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Review article

Effect of tiotropium on COPD exacerbations: A systematic review

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ABSTRACT

Background: Exacerbation frequency is related to disease progression, quality of life, and prognosis in COPD. Earlier diagnosis, along with interventions aimed at preventing exacerbations and delaying progression, may help reduce the global burden of disease. Long-acting inhaled bronchodilators are effective at maintaining symptom relief and are recommended as first-choice therapy for more symptomatic patients and those at risk of exacerbation.

Methods: As prevention of exacerbations is a priority goal in COPD management and a number of different long-acting bronchodilators are available, we conducted a systematic review of exacerbation data from randomized controlled trials (published January 2000 to May 2014) comparing the effect of tiotropium versus placebo and/or other maintenance therapies.

Results: Exacerbations were a primary endpoint in 12 publications (five studies: four comparing tiotropium with placebo; one with active comparator) and a secondary endpoint in 17 publications (seven studies: six comparing tiotropium with placebo; one with active comparator). Overall, tiotropium was associated with a longer time to first exacerbation event and fewer exacerbations (including severe exacerbations/hospitalizations) compared with placebo and long-acting β_2-agonists. Tiotropium also showed similar efficacy to glycopyrronium and a fixed long-acting muscarinic antagonist/long-acting β_2-agonist combination (glycopyrronium/indacaterol), although not all studies were powered to demonstrate differences in exacerbation outcomes. Exacerbation outcomes were comparable with both formulations of tiotropium (HandiHaler® 18 μg/Respimat® 5 μg).

Conclusions: The results of this comprehensive systematic review demonstrate tiotropium is beneficial in reducing exacerbation risk versus placebo or other maintenance treatments.

Contents

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1. Introduction

COPD is characterized by airflow obstruction, and bronchodilators are central to its management [1]. The aims of pharmacological therapy for COPD are to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [1]. Short-acting bronchodilators can produce substantial improvements in lung function, but long-acting bronchodilators are more effective at maintaining symptom relief [1]. Improvements in FEV_1 produced by bronchodilation correlate with improvements in breathlessness and health status as well as reduced exacerbation rates [2].

Exacerbations are an important component of COPD [3,4], significantly impacting on the burden of disease [5], leading to a worsening health status and increased risk of future exacerbations and death [6,7]. Exacerbations are also strong predictors of disease progression, quality of life, and prognosis [7,8]. Some patients may be more prone to exacerbations [4], and the prevention of exacerbations is a priority goal in COPD management [1].

Current maintenance therapies for patients at risk of exacerbations include long-acting anticholinergics (also called long-acting muscarinic antagonists [LAMAs]), long-acting β_2-agonists (LABAs), LABAs combined with inhaled corticosteroids (ICS), and phosphodiesterase type 4 inhibitors [9,10]. For patients at risk of exacerbations in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups C and D, a long-acting anticholinergic or a fixed combination of ICS/LABA is recommended as first-choice therapy [10], while for symptomatic patients at lower risk of exacerbations (group B), a LAMA or LABA is recommended. There is now more evidence to inform these choices, and we have therefore undertaken a systematic review of the effects of tiotropium therapy compared with placebo and/or other maintenance therapies in patients with COPD. Unlike other publications (for example, Karner, et al. [11]), this review includes for the first time all published randomized controlled trials with exacerbation outcomes as prespecified endpoints and with tiotropium as an active treatment arm.

Tiotropium is a once-daily LAMA shown to reduce exacerbations and improve other important outcomes of COPD [12–15]. Tiotropium is approved and marketed as a dry-powder formulation delivered via the HandiHaler® device (18 μg; Boehringer Ingelheim Pharma GmbH and Co KG, Ingelheim am Rhein, Germany) [16] and as an aqueous solution delivered via the Respimat® inhaler (5 μg; two puffs of 2.5 μg once daily; Boehringer Ingelheim Pharma GmbH and Co KG, Ingelheim am Rhein, Germany) in many countries [17].

2. Methods

A systematic literature search (January 2000 to May 2014) of electronic databases was conducted to identify all COPD trials in which exacerbations were a prespecified endpoint and tiotropium was an active treatment arm. As there is no standardized definition of a COPD exacerbation due to the heterogeneity of causes, symptoms and severities [18], our literature search did not limit studies to a specific definition. (For definitions of exacerbation used in selected studies, see Table E1 in the online supplement.) The total hits from the search were assessed for their relevance (based on titles/abstracts), and publications that were deemed potentially relevant were obtained in full and assessed.

Articles were included if they reported on double-blind, randomized, controlled trials of ≥6 months' duration. Both placebo- and active-controlled (i.e., vs. other maintenance therapies) trials were eligible if exacerbation data were included as a primary or secondary endpoint; blinded studies with additional open-label tiotropium arm(s) were included if appropriate. Prospective studies and subgroup analyses of trials were permitted, provided the data were new and not duplicated elsewhere. Non-blinded open-label studies, review articles, methodology papers, retrospective studies, pooled analyses, case studies, conference findings, congress abstracts, pharmacoeconomic studies, and meeting reports were excluded. The search was limited to trials in humans. The literature search results and article selection were reviewed and verified by the authors to ensure their accuracy.

Exacerbation outcomes included time to first event (exacerbation/hospitalization due to exacerbation), exacerbation rate, and the proportion of patients with events (exacerbations/hospitalizations due to exacerbation).

3. Results

3.1. Summary of search findings

The search returned a total of 236 hits (Fig. 1). Of these, 195 publications were excluded based on the title/abstract and identification of duplicates. The remaining 41 publications were deemed potentially relevant based on the title and/or abstract. Of these, a further 14 publications were excluded based on duration of study (i.e., <6 months [$n = 6$]), retrospective nature of study ($n = 1$), non-appropriate comparator ($n = 1$), open-label study ($n = 2$), pooled analysis ($n = 3$), and lack of data on specific treatments ($n = 1$). Two additional recent publications were identified during the search [19,20]. In total, 29 publications were deemed relevant for inclusion in the final analysis [12,14,15,19–44]. Refer to online supplement, Tables E2 and E3, for details of study durations and population size.

Exacerbations were a primary study endpoint (including subgroup analyses and prospective studies) in 12 publications [12,15,21,23,24,30,35,37,38,42–44] and a secondary study endpoint

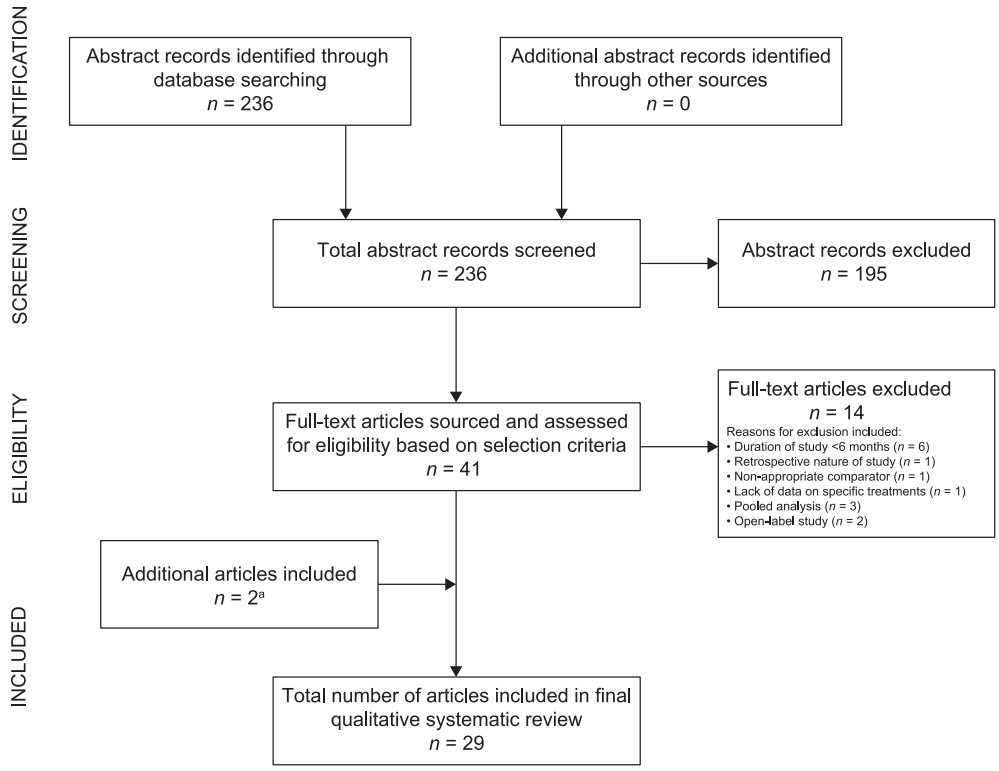

Fig. 1. Systematic review of published manuscripts reporting exacerbation data in trials comparing tiotropium with placebo and/or other maintenance therapies. [a] Two additional articles included following a final check on any relevant, recently published articles (since May 2014 end of search period and submission date).

(including subgroup analyses and prospective studies) in 17 publications [14,19,20,22,25–29,31–34,36,39].

Six studies included an entry criterion that patients must have had one or more exacerbations in the year prior to entry [15,21,29,30,42–44], and one study required one or more exacerbations in the 2 years prior to entry [26].

The exacerbation data reported included time to first event, exacerbation rate, and proportion of patients with an event (online supplement, Tables E2 and E3); severe (hospitalized) exacerbation data have been detailed where available. Of the 209 publications that were excluded, 26 reported exacerbations as "other endpoint". Additional data from open-label comparisons are included for information only [43,45,46].

3.2. Effect of tiotropium versus placebo

Sixteen publications comparing tiotropium with placebo investigated the use of HandiHaler® (18 μg) [14,24–28,30–32,34–37,39–41], and four reported the effects of Respimat® (5 μg [two puffs of 2.5 μg once daily] and/or 10 μg) [12,22,23,38].

3.2.1. Time to first exacerbation event

There were 14 publications (including subgroup analyses) that compared tiotropium with placebo, with time to first exacerbation as the endpoint [12,14,22–25,27,28,30,35,36,38,40,41]. Tiotropium was associated with a significantly ($p < 0.05$) prolonged time to first exacerbation in nine studies [12,14,23–25,30,35,36,40] (online supplement, Table E2). In three studies, the time to first hospitalization (severe exacerbation) was also significantly ($p < 0.05$) prolonged in patients treated with tiotropium compared with placebo (Fig. 2; online supplement, Table E2) [12,14,35].

3.2.2. Exacerbation rate or proportion of patients with exacerbations

Twenty publications (including subgroup analyses) compared the effect of tiotropium with placebo on the rate of exacerbations or proportion of patients experiencing an exacerbation event [12,14,22–28,30–32,34–41]. Fewer patients treated with tiotropium experienced one or more exacerbations [12,23–25,30,35–38]; these differences reached statistical significance in nine publications [12,23–25,30,35–38]. In addition, the number/rate of exacerbations [14,22–25,27,28,30–32,34,36–40] and exacerbation days [14,24,30,36,37,40] were reduced and the probability of remaining exacerbation-free [23] was higher in patients receiving tiotropium versus placebo.

In total, 16 publications examined the effect of tiotropium on severe exacerbations or hospitalizations due to an exacerbation [12,14,23–28,30,31,34–37,39,41]; in five studies, significantly fewer patients experienced a severe/hospitalized exacerbation in the tiotropium arms versus placebo [24,25,35,37,39]. In addition, two studies [24,25] demonstrated that patients receiving tiotropium had significantly fewer hospitalization days due to a severe exacerbation versus those receiving placebo (online supplement, Table E2). However, in two studies [14,26], the number of hospitalizations and hospitalization days due to a severe exacerbation did not differ between tiotropium and placebo (online supplement, Table E2).

3.2.3. Subgroup analyses

In general, the eight subgroup analyses comparing tiotropium with placebo displayed similar trends for exacerbation reductions to those observed in the primary studies, although not all outcomes were statistically significant [27,28,31,32,34,37–39]. In prespecified subgroup analyses of the Understanding Potential Long-term

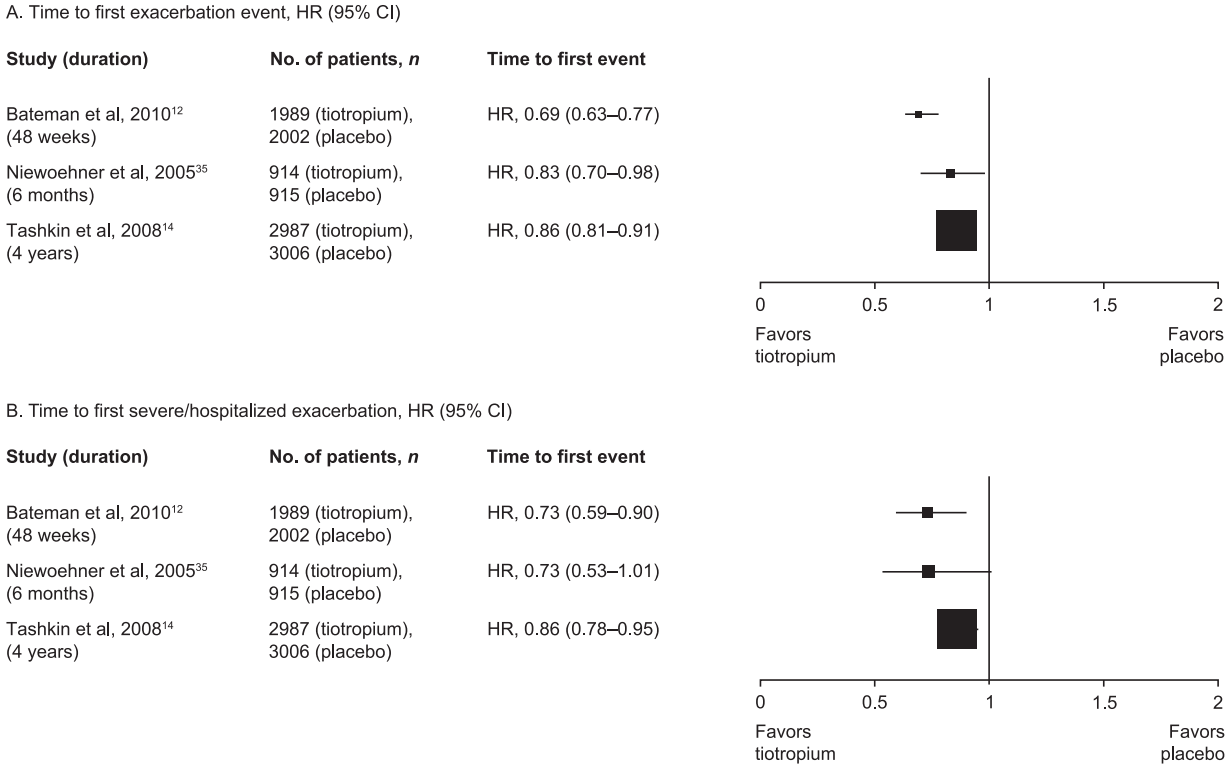

Fig. 2. Hazard ratios for an exacerbation of COPD in patients receiving tiotropium versus placebo.

Impacts on Function with Tiotropium (UPLIFT®) trial, tiotropium significantly reduced the rate of exacerbations in patients with COPD aged <50 years ($p = 0.02$) [34]. Tiotropium reduced the number of exacerbations per patient-year by 16% versus control in patients naïve to maintenance therapy prior to the study; however, this failed to reach statistical significance ($p = 0.08$) [41].

In a *post-hoc* subanalysis of the Veteran Affairs Study (despite not being adequately powered), tiotropium reduced the likelihood of having at least one exacerbation versus placebo in the entire patient group (rate ratio [95% confidence interval (CI)]: 0.81 [0.66–0.99]; $p = 0.037$), with no statistically significant difference between the African American and Caucasian subgroups ($p = 0.34$) [37].

3.3. Effect of tiotropium versus active comparators

3.3.1. Tiotropium monotherapy versus salmeterol

Two publications (including subgroup analyses) directly compared tiotropium with salmeterol [15,42]. In the Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD®) trial, tiotropium significantly prolonged the time to first exacerbation (187 vs. 145 days; hazard ratio [HR] [95% CI], 0.83 [0.77–0.90]; $p < 0.001$) and severe exacerbation (HR [95% CI], 0.72 [0.61–0.85]; $p < 0.001$) in patients with moderate to very severe COPD when compared with salmeterol [15] (Fig. 3; online supplement, Table E3).

In addition, tiotropium reduced the annual rate of exacerbations versus salmeterol (0.64 vs. 0.72; rate ratio [95% CI], 0.89 [0.83–0.96]; $p = 0.002$), as well as the annual rate of moderate exacerbations (0.54 vs. 0.59; rate ratio [95% CI], 0.93 [0.86–1.00]; $p = 0.048$) and severe exacerbations (0.09 vs. 0.13; rate ratio [95% CI], 0.73 [0.66–0.82]; $p < 0.001$) (online supplement, Table E3). Of those patients who experienced an exacerbation in this trial, 44% had moderate (GOLD stage 2) COPD at trial onset.

In subgroup analyses of POET-COPD®, tiotropium significantly prolonged the time to first exacerbation (HR [95% CI], 0.88 [0.79–0.99]; $p = 0.028$) and first severe exacerbation (HR [95% CI], 0.66 [0.48–0.91]; $p = 0.012$), reduced rates of severe exacerbations (rate ratio [95% CI], 0.70 [0.57–0.85]; $p < 0.001$) in GOLD stage 2 patients [42], significantly prolonged the time to first exacerbation (HR [95% CI], 0.79 [0.65–0.97; $p = 0.028$), and reduced the annual exacerbation rate (rate ratio [95% CI], 0.77 [0.63–0.94]; $p = 0.012$) in maintenance therapy-naïve patients when compared with salmeterol [42].

3.3.2. Tiotropium monotherapy versus indacaterol

One publication compared tiotropium with indacaterol [29]. In the second, prespecified superiority analysis, the annualized rate of exacerbations was shown to be higher with indacaterol than with tiotropium (0.90 vs. 0.73; rate ratio [95% CI], 1.24 [1.12–1.37]; $p < 0.0001$), showing superiority of tiotropium [29]. In addition, the time to first moderate or severe exacerbation was longer with tiotropium (HR [95% CI], 1.20 [1.07–1.33]; $p = 0.0012$) over a 1-year period [29]. The HR and 95% CIs presented here for tiotropium versus indacaterol for time to first moderate or severe exacerbation were derived by inverting the HRs and CIs reported in the referenced publication (HR [95% CI], 0.83 [0.75–0.93]; $p = 0.0012$) (Fig. 3; online supplement, Table E3).

In a separate subgroup analysis of patients with exacerbations treated with ICS and/or antibiotics, exacerbation rates were higher in the indacaterol group than in the tiotropium group [29]. However, in patients stratified by ICS at baseline, the rates of severe exacerbations were not significantly different between the two groups. Overall, fewer patients in the tiotropium group experienced an exacerbation during the study than those in the indacaterol group.

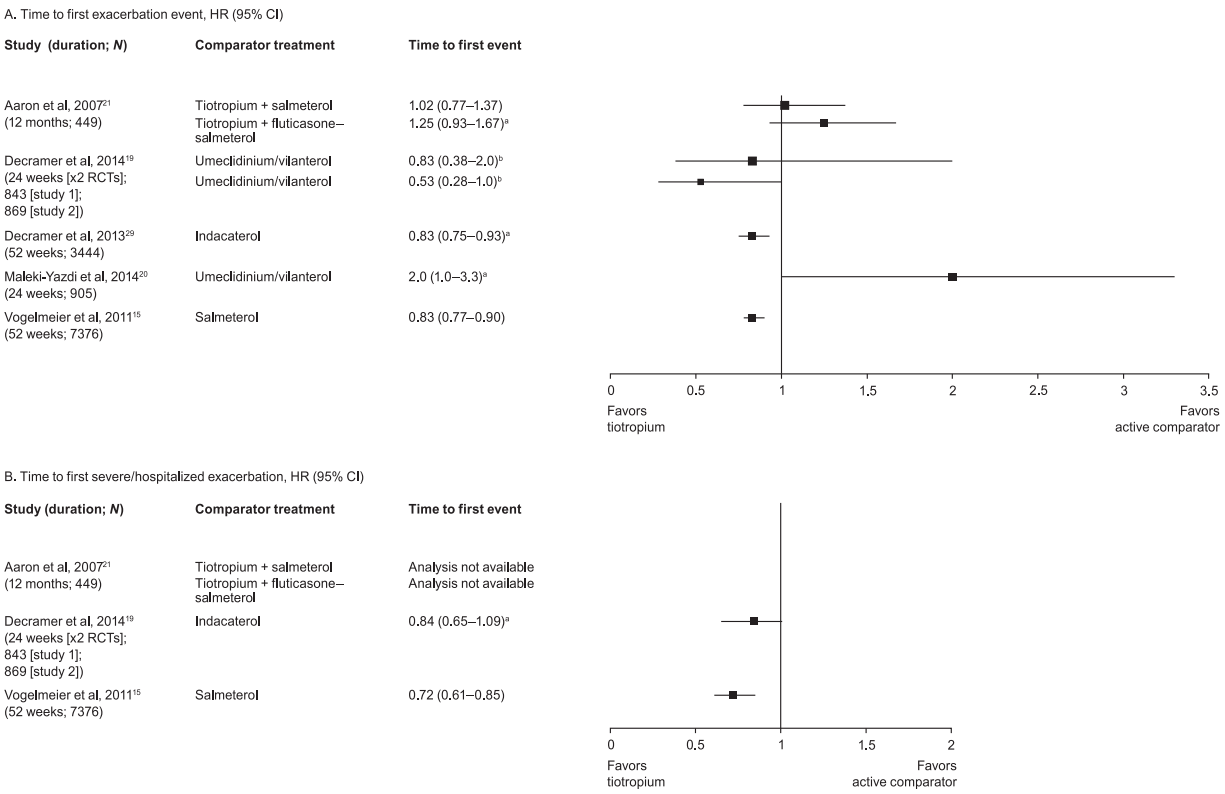

Fig. 3. Hazard ratios for an exacerbation of COPD in patients receiving tiotropium versus an active comparator. [a] Reciprocal HR and 95% CI for tiotropium versus tiotropium plus fluticasone-salmeterol were derived and not as reported in the Aaron et al., 2007 [21] (the reported unadjusted of HR [95% CI], 0.80 [0.60–1.08] are inconsistent with the results presented in the text and are therefore a likely error in the original publication [21]); [b] The reciprocal HR and 95% CIs for tiotropium versus active comparator were derived and not statistically reported in the original publications where values for active comparator versus tiotropium were given.

3.3.3. *Tiotropium monotherapy versus dual and/or triple therapy*

Six publications compared tiotropium with dual (either LABA/LAMA or LABA/ICS) and/or triple therapy (online supplement, Table E3) [19–21,33,43,44].

The Effect of QVA149 Versus NVA237 and Tiotropium on COPD Exacerbations (SPARK) study compared tiotropium versus a combination of glycopyrronium 50 μg/indacaterol 110 μg (QVA149) and glycopyrronium alone (NVA237) in patients at risk of an exacerbation [44]. Overall, the incidence of severe exacerbations was low, with no significant differences observed between tiotropium and the glycopyrronium/indacaterol combination; however, in patients receiving glycopyrronium alone, there was an increase in severe exacerbations compared with tiotropium (rate ratio [95% CI], 1.43 [1.05–1.97]; $p = 0.025$; online supplement, Table E3). The rate of moderate or severe exacerbations was not significantly lower with the glycopyrronium/indacaterol combination versus tiotropium (rate ratio [95% CI], 0.90 [0.79–1.02]; $p = 0.10$), nor with glycopyrronium alone versus tiotropium (rate ratio [95% CI], 1.03 [0.91–1.16]; $p = 0.68$).

Two publications reporting three studies compared the LAMA/LABA combination of umeclidinium/vilanterol with tiotropium [19,20]. In one 24-week blinded study, in which the time to first COPD exacerbation event was an additional endpoint, the risk of an exacerbation was reduced with the LAMA/LABA combination compared with tiotropium (HR [95% CI], 0.5 [0.3–1.0]; $p = 0.044$); however, the number of patients with events was low in both treatment groups ($n = 16$ [4%] vs. 29 [6%], respectively) [20]. Furthermore, a numerically greater proportion of patients who experienced an exacerbation were receiving additional ICS treatment in the umeclidinium/vilanterol group ($n = 12$ [75%]) compared with tiotropium ($n = 20$ [69%]) [20]. In contrast, in two other blinded studies, the risk of a COPD exacerbation was numerically higher in the umeclidinium/vilanterol group when compared with tiotropium, though these results were not significant (HR [95% CI], 1.2 [0.5–2.6]; $p = 0.71$; and HR [95% CI], 1.9 [1.0–3.6]; $p = 0.06$, respectively) [19].

When compared with the salmeterol plus fluticasone combination, tiotropium was not associated with significant differences either in the rate of exacerbations (rate ratio [95% CI], 0.97 [0.84–1.12]; $p = 0.656$) or the rate of hospitalizations (13% vs. 16%; $p = 0.085$) in patients with COPD and a clinical history of exacerbations (online supplement, Table E3) [43]. In a second study, there were no significant differences in exacerbation rates with tiotropium plus salmeterol/fluticasone combination versus tiotropium alone ($p = 0.531$) (online supplement, Table E3) [33].

In a multicenter trial of patients with moderate or severe COPD who had at least one exacerbation treated with corticosteroids or antibiotics in the 12 months prior to randomization [21], neither dual therapy with tiotropium and salmeterol, nor triple therapy with tiotropium, salmeterol, and fluticasone, was associated with any significant differences in the proportion of patients experiencing at least one exacerbation, time to first exacerbation event, or mean number of exacerbations when compared with tiotropium alone. However, unlike dual therapy, triple therapy was associated with a significant reduction in the rate of severe exacerbations requiring hospitalization compared with tiotropium monotherapy (relative risk, 0.53; $p = 0.01$) (online supplement, Table E3).

3.4. *Additional information from open-label comparisons*

3.4.1. *Tiotropium monotherapy versus glycopyrronium and placebo*

One publication compared open-label tiotropium with glycopyrronium bromide [44,45], and another compared each agent with placebo [45].

In the SPARK study, when tiotropium was compared with

glycopyrronium, there were no significant differences for the annual rates of moderate or severe exacerbations (0.93 vs. 0.95) or severe exacerbations (0.08 vs. 0.12) [44].

In a 1-year open-label study, tiotropium reduced the risk of exacerbations (time to first moderate or severe exacerbation) by 34% compared with placebo (HR [95% CI], 0.66 [0.52–0.85]; $p = 0.001$) [45]. The risk reduction was 39% with glycopyrronium versus placebo (HR [95% CI], 0.61 [0.46–0.82]; $p = 0.001$). While glycopyrronium was associated with a 35% reduction in the rate of moderate or severe exacerbations compared with placebo (0.54 vs. 0.80; rate ratio [95% CI], 0.66 [0.50–0.87]; $p = 0.003$), the effect of tiotropium was not significantly different from placebo (rate ratio [95% CI], 0.80 [0.59–1.11]; $p = 0.179$). Both glycopyrronium and tiotropium were superior to placebo in reducing moderate exacerbations treated with systemic corticosteroids (odds ratio [95% CI], 0.61 [0.43–0.87; $p = 0.006$ and 0.62 [0.41–0.93]; $p = 0.021$, respectively) or antibiotics (odds ratio [95% CI], 0.69 [0.50–0.96]; $p = 0.026$ and 0.65 [0.44–0.95]; $p = 0.026$, respectively) [45].

3.4.2. *Tiotropium monotherapy versus indacaterol and placebo*

One publication compared open-label tiotropium with indacaterol and placebo [46]. Over 26 weeks, tiotropium was associated with numerical reductions in exacerbations versus placebo (HR [95% CI], 0.76 [0.56–1.03]; $p = 0.080$) but did not significantly reduce the rate of exacerbations compared with placebo (rate ratio [95% CI], 0.70 [0.48–1.03]; $p = 0.070$). Indacaterol 150 μg did appear to have a significant benefit over placebo in terms of time to first COPD exacerbation (HR [95% CI], 0.69 [0.51–0.94]; $p = 0.019$) and the rate of exacerbations (rate ratio [95% CI], 0.67 [0.46–0.99]; $p = 0.044$) in this study.

4. Discussion

Clinicians need clear advice from guidelines and initiatives such as GOLD on the best first-choice therapies for managing patients with COPD, particularly when considering outcomes such as effects on exacerbation rates. Tiotropium is the most widely studied LAMA and, as such, there is a considerable amount of data available. However, to our knowledge, this is the first systematic review of all published randomized, controlled trials designed to assess exacerbations outcomes (as prespecified endpoints) in patients with COPD who were receiving tiotropium via HandiHaler® or Respimat® (compared with placebo and/or other maintenance therapies).

Overall, tiotropium appears to be associated with a longer time to first exacerbation event and fewer exacerbations (including severe exacerbations/hospitalizations) than either placebo or active comparator treatment. To date, there are limited data available to suggest an additional clinical benefit (in terms of exacerbation reduction) when using LAMA/LABA combinations or a LABA/ICS in combination with a LAMA.

Generally, exacerbation outcomes were comparable with both formulations of tiotropium (HandiHaler® 18 μg/Respimat® 5 μg), a finding in line with evidence from the TIOtropium Safety and Performance In Respimat® (TIOSPIR®) study ($N = 17{,}135$), which demonstrated similar exacerbation efficacy and safety profiles for the two formulations [47].

Both LAMAs and LABAs are effective treatments for patients with COPD and are widely used in clinical practice; however, differences in exacerbation outcomes between various treatments have been demonstrated in the literature. For example, tiotropium, a once-daily LAMA, significantly decreased the annual rate of exacerbations for patients with moderate to very severe COPD compared with salmeterol, a twice-daily LABA [15]. A trend for lower rates of exacerbations was evident with tiotropium compared with indacaterol, a once-daily LABA [29], and indacaterol did not show non-inferiority to tiotropium in terms of the annual rate of exacerbations. These findings indicate that tiotropium may be more effective than LABAs in terms of exacerbation reduction, irrespective of once-daily or twice-daily regimens, suggesting that the effect is not simply related to sustained bronchodilation. It has been postulated that differences in duration and mechanism of action may account for their exacerbation outcome profiles; however, evidence is currently lacking and further prospective, randomized studies are needed to compare directly the exacerbation efficacy of these agents.

Potential mechanisms that may contribute to the preventive effects of tiotropium on COPD exacerbations might include inhibition of the action of acetylcholine in the lung, which may lead to suppression of acetylcholine-mediated release of chemotactic substances involved in the modulation of inflammatory responses [48]. Inhibition of acetylcholine may translate into additional effects beyond that of bronchodilation (i.e., anti-inflammatory effects), and the reduction of proliferation and mucus secretion [48–51].

Although beyond the scope of this review, an important clinical question is whether the exacerbation-prevention properties of tiotropium can be considered a class effect. While LAMAs all demonstrate a high affinity and potency toward the muscarinic M3 receptor, tiotropium has been shown to have a much longer dissociation from the receptors than either aclidinium or glycopyrronium [50,52]. Tiotropium therefore provides an effective and long-lasting (>24 h) blockade of the M3 receptors [53,54]. In line with these kinetic properties, preclinical data suggest that tiotropium should provide the greatest level of bronchoprotection of all three LAMAs when applied at equieffective doses [50]. It is speculative as to whether LAMAs have anti-inflammatory effects: most of the studies suggesting that LAMAs have anti-inflammatory and anti-remodelling properties have been conducted *in vitro*, and clinical studies showing definite anti-inflammatory activity for any LAMA are lacking. Few studies have directly compared the exacerbation efficacy of LAMAs, and this is worthy of further investigation.

Unlike LAMAs, which mediate their bronchodilator effects through inhibition of cholinergic pathways, LABAs mediate their effects, in part, through stimulation of β_2-adrenergic receptors. Recent studies suggest that genetic variation in these receptors may play an important role in treatment response [55], with some genotypes associated with a limited response to β_2-adrenergic drugs and others a full response; however, in clinical practice these genotypes are difficult to identify.

There are both strengths and limitations of this systematic review that should be considered when evaluating the findings. A total of 29 publications were selected for review, including large studies that were specifically powered to evaluate exacerbations [12,15,47], and studies that were large and of a long enough duration to evaluate exacerbations in subgroup analyses [14,15]. In terms of limitations, the results are generally reported in a descriptive manner, and direct comparisons between trials are not conclusive due to differences in study designs and other potential methodological shortcomings. The lack of standardization in endpoints and outcomes between trials precluded the ability to pool data from different studies and perform a formal meta-analysis of the exacerbation data. Definitions used to describe an exacerbation event, including severity, differed between trials, and it is unknown whether these differences may have influenced results; however, there appears to be consistency in the results of the individual studies reviewed here.

Since our search was restricted to English-language papers and mainstream journals (electronic search of the main databases), we

cannot discount the possibility that some studies may have been excluded from this review; however, due to the comprehensive and rigorous literature search process, we are confident that all key studies published at the time were captured and included.

Although not all studies were powered to show differences in exacerbation outcomes, current evidence indicates that tiotropium appears to demonstrate benefits over placebo and the LABAs salmeterol and indacaterol, while providing results comparable with the LAMA glycopyrronium and the fixed LAMA/LABA combination QVA149 (glycopyrronium/indacaterol).

Conflicts of interest

DMGH has received personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim and Novartis, and personal fees from GlaxoSmithKline and Pfizer. CV has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cytos, GlaxoSmithKline, Janssen, Mundipharma, Novartis and Takeda, and grants and personal fees from Grifols. MPP and NM are employees of Boehringer Ingelheim. FR was an employee of Boehringer Ingelheim at the time of manuscript submission. AA has received personal fees from AstraZeneca, Bayer-Schering Pharma, Boehringer Ingelheim, Dey Pharma, GlaxoSmithKline and Pfizer.

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All authors contributed to drafting the article and critically revising the content of the manuscript, and made the decision to submit this work for publication. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.02.012

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