

The sleep apnea cardiovascular endpoints (SAVE) trial: Rationale and start-up phase

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ABSTRACT

The sleep apnea cardiovascular endpoints (SAVE) study (Clinical Trials Registration Number: NCT00738170) is an academic initiated and conducted, multinational, open, blinded endpoint, randomised controlled trial designed to determine whether treatment of obstructive sleep apnea (OSA) with continuous positive airways pressure (CPAP) can reduce the incidence of serious cardiovascular events in patients with established cardiovascular disease. The answer to this question is of major importance to populations undergoing ageing and lifestyle changes all over the world. The SAVE study brings together respiratory, sleep and cardiovascular clinician-scientists in a unique interdisciplinary collaborative effort with industry sponsors to conduct the largest and most ambitious clinical trial yet conducted in the field of sleep apnea, with a global recruitment target of 5000 patients. Following its launch in Australia and China in late 2008, SAVE has now entered a phase of international expansion with new recruitment networks being established in New Zealand, India and Latin America. This article describes the rationale for the SAVE study, the considerations behind its design, and progress thus far in establishing the recruitment network. The report emphasises the important role that Chinese sleep and cardiovascular investigators have played in the start-up phase of this landmark international project.

Key Words:

obstructive sleep apnea; continuous positive airways pressure; sleep apnea cardiovascular endpoints (SAVE) study

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Rationale for the SAVE study

Obstructive sleep apnea (OSA) was first widely recognised as a clinical disorder in the 1970s. OSA is characterised by episodic, complete or partial upper airway obstruction during sleep which leads to sleep fragmentation and intermittent hypoxaemia, tachycardia and surges in systemic and pulmonary arterial blood pressure. In 1981, nasal continuous positive airway pressure (CPAP) was shown to be a highly effective, low-risk treatment for OSA patients (1). The major focus of treatment until now has been to relieve patients of debilitating daytime sleepiness and socially

disruptive snoring. However, over the last two decades, there has been increasing evidence of a possible causal relationship between OSA and cardiovascular disease. A number of pathways have been proposed by which night-time physiological disturbances in OSA patients might lead to cardiovascular disease or cardiovascular events (Fig 1).

Experiments in animals exposed to patterns of intermittent hypoxia similar to those experienced by patients with OSA have shown sustained elevations in blood pressure, central nervous system damage, and abnormalities of glucose and lipid metabolism (2-5). Clinical observational and case-control studies in patients have shown that OSA appears to be independently associated with hypertension, glucose dysregulation and ischaemic heart disease and cerebrovascular disease (6-10). These observations have been supported by the results of several large population surveys which have also shown a possible link between OSA and cardiovascular morbidity (11-14) and mortality (15-17). Short-term CPAP treatment intervention studies in OSA patients have shown

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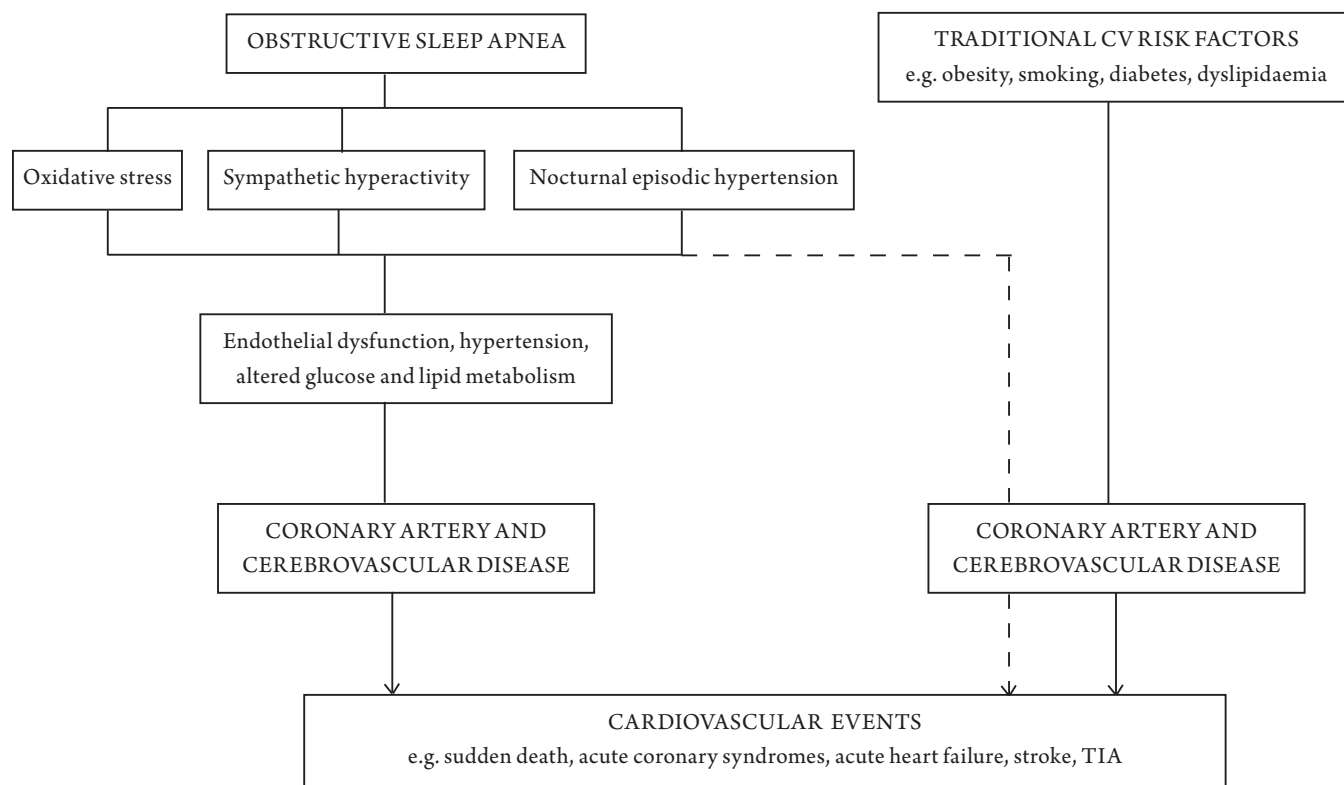


Fig 1. The Sleep Apnea cardiovascular Endpoints (SAVE) trial

small reductions in systemic (18,19) and pulmonary artery pressure (20,21), and improvements in some other biomarkers of cardiovascular risk (22), although not all such treatment intervention studies have been positive (23).

Thus, the evidence has clearly been mounting that OSA may increase the risk of premature cardiovascular disease including myocardial infarction and stroke, and that treatment of OSA may reduce these risks. However, the ultimate test of whether a pathophysiological disorder such as OSA causes premature cardiovascular disease and whether treatment of the disorder reduces cardiovascular risk, requires long-term, large-scale, randomised controlled trials that compare the incidence of “hard” cardiovascular outcomes in patients who are treated for OSA and those who are not. This point has been emphasised in recent leading editorials and scientific consensus statements on the topic (24,25). For example, the 2008 joint American Heart Association and American College of Cardiologists Foundation Scientific statement on sleep apnea (25) concluded that the observational nature of most of the evidence and the possibility of residual confounding by visceral obesity weakened the overall case in favour of a causal link between OSA and cardiovascular disease. This statement concluded that long-term properly designed intervention studies showing benefit from OSA treatment are missing and this lack of evidence is

limiting progress in this field. The SAVE trial (Clinical Trials Registration Number: NCT00738170) has been designed to help fill this evidence gap.

Background planning, study design and trial management

Planning for the SAVE trial began in 2006. An academic partnership was formed between Australian sleep and respiratory clinician scientists at the Adelaide Institute for Sleep Health (AISH), Flinders University, and cardiovascular clinical epidemiologists at the George Institute of Global Health at the University of Sydney, to prepare the ground work for the trial. The George Institute, which has previously conducted a number of large-scale international clinical trials in cardiovascular medicine (e.g. PROGRESS, ONTARGET/TRANSCEND, ADVANCE, INTERACT), provided the necessary expertise and research infrastructure to mount a trial of this size. The AISH had considerable experience in clinical sleep research and, with the assistance of the Australasian Sleep Trials Network, provides the necessary expertise in the areas of sleep apnea diagnosis and CPAP treatment. An untied priming grant was provided by the Respiroics Foundation (USA) in late 2005, to begin a feasibility and scoping exercise

to determine the best way to proceed in the conduct of SAVE. With these funds, extensive discussions were conducted internationally amongst sleep, respiratory and cardiovascular investigators and, with additional equipment grants from the device companies Compumedics and ResMed, a preliminary study was conducted in Shanghai to test the validity of a simple screening device for diagnosing OSA in patients entering the trial. Work then began on the final study design and research plan, and a major untied start-up grant was provided by the Respicronics Foundation to develop and launch the study.

It was decided that the study would be a randomised control trial of CPAP treatment in OSA patients focussing on “hard” cardiovascular endpoints such as myocardial infarction and stroke, rather than confined to surrogate markers of cardiovascular risk such as blood pressure, lipids and glucose metabolism. The rationale for this decision was twofold. First, we believed that the results of such a trial would ultimately have a much greater impact on clinical decision making than another trial focussing on known secondary markers of cardiovascular risk. Secondly, the pathogenic pathways whereby OSA could lead to CV events are likely to be multiple and the relative importance of one mechanism over another is unknown. Thus, we considered an approach that measured the outcome of CPAP treatment on a composite of downstream cardiovascular events, and which did not assume a dominant mechanism or mechanisms for increased cardiovascular risk, was preferable. Having made this decision, there were four important remaining questions. (i) Would the study be best designed as a primary or secondary prevention RCT? (ii) How and where would the patients be recruited? (iii) Should the diagnosis of OSA be made using an ambulatory screening device or would it require hospital sleep laboratory facilities? (iv) What were the important ethical considerations in randomising approximately half the OSA patients to no CPAP treatment for several years? and (v) How would reasonable levels of adherence to CPAP treatment be guaranteed, recognising that most of the patients enrolled in this the trial were likely to be ‘minimally sleepy’ or ‘not at all sleepy’, and therefore, may perceive relatively little symptomatic benefit from the treatment? Also, each patient would need to be followed for several years.

Primary versus secondary prevention trial design

Because of the relatively high cardiovascular event rates amongst patients who have established cardiovascular disease, the numbers of patients that need to be enrolled in a secondary prevention trial are generally in the order of 20-30% of the number needed for a primary prevention trial. While a secondary prevention trial design may target somewhat different pathogenic mechanisms for cardiovascular disease than a primary prevention study (Fig 1), it nevertheless has the

potential to provide highly relevant information with which to inform clinical practice and reduce cardiovascular morbidity and mortality. Furthermore, it increases the overall feasibility of successfully completing such a trial, given the smaller number of patients and shorter period of follow-up required, and thus, ultimately, lower overall trial cost.

Patient recruitment – where and how?

A secondary prevention trial of OSA treatment requires access to a large number of patients with co-existing cardiovascular disease and OSA who are willing to be entered with a 50:50 chance of being allocated to active OSA treatment or usual care control. It was considered that this would not be easily achieved by relying solely on patients referred to sleep medicine services. As well as the numbers of patients referred to sleep services being lower in comparison to the numbers referred to cardiovascular clinics, it is likely that the proportion of sleep clinic patients with co-existing cardiovascular disease is likely to be relatively low (ie in the order of 10% (6)). Even more important, however, is that sleep clinic patients will, in the main, be symptomatic and expect to be offered OSA treatment. The alternative method of recruiting patients directly from cardiovascular clinics is more attractive, although it has its own challenges. It is known that the prevalence of OSA is about 30 to 60% in high cardiovascular risk populations (25-29). Thus, cardiovascular clinics are potentially a rich source of patients for SAVE. However, we were aware that this would either require cardiovascular clinician researchers to develop new skills in sleep apnea diagnosis and CPAP treatment or for respiratory/ sleep and cardiovascular physicians to form strong collaborative working relationships at the local site level. In the end, it was decided to invite both sleep/ respiratory and cardiovascular clinicians to participate in the study, to provide training and support in sleep diagnostics and CPAP therapy where needed, and to encourage collaboration between the medical disciplines at national and local hospital levels.

Diagnosis of OSA - ambulatory sleep apnea monitor versus in-laboratory polysomnography (PSG)

It has become apparent to experts in the sleep field (30) that in-laboratory polysomnography (PSG) is not a cost-effective method to screen and diagnose OSA large numbers of subject that are required for a study such as SAVE. As well as it being a high-cost and labour intensive test to perform, there is considerable cost and effort required to standardise PSG recording and scoring techniques between laboratories (or centralise scoring), which in a study with multiple sites, was considered prohibitive. Furthermore, we were aware that many of our potential recruitment sites in China did not have

access to PSG and many Australian sites with PSG facilities were already heavily booked with clinical work. There has been increasing evidence that simplified home screening devices can be used to identify cases of at least moderate-severe OSA with a high degree of certainty, at least in populations with a high pre-test probability of disease. Since the prevalence of OSA in the proposed study population (i.e. patients with established coronary- or cerebro-vascular disease) was likely to be high, it was decided to validate a simple, automated 2-channel (oximetry and nasal pressure) screening device (the ApneaLink, ResMed, Sydney, Australia) in a high cardiovascular risk population in China with the view to using this device in the main study. Chinese and Australian clinician scientists collaborated on this validation study which was completed in Shanghai in early 2008. It was found in 143 high cardiovascular risk patients that the automatically calculated oxygen desaturation (oximetry) and apnea-hypopnea (nasal pressure) indices had equally high diagnostic accuracy for moderate-severe OSA when compared with full PSG simultaneously performed in the patients' homes (Gantner et al *Respirology* in press). ApneaLink Oximetry had a lower technical failure rate (e.g. loss of signal because of sensor displacement) than nasal pressure recordings making oximetry the preferred primary diagnostic method for identifying OSA patients for SAVE. The nasal pressure trace is used to exclude patients whose predominant pattern of sleep disordered breathing pattern is symmetrical waxing and waning of flow indicating Cheyne-Stokes respiration.

Ethical issues

The main ethical issue relevant to the SAVE study relates to the withholding of CPAP treatment in approximately half the patients who screen positive for OSA, when they may stand to benefit from reduction in daytime sleepiness, and improved driving safety and quality of life with therapy. Since patients in SAVE are recruited from cardiovascular clinics, almost all participants will be unaware of having had OSA prior to the SAVE screening diagnostic evaluations. While previous studies have shown that the great majority of patients with co-existing cardiovascular disease and OSA have little to no daytime symptoms, to minimise any safety concerns it was decided to exclude patients who held a commercial drivers, who demonstrated marked daytime sleepiness (defined as Epworth Sleepiness Scale score > 15), or who reported a fall-asleep accident or near miss accident in the 12 months prior to enrolment. An independent Data Safety Monitoring Board (DSMB) was established to monitor the rates of self-reported accidents in the CPAP-treated and non CPAP-treated groups at regular intervals during the course of the study. At the time of enrolment, all patients are given a full explanation of the possible symptomatic benefits of CPAP and given the option

to seek treatment outside the trial if they wish, and both the patient and their responsible physician must be comfortable about them being randomly allocated to CPAP treatment or no CPAP treatment.

Long term CPAP adherence

It was considered that adherence to CPAP therapy might be a significant problem in a long-term study of several years duration, particularly considering that the majority of subjects were likely to report little or no daytime sleepiness and therefore would be unlikely to experience significant symptomatic benefit. In addition it is known from clinical studies that as many as 30% of sleep apnea patients refuse CPAP treatment outright or in the first few weeks of therapy (31). To exclude those patients who were unwilling or unlikely to adhere to CPAP therapy, we decided to use a one-week sham CPAP run-in phase. Sham CPAP is designed to deliver only a very low, non-therapeutic pressure to the airway, and previous clinic studies have shown similar short-term adherence levels with sham and active CPAP. We argued that if patients were sufficiently motivated and able to wear a CPAP mask for a minimum average period of 3 hours per night, they would likely comply long-term with active treatment during the trial.

Trial management

The trial is led by an Executive Committee who has overall responsibility for the design and proper conduct of the study. Day-to-day operational matters are decided by an Operations Committee. A Principal Investigator (PI) for each participating country or region advises the Executive and Operations Committees on relevant national regulatory issues, clinical practice standards, and patient recruitment strategies. In China, the national PI is assisted by a China PI committee consisting of a small group of experts in sleep and respiratory medicine and stroke and cardiovascular medicine. A DSMB has regular oversight of the study and is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the trial. The DSMB will undertake 2 planned interim analyses and will provide recommendations about stopping or continuing the trial to the trial Executive Committee. Further information regarding the structure and composition of the various SAVE trial committees is provided in Appendix A

Progress during the start-up phase

In China, a total of 40 sites were sequentially initiated over the period from November 2008 to May 2010, and have successfully recruited patients. A total of 15 sites were established in Australia and New Zealand over the same

period. Start-up meetings were conducted in China and Australia in June and October 2008, respectively, at which training in sleep diagnostics, CPAP treatment and patient recruitment and good clinical trial practice was undertaken. This has been reinforced by one-on-one training of site coordinators by SAVE trial clinical research associates at the local hospital level.

As of 2nd July 2010, 590 patients had been randomised in the trial, 477 in China, 102 in Australia and 11 in New Zealand. The average rate of patients recruited per month per active site has varied from about 0.8 to 1.0, with a very large variation in recruitment efficiency between sites. These recruitment rates are lower than initially envisaged and major efforts are currently underway to lift the recruitment rate at individual sites wherever possible, and to expand the recruitment network to include India, Latin America and the United Kingdom.

The impediments to recruitment have varied from time to time, between sites and between countries. The major difficulty experienced by investigators with recruitment relates to the relative complexity and time consuming nature of the screening process. A decision was made in early 2009 to reduce the amount of unnecessary data collection and data entry for investigators. Notwithstanding these changes, the study requires a fairly high level of technical competence and intervention (e.g. sleep apnea diagnosis, sham CPAP run-in, and therapeutic CPAP implementation) that is unavoidable. Access to a suitable high cardiovascular risk patient pool is a problem in some sites but not others. Generally, recruitment rates are highest at sites which have good access to high cardiovascular risk patients and have a highly motivated and well organised study coordinator who has sufficient time to devote to the trial work. Early trends show that average CPAP adherence rates are in the range of 4.5 to 5 hours per night at 6 months, which compares favourably with previously reported CPAP adherence rates in symptomatic clinic population (31). This excellent result is likely due to a combination of factors, including: use of a sham run-in phase to exclude subjects unable to tolerate mask treatment; a study population which by virtue of the serious nature of their cardiovascular problems is motivated to comply with the study procedures; and the intensive training and support in CPAP therapy that has been provided to site investigators, which has led to a high level of proficiency in CPAP despite, in many cases, little or no previous investigator experience in this field.

Summary and conclusions

The SAVE trial is by far the largest and most ambitious clinical trial yet conceived in the field of sleep apnea research. The trial has been made possible by the early generous support of industry. However, SAVE was independently conceived and

designed by academics in sleep and cardiovascular medicine who have complete autonomy with respect to the conduct of the study and analysis of trial data. The SAVE trial is in its early phase but has already attracted considerable international interest and support from leaders in sleep, respiratory and cardiovascular medicine, with over 600 patients enrolled to date. If the results prove that the treatment of OSA reduces the risk of future serious adverse cardiovascular events in high cardiovascular risk patients, it will open the door to a significant new form of therapy for cardiovascular disease risk reduction, which will have global reach. However, a concerted and sustained international effort will be required for the trial to reach a successful conclusion and ultimately, this will hinge on the dedication and enthusiasm of the individual investigators and participating centres to recruit and follow-up sufficient numbers of high-risk patients. Chinese investigators have played a pivotal early role in the study and China will soon have enrolled 500 patients into the study. It is hoped that as the international network expands China will continue to play a major role in the SAVE trial.

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APPENDIX A

SAVE Executive Committee

RD McEvoy (PI), CA Anderson (co-PI), RR Grunstein, B Neal, S Redline, L Palmer, SG Huang, NS Zhong, JG Wang, J Hedner, G Lorenzi-Filho, N Ramakrishnan.

SAVE Operations Committee

E Heeley (Chair), RD McEvoy, CA Anderson, Antic NA

Data Safety Monitoring Board

GG Jennings (Chair), L Wong, G Marks, S Heritier (statistician)

China PI Committee

NS Zhong (Chair), BY Chen, QY He, SG Haung, JG Wang, H Yining

Reference

- Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;1:862-65.
- Li J, Thorne LN, Punjabi NM, Sun CK, Schwartz AR, Smith PL, et al. Intermittent hypoxia induces hyperlipidemia in lean mice. *Circ Res* 2005;97:698-706.
- Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, et al. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. *Am J Respir Crit Care Med* 2007;175:851-7.
- Fletcher EC, Lesske J, Qian W, Miller CC 3rd, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension* 1992;19:555-61.
- Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, et al. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 2004;27:194-201.
- Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046-53.
- Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive Sleep Apnea as a Risk Factor for Stroke and Death. *N Engl J Med* 2005;353:2034-41.
- Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc* 2008;5:207-17.
- McArdle N, Hillman D, Beilin L, Watts G. Metabolic risk factors for vascular disease in obstructive sleep apnea: a matched controlled study. *Am J Respir Crit Care Med* 2007;175:190-5.
- He QY, Feng J, Zhang XL, Liang ZA, Huang SG, Kang J, et al. Relationship of daytime blood pressure and severity of obstructive sleep apnea among Chinese: a multi-center investigation in China. *Chin Med J (Engl)* 2010;123:18-22.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378-84.
- Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163:19-25.
- Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* 1997;157:1746-52.
- Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010;182:269-77.
- Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep* 2008;31:1079-85.
- Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6:e1000132.
- Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;31:1071-8.
- Barbé F, Durán-Cantolla J, Capote F, de la Peña M, Chiner E, Masa JF, et al. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010;181:718-26.
- Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007;50:417-23.
- Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled crossover study. *Eur Heart J* 2006;27:1106-13.
- Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;165:152-8.
- Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007;176:706-12.
- Kohler M, Ayers L, Pepperell JC, Packwood KL, Ferry B, Crosthwaite N, et al. Effects of continuous positive airway pressure on systemic inflammation in patients with moderate to severe obstructive sleep apnoea: a randomised controlled trial. *Thorax* 2009;64:67-73.
- Somers VK. Sleep -- A New Cardiovascular Frontier. *N Engl J Med* 2005;353:2070-3.
- Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008;52:686-717.
- Peker Y, Kraiczki H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J* 1999;14:179-84.
- Moore T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in women: occurrence and association with coronary artery disease. *Am J Med* 1996;101:251-6.
- Moore T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. *Chest* 1996;109:659-63.
- Lee CH, Khoo SM, Tai BC, Chong EY, Lau C, Than Y, et al. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest* 2009;135:1488-95.
- Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. *Prog Cardiovasc Dis* 2009;51:434-51.
- Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-8.