AQUADEX FLEXFLOW ULTRAFILTRATION SYSTEM

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
01/2013

DISCLAIMER

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has not been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya.

Tel: 603 8883 1246

Fax: 603 8883 1230

Available at the following website: http://www.moh.gov.my

Prepared by:
Syful Azlie Md Fuzi
Senior Assistant Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

Reviewed by:
Datin Dr. Rugayah Bakri
Deputy Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia

EXECUTIVE SUMMARY

Introduction

Ultrafiltration in the management of heart failure, while not a new concept, has recently generated greater clinical interest with the development of a portable machine that does not require intensive care unit monitoring or travel to a dialysis ward. Aquadex FlexFlow system ([redacted]) uses the concept of ultrafiltration which can remove up to 500 ml excess salt and water per hour from the circulation of patients with heart failure and fluid overload. The system minimises the risk of haemodynamic interference by using a low blood flow via a small-bore cannula inserted into a peripheral or central vein.

This technology review was conducted based on a request from Consultant Cardiologist in Sarawak General Hospital Heart Centre.

Objective/aim

The objective of this technology review was to review evidence on the effectiveness, safety and cost-effectiveness of using Aquadex FlexFlow ultrafiltration system compared with the intravenous diuretics or conventional techniques in the treatment of patients with congestive heart failure.

Results and conclusions

There was good to fair level of retrievable evidence to indicate that the Aquadex FlexFlow ultrafiltration system was effective in the treatment of patients with congestive heart failure. In a comparative trial versus intravenous diuretics or conventional techniques, results were in favour of the Aquadex FlexFlow treatment. Findings indicated that ultrafiltration efficiently produces greater weight and fluid loss, significantly decreased rehospitalisation rate for heart failure and unscheduled medical visits.

There was no retrievable evidence to suggest that ultrafiltration is unsafe in comparison with conventional therapies. Ultrafiltration is beneficial to patients as it allows fluid to be removed quickly and safely, without compromising renal function or producing other side effects seen with aggressive pharmacological therapy. No other major complications were recorded. The Aquadex FlexFlow is currently the only United States Food & Drug Administration (US FDA) approved portable ultrafiltration device for the treatment of heart failure; has registered as medical device (Class II) and received premarket notification 510(k) (K062922) in 2006.

There was also evidence to suggest that Aquadex FlexFlow ultrafiltration system was likely to be more costly but more effective at fluid reduction and reducing rehospitalisation rates than diuretics in patients with congestive heart failure, though one indicated there was some uncertainty about the budget impact of this technology.

The cost of the Aquadex FlexFlow system, which may be loaned or leased to hospitals, is approximately [redacted] ([redacted]). Typically a treatment (a new filter and blood circuit) will cost [redacted] ([redacted]), and multiple treatments may be required for severe cases of fluid overload.

Based on the above review, Aquadex FlexFlow ultrafiltration system can be used as research purpose or used in research environment for excess fluid removal in patients with congestive heart failure. Further research is needed to establish the patient groups who would benefit most, the optimal rates of fluid removal, and the cost savings associated with long-term quality of life benefits.

Methods

Literatures were searched through electronic databases specifically PubMed, Medline, Cochrane, Ovid, Horizon scanning databases, other websites; US FDA, MHRA and from non scientific database - Google search engine. In addition, a cross-referencing of the articles retrieved was also carried out accordingly to the topic. Relevant articles were critically appraised and evidence graded using US/Canadian Preventive Services Task Force.

AQUADEX FLEXFLOW ULTRAFILTRATION SYSTEM

1.0 INTRODUCTION

Heart failure (HF), often called congestive heart failure (CHF) is a chronic disease of volume overload and sodium retention due to decreased cardiac output whereas acute decompensated heart failure (ADHF) is a worsening of the symptoms, typically shortness of breath (dyspnea), edema and fatigue, in a patient with existing heart disease.[1] A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee 2006 revealed that 90% of one million annual hospitalisations for heart failure are due to volume overload and contributes to heart failure progression and mortality.[2] Guidelines recommend that therapy for heart failure patients be aimed at achieving euvolemia (a term for normal fluid status). An intravenous (IV) loop diuretic remains the current standard or the mainstay of treatment in those with heart failure as diuretics promote both diuresis and natriuresis. However, loop diuretics' effectiveness declines with repeated exposure. Unresolved congestion may contribute to high rehospitalisation rates. Furthermore, loop diuretics may be associated with increased morbidity and mortality because of deleterious effects on neurohormonal activation, electrolyte balance, and cardiac and renal function.[3]

Ultrafiltration (UF) on the other hand, is the extracorporeal filtration of blood to remove water and salt which, unlike haemodialysis, does not change the concentration of urea or creatinine. Ultrafiltration in the management of heart failure, while not a new concept, has recently generated greater clinical interest with the development of a portable machine that does not require intensive care unit monitoring or travel to a dialysis ward. Aquadex FlexFlow system ([redacted]) uses the concept of UF which can remove up to 500 ml excess salt and water per hour from the circulation of patients with HF and fluid overload. The system minimises the risk of haemodynamic interference by using a low blood flow via a small-bore cannula inserted into a peripheral or central vein.[4, 5]

This technology review was conducted based on a request from Consultant Cardiologist in Sarawak General Hospital Heart Centre.

2.0 OBJECTIVE/AIM

The objective of this technology review was to review evidence on the effectiveness, safety and cost-effectiveness of using Aquadex FlexFlow ultrafiltration system compared with the IV diuretics or conventional techniques in the treatment of patients with congestive heart failure

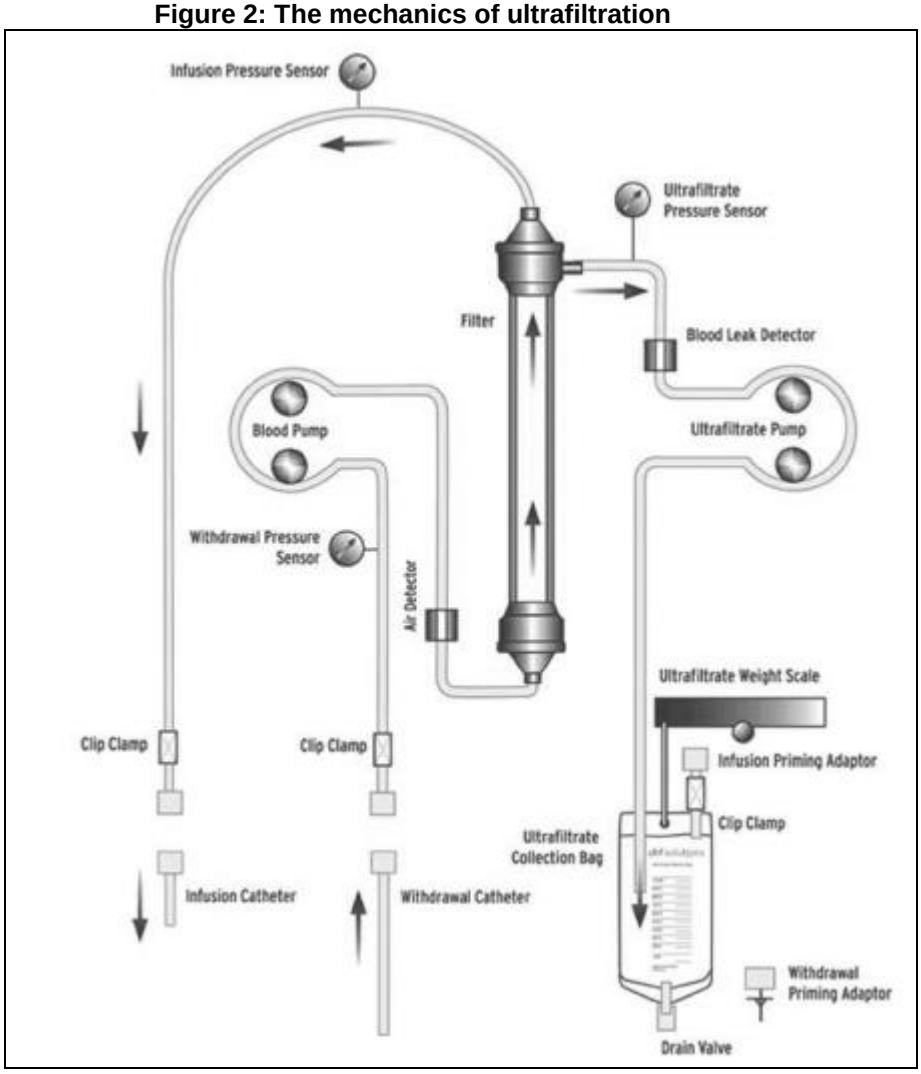
3.0 TECHNICAL FEATURES

The Aquadex FlexFlow (**Figure 1**) is a unique portable ultrafiltration system that allows low blood flow rates of 10 to 40 ml per minute and low extracorporeal blood volume of 33 ml to achieve effective ultrafiltration as compared with conventional ultrafiltration, which typically requires upwards of 200 ml per minute flow and 75 ml of extracorporeal blood volume. The device consists of a console, an extracorporeal blood pump, and venous catheters. The console controls blood removal rates and extracts ultrafiltrate at a user-set maximum rate.[6, 7]

Figure 2 describe the mechanics of ultrafiltration. Blood is withdrawn from a vein through the withdrawal catheter. Tubing connects the withdrawal catheter to the blood pump. Blood passes through the withdrawal pressure sensor just before it enters the blood pump tubing loop. During the operation, the pump loop is compressed by rotating rollers that propel the blood through the tubing. After exiting the blood pump, blood passes through the air detector and enters the hemofilter. The hemofilter is bonded to a clip-on cartridge that mounts onto the ultrafiltrate pump raceway on the side of the console. Blood enters the filter through a port on the bottom, exits through the port at the top of the filter, and passes through the infusion pressure sensor before returning to the patient. Inside the hemofilter, there is a bundle of hollow fibers. The ultrafiltrate passes through the fiber walls, fills the space between these fibers, and exits through a port near the top of the filter case. Ultrafiltrate then passes through a blood leak detector. It sequentially passes through the ultrafiltrate pressure sensor, the ultrafiltrate pump, and the collecting bag that is suspended from the weight scale.[6, 7]

Figure 1: The Aquadex FlexFlow ultrafiltration system

Figure 2: The mechanics of ultrafiltration



4.0 METHODS

4.1. Searching

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – December 2012
- EBM Reviews – Database of Abstracts of Review of Effects – 4th Quarter 2012
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to November 2012
- EBM Reviews – Health Technology Assessment – 4th Quarter 2012
- EBM Reviews - NHS Economic Evaluation Database – 4th Quarter 2012

Other databases:

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- Other websites: US FDA, INAHTA, MHRA

General database such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with congestive heart failure, acute decompensated heart failure
Interventions	Aquadex FlexFlow, fluid removal system, ultrafiltration, aquapheresis
Comparators	Intravenous diuretics/usual care
Outcomes	Weight loss, fluid removal, rehospitalisation, renal function, quality of life, mortality, adverse events
Study design	Systematic reviews (SRs), randomised control trials (RCTs), cross-sectional, cohort, case control, case series
Type of publication	English, full text articles

Exclusion criteria

Study design	Case report, survey, anecdotal, animal studies
Type of publication	Non-English

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US/Canadian Preventive Services Task Force (**Appendix 2**).

5.0 RESULTS AND DISCUSSION

The search strategies yielded an article on the United State Food & Drug Administration (US FDA) related to the Aquadex FlexFlow system ([redacted]) in the treatment of patients with fluid overload who have failed diuretic therapy, and require hospitalization. To date, clinical studies of UF techniques on human subjects have been very limited regarding the impact of this technology on survival, hospitalization, complication rates and quality of life, compared to conventional treatment options. However, studies of UF in this review include four RCT, two cross-sectional, a retrospective cohort and case series. There were also two recent HTA reports; both included economic analysis of the Aquadex FlexFlow. No relevant systematic reviews and meta-analyses were found.

5.1 Effectiveness

The Relief for Acutely Fluid-Overload Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial by Bart BA et al. randomised 40 hospitalized patients to be treated with either ultrafiltration (UF) or usual care, as determined by the attending physician according to best practice standards. The primary end point was weight loss 24 hours post treatment. Other end points included total fluid removal at 24 and 48 hours, CHF and dyspnea assessment, length of hospital stay, and blood chemistry. The trial showed that weight loss after 24 hours was 2.5 kg and 1.9 kg in the UF and usual care group, respectively (greater in the UF group but failed to reach statistical significance, P = 0.240). Fluid removal after 24 hours was 4,650 ml and 2,838 ml in the UF and usual care groups, respectively (P = 0.001). After 48 hours, fluid removal was 8,415 ml and 5,375 ml in the UF and usual care groups, respectively (P = 0.012). Compared to usual care, UF was not associated with significant changes in heart rate, blood pressure, or electrolytes. Dsypnea and CHF symptoms were significantly improved in the UF group compared to usual care at 48 hours (P = 0.039 and P = 0.023 respectively). The median length of hospital stay was six days in the UF group and five days in the usual care group. There was one death in the UF group during the 30-day follow-up period (unrelated to UF) and one catheter site infection. The authors concluded that early use of UF for patients hospitalized with CHF is feasible, well-tolerated, and resulted in significant weight loss and fluid removal.[8 level I]

Costanzo MR et al. conducted a large prospective randomised multicenter trial, the UNLOAD (Ultrafiltration versus Intravenous [IV] Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure). Patients were enrolled from June 2004 until July 2005 at 28 U.S. centres experienced in the use of the Aquadex System 100. In this trial,

100 patients received UF and 100 received treatment with IV diuretics to investigate the primary endpoints of weight loss and dyspnea assessment at 48 hours after randomisation. Secondary endpoints included net fluid loss at 48 hours, functional capacity, HF rehospitalisations, and unscheduled visits in 90-days. Results showed that at 48 hours, weight loss was greater in the UF than in the standard-care group (5.0 ± 3.1 kg versus 3.1 ± 3.5 kg; p = 0.001). Dyspnea score at 48 hours improved to similar degree in the two groups (p = 0.588). Net fluid loss 48 hours after randomisation was greater in the UF than in the standard-care group (4.6 ± 2.6 l versus 3.3 ± 2.6 l; p = 0.001). Length of index hospitalization were comparable (6.3 ± 4.9 days versus 5.8 ± 3.8 days; p = 0.979). At each assessment, New York Heart Association functional class, Minnesota Living with Heart Failure scores, 6-min walk distance, Global Assessment scores, and B-type natriuretic peptide levels were similarly improved in the two groups. At 90 days, the UF group had fewer patients rehospitalized for HF (16 of 89 [18%] versus 28 of 87 [32%]; p = 0.037), HF rehospitalisation (0.22 ± 0.54 versus 0.46 ± 0.76; p = 0.022), rehospitalisation days (1.4 ± 4.2 versus 3.8 ± 8.5; p = 0.022) per patient, and fewer unscheduled office and emergency department (ED) visits (14 of 65 [21%] versus 29 of 66 [44%]; p = 0.009). No clinically significant changes in renal function (serum urea, creatinine, electrolytes) and blood pressure occurred in either group. There were nine deaths (9.6%) in the UF group due to HF (n=3), renal failure (n=1), and causes unrelated to HF or treatment (n=5). Eleven patients (11.6%) died in the standard-care group because of HF (n=5), myocardial infarction (n=1), other causes (n=3), and unknown causes (n=2). The authors concluded that early UF safely produces greater weight and fluid loss than IV loop diuretics in hypervolemic HF patients, significantly decreased rehospitalisations for HF and unscheduled medical visits.[9 level I]

In a post-hoc analysis of the UNLOAD trial, outcomes of 100 patients randomised to UF were compared with those of patients randomised to standard IV diuretic therapy with continuous infusion (n=32) or bolus injection (n=68). In this more recent analysis, the primary and secondary endpoints were compared across the three groups. Overall, weight loss at 48 hours after randomisation differed significantly among the three treatment group (P = 0.002). Pair-wise comparisons, however, showed the weight loss to be: similar in the UF and IV continuous diuretic infusion group (5.0 ± 3.1 kg versus 3.6 ± 3.5 kg; P = 0.145); greater in the UF than in the IV bolus diuretic group (5.0 ± 3.1 kg versus 2.9 ± 3.5 kg; P = 0.001); and similar in the continuous IV and bolus groups (3.6 ± 3.5 kg versus 2.9 ± 3.5 kg; P = 0.358). Differences in the dyspnea score at 48 hours were not statistically significant (P = 0.608). Net fluid loss at 48 hours after randomisation was found to differ significantly between treatment group (P = 0.001). Net fluid loss was similar in the UF and IV continuous diuretic infusion groups (4.6 ± 2.6 l versus 3.9 ± 2.7 l; P = 0.232); greater in the UF

than in the IV bolus diuretic group (4.6 ± 2.6 l versus 3.1 ± 2.6 l; P < 0.001); and similar in the IV bolus and continuous diuretic infusion groups (3.1 ± 2.6 l versus 3.9 ± 2.7 l; P = 0.177). At each assessment, New York Heart Association functional class, Minnesota Living with Heart Failure scores, 6-min walk distance, Global Assessment scores, and B-type natriuretic peptide levels were similarly improved in the three groups. At 90 days, compared with patients treated with continuous IV diuretic infusion, the UF-treated group had: a lower number of HF rehospitalisations per patient (0.23 ± 0.54 versus 0.54 ± 0.79; P = 0.018); fewer HF rehospitalisation days per patient (1.4 ± 4.1 versus 4.9 ± 10.5; P = 0.016), and a smaller percentage of patients requiring unscheduled office and ED visits for worsening HF (14 of 65 [22%] versus 11 of 21 [52%]; P = 0.012). Throughout the study, changes in serum creatinine were similar in the three groups. There were nine deaths (9.6%) in the UF group due to HF (n=3), renal failure (n=1), and causes unrelated to HF or treatment (n=5). Six deaths (19.4%) occurred in the IV continuous diuretic infusion group because of HF (n=2) or causes unrelated to either HF or treatment. Of the five deaths (7.8%) in the IV bolus diuretic group, three were HF-related and two were unrelated to HF or treatment. The results of this analysis from the UNLOAD trial showed that despite the lack of a statistical difference in weight and fluid loss by UF and IV diuretics administered by continuous infusion, UF was associated with fewer rehospitalisations.[10 level I]

The aim of the ULTRADISCO trial (ULTRAfiltration versus DIureticS in DeCOmpensated heart failure) by Giglioni C et al. was to evaluate the clinical, biohumoral, and haemodynamic effects of UF compared with standard IV diuretics therapy in 30 patients (mean age 69.1 ± 16.2 years) with a primary diagnosis of decompensated HF and over-hydration with New York Heart Association (NYHA) functional class III or IV. Haemodynamic variables, including several novel parameters indicating the overall performance of the cardiovascular system, were continuously assessed with the Pressure Recording Analytical Method (PRAM) before, during, at the end of treatment (EoT), and 36 hours after completing treatment (post 36). Aldosterone and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels were also measured. They found that in both treatment groups, body weight was significantly decreased compared with baseline values, but weight loss in the UF group at post 36 was greater (P = 0.001). At post 36, the UF group had a greater cumulative fluid loss compared with the diuretic group (9.7 ± 2.9 l versus 7.8 ± 2.0 l, respectively, P = 0.047). Patients treated with UF had a more pronounced reduction in signs and symptoms of HF at EoT compared with baseline, and a significant decrease in plasma aldosterone (0.24 ± 0.25 nmol/L versus 0.86 ± 1.04 nmol/L; P < 0.001) and NT-proBNP levels (2,823 ± 2,474 ng/L versus 5,063 ± 3,811 ng/L; P < 0.001) compared with the diuretic group. The UF group showed a significant improvement (% of

baseline) in a number of haemodynamic parameters, including stroke volume index (114.0 ± 11.7%; P < 0.001), cardiac index (123.0 ± 20.8%; P < 0.001), cardiac power output (114.0 ± 11.7%; P < 0.001), myocardial contractility index dP/dt_{max} (129.5 ± 19.9%; P < 0.001), and cardiac cycle efficiency (0.24 ± 0.54 versus -0.14 ± 0.50 units; P < 0.05), and a significant reduction in systemic vascular resistance at post 36 (88.0 ± 10.9%; P < 0.001), which was not observed in the diuretic group. The authors concluded that in patients with advanced HF, UF may represent a more beneficial method of fluid removal than diuretic infusion, since its effects go beyond clinical improvement by ameliorating haemodynamic status without a marked increase in aldosterone or NT-proBNP levels.[11] level I

Costanzo MR et al. has also sought to determine if UF before IV diuretics in 20 patients (age range 50.1 to 85.1 years) with decompensated heart failure and diuretic resistance results in euvolemia and early discharge without hypotension or worsening renal function. The study demonstrated that UF, initiated within 4.7 ± 3.5 hours of hospitalization, removed 8,654 ± 4,205 ml of fluid. There were no failed venous cannulations, line malfunctions, phlebitis, or thromboembolism. Twelve patients (60%) were discharge in ≤ 3 days whereas one was readmitted in 30 days. Weight (P = 0.006), Minnesota Living with Heart Failure scores (P = 0.003), and Global Assessment (P = 0.00003) improved after UF and at 30 and 90 days. Median B-type natriuretic peptide levels decreased after UF (from 1,230 pg/ml to 788 pg/ml) and at 30 days (815 pg/ml) (P = 0.035). Blood pressure, renal function, and medications were unchanged. They concluded that early ultrafiltration safely and effectively reduced congestion in ADHF with diuretic resistance. A treatment strategy may decrease length of stay and rehospitalisations in high-risk HF patients. Clinical benefits persist at three months. Thus, early UF may be an alternative to reserving UF for patient's refractory to all other pharmacologic strategies.[12] level II-2

Bartone C et al. performed a cohort study to evaluate short-term effects (clinical and laboratory parameters) of initial treatment strategies for acute decompensated heart failure (ADHF). A total of 25 hospitalized patients treated with UF were retrospectively compared with 25 patients treated with usual care (UC) and 25 patients treated with UC plus adjunctive nesiritide infusion (UN), matched for age, sex, ejection fraction, etiology, and serum creatinine. Ultrafiltration was performed using the Aquadex fluid removal system 100. The study revealed that the median length of hospitalization was six days for UF, four days for UC, and sixth days for UN; do not demonstrated statistically significant differences. There was a tendency for fewer 30-day all-cause hospital readmissions observed in the UF group (16%) compared with either the UC (24%) or UN (24%) groups. All three treatment groups lost weight, although to a greater extent in the

UF group (15.8 lb versus 6.3 lb in UC and 4.7 lb in UN). Concomitantly, UF manifested the greatest increase in serum urea nitrogen, creatinine, and the number of patients with creatinine increases of > 0.5 mg/dL (44% versus 24% in UC and 20% in UN). The authors concluded that for patients with ADHF, UF appears to be more effective for volume removal and possibly prevention of all-cause hospital readmission to 30 days than UC or UN. These findings, as well as the effects on renal function and length of stay, need to be further evaluated in a prospective randomised study.[13 level II-2]

De Maria E et al. reported their experienced with the use of an UF system using a femoral venous inserted catheter (Dedyca system; Bellco, Mirandola, Modena, Italy) in a population of patients with recurrent, diuretic-resistant, acute, decompensated heart failure. The study has a retrospective observational nature. It is a comparison between the post-ultrafiltration and pre-ultrafiltration 6-month event rates (death, heart failure hospitalizations and renal dysfunction) with no control group. Forty two patients (mean age 69 years) were hospitalized for ADHF. Cause of HF was ischemic in 52% of cases, and NYHA class was III (64%) or IV (36%). All patients were on optimal heart failure drugs. Average dose of furosemide before UF was 250 mg. Clinical data were collected from each patient's clinical notes. Potential adverse events related to UF were noted. The study showed that each patient underwent one to four UF treatments (total 70) during the study period. Mean duration of a single UF was six hours. Of the 70 UF treatment, 60 (86%) removed more than 4,000 ml of fluids; 7 (10%) removed 2,000 to 4,000 ml; 3 (4%) removed less than 2,000 ml. Fluid removal ranged from 1,600 ml to 6,900 ml. Mean weight loss at 48 hours was 5 kg. Serum electrolyte levels did not change significantly after UF. Only one (1.4%) UF was aborted because of symptomatic persistent hypotension (SBP < 80 mmHg). Other complications included two cases of significant bleeding from vascular access (2.8% of UF and 4.8% of patients) with more than 2 g/dl reduction in haemoglobin levels (transfusion not required); six cases of worsened renal function (serum creatinine > 3 mg/dl and/or GFR < 30 ml/min) (8% of UF and 14% of patients). One patient required dialysis. Six-month mortality after UF was 26%. Hospitalization rate, 6-months after was 30% (compared with 66% during 6-months before UF). Average furosemide dose, 6-months after UF, was 125 mg. The authors concluded that UF removed fluid overload in diuretic-resistant, severe, CHF. Six months after UF, hospitalization rates were reduced by 36% and furosemide dose was 50% lower, compared to the previous 6-months. Worsened renal function was the most common complication (14% of patients).[14 level II-2]

A case-series by Dahle TG et al. reports on the first nine hospitalized patients (mean age 53.0 ± 12.7 years) with acute decompensated heart failure and resistant to diuretics, underwent peripheral IV catheter insertion

for peripheral ultrafiltration (PUF) therapy. Patient weights and renal function were measured immediately prior to and within 18 hours after PUF therapy. Ultrafiltration stopped when therapeutic objective achieved as specified by attending cardiologist. Results indicated that the mean length of time of UF was 33.3 ± 20.0 hours with a mean volume removed of 7,000 ± 4,900 ml. The patients experienced a statistically significant mean weight loss of 6.2 ± 5.0 kg (P = 0.01). There was no statistically significant change in serum haemoglobin, hematocrit, potassium or renal function as determined by a change in mean blood urea nitrogen or creatinine. None of the patients experienced any major adverse events during PUF therapy. They concluded that the ability to use PUF via peripheral IV catheters will potentially allow this therapy to be implemented more easily in a variety of care settings to treat patients with resistant heart failure.[15 level II-3]

5.2 Safety

The Aquadex FlexFlow system is currently the only US FDA approved portable ultrafiltration device for the treatment of heart failure; has registered as medical device (Class II) and received premarket notification 510(k) (K062922) in 2006. The system is indicated for:

- Temporary (up to eight hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and
- Extended (longer than eight hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization

All treatments must be administered by a health care provider, under physician prescription, both of whom having received training in extracorporeal therapies.[16]

Only the UNLOAD trial [9 level I] studied safety aspect of UF as a primary outcome. Most of other studies reported adverse events, but this should be considered as anecdotal evidence. Nevertheless, the reports of adverse events are generally consistent, and provide an indication of the safety of the technique. The UNLOAD trial found no difference in mortality rate between those treated with UF and those treated with IV diuretics. RAPID-CHF trial [8 level I] also reported one death in the UF group during the 30-day follow-up period but this was unrelated to UF. Infections at the catheter site were reported in both UNLOAD and RAPID-CHF trials, and nothing can be inferred from the absence of reports of catheter site infections in other studies.

5.3. Cost/economic analysis

Pan I and McGregor M from McGill University Health Care (MUHC), Canada in 2010 conducted a health technology assessment of UF using Aquadex FlexFlow for the management of 50 patients suffering from acute, decompensated, diuretic-resistant HF in the cardiology intensive care unit. One of the objectives is to estimate the cost of this technology and the possible budget impact. The anticipated budget impact of the proposed use of UF at the MUHC will depend not only on the cost items listed in **Table 1**, but also on factors such as the duration of hospital stay, and the rate and duration of hospital readmissions associated with standard care and UF. These items are listed in **Table 2**. Analysis indicated that the estimated cost per treatment of UF and standard IV diuretics is CAN$6,606 and CAN$6,193, respectively. Thus, the costs of treating 50 patients per year are as follows:

Ultrafiltration	**CAN$330,318 (95% CI: $282,196 to $410,635)**
Standard care	CAN$309,644 (95% CI: $262,594 to $400,209)

The proposal to treat 50 patients by UF, who would otherwise receive standard care, might result in a budget impact of CAN$20,674 per year (95% CI: -$76,091 to $107,199).[17]

Table 1: Budget impact

Cost items	Ultrafiltration with Aquadex	Standard care
Annual number of patients treated	50	50
Equipment & personnel cost		
Ultrafiltration apparatus ($27,750) amortized over 5 years/patient	*$111.00*	
72-hour treatment cost (use of 1.5 filter per treatment)	$1,200.00	-
Subtotal per patient	$1,311.00	-
Total equipment & personnel cost [Subtotal x 50]	$65,550.00	-
Hospitalization cost		
Average length of stay (day)*	9	10
CCU cost per day	$560.95	$560.95
Subtotal per patient	$5,048.55	$5,609.50
Total index hospitalization cost [Subtotal x 50]	$252,427.50	$280,475.00
Re-admission cost		
Annual number of patients re-admitted**	11	13
Re-admission LOS (day)**	1.4	3.8
CCU cost per day	$560.95	$560.95
Subtotal per patient	$785.33	$2131.61
Total re-admission cost [Subtotal x 11 or 13]	$8,638.63	$27,710.93
TOTAL TREATMENT COST		
per patient	**$6,606**	**$6,193**
per year (assume 50 patients)	**$330,318**	**$309,644**
95% CI (Monte Carlo analysis)	**$282,196-$410,635**	**$262,594-$400,635**

*Source: RCQT report 2008.
**Source: Costanzo et al., 2005

Table 2: Assumptions used in estimation of budget impact

Items influencing budget impact	Best Estimate	Estimated range
Number of new patients treated/year	50	-
Duration of index hospital stay with Standard care (days, average in Quebec in 2005-06 = 9.7[RQCT]	10	8-12
Duration of index Hospital stay with ultrafiltration (days, estimated reduction from standard care by ultrafiltration = 1 day [RQCT]	9	7-11
Readmissions in first year with Standard care, (average readmission rate, 100 Quebec hospitals, 2003-06 = 26%[RQCT])	13	10-16
Readmissions in first year with ultrafiltration (Costanzo et al., 2007 reported 14% fewer readmissions in the first 90 days post-procedure . 13- 14%of 13 = 1.8)	11	8-14
Days of readmission with Standard care (Costanzo et al., 2007 reported 3.8+/-8.5 days per re-admission)	4	3-10
Days of readmission in first year with ultrafiltration (Costanzo et al., 2007 reported 1.4 +/- 4.2 days per re-admission)	2	1-8

Colechin ES, Bowler L, and Sims AJ from United Kingdom conducted cost impact analysis to estimate the difference in total cost per patient of treating fluid overload with Aquadex FlexFlow compared with standard treatment with loop diuretics, by modelling the resource use and associated cost of hospital-based treatment. The model is based on the hospital care costs of initial treatment and readmission, as well as the direct cost for equipment, consumables and drugs related to treatment. The model parameters, resource use and unit costs featured in the analysis are presented in **Tables 3 and 4**.[4]

Table 3: Parameter values for cost impact analysis

Parameter	Ultrafiltration	IV loop diuretics	Reference
Length of stay	6.3 days	5.8 days	Costanzo *et al* [20]
Rate of rehospitalisation	18%	32%	Costanzo *et al* [20]
Length of stay for rehospitalisation	1.4 days	3.8 days	Costanzo *et al* [20]
Rate of emergency hospital visits	21%	44%	Costanzo *et al* [20]
Preparation time	30 minutes	30 minutes	
Number of haematocrit tests required during a 12 h session	15		Rosenthal [36]

Table 4: Unit costs for cost impact analysis

Resource	Cost	Comments	Reference
Cardiac ward	£101	Per bed day	PSSRU 2006 [38]
ICU	£464	Per bed day	PSSRU 2006 [38]
A&E visit	£103	For a high cost investigation	PSSRU 2006 [38]
General inpatient day care attendance	£129	Per day	PSSRU 2006 [38]
Nurse cost per minute	£0.32	For a nurse based on a 24 h ward (excluding qualification costs)	PSSRU 2006 [38]
Haematocrit Laboratory test	£2.35	Accounted for as part of the cost of FBC	Newcastle upon Tyne Hospitals NHS Trust [39]
Aquadex	£12,000	Purchase price	Manufacturer's information
Filter kit	£600	Per session	Manufacturer's information
Cannula	£0.62	Per IV polyurethane 16 g single use cannula	Supply Chain [40]
Saline solution	£0.24	Per 100 ml sachet for preparation	Supply Chain [40]
Heparin bolus injection (1000 units/ml)	£0.19	Per 1 ml ampoule; 10 units/kg; average patient weight 101 kg	BNF 54 [37]
Furosemide bolus injection (10 mg/ml)	£2.50	Per 25 ml ampoule	BNF 54 [37]

Table 5: Estimated cost per patient

Cost item	Aquadex	Diuretics
Preparation costs	£12.22	£9.60
Heparin for anti-coagulation during treatment	£0.19	-
Furosemide	-	£3.62
Aquadex equipment and consumables	£621.97	-
Haematocrit testing	£59.25	-
Hospital care	£636.30	£585.50
Readmission and emergency care	£49.46	£172.37
Total cost per patient	£1,379.39	£771.39

Results for the model are shown in **Table 5**. The cost per patient of treating fluid overload increases significantly using Aquadex FlexFlow compared with IV diuretics therapy when accounting for initial hospital treatment and readmission. Based on the data presented in this main analysis, the additional cost of treatment with Aquadex is £608 per patient. The higher cost is mostly associated with the high cost of the consumables per session.[18]

The cost of the Aquadex FlexFlow system is approximately [redacted] ([redacted]); however the system could be loaned or leased to hospitals. A new filter and blood circuit is required for each UF costing in the region of [redacted] ([redacted]), and multiple treatments may be required for severe cases of fluid overload.[5]

5.4 Limitation

Our review has several limitations. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in the report.

6.0 CONCLUSION

There was good to fair level of retrievable evidence to indicate that the Aquadex FlexFlow ultrafiltration system was effective in the treatment of patients with congestive heart failure. In a comparative trial versus IV diuretics or conventional techniques, results were in favour of the Aquadex FlexFlow treatment. Findings indicated that ultrafiltration efficiently produces greater weight and fluid loss, significantly decreased rehospitalisation rate for heart failure and unscheduled medical visits.

There was no retrievable evidence to suggest that ultrafiltration is unsafe in comparison with conventional therapies. Ultrafiltration is beneficial to patients as it allows fluid to be removed quickly and safely, without compromising renal function or producing other side effects seen with aggressive pharmacological therapy. No other major complications were recorded. The Aquadex FlexFlow is currently the only US FDA approved portable ultrafiltration device for the treatment of heart failure; has registered as medical device (Class II) and received premarket notification 510(k) (K062922) in 2006.

There was also evidence to suggest that Aquadex FlexFlow ultrafiltration system was likely to be more costly but more effective at fluid reduction and reducing rehospitalisation rates than diuretics in patients with CHF, though one indicated there was some uncertainty about the budget impact of this technology.

Based on the above review, Aquadex FlexFlow ultrafiltration system can be used as research purpose or used in research environment for excess fluid removal in patients with congestive heart failure. Further research is needed to establish the patient groups who would benefit most, the optimal rates of fluid removal, and the cost savings associated with long-term quality of life benefits.

7.0 REFERENCES

1. Heart failure. From Wikipedia, the free encyclopaedia. Available at http://en.wikipedia.org/wiki/Heart_failure. Accessed on 15th February 2013
2. Thom T, Haase N, Rosamond W et al. Heart disease and stroke statistics: 2006 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:85-151
3. Costanzo MR. Ultrafiltration in the management of heart failure. Current Opinion in Critical Care. 2008;14:524-530
4. Colechin ES, Bowler L, Sims AJ. Evidence review: ultrafiltration therapy for fluid overload in heart failure. London: Centre for Evidence-Based Purchasing, NHS Purchasing and Supply Agency. 2007. Available at http://nhscep.useconnect.co.uk/ShowDocument.ashx?id=54&i=true. Accessed on 15th February 2013
5. Ultrafiltration for acute decompensated heart failure. University of Birmingham. Horizon Scanning Technology Briefing. 2006
6. Costanzo MR. Ultrafiltration in the management of heart failure. Current Opinion in Critical Care. 2008; 14:524-530
7. Dahle TG, Sobotka P, Boyle AJ et al. A practical guide for ultrafiltration in acute decompensated heart failure. 2007.
8. Bart BA, Boyle A, Bank AJ et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overload patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol. 2005;46(11):2043-2046
9. Costanzo MR, Guglin ME, Saltzberg MT et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure (UNLOAD). J Am Coll Cardiol. 2007;49(6):675-683
10. Costanzo MR, Saltzberg MT, Jessup M et al. Ultrafiltration is associated with fewer rehospitalisations than continuous diuretics infusion in patients with decompensated heart failure: results from UNLOAD. J Cardiac Fail. 2010;16(4):277-284
11. Giglioni C, Landi D, Cecchi E et al. Effect of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study. Eur J Heart Fail. 2011;13:337-346
12. Costanzo MR, Saltzberg M, O'Sullivan J et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol. 2005;46(11):2047-2051
13. Bartone C, Saghir S, Menon SG et al. Comparison of ultrafiltration, nesiritide, and usual care in acute decompensated heart failure. Congest Heart Fail. 2008;14:298-301
14. De Maria E, Pignatti F, Patrizi G et al. Ultrafiltration for the treatment of diuretic-resistant, recurrent, acute decompensated heart failure: experience in a single centre. J Cardiovasc Med. 2010; 11:599-604

15. Dahle TG, Blake D, Ali SS et al. Large volume ultrafiltration for acute decompensated heart failure using standard peripheral intravenous catheters. J Cardiac Fail. 2006;12(5):349-352
16. U.S. Food and Drug Administration 510(k) Premarket Notification Database. Aquadex FlexFlow™ System Summary of Safety and Effectiveness. No K062922. Rockville, MD: FDA. December 2006. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf6/K062922.pdf Accessed on 15th February 2013
17. Pan I, McGregor M. Efficacy, safety and cost of ultrafiltration for the management of acute decompensated heart failure. Montreal: McGill University Health Centre. 2010. Available at http://www.mcgill.ca/files/tau/Ultrafiltration FINAL.pdf. Accessed on 15th February 2013

8.0 APPENDIX

8.1 Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1948 to present

1.	Heart Failure/
2.	(Congestive adj1 heart failure).tw.
3.	(Decompensation adj1 heart).tw.
4.	Cardiac failure.tw.
5.	Myocardial failure.tw.
6.	Heart failure.tw.
7.	1 or 2 or 3 or 4 or 5 or 6
8.	Ultrafiltration/
9.	Hemofiltration.tw.
10.	Micropore Filters.tw.
11.	8 or 9 or 10
12.	Diuretics, Osmotic/ or Diuretics/
13.	7 and 11 and 12

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Aqudex FlexFlow, fluid removal system, ultrafiltration, aquapheresis
INAHTA	
US FDA	

8.2 Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)