# Article Reviews

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***Summaries and commentaries from the section editors present a clinical context for practitioners' application of recently published research relevant to care of patients with pulmonary hypertension.***

### Simonneau S, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension. *Ann Intern Med.* 2008;149:521-530.

This was a multicenter international study, which took place in 41 centers in 11 countries between July 2003 and January 2006. A total of 267 patients with PAH were enrolled. Patients on background continuous intravenous epoprostenol (EPO) therapy were randomized to receive placebo (median EPO dose 28 ng/kg/min) or sildenafil 20 mg 3 times daily (median EPO dose 29 ng/kgmin), titrated to 40 and 80 mg 3 times daily as tolerated. A total of 97% of patients completed the study. The primary endpoint was a change from baseline in 6-minute walk distance (6MWD), and secondary endpoints included hemodynamic measurements, time to clinical worsening, and Borg dyspnea score. Patients should have been on EPO for at least 3 months prior to study enrollment. Inclusion 6MWD was 100-450 meters at baseline.

A placebo-adjusted increase of 28.8 meters (95% CI, 13.9 to 43.8 meters) in 6MWD was seen in the sildenafil group. The sildenafil addition also led to a mean placebo-adjusted reduction in mean pulmonary arterial pressure of 3.8 mm Hg (95% CI, -5.6 to -2.1 mm Hg); cardiac output 0.9 L/min (95% CI, 0.5 to 1.2 L/min); and longer time to clinical worsening, with 6.2% of patients in the sildenafil group experiencing a worsening event by Week 16 vs 19.5% of patients in the placebo group ($P$=0.002). There were no deaths in the sildenafil group vs 7 deaths in the placebo group. Of note, all deaths had a baseline 6MWD <325 meters.

This study revealed that addition of sildenafil to patients who receive background therapy with EPO obtained a clinical benefit—improvement in 6MWD and delay in time to clinical worsening. The clinical findings are supported by the benefit in hemodynamic numbers. The study limitations include an imbalance in missing data between groups, with 8 placebo recipients having no postbaseline walk assessment compared with 1 sildenafil recipient. These patients were excluded from the analysis.—FS

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### Badesch DB, Raskob GE, Elliot CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest.* 2009 Oct 16. (Epub ahead of print)

This article examines the results from the Registry to Evaluate Early And Long-term (REVEAL) pulmonary arterial hypertension (PAH) disease management, established to provide updated characteristics of patients with PAH and to improve diagnosis, treatment, and management.

The study describes the characteristics of PAH patients followed by 54 pulmonary hypertension (PH) centers in the US. It also compares clinical and hemodynamic characteristics of patients with the traditional definition of PAH—pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg—to those with a PCWP between 16-18 mm Hg.

A total of 2864 patients met the study entry criteria (Group I, PAH): 2525 fulfilled the traditional PAH hemodynamic criteria of PCWP ≤15 mm Hg and 239 had a PCWP of 16-18 mm Hg. (See Table.) Idiopathic PAH (IPAH) accounted for 46.2% of patients while associated PAH (APAH) accounted for 50.7%. A 4.1:1 female-to-male ratio among patients with IPAH was found. The most common age at the time of diagnosis was 45 to 54 years (83% of patients ages 19 to 64). At enrollment, 50% of patients were functional class III. The population was overweight (BMI 29 kg/m$^2$). A median 1-year interval delay in referral to PH centers from symptom onset to right heart catheterization was found. Baseline hemodynamics included a mean pulmonary arterial pressure 50.7 mm Hg, mean PCWP 9.1 mm Hg, mean right atrial pressure 9.3 mm Hg, and mean cardiac index 2.4 L/m$^2$. Hemodynamics were similar for IPAH and APAH. At enrollment, 47% of patients were on PAH-specific treatment: 18.5% were on monotherapy; 11.9% were on a combination of 2 oral agents, and 9.2% were using a combination of oral therapy with a prostacyclin analogue.

**Table. Characteristics of traditional PAH definition vs PAH with mildly increased PCWP**

| | PCWP ≤15 mm Hg (n=2525) | PCWP 16-18 mmHg (n=239) | *P*-value |
|---|---|---|---|
| 6MWD, mean | 366 meters | 339 meters | 0.004 |
| Hypertension | 40.2% | 47.6% | 0.02 |
| Sleep Apnea | 21% | 39.9% | <0.001 |
| Diabetes | 12% | 20.2% | <0.001 |
| Beta Blocker | 12.1% | 21.9% | <0.001 |

The study provides important insight into the demographics, diagnosis, and treatment of PAH. Findings such as the delay from presentation to confirmation of the diagnosis and referral to a center, presence of various comorbidities (sleep apnea, systemic hypertension), and widespread empiric use of expensive and complicated drug combinations all have important implications for future educational, therapeutic, and research efforts. Comparison of adult patients with a traditional hemodynamic profile to those with a mildly elevated PCWP reveals important differences that may have therapeutic implications.—FS

### Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. *Circulation.* 2009;120:1248-1254.

Pulmonary hypertension therapy (PHT) is commonly used in pa-

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tients who have chronic thromboembolic pulmonary hypertension (CTEPH), either as sole treatment or as a bridge to pulmonary thromboendarterectomy (PTE). However, the clinical and hemodynamic benefit of such treatment before PTE is not clear.

A retrospective chart review identified 487 consecutive patients referred to the University of California at San Diego (UCSD) between 2005 and 2007 for PTE evaluation. Of these patients, 355 (73%) were found to be PTE candidates. Data were collected for baseline characteristics, hemodynamics, and PHT use. A comparison was made between patients receiving PHT and those who did not (control group). Hemodynamic measurements included cardiac output, mean right atrial pressure, mean pulmonary arterial pressure (mPAP), or total pulmonary resistance (TPR).

A steady increase in PHT use in all CTEPH patients referred to UCSD for PTE evaluation was found over the study duration: 2005 (19.9%), 2006 (31.8%), and 2007 (37%). Bosentan and sildenafil were the most common agents used with an increase in the frequency of combination therapy during the 3-year period (11% in 2005, 14% in 2006, and 26% in 2007).

From a total of 355 patients who underwent PTE, 111 (31%) were on PHT and 244 (69%) did not receive any treatment (control group). No significant difference was found in age, gender, or anticoagulation use between these 2 groups. Those who were on PHT did experience a longer delay to referral: median time of 8.9 months (4-13) vs 4.4 months (2.5-7) in the control group ($P<0.01$). Diuretic and digoxin use was higher in the PHT group. With regard to hemodynamics, only a minimal and likely not clinically significant difference was seen between baseline values (time of diagnosis) and referral values (at the time of evaluation at UCSD) in the 2 groups (PHT vs controls). Post-PTE hemodynamics were not different between the 2 groups. Subgroup analysis suggested some individual hemodynamic benefit such as epoprostenol improving TPR between diagnosis and referral evaluation. However, this did not appear to translate into clinical benefit since no significant differences were observed between the PHT (including individual drug subgroups) and control groups in any of the post-PTE outcomes or complications.

This study demonstrates that the use of pulmonary arterial hypertension medical therapy is increasing in patients with CTEPH. Unfortunately, this usage is also associated with a delay in the time to referral for PTE surgery and only a minimal improvement in preoperative mPAP. Pulmonary hypertension therapy did not result in any significant differences in postoperative outcomes or hemodynamics. Whether these agents might improve outcomes in patients with inoperable CTEPH is still controversial. This study is limited by its retrospective nature and lack of randomization. However, unless a randomized trial is performed, this center's data are the best and most comprehensive available in the literature.—FS

**Degano B, Guillaume M, Savale L, et al. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. *AIDS*. 2009 Sept 16. (Epub ahead of print)**

Characteristics and outcomes of patients with pulmonary arterial hypertension (PAH)-HIV in the current era of highly active antiretroviral therapy (HAART) and specific PAH therapies are unknown. Data were reviewed for 77 consecutive patients treated at the French reference centre for pulmonary hypertension between October 2000 and January 2008. Specific PAH treatment was initiated guided by recommendations for idiopathic PAH and physician's judgment. In patients not receiving HAART at the time of PAH diagnosis, HAART was initiated irrespective of HIV viral load or CD4+ lymphocyte count. Data on functional class (FC), 6-minute walk distance (6MWD), and right heart catheterization were collected. Follow-ups were done approximately every 3-6 months.

A total of 122 patients were seen during the study period: 77 had HIV infection as their only risk factor and 45 had associated risk factors for PAH and were excluded from the analysis. Median duration of HIV infection was 11.1 years (4.1-15.4). Most patients were men (58%), and IV drug use was their main risk factor (36%) for HIV. Median interval between onset of symptoms and PAH diagnosis was 6 months.

At the time of PAH diagnosis, 38 patients (49%) had undetectable viral load and 61 (79%) had a CD4+ lymphocyte count >200 cells/µl. In only one patient was HIV infection discovered at PAH diagnosis. There were 62 patients (81%) receiving HAART at the time of PAH diagnosis. Of all 77 patients, 50 received PAH therapy at the time of diagnosis, and 84% of them remained on monotherapy at the time of follow-up. The other 27 patients were not initially started on therapy but 8 (30%) were subsequently treated. Functional class, 6MWD, cardiac index, and pulmonary vascular resistance all improved significantly with PAH therapy while HAART only led to improvement in 6MWD.

At the cut-off date (May 1, 2008), the mean duration of follow-up was 41 (22-61) months. There were 49 patients alive (64%), with 2 lost to follow-up. Of 26 deaths, 15 of them (58%) were attributable to consequences of PAH. Of all deaths, 14 had received PAH therapy right away while 12 were part of the group not initially treated. Patients with CD4+ count >200 cells/µl (n=61) were more likely to die of PAH vs other causes (21% vs 5% respectively, $P<0.01$). Overall survival rates were 88%, 72%, and 63% at 1, 3, and 5 years, respectively. Survival was dramatically worse for patients in FC IV. Cardiac index <2.8 L/m$^2$ and CD4+ <200 cells/µl were independently related to poor survival by multivariate analysis.

This study revealed that PAH can develop in patients with well controlled HIV infection. While HAART appeared unable to entirely prevent the development of PAH, other recent data suggest that it helps to delay and attenuate the development of PAH. HAART led to improvement in 6MWD in this study, but had no impact on hemodynamic parameters. PAH-HIV carries a lower survival rate at 5 years (63% in this study) when compared to patients without PAH-HIV with similar CD4+ counts. The study is limited by its retrospective nature and the discretion of physicians to decide when to treat PAH-HIV (27 patients were not initially treated), which affects the comparison of PAH therapy impact on disease progression and survival. Based on the data provided, it is not clear whether PAH therapy actually led to improved survival.—FS ■