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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The current trial (1) was the only randomized trial. Three observational studies provided data for survival rate difference on Day 90 (3, 5, 6). Because baseline patient characteristics were not significantly different in any item of these three studies, we believe using raw comparison data is allowed. A random-model meta-analysis on the basis of these three reports with 109 patients yielded Day 90 survival rate difference of 26% in favor of the rhTM arm (95% CI, 13–39%; $P < 0.001$) without heterogeneity ($I^2 = 0\%$; P for heterogeneity = 0.39). Baseline data were different in another observational study with 40 cases (4); however, this study provided adjusted OR for 90-day survival, which made this article eligible for a meta-analysis. Pooled ORs for 90-day survival on the basis of these four studies (3–6) were 3.1 in favor of rhTM-treated patients (95% CI, 1.8–5.3; $P < 0.001$; $I^2 = 0\%$; P for heterogeneity = 0.54). Most of the control subjects in the non-rhTM arm of these four studies were treated with high-dose corticosteroids with a tapering dose. Some of them were also treated with low-molecular-weight heparin, cyclosporine, immunosuppressants, anticoagulants, antiplatelets, and polymyxin. Two studies adopted 0.06 mg/kg/d rhTM, and the other two adopted 380 U/kg/d rhTM on Days 1–6. In short, there was no clear difference of treatment strategy between the current trial (1) and previous observational studies (3–6). Notably, most of the key authors in the four included articles were named in the author list of the recent article by Kondoh and colleagues (1). We suppose many readers would like to know what introduced this large discrepancy between the current trial (1) and previous observations (3–6). Four additional reports that were excluded from our analysis also revealed favorable outcomes for the rhTM arm; three were excluded because they might include the same patients as an included article (3), and one was excluded because of including nonspecific interstitial pneumonia cases.

In any case, we are grateful to Kondoh and colleagues (1) for providing the most up-to-date survival data of AE-IPF cases and alerting us not to use rhTM for AE-IPF. ■

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Reply to Horita and Takeshi

From the Authors:

We thank Dr. Horita and Dr. Takeshi for their interest and important comments regarding our recent randomized trial (1).

The 90-day survival proportion in the non–thrombomodulin alfa arm was much higher than that in previous reports (2–4), as indicated by Horita and Takeshi. Indeed, as well as the 90-day survival proportion in the placebo group, the 90-day survival proportion in all subjects included in the full analysis set in our study was even higher than assumed. Some possible reasons for this unexpected result were discussed in our article, but no clear reason was found.

We also did not anticipate the discrepancy between the results of our study and those of previous studies. Although some possible reasons for this discrepancy were also considered in our article, the definite reason is still unclear.

As we discussed in our article, acute exacerbation of idiopathic pulmonary fibrosis could have a heterogeneous pathology, meaning there would be factors that remain to be elucidated. Consequently, it may be important to examine the prognostic factors of acute exacerbation to select a more homogeneous population and/or to have a more balanced allocation of cases in future studies. ■

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