al. recently published a summary explaining the conflicting results [*Thorax* 2012]. The duration of CPAP, patient age, comorbidities, and the severity of OSA and intermittent hypoxia all appear to be critical factors in the relative success of CPAP in treating OSA.

Statin Use Improves Respiratory-Related Mortality in Patients With COPD

Written by Phil Vinall

There is mounting evidence for an association between statin use and reduced all-cause mortality among patients with chronic obstructive pulmonary disease [Lahousse L et al. *Pulm Pharmacol Ther* 2013; Young RP et al. *Eur Respir Rev* 2009; Janda S et al. *Chest* 2009; Young RP et al. *Postgrad Med J* 2009]. Robert P. Young, MD, PhD, University of Auckland, Auckland, New Zealand, presented results from an observational study indicating that this benefit is of particular significance in terms of respiratory-related mortality.

Prof. Young reported the results of a subanalysis of the data from a recent study, which reported a 30% reduction (HR, 0.69; 95% CI, 0.58 to 0.84; p<0.01) in all-cause mortality after 4 years of follow-up in COPD patients taking statins [Lawes CM et al. *Prim Care Respir J* 2012]. The study comprised 1687 patients (596 statin users; 1091 nonusers; mean age 70.6 years) who were admitted to any New Zealand public hospital during 2006 and had a discharge diagnosis of first episode of COPD. Cases of COPD were identified through national hospital codes. Medication usage was based on a national drug-dispensing database and outcomes for those patients taking statins were compared with patients not taking statins, adjusted for confounding using a propensity score approach. Cause of death was ascertained through death certificate documentation up to the end of 2012 and sub-grouped (respiratory, cardiovascular, and other deaths).

Statin users were significantly more likely to be men (58.4%) and to have a history of cardiovascular disease (58.6%) compared with non-statin users (48.5% and 25.1%, respectively; both p<0.001). Significantly more statin users were taking furosemide (which was used as a proxy for heart failure; 47.7% vs 24.5%) and significantly more had been diagnosed with diabetes (35.4% vs 11.6%; both p<0.001) than statin non-users. The proportion of deaths was similar between the two groups: 242 deaths (40.6%) in the statin group versus 429 deaths (39.3%) among those non-statin users. After adjustment for age, sex, ethnic group, history of cardiovascular disease, diabetes, and prescription for furosemide, the hazard ratio for statin users versus statin non-users for all-cause mortality was 0.69 (95% CI, 0.58 to 0.84; p<0.01).

For their follow-up analysis, Prof. Young and colleagues obtained the specific cause of death for those who died during the follow-up period of 6 years in the Lawes study [Lawes CM et al. *Prim Care Respir J* 2012]. A significant reduction was noted in respiratory death (chest infection, COPD exacerbation, pneumonia, respiratory failure) and "other deaths" with adjusted HRs of 0.55 and 0.55 respectively (95% CI, 0.43 to 0.78 and 0.35 to 0.85; p=0.0009 and p=0.008, respectively). Within the "other deaths" category there was a significant reduction in cancer deaths but no reduction in cardiovascular death.

The investigators concluded that statin therapy confers a benefit on mortality in COPD for respiratory complications leading to death. They noted that although two randomized studies of statin use in patients with COPD have shown significant improvement in exercise tolerance and quality of life [Lee T-M et al. *Am J Cardiol* 2008; McDonald VM et al. *Thorax* 2013] a reduction in mortality is even more important. The results of this study support the hypothesis that the systemic immune-modulatory effects of statins are beneficial in COPD and suggest a need for a randomized controlled trial to assess the role of adjunct statin therapy in reducing systemic and pulmonary inflammation in patients with COPD.

Addition of Spironolactone to Ambrisentan May Be a Novel Treatment Strategy to Improve Outcome in Patients With PAH

Written by Maria Vinall

Bradley Maron, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA, presented the results of a retrospective study that demonstrated a trend toward additional clinical improvement when spironolactone was added to ambrisentan for the treatment of patients with pulmonary arterial hypertension (PAH).

In patients with PAH, levels of the mineralocorticoid hormone aldosterone are increased in the pulmonary arterial circulation and correlate positively with hemodynamic measures of pulmonary vascular remodeling [Maron BA et al. *Eur J Heart Fail* 2013]. In addition, results from recent basic and translational models of PAH suggest that hyperaldosteronism modulates a pulmonary vasculopathy by promoting endothelin receptor type-B (ET_B) dysfunction in pulmonary endothelial cells [Maron BA et al. *Circulation* 2012; Maron BA et al. *Am J Cardiol* 2013. In press], which is required for

maintaining normal bioavailable levels of the vasodilator and anti-remodeling molecule nitric oxide. Together, these observations raised the possibility that coupling the mineralocorticoid-receptor antagonist spironolactone with therapies that inhibit the adverse effects of ET_A-mediated pulmonary vasoconstriction/remodeling may be a useful therapeutic strategy for patients with PAH.

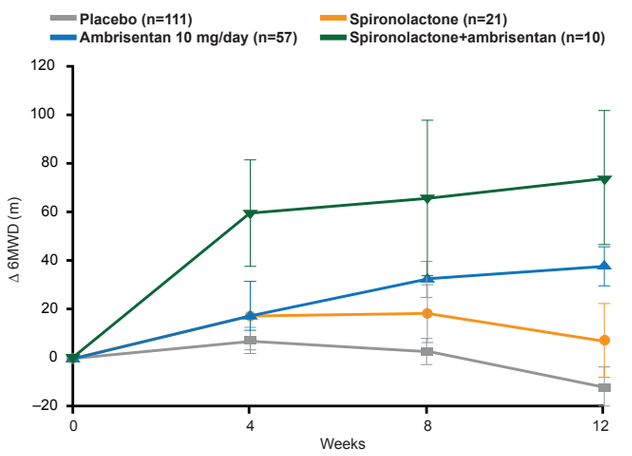
This study analyzed data from patients in the double-blind, placebo-controlled Ambrisentan in Patients With Moderate to Severe Pulmonary Arterial Hypertension studies [ARIES-1 and -2; Galiè N et al. *Circulation* 2008] who were randomized to receive placebo or the selective ET_A antagonist ambrisentan (10 mg daily) and in whom spironolactone use was reported. The investigators elected to study patients randomized to the maximum dose of ambrisentan because it was at this dose that the greatest benefit on clinical outcome was observed in the ARIES trial. Critiera for inclusion in the spironolactone treatment group was as follows: study drug use for ≥28 days, initiation of spironolactone prior to enrollment or ≤28 days after first ARIES study drug day, and discontinuation of spironolactone >28 days prior to the final ARIES study drug dose. Twenty-one patients in the placebo group (21/132; 15.9%) and 10 patients in the ambrisentan group (10/67; 14.9%) met the spironolactone criteria.

Patients treated with ambrisentan plus spironolactone tended to have increased mean pulmonary vascular resistance (14.5±6.0 vs 10.8±5.7 Wood units; p=0.07) and plasma B-type natriuretic peptide (BNP) concentrations (236.7 ng/L; 95% CI, 81.5 to 687.4 vs 131.7 ng/L; 95% CI, 88.0 to 197.2; p=0.24) compared with those treated with ambrisentan alone.

On the primary endpoint of change from baseline in 6-minute walk distance at Week 12, patients treated with ambrisentan plus spironolactone achieved a mean peak mean change of +74.2 meters compared with +38.2 meters for those treated with ambrisentan alone (p=0.11; Figure 1).

A similar trend was observed for the predetermined secondary endpoints: ambrisentan plus spironolactone was associated with a 1.7-fold improvement in BNP levels (p=0.08) compared with ambrisentan alone at Week 12 and a decrease in the geometric BNP mean of 66% compared with 39% decrease for ambrisentan alone at Week 12. World Health Organization functional status improved by ≥1 class in 50.0% of patients treated with ambrisentan plus spironolactone versus 21.6% of placebo-treated patients (p=0.01). Additionally, none of the patients treated with ambrisentan plus spironolactone reached the clinical endpoints of progressive illness, PAH-associated hospitalizations, and/or death versus 5.3% of patients treated with ambrisentan only.

Figure 1. Change From Baseline in the 6-Minute Walk Distance



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Limitations of the study include the retrospective design and small sample size. In addition, aldosterone levels were not measured in the ARIES trial nor were potential mechanisms by which aldosterone influenced outcomes. Additionally, the investigators recognized that use of spironolactone may be a marker of more severe PAH and that the clinical response observed in patients treated with ambrisentan plus spironolactone reflects the enhanced therapeutic efficacy of ambrisentan. Nevertheless, these results support the hypothesis that spironolactone and ET_A antagonism may be beneficial in PAH, and, overall, results from this study provide evidence to support future clinical trials to characterize the efficacy of aldosterone inhibition in the treatment of PAH.

Haloperidol Does Not Prevent Delirium in Ventilated ICU Patients

Written by Emma Hitt, PhD

Treatment of ventilated patients in the intensive care unit (ICU) with haloperidol or intravenous saline resulted in similar rates of delirium- and coma-free days. Valerie Page, MB, BCh, Wirral University Teaching Hospital NHS Foundation Trust, Wirral, United Kingdom, presented data from the Randomised, Double-Blind, Placebo-Controlled Trial to Compare the Early Administration of Intravenous Haloperidol Versus Placebo in the Prevention and Treatment of Delirium in Critically Ill Ventilated Patients [HOPE-ICU; ISRCTN83567338].