Clinical Trial Highlights

ALPHA: T-Wave Alternans Testing Hospital

A noninvasive microvolt T-wave alternans (TWA) test in patients with nonischemic cardiomyopathy can identify patients who do not need an implantable cardiac defibrillator (ICD), said Gaetano M. De Ferrari, MD, of San Matteo Hospital, Pavia, Italy, who presented the results of the T-Wave Alternans in Patients with Heart Failure Trial (ALPHA). ALPHA enrolled 446 patients with New York Heart Association (NYHA) class 2 and 3 heart failure with cardiomyopathy of nonischemic origin and left ventricular ejection fraction (LVEF) of <40%. Patients underwent TWA testing and were followed for 18 to 24 months. Abnormal tests were observed in 65% and normal tests in 35% of patients.

Patients with an abnormal TWA test had a four-fold higher risk of the primary endpoint—cardiac death and life-threatening arrhythmias (p=.001). They also had a four-fold higher total risk of death (p=.002), and a five-fold higher risk of arrhythmic death, life-threatening arrhythmias, and hospitalizations (p=.004). The negative predictive value for the primary endpoint was 98.7% at 12 months and 97.3% at 18 months.

"Patients with a normal TWA test have a very good prognosis and are unlikely to benefit from ICD therapy," Dr. De Ferrari said.

EVEREST: Modest Gains from Tolvaptan in Heart Failure

Results from the EVEREST trial, presented by Marvin A. Konstam, MD, of Tufts-New England Medical Center indicated that in patients with acute decompensated heart failure, tolvaptan, an oral nonpeptide vasopressin V_2-receptor blocker, did not reduce mortality or hospitalizations but did provide modest symptomatic relief.

EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) consisted of two prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe. The combined study population included 4,133 patients who received 30 mg/day of tolvaptan or placebo within 48 hours of hospital admission. The primary composite endpoint was change from baseline at day 7 or hospital discharge in patient global assessment (by visual analog scale) and body weight. Tolvaptan was associated with additional weight loss of 0.6 kg in one trial and 0.9 kg in the other (p<.0001). There were no significant differences in global clinical status improvement in either trial. A number of secondary endpoints were favorably affected by tolvaptan (Table 1).

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.