the effect of inhaled therapy on aPWV. A secondary endpoint was the cardiovascular composite of myocardial infarction, unstable angina, stroke, transient ischemic attack, and cardiovascular death.

We congratulate the authors on conducting this large population-based trial to evaluate an important clinical question. Although inhaled therapy had no effect on aPWV, the finding that aPWV may be useful to predict ACM in patients with COPD merits further consideration. First, we are interested to know what specific adjustments were included in the analysis of aPWV predicting ACM. "Various ischemic and vascular indicators" are mentioned (1). In particular, were adjustments for blood pressure and heart rate included? aPWV is influenced by these factors, and published data from the SUMMIT trial already showed a U-shaped curve of blood pressure to predict both ACM and cardiovascular events, whereas there was a linear relationship with increased heart rate (2–4). Another important question is whether the analysis included adjustment for other established Framingham cardiovascular risk factors, such as diabetes, hypertension, cholesterol level, and diabetes (5).

A further point of interest is the lack of relationship between aPWV and the cardiovascular composite (which included cardiovascular death), despite elevated aPWV predicting ACM. This is striking and leads to the question, what did patients in the study die from? And was aPWV associated with any other cause of death? The authors point out previous studies' findings of elevated aPWV in patients with COPD and speculate on mechanisms linking aPWV to cardiovascular disease in patients with COPD. However, the results of this study do not support an association between aPWV and cardiovascular events in patients with COPD.

Importantly, many of these surrogate markers of cardiovascular risk only add moderately to standard risk factors (6). The importance of routinely assessing cardiovascular risk in patients with COPD using validated risk scores such as Framingham or QRISK and mitigating such risk in individual patients is likely to remain the optimal clinical and cost-effective approach to reduce cardiovascular risk in patients with COPD. ■

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Reply to Fisk and Wilkinson

From the Authors:

We thank Fisk and Wilkinson for their interest in our study showing that higher baseline pulse wave velocity (PWV) was predictive of increased all-cause mortality among patients with chronic obstructive pulmonary disease (COPD) in the SUMMIT (Study to Understand Mortality and Morbidity in COPD) trial (1). They raise several important points in their letter. First, the legend of Figure 1 in our article lists the numerous covariables included in the Cox model. Many of the factors, such as diabetes and cardiovascular disease (CVD) or other risk factors, were included in the model among the "cardiovascular entry criteria" (*see* main paper [2]). Cholesterol concentrations *per se* were not measured. However, blood pressure (in particular) and heart rate are independent predictors of PWV and were not included in the model (3). We acknowledge this as a limitation, but we note that there are numerous covariables already in the model with a wide nonsignificant confidence interval. It is unlikely that adjusting for more variables, including blood pressure, would further strengthen the association.

Fisk and Wilkinson correctly note that the study's primary endpoint was all-cause mortality, and as such, we chose to evaluate the association of PWV with this endpoint. In the entire patient population with moderate airflow limitation, we expected that most deaths would be cardiovascular in nature (4), and in fact, 43% of all deaths in SUMMIT were adjudicated as cardiovascular; of these deaths, 9% were caused by myocardial infarction, 9% were caused by cerebrovascular accidents, 70% were sudden deaths, 1% were cardiac surgery–related procedural deaths, and 10% were of other cardiovascular causes (2). As noted, we did not observe a significant association of PWV with the composite cardiovascular endpoint. Given the fewer number of cardiovascular composite events, our study likely lacked the power to detect this association or statistical

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significance for any of its individual components. We did not separately analyze the adjudicated cause of death for those in the pulse wave analysis subpopulation, and we recognize this limitation as our inability to identify the specific cause of death related to increased PWV in our analysis. Nevertheless, increased PWV has been shown to be an independent predictor of all-cause mortality in prior meta-analyses (5), and we demonstrated in SUMMIT that this association was generally observed in patients with COPD.

Finally, we agree that few novel risk factors are capable of adding incremental risk prognostic information to global risk scores (6). We did not make the claim that clinical practice would be changed by evaluating PWV in patients with COPD, and indeed, we clearly stated that "aggressive treatment focusing on improving CVD risk factors is paramount." Our findings support that future trials should evaluate if a portion of the heightened CVD risk observed in patients with COPD is independently mediated by impaired arterial compliance. Nevertheless, we did not observe that treating COPD with inhaler therapy could reduce PWV, and as such, the mainstay of treatment in such patients with concomitant CVD should be to treat traditional CVD risk factors aggressively. ■

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Thrombomodulin Did Not Benefit Acute Exacerbation of Idiopathic Pulmonary Fibrosis in a Trial

To the Editor:

We read with great interest the report by Kondoh and colleagues regarding rhTM (recombinant human soluble thrombomodulin) therapy for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) (1). Their data were surprising to us in two aspects (1).

First, the 90-day survival in the non-rhTM arm of 89.2% (1) was much higher than that in previous reports, which usually reported 90-day survival $<30\%$ (2). The authors commented that including patients with mild test results and improvement of standard of care may have contributed to this excellent outcome (1). However, these explanations might not be sufficiently persuasive, because life prognosis for patients with AE-IPF was reported to be poor even for those with $Pa_{O_2}/F_{I_{O_2}}$ ratio >250 (3), and no known treatment option has been proven to improve the survival of patients with AE-IPF (2). High-flow nasal cannula and continuous positive airway pressure, which became popular in the last decade, may benefit patient survival because they do not require sedation and do not increase the risk of secondary infection as traditional intubating mechanical ventilation does. The authors also suggested some other possibilities. However, even after taking these factors into account, the 10.8% mortality still seems considerably low (1). We need to learn how Kondoh and colleagues accomplished this excellent survival outcome in the control arm (1).

Second, Kondoh and colleagues described that patients in the rhTM arm trended toward poorer 90-day survival than those in the non-rhTM arm with a marginal significance (rate difference for survival, -16.7% [95% confidence interval (CI), -33.8% to 0.4%]; odds ratio [OR] for survival, 0.32 [95% CI, 0.09 to 1.11]; $P=0.086$) (1), although many previous observational studies reported that rhTM benefits AE-IPF survival (3–6). We systematically searched four electrical databases on February 3, 2020, to identify survival data on Day 90 using the following words: "acute exacerbation idiopathic pulmonary fibrosis thrombomodulin."

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