Tiotropium Respimat increases the risk of mortality: pro

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Tiotropium Respimat increases mortality risk. First do no harm. Tiotropium Respimat should not be prescribed in COPD http://ow.ly/mzPGL

Systematic reviews and meta-analyses of randomised controlled trials of medications provide a high standard of evidence to inform clinical practice, and can be considered the "gold standard" for assessing the risk/benefit profile of treatments [1, 2]. Three systematic reviews and meta-analyses (including a Cochrane Review) of randomised placebo-controlled trials of tiotropium Respimat, each using different methods, have demonstrated a 50% increased risk of mortality, with its use in patients with chronic obstructive pulmonary disease (COPD) [3–5]. These analyses provide substantive evidence that tiotropium Respimat increases mortality in the treatment of COPD [6, 7]. It is informative to review each of the systematic reviews and the issues that have been raised relevant to their interpretation.

In 2011 the *British Medical Journal* (*BMJ*) published the first systematic review and meta-analysis, which included all parallel-group, randomised, placebo-controlled trials of tiotropium Respimat in the treatment of COPD that had reported data on mortality and were of a minimum 30-day duration [3] (table 1 [8–10]). Five trials were included in the analysis, two 12-week trials and three 12-month trials, studying 6522 participants. All five trials were judged to be at low risk of bias. Tiotropium Respimat significantly increased the risk of all-cause mortality, relative risk 1.52 (95% CI 1.06–2.16). There was an apparent dose–response effect on all-cause mortality, with RR 1.46 (95% CI 1.01–2.10) and 2.15 (95% CI 1.03–4.51), for the 5-µg and 10-µg preparations, respectively (fig. 1). The overall estimates were not substantially changed by sensitivity analyses using the random effects model, limiting the analysis to three trials of 1-year duration period each, or the inclusion of additional preliminary data on tiotropium Respimat from an unpublished study. An accompanying editorial calculated, based on these figures, that one excess death is expected for every 121 (COPD) patients treated with a 5 µg dose of tiotropium by Respimat for 12 months [11].

The 2012 Cochrane Review of tiotropium included the same five randomised placebo-controlled clinical trials of tiotropium Respimat, but used the Peto method for pooled estimation of odds ratio, which is arguably more appropriate for the combined analysis of rare events such as death [4]. Tiotropium Respimat significantly increased the risk of mortality, OR 1.47 (95% CI 1.04–2.08). In contrast there was no increased risk of mortality with tiotropium HandiHaler, OR 0.92 (95% CI 0.80–1.05).

In 2012 *Thorax* published a systematic review with direct comparison and mixed treatment comparison meta-analyses of randomised controlled trials of medications used in the treatment of COPD that provided data about overall or cardiovascular death, and were a minimum 6 months in trial duration [5]. In the direct comparison meta-analysis, tiotropium Respimat increased the risk of death compared with placebo, OR 1.49 (95% CI 1.05–2.11). The risk was higher for cardiovascular death, in patients with severe COPD and at a higher daily dose. Tiotropium Respimat also increased the risk of death compared with other commonly used inhaled medications for COPD, including tiotropium HandiHaler, OR 1.65 (95% CI 1.13–2.43), long-acting

TABLE 1 Key characteristics and findings of the published randomised placebo-controlled trials of tiotropium Respimat included in analysis of mortality

	Voshaar [8]			Voshaar [8]			Bateman [9]			Bateman [9]			Bateman [10]	
Year of publication	2008			2008			2010			2010			2010	
ClinicalTrials.gov reference	NCT 00239473			NCT 00240435			NCT 00168844			NCT 00168831			NCT 00387088	
Trial duration weeks	12			12			52			52			52	
Treatment titropium/other	10µg	5µg	Placebo	10µg	5µg	Placebo	10µg	5µg	Placebo	10µg	5µg	Placebo	5µg	Placebo
Number of participants	93	88	91	87	92	90	332	332	319	335	338	334	1989	2002
Participants mean age years	64	64	63	64	64	63	65	65	65	66	65	66	65	65
Mean FEV$_1$ % predicted	39	40	42	39	40	42	38	38	38	38	38	38	40	40
Current smokers	37	37	43	37	37	43	35	38	36	35	38	36	36	36
All-cause mortality	1	0	0	1	1	0	8	9	7	11	7	2	52	38

Data presented as n unless otherwise stated. FEV$_1$: forced expiratory volume in 1 s.

β-agonists, OR 1.63 (95% CI 1.10–2.44), and long-acting β-agonist/inhaled corticosteroid combination therapy, OR 1.90 (95% CI 1.28–2.86).

There have been 10 important issues raised in relation to the interpretation of these systematic reviews and meta-analyses, and the individual studies on which they are based.

Validity of analyses

It has been proposed by Boehringer Ingelheim, the sponsor of the tiotropium clinical trials programme and manufacturer of the tiotropium Respimat and HandiHaler products, that alternative estimates of mortality risk, which are not statistically significant, can be derived by undertaking multiple "sensitivity analyses" based on different mortality datasets [12, 13]. However, the consistent finding of a statistically significant increased risk of mortality with tiotropium Respimat obtained by the three, independent, meta-analyses is more likely to be valid.

Analysis of mortality

It has been proposed that analysing mortality is unjustified as it was not the primary endpoint in the clinical trials and, as such, should be viewed as hypothesis-generating [14]. However, this viewpoint is flawed [15]. Death caused by treatment is clearly a key secondary outcome relevant to both patients and clinicians, and there was a strong *a priori* reason for examining mortality due to the initial clinical trial programmes that suggested that both ipratropium bromide and tiotropium may increase the risk of mortality [16]. The reporting of mortality is mandatory [17], mortality can be reliably and objectively verified and there is no methodological reason to dismiss the findings. A weak argument can be made that choosing different endpoints in secondary analyses may inflate Type I error rates in a relatively limited dataset. However, this issue applies to multiple sensitivity analyses of mortality based on different datasets [12, 13], rather than the primary analysis of mortality as undertaken in the independent meta-analyses. As death is an important adverse outcome and COPD is a common disease, consideration of the mortality findings is crucial in determining the risk/benefit profile of this medication.

All-cause mortality and cause-specific mortality

The critique that the causes of death were diverse [12] is weak, as that is simply the nature of all-cause mortality. Previous research has shown that allocation of the cause of death in clinical trials of tiotropium is not straightforward and that "all-cause" mortality may be a stronger endpoint than cause-specific mortality because of diagnostic uncertainty [18]. Despite this, both the *BMJ* and *Thorax* systematic reviews found an increased risk of cardiovascular death with tiotropium Respimat compared with placebo, RR 2.05 (95% CI 1.06–3.99) [3], and OR 1.96 (95% CI 1.07–3.60) [5], respectively. This twofold increase in cardiovascular mortality accounts for about half the increase in all-cause mortality.

Imbalance in randomisation

The critique that the increase in mortality with tiotropium Respimat could be attributed to an unusually low rate of mortality in the placebo group of these trials [19], challenges the validity of well-designed and conducted, randomised, placebo-controlled trials. A systematic failure of randomisation in all five clinical trials, which provide the evidence base, is highly unlikely. Both the tiotropium Respimat and the placebo
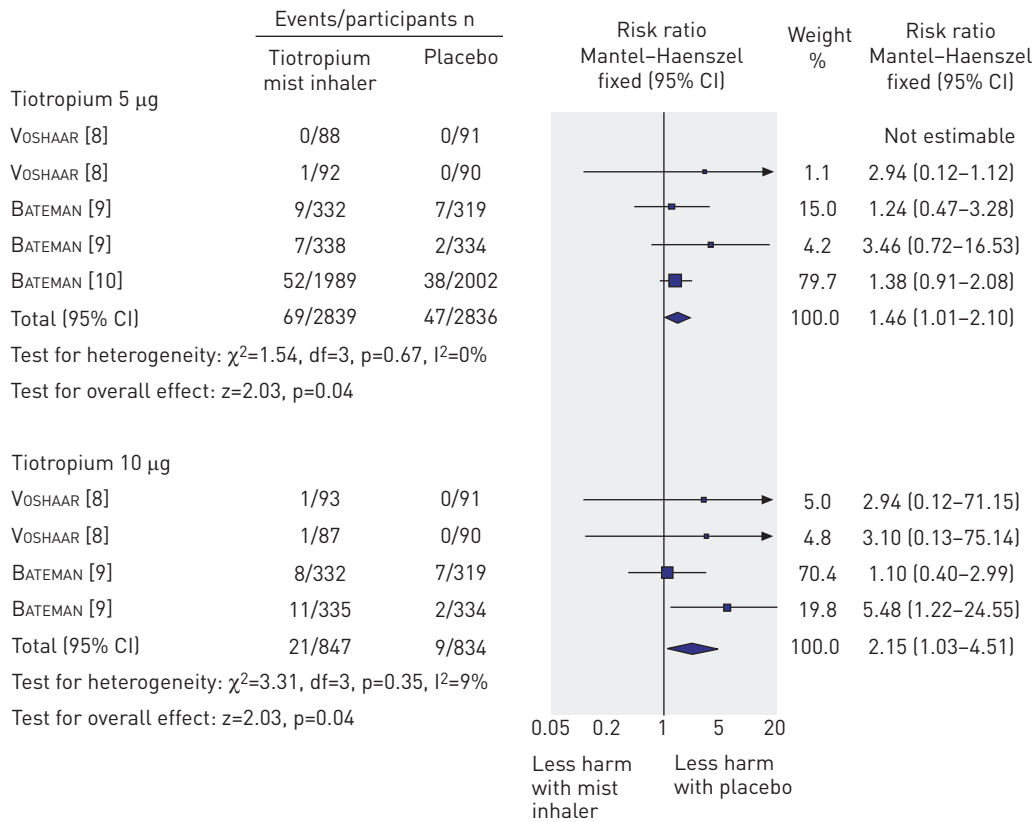
FIGURE 1 Meta-analysis of the risk of all-cause mortality with tiotropium delivered by the Respimat Soft Mist Inhaler (5 μg or 10 μg) from published, randomised, placebo-controlled trials of patients with chronic obstructive pulmonary disease. Reproduced and modified from [3] with permission from the publisher.

groups had comparable baseline characteristics in all the trials (table 1) and there was adequate allocation concealment during randomisation [3, 4].

Higher withdrawal rate with placebo

This potential bias was minimised by the steps taken by the trial investigators to ascertain the vital status of all randomised patients, even if they had discontinued treatment, thereby achieving almost complete capture of the mortality outcomes [3]. For example, in the largest 1-year study the vital status was known for ≥99% of randomised patients for the primary analysis of death by the end of the planned treatment period (day 337) [10]; in the combined analysis of the other two 1-year studies, vital status was known for 97.7% of randomised patients for the primary analysis of death by the end of the planned treatment and 30-day follow-up observation period (day 366) [9, 20].

Inclusion of 10 μg data

The suggestion that 10 μg data should not be included in the meta-analyses because tiotropium Respimat is not marketed in this dose [12] contradicts the Cochrane Handbook that recommends an amalgamation of all treatment arms into one group [21]. Importantly it provides evidence of a probable dose–response relationship of tiotropium Respimat and mortality, which further supports a causal relationship. Inclusion of data from the higher dose arms of the studies is also relevant to patients with renal impairment, as tiotropium is renally excreted and plasma concentrations are around twofold higher in moderate-to-severe renal impairment [22]. Despite this, the two meta-analyses, which reported data on the 5 μg preparation alone, both reported an increased risk of death of 1.46 (95% CI 1.01–2.10) [3] (fig. 1) and 1.46 (95% CI 1.01–2.14) [5], respectively, and a 5 μg dose was also associated with an increased risk of cardiovascular death, OR 2.18 (95% CI 1.15–4.41) [5].

Underestimate of risk

The estimates of risk from the tiotropium Respimat research programme are likely to underestimate the actual risk of mortality in an unselected group of COPD patients with cardiovascular comorbidity. In this

regard, the exclusion criteria in the largest tiotropium Respimat study included a recent history of unstable arrhythmias, myocardial infarction or heart failure requiring hospital admission [10], thereby specifically ensuring the exclusion of patients at highest risk of cardiovascular mortality. The importance of cardiovascular comorbidity in determining this risk is illustrated in the Food and Drug Administration (FDA) review of this study, in which even after exclusion of such high-risk patients, those with a baseline history of cardiac disease or cardiac rhythm disorder had a markedly increased risk of cardiac death with 5 μg of tiotropium Respimat, RR 4.03 (95% CI 1.15–14.13) and 8.61 (95% CI 1.10–67.23), respectively [20].

Differential risk with tiotropium products

Both the Cochrane [4] and *Thorax* [5] meta-analyses have reported no effect of tiotropium HandiHaler on mortality risk, and a significant difference in mortality risk between the HandiHaler and Respimat inhalers. It has been suggested that this difference may weaken the evidence of mortality risk with tiotropium Respimat [12]. There are at least three possible explanations that may account for the differential risk of the two formulations of tiotropium. Firstly, inhalation of the 5 μg and 10 μg doses of tiotropium from the Respimat device may result in greater systemic exposure to tiotropium than the 18 μg dose from the Handihaler device. In pharmacokinetic studies, two to threefold higher peak and steady-state plasma concentrations have been demonstrated with the 10 μg dose by Respimat compared with the 18 μg tiotropium dose from the HandiHaler, whereas the 6–35% higher concentrations with the 5 μg dose *via* Respimat are less marked [23, 24].

The second possibility is that the tiotropium Respimat studies may have been more likely to have included patients at increased risk with tiotropium, in particular those with known cardiac rhythm disorders [7]. This issue has proven difficult to assess, due to the marked inconsistencies in the reporting of exclusion criteria between the sponsor's unpublished study protocols, the publically registered protocols and the published manuscripts for the tiotropium Respimat studies. Furthermore, COPD populations screened for inclusion in the studies are likely to vary between centres, and overarching exclusion criteria such as ''patients who had a disease that might put them at risk because of study participation'' are sensitive to investigator interpretation, resulting in selection biases that may be very difficult to ascertain *post hoc*, making it difficult to determine which patients were excluded [7]. However, in support of this possibility, data submitted to the FDA [25] indicates that patients with a history of cardiac rhythm disorders were more likely to be enrolled in the major tiotropium Respimat study [10], than in the major tiotropium Handihaler study [26], (11.8% *versus* 6.8%, respectively, RR 1.72 (1.54–1.96)).

The third possibility is that repeated exposure to low concentrations of the antibacterial agent benzalkonium chloride included together with the stabilising agent ethylene diamine tetra-acetic acid (EDTA) in the tiotropium Respimat, but not HandiHaler device, may lead to adverse effects [27]. Benzalkonium chloride has bronchoconstrictor properties, being only 7.4 times less potent as a bronchoconstrictor agonist than histamine [28–30]. Furthermore, exposure to benzalkonium chloride is a recognised cause of occupational asthma [31–33]. The administration of placebo Respimat solution containing benzalkonium chloride in a concentration of 100 $\mu g \cdot mL^{-1}$ causes bronchoconstriction with a fall in forced expiratory volume in 1 s (FEV_1) of ⩾15% from baseline in 4.3% of occasions in patients with COPD [34]. While this bronchoconstriction is prevented with the inclusion of tiotropium in the Respimat solution containing benzalkonium chloride it shows the potential acute airways effects of benzalkonium chloride in COPD [34]. The long-term airways effects of repeated administration of benzalkonium chloride and EDTA in COPD have not been studied.

Biological plausibility

There is biological plausibility in that inhaled anticholinergic medications have pro-arrhythmic effects, which have been associated with increased risk of cardiac mortality [35]. Their importance is also suggested by the observation that the increased mortality risk with tiotropium Respimat is present in patients with a history of a cardiac rhythm disorder rather than coronary artery disease [20]. Biological plausibility is also suggested by the observation that ipratropium bromide increases cardiovascular risk, thereby suggesting that the increase in risk may represent a class effect of inhaled anticholinergic agents. This was originally observed in the Lung Health Survey, in which the regular use of ipratropium bromide by metered dose inhaler increased the risk of cardiovascular death, RR 2.57 (95% CI 1.12– 6.62) [36]. Ipratropium bromide was also noted to increase the risk of hospital admission due to arrhythmias with a relatively high prevalence of supraventricular tachycardia. Subsequently, a systematic review and meta-analysis of five trials, including 6,155 subjects, reported that ipratropium bromide increased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction or stroke, RR 1.70 (95% CI 1.19–2.42) [16].

Generalisability

The generalisability of the findings to clinical practice is shown by a recent study from a Dutch general practice database [37]. The use of tiotropium Respimat was associated with an increased risk of dying, hazard ratio 1.27 (95% CI 1.03–1.57) with the highest risk for cardiovascular/cerebrovascular death, HR 1.56 (95% CI 1.08–2.25). The risk was present in patients with coexisting cardiovascular disease, HR 1.36 (95% CI 1.07–1.73) rather than in patients without, HR 1.02 (95% CI 0.61–1.71). This extension of the mortality findings from randomised placebo-controlled trials to a real world non-experimental study provides evidence of a consistent effect with different study designs.

Conclusions

In conclusion, the three systematic reviews and meta-analyses of randomised placebo-controlled trials, undertaken by independent groups of investigators using different methods, provide level 1+ scientific evidence (well conducted meta-analyses of randomised placebo-controlled trials with a low risk of bias) that tiotropium Respimat increases the risk of cardiovascular and all-cause death. To propose otherwise challenges internationally accepted principles of evidence-based medicine. In the absence of evidence of greater clinical benefit with tiotropium Respimat compared with tiotropium HandiHaler [38], a recommendation can be made that the 5 µg and 10 µg preparations of tiotropium Respimat should not be prescribed in the treatment of COPD [6, 7].

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