Online appendix

Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials

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METHODS

Search strategy

Full-text terms and Medical Subject Headings terms used for systematic database searching included chronic obstructive pulmonary disease (COPD), long-acting anticholinergics, long-acting beta-2 agonists (LABA), and inhaled corticosteroids (ICS).

The MEDLINE search strategy through the PubMed filter was as the following: ("chronic obstructive pulmonary disease"[All Fields] OR "chronic obstructive lung disease"[All Fields] OR "chronic obstructive airway disease"[All Fields] OR "pulmonary disease, chronic obstructive"[MeSH Terms] OR "COPD"[All Fields]) AND (("long acting anticholinergic"[All Fields] OR "cholinergic antagonists"[MeSH Terms] OR "tiotropium"[All Fields]) OR ("long acting beta 2 agonist"[All Fields] OR "long acting beta agonist"[All Fields] OR "LABA"[All Fields] OR "adrenergic beta 2 receptor agonists"[MeSH Terms] OR "adrenergic beta agonists"[MeSH Terms] OR "bronchodilator agents"[MeSH Terms] OR "salmeterol"[All Fields] OR "formoterol"[All Fields]) OR ("inhaled corticosteroid"[All Fields] OR "glucocorticoids"[MeSH Terms] OR "anti-inflammatory agents"[MeSH Terms] OR "budesonide"[All Fields] OR "fluticasone"[All Fields] OR "beclomethasone"[All

Fields] OR "triamcinolone"[All Fields]))

For the databases of MEDLINE, CINAHL, and Cochrane Library, the search results were further restricted to randomized controlled trials. For the databases of ClinicalTrials.gov, the search results were restricted to trials with results announced.

All the search strategies were discussed between two investigators, a pharmacist (YHD) and a physician (CHC), and the full consensus was achieved. The investigators also pre-tested whether the search strategies can involve relevant trials according the bibliographies of systematic review articles.

Outcome measures

The primary outcome was overall death. The secondary outcome was cardiovascular death. Most trials did not include cardiovascular death as a predefined outcome and there was no homogeneous definition of this endpoint across the trials. Therefore, for trials without reporting data on the specific endpoint of cardiovascular death, we constructed the composite endpoint of cardiovascular death by retrieving trial data from the serious adverse event reporting and summed the fatal events on the individual cardiovascular endpoints, which include sudden death, cardiac death, sudden cardiac death, and the preferred terms under the cardiac and vascular system organ classes defined by the Medical Dictionary for Regulatory Activities (MedDRA)

version 11.0.[21]

The preferred terms under the cardiac and vascular system organ classes defined by the MedDRA include atrial fibrillation/flutter, supraventricular tachycardia, tachycardia, ventricular tachycardia/fibrillation, palpitations, cardiac arrest, cardiac failure, ischemic heart disease, myocardial infarction, aneurysm, hypertension, and stroke.

Data extraction and assessment of risk of bias

Two investigators (YHD and CHC) independently screened all articles identified based on titles and abstracts. The eligibilities of potentially relevant trials were independently evaluated based on the full-text articles. If trials produced multiple publications, we included the most recent publication or the publication with most complete information. A standardized data extraction form was used to extract the relevant characteristics for each eligible trial, including (a) trial characteristics (author, publication year, design of randomization and blinding, study location and duration, inclusion and exclusion criteria, inhaled medication used, and number of subjects included), (b) patient characteristics at baseline (mean age, proportion of male, percentage of current smokers, mean forced expiratory volume in 1 second (FEV1) % of predicted value, and percentage of subjects with concomitant use of LABA or ICS)

(c) withdrawal rate and the fraction of lost to follow-up, and (d) number of subjects with overall death or with cardiovascular death.

To assess the risk of bias, we applied Cochrane's risk of bias tool to evaluate each trial in terms of sequence generation, allocation concealment, binding of personnel and participants, incomplete outcome addressed (reporting of withdrawal rates and loss to follow-up), and free of selective reporting (reporting of primary and secondary endpoints). We also recorded how adverse events were monitored, including duration, intensity, other measures, and objective adjudication of cause of death.[22] Any disagreement was resolved by discussion and consensus.

Statistical analysis

Direct comparison meta-analysis

We mainly used the Peto method for the direct comparison meta-analysis. The Peto method does not require a continuity correction and has the advantage of providing the best confidence interval coverage when events are rare.[23] To account for the potential imbalance of sample size between treatment groups within trials, we conducted the sensitivity analysis by the Mantel-Haenszel method with different continuity correction factors (0.5, 0.1, 0.01, and without any continuity correction) for trials with zero events in active-treatment or placebo groups.[24] For each pairwise

comparison, the risks of overall and cardiovascular death were estimated with the pooled odds ratio (OR) and 95% confidence interval (CI). If one treatment was given at different doses within a trial, we collapsed the data to obtain an overall estimate. For pairwise comparisons including more than 10 trials, publication bias was assessed by visual inspection of the funnel plot and by the Begg's test and the Egger's test.[22]

MTC meta-analysis

The MTC meta-analysis was conducted using the Bayesian Markov chain Monte Carlo (MCMC) methods.[17] Given the challenge of the homogeneity assumption in the MTC analysis, both fixed effect and random effects models were applied. To address the possible difference of demographic characteristics across trials, we performed meta-regression to adjust for variables of age, proportion of male, percentage of current smoker, study duration, FEV1, and percentage of subjects with concomitant use of LABA or ICS. We applied a vague prior distribution, ran 50,000 MCMC iterations with a thin parameter of 5, and undertook the posterior inference after discarding the initial results of 9,999 iterations. The WinBUGS code for the main analysis was shown as follows, which was based on the code on the website of the Department of Community Based Medicine, University of Bristol, UK (www.bris.ac.uk/cobm/research/mpes/mtc.html) except for the value of absolute log

odds of placebo, which was driven from our trial data.

Fixed effect:

```
model {
#   Model and binomial likelihood
    for(i in 1:N) { logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
                    r[i]~dbin(p[i],n[i]) }
#   Vague priors for trial baselines
    for(j in 1:NS) { mu[j]~dnorm(0,.0001) }
#   Vague priors for basic parameters
    d[1]<-0
    for (k in 2:NT) { d[k] ~ dnorm(0,.0001) }
#   Absolute log odds(overall death) of placebo, based on the crude overall death probability of
    placebo from trial data (5.580%)
    mA ~ dnorm(-2.829,2.763)
#   Absolute log odds(overall death) of tiotropium Soft Mist™ Inhaler, tiotropium HandiHaler®,
    LABA, LABA-ICS and ICS
    for (k in 1:NT) { logit(T[k])<- mA +d[k] }
#   Ranking
    for (k in 1:NT) { rk[k]<- NT+1 - rank(T[],k)
                      best[k]<-equals(rk[k],1) }
#   Pairwise ORs
    for (c in 1:(NT-1))
                    { for (k in (c+1):NT)
                      { lor[c,k] <- d[k] - d[c]
                      log(or[c,k]) <- lor[c,k]
                      }
                    }
}
```

Random effects:

```
model {
for(i in 1:NS){
            w[i,1] <-0
             delta[i,t[i,1]]<-0
#   Vague priors for trial baselines
```

```
            mu[i] ~ dnorm(0,.0001)
#   Model and binomial likelihood
    for (k in 1:na[i]) { r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
                         logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]] }
    for (k in 2:na[i]) {
#   Trial-specific LOR distributions
                         delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
#   Mean of LOR distributions
                         md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
#   Precision of LOR distributions
                         taud[i,t[i,k]] <- tau *2*(k-1)/k
#   Adjustment, multi-arm RCTs
                         w[i,k] <- (delta[i,t[i,k]]    - d[t[i,k]] + d[t[i,1]])
#   Cumulative adjustment for multi-arm trials
                         sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
                           }
#   Vague priors for basic parameters
    d[1]<-0
    for (k in 2:NT){d[k] ~ dnorm(0,.0001) }
#   Vague prior for random effects standard deviation
    sd~dunif(0,2)
    tau<-1/pow(sd,2)
#   Absolute log odds(overall death) of placebo, based on the crude overall death probability of
    placebo from trial data (5.580%)
    mA ~ dnorm(-2.829,2.763)
#   Absolute log odds(overall death) on tiotropium Soft Mist™ Inhaler, tiotropium HandiHaler®,
    LABA, LABA-ICS and ICS
    for (k in 1:NT) { logit(T[k])<- mA +d[k] }
#   Ranking
    for (k in 1:NT) { rk[k]<-NT+1 - rank(T[],k)
                      best[k]<-equals(rk[k],1)}
#   Pairwise ORs
    for (c in 1:(NT-1))
                      { for (k in (c+1):NT)
                        { lor[c,k] <- d[k] - d[c]
                          log(or[c,k]) <- lor[c,k]
                        }
                      }
```

}

RESULTS

Eligible trials

We identified 2248 references through database searching and associated sources. After screening and evaluating these references, 42 eligible trials reporting on overall death[W1-W44] and 31 trials reporting on cardiovascular death[W1-W3, W5, W6, W8 -W12, W15, W17-W23, W25, W27-W44] were included for the meta-analysis (figure 1). Of these trials, three trials assessed tiotropium Soft Mist™ Inhaler and 12 trials assessed tiotropium HandiHaler®. 19, 17, and 16 trials evaluated LABA, LABA-ICS, and ICS, separately. 34 trials were placebo-controlled trials. Based on the predefined treatment arms, 32 trials were two-arm trials, three trials were three-arm trials, and seven trials were four-arm trials.

All these trials excluded patients with significant diseases that might impact the patients' capacity to finish the trials, and 21 trials clearly addressed specific cardiovascular exclusion criteria (table S1). For most of the trials, inhaled short-acting beta-2 agonists, oral corticosteroids, and antibiotics were allowed for as-needed symptom relief and short-course treatment of exacerbations during the study period.

Table S1 Characteristics of included trials

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Bateman, 2010[W2 W9]	TIO-SMI vs PL	3991	336 centers in 31 countries	48 weeks	Recent history of MI, life-threatening cardiac arrhythmia, or hospitalization for cardiac failure
Bateman, 2010*[W3 W10]	TIO-SMI vs PL	983	73 centers in 14 countries	48 weeks	NA
Bateman, 2010*[W3 W11]	TIO-SMI vs PL	1007	78 centers in 14 countries	48 weeks	NA
Tashkin, 2008[W1]	TIO-HH vs PL	5992	490 centers in 37 countries	4 years	Recent history of MI, life-threatening cardiac arrhythmia, or hospitalization for cardiac failure
Tonnel, 2008[W12]	TIO-HH vs PL	554	123 centers in France	9 months	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for either heart failure or pulmonary edema
Ambrosino, 2008[W13]	TIO-HH vs PL	234	12 centers in Italy	25 weeks	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for cardiac failure
Chan, 2007[W14]	TIO-HH vs PL	913	101 centers in Canada	48 weeks	Recent history of MI or cardiac arrhythmia requiring drug therapy
Powrie, 2007[W15]	TIO-HH vs PL	142	Single center in UK	1 year	NA
Dusser, 2005[W16]	TIO-HH vs PL	1010	177 centers in France	48 weeks	NA
Casaburi, 2005[W17]	TIO-HH vs PL	108	17 centers in US	25 weeks	Recent history of MI, cardiac arrhythmia requiring drug therapy, or hospitalization for cardiac failure
Niewoehner, 2005[W18]	TIO-HH vs PL	1829	26 VA centers in US	6 months	Recent history of MI, serious cardiac arrhythmia, or hospitalization for heart failure

Table S1 (Continued)

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Casaburi, 2002[W19]	TIO-HH vs PL	921	50 centers	1 year	Recent history of MI, cardiac arrhythmia requiring drug therapy, or heart failure
Vogelmeier, 2011[W20]	TIO-HH vs LABA	7376	725 centers in 25 countries	1 year	Severe CV disorders or recent history of MI, cardiac arrhythmia requiring medical or surgical treatment, or hospital admission for heart failure
Brusasco, 2003[W21]	TIO-HH vs LABA vs PL	1207	18 countries	6 months	NA
Wedzicha, 2008[W22]	TIO-HH vs LABA-ICS	1323	179 centers in 20 countries	104 weeks	Use of beta blockers
Stockley, 2006[W23]	LABA vs PL	634	84 centers in 19 countries	12 months	NA
Campbell, 2005[W24]	LABA vs PL	657	73 centers in 8 countries	6 months	Significant or unstable cardiovascular disorder
Chapman, 2002[W25]	LABA vs PL	408	52 centers in 6 countries	24 weeks	NA
Shaker, 2009[W26]	ICS vs PL	254	Single center in Denmark	4year	NA
Choudhury, 2007[W27]	ICS vs PL	260	31 centers in UK	1 year	NA
van der Valk, 2002[W28]	ICS vs PL	244	Single center in Netherlands	6 months	Cardiac insufficiency
Burge, 2000[W29]	ICS vs PL	751	18 centers in UK	3 years	Use of beta blockers
Pauwels, 1999[W30]	ICS vs PL	1277	39 centers in 9 countries	3 years	NA
Vestbo, 1999[W31]	ICS vs PL	290	Single center in Denmark	3 years	NA
Paggiaro, 1998[W32]	ICS vs PL	281	Europe, New Zealand, South Africa	6 months	NA
FLTA3025[W33]	ICS vs PL	640	55 centers in US	24 weeks	NA
Calverley, 2010[W34]	LABA-ICS vs LABA	718	76 centers in 8 countries	48 weeks	NA

Table S1 (Continued)

Author, Year	Comparison	No of subjects	Study location	Study duration	Specific CV exclusion criteria
Anzueto, 2009[W35]	LABA-ICS vs LABA	797	98 centers in US and Canada	52 weeks	NA
Ferguson, 2008[W36]	LABA-ICS vs LABA	782	94 centers in US and Canada	52 weeks	Clinically significant and uncontrolled CV disorders
Kardos, 2007[W37]	LABA-ICS vs LABA	994	95 centers in Germany	44 weeks	NA
Wouters, 2005[W38]	LABA-ICS vs LABA	373	39 centers in Netherlands	1 year	Recent history of MI, acute heart failure, or angina pectoris
SCO40041[W39]	LABA-ICS vs LABA	186	31 centers in US	156 weeks	NA
Rennard, 2009[W4]	LABA-ICS vs LABA vs PL	1964	237 centers in US, Europe, Mexico	12 months	Significant or unstable cardiovascular disorder
SFCT01/SCO30002[W40]	LABA-ICS vs ICS vs PL	387	49 centers in Itay and Poland	52 weeks	NA
Zheng, 2007[W41]	LABA-ICS vs PL	445	12 centers in China	24 weeks	NA
Tashkin, 2008[W5]	LABA-ICS vs LABA vs ICS vs PL	1704	194 centers in 5 countries	26 weeks	Significant or unstable cardiovascular disorder
Calverley, 2007[W8]	LABA-ICS vs LABA vs ICS vs PL	6184	444 centers in 42 countries	3 years	NA
Hanania, 2003[W42]	LABA-ICS vs LABA vs ICS vs PL	723	76 centers in US	24 weeks	Abnormal clinically significant electrocardiogram
Calverley, 2003[W6]	LABA-ICS vs LABA vs ICS vs PL	1465	196 centers in 25 countries	12 months	NA
Calverley, 2003[W7]	LABA-ICS vs LABA vs ICS vs PL	1022	109 centers in 15 countries	12 months	Any relevant cardiovascular disorders or use of beta blockers
Szafranski, 2003[W43]	LABA-ICS vs LABA vs ICS vs PL	812	89 centerss in 11 countries	12 months	Any relevant cardiovascular disorders or use of beta blockers
Mahler, 2002[W44]	LABA-ICS vs LABA vs ICS vs PL	674	65 centers in US	24 weeks	Abnormal clinically significant electrocardiogram

*Data from trials NCT00168844[W10] and NCT00168831[W11] were reported together in Bateman and colleagues' article.[W3] Individual information for each trial was retrieved from the U.S. FDA and ClinicalTrials.gov. websites.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; CV, cardiovascular; MI, myocardial infarction; UK, United Kingdom; US, United States; VA, Veterans Affairs; NA, not available.

Table S2 Baseline characteristics of patients and number of events for each outcome in included trials

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Bateman, 2010[W2 W9]	TIO-SMI5 qd	1989 (78.1)	64.8 (9.1)	35.7	45.2 (13.5)	54.2	56.0	16.0	1.1	52	22
	PL	2002 (77.0)	64.8 (9.0)	35.9	45.4 (13.6)	52.6	56.1	18.6	1.4	38	12
Bateman, 2010†[W3 W10 W11]	TIO- SMI5 qd	670 (73.3)	64.7 (8.6)	37.9	46.6 (NA)	30.0	49.0	17.2	1.3	16	6
	TIO- SMI10 qd	667 (74.7)	65.1 (8.5)	34.8	45.3 (NA)	30.0	57.0	20.4	1.7	19	2
	PL	653 (74.6)	65.2 (8.7)	36.1	46.2 (NA)	29.0	55.0	31.4	2.2	9	1
Tashkin, 2008‡[W1]	TIO-HH18 qd	2986 (75.4)	64.5 (8.4)	29.3	47.7 (12.7)	60.1	61.6	36.8	2.1	381	76
	PL	3006 (73.9)	64.5 (8.5)	29.9	47.4 (12.6)	60.1	61.9	45.2	2.5	411	101
Tonnel, 2008[W12]	TIO- HH18 qd	266 (86.8)	64.9 (9.7)	23.7	47.5 (13.3)	NA	NA	14.7	1.1	3	1
	PL	288 (85.4)	63.5 (10.1)	30.2	46.2 (12.4)	NA	NA	25.7	2.1	6	1
Ambrosino, 2008§[W13]	TIO- HH18 qd	117 (82.9)	67.8 (7.8)	NA	42.5 (13.3)	11.1	NA	25.6	1.7	0	NA
	PL	117 (84.6)	66.9 (7.3)	NA	40.3 (12.6)	23.9	NA	23.1	4.3	0	NA
Chan, 2007[W14]	TIO- HH18 qd	608 (59.0)	66.8 (8.7)	32.0	39.4 (13.4)	54.3	65.8	22.2	NA	15	NA
	PL	305 (61.0)	66.9 (9.1)	30.0	39.3 (13.6)	52.8	71.1	27.5	NA	4	NA
Powrie, 2007[W15]	TIO- HH18 qd	69 (69.6)	66.3 (8.1)	59.4	50.9 (14.8)	42.0	73.9	30.4	NA	1	1
	PL	73 (56.2)	66.4 (9.8)	57.5	49.2 (15.6)	43.8	76.7	28.8	NA	2	1
Dusser, 2005‖[W16]	TIO- HH18 qd	500 (89.0)	64.5 (9.1)	27.0	48.2 (12.8)	31.0	65.0	23.4	NA	7	NA
	PL	510 (87.0)	65.0 (9.5)	24.0	47.6 (12.5)	32.5	61.6	28.8	NA	8	NA
Casaburi, 2005[W17]	TIO- HH18 qd	55 (54.5)	65.9 (8.8)	29.1	32.6 (12.4)	NA	NA	NA	NA	1	0
	PL	53 (58.5)	67.3 (6.9)	18.9	36.2 (12.2)	NA	NA	NA	NA	0	0
Niewoehner, 2005[W18]	TIO- HH18 qd	914 (98.0)	67.6 (8.7)	29.0	35.6 (12.6)	38.0	61.0	16.7	0.4	22	7
	PL	915 (99.0)	68.1 (8.5)	30.0	35.6 (12.6)	38.0	58.0	26.8	0.8	19	7

Table S2 (Continued)

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Casaburi, 2002‡[W19]	TIO- HH18 qd	550 (66.5)	65.0 (9.0)	NA	39.1 (13.7)	NA	44.0	18.7	NA	7	6
	PL	371 (62.8)	65.0 (9.0)	NA	38.1 (14.1)	NA	40.0	27.8	NA	7	1
Vogelmeier, 2011[W20]	TIO- HH18 qd	3707 (74.4)	62.9 (9.0)	48.0	49.2 (13.3)	51.5	53.6	15.8	0.2	64	9
	SAL50 bid	3669 (74.9)	62.8 (9.0)	48.3	49.4 (13.1)	51.5	53.3	17.7	0.4	78	7
Brusasco, 2003‡[W21]	TIO- HH18 qd	402 (77.4)	63.8 (8.0)	NA	39.2 (11.6)	NA	NA	15.4	NA	1	1
	SAL50 bid	405 (75.1)	64.1 (8.5)	NA	37.7 (11.7)	NA	NA	18.8	NA	6	1
	PL	400 (76.3)	64.6 (8.6)	NA	38.7 (12.1)	NA	NA	25.8	NA	5	2
Wedzicha, 2008[W22]	TIO-D 18 qd	665 (84.0)	65.0 (NA)	38.0	39.4 (NA)	46.0	51.0	42.0	2.0	38	19
	SAL50/FLU500 bid	658 (81.0)	64.0 (NA)	38.0	39.1 (NA)	43.0	48.0	35.3	2.3	21	9
Stockley, 2006[W23]	SAL50 bid	316 (77.0)	62.4 (9.2)	47.0	46.1 (14.5)	22.0	54.0	24.0	1.6	6	6
	PL	318 (76.0)	62.3 (9.1)	46.0	45.8 (14.1)	22.0	60.0	18.0	2.8	5	2
Campbell, 2005[W24]	FOR9 bid	215 (61.0)	60.0 (NA)	54.0	53.0 (NA)	NA	47.0	14.0	0.5	2	NA
	FOR9 bid and prn	225 (71.0)	60.0 (NA)	56.0	54.4 (NA)	NA	45.0	12.9	0.5	1	NA
	PL	217 (73.0)	60.1 (NA)	55.0	54.1 (NA)	NA	44.0	18.0	0.5	0	NA
Chapman, 2002[W25]	SAL50 bid	201 (64.0)	65.0 (9.0)	44.0	44.0 (NA)	NA	NA	10.0	NA	1	1
	PL	207 (64.0)	64.0 (10.0)	43.0	46.0 (NA)	NA	NA	13.5	NA	2	1
Shaker, 2009[W26]	BUD400 bid	127 (62.0)	63.6 (7.5)	100.0	51.0 (11.0)	NA	NA	43.0	1.6	5	NA
	PL	127 (54.0)	63.6 (7.2)	100.0	53.0 (11.0)	NA	NA	49.0	3.1	5	NA
Choudhury, 2007[W27]	FLU500 bid	128 (48.0)	67.6 (8.9)	40.6	53.2 (18.2)	35.1	NA	43.8	8.6	3	0
	PL	132 (56.0)	67.3 (9.0)	35.6	55.0 (17.1)	31.8	NA	59.0	6.8	0	0

Table S2 (Continued)

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
van der Valk, 2002[W28]	FLU500 bid	123 (85.4)	64.1 (6.8)	22.0	57.5 (14.1)	59.0	86.2	0.8	0.0	4	1
	PL	121 (83.5)	64.0 (7.7)	33.0	56.1 (14.8)	53.0	80.2	0.8	0.0	0	0
Burge, 2000[W29]	FLU500 bid	376 (6.0)	63.7 (7.1)	36.3	50.3 (14.9)	NA	NA	43.6	4.3	32	10
	PL	375 (3.0)	63.8 (7.1)	39.4	50.0 (14.9)	NA	NA	53.3	4.8	36	12
Pauwels, 1999[W30]	BUD400 bid	634 (73.5)	52.5 (7.5)	100.0	76.8 (12.4)	NA	NA	30.0	2.7	8	NA
	PL	643 (72.2)	52.4 (7.7)	100.0	76.9 (13.2)	NA	NA			10	NA
Vestbo, 1999*[W31]	BUD bid	145 (58.6)	59.0 (8.3)	75.9	86.2 (20.6)	NA	NA	24.8	NA	4	3
	PL	145 (62.1)	59.1 (9.7)	77.2	86.9 (21.1)	NA	NA	35.2	NA	5	0
Paggiaro, 1998[W32]	FLU500 bid	142 (70.0)	62.0 (NA)	49.0	59.0 (18.0)	11.0	NA	13.0	0.0	0	0
	PL	139 (78.0)	64.0 (NA)	49.0	55.0 (17.0)	16.0	NA	19.0	1.4	2	0
FLTA3025[W33]	FLU500 bid	218 (66.1)	63.3 (10.0)	NA	NA	NA	NA	33.0	NA	0	0
	FLU250 bid	216 (72.2)	65.2 (8.7)	NA	NA	NA	NA	35.0	NA	0	0
	PL	206 (68.0)	64.8 (9.5)	NA	NA	NA	NA	38.0	NA	0	0
Calverley, 2010[W34]	FOR12/BECLO200 bid	237 (79.3)	63.0 (9.0)	38.8	41.9 (5.6)	44.4	43.5	13.1	1.3	2	NA
	FOR12/BUD400 bid	242 (81.5)	64.1 (9.1)	36.1	42.3 (6.0)	43.2	36.6	12.4	2.1	4	NA
	FOR bid	239 (81.1)	63.7 (8.8)	37.3	42.5 (5.9)	42.9	36.1	14.2	1.3	0	NA
Anzueto, 2009[W35]	SAL50/FLU250 bid	394 (51.0)	65.4 (9.1)	42.0	41.2 (14.3)	8.0	14.0	32.0	1.3	4	0
	SAL50 bid	403 (57.0)	65.3 (8.8)	43.0	40.0 (12.6)	9.0	14.0	39.0	3.0	6	0
Ferguson, 2008[W36]	SAL50/FLU250 bid	394 (58.0)	64.9 (9.0)	40.0	39.8 (13.9)	12.0	15.0	30.0	2.5	6	4
	SAL50 bid	388 (52.0)	65.0 (9.1)	38.0	40.6 (15.4)	11.0	18.0	38.0	2.6	3	1

Table S2 (Continued)

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Kardos, 2007[W37]	SAL50/FLU500 bid	507 (74.0)	63.8 (8.3)	40.6	40.4 (8.9)	53.6	49.7	21.1	0.8	7	1
	SAL50 bid	487 (77.6)	64.0 (8.2)	44.4	40.3 (8.5)	55.4	49.9	19.5	0.6	9	3
Wouters, 2005[W38]	SAL50/FLU500 bid	189 (73.0)	63.0 (7.9)	39.0	47.4 (13.9)	3.0	21.0	18.0	NA	2	1
	SAL50 bid	184 (75.0)	64.0 (7.7)	35.0	48.2 (12.9)	3.0	24.0	25.0	NA	4	3
SCO40041[W39]	SAL50/FLU250 bid	92 (59.8)	65.4 (8.4)	NA	NA	NA	NA	39.0	NA	5	0
	SAL50 bid	94 (62.8)	65.9 (9.5)	NA	NA	NA	NA	41.0	NA	7	2
Rennard, 2009[W4]	FM9/BUD320 bid	494 (62.3)	63.2 (8.9)	NA	38.6 (11.4)	NA	NA	27.1	1.8	5	NA
	FM9/BUD160 bid	494 (62.8)	63.6 (9.2)	NA	39.6 (10.9)	NA	NA	29.0	2.4	2	NA
	FM9 bid	495 (65.3)	62.9 (9.1)	NA	39.3 (11.9)	NA	NA	31.7	2.4	4	NA
	PL	481 (65.3)	62.9 (9.2)	NA	40.8 (11.5)	NA	NA	36.4	2.7	4	NA
SFCT01/SCO30002[W40]	SAL50/FLU500 bid	131 (84.0)	63.9 (10.1)	NA	NA	NA	NA	34.4	NA	1	1
	FLU500 bid	131 (83.2)	64.6 (8.7)	NA	NA	NA	NA	26.0	NA	0	0
	PL	125 (80.0)	65.7 (9.0)	NA	NA	NA	NA	32.0	NA	0	0
Zheng, 2007[W41]	SAL50/FLU500 bid	297 (90.6)	66.0 (8.2)	21.0	47.0 (NA)	NA	NA	12.0	2.0	2	0
	PL	148 (86.5)	66.6 (7.7)	23.0	47.0 (NA)	NA	NA	11.0	0.7	0	0

Table S2 (Continued)

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Tashkin, 2008[W5]	FM9/BUD320 bid	277 (67.9)	63.1 (9.0)	44.4	39.1 (11.8)	35.4	54.2	14.1	1.4	3	1
	FM9/BUD160 bid	281 (64.4)	63.6 (9.0)	44.8	39.9 (11.2)	36.7	52.7	13.5	1.1	4	2
	FM9 bid + Bud320 bid	287 (74.2)	63.7 (9.0)	41.5	39.2 (11.4)	33.1	55.1	16.7	2.1	0	0
	FM9 bid	284 (65.5)	63.5 (9.5)	41.9	39.6 (12.8)	33.1	55.3	21.5	1.4	1	1
	BUD320 bid	275 (67.6)	63.4 (8.8)	42.9	39.7 (12.0)	34.5	52.0	22.9	0.4	2	1
	PL	300 (69.0)	63.2 (9.6)	39.7	41.3 (12.1)	32.7	56.3	25.7	2.3	1	1
Calverley, 2007[W8]	SAL50/FLU500 bid	1546 (75.0)	65.0 (8.3)	43.0	44.3 (12.3)	9.0	19.0	34.6	1.9	193	60
	SAL50 bid	1542 (76.0)	65.1 (8.2)	43.0	43.6 (12.6)	9.0	18.0	37.7	1.0	205	45
	FLU500 bid	1552 (75.0)	65.0 (8.4)	43.0	44.1 (12.3)	8.0	20.0	39.0	1.5	246	61
	PL	1544 (76.0)	65.0 (8.2)	43.0	44.1 (12.3)	8.0	22.0	44.9	1.4	231	71
Hanania, 2003[W42]	SAL50/FLU250 bid	178 (61.0)	63.0 (NA)	43.0	41.0 (11.0)	NA	23.0	30.0	1.8	0	0
	SAL50 bid	177 (58.0)	64.0 (NA)	51.0	42.0 (12.0)	NA	20.0	32.0	1.8	0	0
	FLU250 bid	183 (66.0)	63.0 (NA)	48.0	42.0 (11.0)	NA	28.0	27.0	1.8	0	0
	PL	185 (68.0)	65.0 (NA)	47.0	42.0 (12.0)	NA	30.0	32.0	1.8	0	0
Calverley, 2003[W6]	SAL50/FLU500 bid	358 (75.0)	62.7 (8.7)	52.0	44.8 (14.7)	42.0	50.0	25.0	2.2	2	0
	SAL50 bid	372 (70.0)	63.2 (8.6)	51.0	44.3 (13.8)	42.0	49.0	32.0	2.2	3	1
	FLU500 bid	374 (70.0)	63.5 (8.5)	53.0	45.0 (13.6)	40.0	54.0	29.0	2.1	3	2
	PL	361 (75.0)	63.4 (8.6)	47.0	44.2 (13.7)	38.0	52.0	39.0	1.7	7	4

Table S2 (Continued)

Author, Year	Comparison (inhaled medication and dosage*)	No of subjects (male, %)	Age, mean (SD), yr	Current smoker, %	FEV1 mean (SD), % of predicted value	Subjects with concomitant use of LABA, %	Subjects with concomitant use of ICS, %	Withdrawal rate, %	Lost to follow-up, %	No of subjects with overall death	No of subjects with CV death
Calverley, 2003[W7]	FOR9/BUD320 bid	254 (78.0)	64.0 (NA)	33.0	36.0 (10.0)	31.0	47.0	29.1	0.0	5	NA
	FOR9 bid	255 (75.0)	63.0 (NA)	36.0	36.0 (10.0)	30.0	48.0	43.5	1.2	13	NA
	BUD400 bid	257 (74.0)	64.0 (NA)	39.0	36.0 (10.0)	30.0	51.0	39.7	0.8	6	NA
	PL	256 (75.0)	65.0 (NA)	30.0	36.0 (10.0)	25.0	46.0	41.4	1.2	5	NA
Szafranski, 2003[W43]	FM9/BUD320 bid	208 (76.0)	64.0 (NA)	30.0	36.0 (NA)	17.0	26.0	28.0	NA	6	NA
	FM9 bid	201 (76.0)	63.0 (NA)	38.0	36.0 (NA)	16.0	28.0	32.0	NA	6	NA
	BUD400 bid	198 (80.0)	64.0 (NA)	36.0	37.0 (NA)	17.0	24.0	31.0	NA	5	NA
	PL	205 (83.0)	65.0 (NA)	34.0	36.0 (NA)	20.0	26.0	44.0	NA	9	NA
Mahler, 2002[W44]	SAL50/FLU500 bid	165 (62.0)	61.9 (NA)	46.0	41.0 (NA)	NA	NA	32.0	NA	0	0
	SAL50 bid	160 (64.0)	63.5 (NA)	46.0	40.0 (NA)	NA	NA	28.0	NA	0	0
	FLU500 bid	168 (61.0)	64.4 (NA)	46.0	41.0 (NA)	NA	NA	40.0	NA	0	0
	PL	181 (75.0)	64.0 (NA)	54.0	41.0 (NA)	NA	NA	38.0	NA	3	0

*The unit of dose is mcg. Budesonide was given as 800 mcg in the morning and 400 mcg in the evening for 6 months and 400 mcg bid for 30 months.

†Data from trials NCT00168844[W10] and NCT00168831[W11] were reported together in Bateman and colleagues' article.[W3] Individual information on overall death for each trial was retrieved from the U.S. FDA website. For the trial NCT00168844, number of subjects with overall death was 9 (TIO-SMI5), 8 (TIO-SMI10), and 7 (PL). For the trial NCT00168831, the figure was 7 (TIO-SMI5), 11 (TIO-SMI10), and 2 (PL). Pooled information on cardiovascular death for trials NCT00168844 and NCT00168831 were available in the U.S. FDA website.

‡Information on cardiovascular death was available in the the U.S. FDA website.

§Information on overall death was available in the the U.S. FDA website.

llInformation on overall death was from the material provided by the manufacturer.[W45]

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; SAL, salmeterol; FOR, formoterol; BUD, budesonide; FLU, fluticasone; BECLO, beclomethasone; PL, placebo; qd, once a day; bid, twice a day; prn, as-needed treatment; FEV1, forced expiratory volume in 1 second; CV, cardiovascular; NA, not available.

Table S3 Risk of bias in included trials

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Bateman, 2010[W2 W9]	Yes	Yes	Yes	AEs monitored at baseline, weeks 4, 24, and 48 and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, and ECG; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Bateman, 2010*[W3 W10]	Unclear	Unclear	Yes	AEs and fatal AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, ECG, and Holter monitoring; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Bateman, 2010*[W3 W11]	Unclear	Unclear	Yes	AEs and fatal AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, laboratory test, ECG, and Holter monitoring; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Tashkin, 2008[W1]	Yes	Yes	Yes	AEs, SAEs, and fatal events monitored throughout the treatment period and up to 30 days after the last dose of medication; PE and laboratory test; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes

Table S3 (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Tonnel, 2008[W12]	Yes	Yes	Yes	AEs monitored throughout the treatment period; vital signs and PE	Unclear	Yes	Yes	Yes
Ambrosino, 2008[W13]	Unclear	Unclear	Yes	AEs, vital signs, and PE	Unclear	Yes	Yes	Yes
Chan, 2007[W14]	Unclear	Unclear	Yes	AEs monitored throughout the treatment period; vital signs	Unclear	Yes	No	Yes
Powrie, 2007[W15]	Unclear	Unclear	Yes	AEs monitored throughout the treatment period and up to 30 days after the last dose of medication; vital signs, PE, and laboratory test	Unclear	Yes	No	Yes
Dusser, 2005[W16]	Unclear	Unclear	Yes	AEs monitored throughout the treatment period; PE	Unclear	Yes	No	Yes
Casaburi, 2005[W17]	Unclear	Unclear	Yes	AEs, vital signs, and PE	Unclear	No	No	Yes
Niewoehner, 2005[W18]	Yes	Yes	Yes	SAEs monitored within 30 days of the last dose of medication	Unclear	Yes	Yes	Yes
Casaburi, 2002[W19]	Unclear	Unclear	Yes	AEs collected at baseline, week 1, every 3 weeks throughout the first 13 weeks, and every 6 weeks for the next 36 weeks; PE, laboratory test, and ECG	Unclear	Yes	No	Yes

Table S3 (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Vogelmeier, 2011[W20]	Yes	Yes	Yes	SAEs monitored at baseline, months 2, 4, 8, and 12 and up to 30 days after the last dose of medication; vital signs and PE; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Brusasco, 2003[W21]	Unclear	Unclear	Yes	AEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Wedzicha, 2008[W22]	Yes	Yes	Yes	AEs monitored at weeks 2, 8, and every 12 weeks and up to 1 day after the last dose of medication; SAEs monitored up to 30 days after the last dose of medication; PE and ECG	Unclear	Yes	Yes	Yes
Stockley, 2006[W23]	Yes	Yes	Yes	AEs and SAEs monitored up to 1 day after the last dose of medication	Unclear	Yes	Yes	Yes
Campbell, 2005[W24]	Yes	Yes	Yes	AEs monitored at baseline, months 2, 4, and 6; vital signs, laboratory test, and ECG	Unclear	Yes	Yes	Yes
Chapman, 2002[W25]	Yes	Yes	Yes	AEs and SAE individually monitored up to 1 day and 30 days after the last dose of medication	Unclear	Yes	No	Yes
Shaker, 2009[W26]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Choudhury, 2007[W27]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
van der Valk, 2002[W28]	Yes	Yes	Yes	AEs monitored at 3 and 6 months	Unclear	Yes	Yes	Yes

Table S3 (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Burge, 2000[W29]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period; laboratory test	Unclear	Yes	Yes	Yes
Pauwels, 1999[W30]	Unclear	Unclear	Yes	AEs monitored every 3 months; laboratory test	Unclear	Yes	Yes	Yes
Vestbo, 1999[W31]	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes
Paggiaro, 1998[W32]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
FLTA3025[W33]	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Calverley, 2010[W34]	Yes	Yes	Yes	AEs monitored at baseline, weeks 4, 12, 24, 36, and 48; vital signs, laboratory test, ECG, and Hotering monitoring	Unclear	Yes	Yes	Yes
Anzueto, 2009[W35]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Ferguson, 2008[W36]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Kardos, 2007[W37]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	Yes	Yes
Wouters, 2005[W38]	Yes	Yes	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes

Table S3 (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
SCO40041[W39]	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Rennard, 2009[W4]	Yes	Yes	Yes	AEs monitored at baseline, months 1, 2, 4, 6, 9, and 12 and up to 30 days after the last study visit; vital signs, laboratory test, ECG, and Holter monitoring	Unclear	Yes	Yes	Yes
SFCT01/SCO30002[W40]	Unclear	Unclear	Yes	AEs and SAEs monitored throughout the treatment period	Unclear	Yes	No	Yes
Zheng, 2007[W41]	Unclear	Unclear	Yes	AEs monitored at baseline, weeks 2, 4, 8, 12, 16, 20, and 24 and up to a 2 weeks post-treatment; vital signs, PE, laboratory test, ECG, and Holter monitoring	Unclear	Yes	Yes	Yes
Tashkin, 2008[W5]	Yes	Yes	Yes	AEs monitored at baseline, months 1, 2, 4, and 6 and up to 30 days after the last study visit; vital signs, laboratory test, and ECG	Unclear	Yes	Yes	Yes
Calverley, 2007[W8]	Yes	Yes	Yes	AEs monitored every 12 weeks; PE and laboratory; vital status ascertained after patients prematurely withdrew	Yes	Yes	Yes	Yes
Hanania, 2003[W42]	Unclear	Unclear	Yes	AEs and SAEs monitored up to 1 day after the last dose of medication; vital sign, PE, laboratory test, ECG	Unclear	Yes	Yes	Yes

Table S3 (Continued)

Author, Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of personnel and participants?	Adverse event monitoring	Objective adjudication of cause of death?	Reporting of withdrawal rate?	Reporting of lost to follow-up?	Reporting of primary and secondary endpoints?
Calverley, 2003[W6]	Yes	Yes	Yes	AEs and SAEs monitored at baseline, weeks 2, 4, 8, 16, 24, 32, 40, and 52; PE and laboratory test	Unclear	Yes	Yes	Yes
Calverley, 2003[W7]	Unclear	Unclear	Yes	AEs monitored at month 1, 2, 3, and every 3 months	Unclear	Yes	Yes	Yes
Szafranski, 2003[W43]	Unclear	Unclear	Yes	AEs monitored at baseline, months 1, 2, 3, and every 3 months; laboratory and ECG	Unclear	Yes	No	Yes
Mahler, 2002[W44]	Unclear	Unclear	Yes	AEs and SAE monitored up to 1 day after the last dose of medication; vital signs, PE, laboratory test, ECG and Holter monitoring	Unclear	Yes	No	Yes

*Data from trials NCT00168844[W10] and NCT00168831[W11] were reported together in Bateman and colleagues' article.[W3] Individual information for each trial was retrieved from the U.S. FDA and ClinicalTirals.gov websites.

AE, adverse event; SAE, serious adverse event; PE, physical examination; Electrocardiography, ECG.

Table S4 Risk of overall death and cardiovascular death for each pairwise comparison from the direct comparison meta-analysis using the Mantel-Haenszel method with the fixed effect model and different continuity correction factors

Comparison	Overall death (N=42), fixed effect Mantel-Haenszel OR (95% CI)				Cardiovascular death (N=31), fixed effect Mantel-Haenszel OR (95% CI)			
	Continuity correction factor of 0.5	Continuity correction factor of 0.1	Continuity correction factor of 0.01	Without continuity correction	Continuity correction factor of 0.5	Continuity correction factor of 0.1	Continuity correction factor of 0.01	Without continuity correction
TIO-SMI vs								
PL	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	1.52 (1.05 to 2.18)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)	2.07 (1.06 to 4.01)
TIO-HH vs								
LABA	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	0.76 (0.55 to 1.06)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)	1.24 (0.49 to 3.15)
LABA-ICS*	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	1.84 (1.07 to 3.17)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)	2.12 (0.95 to 4.72)
PL	0.93 (0.81 to 1.07)	0.93 (0.81 to 1.07)	0.93 (0.81 to 1.07)	0.93 (0.80 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)	0.80 (0.61 to 1.06)
LABA vs								
LABA-ICS	1.10 (0.92 to 1.32)	1.10 (0.91 to 1.32)	1.10 (0.91 to 1.32)	1.12 (0.93 to 1.35)	0.84 (0.59 to 1.20)	0.84 (0.59 to 1.20)	0.84 (0.58 to 1.20)	0.79 (0.55 to 1.14)
ICS	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.86 (0.71 to 1.04)	0.74 (0.50 to 1.08)	0.73 (0.50 to 1.07)	0.73 (0.50 to 1.07)	0.73 (0.50 to 1.07)
PL	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.90 (0.75 to 1.08)	0.68 (0.48 to 0.96)	0.67 (0.48 to 0.95)	0.67 (0.47 to 0.95)	0.67 (0.47 to 0.95)
LABA-ICS vs								
ICS	0.78 (0.64 to 0.94)	0.78 (0.64 to 0.94)	0.78 (0.64 to 0.94)	0.77 (0.64 to 0.94)	0.97 (0.69 to 1.38)	0.97 (0.68 to 1.38)	0.97 (0.69 to 1.39)	0.99 (0.69 to 1.41)
PL	0.81 (0.67 to 0.98)	0.81 (0.66 to 0.98)	0.81 (0.66 to 0.98)	0.80 (0.66 to 0.98)	0.81 (0.58 to 1.14)	0.81 (0.58 to 1.14)	0.81 (0.58 to 1.14)	0.84 (0.60 to 1.19)
ICS vs								
PL	1.01 (0.86 to 1.19)	1.01 (0.86 to 1.20)	1.01 (0.86 to 1.20)	1.004 (0.85 to 1.19)	0.88 (0.65 to 1.19)	0.88 (0.65 to 1.20)	0.88 (0.64 to 1.20)	0.83 (0.61 to 1.14)

The denotation of 'N' represented number of trials reporting on each outcome.

*Only 1 trial with the direct comparison of tiotropium HandHaler® and LABA-ICS for the analysis.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; OR, odds ratio; CI, confidence interval.

Table S5 Meta-regression for risk of overall death and cardiovascular death from the MTC meta-analysis, adjusted for age, proportion of male, and percentage of current smokers

Comparison	Overall death (N=42), OR (95% CrI)			Cardiovascular death (N=31) , OR (95% CrI)		
	Adjusted for age	Adjusted for proportion of male	Adjusted for percentage of current smokers	Adjusted for age	Adjusted for proportion of male	Adjusted for percentage of current smokers
Fixed effect						
TIO-SMI vs						
TIO-HH	1.65 (1.13 to 2.45)	1.65 (1.13 to 2.44)	1.62 (1.11 to 2.41)	2.39 (1.21 to 4.97)	2.40 (1.19 to 5.03)	2.47 (1.23 to 5.16)
LABA	1.63 (1.11 to 2.44)	1.63 (1.11 to 2.43)	1.65 (1.12 to 2.47)	3.06 (1.50 to 6.51)	3.07 (1.50 to 6.55)	3.12 (1.53 to 6.67)
LABA-ICS	1.91 (1.29 to 2.86)	1.91 (1.29 to 2.88)	1.92 (1.29 to 2.89)	2.81 (1.39 to 6.00)	2.82 (1.38 to 6.02)	2.82 (1.38 to 6.00)
ICS	1.48 (0.995 to 2.20)	1.47 (0.997 to 2.20)	1.48 (0.998 to 2.20)	2.40 (1.19 to 5.10)	2.41 (1.19 to 5.17)	2.41 (1.18 to 5.11)
PL	1.52 (1.06 to 2.20)	1.52 (1.06 to 2.19)	1.52 (1.06 to 2.20)	2.08 (1.10 to 4.13)	2.09 (1.10 to 4.19)	2.08 (1.10 to 4.14)
Random effects						
TIO-SMI vs						
TIO-HH	1.67 (1.05 to 2.75)	1.66 (1.04 to 2.79)	1.63 (0.98 to 2.71)	2.14 (0.65 to 6.56)	2.16 (0.67 to 6.92)	2.23 (0.83 to 6.39)
LABA	1.59 (0.97 to 2.59)	1.60 (0.998 to 2.65)	1.60 (0.96 to 2.75)	2.93 (0.90 to 9.42)	2.76 (0.83 to 8.81)	3.55 (1.20 to 9.95)
LABA-ICS	1.93 (1.19 to 3.18)	1.93 (1.18 to 3.25)	1.92 (1.14 to 3.31)	3.15 (1.06 to 11.62)	3.04 (0.995 to 10.99)	3.67 (1.35 to 11.52)
ICS	1.50 (0.93 to 2.51)	1.52 (0.94 to 2.68)	1.49 (0.90 to 2.64)	2.46 (0.76 to 8.64)	2.25 (0.64 to 7.66)	2.88 (0.94 to 8.19)
PL	1.50 (0.995 to 2.37)	1.53 (1.002 to 2.44)	1.49 (0.96 to 2.41)	2.31 (0.91 to 6.95)	2.18 (0.85 to 6.78)	2.50 (1.06 to 6.54)

The denotation of 'N' represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval.

Table S6 Meta-regression for risk of overall death and cardiovascular death from the MTC meta-analysis, adjusted for study duration, FEV1, percentage of subjects with concomitant use of LABA or ICS

Comparison	Overall death (N=42), OR (95% CrI)				Cardiovascular death (N=31) , OR (95% CrI)			
	Adjusted for study duration	Adjusted for FEV1	Adjusted for percentage of subjects with concomitant use of LABA	Adjusted for percentage of subjects with concomitant use of ICS	Adjusted for study duration	Adjusted for FEV1	Adjusted for percentage of subjects with concomitant use of LABA	Adjusted for percentage of subjects with concomitant use of ICS
Fixed effect								
TIO-SMI vs								
TIO-HH	1.65 (1.13 to 2.44)	1.65 (1.13 to 2.45)	1.61 (1.10 to 2.38)	1.62 (1.10 to 2.40)	2.39 (1.20 to 5.04)	2.39 (1.21 to 5.04)	2.49 (1.23 to 5.23)	2.38 (1.20 to 5.02)
LABA	1.63 (1.10 to 2.43)	1.63 (1.10 to 2.44)	1.62 (1.09 to 2.43)	1.61 (1.08 to 2.42)	3.05 (1.50 to 6.54)	3.12 (1.53 to 6.73)	3.20 (1.54 to 6.87)	3.16 (1.55 to 6.81)
LABA-ICS	1.91 (1.29 to 2.87)	1.91 (1.28 to 2.88)	1.88 (1.26 to 2.83)	1.89 (1.26 to 2.83)	2.81 (1.38 to 6.05)	2.81 (1.39 to 6.06)	2.86 (1.40 to 6.15)	2.84 (1.40 to 6.07)
ICS	1.47 (0.99 to 2.20)	1.47 (0.99 to 2.21)	1.41 (0.95 to 2.14)	1.42 (0.95 to 2.14)	2.40 (1.18 to 5.12)	2.40 (1.19 to 5.15)	2.51 (1.21 to 5.39)	2.48 (1.22 to 5.36)
PL	1.52 (1.06 to 2.19)	1.52 (1.06 to 2.20)	1.51 (1.06 to 2.19)	1.51 (1.06 to 2.19)	2.07 (1.09 to 4.19)	2.08 (1.10 to 4.20)	2.08 (1.09 to 4.18)	2.07 (1.09 to 4.15)
Random effects								
TIO-SMI vs								
TIO-HH	1.70 (1.001 to 2.90)	1.66 (1.03 to 2.76)	1.57 (0.85 to 2.91)	1.59 (0.87 to 2.90)	1.98 (0.61 to 6.70)	2.17 (0.60 to 7.02)	2.52 (0.83 to 8.68)	2.23 (0.61 to 7.66)
LABA	1.65 (0.96 to 2.78)	1.62 (0.999 to 2.68)	1.59 (0.82 to 3.10)	1.53 (0.80 to 2.85)	2.61 (0.79 to 8.45)	2.03 (0.57 to 8.17)	4.06 (1.16 to 13.93)	3.34 (0.83 to 11.90)
LABA-ICS	1.98 (1.14 to 3.51)	1.96 (1.20 to 3.29)	1.90 (0.93 to 3.82)	1.79 (0.89 to 3.52)	2.72 (0.83 to 10.95)	1.70 (0.51 to 5.90)	4.67 (1.34 to 18.82)	3.80 (0.95 to 15.62)
ICS	1.59 (0.93 to 2.83)	1.55 (0.97 to 2.70)	1.48 (0.74 to 3.13)	1.41 (0.71 to 2.92)	2.07 (0.61 to 7.35)	1.71 (0.46 to 6.37)	3.68 (0.94 to 14.39)	2.94 (0.61 to 11.59)
PL	1.57 (1.02 to 2.49)	1.54 (1.01 to 2.43)	1.57 (0.95 to 2.81)	1.55 (0.94 to 2.69)	2.17 (0.86 to 6.37)	2.16 (0.86 to 6.44)	2.53 (1.002 to 7.82)	2.34 (0.83 to 7.68)

The denotation of 'N' represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval; FEV1, forced expiratory volume in 1 second.

Table S7 Sensitivity analysis for risk of overall death and cardiovascular death from the MTC meta-analysis, excluded trials with the ICS withdrawal design[W27, W28, W38]

Comparison	Overall death (N=39)		Cardiovascular death (N=28)	
	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)	Fixed effect OR (95% CrI)	Random effects OR (95% CrI)
TIO-SMI vs				
TIO-HH	1.65 (1.13 to 2.44)	1.68 (1.06 to 2.79)	2.39 (1.20 to 5.05)	2.22 (0.74 to 6.39)
LABA	1.65 (1.12 to 2.47)	1.65 (1.03 to 2.76)	3.11 (1.53 to 6.73)	2.97 (0.98 to 8.61)
LABA-ICS	1.92 (1.29 to 2.88)	1.97 (1.20 to 3.29)	2.77 (1.37 to 5.91)	2.97 (1.05 to 9.63)
ICS	1.51 (1.02 to 2.26)	1.63 (1.02 to 2.88)	2.42 (1.20 to 5.20)	2.41 (0.81 to 7.30)
PL	1.52 (1.06 to 2.19)	1.55 (1.03 to 2.44)	2.07 (1.10 to 4.21)	2.19 (0.92to 6.02)
TIO-HH vs				
LABA	0.998 (0.83 to 1.20)	0.98 (0.74 to 1.29)	1.30 (0.90 to 1.91)	1.33 (0.71 to 2.52)
LABA-ICS	1.16 (0.95 to 1.41)	1.17 (0.87 to 1.58)	1.16 (0.81 to 1.67)	1.34 (0.75 to 2.88)
ICS	0.91 (0.75 to 1.11)	0.96 (0.73 to 1.43)	1.02 (0.69 to 1.49)	1.08 (0.54 to 2.32)
PL	0.92 (0.81 to 1.04)	0.92 (0.74 to 1.17)	0.87 (0.67 to 1.12)	0.98 (0.64 to 1.84)
LABA vs				
LABA-ICS	1.16 (0.98 to 1.39)	1.19 (0.93 to 1.55)	0.89 (0.63 to 1.26)	1.001 (0.59 to 2.02)
ICS	0.91 (0.77 to 1.09)	0.98 (0.77 to 1.41)	0.78 (0.55 to 1.10)	0.81 (0.44 to 1.62)
PL	0.92 (0.78 to 1.08)	0.94 (0.74 to 1.21)	0.67 (0.49 to 0.91)	0.74 (0.46 to 1.42)
LABA-ICS vs				
ICS	0.79 (0.65 to 0.94)	0.83 (0.64 to 1.18)	0.87 (0.62 to 1.23)	0.81 (0.39 to 1.48)
PL	0.79 (0.67 to 0.94)	0.79 (0.61 to 1.02)	0.75 (0.55 to 1.02)	0.74 (0.41 to 1.32)
ICS vs				
PL	1.01 (0.86 to 1.18)	0.96 (0.70 to 1.19)	0.86 (0.63 to 1.16)	0.91 (0.54 to 1.75)

The denotation of 'N' represented number of trials reporting on each outcome.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS,

inhaled corticosteroids; PL, placebo; MTC, mixed treatment comparison; OR, odds ratio; CrI, credible interval.

Table S8 Sensitivity analysis for risk of cardiovascular death from the Bucher's indirect comparison analysis, based on data of five placebo controlled trials with objective adjudication of cause of death* [W1-W3, W8]

Comparison	Cardiovascular death (N=5), OR (95% CI)
TIO-SMI vs	
TIO-HH	2.60 (1.32 to 5.13)
LABA	3.12 (1.53 to 6.35)
LABA-ICS	2.34 (1.16 to 4.72)
ICS	2.31 (1.15 to 4.65)

* Six trials (with 25 533 subjects) were designed to adjudicate causes of death by an expert committee,[W1-W3, W8, W20] five of which (with 17 341 subjects) were placebo controlled trials.[W1-W3, W8] Given that number of this type of trials was not enough for the MTC meta-analysis, we used the Bucher's approach[25] to indirectly compare the risk of cardiovascular death for each inhaled medication relative to each active control using placebo as a common comparator.

The denotation of 'N' represented number of trials reporting on cardiovascular death.

TIO-SMI, tiotropium solution delivered via Resipmat® Soft Mist™ Inhaler; TIO-HH, tiotropium dry powder delivered via HandiHaler®; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; OR, odds ratio; CI, confidence interval.

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Figure S1 Funnel plot comparing logOR and s.e. of logOR for the test comparisons* and outcomes

*****Publication bias was only assessed for pairwise comparisons including more than 10 trials.[22]

A. LABA vs PL (Overall death). B. LABA vs LABA-ICS (Overall death). C. ICS vs PL (Overall death). D. ICS vs PL (Cardiovascular death). LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; PL, placebo; OR, odds ratio; s.e., standard error.