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Effect of Ultrafiltration versus Intravenous Furosemide for Decompensated Heart Failure in Cardiorenal Syndrome: A Systematic Review with Meta-Analysis of Randomized Controlled Trials

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Key Words
Ultrafiltration · Decompensated heart failure · Cardiorenal syndrome

Abstract
Background: Ultrafiltration is an adjunctive treatment for decompensated heart failure patients with cardiorenal syndrome. The efficacy and safety of ultrafiltration in the patient cohort are still unknown. ***Methods:*** We systematically reviewed and evaluated randomized controlled trials, comparing diuretics with ultrafiltration in adult patients with decompensated heart failure and cardiorenal syndrome through January 2014. The primary outcomes were body weight loss and total fluid removal. ***Results:*** We identified 8 trials including 608 patients. In a random-effects model, the pooled difference of body weight loss was 1.44 kg between patients receiving ultrafiltration and diuretics (95% CI, 0.29–2.59; p = 0.01). The difference of fluid removal was 1.28 l between groups (95% CI, 0.43–2.12; p = 0.003). The RR for mortality was 0.90 for ultrafiltration compared with diuretics (95% CI, 0.61–1.33; p = 0.60) and the RR for renal function deterioration was 1.29 (95% CI, 0.90–1.85; p = 0.17). There is a trend toward reducing readmission rate in ultrafiltration group. ***Conclusions:*** Ultrafiltration is a safe and effective strategy in the treatment of cardiorenal syndrome without increasing the risk of renal deterioration.

Introduction

Pulmonary congestion is the major cause for hospitalization in the great majority of patients with heart failure [1]. Recent studies suggest that nearly half of the patients with acute decompensated heart failure (ADHF) are discharged with unresolved congestion after receiving diuretic-based conventional therapy [2–4]. Development of diuretic resistance is a well-recognized challenge in the care of patients with ADHF and associated with higher morbidity and post-discharge mortality in patients with ADHF [5, 6].

Ultrafiltration (UF) can remove fluid rapidly and sustainably without activation of the neurohumoral axis [7, 8]. We systematically reviewed the literature for randomized controlled trials (RCTs) examining the effect of ultrafiltration in patients with cardiorenal syndrome.

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Method

Data Sources and Searches

We searched Cochrane Library (1993–), PubMed (1988–), OVID (1984–), EBSCO (1984–) through January 2014 using the OVID search engine and 3 comprehensive search themes, which we combined with the Boolean operator 'AND'. The first theme used terms for decompensated heart failure or pulmonary edema or fluid overload, the second used terms for ultrafiltration, whereas the third used terms for diuretics or usual care or medications or pharmacology. Results are filtered for RCTs. We identified additional citations from reference lists of review articles, conferences, and through experts.

The participants were older than the age of 18, and admitted to hospital due to ADHF. The intervention groups were ultrafiltration via any kind of dialysis method, including continuous renal replacement therapy or intermittent hemodialysis. The control groups were any kind of diuretics, given intermittently bolus or continuous.

The screening, selection, data extraction and risk of bias assessment were done independently and in duplicate by two investigators (H.Y.C. and P.T.L.).

Study Outcomes

The primary outcomes were total body weight loss and fluid removal amount during intervention periods, and the secondary outcomes were mortality rate, readmissions, renal function deterioration and adverse events.

Risk of Bias in Individual Studies

Each of the included studies was evaluated using the criteria described in the Cochrane Handbook 5.0 for Systemic Reviews of Interventions.

Quantitative Data Synthesis and Sensitivity Analysis

The study followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. Statistical analysis was performed using Revman 5.2 (Cochrane Collaboration). Data synthesis and analyses were performed using the Cochrane Review Manager software, version 5.2 (Cochrane Collaboration, www.cc-ims.net) according to Cochrane guidelines.

Results

Study Selection and Characteristics of Included Trials

Progress through stages of the systematic review is shown in figure 1. A total of 608 patients were included in 8 RCTs, of whom 304 were treated with ultrafiltration and 304 were treated with diuretic only (table 1). The mean age of patients ranged from 54–75 years, most were male (60–87%) and the body weight ranged from 74.4–106.2 kg. Almost all patients (>93%) had decompensated heart failure reaching NYHA class 3, and the ejection fraction was less than 35%. The mean baseline serum creatinine ranged from 1.4–2.2 mg/dl in the UF group, and 1.4–2.1 mg/dl in the diuretic group.

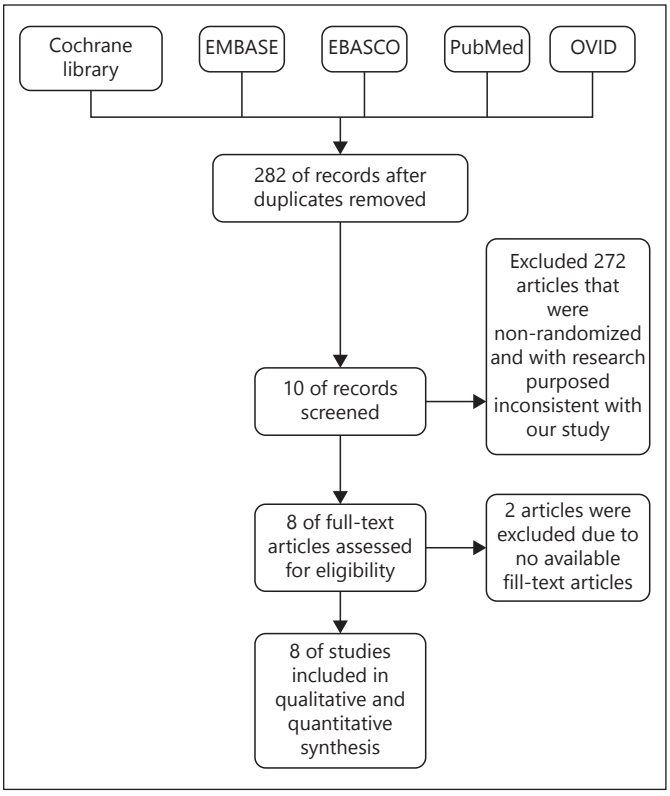

Fig. 1. Literature search and selection.

All eight RCTs used slow continuous UF as the mode of dialysis, of which 3 were Aquadex System 100, 1 was NxStage System, 1 was Dedyca ultrafiltration system, 1 was PRISMA and the other one was Multifiltrate/Prismaflex (table 2). The duration of UF ranged from 8–72 h in 6 trials. The duration was determined by the physicians judged clinically in one trial and by the time required to maintain the PCWP at ≤18 mm Hg for at least 4 h in another trial. Patients in the standard care group were all treated with loop diuretics intravenously, of which two trials used bolus infusion and four trials used continuous infusion. The dosage of diuretics varied from 153–314 mg per day. Three trials illustrated similar hemodynamic parameters including the changes of blood pressure and heart rate between groups [10–12] and one trial demonstrated more inotropic agent in diuretic group (50 vs. 0%) [13].

Risk of Bias

Only 2 RCTs included more than 90 patients. Trial quality was limited (table 3). Given the nature of the intervention, no trial was blinded or used sham procedures. Allocation concealment was not described in any trial. Baseline body weight in each group differed in the trials

Table 1. Characteristics of included studies

	No.		Age, years		BW, kg		Male, %		DM, %		CAD, %		NYHA ≧3, %		EF, %		Baseline SCr, mg/dl	
	UF	D	UF	D	UF	D	UF	D	UF	D	UF	D	UF	D	UF	D	UF	D
Bart (2005)	20	20	67.5	69.5	ND	ND	70	70	35	53	ND	ND	100	100	ND	ND	1.6	1.8
Rogers (2007)	9	9	64	54	91[b]	106[b]	78	60	78	50	78	60	100	100	ND	ND	1.8	1.6
Costanzo (2010)	100	100	62	63	101[b]	96[b]	70	68	50	49	56	48	97	93	ND	ND	1.5	1.5
Hanna (2010)	19	17	60	59	93.2[b]	97.6[b]	84	76	37	29	ND	ND	100	100	19[b]	19[b]	ND	ND
Giglioli (2010)	15	15	72.4	65.8	74.4[b]	83.4[b]	87	87	40	60	60	60	100	100	34[b]	30[b]	2.2	1.9
Badawy (2012)	20	20	64	62	91[b]	94[b]	70	60	60	55	60	65	100	100	ND	ND	1.4	1.4
Bart (2012)	94	94	69	66	94.0[a]	106.2[a]	78	72	65	67	ND	ND	ND	ND	30[a]	35[a]	1.9	2.1
Marenzi (2014)	27	29	75	73	83[b]	89[b]	81	83	59	45	ND	ND	100	100	32[b]	32[b]	1.7	1.9

UF = Ultrafiltration group; D = diuretic group; ND = no data available. [a] Expressed as median; [b] Expressed as mean.

Table 2. Characteristics of treatments in trials for meta-analysis

Study	UF modality	Vascular access	UF method	UF rate	UF duration	Diuretic mode	Diuretic dosage
Bart (2005)	ND	A 35 cm, 16 g catheter over antecubital fossa	Single session UF	Max 500 ml/h	8 h[a]	ND	160 mg/day[a]
Rogers (2007)	Aquadex System 100, using heparin to keep activated clotting time 180–220, 0.12 m^2 polysulphone filter	Combination of central and peripheral vein catheter	Single session UF	Max 500 ml/h	48 h[a]	B	314 mg/day[b]
Costanzo (2010)	Aquadex System 100, using heparin to keep activated clotting time 180–220 s, 0.12 m^2 polysulphone filter	Combination of peripheral and central vein catheter	Single session UF	Max 500 ml/h	Discretion of physician	B/C (68/32)[c]	181 mg/day[b]
Hanna (2010)	NxStage System One, blood flow 200–300 ml/min, heparin infusion 500 U/h	Femoral vein catheter	Single session UF	400 ml/h for 6 h, 200 ml/h till end	Until PCWP ≤18 mm Hg	ND	ND
Giglioli (2010)	PRISMA system, blood flow 150 ml/min, using heparin to keep aPTT 65–85 s	Femoral vein catheter	Slow continuous UF	Max 300 ml/h	46 h[a]	C	250–500 mg/day
Badawy (2012)	Multifiltrate/Prismaflex, blood flow >150 ml/min, heparin loading bolus 5,000 IU and continuous infusion 500–1,000 IU/h to keep activated clotting time 180–220 s	Jugular Vein, subclavian vein or femoral vein	CVVHDF	Max 200 ml/h	72 h[a]	C	ND
Bart (2012)	Aquadex System 100, using heparin to keep aPTT 2–2.5 times normal	2 peripheral IV catheter, or single dual-lumen catheter via peripheral vein, or central vein	Rescue UF therapy	200 ml/h	40 h[a]	C	ND
Marenzi (2014)	Dedyca ultrafiltration, polysulphone filter with a 50,000-Da membrane cutoff, heparin loading bolus 3,000–5,000 IU then continuous 500 IU/h	Central vein double lumen catheter	Single or double session UF	100–500 ml/h	19 h[b]	b	153 mg/day[b]

UF = Ultrafiltration; B = bolus; C = continuous; CVVHDF = continuous veno-venous hemodiafiltration; ND = no data available; PCWP = pulmonary capillary wedge pressure.
[a] Expressed as median; [b] expressed as mean; [c] patient number of each mode.

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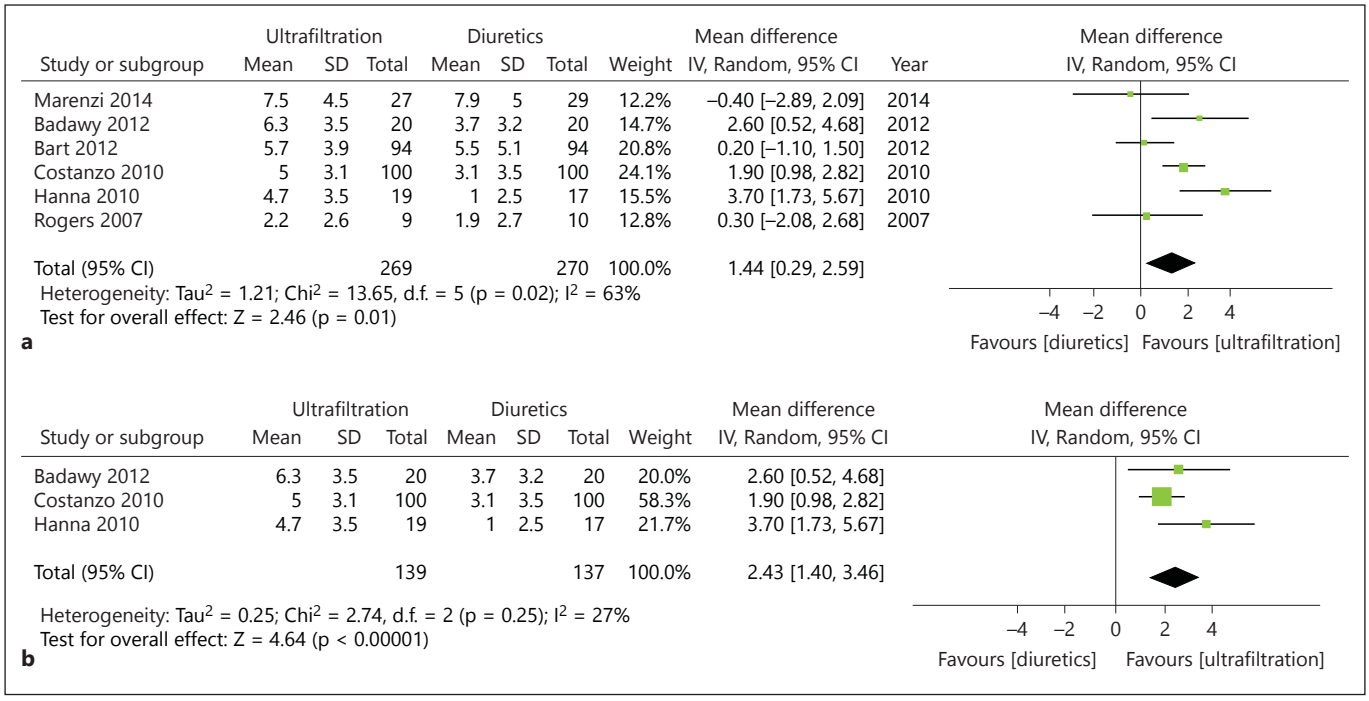

Fig. 2. Forest plot of studies examining the effect of ultrafiltration on total body weight loss in patients with decompensated heart failure and chronic kidney disease.

Table 3. Methodological quality assessment of studies in the meta-analysis

	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias
Bart (2005)	Yes	Unclear	No	Yes	No	No
Rogers (2007)	Yes	Unclear	No	Yes	No	No
Constanzao (2010)	Yes	Unclear	No	Yes	No	No
Hanna (2010)	Yes	Unclear	No	Yes	No	No
Giglioli (2010)	Yes	Unclear	No	Yes	No	No
Badawy (2012)	Yes	Unclear	No	Yes	No	No
Bart (2012)	Yes	Unclear	No	Yes	No	No
Marenzi (2014)	Yes	Unclear	No	Yes	No	No

by Roger et al. (UF group, 91 kg vs. Diuretic group, 106 kg), and Bart et al. (UF group, 94 kg vs. Diuretic group, 106.2 kg). The rate of change of the body weight is not clear and there will be bias in evaluating the result of the outcome by calculating the difference of body weight between two groups.

Outcome Analysis

Our primary outcomes are body weight loss and total fluid removal during the intervention period. The pooled body weight difference between patients receiving UF and diuretics was 1.44 kg (95% CI, 0.29–2.59; p = 0.01; fig. 2a). There was between-trial heterogeneity (I^2 = 63%; Q statistic, p = 0.02). By step-wise approach and exclusion of trials with higher between-groups variation of body weight at baseline, the I^2 statistic decreased from 63 to 27% and the pooled difference remains significant (2.43 kg, 95% CI, 1.4–3.5; p < 0.00001; fig. 2b). Figure 3 shows the analysis of fluid removal during intervention period as primary outcome and shows difference of 1.28 l between UF and diuretic groups (95% CI, 0.43–2.12; p = 0.003), with mild heterogeneity between trials (I^2 = 43%; Q statistic, p = 0.13). There

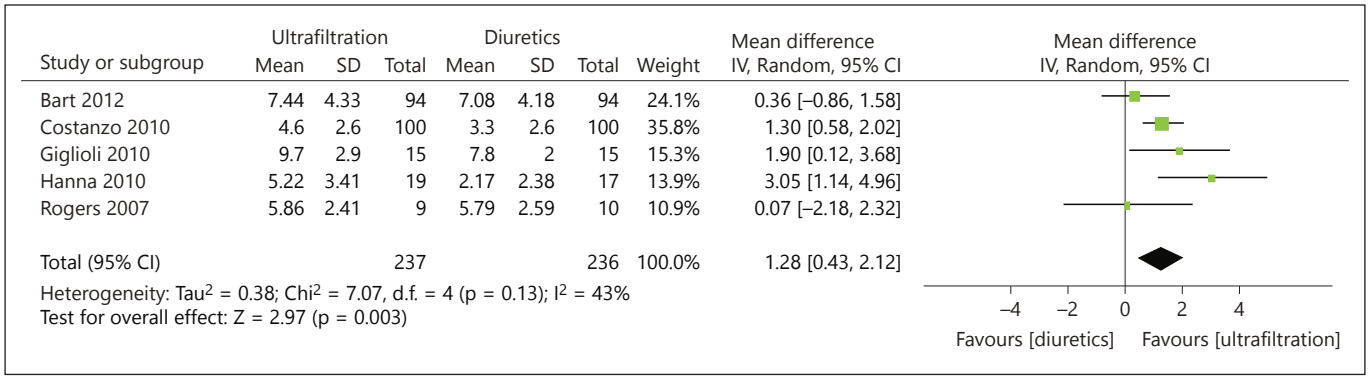

Fig. 3. Forest plot of studies examining the effect of ultrafiltration on total fluid removal in patients with decompensated heart failure and chronic kidney disease.

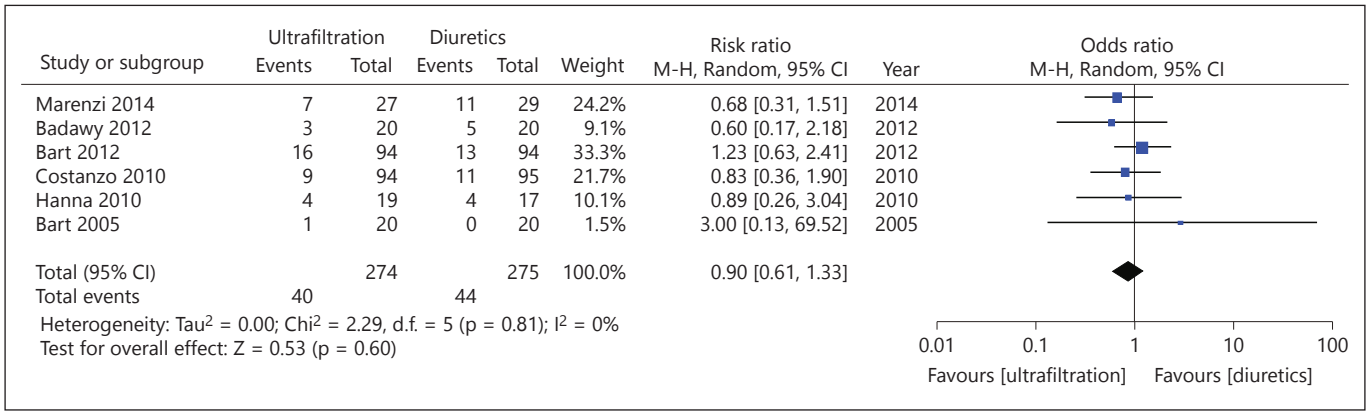

Fig. 4. Forest plot of studies examining the effect of ultrafiltration on total mortality rate in patients with decompensated heart failure and chronic kidney disease.

are four trials mentioning the subjective cardiac assessment and/or patient perception. UF led to significantly improvement of symptoms at 48 h in one trial [14]; and the other three trials all disclosed similar improvement of cardiac assessment [12, 13, 15]. Figure 4 shows the analysis of mortality as an end point and an RR of 0.90 for UF compared with diuretic therapy (95% CI, 0.61–1.33; p = 0.60), with minimal heterogeneity (I^2 = 0%; Q statistic, p = 0.81). The follow-up periods were 30 days by Badawy et al. [10] 60 days by Bart et al. [13, 14], 90 days by Hanna et al. [11] and Costanzo et al. [15] and 12 months by Marenzi et al. [16]. There were four trials demonstrating renal function deterioration. The definition of renal function deterioration was either decreased GFR [13, 17], or rising in serum creatinine of more than 0.3 mg/dl [11, 15]. UF did not increase the risk of renal deterioration, with the pooling risk ratio of 1.29 (95% CI, 0.90–1.85, p = 0.17; fig. 5) without heterogeneity (I^2 = 0%; Q statistic, p = 1.00). Moreover, UF had a trend toward but not statistically significant lower rate of readmission, the pooling risk ratio of 0.71 (95% CI, 0.43–1.18, p = 0.18; fig. 6) with moderate heterogeneity (I^2 = 56%; Q statistic, p = 0.08). However, no study compared the long-term impact on renal function after UF or diuretic therapy. Few data were available for adverse-event rates between treatment arms. There were no gross differences in adverse-event in studies that presented data (table 4). Catheter-related adverse events including catheter infection, catheter associated bleeding or discomfort, ranged from 2.13 to 5% in the UF group.

Discussion

Acute cardiorenal syndrome (ACS) characterized by an acute heart disorder leading to acute kidney injury occurs in about 25% of unselected patients admitted

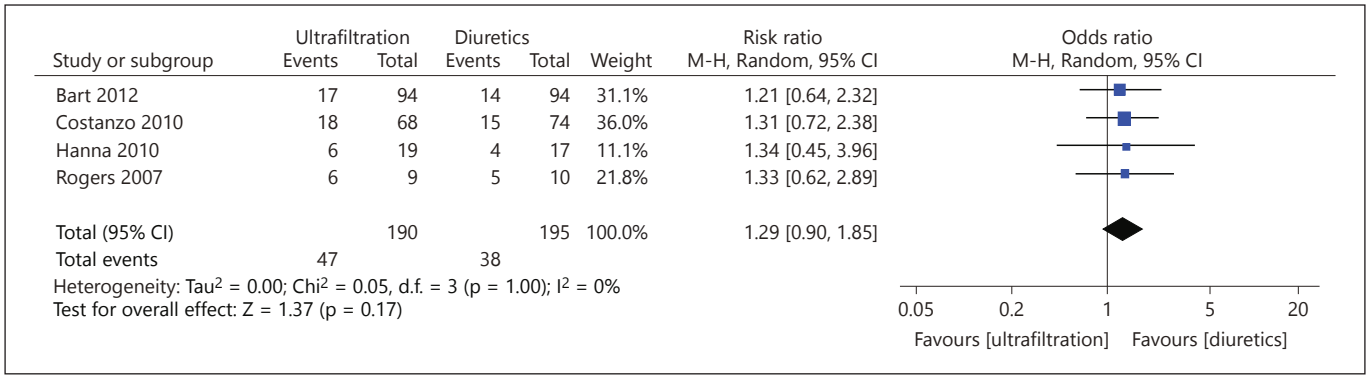

Fig. 5. Forest plot of studies examining the effect of ultrafiltration on renal function deterioration in patients with decompensated heart failure and chronic kidney disease.

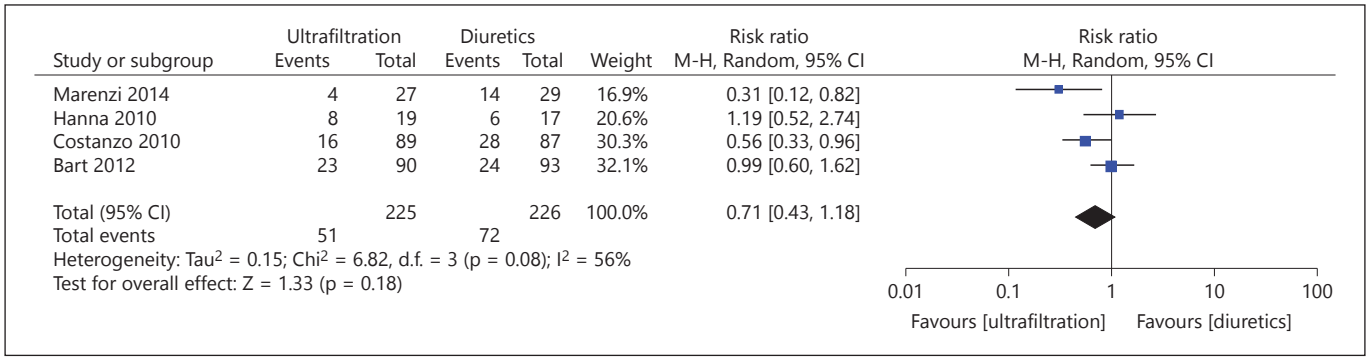

Fig. 6. Forest plot of studies examining the effect of ultrafiltration on readmissions due to heart failure in patients with decompensated heart failure and chronic kidney disease.

Table 4. Summary of adverse events reported

	Adverse events (%)		Catheter-related adverse events (%)	
	UF	D	UF	D
Bart (2005)	ND	ND	5.3	0
Costanzo (2010)	1.01	1.19	4	0
Hanna (2010)	2.68	2.47	ND	0
Bart (2012)	1.85	1.50	2.13	0
Total	1.53	1.43	3.27	0

Event rate expressed as events per patient. UF = Ultrafiltration group; D = diuretic group; ND = no data available.

with ADHF [18]. Renal hypoperfusion, passive venous congestion and reduced renal autoregulation play important roles in the pathogenesis of ACS. ACS represents a clinical challenge regarding its appropriate management; however, the preservation of renal function should receive the same priority as maintaining cardiac function.

Apart from neurohormonal blockade, salt and fluid restriction, intensive diuretic therapy is usually an essential part of therapy in patients with ADHF, but a significant subset of patients receiving diuretics (60%) develop worsening renal function which leads to diuretic resistance [19, 20]. The activation of sympathetic nervous system and exacerbation in renin-angiotensin-aldosterone system following the natriuretic effect of diuretic therapy are the possible reasons [8, 21]. Ultrafiltration, the mechanical extraction of isotonic fluid, has been an alternative treatment for ADHF. This procedure results in increased sodium removal without an increase in sodium delivery to the distal nephron, which could activate the tubuloglomerular feedback system. The lack of neurohormonal activation would theoretically preserve or even improve renal function through the reduction in venous congestion more efficiently, improvement of cardiac output, and increase in renal perfusion [13, 22]. So far, no

studies have approved the beneficial effect of UF on renal function. Further studies using the change of renal function as primary outcome following UF in patients with ADHF will be needed to clarify the issue.

We noted a large apparent effect of UF on body weight loss and fluid removal during intervention, but no apparent effect on readmission or mortality after discharge. Most of the patients in the analysis had poor heart function as reflected by the low ejection fraction and higher NYHA classification of more than 3. Alternatively, death from arrhythmia rather than fluid overload alone is common in patients with ADHF. Thus, the effect of UF on mortality or readmission would be diluted. However, fluid overload or pulmonary edema is associated with poor health-related quality of life and higher in hospital complications, and faster improvement of symptoms by UF remains an important advance for treatment of ADHF.

Although the UF modality in our meta-analysis can be performed via peripheral line, some patients still need central venous access due to difficulty in puncturing the peripheral vein under edematous and hypoperfusion status. It might carry the risk of catheter-associated adverse events in the UF group. Bradley et al. developed a decision-analytic model to explore the potential health economic benefits associated with UF and concluded that it appears unlikely that UF therapy for index and subsequent ADHF hospitalizations is cost-saving from a societal perspective compared to IV diuretics at 90 days from index hospitalization [23]. However, these calculations were based on the use of a recently developed compact device. It would be financially more advantageous to use already existing resources such as nursing staff and conventional cheaper hemofilters; then the results of the decision model analysis would become in favor of ultrafiltration.

At the present time, we would recommend ultrafiltration in patients with ADHF who are unable to achieve decongestion with a rational diuretic regimen and usual hemodynamic care. More RCT data focusing on the impact of long-term, overall kidney outcomes are needed.

Limitations

The included studies were heterogeneous with respect to UF modality, UF or diuretics regimen, patients included, and duration of follow-up. There is lack of diuretic protocol available in most of the trials, which will lead to the suboptimal effect of diuretic therapy in the control group. Most except one study lacked follow-up of renal function with longer duration. Moreover, no study mentioned about the etiology of chronic kidney disease, which may affect the amount of fluid removal.

Conclusions

We conclude that ultrafiltration in patients with cardiorenal syndrome leads to significantly greater body weight loss and fluid removal during intervention periods. Ultrafiltration had similar mortality rate, risk of renal deterioration and adverse event rate compared with diuretics therapy but had a trend toward lower readmission rates.

Acknowledgments

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Disclosure Statement

None declared.

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