DUAL Bronchodilation for the Treatment of COPD

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GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator FEV1)

Figure 2.7

In COPD patients (FEV1/FVC < 0.7):

GOLD 1:	Mild	FEV1 ≥ 80% predicted
GOLD 2:	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3:	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4:	Very Severe	FEV1 < 30% predicted

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Modified MRC Dyspnea Scale

Figure 2.8

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

mMRC Grade 0	mMRC Grade 1	mMRC Grade 2	mMRC Grade 3	mMRC Grade 4
I only get breathless with strenuous exercise	I get short of breath when hurrying on the level or walking up a slight hill	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level	I stop for breath after walking about 100 meters or after a few minutes on the level	I am too breathless to leave the house or I am breathless when dressing or undressing
☐	☐	☐	☐	☐

Reference: ATS (1982) Am Rev Respir Dis. Nov;126(5):952-6.

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CAT™ Assessment

Figure 2.9

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

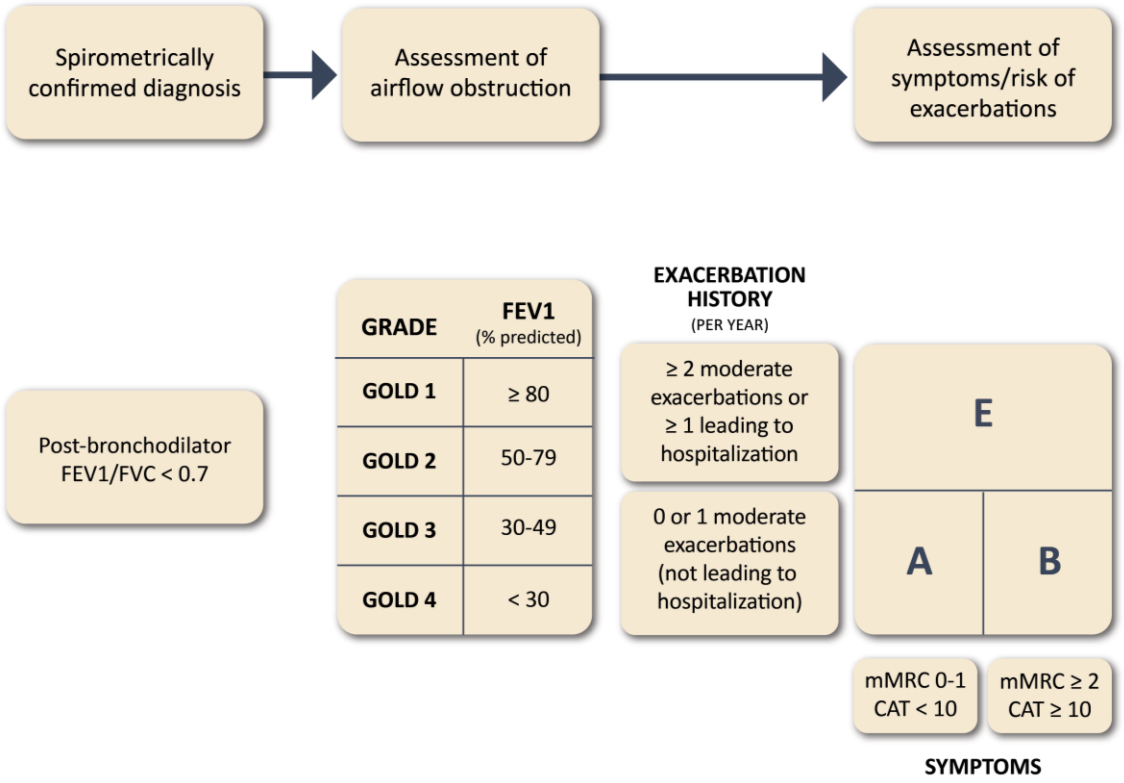
EXAMPLE: I am very happy	0	X	2	3	4	5	I am very sad	Score
I never cough	0	1	2	3	4	5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition	
I have lots of energy	0	1	2	3	4	5	I have no energy at all	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE:

GOLD ABE Assessment Tool

Figure 2.10



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Initial Pharmacological Treatment

Figure 3.7

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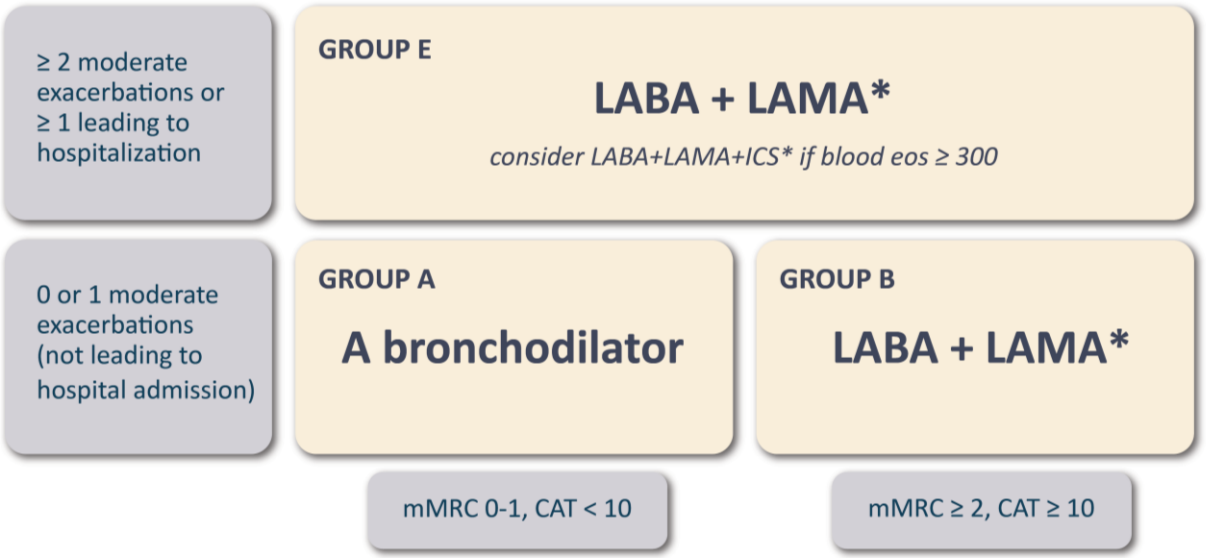

*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment

Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

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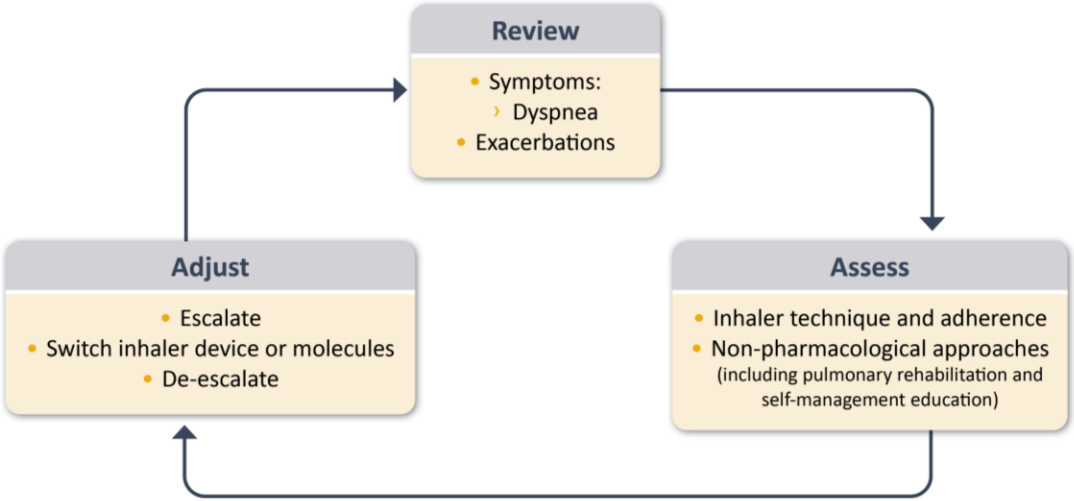
Management Cycle

Figure 3.8



Non-Pharmacological Management of COPD*

Figure 3.12

Patient Group	Essential	Recommended	Depending on Local Guidelines
A	Smoking cessation (can include pharmacological treatment)	Physical activity	Influenza vaccination COVID-19 vaccinations Pneumococcal vaccination Pertussis vaccination Shingles vaccination RSV vaccination
B and E	Smoking cessation (can include pharmacological treatment) Pulmonary rehabilitation	Physical activity	Influenza vaccination COVID-19 vaccinations Pneumococcal vaccination Pertussis vaccination Shingles vaccination RSV vaccination

*Can include pharmacological treatment

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Follow-up Pharmacological Treatment

Figure 3.9

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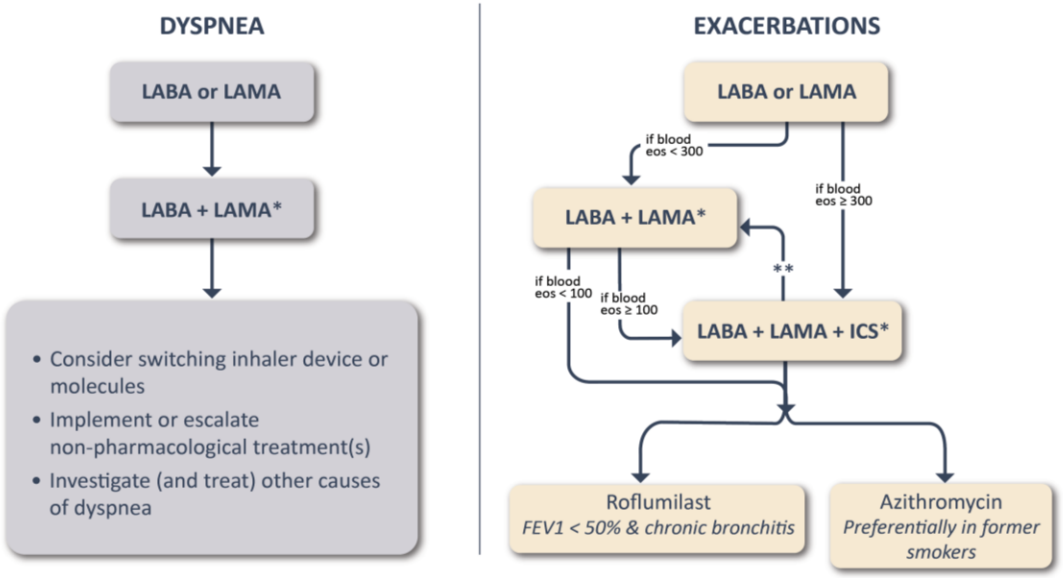
1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

Exacerbations refers to the number of exacerbations per year

Bronchodilators in Stable COPD

Figure 3.19

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- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (**Evidence A**).
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

Factors to Consider when Initiating ICS Treatment

Figure 3.21

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Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.7 & 3.18 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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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 ≥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.

≥ 12 weeks (12-52 weeks), 18 RCT, (n:20185 patients)

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, FEV_1, FVC, HS, RMU
	NCT01202188[25]	Multicenter, 26	474	473/480 (Gly/Tio)	[b]FEV_1, 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, FEV_1, HS, FVC, RMU
Ind/Gly 27.5/15.6 μg bid versus Gly 15.6 μg bid	NCT01727141	Multicenter, 12	260	261	[b]FEV_1 AUC_{0-12h}, 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]FEV_1, Dys, HS, EX, SAF
	NCT01316913[29]		217	215 (Tio)	
	NCT01313650[30]	Multicenter, 24	413	418 (Umec)	[b]FEV_1, FVC, Dys, HS, EX, RMU, SAF
	NCT01777334[31]	Multicenter, 24	454	451 (Tio)	[b]FEV_1, Dys, HS, EX, SAF
Acli/For 400/12 μg bid versus Acli 400 μg bid	NCT01437397[15]	Multicenter, 24	338	340	[b]FEV_1, Dys, HS, EX, RMU, SAF
	NCT01462942[32]	Multicenter, 24	385	385	[b]FEV_1, Dys, HS, EX, RMU, SAF
Tio/Olo 5/5 μg od versus Tio 5 μg od	NCT01431274	Multicenter, 52	522	527	[b]FEV_1, [b]FEV_1 AUC_{0-3h}, [b]HS, Dys, FVC
	NCT01431287[7]		507	506	
	NCT01964352	Multicenter, 12	204	204	[b]HS, [b]FEV_1, AUC_{0-3h}, [b]FEV_1, 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]FEV_1, AUC_{0-12h}, FEV_1, FVC, Dys, HS, RMU, SAF
	NCT01709903[35]	Multicenter, 26	372	369	[b]FEV_1, FEV_1 AUC_{0-4h}, peak FEV_1, FVC, HS, Dys
	NCT01782326[36]	Multicenter, 52	1,678	1,680	[b]EX, FEV_1, 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]FEV_1, Dys, HS, EX, SAF
	NCT01879410[37]		349	348	[b]SAF, FEV_1, EX
	NCT01822899[38]	Multicenter, 12	334	340	[b]FEV_1, Dys, HS, RMU, SAF
Acli/For 400/12 μg bid versus Sal/FP 50/500 μg bid	NCT01908140[39]	Multicenter, 24	467	466	[b]FEV_1, 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; FEV_1, 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 β_2-agonist; LAMA, long-acting muscarinic antagonist; od, once daily; bid, twice daily.

- LABA/LAMAs versus LAMAs: 12 RCT
- LABA/LAMAs with LABA/ICS: 6 RCT

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.

LABA/LAMA compared with both LAMA and LABA/IKS ;
- Trough FEV1
- minimum clinically important difference (MCID ≥100mL) in FEV1
- Peak FEV1 => significantly increased with LABA/LAMA treatment

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)	I^2, % (*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		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		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		–1.34 (–1.94, –0.75)	0 (<0.0001)
Week 52	7, 26	1,987	2,539		–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		–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.

- TDI, SGRQ and MCID was significantly improved in LABA/ LAMA- versus LAMA. But in TDI, no statistically significant difference between LABA/ LAMA and LABA/ICS . At week 26, SGRQ scores had significantly improved in LABA/LAMA- versus LABA/ICS-treated patients.

- Rescue medication use was significantly reduced in LABA/ LAMA-treated patients compared with those treated with either LAMA or LABA/ICS

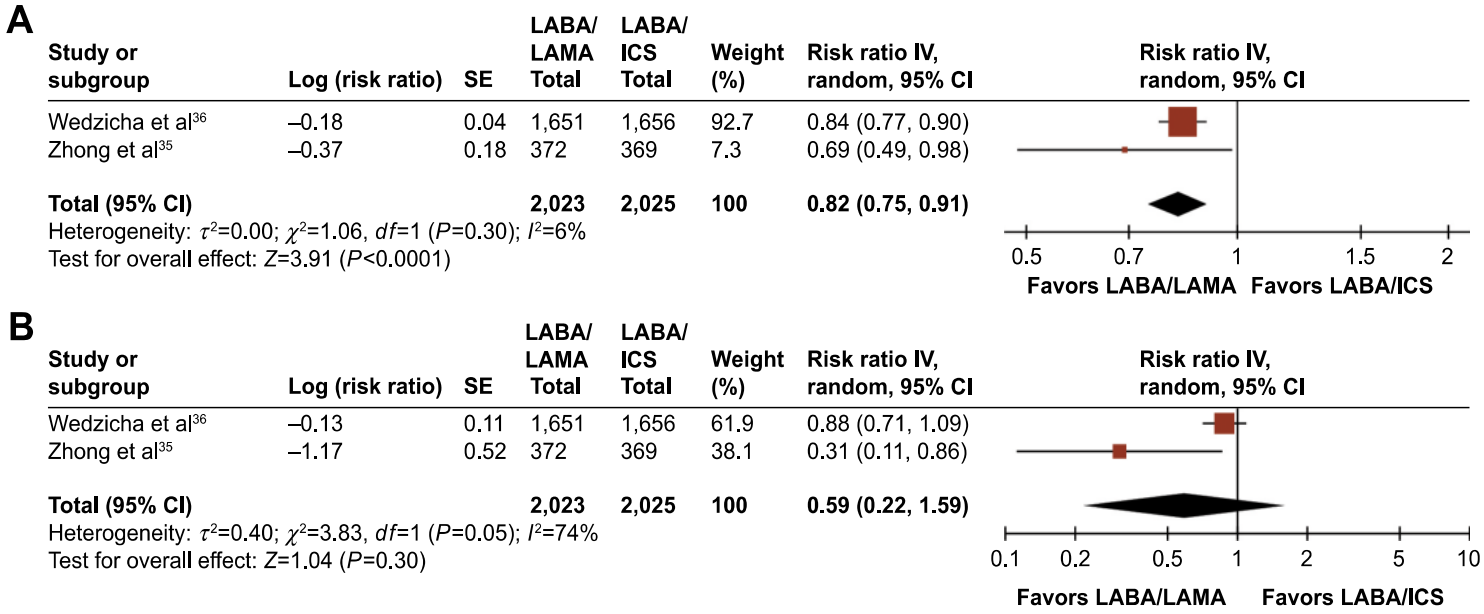

Figure 4 Pooled relative risk of annualized rates of (**A**) moderate and/or severe exacerbations or (**B**) severe exacerbations, with 95% CIs, for eligible studies comparing approved LABA/LAMA combinations with approved LABA/ICS combinations.

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.

- There were insufficient data to conduct a meta-analysis on the effect of treatment on prospectively collected COPD exacerbation rates in LABA/LAMA- versus LAMA-treated patients because such data were available in only one study.

- 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)

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 β_2-agonist; LAMA, long-acting muscarinic antagonist.

- No significant difference in the incidence of AEs was observed in patients treated with LABA/LAMA versus LAMA. Likewise, no significant difference in the incidence of SAEs, pneumonia, CVD.

- Compared with LABA/ICS treatment, however, LABA/ LAMA-treated patients had significantly lower AE rates. Also, there were significantly fewer incidences of pneumonia.

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.

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.

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Review

LABA/LAMA as First-Line Therapy for COPD: A Summary of the Evidence and Guideline Recommendations

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Abstract: Inhaled bronchodilators (alone or in combination) are the cornerstone of treatment for symptomatic patients with COPD, either as initial/first-line treatment or for second-line/treatment escalation in patients who experience persistent symptoms or exacerbations on monotherapy. The Global Initiative for Chronic Obstructive Lung Disease 2022 report recommends initial pharmacological treatment with a long-acting muscarinic antagonist (LAMA) or a long-acting β_2-agonist (LABA) as monotherapy for most patients, or dual bronchodilator therapy (LABA/LAMA) in patients with more severe symptoms, regardless of exacerbation history. The recommendations for LABA/LAMA are broader in the American Thoracic Society treatment guidelines, which strongly recommend LABA/LAMA combination therapy over LAMA or LABA monotherapy in patients with COPD and dyspnea or exercise intolerance. However, despite consistent guideline recommendations, real-world prescribing data indicate that LAMA and/or LABA without an inhaled corticosteroid are not the most

Table 2. Global consensus on LABA/LAMA in the long-term management of COPD.

Guideline	Dyspnea, Infrequent Exacerbations	Dyspnea, Frequent Exacerbations
GOLD [1]	Initial treatment • GOLD A[1]—bronchodilator • GOLD B[2]—LABA or LAMA Follow-up treatment • Escalate to LABA/LAMA if dyspnea not controlled with monotherapy	Initial treatment • GOLD C[3]—LAMA • GOLD D[4]—LAMA or LABA/LAMA (if highly symptomatic) or LABA/ICS (blood eosinophil counts >300 cells/µL) Follow-up treatment • Escalate to LABA/LAMA (from monotherapy) if dyspnea/exacerbations not controlled with monotherapy • Consider LABA/ICS or LABA/LAMA/ICS if blood eosinophil counts ≥300 cells/µL or ≥100 cells/µL and ≥2 moderate exacerbations/1 hospitalization
ATS [13]	• Strong recommendation for LABA/LAMA for patients with dyspnea or exercise intolerance	• Conditional recommendation for LABA/LAMA/ICS over LABA/LAMA for dyspnea or exercise intolerance and ≥1 exacerbation/year • Conditional recommendation for ICS withdrawal (LABA/LAMA/ICS > LABA/LAMA) if no exacerbations in previous year
NICE [18]	• LABA/LAMA for patients who remain breathless or have exacerbations[5] • For patients with asthmatic features: consider LABA/ICS or LABA/LAMA/ICS	• LABA/LAMA for patients who remain breathless or have exacerbations[5] • For patients with asthmatic features: consider LABA/ICS • Consider LABA/LAMA/ICS for those with a severe exacerbation (requiring hospitalization) or 2 moderate exacerbations/year

Spain [19,30]	• Low risk[6]: LAMA as initial treatment, escalated to LABA/LAMA if still symptomatic on monotherapy
	• High risk[7]: LABA/LAMA as initial treatment for all non-exacerbators
		• Low risk[6]: LAMA as initial treatment, escalated to LABA/LAMA if still symptomatic on monotherapy
		• High risk[7]:
		  • Eosinophilic exacerbator (>300 cells/µL): LABA/ICS
		  • Non-eosinophilic exacerbator: initial treatment with LABA/LAMA. ICS may be useful in some cases, although its efficacy is inferior

Germany [20]	• Initial treatment with a long-acting bronchodilator or LABA/LAMA	• Initial treatment with a long-acting bronchodilator or LABA/LAMA • ICS should be considered if exacerbations occur despite adequate treatment with long-acting bronchodilators
Japan [21,31]	• LABA or LAMA monotherapy to address symptoms in moderate COPD • Escalate to LABA/LAMA if symptoms persist despite monotherapy	• LABA or LAMA monotherapy to address symptoms in moderate COPD • Escalate to LABA/LAMA if symptoms persist despite monotherapy • ICS reserved for patients with concomitant asthma

- ATS guideline => Strong recommendation for LABA/LAMA for patients with dyspnea or exercise intolerance.

- Conditional recommendation for LABA/LAMA/ICS over LABA/LAMA for dyspnea or exercise intolerance and ≥1 exacerbation/year.

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Table 3. Comparison of LABA/LAMA with monotherapy, LABA/ICS or triple therapy.

LABA/LAMA versus	Lung Function	Dyspnea	Exacerbations	Exercise Tolerance	Health/Functional Status/Quality of Life	Pneumonia
LAMA	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]
	Calzetta Eur Respir Rev 2017 MA [39]	Calzetta Eur Respir Rev 2017 MA [39]	Calverley Lancet Respir Med 2018 RCT [40]	Calzetta Respir Med 2017 MA [41]	Calzetta Eur Respir Rev 2017 MA [39]	Oba Cochrane Library 2018 SR/MA [34]
	Aziz Int J Chron Obstruct Pulmon Dis 2018 SR/MA [42]	Mahler Eur Respir J 2014 RCT [43]	Ichinose Int J Chron Obstruct Pulmon Dis 2018 RCT [44]	O'Donnell Eur Respir J 2017 PRCT [45]	Ferguson NPJ Prim Care Respir Med 2017 PRCT [46]	
	Mahler Eur Respir J 2014 RCT [43]	Ferguson NPJ Prim Care Respir Med 2017 PRCT [46]	Wedzicha Adv Ther 2020 PRCT [47]	Minakata Int J Chron Obstruct Pulmon Dis 2019 PRCT [48]	Martinez Int J Chron Obstruct Pulmon Dis 2019 PRCT [49]	
	Martinez Int J Chron Obstruct Pulmon Dis 2019 PRCT [49]	Martinez Int J Chron Obstruct Pulmon Dis 2019 PRCT [49]	Chen Ther Adv Respir Dis 2020 SR/MA [35]	Ichinose Int J Chron Obstruct Pulmon Dis 2018 RCT [50]	Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]	
	Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]	Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]	Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]	Maltais Adv Ther 2021 MA/PRCT [52]	Buhl Eur Respir J 2015 PRCT [53]	
	Buhl Eur Respir J 2015 PRCT [53]	O'Donnell Eur Respir J 2017 PRCT [45]		Takahashi Int J Chron Obstruct Pulmon Dis 2020 RCT [54]	Singh Respir Med 2015 PRCT [55]	
	Singh Respir Med 2015 PRCT [55]	Miravitlles Respir Res 2017 SR/MA [56]			Labor Respiration 2018 SR [57]	
	Beeh Pulm Pharmacol Ther 2015 RCT [58]	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]			Miravitlles Respir Res 2017 SR/MA [56]	
	Maltais Adv Ther 2019 RCT [59]	Takahashi Int J Chron Obstruct Pulmon Dis 2020 RCT [54]			Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]	
	Miravitlles Respir Res 2017 SR/MA [56]	Calzetta Chest 2016 SR/MA [60]			Calzetta Chest 2016 SR/MA [60]	
	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]	Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]			Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]	
	Calzetta Chest 2016 SR/MA [60]	Maltais Eur Respir J 2019 RCT [61]				
	O'Donnell Eur Resp J 2017 PRCT [45]					

Compared with LAMA, LABA/LAMA fixed dose combinations;

- In terms of lung function, dyspnea, exacerbations, exercise tolerance and quality of life, it was superior (green) in most studies and equal (yellow) in rare studies.

- When compared in terms of pneumonia, it is equal.

Table 3. *Cont.*

LABA/LAMA versus	Lung Function	Dyspnea	Exacerbations	Exercise Tolerance	Health/Functional Status/Quality of Life	Pneumonia
	Ichinose Int J Chron Obstruct Pulmon Dis 2018 RCT2 [50]					
	Maltais Adv Ther 2021 MA/PRCT [52]					
	Takahashi Int J Chron Obstruct Pulmon Dis 2020 RCT [54]					
LABA	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Oba Cochrane Library 2018 SR/MA [34]
	Calzetta Eur Respir Rev 2017 MA [39]	Calzetta Eur Respir Rev 2017 MA [39]	Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]	O'Donnell Eur Respir J 2017 PRCT [45]	Calzetta Eur Respir Rev 2017 MA [39]	
	Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]	Ferguson NPJ Prim Care Respir Med 2017 PRCT [46]			Ferguson NPJ Prim Care Respir Med 2017 PRCT [46]	
	Beeh Pulm Pharmacol Ther 2015 RCT [58]	Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]			Price Int J Chron Obstruct Pulmon Dis 2017 SR [51]	
	Miravitlles Respir Res 2017 SR/MA [56]	Miravitlles Respir Res 2017 SR/MA [56]			Miravitlles Respir Res 2017 SR/MA [56]	
	Calzetta Chest 2016 SR/MA [60]	Calzetta Chest 2016 SR/MA [60]			Calzetta Chest 2016 SR/MA [60]	
	O'Donnell Eur Respir J 2017 PRCT [45]	O'Donnell Eur Respir J 2017 PRCT [45]			Labor Respiration 2018 SR [57]	
		Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]			Mammen et al. Ann Am Thorac Soc 2020 a SR/MA [36]	
LABA/ICS	Horita Cochrane Database Syst Rev 2017 CR [62]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Horita Cochrane Database Syst Rev 2017 CR [62]		Horita Cochrane Database Syst Rev 2017 CR [62]	Suissa Chest 2019 RWS [63]
	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Miravitlles Respir Res 2017 SR/MA [56]	Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]		Rogliani Int J Chron Obstruct Pulmon Dis 2018 SR [37]	Quint Adv Ther 2021 RWS [64]
	Aziz Int J Chron Obstruct Pulmon Dis 2018 SR/MA [42]	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]		Miravitlles Respir Res 2017 SR/MA [56]	Horita Cochrane Database Syst Rev 2017 CR [62]
	Beeh Int J Chron Obstruct Pulmon Dis 2016 RCT [65]		Quint Adv Ther 2021 RWS [64]		Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]

LABA/LAMA fixed dose combinations compared with LABA and LABA/ICS;

- In terms of lung function, dyspnea, exacerbations, exercise tolerance and quality of life, most studies found superior (green) and rarely equal (yellow).

- When compared in terms of pneumonia, it is equal to LABA and superior to LABA/ICS.

Table 3. *Cont.*

LABA/LAMA versus	Lung Function	Dyspnea	Exacerbations	Exercise Tolerance	Health/Functional Status/Quality of Life	Pneumonia
	Miravitlles Respir Res 2017 SR/MA [56]		Suissa Chest 2019 RWS [63]			
	Rodrigo Int J Chron Obstruct Pulmon Dis 2017 SR/MA [38]					
Triple therapy	Cazzola Eur Respir J 2018 SR/MA [66]	Koarai Respir Res 2021 SR/MA [67]	Cazzola Eur Respir J 2018 SR/MA [66]		Koarai Respir Res 2021 SR/MA [67]	Mammen Annals ATS 2020 bSR/MA [68]
	Koarai Respir Res 2021 SR/MA [67]	Mammen Annals ATS 2020 bSR/MA [68]	Koarai Respir Res 2021 SR/MA [67]		Koarai Respir Investig 2022 SR/MA [69]	Zheng The BMJ 2018 SR/MA [70]
	Koarai Respir Investig 2022 SR/MA [69]		Cabrera Ann Epidemiol 2022 RWS [71]		Zheng The BMJ 2018 SR/MA [70]	Quint Expert Rev Respir Med 2022 RWS [72]
	Zheng The BMJ 2018 SR/MA [70]		Quint Expert Rev Respir Med 2022 RWS [72]			Koarai Respir Res 2021 SR/MA [67]
			Suissa Chest 2020 RWS [73]			Suissa Chest 2020 RWS [73]
			Koarai Respir Investig 2022 SR/MA [69]			Cazzola Eur Respir J 2018 SR/MA [66]
			Lee PLOS Med 2019 SR/MA [74]			Koarai Respir Investig 2022 SR/MA [69]
			Mammen Annals ATS 2020 bSR/MA [68]			Lee PLOS Med 2019 SR/MA [74]
			Zheng The BMJ 2018 SR/MA [70]			

Color code: LABA/LAMA superior ; LABA/LAMA equal ; LABA/LAMA inferior . Although the prespecified crude analysis produced a rate ratio of 0.93 (p-value > 0.01, not significant) comparing LABA/LAMA to LAMA alone, a sensitivity analysis adjusted for the baseline rate of exacerbations and other factors produced a rate ratio of 0.89 (p-value 0.001, significant). CR, Cochrane review; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MA, meta-analysis; PRCT, pooled or post hoc analysis of randomized clinical trials; RCT, randomized clinical trial; RWS, real-world study; SR, systematic review.

Compared with triple therapy, LABA/LAMA;

- Lung function, dyspnea, exacerbations and quality of life were found to be inferior (red) in most studies and equal (yellow) in a few studies.

- When compared in terms of pneumonia, it was superior in most studies.

5. Conclusions

Global and national guidelines for the treatment of COPD consistently recommend bronchodilator monotherapy for symptom control at treatment initiation, stepping up to dual bronchodilator therapy (LABA/LAMA) if symptoms persist. However, there is now extensive evidence showing the benefits of LABA/LAMA versus monotherapy, which has translated into changes to some treatment guidelines, such as those published by ATS, which issues a strong recommendation for LABA/LAMA over monotherapy in patients with COPD and dyspnea or exercise intolerance. The evidence we have presented in this review suggests that LABA/LAMA is an appropriate first-line therapy for the majority of patients with COPD who are symptomatic (i.e., breathless) and infrequent exacerbators. Based on the available evidence, ICS-containing therapy (LABA/ICS and triple therapy) should not be used as an initial treatment for COPD but rather as a step-up from bronchodilator therapy if indicated, per global and national guidelines.

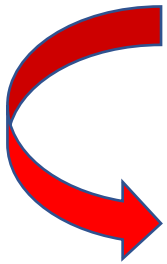
- The evidence we have presented in this review suggests that **LABA/LAMA** is **an appropriate first-line therapy for the majority of patients with** COPD who are symptomatic (i.e., breathless) and infrequent exacerbators.

- Based on patients with COPD who are symptomatic (i.e., breathless) and infrequent exacerbators.the available evidence, **ICS-containing therapy (LABA/ICS and triple therapy)** should **not be used as an initial treatment** for COPD but rather **as a step-up** from bronchodilator therapy if indicated, per global and national guidelines.

In conclusion

- **DUAL Bronchodilators(LABA/LAMA)** for the Treatment of COPD is **first line terapy.**

- If Eos ≥300 cells/µL
- If have concomitant asthma
- Hospitalization for exacerbation
- ≥ 2 moderate exacerbation
- 1 moderate exacerbation and Eos ≥100 cells/µL and/or mMRC ≥ 2



Step-up (Triple treatment- LABA/LAMA/IKS)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