EDITORIAL

Cardiovascular Events in Obstructive Sleep Apnea — Can CPAP Therapy SAVE Lives?

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Obstructive sleep apnea is a common disorder that has been associated with an increased risk of cardiovascular disease.[1] Continuous positive airway pressure (CPAP) is frequently prescribed in patients with obstructive sleep apnea and is effective in reversing hypoxemia and upper airway obstruction. Meta-analyses of randomized trials have shown that CPAP therapy elicits significant reductions in systemic arterial pressure, and the effect is greater with higher adherence.[2,3] Observational studies have shown significantly fewer cardiovascular events in patients adherent to CPAP therapy than in those who are not adherent,[4,5] but the need for large trials has lingered.

The Sleep Apnea Cardiovascular Endpoints (SAVE) trial, the results of which are now reported in the *Journal* by McEvoy et al., is therefore an important and welcome addition to the field.[6] Patients with a history of coronary artery disease or cerebrovascular disease and moderate-to-severe obstructive sleep apnea were randomly assigned to receive CPAP plus usual care (CPAP group) or usual care alone (usual-care group). In the primary analysis performed in the intention-to-treat population (1346 patients in the CPAP group and 1341 patients in the usual-care group), the use of CPAP did not result in a lower rate of the prespecified primary end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack) than usual care alone (hazard ratio with CPAP, 1.10; 95% confidence interval [CI], 0.91 to 1.32; P=0.34). The lack of a significant effect was observed in multiple prespecified subgroups. Despite the negative result for the primary end point, CPAP had a significant beneficial effect on quality of life, mood, daytime sleepiness, and work productivity.

This trial raises several issues. One major issue is whether the results were negative because obstructive sleep apnea does not have clinically significant adverse cardiovascular effects — and thus any treatment would be ineffective in reducing cardiovascular events — or because the patients did not use CPAP for a long enough duration each night to derive cardiovascular benefits. Given the substantial human and animal data that have consistently documented links between obstructive sleep apnea and cardiovascular health, we suspect that it may be the latter. In the SAVE trial, the mean duration of CPAP adherence was only 3.3 hours per night, which is probably less than half the time the patient was asleep. This dose of CPAP may not be adequate to prevent cardiovascular events. In a prespecified propensity-score–matched analysis, 561 patients who used CPAP for more than 4 hours per night were compared with a control group of patients who received usual care alone. Although one must interpret these data cautiously, given the potential for additional confounders, there was a trend toward a slightly lower risk of a primary endpoint event in the CPAP group (hazard ratio, 0.80; 95% CI, 0.60 to 1.07; P=0.13), and the risk of a cerebrovascular event was significantly lower in the CPAP group (hazard ratio, 0.52; 95% CI, 0.30 to 0.90; P=0.02). The potential benefit in patients who were adherent to CPAP therapy is consistent with the findings from two other randomized trials that did not show a lower risk of cardiovascular events in the intention-to-treat analyses but showed a significantly lower risk of cardiovascular events in on-treatment analyses.[3,7]

Another related issue may be the timing of CPAP; when used in the beginning of the night, CPAP may be less effective than when used later in the night. In many of the trial patients, CPAP

may not have been in use during rapid-eye-movement (REM) sleep, the sleep stage that predominates in the early morning hours. This is a concern because apneic or hypopneic events that occur during REM sleep are longer, with greater oxygen desaturation, than those that occur during non-REM sleep; moreover, events that occur during REM sleep have a significantly stronger association with hypertension.[8,9]

To maximize enrollment, the investigators recruited participants from a variety of geographic locations that had limited resources. They took a pragmatic approach and performed a diagnostic test for obstructive sleep apnea (using a home sleep-study screening device [ApneaLink; ResMed]) that is much simpler to perform than polysomnography. However, it is possible that the limited resources at certain participating sites may have affected adherence to CPAP therapy and the trial results, given that the mean duration of adherence was lower than in other studies.[3,10]

Finally, we appreciate that choosing to conduct a secondary prevention trial allowed for a smaller sample size, because rates of cardiovascular events would be higher than rates in a primary prevention trial. However, CPAP may have limited effect in patients with well-established cardiovascular disease. Also, because of recruitment challenges, the investigators revised their original sample-size calculation. The reestimation, however, was based on data from a meta-regression that included mostly primary prevention studies rather than secondary prevention studies. Although it seems doubtful that the recruitment of more patients would have changed the results of the primary analysis, it may have made the results for the patients who were adherent to CPAP therapy clearer.

What do these results mean for clinical practice? We believe that for symptomatic patients with obstructive sleep apnea, a trial of CPAP should be offered. It would also be prudent to offer CPAP to patients with obstructive sleep apnea and severe hypoxemia during sleep regardless of symptoms — these patients were excluded from the SAVE trial. However, on the basis of the results from the SAVE trial, prescribing CPAP with the sole purpose of reducing future cardiovascular events in asymptomatic patients with obstructive sleep apnea and established cardiovascular disease cannot be recommended.[6] Whether increased adherence to CPAP therapy can lead to better cardiovascular outcomes requires further investigation. Ongoing clinical trials such as the ISAACC study (ClinicalTrials.gov number, NCT01335087) will shed further light on the effect of CPAP in nonsleepy patients with obstructive sleep apnea and acute coronary syndromes. Furthermore, although improving CPAP technology to maximize adherence is important, we believe that there is also a need for novel treatment options that allow for better adherence.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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