Reply: Effect of Continuous Positive Airway Pressure Therapy on Cardiovascular Outcomes

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of adherence time to CPAP therapy per night, according to the method used by Peker and colleagues, is needed to confirm the effects of CPAP on cardiovascular outcomes (3).

Furthermore, Steiropoulos and colleagues also classified patients into 21 cases of good adherence (⩾4 h/night) and 20 cases of poor adherence (<4 h/night) and conducted a 6-month follow-up to assess the effect of CPAP therapy on glycemic control in patients without diabetes (4). No significant changes in the homeostasis model assessment of insulin resistance, fasting glucose, or fasting insulin were observed in either group, although CPAP therapy effectively improved the apnea indices. This report suggests that the significant differences in cardiovascular outcomes between CPAP therapy groups with different durations of adherence to CPAP per night, reported by Peker and colleagues, cannot be explained by changes in the glucose homeostasis or insulin resistance. At any rate, Peker and colleagues selected patients with nonsleepy OSA, and the effects of CPAP therapy on the cardiovascular outcomes need to be confirmed by further study. ■

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Reply

From the Authors:

We appreciate Dr. Kawada's comments on our article discussing the RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in Coronary Artery Disease and Obstructive Sleep Apnea) trial, describing the effect of continuous positive airway pressure (CPAP) treatment on cardiovascular outcomes in patients with coronary artery disease and nonsleepy obstructive sleep apnea (1) compared with the results of a much larger cohort of the SAVE (Sleep Apnea Cardiovascular Endpoints Study) trial (2). As pointed out by the commentator, CPAP did not reduce long-term primary adverse outcomes in both trials in an intention-to-treat analysis, but there was a significant reduction after adjustment for baseline comorbidities and compliance with CPAP treatment in the RICCADSA trial but not in the SAVE trial.

We agree that the methodological differences in the *post hoc* analysis of adherent versus nonadherent/no-CPAP groups may partly account for these differences. In the SAVE trial, propensity score matching was applied. Adherent patients, defined as the ones who used the device at least 4 hours per night during the first 2 years, were matched with participants selected from the control group. Thus, patients with poor adherence and unmatched control patients were excluded from the analysis. A strong "benefit" for the adherent group was therefore expected. However, there was no beneficial effect of CPAP regarding the primary composite endpoint in the SAVE study (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.60–1.07; $P = 0.13$) (2). In the RICCADSA trial, an on-treatment analysis was performed using a time-dependent Cox model to estimate the association between CPAP usage and the primary composite endpoint. Because adherence varied strongly within individual patients, this approach considering the time-dependent character of the intervention was chosen. After multivariate adjustment, a significant effect of CPAP use for 4 or more hours per night (HR, 0.29; 95% CI, 0.10–0.86; $P = 0.026$) compared with less than 4 hours was found (1).

The main difference between the two techniques applied here is that the analyzed cohort with propensity score matching in the SAVE study was a selected subset (1,122 of 2,687 patients), whereas in the on-treatment analysis of the RICCADSA trial, all patients with varying treatment intensities were analyzed. Further, intraindividual treatment variabilities were considered in the time-dependent Cox model but not in the propensity score analysis. For instance, a patient who used the device for 4 hours per night between two follow-up visits, and for 3 hours in another interval, is considered more than one time with this technique (1).

Another difference is the longer follow-up of 4.8 years in RICCADSA compared with 3.7 years in the SAVE study, but this should not result in systematic differences. Other possible explanations for the neutral results in the SAVE trial have already been discussed (3, 4). In addition to the "too little" CPAP hours, almost 50% of the participants of the SAVE cohort had more advanced (cerebrovascular) disease at baseline and had more severe obstructive sleep apnea in terms of oxygen desaturation levels. Moreover, 20% of the entire SAVE cohort were "sleepy" (i.e., had an Epworth Sleepiness Scale score >10 at baseline) (2).

We appreciate Dr. Kawada's comments on the article regarding the lack of significant changes in insulin resistance, fasting glucose, or insulin levels in a smaller nondiabetic sleep-clinic cohort stratified by CPAP adherence (5), suggesting the significant differences in the cardiovascular outcomes between CPAP therapy groups in the RICCADSA trial cannot be explained by changes in the glucose homeostasis or insulin resistance. We can neither agree nor disagree, as the results might be different in a coronary artery disease cohort. With available datasets including blood samples at baseline and 3- and 12-month follow-ups, this

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hypothesis is worth testing among the nondiabetic group of the RICCADSA cohort. ■

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