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CORRESPONDENCE

The SAVE Trial: Has the Importance of CPAP for Preventing Cardiovascular Events been Discounted?

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A paper by McEvoy et al. recently appeared in the New England Journal of Medicine concerning the role of continuous positive airway pressure (CPAP) in the prevention of cardiovascular events in patients with obstructive sleep apnea (OSA) [1]. The primary composite end point of the study was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. The results of this paper, apparently showing that CPAP had no protective effect against various forms of cardiovascular disease (CVD), came as a surprise to us in light of the accumulated evidence linking OSA with CVD. The currently available data from randomized controlled trials (RCTs) have shown that CPAP has beneficial effects on factors associated with CVD such as blood pressure, increased sympathetic activity, endothelial function, and insulin sensitivity [2, 3]. In addition, several observational studies have shown that CPAP use reduces the risk of cardiovascular events due to OSA and cardiovascular related death [2, 3].

The associated editorial by Mokhlesi and Ayas (2016) cited several important issues that might have influenced the results of the McEvoy et al. SAVE trial [4]. These included the duration and timing of CPAP use where the average duration of CPAP per night was 3.3 h. Moreover, the variability of resources in certain geographic locations might have affected the outcome measures [4]. Because of recruitment difficulties, the investigators changed their original sample-size calculation. However, the re-estimation was based on primary prevention studies, rather than secondary prevention studies [4].

However, there are other important issues that need to be discussed.

An essential criterion for inclusion in the study was a diagnosis of coronary artery disease (CAD) or cerebrovascular disease, which means that the study assessed secondary, not primary prevention [1]. The title failed to reflect this important aspect of the study.

To diagnose moderate-to-severe OSA, the investigators measured oxygen desaturation index via a portable monitoring device "ApneaLink (AL)". Choosing the appropriate population is extremely important when considering the use of a portable monitoring device to diagnose OSA. The previous studies that showed positive outcomes with AL have been done on patients who had a high likelihood of having OSA, in addition to excluding patients with confounding disorders such as respiratory diseases, cardiac diseases, and cerebrovascular diseases [5, 6]. These findings, therefore, raise the question of whether AL was the appropriate diagnostic tool in this study. One of the inclusion criteria in the McEvoy et al. paper was a diagnosis of CVD and cerebrovascular diseases [1]. Therefore, it is possible that a good proportion of the included patients

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may have had Cheyne–Stokes respiration (CSR) and central apneas, which were missed due to the use of a portable monitoring device. In general, the American Academy of Sleep Medicine (AASM) guidelines did not approve portable home devices for diagnosing CSR [7]. Moreover, AL is not properly validated for diagnosing CSR. The only study that validated AL for detecting CSR in OSA patients included 11 patients with OSA and CSR and used an AL version that provides a classifier for the auto-detection of CSR [6]. No information is provided in McEvoy et al. study about the type of device used [1, 8].

Furthermore, automatic algorithms were used to analyze signals [8]. A previous study that assessed the accuracy of auto and manual scoring of AL raw data in diagnosing patients with moderate-to-severe OSA after excluding patients with CVD and cerebrovascular diseases found that AL manual scoring showed excellent sensitivity, but low specificity, and AL auto scoring showed very good specificity, but low sensitivity [5]. In an important trial such as the McEvoy et al. study, which has far reaching implications for patient's care, management, and prognosis, we believe that detailed information about the scoring techniques and criteria should have been provided.

The investigators used the flow signal to diagnose CSR. However, flow signal has a high chance of signal failure during portable monitoring [9]. No data about signal failure were reported in McEvoy et al. paper [1, 8].

Another point is the age of the cohort. The age of the study group is toward an older age category with a mean age of 61 years. This sample selection is not representative of the typical age profile of OSA sufferers. Most previous studies that validated AL in OSA patients included younger middle-aged patients [5, 6, 10, 11]. In addition, the study recruited Caucasians and Asians. However, it is known that Asians have a higher risk of morbidity from severe OSA than Caucasians at comparable body mass index (BMI) [12].

Finally, 58% of studied subjects had poor adherence to CPAP (<4 h per night). However, data analysis pooled all subjects and the results were analyzed as if all subjects had good adherence. In a subgroup of the cohort who used CPAP >4 h (42%), there was a trend toward a slightly lower risk of a primary cardiovascular endpoint event in the CPAP group. This subgroup ($n = 561$) is much below the needed sample size to have sufficient statistical power to detect a difference. Therefore, it is not fair to conclude that CPAP does not prevent cardiovascular events in moderate-to-severe OSA when the number of patients who had good compliance was insufficient to uncover a significant difference in cardiovascular events.

Consequently, the results of the study are still inconclusive and further evidence is needed to support the authors' claim.

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