Con: continuous positive airway pressure and cardiovascular prevention

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Evidence does not support the use of CPAP treatment to reduce cardiovascular morbidity and mortality http://ow.ly/PgEp30jDipB

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For the last two decades, evidence has been mounting that obstructive sleep apnoea (OSA) may be a cause of cardiovascular disease (CVD). OSA causes repeated acute falls in nocturnal arterial blood oxygen saturation, and rises in blood pressure and heart rate. These physiological changes, combined with the acute mechanical stress placed on the heart from the often very large negative pleural pressure swings during obstructed breathing, were postulated to provide the substrate necessary to induce acute events such as myocardial infarction, arrhythmias, acute heart failure, stroke and sudden cardiovascular death. Observational and case–control studies suggested that OSA is independently associated with daytime increases in some well-accepted markers of long-term cardiovascular risk such as hypertension [1, 2] and diabetes [3, 4], and other likely, yet clinically less well-accepted, markers such as endothelial dysfunction, lipid peroxidation (a marker of oxidative stress [5]) and insulin resistance. Also, community and sleep clinic cohort studies reported an association between OSA and adverse cardiovascular outcomes [6–9] that appeared to be independent of other well-known cardiovascular risk factors such as obesity, smoking, hypertension and diabetes. Furthermore, continuous positive airway pressure (CPAP) treatment studies lasting from a few weeks to several months found a reduction in blood pressure [10], and improvements in endothelial function [11] and insulin sensitivity [12]. Results of studies in animal models designed to mimic the conditions of OSA have tended to support these findings in humans [13, 14].

While strongly supportive of a possible causal link between OSA and CVD, not all the evidence has pointed in that direction. Firstly, after initial reports suggesting that CPAP treatment of OSA resulted in a large fall in mean blood pressure in hypertensive patients [15], the body of evidence from randomised controlled trials (RCTs) now points to a relatively small reduction of about 2–3 mmHg [10, 16], far less than that typically achieved with pharmacological agents [17], with recent studies suggesting that some CPAP-treated OSA patients may even have an adverse response, *i.e.* increase in nocturnal blood pressure [18]. RCTs of CPAP have also failed to show a consistent reduction in new-onset hypertension [19] or clinically significant improvements in blood lipid levels and blood glucose control in patients with hyperlipidaemia [20] and diabetes [21]. Some cohort studies have even suggested that in the elderly, OSA might reduce rather than increase cardiovascular mortality [22], and increasing OSA severity has been associated with reduced cardiac injury during acute myocardial infarction [23], findings postulated to be due to ischaemic pre-conditioning. For these reasons and that previous experience cautions against relying

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on biological plausibility and observational data to direct clinical care [24–26], research efforts have more recently been directed toward conducting RCTs of CPAP treatment that measure hard clinical outcomes such as myocardial infarction, stroke and cardiovascular death.

Foremost amongst these recent RCTs has been the Sleep Apnea Cardiovascular Endpoints (SAVE) study (n=2717) [27]. The results of this study, and several smaller RCTs that were recently combined with SAVE in a meta-analysis [28], have been neutral. Intention-to-treat analyses have shown no reduction in cardiovascular events despite several years of CPAP treatment in patients with moderate to severe OSA. While subanalyses in these trials comparing patients who used CPAP for >4 h per night with non-CPAP-treated patients have suggested possible benefit for myocardial infarction [29] and stroke [27], these results need to be treated with caution; group allocation is no longer random and healthy user effects could explain the differences. The neutral SAVE result was surprising (perhaps shocking) to many who have been researching or practising in this field for the last decade or more, and it is perhaps not surprising therefore that a spirited defence of previous data and intense scrutiny of the SAVE and other RCTs has occurred. However, before jumping to the conclusion that these recent RCTs must have been methodologically flawed and the results "wrong", it is worth remembering that: 1) randomised studies and meta-analyses of such studies remain the highest level of evidence available with which to direct clinical care and allocate scarce health care resources; 2) past experience shows that when RCT evidence becomes available, it is not uncommon to find that the magnitude of association reported previously in observational studies between a putative causative factor and CVD, and/or extent of benefit from treatment of that factor, had been overestimated; and 3) on occasions, it is unexpectedly found that treatment results in harm rather than benefit.

A range of specific criticisms have been raised concerning the design and conduct of SAVE, the largest of the OSA cardiovascular endpoint trials, including the selection of patients, type of diagnostic sleep study used, duration of follow-up and use of a composite cardiovascular endpoint. It has been suggested, for example, that Asian patients, who made up 60% of the study population, or those with established cardiovascular disease or older patients (mean age in SAVE was 60 years) who were minimally sleepy may not be representative of typical OSA patients or be expected to have a cardiovascular benefit from OSA treatment. We know of no evidence to support these hypotheses and refute the criticisms: Chinese people suffer equally from cardiovascular diseases and if anything, appear to have a greater propensity to develop OSA than other races; the age range of 45–75 years of SAVE participants corresponds to a period in the lifespan of high risk for both CVD and OSA; the relative risk reduction from most cardiovascular treatments (*e.g.* blood pressure-, glucose- and lipid-lowering pharmaceuticals) is similar for secondary and primary CVD prevention, and between different racial groups; and the great majority of CVD patients who are found to have OSA actually report little to no daytime sleepiness. The use of a simple screening instrument (ApneaLink; ResMed, San Diego, CA, USA) to diagnose and enrol OSA patients in SAVE was shown in a preliminary validation study [30] to accurately identify moderate to severe OSA patients and, as explained in the main SAVE trial report, strenuous efforts were made to exclude patients with predominant central apnoea. This approach to diagnosing and treating OSA has recently been shown by other groups to be noninferior to polysomnography-based diagnosis [31]. Finally, OSA has been postulated to lead to micro- as well as macrovascular disease, myocardial infarction, stroke, and nonfatal and fatal arrhythmias. The choice therefore of a composite primary cardiovascular endpoint in SAVE was very appropriate and similar to the approach used in trials investigating treatments for other diseases, such as diabetes or hypertension, that have multiple adverse cardiovascular effects.

We submit, therefore, that serious consideration needs now to be given to the possibility that 1) SAVE and the other accumulating RCT evidence on clinical outcomes correctly represents the overall picture with respect to OSA and cardiovascular risk, and 2) CPAP treatment, when given on top of other proven cardiovascular risk-reduction measures, is unlikely to reduce the risk of future cardiovascular events.

Although the results of RCTs and subsequent meta-analyses of such trials are the basis for evidence-based clinical decisions, it is also important to acknowledge the limitations of the RCT evidence. Because of the various patient selection criteria employed, the trials do have some limitations regarding their generalisability in sleep medicine practice. Therefore, it might be that in some patients with specific characteristics (*e.g.* severe OSA, excessive sleepiness and resistant hypertension), optimal adherence to CPAP therapy may reduce cardiovascular risk after all. No RCTs have been performed looking at the effect of CPAP on cardiovascular events in such a selected OSA population and it would be useful to do so, preferably using a sham control. However, it has to be stressed that it is now very difficult to perform RCTs using a sham control arm over several years (or even months) in symptomatic OSA patients because of ethical concerns.

Because average CPAP usage in trials such as SAVE has been rather modest, it has been argued that this might be the reason for the neutral results. SAVE was designed to detect a 25% relative risk reduction in

the primary composite cardiovascular endpoint, based on a metaregression of cohort studies that showed a remarkably strong dose-related association between apnoea–hypopnoea index (AHI) and adverse cardiovascular outcomes, and the anticipated reduction in OSA exposure from a conservative estimate of the average use of CPAP (3–3.5 h per night) [32]. While this level of CPAP adherence was achieved and sufficient cardiovascular events were accumulated in the trial to show a 25% relative risk reduction had it been present, there remains uncertainty about the exact "dose–effect" relationship between OSA (AHI) and cardiovascular outcomes. And at this point, it also has to be kept in mind that a smaller percent reduction in cardiovascular events from OSA treatment, such as is achieved with statin therapy, would still represent a significant advance in cardiovascular care. The difficult question therefore remains as to whether greater levels of CPAP use (and thus lower exposure to OSA) might actually result in a clinically meaningful reduction of cardiovascular events. It is commonly assumed that 4 h of CPAP per night is sufficient to produce some benefit for patients but in fact, there is no firm evidence for this threshold. Although the findings of recent meta-analyses of RCTs strongly support the notion that CPAP usage >4 h per night is associated with a clinically significant reduction in blood pressure [10], this cannot be directly extrapolated to fewer cardiovascular events without caution. A systematic review of currently available RCTs was unable to show any convincing evidence of benefit on cardiovascular events with greater CPAP use [28]. It is extremely laborious and difficult to assess the differential effects of different hours of CPAP usage in an RCT setting. Therefore, the question of how many hours of therapy per night might be required to reduce cardiovascular risk may only be resolved once a highly effective therapy for OSA (*i.e.* a drug) becomes available that is active for the entire night. Only then will it be possible to eliminate low treatment compliance as the reason for the failure of recent RCT trials to show a benefit of OSA treatment on cardiovascular outcomes. Unfortunately though, the ethical concerns of not treating symptomatic patients in an RCT over a longer period of time will remain.

What is the way out of the dilemma? Because patients with OSA often have multiple comorbidities such as obesity, diabetes mellitus and hypertension, maybe we should think more about a holistic approach to treatment in future trials [33]. Rather than focussing solely on the therapy for OSA, we need to answer the question, what is the optimal treatment regimen for such patients? Which combination of therapies leads to the maximal benefit in terms of improvement in quality of life and reduction of morbidity and mortality? There have been some recent attempts in this direction by also including weight reduction in RCTs, but the concept could be taken much further. There may also be a place for defining particular subtypes of OSA patients to enrol in new RCTs (*e.g.* asymptomatic or minimally symptomatic patients with severe OSA and resistant hypertension).

So, what does this all mean for daily clinical practice now? We have enough evidence from RCTs that patients with OSA syndrome should be treated for their symptoms, and this may also be associated with a significant improvement in mood and quality of life, and a minor reduction in blood pressure. However, at the moment, we do not have sufficient evidence that CPAP therapy also reduces the risk of cardiovascular events and thus, we should not treat patients solely to prevent vascular complications. Last but not least, we should start to think about a treatment strategy that addresses all relevant comorbidities in patients with OSA. Clinical guidelines should be updated accordingly.

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