“LATE BREAKING RESULTS OF CARDIOVASCULAR RANDOMISED CONTROLLED TRIALS IN OBSTRUCTIVE SLEEP APNEA ”Co-Chairs: Doug McEvoy and Susan Redline

This symposium brought together epidemiologists, clinical trialists, sleep medicine physicians and cardiologists to discuss the readiness, potential impact, and early results of randomized controlled trials (RCTs) designed to address the role of sleep apnea treatment in mitigating cardiovascular disease.

Dr. Redline introduced the symposium by reviewing the role of RCTs in producing high level evidence needed for patient and provider decision making. The high prevalence of sleep apnea, its substantive co-morbidity, heterogeneity of patients, and growing availability of diverse interventions support the need for RCTs. Although there are challenges related to meeting patient recruitment and retention goals, choosing appropriate control interventions, and changing community equipoise, there are also growing international experience, core laboratories and informatics tools to leverage to overcome such challenges. The International Collaboration of Sleep Apnea Trialists (www.incosact.org) was organized to promote sharing of tools and expertise to further international collaborative trials.

Dr. John Stradling discussed the MOSAIC study, conceived in 2004, started in 2006, and published in 2012, which showed, in a conventional RCT, that patients with newly diagnosed OSA, judged minimally symptomatic, did not appear to derive vascular benefit from 6 months of CPAP in terms of the components of a vascular risk score (including blood pressure, cholesterol, left ventricular hypertrophy, amongst others) despite a clear reduction in subjective and objective sleepiness. However a subset of this study showed that endothelial function, measured by flow mediated dilatation, did improve significantly in the active arm. To explore potential mechanisms of vascular damage, there group is using an alternative to the traditional RCT whereby CPAP is withdrawn in patients with OSA already on CPAP. He reported that compared to continued CPAP, 2 weeks of CPAP withdrawal results in adverse effects on blood pressure, BP, heart rate, flow mediated dilatation, markers of cardiac repolarization and circulating microparticles.

Dr. Miguel Angel Martinez-Garcia reported on results of the “HIPPARACHUS” study, a study from the Spanish Sleep Network, which was designed to evaluate the role of CPAP in the management of resistant hypertension. He reported that 24 hour blood pressure levels were reduced by 3 mmHg after 3 months of CPAP use among 194 patients with resistant hypertension and an AHI > 15, with larger effects observed for nocturnal values. CPAP use of at least 4 hours per day was associated with reductions in blood pressure of 4 to 5mmHg. The results supported the use of CPA for patients with resistant hypertension, and further noted the value of higher levels of CPAP adherence.

Dr. Daniel Gottlieb presented the primary outcome of the NHLBI-funded HeartBEAT Study, a 12-week randomized clinical trial comparing the effects of CPAP, oxygen and an education control intervention on markers of cardiovascular risk. Patients at high risk of cardiovascular disease were screened for the presence of obstructive sleep apnea (OSA), and 318 patients with an AHI of 15-50 were randomized to one of the three treatment arms. Treatment of OSA with CPAP, but not nocturnal supplemental oxygen, resulted in a significant reduction in 24-hour mean arterial pressure by approximately 3 mmHg at 12 weeks despite overall modest levels of CPAP use.

Dr. Emma Heeley presented the design and initial findings from the “Sleep Apnea cardioVascular Endpoints (SAVE) study,” an ongoing, large international trial designed to determine if CPAP treatment for mild-moderate OSA patients with existing CVD will reduce

future heart attack and strokes. To date SAVE has recruited 2300 of 2500 participants, with its primary findings expected to be presented in 2016. An intention-to-treat analysis of the cardiovascular biomarker substudy (n=512) showed that none of the changes in blood lipids, glucose, HbA1C, CRP and pro-BNPat 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 for at least 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 cardiovascular events in OSA, and even small gains in traditional risk markers may be important and have an additive effect.

Dr. Eldrin Lewis concluded the symposium by providing a cardiolovascular trialist's perspective on the topics. He noted that there has been impressive progress in understanding the epidemiology, physiology, and basic science of sleep apnea and cardiovascular disease. Transitions to clinical trials will be important in moving the sleep field into the mainstream of management of CVD and should go beyond use of surrogate outcome measures (e.g., change in AHI) to those that are clinically meaningful such as: a) patient reported outcomes (e.g., sleepiness measures, quality of life, depression), b) exercise capacity, and c) major adverse cardiovascular events (e.g., death, myocardial infarction, heart failure progression, and stroke). Surrogate outcomes also may not reflect "off target" effects of the intervention; examples in cardiovascular literature of RCTs that demonstrated harm with "hard endpoints" despite favorable surrogate outcomes were noted. He recommended that future designs should: a) move forward with humility realizing the uncertainty of optimal treatment and equipoise that exists, b) challenge the norms so that the entire sleep population is eligible for study, and c) establish meaningful endpoints. Accomplishing these traits in the new sleep apnea trial will change the practice of medicine and greatly expand the understanding of management of these patients with concomitant CV disease and sleep disordered breathing.