International Journal of COPD

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REVIEW

Comparative efficacy of inhaled medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD: a systematic review and network meta-analysis

This article was published in the following Dove Press journal:
International Journal of COPD

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Purpose: To assess the comparative efficacy of short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs), LAMA in combination with long-acting beta-agonists (LABAs; LAMA/LABAs) and inhaled corticosteroids (ICS) in combination with LABA (ICS/LABAs) for the maintenance treatment of COPD.

Materials and methods: We systematically reviewed 74 randomized controlled trials (74,832 participants) published up to 15 November 2017, which compared any of the interventions (SAMA [ipratropium], LAMA [aclidinium, glycopyrronium, tiotropium, umeclidinium], LAMA/LABA [aclidinium/formoterol, indacaterol/glycopyrronium, tiotropium/olodaterol, umeclidinium/vilanterol] and ICS/LABA [fluticasone/vilanterol, budesonide/formoterol, salmeterol/fluticasone]) with each other or with placebo. A random-effects network meta-analysis combining direct and indirect evidence was conducted to examine the change from baseline in trough FEV_1, transition dyspnea index, St George's Respiratory Questionnaire and frequency of adverse events at weeks 12 and 24.

Results: Inconsistency models were not statistically significant for all outcomes. LAMAs, LAMA/LABAs and ICS/LABAs led to a significantly greater improvement in trough FEV_1 compared with placebo and SAMA monotherapy at weeks 12 and 24. All LAMA/LABAs, except aclidinium/formoterol, were statistically significantly better than LAMA monotherapy and ICS/LABAs in improving trough FEV_1. Among the LAMAs, umeclidinium showed statistically significant improvement in trough FEV_1 at week 12 compared to tiotropium and glycopyrronium, but the results were not clinically significant. LAMA/LABAs had the highest probabilities of being ranked the best agents in FEV_1 improvement. Similar trends were observed for the transition dyspnea index and St George's Respiratory Questionnaire outcomes. There were no significant differences in the incidences of adverse events among all treatment options.

Conclusion: LAMA/LABA showed the greatest improvement in trough FEV_1 at weeks 12 and 24 compared with the other inhaled drug classes, while SAMA showed the least improvement. There were no significant differences among the LAMAs and LAMA/LABAs within their respective classes.

Keywords: anticholinergics, muscarinic antagonists, frequentist meta-analysis, mixed treatment comparison, indirect treatment comparison, chronic obstructive pulmonary disease

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Introduction

COPD is a chronic disorder characterized by fixed airway obstruction with accompanying respiratory symptoms such as persistent and progressive breathlessness, chronic productive cough and limited exercise capacity. It is predominantly caused by

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http://dx.doi.org/10.2147/COPD.S173472

smoking; however, other factors, particularly occupational exposures, may also contribute to the development of COPD. The impairment of lung function is usually progressive and is not fully reversible. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations. COPD is a global health problem that causes substantial morbidity and mortality. It is the fourth leading cause of death worldwide.[1]

Current disease management guidelines developed by GOLD recommend maintenance therapy with either a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA) in patients with moderate or severe COPD (Groups B–D) when short-acting muscarinic antagonists (SAMAs) fail to control symptoms and exacerbation rates.[2] Patients who have persistent symptoms or exacerbations should be treated with a combination of LAMA and LABA (LAMA/LABA) or inhaled corticosteroids (ICS) and LABA (ICS/LABA). To our knowledge, there is no published systematic review that compares all treatment options. The aim of this network meta-analysis was to comprehensively compare the efficacy and safety of the individual agents under the various therapeutic classes of inhalers commonly used in the treatment of COPD, namely SAMAs, LAMAs, LAMA/LABA fixed-dose combinations (FDCs) and ICS/LABA FDCs. LABA monotherapy was not included in this analysis as it is infrequently used compared to the other classes of inhalers in Singapore.

Materials and methods

This review followed the PRISMA guidelines.

Search strategy

A systematic search of PubMed and Embase was conducted up to 15 November 2017. The search strategy employed a combination of medical subject headings and text words related to the drug classes of interest, the term "COPD" and their synonyms (Table S1). Reference lists from published systematic reviews were hand-searched for additional publications. The searches were limited to English language.

Study selection

Randomized, parallel-group, controlled design studies of ≥12 weeks' duration, which compared LAMA/LABA FDCs (aclidinium/formoterol 400/12 mcg twice a day [AclForm], indacaterol/glycopyrronium 110/50 mcg once a day [IndaGlyco], tiotropium/olodaterol 5/5 mcg once a day [TioOlo], umeclidinium/vilanterol 62.5/25 mcg once a day [UmecVil]), LAMAs (aclidinium 400 mcg once a day [Acl], glycopyrronium 50 mcg once a day [Glyco], tiotropium 18 mcg [Tio18] or 5 mcg [Tio5] once a day, umeclidinium 62.5 mcg once a day [Umec]), ICS/LABA FDC (fluticasone/salmeterol 250/50 mcg [SFC250] or 500/50 mcg [SFC500] twice a day, fluticasone/vilanterol 100/25 mcg once a day [FFVI], budesonide/formoterol 320/9 mcg twice a day [BudeForm]) and SAMA (ipratropium 40 mcg four times a day [Ipra]) with each other or with placebo were selected if they included adults with stable, moderate-to-very severe COPD. The eligible study treatments were restricted to all combinations at their licensed doses which were available at the time of review. Studies were required to report at least one of the following clinical and health status endpoints: trough FEV_1, transitional dyspnea index (TDI), St George's Respiratory Questionnaire (SGRQ) and safety (frequency of adverse events [AEs]). There was considerable heterogeneity in the definition of exacerbation outcomes across the studies, which limited their ability to be pooled in a network. Most of the earlier studies defined exacerbation by the symptoms (eg, at least 3 days of increased sputum production), while more recent studies defined exacerbation by the treatment received (eg, requiring corticosteroids or hospital admission).

Data extraction and risk of bias assessment

Two authors (MIAA and LET) independently reviewed the search results and assessed the eligibility of the studies for selection. Any disagreements were resolved by discussion to achieve consensus. The data extraction was performed independently using a standard template and checked for discrepancies. Specific data points of interest that were only presented in graphs were extracted using WebPlotDigitizer.[3] Risk of bias was assessed using the Cochrane Collaboration Risk of Bias tool.[4] Domains assessed were random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Biases were reported as high or low or unclear. Assumption checking for homogeneity, similarity and consistency was also conducted.

Data synthesis and analysis

A frequentist random-effects network meta-analysis was performed using the "network" routine within the mvmeta package in Stata 15 statistical software (StataCorp, College Station, TX, USA).[5] Network meta-analysis allows for simultaneous analysis of direct comparisons of interventions (head-to-head) within randomized controlled trials and indirect comparisons across trials based on a common

comparator, provided that the studies included are comparable in terms of treatment effect modifiers. The synthesis of direct and indirect evidence produces a more precise and refined estimate of treatment effectiveness by maximizing the use of available data for all treatments within the network. Direct pairwise comparisons were also conducted using the metan package in Stata.[6]

The primary outcome was trough FEV_1 (in mL); secondary outcomes included were TDI, SGRQ and AEs. For the continuous outcomes (FEV_1, SGRQ and TDI), the mean difference (MD) in the change from baseline values between the two arms was used in the analyses. The minimal clinically important difference (MCID) for FEV_1 is 100 mL.[7,8] The proportions of patients who attained the MCID in TDI (TDI responders, a ≥1 unit increase in TDI)[9] and SGRQ (SGRQ responders, a ≥4 unit decrease in SGRQ score)[10] were also analyzed. Observation time points of 12 and 24 weeks were chosen as they were the two consistently reported time points across the studies. A result was considered significant if the 95% CI did not include 0 or one for the continuous and dichotomous outcomes, respectively. The Surface Under the Cumulative RAnking (SUCRA) curve was obtained to determine the relative probability of a treatment being the best option for each outcome measure.[11]

Possible network inconsistency was assessed using the design-by-treatment model approach described by White.[5] This approach provided a global test for inconsistency, with a *P*-value <0.05 indicating violation of the consistency assumption in the network.

Results

Search and selection results

The electronic database search identified 1,611 citations, of which 1,485 were excluded on abstract review (Figure S1). A further 50 were excluded after reviewing the full-text articles, leaving 74 studies reported by 75 articles included in the final selection.

The 74 studies selected for inclusion were published between 2000 and 2017. The study characteristics are presented in Table 1. Thirty-nine studies (53%) were placebo controlled and 35 were active controlled. Overall, there were more published studies for tiotropium 18 mcg compared to the other agents, given it was the first LAMA licensed for COPD. Most studies (67 studies; 91%) had large sample sizes with >200 participants. All studies included patients aged at least 35 years, with a smoking history of at least 10 packs per year. Six studies only included patients with a prior history of exacerbations, while five studies only included patients without

Table 1 Study characteristics of the included trials in NMA

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Kerwin et al, 2012,[13] ACCORD COPD I	MC, DB, PC	Acl	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	376	√ 12	√ 12	√ 12	√ 12	√ 12	
Rennard et al, 2013,[14] ACCORD COPD II	MC, DB, PC	Acl	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	360	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12
Jones et al, 2012,[15] ATTAIN	MC, DB, PC	Acl	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	548	√ 12 24	√ 12 24	√ 24	√ 12 24	√ 24	

(*Continued*)

Table 1 (*Continued*)

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Lee et al, 2015[16]	MC, DB, PC	Acl	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	263	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12
D'Urzo et al, 2011,[17] GLOW1	MC, DB, PC	Glyco	Placebo	–	–	26 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	822	√ 12 24	√ 24	√ 24	√ 24	√ 24	√ 24
Wang et al, 2015,[18] GLOW7	MC, DB, PC	Glyco	Placebo	–	–	26 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years, symptomatic on at least 4 days of the last 7 days	460	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 24
Chapman et al, 2014,[19] GLOW5	MC, DB, AC	Glyco	Tio18	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	657	√ 12	√ 12		√ 12	√ 12	√ 12
Kerwin et al, 2012,[20] GLOW2	MC, DB with open-label Tio18 arm, AC	Glyco	Placebo	Tio18 (open label)	–	52 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	1,066	√ 12 24	√ 12 24	√ 24	√ 12 24	√ 24	
Ambrosino et al, 2008[21]	MC, DB, PC	Tio18	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	234		√ 12 24		√ 12 24		
Brusasco et al, 2003[22]	MC, DB, PC	Tio18	Placebo	–	–	26 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years	802	√ 24	√ 24	√ 24	√ 24	√ 24	
Casaburi et al, 2000[23]	MC, DB, PC	Tio18	Placebo	–	–	13 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years	470	√ 12					√ 12
Casaburi et al, 2002[24]	MC, DB, PC	Tio18	Placebo	–	–	52 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years	921	√ 12 24	√ 12 24		√ 24		

Chan et al, 2007[25]	MC, DB, PC	Tio18	Placebo	–	–	48 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years, had one or more exacerbations (requiring antibiotics/steroids) in past 2 years	913	√ 12					
Covelli et al, 2005[26]	MC, DB, PC	Tio18	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	196	√ 12					
Donohue et al, 2010[27]	MC, DB with open-label Tio arm, AC	Tio18 (open label)	Placebo	–	–	26 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥20 pack years	833	√ 12 24	√ 12 24	√ 12 24	√ 12 24		
Johansson et al, 2008[28]	MC, DB, PC	Tio18	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≥60% (mild/moderate COPD), smoking ≥10 pack years, MRC dyspnea ≥2	224	√ 12					√ 12
Moita et al, 2008[29]	MC, DB, PC	Tio18	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years. Patients excluded if they had more than one exacerbation in the last year	304	√ 12					√ 12
Niewoehner et al, 2005[30]	MC, DB, PC	Tio18	Placebo	–	–	6 months	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	1,829	√ 12 24					
Freeman et al, 2007,[31] SPRUCE	MC, DB, PC	Tio18	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–65%, smoking ≥10 pack years	395	√ 12					√ 12

(*Continued*)

Table 1 (*Continued*)

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Trooster et al, 2014[32]	MC, DB, PC	Tio18	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred 50%–80%, smoking ≥10 pack years. Patients excluded if on maintenance COPD treatment in the last 6 months	457	√ 12 24					
Tashkin et al, 2008,[33] Celli et al, 2009,[34] UPLIFT	MC, DB, PC	Tio18	Placebo	–	–	4 years	≥40 years old, FEV_1 pred ≤80%, smoking ≥10 pack years	5,993	√ 12 24			√ 24		
Verkindre et al, 2006[35]	MC, DB, PC	Tio18	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤50%, smoking ≥10 pack years, with lung hyperinflation	100	√ 12	√ 12		√ 12	√ 12	
Zhou et al, 2017,[36] Tie-COPD	MC, DB, PC	Tio18	Placebo	–	–	1 year	≥40 years old, FEV_1 pred ≥50%	841	√ 24					
Vincken et al 2002,[37] van Noord et al 2000[38]	MC, DB, AC	Tio18	Ipra	–	–	52 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years	535	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12
Bateman et al, 2010[39]	MC, DB, PC	Tio5	Placebo	–	–	48 weeks	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	1,323	√ 24					
Bateman et al, 2010[40]	MC, DB, PC	Tio5	Placebo	–	–	48 weeks	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	3,991	√ 24			√ 24	√ 24	
Voshaar et al, 2008[41]	MC, DB, AC	Tio5	Ipra	Placebo	–	12 weeks	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	539	√ 12					√ 12
Wise et al, 2013,[42] Wise et al, 2013,[43] Anzueto et al, 2015,[44] TIOSPIR	MC, DB, AC	Tio5	Tio18	–	–	Event-driven trial. Median follow-up 2.3 years	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years	11,405	√ 24					

Trivedi et al, 2014[45]	MC, DB, PC	Umec	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	137	√ 12	√ 12	√ 12	√ 12		√ 12
Feldman et al, 2016[46]	MC, DB, PC	Umec	Tio18	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	1,017	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12
Rheault et al, 2015[47]	MC, open label, AC	Umec	Glyco	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	1,034	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12
D'Urzo et al, 2014,[48] AUGMENT	MC, DB, AC	AclForm	Acl	Placebo	–	24 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	1,015	√ 12 24	√ 24	√ 12 24	√ 24	√ 12 24	
Singh et al, 2014,[49] ACLIFORM	MC, DB, AC	AclForm	Acl	Placebo	–	24 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	964	√ 12 24	√ 24	√ 24	√ 24		
Vogelmeier et al, 2016,[50] AFFIRM	MC, DB, AC	AclForm	SFC500	–	–	24 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years, CAT score ≥10	933		√ 24	√ 24		√ 24	√ 24
Bateman et al, 2013,[51] SHINE	MC, DB with open-label Tio18 arm, AC	IndaGlyco	Glyco	Placebo	Tio18 (open label)	26 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years, symptomatic on at least 4 days of the last 7 days	1,659	√ 12 24	√ 12 24	√ 24	√ 24	√ 24	√ 24

(*Continued*)

Table 1 (*Continued*)

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Dahl et al, 2013,[52] ENLIGHTEN	MC, DB, PC	IndaGlyco	Placebo	–	–	52 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years, symptomatic on at least 4 days of the last 7 days	339	√ 12 24					
Vogelmeier et al, 2013,[53] ILLUMINATE	MC, DB, AC	IndaGlyco	SFC500	–	–	26 weeks	≥40 years old, FEV_1 pred 40%–80%, smoking ≥10 pack years. Patients excluded if they had more than one exacerbation in the last year	523	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 24
Wedzicha et al, 2016,[54] FLAME	MC, DB, AC	IndaGlyco	SFC500	–	–	52 weeks	≥40 years old, FEV_1 pred 25%–60%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2, had one or more exacerbations (requiring antibiotics/steroids) in the last year	3,362	√ 12 24			√ 12 24		
Zhong et al, 2015,[55] LANTERN	MC, DB, AC	IndaGlyco	SFC500	–	–	26 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2. Patients excluded if they had more than one exacerbation (requiring antibiotics/steroids) in the last year	744	√ 12 24	√ 12 24		√ 12 24		√ 24

Wedzicha et al, 2013,[56] SPARK	MC, DB with open-label Tio arm, AC	IndaGlyco	Glyco	Tio18 (open label)	–	64 weeks	≥40 years old, FEV_1 pred ≤50%, smoking ≥10 pack years, had one or more exacerbations (requiring antibiotics/ steroids) in the past year	2,224	√ 12 24			√ 12 24	√ 12 24	
Singh et al, 2015,[57] OTEMTO 1	MC, DB, AC	TioOlo	Tio5	Placebo	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	612	√ 12	√ 12		√ 12	√ 12	√ 12
Singh et al, 2015,[57] OTEMTO 2	MC, DB, AC	TioOlo	Tio5	Placebo	–	12 weeks	≥40 years old, FEV_1 pred 30%–80%, smoking ≥10 pack years	607	√ 12	√ 12		√ 12	√ 12	√ 12
Buhl et al, 2015,[58] Buhl et al, 2017,[59] TONADO1	MC, DB, AC	TioOlo	Tio5	–	–	52 weeks	≥40 years old, FEV_1 pred ≤80%, smoking ≥10 pack years	1,049	√ 12 24			√ 24	√ 24	
Buhl et al, 2015,[58] Buhl et al, 2017,[59] TONADO2	MC, DB, AC	TioOlo	Tio5	–	–	52 weeks	≥40 years old, FEV_1 pred ≤80%, smoking ≥10 pack years	1,013	√ 12 24			√ 24	√ 24	
Kerwin et al, 2017[60]	MC, DB, AC	UmecVil	Umec	–	–	12 weeks	≥40 years old, FEV_1 pred 50%–70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 1, and were prescribed with Tio for at least 3 months. Patients were excluded if they had more than two exacerbations in the last year	494	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12

(*Continued*)

Table 1 (*Continued*)

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Siler et al, 2016[61]	MC, DB, PC	UmecVil	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	496	√ 12			√ 12	√ 12	√ 12
Zheng et al, 2015[62]	MC, DB, PC	UmecVil	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	387	√ 12 24	√ 12 24	√ 24	√ 24	√ 24	√ 12
Donohue et al, 2013[63]	MC, DB, AC	UmecVil	Umec	Placebo	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	1,532	√ 12 24	√ 12 24	√ 24	√ 24	√ 24	√ 24
Decramer et al, 2014,[64] study 1	MC, DB, AC	UmecVil	Tio18	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	420	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 24
Decramer et al, 2014,[64] study 2	MC, DB, AC	UmecVil	Tio18	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	432	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 12 24	√ 24
Maleki-Yazdi et al, 2014[65]	MC, DB, AC	UmecVil	Tio18	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	905	√ 12 24			√ 12 24	√ 12 24	√ 24
Donohue et al, 2015,[66] study 1	MC, DB, AC	UmecVil	SFC250	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, mMRC symptoms scale ≥grade 2	707	√ 12	√ 12		√ 12		√ 12

Donohue et al, 2015,[66] study 2	MC, DB, AC	UmecVil	SFC250	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, mMRC symptoms scale ≥grade 2	700	√ 12	√ 12		√ 12		√ 12
Singh et al, 2015[67]	MC, DB, AC	UmecVil	SFC500	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2. Patients were excluded if they had any exacerbation in the last year	716	√ 12	√ 12	√ 12	√ 12	√ 12	√ 12
Tashkin et al, 2008[68]	MC, DB, PC	BudeForm	Placebo	–	–	6 months	≥40 years old, FEV_1 pred ≤50%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2, had one or more exacerbations (requiring antibiotics/steroids) within 1–12 months before screening	577	√ 24			√ 24	√ 24	√ 24
Rennard et al, 2009[69]	MC, DB, PC	BudeForm	Placebo	–	–	12 months	≥40 years old, FEV_1 pred ≤50%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2, had one or more exacerbations (requiring antibiotics/steroids) within 1–12 months before screening	975	√ 24					
Bhatt et al, 2017[70]	MC, DB, PC	FFVI	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years	276	√ 12 24			√ 12 24		

(*Continued*)

Table 1 (*Continued*)

Author, year, study name	Study design	Treatments				Trial duration	Inclusion criteria	No of participants	Outcome measured					
									FEV_1 (weeks)	TDI (weeks)	TDI resp (weeks)	SGRQ (weeks)	SGRQ resp (weeks)	AE (weeks)
Kerwin et al, 2013[71]	MC, DB, PC	FFVI	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	413	√ 24					
Martinez et al, 2013[72]	MC, DB, PC	FFVI	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, mMRC symptoms scale ≥grade 2	409	√ 12 24					
Covelli et al, 2016[73]	MC, DB, AC	FFVI	Tio18	–	–	12 weeks	≥40 years old, FEV_1 pred 30%–70%, smoking ≥10 pack years, at least one cardiovascular risk factor	623	√ 12			√ 12	√ 12	√ 12
Pepin et al, 2014[74]	MC, DB, AC	FFVI	Tio18	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, measured aPWV ≥11.0 m/s	257	√ 12			√ 12		√ 12
Dransfield et al, 2014,[75] study 1	MC, DB, AC	FFVI	SFC250	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years	519	√ 12					
Dransfield et al, 2014,[75] study 2	MC, DB, AC	FFVI	SFC250	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years	511	√ 12					
Dransfield et al, 2014,[75] study 3	MC, DB, AC	FFVI	SFC250	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years	828	√ 12					
Agustí et al, 2014[76]	MC, DB, AC	FFVI	SFC500	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, smoking ≥10 pack years, ≥1 moderate/severe exacerbation in the past 3 years	528	√ 12			√ 12		√ 12

Asai et al, 2015[77]	MC, DB, PC	SFC250	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred 40%–80%	56	√ 12					√ 12
Hanania et al, 2003[78]	MC, DB, PC	SFC250	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥20 pack years, moderate dyspnea	363	√ 12 24					
Mahler et al, 2002[79]	MC, DB, PC	SFC500	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥20 pack years, chronic sputum production for 3 months of a year for 2 years	354	√ 12 24					√ 24
Calverley et al, 2007,[80] Jenkins et al, 2009,[82] Jones et al, 2011,[81] TORCH	MC, DB, PC	SFC500	Placebo	–	–	3 years	≥40 years old, FEV_1 pred ≤60%, smoking ≥10 pack years	6,112	√ 24			√ 24		
Zheng et al, 2007[83]	MC, DB, PC	SFC500	Placebo	–	–	24 weeks	≥40 years old, FEV_1 pred 25%–69%	445	√ 24			√ 24		√ 24
Cazzola et al, 2007[84]	MC, DB, AC	SFC500	Tio18	–	–	12 weeks	≥50 years old, FEV_1 pred ≤80%, smoking ≥20 pack years	60	√ 12					√ 12
Perng et al, 2009[85]	Single-center, open label, AC	SFC500	Tio18	–	–	12 weeks	≥40 years old, FEV_1 pred ≤80%, smoking ≥20 pack years, newly diagnosed or not on medication for 3 months	67	√ 12			√ 12		
Dahl et al, 2001[86]	MC, DB, PC	Ipra	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤70%, symptomatic on at least 4 days of the last 7 days	394				√ 12		√ 12
Taylor et al, 2001[87]	MC, DB, PC	Ipra	Placebo	–	–	12 weeks	≥40 years old, FEV_1 pred ≤65%, smoking ≥10 pack years	187						√ 12

Abbreviations: AC, active-controlled trials; Acl, aclidinium; AclForm, aclidinium/formoterol; AE, adverse event; aPWV, arterial pulse wave velocity; DB, double-blind; FEV_1 pred, FEV_1 percentage predicted; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; MC, multicenter; NMA, network meta-analysis; PC, placebo-controlled trials; resp, responder; SFC250, fluticasone/salmeterol 250/50 mcg; SFC500, fluticasone/salmeterol 500/50 mcg; TDI, transition dyspnea index; SGRQ, St George's respiratory questionnaire; Tio5, tiotropium 5 mcg; Tio18, tiotropium 18 mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

any exacerbation history. The remaining 63 studies did not specify exacerbation history in their inclusion/exclusion criteria. The most commonly reported primary outcome across the studies was lung function (trough FEV_1); limited data for other patient-related outcomes (TDI and SGRQ) were also available. Data from the intention-to-treat and full analysis set for all trials were extracted. The network plots for trough FEV_1 at weeks 12 and 24 are shown in Figure 1.

A total of 74,832 patients were included in the 74 studies. The key patient characteristics and assessment of risk of bias for each study are presented in Table 2. Mean ages ranged from 61 to 73 years; proportion of males and current smokers ranged from 48% to 99% and from 22% to 88%, respectively. The mean FEV_1 predicted at baseline ranged from 35% to 78%. Majority of the studies were assessed to have low or unclear risk of bias. Inconsistency models were not significant for all outcomes, implying that the consistency assumption was not violated.

Efficacy

Trough FEV_1 change from baseline

Trough FEV_1 results were reported in 59 studies at week 12 and in 39 studies at week 24. All LAMAs, LAMA/LABAs and ICS/LABAs led to significantly greater improvement in trough FEV_1 compared to SAMA and placebo at weeks 12 and 24 (Tables 3 and 4). While some of the comparisons among LAMAs, LAMA/LABAs and ICS/LABAs showed statistical significance, the results were generally not clinically significant with respect to an MCID of 100 mL. For example, among the LAMAs, Umec led to statistically significant improvement in trough FEV_1 at week 12 compared to Tio18 (mean difference [MD] of 37 mL, 95% CI 13–62 mL) and Glyco (MD 31 mL, 95% CI 6–57 mL). However, there were no significant differences in trough FEV_1 for all LAMA vs LAMA comparisons at week 24. Among the LAMA/LABAs, there were no significant differences between IndaGlyco, TioOlo and UmecVil at weeks 12 and 24. IndaGlyco and UmecVil showed statistically significant improvement in FEV_1 when compared to AclForm at both weeks 12 and 24. The MDs ranged from 43 to 59 mL (point estimates). Statistically significant improvement at weeks 12 and 24 was also seen for IndaGlyco, TioOlo and UmecVil compared to all LAMAs. The MDs ranged from 48 to 88 mL (point estimates). On the other hand, AclForm exhibited no significant difference compared to any LAMAs. Among the ICS/LABAs, the results were mixed with some showing significant differences between the agents (FFVI vs SFC250 at week 12, MD 40 mL; FFVI vs BudeForm at week 24, MD 58 mL; BudeForm vs SFC250 at week 24, MD −82 mL). When compared to the LAMAs, ICS/LABAs had a similar effect on FEV_1 at week 12, except SFC250 vs Umec (MD −52 mL, 95% CI −85 to −18 mL, favoring Umec) and FFVI vs Tio18 (MD 25 mL, 95% CI 4–47 mL, favoring FFVI). At week 24, ICS/LABAs were generally comparable to the LAMAs, except BudeForm vs Glyco (MD −40 mL, 95% CI −77 to 3 mL, favoring Glyco) and Tio18 (MD −35 mL, 95% CI −69

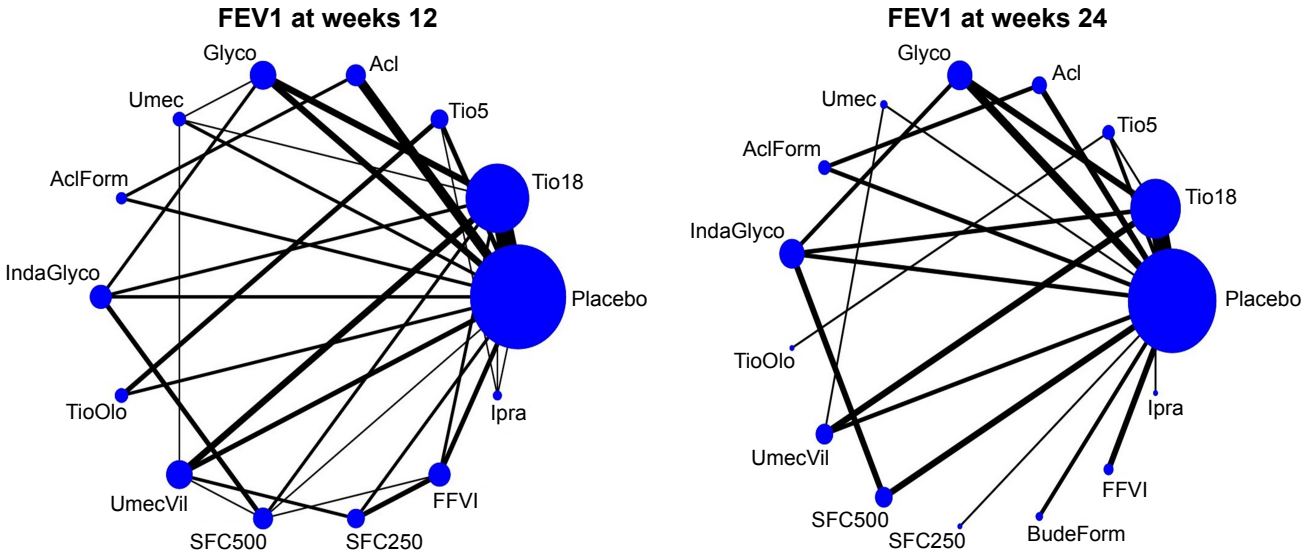

Figure 1 Evidence network of available trials showing direct comparisons of agents with respect to lung function (trough FEV_1) at weeks 12 and 24.
Note: The size of each treatment node is weighted by the number of studies.
Abbreviations: Acl, aclidinium; AclForm, aclidinium/formoterol; BudeForm, budesonide/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; SFC250, fluticasone/salmeterol 250/50 mcg; SFC500, fluticasone/salmeterol 500/50 mcg; Tio5, tiotropium 5 mcg; Tio18, tiotropium 18 mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table 2 Baseline characteristics and risk of bias of the included trials in NMA

Study, year	Proportion of males (%)	Mean age (years)	Proportion of smokers (%)	Mean COPD duration (years)	FEV_1 predicted (%)	Proportion with exacerbation history (%)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
							Random sequence generation	Allocation concealment?	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting
Kerwin et al, 2012,[13] ACCORD COPD I	52	65	44	NR	54	NR	Unclear	Unclear	Unclear	Unclear	Low	Low
Rennard et al, 2013,[14] ACCORD COPD II	53	62	53	NR	53	NR	Unclear	Unclear	Unclear	Unclear	Low	Low
Jones et al, 2012,[15] ATTAIN	68	62	54	NR	56	34	Unclear	Unclear	Unclear	Low	Low	Low
Lee et al, 2015[16]	98	68	NR	NR	53	NR	Low	Low	Low	Unclear	Low	Low
D'Urzo et al, 2011,[17] GLOW1	82	64	34	6.2	55	21.20	Unclear	Unclear	Unclear	High	Low	Low
Wang et al, 2015,[18] GLOW7	96	65	22	4.4	51	23.70	Unclear	Unclear	Unclear	Unclear	Low	Low
Chapman et al, 2014,[19] GLOW5	74	63	45	6.3	54	23.60	Low	Low	Low	Low	Low	Low
Kerwin et al, 2012,[20] GLOW2	64	64	45	6.6	56	26.50	Low	Low	High	High	Low	Low
Ambrosino et al, 2008[21]	84	67	NR	11.1	41	NR	Unclear	Unclear	Low	Low	Low	Low
Brusasco et al, 2003[22]	77	64	NR	9.4	39	NR	Unclear	Unclear	Low	Unclear	High	Low
Casaburi et al, 2000[23]	65	65	NR	9.0	39	NR	High	Unclear	Low	Unclear	Low	Low
Casaburi et al, 2002[24]	65	65	NR	8.4	39	NR	Unclear	Unclear	Low	Unclear	High	Low

(*Continued*)

Table 2 (*Continued*)

Study, year	Proportion of males (%)	Mean age (years)	Proportion of smokers (%)	Mean COPD duration (years)	FEV_1 predicted (%)	Proportion with exacerbation history (%)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
							Random sequence generation	Allocation concealment?	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting
Chan et al, 2007[25]	60	67	30	9.9	39	100	Unclear	Unclear	Low	Unclear	High	Low
Covelli et al, 2005[26]	58	65	39	10.2	39	NR	Unclear	Unclear	Unclear	Unclear	High	Low
Donohue et al, 2010[27]	63	64	NR	NR	55	NR	Low	Low	High	High	High	Low
Johansson et al, 2008[28]	48	61	60	4.8	73	NR	Unclear	Unclear	Low	Unclear	Unclear	Low
Moita et al, 2008[29]	NR	NR	27	NR	41	NR	Unclear	Unclear	Low	Unclear	Low	Low
Niewoehner et al, 2005[30]	99	68	30	12.0	36	NR	Low	Unclear	Low	Low	High	Low
Freeman et al, 2007,[31] SPRUCE	54	65	NR	NR	49	NR	Low	Unclear	Low	Unclear	High	Low
Trooster et al, 2014[32]	68	62	60	NR	66	NR	Unclear	Unclear	Low	Unclear	Low	Low
Tashkin et al, 2008,[33] Celli et al, 2009,[34] UPLIFT	75	65	30	9.9	48	NR	Low	Low	Low	Low	Low	Low
Verkindre et al, 2006[35]	94	61	29	9.4	35	NR	Unclear	Unclear	Low	Unclear	Unclear	Low
Zhou et al, 2017,[36] Tie-COPD	85	64	41	0.6	78	NR	Low	Low	Low	Low	Low	Low
Vincken et al 2002,[37] van Noord et al 2000[38]	85	64	NR	11.3	41	NR	Unclear	Unclear	Low	Unclear	High	Low
Bateman et al, 2010[39]	74	65	37	8.9	46	NR	Unclear	Unclear	Low	Unclear	High	Low
Bateman et al, 2010[40]	78	65	36	8.2	45	NR	Low	Low	Low	Low	High	Low

Voshaar et al, 2008[41]	68	64	40	10	41	NR	Unclear	Unclear	Low	Low	High	Low
Wise et al, 2013,[42] Wise et al, 2013,[43] Anzueto et al, 2015,[44] TIOSPIR	61	66	37	NR	48	NR	Low	Low	Low	Low	Low	Low
Trivedi et al, 2014[45]	62	63	54	NR	46	NR	Low	Low	Low	Unclear	Low	Low
Feldman et al, 2016[46]	72	64	51	NR	51	NR	Low	Low	Low	Unclear	Low	Low
Rheault et al, 2015[47]	69	64	48	NR	51	32.5	Low	Low	High	High	Low	Low
D'Urzo et al, 2014,[48] AUGMENT	53	64	52	NR	54	NR	Unclear	Unclear	Low	Low	High	Low
Singh et al, 2014,[49] ACLIFORM	68	63	47	NR	54	NR	Low	Low	Low	Low	High	Low
Vogelmeier et al, 2016,[50] AFFIRM	65	63	NR	NR	53	32	Unclear	Unclear	Unclear	Unclear	Low	Low
Bateman et al, 2013,[51] SHINE	75	64	40	6.2	55	24.90	Low	Low	High	High	Low	Low
Dahl et al, 2013,[52] ENLIGHTEN	77	63	45	5.64	57	34	Low	Unclear	Low	Unclear	High	Low
Vogelmeier et al, 2013,[53] ILLUMINATE	71	63	48	7.0	60	0	Low	Low	Low	Low	Low	Low
Wedzicha et al, 2016,[54] FLAME	76	65	40	7.3	44	100	Low	Low	Low	Low	Low	Low
Zhong et al, 2015,[55] LANTERN	95	65	25	5.2	52	20.8	Low	Low	Low	Low	Low	Low
Wedzicha et al, 2013,[56] SPARK	74	63	38	7.2	37	100	Low	Low	High	High	Low	Low

(*Continued*)

Table 2 (*Continued*)

Study, year	Proportion of males (%)	Mean age (years)	Proportion of smokers (%)	Mean COPD duration (years)	FEV_1 predicted (%)	Proportion with exacerbation history (%)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
							Random sequence generation	Allocation concealment?	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting
Singh et al, 2015,[57] OTEMTO 1	60	65	49	NR	55	NR	Unclear	Unclear	Low	Unclear	Low	Low
Singh et al, 2015,[57] OTEMTO 2	63	65	46	NR	55	NR	Unclear	Unclear	Low	Unclear	Low	Low
Buhl et al, 2015,[58] Buhl et al, 2017,[59] TONADO1	72	64	37	NR	50	NR	Low	Unclear	Low	Unclear	High	Low
Buhl et al, 2015,[58] Buhl et al, 2017,[59] TONADO2	72	64	37	NR	50	NR	Low	Unclear	Low	Unclear	High	Low
Kerwin et al, 2017[60]	66	64	50	NR	60	34	Low	Low	Low	Low	Low	Low
Siler et al, 2016[61]	59	63	54	NR	47	NR	Low	Low	Low	Unclear	Low	Low
Zheng et al, 2015[62]	93	64	29	NR	47	NR	Low	Low	Low	Unclear	Low	Low
Donohue et al, 2013[63]	71	63	51	NR	47	NR	Low	Low	Low	Unclear	Low	Low
Decramer et al, 2014,[64] study 1	68	64	47	NR	48	48.6	Low	Low	Low	Unclear	Low	Low
Decramer et al, 2014,[64] study 2	68	64	45	NR	48	34.5	Low	Low	Low	Unclear	Low	Low
Maleki-Yazdi et al, 2014[65]	68	62	57	NR	46	NR	Low	Low	Low	Unclear	Low	Low
Donohue et al, 2015,[66] study 1	70	63	43	NR	49	NR	Low	Low	Low	Low	Low	Low

Donohue et al, 2015,[66] study 2	76	64	52	NR	50	NR	Low	Low	Low	High	Low
Singh et al, 2015[67]	72	62	59	NR	51	0	Low	Low	Unclear	Low	Low
Tashkin et al, 2008[68]	68	63	42	NR	40	100	Low	Unclear	Unclear	Low	Low
Rennard et al, 2009[69]	64	63	41	10.5	40	100	Unclear	Unclear	Unclear	Low	Low
Bhatt et al, 2017[70]	81	68	37	NR	NR	NR	Low	Low	Unclear	Low	Low
Kerwin et al, 2013[71]	67	62	54	NR	48	22	Low	Low	Unclear	Low	Low
Martinez et al, 2013[72]	72	62	53	NR	48	22	Low	Low	Unclear	Low	Low
Covelli et al, 2016[73]	65	63	52	NR	50	55	Low	Low	Low	Low	Low
Pepin et al, 2014[74]	86	67	46	NR	46	NR	Unclear	Low	Low	Low	Unclear
Dransfield et al, 2014,[75] study 1	69	61	55	NR	48	NR	Low	Low	Unclear	Low	Low
Dransfield et al, 2014,[75] study 2	69	61	55	NR	49	NR	Low	Low	Unclear	Low	Low
Dransfield et al, 2014,[75] study 3	69	61	55	NR	48	NR	Low	Low	Unclear	Low	Low
Agustí et al, 2014[76]	82	63	NR	NR	48	89	Low	Unclear	Unclear	Low	Unclear
Asai et al, 2015[77]	98	63	50	NR	NR	NR	Low	Unclear	Low	Low	Low
Hanania et al, 2003[78]	64	64	45	NR	42	NR	Unclear	Unclear	Low	Low	Low
Mahler et al, 2002[79]	69	63	50	NR	41	NR	Unclear	Unclear	Low	Unclear	Low

(Continued)

Table 2 (*Continued*)

Study, year	Proportion of males (%)	Mean age (years)	Proportion of smokers (%)	Mean COPD duration (years)	FEV_1 predicted (%)	Proportion with exacerbation history (%)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
							Random sequence generation	Allocation concealment?	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting
Calverley et al, 2007,[80] Jenkins et al, 2009,[82] Jones et al, 2011,[81] TORCH	76	65	43	NR	44	NR	Unclear	Unclear	Low	Unclear	Low	Low
Zheng et al, 2007[83]	89	66	22	NR	47	NR	Unclear	Unclear	Low	Unclear	Low	Low
Cazzola et al, 2007[84]	90	65	88	NR	38	NR	Unclear	Unclear	Low	Unclear	Low	Low
Perng et al, 2009[85]	94	73	61	NR	58	NR	Low	Unclear	High	High	Low	Low
Dahl et al, 2001[86]	74	63	46	8.0	45	NR	Unclear	Unclear	Low	Low	High	Low
Taylor et al, 2001[87]	63	66	NR	9.7	42	NR	Low	Unclear	Low	Unclear	Low	Low

Abbreviations: NMA, network meta-analysis; NR; not reported.

Table 3 Treatment effects on FEV_1 at week 12 – NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)	Direct evidence													
	Placebo	**−54 (−99.08, −8.92)**	**−134.86 (−163.11, −106.62)**	−92.31 (−220.57, 35.95)	**−199.00 (−253.88, −144.12)**	**−161.86 (−201.19, −122.53)**	**−164.00 (−190.33, −137.67)**	**−199.93 (−265.25, −134.62)**	**−136.51 (−160.74, −112.29)**	**−137.62 (−169.5, 105.73)**	**−117.16 (−135.37, −98.95)**	**−113.02 (−127.61, −98.43)**	**−127.32 (−150.06, −104.58)**	**−114.47 (−130.59, −98.36)**
	−8.76 (−44.27, 26.74)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**−64.00 (−109.08, −18.92)**	**−139.20 (−176.44, −101.96)**
	−130.18 (−151.46, −108.90)	**−121.42 (−162.09, −80.74)**	FFVI	**40.91 (13.87, 67.95)**	23.00 (−20.12, 66.12)	NA	NA	NA	NA	NA	NA	NA	NA	12.40 (−16.82, 41.61)
	−90.44 (−115.14, −65.74)	**−81.68 (−124.33, −39.03)**	**39.74 (15.51, 63.96)**	SFC250	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	−118.55 (−140.12, −96.98)	**−109.78 (−150.35, −69.21)**	11.64 (−14.81, 38.08)	−28.10 (−57.80, 1.60)	SFC500	**−90.00 (−125.28, −54.72)**	NA	NA	NA	NA	NA	NA	NA	**41.48 (16.46, 66.49)**
	−183.67 (−201.93, −165.41)	**−174.91 (−213.90, −135.91)**	**−53.49 (−78.10, −28.88)**	**−93.23 (−118.04, −68.41)**	**−65.12 (−88.95, −41.30)**	UmecVil	NA	NA	NA	**56.00 (24.64, 87.36)**	NA	NA	NA	**96.66 (76.84, 116.49)**
	−164.17 (−194.44, −133.90)	**−155.41 (−199.04, −111.77)**	−33.99 (−70.72, 2.74)	**−73.73 (−112.45, −35.01)**	**−45.63 (−82.38, −8.88)**	19.50 (−15.43, 54.42)	TioOlo	NA	NA	NA	NA	NA	**49.13 (22.85, 75.42)**	NA
	−192.99 (−213.93, −172.06)	**−184.23 (−224.48, −143.98)**	**−62.81 (−89.97, −35.66)**	**−102.55 (−132.61, −72.49)**	**−74.45 (−93.95, −54.95)**	−9.32 (−33.70, 15.05)	−28.82 (−65.22, 7.57)	IndaGlyco	NA	NA	**89.35 (50.17, 128.53)**	NA	NA	**84.13 (54.78, 113.48)**
	−134.00 (−164.06, −103.94)	**−125.24 (−171.76, −78.71)**	−3.82 (−40.63, 32.99)	**−43.56 (−82.43, −4.68)**	−15.46 (−52.42, 21.51)	**49.67 (14.53, 84.81)**	30.17 (−12.47, 72.82)	**58.99 (22.39, 95.60)**	AclForm	NA	NA	19.93 (−2.91, 42.76)	NA	NA
	−142.27 (−166.87, −117.67)	**−133.50 (−175.84, −91.16)**	−12.09 (−42.99, 18.81)	**−51.82 (−84.71, −18.94)**	−23.72 (−53.95, 6.51)	**41.40 (14.57, 68.24)**	21.91 (−16.77, 60.58)	**50.73 (21.03, 80.43)**	−8.27 (−47.09, 30.55)	Umec	**33 (5.56, 60.44)**	NA	NA	**53 (25.56, 80.44)**
	−110.92 (−127.58, −94.27)	**−102.16 (−140.51, −63.81)**	19.26 (−6.18, 44.69)	−20.48 (−48.81, 7.85)	7.62 (−16.37, 31.62)	**72.75 (50.48, 95.01)**	**53.25 (18.98, 87.52)**	**82.07 (59.86, 104.29)**	23.08 (−11.27, 57.43)	**31.34 (5.82, 56.87)**	Glyco	NA	NA	0.95 (−13.22, 15.12)
	−111.95 (−131.74, −92.17)	**−103.19 (−143.84, −62.54)**	18.23 (−10.76, 47.21)	−21.51 (−53.05, 10.04)	6.59 (−22.56, 35.75)	**71.72 (44.92, 98.52)**	**52.22 (16.11, 88.33)**	**81.04 (52.35, 109.74)**	22.05 (−7.64, 51.73)	30.31 (−1.17, 61.80)	−1.03 (−26.82, 24.76)	Acl	NA	NA

(*Continued*)

Table 3 (*Continued*)

	Direct evidence												
	−112.16 (−139.57, −84.76)	**−103.40 (−143.61, −63.19)**	18.02 (−16.52, 52.55)	−21.72 (−58.46, 15.02)	6.38 (−28.27, 41.03)	**71.51 (38.80, 104.21)**	**52.01 (26.94, 77.08)**	**80.83 (46.57, 115.09)**	21.84 (−18.84, 62.51)	30.10 (−6.53, 66.74)	−1.24 (−33.12, 30.64)	−0.21 (−34.00, 33.58)	Tio5	NA
	−104.92 (−116.81, −93.02)	**−96.15 (−131.73, −60.58)**	**25.26 (3.71, 46.81)**	−14.48 (−39.53, 10.58)	13.63 (−7.02, 34.27)	**78.75 (61.21, 96.29)**	**59.25 (27.14, 91.37)**	**88.08 (68.02, 108.13)**	29.08 (−3.23, 61.39)	**37.35 (13.17, 61.53)**	6.00 (−10.53, 22.54)	7.03 (−15.98, 30.04)	7.24 (−22.24, 36.73)	Tio18

Notes: Comparisons between treatments should be read from left to right. The MD in milliliters with 95% CI are shown in the cell. MD >0 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in bold. The lower triangle refers to the area below the colored boxes, correspondingly the upper triangle is the area above the colored boxes.

Abbreviations: Acl, aclidinium; AclForm, aclidinium/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; MD, mean difference; NA, results not available; NMA, network meta-analysis; SFC250, fluticasone/salmeterol 250/50 mcg; SFC500, fluticasone/salmeterol 500/50 mcg; Tio5, tiotropium 5 mcg; Tio18, tiotropium 18 mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

Table 4 Treatment effects on FEV_1 at week 24 – NMA results: combining direct and indirect evidence (lower triangle) and direct evidence (upper triangle)

NMA results (combining direct and indirect estimates)															
	Direct evidence														
	Placebo	NA	**−137.07 (−169.35, −104.78)**	**−79.41 (−101.99, −56.83)**	**−161.00 (−223.72, −98.28)**	**−128.66 (−207.25, −50.07)**	**−159.39 (−187.78, −131.00)**	NA	**−185.39 (−228.68, −142.09)**	**−138.87 (−156.97, −120.77)**	**−115.00 (−154.20, −75.80)**	**−125.22 (−142.65, −107.79)**	**−115.24 (−131.16, −99.32)**	**−114.43 (−134.93, −93.93)**	**−120.41 (−133.99, −106.83)**
	48.56 (−3.08, 100.19)	Ipra	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**−161.20 (−200.40, −122.00)**
	−137.27 (−174.32, −100.21)	**−185.82 (−249.39, −122.26)**	FFVI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	−79.45 (−111.25, −47.66)	**−128.01 (−188.65, −67.37)**	**57.81 (8.98, 106.64)**	BudeForm	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	−161.00 (−231.13, −90.87)	**−209.56 (−296.65, −122.46)**	−23.73 (−103.06, 55.59)	**−81.55 (−158.55, −4.54)**	SFC250	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

−95.54 (−117.97, −73.11)	**−144.09 (−199.91, −88.28)**	41.73 (−1.58, 85.03)	−16.08 (−54.99, 22.83)	65.46 (−8.17, 139.10)	SFC500	NA	NA	**−86.15 (−98.06, −74.24)**	NA	NA	NA	NA	NA	NA
−185.89 (−210.29, −161.49)	**−234.45 (−289.94, −178.95)**	**−48.62 (−93.00, −4.24)**	**−106.44 (−146.52, −66.36)**	−24.89 (−99.15, 49.37)	**−90.35 (−123.15, −57.56)**	UmecVil	NA	NA	NA	**52.00 (16.72, 87.28)**	NA	NA	NA	**92.02 (61.25, 122.78)**
−166.97 (−208.69, −125.25)	**−215.53 (−281.26, −149.80)**	−29.71 (−85.52, 26.11)	**−87.52 (−139.98, −35.06)**	−5.97 (−87.58, 75.64)	**−71.44 (−118.97, −23.90)**	18.92 (−28.77, 66.61)	TioOlo	NA	NA	NA	NA	NA	**60.00 (42.36, 77.64)**	NA
−182.82 (−203.61, −162.03)	**−231.37 (−285.98, −176.77)**	**−45.55 (−88.05, −3.06)**	**−103.37 (−141.36, −65.37)**	−21.82 (−94.97, 51.33)	**−87.28 (−107.78, −66.78)**	3.07 (−27.91, 34.05)	−15.85 (−62.17, 30.48)	IndaGlyco	NA	NA	**86.15 (68.77, 103.54)**	NA	NA	**76.09 (57.73, 94.46)**
−139.37 (−167.96, −110.78)	**−187.92 (−246.93, −128.91)**	−2.10 (−48.91, 44.70)	**−59.91 (−102.67, −17.15)**	21.63 (−54.11, 97.37)	**−43.83 (−80.21, −7.45)**	**46.52 (8.96, 84.08)**	27.60 (−22.94, 78.15)	**43.45 (8.10, 78.80)**	AclForm	NA	NA	**26.94 (2.72, 51.17)**	NA	NA
−125.54 (−169.40, −81.68)	**−174.10 (−241.08, −107.11)**	11.73 (−45.70, 69.15)	−46.09 (−100.26, 8.09)	35.46 (−47.26, 118.18)	−30.00 (−79.17, 19.16)	**60.35 (17.31, 103.39)**	41.43 (−18.78, 101.65)	**57.28 (9.13, 105.42)**	13.83 (−38.51, 66.17)	Umec	NA	NA	NA	NA
−119.24 (−138.18, −100.30)	**−167.79 (−221.71, −113.88)**	18.03 (−23.58, 59.64)	**−39.78 (−76.79, −2.78)**	41.76 (−30.88, 114.41)	−23.70 (−50.33, 2.93)	**66.65 (36.86, 96.44)**	**47.73 (2.13, 93.34)**	**63.58 (40.20, 86.96)**	20.13 (−14.18, 54.44)	6.30 (−41.09, 53.69)	Glyco	NA	NA	8.18 (−26.31, 42.67)
−115.15 (−140.60, −89.70)	**−163.71 (−221.26, −106.15)**	22.12 (−22.84, 67.07)	−35.70 (−76.42, 5.03)	45.85 (−28.76, 120.46)	−19.61 (−53.56, 14.33)	**70.74 (35.50, 105.98)**	**51.82 (2.97, 100.67)**	**67.67 (34.81, 100.53)**	24.22 (−7.41, 55.85)	10.39 (−40.31, 61.09)	4.09 (−27.64, 35.82)	Acl	NA	NA
−108.33 (−129.58, −87.07)	**−156.88 (−211.98, −101.78)**	28.94 (−13.79, 71.67)	−28.87 (−67.12, 9.37)	52.67 (−20.61, 125.96)	−12.79 (−43.78, 18.20)	**77.57 (46.08, 109.05)**	**58.65 (22.70, 94.59)**	**74.49 (45.23, 103.76)**	31.04 (−4.55, 66.63)	17.21 (−31.17, 65.60)	10.91 (−17.15, 38.98)	6.82 (−26.30, 39.95)	Tio5	NA
−114.07 (−126.34, −101.80)	**−162.63 (−212.80, −112.45)**	23.20 (−15.84, 62.23)	**−34.62 (−68.70, −0.54)**	46.93 (−24.27, 118.13)	−18.53 (−42.79, 5.72)	**71.82 (47.97, 95.68)**	**52.90 (10.29, 95.52)**	**68.75 (47.19, 90.30)**	25.30 (−5.80, 56.40)	11.47 (−32.97, 55.91)	5.17 (−14.50, 24.84)	1.08 (−27.16, 29.32)	−5.74 (−28.72, 17.23)	Tio18

Notes: Comparisons between treatments should be read from left to right. The MD in milliliters with 95% CI are shown in the cell. MD >0 favors the column-defining treatment (lower triangle) and the row-defining treatment (upper triangle). Statistically significant results in bold.

Abbreviations: Acl, aclidinium; AclForm, aclidinium/formoterol; BudeForm, budesonide/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; MD, mean difference; NA, results not available; NMA, network meta-analysis; SFC250, fluticasone/salmeterol 250/50 mcg; SFC500, fluticasone/salmeterol 500/50 mcg; Tio5, tiotropium 5 mcg; Tio18, tiotropium 18 mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

to −1 mL favoring Tio18). When compared to the LAMA/LABAs, ICS/LABAs conferred significantly less improvement at weeks 12 and 24. The MDs in improvements in FEV_1 between the ICS/LABAs and LAMA/LABAs were smaller with AclForm vs ICS/LABAs than with the other three LAMA/LABAs (IndaGlyco, TioOlo and UmecVil).

Transition dyspnea index

TDI scores were reported in 28 studies at week 12 and in 19 studies at week 24. Significantly greater improvements in TDI scores were observed with all LAMAs, LAMA/LABAs and ICS/LABAs compared to SAMA and placebo at weeks 12 and 24 (Tables S2 and S3). There were no significant differences between the LAMA/LABAs except UmecVil vs TioOlo at week 12 (MD −0.51, 95% CI −0.94 to −0.07, favoring TioOlo). The difference was not considered to be clinically significant (MCID ≥1 point increase). There were no significant differences in TDI scores between all LAMA–LAMA comparisons at weeks 12 and 24. There were, however, some statistically significant improvements in TDI scores for LAMA/LABAs compared to LAMAs. Nonetheless, the magnitudes of difference in TDI scores were all lower than the MCID of ≥1 unit for these comparisons. Similarly, there were some statistically significant (but not clinically significant) differences when LAMA/LABAs were compared to ICS/LABAs. There were no significant differences in TDI scores when LAMAs were compared to ICS/LABAs at both time points.

In terms of the proportion of TDI score responders (who achieved a minimum of 1-point improvement in TDI score), results were reported in 15 studies at week 12 and in 16 studies at week 24. Study participants treated with LAMAs, LAMA/LABAs or ICS/LABAs were more likely to achieve improvement in TDI score than those receiving placebo or SAMA (Tables S4 and S5). There was some evidence to show that LAMA/LABA treatment had higher odds of achieving TDI score improvement compared to LAMAs (UmecVil vs Tio18 at week 12: OR 1.49, 95% CI 1.16–1.93; IndaGlyco vs Tio18 at week 24: OR 1.45, 95% CI 1.11–1.89; AclForm vs Tio18 at week 24: OR 1.37, 95% CI 1.04–1.80). There were no significant differences in TDI score improvement when ICS/LABAs were compared with LAMAs or LAMA/LABAs.

St George's Respiratory Questionnaire

Health-related quality-of-life (HRQoL) benefits as measured by SGRQ scores were reported in 34 studies at week 12 and in 29 studies at week 24. All LAMAs, LAMA/LABAs and ICS/LABAs showed statistically significant improvement in SGRQ score compared to placebo at week 12; however, the point estimates did not achieve clinical significance (MCID ≥4-point decrease) for SFC250, Acl, Glyco, Tio5 and Tio18 (Table S6). At week 24, only some of the LAMAs and LAMA/LABAs showed statistically significant improvements in HRQoL vs placebo (Table S7), but none of the results reached clinical significance. A similar trend was seen when LAMAs, LAMA/LABAs and ICS/LABAs were compared to SAMA. Within each class, the LAMAs, LAMA/LABAs and ICS/LABAs led to similar HRQoL improvements at weeks 12 and 24. While there were some statistically significant differences between LAMA/LABAs and LAMAs, these differences were not clinically significant.

In terms of the proportion of SGRQ score responders (achieving at least a 4-point reduction in SGRQ), results were reported in 21 studies at week 12 and in 19 studies at week 24. At both time points, all LAMAs, LAMA/LABAs and ICS/LABAs led to a significantly higher proportion of study participants achieving an improvement in SGRQ score compared to placebo (Tables S8 and S9). Relative to SAMA, only IndaGlyco and TioOlo showed a statistically significant difference in SGRQ responders at week 12 (Ipra vs IndaGlyco: OR 0.61, 95% CI 0.40–0.94; Ipra vs TioOlo: OR 0.53, 95% CI 0.33–0.85). There were no significant differences within the LAMA, LAMA/LABA and ICS/LABA classes at weeks 12 and 24 for SGRQ responders; however, some evidence was available to suggest that the LAMA/LABAs led to a higher proportion of SGRQ responder compared to the LAMAs at both weeks 12 and 24.

Adverse events

Incidences of AEs were reported in 17 studies at week 12 and in 27 studies at week 24. There were no significant differences in the proportion of patients who experienced AEs for any comparison at week 12 (Table S10). At week 24, a significantly higher proportion of patients receiving SFC500 had AEs compared to those receiving IndaGlyco (SFC500 vs IndaGlyco: OR 1.34, 95% CI 1.04–1.72; Table S11). This translated to a Number Needed to Harm of 14. No other significant differences with respect to AEs were found in other comparisons.

Ranking of treatments

In general, the LAMA/LABAs ranked the highest among the different drug classes for lung function improvement (FEV_1) at weeks 12 and 24, while placebo and SAMA ranked the lowest. The SUCRA values for LAMA/LABAs

Table 5 SUCRA values for all interventions for each outcome

	FEV_1		TDI score		TDI responder		SGRQ score		SGRQ responder		Adverse events	
	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks
Placebo	2.6	6.9	2.4	9.6	1.8	10.8	0.7	6.8	1.0	2.0	25.2	62.1
Tio18	29.5	42.6	29.7	40.1	39.1	38.5	32.9	42.1	33.4	30.2	58.9	62.6
Tio5	40.8	36.1	59.5	NA	NA	NA	27.4	44.6	NA	35.2	75.4	NA
Acl	39.6	43.6	56	47.6	36.6	55.4	23.9	51.7	20.1	72.7	63.3	NA
Glyco	39.2	49.2	36.1	54.5	58.3	61.3	50.5	61.3	48.0	32.7	49.9	72.3
Umec	72.6	53.9	42.2	43.8	58.6	34.2	68.1	68.1	38.5	38.1	31.5	29.4
AclForm	64.5	66.8	NA	88.4	72.8	88.7	NA	61.6	68.2	76.9	NA	74.8
IndaGlyco	97.6	91.7	91.6	94.2	49.1	93.5	93.1	60.6	81.7	76.1	NA	83.9
TioOlo	84.2	82.8	97.8	NA	NA	NA	77.0	66.1	93.4	85.0	75.8	NA
UmecVil	93.0	93.3	71.9	53.5	85.1	54.8	65.6	69.5	62.6	60.7	56.6	33.7
SFC500	48.9	24.5	69.9	66.8	85.6	62.2	71.1	19.2	64.6	72.6	49.3	33.3
SFC250	19.4	76.9	35.7	NA	NA	NA	53.0	NA	NA	NA	40.0	26.2
BudeForm	NA	17.5	NA	NA	NA	NA	NA	60.5	NA	48.4	NA	23.4
FFVI	63.0	64.0	NA	NA	NA	NA	75.6	71.9	70.7	NA	28.8	48.5
Ipra	5.1	0.2	7.2	1.5	13.0	0.4	11.2	15.8	17.8	19.6	45.3	NA

Note: The probabilities of each treatment being ranked best are represented by their SUCRA values.

Abbreviations: Acl, aclidinium; AclForm, aclidinium/formoterol; BudeForm, budesonide/formoterol; FFVI, fluticasone/vilanterol; Glyco, glycopyrronium; IndaGlyco, indacaterol/glycopyrronium; Ipra, ipratropium; NA, results not available; SFC250, fluticasone/salmeterol 250/50 mcg; SFC500, fluticasone/salmeterol 500/50 mcg; SGRQ, St George's Respiratory Questionnaire; SUCRA, Surface Under the Cumulative Ranking; TDI, transitional dyspnea index; Tio5, tiotropium 5 mcg; Tio18, tiotropium 18 mcg; TioOlo, tiotropium/olodaterol; Umec, umeclidinium; UmecVil, umeclidinium/vilanterol.

ranged from 64.5% to 97.6% (Table 5). The trend remained constant for all outcomes, with LAMA/LABAs having the highest SUCRA scores.

Discussion

Our network meta-analysis is the first to utilize a frequentist framework to comprehensively compare the effectiveness of SAMAs, LAMAs, LAMA/LABAs and ICS/LABAs using published randomized controlled studies. A frequentist framework allowed us to make statistical inference/comparisons based on significance testing using *P*-values. With regards to lung function, our results showed that LAMAs, LAMA/LABAs and ICS/LABAs led to a greater improvement in trough FEV_1 compared with placebo and SAMA monotherapy. All LAMA/LABAs except aclidinium/formoterol were significantly better than LAMA monotherapy in improving lung function. Limited evidence also suggested LAMA/LABAs led to greater improvements than ICS/LABAs. Of note, there was markedly more evidence available for lung function than other patient-relevant outcomes. Similar trends were, nonetheless, observed with respect to improvements in TDI and SGRQ scores, although not all results were statistically significant. Improvements with FEV_1 have been correlated with improvements in quality of life as demonstrated in previous analyses.[12] A recent study by Sion et al (2017) reported similar findings that LAMA/LABAs combinations were better than Tio alone or placebo.[88]

Our results did not show any clinically significant differences among the different LAMAs and LAMA/LABAs within their classes, for all outcomes. These results were congruent with other published network meta-analyses which compared outcomes within the drug classes. Cope et al,[89] Karabis et al[90] and Ismaila et al[91] evaluated the comparative efficacy among the LAMA agents through a Bayesian framework and found no differences among them. Similarly, Schlueter et al[92] and Huisman et al[93] evaluated the comparative efficacy among LAMA/LABAs using the Bayesian approach and found no differences among all agents. Our analysis, which employs a frequentist framework and uses a network with more comprehensive treatment options (SAMA, LAMA, LAMA/LABA and ICS/LABA) for stable COPD, adds further confidence to these findings and expands the existing evidence base.

In considering the results, we need to be mindful of the limitations of the analysis. FEV_1 is the only outcome that is consistently reported across the trials. Given TDI and SGRQ outcomes can be reported as either total score or proportion of responders, this resulted in many studies not reporting both types of outcome. Therefore, there was uncertainty in our analysis of TDI and SGRQ outcomes, with the results reflected in wide CIs.

In addition, some included studies were open label (Bateman et al[51] and Kerwin et al[13]), and hence were associated with a high risk of bias in terms of lack of blinding. Incomplete outcome data in some studies also may have increased uncertainty around some results. Small study bias was considered unlikely, given that most included trials had a sample size of at least 100 patients and each arm of all included comparisons had at least 50 patients. Most of the included studies were of a short duration with only 16 studies, out of the 74, reporting outcomes beyond the 24-week time point. Therefore, only the 12- and 24-week time points were selected for evaluation.

When performing network meta-analysis, patients from all pair-wise meta-analysis have not been randomized to different trials and randomization would, therefore, not hold across the set of trials used for the analysis. Thus, it is important to assess imbalance in patient characteristics and effect modifiers across trials to determine the face validity of the analysis. To ensure the assumptions of homogeneity and transitivity are met, the distribution of potential effect modifiers, such as gender distribution, mean age, and proportion of smokers, was assessed and found to be similar across the direct comparisons in the network. However, other effect modifiers, including mean COPD duration and proportion with exacerbation history, were not reported in the majority of the trials, which limited our ability to determine if our assumptions were met with respect to these characteristics. However, despite this limitation, it is unlikely that our results would be substantially biased given the consistency of results demonstrated between the network and direct comparison meta-analyses.

To address the potential influence of certain treatment effect modifiers, network meta-regression would have been appropriate to explore the impact of covariates on all of the data and allow for the simultaneous consideration of continuous and categorical covariates. However, we did not perform a meta-regression mainly due to the fact that the variation in FEV_1 was too small, and also due to the limited number of studies available in parts of the network. Model diagnostics and adequacy are difficult to assess. Even if the network meta-regression was performed, individual patient data would be necessary to avoid ecological bias and to gain greater statistical power to detect differences in treatment effects between the effect modifiers.

It is worth noting that although we have reported the ranking of all treatments using SUCRA curves, large differences in ranking probabilities between two treatments do not necessarily mean significant difference in relative treatment effect. To achieve a more objective assessment, the magnitude of absolute benefit should be accompanied with ranking information in order to minimize potential biased interpretation.

Finally, our approach was based on individual treatments (eg, Acl, Glyco, Tio18, Tio5, Umec) instead of drug classes (eg, LAMAs) as it facilitated comparisons both within and across classes. However, this led to multiple comparisons involving all treatments from each class and, thus, difficulty in drawing conclusions at a therapeutic class level. The number of studies available for each individual treatment was also small, which may have resulted in low statistical power.

Conclusion

LAMA/LABA showed greatest improvement in lung function at weeks 12 and 24 compared with the other inhaled drug classes, while SAMA showed the least improvement. There were no significant differences among the LAMAs and LAMA/LABAs within their respective classes. Results from our analysis may play a role in assisting clinicians make evidence-based treatment decisions and also in advising policymakers on the most effective treatments when making subsidy decisions. Other factors, including cost-effectiveness and patient preferences, may also be taken into account when determining the most optimal treatments for patients with stable COPD.

Acknowledgment

David Bin-Chia Wu left the Agency for Care Effectiveness, Ministry of Health, Singapore during the course of manuscript development.

Disclosure

The authors report no conflicts of interest in this work.

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