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Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial

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Summary

Background Combinations of long-acting bronchodilators are recommended to reduce the rate of chronic obstructive pulmonary disease (COPD) exacerbations. It is unclear whether combining olodaterol, a long-acting beta-agonist, with tiotropium, a long-acting anti-muscarinic, reduces the rate of exacerbations compared with tiotropium alone.

Methods This 52-week, double-blind, randomised, parallel-group, active-controlled trial randomly assigned (1:1) patients with COPD with a history of exacerbations using a randomised block design to receive tiotropium–olodaterol 5 µg–5 µg or tiotropium 5 µg once daily. Patients using inhaled corticosteroids continued this therapy. Treatment was masked to patients, investigators, and those involved in analysing the data. The primary endpoint was the rate of moderate and severe COPD exacerbations from the first dose of medication until 1 day after last drug administration. The primary analysis included all randomly assigned patients who received any dose of study medication but were not from a site excluded due to on-site protocol violations. The trial is registered with ClinicalTrials.gov, number NCT02296138.

Findings Overall, 9009 patients were screened from 818 centres in 51 countries. We recruited 7880 patients between Jan 22, 2015 and March 7, 2016 (mean age 66·4 years [SD 8·5], 5626 [71%] were men, mean FEV_1 percent predicted 44·5% [SD 27·7]): 3939 received tiotropium–olodaterol and 3941 tiotropium. The rate of moderate and severe exacerbations was lower with tiotropium–olodaterol than tiotropium (rate ratio [RR] 0·93, 99% CI 0·85–1·02; p=0·0498), not meeting the targeted 0·01 significance level. The proportion of patients reporting adverse events was similar between treatments.

Interpretation Combining tiotropium and olodaterol did not reduce exacerbation rate as much as expected compared with tiotropium alone.

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Introduction

Symptomatic exacerbations are frequently reported by patients with chronic obstructive pulmonary disease (COPD), and contribute to poor health status, increased risk of death, and increased health-care costs, especially when hospitalisation is necessary.[1] Exacerbation frequency is used by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to assess COPD severity and guide treatment choice.[2] Although several non-pharmacological interventions reduce exacerbation risk, there has been a greater focus on pharmacotherapy, since there is evidence that agents such as long-acting bronchodilators, inhaled corticosteroids (ICS), oral antibiotics, and mucolytic drugs can reduce exacerbation frequency.[1]

Recently, fixed-dose combinations of a long-acting beta-agonist (LABA) and an inhaled long-acting anti-muscarinic (LAMA) drug have been proposed as the initial choice in preventing COPD exacerbations.[2] However, the evidence supporting this approach remains limited. The LAMA tiotropium has proven to be more effective than LABA monotherapy,[3,4] and was equivalent to a LABA–ICS combination in preventing exacerbations.[5] Although exacerbations were less frequent with LAMA–LABA than LABA–ICS treatment,[6] it remains unclear how well LAMA–LABAs perform against tiotropium alone. A combination of indacaterol and glycopyrronium was more effective than glycopyrronium in exacerbation prevention, but was not statistically significantly better than open-label tiotropium, although the study was not powered for the comparison with tiotropium.[7] To date, no study has investigated whether adding a LABA to tiotropium in a fixed-dose combination offers additional benefits over tiotropium in exacerbation prevention. Given that tiotropium alone is effective at reducing risk of exacerbation,[8] this question is of considerable clinical significance.

Combining the LABA olodaterol with tiotropium in a soft mist inhaler has produced statistically significantly greater improvements in lung function and health status than either drug alone over 52 weeks.[9] To determine

Research in context

Evidence before this study

We searched PubMed up to Jan 16, 2018, for published articles in English addressing the question of long-acting anti-muscarinic (LAMA)–long-acting beta-agonist (LABA) versus LAMA for exacerbations in patients with chronic obstructive pulmonary disease (COPD), using the search terms "COPD", "chronic obstructive pulmonary disease", "exacerbation", "bronchodilator", "LAMA", and "LABA". Previous studies have shown that tiotropium reduces the risk of exacerbation compared with placebo. Although there were several COPD exacerbation trials investigating combinations of bronchodilators, including the SPARK trial (which compared another LAMA–LABA combination with a LAMA and open-label tiotropium), there was no study comparing a combination of a LABA and tiotropium with tiotropium alone that was powered to detect a difference in exacerbations between treatments.

Added value of this study

It has previously been shown that adding olodaterol to tiotropium offers improvements in lung function, symptoms, and quality of life compared with tiotropium alone, without additional safety or tolerability concerns. This large trial is the first of its kind to address the question of whether adding a LABA to tiotropium can offer further benefits in terms of reducing exacerbations in patients with COPD. The findings showed that the reduction in exacerbation rate was smaller than anticipated and did not reach the planned level of significance. However, there were larger improvements in some subgroups of patients, such as those receiving triple therapy at baseline, and in exacerbations that required oral corticosteroids.

Implications of all of the available evidence

Tiotropium–olodaterol offers benefits for patients with COPD beyond those provided by tiotropium alone, which extend to a small reduction in the risk of exacerbations requiring treatment with corticosteroids. This reduction might be larger in certain subgroups of patients.

whether tiotropium–olodaterol reduces the annual rate of exacerbations more than tiotropium alone, we did a double-blind, randomised, parallel-group, active-controlled, 52-week study (designated the DYNAGITO trial).

Methods

Study design and participants

This study was a 52-week, randomised, double-blind, active-controlled, parallel-group trial. Patients with COPD were randomly assigned (1:1) to receive either tiotropium–olodaterol 5 μg–5 μg or tiotropium 5 μg, both delivered once daily (in the morning) via two puffs of the Respimat device (Boehringer Ingelheim, Ingelheim am Rhein, Germany). Patients taking ICS at baseline continued this treatment; those receiving ICS in a fixed-dose combination with a LABA were switched to an equivalent corticosteroid monotherapy. Open-label salbutamol was provided for as-needed rescue medication use, but other short-acting beta-agonists, LAMAs, and LABAs (other than the study medication) were not permitted during the study.

We recruited patients aged 40 years or older with a diagnosis of COPD, a smoking history of more than 10 pack-years, stable airflow obstruction with post-bronchodilator FEV_1 less than 60% predicted, a post-bronchodilator FEV_1/forced vital capacity (FVC) less than 0·7, and a history of at least one moderate or severe exacerbation in the preceding year requiring treatment with systemic corticosteroids or antibiotics or both, with or without hospitalisation.

See Online for appendix

Exclusion criteria are listed in the appendix (pp 2, 3), and included a current diagnosis of asthma, severe emphysema requiring endobronchial interventions in the previous 6 months, treatment with antibiotics for any reason within 4 weeks of screening, or phosphodiesterase-4 inhibitor use within 3 months of screening.

Patients gave their written informed consent. The protocol was approved by the ethical review boards of participating centres.

Randomisation and masking

An interactive response technology system was used for randomisation and allocation of trial medication. The randomisation scheme used a randomised block design (block size 4) and was generated using validated randomisation software by Boehringer Ingelheim, which also prepared and coded the medications to maintain the double-blind. As both treatments (tiotropium and tiotropium–olodaterol) were delivered via identical Respimat devices, treatment was masked to patients, investigators, and everyone involved in analysing the trial data. No dummy devices were required.

Procedures

At screening, qualifying lung function could be based on historical data within the last 3 months; if there were no historical spirometry measurements available, a standard spirometry test was performed. After randomisation, patients attended the clinic every 3 months, with interim telephone contact scheduled every 6 weeks.

The COPD Assessment Test (CAT)[10] was completed before any other clinical assessments at baseline, and after 3, 6, 9, and 12 months' treatment.

Patients were provided with a reminder card at clinic visits to note changes in symptoms, missed doses of

medication, or use of health-care resources between visits to assist the description of the event at clinic or telephone appointments.

Outcomes

The primary endpoint was the rate of moderate and severe COPD exacerbations from the first dose of medication until 1 day after last drug administration (see appendix p 1 for details of treatment periods). The main secondary endpoint was time to first moderate or severe COPD exacerbation during the treatment period; other secondary endpoints were rate of exacerbations leading to hospitalisation, time to first exacerbation leading to hospitalisation, and time to all-cause mortality. Other endpoints included the rate of COPD exacerbations treated with corticosteroids, rate of exacerbations treated with antibiotics, and rate of exacerbations treated with corticosteroids and antibiotics.

COPD exacerbations were defined as an increase or new onset of at least two of the following symptoms: shortness of breath, sputum production, change in sputum colour, cough, wheezing, or chest tightness, for a duration of at least 3 days. Exacerbations requiring treatment with oral corticosteroids or antibiotics or both were categorised as moderate, and those additionally requiring hospitalisation or an emergency room visit as severe. COPD exacerbation information was collected during the treatment period for up to 360 plus 1 days for all patients. A CAT responder (based on mean of post-baseline assessments) was defined as an improvement (decrease) of at least 2 units compared with baseline.

All adverse events were collected during the on-treatment period, defined as up to 21 days after the last dose (appendix p 1). A clinical endpoint committee adjudicated the cause of any deaths. As tiotropium–olodaterol is licensed for use in COPD in many countries, a data and safety monitoring board was not needed.

Statistical analysis

A sample size of 3900 patients per group was to provide sufficient power to detect a 12% reduction in rate of exacerbations with tiotropium–olodaterol compared with tiotropium. A 12% reduction was chosen based on the results of a previous study.[7] The dispersion parameter for the negative binomial model was assumed to be between 0·8 and 0·9, with an annual rate of exacerbations in the tiotropium group about 0·85 and a two-sided type I error rate of 0·01. This sample size allowed for 15% loss of data due to patient withdrawals.

Data are expressed as mean and 95% CI, unless otherwise stated. We anticipated that our primary outcome (the mean annual exacerbation rate between treatments) would differ at the 1% significance level, and that other differences would be at the 5% level. A 1% significance level was chosen for regulatory purposes (appendix p 1). For the primary and main secondary endpoint, we report the prespecified rate ratio (RR) and 99% CI, whereas for other outcomes we present the 95% CI. If the primary endpoint was not met, all secondary analyses were to be considered exploratory.

The primary analysis was done on the treated set (all randomly assigned patients who received any dose of study medication and were not from a site excluded due to on-site protocol violations). The primary endpoint was analysed using a negative binomial model including the fixed, categorical effect of treatment, as well as the logarithm of the treatment exposure as an offset. The length of the event was subtracted from the extent of exposure or the length of the observation period, as it is not possible to have another event during an index event. This model was used for all annualised event endpoints.

For the main secondary endpoint (time to first exacerbation) a Cox's proportional hazard model was used to estimate the hazard ratio (HR) and the corresponding 99% CI. A log-rank test was used to obtain the p value for testing the survival curves.

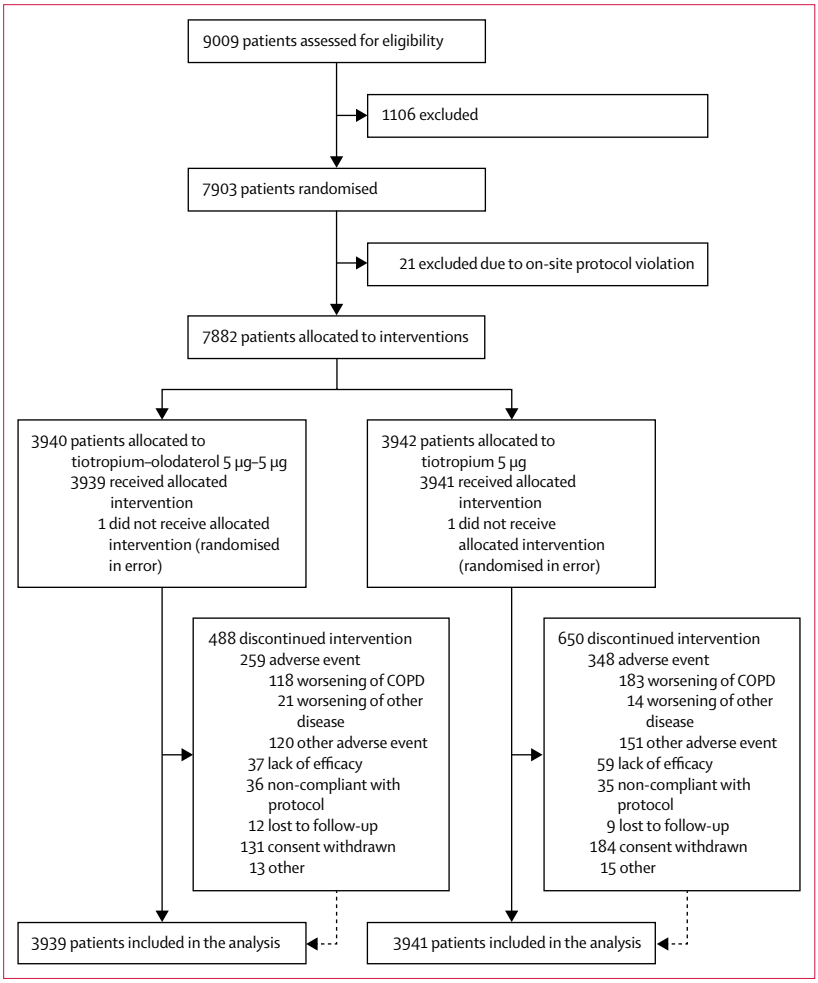

Figure 1: **Trial profile**
Reasons for ineligibility are shown in the appendix (p 4). Number of discontinuations due to adverse events is based on reported reasons for discontinuation. Patients analysed were all randomised patients who received any dose of study medication excluding those due to on-site protocol violation. COPD=chronic obstructive pulmonary disease.

	Tiotropium–olodaterol group (n=3939)	Tiotropium group (n=3941)
Sex		
Male	2785 (71%)	2841 (72%)
Female	1154 (29%)	1100 (28%)
Race		
American Indian–Alaska Native	77 (2%)	64 (2%)
Asian	557 (14%)	607 (15%)
Black–African American	58 (2%)	52 (1%)
Native Hawaiian–Pacific Islander	3 (<1%)	5 (<1%)
White	3134 (80%)	3113 (79%)
Multiple	22 (1%)	20 (1%)
Missing*	88 (2%)	80 (2%)
Age (years)	66·5 (8·4)	66·3 (8·5)
Smoking status		
Current smoker	1434 (36%)	1478 (38%)
Ex-smoker	2505 (64%)	2462 (62%)
Never smoked†	0	1 (<1%)
Smoking history (pack-years)	44·8 (24·4)	44·7 (25·2)
SGRQ (total score)	48·1 (17·7)	47·4 (17·7)
Post-bronchodilator FEV_1‡		
Mean (L)	1·177 (0·385)	1·197 (0·377)
% predicted	44·6 (37·5)	44·5 (11·5)
FEV_1/FVC ratio (%)	46·5 (11·0)	46·7 (11·0)
FVC (L)	2·586 (0·794)	2·622 (0·799)
GOLD class (2017)		
A	260 (7%)	308 (8%)
B	1922 (49%)	1895 (48%)
C	176 (4%)	176 (4%)
D	1569 (40%)	1547 (39%)
Missing	12 (<1%)	15 (<1%)
Patients with ≥2 exacerbations, or ≥1 severe exacerbations in the previous year	1754 (45%)	1733 (44%)
Respiratory medication		
LABA only	122 (3%)	135 (3%)
LAMA only	365 (9%)	350 (9%)
ICS only	107 (3%)	93 (2%)
LABA–ICS	1031 (26%)	1005 (26%)
LAMA–ICS	78 (2%)	88 (2%)
LAMA–LABA	461 (12%)	478 (12%)
LAMA–LABA–ICS	1555 (39%)	1577 (40%)
Neither	220 (6%)	215 (5%)

Data are mean (SD) or n (%). FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease. ICS=inhaled corticosteroid. LABA=long-acting beta-agonist. LAMA=long-acting muscarinic antagonist. SGRQ=St George's Respiratory Questionnaire. *Patients in France had missing race classification, since these data are not collected there. †Patient violated the inclusion criteria of the study. ‡Based on historical data within 3 months of screening.

Table 1: **Patient demographics and baseline characteristics**

Details of subgroups analysed are provided in the appendix (p 1). SAS version 9.4 was used for all analyses. The trial is registered with ClinicalTrials.gov, number NCT02296138.

Role of the funding source

The funder of the study was responsible for the design and analysis of the study, oversaw its conduct, and contributed to study report preparation. The study was overseen by a steering committee comprising five academics and representatives of the sponsor, including the trial statistician. Analyses were done by the sponsor's biostatistics and data sciences department, led by the trial statistician. The manuscript was drafted and revised by the academic authors (PMAC, ARA, CJ, JW, and KFR). Medical writing support for manuscript preparation was paid for by the study sponsor. All authors had access to the data and were responsible for the final decision to submit.

Results

Patients were recruited from Jan 22, 2015, to March 7, 2016, and the study completed on March 30, 2017. In total, 9009 patients were screened from 818 centres in 51 countries. Of these, 7903 were randomly assigned to treatment and 7880 were treated (figure 1). Mean post-bronchodilator FEV_1 at baseline was 1·187 (SD 0·381) L (44·5% predicted). 3132 (40%) patients were receiving LAMA–LABA–ICS, 2036 (26%) were receiving LABA–ICS, and 939 (12%) were receiving LAMA–LABA (table 1). Patients were more likely to complete the study with tiotropium–olodaterol (3451 [88%] of 3939 patients) than tiotropium alone (3291 [84%] of 3941; discontinuation HR 0·73, 95% CI 0·65–0·82; appendix p 9).

The RR for the rate of moderate and severe exacerbations was 0·93 (99% CI 0·85–1·02) with tiotropium–olodaterol compared with tiotropium during the 52-week treatment period (table 2). The targeted significance level of 0·01 (ie, necessitating a p<0·01) was not met, with a p value of 0·0498.

The HR for time to first moderate or severe COPD exacerbation was 0·95 (99% CI 0·87–1·03; p=0·12) with tiotropium–olodaterol versus tiotropium during the 52-week treatment period (figure 2A); the HR for time to first COPD exacerbation leading to hospitalisation was 0·93 (95% CI 0·82–1·06; p=0·28). For severe exacerbations, the RR for tiotropium–olodaterol compared with tiotropium was 0·89 (95% CI 0·78–1·02; p=0·090), and for exacerbations leading to hospitalisation the RR was 0·89 (0·76–1·03; p=0·13; table 2).

Of 5912 moderate and severe exacerbations, 974 (16%) were treated with only corticosteroids, 1734 (29%) were treated with antibiotics only, and 3193 (54%) were treated with corticosteroids and antibiotics together. Tiotropium–olodaterol reduced the rate of exacerbations treated with corticosteroids alone compared with tiotropium (RR 0·80, 95% CI 0·68–0·94), and reduced the rate of exacerbations treated with corticosteroids and antibiotics (RR 0·91, 0·83–1·00; table 2). In a post-hoc analysis, the rate of exacerbations treated with corticosteroids with or without antibiotics was also lower with tiotropium–olodaterol compared with tiotropium

	Adjusted rate of events per patient-year (95% CI)		Rate ratio	95% CI	p value
	Tiotropium–olodaterol group	Tiotropium group			
Primary endpoint					
Moderate and severe exacerbations	0·90 (0·84–0·96)*	0·97 (0·90–1·03)*	0·93	0·85–1·02* (0·87–1·00)†	0·0498
Other prespecified endpoints					
Moderate and severe exacerbations					
Treated with antibiotics only	0·27 (0·25–0·29)	0·25 (0·23–0·27)	1·07	0·96–1·20	0·21
Treated with corticosteroids only	0·14 (0·12–0·15)	0·17 (0·15–0·19)	0·80	0·68–0·94	0·0068
Treated with antibiotics and corticosteroids in combination	0·48 (0·45–0·52)	0·53 (0·50–0·57)	0·91	0·83–1·00	0·045
Severe exacerbations	0·24 (0·22–0·27)	0·27 (0·25–0·30)	0·89	0·78–1·02	0·090
Exacerbations leading to hospitalisation	0·18 (0·16–0·20)	0·20 (0·18–0·22)	0·89	0·76–1·03	0·13

*99% CI, prespecified level of significance. †95% CI.

Table 2: **Annualised rate of exacerbations**

(0·63 *vs* 0·72; RR 0·87, 95% CI 0·78–0·98). There was no difference in exacerbation rate between tiotropium–olodaterol and tiotropium for exacerbations treated with antibiotics only (RR 1·07, 95% CI 0·96–1·20; table 2).

The rate of moderate and severe exacerbations according to baseline therapy is shown in the appendix (p 10). Tiotropium–olodaterol was more effective than tiotropium in patients using triple therapy (LAMA–LABA–ICS) at baseline, and these patients showed the highest exacerbation rates; adjusted incidence rate was 1·11 with tiotropium–olodaterol and 1·31 with tiotropium (RR 0·85, 95% CI 0·77–0·94). In a post-hoc analysis of the subgroup of patients receiving any ICS at baseline, the RR for exacerbations was 0·91 (95% CI 0·84–0·99), whereas there was no difference between tiotropium–olodaterol and tiotropium in the group not receiving any corticosteroid at baseline (RR 1·00, 95% CI 0·86–1·15).

There was an apparently greater effect of tiotropium–olodaterol compared with tiotropium alone in women (n=2254; incidence rate 0·98 *vs* 1·14; RR 0·87, 95% CI 0·76–0·98) than in men (n=5626; incidence rate 0·87 *vs* 0·90; RR 0·96, 95% CI 0·88–1·04). There were no differences according to race, smoking history, or GOLD stage (I–IV) at baseline (appendix p 10).

Tiotropium–olodaterol improved mean CAT score change from baseline compared with tiotropium by –0·4 (SE 0·15) to –0·7 (0·13) units over the 52-week trial period (figure 2B). A responder analysis based on the mean of post-baseline CAT assessments showed that patients were more likely to respond with tiotropium–olodaterol than tiotropium (odds ratio 1·17, 95% CI 1·06–1·28).

Overall, there was no imbalance between groups in the number of patients with an adverse event, and fewer patients reported a serious adverse event with tiotropium–olodaterol (810 [21%] of 3939 patients) compared with tiotropium (862 [22%] of 3941 patients; table 3). Fewer patients reported adverse events leading to study discontinuation in the tiotropium–olodaterol group (219 [6%] of 3939 patients) than in the tiotropium group (302 [8%] of 3941 patients). There was no difference in the number of major adverse cardiac events between treatments (table 3).

At the end of the planned study period (360 plus 21 days after first dose), data on vital status were available from 99·6% of patients. Fewer deaths occurred with tiotropium–olodaterol (107 [3%] of 3939 patients) versus tiotropium (121 [3%] of 3941 patients) during the 360 plus 21 days from the first dose of study drug, and time to all-cause mortality was similar with tiotropium–olodaterol compared with tiotropium (HR 0·88, 95% CI 0·68–1·15). Adjudicated causes of adverse events leading to death are shown in the appendix (p 5). There were 36 (1%) respiratory deaths in the tiotropium–olodaterol group and 52 (1%) in the tiotropium group.

Discussion

In this adequately powered study, there was no significant reduction in the moderate and severe exacerbation rate in patients taking tiotropium–olodaterol compared with tiotropium alone. There was a small difference between treatment groups that met the conventional 5% significance level, but this was below the 1% significance level we targeted. There was no difference in the time to first moderate or severe event between the groups, but patients using ICS during the trial experienced potentially relevant benefits from dual bronchodilator treatment, and exacerbations treated with systemic corticosteroids with or without antibiotics were seen less often with tiotropium–olodaterol treatment. All medications were well tolerated, with an acceptable adverse event profile.

A high significance level was selected to meet regulatory requirements, as pharmaceutical regulators require stronger proof of an effect if the results of a single trial are to be included in a product label. The problems of interpreting marginal p values have been

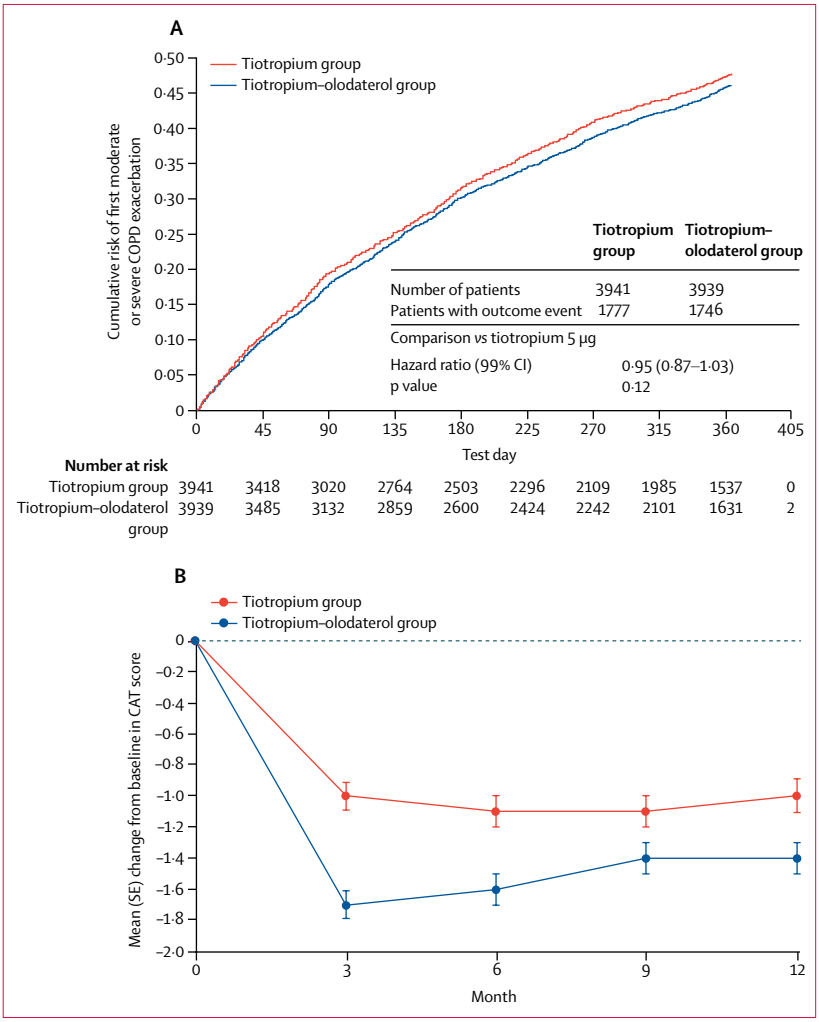

Figure 2: **Treatment effect of tiotropium–olodaterol versus tiotropium**
(A) Time to first moderate or severe exacerbation. (B) Adjusted mean CAT score change from baseline over time. Mean baseline CAT score was 18·8 (SD 7·4) in the tiotropium–olodaterol group and 18·4 (7·4) in the tiotropium group. CAT=COPD Assessment Test. COPD=chronic obstructive pulmonary disease.

	Tiotropium–olodaterol group (n=3939)	Tiotropium group (n=3941)
Adverse events	2920 (74%)	2937 (75%)
Severe adverse events	729 (19%)	810 (21%)
Adverse events leading to discontinuation	219 (6%)	302 (8%)
Serious adverse events	810 (21%)	862 (22%)
Fatal adverse events (onset during on-treatment period)	92 (2%)	98 (2%)
All-cause mortality during 52 weeks plus follow-up period	107 (3%)	121 (3%)
MACE	78 (2%)	85 (2%)
Fatal MACE	33 (1%)	27 (1%)
Fatal MACE including "death unknown"	36 (1%)	41 (1%)
Cardiac arrhythmia	66 (2%)	61 (2%)
Supraventricular tachycardia	11 (<1%)	5 (<1%)
Atrial fibrillation	35 (1%)	26 (1%)
Atrial fibrillation (serious)	18 (<1%)	12 (<1%)
Pneumonia	189 (5%)	199 (5%)

MACE=major adverse cardiac event.

Table 3: **Patients reporting adverse events and serious adverse events (treated patients)**

reviewed elsewhere,[11] although none of the examples considered addressed the failure to achieve as high a level of significance as applies here. Our data about time to first exacerbation are less problematic as there was no difference between treatment groups. A discrepancy between changes in exacerbation rates and time to first exacerbation has been seen with other drugs that prevent exacerbations.[12–14]

As the difference in exacerbation rate between treatment groups was not significant and less than the 12% reduction anticipated when designing the study, we examined reasons why this might have occurred. It seems unlikely that olodaterol was ineffective, as the tiotropium–olodaterol combination produces similar changes in lung function and health status to other LAMA–LABA combinations.[15] The fall in the CAT score is in line with improvements in the St George's Respiratory Questionnaire scores in earlier studies,[9,16] suggesting that LAMA–LABA treatment was more effective than LAMA alone at improving health status.

The assumptions made when designing the study might have impacted the significance of the primary endpoint. We observed that the variance in our population was higher than expected, resulting in a greater dispersion parameter of the negative binomial model (see the appendix p 1 for details). As in most large COPD studies, there was differential study withdrawal between treatments, a factor known to bias the interpretation of randomised trials.[17] The absolute difference (12% discontinued with combination therapy and 16% with tiotropium; HR 0·73, 95% CI 0·65–0·82) was similar to that seen in other studies, including the TORCH trial (at 1 year approximately 15% with combination therapy, 19% with monotherapies, and 25% with placebo)[18] and the UPLIFT study (at 1 year approximately 15% with tiotropium and 20% with placebo; HR at 4 years 0·89, 95% CI 0·85–0·94).[8] We examined whether this difference might account for the wide dispersion of our data, and identified several differences between those who withdrew from the study and those who completed it, including baseline therapies, exacerbation history, and baseline FEV_1 (appendix pp 6, 7). These factors closely resemble those included a priori in the analysis of recent trials investigating differences in exacerbation rates between different treatments.[7,12,14,19] When we applied similar models to our data (ie, implementing covariates in the analysis), we saw again that the difference between exacerbation rates was significant at the expected 1% level (appendix p 8). Our results indicate that the pattern of patient withdrawal and the method of

analysis can have an important effect on the obtained p value and effect size of treatment.

Clinical considerations might also be relevant. Specific subgroups of patients might have been more responsive to combination treatment, especially those patients already using ICS. Patients treated with corticosteroids report more exacerbations[20] and might benefit from additional therapy. There was a higher exacerbation rate among women, a finding consistent with data observed in other COPD trials,[21] although the reasons are not well understood. Alternatively, there might be a ceiling effect in the ability of bronchodilator drugs to reduce exacerbations. Studies with other endpoints such as lung function and health status indicate that combining LABAs and LAMAs produces less improvement than expected from the comparison of the individual components with placebo.[22]

Whatever the explanation for our primary findings, the failure to reach our expected significance level creates problems in interpreting the statistical significance of other study analyses, which could be considered either exploratory or possibly indicative of a true difference between treatments. We prespecified the treatment comparisons between exacerbations managed in different ways by the investigators, who were masked to the maintenance treatment. There was no difference in the number of events treated with antibiotics alone in either study group, a finding also reported in the online supplement of the glycopyrronium–indacaterol exacerbation trial.[7] These events were included in the definition of exacerbations consistent with most guideline recommendations and other COPD clinical trials.[6,7] By contrast, regular tiotropium–olodaterol treatment was associated with a lower rate of events treated with systemic corticosteroids with or without antibiotics than seen in patients receiving tiotropium alone. Systemic corticosteroid-treated events might represent more severe events than those managed by antibiotics alone, as they are associated with worse outcomes.[23] Several other treatments, including ICS and roflumilast, act mainly by decreasing the number of exacerbations treated with oral corticosteroids.[12,18,24,25] Our data suggest that an anti-inflammatory action need not be the only explanation for this finding, and that a general reduction in the severity of the exacerbations might occur with more effective treatment. It is likely that improved resting lung mechanics with the LAMA–LABA treatment mean that the patient must deteriorate further before registering that a more severe event is occurring.[26]

There were no new safety concerns identified in this study, which had relatively open study recruitment criteria compared with earlier studies of tiotropium and olodaterol.[27] The adjudicated mortality of around 3% per year, in this population with FEV_1 45% predicted at baseline, was in line with that in similar study populations treated with inhaled bronchodilators.[18,28]

Our study has strengths and limitations. Among the former are its size, the focus on exacerbations defined by health-care use, and the lack of a lower limit of lung function when enrolling patients. Our population was representative of those where LAMA–LABA treatment has been recommended for exacerbation prevention,[29] and the lack of a run-in period meant that we did not select individuals who could manage without inhaled bronchodilator therapy. Finally, the observed exacerbation rate was close to that anticipated when powering the trial, which means the study was adequately powered. However, as noted above, the variability observed in our study was higher than anticipated, and we did not identify milder events or those not meeting the criteria for a health-care-treated event. The smaller SPARK study was able to identify a signal using that methodology, which might have encouraged earlier exacerbation reporting, although the covariate analysis for the primary endpoint might have been equally important.[7]

Many of the study participants were using ICS, reflecting the use of these drugs in patients more likely to exacerbate.[30] The differences we saw between bronchodilator treatments in patients using ICS might reflect the higher exacerbation rate in these patients rather than a direct interaction of ICS and the treatments under study. One potential weakness of the study is that 40% of patients were already receiving LAMA–LABA–ICS at baseline, so were in effect randomised to either continue triple therapy, or to have LABA removed and receive LAMA–ICS. However, due to the design of the study, it is not appropriate to compare those receiving ICS and those not receiving ICS at baseline as patients were not randomised to receive or not receive ICS.

In conclusion, this is the first trial to directly determine whether adding a LABA to tiotropium reduces the exacerbation rate compared with tiotropium alone. The incremental benefit on prevention of exacerbations by adding a LABA to tiotropium is small, but potentially relevant improvements can be observed on exacerbations treated with systemic corticosteroids. These results with tiotropium–olodaterol are consistent with those seen with glycopyrronium–indacaterol in the SPARK study,[7] and indicate that the LAMA–LABA treatments studied produce a 7–12% reduction in the risk of exacerbating compared with LAMA monotherapy. Our data do not negate the symptomatic benefits associated with these bronchodilator drugs, but emphasise the need to identify those patients where additional bronchodilator therapy might reduce exacerbations.

Contributors

The manuscript was drafted and revised by the academic authors (PMAC, ARA, CJ, JW, and KFR). All authors had access to the data and were responsible for the final decision to submit.

Declaration of interests

PMAC chaired the steering committee of the DYNAGITO study, has received grants and personal fees from GlaxoSmithKline and Takeda, personal fees from AstraZeneca and Novartis, and personal fees and non-financial support from Boehringer Ingelheim, outside of the submitted work. ARA has received personal fees from GlaxoSmithKline,

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