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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. ■

Supported by a grant from the Instituto de Salud Carlos III (Fondo de Investigación Sanitaria project PI18/00682) included in the Acción Estratégica en Salud, Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2013–2016, Instituto de Salud Carlos III, Fondos FEDER.

Author Contributions: J.L.L.-C. conceived the idea of the letter and wrote the initial draft, and A.F.-V. and A.R.-R. improved the manuscript with novel ideas. All authors approved the final content.

Originally Published in Press as DOI: 10.1164/rccm.202012-4386LE on January 14, 2021

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

Acknowledgment: The authors thank Simon Armour from Academia Britannica for improving the English.

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Mortality in ETHOS: A Question of "Power"

To the Editor:

We read with great interest the paper by Martinez and colleagues (1) concerning the additional analyses of all-cause mortality of the ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) trial (2). However, we are puzzled that although mortality was a prespecified secondary endpoint of the ETHOS trial and a large section of the discussion was focused on the reduced risk of death in patients treated with budesonide/glycopyrrolate/formoterol fumarate (BGF) 320/18/9.6 μg compared with glycopyrrolate/formoterol fumarate (GFF) 18/9.6 μg (2), Martinez and colleagues (1) inform the scientific community that data on the vital status of 384 patients (4.51% of the enrolled population) were not included in the primary analysis of the ETHOS trial (2). However, this hasty approach in analyzing an important clinical endpoint such as mortality is somewhat questionable when applied to independent research that has no access to patient-level data of sponsored trials. Furthermore, doubts may arise about whether other data of prespecified secondary endpoints in the ETHOS trial may have been roughly analyzed (2).

Indeed, we recognize that the publication by Martinez and colleagues (1) provides extremely interesting and important findings concerning all-cause mortality in the ETHOS trial, compensating for the flaws of the primary analysis (2). In this respect, the statistically significant superiority in terms of the risk of death of BGF 320/18/9.6 μg over GFF 18/9.6 μg resulted from the analysis of 4,257 patients with chronic obstructive pulmonary disease (COPD) (2,137 plus 2,120, respectively) (1).

Interestingly, the *post hoc* analysis of the power concerning the total adjudicated deaths from the retrieved dataset (1) showed that because of the low mortality prevalence ratio of 0.56 between BGF 320/18/9.6 μg and GFF 18/9.6 μg, data on vital status from at least 5,140 patients with COPD (2,570 each arm) should have been analyzed to have 80% power for observing a statistically significant result ($1 - \alpha = 0.95$) if a truly beneficial effect was present for BGF 320/18/9.6 μg versus GFF 18/9.6 μg (sample-size calculation performed by using OpenEpi [Emory University] [3]). Thus, 883 additional patients with COPD are needed in the current analysis of the retrieved dataset to exclude the possibility that statistical errors (type I or II) may have affected the results published by Martinez and colleagues (1). Definitely, the ETHOS trial was not adequately powered to detect a statistically significant difference between BGF 320/18/9.6 μg and GFF 18/9.6 μg with respect to the risk of all-cause mortality.

Moreover, looking at the problem from a different point of view, the current evidence (1) resulting from the limited number of events does not allow ruling out that BGF 160/18/9.6 μg may also protect against the risk of all-cause mortality when compared with GFF 18/9.6 μg, precluding a potential therapeutic option.

In any case, the IMPACT (Informing the Pathway of COPD Treatment) trial (4) also goes in the same direction with respect to the effect of triple therapy versus dual-bronchodilation therapy on all-cause mortality, with data from the ETHOS trial suggesting that such an effect is dose dependent and that the most protective effect against mortality seems to be related to protection against cardiovascular events (1).

Overall, data on the risk of death resulting from underpowered studies in which the mortality rates are as low as those in the ETHOS trial (2) should be interpreted with caution, while also being considered in light of the fact that selected populations with COPD enrolled in clinical trials are generally only partially representative of real-life populations (5). In this regard, the retrieved analysis of Martinez and colleagues (1) has the unquestionable advantage of providing a solid base to correctly design long-term clinical trials to definitely assess whether triple therapy may really reduce the risk of death in COPD. In conclusion, we should

Author Contributions: P.R. and L.C. analyzed the data, interpreted results, wrote the manuscript, and conceived and managed the project.

Originally Published in Press as DOI: 10.1164/rccm.202012-4328LE on January 14, 2021