Results for the dopamine strategy showed no significant difference between active treatment and placebo in 72-hour urine volume (8.5 vs 8.3 L, respectively; p=0.58), or cystatin-C concentration (0.12 vs 0.11 mg/L; p=0.72). The lack of effect was consistent across prespecified subgroups, except for patients with preserved EF (>50%) who tended to have lower urine volume with dopamine compared with placebo (p=0.01).

No significant treatment effect was seen with dopamine on secondary endpoints related to decongestion, renal function, or symptom relief. There was less study drug dose reduction or discontinuation due to hypotension in the dopamine group, but they were more likely to have study drug dose reduction or discontinuation due to tachycardia. The overall incidence of study drug discontinuation before 72 hours due to any cause was similar between the two groups. As for clinical outcomes, the composite of 60-day death, unscheduled visits, or HF readmission was similar between the two groups (HR, 1.15; 95% CI, 0.74 to 1.78; p=0.53), as was the rate of 180-day mortality (HR, 0.95; 95% CI, 0.54 to 1.68; p=0.87).

In the nesiritide group, there was no significant difference between active treatment and placebo in 72-hour urine volume (8.6 vs 8.3 L, respectively; p=0.25), or cystatin-C concentration (0.07 vs 0.11 mg/L, respectively; p=0.35). The lack of benefit was consistent across prespecified subgroups. There was a nonsignificant trend suggesting a differential effect in patients with reduced EF compared with patients with preserved EF. Patients with reduced EF who received nesiritide tended to have greater urine output volume (p=0.06) and less change in cystatin-C concentration when compared with patients receiving placebo (p=0.09). There was no significant treatment effect on secondary endpoints related to decongestion, renal function, or symptom relief. Patients receiving nesiritide had rates of study drug dose reduction or discontinuation due to hypotension that were numerically higher than in patients receiving placebo (18.8% vs 10.4%; p=0.07). The overall incidence of study drug discontinuation before 72 hours for any reason was similar in both the treatment and placebo group (25% vs 25%; p=0.94). The rate of 180-day mortality was similar between the groups (HR, 0.91; 95% CI, 0.51 to 1.61; p=0.74). The composite rate of 60-day death, unscheduled visits, or HF readmission, however, showed a nonsignificant trend favoring nesiritide (HR, 0.71; 95% CI, 0.44 to 1.15; p=0.16).

In patients with AHF and underlying renal dysfunction, neither low-dose dopamine nor low-dose nesiritide when added to diuretics enhanced decongestion or improved renal function. Further investigations of these, or other, AHF therapies should assess the potential for differential responses in HF with preserved versus reduced EF, stated Dr. Chen.

TOPCAT: Effects of Spironolactone on CV Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

Written by **Mary Mosley**

In adults with heart failure and preserved ejection fraction (HFpEF), the mineralocorticoid receptor antagonist spironolactone did not significantly reduce the composite primary outcome of cardiovascular (CV) mortality, aborted cardiac arrest, or hospitalization for heart failure (HF) compared with placebo, but it did reduce HF hospitalizations (Table 1). Marc A. Pfeffer, MD, PhD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of the Treatment of Preserved Cardiac Function With an Aldosterone Antagonist [TOPCAT; NCT00094302] study.

Table 1. Results for Primary Outcome and Its Components

Outcome	Number and Percentage of Subjects With Event and Event Rate		
	Spironolactone (n=1722)	Placebo (n=1723)	HR (95% CI) p Value
Primary outcome	320 (18.6%) 5.9/100 pt-yr	351 (20.4%) 6.6/100 pt-yr	0.89 (0.77–1.04) p=0.138
Primary components			
CV mortality	160 (9.3%) 2.8/100 pt-yr	176 (10.2%) 3.1/100 pt-yr	0.90 (0.73–1.12) p=0.354
Aborted cardiac arrest	3 (<1%) 0.05/100 pt-yr	5 (<1%) 0.09/100 pt-yr	0.60 (0.14–2.50) p=0.482
Hospitalization for heart failure	206 (12.0%) 3.8/100 pt-yr	245 (14.2%) 4.6/100 pt-yr	0.83 (0.69–0.99) p=0.042

CV=cardiovascular; pt-yr=patient-years.

The hypothesis for the benefit of aldosterone antagonism in HFpEF patients was based upon mechanistic data in combination with the benefits observed in outcomes trials of patients with heart failure and reduced ejection fraction (HFrEF) as well as in the post-myocardial infarction (MI) setting. These included the RALES [Pitt B et al. *N Engl J Med* 1999], EMPHASIS [Zannad F et al. *N Engl J Med* 2011], and the EPHESUS studies [Pitt B et al. *N Engl J Med* 2003].

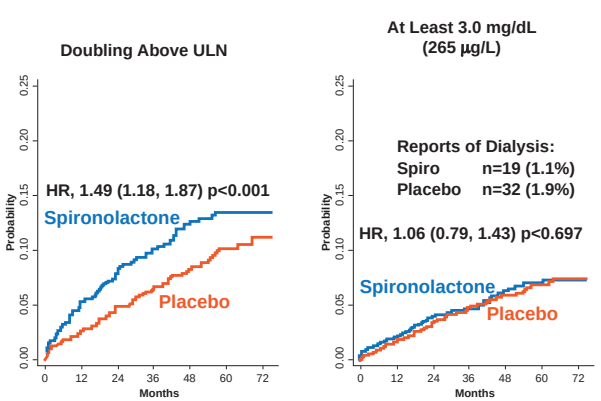
The National Heart, Lung and Blood Institute-funded, international, multicenter, double-blind, placebo-controlled TOPCAT study randomized 3445 patients with symptomatic HF (NYHA II to IV), left ventricular ejection fraction (LVEF) ≥45%, and either HF hospitalization within 1 year prior to randomization or elevated natriuretic peptide levels (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL) within 60 days prior to randomization. Stratification based on

hospitalization in the past year for HF management was performed [Desai A et al. *Am Heart J* 2011]. Patients were started on spironolactone 15 mg/placebo with titration to 30 mg at 4 weeks if there were no tolerability concerns; further titration to 45 mg daily was based on investigator discretion. At 8 months, the mean spironolactone dose was 25 mg. The mean follow-up was 3.3 years. Discontinuation of the study drug increased each year, with 34.3% of spironolactone patients and 31.4% of placebo patients discontinuing by 3 years. Vital status was unknown for 67 spironolactone patients (3.9%) and 65 placebo patients (3.8%).

Within each stratum, 71.5% were hospitalized within the prior year for HF and 28.5% had elevated natriuretic peptides. Baseline characteristics included a median age of 69 years and 52% were women. The median LVEF was 56%. NYHA II was present in 63% and NYHA III in 33% patients. Pertinent baseline findings included history of MI (26%), diabetes mellitus (33%), median systolic blood pressure 130 mm Hg, and eGFR <60 mL/min/1.73 m^2 (39%).

No overall differences were found in the rate of serious adverse events (48.5% spironolactone vs 49.6% placebo). Significantly more patients in the spironolactone group had hyperkalemia (≥5.5 mmol/L; 18.7% vs 9.1%; p<0.001) but fewer had hypokalemia compared with placebo (≤3.5 mmol/L; 16.2% vs 22.9%; p<0.001). In addition, the spironolactone group had a significantly increased risk of elevated creatinine (2x upper limit of normal). However, the percentage of patients requiring dialysis or having a creatinine level of at least 3.0 mg/dL was similar between the groups (Figure 1). Dr. Pfeffer stated that the use of spironolactone in patients with HFpEF requires careful monitoring of potassium and creatinine.

Figure 1. The Effect of Spironolactone on Creatinine and Risk of Dialysis



ULN=upper limit of normal.

Reproduced with permission from MA Pfeffer, MD, PhD.

The overall trial results were consistent across 21 of 22 prespecified subgroups, except in patients with elevated natriuretic peptides who demonstrated a significant reduction in the primary endpoint with spironolactone (HR, 0.65; 95% CI, 0.49 to 0.87; p=0.003). An exploratory post hoc analysis also revealed a significant geographic variation in the placebo event rates and the reduction of the primary endpoint (p=0.122). The primary outcome occurred in 31.8% of the placebo patients in the United States, Canada, Argentina, and Brazil; in these countries, spironolactone was associated with a HR of 0.82 (95% CI, 0.69 to 0.98). In Russia and the Republic of Georgia, the primary outcomes occurred in 8.4%; in these countries, spironolactone was not associated with better outcomes (HR, 1.10; 95% CI, 0.79 to 1.51). Physician judgment should guide the decision whether to use spironolactone to reduce HF hospitalization in a specific patient. However, these data do not support the broad use of spironolactone in patients with HFpEF to reduce CV events.

Adverse Effects Associated With Varespladib in the VISTA-16 Trial

Written by Muriel Cunningham

Inflammation has been implicated in atherosclerosis, and evidence suggests that some of the benefit seen with statin treatment may be related to an anti-inflammatory effect. Secretory phospholipase A_2 ($sPLA_2$) is found in atherosclerotic plaques and has been shown to participate in the inflammatory pathway. The objective of the Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks study [VISTA-16; Nicholls SJ et al. *JAMA* 2013] was to determine whether varespladib, a pan-$sPLA_2$ inhibitor, would have an effect on cardiovascular (CV) outcomes in patients treated for the first 16 weeks after an acute coronary syndrome (ACS).

Stephen J. Nicholls, MD, South Australian Health and Medical Research Institute, Adelaide, Australia, presented the results of the VISTA-16 trial. A total of 5145 patients with ACS were randomized in a double-blind fashion to treatment with varespladib 500 mg/day (n=2572) or placebo (n=2573) in addition to atorvastatin (at least 20 mg/day) and standard care. Eligible patients also had to have one of the following additional risk factors for cardiovascular (CV) events: diabetes, metabolic syndrome, high-density lipoprotein cholesterol <42 mg/dL, estimated glomerular filtration rate <60 mL/minute, stroke or transient ischemic attack, peripheral artery disease, myocardial infarction (MI), or coronary revascularization. Randomized patients began treatment within 96 hours of an ACS and double-blind treatment was continued for 16 weeks. The primary endpoint was the composite of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina.