CORRESPONDENCE



CPAP in Obstructive Sleep Apnea

TO THE EDITOR: The results of the Sleep Apnea Cardiovascular Endpoints (SAVE) study reported by McEvoy et al. (Sept. 8 issue)[1] provide the opportunity to reflect on the story of the glass that is half full. The study shows that if a person is not adherent to continuous positive airway pressure (CPAP) for a mean duration of 3.3 hours per night, he or she should not expect benefits with respect to prevention of secondary composite cardiovascular end points.

Sleep apnea has major genetic determinants, so a study population involving predominantly Asian persons (64%) who are not obese (mean body-mass index [the weight in kilograms divided by the square of the height in meters], 29) and who have asymptomatic moderate-to-severe disease (apnea–hypopnea index [the number of occurrences of apnea or hypopnea per hour of sleep], 29) is a population from which extrapolations should be made carefully. There may also be a cohort effect, since a cohort with a mean age of 61 years may constitute a "survivor" population with lower event rates than those among younger cohorts.

Finally, it is well known that controls in a study involving patients who are receiving standard care actually receive better care than those in observational studies. The effect size may therefore have been attenuated in the study reported by McEvoy et al. The sleep medicine community should be cautious about discarding the benefits of CPAP solely on the basis of this study.

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1. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919-31.

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TO THE EDITOR: Although the study by McEvoy et al. is a provocative contribution to the literature on obstructive sleep apnea, it is important to interpret the results with caution. The level of patient adherence to CPAP therapy was not adequate, with a mean duration of treatment of only 3.3 hours per night. It is notable that this minimal use significantly reduced daytime sleepiness and improved quality of life. However, as mentioned in the corresponding editorial by Mokhlesi and Ayas,[1] it is not surprising that cardiovascular benefits were not derived from inadequate adherence to CPAP therapy.

In contrast, a recent European study involving patients with obstructive sleep apnea and coexisting coronary artery disease showed a significant reduction in cardiovascular risk among persons who used CPAP therapy for 4 or more hours per night.[2] It is well established in the literature that

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CPAP therapy for obstructive sleep apnea is associated with reduced cardiovascular mortality, especially among patients with severe obstructive sleep apnea.[3] Therefore, it remains essential for clinicians to diagnose obstructive sleep apnea and enlist sleep specialists to help patients maintain adherence to CPAP therapy,[4] which produces widespread health benefits.

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THE AUTHORS REPLY: Freire and Chervin et al. state that the average duration of adherence to CPAP of 3.3 hours per night in the SAVE study was not sufficient, and they imply that this was the primary reason for the neutral result with respect to cardiovascular outcomes. The premise underlying the SAVE study was that an average duration of adherence to CPAP of 3.0 to 3.5 hours per night would reduce the average apnea–hypopnea index by approximately 15 points and that this would lead to a 25% reduction in the relative risk of the cardiovascular end point. This was a conservative assumption given that a meta-regression of cohort studies showed a 25 to 32% increase in cardiovascular risk for every increase of 10 events per hour in the apnea–hypopnea index.[1] The level of adherence achieved in the SAVE study tested the study hypothesis.

It is also important to note that this level of adherence reflects "real-world" CPAP usage in many patients with obstructive sleep apnea who, like most of the patients enrolled in the SAVE study, have no or minimal daytime sleepiness. The 42% of SAVE participants who used CPAP for 4 or more hours per night aligns with the rate reported in sleep clinics (range, 17 to 71%).[2]

A beneficial effect with respect to cardiovascular events might have been achieved with greater adherence to CPAP therapy, but experience shows that this adherence is difficult to achieve. As such, the neutral cardiovascular findings of SAVE are highly relevant to clinical practice. Furthermore, the SAVE results suggest that cohort studies have overestimated the direct effects of obstructive sleep apnea on cardiovascular risk. Residual confounding by unadjusted risks such as visceral obesity — which is strongly associated with an increased cardiovascular risk, a decreased upper-airway size, and an increase in the severity of obstructive sleep apnea[3,4] — is one possible explanation. Previous cohort studies and per-protocol analyses of clinical trials may also have overestimated protection from CPAP because of "healthy user" effects and the confounding that can result.

It also seems unlikely that the neutral result is explained by the selection of an older "survivor" patient population or of the high-quality background therapy received by the study participants. Other established treatments for cardiovascular disease such as blood-pressure lowering, lipid lowering, and antithrombotic therapy have all proved to be effective in similar patients. Likewise, it seems unlikely that the inclusion of Asian participants diluted the treatment effect, since, when adequate data become available, other proven therapies have ultimately been shown to provide benefits that are generalizable across diverse populations.[5]

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Variants in *ANGPTL4* and the Risk of Coronary Artery Disease

TO THE EDITOR: Genomic studies of cardiovascular disease that are based on samples obtained from patients have identified variants associated with the risk of disease that do not always predict the onset of disease shown in prospective studies.[1,2] Dewey et al. (March 24 issue)[3] report lower levels of triglycerides and a lower risk of coronary artery disease among carriers of E40K and other inactivating mutations in *ANGPTL4* than among noncarriers. Also, in the same issue of the *Journal*, Stitziel et al. report that in a cross-sectional study, low-frequency coding-sequence variants were associated with a reduced risk of coronary disease.[4]

We carried out an independent, large-scale study and confirmed the role of these genetic variants in incident coronary heart disease. Our study involved data that was collected prospectively from seven cohorts (the Age, Gene/Environment Susceptibility–Reykjavik Study; the Atherosclerosis Risk in Communities Study; the Cardiovascular Health Study; the Framingham Heart Study; the Genetic Studies of Atherosclerosis Risk; the Rotterdam Study; and the Women's Genome Health Study). A total of 5427 of 49,518 persons of European ancestry in these studies had incident coronary heart disease.[5]

We investigated 35,904 autosomal exome-array variants with a minor-allele frequency of greater than 1% for association, with adjustment for age, sex, and population substructure. Significant associations (Bonferroni-corrected P<1.39E-06) are summarized in Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org. We confirm previously reported[6] associations with noncoding common variants at 9p21 and *PHACTR1*, and we also found an association between a low-frequency variant in *ANGPTL4* and a reduced risk of incident coronary heart disease.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the studies reported by Dewey et al. and Stitziel et al., the reduced risk of cardiovascular disease observed among carriers of inactivating variants in *ANGPTL4* suggests a causal role for plasma triglycerides. However, in both studies, lower triglyceride levels in carriers were inextricably linked with elevated levels of high-density lipoprotein (HDL) cholesterol. In another

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