Rescue medication use over 6 weeks was significantly lower with QVA149 versus placebo (–1.43 puffs/day; p<0.001) and tiotropium (–0.45 puffs/day; p=0.002).

QVA149 was well tolerated. The most frequent adverse events (COPD, nasopharyngitis, cough, and dyspnea) occurred with similar frequency to that of placebo and tiotropium.

Results from BLAZE add to the evidence that improved lung function with once-daily QVA149 translates into greater relief of breathlessness and improved patient-reported outcomes, concluded Dr. Mahler.

CPAP in CVD and OSA Does Not Significantly Improve Cardiovascular Biomarkers

Written by **Emma Hitt, PhD**

Patients with cardiovascular disease (CVD) and moderate to severe obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP) and standard CV care demonstrated a small, nonsignificant decrease in fasting blood glucose and HbA1C levels, compared with patients that were randomized to standard care only. Emma Heeley, PhD, The George Institute, Sydney, Australia, presented data from a substudy within the Sleep Apnea Cardiovascular Endpoints Study [SAVE].

Evidence from observational studies suggests that there is an association between CVD and OSA [Loke YK et al. *Circ Cardiovasc Qual Outcomes* 2012]. OSA can lead to oxidative stress, sympathetic hyperactivity, and nocturnal episodic hypertension, causing endothelial dysfunction, hypertension, and altered glucose and lipid metabolism. These factors can lead to coronary artery or cerebrovascular disease and other CV events. The substudy (n=500) tested the hypothesis that 6 months of CPAP treatment would improve biomarkers of CVD risk, such as blood glucose, HbA1C, blood lipid level, C-reactive protein (CRP), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in patients with CVD and OSA, who were participating in the substudy of the SAVE trial.

SAVE is an ongoing, international, prospective, multi-center, open-label, randomized controlled trial. Patients with CVD and diagnosed with moderate to severe OSA (n=2500) received a 1-week sham CPAP treatment and were then randomized to receive standard CV care only, or CPAP treatment plus standard care. Patients received follow-up care at 1, 3, and 6 months thereafter. When the main trial completes in 2016 patients will have an average follow up of 4.5 years.

Prior to the study, patients were screened with overnight oximetry and nasal pressure tests. Patients were excluded from the study if they did not have CVD, or if they had an oxygen desaturation index (ODI) <12, an Epworth sleepiness scale score (ESS) >15, or Cheyne-Stokes respiration. Patients were also excluded if their average adherence to the 1-week CPAP sham was <3 hours per night.

The main SAVE trial has currently recruited 90% of the required sample size, the average adherence to treatment in the CPAP arm is currently about 4 hours/night at 6 and 36 months post randomization. The primary endpoint of the main SAVE study is a composite of CV events, including CV death, myocardial infarction, stroke, and hospitalization for CV-associated events. Secondary endpoints included revascularization procedures, types of CV events, blood pressure, new onset atrial fibrillation, new onset diabetes, daytime sleepiness, and quality of life. Dr. Heeley also presented data from the SAVE substudy, which evaluated CV biomarkers at 6 months.

Patients treated with CPAP experienced a small decrease in blood glucose levels and HbA1C from baseline, as compared with patients that received standard care alone. This effect was more pronounced in individuals with an average nightly CPAP adherence of ≥4 hours. In addition, patients treated with CPAP demonstrated a small decrease in total cholesterol and LDL cholesterol from baseline, as compared with the control arm. There was no apparent difference in CRP, or NT-proBNP levels in either study arm.

Dr. Heeley pointed out that in the intention-to-treat analysis of the substudy none of the changes in CV biomarkers at 6 months between the active and control groups were statistically significant; however, a regression analysis of the change in fasting blood glucose levels, showed a significant CPAP treatment effect with increasing severity of OSA in participants who used the therapy ≥4 hours/night. This finding suggests that CPAP treatment has, at best, only small effects on the traditional biochemical markers of CV risk in OSA, however multiple pathways may be involved in the genesis of CV events in OSA, and even small gains in traditional risk markers may be important and have an additive effect. The SAVE trial is still ongoing to determine if CPAP treatment may play a role in reducing heart attack and stroke in CVD patients.

CPAP Reduces BP in Patients With Resistant Hypertension and Obstructive Sleep Apnea

Written by **Phil Vinall**

In a randomized clinical trial conducted in Spain, blood pressure (BP) in patients with resistant hypertension (RH) and obstructive sleep apnea (OSA) was significantly and

clinically reduced following treatment with continuous positive airway pressure (CPAP). In those patients with good adherence to CPAP therapy, a significant percentage recovered their normal nocturnal dipper pattern and/or reversed their riser pattern. Miguel Ángel Martínez-García, MD, PhD, University and Polytechnic La Fe Hospital, Valencia, Spain, presented the results of the HIPARCO study (Hipertensión Arterial Resistente Control con CPAP).

The objective of this multicenter study was to evaluate the effect of CPAP treatment on the BP levels and nocturnal BP pattern in patients with OSA and RH. Patients with RH and confirmed OSA were randomly assigned to usual medical therapy (n=96) or medical therapy plus tritated fixed CPAP pressure (n=98) for 12 weeks. Patients with 24-hour BP >130/85 mm Hg (determined by ambulatory blood pressure monitoring [ABPM]), an apnea-hypopnea index >15, and with at least an 80% adherence to antihypertensive drug treatment were included in the study. The prevalence of OSA was 82.7% in this population. Patients were monitored at 2, 4, 8, and 12 weeks for CPAP and antihypertensive drug adherence, changes in body mass index (BMI), and new cardiovascular (CV) events. At the 12-week visit, patients underwent a second 24-hour ABPM. All randomized patients independent of their use or not of CPAP were included in the intention-to-treat (ITT) analysis and those patients with a good adherence to CPAP (≥4 hours of CPAP; 68% of randomized patients) use were included in the per protocol (PP) analysis.

Demographics and baseline characteristics were similar in both treatment groups. Mean BMI was 34.1±5.4 kg/m^2; mean number of antihypertensive drug used was 3.8±0.9; 21.4% of participants had past CV events; mean 24-hour BP was 144.2±12.5/83.0±10.5 mm Hg. More than 70% of patients had a nondipper (42.8%) or a riser nocturnal (31.4%) BP pattern. Almost 95% of the patients were on diuretics.

In the ITT analysis, the use of CPAP significantly reduced diastolic (p=0.005) and mean BP (p=0.016) compared with the control group and was associated with a near-significant reduction in 24-hour systolic BP (p=0.09). The reductions (about 3 mm Hg), were clinically relevant. In the PP analysis (only those patients with good CPAP compliance), CPAP use significantly decreased systolic BP, diastolic BP, and mean BP by 4 to 5 mm Hg (p=0.01, p=0.001, and p=0.001, respectively).

The decreases in BP levels were more pronounced during the night especially in those patients with better tolerance to CPAP.

The probability of recovering the dipper pattern and reversing the riser pattern was significantly greater (p≤0.03) in both the ITT and PP analysis in those patients allocated to the CPAP arm. Moreover there was a positive and linear relationship between the number of hours of CPAP use and the decrease in 24-hour BP values, both BP diurnal and nocturnal values. The presence or absence of daytime hypersomnolence, sex, age, years from RH diagnosis and BMI had no impact on treatment effectiveness.

Prof. Martínez-García would like to see future long-term studies that analyze the effect of CPAP on the incidence of CV events or death and BP treatment in these patients with RH and OSA.

Effects of Obesity on COPD

Written by Lori Alexander

The impact of obesity on many chronic diseases is well known, but the effect of obesity on clinical outcomes for people with chronic obstructive pulmonary disease (COPD) is less clear. The number of people with COPD who are obese is expected to increase in line with the obesity pandemic, making it essential to gain a better understanding of the effects of obesity on COPD.

Although classically considered a wasting disease, a link between COPD and obesity is becoming increasingly recognized, and it may influence clinical diversity in COPD, said Frits M. E. Franssen, MD, PhD, CIRO+, Center of Expertise for Chronic Organ Failure, Horn, The Netherlands. Data on the prevalence of obesity in COPD have conflicted, with some studies showing a higher prevalence among patients with COPD and others showing a lower prevalence [Vozoris NT, O'Donnell DE. *Can Respir J* 2012; Montes de Oca M et al. *Respir Med* 2008; Steuten LM et al. *Prim Care Respir J* 2006; Eisner MD et al. *Respir Res* 2007]. Low levels of physical activity have been consistently reported for patients with COPD, and this may contribute to weight gain.

> Increasing evidence suggests a relationship between visceral adipose tissue dysfunction and the pathophysiology of COPD.

Contrary to expectations, obesity is not necessarily associated with worse patient-related outcomes in COPD, said Prof. Franssen. He pointed to an early study in which the risk of mortality was evaluated in obese and normal-weight patients with COPD [Landbo C et al. *Am J Respir Crit Care Med* 1999]. The relative risk of all-cause mortality was increased for obese patients with mild or moderate COPD compared with normal-weight patients. However, in contrast to patients with mild and moderate COPD, among patients with severe disease, the risks of all-cause and COPD-related mortality were lowest for obese patients. These findings are referred to as the obesity paradox.

Studies have also found different effects of obesity on dyspnea. In one study, obese patients with COPD reported increased dyspnea and poorer health-related quality of life