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Sildenafil should be avoided in valve disease with residual pulmonary hypertension

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Sildenafil should not be used to treat residual hypertension in patients with valvular heart disease, according to late-breaking results from the SIOVAC trial presented today in a Hot Line LBCT Session at ESC Congress. The off-label use of the drug led to worse clinical outcomes including a doubled risk of hospitalisation compared to placebo.

"Valvular disease is considered the next cardiac epidemic because of its strong association with age and the rapid aging of the population worldwide," said principal investigator Dr Javier Bermejo, a cardiologist at Hospital General Universitario Gregorio Marañon, Madrid, Spain.

"The only established treatment is repair or replacement of the valve surgically or percutaneously," he continued. "But symptoms often remain or reappear in the long-term. Residual pulmonary hypertension is the most important risk factor for death and disability after successful correction of the valvular lesion."

Pulmonary hypertension refers to increased blood pressure in the pulmonary artery. In patients with long-standing valvular disease, the high pressure in the left side of the heart is transmitted backwards to the lung vessels which react by thickening. This process may not revert after valve treatment, resulting in persistent pulmonary hypertension.

Sildenafil is a potent vasodilator with a strong effect on blood flow. Typically used to treat erectile dysfunction, the drug is also useful for pulmonary hypertension but clinical trials have shown discrepant results

in pulmonary hypertension with a retrograde origin. Sildenafil is believed to be safe and well tolerated and is frequently prescribed as an off-label indication in patients with retrograde pulmonary hypertension.

The SIOVAC trial2 tested the potential of sildenafil to improve long-term outcomes of patients with residual pulmonary hypertension after correction of a valvular lesion. The trial was conducted in 17 public hospitals and coordinated by the Spanish Network Centre for Cardiovascular Research (CIBERCV).

A total of 200 patients were randomised to sildenafil (40 mg three times a day) or placebo for six months. Patients and investigators were blinded to the treatment. Prior to enrolment, patients were screened for contraindications to sildenafil and a catheterisation procedure was performed to confirm elevated pressure in the pulmonary artery.

The primary endpoint was a clinical composite score of all-cause death, hospital admission for heart failure, worsening exercise tolerance (measured by change in functional class), and feeling worse than when starting the medication (assessed by change in a self-assessment score).

Contrary to the expected findings, clinical outcomes were worse in the sildenafil group compared to placebo. At six months, 33 (33%) patients taking sildenafil and 14 (15%) taking placebo had a worse composite clinical score than at the start of the study (odds ratio for improvement, 0.39; 95% confidence interval [CI], 0.22 to 0.67; p

Dr Bermejo said: "Compared to patients taking placebo, the chance for worse clinical outcomes ? as defined by the combined clinical score - was more than twice as high in those taking sildenafil. We were unable to identify any particular subset of patients who could potentially benefit from sildenafil."

Patients taking sildenafil suffered more, and more frequent, hospital admissions due to heart failure decompensations. In fact, the overall risk for hospital admission was double in patients taking the drug. Three patients taking sildenafil and two patients taking placebo died during the study (p = 0.63). Major clinical events ? death or readmission due to heart failure ? occurred earlier and more frequently in the sildenafil group (hazard ratio, 2.0; 95% CI, 1.0 to 4.0; p= 0.044).

"We were surprised to find that decompensations requiring hospital admission were more frequent in patients taking sildenafil," said Dr Bermejo.

"This is the first clinical trial focused on this complication," he continued. "We found that in patients with residual pulmonary hypertension after successfully corrected valvular heart disease, six month treatment with sildenafil leads to worse clinical outcomes than placebo."

Dr Bermejo concluded: "Long-term usage of sildenafil for treating residual pulmonary hypertension in patients with valvular heart disease should be avoided. The high incidence of events during the trial emphasises the need for further research to prevent and treat this complication in patients with valvular disease."

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