Metformin Does Not Improve Diastolic Function in Nondiabetic Patients With STEMI

Written by Brian Hoyle

Metformin has no effect on diastolic function following acute myocardial infarction (MI) in nondiabetic patients. The disappointing finding from the Glycometabolic Interventions in Patients Presenting With ST-Segment Elevation Myocardial Infarction trial [GIPS-III; Lexis CP et al. *JAMA* 2014] was reported by Chris P. H. Lexis, MD, University Medical Center Groningen, Groningen, the Netherlands.

Left ventricular dysfunction following MI occurs in 30% to 50% of patients, of which 15% to 30% will develop heart failure. Left ventricular dysfunction is the strongest predictor of poor outcomes following an ST-segment elevation MI (STEMI). Post-STEMI patients experiencing heart failure at admission or during initial hospitalization are at markedly higher risk when compared to patients with no heart failure [Steg PG et al. *Circulation* 2004]. The researchers became interested in the possible benefit of metformin—the number one–prescribed antihyperglycemic drug—given animal studies that found that metformin improved left ventricular ejection fraction. In addition, some studies found an association between reduced all-cause mortality in patients with diabetes treated with metformin [UK Prospective Diabetes Study Group. *Lancet* 1998].

GIPS-III was a double-blind, placebo-controlled, parallel-group trial that comprised 379 patients. The 371 patients that received at least an assessment of diastolic function were randomly assigned (1:1) to receive metformin (500 mg, twice a day [BID]; n=187) or placebo (BID; n=184). The treatments commenced immediately after percutaneous coronary intervention (PCI) and continued for 4 months. The objective of the study was to evaluate the effect of metformin on left ventricular diastolic function during hospitalization and at 4 months in nondiabetic patients with STEMI.

Patients were eligible if they were at least 18 years old with STEMI, had received a primary PCI with ≥3.0-mm-diameter stents, and had a thrombolysis in MI flow grade ≥2 after PCI. Patients were excluded if they were diabetic, had a prior MI, required cardiothoracic surgery, were contraindicated for magnetic resonance imaging, or had severe renal impairment. Transthoracic echocardiography was done in the left decubital position during hospitalization to assess the short-term effect and again at 4 months. Assessors were blinded to treatment and clinical information. Diastolic individual assessment parameters (grade 0 to 3) included age, heart rate, size and mass, left atrial volume index, E/A ratio, deceleration time, e', E/e' ratio, and estimated pulmonary pressure.

The baseline characteristics of the 2 groups were similar, except for the higher prevalence of dyslipidemia and previous PCI in the placebo group and the longer ischemia time and greater creatinine kinase elevation in the metformin group.

The metformin and placebo groups were not appreciably different in the extent of normal and abnormal diastolic function during hospitalization and at 4 months. Similar grades of diastolic dysfunction and change of diastolic function were evident between groups at both times. Finally, all the assessed parameters were similar during hospitalization and at 4 months.

Dr. Lexis and colleagues concluded that metformin (500 mg, BID) started right after PCI in nondiabetic patients does not improve left ventricular diastolic function after STEMI as compared with placebo, both during hospitalization and at 4 months after discharge.

Spironolactone Misses Primary Endpoint in TOPCAT

Written by Emma Hitt Nichols, PhD

Spironolactone treatment of heart failure (HF) with preserved ejection fraction (HFpEF) did not significantly reduce cardiovascular death, hospitalization due to HF, or resuscitated cardiac arrest compared with placebo. Bertram Pitt, MD, University of Michigan School of Medicine, Ann Arbor, Michigan, USA, presented updated data from the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function trial [TOPCAT; Shah SJ et al. *Circ Heart Fail* 2012].

Previous trials have demonstrated that mineralocorticoid receptor antagonists improve survival in patients with mild to severe reduced ejection fraction and postmyocardial infarction left ventricular dysfunction compared with placebo [Zannad F et al. *N Engl J Med* 2011; Pitt B et al. *N Engl J Med* 2003; Pitt B et al. *N Engl J Med* 1999]. The purpose of the TOPCAT trial was to evaluate the effect of spironolactone in patients with HFpEF.

In the multicenter TOPCAT trial, 3445 patients with HFpEF were randomly assigned to receive a target dose of 30 mg of spironolactone (n=1722) or placebo (n=1723) over a mean follow-up of 3.3 years [Desai AS et al. *Am Heart J* 2011]. Randomly assigned patients had a mean age of 69 years and a New York Health Association class II or III HF, with a mean left ventricular ejection fraction of 56% [Shah SJ et al. *Circ Heart Fail* 2012].

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