been used for more than 30 years, despite inconclusive evidence and poor outcome. In this setting, hemodynamically compensated heart failure (ADHF) suffer from worsening renal function, which is often associated with medical therapy resistance and poor outcome. In this setting, haemofiltration has been used for more than 30 years, despite inconclusive evidence for its advantages. In the last decade, a major technological advances have made available a new technique, ultrafiltration, which works at lower blood flow rates and requires only a venous access. As in a first proof-of-concept study (EU-PHORIA), ultrafiltration proved to be efficacious in fluid removal in ADHF patients; this treatment was further investigated in randomized controlled trials. The RAPID-CHF trial demonstrated that ultrafiltration was more effective than...

**ABSTRACT**

A significant proportion of patients treated for acute decompensated heart failure (ADHF) suffer from worsening renal function, which is often associated with medical therapy resistance and poor outcome. In this setting, haemofiltration has been used for more than 30 years, despite inconclusive evidence for its advantages. In the last decade, a major technological advances have made available a new technique, ultrafiltration, which works at lower blood flow rates and requires only a venous access. As in a first proof-of-concept study (EU-PHORIA), ultrafiltration proved to be efficacious in fluid removal in ADHF patients; this treatment was further investigated in randomized controlled trials. The RAPID-CHF trial demonstrated that ultrafiltration was more effective than...
medical therapy in fluid removal, even though it did not provide a greater weight loss. The UNLOAD trial thereafter showed a greater weight loss with ultrafiltration compared with diuretic therapy at 48 h after admission and a lower readmission rate at 90 days. Based on these results, the AHA/ACC and ESC guidelines consider ultrafiltration as a reasonable approach in ADHF patients with unresolved congestion notwithstanding optimal medical therapy and/or hyponatremia. However, the recently published CARRRESS-HF trial would appear to challenge these recommendations as it failed to demonstrate an advantage of ultrafiltration compared with medical therapy, based on the finding of subtle clinically irrelevant changes in renal function between treatments. This review focused on the current evidence supporting the use of ultrafiltration and on a critical appraisal of the recently published CARRRESS-HF trial.

**Keywords:** cardiorenal syndrome, heart failure, renal failure, ultrafiltration

### INTRODUCTION

A substantial proportion of patients presenting with acute decompensated heart failure (ADHF) manifest a worsening in renal function (WRF), also labelled as acute cardiorenal syndrome [1]. Although the attribute of ‘syndrome’ to coexisting cardiac and renal diseases does not conform to the dictate of standard methodological criteria, namely the definition of criteria for diagnosis, and to stages for prognosis, the synergism of the syndrome components in determining clinical outcomes and the uniqueness of treatment decisions [1], it is undeniable that WRF occurs in about one or two out of five patients with ADHF [2].

The WRF can derive from multiple processes, including intensified use of IV diuretics: in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catherization Effectiveness (ESCAPE) Trial fluid removal was associated with signs of haemoconcentration and with deterioration of renal function [3]. However, in spite of this, WRF predicted substantially improved survival at 180 days (hazard ratio for mortality, 0.31; P = 0.013), suggesting that intensive decongestion protocols even in the setting of an initial worsening of renal function might improve survival [4]. However, it remains possible that in relatively less severe cases with a higher probability of survival, worsening renal function may generate a vicious cycle leading to further aggravation of kidney injury and to adverse clinical outcomes in the medium-long term. In this regard, it is important to reckon that WRF predicts death, and that elevated blood urea nitrogen-to-creatinine ratio (BUN/Cr) at admission has been advocated as a test useful for identifying ADHF patients likely to experience improvement in renal function with treatment [5].

WRF-induced resistance to medical therapy is suspected to be a relevant mechanism, whereby WRF associates with a poorer outcome. On the other hand, the fact that an initial WRF may predict better survival demands caution when WRF is adopted as a surrogate of clinical events in trials in decompensated heart failure. Based on these considerations and on results of several early studies in ADHF, alongside those of some randomized clinical trials on ultrafiltration (UF), the current American Heart Association (AHA)/American College of Cardiology (ACC) and the European Society of Cardiology (ESC) treatment guidelines state that UF is a reasonable approach in patients with congestion that does not respond to medical therapy (Class IIa, level of evidence B) [6, 7]. This review is a narrative appraisal of current evidence supporting this statement along with the results of the recently published The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRRESS-HF) trial [8].

### THE DEVELOPMENT OF THE CONCEPT OF UF IN ADHF

Studies on the use of haemofiltration for resolving congestion in ADHF started in the last few decades of the last century. They were small in size, had a retrospective design, lacked a control group and were conducted before the cornerstone of contemporary treatment of heart failure, e.g. neuro-hormonal blockade, was consistently used [9–15]. Moreover, highly variable types of diuretics, route of administration and continuous versus intermittent extracorporeal therapies were used [9–15]. In addition, the definition of resistance to diuretics was inconsistent across studies and the response to treatment was assessed in heterogeneous ways [9–15]. The impact of haemofiltration on renal function was often not assessed and the length of follow-up was generally short. Besides all these problems, the modalities of extracorporeal fluid removal were highly varied in duration, ranging from a single few-hour treatment to daily therapy repeated over long periods of time. The type of pumps, membranes and therapy were also quite different in that the blood flows (200–400 mL/min) and fluid removal rates (200–1,200 mL/h) accomplished with the only two techniques available in the last decades of the previous century, e.g. haemofiltration or continuous arteriovenous haemofiltration (CAVH), differed markedly [9–15]. Because of this, it was impossible to determine whether and to which extent haemofiltration provided benefits above and beyond those of optimal pharmacological therapy and definitive conclusions could not be drawn on the role of mechanical fluid removal to treat heart failure patients with pulmonary and peripheral congestion. Notwithstanding this, some important messages can be distilled from these early studies: first, extracorporeal fluid removal was generally reserved for patients who had advanced heart failure (HF) of different aetiologies, severe renal impairment and generally refractory fluid overload [9–15]. Second, despite the severity of illness, mechanical fluid removal was consistently associated with substantial weight loss, effective improvement of congestion and also some restoration of responsiveness to diuretics, as indicated by an increased urine output at lower diuretic doses. Third, of much importance, it also became evident that an overly aggressive fluid removal could convert non-oliguric renal dysfunction into oliguric renal failure, likely by decreasing renal perfusion pressure and simultaneously causing additional neuro-hormonal activation [16–18]. An important deduction
was, therefore, that the same rate of fluid removal cannot be universally applied to all subjects, but it must be adjusted to individual patients’ characteristics, including vital signs, underlying renal function, severity of congestion and response to treatment.

**NEWER UF TECHNIQUES**

In the first decade of this century, major technical development allowed valuable advances in simplifying and improving UF. These steps include the availability of 0.12 m² polysulfone filters and peristaltic pumps working at much lower blood flow rates (10–40 mL/min with UF versus 200–300 mL/min with haemofiltration). This translated to a much lower total extracorporeal blood volume (33 mL with UF versus 200–300 mL with haemofiltration) and also in the feasibility of using peripheral, midline or central venous access. However, the low blood flows and UF rates, as well as the small size of the venous catheters, render necessary the use of systemic anticoagulation with heparin in order to prevent clotting of the venous catheter and of the haemofilter. The use of anticoagulation requires meticulous monitoring for the increased risk of bleeding, which is the only major drawback of using these much smaller IV catheters.

A pilot study with this newer UF technique documented for the first time the feasibility of achieving a dose-dependent fluid removal without any adverse haemodynamic consequences [19]. After that, the Early UF in Patients with Decompensated Heart Failure and Observed Resistance to Intervention with Diuretic Agents (The EUPHORIA) trial was conceived as a proof-of-concept study [20]. It enrolled patients with a severely depressed LV ejection fraction (LVEF: 31 ± 16%), who were elderly (mean age: 74 ± 8.5 years), predominantly Caucasians (95%), males (75%) and with an ischaemic aetiology of their heart failure. Early institution of UF within hours of hospital admission resulted in a conspicuous fluid removal (8.653 ± 4.314 mL), which was associated with resolution of signs and symptoms of fluid overload without symptomatic hypotension, renal insufficiency (≥25% increase in serum creatinine) or any other adverse events [20]. Of clinical relevance, this permitted a safe discharge in ≤3 days. Of further interest, UF corrected hyponatraemia when present at baseline and normonatraemia persisted up to 90 days. Likewise, the fall in brain natriuretic peptide seen at discharge persisted for at least 30 days post-discharge, and that of body weight up to 90 days. Thus, an initial UF treatment in elderly diuretic-resistant patients with volume overload was shown to result in reduced length of hospital stay and improved clinical status, which seemed to be preserved for 30–90 days following hospitalization. On the basis of this favourable clinical experience, the authors of this study hypothesized that UF may also have benefits in patients who are responsive to diuretics. On the other hand, a small Mayo Clinic experience showed that WRF might be a problem in patients with impaired renal function at baseline [21]. Indeed, in 11 patients with a baseline serum creatinine of 2.2 mg/dL (range 0.9–3.2) and estimated glomerular filtration rates of 38 mL/min (range 20–87), WRF leading to dialysis occurred in 45% of high-risk patients with diuretic resistant, refractory HF and right ventricular dysfunction.

**THE RANDOMIZED CLINICAL TRIALS WITH UF**

The Relief for Acutely Fluid Overloaded Patients with Decompensated Congestive Heart Failure (The RAPID-CHF) Trial [22] was a multicentre randomized, controlled trial of 40 patients, which compared the effects of a single early 8-h UF treatment strategy (n = 20) with diuretic therapy (n = 20) for patients hospitalized for ADHF of any aetiology. The RAPID-HF missed the primary end point of greater weight loss in the UF arm. Solely based on the finding of a significantly greater fluid removal with UF than with usual diuretic care, and no notable adverse events, the authors hastily concluded that UF was the ‘gold standard’ for salt and water removal, as it was safe in a variety of clinical sites and delivered a predictable clinical response. This study was small and based only on surrogates, and there was no follow-up beyond 48 h. Thus, it remained much uncertain whether in hypervolemic heart failure patients, UF was superior to aggressive IV diuretic therapy in reducing volume overload. UF treatment was further tested in The UF versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure Trial (UNLOAD) [23]. The primary end points of UNLOAD were weight loss and patients’ dyspnoea assessment 48 h after randomization. Weight loss was more pronounced in the UF arm than in the standard-care arm of the study. However, the dyspnoea score improved to a similar degree in the two groups. Thus, UNLOAD failed to show a superiority of UF in alleviating dyspnoea, a cardinal symptom of heart failure. At 90 days, rehospitalizations plus rehospitalization equivalents (unscheduled visits), a secondary end point, were fewer in the UF group (0.65 ± 1.36) than in the continuous infusion (2.29 ± 3.23; P < 0.016 versus UF) and bolus diuretics (1.31 ± 1.87; P < 0.05 versus UF) groups. There were no differences in serum creatinine among groups up to 90 days, and no clinically significant differences at each assessment interval in serum BUN, Na⁺, Cl⁻ and HCO₃⁻ levels. During treatment, hypokalaemia, defined as a serum K⁺ level < 3.5 mEq/L, occurred in 1% of the patients in the UF group and in 22% of the patients in the IV continuous diuretic infusion group (P = 0.003 versus UF), and 8% patients in the IV diuretic bolus group (P = 0.161 versus UF) [24]. Episodes of hypotension during the first 48 h after randomization were similar in the UF and in the standard-care group (4.4 and 3%, respectively) [24]. Of note, UNLOAD did not show a superiority of UF over standard care as for quality of life, another secondary end point, as assessed by an instrument built up specifically for HF patients (The Minnesota quality of life instrument for patients with HF).

**THE GUIDELINES RECOMMENDATIONS**

The current guidelines recommendations from the AHA/ACC [6], ESC [7] and Canadian Cardio-Vascular Society [25], which were therefore based on the results of these RCTs, are reported in Table 1. AHA/ACC and ESC guidelines concur in
suggesting UF as reasonable for patients with refractory congestion not responding to medical therapy, with a class of recommendation IIa, level of evidence B [6, 7]. More specifically, the AHA/ACC guidelines define lack of response to medical therapy as an inadequate response to an initial dose of IV loop diuretic followed by an inadequate response to an increased dose of the same drug. If this measure is not effective, invasive haemodynamic assessment is recommended. Objective evidence of persistent congestion can then be treated with the addition of a thiazide diuretic (metholazone or IV chlorothiazide) or of an aldosterone antagonist or the use of continuous IV infusion of a loop diuretic. If all of these measures fail, mechanical fluid removal can be considered. Hence, according to these guidelines, UF should be considered to reduce fluid overload (pulmonary and/or peripheral oedema) in selected patients and correct hyponatraemia in symptomatic patients refractory to diuretics. In addition, in order to achieve adequate control of fluid overload, UF or haemofiltration may be needed if oedema becomes resistant to treatment and/or if the degree of renal dysfunction is severe, e.g. with increases of serum creatinine to levels >3 mg/dL. Under these conditions, the efficacy of established treatments can be limited by the presence of renal insufficiency and the use of UF can, therefore, produce evident clinical benefits, reduce the risk of uraemia, restore responsiveness to conventional doses of loop diuretics, and also allow the use of drugs routinely used for the management of HF, for example ACE inhibitors or ARBs [6, 7]. The aforementioned recent trials on the use of UF in patients with ADHF have also shown that these effects of UF were sustained for longer periods.

The guidelines from the Canadian Cardio-Vascular Society [25], besides sharing the recommendations from AHA/ACC and ESC guidelines [6, 7] regarding the suggestion to consider UF for volume management in patients with ADHF and diuretic resistance, highlight that UF is potentially associated with risks that include hypotension, catheter-related complications and bleeding due to the need for systemic anticoagulation, which might add further risk for these patients [24]. In addition, based on the literature, the safety of UF cannot be readily extrapolated to a broader population treated at centres without experience and expertise in use of UF. Therefore, according to these guidelines, intermittent slow continuous veno-venous UF may be considered in highly selected patients and under experienced supervision (Weak Recommendation, Low-quality Evidence) [25].

**Table 1. Current guidelines recommendations**

<table>
<thead>
<tr>
<th>Expert Group</th>
<th>Comment</th>
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<tr>
<td>ACC/AHA [6]</td>
<td>UF is reasonable for patients with refractory congestion not responding to medical therapy. (Class of recommendation IIa, level of evidence: B)</td>
</tr>
<tr>
<td>ESC [7]</td>
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**The most recent randomized clinical trial with UF**

The last trial published is the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), a multicentre study designed to compare the effects of UF at a fixed rate (200 ml/h) with those of stepped pharmacologic therapy on renal function and weight loss in heart failure patients with persistent congestion who had WRF with therapies given prior to randomization [26]. In this trial, published in the *New England Journal of Medicine* in December 2012, in 188 patients with ADHF, worsened renal function and persistent congestion, half were randomized to stepped pharmacologic therapy and half to UF. The stepped pharmacologic therapy included loop diuretics, thiazide diuretics, inotropic agents and vasoactive drugs, which had to be carefully adjusted according to the patient’s clinical response (urinary output, etc.).

The primary end point was the bivariante change from baseline in the serum creatinine level and body weight, as assessed 96 h after randomization. Patients were followed for 60 days. According to the authors, UF was found to be inferior to stepped pharmacologic therapy with respect to the bivariante end point 96 h after enrollment (P = 0.003), owing exclusively to an increase in the creatinine level in the UF group [8], since weight loss was very similar. At 96 h, the mean change in the creatinine level was −0.04 ± 0.53 mg/dL (−3.5 ± 46.9 μmol/L) in the stepped pharmacologic-therapy group, when compared with +0.23 ± 0.70 mg/dL (20.3 ± 61.9 μmol/L) in the UF group (P = 0.003). The difference in serum creatinine was, however, no longer present by Day 7 and the levels remained similar in the two groups at 30 days and slightly higher (P = 0.03) in the UF group at 60 days [8]. A higher rate of patients in the UF group than in the stepped pharmacologic-therapy group had serious adverse events (72 versus 57%, P = 0.03) due to an excess of 14 complications (68 versus 54) in the UF arm as compared with the other arm. These complications included HF (likely due to inadequate decongestion) in three cases, and infections, pneumonia, bacteraemia or cellulitis in eight cases [8]. Based on these results, the authors concluded that the use...
of a stepped pharmacologic-therapy algorithm was superior to a strategy of UF for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches and a higher rate of adverse events in the UF group [8].

Undoubtedly, CARRESS-HF provided important information on the usefulness of UF in ADHF in that, for the first time, it was shown that UF at a fixed rate does not offer advantages over well-tailored diuretic therapy in these patients. This trial, like all studies in a complex condition like ADHF, has weak points that were clearly exposed in a series of letters to the New England Journal of Medicine [27–30] after the publication of CARRESS-HF. In particular, the primary end point was based on creatinine, a notoriously inadequate biomarker for monitoring very short-term changes in GFR, as is the case of haemodynamically mediated acute renal failure [31–32]. Cystatin C, a better biomarker than creatinine in chronic kidney disease [33], shares the same limitations of creatinine in acute situations [31]. Moreover, the choice of the bivariate primary end point in the CARRESS-HF trial was unfortunate, because in the patients on UF the fluid excess was mainly removed with UF, which explains why there was a slight transient fall of GFR. In contrast, in the patients treated with escalating doses of loop diuretics, there was an increase of urine output, which reflects an increase of GFR and tubular flow (Figure 1) [28]. Thus, while in the patients with WRF treated with diuretics creatinine was removed through glomerular filtration and tubular secretion, in those undergoing UF it was less removed through these processes and only passively filtered in the ultrafiltrate, given a sieving coefficient of 1, e.g. a concentration of creatinine in the ultrafiltrate equal to that in plasma. Accordingly, the superiority of the stepped pharmacologic-therapy over UF in lowering serum creatinine during the 48–96 h time when UF was performed could easily be anticipated.

Functional magnetic resonance of the kidney has great potential for application in pathophysiological and clinical studies in acute kidney injury [34], but by now its use in the clinical research scenario remains hardly feasible. It should be stressed that even a perfect biomarker of renal function would not provide a definitive answer about the relative merits of UF and stepped pharmacological therapy for the treatment of patients with acute heart failure. WRD is indeed a fairly weak surrogate of clinical events in this very high-risk condition [2] and, as previously discussed, aggressive decongestion in the setting of an initial worsening of renal function was associated with longer survival in the ESCAPE trial [3]. Furthermore, identification of patients with relatively less severe forms of ADHF and higher probability of survival, i.e. a category of patients where timely treatment (with UF or with a pharmacological approach) may attenuate WRF and prevent the evolution of kidney injury, is very problematic. Indeed no clinical score or biomarker exists that can reliably predict the renal response and the simultaneous cardiopulmonary response to fluid subtraction.

**Perspectives and future developments**

In ADHF, decongesting the lung is the absolute priority, and the true challenge in the treatment of these patients is to design strategies tailoring fluid volume removal rate on the basis of serial measurements of lung water. In this regard, CARRESS leaves totally open the question of whether an UF regimen guided by timely and frequent measurements of the degree of pulmonary congestion may translate into better clinical outcomes. Lung congestion is a crucial biomarker in the decision process about treatment in patients with heart failure [35]. As mentioned, correction of fluid overload by diuretics is the central recommendation of current guidelines [6, 7], the underlying assumption being that aggravation of any underlying salt and volume excess is the precipitating event in ADHF. However, fluid accumulation per se does not appear to be the only driver of ADHF in several patients as shown by a study where right ventricular haemodynamics were continuously monitored with an implantable device in heart failure patients over 17 months [36]. The amount of fluid subtraction estimated on the basis of weight loss during hospitalization for ADHF bears no relationship with clinical improvement as
defined on the basis of the degree of fatigue and dyspnoea [37]. The administration of aquaretics like tolvaptan may produce an important weight reduction in heart failure, but reduced fluids volume did not translate into a sustained improvement in symptoms [38]. These observations clearly point to fluid redistribution in the form of pulmonary congestion rather than to the net fluid gain as the critical event precipitating symptoms in ADHF, a phenomenon depending on arterial and venous constriction induced by neural and endocrine mechanisms, inflammation and kidney dysfunction. The degree of lung congestion may be now reliably measured by an ultrasound (US) based, simple, easy to learn, reproducible technique [39]. Lung US has recently been applied in studies in patients with end-stage kidney disease, and these studies have clearly documented that this technique not only serves to refine prognosis in this high-risk population [40], but also reliably detects changes in lung water by dialysis [41]. Lung US allows detection of water accumulation even at a pre-clinical stage and appears therefore well suited to be applied in ADHF trials to tailor UF and diuretic treatment, and its potential for a new breed of clinical trials in heart failure is well recognized [35]. Thus, estimates of lung water by US may represent the biomarker that we need to tailor treatments in these trials.

Accurate assessment of fluid status may also be provided in patients requiring fluid management strategies such as ADHF by electrical impedance measurement, which can help in preventing significant haemodynamic instability associated with over or under removal of fluid under conditions such as ADHF requiring fluid management strategies [42]. Bioimpedance measurement is now available as noninvasive ambulatory monitoring system, which has been shown to accurately assess fluid removal in heart failure and in dialysis patients [42, 43]. In patients with ADHF, this noninvasive fluid monitoring system might, therefore, be applied on the clinical ground to help guide fluid removal.

However, although prognostic studies are fundamental for testing new biomarkers [40, 42, 43], clinical trials remain the conclusive tool for assessing in clinical practice the usefulness of biomarkers. A trial comparing fluid subtraction guided by systematic monitoring of lung water in ADHF via lung US and/or bioimpedance may indeed provide a unique opportunity for establishing whether and when UF may be advantageous when compared with diuretic treatment.

**CONCLUSIONS**

It is altogether evident from what herein reviewed that UF, as most other effective therapeutic strategies, should be reserved for the right patients and should be undertaken by experienced teams. Prospective studies guided by the degree of pulmonary congestion are necessary to establish the correct placing of this novel and effective treatment of congestion in patients with ADHF.

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**CONFLICT OF INTEREST STATEMENT**

L.C., G.M. and C.Z. declare no conflict of interest and no financial disclosure concerning this manuscript to be disclosed. Prof GPR acted as a consultant for Gambro.

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