International Journal of COPD

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ORIGINAL RESEARCH

Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis

This article was published in the following Dove Press journal:
International Journal of COPD
16 November 2015
Number of times this article has been viewed

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Background: Randomized, controlled trials comparing long-acting muscarinic antagonist (LAMA) efficacy in COPD are limited. This network meta-analysis (NMA) assessed the relative efficacy of tiotropium 18 µg once-daily (OD) and newer agents (aclidinium 400 µg twice-daily, glycopyrronium 50 µg OD, and umeclidinium 62.5 µg OD).

Methods: A systematic literature review identified randomized, controlled trials of adult COPD patients receiving LAMAs. A NMA within a Bayesian framework examined change from baseline in trough forced expiratory volume in 1 second (FEV_1), transitional dyspnea index focal score, St George's Respiratory Questionnaire score, and rescue medication use.

Results: Twenty-four studies (n=21,311) compared LAMAs with placebo/each other. Aclidinium, glycopyrronium, tiotropium, and umeclidinium, respectively, demonstrated favorable results versus placebo, for change from baseline (95% credible interval) in 12-week trough FEV_1 (primary endpoint: 101.40 mL [77.06–125.60]; 117.20 mL [104.50–129.90]; 114.10 mL [103.10–125.20]; 136.70 mL [104.20–169.20]); 24-week trough FEV_1 (128.10 mL [84.10–172.00]; 135.80 mL [123.10–148.30]; 106.40 mL [95.45–117.30]; 115.00 mL [74.51–155.30]); 24-week St George's Respiratory Questionnaire score (−4.60 [−6.76 to −2.54]; −3.14 [−3.83 to −2.45]; −2.43 [−2.92 to −1.93]; −4.69 [−7.05 to −2.31]); 24-week transitional dyspnea index score (1.00 [0.41–1.59]; 1.01 [0.79–1.22]; 0.82 [0.62–1.02]; 1.00 [0.49–1.51]); and 24-week rescue medication use (data not available; −0.41 puffs/day [−0.62 to −0.20]; −0.52 puffs/day [−0.74 to −0.30]; −0.30 puffs/day [−0.81 to 0.21]). For 12-week trough FEV_1, differences in change from baseline (95% credible interval) were −12.8 mL (−39.39 to 13.93), aclidinium versus tiotropium; 3.08 mL (−7.58 to 13.69), glycopyrronium versus tiotropium; 22.58 mL (−11.58 to 56.97), umeclidinium versus tiotropium; 15.90 mL (−11.60 to 43.15), glycopyrronium versus aclidinium; 35.40 mL (−5.06 to 76.07), umeclidinium versus aclidinium; and 19.50 mL (−15.30 to 54.38), umeclidinium versus glycopyrronium. Limitations included inhaler-related factors and safety; longer-term outcomes were not considered.

Conclusion: The new LAMAs studied had at least comparable efficacy to tiotropium, the established class standard. Choice should depend on physician's and patient's preference.

Keywords: anticholinergics, muscarinic antagonist, bronchodilator, systematic review, meta-analysis

Introduction

The overarching goals for the management of COPD include prevention of further disease progression, symptom relief, reduction in exacerbations, treatment of complications (eg, infections), and the maintenance or improvement of overall health status.[1] Treatment options for COPD depend on symptom burden and exacerbation risk, but bronchodilators are a cornerstone of therapy. Long-acting muscarinic antagonists

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(LAMAs) are recommended for patients in Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups A to D.[1] LAMAs are associated with improved lung function, improved quality of life, and reduced exacerbations.[2,3]

Until 2012, tiotropium bromide was the only LAMA widely available for the treatment of COPD.[3–5] Tiotropium is a once-daily (OD) treatment, and has been widely prescribed for COPD. However, several new LAMAs have since been introduced, including aclidinium bromide (twice-daily [BD] for COPD maintenance) and glycopyrronium bromide (OD for COPD maintenance), which could be used as alternatives to tiotropium.[6–9] Umeclidinium bromide has been the most recent addition; this is a OD inhaled LAMA approved for COPD maintenance therapy in adults in the EU, USA, and several other countries. Compared with placebo, umeclidinium OD (metered dose 62.5 μg, delivered dose 55 μg) significantly improved lung function, dyspnea, and health status over 12 weeks in a randomized study of 246 patients.[9] With this new addition to the LAMA class, there is a need to understand the relative comparative efficacy of the available agents.

Primary comparative efficacy data from randomized controlled trials for newer LAMAs are limited. With the introduction of new agents, such as umeclidinium, it is often not feasible to conduct clinical trials to compare the new treatment against all alternative agents in clinical trials to determine relative efficacy. Accordingly, there are no published direct head-to-head comparisons on the clinical efficacy between all LAMAs. Therefore, alternative methodologies need to be employed to better inform health care practitioners of the anticipated relative efficacy for important clinical endpoints. A number of network meta-analyses (NMAs) have been published in recent years, comparing LAMAs (tiotropium and glycopyrronium) with other COPD therapies,[10] and aclidinium versus glycopyrronium and tiotropium.[11] However, since the introduction of a new treatment option (umeclidinium), further analyses are needed. A systematic literature review and Bayesian NMA was undertaken to assess the relative efficacy of aclidinium, glycopyrronium, tiotropium, and umeclidinium for the treatment of COPD.

Methods

Study objectives

The primary objective of this study (GSK study number: 201280)[12] was to assess the relative efficacy of all LAMAs available in the market at the licensed doses, namely: aclidinium 400 μg BD (hereafter referred to as aclidinium), glycopyrronium 50 μg OD (glycopyrronium), tiotropium 18 μg OD (tiotropium), and umeclidinium 62.5 μg OD (umeclidinium), by means of lung function (difference in change from baseline for trough forced expiratory volume in 1 second [FEV_1]) at 12 weeks. The doses of each of the four LAMAs chosen for this NMA were the only approved doses for the dry powder inhaler formulations. Other formulations such as tiotropium 5 μg OD via a soft mist device, which is considered as equivalent to 18 μg via the Handihaler, or alternative BD glycopyrronium/glycopyrrolate investigational formulations have not been included. Secondary objectives were to assess the relative efficacy of the LAMA for the following endpoints: 1) difference in change from baseline for trough FEV_1 (at 24 weeks); 2) difference in change from baseline in St George's Respiratory Questionnaire (SGRQ) total score (at 12 and 24 weeks); 3) differences in the transitional dyspnea index (TDI) focal score (at 12 and 24 weeks); and 4) differences in change in rescue medication use (mean number of puffs per day) (at 12 and 24 weeks). The 12- and 24-week time points used in our study were chosen to reflect the expected data availability; these are commonly used time intervals in COPD trials.

Data sources

A systematic review including a broad range of search terms following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was performed.[13] The following databases were searched: MEDLINE (through Ovid platform); MEDLINE In-Process (Ovid); EMBASE (Ovid); The Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE); and Health Technology Assessment (HTA) websites, HTA database and National Institute for Health Research (NIHR). The following clinical trial registries were searched: Clinicaltrials.gov; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); Current Controlled Trials; EU Clinical Trials Register (EU-CTR); Klinische Prüfungen PharmNet.Bund; and The International Prospective Register of Systematic Reviews (PROSPERO). The searches were performed on April 14, 2014–April 16, 2014, for studies in English and German language without time restrictions. Predefined search strategies were used (available in Table S1), tailored for each database.

Inclusion criteria and study selection process for systematic literature review

The relevance of each identified citation was assessed based on the title and abstract according to predefined selection criteria (Table S2). For the abstracts that met the selection

criteria, available publications were obtained and evaluated using the full-text selection criteria. Studies (randomized, controlled trials) had to include adults with COPD reporting on at least one of: umeclidinium; aclidinium; tiotropium; glycopyrronium compared with each other or placebo. The outcomes examined were trough FEV_1, TDI focal score, SGRQ score, and rescue medication. The time points of interest for all outcomes were 12 and 24 weeks, while outcomes between 8 and 16 weeks or 20 and 28 weeks were reported as proxy outcomes for 12 and 24 weeks, respectively. The selection was performed by two researchers independently and any discrepancies were resolved by consensus. The final selected citations were grouped per study.

Data abstraction and quality assessment

Key data from each eligible study were extracted, including study design (treatments, duration, inclusion/exclusion criteria, and background treatment) and patient characteristics (eg, age, sex, and lung function parameters; Table S3) into a data extraction form. Data extraction was performed by one researcher and verified by another researcher. Data of interest presented in graphs were extracted using DigitizeIT version 1.5 software (DigitizeIT, Braunschweig, Germany). The methodological and reporting quality of the included trials was assessed with a checklist based on the guidance by the Institute for Quality and Efficiency in Health Care.[14] The risk of bias in each study was classified as "high" or "low" based on the following items: appropriate generation of a randomization sequence; adequate allocation concealment; blinding of patients, treating staff, and staff responsible for follow-up treatment; reporting of all relevant outcomes independent of results; no other aspects that could lead to bias. The results of the risk of bias assessment are presented in Table S4.

Data synthesis

The existence of a connected network of studies per outcome, as well as the study design and patient characteristics of the identified studies, was used to assess the feasibility of a valid NMA.[15] The identified evidence was used to perform a NMA within a Bayesian framework to simultaneously synthesize the results of the included studies and to obtain relative treatment effects.[16,17] A generalized linear model with normal likelihood distribution was used.[18] Non-informative prior distributions of the relative treatment effects (normal distributions with zero mean and a variance of 10,000) were used as a widely accepted option for all outcomes of interest. The analysis was based on the difference between the least square mean at follow-up or the difference in change from baseline for the active treatment versus the comparator as well as the associated standard error (SE) of the difference. To assess the consistency of the network, the node splitting method was followed by separating and comparing direct and indirect evidence per outcome for each one of these three pairwise comparisons.[19]

For each outcome, a fixed- and a random-effects model was evaluated. The fixed-effects model assumed that the differences in true relative treatment effects across studies in the network of evidence were only due to differences in treatment comparisons (ie, that there was no variation in relative treatment effects for a particular pairwise comparison). The random-effects model assumed that differences in observed treatment effects across the studies in the network were not only caused by the different treatment comparisons, but that there was also heterogeneity in the relative effects for a particular type of comparison caused by factors that modify the relative treatment effect. With the NMA models used, the heterogeneity was assumed to be constant for every treatment comparison. Due to the relatively low number of studies, treatment-by-covariate interactions could not be incorporated into the models; instead, scenario analyses were developed to test the impact of certain studies on the relative treatment estimates.

The goodness of fit of each model to the data was assessed using the Deviance Information Criterion.[20] The posterior densities for the outcomes of interest were estimated using the Markov Chain Monte Carlo simulations for each model. The results were based on 80,000 iterations on three chains, with a burn-in of 20,000 iterations. Convergence assessment was based on visual inspection of trace plots. Accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter (Monte Carlo error $<5\%$ of the posterior standard deviation [SD]). Given the dataset used, the fixed-effects model was chosen over the random-effects model unless there was enough evidence to suggest that the random-effects model was substantially different (ie, Deviance Information Criterion value was lower and Monte Carlo error was not out of proportion). WinBUGS 1.4.3 statistical software was used for the analyses[21] and the models were based on those defined by Dias et al (programs 7(b) and 8(a) in the Appendix of Dias et al).[18]

The NMA provided posterior distributions of the relative treatment effects between interventions for each outcome of interest. The posterior distributions were summarized with the median to reflect the most likely value of the estimate, and the 2.5th and 97.5th percentile to capture the 95% credible interval (CrI).[18] The 95% CrI represents the range of true underlying effects with 95% probability. For each endpoint,

the probability that each treatment was better than a certain comparator was established.

If a study only reported mean differences without a measure of uncertainty (SE, SD, or confidence interval [CI]), the following steps were executed to impute SE values: 1) SD of the difference for each study reporting sufficient data were calculated by the formula SD of difference = SE of difference × square root of N; 2) the average SD of the trials in the network was calculated; 3) the average SD of the trials in the network is imputed for the trial that did not report a SD/SE/95% CI; or 4) the SE of the difference = average SD/square root of N.

Results

Search and selection results

A total of 3,006 citations and 4,720 clinical trials were identified (Figure 1). After screening, 95 citations (publications and trials) reporting on 24 different trials with 21,311 patients were included in the analysis.

Study characteristics

All studies included in the analyses were parallel-group, multicenter, randomized, controlled trials and the number of patients randomized per arm ranged from 46[22] to 3,006[3] (Table 1). All trials were double blind, with the exception of one tiotropium trial that included tiotropium as an open-label arm.[23] Inhaled corticosteroids were allowed in all the studies where information on inhaled corticosteroid background was reported. Long-acting β_2-agonist (LABA) background treatment was allowed in five tiotropium studies (LABA use at baseline ranged from 38% to 61% of the study arms, where data were available).[3,4,24,25] Information on LABA use was missing in three studies,[26–28] and was not allowed in the remaining studies.

Patient characteristics

Patient populations ranged from 49% to 99% male (Table 2), but the mean age was similar across the studies (mean range 60–67 years). Spirometry measures were generally

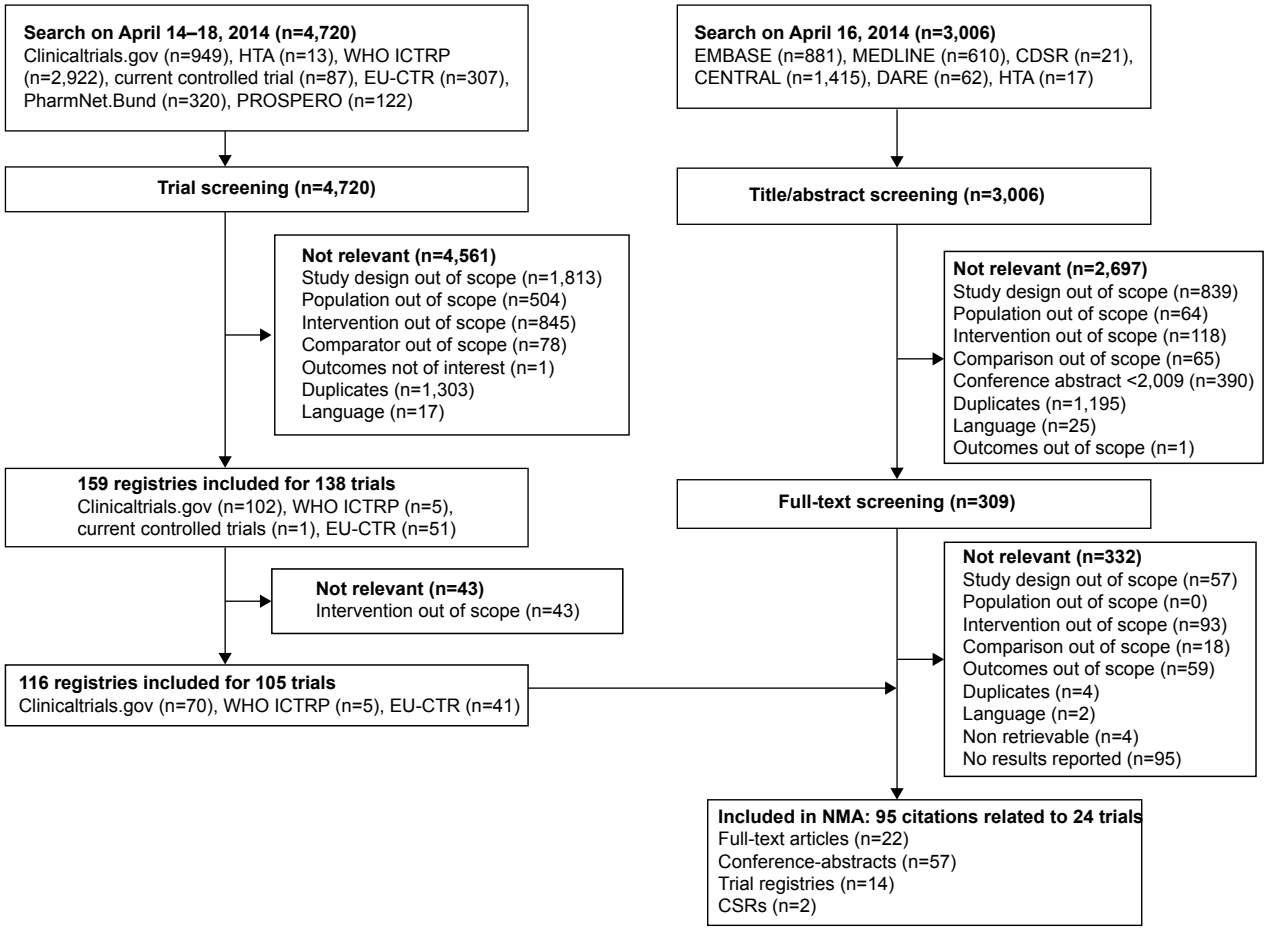

Figure 1 Flow chart of study selection process.

Abbreviations: CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled Trials; CSR, clinical study report; DARE, Database of Abstracts of Reviews of Effects; EU-CTR, EU Clinical Trials Register; HTA, Health Technology Assessment; NMA, network meta-analysis; PROSPERO, International Prospective Register of Systematic Reviews; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Table 1 Key study characteristics for all studies included (only arms of interest)

Study	Treatment	Trial duration	Inclusion criteria	Background treatment
Chan et al,[4] SAFE,[49,50] SAFE-Portugal[51]	Tiotropium 18 μg OD Placebo	48 weeks	≥40 years old; ≥10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%; included if ≥1 exacerbation previous year but not in 6 weeks prior (later amended to include one exacerbation in past 2 years)	Allowed: stable dose oral corticosteroids, ICS, theophylline preparations, mucolytic preparations (not containing bronchodilators), LABAs
TIPHON[35]	Tiotropium 18 μg OD Placebo	36 weeks	≥40 years old; >10 pack-years; FEV_1 20%–70%; FEV_1/FVC ≤70%	Allowed: stable doses of theophylline preparations (excluding 24-hour preparations), mucolytics, ICS, and oral steroids
UPLIFT[3,52]	Tiotropium 18 μg OD Placebo	4 years	≥40 years old; >10 pack-years; FEV_1 ≤70%; FEV_1/FVC ≤70%; excluded if exacerbation 4 weeks prior	Allowed: all respiratory medications, except other inhaled anticholinergic drugs
Niewoehner et al[24]	Tiotropium 18 μg OD Placebo	6 months	≥40 years old; ≥10 pack-years; FEV_1 ≤60%; FEV_1/FVC ≤70%; excluded if not recovered from exacerbation ≥30 days prior	Allowed: all other respiratory medications (including ICS and LABAs) Not allowed: open-label anticholinergic bronchodilator
Brusasco et al[27]	Tiotropium 18 μg OD Placebo	24 weeks	>40 years old; >10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%	NR
Donohue et al[5]	Tiotropium 18 μg OD Placebo	24 weeks	≥40 years old; >10 pack-years; FEV_1 ≤60%; FEV_1/FVC ≤70%	Allowed: usual ICS and oral steroids Not allowed: inhaled anticholinergic LABAs
Casaburi et al[26]	Tiotropium 18 μg OD Placebo	56 weeks	≥40 years old; ≥10 pack-years; FEV_1 ≤65%; FEV_1/FVC ≤70%	Allowed: stable doses of theophylline, ICS, oral prednisone
Donohue et al[23]	Tiotropium 18 μg OD Placebo	26 weeks	Patients aged 40 years or older with a smoking history of 20 pack-years or more and a diagnosis of moderate-to-severe COPD (GOLD criteria) were enrolled. Post-bronchodilator (within 30 minutes of inhaling albuterol 360 μg) FEV_1 <80% and ≥30% predicted and FEV_1/FVC <70%	Patients could continue ICS monotherapy if stable for 1 month before screening; dose and regimen were to remain stable throughout the study. Before the start of the run-in period, treatment with anticholinergic bronchodilators or with β_2-agonists was discontinued with appropriate washout, and patients receiving fixed-combination β_2-agonist/ICS were switched to ICS monotherapy at an equivalent dose. All patients were supplied with albuterol for use as needed
SHINE[29]	Glycopyrronium 50 μg OD Tiotropium 18 μg OD Placebo	26 weeks	≥40 years old; diagnosis of moderate or severe COPD (stage II or III according to GOLD 2008 criteria); post-bronchodilator FEV_1 <80% and ≥30%. Post-bronchodilator FEV_1/FVC <0.70. Smoking history ≥10 pack-years	Allowed: salbutamol/albuterol as rescue medication, inhaled or intranasal corticosteroids in constant doses Not allowed: LABA, LAMA, LABA/ICS
GLOW1[7]	Glycopyrronium 50 μg OD Placebo	26 weeks	≥40 years old; post-bronchodilator FEV_1 ≥30% and <80% of predicted; post-bronchodilator FEV_1/FVC <0.7; ≥10 pack-years	Allowed: ICS, intranasal corticosteroids or H1antagonists Not allowed: LABA
GLOW2[8]	Glycopyrronium 50 μg OD Tiotropium 18 μg OD Placebo	52 weeks	Males and females ≥40 years, with a smoking history of ≥10 pack-years, a diagnosis of moderate-to-severe stable COPD, post-bronchodilator FEV_1 ≥30% and <80% of the predicted normal, and post-bronchodilator FEV_1/FVC <0.70 were enrolled	Allowed: inhaled or intranasal corticosteroids and H1 antagonists; salbutamol/albuterol as rescue medication Not allowed: LAMAs (min 7 days before run-in); LABAs or LABA/ICS combinations (min 48 hours before run-in)
Verkindre et al[22]	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤50%; FEV_1/FVC ≤70%; residual volume ≥125%; excluded if unstable doses oral corticosteroid 6 weeks prior	Allowed: stable doses oral corticosteroids, ICS, theophylline preparations, mucolytic agents Not allowed: use of SABAs, oral β_2-agonists, or LABAs
Casaburi et al[53]	Tiotropium 18 μg OD Placebo	13 weeks	FEV_1 ≤65%; FEV_1/FVC ≤70%; ≥40 years of age; diagnosis of COPD defined by ATS; smoking history of >10 pack-years	Allowed: stable doses of theophylline, ICS, oral prednisone Not allowed: other inhaled or oral bronchodilators

(*Continued*)

Table 1 (*Continued*)

Study	Treatment	Trial duration	Inclusion criteria	Background treatment
Covelli et al[25]	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤60%; FEV_1/FVC ≤70%; excluded if exacerbation in prior 6 weeks	Allowed: ICS, LABAs, theophyllines Not allowed: chromones, leukotriene antagonists, inhaled anticholinergics
Garcia et al[28]	Tiotropium 18 μg OD Placebo	12 weeks	Ambulatory patients of either sex; >40 years old, diagnosed with COPD (FEV_1 <60% of the predicted value and FEV_1/FVC <70%); smokers or ex-smokers with a history of having smoked at least 10 pack-years	NR
Moita et al[54]	Tiotropium 18 μg OD Placebo	12 weeks	FEV_1 ≤70%; FEV_1/FVC ≤70%; excluded if ≥3 exacerbations previous year or exacerbation in 6 weeks prior	Allowed: LABAs, theophylline, mucolytics, ICS, stable doses oral corticosteroids. Temporary increases in theophylline or oral steroids for exacerbations Not allowed: theophylline 24-hour preparation
Vogelmeier et al[55]	Tiotropium 18 μg OD Placebo	24 weeks	FEV_1 <70%, FEV_1/FVC <70%; stable COPD; aged 40 years at COPD onset; smoking history of 10 pack-years	Allowed: salbutamol, ICS monotherapy
ACCORD COPD I[56]	Aclidinium 400 μg BD Placebo	12 weeks	≥40 years old; current or ex-smokers with ≥10 pack-years; diagnosed with moderate-to-severe COPD (post-bronchodilator FEV_1/FVC <70% and FEV_1 ≥30% and <80% of predicted)	Allowed: albuterol (rescue medication); ICS; systemic corticosteroids equivalent to ≤10 mg/day of prednisolone or 20 mg every other day, and theophylline if treatment was stable for ≥4 weeks prior to screening Not allowed: inhaled anticholinergics, LABAs
ACCORD COPD II[30]	Aclidinium 400 μg BD Placebo	12 weeks	≥40 years old; current or ex-smokers with ≥10 pack-years; diagnosed with moderate-to-severe COPD (post-bronchodilator FEV_1/FVC <70% and FEV_1 ≥30% and <80% of predicted)	Allowed: albuterol (rescue medication); theophylline; ICS; oral or parenteral corticosteroids equivalent to ≤10 mg/day of prednisolone or 20 mg every other day, if treatment was stable for ≥4 weeks prior to screening Not allowed: anticholinergics, LABAs
ATTAIN[59]	Aclidinium 400 μg BD Placebo	24 weeks	≥40 years old; post-bronchodilator FEV_1 ≥30% and <80% of predicted; post-bronchodilator FEV_1/FVC <0.7; ≥10 pack-years	Allowed: ICS monotherapy or oral sustained-release theophyllines; systemic corticosteroids at doses equivalent to 10 mg/day of prednisone or 20 mg every other day; and oxygen therapy (<15 hours/day). Inhaled salbutamol was used as a rescue medication
Donohue et al[57]	Umeclidinium 62.5 μg OD Placebo	24 weeks	Outpatient; ≥40 years old; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio <0.70 and a post-salbutamol FEV_1 ≤70%; smoking history ≥10 pack-years	Allowed: ICS at a dose of up to 1,000 μg/day of FP or equivalent, salbutamol/albuterol as rescue Not allowed: LABAs, LABA/ICS combination products, short-acting β_2-agonists, short-acting anticholinergics, SABA/ICS combination products
AC4115408[34]	Umeclidinium 62.5 μg OD Placebo	12 weeks	Outpatient; ≥40 years old; diagnosed with COPD; post-salbutamol FEV_1/FVC ratio <0.70 and a post-salbutamol FEV_1 ≤70%; smoking history ≥10 pack-years; ≥2 on mMRC	Allowed: salbutamol, ICS, mucolytics Not allowed: LABA, tiotropium, theophyllines, inhaled SABA, inhaled SAMA
SPARK[58]	Glycopyrronium 50 μg OD Tiotropium 18 μg OD	24 weeks	≥40 years old; post-bronchodilator FEV_1 <50% of predicted normal and FEV_1/FVC ratio <0.70; history of ≥ exacerbation in the previous 12 months. Smoking history ≥10 pack-years	Allowed: ICS Not allowed: LABAs
GLOW5[45]	Glycopyrronium 50 μg OD Tiotropium 18 μg OD	12 weeks	≥40 years old; post-bronchodilator FEV_1 ≥30% and <80% of predicted; post-bronchodilator FEV_1/FVC <0.7; ≥10 pack-years	Allowed: ICS and SABA for rescue medication Not allowed: LABA

Abbreviations: ATS, American Thoracic Society; BD, twice-daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; NR, not reported; OD, once-daily; SABA, short-acting β_2 agonist.

Table 2 Key patient characteristics at baseline for all studies included (only arms of interest)

Study	Treatment	ITT, n	Male, %	Mean age, years (SD)	Current smokers, %	Severe/very severe COPD, %	ICS use, %	Mean COPD duration, years (SD)	Mean pack-years (SD)	FEV_1 % predicted (SD)
Chan et al,[4] SAFE,[49,50]	Tiotropium 18 μg OD	608	59	67.0 (8.7)	32	NR	66	9.9 (8.1)	50.2 (22.6)	39 (13)
SAFE-Portugal[51]	Placebo	305	61	67.0 (9.1)	30	NR	71	9.9 (7.9)	51.0 (26.3)	39 (14)
TIPHON[35]	Tiotropium 18 μg OD	266	87	65.0 (9.7)	24	57	38	7.9 (7.6)	44.4 (21.3)	47 (13)
	Placebo	288	85	64.0 (10.1)	30	62	36	8.0 (7.9)	43.0 (22.5)	46 (12)
UPLIFT[3,52]	Tiotropium 18 μg OD	2,987	75	65.0 (8.4)	29	52	62	9.9 (7.6)	49.0 (28.0)	40 (12)
	Placebo	3,006	74	65.0 (8.5)	30	53	62	9.7 (7.4)	48.4 (27.9)	39 (12)
Niewoehner et al[24]	Tiotropium 18 μg OD	914	98	67.6 (8.7)	29	NR	61	12.2 (10.4)	67.4 (35.4)	36 (13)
	Placebo	915	99	68.1 (8.5)	30	NR	58	11.9 (10.5)	69.4 (36.6)	36 (13)
Brusasco et al[27]	Tiotropium 18 μg OD	402	77	63.8 (8.0)	NR	NR	NR	9.0 (7.3)	44.1 (22.9)	39 (12)
	Placebo	400	76	64.6 (8.6)	NR	NR	NR	9.8 (7.4)	42.4 (22.7)	39 (12)
Donohue et al[5]	Tiotropium 18 μg OD	209	74	64.5 (7.9)	NR	NR	66	9.2 (7.8)	47.0 (25.0)	41 (NR)
	Placebo	201	75	65.6 (7.8)	NR	NR	66	9.7 (7.9)	46.0 (24.0)	41 (NR)
Casaburi et al[26]	Tiotropium 18 μg OD	550	67	65.0 (9.0)	NR	NR	44	8.6 (7.4)	63.0 (31.0)	39 (14)
	Placebo	371	63	65.0 (9.0)	NR	NR	40	8.1 (6.8)	59.0 (30.0)	38 (14)
Donohue et al[23]	Tiotropium 18 μg OD	420	65	64 (8.8)	NR	NR	35	NR	50.0 (25.1)	54 (16)
	Placebo	425	61	63.6 (8.9)	NR	NR	40	NR	49.7 (23.9)	56 (14)
SHINE[29]	Glycopyrronium 50 μg OD	473	77	64.3 (9.0)	40	37	58	6.5 (5.8)	NR	55 (14)
	Tiotropium 18 μg	480	75	63.5 (8.7)	39	38	59	6.1 (5.5)	NR	55 (14)
	Placebo	232	73	64.4 (8.6)	40	32	58	6.4 (5.7)	NR	55 (13)
GLOW1[7]	Glycopyrronium 50 μg OD	552	83	63.8 (9.5)	33	40	55	5.9 (6.0)	44.9 (28.1)	55 (13)
	Placebo	270	81	64.0 (9.0)	34	38	51	6.5 (6.8)	44.6 (24.8)	54 (13)
GLOW2[8]	Glycopyrronium 50 μg OD	525	65	63.5 (9.1)	45	37	56	7.2 (6.6)	49.0 (25.4)	56 (13)
	Tiotropium 18 μg OD	267	63	63.9 (8.2)	44	NR	52	7.5 (6.6)	50.2 (28.0)	56 (13)
	Placebo	268	65	63.6 (9.1)	46	NR	51	7.4 (6.6)	48.0 (24.0)	56 (14)
Verkindre et al[22]	Tiotropium 18 μg OD	46	94	61.0 (9.5)	24	NR	NR	9.7 (6.9)	45.6 (23.1)	35 (9)
	Placebo	54	94	60.0 (10.2)	33	NR	NR	8.8 (6.6)	41.8 (18.0)	36 (9)
Casaburi et al[53]	Tiotropium 18 μg OD	276	67	65.0 (8.6)	NR	NR	NR	9.3 (8.0)	64.5 (33.1)	39 (14)
	Placebo	188	63	65.0 (9.0)	NR	NR	NR	8.6 (6.9)	60.5 (30.2)	38 (14)
Covelli et al[25]	Tiotropium 18 μg OD	94	66	66.0 (8.9)	40	NR	54	10.1 (8.1)	66 (35.6)	40 (13)
	Placebo	84	49	63.0 (9.2)	37	NR	58	10.4 (7.7)	65 (31.2)	39 (14)
Garcia et al[28]	Tiotropium 18 μg OD	123	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	125	NR	NR	NR	NR	NR	NR	NR	NR
Moita et al[54]	Tiotropium 18 μg OD	147	NR	NR	28	NR	NR	NR	NR	NR
	Placebo	164	NR	NR	25	NR	NR	NR	NR	NR
Vogelmeier et al[55]	Tiotropium 18 μg OD	221	79	63.4 (9.5)	NR	NR	NR	6.9 (6.3)	38.6 (19.3)	52 (11)
	Placebo	209	78	62.5 (8.6)	NR	NR	NR	6.7 (6.1)	40.1 (22.8)	51 (11)
ACCORD COPD I[56]	Aclidinium 400 μg; BD	190	53	64.9 (9.5)	42	NR	47	NR	57.2 (28.5)	54 (13)
	Placebo	186	52	65.1 (9.2)	47	NR	45	NR	52.7 (28.1)	55 (13)

(*Continued*)

Table 2 (*Continued*)

		ITT, n	Male, %	Mean age, years (SD)	Current smokers, %	Severe/very severe COPD, %	ICS use, %	Mean COPD duration, years (SD)	Mean pack-years (SD)	FEV_1 % predicted (SD)
ACCORD COPD	Aclidinium 400 μg BD	177	50	63.2 (9.0)	50	54	42	NR	54.2 (27.7)	50 (13)
II[30]	Placebo	182	55	61.7 (9.3)	56	37	39	NR	52.6 (28.4)	55 (13)
ATTAIN[59]	Aclidinium 400 μg BD	269	68	62.9 (8.4)	55	31	51	NR	41.7 (21.1)	56 (12)
	Placebo	273	69	62.0 (8.0)	53	34	58	NR	38.9 (18.3)	57 (13)
DB2113373[32]; Donohue et al[57]	Umeclidinium 62.5 μg OD	418	71	64.0 (9.2)	50	54	52	NR	46.8 (27.0)	47 (13)
	Placebo	280	70	62.2 (9.0)	54	58	49	NR	47.2 (27.2)	47 (13)
AC4115408[34]	Umeclidinium 62.5 μg OD	69	64	62.3 (9.5)	54	63	22	NR	45.2 (21.2)	45 (14)
	Placebo	68	62	62.5 (8.7)	53	51	26	NR	52.3 (30.2)	47 (13)
SPARK[58]	Glycopyrronium 50 μg OD	740	73	63.1 (8.0)	38	100	75	7.1 (5.3)	44.0 (23.0)	37 (8)
	Tiotropium 18 μg OD	737	75	63.6 (7.8)	37	100	76	7.2 (5.5)	47.0 (28.0)	37 (8)
GLOW5[45]	Glycopyrronium 50 μg OD	327	73	63.2 (7.9)	45	42	50	6.5 (5.1)	39.6 (20.4)	53 (13)
	Tiotropium 18 μg OD	330	75	63.7 (8.0)	44	41	53	6.2 (5.1)	40.2 (21.5)	54 (13)

Abbreviations: SD, standard deviation; ITT, intention to treat population; ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second; NR, not reported; OD, once-daily; BD, twice-daily.

consistent at baseline, with most studies requiring a FEV_1/forced vital capacity of ≤0.70. The mean FEV_1 % predicted ranged between 50% and 56% for aclidinium-treated patients, 37%–56% for glycopyrronium, 35%–55% for tiotropium, and 45%–48% for umeclidinium. The proportion of patients with severe or very severe COPD was reported in seven studies,[3,29–35] and ranged from 31% to 100% (per treatment arm). Across all studies, the proportion of patients per arm who used inhaled corticosteroids at baseline ranged from 22% to 76%. All studies included patients who were current or ex-smokers and most specified a smoking history of at least 10 years; the mean number of pack-years ranged from 38.6 to 69.4 years.

Network meta-analysis

Although there was some degree of variation in patient characteristics across studies, in general the studies were of good quality and homogeneous, and thus a valid NMA was feasible.[36] The network diagram for the randomized clinical trials included in the NMA is shown in Figure 2. Studies were identified that compared aclidinium, glycopyrronium, tiotropium, and umeclidinium with placebo as the common comparator. The NMA results for trough FEV_1 at 12 weeks (primary endpoint) and 24 weeks are presented, as well as secondary endpoints at 24 weeks. Supportive analyses of secondary endpoints at 12 weeks are presented in Tables S5 and S6.

Given the geometry of each network (containing only one closed loop; Figure 2), direct and indirect evidence for all outcomes was only available for the comparative efficacy of tiotropium versus placebo, glycopyrronium versus placebo, and tiotropium versus glycopyrronium. No important deviation between direct and indirect evidence was observed when the network consistency was assessed, suggesting that the consistency assumption was valid.

Trough FEV_1 at 12 weeks (primary outcome)

In total, 17 studies (11,935 patients) were included for the FEV_1 endpoint (Figure 2A and Table 3). The minimal clinically important difference for FEV_1 is 100 mL.[37] All LAMAs investigated were more efficacious than placebo, with a mean change from baseline greater than the minimal clinically important difference (Figure 3A). The mean change from baseline in trough FEV_1 was highest for umeclidinium, with a difference of 136.7 mL (95% CrI: 104.20–169.20) from placebo and a >99% probability of being better than placebo. The probability of umeclidinium being a better treatment than tiotropium, aclidinium, or glycopyrronium was 90%, 96%, or 86%, respectively.

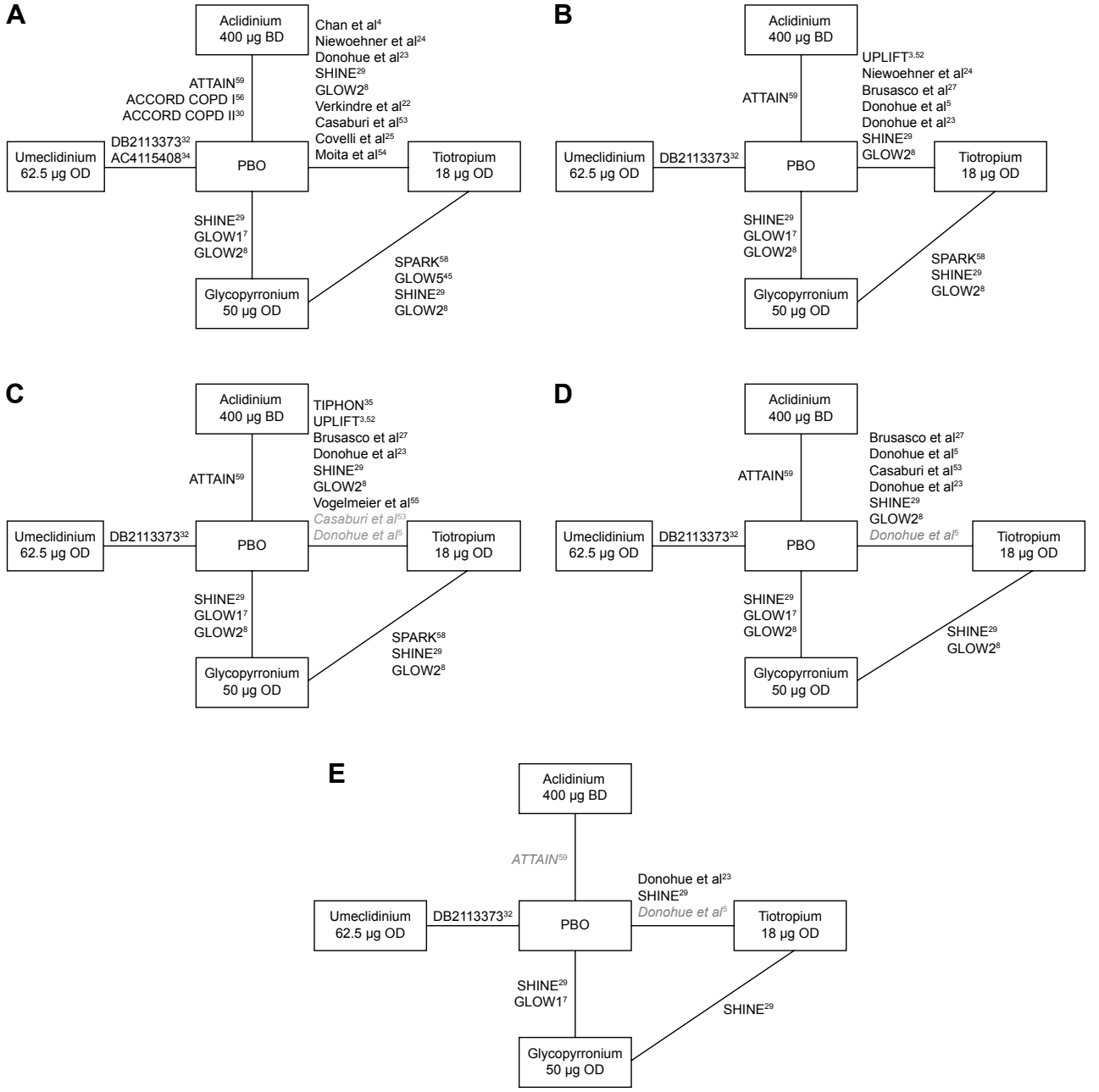

Figure 2 Overall network of studies in the network meta-analysis of umeclidinium versus other LAMAs or placebo for (**A**) trough FEV_1 at 12 weeks, (**B**) trough FEV_1 at 24 weeks, (**C**) SGRQ total score at 24 weeks, (**D**) TDI focal score at 24 weeks, and (**E**) rescue medication use at 24 weeks.

Note: Gray italic text indicates studies that did not report measures of uncertainty.

Abbreviations: BD, twice-daily; FEV_1, forced expiratory volume in 1 second; LAMA, long-acting muscarinic antagonist; OD, once-daily; PBO, placebo; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

Trough FEV_1 at 24 weeks

In total, eleven studies (15,663 patients) were included for the FEV_1 endpoint at 24 weeks (Figure 2B and Table 3). Again, the mean change from baseline was greater than the minimal clinically important difference for all active agents. The highest change from baseline in trough FEV_1 was found with glycopyrronium, with a difference of 135.8 mL (95% CrI: 123.10–148.30). Glycopyrronium had a >99% chance of being better than tiotropium, which had the next highest difference in change from baseline trough FEV_1. The newest agent, umeclidinium, had a mean difference in change from baseline of 115.0 mL compared with placebo (95% CrI: 74.51–155.30), with >99% probability of being better than placebo (Figure 3B). Umeclidinium was comparable to other LAMAs for this endpoint, with only a 66%, 33%, and 17% probability of being better than tiotropium, aclidinium, and glycopyrronium, respectively.

Table 3 Individual study results for trough FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use

Treatment	References	Trough FEV_1 at 12 weeks (mean difference in change from baseline), mL (SE)	Trough FEV_1 at 24 weeks (mean difference in change from baseline), mL (SE)	SGRQ total score at 24 weeks, mean difference in change from baseline (SE)	TDI focal score at 24 weeks, mean difference (SE)	Rescue medication puffs per day at 24 weeks, mean difference in change from baseline (SE)
Tiotropium versus placebo	Chan et al[4]	100 (14.9)	–	–	–	–
	Niewoehner et al[24]	100 (10.2)	100 (12.8)	–	–	–
	Donohue et al[23]	140 (20.4)	140 (20.4)	−1.00 (0.92)	0.90 (0.23)	−0.60 (0.19)
	SHINE[29]	130 (17.9)	130 (17.9)	−0.88 (1.04)	0.58 (0.24)	−0.41 (0.17)
	GLOW2[8]	83 (19.3)	84 (21.6)	−2.52 (1.11)	0.94 (0.30)	–
	Verkindre et al[22]	110 (40.0)	–	–	–	–
	Casaburi et al[53]	150 (14.1)	–	–	–	–
	Covelli et al[25]	184 (37.0)	–	–	–	–
	Moita et al[54]	102 (31.4)	–	–	–	–
	UPLIFT[3,52]	–	100 (7.1)	−2.50 (0.36)		–
	Brusasco et al[27]	–	120 (100)	−2.70 (0.99)	1.10 (0.30)	–
	Donohue et al[5]	–	137 (20.0)	−2.71 (1.31)[a]	1.00 (0.33)[a]	−1.45 (0.25)[a]
	TIPHON[35]	–	–	−3.51 (0.65)	–	–
	Vogelmeier et al[55]	–	–	−2.05 (1.27)	–	–
	Casaburi et al[26]	–	–	−3.08 (0.89)[a]	0.80 (0.19)	–
Aclidinium versus placebo	ATTAIN[59]	105 (21.1)	128 (22.0)	−4.60 (1.10)	1.00 (0.30)	−0.95 (0.22)[a]
	ACCORD COPD I[56]	124 (20.7)	–	–	–	–
	ACCORD COPD II[30]	72 (21.9)	–	–	–	–
Glycopyrronium versus placebo	SHINE[29]	120 (15.3)	120 (17.9)	−1.83 (1.04)	0.89 (0.24)	−0.30 (0.17)
	GLOW2[8]	97 (16.7)	134 (18.9)	−3.38 (0.97)	0.81 (0.26)	–
	GLOW1[7]	108 (14.8)	113 (16.5)	−2.81 (0.96)	1.00 (0.24)	−0.46 (0.16)
Glycopyrronium versus tiotropium	SPARK[58]	10 (14.1)	−10 (13.1)	0.10 (0.88)	–	–
	GLOW5[45]	4 (15.1)	–	–	–	–
Umeclidinium versus placebo	DB2113373[32]	139 (18.1)	115 (20.2)	−4.69 (1.21)	1.00 (0.26)	−0.30 (0.26)
	AC4115408[34]	127 (38.3)	–	–	–	–

Note: [a]Imputed value.

Abbreviations: –, data not available; FEV_1, forced expiratory volume in 1 second; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire total score; TDI, transitional dyspnea index focal score.

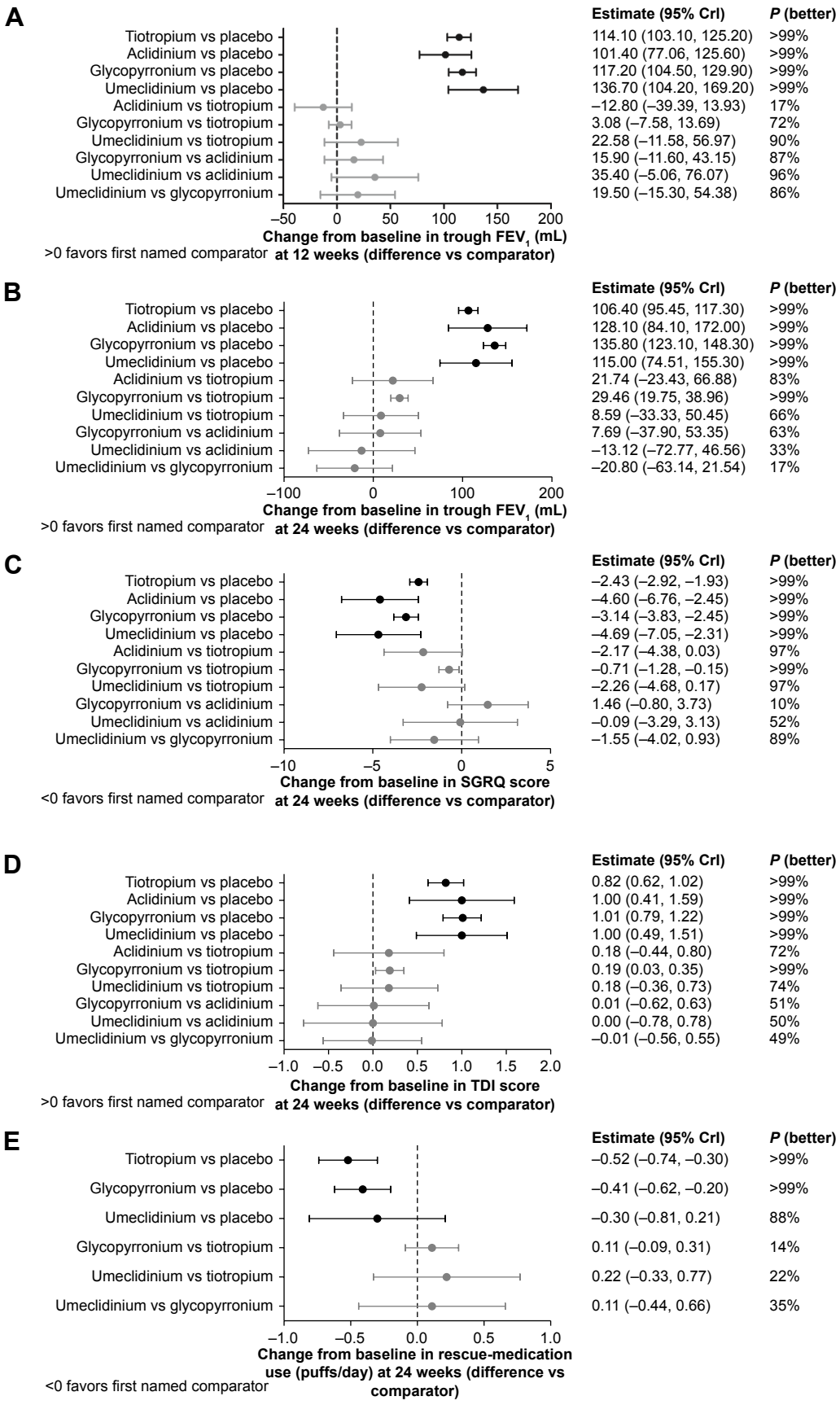

Figure 3 Differences in intervention versus the comparator for change from baseline in (**A**) trough FEV_1 (mL) at 12 weeks, (**B**) trough FEV_1 (mL) at 24 weeks, (**C**) SGRQ total scores at 24 weeks, (**D**) TDI focal scores at 24 weeks, and (**E**) rescue medication use at 24 weeks (95% CrI and probability of the intervention being better than the comparator).
Abbreviations: CrI, credible interval; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

SGRQ total score at 24 weeks

Thirteen studies (15,739 patients) were included in the examination of this endpoint (Figure 2C and Table 3). Two studies reported only the mean difference in change from baseline without any measure of uncertainty, such as SE, SD, or 95% CI.[5,26] An imputed value was calculated based on the average SD of the difference in change from baseline of trials in the network. Imputing this value and adding the studies to the analysis did not impact the results.

The minimal clinically important difference for SGRQ score is 4 units.[38] Relative to placebo, only umeclidinium and aclidinium mean scores were reduced by more than 4 units, although all agents had 99% probability of being better than placebo (Figure 3C). The highest difference was seen with umeclidinium, which had a 97%, 52%, and 89% chance of being better than tiotropium, aclidinium, or glycopyrronium, respectively.

TDI focal score at 24 weeks

Nine studies (7,285 patients) were included (Figure 2D and Table 3). One study[5] did not report any measure of uncertainty or an exact *P*-value; this was imputed and did not impact the results.

The minimal clinically important difference for TDI score is 1 unit.[39] Aclidinium, glycopyrronium, and umeclidinium had a mean difference in change from baseline in TDI score of ≥1.00 (Figure 3D). Only the mean change in TDI score for tiotropium did not reach the minimal clinically important difference.

Rescue medication use at 24 weeks

A total of six studies (4,502 patients) were included (Figure 2E and Table 3). Glycopyrronium, tiotropium, and umeclidinium reduced rescue medication use to comparable extents, with mean changes of −0.41 (95% CrI: −0.62 to −0.20), −0.52 (95 CrI: −0.74 to −0.30), and −0.30 puffs/day (95% CrI: −0.81 to 0.21), relative to placebo (Figure 3E).

Discussion

In the absence of head-to-head study data and in light of new available agents, a systematic literature review and NMA was carried out to assess the relative efficacy of LAMAs for the treatment of COPD. Overall, a large number of patients (21,311) were included in our analyses. Endpoints (change from baseline in trough FEV_1, SGRQ total scores, TDI focal scores, and rescue medication use) were selected because they were consistently reported across all studies and deemed to be clinically important endpoints in those studies. Other endpoints, such as adverse events, exercise tolerance, and exacerbation rate, were not included, for several reasons. First, the definitions and methodology for reporting adverse events and exercise tolerance were variable across trials, precluding accurate comparisons. Second, exacerbations were studied in some longer-term trials, where a history of these events was required at entry, but were not key endpoints in most 3- and 6-month studies. Although exacerbations were beyond the scope of this NMA, another NMA performed without the inclusion of umeclidinium suggested that efficacy was comparable between aclidinium, glycopyrronium, and tiotropium for the prevention of COPD exacerbations; all reduced moderate-to-severe exacerbations, compared with placebo, and all were equally effective.[40]

As expected, this NMA revealed that all the active LAMA treatments (aclidinium, glycopyrronium, tiotropium, and umeclidinium) were more efficacious than placebo, with each of the active therapies providing clinically relevant improvements in trough FEV_1 (>100 mL) at 12 and 24 weeks. Improvements in other measures (SGRQ score, TDI focal score, and rescue medication use), versus placebo, were also observed. The estimates met the minimal clinically important differences for umeclidinium (SGRQ and TDI focal score), aclidinium (SGRQ and TDI focal score), and glycopyrronium (TDI focal score only) versus placebo at 24 weeks. Overall, these findings suggest that all LAMAs are effective, compared with placebo.

Aclidinium and umeclidinium had broadly similar efficacy for lung function and patient-reported outcomes, compared with the other LAMAs examined and each other. Overall, there was no evidence that a BD regimen (ie, aclidinium) was more efficacious than OD regimens. For umeclidinium, the newest agent, there were some modest numerical improvements in 12-week lung function, compared with other LAMAs; however, the CrI crossed zero in all cases. In some cases, there were indications that glycopyrronium had superior efficacy to tiotropium, with the newer agent having a >99% probability of being better in terms of 24-week FEV_1 and SGRQ score than tiotropium. However, it should be acknowledged that the patients in the glycopyrronium trials had predominantly moderately severe COPD, compared with tiotropium trials, which tended to include patients with severe COPD.

Although there have been no direct comparisons of umeclidinium with other LAMAs in the literature (noting that head-to-head trials of umeclidinium versus glycopyrronium

[NCT02236611],[41] and umeclidinium versus tiotropium [NCT02207829],[42] are currently ongoing), there have been recent direct comparisons of aclidinium versus tiotropium. In one randomized, controlled trial aclidinium had comparable bronchodilation and significantly improved symptom control, relative to tiotropium at 6 weeks, in line with our data.[43] A small, randomized crossover study also suggested some improvements for FEV_1 area under the curve and COPD symptoms with aclidinium versus tiotropium.[44] The GLOW5 study concluded that glycopyrronium and tiotropium had similar efficacy, noting that there were non-significant improvements with glycopyrronium for TDI focal score, SGRQ total score, rescue medication use, and the rate of COPD exacerbations.[45] The current analysis failed to entirely corroborate these findings, highlighting small potential efficacy differences in favor of glycopyrronium. As noted previously, this discrepancy could result from differences in baseline COPD severity between glycopyrronium and tiotropium trials.

Limitations

There are some potential limitations to this analysis. Although the endpoints selected were clinically important (and commonly reported in randomized controlled trials), they were also relatively short-term endpoints. At present, all four of the LAMAs investigated here have reported positive effects on exacerbations outcomes relative to placebo,[7,46–48] but differences in study methodology, populations, and reporting methods precluded robust comparisons of LAMAs against one another in our analysis. We also focused on mean outcomes; alternative analyses examining percentage of responders, if performed on patient level data, might highlight incremental differences between the LAMAs that were not apparent when means were used. Differences in the patient populations, particularly the approximately 20% range in mean baseline FEV_1 % predicted values, and background medications may have resulted in some residual confounding influences that could not be adequately addressed with our methodology, despite attempts to select similar studies. Consequently, the findings do not carry the same weight as head-to-head randomized controlled trials; such studies are warranted to corroborate our data. Finally, the data used in the NMA were obtained from highly controlled studies with patients who have been trained in the use of different inhaler devices. Our analysis cannot account for potential handling errors or preferences for a particular device (these factors were likely to have been minimized within studies due to blinding). These inhaler-related factors highlight a need for more pragmatic COPD-effectiveness studies (less controlled) when LAMAs are compared. Such studies may allow for increased differentiation within the LAMA class driven by device choice and posology differences within the drug class. Until such head-to-head studies are available, our findings provide reassurance that umeclidinium has an efficacy profile at least on a par with the standard-of-care LAMA, tiotropium, and a profile at least as effective as other new alternative LAMAs.

Conclusion

The current data on LAMAs suggest that aclidinium, glycopyrronium, tiotropium, and umeclidinium are efficacious, relative to placebo, and the efficacy profile of newer LAMAs appears at least on a par with the standard-of-care LAMA, tiotropium. Until randomized controlled head-to-head trials can be carried out, there is little robust evidence to suggest that one is more efficacious than the others, and the choice of LAMA should depend on physician's and patient's preference.

Acknowledgments

The analysis was sponsored by GSK (GSK study number: 201280). Editorial support in the form of development of the draft outline in consultation with the authors, editorial suggestions to draft versions of this paper, assembling tables and figures, collating author comments, copyediting, fact checking, referencing, and graphic services was provided by Emma McConnell, PhD, at Gardiner-Caldwell Communications (Macclesfield, UK) and was funded by GSK.

Author contributions

ASI, ELH, YSP, and AK contributed to the study design and were involved in the analysis or interpretation of the data. ELH was also involved in the data acquisition. All authors drafted the manuscript.

Disclosure

ASI and YSP are employees of GSK and hold stocks in GSK. ELH and AK are employees of Mapi and received payment from GSK for consultancy during the conduct of this study. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Search strategy for the systematic review

Database	MEDLINE® In-Process and Other Non-Indexed Citations and MEDLINE®
Platform	Ovid
Date of search	April 16, 2014
Time limits	1946–2014 Week 15
Filters	Lines 6–13 are from the search filter: BMJ Clinical Evidence Strategy (MEDLINE randomised controlled trials strategy using Ovid). Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html (accessed on April 14, 2014)

#	Searches	Results, n
1	(formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relvar/breo or zephyr or anoro ellipta).ti,ab,nm.	5,491
2	exp Pulmonary Disease, Chronic Obstructive/or exp Chronic obstructive lung disease/	35,415
3	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ti,ab.	60,286
4	2 or 3	69,295
5	1 and 4	1,647
6	"Randomised controlled trial".pt.	370,219
7	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	782,910
8	(retraction of publication or retracted publication).pt.	6,430
9	6 or 7 or 8	867,607
10	(animals not humans).sh.	3,829,658
11	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomised controlled trial").pt.	3,187,191
12	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomised controlled trial".pt.	47,025
13	9 not (10 or 11 or 12)	649,371
14	5 and 13	637
15	Limit 14 to (English or German)	610

ab, nm, pt, sh, ti: searches performed in abstract, name of substance, publication type, subject heading, and title fields, respectively

Database	EMBASE
Platform	Ovid
Date of search	April 16, 2014
Time limits	1988–2014 Week 15
Filters	Lines 6–12 are from the search filter: BMJ Clinical Evidence Strategy (EMBASE randomized controlled trials strategy using Ovid). Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html (accessed on April 14, 2014)

#	Searches	Results, n
1	(formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA adj "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta).ti,ab.	6,554
2	exp Pulmonary Disease, Chronic Obstructive/or exp Chronic obstructive lung disease/	62,723
3	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema).ti,ab.	65,503
4	2 or 3	87,605
5	1 and 4	2,349
6	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	893,801
7	RETRACTED ARTICLE/	6,430
8	6 or 7	900,087
9	(animal$ not human$).sh,hw.	2,500,858
10	(book or conference paper or editorial or letter or review).pt. not exp randomised controlled trial/	3,608,293
11	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomised controlled trial/	51,550

(*Continued*)

Table S1 (*Continued*)

#	Searches	Results, n
12	8 not (9 or 10 or 11)	681,639
13	5 and 12	914
14	Limit 13 to (English or German)	881

Database	CENTRAL and CDSR
Platform	Cochrane
Date of search	April 16, 2014
Time limits	1988–2014
Filters	n.a.

#	Searches	Results, n
1	(formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA near/3 237) or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta): ti,ab,kw	4,609
2	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	2,533
3	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema): ti,ab,kw	10,689
4	#1 and (#2 or #3) in Trials	1,415
5	#1 and (#2 or #3) (in Cochrane Reviews [Reviews and Protocols])	21

ab, kw, ti: searches performed in abstract, keyword, and title fields, respectively; n.a: not applicable
Line 4 corresponds to the CENTRAL database, line 5 to the CDSR database. Both results were exported.

Database	DARE
Platform	CRD (http://www.crd.york.ac.uk/crdweb/)
Date of search	April 16, 2014
Time limits	No time limits
Filters	n.a.

#	Searches	Results, n
1	(formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA and "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta) [ANY FIELD]	226
2	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) [ANY FIELD]	828
3	1 and 2 in DARE	62

n.a.: not applicable

Database	HTA
Platform	CRD (http://www.crd.york.ac.uk/crdweb/)
Date of search	April 16, 2014
Time limits	No time limits
Filters	n.a.

#	Searches	Results, n
1	(formoterol or eformoterol or foradil or oxis or atimos modulite or atock or perforomist or salmeterol or serevent or tiotropium or spiriva or Ba 679 BR or indacaterol or onbrez or arcapta or NVA-237 or NVA237 or (NVA and "237") or glycopyrronium bromide or glycopyrrolate or seebri or enurev breezhaler or aclidinium bromide or tudorza pressair or eklira genuair or symbicort or advair or seretide or olodaterol or striverdi or umeclidinium or GSK573719 or vilanterol or GW642444 or QVA149 or relovair or zephyr or anoro ellipta) [ANY FIELD]	226
2	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) [ANY FIELD]	828
3	1 and 2 in HTA	116
4	HTA: HTA in progress and HTA published	17

Trial registry	clinicaltrials.gov
URL	http://www.clinicaltrials.gov/
Date of search	April 14, 2014
Search strategy	COPD OR COAD OR "Chronic obstructive pulmonary disease" OR "Chronic obstructive lung disease" OR "chronic obstructive airway disease" OR "chronic bronchitis" OR "emphysema" | Phase 2, 3, 4
Results	949

(*Continued*)

Table S1 (*Continued*)

Trial registry	WHO International Clinical Trials Registry Platform (ICTRP)
URL	http://apps.who.int/trialsearch/AdvSearch.aspx
Date of search	April 14, 2014
Search strategy	COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic bronchitis OR emphysema
Results	3,852 records for 2,922 trials found*
**The WHO ICTRP imports records from several registries. Trials are sometimes recorded in more than one registry. These records can refer to each other using a secondary identification number. The search portal uses this secondary identification number to group records about the same trial together in the search results.* *All results were reported in an excel database. However, WHO ICTRP also collects data from Asian registries. As non-Caucasian population is an exclusion criterion, trials listed on national non-Caucasian registries were excluded for population not of interest. (ie, Chinese Clinical Trial Registry; Clinical Trials Registry – India; Iranian Registry of Clinical Trials; Japan Primary Registries Network).*	
Trial registry	Current controlled trials
URL	http://www.controlled-trials.com/
Date of search	April 15, 2014
Search strategy	(COPD or chronic obstructive pulmonary disease or COAD or chronic obstructive airway disease or chronic obstructive lung disease or chronic bronchitis or emphysema) in Databases: ISRCTN Register (International) – copy of ISRCTN Register; Action Medical Research (UK) – subset from ISRCTN Register; The Wellcome Trust (UK) – subset from ISRCTN Register; UK trials (UK) – subset from ISRCTN Register, UK trials only
Results	87
ClinicalTrials.gov was removed from the list of resources searched in this aggregated database, as clinicaltrials.gov was searched directly in a separate search.	
Trial registry	EU Clinical Trials Register (EU-CTR)
URL	www.clinicaltrialsregister.eu
Date of search	April 15, 2014
Search strategy	(COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic bronchitis OR emphysema) AND (Phase II OR Phase III or Phase IV [Select trial phase])
Results	307
Trial registry	Klinische Prüfungen PharmNet.Bund
URL	http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm
Date of search	April 15, 2014
Search strategy	COPD in Textfelder AND Limit to Phase II or Phase III or Phase IV [Trial phase] AND Limit to therapy or safety or efficacy [Trial scope] AND Limit to patients [Trial population]
Results	320
Trial registry	International Prospective Register of Systematic Reviews (PROSPERO)
URL	http://www.crd.york.ac.uk/NIHR_PROSPERO/
Date of search	April 18, 2014
Search strategy	Separate searches for: COPD [ALL FIELDS] or chronic obstructive pulmonary disease [ALL FIELDS] or COAD [ALL FIELDS] or chronic obstructive airway disease [ALL FIELDS] or chronic obstructive lung disease [ALL FIELDS] or chronic bronchitis [ALL FIELDS] or Emphysema [ALL FIELDS] Review status: Any review status
Results	122
**Please note that search terms have to be searched for manually each and every one of them and then de-duplicated at the end.*	
Trial registry	National Institute for Health Research – Health Technology Assessment (NIHR HTA)
URL	http://www.nets.nihr.ac.uk/projects
Date of search	April 18, 2014
Search strategy	COPD [Keywords] and HTA [programme] in the advanced search
Results	13

Abbreviations: CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled Trials; CSR, clinical study report; DARE, Database of Abstracts of Reviews of Effects; EU-CTR, EU Clinical Trials Register; HTA, Health Technology Assessment; ITC, indirect treatment comparison; PROSPERO, International Prospective Register of Systematic Reviews; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Table S2 Participants, interventions, comparisons, outcomes, and study design (PICOS) criteria

Criteria		Inclusion	Exclusion
Study design	Abstract selection	Randomized controlled trials	Cross-over studies; post hoc or retrospective analyses; cost-effectiveness analyses; observational studies; reviews or meta-analyses; methodology studies or protocols; N of 1 trials (sample size of one patient); studies lasting less than 2 weeks
	Full-text selection		Studies where patients were required to spend time in a sleep laboratory
Treatment/ intervention	Abstract selection	Umeclidinium; tiotropium; aclidinium; glycopyrronium; indacaterol; salmeterol; olodaterol; formoterol	Studies comparing only double or triple therapies (ie, LABA, LAMA, ICS as fixed or open combinations) to each other or to placebo; β-agonists (bambuterol; fenoterol; tulobuterol); short-acting anticholinergics (Ipratropium; Oxitropium); Methylxanthines (theophylline); Inhaled glucocorticosteroids (beclomethasone; budesonide; fluticasone); Leukotriene receptor antagonists (montelukast); combinations of long-acting anticholinergics or LABAs with an ICS; formoterol plus budesonide or fluticasone plus salmeterol that are administered separately; COPD drugs in development or targeting other pathways (roflumilast; polyvalent mechanical bacterial lysate; lipopolysaccharide); all other pharmaceutical interventions not treating COPD (enoxaparin sodium); non-pharmaceutical interventions such as pulmonary rehabilitation
	Full-text selection	Umeclidinium; tiotropium; aclidinium; glycopyrronium; indacaterol; salmeterol; olodaterol; formoterol; administered using any inhalation device	Studies of arformoterol (the (R,R) isomer of formoterol)
Comparator	Abstract and full-text selection	Studies that compare treatments of interest (above) with placebo or to each other	Studies that only compare treatments of interest to treatment not of interest (above) (ie, excluding placebo comparison); studies that only include the treatments of interest in combination with treatments not of interest (ie, prednisolone + formoterol); studies that only include the partial combinations of treatments of interest (ie, Tiotropium + ICS)
Population	Abstract and full-text selection	Patients with COPD as defined by GOLD guidelines (ie, airflow limitation that is not fully reversible); studies that include asthma patients and COPD patients and report data for COPD patients separately; adults; studies that include adults and children and report data for adults separately	Studies with only healthy patients without COPD; studies with patients who have reversible airway or obstructive lung disease; studies with only patients with asthma; studies that include asthma patients and COPD patients but do not report data for COPD patients separately; studies with only patients who have alpha-1-antitrypsin-deficiency-related COPD; studies that include only children; studies that include adults and children but do not report data for adults separately
Outcomes	Abstract and full-text selection	Report results for one of the following outcomes (for all treatments) at any time point ≥10 weeks: trough FEV_1; post-bronchodilator FEV_1; SGRQ total score; proportion of patients with an improvement of at least 4 units in SGRQ total score; TDI focal score; proportion of patients with an improvement of at least 1 unit in TDI score; rate of exacerbations per patient-year over the trial period across definitions; proportion of patients experiencing at least one exacerbation (across definitions) at the end of the study; rescue medication (eg, short-acting β_2-agonists, inhaled corticosteroids) allowed; adverse event rates at the end of the study; serious adverse event rates at the end of the study; withdrawals due to adverse event rates at the end of the study; hospitalization due to adverse event rates at the end of the study; mortality rates at the end of the study	Only report the following outcomes (without any outcomes of interest): bioactivity outcomes or biomarkers of inflammation; lung mucociliary clearance; arterial blood gases or degree of pulmonary hyper-inflation; plethysmography and oscillometry; nocturnal hypoxemia; quality of life in EuroQoL; reporting outcomes at time points <10 weeks

Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β-2 agonist; LAMA, long-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

Table S3 Data extraction

Parameters extracted from studies	
Study characteristics	Author
	Publication year
	Compared interventions including drug name, dose, and administration frequency
	Number of randomized patients
	Trial design
	Centers and countries
	Inclusion criteria
	Background treatments
	Trial duration
	ICS allowed (as background)
	LABAs allowed (as background)
Baseline patient characteristics	Proportion of males
	Age (SD)
	Proportion of current smokers
	Proportion of patients with severe or very severe COPD
	Proportion of patients using ICS
	Duration of COPD (SD)
	Smoking history pack-years (SD)
	FEV_1 % predicted (SD)
	FEV_1/FVC percentage (SD)
	FVC mean (SD)
	BDI mean
	Number of exacerbations in previous year
	Percentage reversibility
	Ethnicity
Outcomes at 12 (8–16 weeks) and 24 weeks (20–28 weeks)	Trough FEV_1
	TDI focal score
	SGRQ total score
	Rescue medication use (number of puffs per day)

Abbreviations: BDI, Baseline Dyspnea Index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-2 agonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

Table S4 Risk of bias assessment for the included studies

Study	Adequate generation of randomization sequence	Adequate allocation concealment	Blinding		Result independent reporting	No other aspects that increase the risk of bias	Risk of bias
			Patients	Caregivers			
Chan et al,[1] SAFE,[2,3] SAFE-Portugal[4]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
TIPHON[5]	Yes	Yes	Yes	Yes	Yes	Yes	Low
UPLIFT[6,7]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Niewoehner et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Brusasco et al[9]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Donohue et al[10]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Casaburi et al[11]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Donohue et al[12]	Unclear	No	No	No	Yes	Yes	High
SHINE[13]	Yes	No	No	No	Yes	Yes	High
GLOW1[14]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
GLOW2[15]	Unclear	Unclear	Yes	Yes	Yes	Yes	Low

(*Continued*)

Table S4 (*Continued*)

Study	Adequate generation of randomization sequence	Adequate allocation concealment	Blinding		Result independent reporting	No other aspects that increase the risk of bias	Risk of bias
			Patients	Caregivers			
Verkindre et al[16]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Casaburi et al[17]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Covelli et al[18]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Garcia et al[19]	Unclear	Yes	Yes	Yes	Yes	Unclear	Low
Moita et al[20]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Vogelmeier et al[21]	Unclear	No	No	No	Yes	Yes	High
ACCORD COPD I[22]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
ACCORD COPD II[23]	No	Yes	Yes	Yes	Yes	Yes	High
ATTAIN[24]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
DB2113373,[25] Donohue et al[26]	Yes	Yes	Yes	Yes	Yes	Yes	Low
AC4115408[27]	Yes	Yes	Yes	Yes	Yes	Yes	Low
SPARK[28]	Yes	No	No	No	No	Yes	High
GLOW5[29]	Unclear	Yes	Yes	Yes	Yes	Yes	Low

Notes: Unclear randomization means that it was mentioned that the study was randomized (and in most cases even with which ratio, eg, 1:1); however, it was not specified how the randomization was generated (eg, by computer). SPARK,[28] SHINE,[13] Vogelmeier et al,[21] and Donohue et al[12] included tiotropium 18 µg as an open-label arm and were categorized as having a high risk of bias. ACCORD COPD II[23] had imbalances in baseline characteristics despite randomization (for FEV_1 and the percentage of patients with GOLD stage II and III); due to these issues in randomization ACCORD COPD II was categorized as having a high risk of bias.
Abbreviation: FEV_1, forced expiratory volume in 1 second.

Table S5 Individual study results for trough SGRQ total scores, TDI focal scores, and rescue medication use

Treatment	References	SGRQ total score at 12 weeks, mean difference in change from baseline (SE)	TDI focal score at 12 weeks, mean difference (SE)	Rescue medication puffs per day at 12 weeks, mean difference in change from baseline (SE)
Tiotropium versus placebo	Donohue et al[12]	−1.10 (0.87)	0.80 (0.22)	–
	SHINE[13]	–	0.59 (0.27)	–
	Verkindre et al[16]	−6.50 (2.90)	1.30 (0.89)	−0.13 (0.25)
	GLOW2[15]	−2.84 (0.97)	0.26 (0.30)	–
	TIPHON[5]	−3.59 (1.22)	–	–
	Casaburi et al[11]	–	0.95 (0.18)	–
Aclidinium versus placebo	ATTAIN[24]	−4.09 (1.02)	0.90 (0.28)	–
	ACCORD COPD I[22]	−2.50 (0.89)	1.00 (0.25)	−0.9 (0.21[a])
	ACCORD COPD II[23]	−1.10 (1.18)	1.00 (0.28)	−0.31 (0.22[a])
Glycopyrronium versus placebo	SHINE[13]	–	0.82 (0.27)	–
	GLOW2[15]	−3.17 (0.84)	0.60 (0.27)	–
Glycopyrronium versus tiotropium	SPARK[28]	−0.50 (0.88)	–	–
	GLOW5[29]	0.65 (0.94)	−0.188 (0.22)	0 (0.15)
Umeclidinium versus placebo	DB2113373[25]	−3.59 (1.06)	0.90 (0.23)	−0.34 (0.25)
	AC4115408[27]	−7.90 (2.19)	1.00 (0.51)	−0.70 (0.31)

Notes: [a]Imputed value; –, no data available.
Abbreviations: SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

Table S6 Differences in intervention versus the comparator for change for SGRQ total scores, TDI focal scores, and rescue medication use at 12 weeks (95% CrI and probability of the intervention being better than the comparator)

Intervention	Comparator				
		Placebo	Tiotropium	Aclidinium	Glycopyrronium
SGRQ total score (difference in change from baseline, units) at 12 weeks					
Tiotropium	Estimate	–2.49			
	95% CrI	–3.56 to –1.41			
	P (better)	>99%			
Aclidinium	Estimate	–2.68	–0.19		
	95% CrI	–3.82 to –1.54	–1.76 to 1.36		
	P (better)	>99%	60%		
Glycopyrronium	Estimate	–2.74	–0.25	–0.06	
	95% CrI	–3.91 to –1.56	–1.07 to 0.56	–1.70 to 1.58	
	P (better)	>99%	73%	53%	
Umeclidinium	Estimate	–4.41	–1.92	–1.73	–1.67
	95% CrI	–6.27 to –2.53	–4.08 to 0.24	–3.92 to 0.47	–3.88 to 0.54
	P (better)	>99%	96%	94%	93%
TDI focal score (difference versus comparator) at 12 weeks					
Tiotropium	Estimate	0.75			
	95% CrI	0.53–0.97			
	P (better)	>99%			
Aclidinium	Estimate	0.97	0.21		
	95% CrI	0.66–1.27	–0.16 to 0.59		
	P (better)	>99%	87%		
Glycopyrronium	Estimate	0.94	0.18	–0.03	
	95% CrI	0.69–1.18	0.04 to 0.33	–0.42 to 0.36	
	P (better)	>99%	>99%	44%	
Umeclidinium	Estimate	0.92	0.16	–0.05	–0.02
	95% CrI	0.51–1.33	–0.30 to 0.63	–0.56 to 0.46	–0.50 to 0.46
	P (better)	>99%	75%	43%	47%
Rescue medication use (difference versus comparator) at 12 weeks					
Tiotropium	Estimate	–0.13			
	95% CrI	–0.62 to 0.36			
	P (better)	0.70			
Glycopyrronium	Estimate	–0.13	0.00		
	95% CrI	–0.70 to 0.44	–0.29 to 0.29		
	P (better)	0.68	50%		
Umeclidinium	Estimate	–0.48	–0.35		–0.35
	95% CrI	–0.86 to –0.10	–0.97 to 0.27		–1.03 to 0.34
	P (better)	>99%	86%		84%

Abbreviations: CrI, credible interval; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index.

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