Medical Policy

Title: Ultrafiltration in Heart Failure

Professional
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<table>
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<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals: With decompensated heart failure</td>
<td>Interventions of interest are: Ultrafiltration</td>
<td>Comparators of interest are: Diuretics</td>
<td>Relevant outcomes include: Overall survival, Quality of life, Hospitalizations, Treatment-related morbidity</td>
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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 policy is to evaluate whether ultrafiltration improves health outcomes in patients with decompensated heart failure compared with diuretics.

BACKGROUND
Heart failure is a relatively common condition that frequently results in hospitalizations and readmissions. Various treatment approaches are being explored, especially when the condition is refractory to conventional therapy. Ultrafiltration (also called 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.

REGULATORY STATUS
In June 2002, the Aquadex™ FlexFlow™ System (Baxter, Deerfield, IL) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. An updated/amended 510(k) approval (classified as a high permeability dialysis system) was given in September 2007 following modifications. The FDA determined that this device was substantially equivalent to existing devices for use in temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and for extended (longer than 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization. FDA product code: KDI.
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
The most recent literature review covers the period of through March 23, 2017.

Heart failure is a condition with a variable natural history and multiple confounders of outcome. Clinical outcomes of interest in treatment of CHF include survival, hospitalization, complications, and quality of life; although removal of fluid and sodium, and weight loss, are important, these are surrogate outcomes that don't necessarily translate into clinical outcomes. Because ultrafiltration does not directly affect ventricular function, its effect on clinical outcomes is difficult to evaluate. Therefore, randomized controlled trials (RCTs) in well-defined, comparable groups are necessary to determine the comparative effectiveness of ultrafiltration and conventional therapy on clinically important outcomes; other study designs will not provide adequate evidence to control for confounding factors and variation in the natural history of heart failure. The following is a summary of key literature.

Heart Failure
Systematic Reviews
A number of systematic reviews of RCTs have been published, with several reported meta-analyses pooling study outcomes. None of the meta-analyses reporting all-cause mortality found significant differences in mortality between ultrafiltration and diuresis.\(^1\)\(^-\)\(^4\) Moreover, all but one\(^5\) of the meta-analyses that reported rehospitalizations found no evidence that ultrafiltration was significantly associated with a decrease in rates.\(^1\)\(^-\)\(^4\) 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.\(^1\)\(^-\)\(^7\)

Most recently, Kwok et al (2017) published a systematic review and meta-analysis of 10 RCTs (total N=857 participants) evaluating ultrafiltration in patients with acute decompensated heart failure.\(^4\) 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; \(p=0.65\)). 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; \(p=0.92\)). However, in a pooled analysis of 9 RCTs, there was significantly greater weight change in the ultrafiltration group than in the control group (MD = -1.86 kg; 95% CI, -4.68 to 0.97 kg; \(p<0.001\)). Pooled analyses of hospitalization rates did not find a statistically significant benefit of ultrafiltration. In a pooled analysis of 3 RCTs, the relative risk for all-cause hospitalization was 0.89 (95% CI, 0.43 to 1.86) and in a pooled analysis of 5 RCTs, the relative risk was 0.71 (95% CI, 0.51 to 1.00; \(p=0.05\)).
Randomized Controlled Trials
UNLOAD was a nonblinded trial that involved 200 patients hospitalized for heart failure and hypervolemia randomized during the first 24 hours of hospitalization to ultrafiltration or to usual care (diuretics). The trial was conducted at 28 U.S. centers. Primary efficacy end points were 48-hour weight loss and dyspnea score (1- to 7-point Likert scale). Primary safety end points 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 end points, 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=0.001), 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=0.037). 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=0.018). Additional subgroup analysis compared outcomes between ultrafiltration and standard intravenous diuretics by continuous infusion or bolus injection. Similar fluid loss was observed for ultrafiltration and continuous diuretic infusion, with outcomes similar to the original UNLOAD trial (ie, fewer rehospitalizations for heart failure at 90 days only in patients who underwent ultrafiltration).

Detailed analysis of UNLOAD identified methodologic concerns that could have influenced trial results. The publication provided insufficient detail of patient status during the trial. The authors 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 study results, as reported, also raise 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 are 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 in outcomes such as rehospitalizations, which are clinically based decisions.

The CARRESS Trial, published by Bart et al (2012), compared fixed-rate ultrafiltration with diuretic-based stepped pharmacologic therapy in 188 patients hospitalized with acute decompensated heart failure and decreased renal function. Unlike the 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 (0.23mg/dL, SD=0.70) compared with the pharmacologic therapy group (0.04mg/dL, SD=0.53), which had a decrease (p=0.003). Mean weight loss did not differ significantly between groups (5.7 kg [SD=3.9] in the ultrafiltration group vs 5.5 kg [SD=5.1] in the pharmacologic therapy group; p=0.58). 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=0.03). Those events included kidney failure, bleeding complications, and complications related to intravenous catheters.

Marenzi et al published findings of the CUORE trial in 2014.11 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 and fluid overload of 4 kg or more of recent weight gain and were partially responsive to diuretic therapy. The primary end point 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=0.002). At the 1-year follow-up, 7 (26%) deaths were reported in the ultrafiltration group versus 11 (38%) in the control group (p=0.33). Weight loss at discharge was similar in both groups (p=0.75).

The most recently published RCT is the AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trial by Costanzo et al (2016).12 This unblinded multicenter RCT tested a strategy of adjustable ultrafiltration and compared it to 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 include 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 study 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=0.106). By 90 days, death occurred in 17 (15%) ultrafiltration patients and 14 (13%) diuretic patients (p=0.827). The proportion of patients who experienced any adverse event or any 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 study therapy than the diuretic group (5%; p=0.026).

Section Summary: Heart Failure
A number of RCTs and meta-analyses of RCTs 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 RCTs did not find significant differences in adverse events in groups receiving ultrafiltration or diuretics, some RCTs (eg, 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 (eg, unblinded outcome assessment, incomplete information on patient status). Moreover, long-term outcomes (ie, >1 year) have not been reported.
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. Some but not all published RCTs reported beneficial effects of ultrafiltration on physiologic measures and intermediate outcomes such as weight loss, and/or reductions in intensive care unit stay or readmissions for heart failure, however, RCTs have not demonstrated improvement in clinical outcomes such as survival. Additionally, significant worsening of renal function and serious adverse events have been reported following ultrafiltration in patients with acute heart failure. Finally, available trials have several methodologic limitations and long-term outcomes have not been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Cardiology Foundation and American Heart Association
The 2013 American College of Cardiology Foundation/American Heart Association Guidelines for the Diagnosis and Management of Heart Failure in Adults (under Recommendations for Hospitalized Patient) lists ultrafiltration as a Class IIb recommendation (benefit greater than or equal to risk, additional studies needed). The recommendations state 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).

European Society of Cardiology and Heart Failure Association
The European Society of Cardiology Task Force’s 2012 guidelines on the diagnosis and treatment of acute heart failure states “ultrafiltration is sometimes used to remove fluid in patients with HF, although is usually reserved for those unresponsive or resistant to diuretics.” The guidelines noted, however, the efficacy and safety of ultrafiltration is unknown.

Heart Failure Society of America
The Heart Failure Society of America’s (HFSA) 2010 Comprehensive Heart Failure Practice Guidelines indicate ultrafiltration may be considered for the treatment of acute decompensated heart failure fluid overload in lieu of diuretics. The HFSA guidelines also indicate 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
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<tr>
<td>NCT02846337</td>
<td>Ultrafiltration Versus Medical Therapies in the Management of the Cardio Renal Syndrome (UF-CARE)</td>
<td>154</td>
<td>Sep 2019</td>
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</table>

NCT: national clinical trial.
CODING
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

CPT/HCPCS
37799 Unlisted procedure, vascular surgery
90999 Unlisted dialysis procedure, inpatient or outpatient

- There are no specific CPT codes for this procedure.
- There is an ICD-9-CM procedure code specific to the procedure: 99.78 Aquapheresis

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

REVISIONS

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<td>Rationale section updated</td>
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<tr>
<td>09-03-2014</td>
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<td>Revised the policy statement to add &quot;compensated&quot; and &quot;who are being treated in the outpatient setting&quot; to read, &quot;The use of ultrafiltration is considered experimental / investigational in patients with compensated congestive heart failure who are being treated in the outpatient setting.&quot;</td>
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REFERENCES

14. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. Jul 2012;33(14):1787-1847. PMID 22611136

Other References
1. Blue Cross and Blue Shield of Kansas Cardiology Liaison Committee, May 2014.