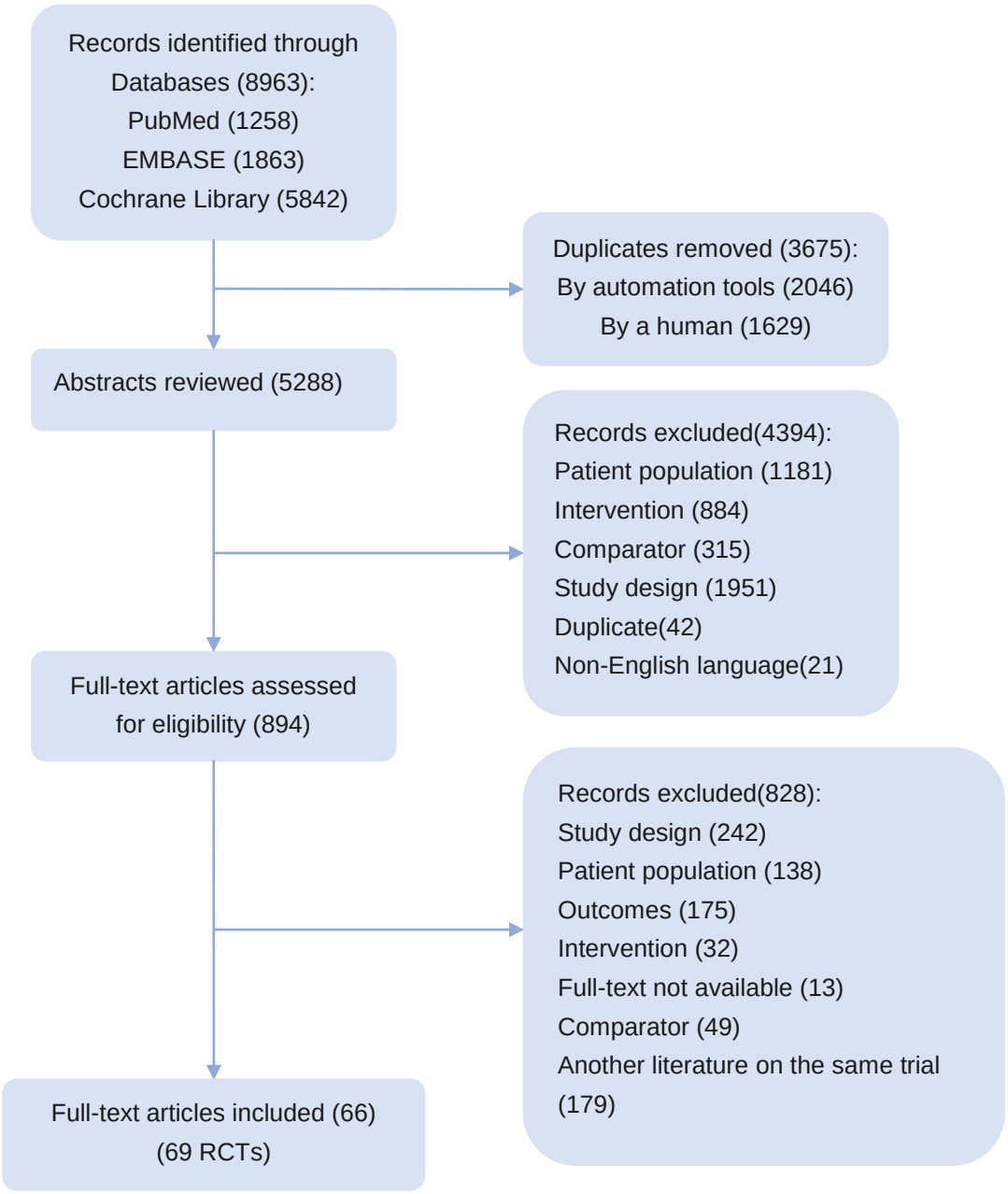
Appendix

Supplementary Table SI. Search strategies

Database	PubMed
Search time	14 June 2023
Strategy	1. (COPD[Title/Abstract]) OR (chronic obstructive pulmonary disease[Title/Abstract]) 2. "Pulmonary Disease, Chronic Obstructive"[Mesh] 3. #1 OR #2 4. ((((((ICSs[Title/Abstract]) OR (Inhaled corticosteroids[Title/Abstract])) OR (budesonide[Title/Abstract])) OR (fluticasone[Title/Abstract])) OR (beclometasone[Title/Abstract])) OR (mometasone[Title/Abstract])) OR (beclomethasone[Title/Abstract]) 5. (((((((LABA[Title/Abstract]) OR (long-acting β2-agonist[Title/Abstract]))) OR (long acting beta-agonists[Title/Abstract])) OR (formoterol[Title/Abstract])) OR (vilanterol[Title/Abstract])) OR (Salmeterol[Title/Abstract])) OR (indacaterol[Title/Abstract])) OR (olodaterol[Title/Abstract]) 6. (((((((LAMA[Title/Abstract]) OR (long-acting muscarinic receptor antagonist[Title/Abstract])) OR (glycopyrrolate[Title/Abstract])) OR (glycopyrronium[Title/Abstract])) OR (aclidinium[Title/Abstract])) OR (umeclidinium[Title/Abstract])) OR (tiotropium[Title/Abstract])) OR (ipratropium[Title/Abstract]) 7. (((Dupilumab[Title/Abstract]) OR (Dupixent[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN-668[Title/Abstract]) 8. #4 OR #5 OR #6 OR #7 9. #3 AND #8 10. #9 AND ((randomizedcontrolledtrial[Filter]) AND (humans[Filter]))
Database	EMBASE
Search time	14 June 2023
Strategy	1. 'chronic obstructive lung disease'/exp 2. 2. 'chronic obstructive lung disease' OR 'copd':ab,kw,ti 3. 3. #1 OR #2 4. 4. 'icss':ab,kw,ti OR 'inhaled corticosteroids':ab,kw,ti OR 'budesonide':ab,kw,ti OR 'fluticasone':ab,kw,ti OR 'mometasone':ab,kw,ti OR 'beclomethasone':ab,kw,ti 5. 5. 'laba':ab,kw,ti OR 'long acting beta-agonists':ab,kw,ti OR 'formoterol':ab,kw,ti OR 'vilanterol':ab,kw,ti OR 'salmeterol':ab,kw,ti OR 'indacaterol':ab,kw,ti OR 'olodaterol':ab,kw,ti 6. 6. 'lama':ab,kw,ti OR 'long-acting muscarinic receptor antagonist':ab,kw,ti OR 'glycopyrrolate':ab,kw,ti OR 'glycopyrronium':ab,kw,ti OR 'aclidinium':ab,kw,ti OR

	'umeclidinium':ab,kw,ti OR 'tiotropium':ab,kw,ti OR 'ipratropium':ab,kw,ti 7. 7. 'Dupilumab':ab,kw,ti OR 'Dupixent':ab,kw,ti OR 'SAR-231893':ab,kw,ti OR 'REGN-668':ab,kw,ti 8. 8. #4 OR #5 OR #6 OR #7 9. 9. #3 AND #8 10. #9 AND 'human'/de AND 'randomized controlled trial'/de
Database	CENTRAL
Search time	14 June 2023
Strategy	1. (COPD or chronic obstructive pulmonary disease):ti,ab,kw 2. MeSH descriptor:[Pulmonary Disease, Chronic Obstructive] explode all trees 3. #1 or #2 4. (ICSs or Inhaled corticosteroids or budesonide or fluticasone or mometasone or beclomethasone):ti,ab,kw 5. (LABA or long acting beta-agonists or formoterol or vilanterol or salmeterol or indacaterol or olodaterol):ti,ab,kw 6. (LAMA or long-acting muscarinic receptor antagonist or glycopyrrolate or glycopyrronium or aclidinium or umeclidinium or tiotropium or ipratropium):ti,ab,kw 7. (Dupilumab or Dupixent or SAR-231893 or REGN-668):ti,ab,kw 8. #4 or #5 or #6 or #7 9. #3 and #8 (Limits:in Trials)

Supplementary Figure S1. Flowchart of selection of included studies



Trial/Author year	Study design	post FEV1%pred inclusion criteria	Median follow-up (m)	Total number	Treatment	Daily dose	Number	All-cause death, n	Patients with≥1 exacerbation, n	Mean			Male(%)	Smoking status		COPD severity(%)		
										Age (y)	BMI (kg/㎡)	post FEV1%pred (%)		Former smokers(%)	Current smokers(%)	Moderate	Severe	Very severe
ETHOS 2020	DB, MC	25%-65%	13	8,509	ICS/LABA/LAMA	ICS budesonide 640μg LABA formoterol 19.2μg LAMA glycopyrronium 36μg	2,137	28	1,026	64.6	NA	43.6	59.0	NA	42.6	28.7	61.1	10.2
					ICS/LABA/LAMA	ICS budesonide 320μg LABA formoterol 19.2μg LAMA glycopyrronium 36μg	2,121	39	1,013	64.6	NA	43.1	61.2	NA	40.8	28.5	59.9	11.6
					LABA/LAMA	LABA formoterol 19.2μg LAMA glycopyrronium 36μg	2,120	49	1,056	64.8	NA	43.5	58.7	NA	40.4	28.1	61.0	10.8
					ICS/LABA	ICS budesonide 640μg LABA formoterol 19.2μg	2,131	34	1,085	64.6	NA	43.4	60.0	NA	40.5	28.8	60.2	10.9
IMPACT 2018	DB, MC	NA	13	10,355	ICS/LABA/LAMA	ICS fluticasone 100μg LABA vilanterol 25μg LAMA umeclidinium 62.5μg	4,151	68	455	65.3	26.6	45.7	66.6	65.0	NA	NA	NA	NA
					ICS/LABA	ICS fluticasone 100μg LABA vilanterol 25μg	4,134	76	472	65.3	26.7	45.5	66.5	66.0	NA	NA	NA	NA
					LABA/LAMA	LABA vilanterol 25μg LAMA umeclidinium 62.5μg	2,070	49	279	65.2	26.6	45.4	65.5	65.0	NA	NA	NA	NA
TRILOGY 2016	DB, MC	＜50%	13	1,367	ICS/LABA/LAMA	ICS beclometasone 400μg LABA formoterol 24μg LAMA glycopyrronium 50μg	687	15	214	63.3	26.3	36.9	74.0	53.0	47.0	NA	77.0	23.0
					ICS/LABA	ICS beclometasone 400μg LABA formoterol 24μg	680	16	240	63.8	26.4	36.2	77.0	53.0	47.0	NA	77.0	23.0
Vestbo 1999	DB, SC, PC	NA	36	290	ICS	ICS budesonide (1200μg 6months, 800μg 30months)	145	4	36	59.0	NA	86.2	58.6	NA	75.9	NA	NA	NA
					Placebo	Placebo	145	5	34	59.1	NA	86.9	62.1	NA	77.2	NA	NA	NA
Szafranski 2003	DB, MC, PC	NA	12	812	ICS/LABA	ICS budesonide 640μg LABA formoterol 18μg	208	6	35	64.0	NA	36.0	76.0	NA	30.0	NA	NA	NA
					ICS	ICS budesonide 800μg	198	5	26	64.0	NA	37.0	80.0	NA	36.0	NA	NA	NA
					LABA	LABA formoterol 18μg	201	6	38	63.0	NA	36.0	76.0	NA	38.0	NA	NA	NA
					Placebo	Placebo	205	9	53	65.0	NA	36.0	83.0	NA	34.0	NA	NA	NA
Calverley 2003	DB,MC, PC	NA	12	1,022	ICS/LABA	ICS budesonide 640μg LABA formoterol 18μg	254	5	48	64.0	NA	36.0	78.0	NA	33.0	NA	NA	NA
					ICS	ICS budesonide 800μg	257	6	62	64.0	NA	36.0	74.0	NA	39.0	NA	NA	NA
					LABA	LABA formoterol 18μg	255	13	73	63.0	NA	36.0	75.0	NA	36.0	NA	NA	NA
					Placebo	Placebo	256	5	79	65.0	NA	36.0	75.0	NA	30.0	NA	NA	NA
Hanania 2019	DB,MC, PC	30%-70%	13	1,071	LABA	LABA formoterol 40μg	541	3	164	62.7	28.3	43.8	47.3	NA	52.1	50.6	48.2	0.6
					Placebo	Placebo	530	10	145	62.5	28.7	44.8	49.6	NA	52.5	51.5	47.2	0.8
Aaron 2007	DB, MC	＜65%	13	449	LAMA	LAMA tiotropium 18μg	156	4	112	68.1	27.6	42.1	53.8	NA	26.9	NA	NA	NA
					LABA/LAMA	LABA salmeterol 100μg LAMA tiotropium 18μg	148	6	104	67.6	27.2	41.2	57.4	NA	24.3	NA	NA	NA
					ICS/LABA/LAMA	ICS fluticasone 1000μg LABA salmeterol 100μg LAMA tiotropium 18μg	145	6	93	67.5	27.8	42.2	57.9	NA	32.4	NA	NA	NA
Calverley 2008	DB,MC, PC	30%-70%	13	911	ICS	ICS mometasone 800μg(800 QD)	308	2	105	65.3	26.7	47.0	69.0	NA	NA	32.0	46.0	20.0
					ICS	ICS mometasone 800μg(400 Bid)	308	5	107	65.0	26.1	46.0	67.0	NA	NA	29.0	44.0	22.0
					Placebo	Placebo	295	3	122	65.0	27.1	47.0	69.0	NA	NA	28.0	43.0	23.0
Calverley 2010	DB, MC	30%-50%	12	703	ICS/LABA	ICS beclomethasone 400μg LABA formoterol 24μg	232	2	64	63.0	NA	41.9	79.3	61.2	38.8	NA	NA	NA
					ICS/LABA	ICS budesonide 800μg LABA formoterol 24μg	238	4	64	64.1	NA	42.3	81.5	63.9	36.1	NA	NA	NA
					LABA	LABA formoterol 24μg	233	0	66	63.7	NA	42.5	81.1	62.7	37.3	NA	NA	NA

Sharafkhaneh 2012	DB, MC	NA	12	1,218	ICS/LABA	ICS budesonide 640µg LABA formoterol 18µg	407	7	169	63.8	NA	37.9	64.4	66.1	NA	NA	NA	NA
					ICS/LABA	ICS budesonide 320µg LABA formoterol 18µg	408	9	173	62.8	NA	37.6	64.7	65.0	NA	NA	NA	NA
					LABA	LABA formoterol 18µg	403	10	182	62.5	NA	37.5	56.8	61.8	NA	NA	NA	NA
Dransfield 2013	DB, MC	≤70%	12	3,255	ICS/LABA	ICS fluticasone 200µg LABA vilanterol 25µg	811	14	338	63.8	NA	45.1	61.9	NA	NA	NA	NA	NA
					ICS/LABA	ICS fluticasone 100µg LABA vilanterol 25µg	806	10	338	63.6	NA	45.7	57.3	NA	NA	NA	NA	NA
					ICS/LABA	ICS fluticasone 50µg LABA vilanterol 25µg	820	16	388	63.6	NA	45.6	60.0	NA	NA	NA	NA	NA
					LABA	LABA vilanterol 25µg	818	13	400	63.6	NA	44.3	58.4	NA	NA	NA	NA	NA
FORWARD 2014	DB	30%-50%	12	1,190	ICS/LABA	ICS beclomethasone 400µg LABA formoterol 24µg	595	11	264	64.6	26.5	41.9	69.0	NA	39.0	NA	NA	NA
					LABA	LABA formoterol 24µg	595	8	294	63.9	26.5	41.6	69.0	NA	40.0	NA	NA	NA
WISDOM 2014	DB, MC	<50%	12	2,485	ICS/LABA/LAMA	ICS fluticasone 1000µg LABA salmeterol 100µg LAMA tiotropium 18µg	1,243	38	564	63.6	NA	34.2	81.5	65.2	NA	NA	61.1	38.1
					LABA/LAMA	LABA salmeterol 100µg LAMA tiotropium 18µg	1,242	43	593	64.0	NA	34.3	83.4	67.9	NA	NA	61.3	38.2
Salford 2016	PC		12	2,799	ICS/LABA	ICS fluticasone 100µg LABA vilanterol 25µg	1,396	45	86	67.0	28.0	NA	50.0	NA	45.0	NA	NA	NA
					Placebo	Placebo	1,403	30	70	67.0	28.0	NA	52.2	NA	47.0	NA	NA	NA
FLAME 2016	DB, MC	25%-60%	13	3,362	ICS/LABA	ICS fluticasone 1000µg LABA salmeterol 100µg	1,682	24	1,374	64.5	NA	44.1	74.8	NA	39.8	NA	NA	NA
					LABA/LAMA	LABA indacaterol 110µg LAMA glycopyrronium 50µg	1,680	24	1,299	64.6	NA	44.0	77.3	NA	39.5	NA	NA	NA
Papi 2017	DB, MC	≤50%	13	1,765	ICS/LABA	ICS fluticasone 1000µg LABA formoterol 40µg	587	21	254	63.8	NA	37.8	75.5	54.3	45.7	NA	NA	NA
					ICS/LABA	ICS fluticasone 500µg LABA formoterol 20µg	588	19	236	63.0	NA	38.0	72.6	50.9	49.1	NA	NA	NA
					LABA	LABA formoterol 24µg	590	13	236	64.0	NA	37.7	75.9	50.0	50.0	NA	NA	NA
TRINITY 2017	DB, MC	<50%	13	2,690	ICS/LABA/LAMA	ICS beclometasone 400µg LABA formoterol 24µg LAMA glycopyrronium 50µg	1,077	20	351	63.4	26.4	36.6	77.0	52.0	48.0	NA	79.0	21.0
					LAMA	LAMA tiotropium 18µg	1,076	29	383	63.3	26.2	36.6	77.0	53.0	47.0	NA	79.0	21.0
					ICS/LABA/LAMA	ICS beclometasone 400µg LABA formoterol 24µg LAMA tiotropium 18µg	537	8	167	62.6	26.3	36.7	74.0	50.0	50.0	NA	79.0	21.0
TRIBUTE 2018	DB, MC	<50%	13	1,532	ICS/LABA/LAMA	ICS beclometasone 348µg LABA formoterol 20µg LAMA glycopyrronium 36µg	764	16	273	64.4	25.7	36.4	72.0	54.0	46.0	NA	80.0	20.0
					LABA/LAMA	LABA indacaterol 85µg LAMA glycopyrronium 43µg	768	21	288	64.5	26.6	36.4	72.0	57.0	43.0	NA	79.0	21.0
Kerwin 2019	DB, MC	25%-80%	13	456	ICS/LABA/LAMA	ICS budesonide 1280µg LABA formoterol 38.4µg LAMA glycopyrronium 72µg	194	3	12	62.6	29.0	NA	52.6	NA	52.1	49.0	44.3	6.7
					ICS/LABA	ICS budesonide 1280µg LABA formoterol 38.4µg	88	0	2	64.0	29.0	NA	60.2	NA	47.7	51.1	42.0	6.8
					LABA/LAMA	LABA formoterol 38.4µg LAMA glycopyrronium 72µg	174	1	9	62.4	29.0	NA	50.0	NA	54.6	52.3	37.4	10.3
Anzueto 2009	DB, MC	≤50%	13	797	ICS/LABA	ICS fluticasone 500µg LABA salmeterol 100µg	394	4	208	65.4	27.6	41.2	51.0	NA	42.0	NA	NA	NA
					LABA	LABA salmeterol 100µg	403	6	234	65.3	27.3	40.0	57.0	NA	43.0	NA	NA	NA
TONADO 2015	DB, MC	<80%	13	5,162	LABA/LAMA	LABA olodaterol 5µg LAMA tiotropium 5µg	1,029	18	332	63.8	NA	49.3	71.2	61.1	38.9	48.8	39.7	11.6
					LABA/LAMA	LABA olodaterol 5µg LAMA tiotropium 2.5µg	1,030	14	301	64.1	NA	50.2	73.5	63.9	36.1	50.4	39.5	10.0
					LAMA	LAMA tiotropium 5µg	1,033	17	340	63.9	NA	49.7	73.1	64.2	35.8	50.0	37.5	12.4
					LAMA	LAMA tiotropium 2.5µg	1,032	12	352	64.0	NA	50.3	73.0	62.4	37.6	50.2	39.6	10.0
					LABA	LABA olodaterol 5µg	1,038	14	370	64.2	NA	50.3	73.6	63.6	36.4	51.3	36.4	12.3
TORCH 2007	DB,MC, PC	NA	36	6,112	ICS/LABA	ICS fluticasone 1000µg LABA salmeterol 100µg	1,533	193	NA	65.0	25.4	44.3	75.0	NA	43.0	NA	NA	NA
					ICS	ICS fluticasone 1000µg	1,534	246	NA	65.0	25.4	44.1	75.0	NA	43.0	NA	NA	NA
					LABA	LABA salmeterol 100µg	1,521	205	NA	65.1	25.4	43.6	76.0	NA	43.0	NA	NA	NA
					Placebo	Placebo	1,524	231	NA	65.0	25.4	44.1	76.0	NA	43.0	NA	NA	NA
D'Urzo 2017	DB,MC, PC	30%-80%	13	918	LABA/LAMA	LABA formoterol 24µg LAMA aclidinium 800µg	182	2	131	63.7	NA	52.1	48.4	NA	53.8	54.4	44.0	NA
					LABA/LAMA	LABA formoterol 12µg LAMA aclidinium 800µg	204	1	159	63.6	NA	55.1	58.8	NA	54.4	62.3	36.8	NA
					LAMA	LAMA aclidinium 800µg	194	1	161	62.9	NA	52.7	53.6	NA	59.3	53.1	45.4	NA
					LABA	LABA formoterol 24µg	192	0	147	62.8	NA	55.1	46.9	NA	53.6	62.0	37.0	NA
					Placebo	Placebo	146	2	104	63.2	NA	53.2	55.5	NA	52.7	54.8	45.2	NA

Dahl 2010	DB, PC	30%-80%	13	1,728	LABA	LABA indacaterol 600µg	425	0	116	63.0	26.0	50.8	76.9	NA	NA	49.9	44.2	3.5
					LABA	LABA indacaterol 300µg	437	1	133	64.0	25.9	51.5	80.3	NA	NA	51.7	43.5	2.1
					LABA	LABA formoterol 24µg	434	3	126	64.0	25.7	52.5	80.2	NA	NA	52.1	41.9	2.3
					Placebo	Placebo	432	4	145	63.0	26.4	52.0	81.5	NA	NA	50.0	43.1	2.1
INVIGORATE 2013	blinded, MC	30%-50%	13	3,439	LABA	LABA indacaterol 150µg	1,721	28	747	64.0	NA	40.2	78.0	65.0	35.0	1.0	98.0	1.0
					LAMA	LAMA tiotropium 18µg	1,718	28	665	64.0	NA	40.7	76.0	66.0	34.0	1.0	98.0	1.0
Donohue 2016	DB, MC	30%-80%	12	590	LABA/LAMA	LABA formoterol 24µg LAMA aclidinium 800µg	392	5	107	63.9	NA	51.8	55.1	NA	46.9	52.8	46.2	NA
					LABA	LABA formoterol 24µg	198	1	59	64.7	NA	50.5	55.1	NA	43.9	51.5	46.5	NA
Ferguson 2008	DB, MC	NA	12	782	ICS/LABA	ICS fluticasone 500µg LABA salmeterol 100µg	394	6	343	64.9	27.3	39.8	58.0	NA	40.0	NA	NA	NA
					LABA	LABA salmeterol 100µg	388	3	335	65.0	27.7	40.6	52.0	NA	38.0	NA	NA	NA
FLIGHT3 2016	DB, MC	30%-80%	13	615	LABA/LAMA	LABA indacaterol 55µg LAMA glycopyrronium 31.2µg	204	1	74	64.0	NA	55.0	64.2	50.5	49.5	62.7	35.8	NA
					LABA/LAMA	LABA indacaterol 55µg LAMA glycopyrronium 62.4µg	204	3	67	63.9	NA	54.2	60.3	48.5	51.5	60.8	38.2	NA
					LABA	LABA indacaterol 75µg	207	5	76	62.8	NA	53.9	72.0	48.3	51.7	62.3	35.7	NA
Hanania 2017	DB, MC	NA	13	3,257	LABA/LAMA	LABA formoterol 19.2µg LAMA glycopyrronium 36µg	1,035	5	238	62.7	NA	43.4	54.3	NA	53.0	NA	NA	NA
					LAMA	LAMA glycopyrronium 36µg	888	1	231	62.8	NA	42.6	55.9	NA	53.0	NA	NA	NA
					LABA	LABA formoterol 19.2µg	884	2	207	62.8	NA	43.4	55.7	NA	55.9	NA	NA	NA
					LAMA	LAMA tiotropium 18µg	450	5	113	62.9	NA	42.7	59.6	NA	52.9	NA	NA	NA
GLOW2 2012	DB,MC, PC	30%-80%	13	1,060	LAMA	LAMA glycopyrronium 50µg	525	3	191	63.5	27.9	55.7	64.6	54.7	45.3	63.2	35.6	1.1
					Placebo	Placebo	268	2	116	63.6	27.5	56.4	64.6	53.7	46.3	64.9	34.3	0.7
					LAMA	LAMA tiotropium 18µg	267	2	90	63.9	27.7	56.0	62.9	55.8	44.2	64.4	35.2	0.0
Koch 2014 (1)	DB,MC, PC	<80%	12	904	LABA	LABA olodaterol 5µg	227	3	77	63.7	NA	52.3	78.0	70.0	30.0	55.1	38.3	6.2
					LABA	LABA olodaterol 10µg	225	6	75	62.6	NA	49.8	75.6	65.3	34.7	50.7	40.4	8.9
					LABA	LABA formoterol 24µg	227	4	62	64.8	NA	52.8	78.9	63.4	36.6	59.9	33.0	7.0
					Placebo	Placebo	225	4	60	64.0	NA	50.0	80.0	61.3	38.7	48.9	42.2	8.9
Koch 2014 (2)	DB,MC, PC	<80%	12	934	LABA	LABA olodaterol 5µg	232	7	54	63.7	NA	52.2	80.6	62.1	37.9	56.0	36.2	7.3
					LABA	LABA olodaterol 10µg	234	6	65	63.8	NA	51.3	78.6	67.5	32.5	48.7	45.3	6.0
					LABA	LABA formoterol 24µg	233	6	69	65.0	NA	51.0	82.4	69.1	30.9	47.6	41.6	9.4
					Placebo	Placebo	235	6	69	63.9	NA	52.0	83.0	69.4	30.6	56.2	32.3	11.1
GEM3 2016	DB, MC	30%-80%	13	507	LABA	LABA indacaterol 75µg	256	1	95	63.2	NA	53.1	58.2	44.5	55.5	55.1	40.6	0.4
					LAMA	LAMA glycopyrronium 31.2µg	251	2	91	63.3	NA	53.1	56.2	45.8	54.2	53.0	43.8	0.0
Rennard 2009	DB,MC, PC	<80%	12	1,964	ICS/LABA	ICS budesonide 640µg LABA formoterol 18µg	494	8	66	63.2	NA	38.6	62.3	60.9	NA	17.0	58.7	24.3
					ICS/LABA	ICS budesonide 320µg LABA formoterol 18µg	494	8	93	63.6	NA	39.6	62.8	58.1	NA	17.2	63.6	19.0
					LABA	LABA formoterol 18µg	495	6	83	62.9	NA	39.3	65.3	54.9	NA	18.0	57.6	24.0
					Placebo	Placebo	481	8	77	62.9	NA	40.8	65.3	56.1	NA	18.9	62.0	18.7
SARAÇ 2016	NA	NA	12	44	ICS/LABA	ICS fluticasone 1000µg LABA salmeterol 100µg	22	0	11	65.7	27.0	63.5	90.9	NA	NA	NA	NA	NA
					LAMA	LAMA tiotropium 18µg	22	0	18	67.4	27.4	67.2	100.0	NA	NA	NA	NA	NA
POET-COPD 2011	DB, MC	≤70%	12	7,376	LAMA	LAMA tiotropium 18µg	3,707	64	1,277	62.9	NA	49.2	74.4	NA	48.0	47.8	43.1	8.9
					LABA	LABA salmeterol 100µg	3,669	78	1,414	62.8	NA	49.4	74.9	NA	48.3	49.6	42.1	7.9
INSPIRE 2008	DB, MC	<50%	24	1,323	ICS/LABA	ICS fluticasone 1000µg LABA salmeterol 100µg	658	21	408	64.0	NA	39.1	81.0	NA	38.0	NA	82.1	15.2
					LAMA	LAMA tiotropium 18µg	665	38	392	65.0	NA	39.4	84.0	NA	38.0	NA	80.8	15.2
SPARK 2013	DB, MC	<50%	16	2,206	LABA/LAMA	LABA indacaterol 110µg LAMA glycopyrronium 50µg	729	23	636	63.1	NA	37.0	76.0	NA	38.0	NA	79.0	21.0
					LAMA	LAMA glycopyrronium 50µg	740	22	651	63.1	NA	37.3	73.0	NA	38.0	NA	79.0	21.0
					LAMA	LAMA tiotropium 18µg	737	25	642	63.6	NA	37.4	75.0	NA	37.0	NA	79.0	21.0

Eric 2010	DB,MC, PC	NA	12	1,990	LAMA	LAMA tiotropium 5μg	670	16	249	64.7	NA	46.6	73.3	NA	37.9	NA	NA	NA
					LAMA	LAMA tiotropium 10μg	667	18	246	65.1	NA	45.3	74.7	NA	34.8	NA	NA	NA
					Placebo	Placebo	653	10	288	65.2	NA	46.2	74.6	NA	36.1	NA	NA	NA
Donohue 2014	DB,MC, PC	35%-80%	13	562	LABA/LAMA	LABA vilanterol 25μg LAMA umeclidinium 125μg	226	0	29	61.4	27.9	55.0	69.0	NA	NA	61.0	39.0	0.0
					LAMA	LAMA umeclidinium 125μg	227	4	34	61.7	28.1	54.2	64.0	NA	NA	57.0	43.0	0.0
					Placebo	Placebo	109	1	26	60.1	27.7	55.1	67.0	NA	NA	65.0	34.0	0.0
Ferguson 2014 (1)	DB,MC, PC	<80%	12	624	LABA	LABA olodaterol 5μg	208	4	50	64.0	NA	48.1	72.1	63.9	36.1	44.7	41.3	13.9
					LABA	LABA olodaterol 10μg	207	2	67	65.0	NA	49.4	74.9	61.4	38.6	44.9	44.9	10.1
					Placebo	Placebo	209	3	71	65.8	NA	49.1	72.7	58.9	41.1	48.3	39.7	12.0
Ferguson 2014 (2)	DB,MC, PC	<80%	12	642	LABA	LABA olodaterol 5μg	209	1	46	64.7	NA	49.2	72.7	53.1	46.9	49.3	40.2	10.5
					LABA	LABA olodaterol 10μg	217	5	59	65.4	NA	48.4	70.0	57.6	42.4	43.3	44.7	11.5
					Placebo	Placebo	216	3	55	63.8	NA	49.1	70.4	57.9	42.1	49.1	33.3	17.1
Zhou 2017	DB,MC, PC	≥50%	24	771	LAMA	LAMA tiotropium 18μg	388	2	112	64.2	22.6	77.9	84.5	37.6	41.2	55.4	NA	NA
					Placebo	Placebo	383	5	150	63.9	22.5	78.1	86.2	39.7	40.2	56.9	NA	NA
Robert 2000	MC, PC	NA	40	1,116	ICS	ICS triamcinolone acetonide 1200μg	559	15	NA	56.2	NA	68.5	64.0	NA	90.5	NA	NA	NA
					Placebo	Placebo	557	19	NA	56.4	NA	67.2	62.1	NA	89.8	NA	NA	NA
ISOLDE 2000	DB,MC, PC	<85%	36	751	ICS	ICS fluticasone 1000μg	376	32	NA	63.7	24.5	50.3	75.0	46.8	36.4	NA	NA	NA
					Placebo	Placebo	375	36	NA	63.8	24.9	50.0	74.1	45.9	39.2	NA	NA	NA
Bateman 2010	DB,MC, PC	NA	12	3,917	LAMA	LAMA tiotropium 5μg	1,952	52	685	64.8	NA	45.2	78.1	64.2	35.7	NA	NA	NA
					Placebo	Placebo	1,965	38	842	64.8	NA	45.4	77.0	64.1	35.9	NA	NA	NA
Andreas 2020	DB, PC	<80%	12	775	LABA	LABA olodaterol 5μg	235	2	NA	62.8	27.4	44.6	69.4	55.7	44.3	50.6	41.7	7.2
					LABA	LABA olodaterol 10μg	234	1	NA	62.8	26.2	44.4	67.1	54.7	45.3	48.7	43.6	7.3
					LABA	LABA formoterol 24μg	80	1	NA	62.5	24.0	44.3	75.0	57.5	42.5	50.0	40.0	10.0
					Placebo	Placebo	226	2	NA	63.9	26.2	46.4	66.4	55.3	44.7	58.4	32.7	8.4
Choudhury 2007	DB, PC	<80%	12	260	ICS	fluticasone 1000μg	128	3	34	67.6	NA	53.2	48.0	NA	40.6	NA	NA	NA
					Placebo	Placebo	132	0	61	67.3	NA	55.0	56.0	NA	35.6	NA	NA	NA
DYNAGITO 2018	DB, MC	<60%	13	7,880	LABA/LAMA	LABA olodaterol 10μg LAMA tiotropium 10μg	3,939	107	1,519	66.5	NA	44.6	71.0	64.0	36.0	49.0	4.0	40.0
					LAMA	LAMA tiotropium 10μg	3,941	121	1,504	66.3	NA	44.5	72.0	62.0	38.0	48.0	4.0	39.0
Casaburi 2002	DB,MC, PC	NA	12	921	LAMA	LAMA tiotropium 18μg	550	7	198	65.0	26.3	39.1	66.5	NA	NA	NA	NA	NA
					Placebo	Placebo	371	7	156	65.0	26.0	38.1	62.8	NA	NA	NA	NA	NA
UPLIFT 2016	DB,MC, PC	≤70%	48	5,992	LAMA	LAMA tiotropium 18μg	2,986	376	1,706	65.0	NA	48.0	75.0	NA	29.0	46.0	44.0	8.0
					Placebo	Placebo	3,006	408	1,743	65.0	NA	47.0	74.0	NA	30.0	45.0	44.0	9.0
Charles 2007	DB,MC, PC	NA	12	913	LAMA	LAMA tiotropium 18μg	608	15	268	66.8	NA	39.4	59.0	NA	32.0	NA	NA	NA
					Placebo	Placebo	305	4	125	66.9	NA	39.3	61.0	NA	30.0	NA	NA	NA
Christopher 2013	DB,MC, PC	≤65%	24	519	LAMA	LAMA tiotropium 18μg	260	6	79	64.7	26.0	44.5	76.5	NA	35.0	37.0	50.0	13.0
					Placebo	Placebo	259	6	79	64.5	26.8	44.2	78.0	NA	32.8	35.0	51.0	14.0
EUROSCOP 1999	DB,MC, PC	50%-100%	36	1,277	ICS	ICS budesonide 800μg	634	8	NA	52.5	25.0	76.8	73.5	NA	NA	NA	NA	NA
					Placebo	Placebo	643	10	NA	52.4	24.7	76.9	72.2	NA	NA	NA	NA	NA
Maltais 2020	DB, MC	50%–70%	36	283	LABA	LABA vilanterol 25μg	142	6	50	66.0	29.1	59.5	51.0	NA	NA	NA	NA	NA
					ICS/LABA	ICS fluticasone 100μg LABA vilanterol 25μg	141	4	54	64.4	28.3	58.9	50.0	NA	NA	NA	NA	NA
Crim 2015	DB, MC	≤70%	13	3,255	LABA	LABA vilanterol 25μg	818	1	NA	63.6	NA	45.2	58.0	44.0	56.0	NA	NA	NA
					ICS/LABA	ICS fluticasone 50μg LABA vilanterol 25μg	820	0	NA	63.6	NA	45.4	58.0	44.0	56.0	NA	NA	NA
					ICS/LABA	ICS fluticasone 100μg LABA vilanterol 25μg	806	1	NA	63.8	NA	46.0	56.0	45.0	55.0	NA	NA	NA
					ICS/LABA	ICS fluticasone 200μg LABA vilanterol 25μg	811	7	NA	63.6	NA	45.2	58.0	43.0	57.0	NA	NA	NA
ENLIGHTEN 2013	DB,MC, PC	30%-80%	13	338	LABA/LAMA	LABA indacaterol 110μg LAMA glycopyrronium 50μg	225	4	63	62.5	NA	56.4	77.3	54.7	45.3	68.4	31.1	0.0
					Placebo	Placebo	113	1	29	62.9	NA	59.4	76.1	54.9	45.1	80.5	18.6	0.9
James 2014	DB,MC, PC	NA	12	841	LABA	LABA arformoterol 30μg	420	12	122	64.2	NA	39.7	56.2	49.0	51.0	NA	NA	NA
					Placebo	Placebo	421	10	132	63.3	NA	39.4	57.7	48.2	51.8	NA	NA	NA

Shaker 2009	DB, SC, PC	NA	36	254	ICS	ICS budesonide 800μg	127	5	69	63.6	25.3	51.0	62.0	NA	NA	NA	NA	NA
					Placebo	Placebo	127	5	62	63.6	25.3	53.0	54.0	NA	NA	NA	NA	NA
Chapman 2011	DB, PC	30%-80%	13	414	LABA	LABA indacaterol 150μg	144	0	34	62.5	NA	53.9	60.0	51.0	NA	NA	NA	NA
					LABA	LABA indacaterol 300μg	146	1	36	62.5	NA	56.6	59.0	48.0	NA	NA	NA	NA
					Placebo	Placebo	124	1	33	62.8	NA	56.3	65.0	51.0	NA	NA	NA	NA
Contoli 2017	blind	50%-80%	12	60	ICS/LABA	ICS fluticasone 1000μg LABA salmeterol 100μg	30	NA	20	70.5	NA	63.1	23.0	NA	NA	NA	NA	NA
					LABA	LABA salmeterol 100μg	30	NA	23	70.6	NA	64.6	25.0	NA	NA	NA	NA	NA
Dusser 2006	DB,MC, PC	NA	12	1,010	LAMA	LAMA tiotropium 18μg	500	NA	250	64.5	NA	48.2	89.0	NA	27.0	NA	NA	NA
					Placebo	Placebo	510	NA	308	65.0	NA	47.6	87.0	NA	24.0	NA	NA	NA
Jones 2011 (1)	DB,MC, PC	＜80%	13	843	LAMA	LAMA aclidinium 200μg	627	7	167	62.6	26.4	54.2	77.8	NA	45.1	NA	NA	NA
					Placebo	Placebo	216	4	56	61.9	26.7	52.9	81.0	NA	45.4	NA	NA	NA
Jones 2011 (2)	DB,MC, PC	＜80%	13	804	LAMA	LAMA aclidinium 200μg	600	6	199	65.1	26.8	50.6	63.8	NA	37.0	NA	NA	NA
					Placebo	Placebo	204	3	81	65.2	26.6	49.4	60.8	NA	38.7	NA	NA	NA
Powrie 2007	DB, SC, PC	NA	12	142	LAMA	LAMA tiotropium 18μg	69	NA	30	66.3	27.1	50.9	69.6	NA	59.4	NA	NA	NA
					Placebo	Placebo	73	NA	47	66.4	27.1	49.2	56.2	NA	57.5	NA	NA	NA
Rossi 2002	MC, PC	NA	12	645	LABA	LABA formoterol 24μg	211	3	68	63.0	NA	47.0	87.0	NA	NA	NA	NA	NA
					LABA	LABA formoterol 48μg	214	1	49	62.0	NA	47.0	83.0	NA	NA	NA	NA	NA
					Placebo	Placebo	220	0	75	63.0	NA	49.0	80.0	NA	NA	NA	NA	NA
Stockley 2006	DB,MC, PC	NA	12	634	LABA	LABA salmeterol 100μg	316	6	146	62.4	NA	46.1	77.0	53.0	47.0	NA	NA	NA
					Placebo	Placebo	318	5	163	62.3	NA	45.8	76.0	54.0	46.0	NA	NA	NA
BOREAS 2023	DB, MC	30%-70%	13	939	ICS/LABA/LAMA /Dupilumab	Dupilumab(皮下注射300mg q2w)	468	7	161	65.0	27.5	50.6	63.7	71.4	28.6	NA	NA	NA
					ICS/LABA/LAMA	NA	471	8	189	65.2	27.6	50.6	68.4	68.6	31.4	NA	NA	NA

Supplementary Table SII. More detailed characteristics of included RCTs

DB – double-blind, MC – multi-centre, SC – single-centre, PC – placebo-controlled, NA – not available, BMI – body mass index, post-FEV1%pred – post-bronchodilation forced expiratory volume in one second as a percentage of the predicted value.

Trial/Author year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ETHOS 2020	Low	Low	Low	Low	Low	Low	Low
IMPACT 2018	Unclear	Unclear	Low	Low	Low	Low	Low
TRILOGY 2016	Low	Low	Low	Low	Low	Low	Low
Vestbo 1999	Low	Low	Low	Low	Low	Low	Unclear
Szafranski 2003	Low	Low	Low	Low	Low	Low	Low
Calverley 2003	Low	Low	Low	Low	Low	Low	Low
Hanania 2019	Low	Low	Low	Low	Low	Low	Low
Aaron 2007	Low	Low	Low	Low	Low	Unclear	Unclear
Calverley 2008	Low	Unclear	Low	Low	Low	Low	Unclear
Calverley 2010	Low	Low	Low	Low	Low	Low	Low
Sharafkhaneh 2012	Low	Low	Low	Low	Low	Low	Low
Dransfield 2013	Low	Low	Low	Low	Low	Low	Low
FORWARD 2014	Low	Low	Low	Low	Low	Low	Low
WISDOM 2014	Low	Low	Low	Low	Low	Low	Low
Salford 2016	Low	Low	High	High	Low	Low	Low
FLAME 2016	Low	Low	Low	Low	Low	Low	Low
Papi 2017	Low	Low	Low	Low	Low	Low	Unclear
TRINITY 2017	Low	Low	Low	Low	Low	Low	Low
TRIBUTE 2018	Low	Low	Low	Low	Low	Low	Low
Kerwin 2019	Low	Low	Low	Low	Low	Low	Low
Anzueto 2009	Low	Low	Low	Low	Low	Low	Unclear
TONADO 2015	Low	Low	Low	Unclear	High	Low	Unclear
TORCH 2007	Low	Low	Low	Low	Low	Low	Low
D'Urzo 2017	Low	Unclear	Low	Unclear	Low	Low	Low
Dahl 2010	Low	Low	Low	Low	Low	Low	Low
INVIGORATE 2013	Low	Low	Low	Unclear	Low	Low	Low
Donohue 2016	Low	Low	Low	Low	High	Low	Low
Ferguson 2008	Low	Unclear	Low	Low	Low	Low	Low
FLIGHT3 2016	Low	Low	Low	Low	Low	Low	Low
Hanania 2017	Low	Unclear	High	High	Unclear	Low	Low
GLOW2 2012	Low	Unclear	High	High	Low	Low	Low
Koch 2014 (1)	Low	Unclear	Low	Unclear	Low	Low	Low
Koch 2014 (2)	Low	Unclear	Low	Unclear	Low	Low	Low
GEM3 2016	Low	Low	Low	Low	Low	Low	Low
Rennard 2009	Low	Low	Low	Low	Low	Low	Low
SARAÇ 2016	Low	Low	Unclear	Unclear	Low	Low	Low
POET-COPD 2011	Low	Low	Low	Low	Low	Low	Low
INSPIRE 2008	Low	Low	Low	Low	Low	Low	Unclear
SPARK 2013	Low	Unclear	High	High	Low	Low	Low
Eric 2010	Low	Low	Low	Low	High	Low	Unclear
Donohue 2014	Low	Low	Low	Low	Low	Low	Low
Ferguson 2014 (1)	Low	Low	Low	Low	Low	Low	Low
Ferguson 2014 (2)	Low	Low	Low	Low	Low	Low	Low
Zhou 2017	Unclear	Unclear	Low	Low	Low	Low	Low
Robert 2000	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
ISOLDE 2000	Low	Low	Low	Low	Low	Low	Low
Bateman 2010	Low	Low	Low	Low	Low	Low	Low
Andreas 2020	Low	Low	Low	Low	Low	Low	Low
Choudhury 2007	Low	Low	Low	Low	Low	Low	Low
DYNAGITO 2018	Low	Low	Low	Low	Low	Low	Low
Casaburi 2002	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
UPLIFT 2016	Unclear	Unclear	Low	Low	Low	Low	Low
Charles 2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Christopher 2013	Low	Low	Low	High	Low	Low	Low
EUROSCOP 1999	Low	Low	Low	Low	Low	Low	Low
Maltais 2020	High	High	Low	Low	Low	Low	Low
Crim 2015	Unclear	Unclear	Low	Low	Low	Low	Low
ENLIGHTEN 2013	Unclear	Low	Low	Low	Low	Low	Low
James 2014	Unclear	Unclear	Low	Low	Low	Low	Low
Shaker 2009	Low	Low	Low	Low	Low	Low	Low
Chapman 2011	Unclear	Unclear	Low	High	Low	Low	High
Contoli 2017	Low	Low	Low	Low	Low	Low	Low
Dusser 2006	Unclear	Unclear	Low	Low	Low	Low	Low
Jones 2011 (1)	Low	Low	Low	Low	Low	Low	Low
Jones 2011 (2)	Low	Low	Low	Low	Low	Low	Low
Powrie 2007	Low	Low	Low	Low	Low	Low	Low
Rossi 2002	Unclear	Unclear	Low	Low	Low	Low	Low
Stockley 2006	Low	Low	Low	Low	Low	Low	Low
BOREAS 2023	Unclear	Low	Low	Low	Low	Low	Low

Supplementary Figure S2. Bias risk assessment of included studies

ICS/LABA/ LAMA/Dupilumab							
0.783 (0.555-1.103)	ICS/LABA/ LAMA						
0.708 (0.491-1.014)	0.904 (0.808-1.009)	LABA/LAMA					
0.676 (0.469-0.973)	0.864 (0.767-0.973)	0.956 (0.865-1.059)	ICS/LABA				
0.679 (0.469-0.977)	0.868 (0.766-0.981)	0.960 (0.872-1.055)	1.004 (0.906-1.108)	LAMA			
0.611 (0.423-0.881)	0.781 (0.688-0.885)	0.864 (0.783-0.953)	0.904 (0.828-0.986)	0.900 (0.829-0.981)	LABA		
0.745 (0.494-1.121)	0.953 (0.762-1.188)	1.053 (0.856-1.300)	1.102 (0.900-1.353)	1.098 (0.901-1.341)	1.219 (1.003-1.486)	ICS	
0.561 (0.387-0.810)	0.717 (0.626-0.817)	0.792 (0.712-0.881)	0.829 (0.747-0.918)	0.825 (0.763-0.893)	0.917 (0.843-0.996)	0.752 (0.621-0.905)	Placebo
I^2=36%, P>0.05							

A

ICS/LABA/ LAMA/Dupilumab							
0.870 (0.299-2.631)	ICS/LABA/ LAMA						
0.677 (0.228-2.080)	0.778 (0.630-0.966)	LABA/LAMA					
0.780 (0.260-2.431)	0.896 (0.721-1.129)	1.152 (0.941-1.406)	ICS/LABA				
0.673 (0.225-2.081)	0.773 (0.610-0.984)	0.993 (0.820-1.204)	0.863 (0.714-1.037)	LAMA			
0.751 (0.248-2.352)	0.862 (0.672-1.130)	1.109 (0.894-1.395)	0.963 (0.812-1.151)	1.114 (0.939-1.352)	LABA		
0.678 (0.221-2.149)	0.773 (0.584-1.093)	0.995 (0.770-1.355)	0.864 (0.701-1.133)	1.002 (0.803-1.328)	0.899 (0.729-1.155)	ICS	
0.691 (0.229-2.165)	0.790 (0.620-1.048)	1.017 (0.825-1.289)	0.883 (0.741-1.077)	1.022 (0.886-1.232)	0.919 (0.773-1.094)	1.021 (0.824-1.236)	Placebo
I^2=0%, P>0.05							

B

Supplementary Table SIII. More primary network meta-analysis results for acute exacerbation (A) and all-cause mortality (B). The odds ratio (OR) and 95% credible interval (95% CI) are presented. No significant heterogeneity (I^2) or inconsistency (p-value) was found for all outcomes

ICS – inhaled corticosteroid, LABA – long-acting β-agonist, LAMA – long-acting muscarinic antagonist, OR – odds ratio, 95% CI – 95% credible interval.

ICS/LABA/ LAMA/Dupilumab							
0.782 (0.558-1.094)	ICS/LABA/ LAMA						
0.711 (0.497-1.008)	0.909 (0.810-1.016)	LABA/LAMA					
0.681 (0.475-0.971)	0.871 (0.771-0.982)	0.958 (0.851-1.082)	ICS/LABA				
0.667 (0.453-0.965)	0.853 (0.712-1.006)	0.939 (0.777-1.120)	0.980 (0.818-1.157)	LAMA			
0.612 (0.421-0.888)	0.783 (0.664-0.922)	0.861 (0.734-1.012)	0.899 (0.797-1.013)	0.917 (0.754-1.130)	LABA		
0.762 (0.484-1.192)	0.974 (0.721-1.319)	1.071 (0.795-1.454)	1.119 (0.841-1.492)	1.143 (0.84-1.569)	1.243 (0.933-1.667)	ICS	
0.407 (0.267-0.610)	0.520 (0.410-0.652)	0.572 (0.453-0.719)	0.597 (0.478-0.738)	0.610 (0.486-0.766)	0.665 (0.527-0.831)	0.534 (0.401-0.702)	Placebo
I^2=7%, P>0.05							

A

ICS/LABA/ LAMA/Dupilumab							
0.866 (0.290-2.578)	ICS/LABA/ LAMA						
0.685 (0.223-2.088)	0.787 (0.628-1.012)	LABA/LAMA					
0.818 (0.266-2.481)	0.944 (0.735-1.213)	1.194 (0.917-1.540)	ICS/LABA				
0.558 (0.174-1.746)	0.640 (0.432-0.945)	0.811 (0.534-1.221)	0.678 (0.458-0.996)	LAMA			
0.778 (0.246-2.413)	0.898 (0.653-1.257)	1.139 (0.815-1.586)	0.952 (0.768-1.194)	1.409 (0.908-2.178)	LABA		
0.668 (0.211-2.099)	0.764 (0.546-1.133)	0.972 (0.682-1.412)	0.810 (0.636-1.095)	1.199 (0.763-1.922)	0.851 (0.665-1.142)	ICS	
0.667 (0.210-2.070)	0.769 (0.536-1.096)	0.974 (0.672-1.386)	0.814 (0.628-1.058)	1.204 (0.757-1.900)	0.855 (0.655-1.107)	1.004 (0.756-1.263)	Placebo
I^2=0%, P>0.05							

B

ICS/LABA/ LAMA/Dupilumab							
0.782 (0.556-1.099)	ICS/LABA/ LAMA						
0.697 (0.488-0.993)	0.891 (0.809-0.981)	LABA/LAMA					
0.683 (0.480-0.975)	0.872 (0.796-0.963)	0.979 (0.891-1.084)	ICS/LABA				
0.653 (0.454-0.937)	0.836 (0.740-0.940)	0.938 (0.842-1.042)	0.958 (0.850-1.068)	LAMA			
0.615 (0.428-0.883)	0.786 (0.700-0.886)	0.882 (0.794-0.984)	0.901 (0.820-0.988)	0.941 (0.841-1.059)	LABA		
0.683 (0.471-0.996)	0.873 (0.749-1.024)	0.980 (0.839-1.151)	1.001 (0.874-1.148)	1.045 (0.889-1.242)	1.111 (0.955-1.296)	ICS	
0.506 (0.348-0.733)	0.647 (0.557-0.750)	0.726 (0.630-0.834)	0.741 (0.645-0.848)	0.774 (0.679-0.883)	0.822 (0.720-0.938)	0.740 (0.621-0.879)	Placebo
I^2=27%, P=NA							

C

ICS/LABA/ LAMA/Dupilumab							
0.861 (0.285-2.489)	ICS/LABA/ LAMA						
0.713 (0.231-2.084)	0.829 (0.682-1.009)	LABA/LAMA					
0.910 (0.296-2.689)	1.053 (0.870-1.276)	1.270 (1.037-1.571)	ICS/LABA				
0.667 (0.213-1.977)	0.773 (0.609-1.003)	0.936 (0.753-1.156)	0.736 (0.579-0.942)	LAMA			
0.866 (0.277-2.584)	1.000 (0.783-1.290)	1.211 (0.945-1.541)	0.952 (0.799-1.138)	1.295 (0.985-1.700)	LABA		
0.728 (0.234-2.178)	0.842 (0.652-1.111)	1.016 (0.779-1.336)	0.799 (0.657-0.985)	1.087 (0.812-1.460)	0.839 (0.681-1.045)	ICS	
0.726 (0.231-2.193)	0.840 (0.647-1.092)	1.014 (0.770-1.321)	0.798 (0.645-0.978)	1.084 (0.812-1.439)	0.836 (0.676-1.033)	0.995 (0.795-1.235)	Placebo
I^2=0%, P>0.05							

D

ICS/LABA/ LAMA/Dupilumab							
0.782 (0.557-1.099)	ICS/LABA/ LAMA						
0.705 (0.495-1.008)	0.902 (0.807-1.004)	LABA/LAMA					
0.682 (0.477-0.978)	0.872 (0.776-0.982)	0.967 (0.874-1.075)	ICS/LABA				
0.675 (0.470-0.968)	0.864 (0.759-0.975)	0.958 (0.862-1.060)	0.990 (0.888-1.096)	LAMA			
0.598 (0.417-0.861)	0.765 (0.674-0.868)	0.848 (0.765-0.943)	0.877 (0.800-0.960)	0.886 (0.813-0.970)	LABA		
0.734 (0.490-1.102)	0.939 (0.752-1.174)	1.042 (0.844-1.287)	1.077 (0.878-1.323)	1.089 (0.894-1.331)	1.228 (1.009-1.496)	ICS	
0.550 (0.381-0.792)	0.704 (0.614-0.803)	0.780 (0.696-0.875)	0.807 (0.722-0.898)	0.815 (0.752-0.885)	0.920 (0.842-1.003)	0.749 (0.621-0.901)	Placebo
I^2=35%, P>0.05							

E

ICS/LABA/ LAMA/Dupilumab							
0.835 (0.279-2.441)	ICS/LABA/ LAMA						
0.648 (0.213-1.922)	0.773 (0.633-0.952)	LABA/LAMA					
0.754 (0.246-2.268)	0.903 (0.729-1.122)	1.164 (0.958-1.432)	ICS/LABA				
0.622 (0.200-1.876)	0.746 (0.591-0.946)	0.965 (0.789-1.185)	0.827 (0.686-0.996)	LAMA			
0.697 (0.228-2.110)	0.833 (0.651-1.081)	1.078 (0.863-1.364)	0.924 (0.782-1.106)	1.118 (0.940-1.341)	LABA		
0.615 (0.201-1.929)	0.739 (0.558-1.015)	0.953 (0.743-1.277)	0.817 (0.668-1.047)	0.989 (0.800-1.278)	0.885 (0.726-1.113)	ICS	
0.621 (0.205-1.886)	0.743 (0.580-0.968)	0.959 (0.771-1.217)	0.822 (0.694-0.997)	0.995 (0.858-1.176)	0.891 (0.756-1.051)	1.007 (0.819-1.208)	Placebo
I^2=0%, P=NA							

F

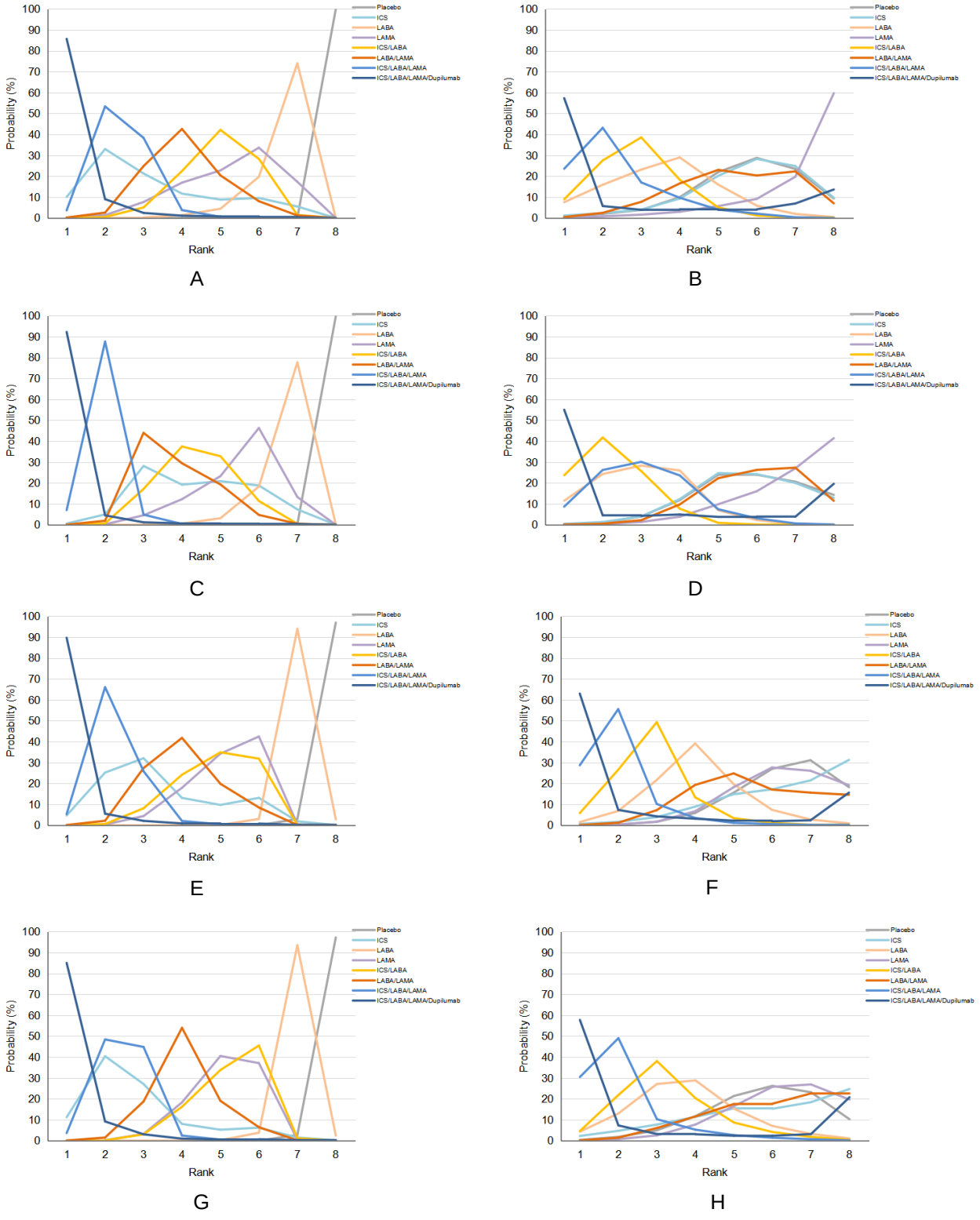
ICS/LABA/ LAMA/Dupilumab							
0.783 (0.560-1.096)	ICS/LABA/ LAMA						
0.709 (0.498-1.007)	0.905 (0.812-1.008)	LABA/LAMA					
0.677 (0.475-0.964)	0.865 (0.770-0.968)	0.955 (0.867-1.053)	ICS/LABA				
0.681 (0.476-0.970)	0.870 (0.770-0.978)	0.961 (0.876-1.051)	1.006 (0.911-1.108)	LAMA			
0.612 (0.429-0.873)	0.781 (0.691-0.884)	0.863 (0.785-0.951)	0.904 (0.829-0.987)	0.898 (0.830-0.977)	LABA		
0.784 (0.516-1.193)	1.002 (0.779-1.290)	1.107 (0.870-1.412)	1.159 (0.915-1.470)	1.152 (0.912-1.459)	1.283 (1.018-1.616)	ICS	
0.564 (0.394-0.806)	0.720 (0.633-0.818)	0.796 (0.718-0.883)	0.833 (0.753-0.922)	0.828 (0.768-0.896)	0.922 (0.849-1.000)	0.719 (0.573-0.901)	Placebo
I^2=30%, P=NA							

G

ICS/LABA/ LAMA/Dupilumab							
0.882 (0.285-2.548)	ICS/LABA/ LAMA						
0.689 (0.220-2.024)	0.783 (0.630-0.973)	LABA/LAMA					
0.788 (0.254-2.335)	0.896 (0.715-1.130)	1.147 (0.931-1.406)	ICS/LABA				
0.683 (0.216-2.027)	0.776 (0.609-0.990)	0.993 (0.815-1.203)	0.866 (0.714-1.045)	LAMA			
0.768 (0.244-2.281)	0.872 (0.675-1.145)	1.116 (0.889-1.410)	0.972 (0.818-1.167)	1.124 (0.939-1.364)	LABA		
0.699 (0.212-2.101)	0.788 (0.588-1.126)	1.009 (0.764-1.393)	0.878 (0.705-1.165)	1.013 (0.807-1.369)	0.904 (0.725-1.176)	ICS	
0.701 (0.216-2.091)	0.794 (0.617-1.053)	1.015 (0.811-1.289)	0.884 (0.745-1.082)	1.020 (0.879-1.231)	0.910 (0.77-1.091)	1.009 (0.797-1.227)	Placebo
I^2=0%, P>0.05							

H

Supplementary Table SIV. More results of 4 sensitivity analyses for acute exacerbation (**A, C, E, G**) and all-cause mortality (**B, D, F, H**). First, the removal of studies with background drug interference (A, B). Second, dealing with background drugs (C, D). Third, excluding relatively high risk of bias studies (E, F). Fourth, removing studies with sample sizes < 300 (G, H). The odds ratio (OR) and 95% credible interval (95% CI) are presented. OR < 1 favors intervention, and 95% CI not including 1 signifies statistical significance. I^2, heterogeneity; *p*-value, inconsistency.



Supplementary Figure S3. Ranking probabilities for each intervention on the two outcomes in four sensitivity analyses. First, the removal of studies with background drug interference (**A, B**). Second, dealing with background drugs (**C, D**). Third, excluding relatively high risk of bias studies (**E, F**). Fourth, removing studies with sample sizes < 300 (**G, H**). Acute exacerbation (A, C, E, G); All-cause mortality (B, D, F, H)

Studies included in this analysis [1-66]

1. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med 2020; 383: 35-48.
2. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med 2018; 378: 1671-80.
3. Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet 2016; 388: 963-73.
4. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999; 353: 1819-23.
5. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 74-81.
6. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 912-9.
7. Hanania NA, Sethi S, Koltun A, Ward JK, Spanton J, Ng D. Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD. Int J Chron Obstruct Pulmon Dis 2019; 14: 117-27.
8. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007; 146: 545-55.
9. Calverley PM, Rennard S, Nelson HS, et al. One-year treatment with mometasone furoate in chronic obstructive pulmonary disease. Respir Res 2008; 9: 73.
10. Calverley PM, Kuna P, Monso E, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med 2010; 104: 1858-68.
11. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study.

Respir Med 2012; 106: 257-68.

12. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med 2013; 1: 210-23.
13. Wedzicha JA, Singh D, Vestbo J, et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. Respir Med 2014; 108: 1153-62.
14. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med 2014; 371: 1285-94.
15. Vestbo J, Leather D, Diar Bakerly N, et al. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. N Engl J Med 2016; 375: 1253-60.
16. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med 2016; 374: 2222-34.
17. Papi A, Dokic D, Tzimas W, et al. Fluticasone propionate/formoterol for COPD management: a randomized controlled trial. Int J Chron Obstruct Pulmon Dis 2017; 12: 1961-71.
18. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 2017; 389: 1919-29.
19. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 2018; 391: 1076-84.
20. Kerwin EM, Ferguson GT, Mo M, DeAngelis K, Dorinsky P. Bone and ocular safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a 52-week randomized study. Respir Res 2019; 20: 167.
21. Anzueto A, Ferguson GT, Feldman G, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD 2009; 6: 320-9.
22. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015; 45: 969-79.
23. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356: 775-89.

24. D'Urzo A, Rennard S, Kerwin E, et al. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. Respir Med 2017; 125: 39-48.
25. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 2010; 65: 473-9.
26. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med 2013; 1: 524-33.
27. Donohue JF, Soong W, Wu X, Shrestha P, Lei A. Long-term safety of aclidinium bromide/formoterol fumarate fixed-dose combination: results of a randomized 1-year trial in patients with COPD. Respir Med 2016; 116: 41-8.
28. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med 2008; 102: 1099-108.
29. Ferguson GT, Taylor AF, Thach C, et al. Long-term maintenance bronchodilation with indacaterol/glycopyrrolate versus indacaterol in moderate-to-severe COPD patients: the FLIGHT 3 study. Chronic Obstr Pulm Dis 2016; 3: 716-28.
30. Hanania NA, Tashkin DP, Kerwin EM, et al. Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel Co-Suspension Delivery Technology in patients with chronic obstructive pulmonary disease. Respir Med 2017; 126: 105-15.
31. Kerwin E, Hebert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J 2012; 40: 1106-14.
32. Koch A, Pizzichini E, Hamilton A, et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat(R) versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis 2014; 9: 697-714.
33. Mahler DA, Gifford AH, Satti A, et al. Long-term safety of glycopyrrolate: a randomized study in patients with moderate-to-severe COPD (GEM3). Respir Med 2016; 115: 39-45.

34. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs 2009; 69: 549-65.
35. Sarac P, Sayiner A. Compare the efficacy and safety of long-acting anticholinergic and a combination of inhaled steroids and long-acting beta-2 agonist in moderate chronic obstructive pulmonary disease. Tuberk Toraks 2016; 64: 112-8.
36. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364: 1093-103.
37. Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008; 177: 19-26.
38. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med 2013; 1: 199-209.
39. Bateman E, Singh D, Smith D, et al. Efficacy and safety of tiotropium RespimatR SMI in COPD in two 1-year randomized studies. Int J Chron Obstruct Pulm Dis 2010; 5: 197-208.
40. Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respir Res 2014; 15: 78.
41. Ferguson GT, Feldman GJ, Hofbauer P, et al. Efficacy and safety of olodaterol once daily delivered via Respimat(R) in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis 2014; 9: 629-45.
42. Zhou Y, Zhong NS, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. N Engl J Med 2017; 377: 923-35.
43. Wise R, Connett J, Weinmann G, Scanlon P, Skeans M. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343: 1902-9.

44. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000; 320: 1297-303.
45. Bateman ED, Tashkin D, Siafakas N, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respir Med 2010; 104: 1460-72.
46. Andreas S, Bothner U, de la Hoz A, Kloer I, Trampisch M, Alter P. A post hoc Holter ECG analysis of olodaterol and formoterol in moderate-to-very-severe COPD. Int J Chron Obstruct Pulmon Dis 2020; 15: 1955-65.
47. Choudhury AB, Dawson CM, Kilvington HE, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res 2007; 8: 93.
48. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. Lancet Respir Med 2018; 6: 337-44.
49. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002; 19: 217-24.
50. Celli BR, Decramer M, Liu D, Metzdorf N, Asijee GM, Tashkin DP. Defining a COPD composite safety endpoint for demonstrating efficacy in clinical trials: results from the randomized, placebo-controlled UPLIFT(R) trial. Respir Res 2016; 17: 48.
51. Chan CKN, Maltais F, Sigouin C, Haddon JM, Ford GT. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Can Respir J 2007; 14: 465-72.
52. Cooper CB, Celli BR, Jardim JR, et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest 2013; 144: 490-7.
53. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999; 340: 1948-53.
54. Maltais F, Schenkenberger I, Wielders P, et al. Effect of once-daily fluticasone furoate/vilanterol versus vilanterol alone on bone mineral density in patients with COPD: a randomized, controlled trial. Ther Adv Respir Dis 2020; 14: 1753466620965145.

55. Crim C, Dransfield MT, Bourbeau J, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Ann Am Thorac Soc 2015; 12: 27-34.
56. Dahl R, Chapman KR, Rudolf M, et al. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. Respir Med 2013; 107: 1558-67.
57. Donohue JF, Hanania NA, Make B, et al. One-year safety and efficacy study of arformoterol tartrate in patients with moderate to severe COPD. Chest 2014; 146: 1531-42.
58. Shaker SB, Dirksen A, Ulrik CS, et al. The effect of inhaled corticosteroids on the development of emphysema in smokers assessed by annual computed tomography. COPD 2009; 6: 104-11.
59. Chapman KR, Rennard SI, Dogra A, et al. Long-term safety and efficacy of indacaterol, a long-acting beta(2)-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest 2011; 140: 68-75.
60. Contoli M, Pauletti A, Rossi MR, et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J 2017; 50: 1700451.
61. Dusser D. The effect of tiotropium on exacerbations and airflow in patients with COPD. European Respir J 2006; 27: 547-55.
62. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. Respir Res 2011; 12: 55.
63. Powrie DJ, Wilkinson TM, Donaldson GC, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. Eur Respir J 2007; 30: 472-8.
64. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest 2002; 121: 1058-69.
65. Stockley RA, Chopra N, Rice L. Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax 2006; 61: 122-8.
66. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. N Engl J Med 2023; 389: 205-14.