Pulmonary Hypertension Drugs Were Never Properly Tested in Heart Failure

To the Editor:

I read with interest the review on pulmonary hypertension (PH) due to left-sided heart disease by Hansdottir et al1 in a recent issue of CHEST (August 2013). It is a thorough and comprehensive review.

Unfortunately, the authors repeated a widespread belief that clinical trials of pulmonary arterial hypertension-specific therapies in heart failure (HF) have been largely disappointing. Specifically, they refer to the Flolan International Randomized Survival Trial (FIRST), which was prematurely stopped because of increased mortality in the epoprostenol arm.2

Although technically this statement is correct, it is worth mentioning that the presence of PH was not required for patients enrolled in this trial. Inclusion criteria for the FIRST trial were New York Heart Association class IIIa or IV, left ventricular ejection fraction of < 25%, low cardiac output and increased wedge pressure, proof of inotrope dependency for patients on inotropes, ineligibility for cardiac transplantation, and eligibility for anticoagulation.3

Elevated pulmonary arterial pressure was not among the inclusion criteria, and normal pulmonary pressure was not among the exclusion criteria. In other words, epoprostrenol in HF was tested in patients who did not necessarily have a target for pharmacologic effects of the drug. When there is no substrate for therapeutic effects, the drug can cause only side effects, and this is exactly what occurred. I doubt anyone could design a trial for a PH drug in the setting of idiopathic pulmonary arterial hypertension without selecting patients with PH. Meanwhile, the FIRST trial did exactly this, in an HF population, and essentially blocked the use of prostacyclin in patients with HF with secondary PH.

Another trial testing sildenafil in HF with preserved ejection fraction (the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure [RELAX] trial)4 had the same flaw in the design. Patients were not required to have PH to enter the study. It is naive to expect the drug to demonstrate its therapeutic effect if you do not select patients who have the target abnormality that the drug is supposed to correct. Predictably, the trial was not effective, with no effect of sildenafil on functional capacity. However, we cannot conclude that sildenafil is useless in HF until we specifically test it in patients with PH due to HF.

Drugs for PH should be tested in patients with PH. If this condition is not met, the results of such trials are inconclusive, and the trials themselves are useless.

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REFERENCES


Response

To the Editor:

We thank Dr Guglin for her comments on our recent article regarding the use of pulmonary hypertension (PH)-speciﬁc therapies in patients with World Health Organization (WHO) group 2 PH due to left-side heart disease (LHD). As Dr Guglin points out,