recurrent CV events observed only in patients in the "no-previous CVD" subgroup with an adjusted hazard ratio (HR) of 1.54 (95% confidence interval [CI], 1.06–2.24). On the contrary, this effect was not observed in patients in the "previous CVD" subgroup (adjusted HR, 0.69; 95% CI, 0.46–1.04). The study reported data on medications that were taken by the two subgroups, namely, lipid-lowering agent, oral antidiabetic medication, insulin, and antiplatelet agents. However, there was no data reported on chronotropic medications (e.g., β-blocker or calcium channel blocker) (2), which may not only affect resting heart rate during wake and sleep but also dampen the autonomic response to respiratory events (3). A secondary analysis from the WSCS (Wisconsin Sleep Cohort Study), consisting of 569 participants with no previous CVD at baseline, were followed up to 15 years (4). Nocturnal total R-R interval dips index (RRDI) was associated with the composite CVD events (HR, 1.24 per 10-unit increment in RRDI [95% CI, 1.10–1.39]; $P < 0.001$). After adjusting for demographic factors (age, sex, and body mass index) and apnea–hypopnea index (4%), individuals with the highest total nocturnal RRDI category (≥28 vs. <15 dips/h) had a significant HR for the increased incidence of CVD and mortality of 7.4 (95% CI, 1.97–27.7; $P = 0.003$). Sleep RRDI was significantly associated with new-onset CVD events, which remained significant after adjusting for demographic factors, apnea–hypopnea index 4%, hypoxemia, and other comorbidities. The mechanism of increased incidence of CVD and association with RRDI can be explained by an increased sympathetic tone and associated endothelial dysfunction from the augmented shear forces (5). Such pathophysiologic changes in patients with OSA have been linked to nocturnal angina, myocyte necrosis leading to cardiomyopathy, and cardiac remodeling (6).

In conclusion, the authors should be praised for their efforts because their results surely expand our understanding of the effect of OSA on CVD. Nonetheless, careful use of predictors for adverse cardiovascular outcomes between subgroups of patients with OSA and the heart rate effect should be considered in future reports. ■

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Reply to Sankari

From the Authors:

We would like to thank Dr. Sankari for his interest in our article (1). In response to his comment on our study, we would like to present detailed information about the medications in the two groups of patients based on the phenotypes analyzed, which included some specific chronotropic drugs. As expected, the percentage of patients treated in the no previous cardiovascular disease (CVD) group was reduced compared with that in the previous CVD group (Table 1). This difference could at least partially justify the finding that in the group of previous patients with CVD, we were not able to observe an increase in the recurrence of cardiovascular events in those patients with obstructive sleep apnea (OSA).

From the initial observation of this ancillary study (1) from the Impact of Sleep Apnea Syndrome on the ISAACC (Continuous Positive Airway Pressure in Patients with Acute Coronary Syndrome [ACS] and OSA) trial (2), future studies should be performed to explore not only the mechanism associated with an increased risk in the recurrence of cardiovascular events and the role of OSA but also the potential therapeutic effect of OSA treatment in this specific profile of patients with no previous CVD in whom OSA would induce a deleterious cardiovascular effect. ■

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Table 1. Medications Administered to Patients at Baseline

	No Previous CVD (*n* = 1,381)	Previous CVD (*n* = 320)	*P* Value
β-Blockers	161 (11.7)	194 (60.6)	<0.001*
Calcium antagonists	122 (8.83)	81 (25.3)	<0.001*
Angiotensin II receptor antagonists	181 (13.1)	65 (20.3)	0.001*
Angiotensin converting enzyme inhibitors	247 (17.9)	144 (45.0)	<0.001*
Diuretics drug	193 (14.0)	79 (24.7)	<0.001*
Antihypertensive drug	567 (41.1)	287 (89.7)	<0.001*

Definition of abbreviation: CVD = cardiovascular disease.
Data are *n* (%).
*Significant *P* values ($P < 0.05$).

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Exposure to Active and Passive Tobacco Smoke on Urinary Eicosanoid Metabolites in Type 2 Asthma

To the Editor:

Data from the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) study reported by Kolmert and colleagues (1) have highlighted the potential value of urinary eicosanoids in identifying type 2 inflammation in asthma. Urinary metabolites of prostaglandin D_2 (PGD_2), tetranor PGD_2 (PGDM) and 2,3-dinor-11β-PGF2α, were elevated in severe asthma compared with mild to moderate asthma, and urinary cysteinyl leukotriene E_4 (LTE_4) concentrations were elevated in mild to severe asthma compared with healthy nonsmoking control subjects. Importantly, high concentrations of urinary PGD_2 and LTE_4 metabolites were associated with markers of type 2 high inflammation in the UBIOPRED cohort and in validation populations of severe asthma and adolescents with asthma. Although metabolite concentrations were unrelated to several demographic factors, the study does not report on the effects of current smoking status or exposure to passive smoke on urinary metabolite eicosanoid concentrations.

Previous studies have found that PGD_2 urinary metabolite PGDM concentrations are increased in current smokers with asthma compared with never-smokers with asthma (2) and that LTE_4 urinary metabolite concentrations are elevated in healthy smokers (2, 3), current smokers with asthma compared with never-smokers (2, 4), and children with asthma exposed to passive smoke and at risk of severe exacerbations (5). Collectively, these findings indicate that exposure to tobacco smoke is an important variable to consider when interpreting urinary PGDM and LTE_4 concentrations as a biomarker of type 2 inflammatory status. Interestingly, urinary LTE_4 (2, 4) and PGDM concentrations (2) are directly associated with sputum eosinophils among current smokers with asthma, suggesting a potential link between urinary eicosanoids and type 2 eosinophilic inflammation, at least in a proportion of this subgroup of smokers. Although the UBIOPRED study included a "smoking" group of 109 current and former smokers with severe asthma, in whom urinary eicosanoid concentration did not differ from the nonsmokers with severe asthma, urinary biomarker results are not reported in the subgroup of current smokers with asthma. It would also be helpful to know whether exposure to passive smoke altered urinary eicosanoid concentrations in the UBIOPRED and validation populations.

Type 2 inflammation occurs in adults with severe asthma and a smoking history (6), although non–type 2 inflammation is a more frequently found phenotype. Current cigarette smoking can alter several biomarkers of type 2 inflammation, for example, by reducing fractional exhaled nitric oxide and serum periostin concentrations, which may hinder stratification of current smokers with asthma for targeted treatments. Further assessment of the role of urinary eicosanoids in identifying and monitoring type 2 inflammation in adults and adolescents with asthma should include data on the effects

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