Table 1. Secondary Endpoints: Symptom Improvement.

Endpoint	Tolvaptan	Placebo	p value
Mean change in body weight Day 1 (kg)	-1.76	-0.97	<.001
Patients with improved dyspnea score Day 1 (%)	74.3	68.0	<.001
Mean change in serum sodium Day 7 (mEq/L)	5.59	1.85	<.001
Patients with ≥2-grade improvement in edema (%)	73.8	70.5	.003

The mortality rate for the combined trials was 25.9% for tolvaptan vs 26.3% for placebo-treated patients; the cardiovascular or heart failure hospitalization rate was 42.0% and 40.2%, respectively. The drug was well tolerated with little or no effect on renal function.

Dr. Konstam said that the evidence does not support widespread use of tolvaptan, but the drug could be useful in patients seeking prompt relief of dyspnea, the leading cause of heart failure hospitalizations. "Tolvaptan improved fluid balance with greater weight loss on top of standard background therapy. This was associated with a number of symptomatic benefits as early as day 1, with just one pill," he said.

FUSION II: No Advantage for Serial Nesiritide Infusions

Outpatient infusions of nesiritide did not prolong survival or prevent future hospitalizations in patients with advanced chronic heart failure and a history of acute decompensation, according to the results of FUSION II, the first large, randomized, controlled study to test the efficacy of this regimen as reported by Clyde W. Yancy, MD, of Baylor University Medical Center, Dallas.

The Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure (FUSION II) trial randomly assigned 911 patients to receive nesiritide as a 2-µg/kg bolus followed by a 0.01-µg/kg/min infusion for 4 to 6 hours or a matching placebo regimen, once or twice a week for 12 weeks. Patients had NYHA class 3 or 4 heart failure and an LVEF <40%, plus a history of at least two prior hospitalizations for heart failure within the past year, the most recent being within the past 2 months.

At the study's end, there were no significant differences in the rates of the primary endpoint of all-cause mortality or cardiovascular or cardiorenal hospitalization, or in rates of the individual component events (Table 1). No particular subgroup derived special benefit from the nesiritide regimen, Dr. Yancy reported.

Table 1. FUSION II: Primary Composite Endpoint Through Week 12.

	Placebo Combined n=306	Nesiritide Combined n=605	*p value
All cause mortality and CV/renal hospitalization	36.8%	36.7%	0.79
All cause mortality	9.6%	9.5%	0.98
CV/renal hospitalization	33.9%	32.9%	0.95

*p value: NES vs placebo stratified by dose group
‡Modified ITT: all treated ITT patients

Event rates were 48% lower than those observed in the FUSION I pilot study. The current study, therefore, was underpowered to find differences, Dr. Yancy suggested. "The most important clinical message from FUSION II is that adherence to guideline-driven therapy and meticulous follow-up defines the benchmark of care for patients with chronic decompensated, or stage D, heart failure," Dr. Yancy concluded.

VALIDD: Lowering Blood Pressure Improves Diastolic Dysfunction

In a first randomized study of its kind, diastolic function, as assessed by noninvasive Doppler technology, was shown to be improved by lowering blood-pressure. The Valsartan in Diastolic Dysfunction (VALIDD) trial evaluated 482 patients from 41 North American sites with stage 1 or 2 essential hypertension using the relatively new method of Doppler tissue imaging to determine myocardial relaxation velocities. Investigators identified 384 patients with evidence of diastolic dysfunction based on low lateral mitral annular relaxation velocities and randomly assigned them to valsartan 320 mg/day or to agents that do not inhibit the renin-angiotensin-aldosterone system (RAAS).

Investigators hypothesized that lowering blood pressure with the RAAS inhibitor valsartan (an angiotensin receptor blocker) would improve diastolic function to a greater extent than is achieved without inhibiting the RAAS. Diastolic dysfunction might represent an early measure of end-organ damage that can precede left ventricular hypertrophy (LVH) in patients with hypertension, explained Scott Solomon, MD, of Brigham and Women's Hospital, Boston, who presented the findings.