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ORIGINAL ARTICLE

Analysis of the usefulness and benefits of ultrafiltration in cardiorenal syndrome: A systematic review

Borja Guerrero Cervera[1], Raquel López-Vilella[1,2]*, Víctor Donoso Trenado[1,2], María Peris-Fernández[3], Paula Carmona[4], Amparo Soldevila[5,6], Sergi Tormo[7], Ramón Devesa[5], María Jesús Montero Hernández[4], Luis Martínez Dolz[1,8], Julio Hernández Jaras[5], Pilar Sánchez-Pérez[5,6] and Luis Almenar-Bonet[1,2,8]

[1]*Cardiology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain;* [2]*Heart Failure and Transplantation Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain;* [3]*Instituto de Investigación Sanitaria La Fe, Valencia, Spain;* [4]*Anesthesia Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain;* [5]*Nephrology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain;* [6]*Nephrology Department, Section of Advanced Chronic Kidney Disease and Renal Replacement Therapies, Advanced Cardiorenal Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain;* [7]*Intensive Care Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain; and* [8]*Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain*

Abstract

Aims Cardiac decompensation in cardiorenal syndrome (CRS) results in systemic congestion usually treated with diuretics. When despite high doses of diuretics, response is poor, ultrafiltration (UF) appears to be a useful and safe technique. The aim of the study was to analyse, by means of a systematic review, the efficacy and safety of UF versus conventional diuretic treatment.

Methods and results Search of the main databases (Pubmed, Embase and Cochrane Central Register of Controlled Trials) identifying comparative studies of UF versus diuretic therapy, from 2000 to the present. After screening the studies, 13 studies were analysed; 1100 patients (UF: 532, diuretic treatment: 568). *Renal function:* UF showed a trend to lower creatinine at discharge (SME = −0.68; 95% CI −1.50 to 0.13; I^2 = 97%) with no difference in glomerular filtration rate (SME = 0.05; 95% CI −0.17 to 0.27; I^2 = 0%). *Diuretic response:* With UF, there was a trend towards greater weight loss (SME = 1.82; 95% CI −0.79 to 4.42; I^2 = 99.7%) and greater volume removed (SME = 3.04; 95% CI −2.13 to 8.20; I^2 = 99.8%). *Morbidity and mortality*: No difference in days of hospital stay (LogOR = −0.14; 95% CI −0.52 to 0.23; I^2 = 66.9%) and mortality at 1 month (LogOR = −0.04; 95% CI −0.34 to 0.44; I^2 = 0%) but reduction in readmissions in patients with UF (LogOR = −0.60; 95% CI −0.94 to −0.26; I^2 = 40.5%).

Conclusions In decompensated HF and CRS with inadequate diuretic response, UF versus diuretic intensification is an effective and safe option; it reduces readmissions with a tendency to decrease weight, creatinine levels and increase volume depletion without affecting mortality. Prospective randomised studies with a sufficient number of patients are needed to corroborate these results.

Keywords Cardiorenal syndrome; Diuretic resistance; Heart failure; Ultrafiltration

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**Correspondence to: Raquel López Vilella, Heart Failure and Transplantation Unit, Hospital Universitari i Politècnic La Fe, Av. Fernando Abril Martorell, No. 106, 46026 Valencia, Spain. Email: lopez_raqvil@gva.es*

Introduction

Heart failure (HF) is a highly prevalent disease that results in frequent clinical decompensations leading to hospital admissions.[1] This results in morbidity, mortality and high healthcare costs.[2] Cardiorenal syndrome (CRS) is a complex clinical entity involving the interrelationship between HF and renal dysfunction. Currently, this pathology presents relevant challenges, particularly in therapeutic management.[3] The usual therapeutic approach to congestive symptoms is

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diuretic therapy; however, high doses, especially when response is poor, lead to renal impairment and worse clinical outcome in congestive patients.[4]

Over the years, several strategies have been explored to address the best therapeutic approach to this syndrome, and among them, ultrafiltration (UF) has emerged as an effective and promising technique. This technique consists of a process of fluid and solute removal through semi-permeable membranes and appears beneficial in improving volume overload and symptoms associated with CRS.[5] The advantages that have been proposed are: predictable fluid and sodium removal, absence of ionic disturbances, more effective decongestion, improved renal function and lower costs.[6] To analyse these issues, some systematic reviews have been published, but they have several relevant limitations as they carry out a comparative analysis from a partial (small number of variables) or very exclusive (biomarkers) point of view, or they have a small sample size and may produce erroneous results with low quality statistical precision. They should therefore be analysed with caution and their external validity should be limited.

On the other hand, data derived from multiple clinical studies will help to draw more precise conclusions about the efficacy of UF in these patients. For all these reasons, this systematic review has been conducted with the intention of gaining a more precise understanding of the true usefulness of this technique in CRS. This review aims to provide a comprehensive and updated view of this topic, which will shed light on the supposed advantages of UF when there is diuretic resistance in systemic congestion and may become a reference for clinicians, researchers and health professionals involved in the care of patients with CRS.

Methods

A literature search of databases Pubmed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) was conducted to identify studies comparing ultrafiltration versus usual treatment (diuretic therapy) in patients with decompensated HF. The date of the search was 9 January 2024, and the search was conducted using the terms 'ultrafiltration' [AND] 'heart failure'. This first search returned 1227 results.

Of these, 506 were excluded if they were not related to the topic. Subsequently, after an exhaustive search, all studies that were not experimental studies (clinical trials) or analytical observational studies (cohorts and case controls) were excluded. In other words, reviews of the topic, case series without comparison with a control group and so on were excluded, amounting to a total of 543 studies. We also excluded studies conducted in animals and not in humans (six studies) and those that did not have an accessible abstract or only in languages other than Spanish, English, Italian or French (15 studies). Finally, studies that did not assess clinical parameters (focusing exclusively on biomarkers or haemodynamic parameters) and those that compared against more than one group (92 studies) were excluded. This left 13 studies comparing ultrafiltration in patients with congestive HF decompensation despite diuretic treatment versus usual management, which are the ones included in the present study (*Figure 1*).

The variables studied were: renal function measured as the difference in creatinine (mg/dL) and glomerular filtration rate (mL/min) between admission and discharge in both groups. Diuretic response collected as volume of diuresis and fluid extracted during admission in mL, and the difference in weight in kg from admission to discharge. All-cause mortality and admissions due to heart failure were analysed. Morbimortality collected as short-term mortality (up to 90 days), readmissions in the first month and hospital stay in days.

Regarding the statistical analysis of the data, for qualitative event variables, absolute frequencies were used to calculate OR and 95% confidence intervals (95% CI) and to represent them as logarithmic transformation (neperian logarithm of OR; LogOR) in the forest plot and funnel plot. For quantitative variables, means and standard deviations were used for the same purpose, calculating Cohen's *d* statistics, expressed as a standardised measurement error (SME) with their corresponding 95% CI. In both cases, the sample sizes of each study analysed for each type of event were taken into account. The overall results of the qualitative variables were also expressed in the text in the form of OR to facilitate their understanding.

For each of the events, the main graph is the forest plot, with its I^2 and H values to study the heterogeneity of the values analysed among the different studies included in the review. For cases in which the value of I^2 is less than 30%, fixed effects models are used, otherwise random effects models are chosen. Possible publication biases were studied with the funnel plot. Finally, in each case, a Galbraith plot was performed to assess the precision of each study in the review and the weights in the overall result.

The analyses were performed with STATA version 18.0. (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Results

Thirteen studies involving 1100 patients with decompensated HF requiring hospital admission and requiring treatment to reduce congestive status were analysed. Of these, 568 received standard drug treatment and 532 received UF therapy, in some cases in combination with diuretic treatment and in others with diuretics being suspended during the use of the technique. The technique was used both centrally and peripherally and extraction rates with ultrafiltration varied from 100 to 400 mL/h between the different studies (*Table 1*).

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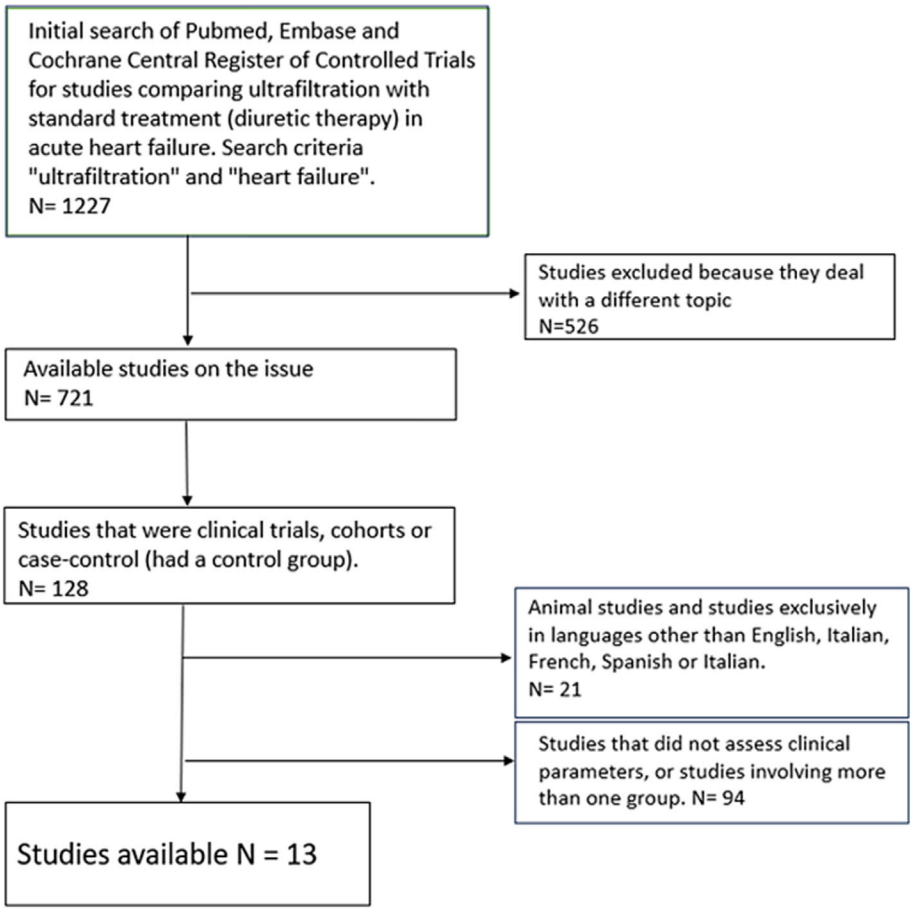
Figure 1 Study selection diagram.



Renal function

Patients undergoing UF therapy were associated with lower creatinine levels at discharge, with no significant differences in glomerular filtration rate.

Creatinine at discharge was analysed in 11 of the studies evaluated involving a total of 979 patients. *Figure 2* shows that the total standardised mean difference of creatinine at discharge shows a negative value close to statistical significance (SME = −0.68; 95% CI −1.50 to 0.13; I^2 = 97%) suggesting an association between UF and a reduction in creatinine values. The I^2 and H values indicate the presence of heterogeneity, which may influence the interpretation and with some of the studies having negative values outside the funnel plot triangle, although all with a very similar contribution (similar weight in the total), indicating that publication bias may exist. Regarding glomerular filtration rate at discharge, this was analysed in four of the studies including a total of 319 patients. For glomerular filtration rate the overall mean shows a value very close to 0 and with a moderate dispersion (SME = 0.05; 95% CI −0.17 to 0.27; I^2 = 0%). None of the studies analysed to assess changes in GFR in patients undergoing UF showed statistically significant results. Neither did they show publication bias in the funnel plot although there are too few studies for this graph to be powerful (*Figure 2*).

Diuretic response

Data on the effects of UF on weight loss were available from 11 trials involving 1030 patients. Data on the effects of UF on volume removed were available from seven trials involving 547 patients. UF treatment produced a positive effect on weight loss and the amount of volume removed close to, but not reaching statistical significance for either variable. In *Figure 3*, we observed that the weighted mean difference for weight loss was +1.82 in patients receiving UF (SME = 1.82; 95% CI −0.79 to 4.42; I^2 = 99.7%), although the heterogeneity between studies was high, when analysing the forest plot and funnel plot, we observed one study completely outside the triangle area contributing to a high I^2 value. Regarding the extracted volume, the overall value of the studies is positive, the total mean shows a value of +3.04 for the group of patients who received UF

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Table 1 Characteristics of included studies

First author and/or study	Year	Type of study	Number of patients (UF/diuretics)	Inclusion criteria	Diuretic dosing	UF rate (mL/h)
RAPID-CHF	2005	RCT	20/20	Acute HF: congestion	Furosemide 160 mg/day	400
UNLOAD	2007	RCT	100/100	Acute HF: congestion	Furosemide equivalent dose 181 mg/day	241
Rogers HL	2008	RCT	9/10	Acute HF: congestion + reduced LVEF	Furosemide 240–520 mg/day	113
ULTRADISCO	2011	RCT	15/15	Acute HF: congestion	Furosemide 250–500 mg/day	100–300
CARRESS-HF	2012	RCT	94/94	Acute HF: congestion + recent ≥ 0.3 mg/dL sCr increase	Furosemide 120 mg/day ± metolazone	200
Hanna MA	2012	RCT	19/17	Acute HF: NYHA III-IV + reduced LVEF + PCWP ≥ 20	Intravenous loop diuretic at physician's discretion ± spironolactone	272 ± 211
CUORE	2014	RCT	27/29	Acute HF: NYHA III–IV + congestion + reduced LVEF	Furosemide 153 mg/day	302 ± 78
Loon YLT	2016	Observational study	18/26	Acute HF: congestion + diuretic resistant (urine output < 125 mL/h)	Furosemide 167 mg/day	314 ± 99
AVOID-HF	2016	RCT	110/114	Acute HF: congestion + on treatment with oral loop diuretics	Furosemide 271 mg/day	138 ± 47
Seker A	2016	RCT	10/20	Acute HF: congestion	Furosemide 164 mg/day	150–400
Tansu SAV	2017	RCT	37/40	Acute HF: congestion	Furosemide 150 mg/day	350
Hu J	2020	RCT	40/60	Acute HF: congestion	Furosemide equivalent dose 80 mg/day + tolvaptan	200–300
López-Vilella R	2023	Observational study	35/21	Acute HF: congestion	Furosemide 249 mg/day ± MRA ± thiazide	131 ± 29

Abbreviations: HF, heart failure; MRA, mineralocorticoid receptor antagonist; PCWP, pulmonary capillary wedge pressure; RCT, randomised clinical trial; sCr, serum creatinine.

(SME = 3.04; 95% CI −2.13 to 8.20; I^2 = 99.8%) and close to statistical significance but without reaching it, the I^2 value is very high indicating significant heterogeneity among the studies; when analysing the funnel plot, we observe again a value totally out of the range of the studies, indicating a high level of heterogeneity among the studies.

Morbidity and mortality indicators

Patients undergoing UF therapy showed lower readmission rates. No significant differences were found in days of hospital stay or short-term mortality between the two groups.

The number of readmissions is reported in six of the studies analysed, with a total of 764 patients studied. *Figure 4* shows the result whose mean value is negative and statistically significant, with moderate heterogeneity (LogOR = −0.60; 95% CI −0.94 to −0.26; I^2 = 40.5%; OR = 0.55 CI 0.39 to 0.77), and when observing the funnel plot we have a triangle that is not symmetrical but no value falls outside the marked area so there is no publication bias. Regarding length of stay, these data were available in five of the analysed studies including a total of 419 patients. Overall, the studies analysed show a total negative mean value in favour of the group that received UF, which does not reach statistical significance as it crosses the neutral effect value (LogOR = −0.14; 95% CI −0.52 to 0.23; I^2 = 66.9%); in this variable, when analysing the funnel plot, we observed publication bias, so these results should be taken with caution (*Figure 5*). Short-term mortality was collected in eight of the studies analysed, including a total of 907 patients. This variable showed no differences between the two groups, resulting in an overall neutral result (LogOR = 0.04; 95% CI −0.34 to 0.44; I^2 = 0%; OR = 1.04 CI 0.70 to 1.55), with an I^2 value indicating high homogeneity and a symmetrical triangle in the Funnel plot with studies on both sides (*Figure 6*).

Discussion

Systemic congestion, as part of CRS in patients with advanced HF, carries a poor prognosis.[7] The measures used to control it have been diuretic treatment with different doses and combinations.[4] However, this intensive treatment is not harmless and is often ineffective due to resistance to these drugs. Therefore, in certain studies and clinical trials, UF has been used as an alternative method due to its less physiological aggressiveness and with the added objective of recovering sensitivity to diuretics.[8] These studies are rather scarce, so the aim of this study was to conduct an in-depth review of the literature and perform a systematic analysis of similar studies/trials, all oriented towards the efficacy and effectiveness of UF. Parameters of renal function (changes in glomerular filtration rate and creatinine), diuretic

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Figure 2 Creatinine and glomerular filtration rate differences at discharge forest plot and funnel plot. CI, confidence interval; SD, standard deviation.

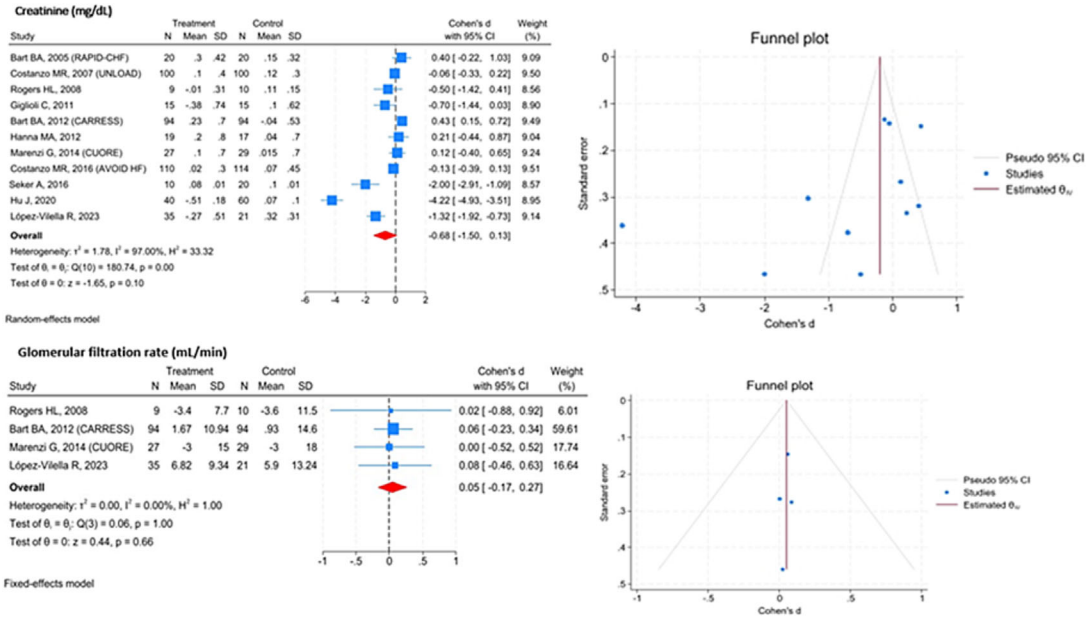
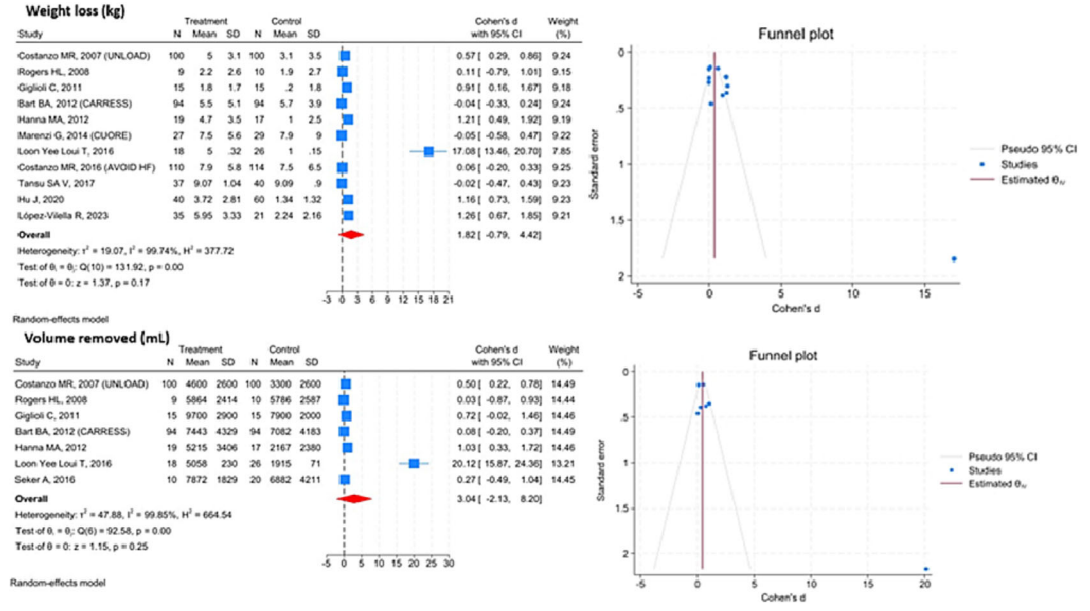


Figure 3 Weight loss and removed volume forest plot and funnel plot. CI, confidence interval; SD, standard deviation.



response (amount of volume extracted and weight loss) and morbimortality (days of stay, readmissions and mortality) were analysed. Significant differences in favour of ultrafiltration have been observed in the reduction of readmissions in the first month and a clear trend towards a reduction in creatinine levels with greater weight loss and no change in mortality.

Focusing on renal function, we observed a favourable trend for UF in the reduction of creatinine values, without a positive effect on glomerular filtration rate. The clinical course of patients with HF and congestion is often characterised by renal dysfunction (CRS) and resistance to diuretics which may be due to multiple mechanisms: neurohormonal activation, adaptation to loop diuretics (hypertrophy

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Figure 4 Readmissions forest plot and funnel plot. CI, confidence interval; SD, standard deviation.

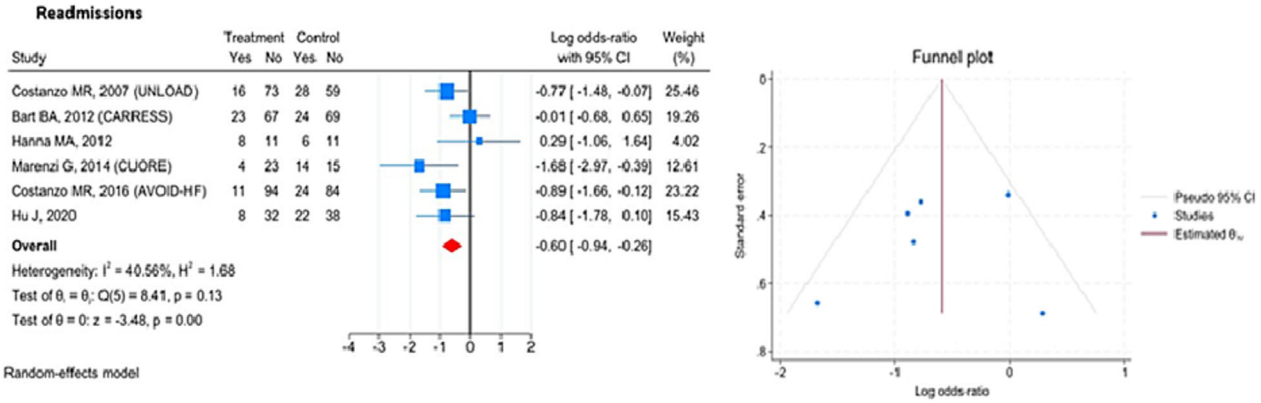


Figure 5 Length of hospital stay forest plot and funnel plot. CI, confidence interval; SD, standard deviation.

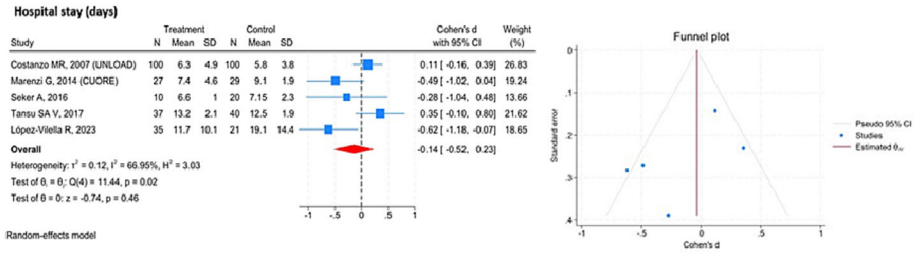
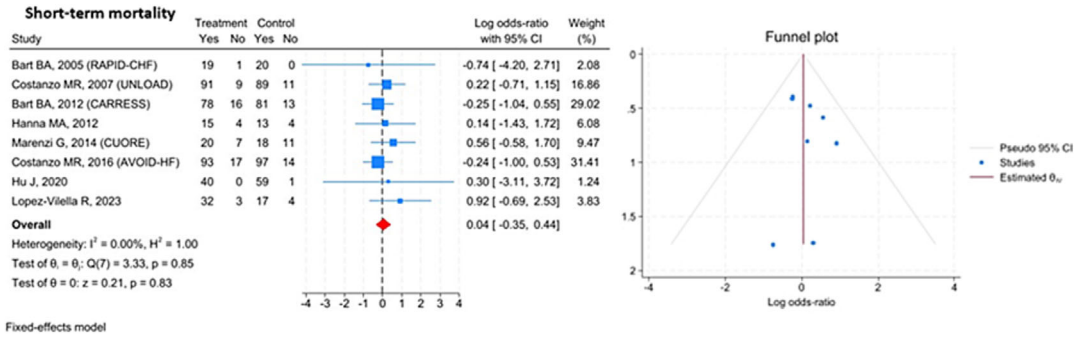


Figure 6 Short-term mortality forest plot and funnel plot. CI, confidence interval.



and hyperfunction of areas of the nephron, increased renin secretion), tubular compensation (increased sodium reabsorption), concomitant proteinuria decreasing drug bioavailability and so on.[8,9] UF avoids some of the mechanisms that lead to a deterioration of renal function. It produces a mechanical elimination of fluids in such a way that water and electrolytes are eliminated without altering the plasma concentration of ions, obtaining an ultrafiltrated fluid that is isotonic and isoosmolar with respect to plasma and a more isotonic urine (diuretics produce hypotonic urine compared to plasma) that contributes to reducing hydrostatic pressure in the nephron and avoids activating the renin angiotensin aldosterone system (RAAS). In addition, UF removes more total body sodium than diuretics and allows recovery of diuretic responsiveness after ['diuretic holidays'].[9,10]

The main studies analysing UF show variable results with respect to renal function. The predominant trend is improvement in renal function. Studies such as RAPID-CHF

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show a benefit of UF in renal protection by reducing creatinine levels.[11] ULTRADISCO and other studies also show an improvement in creatinine levels.[8,12] However, other trials such as CARRES-HF showed an increase in creatinine levels in the UF group.[13] The key to these differences may lie in the UF rates used. It is important to adjust the UF rate according to the patient's vital signs, as intravascular repletion takes time and high UF rates may lead to relative hypovolaemia with associated hypotension.[14] Patients with right ventricular failure and preserved LVEF HF tolerate volume depletion worse and may only tolerate low UF rates.[15] Studies such as CARRES-HF, where worse renal outcomes were obtained, used higher and fixed UF rates, and for less time.[13] Using low (<200 mL/h) and mobile UF rates according to the haemodynamic situation of the patient is the way to obtain the best results with the current evidence.[12,16] In turn, the longer duration of treatment will allow a longer 'rest' of the nephron from diuretic drugs. Regarding glomerular filtration rate, the overall effect obtained is neutral, as is the case in most studies.[11,15] This is probably due to the indirect calculation of glomerular filtration rate by formulae, which use creatinine, but also other variables that may act as confounding factors. On the one hand, it must be taken into account that creatinine can be influenced by muscle mass; in this regard, having cystatin C values would be of great interest, as they would provide relevant information.[17] On the other hand, glomerular filtration rate was analysed in only 319 patients. The low number of studies may have contributed to the lack of statistical significance with the glomerular filtration rate.

In terms of diuretic response, treatment with UF produced a positive effect on weight loss and the amount of volume extracted, showing a clear trend in favour of UF, although without reaching statistical significance. Prolonged use of diuretics may end up decreasing renal capacity to produce adequate diuresis in quantity and sodium content, and despite increasing the dose of diuretics, fluid retention and symptoms of congestion may not be adequately controlled and renal function parameters may worsen.[15,18] Since the RAPID-CHF study (Relief for Acutely Fluid Overload in patients with decompensated congestive heart failure) was published, it has been observed that weight loss and diuresis after 48 hours can be significantly improved.[11] Results that were reproduced in the UNLOAD trial 2 years later where patients receiving UF had greater weight loss and diuresis before discharge.[19] Other studies that have used UF at low rates, for a longer time and partially or totally suspending diuretic treatment, have also shown greater decongestion, weight loss and increased diuresis.[8,10] The plausible physiological explanation for the results obtained is that UF allows precise control of the amount of fluid withdrawn and allows recovery of the response to diuretics after having temporarily suspended them, thus improving diuresis and achieving a more effective decongestion.[20]

When analysing morbidity and mortality indicators, patients undergoing UF therapy showed lower readmission rates, with a tendency to require fewer days of hospital stay that was not statistically significant and no differences compared to the control group in mortality at 1 month. UF appears to reduce all-cause and HF-related readmissions in the first month. In trials such as UNLOAD, the incidence of HF readmissions and 90-day emergency room visits were significantly lower in the UF group, in the CUORE trial, UF-treated patients had a lower incidence of readmissions for heart failure despite similar weight loss at discharge.[19,21] Other studies and the CUORE trial itself also suggest that UF leads to a reduction in hospital stay, although this reduction was not shown to be significant in the overall analysis performed.[8,21] The fact that during the UF process, in addition to the volume of fluid removed by the technique, the loss through diuresis is also preserved and contributes to reaching a state of euvolemia earlier may explain the need for fewer days of hospitalisation. The higher net sodium loss, the lower neurohormonal activity and the higher renal sensitivity after diuretics due to 'diuretic holidays' would explain the reduction of hospital readmissions at 1 month.[10,22] Studies with less favourable results for UF, such as CARRES-HF, simply showed no significant difference in HF hospitalisation, all-cause hospitalisation and mortality versus diuretic therapy.[13]

In most of the studies reviewed, the effect of UF on all-cause mortality at 30 days or less is unclear or null.[10,18] This is partly due to the small sample size, which results in low power for a hard endpoint such as mortality, but also partly due to the high mortality in acute HF, where very few therapeutic strategies have been shown to be effective in its reduction, and the complexity of this pathology.[23] Acute HF has a high mortality rate, which is influenced by a variety of comorbidities, not only heart failure itself.[24] In patients with acute HF, mortality is not determined by fluid loss, but rather by sodium loss. In this sense, UF achieves greater sodium loss, however, with the available results, this is not sufficient to achieve an improvement in mortality.[25] On the other hand, diuretic treatment has not been shown to reduce mortality in acute HF either,[26] and studies such as the DOSE trial in which different strategies were tested with different doses of diuretics showed no improvement in survival.[27] In conclusion, UF treatment is not associated with an increased risk of all-cause mortality, rehospitalisation, or length of admission. However, it does show a decrease in rehospitalisation and a trend towards fewer days of hospitalisation.

Finally, UF is an invasive technique and entails an economic cost. On the other hand, the reported incidence of complications is very low, and the cost of hospital admissions that this technique reduces must be considered. Additionally, in this meta-analysis, we included studies that analyse peripheral access ultrafiltration. These systems can be used via peripheral

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venous access, slowly and at low flow rates; this has been shown not to cause ionic disturbances and to favour the maintenance of renal function.[8]

The limitations of the study are those inherent to any meta-analysis, based on pooling data from different studies, with different designs, objectives and follow-ups. The outcomes of creatinine at discharge and weight loss were the only ones with more than 10 pooled studies. Some of the variables showed publication bias in the funnel plot (asymmetry), suggesting the likelihood that small trials or trials without the desired effect were not published. On the other hand, it can be confirmed in the literature that it is always difficult to find significant evidence in studies conducted on acute heart failure. This may be related to the selected endpoints, which are often chosen for the long term, making it complex to analyse the impact of measures taken in the acute phase. In this regard, it would be highly useful to conduct randomised clinical trials with a large number of patients, careful matching of diuretics, clear definition of diuretic resistance, UF strategy (conventional vs. peripheral access), endpoints, and other key clinical variables.

Conclusions

In patients with decompensated HF, CRS and inadequate diuretic response, ultrafiltration, as opposed to diuretic intensification, is an effective and safe option as it reduces hospital readmissions and has a clear tendency to reduce creatinine levels with decreased body weight and increased volume removed, without affecting mortality. Prospective randomised studies with a sufficient number of patients are needed to corroborate these results.

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Conflict of interest

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