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Sleep Apnea, Pulse Rate Response, and Cardiovascular Events with Special Reference to Biomarkers

To the Editor:

Azarbarzin and colleagues evaluated the association between the pulse rate response to apneas/hypopneas (ΔHR) and cardiovascular disease (CVD) morbidity/mortality (1). The authors used three subclinical CVD biomarkers, namely, coronary artery calcium, N-terminal probrain natriuretic peptide (NT-proBNP), and Framingham risk score, to assess their associations with ΔHR, and U-shaped relationships were exclusively observed. In addition, individuals with obstructive sleep apnea with elevated ΔHR had increased risks of CVD morbidity/mortality. They concluded that the three biomarkers for obstructive sleep apnea were effective for risk stratification of CVD morbidity/mortality. However, I have a query regarding some discrepancies for the risk of CVD morbidity/mortality in patients with low and high ΔHR.

There is an agreement that obesity has an inverse relationship with NT-proBNP (2); however, the progression of apnea/hypopnea cancels the inverse relationship between body mass index (BMI) and NT-proBNP (3). Azarbarzin and colleagues included individuals with mild-to-moderate sleep apnea, and the average BMI was less than 29 (1). I speculate that there is an inverse relationship between BMI and NT-proBNP in this population and that BMI may become a confounding factor in the relationship between ΔHR and CVD morbidity/mortality. Thus, I recommend an additional setting of low ΔHR as a control to compare the risk of CVD morbidity/mortality between patients with low and high ΔHR. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Originally Published in Press as DOI: 10.1164/rccm.202102-0512LE on April 29, 2021

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Reply to Sankari and to Kawada

From the Authors:

We thank Dr. Abdulghani Sankari and Dr. Tomoyuki Kawada for their interest in our work published recently in the *Journal* (1). In our recent study (1), we found a U-shaped relationship between the pulse rate response to sleep apnea (ΔHR) and subclinical cardiovascular biomarkers as well as nonfatal and fatal cardiovascular events. That is, a low ΔHR and a high ΔHR appear to be deleterious. In addition, in our previous studies, we have shown that the ΔHR reflected the severity of preceding respiratory events (2) and the intensity of cortical arousal (3) and was reproducible (4) and heritable (5). Here, we clarify questions raised by Dr. Sankari and Dr. Kawada.

Dr. Sankari wrote to suggest that adjustment for β-blocker use may not adequately deal with a confounding effect of β-blockers on the association between the ΔHR and cardiovascular disease (CVD) outcomes. Indeed, in addition to adding β-blocker use in the main models, we conducted a sensitivity analysis and excluded individuals receiving β-blockers, those with the presence of atrial fibrillation, or those with cardiac pacemakers. The results remained very similar (1). In addition, Dr. Sankari asked about age- and sex-specific associations. The sex-specific associations were included in our study (1) and showed that the associations between a high ΔHR and nonfatal CVD or fatal CVD appeared to be stronger in women than in men (but interactions were not statistically significant). In new, age-specific analyses (age ⩾65 vs. <65 yr), associations also appeared to be

Originally Published in Press as DOI: 10.1164/rccm.202103-0690LE on April 29, 2021

stronger in younger individuals (<65 yr), but interactions were again not statistically significant.

Dr. Kawada wrote to suggest that the body mass index (BMI) may have been an uncontrolled confounder in our bivariate analysis linking ΔHR with NT-proBNP in the Multi-Ethnic Study of Atherosclerosis. Indeed, as suggested, we observed a relationship between the BMI and NT-proBNP in the cohort ($r = -0.06$, $P = 0.03$); however, additional adjustment for the BMI did not affect the U-shaped associations observed. Although a low ΔHR and a high ΔHR were both associated with morbidity and mortality, we emphasize that our goal was not just to find a new cardiovascular biomarker but was to find a cardiovascular biomarker that would explain why some patients with sleep apnea are at greater risk of cardiovascular morbidity and mortality than others. A high ΔHR appears to be a good candidate; for example, in those with sleep apnea (apnea–hypopnea index > 15 events/h) but not in those without sleep apnea, a high ΔHR (vs. a midrange ΔHR) was associated with CVD morbidity, CVD mortality, and all-cause mortality. Interestingly, a group with a low ΔHR does not appear to be an appropriate control group; a low ΔHR (vs. a midrange ΔHR) was associated with all-cause mortality in those *without* sleep apnea (but not in those with sleep apnea). On the basis of these compelling observational data, it appears that although a low ΔHR and a high ΔHR both appear to be deleterious, only a high ΔHR is a good candidate for mediating the impact of sleep apnea on cardiovascular outcomes. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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