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Pharmacologic diuresis is safer than ultrafiltration for cardiorenal syndrome

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ABSTRACT A critical appraisal and clinical application of Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N. Engl. J. Med.* 2012;367:2296-2304. doi: [10.1056/NEJMoa1210357](https://doi.org/10.1056/NEJMoa1210357)

Keywords: Cardiorenal syndrome, pharmacological diuresis, ultrafiltration

Clinical Context

The patient is an 80-year-old Caucasian man with past medical history of hypertension, type 2 diabetes mellitus, heart failure with preserved ejection fraction, and status post living donor renal transplant in 2010. He described symptoms of acute onset nausea and vomiting. His physical exams showed tense ascites and elevated jugular venous pressure suggestive of fluid overload. His labs showed a serum creatinine of 2.5, elevated from a baseline of 1. Due to a calculated FeNa <1% and paracentesis of ascitic fluid with a serum-albumin ascites-albumin ratio of <1.1, he was diagnosed with pre-renal acute kidney injury (AKI) secondary to acute decompensated heart failure and was admitted to the in-patient floor for management of cardiorenal syndrome type 1 by diuresis.

Clinical Question

Is ultrafiltration superior to pharmacologic diuresis in management of acute cardiorenal syndrome?

Research Article

Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N. Engl. J. Med.* 2012;367:2296-2304. doi: [10.1056/NEJMoa1210357](https://doi.org/10.1056/NEJMoa1210357)

Literature Review

Type 1 cardiorenal syndrome occurs when AKI develops secondary to acute decompensation of heart function¹. Volume overload contributes to AKI through several mechanisms: renal venous congestion, neurohormonal activation, intrarenal microvascular changes and cellular dysregulation^{1,2}. A combination of fluid overload and renal injury in cardiorenal syndrome poses a therapeutic challenge. Loop diuretics have been the cornerstone treatment for congestion and volume overload in patients with acute CHF and cardiorenal syndrome^{1,3,4}. However, limitations to this method include diuretic resistance, neuro-hormonal activation and worsening renal function contributing to persistent congestion. These limitations have been correlated with poor outcomes, including re-hospitalization and increased mortality^{3,5}. Alternative treatments are being investigated to determine if there are more effective therapies with better long-term outcomes than pharmacological diuresis.

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Articles used to assess this question were found on Pubmed using the keywords “cardiorenal syndrome treatment” and a filtered search set that included clinical trials, meta-analyses, clinical and comparative studies. The search yielded 65 articles. The chosen article² published the results of the “Cardiorenal Rescue Study in Acute Decompensated Heart Failure” (CARRESS-HF) trial, which compared the standard treatment for cardiorenal syndrome, called pharmacologic diuresis, against a newer method called ultrafiltration. It was the most recent randomized clinical trial that used a head-to-head comparison of different methods of diuresis. Other studies found using these search criteria examined specific novel prognostic markers or new methods of treatment (e.g. ACE inhibitors), or simply did not investigate individuals with cardiorenal syndrome. Prior to this study, the UNLOAD trial⁶ was the largest randomized control trial (n=200) comparing ultrafiltration and intravenous diuretics in patients with acute decompensated heart failure and fluid overload. This study showed a benefit with ultrafiltration in the first 48 hours, improved weight loss and decreased rate of re-hospitalization in patients with acute heart failure. The data directly contradicts the results of the CARRESS-HF trial². Though both studies are similarly designed, there are some distinct differences. The UNLOAD trial did not enroll individuals with AKI due to cardiorenal syndrome nor did they have a strict pharmacologic algorithm. In contrast, the CARRESS-HF trial had prolonged ultrafiltration. Recent trials suggest ultrafiltration is an appropriate and safe method for individuals with volume overload^{1,7}, and that rising creatinine during treatment was not a poor prognostic marker⁸. The RAPID-CHF trial, performed by the same group that conducted the CARRESS-HF trial, studied a significantly smaller population (n=40), but determined the safety and efficacy of ultrafiltration and pharmacologic diuresis compared to pharmacologic diuresis alone. However, due to the small sample size and cross-contamination of this study, it is difficult to draw strong conclusions about the superiority of one method over the other. Additionally, several studies have shown that aggressive and early diuresis by ultrafiltration (CUORE trial⁹) or pharmacological diuresis¹⁰ despite rising creatinine levels was associated with decreased re-hospitalization and more stable renal function. Despite these studies, a recent review by Obi, et al.¹¹ suggests that cardiorenal syndrome type 1 be initially managed with loop diuretics rather than ultrafiltration, supporting the conclusions of the chosen article.

Critical Appraisal

The article by Bart, et al.² was a randomized controlled multicenter clinical trial conducted in 22 sites across the United States and Canada that compared stepped pharmacological diuresis with ultrafiltration (UF) in patients with cardiorenal syndrome. This study provides level 1B evidence using the Oxford and National Guidelines Clearinghouse criteria.

The patient population consisted of 188 individuals who were admitted to hospital with acute decompensated heart failure, and who developed cardiorenal syndrome as defined as an increase in serum creatinine of >0.3 mg/dL from baseline. This definition has been used in other studies on type 1 cardiorenal syndrome^{7,8}. Patients were required to have at least 2 of the following characteristics: 2+ peripheral edema, jugular venous pressure >10 cm water, or pulmonary edema or effusion as assessed by radiography. A notable exclusion criteria was creatinine >3.5 mg/dL, likely excluding any individuals with severe CKD. Other exclusion criteria included those who were hemodynamically unstable, requiring intravenous vasodilators or inotropic agents. These exclusion criteria were likely chosen because of the effects of these agents on renal perfusion, which may be altered with pharmacologic diuresis or ultrafiltration. The majority of those enrolled in the study were Caucasian (80%) and male (80%); this demographic differs from the general patient population served in the clinical context described above.

Patients were randomly assigned to either UF or pharmacologic diuresis. The randomization method was appropriate as there was no significant difference in demographic characteristics between both treatment groups for most criteria. However, there were a significantly greater number of individuals in the UF group who had heart failure secondary to ischemic disease (p=0.007). There was no difference in ejection fractions between the groups. This may have contributed to the overall decreased benefit of the UF group as these patients may not have been able to tolerate the adverse effects of UF and likely have increased renal vascular atherosclerosis. Otherwise, all clinically relevant data was reported in this study.

Confounding variables were decreased by stopping pharmacologic diuresis on anyone assigned to the UF group. Despite this, 30% of individuals on UF went on to receive pharmacologic diuresis, while only 6% in the pharmacological group underwent UF. This may have decreased the difference between treatment groups when assessing long-term outcomes. A significantly long median time to admission and randomization in the study (34 h) likely contributed to the increased cross-contamination between the treatment groups.



The UF method involved an Aquadex system for low-volume continuous veno-venous ultrafiltration with a goal net rate of diuresis of 4.8 L/d, a method chosen to improve hemodynamic stability. However, treatment was not titrated based on clinical response. In contrast, the pharmacologic method involved a high-dose intensity stepped algorithm to prevent variability within the treatment group, with titration of goal urine output 3-5 L/d. Clinical decongestion was scored based on jugular venous pressure, peripheral edema and a subjective measure of dyspnea. Treatment was continued until clinical improvement of congestion was seen. This was a big limitation of the study, because cessation of treatment was entirely subjective and clinical bias potentially affected treatment titration. This was significant for the UF method, as there was no set algorithm in place, which may have contributed to greater variability in this group. A knowledge bias may also have occurred, as physicians may have been more comfortable with pharmacologic diuresis rather than the use of the Aquadex system for UF. The study also did not require physicians to document their clinical reasoning for cessation of diuresis, which may have provided insight into any internal biases.

An intention to treat analysis was appropriate in this study as this most resembles real-world application and guards against bias. All individuals excluded from data analysis were accounted for. The study used a last-observation-carried-forward method for their analysis when the patient died, or was discharged prior to the 96 hour analysis (total of 26 patients; 13 in each treatment group). This could have altered outcomes as the previous data carried forward may have masked the overall effect of the treatment at future time points. The primary outcome was a change in creatinine and weight together as a bivariate endpoint assessed 96 h after enrollment, which was not a patient-oriented outcome. There was a significant change in the bivariate end-point at 96 h ($p=0.003$) in UF compared to pharmacologic diuresis, primarily driven by the increase in creatinine of 0.3 mg/dL in the UF group. This is of questionable clinical significance, as a difference of 0.3 mg/dL may have greater clinical significance at creatinine of 1.0 than it does at a creatinine of 5.0. There was no significant difference in mean weight loss at any time point. In the first 48 hours there was significantly ($P=0.003$) more fluid removed in the UF group than the pharmacologic group. This may have been due to the more rapid and efficient removal of fluid in the UF group in the beginning of treatment, along with prolonged duration (median = 40 h) compared to pharmacologic diuresis which is more time-dependent to reach a steady state. 72% of individuals in the UF group experienced adverse events compared to 57% in the pharmacologic diuresis group. Therefore, the number of patients that would need to be treated with UF to result in one adverse event (number needed to harm) compared to pharmacological diuresis was 7, a relatively small number. Individuals in the UF group experienced more kidney failure, bleeding complications and intravenous-catheter associated complications. The overall rate of re-hospitalization and mortality were similar in both treatment groups at 7 and 60 days and there was no difference between composite rate of death or re-hospitalization for heart failure (UF 38%, pharmacologic diuresis 35%; $p=0.96$). By 60 days, creatinine levels were below baseline in both treatments, though pharmacological diuresis had more significantly ($P=0.003$) improved creatinine.

Overall, the study by Bart, et al., a randomized clinical control trial, provided the best available evidence to determine the most efficacious therapy for management of cardiorenal syndrome type 1. Several limitations to the study included the lack of blinding of treatments, prolonged diuresis by UF, clinical bias and lack of graded algorithm for UF. All of these factors may have contributed to an underestimation of the overall benefit of UF in this study, as well as an increased number of adverse events. The transient rise in serum creatinine by 48 hours in the UF group was likely secondary to hemoconcentration, which has not been associated with poor prognosis³. Nevertheless, based on the number of adverse events in the UF group and increased associated cost with similar long-term outcomes, it is reasonable that pharmacological diuresis continues to be the first-line therapy for patients with cardiorenal syndrome; a suggestion supported by the 2013 ACCF/AHA Guidelines⁴. These guidelines state that patients admitted with heart failure and significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity. Ultrafiltration may be considered for patients with obvious fluid overload to alleviate congestive symptoms and fluid weight. Possible use of a different protocol of UF diuresis in future studies may reveal a benefit with this therapy. Also, as this study was conducted in a primarily Caucasian population, it remains to be seen if these results are as applicable to populations that do not fit the demographics of this study.

Clinical Application

The patient fit within the criteria of the Bart, et al., study population, as he was a white male with cardiorenal syndrome (2+ pitting edema, elevated jugular venous pressure) and creatinine <3.5 mg/dL on admission to hospital. Based on the findings by Bart, et al., initial treatment should be stepped pharmacologic diuresis for management of his volume overload. He was started on IV furosemide with a goal urine output of 2-3 L/d, slightly less than the goal urine output in the study of 3-5 L/d. After 7 days of diuresis with a net fluid loss of 8 kg, the



patient had clinical resolution of symptoms as determined by improvement of pitting edema and non-tense ascites. His serum creatinine improved from 2.50 to 2.20. He was transitioned to oral bumetanide and was discharged from the hospital to continue diuresis at home.

Take Home Points:

- 1.) First-line therapy for acute cardiorenal syndrome is stepped IV pharmacologic diuresis as patients experienced significantly less adverse outcomes and decreased creatinine levels compared to ultrafiltration.
- 2.) Long-term outcomes with respect to weight, number of hospitalizations and mortality were not significantly different in patients in either treatment group. Therefore, consideration of ultrafiltration in patients who develop diuretic resistance may present a reasonable alternative therapy in these patients after a failure of a trial of pharmacologic diuresis.
- 3.) Future studies investigating the role of ultrafiltration in acute cardiorenal syndrome should focus on developing an appropriate treatment algorithm that is based on individual responses to therapy and long-term outcomes.

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