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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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 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 FEV1 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.

CORRESPONDENCE

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