$I^2 = 0\%$) in patients with eosinophil counts <300 cells/μl; however, a significant increase in the rate of exacerbations was found in the subgroup with eosinophil counts ⩾300 cells/μl (RR, 1.63; 95% CI, 1.24–2.14; $P = 0.0005$; $I^2 = 0\%$). In fact, the Global Initiative for Chronic Obstructive Lung Disease guideline also suggested the use of ICSs in patients with eosinophil counts ⩾300 cells/μl or eosinophil counts ⩾100 cells/μl and ⩾2 moderate exacerbations/1 hospitalization (8). All these recommendations (3, 8) indicate the importance of eosinophil count when clinicians consider the withdrawal of ICSs.

In this correspondence, we raised concerns regarding baseline eosinophil count among prior ICS users in this *post hoc* analysis and whether the baseline eosinophil count level would impact the effect of ICS withdrawal. Especially for patients with eosinophil counts ⩾300 cells/μl, the abrupt withdrawal of ICSs in this specific population is expected to have a greater negative impact than that in other groups. Therefore, further subgroup analysis in this study (1) according to baseline eosinophil count among prior ICS users is needed to clarify this issue. ■

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Reply to Wang and Lai

From the Authors:

Thank you for the opportunity to respond to the letter to the editor written by Dr. Cheng-Yi Wang and Dr. Chih-Cheng Lai on our article, "The Effect of ICS Withdrawal and Baseline Inhaled Treatment on Exacerbations in the IMPACT Study: A Randomized, Double-Blind Multicenter Trial" (1). We thank Dr. Wang and Dr. Lai for the opportunity to provide additional data on the relationship between baseline eosinophil level and inhaled corticosteroid (ICS) withdrawal in IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment).

The primary question asked is whether baseline eosinophils impact the effects of ICS withdrawal. To be clear, the intent of IMPACT was not to study ICS withdrawal. Only roughly 14% of the patients in the trial were withdrawn from ICSs. In Figure 1, we show the exacerbation rate for all three treatment arms versus baseline eosinophil count, stratified by ICS use at entry to the study.

To answer Dr. Wang and Dr. Lai's question on ICS withdrawal, we must compare the fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) treatment arm with the UMEC/VI treatment arm among those previously on ICS. In Figure 2, we show the exacerbation rate ratio for FF/UMEC/VI compared with UMEC/VI plotted against baseline eosinophil count. Based on the point estimates alone, we see a numerical reduction in exacerbation rates for FF/UMEC/VI versus UMEC/VI across all eosinophil levels in the prior-ICS group. For Figure 2, the upper bound of the confidence limit for FF/UMEC/VI compared with UMEC/VI falls below unity at approximately 50 eosinophils/μl. There is also a numerical reduction in exacerbation rates for FF/UMEC/VI compared with UMEC/VI for those with eosinophil levels greater than 150 eosinophils/μl in the no-prior-ICS group. It should be noted that the confidence intervals for the individual treatment arms (Figure 1) and the treatment differences (Figure 2) are much wider for the non-ICS group owing to the much smaller sample size and lower event rate in this subgroup.

Overall, in those previously on ICSs, we see a numerical reduction in exacerbations for FF/UMEC/VI compared with UMEC/VI irrespective of baseline eosinophil levels with greater effect among those with higher eosinophil counts. As mean eosinophil

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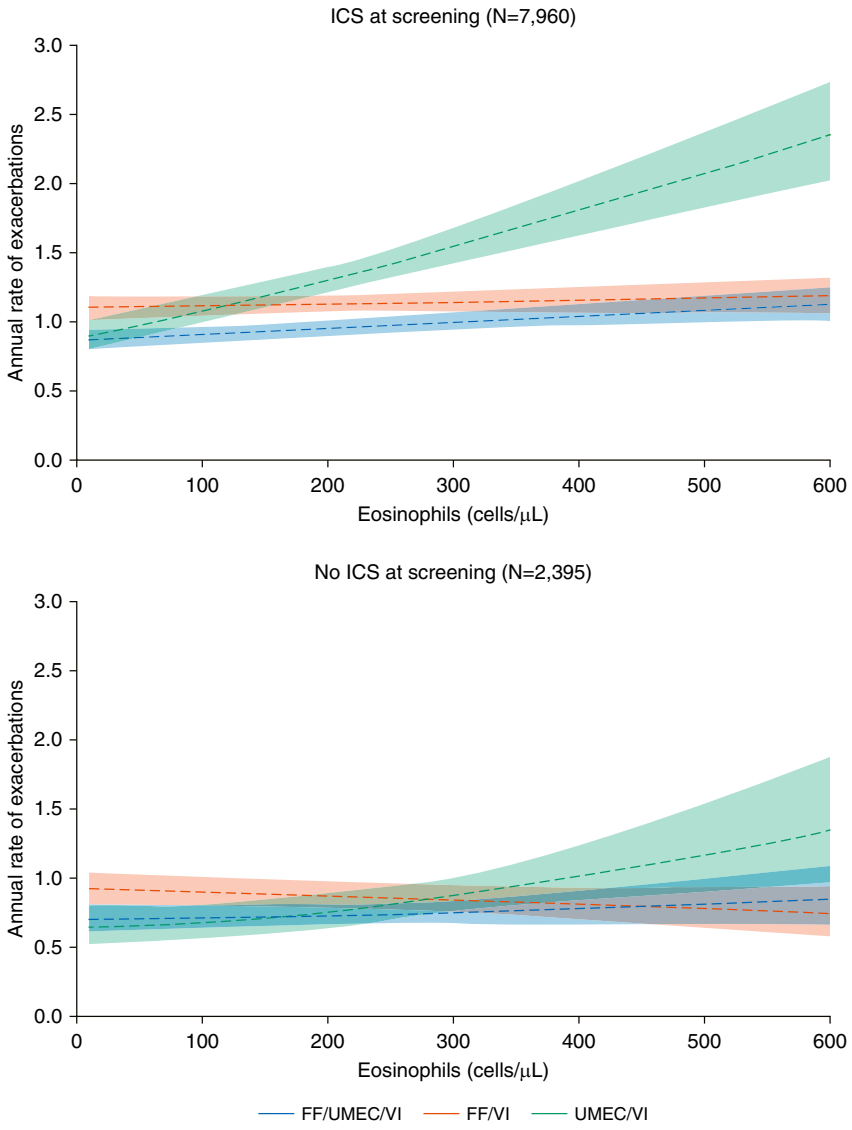

Figure 1. Annual rate of exacerbations in IMPACT by treatment arm stratified by use of ICS at screening. FF/UMEC/VI = fluticasone furoate/umeclidinium/vilanterol; ICS = inhaled corticosteroids; IMPACT = Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment.

counts and eosinophil distribution were very similar between those previously on ICSs and those not, we speculate there are likely other factors that make the minority of subjects not previously on ICSs somehow different. As we showed in the manuscript, this subgroup experienced a relatively low event rate during the trial compared with other subgroups, and here we see that the relationship between ICS effect and higher eosinophil counts is dampened. ■

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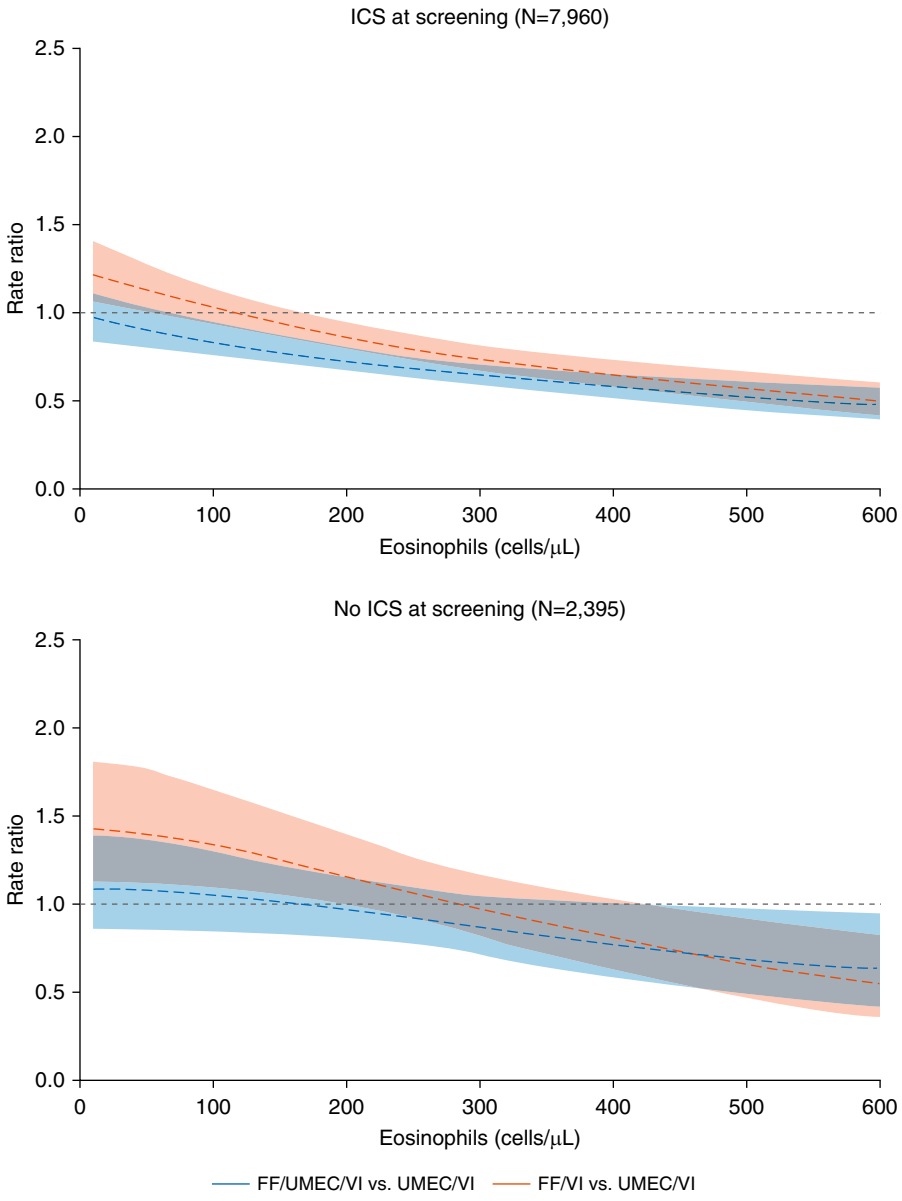

Figure 2. Rate ratio comparing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and FF/VI with UMEC/VI among IMPACT participants stratified by use of ICS at screening. ICS = inhaled corticosteroids; IMPACT = Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment.

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