ICU nephrology

"AVOID"ing harm by a double-edged sword: is there a role for ultrafiltration in heart failure?

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Prior studies comparing ultrafiltration with medical management for acute decompensated heart failure have yielded conflicting results. The AVOID-HF trial was designed as a definitive comparison of optimal ultrafiltration versus optimal diuretic-based medical therapy; unfortunately, the trial was terminated prematurely because of slow recruitment. The results of AVOID-HF nevertheless provide a rationale for well-designed, adequately powered trials to determine whether ultrafiltration has a role in the routine management of acute decompensated heart failure.

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Despite significant advances in the care of chronic heart failure (HF) over the past decade, little progress has been made in management of acute decompensated heart failure (ADHF). It remains the primary reason for hospitalization of older patients, with the highest rate of readmission among all medical conditions.[1]

The Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial is the most recent in a long list of trials evaluating extracorporeal ultrafiltration (UF) therapy as a potential alternative to diuretics for ADHF.[2] It comes after the disappointing results of the landmark Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, which failed to demonstrate a benefit of UF in patients with ADHF and mild to moderate worsening of renal function, despite the promising results of earlier trials.[3] AVOID-HF was a multicenter randomized controlled trial designed to compare the impact of UF with diuretic-based medical therapy in 810 participants hospitalized for ADHF. Due to slow recruitment, the trial was halted by the sponsor prior to interim analysis and after enrollment of only 224 participants, <30% of the planned sample size. Analysis of the available data demonstrated no statistically significant difference in the primary end point of "time to first HF event," defined as HF-related rehospitalization or unscheduled emergency room visit within 3 months (median 62 vs. 34 days in the UF vs. the medical therapy group, $P = 0.106$). There were no significant differences in the secondary end points of 90-day mortality, length of stay, or change in renal function, but UF was associated with significantly greater total fluid removal (18.7 vs. 14 liters in the UF vs. the medical therapy group, $P = 0.015$) and net fluid loss (12.9 vs. 8.9 liters, $P = 0.006$). Although it is not clear whether the observed differences would have translated into improved clinical outcomes if AVOID-HF had been completed, the results provide a rationale for well-designed and adequately powered studies to evaluate the role of UF in the management of ADHF.

Future studies should consider several lessons learned during AVOID-HF and earlier trials. First, the design of AVOID-HF addressed an important shortcoming of the previous landmark studies. The Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial compared an efficient UF therapy with a suboptimal medical regimen and reported superiority of UF, while CARRESS-HF compared a suboptimal UF therapy with an effective pharmacologic regimen and found

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medical management superior.[3,4] Taking these experiences into consideration, AVOID-HF sought to compare optimized medical therapy and UF, using an efficient protocolized pharmacologic regimen as the control group for an adjustable UF therapy that was customized to individual participants. Second, the significance of worsening renal function should be considered when designating study end points. In contrast to CARRESS-HF, AVOID-HF did not demonstrate worsening of renal function with UF as compared to diuretic therapy. The precise mechanisms of worsening renal function in ADHF remain elusive, and emerging data suggest that the impact of worsening renal function on outcomes could be related to the underlying pathophysiological processes.[5] There is a complex and reciprocal link between renal dysfunction and congestion in ADHF, such that worsening renal function that follows effective fluid removal and hemoconcentration may be associated with improved outcomes.[6] As such, there have been proposals to reconsider the current definition of worsening renal function in ADHF, or to revisit its use as a safety end point in this setting.

Third, an important observation in AVOID-HF was that serious adverse events deemed to be related to the study intervention, such as hypotension, were almost 3 times more common in the UF group than in the medical treatment group (14.6% vs. 5.4%, $P = 0.026$). Similarly, adverse events of special interest, including catheter-related bloodstream infection and bleeding, occurred more often with UF (31% vs. 17%, $P = 0.018$). Previous studies have also reported increased risk of serious adverse events with UF.[3,7] Because the UF procedures were largely performed by cardiologists and the reported complications are among those frequently encountered in renal replacement therapy, it is conceivable that the expertise of nephrologists could have been helpful. Nephrologists typically supervise hundreds of dialysis treatments a month; in comparison, the minimum requirement for site selection in AVOID-HF was performance of at least 5 UF treatments.[8] Finally, concerns about the cost and financial justification of UF have been underexplored. UF is one of the most expensive therapies available for ADHF, and its financial viability revolves around how improvements in length of stay, resource utilization, and readmissions relate to the diagnosis-driven reimbursement. Since the high cost is in part due to the UF device and proprietary supplies used in these trials and in cardiology practice, future studies should consider whether using existing nephrology resources may lower the cost of UF.[9]

Despite the early termination and smaller-than-planned sample size, AVOID-HF is the largest study to date comparing the impact of UF with diuretic-based medical therapy on the outcomes of patients hospitalized for ADHF. The results of AVOID-HF suggest that adjustable UF can efficiently remove excess fluid in ADHF without a negative impact on renal function; unfortunately, the study was inadequately powered to determine whether UF is associated with a significant improvement in relevant clinical outcomes. Future studies should evaluate whether collaborative HF programs coupling cardiology and nephrology resources and expertise have the potential to reduce UF-related complications, lower costs, and improve the outcomes of patients with ADHF.

DISCLOSURE

The author declared no competing interests.

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