Treating Heart Failure: Beyond Standard Therapy

Disclosures

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Among the presentations at the American College of Cardiology 52nd Annual Scientific Session (ACC) meeting in Chicago, Illinois, were a number of clinical trial results and late-breaking research developments concerning the understanding and treatment of heart failure, with important clinical implications that will have a significant impact on heart failure management and outcomes for years to come.

COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure)

Of all the clinical trials presented at this ACC meeting, the COMPANION trial was the one that had the most dramatic impact on heart failure patient outcomes. Previous research has demonstrated that 25% to 30% of heart failure patients have QRS widening (ventricular dyssynchrony), which is in itself associated with increased risk of disease progression and mortality. Cardiac resynchronization therapy (biventricular pacing, or CRT) has been developed as a means of restoring synchronization of ventricular contraction. In the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial,[1] the use of CRT in patients with moderate to severe heart failure was demonstrated to significantly reduce heart failure symptoms and to improve exercise capacity and left ventricular ejection fraction (LVEF). CRT also resulted in a reduction in heart failure hospitalizations from 15% to 8%. This led to FDA approval of this form of therapy in 2002. However, the impact of CRT on mortality had not previously been determined.

COMPANION Trial Design

COMPANION was a parallel, randomized clinical trial involving 1634 patients with moderate or severe heart failure with QRS >/= 120 ms and LVEF </= 35%.[2] Patients had to meet the following entry criteria in order to participate:

- At least 1 hospitalization in the past year for heart failure management,
- An outpatient visit in which inotropes or a vasoactive infusion were administered, or
- An emergency room visit of at least 12 hours during which intravenous heart failure medications were administered.

Patients were randomized in a 1:2:2 fashion to optimal pharmacologic therapy (OPT; defined as ACE inhibitors or angiotensin receptor blockers [ARBs]; beta-blockers; and spironolactone, digoxin, with or without diuretics), OPT plus CRT or OPT plus CRT with an implantable cardioverter defibrillator (ICD) (CRT-D).

At baseline, mean age for patients included in this trial was 67 years; 82% were in NYHA class III heart failure; LVEF was 22.8%; and QRS was 156 ms. Background medical therapy was ACE inhibitors/ARBs in 89%, beta-blockers in 66%, and spironolactone in 55% of patients. CRT implants were successful in 90%, occurring within 2 days of randomization. The median implant time was 3 hours, and there were only 4 deaths related to device implants, all occurring early in the trial. Dr. Michael Bristow (University of Colorado Health Sciences Center, Denver) presented the results of this trial, which he described as "preliminary" since reported events have not been fully adjudicated.

COMPANION Results

The primary endpoint of the study, a combination of all-cause mortality and all-cause hospitalizations over 12 months, was significantly reduced by 18.6% for the CRT group and 19.3% for the CRT-D arm of the study. The 1-year mortality rate was 19% with OPT, 14.5% with CRT alone, and 10.8% with CRT-D. Thus, CRT-D therapy resulted in a remarkable 43.4% reduction in all-cause mortality (*P* = .002). CRT alone was also associated with a nonsignificant trend toward a

23.9% reduction in all-cause mortality (*P* = .12). There were no significant differences in treatment effects between patients with ischemic and nonischemic cardiomyopathy, or between other subgroups.

COMPANION Conclusions

Compared with OPT, CRT with or without an ICD can reduce all-cause mortality and all-cause hospitalizations in patients with moderate or severe heart failure. Remarkably, only 12 patients need to be treated with CRT-D in order to prevent 1 death within 1 year of treatment. While other therapies have been used to treat heart failure, CRT is the first therapy developed *specifically* for the heart failure patient that results in improved survival. This represents a major therapeutic advance in heart failure therapy.

EPHESUS

Another multicenter clinical trial presented at the ACC meeting that generated much interest because of its important implications for heart failure management was the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial.[3] This trial tested the hypothesis that selective aldosterone receptor blockade would reduce mortality when given in addition to standard therapy in patients with acute MI (AMI) complicated by left ventricular systolic dysfunction (LVSD) and heart failure. In contrast to the nonselective aldosterone antagonist, spironolactone, eplerenone is a selective aldosterone receptor antagonist that blocks the mineralocorticoid receptor, but not glucocorticoid, progesterone, or androgen receptors (thus avoiding the troublesome hormonal side effects of spironolactone). The study results were presented by Dr. Bertram Pitt (University of Michigan, Ann Arbor) at the late-breaking clinical trial plenary session on March 31, 2003.

ACE inhibitors and beta-blockers have previously been demonstrated to prevent remodeling after AMI and reduce morbidity and mortality in post-MI patients with LVSD. However, even with these medications, morbidity and mortality rates remain relatively high in these patients. Previous experiments, especially RALES (Randomized Aldactone Evaluation Study),[4] have demonstrated that aldosterone receptor blockade prevents ventricular remodeling and collagen deposition. RALES further showed that aldosterone inhibition with spironolactone, in addition to a good level of standard treatment that included an ACE inhibitor, reduced mortality in patients with severe heart failure. However, in the RALES trial, only 10% to 11% of patients were on a beta-blocker.

EPHESUS Trial Design

In EPHESUS, a total of 6632 AMI patients with LVEF </= 40% and rales on physical examination were randomized to receive eplerenone or placebo. (For patients with diabetes, the only requirement was an EF of </= 40%.) Patients were excluded if they had serum creatinine > 2.5 mg/dL or if serum potassium was > 5.0 mmol/L. Eplerenone was administered at a starting dose of 25 mg and titrated to a maximum of 50 mg per day, if tolerated; at study end, the mean dose of eplerenone was 43 mg/day. Therapy was initiated an average of 7 days after the onset of AMI (range, 3 to 14 days). The trial was continued until 1012 deaths had occurred.

Mean age at enrollment was 64 years, mean LVEF was 33%, baseline creatinine was 1.1 mg/dL, and mean blood pressure was 119/72 mm Hg. Background medical treatment included ACE inhibitor or ARB therapy in 86%, beta-blockers in 75%, aspirin in 88%, statin therapy in 47%, and use of revascularization in 45% of patients in this trial. Patients were followed for an average of 16 months.

EPHESUS Results

EPHESUS demonstrated that eplerenone significantly reduced all-cause mortality. The mortality rate was decreased from 16.7% with placebo to 14.4% with eplerenone (RR = 0.85; 95% CI = 0.75-0.96; *P* = .008). There was also a significant reduction in the endpoint of death from cardiovascular causes or hospitalization for cardiovascular events. Additional secondary endpoints were also reduced by eplerenone treatment, including sudden cardiac death (RR = 0.79; 95% CI = 0.64-0.97; *P* = .03).

Subgroup analysis showed a relatively uniform effect of eplerenone treatment. Patients on OPT (defined as treatment with ACE/ARB, a beta-blocker, aspirin, statin, and reperfusion therapy) had a

26% reduction in all-cause mortality with eplerenone. There was a significantly increased incidence of hyperkalemia with eplerenone (1.6% absolute increase), and patients with decreased creatinine clearance (< 50 mL/min) at baseline were at higher risk for hyperkalemia. This finding emphasizes the need to closely monitor serum potassium and adjust eplerenone dosing as necessary. The risk for serious hypokalemia was reduced by eplerenone treatment.

EPHESUS Conclusions

This trial convincingly demonstrates that the addition of eplerenone to OPT results in an improvement in survival and a reduction in hospitalization rates among patients with AMI complicated by LVSD and heart failure. The number needed to treat is 50 to save 1 life in 1 year, and 33 to prevent 1 death from cardiovascular causes or 1 hospitalization for a cardiovascular event in 1 year. Thus, the benefits of aldosterone antagonism, first demonstrated in patients with severe heart failure, have now been shown to apply to patients with mild to moderate heart failure post-MI.

Other Areas of Interesting Heart Failure Research

Reports on progress with **cellular transplantation** using skeletal myoblasts or peripheral stem cells generated much discussion and interest. Although all of the findings presented were from small, uncontrolled safety studies, they demonstrated that it is feasible to perform cellular transplantation with some evidence of improved ventricular function. Larger clinical trials are under way.

There were a number of presentations regarding the clinical utility of measuring **B-type natriuretic peptide** (BNP) in patients with heart failure. Beyond this assay's role in facilitating the diagnosis of heart failure, a number of studies presented demonstrated that this assay provides independent prognostic information. The effects of various heart failure treatments on BNP levels were also the topic of a number of abstracts.

There was significant interest in an observational study from UCLA investigators [5] showing that **statin treatment** was associated with a significant reduction in mortality in patients with advanced heart failure, whether the condition was due to ischemic or to nonischemic cardiomyopathy, irrespective of baseline cholesterol levels. This interesting result needs to be confirmed in prospective randomized clinical trials.

The underuse of **evidence-based guidelines** for heart failure therapies -- including ACE inhibitors, beta-blockers, and aldosterone antagonists -- was a frequent topic of discussion. The ADHERE (Acute Decompensated Heart Failure National Registry)[6] provided interesting data regarding current treatment rates and variation in care across the nation's hospitals. A national hospital-based heart failure quality-of-care improvement program called OPTIMIZE-HF (Organized Program to Initiate Life-Saving Treatments in Hospitalized Patients with Heart Failure) was the primary focus of one of the ACC Satellite Symposiums. This program plans to include 500 US hospitals that will be working together to accelerate adoption of guideline-recommended therapies and improve heart failure patient care. Further information about this program can be found at www.optimize-hf.org (registration required).

References

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