The apparent reduction in mortality with triple therapy among the patients with prior ICS use could be viewed from the opposite perspective, namely that of a sudden and significant early surge in mortality among those randomized to the dual bronchodilator arm (their Figure 3C). This evidence is reinforced by the equal mortality between the triple and LABA–ICS arms. Indeed, depending on the number of patients with asthma in this large stratum of prior ICS users, the withdrawal of ICS at randomization can have a double impact on mortality. First, stopping ICS use in asthma was shown to increase asthma mortality over fourfold in the first 3 months after discontinuation, with a rate ratio of 4.6 (95% CI, 1.1–19.1) compared with patients continuing ICS use (3, 4). Second, treating asthma patients with a LABA, not combined with ICS, is contraindicated following the associated increase in asthma mortality shown for salmeterol in the SNS (Serevent Nationwide Surveillance) and SMART (Salmeterol Multicenter Asthma Research Trial) trials, with relative risks of asthma death with salmeterol of 3.0 (95% CI, 0.7–20.0) and 4.4 (95% CI, 1.2–15.3), respectively (5, 6).

Thus, the unknown subset of patients with asthma in IMPACT among the 70% of patients in whom ICS use before randomization was withdrawn and replaced by a LABA–LAMA inhaler need to be identified and their outcomes reported. Otherwise, this profile confounds the results, leading to the misleading conclusion that triple therapy reduces mortality in all patients with COPD. In the absence of this information, the more likely conclusion of the IMPACT trial is an increased mortality in the LABA–LAMA arm because of the abrupt withdrawal of ICS in patients who needed it and who were given a contraindicated LABA in a LABA–LAMA inhaler.

In the era of precision medicine, in which identifying the right treatment for the right patient is paramount, it is essential to better understand and dissect the heterogeneity of COPD with targeted trials and pertinent stratified analyses. The reanalysis of the IMPACT trial by Lipson and colleagues provides one important stratified analysis but is lacking other key ones. These could help identify the patients who benefit from triple therapy, thereby preventing unnecessary harms from ICS, including cataracts, pneumonia, and fractures, among those patients who do not benefit. ■

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References

1. Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, *et al.*; IMPACT Investigators. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;201: 1508–1516.
2. Suissa S, Drazen JM. Making sense of triple inhaled therapy for COPD. *N Engl J Med* 2018;378:1723–1724.
3. Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018;52:1801848.
4. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332–336.
5. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306: 1034–1037.
6. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129:15–26.

Reply to Suissa

From the Authors:

We read with interest the comments by Dr. Suissa on our manuscript (1) but disagree with his premise that the IMPACT (Informing the Pathway of COPD Treatment) results were driven by the withdrawal of steroids from patients with asthma.

The population enrolled in IMPACT was a typical chronic obstructive pulmonary disease (COPD) population with symptomatic disease and a history of exacerbation. IMPACT was carefully designed (2) on the basis of standard clinical parameters that are not only endorsed by major scientific societies but also routinely used in worldwide clinical practice. All patients within the trial met American Thoracic Society and European Respiratory Society criteria for COPD; current asthma was an exclusion, and investigators enrolled patients only if their symptoms were due to COPD. Clearly, patients with a previous history of asthma can still develop COPD (3). The average age of the population was 65 years and exhibited fixed airflow obstruction with an average FEV_1% predicted of 45.5. All patients were active or former smokers with an average of almost 47 pack-years of cigarette exposure (4). There were no clinically relevant differences from other large COPD trials; in fact, levels of reversibility to albuterol were actually lower in IMPACT (only 18% of patients were reversible to albuterol in IMPACT compared with FLAME [45%], KRONOS [43%], and ETHOS [30.6%]) (5–7) with similar blood eosinophil levels. The IMPACT population is typical of a population with COPD that is clearly recognizable to any clinician caring for such patients.

There were differences in disease severity in the population of patients who came into the trial on inhaled corticosteroids (ICS) compared with those who did not. For example, rates of moderate or severe exacerbations were higher on all arms in the trial for those who came in on a triple regimen compared with those receiving long-acting muscarinic antagonist monotherapy. This would be expected as international recommendations, such as Global Initiative for Chronic Obstructive Lung Disease, suggest the use of ICS in more severe patients (8). Thus, we might expect to see

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a survival benefit in those who came into the trial on ICS because they have the greatest risk for exacerbations and thus the greatest risk for death (9). We believe that the most likely cause of the observed survival benefit was the reduction in recurrent exacerbations, especially those leading to hospitalization, demonstrating the benefit of ICS in this patient population.

It is important to recognize that IMPACT was not an ICS withdrawal study. Although ~77% of patients entered the trial on ICS, because of the 2:2:1 randomization, only approximately 15% of the overall population underwent withdrawal of ICS. The vast majority of the population (85%) did not experience ICS removal. In addition, deaths occurred in all arms throughout the trial, indicating no "surge" in deaths caused by abrupt withdrawal of ICS. Overall mortality on the long-acting muscarinic antagonist–long-acting β_2 agonist arm was actually lower than what has been previously observed in similar patients with advanced COPD (10, 11), also strongly suggesting that abrupt ICS withdrawal was not the cause of the findings.

Even if we were to believe Dr. Suissa's argument that ICS withdrawal was harmful, we would then have to conclude that the addition of ICS was beneficial for these patients in the first place.

What is clear is that most patients who met the IMPACT inclusion criteria benefited from triple therapy compared with dual therapy. Patients with symptomatic COPD and a history of exacerbation who received triple therapy with fluticasone furoate/umeclidinium/vilanterol experienced clinically relevant improvements in lung function and health-related quality of life, reduction in exacerbations and hospitalizations, and now a confirmed additional benefit of improved survival compared with patients randomized to umeclidinium/vilanterol. ■

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References

1. Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, *et al.*; IMPACT Investigators. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;201:1508–1516.
2. Pascoe SJ, Lipson DA, Locantore N, Barnacle H, Brealey N, Mohindra R, *et al*. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. *Eur Respir J* 2016;48: 320–330.
3. Martinez FJ, Han MK, Allinson JP, Barr RG, Boucher RC, Calverley PMA, *et al*. At the root: defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;197: 1540–1551. [Published erratum appears in *Am J Respir Crit Care Med* 198:1463.]
4. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al.*; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–1680.
5. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, *et al.*; FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016;374: 2222–2234.
6. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, *et al*. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018;6:747–758.
7. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, *et al*. A phase III study of triple therapy with budesonide/ glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6 μg and 160/18/9.6 μg using co-suspension delivery technology in moderate-to-very severe COPD: the ETHOS study protocol. *Respir Med* 2019;158:59–66.
8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. [accessed 2020 Apr 21]. Available from: https://goldcopd.org.
9. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;198:464–471.
10. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, *et al*. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med* 2012;186:975–981.
11. Soriano JB, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, Alfageme I, *et al*. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. *Lancet Respir Med* 2015;3:443–450.

One Step at a Time: A Phased Approach to Behavioral Treatment Development in Pulmonary Rehabilitation

To the Editor:

We have read with great interest the article by Barker and colleagues (1). We want to congratulate the authors for their publication and hope to contribute to this important discussion.

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