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Mortality and drug therapy in patients with chronic obstructive pulmonary disease: a network meta-analysis

David A Scott1*, Bethan Woods1,2, Juliette C Thompson1, James F Clark1, Neil Hawkins1, Mike Chambers3, Bartolome R. Celli4 and Peter Calverley5

Abstract

Background: Increasing evidence suggests pharmacological treatments may impact on overall survival in Chronic Obstructive Pulmonary Disease (COPD) patients. Individual clinical trials are rarely powered to detect mortality differences between treatments and may not include all treatment options relevant to healthcare decision makers.

Methods: A systematic review was conducted to identify RCTs of COPD treatments reporting mortality; evidence was synthesised using network meta-analysis (NMA). The analysis included 40 RCTs; a quantitative indirect comparison between 14 treatments using data from 55,220 patients was conducted.

Results: The analysis reported two treatments reducing all-cause mortality; salmeterol/fluticasone propionate combination (SFC) was associated with a reduction in mortality versus placebo in the fixed effects (HR 0.79; 95 % Crl 0.67, 0.94) but not the random effects model (0.79; 0.56, 1.09). Indacaterol was associated with a reduction in mortality versus placebo in fixed (0.28; 0.08 to 0.85) and random effects (0.29; 0.08, 0.89) models. Mean estimates and credible intervals for hazard ratios for indacaterol versus placebo are based on a small number of events; estimates may change when the results of future studies are included. These results were maintained across a variety of assumptions and provide evidence that SFC and indacaterol may lead to improved survival in COPD patients.

Conclusion: Results of an NMA of COPD treatments suggest that SFC and indacaterol may reduce mortality. Further research is warranted to strengthen this conclusion.

Keywords: COPD, COPD treatment, Systematic review, Meta-analysis, Mortality

Background

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity across the world, and the third leading cause of death globally [1, 2]. Primary prevention by a combination of reducing tobacco exposure, decreasing contact with biomass fuels and noxious gases together with improved child health are the most effective ways of decreasing this burden in the longer term, although it takes time for the benefits of interventions on mortality to become apparent [3, 4]. In patients with symptomatic COPD the impact of specific medications on decreasing the risk of dying is an important consideration and merits scientific consideration. The evidence on mortality reduction from individual clinical trials in COPD is inconclusive with relatively few studies of duration and sample size sufficient to demonstrate an impact [5].

Network meta-analysis (NMA) provides a statistical approach to combining direct and indirect trial evidence to generate relative treatment effects between different drugs on outcomes of interest. In the absence of head-to-head trials including all comparators, NMA has been recommended by reimbursement agencies in the UK and Germany [6, 7] and endorsed by influential bodies such as ISPOR [8]. NMA has been applied to COPD mortality data on two previous occasions [9, 10].
We conducted a systematic review and network meta-analysis (NMA) designed to assess whether pharmacotherapy affects mortality reported in COPD clinical trials. NMA was then used to allow all treatment options to be compared in a single analysis [11–13]. The analysis combines survival data reported in two different forms: total number of deaths (r) from (n) subjects subsequently referred to as the ‘binary endpoint’, and hazard ratios which describe the impact of treatment on time to death and account for censoring. Although hazard ratios are more informative they are not reported in all studies and the inclusion of binary data enables the maximum number of trials to be included. Sensitivity analyses permitted us to analyse the robustness of the results to various assumptions supporting the base case analysis.

Primarily, our objective was to estimate the impact of specific COPD treatments on patient mortality using NMA. Secondly, we explored the strengths and limitations of undertaking and interpreting NMA in this context.

Methods

Systematic review

A systematic review was conducted to identify randomised, blinded trials of COPD patients treated with tiotropium, beclomethasone, budesonide, fluticasone propionate, triamcinolone, bambuterol, formoterol, salmeterol, salbutamol, indacaterol, theophylline, roflumilast, indacaterol maleate, ipratropium bromide, vilanterol trifenate, fluticasone furoate or placebo. Dosing and administration method were not specified in the inclusion criteria. Combinations of the listed interventions were allowed; dose comparison studies were not included unless another listed intervention was also incorporated in the study. Studies were required to report all-cause mortality in binary or hazard ratio form for at least 24 weeks of follow-up; mortality could be reported as a study outcome or as a serious adverse event. Only English language full publications were included.

EMBASE (1988), MEDLINE, MEDLINE In-Progress (1946) and CENTRAL (1988) were searched from database inception to October 2012. Searches combined controlled vocabulary and free-text terms for COPD and the treatments of interest; RCT filters were used in EMBASE and MEDLINE. Full publications were reviewed for inclusion by two analysts (JT and JC). Data was extracted from eligible trials by one analyst with validation conducted by the second analyst. Dosages of the same therapy were combined for the purposes of the analysis (indacaterol (150 µg od, 300 µg od, 600 µg od), budesonide (200 µg bid, 400 µg bid, 1200 µg od for 6 months followed by 800 µg od for 30 months), fluticasone propionate (250 µg bid, 500 µg bid), salmeterol (50 µg bid, 100 µg bid), formoterol (6 µg bid, 12 µg bid, 24 µg bid) and salmeterol fluticasone propionate combination (SFC) (50/250 µg bid, 50/500 µg bid)). The Cochrane risk of bias tool was used to assess methods of randomisation, allocation concealment, blinding, patient follow-up and incomplete reporting [14].

Statistical analysis

Binary mortality data: total number of deaths (r) from (n) subjects, and hazard ratios with reported confidence intervals from published studies meeting our inclusion criteria were used as inputs to the analysis. We preferred hazard ratios over binary data where reported. Hazard ratios were taken from the Cox proportional-hazards models as these were consistently reported, in particular the Cox model for TORCH was preferred over that calculated directly from the Kaplan Meier in accordance with the other studies which reported HRs. Hazard ratio data and binary data were combined using the methodology established in Woods [15] which also appropriately incorporates multi-arm trials. Estimated treatment effects were synthesised using network meta-analysis (NMA) in a Bayesian multilevel framework. This method allows simultaneous comparison of outcomes of multiple treatments from trials comparing different sets of treatment options (providing a connected network of treatments can be formed) whilst retaining within-trial randomisation. A study protocol was written and reviewed prior to initiating the systematic review and analysis. Full details of the statistical method and the model code are provided in the Additional file 1.

The base case analysis included all RCTs meeting our inclusion criteria using the intention to treat (ITT) results from these studies, combining different licensed doses of the same medicines as single comparators. Results are presented for active treatments relative to placebo (reference).

Sensitivity analyses

The following pre-planned analyses were conducted to examine the sensitivity of the study results to various assumptions:

(A) Including on-treatment (OT) mortality (excluding deaths that occurred to patients who ceased to receive the allocated study treatment) results in preference to ITT results where available.

(B) Meta-regression controlling for differences in COPD severity assuming a common covariable effect across treatments (assessed by baseline FEV1 % predicted – mean value per study)

(C) Excluding studies where patients had high lung function at baseline (mean FEV1 % predicted >65 %)

(D) Excluding studies where patients received unlicensed doses
(E) Excluding studies of less than 48 weeks duration
(F) Excluding studies not powered to detect a difference in mortality
(G) Excluding studies that failed to meet our specified quality assessment criteria (i.e. 2 or more components of the assessment had a high or unclear risk of bias) as assessed by the Cochrane Collaboration risk of bias [14]
(H) Including studies from the Dong [10] NMA for which mortality data were unavailable in the primary publication. Dong [10] cited a variety of sources for these data, including contacting the study authors and searching website and clinical trial registers; these were not included in the present base case analysis
(I) Separating patients treated with tiotropium by type of inhaler used (SoftMist or HandiHaler). Safety concerns (increased mortality risk) had at the time of the present analysis been raised around the SoftMist inhaler [16]. We also incorporated the results of TIOSPIR [17], a RCT of over 17,000 subjects designed to evaluate efficacy and safety of the two different inhalers, in this sensitivity analysis. TIOSPIR was not published until the final writing up of the present study.

Statistical models were fitted using WinBUGS [18]. As the present study is a Bayesian analysis we refer to credible intervals (the probability that the true value is contained within the interval) rather than confidence intervals; instead of statistically significant differences, we refer to important differences (95 % credible interval does not cross 1.0).

Both fixed and random effect models were fitted. Fixed effect assumes there is one true effect of each treatment and that variation around this is attributed to chance whilst random effects assume a distribution of effects and that variance between studies is attributed to heterogeneity. Larger studies are thus attached relatively less weight in random effects model [19]. The Deviance Information Criteria (DIC) was calculated for each model and used to assess whether any model should be preferred [20]. Each model was run for a burn-in period of 40,000 simulations, which were then discarded, with parameter nodes monitored for a further 200,000 simulations. Caterpillar and Brooks - Gelman - Rubin (BGR) plots were used to compare results obtained using different initial values, thus ensuring that the models had converged [21].

Results and discussion

Systematic review

The systematic review identified 42 studies reporting all-cause mortality in COPD patients (Fig. 1; reasons for excluding full publications: Additional file 2: Table S1). Demographic characteristics of subjects (age, gender) are reported in Table 1; the impact of differences in baseline FEV1 % predicted is assessed in sensitivity analyses B and C. The proportion of current smokers was similar across trials, but three trials (all with patients with less impairment of lung function) reported levels in excess of 75 % [22–24].

Assessment of study quality using the Cochrane risk of bias tool found that the quality of study reporting was generally high (Additional file 2: Table S2). Although all trials were randomised, 17 did not adequately describe the method of randomisation; [22, 24–39] and two studies did not adequately describe methods for allocation concealment [37, 39]. With the exception of FICOPD II where the theophylline arm (not included in analysis) was open-label [36], all studies were double-blind. Reporting of loss to follow-up was unclear in 17 studies; [22, 23, 27, 29, 30, 32, 34, 37, 40–47] imbalanced drop-outs between the treatment groups in two studies was considered to result in a high risk of bias for the reported outcome data [39, 48]. In nine studies two or more components of the assessment were found to be potentially associated with an unclear or high risk of bias [22, 24, 27, 29, 30, 32, 34, 37, 39]. This was thought to reflect incomplete reporting rather than underlying methodological weakness in many cases.

Studies included in the analysis

Two studies were excluded from the statistical analysis. Campbell [49], was excluded since the treatment arms in this trial (formoterol + formoterol as needed, formoterol + terbutaline as needed, placebo + terbutaline as needed) were not included in any of the other trials analysed, and therefore did not link to the evidence network. Similarly, Kerstjens [41], comparing terbutaline with ipratropium bromide + terbutaline and beclomethasone + terbutaline, did not connect to the main evidence network. Two treatments were excluded from the statistical analysis. Theophylline was included in a single trial, FICOPD II (Rossi [36]), which reported no deaths, and so it was not possible for a hazard ratio to be estimated for this treatment. Similarly, the only trial including tiotropium + formoterol combination (Vogelmeier [38]) did not report any deaths for this arm, which was therefore also excluded from the analysis. The other treatment arms of these studies were included in the analysis.

The statistical analysis was based on 40 RCTs including 55,220 randomised subjects and 88,261 person years of experience, allowing the comparison of 14 treatments. Figure 2 shows the base case evidence network weighted by the number of person-years of follow up for each within-trial comparison. Reported binary mortality outcomes are presented in Table 1 and hazard ratios in
Table 2. In the base case analysis hazard ratios for all-cause mortality were available for three studies and binary data were available for the remaining 37 studies.

**Base case results**

Results from the fixed and random effects base case analysis are presented in Fig. 3. Hazard ratios for each treatment are compared to placebo; a hazard ratio below 1.0 indicates that the treatment is associated with reduced mortality compared to placebo. There was no evidence to suggest that the random effects model was a better fit than the fixed effects model; a difference in DIC of 2–3 is required to be indicative of improved model fit [20]. However, if we believe there is true heterogeneity between the trials, the random effects model would be more appropriate.

Two interventions produced a hazard ratio relative to placebo that did not cross 1.0 using the fixed effects model. SFC was associated with a reduction in mortality of 21% (HR 0.79; 95% CrI 0.67, 0.94) and indacaterol with a mortality reduction of 72% (HR 0.28; 95% CrI 0.08, 0.85). Using a random effects model SFC failed to show evidence of effect (HR 0.79; 95% CrI 0.56, 1.09). For indacaterol the result using the random effects model (HR 0.29; 95% CrI 0.08, 0.89) was comparable to that using the fixed effects model. No evidence of effect on all-cause mortality (versus placebo) was found for other treatments. Although the results for most comparators have wide credible intervals suggesting inconclusive results, the HRs for tiotropium + salmeterol, tiotropium + SFC and beclomethasone + formoterol have particularly wide credible intervals; in each case the results are generated by single, relatively small study arms therefore the uncertainty around the estimates is high.

**Sensitivity analyses**

Results of the sensitivity analyses did not in general differ markedly from the base case (Additional file 2: Table S3). For SFC vs placebo the relative treatment effect improved in the fixed effects analysis when unlicensed doses were excluded, but results from the random effects model showed no evidence of effect and were similar to the base case. Similarly, the relative treatment effect for indacaterol vs placebo strengthened slightly (HR 0.17, 95% CrI 0.03, 0.78) when studies with a shorter duration were excluded.

**Conclusion**

In this NMA, data from 40 trials were used to inform comparisons of mortality associated with 14 different pharmacological treatments for COPD. The method allows comparisons of treatments not compared directly
### Table 1 Baseline characteristics of included studies and all-cause mortality (binary data)

| References | Trial | Treatment                  | Dose                                | Study duration (weeks) | n | Mean age (yr.) | Women (%) | Current smokers (%) | FEV1 (mean % predicted) | All-cause mortality (binary) | Subjects | Deaths - ITT | Deaths – OT |
|------------|-------|----------------------------|-------------------------------------|------------------------|---|----------------|-----------|---------------------|--------------------------|--------------------------------|----------|--------------|-------------|
| [53]       | Aaron 2007 | Tiotropium + Salmeterol  | 18 µg od/50 µg bid                 | 52                     |   | 148            | 67.6      | 42.6                | 24.3                     | 41.2                          | 148      | 6            | NR          |
|            |        | Tiotropium + SFC          | 18 µg od/50/500 µg bid              |                        |   | 145            | 67.5      | 42.1                | 32.4                     | 42.2                          | 145      | 6            | NR          |
| [40]       | Anzueto 2009 | SFC                      | 50/250 µg bid                      | 52                     |   | 394            | 65.4      | 49.0                | 42.0                     | 41.2                          | 394      | 4            | NR          |
| [40]       | Anzueto 2009 | Salmeterol               | 50 µg bid                           |                        |   | 403            | 65.3      | 43.0                | 43.0                     | 40.0                          | 403      | 6            | NR          |
| [54]       | Bateman 2010 | Tiotropium                | 5 µg od                             | 48                     |   | 1952           | 64.8      | 21.9                | 35.7                     | 45.2                          | 1952     | 52           | NR          |
| [54]       | Bateman 2010 | Placebo                  | -                                   |                        |   | 1965           | 64.8      | 23.0                | 35.9                     | 45.4                          | 1965     | 38           | NR          |
| [55]       | ISOLDE (Burge 2000) | Fluticasone Propionate    | 500 µg bid                          | 156                    |   | 376            | 63.7      | 25.0                | 36.4                     | 50.3                          | 372      | 32           | NR          |
| [55]       | ISOLDE (Burge 2000) | Budesonide               | 400 µg bid                          |                        |   | 257            | 64.0      | 26.0                | 39.0                     | 36.0                          | 257      | 6            | NR          |
| [55]       | ISOLDE (Burge 2000) | Formoterol               | 9 µg bid                            |                        |   | 255            | 63.0      | 25.0                | 36.0                     | 36.0                          | 255      | 13           | NR          |
| [56]       | Calverley 2003 | Tiotropium               | 320/9 µg bid                        | 52                     |   | 254            | 64.0      | 22.0                | 33.0                     | 36.0                          | 254      | 5            | NR          |
| [56]       | Calverley 2003 | Budesonide               | 400 µg bid                          |                        |   | 257            | 64.0      | 26.0                | 39.0                     | 36.0                          | 257      | 6            | NR          |
| [56]       | Calverley 2003 | Formoterol               | 9 µg bid                            |                        |   | 255            | 63.0      | 25.0                | 36.0                     | 36.0                          | 255      | 13           | NR          |
| [56]       | Calverley 2003 | Placebo                  | -                                   |                        |   | 256            | 65.0      | 25.0                | 30.0                     | 36.0                          | 256      | 5            | NR          |
| [57]       | Calverley 2007 | Roflumilast              | 500 µg od                           | 52                     |   | 760            | 65.0      | 25.0                | 38.0                     | 41.0                          | 760      | 12           | NR          |
| [58]       | M2-124 (Calverley 2009) | Roflumilast             | 500 µg od                           | 52                     |   | 765            | 64.0      | 29.0                | 48.0                     | 37.6                          | 765      | 17           | NR          |
| [58]       | M2-125 (Calverley 2009) | Placebo                  | -                                   |                        |   | 758            | 63.0      | 29.0                | 48.0                     | 37.5                          | 758      | 17           | NR          |
| [59]       | Calverley 2010 | Beclomethasone + Formoterol | 200/12µg bid                       | 48                     |   | 232            | 63.0      | 20.7                | 38.8                     | 41.9                          | 232      | 2            | NR          |
| [49]       | Campbell 2005 | Formoterol + Formoterol  | 9 µg bid / 4.5 µg as needed         | 26                     |   | 225            | 60.0      | 29.0                | 56.0                     | 54.4                          | 225      | 1            | NR          |
| [49]       | Campbell 2005 | Formoterol + Formoterol  | 9 µg bid / 0.5 mg as needed         |                        |   | 215            | 60.0      | 39.0                | 54.0                     | 53.0                          | 215      | 2            | NR          |
| Study Reference | Treatment | Dose | Baseline | Follow-up | Intervention | Mortality | Placebo | Mortality |
|-----------------|-----------|------|----------|-----------|--------------|-----------|---------|-----------|
| [26] Casaburi 2005 | Tiotropium | 18 μg od | 25 | 55 | 65.9 | 45.5 | 29.1 | 32.6 | 55 | 1 | NR |
| | Placebo | - | 53 | 67.3 | 41.5 | 18.9 | 36.2 | 53 | 0 | NR |
| [27] Chan 2007 | Tiotropium | 18 μg od | 48 | 608 | 66.8 | 41.0 | 32.0 | 39.4 | 608 | 15 | 13 |
| | Placebo | - | 305 | 66.9 | 39.0 | 30.0 | 39.3 | 305 | 4 | 2 |
| [28] Choudhury 2007 | Fluticasone Propionate | 500 μg bid | 52 | 128 | 67.6 | 52.0 | 40.6 | 53.2 | 128 | 3 | NR |
| | Placebo | - | 132 | 67.3 | 44.0 | 35.6 | 55.0 | 132 | 0 | NR |
| [29] INVOLVE (Dahl 2010) | Indacaterol (300) | 300μg od | 52 | 437 | 64.0 | 19.7 | NR | 51.5 | 437 | 1 | 1 |
| | Indacaterol (600) | 600μg od | 425 | 63.0 | 23.1 | NR | 50.8 | 428 | 1 | 0 |
| | Formoterol | 12μg (bid) | 434 | 64.0 | 19.8 | NR | 52.5 | 435 | 5 | 3 |
| | Placebo | - | 432 | 63.0 | 18.5 | NR | 52.0 | 432 | 5 | 4 |
| [29] Donohue 2002 | Salmeterol | 50 μg od | 26 | 213 | 64.6 | 25.0 | NR | 40.2 | 213 | 3 | NR |
| | Tiotropium | 18 μg od | 209 | 64.5 | 26.0 | NR | 40.2 | 209 | 0 | NR |
| | Placebo | - | 201 | 65.6 | 25.0 | NR | 40.2 | 201 | 4 | NR |
| [30] INHANCE (Donohue 2010) | Indacaterol (150) | 150 μg od | 26 | 416 | 63.4 | 37.7 | NR | 56.1 | 416 | 1 | 1 |
| | Indacaterol (300) | 300 μg od | 416 | 63.3 | 36.8 | NR | 56.3 | 416 | 0 | NR |
| | Tiotropium | 18 μg od | 415 | 64.0 | 35.2 | NR | 53.9 | 415 | 2 | NR |
| | Placebo | - | 418 | 63.6 | 39.0 | NR | 56.1 | 418 | 0 | NR |
| [31] Ferguson 2008 | SFC | 250/50 μg bid | 52 | 394 | 64.9 | 42.0 | 40.0 | 39.8 | 394 | 6 | NR |
| | Salmeterol | 50 μg bid | 388 | 65.0 | 48.0 | 38.0 | 40.6 | 388 | 3 | NR |
| [32] Hanania 2003 | Fluticasone Propionate | 250 μg bid | 24 | 183 | 63.0 | 34.0 | 48.0 | 42.0 | 183 | 0 | NR |
| | Salmeterol | 50 μg bid | 177 | 64.0 | 42.0 | 51.0 | 42.0 | 177 | 0 | NR |
| | SFC | 250 / 50 μg bid | 178 | 63.0 | 39.0 | 43.0 | 41.0 | 178 | 0 | NR |
| | Placebo | - | 185 | 65.0 | 32.0 | 47.0 | 42.0 | 185 | 0 | NR |
| [33] VIVACE (Kardos 2007) | Salmeterol | 50 μg bid | 44 | 487 | 64.0 | 22.4 | 44.4 | 40.3 | 487 | 9 | NR |
| | SFC | 50/500 μg bid | 507 | 63.8 | 26.0 | 40.6 | 40.4 | 507 | 7 | NR |
| [41] Kerstjens 1992 | Ipratropium Bromide + Terbutaline | 800/2000 μg bid | 130 | 92 | 38.9 | 36.0 | 34.0 | 63.3 | 92 | 0 | NR |
| | Beclomethasone + Terbutaline | 160/2000 μg bid | 91 | 40.2 | 35.0 | 36.0 | 64.6 | 91 | 0 | NR |
| | Placebo + Terbutaline | na/2000 μg bid | 91 | 39.6 | 36.0 | 37.0 | 63.3 | 91 | 0 | NR |
| [42] INLIGHT-2 (Kornmann 2011) | Indacaterol | 150 μg od | 26 | 330 | 63.0 | 28.0 | 46.0 | 54.0 | 330 | 1 | NR |
| | Salmeterol | 50 μg bid | 333 | 63.0 | 25.0 | 46.0 | 53.0 | 333 | 0 | NR |
| | Placebo | - | 335 | 64.0 | 23.0 | 45.0 | 53.0 | 335 | 3 | NR |
| Study          | Intervention                      | Baseline Characteristics | All-Cause Mortality (Binary Data) | Continued |
|---------------|-----------------------------------|--------------------------|-----------------------------------|-----------|
| [34] Mahler 2002 | Fluticasone Propionate 500 μg bid | 24                       | 168                               | 0         | NR |
|               | Salmeterol 50 μg bid              | 160                      | 63.5                               | 39.0      | 46.0 | 41.0b | 168 | 0 | NR |
|               | SFC 50 / 500 μg bid               | 165                      | 61.9                               | 38.0      | 46.0 | 41.0b | 165 | 0 | NR |
|               | Placebo                           | -                        | 181                               | 64.0      | 25.0 | 54.0 | 41.0b | 181 | 3 | NR |
| [61] Niewoehner 2005 | Tiotropium -                     | 26                       | 914                               | 67.6      | 2.0  | 29.0 | 35.6b | 914 | 22 | NR |
|               | Placebo                           | 18 μg od                 | 915                               | 68.1      | 1.0  | 30.0 | 35.6b | 915 | 19 | NR |
| [22] EUROSCOP (Pauwels 1999) | Budesonide 400 μg bid           | 156                      | 634                               | 52.5      | 26.5 | 100.0 | 76.8a | 634 | 8 | NR |
|               | Placebo                           | -                        | 643                               | 52.4      | 27.8 | 100.0 | 76.9a | 643 | 10 | NR |
| [35] Rennard 2009 | Budesonide + Formoterol 320/9 μg bid | 52                       | 494                               | 63.2      | 37.7 | 39.1 | 38.6 | 494 | 8 | 3 |
|               | Budesonide + Formoterol 160/9 μg bid | 494                      | 63.6                               | 37.2      | 41.9 | 39.6 | 494 | 8 | 6 |
|               | Formoterol 9 μg bid                | 495                      | 62.9                               | 34.7      | 45.1 | 39.3 | 495 | 6 | 2 |
|               | Placebo                           | -                        | 481                               | 62.9      | 34.7 | 43.9 | 481 | 8 | 4 |
| [36] FICOPD II (Rossi 2002) | Formoterol 12 12 μg bid         | 52                       | 211                               | 63.0      | 13.0 | NR   | 47.0b | 211 | 3 | NR |
|               | Formoterol 24 24 μg bid           | 214                      | 62.0                               | 17.0      | NR   | 47.0b | 214 | 1 | NR |
|               | Theophylline 200/300 mg bid       | 209                      | 64.0                               | 18.0      | NR   | 46.0b | 209 | 0 | NR |
|               | Placebo                           | -                        | 220                               | 63.0      | 21.0 | NR   | 49.0b | 220 | 0 | NR |
| [62] Schermer 2009 | Fluticasone Propionate 500 μg bid | 156                      | 94                                | 58.4      | 27.0 | 62.0 | 68.7b | 94 | 8 | NR |
|               | Placebo                           | -                        | 96                                | 59.6      | 32.0 | 51.0 | 71.4b | 96 | 3 | NR |
| [23] Shaker 2009 | Budesonide 400 μg bid             | 208                      | 127                               | 63.6      | 38.0 | 100.0 | 51.0b | 127 | 5 | NR |
|               | Placebo                           | -                        | 127                               | 63.6      | 46.0 | 100.0 | 53.0b | 127 | 5 | NR |
| [43] Stockley 2006 | Salmeterol 50 μg bid            | 52                       | 318                               | 62.3      | 24.0 | 46.0 | 45.8b | 216 | 6 | NR |
|               | Placebo                           | -                        | 316                               | 62.4      | 23.0 | 47.0 | 46.1b | 222 | 5 | NR |
| [37] Szafranski 2003 | Budesonide + Formoterol 320/9 μg bid | 52                       | 208                               | 64.0      | 24.0 | 30.0 | 36.0b | 208 | 6 | NR |
|               | Budesonide 400 μg bid             | 198                      | 64.0                               | 20.0      | 36.0 | 37.0b | 198 | 5 | NR |
|               | Formoterol 9 μg bid               | 201                      | 63.0                               | 24.0      | 38.0 | 36.0b | 201 | 6 | NR |
|               | Placebo                           | -                        | 205                               | 65.0      | 17.0 | 34.0 | 36.0b | 205 | 9 | NR |
| [63] Tashkin 2008 | Budesonide + Formoterol 320/9 μg bid | 26                       | 277                               | 63.1      | 32.1 | 44.4 | 39.1 | 277 | 3 | NR |
|               | Budesonide + Formoterol 160/9 μg bid | 281                      | 63.6                               | 35.6      | 44.8 | 39.9 | 281 | 4 | NR |
|               | Budesonide + Formoterol 320 + 9 μg bid (separate) | 287                      | 63.7                               | 25.8      | 41.5 | 39.2 | 287 | 0 | NR |
|               | Budesonide 320 μg bid             | 275                      | 63.4                               | 32.4      | 42.9 | 39.7 | 275 | 2 | NR |
|               | Formoterol 9 μg bid               | 284                      | 63.5                               | 34.5      | 41.9 | 39.6 | 284 | 1 | NR |
|               | Placebo                           | -                        | 300                               | 63.2      | 31.0 | 39.7 | 41.3 | 300 | 1 | NR |
Table 1  Baseline characteristics of included studies and all-cause mortality (binary data) (Continued)

| Study          | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 | Treatment 5 | Treatment 6 |
|----------------|-------------|-------------|-------------|-------------|-------------|-------------|
| [64, 65]       | UPLIFT (Tashkin 2008/Celli 2009) | Tiotropium 18 μg od | 208 | 2986 | 64.5 | 24.6 | 29.3 | 47.7 | 2987 | 446 | 381 |
|                | Placebo     | -           |            |             |             |             |
|                |             | 3006        | 64.5       | 26.1 | 29.9 | 47.4 | 30006 | 495 | 411 |
| [44]           | Tonnel 2008 | Tiotropium 18 μg od | 39 | 266 | 64.9 | 13.2 | 23.7 | 47.5^b | 266 | 3 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 288         | 63.5       | 14.6 | 30.2 | 46.2^b | 288         | 6 | NR |
| [45]           | COPE (van der Valk 2002) | Fluticasone Propionate 500 μg bid | 26 | 123 | 64.1 | 14.6 | 22.0 | 57.5 | 123 | 1 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 121         | 64.0       | 16.5 | 33.3 | 56.1 | 121         | 1 | NR |
| [46]           | CCLS (Vestbo 1999) | Budesonide 800 μg od + 400 μg od for 6 months; 400 μg bid for 30 month | 156 | 145 | 59.0 | 41.4 | 75.9 | 86.2 | 145 | 4 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 145         | 59.1       | 37.9 | 77.2 | 86.9 | 145         | 5 | NR |
| [38]           | Vogelmeier 2008 | Formoterol 10 μg bid | 24 | 210 | 61.8 | 24.3 | NR | 51.6^b | 210 | 0 | NR |
|                | Tiotropium   | 18 μg od    | 221 | 63.4 | 20.8 | NR | 51.6^b | 221 | 0 | NR |
|                | Tiotropium + Formoterol | 18 μg od/10 μg bid | 207 | 62.6 | 20.8 | NR | 50.4 | 207 | 0 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 209         | 62.5       | 22.5 | NR | 51.1 | 209         | 1 | NR |
| [47]           | POET-COPD 2011 (Vogelmeier 2011) | Tiotropium 18 μg od | 52 | 3707 | 62.9 | 25.6 | 48.0 | 49.2 | 3707 | 64 | 66 |
|                | Salmeterol  | 50 μg bid   | 3669 | 62.8 | 25.1 | 48.3 | 49.4 | 3669 | 78 | 73 |
| [66]           | INSPIRE (Wedzicha 2008) | SFC 50/500 μg bid | 104 | 658 | 64.0 | 19.0 | 38.0 | 39.1 | 658 | 21 | 18 |
|                | Tiotropium   | 18 μg od    | 665 | 65.0 | 16.0 | 38.0 | 39.4 | 665 | 38 | 34 |
| [24]           | LHS (Wise 2000) | Triamcinolone 600 μg bid | 156 | 559 | 56.2 | 36.0 | 90.5 | 68.5 | 559 | 15 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 557         | 56.4       | 37.9 | 89.8 | 67.2 | 557         | 19 | NR |
| [39]           | Zheng 2007  | SFC 50/500 μg bid | 24 | 297 | 66.0 | 9.4 | 21.0 | 47.0^b | 297 | 2 | NR |
|                | Placebo     | -           |            |             |             |             |
|                |             | 148         | 66.6       | 13.5 | 23.0 | 47.0^b | 148         | 0 | NR |
| [48]           | Zhong 2012  | Budesonide 320/9 μg bid | 26 | 156 | 65.7 | 1.9 | NR | 36.2 | 156 | 1 | NR |
|                | Budesonide  | 400 μg bid  | 152 | 64.7 | 7.9 | NR | 36.3 | 152 | 0 | NR |

FEV₁ – mean % predicted, post-bronchodilator
*Powered to detect mortality
^Mean % predicted FEV₁ is pre-bronchodilator
^Not stated whether mean % predicted FEV₁ is pre-bronchodilator or post-bronchodilator
^FEV₁ is mean of the three treatment arms
within individual RCTs, and provides additional information on the relative efficacy of treatments for which direct trial comparisons are available. The results show that only indacaterol and the combination of the long-acting β₂-agonist salmeterol and the inhaled corticosteroid fluticasone propionate (SFC) are associated with an important reduction in the risk of all-cause mortality in COPD in fixed effect models. Although the fixed effects model was presented as the base case there was no clear difference between the fixed and random effects models.

### Table 2: All-cause mortality (hazard ratios) of included studies

| Trial   | Treatment | Comparator       | ITT HR   | LCI     | UCI     | p value | On treatment HR   | LCI     | UCI     | p value |
|---------|-----------|------------------|----------|---------|---------|---------|-------------------|---------|---------|---------|
| TORCH   | SFC       | Placebo          | 0.811    | 0.670   | 0.982   | 0.030   | NR                | NR      | NR      | NR      |
|         | SFC       | Salmeterol       | 0.946    | 0.777   | 1.151   | 0.580   | NR                | NR      | NR      | NR      |
|         | SFC       | Fluticasone propionate | 0.768 | 0.636 | 0.927 | 0.006 | NR                | NR      | NR      | NR      |
|         | Salmeterol | Placebo | 0.857    | 0.710   | 1.035   | 0.110   | NR                | NR      | NR      | NR      |
|         | Fluticasone propionate | Placebo | 1.056    | 0.883   | 1.264   | 0.550   | NR                | NR      | NR      | NR      |
| UPLIFT  | Tiotropium | Placebo | 0.890    | 0.790   | 1.020   | 0.086   | 0.840             | 0.730   | 0.970   | 0.016   |
| POET-COPD | Tiotropium | Salmeterol | 0.810    | 0.580   | 1.130   | 0.210   | 0.850             | 0.610   | 1.190   | 0.350   |
| INSPIRE | SFC       | Tiotropium       | NR       | NR      | NR      | NR      | 0.480             | 0.270   | 0.850   | 0.012   |

**Fig. 2 Base case evidence network.** The width of the lines are proportional to the total person years of follow-up for all trials informing that comparison.
The results were consistent across a number of sensitivity analyses including controlling for disease severity.

Results for SFC are based on 233 deaths occurring in 7427 subject years. The results for indacaterol are based on four deaths occurring over 1446 subject years and have wide credible intervals. These results are sensitive to the number of deaths (a small change will have a large impact on the resulting HR) and may change with further research.

The results for many of the treatments are inconclusive, as demonstrated by the wide credible intervals exhibited around a number of the HRs. Whilst tighter credible intervals are observed around the results for tiotropium, salmeterol and fluticasone, our analysis is still inconclusive as to whether the treatments provide a greater benefit or harm to patients.

Two published NMAs have evaluated the relationship between pharmacological agents and mortality in COPD patients [9, 10]. Dong [10] considered all-cause mortality and cardiovascular death as outcomes: 42 trials published up to July 2011 were included, treatments were grouped by class (long-acting β₂ agonists, inhaled corticosteroids etc.) and tiotropium was separated by inhaler type. The authors sourced trial mortality results from secondary sources. The study reported a reduction in mortality for LABAs combined with ICS compared with placebo (HR 0.80; 95 % CrI 0.67, 0.94) based on a fixed effects model. Baker [9] included 28 trials reporting the mortality published up to October 2007: treatments

![Forest plot of results of network meta-analysis. Hazard ratios compared to placebo (DIC 431.9 FE, 431.5 RE). SFC = Salmeterol fluticasone propionate combination; CrI = credible interval; Doses were pooled for the purpose of the analysis: indacaterol (150 µg od, 300 µg od), budesonide (200 µg bid, 400 µg bid, 1200 µg od for 6 months followed by 800 µg od for 30 months), fluticasone propionate (250 µg bid, 500 µg bid), salmeterol (50 µg bid, 100 µg bid), formoterol (6 µg bid, 12 µg bid, 24 µg bid) and salmeterol fluticasone propionate combination (SFC) (50/250 µg bid, 50/500 µg bid).]
were grouped by class. A mortality reduction reported for LABAs in combination with ICS vs placebo (HR 0.71; 95% CI 0.49, 0.96) in the fixed effect model.

The present analysis included an additional 14 months of reported evidence and a wider range of treatments (roflumilast, indacaterol and triamcinolone) compared with Dong [10]. Furthermore, results were not aggregated by class. An assumption of class effects presupposes that the effect of each intervention within a class is identical. Even if the assumption holds for efficacy data it may not translate to safety data as interventions could have physiological effect other than the mechanism of action, therefore we chose estimate effects for each intervention independently [50].

Binary and hazard ratio data were combined in the same analysis, permitting the maximum number of studies to be included and using the best available data from each. We minimised the risk of errors by using data only from citable sources. Sensitivity analyses were undertaken to examine the robustness of the results to the underlying assumptions.

There are a number of limitations of this study. NMA methods depend on the assumptions that effect measures are additive on the selected scale and that relative treatment effects are comparable; [8] heterogeneity between trials may invalidate this assumption. Potential observed or unobserved differences between trials may impact on heterogeneity and thereby relative treatment effects.

The majority of the studies included were not specifically designed to capture mortality as a primary or secondary endpoint. The feasibility of conducting RCTs powered to detect differences in mortality in COPD patients is limited by the need for large sample sizes with sufficient follow-up, as well as the potential for introducing bias associated with differential dropout rates across study arms. Although this is a limitation of the current analysis, where there is an absence of head-to-head trials including all comparators, NMA is a useful tool for healthcare decision makers. In the present analysis we only included studies which reported mortality in the primary study publication. Inclusion of other studies where mortality is available in secondary publications may influence the results however the relatively small number of deaths in these trials makes this unlikely [10].

A potentially beneficial impact on mortality could be masked if a large number of studies with low or ineffectual dosages are included. Whilst there is some evidence that dose responsiveness may not be a significant factor in COPD [17, 51], this could be explored further by extending the network to incorporate dose finding studies and by implementing a three-level hierarchical NMA model with an additional level for each drug class [52].

Whilst we controlled for disease severity (recorded by baseline lung function) we did not control for other potential differences between trials which may impact on relative treatment effects (e.g. background therapy, history of exacerbations) as reporting was less consistent for these indicators.

Further work could examine baseline risk or the response in the placebo arms between studies. For example, similar rates of death per 1000 patient years (PY) were observed in the indacaterol (9.9/1000 PY), budesonide (10.0/1000 PY) and triamcinolone (11.4/1000 PY) placebo arms. Much higher rates were observed in the tiotropium (37.2/1000 PY), fluticasone propionate (43.3/1000 PY), salmeterol (47.0/1000 PY) and SFC (48.7/1000 PY) placebo arms (strongly influenced by the size and number of deaths in TORCH and UPLIFT) (Additional file 2: Table S4).

We conclude that currently available data from clinical trials in COPD suggest that some pharmacological treatments may have a significant impact on mortality, compared with placebo. In particular indacaterol and the combination of salmeterol and fluticasone propionate have shown evidence of reduction in all-cause mortality. The result for indacaterol is however based on a small number of deaths occurring to subjects receiving this therapy. Further research is warranted to strengthen our conclusions.

Additional files

Additional file 1: Statistical Methods. (PDF 376 kb)
Additional file 2: Table S1. Reasons for excluding full publications. Table 2. Risk of bias results. Table S3. Fixed effects network meta-analysis results. Hazard ratios compared to placebo (95% Credible Intervals). Table 4. Placebo mortality by treatment arm. (PDF 352 kb)

Competing interests
Mike Chambers is a GSK employees and owns GSK stock. Funding was provided by GSK.

Authors’ contributions
DAS and JT contributed to the conception and design, acquisition of data and data analysis and interpretation. BW, NH, MC, PC and BC contributed to the conception and design and the data analysis and interpretation. JC contributed to the conception and design and acquisition of data. All authors read and approved the final manuscript.

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References

1. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448–57.

2. World Health Organization. The top 10 causes of death: Fact Sheet No. 310. 2014; http://www.who.int/mediacentre/factsheets/fs310/en/.

3. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.

4. Kohansal R, Soriano JB, Agusti A. Investigating the natural history of lung function: facts, pitfalls, and opportunities. Chest. 2009;135(5):1330–41.

5. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.

6. Institute for Quality and Efficiency in Health Care (IQWiG). General Methods 4.0. 2011.

7. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2014.

8. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Izler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011;14(4):429–37.

9. Baker WL, Baker EL, Coleman CM. Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis. Pharmacotherapy. 2009;29(8):691–905.

10. Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax. 2013;68(1):49–56.

11. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2003;326(7371):997–900.

12. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105–24.

13. Haselbäldt V. Meta-analysis of multitreatment studies. Med Decis Making. 1998;18(1):37–43.

14. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions v5.1.0. The Cochrane Collaboration. 2011. www.cochrane-handbook.org.

15. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol. 2010;10(10):54.

16. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ. 2011;342:d5215.

17. Wije RA, Ankerzén E, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat Inhaler and the Risk of Death in COPD. N Engl J Med. 2013.

18. Spiegelhalter DJ, Thomas A, Best N, Lunn D. WinBUGS User Manual: Version 1.4. Cambridge: MRC Biostatistics Unit. 2003.

19. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to Bayesian analysis. Res Synth Methods. 2010;1(2):97–111.

20. Spiegelhalter DJ, Thomas A, Best N, Carlin B, Van der Linde A. Bayesian Measures of Association. v.5.1.0. The Cochrane Collaboration 2003; 2003.

21. Thomas A, Best N, Carlin B, Van der Linde A. Statistical Discrete Data: R Suite Library. 2008-03-04.

22. Pauwels RA, Lofdahl C-G, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease.

23. Schrafl A, Uphoff M, Barak A, Emser W, Wachtler D, Milsom I, et al. Efficacy of inhaled montelukast in the management of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(3):912–19.

24. Connor RB, El-Kareh M, Benolken D, Whalen J, Whayne GD, et al. Efficacy of an oral inhaled beta-agonist in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(1):14–9.

25. Kerstjens HA, Brand PL, Hughes MD, Robinson DA, Postma DS, et al. Efficacy and safety of salmeterol/fluticasone propionate in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(1):89–96.

26. Calverley PM, Jones PW, Waller L, Celli B, Rabe KF, et al. Salmeterol and fluticasone propionate in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361(9366):449–56.
47. Vogelmeier C, Hederer B, Glab T, Schmidt H, Rutten-van Molken MP, Beeh
KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations
of COPD. N Engl J Med. 2011;364:1093–103.

48. Zhong N, Zheng J, Wen F, Yang L, Chen P, Xiu Q, et al. Efficacy and safety
of budesonide/formoterol via a dry powder inhaler in Chinese patients with
chronic obstructive pulmonary disease. Current Medical Research & Opinion.
2012;28(2):257–65.

49. Campbell M, Eliau A, Johansson G, Tornling G, Nihlen U, Bengtsson T, et al.
Formoterol for maintenance and as needed treatment of chronic
obstructive pulmonary disease. Respir Med. 2005;99(12):1511–20.

50. McAlister FA, Laupacis A, Wells GA, Sackett DL. Users’ Guides to the Medical
Literature: XIX. Applying clinical trial results B. Guidelines for determining
whether a drug is exerting (more than) a class effect. JAMA.
1999;282(14):1371–7.

51. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J,
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(3):210–23.

52. Owen RK, Tincello DG, Keith RA. Network meta-analysis: development of a
three-level hierarchical modeling approach incorporating dose-related
constraints. Value Health. 2015;18(1):116–26.

53. Aaron SD, Vandemheen KL, Fergusson D, Malais F, Bourbeau J, Goldstein R,
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(8):545–55.

54. Bateman ED, Tashkin D, Siafakas N, Dahl R, Towse L, Massey D, et al. A one-
year trial of tiotropium Respimat plus usual therapy in COPD patients. Respir
Med. 2010;104(10):1460–72.

55. Burge PS, Calverley PMA, 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(7249):1297–303.

56. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H.
Maintenance therapy with budesonide and formoterol in chronic
obstructive pulmonary disease.[Erratum appears in Eur Respir J. 2004
Dec;24(6):1075]. Eur Respir J. 2003;22(6):912–9.

57. Calverley PM, Sanchez-Toril F, Michor A, Teichmann P, Bredenbroeker D, Fabbri
LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive
pulmonary disease. Am J Respir Crit Care Med. 2007;176(2):154–61.

58. Calverley PM, Kuna P, Monso E, Costantini M, Petruzzelli S, Sergio F, et al.
Beclomethasone/formoterol in the management of COPD: a randomised
controlled trial. Respir Med. 2010;104(12):1858–68.

59. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha
JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in
primary care: a randomised controlled trial. Respir Med. 2007;101(8):93.

60. Choudhary AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha
JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in
primary care: a randomised controlled trial. Respir Med. 2007;101(8):93.

61. Ewigman BK, Stovall R, Hinson J, Williams A, Bossert A, Tanaka S, et al.
Prevention of exacerbations of chronic obstructive pulmonary disease with
tiotropium, a once-daily inhaled anticholinergic bronchodilator: a
randomised trial. Ann Intern Med. 2005;143(5):317–25.

62. Schermer T, Chavannes N, Delhijuzen R, Wouters E, Morris S, Akerman R,
et al. Fluticasone and N-acetylcysteine in primary care patients with COPD
or chronic bronchitis. Respir Med. 2009;103(4):542–51.

63. Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin LU, Silikoff PE,
et al. Efficacy and safety of budesonide and formoterol in one pressured
metered-dose inhaler in patients with moderate to very severe chronic
obstructive pulmonary disease: Results of a 6-month randomized clinical
trial. Drugs. 2008;68(14):1975–2000.

64. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year
trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med.
2008;359(15):1543–54.

65. Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP. Mortality in the 4-
year trial of tiotropium (UPLIFT) in patients with chronic obstructive
pulmonary disease. Am J Respir Crit Care Med. 2009;180(10):948–55.

66. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA.
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.