



**Title: Ultrafiltration in Heart Failure**

**Professional**

Original Effective Date: April 8, 2013  
 Revision Date(s): April 8, 2013;  
 October 31, 2013; September 3, 2014;  
 September 1, 2015; July 7, 2016;  
 July 1, 2017; July 9, 2018;  
 August 28, 2019; March 23, 2021;  
 July 2, 2021; December 2, 2021  
 Current Effective Date: September 3, 2014

**Institutional**

Original Effective Date: April 8, 2013  
 Revision Date(s): April 8, 2013;  
 October 31, 2013; September 3, 2014;  
 September 1, 2015; July 7, 2016;  
 July 1, 2017; July 9, 2018;  
 August 28, 2019; March 23, 2021;  
 July 2, 2021; December 2, 2021  
 Current Effective Date: September 3, 2014

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Populations	Interventions	Comparators	Outcomes
Individuals: • With decompensated heart failure	Interventions of interest are: • Ultrafiltration	Comparators of interest are: • Diuretics	Relevant outcomes include: • Overall survival • Quality of life • Hospitalizations • Treatment-related morbidity

**DESCRIPTION**

Ultrafiltration is used to remove excess fluid from patients with volume overload and heart failure. It removes fluid from the blood by using pressure differentials with dialysis equipment or similar filtration devices.

**OBJECTIVE**

The objective of this evidence review is to determine whether ultrafiltration improves the net health outcome in patients with decompensated heart failure compared with diuretics.

**BACKGROUND****Heart Failure**

Heart failure is a relatively common condition that frequently results in hospitalizations and readmissions.

**Treatment**

Various treatment approaches are being explored, especially when the condition is refractory to conventional therapy. Ultrafiltration, also referred to as aquapheresis, is a technique being investigated for a possible role in hospitalized patients with marked volume overload from heart failure. It is used to remove fluid from the blood via pressure differentials during treatment with a dialysis machine or similar filtration device.

It has been suggested that ultrafiltration may offer greater and more expeditious volume and sodium removal than conventional therapies, particularly in patients with decompensated heart failure whose fluid overload is unresponsive to medical management.

Newer devices that allow continuous ultrafiltration in ambulatory patients are under investigation to reduce volume overload.

**Outcome Measures**

Heart failure is a condition with a variable natural history and multiple confounders of outcome. Clinical outcomes of interest in the treatment of heart failure include survival, hospitalization, complications, and quality of life; although removal of fluid and sodium, and weight loss, are important, they are surrogate outcomes that do not necessarily translate into clinical outcomes. Because ultrafiltration does not directly affect ventricular function, its effect on clinical outcomes is difficult to evaluate.

**Regulatory Status**

In 2002, the Aquadex FlexFlow™ System (Baxter; acquired by CHF Solutions in 2016) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. An amended 510(k) approval (classified as a high permeability dialysis system) was given in 2007 following system modifications. The FDA determined that this device was substantially equivalent to existing devices for use in temporary ( $\leq 8$  hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and for extended ( $> 8$  hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization. FDA product code: KDI.

In 2020, the FDA approved the Aquadex FlexFlow® System 2.0 for a slightly modified use: "Continuous ultrafiltration therapy for temporary (up to 8 hours) or extended (longer than 8 hours in patients who require hospitalization) use in adult and pediatric patients weighing 20 kilograms or more whose fluid overload is unresponsive to medical management, including diuretics. All treatments must be administered by a healthcare provider, within an outpatient or inpatient clinical setting, under physician prescription, both of whom having received training in extracorporeal therapies."<sup>1</sup>

## **POLICY**

The use of ultrafiltration is considered **experimental / investigational** in patients with compensated heart failure who are being treated in the outpatient setting.

### Policy Guidelines

This policy does not apply to patients with renal failure being treated using dialysis.

## **RATIONALE**

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 11, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## **HEART FAILURE**

### **Clinical Context and Therapy Purpose**

The purpose of ultrafiltration in patients with volume overload and heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does ultrafiltration improve the net health outcome in patients with volume overload and heart failure?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with volume overload and heart failure.

### ***Interventions***

The therapy being considered is ultrafiltration. During ultrafiltration, a small catheter is placed in a vein, and the catheter transports blood to the ultrafiltration machine then back to the patient. After ultrafiltration is complete, the patient restarts on diuretics to keep fluid in balance.

### ***Comparators***

The following therapies are currently being used to manage patients with volume overload and heart failure: diuretics.

### ***Outcomes***

The general outcomes of interest are overall survival, quality of life, hospitalizations, and treatment-related morbidity.

Follow-up of at least 10 years would be preferable to determine outcomes.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

## **REVIEW OF EVIDENCE**

### **Systematic Reviews**

A number of systematic reviews of RCTs have been published. None of the meta-analyses reporting all-cause mortality found significant differences in mortality between ultrafiltration and diuresis.<sup>2,3,4,5</sup> Moreover, all but one<sup>6</sup> of the meta-analyses that reported rehospitalizations found no evidence that ultrafiltration was significantly associated with a decrease in rates.<sup>2,3,4,5</sup> All meta-analyses found that ultrafiltration resulted in significantly greater weight loss and fluid removal than diuretic therapy, and none of the pooled analyses found significant differences between treatments in adverse events.<sup>2,3,4,5,6,7,8</sup>

Kwok et al (2017) published a systematic review and meta-analysis of 10 RCTs (N=857 participants) evaluating ultrafiltration in patients with acute decompensated heart failure.<sup>5</sup> A pooled analysis of 7 RCTs did not find a significant difference between groups in all-cause mortality (relative risk [RR], 1.08; 95% confidence interval [CI], 0.77 to 1.52; p=.65). A pooled analysis of 7 RCTs did not find a significant difference in absolute change in creatinine levels (mean difference [MD], 0.01 mg/dL, 95% CI, -0.17 to 0.19 mg/dL; p=.92). However, in a pooled analysis of 9 RCTs, there was significantly greater weight change in the ultrafiltration group than in the control group (mean difference = -1.86 kg; 95% CI, -4.68 to 0.97 kg; p<.001). Pooled analyses of hospitalization rates did not find a statistically significant benefit of ultrafiltration. In a pooled analysis of 3 RCTs, the RR for all-cause hospitalization was 0.89 (95% CI, 0.43 to 1.86) and, in a pooled analysis of 5 RCTs, the RR was 0.71 (95% CI, 0.51 to 1.00; p=.05).

### Randomized Controlled Trials

Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients with ADvanced Heart Failure (TAVRUNLOAD) was a nonblinded trial that randomized 200 patients hospitalized for heart failure and hypervolemia during the first 24 hours of hospitalization to ultrafiltration or to usual care (diuretics).<sup>9</sup> The trial was conducted at 28 U.S. centers. Primary efficacy endpoints were 48-hour weight loss and dyspnea score (1- to 7-point Likert scale). Primary safety endpoints were changes in blood urea nitrogen, creatinine, and electrolyte levels throughout hospitalization and 90-day follow-up, and episodes of hypotension requiring therapeutic intervention at 48 hours. The trial had at least 13 secondary efficacy endpoints, including length of index hospitalization, quality of life assessments throughout follow-up, and resource utilization (rehospitalization for heart failure, unscheduled office and emergency department visits) during follow-up. Results showed more weight loss in the ultrafiltration group (5.0 kg) than in the usual care group (3.1 kg) from baseline to 48 hours ( $p=.001$ ), with no difference between groups in dyspnea scores. There was no significant difference in the length of stay of the index hospitalization between groups, but the ultrafiltration group (18%) had a smaller percentage of patients rehospitalized for heart failure at 90 days than the diuretics group (32%;  $p=.037$ ). There were no significant differences between treatment groups for quality of life assessments or renal function, except for a greater likelihood of hypokalemia in the diuretics group ( $p=.018$ ). Costanzo et al (2010), in an additional subgroup analysis, compared outcomes between ultrafiltration and standard intravenous diuretics by continuous infusion or bolus injection.<sup>10</sup> Similar fluid loss was observed for ultrafiltration and continuous diuretic infusion, with outcomes similar to the original TAVR UNLOAD trial (i.e., fewer rehospitalizations for heart failure at 90 days only in patients who underwent ultrafiltration).

Detailed analysis of TAVR UNLOAD identified methodologic concerns that could have influenced trial results. The publication provided insufficient detail on patient status during the trial. The investigators reported that 20 patients died during the trial (9 in the ultrafiltration group, 11 in the usual care group), but the timing of deaths was not reported. The trial results, as reported, also raised concerns about dropout rates and patient follow-up for various outcome measures. For example, although 100 patients were randomized to each group, at 48 hours, only 83, 80, and 69 patients in the ultrafiltration group and 84, 83, and 75 patients in the standard care group, respectively, were reported for the 3 primary outcomes (weight loss, dyspnea score, change in serum creatinine level, respectively). For readmission at 90 days, while the denominators were reported as 89 for the treatment group and 87 for the usual care group, information from the report lists 45 and 41 patients at risk, respectively, at 90 days. In addition, it is not clear from the methods that intention-to-treat analyses were performed; and, despite the number of outcomes assessed, there appears to have been no statistical correction for multiple comparisons. Finally, neither participants nor investigators were blinded to treatment, which is a potential source of bias for outcomes such as rehospitalizations, which are clinically based decisions.

Bart et al (2012) reported on the CADriorenal REScue Study in Acute Decompensated Heart Failure (CARRESS) trial, comparing fixed-rate ultrafiltration with diuretic-based stepped pharmacologic therapy in 188 patients hospitalized with acute decompensated heart failure and decreased renal function.<sup>11</sup> Unlike the TAVR UNLOAD trial, outcomes in CARRESS were better in the diuretic group. Primary outcomes were changes in serum creatinine and body weight, as measured 96 hours after randomization. The ultrafiltration group experienced a significant increase in serum creatinine levels (0.23 mg/dL) compared with the pharmacologic therapy

group (0.04 mg/dL), which had a decrease ( $p=.003$ ). Mean weight loss did not differ significantly between groups (5.7 kg in the ultrafiltration group vs. 5.5 kg in the pharmacologic therapy group;  $p=.58$ ). Serious adverse events occurred more frequently in the ultrafiltration group (72%) during the 60-day follow-up period than in the pharmacologic therapy group (57%;  $p=.03$ ). Those events included kidney failure, bleeding complications, and complications related to intravenous catheters.

Marenzi et al (2014) published findings of the CUORE trial.<sup>12</sup> This RCT included 56 hospitalized heart failure patients without severe renal insufficiency who were treated with ultrafiltration ( $n=27$ ) or standard medical therapy ( $n=29$ ). All patients had a left ventricular ejection fraction of 40% or less, fluid overload of 4 kg or more of recent weight gain, and were partially responsive to diuretic therapy. The primary endpoint was the incidence of heart failure-related rehospitalizations during the year after treatment. Four rehospitalizations occurred in the ultrafiltration group, which was significantly fewer instances than the 30 rehospitalizations in the control group (hazard ratio, 0.14; 95% CI, 0.04 to 0.48;  $p=.002$ ). At the 1-year follow-up, 7 (26%) deaths were reported in the ultrafiltration group versus 11 (38%) in the control group ( $p=.33$ ). Weight loss at discharge was similar in both groups ( $p=.75$ ).

Constanzo et al (2016) published results of the Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (Avoid-HF) trial.<sup>13</sup> This unblinded multicenter RCT tested a strategy of adjustable ultrafiltration and compared it with adjustable intravenous loop diuretic treatment. Eligibility included hospitalization with a primary diagnosis of acute decompensated heart failure, and participants were randomized within 24 hours of hospital admission. The trial originally aimed to enroll 810 patients and the sample size calculation determined that this number of participants was needed to have sufficient power for the primary end point. However, after enrolling 224 (27.5%) patients, the trial sponsor terminated the study due to slow enrollment. The analysis reports on 221 (110 patients in the ultrafiltration group, 111 in the diuretic group) enrolled at the time of study termination. The primary end point (a composite of heart failure rehospitalization or unscheduled or outpatient or emergency department treatment for heart failure) occurred in 25% of the ultrafiltration group and 35% of the diuretic group (exact numbers not reported). The difference in event rates between groups was not statistically significant ( $p=.106$ ). By 90 days, death occurred in 17 (15%) ultrafiltration patients and 14 (13%) diuretic patients ( $p=.827$ ). The proportion of patients who experienced any adverse event or serious adverse event did not differ significantly between groups, but the ultrafiltration group (15%) experienced significantly more serious adverse events determined to be related to trial therapy than the diuretic group (5%;  $p=.026$ ).

### Summary of Evidence

For individuals who have decompensated heart failure who receive ultrafiltration, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, quality of life, hospitalizations, and treatment-related morbidity. A number of RCTs and meta-analyses of these controlled trials have been published. Meta-analyses did not find significant differences in all-cause mortality in patients receiving ultrafiltration or diuretics, and nearly all meta-analyses found no significant between-group differences in rehospitalization rates. RCTs and meta-analysis found that patients undergoing ultrafiltration had significantly greater weight loss and more fluid removal than diuretic therapy. Although pooled analyses of randomized controlled trials did not find significant differences in adverse events in groups receiving ultrafiltration or diuretics, some RCTs (e.g., CARESS, AVOID-HR) have reported higher

rates of adverse events after ultrafiltration, including significant worsening of renal function and treatment-related serious adverse events. The available trials have several methodologic limitations (e.g., unblinded outcome assessment, incomplete information on patient status). Moreover, long-term outcomes (i.e., >1 year) have not been reported. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **SUPPLEMENTAL INFORMATION**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **American College of Cardiology Foundation and American Heart Association**

In 2013, the American College of Cardiology Foundation and American Heart Association published joint guidelines on the diagnosis and management of heart failure in adults (under Recommendations for Hospitalized Patient) that list ultrafiltration as a class IIb recommendation (benefit greater than or equal to risk, additional studies needed).<sup>14</sup> The recommendations indicated that ultrafiltration "may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight" (level of evidence B: conflicting evidence) and "for patients with refractory congestion not responding to medical therapy" (level of evidence C: recommendation less well established). A 2017 update from the American College of Cardiology, the American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Failure Society of America did not mention ultrafiltration.<sup>15</sup>

#### **European Society of Cardiology and Heart Failure Association**

In 2012, the European Society of Cardiology and Heart Failure Association released joint guidelines on the diagnosis and treatment of acute heart failure, which stated "ultrafiltration is sometimes used to remove fluid in patients with HF [heart failure], although [it] is usually reserved for those unresponsive or resistant to diuretics."<sup>16</sup> In 2016, an updated note that "ultrafiltration is not recommended and should be confined to patients who fail to respond to diuretic-based strategies" was added.<sup>17</sup>

#### **Heart Failure Society of America**

In 2010, the Heart Failure Society of America's comprehensive heart failure practice guidelines indicated that ultrafiltration may be considered for the treatment of acute decompensated heart failure fluid overload in lieu of diuretics (level B evidence: cohort or smaller studies).<sup>18</sup> The Society's guidelines also indicated ultrafiltration may be considered when congestion continues despite diuretic therapy (level C evidence: opinion).

#### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02846337	Ultrafiltration Versus Medical Therapies in the Management of the Cardio Renal Syndrome (UF-CARE)	154	Sep 2021
<i>Unpublished</i>			
NCT02829450	Home-based Ultrafiltration for Congestive Heart Failure: Impact on Survival, Hospitalizations Rate, Quality of Life, Peritoneal Membrane Characteristics and Residual Renal Function With Different Treatment Modes	40	Oct 2020 (status: unknown)

NCT: national clinical trial.

## **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

### CPT/HCPCS

37799 Unlisted procedure, vascular surgery  
 90999 Unlisted dialysis procedure, inpatient or outpatient  
 0692T Therapeutic ultrafiltration (Use 0692T no more than once per day)  
 Effective 10-01-2021

- There are no specific CPT codes for this procedure.

### ICD-10 Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

## **REVISIONS**

04-08-2012	Policy added to the bcbsks.com web site.
10-31-2013	Description section reviewed
	Rationale section updated
	References updated

09-03-2014	In Policy section: <ul style="list-style-type: none"> <li>Revised the policy statement to add "compensated" and "who are being treated in the outpatient setting" to read, "The use of ultrafiltration is considered experimental / investigational in patients with compensated congestive heart failure who are being treated in the outpatient setting."</li> </ul>
	Rationale section updated
	References updated
09-01-2015	Policy title revised from "Ultrafiltration in Decompensated Heart Failure"
	Updated Description section.
	Updated Rationale section.
07-07-2016	Updated References section.
	Updated Description section.
	Updated Rationale section.
07-01-2017	Updated References section.
	Updated Description section.
	Updated Rationale section.
07-09-2018	Updated References section.
	Updated Description section.
	Updated Rationale section.
08-28-2019	In Coding section: <ul style="list-style-type: none"> <li>Updated Coding bullets.</li> </ul>
	Updated Description section.
	Updated Rationale section.
03-23-2021	Updated References section.
	Updated Description section.
	Updated Rationale section.
07-02-2021	Updated References section.
	Updated Rationale section.
12-02-2021	In the Coding Section <ul style="list-style-type: none"> <li>Added CPT code 0692T</li> </ul>

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## Other References

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