National Institute for Health and Care Excellence

Draft Guideline

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[I] Inhaled triple therapy

NICE guideline NG115

Evidence reviews

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Draft for Consultation

This evidence review was developed by the NICE Guideline Updates Team

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Inhaled triple therapy

Review question

In people with stable COPD, what is the clinical and cost effectiveness of a LAMA plus a LABA plus ICS compared with:

- a LAMA plus LABA?
- a LABA plus an inhaled corticosteroid (ICS)

Introduction

The treatment of moderate to very severe COPD commonly includes the use of long-acting bronchodilators and inhaled corticosteroids to ease symptoms and reduce exacerbations. Inhaled drugs are often used in combination to provide more effective relief. Possible combinations include long-acting muscarinic antagonist with long-acting beta-adrenoceptor (LAMA+LABA) or LABA with inhaled corticosteroids (LABA+ICS).

'Triple therapy' is delivery of a combination of all three inhaled drugs (LAMA+LABA+ICS). Triple therapy can be prescribed as a single inhaler which delivers all three drugs in one dose or as multiple inhalers which deliver separate doses of each drug.

This review aimed to evaluate the effectiveness of triple therapy, either delivered as a combination of inhalers, or as one single inhaler, in managing the symptoms of patients with severe COPD in comparison to the dual therapy combinations of LAMA+LABA and LABA+ICS. Single and multiple inhaler doses of triple therapy were included as separate subgroups in the analyses in this review, but the main comparison of interest was between the effects of dual and triple therapy, rather than inhaler type. Studies which specifically compared the effectiveness of triple therapy alone using a single inhaled device or using separate inhalers were not eligible for inclusion in this review. The protocol for the review is summarised in Table 1Table 1.

PICO table

Table 1 PICO for the comparative effectiveness of combinations of inhaled therapies

Population	• Patients aged > 35 years • Diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2017) or equivalent criteria. • Obstructive ventilator defect should be at least moderate, with a baseline FEV1 less than 80% of predicted.
Interventions	• LAMA + LABA + ICS
Comparator	• LAMA + LABA • LABA + ICS
Outcomes	• COPD exacerbation (moderate to severe and severe) • St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder) • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropouts due to adverse events • Trough FEV1

- Pneumonia
- Fractures (with degree of harm)
- Exercise capacity
- Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

In particular, the following definitions, key outcomes and methods have been adopted:

1. Exacerbations were divided into moderate to severe and severe categories in accordance with the COPD inhaled combination therapy review. A moderate exacerbation is defined as worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics; a severe exacerbation is defined as a rapid deterioration that requires hospitalisation. The moderate to severe exacerbation category included both types of exacerbations.
2. Data for the St George's Respiratory Questionnaire (SGRQ) were presented in 2 ways, depending on the format of data in the included studies: as changes in SGRQ total score and as the number of responders (decrease in SGRQ score of ≥4 units).
3. This review was not intended to evaluate LAMA+LABA versus LABA+ICS and as a result, no pairwise data is presented for these comparisons even if both comparators are included in a triple therapy trial. Comparisons between LAMA+LABA and LABA+ICS are made in the existing NICE COPD guideline (NG115). Only trials that used drug combinations that were within the licensed doses for use or used routinely in UK clinical practice were included as part of the review. The doses used in the included studies are summarised in Table 2.
4. Forest plots are presented showing outcomes that favour triple therapy to the right of the chart. Where lower numbers favoured triple therapy, such as for exacerbation rate, the effect estimate was inverted to maintain consistency in the presentation of the forest plots.
5. The forest plots in the main analysis include subgroups for multiple (medication taken via multiple inhalers) and single inhalers (medication taken via a single inhaler) as all studies provided information on inhaler type. The GRADE tables only report the overall pooled result from the multiple and single inhaler type plots, unless tests for subgroup differences were significant ($p<0.05$). In these cases, the results for each subgroup as well as the pooled result from the inhaler type subgroup analysis are presented in the GRADE tables. To avoid duplication, the pooled results from other subgroup analyses were not reported in the GRADE tables.
6. No data was available to perform some of the pre-specified sub-group analyses. It was not possible to separate whole studies or groups of participants within studies by variation in baseline peak flow, FEV1 variability, asthma, smoking status or pulmonary rehabilitation completion status. However, sub-group analyses for inhaler type, exacerbation history, prior medication and eosinophil count were carried out. Different studies separated people by different eosinophil count thresholds, some by those above or below 200 cells per microliter and others by those above or below 150 cells per microliter. As a result, eosinophil count subgroups were separated into 'higher eosinophil count per microlitre including trials with cut offs of greater than 150 or 200 eosinophils per microlitre' and 'lower eosinophil counts per microlitre' for studies reporting less than 150 or 200 eosinophils per microlitre. To try to assess the effect of including 2 different overlapping cut offs in each subgroup, a sensitivity analysis was carried out removing the study using 200 cells per microlitre as a cut-off (Singh 2016 for triple therapy versus LABA+ICS, Papi 2018 for triple therapy versus LAMA+LABA).

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

This review was conducted as part of an update of the NICE COPD guideline (NG115). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews was conducted from the date of the searches in the previous version of the guideline (May 2003) and this identified 2,133 references. Details of the search strategy are included in appendix C.

All of the abstracts were screened on title and abstract with 114 papers ordered as potentially relevant systematic reviews or RCTs. Another paper (Ferguson 2018), which was published soon after the search date, was also included because it was considered to be directly relevant to the review and had the potential to alter the recommendations. Thirteen papers, reporting 16 RCTs, were included after full text screening. Of these, 2 compared triple therapy with LAMA+LABA, 12 compared triple therapy with LABA+ICS and 2 compared triple therapy with both LAMA+LABA and LABA+ICS.

Details of the review protocol are included in appendix A and the process of study identification is summarised in the diagram in appendix D.

Excluded studies

The excluded studies are listed in appendix J with reasons for their exclusion.

1 Summary of clinical studies included in the evidence review

2 The included studies are summarised in Table 2. For detailed evidence tables refer to appendix E.

3 **Table 2 Summary of studies comparing triple therapy versus dual therapy**

Short Title	Population	Interventions	Relevant outcomes
Aaron (2007) Canadian study	• Sample size: 449 • Split between study groups: Triple: 145 Dual: 148 Mono: 156 • Loss to follow-up: Triple: 2 Dual: 2 • %female: Triple: 42.1% Dual: 42.6% • Mean age (SD): Triple: 67.5 (8.9) Dual: 67.6 (8.2) • Current smoker (%): Dual: 24.3% Triple: 32.4% • FEV1 (mean, SD): Prebronchodilator Dual: 1.00 (0.44) Triple: 1.05 (0.38) Postbronchodilator Dual: 1.08 (0.43) Triple: 1.12 (0.41)	• Dual therapy LAMA+LABA: Tiotropium/Salmeterol *Tiotropium 18 ug, once daily* *Salmeterol 25 ug two puffs, twice daily* • Triple therapy Tiotropium/Fluticasone-Salmeterol *Tiotropium 18 ug, once daily* *Fluticasone 250 ug + Salmeterol 25 ug, two puffs, twice daily*	• Moderate to severe exacerbations • Serious adverse events • Pneumonia • TDI • Severe exacerbations • Mortality • Dropouts due to serious adverse events • Cardiac serious adverse events • COPD serious adverse events
Cazzola (2007) Italian study	• Sample size: 81 • Split between study groups: Triple: 29 Dual: 26 • %female: Triple: 13% Dual: 13% • Mean age (SD): Triple: 66.9 (59.0-74.8) Dual: 64.4 (58.8-70) • Current smoker (%): Triple: 80.0% Dual: 93.3%	• Dual therapy LABA+ICS (Fluticasone-Salmeterol) *Fluticasone propionate 500 ug + Salmeterol 50 ug, twice daily* • Triple therapy Tiotropium/Fluticasone-Salmeterol *Fluticasone propionate 500 ug + Salmeterol 50 ug, twice daily* *Tiotropium 18 ug, once daily*	• Trough FEV1
Ferguson (2018) International study (Canada,	• Sample size: 1902 • Split between study groups: Triple: 640 Dual (LAMA+LABA): 627 Dual (LABA+ICS): 316	• Dual therapy LAMA+LABA: Glycopyrrolate/formoterol *Glycopyrrolate 18 ug + Formoterol fumarate 9.6 ug* LABA+ICS: Budesonide/formoterol	• Moderate to severe exacerbations • SGRQ score • SGRQ responders • Serious adverse events • Pneumonia • TDI

China, Japan, USA)	Open-label dual: 319 • Loss to follow-up: Triple: 10 Dual (LAMA+LABA): 2 Dual (LABA+ICS): 0 • %female: Triple: 28% Dual (LAMA+LABA): 31.2% Dual (LABA+ICS): 28.7% • Mean age (SD): Triple: 64.9 (7.8) Dual (LAMA+LABA): 65.1 (7.7) Dual (LABA+ICS): 65.2 (7.2) • Current smoker (%): Triple: 40.1% Dual (LAMA+LABA): 41.1% Dual (LABA+ICS): 36.6%	*Budesonide 320 ug + Formoterol fumarate 9.6 ug* • Triple therapy Budesonide/glycopyrrolate/formoterol *Budesonide 320 ug + Glycopyrronium 14.4 ug + Formoterol fumarate 10 ug*	• Trough FEV1 • Mortality • Dropout due to serious adverse events • Cardiac serious adverse events
Frith (2015) Australian & New Zealand study	• Sample size: 773 • Split between study groups: Triple (Glycopyrronium): 258 Triple (Tiotropium): 258 Dual: 257 • Loss to follow-up: Triple (Glycopyrronium): 0 Triple (Tiotropium): 0 Dual: 2 • %female: Triple (Glycopyrronium): 36.6% Triple (Tiotropium): 38% Dual: 32.3% • Mean age (SD): Triple (Glycopyrronium): 68.2 (8.38) Triple (Tiotropium): 68.0 (7.74) Dual: 67.8 (8.49) • Current smoker (%): Triple (Glycopyrronium): 35.4% Triple (Tiotropium): 35.7% Dual: 36.2% • Ex-smoker (%): Triple (Glycopyrronium): 64.6% Triple (Tiotropium): 64.3% Dual: 63.8% • FEV1 (mean, SD): Triple (Glycopyrronium): 1.52 (0.50) Triple (Tiotropium): 1.49 (0.47) Dual: 1.55 (0.48)	• Dual therapy LABA+ICS (Fluticasone-Salmeterol) *Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily* • Triple therapy Triple 1: Glycopyrronium + Fluticasone-Salmeterol *Glycopyrronium 50 ug once daily* *Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily* Triple 2: Tiotropium + Fluticasone-Salmeterol *Tiotropium 18 ug, once daily* *Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily*	• Serious adverse events • Pneumonia • Trough FEV1 • Mortality • Dropout due to serious adverse events • Cardiac serious adverse events • COPD serious adverse events
Hoshino (2013) Japanese study	• Sample size: 68 • Split between study groups: Triple: 15 Dual: 16 Mono 1: 15 Mono 2: 14 • %female: Triple: 13% Dual: 20% • Mean age (SD): Triple: 73 (7) Dual: 67 (8) • FEV1 (mean, SD): Triple: 1.38 (0.56) Dual: 1.25 (0.38)	• Dual therapy LABA+ICS (Fluticasone-Salmeterol) *Salmeterol 50 ug + Fluticasone propionate 250 ug, twice daily* • Triple therapy Tiotropium + Fluticasone-Salmeterol *Tiotropium 18 ug once daily* *Salmeterol 50 ug + Fluticasone propionate 250 ug, twice daily*	• SGRQ score

Lipson (2017) and Tabberer (2018) International study (15 countries)	• Sample size: 1811 (extension population 430) • Split between study groups: Triple: 911 Dual: 899 Extension population triple: 210 Extension population dual: 220 • %female: Triple: 26% Dual: 26% Extension population triple: 25% Extension population dual: 26% • Mean age (SD): Triple: 64.2 (8.56) Dual: 63.7 (8.71) Extension population triple: 63.7 (7.76) Extension population dual: 63.3 (8.43) • Current smoker (%): Triple: 44% Dual: 44%	• Dual therapy LABA+ICS: Budesonide/Formoterol *Budesonide 400 ug + formoterol 12 ug, twice daily* • Triple therapy Fluticasone/Umeclidinium/Vilanterol *Fluticasone furoate 100 ug + Umeclindinium 62.5 ug + Vilanterol 25 ug, once daily*	• Moderate to severe exacerbations • SGRQ score • SGRQ responders • Serious adverse events • Pneumonia • TDI • Trough FEV1
Lipson (2018) International study (37 countries)	• Sample size: 10335 • Split between study groups: Dual (LAMA+LABA): 2070 Dual (LABA+ICS): 4134 Triple: 4151 • %female Dual (LAMA+LABA): 34% Dual (LABA+ICS): 34% Triple: 33% • Mean age (SD) Dual (LAMA+LABA): 65.2 (8.3) Dual (LABA+ICS): 65.3 (8.3) Triple: 65.3 (8.2) • Ex-smoker (%): Dual (LAMA+LABA): 65% Dual (LABA+ICS): 66% Triple: 65%	• Dual therapy LAMA+LABA: Umeclidinium/Vilanterol *Umeclidinium 62.5 ug + Vilanterol trifenatate 25 ug* LABA+ICS: Fluticasone/Vilanterol *Fluticasone furoate 100 ug + Vilanterol trifenatate 25 ug* • Triple therapy Fluticasone/Umeclidinium/Vilanterol *Fluticasone furoate 100 ug + Umeclidinium 62.5 ug + Vilanterol trifenatate 25 ug, once daily*	• Moderate to severe exacerbations • SGRQ score • SGRQ responders • Serious adverse events • Pneumonia • Trough FEV1 • Severe exacerbations • Mortality • Dropout due to serious adverse events
Papi (2018) Italian study	• Sample size: 1532 • Split between study groups: Dual: 768 Triple: 764 • Loss to follow-up: Dual: 3 Triple: 4 • %female: Dual: 28% Triple: 28% • Mean age (SD): Dual: 64.5 (7.7) Triple: 64.4 (7.7) • Current smoker (%): Dual: 43% Triple: 46% • Ex-smoker (%): Dual: 57% Triple: 54% • FEV1 (mean, SD): Dual: 1.07 (0.31) Triple: 1.07 (0.31)	• Dual therapy LAMA+LABA: Indacaterol/Glycopyrronium *Indacaterol 85 ug + Glycopyrronium 43 ug, once per day* • Triple therapy Beclometasone/Formoterol/Glycopyrronium *Beclometasone diproprionate 87 ug + Formoterol fumarate 5 ug + Glycopyrronium 9 ug, twice daily*	• Moderate to severe exacerbations • SGRQ responders • Serious adverse events • Pneumonia
Siler (2015) International studies	• Sample size: Study 1: 619 Study 2: 620 • Split between study groups: Study 1 Triple: 206 Study 1 Dual: 206 Study 2 Triple: 206 Study 2 Dual: 206 • Loss to follow-up: Study 1 Triple: 1 Study 1 Dual: 0	• Dual therapy Both studies: LABA+ICS (Fluticasone-Vilanterol) *Fluticasone furoate 100 ug + Vilanterol 25 ug, once daily*	• Moderate to severe exacerbations • SGRQ score • SGRQ responders • Serious adverse events • Pneumonia

(Study 1: Argentina, Canada, Chile, Romania, USA Study 2: Czech Republic, Germany, Korea, USA)	Study 2 Triple: 0 Study 2 Dual: 2 • %female: Study 1 Triple: 33% Study 1 Dual: 32% Study 2 Triple: 33% Study 2 Dual: 39% • Mean age (SD): Study 1 Triple: 64.9 (8.72) Study 1 Dual: 64.7 (7.90) Study 2 Triple: 62.6 (8.12) Study 2 Dual: 62.6 (9.00) • Current smoker (%): Study 1 Triple: 39% Study 1 Dual: 44% Study 2 Triple: 58% Study 2 Dual: 58% • FEV1 (mean, SD): Study 1 Triple: 1.12 (0.45) Study 1 Dual: 1.16 (0.46) Study 2 Triple: 1.24 (0.44) Study 2 Dual: 1.29 (0.47)	• Triple therapy Both studies: Umeclidinium + Fluticasone-Vilanterol *Umeclidinium 62.5 ug, once daily* *Fluticasone furoate 100 ug + Vilanterol, 25 ug, once daily*	• Trough FEV1 • Mortality • Dropout due to adverse events
Siler (2016) International studies (Study 1: Canada, Germany, Korea, USA Study 2: Chile, Czech Republic, Korea, USA)	• Sample size: Study 1: 617 Study 2: 608 • Split between study groups: Study 1 Triple: 204 Study 1 Dual: 205 Study 2 Triple: 203 Study 2 Dual: 201 • Loss to follow-up: Study 1 Triple: 14 Study 1 Dual: 27 Study 2 Triple: 25 Study 2 Dual: 31 • %female: Study 1 Triple: 35% Study 1 Dual: 36% Study 2 Triple: 31% Study 2 Dual: 39% • Mean age (SD): Study 1 Triple: 62.7 (7.84) Study 1 Dual: 63.4 (8.27) Study 2 Triple: 64.5 (8.31) Study 2 Dual: 65.7 (7.92) • Current smoker (%): Study 1 Triple: 50% Study 1 Dual: 57% Study 2 Triple: 36% Study 2 Dual: 38% • FEV1 (mean, SD): Study 1 Triple: 1.31 (0.47) Study 1 Dual: 1.31 (0.46) Study 2 Triple: 1.15 (0.44) Study 2 Dual: 1.13 (0.45)	• Dual therapy Both studies: LABA+ICS (Fluticasone-Salmeterol) *Fluticasone propionate 250 ug + Salmeterol 50 ug, twice daily* • Triple therapy Both studies: Umeclidinium + Fluticasone-Salmeterol *Umeclidinium 62.5 ug, once daily* *Fluticasone propionate 250 ug + Salmeterol 50 ug, twice daily*	• Moderate to severe exacerbations • SGRQ score • Serious adverse events • Pneumonia • Trough FEV1 • Mortality • Dropout due to serious adverse events
Singh (2016) International study (14 countries)	• Sample size: 1368 • Split between study groups: Triple: 687 Dual: 681 • Loss to follow-up: Triple: 2 Dual: 5 • %female: Triple: 26% Dual: 23% • Mean age (SD): Triple: 63.3 (7.9) Dual: 63.8 (8.2) • Current smoker (%): Triple: 47% Dual: 47% • Ex-smoker (%): Triple: 53% Dual: 53% • FEV1 (mean, SD): Triple: 1.11 (0.32) Dual: 1.10 (0.33)	• Dual therapy LABA+ICS: Beclometasone/Formoterol *Beclometasone dipropionate 100 ug + Formoterol fumarate 6 ug, two puffs, twice per day* • Triple therapy Beclometasone/Formoterol/Glycopyrronium *Glycopyrronium bromide 12.5 ug + Beclometasone diproprionate 100 ug + Formoterol fumarate 6 ug, two puffs, twice per day*	• SGRQ responders • Serious adverse events • Pneumonia • TDI

Sousa (2016) European study (Czech Republic, Germany, Greece, Netherlands)	• Sample size: 236 • Split between study groups: Triple: 119 Dual: 117 • Loss to follow-up: Dual: 0 Triple: 1 • %female: Dual: 36% Triple: 30% • Mean age (SD): Dual: 63.1 (7.9) Triple: 65.2 (7.5) • Current smoker (%): Dual: 61% Triple: 49% • FEV1 (mean, SD): Triple: 1.33 (0.49) Dual: 1.37 (0.50)	• Dual therapy ICS/LABA combinations *Range of ICS/LABA (exact combinations not stated) at approved doses* • Triple therapy Umeclidinium/ICS/LABA *Umeclidinium 62.5 ug + Range of ICS/LABA (exact combinations not stated) at approved doses*	• SGRQ score • SGRQ responders • Trough FEV1

Abbreviations
FEV1: Forced expiratory volume
SGRQ: St George's Respiratory Questionnaire (SGRQ score = continuous outcome; SGRQ responders = dichotomous outcome)
TDI: Transition Dyspnoea Index

1

Quality assessment of clinical studies included in the evidence review

The RCTs were assessed for risk of bias and applicability and this information is presented in the evidence tables in appendix E. See appendix G for full GRADE tables.

Economic evidence

Included studies

A systematic search was carried out for this review question. The search returned 1,421 records, of which 1,419 were excluded on title and abstract. The remaining 2 papers were screened in full, and 1 was included in the evidence review.

Since a relevant UK-based analysis was identified, and *de novo* economic modelling was conducted for this review question, only studies using an NHS perspective were included in the evidence review.

Excluded studies

Details of the studies excluded at full text review are given in Appendix J.

Summary of studies included in the economic evidence review

Hertel et al. (2012) conducted a cost-utility analysis comparing various combinations of LAMA, LABA, ICS and roflumilast in patients with severe and very severe COPD (summarised in Table 3 below). The evaluation used a lifetime horizon, and was conducted from the perspective of the NHS.

The authors used a Markov structure to model COPD treatment, with states based on GOLD stages 3 and 4 (30%–50% predicted FEV1 and < 30% predicted FEV1 respectively). In each cycle, patients could remain in the same state, progress to a more severe state or die. Patients were also at risk of exacerbations, which could be community- or hospital-treated. The model also allowed patients to "step up" to a second line regimen (add in another drug) in each cycle.

The probability of progressing to a more severe GOLD stage was modelled based on the mean rate of FEV1 decline in COPD patients. Mortality was incorporated by applying a standardised mortality ratio for COPD to the background mortality rate for the UK general population. In addition, hospitalised exacerbations were associated with a probability of death. Treatment effects were implemented through relative exacerbation rates, which were derived from a network meta-analysis.

The analysis included 3 cost categories: (1) maintenance costs (estimated using resource use data from a tiotropium trial and unit costs data from NHS Reference Costs); (2) exacerbation costs (estimated using resource use data from the GOLD strategy group, and unit cost data from NHS Reference Costs); and (3) drug costs (from the BNF). Utilities were incorporated as baseline QoL scores stratified by GOLD stage, to which utility decrements were applied for patients experiencing exacerbations.

Results showed that triple therapy produces an ICER of £4,300 per QALY compared to LAMA+LABA and an ICER of £6,960 compared to LABA+ICS (calculated manually as the authors do not report ICERs).

This analysis was categorised as being partially applicable as it was conducted prior to the introduction of single fixed-dose triple therapy inhalers, and therefore uses outdated costs and clinical evidence. It was classified as having potentially serious limitations, as it relies on assumed exacerbation rates with no empirical basis, does not a conduct a probabilistic sensitivity analysis for the comparisons of interest, and is subject to a potential conflict of interest (the study was funded by a manufacturer of roflumilast).

Table 3 – Summary of Hertel et al. (2012)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty

Hertel et al. (2012)	1. Partially applicable [a] 2. Potentially serious limitations [b]	• Triple therapy • LABA+ICS • LAMA+LABA	UK	Lifetime 3.5% for costs and health effects	Triple therapy produces an ICER of £6,960/QALY compared to LABA+ICS. Triple therapy produces an ICER of £4,300/QALY compared to LAMA+LABA	The authors did not report sensitivity analysis results for the comparisons of interest

(a) Analysis conducted prior to introduction of single fixed-dose triple therapy inhalers (uses outdated costs and clinical evidence)
(b) Relies on an assumed exacerbation rates, does not conduct probabilistic sensitivity analysis for the comparison of interest, subject to a potential conflict of interest (funded by a manufacturer of roflumilast)

1

Economic model

This section summarises the *de novo* economic modelling conducted for this review question. For a full description of methods, results and conclusions please refer to the model report in Chapter C.

This analysis is based on the economic modelling conducted for the 2018 update of this guideline, which assessed the cost effectiveness of mono and dual long-acting bronchodilator regimens.

Population

Adults diagnosed with COPD who continue to experience breathlessness or exacerbations, despite treatment with a dual long-acting bronchodilator regimen (LAMA+LABA or LABA+ICS).

Comparators

Three treatment regimens are included in the analysis:

1. Triple therapy (LAMA+LABA+ICS)
2. LAMA+LABA
3. LABA+ICS

Since the review question focuses on the clinical and cost effectiveness of triple therapy compared with dual therapy (rather than on dual therapy regimens compared with each other), the model assesses 2 separate decision problems:

1. Triple therapy versus LAMA+LABA
2. Triple therapy versus LABA+ICS

Methods

Model structure

In order to represent the natural history of COPD over time, the model uses a Markov structure, with states based on GOLD severity stages 1-4, defined by FEV1 percent predicted (mild COPD = FEV1 ≥ 80% predicted; moderate COPD = 50% ≤ FEV1 < 80%; severe COPD = 30% ≤ FEV1 < 50% predicted; very severe COPD = FEV1 < 30% predicted). The model structure is shown in Figure 1. In each cycle of the model, patients have a probability of moving to a more severe GOLD stage (defined by the natural rate of FEV1 decline over time), and a probability of death (defined by stage-specific mortality rates). In the first cycle of the model, patients can move to a less severe GOLD stage, in order to reflect the initial FEV1 benefit for patients stepping up from dual therapy to triple therapy.

In each cycle, patients can also experience a hospitalised or non-hospitalised exacerbation, or an adverse event. The model uses a 3-month cycle length, which was deemed an appropriate period of time to capture progression between states, as well as interfacing well with clinical trial data on long-acting bronchodilators, which typically use 3-, 6-, or 12-month endpoints.

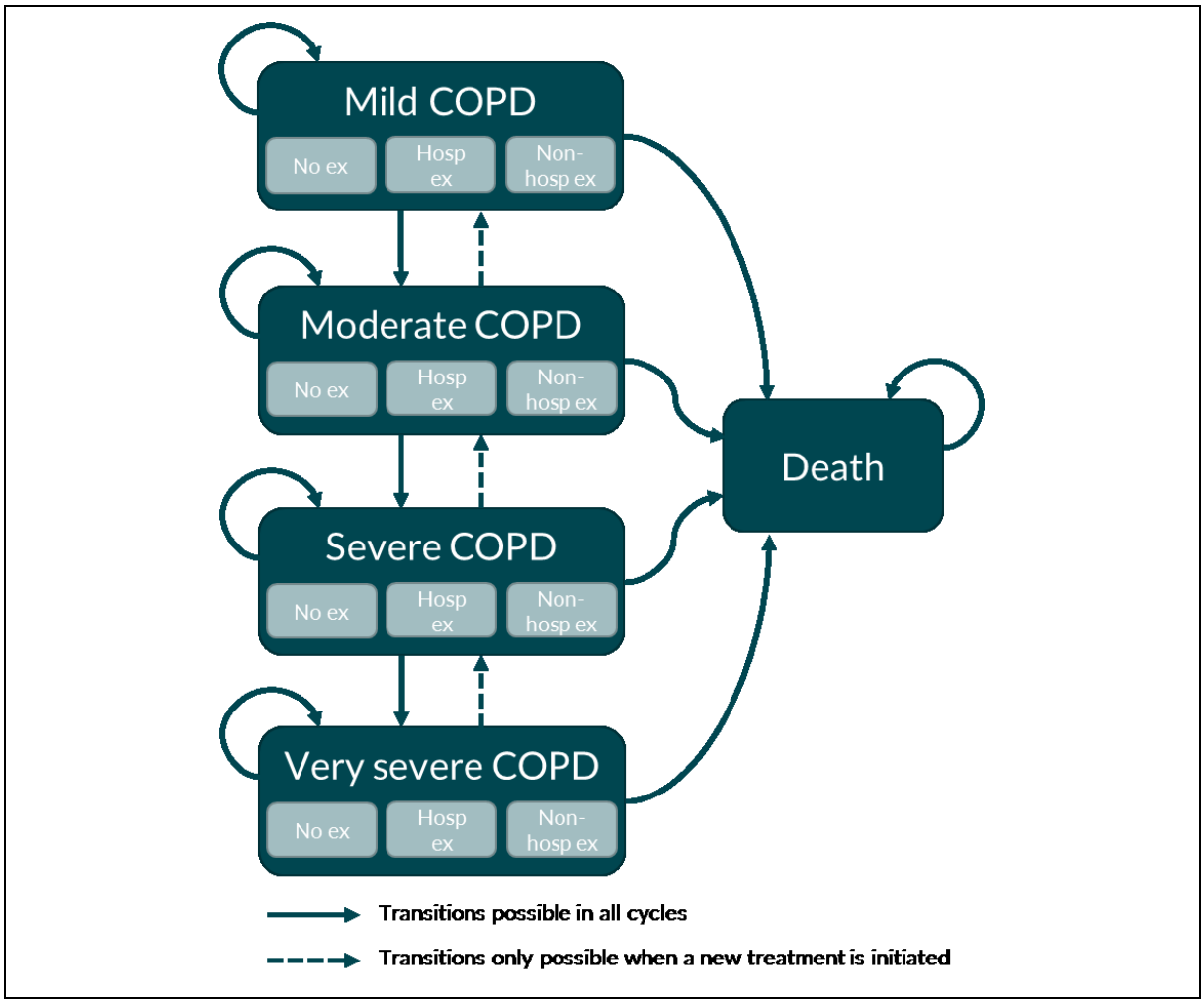

Figure 1 – Overall structure of the model

The model also simulates patients' treatment progression over time. In each cycle, patients treated with dual therapy regimen (LAMA+LABA or LABA+ICS) have a probability of either stepping up to triple therapy, or switching to an alternative dual therapy regimen (patients on a LAMA+LABA switch to a LABA+ICS, and vice versa). The pathway for treatment progression is shown in Figure 2. We made the assumption that no further stepping up or switching occurs once patients are initiated onto triple therapy.

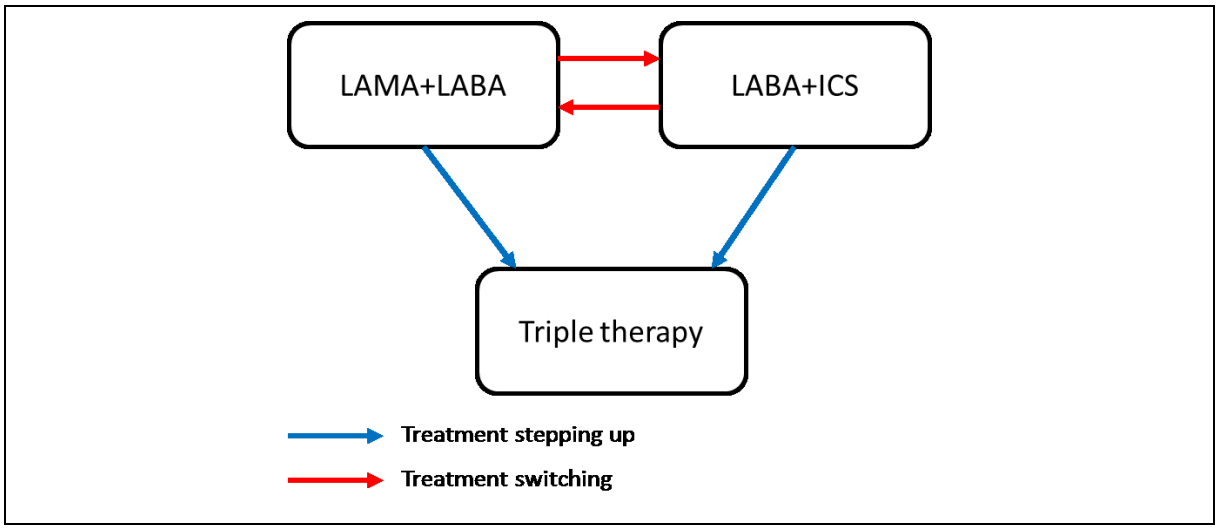

Figure 2 – treatment progression pathway in the model

Baseline patient population and natural history

To inform the initial distribution of patients' FEV1 at baseline, we used data on patients identified through the Clinical Practice Research Datalink (CPRD) who had a diagnosis of COPD, received treatment with either a LABA+ICS or LAMA+LABA, and were coded as having breathlessness or exacerbations in the year after initiating dual therapy.[a] Other baseline and natural history data were the same as in the original 2018 model.

Incorporating treatment effects

Treatment benefits

We used the pairwise meta-analyses conducted for this review question comparing triple therapy with LAMA+LABA, and triple therapy with LABA+ICS to inform treatment effects in the model. These provided a number of outcomes which could be used to model relative treatment benefit: exacerbations, FEV1, breathlessness (TDI), and condition-specific quality of life (SGRQ). However, incorporating all of these outcomes simultaneously in the model would introduce double-counting of benefits. Therefore, we modelled a number of scenarios, using the following combinations of outcomes:

- **Scenario 1: Exacerbations alone**
- **Scenario 2: SGRQ and exacerbations**
- **Scenario 3: FEV1 and exacerbations** – this scenario allows differences in transition probabilities in the first cycle of the model, with more effective treatments associated with a greater probability of moving to a less severe GOLD stage, as well as including effects of exacerbations on quality of life
- **Scenario 4: TDI and exacerbations** – this scenario uses coefficients from a regression analysis in order to predict the effect of breathlessness on SGRQ score, as well as including effects of exacerbations on quality of life
- **Scenario 5: FEV1, TDI and exacerbations** – as above, this scenario uses coefficients from a multiple regression analysis in order to predict the independent effect of FEV1, breathlessness and exacerbations in the previous year on SGRQ, as well as including effects of exacerbations on quality of life

Effect on treatment progression

Differences in the probability of stepping up treatment were implemented by assuming an inverse relationship with treatment effect on TDI, since breathlessness provides a reasonable indication of how well patients' disease symptoms are managed. Differences in the

[a] Thanks to Jennifer Quint of Imperial College London for CPRD data analysis

probability of treatment switching were implemented using treatment effects on discontinuation due to adverse events.

Treatment effects on mortality and adverse events

Treatment effects on mortality were applied directly to baseline mortality for each GOLD stage.

Adverse events were categorised as either cardiac, pneumonia, or 'other' events. Treatment effects from the clinical evidence review for the appropriate adverse event category were applied to these, using total serious adverse events as a proxy for the 'other' events category.

Since the mortality and adverse event outcomes were generally associated with a high degree of uncertainty, the model explores the impact of including and excluding these treatment effects through 3 scenarios:

- **Option A:** Treatment-specific differences in adverse events and mortality excluded
- **Option B:** Treatment-specific differences in adverse events, but not mortality, included
- **Option C:** Treatment-specific differences in adverse events and mortality included

Costs

Five categories of cost were used in the model:

1. **Drug costs** – acquisition costs of long-acting bronchodilators
2. **Maintenance costs** – routine healthcare resource use for each GOLD severity stage
3. **Exacerbation costs** – resource use associated with a hospitalised or non-hospitalised exacerbation
4. **Adverse event costs** – costs associated with treating acute and chronic adverse events
5. **Treatment progression costs** – healthcare costs associated with switching or stepping up treatment

In the base case, we assumed that all regimens were delivered as single fixed-dose inhalers, rather than as separate devices. This assumption was relaxed in a scenario analysis where triple therapy is delivered via 2 separate inhaler devices: a LABA+ICS combination inhaler plus a LAMA inhaler.

Health-related quality of life

Patients' stable quality of life (QoL) initially depended upon their GOLD stage, with disutilities applied depending on whether patients experienced an exacerbation or adverse event within each cycle.

SGRQ values were used to inform patients' baseline QoL. These were converted to EQ-5D scores via a mapping algorithm in line with the NICE Reference Case.

Results

Results presented in this section are means of 5,000 probabilistic iterations. Structural uncertainty in the model is also addressed stochastically, by randomly selecting 1 of the 5 scenarios for implementing treatment benefit in each iteration. Individual results for these scenarios and additional sensitivity analyses are reported in Chapter C (economic model report).

Triple therapy versus LAMA+LABA

Table 4 shows results comparing triple therapy to LAMA+LABA when treatment-specific differences in adverse events and mortality are excluded. These results indicate that triple therapy produces an ICER of £5,182 per QALY compared with LAMA+LABA and has an 89.6% probability of being cost effective when QALYs are valued at £20,000.

Table 4 – Mean probabilistic results for triple therapy versus LAMA+LABA. Option A: treatment-specific differences in adverse events and mortality excluded

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£28,438	4.97	-	-	-	10.4%
Triple therapy	£28,637	5.01	£199	0.038	£5,182	89.6%

Table 5 shows results when treatment-specific differences in adverse events are included. These results indicate that triple therapy dominates LAMA+LABA (is both more effective and less costly), and has a 70.1% probability of being cost effective when QALYs are valued at £20,000.

Table 5 – Mean probabilistic results for triple therapy versus LAMA+LABA. Option B: treatment-specific differences in adverse events (but not mortality) included

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
Triple therapy	£28,735	5.01	-	-	-	70.1%
LAMA+LABA	£29,064	4.94	£329	-0.075	dominated	29.9%

Table 6 shows results when treatment-specific differences in both adverse events and mortality are included. These results indicate that triple therapy produces an ICER of £4,979 per QALY compared to LAMA+LABA and has an 89.9% probability of being cost effective when QALYs are valued at £20,000.

Table 6 – Mean probabilistic results for triple therapy versus LAMA+LABA. Option C: treatment-specific differences in adverse events and mortality included

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
LAMA+LABA	£27,279	4.69	-	-	-	10.1%
Triple therapy	£28,911	5.02	£1,632	0.328	£4,979	89.9%

Table 7 summarises results for other scenario analyses which test key model assumptions for Option A. These results show that using the acquisition cost of triple therapy delivered as 2 separate inhalers, rather than 1 combination product, produces an ICER of above £20,000 per QALY (£22,313 per QALY), with a low probability of being cost effective if QALYs are valued at £20,000 (38.6%). However, triple therapy remains cost effective across all other scenarios.

Table 7 – Results for other scenario analyses testing key model assumptions – triple therapy versus LAMA+LABA. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Incremental: triple therapy versus LAMA+LABA			Prob triple therapy CE at £20k/QALY
	Cost	QALYs	ICER	
Triple therapy delivered as 2 separate inhalers	£847	0.038	£22,313	38.6%
Drug costs not adjusted for adherence	£288	0.039	£7,379	83.7%
Continuous treatment effect at 3, 6 and 12 mo	£181	0.054	£3,330	92.3%
No FEV1 benefit when switching and stepping up	£173	0.051	£3,434	93.6%
Trelegy trial data for baseline FEV1 distribution	£125	0.040	£3,151	92.9%
Cheapest product used for every regimen	£237	0.039	£6,107	87.7%
More severe values for baseline breathlessness	£198	0.036	£5,451	89.6%
Baseline GOLD distribution for comparison of triple therapy versus LABA+ICS used	£188	0.040	£4,698	91.4%

Triple therapy versus LABA+ICS

Table 8 shows results comparing triple therapy to LABA+ICS when treatment-specific differences in adverse events and mortality are excluded. These results indicate that triple therapy produces an ICER of £881 per QALY compared with LABA+ICS, and has a 99.2% probability of being cost effective when QALYs are valued at £20,000.

Table 8 – Mean probabilistic results for triple therapy versus LABA+ICS. Option A: treatment-specific differences in adverse events and mortality excluded

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA+ICS	£28,567	4.90	-	-	-	0.8%
Triple therapy	£28,631	4.98	£64	0.073	£881	99.2%

Table 9 shows results when treatment-specific differences in adverse events are included. Results indicate that triple therapy produces an ICER of £138 per QALY compared with LABA+ICS, and has a 74.6% probability of being cost effective when QALYs are valued at £20,000.

Table 9 – Mean probabilistic results for triple therapy versus LABA+ICS. Option B: treatment-specific differences in adverse events (but not mortality) included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA+ICS	£28,261	4.92	-	-	-	25.4%
Triple therapy	£28,273	5.01	£11	0.083	£138	74.6%

Table 10 shows results when treatment-specific differences in adverse events and mortality are included. Results indicate that triple therapy produces an ICER of £3,437 per QALY compared with LABA+ICS and has a 75.7% probability of being cost effective when QALYs are valued at £20,000.

Table 10 – Mean probabilistic results for triple therapy versus LABA+ICS. Option C: treatment-specific differences in adverse events and mortality included

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
LABA+ICS	£28,094	4.90	-	-	-	24.3%
Triple therapy	£28,517	5.02	£423	0.123	£3,437	75.7%

Table 11 summarises results for other scenario analyses which test key model assumptions for Option A. These results show that using an acquisition cost for triple therapy that reflects use of two separate inhalers, rather than 1 combination product, increases the ICER to £9,493 per QALY; substantially higher than the base case ICER. Triple therapy retains a relatively low ICER across all other scenarios.

Table 11 – Results for other scenario analyses testing key model assumptions – triple therapy versus LABA+ICS. Option A (treatment-specific differences in adverse events and mortality excluded)

Scenario	Incremental: triple therapy versus LAMA+ICS			Prob triple therapy CE at £20k/QALY
	Cost	QALYs	ICER	
Triple therapy delivered as 2 separate inhalers	£683	0.072	£9,493	82.5%
Drug costs not adjusted for adherence	£168	0.073	£2,308	98.3%
Continuous treatment effect at 3, 6 and 12 months	£75	0.068	£1,091	93.8%
No FEV1 benefit when switching and stepping up	-£51	0.124	Dominant	99.3%
Trelegy trial data for baseline FEV1 distribution	-£74	0.075	Dominant	99.8%
Cheapest product used for every regimen	£358	0.073	£4,918	93.5%
More severe values for baseline breathlessness	£61	0.069	£892	99.4%

Discussion

Results show that triple therapy is likely to be cost effective compared to both LAMA+LABA and LABA+ICS in patients who continue to exacerbate or remain breathless on dual therapy if QALYs are valued at £20,000. This finding is primarily due to favourable treatment effects of triple therapy on exacerbations, FEV1, TDI and SGRQ (even though, in some cases, the data are consistent with no effect at a 95% confidence level). While the acquisition cost of triple therapy is higher than that of either dual therapy regimen, this difference is relatively modest in relation to the health benefits; triple therapy costs an additional £16 per 30 days of treatment versus LABA+ICS, and an additional £12 per 30 days of treatment versus LAMA+LABA (assuming full adherence). Furthermore, this cost is at least partially offset by savings from prevented exacerbations.

Probabilistic sensitivity analysis shows a high degree of certainty that triple therapy is cost effective compared with both LAMA+LABA and LABA+ICS when treatment-specific differences in adverse events and mortality are excluded. This is because triple therapy produces strong treatment benefits across a number of outcomes. Contrastingly, including treatment effects on adverse events and mortality produces a higher degree of uncertainty in results, although triple therapy still retains a >70% probability of being cost effective at a threshold of £20,000 per QALY compared with both LAMA+LABA and LABA+ICS. This is due to the relatively wide confidence intervals around these effects, in particular the treatment effect on cardiovascular events.

Scenario analyses show that results are generally robust to key model assumptions. The exception to this is the scenario in which triple therapy is assumed to be delivered as 2 separate inhalers, which produces a substantial increase in ICERs, particularly for the

comparison of triple therapy with LAMA+LABA, for which the ICER exceeds £20,000 per QALY. This is because delivering triple therapy as 2 inhalers is more costly than using a single combination inhaler: £56.48 versus £45.50 per 30 days of treatment. While this difference may not appear excessive, it constitutes a considerable proportional increase in the incremental cost of triple therapy compared with dual therapies.

Evidence statements

Clinical evidence statements

The format of the evidence statements is explained in the methods in appendix B. Where possible, outcomes were analysed at 3, 6 and 12 months from the beginning of the intervention. If no time points are specified in the evidence statement for a particular outcome then this statement applies to all the time points where evidence was available for that outcome.

Triple therapy versus LAMA+LABA

Moderate quality evidence from up to 4 studies with up to 9,310 people showed a reduction in dropouts due to serious adverse events but a greater number of people experiencing pneumonia in people offered triple therapy compared to LAMA+LABA.

Low to high quality evidence from up to 2 studies with up to 7,753 people showed a reduction in the rate of severe exacerbations per person per year and an increase in SGRQ responders at 12 months for people offered triple therapy compared to LAMA+LABA, but the point estimates were less than the defined individual minimal clinically important differences.

High quality evidence from up to 4 studies with up to 9,310 people found no meaningful difference in the rate of moderate to severe exacerbations per patient per year, the numbers of people experiencing serious adverse events, change in FEV1, SGRQ responders at 6 months, change in TDI at 6 months or change in total SGRQ score at 12 months for people offered triple therapy compared to LAMA+LABA.

Low to moderate quality evidence from up to 4 studies with up to 9,310 people could not differentiate mortality, the number of people experiencing moderate to severe or severe exacerbations, the number of COPD or cardiac serious adverse events or TDI scores at 12 months for people offered triple therapy compared to LAMA+LABA.

Triple therapy versus LAMA+LABA: subgroup analyses

No subgroup differences were identified between the following categories:

- studies using multiple inhaler triple therapy compared to those using single triple therapy for all of the outcomes examined
- studies with patients taking LAMA+LABA prior to the intervention compared to those taking any other combination of medications
- studies including patients with a higher eosinophil count per microlitre compared to those with a lower eosinophil count per microlitre
- studies which included patients with an exacerbation in the past 12 months compared to those with either no exacerbation in the past 12 months or studies that didn't have previous exacerbations in the inclusion criteria.

Subgroup analyses were not possible for the following categories because insufficient data was provided to separate whole studies or groups of participants within studies:

- variation in baseline peak flow
- FEV1 variability

- asthma status
- smoking status
- pulmonary rehabilitation completion status

Triple therapy versus LAMA+LABA: eosinophil sensitivity analysis (removing study with cut off of 200 cells per microlitre)

No meaningful differences in results were identified compared to the analysis including this study.

Triple therapy versus LABA+ICS

Very low to high quality evidence from up to 8 studies with up to 11,884 people showed a lower rate of severe exacerbations per patient per year, an improvement in FEV1 and fewer dropouts due to serious adverse events for people offered triple therapy compared to LABA+ICS.

Low to moderate quality evidence from up to 7 studies with up to 10,080 people showed a reduction in the number of people experiencing moderate to severe exacerbations, an increase in SGRQ responders at 6 and 12 months, but the point estimates were less than the defined individual minimal clinically important differences.

Very low to high quality evidence from up to 5 studies with up to 10,605 people found no meaningful difference in the rate of moderate to severe exacerbations per patient per year, total SGRQ score or TDI score at 6 and 12 months for people offered triple therapy compared to LABA+ICS.

Very low to moderate quality evidence from up to 9 studies with up to 13,252 people could not differentiate mortality, serious adverse events, COPD serious adverse events, pneumonia or the number of SGRQ responders at 3 months for people offered triple therapy compared to LABA+ICS.

Triple therapy versus LABA+ICS: subgroup analysis

- Moderate quality evidence from 3 RCTs with up to 4,953 people who had a lower eosinophil count per microlitre showed a reduction in the rate of moderate to severe exacerbations for people offered triple therapy compared to LABA+ICS, although this was less than the MID. High quality evidence from 3 studies with up to 5,648 people who had a higher eosinophil count per microlitre showed a reduction in the rate of moderate to severe exacerbations for people offered triple therapy compared to LABA+ICS.
- No subgroup differences were identified between studies using multiple inhaler triple therapy compared to single inhaler triple therapy for most of the outcomes apart from change in FEV1 at 3 months.
    - Very low quality evidence from 8 studies with 2,653 people showed an increase in FEV1 at 3 months for people offered multiple inhaler triple therapy compared to LABA+ICS, but the point estimate was less than the defined MID.
    - Moderate quality evidence from 1 study with 1,810 people showed an increase in FEV1 at 3 months for people offered single inhaler triple therapy compared to LABA+ICS.
- No subgroup differences were identified between studies which included patients with an exacerbation in the past 12 months compared to those with either no exacerbation in the past 12 months or which didn't have previous exacerbations in the inclusion criteria apart from change in FEV1 at 12 months.
    - Moderate quality evidence from 1 study with 6,426 people who had an exacerbation in the past 12 months showed an improvement in FEV1 at 12 months for people offered triple therapy compared to LABA+ICS, but the point estimate was less than the defined MID.

  - Moderate quality evidence from 1 study with 430 people who were not required to have had an exacerbation in the past 12 months as part of the study inclusion criteria showed an improvement in FEV1 at 12 months for people offered triple therapy compared to LABA+ICS.
- No subgroup differences were identified between studies with patients taking LABA+ICS prior to the intervention compared to those taking any other combination of medications prior to the intervention.

Subgroup analyses were not possible for the following categories because insufficient data was provided to separate whole studies or groups of participants within studies:

- variation in baseline peak flow
- FEV1 variability
- asthma status
- smoking status
- pulmonary rehabilitation completion status

Triple therapy versus LABA + ICS: eosinophil sensitivity analysis (removing study with cut off of 200 cells per microlitre)

No meaningful differences in results were identified compared to the analysis including this study.

Economic evidence statements

A directly applicable original model with minor limitations found that triple therapy has a high probability of being cost effective compared to LAMA+LABA (90%) and compared to LABA+ICS (99%) in the base case if QALYs are valued at £20,000. These results are generally robust to sensitivity analysis, although making the assumption that triple therapy is delivered as 2 separate inhalers, rather than as 1 combined device, reduces the probability that triple therapy is cost effective to 39% versus LAMA+LABA and 83% versus LABA+ICS.

A partially applicable study with potentially serious limitations (Hertel et al. 2012) found that triple therapy has an ICER of £4,300 per QALY compared to LAMA+LABA, and an ICER of £6,960 compared to LABA+ICS.

Recommendations

1. In people with COPD who are taking LABA+ICS, offer LAMA+LABA+ICS if:
   - their symptoms continue to interfere with activities of daily living **or**
   - they have a severe exacerbation[b] (requiring hospitalisation) **or**
   - they have 2 moderate exacerbations[c] within a year. [2019]

2. In people with COPD who are taking LAMA+LABA, consider LAMA+LABA+ICS if:
   - they have a severe exacerbation[b] (requiring hospitalisation) **or**
   - they have 2 moderate exacerbations[c] within a year. [2019]

3. In people with COPD who are taking LAMA+LABA and whose symptoms continue to interfere with daily living, consider a 3-month trial of LAMA+LABA+ICS, and:
   - if symptoms improve, continue with LAMA+LABA+ICS
   - if symptoms do not improve, switch back to LAMA+LABA. [2019]

[b] The person experiences a rapid deterioration in respiratory status that requires hospitalisation.
[c] The person has a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics.

Rationale and impact

Why the committee made the recommendations

The committee decided that there should be separate recommendations on triple therapy for people who are currently taking LABA+ICS and for people taking LAMA+LABA. They agreed that there was stronger evidence from a greater number of studies that triple therapy benefits people taking LABA+ICS, compared with people taking LAMA+LABA.

For people currently taking LABA+ICS, the evidence showed that LAMA+LABA+ICS reduced the rate of severe exacerbations, improved FEV1, and did not increase the risk of pneumonia or other serious adverse events.

For people currently taking LAMA+LABA, the evidence showed that LAMA+LABA+ICS reduced the rate of serious exacerbations and provides some quality of life improvement. However, these improvements were smaller than the ones for people who were taking LABA+ICS before they started triple therapy. In addition, people who switched from LAMA+LABA to triple therapy were more likely to get pneumonia.

The criteria for starting triple therapy are based on the inclusion criteria for the studies the committee reviewed. For people who are currently taking LAMA+LABA, the committee made separate recommendations for:

- people who are having severe or frequent exacerbations, for whom the benefit of fewer exacerbations outweighs the increased risk of pneumonia
- people with less severe symptoms, for whom it is less clear if triple therapy provides enough benefits to outweigh the risk of pneumonia.

The committee looked at making recommendations for people with asthmatic features. However, the evidence excluded people with asthma and did not provide much information on asthmatic features (such as eosinophil count). Because of this, and because people with asthmatic features are likely to be covered by the recommendation for people taking LABA+ICS, the committee agreed not to make a specific recommendation for this group.

The committee did not make a recommendation in favour of single or multiple inhaler devices as the included evidence did not show a meaningful difference in clinical effectiveness between triple therapy compared to dual therapy based on the number of devices. From the economic evidence, using a single inhaler device was more cost effective, but the committee agreed that there were circumstances where using multiple inhalers could be better for the person with COPD. Finally, the committee had already made a recommendation about the factors to be taken into account when choosing an inhaler device and these included costs and minimising the numbers of inhalers where possible so an additional recommendation on this issue was unnecessary.

Impact of the recommendations on practice

The recommendations may result in an increase in the number of people who are prescribed triple therapy and an increase in the number of people who need treatment for pneumonia, although this may be mitigated by the relatively widespread current use of triple therapy. However, the criteria for who should be offered triple therapy and the recommendation for a trial period should limit the impact of both of these changes.

Triple therapy regimens have a higher cost than dual long-acting bronchodilator regimens. However, this cost is likely to be at least partially offset by savings from reduced numbers of exacerbations and better management of symptoms for people switching to triple therapy.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Exacerbations and quality of life were considered to be the most important outcomes. It was highlighted that a reduction in exacerbations, in particular severe exacerbations which require hospitalisation, is seen as the critical outcome by people with COPD. Quality of life was raised as an important indicator of the impact of COPD on the functional aspects of a person's daily life. Quality of life at 12 months was considered particularly important as this indicates whether the step-up to triple therapy provides long-term benefits. Pneumonia was highlighted as an important negative outcome as an increased risk of pneumonia could outweigh the benefits of triple therapy and have a detrimental impact on a person's life. However, it was highlighted that small increases in this risk are unlikely to outweigh more pronounced reductions in the risk of being hospitalised with an acute exacerbation of COPD.

Other outcomes, such as change in trough FEV1, were suggested to be less useful as an improvement in FEV1 alone is not necessarily enough to provide a noticeable difference to someone with COPD if it is not accompanied by changes in other outcomes such as exacerbations. The committee agreed that although dropouts due to adverse events provide an indication about the relative effectiveness of treatments, caution is needed as some of these could reflect study design and be the effects of the step-down in medication for some people who were taking triple therapy before being randomised to a dual therapy combination. For instance, of those randomised to LAMA/LABA in Ferguson (2018), 25% were using triple therapy prior to randomisation, while 32% of people randomised to LABA/ICS were previously using triple therapy. In Lipson (2018), 35% of people randomised to the LABA/LAMA and LABA/ICS groups were previously using triple therapy. Some studies did not provide full details of the breakdown of inhaled therapy treatments used prior to randomisation. The committee agreed that this step-down in medication may have resulted in withdrawal effects that were not relevant to their aim of evaluating the effects of a step-up to triple therapy.

The quality of the evidence

For comparisons between triple therapy and LAMA+LABA the evidence ranged from low- to high-quality and no studies were based in the UK. However, all studies were considered directly applicable to the review question and at low risk of bias. A greater number of studies compared the effects of triple therapy and LABA+ICS, with evidence ranging from very low- to high-quality. No studies were based in the UK, but all were directly applicable. The majority of studies were at moderate risk of bias due to limited information on allocation concealment and blinding of participants and outcomes. However, the low heterogeneity in the majority of the results indicated that the inclusion of these studies did not change the results for any of the outcomes. More detail on the risk of bias and applicability of each study is available in appendix E.

The committee raised concerns about the doses used in one of the LABA+ICS studies (Siler 2016). This study used a lower dose of fluticasone propionate and salmeterol in both treatment arms than would typically be prescribed to people with COPD in the UK. Although this dose was lower than what is most commonly prescribed, it is still taken by some people in the UK, leading to its inclusion in the review. There was concern that prescribing a lower dose of steroids may have resulted in fewer people developing pneumonia than might otherwise be seen in people who were prescribed the licensed dose, making the potential negative effects of triple therapy less apparent. The committee discussed whether recommendations based on these results could result in clinicians prescribing triple therapy but at the higher dosage, potentially resulting in a greater number of side-effects. However, heterogeneity was low in the majority of outcomes in which this study was included and so it

was decided that the study should remain part of the review as it did not skew the results to favour triple therapy unduly.

A key discussion point was the methods used in many of the studies. The committee noted that study design meant that some people who were previously taking LABA+ICS were randomised to LAMA+LABA, and some who were taking triple therapy were randomised to dual therapy. Both scenarios may have led to the studies detecting withdrawal effects from a person's step-down in medication rather than the effects of dual and triple therapy. The committee were particularly concerned about one of the studies (IMPACT trial, Lipson 2018), which included a large number of participants and had a high weighting in many of the outcomes for the meta-analysis. It was noted that 69% of people who were randomised to the LAMA+LABA arm of the trial were previously on medication that included an ICS component. This may have resulted in the study detecting a withdrawal effect from the removal of steroids from these people's medication. In addition, 34% of people randomised to triple therapy had already been prescribed triple therapy. It was suggested that this may have skewed the results towards favouring triple therapy, particularly during the first month of the study where the exacerbation rate was higher for dual therapy than triple therapy. However, the committee noted that the study reported a greater number of SGRQ responders at 12 months for triple therapy, indicating that there may be long-term benefits of triple therapy for outcomes other than exacerbations. These long-term benefits, alongside the low heterogeneity in results for the majority of outcomes in which this study was included, led the committee to include the study as part of the evidence review.

An additional issue was the combination of drugs used in some studies (TRIBUTE trial (Papi 2018), IMPACT trial (Lipson 2017)) where the drugs used in triple therapy were different to those used in dual therapy. It was suggested that the results of these studies may reflect the differences in the effects of individual drugs in addition to any differences between dual and triple therapy. The issue of appropriate wash-out and run-in periods to reduce the effects of changing medication was also raised. This was not clearly reported in some of the studies and it was suggested that these could have helped to reduce the withdrawal effects that the committee were concerned were being detected. However, the committee decided that despite these methodological issues, and those potentially associated with withdrawal effects, there was still strong enough evidence to make recommendations in relation to the use and potential benefits of triple therapy.

The committee considered the results from a number of subgroup analyses, with comparisons made between the effects of using either a single inhaler or multiple inhalers to deliver triple therapy. There were no detectable subgroup differences between single and multiple inhalers for comparisons with LAMA+LABA and only one outcome (change in trough FEV1 at 3 months) showed a difference for comparisons with LABA+ICS. This evidence, favouring triple therapy over LABA+ICS for both single and multiple inhalers was low- to moderate-quality with only one study evaluating the effects of using a single inhaler compared to several studies with multiple inhalers. The committee, agreed that the difference in change in trough FEV1 alone, in the absence of effects on other key outcomes such as exacerbations, was insufficient to allow any specific recommendations on how triple therapy should be delivered.

Additional subgroup comparisons were made between people who had an exacerbation in the 12 months prior to the study and those who had not had any exacerbations in the previous 12 months or where exacerbations were not part of the inclusion criteria. However, a number of studies did not report detailed information on exacerbation history and it is possible that some of these may have included people who had prior exacerbations and should therefore have been in the other subgroup.

The committee were also interested in whether the medication that a person was taking prior to being prescribed triple therapy has an impact on the effects of triple therapy. However, although two studies (Cazzola 2007, Sousa 2016) only included people who had previously

been taking LABA+ICS, other studies either did not report the medication that people were taking prior to the study or included people who were taking any combination of mono, dual or triple therapy. This made it difficult to separate the studies into meaningful subgroups to help the committee make further recommendations based on the type of dual therapy taken currently.

Benefits and harms

This update is linked to the 2018 inhaled combination therapy review (evidence review F) which considered which long-acting therapies were most beneficial for people with COPD when short-acting therapy ceased to be sufficient to manage their symptoms. The 2018 update recommends that people with COPD who do not have asthmatic features/features suggesting steroid responsiveness[d] are offered LAMA+LABA. It also recognises that steroids are an important component of treatment for people with COPD who have asthma and so recommends LABA+ICS for people with both COPD and asthmatic features. It recommends that the choice of medication should be based on the trade-off between how much they improve symptoms and reduce exacerbations against the potential side-effects. The current review had a similar aim, but for people with more severe COPD who still experience symptoms despite being prescribed dual therapy. Given that both LAMA+LABA and LABA+ICS were recommended for use in the 2018 update, the current update aimed to determine whether people who are currently prescribed either of these medications should be offered triple therapy. However, the committee noted that there were limitations in the available evidence as few studies examined the effects of triple therapy for people who were previously taking either LAMA+LABA or LABA+ICS. Instead the majority of studies included people with COPD who were taking any combination of mono, dual or triple therapy. This made it difficult to make direct recommendations on the effectiveness of triple therapy for people currently taking either LAMA+LABA or LABA+ICS. Instead, the committee had to use the evidence to infer which treatment options may be best for people with COPD who are taking dual therapy, but still experiencing symptoms.

Based on the available evidence, the committee agreed that there were clear benefits for the use of triple therapy over LABA+ICS, in particular a reduction in the rate of severe exacerbations per patient per year and improvements in FEV1. There was also a reduction in the number of people experiencing moderate to severe exacerbations, and an increase in the numbers of SGRQ responders at 6 and 12 months, but these values were less than the defined individual minimal clinically important differences. In addition, there was no detectable difference in the number of people experiencing pneumonia between the 2 groups. A reduction in the number of severe exacerbations may help to improve a person's quality of life by reducing the number of hospitalisations and use of rescue packs of antibiotics and/or corticosteroids that people might otherwise need if their COPD were less well controlled on dual therapy. Taking these results and those from the economic model into account, the committee decided to recommend that triple therapy be offered to people with severe COPD who were taking LABA+ICS, but with a number of caveats. The committee envisaged that if people taking LABA+ICS currently had their symptoms controlled by this medication then it was unnecessary for them to switch to triple therapy. However, if their symptoms proved limiting (i.e. stopped them from having a reasonable quality of life) or they were having frequent or severe exacerbations, then the committee agreed that these people could benefit from triple therapy and it would be appropriate for these people to switch to this medication. They decided to set the exacerbation requirement as 1 severe (requiring hospitalisation) or 2 moderate based on their clinical experience and the inclusion criteria reported in the studies, the most common of which was one severe or two moderate exacerbations in the previous year.

[d] This includes any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).

The committee commented that it was not unexpected that there was no detectable difference in the number of people experiencing pneumonia between the people offered triple therapy compared to LABA+ICS (risk ratio 0.83 (0.69, 1.01), where values greater than 1 favour triple therapy). This was because the increased risk of pneumonia was associated with the use of ICS and the people using LABA+ICS were already exposed to this risk. They also noted that the addition of a LAMA to LABA+ICS to give triple therapy was also expected to be beneficial for people with severe COPD based on the findings of the inhaled therapy combinations review in the 2018 update. This review examined the clinical and cost effectiveness of dual versus monotherapy and found that LAMA+LABA was the most effective option for people with COPD. However, the committee recommended that people with asthmatic features/features suggesting steroid responsiveness[e] follow a different pathway that involved LABA+ICS instead as they agreed that it was inappropriate not to treat these people with ICS. They also amended a 2010 triple therapy recommendation, which referred to the conditions that needed to be met before people who were already taking LABA+ICS could move to triple therapy, by including a reference to asthmatic features/features suggesting steroid responsiveness to link this recommendation to the new treatment pathway.

In the current update, the committee looked for evidence in the included trials to help them improve the definition of the population of people who would benefit from moving to triple therapy. However, the trials excluded people with a current diagnosis of asthma and provided limited information on other asthmatic features such as eosinophil count. As a result, the committee felt that there was insufficient evidence to make recommendations with a specific reference to asthmatic features and therefore removed asthmatic features/features suggesting steroid responsiveness from the recommendation to step up to triple therapy from LABA+ ICS.

The committee also discussed the evidence for the clinical and cost effectiveness of triple therapy compared to LAMA+LABA. Triple therapy resulted in a reduction in dropouts due to severe adverse events in comparison to LAMA+LABA. It also resulted in a reduction in the rate of severe exacerbations per person per year and an increase in SGRQ responders at 12 months, but these values were less than the defined individual minimal clinically important differences. However, the committee noted that the minimal clinically important differences used for these outcomes were based on default statistical values of 0.8 for the lower limit and 1.25 for the upper limit, which correspond to a 20% decrease or a 25% increase in rates of events or the risk of an event, depending on the way an outcome was measured. The committee agreed that for some outcomes, such as exacerbations, a reduction in the risk or rate of exacerbations that was below the MID of 20% might be clinically meaningful, particularly if it was associated with improvements across multiple outcomes. This was in keeping with their approach to the interpretation of the results of the network meta-analyses in the inhaled combination therapy review from the 2018 update of this guideline. The committee also noted the advantage of using an economic model to synthesise the different levels of benefits and harms across multiple outcomes.

Although triple therapy showed some benefits over LAMA+LABA, there was also evidence of a potential harm, with an increased risk of pneumonia with the use of triple therapy (risk ratio 0.65 (0.50, 0.84) for triple therapy compared to LAMA+LABA, where values greater than 1 favour triple therapy). However, the committee noted that although there was an increase in pneumonia with triple therapy, there were no meaningful differences between the two treatments for serious adverse events, suggesting that the increased cases of pneumonia may not have been severe and need to be weighed against the occurrence of other adverse events, most obviously hospitalisation with severe acute COPD exacerbations. It was however raised that some of the doses that will be prescribed to people may be higher than those used in some of the studies or involve more potent formulations of ICS (namely

[e] This includes any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV1 over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).

fluticasone proprionate and fluticasone furoate), potentially further increasing the risk of pneumonia. The committee therefore agreed that the increased risk of pneumonia due to the addition of ICS, particularly in comparison to LAMA+LABA, is something that should be discussed with patients who are offered triple therapy. They noted that the increased risk of pneumonia was mentioned in an existing recommendation (1.2.9) in the 2018 update.

Although there was less evidence available to compare the effects of triple therapy and LAMA+LABA the committee still felt that the results, particularly the reduction in severe exacerbations, were important enough to include a recommendation in favour of its use for people with COPD who continue to experience severe symptoms despite being prescribed LAMA+LABA. It was therefore agreed that the use of triple therapy should be considered for people taking LAMA+LABA who continue to have severe or frequent exacerbations because, for this group of people, the potential harm of pneumonia is outweighed by the potential benefits.

The committee's main concern about people being stepped up from LAMA+LABA to triple therapy was that the benefits may not outweigh the harms for people who have less severe symptoms. There was also a suggestion that recommendations to use triple therapy may lead to over-medication, with people being prescribed triple therapy who may otherwise have experienced the same benefits using dual therapy. However, although Ferguson (2018) did not report recent exacerbations as part of the inclusion criteria and did not detect an effect on the rate of moderate to severe exacerbations, they did report improvements in quality of life at 6 months. This suggests that there may still be some benefits in the use of triple therapy for people with less severe COPD symptoms. The committee therefore agreed on an additional recommendation which indicates that people who are currently prescribed LAMA+LABA and do not meet the exacerbation criteria, but continue to have less severe, uncontrolled, symptoms should initially be considered for a 3 month trial period of triple therapy. They envisaged that this would provide clinicians with an opportunity to see if there is a benefit from the step-up in medication as well as monitoring any potential side-effects. If there are any adverse effects or no clear benefits then the recommendation supports a return to dual therapy, avoiding any long-term harms and reducing the risk of over-medication. The committee also expected that anyone who is prescribed triple therapy on a long-term basis would have regular reviews of their medication to ensure it is still beneficial, as highlighted in recommendation 1.2.134 and Table 6 (Summary of follow-up of people with COPD in primary care) in the 2018 COPD guideline. Given the potential harm of pneumonia and the smaller evidence base available to support the benefits of triple therapy for this group of people with less severe symptoms, the committee made a weak recommendation for a step up to triple therapy.

The committee discussed the use of single versus multiple inhalers to deliver triple therapy. They noted that although the results of the economic model suggested that single inhaler triple therapy was more cost-effective than using multiple inhaler devices (see discussion in the cost effectiveness and resource section below), subgroup analyses of the clinical data did not detect a difference in effectiveness between these groups. In addition, this review specifically did not include trials that only compared different types of device (i.e. triple therapy versus triple therapy). The committee also agreed that, when making the step-up to triple therapy, it may be preferable to start with multiple inhalers by adding the extra inhaler to a person's current treatment, making it easier for a person to return to their previous dual therapy combination if they fail to experience any benefits or if they experience any serious side effects. The committee therefore decided against making a specific recommendation for the use of single inhaler triple therapy. Although their recommendations did not specifically make reference to the cost-effectiveness of single inhaler triple therapy, the choice of inhaler is covered by recommendation 1.2.17 in the 2018 COPD guideline and this recommendation takes into account issues such as cost and minimising inhaler number.

The committee noted that the included studies had high levels of current smokers (average of 40%, but as high as 93.3% in 1 study) and that large numbers of people in the UK with

severe COPD still smoke. They stressed the importance of continuing to treat tobacco dependence in people with all levels of severity of COPD to improve their quality of life. They also noted that the conditions listed in the recommendations for dual therapy (offering treatment for tobacco dependence if they smoke and optimised non-pharmacological management (including pulmonary rehabilitation) and relevant vaccinations) were still relevant for people with severe COPD. The committee did not restate these conditions as they expected that, based on the treatment pathway outline in the guideline, people would transition to triple therapy from dual therapy and thus already have had these discussions with healthcare professionals. However, they stressed the continuing importance of offering these interventions, and in particular treatment for tobacco dependence, at multiple points in the pathway. This is made clear by the algorithm, which places these treatment options alongside the pathway for inhaled therapy.

Cost effectiveness and resource use

The committee were presented with economic evidence on the cost effectiveness of triple therapy, both from the *de novo* economic model developed for this guideline, and from the existing literature. The committee prioritised the evidence from the original model, since the 1 study identified by the economic literature review was considered to be only partially applicable, and had potentially serious limitations.

The committee considered the evidence from the de novo model and noted that, in the base case, triple therapy is highly cost effective compared to LABA+ICS (ICER of £881 per QALY). Probabilistic sensitivity analysis and scenario analyses also demonstrated that this result is highly robust. The committee noted that this finding is logical, given that results of the clinical evidence review show that triple therapy has favourable treatment effects versus LABA+ICS across a number of outcomes. It was also noted that, while the acquisition cost of triple therapy is higher than that of LABA+ICS, the incremental cost is relatively minor in relation to the magnitude of health benefits. In addition, this cost is partially offset by reduced numbers of exacerbations. For this reason, the committee were confident in making a strong recommendation for triple therapy in patients who are limited by symptoms or continue to exacerbate despite treatment with LABA+ICS.

The committee observed that the economic model also shows that triple therapy is cost effective compared with LAMA+LABA in the base case (ICER of £5,182), and probabilistic sensitivity analysis shows that triple therapy has a relatively high probability (89.6%) of being cost effective at a threshold of £20,000 per QALY. However, it was also noted that triple therapy has both a higher ICER and a lower probability of being cost effective compared with LAMA+LABA than compared with LABA+ICS, due to clinical benefits of triple therapy versus LAMA+LABA being less pronounced and more uncertain. The committee observed that this finding is consistent with previous evidence on the relative effectiveness of mono and dual long-acting bronchodilator regimens: adding in a LAMA generally produces more clinical benefit than adding an ICS. The majority of scenario analyses showed that triple therapy remains cost effective compared to LAMA+LABA. However, when the assumption is made that triple therapy is delivered as 2 separate devices, the ICER rises to £22,313 per QALY. The committee noted that this is due to the higher acquisition cost of providing triple therapy as 2 inhalers, rather than as 1 combination inhaler.

Based on this evidence, the committee felt confident in making a recommendation in favour of triple therapy for patients whose symptoms are not adequately managed by LAMA+LABA. However, they also determined that the threshold for prescribing triple therapy should be higher for patients treated with a LAMA+LABA than for patients treated with a LABA+ICS, for a number of reasons. First, the evidence shows that addition of an ICS produces less clinical benefit than addition of a LAMA for patients on dual therapy. Second, ICS is associated with an increased incidence of pneumonia, the disbenefit of which must be balanced against the benefits of treatment. Third, the committee felt that patients do not have a uniform capacity to benefit from ICS; some patients may respond better than others to treatment. Therefore, the

committee opted to recommend that patients with 1 severe or 2 moderate exacerbations per year while treated with a LAMA+LABA should be offered triple therapy, and that a trial of triple therapy should be considered in patients whose symptoms continue to interfere with daily living while on a LAMA+LABA.

Since results of the economic model showed that triple therapy is less cost effective when provided as 2 devices, the committee considered the appropriateness of explicitly recommending that triple therapy should be provided as a single combination inhaler. They determined that such a recommendation would be unnecessary, as the existing guideline already states that the number of inhalers should be minimised for all inhaled therapies. Furthermore, the committee indicated that it may be appropriate in some instances to provide an initial trial of triple therapy as 2 inhalers for patients stepping up from dual therapy, so that they can easily revert to their original treatment if triple therapy is not tolerated.

The committee discussed the resource impact of their recommendations. They determined that the number of patients treated with triple therapy may increase as a result, and therefore the recommendations may produce an increase in spending (although this is likely to be mitigated by widespread current use of triple therapy). However, the committee were confident in their recommendations, given the robust economic and clinical evidence supporting them. Furthermore, the additional spend may be (at least partially) offset by savings from prevented exacerbations and better management of symptoms.

Other factors the committee took into account

In addition, the committee agreed that, although there is emerging evidence on eosinophils and their role in COPD, currently it is unclear whether they should be used to initiate triple therapy or what the cut off level should be and they noted that it was important not to rely on eosinophil counts to make decisions on predicting response to therapy.

Appendices

Appendix A – Review protocols

Review protocol for inhaled triple therapy

Field (based on PRISMA-P)	Content
Review question	In people with stable COPD, what is the clinical and cost effectiveness of a LAMA plus a LABA plus ICS compared with: • a LABA plus an inhaled corticosteroid (ICS) • a LAMA plus LABA?
Type of review question	Intervention
Objective of the review	To determine the comparative effectiveness of different drug classes for managing stable COPD
Eligibility criteria – population	People diagnosed with COPD Inclusion criteria from Cochrane Review: • Patients aged > 35 years • Diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society (ATS/ERS 2004), GOLD report (GOLD 2017) or equivalent criteria. • Obstructive ventilator defect should be at least moderate, with a baseline FEV1 less than 80% of predicted.
Eligibility criteria – interventions	• LAMA+LABA+ICS
Eligibility criteria – comparators	• LAMA + LABA • LABA + ICS Trials looking at LAMA+LABA versus LABA+ICS may be included to increase network strength if fewer than 3 trials are

	found for either comparison. In this case, only those trials with similarly severe populations of people as the triple therapy trials will be included.
Outcomes	• COPD exacerbation (moderate to severe and severe) • St George's Respiratory Questionnaire (SGRQ) score and decrease in SGRQ score ≥ 4 units (responder) • Transition Dyspnoea Index (TDI) • Mortality • Total serious adverse events (SAEs) • Cardiac and COPD SAEs • Dropout due to adverse event • Trough FEV1 • Pneumonia • Fractures (with degree of harm) • Exercise capacity • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other inclusion exclusion criteria	• Trials with a follow-up of less than 12 weeks

Proposed sensitivity/sub-group analysis	Subgroups:
	• asthmatic features/features suggesting steroid responsiveness or no asthmatic features/features suggesting steroid responsiveness including
	  ○ eosinophil count
	  ○ variation in peak flow
	  ○ FEV1 variability
	  ○ asthma/atopy
	• previous exacerbation history (exacerbation within the last 12 months or no exacerbation within the last 12 months/ not stated)
	• smoking status (current vs ex-smokers)
	• single inhalers used in combination for triple therapy versus single combined inhaler

	• pulmonary rehabilitation completion status (completed versus not completed/ not eligible) • multimorbidities (including COPD with asthma, bronchopulmonary dysplasia, bronchiectasis, anxiety or depression)
Selection process – duplicate screening/selection/ analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C
Identify if an update	Update of 2010 COPD guideline questions: What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus inhaled corticosteroids in the management of people with stable COPD? What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus long-acting muscarinic antagonists in the management of people with stable COPD?
Author contacts	Guideline update

Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Andrew Molyneux in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where

	appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

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Appendix B – Methods

Evidence synthesis and meta-analyses of pair-wise data

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where

the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence was identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 12. For other mean differences where no MID is given below the line of no effect is used.

Table 12: Identified MIDs

Outcome	MID	Source
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.
Change in Transition Dyspnoea Index (TDI)	1 point (-1, +1)	Witek TJ, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. The European respiratory journal 2003; 21:267-272.
Change in FEV1	100ml (-100, +100)	Cazzola M, MacNee W, Martinez M et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.

The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. For relative risks where no other MID was available, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. Incidence rate ratios were treated in the same way as relative risks, with a default MID interval of 0.8 and 1.25 used for analysis.

In cases where the point estimate of effect fell on an MID boundary, it was taken as being within the MID and therefore not being a clinically meaningful effect. If the 95% CI of the point estimate fell on either or both of the MID boundaries it was taken as being within/inside the MID.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 13

Table 13: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (1 corresponding to meaningful benefit; 1 corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- We state the evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology 'up to' in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 14.

Table 14 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 15.

Table 15 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Clinical literature search

What is the clinical effectiveness of triple therapy for COPD (LAMA+LABA+ICS)?

Sources searched to identify the clinical evidence:

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	5th Sept 2018	Issue 8 of 12, August 2018	714
Embase (Ovid)	28th Aug 2018	Embase <1974 to 2018 Week 35>	1934
MEDLINE (Ovid)	28th Aug 18	Ovid MEDLINE(R) ALL <1946 to August 27, 2018>	664
MEDLINE In-Process (Ovid)	28th Aug 18	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 27, 2018>	52
MEDLINE Epub Ahead of Print[f]	28th Aug 18	Ovid MEDLINE(R) Epub Ahead of Print <August 27, 2018>	14
MHRA – Drug Safety Alerts [2]	30th Aug 18		0

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked. A Randomised Controlled Trial filter was used to identify the study design specified in the Review Protocol.

1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.

[f] Please search for both development and re-run searches

9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 Muscarinic Antagonists/
14 Parasympatholytics/
15 Cholinergic Antagonists/
16 (muscarinic* or antimuscarinic* or anti-muscarinic* or cholinergic* or anticholinergic* or anti-cholinergic* or parasympatholy*).tw.
17 (lama or lamas).tw.
18 Tiotropium Bromide/
19 tiotropium*.tw.
20 tiova*.tw.
21 spiriva*.tw.
22 braltus*.tw.
23 Glycopyrrolate/
24 glycopyr*.tw.
25 glicopir*.tw.
26 seebri*.tw.
27 umeclidinium*.tw.
28 incruse*.tw.
29 aclidinium*.tw.
30 eklira*.tw.
31 or/13-30
32 Adrenergic beta-2 Receptor Agonists/
33 (beta* adj5 (receptor* or agonist*)).tw.
34 (beta2 or beta-2 or "beta* 2" or B2 or B-2 or "B 2").tw.
35 (laba or labas).tw.
36 Formoterol Fumarate/
37 formoterol*.tw.
38 foradil*.tw.
39 oxis*.tw.
40 Salmeterol Xinafoate/
41 salmeterol*.tw.
42 serevent*.tw.
43 indacaterol*.tw.
44 onbrez*.tw.
45 olodaterol*.tw.
46 striverdi*.tw.
47 vilanterol*.tw.
48 or/32-47
49 Glucocorticoids/
50 (steroid* or corticosteroid* or cortico-steroid* or glucocortico* or gluco-cortico*).tw.
51 ics.tw.
52 Budesonide/
53 budesonide*.tw.
54 pulmicort*.tw.
55 budelin*.tw.
56 Fluticasone/
57 fluticasone*.tw.
58 flixotide*.tw.
59 Beclomethasone/
60 (beclomethasone* or beclometasone*).tw.
61 exp Mometasone Furoate/

62 mometasone*.tw.
63 asmanex*.tw.
64 ciclesonide*.tw.
65 alvesco*.tw.
66 or/49-65
67 31 and 48 and 66
68 12 and 67
69 ((triple* or three) adj5 (therap* or treat* or combin* or inhal* or drug*)).tw.
70 (3-in-1 or "3 in 1").tw.
71 trelegy*.tw.
72 trimbow*.tw.
73 or/69-72
74 12 and 73
75 68 or 74
76 Randomized Controlled Trial.pt.
77 Controlled Clinical Trial.pt.
78 Clinical Trial.pt.
79 exp Clinical Trials as Topic/
80 Placebos/
81 Random Allocation/
82 Double-Blind Method/
83 Single-Blind Method/
84 Cross-Over Studies/
85 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
86 (random$ adj3 allocat$).tw.
87 placebo$.tw.
88 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
89 (crossover$ or (cross adj over$)).tw.
90 or/76-89
91 animals/ not humans/
92 90 not 91
93 75 and 92
94 limit 93 to english language

Health economic literature search

Economic evaluations and quality of life data

Sources searched to identify economic evaluations:

Economics	Date searched
MEDLINE (Ovid)	29th Aug 2018
MEDLINE in Process (Ovid)	29th Aug 2018
Embase (Ovid)	29th Aug 2018
EconLit (Ovid)	29th Aug 2018

Search filters to retrieve economic evaluations and quality of life papers were appended to the search strategy to identify relevant evidence. The MEDLINE economic evaluations and

quality of life search filters are presented below. They were translated for use in MEDLINE in Process and Embase databases.

Economic evaluations

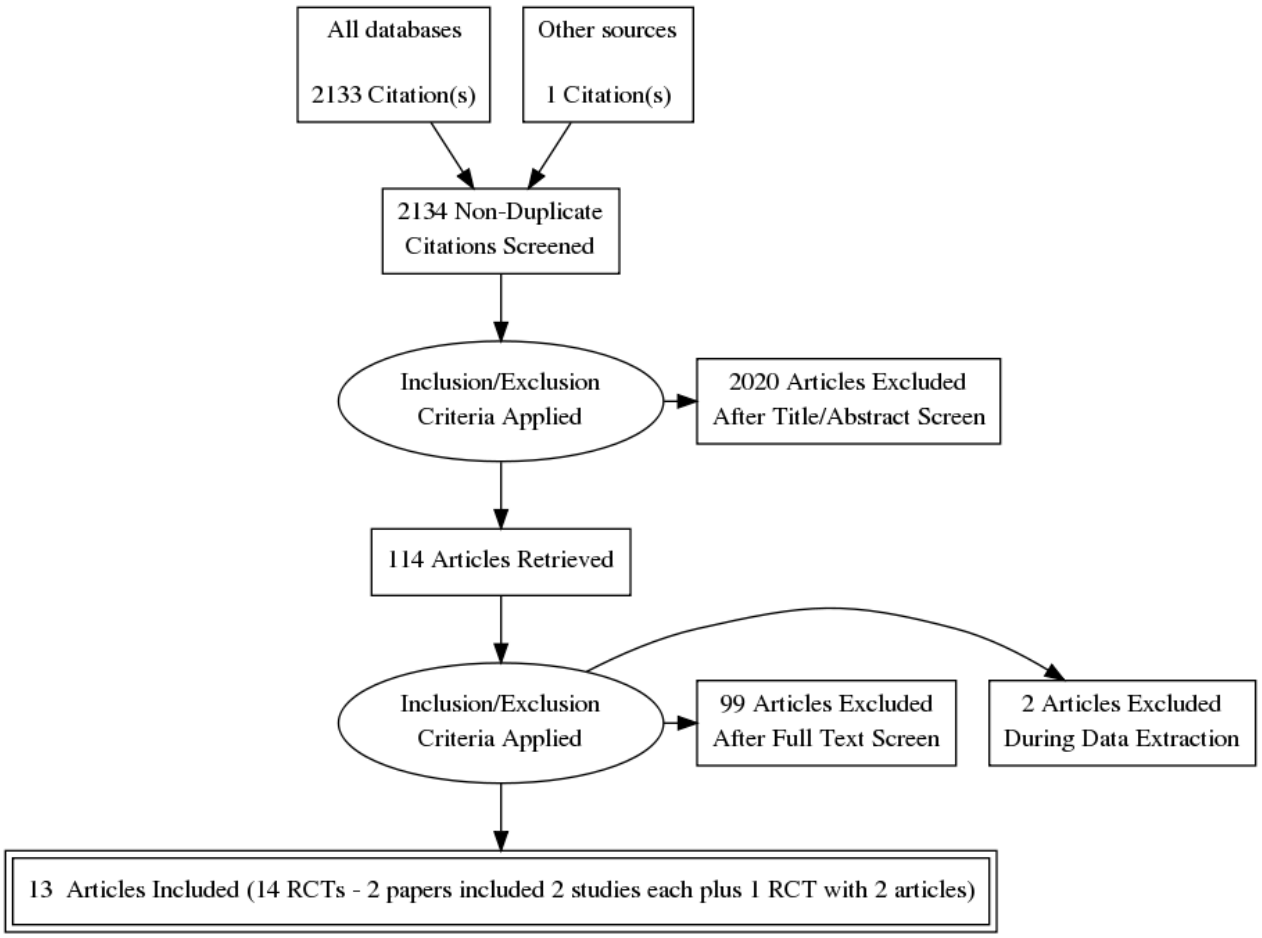
1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25

Quality of Life

1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.

18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

Appendix D – Clinical evidence study selection



1 # Appendix E – Clinical evidence tables

Short Title	Title	Study characteristics	Risk of bias and directness
Aaron 2007	Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease	**Study type** Randomised controlled trial **Study details** Study location *Canada* Study setting *Multi-centre study* Study dates *October 2003 - January 2006* Duration of follow-up *52 weeks* Sources of funding *Canadian Institutes of Health Research The Ontario Thoracic Society* **Inclusion criteria** Age *>35* Current or ex-smokers *History of 10+ pack-years of smoking* FEV1 *<65%* Recent moderate/severe exacerbation *At least 1 in past 12 months* **Exclusion criteria** Asthma diagnosis *Before 40 years of age* Women who are pregnant or planning on becoming pregnant *Pregnant or breastfeeding*	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low

Short Title	Title	Study characteristics	Risk of bias and directness
		Chronic congestive heart failure Previous lung transplantation or lung resection **Sample characteristics** Sample size *449* Split between study groups *Triple: 145 Dual: 148 Mono: 156* Loss to follow-up *Triple: 2 Dual: 2* %female *Triple: 42.1% Dual: 42.6%* Mean age (SD) *Triple: 67.5 (8.9) Dual: 67.6 (8.2)* Current smoker (%) *Dual: 24.3% Triple: 32.4%* FEV1 (mean, SD) *Prebronchodilator Dual: 1.00 (0.44) Triple: 1.05 (0.38)* *Postbronchodilator Dual: 1.08 (0.43) Triple: 1.12 (0.41)* **Interventions** Dual therapy *LAMA+LABA: Tiotropium/Salmeterol* *Tiotropium 18 ug, once daily* *Salmeterol 25 ug two puffs, twice daily* Triple therapy *Tiotropium/Fluticasone-Salmeterol* *Tiotropium 18 ug, once daily* *Fluticasone 250 ug + Salmeterol 25 ug, two puffs, twice daily*	**Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Outcome measure(s) Moderate to severe exacerbations during follow-up SGRQ score - *SD not provided so data was not extractable* Serious adverse events Pneumonia TDI Severe exacerbation Mortality Dropout due to SAEs Cardiac SAEs COPD SAEs	
Cazzola (2007)	A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD.	**Study type** Randomised controlled trial **Study details** Study location *Italy* Duration of follow-up *12 weeks* Sources of funding *None reported* **Inclusion criteria** Age *>50* Current or ex-smokers *History of 20+ pack-years of smoking* FEV1:FVC <0.7 FEV1	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Unclear risk of bias *Insufficient information provided* **Blinding of outcome assessment**

Short Title	Title	Study characteristics	Risk of bias and directness
		<50% **Exclusion criteria** Asthma diagnosis Unstable respiratory disease *Requiring corticosteroids up to 4 weeks before screening* Alcohol abuse **Sample characteristics** Sample size *81* Split between study groups *Triple: 29 Dual: 26* %female *Triple: 13% Dual: 13%* Mean age (SD) *Triple: 66.9 (59.0-74.8) Dual: 64.4 (58.8-70)* Current smoker (%) *Triple: 80.0% Dual: 93.3%* **Interventions** Dual therapy *LABA+ICS (Fluticasone-Salmeterol)* *Fluticasone propionate 500 ug + Salmeterol 50 ug, twice daily* Triple therapy *Tiotropium/Fluticasone-Salmeterol* *Fluticasone propionate 500 ug + Salmeterol 50 ug, twice daily* *Tiotropium 18 ug, once daily* **Outcome measure(s)** Trough FEV1	Unclear risk of bias *Insufficient information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Insufficient information provided for allocation concealment and blinding of participants and outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
Ferguson (2018)	Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial.	**Study type** Randomised controlled trial **Study details** Study location *Canada, China, Japan and USA* Study setting *Multi-centre study* Study dates *August 2015 - January 2018* Duration of follow-up *24 weeks* Sources of funding *Pearl* **Inclusion criteria** Age *40-80* Current or ex-smokers *History of 10+ pack-years of smoking* FEV1 *25% - 80%* Clinical history of COPD as defined by ATS guidelines **Exclusion criteria** Asthma diagnosis Recent exacerbation *In 6 weeks before screening* Hospitalisation for COPD or pneumonia within 12 weeks of study Use of LTOT *>15 hours per day*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Unclear risk of bias *Funding source had role in study design, data collection, data analysis*

Short Title	Title	Study characteristics	Risk of bias and directness
		Any respiratory disease other than asthma **Sample characteristics** Sample size *1902* Split between study groups *Triple: 640 Dual (LAMA+LABA): 627 Dual (LABA+ICS): 316 Open-label dual: 319* Loss to follow-up *Triple: 10 Dual (LAMA+LABA): 2 Dual (LABA+ICS): 0* %female *Triple: 28% Dual (LAMA+LABA): 31.2% Dual (LABA+ICS): 28.7%* Mean age (SD) *Triple: 64.9 (7.8) Dual (LAMA+LABA): 65.1 (7.7) Dual (LABA+ICS): 65.2 (7.2)* Current smoker (%) *Triple: 40.1% Dual (LAMA+LABA): 41.1% Dual (LABA+ICS): 36.6%* **Interventions** Dual therapy *LAMA+LABA: Glycopyrrolate 18 ug + Formoterol fumarate 9.6 ug* *LABA+ICS: Budesonide 320 ug + Formoterol fumarate 9.6 ug* Triple therapy *Budesonide 320 ug + Glycopyrronium 14.4 ug + Formoterol fumarate 10 ug* **Outcome measure(s)** Moderate to severe exacerbations during follow-up SGRQ score Serious adverse events Pneumonia TDI Trough FEV1	*and write-up* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Mortality Dropout due to SAEs Cardiac SAEs	
Frith (2015)	Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial.	**Study type** Randomised controlled trial **Study details** Study location *Australia and New Zealand* Study setting *Multicentre study* Study dates *April 2012 - September 2013* Duration of follow-up *12 weeks* Sources of funding *Novartis Pharmaceuticals Australia Pty Limited.* **Inclusion criteria** Age *>40* COPD diagnosis *Moderate to severe stable COPD* FEV1:FVC <0.7 FEV1 *>30% and <80%* **Exclusion criteria** Asthma diagnosis Recent exacerbation	**Random sequence generation** Unclear risk of bias *Insufficient information provided* **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Unclear risk of bias *Insufficient information provided* **Blinding of outcome assessment** Unclear risk of bias *Insufficient information provided* **Incomplete outcome data**

Short Title	Title	Study characteristics	Risk of bias and directness
		In 6 weeks before screening **Sample characteristics** Sample size *773* Split between study groups *Triple (Glycopyrronium): 258 Triple (Tiotropium): 258 Dual: 257* Loss to follow-up *Triple (Glycopyrronium): 0 Triple (Tiotropium): 0 Dual: 2* %female *Triple (Glycopyrronium): 36.6% Triple (Tiotropium): 38% Dual: 32.3%* Mean age (SD) *Triple (Glycopyrronium): 68.2 (8.38) Triple (Tiotropium): 68.0 (7.74) Dual: 67.8 (8.49)* Current smoker (%) *Triple (Glycopyrronium): 35.4% Triple (Tiotropium): 35.7% Dual: 36.2%* Ex-smoker (%) *Triple (Glycopyrronium): 64.6% Triple (Tiotropium): 64.3% Dual: 63.8%* FEV1 (mean, SD) *Triple (Glycopyrronium): 1.52 (0.50) Triple (Tiotropium): 1.49 (0.47) Dual: 1.55 (0.48)* **Interventions** Dual therapy *LABA+ICS: Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily* Triple therapy *Triple 1: Glycopyrronium 50 ug once daily* *Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily* *Triple 2: Tiotropium 18 ug, once daily* *Salmeterol 50 ug + Fluticasone propionate 500 ug, twice daily*	Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Insufficient information provided for random sequence generation, allocation concealment and blinding of participants and outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Outcome measure(s) Serious adverse events Pneumonia Trough FEV1 Mortality Dropout due to SAEs Cardiac SAEs COPD SAEs	
Hoshino (2013)	Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease.	**Study type** Randomised controlled trial **Study details** Study location *Japan* Duration of follow-up *16 weeks* **Inclusion criteria** Age *>40* Current or ex-smokers *History of 10+ pack-years of smoking* COPD diagnosis FEV1:FVC <0.7 FEV1 *<70%* **Exclusion criteria** Asthma diagnosis	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Unclear risk of bias *Insufficient information provided* **Blinding of outcome assessment** Unclear risk of bias *Insufficient information*

Short Title	Title	Study characteristics	Risk of bias and directness
		Clinically significant medical disorder other than COPD **Sample characteristics** Sample size *68* Split between study groups *Triple: 15 Dual: 16 Mono 1: 15 Mono 2: 14* %female *Triple: 13% Dual: 20%* Mean age (SD) *Triple: 73 (7) Dual: 67 (8)* FEV1 (mean, SD) *Triple: 1.38 (0.56) Dual: 1.25 (0.38)* **Interventions** Dual therapy *LABA+ICS: Salmeterol 50 ug + Fluticasone propionate 250 ug, twice daily* Triple therapy *Tiotropium 18 ug once daily* *Salmeterol 50 ug + Fluticasone propionate 250 ug, twice daily* **Outcome measure(s)** SGRQ score	*provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Insufficient information provided for allocation concealment and blinding of participants, personnel and outcomes data* **Directness** Directly applicable
Lipson (2017)	FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease.	**Data extraction (intervention)** Associated studies (qualitative outcomes) *Tabberer,M, Lomas,D A., Birk,R., et al. (2018) Once-Daily Triple Therapy in Patients with COPD: Patient-Reported Symptoms and Quality of Life*	**Random sequence generation** Unclear risk of bias *Insufficient information provided*

Short Title	Title	Study characteristics	Risk of bias and directness
		Study type Randomised controlled trial **Study details** Study location *International* Study setting *Multi-centre study* Study dates *January 2015 - April 2016* Duration of follow-up *24 weeks (52 weeks for extension population)* Sources of funding *GlaxoSmithKline* FULFIL Trial **Inclusion criteria** Age *>40* FEV1 *<50%* Recent moderate/severe exacerbation *Either minimum of 2 moderate exacerbations or at least 1 severe exacerbation in past 12 months* COPD Assessment Test score of at least 10 Using monotherapy or dual therapy before screening *Minimum 3 months before* **Exclusion criteria** Asthma diagnosis Recent exacerbation	**Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *Insufficient information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Insufficient information provided for random*

Short Title	Title	Study characteristics	Risk of bias and directness
		Severe exacerbation at time of screening Pneumonia **Sample characteristics** Sample size *1811 (extension population 430)* Split between study groups *Triple: 911 Dual: 899 Extension population triple: 210 Extension population dual: 220* %female *Triple: 26% Dual: 26% Extension population triple: 25% Extension population dual: 26%* Mean age (SD) *Triple: 64.2 (8.56) Dual: 63.7 (8.71) Extension population triple: 63.7 (7.76) Extension population dual: 63.3 (8.43)* Current smoker (%) *Triple: 44% Dual: 44%* **Interventions** Dual therapy *LABA+ICS: Budesonide 400 ug + formoterol 12 ug, twice daily* Triple therapy *Fluticasone furoate 100 ug + Umeclindinium 62.5 ug + Vilanterol 25 ug, once daily* **Outcome measure(s)** Moderate to severe exacerbations during follow-up Decrease in SGRQ score >4 points Serious adverse events Pneumonia TDI	*sequence generation, allocation concealment and blinding of outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Trough FEV1	
Lipson (2018)	Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.	**Study type** Randomised controlled trial **Study details** Study location *International* Study setting *1070 centres* Study dates *June 2014 - July 2017* Duration of follow-up *52 weeks* Sources of funding *GlaxoSmithKline* **Inclusion criteria** Age *>40* Current or ex-smokers FEV1 *<50%* Recent moderate/severe exacerbation *Two or more within previous year* Using monotherapy or dual therapy before screening *Minimum 3 months before* **Exclusion criteria** Asthma diagnosis *Requiring inhaled or oral corticosteroid therapy*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Women who are pregnant or planning on becoming pregnant Inpatients **Sample characteristics** Sample size *10335* Split between study groups *Dual (LAMA+LABA): 2070 Dual (LABA+ICS): 4134 Triple: 4151* %female *Dual (LAMA+LABA): 34% Dual (LABA+ICS): 34% Triple: 33%* Mean age (SD) *Dual (LAMA+LABA): 65.2 (8.3) Dual (LABA+ICS): 65.3 (8.3) Triple: 65.3 (8.2)* Ex-smoker (%) *Dual (LAMA+LABA): 65% Dual (LABA+ICS): 66% Triple: 65%* **Interventions** Dual therapy *LAMA+LABA: Umeclidinium 62.5 ug + Vilanterol trifenatate 25 ug* *LABA+ICS: Fluticasone furoate 100 ug + Vilanterol trifenatate 25 ug* Triple therapy *Fluticasone furoate 100 ug + Umeclidinium 62.5 ug + Vilanterol trifenatate 25 ug, once daily* **Outcome measure(s)** Moderate to severe exacerbations during follow-up SGRQ score Serious adverse events Pneumonia Trough FEV1 Severe exacerbation Mortality	**Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Dropout due to SAEs	
Papi (2018)	Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.	**Study type** Randomised controlled trial **Study details** Study location *Italy* Study setting *Multi-centre study* Study dates *May 2015 - July 2017* Duration of follow-up *52 weeks* Sources of funding *Chiesi Farmaceutici* **Inclusion criteria** Age *>40* Current or ex-smokers COPD diagnosis FEV1:FVC <0.7 FEV1 *<50%* Recent moderate/severe exacerbation *One or more within previous year* COPD Assessment Test score of at least 10 Using monotherapy or dual therapy before screening *Minimum 2 months before*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Exclusion criteria Asthma diagnosis *Requiring inhaled or oral corticosteroid therapy* Using triple therapy **Sample characteristics** Sample size *1532* Split between study groups *Dual: 768 Triple: 764* Loss to follow-up *Dual: 3 Triple: 4* %female *Dual: 28% Triple: 28%* Mean age (SD) *Dual: 64.5 (7.7) Triple: 64.4 (7.7)* Current smoker (%) *Dual: 43% Triple: 46%* Ex-smoker (%) *Dual: 57% Triple: 54%* FEV1 (mean, SD) *Dual: 1.07 (0.31) Triple: 1.07 (0.31)* **Interventions** Dual therapy *LAMA+LABA: Indacaterol 85 ug + Glycopyrronium 43 ug, once per day* Triple therapy *Beclometasone diproprionate 87 ug + Formoterol fumarate 5 ug + Glycopyrronium 9 ug, twice daily*	**Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Outcome measure(s) Moderate to severe exacerbations during follow-up Decrease in SGRQ score >4 points Serious adverse events Pneumonia	
Siler (2015)	Efficacy and Safety of Umeclidinium Added to Fluticasone Furoate/Vilanterol in Chronic Obstructive Pulmonary Disease: Results of Two Randomized Studies.	**Study type** Randomised controlled trial **Study details** Study location *Study 1: Argentina, Canada, Chile, Romania, USA Study 2: Czech Republic, Germany, Korea, USA* Study setting *Multi-centre study* Duration of follow-up *12 weeks* Sources of funding *GlaxoSmithKline* **Inclusion criteria** Age *>40* Current or ex-smokers *History of 10+ pack-years of smoking* FEV1:FVC <0.7 FEV1 *<70%* Clinical history of COPD as defined by ATS guidelines	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *Insufficient information provided* **Incomplete outcome data** Low risk of bias

Short Title	Title	Study characteristics	Risk of bias and directness
		Exclusion criteria Asthma diagnosis Hospitalisation for COPD or pneumonia within 12 weeks of study Any respiratory disease other than asthma **Sample characteristics** • Sample size *Study 1: 619 Study 2: 620* • Split between study groups *Study 1 Triple: 206 Study 1 Dual: 206 Study 2 Triple: 206 Study 2 Dual: 206* • Loss to follow-up *Study 1 Triple: 1 Study 1 Dual: 0* *Study 2 Triple: 0 Study 2 Dual: 2* • %female *Study 1 Triple: 33% Study 1 Dual: 32%* *Study 2 Triple: 33% Study 2 Dual: 39%* • Mean age (SD) *Study 1 Triple: 64.9 (8.72) Study 1 Dual: 64.7 (7.90)* *Study 2 Triple: 62.6 (8.12) Study 2 Dual: 62.6 (9.00)* • Current smoker (%) *Study 1 Triple: 39% Study 1 Dual: 44%* *Study 2 Triple: 58% Study 2 Dual: 58%* • FEV1 (mean, SD) *Study 1 Triple: 1.12 (0.45) Study 1 Dual: 1.16 (0.46)* *Study 2 Triple: 1.24 (0.44) Study 2 Dual: 1.29 (0.47)* **Interventions** Dual therapy *Both studies: LABA+ICS Fluticasone furoate 100 ug + Vilanterol 25 ug, once daily* Triple therapy *Both studies: Umeclidinium 62.5 ug, once daily* *Fluticasone furoate 100 ug + Vilanterol, 25 ug, once daily*	**Selective reporting** Low risk of bias **Other sources of bias** Unclear risk of bias *Funding source had role in editing of article* **Overall risk of bias** Moderate *Insufficient information provided for allocation concealment and blinding of outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Outcome measure(s) Moderate to severe exacerbations during follow-up SGRQ Responders SGRQ score Serious adverse events Pneumonia Trough FEV1 Mortality Dropout due to SAEs	
Siler (2016)	Efficacy and Safety of Umeclidinium Added to Fluticasone Propionate/Salmeterol in Patients with COPD: Results of Two Randomized, Double-Blind Studies.	**Study type** Randomised controlled trial **Study details** Study location *Study 1: Canada, Germany, Korea, USA Study 2: Chile, Czech Republic, Korea, Poland, U* Study setting *Multi-centre study* Duration of follow-up *12 weeks* Sources of funding *GlaxoSmithKline* **Inclusion criteria** Age *>40* Current or ex-smokers *History of 10+ pack-years of smoking* FEV1:FVC <0.7 FEV1	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *Insufficient information provided*

Short Title	Title	Study characteristics	Risk of bias and directness
		<70% Clinical history of COPD as defined by ATS guidelines **Exclusion criteria** Asthma diagnosis Hospitalisation for COPD or pneumonia within 12 weeks of study Any respiratory disease other than asthma **Sample characteristics** Sample size *Study 1: 617 Study 2: 608* Split between study groups *Study 1 Triple: 204 Study 1 Dual: 205 Study 2 Triple: 203 Study 2 Dual: 201* Loss to follow-up *Study 1 Triple: 14 Study 1 Dual: 27 Study 2 Triple: 25 Study 2 Dual: 31* %female *Study 1 Triple: 35% Study 1 Dual: 36% Study 2 Triple: 31% Study 2 Dual: 39%* Mean age (SD) *Study 1 Triple: 62.7 (7.84) Study 1 Dual: 63.4 (8.27) Study 2 Triple: 64.5 (8.31) Study 2 Dual: 65.7 (7.92)* Current smoker (%) *Study 1 Triple: 50% Study 1 Dual: 57% Study 2 Triple: 36% Study 2 Dual: 38%* FEV1 (mean, SD) *Study 1 Triple: 1.31 (0.47) Study 1 Dual: 1.31 (0.46) Study 2 Triple: 1.15 (0.44) Study 2 Dual: 1.13 (0.45)* **Interventions** Dual therapy *Both studies: LABA+ICS Fluticasone propionate 250 ug + Salmeterol 50*	**Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Unclear risk of bias *Funding source had role in editing of article* **Overall risk of bias** Moderate *Insufficient information provided for allocation concealment and blinding of outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		ug, twice daily Triple therapy *Both studies: Umeclidinium 62.5 ug, once daily* *Fluticasone propionate 250 ug + Salmeterol 50 ug, twice daily* **Outcome measure(s)** Moderate to severe exacerbations during follow-up SGRQ score Serious adverse events Pneumonia Trough FEV1 Mortality Dropout due to SAEs	
Singh (2016)	Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.	**Study type** Randomised controlled trial **Study details** Study location *International* Study setting *Multi-centre study* Study dates *March 2014 - January 2016* Duration of follow-up *52 weeks* Sources of funding *Chiesi Farmaceutici* **Inclusion criteria** Age *>40*	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment**

Short Title	Title	Study characteristics	Risk of bias and directness
		COPD diagnosis FEV1:FVC <0.7 FEV1 *<50%* Recent moderate/severe exacerbation *At least 1 in past 12 months* COPD Assessment Test score of at least 10 Using monotherapy or dual therapy before screening *Minimum 2 months before* BDI score <10 **Exclusion criteria** Asthma diagnosis Recent exacerbation *In 4 weeks before screening* **Sample characteristics** Sample size *1368* Split between study groups *Triple: 687 Dual: 681* Loss to follow-up *Triple: 2 Dual: 5* %female *Triple: 26% Dual: 23%* Mean age (SD) *Triple: 63.3 (7.9) Dual: 63.8 (8.2)* Current smoker (%) *Triple: 47% Dual: 47%* Ex-smoker (%) *Triple: 53% Dual: 53%*	Low risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Unclear risk of bias *Funding source had role in editing of article* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		FEV1 (mean, SD) *Triple: 1.11 (0.32) Dual: 1.10 (0.33)* **Interventions** Dual therapy *LABA+ICS: Beclometasone dipropionate 100 ug + Formoterol fumarate 6 ug, two puffs, twice per day* Triple therapy Beclometasone/Formoterol/Glycopyrronium *Glycopyrronium bromide 12.5 ug + Beclometasone diproprionate 100 ug + Formoterol fumarate 6 ug, two puffs, twice per day* **Outcome measure(s)** SGRQ score Serious adverse events Pneumonia TDI	
Sousa (2016)	The effect of umeclidinium added to inhaled corticosteroid/long-acting beta2-agonist in patients with symptomatic COPD: a randomised, double-blind, parallel-group study.	**Study type** Randomised controlled trial **Study details** Study location *Czech Republic, Germany, Greece and the Netherlands* Study setting *Multi-centre study* Study dates *September 2014 - March 2015* Duration of follow-up *12 weeks* Sources of funding	**Random sequence generation** Low risk of bias **Allocation concealment** Unclear risk of bias *Insufficient information provided* **Blinding of participants and personnel**

Short Title	Title	Study characteristics	Risk of bias and directness
		GlaxoSmithKline **Inclusion criteria** Age *>40* Current or ex-smokers FEV1:FVC <0.7 FEV1 *<70%* Using monotherapy or dual therapy before screening *Minimum 1 month before* Dyspnoea score >2 **Exclusion criteria** Asthma diagnosis Hospitalisation for COPD or pneumonia within 12 weeks of study Use of LTOT *Prescribed for >12 hours per day* Previous lung transplantation or lung resection *Lung volume reduction within previous 12 months* **Sample characteristics** Sample size *236* Split between study groups *Triple: 119 Dual: 117* Loss to follow-up *Dual: 0 Triple: 1* %female *Dual: 36% Triple: 30%* Mean age (SD)	Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *Insufficient information provided* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate *Insufficient information provided for allocation concealment and blinding of outcome assessment* **Directness** Directly applicable

Short Title	Title	Study characteristics	Risk of bias and directness
		Dual: 63.1 (7.9) Triple: 65.2 (7.5) Current smoker (%) *Dual: 61% Triple: 49%* FEV1 (mean, SD) *Triple: 1.33 (0.49) Dual: 1.37 (0.50)* **Interventions** Dual therapy *Range of ICS/LABA (exact combinations not stated) at approved doses* Triple therapy *Umeclidinium 62.5 ug + Range of ICS/LABA (exact combinations not stated) at approved doses* **Outcome measure(s)** SGRQ score Decrease in SGRQ score >4 points Trough FEV1	

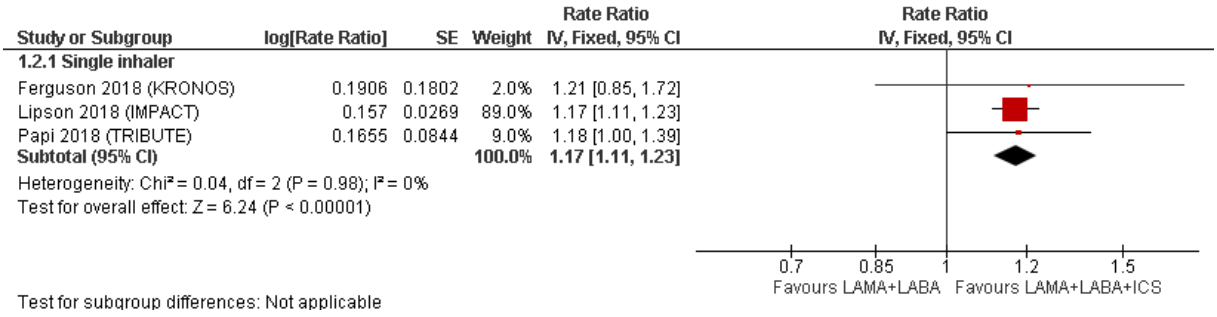
Appendix F – Forest plots

Forest plots are presented showing outcomes that favour triple therapy to the right of the chart. Where lower numbers favoured triple therapy, such as for exacerbation rate, the effect estimate was inverted to maintain consistency in the presentation of the forest plots.

Triple therapy (LAMA+LABA+ICS) versus LAMA+LABA dual therapy

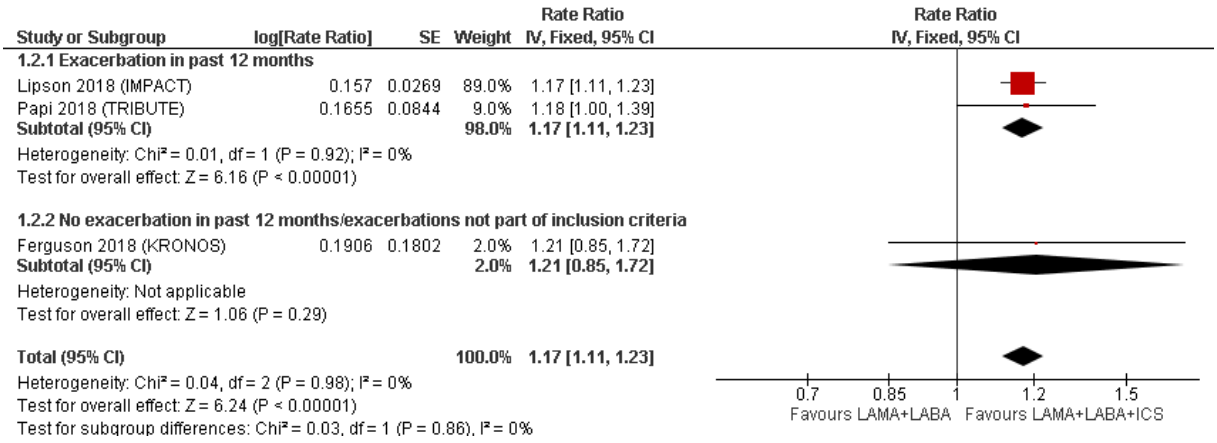
Rate of moderate to severe exacerbations per patient per year by:

Number of inhalers (multiple or single inhalers)



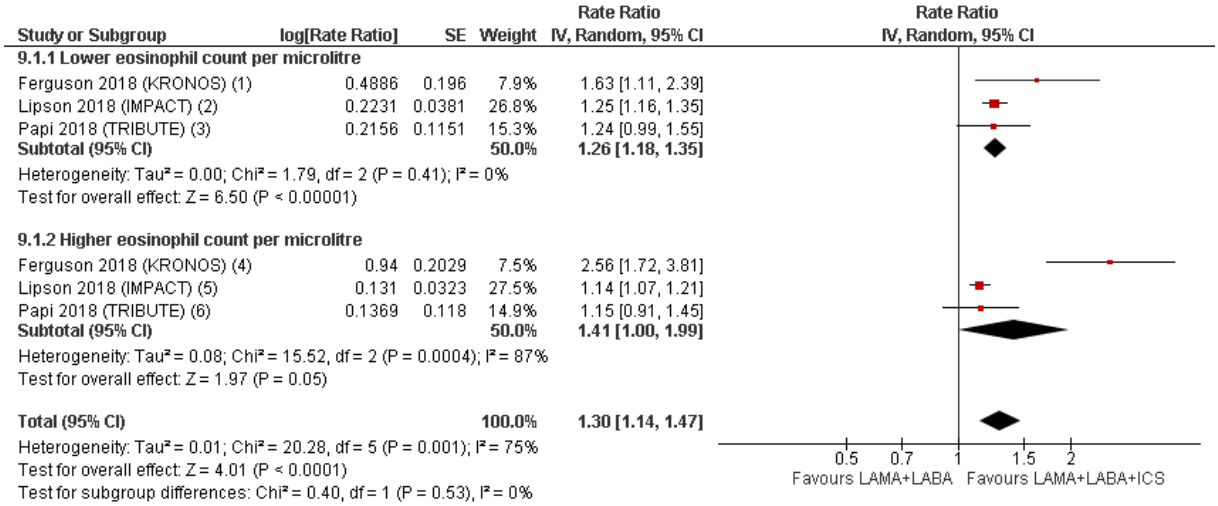
Test for subgroup differences: Not applicable

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%

1 ***Eosinophil count***

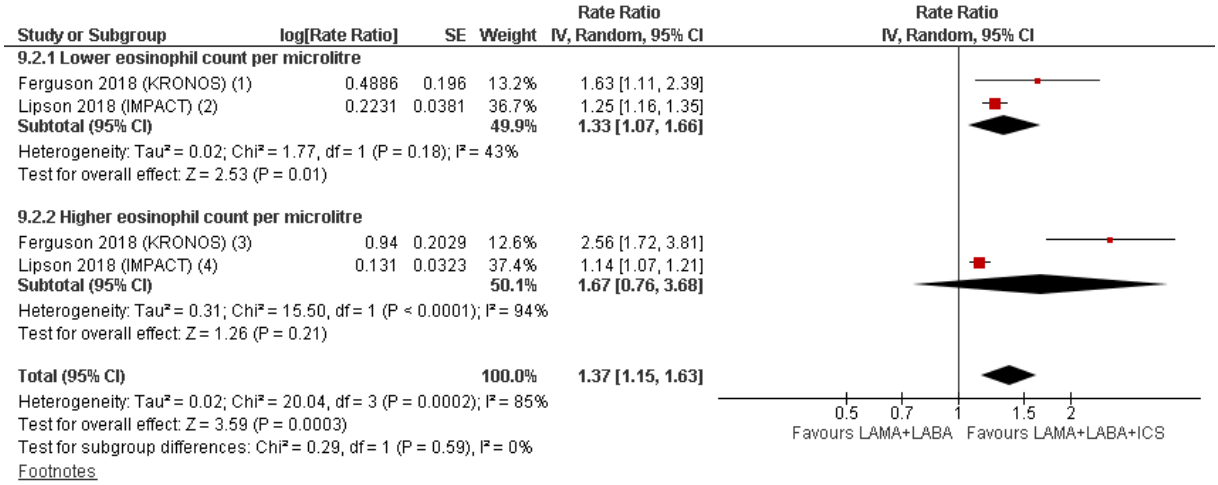


Footnotes

(1) <150 cells/ul
(2) <150 cells/ul
(3) <200 cells/ul
(4) >150 cells/ul
(5) >150 cells/ul
(6) >200 cells/ul

2

3 *Sensitivity analysis removing the study using a 200ul eosinophil count cut off*

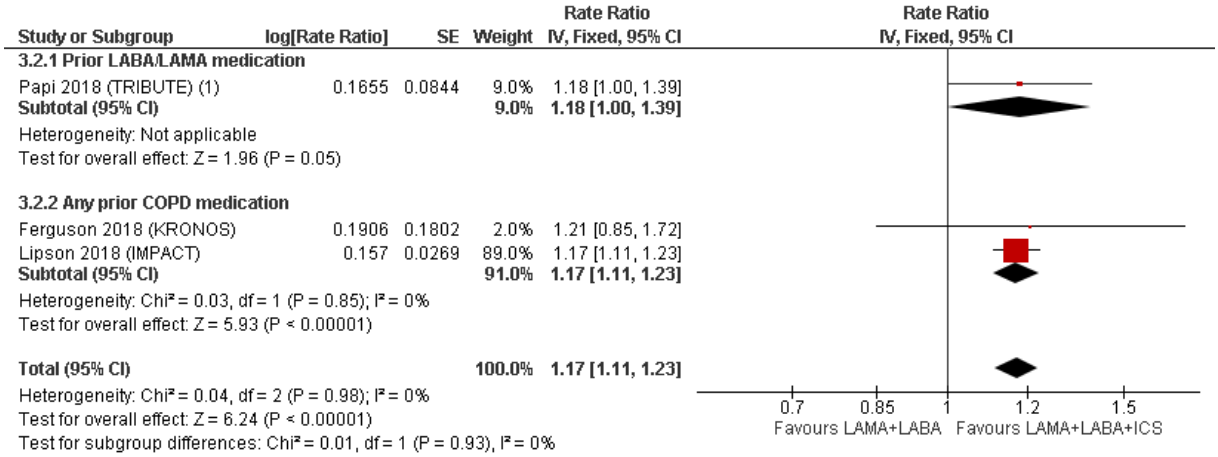


Footnotes

(1) <150 cells/ul
(2) <150 cells/ul
(3) >150 cells/ul
(4) >150 cells/ul

4

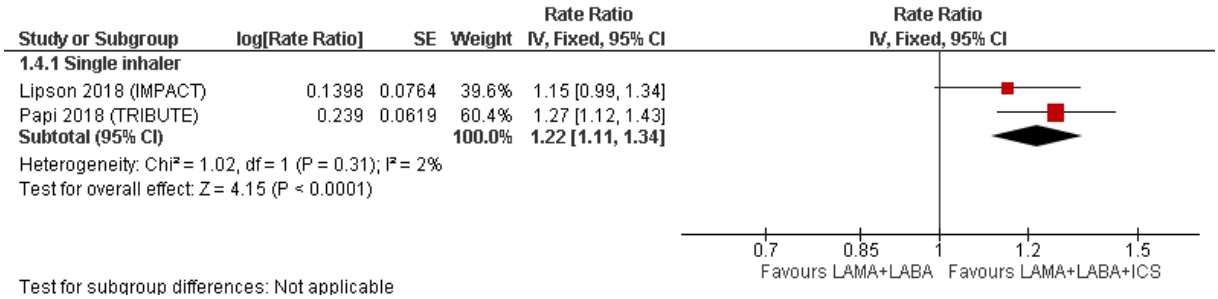
1 ***Previous medication***



2

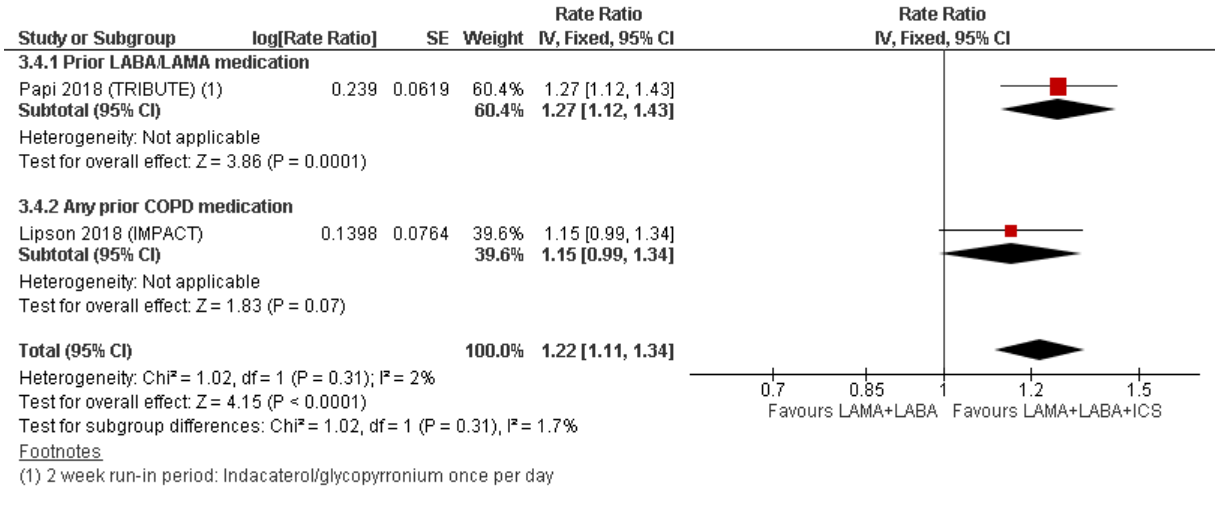
3 **Rate of severe exacerbations per patient per year by:**

4 ***Number of inhalers (multiple or single)***



5 Test for subgroup differences: Not applicable

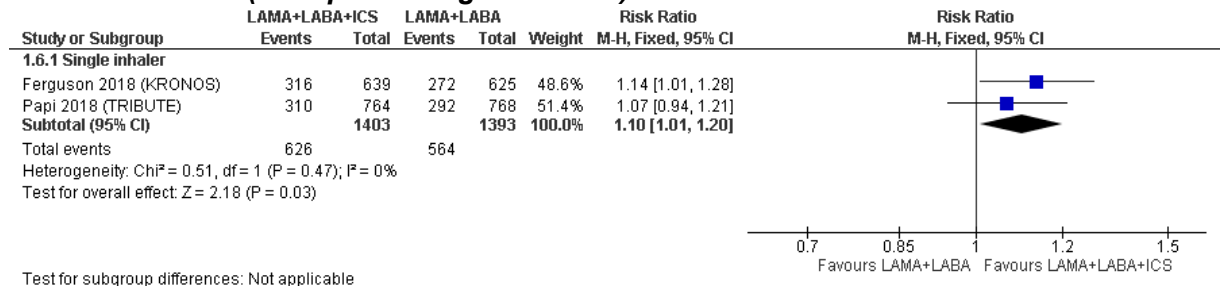
6 ***Previous medication***



7

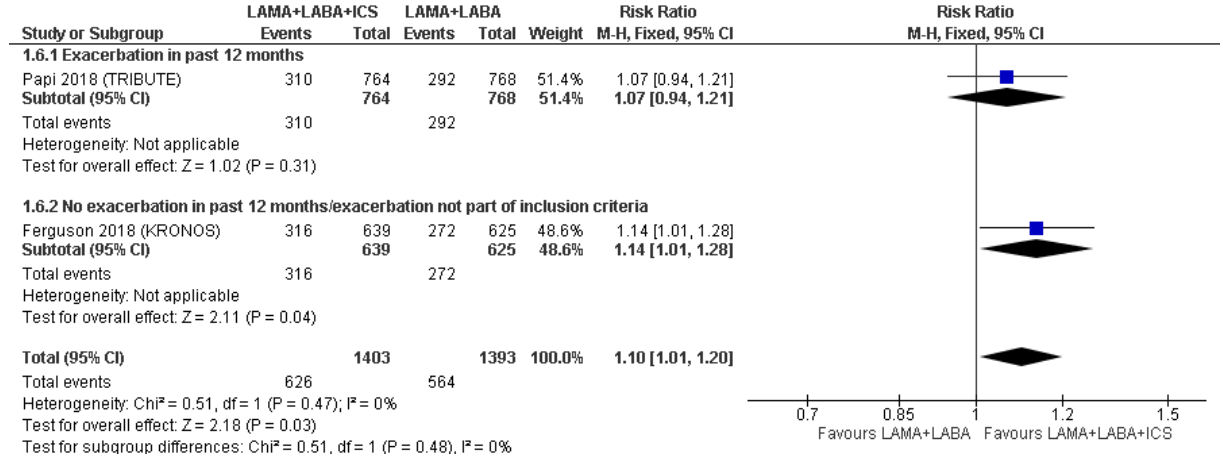
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 6 months by:

Number of inhalers (multiple or single inhalers)

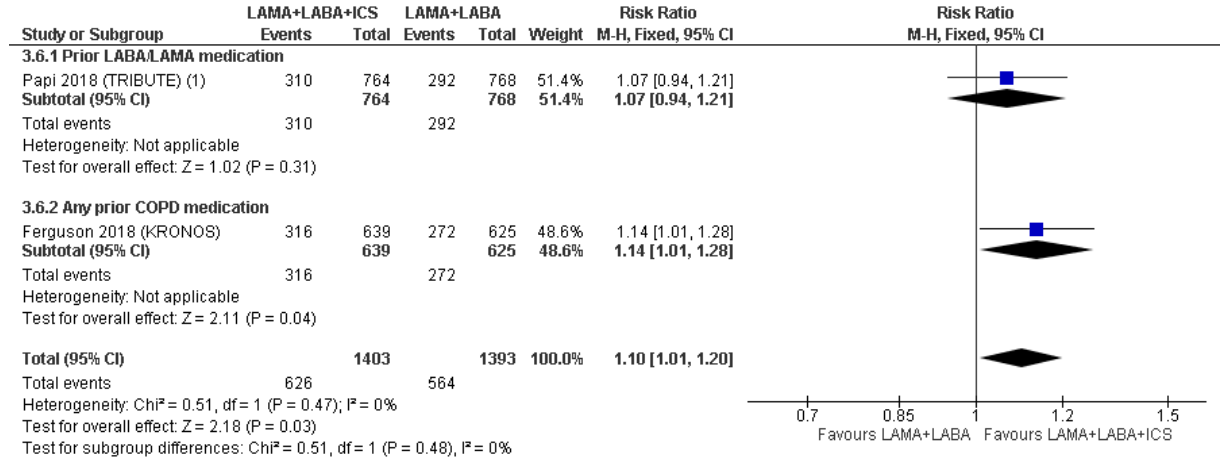


Test for subgroup differences: Not applicable

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

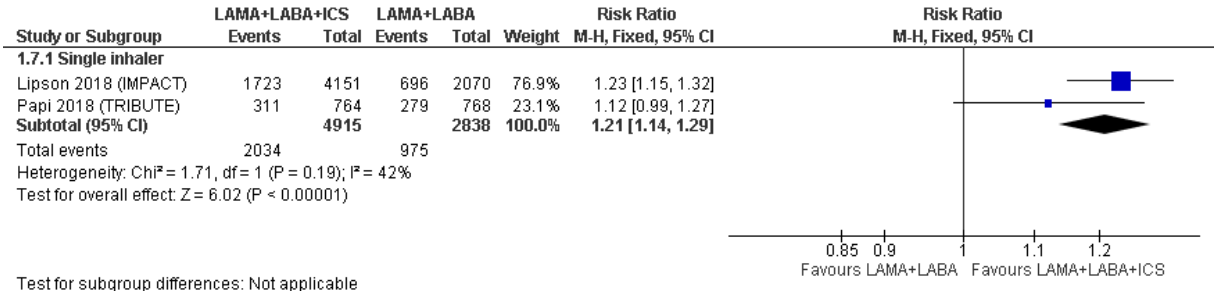


Previous medication



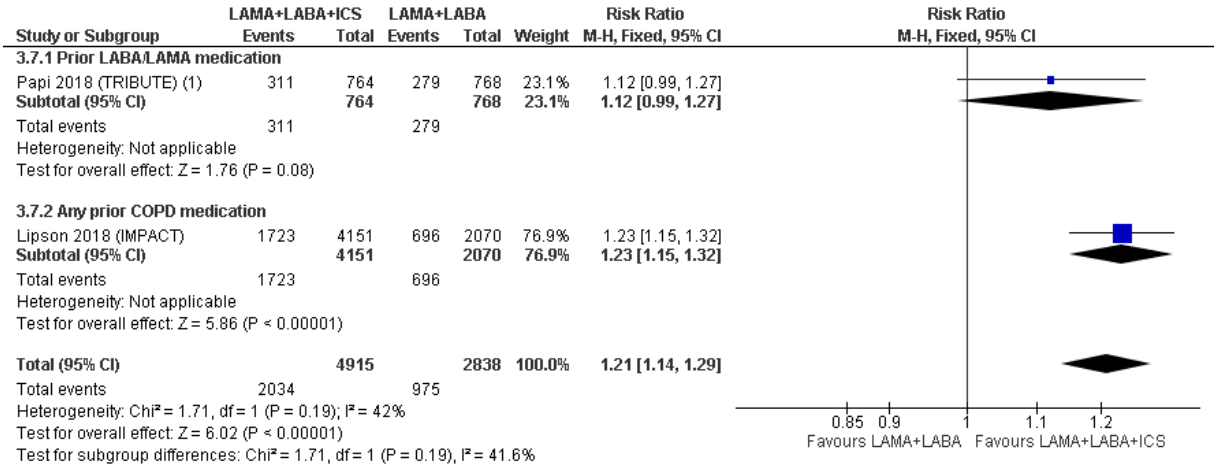
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 12 months by:

Number of inhalers (multiple or single inhalers)



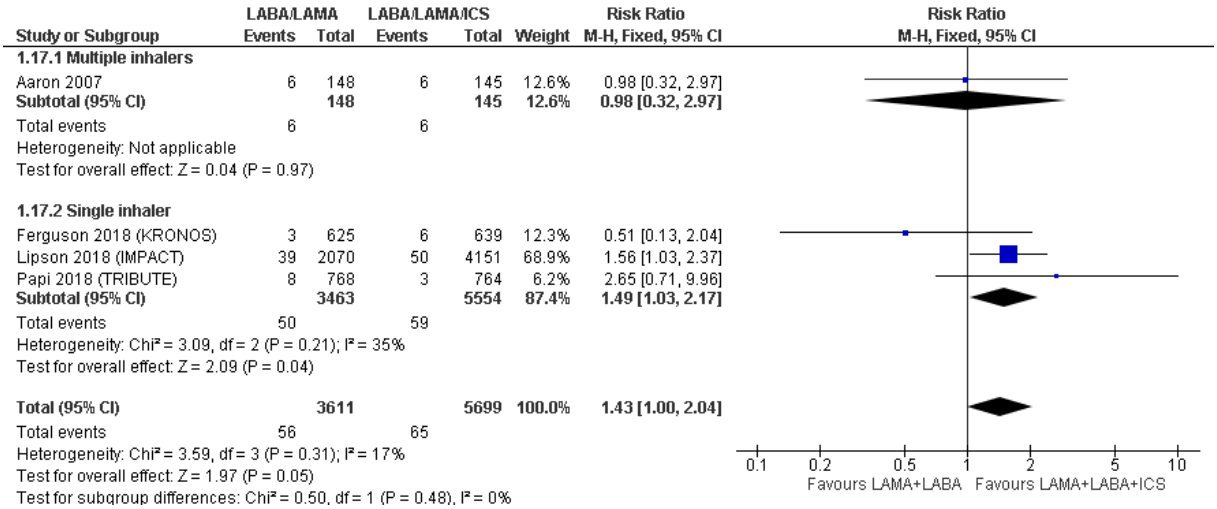
Test for subgroup differences: Not applicable

Previous medication

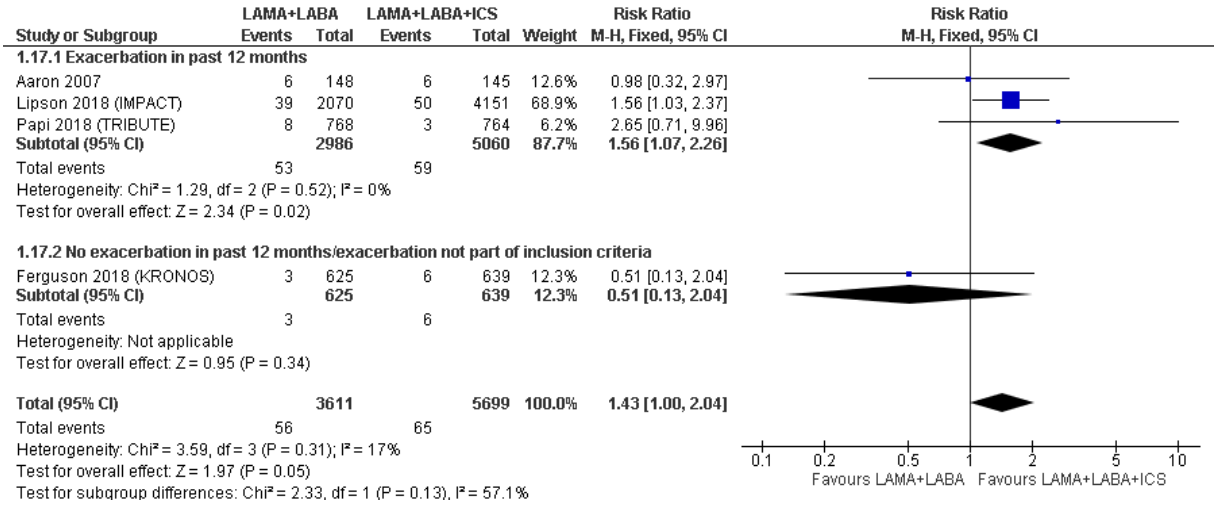


All-cause mortality by:

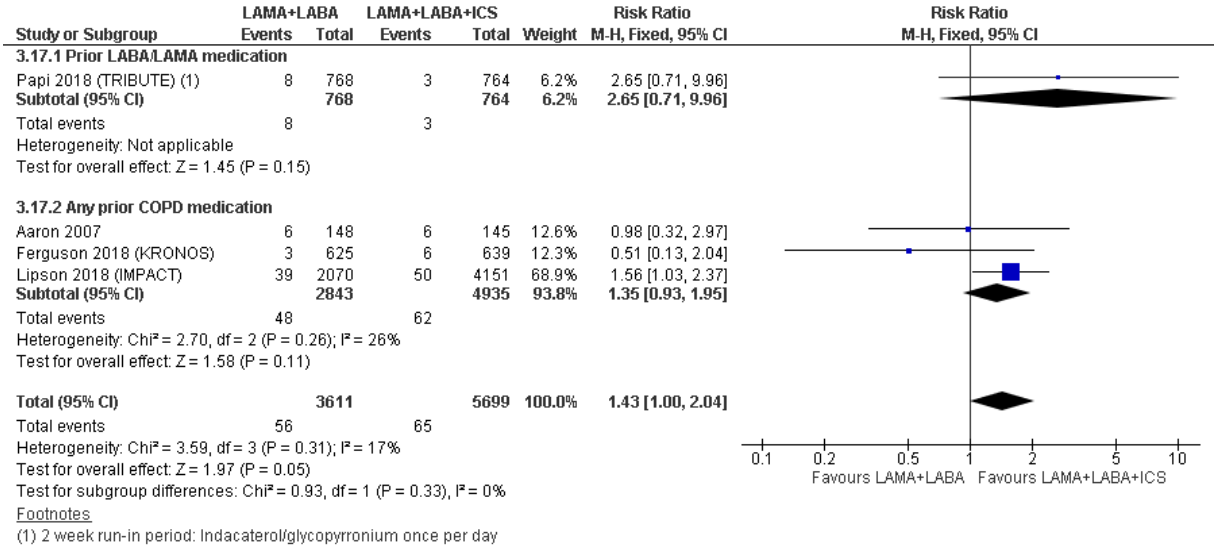
Number of inhalers (multiple or single inhalers)



Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

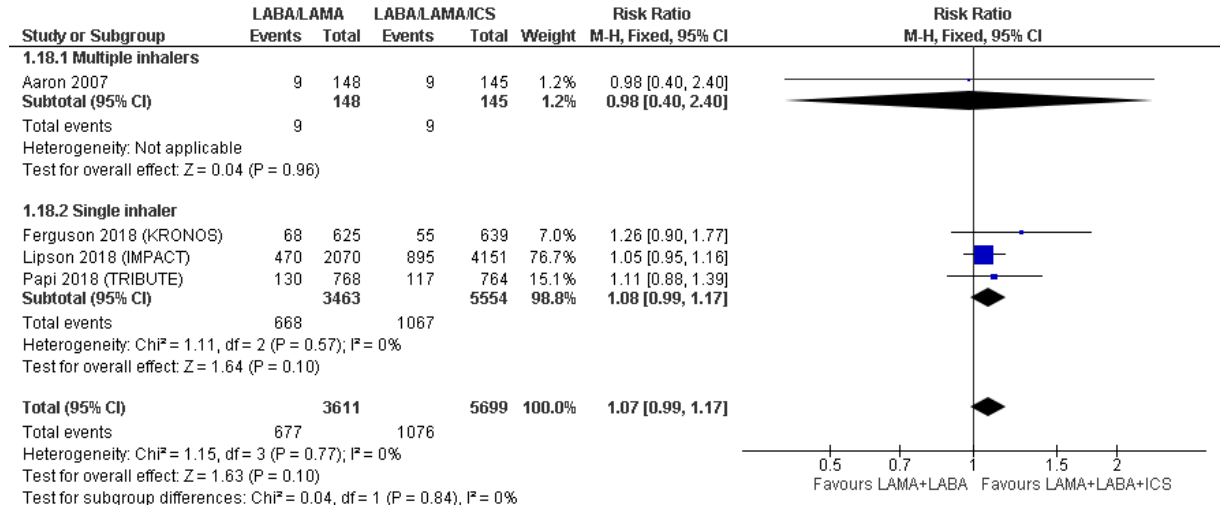


Previous medication



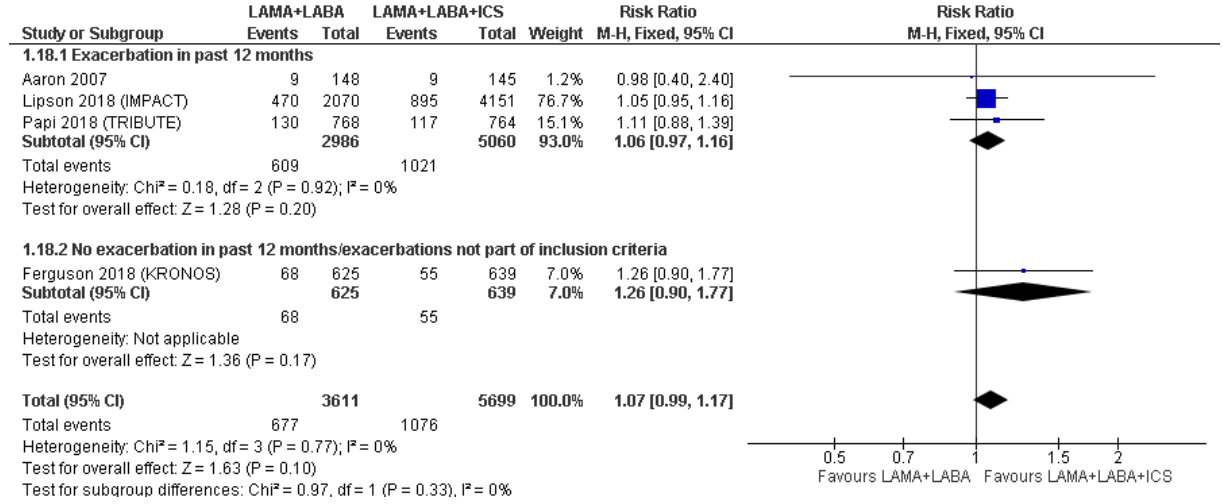
1 **Total serious adverse events by:**

2 ***Number of inhalers (multiple or single inhalers)***



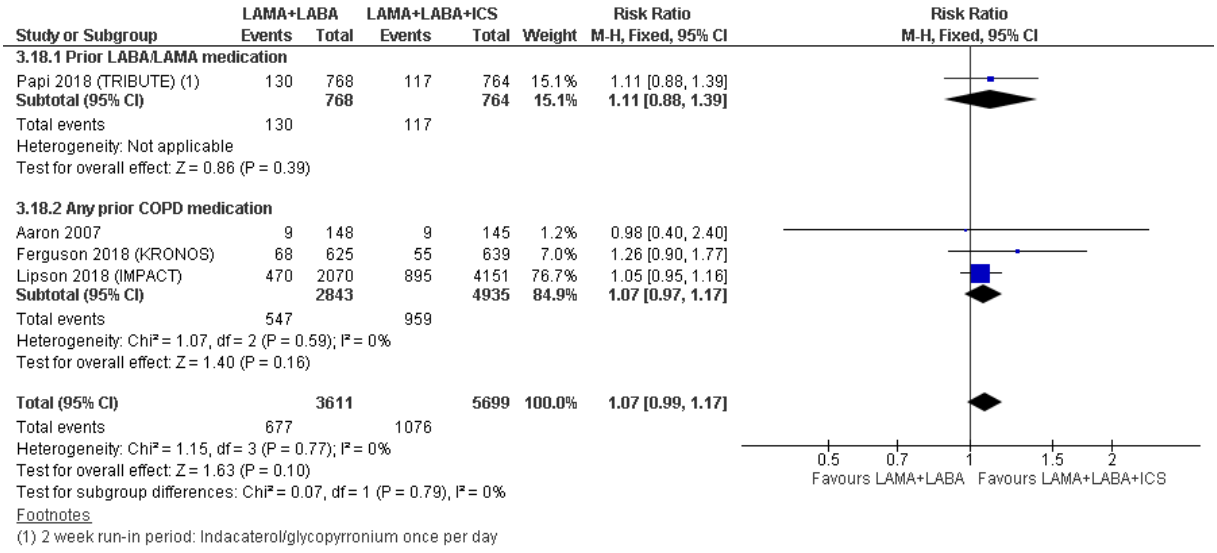
3

4 ***Previous exacerbation (occurrence or no exacerbations in past 12 months as part of***
5 ***inclusion criteria)***



6

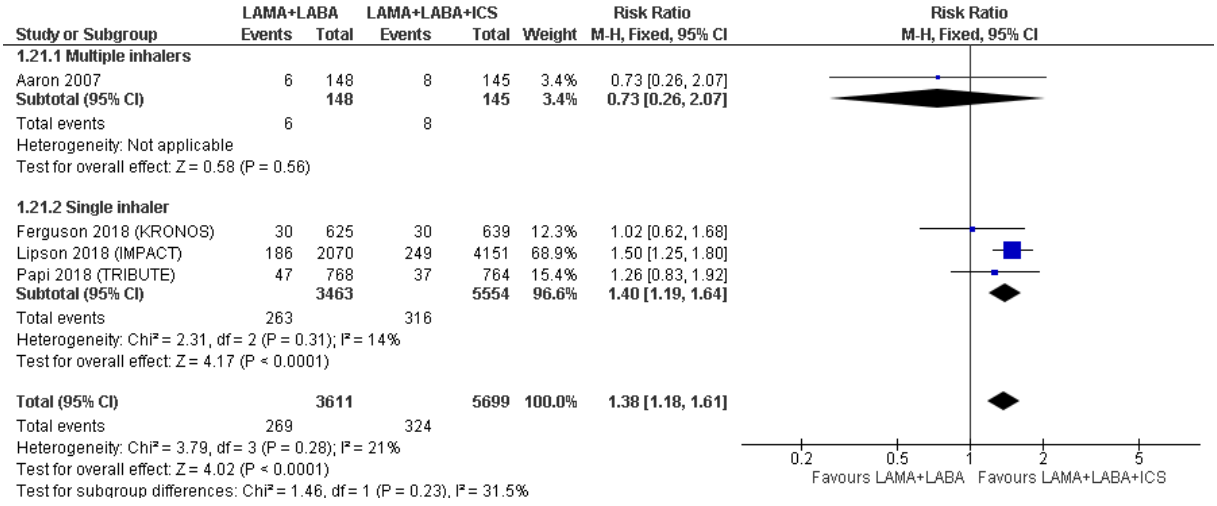
1 ***Previous medication***



2

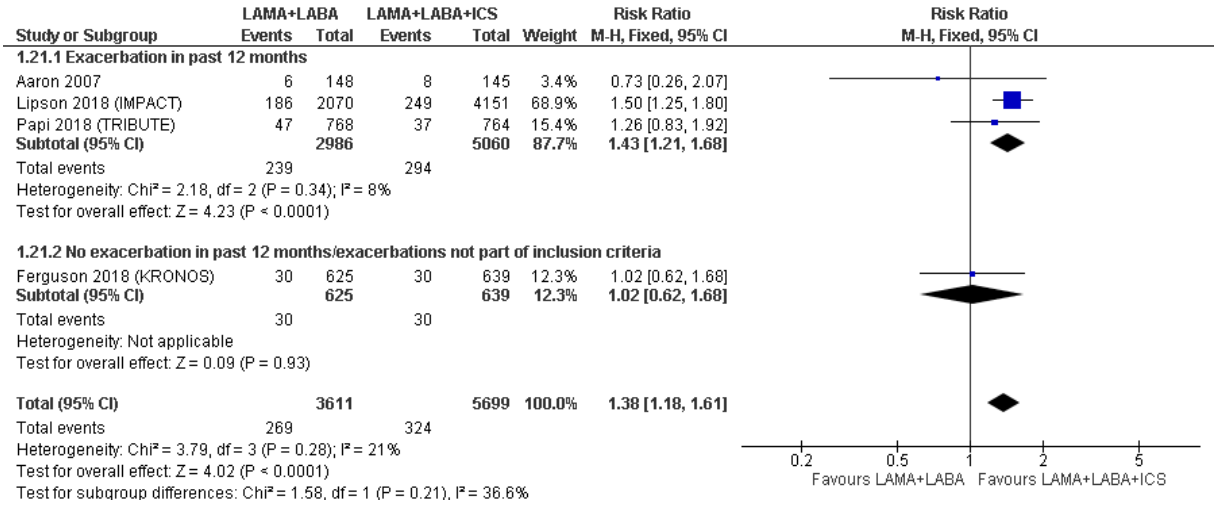
3 **Dropout due to adverse events by:**

4 ***Number of inhalers (multiple or single inhaler)***

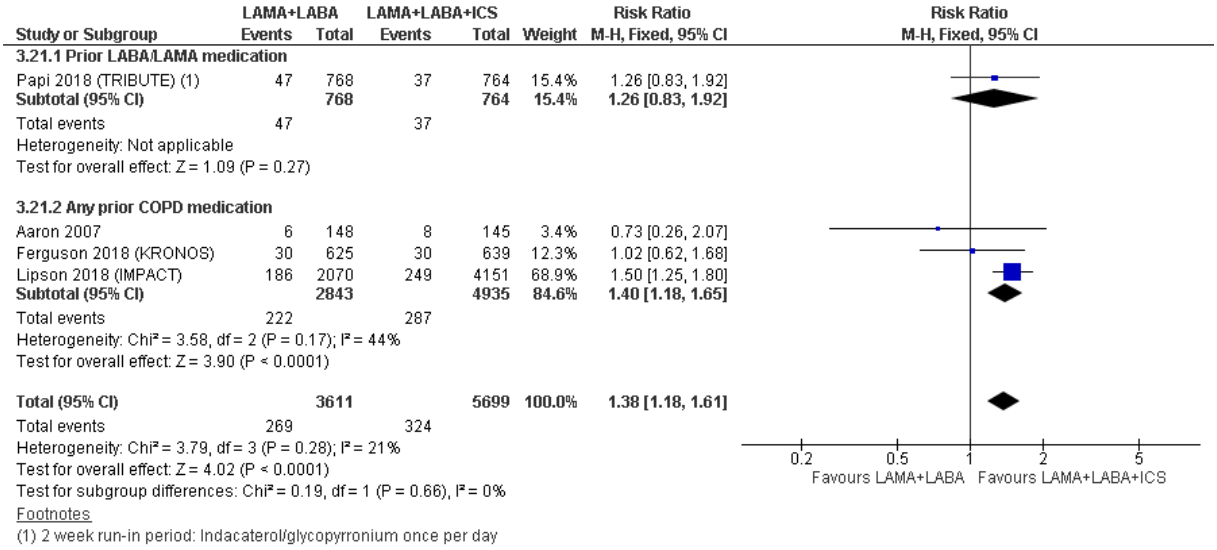


5

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

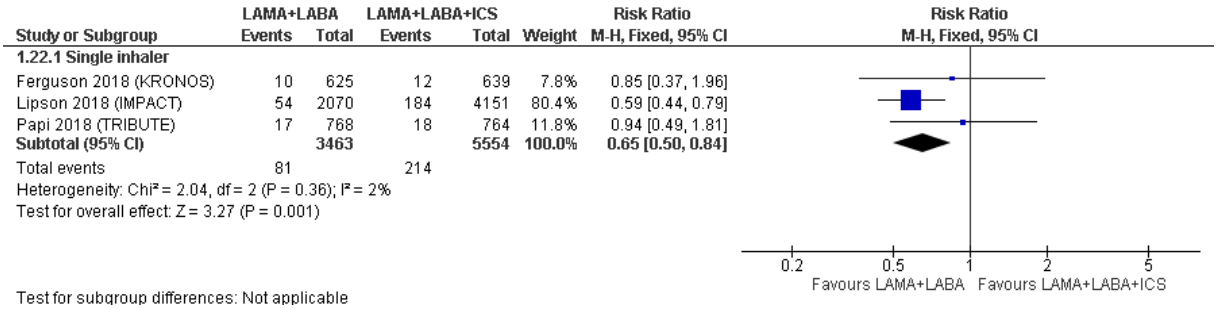


Previous medication



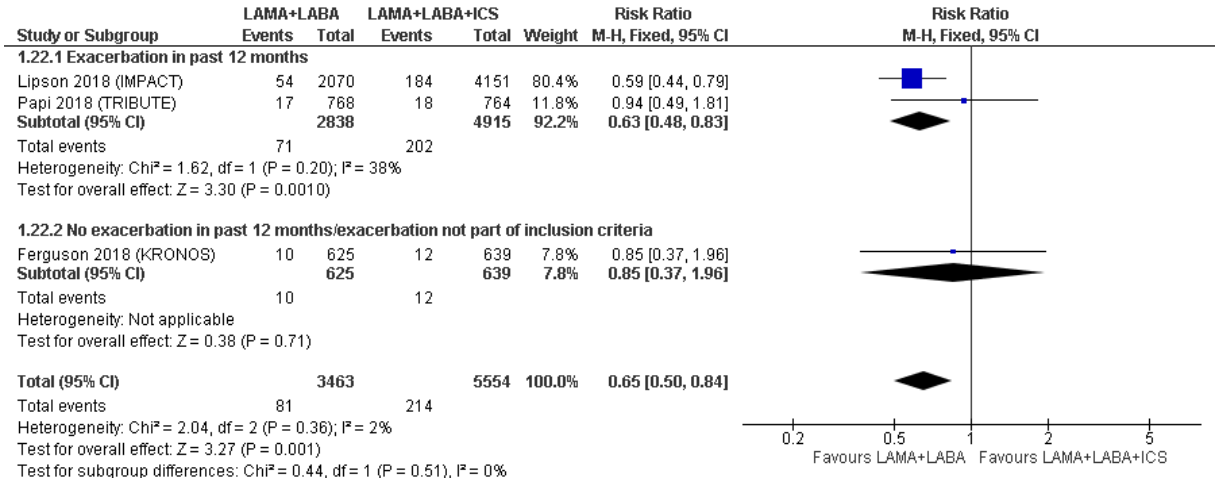
Pneumonia by:

Number of inhalers (multiple or single inhaler)

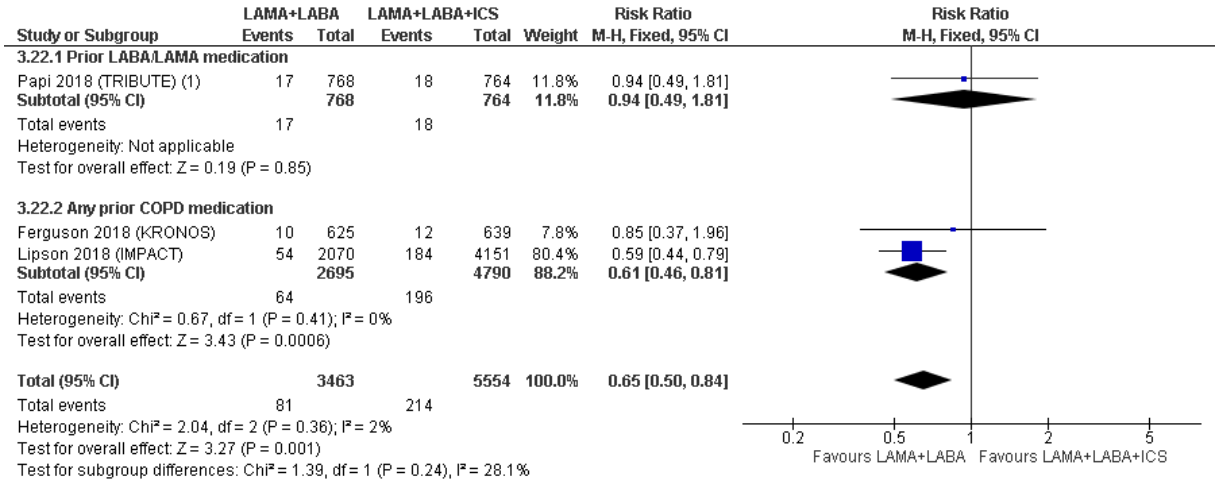


Test for subgroup differences: Not applicable

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



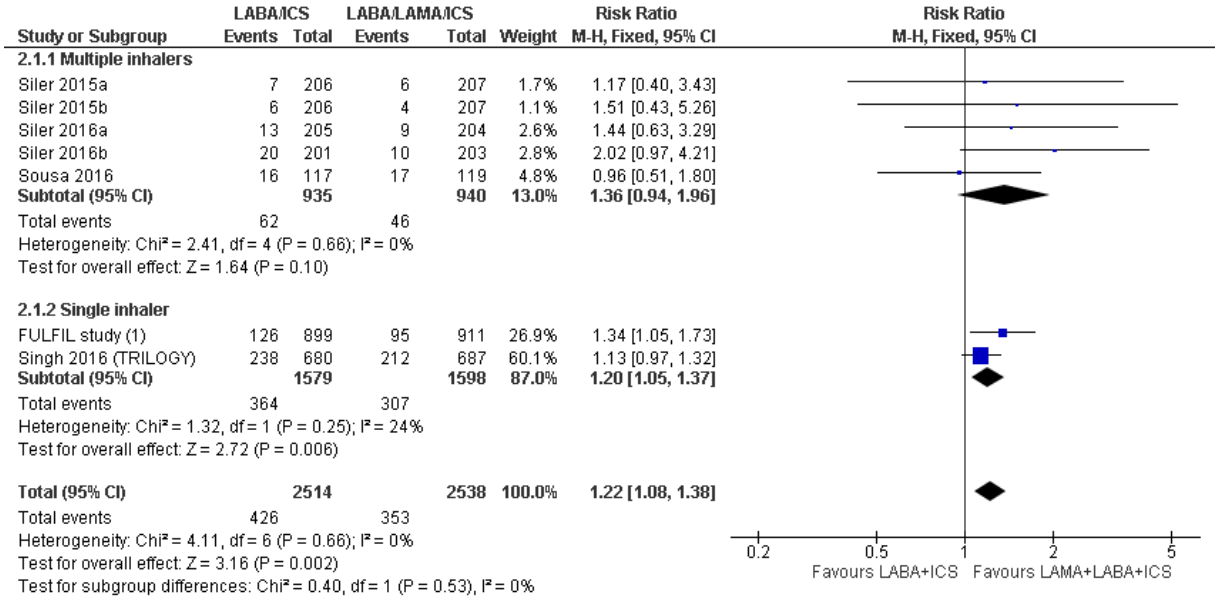
Previous medication



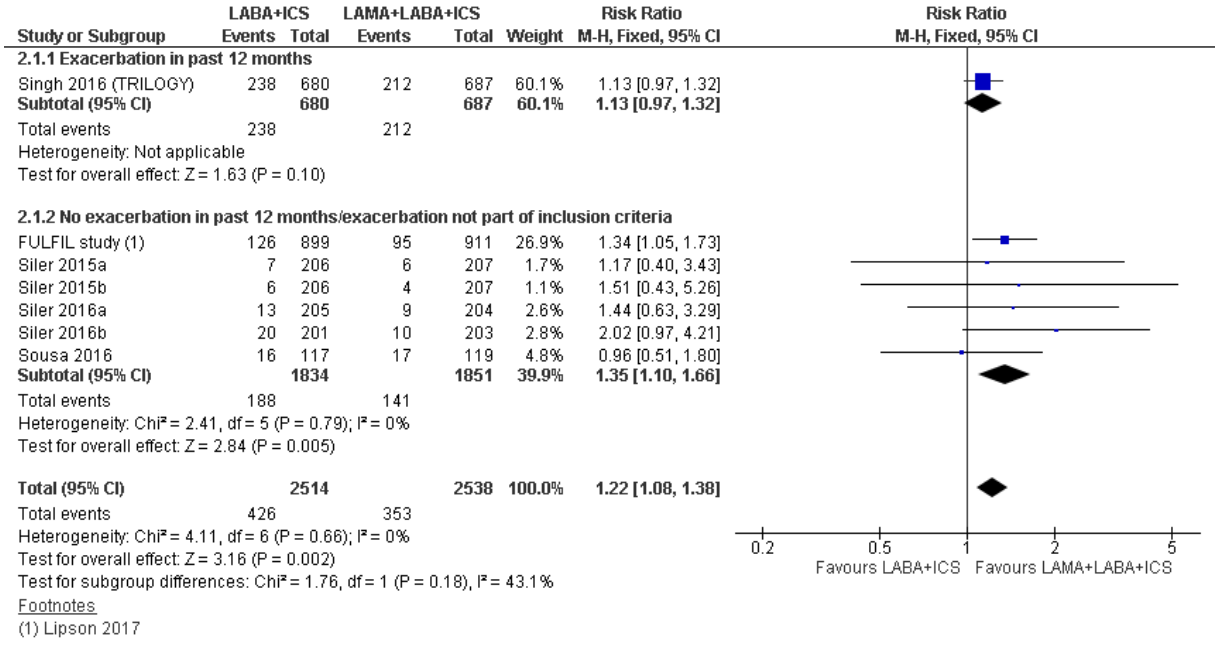
Triple therapy (LAMA+LABA+ICS) versus LABA+ICS dual therapy

Moderate to severe exacerbations by:

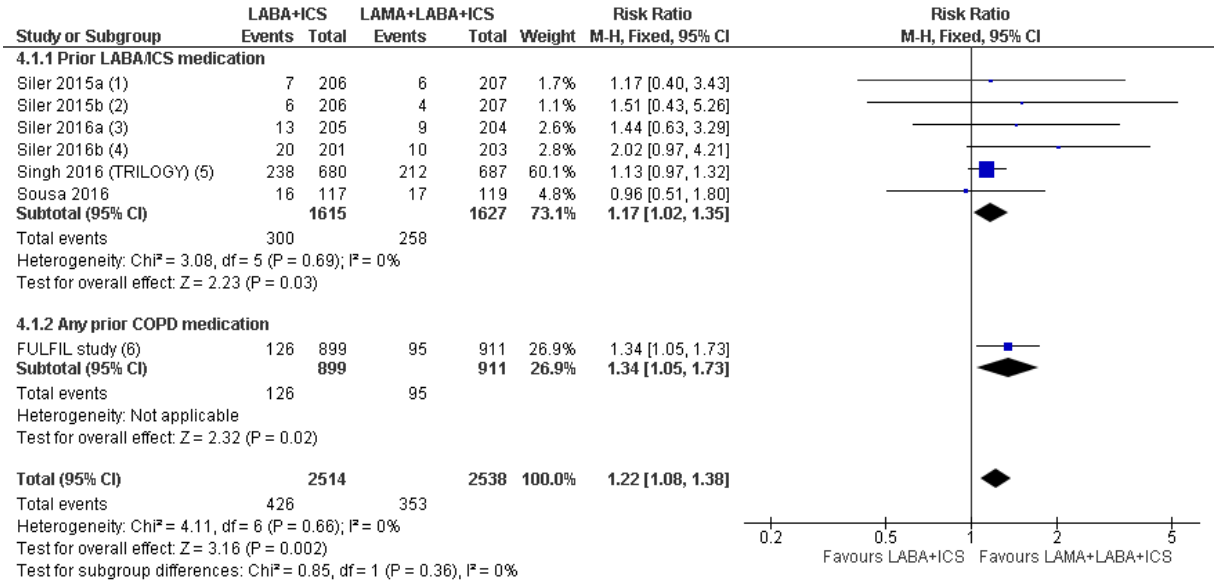
Number of inhalers (multiple or single inhalers)



Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



Prior medication



Footnotes

(1) 4 week run-in period: salmeterol/fluticasone

(2) 4 week run-in period: salmeterol/fluticasone

(3) 4 week run-in period: salmeterol/fluticasone

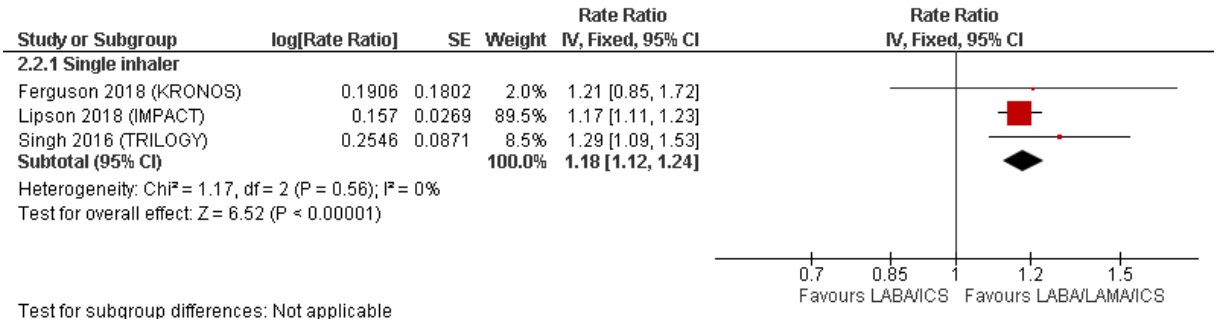
(4) 4 week run-in period: salmeterol/fluticasone

(5) 2 week run-in period: Beclometasone/formoterol twice per day

(6) Lipson 2017

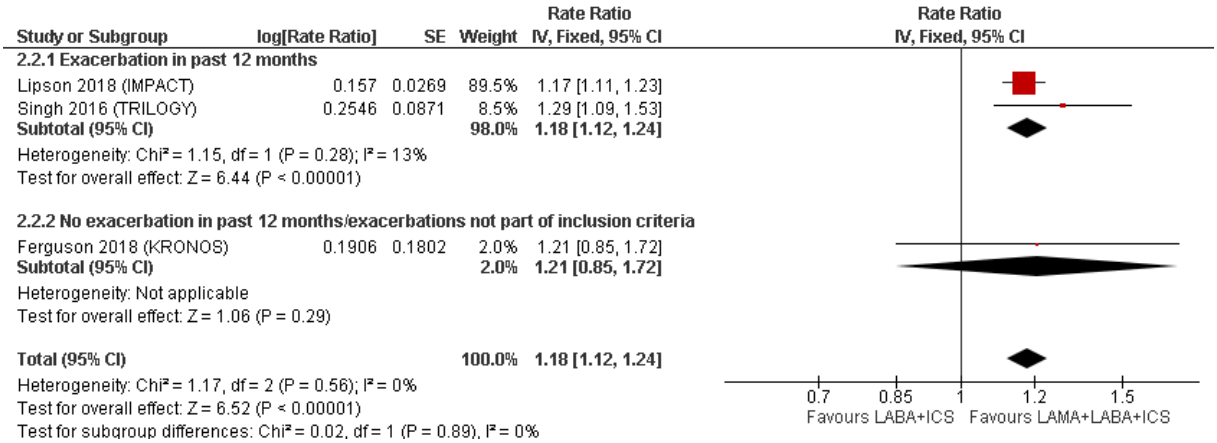
Rate of moderate to severe exacerbations per patient per year by:

Number of inhalers (multiple or single inhalers)

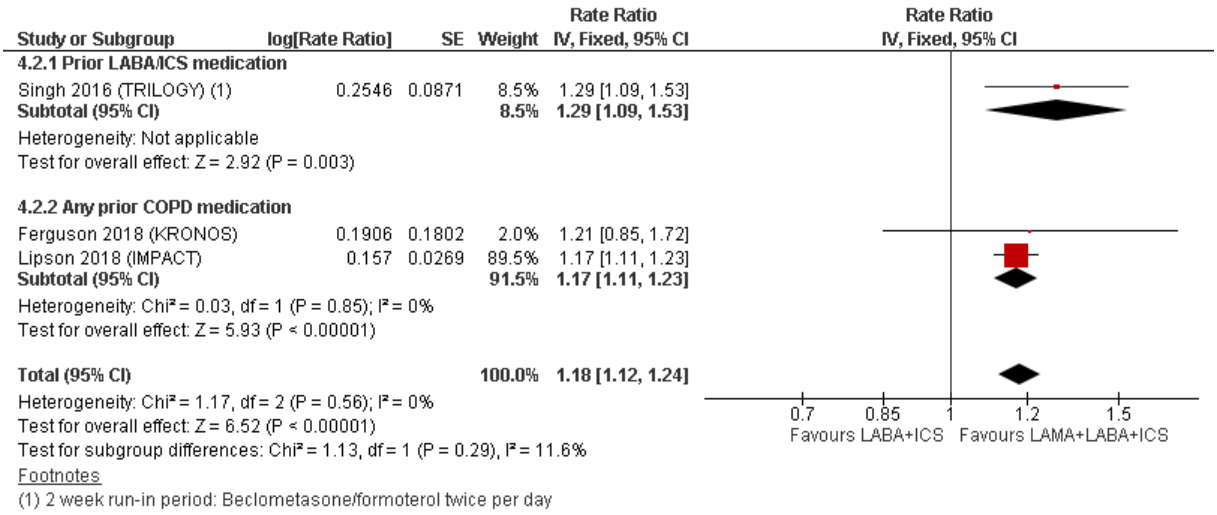


Test for subgroup differences: Not applicable

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



1 ***Prior medication***

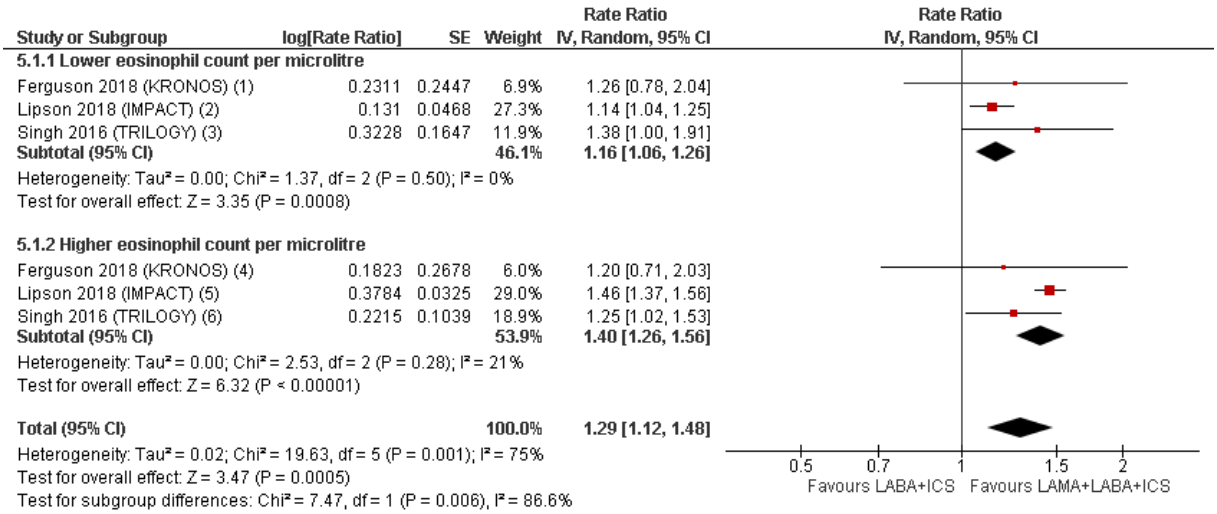


Footnotes

(1) 2 week run-in period: Beclometasone/formoterol twice per day

2

3 ***Eosinophil count***

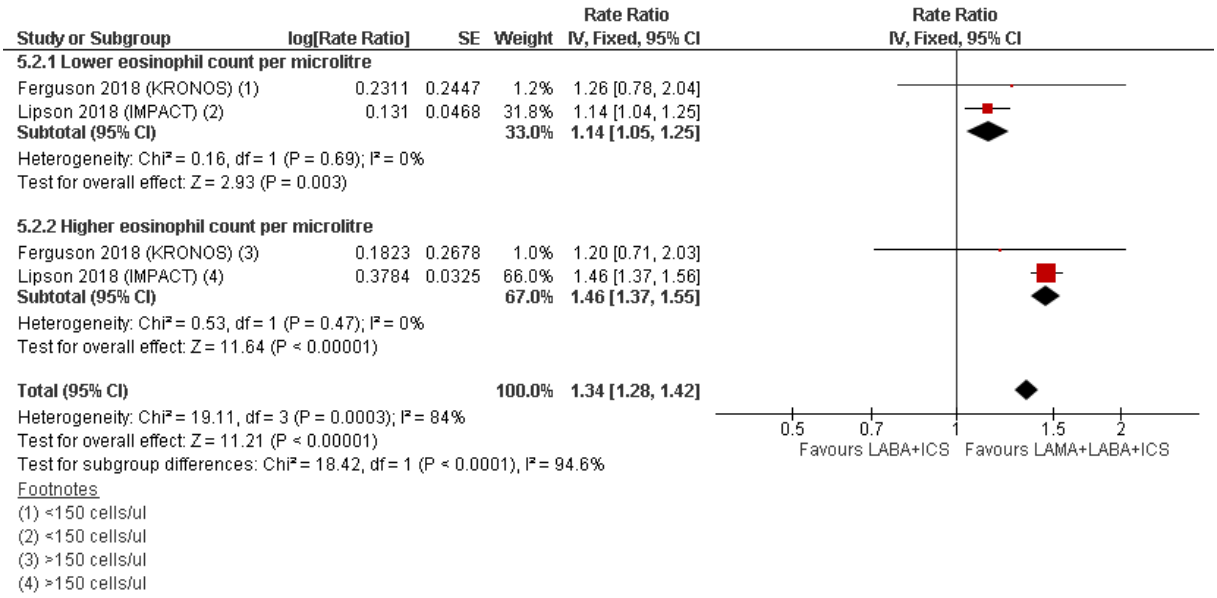


Footnotes

(1) <150 cells/ul
(2) <150 cells/ul
(3) <200 cells/ul
(4) >150 cells/ul
(5) >150 cells/ul
(6) <200 cells/ul

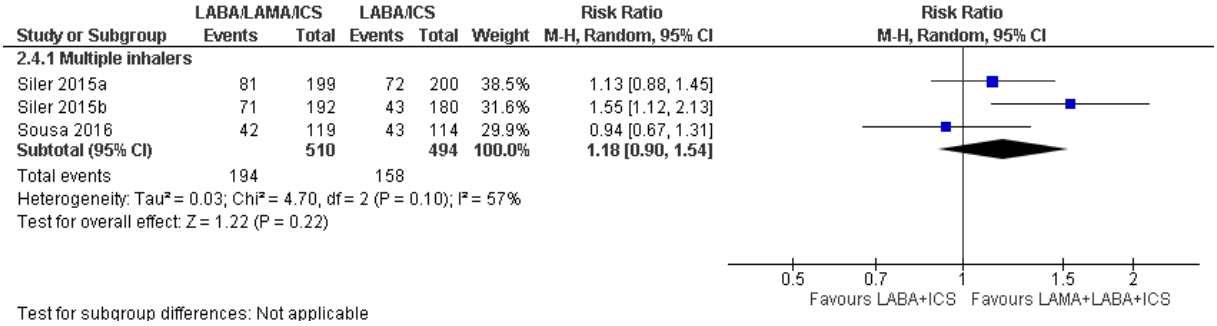
4

Sensitivity analysis removing the study using a 200ul eosinophil count cut off



People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 3 months by:

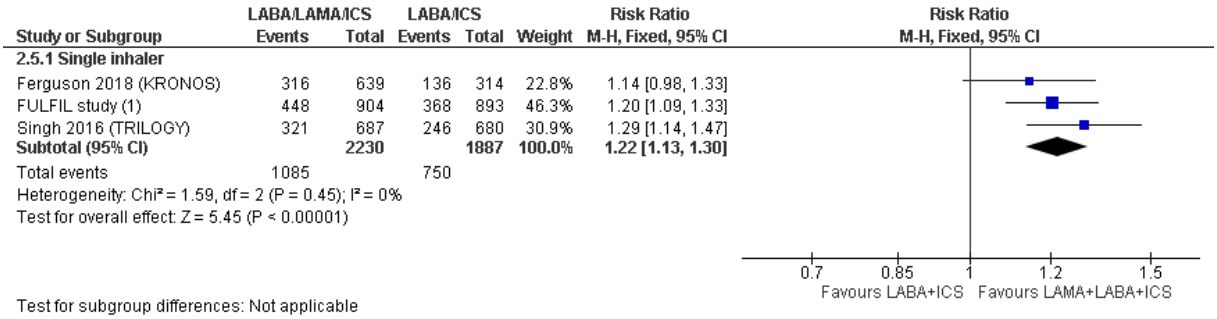
Number of inhalers (multiple or single inhalers)



Test for subgroup differences: Not applicable

People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 6 months by:

Number of inhalers (multiple or single inhalers)

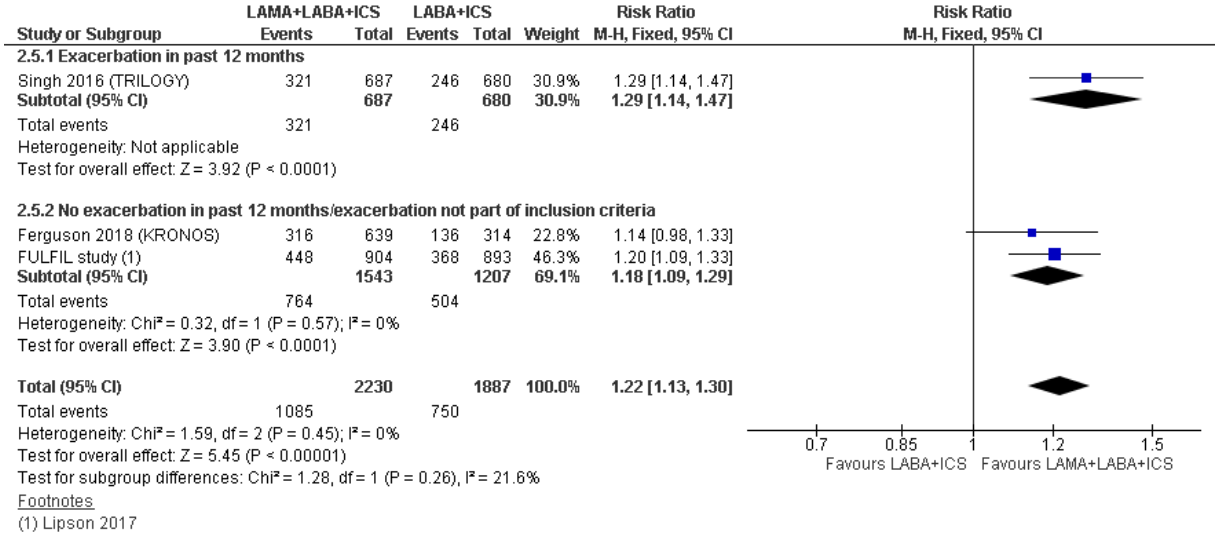


Test for subgroup differences: Not applicable

Footnotes

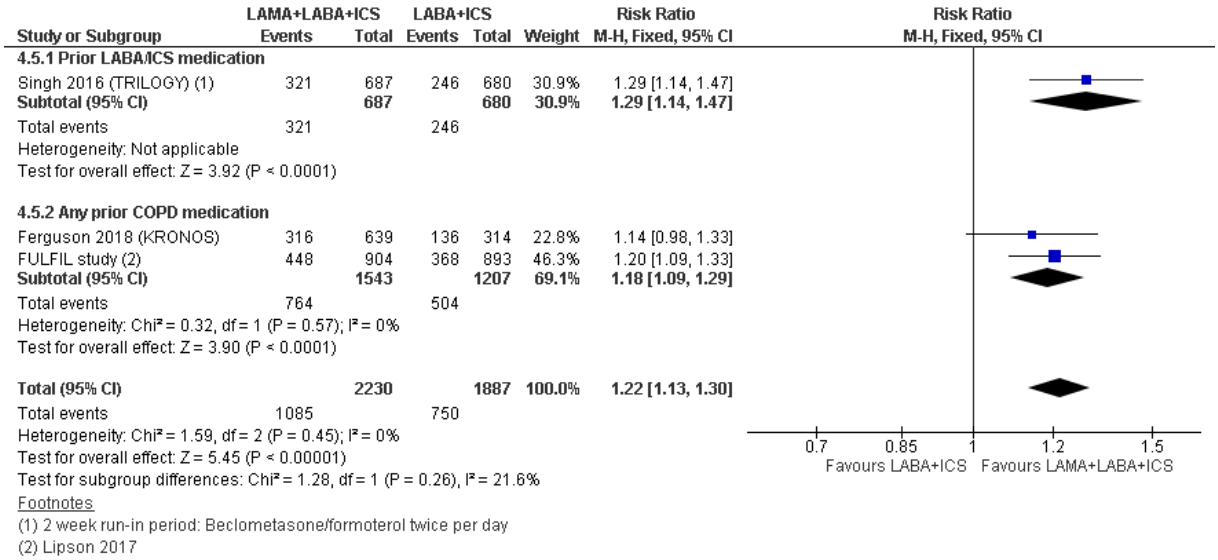
(1) Lipson 2017

1 ***Exacerbations (exacerbation or no exacerbation in past 12 months)***



2

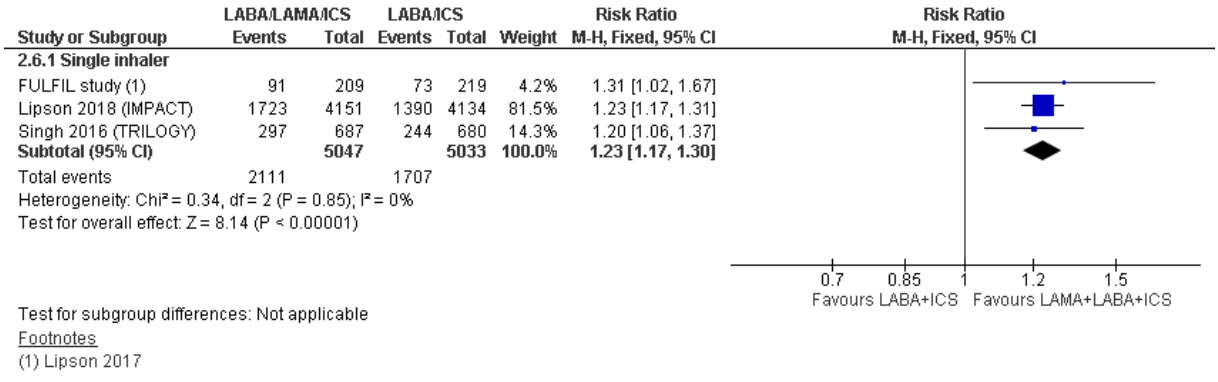
3 ***Prior medication***



4

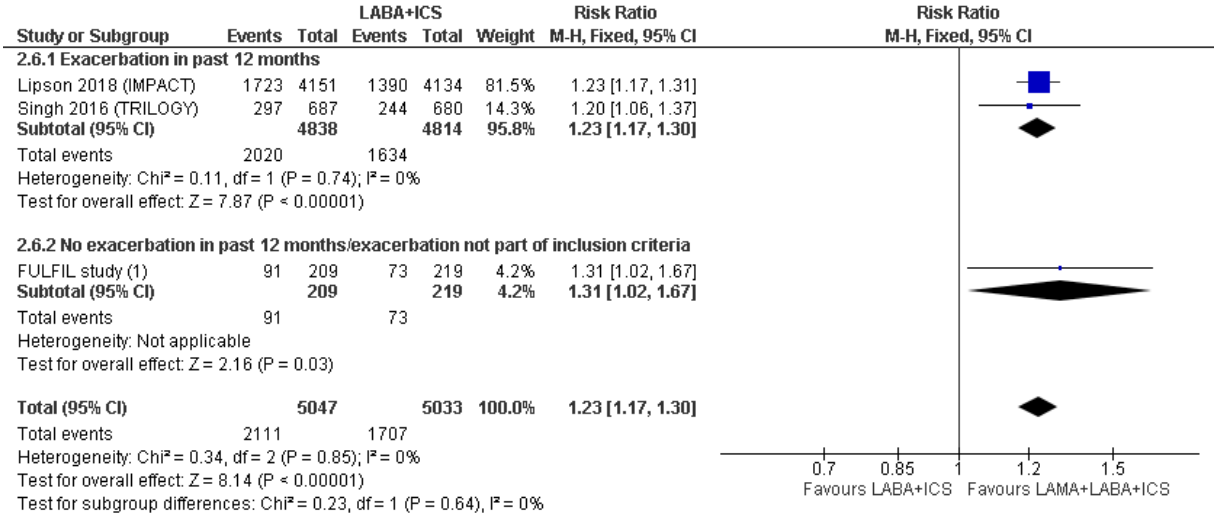
5 **People with ≥ 4 units improvement in quality of life (St. George's Respiratory**
6 **Questionnaire responders) at 12 months by:**

7 ***Number of inhalers (multiple or single inhalers)***

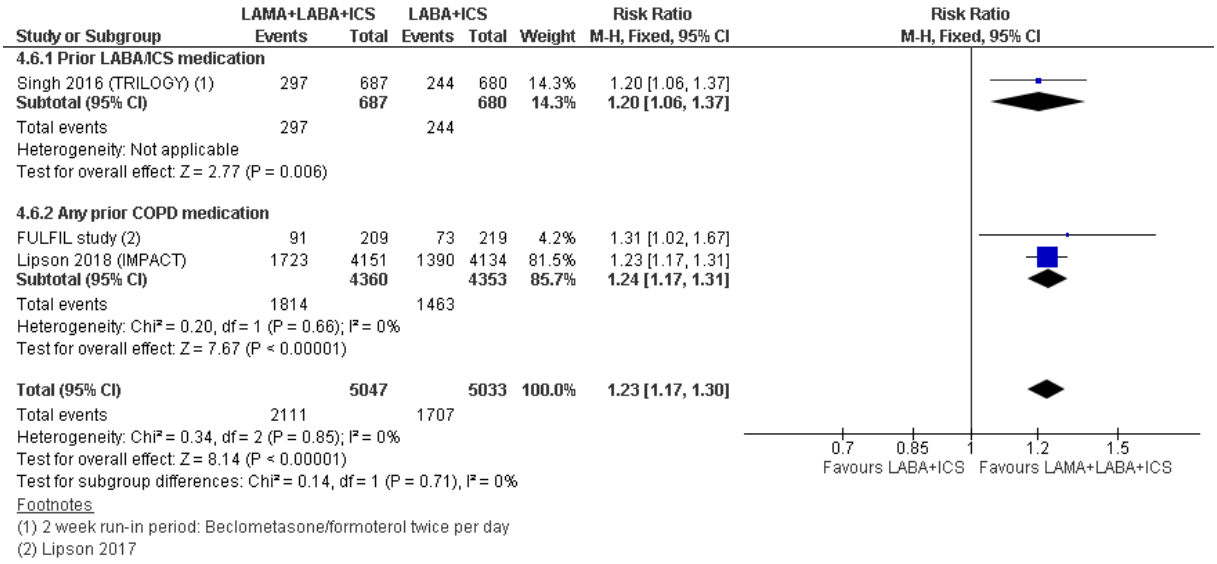


8

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

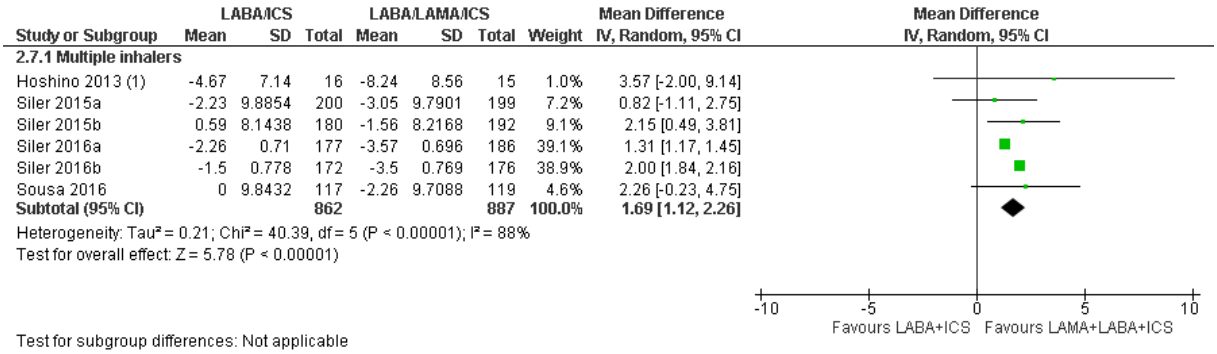


Prior medication



Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 3 months by:

Number of inhalers (multiple or single inhalers)

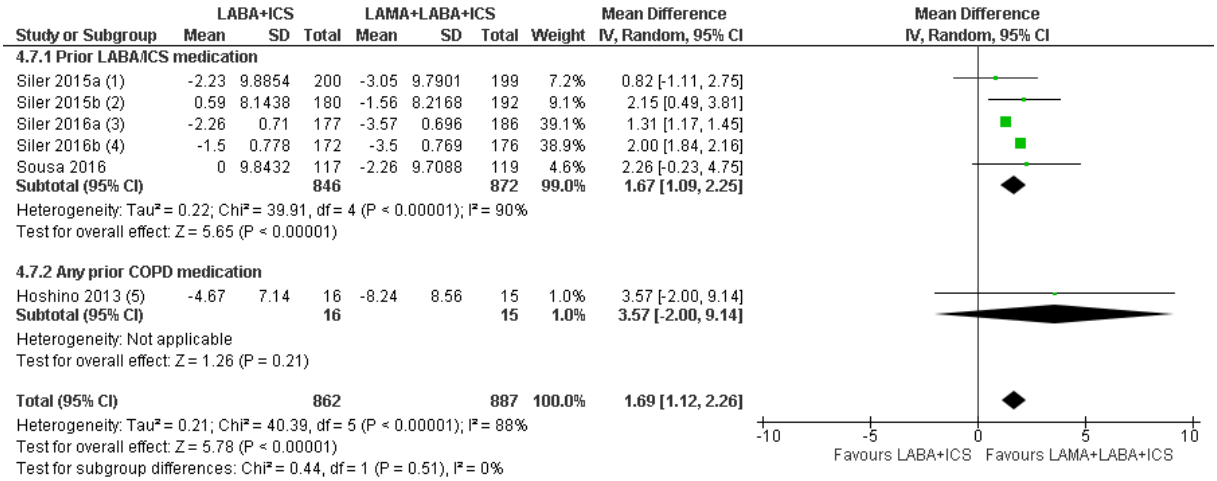


Test for subgroup differences: Not applicable

Footnotes

(1) 4 months

Prior medication



Footnotes

(1) 4 week run-in period: salmeterol/fluticasone

(2) 4 week run-in period: salmeterol/fluticasone

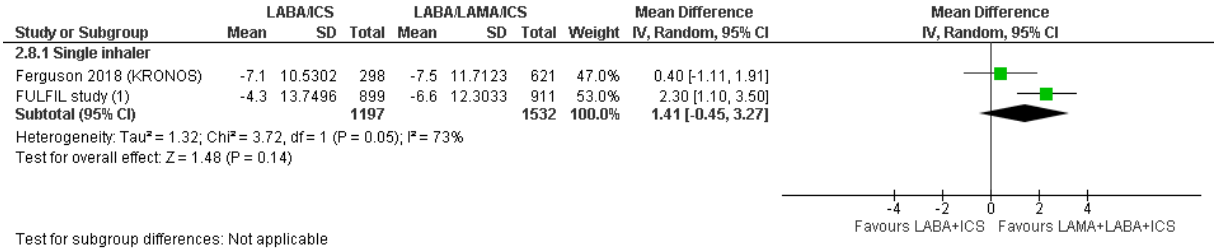
(3) 4 week run-in period: salmeterol/fluticasone

(4) 4 week run-in period: salmeterol/fluticasone

(5) 4 months

Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 6 months by:

Number of inhalers (multiple or single inhalers)



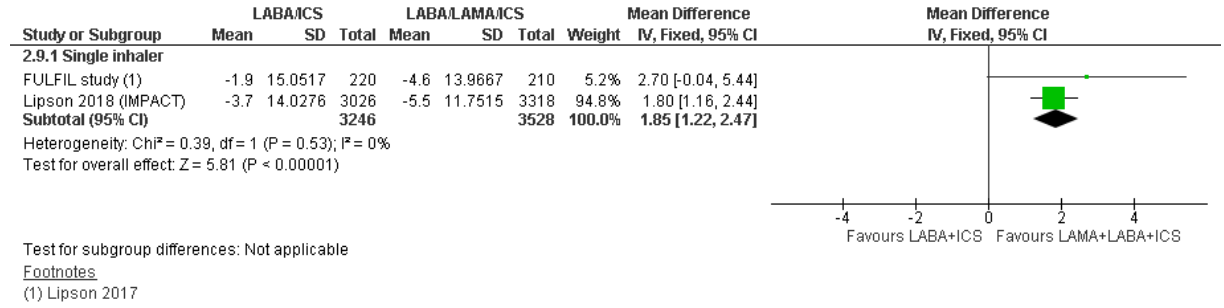
Test for subgroup differences: Not applicable

Footnotes

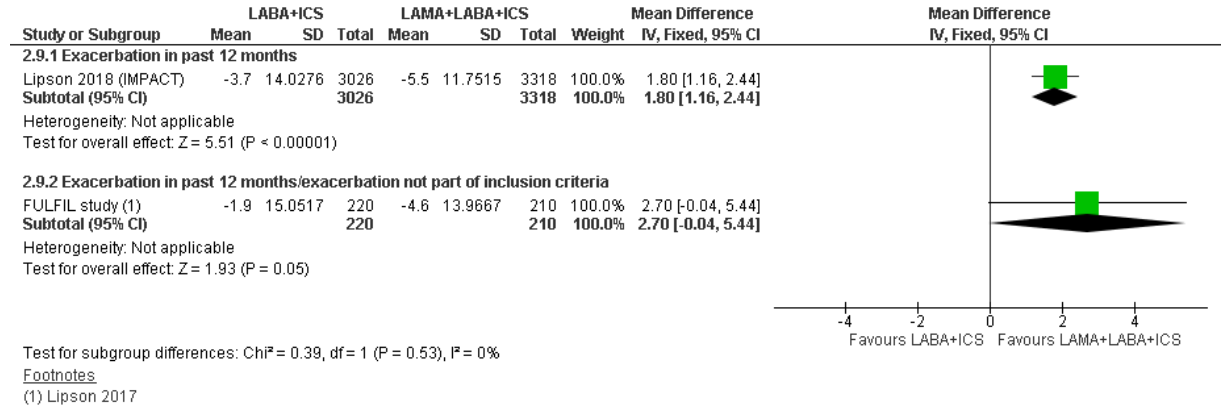
(1) Lipson 2017

Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 12 months by:

Number of inhalers (multiple or single inhalers)

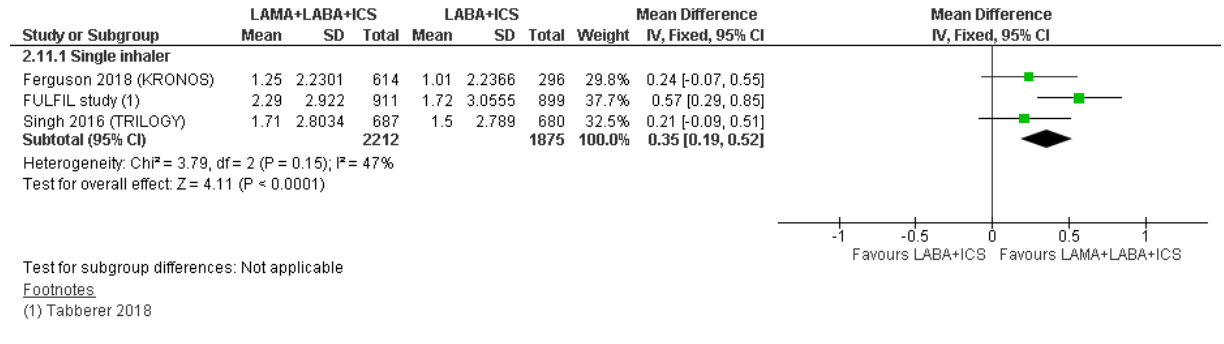


Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

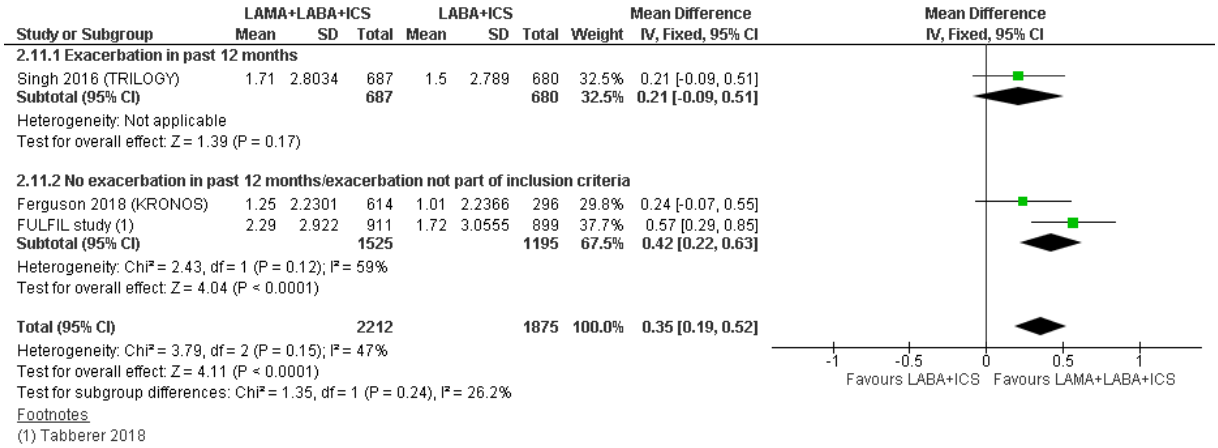


Transition Dyspnoea Index (TDI) at 6 months by:

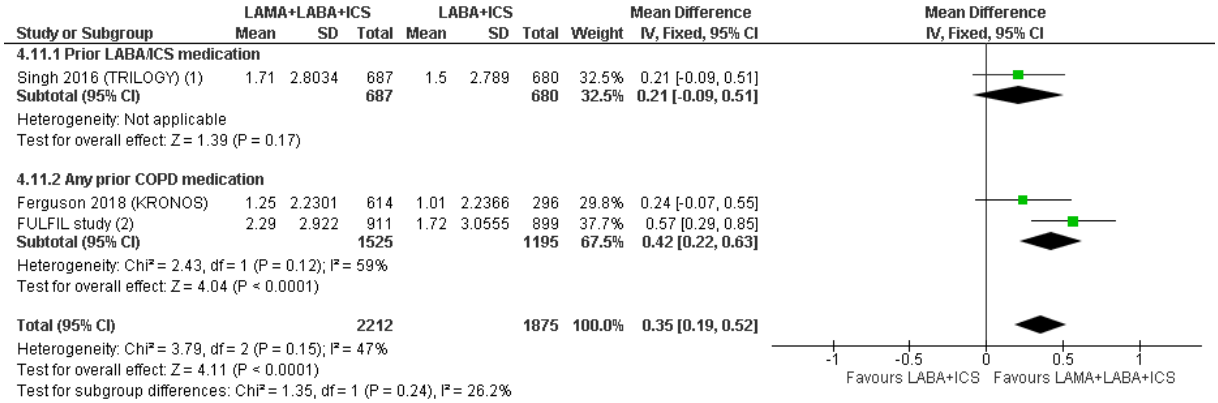
Number of inhalers (multiple or single inhalers)



Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

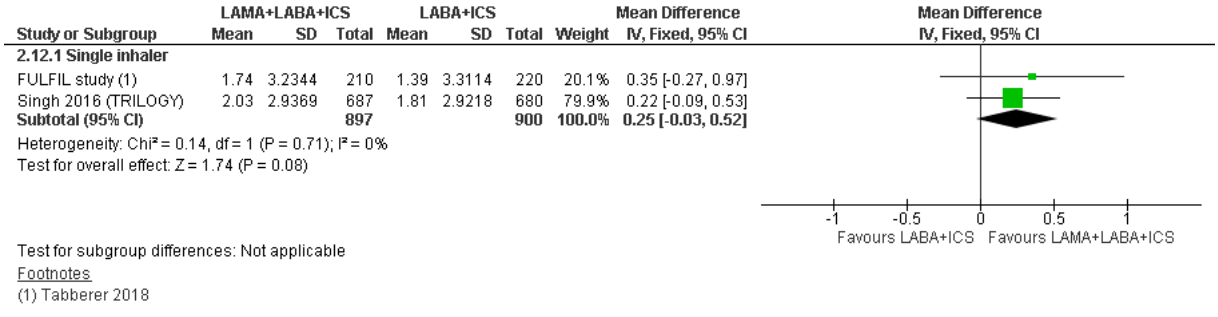


Prior medication

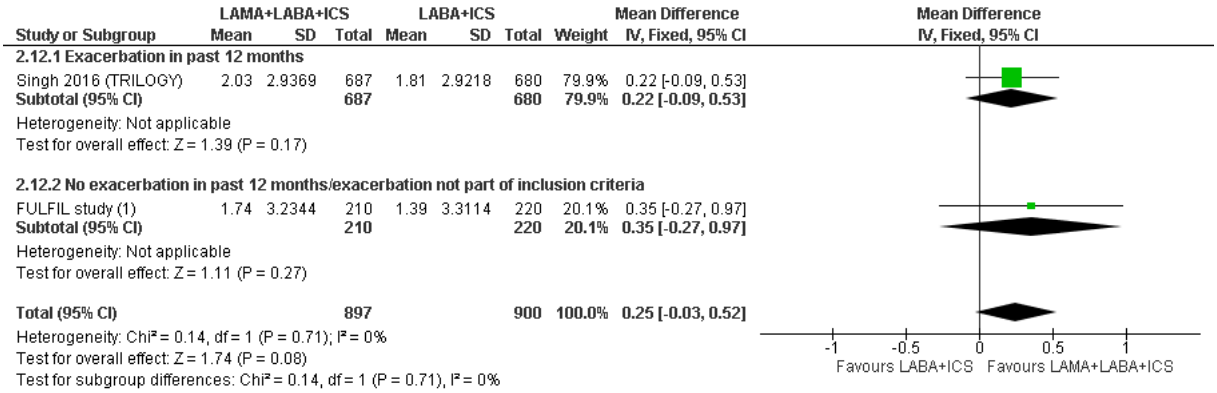


Transition Dyspnoea Index (TDI) at 12 months by:

Number of inhalers (multiple or single inhalers)



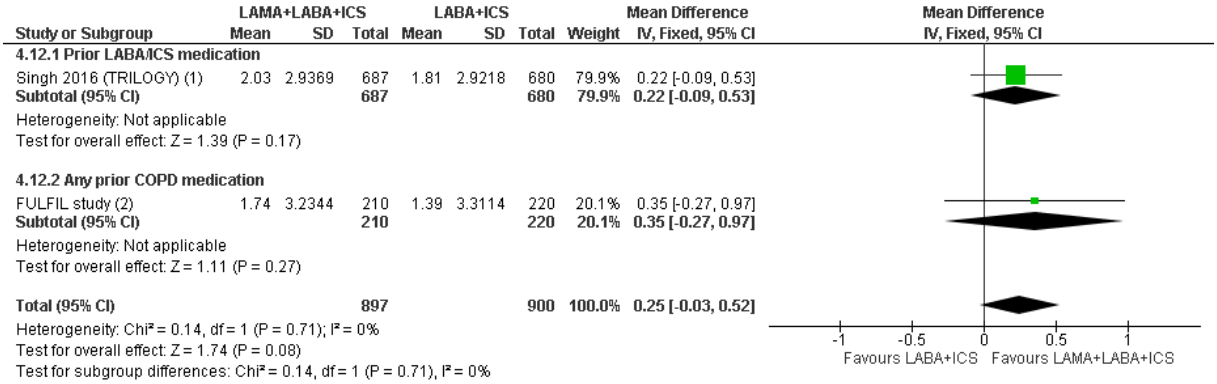
Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



Footnotes

(1) Tabberer 2018

Prior medication



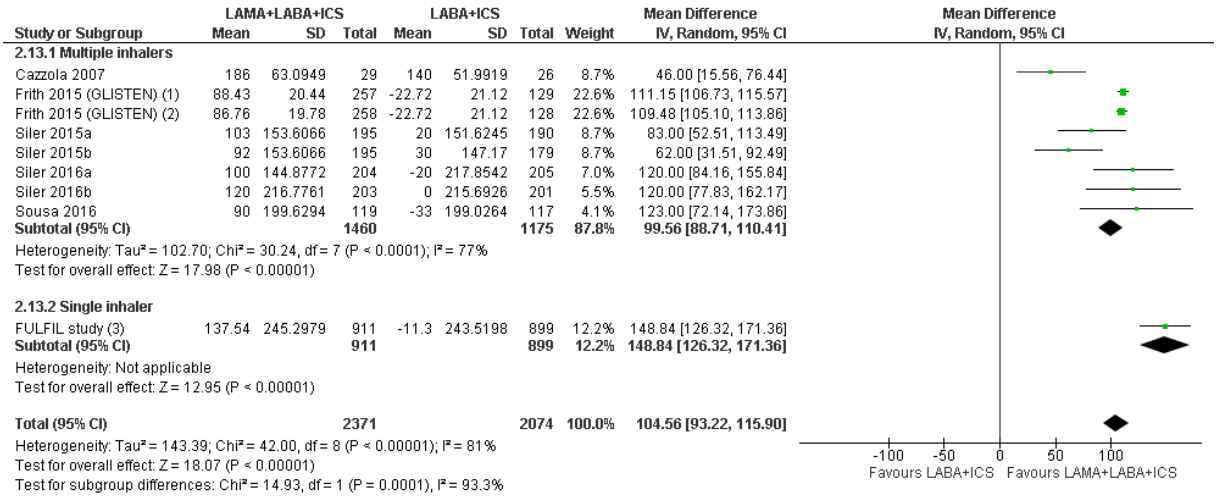
Footnotes

(1) 2 week run-in period: Beclometasone/formoterol twice per day

(2) Tabberer 2018

Change from baseline in FEV1 at 3 months by:

Number of inhalers (multiple or single inhalers)



Footnotes

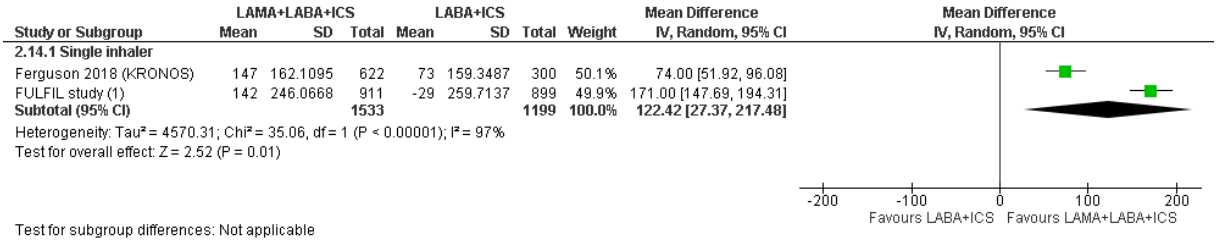
(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone

(2) Triple therapy: Tiotropium + salmeterol/fluticasone

(3) Lipson 2017

Change from baseline in FEV1 at 6 months by:

Number of inhalers (multiple or single inhalers)



Study or Subgroup	LAMA+LABA+ICS Mean	SD	Total	LABA+ICS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.14.1 Single inhaler								
Ferguson 2018 (KRONOS)	147	162.1095	622	73	159.3487	300	50.1%	74.00 [51.92, 96.08]
FULFIL study (1)	142	246.0668	911	-29	259.7137	899	49.9%	171.00 [147.69, 194.31]
Subtotal (95% CI)			**1533**			**1199**	**100.0%**	**122.42 [27.37, 217.48]**

Heterogeneity: Tau² = 4570.31; Chi² = 35.06, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.52 (P = 0.01)

Mean Difference IV, Random, 95% CI

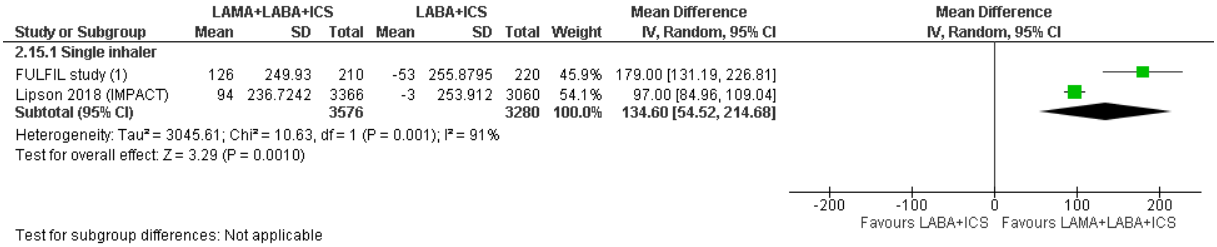
-200 -100 0 100 200
Favours LABA+ICS Favours LAMA+LABA+ICS

Test for subgroup differences: Not applicable

Footnotes
(1) Lipson 2017

Change from baseline in FEV1 at 12 months by:

Number of inhalers (multiple or single inhalers)



Study or Subgroup	LAMA+LABA+ICS Mean	SD	Total	LABA+ICS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.15.1 Single inhaler								
FULFIL study (1)	126	249.93	210	-53	255.8795	220	45.9%	179.00 [131.19, 226.81]
Lipson 2018 (IMPACT)	94	236.7242	3366	-3	253.912	3060	54.1%	97.00 [84.96, 109.04]
Subtotal (95% CI)			**3576**			**3280**	**100.0%**	**134.60 [54.52, 214.68]**

Heterogeneity: Tau² = 3045.61; Chi² = 10.63, df = 1 (P = 0.001); I² = 91%
Test for overall effect: Z = 3.29 (P = 0.0010)

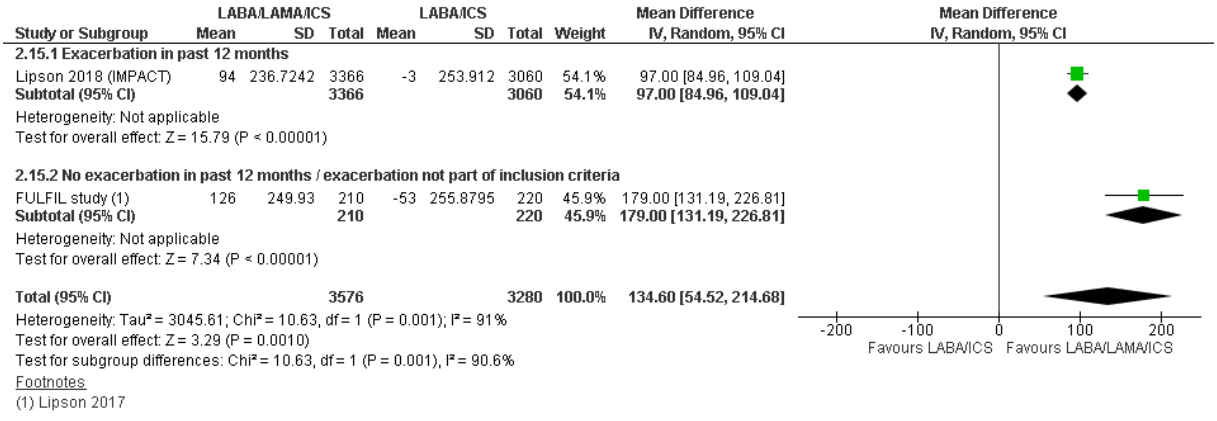
Mean Difference IV, Random, 95% CI

-200 -100 0 100 200
Favours LABA+ICS Favours LAMA+LABA+ICS

Test for subgroup differences: Not applicable

Footnotes
(1) Lipson 2017

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)



Study or Subgroup	LABA/LAMA/ICS Mean	SD	Total	LABA/ICS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.15.1 Exacerbation in past 12 months								
Lipson 2018 (IMPACT)	94	236.7242	3366	-3	253.912	3060	54.1%	97.00 [84.96, 109.04]
Subtotal (95% CI)			**3366**			**3060**	**54.1%**	**97.00 [84.96, 109.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 15.79 (P < 0.00001)								
2.15.2 No exacerbation in past 12 months / exacerbation not part of inclusion criteria								
FULFIL study (1)	126	249.93	210	-53	255.8795	220	45.9%	179.00 [131.19, 226.81]
Subtotal (95% CI)			**210**			**220**	**45.9%**	**179.00 [131.19, 226.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.34 (P < 0.00001)								
Total (95% CI)			**3576**			**3280**	**100.0%**	**134.60 [54.52, 214.68]**

Heterogeneity: Tau² = 3045.61; Chi² = 10.63, df = 1 (P = 0.001); I² = 91%
Test for overall effect: Z = 3.29 (P = 0.0010)
Test for subgroup differences: Chi² = 10.63, df = 1 (P = 0.001), I² = 90.6%

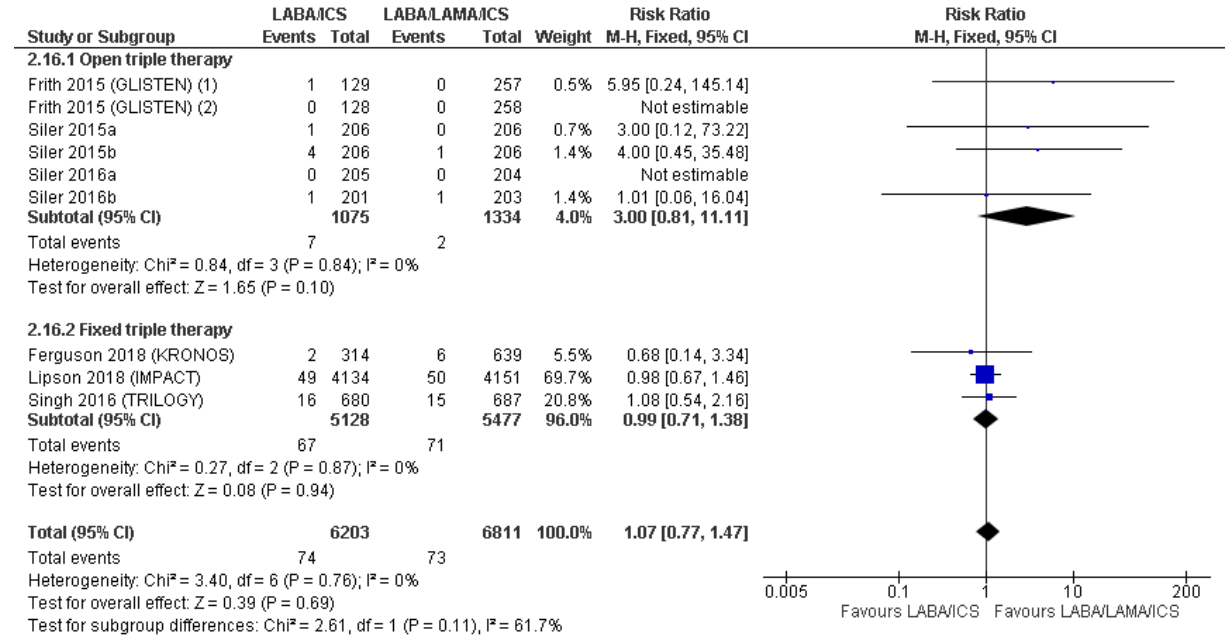
Mean Difference IV, Random, 95% CI

-200 -100 0 100 200
Favours LABA/ICS Favours LABA/LAMA/ICS

Footnotes
(1) Lipson 2017

All-cause mortality by:

Number of inhalers (multiple or single inhalers)

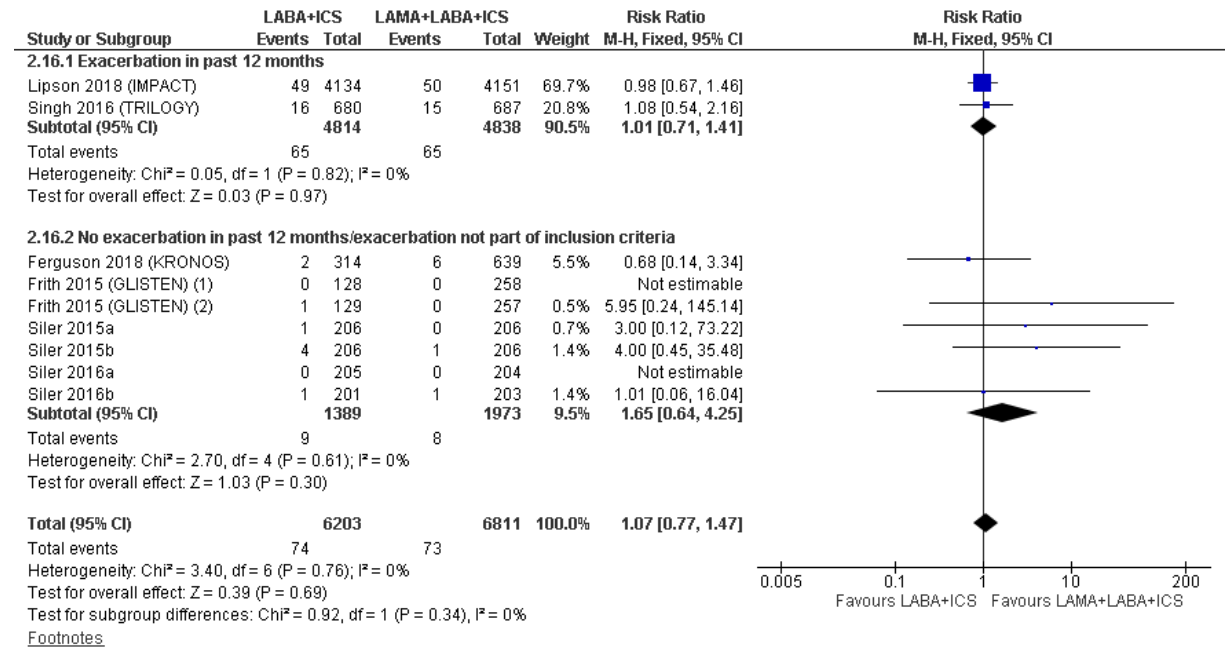


Footnotes

(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

(2) Triple therapy: Tiotropium + salmeterol/fluticasone. 1 death for LABA/ICS but not reported because data was split to allow comparisons with two triple...

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

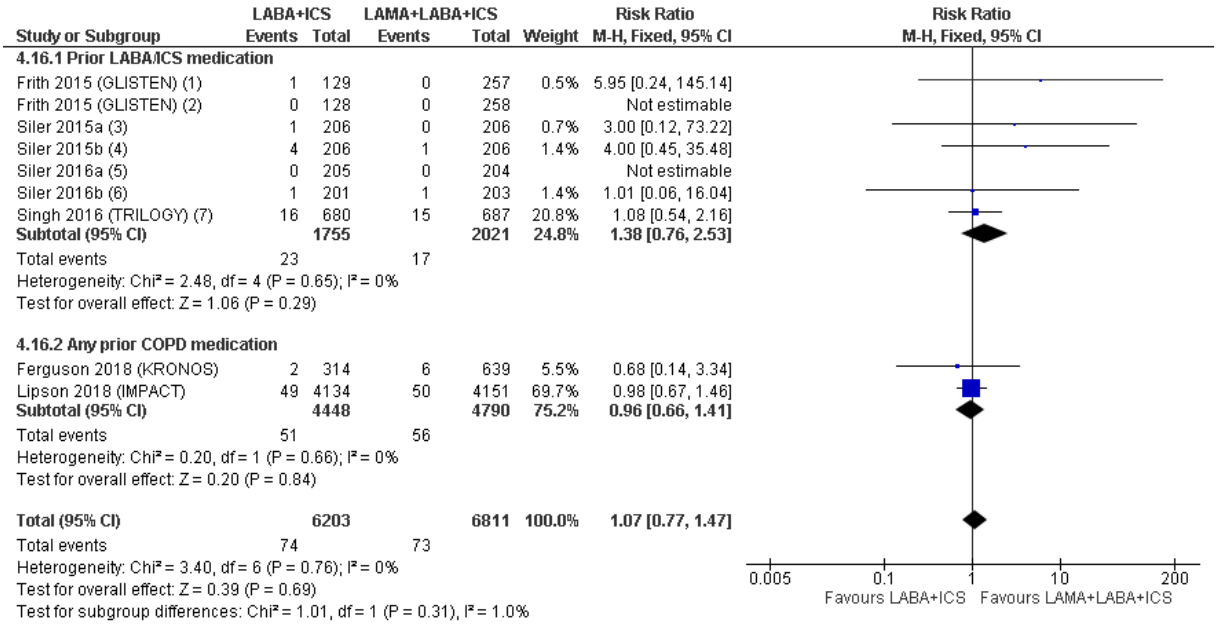


Footnotes

(1) Triple therapy: Tiotropium + salmeterol/fluticasone. 1 death for LABA/ICS but not reported because data was split to allow comparisons with two triple...

(2) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

1 ***Prior medication***



Footnotes

(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations. 1 week run-in...

(2) Triple therapy: Tiotropium + salmeterol/fluticasone. 1 death for LABA/ICS but not reported because data was split to allow comparisons with two triple...

(3) 4 week run-in period: salmeterol/fluticasone

(4) 4 week run-in period: salmeterol/fluticasone

(5) 4 week run-in period: salmeterol/fluticasone

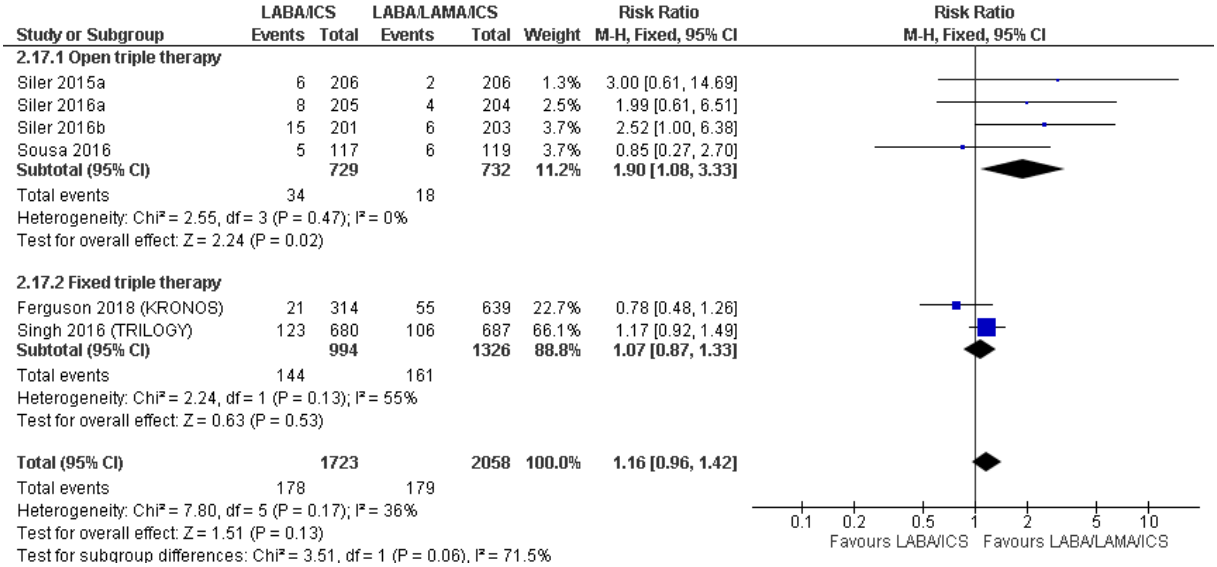
(6) 4 week run-in period: salmeterol/fluticasone

(7) 2 week run-in period: Beclometasone/formoterol twice per day

2

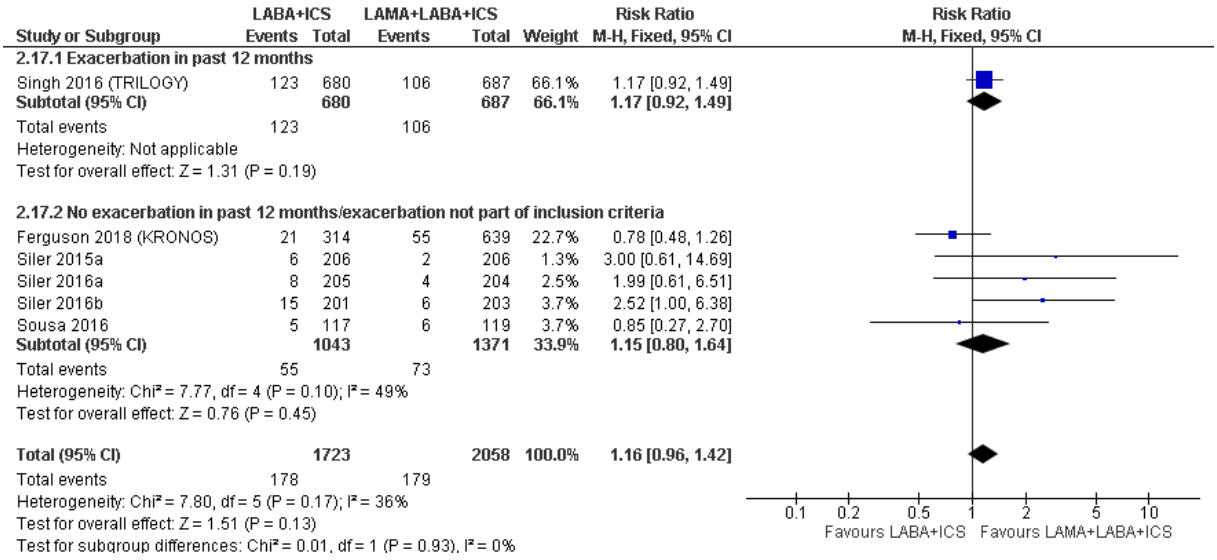
3 **Total serious adverse events by:**

4 ***Number of inhalers (multiple or single inhalers)***

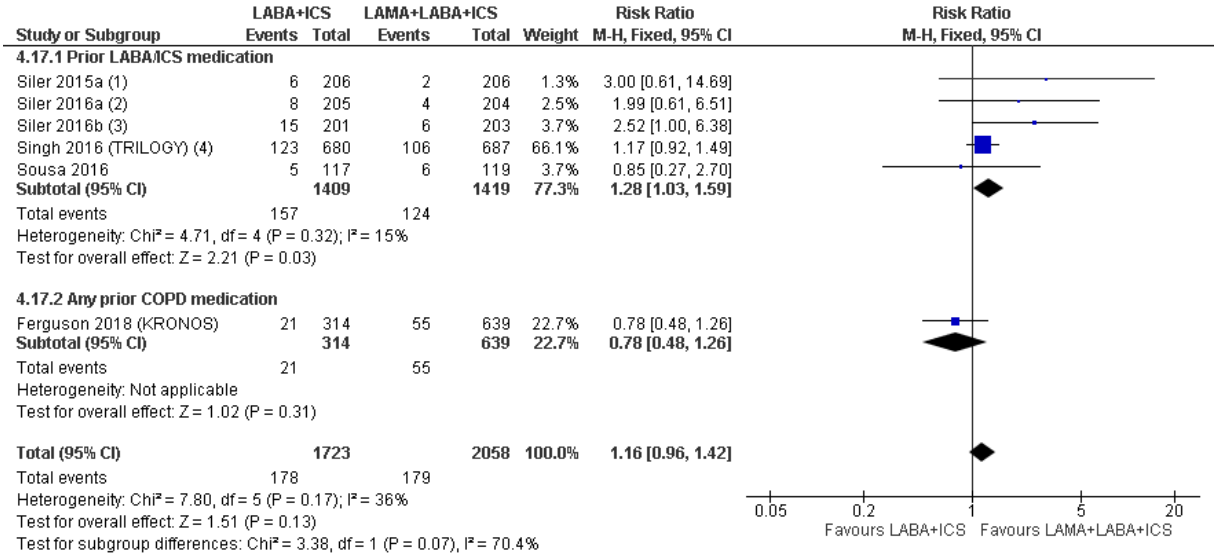


5

Previous exacerbation (occurrence or no exacerbations in past 12 months as part of inclusion criteria)

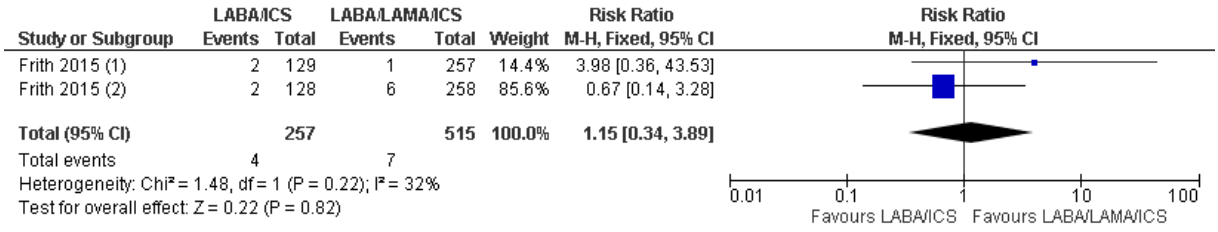


Prior medication



1 **Cardiac serious adverse events by:**

2 ***Number of inhalers (multiple or single inhalers)***



Study or Subgroup	LABA/ICS Events	LABA/ICS Total	LABA/LAMA/ICS Events	LABA/LAMA/ICS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frith 2015 (1)	2	129	1	257	14.4%	3.98 [0.36, 43.53]
Frith 2015 (2)	2	128	6	258	85.6%	0.67 [0.14, 3.28]
Total (95% CI)		**257**		**515**	**100.0%**	**1.15 [0.34, 3.89]**
Total events	4		7			

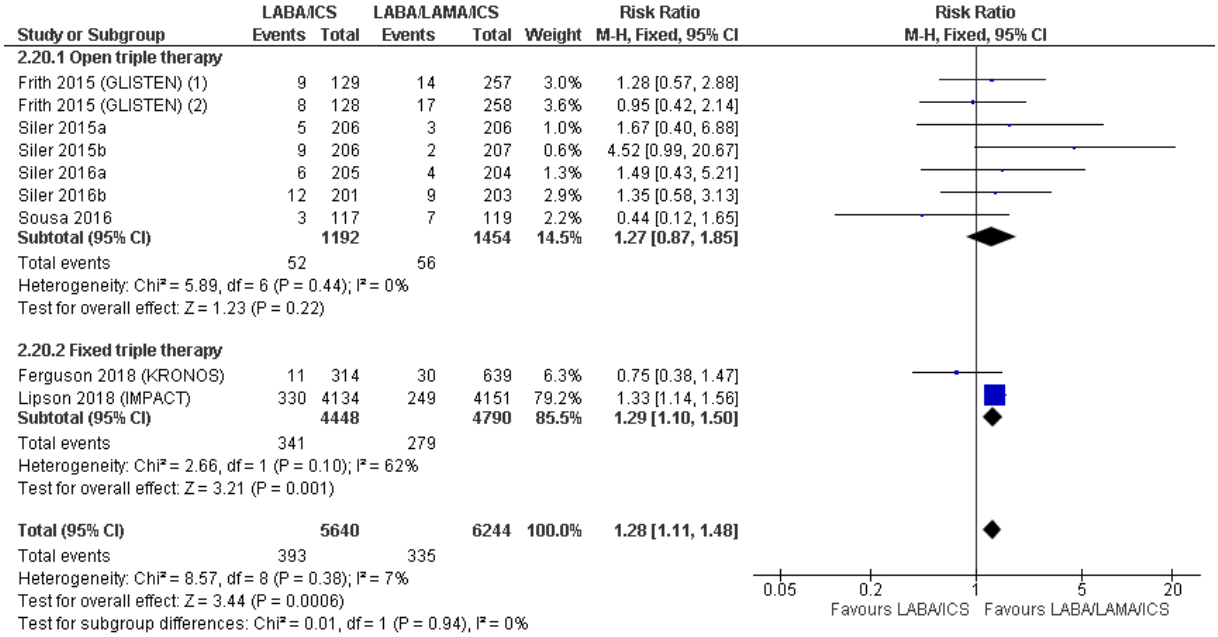
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 0.22 (P = 0.82)

Footnotes
(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations
(2) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

3

4 **Dropout due to adverse events by:**

5 ***Number of inhalers (multiple or single inhalers)***

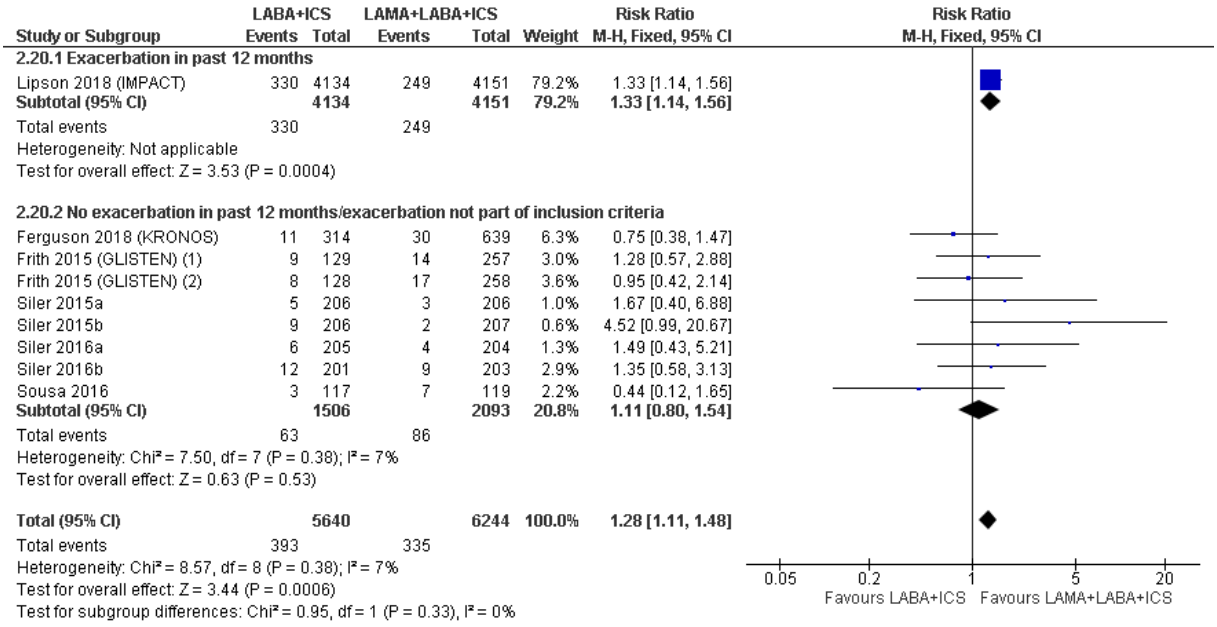


Study or Subgroup	LABA/ICS Events	LABA/ICS Total	LABA/LAMA/ICS Events	LABA/LAMA/ICS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.20.1 Open triple therapy						
Frith 2015 (GLISTEN) (1)	9	129	14	257	3.0%	1.28 [0.57, 2.88]
Frith 2015 (GLISTEN) (2)	8	128	17	258	3.6%	0.95 [0.42, 2.14]
Siler 2015a	5	206	3	206	1.0%	1.67 [0.40, 6.88]
Siler 2015b	9	206	2	207	0.6%	4.52 [0.99, 20.67]
Siler 2016a	6	205	4	204	1.3%	1.49 [0.43, 5.21]
Siler 2016b	12	201	9	203	2.9%	1.35 [0.58, 3.13]
Sousa 2016	3	117	7	119	2.2%	0.44 [0.12, 1.65]
Subtotal (95% CI)		**1192**		**1454**	**14.5%**	**1.27 [0.87, 1.85]**
Total events	52		56			
Heterogeneity: Chi² = 5.89, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.23 (P = 0.22)						
2.20.2 Fixed triple therapy						
Ferguson 2018 (KRONOS)	11	314	30	639	6.3%	0.75 [0.38, 1.47]
Lipson 2018 (IMPACT)	330	4134	249	4151	79.2%	1.33 [1.14, 1.56]
Subtotal (95% CI)		**4448**		**4790**	**85.5%**	**1.29 [1.10, 1.50]**
Total events	341		279			
Heterogeneity: Chi² = 2.66, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 3.21 (P = 0.001)						
Total (95% CI)		**5640**		**6244**	**100.0%**	**1.28 [1.11, 1.48]**
Total events	393		335			
Heterogeneity: Chi² = 8.57, df = 8 (P = 0.38); I² = 7%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						

Footnotes
(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations
(2) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

6

1 ***Previous exacerbation (occurrence or no exacerbations in past 12 months as part of***
2 ***inclusion criteria)***



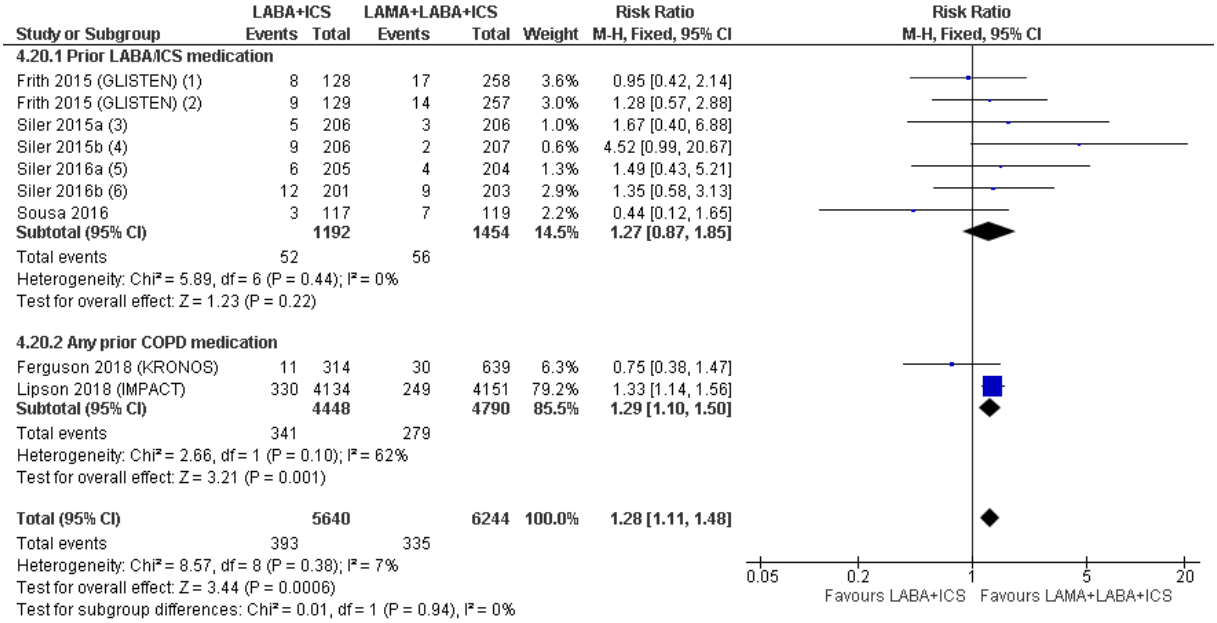
Footnotes

(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

(2) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

3

4 ***Prior medication***



Footnotes

(1) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations. 1 week run-in...

(2) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations. 1 week run-in...

(3) 4 week run-in period: salmeterol/fluticasone

(4) 4 week run-in period: salmeterol/fluticasone

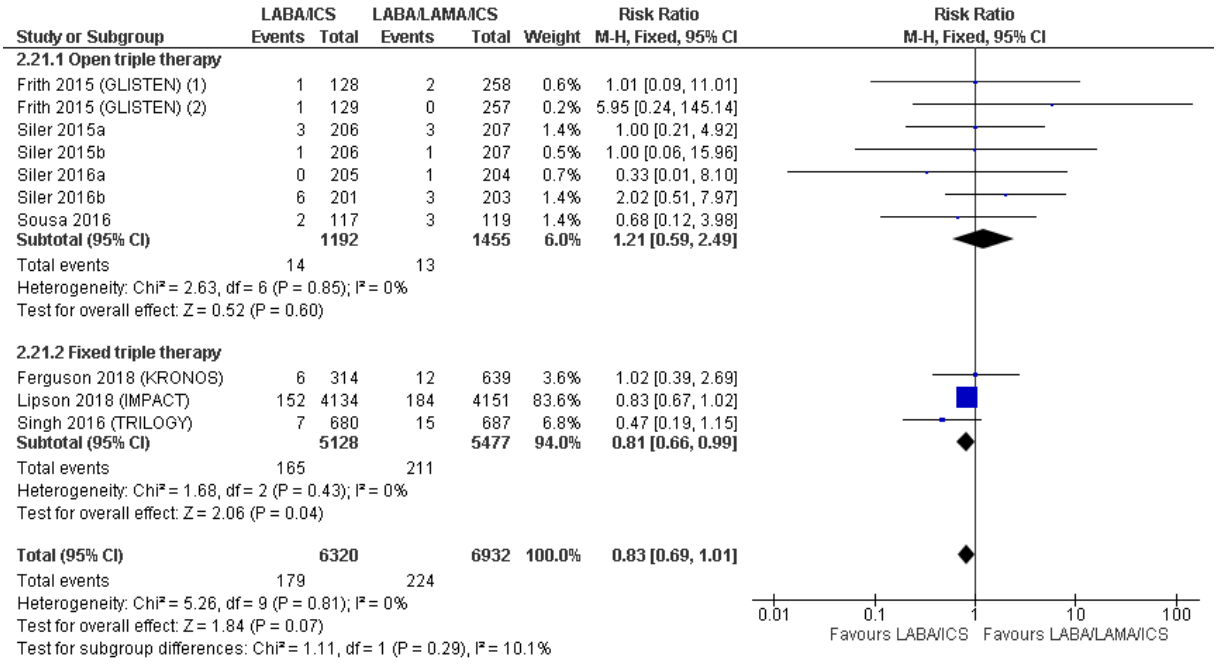
(5) 4 week run-in period: salmeterol/fluticasone

(6) 4 week run-in period: salmeterol/fluticasone

5

1 **Pneumonia by:**

2 ***Number of inhalers (multiple or single inhalers)***



Study or Subgroup	LABA/ICS Events	LABA/ICS Total	LABA/LAMA/ICS Events	LABA/LAMA/ICS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.21.1 Open triple therapy						
Frith 2015 (GLISTEN) (1)	1	128	2	258	0.6%	1.01 [0.09, 11.01]
Frith 2015 (GLISTEN) (2)	1	129	0	257	0.2%	5.95 [0.24, 145.14]
Siler 2015a	3	206	3	207	1.4%	1.00 [0.21, 4.92]
Siler 2015b	1	206	1	207	0.5%	1.00 [0.06, 15.96]
Siler 2016a	0	205	1	204	0.7%	0.33 [0.01, 8.10]
Siler 2016b	6	201	3	203	1.4%	2.02 [0.51, 7.97]
Sousa 2016	2	117	3	119	1.4%	0.68 [0.12, 3.98]
Subtotal (95% CI)		**1192**		**1455**	**6.0%**	**1.21 [0.59, 2.49]**
Total events	14		13			
Heterogeneity: Chi² = 2.63, df = 6 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
2.21.2 Fixed triple therapy						
Ferguson 2018 (KRONOS)	6	314	12	639	3.6%	1.02 [0.39, 2.69]
Lipson 2018 (IMPACT)	152	4134	184	4151	83.6%	0.83 [0.67, 1.02]
Singh 2016 (TRILOGY)	7	680	15	687	6.8%	0.47 [0.19, 1.15]
Subtotal (95% CI)		**5128**		**5477**	**94.0%**	**0.81 [0.66, 0.99]**
Total events	165		211			
Heterogeneity: Chi² = 1.68, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)		**6320**		**6932**	**100.0%**	**0.83 [0.69, 1.01]**
Total events	179		224			
Heterogeneity: Chi² = 5.26, df = 9 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 10.1%						

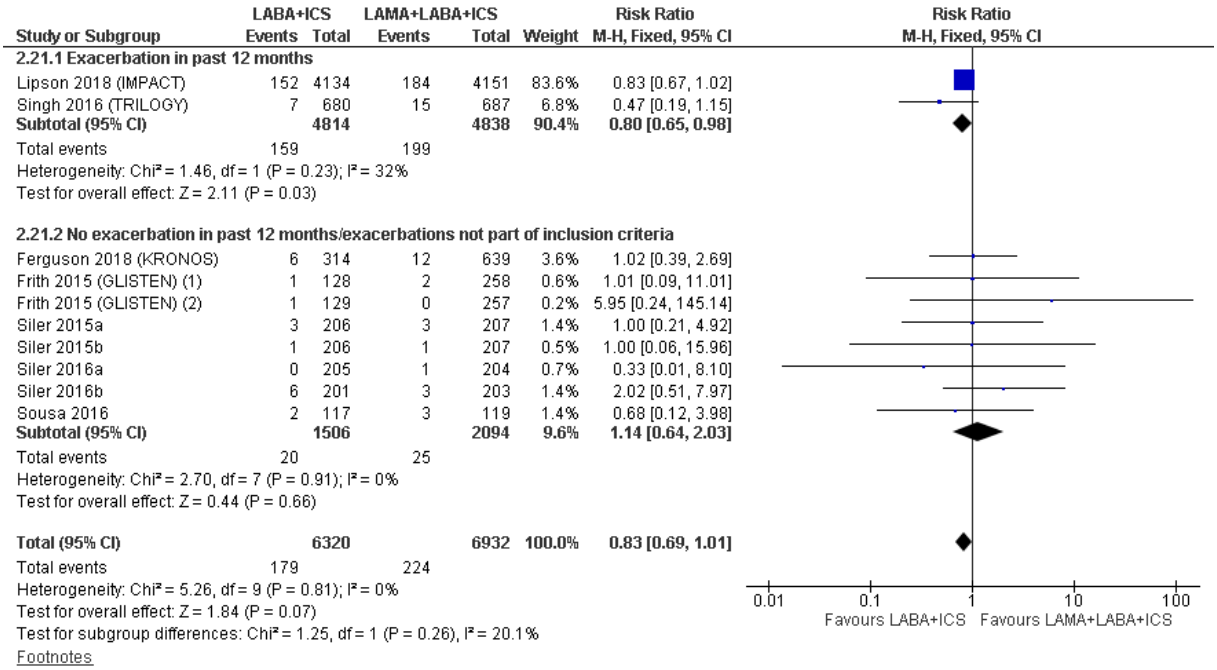
Footnotes

(1) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

(2) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

3

4 ***Previous exacerbation (occurrence or no exacerbations in past 12 months as part of***
5 ***inclusion criteria)***



Study or Subgroup	LABA+ICS Events	LABA+ICS Total	LAMA+LABA+ICS Events	LAMA+LABA+ICS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.21.1 Exacerbation in past 12 months						
Lipson 2018 (IMPACT)	152	4134	184	4151	83.6%	0.83 [0.67, 1.02]
Singh 2016 (TRILOGY)	7	680	15	687	6.8%	0.47 [0.19, 1.15]
Subtotal (95% CI)		**4814**		**4838**	**90.4%**	**0.80 [0.65, 0.98]**
Total events	159		199			
Heterogeneity: Chi² = 1.46, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 2.11 (P = 0.03)						
2.21.2 No exacerbation in past 12 months/exacerbations not part of inclusion criteria						
Ferguson 2018 (KRONOS)	6	314	12	639	3.6%	1.02 [0.39, 2.69]
Frith 2015 (GLISTEN) (1)	1	128	2	258	0.6%	1.01 [0.09, 11.01]
Frith 2015 (GLISTEN) (2)	1	129	0	257	0.2%	5.95 [0.24, 145.14]
Siler 2015a	3	206	3	207	1.4%	1.00 [0.21, 4.92]
Siler 2015b	1	206	1	207	0.5%	1.00 [0.06, 15.96]
Siler 2016a	0	205	1	204	0.7%	0.33 [0.01, 8.10]
Siler 2016b	6	201	3	203	1.4%	2.02 [0.51, 7.97]
Sousa 2016	2	117	3	119	1.4%	0.68 [0.12, 3.98]
Subtotal (95% CI)		**1506**		**2094**	**9.6%**	**1.14 [0.64, 2.03]**
Total events	20		25			
Heterogeneity: Chi² = 2.70, df = 7 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**6320**		**6932**	**100.0%**	**0.83 [0.69, 1.01]**
Total events	179		224			
Heterogeneity: Chi² = 5.26, df = 9 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 1.25, df = 1 (P = 0.26), I² = 20.1%						

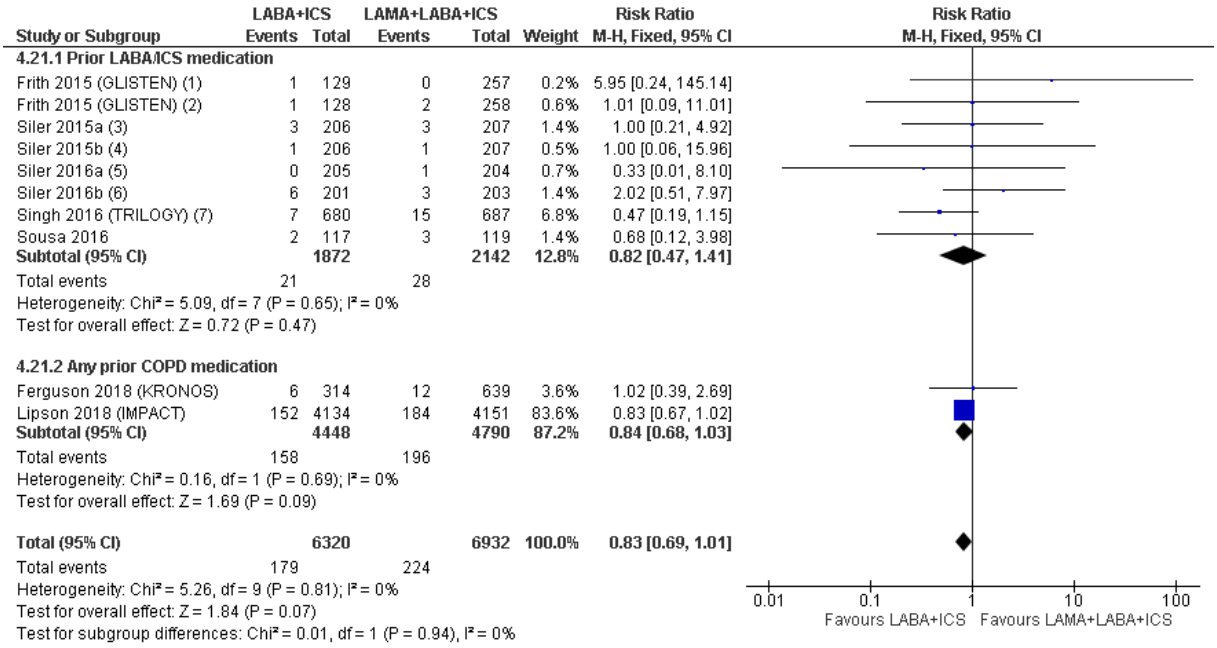
Footnotes

(1) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

(2) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations

6

1 ***Prior medication***



Footnotes

(1) Triple therapy: Glycopyrronium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations. 1 week run-in...
(2) Triple therapy: Tiotropium + salmeterol/fluticasone. Events and n halved to allow for comparisons with two triple therapy combinations. 1 week run-in...
(3) 4 week run-in period: salmeterol/fluticasone
(4) 4 week run-in period: salmeterol/fluticasone
(5) 4 week run-in period: salmeterol/fluticasone
(6) 4 week run-in period: salmeterol/fluticasone
(7) 2 week run-in period: Beclometasone/formoterol twice per day

2

Appendix G – GRADE tables

Triple therapy versus LAMA+LABA

Pooled results are shown (based on the inhaler subgroup meta-analyses), unless subgroup differences were detected. In these cases the relevant subgroup analyses are also presented.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Moderate to severe exacerbations (events) (RR>1 favours triple therapy)										
1 (Aaron 2007)	RCT	293	RR 1.08 (0.90, 1.29)	65 per 100	60 per 100 (45, 72)	Not serious	N/A	Not serious	Serious[2]	Moderate
Rate of moderate to severe exacerbations (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)										
3	RCT	9,017	IRR 1.17 (1.11, 1.23)	-	-	Not serious	Not serious	Not serious	Not serious	High
Severe exacerbations (events) (RR>1 favours triple therapy)										
1 (Aaron 2007)	RCT	293	RR 1.43 (0.92, 2.23)	26 per 100	18 per 100 (11, 28)	Not serious	N/A	Not serious	Serious[2]	Moderate
Rate of severe exacerbations (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)										
2	RCT	7,753	IRR 1.22 (1.11, 1.34)	-	-	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 6 months (RR>1 favours triple therapy)										
2	RCT	2,796	RR 1.10 (1.01, 1.20)	44 per 100	48 per 100 (44, 52)	Not serious	Not serious	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 12 months (RR>1 favours triple therapy)										
2	RCT	7,753	RR 1.21 (1.14, 1.29)	34 per 100	42 per 100 (39, 44)	Not serious	Serious[1]	Not serious	Serious[2]	Low
Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 12 months (MD>0 favours triple therapy)										
1 (Ferguson 2018)	RCT	1,216	MD 1.20 (-0.10, 2.50)	-	-	Not serious	N/A	Not serious	Not serious	High
Transition Dyspnoea Index (TDI) at 6 months (MD>0 favours triple therapy)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Ferguson 2018)	RCT	1,201	MD 0.18 (-0.07, 0.43)	-	-	Not serious	N/A	Not serious	Not serious	High
Transition Dyspnoea Index (TDI) at 12 months (MD>0 favours triple therapy)										
1 (Aaron 2007)	RCT	293	MD 0.44 (-0.46, 1.34)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
Change from baseline in FEV1 at 6 months (MD>0 favours triple therapy)										
1 (Ferguson 2018)	RCT	1,223	MD 22.00 (3.84, 40.16)	-	-	Not serious	N/A	Not serious	Not serious	High
Change from baseline in FEV1 at 12 months (MD>0 favours triple therapy)										
1 (Lipson 2018)	RCT	6,221	MD 54.00 (39.58, 68.42)	-	-	Not serious	N/A	Not serious	Not serious	High
All-cause mortality (RR>1 favours triple therapy)										
4	RCT	9,310	RR 1.43 (1.00, 2.04)	2 per 100	1 per 100 (1, 2)	Not serious	Not serious	Not serious	Serious[2]	Moderate
Total serious adverse events (RR>1 favours triple therapy)										
4	RCT	9,310	RR 1.07 (0.99, 1.17)	19 per 100	17 per 100 (16, 19)	Not serious	Not serious	Not serious	Not serious	High
COPD serious adverse events (RR>1 favours triple therapy)										
1 (Papi 2018)	RCT	1,532	RR 1.13 (0.81, 1.56)	9 per 100	8 per 100 (6, 11)	Not serious	N/A	Not serious	Serious[2]	Moderate
Cardiac serious adverse events (RR>1 favours triple therapy)										
1 (Papi 2018)	RCT	1,532	RR 1.16 (0.39, 3.44)	1 per 100	1 per 100 (0, 2)	Not serious	N/A	Not serious	Very serious[3]	Low
Dropout due to adverse events (RR>1 favours triple therapy)										
4	RCT	9,310	RR 1.38 (1.18, 1.61)	7 per 100	5 per 100 (5, 6)	Not serious	Not serious	Not serious	Serious[2]	Moderate
Pneumonia (RR>1 favours triple therapy)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3	RCT	9,017	RR 0.65 (0.50, 0.84)	2 per 100	4 per 100 (3, 5)	Not serious	Not serious	Not serious	Serious[2]	Moderate

1. I^2 between 33.3% and 66.7%
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% confidence interval crosses both ends of a defined MID interval

1 Triple therapy versus LABA+ICS

2 Pooled results are shown (based on the inhaler subgroup meta-analyses), unless subgroup differences were detected. In these cases the relevant
3 subgroup analyses are also presented.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Moderate to severe exacerbations (events) (RR>1 favours triple therapy)										
7*	RCT	5,052	RR 1.22 (1.08, 1.38)	17 per 100	14 per 100 (12, 16)	Serious[1]	Not serious	Not serious	Serious[5]	Low
Rate of moderate to severe exacerbations (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)										
3	RCT	10,605	IRR 1.18 (1.12, 1.24)	-	-	Not serious	Not serious	Not serious	Not serious	High
Eosinophil count subgroup analysis ***Subgroup analysis: Rate of moderate to severe exacerbations: Lower eosinophils per microlitre subgroup (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)***										
3	RCT	4,953	IRR 1.16 (1.06, 1.26)	-	-	Not serious	Not serious	Not serious	Serious[5]	Moderate
Subgroup analysis: Rate of moderate to severe exacerbations: Higher eosinophils per microlitre subgroup (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)										
3	RCT	5,648	IRR 1.40 (1.26, 1.56)	-	-	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Rate of severe exacerbations (rate per patient per year) (Incidence rate ratio>1 favours triple therapy)										
1 (Lipson 2018)	RCT	8,285	IRR 1.51 (1.28, 1.78)	-	-	Not serious	N/A	Not serious	Not serious	High
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 3 months (RR>1 favours triple therapy)										
3	RCT	1,004	RR 1.18 (0.90, 1.54)	32 per 100	27 per 100 (20, 36)	Serious[1]	Serious[3]	Not serious	Serious[5]	Very low
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 6 months (RR>1 favours triple therapy)										
3	RCT	4,117	RR 1.22 (1.13, 1.30)	40 per 100	48 per 100 (45, 52)	Serious[1]	Not serious	Not serious	Serious[5]	Low
People with ≥ 4 units improvement in quality of life (St. George's Respiratory Questionnaire responders) at 12 months (RR>1 favours triple therapy)										
3	RCT	10,080	RR 1.23 (1.17, 1.30)	34 per 100	42 per 100 (40, 44)	Not serious	Not serious	Not serious	Serious[5]	Moderate
Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 3 months (MD>0 favours triple therapy)										
5	RCT	1,749	MD 1.69 (1.12, 2.26)	-	-	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 6 months (MD>0 favours triple therapy)										
2	RCT	2,729	MD 1.41 (-0.45, 3.27)	-	-	Serious[1]	Very serious[2]	Not serious	Not serious	Very low
Change from baseline in St. George's Respiratory Questionnaire (SGRQ), total score at 12 months (MD>0 favours triple therapy)										
2	RCT	6,774	MD 1.85 (1.22, 2.47)	-	-	Not serious	Not serious	Not serious	Not serious	High
Transition Dyspnoea Index (TDI) at 6 months (MD>0 favours triple therapy)										
3	RCT	4,087	MD 0.35 (0.19, 0.52)	-	-	Serious[1]	Serious[3]	Not serious	Not serious	Low
Transition Dyspnoea Index (TDI) at 12 months (MD>0 favours triple therapy)										
2	RCT	1,797	MD 0.25 (-0.03, 0.52)	-	-	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change from baseline in FEV1 at 3 months (MD>0 favours triple therapy)										
9**	RCT	4,445	MD 104.56 (93.22, 115.90)	-	-	Serious[1]	Very serious[2]	Not serious	Serious[5]	Very low
Inhaler type subgroup analysis ***Subgroup analysis change from baseline in FEV1 at 3 months: multiple inhaler triple therapy subgroup (MD>0 favours triple therapy)***										
8**	RCT	2,635	MD 99.56 (88.71,110.41)	-	-	Serious[1]	Very serious[2]	Not serious	Serious[5]	Very low
Subgroup analysis: change from baseline in FEV1 at 3 months: single inhaler triple therapy subgroup (MD>0 favours triple therapy)										
1 (Lipson 2017)	RCT	1,810	MD 148.84 (126.32, 171.36)	-	-	Serious[6]	N/A	Not serious	Not serious	Moderate
Change from baseline in FEV1 at 6 months (MD>0 favours triple therapy)										
2	RCT	2,732	MD 122.42 (27.37, 217.48)	-	-	Serious[1]	Very serious[2]	Not serious	Serious[5]	Very low
Change from baseline in FEV1 at 12 months (MD>0 favours triple therapy)										
2	RCT	6,856	MD 134.60 (54.52, 214.68)	-	-	Serious[1]	Very serious[2]	Not serious	Serious[5]	Very low
Previous exacerbation subgroup analysis ***Subgroup analysis: change from baseline in FEV1 at 12 months: exacerbation in past 12 months subgroup (MD>0 favours triple therapy)***										
1 (Lipson 2018)	RCT	6,426	MD 97.00 (84.96, 109.04)	-	-	Not serious	N/A	Not serious	Serious	Moderate
Subgroup analysis: change from baseline in FEV1 at 12 months: no exacerbation in past 12 months/exacerbations not part of inclusion criteria subgroup (MD>0 favours triple therapy)										
1 (Lipson 2017)	RCT	430	MD 179.00 (131.19, 226.81)	-	-	Serious[6]	N/A	Not serious	Not serious	Moderate
All-cause mortality (RR>1 favours triple therapy)										
8**	RCT	13,014	RR 1.07 (0.77, 1.47)	1 per 100	1 per 100 (1, 2)	Not serious	Not serious	Not serious	Very serious[4]	Low
Total serious adverse events (RR>1 favours triple therapy)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6	RCT	3,781	RR 1.16 (0.96, 1.42)	10 per 100	9 per 100 (7, 11)	Not serious	Serious[3]	Not serious	Serious[5]	Low
COPD serious adverse events (RR>1 favours triple therapy)										
1 (Singh 2016)	RCT	1,367	RR 1.17 (0.82, 1.65)	11 per 100	9 per 100 (7, 13)	Not serious	N/A	Not serious	Serious[5]	Moderate
Cardiac serious adverse events (RR>1 favours triple therapy)										
1** (Frith 2015)	RCT	772	RR 1.15 (0.34, 3.89)	2 per 100	1 per 100 (0, 5)	Serious[1]	N/A	Not serious	Very serious[4]	Very low
Dropout due to adverse events (RR>1 favours triple therapy)										
8**	RCT	11,884	RR 1.28 (1.11, 1.48)	7 per 100	5 per 100 (5, 6)	Not serious	Not serious	Not serious	Serious[5]	Moderate
Pneumonia (RR>1 favours triple therapy)										
9**	RCT	13,252	RR 0.83 (0.69, 1.01)	3 per 100	3 per 100 (3, 4)	Not serious	Not serious	Not serious	Serious[5]	Moderate

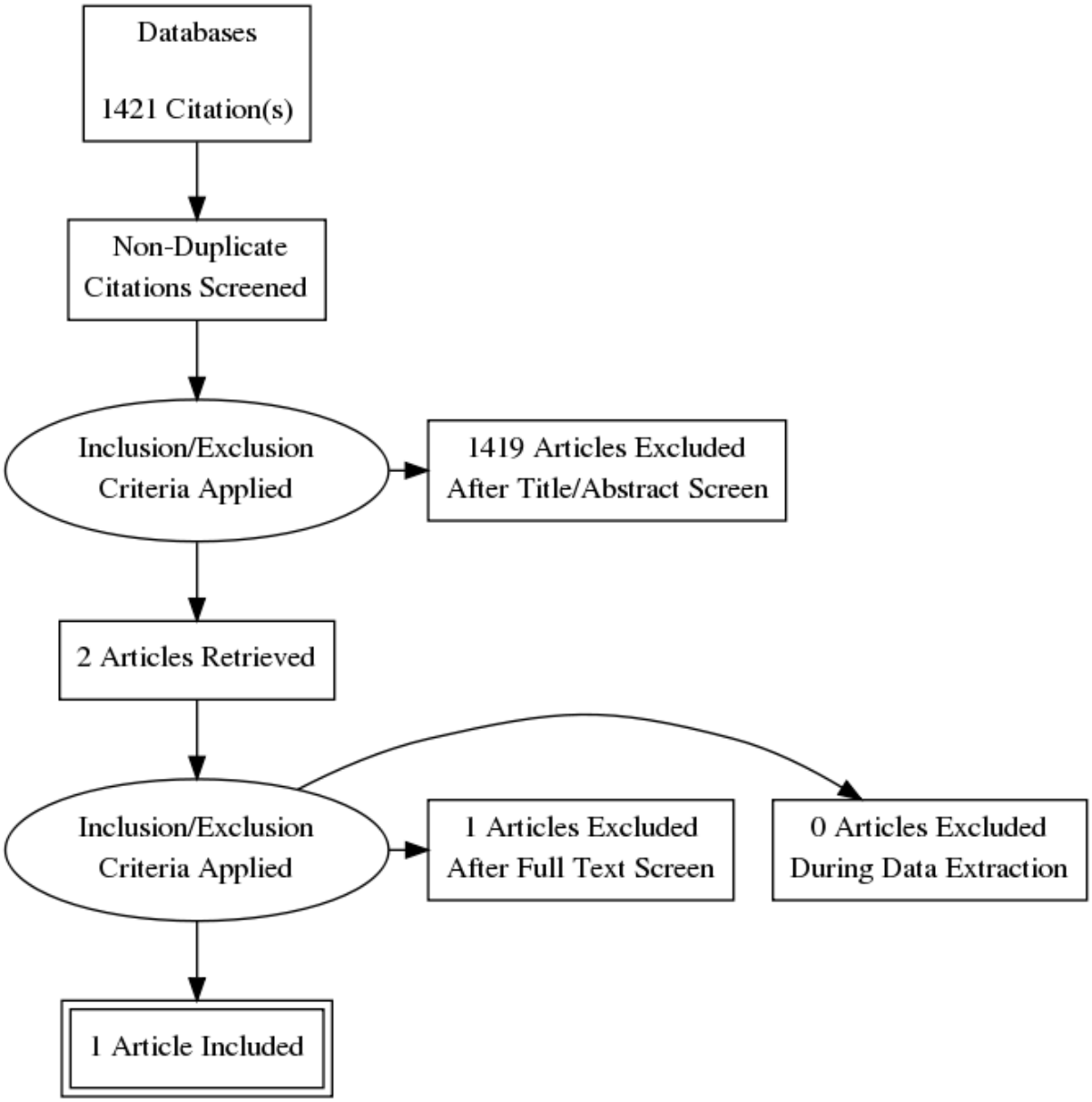
*Includes 2 papers each reporting 2 different studies

**Includes 2 comparisons from 1 study (two triple therapy arms in Frith 2015)

1. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. I^2 > 66.7%
3. I^2 between 33.3% and 66.7%
4. 95% confidence interval crosses both ends of a defined MID interval
5. 95% confidence interval crosses one end of a defined MID interval
6. One study at moderate risk of bias

1

Appendix H – Economic evidence study selection



1 Appendix I – Economic evidence tables

Study, population, comparators, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Hertel et al. (2011) **Population:** Patients with severe or very severe COPD **Comparators (relevant to review question):** Triple therapy LABA+ICS LAMA+LABA **Country:** UK **Partially applicable**[a] **Potentially serious limitations**[b]	**Treatment effects** Treatment-specific differences in exacerbation rates taken from a network meta-analysis of RCTs. **Costs and resource use** Unit costs taken from standard NHS sources (NHS Reference Costs, BNF) Resource use data taken from tiotropium clinical trial (maintenance resource use) and from the GOLD strategy group (estimates of exacerbation resource use). **Utilities** Health state utilities taken from roflumilast clinical trials. Exacerbation disutilities taken from a health preference study which used the time trade-off method to establish quality of life decrements.	Lifetime time horizon Costs and QALYs discounted at 3.5% per annum	Triple therapy versus LABA+ICS			Triple therapy is cost effective compared to both LABA+ICS and LAMA+LABA when QALYs are valued at £20,000 each.	The authors did not conduct sensitivity analysis for the comparisons of interest.
			£348	0.05	£6,960		
			Triple therapy versus LAMA+LABA				
			£129	0.03	£4,300		

a) *Analysis conducted prior to introduction of single fixed-dose triple therapy inhalers (uses outdated costs and clinical evidence)*
b) *Relies on an assumed exacerbation rates, does not conduct probabilistic sensitivity analysis for the comparison of interest, subject to a potential conflict of interest (funded by a manufacturer of roflumilast)*

2

1

1 Appendix J – Excluded studies

2 Clinical studies

Study	Reason for exclusion
Agusti, A.; De Teresa, L.; De Backer, W.; Zvarich, M. T.; Locantore, N.; Barnes, N.; Bourbeau, J.; Crim, C., A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/ salmeterol in moderate to very severe COPD, European Respiratory Journal, 43, 3, 763-772, 2014	Study does not contain a relevant intervention
Alexander, M. J.; Zappetti, D., Is Combination Long-acting Beta-Agonist and Long-acting Muscarinic Antagonist Therapy the Future of COPD Therapy?, Clinical Pulmonary Medicine, 23, 6, 288-289, 2016	Review article but not a systematic review
Anonymous, Erratum: Triple therapy with salmeterol/fluticasone propionate 50/250 plus tiotropium bromide improve lung function versus individual treatments in moderate-to-severe Japanese COPD patients: a randomized controlled trial - Evaluation of Airway sGaw after treatment with tripLE [Corrigendum], International journal of chronic obstructive pulmonary disease, 11, 1031-1033, 2016	Duplicate reference
Anonymous, Triple therapy benifits COPD patients, Australian Journal of Pharmacy, 91, 1078, 78, 2010	Conference abstract
Anthonisen, N. R., Tiotropium and the treatment of chronic obstructive pulmonary disease, Canadian Respiratory Journal, 14, 8, 460-462, 2007	Not a peer-reviewed publication
Antohe, Ileana; Antoniu, Sabina A.; Gavrilovici, Cristina, Triple fixed inhaled therapy in frequent chronic obstructive pulmonary disease exacerbators: potential advantages for various degrees of airways obstruction, Expert opinion on pharmacotherapy, 19, 3, 287-289, 2018	Full text paper not available
Antoniu, S. A., Long-term bronchodilator inhaled therapy in COPD: The role of tiotropium bromidum, Reviews on Recent Clinical Trials, 4, 2, 89-98, 2009	Review article but not a systematic review
Anzueto, Antonio R.; Kostikas, Konstantinos; Mezzi, Karen; Shen, Steven; Larbig, Michael; Patalano, Francesco; Fogel, Robert; Banerji, Donald; Wedzicha, Jadwiga A., Indacaterol/glycopyrronium versus salmeterol/fluticasone in the prevention of clinically important deterioration in COPD: results from the FLAME study, Respiratory research, 19, 1, 121, 2018	Secondary publication of an included study that does not provide any additional relevant information
Anzueto, Antonio R.; Vogelmeier, Claus F.; Kostikas, Konstantinos; Mezzi, Karen; Fucile, Sebastian; Bader, Giovanni; Shen, Steven; Banerji, Donald; Fogel, Robert, The effect of indacaterol/glycopyrronium versus tiotropium or salmeterol/fluticasone on the prevention of clinically important deterioration in COPD, International journal of chronic obstructive pulmonary disease, 12, 1325-1337, 2017	Secondary publication of an included study that does not provide any additional relevant information
Baker, William L.; Baker, Erica L.; Coleman, Craig I., Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis, Pharmacotherapy, 29, 8, 891-905, 2009	Study does not contain a relevant intervention
Banerji, Donald; Mahler, Donald A.; Hanania, Nicola A., Efficacy and safety of LABA/LAMA fixed-dose combinations approved in the US for the management of COPD, Expert review of respiratory medicine, 10, 7, 767-80, 2016	Review article but not a systematic review
Bateman, Eric D.; Mahler, Donald A.; Vogelmeier, Claus F.; Wedzicha, Jadwiga A.; Patalano, Francesco; Banerji, Donald, Recent advances in COPD disease management with fixed-dose long-acting combination therapies, Expert review of respiratory medicine, 8, 3, 357-79, 2014	Study does not contain a relevant intervention

Study	Reason for exclusion
Black, P., Preventing exacerbations of COPD - What should we do?, International Journal of Respiratory Care, 4, 1, 5-6, 2008	Full text paper not available
Bremner, Peter R.; Birk, Ruby; Brealey, Noushin; Ismaila, Afisi S.; Zhu, Chang-Qing; Lipson, David A., Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study, Respiratory research, 19, 1, 19, 2018	Triple v triple
Cazzola, Mario; Matera, Maria Gabriella, Triple combinations in chronic obstructive pulmonary disease - is three better than two?, Expert opinion on pharmacotherapy, 15, 17, 2475-8, 2014	Review article but not a systematic review
Chapman, K. R.; Roche, N.; Ayers, Tim; FowlerTaylor, A.; Thach, C.; Ahlers, N., Indacaterol/glycopyrronium (IND/GLY) is superior to salmeterol/fluticasone (SFC) in improving the health status of patients with moderate-to-very severe COPD: results from the FLAME study, European respiratory journal, 48, suppl60, pa982, 2016	Study does not contain a relevant intervention
Criner, G. J., Optimal treatment of chronic obstructive pulmonary disease: The search for the magic combination of inhaled bronchodilators and corticosteroids, Annals of Internal Medicine, 146, 8, 606-608, 2007	Review article but not a systematic review
Do Lee, S.; Xie, C. M.; Yunus, F.; Itoh, Y.; Su, R., Efficacy and tolerability of budesonide/formoterol (B/F) added to tiotropium (T) vs T alone in East-Asian patients (pts) with severe/very severe chronic obstructive pulmonary disease (COPD), European respiratory journal, 44, suppl58, p282, 2014	Not a peer-reviewed publication
Donohue, James F.; Worsley, Sally; Zhu, Chang-Qing; Hardaker, Liz; Church, Alison, Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations, Respiratory medicine, 109, 7, 870-81, 2015	Not a peer-reviewed publication
Dransfield, M. T.; Feldman, G.; Korenblat, P.; Laforce, C. F.; Locantore, N.; Pistolesi, M.; Watkins, M. L.; Crim, C.; Martinez, F. J., Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients, Respiratory Medicine, 108, 8, 1171-1179, 2014	Study does not contain a relevant intervention
Farne, Hugo A.; Cates, Christopher J., Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease, The Cochrane database of systematic reviews, , 10, cd008989, 2015	Study does not contain a relevant intervention
Fogel, R.; Chapman, K. R.; Vogelmeier, C. F.; FowlerTaylor, A.; Ayers, T.; Thach, C., Once-daily indacaterol/glycopyrronium (IND/GLY) reduces use of rescue medication versus twice-daily salmeterol/fluticasone (SFC) in patients with moderate-to-very severe COPD: results from the FLAME study, European respiratory journal, 48, suppl60, pa990, 2016	Study does not contain a relevant intervention
Frampton, James E., QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease, Drugs, 74, 4, 465-88, 2014	Review article but not a systematic review
Halpin, D. M. G.; Birk, R.; Brealey, N.; Criner, G. J.; Dransfield, M. T.; Hilton, E.; Lomas, D. A.; Zhu, C. Q.; Lipson, D. A., Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses, ERJ open research, 4, 2nopagination, 2018	Duplicate reference

Study	Reason for exclusion
Halpin, David M. G.; Birk, Ruby; Brealey, Noushin; Criner, Gerard J.; Dransfield, Mark T.; Hilton, Emma; Lomas, David A.; Zhu, Chang-Qing; Lipson, David A., Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses, ERJ open research, 4, 2, 2018	Secondary publication of an included study that does not provide any additional relevant information
Hanania, Nicola A.; Crater, Glenn D.; Morris, Andrea N.; Emmett, Amanda H.; O'Dell, Dianne M.; Niewoehner, Dennis E., Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD, Respiratory medicine, 106, 1, 91-101, 2012	Triple v monotherapy
Herman, J. B.; West, F. M.; Zappetti, D., Are We FULFIL-led by a Once-daily Triple-therapy Inhaler for Chronic Obstructive Pulmonary Disease?, Clinical Pulmonary Medicine, 25, 2, 77-78, 2018	Secondary publication of an included study that does not provide any additional relevant information
Hizawa, Nobuyuki, LAMA/LABA vs ICS/LABA in the treatment of COPD in Japan based on the disease phenotypes, International journal of chronic obstructive pulmonary disease, 10, 1093-102, 2015	Review article but not a systematic review
Horita, Nobuyuki; Goto, Atsushi; Shibata, Yuji; Ota, Erika; Nakashima, Kentaro; Nagai, Kenjiro; Kaneko, Takeshi, Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD), The Cochrane database of systematic reviews, 2, cd012066, 2017	Study does not contain a relevant intervention
Horita, Nobuyuki; Kaneko, Takeshi, Triple therapy vs. dual bronchodilator therapy for chronic obstructive pulmonary disease: Is it worth the cost?, Respiratory investigation, 53, 4, 173-5, 2015	Not a peer-reviewed publication
Horita, Nobuyuki; Miyazawa, Naoki; Tomaru, Koji; Inoue, Miyo; Kaneko, Takeshi, Long-acting muscarinic antagonist+long-acting beta agonist versus long-acting beta agonist+inhaled corticosteroid for COPD: A systematic review and meta-analysis, Respirology (Carlton, Vic.), 20, 8, 1153-9, 2015	Systematic review not used as a source of primary studies
Hoshino, Makoto; Ohtawa, Junichi, Effects of adding salmeterol/fluticasone propionate to tiotropium on airway dimensions in patients with chronic obstructive pulmonary disease, Respirology (Carlton, Vic.), 16, 1, 95-101, 2011	Triple v monotherapy
Huisman, E. L.; Cockle, S. M.; Ismaila, A. S.; Punekar, Y. S., Comparative efficacy of combination bronchodilator therapies in COPD: A network meta-analysis, International Journal of COPD, 10, 1, 1863-1881, 2015	Systematic review not used as a source of primary studies
Ismaila, Afisi S.; Birk, Ruby; Shah, Dhvani; Zhang, Shiyuan; Brealey, Noushin; Risebrough, Nancy A.; Tabberer, Maggie; Zhu, Chang-Qing; Lipson, David A., Once-Daily Triple Therapy in Patients with Advanced COPD: Healthcare Resource Utilization Data and Associated Costs from the FULFIL Trial, Advances in therapy, 34, 9, 2163-2172, 2017	Secondary publication of an included study that does not provide any additional relevant information
Jung, Ki Suck; Park, Hye Yun; Park, So Young; Kim, Se Kyu; Kim, Young-Kyoon; Shim, Jae-Jeong; Moon, Hwa Sik; Lee, Kwan Ho; Yoo, Jee-Hong; Lee, Sang Do; Korean Academy of, Tuberculosis; Respiratory Diseases study, group; Korea Chronic Obstructive Pulmonary Disease study, group, Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study, Respiratory medicine, 106, 3, 382-9, 2012	Triple v monotherapy
Kaplan, A., Effects of tiotropium combined with either salmeterol or salmeterol/fluticasone in moderate to severe COPD, Primary care respiratory journal, 16, 4, 258260, 2007	Conference abstract

Study	Reason for exclusion
Kaplan, Alan, Effect of tiotropium on quality of life in COPD: a systematic review, Primary care respiratory journal : journal of the General Practice Airways Group, 19, 4, 315-25, 2010	Systematic review not used as a source of primary studies
Karner, Charlotta; Cates, Christopher J., Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease, The Cochrane database of systematic reviews, , 3, cd008532, 2011	Systematic review not used as a source of primary studies
Karner, Charlotta; Cates, Christopher J., The effect of adding inhaled corticosteroids to tiotropium and long-acting beta(2)-agonists for chronic obstructive pulmonary disease, The Cochrane database of systematic reviews, , 9, cd009039, 2011	Systematic review not used as a source of primary studies
Kerwin, E.; Ferguson, G. T.; Sanjar, S.; Goodin, T.; Yadao, A.; Fogel, R.; Maitra, S.; Sen, B.; Ayers, T.; Banerji, D., Dual Bronchodilation with Indacaterol Maleate/Glycopyrronium Bromide Compared with Umeclidinium Bromide/Vilanterol in Patients with Moderate-to-Severe COPD: Results from Two Randomized, Controlled, Cross-over Studies, Lung, 195, 6, 739-747, 2017	Study does not contain a relevant intervention
Kwak, Min-Sun; Kim, Eunyoung; Jang, Eun Jin; Kim, Hyun Jung; Lee, Chang-Hoon, The efficacy and safety of triple inhaled treatment in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis using Bayesian methods, International journal of chronic obstructive pulmonary disease, 10, 2365-76, 2015	Systematic review not used as a source of primary studies
Larbig, M.; Vogelmeier, C. F.; N, Roche; Ayers, T.; FowlerTaylor, A.; Thach, C.; Shrinivasan, A.; Fogel, R.; Patalano, F.; Banerji, D., Efficacy of indacaterol/glycopyrronium (IND/GLY versus salmeterol/fluticasone (SFC) on exacerbations and health status in GOLD Group D COPD patients: the FLAME study, Respirology (carlton, vic.), 22, suppl2, 131tp050, 2017	Study does not contain a relevant intervention
Lee, Sang-Do; Xie, Can-Mao; Yunus, Faisal; Itoh, Yohji; Ling, Xia; Yu, Wai-cho; Kiatboonsri, Sumalee, Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: A randomized, multicentre study in East Asia, Respirology (Carlton, Vic.), 21, 1, 119-27, 2016	Triple v monotherapy
Lipson, David A.; Barnacle, Helen; Birk, Ruby; Brealey, Noushin; Locantore, Nicholas; Lomas, David A.; Ludwig-Sengpiel, Andrea; Mohindra, Rajat; Tabberer, Maggie; Zhu, Chang-Qing; Pascoe, Steven J., FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease, American journal of respiratory and critical care medicine, 196, 4, 438-446, 2017	Duplicate reference
Lomas, D.; Lipson, D.; Barnacle, H.; Birk, R.; Brealey, N.; Zhu, C. Q., Single inhaler triple therapy (ICS/LAMA/LABA) in patients with advanced COPD: results of the FULFIL trial, European respiratory journal, 48, suppl60, pa4629, 2016	Conference abstract
Mahler, Donald A.; Keininger, Dorothy L.; Mezzi, Karen; Fogel, Robert; Banerji, Donal, Efficacy of Indacaterol/Glycopyrronium in Patients with COPD Who Have Increased Dyspnea with Daily Activities, Chronic obstructive pulmonary diseases (Miami, Fla.), 3, 4, 758-768, 2016	Secondary publication of an included study that does not provide any additional relevant information
Maltais, Francois; Mahler, Donald A.; Pepin, Veronique; Nadreau, Eric; Crater, Glenn D.; Morris, Andrea N.; Emmett, Amanda H.; Ferro, Thomas J., Effect of fluticasone propionate/salmeterol plus tiotropium	Study does not contain a relevant intervention

Study	Reason for exclusion
versus tiotropium on walking endurance in COPD, The European respiratory journal, 42, 2, 539-41, 2013	
Mehta, Rashmi; Pefani, Eleni; Beerahee, Misba; Brealey, Noushin; Barnacle, Helen; Birk, Ruby; Zhu, Chang-Qing; Lipson, David A., Population Pharmacokinetic Analysis of Fluticasone Furoate/Umeclidinium/Vilanterol via a Single Inhaler in Patients with COPD, Journal of clinical pharmacology, , 2018	Study does not contain a relevant intervention
Mills, Edward J.; Druyts, Eric; Ghement, Isabella; Puhan, Milo A., Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis, Clinical epidemiology, 3, 107-29, 2011	Systematic review not used as a source of primary studies
Miravitlles, M.; Anzueto, A.; Jardim, J. R., Optimizing bronchodilation in the prevention of COPD exacerbations, Respiratory Research, 18, 1, 125, 2017	Review article but not a systematic review
Mittmann, Nicole; Hernandez, Paul; Mellstrom, Carl; Brannman, Lance; Welte, Tobias, Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives, PharmacoEconomics, 29, 5, 403-14, 2011	Study does not contain outcomes of interest
Molino, Antonio; Calabrese, Giovanna; Maniscalco, Mauro, Patient considerations in the treatment of COPD: focus on the new combination inhaler fluticasone furoate/umeclidinium/vilanterol, Patient preference and adherence, 12, 993-1001, 2018	Review article but not a systematic review
Oba, Yuji; Chandran, Arul V.; Devasahayam, Joe V., Long-acting Muscarinic Antagonist Versus Inhaled Corticosteroid when Added to Long-acting beta-agonist for COPD: A Meta-analysis, COPD, 13, 6, 677-685, 2016	Study does not contain a relevant intervention
Olsson, P.; Roche, N.; Vestbo, J.; FowlerTaylor, A.; Ayers, T.; Thach, C., Cardiovascular (CV) safety of indacaterol/glycopyrronium (IND/GLY) compared with salmeterol/fluticasone combination (SFC) in moderate-to-very severe COPD patients with prior exacerbations: the FLAME study, European respiratory journal, 48, suppl60, pa311, 2016	Study does not contain a relevant intervention
Pascoe, Steven J.; Lipson, David A.; Locantore, Nicholas; Barnacle, Helen; Brealey, Noushin; Mohindra, Rajat; Dransfield, Mark T.; Pavord, Ian; Barnes, Neil, A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol, The European respiratory journal, 48, 2, 320-30, 2016	Not a relevant study design [IMPACT Protocol]
Patalano, F.; Wedzicha, J. A.; Vestbo, J.; FowlerTaylor, A.; Ayers, T.; Thach, C.; Ruparelia, N.; Fogel, R.; Banerji, D., Indacaterol/glycopyrronium (IND/GLY) reduces exacerbation and improves lung function versus salmeterol/fluticasone (SFC) in patients with and without prior ICS use: the FLAME study, Respirology (carlton, vic.), 22, suppl2, 137tp063, 2017	Study does not contain a relevant intervention
Petite, Sarah E., Role of Long-Acting Muscarinic Antagonist/Long-Acting beta2-Agonist Therapy in Chronic Obstructive Pulmonary Disease, The Annals of pharmacotherapy, 51, 8, 696-705, 2017	Systematic review not used as a source of primary studies
Puhan, Milo A.; Bachmann, Lucas M.; Kleijnen, Jos; Ter Riet, Gerben; Kessels, Alphons G., Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis, BMC medicine, 7, 2, 2009	Systematic review not used as a source of primary studies
Rees, P. J., Tiotropium in the management of chronic obstructive pulmonary disease, European Respiratory Journal, 19, 2, 205-206, 2002	Not a peer-reviewed publication

Study	Reason for exclusion
Rennard, S. I., Combination bronchodilator therapy in COPD, Chest, 107, 5suppl, 171S-175S, 1995	Study does not contain a relevant intervention
Rice-McDonald, G., Using tiotropium in the treatment of COPD, Medicine Today, 5, 9, 75-76, 2004	Not a peer-reviewed publication
Rodrigo, Gustavo J.; Plaza, Vicente; Castro-Rodriguez, Jose A., Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review, Pulmonary pharmacology & therapeutics, 25, 1, 40-7, 2012	Systematic review not used as a source of primary studies
Rodrigo, Gustavo J.; Price, David; Anzueto, Antonio; Singh, Dave; Altman, Pablo; Bader, Giovanni; Patalano, Francesco; Fogel, Robert; Kostikas, Konstantinos, LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis, International journal of chronic obstructive pulmonary disease, 12, 907-922, 2017	Systematic review not used as a source of primary studies
Roisman, G., Tiotropium in combination with placebo, salmeterol, or fluticasone- salmeterol for treatment of chronic obstructive pulmonary disease. A randomized trial, Revue de pneumologie clinique, 63, 6, 390391, 2007	Conference abstract Study not reported in English
Rojas-Reyes, Maria Ximena; Garcia Morales, Olga M.; Dennis, Rodolfo J.; Karner, Charlotta, Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease, The Cochrane database of systematic reviews, , 6, cd008532, 2016	Duplicate reference
Saito, Takefumi; Takeda, Akinori; Hashimoto, Katsuji; Kobayashi, Akihiro; Hayamizu, Tomoyuki; Hagan, Gerald W., Triple therapy with salmeterol/fluticasone propionate 50/250 plus tiotropium bromide improve lung function versus individual treatments in moderate-to-severe Japanese COPD patients: a randomized controlled trial - Evaluation of Airway sGaw after treatment with tripLE, International journal of chronic obstructive pulmonary disease, 10, 2393-404, 2015	Study does not contain a relevant intervention
Schlueter, Max; Gonzalez-Rojas, N.; Baldwin, Michael; Groenke, Lars; Voss, Florian; Reason, Tim, Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting beta2-agonists: a systematic review and network meta-analysis, Therapeutic advances in respiratory disease, 10, 2, 89-104, 2016	Systematic review not used as a source of primary studies
Siler, Thomas M.; Kerwin, Edward; Sousa, Ana R.; Donald, Alison; Ali, Rehan; Church, Alison, Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies, Respiratory medicine, 109, 9, 1155-63, 2015	Duplicate reference
Singh, D.; Papi, A.; Corradi, M.; Montagna, I.; Francisco, C.; Cohuet, G., TRILOGY: a phase III study to evaluate the efficacy and safety of an extrafine triple combination of beclometasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium bromide (GB) pMDI (CHF5993) in COPD patients, European respiratory journal, 48, suppl60, pa995, 2016	Conference abstract
Singh, D.; Worsley, S.; Zhu, C. Q.; Hardaker, L.; Church, A., Umeclidinium/vilanterol (UMEC/VI) once daily (OD) vs fluticasone/salmeterol combination (FSC) twice daily (BD) in patients with moderate-to-severe COPD and infrequent COPD exacerbations, European respiratory journal, 44, suppl58, p290, 2014	Study does not contain a relevant intervention
Singh, Dave, Single inhaler triple therapy with extrafine beclomethasone, formoterol, and glycopyrronium for the treatment of	Full text paper not available

Study	Reason for exclusion
chronic obstructive pulmonary disease, Expert opinion on pharmacotherapy, 19, 11, 1279-1287, 2018	
Singh, Dave; Corradi, Massimo; Spinola, Monica; Papi, Alberto; Usmani, Omar S.; Scuri, Mario; Petruzzelli, Stefano; Vestbo, Jorgen, Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide, International journal of chronic obstructive pulmonary disease, 12, 2917-2928, 2017	Review article but not a systematic review
Thompson, P.; Frith, P.; Frenzel, C.; Kurstjens, N., Randomized controlled trial of glycopyrronium added to fixed combination salmeterol-fluticasone in COPD: primary care and specialist site differences in the glisten study, Respirology (carlton, vic.), 20, suppl2, 80tp045, 2015	Conference abstract
Tricco, Andrea C.; Strifler, Lisa; Veroniki, Areti-Angeliki; Yazdi, Fatemeh; Khan, Paul A.; Scott, Alistair; Ng, Carmen; Antony, Jesmin; Mrklas, Kelly; D'Souza, Jennifer; Cardoso, Roberta; Straus, Sharon E., Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis, BMJ open, 5, 10, e009183, 2015	Systematic review not used as a source of primary studies
Vestbo, J.; Corradi, M.; Montagna, I.; Cohuet, G.; Francisco, C.; Vezzoli, S., TRINITY: a phase III study to compare the efficacy and safety of an extrafine triple combination of beclometasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium bromide (GB) pMDI (CHF5993) with tiotropium (Tio) and a free triple combination of BDP/FF (Foster®) + Tio in COPD patients, European respiratory journal, 48, suppl60, oa1972, 2016	Conference abstract
Vestbo, Jorgen; Papi, Alberto; Corradi, Massimo; Blazhko, Viktor; Montagna, Isabella; Francisco, Catherine; Cohuet, Geraldine; Vezzoli, Stefano; Scuri, Mario; Singh, Dave, Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial, Lancet (London, England), 389, 10082, 1919-1929, 2017	Triple v triple
Vogelmeier, C.; Paggiaro, P. L.; Dorca, J.; Sliwinski, P.; Mallet, M.; Kirsten, A. M., The efficacy and safety of aclidinium/formoterol fixed-dose combination compared with salmeterol/fluticasone in patients with COPD: results from a phase III study, American journal of respiratory and critical care medicine, 191, meetingabstracts, a3974, 2015	Conference abstract
Vogelmeier, C.; Paggiaro, P. L.; Dorca, J.; Sliwinski, P.; Mallet, M.; Kirsten, A. M., Efficacy of aclidinium/formoterol fixed-dose combination versus salmeterol/fluticasone in COPD, European respiratory journal, 46, 2015	Conference abstract
Vogelmeier, Claus; Zhong, Nanshan; Humphries, Michael J.; Mezzi, Karen; Fogel, Robert; Bader, Giovanni; Patalano, Francesco; Banerji, Donald, Indacaterol/glycopyrronium in symptomatic patients with COPD (GOLD B and GOLD D) versus salmeterol/fluticasone: ILLUMINATE/LANTERN pooled analysis, International journal of chronic obstructive pulmonary disease, 11, 3189-3197, 2016	Secondary publication of an included study that does not provide any additional relevant information
Wedzicha, Jadwiga A.; Banerji, Donald; Chapman, Kenneth R.; Vestbo, Jorgen; Roche, Nicolas; Ayers, R. Timothy; Thach, Chau; Fogel, Robert; Patalano, Francesco; Vogelmeier, Claus F.; Investigators, Flame, Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD, The New England journal of medicine, 374, 23, 2222-34, 2016	Study does not contain a relevant intervention
Wedzicha, Jadwiga A.; Zhong, Nanshan; Ichinose, Masakazu; Humphries, Michael; Fogel, Robert; Thach, Chau; Patalano, Francesco; Banerji, Donald, Indacaterol/glycopyrronium versus	Study does not contain a relevant intervention

Study	Reason for exclusion
salmeterol/fluticasone in Asian patients with COPD at a high risk of exacerbations: results from the FLAME study, International journal of chronic obstructive pulmonary disease, 12, 339-349, 2017	
Welte, T., Optimising treatment for COPD--new strategies for combination therapy, International journal of clinical practice, 63, 8, 1136-49, 2009	Review article but not a systematic review
Welte, T.; Miravitlles, M.; Hernandez, P.; Hartman, L.; Polanowski, T.; Kessler, R., Budesonide/formoterol added to tiotropium improves lung function, health status, symptoms & morning activities in COPD patients, European respiratory society annual congress, vienna, austria, september 12-16, , p2005, 2009	Conference abstract
Welte, Tobias; Miravitlles, Marc; Hernandez, Paul; Eriksson, Goran; Peterson, Stefan; Polanowski, Tomasz; Kessler, Romain, Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease, American journal of respiratory and critical care medicine, 180, 8, 741-50, 2009	Triple v monotherapy
Wheeler, K., Umeclidinium triple therapy for patients with COPD: Two studies, Drug Topics, 160, 5, 2016	Conference abstract
Zhu, Ying; Zhang, Tong; Li, Haiyan; Yang, Yang; Chen, Qiong; Kong, Lei; Tai, Bo, Discovering the Relative Efficacy of Inhaled Medications for Chronic Obstructive Pulmonary Disease: Multiple Treatment Comparisons, Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology, 41, 4, 1532-1546, 2017	Systematic review not used as a source of primary studies

1 **Economic studies**

Author (year)	Reason for exclusion
Najafzadeh, M., Marra, C.A., Sadatsafavi, M., Aaron, S.D., Vandemheem, K.L., Sullivan, S., Jones, P.W. and Fitzgerald, M.J., 2008. Cost-Effectiveness of Therapy with Combinations of Long-Acting Bronchodilators and Inhaled Steroids for Treatment of COPD. Thorax.	Non-UK healthcare system perspective

2

Appendix K – References

Included clinical studies

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, Bishop G, Anthony J, Cowie R, Field S, Hirsch A, Hernandez P, Rivington R, Road J, Hoffstein V, Hodder R, Marciniuk D, McCormack D, Fox G, Cox G, Prins HB, Ford G, Bleskie D, Doucette S, Mayers I, Chapman K, Zamel N, and FitzGerald M (2007) Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease. Annals of Internal Medicine 146, 545-555

Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, and D'Amato M (2007) A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulmonary pharmacology & therapeutics 20(5), 556-61

Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, Bourne E, Ballal S, Darken P, DeAngelis K, Aurivillius M, Dorinsky P, and Reisner C (2018) Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial.. The Lancet. Respiratory medicine 6(10), 747-758

Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, Frenzel C, and Kurstjens N (2015) Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial.. Thorax 70(6), 519-27

Hoshino M, and Ohtawa J (2013) Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. Respiration, and international review of thoracic diseases 86(4), 280-7

Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, and Pascoe SJ (2017) FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease.. American journal of respiratory and critical care medicine 196(4), 438-446

Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, and Pascoe SJ (2018) Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.. The New England journal of medicine 378(18), 1671-1680

Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, and Singh D (2018) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.. Lancet (London, and England) 391(10125), 1076-1084

Siler TM, Kerwin E, Sousa AR, Donald A, Ali R and Church A (2015) Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. Respiratory medicine, 109(9), 1155-63

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