between asthma and obstructive sleep apnea (OSA) (1). However, to develop a personalized approach toward the treatment of comorbid pulmonary diseases with systemic spillover of inflammation (1), we have to appreciate their cardiovascular interactions (2). Because the cardiovascular impact of OSA and chronic obstructive pulmonary disease is relatively well described (2), a brief discussion with regard to asthma and cardiovascular disease (CVD) is warranted.

A recent large retrospective cohort of patients admitted to National Health Service hospitals in the United Kingdom reported a strong and independent association of asthma, chronic obstructive pulmonary disease, and interstitial lung disease with CVD (3). Asthma was independently associated with ischemic heart disease, and heart failure (hazard ratio, 1.81; 95% confidence interval, 1.75–1.87) and ischemic heart disease (hazard ratio, 1.04; 95% confidence interval, 1.01–1.07) were among the variables that were independently associated with mortality in patients with asthma (3). In another large study, late-onset asthma, diagnosed at age ⩾18 years, was associated with an increased risk of incident CVD events after adjustment for age, sex, and CVD risk factors (4). In a biracial, community-based, long-term investigation of risk factors and natural history of CVD, young adults with a history of asthma were found to have a significantly greater risk of increased left ventricular mass index independently of other major cardiovascular risk factors (5).

Many similarities exist between the biochemical and cellular pathways of cardiac and pulmonary fibrosis (6). As we read the article by Prasad and colleagues and appreciate the multifaceted overlap between asthma and OSA, we have to remind ourselves of the current evidence and knowledge gaps regarding cardiopulmonary interactions in asthma to help improve risk stratification, devise precise management strategies, and identify novel therapeutic targets. ■

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Reply to Mehmood

From the Authors:

We appreciate the point made by Dr. Mehmood in his letter with regard to our review of the evidence supporting the overlap between asthma and obstructive sleep apnea (OSA) (1). Several reviews on this topic have been published over time, presenting multiple putative pathways whereby asthma and OSA could interact (2–5). Among them, the role of cardiopulmonary interactions in this relationship was brought forward more than a decade ago (2, 4). Since then, much of the evidence has remained at the epidemiologic, database level, as referenced in the letter, with a lack of evidence from well-characterized patients or experimental studies. Furthermore, none of the cited epidemiologic studies that focused on individuals with asthma included OSA in their analyses (6–8), even though objective, standard laboratory-based sleep data were readily available (8). This raises several questions: *1*) does OSA independently modulate the interaction of asthma with cardiovascular disease, *2*) is there any bidirectionality in the relationship of asthma with cardiovascular disease, and *3*) what are the underlying pathways?

The *a priori* set goal of our review was to focus on mechanisms for which *multiple lines of evidence* (epidemiologic, clinical, and experimental) have amassed, as detailed for each direction of the relationship (1). Although many other mechanisms (3, 4), including cardiopulmonary interactions, may play a role in the asthma–OSA relationship, in our opinion, the underlying mechanism (or mechanisms) remains to be identified by testing in clinical and experimental studies. ■

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Too Premature to Deny the Potential of Thrombomodulin Alfa in Idiopathic Pulmonary Fibrosis

To the Editor:

We read with much interest the recent work reported by Kondoh and colleagues regarding the effect of thrombomodulin alfa (TM-alfa) in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF) in a randomized, double-blind, placebo-controlled clinical trial (1). Surprisingly, the reported results contradict the clinical benefits shown by TM-alfa in previous open-label and nonrandomized clinical studies (2).
We congratulate the authors for their excellent work in successfully completing this randomized trial in IPF. The study, however, has serious limitations that argue against the author's conclusions about the potential of TM-alfa in IPF. The baselines of the TM-alfa and placebo groups were not matched. Patients treated with TM-alfa had advanced disease (stage IV) and a $Pa_{O_2}/F_{I_{O_2}}$ ratio of ⩽250, and used noninvasive respiratory support or supplemental oxygen almost twice as often as the patients receiving placebo. In addition, there were three times as many patients with worse high-resolution computed tomography findings in the TM-alfa arm than in the placebo group. Although subgroup stratification favored the placebo group, the small sample size together with the significant number of confounding factors mentioned above (stage, hypoxemia, respiratory support, and radiological findings) casts doubt on the results. The use of a multivariate model is the best statistical approach to correct the influence of multiple confounding factors (3). The authors mentioned the use of "a *post hoc* baseline adjustment analysis," but neither the specific statistical method used nor the data were reported. This information is critical to predict the potential of TM-alfa in future clinical trials. Another important drawback in this study is the concurrent use of corticosteroids with TM-alfa. The authors provided no rationale for the concurrent therapeutic approach. Corticosteroids may downregulate the expression of anticoagulant factors and cell-surface receptors that mediate the antiinflammatory activity of TM-alfa (4, 5). TM-alfa also inhibits epithelial–mesenchymal transition and apoptosis, two well-recognized pathogenic pathways of tissue fibrosis, through a receptor-mediated mechanism (6, 7). Therefore, a sequential therapeutic approach would have been ideal to maximize the beneficial effects of TM-alfa and to avoid the disadvantageous biological consequences of high-dose corticosteroids. Given these limitations, we believe it is too early to deny the potential of TM-alfa for the treatment of patients with IPF. ■

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