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ORIGINAL RESEARCH

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

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Background: Randomized controlled trials (RCTs) indicate that long-acting bronchodilator combinations, such as β_2-agonist (LABA)/muscarinic antagonist (LAMA), have favorable efficacy compared with commonly used COPD treatments. The objective of this analysis was to compare the efficacy and safety of LABA/LAMA with LAMA or LABA/inhaled corticosteroid (ICS) in adults with stable moderate-to-very-severe COPD.

Methods: This systematic review and meta-analysis (PubMed/MEDLINE, Embase, Cochrane Library and clinical trial/manufacturer databases) included RCTs comparing $\geq$12 weeks' LABA/LAMA treatment with LAMA and/or LABA/ICS (approved doses only). Eligible studies were independently selected by two authors using predefined data fields; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results: Eighteen studies (23 trials) were eligible (N=20,185). LABA/LAMA significantly improved trough forced expiratory volume in 1 second (FEV_1) from baseline to week 12 versus both LAMA and LABA/ICS (0.07 L and 0.08 L, $P<0.0001$), with patients more likely to achieve clinically important improvements in FEV_1 of >100 mL (risk ratio [RR]: 1.33, 95% confidence interval [CI]: [1.20, 1.46] and RR: 1.44, 95% CI: [1.33, 1.56], respectively, the number needed to treat being eight and six, respectively). LABA/LAMA improved transitional dyspnea index and St George's Respiratory Questionnaire scores at week 12 versus LAMA (both $P<0.0001$), but not versus LABA/ICS, and reduced rescue medication use versus both ($P<0.0001$ and $P=0.001$, respectively). LABA/LAMA significantly reduced moderate/severe exacerbation rate compared with LABA/ICS (RR 0.82, 95% CI: [0.75, 0.91]). Adverse event (AE) incidence was no different for LABA/LAMA versus LAMA treatment, but it was lower versus LABA/ICS (RR 0.94, 95% CI: [0.89, 0.99]), including a lower pneumonia risk (RR 0.59, 95% CI: [0.43, 0.81]). LABA/LAMA presented a lower risk for withdrawals due to lack of efficacy versus LAMA (RR: 0.66, 95% CI: [0.51, 0.87]) and due to AEs versus LABA/ICS (RR: 0.83, 95% CI: [0.69, 0.99]).

Conclusion: The greater efficacy and comparable safety profiles observed with LABA/LAMA combinations versus LAMA or LABA/ICS support their potential role as first-line treatment options in COPD. These findings are of direct relevance to clinical practice because we included all currently available LABA/LAMAs and comparators, only at doses approved for clinical use.

Keywords: LABA/LAMA combinations, COPD, LAMA, LABA/ICS, meta-analysis

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Introduction

Long-acting bronchodilators, whether β_2 agonists (LABAs) or muscarinic antagonists (LAMAs), are central to symptom management in patients with COPD.[1] As well as improving lung function and health-related quality of life (HRQoL), they help prevent exacerbations and increase exercise endurance by reducing pulmonary hyperinflation

and dyspnea.[2] LABA/inhaled corticosteroid (ICS) combinations are indicated for patients with severe-to-very-severe COPD and a history of repeated exacerbations. Despite these indications, however, LABA/ICS combinations remain the second-most commonly prescribed first-line treatments (after LAMA monotherapy) across the range of COPD severities.[3,4] The use of LABA/ICS combinations has been associated with a decrease in the rate of COPD exacerbations but with an increased risk of pneumonia.[5]

LAMAs and LABAs achieve bronchodilation through different mechanisms: muscarinic antagonists block acetylcholine-mediated bronchoconstriction by binding to M_3 receptors in airway smooth muscle,[6] whereas β_2 agonists induce smooth muscle relaxation by stimulating β_2-adrenergic receptors.[7,8] These distinct mechanisms result in differences in observed efficacy between the two classes of bronchodilators. Hence, some data suggest that LABAs are more effective at improving symptoms and HRQoL than LAMAs, while LAMAs are superior to LABAs in reducing exacerbations, with the differential efficacy likely occurring through modes of action beyond bronchodilation.[8–12] Such differences provide the opportunity of combining LABAs and LAMAs in an attempt to improve treatment outcomes.

Accumulating evidence from randomized controlled trials (RCTs) has shown that LABA/LAMA fixed-dose combinations (FDCs) have beneficial effects on lung function and patient-reported outcomes compared with LAMA or LABA/ICS treatments, while demonstrating a similar safety profile.[13–15] In a recent network meta-analysis, LABA/LAMA combinations have also been shown to be more effective than either of the monotherapy component in improving lung function, QoL, symptom scores and exacerbation rates while maintaining similar safety profiles.[16] Building on this, the aim of this meta-analysis was to compare the pooled efficacy and safety data from trials of FDCs of LABA/LAMAs with the two most commonly prescribed first-line treatments: LAMAs and LABA/ICS combinations.

Materials and methods
Literature search and terms used
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to perform this systematic review.[17] Full details are provided in the online Supplementary materials.

Inclusion criteria and outcome assessments
Randomized, parallel-group, controlled design of >4 weeks' duration, which compared LABA/LAMA FDCs with LAMA monotherapy or LABA/ICS combinations, were included. The studies were to have been conducted in adult patients aged ≥40 years with stable, moderate-to-very severe COPD.[1]

Study treatments were restricted to all currently available LABA/LAMA combinations at the approved doses of these combinations and their comparators (in the US or EU; Table S1).

Studies were required to report at least one of the following outcomes: trough and/or peak FEV_1; transitional dyspnea index (TDI) total score; St George's Respiratory Questionnaire (SGRQ) total score; rescue medication use (puffs/day); COPD exacerbations (as a study end point); safety (frequency of adverse events [AEs], serious AEs [SAEs] and cardiovascular events); pneumonia incidence; withdrawal from treatment (due to AEs or lack of efficacy); or deaths while on treatment.

The primary outcome was trough FEV_1; secondary outcomes included peak FEV_1, TDI, SGRQ, rescue medication use, prospectively collected annualized rate of COPD exacerbations, AEs and related safety measures. The effect of treatments was established at weeks 12, 24 or 26, and 52 (dependent on the trial) for efficacy end points, as well as throughout the trial duration for safety outcomes. In addition, in studies in which the data were evaluated, the proportions of patients who achieved minimal clinically important differences (MCIDs) in FEV_1, TDI and SGRQ have also been presented; these are defined as a >100 mL increase over baseline for FEV_1,[18] a ≥1 unit increase in TDI,[19] and a ≥4 unit decrease in SGRQ score.[20]

Data extraction and risk of bias assessment
Two authors (GJR and DP) reviewed the search results for relevant article titles meeting the inclusion criteria. The reviewers worked independently during study selection and data extraction; disagreements, if any, were resolved by discussion to obtain consensus.

Risk of bias of eligible trials was assessed by applying the Cochrane collaborations tool;[21] further details are provided in the online Supplementary materials.

Data analysis
The meta-analysis was performed using Review Manager, version 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) as described in detail in the online Supplementary materials. In all analyses, the P-values were based on a two-tailed test with P<0.05 considered statistically significant.

Outcomes were pooled as forest plots using mean differences (inverse variance [IV] or generic IV method), Mantel–Haenszel risk ratios (RRs) or risk differences (RDs). Precision of the estimates was quantified with 95% confidence intervals (CIs), and heterogeneity was assessed using the I^2 test.[22] Random-effects models were used to address variations across studies.[23]

Results
Studies included in the analyses

The study selection process is described in Figure 1, with further details supplied in the online Supplementary materials. Eighteen studies (comprising 23 clinical trials in total) fulfilled the eligibility criteria, and all were included in the analysis (N=20,185); both reviewers were in full agreement as to their inclusion. Details of the studies are summarized in Table 1; five comprised pooled data from two clinical trials. One of four pharmaceutical companies (AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis) sponsored each of the studies, all of which involved randomized

comparisons of approved doses of COPD treatments or placebo. Twelve of the studies compared LABA/LAMA with LAMA,[7,15,24–33] while six compared LABA/LAMA with LABA/ICS (salmeterol/fluticasone propionate);[34–39] two of the trials[25,26] included two or more comparators. Further details for each of the studies can be found at https://ClinicalTrials.gov/ or in their respective primary publications.[7,15,24–39]

Most of the studies showed a low risk of bias in the six items of the Cochrane instrument[21] (online Supplementary materials; Figures S1–S3).

Effect of treatments on lung function (trough and peak FEV$_1$)

The overall treatment effect for each of the treatment comparisons are shown in Table 2 for each outcome measure at each of the protocol-defined time points. At week 12, significant increases from baseline were observed in trough FEV$_1$ for the LABA/LAMAs indacaterol (Ind)/glycopyrronium (Gly) (both dose regimens), umeclidinium (Umec)/vilanterol (Vi) and tiotropium (Tio)/olodaterol (Olo)
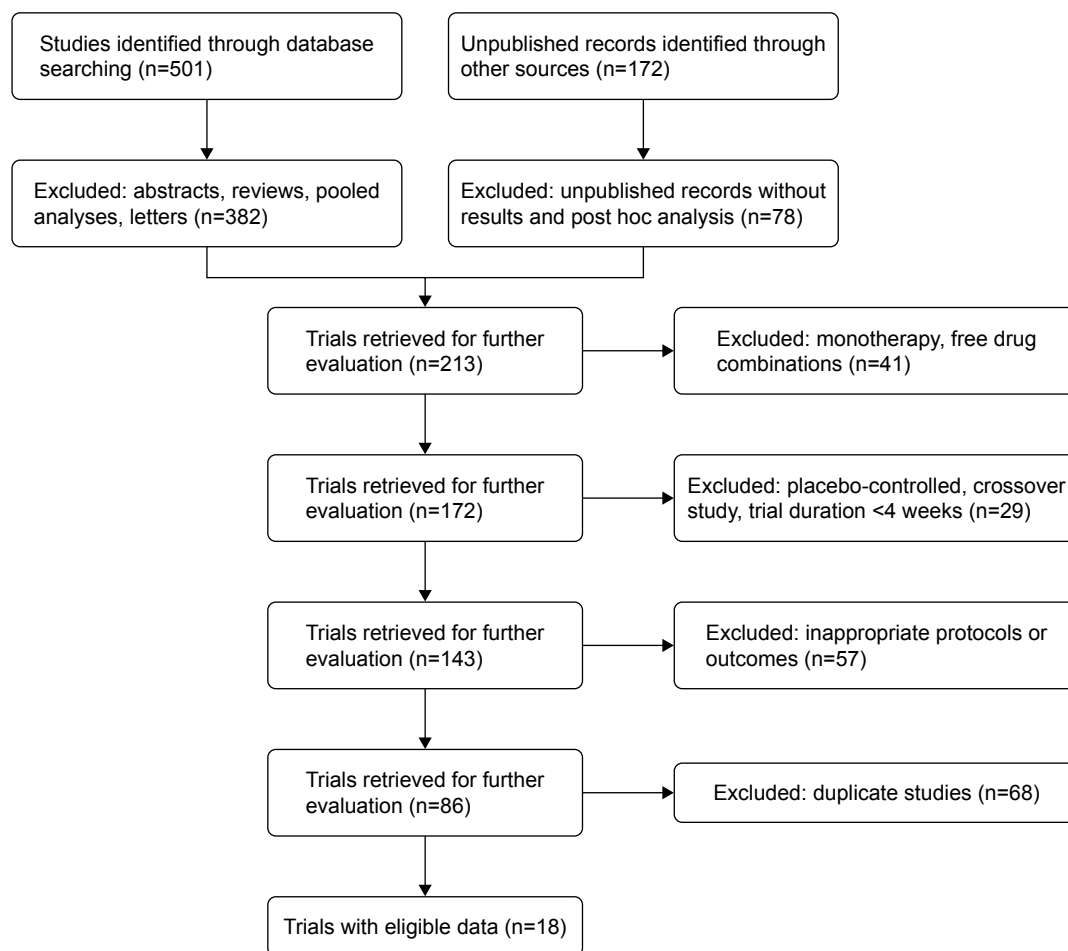

Figure 1 Study selection process: PRISMA flow diagram identifying studies included in the meta-analysis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Characteristics of included studies

Comparisons of interest[a]	Study with reference no	Study type, duration, weeks	No of randomized patients analyzed		Outcomes measured
			LABA/LAMA	Comparator	
LABA/LAMAs versus LAMAs					
Ind/Gly 110/50 μg od versus Tio 18 μg od and Gly 50 μg od	NCT01285492[24]	Multicenter, 52	119	39	[b]AE, FEV1, FVC, HS, RMU
	NCT01202188[25]	Multicenter, 26	474	473/480 (Gly/Tio)	[b]FEV1, Dys, HS, RMU, With, EX, AE
	NCT01120691[26]	Multicenter, 64	741	741/742 (Gly/Tio)	EX, [b]HS, RMU, With, AE
	NCT01610037[27]	Multicenter, 52	407	405 (Tio)	[b]SAE, SAF, FEV1, HS, FVC, RMU
Ind/Gly 27.5/15.6 μg bid versus Gly 15.6 μg bid	NCT0172714l	Multicenter, 12	260	261	[b]FEV1, AUC0–12h, Dys, HS, RMU
	NCT01712516[28]		250	251	
Umec/Vi 62.5/25 μg versus Tio 18 μg od and Umec 62.5 μg od	NCT01316900	Multicenter, 24	212	208 (Tio)	[b]FEV1, Dys, HS, EX, SAF
	NCT01316913[29]		217	215 (Tio)	
	NCT01313650[30]	Multicenter, 24	413	418 (Umec)	[b]FEV1, FVC, Dys, HS, EX, RMU, SAF
	NCT01777334[31]	Multicenter, 24	454	451 (Tio)	[b]FEV1, Dys, HS, EX, SAF
Acli/For 400/12 μg bid versus Acli 400 μg bid	NCT01437397[15]	Multicenter, 24	338	340	[b]FEV1, Dys, HS, EX, RMU, SAF
	NCT01462942[32]	Multicenter, 24	385	385	[b]FEV1, Dys, HS, EX, RMU, SAF
Tio/Olo 5/5 μg od versus Tio 5 μg od	NCT01431274	Multicenter, 52	522	527	[b]FEV1, [b]FEV1 AUC0–3h, [b]HS, Dys, FVC
	NCT01431287[7]		507	506	
	NCT01964352	Multicenter, 12	204	204	[b]HS, [b]FEV1, AUC0–3h, [b]FEV1, Dys, FVC, SAF
	NCT02006732[33]		202	203	
LABA/LAMAs versus LABA/ICS					
Ind/Gly 110/50 μg od versus Sal/FP 50/500 μg bid	NCT01315249[34]	Multicenter, 26	258	264	[b]FEV1, AUC0–12h, FEV1, FVC, Dys, HS, RMU, SAF
	NCT01709903[35]	Multicenter, 26	372	369	[b]FEV1, FEV1 AUC0–4h, peak FEV1, FVC, HS, Dys
	NCT01782326[36]	Multicenter, 52	1,678	1,680	[b]EX, FEV1, HS, RMU, SAF, FVC, AE
Umec/Vi 62.5/25 μg od versus Sal/FP 50/250 or 500 μg bid	NCT01817764	Multicenter, 12	353	353	[b]FEV1, Dys, HS, EX, SAF
	NCT01879410[37]		349	348	[b]SAF, FEV1, EX
Acli/For 400/12 μg bid versus Sal/FP 50/500 μg bid	NCT01822899[38]	Multicenter, 12	334	340	[b]FEV1, Dys, HS, RMU, SAF
	NCT01908140[39]	Multicenter, 24	467	466	[b]FEV1, Dys, HS, EX, SAF

Notes: [a]Only patients randomized to approved doses were included in the meta-analysis; some trials included additional comparisons. [b]Primary end point.
Abbreviations: Acli, aclidinium; AE, adverse events (including serious AEs/deaths); AUC, area under the curve; bid, twice daily; Dys, dyspnea; EX, exacerbation; FEV1, forced expiratory volume in 1 second; For, formoterol; FVC, forced vital capacity; Gly, glycopyrronium; HS, health status; Ind, indacaterol; NA, data not available; SAF, safety; od, once daily; Olo, olodaterol; Pl, placebo; QVA149, fixed-dose combination of indacaterol and glycopyrronium; RMU, rescue medication use; Sal/FP, salmeterol/fluticasone propionate; Tio, tiotropium; Umec, umeclidinium; Vi, vilanterol; With, withdrawal; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; od, once daily; bid, twice daily.

Table 2 Effect of LABA/LAMA versus LAMA or LABA/ICS on trough and peak FEV$_1$

Outcome measure	Studies included	No of patients		Estimate	Effect (95% CI)	I^2, % (P-value)
		LABA/LAMA	**Comparator**			
Trough FEV$_1$ (L) from baseline to LABA/LAMA versus LAMA						
Week 12	7, 15, 24–33	5,565	6,615	Mean difference	0.07 (0.05, 0.09)	91 (<0.0001)
Week 24–26	15, 24–33	4,584	5,552		0.07 (0.05, 0.08)	56 (<0.0001)
Week 52	24, 26, 27, 33	2,015	2,488		0.07 (0.05, 0.10)	63 (<0.0001)
Total assessed for MCID[a]	25, 29–31	1,765	2,240	Relative risk	1.33 (1.20, 1.46)	55 (<0.0001)
Total with MCID		1,018	978	NNTB	8 (6, 9)	
LABA/LAMA versus LABA/ICS						
Week 12	34–36, 39	3,142	3,123	Mean difference	0.08 (0.07, 0.09)	0 (<0.0001)
Week 24–26	34–38	2,563	2,537		0.06 (0.00, 0.12)	90 (0.04)
Total assessed for MCID	35, 37, 38	1,371	1,383	Relative risk	1.44 (1.33, 1.56)	0 (<0.0001)
Total with MCID				NNTB	6 (5, 7)	
Peak FEV$_1$ (L) from baseline to LABA/LAMA versus LAMA						
Week 12	28, 32	893	868	Mean difference	0.10 (0.08, 0.12)	0 (<0.0001)
Week 24–26	25, 29–32	2,150	2,625		0.11 (0.09, 0.12)	0 (<0.0001)
LABA/LAMA versus LABA/ICS						
Week 12	34, 35, 37, 38	1,552	1,544	Mean difference	0.12 (0.10, 0.14)	0 (<0.0001)
Week 24–26	34, 35, 39	953	932		0.12 (0.09, 0.15)	62 (<0.0001)

Note: [a]MCID ≥100 mL above baseline.
Abbreviations: CI, confidence interval; MCID, minimum clinically important difference; NNTB, number needed to treat for benefit; ICS, inhaled corticosteroid; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist; FEV$_1$, forced expiratory volume in 1 second; TDI, transitional dyspnea index.

relative to the respective LAMAs evaluated in their studies (mean differences: 0.06–0.10 L; P<0.0001; Figure 2). The between-treatment difference for aclidinium (Acli)/formoterol (For) versus Acli was not statistically significantly different (P=0.06), but a trend in favor of Acli/For was evident.

Overall, for all LABA/LAMA versus LAMA comparisons, a significant improvement in trough FEV$_1$ with LABA/LAMA treatment was observed at week 12 (mean overall difference: 0.07 L, 95% confidence interval [CI]: [0.05, 0.09]; P<0.0001 relative to LAMA monotherapy). This improvement was maintained at weeks 24–26 and at week 52 (mean difference: 0.07 L, 95% CI: [0.05, 0.08], and mean difference: 0.07 L, 95% CI: [0.05, 0.10], respectively; both P<0.0001; Table 2; Figure S4). In addition, in studies where MCID was evaluated, 33% more patients receiving LABA/LAMA rather than LAMA treatments achieved the MCID in trough FEV$_1$ of >100 mL above baseline (RR: 1.33; 95% CI [1.20, 1.46]; Table 2). The number needed to treat to achieve this treatment benefit (NNTB) was 8 (95% CI [6, 9]; Table 2). The absolute proportions of patients achieving any MCID were 58% (1,018 of 1,765) and 44% (978 of 2,240), respectively.

LABA/LAMA treatment also significantly increased trough FEV$_1$ relative to LABA/ICS, both at the week 12 and week 24–26 time points (overall mean differences: 0.08 L, 95% CI: [0.07, 0.09], P<0.0001; and 0.06 L, 95% CI: [0.00, 0.12], P=0.04, respectively; Figure 3; Table 2).

LABA/LAMA-treated patients had a 44% greater likelihood of achieving an MCID in trough FEV$_1$ than those receiving LABA/ICS (RR: 1.44; 95% CI: [1.33, 1.56]; Table 2), with an NNTB of 6 at week 12 (95% CI: [5, 7]; Table 2). The absolute proportions of patients achieving any MCID (where evaluated) were 59% (803 of 1,371) and 41% (562 of 1,383), respectively.

Peak FEV$_1$ at week 12 and at weeks 24–26 was also higher in LABA/LAMA-treated patients versus both LAMA- or LABA/ICS-treated patients (overall mean differences: 0.10–0.12 L; all P<0.0001; Table 2; Figure S5).

Effect of treatments on dyspnea, health status and rescue medication use

The effects of each treatment on dyspnea and health status (assessed by TDI and SGRQ, respectively), as well as rescue medication use, were determined at protocol-defined time points for individual trials and for treatment comparison subgroups. Overall treatment effects for all study subgroups combined are shown in Table 3.

TDI focal score was significantly improved in LABA/LAMA- versus LAMA-treated patients at weeks 12 and 24 (mean difference: 0.5 points, 95% CI: [0.32, 0.68], P<0.0001, and mean difference: 0.29 points, 95% CI: [0.12, 0.46], P=0.0006, respectively; Table 3; Figure S6A). Furthermore, in studies wherein it was evaluated, LABA/
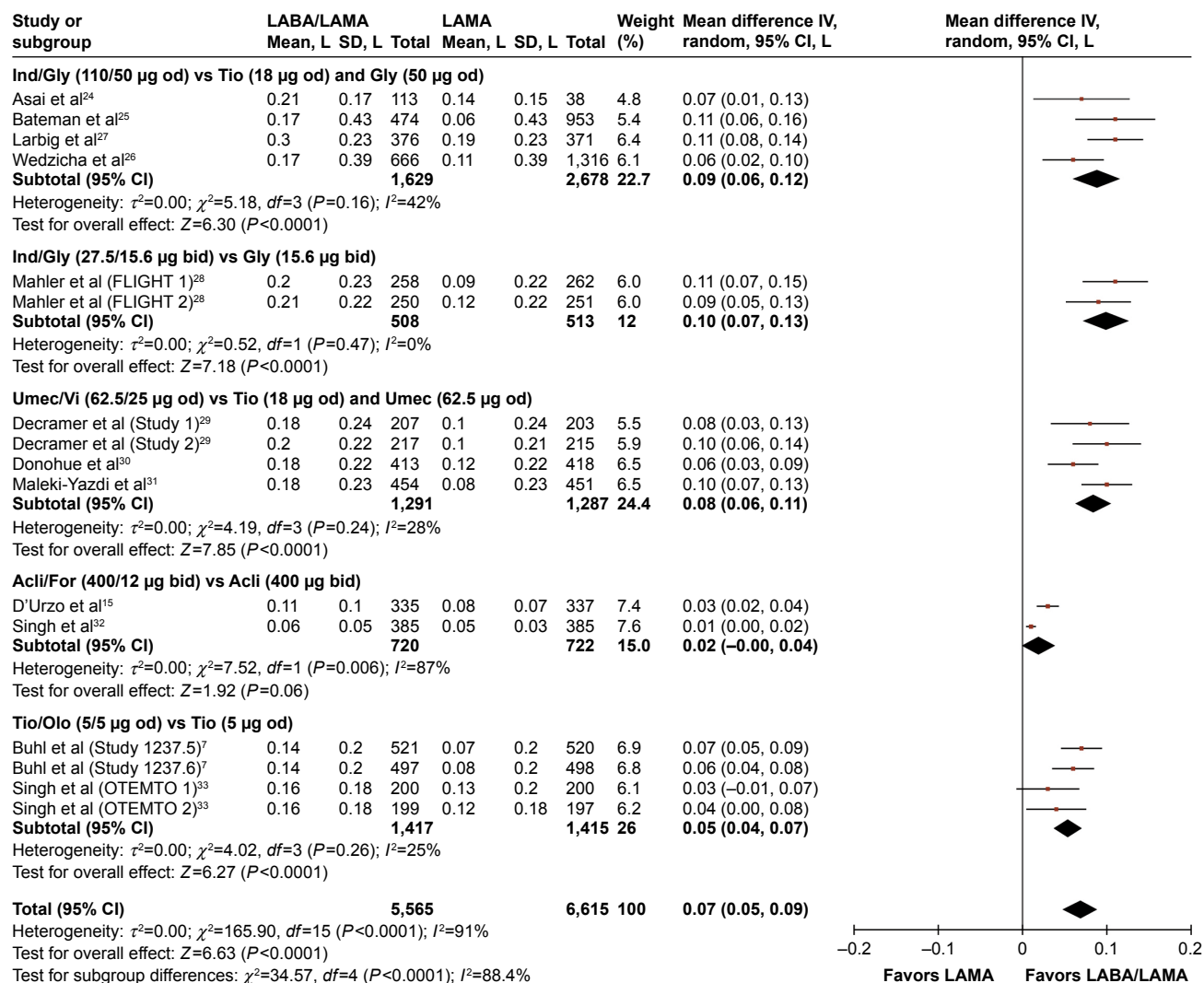
Study or subgroup	LABA/LAMA Mean, L	SD, L	Total	LAMA Mean, L	SD, L	Total	Weight (%)	Mean difference IV, random, 95% CI, L	Mean difference IV, random, 95% CI, L
Ind/Gly (110/50 µg od) vs Tio (18 µg od) and Gly (50 µg od)									
Asai et al[24]	0.21	0.17	113	0.14	0.15	38	4.8	0.07 (0.01, 0.13)	
Bateman et al[25]	0.17	0.43	474	0.06	0.43	953	5.4	0.11 (0.06, 0.16)	
Larbig et al[27]	0.3	0.23	376	0.19	0.23	371	6.4	0.11 (0.08, 0.14)	
Wedzicha et al[26]	0.17	0.39	666	0.11	0.39	1,316	6.1	0.06 (0.02, 0.10)	
Subtotal (95% CI)			1,629			2,678	22.7	**0.09 (0.06, 0.12)**	
Heterogeneity: τ^2=0.00; χ^2=5.18, df=3 (P=0.16); I^2=42%									
Test for overall effect: Z=6.30 (P<0.0001)									
Ind/Gly (27.5/15.6 µg bid) vs Gly (15.6 µg bid)									
Mahler et al (FLIGHT 1)[28]	0.2	0.23	258	0.09	0.22	262	6.0	0.11 (0.07, 0.15)	
Mahler et al (FLIGHT 2)[28]	0.21	0.22	250	0.12	0.22	251	6.0	0.09 (0.05, 0.13)	
Subtotal (95% CI)			508			513	12	**0.10 (0.07, 0.13)**	
Heterogeneity: τ^2=0.00; χ^2=0.52, df=1 (P=0.47); I^2=0%									
Test for overall effect: Z=7.18 (P<0.0001)									
Umec/Vi (62.5/25 µg od) vs Tio (18 µg od) and Umec (62.5 µg od)									
Decramer et al (Study 1)[29]	0.18	0.24	207	0.1	0.24	203	5.5	0.08 (0.03, 0.13)	
Decramer et al (Study 2)[29]	0.2	0.22	217	0.1	0.21	215	5.9	0.10 (0.06, 0.14)	
Donohue et al[30]	0.18	0.22	413	0.12	0.22	418	6.5	0.06 (0.03, 0.09)	
Maleki-Yazdi et al[31]	0.18	0.23	454	0.08	0.23	451	6.5	0.10 (0.07, 0.13)	
Subtotal (95% CI)			1,291			1,287	24.4	**0.08 (0.06, 0.11)**	
Heterogeneity: τ^2=0.00; χ^2=4.19, df=3 (P=0.24); I^2=28%									
Test for overall effect: Z=7.85 (P<0.0001)									
Acli/For (400/12 µg bid) vs Acli (400 µg bid)									
D'Urzo et al[15]	0.11	0.1	335	0.08	0.07	337	7.4	0.03 (0.02, 0.04)	
Singh et al[32]	0.06	0.05	385	0.05	0.03	385	7.6	0.01 (0.00, 0.02)	
Subtotal (95% CI)			720			722	15.0	**0.02 (−0.00, 0.04)**	
Heterogeneity: τ^2=0.00; χ^2=7.52, df=1 (P=0.006); I^2=87%									
Test for overall effect: Z=1.92 (P=0.06)									
Tio/Olo (5/5 µg od) vs Tio (5 µg od)									
Buhl et al (Study 1237.5)[7]	0.14	0.2	521	0.07	0.2	520	6.9	0.07 (0.05, 0.09)	
Buhl et al (Study 1237.6)[7]	0.14	0.2	497	0.08	0.2	498	6.8	0.06 (0.04, 0.08)	
Singh et al (OTEMTO 1)[33]	0.16	0.18	200	0.13	0.2	200	6.1	0.03 (−0.01, 0.07)	
Singh et al (OTEMTO 2)[33]	0.16	0.18	199	0.12	0.18	197	6.2	0.04 (0.00, 0.08)	
Subtotal (95% CI)			1,417			1,415	26	**0.05 (0.04, 0.07)**	
Heterogeneity: τ^2=0.00; χ^2=4.02, df=3 (P=0.26); I^2=25%									
Test for overall effect: Z=6.27 (P<0.0001)									
Total (95% CI)			5,565			6,615	100	**0.07 (0.05, 0.09)**	
Heterogeneity: τ^2=0.00; χ^2=165.90, df=15 (P<0.0001); I^2=91%									
Test for overall effect: Z=6.63 (P<0.0001)									
Test for subgroup differences: χ^2=34.57, df=4 (P<0.0001); I^2=88.4%									

−0.2 −0.1 0 0.1 0.2
Favors LAMA   Favors LABA/LAMA

Figure 2 Pooled mean difference for trough FEV_1 (change from baseline, L) at week 12, with 95% CIs, for eligible studies comparing approved doses of LABA/LAMA combinations with approved LAMAs.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation; IV, intravenous; od, once daily; bid, twice daily.

LAMA-treated patients were 12% more likely to achieve an MCID in TDI (≥1 point increase) compared with LAMA-treated patients (RR: 1.12; 95% CI: [1.06, 1.18]; Table 3), with an NNTB of 19 patients (95% CI: [12, 36]). The absolute proportions of patients achieving any MCID were 61% (1,500 of 2,444) and 56% (1,604 of 2,865), respectively.

No statistically significant difference between LABA/LAMA and LABA/ICS treatments with respect to TDI focal scores at weeks 12 and 26 were observed (P=0.09 and P=0.29, respectively; Table 3; Figure S6B), although a trend in favor of LABA/LAMA treatment was observed.

With respect to the effect of different treatments on health status, SGRQ total scores (mean difference from baseline) at the week 12 and 24 time points were significantly improved in LABA/LAMA- versus LAMA-treated patients

(mean difference: −1.84, 95% CI: [−2.31, −1.37], and mean difference: −1.34, 95% CI: [−1.94, −0.75] points, respectively, both P<0.0001; Table 3; Figure S7A [i] and [ii]). By week 52, the intertreatment difference was no longer statistically significant (mean difference: −1.21, 95% CI: [−2.64, 0.21], P=0.09; Table 3; Figure S7A [iii]), although the direction of the treatment benefit remained in favor of LABA/LAMA treatment. Furthermore, SGRQ scores at week 52 were only captured in three studies, compared with 11 and 8 in the earlier time points; therefore, this finding may not be as robust as the earlier time points because the end point was tested in a comparatively smaller population. Heterogeneity between the three trials comprising the week 52 end point was also relatively high, at an I^2 of 58%. In studies where MCID was evaluated, at the end of treatment, LABA/LAMA-treated
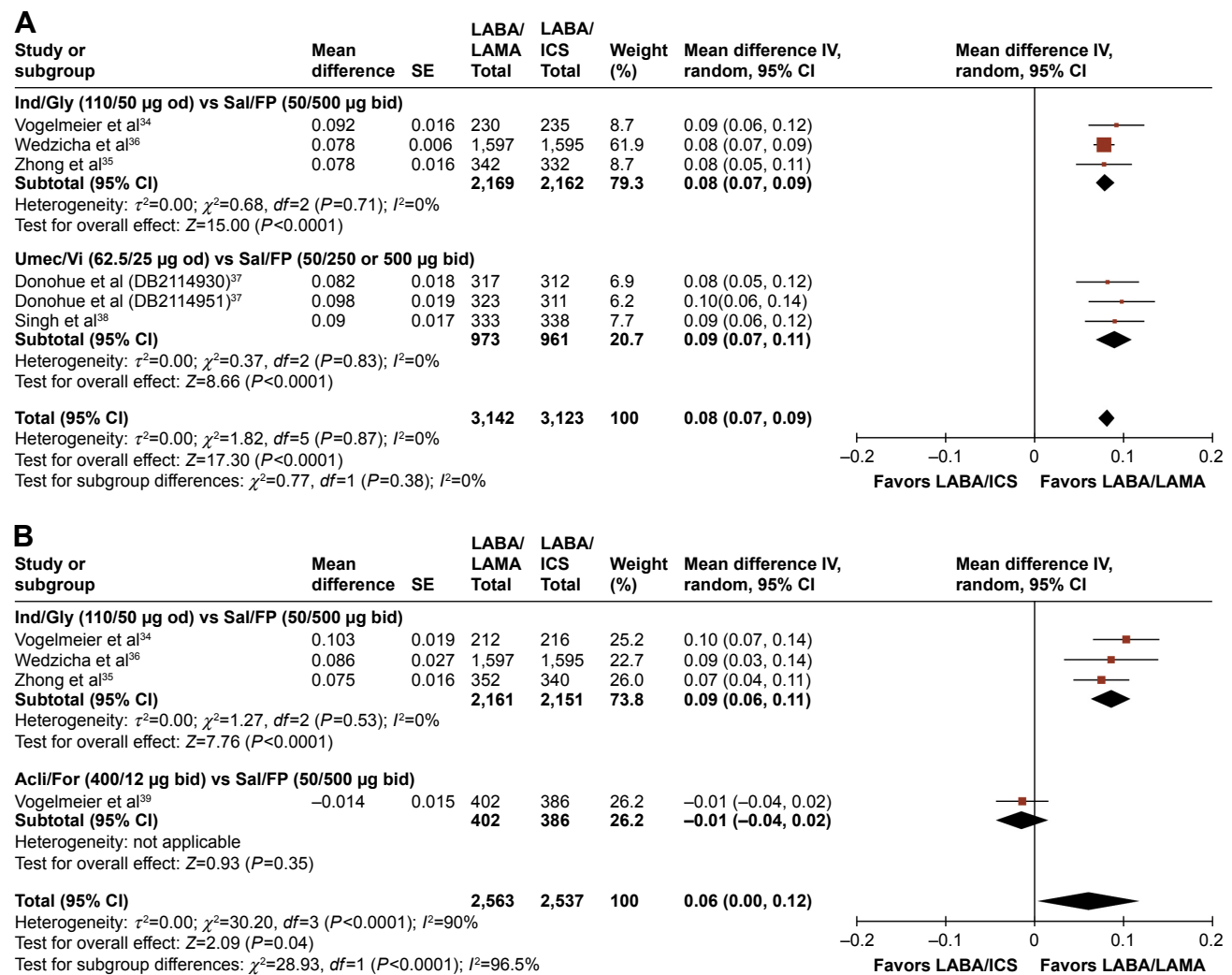
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Study or subgroup	Mean difference	SE	LABA/ LAMA Total	LABA/ ICS Total	Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Ind/Gly (110/50 µg od) vs Sal/FP (50/500 µg bid)							
Vogelmeier et al[34]	0.092	0.016	230	235	8.7	0.09 (0.06, 0.12)	
Wedzicha et al[36]	0.078	0.006	1,597	1,595	61.9	0.08 (0.07, 0.09)	
Zhong et al[35]	0.078	0.016	342	332	8.7	0.08 (0.05, 0.11)	
Subtotal (95% CI)			2,169	2,162	79.3	0.08 (0.07, 0.09)	
Heterogeneity: τ^2=0.00; χ^2=0.68, df=2 (P=0.71); I^2=0%							
Test for overall effect: Z=15.00 (P<0.0001)							
Umec/Vi (62.5/25 µg od) vs Sal/FP (50/250 or 500 µg bid)							
Donohue et al (DB2114930)[37]	0.082	0.018	317	312	6.9	0.08 (0.05, 0.12)	
Donohue et al (DB2114951)[37]	0.098	0.019	323	311	6.2	0.10 (0.06, 0.14)	
Singh et al[38]	0.09	0.017	333	338	7.7	0.09 (0.06, 0.12)	
Subtotal (95% CI)			973	961	20.7	0.09 (0.07, 0.11)	
Heterogeneity: τ^2=0.00; χ^2=0.37, df=2 (P=0.83); I^2=0%							
Test for overall effect: Z=8.66 (P<0.0001)							
Total (95% CI)			**3,142**	**3,123**	**100**	**0.08 (0.07, 0.09)**	
Heterogeneity: τ^2=0.00; χ^2=1.82, df=5 (P=0.87); I^2=0%							
Test for overall effect: Z=17.30 (P<0.0001)							
Test for subgroup differences: χ^2=0.77, df=1 (P=0.38); I^2=0%							

-0.2 -0.1 0 0.1 0.2
Favors LABA/ICS   Favors LABA/LAMA

B

Study or subgroup	Mean difference	SE	LABA/ LAMA Total	LABA/ ICS Total	Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Ind/Gly (110/50 µg od) vs Sal/FP (50/500 µg bid)							
Vogelmeier et al[34]	0.103	0.019	212	216	25.2	0.10 (0.07, 0.14)	
Wedzicha et al[36]	0.086	0.027	1,597	1,595	22.7	0.09 (0.03, 0.14)	
Zhong et al[35]	0.075	0.016	352	340	26.0	0.07 (0.04, 0.11)	
Subtotal (95% CI)			2,161	2,151	73.8	0.09 (0.06, 0.11)	
Heterogeneity: τ^2=0.00; χ^2=1.27, df=2 (P=0.53); I^2=0%							
Test for overall effect: Z=7.76 (P<0.0001)							
Acli/For (400/12 µg bid) vs Sal/FP (50/500 µg bid)							
Vogelmeier et al[39]	−0.014	0.015	402	386	26.2	−0.01 (−0.04, 0.02)	
Subtotal (95% CI)			**402**	**386**	**26.2**	**−0.01 (−0.04, 0.02)**	
Heterogeneity: not applicable							
Test for overall effect: Z=0.93 (P=0.35)							
Total (95% CI)			**2,563**	**2,537**	**100**	**0.06 (0.00, 0.12)**	
Heterogeneity: τ^2=0.00; χ^2=30.20, df=3 (P<0.0001); I^2=90%							
Test for overall effect: Z=2.09 (P=0.04)							
Test for subgroup differences: χ^2=28.93, df=1 (P<0.0001); I^2=96.5%							

-0.2 -0.1 0 0.1 0.2
Favors LABA/ICS   Favors LABA/LAMA

Figure 3 Pooled mean difference for trough FEV$_1$ (change from baseline, L) at (**A**) week 12 and (**B**) weeks 24–26, with 95% CIs, for eligible studies comparing approved LABA/LAMA combinations with approved LABA/ICS combinations.
Abbreviations: CI, confidence interval; FEV$_1$, forced expiratory volume in 1 second; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SE, standard error; od, once daily; bid, twice daily; FP, fluticasone propionate.

patients were found to be 14% more likely to have achieved an MCID in SGRQ (≥4 unit decrease) than LAMA-treated patients (RR: 1.14, 95% CI: [1.09, 1.20]); the NNTB was 16 (95% CI: [12, 22]) (Table 3). The absolute proportions of patients achieving any MCID were 56% (2,493 of 4,450) and 50% (2,668 of 5,385), respectively.

Overall, no statistically significant difference was observed between LABA/LAMA and LABA/ICS treatments with respect to SGRQ total score at week 12 (mean difference: −0.43, 95% CI: [−1.28, 0.42], P=0.32), potentially driven by the considerable heterogeneity between the trials, providing an overall I^2 of 48%. At week 26, SGRQ scores had significantly improved in LABA/LAMA- versus LABA/ICS-treated patients (mean difference: −1.13, 95% CI: [−1.78, −0.48], P=0.0006; Table 3; Figure S7B), an effect driven by the data of the Ind/Gly data available at that

time point. Interestingly, the trial that contributed the greatest weight to the analysis of this comparison, FLAME,[36] was highly significantly in favor of LABA/LAMA at both time points (Figure S7B).

At the end of treatment, rescue medication use relative to baseline use was significantly reduced in LABA/LAMA-treated patients compared with those treated with either LAMA or LABA/ICS (reduction of −0.58 puffs/day, 95% CI: [−0.70, −0.45]; P<0.0001; and −0.18 puffs/day, 95% CI: [−0.28, −0.07], P=0.001, respectively) (Table 3; Figure S8).

Effect of treatments on COPD exacerbations and hospitalizations

There were insufficient data to conduct a meta-analysis on the effect of treatment on prospectively collected COPD

Table 3 Effect of LABA/LAMA versus LAMA or LABA/ICS on secondary COPD outcomes

Outcome measure	Studies included	No of patients		Estimate	Effect (95% CI)	I², % (P-value)
		LABA/LAMA	Comparator			
TDI focal score from baseline to						
LABA/LAMA versus LAMA						
Week 12	25, 28–30, 33	2,059	2,471	Mean difference	0.50 (0.32, 0.68)	0 (<0.0001)
Week 24	7, 25, 29, 30, 32	2,653	3,064	Mean difference	0.29 (0.12, 0.46)	0 (0.0006)
Total assessed for MCID[a]	7, 15, 25, 28–31, 33	2,444	2,865	Relative risk	1.12 (1.06, 1.18)	18 (0.0002)
Total with MCID		1,500	1,604	NNTB	19 (12, 36)	
LABA/LAMA versus LABA/ICS						
Week 12	34, 35, 37, 38	1,581	1,567	Mean difference	0.20 (−0.03, 0.42)	3 (0.09)
Week 26	34, 35	579	575	Mean difference	0.33 (−0.28, 0.95)	0 (0.29)
Health status (SGRQ) from baseline to						
LABA/LAMA versus LAMA						
Week 12	7, 25, 26, 28–31, 33	4,101	5,189	Mean difference	−1.84 (−2.31, −1.37)	0 (<0.0001)
Week 24	7, 25, 26, 29, 31, 32	3,679	4,750	Mean difference	−1.34 (−1.94, −0.75)	0 (<0.0001)
Week 52	7, 26	1,987	2,539	Mean difference	−1.21 (−2.64, 0.21)	58 (0.09)
Total assessed for MCID[b]	7, 15, 25, 26, 28–31, 33	4,450	5,385	Relative risk	1.14 (1.09, 1.20)	39 (<0.0001)
Total with MCID		2,493	2,668	NNTB	16 (12, 22)	
LABA/LAMA versus LABA/ICS						
Week 12	34–38	3,122	3,099	Mean difference	−0.43 (−1.28, 0.42)	48 (0.32)
Week 26	34–36	2,160	2,143	Mean difference	−1.131 (−1.78, −0.48)	0 (0.0006)
Rescue medication use at EOT versus baseline						
LABA/LAMA versus LAMA						
Treatment period range (12–64 weeks)	25, 26, 28–31	2,769	3,744	Mean difference	−0.58 (−0.70, −0.45)	0 (<0.0001)
LABA/LAMA versus LABA/ICS						
Treatment period range (12–26 weeks)	34–38	3,275	3,289	Mean difference	−0.18 (−0.28, −0.07)	0 (0.001)

Notes: [a]MCID of TDI: ≥1 unit. [b]MCID of SGRQL ≥4 units.
Abbreviations: CI, confidence interval; EOT, end of treatment; MCID, minimum clinically important difference; NNTB, number needed to treat for benefit; SGRQ, St George's Respiratory Questionnaire; TDI, transitional dyspnea index; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

exacerbation rates in LABA/LAMA- versus LAMA-treated patients because such data were available in only one study.[26] However, compared with LABA/ICS treatment, LABA/LAMA significantly reduced the annualized rate of moderate and/or severe exacerbations (RR: 0.82, 95% CI: [0.75, 0.91]; $P<0.001$; Figure 4A). A trend in favor of LABA/LAMA was also observed for severe exacerbations alone, with one study[35] revealing a significant benefit in favor of LABA/LAMA, and another[36] showing a numerical benefit. However, heterogeneity between the two studies was high for this end point, at $I^2=74\%$ (Figure 4B).

Effect of treatments on safety outcomes

The relative effects of each COPD treatment class on the safety end points of AE and SAE incidence, numbers of withdrawals (due to AEs or lack of efficacy) and deaths, as well as the effect of treatment on annualized exacerbation rate, are presented in Table 4.

No significant difference in the incidence of AEs was observed in patients treated with LABA/LAMA combinations versus those on LAMA monotherapy (RR: 1.00, 95% CI: [0.98, 1.02], $P=0.95$; Table 4; Figure 5A). Likewise, no significant difference in the incidence of SAEs (RR: 1.01, 95% CI: [0.88, 1.15], $P=0.94$) nor in the incidence of pneumonia or cardiovascular-related events (RR: 1.04, 95% CI: [0.78, 1.38], $P=0.79$, and RR: 1.09, 95% CI: [0.77, 1.55], $P=0.62$, respectively; Figures S9A, S10 and S11A) was observed.

Compared with LABA/ICS treatment, however, LABA/LAMA-treated patients had significantly lower AE rates (RR: 0.94, 95% CI: [0.89, 0.99], $P=0.02$), with a number needed

to treat for harm (NNTH) of 32 (95% CI: 18, 100) (Table 4; Figure 5B). There were significantly fewer incidences of pneumonia in the LABA/LAMA treatment arm versus the LABA/ICS treatment arm (RR: 0.59, 95% CI: [0.43, 0.81], $P=0.001$), with an NNTH of 84 (95% CI: 54, 184) (Table 4; Figure 6). Neither the incidence of SAEs nor cardiovascular-related events were significantly different between the LABA/LAMA and LABA/ICS groups (RR: 0.90, 95% CI: [0.74, 1.10], $P=0.32$, and RR: 1.17, 95% CI: [0.78, 1.76], $P=0.45$, respectively; Figures S9B and S11B).

The overall rates of death were low across treatment groups, with no significant differences observed between patients treated with LABA/LAMA and those on either LAMA or LABA/ICS ($P=0.46$ and 0.65, respectively; Table 4; Figure S12).

The rate of withdrawal from treatment due to AEs was significantly lower in LABA/LAMA-treated patients compared with those treated with LABA/ICS (RR: 0.83, 95% CI: [0.69, 0.99], $P=0.05$; Table 4) but not when compared with those treated with LAMA alone (Figure S13). However, significantly more LAMA- versus LABA/LAMA-treated patients withdrew due to lack of efficacy (RR: 0.66, 95% CI: [0.51, 0.87], $P=0.003$; NNTH 90, 95% CI: [56, 218]), with no such difference apparent between LABA/LAMA- and LABA/ICS-treated patients (Table 4; Figure S14).

Discussion

In this meta-analysis of 23 RCTs in 20,185 patients with stable moderate-to-very severe COPD, we compared the efficacy and safety of dual bronchodilation with four
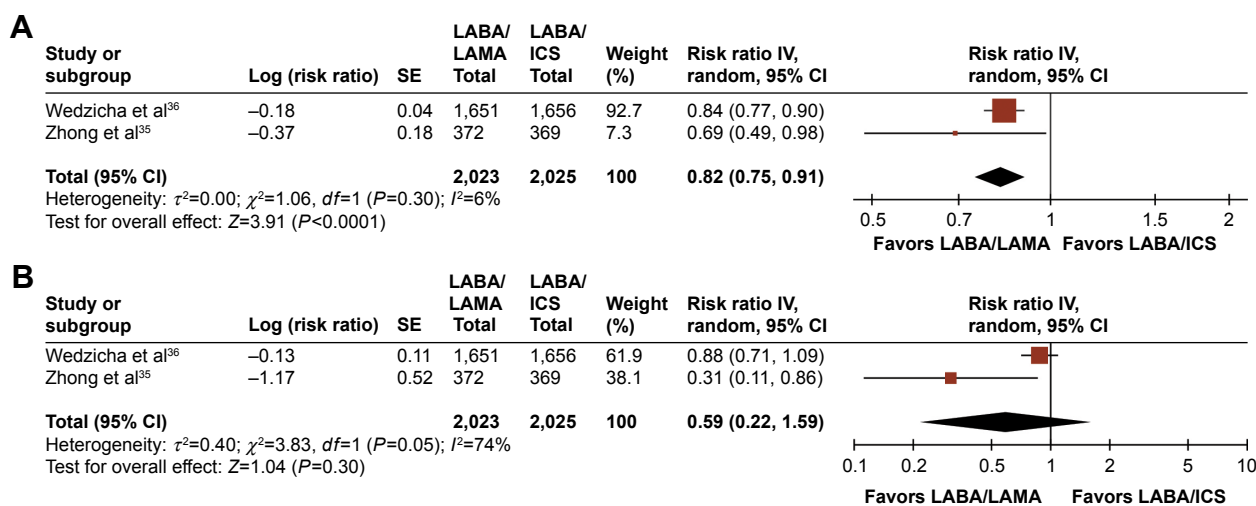
Figure 4 Pooled relative risk of annualized rates of (**A**) moderate and/or severe exacerbations or (**B**) severe exacerbations, with 95% CIs, for eligible studies comparing approved LABA/LAMA combinations with approved LABA/ICS combinations.
Note: Insufficient data prevented a similar analysis to be conducted versus approved LAMAs.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; FEV$_1$, forced expiratory volume in 1 second; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Table 4 Effect of LABA/LAMA versus LAMA or LABA/ICS on safety outcomes

Outcome measure	Studies included	No of patients		Relative risk	
		LABA/LAMA	**Comparator**	**Effect (95% CI)**	I^2, % (*P*-value)
Any AE					
LABA/LAMA versus LAMA	7, 15, 24–33	5,687	6,840	1.00 (0.98, 1.02)	0 (0.95)
LABA/LAMA versus LABA/ICS	34–39	3,835	3,838	0.94 (0.89, 0.99)	23 (0.02)
				NNTH: 32 (18, 100)	
Serious AEs					
LABA/LAMA versus LAMA	7, 15, 24–33	5,687	6,840	1.01 (0.88, 1.15)	21 (0.94)
LABA/LAMA versus LABA/ICS	34–39	3,616	3,656	0.90 (0.74, 1.10)	18 (0.32)
Pneumonia					
LABA/LAMA versus LAMA	7, 24–27, 29–32, 36	4,439	5,584	1.04 (0.78, 1.38)	0 (0.79)
LABA/LAMA versus LABA/ICS	34–39	3,835	3,838	0.59 (0.43, 0.81)	0 (0.001)
				NNTH: 84 (54, 184)	
Cardiac/cardiovascular disorders					
LABA/LAMA versus LAMA	24–31	3,533	4,679	1.09 (0.77, 1.55)	32 (0.62)
LABA/LAMA versus LABA/ICS	34–39	3,835	3,838	1.17 (0.78, 1.76)	0 (0.45)
Deaths					
LABA/LAMA versus LAMA	7, 15, 24–32	5,282	6,434	−0.00 (−0.00, 0.00)	0 (0.46)
LABA/LAMA versus LABA/ICS	34–39	3,835	3,838	0.00 (−0.00, 0.00)	0 (0.65)
Withdrawals due to AEs					
LABA/LAMA versus LAMA	7, 15, 24–26, 28–33	5,300	6,448	0.97 (0.80, 1.18)	19 (0.78)
LABA/LAMA versus LABA/ICS	34–39	3,836	3,841	0.83 (0.69, 0.99)	0 (0.04)
				NNTH: 88 (45, 1,228)	
Withdrawals due to lack of efficacy					
LABA/LAMA versus LAMA	15, 25, 26, 28–33	3,947	5,173	0.66 (0.51, 0.87)	0 (0.003)
				NNTH: 90 (56, 218)	
LABA/LAMA versus LABA/ICS	34–38	1,691	1,695	1.10 (0.60, 2.03)	0 (0.75)

Abbreviations: AE, adverse event; CI, confidence interval; NNTH, number needed to treat for harm; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist.

approved LABA/LAMA FDCs (Ind/Gly, Umec/Vi, Acli/For and Tio/Olo) with treatment using LAMA or LABA/ICS. We have shown that LABA/LAMA combinations provided superior efficacy and comparable safety profiles compared with either LAMA or LABA/ICS treatment.

The efficacy and safety of LABA/LAMA combinations has been evaluated in previous meta-analyses.[13,14,40] Single LABA/LAMA combinations have been evaluated in two studies,[13,14] whereas in a recent meta-analysis,[40] all doses of LABA/LAMA combinations were pooled and treatment effects were compared with the combined pooled effect of the monocomponents (LABA or LAMA) and not with LABA/ICS combinations. In our analysis, we also pooled the data from trials using the same treatments and dose regimens to facilitate comparisons between treatment subgroups. Pooling of data in this manner is recommended in meta-analyses in which there are only a few studies per subgroup because estimates within subgroups are likely to be imprecise; in such instances, the increased accuracy obtained using pooled estimates is likely to exceed any real differences between groups in the true value. The difference in our analysis compared with previous analyses is that we included all

currently available LABA/LAMA combinations and chose only approved doses of these combinations and their comparators. Including all available LABA/LAMA combinations also allowed us to provide indirect insights on the potential relative efficacy of these drugs (although we also recognize that any conclusions drawn will need to be confirmed in prospective, head-to-head studies). In addition, we used as comparators the treatments most commonly prescribed in COPD clinical practice (ie, LAMAs or LABA/ICS). Finally, we elected to implement the robust methodology of a standard meta-analysis design that involved a direct, pooled analysis of LABA/LAMA with their comparators. Based on all of the above, we believe that our analysis provides clinically relevant, high-quality evidence that is applicable to daily clinical practice.

After 12 weeks of treatment, significant improvements in lung function (trough and peak FEV_1) were observed with LABA/LAMA combinations compared with the results with LAMA or LABA/ICS. Furthermore, the percentage of LABA/LAMA-treated patients achieving MCIDs in trough FEV_1 was significantly higher than that with LAMA or LABA/ICS, with NNTBs of 8 and 6, respectively. These magnitudes of

treatment effects and NNTBs are similar to those of previous meta-analyses comparing LABA/LAMA with LAMA and/or LABA/ICS[10,14] and were maintained versus both comparators after longer periods of treatments (24–26 weeks or 52 weeks). Significant improvements in peak FEV_1 relative to baseline measurements were also observed at week 12 for LABA/LAMA treatment versus both comparators (mean differences

of 0.1–0.2 L). As with trough FEV_1, these improvements were still evident after several weeks of treatment.

Previous analyses have shown that improvements in FEV_1 are likely to be associated with improvements in patient-reported outcomes in COPD patients.[41] In our analysis, LABA/LAMA versus LAMA alone improved the patient-reported outcomes of dyspnea (TDI) and HRQoL (SGRQ) at week
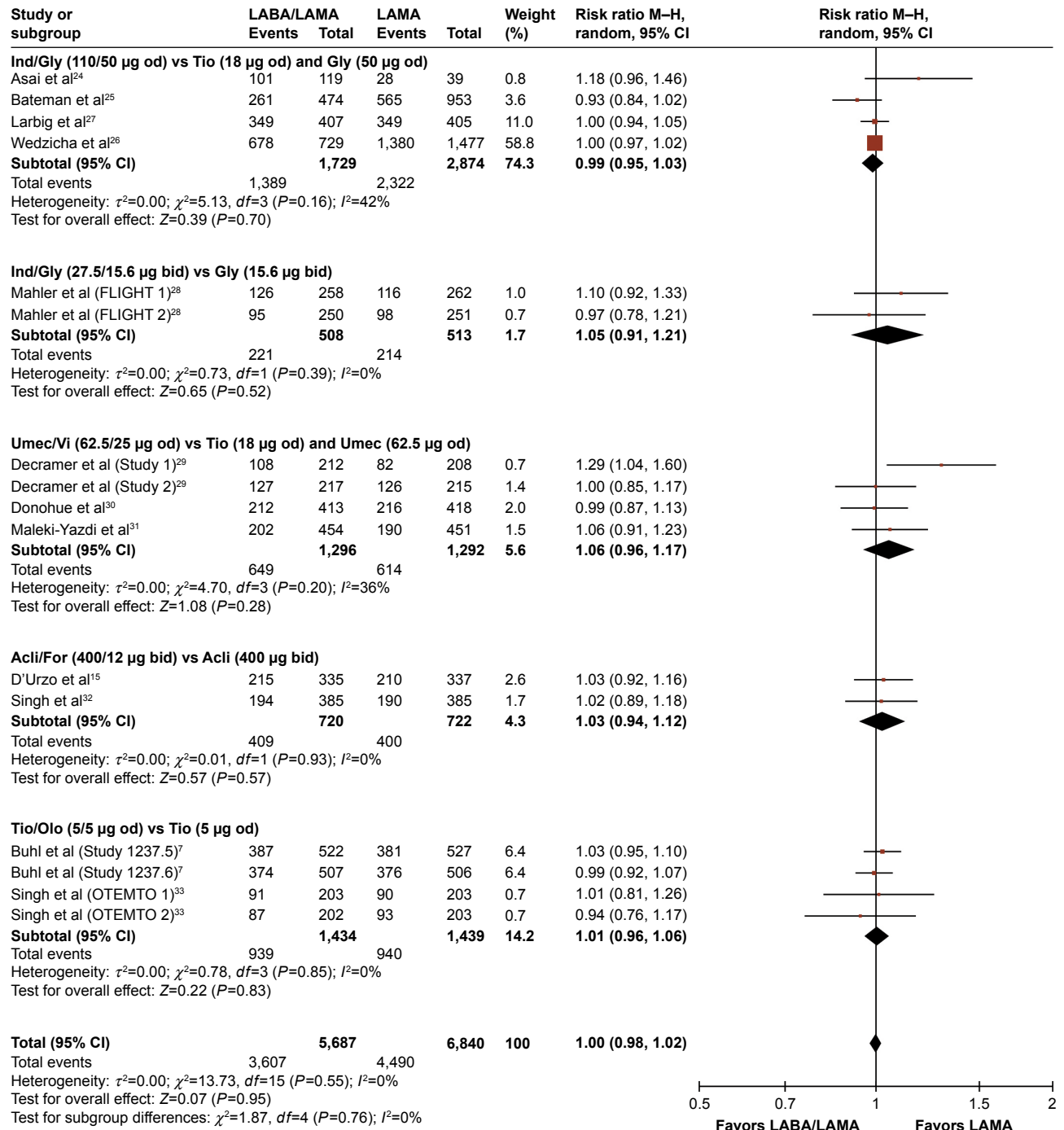
A

Study or subgroup	LABA/LAMA Events	Total	LAMA Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Ind/Gly (110/50 µg od) vs Tio (18 µg od) and Gly (50 µg od)						
Asai et al[24]	101	119	28	39	0.8	1.18 (0.96, 1.46)
Bateman et al[25]	261	474	565	953	3.6	0.93 (0.84, 1.02)
Larbig et al[27]	349	407	349	405	11.0	1.00 (0.94, 1.05)
Wedzicha et al[26]	678	729	1,380	1,477	58.8	1.00 (0.97, 1.02)
Subtotal (95% CI)		**1,729**		**2,874**	**74.3**	**0.99 (0.95, 1.03)**
Total events	1,389		2,322			
Heterogeneity: τ^2=0.00; χ^2=5.13, df=3 (P=0.16); I^2=42%						
Test for overall effect: Z=0.39 (P=0.70)						
Ind/Gly (27.5/15.6 µg bid) vs Gly (15.6 µg bid)						
Mahler et al (FLIGHT 1)[28]	126	258	116	262	1.0	1.10 (0.92, 1.33)
Mahler et al (FLIGHT 2)[28]	95	250	98	251	0.7	0.97 (0.78, 1.21)
Subtotal (95% CI)		**508**		**513**	**1.7**	**1.05 (0.91, 1.21)**
Total events	221		214			
Heterogeneity: τ^2=0.00; χ^2=0.73, df=1 (P=0.39); I^2=0%						
Test for overall effect: Z=0.65 (P=0.52)						
Umec/Vi (62.5/25 µg od) vs Tio (18 µg od) and Umec (62.5 µg od)						
Decramer et al (Study 1)[29]	108	212	82	208	0.7	1.29 (1.04, 1.60)
Decramer et al (Study 2)[29]	127	217	126	215	1.4	1.00 (0.85, 1.17)
Donohue et al[30]	212	413	216	418	2.0	0.99 (0.87, 1.13)
Maleki-Yazdi et al[31]	202	454	190	451	1.5	1.06 (0.91, 1.23)
Subtotal (95% CI)		**1,296**		**1,292**	**5.6**	**1.06 (0.96, 1.17)**
Total events	649		614			
Heterogeneity: τ^2=0.00; χ^2=4.70, df=3 (P=0.20); I^2=36%						
Test for overall effect: Z=1.08 (P=0.28)						
Acli/For (400/12 µg bid) vs Acli (400 µg bid)						
D'Urzo et al[15]	215	335	210	337	2.6	1.03 (0.92, 1.16)
Singh et al[32]	194	385	190	385	1.7	1.02 (0.89, 1.18)
Subtotal (95% CI)		**720**		**722**	**4.3**	**1.03 (0.94, 1.12)**
Total events	409		400			
Heterogeneity: τ^2=0.00; χ^2=0.01, df=1 (P=0.93); I^2=0%						
Test for overall effect: Z=0.57 (P=0.57)						
Tio/Olo (5/5 µg od) vs Tio (5 µg od)						
Buhl et al (Study 1237.5)[7]	387	522	381	527	6.4	1.03 (0.95, 1.10)
Buhl et al (Study 1237.6)[7]	374	507	376	506	6.4	0.99 (0.92, 1.07)
Singh et al (OTEMTO 1)[33]	91	203	90	203	0.7	1.01 (0.81, 1.26)
Singh et al (OTEMTO 2)[33]	87	202	93	203	0.7	0.94 (0.76, 1.17)
Subtotal (95% CI)		**1,434**		**1,439**	**14.2**	**1.01 (0.96, 1.06)**
Total events	939		940			
Heterogeneity: τ^2=0.00; χ^2=0.78, df=3 (P=0.85); I^2=0%						
Test for overall effect: Z=0.22 (P=0.83)						
Total (95% CI)		**5,687**		**6,840**	**100**	**1.00 (0.98, 1.02)**
Total events	3,607		4,490			
Heterogeneity: τ^2=0.00; χ^2=13.73, df=15 (P=0.55); I^2=0%						
Test for overall effect: Z=0.07 (P=0.95)						
Test for subgroup differences: χ^2=1.87, df=4 (P=0.76); I^2=0%						

Risk ratio M–H, random, 95% CI

0.5 0.7 1 1.5 2

Favors LABA/LAMA   Favors LAMA

Figure 5 (*Continued*)

B

Study or subgroup	LABA/LAMA Events	Total	LABA/ICS Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Ind/Gly (110/50 μg od) vs Sal/FP (50/500 μg bid)							
Vogelmeier et al[34]	143	258	159	264	10.6	0.92 (0.79, 1.07)	
Wedzicha et al[36]	1,459	1,678	1,498	1,680	52.1	0.98 (0.95, 1.00)	
Zhong et al[35]	149	372	175	369	8.7	0.84 (0.72, 1.00)	
Subtotal (95% CI)		2,308		2,313	71.4	0.93 (0.85, 1.03)	
Total events	1,751		1,832				
Heterogeneity: $\tau^2=0.00$; $\chi^2=4.51$, $df=2$ ($P=0.10$); $I^2=56\%$							
Test for overall effect: $Z=1.44$ ($P=0.15$)							
Umec/Vi (62.5/25 μg od) vs Sal/FP (50/250 or 500 μg bid)							
Donohue et al (DB2114930)[37]	93	353	96	353	4.3	0.97 (0.76, 1.24)	
Donohue et al (DB2114951)[37]	104	349	108	348	5.0	0.96 (0.77, 1.20)	
Singh et al[38]	99	358	105	358	4.7	0.94 (0.75, 1.19)	
Subtotal (95% CI)		1,060		1,059	14.1	0.96 (0.84, 1.09)	
Total events	296		309				
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.03$, $df=2$ ($P=0.99$); $I^2=0\%$							
Test for overall effect: $Z=0.64$ ($P=0.52$)							
Acli/For (400/12 μg bid) vs Sal/FP (50/500 μg bid)							
Vogelmeier et al[39]	235	467	265	466	14.5	0.88 (0.78, 1.00)	
Subtotal (95% CI)		467		466	14.5	0.88 (0.78, 1.00)	
Total events	235		265				
Heterogeneity: not applicable							
Test for overall effect: $Z=2.00$ ($P=0.05$)							
Total (95% CI)		3,835		3,838	100	0.94 (0.89, 0.99)	
Total events	2,282		2,406				
Heterogeneity: $\tau^2=0.00$; $\chi^2=7.82$, $df=6$ ($P=0.25$); $I^2=23\%$							
Test for overall effect: $Z=2.26$ ($P=0.02$)							
Test for subgroup differences: $\chi^2=0.80$, $df=2$ ($P=0.67$); $I^2=0\%$							

0.5 0.7 1 1.5 2

Favors LABA/LAMA   Favors LABA/ICS

Figure 5 Pooled relative risk of AE incidence at end of treatment, with 95% CIs, for eligible studies comparing approved doses of LABA/LAMAs with approved doses of (**A**) LAMAs and (**B**) LABA/ICS combinations.
Abbreviations: AE, adverse event; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; M–H, Mantel–Haenszel test.

12; 28% and 14% of LABA/LAMA- versus LAMA-treated patients, respectively, were also more likely to achieve MCIDs in these outcome measures (NNTB: 26 and 16, respectively). LABA/LAMA-treated patients also had significantly reduced requirements for rescue medications during the trial than both LAMA- and LABA/ICS-treated patients. A trend in favor of LABA/LAMA versus LABA/ICS treatment was also observed with respect to TDI score and, for health status, a significant benefit in favor of LABA/LAMA was observed at week 26 but not at week 12 versus LABA/ICS. These differences were mainly driven by the Ind/Gly trials; however, significant heterogeneity in component studies prevented firm conclusions to be drawn. As mentioned previously, LABAs improve symptoms and HRQoL more effectively than LAMAs, while LAMAs are superior to LABAs in reducing exacerbations.[9,11] Given that the severity and frequency of exacerbations are associated with impaired HRQoL,[42] the improvements in HRQoL with LABA/LAMA versus LABA/ICS were more evident in studies including patients with more severe exacerbations.[36]

A protocol-defined end point of this meta-analysis was to examine the annualized rate of COPD exacerbations prospectively collected as an efficacy end point. Only three studies (two LABA/LAMA versus LABA/ICS comparisons[35,36] and one LABA/LAMA versus LAMA comparison[26]) prospectively collected exacerbation rates, and therefore a meta-analysis of LABA/LAMA versus LAMA was not possible. Nevertheless, a positive signal for LABA/LAMA versus LAMA treatment was evident in the SPARK study,[26] and the inclusion of data from ongoing studies such as DYNAGITO (Tio/Olo versus Tio) will clarify the role of LABA/LAMA versus LAMA treatment in the prevention of COPD exacerbations, especially in high-risk populations. Compared with LABA/ICS, however, LABA/LAMA treatment significantly reduced the rate of moderate and/or severe exacerbations, and a trend in favor of LABA/LAMA was also observed for reducing severe exacerbations. Whether this finding represents an effect of Ind/Gly, which was the comparator LABA/LAMA used in the two evaluated studies,[35,36] or an overall effect of the LABA/LAMA class needs to be defined in prospective studies using the other available combinations.

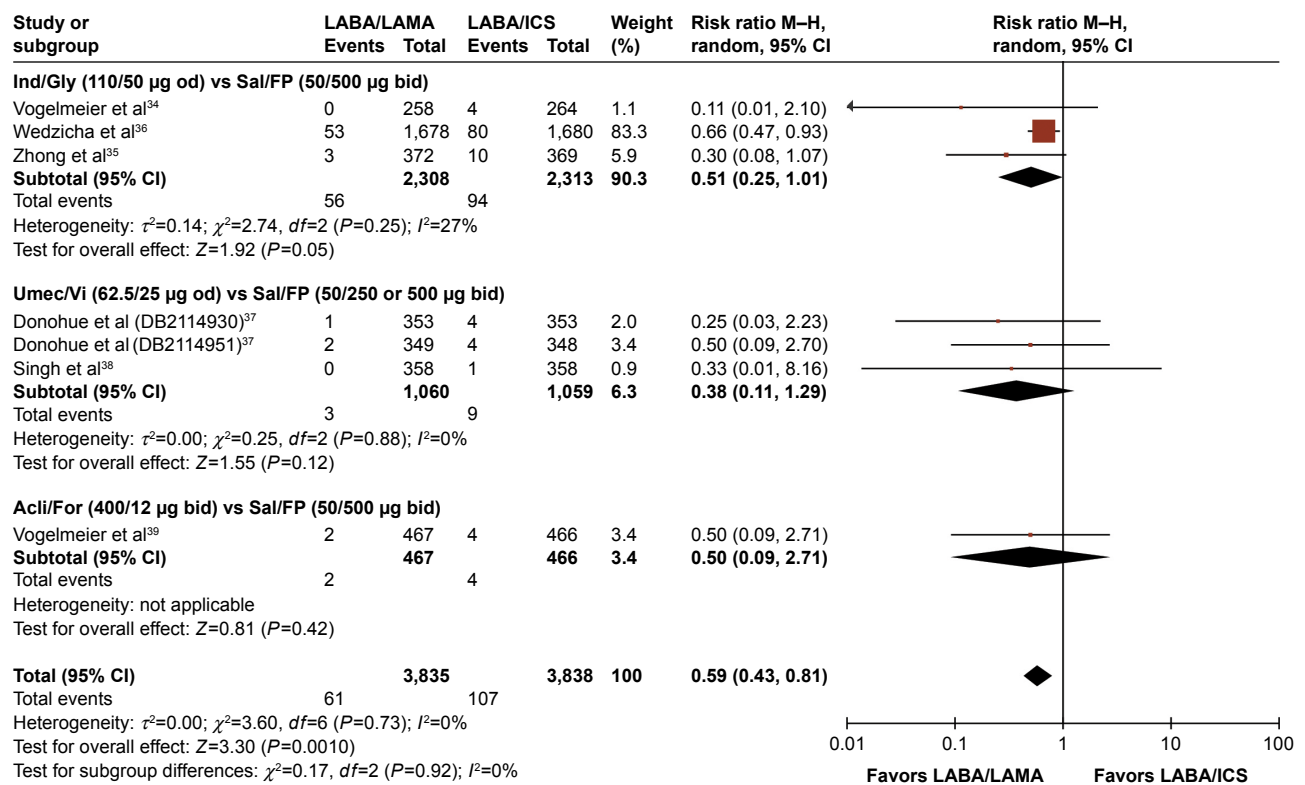AE incidence was significantly lower in LABA/LAMA- versus LABA/ICS-treated patients (NNTH =32), with the

Study or subgroup	LABA/LAMA Events	Total	LABA/ICS Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Ind/Gly (110/50 µg od) vs Sal/FP (50/500 µg bid)							
Vogelmeier et al[34]	0	258	4	264	1.1	0.11 (0.01, 2.10)	
Wedzicha et al[36]	53	1,678	80	1,680	83.3	0.66 (0.47, 0.93)	
Zhong et al[35]	3	372	10	369	5.9	0.30 (0.08, 1.07)	
Subtotal (95% CI)		**2,308**		**2,313**	**90.3**	**0.51 (0.25, 1.01)**	
Total events	56		94				
Heterogeneity: τ^2=0.14; χ^2=2.74, df=2 (P=0.25); I^2=27%							
Test for overall effect: Z=1.92 (P=0.05)							
Umec/Vi (62.5/25 µg od) vs Sal/FP (50/250 or 500 µg bid)							
Donohue et al (DB2114930)[37]	1	353	4	353	2.0	0.25 (0.03, 2.23)	
Donohue et al (DB2114951)[37]	2	349	4	348	3.4	0.50 (0.09, 2.70)	
Singh et al[38]	0	358	1	358	0.9	0.33 (0.01, 8.16)	
Subtotal (95% CI)		**1,060**		**1,059**	**6.3**	**0.38 (0.11, 1.29)**	
Total events	3		9				
Heterogeneity: τ^2=0.00; χ^2=0.25, df=2 (P=0.88); I^2=0%							
Test for overall effect: Z=1.55 (P=0.12)							
Acli/For (400/12 µg bid) vs Sal/FP (50/500 µg bid)							
Vogelmeier et al[39]	2	467	4	466	3.4	0.50 (0.09, 2.71)	
Subtotal (95% CI)		**467**		**466**	**3.4**	**0.50 (0.09, 2.71)**	
Total events	2		4				
Heterogeneity: not applicable							
Test for overall effect: Z=0.81 (P=0.42)							
Total (95% CI)		**3,835**		**3,838**	**100**	**0.59 (0.43, 0.81)**	
Total events	61		107				
Heterogeneity: τ^2=0.00; χ^2=3.60, df=6 (P=0.73); I^2=0%							
Test for overall effect: Z=3.30 (P=0.0010)							
Test for subgroup differences: χ^2=0.17, df=2 (P=0.92); I^2=0%							

0.01   0.1   1   10   100
Favors LABA/LAMA   Favors LABA/ICS

Figure 6 Pooled relative risk of pneumonia incidence, with 95% CIs, for eligible studies comparing approved doses of LABA/LAMAs with approved doses of LABA/ICS combinations.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; M–H, Mantel–Haenszel test.

excess in the LABA/ICS arm plausibly related to the ICS component. This difference, however, did not translate through to SAEs, with no significant differences in SAE incidence observed between LABA/LAMA- and either LABA/ICS- or LAMA-treated patients. The incidence of pneumonia, however, was significantly lower in the LABA/LAMA group versus the LABA/ICS-treated patients (RR: 0.34). Several studies and systematic reviews comparing pneumonia risk in patients receiving ICS alone or in combination with LABA have reported a greater incidence of pneumonia in the LABA/ICS or ICS arms relative to the LABA arm.[5,43] Regarding potential differences between different ICS treatments, some evidence of a higher risk of any pneumonia event has been reported with fluticasone versus budesonide, but no significant differences between the two drugs were observed in terms of SAEs (either pneumonia-related or all-cause) or mortality.[44] In the studies included in the current analysis, salmeterol/fluticasone propionate was the only LABA/ICS used as a comparator; therefore, in our systematic review, we were not able to provide additional data in this regard.

Cardiovascular events were also of particular interest as single-agent LABAs have been associated with increased risk

of arrhythmias,[45] whereas retrospective analyses of LABA/ICS studies have shown a potential benefit for LABA/ICS on the risk of cardiovascular AEs versus placebo.[46] A recent study demonstrated that LABA/ICS did not reduce mortality versus LABA/placebo in patients with, or at risk of, cardiovascular events,[47] disputing the notion that ICS-induced decreases in systemic inflammation can reduce mortality. In the current analysis, no significant differences were observed between any of the treatment classes with respect to cardiac or cardiovascular disorders; this is in accordance with a pooled analysis of safety data showing no increase in the risk of major cardiovascular events in COPD patients treated with LABA/LAMA (Ind/Gly) versus placebo (RR: 1.04, 95% CI: [0.45, 2.42]).[48]

Withdrawals due to AEs were significantly higher in LABA/ICS-treated patients compared with LABA/LAMA-treated patients, presumably due to AEs of pneumonia or other respiratory or extrapulmonary events associated with ICS use. Indeed, a significantly higher incidence of pneumonia (P=0.02) was observed in the LABA/ICS arm of one of the composite studies included in this meta-analysis, while a threefold higher incidence was reported in other studies.[35,36] Withdrawals due to lack of efficacy, however, occurred in

significantly more LAMA- versus LABA/LAMA-treated patients, a finding that was driven largely by two of the component trials.[26,31]

There are certain potential limitations in the current analysis. 1) Open-label tiotropium was used as comparator in some studies;[24,26] this may have affected patient-reported outcomes (TDI and SGRQ), although it should not bias objective outcomes such as FEV_1. 2) As our sample was largely composed of patients with stable COPD and infrequent exacerbations, our findings cannot readily be applied to all patients with frequent exacerbations; nevertheless, a significant proportion of patients with frequent exacerbations were included in the two studies that evaluated exacerbations as an outcome.[26,36] 3) In this analysis, we do not provide any comparisons of LABA/LAMA versus LABA, as we wanted to evaluate the available evidence compared with the most commonly prescribed medications for COPD, namely, LABA/ICS or LAMA. That said, however, the recent network meta-analysis by Oba and Lone[16] did include this comparison, finding LABA/LAMA combinations to be associated with significantly improved efficacy outcomes versus LABAs while maintaining similar safety profiles. 4) Based on the design of the studies identified for this systematic review, we are unable to provide data on outcomes beyond 52/64 weeks or on mortality or disease progression. Further studies using LABA/LAMA combinations are required to address these important scientific questions. 5) Given the heterogeneity of COPD, it would have been of interest to evaluate further parameters such as additional spirometric measures (eg, forced vital capacity [FVC][49] or other markers of small airways dysfunction) or the effects of treatments on physical activity.[50,51] Data on such parameters are, however, not uniformly presented in RCTs; therefore, in this meta-analysis, the most commonly used clinically relevant outcomes were prespecified as the outcomes of interest. 6) Definitive conclusions on the relative efficacy of different treatments within the LABA/LAMA class cannot be made as the individual treatments were not compared head to head. Nevertheless, we observed differences between different drugs, and the clinical significance of these differences needs to be further evaluated.

Conclusion

This meta-analysis of 23 RCTs provides evidence that LABA/LAMA FDCs offer superior efficacy and comparable safety to LAMA or LABA/ICS in patients with stable moderate-to-very severe COPD, indicating their potential as first-line treatment options for this population of patients.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd, UK and 74% of Observational and Pragmatic Research Institute Pte Ltd, Singapore; and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, HTA, and Medical Research Council. AA has acted as a Consultant and has served on advisory boards for Novartis Pharma AG, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Sunnovion. DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies, including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Glenmark, Merck, Napp, Novartis, Pfizer, Respivert, Skyepharma, Takeda, Teva, Therevance and Verona. PA, GB, FP, RF and KK are employees and shareholders of Novartis Pharma AG. KK had previously received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, Elpen, and Novartis, and participated on advisory boards arranged by AstraZeneca, Chiesi, Elpen, and Novartis. The authors report no other conflicts of interest in this work.

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