



## One More Time: The Impact of Inhaled Corticosteroid Withdrawal on IMPACT

We thank the editors for the opportunity to respond to the editorial written by Dr. Samy Suissa on our original article, “The Effect of Inhaled Corticosteroid Withdrawal and Baseline Inhaled Treatment on Exacerbations in the IMPACT Study: A Randomized, Double-Blind, Multicenter Clinical Trial,” in this issue of the *Journal* (pp. 1237–1243) (1). We thank Dr. Suissa for his contribution to the ongoing scientific dialogue on this important topic. We would, however, like to take this opportunity to clarify several points.

The first point is that Dr. Suissa notes that the IMPACT (The Informing the Pathway of COPD Treatment) study included patients with a history of asthma. Although this is true, it is important to note that patients with a *current diagnosis* of asthma were excluded. All patients met American Thoracic Society/European Respiratory Society and Global Initiative for Chronic Obstructive Lung Disease criteria for chronic obstructive pulmonary disease (COPD), had a mean age of approximately 65 years, tobacco exposure of nearly 47 pack-years, and fixed airflow obstruction with an FEV<sub>1</sub>% predicted of 45.5. Furthermore, investigators also excluded patients whose symptoms were not believed to be due to COPD. As a prior diagnosis of asthma in current COPD is also relatively common, we believe these inclusion criteria better represent the patient population physicians might actually encounter in practice and underscores the generalizability of the IMPACT trial data.

Dr. Suissa also incorrectly notes in his editorial that we examined a “large number of patients (7,360) who had ICS abruptly withdrawn.” Because of the 2:2:1 randomization schema (inhaled corticosteroid [ICS]/long-acting muscarinic antagonist [LAMA]/long-acting  $\beta_2$ -agonist [LABA]:ICS/LABA:LAMA/LABA), only 20% of these patients ( $n = 1,481$ ) would have had ICS withdrawn (not 7,360 patients), which is 14% of the total IMPACT patient population. The remaining 86% of patients continued seamlessly on an ICS or had not been on an ICS because IMPACT did not employ an artificial washout period, again mimicking clinical practice.

A further concern raised by the editorial was a semantic one, noting that we should have reversed the estimates to compare LAMA/LABA therapy versus triple therapy, termed by Dr. Suissa “effect of ICS withdrawal” as opposed

to triple therapy versus LAMA/LABA therapy “exacerbation reduction.” Regardless, we believe it is important to point out that we clearly see a statistically significant 35% decrease in severe exacerbations (risk ratio, 0.65) comparing triple therapy with LAMA/LABA therapy *regardless of prior ICS use*. Hence, the effect of triple therapy on severe exacerbations cannot be attributed to ICS withdrawal.

Dr. Suissa also raises the point that our analysis excludes “early exacerbations” but fails to exclude “early exacerbators,” suggesting that the majority of ICS effect is being driven by a small group of patients who are in fact harmed by ICS withdrawal as opposed to a patient population that experiences longer-term benefits. Again, this concept fails to account for the benefit of triple therapy versus LAMA/LABA therapy on severe exacerbations, irrespective of ICS use. Dr. Suissa also states that “by pooling rather than splitting, this analysis fails to identify the key patient groups who could benefit from ICS withdrawal or from continuation.” We would like to clarify that we have not pooled data, but we present the entire intention-to-treat population. Furthermore, it would have been statistically irresponsible to “split” off a subgroup of patients from an analysis after randomization, particularly on the basis of events that occurred after randomization. Furthermore, our graphs of cumulative exacerbation data demonstrate that events continue to increase throughout the trial.

Finally, we must underscore that when considering the risk-benefit profile of triple therapy, in prespecified secondary analyses, we see a reduction in all-cause mortality among patients treated with triple therapy compared with those treated with LAMA/LABA therapy. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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## References

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# Angels Dancing on the Tip of a Needle: Interpreting Clinical Trials in Chronic Obstructive Pulmonary Disease

St. Thomas Aquinas was a distinguished medieval scholar who successfully reconciled Christian theology with Aristotelian philosophy. Sadly, he is best known today for the taunts of his critics who likened him to someone counting the number of angels who could stand on a needle tip, a metaphor for debating topics of no consequence when more urgent matters need attention. In this issue of the *Journal*, Han and colleagues (pp. 1237–1243) conduct a further analysis of the data from the very large 1-year IMPACT (Informing the Pathway of COPD Treatment) trial comparing the effectiveness of different inhaled combination treatments (long-acting antimuscarinic [LAMA] + long-acting  $\beta_2$ -agonist [LABA] bronchodilators, LABA + inhaled corticosteroids [ICS], and LABA + LAMA + ICS) given in single inhalers once daily (1). The primary outcome measure in IMPACT was the rate of exacerbation, and triple therapy was more effective in exacerbation prevention than the bronchodilators alone.

Large clinical trials are required because the expected difference between treatments is small and/or the events of interest are clinically important but infrequent. Given the time (and expense) of conducting these investigations, secondary analyses, ideally prespecified before treatment unblinding, are conducted either to generate new hypotheses or, as in the case of the paper by Han and colleagues, to test the robustness of the primary result (1). In an accompanying editorial, Prof. Suissa, a long-standing critic of many studies of ICS in chronic obstructive pulmonary disease (COPD), outlines his concerns about the completeness of the data reporting and analysis, and the distinguished study authors rebut his assertions in a second editorial comment. Are they simply counting angels?

The new analysis highlights some important features of the IMPACT population. Among the 71% using ICS before study randomization, lung function and health status were rather worse than ICS-naïve subjects, but the reported exacerbation history was similar in each group. The observed exacerbation rate after randomization was significantly higher in those taking ICS beforehand, irrespective of the

treatment to which they were randomized. This is in keeping with other analyses showing that patients taking ICS are more likely to report exacerbations than those not doing so, irrespective of their prior exacerbation history (2). It seems that clinicians do identify some patients who benefit from ICS treatment! Indeed, those taking the least intense baseline treatment (LAMA alone) showed no benefit from triple treatment, although whether this reflects their disease severity or the smaller sample size of this group is unclear. The cumulative event plots resolve the previous confusion around the misinterpreted time to first event plots (3) about whether the benefit of triple therapy is maintained, and this point is further emphasized by the analysis of data from 30 days after randomization where a positive treatment signal is still seen in the triple therapy group.

Suissa views the present study as an ICS withdrawal study, although only 14% of patients had ICS stopped for the study. The IMPACT patients were sicker than those in either the INSTEAD (4) or even the WISDOM (Withdrawal of Inhaled Steroids during Optimal Bronchodilator Management) (5) studies to which he refers, with over 50% of IMPACT patients having two or more moderate or severe events and approximately a quarter reporting hospitalization in the year before randomization. This emphasizes the importance of understanding which patients have been studied and explains apparently contradictory results between different trials. Even the extreme view that the difference in treatments is driven by exacerbations occurring when ICS treatment is stopped implies that ICS were doing something useful beforehand. Identifying appropriate therapy is key to personalized treatment selection, but the suggestion that prior asthma explains the positive signal seems optimistic, especially as we have no knowledge of what led to an initial diagnosis of asthma before it was amended to COPD. Blood eosinophil count and exacerbation history both predict relapse when ICS are stopped (6), and the IMPACT group have already shown how important eosinophil counts can be in a population at high risk for exacerbation based on their history at study entry (7).

Karl Popper believed that science proceeds by a process of refutability. Any hypothesis can only be considered correct until evidence emerges that it cannot adequately explain. By that standard, the hypothesis that taking ICS in addition to optimized inhaled bronchodilators in patients meeting the entry criteria for the IMPACT study seems to be intact. Robust

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