Editorial

The Sleep Apnea Cardiovascular Endpoints (SAVE) study: implications for health services and sleep research in China and elsewhere

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The results of the Sleep Apnea Cardiovascular Endpoints (SAVE) study were recently published in the *New England Journal of Medicine* (1). The study recruited 2,717 patients from 89 sites in seven countries. Chinese investigators played a pivotal role in the study with approximately 60% of trial participants recruited from 47 hospital sites. Eight of the top ten recruiting sites were in China including the study's top recruiting centre.

The study was first conceptualised in 2005 as a randomised controlled trial to provide high level evidence on the question of whether or not treatment of OSA would reduce the risk of cardiovascular (CV) morbidity and mortality. Studies in the previous decade had pointed to a possible causal relationship between OSA and CV disease (2). The observational co-cohort data pointed to a potentially large independent effect of OSA on CV risk and an observational study in Spain suggested that CPAP treatment of patients with severe OSA might substantially reduce that risk. However, as has been found in other areas of medicine, evidence derived solely from observational data or arguments of biological plausibility can be misleading, with subsequent randomised trials sometimes showing treatment to have either little or no benefit, or even harm. The lack of randomised trial evidence on clinically important CV endpoints such as stroke and myocardial infarction was thus considered to be impeding progress in this area of sleep and cardiovascular medicine. The SAVE study was undertaken to help fill this evidence gap.

The primary collaboration was between leading sleep researchers at the Adelaide Institute for Sleep Health, South Australia and stroke and cardiovascular epidemiologists at the George Institute for Global Health in New South Wales, Australia. The George Institute researchers had already established a stroke clinical trials network in China and a trials monitoring team in Beijing, which provided the initial structural framework for the study in China. A preliminary study was undertaken in Shanghai in 2007 to validate a simple diagnostic screening strategy for OSA (3). Several meetings were then held between the SAVE Steering Committee and Chinese key opinion leaders in respiratory, sleep and cardiovascular medicine. These meetings helped the Steering Committee refine the study protocol and confirmed that clinical equipoise existed regarding the study's primary question amongst clinicians in China and that the study's aims were relevant to the Chinese population and its health system. It seemed likely that significant numbers of patients could be enrolled in the study in China. The China network was then expanded by bringing together respiratory, sleep, CV clinicians and scientists in an inter-disciplinary collaboration (4). The main study was launched in Australia and China in late 2008 with industry and government sponsorship and the recruitment network subsequently expanded across 89 sites including in New Zealand, India, Spain, the USA, and Brazil with a total of 2,717 patients randomised by December 2013. Trial close-out occurred in January 2016. SAVE is the largest and most ambitious clinical trial yet undertaken in sleep apnea.

Adults aged between 45 and 75 years with moderate-to-severe OSA and coronary or cerebrovascular disease were

randomised, after a 1-week sham CPAP run in period, to CPAP treatment plus usual care or usual care alone. The primary composite endpoint included death from CV causes, myocardial infarction, stroke, and hospitalization for unstable angina, heart failure or transient ischemic attack. Secondary outcomes included other single disease and composite CV outcomes, health-related quality of life, OSA symptoms and mood. Participants had moderate-to-severe OSA but were minimally sleepy, and were approximately evenly divided between those with coronary artery disease and those with cerebrovascular disease. Eighty percent were male in keeping with the known increased risk of OSA and CV disease amongst men. In the CPAP group, average adherence was 3.3 hours per night, and the mean apnea-hypopnea index (AHI) on CPAP was 3.7 events per hour, which compared with 29.0 events per hour during the diagnostic sleep study. After an average follow-up of 3.7 years, there were 229 (17.0%) primary composite CV endpoints with CPAP treatment and 207 (15.4%) with usual care [hazard ratio with CPAP treatment, 1.10; 95% confidence interval (CI), 0.91 to 1.32; P=0.34]. There was no effect on any individual or other composite CV outcome and there was no evidence of heterogeneity of CPAP treatment effect when comparing Chinese versus non-Chinese participants. A pre-planned per protocol analysis, in which 561 patients with good adherence to CPAP therapy (≥4 hours per night) were compared with the same number of patients in the usual-care group matched by propensity scores, also showed no statistically significant benefit of CPAP treatment with respect to the composite primary outcome. However, there was a trend toward a lower risk of stroke for those with good CPAP adherence (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05), as well as a lower risk of the composite end point of cerebral events (hazard ratio, 0.52; 95% CI, 0.30 to 0.90; P=0.02). The intention-to-treat analysis showed that CPAP treatment significantly improved snoring, daytime sleepiness (mean between-group difference in the change from baseline in Epworth Sleepiness Scale score, –2.5; 95% CI, –2.8 to –2.2; P<0.001) and health-related quality of life. The percentage of patients with clinically relevant depression scores was 25% to 30% lower in the CPAP group, and there were approximately 20% fewer work days lost due to ill health amongst CPAP-treated patients.

How should we to interpret these findings; and what are the implications for clinical practice and future sleep apnea research in China and elsewhere?

Firstly, it must be acknowledged that the neutral result with respect to CV outcomes came as a surprise to a number of those involved in the planning and conduct of the SAVE study. As indicated above, observational data suggested that OSA in adults carried a markedly increased risk of adverse cardiovascular events, including sudden death; and that CPAP treatment might ameliorate that risk. Considerable discussion has occurred since publication of the SAVE primary findings as to the possible reasons for the neutral CV result.

A concern expressed in the accompanying editorial (5) and by other commentators was that, on average, patients assigned to CPAP used the treatment for only about half the night (i.e., 3.3 hours), raising the possibility that had they been able to use the treatment longer a treatment benefit may have been observed. We cannot entirely exclude this possibility. However, in designing the study we assumed that, because most CV patients with OSA report relatively little sleepiness, average CPAP adherence would be somewhere between 3.0 and 3.5 hours per night. As explained in the SAVE protocol paper (6), we calculated that this level of CPAP adherence would be sufficient to show at least a 25% relative risk reduction in the composite CV endpoint given the very strong association between OSA and CV risk in prior epidemiological studies. It is also important to note that the level of CPAP adherence achieved in the SAVE trial reflects current "real world" clinical experience in OSA patients with minimal daytime symptoms (7). It is noteworthy that similar average adherence levels were found between the various countries participating in the trial [CPAP hours/night, mean (SD): Australia 3.6 (2.54), Brazil 3.9 (1.85), China 3.1 (2.21), India 2.9 (2.12), New Zealand 3.9 (2.77), and Spain 3.5 (2.43)]. This we believe reflects the fact that with suitable training (as in the SAVE trial) doctors, nurses and technicians can quickly accumulate the skills and experience needed to successfully manage OSA. The difference in average adherence was only 0.5 hours between Australia, where clinicians had had almost 30 years of experience with CPAP treatment and China, where many of the sites had little to no prior experience in sleep apnea diagnosis or treatment. While patients with very severe sleepiness and very severe oxygen desaturation were excluded for the SAVE trial, in practice less than 5% of patients were excluded on these grounds. The SAVE result therefore is highly relevant to clinical practice in patients with CV disease and co-occurring OSA, globally.

Although China is sometimes rated as the world's largest

economy, many people who live in rural area are still very poor and are dependent on an income of less than a thousand US dollars per year. The results are particularly pertinent to China where sleep apnea clinical services are still being developed, and where the incidence and burden of cardiovascular disease is large and likely to increase greatly in the future because of an ageing demographic and increasing overweight and obesity. Relatively scarce health care resources need to be allocated wisely given the many competing demands on the Chinese health care system. The SAVE result suggests that CPAP treatment of OSA cannot be justified for CV risk reduction alone. The study, however, confirmed that CPAP treatment is beneficial for daytime sleepiness and quality of life; and it provided the first high-level evidence that CPAP treatment of OSA can reduce depression and improve work place productivity. Thus, it would seem reasonable to direct sleep apnea services toward symptomatic OSA patients. The preliminary SAVE validation study demonstrated the accuracy and practicality of using a simple ambulatory sleep test to diagnose OSA. And experience in the main trial showed that health professionals, including nurses and clinical scientists, can quickly become proficient in sleep apnea management, which fits with the results of previously published studies in Australia and elsewhere (8,9). If the Chinese investigators were to deploy this new knowledge and experience when designing new sleep services, it would undoubtedly enhance the reach, and the effectiveness and cost-effectiveness of these services.

There is clearly room for further research and clinical trials to examine the clinical importance of OSA in patients with CV disease. For example, trials to explore further whether OSA treatment will benefit patients with stroke or reduce the risk of atrial fibrillation; research to see whether specific patient characteristics or phenotypes can be identified that render some OSA patients more susceptible to adverse CV outcomes than others and therefore more amenable to beneficial treatment effects; and research to explore whether the types of neurobehavioral and quality of life benefits from CPAP treatment that were shown in the SAVE study will translate into fewer hospital admissions and lower overall health costs for patients with advanced CV disease. Hopefully, the experience and knowledge gained by Chinese investigators from working on the SAVE study will enthuse and equip them to join the international effort to address these important questions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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