<u>Author disclosures</u> are available with the text of this article at www.atsjournals.org.

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∂ Using Real-World Data to Understand Who Has Cardiovascular Benefits from Continuous Positive Airway Pressure: The Importance of Male Sex, Excessive Sleepiness, and Primary Prevention

Although there is a wide consensus about the positive impact of continuous positive airway pressure (CPAP) on symptomatic patients with obstructive sleep apnea (OSA), there are conflicting results about the ability of CPAP to reduce cardiovascular risk and mortality (1–3). Secondary prevention studies in patients diagnosed with OSA after a prior cardiovascular event, such as SAVE (Sleep Apnea Cardiovascular Endpoints study) (4), ISAACC (the Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome - effect of intervention with CPAP) (5) or RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) (6), were neutral or negative with respect to the benefits of CPAP, probably because of poor CPAP adherence, the less symptomatic patients enrolled, and the difficulty to reverse an altered vascular structure in patients with established cardiovascular disease (3, 7–9). It is reasonable to suspect that primary prevention studies with better CPAP adherence and inclusion of more "real-world" patients (e.g., more symptomatic patients with more severe hypoxemia, who reflect individuals seen in sleep clinics) would find cardiovascular benefits of treatment. To demonstrate the positive impact of CPAP on cardiovascular risk and

mortality in this regard, large randomized controlled trials (RCTs) are the assumed standard approach. Unfortunately, this type of trial is neither ethical nor feasible, because it would require decades of follow-up with high costs and randomization to no therapy for a long period of time in symptomatic patients with OSA.

In the current issue of the *Journal*, Gervès-Pinquié and colleagues (pp. 1393–1404) used an alternative approach to address this important question based on the analysis of a real-world clinical cohort of patients diagnosed with OSA (10). After a mean follow-up of 6.6 years, they found a dose–response relationship between CPAP adherence and reduced incidence of a composite outcome of major adverse cardiovascular events and all-cause mortality (MACE) based on the French insurance database. Patients using their CPAP at least 6 h/night had a significant reduction of incident MACE compared with nonadherent subjects (<4 h/night). Interestingly, this association was stronger in patients without overt cardiovascular disease at diagnosis, in males, and in the excessively sleepy symptom subtype of OSA. This suggests that CPAP could be used as primary prevention for MACE in specific clinical subgroups of patients with OSA, provided that CPAP adherence is adequate. These results, if confirmed in other cohorts, could help clinicians to prioritize treatment on the basis of the likelihood of individual patients to benefit from it.

Understanding which patients with OSA are at increased cardiovascular risk and would benefit from therapy is an active area of sleep research. The observation that patients without a history of cardiovascular disease had greater benefits of CPAP is consistent with a larger role for OSA treatment in primary prevention. Gervès-Pinquié and colleagues (10) also found greater benefit of CPAP in men than in women, which was not observed in two prior RCTs (4, 5). The relatively smaller number of women overall and among those experiencing MACE may in part explain this result, as women using CPAP ≥ 7 h/night showed a positive benefit. Although data support sex differences in OSA etiology, presentation, and physiology (11), literature is mixed regarding differences in cardiovascular consequences of OSA (12). Ultimately, more studies are needed to identify mechanisms through which CPAP may differentially benefit cardiovascular risk in men and women. Interestingly, the present article also supports different cardiovascular benefits of CPAP across symptom subtypes of OSA, with the greatest benefit among the excessively sleepy subtype. Although there was a greater cardiovascular benefit of CPAP in those with more severe hypoxic burden, there was not significant evidence of a differential effect across hypoxic burden severity groupings. A prior article in a subset of this same cohort identified hypoxic burden as a key marker of cardiovascular risk, suggesting symptom subtypes were not important (13). In contrast, these new data are supportive of excessive sleepiness as a marker of underlying cardiovascular risk specific to OSA, which is more consistent with prior literature (3, 14–18).

Taken together, these data support the notion that the focus on secondary prevention and the exclusion of more severe and more symptomatic patients may explain recent neutral or negative randomized trials on the cardiovascular benefits of CPAP. Alternative approaches to randomization are needed to study these real-world patients. In this regard, the present article provides a roadmap for other researchers embarking on studies estimating treatment effects in observational data. To overcome the limitations of nonrandomized treatment assignments, the authors applied causal inference techniques of inverse probability of treatment weighting. To understand possible healthy adherer bias, Gervès-Pinquié and colleagues summarize and adjust for a cardiovascular-specific medication possession ratio; greater adherence to multiple classes of cardiovascular active drugs was observed with higher CPAP adherence. Thus, including the medication possession ratio in covariate-adjusted and inverse probability of treatment weighting analyses is an important strength, as healthy adherer bias is a key confounding factor in nonrandomized treatment studies. Ultimately, weighted analyses were consistent with the unweighted results, supporting a causal effect of CPAP. Moreover, application of the more recently established E-value (19), which quantifies the potential for unmeasured confounding to negate observed treatment effects, is supportive of the robustness of the results. More widespread applications of these techniques within existing large-scale datasets (including electronic health records) or new prospective studies have the potential to greatly enhance knowledge, particularly given the inability to randomize many real-world patients with OSA.

The study is not without limitations. Most notably, data on the specific causes of death were unavailable, which prohibited understanding of the role of CPAP and subgroup benefits for cardiovascular-specific mortality. Although the authors argue that an impact on cardiovascular mortality is supported by the fact that cardiovascular disease is a leading cause of death combined with a lack of previous associations of CPAP with cancer risk (another leading cause of mortality) in this cohort, at present this remains a conjecture. Relatedly, although statistically significant effects of CPAP were observed on the composite MACE endpoint and on all-cause mortality alone, nonsignificant effects on cardiovascular morbidity were observed when examining individual components of the composite MACE endpoint. The association with all-cause mortality corroborates another recent real-world cohort analysis in France demonstrating that CPAP termination was associated with increased all-cause mortality (20). However, questions remain as to the specificity of the present association with respect to cardiovascular endpoints.

In the end, Gervès-Pinquié and colleagues (10) have provided important new information supporting a benefit of CPAP for cardiovascular endpoints in real-world patients, many of whom are not and, because of ethical and feasibility concerns, will not be adequately represented in randomized studies. Patients with OSA who are male, do not have existing cardiovascular disease (e.g., primary prevention), or are in the excessively sleepy OSA symptom subtype are more likely to have cardiovascular-specific benefits from CPAP. If confirmed in other cohorts, ideally with more detailed information on mortality, these factors are likely to have clinical utility for prioritizing and personalizing OSA treatment. ■

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