7. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, *et al*. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax* 2012;67:804–810.
8. Swigris JJ, Andrae DA, Churney T, Johnson N, Scholand MB, White ES, *et al*. Development and initial validation analyses of the Living with Idiopathic Pulmonary Fibrosis Questionnaire. *Am J Respir Crit Care Med* 2020;202: 1689–1697.
9. Glaspole IN, Watson AL, Allan H, Chapman S, Cooper WA, Corte TJ, *et al*. Determinants and outcomes of prolonged anxiety and depression in idiopathic pulmonary fibrosis. *Eur Respir J* 2017;50:1700168.
10. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J* 2018;51:1800692.
11. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, *et al*.; INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381: 1718–1727.

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Opportunities for Cardiovascular Benefits in Treating Obstructive Sleep Apnea in the Secondary Prevention Scenario

Understanding the cardiovascular (CV) impact of obstructive sleep apnea (OSA) is now a mature research field. After more than four decades of experimental, translational, and clinical studies (most of them observational or small randomized trials) showing a myriad of OSA consequences such as hypertension, heart failure, arrhythmias, and coronary artery disease (CAD), we were recently challenged for reaching the top of the scientific evidence (1). Like in any other field, randomization reduces bias and provides a rigorous tool to examine cause–effect relationships between an intervention and outcome (2). The obvious initial strategy is to select patients with a high-CV-risk profile to increase the chance of detecting differences during a relatively short period of time and aiming for feasibility; events in the primary prevention scenario usually have lower incidence, requiring greater than twofold the number of patients and follow-up time than secondary prevention studies. However, expectations based on promising previous observational studies in primary prevention (3–5) did not come true for secondary prevention: recent randomized trials comprising patients with OSA with previous CAD or cerebrovascular disease (SAVE [Sleep Apnea Cardiovascular Endpoints]) (6), CAD only (RICCADSA [Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea]) (7), and acute coronary syndrome (ACS) (ISAACC [Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome]) (8) showed neutral results in their primary outcomes. Although subanalysis suggested significant effects in patients with good adherence of continuous positive airway pressure (CPAP) for preventing cerebrovascular events in SAVE (6) and composite CV endpoints in RICCADSA (7), the ISAAC trial resulted in a tough scenario: not only did CPAP not prevent CV events, untreated patients with OSA did not have a poorer prognosis than a control group without OSA (8). Therefore, it is natural to ask whether we should ignore the aforementioned evidence because it did not fit the most recommended evidence. What kind of previous lessons and reflections do we consider before determining OSA to be a nonrelevant cardiology issue? Recently, at least three reviews highlighted this matter and proposed alternatives for future studies (1, 9, 10). Beyond CPAP compliance issues, these randomized studies shared a common profile: patients with OSA were minimally or not sleepy. Although the inclusion of sleepy patients sounds unethical, they may prevent us from understanding the impact of treating symptomatic patients on cardiovascular outcomes. Indeed, recent evidence in the Sleep Heart Health Study showed that excessive sleepiness is associated with poor CV outcomes in patients with OSA (11). Moreover, it is reasonable to speculate that physiological traits, characteristics of the nocturnal hypoxemia, biomarkers, and the baseline characteristics of patients may modulate clinical response and outcomes in OSA treatment (12).

In this issue of the *Journal*, Zapater and colleagues (pp. 1698–1706) shed light upon the phenotypes and therapeutic opportunities for mitigating CV risk in OSA (13). They reported the results of a secondary analysis of the ISAACC study, aimed at understanding the impact of moderate–severe OSA on the incidence of CV disease in 1,701 patients with ACS of different CV risk phenotypes (13). The authors define CV risk phenotypes using unsupervised approaches to help tease out the known clinical heterogeneity of OSA, a strategy that has been demonstrated to be valuable in understanding CV disease risk in other clinical domains in OSA such as clinical symptoms (11) and polysomnographic characteristics (14). In the current study, the authors used latent class analysis on categorized representation of 12 clinical factors commonly associated with CV risk (e.g., age, sex, lifestyle habits, comorbidities, and lipid levels) and identified two distinct CV risk phenotypes: "no previous CVD" and "previous CVD." These distinct subgroups of patients with ACS differed mostly based on the prevalence of previous CV diseases, but they also differed in age, smoking status, and prevalence of other comorbidities.

The main findings of the study indicate a significant effect of moderate–severe OSA on the risk of recurrent CV events observed only in patients in the "no-previous-CVD" subgroup (13). Patients with OSA in this subgroup had an increased risk of recurrent CV events with an adjusted hazard ratio (HR) of 1.54 (95% confidence interval [95% CI], 1.06–2.24). Conversely, this effect was not

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observed in patients in the "previous-CVD" subgroup (adjusted HR, 0.69; 95% CI, 0.46–1.04). This represents a significant interaction between moderate–severe OSA status and CV risk phenotype with an adjusted HR of 2.32 (95% CI, 1.34–3.96; $P = 0.002$). The authors also presented additional analyses excluding patients under CPAP therapy and demonstrated similar results ("no previous CVD": HR, 1.65; 95% CI, 1.15–2.36; "previous CVD": 0.75; 95% CI, 0.49–1.08). A dose–response relationship between OSA severity based on the apnea–hypopnea index and CV risk was also described, but only for patients in the "no-previous CVD" subgroup.

It is important to notice that all patients were admitted for ACS, and therefore, patients in the "no-previous-CVD" subgroup were more likely to be admitted with their first CV event when compared with the "previous-CVD" phenotype. Hence, the study suggests clinical relevance of risk stratification based on OSA diagnosis focused on secondary prevention (i.e., recurrent events). This high-risk subgroup, defined as patients admitted for their first ACS, diagnosed with moderate–severe OSA and without previous CV disease, could be a candidate target for improvement of OSA therapeutic efforts. To address this point, the authors described the effect of CPAP treatment on CV risk in patients with OSA of each phenotype as a follow-up, secondary analysis of the ISAACC randomized trial (5). However, the authors did not find a significant effect of CPAP therapy on CV incidence when stratifying the study sample based on CV risk phenotypes using latent class analysis ("no previous CVD": HR, 0.86; 95% CI, 0.62–1.21; "previous CVD": 0.96; 95% CI, 0.58–1.60), although the effect estimates were larger toward CPAP benefit in the

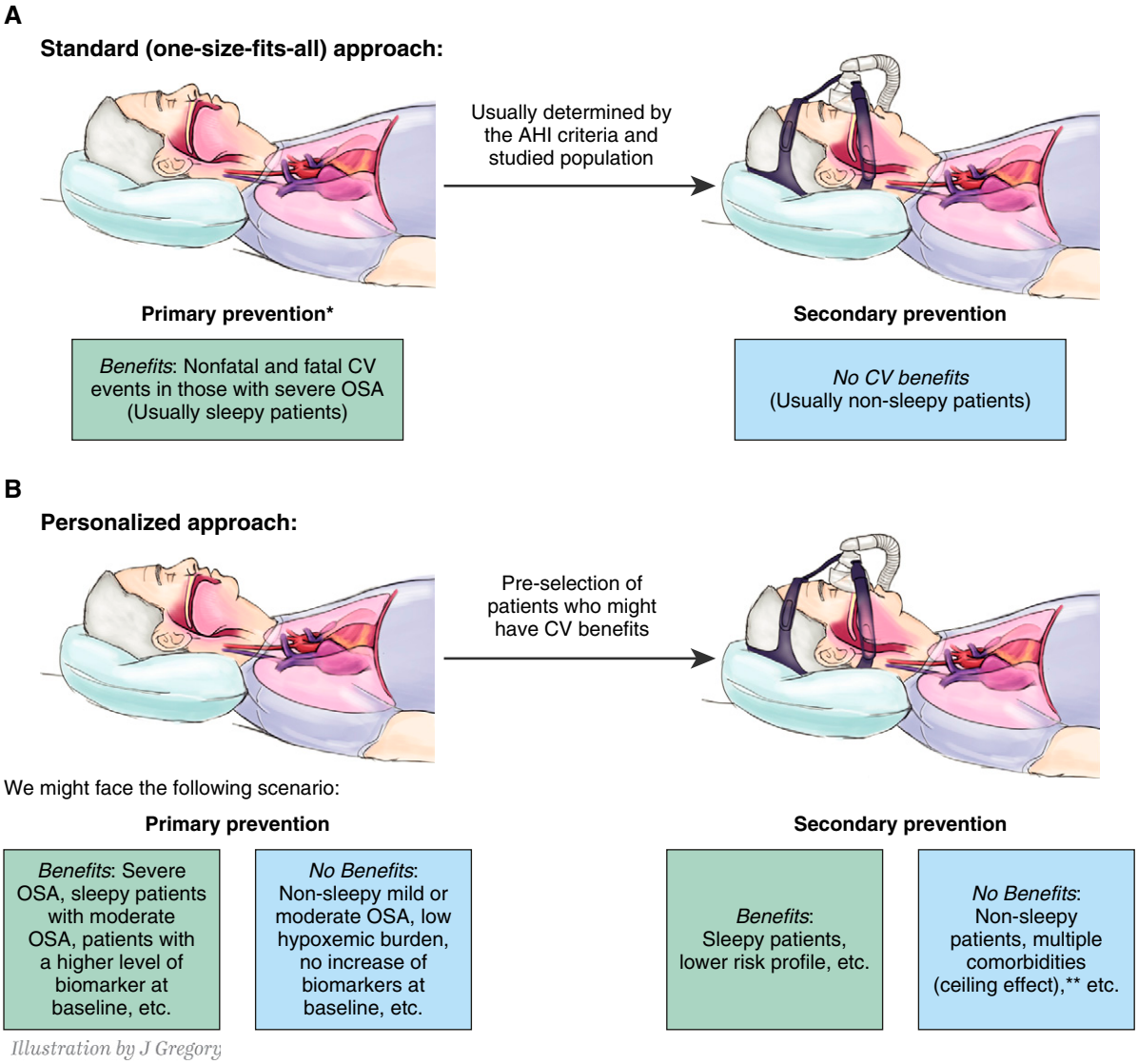

Figure 1. Cardiovascular (CV) benefits in treating obstructive sleep apnea (OSA) and potential windows of opportunities (patients' profile, biomarkers, etc.). (*A*) Standard (one-size-fits-all) approach. (*B*) Personalized approach. Green boxes represent favorable CV effects and blue boxes neutral CV effects. *Current evidence based on observational studies. **Ceiling effect: Under multiple comorbidities, OSA may not represent an independent risk factor, and CPAP therapy therefore would not provide additional CV benefits. Specific and predictive biomarkers for OSA are currently unavailable in clinical practice. Other benefits beyond CV diseases are not considered here yet have major importance in OSA treatment. AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure.

"no-previous-CVD" subgroup, thus highlighting this potential treatment opportunity window. Additional evidence from observational studies looking at recurrent events in patients at lower CV risk, as well as randomized clinical trials evaluating the effect of OSA therapy in this specific subgroup of patients, is still warranted to confirm this hypothesis.

This study has several strengths, including a large population of patients originated from a multicentric design with standardized collection, well-adjudicated CV events, and robust characterization of clinical heterogeneity based on CV risk using unsupervised clustering. Nevertheless, this study might be applied only to a specific population of patients with ACS and moderate–severe OSA that are nonsleepy. Although this is a limitation attributed to the ethical concerns of randomizing patients with OSA that are excessively sleepy to no CPAP therapy owing to higher risk of motor vehicle accidents, the results of the study could not be extrapolated to this specific symptomatic subtype of the disease. As previously mentioned, excessively sleepy patients with moderate–severe OSA were at increased CV risk in the Sleep Heart Health Study (11), and CPAP therapy has been shown to significantly improve symptoms in patients with this subtype (15). Therefore, CV risk stratification of excessively sleepy patients with OSA could refine even more the patient population that could benefit the most from CPAP therapy (Figure 1). Therefore, this interesting study reinforces a strong need for using personalized medicine in OSA and cardiovascular interactions. Sometimes, less is more! ■

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References

1. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S; INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation* 2017;136: 1840–1850.
2. Rosen L, Manor O, Engelhard D, Zucker D. In defense of the randomized controlled trial for health promotion research. *Am J Public Health* 2006;96:1181–1186.
3. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–1053.
4. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. *Ann Intern Med* 2012;156:115–122.
5. Martínez-García MA, Campos-Rodríguez F, Catalán-Serra P, Soler-Cataluña JJ, Almeida-Gonzalez C, De la Cruz Morón I, *et al*. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. *Am J Respir Crit Care Med* 2012;186:909–916.
6. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, *et al*.; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016; 375:919–931.
7. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
8. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, *et al*.; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;8:359–367.
9. Floras JS. Sleep apnea and cardiovascular disease: an enigmatic risk factor. *Circ Res* 2018;122:1741–1764.
10. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F. CPAP treatment and cardiovascular prevention: we need to change the design and implementation of our trials. *Chest* 2019;156:431–437.
11. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019;200: 493–506.
12. Lebkuchen A, Freitas LS, Cardozo KHM, Drager LF. Advances and challenges in pursuing biomarkers for obstructive sleep apnea: implications for the cardiovascular risk. *Trends Cardiovasc Med* [online ahead of print] 12 May 2020; DOI: 10.1016/j.tcm.2020. 04.003.
13. Zapater A, Sánchez-de-la-Torre M, Benítez ID, Targa A, Bertran S, Torres G, *et al*.; Spanish Sleep Network. The effect of sleep apnea on cardiovascular events in different acute coronary syndrome phenotypes. *Am J Respir Crit Care Med* 2020;202:1698–1706.
14. Zinchuk AV, Jeon S, Koo BB, Yan X, Bravata DM, Qin L, *et al*. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. *Thorax* 2018;73:472–480.
15. Pien GW, Ye L, Keenan BT, Maislin G, Björnsdóttir E, Arnardottir ES, *et al*. Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic sleep apnea cohort. *Sleep* 2018;41:zsx201.

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