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Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

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ABSTRACT

OBJECTIVES The AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trial tested the hypothesis that patients hospitalized for HF treated with adjustable ultrafiltration (AUF) would have a longer time to first HF event within 90 days after hospital discharge than those receiving adjustable intravenous loop diuretics (ALD).

BACKGROUND Congestion in hospitalized heart failure (HF) patients portends unfavorable outcomes.

METHODS The AVOID-HF trial, designed as a multicenter, 1-to-1 randomized study of 810 hospitalized HF patients, was terminated unilaterally and prematurely by the sponsor (Baxter Healthcare, Deerfield, Illinois) after enrollment of 224 patients (27.5%). Aquadex FlexFlow System (Baxter Healthcare) was used for AUF. A Clinical Events Committee, blinded to the randomized treatment, adjudicated whether 90-day events were due to HF.

RESULTS A total of 110 patients were randomized to AUF and 114 to ALD. Baseline characteristics were similar. Estimated days to first HF event for the AUF and ALD group were, respectively, 62 and 34 ($p = 0.106$). At 30 days, compared with the ALD group, the AUF group had fewer HF and cardiovascular events. Renal function changes were similar. More AUF patients experienced an adverse effect of special interest ($p = 0.018$) and a serious study product-related adverse event ($p = 0.026$). The 90-day mortality was similar.

CONCLUSIONS Compared with the ALD group, the AUF group trended toward a longer time to first HF event within 90 days and fewer HF and cardiovascular events. More patients in the AUF group experienced special interest or serious product-related adverse event. Due to the trial's untimely termination, additional AUF investigation is warranted.
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ABBREVIATIONS AND ACRONYMS

ALD = adjustable loop diuretics

AUF = adjustable ultrafiltration

BNP = B-type natriuretic peptide

CV = cardiovascular

HF = heart failure

IV = intravenous

LD = loop diuretics

SEC = Study Endpoint Committee

UF = ultrafiltration

Persistent congestion in patients hospitalized with heart failure (HF) is associated with worse prognosis regardless of age and underlying renal function (1,2). Most pharmacologic approaches to treat congestion have not reduced HF events, renal dysfunction, or mortality (3-6). These unmet therapeutic needs underlie the interest in the role of fluid removal with isolated venovenous ultrafiltration (UF) in acutely decompensated HF patients (7). The UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) trial showed that, compared with patients receiving intravenous (IV) loop diuretics (LD), those randomized to the UF arm had greater weight and net fluid loss at 48 h and a 53% reduction in the 90-day risk of rehospitalization for HF ($p = 0.037$) (8). In contrast to the results of the UNLOAD trial, which tested the effects of *early* decongestive strategies, the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial showed that a stepped pharmacologic therapy algorithm was both superior and safer than a fixed 200 ml/h UF rate for the preservation of renal function at 96 h (9). The discouraging results of CARRESS-HF do not disprove the potential physiological benefits of UF (10,11). Recently, in the CUORE (Continuous Ultrafiltration for Congestive Heart Failure) trial, HF patients meeting the inclusion criteria of a >4 kg weight gain had a greater freedom from HF events at 1 year when treated with UF compared to IV LD (12).

The primary objective of the AVOID-HF (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) study (NCT01474200) was to determine whether UF prolonged the time to first HF event within 90 days of hospital discharge when fluid removal therapy is adjusted in *both* arms according to the patients' vital signs and renal function. Thus the AVOID-HF study's design went beyond the assessment of fluid removed and symptoms by exploring whether titrated UF impacts HF events.

METHODS

STUDY DESIGN, PATIENT POPULATION, AND INCLUSION/EXCLUSION CRITERIA. This was a multicenter, prospective, unblinded, 1-to-1 randomized study. A total of 810 patients hospitalized with the primary diagnosis of HF were to be enrolled in the trial. The AVOID-HF trial was initially supported by Gambro (Lund, Sweden) and subsequently by Baxter Healthcare (Deerfield, Illinois), which acquired Gambro in September 2013. The determination that acutely decompensated HF was the primary cause of hospitalization was made by the site's principal investigator, based on the assessment of the clinical signs and symptoms that triggered the admission. Patients meeting all of the inclusion criteria and none of the exclusion criteria for this study (Online Table 1) and considered treatable with either adjustable UF (AUF) or adjustable IV LD (ALD) were eligible for enrollment. All participants provided written informed consent. Patients had to be randomized within 24 h of hospital admission. Up to 2 doses of IV LD were allowed before randomization to reflect events typical of clinical practice. Using a central web-based system, study subjects were randomized to one or the other fluid removal therapies during their index hospitalization. Subjects' monitoring schedule has been previously described (13). Resolution of congestion was defined as a jugular venous pressure <8 mm Hg, absence of dyspnea, and trace or no peripheral edema. Treatment failure was defined as death, worsening or persistent HF as indicated by requirement for vasoactive drugs or renal replacement therapy, or technical failures in the AUF arm. Following discharge patients were evaluated at 30, 60, and 90 days.

All adverse events were evaluated according to severity, causality, expectedness, and relationship to study product and treatment. Adverse events of special interest (central line-associated bloodstream infections, bleeding requiring transfusion, symptomatic hypotension necessitating intervention, drop in hemoglobin >3 g/dl, acute coronary syndrome) were documented and followed throughout the study (13). Requirements for site selection have also been specified earlier and study sites are listed in the Online Appendix (13).

PRIMARY ENDPOINT. The primary hypothesis of AVOID-HF was that patients hospitalized with a primary diagnosis of decompensated HF who are treated with AUF will have a longer time to first HF event within 90 days after discharge from index hospitalization compared with patients treated with ALD. HF events were defined as either a HF rehospitalization or as an unscheduled outpatient or emergency room treatment with IV LD or UF.

SECONDARY OBJECTIVES. Secondary endpoints were classified as efficacy, clinical, and safety variables. The pre-specified clinical and safety endpoints were assessed at 30 and 90 days (Online Table 2) (13).

TREATMENT DETAILS. In both the AUF and ALD arms, patients had a daily fluid and sodium restriction of 1500 cc and 1.5 g, respectively. Guidelines-Directed