Reply to Chen *et al.*

From the Authors:

We thank Dr. Chen and collaborators for their positive comments on our randomized controlled trial, which explored the carbonic anhydrase inhibitor sulthiame (STM) in obstructive sleep apnea (OSA) (1). Indeed, the study was the first to demonstrate a reduction of OSA severity after STM and, in addition, to demonstrate one of the strongest effects ever shown by a single drug administered for an extended period of 4 weeks. The study was designed to explore safety and tolerability, and the clinical effect encompassed several polysomnographic metrics, including improved overnight saturation, reduced arousal frequency, and improvement of sleep quality. In addition, a trend toward improved metabolic function was observed after STM. On the other hand, the data were inconclusive in terms of daytime symptomatic effects on, for example, sleepiness. Failure to demonstrate reduced sleepiness may, as pointed out by Chen and colleagues, have several explanations, including treatment duration and study size. A clinical development program including the ongoing FLOW study (a 12-week, multicenter, randomized, double-blind, placebo-controlled, dose-finding, four-arm, parallel-assignment study) has been sized to address the safety and efficacy of STM in OSA on respiratory function as well as OSA-associated symptoms and potential effects on cardiovascular and metabolic function (NCT 05236842). Studies in this field are advancing, and these areas of research and results so far are certainly promising (2).

In their letter, Chen and colleagues point to the solid theoretical basis for exploring long-term treatment effects on OSA within this drug class. Indeed, research has provided data showing a dampening effect of carbonic anhydrase inhibition (e.g., acetazolamide) on loop gain, a mechanism that contributes substantially to the pathogenesis of OSA (3). For STM, a direct central respiratory–stimulating effect and reanimation of upper airway muscle tone may also contribute to this striking improvement. A further step to evaluate the therapeutic effects of carbonic anhydrase inhibition might be to link blood- or tissue-borne carbonic anhydrase activity to the degree of hypoxic burden or to other metrics of apnea severity (4, 5).

Finally, Chen and colleagues also speculate on the position and clinical application of a drug such as STM in therapy for OSA. We agree that phenotyping of subjects with OSA may certainly enable early recognition of patients with OSA who may benefit most from STM treatment. We speculate that a future target group for STM treatment might include patients with metabolic derangement, residual apnea after treatment of positive airway pressure, mandibular advancement devices, or upper airway surgery and that STM may be combined with other therapies (6). ■

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Selecting the Right Patient: The Achilles Heel of COPD Clinical Trials

To the Editor:

We read with interest the article by Wise and colleagues which reported that, in 2020, patients with moderate chronic obstructive pulmonary disease (COPD) and emphysema, the angiotensin II receptor blocker losartan administered over 48 weeks did not prevent emphysema progression (1). Several previous studies suggested a potential benefit from angiotensin receptor blockers, as well as angiotensin-II receptor blocker losartan inhibitors, in delaying the progression of COPD-related pulmonary and systemic pathologies

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(2–4). Testing the efficacy of these drugs in patients with COPD was the natural extension of this previous body of work.

COPD is a complex and heterogeneous disease, both at the clinical and biological levels. However, most of the clinical trials still enroll patients with COPD according to simple clinical variables (e.g., severity of airflow limitation, symptoms, and frequency of previous exacerbations). In line with previous trials, Wise and colleagues included patients' age ⩾40 years, with stable mild to moderate COPD defined by a FEV_1/FVC ratio of ⩽0.70 and FEV_1 of 20–80% for predicted, current, or former smokers with ⩾10 pack-years of exposure, and with an inspiratory high-resolution computed tomographic scan with mild to moderate emphysema. No information on coexisting systemic pathologies was used to stratify this study population, nor was a biomarker of endothelial dysfunction, such as microalbuminuria (MAB), used to select patients likely to respond to these agents. Among these pathologies, preexisting cardiovascular disease has been recognized as an important comorbidity of COPD independent of the degree of airflow limitation (5), suggesting that cardiovascular disease could be used to stratify patients with COPD.

To date, only a few biomarkers have been accepted as being clinically useful (6, 7). Notably, MAB, a marker of systemic endothelial dysfunction/injury and inflammation (2, 8), is associated with poor cardiovascular outcomes in patients with diabetes mellitus; hypertension; and, it is important to note, in the general population. Approximately 24% of patients with COPD (versus 4% of control subjects) have persistent MAB (9, 10), the severity of which correlates with degree of hypoxemia in patients with stable COPD and during exacerbations (9, 10). In addition, using electron microscopy, we have detailed the renal endothelial lesions affecting patients with COPD that help explain the MAB seen in many of those patients (7).

We believe that the study by Wise and colleagues (1), although well conducted and important, missed the opportunity to target the right patient population. In fact, stratifying the COPD patients on the basis of the specific biomarkers of endothelial dysfunction (e.g., the easily measurable MAB) might have changed the outcome of the trial by narrowing the target COPD subpopulation most likely to benefit from treatment with angiotensin receptor blockers.

Many clinical trials with negative results have led to the exclusion of potentially beneficial drugs for the treatment of COPD. Thus, careful consideration of the target population must be paid before ruling out the efficacy of such drugs. In the era of precision medicine, the goal of improving clinical outcomes for individual patients on the basis of the pathobiological mechanism (i.e., endotypes) should be prioritized over the selection of patients falling under the general umbrella diagnosis of "COPD." ■

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