associated with the use of our product, Limbrel (flavocoxid). I wish to thank them for their clear and concise description of the clinical presentation and appropriate treatment of this rare event.

Limbrel was first marketed nationally in April 2004. At that time, no instances of hypersensitivity pneumonitis had been reported in clinical trials or test marketing surveillance. By 2008, three cases had been reported, and the package insert was revised to reflect this complication. At the time of its most recent revision, in mid-2010, the package insert was again revised to reflect seven confirmed cases reported in post-marketing surveillance and through the US Food and Drug Administration’s MedWatch. As of that time, approximately 270,000 people had been exposed to the product as judged by the number of new prescriptions filled. Thus, the apparent incidence of hypersensitivity pneumonitis, as nearly as we can estimate it, is approximately 0.0023%, or somewhere around two to three per 100,000.

Given such a low incidence, it is unlikely that any individual physician would encounter the problem. The report by Youssef and Tomic should increase awareness of this rare event and enable more rapid institution of appropriate therapy and avoidance of unnecessary and inappropriate treatments.

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Response

To the Editor:

We appreciate the comments from Dr Robert Levy about our case presentation. First, we would like to applaud the pharmaceutical company for their efforts in careful monitoring of published literature concerning their products. It is encouraging that their safety packets are regularly updated to reflect new reports of possible side effects.

Hypersensitivity pneumonitis represents a complex pulmonary disorder of varying intensity and clinical presentation, which is characterized by a diffuse Tc1 immune response of lung parenchyma in patients previously sensitized to one of >300 causative agents that may favor the hypersensitivity pneumonitis reaction. It remains an elusive diagnosis that is achieved by performing clinical, radiologic, physiologic, and immunologic evaluations. Hypersensitivity pneumonitis is known to be caused by a large number of different medications. This possible side effect can go unnoticed and misdiagnosed if physicians do not report their experiences. Possible consequences can include many unnecessary procedures that can cause an increase in morbidity and mortality for the patients.

The purpose of our case presentation was to bring to light a possible, though rare, side effect that patients may experience when their doctors administer flavocoxid (Limbrel). Increasing the awareness of yet another possible cause of hypersensitivity pneumonitis will help physicians to reach the right diagnosis and avoid unnecessary and potentially harmful diagnostic procedures.

Also, it will be useful to review all published reports of flavocoxid causing hypersensitivity pneumonitis in order to assess the common characteristics among these patients that could have predisposed them to hypersensitivity pneumonitis. This will help us to identify groups of patients who should avoid flavocoxid. We believe that our report will help physicians and increase the awareness of this rare but possible cause of hypersensitivity pneumonitis.

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Can Pulmonary Arterial Hypertension Be Diagnosed by an Elevated Pulmonary Capillary Wedge Pressure Outside of the Guideline Criteria?

To the Editor:

We read with interest the report by Frost and colleagues in a recent issue of CHEST (July 2011) comparing the results of the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) with the other registries of pulmonary arterial hypertension (PAH). We are troubled by the inclusion of patients with a pulmonary capillary wedge pressure (PCWP) > 15 mm Hg, a value > 2 SD higher
than normal, in this most recent and other publications from the REVEAL Registry. Since the 1979 National Institutes of Health registry, a PCWP \( \leq 15 \) mm Hg has been accepted as a requirement for diagnosing PAH by professional societies and for entrance into clinical trials of PAH. Of 2,967 subjects in the REVEAL Registry, 239 (8\%) had a PCWP > 15 mm Hg, suggesting either a proper diagnosis of pulmonary venous hypertension from unrecognized left-sided heart disease (LHD) or coexistent PAH and LHD. Obesity, female sex, hypertension, sleep apnea, and renal insufficiency, characteristics associated with left-sided heart disease, particularly heart failure with preserved ejection fraction, were more common among subjects with a PCWP > 15 mm Hg. The primary disease process in these patients may be quite different from that in patients with PAH. Including this heterogeneous population in REVEAL Registry analyses may confound the true picture of PAH.

Risks of inaccurate diagnosis include psychologic stress and adverse effects of therapy. Risks may be higher in patients treated with PAH-specific therapy who have unrecognized LHD. In patients with heart failure with reduced ejection fraction, a trial of epoprostenol was stopped early because of a trend toward increased mortality. Studies of bosentan, enrasentan, tezosentan, and darusentan in heart failure with reduced ejection fraction showed increased transaminases, fluid retention, and hospitalization for heart failure in the treatment arms. Adequate trials to assess the safety of sildenafil in LHD have not yet been performed. Unrecognized and untreated LHD could result in further preventable morbidity and mortality. Well-designed and executed studies of patients with characteristics of PAH but PCWP > 15 mm Hg are mandatory before the accepted definition of PAH is modified and patients who do not meet these criteria are treated with PAH-specific therapy.

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Response

To The Editor:

We appreciate the letter from Drs Barnett and De Marco regarding our recent article in CHEST; because it highlights several important points from this and other Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) articles. Drs Barnett and De Marco emphasize that patients with pulmonary arterial hypertension (PAH) should not be confused with patients with pulmonary venous hypertension related to unrecognized left-sided heart disease (LHD) and that such an erroneous diagnosis can have a major impact on the patients as well as on the database. We completely concur with these important points and agree with the comments that proven therapies for patients with LHD-associated pulmonary hypertension are lacking and that there is no proven role for PAH-specific therapies in treating these patients.

It is important to emphasize that those patients with a higher than traditional pulmonary capillary wedge pressure (PCWP) included in the REVEAL Registry were considered to have group 1 pulmonary hypertension (ie, PAH) by the enrolling physician. Although not mandated by the study protocol, it is assumed that the enrolling physician performed the necessary evaluations to ensure the diagnosis of PAH.

The design of the REVEAL Registry permitted the inclusion of such patients because:

1. The level of PCWP allowed for definition of PAH has increased over time (PCWP was \( \leq 12 \) mm Hg in the National Institutes of Health idiopathic PAH registry, not the more recent 15 mm Hg). This change has been driven by expert opinion and enrollment criteria for clinical studies, both of which strive to exclude patients with unrecognized LHD while maximizing enrollment of appropriate patients.

2. Having a risk factor for LHD does not confer protection from development of true intrinsic pulmonary vascular disease (ie, PAH).

3. Ventricular interdependence can result in elevated left-sided pressures (PCWP or left ventricular end-diastolic pressure) in the absence of LHD in a patient with severe PAH.

4. Characterization of these patients and their treatment in clinical practice needs further exploration.

The emphasis of this article was on the comparison of historical and contemporary registries of PAH with the REVEAL Registry database. The size of the REVEAL Registry database permitted comparison of subgroups with enrollment characteristics identical to traditionally defined patients with PAH: the 1,072 patients in the REVEAL Registry National Institutes of Health Comparison Cohort subgroup had idiopathic PAH, familial PAH, and PCWP \( \leq 12 \) mm Hg, whereas the 2,355 patients