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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 Hansdottr 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 IIIB 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.²

Elevated pulmonary arterial pressure was not among the inclusion criteria, and normal pulmonary pressure was not among the exclusion criteria. In other words, epoprostenol 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)³ 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 negative, 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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Response

To the Editor:

We thank Dr Guglin for her comments on our recent article¹ 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,

elevated pulmonary arterial pressures were not required for enrollment in the Flolan International Randomized Survival Trial (FIRST).² However, all patients underwent right-sided heart catheterization, and most subjects (> 75%) did, in fact, have PH as defined by mean pulmonary arterial pressure > 25 mm Hg. This makes it unlikely that epoprostenol is of significant benefit in patients with systolic heart failure and PH. The same is true for the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial. The rationale behind the RELAX trial was to target the pleiotropic (cardiac, vascular, and neurohormonal) effects of phosphodiesterase-5 inhibition on cardiovascular function in patients with heart failure with reduced ejection fraction regardless of the pulmonary pressures.³ Based on echocardiographic estimates (which are admittedly imprecise), approximately two-thirds of subjects in this trial also had elevated pulmonary arterial systolic pressure (> 35 mm Hg).

Recently, Bonderman and colleagues⁴ reported the results of the Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT). Riociguat, a guanylate cyclase stimulator, is efficacious in the treatment of pulmonary arterial hypertension and in PH due to chronic thromboembolic disease; it received US Food and Drug Administration approval for these indications in October 2013. LEPHT was a phase 2 trial that examined the hemodynamic effects of riociguat in patients with hemodynamically confirmed PH due to heart failure with reduced ejection fraction. In this study, riociguat failed to reduce mean pulmonary arterial pressure, and there was no significant improvement in N-terminal pro-brain natriuretic peptide or 6-min walk test distance after 16 weeks of treatment. On a more positive note, subjects receiving riociguat had significantly increased cardiac index and a decrease in the Minnesota Living With Heart Failure score.

To conclude, the clinical trials to date have been disappointing, and the use of PH-specific therapies for PH due to LHD should be discouraged outside of the context of clinical trials. We do agree with Dr Guglin that additional, adequately powered, trials looking at subgroups of patients with LHD and a fixed component of PH are needed.

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Just Because We Can Does Not Mean We Should

A Perspective on Combined Tracheostomy and Percutaneous Endoscopic Gastrostomy Tube Insertion

To the Editor:

We read with interest the article from Yarmus et al¹ in *CHEST* (August 2013) about the feasibility of percutaneous endoscopic gastrostomy (PEG) tube insertion by interventional pulmonologists. For reasons that are unclear, a combination procedure of PEG and tracheostomy has been advocated by some. In the current work, more than one-half of the patients (n = 41) underwent a combined procedure. There is some historic observational data on the feasibility of this approach^{2,3}; however, efficacy and safety of this approach has not been previously studied in prospective randomized trials.

Consensus guidelines would suggest that PEG tube insertion be considered for patients who are likely to have a requirement for enteral nutrition of > 30 days.⁴ PEG, while safe and reasonably well tolerated, is not a frivolous procedure. Thirty-day mortality after PEG tube insertion has been noted to range between 10% and 26% in some series, largely driven by poor patient selection.^{4,5} Indeed, in one of the largest published series, a 1-week mortality of 43% was seen in a national confidential inquiry into patient deaths in the National Health Service, of which 19% of procedures were deemed futile upon expert review.⁶ It is with this knowledge that the selection of critically ill patients undergoing tracheostomy as suitable subjects for PEG tube insertion needs to be questioned. By virtue of their complex critical illness, patients undergoing tracheostomy insertion are sick and not optimal subjects. Reported 30-day mortality rates after tracheostomy insertion alone vary but have been reported to be on the order of 30%.⁶⁻⁸ For similar reasons, the policy of placing PEG tubes in patients early in the course of their critical illness (as early as 4 days in the current report) and prior to declaration of medical stability is questionable.

In the current series, Yarmus et al¹ reported mortality at 30 days of 11%. The mortality in the group that underwent simultaneous PEG and tracheostomy tube insertion was not reported; we would be interested to see these data.

PEG tubes were removed in 73% of surviving patients within a median of 76 days (range, 24-611 days). This would seem to