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.

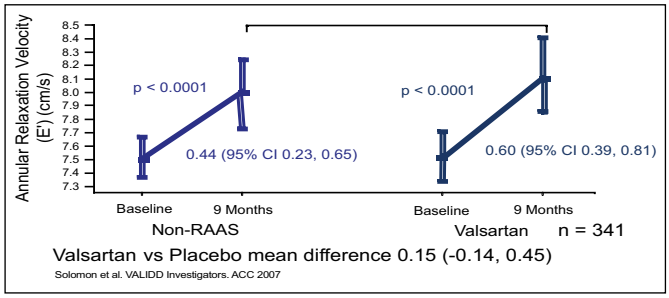
VALIDD: Lowering Blood Pressure Improves Diastolic Dysfunction

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.

Both antihypertensives lowered blood pressure by >10 mm Hg and both improved diastolic function to a similar degree. After 38 weeks of treatment, diastolic function, as assessed by diastolic relaxation velocities, increased from 7.5 cm/s at baseline to 8.1 cm/s in the valsartan group and 8.0 cm/s in the non-RAAS inhibitor group. Improvements in diastolic function in both groups were accompanied by small but significant reductions in left ventricular mass, Dr. Solomon reported.

Figure 1. Change in Mitral Annular Relaxation Velocity (E') from Baseline to Follow-Up.



Dr. Solomon noted that, despite having hypertension, LVH was observed in only 4% of patients. "We thought we would have seen a higher prevalence of LVH and myocardial fibrosis and, if we had, we may have shown a more pronounced effect in the valsartan group. We may have seen a difference between the two groups if the condition of the population had not been so benign," he speculated.

Torcetrapib Fails to Meet Expectations

Increased levels of high-density lipoprotein cholesterol (HDL-C) decrease the risk of cardiovascular disease. Torcetrapib, a cholesteryl-ester-transfer protein (CETP) inhibitor, has a potent effect on increasing HDL-C levels that was hoped would translate into the halting or reversal of atherosclerosis. The results from three clinical trials of torcetrapib were presented by Steven Nissen, MD, FACC, president of the American College of Cardiology, and John Kastelein, MD, PhD, of the Academic Medical Center in Amsterdam, The Netherlands.

Dr. Nissen reviewed the results of the ILLUSTRATE trial, which was terminated prematurely in early December 2006 due to an excess in total mortality in patients who were randomized to torcetrapib. A total of 1,188 patients participated in the ILLUSTRATE study at 137 centers in the United States and Europe. Intravascular ultrasound (IVUS) was performed on study subjects, who were then treated with atorvastatin to decrease levels of low-density lipoprotein-cholesterol (LDL-C) to <100 mg/dL. Subjects were subsequently randomized to treatment with atorvastatin monotherapy or atorvastatin combined with torcetrapib 60 mg/day. After 24 months of treatment, IVUS was repeated in 910 subjects (77%). The primary efficacy measure was change in the percent atheroma volume.

There were no significant differences in any of the baseline demographic variables. The torcetrapib-atorvastatin group (n=464) had a significant increase in HDL-C, significant decrease in LDL-C, and a decrease in LDL-C/HDL-C ratio (all p<0.001) compared with the atorvastatin monotherapy group (n=446; Table 1). According to Dr. Nissen, this study exhibited the lowest magnitude of LDL-C/HDL-C ratio ever observed. The change in percent atheroma volume increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib–atorvastatin group (p=0.72). The HDL levels increased slowly, over 6-9 months after randomization.

Table 1. Final Lipid Values and Percentage Change.

Lipid Value (mg/dL)	Atorvastatin monotherapy (n=446)		Torcetrapib Atorvastatin n=464		*p* value
	Final Value	Change (%)	Final Value	Change (%)	
Total Cholesterol	157.2	1.9%	167.5	7.2%	<0.001
LDL-cholesterol	87.2	6.6%	70.1	-13.3%	<0.001
HDL-cholesterol	43.9	-2.2%	72.1	58.6%	<0.001
LDL-C/HDL-C ratio	2.03	NA	0.93	NA	<0.001
Triglycerides	110	-8.2%	104	-14.3%	<0.001
C-Reactive Protein	1.5	-0.2	1.85	-0.1	0.19

Unfortunately torcetrapib did not slow the progression of atherosclerosis, nor were there any significant differences in secondary measures. Torcetrapib-treated patients experienced a mean increase of 4.6 mm in systolic blood pressure (Figure 1). The main trial was stopped because of an increase in all-cause mortality of approximately 60% in the torcetrapib/atorvastatin group when compared with the atorvastatin group. "We just don't know what the toxicity is, and that makes it difficult to interpret the trial," summarized Dr. Nissen.