Arch Bronconeumol. 2018;54(5):241–242

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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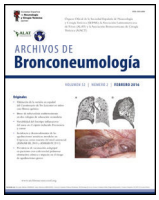

Editorial

Sleep Apneas and Cardiovascular Risk After Sleep Apnea Cardiovascular Endpoints Study (SAVE). What Next?☆

Síndrome de apneas del sueño y riesgo cardiovascular después del Sleep Apnea Cardiovascular Endpoints Study (SAVE). ¿Y ahora qué

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The Sleep Apnea Cardiovascular Endpoints (SAVE) Study[1] is one of the most important investigations into sleep apnea in recent times. Patients with established cardiovascular disease and sleep apnea–hypopnea syndrome (SAHS) were randomized to receive either conventional treatment or continuous positive airway pressure (CPAP) plus conventional treatment. The main objective was to determine if CPAP improved cardiovascular morbidity and mortality in this group of patients. The use of CPAP did not decrease the number of events in the intent-to-treat analysis of the main objective (a composite of cardiovascular death, myocardial infarction, stroke, admission for angina pectoris, congestive heart failure, stroke, and transient ischemic attack). In contrast, a significant improvement was reported in daytime sleepiness, quality of life, mood, and work productivity in patients who received CPAP.

The limitations and strengths of the study must be examined when interpreting the results. One of the most important limitations involves defining the presence of moderate-severe SAHS as a desaturation index greater than 12 (number of desaturations ≥4%/h), calculated using a screening device (Apnealink, ResMed). Although this simplified method is not the gold standard used in clinical practice, it fulfills the purpose of the trial: it would have been impossible to randomize 2717 patients in 7 countries and 89 different centers in a reproducible manner for centralized analysis without using a simple method. One thing we have learnt about simplified methods is that they can detect patients with significant SAHS in a large population of individuals. This diagnostic test is further limited by its inability to identify central events due to the absence of plethysmography bands. However, in this study, severe heart failure was an exclusion criterion, as was Cheyne–Stokes respiration. This minimized the inclusion of patients with central events, and treatment also was monitored by recording possible residual central events on the CPAP machine memory card.

The main limitation of the study, however, was CPAP adherence. Mean compliance was 3.3 h per night, so patients on average spent more than half the night without treatment. The per-protocol analysis of 561 of the 1346 patients in the CPAP arm (41%) found no improvement in more compliant patients (≥4 h/night), but it is unclear whether better compliance would have produced different results.

One of the strengths of the SAVE study is that it is the only SAHS study that has managed to randomize 2717 patients of different nationalities, while maintaining diagnostic and therapeutic uniformity over long-term follow-up. Furthermore, the study's sound methodology and robust data collection strengthen the author's conclusions.

Regarding the clinical application of the results, it is worth pointing out that the clinical characteristics of these patients differ in some respects from those usually seen in pulmonology and sleep clinics. The patients were non-obese, mostly Asian, with a mean age of 63 years, and generally asymptomatic. Consequently, the study conclusions do not significantly impact on our daily clinical practice, where patients of a different phenotype are usually seen: younger, more symptomatic, with a higher body mass index, etc. One of major implications of the study may be that, given the lack of improvement in the morbidity and mortality of the study patients, it does not seem justified to actively screen for SAHS among patients with vascular disease if they are symptom-free. Of course, specialists must continue to refer patients with suspected SAHS for further study, and those who require treatment should receive it according to current guidelines.

It must be remembered that the SAVE study was designed for secondary prevention, so the results should not be directly extrapolated to primary prevention. The patients' age and their established vascular disease could have minimized the positive effect of CPAP.

☆ Please cite this article as: Mediano O, Masdeu MJ, McEvoy D, Barbé F. Síndrome de apneas del sueño y riesgo cardiovascular después del Sleep Apnea Cardiovascular Endpoints Study (SAVE). ¿Y ahora qué. Arch Bronconeumol. 2018;54:241–242.

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The study patients may have been "survivors" who have developed compensatory mechanisms that make them more resistant to insult (the ischemic preconditioning theory). This observation raises questions that could constitute an important new challenge in research.

In the per-protocol analysis, CPAP did show a possible protective effect against new cerebrovascular events in the most compliant patients (OR: 0.52; 95% CI: 0.30–0.90; *P*<.02). Although this finding may have been influenced by confounding factors and should be regarded with caution, it suggests that the impact of SAHS on the heart and the brain may be different. Perhaps the heart, when exposed to insult over time, is capable of developing protective mechanisms while the brain is not, and therefore continues to be susceptible. In this respect, the SAVE study opens a wide range of possibilities for future research, signaling the way toward several lines of investigation.

Two positive outcomes of the study were that CPAP significantly improved patients' quality of life and fewer days were missed from work due to SAHS. The financial consequences of these results are not insignificant. Moreover, these results should compel us to rethink our attitude toward therapeutic interventions and to reassess our management of patients with a diagnosis of SAHS who can cope with their symptoms; these patients may benefit from a clear improvement in their activities of daily living.

Clinical trials are still in progress and no doubt will contribute revealing results to this field. The ISAAC study (NCT01335087), for example, has certain methodological differences from the SAVE study, and may provide additional information on the potential benefit of earlier application of CPAP after a cardiovascular event.

The SAVE study has contributed significantly to our current understanding of sleep apnea, and will help improve the clinical management of our patients, since it provides information on the effect of CPAP in a certain group of subjects, and points us toward new research lines for the future.

Reference

1. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al., SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919–31.