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The full report is titled "Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension. A Randomized Trial." It is in the 21 October 2008 issue of *Annals of Internal Medicine* (volume 149, pages 521-530). The authors are G. Simonneau, L.J. Rubin, N. Galiè, R.J. Barst, T.R. Fleming, A.E. Frost, P.J. Engel, M.R. Kramer, G. Burgess, L. Collings, N. Cossons, O. Sitbon, and D.B. Badesch, for the PACES Study Group.

## A Combination Treatment for Pulmonary Hypertension

### What is the problem and what is known about it so far?

Pulmonary hypertension is high blood pressure in the arteries that deliver blood to the lungs. It is usually caused by scar tissue that narrows or destroys small arteries. The damaged arteries make it harder for blood to flow through the lungs. As pressure builds, the right side of the heart must contract more vigorously than normal to maintain blood flow. This weakens the heart muscle and leads to heart failure. As the disease worsens, the lungs and heart have difficulty providing oxygen to the body.

Pulmonary hypertension is a rare and very serious disease. It causes disabling shortness of breath and is often fatal. Various treatments may help reduce symptoms, but there is no cure for the disease. Treatment include a drug (epoprostenol) that is given intravenously through a small tube and a pill whose active ingredient is more commonly used for erectile dysfunction. Despite such therapy, many patients with pulmonary hypertension do poorly. Whether treating patients with 2 drugs rather than a single drug would improve their outcomes is unclear.

### Why did the researchers do this particular study?

To see whether a combination of sildenafil and epoprostenol improves outcomes more than epoprostenol alone in patients with pulmonary hypertension.

### Who was studied?

267 patients with pulmonary hypertension. All had received intravenous epoprostenol for at least 3 months.

### How was the study done?

The researchers recruited patients already receiving epoprostenol therapy from 41 centers in 11 countries. They randomly assigned these patients to receive either a dummy pill or sildenafil (20 mg) 3 times daily. They followed the patients monthly for 16 weeks and increased pill dosages to 4 pills 3 times daily, if tolerated. Neither the researchers nor the patients knew which pills the patients received. At baseline and follow-up visits, the researchers measured patients' exercise capacity (distance walked in 6 minutes) and pulmonary artery pressure and asked about symptoms of breathlessness and adverse events.

### What did the researchers find?

At follow-up, patients given sildenafil could walk longer distances in 6 minutes and had greater decreases in pulmonary arterial pressures than did those given the dummy pills. Neither sildenafil nor the dummy pills affected breathlessness symptoms. None of the 134 patients given sildenafil died; however, 7 of the 131 patients given dummy pills died. More patients given dummy pills required changes in epoprostenol doses because of clinical deterioration. More patients given sildenafil reported side effects, such as headaches and abdominal discomfort (dyspepsia).

### What were the limitations of the study?

The study duration was short. The improvements in walking distances with sildenafil were seen mostly in a subgroup of patients who had walked further than 324 meters in 6 minutes at their baseline visits.

### What are the implications of the study?

Adding sildenafil to epoprostenol therapy may improve outcomes for some patients with pulmonary hypertension.

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