

**VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM**

BRIEF OVERVIEW:

ULTRAFILTRATION FOR HEART FAILURE

Prepared by
Karen Flynn, DDS, MS
Program Manager

May 2008

TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

TAP has two categories of products directed toward filling urgent information needs of its VA clients. TAP assigns a category to each new request based largely on the availability of studies from results of initial searches of peer-reviewed literature databases:

- The **Short report** is a self-contained, rapidly-produced qualitative systematic review between 5 and 20 pages in length. It provides sufficient background information and clinical context to its subject to be accessible to a wide audience, including non-clinician managers.
- The **Brief overview** originated as an internal memo to VA clients with both well-defined and urgent information needs. It usually comprises 2 to 10 pages and assumes sufficient existing knowledge regarding clinical context and technology issues by its readers to omit these components. It often requires some additional reading of documents (provided with the overview for the client) to obtain a full and comprehensive picture of the state of knowledge on the topic.

All TAP products are reviewed internally by TAP's physician advisor and key experts in VA. Additional comments and information on this report can be sent to:

VA Technology Assessment Program • Office of Patient Care Services
Boston VA Healthcare System (11T) • 150 S. Huntington Ave. • Boston, MA 02130
Tel. (857) 364-4469 • Fax (857) 364-6587 • VATAP@va.gov

A SUMMARY FOR HTA REPORTS
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VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist[®] as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP added this checklist[®] to its reports in 2002.

This summary form is intended as an aid for those who want to record the extent to which an HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

Brief Overview: Ultrafiltration for Heart Failure May 2008			
Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?			√
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

ABBREVIATIONS IN THIS REVIEW

AKI , acute kidney injury	LOS , length of stay
ACE , angiotension-converting enzyme	LR , likelihood ratio
ACS , acute coronary syndrome	LVEF left ventricular ejection fraction
ADHF , acute decompensated heart failure	MI , myocardial infarction
AHRQ , Agency for Healthcare Research and Quality	NHSC , National Horizon Scanning Centre (UK)
AMI , acute myocardial infarction	NHLBI , National Heart, Lung, and Blood Institute
BNP , B-type natriuretic peptide	NHS , National; Health Service (UK)
BP , blood pressure	NIH , National Institutes of Health
CEP , center for Evidence-based Purchasing (UK-NHS)	NIV , non-invasive ventilation
CHF , congestive heart failure	NIPSV , noninvasive pressure support ventilation
CHF Solutions/CHFS , device manufacturer	NNT , number needed to treat
CI , 95% confidence interval	NYHA , New York Heart Association
CPAP , continuous positive airway pressure	NS , not significant
CS , clinical scenario	NT-proBNP , N-terminal pro-B-type natriuretic peptide
CVA , cerebrovascular accident	OR , odds ratio
ED , emergency department	RCT , randomized controlled trial
EF , ejection fraction	RR , relative risk
FDA , Food and Drug Administration	RRT , renal replacement therapy
GP , general practitioner	SBP , systolic blood pressure
GFR , glomerular filtration rate	TAAG , Technology Assessment Advisory Group (VHA Office of Patient Care Services)
HF , hemofiltration	UF , ultrafiltration
HFSA , Heart Failure Society of America	
IV , intravenous	

BRIEF OVERVIEW:

ULTRAFILTRATION FOR HEART FAILURE

“Acute heart failure syndrome (AHFS) is defined as a gradual or rapid change in heart failure signs and symptoms resulting in the need for urgent therapy. The syndrome is complex and encompasses multiple diagnoses and etiologies.” Mezabaa (2008)

“Large databases obtained in the past decade from registries and clinical trials have allowed a better characterization of the clinical profile of patients admitted to hospitals for decompensated heart failure (DHF). This new information has clearly recognized fluid overload and pulmonary congestion as the main reasons for hospitalization in the great majority of these patients.” Elkayam (2007)

“Although used routinely in pediatric patients, ultrafiltration techniques that reverse hemodilution are infrequently used in adults. Data from small, unblinded clinical trials suggest that the use of ultrafiltration can reduce inflammatory mediators, improve cardiac function, and reverse hemodilution....” Boodhwani (2006)

“...Ultrafiltration is an alternative therapy that has theoretic advantages over management with diuretics but has not been widely used in the clinical setting. Interest in this technology, however, has grown with the recent development of a portable, bedside device (Aquadex Flex Flow; CHF Solutions, Inc, Brooklyn Park MN) that can accomplish ultrafiltration by continuous venovenous hemofiltration through peripherally inserted intravenous catheters. This device is essentially an extracorporeal circuit that permits removal of an isotonic ultrafiltrate composed primarily of free water with sodium, potassium, and other small molecules from whole blood through use of a specialized hemofilter...” Levy (2008)

“Heart failure is a condition that affects nearly 5 million people in the United States and costs the nation an estimated \$35 billion a year. Although common, the condition presents treating clinicians with real challenges. There are currently few effective therapies for people with acute decompensated disease...” Bart (2007)

Despite the significant investment of money and health care resources, mortality from HF continues to rise, increasing 155% from 1979 to 2001. Within the same time interval, over 80% of patients seen in an emergency room with HF were admitted to the hospital, representing a 164% increase in hospital admissions. Regrettably, ambulatory management of patients with advanced HF has been largely unsuccessful, necessitating more frequent hospitalization in these recalcitrant patients...

“Today, for those advanced HF patients who remain symptomatic despite optimal conventional therapy, limited treatments exist; but as newer therapies evolve, the options will expand to include more than palliative care, heart transplant, and ventricular assist devices.” Mehta (2005)

“Pharmacological therapy is the current standard of care for ADHF, but non-pharmacological devices and assistance can be beneficial. Respiratory therapies such as positive pressure and mechanical ventilation should be an integral part of therapy in cardiogenic shock to maintain oxygen saturation within the normal range to prevent end-organ dysfunction, decrease diaphragmatic activity, and increase functional residual capacity.” Gauthier (2008)

“ADHF accounts for over 1 million hospital admissions each year in the USA. Of these, 75% occur in the 12.4% of the population over 65 years of age, and more than 60%

occur in the 6.2% of the population that is over 75 years of age...it is the most costly medical illness to the Medicare system. In addition, it is anticipated that the number of hospitalizations for ADHF will double in the next 25 years due to the progressive aging of the population.” Rich (2007)

“Although AHF is associated with a poor prognosis only recently guidelines from Europe and USA have begun to address management of AHF syndromes (AHFS), and the clinical trial data supporting these recommendations are limited. Moreover, most of these clinical trials failed to show a decrease in mortality. A potential explanation is the heterogeneity of AHFS and the lack of a classification which could help design appropriate treatment algorithms...” Filippatos (2007)

“Acute decompensated heart failure is the most common cause for hospitalization among patients over 65 years of age...In-hospital mortality remains high for both systolic and diastolic forms of the disease. Therapy is largely empirical as few randomized, controlled trials have focused on this population and consensus practice guidelines are just beginning to be formulated. Treatment should be focused on correction of volume overload, identifying potential precipitating causes, and optimizing vasodilator and beta-adrenergic blocker therapy. The majority of patients (>90%) will improve without the use of positive inotropic agents, which should be reserved for patients with refractory hypotension, cardiogenic shock, end-organ dysfunction or failure to respond to conventional oral and/or intravenous diuretics and vasodilators” Dec (2007)

“Diuretic therapy in the management of volume-overloaded patients with ADHF can be dramatically effective. Diuretic therapy is inexpensive, easily administered, and applicable in a variety of treatment settings including emergency departments, intensive care units, and monitored and unmonitored units. For the patient with normal blood pressure and intact renal function, diuretic therapy may be sufficient to relieve the acute symptoms of decompensated HF. However, there are important limitations associated with the utility and tolerability of diuretic use.” Hill (2006)

“In the U.S, 90% of the one million annual hospitalizations for heart failure (HF) are due to symptoms of volume overload. Hypervolemia contributes to HF progression and mortality. Treatment guidelines recommend that therapy of patients with HF be aimed at achieving euvolemia.” Costanzo (2007)

“Congestive heart failure (CHF) is an increasingly common medical condition and the fastest growing cardiovascular diagnosis in North America. Over one-third of patients with heart failure also have renal insufficiency. It has been shown that renal insufficiency confers worsened outcomes to patients with heart failure. However a majority of the larger and therapy-defining heart failure medication and device trials exclude patients with advanced renal dysfunction. These studies also infrequently perform subgroup analyses based on degree of renal dysfunction. The lack of information on heart failure patients who have renal insufficiency likely contributes to their being prescribed mortality and morbidity reducing medications and receiving diagnostic and therapeutic procedures at lower rates than heart failure patients with normal renal function...”

“...Studies are now being conducted to evaluate the utility of ultrafiltration for treatment of ADHF secondary to volume overload. Two of these studies, The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial and the larger and more recent Ultrafiltration Versus intravenous Diuretics for Acute Decompensated heart Failure (UNLOAD) trial, have shown benefits of greater weight loss at 48 h, and fewer re-hospitalizations, unscheduled clinic visits, and emergency room visits.” Saltzman (2007)

“The pathophysiology of the cardiorenal syndrome is poorly understood and likely involves interrelated hemodynamic and neurohormonal mechanisms. When conventional therapy for acute decompensated heart failure fails, mechanical fluid removal via ultrafiltration, hemofiltration, or hemodialysis may be needed. While ultrafiltration can

address diuretic resistance, whether ultrafiltration prevents worsening renal function or improves outcomes in patients with cardiorenal syndrome remains unclear. Evidence regarding the potential renal-preserving effects of nesiritide is mixed, and further studies on the efficacy and safety of nesiritide in heart failure therapy are warranted. Newer therapeutic agents, including vasopressin antagonists and adenosine antagonists, hold promise for the future, and clinical trials of these agents are under way.” Liang (2008)

“The clinical classification of patients with ADHF continues to evolve and reflects ongoing changes in our understanding of the pathophysiology of this syndrome. Worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function all seem to play a role. Decompensation also commonly occurs without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications related to inadequate financial resources, poor compliance, and lack of education or an inadequate medical regimen may lead to hospitalization without a worsening of underlying circulatory function.” HFSA (2006)

“Noninvasive ventilation (NIV) is a modality for ventilatory support without endotracheal intubation and sedation that has demonstrated to be useful in several forms of respiratory failure. In patients with severe exacerbation of chronic obstructive pulmonary disease, it has been shown to reduce mortality. In the setting of acute pulmonary edema, NIV has been shown to reduce the intubation rate in several randomized trials, using either CPAP or bilevel NIPSV...acute pulmonary edema is currently the second most common indication for NIV in clinical practice, but its use is often based more on perceived efficacy than on scientific evidence. This may be explained because no single trial has shown an impact on hospital mortality, and considerable controversy remains over which technique is superior to the other.” Masip (2005)

“In heart failure, as the heart gets worse, often so do the kidneys, complicating the treatment of heart failure and worsening the prognosis...challenges in the use of diuretics, angiotensin-converting enzyme (ACE)inhibitors, and other therapies in the cardiorenal syndrome...novel therapies that hold promise, such as argeninine vasopressin antagonists, adenosine A₁ receptor antagonists, and ultrafiltration....

“...Although renal function may remain stable at a diminished level in heart failure, in many it eventually leads to worsening end-organ damage, resistance to standard therapy, frequent hospitalizations, exacerbation of symptoms, inability to maintain a good quality of life, and, eventually, death.” Geisberg (2006).

“Acute renal failure (ARF) with the concomitant need for renal replacement therapy (RRT) is a common complication of critical care medicine that is still associated with high mortality. Different RRT strategies, like intermittent hemodialysis, continuous venovenous hemofiltration, or hybrid forms that combine the advantages of both techniques, are available....Since a general survival benefit has not been demonstrated for either method, it is the task of the nephrologist or intensivist to choose the RRT strategy that is most advantageous for each individual patient...”

“...The underlying disease, its severity and stage, the etiology of ARF, the clinical and hemodynamic status of the patient, the resources available, and the different costs of therapy may all influence the choice of RRT strategy. ARF, with its risk of uremic complications, represents an independent risk factor for outcome in critically ill patients. In addition, the early initiation of RRT with adequate doses is associated with improved survival...” John (2007)

“The indication to use device therapy in acute heart failure is predicated on the assumption that continued pharmacologic support is either ineffective or associated with excessive morbidity or mortality....For the volume overloaded patient with heart failure in the intensive care unit, peripheral ultrafiltration does appear effective and safe in treating volume overload and may be especially useful when blood pressure, renal insufficiency, and/or diuretic resistance complicate the clinical picture.” Kale (2008).

BACKGROUND

VHA's TAAG asked the VA Technology Assessment Program (TAP) for a review of the literature as support for use of ultrafiltration in heart failure patients. TAP searched first for available systematic reviews, technology assessments, and guidelines as a means of quickly gauging the overall status of research on ultrafiltration in this context.

The most recent guideline developers (Mebazaa, 2008) report consensus recommendations of a group of European and American clinical experts for pre-hospital and early in-hospital management of acute heart failure syndromes: as a narrative review focusing on early treatment (ultrafiltration not addressed), Mebazaa (2008) is not included in the Appendix tables. However, Mebazaa does provide a useful clinical classification (Figure 1, below):

Figure 1. Classification system for presenting characteristics of acute heart failure syndrome patients

Adapted from Mebazaa (2008)

Class	Description
CS1	<ul style="list-style-type: none"> • SBP>140mm Hg; • Abrupt symptom development; • Diffuse pulmonary edema; • Minimal systemic edema (patient eu- or hypo-volemic); • Acute elevation of filling pressure often with preserved LVEF; • Vascular pathophysiology
CS2	<ul style="list-style-type: none"> • SBP 100-140 mm Hg; • Gradual development of symptoms with gradual increase in body weight; • Predominately systemic edema; • Minimal pulmonary edema; • Chronic filling pressure elevation with increased venous and pulmonary artery pressure; • Manifestations of organ dysfunction: renal and liver, anemia, hyper-albuminemia;
CS3 and subsets	<ul style="list-style-type: none"> • SBP< 100 mm Hg; • Rapid or gradual symptom onset; • Signs of hypo perfusion predominate; • Minimal systemic and pulmonary edema; • Elevated filling pressure;
	Clear hypoperfusion or cardiogenic shock
	No hypoperfusion/cardiogenic shock
CS4	<ul style="list-style-type: none"> • Signs and symptoms of acute heart failure; • Evidence of ACS; • Isolated cardiac troponin is inadequate for this classification;
CS5	<ul style="list-style-type: none"> • Rapid or gradual onset; • No pulmonary edema; • Right ventricular dysfunction; • Systemic venous congestion;

METHODS

Search strategy

TAP searched Medline via PubMed and Dialog, Embase, and Cochrane databases from 1990 to April 2008. Search terms were: ultrafiltration, heart failure, and hemodialysis. All searches were restricted to adult human patients and English language publications. TAP also included search terms to identify existing systematic reviews, meta-analyses, economic analyses, and technology assessments i.e., syntheses of the literature that would enhance TAP's ability to meet the information needs of OPCS quickly. Hand searching reference lists of articles initially retrieved allowed TAP to identify and retrieve additional full-text publications.

Finally, the databases of the International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org), the AHRQ guideline clearinghouse (www.guideline.gov), and the NIH listing of clinical trials(www.clinicaltrials.gov) were searched, and an electronic query addressed to TAP's colleague INAHTA members requested information on completed or in-progress reviews and technology assessments. One reviewer (KF) selected, read, and abstracted all retrievals.

Analytic framework: epidemiologic study cycle

The progression of epidemiologic studies, or the epidemiologic study cycle, confirming the existence and strength of an observed association between exposure and disease (or intervention and outcome) is both well-documented and the foundation for the systematic review framework outlined below (Ibrahim, 1985; Mausner and Kramer, 1985; Lilienfeld and Stolley, 1994; Muir Gray, 1997): it begins with observational, hypothesis-generating studies such as single case or case series reports, then on to cross-sectional (also known as survey, correlational, or ecological) studies, which ascertain exposure and disease at the same point in time, then progresses through analytic, hypothesis-testing studies (case-control or cohort, from which relative risk or estimates can be calculated), and culminates in the randomized controlled trial confirming causality.

Inclusion criteria

The Appendix tables abstract published studies worthy of consideration by the TAAG: systematic reviews, technology assessments, cost-effectiveness or-utility analyses, or other studies clearly based on systematic reviews, and subsequently published papers representing credible research and reporting survival, functional outcomes, or adverse events for ultrafiltration in acutely decompensated heart failure.

Exclusion criteria

- non-English language articles;
- studies in pediatric populations;
- animal studies;
- single case reports;
- case series;
- narrative reviews, editorials, and other articles lacking primary clinical data;
- guidelines or policy statements not explicitly addressing ultrafiltration.
- primary studies included in available systematic reviews or assessments, which TAP generally considers redundant. However, in this case, the single most relevant recent RCT [Costanza (2007; the UNLOAD trial)], cited in reviews and assessments, is abstracted Appendix Table 1 as a point of reference for ongoing research.

Analytic framework: systematic reviews

Cook (1997) and Mulrow (1997) define systematic reviews: “*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their “subjects”. They synthesize the results of multiple primary investigations by using strategies that limit bias and random error...*”

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible science.

Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook, 1995; Guyatt 1995), where they receive the highest level designation.

RESULTS

Appendix Table 1 abstracts available systematic reviews and technology assessments; Table 2 lists in-progress clinical studies.

CONCLUSIONS AND DISCUSSION

One ultrafiltration device, the Aquadex FlexFlow system (CHF Solutions, Brooklyn Park MN) has been FDA approved for marketing in the US since December 2006 for temporary (up to eight hours) treatment of patients with fluid overload who have failed diuretic therapy and for extended (longer than eight hours) treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization.

FDA stipulates that treatment be administered by a health care provider under physician supervision and that both provider and physician have been trained in extracorporeal therapies. The FDA approval letter does not explicitly reference published studies, but it is reasonable to assume that FDA reviewers identified the same trials included by Colechin (2007; Appendix Table 1), with the exception of Costanzo (2007) (also in Appendix Table 1), which was published after the date of the FDA letter. Colechin (2007) thus remains the most recent and comprehensive systematic review of ultrafiltration for acute decompensated heart failure and provides the core evidence considered by TAP in the present review.

TAP identified no recently published evidence to materially change NHS/CEP conclusions (Colechin, 2007):

“CEP finds that ultrafiltration has significant potential to become a routine therapy for excess fluid removal in patients with congestive heart failure. However, further work is needed to establish the patient groups who would benefit most, the optimal rates of fluid

removal, the conditions for termination of therapy, and the cost savings associated with long-term quality of life benefits.”

These conclusions can be transferred to the US in 2008. Additional shortcomings of the available literature include:

- Lack of blinding, which may be understandably difficult in the case of a bulky bedside device;
- Lack of explicit power calculations and correspondingly small numbers of patients in clinical trials, which may reflect the relative lack of reliable estimates of clinically significant effects for ultrafiltration in available research on which such calculations would be based;
- Lack of follow up beyond two to three months;
- Reliance on intermediate or surrogate outcomes such as fluid volume removed or weight lost, rather than longer term outcomes such as quality of life or heart failure-specific mortality.
- The device manufacturer is a significant presence in published and ongoing trials.

Finally, the systematic reviews and assessments in Table 1 do not report significant adverse events or safety concerns, but studies may not have been adequately powered or followed patients for long enough to detect uncommon adverse events. Post-marketing surveillance for a device only available since late 2006 also may be inadequate to detecting uncommon or late adverse events.

APPENDIX

Table 1. Systematic reviews, technology assessments, and recent primary research of ultrafiltration in heart failure patients

Reference	Purpose/details	Results/Comments/Recommendations
Systematic reviews, guidelines, or assessments		
Colechin (2007)	<p>NHS Centre for evidence-based purchasing systematic review with cost impact analysis: Can ultrafiltration be used as an alternative to intravenous diuretics for heart failure patients admitted with fluid overload?</p> <ul style="list-style-type: none"> • Medline searches conducted March 2007; • Included: clinical trials in humans with heart failure. • Cost impact analysis: differences in costs/patient with 12 hr Aquadex system treatment Vs standard treatment with loop diuretics. 	<p>39 studies with 1174 patients (mean study size, 30.2; range, 4-200):</p> <p>Study availability:</p> <ul style="list-style-type: none"> • 7 experimental studies used a broadly similar study design(heart failure patients randomized to treatment with UF Vs conventional diuretics) and enrolled a total of 358 patients (mean 60, median 38, range 16-200, mean age 62 years); • One study compared two different UF protocols; • None of the 32 observational studies used a formal cohort or case-control design; <p>Heterogeneity among studies:</p> <ul style="list-style-type: none"> • The studies used different protocols for UF (including termination conditions), had different primary outcome measures, and different durations of follow up; • In some of the experimental studies, patients receiving UF continued to receive diuretics; • Total volume of fluid removed was the only common outcome measure, but this depended on UF protocol; • There was insufficient homogeneity among the RCTs to conduct a meta-analysis for any outcome measure • Two of the RCTs were supported by the device manufacturer; <p>Study patients:</p> <ul style="list-style-type: none"> • RCTs: no differences in severity of heart failure (as measured by NYHA score) or urinary output prior to UF between groups; • In one study all patients had severe left ventricular systolic dysfunction, but remaining studies did not specify; • Comorbidities: no common inclusion or exclusion criteria. In general, patients with hemodynamic instability, arrhythmia, valvular heart disease, or artificial pacemakers were excluded. Some studies excluded patients with anginas pectoris, systolic hypotension, or conditions related to lung water, but other studies included patients with these conditions <p>Overall:</p> <ul style="list-style-type: none"> • Insufficient evidence from RCTs to permit a systematic review or meta-analysis satisfying Cochrane criteria; • Authors acknowledge practical and ethical difficulties of conducting RCTs in this patient group. <p>Cost analysis:</p> <ul style="list-style-type: none"> • Assumptions: both UF and diuretic require 30 min preparation time for patient and equipment; hematocrit test requiring 5 minutes of RN time carried out every 15 min for first hour of UF to establish flow rate; diuretic treatment based on Costanzo (2007, below) with bolus injections at an average dose of 181mg daily for 48 hrs; and post-discharge care would be the same for both groups; • Costs related to direct hospital treatment of fluid overload in heart failure only, no after-discharge care or

Reference	Purpose/details	Results/Comments/Recommendations
		<p>adverse events included.</p> <p>Cost/patient results:</p> <ul style="list-style-type: none"> • Non-ICU: £2379.39 for UF; £771.39 for diuretics; • ICU: £3758 for UF; £3318 for diuretics; • Results were sensitive to changes in rates of readmission and emergency visits; • Analysis was limited by the data available: further research is needed on resource use associated with UF in subgroups of CHF patients, particularly those with diuretic resistance, where there may be greater potential for UF benefit. Further collection of data on adverse events, long-term quality of life, and post-discharge care is also needed. <p>Conclusions for cost analysis: <i>"The cost impact analysis was used to estimate the impact that treating fluid overload with Aquadex in heart failure patients would have on NHS resources associated with hospital care, compared with standard diuretic treatment. The analysis showed that the cost of treatment was significantly increased, but hospital care costs were reduced overall and the cost of consumables accounted for the majority of the higher treatment cost."</i></p> <p>Among RCTs which compared a single UF treatment with IV diuretics:</p> <ul style="list-style-type: none"> • U F was at least as effective in removing fluid; • UF was effective in diuretic-resistant patients; • UF-treated patients showed sustained (up to 3 months) improvement in exercise test performance; • UF effectiveness on observational studies was in broad agreement with results from RCTs; • No evidence suggested that UF is unsafe, but some studies suggested that UF carries greater risk at high rates of fluid removal, particularly in heart failure patients. <p>Summary: <i>"Ultrafiltration appears to be safe and well tolerated by most CHF patients. Further studies are needed to establish the safe maximum rate of fluid removal, especially for patients in advanced stages of the disease and also to measure the long-term mortality rate"</i></p> <p>Conclusions: <i>"CEP finds that ultrafiltration has significant potential to become a routine therapy for excess fluid removal in patients with congestive hear failure. However, further work is needed to establish the patient groups who would benefit most, the optimal rates of fluid removal, the conditions for termination of therapy, and the cost savings associated with long-term quality of life benefits."</i></p>
HFSA (2006)	<p>Professional society guideline: evaluation and management of patients with acute decompensated heart failure:</p> <ul style="list-style-type: none"> • Quasi-systematic qualitative review (some detail on search but none on election criteria or quality assessment of individual studies) plus expert 	<p><i>"When congestion fails to improve in response to diuretic therapy, the following options should be considered:</i></p> <ul style="list-style-type: none"> • <i>Sodium and fluid restriction ,</i> • <i>Increasing doses of loop diuretic,</i> • <i>Continuous infusion of a loop diuretic, or</i> • <i>Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide)."</i>

Reference	Purpose/details	Results/Comments/Recommendations
	<p>opinion;</p> <ul style="list-style-type: none"> • Interventions considered: evaluation of signs and symptoms; determination of plasma BNP or NT-proBNP; hospital admission (with careful monitoring of weight, fluid intake and output, vital signs, signs, symptoms, electrolytes, and renal function); loop diuretics; careful observation for development of renal dysfunction and other side effects; sodium and fluid restriction, increased doses of loop diuretics, continuous infusion of a loop diuretic, addition of a second oral or IV diuretic, or ultrafiltration; • IV nitroglycerin, nitroprusside, or nesiritide; • IV inotropes; • Invasive hemodynamic monitoring; • Evaluation of admitted patients for precipitating factors; • Discharge planning. 	<p><i>"A fifth option, ultrafiltration, may be considered (Strength of Evidence = C (expert opinion, observational studies, or post-marking safety surveillance))"</i></p>
<p>NHSC (2006)</p>	<p>Horizon scanning briefing: Ultrafiltration: (Aquadex FlexFlow aquapheresis system):</p> <ul style="list-style-type: none"> • Target group: acute decompensated heart failure patients (with very severe peripheral edema and fluid overload who have not responded adequately or rapidly to conventional therapy); • Place of use: secondary care/general non-specialist hospital; or tertiary care. • Other related guidance under development: Nesiritide for acute decompensated heart failure. 	<p>3 RCTs with 261 patients tabulated:</p> <ul style="list-style-type: none"> • Primary outcomes: weight loss, fluid removal, dyspnea score change; • At 48 hrs: 38% greater weight loss and 28% greater fluid removal Vs standard care; • At 90 days: 50% reduction in readmissions and 52% reduction in emergency or clinic visits Vs standard care; • Hemodynamic stability, median 3213 ml fluid removed; • Weight loss, 91.9±17.5 kg to 89.3±17.3 kg. • Adverse events: none in 2/3 trials; 1 catheter site infection in one trial <p>Existing comparators/treatments:</p> <ul style="list-style-type: none"> • Diuretic in acute pulmonary edema; • IV vasodilators (nitrates); • IV inotropes: in severe exacerbations, usually in intensive care; • Treatment of precipitating cause: infection, arrhythmia, hypertension, myocardial infarction, anemia; • Conventional ultrafiltration: high blood flow rates and large bore vascular access, mainly in intensive care or renal department settings; • Once stable, treatment aims to relieve symptoms, improve exercise tolerance, reduce exacerbations and mortality by: ACE inhibitors or angiotensin-II receptor antagonists; diuretics; beta-blockers (stable heart failure); digoxin (for patients with atrial fibrillation); cardiac resynchronization.

Reference	Purpose/details	Results/Comments/Recommendations
		<p>Costs: Aquadex FlexFlow, £12,000; new filter and blood circuit for each patient, £600 (multiple treatments may be required for severe cases).</p> <p>Potential or intended impact: Speculative, but may include decreased length of stay, reduced referrals, and reduced re-admissions.</p>
Hunt (2005)	<p>ACC/AHA guideline update: diagnosis and management of chronic heart failure in the adult: Quasi-systematic review:</p> <ul style="list-style-type: none"> • some information on searches and selection criteria; • quality appraisal limited to assignment to a level of evidence 	<p>Management of fluid status:</p> <ul style="list-style-type: none"> • Many patients with advanced HF have symptoms related to retention of salt and water, thus will respond favorably to interventions designed to restore sodium balance: low doses of loop diuretic with moderate dietary sodium restriction; • As renal function declines, control of fluid retention may require progressive increments in the dose of a loop diuretic or addition of a second diuretic with a different mode of action; • Patients continuing to show evidence of volume overload generally require hospitalization for further adjustment of therapy, possibly intravenous dopamine or dobutamine; • <i>"If the degree of renal dysfunction is severe or if the edema becomes resistant to treatment, ultrafiltration or hemofiltration may be needed to achieve adequate control of fluid retention. The use of such mechanical methods of fluid removal can produce meaningful clinical benefits in patients with diuretic-resistant HF and may restore responsiveness to conventional doses of loop diuretics."</i>
Related reviews/alternate interventions		
Bagshaw (2008)	<p>Systematic review: continuous Vs intermittent renal replacement therapy for critically ill patients with acute kidney injury</p> <ul style="list-style-type: none"> • Randomized trials; • Multiple databases, through Dec 2006 • No language restrictions; • Multiple databases, 1990-2002; • Adult ICU patients with AKI; • Trials assessed for: allocation concealment; description of losses to follow-up or missing outcome data; evidence of important baseline differences; number of centers; predefined outcomes; treatment crossover; power calculation; funding sources. 	<p>9 RCTs with 1403 subjects:</p> <ul style="list-style-type: none"> • No trial satisfied all quality indicators and several had limitations: selection bias; randomization; imbalances in patient characteristics; treatment crossover; • No trial standardized timing, criteria for initiation; or dose of RRT; • No statistical evidence that initial modality influenced mortality (OR, .99; CI, 0.78-1.26, p = .94) or recovery to RRT independence (OR, 0.76; CI, 0.28-2.07; p = .59); • There was suggestion that continuous RRT had fewer episodes of hemodynamic instability and better control of fluid balance. <p>Conclusions: <i>"We identified numerous issues related to study design, conduct, and quality that dispute the validity and question any inferences that can be drawn from these trials. In the context of these limitations, the initial RRT modality does not seem to affect mortality or recovery to RRT independence. There is urgent need for additional high-quality and suitably powered trials to adequately address this issue."</i></p>
Masip (2005)	Systematic review: noninvasive ventilation in acute cardiogenic pulmonary edema:	<p>15 parallel studies included:</p> <ul style="list-style-type: none"> • Overall, noninvasive ventilation significantly reduced mortality rate by 45% Vs conventional therapy(RR, 0.55;

Reference	Purpose/details	Results/Comments/Recommendations
	<ul style="list-style-type: none"> Multiple databases, 1988-2005; RCTs , parallel studies and systematic reviews comparing noninvasive ventilation to conventional oxygen therapy in patients with acute pulmonary edema; CPAP or bilevel NIPSV also included 	<p>CI, 0.40-0.78; P= .72;</p> <ul style="list-style-type: none"> Rates significant for CPAP (RR, 0.53; CI, 0.35-0.82; P = .44) but not for NIPSV (RR, 0.60; CI, 0.34-1.05; P = .76); Both modalities showed significant decrease in need to intubate rate: CPAP (RR, 0.40; CI, 0.27-0.58; P = .21); NIPSV (RR, 0.48; CI, 0.32-0.57; P = .20); together (RR, 0.43; CI, 0.32-0.57; P = .20); There were no differences in intubation or mortality rates in the analysis of studies comparing the 2 techniques. <p>Conclusions: <i>"Noninvasive ventilation reduces the need for intubation and mortality in patients with acute cardiogenic pulmonary edema. Although the level of evidence is higher for CPAP, there are no significant differences in clinical outcomes when comparing CPAP vs NIPSV."</i></p>
Recent primary research		
Rogers (2008)	<p>RCT:</p> <ul style="list-style-type: none"> Consequences of UF Vs standard IV diuretic (furosemide) on renal function; Patient selection: hospitalized for ADHF; EF < 40%; ≥ 2 signs of hypervolemia; Primary outcomes: GFR (iothalamate), renal plasma flow (measured by para-aminohippurate); before fluid removal and at 48 hrs; Secondary end points: urine output and net fluid removal at 48 hrs. 	<p>19 patients (59±16 yrs; 68% male):</p> <ul style="list-style-type: none"> 9 randomized to UF, 10 to IV furosemide; Change in GFR (-3.4 ±7.7 ml/min Vs -3.6 ± 115 ml/min; P = .966) and filtration fraction (-6.9 ± 13.6 ml/min Vs. -3.9 ± 13.6ml/min; P = .644) after treatment were not significantly different between UF and furosemide groups. There was no significant difference in net fluid removal (-3211±2345ml for UF Vs -2725±2330ml for furosemide; P = .682); Urine output during 48 hrs was significantly greater for furosemide (5786 ±2587ml) Vs UF (2286±915ml); P<.001. <p>Conclusions: <i>"During a 48-hour period, UF did not cause any significant differences in renal hemodynamics compared with the standard treatment of intravenous furosemide."</i></p>
Costanzo (2007)	<p>RCT: included by Colechin (2007)</p> <ul style="list-style-type: none"> Patients over 18 yrs hospitalized for HF (28 US centers with experience in ultrafiltration) with ≥2 signs of hypervolemia randomized to UF or IV diuretics and followed 90 days or until death; All patients had dietary sodium and fluid restrictions; Power calculations not reported; Not blinded; Sponsored by and with investigator ties to device manufacturer; Exclusions: acute coronary syndrome; serum creatinine >3.0mg/dL; systolic BP ≤ 90 mm Hg; 	<p>200 patients randomized:</p> <ul style="list-style-type: none"> 100/group; 63 ±15 years; 79% male; 71% with EF ≤40% <p>Results:</p> <ul style="list-style-type: none"> At 48 hrs: weight (5.0±3.1kg Vs 3.1±kg; p = 0.001) and net fluid loss (4.6 Vs 3.1 L; p = 0.001) were greater in UF group; Dyspnea scores were similar; At 90 days; UF group had fewer patients hospitalized for HF(18% Vs 32%; p = 0.037); HF rehospitalizations (0/22 ±0.54 Vs 0.46 ±0.76; p = 0.022); rehospitalization days/patient (1.4±4.2 Vs 3.8; p = 0.022); and unscheduled visits (21% Vs 44%; p = 0.009);

Reference	Purpose/details	Results/Comments/Recommendations
	<p>hematocrit > 45%; unattainable venous access; requirement for IV pressors; vasoactive drug use during hospitalization before randomization; used of iodinated radiocontrast; comorbidities expected to prolong hospitalization; contraindication to anticoagulation; systemic infection; heart transplant;</p> <ul style="list-style-type: none"> • Primary end points: weight loss and dyspnea at 48 hrs after randomization; • Secondary endpoints: 48 hr functional capacity; HF re-hospitalizations or unscheduled visits in 90 days; • Safety endpoints: renal function; electrolytes; blood pressure. 	<ul style="list-style-type: none"> • No serum creatinine differences between groups; • Deaths: 9 in UF group; 11 in diuretics group; <p>Conclusions: <i>"In decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternate therapy."</i></p>

Table 2. Ongoing studies of ultrafiltration for heart failure

- Listed by NIH at www.clinicaltrials.gov (accessed 4/30/08)
- Does not include withdrawn , discontinued, or no longer recruiting trials

Purpose/outcomes/FU	Location	Projected completion (if noted)
<ul style="list-style-type: none"> • Ability of UF to maintain patients in stable condition and reduce hospitalizations or use of emergency services; • Safety: long term (1 year) major clinical events such as death 	Italy	August 2008
<p>RCT: Effectiveness of UF Vs standard drug treatment for ADHF and cardiorenal syndrome (CARRESS study):</p> <ul style="list-style-type: none"> • Primary outcome: Bivariate (change in weight and creatinine) outcome at 7 days; • Secondary outcomes weight loss and renal improvement at 7 days; change in renal function at 60 days; change in electrolytes at 7 days; weight change at 60 days; clinical decongestion at 60 days; net fluid loss at 7 days; biomarker change at 60 days; global assessment change at 7 days; LOS; change in oral diuretic dose at 30 and 60 days. 	NHLBI and CHFS; multiple US sites	November 2009

REFERENCES

- Allen LA, O'Connor CM. Management of acute decompensated heart failure. *CMAJ: Canadian Medical Association Journal*, 2007; 176(6): 797-805.
- Antczak-Bouckoms A, Burdick E, Klawansky S, Mosteller F. Using medical registries and data sets for technology assessment. *International Journal of Technology Assessment in Health Care*, 1991; 7(2): 123-128.
- Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Critical Care Medicine*, 2008; 36(2): 610-617.
- Bart BA. Advances in heart failure: Minnesota's role in the NHLBI's Heart Failure Network. *Minnesota Medicine*, 2008; 91(1): 40-42.
- Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial. *Journal of the American College of Cardiology*, 2005; 46(11): 2043-2046.
- Blais R. Using administrative data bases for technology assessment in health care. Results of an international survey. *International Journal of Technology Assessment in Health Care*, 1991; 7(2): 203-208.
- Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens FD. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. *European Journal of Cardio-Thoracic Surgery*, 2006; 30(6): 892-897.
- Colechin ES, Bower L, Sims AJ. (NHS. Centre for Evidence-based Purchasing): Newcastle upon Tyne. Ultrafiltration therapy for fluid overload in heart failure, 45 Pgs. 2007. Report Number: CEP 07016, <http://www.pasa.nhs.uk/PASAWeb/NHSprocurement/CEP> [Website].
- Cook DJ, Guyatt GH, Laupacis A, Sackett DL, Goldberg RJ. Clinical recommendations using levels of evidence for antithrombotic agents. *Chest*, 1995; 108(4 Suppl): 227S-230S.
- Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *Journal of the American College of Cardiology*, 2007; 49(6): 675-683.
- Dec GW. Management of Acute Decompensated Heart Failure. *Current Problems in Cardiology*, 2007; 32(6): 321-366.
- Elkayam U, Hatamizadeh P, Janmohamed M. The challenge of correcting volume overload in hospitalized patients with decompensated heart failure. *Journal of the American College of Cardiology*, 2007; 49(6): 684-686.
- FDA. Food and Drug Administration. (FDA Center for Devices and Radiological Health, Office of Device Evaluation): Rockville. 510(k) Summary Aquadex FlexFlow System, 4 Pgs., December 13, 2006. <http://www.fda.gov/cdrh/pdf6/K062922.pdf> [Website].
- Filippatos G, Zannad F, Filippatos G. An introduction to acute heart failure syndromes: Definition and classification. *Heart Failure Reviews*, 2007; 12(2): 87-90.
- Gauthier N, Anselm AH, Haddad H. New therapies in acute decompensated heart failure. *Current Opinion in Cardiology*, 2008; 23(2): 134-140.

Geisberg C, Butler J. Addressing the challenges of cardiorenal syndrome. *Cleveland Clinic Journal of Medicine*, 2006; 73(5): 485-491.

Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. *JAMA*, 1995; 274(22): 1800-1804.

Heart Failure Society of America. Evaluation and management of patients with acute decompensated heart failure. *Journal of Cardiac Failure*, 2006; 12(1): e86-e103.

Hill JA, Yancy CW, Abraham WT. Beyond diuretics: management of volume overload in acute heart failure syndromes. *The American Journal of Medicine*, 2006; 119(12 Suppl 1): S37-S44.

Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*, 2005; 112(12): e154-e235.

Ibrahim MA. Epidemiology and Health Policy. Rockville: Aspen, 1985.

John S, Eckardt KU. Renal replacement strategies in the ICU. *Chest*, 2007; 132(4): 1379-1388.

Kale P, Fang JC. Devices in acute heart failure. *Critical Care Medicine*, 2008; 36(1 Suppl): S121-S128.

Levy PD, Penugonda N, Guglin M, phillevy_@yahoo.com. Treatment of massive fluid overload as a result of constrictive pericarditis with ultrafiltration in the emergency department. *Annals of Emergency Medicine*, 2008; 51(3): 247-250.

Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. *Critical Care Medicine*, 2008; 36(1 Suppl): S75-S88.

Lilienfeld DE, Stolley PD. Foundations of Epidemiology. 3rd. New York: Oxford University Press, 1994.

Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA*, 2005; 294(24): 3124-3130.

Mausner JS, Kramer S. Mausner & Bahn Epidemiology: An Introductory Text. 2nd. Philadelphia: WB Saunders, 1985.

Mebazaa A, Plaisance P, Gheorghiane M, Pina IL, Harjola VP, Nieminen M, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Critical Care Medicine*, 2008; 36(1 Suppl): S129-S139.

Mehta R, Feldman D. Acute decompensated heart failure: best evidence and current practice. *Minerva Cardioangiologica* 2005; 53(6): 537-547.

Muir Gray JA. Evidence-Based Healthcare: How to Make Health Policy and Management Decisions. New York: Churchill Livingstone, 1997.

Mulrow CD, Cook DJ, Davidoff F. Systematic reviews: critical links in the great chain of evidence. *Annals of Internal Medicine*, 1997; 126(5): 389-391.

National Horizon Scanning Centre. (NHS): Birmingham. Ultrafiltration for acute decompensated heart failure: horizon scanning technology briefing, 6 Pgs. *Technology Briefing*, March 30, 2006. http://pcpoh.bham.ac.uk/publichealth/horizon/PDF_files/2006reports/December06/Ultrafiltration.pdf Accessed: April 16. [Website].

Rich MW. Advances in the treatment of acute decompensated heart failure in the elderly. *Future Cardiology*, 2007; 3(2): 165-174.

Rogers HL, Marshall J, Bock J, Dowling TC, Feller E, Robinson S, et al. A randomized, controlled trial of the renal effects of ultrafiltration as compared to furosemide in patients with acute decompensated heart failure. *Journal of Cardiac Failure*, 2008; 14(1): 1-5.

Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd. Boston: Little Brown & Company, 1991.

Saltzman HE, Sharma K, Mather PJ, Rubin S, Adams S, Whellan DJ. Renal dysfunction in heart failure patients: what is the evidence? *Heart Failure Reviews*, 2007; 12(1): 37-47.

Sharma A, Hermann DD, Mehta RL. Clinical benefit and approach of ultrafiltration in acute heart failure. *Cardiology*, 2001; 96(3-4): 144-154.

TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services