Medical University of Graz, Graz, Austria, showed that spironolactone significantly improves diastolic function and blood pressure (BP) control, but not exercise capacity, in patients with diastolic heart failure (DHF).

DHF accounts for more than 50% of all HF cases and clinical outcomes for these patients are poor. While no established therapy exists for DHF, there is strong evidence for a benefit from aldosterone antagonists in patients with reduced left ventricular ejection fraction (LVEF) [Chatterjee S et al. *Am J Med* 2012], and aldosterone has been implicated in the pathogenesis of DHF via aldosterone receptor mediated myocardial fibrosis, hypertrophy, and vascular stiffening.

Aldo-DHF was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study conducted to assess the safety and efficacy of the aldosterone receptor antagonist spironolactone on diastolic function and exercise capacity in patients with DHF after 1 year of therapy. Subjects were required to have documented stable chronic HF (NYHA II/III), echocardiographic evidence of diastolic dysfunction ≥Grade 1 or atrial fibrillation, EF ≥50%, and peak VO_2 <25 mL/kg/min. Co-primary endpoints were change in diastolic function (mitral inflow E velocity to tissue Doppler e´ [E/e´ ratio]) and maximal exercise capacity (peak VO_2 on bicycle spiroergometry) at 12 months [Edelmann F et al. *Eur J Heart Fail* 2010].

Subjects (mean age 67 years, 52% women, ≥85% NYHA class II) were randomized to spironolactone (n=213) or placebo (n=209). Baseline E/e´ was 12.7±3.6 and 12.8±4.4 and peak VO_2 was 16.3±3.6 and 16.4±3.5 mL/kg/min in the spironolactone and placebo groups, respectively. Median NT-proBNP was 179 ng/L in the spironolactone group (range, 81 to 276) and 148 ng/L (range, 80 to 276) in the placebo group. Approximately 92% of patients had controlled hypertension at study entry. Mean estimated glomerular filtration rate was ~78 mL/min/1.73 m^2.

Spironolactone (25 mg QD) significantly improved diastolic function (p<0.001) but did not improve exercise capacity. Treatment effects were consistent across all subgroups analyzed. Spironolactone induced significant structural reverse remodeling (LV mass index p=0.009) and significant reductions in NT-proBNP plasma levels (p=0.03), but did not improve NYHA class, left atrial volume index, or quality of life.

Spironolactone was also associated with significant reductions in both systolic and diastolic BP beginning at 3 months, yet the effects of spironolactone on cardiac structure and function remained significant after adjusting for BP changes. Adverse events occurred significantly more often with spironolactone, including mild worsening of renal function (36% of spironolactone subjects vs 21% of placebo subjects; p<0.001); new or worsening anemia (16% vs 9%; p=0.03), gynecomastia (4% vs <1%; p=0.02), and nonsevere (<5.0 mmol/L) increases in serum potassium levels (21% vs 11%; p=0.005). One patient in the spironolactone group died (vs none of the placebo subjects). There was no difference in the rate of hospitalization.

Additional data on the long-term efficacy and safety of spironolactone in patients with DHF will come from the Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure [TOPCAT; NCT00094302] study, which is expected to report during 2013. TOPCAT is a multicenter, international, randomized, double-blind, placebo-controlled trial of spironolactone in 3515 adults with HF and LVEF ≥45%. The trial duration is ~6 years with an expected average subject follow-up of 3.45 years. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF.

FAME 2 Results

Written by Lori Alexander

Percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR) plus the best available medical therapy (MT) improves outcomes in patients with stable coronary artery disease (CAD) compared with optimal MT alone. The benefit is primarily due to a lower rate of rehospitalization for urgent revascularization (UR). These findings, from the Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Therapy versus Optimal Medical Therapy Alone in Patients with Stable Coronary Artery Disease [FAME 2; NCT01132495] trial, were reported by Bernard De Bruyne, MD, PhD, Onze-Lieve-Vrouw Clinic, Aalst, Belgium.

In prior studies, PCI has failed to to improve the prognosis for patients with stable CAD. However, Prof. De Bruyne and the FAME 2 investigators hypothesized that PCI plus MT would improve outcomes for patients with stable CAD if the presence of lesions that produced ischemia were confirmed by measurement of FFR. FFR-guided PCI was superior to angiography-guided PCI in the initial FAME trial [Tonino PA et al. *N Engl J Med* 2009]. The results of FAME 2 were simultaneously published to coincide with the presentation of the study [De Bruyne B et al. *N Engl J Med* 2012].

The researchers measured FFR in patients with stable CAD for whom PCI was being considered. Patients who had at least 1 functionally significant stenosis (FFR ≤0.80)

were randomly assigned to FFR-guided PCI plus the best available MT or the best available MT alone. Patients who had no evidence of ischemia (FFR >0.80) were treated with MT alone and were followed in a registry. The primary endpoint was a composite of death, myocardial infarction (MI), or UR. The trial was designed as a superiority study in 1632 patients and powered to test whether FFR-guided PCI resulted in a 30% relative risk reduction of the primary endpoint over an intended average follow-up of 2 years.

An important first finding was that 27% (n=322) of the patients evaluated for the study had no hemodynamically significant stenosis, and were thus followed in the trial registry. The remaining 73% (n=888) had an FFR ≤0.80 in at least 1 large epicardial artery and were randomly assigned to FFR-guided PCI plus MT (n=447) or MT alone (n=441). The trial was stopped prematurely in January 2012 after 1220 patients were randomized with an average follow-up of 7 months, when the independent Data Safety Monitoring Board judged highly significant differences in the primary endpoint rates between patients randomized to MT alone compared with those who recieved FFR-guided PCI plus MT (4.3% vs 12.7%; HR with PCI, 0.32; 95% CI, 0.19 to 0.53; p<0.001). A large difference in the rate of UR (1.6% vs 11.1%; HR, 0.13; 95% CI, 0.06 to 0.30; p<0.001) was the major factor responsible for the difference in the composite endpoint between the groups. Rates of mortality or MI were infrequent and did not differ significantly between the 2 randomized groups. In the registry, MT alone led to an excellent outcome for patients without FFR-determined ischemia, regardless of the angiographic appearance of the stenoses; the primary endpoint occurred in only 5/166 (3.0%) patients with FFR >0.80.

Science Advisors' Note

Although the reduction in the composite primary endpoint with PCI is provocative, it is worth noting that this observation was predominantly dependent on a difference in the "softer" endpoint of UR, and that the premature termination of this randomized study resulted in the enrollment of only 75% of the patients planned with less than a third of the intended average follow-up. Two additional limitations warrant mention. First, an early signal towards a potential harm as a result of definite or probable stent thrombosis in patients randomized to FFR-guided PCI plus MT (all of whom received a second-generation drug-eluting stent) compared with MT alone (1.1% vs. 0.2% by 12 months; HR with PCI, 4.98; 95% CI, 0.59 to 42.25) could have been better defined with further follow-up and greater event accrual. Second, the non-blinded nature of this study (the patients managed with MT alone did not undergo sham PCI) could have led to a selection bias in referral for "urgent" revascularization, with a lower threshold to refer patients to PCI if they had been randomized to optimal MT without PCI. As Dr. William Boden, one of the lead investigators of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial, concluded in his editorial to FAME-2, neither FAME-2 with 7 months of mean follow-up or the COURAGE trial with 55 months of mean follow-up showed a reduction with PCI in "hard" clinical endpoints, such as death or MI [Boden WE. *N Engl J Med* 2012]. Further insight regarding the comparison of PCI with best available MT in patients with stable CAD and moderate-to-severe ischemia may come from the results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial [ISCHEMIA; NCT01471522].

Results from the IABP-SHOCK II Trial

Written by Maria Vinall

The Intra-Aortic Balloon Pump (IABP) in Cardiogenic Shock II [IABP-SHOCK II; NCT00491036] trial, presented by Holger Thiele, MD, University of Leipzig Heart Center, Leipzig, Germany, failed to demonstrate a significant reduction in 30-day mortality with use of an IABP compared with best available medical therapy (BAT) alone in patients with acute myocardial infarction (AMI) complicated by cardiogenic shock.

IABPs have been used for almost 5 decades in the treatment of cardiogenic shock [Thiele H et al. *Eur Heart J* 2010]. Although considered a Class I recommendation in patients with AMI complicated by cardiogenic shock in both US and European guidelines [Van de Werf EM et al. *Eur Heart J* 2008; Wijns F et al. *Eur Heart J* 2010; Antman W et al. *Circulation* 2004], there is no evidence for a mortality benefit. IABP-SHOCK II was an investigator-initiated, randomized, prospective, open-label, multicenter trial, designed to compare IABP with BAT in patients presenting with an AMI complicated by cardiogenic shock and for whom early revascularization (using either percutaneous coronary intervention [PCI] or coronary artery bypass graft) was planned. Subjects were assigned to IABP (n=301) or BAT (n=299). The primary efficacy end point was 30-day all-cause mortality. Secondary endpoints included hemodynamic parameters, serum-lactate, Simplified Acute Physiology Score–II (SAPS-II), serial creatinine level and creatinine clearance, and inflammatory reaction (as measured by C-reactive protein). Safety assessments included major bleeding, peripheral ischemic complications, sepsis, and stroke [Thiele H et al. *Am Heart J* 2012; Thiele H et al. *N Engl J Med* 2012].

The median age of subjects was 70 years and 77% were men. Almost 50% had undergone resucitation (for 30 or fewer minutes) before randomization and about 80% had