The primary outcome was a composite of cardiovascular death, hospitalization due to HF, or resuscitated cardiac arrest. In the spironolactone and placebo arms, 34.3% and 31.4% of patients prematurely discontinued the medication by the end of the study, respectively.

There was no significant difference in the primary outcome with spironolactone (18.6%) compared to placebo (20.4%) at 72 months (HR, 0.89; 95% CI, 0.77 to 1.04; p=0.138) [Pitt B et al. *N Engl J Med* 2014]. Although the primary end point was not significant, there were promising trends for the individual components, including a lower rate of HF hospitalization with spironolactone compared with placebo at 72 months (HR, 0.83; 95% CI, 0.69 to 0.99; p=0.042).

Interestingly, the rate of reaching the primary outcome varied by geographic region. Patients from the United States, Canada, Argentina, and Brazil had a rate of 12.6 per 100 patient-years, compared with 2.3 per 100 patient-years in patients from Russia and the Republic of Georgia. Similarly, the HR varied. In the United States, Canada, Argentina, and Brazil, the HR was 0.82 (95% CI, 0.69 to 0.98), compared with 1.10 (95% CI, 0.79 to 1.51) in Russia and the Republic of Georgia; however, these differences did not result in a statistically significant interaction (interaction p=0.122).

There were no significant differences in the number of patients who experienced serious adverse events or total reports of adverse events. However, hyperkalemia occurred in 18.7% of patients who received spironolactone, compared with 9.1% who received placebo (p<0.001). In contrast, the placebo arm demonstrated greater rates of hypokalemia compared with the spironolactone arm (p<0.001). In addition, creatinine above the upper limit of reference occurred more frequently in the spironolactone arm compared with the placebo arm (HR, 1.49; 95% CI, 1.18 to 1.87; p<0.001).

Dr. Pitt concluded by stating that the results of the TOPCAT trial do not show a benefit of spironolactone treatment in patients with HFpEF, although the observation of an associated decrease in hospitalization for HF as an individual component is promising and warrants further study. The geographic heterogeneity in patient risk complicates the conclusions of this study.

Stem Cell Promotor JVS-100 Appears Safe and Shows Promising Trends in HF After MI

Written by Emma Hitt Nichols, PhD

Patients with heart failure (HF) and previous myocardial infarctions (MIs) demonstrated favorable outcomes after treatment with JVS-100, a plasmid that encodes for stromal cell–derived factor-1. Marc S. Penn, MD, PhD, Summa Cardiovascular Research, Akron, Ohio, USA, presented data from the Study to Evaluate the Safety and Efficacy of JVS-100 Administered to Adults With Ischemic Heart Failure trial [STOP-HF; NCT01643590].

Although ischemic tissue could potentially be repaired by stem cells, it may be inefficient because key molecular signals are either dysfunctional or expressed short term. Early studies suggest that adult stem cells induce tissue repair by activating endogenous stem cells through the stromal cell–derived factor-1/chemokine receptor type 4 axis. JVS-100 is a DNA plasmid encoding human stromal cell–derived factor-1; therefore, it has been hypothesized that administration in patients with HF could improve outcomes through improved stem cell homing. This was previously investigated in a Phase 1 open-label trial demonstrating that JVS-100 was safe, with initial signs of potential efficacy [Penn MS et al. *Circ Res* 2013]. The purpose of the current trial was to further evaluate the efficacy and safety of JVS-100 in patients with HF.

In the multicenter, Phase 2 STOP-HF trial, 93 patients with HF and prior MIs were randomly assigned to receive placebo (cohort 1), 15 mg of JVS-100 (cohort 2), or 30 mg of JVS-100 (cohort 3) by endomyocardial injection. Patients qualified if they had 6-minute walk distances ≤400 m, left ventricular ejection fractions (LVEF) ≤40%, and Minnesota Living With Heart Failure Questionnaire scores ≥20. Baseline characteristics included a mean age of 65 years, history of MI 11 years previously with a mean LV end-systolic volume (LVESV) of 168 mL and a mean LVEF of 28.5%.

The primary end points for this analysis were (1) the impact of the JVS-100 injection on 6-minute walk distance compared with placebo at 4-month follow-up and (2) the impact of the injection on the quality of life. Safety assessments included the numbers of major adverse cardiac events, serious adverse events, and adverse events up to 12 months.

At 4 months, there were no significant differences in clinical or structural parameters of efficacy with JVS-100. There were, however, trends that favored 30 mg of JVS-100 compared with placebo. Treatment with either dose of JVS-100 resulted in a decrease in LVESV from baseline compared with placebo. There was a promising trend toward a greater negative change from baseline in left ventricular end-diastolic volume (LVEDV) with 30 mg of JVS-100 compared with placebo and 15 mg of JVS-100 (p=0.11). In addition, patients who received 15 or 30 mg of JVS-100 experienced a trend toward a greater positive change from baseline in ejection fraction compared with patients who received placebo, who experienced

a negative change from baseline. Similarly, there was a dose-dependent decrease in N-terminal prohormone of brain natriuretic peptide. Although there were no significant differences with therapy, the observed trends were seen primarily in patients with LVESVs above the median at baseline, whereas patients with LVESVs below the median did not demonstrate the same beneficial trends in change from baseline in LVESV, LVEDV, or LVEF. Although there was no significant difference in terms of efficacy with this early phase trial, JVS-100 appeared to be well tolerated with no serious adverse events reported.

Dr. Penn concluded that the data from the STOP-HF study suggest that JVS-100 may provide benefits in patients with HF and previous MIs. Although there was no significant benefit in this early-phase trial of treatment with JVS-100, it appeared safe and showed promising trends for efficacy.

Parachute Implant Promising In HF

Written by Emma Hitt Nichols, PhD

A novel Parachute implant system was found to improve the New York Heart Association (NYHA) class and 6-minute walk distance (6MWD) in patients with heart failure (HF). William T. Abraham, MD, Director of the Division of Cardiovascular Medicine, Ohio State University Wexner Medical Center, Columbus, Ohio, USA, presented data from the Percutaneous Ventricular Restoration in Chronic Heart Failure Due to Ischemic Heart Disease trial.

HF results in at least 1 million hospitalizations per year, with 279,000 deaths and a 5-year mortality rate of about 50% [American Heart Association. *Circulation* 2014]. After an anterior wall myocardial infarction (AWMI), eccentric wall motion during the AWMI causes left ventricular (LV) remodeling. Over time, the LV enlarges and wall tension rises, which impairs contractility of the myocardium. Therefore, an improvement in LV contraction is needed to resolve symptoms. The purpose of this study was to evaluate the safety and efficacy of the Parachute system in the treatment of HF after a remote MI.

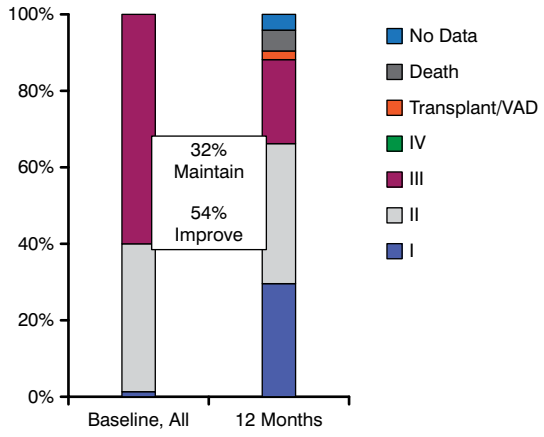
The Parachute system is a collapsible, cuplike implant. Its dual-layer, occlusive membrane is made of polytetrafluoroethylene, which is supported at the edges with polypropylene sutures and a 16-arm frame. A urethane foot at the bottom of the Parachute implant functions as a shock absorber. The implant is delivered and anchored via a 20-cc balloon, which is guided by a catheter (available in 3 sizes). The Parachute implant decreases wall stress in the upper chamber of the heart by decreasing the volume of the LV. It also provides a trampoline effect, replacing scar tissue with a more compliant material that creates an outward force to enhance diastolic filing. Improved diastolic compliance reduces the end-diastolic filling pressure.

The first results from this trial are reported. The cohort comprised 111 consecutive, intent-to-treat patients with NYHA Class III to IV ischemic HF who had received a Parachute implant and were followed for 12 months. These patients were from the USA and Europe, were enrolled on or before December 31, 2012, and were treated for 1 year.

The mean age of the study population was 60.7 years and the mean body mass index was 28.5. Most patients were male (84%). Prior tobacco abuse (74%), hypertension (69%) and diabetes (35%) were common. The use of revascularization with either percutaneous coronary intervention (76%) or coronary artery bypass (17%) or the use of advanced heart failure therapies, such as implantable cardiac defibrillator (38%) or cardiac resynchronization therapy (18%), were also common.

The Parachute implant led to an improvement in NYHA class in 54% patients and maintained the class in 32% patients at the 1-year time point (Figure 1). In addition, patients with the Parachute implant experienced a significant improvement in their 6MWD ($p<0.05$).

Figure 1. Effect of the Parachute Implant on NYHA Class



NYHA=New York Heart Association.
n=106 and refers to the number of patients discharged with the Parachute device.
*NYHA II at baseline had to be NYHA III or IV in the last 3 months.
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The 12-month stroke rate was 3%, the all-cause mortality was 6%, and the mortality plus HF hospitalization rate was 22%.

Dr. Abraham concluded that the Parachute implant could benefit some patients with congestive heart failure. The device is currently undergoing further evaluation in the PARACHUTE IV trial, which is now enrolling in the USA [NCT01614652].