References

1. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. *Am J Respir Crit Care Med* [online ahead of print] 14 Oct 2020; DOI: 10.1164/rccm.202004-0993OC. Published in final form as *Am J Respir Crit Care Med* 2021;203:831–840 (this issue).
2. Khan F, Mat A, Hogan AE, Kent BD, Eigenheer S, Corrigan MA, *et al*. Preliminary asthma-related outcomes following glucagon-like peptide 1 agonist therapy. *QJM* 2017;110:853–854.
3. Jin T, Weng J. Hepatic functions of GLP-1 and its based drugs: current disputes and perspectives. *Am J Physiol Endocrinol Metab* 2016;311:E620–E627.
4. Zhu T, Wu X-L, Zhang W, Xiao M. Glucagon Like Peptide-1 (GLP-1) modulates OVA-induced airway inflammation and mucus secretion involving a Protein Kinase A (PKA)-dependent Nuclear Factor-κB (NF-κB) signaling pathway in mice. *Int J Mol Sci* 2015;16:20195–20211.
5. Dougherty RH, Sidhu SS, Raman K, Solon M, Solberg OD, Caughey GH, *et al*. Accumulation of intraepithelial mast cells with a unique protease phenotype in T(H)2-high asthma. *J Allergy Clin Immunol* 2010;125:1046–1053, e8.
6. Ojima A, Ishibashi Y, Matsui T, Maeda S, Nishino Y, Takeuchi M, *et al*. Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of streptozotocin-induced diabetic rats by blocking advanced glycation end product-induced protein arginine methyltranferase-1 expression. *Am J Pathol* 2013;182:132–141.

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Reply to Watchorn *et al.*

From the Authors:

We appreciate the insightful comments by Watchorn and colleagues in response to our report on the association between asthma exacerbations and GLP-1RA (glucagon-like peptide-1 receptor agonist) use in patients with comorbid asthma and type 2 (T2) diabetes mellitus (T2DM) (1). The intersection of metabolic disease and asthma is a complex and compelling area of study with direct implications for treatment strategies (2) and clinical outcomes (3). Increasingly, work is being done to try to disentangle the confounding effects of body mass index, insulin resistance, and other features of the metabolic syndrome (which also increase the likelihood of cardiovascular disease) in asthma (4). Inclusion of atherosclerotic cardiovascular disease (defined as $\geqslant$1 International Classification of Diseases, ninth edition, or International Classification of Diseases, tenth edition, codes) as a variable in our model did not change the primary outcome, as follows: counts of asthma exacerbations in all comparator groups remained significantly ($P \leqslant 0.05$) higher than in the GLP-1RA user group. Atherosclerotic cardiovascular disease was also not a significant predictor ($P = 0.97$) in the primary outcome model. This is consistent with the clinical context, as asthma symptoms (secondary outcome) may be nonspecific, but asthma exacerbations (defined as corticosteroid prescriptions) may be far less so.

Importantly, the authors also raise the question of mechanism as it relates to the heterogeneity of asthma phenotypes on the inflammatory spectrum. Our study cohort was comprised of adults with asthma and T2DM, with a mean body mass index ranging from 34 to 39, clinical characteristics associated with non-T2 asthma (5). In a lean murine model of allergic airway inflammation, the GLP-1RA liraglutide inhibited T2-inflammation pathways (6). Additional preclinical and clinical investigations are underway in our research groups to determine the actions of GLP-1R agonists in T2 and non-T2 airway inflammation. Obese asthma models and patient-oriented biomarker studies would be helpful in providing additional insight to the question of mechanism and would inform the design of prospective studies. Our retrospective observational study was conducted within the context of routine care and was not designed to compare the effects of GLP-1 analogs with exendin-based GLP-1 agents, which would require much larger sample sizes (particularly for detection of a rare outcome) or a prospective study.

In conclusion, Watchorn and colleagues' letter highlights the need for prospective studies of GLP-1RA therapy using single agents within the class (e.g., GLP-1 analogs or exendin-based therapies) in well-phenotyped asthma populations with outcomes aligned with regulatory approval metrics—we absolutely agree, and we look forward to this unfolding area of investigation. ■

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Dinah Foer, M.D.
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Patrick E. Beeler, M.D.
Brigham and Women's Hospital
Boston, Massachusetts
and
University of Zurich
Zurich, Switzerland

Jing Cui, M.D., Ph.D.
Elizabeth W. Karlson, M.D., M.S.
David W. Bates, M.D., M.Sc.
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Katherine N. Cahill, M.D.*
Vanderbilt University Medical Center
Nashville, Tennessee

On behalf of all the authors

ORCID IDs: 0000-0002-0717-5714 (D.F.); 0000-0002-8549-1835 (K.N.C.).

*Corresponding author (e-mail: katherine.cahill@vumc.edu).

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References

1. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. *Am J Respir Crit Care Med* [online ahead of print] 14 Oct 2020; DOI: 10.1164/rccm.202004-0993OC. Published in final form as *Am J Respir Crit Care Med* 2021; 203:831–840 (this issue).
2. Wu TD, Keet CA, Fawzy A, Segal JB, Brigham EP, McCormack MC. Association of metformin initiation and risk of asthma exacerbation: a claims-based cohort study. *Ann Am Thorac Soc* 2019;16:1527–1533.
3. Yang G, Han Y-Y, Forno E, Yan Q, Rosser F, Chen W, *et al*. Glycated hemoglobin A1c, lung function, and hospitalizations among adults with asthma. *J Allergy Clin Immunol Pract* 2020;8:3409–3415, e1.
4. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, *et al*. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. *Am J Respir Crit Care Med* 2020;202:973–982.
5. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, *et al*.; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;4:574–584.
6. Toki S, Goleniewska K, Reiss S, Zhang J, Bloodworth MH, Stier MT, *et al*. Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo. *J Allergy Clin Immunol* 2018;142: 1515–1528, e8.

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Triple-Therapy Trials for Chronic Obstructive Pulmonary Disease: Methodological Considerations in the Mortality Effect

To the Editor:

Currently, modern epidemiology identifies a number of necessary methodological requirements in the design of clinical trials. Three of these measures are intention-to-treat (ITT) analysis, correction for multiplicity, and adjustment of the analysis for confounding variables. Two large clinical trials have recently been published evaluating the efficacy and safety of a triple therapy in a single inhalation device, both of which analyzed mortality. The IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment) study evaluates the combination of fluticasone furoate, umeclidinium, and vilanterol (1), whereas the ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) study assesses combined treatment with budesonide, glycopyrronium, and formoterol fumarate (2). Because of the recent publication of a mortality analysis from the ETHOS study (3), we would like to comment on these three methodological aspects in the mortality analysis of these clinical trials.

First, the potential confounders for the mortality analysis in both studies are clearly insufficient. In the IMPACT trial, time to all-cause mortality included age and sex as covariates (1). The ETHOS trial's time to death was adjusted by the covariates of baseline post-bronchodilator percent-predicted FEV_1 and baseline age (2). However, a considerable number of predictors of mortality have been described (4). This is highly relevant, as more covariates would have an effect on current results and might also change the effect estimations.

Second, all analyses must be performed under the ITT principle. This analysis requires that all patients be analyzed according to their original random allocation. The IMPACT and ETHOS trials use confusing terminology when identifying the test population, with their use of the terms "on treatment" and "off treatment." Interestingly, the main mortality analysis of IMPACT refers to on-treatment patients, who do not correspond to the ITT population (1). In the IMPACT study, the inclusion of off-treatment cases maintained significance, but it was an unadjusted analysis. The ETHOS trial also provides an unadjusted association for the on/off population. In addition, in ETHOS, deaths were taken into account inconsistently for the survival analysis between groups. The mortality database had to be completed by contacting patients or next of kin using information found by searching public records or via social media. In the final retrieved dataset, the numbers of deaths used in the analysis were 30 out of 37 identified deaths (81.0%) for budesonide/glycopyrronium/formoterol fumarate 320, 44 out of 55 identified deaths (80.0%) for budesonide/glycopyrronium/formoterol fumarate 160, 56 out of 64 identified deaths (87.5%) for glycopyrronium/formoterol fumarate, and 40 out of 46 identified deaths (86.9%) for budesonide/formoterol fumarate. As a result, fewer deaths in the triple-therapy experimental arms were included in the analysis. With such a low number of deaths in each group, additional deaths included in the analysis might have changed the results significantly. For example, this could have occurred if there had been a difference in the effort of retrieving deaths between groups.

Finally, it is well known that clinical trials that include the evaluation of multiple outcomes have an increased probability of finding an association. Therefore, it is essential to select a suitable statistical strategy to deal with this multiplicity to make reliable inferences (5). Consequently, conducting the analysis of these data without the correct statistical adjustment leads to a greater probability of drawing incorrect conclusions. In both trials, the assessment of the association with mortality was performed without adjustment for multiplicity.

Altogether, these mortality analyses have some methodological limitations. Because correcting these factors may yield different conclusions, these results should be considered merely as hypothesis-generating data to be further explored after a reanalysis of the data or an *ad hoc* clinical trial with mortality as the primary outcome. ■

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