Tiotropium Respimat Inhaler and the Risk of Death in COPD

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ABSTRACT

BACKGROUND
Tiotropium delivered at a dose of 5 μg with the Respimat inhaler showed efficacy similar to that of 18 μg of tiotropium delivered with the HandiHaler inhalation device in placebo-controlled trials involving patients with chronic obstructive pulmonary disease (COPD). Although tiotropium HandiHaler was associated with reduced mortality, as compared with placebo, more deaths were reported with tiotropium Respimat than with placebo.

METHODS
In this randomized, double-blind, parallel-group trial involving 17,135 patients with COPD, we evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 μg or 5 μg, as compared with tiotropium HandiHaler at a once-daily dose of 18 μg. Primary end points were the risk of death (noninferiority study, Respimat at a dose of 5 μg or 2.5 μg vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study, Respimat at a dose of 5 μg vs. HandiHaler). We also assessed cardiovascular safety, including safety in patients with stable cardiac disease.

RESULTS
During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.96; 95% confidence interval [CI], 0.84 to 1.09; Respimat at a dose of 2.5 μg vs. HandiHaler: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) and not superior to HandiHaler with respect to the risk of the first exacerbation (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.98; 95% CI, 0.93 to 1.03). Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

CONCLUSIONS
Tiotropium Respimat at a dose of 5 μg or 2.5 μg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 μg in patients with COPD. (Funded by Boehringer Ingelheim; TIOSPIR ClinicalTrials.gov number, NCT01126437.)

*Investigators in the Tiotropium Safety and Performance in Respimat (TIOSPIR) study are listed in the Supplementary Appendix, available at NEJM.org.

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TIOTROPIUM (SPIRIVA, BOEHRINGER INGELHEIM), a long-acting inhaled anticholinergic bronchodilator, improves lung function, quality of life, and exercise endurance and reduces exacerbations in patients with chronic obstructive pulmonary disease (COPD). Cross-study comparisons have suggested the potential superiority of tiotropium Respimat in terms of COPD exacerbations, as compared with HandiHaler. Concern about the safety of tiotropium Respimat was expressed when a post hoc pooled analysis of three 1-year trials and one 6-month placebo-controlled trial showed that tiotropium Respimat at a dose of 5 μg was associated with excess mortality in the planned treatment period (rate ratio, 1.33; 95% confidence interval [CI], 0.93 to 1.92), particularly among patients with known cardiac rhythm disorders. Subsequent meta-analyses and reviews of the Respimat trials database by various authors showed a significant increase in the risk of death associated with tiotropium Respimat, as compared with placebo. These concerns have driven a continuing debate about the cardiac safety of anticholinergic agents in general and the Respimat formulation in particular.

The results were contrary to the experience with tiotropium HandiHaler in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, in which fewer deaths were observed with HandiHaler treatment than with placebo in the planned treatment period (14.4% vs. 16.3%; hazard ratio, 0.87; 95% CI, 0.76 to 0.99). The findings also differed from the results of several meta-analyses and data reviews, which have shown no link between tiotropium HandiHaler or Respimat and cardiovascular events or death in patients with COPD. Given the small amount of safety data for tiotropium Respimat at a dose of 5 μg (6448 patients, with 5487 patient-years at risk), and as compared with HandiHaler at a dose of 18 μg (17,014 patients, with 23,934 patient-years at risk), a relationship between tiotropium Respimat and the risk of death could not be established.

On the basis of the results of the initial pooled safety analysis of tiotropium Respimat at a dose of 5 μg, we initiated the Tiotropium Safety and Performance in Respimat (TIOSPIR) trial. Here, we report the primary results of this large-scale, randomized, prospective evaluation of the safety and efficacy of tiotropium Respimat, as compared with tiotropium HandiHaler.

METHODS

STUDY DESIGN AND OVERSIGHT

The study methods have been described in detail previously, and the complete study protocol is available with the full text of this article at NEJM.org. The trial was performed in accordance with the provisions of the Declaration of Helsinki, and the study protocol and procedures were approved by relevant institutional review boards and ethics committees. All the patients provided written informed consent.

In this event-driven study, which was designed to continue until at least 1266 deaths had occurred, patients were randomly assigned to one of three groups: once-daily tiotropium at a dose of 2.5 μg or 5 μg delivered by means of the Respimat soft-mist inhaler or at a dose of 18 μg delivered by means of the HandiHaler inhalation device. The Respimat 2.5-μg group was included because the drug dose is being investigated in clinical trials.
committee reviewed adverse events and deaths according to study group every 4 months. No formal interim analyses were planned, but the data and safety monitoring committee could recommend modification of the study protocol if one study group was superior to another (defined as P<0.01). A mortality adjudication committee, whose members were unaware of the study-group assignments, reviewed medical documentation, case-report forms, and witness statements to attribute the cause of each death (see Section 3 in the Supplementary Appendix, available at NEJM.org). Nonfatal major adverse cardiovascular events, as defined in the study protocol, were reported by site investigators, and the accuracy of classification was verified by central reviewers who were unaware of the study-group assignments.

STUDY PATIENTS
Full inclusion and exclusion criteria have been reported previously\textsuperscript{19} and are included in the protocol. In brief, we enrolled patients who were 40 years of age or older and who had received a clinical diagnosis of COPD, had at least 10 pack-years of smoking history, had a postbronchodilator ratio of the forced expiratory volume in 1 second (FEV\textsubscript{1}) to the forced vital capacity (FVC) of 0.70 or less, and had an FEV\textsubscript{1} of 70% or less of the predicted value. Patients with concomitant cardiac disease were included unless they had had a myocardial infarction within the previous 6 months, were hospitalized for class III or IV heart failure, or had unstable or life-threatening arrhythmia requiring new treatment within the previous 12 months. Also excluded were patients with other clinically significant lung diseases or a COPD exacerbation within the previous 12 months. Furthermore, cancer requiring therapy within the previous 4 years, drug or alcohol abuse within the previous 12 months, or exclusions that were stipulated in drug labeling for tiotropium treatment were allowed. Patients with other clinically significant lung diseases or a COPD exacerbation within the previous 12 months, or exclusions that were stipulated in drug labeling for tiotropium treatment were allowed. Patients with other clinically significant lung diseases or a COPD exacerbation within the previous 12 months, or exclusions that were stipulated in drug labeling for tiotropium treatment were allowed.

PROCEDURES
Randomization was based on permuted blocks of nine, stratified according to center. Each patient received one of two possible Respimat inhalers: either 1.25 μg or 2.5 μg per inhalation, and a HandiHaler device; in each case, one of the inhalers held active medication and the other one contained placebo. Thus, patients received tiotropium Respimat 2.5 μg (two inhalations of 1.25 μg), tiotropium Respimat 5 μg (two inhalations of 2.5 μg), or tiotropium HandiHaler 18 μg, plus the corresponding placebo. Patients were seen at local clinical centers every 12 weeks with a final visit 30 days after the end of treatment. Detailed descriptions of assessments undertaken at each visit, methods for measuring exacerbations, and adherence rates are included in the protocol.

Outcome Measures
The primary safety outcome was the time to death from any cause, which was used to calculate the proportional-hazards ratio, or relative risk of death, between groups. The primary efficacy outcome was the risk of the first COPD exacerbation. COPD exacerbations were defined as the worsening of two or more major respiratory symptoms (dyspnea, cough, sputum, chest tightness, or wheezing) with a duration of at least 3 days requiring specified treatment changes. Mild exacerbations required a new prescription for a maintenance bronchodilator only; moderate exacerbations required a prescription for antibiotics, systemic glucocorticoids, or both; and severe exacerbations required hospitalization.

Secondary outcome measures included the number of COPD exacerbations, the time to the first moderate or severe exacerbation, the time to and number of severe exacerbations, and the time to major adverse cardiovascular events.

Statistical Analysis
We used a Cox proportional-hazard model (with no covariate adjustment) to perform the primary analyses, using a hierarchical analysis plan. The comparisons were tested in the following order with HandiHaler 18 μg as the reference treatment: first, a noninferiority analysis for the risk of death with Respimat 5 μg; second, a noninferiority analysis for the risk of death with Respimat 2.5 μg; and third, a superiority analysis for the risk of the first COPD exacerbation with Respimat 5 μg.

We estimated that a target sample of 16,800 patients was required in order to observe 1266 deaths within 3.5 years of follow-up, assuming a power of 90% with a one-sided P value of 0.025.
for the test of noninferiority, with the use of a noninferiority hazard ratio margin of 1.25. The primary mortality analysis (modified intention-to-treat analysis) involved all patients who received at least one dose of a study drug, regardless of whether the patient discontinued the drug prematurely. All patients (including those with premature discontinuation) were followed for vital status until the end of the study. Data from patients who were lost to follow-up were censored at the time of the last known vital status. A sensitivity analysis of fatal adverse events censored the data 30 days after discontinuation of a study drug.

The primary exacerbation analysis censored data for patients at the time of discontinuation of the study drugs. For the analysis of the time to the first exacerbation, the trial had a power of 90% with a two-sided P value of 0.05 to detect a relative reduction of 8% in the hazard ratio, assuming a 35% treatment discontinuation rate and 60% exacerbation rate in the HandiHaler group.

We performed subgroup analyses for the two primary outcomes for 13 prespecified baseline characteristics. We used a Cox proportional-hazards model to analyze secondary time-to-event end points and used the negative binomial model (with treatment exposure as the offset term to account for different exposure times) to analyze the number of end-point events.

### Table 1. Baseline Characteristics of the Patients in the As-Treated Population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tiotropium Respimat 2.5 μg (N = 5724)</th>
<th>Tiotropium Respimat 5 μg (N = 5705)</th>
<th>Tiotropium HandiHaler 18 μg (N = 5687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>73.1 ± 9.1</td>
<td>70.5 ± 9.1</td>
<td>69.3 ± 9.0</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.1 ± 9.1</td>
<td>64.9 ± 9.1</td>
<td>65.0 ± 9.0</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>37.9</td>
<td>38.7</td>
<td>37.7</td>
</tr>
<tr>
<td>Smoking history (pack-yr)</td>
<td>39.6 ± 24.6</td>
<td>41.4 ± 25.0</td>
<td>43.2 ± 24.7</td>
</tr>
<tr>
<td>Spirometry after bronchodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>Mean (liters)†</td>
<td>1.328 ± 0.481</td>
<td>1.352 ± 0.481</td>
</tr>
<tr>
<td></td>
<td>Percent of predicted value</td>
<td>48.0 ± 13.9</td>
<td>48.5 ± 13.8</td>
</tr>
<tr>
<td></td>
<td>FVC (liters)</td>
<td>2.696 ± 0.848</td>
<td>2.726 ± 0.843</td>
</tr>
<tr>
<td></td>
<td>Ratio of FEV1 to FVC</td>
<td>0.498 ± 0.115</td>
<td>0.501 ± 0.114</td>
</tr>
<tr>
<td>Previous cardiac arrhythmia (%)</td>
<td>10.6</td>
<td>10.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>5.9</td>
<td>5.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>2.2</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Previous ischemic heart disease or coronary artery disease (%)</td>
<td>14.8</td>
<td>15.0</td>
<td>15.7</td>
</tr>
<tr>
<td>Use of respiratory medication (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>90.8</td>
<td>90.3</td>
<td>90.7</td>
</tr>
<tr>
<td>Long-acting inhaled beta-agonist‡</td>
<td>61.9</td>
<td>61.2</td>
<td>62.3</td>
</tr>
<tr>
<td>Inhaled glucocorticoid‡</td>
<td>58.9</td>
<td>58.8</td>
<td>59.4</td>
</tr>
</tbody>
</table>

† P < 0.05 for baseline FEV1; ‡ P values are based on F-tests for the continuous variables and on chi-square tests for the categorical variables.

### RESULTS

#### Study Patients

Patients were recruited from May 2010 through April 2011; the study ended in May 2013. Of the 20,313 patients who were screened, 17,183 underwent randomization, and 17,135 received at least one dose of the assigned treatment (Fig. S1 in Section 4 in the Supplementary Appendix). Vital status at the end of study was known for 99.7% of patients, including those who discontinued treatment prematurely. Among the treated patients, 13,199 (77.1%) did not discontinue a study drug prematurely but continued treatment until the study was officially terminated, when the predefined number of fatal events had been reached. The numbers of patients who discontinued treatment in the three study groups were similar throughout the trial (see Section 5 in the Supplementary Appendix). A majority of premature discontinuations were due to adverse events.

In total, 90% of patients complied with the study protocol, using 80 to 120% of the assigned study drug doses, on average, throughout the study. The median duration of treatment was 835 days in all three study groups, with a mean follow-up of 2.3 years. The study-drug exposure was 11,405 patient-years in the group receiving 2.5 μg of Respimat, 11,343 patient-years in the group receiving 5 μg of Respimat, and 11,337 patient-years in the group receiving 18 μg of HandiHaler.

The baseline characteristics of the patients and the use of respiratory and cardiovascular medications were similar in the three study groups (Table 1, and Table S1 in Section 8 in the Supplementary Appendix). The mean (±SD) age was 65±9 years, 71% of patients were men, 38% were current smokers, and the mean FEV1...
was 48% of the predicted value. At baseline, approximately 50% of the patients were receiving cardiovascular medications other than statins, and 11% had a history of cardiac arrhythmia; 62% were taking a long-acting β₂-agonist, and 68% did so during the trial, with corresponding proportions of patients of 59% and 68%, respectively, taking inhaled glucocorticoids.

DEATH

For the primary end point of the risk of death from any cause, the hazard ratio for Respimat 5 μg versus HandiHaler was 0.96 (95% CI, 0.84 to 1.09); for Respimat 2.5 μg versus HandiHaler, the hazard ratio was 1.00 (95% CI, 0.87 to 1.14) (Table 2 and Fig. 1A and 1B). Since the upper limits of the 95% confidence intervals for the two comparisons were well below the predefined noninferiority margin of 1.25, the primary comparisons of Respimat 5 μg and 2.5 μg with HandiHaler 18 μg for death from any cause achieved noninferiority (Fig. 1B).

Death from any cause during the observation period (regardless of treatment discontinuation) occurred in 7.7% of patients in the Respimat 2.5-μg group, 7.4% in the Respimat 5-μg group, and 7.7% in the HandiHaler group. Similar results were observed in the as-treated analysis of fatal events of any cause (with 6.3%, 5.7%, and 6.3% of patients in the three groups, respectively) (Table 2 and Fig. 1C and 1D). Causes of death were similar across the treatment groups, including death from cardiovascular causes (2.1%, 2.0%, and 1.8% for Respimat 2.5 μg, Respimat 5 μg, and HandiHaler, respectively).

Predefined subgroup analyses of mortality are shown in Section 7 in the Supplementary Appendix.

### Table 2. Risk of Death.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tiotropium Respimat 2.5 μg (N = 5730)</th>
<th>Tiotropium Respimat 5 μg (N = 5711)</th>
<th>Tiotropium HandiHaler 18 μg (N = 5694)</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death in follow-up analysis†</td>
<td>440 (7.7)</td>
<td>423 (7.4)</td>
<td>439 (7.7)</td>
<td>1.00 (0.87–1.14)</td>
</tr>
<tr>
<td>Death in as-treated analysis</td>
<td>359 (6.3)</td>
<td>326 (5.7)</td>
<td>357 (6.3)</td>
<td>1.00 (0.86–1.16)</td>
</tr>
<tr>
<td>Adjudicated primary cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>119 (2.1)</td>
<td>113 (2.0)</td>
<td>101 (1.8)</td>
<td>1.17 (0.90–1.53)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (0.2)</td>
<td>11 (0.2)</td>
<td>3 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Sudden death‡</td>
<td>82 (1.4)</td>
<td>67 (1.2)</td>
<td>68 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (0.2)</td>
<td>14 (0.2)</td>
<td>11 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular cause§</td>
<td>17 (0.3)</td>
<td>21 (0.4)</td>
<td>19 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Respiratory cause¶</td>
<td>143 (2.5)</td>
<td>148 (2.6)</td>
<td>155 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>110 (1.9)</td>
<td>100 (1.8)</td>
<td>95 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Undetermined or unknown cause</td>
<td>35 (0.6)</td>
<td>27 (0.5)</td>
<td>37 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other cause‖</td>
<td>33 (0.6)</td>
<td>35 (0.6)</td>
<td>51 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Death of patients with previous cardiac arrhythmia, according to vital status at follow-up**</td>
<td>79 (13.1)</td>
<td>65 (10.6)</td>
<td>78 (12.9)</td>
<td>1.02 (0.74–1.39)</td>
</tr>
</tbody>
</table>

* Hazard ratios and 95% confidence intervals are provided for all prespecified analyses.
† P<0.05 for the test for noninferiority. The rates of death per 100 patient-years were 3.35 in the Respimat 2.5-μg group, 3.22 in the Respimat 5-μg group, and 3.36 in the HandiHaler group.
‡ This category includes both cardiac death and sudden death. (Details are provided in Section 3 in the Supplementary Appendix.)
§ Other cardiovascular causes include all other terms not included in the categories of myocardial infarction, sudden death, or stroke. Details are provided in Table S3 in Section 9 in the Supplementary Appendix.
¶ Respiratory causes include death in the respiratory-system organ class and deaths from respiratory-tract infection (including pneumonia).
‖ Other causes of death are provided in Table S2 in Section 9 in the Supplementary Appendix.
** Listed are data for 1825 patients in the subgroup with cardiac arrhythmia (604 patients in the Respimat 2.5-μg group, 614 in the Respimat 5-μg group, and 607 in the HandiHaler group).
A Death during Follow-up

No. at Risk
Tiotropium Respimat 2.5 µg 5730 5694 5637 5582 5499 5423 5157 3575 3504
Tiotropium Respimat 5 µg 5711 5675 5626 5576 5510 5429 5167 3585 467
Tiotropium HandiHaler 18 µg 5694 5660 5601 5544 5471 5388 5097 3544 488

B Death during Follow-up

Hazard Ratio (95% CI)
0.84 0.96 1.09
Tiotropium Respimat 5 µg vs. Tiotropium HandiHaler 18 µg
0.87 1.00 1.14
Tiotropium Respimat 2.5 µg vs. Tiotropium HandiHaler 18 µg

C Death in As-Treated Analysis

No. at Risk
Tiotropium Respimat 2.5 µg 5730 5387 5179 5015 4822 4671 4423 3183 385
Tiotropium Respimat 5 µg 5711 5333 5138 4978 4809 4662 4427 3171 364
Tiotropium HandiHaler 18 µg 5694 5351 5146 4998 4811 4659 4398 3141 373

D Death in As-Treated Analysis

Hazard Ratio (95% CI)
0.79 0.91 1.06
Tiotropium Respimat 5 µg vs. Tiotropium HandiHaler 18 µg
0.86 1.00 1.16
Tiotropium Respimat 2.5 µg vs. Tiotropium HandiHaler 18 µg

E COPD Exacerbation

No. at Risk
Tiotropium Respimat 2.5 µg 5724 4415 3760 3266 2828 2532 2285 1335 94
Tiotropium Respimat 5 µg 5705 4381 3716 3279 2912 2384 2336 1332 95
Tiotropium HandiHaler 18 µg 5687 4407 3725 3256 2881 2571 2266 1300 105

F COPD Exacerbation

Hazard Ratio (95% CI)
0.93 0.98 1.03
Tiotropium Respimat 5 µg vs. Tiotropium HandiHaler 18 µg
0.96 1.02 1.07
Tiotropium Respimat 2.5 µg vs. Tiotropium HandiHaler 18 µg
dix. No significant interaction with treatment was seen for either Respimat dose, as compared with HandiHaler. In particular, there was no increased risk of death among the 1221 patients with a history of cardiac arrhythmia in the Respimat 5-μg group, as compared with the HandiHaler group (10.6% and 12.9%, respectively; hazard ratio, 0.81; 95% CI, 0.58 to 1.12).

EXACERBATIONS
For the second primary end point of the risk of the first exacerbation, the hazard ratio for Respimat 5 μg versus HandiHaler was 0.98 (95% CI, 0.93 to 1.03) (Table 3 and Fig. 1E and 1F), a difference that was not significant (P = 0.42). The proportions of patients with a COPD exacerbation were 47.9% for the Respimat 5-μg group and 48.9% for the HandiHaler group (median times to the first COPD exacerbation, 756 days and 719 days, respectively). Rates of exacerbations, moderate or severe exacerbations, and severe exacerbations were similar in the three study groups. Relative differences in COPD exacerbations among the study groups across predefined subgroups were consistent (see Section 7 in the Supplementary Appendix).

SPIROMETRY SUBSTUDY
The spirometry substudy in 1370 patients showed that Respimat 5 μg was noninferior to HandiHaler for the trough FEV₁ (difference in FEV₁, −10 ml; 95% CI, −38 to 18; average for weeks 24 to 120), but noninferiority was not shown for Respimat 2.5 μg (difference in FEV₁ favoring the HandiHaler, −37 ml; 95% CI, −65 to −9) (see Section 6 in the Supplementary Appendix).

SAFETY
Serious adverse events were reported in 33% of the patients (Table 4). As expected, the highest rates of serious adverse events were lung disorders in all three study groups (17.8%, 16.8%, and 17.0%, for Respimat 2.5 μg, Respimat 5 μg, and HandiHaler, respectively). Details of serious adverse events, adverse events leading to discontinuation, and drug-related adverse events are provided in Section 9 in the Supplementary Appendix.

The overall incidence of major adverse cardiovascular events was 3.9%, 3.9%, and 3.6% in the Respimat 2.5-μg, Respimat 5-μg, and HandiHaler groups, respectively (Table 4); the corresponding rates of cardiac arrhythmia were 2.3%, 2.1%, and 2.1%.

DISCUSSION
A careful review of adverse events that are reported in clinical trials plays an essential role in ensuring the safety of prescription medicines. When an unexplained increase in mortality was observed in COPD trials of tiotropium Respimat 5 μg,6,9 we designed the TIOSPIR trial to have sufficient power to estimate the difference in mortality between tiotropium delivered by the Respimat and tiotropium delivered by an active control (the HandiHaler).

During the course of our study, 1302 patients died, as compared with 137 patients who died in the initial meta-analysis.10 In the UPLIFT trial, tiotropium HandiHaler was associated with lower mortality (assessed as a secondary end point) than was placebo.4,20 In contrast, mortality with tiotropium Respimat was reported to be higher than with placebo in the Respimat trials.6 Our study did not support these contrasting results for the same active substance in two formulations with similar pharmacokinetic properties.7,8

We found that rates of death per 100 patient-years were 3.22 and 3.36 for tiotropium Respimat 5 μg and HandiHaler, respectively, which were similar to the rates seen in the tiotropium groups in the pooled analysis of trials of Respimat 5 μg (with a rate of 2.64)14 and UPLIFT (with a rate of 3.94) (Table S7 in Section 10 in the Supplementary Appendix), taking into account the variable duration of the studies from 6 months to 4 years. In the UPLIFT trial, the probability of death over a period of 4 years was 14.4% in the tiotropium group and 16.3% in the placebo...
In the Towards a Revolution in COPD Health (TORCH) study, the probability of death during the 3-year period was 16.0% in the fluticasone group, 13.5% in the salmeterol group, and 12.6% in the group that received both fluticasone and salmeterol.

In our study, tiotropium Respimat was not associated with higher mortality than tiotropium HandiHaler among patients with previous cardiac disease, including stable arrhythmias at baseline; Respimat was also not associated with a higher incidence of arrhythmias during the study. Our results contradict findings from a recent database study in which higher mortality was observed with tiotropium Respimat than with HandiHaler. The authors noted that patients who received the Respimat inhaler had more severe COPD and coexisting cardiovascular conditions at baseline than did those who received the HandiHaler device, leading to potential confounding by indication, which could be an explanation for their results. In our study, there were fewer fatal myocardial infarctions in the HandiHaler group than in either Respimat group. However, the numbers were small, and the incidence was lower than in the UPLIFT trial.

Overall, there were no significant differences among the three study groups in terms of serious adverse events and nonfatal and fatal major adverse cardiovascular events.

We did not see a greater effect of tiotropium Respimat on the risk of the first exacerbation, the risk of the first severe (hospitalized) exacerbation, or exacerbation frequency, as compared with HandiHaler. The overall exacerbation rate per patient-year (0.59 in all three study groups), which was driven by moderate or severe episodes, was lower than in earlier studies in similar populations of patients (0.69 for Respimat 5 μg in a previous 1-year trial; 0.73 for HandiHaler

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tiotropium Respimat 2.5 μg (N=5724)</th>
<th>Tiotropium Respimat 5 μg (N=5705)</th>
<th>Tiotropium HandiHaler 18 μg (N=5687)</th>
<th>Tiotropium Respimat 2.5 μg vs. HandiHaler Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Tiotropium Respimat 5 μg vs. HandiHaler Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any exacerbation</td>
<td>2827 (49.4)</td>
<td>2733 (47.9)</td>
<td>2782 (48.9)</td>
<td>1.02 (0.96–1.07)</td>
<td>0.56</td>
<td>0.98 (0.93–1.03)</td>
<td>0.42</td>
</tr>
<tr>
<td>No. of events</td>
<td>6565</td>
<td>6425</td>
<td>6504</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted rate of events per patient-yr (95% CI)</td>
<td>0.59 (0.57–0.62)</td>
<td>0.59 (0.56–0.61)</td>
<td>0.59 (0.57–0.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe exacerbation</td>
<td>2769 (48.4)</td>
<td>2694 (47.2)</td>
<td>2732 (48.0)</td>
<td>1.01 (0.96–1.07)</td>
<td>0.68</td>
<td>0.98 (0.93–1.04)</td>
<td>0.54</td>
</tr>
<tr>
<td>No. of events</td>
<td>6423</td>
<td>6308</td>
<td>6362</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted rate of events per patient-yr (95% CI)</td>
<td>0.58 (0.56–0.61)</td>
<td>0.58 (0.55–0.60)</td>
<td>0.58 (0.55–0.60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>869 (15.2)</td>
<td>826 (14.5)</td>
<td>811 (14.3)</td>
<td>1.07 (0.97–1.18)</td>
<td>0.18</td>
<td>1.02 (0.93–1.13)</td>
<td>0.64</td>
</tr>
<tr>
<td>No. of events</td>
<td>1316</td>
<td>1284</td>
<td>1216</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted rate of events per patient-yr (95% CI)</td>
<td>0.12 (0.11–0.13)</td>
<td>0.12 (0.11–0.13)</td>
<td>0.11 (0.10–0.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A COPD exacerbation was defined as an event that led to a new prescription of medication: mild exacerbation, maintenance bronchodilator only; moderate exacerbation, antibiotics or glucocorticoids without hospitalization; or severe exacerbation, antibiotics or glucocorticoids with hospitalization. If the cause of death was adjudicated to be a COPD exacerbation, yet no medication was prescribed, the duration was less than 3 days, and neither antibiotics nor systemic glucocorticoids had been taken, the event was counted as a fatal COPD exacerbation.

†Hazard ratios and P values are provided for all prespecified analyses.
The lower rate of exacerbations has been observed in all recent studies, except for those performed in selected patients who have COPD with frequent exacerbations. This finding probably reflects the progressive improvement in the management of this disease. Finally, the lack of difference in exacerbation outcomes between Respimat 5 μg and HandiHaler is in line with the results observed with the two formulations with respect to mortality, as well as with spirometry findings in a study subpopulation.

Our conclusions differ from those in previous meta-analyses and observational trials. Several explanations may account for these differences. First, in placebo-controlled trials of bronchodilators in COPD, early discontinuation in the placebo group may bias results. In our study, rates of discontinuation were similar in the three study groups and were lower overall than rates in the UPLIFT and TORCH studies. In the UPLIFT and TORCH trials, a higher proportion of patients discontinued in the placebo group than in the active treatment groups. Second, previous meta-analyses were post hoc without an a priori hypothesis and should therefore be considered hypothesis-generating rather than definitive.

Observational studies may be flawed because of residual confounding by indication or other unknown factors that are presumably balanced in a randomized clinical trial. Although increased systemic exposure to tiotropium through Respimat was a proposed explanation of earlier findings, pharmacokinetic studies have shown similar drug exposure, regardless of delivery system.

Our study has several strengths. First, it was a large study with more than 34,000 patient-years of exposure to tiotropium and was powered to precisely estimate rates of death and exacerbations. Rates of vital-status ascertainment were very high, allowing little leeway for bias owing to differential follow-up. The patients who were enrolled were similar to those in previous Respimat studies with respect to disease severity and background therapy. Moreover, we enrolled a substantial number of patients with a history of cardiac disorders (1825 patients with cardiac arrhythmia and 3152 with ischemic heart disease, coronary artery disease, or heart failure). Tiotropium HandiHaler may be associated with reduced mortality, including among patients with coexisting cardiac conditions, a finding that strengthens the conclusion that tiotropium

Table 4. Serious Adverse Events and Major Adverse Cardiovascular Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Tiotropium Respimat 2.5 μg (N = 5724)</th>
<th>Tiotropium Respimat 5 μg (N = 5705)</th>
<th>Tiotropium HandiHaler 18 μg (N = 5687)</th>
<th>Tiotropium Respimat 2.5 μg vs. HandiHaler</th>
<th>Tiotropium Respimat 5 μg vs. HandiHaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>1937 (33.8)</td>
<td>1846 (32.4)</td>
<td>1842 (32.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, or mediastinal disorder</td>
<td>1017 (17.8)</td>
<td>957 (16.8)</td>
<td>964 (17.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection or infestation</td>
<td>497 (8.7)</td>
<td>502 (8.8)</td>
<td>495 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>293 (5.1)</td>
<td>273 (4.8)</td>
<td>270 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse cardiovascular events ‡</td>
<td>224 (3.9)</td>
<td>222 (3.9)</td>
<td>202 (3.6)</td>
<td>1.11 (0.91–1.34)</td>
<td>0.30</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (1.0)</td>
<td>52 (0.9)</td>
<td>57 (1.0)</td>
<td>0.98 (0.68–1.41)</td>
<td>0.90</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>25 (0.4)</td>
<td>30 (0.5)</td>
<td>20 (0.4)</td>
<td>1.24 (0.69–2.24)</td>
<td>0.47</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>70 (1.2)</td>
<td>73 (1.3)</td>
<td>52 (0.9)</td>
<td>1.34 (0.94–1.92)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* Events are listed according to the system organ class in the Medical Dictionary for Regulatory Activities. A complete list of serious adverse events is provided in Table S4 in Section 9 in the Supplemen- tary Appendix.
† Hazard ratios and P values are provided for all prespecified analyses.
‡ Major adverse cardiovascular events include stroke, transient ischemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death, or fatal event in system organ classes for cardiac and vascular disorders. Data for patients who died from a fatal major adverse cardiovascular event are listed in Table 2.
Respirin does not increase risk of death or cardiac adverse events in these patients.

Our study has limitations, most notably the absence of a placebo group. One was not included because it would have been impractical to maintain high levels of adherence and follow-up without effective symptom control in such a large population; instead, we used as a control tiotropium HandiHaler, which has been associated with improved survival.\(^4,20,26\) In addition, we excluded patients with unstable cardiovascular conditions (myocardial infarction within the previous 6 months, hospitalization for class III or IV heart failure, or unstable or life-threatening arrhythmia) or moderate or severe renal impairment, so the study findings cannot be extended to these populations.

In conclusion, the results from this large-scale trial offer a need for caution when interpreting safety outcomes from meta-analyses of small data sets and observational studies. We found that tiotropium at a dose of 5 \(\mu\)g or 2.5 \(\mu\)g, delivered by the Respimat inhaler, had a safety profile and exacerbation efficacy similar to those of tiotropium at a dose of 18 \(\mu\)g delivered by the HandiHaler device.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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