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Cardiac safety of tiotropium in patients with COPD: a combined analysis of Holter-ECG data from four randomised clinical trials

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Disclosures
J.M. Hohlfeld is a consultant to Boehringer Ingelheim and has served on the Boehringer Ingelheim Advisory Board for Early Clinical Development. E.D. Bateman has served as an advisor or consultant for Actelion Pharmaceuticals Ltd, Almirall Prodesfarma, S.A.; Alk Abello; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim Pharmaceuticals, Inc.; Elevation Pharmaceuticals; Chiesi Farmaceutici SpA, Forest Laboratories, Inc.; GlaxoSmithKline; La Roche Ltd; IMS Health; Merck & Co., Inc.; Napp Pharmaceuticals Limited; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Takeda Pharmaceuticals. He has also served as a speaker or a member of a speaker's bureau

SUMMARY

Background: Tiotropium is generally well tolerated; however, there has been debate whether antimuscarinics, particularly tiotropium administered via Respimat® Soft Mist™ Inhaler, may induce cardiac arrhythmias in a vulnerable subpopulation with cardiovascular comorbidity. The aim of this study was to provide evidence of the cardiac safety of tiotropium maintenance therapy. **Methods:** Combined analysis of Holter electrocardiogram (ECG) data from clinical trials of tiotropium in chronic obstructive pulmonary disease (COPD). Trials in the Boehringer Ingelheim clinical trials database conducted between 2003 and 2012, involving tiotropium HandiHaler® 18 μg and/or tiotropium Respimat® (1.25-, 2.5-, 5.0- and 10-μg doses) were reviewed. All trials involving Holter-ECG monitoring during this period were included in the analysis. Men and women aged ≥ 40 years with a smoking history of ≥ 10 pack-years, and a clinical diagnosis of COPD were included. Holter ECGs were evaluated for heart rate (HR), supraventricular premature beats (SVPBs), ventricular premature beats (VPBs) and pauses. Quantitative and categorical end-points were derived for each of the Holter monitoring days. **Results:** Four trials (n = 727) were included in the analysis. Respimat® (1.25–10 μg) or HandiHaler® (18 μg) was not associated with changes in HR, SVPBs, VPBs and pauses compared with placebo or the pretreatment baseline period. In terms of cardiac arrhythmia end-points, there was no evidence for an exposure–effect relationship. **Conclusions:** In this analysis, tiotropium maintenance therapy administered using Respimat® (1.25–10 μg) or HandiHaler® (18 μg) once daily for periods of up to 48 weeks was well tolerated with no increased risk of cardiac arrhythmia in patients with COPD.

What's known
Extensive clinical trial data have shown that tiotropium, administered via either the HandiHaler or Respimat Soft Mist™ Inhaler, improves lung function, quality of life and reduces exacerbations in patients with chronic obstructive pulmonary disease (COPD). However, a variety of reports, the majority of which were retrospective database analyses, have raised concerns about the cardiovascular (CV) safety of tiotropium, particularly in vulnerable subpopulations with CV comorbidity.

What's new
This combined analysis of all tiotropium trials in COPD involving Holter electrocardiogram monitoring that were conducted between 2003 and 2012, confirms that neither formulation of tiotropium was associated with an increased risk of cardiac arrhythmia. However, more data are required on the safety of tiotropium and other anticholinergics in patients with unstable CV disorders, who might have been excluded from clinical trials.

Introduction

The long-acting anticholinergic, tiotropium bromide (SPIRIVA®; Boehringer Ingelheim Pharma GmbH & Co K.G., Ingelheim, Germany) is a competitive muscarinic receptor antagonist that has gained widespread acceptance as a maintenance treatment for patients with chronic obstructive pulmonary disease (COPD). It is available as both a dry-powder formulation delivered via HandiHaler® (18 μg nominal dose) and as an aqueous solution delivered via the Respimat® Soft Mist™ Inhaler (SMI; 5 μg delivered dose) (1–3). Tiotropium Respimat® is a new-generation, propellant-free inhaler developed as an innovative approach to inhalation therapy. It delivers a metered dosage of medication as a fine mist, with design features that improve lung deposition, allowing for a lower dose of tiotropium than in the HandiHaler® (4).

Extensive clinical trial data have shown that tiotropium improves lung function, quality of life and exercise endurance and reduces exacerbations in patients with COPD. Both formulations (HandiHaler® 18 μg and Respimat® 5 μg) have similar efficacy (5–10) and provide similar systemic exposure to the drug (4, 11, 12). Since the first approval of tiotropium HandiHaler® in 2002, tiotropium has become available in 110 countries around the world and there are now more than 30 million patient-years of clinical experience with the drug (1).

Although clinical trial data indicate that tiotropium is generally well tolerated (13, 14), there is ongoing debate whether antimuscarinics, in general, and particularly tiotropium administered via the Respimat

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SMI, may induce cardiac arrhythmias in a vulnerable subpopulation with cardiovascular (CV) comorbidity (15). Concerns regarding the safety of tiotropium delivered by Respimat® were triggered by *post hoc* pooled analyses of data from placebo-controlled trials in which a numerical increase in all-cause mortality was seen in patients treated with Respimat® [$n = 68$; incidence rate (IR): 2.64 cases per 100 patient-years] compared with placebo [$n = 51$; IR: 1.98; rate ratio (RR) 95% confidence interval (CI): 1.33 (0.93–1.92) for the planned treatment period]; the excess in mortality was observed in patients who, at study entry, were recorded as having a cardiac rhythm disorder (3). Subsequent meta-analyses and reviews of the same Respimat® clinical trials have reported similar findings (13, 16, 17). In addition, and based on an analysis of an integrated primary care information database, Verhamme et al. reported that tiotropium Respimat® was associated with an almost 30% increase of mortality compared with tiotropium HandiHaler® (18).

While these mortality data are of some concern, they are in contrast with those reported for the tiotropium HandiHaler® 18 μg in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) study (8), in which there were fewer deaths with tiotropium delivered via Handi Haler® 18 μg than placebo (14.9% vs. 16.5%; hazard ratio: 0.89; 95% CI: 0.79–1.02) during a period of 4 years plus 30 days (1491 days). Additional meta-analyses showed no association between tiotropium and CV events or mortality in patients with COPD (8, 14, 19–21). Furthermore, in the recently completed Tiotropium Safety and Performance in Respimat® (TIOSPIR™) trial, tiotropium Respimat 5 or 2.5 μg had an overall and CV safety profile similar to that of tiotropium HandiHaler® 18 μg in patients with COPD. The TIOSPIR™ population included patients with stable cardiac disease; 11% (1825 of 17,135 patients) of the study population were reported to have a cardiac arrhythmia of any variety at study entry (10).

In view of the debate regarding the cardiac safety of tiotropium, we performed a combined analysis of Holter ECG data from four Phase II/III/IIIb clinical trials of tiotropium in COPD with the primary objective to provide additional evidence of the cardiac safety of tiotropium maintenance therapy.

Methods

Clinical trial selection

Trials in the Boehringer Ingelheim clinical trials database involving tiotropium HandiHaler® 18 μg and/or tiotropium Respimat® (1.25-, 2.5-, 5.0- and 10-μg doses) conducted between 2003 and 2012 were reviewed and all trials that involved Holter ECG monitoring were included in the combined analysis; details of the trials are presented in Table S1.

Analysis

The design and methodology of the four trials included in this analysis have been previously described (5, 12, 22).

The Holter ECGs were evaluated for heart rate (HR), supraventricular premature beats (SVPBs), ventricular premature beats (VPBs) and pauses (defined as absence of a heart beat for more than 3 s). Quantitative and categorical end-points referring to the monitoring periods (6.5–24 h) were derived for each of the Holter monitoring days.

Quantitative end-points

Quantitative end-points included mean, maximum and minimum HR [beats per min (BPM)], number of SVPB/VPB events per hour (totals, runs, pairs and single events), and the HR of the fastest SVPB/VPB run (HR in BPM). Ventricular 'runs' included ventricular tachycardia, idioventricular rhythm and other events with at least three consecutive premature ventricular beats, while a 'pair' comprised two consecutive premature beats. 'Total' denoted the total number of premature beats observed during the entire monitoring period. For all trials, single VPBs included early as well as non-early VPBs. Early VPBs were defined as VPBs with a prematurity index of 20% or greater (i.e. VPB coupling interval < 80% of baseline RR interval). Non-early VPBs were defined as VPBs with a prematurity index < 20% (i.e. not early enough to be counted as an early VPB).

Categorical end-points

These included overall Holter evaluation (normal, abnormal, unable to evaluate), occurrence (number of patients) of pauses and categorisation by the number of pauses, occurrence (number of patients) of runs, pairs or single SVPB/VPB events, number of SVPB/VPB events per hour (categorised as no events, 1 to < 10, 10 to < 30, 30 to < 50, 50 to < 100, 100 to < 500, 500 to < 1000, 1000 to < 2000 and ≥ 2000 events), number of beats in the longest VPB event, occurrence of 0, 1, 2, 3 to < 5, 5 to < 10 or ≥ 10 beats in the longest VPB event.

In addition, the number of patients who 'worsened' or 'improved' on treatment was displayed using two-way shift tables to allow for comparisons between treatments. An analysis of tiotropium peak exposure [peak plasma concentration at steady state ($C_{max,ss}$)] and overall exposure [amount of drug excreted in urine from 0 to 6 h at steady state

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($Ae_{0\text{-}6,ss}$)] between patients with SVPB/VPB events and those without was conducted for the pharmacokinetic trial 205.458 to assess any potential exposure–effect relationships (supporting information).

Statistical analysis

The combined analysis of Holter ECG data was performed on the Holter full analysis set (FAS), which included all patients who were dispensed study medication, were documented to have taken ≥ 1 dose of investigational treatment, and for whom an evaluable (i.e. analysed time > 0 s) continuous Holter ECG was recorded on at least one occasion. The analysis set used for the combined analysis could deviate from the analyses sets described in the individual trial reports and respective publications, as for this combined analysis: (i) Holter recordings with analysed times between 0 s and 18 h were not excluded; (ii) patients with artificial pacemakers were not excluded and (iii) 'invalid' baseline values, i.e. those taken after the first dose of randomised treatment were excluded.

The ECG data from the trials included in this combined analysis were not pooled because of the different trial designs applied. While the initial statistical analysis for the single trials varied, a common analysis strategy has been used for the combined analysis. In contrast to previous analyses, the number of patients with any arrhythmia event was evaluated in addition to hourly event rates in the overall population. Data were summarised by descriptive statistical methods. Inferential statistical analysis was not performed.

Results

Four trials that included ECG Holter monitoring were included in the study (Table S1). All four trials recruited men and women aged ≥ 40 years with a smoking history of ≥ 10 pack-years, and a clinical diagnosis of COPD. Patients were required to have a forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio of ≤ 70%, but requirements for severity of airflow limitation varied. In trial 205.284/NCT00239460 patients with a predicted FEV_1 ≤ 60% were recruited, trial 205.458/NCT01222533 included those with a predicted FEV_1 < 80% and trials 205.254/NCT00168844 and 205.255/NCT00168831 included patients with a predicted FEV_1 ≤ 60%. All trials included patients with pre-existing CV disease as long as they had no recent history (i.e. ≤ 6 months) of myocardial infarction or unstable or life threatening cardiac arrhythmia and had not been hospitalised for cardiac failure during the past year. The continuing use and introduction of CV drugs including anti-arrythmics were permitted throughout the trials.

Trials ranged from 4 to 48 weeks' treatment duration and included both parallel-group and cross-over designs. A total of 727 patients with COPD were included in the Holter FAS [192 patients (trial 205.284); 412 patients (trials 205.254/205.255); and 123 patients (trial 205.458)]. Of these, 117 patients each received tiotropium Respimat® 1.25 and 2.5 μg, while 265 patients received tiotropium Respimat® 5 μg, 133 patients received tiotropium Respimat® 10 μg and 214 patients received tiotropium HandiHaler® 18 μg (Table S1).

The mean age across all four trials was 64.7 ± 8.7 years (mean ± SD); 67.7% were male, and 95.9% were Caucasian (Table S2a). The mean duration of COPD was 9.8 ± 7.7 years and the mean body mass index was 26.5 ± 5.5 kg/m^2. COPD severity and other variables were largely comparable across treatments. Overall, the prevalence of concomitant cardiac conditions at baseline (for total population) was similar across treatment groups within the individual trials included. For the Phase III trials, the prevalence of concomitant cardiac conditions in the total populations of the 205.284 and 205.254/205.255 studies were higher (29.1% and 29.6%, respectively) than in the Phase II study (13.8%). The most prevalent cardiac diagnoses were coronary artery disease (10.2% in trial 205.284 and 8.2% in trials 205.254/205.255) and myocardial ischaemia (2.4% in trial 205.458). At baseline, the majority of patients were receiving short-acting/inhaled beta-adrenergics in trial 205.284 and trials 205.254/205.255; however, in the cross-over trial (trial 205.458) long-acting beta-agonists (LABAs) were most frequently used [it should be noted that concomitant use of LABAs was permitted in trials 205.284 and 205.458 (washed out for 24 h before Holter monitoring days) but not in trials 205.254/205.255]. Patient baseline characteristics data (Holter FAS) for the individual trials are included in Tables S2a and b.

In terms of discontinuations, 27 patients discontinued treatment in trial 205.284 [placebo (n = 17), tiotropium HandiHaler® 18 mg (n = 10)]; 456 patients in trials 205.254/255 [placebo (n = 205), tiotropium Respimat® 5 mg (n = 115), tiotropium Respimat® 10 mg (n = 136)]; and 16 in the cross-over trial (205.458) [placebo (n = 3), tiotropium Respimat® 1.25 mg (n = 3), tiotropium Respimat® 5 mg (n = 5), tiotropium HandiHaler® 18 mg (n = 5)]. Overall treatment compliance was high across all the trials. In trials 205.254/255 92.8% of patients took > 80% of the prescribed treatment. In trial 205.458 100% of patients took > 80% of the prescribed treatment.

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Heart rates and pauses

Summary statistics for mean, maximum and minimum HR over the entire Holter monitoring period revealed similar results for tiotropium and placebo in all trials (Table 1). Treatment group means for average HR ranged from 76 to 81 BPM when on placebo, 78 to 81 BPM at baseline and from 75 to 81 BPM when on tiotropium treatment. Treatment group means for maximum HR ranged from 109 to 124 BPM when on placebo, 118 to 122 BPM at baseline and from 108 to 122 BPM when on tiotropium treatment. Treatment group means for minimum HR ranged from 54 to 59 BPM when on placebo, 54 to 56 BPM at baseline and from 53 to 59 BPM when on tiotropium treatment. Within each of the trials, the mean, maximum and minimum HR was similar between all treatment groups. Mean HRs differed by less than 1 BPM from placebo for all four active treatment groups in the cross-over trial and by less than 2 BPM compared with baseline for the parallel-group trials. Maximum and minimum HRs differed by less than 2 BPM from placebo for all four active treatment groups in the cross-over trial and by less than 3 BPM compared with baseline for the parallel-group trials. No treatment-dependent trends regarding decreases or increases in mean, maximum or minimum HR were apparent.

Overall, the proportion of patients who experienced a pause in the tiotropium Respimat® 5 or 10 μg, HandiHaler® 18 μg and placebo groups ranged from 0.9% to 3.5% (Table 1). Again, there were no treatment-related patterns in the frequency of pauses.

Proportion of patients with SVPB and VPB events

Overall, the proportions of patients on tiotropium treatment, who experienced a SVPB or VPB event, were in the same range as those who were not on tiotropium treatment (during baseline or placebo treatment periods). In the trials that included a 24-h Holter monitoring period (205.284 and 205.254/205.255), the proportion of patients with any VPBs ranged from 76.9% to 90.4% when on placebo, 82.4% to 93.4% at baseline (tiotropium group) and from 82.6% to 86.3% when on tiotropium treatment. In the trial with a 6.5-h Holter monitoring period (205.458) the proportion of patients with any VPBs ranged from 78.4% to 79.5% when on placebo and from 73.0% to 86.1% on treatment (Table S3a). SVPBs (runs and/or pairs and/or singles taken together) were detected in the majority of patients in all trials without any observable differences between tiotropium and placebo or baseline. Overall, neither treatment affected the proportion of patients with VPB and SVPB and events (Tables S3a and b).

Proportion of patients with VPB runs

In the three trials with a 24-h Holter monitoring period (Table 2), the proportion of patients with VPB runs ranged from 9.2% to 14.9% at baseline, 6.0% to 17.0% when on placebo and from 7.6% to 13.6% when on tiotropium treatment. Of note, the proportion of patients with VPB runs on treatment in the group that received the highest dose of tiotropium (10 μg/day via Respimat®) was in a similar range to patients who received lower doses or placebo (Table 2).

As a result of the shorter Holter monitoring period (6.5 h), the proportion of patients with VPB runs was lower in trial 205.458 (2.6–8.6%) than in trials with a 24-h monitoring period (205.284 and 205.254/205.255). The proportions of patients with VPB runs in trial 205.458 (days 26 and 29 taken together) ranged from 7.9% to 8.6% in the higher tiotropium dose groups (5 and 18 μg), compared with 3.4% to 7.0% in the lower dose groups (1.25 and 2.5 μg) and 2.6% to 6.8% in those receiving placebo. In trial 205.458, on day 29 of treatment, 2.6% of patients developed VPB runs with placebo, 4.3% with Respimat® 1.25 μg and 3.4% with Respimat® 2.5 μg while the respective proportions were higher with Respimat® 5 μg (8.6%) and HandiHaler® 18 μg (7.9%). The day 26 data did not reveal differences between treatments (placebo, 6.8%; active, 6.3–8.0%). An adjudication of VPB runs performed *post hoc* for trial 205.458 by a group of independent cardiologists blinded to treatment assignment revealed similar differences between the lower and the higher tiotropium dose levels to those observed in the original analyses.

There were no treatment- or dose-dependent effects regarding the proportion of patients with VPB pairs or singles (Table S3b). For example, in the trials with 24-h monitoring periods, the proportion of patients with VPB pairs ranged from 30.8% to 38.8% at baseline (tiotropium group), 21.8% to 35.8% when on placebo, and from 19.6% to 34.2% when on tiotropium treatment; the proportion of patients with VPB singles ranged from 82.4% to 92.6% at baseline, 74.4% to 90.4% when on placebo and from 81.5% to 86.3% when on tiotropium treatment.

Shifts across categories of VPB runs

For the parallel-group trials, patients 'worsening under treatment' are defined as patients without VPB runs at baseline but with VPB runs on treatment, while patients 'improving under treatment' are defined as patients with VPB runs at baseline but without VPB runs on treatment. For the cross-over trial 205.458, patients 'worsening under treatment'

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Table 1 Heart rate and pauses (Holter FAS)

	Placebo	Respimat® 1.25 μg	Respimat® 2.5 μg	Respimat® 5 μg	HandiHaler® 18 μg	Respimat® 10 μg
Average heart rate (BPM), mean ± SD (min–max)						
205.284						
Baseline	81.35 ± 9.14 (52–97)	–	–	–	79.89 ± 10.88 (59–108)	–
Day 56	81.17 ± 11.49 (58–141)	–	–	–	80.41 ± 11.00 (53–117)	–
Day 84	81.12 ± 12.36 (54–140)	–	–	–	80.19 ± 9.78 (61–103)	–
205.254/255						
Baseline	79.26 ± 11.56 (55–136)	–	–	77.64 ± 10.05 (50–100)	–	80.10 ± 9.86 (60–108)
Day 113	78.97 ± 11.27 (56–129)	–	–	76.33 ± 10.00 (48–97)	–	80.87 ± 8.72 (60–101)
Day 281	77.62 ± 11.21 (53–111)	–	–	77.23 ± 9.68 (56–99)	–	81.30 ± 8.58 (59–104)
205.458						
Day 26	75.91 ± 10.91 (56–106)	75.14 ± 10.84 (51–102)	76.13 ± 11.93 (52–119)	75.36 ± 10.77 (51–108)	75.83 ± 10.35 (58–100)	–
Day 29	77.02 ± 10.36 (59–103)	76.37 ± 10.69 (53–110)	77.75 ± 10.90 (54–103)	76.87 ± 10.82 (54–104)	77.39 ± 10.44 (55–104)	–
Maximum heart rate (BPM), mean ± SD (min–max)						
205.284						
Baseline	121.58 ± 12.89 (71–145)	–	–	–	121.78 ± 18.55 (87–200)	–
Day 56	124.45 ± 15.63 (91–177)	–	–	–	121.59 ± 18.18 (81–171)	–
Day 84	124.32 ± 16.56 (92–200)	–	–	–	120.12 ± 16.15 (78–192)	–
205.254/255						
Baseline	121.94 ± 19.21 (72–203)	–	–	118.15 ± 16.91 (80–200)	–	121.58 ± 17.36 (77–189)
Day 113	120.99 ± 18.21 (72–192)	–	–	115.96 ± 14.70 (77–174)	–	120.06 ± 16.38 (88–225)
Day 281	119.0 ± 18.14 (77–180)	–	–	116.73 ± 13.94 (86–147)	–	119.27 ± 14.47 (83–158)
205.458						
Day 26	108.82 ± 16.58 (74–143)	107.71 ± 14.28 (76–141)	109.07 ± 15.77 (61–166)	107.72 ± 16.25 (68–155)	109.85 ± 14.93 (74–160)	–
Day 29	109.57 ± 15.46 (67–162)	109.57 ± 15.29 (72–141)	110.05 ± 15.45 (66–143)	109.34 ± 14.36 (67–138)	108.94 ± 14.48 (74–141)	–
Minimum heart rate (BPM), mean ± SD (min–max)						
205.284						
Baseline	55.12 ± 7.16 (34–74)	–	–	–	54.54 ± 8.39 (38–90)	–
Day 56	54.69 ± 9.30 (24–86)	–	–	–	55.07 ± 8.91 (20–78)	–
Day 84	55.42 ± 10.07 (22–96)	–	–	–	54.77 ± 8.49 (27–82)	–
205.254/255						
Baseline	55.07 ± 10.29 (28–103)	–	–	53.85 ± 8.35 (34–78)	–	55.48 ± 8.62 (34–75)
Day 113	54.04 ± 9.50 (28–93)	–	–	53.36 ± 9.33 (34–89)	–	56.36 ± 8.55 (35–80)
Day 281	54.19 ± 10.97 (31–93)	–	–	53.77 ± 7.78 (35–71)	–	57.73 ± 8.03 (40–82)
205.458						
Day 26	58.56 ± 9.03 (40–92)	57.34 ± 9.26 (40–87)	58.01 ± 9.37 (41–83)	57.62 ± 9.26 (37–81)	56.98 ± 9.15 (28–79)	–
Day 29	58.71 ± 8.51 (40–90)	58.56 ± 9.32 (39–95)	59.25 ± 9.20 (38–82)	58.34 ± 9.15 (34–81)	58.49 ± 8.51 (42–85)	–

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Table 1 Continued

	Placebo	Respimat® 1.25 µg	Respimat® 2.5 µg	Respimat® 5 µg	HandiHaler® 18 µg	Respimat® 10 µg
Pauses						
205.284						
Baseline, *n*/*N* (%)	1/65 (1.5)	–	–	–	2/74 (2.7)	–
Day 56, *n*/*N* (%)	0/84 (0)	–	–	–	3/92 (3.3)	–
Day 84, *n*/*N* (%)	0/78 (0)	–	–	–	3/86 (3.5)	–
205.254/255						
Baseline, *n*/*N* (%)	3/109 (2.8)	–	–	2/121 (1.7)	–	1/104 (1.0)
Day 113, *n*/*N* (%)	2/100 (2.0)	–	–	2/117 (1.7)	–	1/100 (1.0)
Day 281, *n*/*N* (%)	2/73 (2.7)	–	–	1/103 (1.0)	–	0/89 (0)
205.458						
Day 26, *n*/*N* (%)	0/117 (0)	0/112 (0)	0/115 (0)	0/112 (0)	1/113 (0.9)	–
Day 29, *n*/*N* (%)	0/116 (0)	0/115 (0)	0/116 (0)	0/116 (0)	0/114 (0)	–

BPM, beats per minute; FAS, full analysis set; SD, standard deviation; *N*, number of patients with non-missing data; *n*, number of patients with pauses.

are defined as patients without VPB runs on placebo but with VPB runs on active treatment, while patients 'improving under treatment' are defined as patients with VPB runs on placebo but without VPB runs on active treatment.

The comparison of the numbers of patients 'worsening' and 'improving' revealed balanced changes between active treatment and placebo regarding the development of VPB runs (Table 3). Across trials 205.284 and 205.254/205.255, the proportion of patients 'worsening' on placebo ranged from 5.3% to 13.0%, while the proportion of patients 'improving' on placebo ranged from 3.7% to 8.5%. The corresponding results for tiotropium (Respimat® and HandiHaler®) were similar: 4.3 to 11.0% patients 'worsened' on tiotropium, while 4.6 to 7.5% patients 'improved' on tiotropium.

For trial 205.458 alone, the shift tables for absence/presence of VPB runs off treatment/on treatment showed a trend for differences between the lower (1.25, 2.5 µg) and higher (5 µg) tiotropium Respimat® doses. With the lower doses, the proportion of patients 'worsening' was comparable to the proportion 'improving' (3.6–4.5% vs. 2.7–5.4%, respectively). However, with the 5-µg tiotropium Respimat® dose, the proportion of patients 'worsening' exceeded the proportion 'improving' (4.5–8.8% vs. 2.7–3.6%, respectively). This finding was in line with the overall analysis of VPB runs in this trial. Similarly, for the 18-µg tiotropium HandiHaler® dose, the proportion of patients 'worsening' also exceeded the proportion 'improving' (range 5.4–8.0% vs. 2.7–4.5%, respectively). Across all the trials, only a few patients ($n = 15$) had VPB runs ≥ 10 beats, with no evidence of a relationship with the administered dose strengths.

Furthermore, a comparison of tiotropium peak exposure ($C_{max,ss}$) and overall exposure ($Ae_{0\text{-}6,ss}$) for patients with SVPB/VPB events and those without in trial 205.458 did not reveal a relationship between exposure and events (Figures S1 and S2).

Discussion

The clinical evidence supporting the efficacy and safety of tiotropium in patients with COPD is considerable. However, questions have been raised regarding the potential for anticholinergic agents, particularly tiotropium delivered via Respimat®, to cause arrhythmias in patients with COPD and CV comorbidity. Our analysis of Holter ECG variables in patients with COPD treated with tiotropium provides evidence against an adverse effect of tiotropium in patients with COPD when delivered by either the HandiHaler® device or the Respimat® SMI.

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Table 2 VPB runs (number of patients with events; Holter FAS)

	Placebo	Respimat® 1.25 μg	Respimat® 2.5 μg	Respimat® 5 μg	HandiHaler® 18 μg	Respimat® 10 μg
205.284						
Baseline, *n*/*N* (%)	6/65 (9.2)	–	–	–	10/74 (13.5)	–
Day 56, *n*/*N* (%)	5/84 (6.0)	–	–	–	7/92 (7.6)	–
Day 84, *n*/*N* (%)	7/78 (9.0)	–	–	–	11/86 (12.8)	–
205.254/255						
Baseline, *n*/*N* (%)	13/109 (11.9)	–	–	18/121 (14.9)	–	10/104 (9.6)
Day 113, *n*/*N* (%)	17/100 (17.0)	–	–	12/117 (10.3)	–	10/100 (10.0)
Day 281, *n*/*N* (%)	9/73 (12.3)	–	–	14/103 (13.6)	–	7/89 (7.9)
205.458						
Day 26, *n*/*N* (%)	8/117 (6.8)	7/112 (6.3)	8/115 (7.0)	9/112 (8.0)	9/113 (8.0)	–
Day 29, *n*/*N* (%)	3/116 (2.6)	5/115 (4.3)	4/116 (3.4)	10/116 (8.6)	9/114 (7.9)	–

FAS, full analysis set; VPB, ventricular premature beat; *N*, number of patients with non-missing data; *n*, number of patients with VPB runs.

Table 3 Number of patients without VPB runs at baseline/placebo but runs on active treatment compared with patients with VPB runs at baseline/placebo but absent when on active treatment (Holter FAS)

	Placebo	Respimat® 1.25 μg	Respimat® 2.5 μg	Respimat® 5 μg	HandiHaler® 18 μg	Respimat® 10 μg
205.284			**Shifts vs. baseline**			
Day 56, *n*/*N* (%)	↑3/57 (5.3), ↓3/57 (5.3)	–	–	–	↑5/68 (7.4), ↓4/68 (5.9)	–
Day 84, *n*/*N* (%)	↑2/54 (3.7), ↓5/54 (9.3)	–	–	–	↑4/62 (6.5), ↓4/62 (6.5)	–
205.254/255			**Shifts vs. baseline**			
Day 113, *n*/*N* (%)	↑5/77 (6.5), ↓10/77 (13.0)	–	–	↑7/93 (7.5), ↓4/93 (4.3)	–	↑4/74 (5.4), ↓5/74 (6.8)
Day 281, *n*/*N* (%)	↑5/59 (8.5), ↓4/59 (6.8)	–	–	↑6/82 (7.3), ↓9/82(11.0)	–	↑3/65 (4.6), ↓3/65 (4.6)
205.458			**Shifts vs. placebo**			
Day 26, *n*/*N* (%)	–	↑4/110 (3.6), ↓4/110 (3.6)	↑6/112 (5.4), ↓5/112 (4.5)	↑4/110 (3.6), ↓5/110 (4.5)	↑5/112 (4.5), ↓6/112 (5.4)	–
Day 29, *n*/*N* (%)	–	↑3/113 (2.7), ↓5/113 (4.4)	↑3/113 (2.7), ↓4/113 (3.5)	↑3/113 (2.7), ↓10/113 (8.8)	↑3/113 (2.7), ↓9/113 (8.0)	–

FAS, full analysis set; VPB, ventricular premature beat; *N*, number of patients with non-missing data at baseline and on the respective treatment day; ↑*n*, number of patients with VPB runs at baseline/placebo but without runs on active treatment ('improving'); ↓*n*, number of patients without VPB runs at baseline/placebo but with VPB runs on active treatment ('worsening').

Overall, there were no discernable treatment-dependent effects on HR, pauses and SVPB/VPB events across the four trials; however, in the individual trials there was a high degree of variability, particularly in parameters with low event rates, such as the number of patients with VPB runs. For example, in trial 205.458 (12) a tendency towards a higher frequency of VPB runs was observed in patients receiving tiotropium Respimat® 5 μg and tiotropium HandiHaler® 18 μg compared with placebo or lower tiotropium Respimat® doses on one study day (day 29) but not on another study day (day 26). This imbalance in the number of patients with VPB runs was not seen in the other three trials, two of which included a higher dose level of tiotropium (Respimat® 10 μg in trials 205.254 and 205.255) (6) and with longer treatment duration (up to 48 weeks). In general, in trials with 24-h Holter monitoring, the proportion of patients with VPB runs who received tiotropium treatment was similar to those who did not. The tendency for a higher frequency of VPB runs on day 29 of trial 205.458 (12) may be explained by the low proportion of patients with VPB runs on placebo, which is not seen on day 26, reflecting natural variability. On day 26 of the placebo period, the proportion of patients with VPB

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runs was higher (6.8%) and thus comparable to the respective day 26 results in the tiotropium treatment periods (6.3–8.0%). Taking all the trials together, the proportion of patients with VPB runs did not suggest a dose relationship. Likewise, there was no evidence for an exposure–effect relationship regarding other cardiac arrhythmia end-points.

The findings of this combined analysis are in line with the results of the recently published TIOSPIR™ trial (10), which did not support the theory that the tiotropium Respimat® formulation is associated with an increased risk of mortality in patients with COPD, especially in patients with cardiac arrhythmia or cardiac disease in general (16–18). Of note, and in contrast to the *post hoc* pooled analyses of data from smaller placebo-controlled trials (2, 3), survival rates in the TIOSPIR™ trial were similar for both tiotropium Respimat® 5 μg and tiotropium HandiHaler® 18 μg not only in the overall population but also among the 1221 patients with a history of cardiac arrhythmia, numerically even favouring tiotropium Respimat® 5 μg (hazard ratio: 0.81; 95% CI: 0.58–1.12).

Our analysis has both strengths and limitations. One strength is that a considerable number of patients have been investigated using double (10 μg) the therapeutic tiotropium Respimat® dose for 48 weeks. Another strength is that patients with concomitant CV conditions were not excluded from these studies, although it is acknowledged that patients at highest risk were excluded, such as those with 'unstable' arrhythmias, cardiac failure or a recent myocardial infarction (defined as occurring within the last 6 months). Consequently, our findings cannot be extended to these patient populations and more 'real-life' studies will be required before any firm conclusions can be drawn. Furthermore, because of study differences (parallel vs. cross-over design, duration of treatment/Holter monitoring periods, and use of baseline Holter recording), pooling of individual patient data from the four trials was not possible.

We conclude that, tiotropium administered using the Respimat® SMI (1.25–10 μg) or HandiHaler® (18 μg) for periods of up to 48 weeks is not associated with changes in HR, SVPBs, VPBs and pauses measured by Holter ECG monitoring when compared with placebo or the pretreatment baseline period. These findings support data from other prospective studies that did not confirm cardiac side effects from tiotropium in patients with COPD that were suggested on the basis of smaller studies and retrospective analyses. At the same time, it is recognised that more data are required on the safety of tiotropium in patients with unstable CV disorders who might have been excluded from the trials analysed.

Author contributions

A.F. prepared the preliminary draft; all authors (J.H., A.F., M.K.B., G.W., B.W. and E.B.) reviewed and contributed to each draft, and approved the final version for publication.

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References

1 Boehringer Ingelheim. Innovative solutions to help millions breathe easier, 2013. http://www.boehringer-ingelheim.com/content/dam/internet/opu/com_EN/document/01_news/05_Media_Material/Pipeline_backgrounder_2013.PDF (accessed 25 October 2013).

2 Boehringer Ingelheim. Summary of Product Characteristics (SPC): Spiriva 18 microgram inhalation powder, hard capsule. EMC, 2013. http://www.medicines.org.uk/emc/medicine/10039 (accessed 25 October 2013).

3 Boehringer Ingelheim. Summary of Product Characteristics (SPC): Spiriva Respimat 2.5 microgram solution for inhalation. EMC, 2013. http://www.medicines.org.uk/emc/medicine/20134 (accessed 19 July 2013).

4 van Noord JA, Cornelissen PJ, Aumann JL, Platz J, Mueller A, Fogarty C. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. *Respir Med* 2009; **103**: 22–9.

5 Bateman E, Singh D, Smith D et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *Int J Chron Obstruct Pulmon Dis* 2010; **5**: 197–208.

6 Bateman ED, Tashkin D, Siafakas N et al. A one--year trial of tiotropium Respimat plus usual therapy in COPD patients. *Respir Med* 2010; **104**: 1460–72.

7 Cooper CB, Celli BR, Jardim JR et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. *Chest* 2013; **144**: 490–7.

8 Tashkin DP, Celli B, Senn S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359**: 1543–54.

9 Vogelmeier C, Hederer B, Glaab T et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011; **364**: 1093–103.

10 Wise RA, Anzueto A, Cotton D et al. Tiotropium respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; **369**: 1491–501.

11 Ichinose M, Fujimoto T, Fukuchi Y. Tiotropium 5microg via Respimat and 18microg via HandiHaler; efficacy and safety in Japanese COPD patients. *Respir Med* 2010; **104**: 228–36.

12 Hohlfeld JM, Sharma A, van Noord JA et al. Pharmacokinetics and pharmacodynamics of tiotropium solution and tiotropium powder in chronic obstructive pulmonary disease. *J Clin Pharmacol* 2014; **54**: 405–14.

13 Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; **7**: CD00 9285.

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14 Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest* 2010; **137**: 20–30.
15 Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax* 2013; **68**: 114–6.
16 Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax* 2013; **68**: 48–56.
17 Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2011; **342**: d3215.
18 Verhamme KM, Afonso A, Romio S, Stricker BC, Brusselle GG, Sturkenboom MC. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD. *Eur Respir J* 2013; **42**: 606–15.
19 Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; **61**: 854–62.
20 Kesten S, Leimer I, Jara M. Risk of major adverse cardiovascular events with inhaled anticholinergics in patients with chronic obstructive pulmonary disease. *JAMA* 2009; **301**: 1224–6.
21 Rodrigo GJ, Castro-Rodriguez JA, Nannini LJ, Plaza Moral V, Schiavi EA. Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. *Respir Med* 2009; **103**: 1421–9.
22 Covelli H, Bhattacharya S, Cassino C, Conoscenti C, Kesten S. Absence of electrocardiographic findings and improved function with once-daily tiotropium in patients with chronic obstructive pulmonary disease. *Pharmacotherapy* 2005; **25**: 1708–18.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Trials included in the combined analysis of Holter electrocardiogram (ECG) data.

Data S2. Analysis of exposure–effect relationship in trial 205.458.

Table S1. Design and patient numbers in tiotropium trials in which Holter ECG recording was performed (Holter FAS).

Table S2a. Patient baseline demographics by trial (Holter FAS).

Table S2b. Patient baseline prebronchodilator spirometry by trial (Holter FAS).

Table S3a. VPB pairs and singles (number of patients with events; Holter FAS).

Table S3b. SVPBs runs, pairs and singles (number and proportion of patients with events; Holter FAS).

Figure S1. Box plot comparing $C_{max,ss}$ (A) and $Ae_{0–6,ss}$ (B) values in patients with and without VPB runs on days 26 and 29.

Figure S2. Box plot comparing $C_{max,ss}$ (A) and $Ae_{0–6,ss}$ (B) values in patients with and without SVPB runs on days 26 and 29.

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