Authors' reply to 'Explaining differential effects of tiotropium on mortality in COPD'

We thank Dr Lipworth[1] for his response to our editorial,[2] which we emphasise related to the safety of tiotropium by Respimat, not by Handihaler. We agree that UPLIFT provides very reassuring data regarding the safety of tiotropium administered by the Handihaler device in a chronic obstructive pulmonary disease (COPD) population from which people with significant diseases other than COPD, which could compromise participation or put the patient at risk, were excluded. Patients with a range of commonly encountered comorbidities, including myocardial infarction in the recent 6 months, unstable arrhythmia or hospitalisation for heart failure in the recent 12 months, or need for oxygen therapy >12 h/day, and moderate renal impairment were not eligible for UPLIFT, thereby limiting the generalisability of the findings. We also agree that a real-life analysis, such as undertaken using the Tayside data, confirming the mortality reduction on tiotropium is reassuring, although based on data from a retrospective, observational database. As well, 90% of these patients were taking tiotropium by Handihaler, and in our editorial we do not contest the safety of this tiotropium dose and mode of administration. The non-experimental study of greater relevance to the Respimat device is the Dutch general practice database analysis which reported that the use of tiotropium Respimat was associated with an increased risk of dying (HR 1.52, 95% CI 1.24 to 1.87), an association that remained upon adjustment (HR 1.33, 95% CI 1.07 to 1.65).[3]

There is no question that a wide CI around the estimate of the number needed to treat to cause harm reduces the degree of certainty. However, we do not agree with the suggestion that a meta-analysis which does not have mortality as its primary endpoint cannot provide important information on this endpoint, particularly when that evidence aligns with other meta-analyses and data obtained from large randomised controlled trials.[4] Many would argue that when an efficacious and safer alternative is available, it should be chosen until further studies narrow such CI's and nail the verdict, or exonerate the Respimat. In taking a precautionary approach and maximising patient safety until these data are available, it is not unreasonable to reflect on the possibility of the worst scenario (ie, 1 additional death for every 52 patients treated with 5 μg tiotropium Respimat for 1 year), rather than the best.

With regard to the biological plausibility, we would argue there are several possible mechanisms, as yet poorly elucidated,[5] and that these are not incongruous, nor inconsistent with the Handihaler data, but fit entirely with the at-risk COPD population and the observations made in clinical trials

of tiotropium administered by Respimat.[5] They include higher peak plasma tiotropium levels with Respimat, removal of cholinergic tone from the SA node, slower renal excretion and greater propensity to arrhythmias in older patients.

We await with interest the new data which will emerge from the TIOSPIR study (NCT01126437), but its findings may not be definitive for many patients with COPD, as TIOSPIR also excludes patients with significant diseases other than COPD, a recent history of myocardial infarction, hospitalisation for cardiac failure, or any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year. Hopefully, TIOSPIR will inform clinicians regarding the risk of tiotropium Respimat at several doses relative to tiotropium Handihaler, although it will not be able to determine the actual risk with tiotropium Respimat, as the study does not contain a placebo arm. Until adequately powered, prospective randomised trials provide data that reassure us of the safety of Respimat,[6] we do not resile from our recommendation that it is wiser not to prescribe tiotropium by this device.

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