



Fixed Triple Therapy in Chronic Obstructive Pulmonary Disease and Survival Living Better, Longer, or Both?

Does regular pharmacological treatment including inhaled corticosteroids (ICS) reduce mortality in patients with chronic obstructive pulmonary disease (COPD)? Few questions have attracted more attention in COPD, and the number of commentaries, editorials, and reviews on this topic by far exceeds the limited number of original papers addressing the topic. However, here is one more.

In this issue of the *Journal*, Lipson and colleagues (pp. 1508–1516) report findings from a *post hoc* analysis of the IMPACT (Informing the Pathway of COPD Treatment) trial (1). The trial was enriched for exacerbators, and the primary outcome was the annual rate of on-treatment moderate and severe exacerbations comparing a fixed combination of fluticasone furoate (FF), umeclidinium (UMEC), and vilanterol (VI) with fixed combinations of UMEC/VI and FF/VI. Mortality was listed among “other efficacy outcomes” (2), and the article presents an expanded analysis of mortality compared with the one reported in their primary report (3). By obtaining information on vital status at end of the trial for an additional 574 patients, the authors had information on vital status for 10,313 of the 10,355 patients included in the trial. The authors compared mortality in patients randomized to FF/UMEC/VI with those randomized to either a fixed combination of FF/VI or a fixed combination of UMEC/VI. After 1 year, there were significantly fewer deaths in the triple-combination group (FF/UMEC/VI) than in the UMEC/VI group (absolute risk reduction [ARR], 0.83%; relative risk reduction [RRR], 28%; $P = 0.042$) but not when comparing the FF/VI group with the UMEC/VI group (ARR, 0.55%; RRR, 18%; $P = 0.190$). When analyses were restricted to on-treatment mortality, both these group analyses were statistically significant. The authors convincingly showed that missing outcome data on the 0.4% of the patient population were very unlikely to have had an impact on the reported estimates.

Only a few previous trials of an ICS-containing treatment have had mortality as a primary outcome. The TORCH (Toward a Revolution in COPD Health) study (4) found a 2.6% ARR and a 17.5% RRR in deaths when comparing the combination of salmeterol and fluticasone propionate with placebo. However, the P value was adjusted from 0.041 to 0.052 to take a late interim analysis into account, and the study has since been referred to as “negative.” The SUMMIT (Study to Understand Mortality and Morbidity) (5) compared a combination of vilanterol and fluticasone furoate with placebo in patients with moderate COPD

at heightened cardiovascular risk and could not demonstrate an effect on overall mortality (ARR, 0.7%; RRR, 12%; $P = 0.137$). Observational studies had previously indicated a beneficial effect of ICS on mortality, but these are all open to criticism as they lack randomization (6). In neither TORCH nor SUMMIT did the long-acting β -agonist have any effect on mortality. In the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial, an effect on mortality, which was not the primary outcome, was likely present but depended on choice of analysis (7). No other single study of a fixed triple combination has analyzed mortality, but a recent pooled *post hoc* analysis indicated a favorable effect on mortality of the fixed combination of extrafine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (8).

It is unlikely that there will be any more studies of inhaled medications with mortality as primary outcome. Even though treatment before entering a study is unlikely to affect the study findings (9), studies including patients who will have their existing treatment changed—and sometimes reduced—will always be open to criticism (10). Studies of symptomatic treatment-naïve patients with COPD are not possible, and placebo-controlled trials are unethical. Withdrawal from longer-term studies is inevitable and will dilute study findings (11), and one could always question whether the findings from rigorous efficacy trials are transferable to usual clinical practice (12). Nonetheless, the IMPACT findings are probably the best we will have, and we cannot shy away from having an opinion on the effects seen, with the usual “more studies are needed.”

Now, should the discussion of these new IMPACT findings then focus on the small ARRs, the importance of the findings for the large patient group, the risk of pneumonia in the many versus the survival gain in the few, or the strengths and weaknesses of these findings? I would argue that this would be a waste of time. I would rather ask why we keep looking for reasons why a “proper” pharmacological treatment in COPD should *not* lead to a reduction in mortality in symptomatic COPD patients with a history of exacerbations. By “proper,” I mean a treatment that affects lung function, health status, and frequency of moderate and severe exacerbations—which we can achieve with long-acting bronchodilators in the majority of patients and with ICS in a proportion of these (13). To a COPD clinician it is clear that not all patients have marked benefits from the treatments, but to a vast number of patients, new long-acting inhaled drugs in simple combination inhalers have made a marked impact on their well-being and their ability to keep up with daily activities. Given what we know about risk factors for mortality in multimorbidity in general and COPD in particular, it really does not surprise me that these patients live longer. The challenge is now the same as for all other areas where individualized management is “the thing.”

©This article is open access and distributed under the terms of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

Supported by the National Institute for Health Research Manchester Biomedical Research Centre (J.V.).

Originally Published in Press as DOI: 10.1164/rccm.202003-0622ED on March 26, 2020

How do we provide ICS-containing treatment to those who will benefit the most with the fewest side effects, in particular pneumonia? Blood eosinophils is undoubtedly a step in the right direction (13, 14), but better understanding and application of this and future biomarkers could help us better identify those with the biggest benefit. In the meantime, we can appreciate that for patients with COPD with frequent exacerbations we can already provide treatments that make them live both better and longer. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Jørgen Vestbo, D.M.Sc.
Division of Infection, Immunity, and Respiratory Medicine
The University of Manchester
Manchester, United Kingdom
and
North West Lung Centre
Manchester University NHS Foundation Trust
Manchester, United Kingdom

ORCID ID: 0000-0001-6355-6362 (J.V.).

References

- 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.
- Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al.* Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–1680.
- 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.
- Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al.*; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
- Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, *et al.*; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–1826.
- Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. *N Engl J Med* 2020;382:674–678.
- Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP; UPLIFT Study Investigators. Mortality in the 4-year trial of Tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:948–955.
- Vestbo J, Fabbri L, Papi A, Petruzzelli S, Scuri M, Guasconi A, *et al.* Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J* 2018;52:1801230.
- Vestbo J, Dransfield M, Anderson JA, Brook RD, Calverley PMA, Celli BR, *et al.* Impact of pre-enrolment medication use on clinical outcomes in SUMMIT. *ERJ Open Res* 2019;5:00203-2018.
- Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur Respir J* 2008;31:927–933.
- Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, *et al.* Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J* 2011;5:44–49.
- Woodcock A, Boucot I, Leather DA, Crawford J, Collier S, Bakerly ND, *et al.* Effectiveness versus efficacy trials in COPD: how study design influences outcomes and applicability. *Eur Respir J* 2018;51:1701531.
- Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019;53:1900164.
- Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, *et al.* Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *Lancet Respir Med* 2019;7:745–756.

Copyright © 2020 by the American Thoracic Society



Increasing Pulmonary Rehabilitation Uptake after Hospitalization for Chronic Obstructive Pulmonary Disease Exacerbation

Let's Rise to the Challenge

Acute exacerbations of chronic obstructive pulmonary disease (COPD) worsen the symptoms, airflow obstruction, functional disability, and quality of life, and increase mortality risk for those with the disease (1), particularly among those requiring hospitalization. Recovery from COPD exacerbations is often slow; symptoms may take months to resolve and hospital readmissions are common (1, 2). Pulmonary rehabilitation (PR) is an essential

component of the integrated care of individuals with COPD and other chronic respiratory diseases (3) and is effective in fostering patients' recovery after hospitalization for COPD exacerbation (4, 5). When delivered within 4 weeks of exacerbation, it improves exercise capacity, symptoms, and quality of life and reduces hospital readmission risk (4); it is recommended in disease management guidelines (1, 6). Studies have also shown a survival advantage related to postexacerbation PR (4, 7). However, few patients are referred to PR after hospitalization for COPD exacerbation (8, 9). Moreover, when offered, patients' uptake of PR is low (10, 11).

In this issue of the *Journal*, Barker and colleagues (pp. 1517–1524) report the findings of a randomized controlled trial evaluating the effects of a novel video intervention on PR uptake

Ⓜ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202003-0705ED on April 27, 2020