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Letter to the Editor

LETTER TO THE EDITOR

Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias

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In their recent provocative commentary, Pack et al. [1] contend that the neutral results of randomized controlled trials (RCTs) of continuous positive airways pressure (CPAP) for secondary cardiovascular (CV) prevention in obstructive sleep apnea (OSA) are flawed due to design biases, in particular, the inclusion of OSA patients without excessive sleepiness from CV clinics and inpatient services. They cite Mazzotti et al.'s [2] analysis of the Sleep Heart Health Study (SHHS), where only an excessively sleepy OSA patient cluster (mean Epworth sleepiness score [ESS] 13.7) had increased CV events and also highlight the lower CPAP adherence in RCTs than clinical practice, and criticize the use of composite CV primary endpoints. Pack et al. [1] conclude that only propensity score analysis of prospective clinical registries will effectively resolve uncertainties over causal pathways for OSA and CV disease.

We acknowledge that the results of RCTs in OSA have been unexpected [3–5], but consider Pack et al. [1] have been too hasty in dismissing their value in advancing knowledge and clinical decision-making and appear misinformed in their belief that only sleepy patients are at increased CV risk. Moreover, their proposed solution to the challenges of RCTs—propensity score analysis of observational data—is fraught with limitations.

Several RCTs [3–5] were specifically designed to determine whether treatment of OSA would lower the risk of recurrent serious CV events and took a pragmatic approach to enhance both internal and external validity. The use of composite CV primary endpoints provides statistical efficiencies and is

supported by strong epidemiological and mechanistic studies of an association of OSA with both cardiac and stroke events [6]. Recruiting OSA patients from CV clinics not only targets a high-risk comorbid CV-OSA population but also tests the potential translation of the findings into a clinical setting with a high frequency of undiagnosed OSA [6]. The RCTs used broad inclusion criteria, deployed simplified home-based sleep studies, and initiation and follow-up of patients allocated to CPAP were consistent with specialist sleep clinic processes. All these aspects allowed the participating health systems to be effectively reorganized to accommodate screening, assessment, and uptake of a widely applicable treatment had the results been positive. OSA patient recruitment from CV rather than sleep clinics should not be described as a particular form of "selection bias," as it was an entirely appropriate place to source OSA patients for RCTs addressing secondary CV prevention. While RCTs can never include all "real-world" patients, their primary purpose is to provide a reliable answer to a clinically meaningful question, based on sensible estimates of the treatment effect and in an efficient manner over a realistic time frame.

While the RCTs excluded patients with varying degrees of excessive sleepiness (ESS ≥16 [3], ≥10 [4], and ≥ 11 [5]), we disagree with Pack et al. [1] who contend that this has seriously jeopardized the findings. It is possible that excessive daytime sleepiness constitutes an additional CV risk factor in OSA patients, but there is limited supporting data. The Mazzotti et al.'s [2] study identified four different clinical clusters in 1207 SHHS participants with OSA (apnea-hypopnea index [AHI] ≥15) and found that only the small "excessively sleepy" patient cluster (n = 201 [17%]; mean ESS 13.7) had increased CV risk compared with the other clusters and participants without OSA (AHI < 5). This could simply be a chance finding and ignores the role of other predictors of adverse CV outcomes such as cumulative nocturnal hypoxic burden [7–9], reduced slow-wave sleep [10], shorter obstructive events [11], and increased heart rate in response to respiratory events [12] some of which clearly show no effect modification by excessive sleepiness [7, 12]. The Sleep Apnea cardioVascular Endpoint (SAVE) trial raises further doubt over the hypothesis that only excessive sleepy OSA patients have increased CV risk amenable to CPAP treatment. There was no difference in the composite CV outcome between CPAP and usual care in the approximately one-fifth (n = 550) of the study population with "excessive sleepiness" (ESS values: 11–15, hazard ratio [HR]: 1.08, 95% confidence interval [CI]: 0.71 to 1.66) compared with the "non-sleepy" group (ESS values: 0–10, HR: 1.10, 95% CI: 0.89 to 1.35) [3]. Mazzotti et al. [2] did not control for sleep duration, a robust predictor of CV outcomes [13] and a major determinant of excessive sleepiness. Daytime sleepiness in the community is common and strongly associated with insufficient sleep duration and conditions other than sleep apnea (eg, depression, diabetes, obesity, and sedating medications) [14]. An earlier SHHS study [15] found excessive daytime sleepiness (ESS >10) in approximately one-third of individuals with OSA and in one-fifth of those without OSA, suggesting that a significant proportion of the sleepiness in OSA is likely due to other factors that are related to CV morbidity and mortality but cannot be reversed by treating OSA.

We contend that it is too early to conclude that OSA-related CV risk occurs only, or even predominantly, in those with excessive sleepiness. Moreover, focusing just on patients with excessive daytime sleepiness may exacerbate sex inequities in sleep health as women, who are also at increased CV risk with OSA, often do not report sleepiness [16]. Further studies are needed to identify and confirm specific OSA endotypes or clinical phenotypes with CV risk, to ensure inequities are not propagated by sex and other factors, and also whether OSA confers cardioprotection in certain subgroups. Post hoc analyses of RCTs [17, 18] can contribute to this effort and strengthen mechanistic hypotheses for future testing in RCTs.

We cannot abandon RCTs in search for causal links between OSA and CV disease as they ultimately provide the most robust evidence of the effectiveness of interventions that underpin Level A guideline recommendations. Propensity score and other adjusted analyses provide information on the utility of evidence in real-world settings but cannot establish effectiveness, may overestimate CV treatment effects, and even conflict with RCT findings [19]. There are likely challenges in identifying sufficiently large numbers of adherent patients and achieving sufficient propensity score matching to nonadherent patients in sleep clinic populations, given differences in the management and follow-up between these two groups, and the various other variables, known and unknown, between OSA and CV events.

As has been shown in the SAVE study [3] and in the ongoing Sleep SMART (sleep for stroke management and recovery trial) poststroke trial [20], it is possible to ethically design and conduct RCTs in a broad range of OSA-CV disease populations, including those with marked hypoxemia and at least moderately severe sleepiness. Fewer than 5% of patients who screened positive for moderate–severe OSA in SAVE were excluded due to severe daytime sleepiness (ESS ≥16) or nocturnal hypoxemia (SaO_2 < 80% for >10% of time). Pack et al.'s [1] assertion that 10 000 patients per arm are required to conduct OSA RCTs for secondary CV event reduction is incorrect, as a plausible treatment effect of 25% to 35% relative risk reduction can be detected with far fewer patients in the context of a high annual composite CV event rate [3, 20, 21]. However, future RCTs need to consider efficiency gains through the use of adaptive designs [22, 23] and recruitment via clinical registries [24]. An adaptive enrichment design [22] could be used in which preplanned interim analysis can ascertain whether a treatment has more promising results in a particular subgroup (eg, patients with excessive sleepiness, prominent nocturnal hypertension, or severe nocturnal hypoxia). This latter feature can allow eligibility criteria to be modified such that future enrollment is enriched with that subgroup and for the sample size to be reassessed. The use of SMART (sequential, multiple assignments, randomized trials) designs could allow patients with early poor CPAP adherence to be re-randomized to alternative interventions (eg, mandibular repositioning device, hypoglossal nerve stimulation, and surgery) or enhanced behavioral support.

While the average "intention-to-treat" CPAP adherence of approximately 3–3.5 hours per night in RCTs was suboptimal, it is comparable to standard-of-care CPAP adherence (~3.5–4 hours per night) in short-term sleep clinic RCTs [25] and may reflect a lower symptom burden of patients in CV clinics. Greater patient education and support, including telehealth, may improve adherence by as much as 1 hour per night [25].

While current RCT evidence does not support the use of CPAP treatment primarily for CV prevention, research on the link between OSA and CV disease has entered a new and exciting

phase. A sustained and coordinated effort between sleep and CV researchers is needed to solve the riddle [26] through a reevaluation of the evidence and achieving a better understanding of the impact of specific disturbances in nighttime cardiorespiratory and neurophysiology in OSA and across different clinical phenotypes. It is far too early to throw the baby (RCTs) out with the bathwater.

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