Sildenafil for heart failure does not result in significant improvement in exercise capacity

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Among patients with heart failure with preserved ejection fraction (a measure of heart function), administration of sildenafil (commercially known as Viagra) for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or clinical status, according to a study published online by *JAMA*. Some studies have suggested that phosphodiesterase-5 inhibitors (a class of drugs that includes sildenafil) may improve cardiovascular function.

Heart failure with preserved ejection fraction (HFPEF) or diastolic heart failure is a common condition with a high level of illness. "Clinical trials of renin-angiotensin system antagonists have not demonstrated improvement in outcomes or clinical status in HFPEF, and effective therapies are needed," according to background information in the article. "Preclinical studies suggest that inhibition of phosphodiesterase-5 (PDE-5) reverses adverse cardiac structural and functional remodeling and enhances vascular, neuroendocrine, and renal function. In clinical studies, PDE-5 inhibitor therapy improved exercise tolerance and clinical status in patients with idiopathic pulmonary arterial hypertension and in patients with heart failure and reduced ejection fraction."

Margaret M. Redfield, M.D., of the Mayo Clinic, Rochester, Minn., and colleagues conducted a study to test the hypothesis that, compared with placebo, therapy with the PDE-5 inhibitor sildenafil would improve exercise capacity in HFPEF after 24 weeks of therapy, assessed by the change in peak oxygen consumption. The multicenter, randomized clinical trial included 216 stable outpatients with heart failure, reduced exercise capacity and other certain criteria. Participants were randomized from October 2008 through February 2012 at 26 centers in North America. Sildenafil (n = 113) or placebo (n = 103) was administered orally at 20 mg 3 times daily for 12 weeks, followed by 60 mg 3 times daily for 12 weeks. Follow-up was through August 2012.

The primary end point for the study was change in peak oxygen consumption after 24 weeks of therapy. Secondary end points included change in 6-minute walk distance and a hierarchical composite clinical status score based on time to death, time to cardiovascular or cardiorenal hospitalization, and change in quality of life for participants without cardiovascular or cardiorenal hospitalization at 24 weeks. The median (midpoint) age was 69 years, and 48 percent of patients were women.

The researchers found that at 24 weeks, the median change in peak oxygen consumption from the beginning of the study was not significantly different in patients treated with placebo and patients treated with sildenafil. Also, there were no significant differences in the clinical rank score, change in 6-minute walk distance at 24 weeks, or change in peak oxygen consumption or 6-minute walk distance at 12 weeks between treatment groups .

Adverse events occurred in 78 patients (76 percent) who received placebo and 90 patients (80 percent) who received sildenafil. Serious adverse events occurred in 16 patients (16 percent) who received placebo and 25 patients (22 percent) who received sildenafil.

"To our knowledge, [this] trial is the first multicenter study to investigate the effect of PDE-5 inhibition in HFPEF. Contrary to our hypothesis, long-term PDE-5 inhibition in HFPEF had no effect on maximal or submaximal exercise capacity, clinical status, quality of life, left ventricular remodeling, diastolic function parameters, or pulmonary artery

systolic pressure. Renal function worsened more and NT-proBNP, endothelin-1, and uric acid levels increased more in patients treated with sildenafil. Furthermore, there were more (but not significantly more) patients in the sildenafil group who withdrew consent, died, or were too ill to perform the cardiopulmonary exercise test, and patients treated with sildenafil had a higher incidence of vascular adverse events. These findings do not suggest that therapy with the PDE-5 inhibitor sildenafil provides clinical benefit in the general HFPEF population," the authors write.

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The study is being released early to coincide with its presentation at the American College of Cardiology's annual Scientific Sessions.

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