Supplementary

Efficacy and cardiovascular safety of LAMA in patients with COPD: a systematic review and meta-analysis

Chuchu Zhang[1,2], Meng Zhang[1,2], Yalei Wang[1,2], Huaiyu Xiong[1,2], Qiangru Huang[1,2], Tiankui Shuai[1,2], Jian Liu[1*]

1. Department of Intensive Care Unit, Lanzhou University First Affiliated Hospital, Lanzhou University, Lan Zhou, Gansu Province, China

2. The First Clinical Medical College of Lanzhou University, Lanzhou University, Lanzhou, Gansu Province, China

Short Title: LAMA in patients with COPD: a systematic review and meta-analysis.

Corresponding Author:

Jian Liu

Department of Intensive Care Unit, Lanzhou University First Affiliated Hospital, Lanzhou University.

No.199 Donggang West Road, Lanzhou, Gansu Province, 730000, China.

Tel: +86 13609354197

E-mail: medecinliu@sina.com

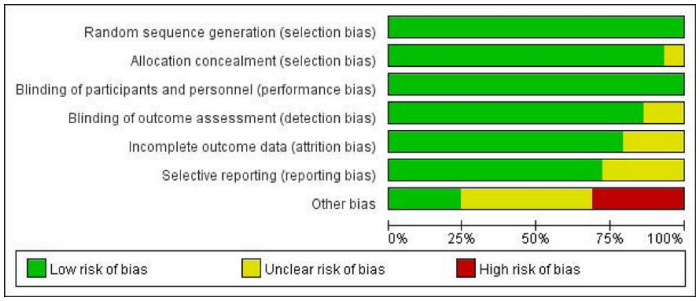

Fig. S1. Risk of bias summary for included studies, showing each risk of bias item for every included study.

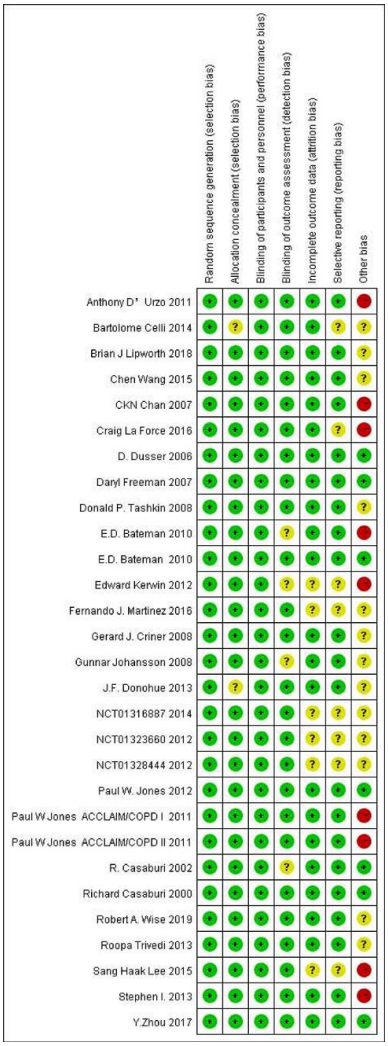

Fig. S2. Risk of bias graph presenting each risk of bias item as percentages across all included studies.

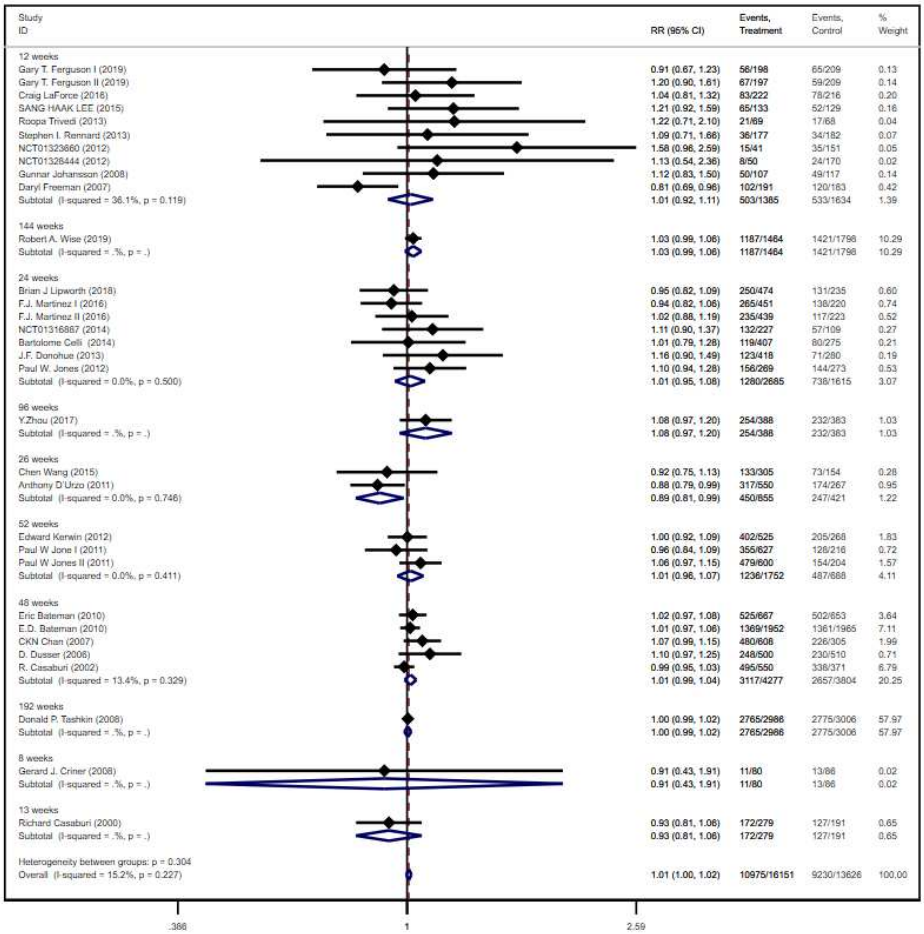

Fig. S3. Subgroup analysis of all adverse events based on the duration.

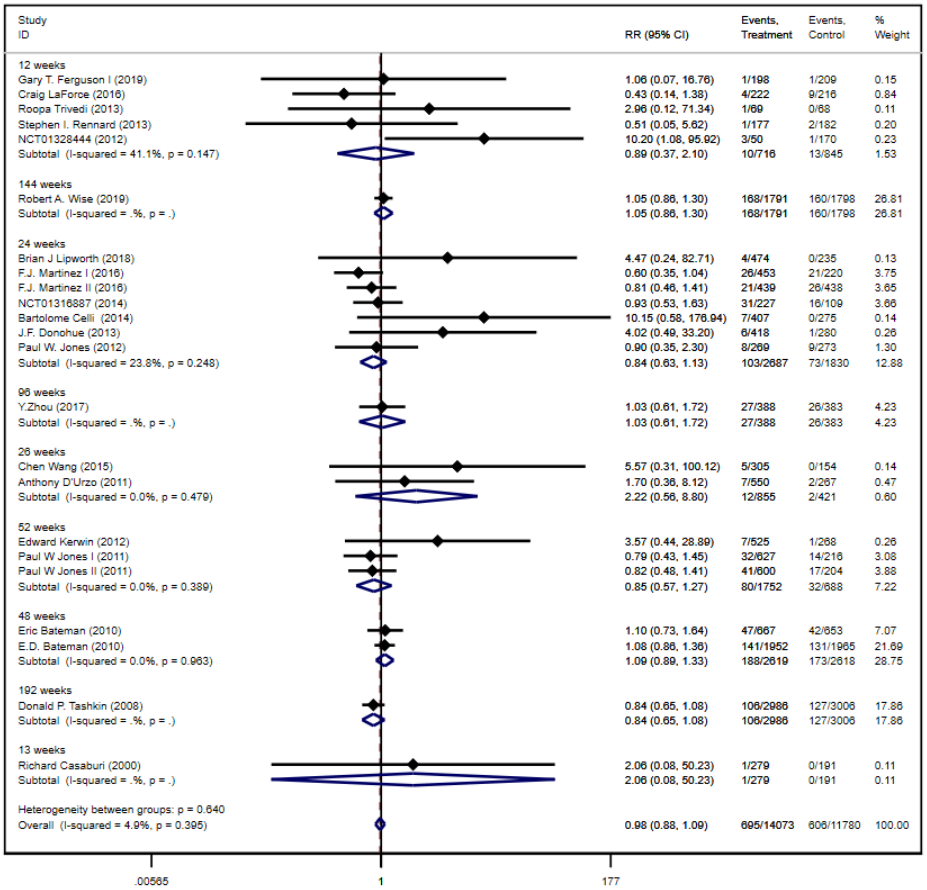

Fig. S4. Subgroup analysis of cardiovascular disease based on the duration.

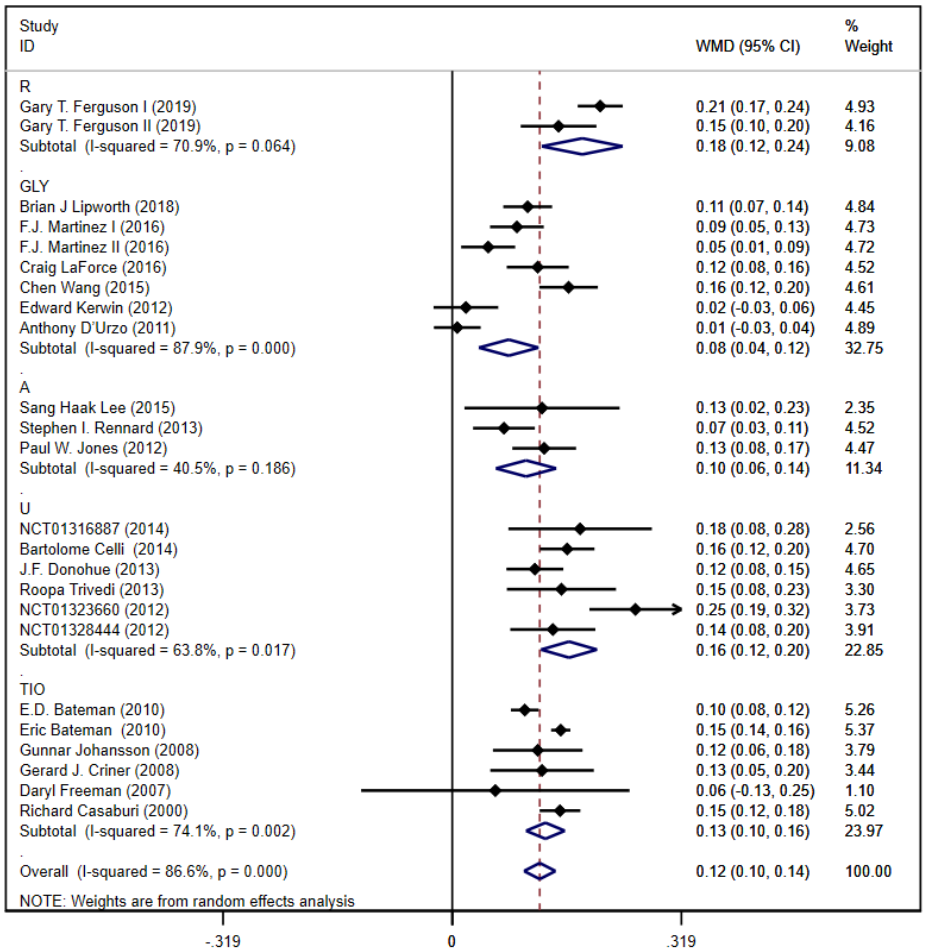

Fig. S5. Subgroup analysis of trough FEV_1 based on the drug type. Abbreviation: A: Aclidinium, Gly: Glycopyrronium, Tio: Tiotropium, U:umeclidinium, R: revefenacin.

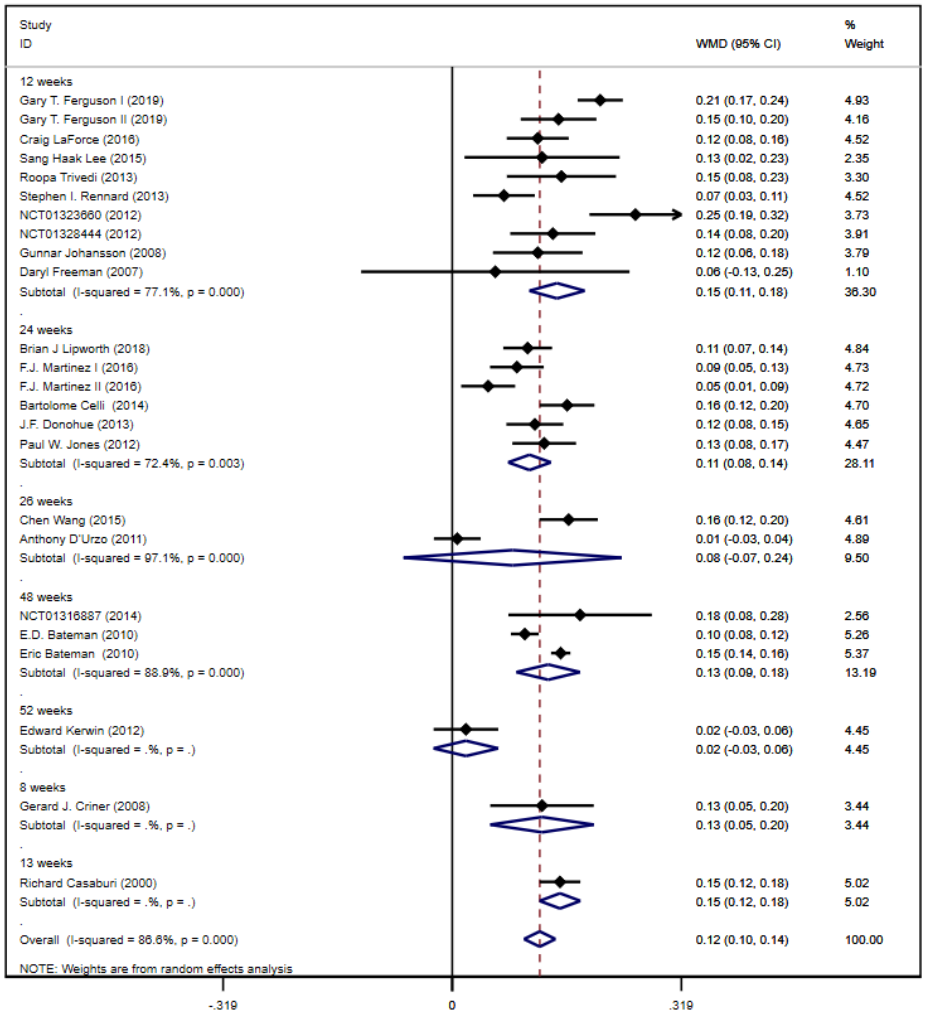

Fig. S6. Subgroup analysis of trough FEV_1 based on the treatment duration.

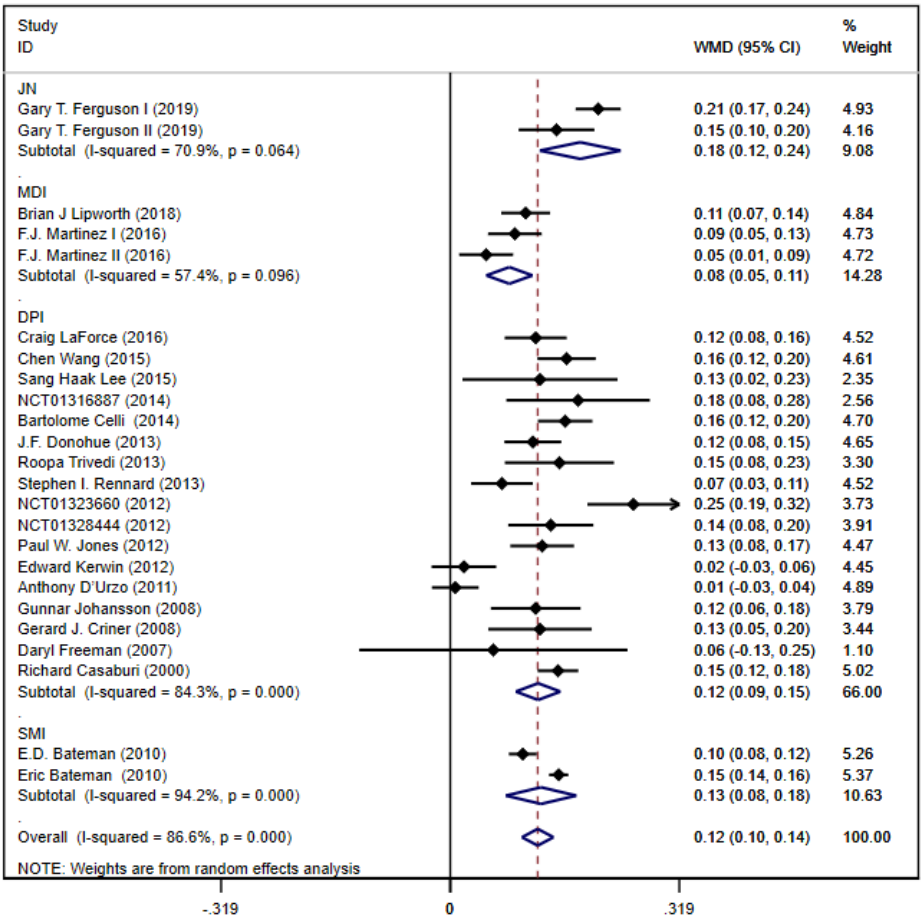

Fig. S7. Subgroup analysis of trough FEV_1 based on the inhaler of LAMA. Abbreviation: DPI: Dry Powder Inhaler, JN: Jet Nebulizer, MDI: Metered Dose Inhaler, SMI: Soft Mist Inhaler.

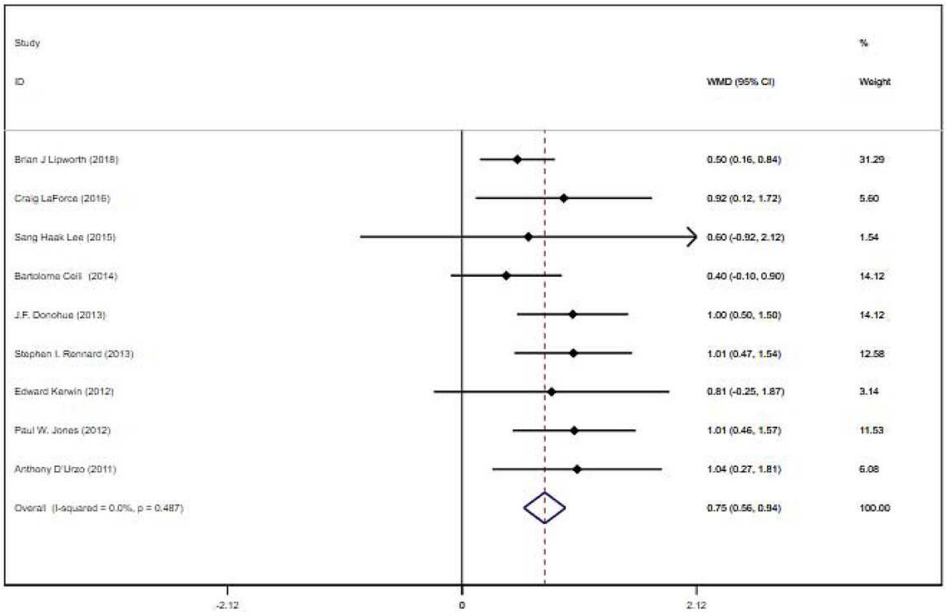

Fig. S8. Forest plot of TDI focal score in COPD patients with LAMAs versus placebo.

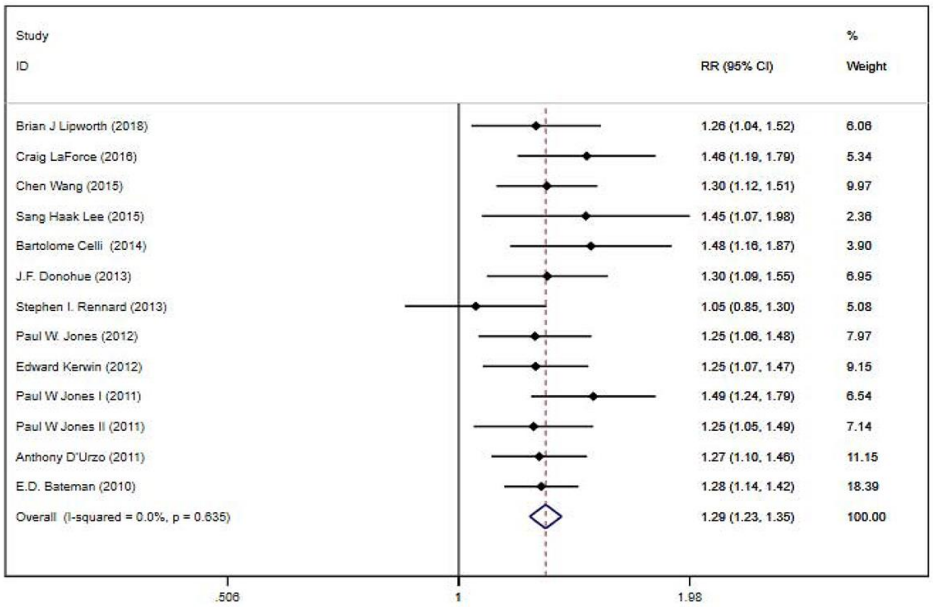

Fig. S9. Forest plot of TDI responders in COPD patients with LAMAs versus placebo

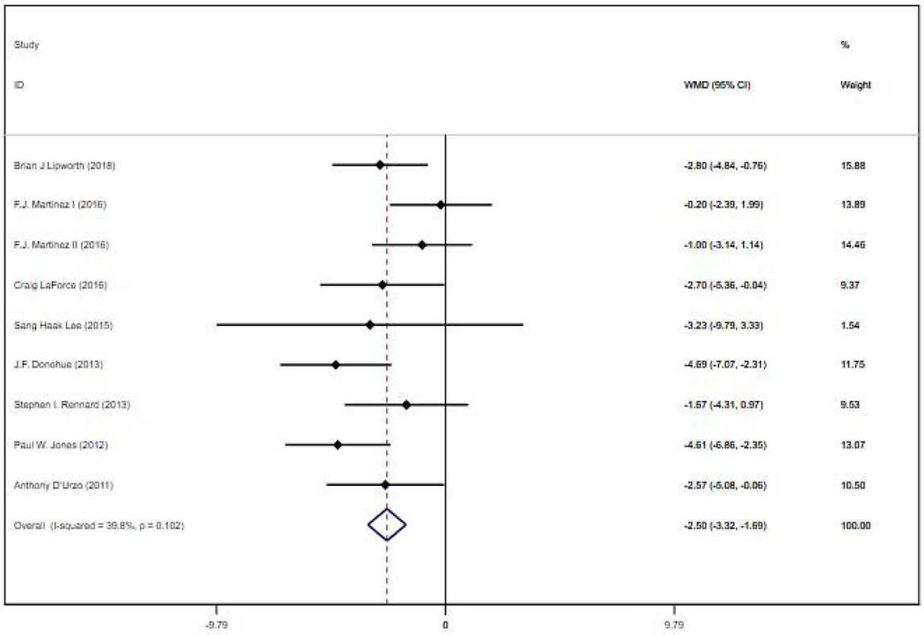

Fig. S10. Forest plot of SGRQ score in COPD patients with LAMAs versus placebo.

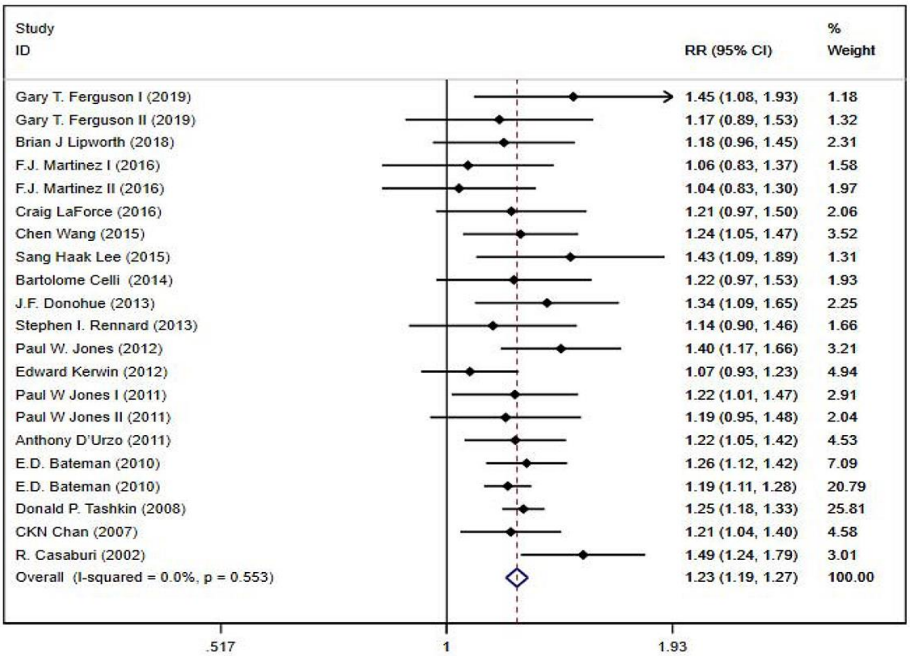

Fig. S11. Forest plot of SGRQ responders in COPD patients with LAMAs versus placebo.

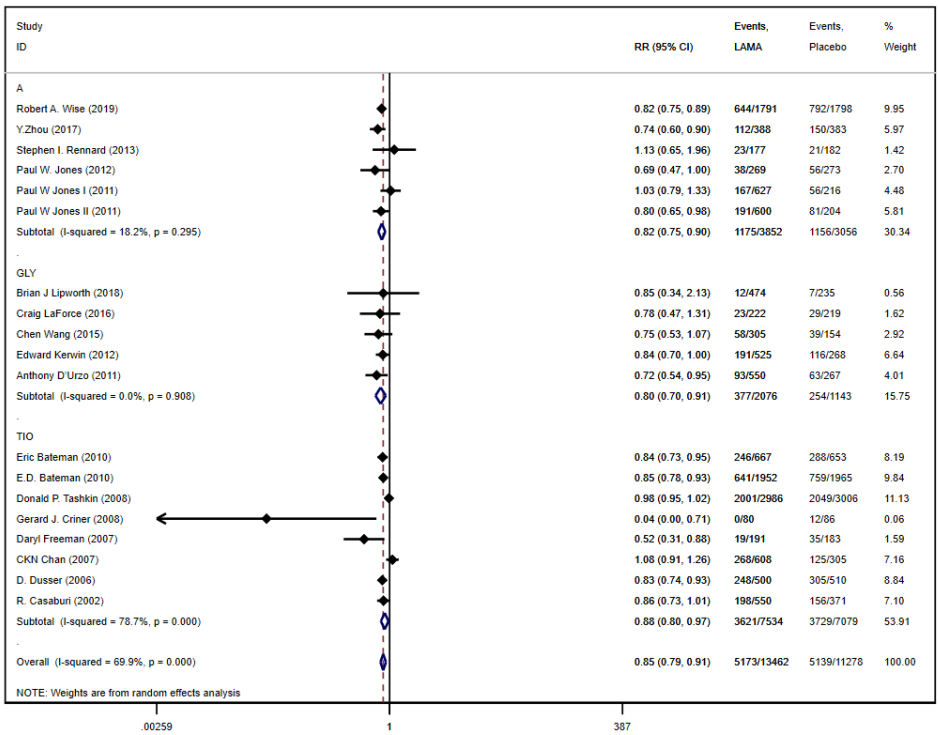

Fig. S12. Forest plot of the number of patients with at least one moderate or severe exacerbations with LAMAs versus placebo (subgroup analysis based on the drug type). Abbreviation: A: Aclidinium, Gly: Glycopyrronium, Tio: Tiotropium, U:umeclidinium, R: revefenacin.

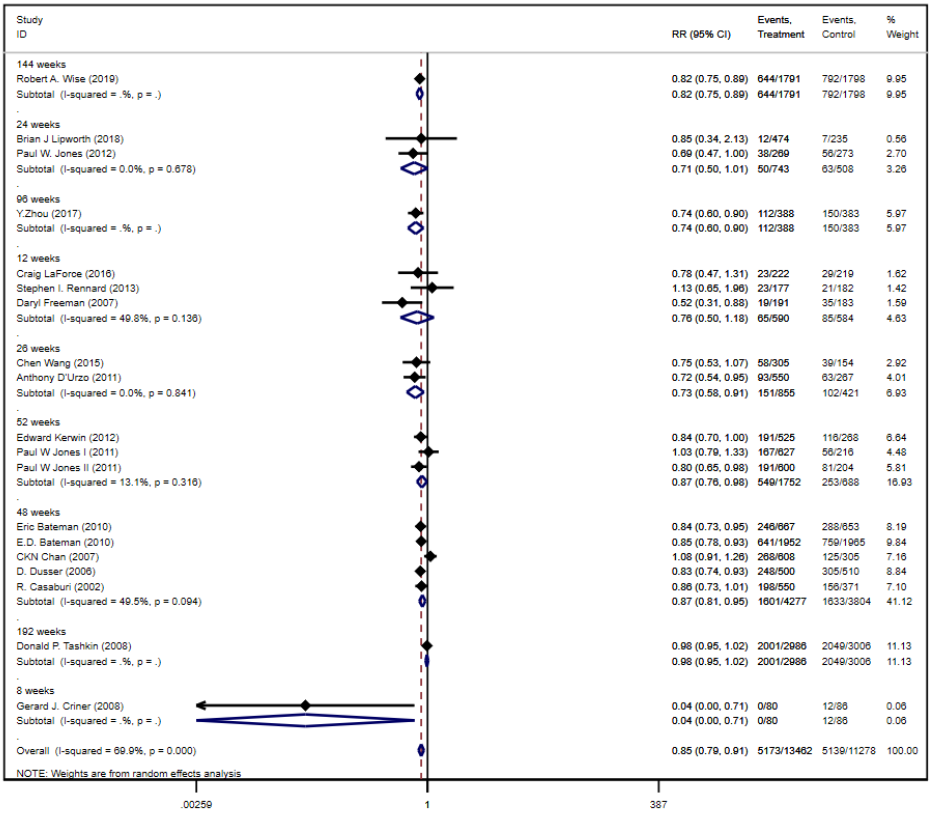

Fig. S13. Forest plot of the number of patients with at least one moderate or severe exacerbations with LAMAs versus placebo (subgroup analysis based on the duration)

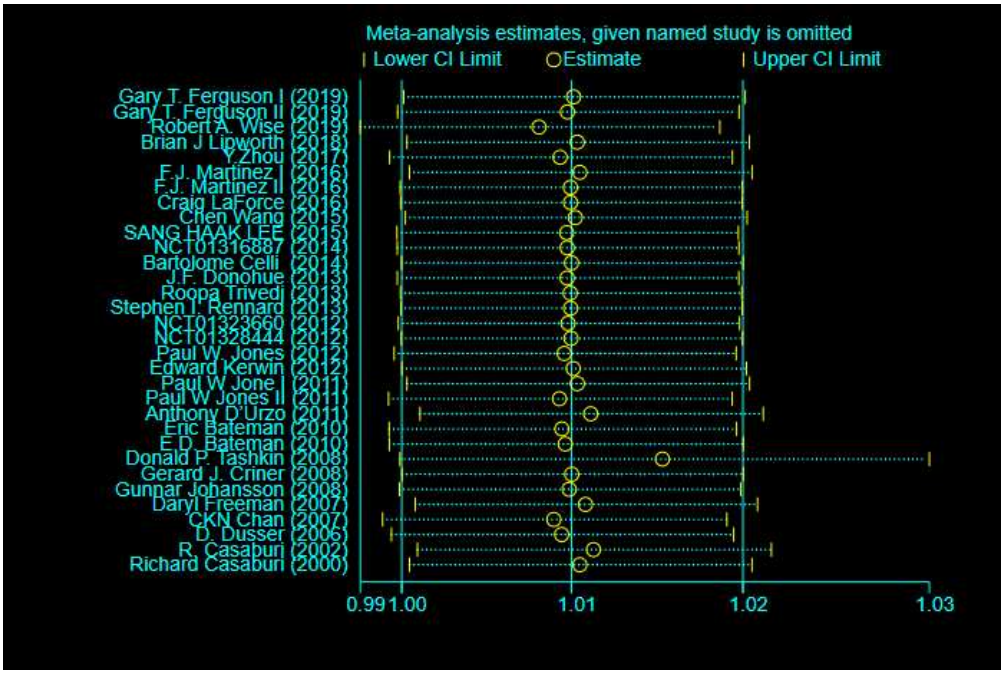

Fig. S14. Sensitivity analysis of all adverse events.

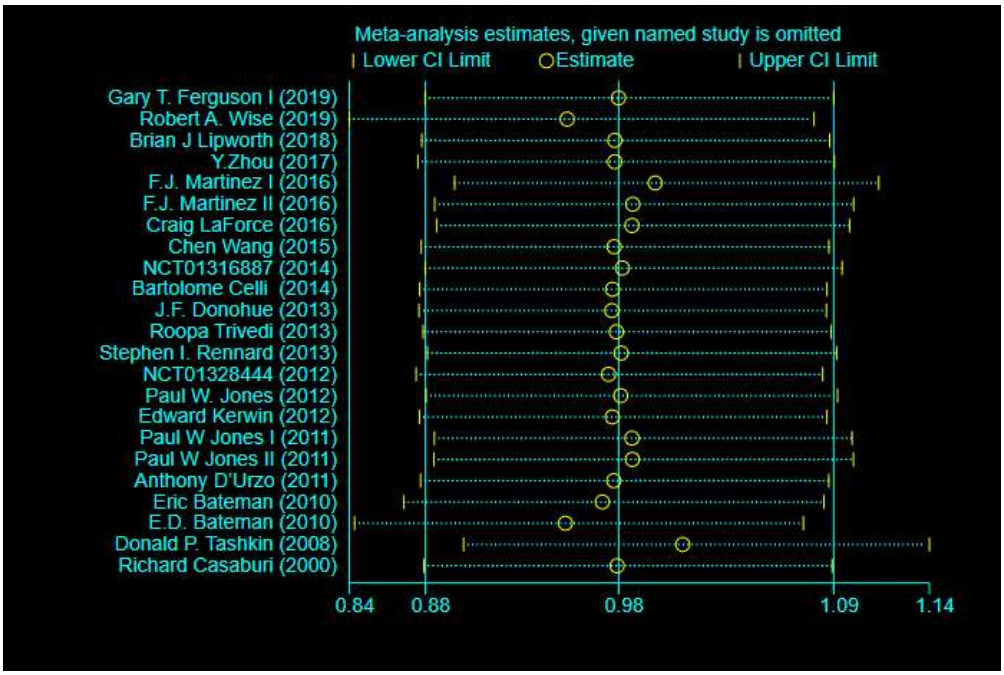

Fig. S15. Sensitivity analysis of cardiovascular events.

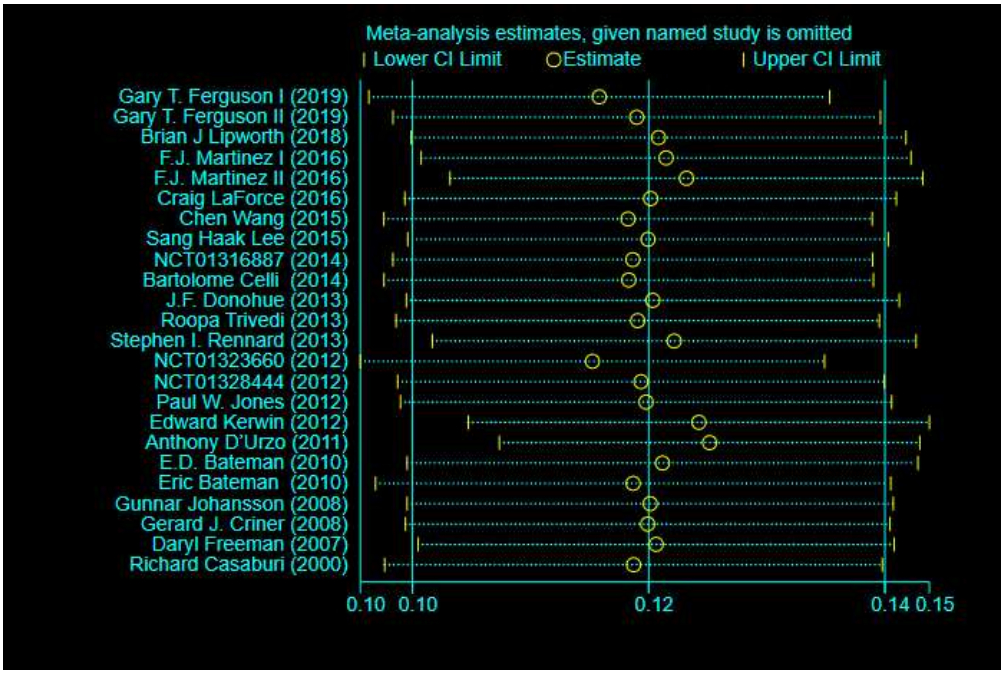

Fig. S16. Sensitivity analysis of trough FEV1.

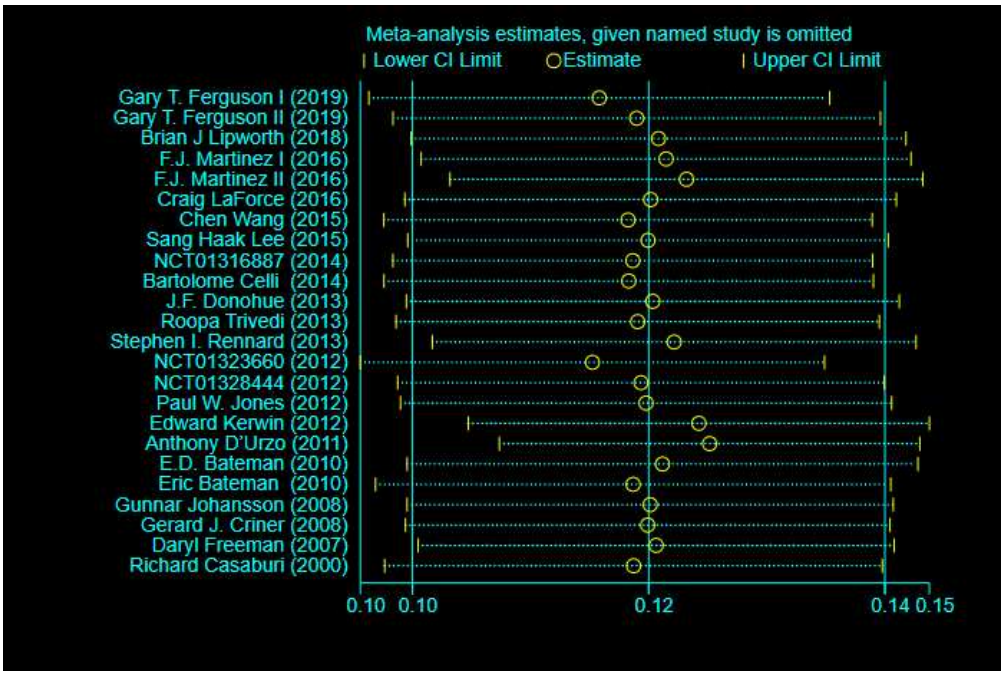

Fig. S17. Sensitivity analysis of the reduction of COPD exacerbation.

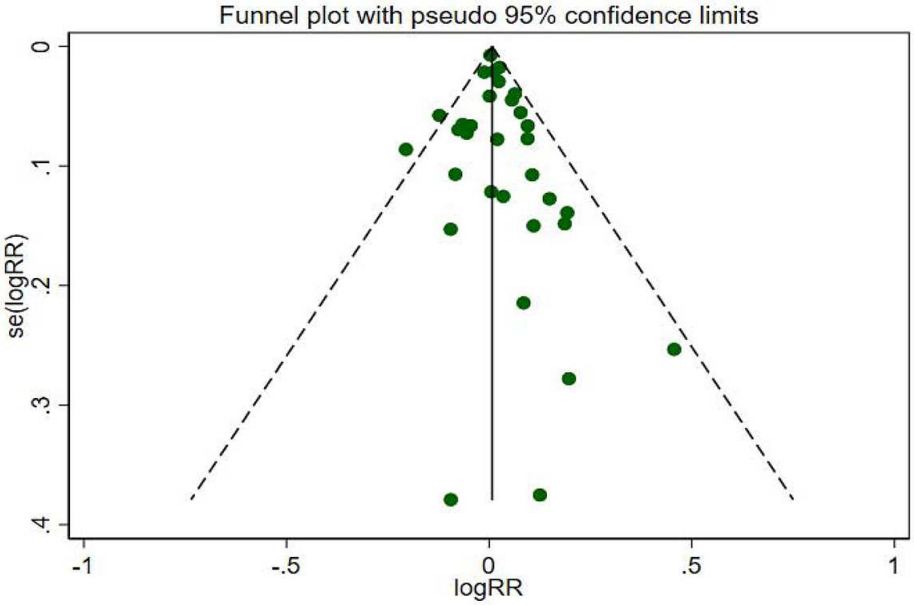

Fig. S18. Funnel plot for publication bias.

Table S1. Characteristic of included studies.

Study	Year	country	N	smoker (%)	pack-years	β2- agonists use(%)	COPD severity(%)				Drug	Inhaler	Duration	outcome
				LAMA/Placebo			mild	moderate	severe	very severe			weeks	
Ferguson G.T.*	2019	US	198/209	48.5/49.3	NA	39.9/35.4	NA				R175 μg qd	JN	12	①②③⑦
			197/208	47.7/45.7	NA	37.6/35.1	NA				R 175μg qd	JN	12	①③⑦
Robert A. Wise	2019	Multinational	1791/1798	43.8/43.3	NA	86.4/89.3	1.9/1.8	44.4/44.9	41.4/39.7	12.3/13.6	A 400 μg bid	DPI	144	①②⑧
Brian J Lipworth	2018	Multinational	480/238	44.1/48.1	44.8±25.5/ 45.7±26.4	NA	1.9/2.6	59.7/58.3	35.4/36.6	3.0/2.6	Gly 18 μg bid	MDI	24	①②③④⑤⑥⑦⑧
Y.Zhou	2017	China	388/383	41.2/40.2	50.6±57.8/ 55.1±86.1	NA	43.1/44.6	56.9/55.4	0/0	0/0	Tio 18 μg qd	DPI	96	①②③⑧
Fernando J. Martinez*	2016	Multinational	451/219	54.3/52.8	50.4±25.1/ 50.8±27.5	NA	0.2/0	52.8/53.0	39.9/39.3	7.1/7.8	Gly 18 μg bid	MDI	24	①②③⑥⑦
			439/223	51.5/49.3	50.4±26.4/ 53.2±25.5	6.4/8.5	0/0	53.8/52.5	40.8/44.8	5.5/2.7	Gly 18 μg bid	MDI	24	①②③⑥⑦
Craig LaForce	2016	US	222/219	61.7/60.3	NA	NA	NA	62.2/65.8	37.4/33.3	NA	Gly 15.6 μg bid	DPI	12	①②③④⑤⑥⑦⑧
Chen Wang	2015	Multinational	305/154	22.3/22.1	38.3±20.78/ 38.3±21.13	NA	0/0	49.2/53.2	50.8/46.8	0/0	Gly 50 μg qd	DPI	26	①②③⑤⑦⑧
Sang Haak Lee	2015	Korea	133/129	NA	39.4±17.3/ 42.5±18.3	NA	NA	56.6/56.6	41.4/43.4	NA	A 400 μg bid	DPI	12	①③④⑤⑥⑦
NCT01316887	2014	Multinational	407/275	53.0/52.0	NA	NA	NA				U 125 μg qd	DPI	24	①②③④⑤⑦
Bartolome Celli	2014	Multinational	227/109	NA	44.0±23.32/ 43.6±23.06	NA	0/0	48/44	44/48	8/8	U 125 μg qd	DPI	24	①②③
J.F. Donohue	2013	Multinational	418/280	50.0/54.0	46.8±27.03/ 47.2±27.21	NA	0/0	46/43	41/48	13/10	U 62.5 μg qd	DPI	24	①②③④⑤⑥⑦
Roopa Trivedi	2013	Multinational	69/68	57.0/53.0	47.5±18.6/ 52.3±30.2	NA	0/0	49/49	36/38	14/13	U 125 μg qd	DPI	12	①②③

Study	Year	country	N	smoker (%)	pack-years	β2- agonists use(%)	COPD severity(%)				Drug	Inhaler	Duration	outcome
				LAMA/Placebo			mild	moderate	severe	very severe			weeks	
Stephen I. Rennard	2013	Multinational	177/182	50.3/56.0	54.2±27.7/ 52.6±28.4	61.0/54.4	0/1.1	44.6/62.1	54.2/36.8	0/0	A 400 μg bid	DPI	12	①②③④⑤⑥⑦⑧
NCT01323660	2012	Multinational	307	NA	NA	NA	NA				U 125 μg qd	DPI	12	①③
NCT01328444	2012	Multinational	348	NA	NA	NA	NA				U 125 μg qd	DPI	12	①②③
Paul W. Jones	2012	Multinational	269/273	55.0/52.8	41.7±21.1/ 38.9±18.3	82.5/83.2	0/0	68.7/65.9	31.3/34.1	0/0	A 400 μg bid	DPI	24	①②③④⑤⑥⑦⑧
Edward Kerwin	2012	Multinational	525/268	45.3/46.3	49.0±25.4/ 48.0±24.0	54.9/53.4	0/0	63.2/64.9	35.6/34.3	1.1/0.7	Gly 50 μg qd	DPI	52	①②③④⑤⑦⑧
Paul W Jone*	2011	Multinational	627/216	45.1/45.4	40.4±21.0/ 38.4±18.3	68.6/59.7	NA				A 200 μg qd	DPI	52	①②⑤⑦⑧
			600/204	37.0/38.7	57.8±29.9/ 58.2±28.4	74.3/87.0	NA				A 200 μg qd	DPI	52	①②⑤⑦⑧
Anthony D'Urzo	2011	Multinational	550/267	32.7/34.1	NA	NA	0/0	60.2/62.2	39.5/37.1	0.4/0.7	Gly 50 μg qd	DPI	26	①②③④⑤⑥⑦⑧
Eric Bateman	2010	Multinational	667/653	34.8/36.1	NA	87/82	NA				Tio 10 μg qd	SMI	48	①②③⑤⑦⑧
E.D. Bateman	2010	Multinational	1952/1965	35.7/35.9	46.0±26.1/ 45.0±26.5	90.9/89.8	NA				Tio 5 μg qd	SMI	48	①②③⑦⑧
Donald P. Tashkin	2008	Multinational	2986/3006	29.3/29.9	49.0±28.0/ 48.4±27.9	68.5/68.1	2/2	46/45	44/44	8/9	Tio 18 μg qd	DPI	192	①②⑦⑧
Gerard J. Criner	2008	US	80/86	52.5/41.9	45.6 ± 26.7/ 47.1 ± 26.0	68.8/57.0	NA				Tio 18 μg qd	DPI	8	①③⑧
Gunnar Johansson	2008	Sweden	107/117	57.0/63.0	31.4±11.9/ 31.6±12.2	0.9/0	28.6/27.8	68.6/68.7	2.9/3.5	0/0	Tio 18 μg qd	DPI	12	①③
Daryl Freeman	2007	UK	191/183	NA	36.9±16.9/ 37.9±17.7	31.27/31.51	45.0/50.3		50.8/48.1	4.2/1.6	Tio 18 μg qd	DPI	12	①③⑧
CKN Chan	2007	Canada	608/305	32.0/30.0	50.2±22.6/ 51.0±26.3	64.0/69.8	NA				Tio 18 μg qd	DPI	48	①⑦⑧

Study	Year	country	N	smoker (%)	pack-years	β2- agonists use(%)	COPD severity(%)				Drug	Inhaler	Duration	outcome
				LAMA/Placebo			mild	moderate	severe	very severe			weeks	
D. Dusser	2006	France	500/510	27.0/24.0	NA	93.4/93.5	NA				Tio 18 μg qd	DPI	48	①⑧
R. Casaburi	2002	US	550/371	NA	63±31/ 59±30	99/99	NA				Tio 18 μg qd	DPI	48	①⑦⑧
Richard Casaburi	2000	US	279/191	NA	64.5±33.1/ 60.5±30.2	NA	NA				Tio 18 μg qd	DPI	13	①②③

Outcomes: ①all adverse events;②cardiovascular events;③trough FEV_1;④TDI focal score;⑤responder of TDI;⑥SGRQ score;⑦responder of SGRQ;⑧the number of patients with at least one moderate or severe exacerbations. Abbreviations: A: aclidinium; Tio: tiotropium; Gly: glycopyrronium; NA: not applicable. *: studies that one article reported two RCTs.

Table S2. The sensitivity analysis of included studies with regard to trough FEV_1

sensitivity analysis	Heterogeneity test		Effect size	
	I^2	tau^2	WMD and 95%CI	*P*
overall	86.60%	0.0023	0.122 (0.100, 0.144)	0
excluding Gary T. Ferguson I	84.80%	0.002	0.117 (0.096, 0.139)	0
excluding Gary T. Ferguson II	87.10%	0.0023	0.121 (0.098, 0.143)	0
excluding Brian J Lipworth	87.10%	0.0024	0.123 (0.100, 0.146)	0
excluding F.J. Martinez I	86.90%	0.0023	0.123 (0.101, 0.146)	0
excluding F.J. Martinez II	85.90%	0.0021	0.125 (0.103, 0.147)	0
excluding Craig LaForce	87.20%	0.0024	0.122 (0.099, 0.145)	0
excluding Chen Wang	87.00%	0.0023	0.120 (0.097, 0.142)	0
excluding Sang Haak Lee	87.20%	0.0023	0.122 (0.099, 0.144)	0
excluding NCT01316887	87.10%	0.0023	0.120 (0.098, 0.143)	0
excluding Bartolome Celli	86.90%	0.0023	0.120 (0.097, 0.143)	0
excluding J.F. Donohue	87.20%	0.0024	0.122 (0.099, 0.145)	0
excluding Roopa Trivedi	87.20%	0.0023	0.121 (0.098, 0.143)	0
excluding Stephen I. Rennard	86.70%	0.0023	0.124 (0.102, 0.147)	0
excluding NCT01323660	85.90%	0.0021	0.117 (0.095, 0.138)	0
excluding NCT01328444	87.20%	0.0023	0.121 (0.099, 0.144)	0
excluding Paul W. Jones	87.20%	0.0024	0.122 (0.099, 0.144)	0
excluding Edward Kerwin	85.40%	0.002	0.126 (0.105, 0.148)	0
excluding Anthony D'Urzo	81.60%	0.0016	0.127 (0.108, 0.147)	0
excluding E.D. Bateman	86.70%	0.0026	0.123 (0.099, 0.147)	0
excluding Eric Bateman	85.50%	0.0026	0.120 (0.096, 0.144)	0
excluding Gunnar Johansson	87.20%	0.0023	0.122 (0.099, 0.144)	0
excluding Gerard J. Criner	87.20%	0.0023	0.122 (0.099, 0.144)	0
excluding Daryl Freeman	87.20%	0.0023	0.122 (0.100, 0.145)	0
excluding Richard Casaburi	87.00%	0.0024	0.120 (0.097, 0.143)	0

Detailed search strategy

PubMed

Search: ((((((((((COPD[Title/Abstract]) OR (Chronic Obstructive Pulmonary Disease[Title/Abstract])) OR (Chronic Obstructive Airway Disease[Title/Abstract])) OR (Chronic Obstructive Lung Disease[Title/Abstract])) OR (Airflow Obstruction, Chronic[Title/Abstract])) OR (Airflow Obstructions, Chronic[Title/Abstract])) OR (Chronic Airflow Obstructions[Title/Abstract])) OR (Chronic Airflow Obstruction[Title/Abstract])) OR (COBD[Title/Abstract])) OR ("Pulmonary Disease, Chronic Obstructive"[Mesh])) AND ((((((((((((((LAMA[Title/Abstract]) OR (long-acting muscarinic antagonists[Title/Abstract])) OR (long acting muscarinic antagonists[Title/Abstract])) OR (aclidinium bromide[Title/Abstract])) OR (glycopyrronium bromide[Title/Abstract])) OR (tiotropium bromide[Title/Abstract])) OR (umeclidinium bromide[Title/Abstract])) OR

(aclidinium[Title/Abstract])) OR (glycopyrronium[Title/Abstract])) OR (tiotropium[Title/Abstract])) OR (umeclidinium[Title/Abstract])) OR (revefenacin[Title/Abstract])) OR (Glycopyrrolate[Title/Abstract])) OR (TD-4208[Title/Abstract])) OR (GSK573719[Title/Abstract])) Filters: Randomized Controlled Trial

Embase

('chronic obstructive lung disease'/exp OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchitis' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive lung disorder' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive pulmonary disorder' OR 'chronic obstructive respiratory disease' OR 'copd' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'lung diseases, obstructive' OR 'obstructive lung disease' OR 'obstructive lung disease, chronic' OR 'obstructive pulmonary disease' OR 'obstructive respiratory disease' OR 'obstructive respiratory tract disease' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive') AND ('long-acting muscarinic antagonists' OR 'aclidinium bromide'/exp OR '3 [(hydroxy) di (thiophen 2 yl) acetyloxy] 1 (3 phenoxypropyl) 1 azabicyclo [2.2.2] octan 1 ylium bromide' OR '3 [[hydroxy (di 2 thienyl) acetyl] oxy] 1 (3 phenoxypropyl) 1 azoniabicyclo [2.2.2] octane bromide' OR '3 [[hydroxydi (thiophen 2 yl) acetyl] oxy] 1 (3 phenoxypropyl) 1 azoniabicyclo [2.2.2] octane bromide' OR '3 [hydroxybis (2 thienyl) acetoxy] 1 (3 phenoxypropyl) quinuclidinium bromide' OR 'aclidinium' OR 'aclidinium bromide' OR 'bretaris' OR 'bretaris genuair' OR 'eklira' OR 'eklira genuair' OR 'las 34273' OR 'las34273' OR 'tudorza' OR 'tudorza pressair' OR 'glycopyrronium'/exp OR '3 (2 cyclopentyl 2 hydroxy 2 phenylacetoxy) 1, 1 dimethylpyrrolidinium' OR '3 (2 cyclopentyl 2 hydroxy 2 phenylacetoxy) 1, 1 dimethylpyrrolidinium 4-methylbenzenesulfonate monohydrate' OR '3 (2 cyclopentyl 2 hydroxy 2 phenylacetoxy) 1, 1 dimethylpyrrolidinium bromide' OR '3 (2 cyclopentyl 2 hydroxy 2 phenylacetoxy) 1, 1 dimethylpyrrolidinium tosylate' OR 'ad 237' OR 'ad237' OR 'ahr 504' OR 'ahr504' OR 'asecryl' OR 'cuvposa' OR 'drm 04' OR 'drm04' OR 'enurev' OR 'enurev breezhaler' OR 'gastrodyn' OR 'gastrodyn inj' OR 'glersa' OR 'glycopyrrolate' OR 'glycopyrrolate inj' OR 'glycopyrronium' OR 'glycopyrronium bromide' OR 'glycopyrronium tosylate' OR 'glyrx-pf' OR 'lonhala magnair' OR 'mobinul' OR 'nodapton' OR 'nva 237' OR 'nva237' OR 'robinal' OR 'robinol' OR 'robinul' OR 'robinul forte' OR 'robinul inj.' OR 'robinul v' OR 'seebri' OR 'seebri breezhaler' OR 'seebri neohaler' OR 'sialanar' OR 'sroton' OR 'strodin' OR 'tarodyl' OR 'tarodyn' OR 'tovanor' OR 'tovanor breezhaler' OR 'tiotropium bromide'/exp OR '7beta [[hydroxybis (2 thienyl) acetyl] oxy] 9, 9 dimethyl 3 oxa 9 azoniatricyclo [3.3.1.0 2, 4] nonane bromide' OR '7beta [hydroxybis (2 thienyl) acetoxy] 9, 9 dimethyl 3 oxa 9 azoniatricyclo [3.3.1.0 2, 4] nonane bromide' OR 'ba 679 br' OR 'ba679 br' OR 'braltus' OR 'favynd' OR 'gregal' OR 'spiriva' OR 'spiriva handihaler' OR 'spiriva respimat' OR 'srivasso' OR 'tiotropium' OR 'tiotropium bromide' OR 'tiotropium bromide monohydrate' OR 'tiotrus' OR 'tiova rotacaps' OR 'umeclidinium'/exp OR '1 [2 (benzyloxy) ethyl] 4 (alpha hydroxybenzhydryl) quinuclidinium bromide' OR '1 [2 (benzyloxy) ethyl] 4 (hydroxydiphenylmethyl) 1 azoniabicyclo [2.2.2] octane' OR '1 [2 [(benzyl) oxy] ethyl] 4 [hydroxydi (phenyl) methyl] 1 azabicyclo [2.2.2] octan 1 ium bromide' OR '4 (hydroxydiphenylmethyl) 1 [2 (phenylmethoxy) ethyl] 1 azoniabicyclo [2.2.2] octane' OR 'ellipta' OR 'ellipta incruse' OR 'encruse ellipta' OR 'gsk 573719' OR 'gsk 573719a' OR 'gsk-573719' OR 'gsk-573719a' OR 'gsk573719' OR 'gsk573719a' OR 'incruse' OR 'incruse ellipta' OR 'rolufta' OR 'rolufta ellipta' OR 'umeclidinium' OR 'umeclidinium bromide' OR 'ipratropium bromide'/exp OR '3 (3 hydroxy 1 oxo 2 phenylpropoxy) 8

methyl 8 (1 methylethyl) 8 azoniabicyclo [3.2.1] octane bromide' OR 'aerovent' OR 'altyonz' OR 'altyonz inhaler' OR 'apo-ipravent' OR 'apovent' OR 'aproven' OR 'atem' OR 'atroaldo' OR 'atrodil' OR 'atronase' OR 'atrovent' OR 'atrovent aerosol' OR 'atrovent enfants' OR 'atrovent forte' OR 'atrovent hfa' OR 'atrovent inhaler' OR 'atrovent n' OR 'atrovent nasal' OR 'broncovent' OR 'inhalvent' OR 'ipra uni-dose' OR 'ipratropium' OR 'ipratropium bromide' OR 'ipratropium salt' OR 'ipravent' OR 'ipraxa' OR 'iprohalex' OR 'ipvent' OR 'itrop' OR 'n isopropylatropinium' OR 'narilet' OR 'nebu trop' OR 'nebu-trop' OR 'respontin' OR 'respontin nebules' OR 'rhinatec' OR 'rinatec' OR 'sch 1000' OR 'sch1000') AND ('placebo'/exp OR 'placebo' OR 'placebo gel' OR 'placebos') AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	5838
#2	COPD	17120
#3	Chronic Obstructive Pulmonary Disease	14572
#4	COBD	90
#5	Chronic Airflow Obstruction	742
#6	Chronic Airflow Obstructions	5
#7	Airflow Obstructions, Chronic	5
#8	Airflow Obstruction, Chronic	742
#9	Chronic Obstructive Lung Disease	11668
#10	Chronic Obstructive Airway Disease	2042
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	22261
#12	MeSH descriptor: [Muscarinic Antagonists] explode all trees	907
#13	long-acting muscarinic antagonists	288
#14	revefenacin	38
#15	umeclidinium	388
#16	tiotropium	2378
#17	glycopyrronium	1042
#18	aclidinium	346
#19	umeclidinium bromide	110
#20	tiotropium bromide	1453
#21	glycopyrronium bromide	662
#22	aclidinium bromide	309
#23	long acting muscarinic antagonists	302
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	4493
#25	#11 AND #24	2893
#26	RCT	35501
#27	Randomized Controlled Trial	1045668
#28	#26 OR #27	1050695
#29	#25 AND #28	1583

Web Of Science

#1 **TOPIC:** (COBD) *OR* **TOPIC:** (Chronic Airflow Obstructions) *OR* **TOPIC:** (COPD) *OR* **TOPIC:** (Chronic Obstructive Pulmonary Disease) *OR* **TOPIC:** (Chronic Obstructive Airway Disease) *OR* **TOPIC:** (Chronic Obstructive Lung Disease) *OR* **TOPIC:** (Airflow Obstruction, Chronic) *OR* **TOPIC:** (Airflow Obstructions, Chronic) *OR* **TOPIC:** (Chronic Airflow Obstruction)
Databases= WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO Timespan=All years
Search language=Auto
#2 **TOPIC:** (revefenacin) *OR* **TOPIC:** (long-acting muscarinic antagonists) *OR* **TOPIC:** (LAMA) *OR* **TOPIC:** (long acting muscarinic antagonists) *OR* **TOPIC:** (aclidinium bromide) *OR* **TOPIC:** (glycopyrronium bromide) *OR* **TOPIC:** (tiotropium bromide) *OR* **TOPIC:** (umeclidinium bromide) *OR* **TOPIC:** (aclidinium) *OR* **TOPIC:** (glycopyrronium) *OR* **TOPIC:** (tiotropium) *OR* **TOPIC:** (umeclidinium)
Databases= WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO Timespan=All years
Search language=Auto
#3 #2 AND #1
Databases= WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO Timespan=All years
Search language=Auto