Ultrafiltration Bests Loop Diuretics in Acute HF

The FDA-approved device allows fluid to be extracted from a patient's blood at a controlled rate.

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Peripheral ultrafiltration trounced aggressive intravenous diuretics—the long-standard, yet previously unchallenged, therapy for acute decompensated heart failure—in a major randomized trial presented at the annual meeting of the American College of Cardiology.

The novel mechanical ultrafiltration method safely produced greater weight and fluid loss than did loop diuretics. It also cut total rehospitalization days and emergency department visits by more than half during the 90 days after discharge, reported Dr. Maria Rosa Costanzo, principal investigator in the Ultrafiltration vs. IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial.

"We believe that the results of this trial are immediately applicable to a large proportion of patients admitted with decompensated heart failure," said Dr. Costanzo, medical director at the Edward Hospital Center for Advanced Heart Failure, Naperville, Ill.

UNLOAD was a 28-center study involving 200 patients hospitalized for decompensated heart failure and volume overload. Patients were randomized to peripheral ultrafiltration or aggressive use of loop diuretics—the standard therapy—with the goals of getting them stabilized, feeling better, and out of the hospital as quickly as possible.

Patients in the ultrafiltration arm averaged a weight loss of 5.0 kg at 48 hours, with no adverse impact on renal function, compared with 3.1 kg with standard care. The mean net fluid loss of 4.6 L in the ultrafiltration group at 48 hours was also significantly greater than the 3.3 L in the standard care group.

But what really grabbed the attention of heart failure specialists in the audience was the difference in 90-day outcomes. That's because decompensated heart failure is the number one cause of hospital admission in the United States, with 90% of these hospitalizations resulting from volume overload—and health policy officials are desperate to reduce that enormous burden on resources.

Patients in the ultrafiltration group were rehospitalized for heart failure for a collective 123 days during the 3 months after discharge, compared with 330 days in the standard care group. The ultrafiltration group also fared markedly better in terms of other resource-utilization end points (see box).

Dr. Costanzo attributed the sustained benefits of ultrafiltration to three factors: It doesn't activate neurohormonal systems, as do loop diuretics; it is more efficient in that it removes proportionately more sodium per unit fluid removed; and it allows patients to take "a diuretic holiday," as reflected in their lower dose of oral diuretics at discharge, compared with patients who had received loop diuretics.

The use of high-dose intravenous diuretics has been linked to increased short-term morbidity and mortality. Most physicians will be surprised to learn that the safety and efficacy of this long-standard therapy has never been tested in a randomized trial, she added.

Dr. Gregg C. Fonarow called the UNLOAD data "very impressive and something that I think should influence clinical practice now. The adverse consequences of high-dose loop diuretics have been underappreciated. Anything we can do to get fluid off while limiting the amount of loop diuretics needed is good from a physiologic standpoint," he said in an interview.

UNLOAD sets the stage for a larger, more definitive outcomes study, added Dr. Fonarow, professor of medicine at the University of California, Los Angeles and director of the Ahmanson-UCLA Cardiomyopathy Center.

Ultrafiltration was accomplished using a Food and Drug Administration–approved device marketed by CHF Solutions Inc. Unlike older ultrafiltration methods, which never caught on because they required central venous access and intensive patient monitoring, the CHF Solutions device is easy to use, requires only peripheral venous access, and takes only 33 mL of blood extracorporeally at any given time. The device can remove up to 500 cc of fluid per hour, with most patients requiring one or two 8-hour treatment sessions.

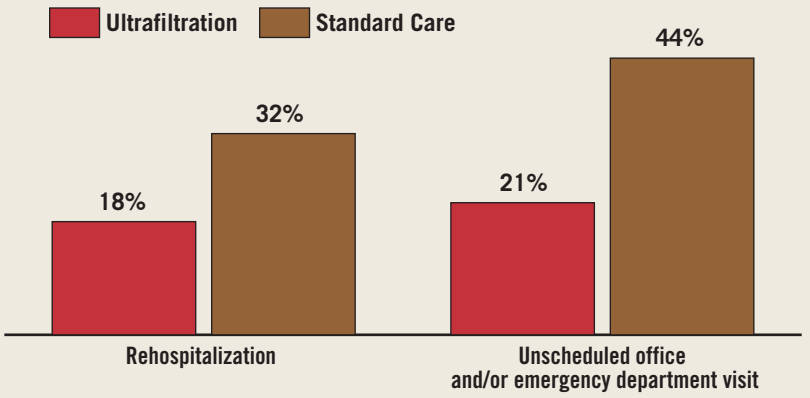
The single-use filter costs about $800; however, that pales next to the potential cost savings through reduced rehospitalization, especially because Medicare won't reimburse for rehospitalization within 30 days, Dr. Costanzo observed.

However, results showed that the markedly greater fluid loss achieved with ultrafiltration did not translate into greater symptom relief. Dyspnea scores at 48 hours were similar in the two treatment arms. In fact, change in dyspnea score did not significantly correlate with weight loss at 48 hours. This challenges the traditional practice of using congestive symptoms to decide when to start and stop therapy in decompensated heart failure.

Indeed, the observation that symptoms of congestion aren't a sufficiently sensitive guide to fluid volume provides a further boost to ongoing efforts to develop implantable hemodynamic monitors for this clinical application.

Dr. Costanzo is on the medical advisory board of CHF Solutions, which sponsored UNLOAD. ■

Resource Allocation for Heart Failure Patients 90 Days After Discharge



Note: Based on 200 heart failure patients in the UNLOAD trial.
Source: Dr. Costanzo

ELSEVIER GLOBAL MEDICAL NEWS

Investigational Renin Blocker May Reduce End-Organ Damage

BY MITCHEL L. ZOLER
Philadelphia Bureau

ATLANTA — Treatment with aliskiren, a drug from a new class of antihypertensive agents, led to safe and effective blood pressure lowering in a phase III study with 672 patients.

"Aliskiren has the potential to be an important new treatment for hypertension, with placebolike tolerability and sustained, 24-hour action," Dr. Byung-Hee Oh said at the annual meeting of the American College of Cardiology.

But what some experts find even more compelling is the potential aliskiren might have for preventing end-organ damage, such as heart failure, because it works by blocking renin, the rate-limiting enzyme for the entire renin-angiotensin-aldosterone system (RAAS). Two existing classes of antihypertensive drugs also act by inhibiting elements of the RAAS: ACE inhibitors and angiotensin-receptor blockers (ARBs).

"As good as the ACE inhibitors and ARBs have been, there is still some unfulfilled promise. It may be that we need to inhibit the whole RAAS rather than one or two components. The hope is that renin inhibitors can do what the other RAAS-active drugs do, but do it even better," commented Dr. Thomas D. Giles, a professor of medicine at Louisiana State University, New Orleans, and president of the American Society of Hypertension Inc. Dr. Giles has been a consultant to, a speaker for, and received research support from Novartis.

Clinical studies are planned to test aliskiren's efficacy for preventing end-organ damage. In the meantime, Novartis, the company developing aliskiren, has filed a new drug application with the Food and Drug Administration. The company is seeking an indication of blood pressure lowering, based in part on the results reported by Dr. Oh, said a company spokeswoman.

The study run by Dr. Oh and his associates enrolled patients with mild to moderate hypertension (defined as an average diastolic blood pressure of 95-109 mm Hg and an average systolic blood pressure of less than 180 mm Hg) at 68 centers in five countries, including the United States. Patients were randomized to daily treatment with placebo or one of three dosages of aliskiren: 150 mg, 300 mg, or 600 mg once daily. Treatment continued for 8 weeks, and 608 patients completed the full study course.

After 8 weeks of treatment, systolic blood pressure fell by an average of 13.0, 14.7, and 15.8 mm Hg in patients taking 150 mg, 300 mg, and 600 mg of aliskiren, respectively, compared with an average drop of 3.8 mm Hg in the placebo group. Diastolic pressure fell by an average of 10.3, 11.1, and 12.5 mm Hg in the three aliskiren arms, compared with a 4.9–mm Hg decline in the placebo group, reported Dr. Oh, chief of the division of cardiology at Seoul (South Korea) National University. Substantial reductions in blood pressure were seen after 2 weeks of treatment, and the drops in pressure reached near-maximal levels after 4 weeks and then were maintained out to week 8.

Between 59% and 69% of patients treated with aliskiren achieved at least a 10–mm Hg fall in their diastolic pressure or reached a pressure of less than 90 mm Hg, compared with 36% of patients having this level of decline while on placebo.

Serum analyses showed that plasma renin activity fell by an average of 75%-81% in patients treated with aliskiren, compared with a 20% rise in the control group. Despite these drops in activity, the level of plasma renin rose substantially, by 52%-229%, in patients taking aliskiren.

Treatment with aliskiren was generally well tolerated; the overall rate of all reported adverse effects was roughly similar in all four treatment groups. The incidence of serious adverse events was 0, 2.4%, and 1.8% in the three groups taking aliskiren, compared with 0.6% in the placebo group. Fewer patients discontinued aliskiren because of adverse effects, compared with patients in the placebo group. The most common adverse event associated with aliskiren use was diarrhea, which occurred in 11.8% of patients taking 600 mg daily, compared with rates of 1.2%-1.8% in the other two dosage groups and in patients who received placebo. ■