chf solutions

CARRESS-HF STUDY REVIEW

CARRESS-HF STUDY REVIEW

STUDY DESIGN

The CARRESS-HF study[1] was a randomized, prospective, multi-center study designed and funded by the National Heart, Lung, and Blood Institute (NHLBI).

STUDY PURPOSE

The purpose of this study was to compare the effect of ultrafiltration (UF) to stepped pharmacologic therapy (SPT) on renal function and weight loss in patients with acute decompensated heart failure (ADHF) who have persistent congestion and worsening renal function (WRF).

STUDY POPULATION

A total of 188 patients were randomized among 22 centers. Patients hospitalized with ADHF with $\geq$ 2 signs of congestion and had WRF as defined by an increasing serum creatinine (SCr of $\geq$ 0.3 mg/dL) after or before hospitalization (12 weeks before or 10 days after the index admission for HF) were enrolled in the study.

PRIMARY ENDPOINT

The primary endpoint was the bivariate change from baseline in serum creatinine level and body weight, assessed at 96 h after randomization.

METHODS

Patients were randomly assigned in a 1:1 ratio via automated web-based system. There was no pre-determined treatment duration. Treatment in both arms was continued until the signs and symptoms of congestion were optimized.

- **UF arm:** Fluid removal rate was fixed at 200 mL/h and continued until the subject's signs and symptoms of congestion were optimized. Loop diuretics were discontinued for the duration of UF treatment. The use of vasodilators or inotropes agents after randomization were prohibited unless necessary for rescue therapy.
- **SPT arm:** Diuretic dosage was administered per a defined stepped care algorithm that allowed investigators to decrease, increase, or continue on current doses of diuretics depending on urine output and clinical response, which was assessed daily. The use of vasodilators or inotropes agents were based on the individual patient's blood pressure, ejection fraction, and the presence or absence of right ventricular failure at 48 h.

CARRESS-HF STUDY REVIEW

Study Arm	Mean SCr Change (p=0.003)	Mean Weight Loss (p=0.58)	% of Patients with Serious Adverse Events (p=0.03)
UF	+0.23 ± 0.70 mg/dL	5.7 ± 3.9 kg	72%
SPT	-0.04 ± 0.53 mg/dL	5.5 ± 5.1 kg	57%

TRANSIENT RISE IN SERUM CREATININE MAY NOT INDICATE POOR OUTCOMES

Recent publications challenge the rationale for use of acute serum creatinine changes as a prognostic factor for clinical outcomes. Results suggest that temporary elevations in serum creatinine in the setting of aggressive diuresis are not associated with adverse outcomes. These publications suggest that effective decongestion is needed to improve outcomes in fluid overloaded heart failure patients (see Table 1).[2,3,4,5,6,7,8]

ADDITIONAL CARRESS-HF STUDY DESIGN LIMITATIONS[9]

- The rate of fluid removal was mandated to be the same (200 ml/h) in ALL patients assigned to UF arm while patients in the SPT arm received care tailored to their characteristics. Regardless of the method used, removal of fluid should be tailored to patient's blood pressure, renal function, urine output, and body mass.
- Patients assigned to UF were not allowed to receive vasodilators or inotropic drugs except as a rescue therapy, whereas, it was allowed in the SPT arm per investigator discretion.
- The median UF duration was 40 h vs. 92 h for SPT for the same amount of fluid removal.
- Crossover rate was 20% (38/188).
- 39% in the UF group received only diuretic agents or were given diuretic agents before the assessment of the primary endpoint at 96 h, which impairs adjudication of adverse events to one or the other therapy.

PER-PROTOCOL ANALYSIS OF CARRESS-HF[10]

A per-protocol analysis of CARRESS-HF evaluated patient results at baseline, 24 h, 48 h, 72 h, and 96 h but adjusted for the substantial dropout or crossover of the subjects in this trial. Sixty (60) day outcomes were also evaluated.

Per-protocol Analysis Results

- UF was associated with higher serial cumulative fluid loss (p=0.003), higher net fluid loss (p=0.001), and a greater relative reduction in weight over time (p=0.02) than SPT.
- UF was associated with significantly higher SCr at 72 h (P-interaction=0.001) & 96 h (P-interaction<0.001) after being on treatment.
- There was no difference in 60-day outcomes between UF and SPT.

Per-protocol Analysis Key Takeaways

- UF was associated with significant fluid loss and reduction in weight than SPT, which contrasts to the primary findings of the original CARRESS-HF intent-to-treat analysis.
- There was no significant difference in long term outcomes between subjects in the UF and SPT arms, which calls into question the prognostic relevance of UF-mediated rise in SCr.

SUMMARY

It is important to consider the following points when evaluating the CARRESS-HF study results:

1. The CARRESS-HF study cohort presented with more advanced disease (i.e. pre-existing baseline renal dysfunction).
2. UF was conducted at a fixed fluid removal rate. It is recommended that UF therapy is tailored to each patient's clinical characteristics.
3. The per-protocol analysis of the CARRESS-HF study cohort showed UF was associated with more efficient decongestion in comparison to an aggressive urine output-guided diuretic-based SPT protocol.
4. Although serum creatinine levels increased in the UF arm, it may not be clinically relevant as multiple publications have reported that transient increases in SCr are not associated with adverse outcomes.[2,3,4,5,6,7,8]

Table 1: Publications on Transient Changes in Serum Creatinine

Lead Author/Publication	Study Design/Objective	Conclusions
Ahmad T et al.[2] Circulation 2018 (epub ahead of print)	■ Post-hoc analysis of ROSE-AHF trial[i] ■ Objective: Determine whether tubular injury biomarkers are associated with WRF in the setting of aggressive diuresis and its association with prognosis	WRF occurred in 21.2% of the population and was not associated with an increase in any marker of renal tubular injury. WRF was not associated with worsened 180-day survival, and paradoxically, increases in NGAL, NAG, and KIM-1 were paradoxically associated with improved survival (adjusted HR: 0.80 per 10 percentile increase). These findings reinforce the notion that the small to moderate deteriorations in renal function commonly encountered with aggressive diuresis are dissimilar from traditional causes of acute kidney injury.
Coca et al.[3] J Am Soc Nephrol 2016;27(8):2529-2542	■ Systematic review of a meta-analysis of 14 RCTs (a total of 5,817 patients, up to 12 months follow-up) ■ Objective: Quantify the relationship between positive or negative short–term effects of interventions on change in serum creatinine level and more meaningful clinical outcomes.	Interventions that affected the risk (increased risk or decreased the risk) of acute mild to moderate, temporary elevations in serum creatinine level in randomized trials showed no appreciable effect on CKD or mortality months later, raising questions about the value of using small to moderate changes in serum creatinine level as end points in clinical trials.
Brisco et al.[4] J Card Fail. 2016;22(10):753-60	■ Limited dataset from DOSE trial[ii] ■ Objective: Investigated the association between changes in creatinine and the composite endpoint of death, rehospitalization or emergency room visit within 60 days in 301 patients DOSE trial	Worsening in serum creatinine during the randomized intervention was not associated with an increase in adverse outcomes. On the contrary, decreases in serum creatinine were associated with a substantially increased risk for adverse events. This finding suggests the practice of using mild to moderate-sized changes in serum creatinine as an endpoint in ADHF clinical trials may be inappropriate.
Van der Meer et al.[5] J Am Coll of Cardiol 2013;61 (19) 1973-1981	■ Post hoc analysis PROTECT[iii] trial ■ Objective: Investigate the clinical correlates and prognostic role of anemia and changes in hemoglobin in patients hospitalized for acute decompensated heart failure (AHF).	In patients with ADHF and mild to moderate impaired renal function, 69% achieved an increase in hemoglobin. A rapid increase in hemoglobin during the first week was independently associated with a favorable outcome, despite a slight decrease in renal function, supporting the notion that the driver of outcomes is hemoconcentration and not renal function.
Metra et al.[6] Circ Heart Fail. 2012;5(1):54-62	■ Single center study on 599 patients admitted for AHF and measured serum creatinine level on a daily basis during hospitalization ■ Objective: Assess relationship between WRF, clinical signs, and prognosis of the patients admitted for AHF	Patients with WRF and no congestion had similar outcomes compared with those with no WRF and no congestion, whereas the risk of death or AHF readmission was increased in the patients with persistent congestion alone and in those with both WRF and congestion. The data suggests again, WRF did not drive clinical outcomes, instead, decongestion was the driver.

[i] The renal optimization strategies evaluation (ROSE) study was a multi-center double-blind, placebo-controlled trial designed to assess the potential renoprotective effects of low-dose nesiritide and dopamine in AHF patients with renal dysfunction.
[ii] DOSE trial is Diuretic Optimization Strategies Evaluation randomized trial to 308 patients with acute decompensated HF in a 2x2 factorial design to intermittent vs. continuous and low-dose (home dose) vs. high-dose therapy (2.5x home dose) with IV loop diuretics.
[iii] PROTECT trial is Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study in 1,969 patients with AHF and mild to moderate impaired renal function. Hemoglobin levels were measured daily for the first 4 days and at day 7. The endpoint was 180-day all-cause mortality.

CARRESS-HF STUDY REVIEW

Lead Author/Publication	Study Design/Objective	Conclusions
Testani et al.[7] European Journal of Heart Failure. 2011;13(8):877-884	■ Limited dataset from ESCAPE[iv] trial ■ Objective: Investigate if reduction in blood pressure during the treatment of DHF would be associated with WRF and evaluate the prognostic significance of WRF	Larger reductions in SBP were associated with greater odds for WRF. In patients with SBP-reduction, WRF was not associated with worsened survival. However, in patients without SBP-reduction, WRF was strongly associated with increased mortality (adjusted HR 5.3). The data suggests that WRF may represent the final common pathway of several mechanistically distinct processes, each with potentially different prognostic implications.
Testani et al.[8] Circulation. 2010;122:265-272	■ Limited dataset from ESCAPE trial ■ Objective: Determine if intravascular volume depletion is a relevant mechanism in cardiorenal interactions, hemoconcentration would be highly associated with changes in renal function during diuresis, WRFv is a direct cause of adverse outcomes or advanced disease state.	Interventions that affected the risk (increased risk or decreased the risk) of acute mild to moderate, temporary elevations in serum creatinine level in randomized trials showed no appreciable effect on CKD or mortality months later, raising questions about the value of using small to moderate changes in serum creatinine level as end points in clinical trials.

[iv] ESCAPE trial is The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial was a National Heart, Lung, and Blood Institute (NHLBI)–sponsored, randomized, multicenter trial of therapy guided by pulmonary artery catheter (PAC) versus clinical assessment in hospitalized patients with acute decompensated heart failure. A total of 433 patients were enrolled at 26 sites from January 2000 to November 2003.

REFERENCES

[1]Bart BA, et al. NEJM. 2012 Dec; 367(24):2296-2304.
[2]Ahmad T, et al. Circulation. 2018;(137), issue 8.
[3]Coca SG, et al. JASN. 2016;27(8):2529-2542.
[4]Brisco MA, et al. J Card Fail.2016; 22(10):753-60.
[5]van der Meer P, et al. J Am Coll of Cardiol. 2013; 61(19) 1973-1981.
[6]Metra M, et al. Circ Heart Fail. 2012; 5(1):54-62.
[7]Testani JM, et al. Eur J of Heart Fail. 2011;13(8):877-884.
[8]Testani JM, et al. Circulation. 2010; 122:265-272.
[9]Costanzo MR, et al. J Am Coll Cardiol. 2017 May 16;69(19):2428-2445.
[10]Grodin JL, et al. Eur J of Heart Fail. 2018 Mar.

RX ONLY

INDICATION: The Aquadex FlexFlow System is indicated for temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy; and extended (longer than 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization. All treatments must be administered by a healthcare provider, under physician prescription, both of whom having received training in extracorporeal therapies.

AQUADEX FLEXFLOW® SYSTEM
www.chf-solutions.com
12988 Valley View Road
Eden Prairie, MN 55344

chf solutions