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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

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never forget the lessons from the TORCH (Towards a Revolution in COPD Health) trial (6). ■

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Reply to López-Campos *et al.* and to Rogliani and Calzetta

From the Authors:

We thank Dr. López-Campos and colleagues and Drs. Rogliani and Calzetta for their interest in our work published recently in the *Journal* (1). They raise several methodological queries regarding ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) that we wish to clarify.

First, the mortality analyses in ETHOS followed the intent-to-treat principle, using a treatment policy estimand that analyzed data from all randomized and treated patients, regardless of whether they discontinued treatment. The "on- and off-treatment" terminology used in our manuscript is a simpler way to describe this approach. In ETHOS, the secondary endpoint of all-cause mortality was prespecified to include both on- and off-treatment data. This analysis was reported in both the primary and secondary publications (1, 2). We published the "on-treatment only" analysis in our secondary publication to provide a comparison with other studies that used this approach.

We acknowledge that ETHOS was not designed primarily as a mortality study, and the sample size was therefore not selected on the basis of considerations of power for this secondary endpoint. However, we disagree with the conclusions of the *post hoc* power analysis conducted by Rogliani and Calzetta. Such an analysis is of limited usefulness when a significant effect was shown, and the fact that a treatment effect of budesonide/glycopyrrolate/formoterol fumarate (BGF) 320 versus glycopyrrolate/formoterol fumarate (GFF) was detected means that this comparison was not affected by type II error (failing to show a difference when one truly exists). Although we cannot rule out a type II error in the comparisons of BGF 160 with dual therapies, which did not reach $P < 0.05$, we did not make any conclusive claims of a benefit, or lack thereof, with this dose. It should also be noted that the original analysis for this endpoint, published in our primary publication, was in fact included in the testing hierarchy for type I error control (2). However, the *P* values for this endpoint are described as unadjusted because of the results for severe exacerbations higher in the hierarchy, which did not reach significance. Although there was no adjustment for multiplicity for the supplemental analyses published in our secondary manuscript (1), a type I error (detecting a difference that does not truly exist) is unlikely given the size of the *P* value, the prespecification of the endpoint as secondary, the consistency with the original analysis, and the corroborating evidence from other studies.

We also wish to clarify that the original mortality analyses, published in the primary publication (2), were not missing 384 patients. These patients were included, but their vital status information did not extend to 52 weeks. The extensive follow-up conducted to retrieve 52-week vital status data for these patients did not apply to the other endpoints presented in the primary publication, which were analyzed without postdiscontinuation data. Although posttreatment data were collected for other endpoints, post-study information other than vital status could not have been collected because informed consent was no longer in place. Therefore, except for mortality, the results represent the final analyses with all available data.

Regarding the choice of covariates in the model, we disagree with the assertion that including more covariates in the model would have affected the results. As ETHOS was a randomized study, potential confounders were balanced across groups (2). Therefore, there is no reason to expect a large impact of additional covariates on the estimates. We have performed sensitivity analyses including eosinophil counts or prior inhaled corticosteroid use as additional covariates in the model; in both analyses, the hazard ratio for BGF 320 versus GFF remained 0.51. Furthermore, the subgroup analyses reported in our paper show that the incidence of death was lower with BGF 320 than with GFF across all subgroups examined for exacerbation history, FEV_1% predicted, and prior medication (except for patients not

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