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RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
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ASTHMA + COPD

Systematic literature review: full report

Consensus conference
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1 Abbreviations

Abbreviation	Meaning
6MWT	6-minute walking test
ACQ	Asthma control questionnaire
AE	Adverse event
AQoL (or AQLQ)	Asthma Quality of Life Questionnaire
ARR:	Absolute risk reduction
ASFD	Asthma symptom-free days questionnaire
ASUI	Asthma symptom utility index
CI	Confidence interval
CO	Crossover RCT
DB	Double blind
FEV1	Forced expiratory volume in one second
HR	Hazard ratio
ICS	Inhaled corticosteroid
ITT	Intention-to-treat analysis
LABA	Long-acting beta2-agonist
LAMA	Long-acting muscarinic antagonist
LRTI	Lower respiratory tract infection
LSM-TD	Least squares mean – treatment difference
MA	Meta-analysis
mab	Monoclonal antibody
MCID	Minimal clinically important difference
MD	Mean difference
MID	Minimally important difference
mMRC	Modified Medical Research Council dyspnea scale
MRMM	Mixed-effect Model Repeated Measure
n	Number of patients
N	Number of studies
NR	Not reported
NS	Not statistically significant
NT	No statistical test
OCS	Oral corticosteroid
OL	Open label
PC	Placebo controlled
PG	Parallel group
PO	Primary outcome
SAE	Severe adverse event
SB	Single blind
SGRQ	St George respiratory questionnaire
SO	Secondary outcome
TDI	Transitional dyspnea index
UT	Urinary tract

Table 1

2 COPD study names

A lot of COPD studies have an abbreviation or study name. This report tends to use “author – date” style, followed by reference number. We have made the following list to clarify which references correspond to which study name. When ambiguous, we try to mention the study name as well as the author name, date and reference number.

Name of the study	Reference
ACLIFORM COPD	Singh 2014 (1)
AFFIRM	Vogelmeier 2016 (2)
ANHELTO 1, ANHELTO 2	ZuWallack 2014 (3)
AUGMENT COPD	D’urzo 2014 (4)
BLAZE	Mahler 2012 (5)
FLAME	Wedzicha 2016 (6)
FLIGHT 1, FLIGHT 2	Mahler 2015 (7)
FORWARD	Wedzicha 2014 (8)
GLISTEN	Frith 2015 (9)
GLOW6	Vincken 2014 (10)
ILLUMINATE	Vogelmeier 2013 (11)
INSTEAD	Rossi 2014 (12)
LANTERN	Zhong 2015 (13)
OTEMTO 1, OTEMTO 2	Singh 2015 (14)
PINNACLE 1, PINNACLE 2	Martinez 2016 (15)
QUANTIFY	Buhl 2015 (16)
SHINE	Bateman 2013 (17)
SPARK	Wedzicha 2013 (18)
SPARK	Wedzicha 2013 (18)
SUMMIT	Vestbo 2016 (19)
TORCH	Calverley 2007 (20)
TRILOGY	Singh 2016 (21)
TRISTAN	Calverley 2003 (22)

Table 2

3 Methodology

3.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference "asthma + COPD", which will take place on the 11th of May 2017.

3.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

QUESTION/VRAAG 1
Concernant l'asthme et la BPCO : observance thérapeutique
Comment évaluer l'observance thérapeutique et comment l'améliorer ?
Quels indicateurs pour quels intervenants ?
Met betrekking tot astma en COPD: therapietrouw
Hoe kan de therapietrouw worden geëvalueerd en verbeterd?
Welke indicatoren moeten voor welke actoren worden gehanteerd?

QUESTION/VRAAG 2
Concernant l'asthme et la BPCO : observance thérapeutique
Quelle est l'importance du type de dispositif d'administration dans l'observance thérapeutique ?
Met betrekking tot astma en COPD: therapietrouw
Wat is het belang van het soort inhalator voor de therapietrouw?

QUESTION/VRAAG 3
Pour l'asthme :
Quelle est la place des LAMA dans le traitement de l'asthme ?
Efficacité, sécurité.
Voor astma:
Welke rol spelen de LAMA's bij de behandeling van astma?
Werkzaamheid, veiligheid.

QUESTION/VRAAG 4
Pour l'asthme :
Quelle est la place des mab (anticorps monoclonaux anti IgE – neutralisant de l'interleukine-5) dans le traitement de l'asthme ?
Efficacité, sécurité, durée du traitement.
Voor astma:
Welke rol spelen de mab's (anti-IgE-monoklonale antilichamen - interleukine-5-neutraliserende stoffen) bij de behandeling van astma?
Werkzaamheid, veiligheid, behandelingsduur.

QUESTION/VRAAG 5

Quelle est la place d'un traitement au long cours avec de l'azithromycine pour l'asthme ? Efficacité, sécurité.

Welke rol speelt een langdurige behandeling met azitromycine bij de behandeling van astma? Werkzaamheid, veiligheid.

QUESTION/VRAAG 6

Pour l'asthme : quel choix de traitement chronique inhalé initial et quelle stratégie d'augmentation thérapeutique, voire d'arrêt de certains médicaments ?

Voor astma: welke initiële chronische inhalatiebehandeling en welke therapeutische verhogingsstrategie moet er worden gekozen; of moet het gebruik van sommige geneesmiddelen zelfs worden stopgezet?

QUESTION/VRAAG 7

BPCO

Quelle est la place des associations bronchodilatatrices inhalées (fixes et autres) versus monothérapies ?

COPD

Welke rol spelen de combinaties van inhalatiebronchodilatoren (vaste en andere) in vergelijking met monotherapieën?

QUESTION/VRAAG 8

BPCO

Quelle est la place des associations d'un (de) bronchodilatateur(s) inhalé(s) avec un corticostéroïde inhalé (CSI) (LAMA, LABA ou les 2, + CSI, associations fixes ou non).

COPD

Welke rol spelen de combinaties van een (van de) inhalatiebronchodilator(en) met een inhalatiecorticosteroïde (ICS) (LAMA, LABA of beide, + ICS, al dan niet in vaste combinaties).

QUESTION/VRAAG 9

Quelle est la place d'un traitement au long cours avec de l'azithromycine pour la BPCO ? Efficacité et sécurité.

Welke rol speelt een langdurige behandeling met azitromycine bij de behandeling van COPD? Werkzaamheid en veiligheid.

QUESTION/VRAAG 10

Pour la BPCO : quel choix de traitement inhalé initial et quelle stratégie d'augmentation thérapeutique ?

Voor COPD: welke initiële inhalatiebehandeling en welke therapeutische verhogingsstrategie moet er worden gekozen?

QUESTION/VRAAG 11

Concernant l'asthme et la BPCO : effets indésirables des traitements inhalés

Quelles sont les effets indésirables sérieux et quelles sont les nouveautés des 5 dernières années dans ce domaine ?

Met betrekking tot astma en COPD: ongewenste bijwerkingen van inhalatiebehandelingen
Welke zijn de ernstige ongewenste effecten en welke nieuwigheden zijn er op dat vlak de laatste 5 jaar te vermelden ?

The answers to these questions can be found in the following chapters of this document:

Question	Chapters
question 1	Guidelines: 5.1.7and 5.2.6 RCTs: 9
question 2	9.3
question 3	Guidelines: 5.1.4 RCTs: 7.1 Adverse effects: 7.1.5; 10.2and 11.1.2
question 4	Guidelines: 5.1.6 RCTs: 7.2 Adverse effects: 7.2.5; 10.3and 11.2
question 5	Guidelines: 5.1.5 RCTs: 8.2 Adverse effects: 8.3and 11.3
question 6	Guidelines: 5.1.3
question 7	Guidelines: 5.2.3 RCTs: 6.1 (LABA/LAMA); 6.2(LABA / ICS) 6.3 (triple therapy); 6.4(ICS withdrawal) Adverse effects: 6.1.5; 6.3.6; 6.4.2; 6.1.5 ;10.1;10.2 and 11.1
question 8	Guidelines: 5.2.4 RCTs: 6.2 (LABA+ICS); 6.3 (triple therapy); 6.4 (ICS withdrawal) Adverse effects: 6.2.5; 6.3.6; 6.4.2; 10.1; 10.2and 11.1
question 9	Guidelines: 5.2.5 RCTs: 8.1 Adverse effects: 8.3and 11.3
question 10	Guidelines: 5.2.2
question 11	10

Table 3

3.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- Question 1:
  - Discuss selected guidelines
  - Perform a systematic search, summarize and assess the quality of the evidence
- Question 2:
  - Discuss selected guidelines
  - Perform a systematic search, summarize and assess the quality of the evidence
- Question 3:
  - Discuss selected guidelines
  - Perform a systematic search, summarize and assess the quality of the evidence
- Question 4:
  - Discuss selected guidelines

- Question 5:
    - Discuss selected guidelines
    - Perform a systematic search, summarize and assess the quality of the evidence
- Question 6:
    - Discuss selected guidelines
    - Perform a systematic search of MABs, summarize and assess the quality of the evidence
- Question 7:
    - Discuss selected guidelines
    - Perform a systematic search, summarize and assess the quality of the evidence
- Question 8:
    - Discuss selected guidelines
- Question 9:
    - Due to time constraints, do not perform a systematic search for side effects only, however discuss the evidence about side effects found in the other systematic searches
    - Discuss the articles selected by the organizing committee
    - Discuss selection of articles with expert speaker and if necessary add other articles recommended by them
    - Refer to Belgian EBM-sources such as the Folia and CBIP and collect information about side effects of the selected interventions (see item "*Interventions*" below) from the last 5 years (01/01/2011- 31/12/2016)
- Question 10:
    - Discuss selected guidelines
    - Perform a systematic search and summarize the evidence that corresponds to the two points of interest only
    - Discuss selection of articles with expert speaker and if necessary add other articles recommended by them

3.1.2.1 *Populations*

The following population is to be evaluated:

- Adults with asthma or COPD

Studies in which children have been included should not be considered. However, in the case of asthma, studies investigating *efficiency* that include adolescents (15 years and up) will not be excluded. The population characteristics will be described in the evidence tables. Studies investigating *adherence* that include adolescents will be excluded due to the particular problem of adherence to medication during adolescence (see "*Critical Reflexions"* further)
Excluded from the literature search are:

- People suffering from both asthma and COPD (ACOS)
- Pregnant women
- Children <12 years of age in all cases

3.1.2.2 *Interventions and comparisons*

Selected interventions are:

Long acting muscarinic antagonists (LAMA's)
Aclidinium
Glycopyrronium
Tiotropium
Umeclidinium
Long acting beta-antagonists (LABAs)
Formoterol
Indacaterol
Olodaterol
Salmeterol
Vilanterol (when combined)
Inhaled corticosteroids (ICS)
Beclomethasone
Budesonide
Fluticasone
Mometasone (when combined)
MABs
Omalizumab
Mepolizumab

All possible salts were included (e.g. fluticasone furoate, fluticasone propionate etc.).
In the chapters on inhaled medicine, this literature review studies combinations of a number of molecules (sometimes in a single inhaler). Theoretically all combinations of a LABA, LAMA and/or ICS could be selected. However only certain combinations are available and not all combinations have been studied. A greyed out cell indicates that the combination has been investigated and selected in our literature review. If the combination is available in a single inhaler on the Belgian market the commercial name is given.

LAMA and LABA combinations:

LAMA / LABA	Aclinidium	Glycopyrronium	Tiotropium	Umeclidinium
Formoterol	Duaklir ®			
Indacaterol		Ultibro ®		
Olodaterol			Spiolto ®	
Salmeterol				
Vilanterol*				Anoro ®

Table 4

(* see "*comparisons*" below)

LABA and ICS combinations:

ICS / LABA	Beclomethasone	Budesonide	Fluticasone	Mometasone*
Formoterol	Inuvair®	Bufomix®	Flutiform®	

		Symbicort®		
Indacaterol				
Olodaterol				
Salmeterol		Zephirus®	Seretide ® Salmeterol/flutic. Cipla®	
Vilanterol*			Relvar®	

Table 5

(* see "*comparisons*" below)

Were excluded as comparators:

- Molecules that are on the market in Belgium as a combination but that aren't available individually as treatment for asthma or COPD (such as vilanterol, or mometasone)
- Comparators consisting of placebo only (for example without ICS background treatment)

3.1.2.3 *Endpoints*

- COPD
  - SGRQ
  - Trough FEV1
  - Hospitalisations
  - Exacerbations
  - Mortality
- Asthma
  - AQoL
  - ACQ
  - Asthma Symptom Utility Index
  - Trough FEV1
  - Hospitalisations
  - Exacerbations
  - Oral corticoid use
- Safety endpoints
  - Atrial fibrillation with inhaled bronchodilators
  - Pneumonia with ICS
  - Other serious adverse events (with any product)
- Adherence intervention
  - Medication adherence
  - Clinical endpoints (as described above)

3.1.2.4 *Study criteria*

To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases

- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

RCT's

- Blinded studies are preferred, but we will not exclude unblinded trials
- Duration: minimum duration of 12 weeks is required
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Post hoc subgroup analyses according to COPD severity

Other sources for safety and dosing

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), ,-Folia Pharmacotherapeutica
- The SPC (Summary of Product Characteristics) is consulted if additional information is necessary

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

3.1.2.5 *Guidelines*

Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2012 onwards are to be selected.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/. [1]

Table 6 gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described

10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 6: Items assessed by the domain "Rigour of development" in AgreeII score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

3.2 Search strategy

3.2.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

- As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, TRIPP database) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.
- In a second step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library (CDSR)

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links

to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like National Guideline Clearinghouse and G-I-N.

3.2.2 Search strategy details

The following systematic review were selected as source documents and starting points to find relevant publications:

For the comparisons LABA + LAMA vs LABA or vs LAMA in COPD

Farne Hugo, A. and J. Cates Christopher (2015). "Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews.

For the comparison LABA + ICS vs LABA in COPD

Nannini Luis, J., J. Lasserson Toby and P. Poole (2012). "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews(9).

For the comparison LABA + ICS vs ICS in COPD

Nannini Luis, J., P. Poole, J. Milan Stephen and A. Kesterton (2013). "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews(8).

For the comparison triple therapy vs LABA + LAMA in COPD

Tan, D. J., et al. (2016). "Inhaled corticosteroids with combination inhaled long-acting beta2-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease." Cochrane Database Syst Rev 11: Cd011600.

For the comparison triple therapy vs LAMA in COPD

Rojas-Reyes, M. X., O. M. Garcia Morales, R. J. Dennis and C. Karner (2016). "Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease." Cochrane Database Syst Rev(6): Cd008532.

For the comparison LAMA + ICS vs ICS in asthma:

Anderson, D. E., K. M. Kew and A. C. Boyter (2015). "Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma." Cochrane Database Syst Rev(8): Cd011397.

For the comparison LAMA + ICS vs higher dose ICS in asthma:

Evans, D. J., K. M. Kew, D. E. Anderson and A. C. Boyter (2015). "Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma." Cochrane Database Syst Rev(7): Cd011437.

For the comparison LAMA + ICS vs LABA + ICS in asthma:

Kew, K. M., D. J. Evans, D. E. Allison and A. C. Boyter (2015). "Long-acting muscarinic antagonists

(LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma." Cochrane Database Syst Rev(6): Cd011438.

For the comparison triple therapy vs LABA + ICS in asthma:

Kew, K. M. and K. Dahri (2016). "Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma." Cochrane Database Syst Rev(1): Cd011721.

For mepolizumab:

Powell, C., S. J. Milan, K. Dwan, L. Bax and N. Walters (2015). "Mepolizumab versus placebo for asthma." Cochrane Database Syst Rev(7): Cd010834.

For omalizumab:

Normansell, R., S. Walker, S. J. Milan, E. H. Walters and P. Nair (2014). "Omalizumab for asthma in adults and children." Cochrane Database Syst Rev(1): Cd003559.

For long term prophylactic use of macrolides in COPD:

Herath, S. C. and P. Poole (2013). "Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)." Cochrane Database Syst Rev(11): Cd009764.

For long term prophylactic use of macrolides in asthma:

Kew, K. M., K. Undela, I. Kotortsi and G. Ferrara (2015). "Macrolides for chronic asthma." Cochrane Database Syst Rev(9): Cd002997.

For adherence in asthma:

British Thoracic Society and Scottish Intercollegiate Guidelines Network (2016). "British guideline on the management of asthma - A national clinical guideline."

For adherence in COPD:

Bryant, J., V. M. McDonald, A. Boyes, R. Sanson-Fisher, C. Paul and J. Melville (2013). "Improving medication adherence in chronic obstructive pulmonary disease: a systematic review." Respir Res 14: 109.

For safety:

Cates, C. J., L. S. Wieland, M. Oleszczuk and K. M. Kew (2014). "Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews." Cochrane Database Syst Rev(2): Cd010314.

Kew, K. M. and A. Seniukovich (2014). "Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease." Cochrane Database Syst Rev(3): Cd010115.

Due to the high precision and well defined comparison of most of those reviews, a number of them were used to cover the full scope of our search. Searches were done upwards of the oldest search date.
Sometimes source documents were replaced by more recent or better systematic reviews and meta-analyses that we found in our search.
The full search strategy can be found in appendix 1.

3.3 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.
The list of articles excluded after reading of the full text can be found in Appendix 2.

3.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 7. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance

- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

3.5 Synopsis of the study results

The complete report contains per research question

- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based

- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- (Brief) summary of selected guidelines
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

4 Critical reflections of the reading committee and the literature group

4.1 General remarks

The most important aspect of COPD treatment is smoking cessation, if the patient is still a smoker. In most studies a fair amount of the patients are smokers (numbers vary but are somewhere between 30% to 50% usually). One can wonder about the purpose of heavier pharmacotherapy in a smoking COPD patient. Treatment with bronchodilating medication or other medication is not disease modifying. They do not fundementally change the development of the disease.
Most studies in this report are industry-sponsored.
Most studies are of medium length. 12 weeks was the minimal duration to be included in this literature review. A lot of studies lasted 6 months, some lasted a year. A few studies with mortality as primary endpoint lasted several years. 12 weeks or 6 months is sufficient for certain endpoints (trough FEV1 for example) but not for others, like hospitalizations or mortality, where the amount of events is much lower. It is also an insufficient length to evaluate the effect of antibiotic use on resistance, and to evaluate the risks or side-effects of monoclonal antibodies
Patient inhaler technique remains sub-par and it's one of the first things that should be evaluated when a prescriber considers adding another molecule to the treatment. Incorrect inhaler technique remains very frequent (around 40%) (23).
Some COPD trials are "twin trials", two studies with the same inclusion and exclusion criteria, measuring the same endpoints, which are performed at the same time. This is done on the request of the FDA.
Albuterol is the name given in the USA to salbutamol.

An important reservation for the use of antibiotics is the problem of resistance. Recently the WHO released a list of a dozen antibiotic resistant superbugs that pose an enormous threat to human health[1]. It is much complicated to calculate the harm that can be done by (ab)using antibiotics, but today antibiotic resistance already kills people worldwide. This needs to be taken into consideration when evaluating the results we report on antibiotic use.

4.2 Population

COPD

Most of the patients included in the studies in this report have moderate to severe forms of COPD (depending on the GOLD version: Stage II or Stage III patients, Gold category B or D). Very severe COPD, with multiple exacerbations in the previous year, are usually excluded. Patients with a very mild form of COPD (category A) are often excluded and generally don't start their treatment with a double bronchodilator therapy, which is the focus of this report. Those patients are the one most usually treated in general or family practice (pneumologists see more severe patients than the general practitioner does).

[1] http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

Some things need to be said about reversibility. The term bronchodilator reversibility implies the complete or near complete correction of an obstructive spirometric abnormality. This is mostly seen in patients that are close to predicted normal values before the drug is given, and not in those with a more severe disease (if this response was shown, the patient would then be regarded as asthmatic). However, many patients show some improvement. Those patients are often excluded in European studies but not in those performed in the USA. Highly reversible patients are also more likely to be strong responders to ICS. There are some issues regarding the test protocol for reversibility (24).
Overall the studies included in this report tend to represent the same kind of patient: an older male between 63 and 65 years, with ≥10 pack-years and no major comorbidities. There are fewer women included, so this is one area where there might be some uncertainty. There are also few patients with very severe COPD or mild COPD. Another area of uncertainty is the efficacy of the treatment in case of comorbidities.
A lot of large trials recruit patients from different centers, scattered all over the world (it's not unusual to see a mix of USA, Eastern Europe, Africa, Latin-America, Russia etc). Sometimes the exact repartition of patients is known, but usually it is not. A lot of the time a protocol to certify excellence is put in place but it still can raise some questions about external validity.
Asthma
Most of our source documents for asthma include adults and adolescents (cut-off value in those cases often ≥12 years). For efficiency endpoints this didn't strike us as a problem, but we did exclude studies with mixed groups or focusing on adolescents when it came to adherence, since in this case adolescents are a group with specific issues.
Both
Some patients have symptoms of both asthma and COPD. They are excluded from all of the reported studies, and so we have little to no information on how to treat those patients.
The Hawthorne effect is when patients, due to being enrolled in a study, have better results than what would be seen in real-life. This can be due to the high quality follow-up they receive, the multiple study visits, the fact that study nurses take a lot of time to explain the proper way to use the inhaler devices, … This needs to be kept in mind when interpreting the clinical significance of results.

4.3 Comparisons

Comparisons versus placebo are quite common, despite the fact that COPD usually doesn't remain untreated. Especially statistical testing was often done versus placebo, which wasn't of interest for this report. When the main objective of a study was to prove efficacy of a treatment versus placebo it might mean that the study is underpowered for comparisons vs control, where the differences are generally smaller. Also, drop-outs tended to be larger in placebo groups, further skewing the perspective.
There is a lack of head to head trials comparing different molecules of the same class, or different combinations. The information available for this is often limited to network meta-analysis, which need to be considered with a lot of caution, and weren't selected for this literature review.
Sometimes comparisons are analyzed on the level of the specific combination, sometimes they are considered by class of molecule.
- In the case of a bronchodilator + ICS combinations, there are suggestions that different ICS can have different effects, mostly suspected for pneumonia's. In this case results are shown by molecule combination.

- For the LABA and LAMA combinations, even if the kinetic properties differ, there doesn't seem to be an indication of differences in treatment outcomes between different molecules. Indirect comparisons found no significant differences between LAMA/LABA combinations in terms of trough FEV1, TDI and SGRQ scores (25). On top of that, we report on a large number of trials without pooling the results, and with the information provided in the tables the reader can isolate the specific combination that is of interest to them. When we report a meta-analysis, results are pooled however. We are aware that the pooling of heterogeneous trials in a meta-analysis can give rise to a false impression of general class effect. However, almost all meta-analyses that we use also report results per combination, and we invite the reader to consult those if they wish more detail. Since the questions to the jury were on the place of combination therapies as a whole and not on which specific choice to make in this case, we preferred not to oversaturate the report with information.

4.4 Outcomes

When evaluating outcomes one needs to pay special attention to the difference between a statistically significant endpoint and a clinically significant endpoint: not every difference that proves to be statistically significant will be translated to a tangible effect for the patient.
The following table gives an overview of the minimally clinically important differences for the endpoints that are often reported in our literature review.

Outcome	MCID	Interpretation	Reference
Asthma control questionnaire (ACQ)	0.5	Higher score indicates more impairment	Juniper 1999(26)
Asthma-related Quality of Life Questionnaire (AQLQ)	0.5	Higher score indicates better quality of life	Juniper 1994(27)
6-minute walking test (6MWT)	35 meter	Longer distance corresponds to more exercise capacity	NHG COPD(28)
Modified Medical Research Council (mMRC) dyspnea scale	1	Higher score indicates more dyspnea	NHG COPD(28)
St George respiratory questionnaire (SGRQ)	4	Higher score indicates more limitations	NHG COPD(28)
Transitional dyspnea index (TDI)	1	Higher score corresponds to less deterioration in severity of dyspnea	Witek 2003(29)
Trough FEV1	100 mL	higher volume corresponds to better lung function	Donohue 2005(30)

Table 8 : MCID: minimal clinically important difference

Endpoints related to exacerbations are difficult to measure with traditional RCTs, because the patient is usually followed more closely, and exacerbations that could have spiralled out of control and led to a hospitalization might get identified and treated earlier.
The way in which exacerbations are reported can also raise some issues. It is not sufficient to report only the rate of exacerbations per participant per year. This is because some participants have no exacerbations, some participants have one, some have multiple (usually a small fraction). When all the exacerbations are put together, and all the patients are put together for the calculations (regardless of who did or didn't have an exacerbation), it gives a wrong impression. For example, if

two patients had zero exacerbations, one patient had one exacerbation and a third patient had three, calculating the rate (4 exacerbations, 4 patients) makes it look wrongly like every patient had one exacerbation. To make sure results are interpreted clearly, one needs to see how many patients did actually have an exacerbation, and if that is different between the active and the control group; that is the outcome "amount of patients with one or more exacerbations". Another problem with exacerbation rates are that not all patients included in the calculations are followed for the entire duration of the study. For example, a patient that was followed only six months during a one year study might have done an exacerbation later.
One needs to be especially cautious with NNTs (or NNH) calculated on exacerbation rates due to the above mentioned limitations. A correct NNT is calculated on the percentage of patients that have done exacerbations. More in-depth explanations on this are available in the references(31, 32).

Lastly, it is important to note that what constitutes an exacerbation isn't always well defined or explicited. Sometimes an exacerbation is only considered as such if it required hospitalization or oral corticosteroids, sometimes it's considered as an exacerbation the moment antibiotics were needed.

The link between FEV1, pulmonary distention and a better quality of life is not always straightforward. FEV1 can improve without the patients reporting a big difference in quality of life or breathlessness (24).
When the efficiency of (a) bronchodilator(s) is evaluated by spirometry, it generates a lot of different measurements one can report on: FEV1, FVC, FEV1/FVC, RV. Each of these can be measured in different ways, for example one can take the FEV1 24 hours post dose (for a medication taken once a day), or an area under the curve measurement can be used, where one takes repeated measurements of the parameter shortly after administration and computes the AUC for example. However those repeated measurements are hard to execute, are often done on smaller populations, and it's one reason of the choice for trough FEV1. AUC measurements are still very useful when trying to define the moment a medication starts working.
Consider also that COPD and asthma are long term conditions, sometimes requiring life-long treatments. So, how important are those measurements of effect inception when considering medication taken chronically (if, of course, the medication considered is effective until the next dose)? This is another reason why trough FEV1 is the reported outcome of choice. Trough FEV1 should however not be considered on its own, but together with quality of life, dyspnea, exacerbations, etc., so patient-centered outcomes. One must not forget that it is a patient that is being treated, not a spirometry.

4.5 Adverse events

It is difficult to draw conclusions from adverse events reported in RCTs, since they are usually set up in a way to minimize adverse events.
Also, some adverse events are rare occurrences. The less common they are, the longer the studies need to be to identify a difference between active and control group.
In a number of COPD studies, exacerbations were considered as an adverse event, not a secondary endpoint. In quite a number of studies considering exacerbations as AE, no statistical testing was provided. Hospitalizations, which were an endpoint of interest, are also often lumped in with adverse events. Often the precise endpoint is "adverse events leading to hospitalization" which can include many other things aside from exacerbations.

What is considered a serious adverse event can differ between study authors and can be especially problematic when pooled.
Due to time constraints we didn't perform a systematic search for adverse events. How we searched for evidence is detailed at the beginning of the chapter "adverse events".

Some adverse events that pose a risk at medium-long term such as glaucoma or prostate problems are often prevented by excluding patients with a history of those problems.

5 Guidelines

5.1 Guidelines on asthma

5.1.1 General information on selected guidelines

5.1.1.1 *Selected guidelines*

The selected guidelines and their abbreviations as used in this report can be found in the table below.

Abbreviation	Guideline
ERS/ATS 2014(33)	The European Respiratory Society/American Thoracic Society Task Force - International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, 2014.
GINA 2016(34)	Global Initiative For Asthma – Global Strategy for Asthma Management and Prevention, 2016.
NHG ASTMA 2015(35)	Nederlands Huisartsen Genootschap – NHG-Standaard Astma bij volwassenen, 2015.
SIGN/BTS 2016(36)	Scottish Intercollegiate Guidelines Network/British Thoracic Society – SIGN 153: British Guideline on the management of asthma, 2016.

Table 9: Selected guidelines and their abbreviations as used in this report.

5.1.1.2 *Grades of recommendation*

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the tables below.

ERS/ATS 2014		
Grades of recommendation	Strong	"We recommend…"
	Conditional	"We suggest…"
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table 10: Levels of evidence of the ERS/ATS 2014 guideline

GINA 2016		
Levels of evidence	A	RCTs and meta-analyses. Rich body of data.
	B	RCTs and meta-analyses. Limited body of data.
	C	Nonrandomized trials. Observational studies.
	D	Panel consensus judgment.

Table 11: Levels of evidence of the GINA 2016 guideline

The **NHG** guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended). (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

NHG ASTMA 2015		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/
	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 12: Grades of recommendation and Level of evidence of NHG ASTMA 2015 guideline.

SIGN/BTS 2016		
Grades of recommendation:	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
	B	A body of evidence including studies rate das 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
	✓	Good practice points: Recommended best practice based on the clinical experience of the guideline development group
Levels of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, e.g. case reports, case series
	4	Expert opinion

Table 13: Levels of evidence of the SIGN/BTS 2016 guideline

5.1.1.3 *Agree II score*

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the table below. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score (%)
ERS/ATS 2014	7	4	7	2	7	7	1	5	**40**	**71**
NHG ASTMA 2015	5	4	4	1	6	6	5	3	**34**	**61**
GINA 2016	6	6	5	5	6	6	5	7	**46**	**82**
BTS/SIGN 2016	7	7	7	2	7	7	7	5	**49**	**88**

Table 14: AGREE score of selected guidelines on item “Rigour of development”

5.1.1.4 *Included populations – interventions – main outcomes*

In the tables below, the populations, interventions and main outcomes considered in the selected guidelines are represented.

ERS/ATS 2014	
Population	Children and adults with severe or therapy-resistant asthma.
Interventions	Diagnosis, monitoring, management (Anti-IgE antibody, methotrexate, macrolide antibiotics, antifungal agents, bronchial thermoplasty)
Outcomes	Not specified.

Table 15: Included population, intervention and main outcomes of the ERS/ATS 2014 guideline.

GINA 2016	
Population	Children, adolescents and adults with asthma.
Interventions	Diagnosis, assessment, treatment, asthma exacerbations, COPD overlap, prevention of asthma, management in children <5 years.
Outcomes	Not specified.

Table 16: Included population, intervention and main outcomes of the GINA 2016 guideline.

NHG ASTMA 2015	
Population	Adults with asthma.
Interventions	Diagnosis, management, monitoring.
Outcomes	Not specified.

Table 17: Included population, intervention and main outcomes of the NHG ASTMA 2015 guideline.

SIGN/BTS 2016	
Population	Children and adults with a diagnosis of asthma
Interventions	Diagnosis, monitoring, management of asthma, acute asthma, difficult asthma, asthma in pregnancy, occupational asthma
Outcomes	Pulmonary function, symptoms, exacerbations, adverse effects

Table 18: Included population, intervention and main outcomes of the SIGN/BTS 2016 guideline.

5.1.1.5 *Members of development group – target audience*

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the tables below.

ERS/ATS 2014	
Development group	Clinicians and researchers with expertise in severe asthma and a methodologist.
Target audience	Specialists in respiratory medicine and allergy managing adults and children with severe asthma. *General internists, paediatricians, primary care physicians, and other healthcare professionals and policy makers may also benefit from these guidelines.*

Table 19: Members of the development group and target audience of the ERS/ATS 2014 guideline.

GINA 2016	
Development group	"recognized leaders in asthma research and clinical practice with scientific expertise"
Target audience	Primary care and specialist physicians.

Table 20: Members of the development group and target audience of the GINA 2016 guideline.

NHG ASTMA 2015	
Development group	General practitioners, pulmonologists, an epidemiologist.
Target audience	General practitioners.

Table 21: Members of the development group and target audience of the NHG ASTMA 2015 guideline.

SIGN/BTS 2016	
Development group	Paediatricians, respiratory physicians, pharmacists, general practitioners, information scientists, nurses, lay representative
Target audience	General practitioners, consultants and specialists in respiratory medicine, nurses and pharmacists; patients and carers

Table 22: Members of the development group and target audience of the SIGN/BTS 2016 guideline.

5.1.1.6 *Method of reporting of the recommendations and notes*

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Even though the NHG ASTMA 2015 guideline did not grade its recommendations, it does appraise the studies leading to the recommendations. For that reason, the recommendations of the NHG ASTMA 2015 guideline are also written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

5.1.2 Definitions

5.1.2.1 *Summary*

"Severe" or "difficult" asthma is defined in 3 guidelines (ERS/ATS 2014, GINA 2016, SIGN/BTS 2016) as:

Asthma which requires treatment with high dose therapies (e.g. LABA + high-dose ICS) to prevent it from becoming uncontrolled, or asthma that remains "uncontrolled" despite this treatment.

5.1.2.2 *ERS/ATS 2014*

Definition of severe asthma for patients aged ≥ 6 years:

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS# and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming ''uncontrolled'' or which remains ''uncontrolled'' despite this therapy.

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or ''not well controlled'' by NAEPP/GINA guidelines)

2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year

3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

#: the definition of high dose inhaled corticosteroids (ICS) is age-specific. GINA: Global Initiative for Asthma; LABA: long-acting b2agonists; CS: corticosteroids; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; NAEPP National Asthma Education and Prevention Program.

5.1.2.3 *GINA 2016*

Asthma severity can be assessed when the patient has been on regular controller treatment for several months:

- *Mild asthma is asthma that is well controlled with Step 1 or Step 2 treatment, i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.*

- *Moderate asthma is asthma that is well controlled with Step 3 treatment e.g. low dose ICS/LABA.*
- *Severe asthma is asthma that requires Step 4 or 5 treatment,, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete*

5.1.2.4 *NHG ASTMA 2015*

No definition for severe asthma is given.

5.1.2.5 *SIGN/BTS 2016*

Note: The SIGN/ BTS guideline uses the term "severe asthma" in the context of severe acute asthma exacerbations.

In this guideline difficult asthma is defined as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose therapies or continuous or frequent use of oral steroids.

5.1.3 What inhaled treatment is first choice in the initial chronic treatment of asthma, and what strategy may be used for step-up or step-down of treatment?

5.1.3.1 *Summary*

Three guidelines provide a stepwise strategy for initiating and intensifying treatment (GINA 2016, NHG ASTMA 2015, SIGN/BTS 2016).

The first choice in the *chronic* treatment of asthma is a low dose ICS, according to all three guidelines.

All three guidelines agree that the first step-up for chronic treatment of asthma is to add a LABA to the low dose ICS.
GINA 2016 and SIGN/BTS 2016 agree that in the second and third intensification step, the dose of ICS can be gradually increased.
For step-up 4, GINA 2016 advises to consider adding a monoclonal antibody, while SIGN/BTS 2016 advises to try daily oral steroids first.
In all three guidelines, the advised timing of a referral to a specialist differs.

Guideline	GINA 2016	NHG ASTMA 2015	SIGN/BTS 2016
Initial treatment	Low dose ICS	Low dose ICS	Low dose ICS
Step-up 1	Low dose ICS + LABA	Low dose ICS + LABA	Low dose ICS + LABA
Step-up 2	Medium dose ICS + LABA	Referral to specialist	Medium dose ICS + LABA
Step-up 3	High dose ICS + LABA	/	High dose ICS + LABA Referral advised
Step-up 4	Consider adding a different drug (e.g. monoclonal antibodies) Referral advised	/	Daily oral steroids Referral advised

Table 23 First choice chronic controller medication in asthma, according to guidelines

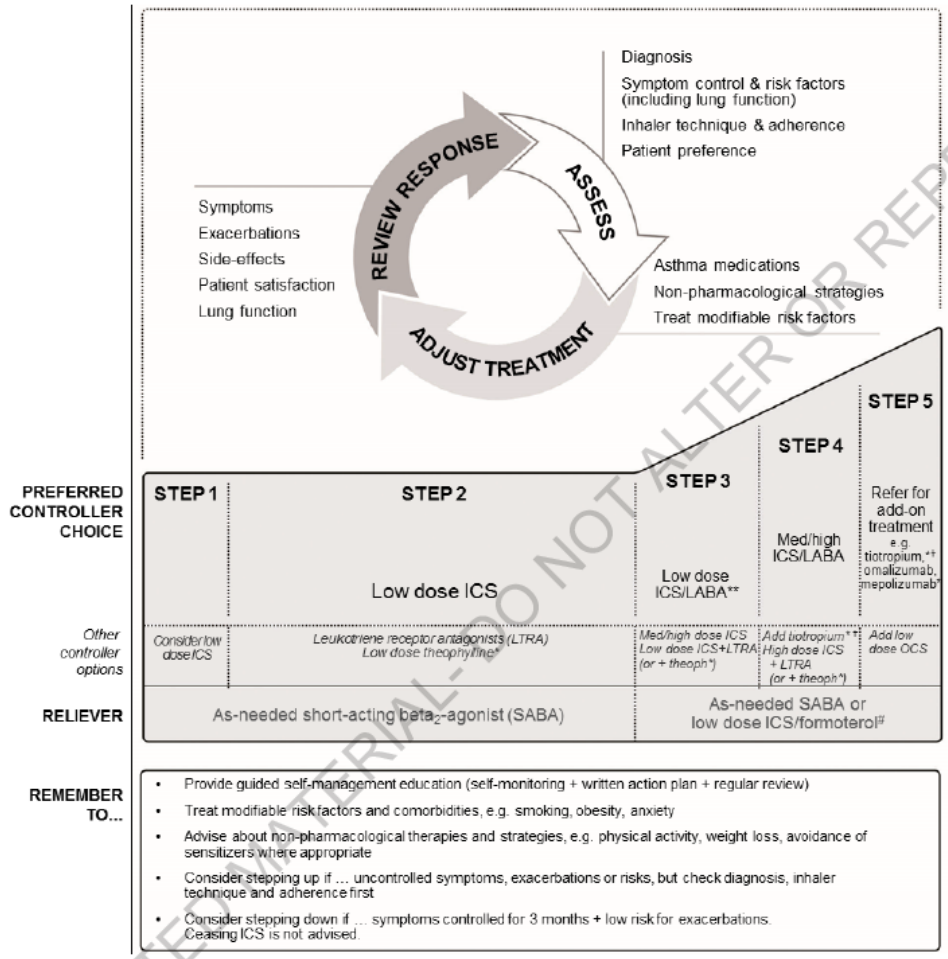
All three guidelines agree that a medication step-down should be considered when good asthma control has been maintained for 3 months.

5.1.3.2 *ERS/ATS 2014*

As this guideline concerns severe asthma only (at which, by definition, GINA medication steps 4-5 are required), no formal recommendations are made for an initial chronic treatment of asthma, or for step-up or step-down of treatment.

5.1.3.3 *GINA 2016*

Box 3-5. Stepwise approach to control symptoms and minimize future risk



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.65) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.

** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.

Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.

† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

Step 1: As-needed reliever inhaler

Step 2: Low dose controller medication plus as-needed reliever medication

Step 3: One or two controllers plus as-needed reliever medication

Step 4: Two or more controllers plus as-needed reliever medication

Step 5: Higher level care and/or add-on treatment

Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma. (Evidence D)

5.1.3.4 *NHG ASTMA 2015*

Step 1: Short-acting bronchodilator (SABA) as needed

Provide patients with infrequent symptoms (twice a week or less) with a SABA "as needed". **In patients with exercise-induced asthma, preference is given to a SABA as well, ten to fifteen minutes before the exercise***; this gives approximately two hours of protection*.

When using a SABA, adverse effects such as tremors of the hands and fingers, headache, peripheral vasodilation, an increase in heart rate and hyper- or hypokalaemia may occur.

Step 2: Maintenance treatment with ICS

Give an ICS in a starting dose to patients who report symptoms three times a week or more at a first presentation, or who report needing a SABA three times a week or more at a follow-up visit.

A SABA can be given up to the maximum daily dose for a few days "as needed", if asthma symptoms worsen.

Four to six weeks after the patient started an ICS, check if the (personal) treatment goals have been achieved. Also discuss the adverse effects, therapeutic adherence, inhalation technique, the avoidance of stimuli that trigger or aggravate symptoms, and smoking status.

Continue the ICS for three months and, if necessary, monitor one or more times until the personal treatment goals have been achieved. After this, or if good asthma control has been achieved, it can be attempted to reduce ICS. *In patients experiencing local adverse effects of ICS, such as persistent hoarseness and oral candidiasis, a dose aerosol with a spacer is preferred. When local reactions are persistent, the dose may be temporarily reduced. An LTRA (montelukast) can also be an alternative, although it is less effective.*

If despite adequate diagnosis and appropriate management, good asthma control is not achieved with a starting dose of ICS, the ICS dose may be doubled.

Step 3: Maintenance treatment with ICS and LABA

Reconsider the asthma diagnosis and management of patients whose asthma control does not improve or who fail to achieve the personal treatment goals despite the proper use of an initial ICS dose. Also discuss the therapeutic adherence, inhalation technique, the avoidance of stimuli that trigger or aggravate symptoms and the smoking status.

Note that the efficacy of ICS is reduced in patients who continue to smoke and consider other conditions or - in patients over forty years - the development of COPD in addition to asthma. **Also remember to adequately treat allergic rhinitis and the complicating effect of obesity on treatment when good asthma control is not achieved.**

Add a LABA to ICS if good asthma control is not achieved with a starter dose ICS despite a correct diagnosis and adequate management. *If the patient experiences adverse effects of LABA, such as palpitations and tremors, a further increase in the dose of ICS in one or more steps is a possibility, or alternatively the addition of a LTRA. In case of exacerbation of asthma symptoms, a SABA 'as needed' can be added for several days up to the maximum daily dose.*

An alternative for patients on a maintenance treatment with a combination preparation of beclomethasone /formoterol ("100/6") or budesonide/formoterol ("100/6") are "as needed" extra doses of this combination preparation, for up to 8 inhalations a day. Prescribe this "as needed" use only after proper instruction and when the patient has sufficient awareness of the disease. **Try reducing the dose to the lowest effective ICS dose, whether in combination with a LABA or not, when asthma control is good, or if the achievement of personal treatment goals have been maintained during some time (3 months).**

If despite adequate diagnosis and management, good asthma control is not achieved with a starter dose ICS plus LABA, the ICS dose can be doubled, whether or not in combination with a maximum dose of LABA.

Step 4: Consultation pulmonologist

A consultation with or a referral to the pulmonologist is indicated if the treatment goals in the above steps were not met within three months.

5.1.3.5 *SIGN/BTS 2016*

INTERMITTENT RELIEVER THERAPY

Prescribe an inhaled short-acting β2 agonist as short term reliever therapy for all patients with symptomatic asthma. A

REGULAR PREVENTER THERAPY

Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals. A

Inhaled corticosteroids should be considered for patients with any of the following asthma-related features:

- **asthma attack in the last two years B**
- **using inhaled β2 agonists three times a week or more B**
- **symptomatic three times a week or more B**
- **waking one night a week. B**

Give inhaled corticosteroids initially twice daily (except ciclesonide which is given once daily). A

Once a day inhaled corticosteroids at the same total daily dose can be considered if good control is established. A

INITIAL ADD-ON THERAPY

The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting β2 agonist, which should be considered before increasing the dose of inhaled corticosteroid. A

MAINTENANCE AND RELIEVER THERAPY

In adults over the age of 18, combined maintenance and reliever therapy can be considered for patients who have a history of asthma attacks on medium dose ICS or ICS/LABA. A

ADDITIONAL ADD-ON THERAPIES

If asthma control remains suboptimal after the addition of an inhaled long-acting β2 agonist then the dose of inhaled corticosteroids should be increased from low dose to medium dose in adults or from very low dose to low dose in children (5–12 years), if not already on these doses. D

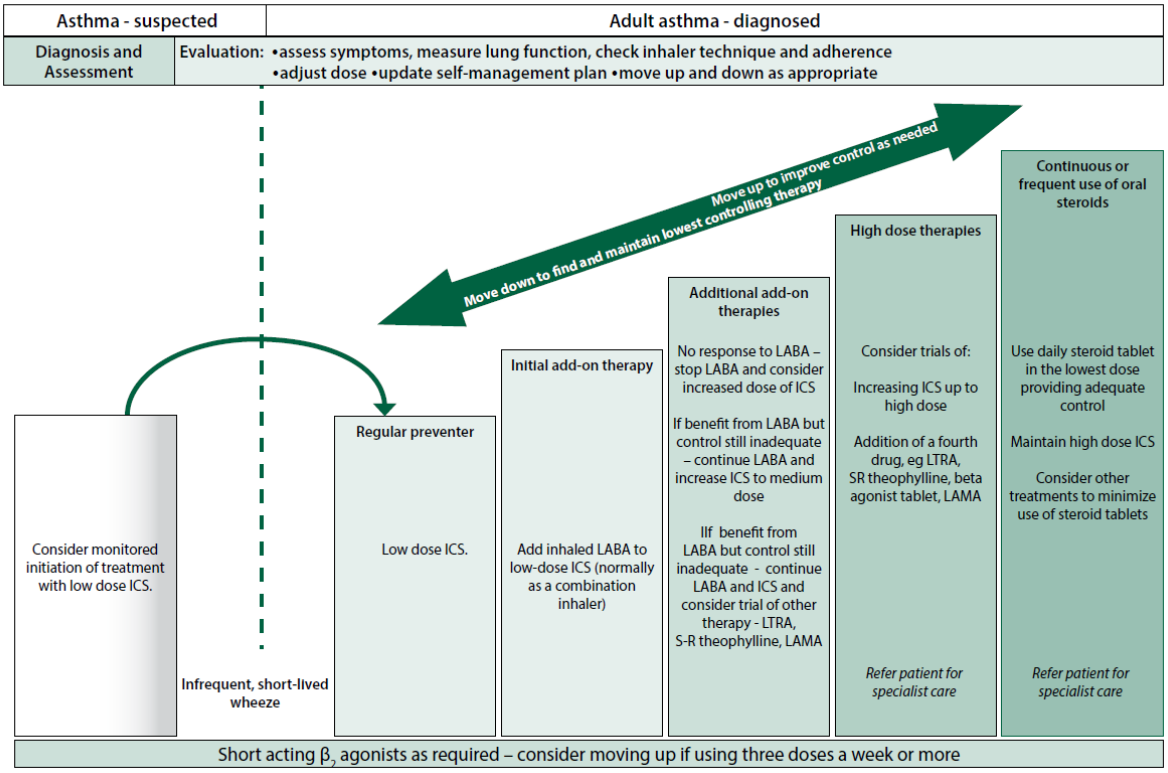
If control remains inadequate on medium dose (adults) or low dose (children) of an inhaled corticosteroid plus a long-acting β2 agonist, the following interventions can be considered: (D)

- **increase the inhaled corticosteroids to high dose (adults) or**
- **add a leukotriene receptor antagonist or**
- **add a theophylline or**
- **add slow-release β2 agonist tablets, although caution needs to be**
- **used in patients already on long-acting β2 agonists, or**
- **add tiotropium (adults).**

DECREASING THERAPY

Regular review of patients as treatment is decreased is important. When deciding which drug to decrease first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account. ✓

Patients should be maintained at the lowest possible dose of inhaled corticosteroid. Reduction in inhaled corticosteroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25–50% each time. ✓


Asthma - suspected
Adult asthma - diagnosed
Diagnosis and Assessment
Evaluation: •assess symptoms, measure lung function, check inhaler technique and adherence
•adjust dose •update self-management plan •move up and down as appropriate
Move up to improve control as needed
Move down to find and maintain lowest controlling therapy
Consider monitored initiation of treatment with low dose ICS.
Infrequent, short-lived wheeze
Regular preventer
Low dose ICS.
Initial add-on therapy
Add inhaled LABA to low-dose ICS (normally as a combination inhaler)
Additional add-on therapies
No response to LABA – stop LABA and consider increased dose of ICS
If benefit from LABA but control still inadequate – continue LABA and increase ICS to medium dose
IIf benefit from LABA but control still inadequate - continue LABA and ICS and consider trial of other therapy - LTRA, S-R theophylline, LAMA
High dose therapies
Consider trials of:
Increasing ICS up to high dose
Addition of a fourth drug, eg LTRA, SR theophylline, beta agonist tablet, LAMA
Refer patient for specialist care
Continuous or frequent use of oral steroids
Use daily steroid tablet in the lowest dose providing adequate control
Maintain high dose ICS
Consider other treatments to minimize use of steroid tablets
Refer patient for specialist care
Short acting β2 agonists as required – consider moving up if using three doses a week or more

5.1.4 What is the place of LAMA in the treatment of asthma?

5.1.4.1 *Summary*

One guideline (ERS/ATS 2014) did not provide recommendations concerning the use of LAMA in (severe) asthma.

One guideline (NHG ASTMA 2015) states that LAMA have no place in the treatment of asthma in primary care.

One guideline (GINA 2016) recommends to consider tiotropium as an add-on to ICS/LABA, when asthma control is insufficient with medium to high dose ICS/LABA.

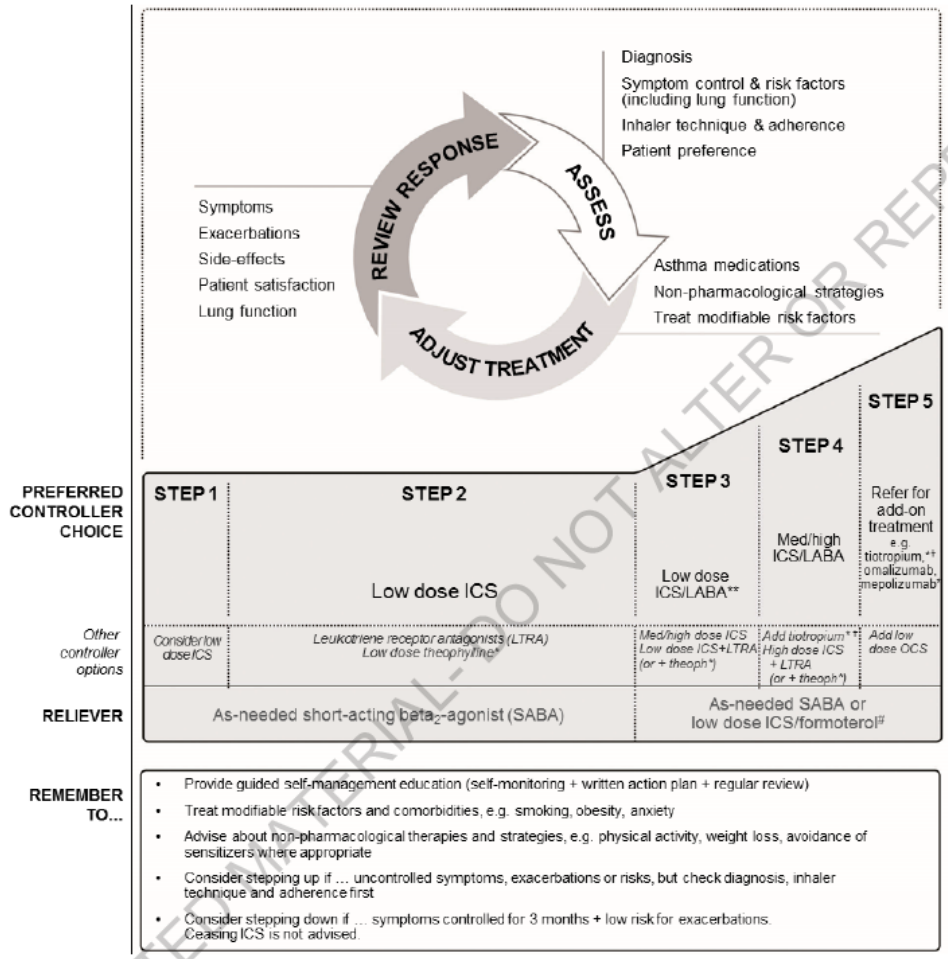
One guideline (SIGN/BTS 2016) recommends to consider a LAMA if control remains poor on a low-dose ICS/LABA, either as third medication added to ICS/LABA, or in combination with ICS, without LABA.

5.1.4.2 *ERS/ATS 2014*

The ERS/ATS 2014 guideline does not provide recommendations concerning the use of LAMA in severe asthma.

5.1.4.3 *GINA 2016*

Box 3-5. Stepwise approach to control symptoms and minimize future risk



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.65) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

Step 1: As-needed reliever inhaler
Step 2: Low dose controller medication plus as-needed reliever medication
Step 3: One or two controllers plus as-needed reliever medication
Step 4: Two or more controllers plus as-needed reliever medication
Step 5: Higher level care and/or add-on treatment

Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma. (Evidence D)

Treatment options that may be considered at Step 5 (if not already tried) include:

• Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years with a history of exacerbations despite Step 4 treatment. Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation (Evidence B).

• Add-on omalizumab (anti-immunoglobulin E (anti-IgE) treatment: for patients with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment (Evidence A).

• Add-on mepolizumab (anti-interleukin-5 treatment): for patients aged ≥12 yrs with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).

• Sputum-guided treatment: for patients with persisting symptoms and/or exacerbations despite high-dose ICS or ICS/LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS (Evidence A).

• Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma (Evidence B). *Evidence is limited and in selected patients (see p.51 and Appendix Chapter 6). The long term effects compared with control patients, including for lung function, are not known.*

• Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma (Evidence D); but are often associated with substantial side effects (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors. Patients should be counseled about potential side-effects (Evidence D). *They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).*

5.1.4.4 *NHG ASTMA 2015*

The long-acting anticholinergic tiotropium is not registered for the treatment of asthma at present (2014). There is only limited evidence for the efficacy of tiotropium in asthma. Tiotropium added to ICS (Step 3) is therefore not recommended in primary care.

5.1.4.5 *SIGN/BTS 2016*

ADDITIONAL ADD-ON THERAPIES

If control remains poor on low-dose ICS plus a LABA, recheck the diagnosis, assess adherence to existing medication and check inhaler technique before increasing therapy. If more intense treatment is appropriate, then the following alternatives can be considered.

If there is an improvement when a LABA is added but control remains inadequate:

- *continue the LABA and increase the dose of ICS*
- *continue the LABA and the ICS and add an LTRA or a long acting muscarinic agent*
- *(LAMA) or a theophylline*

If there is no improvement when a LABA is added, stop the LABA and try:

- *an increased dose of ICS*
- *an LTRA*
- *a LAMA. LAMA are not licensed for this indication.*

5.1.5 What is the place of a long-term treatment with macrolides in asthma?

5.1.5.1 *Summary*

None of the selected guidelines recommend a long-term treatment with macrolides in asthma.

5.1.5.2 *ERS/ATS 2014*

We suggest that clinicians do not use macrolide antibiotics in adults and children with severe asthma for the treatment of asthma. (Conditional, Very Low)
This recommendation places a relatively higher value on prevention of development of resistance to macrolide antibiotics, and relatively lower value on uncertain clinical benefits.

5.1.5.3 *GINA 2016*

The GINA 2016 guideline does not mention the long-term use of macrolides in asthma.

5.1.5.4 *NHG ASTMA 2015*

The NHG 2015 guideline does not mention the long-term use of macrolides in asthma.

5.1.5.5 *SIGN/BTS 2016*

A systematic review of the use of macrolides in patients with chronic asthma concluded that they confer no benefit over placebo in terms of clinical outcomes. There was some evidence of possible benefit in improved lung function but concern about the risk of increased antimicrobial resistance. Subgroup analyses in two of the included studies suggested improved outcomes in patients with non-eosinophilic asthma, but patient numbers were small and no conclusions can be drawn from the data available. There is insufficient evidence to support the addition of macrolides to existing treatment for patients with severe asthma.

5.1.6 What is the place of monoclonal anti-IgE-antibodies in the treatment of asthma?

5.1.6.1 *Summary*

Monoclonal antibodies may be considered, according to two guidelines (ERS/ATS 2014, GINA 2016), in patients with severe asthma which is uncontrolled despite optimal management. According to one guideline (SIGN/BTS 2016), it may be considered in patients with a high (oral) steroid burden.

In three guidelines (GINA 2016, NHG ASTMA 2015, SIGN/BTS 2016), it is recommended to refer the patient for specialist care when considering initiation of a monoclonal antibody in asthma. The fourth selected guideline, the ERS/ATS 2014 guideline, is aimed at specialists in respiratory medicine.

Omalizumab may be considered, according to three guidelines (ERS/ATS 2014, GINA 2016, NHG ASTMA 2015) in patients with severe allergic asthma. Mepolizumab may be considered, according to one guideline (GINA 2016), in severe eosinophilic asthma.

5.1.6.2 *ERS/ATS 2014*

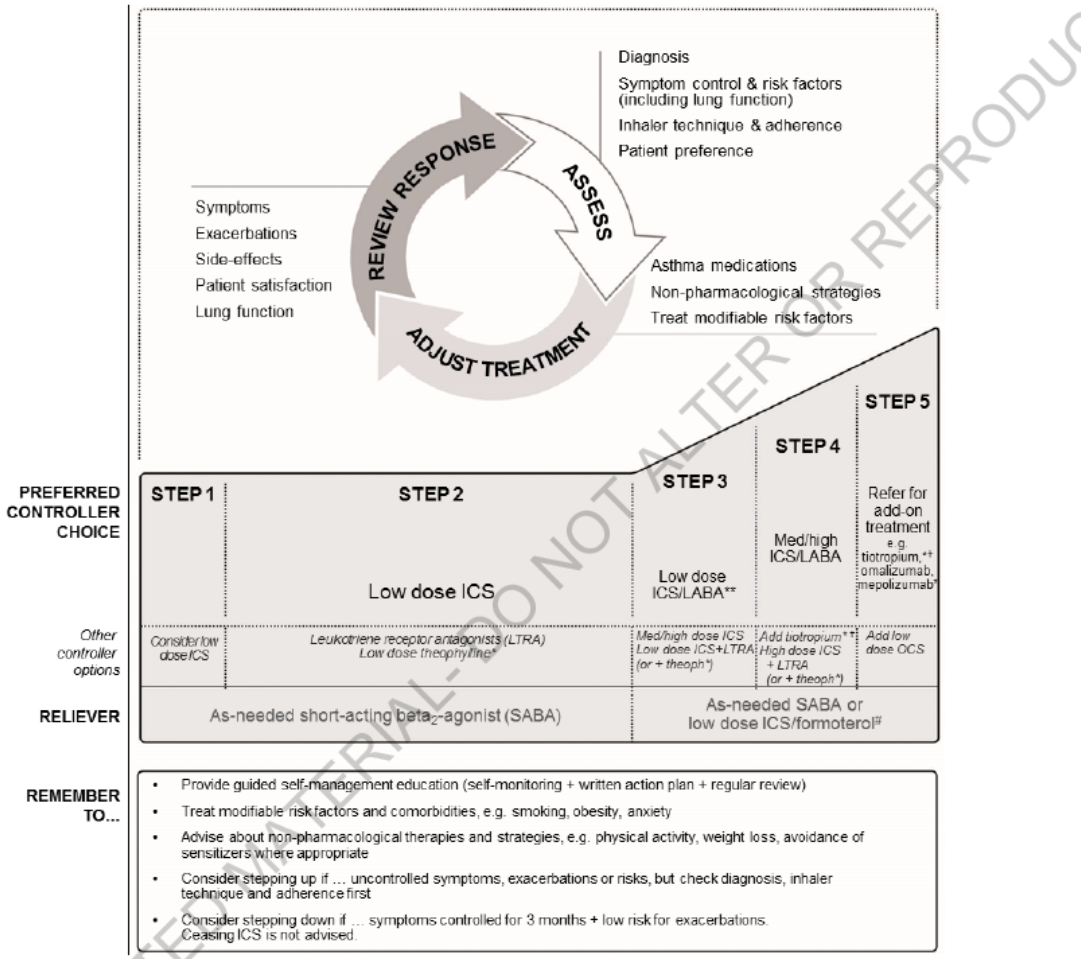
In patients with severe allergic asthma we suggest a therapeutic trial of omalizumab both in adults and in children. (Conditional, Low (adults))

This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use.

Those adults and children aged ≥6 years with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30–700 IU/mL (in three studies the range was wider: 30–1300 IU/mL) Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, and improvement in quality of life If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.

5.1.6.3 *GINA 2016*

Box 3-5. Stepwise approach to control symptoms and minimize future risk



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.65) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

Step 1: As-needed reliever inhaler
Step 2: Low dose controller medication plus as-needed reliever medication
Step 3: One or two controllers plus as-needed reliever medication
Step 4: Two or more controllers plus as-needed reliever medication
Step 5: Higher level care and/or add-on treatment

Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma. (Evidence D)

Treatment options that may be considered at Step 5 (if not already tried) are described in Box 3-14 (p.70). They include:

• Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years with a history of exacerbations despite Step 4 treatment. Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation (Evidence B).

• Add-on omalizumab (anti-immunoglobulin E (anti-IgE) treatment: for patients with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment (Evidence A).

• Add-on mepolizumab (anti-interleukin-5 treatment): for patients aged ≥12 yrs with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).

• Sputum-guided treatment: for patients with persisting symptoms and/or exacerbations despite high-dose ICS or ICS/LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS (Evidence A).

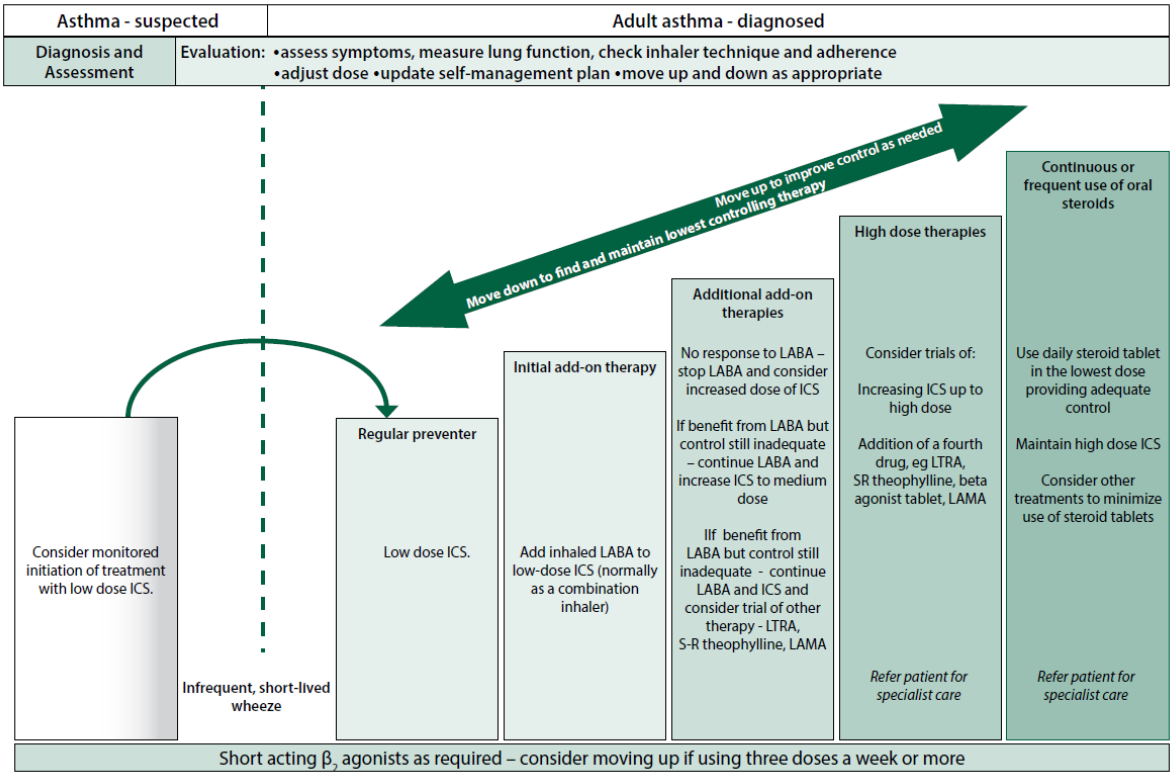
• Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma (Evidence B). *Evidence is limited and in selected patients (see p.51 and Appendix Chapter 6). The long term effects compared with control patients, including for lung function, are not known.*

• Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma (Evidence D); but are often associated with substantial side effects (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors. Patients should be counseled about potential side-effects (Evidence D). *They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).*

5.1.6.4 *NHG ASTMA 2015*

Second-line treatment options for certain subgroups of patients are subcutaneous immunotherapy in patients with (predominantly) a mono-allergy and subcutaneous administration of omalizumab, a monoclonal antibody against IgE, in severe allergic asthma.

5.1.6.5 *SIGN/BTS 2016*



Other medications and potential steroid tablet-sparing treatments

Omalizumab given by subcutaneous injection may be considered in patients with a high steroid burden. (B)

Omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma. (✓)

5.1.7 Adherence

5.1.7.1 *Summary*

Three of the selected guidelines (ERS/ATS 2014, GINA 2016, SIGN/BTS 2016) discuss strategies to assess and improve adherence.

Possible strategies for identifying poor adherence:

- Empathic, non-judgemental question
- Checking the date of the last prescription or the date on the inhaler
- Confirmation that patients have picked up prescriptions from pharmacies
- Biomarker testing in severe/difficult asthma (FeNO or biochemical urinary assays)

Possible strategies for improving adherence:

- Patient empowerment, shared decision making
- Consider cost
- Information
- Practical support: e.g. Inhaler reminders
- Simple dosage regimes: e.g. ICS prescribed once-daily versus twice daily
- Behavioural support: e.g. counselling
- Home visits by an asthma nurse

5.1.7.2 *ERS/ATS 2014*

No formal recommendation:

Difficult-to-control and severe asthma are often associated with coexisting conditions. Non-adherence to treatment should be considered in all difficult-to-control patients, as reports show that non-adherence can be as high as 32–56%. Poor inhaler technique is also common and should be addressed. Detecting poor adherence can be challenging.

Measuring serum prednisolone, theophylline, systemic corticosteroid (CS) side effects and suppression of serum cortisol levels can be used to evaluate adherence to oral medications, but methods for measuring inhaled CS compliance, such as canister weight, pressure-actuated or electronic counters, are not widely available in clinical practice. Confirmation that patients have picked up prescriptions from pharmacies can also provide insight. If non-adherence is present, clinicians should empower patients to make informed choices about their medicines and develop individualised interventions to manage non-adherence. Cost alone can have substantial impact on adherence.

5.1.7.3 *GINA 2016*

ADHERENCE WITH MEDICATIONS AND OTHER ADVICE

Identifying poor adherence

Poor adherence is defined as the failure of treatment to be taken as agreed upon by the patient and the health care provider. There is increasing awareness of the importance of poor adherence in chronic diseases, and of the potential to develop interventions to improve adherence. Approximately 50% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.

In clinical practice, poor adherence may be identified by an empathic question that acknowledges the likelihood of incomplete adherence and encourages an open discussion. See table below for examples.

Checking the date of the last prescription or the date on the inhaler may assist in identifying poor adherence. In some health systems, pharmacists can assist in identifying poorly adherent patients by monitoring dispensing records. In clinical studies, poor adherence may be identified by short adherence behavior questionnaires, or from dispensing records; dose or pill counting; electronic inhaler monitoring; and drug assay such as for prednisolone.

<u>Interventions to improve adherence in asthma</u>

Few adherence interventions have been studied comprehensively in asthma. Some examples are:

- *Shared decision-making for medication/dose choice improved adherence and asthma outcomes.*
- *Inhaler reminders for missed doses improved adherence and reduced exacerbations.*
- *Adherence was higher with ICS prescribed once-daily versus twice-daily. In a difficult inner-city environment, home visits for a comprehensive asthma program by an asthma nurse led to improved adherence and reduced prednisone courses over the following several months.*
- *Providing adherence information to clinicians did not improve ICS use among patients with asthma unless clinicians chose to view the details of their patients' medication use.*

Further studies are needed of adherence strategies that are feasible for implementation in primary care.

Factors contributing to poor adherence	*How to identify poor adherence in clinical practice*
<u>Medication/regimen factors</u> *• Difficulties using inhaler device (e.g. arthritis)* *• Burdensome regimen (e.g. multiple times per day)* *• Multiple different inhalers* *<u>Unintentional poor adherence</u>* *• Misunderstanding about instructions* *• Forgetfulness* *• Absence of a daily routine* *• Cost* *<u>Intentional poor adherence</u>* *• Perception that treatment is not necessary* *• Denial or anger about asthma or its treatment*	*<u>Ask an empathic question</u>* *• Acknowledge the likelihood of incomplete adherence and encourage an open non-judgemental discussion.* *Examples are:* *• 'Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1, 2, 3 or more days a week?'* *• 'Do you find it easier to remember your inhaler in the morning or the evening?'* *<u>Check medication usage</u>*

• *Inappropriate expectations* • *Concerns about side-effects (real or perceived)* • *Dissatisfaction with health care providers* • *Stigmatization* • *Cultural or religious issues* • *Cost*	• *Check the date of the last controller prescription* • *Check the date and dose counter on the inhaler* • *In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists*
Examples of successful adherence interventions	
• *Shared decision-making for medication/dose choice* • *Inhaler reminders for missed doses* • *Prescribing ICS once-daily versus twice-daily* • *• Home visits for a comprehensive asthma program by an asthma nurse*	

Table 24

5.1.7.4 *NHG ASTMA 2015*

No recommendations about strategies to assess nonadherence or to improve adherence.

5.1.7.5 *SIGN/BTS 2016*

ASSESSING MEDICATION ADHERENCE

In most clinical contexts, the key strategies for assessing adherence are self reporting and the prescribing record, although biochemical assays may have a role in asthma clinics for patients with severe asthma. In a research context electronic dose monitoring is the gold standard; counting doses used is another approach that is frequently used.

Patient self reporting is simple, inexpensive and feasible in most clinical settings. Self reporting typically overestimates adherence by a third compared to electronic monitoring or dose counting. This applies both in trial populations and clinical settings. Underuse is over-reported and overuse is underreported, reflecting socially acceptable answers. Patients/caregivers who report missing doses or not taking medication are likely to be non-adherent, though their estimate of dosages taken may still be inaccurate. Being non-judgemental, and asking specific questions about use of a treatment over a short time period (for example, in the last week/month) can help elicit an accurate response. Questionnaires have been validated for use in research, but have not been validated as a tool in clinical use.

<u>Computerised prescribing records</u>

Computerised prescribing records, normally readily available in primary care consultations and/or pharmacy dispensing records, provide a useful indication of adherence to prescribed asthma regimens. At an individual level, prescribing data does not correlate with self-reported adherence and may be a useful strategy for opening a discussion about suspected poor adherence. At a population

level, formulae (such as 'proportion of days covered' by the prescription recorded over a defined period) have been devised to assess adherence from routine prescribing/dispensing databases.

Biomarker testing

Biomarker testing with FeNO or biochemical urinary assays (for example a metabolite of fluticasone propionate) may have a role in establishing (non-)adherence in people with severe/difficult asthma. Suppression of FeNO after five days of directly observed inhaled steroid dosage has been shown to be an objective test to distinguish adherent from non-adherent patients with difficult asthma (see section 10.2.1).

Electronic monitoring

Electronic monitoring is the gold standard for assessing adherence in the research context, although not normally available in routine clinical practice. Dose counting is also used as a comparator, although unlikely to be feasible in a clinical context.

To assess adherence, ask specific questions about medication use and assess prescribing and any other data available. Explore attitudes to medication as well as practical barriers to adherence in a non-judgemental way. (D)

Questions about adherence should be open ended, acknowledge that poor adherence is the norm, and avoid use of potentially judgmental terminology. The questions are designed to stimulate an open discussion. (✓)

- **Explore perceived benefits ("How do you think that the inhaler is helping you control your asthma?" "Are there times when you find that you don't need your inhaler?")**
- **Ask about adverse reactions ("How much bother do you have from side effects?")**
- **Acknowledge general concerns about regular medication ("Some people worry about taking regular medication… what do you think?")**
- **Acknowledge practical difficulties with regular medication ("People sometimes find it difficult to remember to take regular treatment…")**
- **Ask about adherence over a specific time period ("How often did you use your preventer inhaler last week?")**

INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

Six systematic reviews were identified that evaluated interventions to improve adherence, one specifically in asthma, and five including a number of long-term conditions including asthma. The body of evidence represents 26 unique asthma trials.

The interventions were divided into 'informational' interventions (individual and/ or group sessions with or without written/electronic materials), or 'behavioural' interventions (including dosage simplification, regular monitoring including assessment of medication use with feedback, psychological therapies) or a combination of these two approaches.

Multifaceted interventions to improve adherence have:

- *modest effects on adherence*
- *less, or sometimes no, effect on clinical outcomes.*

The effect is greater if the intervention:

- *includes behavioural components*
- *includes practical facilitators (such as simplified dosage regimes), strategies to aid integration into daily routines, automated reminders, monitoring and follow up*
- *is monitored, delivered and sustained as part of a comprehensive programme of accessible proactive asthma care.*

Innovative, IT-based ways to support adherence show some promise (for example, providing daily medication reminders, feedback on adherence, refill reminders) especially if they are interactive, but as components of, as opposed to replacement for, on-going supportive care.

Adherence to long-term asthma treatment should be routinely and regularly addressed by all healthcare professionals within the context of a comprehensive programme of accessible proactive asthma care. (D)

Initiatives to promote adherence to regular treatment should consider: (✓)

- **information requirements, for example individual and/or group sessions, written/electronic materials, ongoing access to information**
- **practical facilitators, for example simple dosage regimes, dose counters, reminders**
- **behavioural support, for example regular monitoring including assessment of medication use with feedback, counselling, psychological therapies**
- **context – accessible proactive asthma care, for example Chronic Care Model**
- **consultation skills required to achieve shared decision making: adherence is more likely when the patient and the healthcare professional agree that the action is appropriate.**

PHARMACIST-LED INTERVENTIONS

Pharmacists have opportunities to provide education for people with asthma, and furthermore, may be able to identify those with poor asthma control. The body of evidence for pharmacy-based interventions is, however, methodologically weak or of limited relevance. Two systematic reviews were assessed. One review addressed interventions in low and middle income countries, while another addressed pharmacy interventions more generally.

Interventions generally involved educating community pharmacists to, in turn, educate patients. Other models or elements included follow-up reviews for newly prescribed medication, identifying those with poor control by using questionnaires such as the Asthma Control Test searching prescribing databases for patients using large numbers of reliever inhalers, and targeting reviews or referral to general practitioners. Overall, the most consistent improvements in outcomes were seen in inhaler technique, with a few studies showing improvements in reduced dispensing of, or need for, reliever inhalers. There was no convincing evidence of reduction in healthcare use.

Further high-quality randomised trials testing pharmacist-led interventions to improve asthma outcomes are needed.

Consider training pharmacists to provide education for people with asthma.(✓)

5.2 Guidelines on COPD

5.2.1 General information on selected guidelines

5.2.1.1 *Selected guidelines*

The selected guidelines and their abbreviations as used in this report can be found in the table below.

Abbreviation	Guideline
AECOPD 2015(37)	American College of Chest Physicians and Canadian Thoracic Society – Prevention of Acute Exacerbations of COPD, 2015.
GOLD 2017(38)	Global Initiative for Chronic Obstructive Lung Disease – Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2017.
NHG COPD 2015(28)	Nederlands Huisartsen Genootschap – NHG-Standaard COPD, 2015.
VA/DoD 2014(39)	The Department of Veterans Affairs/ the Department of Defense – VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease, 2014.

Table 25: Selected guidelines and their abbreviations as used in this report.

5.2.1.2 *Grades of recommendation*

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the tables below.

AECOPD 2015		
Grades of recommendation	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High-quality evidence: RCTs without important limitations or exceptionally strong evidence from observational studies
	B	Moderate-quality evidence: RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies
	C	Low or very low-quality evidence: at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence
	Nongraded CB	Consensus based: insufficient evidence for a graded recommendation

Table 26: Levels of evidence of the AECOPD 2015 guideline

GOLD 2017		
Levels of evidence	A	Randomized controlled trials (RCTs). Rich body of high quality evidence without any significant limitation or bias.
	B	Randomized controlled trials (RCTs) with important limitations. Limited body of evidence.
	C	Nonrandomized trials. Observational studies.
	D	Panel consensus judgment.

Table 27: Levels of evidence of the GOLD 2017 guideline

The **NHG** guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended). (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

NHG COPD 2015		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/
	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.

Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 28: Grades of recommendation and Level of evidence of NHG COPD 2015 guideline.

VA/DoD 2014		
Grades of recommendation/ Levels of evidence	Strong For	"We recommend offering this option…"
	Weak For	"We suggest offering this option…"
	Weak Against	"We suggest not offering this option…"
	Strong against	"We recommend against offering this option…"

Table 29: Levels of evidence of the VA/DoD 2014 guideline

5.2.1.3 *Agree II score*

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the table below. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score (%)
AECOPD 2015	6	7	7	6	7	6	1	7	**47**	**84**
GOLD 2017	5	5	6	6	7	7	5	7	**48**	**86**
NHG COPD 2015	5	4	4	1	6	6	5	3	**34**	**61**
VA/DoD 2014	7	7	7	5	7	7	1	1	**42**	**75**

Table 30: AGREE score of selected guidelines on item "Rigour of development"

5.2.1.4 *Included populations – interventions – main outcomes*

In the tables below, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AECOPD 2015	
Population	Patients with COPD (>40 yrs of age, previous or current smoker, post bronchodilator FEV1/FVC <0.70)
Interventions	Nonpharmacological therapies, inhaled therapies, oral therapies
Outcomes	Preventing acute exacerbations, including those requiring change in medication (antibiotic, prednisone, or both), emergency room visits and hospital admissions and readmissions, unscheduled physician

	visits, change in location of care, time to first exacerbation, or exacerbation rate.

Table 31: Included population, intervention and main outcomes of the AECOPD 2015 guideline.

GOLD 2017	
Population	Patients with COPD
Interventions	Diagnosis and assessment, therapeutic options, management of stable COPD, exacerbations, COPD and comorbidities
Outcomes	Not specified.

Table 32: Included population, intervention and main outcomes of the GOLD 2017 guideline.

NHG COPD 2015	
Population	Patients with COPD
Interventions	Diagnosis, monitoring, management, comorbidity, exacerbations
Outcomes	Dyspnea, exercise tolerance, health status, lung function, prevention of exacerbations, prevention of disability, workplace absence and mortality, serious adverse effects (pneumonia)

Table 33: Included population, intervention and main outcomes of the NHG COPD 2015 guideline.

VA/DoD 2014	
Population	Adults with a diagnosis or a suspicion of COPD. Excluded: patients with bronchiectasis, asthma, cystic fibrosis or other lung diseases but without COPD.
Interventions	Non-pharmacologic treatments, inhaled and systemic pharmacologic treatments used in acute and maintenance management of COPD.
Outcomes	Outcomes considered included QoL, morbidity, dyspnea, functional capacity, exacerbation rate and/or severity, mortality, harms, health care utilization (only for the KQs assessing pulmonary rehabilitation or chronic disease management), and diagnostic test accuracy (only for the KQ assessing tests used to distinguish between COPD exacerbation and other causes of acute symptoms).

Table 34: Included population, intervention and main outcomes of the VA/DoD 2014 guideline.

5.2.1.5 *Members of development group – target audience*

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the tables below.

AECOPD 2015	
Development group	"Interdisciplinary clinicians who have special expertise in COPD clinical research and care, with the assistance of methodologists"
Target audience	Clinicians treating patients with COPD.

Table 35: Members of the development group and target audience of the AECOPD 2015 guideline.

GOLD 2017	
Development group	Specialists in respiratory medicine.
Target audience	General practitioners.

Table 36: Members of the development group and target audience of the GOLD 2017 guideline.

NHG COPD 2015	
Development group	General practitioners, pulmonologists, expert in preventative medicine, biomedical sciences, an epidemiologist
Target audience	General practitioners

Table 37: Members of the development group and target audience of the NHG COPD 2015 guideline.

VA/DoD 2014	
Development group	Multidisciplinary: specialties and clinical areas of interest included family practice, internal medicine, nurse case management, nursing, pharmacy, pulmonology, social work, primary care, physical therapy, nutritional service, and dietetics
Target audience	Primary care providers

Table 38: Members of the development group and target audience of the VA/DoD 2014 guideline.

5.2.1.6 *Method of reporting of the recommendations and notes*

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Even though the NHG COPD 2015 guideline did not grade its recommendations, it does appraise the studies leading to the recommendations. For that reason, the recommendations of the NHG COPD 2015 guideline are also written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

5.2.2 What inhaled treatment is the initial choice and what intensification strategy may be used ?

5.2.2.1 *Summary*

Three of the selected guidelines (GOLD 2017, NHG COPD 2015, VA/DoD 2014) provide recommendations on initial choice and intensification strategy of inhaled medication in COPD.

All three strategies differ.
The GOLD 2017 guideline selects initial and step-up inhaled treatments according to the disease burden and exacerbation risk of the patient.
The NHG COPD 2015 guideline recommends to initiate treatment with any short-acting bronchodilator or a combination of short-acting bronchodilators, and to step-up to any long-acting bronchodilator if necessary.
The VA/DoD 2014 guideline makes specific first choices for initial treatment and step-up treatments.

Guidelines	GOLD 2017	NHG COPD 2015	VA/DoD 2014
Initial treatment	Group A : any bronchodilator Group B : LABA or LAMA Group C :LAMA Group D : LABA + LAMA	SABA or SAMA or SABA + SAMA	SABA
Step-up 1	Group A : continue, stop or try alternative class Group B : LABA + LAMA Group C : LAMA + LABA Group D : LABA + LAMA + ICS	LABA or LAMA	Tiotropium
Step-up 2	/	/	Tiotropium + LABA
Step-up 3	/	/	Tiotropium + LABA+ ICS

Table 39: Initial choice of inhaled treatment and intensification strategy, according to the selected guidelines

5.2.2.2 *AECOPD 2015*

AECOPD 2015 does not provide a strategy for initiating therapy, for step-up or step-down.

5.2.2.3 *GOLD 2017*

Key points for the use of bronchodilators:

- **LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (Evidence A).**
- **Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator treatment should be escalated to two (Evidence A).**
- **Inhaled bronchodilators are recommended over oral bronchodilators (Evidence A).**

- **Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (Evidence B).**

Key points for the use of anti-inflammatory agents

- **Long-term monotherapy with ICS is not recommended (Evidence A)**
- **Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (Evidence A).**
- **Long-term therapy with oral corticosteroids is not recommended (Evidence A).**

Figure 2.4. The refined ABCD assessment tool

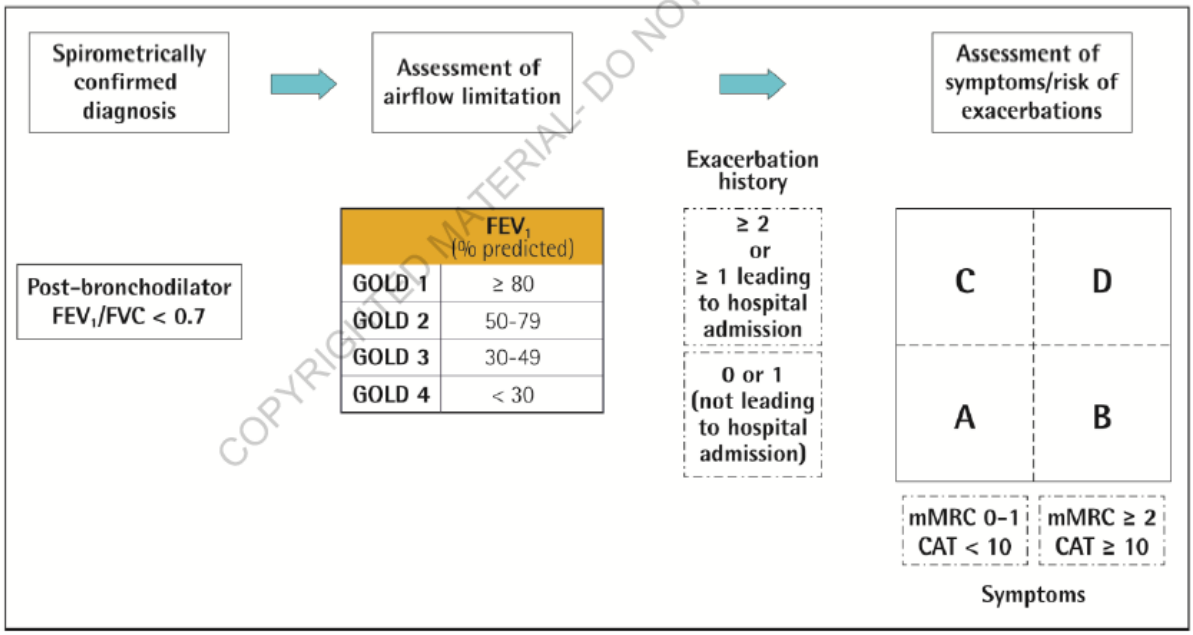
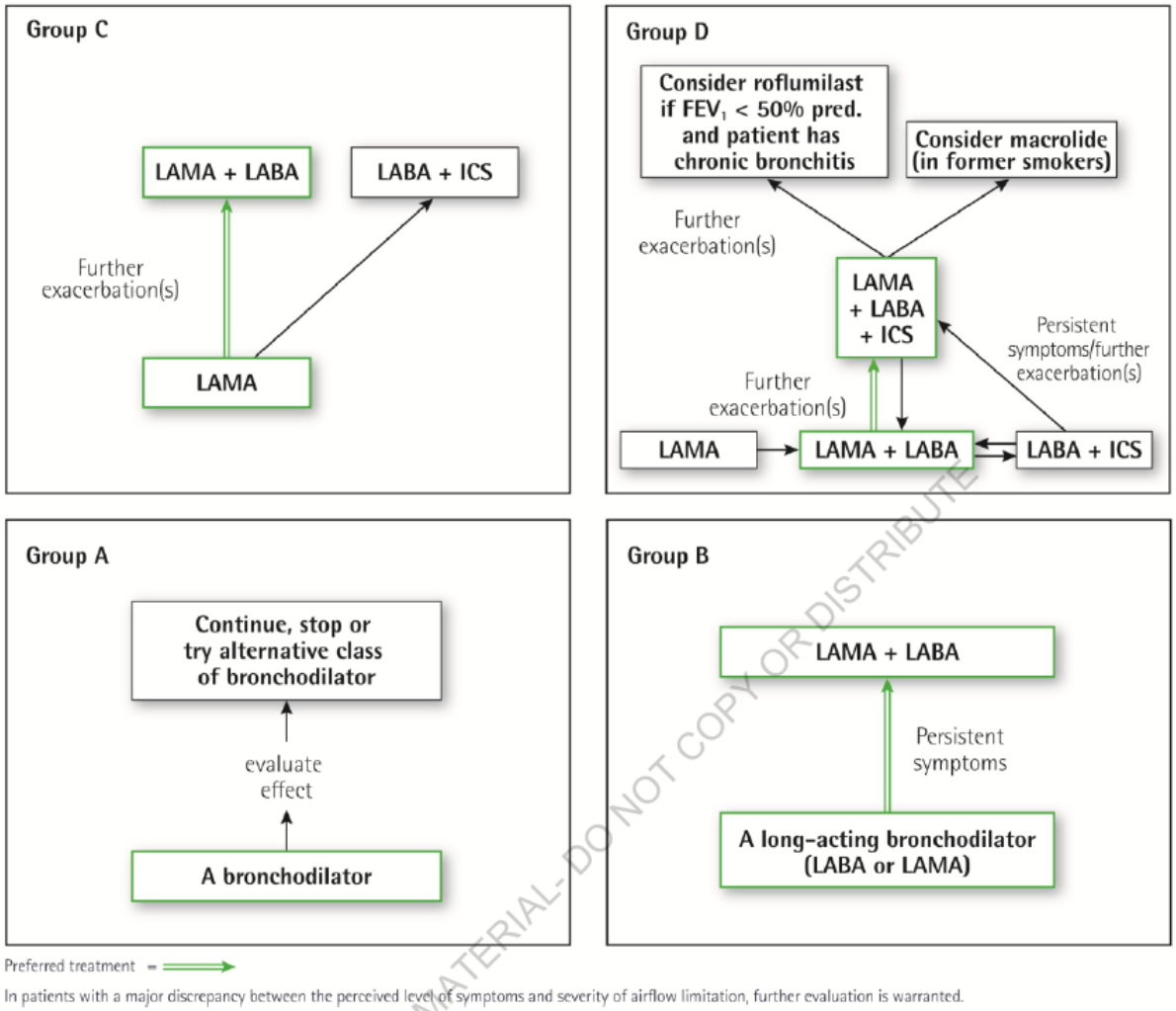


Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Group A

All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.
This should be continued if symptomatic benefit is documented.

Group B

Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., pro re nata (prn) and are therefore recommended.

There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.

For patients with persistent breathlessness on monotherapy, the use of two bronchodilators is recommended.

For patients with severe breathlessness initial therapy with two bronchodilators may be considered.

If the addition of a second bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to a single bronchodilator.

Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.

<u>Group C</u>

Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.

Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting beta2-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.

<u>Group D</u>

We recommend starting therapy with a LABA/LAMA combination because:

- **In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs.**
- **A LABA/LAMA combination was superior to a LABA/ICS combination in prevention exacerbations and other patient reported outcomes in Group D patients.**
- **Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.**

In patients who develop further exacerbations on LABA/LAMA we suggest two alternative pathways:
Escalation to LABA/LAMA/ICS. Studies are underway comparing the effects of LABA/LAMA vs. LABA/LAMA/ICS for exacerbation prevention.

Switch to LABA/ICS. However, there is no evidence that switching from LABA/LAMA to LABA/ICS results in better exacerbation prevention. If LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added.

If patients treated with LABA/LAMA/ICS still have exacerbations the following options may be considered:

- **Add roflumilast. This may be considered in patients with an FEV1 <50% predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.**
- **Add a macrolide. The best available evidence exists for the use of azithromycin. Consideration to the development of resistant organisms should be factored into decision making.**
- **Stopping ICS. A reported lack of efficacy, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports this recommendation.**

5.2.2.4 *NHG COPD 2015*

In "new" patients with COPD, assess empirically which short-acting bronchodilator or combination of bronchodilators is the most efficacious. **In patients with COPD and little symptoms (e.g. MRC <2 or CCQ <1), inhalation medication can be left out.**

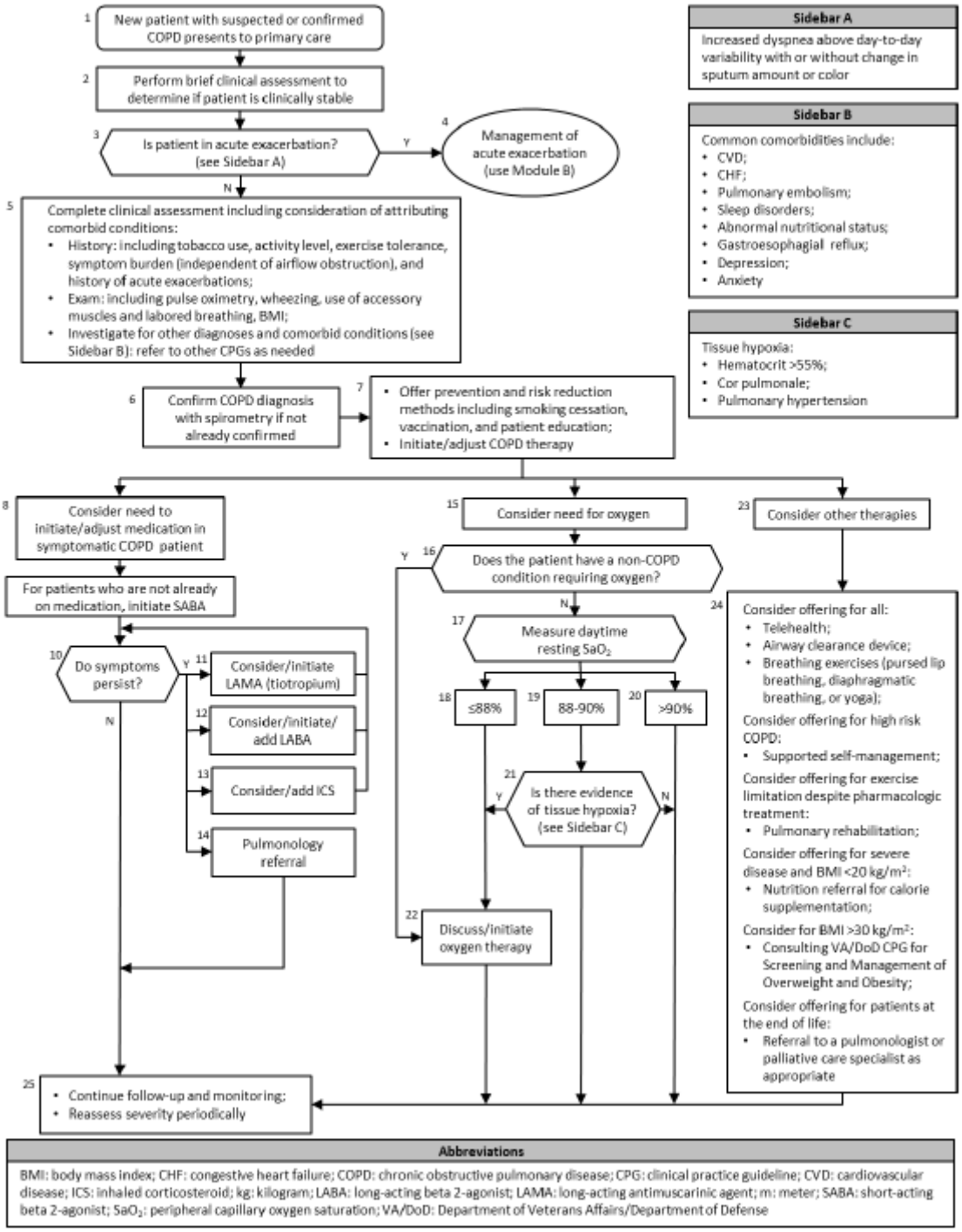
- **Start with one of both kinds of short-acting bronchodilators:**
  - *A SABA (short-acting beta2-agonist) (salbutamol, terbutaline) or;*
  - *A SAMA (short-acting muscarinic antagonist) (ipratropium).*
- **Choose the other kind of bronchodilator when there is insufficient improvement (persistent symptoms of dyspnoea) after two weeks, or add a product of the other kind.**
- **When treatment goals are not met (persistent complaints of dyspnoea, exacerbations, nocturnal symptoms) in patients with (moderate) severe airway obstruction (FEV1 <80% of predicted), a switch to maintenance treatment with a long-acting bronchodilator is initiated.**
  - *A LABA (long-acting beta2 agonist) like formoterol or salmeterol or;*
  - *A LAMA (long-acting muscarinic antagonist) like tiotropium.*

According to the working group, there are no clinical reasons for a preference for LABA or LAMA; the choice is determined on the basis of efficiency.

In recent years a number of new products have appeared on the market (eg roflumilast tablets, and inhalants such as indacaterol, olodaterol, glycopyrronium, aclidinium and a combination preparation indacaterol/ glycopyrronium. These new agents have not demonstrated a clinically significant added value compared to existing long-acting agents regarding lung function, quality of life, exacerbations and mortality. Because of unknown long-term efficacy and adverse effects, these products are not recommended.

5.2.2.5 *VA/DoD 2014*

Algorithm A: Management of COPD in Primary Care



- **We recommend prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. Strong For**
  Modified from the 2007 CPG without an updated systematic review of the evidence.
- **We recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). Strong For**
- **We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). Weak For**

- **We recommend inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1<50%) or a history of COPD exacerbations. Strong For**
- **For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), we suggest continuing with this treatment, rather than switching to long-acting bronchodilators. Weak For**
  Modified from the 2007 CPG without an updated systematic review of the evidence.
- **For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, we suggest discontinuing the SAMA. Weak For**
  Modified from the 2007 CPG without an updated systematic review of the evidence.
- **We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy. Strong Against**
- **In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of rugs. Strong For**
- **In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication. Weak For**

5.2.3 What is the place of associations of inhaled bronchodilators (fixed and others) versus monotherapy?

5.2.3.1 *Summary*

In the AECOPD 2015 guideline, LABA + LAMA is recommended to prevent exacerbations, but it is not clear to which step of the treatment this recommendation applies.

In the GOLD 2017 guideline, LABA + LAMA is recommended as a first-choice, first step therapy for Group D patients (high risk of exacerbations and high disease burden), and as a step-up therapy for patients in Group B (high disease burden, low risk of exacerbations) and C (high risk of exacerbations, low disease burden), who are not controlled in monotherapy.

In the VA/DoD 2014 guideline, LABA + LAMA is recommended as a step-up therapy for patients who have persistent symptoms on monotherapy.

In the NHG COPD 2015 guideline, LABA + LAMA is presented as a possible choice if monotherapy is insufficient, but it is not actively recommended.

5.2.3.2 *AECOPD 2015*

The AECOPD 2015 guideline does not provide a treatment strategy. It is not clear to what stage of disease or treatment the following recommendation pertains.

For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting b 2 -agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

5.2.3.3 *GOLD 2017*

Group B

Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., pro re nata (prn) and are therefore recommended.
There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.
For patients with persistent breathlessness on monotherapy, the use of two bronchodilators is recommended.
For patients with severe breathlessness initial therapy with two bronchodilators may be considered.

If the addition of a second bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to a single bronchodilator.
Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.

Group C

Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.
Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting beta2-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.

Group D

We recommend starting therapy with a LABA/LAMA combination because:

- **In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs.**
- **A LABA/LAMA combination was superior to a LABA/ICS combination in prevention exacerbations and other patient reported outcomes in Group D patients.**
- **Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.**

5.2.3.4 *NHG COPD 2015*

If needed, a LABA can be combined with a LAMA, *even though the evidence of efficacy and the added value of this combination are very sparse.*

5.2.3.5 *VA/DoD 2014*

- **In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of drugs. Strong For**

5.2.4 What is the place of associations of one inhaled bronchodilator with an inhaled corticosteroid (LAMA, LABA or both, + CSI, fixed association or not)

5.2.4.1 *Summary*

The AECOPD 2015 guideline recommends the combination of LABA + ICS and triple therapy (LABA + LAMA + ICS) as treatments to prevent exacerbations. However, as the AECOPD 2015 guideline does not provide a treatment strategy, it is not clear in what stage of treatment these combinations should be used.

The GOLD 2017 guideline recommends triple therapy (LAMA + LABA + ICS) as a first-choice step-up therapy in Group D patients (high disease burden and high exacerbation risk), who are not controlled with LABA + LAMA. The combination of LABA + ICS is presented as a possible alternative, but not as a first choice, in Group C (low disease burden, high exacerbation risk) and Group D patients who are not controlled with initial therapy.

The NHG COPD 2015 guideline states that adding ICS for one year can be considered as a step-up treatment in patients with two or more severe exacerbations, despite maintenance treatment with a LABA or LAMA. The NHG guideline does not recommend initiating ICS maintenance therapy in primary care.

The VA/DoD 2014 guideline recommends triple therapy (LAMA + LABA + ICS) as a step-up therapy in COPD patients who are uncontrolled on LABA + LAMA.

5.2.4.2 *AECOPD 2015*

The AECOPD 2015 guideline does not provide a treatment strategy. It is not clear to what stage of disease or treatment the following recommendations pertain.

For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting b 2 -agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).
For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting b 2 -agonist therapy compared with long-acting b 2 -agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).
For patients with stable moderate to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting b 2 -agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).
For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/ long-acting b 2 -agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).
For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting b 2 -agonist therapy or inhaled long-acting

anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

5.2.4.3 *GOLD 2017*

Group C

Initial therapy should consist of a single long acting bronchodilator. In two head-to-head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.
Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting beta2-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.

Group D

We recommend starting therapy with a LABA/LAMA combination because:

- **In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs.**
- **A LABA/LAMA combination was superior to a LABA/ICS combination in prevention exacerbations and other patient reported outcomes in Group D patients.**
- **Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.**

In patients who develop further exacerbations on LABA/LAMA we suggest two alternative pathways:
Escalation to LABA/LAMA/ICS. Studies are underway comparing the effects of LABA/LAMA vs. LABA/LAMA/ICS for exacerbation prevention.
Switch to LABA/ICS. However, there is no evidence that switching from LABA/LAMA to LABA/ICS results in better exacerbation prevention. If LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added.

5.2.4.4 *NHG COPD 2015*

Consider adding inhaled corticosteroids (ICS) for one year in patients with frequent severe exacerbations (two or more courses of prednisolone or antibiotics or hospitalizations associated with COPD per year), despite maintenance treatment with long-acting bronchodilator. *The treatment is continued when there is a decrease in the number of exacerbations, measured by the number of courses of prednisolone or an antibiotic or hospitalizations associated with COPD.*

Treatment with ICS is associated with an increased risk of pneumonia. If the number of exacerbations are not significantly reduced after one year, or if there are no exacerbations for a longer period (two years), treatment with ICS is therefore discontinued. *Evaluate three months after discontinuation of ICS.*

The general practitioner generally does not initiate a maintenance therapy with a combination preparation of an ICS and a LABA, due to limited indication of ICS in COPD. For this reason, the combination preparations have not been included.

5.2.4.5 *VA/DoD 2014*

In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication. Weak For

5.2.5 What is the place of a long-term treatment with azithromycin for COPD?

5.2.5.1 *Summary*

Two guidelines (AECOPD 2015, GOLD 2017) advise to consider long-term macrolides in COPD patients who are former smokers and have exacerbations despite optimal inhaler therapy.

Chronic macrolide use is not recommended in primary care by two other guidelines (NHG COPD 2015, VA/DoD 2014).

5.2.5.2 *AECOPD 2015*

Note: the AECOPD 2015 guideline does not provide a treatment strategy, so it is unclear to which stage of treatment/disease the following recommendation applies.

PICO 3: In Patients Aged >40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?
For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).
Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

5.2.5.3 *GOLD 2017*

In former smokers with exacerbations despite appropriate therapy, macrolides can be considered (Evidence B).
If patients treated with LABA/LAMA/ICS still have exacerbations the following options may be considered:

- **Add roflumilast. This may be considered in patients with an FEV1 <50% predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.**
- **Add a macrolide. The best available evidence exists for the use of azithromycin. Consideration to the development of resistant organisms should be factored into decision making.**
- **Stopping ICS. A reported lack of efficacy, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports this recommendation.**

5.2.5.4 *NHG COPD 2015*

Maintenance treatment with antibiotics is not recommended in primary care *because the disadvantages outweigh the benefits.*

5.2.5.5 *VA/DoD 2014*

We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. Weak Against

5.2.6 Adherence

5.2.6.1 *Summary*

None of the selected guidelines gave recommendations on how to assess nonadherence or strategies on how to improve adherence in COPD.

5.2.6.2 *AECOPD 2015*

No recommendations about strategies to assess nonadherence or to improve adherence.

5.2.6.3 *GOLD 2017*

No recommendations about strategies to assess nonadherence or to improve adherence.

5.2.6.4 *NHG COPD 2015*

No recommendations about strategies to assess nonadherence or to improve adherence.

5.2.6.5 *VA/DoD 2014*

No recommendations about strategies to assess nonadherence or to improve adherence.

6 COPD – Evidence tables and conclusions

6.1 Combination of two bronchodilators

6.1.1 LABA +LAMA vs LABA

6.1.1.1 *Clinical evidence profile*

Meta-analysis: Farne 2015 (40)"Long-acting beta2-agonist plus tiotropium versus tiotropium alone for chronic obstructive pulmonary disease"

Inclusion criteria: RCTs with a parallel group design of at least 12 weeks duration. Population with a diagnosis of COPD and that used an external set of criteria to diagnose participants (like GOLD or American Thoracic Society). Participants needed to have received inhaled LABA in addition to tiotropium, tiotropium, or LABA alone.
Search strategy: Up to july 2015.
Trials were searched for in CAGR, CENTRAL, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, with handsearching of respiratory journals and meeting abstract.
clinicaltrials.gov was searched until april 2015.
Assessment of quality of included trials: yes
Other methodological remarks: Dichotomous data was analysed using participants as the unit of analysis rather than events (to avoid counting the same patient twice).

Table 40

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Farne 2015 (40) Design:	**LABA + tiotropium** **vs tiotropium**	N= 5 n= 6709 (Aaron 2007, Vogelmeier 2008, Buhl 2015a, Buhl 2015b,	**Change in SGRQ**	MD: -1.34 [-1.87 to -0.70] SS (Favours LABA + LAMA)

Search date: (month-year)		ZuWallack 2014a)		
		N= 4 n= 4856 (Aaron 2007, Vogelmeier 2008, Buhl 2015a, Buhl 2015b)	**Hospital admissions (all causes)**	OR: 1.01 (0.86 to 1.19) NS
		N= 4 n= 4856 (Aaron 2007, Vogelemeir 2008, Buhl 2015a, Buhl 2015b)	**Hospital admissions (exacerbations)**	OR: 1.02 (0.80 to 1.28) NS
		N= 8 n=9633 (Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Mahler 2010a, Mahler 2010b, Buhl 2015a, Buhl 2015b, ZuWallack 2014a)	**Mortality (all cause)**	OR: 1.24 (0.81 to 1.90) NS
		N= 7 n=6391 (Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Buhl 2015a & Buhl 2015b, ZuWallack 2014a & ZuWallack 2014b)	**Exacerbation**	OR: 0.94 (0.79 to 1.11) NS
		N= 8	**Trough FEV1**	MD: 0.06 (0.05 to 0.07)

		n=9573 (Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Hoshino 2014, Mahler 2010a & 2010b, Buhl 2015a & 2015b, ZuWallack 2014a & 2014b)		SS (Favours LABA + LAMA)

Table 41

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Farne 2015 (40) Design: Search date: (month-year)	**LABA + tiotropium** **vs LABA**	N=4 n= 3378 (Buhl 2015b, Buhl 2015a, Hoshino 2014, Vogelmeier 2008)	**Change in SGRQ**	MD: -1.03 (-2.36 to 0.30) **SS** **Favours LABA + LAMA**
		N= 3 n= 3514 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	**Hospital admissions (all causes)**	OR: 0.93 (0.76 to 1.14) NS
		N= 3 n= 3514 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	**Hospital admissions (exacerbations)**	OR: 0.90 (0.66 to 1.22) NS
		N= 3 n=3514 (Buhl 2015b, Buhl	**Mortality (all cause)**	OR: 1.15 (0.62 to 2.13) NS

		2015a, Vogelmeier 2008)		
		N= 3 n=3514 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	**Exacerbation**	OR: 0.80 (0.69 to 0.93) NS
		N= 4 n=3513 (Buhl 2015b, Buhl 2015a, Hoshino 2014, Vogelmeier 2008)	**Trough FEV1**	MD: 0.07 (0.06 to 0.09) **SS** **Favours LABA+LAMA**

Table 42

Ref + design	n	Population	Duration (of treatment)	Comparison	Methodology (as assessed by cochrane authors)
Aaron 2007 RCT DB PC PG Canada	304	- clinical history of moderate or severe COPD as definedby ATS and GOLD guidelines - mean age 68 years - COPD severity moderate to severe with mean FEV1 predicted of 38% - 57% men - at least 1 exacerbation of COPD in the previous 12 months - ≥ 10 pack-years of cigarette smoking - FEV1/FVC ratio < 0.70	1 year	*LABA+LAMA vs Placebo + LAMA* tiotropium 18 µg once daily using a HandiHaler + salmeterol 25 µg/puff, 2 puffs twice daily using a pressurised metered-dose inhaler using a spacer device VS	ALLOCATION CONC: unclear risk of bias RANDO: low risk of bias BLINDING : Participants/ personnel = adequate assessors: unclear SELECTIVE REPORTING: low risk FUNDING: Canadian Institutes of Health Research & the Ontario Thoracic Society CO-MEDICATION:

		- post-bronchodilator FEV1 < 65% predicted <u>Exclusion:</u> - physician-diagnosed asthma before 40 years - history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction - receiving oral prednisone - known hypersensitivity or intolerance to study components - having had a lung transplant or volume reduction surgery - having diffuse bilateral bronchiectasis - pregnant/breastfeeding - history of glaucoma or severe UT obstruction		tiotropium, 18 µg once daily, + placebo inhaler, 2 puffs twice daily	At baseline tiotropium+ placebo group 52% on combined inhalers (ICS+LABA), 25% on ICS inhaler tiotropium +salmeterol group: 44% on combined inhalers (ICS+LABA) and 35%on ICS inhalers. Any treatment with ICS, LABA, and anticholinergics that the person may have been using before entry was discontinued on entry into the study. Therapy with other respiratory medications, such as oxygen, anti-leukotrienes, and methylxanthines, was continued in all participant groups
Buhl 2015a (16) RCT DB PG phase III	2624	- mean age 64.2y - men: 74% - 38% current smokers - 50% GOLD stage 2 (FEV1 50-80% pred.); 39% GOLD stage 3 (FEV1 30-50% pred.); 11% GOLD stage 4 (FEV1 <30% pred.) - 86% with comorbidities at baseline <u>EXCLUSION:</u> - critically abnormal baseline parameters - history of asthma	52 weeks (nearly all endpoints reported after 24 weeks, including trough FEV1)	*LAMA + LABA (different doses) vs LABA* *vs LAMA (different doses)* • tiotropium 5 µg + olodaterol 5 µg fixed-dose combination via Respimat 1x/d • tiotropium 2.5 µg + olodaterol 5 µg fixed-dose combination via Respimat	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk SELECTIVE REPORTING: low risk OTHER BIAS: More drop out for monotherapy arms for all outcomes except trough FEV1 at 6 months FUNDING: NCT01431274 sponsored by Boehringer Ingelheim

		- MI within 1 year of screening - hospitalized within the past year - unstable / life-threatening cardiac disease - diagnosed thyrotoxicosis or paroxysmal tachycardia - previous pulmonary resection - regular use of daytime oxygen and unable to abstain during clinic visits - currently enrolled in pulmonary rehabilitation programme		once daily • Olodaterol µg Respimat once daily • tiotropium 5 µg Respimat once daily • tiotropium 2.5 µg Respimat once daily	COMEDICATION: 48% were taking ICS Continued use of ICS that were stable prior to study entry were permitted Temporary increase of the dose or addition of oral corticosteroids and methylxanthines permitted.
Buhl 2015b (16) RCT DB PG phase III		- mean age 63.8 years - men: 72% - 36% current smokers - 50% GOLD stage 2 (FEV1 50-80% pred.); 38% GOLD stage 3 (FEV1 30-50% pred.); 12% GOLD stage 4 (FEV1 <30% pred.) - 87% with comorbidities at baseline <u>EXCLUSION</u>: - critically abnormal baseline parameters - history of asthma - MI within 1 year of screening - hospitalized within the past year - unstable / life-threatening cardiac disease - diagnosed thyrotoxicosis or paroxysmal tachycardia - previous pulmonary resection - regular use of daytime oxygen and unable to abstain during clinic visits	52 weeks (nearly all endpoints reported after 24 weeks, including trough FEV1)	*LAMA + LABA (different doses) vs LABA* *vs LAMA (different doses)* • tiotropium 5 µg + olodaterol 5 µg fixed-dose combination via Respimat 1x/d • tiotropium 2.5 µg + olodaterol 5 µg fixed-dose combination via Respimat once daily • Olodaterol µg Respimat once daily • tiotropium 5 µg Respimat once daily • tiotropium 2.5 µg Respimat once daily	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: unclear risk SELECTIVE REPORTING: low risk OTHER BIAS: More drop out for monotherapy arms for all outcomes except trough FEV1 at 6 months FUNDING: NCT01431287 sponsored by Boehringer Ingelheim COMEDICATION: 47% were taking ICS Temporary increase of the dose or addition of oral corticosteroids and methylxanthines permitted

		- currently enrolled in pulmonary rehabilitation programme			
Hoshino 2014 RCT OL PG Japan	62	- diagnosis of moderate or severe COPD as defined by GOLD (FEV1 <70%) - mean age 71 y - 93% male -mean FEV1 1.46 – 1.63L - mean FEV1 predicted 64-67% <u>EXCLUSION:</u> - diagnosis of asthma - patients on supplemental oxygen - patients judged unsuitable by doctors	16 weeks	• Indacaterol 150 µg through SDDPI Breezhaler, once daily + tiotropium 18 µg through SDDPI HandiHaler, once daily • tiotropium 18 µg through SDDPI HandiHaler, once daily • Indacaterol 150 µg through SDDPI Breezhaler, once daily	ALLOCATION CONC: unclear RANDO: low risk of bias BLINDING : Participants/ personnel = open study assessors: adequate INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low risk FUNDING: self-funded COMEDICATION: patients were either newly diagnosed or discontinued the use of any COPD medications
Mahler 2010a RCT DB PG Multinational	1134	- moderate or severe COPD as defined by GOLD guidelines - mean age 64 y - mean FEV1 1.3L - mean FEV1 49% of predicted value - mean pack-years smoking history: 47 years - 67% men <u>EXCLUSION</u> - having received systematic corticosteroids or antibiotics or being hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during run-in - having a respiratory tract infection	12 weeks	• Indacaterol 150 µg through SDDPI, once daily + tiotropium 18 µg through SDDPI HandiHaler, once daily • Placebo to indacaterol + tiotropium 18 µg through SDDPI HandiHaler, once daily	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: / FUNDING: Novartis COMEDICATION: abulterol for rescue 53% of patients had ICS at baseline and continued treatment at equivalent dose and regimen throughout study

		whithin 6 weeks prior to screening - concomitant pulmonary disease - history of asthma - diabetes type I - uncontrolled diabetes type II - (a history of) lung cancer - certain cadriovascular comorbidities			
Mahler 2010b RCT DB PG Multinational	1142	- moderate or severe COPD as defined by GOLD guidelines - mean age 63 y - mean FEV1 1.3L - mean FEV1 49% of predicted value - mean pack-years smoking history: 46 years - 67% men <u>EXCLUSION</u> - having received systematic corticosteroids or antibiotics or being hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during run-in - having a respiratory tract infection whithin 6 weeks prior to screening - concomitant pulmonary disease - history of asthma - diabetes type I - uncontrolled diabetes type II - (a history of) lung cancer - certain cadriovascular comorbidities	12 weeks	• Indacaterol 150 µg through SDDPI, once daily + tiotropium 18 µg through SDDPI HandiHaler, once daily • Placebo to indacaterol + tiotropium 18 µg through SDDPI HandiHaler, once daily	RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: / FUNDING: Novartis COMEDICATION: abulterol for rescue 53% of patients had ICS at baseline and continued treatment at equivalent dose and regimen throughout study
Tashkin 2009a	255	- clinical history of COPD - mean age 64 yaers	12 weeks	• formoterol (Foradil Aerolizer) 12 µg twice daily	ALLOCATION CONC: unclear RANDO: adequate

RCT DB PG USA		- post-bronchodilator FEV1 <70% and >30% predicted - FEV1/FVC <0.70 at screening and run-in - daytime or nighttime symptoms of COPD, including dyspnoea present ≥4 of the 7 days before baseline visit <u>EXCLUSION</u> - current or previous history of asthma - significant condition that might interfere with study treatment - use of oxygen (≥2L/min for >2h/day) - initiation of pulmonary rehabilitation within the previous 3 months - ventilator support for respiratory failure within previous 3 months - needing nasal CPAP - clinically significant lung disease other than COPD - sleep apnea - chronic narrow-angle glaucoma - symptomatic prostatic hyperplasia - bladder neck obstruction - need for chronic		and tiotropium (HandiHaler) 18 µg once daily in the morning delivered via 2 separate inhalers • formoterol-matched placebo twice daily and tiotropium 18 µg once daily delivered via 2 separate inhalers	BLINDING : Participants/ personnel: adequate assessors: unclear INCOMPLETE OUTCOME DATA: unclear risk, uneven withdrawals (14.5% LABA+LAMA group, 6.1% LAMA group) SELECTIVE REPORTING: low risk FUNDING: Schering Corporation COMEDICATION: continued use of prior stable ICS (27%) regimens and systemic corticosteroids for the treatment of exacerbations was permitted throughout the study
Vogelmeier 2008 R partly blind partly placebo controlled PG	638	- mean age 63 years - mean FEV1 predicted of 52% - 78% men - clinical history of moderate-to-very severe COPD as defined by GOLD guidelines	24 weeks	• formoterol 10 µg twice daily via MDDPI • tiotropium 18 µg once daily via the HandiHaler + formoterol 10 µg via MDDPI	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel: inadequate, no placebo tiotropium inhaler Assessors: adequate INCOMPLETE OUTCOME DATA: low

Multi-national		- smoking history of ≥ 10 pack-years - be symptomatic on at least 4 of 7 days prior to randomisation EXCLUSION - respiratory tract infection or had been hospitalised for an acute exacerbation of COPD within the month prior to screening - participants with a clinically significant condition such as ischaemic heart disease that might compromise person's safety or compliance			risk SELECTIVE REPORTING: low risk FUNDING: Novartis COMEDICATION: Participants (40-44%) could receive ICS at a stable daily dose (any participants receiving fixed combinations of ICS and beta2-agonists were switched to receive the same dose of ICS and as-needed salbutamol)
ZuWallack 2014a (3) RCT DB PC PG USA	1132	- mean age 64 y - 50% men - mean FEV1 1.45L (54% predicted) - clinical history of moderate-to-severe COPD as defined by GOLD guidelines (FEV1 < 80% and ≥ 30% predicted) - smoking history ≥ 10 pack-years EXCLUSION - prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day - oxygen use > 1 h/day - pulmonary rehabilitation in the last 6 weeks - significant disease other than COPD	12 weeks	• Olodaterol 5 µg through SDDPI Respimat, once daily + tiotropium 18 µg through SDDPI HandiHaler, once daily • Placebo to olodaterol + tiotropium 18 µg through SDDPI HandiHaler, once daily	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk FUNDING: NCT01694771, by Boehringer Ingelheim
ZuWallack 2014b (3)	1132	- mean age 64 y - 50% men	12 weeks	• Olodaterol 5 µg through SDDPI Respimat, once daily +	ALLOCATION CONC: adequate RANDO: adequate

RCT DB PC PG USA		- mean FEV1 1.45L (54% predicted) - clinical history of moderate-to-severe COPD as defined by GOLD guidelines (FEV1 < 80% and ≥ 30% predicted) - smoking history ≥ 10 pack-years <u>EXCLUSION</u> - prednisolone at an unstable dose (i.e. changed in < 6 weeks) or > 10 mg/day - oxygen use > 1 h/day - pulmonary rehabilitation in the last 6 weeks - significant disease other than COPD		tiotropium 18 µg through SDDPI HandiHaler, once daily • Placebo to olodaterol + tiotropium 18 µg through SDDPI HandiHaler, once daily	BLINDING : Participants/ personnel: unclear risk Assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk FUNDING: NCT01696058 sponsored by Boehringer Ingelheim

Table 43

Remarks: The exclusion list of this MA was reviewed by the literature group to make sure that we had selected all studies that matched our selection criteria but that might have been excluded from this publication (for example due to the LAMA being another molecule than tiotropium)

Author's conclusions:
The combination of tiotropium plus LABA resulted, on average, in a slightly better quality of life and lung function for the participants compared to using only either tiotropium or a LABA alone, but did not show a difference in hospital admissions or death. The combination treatment also reduced the risk of episodes of acutely worse symptoms ('exacerbations'), compared to a LABA alone but not tiotropium. There were not enough data to determine the risks and benefits of the different types of LABA.

BATEMAN 2013

Study details	n/Population	Comparison	Outcomes		Methodological
Bateman 2013 (17) Design: RCT DB/ partial blind (comparison reported all blinded) PC Duration of follow-up: 26 weeks	n= 2144 Mean age: 64 y % male: 75.2 % Currently smoking: 40% % taking ICS at inclusion: 57.5% ICS policy: continued if stable other background medications allowed: H1 antagonists GOLD (2008)-classification of patients: patients were stage II or III Baseline FEV1 55.5% predicted % reversible :20.2% <u>Inclusion:</u> aged >40 years	Indacaterol 150µg + glycopyrronium 50µg (n=475) vs Indacaterol 150µg (n=477) vs glycopyrronium 50µg (n=475) vs open-label tiotropium 18µg (n=483) vs placebo (n=234)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear POWER CALCULATION: Yes FOLLOW-UP: Completed: 89 % • Described: yes • Balanced across groups: yes ITT: yes efficacy: all randomised patients safety: at least on dose of study drug SELECTIVE REPORTING: possible, no statistical test found for certain comparisons
			trough FEV1 (PO)	IND+GLY vs IND IND+GLY: 0.20 (0.17 – 0.24) IND: 0.13 (0.10 – 0.16) Diff: 0.07L **SS** **p<0.001**	
				IND+GLY vs GLY IND+GLY: 0.20 (0.17 – 0.24) GLY: 0.12 (0.08 – 0.15) Diff: 0.09L **SS** **p<0.001**	
			SGRQ	IND+GLY: -10.03 IND: -8.59 No statistical test found	
				IND+GLY: -10.03 GLY: -8.91 LSM diff: -1.84 **p = 0.020** **SS**	
			Exacerbations no stat tests	IND+GLY: 28.9% IND: 32.1% GLY: 31.7%	
			Deaths	IND+GLY: 1 (0.2%)	

	moderate-to-severe stable COPD ≥10 pack-years smoking history FEV1/forced vital capacity (FVC) ratio <0.70 FEV1 % predicted normal: Y, ≥30% but <80% <u>Exclusion</u> - pregnant, nursing, or of child-bearing potential - patients contraindicated with treatment patients with: - long QT syndrome - clinically significant ECG abnormalities - diabetes (TI and TII) - narrow angle glaucoma, symptomatic prostatic hyperplasia, bladder neck obstruction - history of malignancy			IND: 2 (0.4%) GLY: 1 (0.2%)	Sponsor: Novartis
			Atrial Fibrillation	IND+GLY: 2 (0.4%) IND: 3 (0.6%) GLY:2 (0.4%)	

	in any organ system COPD specific: - requiring long term O2 therapy - exacerbation requiring antibiotics in the 10 weeks before randomization - RTI before run-in phase - patients with a concomitant pulmonary disease - with lung resection or volume reduction - patients with any history of asthma - with allergic rhinits using H1 antagonists - with eczema or high IgE levels - patients enrolled in a pulmonary rehabilitation programme				

Table 44

CELLI 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Celli 2014 (41) Design: RCT (SB DB OL) (PG CO) Duration of follow-up: 24 weeks	n= 1439 Mean age: 63y % females: 34.5% currently smoking: 52% % taking ICS at inclusion: 47% ICS policy: regular use of inhaled corticosteroids (ICS) at a stable dose (≤1000 mcg/day of fluticasone propionate or equivalent) was allowed other background medications allowed: GOLD (yr)-classification of patients: Stage II: 47% Stage III: 45% Stage IV: 8% Baseline postalbuterol FEV1 48.2% predicted	umeclidinium/ vilanterol 125/25µg (n = 403) vs umeclidinium 125µg (n = 407) vs vilanterol 25µg (n = 404) vs placebo (n = 275)	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: states randomized, double blind but gives no detail in article or appendix POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 25% • Described: yes • Balanced across groups: no, more drop-out in placebo (33%), less in umec/vi (19%)
			Trough FEV1 (PO)	<u>LSM change from baseline:</u> UMEC 125µg: 0.129 (SE: 0.0119) VI 25 µg: 0.093 (SE: 0.0121) UMEC/VI 125/25 µg : 0.207 (0.0119) Placebo : -0.0031 (0.0153) UMEC/VI 125/25 µg vs VI 25µg: Difference: 0.114L 95% CI: 0.081 to 0.148 **SS** **p<0.001** UMEC/VI 125/25 µg vs UMEC 125µg: Difference: 0.079 95% CI: 0.046 to 0.112 **SS** **p<0.001**	
			TDI focal score	<u>LSM (SE) at day 168</u> UMEC 125µg: 1.2 (0.16) VI 25 µg: 1.3 (0.16) UMEC/VI 125/25 µg: 1.8 (0.15) Placebo: 0.8 (0.20)	

	% reversibility to albuterol: 13.2% <u>Inclusion:</u> ≥40 years of age with a history of COPD, 1 current or former smoker with a smoking history of ≥10 pack-years, postalbuterol (salbutamol) FEV1 /FVC ratio <0.70, FEV1 ≤70% of predicted normal, 19 and a score of ≥2 on the modified Medical Research Council dyspnea scale at screening <u>Exclusion</u> current diagnosis of asthma or other known respiratory disorder, any clinically significant			UMEC/VI 125/25 µg vs VI 25µg: Difference: 0.5 (0.1, 1.0) SS p<0.05 UMEC/VI 125/25 µg vs UMEC 125µg: Difference: 0.6 (95% CI: 0.2, 1.0) SS p<0.01	ITT: Yes (=all randomized patients who had received at least one dose of the study medication) SELECTIVE REPORTING: no Sponsor: GlaxoSmithKline
			SGRQ score	<u>LSM (SE) at day 168</u> UMEC 125µg: 43.38 (0.664) VI 25 µg: 42.82 (0.681) UMEC/VI 125/25 µg: 40.10 (0.665) Placebo: 43.69 (0.875) UMEC/VI 125/25 µg vs VI 25µg: -2.72 (95% CI: -4.59, -0.86) **SS** **p<0.01** Umec/VI vs UMEC: - 3.29 (95% CI: -5.13, -1.44) **SS** **p≤0.001**	
			Deaths	6 deaths, none related to study drug	

	uncontrolled disease, an abnormal and significant electrocardiogram (ECG) or 24-h Holter finding or significantly abnormal clinical laboratory findings.				

Table 45

DECRAMER 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Decramer 2014 (42) NCT01316900 Design: TWIN STUDY RCT DB PG Duration of follow-up: 24 weeks	n= 1141 Mean age: 62.9y % females: 31 Current smoker: 51% % taking ICS at inclusion: 44.3% ICS policy: stable doses up to 1000µg/d of fluticasone propionate or equivalent permitted other background medications allowed: salbutamol GOLD -classification of patients: B or D bc of exclusion criterias stage II: 46.5% stage III: 41.75% stage IV: 10.75% Baseline FEV1 48% of predicted	Tiotropium 18µg (n = 208) vs Vilanterol 25µg (n = 209) vs Umeclidinium 125 µg + vilanterol 25 µg (n = 214) vs umeclidinium 62.5µg + vilanterol 25 µg (n = 212)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.4%% Drop-out and Exclusions: 17.4 % • Described: yes • Balanced across groups: no analysis, raw numbers: • TIO = 15%; VI:=21%; UMEC125µg+VI=19%; UMEC62.5µg+VI=14.6% ITT: Yes (= received at least 1 dose of study medication)
			Trough FEV1 on day 169(PO)	Least square means change from baseline TIO: 0.121 L (0.019) VI: 0.121 L (0.019) UMEC 125µg+VI: 0.209 L (0.019) UMEC 62.5µg+VI: 0.211 L (0.018) <u>UMEC+VI vs LAMA (TIO)</u> UMEC 125µg+VI vs TIO: 0.088 (95% CI: 0.036 – 0.140) **p=0.001** **SS** UMEC62.5µg+VI vs TIO : 0.090 (95% CI : 0.039 – 0.141) **p = 0.0006** **SS** <u>UMEC+VI vs LABA (VI)</u> UMEC 125µg+VI vs VI : 0.088 (95% CI : 0.036 – 0.140) **p=0.001** **SS** UMEC62.5µg+VI vs VI : 0.090 (95% CI : 0.039 – 0.142)	

	% reversible to salbutamol : 13% Exacerbations in the previous year : 46% <u>Inclusion:</u> current or former smokers aged 40 years or more with moderate to very severe COPD as defined by ATS–ERS - smoking history of 10 pack-years or more - post-salbutamol FEV1-FVC ratio <0·70 - post-salbutamol FEV1 of 70% of predicted normal values or less - score of 2 or higher on the modifi ed Medical Research Council Dyspnoea Scale17 at study visit 1 <u>Exclusion</u> hospital admission for COPD or pneumonia			**p=0.0006** **SS**	SELECTIVE REPORTING: no Other important methodological remarks 12 week run-in Sponsor: Glaxo Smith Kline
			Exacerbations (number of patients with exacerbations)	Patients with exacerbations removed from study TIO: 11 (5%) VI: 17 (8%) UMEC 125µg+VI: 11 (5%) UMEC 62.5µg+VI:14 (7%) No statistical analysis	
			Dyspnea/ TDI score	TIO: 2.4 (0.2) VI: 2.1 (0.2) UMEC 125µg+VI: 2.9 (0.2) UMEC 62.5µg+VI: 2.3 (0.2) <u>UMEC+VI vs LAMA (TIO)</u> UMEC 125µg+VI vs TIO: 0.5 (95% CI : -0.2 to 1.1) NS UMEC62.5µg+VI vs TIO : -0.1 (95 CI : -0.7 to 0.5) NS <u>UMEC+VI vs LABA (VI)</u> UMEC 125µg+VI vs VI : 0.8 (95% CI : 0.2 to 1.5) **SS**	

	within the 12 weeks before study visit 1. Patients were excluded if they had a present diagnosis of asthma or other known respiratory disorder..			**p=0.0126** UMEC62.5µg+VI vs VI : 0.2 (-0.4 to 0.8) NS	
			SGRQ	LS mean change from baseline TIO: -7.62 (1.05) VI:-8.29 (0.2) UMEC 125µg+VI: -9.03 (1.05) UMEC 62.5µg+VI: -6.87 (1.02) No statistical analysis	

Table 46

DECRAMER 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Decramer	n= 1191	Tiotropium (n =	Efficacy		RANDO:
2014		215)	Trough FEV1 on day	Least square means change from	Adequate
(42)	Mean age: 64.6y	vs	169 (PO)	baseline	ALLOCATION CONC:
	% male: 68%			TIO: 0.149L (0.018)	Adequate
NCT01316913	current smoker: 44.5%	Umeclidinium		UMEC 125µg: 0.186 L(0.018)	BLINDING :
	% taking ICS at inclusion:	125µg (n = 222)		UMEC 125µg+VI: 0.223L (0.018)	Participants: yes
Design:	52%			UMEC 62.5µg+VI: 0.208L (0.018)	Personnel: yes
TWIN STUDY	ICS policy: stable doses up	vs			Assessors: yes
	to 1000µg/d of			<u>UMEC+VI vs LAMA (TIO)</u>	
RCT	fluticasone propionate or	Umeclidinium 125		UMEC 125µg+VI vs TIO: 0.074 (95% CI :	
DB	equivalent permitted	µg + vilanterol 25		0.025 to 0.123)	POWER CALCULATION:

PG Duration of follow-up: 24 weeks	other background medications allowed: salbutamol GOLD-classification of patients: B or D bc of exclusion criterias stage II: 44.25% stage III: 43% stage IV: 12.25% Baseline FEV1 47.1% predicted % reversibility to salbutamol : 15.3% <u>Inclusion:</u> current or former smokers aged 40 years or more with moderate to very severe COPD as defined by ATS–ERS - smoking history of 10 pack-years or more - post-salbutamol FEV1-FVC ratio <0·70	µg (n = 215) vs umeclidinium 62.5µg + vilanterol 25 µg (n = 217)		**p=0.0031** **SS** UMEC 62.5µg+VI vs TIO : 0.060 (95% CI : 0.010 to 0.109) p=0.0182 **SS** <u>UMEC+VI vs LAMA (UMEC)</u> UMEC 125µg+VI vs UMEC 125µg: 0.037 (95% CI : -0.012 to 0.087) p = 0.14 NS UMEC62.5µg+VI vs UMEC 125µg: 0.022 (95% CI: -0.027 to 0.072) p=0.38 NS	Yes FOLLOW-UP: Lost-to follow-up: 0.3% Drop-out and Exclusions: 22.9 % • Described: yes • Balanced across groups: no analysis, raw numbers: • TIO = 18.1%; UMEC125µg:=25.7%; UMEC125µg+VI=22.8%; UMEC62.5µg+VI=24.9% ITT: Yes (= received at least 1 dose of study medication) SELECTIVE REPORTING: no Other important methodological remarks 12 week run-in Sponsor: Glaxo Smith Kline
			Exacerbations (number of patients with exacerbations)	Patients with exacerbations removed from study TIO: 14 (7%) UMEC 125µg: 26 (12%) UMEC 125µg+VI: 16 (7%) UMEC 62.5µg+VI: 26 (12%) No statistical analysis	
			Dyspnea/ TDI score	TIO: 2.1 (0.2 SD) UMEC 125µg : 1.9 (0.2) UMEC 125µg+VI: 2.4 (0.2)	

	- post-salbutamol FEV1 of 70% of predicted normal values or less - score of 2 or higher on the modifi ed Medical Research Council Dyspnoea Scale17 at study visit 1 <u>Exclusion</u> hospital admission for COPD or pneumonia within the 12 weeks before study visit 1. Patients were excluded if they had a present diagnosis of asthma or other known respiratory disorder.			UMEC 62.5µg+VI: 2.3 (0.3) <u>UMEC+VI vs LAMA (TIO)</u> UMEC 125µg+VI vs TIO: 0.3 (95% CI: -0.4 to 1.0) p=0.38 NS UMEC62.5µg+VI vs TIO : 0.2 95% CI: -0.5 to 0.9) p=0.55 NS <u>UMEC+VI vs LABA (VI)</u> UMEC 125µg+VI vs UMEC 125µg: 0.5 (95%CI: -0.2 to 1.2) p=0.15 NS UMEC62.5µg+VI vs UMEC 125µg : 0.4 (95% CI: -0.3 to 1.1) p=0.25 NS	
			SGRQ	LS mean change from baseline TIO: -9.78 (0.95 SD) UMEC 125µg: -8.40 (0.97) UMEC 125µg+VI: -10.52 (0.97) UMEC 62.5µg+VI: -9.95 (0.98)	

				No statistical analysis	

Table 47

DONOHUE 2013

Study details	n/Population	Comparison	Outcomes		Methodological
Donohue 2013 (43) Design: RCT DB PG PC Duration of follow-up: 24 weeks	n= 1536 Mean age: 63 y % females: 29% current smokers: 50% % taking ICS at inclusion: 50.5% ICS policy: allowed at a stable dose of <1000 mcg/day of fluticasone propionate or equivalent from 30 days prior to screening onward other background medications allowed: salbutamol rescue GOLD (classification of patients: stage II: 46% stage III: 43% stage IV: 11% Baseline FEV1 47.4% predicted normal	umeclidinium 62.5 µg/d + vilanterol 25µg (n = 413) vs umeclidinium 62.5 µg/d (n = 418) vs vilanterol 25µg (n = 421) vs placebo (n = 280)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: the blinding method is described in supplementary materials to be found at clinicalstudydatarequest.com but a bad gateway error (502) prevented us to access it POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 22% • Described: yes • Balanced across groups: yes (more in placebo group but not of interest for us)
			Trough FEV1 on day 169 (PO)	<u>LS mean change from baseline (SE)</u> Placebo: 0.004 L (0.0158) UMEC: 0.119 L (0.0126) VI:0.076 L (0.0127) UMEC/VI: 0.171 L (0.0126) <u>Différence</u> UMEC/VI vs UMEC : 0.052 L (95% CI: 0.017 to 0.087) **SS** **p≤0.01** UMEC/VI vs VI : 0.095 L (95% CI : 0.060 to 0.130) **SS** **p≤0.001**	
			TDI	<u>LS mean change from baseline (SE)</u> Placebo: 1.2 (0.20) UMEC: 2.2 (0.16) VI: 2.1 (0.16) UMEC/VI: 2.4 (0.16) <u>Difference</u> UMEC/VI vs UMEC: 0.3 (95% CI: -0.2 to 0.7)	

	% reversibility to salbutamol : 14.7% <u>Inclusion:</u> - current or former cigarette smokers - aged > 40 years - clinically established history of COPD characterised by airflow limitation that is not fully reversible - FEV1/FVC ratio <0.70 and post-salbutamol FEV1 of <70% of predicted normal value <u>Exclusion</u> current diagnosis of asthma or other known respiratory disorders - abnormal and clinically significant electrocardiogram (ECG) or 24-h Holter ECG - women who are pregnant, lactating or planning to become pregnant - hospitalization for COPD			NS UMEC/VI vs VI: 0.4 (95% CI: -1.0 to 0.8) NS	ITT: Yes (= received at least 1 dose of study drug) SELECTIVE REPORTING: no Other important methodological remarks : 7-14 days run in Sponsor: GlaxoSmithKline
			Exacerbation : time to first COPD exacerbation	only vs placebo	
			SGRQ score	<u>Change from baseline (SE)</u> PLACEBO: -2.56 (0.950) UMEC: -7.25 (0.753) VI: -7.75 (0.760) UMEC/Vi: -8.07 (0.749) UMEC/VI vs UMEC: -0.82 (95% CI: -2.90 to 1.27) NS UMEC/VI vs VI : -0.32 (95% CI : -2.41 to 1.78) NS	

	within 12weeks prior to screening - Use of systemic corticosteroids, antibiotics for respiratory tract infections, strong cytochrome P450 3A4 inhibitors, high dose inhaled steroids (>1000mcg fluticasone propionate or equivalent), PDE4 inhibitors, tiotropium, oral beta2-agoinists, short- and long-acting inhaled beta2-agonists, ipratropium, inhaled sodium cromoglycate or nedocromil sodium, or investigational medicines for defined time periods prior to the screening visit - Participation in the acute phase of a pulmonary rehabilitation program				

Table 48

DONOHUE 2016

Study details	n/Population	Comparison	Outcomes	Methodological
Donohue	n= 590	aclinidium 400	Efficacy	RANDO:

2016 (44) Design: Phase III RCT PG AC USA Duration of follow-up: 1 year	 Mean age: 64.7y % male: 55.1% Current smoker: 45.4% % taking ICS at inclusion: 34.8% ICS policy: allowed at ≤10 mg/day other background medications allowed: - albuterol as needed, but not within 6 h before a visit, - oral or parenteral corticosteroids at doses ≤10 mg/day - theophylline and H1-antihistamine were permitted for chronic use provided the dosage was stable for ≥4 weeks prior to screening - Chronic use of oxygen therapy was permitted for up to 15 h/day provided the dosage was stable for ≥4 weeks prior to screening - Atenolol,	µg + formoterol 12 µg (n = 392) vs formoterol 12 µg (n = 198)	Trough FEV (not PO!)	LSM difference: 81.5 mL (95% CI: 12.5 to 150.5) **p<0.05** **SS**	Adequate ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: adequate POWER CALCULATION: Yes for safety FOLLOW-UP: 100% in safety analysis 98% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes, 32.4% in AB/FF; 32.8% in FF ITT: Yes (= at least one dose of study drugs) SELECTIVE REPORTING: yes/no (describe if yes)
			Mortality	AB+FF: 5 (1.3%) FF: 1 (0.5%) No statistical test reported	
			Exacerbations (patients with at least one)	AB+FF: 27.3% FF: 29.8% No statistical test reported	

	metoprolol, nebivolol were permitted for chronic use if the dosage was stable for ≥2 weeks prior to screening GOLD -classification of patients: stage II or moderate: 52.2% stage III or severe: 46.4% Baseline FEV1 52.2% predicted % reversibility to salbutamol : unknown ≥1 exacerbation during last 12 months: 24.5% <u>Inclusion:</u> - current or ex-smokers with history ≥10 pack years - diagnosis of COPD - post-bronchodilator FEV1/FVC <70; FEV1 ≥30% but <80% predicted <u>Exclusion</u> - any respiratory infection or COPD exacerbation ≤6 weeks before screening				Other important methodological remarks: - 2-3 weeks run-in - Safety study, so it wasn't powered to detect between-groups statistical differences for exacerbations Sponsor: Forest laboratories, subsidiary of Allergan + Almirall

	- pulmonary rehabilitation within 3 months of screening or an intention to start during the trial - clinically significant cardiovascular conditions, including myocardial infarction ≤6 months; - newly diagnosed arrhythmia ≤3 months; - unstable angina; - unstable arrhythmia that had required changes in pharmacological therapy or other interventions ≤6 months; - use of an automated implantable cardioverter-defibrillator; - history of thoracic surgery ≤1 year of screening; - hospitalization ≤12 months for heart failure (New York Heart Association [NYHA] class III) or history of thoracic surgery ≤1				

	year of screening and NYHA class IV [14]; - QTcB >470 ms at rest; - body mass index ≥40 kg/m2				

Table 49

D'URZO 2014

Study details	n/Population	Comparison	Outcomes		Methodological
D'Urzo 2014 (4) Design: RCT phase III DB Duration of follow-up: 24 weeks	n= 1692 Mean age: 64y % females: 47% Smoking: 51.5% % taking ICS at inclusion:NR ICS policy: allowed if stable ≥4weeks prior to screening other background medications allowed: - use of long-acting bronchodilators other than study medication was not permitted - other COPD medications, oral or parenteral corticoids (≤10 mg/day or 20 mg every other day of prednisone) allowed if stable ≥4 weeks - albuterol / salbutamol as rescue GOLD-classification of patients: moderate: 57%	aclinidium 400µg + formoterol 12 µg (n= 335) vs aclinidium 400µg + formoterol 6µg (n=333) vs aclinidium 400µg (n=337) vs formoterol 12µg (n=332) vs placebo	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: yes Remarks on blinding method: states randomized and double blind but gives no details on method, not in article, suppl materials or clinical trial registration POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 3.5% Drop-out and Exclusions: 18.3% • Described: yes • Balanced across groups: no, 10% more in placebo group ITT:
			Trough FEV1 (co-PO) (at week 24)	<u>LS mean difference:</u> ACL/FOR12µg vs FOR 12µg: 45mL (no 95% CI) **p=0.01** **SS** ACL/FOR6µg vs FOR 12µg: 26 mL (no 95% CI) p=0.133 NS no numerical values for other comparisons	
			SGRQ total score (at week 24)	<u>LS mean changes from baseline</u>: Placebo: -2.21 ACL/FOR12: -6.57 ACL/FOR6: -5.94 ACL: -6.44 FOR12: -4.70 Only statistical testing vs placebo	
			TDI focal score (at week 24)	<u>LS mean changes from baseline:</u> placebo: 0.58 ACL/FOR12: 2.02 ACL/FOR6: 1.98	

	severe: 42% Baseline FEV1 53.5% predicted % reversibility : 15.2% <u>Inclusion:</u> ≥40 years former smokers (≥10 pack-years) - diagnosed with stable, moderate to severe expiratory airflow obstruction according to GOLD guidelines: FEV1/FVC <70% and FEV1 ≥30% and <80% predicted Dyspnea: not a criteria <u>Exclusion</u> - COPD exacerbation or respiratory tract infection ≤6 weeks (≤3 months if hospitalized for exacerbation	(n=332)		ACL: 1.56 FOR: 1.52 “resulted in numerically greater improvements in TDI focal score compared to either monotherapy”	Yes (=all randomized patients who took ≥1 dose of study medication and had a baseline and at least one post-baseline FEV1 assessment) SELECTIVE REPORTING: yes, lack of 95% CI. not all comparisons that were reported for 1-hour postdose FEV1 were also reported for trough FEV1 Other important methodological remarks: 2 – 3 weeks run-in Sponsor: Forest Laboratories LLC, a subsidiary of Actavis plc, and by Almirall, S.A

	- clinically significant respiratory conditions (including asthma) - clinically significant cardiovascular conditions including MI within previous 6 mo - unstable angina - unstable arrhythmia that required changes in pharmacological therapy or other intervention within the previous 6 months				

Table 50

MAHLER 2015

Study details	n/Population	Comparison	Outcomes		Methodological
Mahler 2015 (7) FLIGHT 1 FLIGHT 2 twin studies Design: phase III RCT PG DB Duration of follow-up: 12 weeks USA	n(Flight 1 & flight 2) = 2038 Mean age: 63.4 y % females: 36.7% Smoking: 51.6% % taking ICS at inclusion: 45.8% ICS policy: allowed and continued if stable dose for at least 30 days before visit 1 other background medications allowed: SSRI stable dose for at least 30 days prior to visit 1 albuterol as rescue COPD (2011) -classification of patients: Moderate: 57.1% Severe: 38.5% GOLD classification: Gold B: 57.2% Gold D: 42.1% Baseline FEV1 54.6%	indacaterol 27.5µg / glycopyrrolate 15.6 µg 2x/d (n = 510) vs indacaterol 27.5 µg 2x/d (n = 511) vs glycopyrrolate 15.6 µg 2x/d (n = 512) vs placebo (n = 510)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: unknown% in safety analysis "full set" in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: higher in placebo approx 94% finished in active drug treatment arms but 87% in placebo arms across both studies ITT:
			Trough FEV1 FLIGHT 1&2	<u>LS mean ±SE</u> IND/GLY: 0.208L (0.0101) IND: 0.129L (0.0100) GLY: 0.110L (0.0100) PLA:0.015L (0.0104) <u>Difference</u> IND/GLY vs IND: 0.079L (0.051 to 0.107) **SS** **p<0.001** IND/GLY vs GLY: **0.098L (0.071 to 0.126)** **SS** **p<0.001**	
			SGRQ total score	<u>Difference</u> IND/GLY vs IND: -1.7 (-3.1 to -0.3) **SS** **p<0.05** IND/GLY vs GLY: -1.5 (-3.0 to -0.1) **SS** **p< 0.05**	
			TDI total score	IND/GLY vs IND: 0.78 (0.43 to 1.13) **SS** **p<0.001** IND/GLY vs GLY: 0.73 (0.39 to 1.08) **SS**	

	predicted % reversibility to salbutamol :22.8% <u>Inclusion:</u> - 40 years or older - current or ex-smokers with at least 10 pack years history - stable but symptomatic moderate-to-severe COPD according do GOLD 2011 - FEV1 post-bronchodilator ≥30 but <80% of predicted normal <u>Exclusion :</u> - pregnant or nursing women - women of child-bearing potential - type I or uncontrolled type II diabetes - history of long QT-syndrome or prolonged QTc at visit 101 (>450 ms) - clinically significant ECG or laboratoy abnormality - BMI ≥40kg/m² - clinically significant renal,			**p<0.001**	Yes (all randomized patients who received at least one dose) SELECTIVE REPORTING: no Other important methodological remarks: the FLIGHT 1 and FLIGHT 2 studies are separate studies but all analyses are done on the pooled populations and results. 14 day run-in period missing values for reported endpoints by LOCF Sponsor: Novartis
			Death (flight 1 & 2 pooled)	IND/GLY: 0 IND: 2 (0.4%) GLY: 1 (0.2%) Placebo: 11 (2.2%)	

	cardiovascular, neurological, endocrine, immunological, psychiatric, G-I, hepatic, or hematological abnormalities which could interfere with assessments - paroxysmal atrial fibrillation. Persistent atrial fibrillation controlled with a rate control strategy could be considered though - patients contra-indicated for treatment - history of malignancy in any organ system - narrow-angle glaucoma, symptomatic benign prostatic hyperplasia - COPD exacerbations between screening and treatment were not eligible but were permitted to be rescreened 6 weeks after the resolution - RTI 4 weeks before screening - requiring long-term oxygen therapy >12h/d - any history of asthma				

	- onset of respiratory symptoms or COPD diagnosis before 40 years - blood eosinophil > 600/mm³ - allergic rhinitis on H1 antagonists or on intermittent intra-nasal corticoids - concomitant pulmonary disease - participating in a pulmonary rehabilitation program				

Table 51

SINGH 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2014 (1) ACLIFORM-COPD Design: RCT DB PG AC & PC Phase III Duration of follow-up: 24 weeks	n= 1729 Mean age: 63.2 % females: 32.4 Smoking:47.3 % taking ICS at inclusion:19.8 ICS policy: could be continued if stable ≥4 weeks pre-screening other background medications allowed: salbutamol as relief; oral sustained-release methylxanthines, oxygen therapy (<15 hours/day) and oral or parenteral corticosteroids equivalent to ≤10 mg/day of prednisone or 20 mg every other day, provided treatment was stable ≥4 weeks pre-screening GOLD (yr)-classification of	placebo (n = 194) vs ACL/FOR 400/12µg (n = 385) vs ACL/FOR 400/6µg (n = 381) vs Aclinidium 400µg (n = 385) vs formoterol 12µg (n = 384)	Efficacy		RANDO: Adequate, stratified by smoker status ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: unclear Assessors: unclear Remarks on blinding method: centralised interactive voice response system POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 1 % Drop-out and Exclusions: 11.3% • Described: yes • Balanced across groups: more drop out in placebo group (17.5%) compared to active groups (11%)
			Trough FEV1 (co-PO)	ACL/FOR 12µg vs FOR 12µg: 85 ml (no CI) **SS** **p<0.001** ACL/FOR 6µg vs FOR 12µg: 53mL (no CI) **SS** **p<0.01** (the following comparisons are not part of the co-PO) ACL/FOR 12µg vs ACL: NS ACL/FOR 6µg vs ACL: NS	
			TDI focal score improvement (units)	ACL/FOR 12µg: 2.5 ACL/FOR 6µg: 2.4 FOR 12µg: 2.1 ACL 400µg: 2.1 PLA: 1.2 only statistical tests vs placebo are reported	
			SGRQ total score (change from baseline)	ACL/FOR 12µg: -7.2 ACL/FOR 6µg: -8.3 FOR 12µg: -5.6	

	patients: Moderate: 60.1% Severe: 39.7% Baseline post-bronchodilator FEV1 54.3% predicted % reversibility:32.8 <u>Inclusion:</u> - ≥40 years - current or former smoker with ≥10 pack years - diagnosed with moderate to severe COPD according to GOLD 2010 criteria - FEV1/FVC <70% and FEV1 <80% and ≥30% of normal <u>Exclusion</u> history/current diagnosis of asthma; respiratory tract infection or chronic obstructive pulmonary disease (COPD) exacerbation within 6 weeks (3 months if hospitalisation required)		(in units)	ACL 400µg: -5.8 PLA: -6.5 only statistical tests vs placebo are reported	ITT: Yes (= patients who took ≥1 dose of study medication, had a baseline and ≥1 post-baseline FEV1 assessment) Safety population= at least one dose of study medication SELECTIVE REPORTING: yes trough FEV1 is primary endpoint unable to locate numerical values for confidence intervals for statistically significant results in article or in supplements Other important methodological remarks: 3 or 2 weeks placebo run in MMRM model for statistical analysis Sponsor:
			Atrial Fibrilation	"no clinically significant differences between treatment groups in ECG including 24h holter ECG monitoring"	
			Mortality	ACL/FOR 400/12µg: 1 patient ACL/FOR 400/6µg: 2 patients FOR 12µg: 1 ACL 400µg: 0 PLA: 0	

	pre-screening; clinically relevant respiratory conditions other than COPD; clinically significant cardiovascular conditions; and contraindications to anticholinergics.				

Table 52

VINCKEN 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Vincken 2014 (10) Design: RCT DB PG Duration of follow-up:	n= 449 Mean age: 64 y % females: 18% currently smoking: 42% % taking ICS at inclusion: 63% ICS policy: Those on fixed-dose LABA/ICS combinations were switched to ICS monotherapy at a dose equivalent to that contained in the fixed-dose combination other background medications allowed:	IND/GLY 150/50 µg (n = 226) vs IND 150µg + placebo (n = 223)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: 99.5% for safety analysis % for efficacy analysis not clearly detailed
			trough FEV1 (PO)	LSMD: 0.064L (95% CI: 0.028 to 0.099) **SS** **p<0.001**	
			TDI total score	LSMD: 0.494 (95% CI: 0.030 to 0.958) **SS** **p=0.037**	
			SGRQ total score	LSMD: -1.47 (95% CI: -3.42 to 0.48) NS	
			Mortality	IND/GLY: 0 IND: 0	
			Pre-specified subgroup analysis according to COPD status		
			trough FEV1	Moderate or less airflow limitation: 0.045 (95% CI: 0.001–0.089)	

12 weeks	rescue medication GOLD (2013)-classification of patients: moderate: 64% severe: 36% Baseline FEV1 55% predicted (post-bronchodilator) % reversibility to bronchodilator : 19.5% <u>Inclusion:</u> men and women ≥40 years of age, with moderate-to-severe stable COPD (GOLD stage II or III according to the 2010 GOLD guidelines) who were current or ex-smokers with a smoking history of at least 10 pack-years, and had a post-bronchodilator forced expiratory volume in 1 second (FEV1) $30% and ,80% of the predicted normal and post-bronchodilator FEV1/forced vital capacity (FVC) ratio of ,0.70 at screening (GOLD stage II or			**SS** **p<0.047** Severe or worse airflow limitation: 0.098 (95% CI: 0.039–0.157) **SS** **p<0.001**	Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: called FAS: full analysis set (FAS) included all randomized patients who received at least one dose of the study drug Others: PPS: all patients in the FAS who had no major protocol deviations Safety population: all patients who received at least one dose of the study medication, irrespective of randomization SELECTIVE REPORTING: no Other important methodological remarks: 7 days washout and 14 day run in period Sponsor: Novartis

	III) <u>Exclusion</u> respiratory tract infection within 6 weeks prior to screening; COPD exacerbation requiring treatment with antibiotics and/or oral corticosteroids and/or hospitalization 6 weeks prior to screening; concomitant pulmonary disease (such as lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis, pulmonary tuberculosis); history of asthma, diabetes (with the exception of controlled type II diabetes), malignancy of any organ system, long QT syndrome or QTc >450 ms at screening, symptomatic prostatic hyperplasia, bladder-neck obstruction, moderate/severe renal				

	impairment, urinary retention, narrow-angle glaucoma, a known history of α1-antitrypsin deficiency, or paroxysmal atrial fibrillation; clinically significant renal, cardiovascular (such as, but not limited to, unstable ischemic heart disease, New York Heart Association class III/IV left ventricular failure, myocardial infarction), neurological, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormality that could have interfered with the assessment of efficacy and safety of the study treatment; participation in the active phase of a supervised pulmonary rehabilitation program; and contraindications for tiotropium or ipratropium, or history of adverse reactions to inhaled anticholinergics				

Table 53

6.1.1.2 *Summary and conclusions*

LABA & LAMA vs LABA

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Farne 2015 (40)	N= 4 n = 3378 (Buhl 2015a & 2015b (16), Vogelmeier 2008 (45), Hoshino 2014 (46))	16 weeks to 52 weeks	LABA (different molecules) + Tiotropium vs LABA	COPD mostly older, predominantly male	- 2 studies by Buhl had more drop out in monotherapy arms - in almost all studies a large amount of participants were on ICS and could continue the ICS therapy.

Table 54

Bibliography of included studies							
	n	duration	exact comparison	population (+ remarks*)	GOLD cat.	%ICS	methodological remarks
Bateman 2013 (17) [ref]	2144 (902 in comp. of inte-rest)	26 weeks	IND+GLY 150/50µg vs IND 150µg	COPD older males FEV1% pred.: 55.5% reversib. : 20%	stage II or III	57.5% cont.	
Celli 2014 (41)	1439 (807 in comp.)	24 weeks	UMEC+VI 125/25µg vs VI 25µg	COPD mean age:63 y FEV1% pred.: 48.2% reversib.: 13.2%	ST II: 47% St III: 45% St IV: 8%	47%, cont	
Decramer 2014 (42)	1141 (844)	24 weeks	UMEC+VI 125/25µg UMEC+VI 62.5/25 µg vs VI 25µg	COPD mean age: 63y mostly male FEV1% pred.: ±47.5% revers.:±14%	Trial 1: St II: 47% St III: 42% St IV: 11% Trial 2: St II: 44% St III: 43% St IV: 12%	Trial 1: 44% Trial 2: 52%	- twin trials - analysis on each trial, results not pooled - through FEV LABA+LAMA vs LABA only analysed on one trial
Donohue 2013 (43)	1536 (834)	24 weeks	UMEC+VI 62.5/25µg vs	COPD older males FEV1% pred.: 47.4%	St II: 46% St III: 43% St IV: 11%	50% cont.	

			VI 25µg	reversib.: 15%			
Donohue 2016 (44)	590 (590)	52 weeks	ACL+FOR 400/12 µg vs FOR 12µg	COPD mean age: 65y 55% male FEV1% pred: 52.2% reversib.: NR	St II: 52.2% St III: 46.4%	35% cont.	high dropout: ±32% in both groups
D'urzo 2014 (4)	1692 (1000)	24 weeks	ACL+FOR 400/12 µg & ACL+FOR 400/6 µg vs FOR 12µg	COPD mean age: 64y 53% male FEV1% pred.: 53.5% Reversib: 15%	moderate 57% severe: 42%	NR cont.	Around 18% drop out in both groups Unclear randomization and blinding
Mahler 2015 (7)	2038 (1021)	12 weeks	IND+GLY 27.5/15.6 µg vs IND 27.5 µg	COPD mean age:63y 63% male FEV1% pred: 54.6% Reversib: 22.8%	GOLD B: 57.2% GOLD D: 42.1%	46% cont.	Article reports on Flight1 and Flight2 studies. The analyses were done on pooled results
Singh 2014 (1)	1729 (1150)	24 weeks	ACL/FOR 400/12 µg & ACL/FOR 400/6 µg vs FOR 12µg	COPD mean age 63y 68% male FEV1% pred: 54% reversib: 32.8%	moderate 60% severe 40%	19.8% cont	highly reversible population
Vincken 2014 (10)	449	12 weeks	IND+GLY 150/50 µg vs IND 150µg	COPD mean age 63 82% males FEV1% pred: 55% reversib: 19.5%	moderate : 64% severe: 36%	63% cont	- 63% took ICS at inclusion, continued during study
* FEV1% predicted reported here are always post-bronchodilator							

Table 55

The **meta-analysis** by Farne and colleagues searched for all studies where a LABA and tiotropium were compared either with the LABA in monotherapy or tiotropium in monotherapy. 4 studies were mentioned in the outcomes of interest for this report. The LABA's used in the studies are olodaterol, indacaterol and formoterol.

In almost all studies, around roughly 50% of participants were on ICS and were allowed to continue those during the study. Sometimes randomization was stratified for ICS use, but not always so. This means that a certain percentage of patients was on triple therapy and a certain percentage in the

control group was taking a LAMA + ICS combination. An exception is Hoshino 2014, who included newly diagnosed patients that weren't on any medication yet.

Most of the patients had a % predicted FEV1 around 50%. Hoshino, who included newly diagnosed patients, had a post-bronchodilator FEV1 around 65% predicted.

The **other studies** that also investigated LABA & LAMA vs LABA are also reported.
The LABA's used in the studies are indacaterol, formoterol and vilanterol.

9 RCTs with duration of 12 to 52 weeks were found.

These studies have similar population: most of them are older males and the mean age is generally situated around 60-65. The mean FEV1 is also generally similar, lowest number being 47.5% of FEV1 predicted and the highest 55.5%. The severity of COPD is also more or less constant throughout the studies, with more patients with moderate forms of COPD being included.

On the other hand they differ in percentage of reversibility to a bronchodilator, some studies have up to 32.8% reversibility but others are around 15-20%. The percentage of patients on ICS at baseline is also different. For some studies the numbers are even higher than in the meta-analysis with around 60% of patients taking ICS at inclusion (Bateman 2013 and Vincken 2014). In other studies that number is lower: Singh 2014 has only 19.8% of patients on ICS and Donohue 2016 only 35%, but this last study only reports on one endpoint of interest. In all studies, patients who were on stable doses that weren't too high could continue (definition differs but generally at least one month stable on a dose of ≤1000mcg/d).

Mahler 2015 and Decramer 2014 are articles that report the results of twin trials. However, Mahler 2015 makes his statistical analyses on pooled results, and Decramer 2014 doesn't, thus reporting two results and 95% CI for each endpoint. On top of that Decramer compares two different dosages of formoterol (added to a LAMA) with formoterol 12µg alone, but only does this in one of his two twin trial.

Endpoint: Through FEV		
(n= 9473 (MA) + 7597) duration : 12 to 52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for ICS use and policy Imprecision: ok	
Studies	Results	
Farne 2015 (Buhl 2015b, Buhl 2015a, Hoshino 2014, Vogelmeier 2008)	MD: 0.070L (0.060L to 0.09)	**SS** **favours LABA+LAMA**
Bateman 2013	0.070L (no CI)	**SS** **p<0.001** **favours LABA+LAMA**

Celli 2014	0.114L (0.081 to 0.148)	**SS** **p<0.001**
Decramer 2014	UMEC125µg+VI vs VI: MD: 0.088 (0.036 to 0.140) UMEC 62.5µg+VI vs VI: MD: 0.090 (0.039 to 0.142)	**SS** **p=0.001** **SS** **p=0.0006**
Donohue 2013	MD: 0.095L (0.060 to 0.130)	**SS** **p<0.001**
Donohue 2016	MD: 0.0815L (0.0125 to 0.1505L)	**SS** **p<0.05**
D'Urzo 2014	ACL/FOR12µg vs FOR12µg MD: 0.045L (no 95% CI) ACL/FOR 6µg vs FOR12µg: MD: 0.026L (no 95% CI)	**SS** **p<0.01** NS
Mahler 2015	MD: 0.079L (0.051 to 0.107)	**SS** **p<0.001**
Singh 2014	ACL/FOR 12µg vs FOR 12µg: 85 ml (no CI) ACL/FOR 6µg vs FOR 12µg: 53mL (no CI)	**SS** **p<0.001** **SS** **p<0.01**
Vincken 2014	0.064L (95% CI: 0.028 to 0.099)	**SS** **p<0.001**

Table 56

Vincken 2014 also reports on a subgroup analysis according to COPD severity:

- Moderate or less airflow limitation: 0.045 (95% CI: 0.001–0.089) SS; p<0.047
- Severe or worse airflow limitation: 0.098 (95% CI: 0.039–0.157), SS; p<0.001

The results of these studies suggest that trough FEV1 is increased with LABA+LAMA compared to a LABA alone

For this meta-analysis and series of studies, almost all results are statistically significant.
Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: TDI focal score	
(n= 3955)	**GRADING** ⊕⊕⊕⊖ **MODERATE**

12 to 24 weeks	Study quality: ok Consistency: ok Directness: -1 for ICS use and policy Imprecision: ok

Studies	Results	
Celli 2014	LSMD: 0.5 (0.1 to 1.0)	**SS** **p<0.05**
Decramer 2014	LSMD: 0.8 (0.2 to 1.5)	**SS** **p=0.0126**
Donohue 2013	LSMD: 0.4 (-1.0 to 0.8)	NS
Mahler 2015	LSMD: 0.78 (0.43 to 1.13)	**SS** **p<0.001**
Vincken 2014	0.494 (95% CI: 0.030 to 0.958)	**SS** **p=0.037**

Table 57

The results of these studies suggest that the TDI focal score is increased with LABA+LAMA compared to LABA.
D'Urzo 2014 also reports that the results for TDI focal score were numerically greater for the LABA+LAMA group but reports no statistical testing. Singh 2014 reports similar numerical values for the TDI scores but only provides statistical tests vs placebo.

For this series of studies,
Most results are statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: SGRQ	
(n= 3378 (MA) + 3111) 12 weeks to 24 weeks	**GRADING** ⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: ok Directness: -1 for ICS use and policy Imprecision: -1, wide CI

Studies	Results	
Farne 2015 (Buhl 2015b, Buhl 2015a, Hoshino 2014, Vogelmeier 2008)	MD: -1.03 (-2.36 to 0.30)	**SS** **Favours LABA + LAMA**
Celli 2014	MD: -2.72 (-4.59 to -0.86)	**SS** **p<0.01**
Donohue 2013	MD: -0.32 (-2.41 to 1.78)	NS
Mahler 2015	MD: -1.7 (-3.1 to -0.3)	**SS** **p<0.05**
Vincken 2014	LSMD: -1.47 (-3.42 to 0.48)	NS

Table 58

The results of these studies suggest that SGRQ total score is decreased with LABA+LAMA compared to LABA.

For this series of studies,

Most results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Mortality		
(n= 3514 (MA)) duration: 12 weeks to 52 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1, most studies too short to correctly assess mortality Consistency: n/a Directness: -1, for ICS use and policy Imprecision: ok	
Studies	Results	
Farne 2015 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	OR: 1.15 (0.62 to 2.13)	NS

Table 59

The results of these studies do not suggest an effect on mortality of LABA+LAMA vs LABA alone.

For this meta-analysis, the result isn't statistically significant.

Other studies report numerical values for mortality (Bateman 2013, Singh 2014, Vincken 2014). The amount of events is very low (0, 1 or 2). No statistical testing is performed.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Exacerbations		
(n= 3514) 12 weeks to 52 weeks	**GRADING** ⊕⊕⊕⊖ **LOW** Study quality: ok Consistency: -1, see below Directness: -1 for ICs use and policy Imprecision: ok	
Studies	Results	
Farne 2015 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	OR: 0.80 (0.69 to 0.93)	NS

Table 60

The results of these studies do not suggest an effect on exacerbationsof LABA+LAMA vs LABA alone.

For this meta-analysis, the result isn't statistically significant.

Exacerbations however are frequently reported in the other RCTs we found.
In the study by Bateman 2013 around 30% of patients had exacerbations, but no statistical testing is reported. Decramer 2014 reports that only 5 to 8% of the patients in various groups had exacerbations. Donohue 2013 only reports testing of exacerbations vs placebo, and Donohue 2016 also reports a percentage of between 27 and 30% but doesn't run statistical tests on those numbers. Because of the confusing picture painted by the results and these numbers, we downgraded the grading by one for the overall consideration of the effect of LABA+LAMA on exacerbations.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Hospital admissions (all causes)		
(n= 3514) 12 weeks to 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1 for ICS use and policy Imprecision: ok	
Studies	Results	
Farne 2015 (Buhl 2015b, Buhl 2015a, Vogelmeier 2008)	OR: 0.93 (0.76 to 1.14)	NS

Table 61

The results of these studies do not suggest an effect in any direction.
For this meta-analysis, the result isn't statistically significant.

No other study reported on this endpoint.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.1.2 LABA +LAMA vs LAMA

6.1.2.1 *Clinical evidence profile*

Studies shared with LABA + LAMA vs LABA

Meta-analysis Farne 2015: See Table 40, Table 41, Table 42 and Table 43

Bateman 2013 : See Table 44

Celli 2014 : See Table 45

Decramer 2014 : See Table 46, Table 47

Donohue 2013 : See Table 48

Mahler 2015 : See Table 51

MAHLER 2012

Study details	n/Population	Comparison	Outcomes		Methodological
Mahler 2012 (5) Design: twin trials Study 1 RCT DB PG multinational Duration of follow-up: 12 weeks	n= 1134 Mean age: 64y % females: 31.5% currently smoking: 38% % taking ICS at inclusion: 48 ICS policy: continued at equivalent dose and regimen other background medications allowed: salbutamol (rescue) GOLD (2007)-classification of patients: moderate: 47% (very) severe: 53% Baseline FEV1 48.6% predicted (post salbutamol) % reversibility to salbutamol : 16.9% <u>Inclusion:</u>	indacaterol 150µg / tiotropium 18µg (n = 570) vs placebo / tiotropium 18µg (n = 564)	Efficacy		RANDO: Adequate ALLOCATION CONC: adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on randomization: stratified by COPD severity POWER CALCULATION: Yes Lost-to follow-up: 0.4% Drop-out and Exclusions: 5.6% Completed: 94% • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no
			trough FEV1	Difference: IND/TIO vs TIO: 80mL (95% CI: 50 to 100) **SS** **p<0.001**	
			prespecified subgroup analysis according to COPD severity		
			trough FEV1 moderate COPD	Diff: 90 mL (95% CI: 50 to 130) **SS**	
			trough FEV1 severe COPD	70 mL (30 to 110) **SS**	
			Deaths	IND+TIO: 2 TIO: 0	

	patients aged ≥40 years with moderate to severe COPD (defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 criteria), with a smoking history ≥10 pack-years and postbronchodilator (salbutamol 100 mg 3 four puffs) forced expiratory volume in 1 s (FEV1) ≤65% and ≥30% of predicted normal, and post-bronchodilator FEV1/forced vital capacity <70% at screening. <u>Exclusion</u> patients were not eligible if they had a history of asthma or had experienced a respiratory tract infection or COPD exacerbation within the previous 6 weeks				Other important methodological remarks : The midpoint of GOLD stage II, namely FEV1 65% of predicted, was chosen as the upper limit for the protocol of this study evaluating two long-acting bronchodilators to target a more 'severe' GOLD II patient population Sponsor: Novartis

Table 62

Study details	n/Population	Comparison	Outcomes		Methodological
Mahler 2012 (5) Design: twin trials Study 2 RCT DB PG Duration of follow-up: 12 weeks	n= 1142 Mean age: 63 y % females: 34.5% currently smoking: 40.5% % taking ICS at inclusion: 46% ICS policy: continued at equivalent dose and regimen other background medications allowed: salbutamol (rescue) GOLD (2007)-classification of patients: moderate: 46% (very) severe: 54% Baseline FEV1 48.6% predicted (post-salbutamol) % reversibility to salbutamol : 16.4%	indacaterol 150µg / tiotropium 18µg Vs placebo / tiotropium 18µg	Efficacy		Idem study 1 POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.7% Drop-out and Exclusions: 5.1% Completed: 94% • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no Other important method: see study 1 Sponsor: Novartis
			trough FEV1 (PO)	Difference: IND/TIO vs TIO: 70mL (95% CI: 50 to 90) **SS** **p<0.01**	
			Prespecified subgroup analysis according to COPD severity		
			trough FEV1 moderate COPD	Diff: 90 mL (60 to 120mL) **SS** **no p value**	
			trough FEV1 severe COPD	Diff: 60 mL (30 to 90mL) **SS** **no p value**	
			Deaths	IND+TIO: 1 TIO: 2	

	Inclusion: idem study 1 Exclusion : idem study 1				

MALEKI-YAZDI 2014

Study details	n/Population	Comparison	Outcomes		Methodological
Maleki-Yazdi 2014 Design: RCT DB PG Phase III Duration of follow-up: 24 weeks	n= 905 Mean age: 62.3 y % females: 32.5% Currently smoking: 56.5% % taking ICS at inclusion: 53.5% ICS policy: permitted provided the dose did not exceed 1000 mcg of FP or equivalent; ICS use was not to be initiated or discontinued within 30 days prior to Visit 1 other background medications allowed: albuterol/salbutamol as a rescue medication GOLD (2014)-classification of patients: Stage II: 41.5% Stage III: 46% Stage IV: 13%	Umeclidinium / vilanterol 62.5/25µg (n = 454) vs tiotropium 18µg (n = 451)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 13% • Described: yes • Balanced across groups: yes ITT: Yes (all randomized patients who had received at least one dose of study drug during the treatment period)
			Trough FEV1 (PO) (MMRM)	UMEC/VI: 0.205 L (SE: 0.0114) TIO: 0.093 L (SE : 0.0115) Difference: 0.112L 95% CI: 0.081 to 0.144 **SS** **p<0.001**	
			SGRQ total score	LS mean change: UMEC/VI: -7.27 (0.538) TIO: -5.17 (0.548) Difference: -2.1 95% CI: -3.61 to -0.59 **SS** **p = 0.006**	
			Time to 1st COPD exacerbation	UMEC/VI vs TIO HR: 0.5 (95% CI: 0.3 to 1.0) **SS** **p = 0.044** **favors UMEC/VI**	
			Subjects with on-treatment exacerbation	UMEC/VI: 16 (4%) TIO: 29 (6%) no statistical analysis	

	Baseline FEV1 46.4% predicted post-salbutamol % reversibility to salbutamol : 29% %reversibility to salbutamol and ipratropium: 53.5% <u>Inclusion:</u> Patients aged ≥40 years with moderate-to-very severe COPD and an established clinical history of COPD as defined by ATS/ERS Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years A pre and post-albuterol/salbutamol forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of <0.70 and a pre- and post-albuterol/ salbutamol FEV1 of ≤70% of predicted normal values		Cardiac arrhythmias	UMEC/VI: 3 (<1%) TIO: 4 (<1%)	SELECTIVE REPORTING: no Other important methodological remarks: no run in Sponsor: GlaxoSmithKline
			Fatal AE (deaths)	UMEC/VI: 2 TIO: 2	

	<u>Exclusion</u> - hospitalized for COPD or pneumonia within 12 week - Women who were pregnant or lactating or were planning on becoming pregnant during the study. - Asthma: A current diagnosis of asthma. - Other respiratory disorders - Other diseases /abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 - A history of allergy or hypersensitivity to any anticholinergic/muscarinic				

	receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction - An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1 - Unable to withhold albuterol/salbutamol for the 4-h period required prior to spirometry testing - Use of long-term oxygen therapy ≥12h/d				

Table 63

SINGH 2015

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2015 (14) **OTEMTO 1** (twin studies, see below for OTEMTO2) Design: RCT DB PG Duration of follow-up: 12 weeks	n (OTEMTO 1) = 814 Mean age: 64.85 y % females: 41% currently smoking: 48.7% % taking ICS at inclusion: 38.3% ICS policy: allowed to continue (if they were on a stable dose for 6 weeks prior to screening). other background medications allowed: salbutamol as rescue GOLD (2014) classification of patients: cat 1: 0% cat 2: 65% cat 3: 34% cat 4: 0.5%	tiotropium/ olodaterol 5/5µg (n = 204) vs tiotropium / olodaterol 2.5/5µg (n = 202) vs tiotropium 5µg (n = 204) vs placebo (n = 204)	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: no description POWER CALCULATION: Yes, but vs placebo FOLLOW-UP: variable% in safety analysis variable% in efficacy analysis (amount included depends on endpoint) Drop-outs and Exclusions: • Described: yes • Balanced across groups: slightly more drop-out in placebo group (87.3%) than in
			SGRQ total score (PO) (full analysis set: otemto 1&2)	<u>Difference</u>: TIO/OLO 5/5µg vs TIO 5µg: mean diff (SE): -2.1 (0.70) 95% CI: -3.47 to -0.72 **p<0.01** **SS** TIO/OLO 2.5/5µg vs TIO 5µg: mean diff (SE): -1.27 (0.70) 95% CI: -2.65 to 0.10 NS	
			SGRQ total score (OTEMTO 1)	TIO/OLO 5/5µg vs TIO 5µg: mean diff: -2.49(95% CI: -4.47 to -0.51) **p<0.05** **SS** TIO/OLO 2.5/5µg vs TIO 5µg: mean diff: -1.72 95% CI: -3.70 to 0.26 NS	
			Trough FEV1 (OTEMTO 1 + 2)	not calculated	
			Trough FEV1 (L)	TIO/OLO 5/5µg vs TIO 5µg	

	Baseline FEV1 55.4% predicted (post-bronchodilator) % reversibility to salbutamol : nr <u>Inclusion:</u> Patients aged ≥40 years with moderate to severe COPD (GOLD; post-bronchodilator forced expiratory volume in 1 s [FEV1] ≥30% and <80% of predicted normal), FEV1/forced vital capacity (FVC) <70% predicted and a smoking history of >10 pack-years <u>Exclusion</u> history of asthma, another significant disease, COPD exacerbation or symptoms of lower respiratory tract		(OTEMTO 1)	mean diff (SE): 0.028 (0.019) 95% CI/ -0.009 to 0.066 NS TIO/OLO 2.5/5µg vs TIO 5µg mean diff (SE): 0.017 (0.019) 95% CI: -0.021 to 0.054 NS	others (T5µg: 94.6%; T/O2.5/5: 97%; T/O 5/5: 96.1%) ITT: Yes (all patients who received at least one dose of study medication and had baseline and at least one post-baseline measurement for any of the primary end points) SELECTIVE REPORTING: no Other important methodological remarks - run in van 2 weken - testing strategy primarily vs placebo - amount of patients included for calculations of FEV1 AUC0-3 is not the same as amount of patients for trough FEV1 Sponsor: Boehringer Ingelheim
			TDI focal score (OTEMTO 1 + 2)	TIO/OLO 5/5µg vs TIO 5µg mean diff (SE): 0.59 (0.19) 95% CI: 0.22 to 0.97 **SS** **p<0.01** TIO/OLO 2.5/5µg vs TIO 5µg mean diff (SE): 0.58 (0.19) 95% CI: 0.21 to 0.96 **SS** **p<0.01**	
			TDI focal score (OTEMTO 1)	TIO/OLO 5/5µg vs TIO 5µg mean diff (SE): 0.61 (0.27) 95%CI: 0.08 to 1.14 **SS** **p<0.05** TIO/OLO 2.5/5µg vs TIO 5µg mean diff (SE): 0.51 (0.27) 95% CI: -0.02 to 1.04 NS	

	infection within the previous 3 months, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year, a history ofmyocardial infarction within 1 year of screening or a history of life-threatening pulmonary obstruction		AF	not measured or reported	

Table 64

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2015 (14) **OTEMTO 2** (twin studies) Design: RCT DB PG	n (OTEMTO 2) = 809 Mean age: 64.6y % females: 37% currently smoking: 45.5% % taking ICS at inclusion: 36.7% ICS policy: allowed to continue (if they were on a stable dose for 6 weeks prior to screening).	tiotropium/ olodaterol 5/5µg (n = 202) vs tiotropium / olodaterol 2.5/5µg (n = 202) vs	Efficacy		idem Otemto 1 FOLLOW-UP: variable % in safety analysis variable% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: slightly more drop-out in placebo group (90.1%%) than in others (T5µg: 94.1%%; T/O2.5/5: 95.5%; T/O 5/5: 98%)
			SGRQ total score (OTEMTO 2)	TIO/OLO 5/5µg vs TIO 5µg: mean diff (SE): -1.72 (0.97) 95% CI: -3.63 to 0.19 NS TIO/OLO 2.5/5µg vs TIO 5µg: mean diff (SE): -0.82 (0.98) 95% CI: -2.74 to 1.10 NS	
			Trough FEV1 (L)	TIO/OLO 5/5µg vs TIO 5µg:	

Duration of follow-up: 12 weeks	other background medications allowed: salbutamol as rescue GOLD (2014)-classification of patients: cat 1: 0% cat 2: 63.4% cat 3: 36.1% cat 4: 0.5% Baseline FEV1 54.8% predicted (post-bronchodilator) % reversibility: nr <u>Inclusion & exclusion :</u> idem OTEMTO 1	tiotropium 5µg (n = 203) vs placebo (n = 202)	(OTEMTO2)	mean diff (SE): 0.039 (0.019) 95% CI: 0.002 to 0.076 **SS** **p<0.05** TIO/OLO 2.5/5µg vs TIO 5µg mean diff (SE): 0.042 (0.019) 95% CI: 0.005 to 0.079 **SS** **p<0.05**	
			TDI focal score (OTEMTO 2)	TIO/OLO 5/5µg vs TIO 5µg mean diff (SE): 0.58 (0.27) 95%CI: 0.06 to 1.11 **SS** **p<0.05** TIO/OLO 2.5/5µg vs TIO 5µg mean diff (SE): 0.65 (0.27) 95% CI: 0.12 to 1.18 **SS** **p<0.05**	
			AF	not measured or reported	

Table 65

WEDZICHA 2013

Study details	n/Population	Comparison	Outcomes		Methodological
Wedzicha 2013 (18) Design: RCT PG DB for some comparisons OL for Tio Duration of follow-up: 64 weeks	n= 2224 Mean age: 63.3 y % females: 25% currently smoking: 38% % taking ICS at inclusion: 75% ICS policy: Patients receiving inhaled corticosteroids at baseline continued treatment at the same or equivalent dose and regimen during the study. other background medications allowed: GOLD (2010)-classification of patients: Severe: 79%	Indacaterol/glycopyrronium 110/50 µg (n = 741) vs glycopyrronium 50µg (n = 741) vs tiotropium 18µg (n = 742)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes but not for TIO Personnel: yes but not for TIO Assessors: yes but not for TIO POWER CALCULATION: Yes FOLLOW-UP: • Lost-to follow-up: <1% • Drop-out and Exclusions: 25% Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: yes
			moderate to severe COPD exacerbations (PO) (rate ratio)	IND/GLY: 812 GLY: 900 TIO: 898 <u>Mean exacerb per patient</u> IND/GLY: 1.11 (SD: 1.35) GLY: 1.22 (SD: 1.48) TIO: 1.22 (SD: 1.66) <u>Annualized rate</u> IND/GLY: 0.84 (0.75 to 0.94) GLY: 0.95 (0.85 to 1.06) TIO: 0.93 (0.83 to 1.04) <u>Difference (rate ratio)</u> IND/GLY vs GLY: 0.88 (0.77 to 0.99) **SS** **p=0.038** IND/GLY vs TIO: 0.90 (0.79 to 1.02) NS p=0.096
			Trough FEV1	IND/GLY vs GLY: 70–80 mL;	

	Very severe: 21% post-bronchodilator baseline FEV1 37.2% predicted % reversibility: 18.3% COPD exacerbations in the previous year: 0 : 1% 1 : 76% ≥2: 22% <u>Inclusion:</u> men and women; aged ≥40 years) at risk of exacerbations, defined as patients with severe to very severe airflow limitation (Stage III or IV according to Global Initiative for Chronic Obstructive			**SS** **p<0·0001** IND/GLY vs TIO: differences 60–80 mL; **SS** **p<0·0001**	results for trough FEV1 and SGRQ total score only reported visually, no exacts numbers, "ranged from", reporting unclear Other important methodological remarks: - 14 day run-in - Longacting bronchodilators were discontinued with a washout of up to 7 days (for theophylline, indacaterol, and tiotropium) before screening Sponsor: Novartis
			SGRQ total score	IND/GLY: improvement from baseline was 8–9 units with QVA149, GLY: improvement 6 units TIO: 5–6 units <u>Differences</u> IND/GLY vs GLY: differences ranged from −1·9 to −2·8 (all p<0·01) IND/GLY vs TIO: differences ranged from −1·7 to −3·1 (all p<0·05)	
			Pneumonia	IND/GLY: 33 (5%) GLY: 36 (5%) TIO: 34 (5%) p>0.05	
			Atrial Fibrillation	IND/GLY: 11 (2%) GLY: 10 (1%) TIO: 8 (1%) p>0.05	

	Lung Disease [GOLD] 2008 criteria, post-bronchodilator forced expiratory volume in 1 s [FEV1] <50% of predicted normal and FEV1 /forced vital capacity [FVC] <0·70 at screening), and a documented history of at least one exacerbation in the previous 12 months requiring treatment with systemic corticosteroids or antibiotics, or both. Patients were to be current or ex-smokers with a smoking history of 10 or more pack-years				

	<u>Exclusion</u> a COPD exacerbation that needed treatment with antibiotics, systemic corticosteroids (oral or intravenous), or hospitalisation in the 6 weeks before prescreening or during screening, developed a COPD exacerbation during prescreening or screening, or had a respiratory tract infection within 4 weeks before prescreening				

6.1.2.2 *Summary and conclusions*

Laba & Lama vs LAMA

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Farne 2015 (40)	N= 10 (articles: 7) n = 9633 (Aaron 2007(47), Buhl 2015a & Buhl 2015b (16), Hoshino 2014 (46), Mahler 2010a & 2010b, (48), Tashkin 2009a (49), Vogelemeier 2008 (45), ZuWallack 2014a & 2014b (3)	12 weeks to 52 weeks	Laba (different molecules) + Tiotropium vs same dose tiotropium	COPD mostly older, predominantly male	- 2 studies by Buhl had more drop out in monotherapy arms - in almost all studies a large amount of participants were on ICS and could continue the ICS therapy.

Table 66

Bibliography of included RCTs							
	n	duration	exact comparison	population (+ remarks)	GOLD cat.	%ICS	methodological remarks
Bateman 2013 (SHINE) (17)	2144 (950)	26 weeks	IND+GLY 150/50µg vs GLY 50µg	COPD older males FEV1% pred.: 55.5% reversib. : 20%	stage II or III	57.5 % cont.	
Celli 2014 (41)	1439 (810)	24 weeks	UMEC+VI 125/25µg vs TIO 18µg	COPD mean age:63 y FEV1% pred.: 48.2% reversib.: 13.2%	ST II: 47% St III: 45% St IV: 8%	47%, cont	
Decramer	2332	24	UMEC+VI	COPD	Trial 1:	Trial	- twin trials

2014 (42)	(1825)	weeks	125/25µg UMEC+VI 62.5/25 µg vs TIO 18 µg	mean age: 63y mostly male FEV1% pred.: ±47.5% revers.:±14%	St II: 47% St III: 42% St IV: 11% Trial 2: St II: 44% St III: 43% St IV: 12%	1: 44% Trial 2: 52%	- analysis on each trial, results not pooled
Donohue 2013 (43)	1536 (831)	24 weeks	UMEC+VI 62.5/25µg vs UMEC 62.5 µg	COPD older males FEV1% pred.: 47.4% reversib.: 15%	St II: 46% St III: 43% St IV: 11%	50% cont.	
Mahler 2012 (5)	1134 (1134)	12 weeks	IND+TIO 150/18µg vs TIO 18µg	COP older males (59.5%) FEV1% pred: 48.6% Reversib: 17%	moderate : 47% severe or very severe: 53%	48%	- FEV1 65% of predicted, was chosen as the upper limit to target a more 'severe' GOLD II patient population - twin trials, analyzed separately
Mahler 2015 (7)	2038 (1022)	12 weeks	IND+GLY 27.5/15.6 µg (2x/d) vs GLY 15.6 µg (2x/d)	COPD mean age:63y 63% male FEV1% pred: 54.6% Reversib: 22.8%	GOLD B: 57.2% GOLD D: 42.1%	46% cont.	Article reports on Flight1 and Flight2 studies. The analyses were done on pooled results
Maleki-Yazdi 2014 (50)	905 (905)	24 weeks	UMEC+VI 62.5/25µg vs TIO 18µg	COPD older males FEV1 46.4% predicted % reversibility to salbutamol : 29% %reversibility to salbutamol & ipratropium: 53.5%	Stage II: 41.5% Stage III: 46% Stage IV: 13%	53.5 % cont.	no run in
Singh 2015 (14)	814 (814)	12 weeks	TIO+OLO 5/5 µg &	COPD older males	cat 1: 0% cat 2: 65%	38.3 %, conti	- twin trial, results are given for each

			TIO+OLO5 /2.5µg vs TIO 5µg	FEV1 55.4% predicted Reversibility: NR	cat 3: 34% cat 4: 0.5%	nued	trial alone and for pooled trials (not on all endpoints)
Wedzicha 2013 (SPARK) (18)	2224 (2224)	64 weeks	IND+GLY 110/50 µg vs GLY 50µg vs TIO 18µg	COPD older males FEV1 37.2% predicted 18.3% reversib.	Severe: 79% Very severe: 21%	75%	drop-out and exclusions of 25% all patients had had an exacerbation in the previous year
*FEV1% predicted reported here are always post-bronchodilator							

Table 67

The **meta-analysis** by Farne and colleagues searched for all studies where a LABA and tiotropium were compared either with the LABA in monotherapy or tiotropium in monotherapy. 8 studies were mentioned in the outcomes of interest for this report. The LABA's used in the studies are salmeterol, olodaterol, indacaterol, formoterol. The LAMA in the comparison group is not always the same as in the active group.

In almost all studies, around roughly 50% of participants were on ICS and were allowed to continue those during the study (in Tashkin 2009 only 27% were taking ICS). Sometimes randomization was stratified for ICS use, but not always so. This means that a certain percentage of patients was on triple therapy and a certain percentage in the control group was taking a LAMA + ICS combination. Exceptions were Aaron 2007, were ICS was discontinued, and Hoshino 2014 who included newly diagnosed patients that weren't on any medication yet.

Most of the patients had a % predicted FEV1 around 50%. A first exception is Aaron 2007, with post-bronchodilator FEV1 around 38% predicted, and Hoshino 2014, who included newly diagnosed patients, and thus had a post-bronchodilator FEV1 around 65% predicted.

The second table lists the **other studies** that also investigated LABA & LAMAvs LAMA.
9 RCTs lasting 12 to 64 weeks were found.

These studies have similar population: most of them are older males and the mean age is generally situated around 60-65. The studies have included patients with moderate, severe or very severe forms of BPCO. 5 out of 9 studies included very severe patients (making up around 10% of participants included), and in one study 21% of patients had very severe COPD. Two studies are slightly different: patients in Singh 2015 tend to have a more moderate form of COPD, and Wedzicha 2013 have a more severe form (this shows also in the percentage of patients under ICS: 75%!). When mentioned, reversibility is usually between 15-20%. Aside from exceptions, approximately half of the patients were also taking ICS, which could be continued provided they were stable and below a certain dose.

There were 4 twin trials. One gave both pooled and separate results, one gave the pooled results, and two analyzed both trials separately. Decramer compares two different dosages of formoterol (added to a LAMA) with formoterol 12µg alone, but only does this in one of his two twin trial.

Endpoint: Trough FEV1	
(n= 9573 (MA) + 10515) duration: 12 weeks to 64 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: -1, some trials SS and clinically sign., some only SS significant, some barely significant, some NS Directness: -1, some heterogeneity present in Farne 2015, differences in trial analysis for others, in trial conception, % ICS users, etc Imprecision: ok

Studies	Results	
Farne 2015 (Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Hoshino 2014, Mahler 2010a & 2010b, Buhl 2015a & 2015b, ZuWallack 2014a & 2014b)	MD: 0.06 (0.05 to 0.07)	**SS** (Favours LABA + LAMA)
Bateman 2013	MD: 0.090L (no 95% CI)	**SS** p<0.001 **Favours LABA+LAMA**
Celli 2014	MD: 0.079L (0.046 to 0.112)	**SS** **p<0.001** **Favours LABA+LAMA**
Decramer 2014	Study 1: - UMEC 125µg+VI vs TIO 18µg MD: 0.088L (0.036 to 0.140) - UMEC 62.5µg + VI vs TIO 18µg MD: 0.090L (0.039 to 0.141)	**SS** **p=0.001,** favours combination **SS** **p = 0.001,** favours combination
	Study 2: - UMEC 125µg+VI vs TIO 18µg MD: 0.074L (0.025 to 0.123) - UMEC 62.5µg + VI vs TIO MD: 0.060L (0.010 to 0.109) - UMEC 125µg+VI vs UMEC 125µg MD: 0.037 (-0.012 to 0.087) - UMEC 62.5µg + VI vs UMEC 125µg MD: 0.022L (-0.027 to 0.072)	 **SS** **p = 0.0031** **SS** **p=0.0182** NS NS
Donohue 2013	MD: 0.052 (0.017 to 0.087)	**SS** **p≤0.001**
Mahler 2012	MD: 0.080L (0.050 to 0.100)	**SS** **p<0.001**
	MD: 0.070L (0.050 to 0.090)	**SS** **p<0.01**
Mahler 2015	MD: 0.098L (0.071 to 0.126)	**SS**

		p<0.001
Maleki-Yazdi 2014	MD: 0.112L (0.081 to 0.144)	**SS** **p<0.001**
Singh 2015*	Otemto1: - TIO/OLO 5/5µg vs TIO 5µg: MD: 0.028L (-0.009 to 0.066) - TIO/OLO 2.5/5 µg vs TIO 5µg MD: 0.017 (-0.021 to0.054)	 NS NS
	Otemto2: - TIO/OLO 5/5µg vs TIO 5µg: MD: 0.039L (0.002 to 0.076) - TIO/OLO 2.5/5 µg vs TIO 5µg MD: 0.042 L (0.005 to 0.079)	 **SS** **p<0.05** **SS** **p<0.05**
Wedzicha 2013	IND/GLY vs GLY: 70-80mL† IND/GLY vs TIO: 60-80mL†	**SS** **p<0.0001** **SS** **p<0.0001**
* For some outcomes the results on pooled population are given, however not on trough FEV1 † Numbers given as range, this is not a 95% CI		

Table 68

The results of these studies suggest that trough FEV1 is increased with LABA/LAMA compared to LAMA alone.
Mahler 2012 had a prespecified subgroup analysis according to COPD severity:
For Study 1

- Moderate COPD: MD: 90 mL (50 to 130ml), SS
- Severe COPD: MD: 70 mL (30 to 110ml), SS

For study 2:

- Moderate COPD: MD: 90 mL (60 to 120 mL), SS
- Severe COPD: MD: 60 mL (30 to 90 mL), SS

For this series of studies, most results are statistically significant.
Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: TDI focal score		
(n= 5302) duration: 12 to 24 weeks	**GRADING** ⨁⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: -1, some trials SS, some NS, and effect direction not consistent Directness: -1, % ICS users Imprecision: -1, take into account that the MCI difference is 1, a CI of >MCID happens quite often	
Studies	Results	
Celli 2014	MD: 0.6 (0.2 to 1.0)	**SS**
Decramer 2014	- UMEC 125µg+VI vs TIO 18µg	NS

	MD: 0.5 (-0.2 to 1.1) - UMEC 62.5µg + VI vs TIO MD: -0.1 (-0.7 to 0.5)	NS
	- UMEC 125µg+VI vs TIO 18µg MD: 0.3 (0.4 to 1.0) - UMEC 62.5µg + VI vs TIO 18µg MD: 0.2 (-0.5 to 0.9) - UMEC 125µg+VI vs UMEC 125µg MD: 0.5 (-0.2 to 1.2) - UMEC 62.5µg + VI vs UMEC 125µg MD: 0.4 (-0.3 to 1.1)	**SS** NS NS NS
Donohue 2013	MD: 0.3 (-0.2 to 0.7)	NS
Mahler 2015	MD: 0.73 (0.39 to 1.08)	**SS** **p<0.001**
Singh 2015	TIO/OLO 5/5µg vs TIO 5µg: MD: 0.59 (0.22 to 0.97) TIO/OLO 5/2.5µg vs TIO 5µg: MD: 0.58 (0.21 to 0.96)	**SS** **p<0.01** **SS** **p<0.01**

Table 69

We can't make any conclusions about the direction of the effect.
The interpretation is complicated by the fact that not all results are SS, and not all results unambiguously show an increase or a decrease. Mahler 2015 and Singh 2015 have a population with a better mean FEV1% predicted (around 55%) compared to Celli 2014 and Decramer 2014 (47-48% FEV1 predicted).

For this series of studies, some results are significant, some are not (50/50).

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: SGRQ		
(n= 6709 (MA) + 7556) duration: 12 weeks	**GRADING** ⊕⊕⊕⊕ **HIGH** ⊕⊕⊕⊖ **MODERATE** ⊕⊕⊖⊖ **LOW** ⊕⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: -1 Directness: -1 for %ICS users Imprecision: ok	
Studies	Results	
Farne 2015 (Aaron 2007, Vogelmeier 2008, Buhl 2015a, Buhl 2015b, ZuWallack 2014a)	MD: -1.34 [-1.87 to -0.70]	**SS** **(favours LABA+LAMA)**

Bateman 2013	LSMD: -1.84 (no 95% CI)	**SS** **p=0.020**
Celli 2014	MD: -3.29 (-5.13 to -1.44)	**SS** **p<0.001**
Donohue 2013	MD: -0.82 (-2.90 to 1.27)	NS
Mahler 2015	MD: -1.5 (-3.0 to -0.3)	NS
Maleki-Yazdi 2014	MD-2.1 (-3.61 to -0.59)	**SS** **p = 0.006**
Singh 2015	Otemto1&2: TIO/OLO 5/5µg vs TIO 5µg: -2.1 (-3.47 to -0.72) TIO/OLO 2.5/5µg vs TIO 5µg: -1.27 (-2.65 to 0.10)	**p<0.01** **SS** NS
	Otemto 1 TIO/OLO 5/5µg vs TIO 5µg: -2.49 (-4.47 to -0.51) TIO/OLO 2.5/5µg vs TIO 5µg: -1.72 (-3.70 to 0.26)	 **p<0.05** **SS** NS
	Otemto 2 TIO/OLO 5/5µg vs TIO 5µg: -1.72 (-3.63 to 0.19) TIO/OLO 2.5/5µg vs TIO 5µg: -0.82 (-2.74 to 1.10)	 NS NS
Wedzicha 2013	IND/GLY vs GLY: "difference ranged from -1.9 to -2.8" IND/GLY vs TIO: "differences ranged from -1.7 to -3.1	 "all were p<0.01" "all were p<0.05"

Table 70

The results of these studies suggest that the SGRQ-score decreased with LABA+LAMA compared to LAMA.

For this series of studies, about half the results are statistically significant. Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Mortality		
(n= 9633 (MA) duration: 12 weeks to 52 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1, most studies too short to correctly assess mortality Consistency: n/a Directness: -1, for ICS use and policy Imprecision: ok	
Studies	Results	
Farne 2015	OR: 1.24 (0.81 to 1.90)	NS

(Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Mahler 2010a, Mahler 2010b, Buhl 2015a, Buhl 2015b, ZuWallack 2014a)		

Table 71

The results of these studies suggest that there is no effect on mortality.

For this meta-analysis the result isn't statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations		
(n= 6391(MA) + 905) duration: 12 to 52 weeks	**GRADING** ⨁⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: -1 Directness: -1 Imprecision: -1, unclear CI	
Studies	Results	
Farne 2015 (Aaron 2007, Tashkin 2009a, Vogelmeier 2008, Buhl 2015a & Buhl 2015b, ZuWallack 2014a & ZuWallack 2014b)	OR: 0.94 (0.79 to 1.11)	NS
Maleki-Yazdi 2014	(time to first exacerbation) HR: 0.5 (0.3 to 1.0*)	SS p = 0.044* favours combination
* We double checked these numbers and this is how they are reported in the article supplements, we suppose the HR = 1.0 (which would be NS) is because of rounding up.		

Table 72

The results of these studies do not suggest an effect on exacerbations of LAMA / LABA versus LAMA. Because the amount of patients in the meta-analysis is many times larger, because the CI of that result both shows increased and decreased risk, and because of the uncertainty about the CI from Maleki-Yazdi 2014, we concluded that there is likely no effect.

For this study and meta-analysis, the result from the study is statistically significant but needs to be interpreted with caution; the one from the meta-analysis is not statistically significant.

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Hospitalizations (all causes)	
(n= 4856) duration: 12 to 52 weeks	**GRADING** ⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: n/a Directness: -1 for ICS use and policy

	Imprecision: ok	
Studies	Results	
Farne 2015 (Aaron 2007, Vogelmeier 2008, Buhl 2015a, Buhl 2015b)	OR: 1.01 (0.86 to 1.19)	NS

Table 73

The results of these studies do not suggest an effect in any direction.
For this meta-analysis, the result isn't statistically significant.

No other study reported on this endpoint.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.1.3 LABA +LAMA vs LABA + ICS

6.1.3.1 *Clinical evidence profile*

DONOHUE 2015

Study details	n/Population	Comparison	Outcomes		Methodological
Donohue 2015 (51) Twin trials DB2114930 Design: RCT DB PG Duration of follow-up: 12 weeks	n= 706 Mean age: 62.8 % females: 30 currently smoking: 43% % taking ICS at inclusion: 6% ICS policy: stopped with a 30 day wash out period other background medications allowed: albuterol as rescue GOLD (2014)-classification of patients: Stage II: 49% Stage III: 51% Stage IV: 0% Baseline FEV1 49.4% predicted (post-albuterol)	Umeclidinium / Vilanterol 62.5/25 µg (n = 353) vs Fluticasone propionate / salmeterol 250/50 µg (n = 353)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.7% Drop-out and Exclusions: 9.5% • Described: yes • Balanced across groups: yes ITT: Yes (at least one dose of study medication)
			Trough FEV1 (SO)	LS mean change from baseline (SD): UMEC/VI: 0.154 (0.0133) FP/SAL: 0.072 (0.0134) Difference: 0.082 (0.045 , 0.119) **SS** **p<0.001** favours UMEC/VI	
			Trough FEV1 (SO) *Subgroup: GOLD Stage II*	LS mean change from baseline (SD) UMEC/VI: 0.143 (SD: 0.2613) FP/SAL: 0.064 (0.2714)	
			Trough FEV1 (SO) *Subgroup: GOLD Stage III*	LS mean change from baseline (SD) UMEC/VI: 0.167 (0.2412) FP/SAL: 0.084 (0.1943)	
			TDI focal score	LS mean change from baseline (SE): UMEC/VI: 2.0 (0.16) FP/SAL: 1.7 (0.16)	

	% reversibility to albuterol : 11.3 <u>Inclusion:</u> males or females ≥40 years old with established COPD; a post-albuterol (salbutamol) forced expiratory volume in 1 s (FEV1) ≥30% and ≤70% predicted normal and a pre- and post- albuterol FEV1/forced vital capacity (FVC) ratio ≤0.70 [2,3]; a dyspnea score ≥2, modified Medical Research Council [mMRC] Dyspnea Scale); current or former (stopped smoking for ≥6months) cigarette smokers with a history of cigarette smoking of ≥10 pack-years. <u>Exclusion</u> asthma/other respiratory disorders; hospitalization for pneumonia within ≤12 weeks of screening; a			Difference: 0.3 (–0.2 to 0.7) *p* = 0.246 NS	SELECTIVE REPORTING: no Other important methodological remarks: has a run in Sponsor: GlaxoSmithKline
			SGRQ total score	LS mean change from baseline (SE): UMEC/VI: –4.14 (0.566) FP/ SAL: –4.25 (0.562) Difference: 0.10 (–1.46-1.67) *p* = 0.898 NS	
			Cardiac arrhythmias	UMEC/VI: n = 2; <1% FP/SAL: n = 2; <1%	
			Pneumonia	UMEC/VI: n = 1 ; <1% FP/ SAL: n = 4 ; 1%	

	documented history of ≥1 COPD exacerbation requiring oral corticosteroids, antibiotics and/or hospitalization in the year before screening				

Table 74

SINGH 2015

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2015 (52) Design: RCT phase III DB PG Duration of follow-up: 12 weeks	n= 717 Mean age: 61.8 % females: 28% currently smoking: 59% % taking ICS at inclusion: NR ICS policy: stopped other background medications allowed: salbutamol, mucoltics, as-needed oxygen therapy ≤12h/d GOLD (2014)-classification of	umeclidinium/ vilanterol 62.5/25 µg vs fluticasone propionate / salmeterol 500/50 µg	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear POWER CALCULATION: Yes, sufficiently powered FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 6% • Described: yes • Balanced across groups: yes
			Trough FEV1 (MRMM)	UMEC/VI: 0.151 (0.0126) FP/SAL: 0.062 (0.0125) Difference: 0.090 L 95% CI: 0.055 – 0.125 **SS** **p<0.001** **favours UMEC/VI**	
			SGRQ total score	LS mean change (SE) UMEC/VI: -3.83 (0.552) FP/SAL: -5.05 (0.544) Difference: 1.11 95% CI: -0.30 to 2.75 NS p = 0.116	
			Cardiac arrhythmia	UMEC/VI: 3 (<1%)	

	patients: Stage B: 55% Stage D: 45% Baseline FEV1 50.6% predicted post-salbutamol % reversibility to salbutamol : 10.8 <u>Inclusion:</u> male or female patients ≥40 years old; an established COPD clinical history; a post-salbutamol FEV1/forced vital capacity (FVC) ratio <0.70 and a post-salbutamol FEV1 of ≥30 % and ≤70 % of predicted normal values; a dyspnoea score of ≥2 (modified Medical Research Council			FP/SAL: 2 (<1%)	ITT: Yes (= (all randomised patients who took at least one dose of study medication) SELECTIVE REPORTING: no Other important methodological remarks: 7 to 14 day run in patients selected specifically to not have a history of exacerbations Sponsor: GSK
			Pneumonia	UMEC/VI: 0 FP/SAL: 1 (<1%)	
			COPD exacerbations	UMEC/VI: n = 8 (2%) FP/SAL: n = 3 (<1%)	

	[mMRC] Dyspnoea Scale); current or former (stopped smoking for ≥6 months) cigarette smokers with a history of cigarette smoking of ≥10 pack-years. <u>Exclusion</u> asthma/ other respiratory disorders; hospitalisation for pneumonia within 12 weeks of screening; a documented history of ≥1 COPD exacerbation requiring oral corticosteroids, antibiotics and/or hospitalisation in the 12 months preceding screening.				

Table 75

VOGELMEIER 2013

Study details	n/Population	Comparison	Outcomes		Methodological
Vogelmeier 2013 (11) ILLUMINATE Design: RCT DB PG Duration of follow-up: 26 weeks	n= 523 Mean age: 63.3 % females: 29.1 currently smoking: 47.9% % taking ICS at inclusion: 35% ICS policy: stopped 48 hours before run in other background medications allowed: salbutamol as rescue, SSRI, intranasal corticoids, H1 antagonists (constant doses) GOLD (2009)-classification of patients: moderate: 80.25% severe: 19.75% Baseline FEV1 50.9% predicted % reversibility to salbutamol : 20.4%	Indacaterol / glycopyrronium 110/50 µg 1x/d (n = 259) vs salmeterol / fluticasone 50/500 µg 2x/d (n = 264)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes, calculated for PO which was FEV1 AUC(0->12h) FOLLOW-UP: 99.8% in safety analysis 81.8% in efficacy analysis Drop-outs and Exclusions: • Described: yes, 17.4% • Balanced across groups: yes ITT: YES Full analysis set: all patients who received at least one dose of the study drug Safety pop.: all patients who received at least one dose of the study drug
			Trough FEV1 (SO)	IND/GLY: 1.601L (0.027) SAL/FLU: 1.498L (0.025) Difference of LSMs: 0.103L (95% CI: 0.065 to 0.141) **SS in favour of IND/GLY** **p<0.0001**	
			TDI focal score	increase from baseline at 26 weeks (LSM): IND/GLY: 2.36 SAL/FLU: 1.60 Difference: 0.76 (0.26 to 1.26) SS p = 0.0031 favours IND/GLY	
			SGRQ total score	mean total score at 26 weeks (LSM): IND/GLY: 35.45 SAL/FLU: 36.68 Difference: -1.24 (-3.33 to 0.85) NS	
			Atrial Fibrillation	IND/GLY: n = 1 (0.4%) SAL/FLU: 0	

	Inclusion: men and women 40 years of age or older, current or former smokers with a smoking history of at least 10 pack-years, post-bronchodilator FEV1 between 40% and 80% of predicted value, and post-bronchodilator FEV1 to forced vital capacity (FVC) ratio less than 0·70 Exclusion history of COPD exacerbations needing treatment with antibiotics, systemic corticosteroids, or hospitalisation in the year leading up to and including randomisation were excluded - Patients with a history of long QT syndrome or a clinically significant abnormality on the visit 2 ECG				
			Pneumonia	IND/GLY: 0 SAL/FLU: 1 (0.4%)	SELECTIVE REPORTING: no Other important methodological remarks: 7 day pre-screening wash-out period and 14 day run-in period Confusion between claimed ITT and numbers on which the efficacy analyses are performed Sponsor: Novartis

	- a history of malignancy of any organ system -Patients requiring long-term oxygen therapy on a daily basis for chronic hypoxaemia - a respiratory tract infection within 4 weeks prior to visit 1 - patients with concomitant pulmonary disease - any history of asthma - blood eosinophil count >600/mm3 - Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently - patients in the active phase of a supervised pulmonary rehabilitation programme				

Table 76

VOGELMEIER 2016

Study details	n/Population	Comparison	Outcomes		Methodological
Vogelmeier 2016 (2) AFFIRM Design: RCT DB PG Duration of follow-up: 24 weeks	n= 933 Mean age: 63.4 % females: 34.9% currently smoking: NR % taking ICS at inclusion: 38.3% ICS policy: stopped the day before randomisation other background medications allowed: salbutamol as rescue GOLD (2015)-classification of patients: Gold B: 55.85% Gold D: 44.15% Baseline FEV1 53.3% predicted % reversibility to salbutamol : 11.8% ≥1 exacerbation in previous year: 32.05%	aclinidium bromide / formoterol fumarate 400/12 µg 2x/d vs fluticasone propionate / salmeterol 500/50 µg 1x/d	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: unclear Assessors: unclear Remarks on blinding method: (vrij te omschrijven, schrappen als nvt) POWER CALCULATION: Yes, allowing for 10% dropout Drop-outs and Exclusions: • Described: yes, 15.5% • Balanced across groups: yes, 14.1% in ACL/FOR, 17.0% in SAL/FLU <u>ITT</u> population: patients with a baseline FEV1 assessment who took one or more doses of study
			trough FEV1	ACL/FOR: 1.405L SAL/FLU: 1.419 difference / 95% CI: not given p = 0.3635 NS	
			TDI focal score (PPA)	ACL/FOR: 1.9 SAL/FLU: 1.9 Difference: -0.001 95% CI: -0.46 to 0.46 NS ACL/FOR non-inferior to SAL/FLU	
			SGRQ score	ACL/FOR: -4.7 SAL/FLU: -5.7 NS p = 0.27	
			Exacerbations	ACL/FOR: 15.8% of patiens with ≥1 SAL/FLU: 16.6% of patients with ≥1 NS no CI given	
			Pneumonia	ACL/FOR: n = 3 (0.6%) SAL/FLU: n = 9 (1.9%)	

	Inclusion: ⩾40 years of age with a smoking history ⩾10 pack-years and diagnosed with moderate-to-severe COPD (GOLD 2013 criteria: post-bronchodilator FEV1/forced vital capacity <70% and FEV1 <80% predicted) CAT score ≥10 Exclusion respiratory tract infection or COPD exacerbation within 6 weeks of screening or during run-in, pulmonary rehabilitation within 3 months, or use of triple therapy (LAMA/LABA/ICS) within 4 weeks of the screening visit				medication Safety population: patients who received one or more doses of study medication SELECTIVE REPORTING: yes, lack of CI for trough FEV1 or exacerbations Other important methodological remarks: 7 to 10 day run-in period no pre-treatment washout period, patients discontinued all bronchodilators and ICS medication the night before randomisation visit Sponsor: AstraZeneca

Table 77

WEDZICHA 2016

Study details	n/Population	Comparison	Outcomes		Methodological
Wedzicha 2016 (6) FLAME Design: RCT DB PG non-inferiority Duration of follow-up: 52 weeks	n = 3362 Mean age: 64.6 % females: 23.9 currently smoking: 39.6% % taking ICS at inclusion: 56.3% ICS policy: stopped other background medications allowed: salbutamol as rescue GOLD (2015)-classification of patients: Group B: 24.4% Group C: 0.1% Group D: 74.8% Baseline FEV1 44.1% predicted % reversibility to salbutamol : 22.4% <u>Inclusion:</u> patients 40 years of age or	indacaterol / glycopyrronium 110/50 µg 1x/d (n = 1680) vs fluticasone / salmeterol 500 / 50 µg 2x/d (n = 1682)	Efficacy		RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes, dropouts and deviations assumed at 30% FOLLOW-UP: 91.7% in PPA analysis 99.75% in mITT analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes, 16.9% in UMEC/VI group, 19% in FP/SAL mITT (modified intention to treat): all patients who underwent randomization, received at least one dose of a
			Annual rate of COPD exacerbations (PO) (PPA)	IND/GLY: 3.59 (95% CI: 3.28 to 3.94) FLU/SAL: 4.03 (95% CI: 3.68 to 4.41) Rate ratio: 0.89 (95% CI: 0.83 to 0.96) (represents an 11% lower rate) p = 0.003 IND/GLY is non-inferior to FLU/SAL	
			Annual rate of COPD exacerbation in mITT analysis	IND/GLY: 3.59 (95% CI: 3.29 to 3.92) FLU/SAL: 4.09 (95% CI: 3.75 to 4.46) Rate ratio: 0.88 (95% CI: 0.82 to 0.94) p<0.001 favours IND/GLY	
			Subgroup analysis according to COPD group	Rate Ratio Group B: 0.98 (0.85 to 1.14) NS Rate Ratio Group D: 0.85 (0.78 to 0.92) **SS**	
			trough FEV1 (mITT)	IND/GLY: 15mL FLU/SAL: -48 mL Between-group difference: 62m L; (0.048 to 0.077)	

	older who had COPD with a grade of 2 or higher on the modified Medical Research Council scale (which ranges from 0 to 4, with higher grades indicating more severe dyspnea; a minimum clinically important difference has not been determined), a post-bronchodilator forced expiratory volume in 1 second (FEV1) of at least 25% to less than 60% of the predicted value, and a postbronchodilator ratio of FEV1 to forced vital capacity (FVC) of less than 0.70 at least one COPD exacerbation during the previous year for which they received treatment with systemic glucocorticoids, antibiotic			p<0.001 **SS** **favours IND/GLY**	drug during treatment period, and did not have major violations of compliance with GCP PP (per protocol population): all patients in the mITT who did not have any major protocol deviations SELECTIVE REPORTING: no Other important methodological remarks : one week screening then 4 week run-in period during which all people received tiotropium 18µg 1x/d and then patients were switched on study medication Non-inferiority margin of 15% Sponsor: novartis
			SGRQ total score (mITT)	IND/GLY: -3.1 FLU/SAL: -1.9 Difference: -1.3 95% CI: –2.1 to –0.4 SS p = 0.003	
			Mortality	IND/GLY: n = 24 (1.4%) FLU/SAL: n = 24 (1.4%)	
			Pneumonia	IND/GLY: 53 (3.2%) FLU/SAL: 80 (4.8%)	

	agents, or both <u>Exclusion</u> pregnant or nursing (lactating) women or of child-bearing potential Patients with Type I or uncontrolled Type II diabetes. history of long QT syndrome or whose QTc measured at the start of the run-in epoch was prolonged or a clinically significant electrocardiogram abnormality clinically significant laboratory abnormality clinically significant renal, cardiovascular, arrhythmia, neurological, endocrine, immunological, psychiatric,				

	gastrointestinal, hepatic, or hematological abnormalities Patients with paroxysmal (e.g. intermittent) atrial fibrillation history of malignancy of any organ system Patients who had a COPD exacerbation that resulted in treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1				

Table 78

ZHONG 2015

Study details	n/Population	Comparison	Outcomes		Methodological
Zhong 2015 (13) LANTERN Design: RCT DB PG Duration of follow-up: 26 weeks	n= 744 Mean age: 65.05 y % females: 9.3% currently smoking: 25.9% % taking ICS at inclusion: 54.8% ICS policy: other background medications allowed: SSRI, intra-nasal corticoids, H1 antagonists GOLD (2014)-classification of patients: GOLD B: 53% GOLD D: 47% Baseline FEV1 51.8% predicted % reversibility to salbutamol : 24.05% Exacerbations: ≤1 exacerbation the previous year	Indicaterol / glycopyrronium 110/50 µg 1x/d vs salmeterol / fluticasone 50/500 µg 2x/d	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes/no/unclear Remarks on blinding method: (vrij te omschrijven, schrappen als nvt) POWER CALCULATION: Yes FOLLOW-UP: 99.6% in safety analysis 99.6% in FAS 90.7% in PPS Drop-outs and Exclusions: 9.1% • Described: yes • Balanced across groups: yes ITT: not really defined as such. Two sets:
			trough FEV1 (PO) (non-inferiority on PPS) (superiority on FAS) (LOCF)	FAS: IND/GLY: 1159mL SAL/FLU: 1186 mL Treatment difference in PPS: 72ml 95% CI: 40 to 140 mL no p reported **IND/GLY non-inferior to SAL/FLU** Treatment difference in FAS: 75 mL 95% CI: 44 to 107mL **p<0.001** **SS** **IND/GLY superior to SAL/FLU**	
			Exacerbations	<u>Total number:</u> IND/GLY: 105 SAL/FLU: 131 <u>Rate of exacerbations per year:</u> IND/GLY: 0.59 SAL/FLU: 0.75 Ratio of rate: 0.79 (95% CI : 0.58 to 1.07) NS	

	Inclusion: male and female patients aged ・40 years with moderate-to-severe COPD (stage II and III, as defined in the GOLD 2010 criteria). All patients had a modified Medical Research Council (mMRC) grade ≥2 at screening Exclusion more than one documented COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the year before the screening visit or during the run-in period		TDI focal score	LS square mean change (SE) IND/GLY: 2.91(0.27) SAL/FLU: 2.77 (0.27) Difference 0.13 (-0.20 to 0.47) NS	PPS: per protocol set (=all patients in the full analysis set population without any major protocol deviations) FAS: full analysis set (= all randomized patients who received at least one dose of the study drug) Safety population: all patients who received at least one dose of study drug, regardless of whether the patient was randomized SELECTIVE REPORTING: yes Other important methodological remarks washout period of 1 week and 14 day run-in Sponsor: Novartis
			SGRQ (week 26)	IND/GLY: 31.74 (1.136) SAL/FLU: 32.43 (1.130) Difference: -0.69 (-2.38 to 1.00) NS	
			Hospitalizations	IND/GLY: n =24 SAL/FLU: n =51 no statistical testing	
			Pneumonia	IND/GLY: n = 3 (0.8%) SAL/FLU: n = 10 (2.7%) no statistical testing	

	Patients who have a clinically significant abnormality on the ECG at the run-in Pregnant, lactating or childbearing women Type I or uncontrolled Type II diabetes body mass index of >40 kg/m2 - requiring long-term oxygen therapy (>12 hours a day) on a daily basis - a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous), or hospitalization in the 6 weeks prior to screening - respiratory tract				

	infection within 4 weeks prior to screening - concomitant pulmonary disease				

Table 79

6.1.3.2 *Summary and conclusions*

Bibliography summary RCTs							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Donohue 2015 (51)	706	12 weeks	UMEC/VI 62.5/ 25µg vs FP/SAL 250 /50 µg	Mean age: 62.8y % females: 30% currently smoking: 43% Baseline FEV1:49.4% predicted % reversibility: 11.3%	GOLD 2014 Stage II: 49% Stage III: 51%	6%	Twin trials patients with ≥1 exacerbations the year before screening excluded
Singh_2015 (52)	717	12 w	UMEC/VI 62.5/25 µg vs FP/SAL 250/50 µg	Mean age: 61.8 % fem.: 28% currently smoking: 59% Baseline FEV1 50.6% predicted 10.8% reversibility	Stage B: 55% Stage D: 45%	NR	patients with ≥1 exacerbations the year before screening excluded
Vogelmeier 2013_121 (ILLUMINATE) (11)	523	26w	IND/GLY 110/50µg vs FP/SAL 500/50 µg	Mean age: 63.3 % females: 29.1 currently smoking: 47.9% Baseline FEV1 50.9% predicted % reversibility to salbutamol : 20.4%	GOLD (2009)-classification of patients: moderate: 80.25% severe: 19.75%	35%	dropout of around 17% for both groups
Vogelmeier 2016 (2)	933	24 w	ACL/FOR 400/12 µg vs FP/SAL 500/50 µg	Mean age: 63.4 % females: 34.9% currently smoking: NR Baseline FEV1	GOLD (2015)-classification of patients: Gold B:55.85% Gold D:44.15%	38.3 %	unclear randomisation and allocation concealment approx. 15% dropout, power calculation

				53.3% predicted % reversibility to salbutamol : 11.8%			allowed for 10% all medications except study medication discontinued the night before randomization visit
Wedzicha 2016 (FLAME) (6)	3362	52 w	IND/GLY 110/50 µg vs FP/SAL 500/50 µg	Mean age: 64.6 % females: 23.9 currently smoking: 39.6% Baseline FEV1 44.1% predicted % reversibility to salbutamol : 22.4%	GOLD (2015)-classification of patients: Group B: 24.4% Group C: 0.1% Group D: 74.8%	56.3 %	- noninferiority study (with a 15% margin) - patients had to have at least one exacerbation in the previous year to be included
Zhong 2015 (LANTERN) (13)	744	26 weeks	IND/GLY 110/50 µg vs FP/SAL 500/50 µg	Mean age: 65.05 y % females: 9.3% currently smoking: 25.9% Baseline FEV1 51.8% predicted % reversibility to salbutamol : 24.05%	GOLD (2014)-classification of patients: GOLD B: 53% GOLD D: 47%	54.8 %	- non-inferiority and superiority study - patients excluded if >1 exacerbation in the year before screening visit

Table 80

No meta-analysis or systematic review was found for this comparison, all of the 6 selected studies are RCTs.

All trials have a run-in. All trials were industry sponsored.

They differ in study design: two studies were non-inferiority studies, with one calculating also superiority. Some studies have a high percentage in reversibility to a bronchodilator. The proportion

of patients in COPD categories also vary. Wedzicha 2016 (FLAME) includes people who had at least one exacerbation during the previous year, which is an exclusion criteria for other studies.
There is also a large variation in the percentage of patients taking corticosteroids before study inception. They were always discontinued before or during run-in phase.

Donohue 2015 reports two twin trials. Results reported below are always from the pooled trials.

We are not able to perform a heterogeneity test, but the differences in included populations should be kept in mind.

Endpoint: Trough FEV1		
n=6985 duration: 12 – 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1, ≥1 exacerbation in the previous year sometimes inclusion, sometimes exclusion criteria, % of patients on ICS before study differs a lot between certain studies Imprecision: ok	
Studies	Results	
Donohue 2015	LSM Difference: 0.082 L **†** (0.045 to 0.119)	**SS** **p<0.001** favours UMEC/VI
Singh 2015	LSMD: 0.090 L 95% CI: 0.055 to 0.125 L	**SS** **p<0.001** favours UMEC/VI
Vogelmeier 2013	LSMD: 0.103L 95% CI: 0.065 to 0.141 L	**SS** **p<0.0001** in favour of IND/GLY
Vogelmeier 2016	figures not given	NS p = 0.3635
Wedzicha 2016	Difference: 0.062 L (0.048 to 0.077)	**p<0.001** **SS** favours IND/GLY
Zhong 2015	D: 0.075L* 95% CI: 0.044 to 0.107 L	**p<0.001** **SS** IND/GLY superior* to SAL/FLU
		†pooled results of twin trials ***figures of superiority analysis reported

Table 81

The results of these studies suggest that trough FEV1 is increased with LABA + LAMA compared to LABA + ICS.

For this series of studies,

Most results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: TDI focal score		
(n=2906) duration: 12 -26 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok	
Studies	Results	
Donohue 2015	LSMD: 0.3 (–0.2 to 0.7)	*p* = 0.246 NS
Vogelmeier 2013	LSMD: 0.76 (0.26 to 1.26)	**SS** **p = 0.0031** favours IND/GLY
Vogelmeier 2016	LSMD: -0.001 (-0.46 to 0.46)	NS
Zhong 2015	LSMD: 0.13 (-0.20 to 0.47)	NS

Table 82

The results of these studies suggest that there is no effect.

For this series of studies, most results aren't statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: SGRQ		
(n=6985) duration: 12 – 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1, see trough FEV1 Imprecision: ok	
Studies	Results	
Donohue 2015	LSMD: 0.10 (–1.46-1.67)	NS
Singh 2015	LSMD: 1.11 (-0.30 to 2.75)	NS
Vogelmeier 2013	LSMD: -1.24 (-3.33 to 0.85)	NS
Vogelmeier 2016	*figures not given*	NS
Wedzicha 2016	LSMD: -1.3 (–2.1 to –0.4)	**SS** p = 0.003 favours IND/GLY
Zhong 2015	LSMD: -0.69 (-2.38 to 1.00)	NS

Table 83

The results of these studies do not suggest an effect in any direction.

For this series of studies, most results aren't statistically significant.
As already mentioned above, Wedzicha 2016 (FLAME) selected specifically patients who had gone through an exacerbation.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: exacerbation rates		
(n= 4106) duration: 26-52 weeks	**GRADING** ⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: ok, CI even if not SS shows decrease Directness: -1 for difference in populations Imprecision: ok	
Studies	Results	
Wedzicha 2016	Rate ratio: 0.88 (95% CI: 0.82 to 0.94)	**SS** **p<0.001** **favours IND/GLY**
Zhong 2015	RR: 0.79 (0.58 to 1.07)	NS

Table 84

The results suggest a decrease in the exacerbation rates with LABA/LAMA vs LABA/ICS.

For this series of studies, some results are statistically significant.

It is useful to note that Wedzicha 2016 (FLAME) selected a population at a higher risk of exacerbations than other trials. The trial is also bigger than the other two (provides 81% of patients for this endpoint) and it is of a longer duration (52w).
On top of that Wedzicha performs a pre-specified subgroup analysis according to COPD severity:

- Rate Ratio Group B: 0.98 (0.85 to 1.14), NS
- Rate Ratio Group D: 0.85 (0.78 to 0.92), **SS**

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.1.4 LABA + LAMA vs other LABA + LAMA

6.1.4.1 *Indacaterol + glycopyrronium vs tiotropium + formoterol*

6.1.4.1.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Buhl 2015(16) Design: RCT (DB) (PG) Duration of follow-up: 26 weeks	n= 934 Mean age: 63y % females: 34% Current smoker: 49% % taking ICS at inclusion: 41% ICS policy: patients receiving ICS at baseline continued treatment (or the ICS component alone if taken as a fixed combination with a bronchodilator) at the same or equivalent dose and regimen other background medications allowed: ICS	Indacaterol/ glycopyrronium 110/50 mcg 1x/d Vs Tiotropium 18 mcg 1x/d + formoterol 12 mcg 2x/d Salbutamol as rescue drug	Efficacy		RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.6 % Drop-out and Exclusions: 11 % • Described: yes • Balanced across groups: yes ITT: full analysis set; all randomized
			SGRQ-C (PO)	Difference -0.69 (95%CI -2.31 to 0.92) NS	
			TDI total score	Difference -0.38 (95%CI -0.06 to 0.82) NS	
			Trough FEV1	Indacaterol/ glycopyrronium: Tiotropium + formoterol: **Difference 68 mL (95%CI 37 to 100)** **SS and p<0.001** **In favour of indacaterol/glycopyrronium**	
			Rate of moderate and severe COPD exacerbations Over 26 weeks	Indacaterol/ glycopyrronium: 62 Tiotropium + formoterol: 70 RR 0.85 (95%CI 0.62 to 1.17) NS and p<0.323	
			Pneumonia	Indacaterol/ glycopyrronium: 1/476 Tiotropium + formoterol: 8/457	

	GOLD (2010)-classification of patients: II-III Baseline FEV1 53.2% predicted % reversibility to salbutamol : 19.4% <u>Inclusion:</u> ≥40y ≥10 pack years COPD 2010 gold II or III FEV1 ≥30% and <80% FEV1/FVC <0.7 <u>Exclusion</u> COPD exacerbation in the 6 weeks before screening			**RR 0.12 (95%CI 0.03 to 0.96)** **SS** **In favour of indacaterol/glycopyrronium**	patients were included SELECTIVE REPORTING: yes; not all outcome data reported Other important methodological remarks: Run-in period up to two weeks Sponsor: Novartis
			Patients with serious adverse events	Indacaterol/ glycopyrronium: 30/476 Tiotropium + formoterol: 24/457 RR 1.20 (95%CI 0.72 to 2.01) NS	
			Deaths	Indacaterol/ glycopyrronium: 3/476 Tiotropium + formoterol: 3/457 RR 0.96 (95%CI 0.22 to 4.21) NS	

Table 85

6.1.4.1.2 Summary and conclusions

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Buhl 2015(16)	934	26 weeks	Indacaterol/ glycopyrronium 110/50 mcg 1x/d Vs Tiotropium 18 mcg 1x/d + formoterol 12 mcg 2x/d	Mean age: 63y Females: 34% Current smoker: 49%	II-III	41	not all outcome data reported

Table 86

This double-blind RCT compared a combination of indacaterol and glycopyrronium with tiotropium and formoterol in 934 patients with moderate to severe COPD.

The duration of this RCT was 26 weeks.

This RCT did not report all outcome data.

Endpoint: Trough FEV1		
n=934 26 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 possible selective reporting, only RCT Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Buhl 2015	**Difference 68 mL (95%CI 37 to 100)**	**SS** **In favour of indacaterol/glycopyrronium**

Table 87

The results of these studies suggest that trough FEV1 is increased with indacaterol/glycopyrronium compared to tiotropium + formoterol.

For this study,

The result is statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: SGRQ-C		
n=934 26 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 possible selective reporting, only RCT Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Buhl 2015	Difference -0.69 (95%CI -2.31 to 0.92)	NS

Table 88

The results of this study do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: TDI total score		
n=934 26 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 possible selective reporting, only RCT Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Buhl 2015	Difference -0.38 (95%CI -0.06 to 0.82)	NS

Table 89

The results of this study do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Rate of moderate and severe COPD exacerbations		
n=934 26 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 possible selective reporting, only RCT Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Buhl 2015	RR 0.85 (95%CI 0.62 to 1.17)	NS

Table 90

The results of this study do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.1.4.2 *Umeclidinium + vilanterol vs tiotropium + indacaterol*

6.1.4.2.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Kalberg 2016(53) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 967 Mean age: 64y % females: 28% Current smoker: 43% % taking ICS at inclusion: 53% ICS policy: ICS in stable dose <1000 mcg/day allowed; ICS/LABA combination not allowed other background medications allowed: ICS in stable dose <1000 mcg/day GOLD (2010)-classification of patients: II: 43% III: 46%	Umeclidinium/ vilanterol 62.5/25 mcg 1x/d Vs Tiotropium 18 mcg 1x/d+ indacaterol 150 mcg 1x/d Salbutamol as rescue medication	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.1% Drop-out and Exclusions: 4% • Described: yes • Balanced across groups: yes ITT: Defined as all patients randomized to treatment who received at least one dose of
			Trough FEV1 (PO) 12 weeks	Umeclidinium/ vilanterol: 172 mL Tiotropium + indacaterol: 171 mL LS MD 1 mL (95%CI -29 to 30) Umeclidinium/vilanterol non-inferior to tiotropium + indacaterol	
			Transition Dyspnea Index (TDI) focal score	Umeclidinium/ vilanterol: 2.32 Tiotropium + indacaterol: 2.62 LS MD -0.30 (95%CI -0.65 to 0.05) NS	
			SGRQ total score	Umeclidinium/ vilanterol: -4.93 Tiotropium + indacaterol: -5.01 LS MD 0.08 (95%CI -1.52 to 1.67) NS	
			Non-fatal serious adverse events	Umeclidinium/ vilanterol: 17/482 Tiotropium + indacaterol: 15/479	

	IV: 11% Baseline FEV1 % predicted:NR % reversibility to salbutamol :12.3 <u>Inclusion:</u> ≥40y ≥10 pack years FEV1/FVC <0.7 FEV1 ≤70% predicted Modified Medical Research Council Dyspnea Scale ≥2 QTc <450 or <480 ms (if bundle branch block) <u>Exclusion</u> Of childbearing potential Asthma Other clinically significant disease/abnormality Abnormal ecg Hospitalized for COPD or pneumonia within			NT	randomized study medication
			Fatal adverse events	Umeclidinium/ vilanterol: 4/482 Tiotropium + indacaterol: 1/479 NT	SELECTIVE REPORTING: no Other important methodological remarks: 5-7 day run-in period Margin of non-inferiority for the PO was -50 mL Sponsor: GlaxoSmithKline

	12 weeks prior to visit 1 Long-term oxygen therapy				

Table 91

6.1.4.2.2 Summary and conclusions

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Kalberg 2016(53)	967	12 weeks	Umeclidinium/ vilanterol 62.5/25 mcg 1x/d Vs Tiotropium 18 mcg 1x/d+ indacaterol 150 mcg 1x/d	Mean age: 64y % females: 28% Current smoker: 43%	II: 43% III: 46% IV: 11%	53%	No remarks

Table 92

This double-blind RCT compared a combination of umeclidinium and vilanterol with tiotropium and indacaterol in 967 patients with moderate to very severe COPD.

The duration of this RCT was 12 weeks.

There are no methodological remarks on this study.

Endpoint: trough FEV1		
n=967 12 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: - short duration Imprecision: ok	
Studies	Results	
Kalberg 2016	LS MD 1 mL (95%CI -29 to 30)	Umeclidinium/vilanterol non-inferior to tiotropium + indacaterol

Table 93

The results of these studies do not suggest an effect in any direction.

For this study

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: Transition Dyspnea Index (TDI) focal score	
	GRADING

n=967 12 weeks	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: - short duration Imprecision: ok	
Studies	Results	
Kalberg 2016	LS MD -0.30 (95%CI -0.65 to 0.05)	NS

Table 94

The results of these studies do not suggest an effect in any direction.

For this study

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: SGRQ total score		
n=967 12 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: - short duration Imprecision: ok	
Studies	Results	
Kalberg 2016	LS MD 0.08 (95%CI -1.52 to 1.67)	NS

Table 95

The results of these studies do not suggest an effect in any direction.

For this study

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

6.1.5 Adverse events from RCTs

6.1.5.1 *LABA + LAMA vs LABA*

The meta-analysis by Farne 2015 (40) found **no statistical difference** in SAE between a LABA/LAMA combination and LABA (OR: 0.94 (95% CI: 0.77 to 1.14)). Other studies also report no difference in SAE.

Mortality and **exacerbations** are reported as endpoints in the conlusions, since Farne 2015 performs a statistical analysis. Many studies report those events numerically but do not perform statistical analysis. No differences are seen.

Atrial fibrillation is seldom reported as is. In some studies a subset of patients gets a 12 lead/24 h holter monitoring. Celli 2014 does this and reports no differences.

Pneumonia is again most often reported as an adverse event, and only numerically. One study, Donohue 2016 mentions that the frequency of pneumonia was greater in patients on aclidinium and formoterol vs formoterol , however half of the patients were on ICS. The large percentage of patients taking ICS is a problem when trying to evaluate the risk pneumonia for this comparisons.

6.1.5.2 *LABA + LAMA vs LAMA*

The meta-analysis by Farne 2015 (40) found **no statistical difference** in SAE between a LABA/LAMA combination and LAMA (OR: 1.07 (95% CI: 0.54 to 2.13)). Other studies also report no difference in SAE.

Mortality and **exacerbations** are reported as endpoints in the conlusions, since Farne 2015 performs a statistical analysis.

Some studies report numbers for **mortality**. They are always low. Donohue 2013 lists 9 fatal AE, Mahler 2012 recorded 2 deaths in study 1 and 3 in study 2, all unrelated to study treatment.

Two studies report **exacerbations** as side effets numerically. Mahler 2012 reports 1.1% and 1.6% for the IND/TIO groups (twin trials) and 2.1% and 1.6% for the TIO groups. Mahler 2015 reports “COPD worsening” but here we see a numerical difference: 15.2% of patients IND/GLY group versus 17.4%. However, since no statistical testing is performed, we do not know if this is statistically significant.

Atrial fibrillation is not reported. Some studies mention “adverse cardiovascular effects” (Mahler 2015) or “cardiac arrhytmia’s” (Maleki-Yazdi 2014), with no differences between groups.

Pneumonia was not mentioned.

6.1.5.3 *LABA + LAMA vs LABA + ICS*

Two studies reported on **cardiac arrhythmia** (Donohue 2015 (51) and Singh 2015 (52)) but only numerically, and very low numbers (2 or 3 in each group at most), showing no difference. One study reports on **atrial fibrillation** (Vogelmeier 2013 (11)), with only 1 case in the IND/GLY group and none in the other.

All six included studies report on **pneumonia**, but only numerically, none reports a statistical test. Usually the number is higher in the ICS group, but we don’t know whether that is statistically significant or not. There are usually only a handful of cases except for Wedzicha 2016 (6) (53 pneumonia’s in IND/GLY group, 80 in the FLU/SAL group)

Two studies report **exacerbations** as adverse events; Vogelmeier 2016 (2) performs a statistical test: the difference is not significant.

Finally, Zhong 2015 (13) reports hospitalizations. The number is higher for SAL/FLU group (51) compared with IND/GLY group (24) but again, we don't know if this is statistically significant.

6.1.5.4 *LABA+ LAMA vs other LABA + LAMA*

6.1.5.4.1 Indacaterol/ glycopyrronium Vs tiotropium + formoterol

One RCT (Buhl 2015(16)) found a **statistically significant decrease of pneumonia** with indacaterol + glycopyrronium, compared to tiotropium + formoterol.
There were no statistical differences of patients with **serious adverse events** or of **deaths** between the groups for this comparison.

6.1.5.4.2 Umeclidinium/ vilanterol vs tiotropium + indacaterol

One RCT (Kalberg 2016(53)) found similar rates of **non-fatal serious adverse events** and **fatal adverse events** for umeclidinium + vilanterol versus tiotropium + indacaterol, but no statistical testing was performed.

6.2 Single bronchodilator + inhaled corticosteroids

6.2.1 LABA +ICS vs ICS

6.2.1.1 *Fluticasone + salmeterol vs fluticasone*

6.2.1.1.1 Clinical evidence profile

Meta-analysis: Nannini 2013 (54) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive
pulmonary disease"

Inclusion criteria: Randomised, double-blind, parallel-group clinical trials of at least four weeks' duration comparing combination ICS and LABA with its component ICS alone. Population included were adult patients (age > 40 years) with known, stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society
(ERS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria.
Search strategy: Investigators searched the Cochrane Airways Group Specialised Register of trials (the Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO). The investigators also handsearched respiratory journals and meeting abstracts.
The search was conducted until june 2013.
Assessment of quality of included trials: yes
Other methodological remarks:

- Studies in which the ICS dose in the ICS/LABA arm was less than 80% of the ICS dose in the ICS-only arm were excluded
- trials in which participants were randomly assigned to tiotropium+combined ICS/LABA therapy versus tiotropium+ICS were excluded

Table 96

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini_2013_105 Design: SR+	Fluticasone / salmeterol vs	N= 2 n= 3824 (TORCH, TRISTAN)	Exacerbation rates	OR: 0.88 (0.80 to 0.98) **SS** **(Favours LABA + ICS)**
		N= 5	Amount of participants	OR: 1.0 (0.76 to 1.31)

MA Search date: june 2013	fluticasone	n= 1876 (Hanania 2003, Mahler 2002, SFCT01, Sin 2008, TRISTAN)	with one or more exacerbations	NS
		N= 5 n= 4784 (Hanania 2003, Mahler 2002, SFCT01, TORCH, TRISTAN)	Hospitalisations due to COPD exacerbations	OR: 0.93 (0.79 to 1.10) NS
		N=6 n= 4836 (Hanania 2003, Mahler 2002, NCT00358358, SFCT01, TORCH, TRISTAN)	Mortality	OR: 0.76 (0.62 to 0.92) **SS** **Favours LABA + ICS**
		N= 7 n= 5044 (Hanania 2003, Mahler 2002, NCT 00358358, SFCT01, Sin 2008, TORCH, TRISTAN)	Pneumonia	OR: 1.06 (0.89 to 1.27) NS
		N = 3 n = 4080 (SFCT01, TORCH, TRISTAN)	Change from baseline in SGRQ	SGRQ units: -1.30 (-2.04 to -0.57) SS favours LABA+ ICS
		N= 2 n= 690	Change from baseline in TDI	Mean diff: 0.31 (-0.45 to 1.08) NS

Table 97

FOR THE INFORMATION ON THE INCLUDED RCTS SEE Table 118

6.2.1.1.2 Summary and conclusions

Fluticasone + salmeterol vs fluticasone

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2013 (54)	N= 7 (Hanania 2003, Mahler 2002, NCT 00358358, SFCT01, Sin 2008, TORCH, TRISTAN)	4 weeks to 3 years (most studies 24 or 52 weeks)	LABA/ICS vs ICS broken down into: - FLU/SAL vs FLU (N = 6) - BUD/FOR vs BUD (N = 4) - MOM/FOR vs MOM (N = 2)	COPD poorly reversible mostly	- PO from TORCH was mortality - aside from Sin 2008 (4 w study), all included studies had high dropout rates (±20%)

Table 98

This meta-analysis searched for studies that compared a combination of LABA and ICS with the same ICS. These are the results specifically for the studies comparing fluticasone and salmeterol with fluticasone.

7 RCTs with a duration of 4 weeks (Sin 2008) to 3 years (TORCH) were found.

These studies have similar population, the mean FEV1 % predicted is roughly around 45% and sometimes reversibility to a bronchodilator is an exclusion criteria. Whenever reported, the studies are industry sponsored and have a run-in phase.
Almost all studies had high drop-out rates. For the TORCH study this was up to 38% in the ICS arm. TORCH's primary endpoint was mortality and they obtained data on this endpoints for all patients regardless, which lessens the risk of incomplete outcome date. For other endpoints the large drop-out remains a problem. In most studies the rates in the ICS group were numerically higher than the rate in the LABA/ICS group.
Only one study (TRISTAN) specified that patients needed to have had an exacerbation in the previous year to be included.

Endpoint: trough FEV1
Not reported

Endpoint: Exacerbation rates (per participant per year)	
(n= 3824)	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropout rates

duration: 52 weeks – 3 years	Consistency: ok Directness: ok Imprecision: ok

Studies	Results	
Nannini 2013 (TORCH, TRISTAN)	OR: 0.88 (0.80 to 0.98)	**SS** (Favours LABA + ICS)

Table 99

The result of these studies suggest that exacerbation rates are decreased with LABA + ICS compared to ICS

For this meta-analysis, the result is statistically significant.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: amount of patients with one or more exacerbation	
(n=1876) 4 weeks – 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropouts Consistency: ok Directness: ok Imprecision: ok

Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, SFCT01, Sin 2008, TRISTAN)	OR: 1.0 (0.76 to 1.31)	NS

Table 100

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result isn't statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: hospitalization due to COPD exacerbation	
n= 4784 duration 24w – 3 years	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 for high dropout rates Consistency: ok Directness: ok Imprecision: ok

Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, SFCT01, TORCH, TRISTAN)	OR: 0.93 (0.79 to 1.10)	NS

Table 101

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result isn't statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: mortality (all causes)		
(n=4836) 12 weeks – 3 years	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1, large dropouts Consistency: -1, difference in statistical significance when TORCH removed Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, NCT00358358, SFCT01, TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	OR: 0.78 (0.64 to 0.94)	**SS** **favours combination**
Nannini 2013 Sensitivity analysis Idem as above, without TORCH trial	not reported	NS

Table 102

Some results from the studies suggest a decrease in mortality with LABA+ICS, some suggest that there is no effect.

TORCH was the only trial in Nannini 2013 where mortality was the primary endpoint and showed a decrease in mortality (8554 patients randomized, 3067 for our comparison).
Later in the report it is compared also with SUMMIT (Vestbo 2016), another trial with mortality as PO.

In this meta-analysis, some results are statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Pneumonia		
(n= 5044) duration: 4 weeks to 3 years	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropout rates Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	

Nannini 2013 (Hanania 2003, Mahler 2002, NCT 00358358, SFCT01, Sin 2008, TORCH, TRISTAN)	OR: 1.08 (0.91 to 1.28)	NS

Table 103

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result isn't statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.2.1.2 *Fluticasone + vilanterol vs fluticasone*

6.2.1.2.1 Clinical evidence profile

Meta-analysis: Rodrigo 2016 (55) "A systematic review with meta-analysis of fluticasone furoate/vilanterol combination for the treatment of stable COPD"

Inclusion criteria: Randomized, placebo-controlled trials of >8 weeks of duration were included. Primary end points were pulmonary function, COPD exacerbations and serious adverse events. FF/VI was compared with its mono-components.
To be included, studies had to meet all the following three criteria: 1) patients aged 40 years with a diagnosis of moderate to very severe stable COPD according to current guidelines, 2) comparison of FF/VI 100/25 mcg OD (the approved dose) with fluticasone furoate (FF) 100 mcg OD or vilanterol (VI) 25 mcg OD; and 3) randomized (parallel group or cross-over) controlled trials (RCTs) of >8 weeks of duration.
Search strategy: Published studies were identified from MEDLINE, EMBASE, CINAHL, SCOPUS and the Cochrane Controlled Trials Register (CENTRAL) databases
Assessment of quality of included trials: yes
Other methodological remarks: /

Table 104

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Rodrigo 2016 (55) Design: SR MA Search date: (july 2016)	fluticasone furoate / vilanterol 100/25 µg vs fluticasone furoaat 25µg	N= 2 n= 574 (Kerwin 2013, Martinez 2013)	Trough FEV1	Mean difference: 100 mL (40 to 160 mL) SS p<0.001 (I^2 = 59%) Favours FF/VI
		N=3 n= 9117 (Kerwin 2013, Martinez 2013, Vestbo 2016)	Patients with at least one moderate to severe COPD exacerbation	RR: 0.84 (0.78 to 0.90) SS p<0.000001 (I^2: 0%) Favours FF/VI
		N=3 n= 9117 (Kerwin 2013, Martinez 2013, Vestbo 2016)	Pneumonia	Risk difference: 0.00 (-0.01 to 0.01) NS

		N = 5 n = 9076 (NCT01336608, Dransfield 2013 trial 1, Dransfield 2013 trial 2, Kerwin 2013, Martinez 2013, Vestbo 2016)	All-cause mortality	Risk difference: 0.00 (-0.01 to 0.01) NS

Table 105

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Rodrigo et al.°)
NCT01336608 *unpublished results*	289	Inclusion and exclusion criteria's not reported Baseline char.: Mean baseline post-bronchodil FEV1: 50% predicted Previous COPD exacerbation: NR Current smokers 50% Previous CV history: inclusion criteria	24 weeks	FF/VI 100/25 µg vs VI 25 µg	ALLOCATION CONC: unclear RANDO: adequate BLINDING : Participants/ personnel/: adequate assessors: unclear INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: no FUNDING: Industry-sponsored (bij COPD) COMEDICATION (ICS): NR
Dransfield 2013 (study 1 and study 2) (56)	812 and 812	Inclusion and exclusion criteria's not reported Baseline char.: Mean baseline post-bronchodil FEV1: 46% predicted; and 45% Previous COPD exacerbation: 92%, and 93% Current smokers 46% and 43%	52 weeks	FF/VI 100/25 µg vs VI 25 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: no FUNDING: industry sponsored

		Previous CV history: 63% and 60%			(bij COPD) COMEDICATION (ICS): NR
Kerwin 2013 (57)	617	Inclusion and exclusion criteria's not reported Baseline char.: Mean baseline post-bronchodil FEV1: 47% predicted Previous COPD exacerbation: 20% Current smokers 54% Previous CV history: no	24 weeks	FF/VI 100/25 µg vs VI 25 µg vs FF 100 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: no FUNDING: industry sponsored (bij COPD) COMEDICATION (ICS): NR
Martinez 2013 (56)		Inclusion and exclusion criteria's not reported Baseline char.: Mean baseline post-bronchodil FEV1: 47% predicted Previous COPD exacerbation: 20% Current smokers 54% Previous CV history: no	24 weeks	FF/VI 100/25 µg vs VI 25 µg vs FF 100µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: no FUNDING: industry sponsored (bij COPD) COMEDICATION (ICS): NR
Vestbo 2016 SUMMIT (19)	12374	Inclusion and exclusion criteria's not reported Baseline char.: Mean baseline post-bronchodil FEV1: 59% predicted Previous COPD exacerbation: 39% Current smokers 46% Previous CV history: inclusion criteria%	162 weeks	FF/VI 100/25 µg vs VI 25 µg vs FF 100µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: no FUNDING: industry sponsored <u>Other remarks:</u> 48 hour run in (which is considered short)

Table 106

6.2.1.2.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Rodrigo 2016 (55)	N = 6	24 weeks to 3 years and 6 weeks	Fluticasone furoate / vilanterol vs fluticasone furoate	COPD - patients were included only if previous CV incident in 2 studies - in some studies almost all patients had an exacerbation in the previous year (Dransfield 2013), some few (±20%) (Kerwin 2013 and Martinez 2013)	- I^2 for pooling of Trough FEV1 outcome = 59% (other outcomes I^2=0%) - PO from SUMMIT (Vestbo 2016) was mortality

The systematic review and meta-analysis searched for studies that compared fluticasone and vilanterol with fluticasone alone (or vilanterol alone, not reported here).
6 RCTs were included in the meta-analysis. Of those 6, one is an unpublished trial, and 2 are twin trials. Duration is at least 24 weeks, and for one study over 3 years (SUMMIT / Vestbo 2016).

Two trials specifically included people with a previous cardiovascular history (SUMMIT / Vestbo 2016, and an unpublished one). Whenever reported, the trials are industry-sponsored.

Definitions for exacerbations were mostly similar (hospitalization and / or oral corticoids due to worsening of symptoms). Some studies also included need for antibiotic treatment as criteria for exacerbation.

Endpoint: Trough FEV1		
(n= 574) 24 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 for high I^2 Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Rodrigo 2016 (Kerwin 2013, Martinez 2013)	Mean difference: 100 mL (40 to 160 mL)	**SS** **p<0.001** Favours LABA+ICS

The results of these studies suggest that trough FEV1 is increased with fluticasone + vilanterol compared to fluticasone

For this meta-analysis, the result is statistically significant.
Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

The population selected in the two studies had a low rate of exacerbations in the previous year.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Patients with at least one moderate to severe COPD exacerbation		
(n = 9117) 24 weeks – 3 years	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1, other studies of LABA/ICS vs ICS or FLU/SAL vs FLU are NS Directness: ok Imprecision: ok	
Studies	Results	
FLU+VIL vs FLU *Rodrigo 2016* (Kerwin 2013, Martinez 2013, Vestbo 2016)	RR: 0.84 (0.78 to 0.90)	**SS** p<0.000001 **Favours FLU + VIL**

The results of these studies suggest that there is a decrease in the amount of patients with at least one moderate to severe exacerbation with fluticasone + vilanterol compared to fluticasone

The population selected in the three studies from Rodrigo 2016 had a low rate of exacerbations in the previous year.

We have moderate confidence that the results of the studies in Rodrigo 2016 reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Mortality (all cause)		
(n= 16594) 12 weeks – 3 years	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for differences in previous exacerbations and CV history Imprecision: ok	
Studies	Results	
Rodrigo 2016 (NCT01336608, Dransfield 2013 trial 1, Dransfield 2013 trial 2,	Risk difference: 0.00 (-0.01 to 0.01)	NS

Kerwin 2013, Martinez 2013, Vestbo 2016)		

The results from the studies suggest no effect on mortality with fluticasone + vilanterol vs fluticasone.

SUMMIT (Vestbo 2016) is the largest trial, with the longest duration of all the included trials and has mortality as PO. It randomized 16590 patients with cardiovascular comorbidities, 8256 of which were included in these analyses.

In this meta-analysis, the result isn't statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Pneumonia		
(n = 9117) 6 mo weeks to 3 years	**GRADING** ⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Rodrigo 2016 (Kerwin 2013, Martinez 2013, Vestbo 2016)	Risk difference: 0.00 (-0.01 to 0.01)	NS

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result is not statistically significant.

The population selected in the three studies had a low rate of exacerbations in the previous year.

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

6.2.1.3 *Budesonide + formoterol vs budesonide*

6.2.1.3.1 Clinical evidence profile

Meta-analysis: Nannini 2013 (54) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease"

See Table 96

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini_2013_105 Design: SR+ MA Search date: june 2013	Budesonide/ formoterol vs budesonide	N= 4 n= 1777 (Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012)	Exacerbation rates	OR: 0.84 (0.73 to 0.97) **SS** **(Favours LABA + ICS)**
		N= 3 n= 1371 (Calverley 2003, Tashkin 2008, Zhong 2012)	Hospitalisation due to COPD exacerbation	OR: 0.85 (0.60 to 1.20) NS
		N= 4 n= 1777 (Calverley 2003, Szafrasnski 2003, Tashkin 2008, Zhong 2012)	Mortality	OR: 1.13 (0.54 to 2.37) NS
		N = 3 n= 1371 (Calverley 2003, Tashkin 2008, Zhong 2012)	Pneumonia	OR: 1.11 (0.47 to 2.63) NS

FOR THE INFORMATION ON THE INCLUDED RCTS SEE Table 118

6.2.1.3.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2013	N= 4 n = 1777 (Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012)	24 w – 52 weeks	budesonide & formoterol vs budesonide	COPD poorly reversible ≥1 exacerbation in the previous year	- high dropout rates overal, slightly better for Tashkin 2008 (up to 22%), worse for Szafranski 2003 (up to 31% in one group) - unclear randomisation and blinding for Calverley 2003 - Tashkin 2008 had patients continue ICS during run-in and then switched to study medication without washout

Table 107

This systematic review and meta-analysis searched for studies that compared a combination of LABA and ICS with the same ICS. These are the results specifically for the studies comparing budesonide and formoterol with budesonide.

4 RCT's with a duration of 6 months to 1 year were found.

These studies have similar patient population: all studies included patients with ≥1 exacerbations during the previous year. No study has a substantially larger patients population than others (range from 308 patients (Zhong 2012) to 511 (Calverley 2003)).

There are methodological issues with the high drop-out rates, with the difference between LABA/ICS and the ICS drop-outs percentages, and with the different set-ups of the run-in phase.

Endpoint: trough FEV1
Not reported

Endpoint: Exacerbation rates (per participant per year)		
(n=1652) duration: 6 mo to 1 y	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: - 1, high dropout rates, lack of wash-out in one study Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013	OR: 0.84 (0.73 to 0.97)	**SS**

(Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012)		(Favours BUD + FOR)

Table 108

The results of these studies suggest that exacerbation rates are decreased with budesonide + formoterol compared to budesonide

For this meta-analysis,

The results are statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: hospitalization due to COPD exacerbation		
(n= 1371) duration: 6 mo – 1 year	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: - 1, high dropout rates, lack of wash-out in one study Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Calverley 2003, Tashkin 2008, Zhong 2012)	OR: 0.85 (0.60 to 1.20)	NS

Table 109

The results of these studies do not suggest an effect.

For this meta-analysis,

No result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Mortality		
(n= 1777) duration: 6 months – 1 year	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: ok Directness: ok Imprecision: -1, large CI	
Studies	Results	
Nannini 2013 (Calverley 2003, Szafrasnski 2003, Tashkin 2008, Zhong 2012)	OR: 1.13 (0.54 to 2.37)	NS

Table 110

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result is not statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Pneumonia		
(n= 1371) duration : 24 to 52 weeks	**GRADING** ⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: ok Directness: ok Imprecision: -1, large CI	
Studies	Results	
Nannini 2013 (Calverley 2003, Tashkin 2008, Zhong 2012)	OR: 1.11 (0.47 to 2.63)	NS

Table 111

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result is not statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

6.2.1.4 *Mometasone + formoterol vs mometasone*

6.2.1.4.1 Clinical evidence profile

Meta-analysis: Nannini 2013 (54) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease" See Table 96

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini_2013_105 Design: SR+ MA Search date: june 2013	Mometasone / formoterol vs mometasone	n/a	Exacerbation rates	n/a
		N= 2 n= 905 (Doherty 2012, Tashkin 2012)	Amount of participants with one or more exacerbations	OR: 0.67 (0.45 to 0.98) **SS** **Favours LABA + ICS**
		N= 2 n= 905 (Doherty 2012, Tashkin 2012)	Hospitalisations due to COPD exacerbations	OR: 1.46 (0.66 to 3.21) NS
		N= 2 n=905 (Doherty 2012, Tashkin 2012)	Mortality	0.89 (0.27 to 2.91) NS
		N= 2 n = 905	Pneumonia	OR: 1.92 (0.66 to 5.57) NS

		(Doherty 2012, Tashkin 2012)		

FOR THE INFORMATION ON THE INCLUDED RCTS SEE Table 118

6.2.1.4.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2013	N= 2 n= 905 (Doherty 2012, Tashkin 2012)	26-52 weeks	mometasone & formoterol vs mometasone	copd, poorly reversible	- high drop outs (around 20%)

Table 112

This meta-analysis searched for studies that compared a combination of LABA and ICS with the same ICS. These are the results specifically for the studies comparing mometasone and formoterol with mometasone.

2 RCTs were found, one of 6 months, one of 1 year.

These studies have similar number of patients included, and a similar population. Compared to other studies from Nannini 2013 the % of FEV1 predicted is on the low end (38-40%), as were the selection criteria's (post-bronchodilator had to be <60% for both)

There are methodological issues with the drop-out rates.

Endpoint: trough FEV1
Not reported

Endpoint: Exacerbation rates
Not reported

Endpoint: amount of participants with one or more exacerbations		
(n=905) 24 weeks-52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: - 1 for high dropouts Consistency: -1, pooled LABA/ICs vs ICS and other LABA/ICS combinations are not SS Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Doherty 2012, Tashkin 2012)	OR: 0.67 (0.45 to 0.98)	**SS** **Favours MOM + FOR**

Table 113

The results of these studies suggest that the amount of participants with one or more exacerbation is decreased with LABA/ICS compared to ICS.

For this meta-analysis, the result was statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Hospitalizations due to exacerbation		
(n= 905) duration: 6 mo – 1 y	**GRADING** ⨁⨁⊖⊖ **LOW** Study quality: - 1 for high dropouts Consistency: ok Directness: ok Imprecision: -1 for large CI	
Studies	Results	
Nannini 2013 (Doherty 2012, Tashkin 2012)	OR: 1.46 (0.66 to 3.21)	NS

Table 114

The results of these studies do not suggest an effect on hospitalizations due to exacerbations for of mometasone and formoterol vs mometasone.

For this meta-analysis, the result isn't statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Mortality		
(n= 905) duration: 6 mo – 1 year	**GRADING** ⨁⨁⊖⊖ **LOW** Study quality: - 1 for high dropouts Consistency: ok Directness: ok Imprecision: -1 for large CI	
Studies	Results	
Nannini 2013 (Doherty 2012, Tashkin 2012)	0.89 (0.27 to 2.91)	NS

Table 115

The results of these studies do not suggest an effect on mortality.

For this meta-analysis, the result isn't statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Pneumonia

(n= 905) duration: 6 mo – 1 year	**GRADING** ⨁⨁⊖⊖ **LOW** Study quality: - 1 for high dropouts Consistency: ok Directness: ok Imprecision: -1 for large CI

Studies	Results	
Nannini 2013 (Doherty 2012, Tashkin 2012)	OR: 1.92 (0.66 to 5.57)	NS

Table 116

The results of these studies do not suggest an effect on pneumonia.

For this meta-analysis, the result isn't statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

6.2.1.5 *All combined LABA + ICS vs ICS*

6.2.1.5.1 Clinical evidence profile

Meta-analysis: Nannini 2013 (54) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease" See Table 96

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini_2013 (54) Design: SR+ MA Search date: june 2013	LABA + ICS vs ICS (ALL COMBINED)	N= 6 n= 5601 (TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012)	Exacerbation rates (per participant per year)	OR: 0.87 (0.80 to 0.94) SS (Favours LABA + ICS)
		N= 7 n= 2781 (Hanania 2003, Mahler 2002, SFCT01, Sin 2008, TRISTAN, Doherty 2012, Tashkin 2012)	Amount of participants with one or more exacerbations	OR: 0.87 (0.70 to 1.09) NS
		N= 10 n= 7060 (Hanania 2003, Mahler 2002, SFCT01, TORCH, TRISTAN, Calverley 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin	Hospitalisations due to exacerbations	OR: 0.93 (0.80 to 1.07) NS

		2012)		
		N= 12 n= 7518 (Hanania 2003, Mahler 2002, NCT00358358, SFCT01, TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	Mortality	OR: 0.78 (0.64 to 0.94) **SS** **(Favours LABA + ICS)**
		N= 12 n= 7320 (Hanania 2003, Mahler 2002, NCT0358358, SFCT01, Sin 2008, TORCH, TRISTAN, Calverley 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	Pneumonia	OR:1.08 (0.91 to 1.28) NS

Table 117

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Nannini et al.)
Calverley 2003 (58) RCT DB PG	511	- GOLD defined COPD (stages 3 and 4); ≥ 40 years - COPD symptoms > 2 years; smoking history ≥ 10 pack-years - FEV1/VC ≤ 70% pre-BD; FEV1 ≤ 50% predicted - use of SABAs as reliever medication	52 weeks	Budesonide / formoterol vs budesonide	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: high risk (40% withdrawal on ICS, 29% withdrawal on LABA+ICS)

		- ≥ 1 COPD exacerbation requiring OCS/antibiotics 2 to 12 months before 1st clinic visit - poorly reversible population - mean FEV1 36% predicted			SELECTIVE REPORTING: low risk OTHER BIAS: FUNDING: GlaxoSmithKline COMEDICATION (ICS): ICS aside from study medication not allowed
Doherty 2012 (59) RCT PC DB	478	Inclusion: - males or females ≥ 40 years old - with FEV1/FVC ≤ 0.70, with a post-bronchodilator FEV1 of 25% to 60% predicted - symptoms of COPD for at least 24 months before enrolment; current or ex-smokers with ≥ 10 pack-year history; no use of parenteral steroids, oral steroids or antibiotics within 4 weeks before screening - clinically acceptable laboratory tests at screening Exclusion: exhibited marked bronchodilator reversibility (increase in FEV1 ≥ 400 mL) Baseline lung function: mean % predicted FEV1 (SD) post BD: 38.1 (10.8) MF/F, 40.2 (11.7)	52 weeks	Mometasone furoate / formoterol (MF) vs formoterol (F)	ALLOCATION CONC: unclear RANDO: unclear BLINDING : adequate INCOMPLETE OUTCOME DATA: unclear risk (15 % withdrawal on M/F and 20% on F) SELECTIVE REPORTING: low risk FUNDING: Merck Sharp & Dohme Corp COMEDICATION (ICS): washed out during run-ins
Hanania 2003 (60) RCT PG DB	366	Inclusion: - stable COPD, FEV1 40% to 65% predicted, FEV1/FVC <70% predicted - symptoms of chronic bronchitis and moderate dyspnoea Exclusion: current diagnosis of asthma, use of oral	24 weeks	Fluticasone propionate / salmeterol vs fluticasone propionate	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk (30% withdrawal on FPS and 27% on fluticasone) SELECTIVE REPORTING: low risk

		steroids in past 6 weeks, abnormal ECG, LTOT, moderate to severe exacerbation in run-in. Other significant medical disorder Baseline characteristic: mean FEV1: 1.27 L (42% predicted) FEV1 reversibility < 12%			FUNDING: NR COMEDICATION (ICS): NR
Mahler 2002 (61) PG RCT	333	Inclusion: participants with COPD according to ATS guidelines. - Baseline pre-bronchodilation FEV1 < 65% predicted and > 0.70 L. Baseline prebronchodilation FEV1/FVC < 70% predicted. - Age > 40 - 20 pack-year history smoking - day or night symptoms present on 4 out of last 7 days during run-in period Exclusion: current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, LTOT, moderate to severe exacerbation in run-in. Baseline characteristics: Mean FEV1 reversibility 11.0%	24 weeks	Fluticasone propionate / salmeterol vs fluticasone	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk (30% withdrawal on FPS and 27% on FP) SELECTIVE REPORTING: low risk FUNDING: NR COMEDICATION (ICS): NR
NCT00358358 Data extracted from: (62)	81	Inclusion: Males or females of non-childbearing potential ≥ 40 years of age were eligible to participate if they had an established clinical history of COPD,	12 weeks	fluticasone propionate / salmeterol 500/50 µg vs	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/ personnel/ assessors: low risk INCOMPLETE OUTCOME DATA:

		evidence of bronchitis as a component of the COPD disease and a current or prior history of at least 10 pack-years of cigarette smoking. Participants had measured post-albuterol FEV1/FVC ≤ 70% at Visit 1 (screening) and measured post-albuterol FEV1 ≥ 30% and ≤ 70% of predicted normal		fluticasone propionate 500µg	unclear risk (10% withdrew on FPS and 17% on F) SELECTIVE REPORTING: low risk FUNDING: GlaxoSmithKline COMEDICATION (ICS): not reported
SFCT01 *unpublished study obtained from ctr.gsk.co.uk* RCT PG DB	256	Inclusion: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-year; FEV1 < 70% predicted and > 800 mL; reversibility < 10% predicted normal (and <200 mL) Exclusion: not described	52 weeks	fluticasone propionate / salmeterol 500/50 µg vs fluticasone propionate 500 µg	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk SELECTIVE REPORTING: low risk FUNDING: GlaxoSmithKline COMEDICATION (ICS): not reported
Sin 2008 (63)	179	Inclusion: - FEV1 of less than 80% of predicted with an FEV1 to FVC ratio of less than 0.70 (post-bronchodilator values). - Cigarette smoking history of more than 10 pack-years, clinical stability as defined by the absence of exacerbations for at least 4 weeks, age ≥ 40 years and absence of known chronic systemic infections or inflammatory conditions Exclusion: - any known disseminated malignancy, known chronic systemic infection	4 weeks	fluticasone propionate / salmeterol 500/50 µg vs fluticasone propionate 500 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk FUNDING: GlaxoSmithKline COMEDICATION (ICS): all withdrawn during a pre-study phase

		or inflammatory condition - previous solid organ transplantation, - myocardial infarction or cerebrovascular accident within the past 3 months before study enrolment			
Szafranski 2003 (64) RCT PG	406	Inclusion: - age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack-years; FEV1 ≤ 50% predicted; FEV1/FVC ≤ 70%; - use of bronchodilators for reliever medication - ≥ 1 severe COPD exacerbation within 2 to 12 months before study entry Baseline characteristics: mean age: 64 years; mean FEV1 % predicted: 36%; mean reversibility 6% predicted normal	52 weeks	budesonide / formoterol 320/9 µg vs budesonide 9 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: high risk (28% withdrew on BDF and 31% on BUD) SELECTIVE REPORTING: low risk FUNDING: not reported COMEDICATION (ICS): stopped during run-in
Tashkin 2008 (65) RCT DB PC PG	552	Inclusion: - ≥ 40 years of age. - Clinical diagnosis of COPD and symptoms for > 2 years - a history of at least 1 COPD exacerbation treated with a course of oral corticosteroids and/or antibiotics within 1 to 12 months before screening (visit 1), - use of an inhaled SABA as rescue medication - pre-bronchodilator FEV1 ≤ 50% of predicted normal, pre-bronchodilator FEV1/FVC < 70% - Smoking history ≥ 10 pack-years, score	6 months	budesonide / formoterol 320/9µg vs budesonide 320µg	ALLOCATION CONC: unclear RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk, (14.1% withdrawal on BUD/FOR and 22.9% on BUD alone) SELECTIVE REPORTING: low risk FUNDING: astra zeneca COMEDICATION (ICS): participants continued their usual ICS during run-in but anticholinergics were switched to ipratropium bromide. ICS were stopped at the beginning

		≥ 2 on the modified MRC dyspnoea scale Exclusion: - If additions or alterations to their usual COPD maintenance therapy needed or an increment in rescue therapy due to worsening symptoms within 30 days before screening or during the run-in period - history of asthma or allergic rhinitis before 40 years of age - significant/ unstable cardiovascular disorder - clinically significant respiratory tract disorder other than COPD Baseline lung function: mean % predicted FEV1 (SD) post-bronchodilator: 39.05 (11.78) Sym, 39.72 (12.01) bud			of study and participants were then given study medication
Tashkin 2012 (66) RCT PG DB	427	Inclusion: - adult males and females who were current or former smokers with a smoking history of ≥ 10 pack-years - ≥ 40 years of age, diagnosis of moderate to very severe COPD, based on a pre-bronchodilator FEV1/forced vital capacity (FVC) ratio ≤0.70. - Symptoms of COPD (chronic cough and sputum production not attributable to	26 weeks	Mometasone furoate / formoterol 400/10 gμ vs mometasone furoaat 400 μg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: high risk, 19% withdrew on MF/F and 22% on MF SELECTIVE REPORTING: no FUNDING: Merck Sharp & Dohme Corp

		another disease process) for ≥ 24 months, post-bronchodilator FEV1 ≤ 60% predicted normal and ≥ 25% predicted normal at screening Exclusion: - patients with an increase in absolute volume ≥400mL at the screening visit or before the baseline visit within 30 minutes after administration of 4 inhalations of albuterol/salbutamol (total dose of 360 to 400 mcg) or nebulised 2.5 mg albuterol/salbutamol. - Patients requiring long-term administration of oxygen (.15 hours per day) - patients who experienced an exacerbation of COPD requiring medical intervention within four weeks before randomisation, -blocking agents Baseline characteristics: Baseline FEV1 AUC(0-12 h); LS mean mL 1186 (MF/F), 1255 (MF).			COMEDICATION (ICS): discontinued during open label run-in period SABA and anticholinergic fixed-dose combination was given
TORCH (20) RCT PG	3091	Inclusion: M/F 40 to 80 years of age; diagnosis of COPD (ERS); < 10% reversibility of predicted FEV1; FEV1/FVC ratio < 70%; FEV1 < 60% predicted; ≥ 10 pack-year smoking history	156 weeks	fluticasone / salmeterol 500/50 µg vs fluticasone 500 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: all adequate INCOMPLETE OUTCOME DATA: 34.1% withdrew on FPS and 38.3% on fluticasone, except for mortality (vital status was checked in for

		Exclusion: asthma or respiratory diseases other than COPD; LVRS/lung transplant; requirement for > 12 hours/d LTOT; long-term OCS therapy; serious uncontrolled disease likely to interfere with medication/cause of death in next three years			those who withdrew) SELECTIVE REPORTING: low risk FUNDING: GlaxoSmithKline COMEDICATION (ICS): two weeks run in, all maintenance treatment with ICS and LABA ceased
TRISTAN (67) RCT PG	733	Inclusion criteria: baseline FEV1 25% to 75% predicted; FEV1/ FVC ratio ≤70%; poor reversibility < 10% increase of predicted FEV1 30 minutes after inhaling 400 mcg salbutamol; at least 10 pack-year smoking history; history of exacerbations (at least 1 in the last year) requiring OCS and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years Exclusion criteria: respiratory disorders other than COPD. Oxygen treatment, systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the 2-week run-in period Baseline characteristics: mean age 63 years, mean FEV1 1.26 L (44% predicted)	52 weeks	fluticasone propionate / salmeterol 50/500 µg vs fluticasone propionate 500 µg	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk, 25% withdrew on FPS and 29% on fluticasone SELECTIVE REPORTING: low risk FUNDING: COMEDICATION (ICS): Run-in: 2 weeks. All maintenance treatment with ICS and LABA ceased

Zhong 2012 RCT DB PG	308	Inclusion criteria: male or female outpatients ≥ 40 years with diagnosis of COPD; prebronchodilator FEV1 ≤ 50% predicted; FEV1/FVC < 70%; at least 1 COPD exacerbation (defined as use of oral/IV corticosteroids and/or antibiotics and/or emergency room treatment/hospitalisation due to respiratory symptoms) during 2 to 12 months before the study; a smoking history of ≥ 10 pack-years Exclusion criteria: a history of asthma; seasonal allergic rhinitis with onset < 40 years; COPD exacerbation within 4 w of study entry or during the run-in period; post-bronchodilator FEV1 ≥ 80% of predicted normal value during the reversibility test at baseline; any other serious diseases or disorders that were considered to influence the study results or to increase the risk of participation in the study Baseline characteristics: COPD severity: BUD/FOR moderate: 7 (4.5%) severe: 98 (62.8%) very severe: 51 (32.7%) BUD only moderate: 5 (3.3%) severe: 94 (61.8%),	24 w	budesonide / formoterol (160 / 4.5 µg/dose) 2x/d vs budesonide 200 µg/dose 2x/d	ALLOCATION CONC: adequate RANDO: adequate BLINDING : Participants/ personnel/ assessors: adequate INCOMPLETE OUTCOME DATA: high risk, 14.7% withdrew on BDF and 23% withdrew on bud SELECTIVE REPORTING: low risk FUNDING:Astra Zeneca COMEDICATION (ICS): no other bronchodilator except trial medication and rescue was allowed

		very severe: 53 (34.9%) Baseline lung function (post-bronchodilator): mean % predicted FEV1 (SD): 36.15% (10.97) for group BUD/FOR, 36. 28 (10.40) for group BUD			

Table 118

6.2.1.5.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2013 (54)	N= 12 (Hanania 2003, Mahler 2002, NCT00358358, SFCT01, TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012	4 weeks to 3 years (most studies 24 or 52 weeks)	LABA/ICS vs ICS broken down into: - FLU/SAL vs FLU (N = 6) - BUD/FOR vs BUD (N = 4) - MOM/FOR vs MOM (N = 2)	COPD poorly reversible mostly	- 10 out of 12 studies reported high drop-out rates (around 20% usually but one even up to 38% dropout in one arm) - PO from TORCH was mortality

Table 119

This systematic review and meta-analysis searched for studies that compared a LABA and an ICS with the same ICS.

In Nannini 2013 twelve RCTs with a duration from 4 weeks (only one) to 3 years of were found. Two were unpublished trials.

The studies selected in Nannini often have the following profile: mean % of FEV1 predicted in Nannini 2013 is overall roughly around 40-45% (when reported). The studies selected in Nannini 2013 often have a high drop-out and withdrawal rate, almost all studies report rates around 20%, some much higher. Numerically drop-outs in the ICS group are always higher.
Whenever reported, the trials are industry-sponsored.

Endpoint: Exacerbation rates (per participant per year)		
(n= 5601) 24 weeks – 3 years	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropout rates Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012)	OR: 0.87 (0.80 to 0.94)	**SS** (Favours LABA + ICS)

Table 120

The results of these studies suggest that exacerbation rates are decreased with LABA + ICS compared to ICS.
For this meta-analysis,
The results are statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: amount of patients with one or more exacerbation		
(n=2781 for pooled analysis) 4 weeks – 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropouts Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, SFCT01, Sin 2008, TRISTAN, Doherty 2012, Tashkin 2012)	OR: 0.87 (0.70 to 1.09)	NS

Table 121

The results of these studies suggest that there is a decrease in the amount of patients with at least one moderate to severe exacerbation with LABA + ICS compared to ICS

The odds ratio for the studies examining mometasone + formoterol vs mometasone was statistically significant.

We have moderate confidence that the results of the studies in Nannini 2013 reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: hospitalization due to COPD exacerbation		
(n= 7060) 24 weeks – 52 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 for high dropout rates Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, SFCT01, TORCH, TRISTAN, Calverley 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	OR: 0.93 (0.80 to 1.07)	NS

Table 122

The results of these studies do not suggest an effect in any direction.

For this meta-analysis, the result isn't statistically significant.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Mortality (all cause)		
(n= 16594) 12 weeks – 3 years	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1, large dropouts Consistency: -1, see explanation below Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, NCT00358358, SFCT01, TORCH, TRISTAN, Calverley 2003, Szafranski 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	OR: 0.78 (0.64 to 0.94)	**SS** **favours combination**
Nannini 2013 Idem as above, without TORCH trial	not reported	NS

The results from the studies suggest a decrease in mortality with LABA+ICS versus ICS.

However, TORCH was the only trial in Nannini 2013 where mortality was the primary endpoint and showed a decrease in mortality (8554 patients randomized, 3067 for our comparison). Other results in Nannini 2013 show no effect.
Another large trial had mortality as PO, and was published after this meta-analysis (and reported elsewhere as part of a meta-analysis by Rodrigo 2016). This trial was the SUMMIT (Vestbo 2016), which used another combination of LABA and ICS: fluticasone and vilanterol. It randomized 16590 patients with cardiovascular comorbidities, 8256 of which were included in the analyses by Rodrigo 2016, but showed no effect on mortality, and also not when pooled with other results. Both of these large-scale trials, who give most weight to the analyses, lasted 3 years.
This motivates our removal of 1 point for consistency.

In these meta-analyses, the result is statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Pneumonia

Endpoint: Pneumonia	
(n = 7320) (n = 9117 Rodrigo) 4 weeks to 3 years	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: - 1 for high dropout rates Consistency: ok Directness: ok Imprecision: ok

Studies	Results	
Nannini 2013 (Hanania 2003, Mahler 2002, NCT0358358, SFCT01, Sin 2008, TORCH, TRISTAN, Calverley 2003, Tashkin 2008, Zhong 2012, Doherty 2012, Tashkin 2012)	OR: 1.08 (0.91 to 1.28)	NS

The results of these studies do not suggest an effect in any direction.

For this series of studies, no result is statistically significant.

We have moderate to low confidence that the results of the studies reflect the true effect.
GRADE: MODERATE to LOW quality of evidence

6.2.2 LABA + ICS vs LAMA

6.2.2.1 *Clinical evidence profile*

Meta-analysis: Welsh 2013(68) "Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease" Inclusion criteria: RCTs with parallel group design >12 weeks; population: diagnosis of COPD, comparison combination ICS and LABA versus tiotropium bromide. Search strategy: systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts. Latest search November 2012. Assessment of quality of included trials: yes Other methodological remarks:/

Table 123

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Welsh 2013(68) Design: SR/ MA Search date: (November-2012)	fluticasone/ salmeterol vs tiotropium	N= 2 n= 1448 (INSPIRE, SCO40034)	Mortality (all-cause)	**Peto OR: 0.55 (0.33 to 0.93)*** **SS** **Favours fluticasone/salmeterol** *result from INSPIRE only, as SCO40034 recorded no events
		N= 2 n= 1448 (INSPIRE, SCO40034)	Hospital admissions	**Peto OR: 1.32 (1.04 to 1.67)** **SS** **Favours tiotropium**
				Peto OR: 0.53 (0.05 to 5.22) NS
		N= 1 n= 1323 (INSPIRE)	Exacerbations (number of patients experiencing one or more exacerbations over two years)	OR 1.13 (0.91 to 1.41) NS
		N= 1	Exacerbations (mean number of	Rate ratio 0.97 (0.84 to 1.12)

		n= 1323 (INSPIRE)	exacerbations per patient per year)	NS
		N= 1 n= 1323 (INSPIRE)	SGRQ at 104 weeks	**MD -2.07 (-4.02 to -0.12)** **SS** **Favours fluticasone/salmeterol**
		N= 1 n= 1323 (INSPIRE)	FEV1 at 2 years	MD -0.02L (-0.05 to 0.01) NS
		N= 2 n= 1448 (INSPIRE, SCO40034)	Serious adverse events	**Peto OR: 1.55 (1.21 to 1.92)** **SS** **Favours tiotropium**
				Peto OR: 0.53 (0.05 to 5.22) NS
		N= 2 n= 1448 (INSPIRE, SCO40034)	Pneumonia	**Peto OR: 2.13 (1.33 to 3.40)*** **SS** **Favours tiotropium** *result from INSPIRE only, as SCO40034 recorded no events

Table 124

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
INSPIRE(69) RCT double blind	1323	**Baseline characteristics**: mean age 64 years. FEV1 39% predicted. Inhaled corticosteroids used previously by 50% of participants. Exacerbation in previous 12 months in 86%of participants. 48%of participants on FPS and 51%on tiotropium stopped taking	104 weeks	fluticasone/salmeterol 500/50 mcg 2x/d vs	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk: 35% withdrew in fluticasone/salmeterol group and

		inhaled corticosteroids at baseline **Inclusion criteria**: aged 40 to 80 years, with a smoking history of 10 o rmore pack-years, a clinical history of COPD exacerbations, post-bronchodilator FEV1 less than 50% of predicted, bronchodilator reversibility of less than 10% in FEV1 to 400 mg salbutamol, score of 2 or more on the Modified Medical Research Council dyspnoea scale **Exclusion criteria**: asthma or atopic disease, a lung disease likely to confound the drug response other than COPD, a recent exacerbation (within 6 weeks of screening or during run-in); receiving long-termoxygen therapy or pulmonary rehabilitation or had a known or suspected hypersensitivity to beta2-agonists, inhaled corticosteroids, anticholinergic agents or any components of these formulations		tiotropium 18 mcg 1x/day	42% from tiotropium group FUNDING: GlaxoSmithKline COMEDICATION (ICS): Participants were allowed to use short-acting inhaled beta2-agonists and standardized short courses of oral corticosteroids
SCO40034(70) RCT double-blind	125	**Population**: 125 adults with a clinical history of moderate to severe COPD as defined by the Global Initiative for Obstructive Lung Disease 2001 guidelines **Inclusion criteria**: aged 40 to 80 years inclusive. Post-bronchodilator FEV1 less than 70% of predicted normal. Participants must have had a smoking history (current or former smokers) of more than 10 pack-years. Mean FEV1 1.4 L	12 weeks	fluticasone/salmeterol 500/50 mcg 2x/d vs tiotropium 18 mcg 1x/day	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk: small but imbalanced withdrawals (more from tiotropium arm) FUNDING: GlaxoSmithKline

		Exclusion criteria: within 4 weeks prior to visit 1; COPD exacerbation; received oral, parenteral or depot corticosteroids for a COPD exacerbation; received antibiotic therapy and/or been hospitalised for either a lower respiratory tract infection or for COPD exacerbation, or had any changes in their COPD medication			

Table 125

Remarks:

We searched the studies that were excluded from this systematic review. None met our inclusion criteria (because of duration, sample size, or unpublished status).

Study details	n/Population	Comparison	Outcomes		Methodological
Covelli 2016(71) Design: RCT (DB) (PG)	n= 623 Mean age: 62 y % females: 35.5% Smoking: current 52% % taking ICS at	Fluticasone/ vilanterol 100/25 mcg 1x/d	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes
			Trough FEV1	Fluticasone/vilanterol: 0.098 L tiotropium: 0.093 L LS MD 0.005 L (95%CI -0.029 to 0.039) NS	

Duration of follow-up: 12 weeks	inclusion: NR ICS policy: only allocated treatment other background medications allowed: mucolytics, rescue salbutamol GOLD (2010)-classification of patients: II-III Baseline FEV1 49% predicted % reversibility to salbutamol : NR <u>Inclusion:</u> ≥40 years ≥10 packyears FEV1 ≥30% to ≤70% of predicted FEV1/FVC <70% History of CVD event OR current smoker + CV risk factor (hypertension ,	Vs tiotropium 18 mcg 1x/d rescue medication: salbutamol	SGRQ score	LS MD -1.38 (95%CI -3.38 to 0.62) NS	Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.6% Drop-out and Exclusions: 8.6 % • Described: yes • Balanced across groups: no; fluticasone/vilanterol 5.8% tiotropium 11.5% ITT: defined as "all subjects randomized to treatment and who had received at least one dose of study medication" SELECTIVE REPORTING: no Other important methodological remarks: 2 week placebo run-in Sponsor: GlaxoSmithKline
			Serious adverse events	Fluticasone/vilanterol: 10/310 tiotropium: 10/313 NT	
			Cardiovascular effects	Fluticasone/vilanterol: 13/310 tiotropium: 15/313 NT	
			Pneumonia	Fluticasone/vilanterol: 3/310 tiotropium: 0/313 NT	

	hypercholesterolemia, treated diabetes) Female : effective contraception or postmenopauzal <u>Exclusion</u> asthma or other respiratory disorders clinically significant abnormal X-ray, laboratory, Holter or ECG at screening recent≤12 weeks hospitalization for COPD recent ≤6 week acute worsening of COPD oxygen therapy >12h/d noncompliance				

Table 126

6.2.2.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Welsh 2013(68)	N=2 (INSPIRE(69), SCO40034(70))	12-104 weeks	LABA +ICS v vs tiotropium (both RCTs studies fluticasone/ salmeterol vs tiotropium)	COPD	• High and unbalanced dropout in one RCT (INSPIRE)

Table 127

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Covelli 2016{Covelli, 2016 #151	623	12 weeks	Fluticasone/ vilanterol 100/25 mcg 1x/d Vs tiotropium 18 mcg 1x/d	Mean age: 62 y % females: 35.5% Smoking: current 52% CVD history or current smoker + CVD risk factor	II-III	NR	unbalanced dropout: more in tiotropium group

Table 128

A systematic review and meta-analysis searched for RCTs that compared LABA/ICS combination with tiotropium, in adults with a COPD diagnosis.

Two RCTs with a duration of 12 to 104 weeks were found. Both compared fluticasone/salmeterol to tiotropium.

One of both RCTs had high (>30%) and unbalanced dropout (more dropout in the tiotropium group). This could lead to bias and limits our confidence in the results.

An additional RCT, published after the final search date of the systematic review described above, compared fluticasone/vilanterol to tiotropium in COPD patients with moderate to severe COPD and at higher CVD risk.

The duration of this RCT was 12 weeks.

This RCT had unbalanced dropout with more dropout in the tiotropium group. This could lead to bias even if the dropout was <20%.

Endpoint: Mortality		
n=1448 12-104 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 high unbalanced dropout Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE, SCO40034) n= 1448	**Peto OR: 0.55 (0.33 to 0.93)***	**SS** **Favours fluticasone/salmeterol**

Table 129

The results of these studies suggest that mortality is decreased with fluticasone/salmeterol compared to tiotropium.

For this meta-analysis,

The result is statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: FEV1		
n=1946 12- 104 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 high unbalanced dropout Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE) n= 1323	MD -0.02L (-0.05 to 0.01)	NS
Covelli 2016 n=623	LS MD 0.005 L (95%CI -0.029 to 0.039)	NS

Table 130

The results of these studies do not suggest an effect in any direction.

For this series of studies,

No result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: SGRQ		
n=1946 12- 104 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1 high unbalanced dropout Consistency: -1 Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE) n= 1323	**MD -2.07 (-4.02 to -0.12)**	**SS** **Favours fluticasone/salmeterol**
Covelli 2016 n=623	LS MD -1.38 (95%CI -3.38 to 0.62)	NS

Table 131

The results of these studies suggest that SGRQ score is decreased with fluticasone/salmeterol compared to tiotropium.

For this series of studies,
Some are significant, some are not (50/50)
Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations (number of patients experiencing one or more exacerbations over 2 years)		
n=1323 104 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 high unbalanced dropout Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE) n= 1323	OR 1.13 (0.91 to 1.41)	NS

Table 132

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,
The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Exacerbations (mean number of exacerbations per patient per year)		
n=1323 104 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 high unbalanced dropout Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE) n= 1323	Rate ratio 0.97 (0.84 to 1.12)	NS

Table 133

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Hospital admissions		
n= 1448 12-104 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1 high unbalanced dropout Consistency: -1 Directness: ok Imprecision: ok	
Studies	Results	
Welsh 2013 (INSPIRE) n= 1323	**Peto OR: 1.32 (1.04 to 1.67)**	**SS** **Favours tiotropium**
Welsh 2013 (SCO40034) n= 125	Peto OR: 0.53 (0.05 to 5.22)	NS

Table 134

The results of these studies suggest that hospital admissions are increased with fluticasone/salmeterol compared to tiotropium.

For this series of studies,

Some are significant, some are not (50/50)

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

6.2.3 LABA + ICS vs LABA

6.2.3.1 *Fluticasone + salmeterol vs salmeterol*

6.2.3.1.1 Clinical evidence profile

Meta-analysis: Nannini 2012(72) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease"

Inclusion criteria:
Double-blind RCTs. Population: adult COPD patients, no exacerbation for one month prior to entry. Comparison: fluticasone and salmeterol versus salmeterol; budesonide and formoterol versus formoterol
Search strategy:
Last search November 2011
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts." "In addition, we performed a search of LILACS (all years to March 2011) and CENTRAL"
Assessment of quality of included trials: yes
Other methodological remarks:/

Table 135

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini 2012(72) Design: SR+MA Search date: November 2011	Fluticasone & salmeterol Vs salmeterol	N= 4 n= 5397 (TRISTAN, TORCH, Ferguson 2008, Anzueto 2009)	Exacerbations (requirement for oral steroids)	**Rate ratio: 0.71 (95%CI 0.62 to 0.81)** **SS** **In favour of fluticasone + salmeterol**
		N= 3 n= 4879 (Kardos 2007, TORCH, Anzueto 2009)	Exacerbations (hospitalisation)	Rate ratio: 0.79 (95%CI 0.55 to 1.13) NS

		N= 6 n= 6868 (TORCH, SCO 100470, TRISTAN, Kardos 2007, Ferguson 2008, Anzueto 2009)	Mortality	OR 0.93 (95%CI 0.76 to 1.13) NS
		N= 6 n= 7441 (SCO 100470, TRISTAN, TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009)	SGRQ – total score	**-1.58 (95%CI -2.15 to -1.01)** **SS** **In favour of fluticasone+ salmeterol**
		N= 5 n= 2390 (Mahler 2002, Hanania 2003, O'Donnell 2006, Ferguson 2008, Anzueto 2009)	Trough FEV1	**0.07 L (95%CI 0.05 to 0.10)** **SS** **In favour of fluticasone + salmeterol**
		N= 9 n= 8242 (SCO 100470, Mahler 2002, O'Donnell 2006, Hanania 2003, TRISTAN,	Adverse events- pneumonia	**OR: 1.75 (95%CI 1.25 to 2.45)** **SS** **In favour of salmeterol (less pneumonia with salmeterol)**

		TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009)		
		N= 2 n= 677 (Mahler 2002, Hanania 2003)	Change from baseline in transitional dyspnoea index (TDI)	MD 0.61 (-0.47 to 1.68) NS

Table 136

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group°)
Anzueto 2009(73)	797	Mean age: 65.4. Mean FEV1: 0.98L INCLUSION: aged ≥40 yrs. History ≥ 10 pack-years, a pre-albuterol FEV1/FVC ≤ 0.70, a FEV1 ≤ 50% of predicted normal and a documented history of at least 1 COPD exacerbation the year prior to the study that required treatment with antibiotics, oral corticosteroids, and/or hospitalisation. EXCLUSION: current diagnosis of asthma, a respiratory disorder other than COPD, historical or current evidence of a clinically significant uncontrolled disease, or had a COPD exacerbation that was not resolved at	52 weeks	Fluticasone/salmeterol 250/50 2x/d Vs Salmeterol 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (39% discontinued on salmeterol and 32% on fluticasone/salmeterol) SELECTIVE REPORTING: Low risk

		screening			
Ferguson 2008(74)	782	Mean age: 64 years; mean FEV1: 0.94L. INCLUSION: 40 years of age or older with a diagnosis of COPD,16 a cigarette smoking history of greater than or equal to 10 pack-years, a pre-albuterol FEV1/FVC of 0.70 or less, a FEV1 of 50% of predicted normal or less and a history of one or more exacerbations of COPD in the year prior to the study that required treatment with oral corticosteroids, antibiotics, or hospitalisation. EXCLUSION: diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening.	52 weeks	Fluticasone/salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Unclear risk (method unclear) INCOMPLETE OUTCOME DATA: High risk (38% discontinued on salmeterol and 30% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
Hanania 2003(75)	360	mean age: 64; mean FEV1: 1.27 L (42% predicted). INCLUSION: stable COPD, FEV1 40-65% predicted, FEV1/FVC < 70% predicted, symptoms of chronic bronchitis and moderate dyspnoea. EXCLUSION: current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, LTOT, moderate - severe exacerbation in run-in. Other	24 weeks	Fluticasone/salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Unclear risk (No information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on salmeterol and 30% on combination) SELECTIVE REPORTING: High risk

		significant medical disorder.			(not all outcome data reported) FUNDING: GlaxoSmithKline
Kardos 2007(76)	994	64 years. 40% predicted FEV1; mean reversibility 7% predicted; Mean duration of COPD: 11 years. INCLUSION: M/F ≥40 years of age; diagnosis of severe or very severe COPD (according to GOLD criteria III or IV); FEV1 <50% predicted at visit 1 (FEV1 ±20% of visit one at visit two); 2 exacerbations prompting medical consultation in previous 12 months; Smoking history of >10 pack years. EXCLUSION: Exacerbtion in 4 weeks prior to visit 1; LTOT; chronic systemic steroids.	52 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	ALLOCATION CONC: Low risk RANDO: Low risk) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (21% withdrew on salmeterol and 20% on combination) SELECTIVE REPORTING: Low risk FUNDING: GlaxoSmithKline
Mahler 2002(77)	325	Mean age: 63; FEV1: 1.2-3 L. INCLUSION: Participants with COPD according to ATS guidelines. Baseline pre-bronchodilation FEV1 < 65% predicted and > 0.70L. Baseline prebronchodilation FEV1/FVC < 70% predicted. Age > 40, 20 pack-year history smoking, day or night symptoms present on 4 out of last 7 days during run-in period. EXCLUSION: history of asthma, corticosteroid use in last 6 weeks, abnormal ECG, oxygen therapy, moderate or severe exacerbation during run-in, significant concurrent	24 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (28% withdrew on salmeterol and 32% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline

		disease.			
SCO 100470(78)	1050	Mean age: 64 years; FEV1: 1.67L; am PEF: 274; SGRQ: 48. INCLUSION: M/F 40-80 years of age; diagnosis of COPD (according to GOLD criteria); ≥ 2 on MRC dyspnoea scale; poor reversibility of < 10% predicted normal (and < 200 mL); FEV1/FVC ratio < 70% predicted; ≥10 pack year smoking history. EXCLUSION: Not described.	24 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (14% withdrew on salmeterol and 11% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GSK
TORCH(79)	3088	65 years; Male: 76%. INCLUSION: M/F 40-80 years of age; diagnosis of COPD (ERS); <10% reversibility of predicted FEV1; FEV1/FVC ratio <70%; FEV1< 60% predicted; ≥10 pack year smoking history. EXCLUSION: Asthma or respiratory diseases other than COPD; LVRS/lung transplant; requirement for >12hrs/day LTOT; long-term OCS therapy; 'serious uncontrolled disease likely to interfere with medication/cause death in next three years'.	156 weeks (3 years)	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (36.9 % withdrew on salmeterol and 34.1 % on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
TRISTAN(22)	730	Mean age 63 years, mean FEV1 = 1.26 L (44% predicted). INCLUSION: Baseline FEV1 25 - 75%	52 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/

		predicted; FEV1/ FVC ratio ≤ 70%; Poor reversibility: < 10% increase of predicted FEV1 30 minutes after inhaling 400 mcg salbutamol; at least 10 pack years smoking history; history of exacerbations (at least 1 in the last year) requiring OCS and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years. EXCLUSION: respiratory disorders other than COPD. Oxygen treatment, systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the 2 week run-in period.		Vs Salmeterol 50 mcg 2x/	assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32 % withdrew on salmeterol and 25% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
O'Donnell 2006(80)	*126*		*8 weeks*		*RCT did not meet our inclusion criteria (minimum 12 weeks' duration)*

Table 137

Study details	n/Population	Comparison	Outcomes		Methodological
Ohar 2014(81) Design: RCT (DB) (PG)	n= 639 Mean age: 63y % females: 46% Smoking: NR % taking ICS at inclusion: NR	Fluticasone/ salmeterol 250/50 mcg 2x/d Vs	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes
			Severe exacerbations (PO) Mean annualized rate	Fluticasone/salmeterol: 0.44 salmeterol: 0.48 Ratio: 0.92 (95%CI 0.58 to 1.45) NS and p=0.710	
			Moderate/severe	Fluticasone/salmeterol: 1.49	

Duration of follow-up: 26 weeks	ICS policy: not allowed outside of allocated treatment other background medications allowed: All background COPD medications, with the exception of inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA), alone or in combination, were allowed GOLD (yr)-classification of patients: NR Baseline FEV1 40% predicted % reversibility to salbutamol : 14 <u>Inclusion:</u> ≥40y ≥10 pack years FEV1 ≤70% predicted Recent (≤14 days)	Salmeterol 50 mcg 2x/d	exacerbations (PO) Mean annualized rate	salmeterol: 1.81 Ratio: 0.82 (95%CI 0.64 to 1.06) NS and p=0.136	Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 3% Drop-out and Exclusions: 33% • Described: yes • Balanced across groups: salmeterol 35%; combination 31% ITT: Yes, all eligible patients randomized to study treatment SELECTIVE REPORTING: no (describe if yes) Other important methodological remarks : 21-day stabilization period after randomization Sponsor: GlaxoSmithKline
			Trough FEV1	Fluticasone/salmeterol: 0.14 salmeterol: 0.04 **LS MD: 0.10 (95%CI 0.04 to 0.16)** **SS in favour of fluticasone/salmeterol**	
			Pneumonia	Fluticasone/salmeterol: 13/314 salmeterol: 10/325 NT	
			Fatal AEs	Fluticasone/salmeterol: 4/314 salmeterol: 3/325 NT	
			Severe AEs	Fluticasone/salmeterol: 75/314 salmeterol: 82/325 NT	

	history of exacerbation requiring hospitalization, emergency room observation ≥24h during which OCS was administered or physician's office or emergency room visit of <24 hours with OCS treatment PLUS 6-month history of exacerbation-related hospitalization Exclusion Pneumonia, or other complicating comorbid condition while hospitalized in last 6 months Clinically significant uncontrolled disease				

Table 138

6.2.3.1.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2012(72)	N=9 (TORCH(79), SCO 100470(78), TRISTAN(22), Kardos 2007(76), Ferguson 2008(74), Anzueto 2009(73), Mahler 2002(77), Hanania 2003(75), O'Donnell 2006(80))	8weeks -3 years	fluticasone and salmeterol versus salmeterol	adult COPD patients, no exacerbation for one month prior to entry.	• One RCT did not meet our inclusion criterium for duration (O'Donnel 2006) • 5 RCTs had unclear allocation concealment (SCO100470, Ferguson 2008, Anzuaeto 2009, Mahler 2002, Hanania 2003) • 3 RCTs had an unclear randomization method (SCO100470, Mahler 2002, Hanania 2003) • 1 RCT had an unclear blinding method (Ferguson 2008) • 7 RCTs had high drop-out (>20%, often unbalanced) (TORCH, TRISTAN, Kardos 2007, Ferguson 2008, Anzueto 2009, Mahler 2002, Hanania 2003) • 6 RCTs reported selectively (TORCH, SCO100470, TRISTAN, Ferguson 2008, Mahler 2002, Hanania 2003)

Table 139

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Ohar 2014(81)	639	26 weeks	Fluticasone/ salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	Mean age: 63y % females: 46% Smoking: NR INCLUSION CRITERIUM : Recent (≤14 days) history of exacerbation requiring	FEV1 ≤70% predicted	NR	high dropout: 33% (salmeterol 35%; combination 31%)

				hospitalization, emergency room observation ≥24h during which OCS was administered or physician's office or emergency room visit of <24 hours with OCS treatment PLUS 6-month history of exacerbation-related hospitalization			

Table 140

A systematic review and meta-analysis searched for RCTs that compared a combination of fluticasone and salmeterol to salmeterol alone, in adult COPD patients who did not have an exacerbation for one month prior to entry.

9 RCTs were found, with a duration ranging from 8 weeks to 156 weeks (3 years).

One of the 9 RCTs did not meet our inclusion criterium for duration. 5 RCTs had unclear allocation concealment, 3 RCTs had an unclear randomization method, and 1 RCT had an unclear blinding method. 7 RCTs had high drop-out, ranging from 28% to 39%. This drop-out was often unbalanced between groups. 6 RCTs reported selectively. These methodological remarks severely limit our confidence in the results.

An additional RCT, published after the final search date of the systematic review described above, also compared a combination of fluticasone and salmeterol to salmeterol alone in 539 adult COPD patients. Contrary to the RCTs in the systematic review, this RCT specifically included patients who had a recent (<14 days) history of an exacerbation requiring hospitalisation.

The duration of this RCT was 26 weeks.

Like the RCTs included in the systematic review, this RCT had high drop-out (33% of all randomized participants). This limits our confidence in the results.

Endpoint: Mortality	
n=6868 24 weeks – 3 years	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: ok Directness: ok

	Imprecision: ok	
Studies	Results	
Nannini 2012 (TORCH, SCO 100470, TRISTAN, Kardos 2007, Ferguson 2008, Anzueto 2009) n= 6868	OR 0.93 (95%CI 0.76 to 1.13)	NS

Table 141

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Trough FEV1		
n= 3029 8 weeks – 52 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (Mahler 2002, Hanania 2003, O'Donnell 2006, Ferguson 2008, Anzueto 2009) n= 2390	**0.07 L (95%CI 0.05 to 0.10)**	**SS** **In favour of fluticasone + salmeterol**
Ohar 2014 n=639	**LS MD: 0.10 (95%CI 0.04 to 0.16)**	**SS** **in favour of fluticasone/salmeterol**

Table 142

The results of these studies suggest that trough FEV1 is increased with fluticasone/salmeterol compared to salmeterol alone.

For this series of studies,

All results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: SGRQ- total score

n= 7441 24 weeks – 3 years	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (SCO 100470, TRISTAN, TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009) n= 7441	**-1.58 (95%CI -2.15 to -1.01)**	**SS** **In favour of fluticasone+ salmeterol**

Table 143

The results of these studies suggest that SGRQ total score is decreased with fluticasone/salmeterol compared to salmeterol alone.

For this meta-analysis,

The results is statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: TDI		
n=677 24 weeks	**GRADING** ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: -1 (I^2 >70%) Directness: ok Imprecision: -1 (wide CI)	
Studies	Results	
Nannini 2012 (Mahler 2002, Hanania 2003) n= 677	MD 0.61 (-0.47 to 1.68)	NS

Table 144

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.

GRADE: VERY LOW quality of evidence

Endpoint: Moderate/severe exacerbations (mean annualized rates)		
n=639 26 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 very high dropout (>30%) Consistency: NA Directness: -1 only COPD patients with very recent hospitalization for exacerbation Imprecision: ok	
Studies	Results	
Ohar 2014 n=639	Ratio: 0.82 (95%CI 0.64 to 1.06)	NS

Table 145

The results of these studies do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Exacerbations (requiring oral steroids)		
n=5397 1-3 years	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (TRISTAN, TORCH, Ferguson 2008, Anzueto 2009) n= 5397	**Rate ratio: 0.71 (95%CI 0.62 to 0.81)**	**SS** **In favour of fluticasone + salmeterol**

Table 146

The results of these studies suggest that the number of exacerbations requiring oral steroids is decreased with fluticasone/salmeterol compared to salmeterol alone.

For this meta-analysis,

the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: severe exacerbations (requiring hospitalisation)

n= 5518 1-3 years	**GRADING** ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment Consistency: -1 (I^2=70%) Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (Kardos 2007, TORCH, Anzueto 2009) n= 4879	Rate ratio: 0.79 (95%CI 0.55 to 1.13)	NS
Ohar 2014 n=639	Rate Ratio: 0.92 (95%CI 0.58 to 1.45)	NS

Table 147

The results of these studies do not suggest an effect in any direction.

For this series of studies,

No result is statistically significant

We have very low confidence that the results of the studies reflect the true effect.

GRADE: VERY LOW quality of evidence

6.2.3.2 *Budesonide + formoterol vs formoterol*

6.2.3.2.1 Clinical evidence profile

Meta-analysis: Nannini 2012(72) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease"

Inclusion criteria:
Double-blind RCTs. Population: adult COPD patients, no exacerbation for one month prior to entry. Comparison: fluticasone and salmeterol versus salmeterol; budesonide and formoterol versus formoterol
Search strategy:
Last search November 2011
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts." "In addition, we performed a search of LILACS (all years to March 2011) and CENTRAL"
Assessment of quality of included trials: yes
Other methodological remarks:/

Table 148

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini 2012(72) Design: SR+MA Search date: November 2011	Budesonide & formoterol Vs formoterol	N= 4 n= 3442 (Calverley 2003, Rennard 2009, Szafranski 2003, Tashkin 2008)	SGRQ – change scores	**-2.69 (95%CI -3.82 to -1.55)** **SS** **In favour of budesonide + formoterol**
		N= 2 n= 1203 (Tashkin 2008,	Trough FEV1	MD 0.05 (95%CI 0.00 to 0.009) NS

		Rennard 2009)		
		N= 4 n= 3243 (Calverley 2003, Szafranski 2003, Tashkin 2008, Rennard 2009)	Serious adverse events	OR 0.92 (95%CI 0.69 to 1.25) NS

Table 149

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group°)
Calverley 2003(82)	509	mean age: 64; mean FEV1 L: 1; mean FEV1 % predicted: 36; mean SGRQ: 48. INCLUSION: GOLD defined COPD (stages III and IV); ≥ 40 years; COPD symptoms >2 years; smoking history ≥ 10 pack years; FEV1/VC ≤ 70% pre-BD; FEV1 ≤ 50% predicted; use of SABAs as reliever medication; >/= 1 COPD exacerbation requiring OCS/antibiotics 2-12 months before 1st clinic visit. EXCLUSION: History of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention	12 months	Budesonide/formoterol 320/9 mcg 2x/d Vs Formoterol 9 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Unclear risk (No information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (44% withdrew on formoterol and 29% on combination) SELECTIVE REPORTING: High risk (not all outcomes reported) FUNDING: AstraZeneca (bij COPD) COMEDICATION (ICS):

		within 4 weeks of run-in/during run-in phase			non-allowed medications: O2 therapy; ICS - (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, BD (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, ß-blocking agents
Rennard 2009(83)	1483	Mean age: 63 years. FEV1 1L. INCLUSION: Moderate to very severe COPD with previous exacerbations age > 40 years, diagnosis of symptomatic COPD for >2 years, >10 pack-year smoking history, pre-bronchodilator FEV1 of < 50% of predicted normal and prebronchodilator FEV1/FVC of <70%. Patients were to have a Modified Medical Research Council dyspnoea scale score of >2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1-12 months before the first study visit. EXCLUSION: I) a history of asthma; (ii) a history of allergic rhinitis before 40 years of age; (iii) significant/unstable cardiovascular disorder; (iv) clinically significant respiratory tract disorder (v) homozygous -1 antitrypsin deficiency. Oral or ophthalmic non-cardioselective	12 months	Budesonide/formoterol 160/4.5 mcg 2x/d Vs Budesonide/formoterol 80/4.5 mcg 2x/d vs Formoterol 4.5 mcg 2x/d Vs placebo	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on formoterol and 28% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: AstraZeneca

		-adrenoceptor antagonists, oral corticosteroids, pregnancy and breast-feeding.			
Szafranski 2003(84)	409	Mean age: 64 years mean FEV1 %predicted: 36%, mean reversibility 6% predicted normal. INCLUSION: Age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack years; FEV1 ≤ 50% predicted; FEV1/FVC ≤ 70%; Symptom score ≥ 2 during at least 7 days of run-in; use of bronchodilators for reliever medication; ≥ 1 severe COPD exacerbation within 2-12 months before study entry. EXCLUSION: history of asthma/rhinitis before age of 40; using beta-blockers; current respiratory tract disease other than COPD.	52 weeks	Budesonide/formoterol 320/9 mcg 2x/d Vs Formoterol 9 mcg 2x/d	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on formoterol and 28% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: AstraZeneca
Tashkin 2008(85)	1129	Mean age: 63.5 years; FEV1: 1.04L. INCLUSION: Moderate to very severe COPD with previous exacerbations age > 40 years, diagnosis of symptomatic COPD for >2 years, >10 pack-year smoking history, pre-bronchodilator FEV1 of < 50% of predicted normal and prebronchodilator FEV1/FVC of <70%. Patients were to have a Modified Medical Research Council dyspnoea scale score of >2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1-12 months before the first study visit.	6 months	budesonide/formoterol pressurised metered dose inhaler (pMDI) 160/4.5 µg 2x/d vs budesonide/formoterol pMDI 80/4.5 µg 2x/d vs budesonide pMDI 160 µg 2x/d plus formoterol dry powder inhaler (DPI) 4.5 µg	ALLOCATION CONC: Unclear (information not available) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (21% withdrew on formoterol and 14% on combination) SELECTIVE REPORTING: Unclear risk (not all outcome data reported) FUNDING: AstraZeneca

		EXCLUSION: I) a history of asthma; (ii) a history of allergic rhinitis before 40 years of age; (iii) significant/unstable cardiovascular disorder; (iv) clinically significant respiratory tract disorder (v) homozygous -1 antitrypsin deficiency. Oral or ophthalmic non-cardioselective -adrenoceptor antagonists, oral corticosteroids, pregnancy and breast-feeding.		2x/d vs budesonide pMDI 160 µg 2x/d; vs formoterol DPI 4.5 µg 2x/d; vs placebo	

Table 150

Study details	n/Population	Comparison	Outcomes		Methodological
Fukuchi 2013(86) Design: RCT (DB) (PG) Duration of follow-up:	n= 1293 Mean age: 65y % females: 11% Smoking: Current: 34% Former:66% % taking ICS at inclusion: NR ICS policy: no ICS use permitted outside of allocated intervention other background	Budesonide/ formoterol 2x 160/4.5 mcg 2x/day Vs formoterol 2x 4.5 mcg 2x/day	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP:
			Trough FEV1 (PO)	Formoterol/budesonide: 44mL formoterol: 14mL **ratio 1.032 (95%CI 1.013 to 1.052)** **P=0.0011** **SS in favour of formoterol/budesonide**	
			COPD exacerbations (number of patients)	Formoterol/budesonide: 76/636 formoterol: 111/657 NT	
			COPD exacerbations (number of exacerbations)	Formoterol/budesonide: 93 formoterol: 151	

12 weeks	medications allowed: none GOLD (yr)-classification of patients: II to III Baseline FEV1 36% predicted 14% reversibility to salbutamol : <u>Inclusion:</u> • ≥40y • Moderate to severe COPD • FEV1≤50% predicted • FEV1/FVC <70% • ≥10 pack years • At least one COPD exacerbation in last 12 months <u>Exclusion</u> • Asthma or atopy • Significant cardiovascular disease • COPD exacerbation in 4 weeks prior to enrollment or			**p=0.0006** **SS in favour of formoterol/budesonide**	Lost-to follow-up: NR Drop-out and Exclusions:7.6% • Described: yes • Balanced across groups: combination: 6.6%; formoterol: 8.5% ITT: Unclear, not defined SELECTIVE REPORTING: yes, not all outcome data reported Other important methodological remarks: 1-2 week run-in with formoterol Sponsor: AstraZeneca
			SGRQ total score	Formoterol/budesonide: -4.37 formoterol: -2.90 **-1.60 (95%CI -3.08 to -0.11)** **P=0.035** **SS in favour of formoterol/budesonide**	
			Pneumonia	Formoterol/budesonide: 3 formoterol: 1 NT	
			Death	Formoterol/budesonide: 4 formoterol: 5 NT	
			Serious AE other than death	Formoterol/budesonide: 39 formoterol: 41 NT	

	during run-in • Using oxygen therapy				

Table 151

Study details	n/Population	Comparison	Outcomes		Methodological
Sharafkhaneh 2012(87) Design: RCT (DB) (PG) Duration of follow-up: 12 months	n= 1219 Mean age: 63y % females: 38% Smoking: Current smoker: 36% Ex-smoker: 64% % taking ICS at inclusion: 28% ICS policy: only allocated treatment other background medications allowed: none GOLD (2010)-classification of patients: ≥III	Budesonide/ formoterol 2x 320/9 mcg 2x/d OR Budesonide/ formoterol 2x 160/9 mcg 2x/d Vs Formoterol 2x 9 mcg 2x/d albuterol as	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 2% Drop-out and Exclusions: 28% • Described: yes • Balanced across groups: lower in the combination groups (29%) than in the formoterol
			Number of COPD exacerbations (PO) per patient-treatment year	BUD/FORM 320/9 vs FORM **Ratio 0.654 (95%CI 0.535 to 0.798)** **SS and p<0.001** **In favour of BUD/FORM 320/9** BUD/FORM 160/9 vs FORM **Ratio 0.741 (95%CI 0.610 to 0.899)** **SS and p=0.002** **In favour of BUD/FORM 160/9**	
			Trough FEV1	BUD/FORM 320/9: 0.07 BUD/FORM 160/9: 0.07 FORM: 0.04 BUD/FORM vs FORM	

	Baseline FEV1 37.6% predicted % reversibility to salbutamol : NR <u>Inclusion:</u> ≥40y ≥10 pack years ≥1 COPD exacerbation within 1-12 months before screening FEV1 ≤50% predicted FEV1/FVC <70% <u>Exclusion</u> (planned) enrollment in a COPD pulmonary rehabilitation program Treatment with OCS	rescue medication		**P< 0.05** **SS in favour of BUD/FORM**	group (33%) ITT: All randomized patients who received ≥1 dose of study medication and contributed sufficient data for ≥1 efficacy end point SELECTIVE REPORTING: yes; not all outcome data provided Other important methodological remarks : 2-week run-in period Sponsor: AstraZeneca
			SGRQ	BUD/FORM 320/9: -7.2 BUD/FORM 160/9: -5.5 FORM: -5.9 BUD/FORM vs FORM NS	
			Serious adverse events	BUD/FORM 320/9: 76/407 BUD/FORM 160/9: 54/408 FORM: 68/403 NT	
			Pneumonia	BUD/FORM 320/9: 5/407 BUD/FORM 160/9: 2/408 FORM: 0/403 NT	

Table 152

6.2.3.2.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2012(72)	N=4 (Calverley 2003(82), Rennard 2009(83), Szafranski 2003(84), Tashkin 2008(85))	6-12 months	Budesonide & formoterol Vs formoterol	adult COPD patients, no exacerbation for one month prior to entry.	• 3 RCTs had unclear allocation concealment (Calverley 2003, Rennard 2009, Tashkin 2008) • 2 RCTs had unclear randomization method (Calverly 2003, Rennard 2009) • 3 RCTs had high dropout (>20%) (Calverley 2003, Rennard 2009, Szafranski 2003) • All RCTs had unclear or high risk of selective reporting

Table 153

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Fukuchi 2013(86)	1293	12 weeks	Budesonide/ formoterol 2x 160/4.5 mcg 2x/day Vs formoterol 2x 4.5 mcg 2x/day	Mean age: 65y % females: 11% Smoking: Current: 34% Former:66%	II to III	NR	Unclear randomization and allocation concealment Not all outcome data reported
Sharafkhaneh 2012(87)	1219	12 months	Budesonide/ formoterol 2x 320/9 mcg 2x/d OR Budesonide/ formoterol 2x 160/9 mcg 2x/d Vs	Mean age: 63y % females: 38% Smoking: Current smoker: 36% Ex-smoker: 64%	≥III	28%	high drop-out: lower in the combination groups (29%) than in the formoterol group (33%) SELECTIVE REPORTING: yes; not all outcome data provided

			Formoterol 2x 9 mcg 2x/d				

Table 154

A systematic review and meta-analysis searched for RCTs that compared a combination of budesonide and formoterol to formoterol alone, in adult COPD patients who did not have an exacerbation for one month prior to entry.

4 RCTs were found, with a duration ranging from 6-12 months.

3 RCTs had unclear allocation concealment, 2 RCTs had an unclear randomization method and 3 RCTs had high dropout (>20%). All RCTs had unclear or high risk of selective reporting These methodological remarks severely limit our confidence in the results.

Two additional RCTs, published after the final search date of the systematic review described above, also compared a combination of budesonide and formoterol to formoterol alone in COPD patients.

One RCT had a duration of 12 weeks, the other of 12 months.

There was unclear reporting of allocation concealment and randomization method in one RCT. The dropout in the longer RCT was high. Both RCTs reported selectively.

Endpoint: Trough FEV1		
n= 3715 12- 52 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando and allocation concealment, selective reporting, high dropout Consistency: -1 Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (Tashkin 2008, Rennard 2009) n= 1203	MD 0.05 L (95%CI 0.00 to 0.009)	NS
Fukuchi 2013 n=1293	**ratio 1.032 (95%CI 1.013 to 1.052)**	**SS in favour of formoterol/budesonide**
Sharafkhaneh 2012 n=1219	BUD/FORM 320/9: 0.07 L BUD/FORM 160/9: 0.07 L FORM: 0.04 L **P< 0.05**	**SS in favour of BUD/FORM**

Table 155

The results of these studies suggest that trough FEV1 is increased with budesonide/formoterol compared to formoterol alone.

For this series of studies,

Most results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: SGRQ		
n= 5954 12-52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando and allocation concealment, selective reporting, high dropout Consistency: -1 Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (Calverley 2003, Rennard 2009, Szafranski 2003, Tashkin 2008) n= 3442	**-2.69 (95%CI -3.82 to -1.55)**	**SS** **In favour of budesonide + formoterol**
Fukuchi 2013 n=1293	**-1.60 (95%CI -3.08 to -0.11)**	**SS** **in favour of formoterol/budesonide**
Sharafkhaneh 2012 n=1219	BUD/FORM 320/9: -7.2 BUD/FORM 160/9: -5.5 FORM: -5.9	NS

Table 156

The results of these studies suggest that SGRQ is decreased with budesonide/formoterol compared to formoterol alone.

For this series of studies,

Most results are statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Exacerbations (number of exacerbations)		
n= 2512 12 -52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear rando and allocation concealment, selective reporting, high dropout Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Fukuchi 2013	Formoterol/budesonide: 93	**SS**

n=1293	formoterol: 151 **p=0.0006**	**in favour of formoterol/budesonide**
Sharafkhaneh 2012 n=1219	BUD/FORM 320/9 vs FORM **Ratio 0.654 (95%CI 0.535 to 0.798)** BUD/FORM 160/9 vs FORM **Ratio 0.741 (95%CI 0.610 to 0.899)**	**SS and p<0.001** **In favour of BUD/FORM 320/9** **SS and p=0.002** **In favour of BUD/FORM 160/9**

Table 157

The results of these studies suggest that the number of exacerbations is decreased with budesonide/formoterol compared to formoterol alone.

For this series of studies,

All results are statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.2.3.3 *All combined LABA + ICS vs LABA*

6.2.3.3.1 Clinical evidence profile

Meta-analysis: Nannini 2012(72) "Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease"

Inclusion criteria:
Double-blind RCTs. Population: adult COPD patients, no exacerbation for one month prior to entry. Comparison: fluticasone and salmeterol versus salmeterol; budesonide and formoterol versus formoterol
Search strategy:
Last search November 2011
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts." "In addition, we performed a search of LILACS (all years to March 2011) and CENTRAL"
Assessment of quality of included trials: yes
Other methodological remarks:/

Table 158

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Nannini 2012(72) Design: SR+MA Search date: November 2011	LABA + ICS Vs LABA	N= 9 n= 9921 (TRISTAN, TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009, Szafranski 2003, Calverley 2003, Tashkin 2008, Rennard 2009)	Exacerbation rates	**Rate ratio: 0.77 (95%CI 0.66 to 0.89)** **SS** **In favour of LABA + ICS**

		N= 6 n= 3357 (Mahler 2002, Hanania 2003, O'Donnell 2006, Kardos 2007, Ferguson 2008, Anzueto 2009)	Number of participants with one or more exacerbation	**OR: 0.83 (95%CI 0.70 to 0.98)** **SS** **In favour of LABA + ICS*** (all included studies evaluated fluticasone/salmeterol versus salmeterol)
		N= 3 n= 4879 (TORCH, Kardos 2007, Anzueto 2009)	Hospitalisations	Rate ratio: 0.79 (95%CI 0.55 to 1.13) NS
		N= 10 n= 10681 (SCO 100470, TRISTAN, Kardos 2007, TORCH, Ferguson 2008, Anzueto 2009, Calverley 2003, Szafranski 2003, Tashkin 2008, Rennard 2009)	Mortality	OR: 0.92 (95%CI 0.76 to 1.11) NS
		N= 12 n= 11076 (Mahler 2002, SCO 100470, TRISTAN,	Pneumonia	**OR 1.55 (95%CI 1.20 to 2.01)** **SS** **In favour of LABA (less pneumonia with LABA)**

		Hanania 2003, O'Donnell 2006, TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009, Calverley 2003, Tashkin 2008, Rennard 2009)		

Table 159

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group°)
Anzueto 2009(73)	797	Mean age: 65.4. Mean FEV1: 0.98L INCLUSION: aged ≥40 yrs. History ≥ 10 pack-years, a pre-albuterol FEV1/FVC ≤ 0.70, a FEV1 ≤ 50% of predicted normal and a documented history of at least 1 COPD exacerbation the year prior to the study that required treatment with antibiotics, oral corticosteroids, and/or hospitalisation. EXCLUSION: current diagnosis of asthma, a respiratory disorder other than COPD, historical or current evidence of a clinically significant uncontrolled disease, or had a COPD exacerbation that was not resolved at screening	52 weeks	Fluticasone/salmeterol 250/50 2x/d Vs Salmeterol 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (39% discontinued on salmeterol and 32% on fluticasone/salmeterol) SELECTIVE REPORTING: Low risk

Calverley 2003(82)	509	mean age: 64; mean FEV1 L: 1; mean FEV1 % predicted: 36; mean SGRQ: 48. INCLUSION: GOLD defined COPD (stages III and IV); ≥ 40 years; COPD symptoms >2 years; smoking history ≥ 10 pack years; FEV1/VC ≤ 70% pre-BD; FEV1 ≤ 50% predicted; use of SABAs as reliever medication; >/= 1 COPD exacerbation requiring OCS/antibiotics 2-12 months before 1st clinic visit. EXCLUSION: History of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention within 4 weeks of run-in/during run-in phase	12 months	Budesonide/formoterol 320/9 mcg 2x/d Vs Formoterol 9 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Unclear risk (No information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (44% withdrew on formoterol and 29% on combination) SELECTIVE REPORTING: High risk (not all outcomes reported) FUNDING: AstraZeneca (bij COPD) COMEDICATION (ICS): non-allowed medications: O2 therapy; ICS - (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, BD (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, ß-blocking agents
Ferguson 2008(74)	782	Mean age: 64 years; mean FEV1: 0.94L. INCLUSION: 40 years of age or older with a diagnosis of COPD,16 a cigarette smoking history of greater than or equal to 10 pack-years, a pre-albuterol FEV1/FVC of 0.70 or less, a FEV1 of 50% of predicted normal or less and a history of one or more exacerbations of	52 weeks	Fluticasone/salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Unclear risk (method unclear) INCOMPLETE OUTCOME DATA: High risk (38% discontinued on

		COPD in the year prior to the study that required treatment with oral corticosteroids, antibiotics, or hospitalisation. EXCLUSION: diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening.			salmeterol and 30% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
Hanania 2003(75)	360	mean age: 64; mean FEV1: 1.27 L (42% predicted). INCLUSION: stable COPD, FEV1 40-65% predicted, FEV1/FVC < 70% predicted, symptoms of chronic bronchitis and moderate dyspnoea. EXCLUSION: current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, LTOT, moderate - severe exacerbation in run-in. Other significant medical disorder.	24 weeks	Fluticasone/salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	ALLOCATION CONC: Unclear risk (No information) RANDO: Unclear risk (No information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on salmeterol and 30% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
Kardos 2007(76)	994	64 years. 40% predicted FEV1; mean reversibility 7% predicted; Mean duration of COPD: 11 years. INCLUSION: M/F ≥40 years of age; diagnosis of severe or very severe COPD	52 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs	ALLOCATION CONC: Low risk RANDO: Low risk) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High

		(according to GOLD criteria III or IV); FEV1 <50% predicted at visit 1 (FEV1 ±20% of visit one at visit two); 2 exacerbations prompting medical consultation in previous 12 months; Smoking history of >10 pack years. EXCLUSION: Exacerbtion in 4 weeks prior to visit 1; LTOT; chronic systemic steroids.		Salmeterol 50 mcg 2x/d	risk (21% withdrew on salmeterol and 20% on combination) SELECTIVE REPORTING: Low risk FUNDING: GlaxoSmithKline
Mahler 2002(77)	325	Mean age: 63; FEV1: 1.2-3 L. INCLUSION: Participants with COPD according to ATS guidelines. Baseline pre-bronchodilation FEV1 < 65% predicted and > 0.70L. Baseline prebronchodilation FEV1/FVC < 70% predicted. Age > 40, 20 pack-year history smoking, day or night symptoms present on 4 out of last 7 days during run-in period. EXCLUSION: history of asthma, corticosteroid use in last 6 weeks, abnormal ECG, oxygen therapy, moderate or severe exacerbation during run-in, significant concurrent disease.	24 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (28% withdrew on salmeterol and 32% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
Rennard 2009(83)	1483	Mean age: 63 years. FEV1 1L. INCLUSION: Moderate to very severe COPD with previous exacerbations age > 40 years, diagnosis of symptomatic COPD for >2 years, >10 pack-year smoking history, pre-bronchodilator FEV1 of < 50% of predicted normal and prebronchodilator FEV1/FVC of <70%.	12 months	Budesonide/formoterol 160/4.5 mcg 2x/d Vs Budesonide/formoterol 80/4.5 mcg 2x/d	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on formoterol

		Patients were to have a Modified Medical Research Council dyspnoea scale score of >2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1-12 months before the first study visit. EXCLUSION: I) a history of asthma; (ii) a history of allergic rhinitis before 40 years of age; (iii) significant/unstable cardiovascular disorder; (iv) clinically significant respiratory tract disorder (v) homozygous -1 antitrypsin deficiency. Oral or ophthalmic non-cardioselective -adrenoceptor antagonists, oral corticosteroids, pregnancy and breast-feeding.		vs Formoterol 4.5 mcg 2x/d Vs placebo	and 28% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: AstraZeneca
SCO 100470(78)	1050	Mean age: 64 years; FEV1: 1.67L; am PEF: 274; SGRQ: 48. INCLUSION: M/F 40-80 years of age; diagnosis of COPD (according to GOLD criteria); ≥ 2 on MRC dyspnoea scale; poor reversibility of < 10% predicted normal (and < 200 mL); FEV1/FVC ratio < 70% predicted; ≥10 pack year smoking history. EXCLUSION: Not described.	24 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Unclear risk (no information) RANDO: Unclear risk (insufficient information) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (14% withdrew on salmeterol and 11% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GSK
Szafranski 2003(84)	409	Mean age: 64 years mean FEV1	52 weeks	Budesonide/formoterol	ALLOCATION CONC: Low risk

		%predicted: 36%, mean reversibility 6% predicted normal. INCLUSION: Age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack years; FEV1 ≤ 50% predicted; FEV1/FVC ≤ 70%; Symptom score ≥ 2 during at least 7 days of run-in; use of bronchodilators for reliever medication; ≥ 1 severe COPD exacerbation within 2-12 months before study entry. EXCLUSION: history of asthma/rhinitis before age of 40; using beta-blockers; current respiratory tract disease other than COPD.		320/9 mcg 2x/d Vs Formoterol 9 mcg 2x/d	RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32% withdrew on formoterol and 28% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: AstraZeneca
Tashkin 2008(85)	1129	Mean age: 63.5 years; FEV1: 1.04L. INCLUSION: Moderate to very severe COPD with previous exacerbations age > 40 years, diagnosis of symptomatic COPD for >2 years, >10 pack-year smoking history, pre-bronchodilator FEV1 of < 50% of predicted normal and prebronchodilator FEV1/FVC of <70%. Patients were to have a Modified Medical Research Council dyspnoea scale score of >2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1-12 months before the first study visit. EXCLUSION: I) a history of asthma; (ii) a history of allergic rhinitis before 40 years of age; (iii) significant/unstable cardiovascular disorder; (iv) clinically	6 months	budesonide/formoterol pressurised metered dose inhaler (pMDI) 160/4.5 µg 2x/d vs budesonide/formoterol pMDI 80/4.5 µg 2x/d vs budesonide pMDI 160 µg 2x/d plus formoterol dry powder inhaler (DPI) 4.5 µg 2x/d vs	ALLOCATION CONC: Unclear (information not available) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (21% withdrew on formoterol and 14% on combination) SELECTIVE REPORTING: Unclear risk (not all outcome data reported) FUNDING: AstraZeneca

		significant respiratory tract disorder (v) homozygous -1 antitrypsin deficiency. Oral or ophthalmic non-cardioselective - adrenoceptor antagonists, oral corticosteroids, pregnancy and breast-feeding.		budesonide pMDI 160 µg 2x/d; vs formoterol DPI 4.5 µg 2x/d; vs placebo	
TORCH(79)	3088	65 years; Male: 76%. INCLUSION: M/F 40-80 years of age; diagnosis of COPD (ERS); <10% reversibility of predicted FEV1; FEV1/FVC ratio <70%; FEV1< 60% predicted; ≥10 pack year smoking history. EXCLUSION: Asthma or respiratory diseases other than COPD; LVRS/lung transplant; requirement for >12hrs/day LTOT; long-term OCS therapy; 'serious uncontrolled disease likely to interfere with medication/cause death in next three years'.	156 weeks (3 years)	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (36.9 % withdrew on salmeterol and 34.1 % on combination) SELECTIVE REPORTING: High risk (not all outcome data reported) FUNDING: GlaxoSmithKline
TRISTAN(22)	730	Mean age 63 years, mean FEV1 = 1.26 L (44% predicted). INCLUSION: Baseline FEV1 25 - 75% predicted; FEV1/ FVC ratio ≤ 70%; Poor reversibility: < 10% increase of predicted FEV1 30 minutes after inhaling 400 mcg salbutamol; at least 10 pack years smoking history; history of exacerbations (at least 1 in the last	52 weeks	Fluticasone/salmeterol 500/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (32 % withdrew on salmeterol and 25% on combination) SELECTIVE REPORTING: High risk (not all outcome data reported)

		year) requiring OCS and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years. EXCLUSION: respiratory disorders other than COPD. Oxygen treatment, systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the 2 week run-in period.			FUNDING: GlaxoSmithKline
O'Donnell 2006(80)	*126*		*8 weeks*		*RCT did not meet our inclusion criteria (minimum 12 weeks' duration)*

Table 160

Study details	n/Population	Comparison	Outcomes		Methodological
Rossi 2014(12) Design: RCT (DB) (PG) Duration of	n= 581 Mean age: 66y % females: 31% Smoking: 36% current smokers 74% ex-smokers % taking ICS at inclusion: taking fluticasone/salmeterol combination was an inclusion criterium	Fluticasone/ salmeterol 500/50 mcg 2x/d Vs Indacaterol 150 mcg/d Salbutamol as rescue	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes
			Trough FEV1 (PO) At 12 weeks	Fluticasone/ salmeterol: 1.593 Indacaterol: 1.584 LS MD -0.009 (95%CI -0.045 to 0.026) (per protocol population) LS MD -0.014 (95%CI -0.046 to 0.019) (Full analysis set) Indacaterol non-inferior to fluticasone/salmeterol	
			Trough FEV1 At 26 weeks	LS MD -0.008 (95%CI -0.045 to 0.028) NS	

follow-up: 26 weeks	ICS policy: not outside of allocated treatment other background medications allowed: no GOLD (2010)-classification of patients: II Baseline FEV1 64% predicted % reversibility to salbutamol : 10% <u>Inclusion:</u> ≥40y ≥10 pack years Moderate COPD (stage II GOLD 2010) Receiving fluticasone/salmeterol 500/50 mcg 2x/d <u>Exclusion</u> COPD exacerbation in the year before screening	medication			FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 14 % • Described: yes • Balanced across groups: indacaterol 16%, fluticasone/salmeterol 13% ITT: Per protocol population used for primary outcome (non-inferiority testing) Full analysis set (= all randomized patients who received at least one dose of study drug) for all other outcomes SELECTIVE REPORTING: no Other important methodological remarks : Primary outcome was trough FEV1 at 12 weeks; non-inferiority margin -0.06 L Sponsor: Novartis
			TDI total score Week 26	Fluticasone/ salmeterol: 2.70 Indacaterol: 2.58 Difference -0.12 (95%CI -0.71 to 0.48) NS and p=0.694	
			SGRQ total score Week 26	Fluticasone/ salmeterol: 33.5 Indacaterol: 33.1 Difference -0.40 (95%CI -2.5 to 1.6) NS and p=0.693	
			Exacerbations Rate of exacerbations per year	Fluticasone/ salmeterol: 0.67 Indacaterol: 0.57 Rate ratio: 0.86 (95%CI 0.62 to 1.20) NS and p=0.367	
			Serious adverse events	Fluticasone/ salmeterol: 17/288 Indacaterol: 5/293 NT	
			Death	Fluticasone/ salmeterol: 2/288 Indacaterol: 0/293 NT	
			Atrial fibrillation	Fluticasone/ salmeterol: 2/288 Indacaterol: 0/293 NT	

	Asthma Any other maintenance treatment for COPD		Pneumonia	Fluticasone/ salmeterol: 2/288 Indacaterol: 0/293 NT	

Table 161

Study details	n/Population	Comparison	Outcomes		Methodological
Wedzicha 2014(8) Design: RCT (DB) (PG) Duration of follow-up: 48 weeks	n= 1199 Mean age: 64y % females: 32% Current smokers: 39% % taking ICS at inclusion: NR ICS policy: not outside of allocated treatment other background medications allowed: theophylline and tiotropium allowed if stable dose before screening and maintained constant throughout study GOLD (2010)-	Beclomethasone/ formoterol 2x 100/6 mcg 2x/d Vs formoterol 12 mcg 1x/d salbutamol as rescue medication	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (no information) BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.6% Drop-out and Exclusions: 15% • Described: yes • Balanced across groups: 13% combination; 17% formoterol
			Exacerbation rate over the entire treatment period (PO)	Beclomethasone/formoterol: 0.804/patient per year Formoterol: 1.118 per patient per year **Adj. rate ratio: 0.719 (95%CI 0.619 to 0.837)** **SS and p<0.001** **In favour of beclomethasone/formoterol**	
			Trough FEV1 (L) Week 12 (PO)	Beclomethasone/formoterol: 0.081 L Formoterol: 0.012 L **Adj. MD: 0.069 L (95%CI 0.043 to 0.095)** **SS and p<0.001** **In favour of beclomethasone/formoterol**	
			Trough FEV1 48 weeks	**SS and p<0.05** **In favour of**	

	classification of patients: III Baseline FEV1 41% predicted % reversibility to salbutamol : 11 <u>Inclusion:</u> ≥40y ≥10 pack years FEV1/FVC <70% FEV1 30-<50% predicted ≥1 COPD exacerbation <u>Exclusion</u> Asthma diagnosis Other unstable concurrent disease			**beclomethasone/formoterol** (no numerical data reported)	ITT: Defined as all patients with efficacy data SELECTIVE REPORTING: yes, no numerical data reported for some secondary outcomes Other important methodological remarks : 2-week run-in period under formoterol 12 mcg 2x/d Sponsor: Chiesi Farmaceutici
			SGRQ	Beclomethasone/formoterol: -3.55 Formoterol: -0.77 **Adj. MD: -2.78 (95%CI -4.51 to -1.05)** **SS and p=0.002** **In favour of beclomethasone/formoterol**	
			Serious adverse events	Beclomethasone/formoterol: 189 events (n=601) Formoterol: 158 events (n=596) NT	
			Pneumonia	Beclomethasone/formoterol: 26 events (n=601) Formoterol: 11 events (n=596) NT	
			Atrial fibrillation	Beclomethasone/formoterol: 7 events (n=601) Formoterol: 3 events (n=596) NT	

Table 162

Study details	n/Population	Comparison	Outcomes		Methodological
Fukuchi 2013(86) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 1293 Mean age: 65y % females: 11% Smoking: Current: 34% Former:66% % taking ICS at inclusion: NR ICS policy: no ICS use permitted outside of allocated intervention other background medications allowed: none GOLD (yr)-classification of patients: II to III	Budesonide/ formoterol 2x 160/4.5 mcg 2x/day Vs formoterol 2x 4.5 mcg 2x/day	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: NR Drop-out and Exclusions:7.6% • Described: yes • Balanced across groups: combination: 6.6%; formoterol: 8.5%
			Trough FEV1 (PO)	Formoterol/budesonide: 44mL formoterol: 14mL **ratio 1.032 (95%CI 1.013 to 1.052)** **P=0.0011** **SS in favour of formoterol/budesonide**	
			COPD exacerbations (number of patients)	Formoterol/budesonide: 76/636 formoterol: 111/657 NT	
			COPD exacerbations (number of exacerbations)	Formoterol/budesonide: 93 formoterol: 151 **p=0.0006** **SS in favour of formoterol/budesonide**	
			SGRQ total score	Formoterol/budesonide: -4.37 formoterol: -2.90 **-1.60 (95%CI -3.08 to -0.11)**	

	Baseline FEV1 36% predicted 14% reversibility to salbutamol : <u>Inclusion:</u> • ≥40y • Moderate to severe COPD • FEV1≤50% predicted • FEV1/FVC <70% • ≥10 pack years • At least one COPD exacerbation in last 12 months <u>Exclusion</u> • Asthma or atopy • Significant cardiovascular disease • COPD exacerbation in 4 weeks prior to enrollment or during run-in • Using oxygen therapy			**P=0.035** **SS in favour of formoterol/budesonide**	ITT: Unclear, not defined SELECTIVE REPORTING: yes, not all outcome data reported Other important methodological remarks: 1-2 week run-in with formoterol Sponsor: AstraZeneca
			Pneumonia	Formoterol/budesonide: 3 formoterol: 1 NT	
			Death	Formoterol/budesonide: 4 formoterol: 5 NT	
			Serious AE other than death	Formoterol/budesonide: 39 formoterol: 41 NT	

Table 163

Study details	n/Population	Comparison	Outcomes	Methodological
Sharafkhaneh	n= 1219	Budesonide/	Efficacy	RANDO:

2012(87) Design: RCT (DB) (PG) Duration of follow-up: 12 months	Mean age: 63y % females: 38% Smoking: Current smoker: 36% Ex-smoker: 64% % taking ICS at inclusion: 28% ICS policy: only allocated treatment other background medications allowed: none GOLD (2010)-classification of patients: ≥III Baseline FEV1 37.6% predicted % reversibility to salbutamol : NR <u>Inclusion:</u> ≥40y ≥10 pack years ≥1 COPD exacerbation	formoterol 2x 320/9 mcg 2x/d OR Budesonide/ formoterol 2x 160/9 mcg 2x/d Vs Formoterol 2x 9 mcg 2x/d albuterol as rescue medication	Number of COPD exacerbations (PO) per patient-treatment year	BUD/FORM 320/9 vs FORM **Ratio 0.654 (95%CI 0.535 to 0.798)** **SS and p<0.001** **In favour of BUD/FORM 320/9** BUD/FORM 160/9 vs FORM **Ratio 0.741 (95%CI 0.610 to 0.899)** **SS and p=0.002** **In favour of BUD/FORM 160/9**	Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 2% Drop-out and Exclusions: 28% • Described: yes • Balanced across groups: lower in the combination groups (29%) than in the formoterol group (33%) ITT: All randomized patients who received ≥1 dose of study medication and contributed sufficient data for ≥1 efficacy end point
			Trough FEV1	BUD/FORM 320/9: 0.07 BUD/FORM 160/9: 0.07 FORM: 0.04 BUD/FORM vs FORM **P< 0.05** **SS in favour of BUD/FORM**	
			SGRQ	BUD/FORM 320/9: -7.2 BUD/FORM 160/9: -5.5 FORM: -5.9 BUD/FORM vs FORM NS	

	within 1-12 months before screening FEV1 ≤50% predicted FEV1/FVC <70% Exclusion (planned) enrollment in a COPD pulmonary rehabilitation program Treatment with OCS				SELECTIVE REPORTING: yes; not all outcome data provided Other important methodological remarks : 2-week run-in period Sponsor: AstraZeneca
			Serious adverse events	BUD/FORM 320/9: 76/407 BUD/FORM 160/9: 54/408 FORM: 68/403 NT	
			Pneumonia	BUD/FORM 320/9: 5/407 BUD/FORM 160/9: 2/408 FORM: 0/403 NT	

Table 164

Study details	n/Population	Comparison	Outcomes		Methodological
Ohar 2014(81) Design: RCT (DB) (PG)	n= 639 Mean age: 63y % females: 46% Smoking: NR % taking ICS at	Fluticasone/ salmeterol 250/50 mcg 2x/d Vs	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes
			Severe exacerbations (PO) Mean annualized rate	Fluticasone/salmeterol: 0.44 salmeterol: 0.48 Ratio: 0.92 (95%CI 0.58 to 1.45) NS and p=0.710	

Duration of follow-up: 26 weeks	inclusion: NR ICS policy: not allowed outside of allocated treatment other background medications allowed: All background COPD medications, with the exception of inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA), alone or in combination, were allowed GOLD (yr)-classification of patients: NR Baseline FEV1 40% predicted % reversibility to salbutamol : 14 <u>Inclusion:</u> ≥40y ≥10 pack years FEV1 ≤70% predicted	Salmeterol 50 mcg 2x/d	Moderate/severe exacerbations (PO) Mean annualized rate	Fluticasone/salmeterol: 1.49 salmeterol: 1.81 Ratio: 0.82 (95%CI 0.64 to 1.06) NS and p=0.136	Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 3% Drop-out and Exclusions: 33% • Described: yes • Balanced across groups: salmeterol 35%; combination 31% ITT: Yes, all eligible patients randomized to study treatment SELECTIVE REPORTING: no (describe if yes) Other important methodological remarks : 21-day stabilization period after randomization Sponsor: GlaxoSmithKline
			Trough FEV1	Fluticasone/salmeterol: 0.14 salmeterol: 0.04 **LS MD: 0.10 (95%CI 0.04 to 0.16)** **SS in favour of fluticasone/salmeterol**	
			Pneumonia	Fluticasone/salmeterol: 13/314 salmeterol: 10/325 NT	
			Fatal AEs	Fluticasone/salmeterol: 4/314 salmeterol: 3/325 NT	
			Severe AEs	Fluticasone/salmeterol: 75/314 salmeterol: 82/325 NT	

	Recent (≤14 days) history of exacerbation requiring hospitalization, emergency room observation ≥24h during which OCS was administered or physician's office or emergency room visit of <24 hours with OCS treatment PLUS 6-month history of exacerbation-related hospitalization <u>Exclusion</u> Pneumonia, or other complicating comorbid condition while hospitalized in last 6 months Clinically significant uncontrolled disease				

Table 165

6.2.3.3.2 Summary and conclusions

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Nannini 2012(72)	N=13 (Anzueto 2009(73), Calverley 2003(82), Ferguson 2008(74), Hanania 2003(75), Kardos 2007(76), Mahler 2002(77), O'Donnell 2006(80), Rennard 2009(83), SCO 100470(78), Szafranski 2003(84), Tashkin 2008(85), TORCH(79), TRISTAN(22))	8 weeks – 3 years	LABA + ICS Vs LABA	adult COPD patients, no exacerbation for one month prior to entry	• One RCT did not meet our inclusion criterium for duration (O'Donnel 2006) • 8 RCTs had unclear allocation concealment (SCO100470, Ferguson 2008, Anzuaeto 2009, Mahler 2002, Hanania 2003, Calverley 2003, Rennard 2009, Tashkin 2008)) • 5 RCTs had an unclear randomization method (SCO100470, Mahler 2002, Hanania 2003, Calverly 2003, Rennard 2009) • 1 RCT had an unclear blinding method (Ferguson 2008) • 10 RCTs had high drop-out (>20%, often unbalanced) (TORCH, TRISTAN, Kardos 2007, Ferguson 2008, Anzueto 2009, Mahler 2002, Hanania 2003, Calverley 2003, Rennard 2009, Szafranski 2003) • 10 RCTs had

					unclear or high risk of selective reporting (TORCH, SCO100470, TRISTAN, Ferguson 2008, Mahler 2002, Hanania 2003, Calverley 2003, Rennard 2009, Szafranski 2003, Tashkin 2008)

Table 166

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Rossi 2014(12)	581	26 weeks	Fluticasone/ salmeterol 500/50 mcg 2x/d Vs Indacaterol 150 mcg/d	Mean age: 66y % females: 31% Smoking: 36% current smokers 74% ex-smokers	II	100% taking fluticasone/ salmeterol combination was an inclusion criterium	No remarks
Wedzicha 2014(8)	1199	48 weeks	Beclomethasone/ formoterol 2x 100/6 mcg 2x/d Vs formoterol 12 mcg 1x/d	Mean age: 64y % females: 32% Current smokers: 39	III	NR	Unclear allocation concealment and randomization Not all outcome data reported
Ohar 2014(81)	639	26 weeks	Fluticasone/ salmeterol 250/50 mcg 2x/d Vs Salmeterol 50 mcg 2x/d	Mean age: 63y % females: 46% Smoking: NR INCLUSION CRITERIUM : Recent (≤14 days) history	FEV1 ≤70% predicted	NR	high dropout: 33% (salmeterol 35%; combination 31%)

				of exacerbation requiring hospitalization, emergency room observation ≥24h during which OCS was administered or physician's office or emergency room visit of <24 hours with OCS treatment PLUS 6-month history of exacerbation-related hospitalization			
Fukuchi 2013(86)	1293	12 weeks	Budesonide/ formoterol 2x 160/4.5 mcg 2x/day Vs formoterol 2x 4.5 mcg 2x/day	Mean age: 65y % females: 11% Smoking: Current: 34% Former:66%	II to III	NR	Unclear randomization and allocation concealment Not all outcome data reported
Sharafkhaneh 2012(87)	1219	12 months	Budesonide/ formoterol 2x 320/9 mcg 2x/d OR Budesonide/ formoterol 2x 160/9 mcg 2x/d Vs	Mean age: 63y % females: 38% Smoking: Current smoker: 36% Ex-smoker: 64%	≥III	28%	high drop-out: lower in the combination groups (29%) than in the formoterol group (33%) SELECTIVE REPORTING: yes; not all outcome

			Formoterol 2x 9 mcg 2x/d				data provided

Table 167

A systematic review and meta-analysis searched for RCTs that compared a combination of LABA and ICS to LABA alone, in adult COPD patients who did not have an exacerbation for one month prior to entry.

13 RCTs were found, with a duration ranging from 8 weeks to 3 years.

All the RCTs compared either fluticasone and salmeterol to salmeterol alone, or budesonide and formoterol to formoterol alone.

One RCT did not meet our inclusion criterion for duration. 8 RCTs had unclear allocation concealment, 5 RCTs had an unclear randomization method, and 1 RCT had an unclear blinding method. 10 RCTs had high drop-out (>20%, often unbalanced) and 10 RCTs had unclear or high risk of selective reporting. These problems severely limit our confidence in the results.

Five additional RCTs, published after the final search date of the systematic review described above, also compared a combination LABA and ICS to LABA alone in COPD patients.

The duration of these RCTs ranged from 12 to 52 weeks.

Two RCTs compared budesonide and formoterol to formoterol alone, one compared fluticasone and salmeterol to salmeterol alone. One RCT compared beclomethasone and formoterol to formoterol alone. One RCT compared fluticasone and salmeterol to indacaterol alone.

There was unclear reporting of allocation concealment and randomization method in two RCTs. Two RCTs had high dropout (>20%). Three RCTs reported selectively. This limits our confidence in the results.

Endpoint: Mortality		
n= 10681 median 1 year	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 high dropout, high risk of selective reporting, unclear allocation concealment and randomization method Consistency: ok Directness: -1 different comparisons Imprecision: ok	
Studies	Results	
Nannini 2012 (SCO 100470, TRISTAN, Kardos 2007, TORCH, Ferguson 2008, Anzueto 2009, Calverley 2003, Szafranski 2003, Tashkin 2008, Rennard 2009)	OR: 0.92 (95%CI 0.76 to 1.11)	NS

n= 10681		

Table 168

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Trough FEV1		
n= 4931 12 – 52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 high dropout, selective reporting, unclear allocation concealment and randomization method Consistency: ok Directness: -1 different comparisons Imprecision: ok	
Studies	Results	
Wedzicha 2014 n=1199 endpoint at 12 weeks	**Adj. MD: 0.069 L (95%CI 0.043 to 0.095)**	**SS** **In favour of LABA +ICS**
Rossi 2014 n=581	LS MD -0.008 (95%CI -0.045 to 0.028)	NS
Ohar 2014 n=639	**LS MD: 0.10 (95%CI 0.04 to 0.16)**	**SS** **in favour of LABA +ICS**
Fukuchi 2013 n=1293	**ratio 1.032 (95%CI 1.013 to 1.052)**	**SS in favour of LABA +ICS**
Sharafkhaneh 2012 n=1219	BUD/FORM 320/9: 0.07 L BUD/FORM 160/9: 0.07 L FORM: 0.04 L **P< 0.05**	**SS in favour of LABA +ICS**

Table 169

The results of these studies suggest that trough FEV1 is increased with LABA+ICS compared to LABA alone.

For this series of studies,

Most results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: SGRQ total score		
n= 4292 12- 52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 high dropout, selective reporting, unclear allocation concealment and randomization method Consistency: -1 Directness: -1 different comparisons Imprecision: ok	
Studies	Results	
Wedzicha 2014 n=1199	**Adj. MD: -2.78 (95%CI -4.51 to -1.05)**	**SS** **In favour of LABA +ICS**
Rossi 2014 n=581	Difference -0.40 (95%CI -2.5 to 1.6)	NS
Fukuchi 2013 n=1293	**-1.60 (95%CI -3.08 to -0.11)**	**SS** **in favour of LABA+ICS**
Sharafkhaneh 2012 n=1219	BUD/FORM 320/9: -7.2 BUD/FORM 160/9: -5.5 FORM: -5.9	NS

Table 170

The results of these studies suggest that SGRQ score is decreased with LABA+ICS compared to LABA alone.

For this series of studies,

Some are significant, some are not (50/50)

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: TDI total score		
n=581 26 weeks	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Rossi 2014 n=581	Difference -0.12 (95%CI -0.71 to 0.48)	NS

Table 171

The results of these studies do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Hospitalisations		
n=4879 1-3 years	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -1 high dropout, selective reporting Consistency: -1 (I^2 = 70%) Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (TORCH, Kardos 2007, Anzueto 2009) n= 4879	Rate ratio: 0.79 (95%CI 0.55 to 1.13)	NS

Table 172

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Number of patients with an exacerbation		
n= 3357 median 1 year	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment and randomization method, short duration Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Nannini 2012 (Mahler 2002, Hanania 2003, O'Donnell 2006, Kardos 2007, Ferguson 2008, Anzueto 2009) n= 3357	**OR: 0.83 (95%CI 0.70 to 0.98)**	**SS** **In favour of LABA + ICS**

Table 173

The results of these studies suggest that the number of patients with an exacerbation is decreased with LABA+ICS compared to LABA alone.

For this meta-analysis,

The result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations rates		
n= 14852 12 weeks – 3 years	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 high dropout, selective reporting, unclear allocation concealment and randomization method Consistency: -1 Directness: -1 different comparisons Imprecision: ok	
Studies	Results	
Nannini 2012 (TRISTAN, TORCH, Kardos 2007, Ferguson 2008, Anzueto 2009, Szafranski 2003, Calverley 2003, Tashkin 2008, Rennard 2009) n= 9921	**Rate ratio: 0.77 (95%CI 0.66 to 0.89)**	**SS** **In favour of LABA + ICS**
Wedzicha 2014 n=1199	**Adj. rate ratio: 0.719 (95%CI 0.619 to 0.837)**	**SS** **In favour of LABA +ICS**
Rossi 2014 n=581	Rate ratio: 0.86 (95%CI 0.62 to 1.20)	NS
Ohar 2014 n=639	Ratio: 0.82 (95%CI 0.64 to 1.06)	NS
Fukuchi 2013 n=1293	Formoterol/budesonide: 93 formoterol: 151 **p=0.0006**	**SS** **in favour of LABA +ICS**
Sharafkhaneh 2012 n=1219	<u>BUD/FORM 320/9 vs FORM</u> **Ratio 0.654 (95%CI 0.535 to 0.798)** <u>BUD/FORM 160/9 vs FORM</u> **Ratio 0.741 (95%CI 0.610 to 0.899)**	**SS** **In favour of LABA +ICS** **SS** **In favour of LABA +ICS**

Table 174

The results of these studies suggest that exacerbation rates are decreased with LABA+ICS compared to LABA alone.

For this series of studies,

Most results are statistically significant

We have very low confidence that the results of the studies reflect the true effect.

GRADE: VERY LOW quality of evidence

Endpoint: Severe exacerbations

n=639 26 weeks	**GRADING** ⊕⊕⊕⊖ **MODERATE** Study quality: -1 high dropout Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Ohar 2014 n=639	Rate Ratio: 0.92 (95%CI 0.58 to 1.45)	NS

Table 175

The results of these studies do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.2.4 LABA + ICS vs other LABA + ICS

6.2.4.1 *Beclomethasone + formoterol vs fluticasone + salmeterol*

6.2.4.1.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2014(88) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 419 Mean age: 64y % females: 29% Current smokers: 54% % taking ICS at inclusion: 74% ICS policy: only allocated treatments other background medications allowed: no other COPD medications permitted GOLD (yr)-classification of patients: ≥II	Extrafine beclomethasone/formoterol 2x 100/6 mcg 2x/d Vs Fluticasone/salmeterol 500/50 mcg 2x/d Salbutamol as rescue medication	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.7% Drop-out and Exclusions: 10% • Described: yes • Balanced across groups: beclo/formo 8.5%; flut/salme 12%
			TDI score (PO) Week 12	beclomethasone/formoterol: 1.32 Fluticasone/salmeterol: 1.15 MD 0.17 (-0.39 to 0.72) p=0.56 Beclomethasone/formoterol is equivalent to fluticasone/salmeterol	
			Trough FEV1 (L)	beclomethasone/formoterol: 0.08L Fluticasone/salmeterol: 0.06L Between-group p value 0.58 NS	
			SGRQ	beclomethasone/formoterol: -5.92 Fluticasone/salmeterol: -3.80 Between-group p value 0.08 NS	
			6MWT (meters)	beclomethasone/formoterol: 31.62 Fluticasone/salmeterol: 22.23	

	Baseline FEV1 46.5% predicted % reversibility to salbutamol : 17.6% <u>Inclusion:</u> ≥40y ≥10 pack years FEV1/FVC <0.7 FEV1 <60% predicted Increase in FEV1 ≥5% following 400 mcg salbutamol Baseline Dyspnoea Index focal score ≤10 History of ≤1 COPD exacerbation in last 12 months <u>Exclusion</u> Other respiratory disorders Other clinically relevant condition			Between-group p value 0.33 NS	ITT: Not defined; not all randomized patients were analysed SELECTIVE REPORTING: yes; between-group differences of secondary outcomes not reported Other important methodological remarks 2-week run-in period with ipratropium bromide Equivalence in TDI score was demonstrated if the two-sided 95%CI for the adjusted MD lied entirely within the equivalence margins fixed at +/- 1 Sponsor: Chiesi Farmaceutici

Table 176

6.2.4.1.2 Summary and conclusions

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Singh 2014(88)	419	12 weeks	Extrafine beclomethasone/formoterol 2x 100/6 mcg 2x/d Vs Fluticasone/salmeterol 500/50 mcg 2x/d	Mean age: 64y % females: 29% Current smokers: 54%	≥II	74%	higher % dropout in fluticasone/ salmeterol group (12% vs 8.5%) not all outcome data reported

Table 177

This double-blind RCT compared a combination of beclomethasone and formoterol with fluticasone and salmeterol in 419 patients with COPD (FEV1 <60% predicted).

The duration of this RCT was 12 weeks.

This RCT did not report all outcome data. There was a higher percentage of drop-out in the fluticasone/salmeterol group compared to the beclomethasone/formoterol group. This limits our confidence in the results.

Endpoint: trough FEV1		
n=419 12 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 possible selective reporting, unbalanced dropout Consistency: NA Directness: -1 short duration Imprecision: -1 no CI	
Studies	Results	
Singh 2014	beclomethasone/formoterol: 0.08L Fluticasone/salmeterol: 0.06L Between-group p value 0.58	NS

Table 178

The results of this study do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: TDI score		
n=419 12 weeks	**GRADING** ⨁⨁⨀⨀ **LOW** Study quality: -1 possible selective reporting, unbalanced dropout Consistency: NA Directness: -1 short duration Imprecision: ok	
Studies	Results	
Singh 2014	MD 0.17 (-0.39 to 0.72)	Beclomethasone/formoterol is equivalent to fluticasone/salmeterol

Table 179

The results of this study do not suggest an effect in any direction.

For this study,
The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: SGRQ		
n=419 12 weeks	**GRADING** ⨁⨀⨀⨀ **VERY LOW** Study quality: -1 possible selective reporting, unbalanced dropout Consistency: NA Directness: -1 short duration Imprecision: -1 no CI	
Studies	Results	
Singh 2014	beclomethasone/formoterol: -5.92 Fluticasone/salmeterol: -3.80 Between-group p value 0.08	NS

Table 180

The results of this study do not suggest an effect in any direction.

For this study,
The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: 6MWT		
n=419 12 weeks	GRADING ⨁⊖⊖⊖ **VERY LOW** Study quality: -1 possible selective reporting, unbalanced dropout Consistency: NA Directness: -1 short duration Imprecision: -1 no CI	
Studies	Results	
Singh 2014	beclomethasone/formoterol: 31.62 Fluticasone/salmeterol: 22.23 Between-group p value 0.33	NS

Table 181

The results of this study do not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.

GRADE: VERY LOW quality of evidence

6.2.4.2 *Fluticasone + vilanterol vs fluticasone + salmeterol*

6.2.4.2.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Agusti 2014 (89) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 528 Mean age: 63 y % females: 18 Smoking: NR % taking ICS at inclusion:18% taking fluticasone proprionate; other ICS unknown ICS policy: not outside of allocated treatments other background medications allowed: ipratropium, mucolytics and oxygen for ≤12 h were allowed (stable dose)	Fluticasone furoate/vilanterol 100/25 mcg 1x/d Vs Fluticasone proprionate/salmeterol 500/50 mcg 2x/d Salbutamol as rescue medication	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.8% Drop-out and Exclusions: 6.6% • Described: yes • Balanced across groups: yes ITT: Defined as all patients who were randomized to treatment and who received at least one dose
			Trough FEV1 Week 12	Fluticasone/vilanterol: 111 mL Fluticasone/salmeterol: 88 mL LS MD 23 mL (95%CI -20 to 66) NS	
			SGRQ total score Week 12	Fluticasone/vilanterol: -4.3 Fluticasone/salmeterol: -3.0 LS MD -1.3 (95%CI -3.5 to 0.8) NS	
			Serious adverse events	Fluticasone/vilanterol: 6/266 Fluticasone/salmeterol: 3/262 NT	
			Atrial fibrillation	Fluticasone/vilanterol: 2/266 Fluticasone/salmeterol: 0/262 NT	
			Pneumonia	Fluticasone/vilanterol: 1/266	

	GOLD (yr)-classification of patients: ≥II Baseline FEV1 43% predicted % reversibility to salbutamol : 11.8 <u>Inclusion:</u> ≥40 years ≥10 pack years FEV1/FVC <0.7 FEV1 ≤70% predicted At least one moderate or severe exacerbation within the past 3 years <u>Exclusion</u> Asthma Serious underlying disease Hospitalisation due to COPD exacerbation within 12 weeks of screening			Fluticasone/salmeterol: 2/262 NT	of study medication SELECTIVE REPORTING: no Other important methodological remarks: PO was 24-h effect on FEV1 after 12 weeks; not reported by us Sponsor: GlaxoSmithKline

Table 182

Study details	n/Population	Comparison	Outcomes		Methodological
Dransfield 2014(90) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 828 Mean age: 61y % females: 28% Current smoker: 58% % taking ICS at inclusion: NR ICS policy: not outside allocated treatments other background medications allowed: ipratropium, mucolytics, oxygen therapy ≤12h a day GOLD (2010)-classification of patients: ≥II Baseline FEV1 43 % predicted % reversibility to salbutamol : 12%	Fluticasone furoate/vilanterol 100/25 mcg 1x/d Vs Fluticasone proprionate/salmeterol 250/50 mcg 2x/d Open-label salbutamol as rescue medication	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.5 % Drop-out and Exclusions: 10.5% • Described: yes • Balanced across groups: yes ITT: Yes; not defined in article, but all randomized patients were included in analysis SELECTIVE REPORTING: yes; pooled data of three trials for
			Trough FEV1 12 weeks *(only study 3; see other important methodological remarks*)*	Fluticasone/vilanterol: 151 mL Fluticasone/salmeterol 121 mL LS MD 30 mL (95%CI-5 to 65) NS	
			Atrial fibrillation	Fluticasone/vilanterol: 1/412 Fluticasone/salmeterol: 0/416 NT	
			Pneumonia	Fluticasone/vilanterol: 4/412 Fluticasone/salmeterol: 4/416 NT	

	Inclusion: ≥40y ≥10 pack years FEV1/FVC <0.7 FEV1 ≤70% predicted Exclusion asthma				outcome “trough FEV1” presented in table (SS difference); yet in text explained that this was only a prespecified endpoint in trial 3 (NS) Other important methodological remarks: 2-week single-blind placebo run-in period PO was 0-24h weighted mean FEV1; we did not report this outcome *This study was part of a triple trial; however, only one trial had a prespecified outcome of interest for this report. We will not report the results of the other two trials. Sponsor: GlaxoSmithKline

Table 183

6.2.4.2.2 Summary and conclusions

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Agusti 2014 (89)	528	12 weeks	Fluticasone furoate/vilanterol 100/25 mcg 1x/d Vs Fluticasone proprionate/salmeterol 500/50 mcg 2x/d	Mean age: 63 y females: 18% Smoking: NR	FEV1 ≤70% predicted	18% taking fluticasone proprionate; other ICS unknown	No remarks
Dransfield 2014(90)	828	12 weeks	Fluticasone furoate/vilanterol 100/25 mcg 1x/d Vs Fluticasone proprionate/salmeterol 250/50 mcg 2x/d	Mean age: 61y % females: 28% Current smoker: 58%	FEV1 ≤70% predicted	NR	This study was part of a triple trial; however, only one trial had a prespecified outcome of interest for this report. We will not report the results of the other two trials. SELECTIVE REPORTING: yes; pooled data of three trials for outcome "trough FEV1" presented in table (SS difference); yet in text explained that this was only a prespecified

							endpoint in trial 3 (NS)

Table 184

Two double-blind RCTs were found that compared a combination of fluticasone and vilanterol to fluticasone and salmeterol in COPD patients with FEV1 <70% predicted.

The duration of both RCTs was 12 weeks.

There were no methodological remarks on one RCT. There was some evidence of selective reporting in the other RCT.

Endpoint: Trough FEV1		
n= 1356 12 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 selective reporting Consistency: ok Directness: -1 short duration Imprecision: ok	
Studies	Results	
Agusti 2014 n= 528	LS MD 23 mL (95%CI -20 to 66)	NS
Dransfield 2014 n= 828	LS MD 30 mL (95%CI-5 to 65)	NS

Table 185

The results of these studies do not suggest an effect in any direction.

For this series of studies,

No result is statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: SGRQ total score		
n=528 12 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 short duration Imprecision: ok	
Studies	Results	
Agusti 2014 n= 528	LS MD -1.3 (95%CI -3.5 to 0.8)	NS

Table 186

The results of this study does not suggest an effect in any direction.

For this study,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.2.5 Adverse events from RCTs

6.2.5.1 *LABA + ICS vs ICS*

6.2.5.1.1 Fluticasone/salmeterol vs fluticasone

A meta-analysis of 7 RCTs (Nannini 2013 (54)) found a **statistically significant difference** in **mortality** between fluticasone + salmeterol vs fluticasone, in favour of the combination. It did **not** find a statistically significant difference for pneumonia, exacerbations or hospitalizations due to exacerbations.

6.2.5.1.2 Fluticasone / vilanterol vs fluticasone

A meta-analysis of 6 RCTs (Rodrigo 2016 (55)) found **no statistically significant difference** in **mortality and pneumonia** between fluticasone and vilanterol vs fluticasone.

6.2.5.1.3 Budesonide/formoterol vs budesonide

A meta-analysis of 4 RCTs (Nannini 2013 (54)) found **no statistically significant difference** for **hospitalizations** due to COPD exacerbation**, mortality or pneumonia.**

6.2.5.1.4 Mometasone / formoterol vs mometasone

A meta-analysis of 2 RCTs (Nannini 2013 (54)) found **no statistically significant difference** for **hospitalizations** due to COPD exacerbation**, mortality or pneumonia.**

6.2.5.1.5 All combined LABA/ICS vs ICS

A meta-analysis of 12 RCTs (Nannini 2013 (54)) found a **statistically significant difference** in **mortality** between LABA + ICS vs ICS, in favour of the combination. There was no difference for **pneumonia** or **hospitalizations** due to COPD exacerbations.

6.2.5.2 *LABA + ICS vs LAMA*

6.2.5.2.1 fluticasone/ salmeterol vs tiotropium

One RCT (INSPIRE (69)) found a **statistically significant increase of serious adverse events** with LABA + ICS versus tiotropium, while a different RCT SCO40034(70) did not find a difference.
One RCT (INSPIRE (69)) found a **statistically significant increase of pneumonia** with LABA + ICS versus tiotropium.

6.2.5.3 *LABA + ICS vs LABA*

A meta-analysis of 12 RCTs (Nannini 2012 (72)) found a **statistically significant increase of pneumonia** with LABA + ICS versus LABA alone.

6.2.5.3.1 Fluticasone & salmeterol Vs salmeterol

A meta-analysis of 9 RCTs (Nannini 2012(72)) found a **statistically significant increase of pneumonia** with fluticasone + salmeterol versus salmeterol alone.

6.2.5.3.2 Budesonide & formoterol Vs formoterol

A meta-analysis of 4 RCTs (Nannini 2012(72)) found no difference of **serious adverse events** between budesonide + formoterol versus formoterol alone.

6.2.5.4 *LABA + ICS vs other LABA + ICS*

6.2.5.4.1 Fluticasone + vilanterol vs fluticasone + salmeterol

One RCT (Agusti 2014 (89)) assessed **serious adverse events**, **atrial fibrillation** and **pneumonia** with fluticasone + vilanterol versus fluticasone + salmeterol. The rates of these outcomes were similar between groups, but no statistical test was performed.

6.3 Triple therapy: LABA + LAMA + ICS

6.3.1 Triple therapy vs LABA

6.3.1.1 *Clinical evidence profile*

For this comparison, we did not find any systematic reviews or RCTs that met our inclusion criteria.

6.3.1.2 *Summary and conclusions*

For this comparison, we did not find any systematic reviews or RCTs that met our inclusion criteria.

6.3.2 Triple therapy vs LAMA

6.3.2.1 *Clinical evidence profile*

Meta-analysis: Rojas-Rejes 2016(91) "Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease"

Inclusion criteria:
Parallel group RCTs, at least 12 weeks' duration. Population: COPD patients. Comparison: ICS +LABA + tiotropium versus tiotropium alone or ICS + LABA
Search strategy:
Last search April 2015
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts." "We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 187

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Rojas-Rejes 2016(91) Design: SR+MA Search date:	**LABA + ICS + tiotropium vs tioptropium**	N= 2 n= 961 (Welte 2009, Aaron 2007)	Mortality	Triple: 7/474 Tiotropium: 4/487 OR:1.80(95%CI 0.55 to 5.91) NS
		N= 2 n= 961 (Welte 2009,	Hospital admission	**Triple: 50/474** **Tiotropium: 76/487** **OR:0.60(95%CI 0.40 to 0.92)**

April 2015		Aaron 2007)		**SS** **In favour of triple treatment**
		N= 1 n= 660 (Welte 2009)	Exacerbations At 3-month follow-up	**Triple: 25/329** **Tiotropium: 61/331** **OR:0.36 (95%CI 0.22 to 0.60)** **SS** **In favour of triple treatment**
		N= 1 n= 455 (Jung 2012)	Exacerbations At 6-month follow-up	Triple: 39/223 Tiotropium: 47/323 OR:0.83(95%CI 0.52 to 1.34) NS
		N= 1 n= 301 (Aaron 2007)	Exacerbations At 12-month follow-up	Triple: 87/145 Tiotropium: 98/156 OR: 0.89(95%CI 0.56 to 1.41) NS
		N= 4 n= 1618 (Hoshino 2011, Jung 2012, Aaron 2007, Welte 2009)	SGRQ	**MD: -3.46 (95%CI -5.05 to -1.87)** **SS** **In favour of triple treatment**
		N= 4 n= 1678 (Cazzola 2007, Jung 2012, Welte 2009, Aaron 2007)	Trough FEV1 At 3-6 months	**MD: 0.06 (95%CI 0.04 to 0.08)** **SS** **In favour of triple treatment**
		N= 1 n= 449 (Aaron 2007)	Trough FEV1 at 1 year	MD: 0.06 (95%CI 0.00 to 0.12) NS
		N= 4 n= 1758 (Hanania 2011,	Serious adverse events	Triple: 45/870 Tiotropium: 53/888 OR: 0.86 (95%CI 0.57 to 1.30)

		Welte 2009, Aaron 2007, Jung 2012)		NS
		N= 4 n= 1758 (Welte 2009, Jung 2012, Hanania 2011, Aaron 2007)	Pneumonia	Triple: 8/870 Tiotropium: 5/888 OR: 1.62 (95%CI 0.54 to 4.82) NS

Table 188

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group°)
Aaron 2007(47)	449	**Inclusion criteria:** at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomisation; age older than 35 years; history of 10 or more pack-years of cigarette smoking; documented chronic airflow obstruction, with an FEV1/FVC ratio < 0.70 and a post-bronchodilator FEV1 < 65% of predicted value **Exclusion criteria**: history of physician-diagnosed asthma before 40 years of age; history of physician-diagnosed chronic congestive heart failure with	52 weeks	Tiotropium 18 mcg 1x/d+ salmeterol/fluticasone 2x 250/25 mcg 2x/d Vs Tiotropium 18 mcg 1x/d+ salmeterol 2x25 mcg 2x/d Vs Tiotropium 18 mcg 1x/d + placebo 2 puffs 2x/d	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (variation in drop-out between groups (19% tiotropium vs 10% triple); sensitivity analysis was done) SELECTIVE REPORTING: Low risk FUNDING: The Canadian Institutes of Health Research and The Ontario Thoracic Society provided peer-reviewed funding for this study

		known persistent severe left ventricular dysfunction; those receiving oral prednisone; those with a known hypersensitivity or intolerance to tiotropium, salmeterol or fluticasone-salmeterol; history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery or diffuse bilateral bronchiectasis; those who were pregnant or breastfeeding			COMEDICATION (ICS): • Albuterol as rescue medication • ICS, LABA and anticholinergics were discontinued on entry • Oxygen, antileukotrienes and methylxanthines were continued
Hanania 2011(92)	342	mean age 61 years. Moderate to severe COPD with mean FEV1 predicted of 56% Inclusion criteria: age ≥ 40 years; diagnosis of COPD according to ATS-ERS criteria; history of 10 ormore pack-years of cigarette smoking; post-albuterol FEV1 > 40 to < 80% of predicted normal and post-albuterol FEV1/FVC ratio < 0.70 according to NHANES III reference values Exclusion criteria: clinical diagnosis of respiratory disorder other than COPD; longterm oxygen; BMI > 40 kg/m2; clinically significant and uncontrolled medical disorder; lung resection surgery within the past year; inability to give informed consent	24 weeks	Tiotropium 18 mcg 1x/d+ fluticasone/salmeterol 250/25 mcg 2x/d Vs Tiotropium 18 mcg 1x/d + placebo 2x/d	ALLOCATION CONC: Unclear risk (no details) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (drop-out rate:23%) SELECTIVE REPORTING: Low risk FUNDING: GlaxoSmithKline COMEDICATION (ICS): • Albuterol as rescue medication • LAMA, LABA, ICS, OCS, ipratropium/albuterol combination, oral beta2-agonists, theophylline not allowed
Jung 2012(93)	479	mean age 67 years.Moderate to very	24 weeks	Tiotropium 18 mcg 1x/d	ALLOCATION CONC: Low risk

		severe COPD with mean FEV1 predicted of 50.8%. 98% men Inclusion criteria: participants diagnosed with COPD who had a post-bronchodilator FEV1/FVC ratio < 0.70 and FEV1 < 65% of predicted value in the past 1 year or at screening. Eligible participants were 40 to 80 years of age and had a smoking history of 10 or more pack-years Exclusion criteria: a history of physician-diagnosed asthma or a chronic respiratory disorder other than COPD that was clinically significant; any uncontrollable or serious disease that might affect participation in the study; use of systemic corticosteroids or immunosuppressants within 4 weeks before study entry; any malignant disease; a history of severe glaucoma, urinary tract obstruction or previous lung volume reduction surgery; women who were pregnant or lactating; known hypersensitivity or intolerance to tiotropium or FSC		Vs Tiotropium 18 mcg 1x/d + fluticasone/ salmeterol 250/50 2x/d	RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Unclear risk (no details) INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Korea Healthcare Technology R&D Project, Ministry for Health and Welfare, Republic of Korea (A102065), and from GlaxoSmithKline Korea COMEDICATION (ICS): • Salbutamol as rescue medication • ICS, LABA, LAMA stopped before run-in • Oxygen, mucolytics, methylxanthines allowed
Welte 2009(94)	660	mean age 62 years. Moderate, severe or very severe COPD with mean FEV1	12 weeks	Tiotropium 18 mcg 1x/d + budesonide/formoterol	ALLOCATION CONC: Low risk RANDO: Low risk

		predicted of 38%. 25% women		320/9 mcg 2x/d Vs Tiotropium 18 mcg 1x/d + placebo 2x/d	BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: AstraZeneca COMEDICATION (ICS): • Terbutaline as rescue medication
Cazzola 2007(95)	*90*			*3 arms*	*RCT did not meet our inclusion criteria*
Hoshino 2011(96)	*30*		*12 weeks*		*RCT did not meet our inclusion criteria*

Table 189

Study details	n/Population	Comparison	Outcomes		Methodological
Lee 2016(97) Design: RCT (OL) (PG)	n= 577 Mean age: 66.8 % females: 4.3% Smoking: NR % taking ICS at inclusion: NR other background medications allowed: Salbutamol as reliever therapy	Tiotropium 18 mcg once daily + budesonide/formoterol 160/4.5 mcg 2 inhalations twice daily Vs Tiotropium 18 mcg once daily	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: Open-label
			Trough FEV1 (PO) (% difference)	**TD: 4.4 (1.9 to 6.9)** **SS and p=0.0004** **In favour of triple therapy**	
			Number of patients with at least one COPD exacerbation	triple: 40/287 tiotropium: 61/291 **HR: 0.61 (0.41 to 0.92)** **SS and p=0.017** **In favour of triple therapy**	
			Time to first exacerbation	**Risk reduction -38.6% (-8.4 to -58.8)** **SS and p=0.017**	

Duration of follow-up: 12 weeks	GOLD (2010)-classification: • II (moderate): 7.5% • III (severe): 74.4% • IV (very severe): 18.2% Baseline FEV1 : 36.4% predicted Baseline FVC : NR % reversible : NR <u>Inclusion:</u> Dyspnea: not a criterium FEV1 % predicted: Y, ≤50% Exacerbations: Y, ≥1 requiring OCS or AB within 1 year East-Asian patients ≥40y FEV1/FVC <70% <u>Exclusion</u> Asthma or seasonal allergic rhinitis Significant			**In favour of triple therapy**	POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.9% Drop-out and Exclusions: 8.5% • Described: yes • Balanced across groups: triple therapy: 7.7%; tiotropium: 9.3% ITT: No; Full analysis set: all patients who took ≥1 dose of study medication and who had ≥1 efficacy assessment SELECTIVE REPORTING: yes, not all outcome data reported Other important methodological remarks : 14-day run-in period Sponsor: AstraZenica
			SGRQ-C total score	triple: -10.00 tiotropium: -4.80 **LS MD -5.20 (-8.03 to -2.38)** **SS and p=0.0003** **In favour of triple therapy**	
			Proportion of patients achieving a clinically meaningful improvement in SGRQ-C score (≥4 units)	triple: 59.6% tiotropium: 46.2% **SS and p=0.0015** **In favour of triple therapy**	

	cardiocascular disorder Glaucoma, prostatic hyperplasia, bladder neck obstruction				

Table 190

6.3.2.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Rojas-Rejes 2016(91)	N=6 (Aaron 2007(47), Hanania 2011(92), Hoshino 2011(96), Jung 2012(93), Aaron 2007(47), Welte 2009(94)	12-52 weeks	ICS +LABA + tiotropium versus tiotropium alone	COPD patients	• 2 RCTs did not meet our inclusion criteria (sample size) (Cazzola 2007, Hoshino 2011) • 1 RCT with unclear allocation concealment (Hanania 2011) • 1 RCT with unclear blinding • 1 RCT with unbalanced dropout (Aaron 2007) • 1 RCT with high dropout rate (Hanania 2011)

Table 191

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Lee 2016(97)f	577	12 weeks	Tiotropium 18 mcg once daily + budesonide/formoterol 160/4.5 mcg 2 inhalations twice daily Vs Tiotropium 18 mcg once daily	Mean age: 66.8 % females: 4.3% Smoking: NR	II: 7.5% III : 74.4% IV: 18.2%	NR	unclear randomization and allocation concealment open-label trial not all outcome data reported

Table 192

A systematic review and meta-analysis searched for RCTs that compared ICS+ LABA+ tiotropium with tiotropium alone in COPD patients.

6 RCTs of 12-52 weeks' duration were found.

2 of these RCTs did not meet our inclusion criteria because of a small sample size. One RCT had unclear allocation concealment. One RCT had unclear blinding. One RCT had unbalanced dropout, and one RCT had a high dropout rate. This limits our confidence in the results.

An additional RCT, published after the final search date of the systematic review described above, also compared tiotropium + LABA/ ICS with tiotropium alone in COPD patients.

The duration of this RCT was 12 weeks.

This RCT had unclear reporting of allocation concealment and randomization. It was not blinded. Not all outcome data was reported. This severely limits our confidence in the results.

Endpoint: Mortality		
n=961 12-24 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: ok Directness: ok Imprecision: -1 wide CI	
Studies	Results	
Rojas-Rejes 2016 (Welte 2009, Aaron 2007) n= 961	OR:1.80(95%CI 0.55 to 5.91)	NS

Table 193

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Trough FEV1 (at 3-6 months)		
n=2255 12-24 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 unbalanced dropout, small sample size, one study with severe limitations (open label, unclear rando and alloc conc., selective reporting) Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016 (Cazzola 2007, Jung 2012, Welte 2009, Aaron 2007) n= 1678	**MD: 0.06 L (95%CI 0.04 to 0.08)**	**SS** **In favour of triple treatment**
Lee 2016 n= 577	**TD: 4.4 %difference (1.9 to 6.9)** **(absolute difference: 0.04L)**	**SS** **In favour of triple treatment**

Table 194

The results of these studies suggest that trough FEV1 is increased with triple therapy compared to LAMA alone.

For this series of studies,

All results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Trough FEV1 (at 12 months)		
n=449 52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unbalanced dropout Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016 (Aaron 2007) n= 449	MD: 0.06 L(95%CI 0.00 to 0.12)	NS

Table 195

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: SGRQ-C total score		
n= 2195 12-52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unbalanced dropout, small sample size Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016(Hoshino 2011, Jung 2012, Aaron 2007, Welte 2009) n= 1618	**MD: -3.46 (95%CI -5.05 to -1.87)**	**SS** **In favour of triple treatment**
Lee 2016 n= 577	**LS MD -5.20 (-8.03 to -2.38)**	**SS** **In favour of triple treatment**

Table 196

The results of these studies suggest that SGRQ total score is decreased with triple therapy compared to LAMA alone.

For this series of studies,

All results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: Proportion of patients with at least one COPD exacerbation		
n=577 12 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 open-label, unclear rando and alloc conc, selective reporting, only study Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Lee 2016 n= 577	**HR: 0.61 (0.41 to 0.92)**	**SS** **In favour of triple therapy**

Table 197

The results of these studies suggest that the proportion of patients with at least one COPD exacerbation is decreased with triple therapy compared to LAMA alone.

For this study,

The result is statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Number of exacerbations at 3 months		
n=660 12 weeks	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016(Welte 2009) n= 660	**OR: 0.36 (95%CI 0.22 to 0.60)**	**SS** **In favour of triple treatment**

Table 198

The results of these studies suggest that the number of exacerbations at 3 months is decreased with triple therapy compared to LAMA alone.

For this meta-analysis,

The result is statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Number of exacerbations at 6 months		
n=455 24 weeks	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016(Jung 2012) n= 455	OR:0.83 (95%CI 0.52 to 1.34)	NS

Table 199

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Number of exacerbations at 12 months		
n=301 52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unbalanced dropout Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016(Aaron 2007) n= 301	OR: 0.89 (95%CI 0.56 to 1.41)	NS

Table 200

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

Endpoint: Hospital admission		
n=961 12-52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unbalanced dropout Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Rojas-Rejes 2016 (Welte 2009, Aaron 2007) n= 961	**OR:0.60(95%CI 0.40 to 0.92)**	**SS** **In favour of triple treatment**

Table 201

The results of these studies suggest that hospital admission is decreased with triple therapy compared to LAMA alone.
For this meta-analysis,
The result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.3.3 Triple therapy vs LABA + LAMA

6.3.3.1 *Clinical evidence profile*

Meta-analysis: Tan 2016(98) "Inhaled corticosteroids with combination inhaled long-acting beta$_2$-agonists and long-acting muscarinic antagonists for chronic obstructive pulmonary disease" Inclusion criteria: Parallel-group RCTs, >3 weeks' duration. Population: all participants with a diagnosis of stable COPD. Comparison: LABA/LAMA combination inhaler plus ICS versus LABA/LAMA combination inhaler without ICS. Search strategy: Assessment of quality of included trials: yes Other methodological remarks:/

Table 202

Remarks: No RCTs that met the inclusion criteria were found.

The RCTs comparing LAMA + LABA + ICS versus LABA + LAMA that were excluded from this review because they did not use a combination inhaler LABA/LAMA, were further examined by us but they did not meet our inclusion criteria because of insufficient sample size.

6.3.3.2 *Summary and conclusions*

A systematic review (Tan 2016(98)) searched for RCTs that compared LABA/LAMA combination inhaler plus ICS versus LABA/LAMA combination inhaler without ICS did not find any RCTs that met its inclusion criteria.

The RCTs comparing LAMA + LABA + ICS versus LABA + LAMA that were excluded from this review because they did not use a combination inhaler LABA/LAMA, were further examined by us, but they did not meet our inclusion criteria because of insufficient sample size.

6.3.4 Triple therapy vs LABA + ICS

6.3.4.1 *Clinical evidence profile*

Meta-analysis: Rojas-Rejes 2016(91) "Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease"

Inclusion criteria:
Parallel group RCTs, at least 12 weeks' duration. Population: COPD patients. Comparison: ICS +LABA + tiotropium versus tiotropium alone or ICS + LABA
Search strategy:
Last search April 2015
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts." "We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 203

For the comparison LABA + ICS + tiotropium vs LABA + ICS only one RCT was found. We did not report it because it did not meet our inclusion criteria (n=30 per study arm).

Study details	n/Population	Comparison	Outcomes		Methodological
Frith 2015(9) GLISTEN Design: RCT (SB)	n= 773 Mean age: 68y % females: 35.6% • Smoking: • Current: 36% Ex-smoker: 64%	**Glycopyrronium 50 mcg** 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Placebo** 1x/d +	Trough FEV1 (PO for glycopyrronium vs tiotropium)	Glycopyrronium vs tiotropium LSM TD -7 mL (97.16%CI -45 to 31 mL) **Glycopyrronium non-inferior to tiotropium** **Glycopyrronium vs placebo:**	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: unclear

(PG) Duration of follow-up: 12 weeks	% taking ICS at inclusion: 66% ICS policy: All participants were randomized to same LABA+ICS combination other background medications allowed: GOLD (2010)-classification of patients: II: 68% III: 32% Baseline FEV1 57% predicted % reversible : 22 <u>Inclusion:</u> Dyspnea: not a criterium FEV1 % predicted: Y,	Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Tiotropium 18 mcg** 1x/d + salmeterol/fluticasone 50/500 mcg 2x/d Salbutamol as rescue medication (Glycopyrronium was compared to tiotropium and to placebo, but tiotropium was not analysed versus placebo)		**LSM TD 101 mL** **P<0.001** **SS in favour of glycopyrronium**	Assessors: unclear Remarks on blinding method: Trial described as “blinded”; not clear if personnel and assessors were aware of allocation POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.3% Drop-out and Exclusions: 15% • Described: yes • Balanced across groups: no; higher % of patients discontinued in placebo arm (22%) compared to glycopyrronium arm (11%), and tiotropium arm (12%); p<0.00012 ITT: No: full analysis set (FAS) Primary outcome (non-inferiority of glycopyrronium vs tiotropium for trough FEV1)was
			SGRQ-C total score	<u>Glycopyrronium vs tiotropium</u> TD -1.1 (-0.719 to 2.911) P= 0.236 NS **<u>Glycopyrronium vs placebo:</u>** **LSM TD -2.15 (95%CI -3.972 to -0.336)** **P=0.02** **SS in favour of glycopyrronium**	
			Number of patients experiencing a moderate or severe COPD exacerbation	Glycopyrronium: 29/257 Tiotropium: 24/258 Placebo: 32/257 <u>Glycopyrronium vs tiotropium</u> NS <u>Glycopyrronium vs placebo:</u> NS	
			SAFETY		
			Atrial fibrillation	Glycopyrronium: 0/257 Tiotropium: 2/258 Placebo: 1/257 NT	

	≥30 - <80% Exacerbations: not a criterium Moderate to severe stable COPD (GOLD 2010) ≥40 years ≥10 pack years <u>Exclusion</u> • LRTI/COPD exacerbations in the 6 weeks prior to screening • Significant co-existing pulmonary, renal, or cardiovascular disease • Pre-existing conditions that might be worsened by anticholinergic therapy		Pneumonia	Glycopyrronium: 0/257 Tiotropium:2/258 Placebo: 2/257 NT	assessed in per protocol population SELECTIVE REPORTING: yes; not all outcome data was fully reported Other important methodological remarks: Washout period, followed by 7-day run-in period Sponsor: Novartis Pharmaceuticals

Table 204

Study details	n/Population	Comparison	Outcomes		Methodological
Siler 2015(99) NCT01957163	n= 619 Mean age: 64.5 % females: 34	**Umeclidinium 62.5 mcg** + open- label fluticasone/vilanterol 100/25 mcg	Efficacy Trough FEV1 (PO)	Ume 62.5mcg: 0.103 Ume 125 mcg: 0.108 Placebo: -0.020	RANDO: Adequate ALLOCATION CONC: Unclear (not described)

Design: RCT (DB) (PG) Twin trials Duration of follow-up: 12 weeks	Smoking: current: 42% % taking ICS at inclusion: 63% ICS policy: all participants were allocated to open-label LABA/ICS combination other background medications allowed: no GOLD (yr)-classification of patients: II: 40% III: 46% IV: 14% Baseline FEV1 45.2% predicted % reversible : 14.3% <u>Inclusion:</u> Dyspnea: Y, modified Medical Research	OR **Umeclidinium 125 mcg** + open- label fluticasone/vilanterol 100/25 mcg Vs **Placebo** + open-label fluticasone/vilanterol 100/25 mcg Salbutamol as rescue medication		**Ume 62.5 mcg vs placebo** **Difference: 0.124(95%CI 0.093 to 0.154)** **SS en p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **Difference: 0.128 (95%CI 0.098 to 0.159)** **SS en p<0.001** **In favour of Umeclidinium 125 mcg**	BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.2 % Drop-out and Exclusions: 7% • Described: yes • Balanced across groups: placebo 7%, umeclidinium 62.5 mcg 5%, umeclidinium 125 mcg 9% • ITT: All patients randomized to treatment who received at least one dose of study drug SELECTIVE REPORTING: no Other important methodological remarks : 4 weeks run-in treatment with
			Proportion of patients achieving an increase of >0.100 L above baseline in trough FEV1	Ume 62.5mcg: 94/206 Ume 125 mcg: 89/206 Placebo: 27/205 **Ume 62.5 mcg vs placebo** **OR: 5.6(95%CI 3.4 to 5.1)** **SS en p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **OR: 5.1 (95%CI 3.1 to 8.3)** **SS en p<0.001** **In favour of Umeclidinium 125 mcg**	
			SGRQ-C	Ume 62.5mcg: -3.05 Ume 125 mcg: -1.77	

	Council dyspnea scale score ≥2 FEV1 % expected: Y, ≤70% Exacerbations: N, not a criterium ≥40 years ≥10 pack years FEV1/FVC<0.7 <u>Exclusion</u> • Other known respiratory disease • Hospitalization for COPD or pneumonia in the 12 weeks previous to visit 1 • Pregnancy • Use of long-term oxygen therapy			Placebo: -2.23 Ume 62.5 mcg vs placebo Difference: -0.82(95%CI -2.76 to 1.12) NS Ume 125 mcg vs placebo Difference: 0.46 (95%CI -1.49 to 2.41) NS	fluticasone/vilanterol Sponsor: GSK
			Exacerbations (worsening of symptoms requiring the use of any treatment beyond study medication or rescue salbutamol)	Ume 62.5mcg: 6/206 Ume 125 mcg: 14/206 Placebo: 7/206 NT	
			SAFETY		
			Atrial fibrillation	Ume 62.5mcg: 1/206 Ume 125 mcg: 1/206 Placebo: 3/206 NT	
			pneumonia	Ume 62.5mcg: 0/206 Ume 125 mcg: 3/206 Placebo: 3/206 NT	
			Fatal AEs	Ume 62.5mcg: 0/206	

				Ume 125 mcg: 0/206 Placebo: 1/206 NT	

Table 205

Study details	n/Population	Comparison	Outcomes		Methodological
Siler 2015(99) NCT02119286 Design: RCT (DB) (PG) Twin trials Duration of follow-up:	n= 620 Mean age: 62.9 % females: 37 Smoking: current: 57% % taking ICS at inclusion: 46% other background medications allowed: no GOLD (yr)-classification of patients:	**Umeclidinium 62.5 mcg** + open- label fluticasone/vilanterol 100/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/vilanterol 100/25 mcg Vs **Placebo** + open-	Efficacy		FOLLOW-UP: Lost-to follow-up: 0.5 % Drop-out and Exclusions: 7% • Described: yes • Balanced across groups: placebo: 12%, umeclidinium 62.5 mcg: 5%, umeclidinium 125 mcg: 3%
			Trough FEV1 (PO)	Ume 62.5mcg: 0.092 Ume 125 mcg: 0.081 Placebo: -0.030 **Ume 62.5 mcg vs placebo** **Difference: 0.122(95%CI 0.091 to 0.152)** **SS en p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **Difference: 0.111 (95%CI 0.081 to 0.141)** **SS en p<0.001** **In favour of Umeclidinium 125 mcg**	

12 weeks	II: 48% III: 41% IV: 11% Baseline FEV1 : 47.2% predicted % reversible : 12.1	label fluticasone/vilanterol 100/25 mcg Salbutamol as rescue medication			
			Proportion of patients achieving an increase of >0.100 L above baseline in trough FEV1	Ume 62.5mcg: 88/206 Ume 125 mcg: 84/206 Placebo: 28/205 **Ume 62.5 mcg vs placebo** **OR: 4.8(95%CI 2.9 to 7.8)** **SS en p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **OR: 4.4 (95%CI 2.7 to 7.2)** **SS en p<0.001** **In favour of Umeclidinium 125 mcg**	
			SGRQ-C score	Ume 62.5mcg: -1.56 Ume 125 mcg: -1.04 Placebo: 0.59 **Ume 62.5 mcg vs placebo** **Difference: -2.16(95%CI -3.83 to -0.49)** **SS and p<0.01** **In favour of Umeclidinium 62.5mcg** Ume 125 mcg vs placebo Difference: -1.63 (95%CI -3.29 to 0.02) NS	
			Exacerbations	Ume 62.5mcg: 6/206	

			(worsening of symptoms requiring the use of any treatment beyond study medication or rescue salbutamol)	Ume 125 mcg: 4/206 Placebo: 17/206 NT	
			SAFETY		
			Atrial arrhythmias	Ume 62.5mcg: 1/206 Ume 125 mcg: 2/206 Placebo: 2/206 NT	
			pneumonia	Ume 62.5mcg: 2/206 Ume 125 mcg: 1/206 Placebo: 1/206. NT	
			Fatal AEs	Ume 62.5mcg: 1/206 Ume 125 mcg: 0/206 Placebo: 4/206 NT	

Table 206

Study details	n/Population	Comparison	Outcomes		Methodological
Siler 2016(100) NCT01772134 Design: RCT (DB) (PG) Duration of follow-up: 12 weeks	n= 617 Mean age: 63 % females: 34 Smoking: current: 54% % taking ICS at inclusion: 51% ICS policy: all participants allocated to LABA+ICS other background medications allowed: none GOLD -classification of patients: II: 45% III: 43%	**Umeclidinium 62.5 mcg** + open- label fluticasone/salmeterol 250/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/salmeterol 250/25 mcg Vs **Placebo** + open- label fluticasone/salmeterol 250/25 mcg	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.3% Drop-out and Exclusions: 9.7% • Described: yes • Balanced across groups: placebo 12%, umeclidinium 62.5 mcg 7%, umeclidinium 125 mcg
			Trough FEV1 (PO)	**Ume 62.5 mcg vs placebo** **LS mean Difference: 0.147(95%CI 0.107 to 0.187)** **SS and p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **Difference: 0.138 (95%CI 0.098 7 to 0.178)** **SS and p<0.001** **In favour of Umeclidinium 125 mcg**	
			Proportion of patients achieving an increase of >0.100 L above baseline in trough FEV1	**Ume 62.5 mcg vs placebo** **OR: 5.6 (95%CI 3.5 to 8.9)** **SS and p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **OR: 4.5 (95%CI 2.8 to 7.2)**	

	IV:11% Baseline FEV1 47% predicted % reversible :15.6 <u>Inclusion:</u> Dyspnea: Y, modified Medical Research Council dyspnea scale score ≥2 FEV1 % expected: Y, ≤70% Exacerbations: N, not a criterium ≥40 years ≥10 pack years FEV1/FVC<0.7 <u>Exclusion</u> • Other known respiratory disease • Hospitalization for COPD or pneumonia in the 12 weeks previous to visit 1	Salbutamol as rescue medication		**SS and p<0.001** **In favour of Umeclidinium 125 mcg**	10% ITT: Defined as all patients randomized to treatment who received at least one dose of study drug SELECTIVE REPORTING: yes, not all outcome data reported Other important methodological remarks : 4 weeks run-in treatment with fluticasone/salmeterol Sponsor: GSK
			SGRQ-C	Ume 62.5mcg: -3.57 Ume 125 mcg: -2.77 Placebo: -2.26 Ume 62.5 mcg vs placebo LS mean Difference: -1.32 (95%CI -3.27 to 0.64) NS Ume 125 mcg vs placebo Difference: -0.51 (95%CI -2.47 to 1.44) NS	
			Exacerbations (worsening of symptoms requiring the use of any treatment beyond study medication or rescue salbutamol, number of patients)	Ume 62.5mcg: 9/204 Ume 125 mcg: 7/205 Placebo: 13/205 NT	
			SAFETY		
			pneumonia	Ume 62.5mcg: 1/204 Ume 125 mcg: 2/205 Placebo: 0/205	

				NT	
			Fatal AEs	Ume 62.5mcg: 0/204 Ume 125 mcg: 1/205 Placebo: 0/205 NT	

Table 207

Study details	n/Population	Comparison	Outcomes		Methodological
Siler 2016(100) NCT01772147 Design: RCT (DB) (PG)	n= 608 Mean age: 65 % females: 37 Smoking: current: 38% % taking ICS at inclusion: 58% other background medications allowed: no GOLD (yr)-	**Umeclidinium 62.5 mcg** + open- label fluticasone/vilanterol 100/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/vilanterol 100/25 mcg Vs	Efficacy		FOLLOW-UP: Lost-to follow-up: 0.3 % Drop-out and Exclusions: 12% • Described: yes • Balanced across groups: placebo: 15%, umeclidinium 62.5 mcg: 12%, umeclidinium 125 mcg: 8%
			Trough FEV1 (PO)	**Ume 62.5 mcg vs placebo** **LS mean Difference: 0.127 (95%CI 0.089 to 0.164)** **SS and p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **Difference: 0.148 (95%CI 0.111 to 0.185)** **SS and p<0.001** **In favour of Umeclidinium 125 mcg**	
			Proportion of patients	**Ume 62.5 mcg vs placebo**	

Duration of follow-up: 12 weeks	classification of patients: II: 39% III: 47% IV: 12% Baseline FEV1 : 45.4% predicted % reversible : 15.4	**Placebo** + open-label fluticasone/vilanterol 100/25 mcg Salbutamol as rescue medication	achieving an increase of >0.100 L above baseline in trough FEV1	**OR: 4.1 (95%CI 2.6 to 6.5)** **SS and p<0.001** **In favour of Umeclidinium 62.5 mcg** **Ume 125 mcg vs placebo** **OR: 5.7 (95%CI 3.6 to 9.1)** **SS and p<0.001** **In favour of Umeclidinium 125 mcg**	
			SGRQ-C score	Ume 62.5mcg: -3.50 Ume 125 mcg: -4.54 Placebo: -1.50 Ume 62.5 mcg vs placebo LS mean Difference: -1.99 (95%CI -4.14to 0.16) NS **Ume 125 mcg vs placebo** **Difference: -3.04 (95%CI -5.19 to -0.89)** **SS and p<0.05** **In favour of umeclidinium 125 mcg**	
			Exacerbations (worsening of symptoms requiring the use of any treatment beyond study	Ume 62.5mcg: 10/203 Ume 125 mcg: 8/202 Placebo: 20/201 NT	

			medication or rescue salbutamol) number of patients		
			SAFETY		
			pneumonia	Ume 62.5mcg: 3/203 Ume 125 mcg: 5/202 Placebo: 6/201 NT	
			Fatal AEs	Ume 62.5mcg: 1/203 Ume 125 mcg: 0/202 Placebo: 1/201 NT	

Table 208

Study details	n/Population	Comparison	Outcomes		Methodological
Singh 2016(21) TRILOGY	n= 1368 Mean age: 63.5y % females: 24%	Glycopyrronium bromide 12.5 mcg + beclometasone/formoterol 100/6 mcg	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate
			Trough FEV1 (PO)	triple: 0.071 beclo/formo: 0.008	

Design: RCT (DB) (PG) Duration of follow-up: 52 weeks	Smoking: current: 47%; ex: 53% % taking ICS at inclusion: 74% ICS policy: all participants were allocated to ICS+LABA other background medications allowed: GOLD -classification of patients: III: 77% IV: 23% Baseline FEV1% predicted : • 30-<50% : 77% • <30% :23% % reversible : 10.4 <u>Inclusion:</u> Dyspnea: Y, baseline dyspnea index focal score of ≤10	Vs beclometasone/formoterol 100/6 mcg Salbutamol as rescue medication		**Adj. Mean diff 0.063 (95%CI 0.032 to 0.094)** **SS and p <0.001** **In favour of triple therapy**	BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.5% Drop-out and Exclusions: 13% • Described: yes • Balanced across groups: triple: 12%; beclo/formo: 14% ITT: Defined as all patients who were randomly assigned and received at least one dose of study drug and had at least one post-baseline efficacy assessment SELECTIVE REPORTING: yes, not all outcome data reported
			SGRQ- total score	**Mean diff -1.69 (95%CI -3.20 to -0.17)** **SS and p <0.029** **In favour of triple therapy**	
			SGRQ response (decrease from baseline ≥4)	triple: 297/687 beclo/formo: 244/680 **OR 1.33 (95%CI 1.06 to 1.66)** **SS and p = 0.014** **In favour of triple therapy**	
			Moderate to severe exacerbations (requiring systemic corticoids, antibiotics, or hospital admission); percentage of patients	triple: 31% beclo/formo: 35% NT	
			Adjusted annual rate of moderate-to severe exacerbations	triple: 0.41 beclo/formo: 0.53 **Rate ratio 0.77 (95%CI 0.65 to 0.92)** **SS and p = 0.005** **In favour of triple therapy**	
			SAFETY		
			Major adverse cardiovascular events	triple: 15/687 beclo/formo: 15/680	

	FEV1 % expected: Y, <50% Exacerbations: Y, at least one moderate or severe COPD exacerbation in the previous 12 months ≥40 years Use of ICS+ LABA or ICS+ LAMA or LABA + LAMA or LAMA CAT-score ≥10 ≥10 pack year <u>Exclusion</u> Asthma, allergic rhinitis or atopy COPD exacerbation in the 4 weeks before screening or during run-in Clinically significant cardiovascular conditions or laboratory abnormalities, unstable concurrent disease			NT	Other important methodological remarks: 2-week open-label run-in with beclomatasone/formoterol Sponsor: Chiesi Farmaceutici SpA
			Pneumonia	triple: 15/687 beclo/formo: 7/680 NT	
			Treatment-emergent adverse events leading to death	triple: 15/687 beclo/formo: 16/680 NT	

Table 209

6.3.4.2 *Summary and conclusions*

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Frith 2015(9) GLISTEN	773	12 weeks	**Glycopyrronium** 50 mcg 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Placebo** 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d	Mean age: 68y % females: 35.6% Current: 36% Ex-smoker: 64% % taking ICS at inclusion: 66%	II: 68% III: 32%	66	unclear randomization and allocation concealment Trial described as "blinded"; not clear if personnel and assessors were aware of allocation higher % of patients discontinued in placebo arm (22%) compared to glycopyrronium arm (11%), and tiotropium arm (12%); p<0.00012 not all outcome data was fully reported
Siler 2015a(99) NCT01957163	619	12 weeks	**Umeclidinium 62.5 mcg** + open- label fluticasone/vilanterol 100/25 mcg OR **Umeclidinium 125 mcg** + open- label	Mean age: 64.5 % females: 34 Smoking: current: 42%	II: 40% III: 46% IV: 14%	63	unclear allocation concealment

			fluticasone/vilanterol 100/25 mcg Vs **Placebo** + open-label fluticasone/vilanterol 100/25 mcg				
Siler 2015b(99) NCT02119286	620	12 weeks	**Umeclidinium 62.5 mcg** + open- label fluticasone/vilanterol 100/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/vilanterol 100/25 mcg Vs **Placebo** + open-label fluticasone/vilanterol 100/25 mcg	Mean age: 62.9 % females: 37 Smoking: current: 57%	II: 48% III: 41% IV: 11%	46	unclear allocation concealment higher % drop-out in placebo group vs umeclidinium groups
Siler 2016a(100) NCT01772134	617	12 weeks	**Umeclidinium 62.5 mcg** + open- label fluticasone/salmeterol 250/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/salmeterol 250/25 mcg Vs **Placebo** + open-label fluticasone/salmeterol 250/25 mcg	Mean age: 63 % females: 34 Smoking: current: 54%	II: 45% III: 43% IV:11%	51	higher % dropout in placebo arm vs umeclidinium arms not all outcome data reported
Siler	608	12	**Umeclidinium 62.5**	Mean age:	II: 39%	58	not all

2016b(100) NCT01772147		weeks	**mcg** + open- label fluticasone/salmeterol 250/25 mcg OR **Umeclidinium 125 mcg** + open- label fluticasone/salmeterol 250/25 mcg Vs **Placebo** + open-label fluticasone/salmeterol 250/25 mcg	65 % females: 37 Smoking: current: 38%	III: 47% IV: 12%		outcome data reported
Singh 2016(21) TRILOGY	1368	52 weeks	Glycopyrronium bromide 12.5 mcg + beclometasone/formoterol 100/6 mcg Vs beclometasone/formoterol 100/6 mcg	Mean age: 63.5y % females: 24% Smoking: current: 47%; ex: 53%	III: 77% IV: 23%	74	not all outcome data reported

Table 210

A systematic review and meta-analysis (Rojas-Reyes 2016(91)) searched for RCTs that compared LABA+ ICS+ tiotropium vs tiotropium + ICS.

For the comparison LABA + ICS + tiotropium vs tiotropium + ICS only one RCT was found. We did not report it because it did not meet our inclusion criteria (n=30 per study arm).

6 additional RCTs, published after the final search date of the systematic review described above, also compared triple therapy to treatment with LABA +ICS.

The mean age and percentage women was similar in the trials. Participants with moderate to very severe COPD (in two trials) were included.

5 RCTs had a duration of 12 weeks, while one had a duration of 52 weeks.

In 5 RCTs the ICS used was fluticasone. In one RCT the ICS used was beclomethasone.
In 3 RCTs the LABA used was salmeterol. In 2 RCTs the LABA used was vilanterol. In one RCT the LABA used was formoterol.
In 2 RCTs the LAMA used was glycopyrronium. In four RCTs the LAMA used was umeclidinium.

Three RCTs had unclear reporting of allocation concealment. One RCT had unclear reporting of randomization and blinding methods. The dropout was large or unbalanced in three RCTs. The reporting of outcome data was selective in four trials. This severely limits our confidence in the results.

Endpoint: Trough FEV1		
n=4605 12-52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 unclear rando, alloc concealment, blinding, unbalanced dropout, selective reporting Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Frith 2015 n=773	**LSM TD 101 mL**	**SS** **in favour of triple therapy**
Siler 2015a n=619	**<u>Ume 62.5 mcg vs placebo</u>** **Difference: 0.124(95%CI 0.093 to 0.154)** **<u>Ume 125 mcg vs placebo</u>** **Difference: 0.128 (95%CI 0.098 to 0.159)**	**SS** **In favour of triple therapy** **SS** **In favour of triple therapy**
Siler 2015b n=620	**<u>Ume 62.5 mcg vs placebo</u>** **Difference: 0.122(95%CI 0.091 to 0.152)** **<u>Ume 125 mcg vs placebo</u>** **Difference: 0.111 (95%CI 0.081 to 0.141)**	**SS** **In favour of triple therapy** **SS** **In favour of triple therapy**
Siler 2016a n= 617	**<u>Ume 62.5 mcg vs placebo</u>** **LS mean Difference: 0.147(95%CI 0.107 to 0.187)** **<u>Ume 125 mcg vs placebo</u>** **Difference: 0.138 (95%CI 0.098 7 to 0.178)**	**SS** **In favour of triple therapy** **SS** **In favour of triple therapy**
Siler 2016b n=608	**<u>Ume 62.5 mcg vs placebo</u>** **LS mean Difference: 0.127 (95%CI 0.089 to 0.164)** **<u>Ume 125 mcg vs placebo</u>** **Difference: 0.148 (95%CI 0.111**	**SS** **In favour of triple therapy** **SS** **In favour of triple therapy**

	to 0.185)	
Singh 2016 n=1368	**<u>Adj. Mean diff</u> 0.063 (95%CI 0.032 to 0.094)**	**SS** **In favour of triple therapy**

Table 211

The results of these studies suggest that trough FEV1 is increased with triple therapy compared to LABA+ICS.

For this series of studies,

All results are statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: SGRQ-total score		
n=4605 12-52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 unclear rando, alloc concealment, blinding, unbalanced dropout, selective reporting Consistency: -1 NS and SS Directness: ok Imprecision: ok	
Studies	Results	
Frith 2015 n=773	**LSM TD -2.15 (95%CI -3.972 to -0.336)**	**SS** **In favour of triple therapy**
Siler 2015a n=619	<u>Ume 62.5 mcg vs placebo</u> Difference: -0.82(95%CI -2.76 to 1.12) <u>Ume 125 mcg vs placebo</u> Difference: 0.46 (95%CI -1.49 to 2.41)	NS NS
Siler 2015b n=620	**<u>Ume 62.5 mcg vs placebo</u>** **Difference: -2.16(95%CI -3.83 to -0.49)** <u>Ume 125 mcg vs placebo</u> Difference: -1.63 (95%CI -3.29 to 0.02)	**SS** **In favour of triple therapy** NS
Siler 2016a n= 617	<u>Ume 62.5 mcg vs placebo</u> LS mean Difference: -1.32 (95%CI -3.27 to 0.64) <u>Ume 125 mcg vs placebo</u> Difference: -0.51 (95%CI -2.47 to 1.44)	NS NS

Siler 2016b n=608	Ume 62.5 mcg vs placebo LS mean Difference: -1.99 (95%CI -4.14to 0.16) **Ume 125 mcg vs placebo** **Difference: -3.04 (95%CI -5.19 to -0.89)**	NS **SS** **In favour of triple therapy**
Singh 2016 n=1368	**Mean diff -1.69 (95%CI -3.20 to -0.17)**	**SS** **In favour of triple therapy**

Table 212

We cannot make a statement about the direction of the effect of triple therapy versus LABA+ICS on SGRQ-total score.

For this series of studies,

Most results aren't statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Exacerbations (number of patients with moderate or severe exacerabtions)		
n=3366 12-52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 unclear rando, alloc concealment, blinding, unbalanced dropout, selective reporting Consistency: NA without statistical testing Directness: ok Imprecision: -1 no statistical testing	
Studies	Results	
Frith 2015 n=773	NR	NS
Siler 2016a n= 617	Ume 62.5mcg: 9/204 Ume 125 mcg: 7/205 Placebo: 13/205	NT
Siler 2016b n=608	Ume 62.5mcg: 10/203 Ume 125 mcg: 8/202 Placebo: 20/201	NT
Singh 2016 n=1368	triple: 31% beclo/formo: 35%	NT

Table 213

We cannot make a statement about the direction of the effect of triple therapy versus LABA+ICS on number of patients with moderate or severe exacerbations.

Most trials did not perform a statistical test.

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Exacerbations (number of moderate or severe exacerbations)

n=2607 12-52 weeks	**GRADING** ⨁⨀⨀⨀ **VERY LOW** Study quality: -1 unclear alloc conceal, unbalanced dropout, selective reporting Consistency: -1 more exacerbations with triple in Siler 2015a Directness: ok Imprecision: -1 no statistical testing	
Studies	Results	
Siler 2015a n=619	Ume 62.5mcg: 6/206 Ume 125 mcg: 14/206 Placebo: 7/206	NT
Siler 2015b n=620	Ume 62.5mcg: 6/206 Ume 125 mcg: 4/206 Placebo: 17/206	NT
Singh 2016 n=1368	**Rate ratio 0.77 (95%CI 0.65 to 0.92)**	**SS** **In favour of triple therapy**

Table 214

We cannot make a statement about the direction of the effect of triple therapy versus LABA+ICS on number of moderate or severe exacerbations.

Most trials did not perform a statistical test.

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

6.3.5 Triple therapy vs other triple therapy

6.3.5.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Frith 2015(9) GLISTEN Design: RCT (SB) (PG) Duration of follow-up: 12 weeks	n= 773 Mean age: 68y % females: 35.6% • Smoking: • Current: 36% Ex-smoker: 64% % taking ICS at inclusion: 66% ICS policy: All participants were randomized to same LABA+ICS combination other background medications allowed: GOLD (2010)-	**Glycopyrronium 50 mcg** 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Placebo** 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Tiotropium 18 mcg** 1x/d + salmeterol/fluticasone 50/500 mcg 2x/d			RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: unclear Assessors: unclear Remarks on blinding method: Trial described as "blinded"; not clear if personnel and assessors were aware of allocation POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.3%
			Trough FEV1 (PO for glycopyrronium vs tiotropium)	<u>Glycopyrronium vs tiotropium</u> LSM TD -7 mL (97.16%CI -45 to 31 mL) **Glycopyrronium non-inferior to tiotropium** **<u>Glycopyrronium vs placebo:</u>** **LSM TD 101 mL** **P<0.001** **SS in favour of glycopyrronium**	
			SGRQ-C total score	<u>Glycopyrronium vs tiotropium</u> TD -1.1 (-0.719 to 2.911) P= 0.236 NS **<u>Glycopyrronium vs placebo:</u>** **LSM TD -2.15 (95%CI -3.972 to -0.336)** **P=0.02** **SS in favour of glycopyrronium**	

	classification of patients: II: 68% III: 32% Baseline FEV1 57% predicted % reversible : 22 <u>Inclusion:</u> Dyspnea: not a criterium FEV1 % predicted: Y, ≥30 - <80% Exacerbations: not a criterium Moderate to severe stable COPD (GOLD 2010) ≥40 years ≥10 pack years <u>Exclusion</u> • LRTI/COPD exacerbations in the 6 weeks prior to screening • Significant co-existing pulmonary, renal,	Salbutamol as rescue medication (Glycopyrronium was compared to tiotropium and to placebo, but tiotropium was not analysed versus placebo)	Number of patients experiencing a moderate or severe COPD exacerbation	Glycopyrronium: 29/257 Tiotropium: 24/258 Placebo: 32/257 <u>Glycopyrronium vs tiotropium</u> NS <u>Glycopyrronium vs placebo:</u> NS	Drop-out and Exclusions: 15% • Described: yes • Balanced across groups: no; higher % of patients discontinued in placebo arm (22%) compared to glycopyrronium arm (11%), and tiotropium arm (12%); p<0.00012 ITT: No: full analysis set (FAS) Primary outcome (non-inferiority of glycopyrronium vs tiotropium for trough FEV1)was assessed in per protocol population SELECTIVE REPORTING: yes; not all outcome data was fully reported Other important methodological remarks: Washout period, followed by 7-day run-in period Sponsor: Novartis
			SAFETY		
			Atrial fibrillation	Glycopyrronium: 0/257 Tiotropium: 2/258 Placebo: 1/257 NT	
			Pneumonia	Glycopyrronium: 0/257 Tiotropium:2/258 Placebo: 2/257 NT	

	or cardiovascular disease • Pre-existing conditions that might be worsened by anticholinergic therapy				Pharmaceuticals

Table 215

6.3.5.2 *Summary and conclusions*

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Frith 2015(9) GLISTEN	773	12 weeks	**Glycopyrronium** 50 mcg 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d Vs **Tiotropium** 18 mcg 1x/d + salmeterol/fluticasone 50/500 mcg 2x/d	Mean age: 68y % females: 35.6% • Smoking : • Current: 36% Ex-smoker: 64% % taking ICS at inclusion: 66%	II: 68% III: 32%	66%	unclear randomization and allocation concealment Trial described as "blinded"; not clear if personnel and assessors were aware of allocation not all outcome data was fully reported

Table 216

A blinded parallel group RCT compared triple therapy with **glycopyrronium** 50 mcg 1x/d + Salmeterol/fluticasone 50/500 mcg 2x/d to triple therapy with **tiotropium** 18 mcg 1x/d + salmeterol/fluticasone 50/500 mcg 2x/d in 773 patients with moderate to severe COPD.

The duration of this RCT was 12 weeks.

This RCT had unclear reporting of randomization and allocation concealment. It was not clear whether the assessors were blinded. The reporting of outcome data was incomplete. This severely limits our confidence in the results.

Endpoint: Trough FEV1		
n=773 12 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -2 unclear randomization, allocation concealment and blinding; selective reporting Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Frith 2015	LSM TD -7 mL (97.16%CI -45 to 31 mL)	Glycopyrronium non-inferior to tiotropium

Table 217

The result of this study suggests that triple therapy with glycopyrronium/salmeterol/fluticasone is non-inferior to triple therapy with tiotropium/salmeterol/fluticasone for trough FEV1.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: SGRQ		
n=773 12 weeks	**GRADING** ⊕⊕⊖⊖ **LOW** Study quality: -2 unclear randomization, allocation concealment and blinding; selective reporting Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Frith 2015	TD -1.1 (-0.719 to 2.911)	NS

Table 218

The results of these studies do not suggest an effect in any direction.

For this study,
The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Number of patients experiencing a moderate or severe COPD exacerbation		
n=773 12 weeks	**GRADING** ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 unclear randomization, allocation concealment and blinding; selective reporting Consistency: NA Directness: ok Imprecision: -1 no CI	
Studies	Results	
Frith 2015	Glycopyrronium: 29/257 Tiotropium: 24/258	NS

Table 219

The results of these studies do not suggest an effect in any direction.

For this study,
The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

6.3.6 Adverse events from RCTs

6.3.6.1 *Triple therapy vs LAMA*

A meta-analysis of 4 RCTs (Rojas-Rejes 2016(91)) found no difference of **serious adverse events** with triple therapy versus tiotropium alone.
A meta-analysis of 4 RCTs (Rojas-Rejes 2016(91)) found no difference of **pneumonia** with triple therapy versus tiotropium alone.

6.3.6.2 *Triple therapy vs LABA + ICS*

Pneumonia was assessed in 6 RCTs (Singh 2016(21), Siler 2016a(100), Siler 2016b(100), Siler 2015a(99), Siler 2015b(99), Frith 2015(9)) comparing triple therapy to LABA + ICS. Rates were similar between groups, but no statistical testing was performed.
Atrial fibrillation/arrythmia was assessed in 4 RCTS (Frith 2015(9), Siler 2015a(99), Siler 2015b(99), Singh 2016(21)) comparing triple therapy to LABA + ICS. Rates were similar between groups, but no statistical testing was performed.
Fatal adverse events were assessed in 5 RCTs (Siler 2015a(99), Siler 2015b(99), Siler 2016a(100), Siler 2016b(100), Singh 2016(21)) comparing triple therapy to LABA + ICS. Rates were similar between groups, but no statistical testing was performed.

6.3.6.3 *Triple therapy vs other triple therapy*

In an RCT (Frith 2015(9)) where triple therapy with glycopyrronium + Salmeterol/fluticasone was compared to tiotropium + salmeterol/fluticasone, similar rates of **atrial fibrillation** and **pneumonia** were seen. No statistical testing was performed for these outcomes.

6.4 Corticoid withdrawal as intervention

6.4.1 Corticoid withdrawal as intervention

6.4.1.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Magnussen 2014(101)(WISDOM) Design: RCT (DB) (PG) Duration of follow-up: 12 months	n= 2485 Mean age: 63.8y % females: 17.5% former smoker:66.6% % taking ICS at inclusion: 69.9% ICS policy: at the investigator's discretion, randomized treatment could be discontinued and open-label fluticasone could be initiated for the remainder of the trial other background medications allowed: xanthines, mucolytic	During 6-week run-in, all patients received triple therapy with tiotropium 18 mcg 1x/day + salmeterol 50 mcg 2x/day + fluticasone 500 mcg 2x/day, then randomised to : **continued triple therapy** Vs	Efficacy		RANDO: unclear (not well described) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.6% Drop-out and Exclusions: 17.8 % • Described: yes • Balanced across groups: yes ITT:
			Time to first moderate or severe COPD exacerbation (PO)	HR:1.06 (95%CI 0.94 to 1.19) p=0.35 non-inferiority of ICS withdrawal compared to continued triple therapy	
			Number of moderate or severe COPD exacerbations	triple: 0.91 per patient-year ICS withdrawal: 0.95 per patient-year NT or NR	
			Trough FEV1 change from baseline	**Adj. MD 43 mL** **p<0.001** **SS in favour of triple therapy**	
			SGRQ	triple: -0.07 ICS withdrawal: 1.15 **p=0.047** **SS in favour of triple therapy**	
			Dyspnea: modified Medical Research Council (mMRC)	triple: 0.035 ICS withdrawal: -0.028 p=0.06	

	agents GOLD (yr)-classification of patients: III: 61.2% IV: 38.1% Baseline FEV1 32.8% predicted % reversibility to salbutamol : NR <u>Inclusion:</u> ≥40y ≥10 pack years severe or very severe COPD FEV1<50% predicted FEV1/FVC<70% at least one exacerbation in the 12 months before screening <u>Exclusion</u> significant diseases other than COPD	**withdrawal fluticasone in three steps over 12-week period** (dose reduction every 6 weeks from 1000 mcg to 500 mcg to 200 mcg, to placebo) salbutamol as rescue medication		NS	defined as all patients who received at least one dose of a study drug SELECTIVE REPORTING: yes (not all outcome data reported) Other important methodological remarks : prespecified noninferiority margin of 1.20 was defined as the upper limit of the 95%CI for the hazard ratio for the PO Sponsor: Boehringer Ingelheim Pharma
			Serious adverse events	triple: 292/1243 ICS withdrawal: 300/1242 NT	
			Death	triple: 34/1243 ICS withdrawal: 40/1242 NT	
			Pneumonia	triple: 72/1243 ICS withdrawal: 68/1242 NT	
			Major adverse cardiac event	triple: 25/1243 ICS withdrawal: 27/1242 NT	

	use of daytime oxygen therapy >1 h per day use of systemic corticosteroids >5mg/day				

Table 220

A 5-year **observational** follow-up (Kunz 2015(102)) of participants from the GLUCOLD 1 study (Laperre 2009), evaluated FEV1 and QoL of patients previously randomized to a 6- or 30-month treatment with fluticasone, a 30 month treatment with fluticasone and salmeterol , or placebo.

Patients that were allocated to ICS during the interventional part of the study, had a significantly accelerated annual decline of FEV1 if they discontinued ICS during the observational follow-up (= ICS use 0-50% of the time), compared to the interventional part of the study.

This is an observational study with a very small sample size (79 patients started and 58 patients completed the study). For this reason we have very little confidence that these results represent the true effect.

6.4.1.2 *Summary and conclusions*

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Magnussen 2014(101)(WISDOM)	2485	52 weeks	During 6-week run-in, all patients received triple therapy with tiotropium 18 mcg 1x/day + salmeterol 50 mcg 2x/day + fluticasone 500 mcg 2x/day, then randomised to : **continued triple therapy** Vs **withdrawal fluticasone in three steps over 12-week period** (dose reduction every 6 weeks from 1000 mcg to 500 mcg to 200	Mean age: 63.8y % females: 17.5% former smoker:66.6 %	III: 61.2% IV: 38.1%	69.9 %	unclear randomization, selective reporting

			mcg, to placebo)				

Table 221

A double-blind parallel group RCT compared the withdrawal of ICS in three steps over a 12-week period to continued triple therapy, after all patients had been receiving triple therapy during a 6-week run-in.

The duration of this RCT was 52 weeks.

This RCT had unclear reporting of randomization. The reporting of outcome data was incomplete. This limits our confidence in the results.

An additional 5-year **observational** follow-up (Kunz 2015(102)) of participants from the GLUCOLD 1 study (Lapperre 2009(103)), evaluated FEV1 and QoL of patients previously randomized to a 6- or 30-month treatment with fluticasone, a 30 month treatment with fluticasone and salmeterol , or placebo.
Patients that were allocated to ICS during the interventional part of the study, had a significantly accelerated annual decline of FEV1 if they discontinued ICS during the observational follow-up (= ICS use 0-50% of the time), compared to the interventional part of the study.
This is an observational study with a very small sample size (79 patients started and 58 patients completed the study). For this reason we have very little confidence that these results represent the true effect.

Endpoint: Trough FEV1		
n=2485 52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando, selective reporting Consistency: NA Directness: ok Imprecision: -1 no CI	
Studies	Results	
Magnussen 2014 n=2485	**Adj. MD 43 mL**	**SS** **in favour of triple therapy**

Table 222

The results of these studies suggest that trough FEV1 is decreased with ICS withdrawal compared to continuation of triple therapy.

For this study,
The result is statistically significant
Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: SGRQ		
n=2485 52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando, selective reporting Consistency: NA Directness: ok Imprecision: -1 no CI	
Studies	Results	
Magnussen 2014 n=2485	triple: -0.07 ICS withdrawal: 1.15 **p=0.047**	**SS** **in favour of triple therapy**

Table 223

The results of these studies suggest that SGRQ is increased with ICS withdrawal compared to continuation of triple therapy.

For this study,

The result is statistically significant

Please refer to Table 1 (in the critical reflexions section on page24) for the clinical significance of the reported results.

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Dyspnea (mMRC)		
n=2485 52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando, selective reporting Consistency: NA Directness: ok Imprecision: -1 no CI	
Studies	Results	
Magnussen 2014 n=2485	triple: 0.035 ICS withdrawal: -0.028 p=0.06	NS

Table 224

The results of this study does not suggest an effect in any direction.

For this study,

the result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: Time to first moderate or severe COPD exacerbation		
n=2485 52 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear rando, selective reporting Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Magnussen 2014 n=2485	HR:1.06 (95%CI 0.94 to 1.19)	non-inferiority of ICS withdrawal compared to continued triple therapy

Table 225

The result of this study suggests that ICS withdrawal is non-inferior to continued triple therapy for time to the first moderate or severe COPD exacerbation.

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

6.4.2 Adverse events from RCTs

In one RCT (Magnussen 2014(101)) where corticoid withdrawal was compared to continued triple therapy, **serious adverse events**, **death**, **pneumonia**, and **major adverse cardiac events** were reported. Rates between groups were similar, but no statistical testing was performed.

7 Asthma – Evidence tables and conclusions

7.1 Place of LAMAs

7.1.1 LAMA + ICS vs same dose ICS

7.1.1.1 *Clinical evidence profile*

Meta-analysis: Anderson 2015(104) "Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma"

Inclusion criteria:
RCTs of at least 12 weeks' duration. Population: adults >18 years, whose asthma was not well controlled by ICS alone. Comparisons: LAMA added to any dose of ICS therapy versus continued use of ICS at the same dose.

Search strategy:
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts." "We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and industry trial registries." Last search on 9 April 2015.

Assessment of quality of included trials: yes
Other methodological remarks:

Table 226

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Anderson 2015(104) Design: SR + MA	**LAMA + ICS vs ICS alone**	N= 3 n= 1713 (Bateman 2011, Kerstjens	**AQoL**	MD: 0.05 (-0.03; 0.12) NS

Search date: April 2015		2015a, Kerstjens 2015b)		
		N= 3 n= 2277 (Bateman 2011, Kerstjens 2015a, Paggiaro 2014)	**Exacerbations requiring oral corticosteroids**	73/1473 vs 64/804 **OR: 0.65 (0.46; 0.93)** **SS** **Favours LAMA + ICS**
		N= 5 n= 2562 (Bateman 2011, Kerstjens 2015a, Kerstjens 2015b, Paggiaro 2014, Ohta 2015)	**Exacerbations requiring hospital admission**	OR: 0.42 (0.12; 1.47) NS
		N= 5 n= 2459 (Ohta 2015, Paggiaro 2014, Bateman 2011, Kerstjens 2015b, Kerstjens 2015a)	**Trough FEV1 (litres change from baseline)**	**MD: 0.14 (0.10; 0.17)** **SS** **Favours LAMA + ICS**
		N=3 N=1916	**Asthma control (ACQ)**	MD -0.08 (-0.19 to 0.03) NS

		(2015a, Kerstjens 2015b, Paggiaro 2014)		
		N=3 N=2009 (2015a, Kerstjens 2015b, Paggiaro 2014)	**Asthma control (ACQ responder)**	850/1337 vs 390/672 OR 1.23 (0.87 to 1.74) NS
		N=5 n=2562 (Ohta 2015, Paggiaro 2014, Bateman 2011, Kerstjens 2015b, Kerstjens 2015a)	**Serious adverse events**	34/1701 vs 25/861 OR 0.60 (0.23 to 1.57) NS

Table 227

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Bateman 2011(105) RCT	254	- Age: 18-65 - patients homozygous for arginine at the 16th amino acid position of the beta2-adrenergic receptor (B16 Arg/Arg) - Maintenance treatment with ICS	16 weeks	tiotropium 2x2.5 mcg daily+ ICS vs ICS alone ICS= budesonide 400-1000 mcg or equivalent	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk

		- EXCLUSION of significant cardiovascular disease, malignancy, COPD			SELECTIVE REPORTING: Low risk FUNDING: Boehringer Ingelheim, with collaboration from Pfizer
Kerstjens 2015a, Kerstjens 2015b (106) RCT Twin trials	a: 795 b: 764	- Age: 18-75 - Asthma - Pre-bronchodilator FEV1 60% to 90% of predicted normal at screening; variation in absolute FEV1 at screening (pre-bronchodilator) as compared with visit 2 (pre-dose)within ± 30% - ability to use inhalers and perform trial procedures correctly - EXCLUSION of significant cardiovascular disease, malignancy, COPD, women of childbearing potential not using effective birth control	24 weeks	tiotropium (2.5 mcg daily) + ICS vs tiotropium (5 mcg daily) + ICS vs ICS alone (medium dose)	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Boehringer Ingelheim , with collaboration from Pfizer
Paggiaro 2014(107) RCT	456	- Age: 18-75 - Asthma - Pre-bronchodilator FEV1 60% to 90% of predicted normal at visit 1; variation in absolute pre-BD FEV1 values at visit 1 vs visit 2 within ± 30% - symptomatic despite low doses of ICS - ability to use Respimat inhaler correctly EXCLUSION of significant cardiovascular disease, malignancy, COPD, women of childbearing potential not using effective birth control	12 weeks	tiotropium (2.5 mcg daily)+ ICS vs tiotropium (5 mcg daily) + ICS vs ICS (low dose)	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Boehringer Ingelheim, with collaboration from Pfizer

Ohta 2015(108) RCT	285	- Age: 18-75 - Asthma - On maintenance therapy with medium, stable dose of ICS - FEV1 60-90% of predicted normal at visit 1 - symptomatic despite low doses of ICS - ability to perform all trial-related procedures EXCLUSION of significant cardiovascular disease, malignancy, COPD, women of childbearing potential not using effective birth control	52 weeks	tiotropium (2.5 mcg daily)+ ICS vs tiotropium (5 mcg daily) + ICS vs ICS (medium dose)	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Boehringer Ingelheim, with collaboration from Pfizer

Table 228

Study details	n/Population	Comparison	Outcomes		Methodological
Paggiaro 2016(109) Design: RCT DB PG Duration of follow-up: 12 weeks treatment+ 3	n= 465 Mean age: 43 %female: 61% Smoking: 0% (never 82%, ex-smoker: 18%) Asthma severity: mean FEV1 78% of predicted Phenotyping: N <u>Inclusion:</u> - Age 18-75 - Asthma - FEV1≥60% and ≤90% of predicted normal - Never and ex-	Tiotropium 2.5 mcg once daily And Tiotropium 5 mcg once daily Vs Placebo As add-on to low-to medium dose ICS	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear (not specified) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 2% • Described: yes • Balanced across groups: 0% in placebo group, 3% in tio 2.5 mcg and 2% in tio 5 mcg group
			Trough FEV1 (mL)	Tiotropium 2.5mcg: 125 mL Tiotropium 5mcg: 137 mL Placebo: 15 mL **Tio 2.5 mcg vs placebo** **Adj. MD 110 mL (95%CI 38 to 182)** **P= 0.003** **SS in favour of tiotropium 2.5 mcg** **Tio 5 mcg vs placebo** **Adj. MD 122 mL (95%CI 49 to 194)** **P= 0.001** **SS in favour of tiotropium 5 mcg**	

weeks follow-up	smokers - Symptomatic ACQ-7 ≥1.5 - Asthma mild and symptomatic despite current maintenance with low-to medium dose ICS (200-400 mcg budesonide or equivalent) <u>Exclusion:</u> - COPD - Serious coexisting illness - Concurrent SAMA or LAMA use - LABA use within 4 weeks before enrollment		**ACQ-7 total score**	Tiotropium 2.5mcg: 1.438 Tiotropium 5mcg: 1.391 Placebo: 1.377 Tio 2.5 mcg vs placebo Adj. MD 0.061 (95%CI -0.071 to 0.194) P= 0.36 NS Tio 5 mcg vs placebo Adj. MD 0.014 (95%CI -0.118 to 0.146) P= 0.83 NS	ITT:Defined as all randomized patients who received at least 1 documented dose of trial drug SELECTIVE REPORTING: no Other important methodological remarks: - 4 week screening period before randomization - Primary endpoint peak FEV1 (not reported by us) Sponsor: Boehringer-Ingelheim

Table 229

7.1.1.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Anderson 2015(104)	N=5 (Ohta 2015, Paggiaro 2014, Bateman 2011, Kerstjens 2015b, Kerstjens 2015a)	12-52 weeks	LAMA + ICS vs ICS alone at the same dose	adults >18 years, whose asthma was not well controlled by ICS alone	No remarks

Table 230

Bibliography summary						
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	methodological remarks
Paggiaro 2016(109)	465	15 weeks	Tiotropium 2.5 mcg once daily And Tiotropium 5 mcg once daily Vs Placebo As add-on to low-to medium dose ICS	Mean age: 43 %female: 61% Smoking: 0% (never 82%, ex-smoker: 18%) Asthma severity: mean FEV1 78% of predicted	FEV1≥60% and ≤90% of predicted normal Asthma mild and symptomatic despite current maintenance with low-to medium dose ICS (200-400 mcg budesonide or equivalent)	Allocation concealment unclear

Table 231

A systematic review and meta-analysis searched for RCTs that compared treatment with a LAMA + ICS to treatment with ICS alone, at the same dose, in adults whose asthma was not well controlled by ICS alone.

Five RCTs were found, with a duration of 12-52 weeks.

There were no methodological remarks on these RCTs.

An additional RCT, published after the final search date of the systematic review described above, also compared treatment with a LAMA + ICS to treatment with ICS alone, at the same dose, in 465 adult asthma patients who were symptomatic despite maintenance with low-to-medium dose ICS.

The duration of this RCT was 15 weeks.

This RCT had unclear reporting of allocation concealment.

Endpoint: Trough FEV1		
12-52 weeks n=3014	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Anderson 2015 (Ohta 2015, Paggiaro 2014, Bateman 2011, Kerstjens 2015b, Kerstjens 2015a) n= 2459	**MD: 0.14 L (0.10; 0.17)**	**SS** **In favour of LAMA + ICS**
Paggiaro 2016 n=465	**Tio 2.5 mcg +ICS vs ICS** **Adj. MD 110 mL (95%CI 38 to 182)** **Tio 5 mcg+ ICS vs ICS** **Adj. MD 122 mL (95%CI 49 to 194)**	**SS** **In favour of LAMA+ICS**

Table 232

The results of these studies suggest that trough FEV1 is increased with LAMA+ICS compared to ICS alone.

For this series of studies,

All results are statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: ACQ		
12-24weeks n= 2381	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Anderson 2015 (Kerstjens 2015a, Kerstjens 2015b,	MD -0.08 (-0.19 to 0.03)	NS

Paggiaro 2014) n= 1916		
Paggiaro 2016 n=465	Tio 2.5 mcg vs placebo Adj. MD 0.061 (95%CI -0.071 to 0.194) Tio 5 mcg vs placebo Adj. MD 0.014 (95%CI -0.118 to 0.146)	NS

Table 233

The results of these studies do not suggest an effect in any direction.

For this series of studies,

No result is statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: AQLQ		
16-24 weeks n= 1713	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Anderson 2015 (Bateman 2011, Kerstjens 2015a, Kerstjens 2015b) n= 1713	MD: 0.05 (-0.03; 0.12)	NS

Table 234

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

the result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Exacerbations requiring oral corticoids	
12-24 weeks n= 2277	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Studies	Results

Anderson 2015 (Bateman 2011, Kerstjens 2015a, Paggiaro 2014) n= 2277	**OR: 0.65 (0.46; 0.93)**	**SS** **Favours LAMA + ICS**

Table 235

The results of these studies suggest that the number of exacerbations requiring oral corticoids is decreased with LAMA+ICS compared to ICS alone.

For this meta-analysis,

the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Exacerbations requiring hospital admission		
12-52 weeks n= 2562	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (wide CI)	
Studies	Results	
Anderson 2015 (Bateman 2011, Kerstjens 2015a, Kerstjens 2015b, Paggiaro 2014, Ohta 2015) n= 2562	OR: 0.42 (0.12; 1.47)	NS

Table 236

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.

GRADE: MODERATE quality of evidence

7.1.2 LAMA + ICS vs higher dose ICS

7.1.2.1 *Clinical evidence profile*

Meta-analysis: Evans 2015(110)"Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma" Inclusion criteria: Double-blinded parallel or cross-over RCTs, at least 12 weeks' duration. Population >18 years old, asthma not well controlled on ICS alone. Comparison: any dose of tiotropium, aclidinium bromide or glycopyrronium bromide as an add-on to any dose of ICS versus an increased ICS dose. Search strategy: "systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts." "We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and industry trial registries." Last search April 2015. Assessment of quality of included trials: yes Other methodological remarks:/

Table 237

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Evans 2015(110)" Design: SR+ MA Search date: April 2015	**LAMA + ICS vs higher dose ICS**	N= 1 n= 210 (Peters 2010)	**AQoL**	MD 0.10 (-0.07 to 0.27) NS
		N= 1 n= 210 (Peters 2010)	**Exacerbations requiring a course of oral corticosteroids**	OR: 0.57 (0.22 to 1.43) NS
		N= 1 n= 210 (Peters 2010)	**Exacerbations requiring hospital admission**	OR 1.00 (0.06 to 16.24) NS

		N= 1 n= 210 (Peters 2010)	**Exacerbations**	OR 0.49 (0.09 to 2.77) NS
		N= 1 n= 210 (Peters 2010)	**FEV1 pre-albuterol**	**MD 0.10 L (0.03 to 0.17)** **SS** **Favours LAMA + ICS**
		N= 1 n= 210 (Peters 2010)	**Asthma Control Questionnaire score**	**MD -0.18 (-0.34 to -0.02)** **SS** **Favours LAMA + ICS**
		N= 1 n= 210 (Peters 2010	**Severe adverse events**	OR 1.00 (0.20 to 5.09) NS

Table 238

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Peters 2010(111) RCT Cross-over	210	- Age: at least 18 - Asthma - received prescription for or used asthma controller in previous 12months;OR symptoms > twice a week and not on asthma controller; if on ICS, stable dose for at least two weeks not exceeding 1000 mcg fluticasone or equivalent daily - ≥ 75% adherence with study medication during run-in - EXCLUSION: COPD, history of life threatening asthma, pregnant	14 week treatment period followed by 2-week washout	Beclomethasone 80 mcg twice daily + tiotropium 18 mcg once daily Vs Beclomethasone 160 mcg twice daily	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: High risk; “Although minimal carryover effects between periods were observed for measures of lung function, an effect was seen for asthma control days.” FUNDING: National Heart, Lung, and Blood Institute

Table 239

7.1.2.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Evans 2015(110)“	N=1 (Peters 2010)	14 weeks	LAMA + ICS vs higher dose ICS	>18 years old, asthma not well controlled on ICS alone	• Cross-over study: carryover effect seen for asthma control days

Table 240

A systematic review and meta-analysis searched for RCTs that compared LAMA+ICS with ICS alone in a higher dose, in adults with asthma not well controlled on ICS alone.

Only one cross-over RCT with a duration 14 weeks was found (and a 2-week washout period).

A carry-over effect was observed for asthma control days.

Endpoint: trough FEV1		
14 weeks n= 210	GRADING ⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 only known for tiotropium + beclomethasone vs beclomethasone Imprecision: ok	
Studies	Results	
Evans 2015 (Peters 2010)	**MD 0.10L (0.03 to 0.17)**	**SS** **Favours LAMA + ICS**

Table 241

The results of these studies suggest that trough FEV1 is increased with LAMA+ICS compared to ICS alone in a higher dose.

For this meta-analysis,
the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: ACQ	
14 weeks n= 210	GRADING ⨁⨁⊖⊖ **LOW** Study quality: -1 possible carryover effect Consistency: NA Directness:-1 only known for tiotropium + beclomethasone vs beclomethasone Imprecision: ok
Studies	Results

Evans 2015 (Peters 2010)	**MD -0.18 (-0.34 to -0.02)**	**SS** **Favours LAMA + ICS**

Table 242

The results of these studies suggest that the ACQ score is decreased with LAMA+ICS compared to ICS alone in a higher dose.

For this meta-analysis,
the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: AQLQ		
14 weeks n= 210	GRADING ⨁⨁⊖⊖ **LOW** Study quality: -1 possible carryover effect Consistency: NA Directness: -1 only known for tiotropium + beclomethasone vs beclomethasone Imprecision: ok	
Studies	Results	
Evans 2015 (Peters 2010)	MD 0.10 (-0.07 to 0.27)	NS

Table 243

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,
the result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations		
14 weeks n= 210	GRADING ⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 only known for tiotropium + beclomethasone vs beclomethasone Imprecision: -1 (wide CI)	
Studies	Results	
Evans 2015 (Peters 2010)	OR 0.49 (0.09 to 2.77)	NS

Table 244

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,
the result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

7.1.3 LAMA + ICS vs LABA + ICS

7.1.3.1 *Clinical evidence profile*

Meta-analysis: Kew 2015(112) "Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta$_2$-agonists (LABA) for adults with asthma"

Inclusion criteria:
parallel or cross-over RCTs of at least 12 weeks' duration. Population: 18 years and older, asthma not well controlled with ICS alone. Comparisons: LAMA (tiotropium, aclidinium or glycopyrronium) + any dose of ICS versus LABA (formoterol 12 or 24 mcg twice daily, salmeterol 50 mcg twice daily, vilanterol 22 mcg once daily) + same dose ICS

Search strategy:
"systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts." "We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and industry trial registries." Last search in April 2015.

Assessment of quality of included trials: yes
Other methodological remarks:/

Table 245

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Kew 2015(112) Design: SR+ MA Search date: April 2015	**LAMA + ICS** **Vs** **LABA + ICS**	N= 2 n= 998 (Peters 2010, Kerstjens 2015a)	**Exacerbations (oral corticosteroid)**	OR: 1.05 (0.50 to 2.18) NS
		N= 4 n= 2026 (Bateman	**AQLQ**	**MD: -0.12 (-0.18 to -0.05)** **SS** **Favours LABA + ICS**

		2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b)		
		N= 4 n= 2026 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b)	**Exacerbations (hospital)**	OR: 0.72 (0.18 to 2.92) NS
		N= 4 n= 2026 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b)	**Trough FEV1 (L)**	**MD: 0.05 (0.01 to 0.09)** **SS** **Favours LAMA + ICS**
		N= 3 n= 1764 (Kerstjens 2015a, Kerstjens 2015b, Peters 2010)	**Asthma Control Questionnaire (ACQ)**	0.06 (0.00 to 0.13) NS
		N= 2 n=1563 (Kerstjens 2015a, Kerstjens	**ACQ response**	OR 0.91 (0.73 to 1.13) NS

		2015b)		

Table 246

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Bateman 2011(105) RCT	262	- Age: 18-65 - patients homozygous for arginine at the 16th amino acid position of the beta2-adrenergic receptor (B16 Arg/Arg) - Maintenance treatment with ICS - EXCLUSION of significant cardiovascular disease, malignancy, COPD	16 weeks	tiotropium 2x2.5 mcg daily+ ICS vs salmeterol 50 mcg twice daily + ICS ICS was 400-1000 mcg of budesonide/equivalent	ALLOCATION CONC: Unclear risk “Not sufficiently described in the available reports but previous contact with study sponsors confirmed that a concealed allocation system was used” RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk “Demographic characteristics were well balanced across the treatment groups, with slightly more female patients in the tiotropium group and slightly more patients who had never smoked in the salmeterol group” FUNDING: Boehringer Ingelheim, with collaboration from Pfizer
Kerstjens 2015a,	a:	- Age: 18-75	24 weeks	tiotropium 2x2.5 mcg daily+	ALLOCATION CONC: Low risk

Kerstjens 2015b (106) RCT Twin trials	778 b: 776	- Asthma - Pre-bronchodilator FEV1 60% to 90% of predicted normal at screening; variation in absolute FEV1 at screening (pre-bronchodilator) as compared with visit 2 (pre-dose)within ± 30% - ability to use inhalers and perform trial procedures correctly - EXCLUSION of significant cardiovascular disease, malignancy, COPD, women of childbearing potential not using effective birth control		ICS vs tiotropium 2x5 mcg daily+ ICS vs salmeterol 50 mcg twice daily + ICS ICS was medium dose	RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Boehringer Ingelheim , with collaboration from Pfizer
Peters 2010(111) RCT Cross-over	210	- Age: at least 18 - Asthma - received prescription for or used asthma controller in previous 12months;OR symptoms > twice a week and not on asthma controller; if on ICS, stable dose for at least two weeks not exceeding 1000 mcg fluticasone or equivalent daily - ≥ 75% adherence with study medication during run-in - EXCLUSION: COPD, history of life threatening asthma, pregnant	14 week treatment period followed by 2-week washout	tiotropium 18 mcg daily+ beclomethasone 80 mcg twice daily vs salmeterol 50 mcg twice daily + beclomethasone 80 mcg twice daily	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: National Heart, Lung, and Blood Institute

Table 247

Study details	n/Population	Comparison	Outcomes		Methodological
Wechsler 2015(113) (BELT)	n= 1070 Mean age: 45	Tiotropium 18 mcg once daily	Efficacy		RANDO: Adequate ALLOCATION CONC:
			Exacerbations (mean number per person-	Tiotropium: 0.37/person-year LABA: 0.42/person-year	

Design: RCT (OL) (PG) Duration of follow-up: 12 months (some patients were followed until 18 months)	%female: 76% Smoking: 0% Asthma severity: • FEV1% predicted: • <60: 15% • 60-79: 37% • ≥80: 48% Phenotyping: Y • Arg/Arg: 24% • Gly/Gly: 25% • Arg/Gly: 51% <u>Inclusion:</u> • Black patients • Age 18-75 • Asthma • Receiving combination LABA+ICS or taking ICS and having an ACQ >1.25 <u>Exclusion:</u> • Current smokers • FEV1 <40% of predicted • Exacerbation	Vs LABA (salmeterol 50 mcg or formoterol 9 mcg) On top of baseline ICS dose	year)	Rate ratio: 0.90 (0.73 to 1.11) P=0.31 NS	Adequate BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: Open label FOLLOW-UP: Lost-to follow-up: 12% (at 12 months) Drop-out and Exclusions: 16% • Described: yes • Balanced across groups: yes ITT: Yes (all randomized participants were analysed) SELECTIVE REPORTING: yes, limited reporting of numerical results Other important methodological remarks :
			Exacerbations (proportion of patients with at least one exacerbation)	Tiotropium: 20.9% LABA: 22.7% difference: 1.8% (-3.1% to 6.8%) P=0.51 NS	
			Patients with hospitalization for asthma exacerbation	Tiotropium: 19/532 (3.6%) LABA: 10/538 (1.9%) P=0.09 NS	
			AQLQ score ASFD annualized score ASUI score	Improved within groups (p<0.001), but no difference between groups NS (exact figures not reported)	
			ACQ score	Tiotropium: -0.70 LABA: -0.66 Between-group difference: 0.04 (-0.011 to 0.20) P=0.33 NS	

	requiring oral steroids within 3 months		FEV1	Tiotropium: -0.018 L LABA: 0.003 L Between-group difference: 0.020 (-0.021 to 0.061) P=0.33 NS	Primary outcome, time to first exacerbation, did not differ significantly between groups Sponsor: AHRQ

Table 248

7.1.3.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Kew 2015(112)	4 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b)	14-24 weeks	LAMA + ICS Vs LABA + ICS	18 years and older, asthma not well controlled with ICS alone	No remarks

Table 249

Bibliography summary						
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	methodological remarks
Wechsler 2015(113) (BELT)	1070	12 months	Tiotropium 18 mcg once daily Vs LABA (salmeterol 50 mcg or formoterol 9 mcg) On top of baseline ICS dose	Black patients Mean age: 45 %female: 76% Smoking: 0% Asthma severity: FEV1% predicted: <60: 15% 60-79: 37% ≥80: 48% Phenotyping: Y Arg/Arg: 24% Gly/Gly: 25% Arg/Gly: 51%	Receiving combination LABA+ICS or taking ICS and having an ACQ >1.25	open label limited reporting of numerical results

Table 250

A systematic review and meta-analysis searched for RCTs that compared LAMA+ICS versus LABA+ICS, in adults with asthma not well controlled with ICS alone.

Four RCTs with a duration of 14-24 weeks was found.

There were no methodological remarks on these RCTs.

An additional RCT, published after the final search date of the systematic review described above, also compared LAMA+ICS versus LABA+ICS, in adults with asthma not well controlled with ICS alone.

The duration of this RCT was 12 months.

This RCT had an open-label design, and did not report all results numerically. This limits our confidence in the results.

Endpoint: Trough FEV1		
n=3096 14-52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 open label Consistency: -1 Directness: -1 study with only black patients Imprecision: ok	
Studies	Results	
Kew 2015 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b) n= 2026	**MD: 0.05L (0.01 to 0.09)**	**SS** **Favours LAMA + ICS**
Wechsler 2015 (BELT) n= 1070	Between-group difference: 0.020L (-0.021 to 0.061)	NS

Table 251

The results of these studies suggest that trough FEV1 is increased with LAMA+ ICS compared to LABA+ICS.

For this series of studies,

Most results are statistically significant.

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: ACQ		
n=2834 14-52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 study with only black patients Imprecision: ok	
Studies	Results	
Kew 2015 (Kerstjens 2015a, Kerstjens 2015b, Peters 2010) n= 1764	0.06 (0.00 to 0.13)	NS
Wechsler 2015 (BELT) n= 1070	Between-group difference: 0.04 (-0.011 to 0.20)	NS

Table 252

The results of these studies do not suggest an effect in any direction.

For this series of studies,

No result is statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

Endpoint: AQLQ		
n=3096 14-52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 open label, selective reporting Consistency: -1 Directness: -1 study with only black patients Imprecision: ok	
Studies	Results	
Kew 2015 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b) n= 2026	**MD: -0.12 (-0.18 to -0.05)**	**SS** **Favours LABA + ICS**
Wechsler 2015 (BELT) n= 1070	*figures not reported*	NS

Table 253

We cannot make a statement about the direction of the effect of LAMA+ICs versus LABA+ICS on AQLQ score.

For this series of studies,

Some are significant, some are not (50/50)

We have very low confidence that the results of the studies reflect the true effect.

GRADE: VERY LOW quality of evidence

Endpoint: Number of exacerbations (requiring oral corticosteroid)		
n=2068 14-52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: ok Directness: -1 study with only black patients Imprecision: ok	
Studies	Results	
Kew 2015 (Peters 2010, Kerstjens 2015a) n= 998	OR: 1.05 (0.50 to 2.18)	NS
Wechsler 2015 (BELT) n= 1070	Rate ratio: 0.90 (0.73 to 1.11)	NS

Table 254

The results of these studies do not suggest an effect in any direction.

For this series of studies,

None of the results are statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations requiring hospital admission		
n=3096 14-52 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 open label, selective reporting Consistency: ok Directness: -1 study with only black patients Imprecision: -1 (wide CI)	
Studies	Results	
Kew 2015 (Bateman 2011, Peters 2010, Kerstjens 2015a, Kerstjens 2015b) n= 2026	OR: 0.72 (0.18 to 2.92)	NS
Wechsler 2015 (BELT) n= 1070	*figures not reported*	NS

Table 255

The results of these studies do not suggest an effect in any direction.

For this series of studies,
No result is statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: proportion of patients with at least one exacerbation		
n=1070 52 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 open label Consistency: NA Directness: -1 study with only black patients Imprecision: ok	
Studies	Results	
Wechsler 2015 (BELT) n= 1070	difference: 1.8% (-3.1% to 6.8%)	NS

Table 256

The results of these studies do not suggest an effect in any direction.

For this study,
the result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

7.1.4 Triple therapy vs LABA + ICS

7.1.4.1 *Clinical evidence profile*

Meta-analysis: Kew 2016(114) "Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta$_2$-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma"

Inclusion criteria:
parallel and cross-over RCTs, at least 12 weeks' duration. Population: 18 years or older, asthma, taking LABA/ICS combination therapy. Comparison: LAMA (tiotropium, aclidinium, glycopyrronium) add-on to any dose of LABA/ICS combination therapy versus the same dose of LABA/ICS alone.

Search strategy:
"systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO. The CAGR also includes records identified by handsearching respiratory journals and meeting abstracts" "We also conducted a search of www.ClinicalTrials.gov and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/)". Last search in January 2016.

Assessment of quality of included trials: yes
Other methodological remarks:/

Table 257

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Kew 2016(114) Design: SR + MA Search date: January	**LAMA + LABA + ICS** **vs** **LABA + ICS**	N= 2 n= 907 (Kerstjens 2012a, Kerstjens 2012b)	**Exacerbations requiring oral corticosteroids (patients with at least one)**	122/453 vs 149/454 OR: 0.76 (0.57 to 1.02) NS
		N= 2 n= 907	**Exacerbations requiring oral corticosteroids (number per patient)**	Rate ratio: 0.79 (0.53 to 1.17) NS

2061		(Kerstjens 2012a, Kerstjens 2012b)		
		N= 2 n= 907 (Kerstjens 2012a, Kerstjens 2012b)	**AQLQ**	MD: 0.09 (-0.03 to 0.20) NS
		N= 3 n= 1191 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014)	**Exacerbations requiring hospital admission**	17/681 vs 22/510 Risk difference: -0.01 (-0.04 to 0.01) NS
		N= 3 n= 1191 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014)	**Lung function (change in trough FEV1 L)**	**MD 0.07 (0.02 to 0.13)** **SS** **Favours LAMA + LABA+ICS**
		N= 2 n=907 (Kerstjens 2012a, Kerstjens 2012b)	**Time to first exacerbation requiring oral corticosteroids**	HR 0.80 (0.63 to 1.01) NS
		N= 2 n=907 (Kerstjens	**Asthma control (ACQ)**	**MD -0.13 (-0.23 to -0.02)** **SS** **Favours LAMA + LABA+ ICS**

		2012a, Kerstjens 2012b)		
		N= 2 n=1192 (Kerstjens 2012a, Ohta 2014)	**Asthma control (ACQ responder)**	OR: 1.42 (0.88 to 2.29) NS
		N=3 n=1197 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014)	**Serious adverse events**	45/684 vs 49/513 OR 0.60 (0.24 to 1.47) NS

Table 258

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group)
Kerstjens 2012a and Kerstjens 2012b (115) RCT Twin trials	a: 459 b: 453	- Age: 18-75 - Diagnosis of severe or persistent asthma that is symptomatic despite treatment with high, stable doses of ICS and a LABA - History of ≥1 asthma exacerbations in the past year - Able to use the Respimat inhaler correctly - able to use the Respimat inhaler correctly; able to perform all trial-	48 weeks	Tiotropium Respimat 5 mcg once daily Vs placebo On top of usual treatment with high stable doses of ICS and a LABA	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: Boehringer Ingelheim with collaboration from Pfizer

		related procedures - EXCLUSION: - Significant disease other than asthma - Clinically relevant abnormal screening haematology or blood chemistry - Recent history of cardiac disease - Malignancy, women of childbearing potential not using a highly effective method of birth control			
Ohta 2014(116) RCT	285	- Age: 18-75 - Asthma on maintenance treatment with a medium, stable dose of ICS (alone or in a fixed combination with a LABA) - pre-bronchodilator FEV1 60%-90% of predicted normal at visit 1 - able to use the Respimat inhaler correctly; able to perform all trial-related procedures - EXCLUSION: - Significant disease other than asthma - Recent history of cardiac disease - Malignancy, women of childbearing potential not using a highly effective method of birth control	52 weeks	Tiotropium Respimat 2.5 mcg Vs Triotopium Respimat 5 mcg Vs Placebo On top of a medium, stable dose of ICS with or without a LABA	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: Boehringer Ingelheim with collaboration from Pfizer

Table 259

Study details	n/Population	Comparison	Outcomes		Methodological
Ohta 2015(117)	n= 285	tiotropium (2.5 mcg daily)+	Efficacy		RANDO: Adequate
			Trough FEV1	**Tiotropium 5 mcg vs placebo**	

Design: RCT (DB) (PG) Duration of follow-up: 52 weeks + additional 3 weeks	Mean age: 44.5 %female: 62 Smoking: • Never smoker 75% • Ex-smoker: 25% Asthma severity: Mean FEV1: 80% predicted Phenotyping: N <u>Inclusion:</u> - Age: 18-75 - Asthma - On maintenance therapy with medium, stable dose of ICS (≥ 400 mcg and ≤800 mcg budesonide or equivalent dose) - FEV1 60-90% of predicted normal at visit 1 - symptomatic despite low doses of ICS - ability to perform all trial-related procedures	ICS+/- LABA vs tiotropium (5 mcg daily) + ICS +/- LABA vs Placebo + ICS (medium dose) +/- LABA		**Adj. MD: 112 mL (95%CI 18 to 207)** **P=0.02** **SS** **Favours tiotropium 5 mcg** Tiotropium 2.5 mcg vs placebo Adj. MD: 12 mL (95%CI -82 to 106) P=0.80 NS	ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Power calculation: y FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 7% • Described: yes • Balanced across groups: yes ITT: all treated patients with baseline data and at least one on-treatment efficacy measurement SELECTIVE REPORTING: no Other important methodological remarks : 4 week screening period before randomization Sponsor: Boehringer Ingelheim,
			ACQ-7 responder rate (MID of 0.5)	Tiotropium 2.5 mcg: 71.1% Tiotropium 5 mcg: 76.3% Placebo: 73.2% No statistical analysis	

	<u>Exclusion:</u> significant cardiovascular disease, malignancy, COPD, women of childbearing potential not using effective birth control failed to complete ≥80% of electronic diary during the run-in period				with collaboration from Pfizer

Table 260

7.1.4.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
Kew 2016(114)	N= 3 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014)	48-52 weeks	LAMA + LABA + ICS vs LABA + ICS	18 years or older, asthma, taking LABA/ICS combination therapy	No remarks

Table 261

Bibliography summary						
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	methodological remarks
Ohta 2015(117)	285	55 weeks	tiotropium (2.5 mcg daily)+ ICS+/- LABA vs tiotropium (5 mcg daily) + ICS +/- LABA vs Placebo + ICS (medium dose) +/- LABA	Mean age: 44.5 %female: 62 Never smoker 75% Ex-smoker: 25% Asthma severity: Mean FEV1: 80% predicted	FEV1 60-90% of predicted normal at visit 1 symptomatic despite low doses of ICS	No remarks

Table 262

A systematic review and meta-analysis searched for RCTs that compared treatment with LABA+LAMA+ICS (triple therapy) versus LABA+ICS , in adults already on a maintenance therapy with LABA+ICS.

Three RCTs with a duration of 48-52 weeks were found.

There were no methodological remarks on these RCTs.

An additional RCT, published after the final search date of the systematic review described above, also compared LABA+LAMA+ICS (triple therapy) versus LABA+ICS , in adults who were symptomatic despite low doses of ICS.

The duration of this RCT was 55 weeks.

There were no methodological remarks on this RCT.

Endpoint: Trough FEV1		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014) n=1191	**MD 0.07L (0.02 to 0.13)**	**SS** **Favours LAMA + LABA+ICS**
Ohta 2015{ n=285	**Tiotropium 5 mcg vs placebo** **Adj. MD: 112 mL (95%CI 18 to 207)** Tiotropium 2.5 mcg vs placebo Adj. MD: 12 mL (95%CI -82 to 106)	**SS** **Favours tiotropium 5 mcg** NS for tiotropium 2.5 mcg

Table 263

The results of these studies suggest that trough FEV1 is increased with triple therapy compared to LABA+ICS.

For this series of studies,

Most results are statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: ACQ		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016 (Kerstjens 2012a, Kerstjens 2012b) n=907	**MD -0.13 (-0.23 to -0.02)**	**SS** **Favours LAMA + LABA+ ICS**

Table 264

The results of these studies suggest that ACQ score is decreased with triple therapy compared to LABA+ICS.

For this meta-analysis,

the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: AQLQ		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016(Kerstjens 2012a, Kerstjens 2012b) n=907	MD: 0.09 (-0.03 to 0.20)	NS

Table 265

The results of these studies do not suggest an effect in any direction.

For this meta-analysis
The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: Number of patients with at least one exacerbation (requiring oral corticosteroids)		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016(Kerstjens 2012a, Kerstjens 2012b) n=907	OR: 0.76 (0.57 to 1.02)	NS

Table 266

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,
The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: Number of exacerbations (requiring oral corticosteroids) per patient		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016 (Kerstjens 2012a, Kerstjens 2012b) n=907	Rate ratio: 0.79 (0.53 to 1.17)	NS

Table 267

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Exacerbations requiring hospital admission		
	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Kew 2016 (Kerstjens 2012a, Kerstjens 2012b, Ohta 2014) n=1191	Risk difference: -0.01 (-0.04 to 0.01)	NS

Table 268

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

The result is not statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

7.1.5 Adverse events from RCTs

7.1.5.1 *LAMA + ICS vs same dose ICS*

A meta-analysis of five RCTs(Anderson 2015(104)) did not find a difference of **serious adverse events** in LAMA + ICS vs the same dose ICS.

7.1.5.2 *LAMA + ICS vs higher dose ICS*

One RCT (Peters 2010(111)) did not find a difference of **severe adverse events** in LAMA +ICS versus a higher dose of ICS.

7.1.5.3 *Triple therapy vs LABA + ICS*

A meta-analysis of 3 RCTs (Kew 2016(114)) did not find a difference of **serious adverse events** with triple therapy versus LABA + ICS in asthma patients.

7.2 Monoclonal antibodies

7.2.1 Mepolizumab vs placebo (+/- cointerventions)

7.2.1.1 *Clinical evidence profile*

Meta-analysis: Powell 2015 (118)"Mepolizumab versus placebo for asthma"

Inclusion criteria:
RCTs, minimum of 16 weeks' duration; population: adults and children with asthma diagnosis. Comparisons: mepolizumab versus placebo; co-interventions allowed: leukotriene antagonists, inhaled bronchodilators, systemic and inhaled steroids, oral aminophylline and macrolide antibiotics.
Search strategy:
"systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO. We also handsearched respiratory journals and meeting abstracts" "We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/)." Last search date November 2014.
Assessment of quality of included trials: yes
Other methodological remarks:/

Table 269

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Powell 2015(118) Design: SR+MA Search date: November 2014	**SC mepolizumab vs placebo**	N= 1 n= 385 (Ortega 2014)	**HRQoL as assessed by SGRQ**	**MD -7.00 (-10.19 to -3.81)** **SS** **Favours mepolizumab**
		N= 1 n= 385 (Ortega 2014)	**Rate of exacerbations requiring admission**	**RR 0.31 (0.11 to 0.91)** **SS** **Favours mepolizumab**
		N= 1 n= 385 (Ortega 2014)	**Rate of exacerbations requiring ED or admission**	**RR 0.39 (0.18 to 0.83)** **SS** **Favours mepolizumab**
		N= 1	**Rate of clinically significant**	**RR 0.47 (0.35 to 0.63)**

		n= 385 (Ortega 2014)	**exacerbations**	**SS** **Favours mepolizumab**
		N= 1 n= (Ortega 2014)	**Pre-bronchodilator FEV1 (L) at week 32**	**MD 0.10 (0.02 to 0.18)** **SS** **Favours mepolizumab**
		N= 1 n= 385 (Ortega 2014)	**Asthma symptoms**	**MD -0.44 (-0.64 to -0.24)** **SS** **Favours mepolizumab**

Table 270

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Ortega 2014(119) RCT	576	• At least 12 years of age • Well-documented requirement for regular treatment with high dose ICS in 12 months prior to first visit, with or without maintenance oral corticosteroids • Current treatment with additional controller medication besides ICS for at least 3 months; or documented failure • Confirmed history of 2 or more exacerbations requiring treatment with systemic corticosteroids EXCLUSION: • Current smokers or >10 pack-years • Clinically important lung condition other than asthma • Concurrent clinically significant	1-6 weeks run-in 32 weeks intervention + 8 weeks safety follow-up	Mepolizumab 75 mg IV Vs Mepolizumab 100 mg SC Vs placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: GlaxoSmithKline

		medical conditions • QTc(F)a ≥ 450 ms or QTc(F) ≥ 480 ms • Known evidence of lack of adherence to controller medications, inability to follow physician's recommendations, or both			

Table 271

Study details	n/Population	Comparison	Outcomes		Methodological
Bel 2014(120) Design: RCT (DB) (PG) Duration of follow-up: 32 weeks	n= 135 Mean age: 50 %female: • 45% in placebo group • 64% in mepolizumab group Smoking: none Former smoker: 39% Asthma severity: • Placebo: 57.8% predicted, mepolizumab: 59.6% predicted Phenotyping: N	Mepolizumab 100 mg SC Vs Placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: no "formulations of mepolizumab and placebo were prepared by staff members who were aware of study-group assignments but were not involved in study assessments" Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 5%
			Degree of reduction in oral glucocorticoid dose (PO)	placebo: • 90-100%: 7/66 • 75-<90%:5/66 • 50-<75%: 10/66 • >0 to <50%: 7/66 • No decrease, lack of asthma control, or withdrawal: 37/66 mepolizumab: • 90-100%: 16/69 • 75-<90%: 12/69 • 50-<75%: 9/69 • >0 to <50%: 7/69 • No decrease, lack of asthma control, or withdrawal: 25/69 **OR: 2.39 (95%CI 1.25 to 4.56)** **P= 0.008** **SS in favour of mepolizumab**	

	<u>Inclusion:</u> • At least a 6- month history of maintenance treatment with systemic glycocorticoids (5-35 mg per day of prednisone or its equivalent) • Presence of eosinophilic inflammation • Treated with high-dose inhale glucocorticoids and an additional controller <u>Exclusion:</u>		Reduction in daily oral glucocorticoid dose of ≥50%	placebo: 22/66 mepolizumab: 37/69 **OR: 2.26 (95%CI 1.10 to 4.65)** **P= 0.03** **SS in favour of mepolizumab**	• Described: yes • Balanced across groups: yes ITT: Yes (all patients who underwent randomization) SELECTIVE REPORTING: yes Some secondary outcomes not fully reported Other important methodological remarks: 3-8 weeks run-in phase Sponsor: GlaxoSmithKline
			Reduction in daily oral glucocorticoid dose to a level ≤5 mg	placebo: 21/66 mepolizumab: 37/69 **OR: 2.45 (95%CI 1.12 to 5.37)** **P= 0.02** **SS in favour of mepolizumab**	
			Reduction of 100% in oral glucocorticoid dose	placebo: 5/66 mepolizumab: 10/69 OR: 1.67 (95%CI 0.49 to 5.75) P= 0.41 NS	

	• Current smokers or ≥10 pack years • Concurrent respiratory disease • Malignancy • Liver disease • Clinically significant cardiovascular disease • ECG assessment QTcF ≥ 450msec or QTcF ≥ 480 msec for subjects with Bundle Branch Block • Eosinophilic disease • Immunodeficiency • Pregnancy • Known lack of adherence to controller medications		Median percent reduction from baseline in daily oral glucocorticoid dose	Placebo: 0.0 mepolizumab: 50.0 **OR: NA** **P= 0.007** **SS in favour of mepolizumab**	
			Annualized rates of exacerbations	Placebo: 2.12 per year mepolizumab: 1.44 per year **Rate ratio: 0.68 (95%CI 0.47 to 0.99)** **P= 0.04** **SS in favour of mepolizumab**	

	• Lack of ability to follow physician's recommendations		ACQ-5 score	Placebo: NR mepolizumab: NR **Between-group difference: -0.52 (95%CI -0.87 to -0.17)** **P= 0.004** **SS in favour of mepolizumab**	
			SGRQ score	Placebo: NR mepolizumab: NR **Between-group difference: -5.8 (95%CI -10.6 to -1.0)** **P= 0.02** **SS in favour of mepolizumab**	

			FEV1 before bronchodilation	Placebo: NR mepolizumab: NR Between-group difference: 114 mL (95%CI NR) P= 0.15 NS	

Table 272

7.2.1.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Powell 2015(118)	N= 1 (Ortega 2014(119))	32 weeks	Mepolizumab 100mg SC vs placebo	adults and children with asthma diagnosis	• No remarks

Table 273

	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	methodological remarks
RCT Bel 2014(120)	135	32 weeks	Mepolizumab 100mg SC vs placebo	Mean age: 50y %female: 45% in placebo group and 64% in mepolizumab group Asthma severity: Placebo: 57.8% predicted, mepolizumab: 59.6% predicted	Treated with high-dose inhaled glucocorticoids and an additional controller and at least a 6-month history of maintenance treatment with systemic glycocorticoids (5-35 mg per day of prednisone or its equivalent)	Unclear allocation concealment; Some secondary outcomes not fully reported

Table 274

A systematic review and meta-analysis searched for RCTs that compared subcutaneous mepolizumab with placebo, in children and adults with a diagnosis of asthma.

Only one RCT with a duration 32 weeks was found.

There were no methodological remarks on this RCT.

An additional RCT, published after the final search date of the systematic review described above, also compared subcutaneous mepolizumab with placebo in 616 asthma patients treated with high-dose ICS and an additional controller, as well as OCS.

The duration of this RCT was 32 weeks.

This RCT had unclear reporting of allocation concealment. The reporting of outcome data was incomplete. This limits our confidence in the results.

Endpoint: Trough FEV1		
n=520 32 weeks	GRADING ⨁⊖⊖⊖ **VERY LOW** Study quality:-1 Unclear allocation concealment; Some secondary outcomes not fully reported Consistency: -1 Directness: ok Imprecision: -1 no CI	
Studies	Results	
Powell 2015 (Ortega 2014) n= 385	**MD 0.10L (0.02 to 0.18)**	**SS** **Favours mepolizumab**
Bel 2014 n= 135	114 mL (95%CI NR)	NS

Table 275

The results of these studies suggest that trough FEV1 is increased with mepolizumab compared to placebo.

For this series of studies,

Some are significant, some are not (50/50)

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Health-related quality of life (As assessed by SGRQ)		
n=520 32 weeks	GRADING ⨁⨁⨁⊖ **MODERATE** Study quality: -1 Unclear allocation concealment; Some secondary outcomes not fully reported Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Powell 2015 (Ortega 2014) n= 385	**MD -7.00 (-10.19 to -3.81)**	**SS** **Favours mepolizumab**
Bel 2014 n= 135	**MD -5.8 (95%CI -10.6 to -1.0)**	**SS in favour of mepolizumab**

Table 276

The results of these studies suggest that SGRQ score is decreased with mepolizumab compared to placebo.

For this series of studies,

All results are statistically significant

We have moderate that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Asthma symptoms - ACQ		
n=520 32 weeks	GRADING ⨁⨁⨁⊖ **MODERATE** Study quality: -1 Unclear allocation concealment; Some secondary outcomes not fully reported Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
Powell 2015 (Ortega 2014) n= 385	**MD -0.44 (-0.64 to -0.24)**	**SS** **Favours mepolizumab**
Bel 2014 n= 135	**MD -0.52 (95%CI -0.87 to -0.17)**	**SS in favour of mepolizumab**

Table 277

The results of these studies suggest that ACQ score is decreased with mepolizumab compared to placebo.

For this series of studies,
All results are statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Exacerbations requiring hospital admission		
n=3851 32 weeks	GRADING ⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Powell 2015 (Ortega 2014) n= 3851	**RR 0.31 (0.11 to 0.91)**	**SS** **Favours mepolizumab**

Table 278

The results of these studies suggest that the number of exacerbations requiring hospital admission is decreased with mepolizumab compared to placebo.

For this meta-analysis,
the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Clinically significant exacerbations		
n=385 32 weeks	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok	
Studies	Results	
Powell 2015 (Ortega 2014) n= 385	**RR 0.47 (0.35 to 0.63)**	**SS** **Favours mepolizumab**

Table 279

The results of these studies suggest that the number of clinically significant exacerbations is decreased with mepolizumab compared to placebo.

For this meta-analysis,
the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: Annualized rate of exacerbations		
n=135 32 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 Unclear allocation concealment; Some secondary outcomes not fully reported Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Bel 2014 n= 135	**Rate ratio: 0.68 (95%CI 0.47 to 0.99)**	**SS** **Favours mepolizumab**

Table 280

The results of these studies suggest that the annualized rate of exacerbations is decreased with mepolizumab compared to placebo.

For this study,
the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Degree of reduction in oral glucocorticoid dose		
n=135 32 weeks	GRADING ⨁⨁⨁⊖ **MODERATE** Study quality: -1 unclear allocation conc., selective reporting Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
Bel 2014 n= 135	**OR: 2.39 (95%CI 1.25 to 4.56)**	**SS** **Favours mepolizumab**

Table 281

The results of these studies suggest that there is a greater reduction in oral steroid use with mepolizamab compared to placebo.

For this series of studies,

the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

7.2.2 Omalizumab vs placebo (+/- ICS or OCS in stable dose)

7.2.2.1 *Clinical evidence profile*

Meta-analysis: Normansell 2014(121)"Omalizumab for asthma in adults and children" Inclusion criteria: Double blind, parallel group RCTs. Population: adults and children with chronic asthma. Comparisons: Anti-IgE therapy at any dose or route versus placebo; with or without background therapy (analysed separately). Search strategy: "Systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts." We also checked the reference lists of included trials and searched online trial registries and drug company websites." Last search in June 2013. Assessment of quality of included trials: yes Other methodological remarks: /

Table 282

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Normansell 2014(121)" Design: SR+ MA Search date: June 2013	**SC omalizumab + steroid Versus Placebo+ steroid (stable steroid)**	N= 10 n= 3261 (Busse 2001, Busse 2011, Milgrom 2001, NCT00096954, Ohta 2009, SOLAR, Solèr 2001, Chanez 2010, Holgate 2004a, Holgate	Number of participants with at least one exacerbation (ICS and OCS users)	Omalizumab: 285/ 1697 Placebo: 410/1564 **OR: 0.55 (0.46 to 0.65)** **SS** **In favour of omalizumab**

		2004b)		
		N= 3 n= (INNOVATE, Lanier 2009, Hanania 2011)	Exacerbations requiring oral steroids	Moderate to severe asthma (ICS + mixed treatments) **Rate ratio: 0.52 (0.37 to 0.73)** **SS** **In favour of omalizumab** Severe asthma **Rate ratio: 0.66 (0.45 to 0.97)** **SS** **In favour of omalizumab** Severe asthma (ICS + LABA + other treatment) **Rate ratio: 0.72 (0.53 to 0.98)** **SS** **In favour of omalizumab**
		N= 4 n= 1824 (Busse 2001, Busse 2011, Milgrom 2001, Solèr 2001)	Hospitalisations	Omalizumab: 4/ 975 Placebo: 26/849 **OR: 0.16 (0.06 to 0.42)** **SS** **In favour of omalizumab**
		N= 9 n= 4245 (Busse 2001, Busse 2011, Lanier 2009, Massanari 2010, Ohta 2009, SOLAR, Solèr 2001,	Mortality	Omalizumab: 0/ 2240 Placebo: 4/2005 OR 0.19 (0.02 to 1.67) NS

		Bardelas 2012, Hanania 2011)		
		N= 5 n= 1463 (Ohta 2009, SOLAR, Bardelas 2012, INNOVATE, NCT01007149)	Change in FEV1 (mL)	**MD 56.39 (16.82 to 95.96)** **SS** **In favour of omalizumab**
		N= 10 n= 2197 (Busse 2001, Busse 2011, Lanier 2009, NCT00096954, Ohta 2009, Solèr 2001, Bardelas 2012, Hanania 2011, Holgate 2004a, NCT01007149)	Symptom scores	No meaningful meta-analysis possible: different scoring systems used by trials
				MD: **-0.44 [-0.70, -0.18] SS**
				MD: **-0.48 [-0.76, -0.20] SS**
				MD: **-0.13 [-0.25, -0.01] SS**
				MD: 0.01 [-0.15, 0.17] NS
				MD: -1.73 [-3.60, 0.14] NS
				MD: **-0.53 [-0.82, -0.24] SS**
				MD: -0.25 [-0.81, 0.31] NS
				MD: -0.25 [-0.50, 0.00] NS
				MD: **-0.40 [-0.75, -0.05] SS**
				MD: 0.30 [-0.64, 1.24] NS
		N= 1 n= 246 (Holgate 2004a)	AQLQ change from baseline	**MD: 0.26 (0.05 to 0.47)** **SS** **In favour of omalizumab**
		N= 15 n= 5713 (Busse 2001,	Serious adverse events	Omalizumab: 138/ 3035 Placebo: 171/2678

		Busse 2011, Lanier 2009, Massanari 2010, Milgrom 2001, NCT00096954, Ohta 2009, SOLAR, Solèr 2001, Bardelas 2012, Chanez 2010, Hanania 2011, Holgate 2004a, INNOVATE, NCT01007149)		**OR 0.72 (0.57 to 0.91)** **SS** **In favour of omalizumab**

Table 283

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Bardelas 2012(122)	271	Treatment group: 136. Age: 41.9 (14.6). Males: 43 (31.6%). Baseline lung function: mean % predicted FEV1 (SD): 74.4 (17.5) Control group: 135. Age: 40.7 (14.9).Males: 48 (35.6%). Baseline lung function: mean % predicted FEV1 (SD): 76.5 (17.0) Inclusion criteria stated as: males and	24 weeks	Omalizumab 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks Vs placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Unclear risk (no details) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (all outcome measures reported. However, subgroup analysis was ad

		females; 12 years or over; inadequately controlled persistent allergic asthma (ACT score equal to or less than 19) and positive skin prick test; on step 4 or above of NHLBI maintenance treatment (ICS + LABA/leukotriene receptor antagonist/theophylline/zileuton); total serum IgE 30 to 700 IU/mL. One or more of the following with four weeks of screening phase: symptoms > 2 days/wk; nighttime awakenings ≥ 1 time/wk; use of SABA > 2 days/wk; FEV1 ≤ 80% predicted Exclusion criteria stated as: body weight > 150 kg; current smoker or ex-smoker within last year, or pack-year history ≥10 years; history of intubation for asthma or anaphylaxis; systemic steroids within last four weeks; active lung disease other than asthma; current or anticipated use of beta-blockers or methotrexate, gold, cyclosporine or troleandomycin within three months of enrolment; elevated serum IgE levels for reasons other than atopy or a combination of serum IgE levels and weight requiring doses of omalizumab greater than 750 mg per four weeks			hoc and produced the only significant results) FUNDING: Novartis
Busse 2001(123)	525	Participants with moderate to severe asthma were recruited Inclusion criteria: asthma diagnosed for longer than one year; positive response	28 weeks: 16 weeks stable steroid	SC omalizumab 0.016 mg/kg IgE (IU/mL) per 4 weeks 150 or 300 mg every four weeks or 225, 300 or 375 mg	ALLOCATION CONC: Unclear risk (no details) RANDO: Low risk BLINDING : Participants/

		to skin prick to one common allergen; total IgE serum > 30 IU/mL and < 700 IU/mL; FEV1 reversibility of 12%	phase + 12 weeks steroid reduction	every two weeks Vs placebo	personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Genentech and Novartis Pharmaceuticals
Hanania 2011(124)	850	Age: 43.7 (14.3).Males: 165 (38.6%). Baseline lung function: mean % predicted FEV1 (SD): 65.4 (15.2) Control group: 423 (421 completed). Age: 45.3 (13.9). Males: 126 (29.9%). Baseline lung function: mean % predicted FEV1 (SD): 64.4 (13.9) Inclusion criteria stated as: The study included participants 12 to 75 years of age with a history of severe allergic asthma for at least one year before screening. Participants received a diagnosis of asthma from physician investigators at each site on the basis of criteria specified by the NAEPP guidelines. Patients whose asthma was not well controlled despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS) were enrolled. Asthma was considered not well controlled if participants had persistent asthma symptoms with current therapy, defined as an average of one or more night-time awakenings per week and	48 weeks	Omalizumab Minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every two weeks or 0.016 mg/kg per IgE (IU/mL) every four weeks Versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Genentech and Novartis Pharmaceuticals

		daytime asthma symptoms requiring the use of rescue medication for two or more days per week during the four weeks before screening and for two consecutive weeks up to four weeks before randomisation. In addition, participants were required to have at least one documented asthma exacerbation during the previous 12months, defined as increased asthma symptoms requiring treatment with systemic corticosteroid rescue therapy. High-dose ICS was given at a minimum dose of 500 mcg of fluticasone dry powder inhaler twice daily or its similar ex-valve dose for at least eight weeks before screening. Long-acting beta2-agonist treatment could consist of salmeterol 50 mcg twice daily or formoterol 12 mcg twice daily for at least eight weeks before screening. Patients were also required to have objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radioallergosorbent test) to dog, cat, cockroach, Dermatophagoides farinae (dust mite) or D. pteronyssinus documented in the 12 months before screening. Consistent with earlier pivotal studies, participants were also required to have baseline pre-bronchodilator FEV1 of 40%to			

		80%of predicted values, serum IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg Exclusion criteria stated as: Persons were excluded if they had an asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatmentwith systemic corticosteroids (or an increase in the baseline dose ofOCS) in the 30 days before screening. Other exclusion criteria included active lung disease other than asthma, treatment with omalizumab in the 12 months before screening, elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich syndrome, bronchopulmonary aspergillosis) or smoking history of 10 or more pack-years			
Holgate 2004 (125)	246	Mean age (placebo): 40.5 (12 to 71); treatment group: 41.1 (12 to 75). Female/Male percentage: placebo: 57.5/42.5; treatment: 64.3/35.7. Severe asthmatic participants optimally controlled, requiring high-dose fluticasone. FP dose: between 1000 and 2000 mcg/d Inclusion criteria stated as: male/females 12 to 75 years of age, severe asthma according	44 weeks: 16 week steroid-stable phase, 16-week steroid reduction phase, 12-week follow-up	SC omalizumab 0.016 mg/kg/IgE (IU/mL) at two- or four-weekly intervals depending on body weight versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis

		to ATS guidelines, allergic response (> one positive skin prick test to one or more aeroallergens, mean total daily symptom score ≥ four over seven days before randomisation, ≥ 12% reversibility, FEV1 within 30 minutes of salbutamol in 12 months before or at randomisation, stable medication four weeks before randomisation, IgE between 30 and 700 IU/mL Exclusion criteria stated as: females forwhomcurrent or future pregnancy could not be excluded, evidence/history of drug or alcohol abuse, history of non-compliance with medical regimens, those considered potentially unreliable, known sensitivity to study drugs (omalizumab, corticosteroids, salbutamol and terbutaline), those using theophylline, those suffering from live/kidney disease, haematological abnormality, anaphylaxis, nearfatal asthma exacerbation in last three years, elevated serum IgE for reasons other than atopy (parasitic infections, etc).			
Holgate 2004b(125)	95	Mean age: not specified (likely to be similar to Holgate 2004). FEV1 (%	Identical to	Identical to Holgate 2004a	ALLOCATION CONC: Low risk RANDO: Low risk

		predicted): treatment: 60; control: 57 In-and exclusion criteria: Identical to Holgate 2004a	Holgate 2004a		BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis
INNOVATE(126)	482	Mean age: omalizumab: 43.4; placebo: 43.3. FEV1: omalizumab: 61; placebo: 61.6; Inclusion criteria: +ve skin prick test to ≥ one aeroallergen; serum IgE: 30 to 700 IU/ mL; severe persistent asthma requiring > 1000 BDP or equivalent and LABA treatment; FEV1 40% to 80%; FEV1 reversibility ≥ 12% post SABA; ≥ two exacerbations requiring OCS in previous 12 months or one severe exacerbation resulting in hospitalisation Exclusion criteria: smokers/smoking history of ≥ 10 pack-years; treatment for exacerbation four weeks before randomisation; use of methotrexate/gold salts/troleandomycin/ cyclosporin within three months of first visit; prior omalizumab treatment	28 weeks	Subcutaneous omalizumab (0.016 mg/kg per IU/mL) (plus usual care) versus placebo (plus usual care).	ALLOCATION CONC: Unclear risk (method not reported) RANDO: Unclear risk (method not reported) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: NR
Massanari 2010(127)	275	Age: 38.2 (9.89).Males: 51 (37%). Baseline lung function: mean % predicted FEV1 (SD): 86.1 Inclusion criteria stated as: male or	26 weeks	At least 0.016mg/kg/IgE (IU/mL) omalizumab subcutaneous per four weeks	ALLOCATION CONC: Unclear risk (method not reported) RANDO: Unclear risk (no details) BLINDING : Participants/

		female, any race, ages 18 to 55 years, body weight ≥ 20 kg and ≤ 150 kg, total serum IgE concentration ≥ 30 and ≤ 700 IU/mL at visit 0. History of at least moderate persistent allergic asthma of ≥ one year in duration, on a stable asthma treatment regimen including inhaled corticosteroids for the preceding four weeks, an FEV1 while withholding short-acting beta-agonists for at least six hours and long-acting beta-agonists for at least 12 hours, of ≥ 75% of predicted value at visit 0, reversibility (increase in FEV1 of ≥ 12% between 20 and 30 minutes after four puffs), positive skin test to at least one perennial allergen (house dust mite, cat or dog), average PEFR variability ≤ 20%, prespecified level of nocturnal asthma symptoms, non-smoker for at least one year before visit 1, with a smoking history of no more than 10 pack-years, good physical and mental health Exclusion criteria stated as: history of intubation for asthma or requiring systemic steroids in last three months, asthma requiring ED visit on admission in the preceding six months, URTI or sinusitis within the preceding four weeks, history of an anaphylactic allergic reaction (except to stinging insects, foods or drugs other than omalizumab), history of treatment with		Vs placebo	personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (high dropout and unbalanced between groups (75% placebo; 61% omalizumab) SELECTIVE REPORTING: Low risk FUNDING: Novartis

		immunotherapy to any allergen within past three years, history of aspirin- or non-steroidal anti-inflammatory drug (NSAID)-related asthma, history of or current malignancy, any clinically significant uncontrolled systemic disease or a history of such disease within the previous three months, clinically significant laboratory abnormalities at visit 1, platelet levels ≤ 130 × 109/L at visit one, pregnant or breastfeeding women or women using inadequate contraception, history of hypersensitivity to the study medication or drugs related to omalizumab (e.g. monoclonal antibodies, polyclonal gammaglobulin), Previous treatment with omalizumab within one year of screening, Considered by investigator to be potentially unreliable or who may not have reliably attended study visits, history of drug or alcohol abuse			
NCT00096954(128)	333	Treatment group: 159. Age: 36.0 (14.7).Males: 47 (30%). Baseline lung function: mean % predicted FEV1 (SD): not stated Control group: 174. Age: 38.1 (15.1). Males: 55 (32%). Baseline lung function: mean % predicted FEV1 (SD): not stated Patients with 'difficult to treat atopic asthma' Inclusion criteria stated as: documented	24 weeks	Omalizumab SC every two or four weeks Vs placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Unclear risk (no details) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk FUNDING: Genentech

		history of asthma as well as evidence of ≥ 12% reversibility of FEV1; baseline FEV1 ≥ 80% predicted normal value before randomisation; positive skin test (diameter of wheal ≥ 3 mm vs control) or in vitro radioallergosorbent test (RAST(R)) or ImmunoCap(R) to one relevant perennial aeroallergen such as cat or house dust mites documented within the previous year; receiving at least an inhaled corticosteroid dosage of fluticasone dry powder inhaler (DPI) ≥ 200 μg/d or equivalent; during four-week run-in period before randomisation demonstrate evidence of inadequate asthma symptom control; inadequate asthma symptom control defined as at least one of the following reported on the participant diary card during four-week run-in period: daytime asthma symptoms as a score of ≥ one (scale of zero to four) on at least 20 of 28 days (missing data to be treated as a day with no symptoms) and mean symptom score ≥ 1.5 or night-time awakening because of asthma symptoms (more than four times during four-week run-in period); meet study drug-dosing table eligibility criteria (serum baseline IgE level ≥ 30 to ≤ 1300 IU/mL and body weight ≥ 20 to ≤ 150 kg); if female of child-bearing potential, using an effective method of			

		contraception Exclusion criteria stated as: received long-term systemic corticosteroids (oral or intravenous) within three months or received a burst of oral corticosteroids within the last two weeks before screening; received Xolair therapy at any time within 12 months before screening; pregnant or lactating; known hypersensitivity to any ingredients of Xolair, including excipients (sucrose, histidine, polysorbate 20); lifetime history of smoking > 10 pack-years; active lung disease other than asthma (e.g. chronic bronchitis, emphysema, cystic fibrosis, chronic obstructive pulmonary disease); history of upper respiratory infection or lower respiratory infection within 30 days before randomisation; diagnosis of aspirin- or nonsteroidal anti-inflammatory drug-induced asthma; immunosuppressants or other investigational drugs within 30 days before screening; significant medical illness other than asthma			
Ohta 2009(129)	327	Treatment group: 158. Age: 48.8 (14.88). Males: 74 (46.8%). Baseline lung function: mean % predicted FEV1 (SD): 74.06 (19.91) Control group: 169. Age: 49.2 (14.42).Males: 70 (42.7%). Baseline lung function:mean % predicted FEV1 (SD): 75.81 (20.89) Inclusion criteria stated	28 weeks	SC omalizumab at least 0.016 mg/kg/IgE (IU/mL) every four weeks or 0.008 mg/kg/IgE (IU/mL) every two weeks Versus	ALLOCATION CONC: Unclear risk (no details) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (Unbalanced withdrawals from groups (8.2%

		as: males and females with inadequately controlled allergic asthma for > one year (positive skin prick test), 20 to 75 years, weighing 30 to 150 kg, with allergic asthma, IgE level 30 to 700 IU/mL, taking inhaled corticosteroids at a dosage of BDP 800 µg/d (or equivalent) and at least one more drug for managing their asthma at least three months before trial observation (e.g. oral corticosteroids, β2- agonists (oral, inhaled or patch-type) theophylline, leukotriene-3 antagonists or a thromboxane A2 inhibitor/antagonist) Exclusion criteria stated as: pregnant or breast-feeding, history of severe anaphylactic reaction or anaphylactoid reaction, patients taking unacceptable medications (e.g. > 10 mg of prednisolone-equivalent oral corticosteroids, immunosuppressants), significant underlying medical conditions that could impact interpretation of results		placebo	from treatment group vs 16.6% from placebo group) SELECTIVE REPORTING: Unclear risk (not all outcome measures reported) FUNDING: Novartis
SOLAR(130)	405	Age range: 12 to 75 years. Mean steroid dose (BUD equivalent mcg/d): treatment: 842; control: 901. Mean exacerbations requiring OCS in past year: treatment: 2.1; control: 2.1 Inclusion criteria: FEV1 reversibility ≥ 12%; IgE level ≥ 30 to ≤ 1300 IU/mL; +ve skin prick test to one or more indoor allergen; co-existing moderate to	28 weeks	omalizumab 0.016 mg/kg/IgE (IU/mL) every four weeks versus placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Unclear risk (no details) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (No apparent indication of selective

		severe perennial rhinitis; ≥ 400 mch/d ICS; ≥ two unscheduled medical visits for asthma in past year; score ≥ 64/192 on AQLQ Exclusion criteria: patients taking systemic steroids; long-acting antihistamines; cromolyn sodium, oral beta-agonists; theophylline; leukotriene antagonists; inhaled anticholinergics; methotrexate; gold salts; cyclosporin; allergen-specific immunotherapy; non-allergic rhinitis; pregnancy; platelet count ≤ 130 × 10(9)/one			reporting bias) FUNDING: Novartis and Genentech
Solèr 2001(131)	546	Age range: 12 to 75, 268 male participants. Asthma diagnosed according to ATS guidelines Inclusion criteria: asthma diagnosed for longer than one year, positive skin prick test to at least one allergen, serum total IgE level > 30 and < 700 IU/mL-1, body weight < 150 kg, baseline FEV1 > 40% and < 80% predicted, increasing by > 12% within 30 minutes of taking salbutamol, mean total daily symptom score > 3 (max 9) during 14 days before randomisation, treatment with ICS 200 mcg BDP per day for > three months before randomisation, use of beta-agonists on an as-needed/regular basis Exclusion criteria: unstable asthma, significant alteration to regular medication and acute exacerbation requiring additional corticosteroid	28 weeks + trial extension of 32 weeks	Subcutaneous omalizumab ≥ 0.016 mg/kg/IgE (IU/mL) Versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (not all outcome measures reported) FUNDING: Novartis and Genentech

		treatment > one month before screening visit, oral steroids.			
Chanez 2010(132)	*31*				*RCT did not meet our inclusion criteria*
Lanier 2009(133)	*627*	*aged 6 to less than 12 years*			*RCT did not meet our inclusion criteria*
Milgrom 2001(134)	*334*	*Age range: six to 12 years*			*RCT did not meet our inclusion criteria*
NCT01007149(135)	*41*				*RCT did not meet our inclusion criteria*

Table 284

Study details	n/Population	Comparison	Outcomes		Methodological
Li 2016(136) Design: RCT (DB) (PG) Duration of follow-up: 24 weeks	n= 616 Mean age: 46.5y %female: 54% Smoking: NR Asthma severity: FEV1 % predicted • Omalizumab: 63.5% • Placebo: 63.0% Phenotyping: N <u>Inclusion:</u> • Age: 18-75y • Confirmed	Omalizumab (≥0.016 mg/kg/IgE-IU/mL every 4 weeks) Vs Placebo Rescue inhaled salbutamol as needed	Efficacy		RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (not reported) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0.3 % Drop-out and Exclusions: 4% • Described: yes • Balanced across groups: omalizumab: 3.4% Placebo: 5.1%
			FEV1% predicted	Omalizumab: NR Placebo: NR **LSM-TD 4.12%** **P= 0.001** **SS in favour of omalizumab**	
			ACQ	Omalizumab: LSM change from baseline: -0.51 Placebo: NR **LSM-TD 0.17** **P= 0.002** **SS in favour of omalizumab**	
			ACQ- Proportion of patients achieving clinically meaningful	Omalizumab: 104/210 Placebo: 75/211.	

	diagnosis of moderate-to severe persistent allergic asthma (inadequately controlled symptoms despite medium-to-high dose ICS+ LABA therapy) for ≥ 1 year duration • Serum total IgE 30-700 IU/mL • Documented positive reaction to at least 1 perennial aeroallergen • Reported ≥ 2 exacerbation events in previous 12 or ≥ 3 in 24 months • FEV1 of 40-80% predicted normal • Post-bronchodilator reversibility of ≥12% within 30 minutes • Compliance during run-in period <u>Exclusion:</u>		improvement	*Approximately 30% of patients in both treatment groups had missing ACQ data* No statistical analysis	ITT: no "full analysis set": all patients who received ≥1 dose of the study drug SELECTIVE REPORTING: yes (incomplete reporting of outcome data) Other important methodological remarks • 2 week therapy optimization period and 4 week run-in period Sponsor: Novartis Pharma AG
			AQLQ- Proportion of patients achieving clinically meaningful improvement (≥0.5 point change from baseline)	Omalizumab:106/182 Placebo: 2/178 *Approximately 40% of patients in both treatment groups had missing AQLQ data* **P< 0.001** **SS in favour of omalizumab**	
			Asthma exacerbations	Omalizumab: 7.2% Placebo: 10.9% **Rate ratio: 0.61** **P= 0.097** **SS in favour of omalizumab**	

	History of malignancy, lung disease other than asthma, clinically significant ECG or chest X-ray abnormality, elevated total serum IgE level without increase in specific IgE				

Table 285

7.2.2.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Normansell 2014(121)“	N= 15 (Bardelas 2012(122) Busse 2001(123) Chanez 2010(132) Hanania 2011(124) Holgate 2004a(125) Holgate 2004b(125) INNOVATE(126) Lanier 2009(133) Massanari 2010(127) Milgrom 2001(134) NCT00096954(128) NCT01007149(135) Ohta 2009(129) Solèr 2001(131) SOLAR(130))	24-60 weeks	SC omalizumab + ICS or OCS versus placebo + ICS or OCS (stable steroid)	adults and children with chronic asthma	• 4 RCTs did not meet our inclusion criteria (Chanez 2010, Lanier, Milgrom 2001, NCT01007149) • 7 RCTs with unclear reporting of allocation concealment (Ohta, SOLAR, Massanari, NCT00096954, Bardelas, Busse, INNOVATE) • 5 RCTs with unclear reporting of randomization method (Massanari, NCT00096954, Bardelas, INNOVATE, SOLAR) • 2 RCTs with unbalanced withdrawal (Massanari, Ohta) • 3 RCTs with selective reporting (Bardelas, Ohta, Solèr)

Table 286

RCT	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	methodological remarks

Li 2016(136)	616	24 weeks	Omalizumab (≥0.016 mg/kg/IgE-IU/mL every 4 weeks) Vs Placebo	Mean age: 46.5y %female: 54% Smoking: NR Asthma severity: FEV1 % predicted • Omalizumab: 63.5% • Placebo: 63.0%	Moderate-to severe persistent allergic asthma	Unclear randomization and allocation concealment; Incomplete reporting of outcome data

Table 287

A systematic review and meta-analysis searched for RCTs that compared subcutaneous omalizumab with placebo, on top of a stable dose of inhaled or oral steroids, in children and adults with a diagnosis of chronic asthma.

Fifteen RCTs with a duration 24 to 52 weeks were found.

4 of the fifteen RCTs did not meet our inclusion criteria , 7 RCTs had unclear reporting of allocation concealment , 5 RCTs had unclear reporting of randomization method, 2 RCTs had unbalanced withdrawal and 3 RCTs had selective reporting. This limits our confidence in the results.

An additional RCT, published after the final search date of the systematic review described above, also compared subcutaneous omalizumab with placebo, on top of a stable dose of inhaled steroids, in 616 children and adults with a diagnosis of moderate to severe allergic asthma.

The duration of this RCT was 24 weeks.

This RCT had unclear reporting of randomization and of allocation concealment. The reporting of outcome data was incomplete. This limits our confidence in the results.

Endpoint: Trough FEV1		
n=1463 24-28 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear rando, unclear alloc conc, selective reporting Consistency: -1 (I^2=71%) Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Ohta	**MD 56.39mL (16.82 to 95.96)**	**SS**

2009, SOLAR, Bardelas 2012, INNOVATE, NCT01007149) n= 1463		**In favour of omalizumab**

Table 288

The results of these studies suggest that trough FEV1 is increased with omalizumab compared to placebo.

For this meta-analysis,
the results is statistically significant.

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: ACQ		
n=616 24 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 Unclear randomization and allocation concealment; Incomplete reporting of outcome data Consistency: NA Directness: ok Imprecision: -1 no CI reported	
Studies	Results	
RCT Li 2016	**LSM-TD 0.17 (95%CI NR)** **P= 0.002**	**SS** **In favour of omalizumab**

Table 289

The results of these studies suggest that theACQ score is decreased with omalizumab compared to placebo.

For this study,
the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: AQLQ		
n=246 44 weeks	GRADING ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014	**MD: 0.26 (0.05 to 0.47)**	**SS**

(Holgate 2004a) n= 246		**Favours omalizumab**

Table 290

The results of these studies suggest that AQLQ score is increased with omalizumab compared to placebo.

For this meta-analysis,

the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.
GRADE: HIGH quality of evidence

Endpoint: Hospitalisations		
n=1824 28-60 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear rando, allocation conc Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Busse 2001, Busse 2011, Milgrom 2001, Solèr 2001) n= 1824	**OR: 0.16 (0.06 to 0.42)**	**SS** **In favour of omalizumab**

Table 291

The results of these studies suggest that hospitalisations are decreased with omalizumab compared to placebo.
For this meta-analysis,

the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Number of participants with at least one exacerbation	
n=3261 16-60 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok
Studies	Results

SR/MA Normansell 2014 (Busse 2001, Busse 2011, Milgrom 2001, NCT00096954, Ohta 2009, SOLAR, Solèr 2001, Chanez 2010, Holgate 2004a, Holgate 2004b) n= 3261	**OR: 0.55 (0.46 to 0.65)**	**SS** **In favour of omalizumab**

Table 292

The results of these studies suggest that the number of participants with at least one exacerbation is decreased with omalizumab compared to placebo.

For this meta-analysis,

the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Asthma exacerbation (rate of exacerbations)		
n=616 24 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality:-1 (Unclear randomization and allocation concealment; Incomplete reporting of outcome data) Consistency: NA Directness: ok Imprecision: -1 no CI	
Studies	Results	
RCT Li 2016 N=616	**Rate ratio: 0.61 (95%CI NR)** **P= 0.097**	**SS** **In favour of omalizumab**

Table 293

The result of this study suggest that the rate of asthma exacerbations is decreased with omalizumab compared to placebo.

For this study

the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

7.2.3 Omalizumab vs placebo (+/- ICS or OCS in decreasing dose)

7.2.3.1 *Clinical evidence profile*

Meta-analysis: Normansell 2014(121)"Omalizumab for asthma in adults and children"

Inclusion criteria:
Double blind, parallel group RCTs. Population: adults and children with chronic asthma. Comparisons: Anti-IgE therapy at any dose or route versus placebo; with or without background therapy (analysed separately).
Search strategy:
"Systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts." We also checked the reference lists of included trials and searched online trial registries and drug company websites." Last search in June 2013.
Assessment of quality of included trials: yes
Other methodological remarks: /

Table 294

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Normansell 2014(121)" Design: SR+ MA Search date: June 2013	**SC omalizumab + steroid Versus Placebo+ steroid (steroid reduction)**	N= 5 n= 1726 (Busse 2001, Milgrom 2001, Solèr 2001, Holgate 2004a, Holgate 2004b)	Number of participants with exacerbation	Omalizumab: 179/934 Placebo: 250/792 **OR 0.49 (0.39 to 0.62)** **SS** **In favour of omalizumab**
		N= 3 n= 1405 (Busse 2001, Milgrom 2001,	Exacerbations requiring hospitalisation	Omalizumab: 1/767 Placebo: 13/638

		Solèr 2001)		**OR 0.11 (0.03 to 0.48)** **SS** **In favour of omalizumab**
		N= 1 n= 246 (Holgate 2004a)	QoL change from baseline	**MD 0.42 (0.17 to 0.67)** **SS** **In favour of omalizumab**
		N= 1 n= 246 (Holgate 2004a	Numbers of participants achieving clinically relevant improvement in quality of life (>0.5)	Omalizumab: 73/126 Placebo: 46/120 **OR 2.22 (1.33 to 3.69)** **SS** **In favour of omalizumab**

Table 295

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Busse 2001(123)	525	Participants with moderate to severe asthma were recruited Inclusion criteria: asthma diagnosed for longer than one year; positive response to skin prick to one common allergen; total IgE serum > 30 IU/mL and < 700 IU/mL; FEV1 reversibility of 12%	28 weeks: 16 weeks stable steroid phase + 12 weeks steroid reduction	SC omalizumab 0.016 mg/kg IgE (IU/mL) per 4 weeks 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks Vs placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Genentech and Novartis Pharmaceuticals
Holgate 2004a (125)	246	Mean age (placebo): 40.5 (12 to 71); treatment group: 41.1 (12 to 75).	44 weeks:	SC omalizumab 0.016 mg/kg/IgE (IU/mL) at two-	ALLOCATION CONC: Low risk RANDO: Low risk

		Female/Male percentage: placebo: 57.5/42.5; treatment: 64.3/35.7. Severe asthmatic participants optimally controlled, requiring high-dose fluticasone. FP dose: between 1000 and 2000 mcg/d Inclusion criteria stated as: male/females 12 to 75 years of age, severe asthma according to ATS guidelines, allergic response (> one positive skin prick test to one or more aeroallergens, mean total daily symptom score ≥ four over seven days before randomisation, ≥ 12% reversibility, FEV1 within 30 minutes of salbutamol in 12 months before or at randomisation, stable medication four weeks before randomisation, IgE between 30 and 700 IU/mL Exclusion criteria stated as: females forwhomcurrent or future pregnancy could not be excluded, evidence/history of drug or alcohol abuse, history of non-compliance with medical regimens, those considered potentially unreliable, known sensitivity to study drugs (omalizumab, corticosteroids, salbutamol and terbutaline), those	16 week steroid-stable phase, 16-week steroid reduction phase, 12-week follow-up	or four-weekly intervals depending on body weight versus placebo	BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis

		using theophylline, those suffering from live/kidney disease, haematological abnormality, anaphylaxis, nearfatal asthma exacerbation in last three years, elevated serum IgE for reasons other than atopy (parasitic infections, etc).			
Holgate 2004b(125)	95	Mean age: not specified (likely to be similar to Holgate 2004). FEV1 (% predicted): treatment: 60; control: 57 In-and exclusion criteria: Identical to Holgate 2004a	Identical to Holgate 2004a	Identical to Holgate 2004a	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis
Solèr 2001(131)	546	Age range: 12 to 75, 268 male participants. Asthma diagnosed according to ATS guidelines Inclusion criteria: asthma diagnosed for longer than one year, positive skin prick test to at least one allergen, serum total IgE level > 30 and < 700 IU/mL-1, body weight < 150 kg, baseline FEV1 > 40% and < 80% predicted, increasing by > 12% within 30 minutes of taking salbutamol, mean total daily symptom score > 3 (max 9) during 14 days before randomisation, treatment with ICS 200 mcg BDP per day for > three months before randomisation, use of beta-	28 weeks + trial extension of 32 weeks	Subcutaneous omalizumab ≥ 0.016 mg/kg/IgE (IU/mL) Versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (not all outcome measures reported) FUNDING: Novartis and Genentech

		agonists on an as-needed/regular basis Exclusion criteria: unstable asthma, significant alteration to regular medication and acute exacerbation requiring additional corticosteroid treatment > one month before screening visit, oral steroids.			
Milgrom 2001(134)	*334*	*Age range: six to 12 years*			*RCT did not meet our inclusion criteria*

Table 296

7.2.3.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Normansell 2014(121)	N= 5 (Busse 2001(123), Milgrom 2001(134), Solèr 2001(131), Holgate 2004a(125), Holgate 2004b(125))	28-44 weeks	SC omalizumab + ICS or OCS versus placebo + ICS or OCS (steroid reduction)	adults and children with chronic asthma	• One RCT included only children (Milgrom 2001) • One RCT with unclear allocation concealment (Busse 2001) • One RCT with selective outcome reporting (Solèr)

Table 297

A systematic review and meta-analysis searched for RCTs that compared subcutaneous omalizumab with placebo, on top of inhaled or oral steroids that were reduced in dose during the trial, in children and adults with a diagnosis of chronic asthma.

Five RCTs with a duration 28 to 44 weeks were found.

One of the five RCTs did not meet our inclusion criteria , one RCT had unclear reporting of allocation concealment and one RCT had selective reporting. This limits our confidence in the results.

Endpoint: AQLQ		
n=246 44 weeks	**GRADING** ⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Holgate 2004a) n= 246	**MD 0.42 (0.17 to 0.67)**	**SS** **In favour of omalizumab**

Table 298

The results of these studies suggest that AQLQ is increased with omalizumab compared to placebo.

For this meta-analysis,

the result is statistically significant

We have high confidence that the results of the studies reflect the true effect.

GRADE: HIGH quality of evidence

Endpoint: Number of participants with exacerbation		
n=1726 28-44 weeks	GRADING ⨁⨁⨀⨀ **LOW** Study quality: -1 unclear allocation concealment, selective reporting Consistency: ok Directness: -1 one RCT included only children Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Busse 2001, Milgrom 2001, Solèr 2001, Holgate 2004a, Holgate 2004b) n= 1726	**OR 0.49 (0.39 to 0.62)**	**SS** **In favour of omalizumab**

Table 299

The results of these studies suggest that the number of participants with an exacerbation is decreased with omalizumab compared to placebo.

For this meta-analysis,
the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations requiring hospital admission		
n=246 44 weeks	GRADING ⨁⨁⨁⨀ **MODERATE** Study quality: -1 unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Holgate 2004a) n= 246	**OR 0.11 (0.03 to 0.48)**	**SS** **In favour of omalizumab**

Table 300

The results of these studies suggest that the number of exacerbations requiring hospital admission is decreased with omalizumab compared to placebo.

For this meta-analysis,
the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

7.2.4 Omalizumab vs placebo (+/- ICS AND OCS in decreasing dose)

7.2.4.1 *Clinical evidence profile*

Meta-analysis: Normansell 2014(121)"Omalizumab for asthma in adults and children" Inclusion criteria: Double blind, parallel group RCTs. Population: adults and children with chronic asthma. Comparisons: Anti-IgE therapy at any dose or route versus placebo; with or without background therapy (analysed separately). Search strategy: "Systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts." We also checked the reference lists of included trials and searched online trial registries and drug company websites." Last search in June 2013. Assessment of quality of included trials: yes Other methodological remarks: /

Table 301

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Normansell 2014(121)" Design: SR+ MA Search date: June 2013	**SC omalizumab + ICS and OCS Versus Placebo+ ICS and OCS (steroid reduction)**	N= 1 n= 95 (Holgate 2004b)	Numbers of participants achieving complete oral steroid withdrawal	Omalizumab: 21/50 Placebo: 19/45 OR 0.99 (0.44 to 2.24) NS
		N= 1 n= 92 (Holgate 2004b)	Number of participants with exacerbation	Omalizumab: 21/50 Placebo: 19/42

				OR 0.88 (0.38 to 2.01) NS
		N= 5 n= (Busse 2001, SOLAR, Solèr 2001, Hanania 2011, Holgate 2004a, INNOVATE)	Mean change in AQLQ scores	**MD 0.31 (0.23 to 0.39)** **SS** **In favour of omalizumab**

Table 302

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane authors)
Busse 2001(123)	525	Participants with moderate to severe asthma were recruited Inclusion criteria: asthma diagnosed for longer than one year; positive response to skin prick to one common allergen; total IgE serum > 30 IU/mL and < 700 IU/mL; FEV1 reversibility of 12%	28 weeks: 16 weeks stable steroid phase + 12 weeks steroid reduction	SC omalizumab 0.016 mg/kg IgE (IU/mL) per 4 weeks 150 or 300 mg every four weeks or 225, 300 or 375 mg every two weeks Vs placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Genentech and Novartis Pharmaceuticals
Hanania 2011(124)	850	Age: 43.7 (14.3).Males: 165 (38.6%). Baseline lung function: mean % predicted FEV1 (SD): 65.4 (15.2) Control group: 423 (421 completed).	48 weeks	Omalizumab Minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every two weeks or 0.016	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk

		Age: 45.3 (13.9). Males: 126 (29.9%). Baseline lung function: mean % predicted FEV1 (SD): 64.4 (13.9) Inclusion criteria stated as: The study included participants 12 to 75 years of age with a history of severe allergic asthma for at least one year before screening. Participants received a diagnosis of asthma from physician investigators at each site on the basis of criteria specified by the NAEPP guidelines. Patients whose asthma was not well controlled despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS) were enrolled. Asthma was considered not well controlled if participants had persistent asthma symptoms with current therapy, defined as an average of one or more night-time awakenings per week and daytime asthma symptoms requiring the use of rescue medication for two or more days per week during the four weeks before screening and for two consecutive weeks up to four weeks before randomisation. In addition, participants were required to have at least one documented asthma exacerbation during the previous 12months, defined as increased asthma symptoms requiring treatment with systemic corticosteroid rescue		mg/kg per IgE (IU/mL) every four weeks Versus placebo	INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Genentech and Novartis Pharmaceuticals

		therapy. High-dose ICS was given at a minimum dose of 500 mcg of fluticasone dry powder inhaler twice daily or its similar ex-valve dose for at least eight weeks before screening. Long-acting beta2-agonist treatment could consist of salmeterol 50 mcg twice daily or formoterol 12 mcg twice daily for at least eight weeks before screening. Patients were also required to have objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radioallergosorbent test) to dog, cat, cockroach, Dermatophagoides farinae (dust mite) or D. pteronyssinus documented in the 12 months before screening. Consistent with earlier pivotal studies, participants were also required to have baseline pre-bronchodilator FEV1 of 40%to 80%of predicted values, serum IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg Exclusion criteria stated as: Persons were excluded if they had an asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatmentwith systemic corticosteroids (or an increase in the baseline dose ofOCS) in the 30 days before screening. Other exclusion criteria included active lung disease			

		other than asthma, treatment with omalizumab in the 12 months before screening, elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich syndrome, bronchopulmonary aspergillosis) or smoking history of 10 or more pack-years			
Holgate 2004a (125)	246	Mean age (placebo): 40.5 (12 to 71); treatment group: 41.1 (12 to 75). Female/Male percentage: placebo: 57.5/42.5; treatment: 64.3/35.7. Severe asthmatic participants optimally controlled, requiring high-dose fluticasone. FP dose: between 1000 and 2000 mcg/d Inclusion criteria stated as: male/females 12 to 75 years of age, severe asthma according to ATS guidelines, allergic response (> one positive skin prick test to one or more aeroallergens, mean total daily symptom score ≥ four over seven days before randomisation, ≥ 12% reversibility, FEV1 within 30 minutes of salbutamol in 12 months before or at randomisation, stable medication four weeks before randomisation, IgE between 30 and	44 weeks: 16 week steroid-stable phase, 16-week steroid reduction phase, 12-week follow-up	SC omalizumab 0.016 mg/kg/IgE (IU/mL) at two- or four-weekly intervals depending on body weight versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis

		700 IU/mL Exclusion criteria stated as: females forwhomcurrent or future pregnancy could not be excluded, evidence/history of drug or alcohol abuse, history of non-compliance with medical regimens, those considered potentially unreliable, known sensitivity to study drugs (omalizumab, corticosteroids, salbutamol and terbutaline), those using theophylline, those suffering from live/kidney disease, haematological abnormality, anaphylaxis, nearfatal asthma exacerbation in last three years, elevated serum IgE for reasons other than atopy (parasitic infections, etc).			
Holgate 2004b(125)	95	Mean age: not specified (likely to be similar to Holgate 2004). FEV1 (% predicted): treatment: 60; control: 57 In-and exclusion criteria: Identical to Holgate 2004a	Identical to Holgate 2004a	Identical to Holgate 2004a	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: Novartis
INNOVATE(126)	482	Mean age: omalizumab: 43.4; placebo: 43.3. FEV1: omalizumab: 61; placebo: 61.6;	28 weeks	Subcutaneous omalizumab (0.016 mg/kg per IU/mL) (plus usual care)	ALLOCATION CONC: Unclear risk (method not reported) RANDO: Unclear risk (method not

		Inclusion criteria: +ve skin prick test to ≥ one aeroallergen; serum IgE: 30 to 700 IU/ mL; severe persistent asthma requiring > 1000 BDP or equivalent and LABA treatment; FEV1 40% to 80%; FEV1 reversibility ≥ 12% post SABA; ≥ two exacerbations requiring OCS in previous 12 months or one severe exacerbation resulting in hospitalisation Exclusion criteria: smokers/smoking history of ≥ 10 pack-years; treatment for exacerbation four weeks before randomisation; use of methotrexate/gold salts/troleandomycin/ cyclosporin within three months of first visit; prior omalizumab treatment		versus placebo (plus usual care).	reported) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (no apparent indication of selective reporting bias) FUNDING: NR
SOLAR(130)	405	Age range: 12 to 75 years. Mean steroid dose (BUD equivalent mcg/d): treatment: 842; control: 901. Mean exacerbations requiring OCS in past year: treatment: 2.1; control: 2.1 Inclusion criteria: FEV1 reversibility ≥ 12%; IgE level ≥ 30 to ≤ 1300 IU/mL; +ve skin prick test to one or more indoor allergen; co-existing moderate to severe perennial rhinitis; ≥ 400 mch/d ICS; ≥ two unscheduled medical visits for asthma in past year; score ≥ 64/192 on AQLQ Exclusion criteria: patients taking	28 weeks	omalizumab 0.016 mg/kg/IgE (IU/mL) every four weeks versus placebo	ALLOCATION CONC: Unclear risk (no details) RANDO: Unclear risk (no details) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (No apparent indication of selective reporting bias) FUNDING: Novartis and Genentech

		systemic steroids; long-acting antihistamines; cromolyn sodium, oral beta-agonists; theophylline; leukotriene antagonists; inhaled anticholinergics; methotrexate; gold salts; cyclosporin; allergen-specific immunotherapy; non-allergic rhinitis; pregnancy; platelet count ≤ 130 × 10(9)/one			
Solèr 2001(131)	546	Age range: 12 to 75, 268 male participants. Asthma diagnosed according to ATS guidelines Inclusion criteria: asthma diagnosed for longer than one year, positive skin prick test to at least one allergen, serum total IgE level > 30 and < 700 IU/mL-1, body weight < 150 kg, baseline FEV1 > 40% and < 80% predicted, increasing by > 12% within 30 minutes of taking salbutamol, mean total daily symptom score > 3 (max 9) during 14 days before randomisation, treatment with ICS 200 mcg BDP per day for > three months before randomisation, use of beta-agonists on an as-needed/regular basis Exclusion criteria: unstable asthma, significant alteration to regular medication and acute exacerbation requiring additional corticosteroid treatment > one month before screening visit, oral steroids.	28 weeks + trial extension of 32 weeks	Subcutaneous omalizumab ≥ 0.016 mg/kg/IgE (IU/mL) Versus placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Unclear risk (not all outcome measures reported) FUNDING: Novartis and Genentech

Table 303

7.2.4.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Normansell 2014(121)“	N= 6 (Busse 2001(123), SOLAR(130), Solèr 2001(131), Hanania 2011(124), Holgate 2004a(125), Holgate 2004b(125), INNOVATE(126))	28-48 weeks	SC omalizumab + ICS + OCS versus placebo + ICS + OCS (steroid reduction)	adults and children with chronic asthma	• 2 RCT with unclear randomization (SOLAR, INNOVATE) • 3 RCTs with unclear allocation concealment (Busse 2001, SOLAR, INNOVATE) • One RCT with selective outcome reporting (Solèr)

Table 304

A systematic review and meta-analysis searched for RCTs that compared subcutaneous omalizumab with placebo, on top of of inhaled AND oral steroids ,that were reduced in dose during the trial, in children and adults with a diagnosis of chronic asthma.

Six RCTs with a duration 28 to 48 weeks were found.

Two of the six RCTs had unclear reporting of randomization, three had unclear allocation concealment and one RCT had selective reporting. This limits our confidence in the results.

Endpoint: AQLQ score		
n=2964 28-48 weeks	GRADING ⨁⨁⨁⊖ **MODERATE** Study quality: -1 unclear randomization, alloc concealment; selective outcome reporting Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Normansell 2014 (Busse 2001, SOLAR, Solèr 2001, Hanania 2011, Holgate 2004a, INNOVATE) n= 2964	**MD 0.31 (0.23 to 0.39)**	**SS** **In favour of omalizumab**

Table 305

The results of these studies suggest that the AQLQ score is increased with omalizumab compared to placebo.

For this meta-analysis,

the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Number of participants with exacerbation		
n=92 44 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: -1 (wide CI)	
Studies	Results	
SR/MA Normansell 2014 (Holgate 2004b) n=92	OR 0.88 (0.38 to 2.01)	NS

Table 306

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

the result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Numbers of participants achieving complete oral steroid withdrawal		
n=92 44 weeks	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness:ok Imprecision: -1 (wide CI)	
Studies	Results	
SR/MA Normansell 2014 (Holgate 2004b) n=92	OR 0.99 (0.44 to 2.24)	NS

Table 307

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,

the result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

7.2.5 Adverse events from RCTs

7.2.5.1 *Omalizumab vs placebo (+/- ICS or OCS in stable dose)*

A meta-analysis of 15 RCTs (Normansell 2014(121)) found a **statistically significant decrease of serious adverse events** with omalizumab, compared to placebo.

8 Questions pertaining to both asthma and COPD – Evidence tables and conclusions

8.1 Long-term prophylactic use of macrolides in COPD

8.1.1 Azithromycin vs placebo

8.1.1.1 *Clinical evidence profile*

Meta-analysis: Ni 2015(137) "Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: A meta-analysis" Inclusion criteria: RCTs. Population: adults >18y with a diagnosis of stable COPD Search strategy: Searched PubMed, Embase and the Cochrane Library from their inception until September 30th 2014. In addition, the reference lists of reports identified by this search strategy were also searched to select relevant articles. Assessment of quality of included trials: yes Other methodological remarks: no

Table 308

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Ni 2015(137) Design: SR+ MA	**Azithromycin (3 months) vs placebo**	N= 1 n= 84 (Berkhof 2013)	Number of patients with exacerbations	RR: 0.46(0.18 to 1.18) NS and p =0.11

Search date: September 2014				

Table 309

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Ni 2015(137) Design: SR+ MA Search date: September 2014	**Azithromycin (6-12 months) vs placebo**	N= 2 n= 1209 (Uzun 2014, Albert 2011)	Number of patients with exacerbations	**RR: 0.82(0.76 to 0.90)** **SS and p <0.01** **In favour of azithromycin 6-12 months**
		N= 3 n= 1231 (Uzun 2014, Albert 2011, Blasi 2010)	Rate of exacerbations per patient per year	**RR: 0.59(0.37 to 0.93)** **SS and p =0.02** **In favour of azithromycin 6-12 months**

Table 310

Ref + design	n	Population	Duration	Comparison	Methodology (Jadad score as assessed by Ni et al.; added comments by Cochrane author Herath et al. 2013)
Albert 2011(138)	1117	Mean age 65 years (azithromycin) and 66 (placebo)	12 months	Azithromycin 250 mg once daily	Jadad score: 3 ALLOCATION CONC: Low risk

		41% female INCLUSION • Aged 40 or over. • Severity of COPD moderate or worse as defined by GOLD criteria • Mean FEV1 1.10±0.50 (azithromycin) and 1.12±0.52 (placebo) • Presence of either a) using continuous supplemental oxygen or b) received systemic glucocorticoids within the previous year /had gone to an emergency room/ hospitalization for an acute exacerbation • No acute exacerbation of COPD for at least 4 weeks EXCLUSION asthma, resting heart rate>100/min, Prolonged QT interval > 450 ms, using medications that prolong QTc, hearing impairment documented by audiometry		Vs placebo	RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Unclear risk (loss to follow-up of 20% in AB arm and 18% in placebo arm, reasons not given) SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: Grants listed from National Institutes of Health
Berkhof 2013(139)	82	Mean age of participants was 68 years and mean FEV1 was 1.36L INCLUSION age of ≥40 years, COPD GOLD stage ≥2 and chronic productive cough. Exclusion criteria were a prior history of asthma; use of intravenous or oral corticosteroids and/or antibiotics for an exacerbation three weeks before inclusion; other relevant lung or liver diseases at the discretion of the	3 months	Azithromycin 250 mg once 3 days/week Vs placebo	Jadad score: 5

		treating physician; pregnancy or lactation; use of macrolides in the last six weeks prior to inclusion; allergy or intolerance to macrolides; or use of other investigational medication started two months prior to inclusion.			
Uzun 2014(140)	92	Patients (≥18 years) with a diagnosis of COPD who had received treatment for three or more exacerbations in the previous year	12 months	Azithromycin 500 mg once 3 days/week Vs placebo	Jadad score: 5
Blasi 2010(141)	*22*	*RCT did not meet our inclusion criteria*			

Table 311

8.1.1.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Ni 2015(137)	N= 4 (Berkhof 2013(139), Uzun 2014(140), Albert 2011(138), Blasi 2010(141))	3-12 months	Long-term azithromycin vs placebo	adults >18y with a diagnosis of stable COPD	• One RCT with loss to follow-up of 20% (Albert 2011) • one small RCT n=22 (Blasi 2010)

Table 312

This systematic review and meta-analysis searched for RCTs that compared long-term azithromycin with placebo in adults with a diagnosis of stable COPD.

Four RCTs with a duration of 3 to 12 months were found.

One RCT has a loss to follow-up of 20%, and one of the included RCTs had a very small sample size.

Endpoint: exacerbations 3 months		
(n=84) 3 months	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 small sample size Consistency: NA Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Ni 2015 (Berkhof 2013)	RR: 0.46(0.18 to 1.18)	NS

Table 313

The results of these studies do not suggest an effect in any direction.

For this meta-analysis,
the result is not statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: exacerbations 6-12 months	
(n= 1209) 6-12 months	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 high loss to follow-up Consistency: -1 high clinical heterogeneity Directness: ok Imprecision: ok

Studies	Results	
SR/MA Ni 2015 (Uzun 2014, Albert 2011)	**RR: 0.82(0.76 to 0.90)**	**SS and p <0.01** **In favour of azithromycin 6-12 months**

Table 314

The results of these studies suggest that the number of exacerbations at 6-12 months is decreased with azithromycin compared to placebo.

For this meta-analysis,
the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: rate of exacerbations per patient per year		
(n=1231 6-12 months	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 high loss to follow-up, small study Consistency: -1 high clinical heterogeneity Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Ni 2015 (Uzun 2014, Albert 2011, Blasi 2010)	**RR: 0.59(0.37 to 0.93)**	**SS and p =0.02** **In favour of azithromycin 6-12 months**

Table 315

The results of these studies suggest that the rate of exacerbations per patient per year is decreased with azithromycin compared to placebo.

For this meta-analysis
the result is statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

8.1.2 Erythromycin vs placebo

8.1.2.1 *Clinical evidence profile*

Meta-analysis: Ni 2015(137) "Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: A meta-analysis" Inclusion criteria: RCTs. Population: adults >18y with a diagnosis of stable COPD Search strategy: Searched PubMed, Embase and the Cochrane Library from their inception until September 30th 2014. In addition, the reference lists of reports identified by this search strategy were also searched to select relevant articles. Assessment of quality of included trials: yes Other methodological remarks: no

Table 316

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Ni 2015(137) Design: SR+ MA Search date: September 2014)	**Erythromcyin (6-12 months)** **Vs placebo**	N= 3 n= 254 (Suzuki 2001, Seemungal 2008, He 2010)	Number of patients with exacerbations	**RR: 0.49(0.26 to 0.91)** **SS and p =0.02** **In favour of erythromycin**
		N= 3 n= 254 (Suzuki 2001, Seemungal 2008, He 2010)	Rate of exacerbations per patient per year	**RR: 0.53(0.43 to 0.83)** **SS and p =0.01** **In favour of erythromycin**

Table 317

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Jadad score as assessed by Ni et al.; added

					comments by Cochrane author Herath et al. 2013)
Seemungal 2008(142)	109	Mean age 66 (treatment arm) versus 68 in placebo arm Females 38% (treatment arm) versus 36% in placebo arm Patients recruited from outpatient chest clinic from a single centre Mean FEV1 1.27 (treatment arm) versus1.36 (placebo arm) INCLUSION Severity of COPD was moderate to severe. FEV1 between 30-70%). EXCLUSION: History of asthma, bronchiectasis, neoplasia, unstable cardiac status (including prolonged QTc and arrhythmias), macrolide allergy or history of abnormal liver functions	12 months	Erythromcyin 250 mg twice daily Vs placebo	Jadad score: 5 ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: British Lung Foundation
Suzuki 2001(143)	109	Mean age 69y in erythromycin group and 72 in placebo group Mean FEV1 1.47 in erythromycin group versus1.30 in placebo group Females 13% in erythromycin group versus 18% in placebo group All study participants were treated with sustained release theophylline and inhaled anticholinergic agents EXCLUSION Patients diagnosed with bronchiectasis or diffuse pan bronchiolitis	12 months	Erythromycin 200-400 mg once daily vs placebo	Jadad score: 2 ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: High risk (not blinded) INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: not stated
He 2010(144)	*36*	*RCT did not meet our inclusion criteria*			

Table 318

8.1.2.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Ni 2015(137)	N= 3 (Suzuki 2001(143), Seemungal 2008(142), He 2010(145))	6-12 months	Long-term erythromycin vs placebo	adults >18y with a diagnosis of stable COPD	• unblinded study (Suzuki 2001) • one small RCT n=36 (He 2010)

Table 319

This systematic review and meta-analysis searched for RCTs that compared long-term erythromycin with placebo in adults with a diagnosis of stable COPD.

Three RCTs with a duration of 6 to 12 months were found.

One RCT was unblinded and one of the included RCTs had a very small sample size.

Endpoint: Exacerbations (number of patients)		
n= 254 6-12 months	GRADING ⊕⊕⊕⊖ **MODERATE** Study quality: -1 unblinded study, small sample size Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Ni 2015 (Suzuki 2001, Seemungal 2008, He 2010)	**RR: 0.49(0.26 to 0.91)**	**SS and p =0.02** **In favour of erythromycin**

Table 320

The results of these studies suggest that the number of patients with an exacerbation is decreased with erythromycin compared to placebo.

For this meta-analysis,
the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

Endpoint: Rate of exacerbations per patient per year	
n= 254	GRADING ⊕⊕⊕⊖ **MODERATE**

6-12 months	Study quality: -1 unblinded study, small sample size Consistency: ok Directness: ok Imprecision: ok	
Studies	Results	
SR/MA Ni 2015 (Suzuki 2001, Seemungal 2008, He 2010)	**RR: 0.53(0.43 to 0.83)**	**SS and p =0.01** **In favour of erythromycin**

Table 321

The results of these studies suggest that the rate of exacerbations per patient per year is decreased with erythromycin compared to placebo.

For this meta-analysis,
the result is statistically significant

We have moderate confidence that the results of the studies reflect the true effect.
GRADE: MODERATE quality of evidence

8.1.3 Clarithromycin vs placebo

8.1.3.1 *Clinical evidence profile*

SR/MA Ni 2015(137) found one RCT comparing long-term clarithromycin and placebo in COPD. However, this RCT did not meet our inclusion criteria (n=67).

8.1.3.2 *Summary and conclusions*

SR/MA Ni 2015(137) found one RCT comparing long-term clarithromycin and placebo in COPD. However, this RCT did not meet our inclusion criteria (n=67).

8.1.4 Roxithromycin vs placebo

8.1.4.1 *Clinical evidence profile*

Study details	n/Population	Comparison	Outcomes		Methodological
Shafuddin 2015(146) Design: RCT (DB) (PG) Duration of follow-up: 12 weeks intervention + 48 weeks follow-up	n= 292 Mean age: 67 % females: 21 Smoking: • Current: 18% • Ex-smoker: 82% % taking ICS at inclusion: NR other background medications allowed: NR, probably yes GOLD (yr)-classification: NR Baseline FEV1 : 34.9% predicted Baseline FVC : 2.29 L % reversible : NR	Roxithromycin 300mg/d + doxycycline 100mg/d combination* Vs **Roxithromycin 300mg/d** **Vs** **Placebo** *We will not report this combination	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 1.6% Drop-out and Exclusions:10.5% • Described: yes • Balanced across groups: yes ITT: Yes (analysis of all randomized participants)
			Moderate and severe COPD exacerbations (through 48-week period post treatment)(PO)	Roxithromycin: 2.69 per patient year (2.26 to 3.21) Placebo: 2.50 per patient year (2.08 to 3.03) NS and p=0.5832	
			Mean time to first moderate or severe COPD exacerbation (through 48-week period post treatment)(	Roxithromycin: 140 (SD 117) Placebo: 147 (SD 115) NS and p=0.254	
			Moderate and severe COPD exacerbations (through 12-week active treatment period)	Roxithromycin: 1.74 per patient year Placebo: 2.25 per patient year NS and p=0.2545	
			Moderate and severe COPD exacerbations (during first 24-week period post treatment)	Roxithromycin: 2.57 per patient year Placebo: 2.59 per patient year	

	Inclusion: Dyspnea: not a criterium FEV1 % predicted: Y, ≤70% Exacerbations: Y, ≥3 moderate or severe in the past two years 45 years or older Smoking history ≥20 pack years Exclusion • Pulmonary disease other than COPD • Hypersensitivity to macrolides • Serious cardiovascular, hepatic, renal or other systemic diseases • Long QT • Imparaired hepatic function • Unlikely to comply			NS and p=0.9577	SELECTIVE REPORTING: no Other important methodological remarks: 2-week run-in period Sponsor: Sanofi-Aventis
			Moderate and severe COPD exacerbations (during last 24-week period post treatment)	Roxithromycin: 2.81 per patient year Placebo: 2.40 per patient year NS and p=0.3496	

Table 322

8.1.4.2 *Summary and conclusions*

Bibliography summary							
	n	duration	exact comparison	population (+ remarks)	GOLD / asthma categories	%ICS	methodological remarks
Shafuddin 2015(146)	292	12 weeks intervention + 48 weeks follow-up	Roxithromycin 300mg/d Vs Placebo	Mean age: 67 % females: 21 Baseline FEV1 : 34.9% predicted	≥II	NR	Unclear method of randomization and allocation concealment

Table 323

This RCT compared roxithromycin versus placebo in 292 COPD patients.

The intervention had a duration of 12 weeks, with an additional follow-up of 48 weeks.

The method of randomization and allocation concealment in this RCT was not clearly described, which limits our confidence in the results.

Endpoint: Number of moderate and severe exacerbations		
n=292 48 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: -1 unclear randomization and allocation concealment Consistency: NA Directness: ok Imprecision: -1 no numerical result for between-group differences	
Studies	Results	
Shafuddin 2015 n=292 48 weeks	Roxithromycin: 2.69 per patient year (2.26 to 3.21) Placebo: 2.50 per patient year (2.08 to 3.03)	NS

Table 324

The results of these studies do not suggest an effect in any direction.

For this study,

the result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.

GRADE: LOW quality of evidence

8.2 Long-term prophylactic use of macrolides in ASTHMA

8.2.1 Macrolides vs placebo

8.2.1.1 *Clinical evidence profile*

Meta-analysis: Kew 2015(147) "Macrolides for chronic asthma"

Inclusion criteria:
Parallel group and cross-over RCTs. Population: children and adults with chronic asthma. Comparisons: macrolides, administered for more than four weeks, versus placebo.
Search strategy:
"Systematic searching of electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts" "We also manually searched bibliographies of previously published reviews and conference proceedings and contacted study authors." Last search date april 2015.
Assessment of quality of included trials: yes
Other methodological remarks: /

Table 325

Ref	Comparison	N/n	Outcomes	Result(95%CI)
Kew 2015(147) Design: SR+ MA Search date: April 2015	Macrolide versus placebo	N= 2 n= 143 (Amayasu 2000, Brusselle 2013)	Exacerbation requiring hospitalisation	Macrolide: 2/72 Placebo: 2/71 OR: 0.98 (0.13 to 7.23) NS
		N= 5 n= 290 (Amayasu 2000, Brusselle	Severe exacerbation – requiring at least OCS	Macrolide: 31/158 Placebo: 32/132 OR: 0.82 (0.43 to 1.57)

		2013, Hahn 2006, Kostadima 2004, Strunk 2008)		NS
		N= 4 n= 353 (Brusselle 2013, Cameron 2012, Hahn 2012, Sutherland 2010)	Asthma Control Questionnaire	Std. MD -0.05 (-0.26 to 0.15) NS
		N= 5 n= 389 (Brusselle 2013, Cameron 2012, Hahn 2006, Hahn 2012, Sutherland 2010)	AQLQ	MD 0.06 (-0.12 to 0.24) NS
		N= 9 n= 631 (Amayasu 2000, Cameron 2012, He 2009, Kraft 2002, Shoji 1999, Sutherland 2010, Wang 2014, Xiao 2013, Yan	FEV1 (unclear whether trough or peak)	**MD 0.08 (0.02 to 0.14)** **SS** **Favours macrolide**

		2008)		
		N= 7 n= 434 (Amayasu 2000, Brusselle 2013, Cameron 2012, Hahn 2006, Hahn 2012, Kamada 1993, Sutherland 2010)	Serious adverse events	Macrolide: 4/221 Placebo: 5/213 OR 0.80 (0.24 to 2.68) NS

Table 326

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group°)
Brusselle 2013(148) RCT	109	18 to 75 years of age; diagnosis of persistent asthma; history consistent with Global Initiative for Asthma step 4 or 5 clinical features; received high doses of ICS (≥ 1000 mg fluticasone or equivalent) plus inhaled LABA for at least 6 months prior to screening and had at least two independent severe asthma exacerbations requiring systemic corticosteroids, LRTI requiring antibiotics or both within the previous 12 months; never smokers or ex-smokers with a smoking history of≤10 pack-years; FeNO-level was below the	26 weeks	Azithromycin 250 mg/d for 5 days and then 1 capsule 3x/week vs placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Low risk FUNDING: Agency for Innovation by Science and Technology. No industry funding.

		upper limit of normal **Exclusion criteria**: Prolonged corrected QT interval, severe bronchiectasis, significant medical conditions or significant laboratory abnormalities that might interfere with the study conduct or patient's safety, pregnancy or breastfeeding, prohibited concomitant medication including anti-IgE treatment and treatment with macrolide antibiotics within the last 3 months			
Sutherland 2010(149)	92	history of physician-diagnosed asthma; methacholine PC20 less than or equal to 16 mg/mL, FEV1 improvement greater than or equal to 12% in response to 180 µg albuterol, or both; stable asthma for at least 6 weeks prior to study entry; FEV1 greater than or equal to 60% of predicted result following 180 µg albuterol; Juniper ACQ score greater than or equal to 1.5 (optimal ACQ score cut-off point for asthma that is 'not well controlled' by NIH/GINA guidelines); non-smoker (less than 10 pack-per-year lifetime smoking history and no smoking in the year prior to study entry); able to perform spirometry, as per ATS criteria; 75% adherence with diary cards, fluticasone (monitored with Doser), and placebo pill trial (monitored electronically with	16 weeks	Clarithromycin 500 mg 2x/day + fluticasone propionate 88 mcg 2x/day Vs Placebo + fluticasone propionate 88 mcg 2x/day	ALLOCATION CONC: Unclear risk (not described) RANDO: Unclear risk (method not described) BLINDING : Participants/ personnel/ assessors: Low risk INCOMPLETE OUTCOME DATA: High risk (ITT; dropout was 17% and 11% in clarithromycin and placebo groups respectively, does not appear to have imputed for missing participants) SELECTIVE REPORTING: High risk (Some outcomes not fully reported; only primary outcome and adverse effects have been uploaded to ClinicalTrials.gov) OTHER BIAS: Low risk FUNDING: Milton S Hershey Medical Center with collaboration from the

		electronic Drug Exposure Monitor (eDEM) pill dose counter) for the final 2 weeks of the 4-week run-in period; at visit 1, in steroid-naive participants, no significant adrenal suppression, defined as a plasma cortisol concentration less than 5 µg/dL (if adrenal suppression occurs, a 250 µg corticotropin (ACTH) stimulation test was performed. Plasma cortisol levels were collected at baseline, and 30 and 60 minutes after the ACTH stimulation test. Participants must have a cortisol concentration greater than 20 µg/ dL on at least one of the post-ACTH time points); absence of bronchoscopy-induced exacerbation (if bronchoscopy-induced exacerbation has occurred, prednisone therapy must have stopped at least 6 weeks prior to study entry); absence of respiratory tract infection (if infection has occurred, infection-related symptoms must have stopped at least 6 weeks prior to study entry); has experienced no more than two exacerbations or respiratory tract infections prior to study entry; if female and able to conceive, willing to utilise two medically acceptable forms of contraception (one non-barrier method with single barrier method or a double barrier method)			National Heart, Lung and Blood Institute (NHLBI)

		Exclusion criteria: • presence of lung disease other than asthma • significant medical illness other than asthma • history of atrial or ventricular tachyarrhythmia • use of any medication that has a significant interaction with clarithromycin • asthma exacerbation within 6 weeks of the screening visit or during the run-in period prior to bronchoscopy • use of systemic steroids or change in dose of controller therapy within 6 weeks of the screening visit • inability, in the opinion of the study investigator, to coordinate use of dry powder or metred-dose inhaler or to comply with medication regimens • QT interval (greater than 450 ms in women and greater than 430 ms in men) on ECG at study entry; low potassium or magnesium levels (based on local Asthma Clinical Research Network laboratory definitions); abnormal elevation of liver function tests (AST, ALT, total bilirubin or alkaline phosphatase); abnormal prothrombin time (PT) or partial thromboplastin time (PTT)			

		results; reduced creatinine clearance; contraindication to bronchoscopy, as determined by medical history or physical examination; regular consumption of grapefruit or grapefruit juice; pregnant or breastfeeding			
Xiao 2013(150)	210	"We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma"" Exclusion criteria: Not reported	12 weeks	Roxithromycin 150 mg twice daily Vs placebo	ALLOCATION CONC: Unclear risk (no information) RANDO: Low risk BLINDING : Participants/ personnel/ assessors: Unclear risk (placebo control was used, but methods of blinding not adequately described) INCOMPLETE OUTCOME DATA: Unclear risk (no information) SELECTIVE REPORTING: Unclear risk (no information)ClinicalTrials.gov) OTHER BIAS: Unclear risk (no information) FUNDING: unknown
Amayasu 2000(151)	*17*			*clarithromycin 200 mg twice a day*	*RCT did not meet our inclusion criteria*
Cameron 2012(152)	*77*			*Azithromycin 250 mg/day* *Vs* *Placebo*	*RCT did not meet our inclusion criteria*
Hahn 2006(153)	*45*			*Azithromycin 600mg/day for 3 days, followed by 600 mg weekly for an additional 5 weeks* *Vs* *placebo*	*RCT did not meet our inclusion criteria*

Hahn 2012(154)	*75*		*Azithromycin 600 mg/day for 3 days, followed by 600 mg/week for 11 weeks*	*RCT did not meet our inclusion criteria*
He 2009(145)	*40*		*Azithromycin 250 mg 2x/week*	*RCT did not meet our inclusion criteria*
Kamada 1993(155)	*19*		*Troleandomycin 250 mcg Vs placebo*	*RCT did not meet our inclusion criteria*
Kostadima 2004(156)	*75*		*Clarithromycin 250 mg 2x/day or Clarithromycin 250 mg 3x/day Vs placebo*	*RCT did not meet our inclusion criteria*
Kraft 2002(157)	*55*		*Clarithromycin 500 mg twice daily*	*RCT did not meet our inclusion criteria*
Shoji 1999(158)	*14*		*Roxithromycin 150 mg twice daily*	*RCT did not meet our inclusion criteria*
Strunk 2008(159)	*55*		*Azithromycin 250 or 500 mg/day Vs placebo*	*RCT did not meet our inclusion criteria*
Wang 2014(160)	*58*		*Azithromycin 250 mg twice weekly Vs placebo*	*RCT did not meet our inclusion criteria*
Yan 2008(161)	*40*	*(160)*	*Roxithromycin 150 mg twice daily Vs placebo*	*RCT did not meet our inclusion criteria*

Table 327

8.2.1.2 *Summary and conclusions*

Summary: meta-analysis					
	N (studies)	Duration	Comparison	Population	methodological remarks on included studies
SR/MA Kew 2015(147)	N= 15 (Amayasu 2000(151), Brusselle 2013(148), Cameron 2012(152), Hahn 2006(153), Hahn 2012(154), He 2009(145), Kamada 1993(155), Kostadima 2004(156), Kraft 2002(157), Shoji 1999(158), Strunk 2008(159), Sutherland 2010(149), Wang 2014(160), Xiao 2013(150), Yan 2008(161))	12-26 weeks	Azithromycin vs placebo (7) Clarithromycin vs placebo (3) Roxithromycin vs placebo (3) Troleandomycin vs placebo (1)	children and adults with chronic asthma	• 12/15 RCTs did not meet our inclusion criteria (sample size <40/arm) (Amayasu 2000, Cameron 2012, Hahn 2012, He 2009, Kamada 1993, Kostadima 2004, Kraft 2002, Shoji 1999, Strunk 2008, Wang 2014, Yan 2008) • One RCT with unbalanced drop-out between groups, unclear randomization and allocation concealment, and selective reporting (Sutherland 2010) • One RCT unclear information (unpublished data taken from a different review) (Xiao 2013)

Table 328

This systematic review and meta-analysis searched for RCTs that compared long-term macrolides with placebo in adults and children with a diagnosis of chronic asthma.

Fifteen RCTs with a duration of 12-26 weeks were found. Seven RCTs compared azithromycin with placebo, three compared clarithromycin with placebo, three compared roxithromycin with placebo, and one RCT compared troleandomycin (not available on the Belgian market) with placebo.

Twelve out of the fifteen RCTs did not meet our inclusion criteria because of a very small sample size. Of the three remaining RCTs, one had unbalanced drop-out between groups, unclear randomization

and allocation concealment, and displayed selective reporting. We had little information regarding another unpublished RCT. These problems severely limit our confidence in the results.

As the pool of evidence was so small, we did not report the comparisons of separate antibiotics.

Endpoint: Exacerbations requiring hospitalisation		
n= 143 12-26 weeks	GRADING ⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1 different antibiotics Imprecision: -1 (wide confidence interval)	
Studies	Results	
Kew 2015 (Amayasu 2000, Brusselle 2013)	OR: 0.98 (0.13 to 7.23)	NS

Table 329

The results of these studies do not suggest an effect in any direction.

For this meta-analysis of studies,

The result is not statistically significant

We have low confidence that the results of the studies reflect the true effect.
GRADE: LOW quality of evidence

Endpoint: Exacerbations (severe- requiring at least OCS)		
n= 290 mean 18 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -1 small sample size of included studies Consistency: ok Directness: -1 different antibiotics Imprecision: -1 (wide confidence interval)	
Studies	Results	
Kew 2015 (Amayasu 2000, Brusselle 2013, Hahn 2006, Kostadima 2004, Strunk 2008)	OR: 0.82 (0.43 to 1.57)	NS

Table 330

The results of these studies do not suggest an effect in any direction.

For this meta-analysis of studies,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: Asthma control questionnaire	
	GRADING

n= 353 mean 17 weeks	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 small sample size of included studies; larger RCT with unbalanced drop-out between groups, unclear randomization and allocation concealment, and selective reporting Consistency: ok Directness: -1 different antibiotics Imprecision: ok

Studies	Results	
Kew 2015 (Brusselle 2013, Cameron 2012, Hahn 2012, Sutherland 2010)	Std. MD -0.05 (-0.26 to 0.15)	NS

Table 331

The results of these studies do not suggest an effect in any direction.

For this meta-analysis of studies,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: AQLQ	
n= 389 mean 16 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 small sample size of included studies; larger RCT with unbalanced drop-out between groups, unclear randomization and allocation concealment, and selective reporting Consistency: ok Directness: -1 different antibiotics Imprecision: ok

Studies	Results	
Kew 2015 (Brusselle 2013, Cameron 2012, Hahn 2006, Hahn 2012, Sutherland 2010)	MD 0.06 (-0.12 to 0.24)	NS

Table 332

The results of these studies do not suggest an effect in any direction.

For this meta-analysis of studies,

The result is not statistically significant

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

Endpoint: FEV1 (*Unclear whether trough or peak)*	
n= 631 mean 15 weeks	GRADING ⊕⊖⊖⊖ **VERY LOW** Study quality: -2 small sample size of included studies; larger RCT with

	unbalanced drop-out between groups, unclear randomization and allocation concealment, and selective reporting Consistency: ok Directness: -1 different antibiotics Imprecision: ok	
Studies	Results	
Kew 2015 (Amayasu 2000, Cameron 2012, He 2009, Kraft 2002, Shoji 1999, Sutherland 2010, Wang 2014, Xiao 2013, Yan 2008)	**MD 0.08 L (0.02 to 0.14)**	**SS** **Favours macrolide**

Table 333

For this meta-analysis of studies,

The result is statistically significant

When comparing macrolides with placebo, the results from the studies show an effect in favour of macrolides on FEV1, and it is statistically significant.

We have very low confidence that the results of the studies reflect the true effect.
GRADE: VERY LOW quality of evidence

8.3 Adverse events from RCTs

8.3.1 Long-term prophylactic use of macrolides in COPD

A meta-analysis{Ni, 2015 #82} of three studies (comparing erythromycin and azithromycin versus placebo) including 212 patients reported 4 **cardiovascular events** in the treatment group and 2 in the placebo group, which was a statistically significant difference (P = 0.43).

One RCT (Albert 2011{Albert, 2011 #184}) found no significant difference of the **rate of death due to cardiovascular or respiratory events,** and of **serious adverse events causing drop-out** between azithromycin and placebo.

8.3.2 Long-term prophylactic use of macrolides in ASTHMA

A meta-analysis of 7 RCTs (Kew 2015(147)) did not find a statistically significant difference of **serious adverse events** with the long-term prophylactic use of macrolides, compared to placebo, in asthma patients.

9 Adherence

9.1 Adherence in asthma

9.1.1 Identifying non-adherence

See guideline section for details.

9.1.2 Interventions to improve adherence

We found the following systematic reviews about (interventions to improve) adherence in asthma.

9.1.2.1 *Systematic review. Interventions (with components of the chronic care model) to improve adherence to inhaled corticosteroids.*

Moullec 2012 (162) is the only systematic review found by BTS/SIGN 2016(36) that specifically addresses asthmatic patients.

Moullec 2012 (162) performed a systematic review on **interventions to improve adherence to inhaled corticosteroids** and more specifically, whether the use of components of Wagner's chronic care model (CCM) in these interventions, had an impact on adherence. The components of the chronic care model are: self-management skills, providing decision support, delivery system design and clinical information systems. 18 studies were included. Inclusion of a greater number of CCM components within interventions was associated with stronger effects on ICS adherence outcomes.

9.1.2.2 *Systematic review. Any intervention to improve adherence to inhaled corticosteroids*

Barnes 2015(163) performed a systematic literature search on **adherence to inhaled corticosteroids** (ICS), the effects of poor adherence and means to improve adherence (last updated april 2014). Concerning interventions to improve adherence, 7 studies were identified (RCT's, observational or non-comparative intervention studies). 3 of the RCT's met our inclusion criteria, but they were all included in one or more of the other systematic review in this chapter.

Barnes(163) concludes '*Interventions to improve adherence show varying results, with most studies reporting an increase in adherence but unfortunately not necessarily an improvement in outcome. Even following successful interventions, adherence remains low.'*

9.1.2.3 *Systematic review. The use of mobile applications to support self-management*

Hui (164) did a systematic review on **the use of mobile applications to support self-management** for people with asthma. Clinical outcomes were reported. Adherence was only reported on the use of the application, not on the use of medication.

12 RCT's were included. The interventions could be grouped in 7 categories (education, monitoring/electronic diary, action plans, medication reminders/prompts, facilitating professional support, raising patient awareness of asthma control, and decision support for professionals).

In 6 of 11 studies, an improvement in **asthma control** was reported.

A meta-analysis of 3 RCT's was performed for the outcome asthma control (using the ACQ or Asthma control questionnaire) at 6 to 12 months. There was statistically significantly improved asthma control in the intervention group (mean difference -0.25, [95% CI, -0.37 to -0.12]), but Hui stated that '*the confidence interval did not include the minimum clinically important difference of 0.5*'.

In 4 of the 8 studies that reported **quality of life,** QOL was improved with the intervention.
In 5 RCT's that reported on **exacerbations**, none of the interventions was associated with a significant reduction in exacerbation related outcomes.

Hui (164) concludes: the most successful interventions include multiple features, but the effect on clinical outcomes are inconsistent.

9.1.2.4 *Systematic review. Patient reminder systems and asthma medication adherence.*

BTS/SIGN 2016(36) identified one systematic review on reminder systems in adults:
Tran 2014 (165) conducted a systematic review of the literature to identify randomized controlled trials (RCTs) which assessed the **effect of reminder systems** on daily asthma medication adherence. Five RCTs and one pragmatic RCT were included in the analysis. Median follow-up time was 16 weeks. All of the six studies suggested that the **reminder system intervention was associated with greater levels of asthma medication adherence** compared to those participants in the control group. None of the studies documented a change in asthma-related quality of life or clinical asthma outcomes.
BTS/SIGN 2016(36) identified 1 other RCT about inhaler reminders (Foster 2014 (166)), that came to the same conclusion.

9.1.2.5 *Systematic review. SMS and voice call interventions to improve adherence*

A systematic review by Yasmin 2016 (167) about SMS and **voice call interventions** on adherence and health outcomes in chronic disease found 2 RCT's in asthmatic patients, both of which were included in Tran 2014 (165).

9.1.2.6 *Systematic review. Cognitive behavior therapy (CBT) in adolescents and adults with asthma.*

A Cochrane systematic review by Kew 2016 (168) found insufficient evidence to evaluate the effect of **CBT** on adherence to medication (1 RCT, 12 participants).

9.1.2.7 *Systematic review: pharmacist-led interventions*

BTS/SIGN 2016(36) identified 2 reviews: one Cochrane systematic review that examined pharmacist interventions in different chronic illnesses (Pande 2013 (169)), and 1 review that assessed pharmacist interventions in asthma (Benavides 2009 (170)).
Pande (169) found 3 RCT's in asthma and 1 RCT in asthma/COPD. Benavides (170) found 25 studies. Quality of the studies was variable, so were interventions used (education, monitoring, self-management). The main interest was in clinical outcomes. Adherence to medication was not measured.

The results are discussed in the Guidelines chapter.

9.1.2.8 *RCT's that were found by our search*

9.1.2.8.1 Web based management system

- Ahmed 2016 (171) was a pilot study that included 100 patients with poor asthma control. They were randomly assigned to a **web-based asthma management system** (MAP – My Asthma Portal) or to usual care for 6 months. At 6 months, no statistically significant difference in quality of life or asthma control was found. Adherence to medication was not measured.

9.1.2.8.2 Multifactorial - pharmacist

- Olivera 2016 (172) randomized 119 patients with asthma to 5 **pharmacist-led education sessions about a self-management program** or to usual care. After 4 months, asthma knowledge, lifestyle, inhaler techniques, adhesion to treatment, pulmonary function and quality of life was evaluated.
  Inhaler technique knowledge was improved from baseline, and was better at 4 months in the intervention group compared to the control group for 2 of the 3 inhalers studied. Compared to the baseline values, patients in the intervention group developed **a better adherence** to medicinal treatment, a better quality of life, an increased uptake of physical exercise. The differences between intervention and control group were not reported.

9.1.3 Conclusions – Improving medication adherence in asthma

There are different ways to measure adherence in a clinical setting. (See chapter guidelines). Several interventions to improve adherence to asthma medication have been studied. These interventions involve different medications.

Most interventions to improve adherence are **multifaceted**: they target different aspects of asthma management and can include educational and behavioural components. A better adherence is usually seen, but not always accompanied by a measurable clinical improvement (162), (163).

Some (mobile) applications to improve self-management can improve asthma outcomes and quality of life. We do not know whether they improve medication adherence. Since every study had a different (multifactorial) intervention, and not all studies produced statistically significant improvements, it is unclear what factors contribute to success (164), (171).

Patient reminder systems, for example via SMS or automated telephone calls improve adherence. We have no information whether they improve clinical outcomes (165), (166), (167).

There is insufficient evidence about **cognitive behavior therapy** for improving medication adherence in asthma (168).

A **pharmacist-led intervention** may be useful to improve inhaler technique. More studies are needed to assess impact on clinical outcomes and adherence (169), (170), (172).

9.2 Adherence in COPD

9.2.1 Identifying non-adherence

None of the selected guidelines for COPD discussed adherence.

A systematic review by Bryant 2013 (173) stated that non-adherence to medication in COPD is high, with adherence between 41.3% and 57% . Underuse is most common: up to 49.4% are not taking nebulised treatments as prescribed; 31% employ ineffective inhaler dosing techniques and more than 50% over-utilise medications during periods of respiratory distress.
There is intentional and unintentional non-adherence.
Intentional non-adherence is deliberate, usually during periods of symptom remission, often due to an erroneous understanding of the disease course and the treatment goals.
Unintentional non-adherence is due to reasons beyond the control of the patient. The most common are:

- complex medication regimes
- poly-pharmacy

other factors include

- cognitive impairments
- language barriers
- physical disability, like impaired vision or musculoskeletal problems affecting patient ability to use inhaled medications
- multiple devices
- poor awareness and understanding of the nature of COPD
- confusion about prescribed medication regimes
- high rates of depression

9.2.2 Interventions to improve adherence

9.2.2.1 *Systematic review. interventions to improve medication adherence in COPD*

Bryant 2013 (173) performed a systematic review about **interventions to improve medication adherence in COPD**. 7 RCT's were included. The interventions that were studied were: brief counselling, monitoring and feedback about inhaler use through electronic medication delivery devices; and multi-component interventions consisting of self-management and care co-ordination delivered by pharmacists and primary care teams.
Medications that were studied varied: beta 2 agonists, theophylline, steroids, antibiotics… and consisted of inhaled and/or oral medication.
Outcomes were measured directly (blood serum ratios, observation of inhaler technique) and indirectly (prescription refills, adherence scales, inhaler device data, patient self-report, pharmacy data, canister weighing and tablet counts).

The studies from Bryant that met our inclusion criteria are listed in a table on the next page.

Reference Country Design	**Sample** N; Age; Setting; Medication types	**Eligibility** Inclusion criteria;	**Intervention**	**Outcome measures** **Follow-up time points**	**Findings**
Garcia-Aymerich 2007(174) Spain RCT	**N:** 113 **Setting:** Tertiary hospital clinic.	**Inclusion criteria:** Admitted because of exacerbation requiring hospitalisation for >48 hours.	**Intervention:** Assessment of the patient at discharge; 2 hour **educational session** on self-management including written information; possibility to **phone nurse** if symptoms worsened; joint **visit by nurse** and **primary care team** within 72 hours post-discharge; **weekly phone call** first month post-discharge and one phone call at 3 and 9 months. **Control:** Usual care.	**Measures:** i) Medication Adherence Scale (MAS); ii) Inhaler Adherence Scale (IAS); iii) Observed skills for administration of inhaled drugs. **Follow up:** 6 and 12 months.	• Significant difference in inhaled treatment adherence at 12 months (I: 71%; C: 37%; *p*=.009). • Significant difference in correct inhaler use (I: 86%; C: 24%; *p*≤.001). • No significant difference in adherence to oral treatment at 12 months (I: 90%; C: 85%; *p*=.57).
Jarab 2012(175) Jordan RCT	**N:** 133 **Age:** I: Median=61 (IQR=14); C: Median=64 (IQR=15).	**Inclusion criteria:** Attend outpatient COPD clinic; confirmed diagnosis by hospital consultant for >1 year; >35 years old; FEV_1 of 30–80% of predicted; consultant agreement that patient suitable for trial.	**Intervention:** Structured **face-to-face motivational interviewing** provided by **clinical pharmacist** at an outpatient clinic. Education included symptom control, technique for sputum expectoration and importance of simple exercises for physical activity. Clinical pharmacist completed medication table and provided take-home booklet. Referral to **smoking cessation program**. **Control:** Usual care.	**Measures:** Morisky scale. **Follow up:** 6 months.	• Significant difference in proportion of non-adherent patients in I (28.6%) compared to C (48.4%) at 6 months (*p*<.05).
Khdour 2009(176)	**N:** 173 **Age:** I: M=65.63	**Inclusion criteria:** Confirmed diagnosis of COPD	**Intervention:** . i) Assessment of disease knowledge; smoking status; medication adherence; self-efficacy in	**Measures**: Morisky Scale.	• At 6 months follow-up, significantly higher adherence to

UK RCT	(SD=10.1); C: M=67.3 (SD=9.2). **Setting:** Hospital based outpatient clinic.	by the hospital consultant for > 1 year; FEV_1 of 30–80% of predicted normal value; >45 years old.	managing breathing difficulty; exercise and diet habits conducted by researchers and results forwarded to clinical pharmacist to allow tailoring of intervention; ii) **One hour face-to-face education delivered by clinical pharmacist** on disease state, medications and breathing techniques. Patients given booklets and a customised action plan. Motivational interviewing provided to participants who smoked, and referral to hospital **smoking cessation program** made. At outpatient clinic visits (every 6 months) participants received **reinforcement** of education by clinical pharmacist, as well as telephone calls at 3 and 9 months. **Control:** Usual care.	**Follow up:** 6 and 12 months.	medication in I (81%) compared to C (63%); *p*=.019. • At 12 months follow-up, significantly higher adherence to medication in I (77.8%) compared to C (60%); *p*=.019.
Nides 1993 (177) USA CCT	**N:** 251 **Age:** I: M=49 (SD=6.4); C: M=50.3 (SD=6.3). **Setting:** University of California and Johns Hopkins University centres.	**Inclusion criteria:** Aged 35-60 years; active cigarette smokers; spirometric evidence of mild to moderate airflow obstruction as indicated by FEV_1/FVC of ≤70% and FEV_1 of 55-90% of predicted.	**Intervention:** **Nebuliser chronolog** (NC) provided to patients. Patients instructed about ability of the NC to record the time and date of each actuation. Provided with printed copies of own NC record at end of weeks 1 and 7 of the 12-week smoking cessation program. **Health educator and participant jointly reviewed feedback about adherence** (5 min sessions). Praise given for satisfactory use. **Behavioural strategies** such as anchoring inhaler use to daily routines were collaboratively developed to address problem areas. **Brief feedback sessions** continued at each 4-month follow-up visit. **Control:** Patients provided with NC monitor and told monitor would record the amount of inhaled drug used. No feedback provided.	**Measures:** i) NC device data on number and intervals of actuations; ii) Self-reported adherence "how frequently on average are you using your inhaler at present" with seven response options ranging from "not at all" to "4 or more times per day"; iii) Inhaler canister weighing before being dispensed and at follow-up. **Follow up:** 4 months.	• I participants adhered more closely to the prescribed three sets per day (M=1.95; SD=0.68) compared to C (M=1.63; SD=0.82); *p*=.003. • I participants had greater proportion of adherent days (M=60.2; SD=25.9) compared to C (M=40.4; SD=28.2); *p*<.0001. • I participants had greater proportion of actuations taken as prescribed (M=88.8; SD=9.6) compared to C (M=68.8; SD=25.7); *p*<.0001. • 28% of I participants had

					>80% adherent days compared to only 7.9% of C participants; *p*<.002.
Simmons 1996(178) USA CCT	**N:** 231 **Age:** I: M=50.3; C: M=48.4 **Setting:** University of California, Los Angeles and Johns Hopkins University. .	**Inclusion criteria:** Aged 35-60 years; active cigarette smokers; spirometric evidence of mild to moderate airflow obstruction as indicated by FEV_1/FVC of ≤70% and FEV_1 of 55-90% of predicted.	**Intervention** Aware that inhaler had a nebuliser chronolog (NC) to record date and time of each use. Readings of actuation dates and times used to provide feedback at weeks 1 and 10 following their groups quit date and each 4 month follow-up. **Control:** Not aware of ability of NC to record date and time, however aware that the NC would monitor total medication used.	**Measures:** NC device data examining: i) Mean number of daily sets of use (mean number of times inhaler is used each day) in two week interval following issue of NC and each subsequent follow-up visit; ii) Changes in mean number of sets per day (comparison of last 2 week period before the follow-up visit and first 2 week period after the follow-up visit). **Follow up:** 4, 8, 12, 16, 20 and 24 months.	• I group had significantly greater mean number of daily sets of use at each follow up compared to C: 4 months- I: M=1.93 (SD=.69); C: M=1.6 (SD=0.83); *p*<.0035. 12 months- I: M=1.74 (SD=.89); C: M=1.29 (SD=.91); *p*=.0007. 24 months- I: M=1.65 (SD=.89); C: M=1.16 (SD=.95); *p*=.0006. • No significant differences between groups in mean number of sets per day from last 2 week period before follow-up and first 2 week period after follow-up.
Solomon 1998(179) USA RCT	**N:** 98 **Age:** I: M=69.3 (SD=5.9); C: M=69.3 (SD=9.2).	**Inclusion criteria:** ≥40 years; ambulatory patient; pulmonary function tests to diagnose COPD;	**Intervention:** Patient-centred **pharmaceutical care** provided **face-to-face and via telephone by clinical pharmacist** and pharmacy residents. Included: management of drug therapy; collaboration with physician to implement patient-specific stepped care; education about COPD; counselling to	**Measures**: i) Morisky scale; ii) Tablet counts. **Follow up:** 6 months.	• Authors state no significant difference in medication compliance. Data not reported.

	Setting: 10 Department of Veterans Affairs medical centres and 1 academic medical centre. **Medication type:** Not reported.	currently receiving treatment that included ≥1 metered dose inhaler (MDI); mentally and physically able to use MDI/spacer inhaler; read and write English; understand study protocols; telephone access.	address patient concerns; patient assessment and care through clinic visits and telephone follow-up. **Control:** Usual pharmacy care.		

Table 334

Bryant concludes: *"Most interventions studied were multi-component interventions. Most interventions achieved a better adherence compared to a control intervention. It is not clear wat intervention is best to achieve a better adherence, and what are the influencing factors in a multi-component approach to make it work".*

9.2.2.2 *RCT's that were found by our search*

9.2.2.2.1 Tele-monitoring

- Pinnock 2013(180) examined **tele-monitoring** (with on-line questionnaire and oxygen saturation measurements) integrated into existing clinical services and compared it to conventional self-monitoring in 256 COPD patients that had had a hospitalization for a COPD exacerbation in the last year. Outcomes that were assessed included time to hospital admission for COPD exacerbation, quality of life, adherence to treatment, etc… After 1 year, there was **no statistically significant difference** in time to **hospital admission** between groups (adjusted HR 0.98, 95% CI 0.66 to 1.44), neither was there an statistically significant difference in the number of hospitalisations, in quality of life scores and in **adherence scores**.

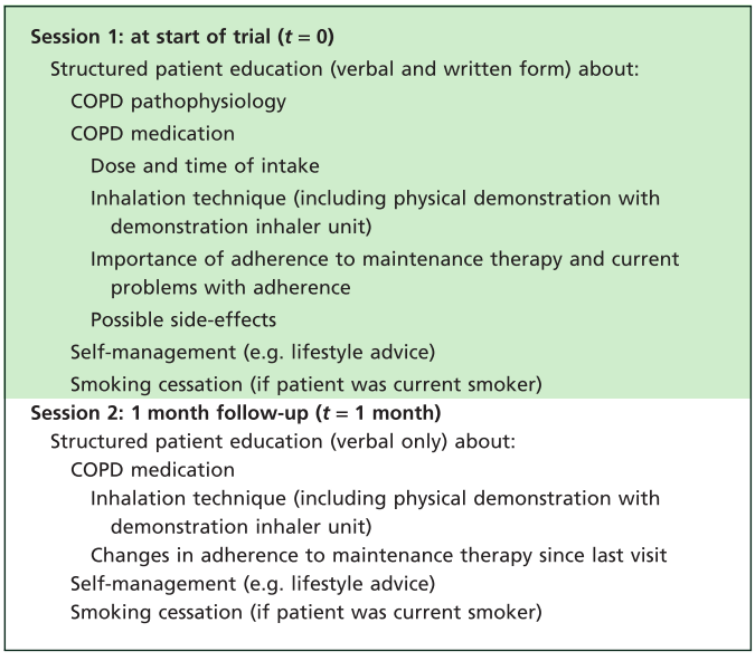
9.2.2.2.2 Multifactorial – unknown professional

- Leiva-Fernandez 2014(181) randomised 146 patients with COPD to a **multifactorial intervention to improve adherence** or to usual care. The intervention consisted of a group session on motivational aspects related to **adherence** (beliefs and behaviour), **information** about the illness and training in **inhalation** techniques and of individual visits. The intervention was given by 'trained professionals'. Follow-up was 12 months.
  Patients were defined as 'adherent' when they took between 80% and 110% of their prescribed doses (dose/pill count).
  41.1% reported adherence (41.9% of the control group and 40.3% of the intervention group). When multifactorial intervention was applied, the reported adherence was 32.4% for the control group and 48.6% for the intervention group, which showed **a statistically significant difference** (p = 0.046). **Number needed to treat is 6.37**. In the intervention group, cognitive aspects increased by 23.7% and skilled performance of inhalation techniques increased by 66.4%. A better adherence was associated with fewer exacerbations, fewer number of devices, fewer use of beta-adrenergics.

9.2.2.2.3 Multifactorial – pharmacist

- **Belgium**

Tommelein 2014 (182) randomised 734 patients from 170 Belgian community pharmacies to **a protocol defined pharmacist care** (2 sessions, 1 month apart, face to face), or to usual pharmacist care. Interventions were focused on **inhalation technique and adherence** to maintenance therapy.



Inhalation technique was scored using a checklist. Adherence was assessed by medication refill data (MRA: medication refill assessment). An MRA ≥ 80 was considered adherent.

At 3 months**, inhalation scores and medication adherence scores were significantly higher in the intervention group** compared to the control group.

At 3 months – inhalation scores
Intervention: 93.4% correct steps
Control: 79.0% correct steps
Difference 13.5 (95%CI 10.8-16.1)

At 3 months – MRA scores
Intervention: 93.9
Control: 85.7
Difference: 8.51 (95%CI 4.63-12.4)

A **lower hospitalization rate** was observed in the intervention group, as well as a **lower rate of serious exacerbations**, compared to the control group.

Hospitalizations (patients with an event)
Intervention: 2.2%
Control: 6.6%
OR 0.31 (95%CI 0.14 – 0.71)
Severe exacerbations (patients with an event)
Intervention: 5.1%
Control: 9.1%
OR 0.55 (95% CI 0.31 – 0.98)

- **China**

Wei 2014 (183) randomized 117 Chinese COPD patients with suboptimal adherence to receive a **pharmaceutical care program** or usual care for 6 months. The intervention consisted of individualized education (use of **inhalers**, **disease** and medication information, **adherence**) and telephone counseling.
Adherence was measured by pill count and direct interview.
At 6 months and at 1 y, **adherence was higher** in the intervention group compared to the control group: At 6-month pharmaceutical care and one-year follow-up, the pharmaceutical care group exhibited higher medication adherence than the usual care group (73.4±11.1 vs. 55.7±11.9, P=0.016 and 54.4±12.5 vs. 66.5±8.6, P=0.039, respectively).
Patients in the intervention group had **fewer hospital admissions** for COPD exacerbation compared to patients in the control group. There are 60 acute exacerbations resulted in a hospital admission in the usual group while 37 ones in the pharmaceutical care group during one-year follow-up (P=0.01).

9.2.3 Conclusions – Improving medication adherence in COPD

Based on the following references: Bryant 2013 (173), Pinnock 2013(180), Leiva-Fernandez 2014(181), Tommelein 2014 (182), Wei 2014 (183),
Most interventions to improve medication adherence in COPD in the included RCT's were **multifaceted** (education about disease, inhalers, adherence support…).
In 5 RCT's, the interventions were led by a **pharmacist**, in 1 RCT by a primary care team (mostly nurse) and in 1 RCT it is unspecified who delivered the intervention.
Most interventions achieved **a better medication adherence** compared to usual care, sometimes resulting in fewer hospitalizations for exacerbations (but in most studies this was not measured).

2 RCT's used an intervention with an electronic inhaler device that registered adherence. This is not used in a clinical setting.

9.3 Adherence - Type of device

We consulted the ADMIT series on Issues in inhalation therapy(184), (185), (186) and the ERS/ISAM task force report on new inhalation therapies(187).
The different types of inhaler all require different skills/capacities.

- pMDI – pressurized metered dose inhaler
  This device requires co-ordination of inspiration and actuation
- pMDI - with spacer (>100 ml)
- Breath actuated pMDI
  Requires a higher inspiratory low to be triggered
- DPI – dry powder inhaler
  Moderate to high inspiratory flow required

A correct inhalation therapy requires

- Precise instructions/knowledge of the inhalation manoevre.
  This requires adequate knowledge of the technique by the health professional.
  The health professional should adequately instruct the patient.
  Checking and instructing should be repeated regularly.
- Inhaler characteristics that are suitable to the user.
  - Good coordination, poor inspiratory flow: pMDI is first choice.
  - Inadequate co-ordination, sufficient inspiratory flow: DPI, pMDI + spacer or breath-actuated pMDI.
  - Elderly COPD patient with intact cognitive function: DPI, pMDI + spacer or breath-actuated pMDI (avoid pMDI).
  - Unable to co-ordinate and/or insufficient flow: pMDI + spacer.
  - Acute setting: nebulizer may be used.

Prescribing a single type of device for different drugs for an individual patient is preferable (because the inhalation technique of different types of device is so different).
Patients may be more adherent with an inhaler that combines two drugs (i.e. LABA and ICS) in the same dose, compared with using two separate inhalers.

Take into account availability and affordability of the device, as well as patient preference.

9.3.1 Conclusions – Type of device

Based on the following references: (184), (185), (186, 187).

There are different inhaler devices on the market, all requiring a different technique to use them correctly.
The choice of device should take into account patient characteristics (co-ordination, inspiratory flow).
Each patient should receive adequate instruction as to the correct inhalation technique and this should be checked and repeated regularly. This means that the health professional should have

adequate knowledge about the devices to choose the appropriate type of device and (importantly) to be able to instruct the use of the device correctly.
An inhaler that combines multiple drugs, or the same type of inhaler for different drugs may improve adherence and limit mistakes.

10 Serious adverse events from RCTs and observational studies

This chapter is based on information from RCTs and observational (cohort) studies. Due to time constraints, we could not perform a systematic search.
For this question, we:

Searched the last five years (2011 onwards) of the Folia pharmacotherapeutica for relevant information on serious adverse events of the drugs studied in this literature report.

Searched for the large observational studies (using health-care databases) done by Suissa S. and colleagues on pneumonia in ICS and cardiovascular adverse events in inhalation bronchodilators, following the advice of the Organising Committee.
We did not perform a GRADE evaluation of the outcomes, as it is unclear whether our selection comprises the whole body of evidence available.

10.1 ICS and pneumonia

10.1.1 Information from the Folia Pharmacotherapeutica

In the TORCH 2007(20) study (a large RCT of 3 years' duration), an elevated risk of pneumonia in COPD patients taking ICS-containing products was first identified. Other subsequent RCTs also reported on this risk.
In 2016, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA)(188) published a benefit-risk balance evaluation of ICS-containing medicinal products indicated in the treatment of COPD.

Data from randomized studies

Study	Study type (pneumonia-related outcome)	Included	Main results
Calverley et al 2007 TORCH study	Randomised controlled trial (pneumonia adverse events)	6,184 patients (1,544 placebo, 1,542 salmeterol, 1,552 fluticasone, 1,546 combination)	% of patients with pneumonia: placebo 12.3%, salmeterol 13.3%, fluticasone 18.3%, combination 19.6%; p<0.001 for fluticasone-containing treatment vs placebo
Crim et al 2009	post hoc analysis of the TORCH data (time to first pneumonia; risk factors)	6,184 patients (1,544 placebo, 1,542 salmeterol, 1,552 fluticasone, 1,546 combination)	HR vs placebo: Fluticasone HR 1.53; 95% CI 1.24-1.89 Combination HR 1.64; 95% CI 1.33-2.02 Risk factors: age ≥55, FEV_1 <50% predicted, COPD exacerbations in year prior to study, worse dyspnoea score and BMI <25 kg/m
Drummond et al 2008	meta-analysis (effects of ICS treatment on mortality and adverse effects in patients with stable COPD)	7 studies with pneumonia data (10,776 patients: 5,405 treatment, 5,371 control)	Incidence of pneumonia with ICS: RR, 1.34; 95% CI, 1.03-1.75: p=0.03

Sobieraj et al 2008	meta-analysis (pneumonia adverse events)	9 studies of ICS in COPD	Incidence of pneumonia with ICS: RR 1.68; 95% CI 1.28-2.21
Rodrigo et al 2009	meta-analysis (pneumonia adverse events)	18 randomised controlled trials	Risk of pneumonia with ICS: RR 1.63; 95% CI 1.35–1.98
Sin et al 2009	meta-analysis (pneumonia adverse events, pneumonia SAEs and time to pneumonia as AE)	7 randomised controlled trials using budesonide	Incidence of pneumonia with budesonide: AEs: HR 1.05; 95% CI 0.81 – 1.37 SAEs: HR 0.92; 95% CI 0.62-1.35
Singh & Loke 2010	meta-analysis (pneumonia adverse events)	24 randomised controlled trials (23,096 patients)	Risk of pneumonia with ICS: RR 1.57; 95% CI 1.41–1.75
Halpin et al 2011	meta-analysis (pneumonia adverse events, pneumonia SAEs – OR given for budesonide/ fluticasone comparison only)	8 fluticasone/ salmeterol trials, 4 budesonide/ formoterol trials	Pneumonia AE: budesonide/ formoterol vs fluticasone/salmeterol OR 0.47; 95% CI 0.28-0.80 Pneumonia SAE: budesonide/ formoterol vs fluticasone/salmeterol OR 0.41; 95% CI 0.19-0.86
Spencer et al 2011	Cochrane review (pneumonia adverse events and pneumonia SAEs)	7 randomised trials	Incidence of pneumonia AE with ICS: OR 1.38; 95% CI 1.10 to 1.73 Incidence of pneumonia SAE with ICS: OR 1.48; 95% CI 1.13 to 1.94
Nannini et al 2012	Cochrane review (pneumonia adverse events)	14 studies (11,794 severe COPD patients)	Incidence of pneumonia with ICS/LABA vs LABA: OR 1.55; 95% CI 1.20-2.01
Nannini et al 2013a	Cochrane review (pneumonia adverse events)	19 randomised studies (10,400 patients)	Risk of pneumonia with ICS/LABA vs placebo: OR 1.62; 95% CI 1.36-1.94
Kew and Seniukovich 2014	Cochrane review (non-fatal pneumonia SAEs requiring hospital admission, all pneumonia events)	43 studies	Risk of pneumonia (non-fatal SAE) with fluticasone: OR 1.78; 95% CI 1.50-2.12 Risk of pneumonia (non-fatal SAE) with budesonide: OR 1.62; 95% CI 1.00-2.62

Table 335: data from randomized studies, table from the PRAC 2016 report

Data from observational studies

Study	**Study type (pneumonia-related outcome)**	**Included**	**Main results**

Ernst et al 2007	Nested case-control study (pneumonia hospitalisation)	175,906 (23,942 hospitalised with pneumonia)	RR 1.70 (95% CI 1.63–1.77)
Almirall et al 2010	Case-control study (community acquired pneumonia)	94 with pneumonia, 33 controls	OR 3.26 (95% CI 1.07– 9.98)
Joo et al 2010	Nested case-control study (pneumonia hospitalisation)	145,586 (13,995 pneumonia)	Current ICS use: aOR 1.38 (95% CI 1.31-1.45)
Snider et al 2012	Nested case-control study (pneumonia)	83,455 (13,778 pneumonia, 36767 controls)	OR 1.11 (95% CI 1.05–1.18) for ICS in past year; OR 1.26 (95% CI 1.16–1.36) for current use
Janson et al 2013	Retrospective pairwise cohort study (pneumonia)	2734 each for fluticasone/salmeterol and budesonide/formoterol; 2115 in matched groups	Pneumonia event rate: 11.0 events per 100 Pt years (95% CI 10.4-11.8) for fluticasone 6.4 events per 100 Pt years (95% CI 6.0-6.9) for budesonide
Lin et al 2013	Retrospective chart review (pneumonia)	2630 (402 pneumonia)	aHR 1.60 (95%CI 1.30–1.96)
Eurich et al 2013	Nested case-control study (pneumonia)	2652	aOR 1.72 (95% CI 1.17–2.55)
Suissa et al 2013	Nested case-control study (pneumonia)	163,514 (20,344 pneumonia)	RR 1.69 (95% CI 1.63-1.75)
Yawn et al 2013	Retrospective cohort analysis	135,445	HR 1.51 (95% CI 1.42–1.61)
Flynn et al 2014	Record linkage analysis (pneumonia hospitalisation)	4305 (3243 exposed to ICS, 550 pneumonia)	HR 1.42 (95% CI 1.07-1.88

DiSantostefano et al 2014	New user cohort study (pneumonia)	11,555 ICS/LABA & ICS, 6492 controls	Pneumonia hospitalisation: HR 1.55 (95% CI: 1.14-2.10) Any pneumonia: HR 1.49 (95% CI: 1.22-1.83)
Mapel et al 2010	Nested case control study (pneumonia)	5245	ICS/LABA (90 days prior to case): aOR 0.58 (95% CI 0.30-1.12) ICS alone (90 days prior to case): aOR 1.29 (95% CI 0.96-1.73)
Festic et al 2014	Prospective cohort study (pneumonia hospitalisation)	5584 (495 on ICS, 1234 pneumonia hospitalisation)	aOR 1.40 (95% CI 0.95-2.09)
Gershon et al 2014	Longitudinal cohort study (pneumonia hospitalisation)	8712 LABA/ICS, 3160 LABA only	HR 1.01 (95% CI 0.93-1.08)
Lee et al 2013	Case-crossover study	186,018 pneumonia	ICS alone: aOR 1.73 (95% CI 1.64–1.83) ICS/LABA: aOR 0.63 (95% CI: 0.61–0.66)

Table 336: data from observational studies, table from the PRAC 2016 report

Its conclusions are as follows:

- Analysis of the data from randomized studies confirms a risk of pneumonia (increase of 40 to 70%) in patients with COPD who are being treated with inhaled corticosteroids.
- Data from observational studies are fully consistent with the data from randomized trials.
- There is no evidence that this risk differs for different inhaled corticosteroids.
- In some, but not all studies, dose-dependency of the risk is determined.
- One cannot rule on the possible effect of simultaneous intake of other drugs (among other things, long-acting beta-agonists) on the risk of pneumonia.

- The risk of pneumonia does not change the risk-benefit balance of inhaled corticosteroids, according to the PRAC.

10.1.2 Large observational studies

- The Suissa 2013(189) nested case-control study was included in the PRAC-report, and described above.
- We found an additional cohort study (Suissa 2015(190)) of 103 386 COPD patients that used ICS at baseline. A nested case-control analysis of the cohort was used to estimate the rate ratio of serious pneumonia associated with the discontinuation of ICS use, compared with continued use. The discontinuation of ICS us in COPD was associated with a reduction in the elevated risk of serious pneumonia, compared to current use (adj. RR 0.63 (95%CI 0.60 to 0.66)).

10.1.3 Conclusion

The current evidence finds an **increased risk of pneumonia**, consistent across randomized and observational data, with the use of **ICS in COPD**.
The body of evidence is too limited to conclude whether the risk differs for different inhaled corticosteroids, whether the risk is dose-dependent, and whether there is an effect of the simultaneous intake of other drugs (e.g. LABA) on the risk of pneumonia.
An additional large cohort study finds a reduction in the elevated risk of serious pneumonia, associated with the discontinuation of ICS use in COPD. It is not clear whether this is a causal association.

10.2 Cardiovascular events and inhaled bronchodilators

10.2.1 Information from the Folia Pharmacotherapeutica

- A meta-analysis of 5 RCTs (Singh 2011(191)) found a statistically significant increase of **mortality** with tiotropium delivered via mist inhaler (Spiriva Respimat®), compared to placebo (RR 1.52 (95%CI 1.06 to 2.16)). The NNH for one year with the 5 mcg dose to see one additional death was estimated to be 124 (95%CI 52 to 5682).
- A subsequent RCT (Wise 2013, TIOSPIR(192)),in which 17135 patients with COPD were followed up for a mean of 2.3 years, the safety of tiotropium Respimat® was compared to tiotropium HandiHaler®. Respimat® was non-inferior to HandiHaler® for risk of **death** (HR: 0.96 (95%CI 0.84 to 1.09)). Incidences of **major cardiovascular adverse events** were similar between groups. In the subgroup of participants with previous cardiac arrhythmia, there was likewise no significant different in the risk of death between groups.

10.2.2 Large observational studies

- A cohort study (Wilchesky 2012a(193)) followed 6018 COPD patients for a hospital admission for, or death from, arrhythmia. The rate ratio of arrhythmia associated with a new use of bronchodilators was estimated. A new use of the SAMA ipratropium (RR 2.4 (95%CI 1.4-4.0)) and of LABAs (RR 4.5 (96%CI 1.4 to 14.4)) was associated with an increase of **arrhythmia**. There was no increase for SABAs or for methylxanthines. Tiotropium was not yet available at the time of the study.
- The association found in the first cohort study was reassessed in a larger cohort of 76 661 COPD patients (Wilchesky 2012b(194)). The rate of **cardiac arrhythmias** was increased with the new use of SABAs (RR 1.27 (95%CI 1.03 to 1.57)) and LABAs (RR 1.47 (95%CI 1.01 to 2.15)). There was no significant increase with the new use of ipratropium bromide or methylxanthines. Tiotropium was not yet available at the time of the study.
- A 1-year cohort study (Suissa 2017(195)) in 52 884 new users of long-acting bronchodilators, compared tiotropium initiators to matched LABA initiators for the occurrence of **acute myocardial infarction**, **stroke**, **heart failure**, **arrhythmia**, and pneumonia. There was no significant difference between groups for any of the cardiovascular endpoints. The new use of LABAs was associated with an elevated risk of **pneumonia**, compared to the new use of tiotropium. According to the authors, this is likely due to the common association of LABA with ICS.

10.2.3 Conclusion

A meta-analysis of 5 RCTs found a statistically significant increase of **mortality** with tiotropium via Respimat inhaler. A subsequent RCT found no difference of **mortality** or **major cardiovascular events** between tiotropium via Respimat® and tiotropium via HandiHaler®.

It remains unclear whether there is a higher risk of mortality or cardiovascular events with tiotropium versus placebo, versus other LAMAs, or versus LABAs.

In two cohort studies, a new use of LABAs was associated with an increased risk of **cardiac arrhythmias**. In one cohort study, there was no difference of **cardiovascular events** between new use of tiotropium and new use of LABAs. It is not clear whether the associations are causal.

10.3 Monoclonal antibodies

We found a prospective cohort study (Iribarren 2016, EXCELS(196)) in patients with moderate to severe asthma receiving omalizumab. The aim of this study was to examine a potential association between omalizumab and cardiovascular or cerebrovascular events.

7836 patients who were or were not being treated with omalizumab, were followed up for ≤ 5 years. Patients treated with omalizumab had a higher rate of cardiovascular or cerebrovascular events than did non-omalizumab-treated patients (13.4 per 1000 patient-years versus 8.1 per 1000 patient-years). More patients in the omalizumab-treated group had severe asthma in comparison to the non-omalizumab group, which could have contributed to the difference, but the increase in risk cannot be excluded.

10.3.1 Conclusion

One cohort study with 5 years' follow-up found a higher rate of **cardiovascular or cerebrovascular events** in omalizumab-treated patients with moderate-to-severe asthma, compared with non-omalizumab-treated patients. It is not clear whether this is a causal association.

11 Adverse effects from other sources

11.1 Inhalation medication

11.1.1 LABA

- The undesirable effects of the different β2-mimetics are similar.[2]
- Nervousness, insomnia, headaches, tremors, tachycardia.[2]
- Cardiac stimulation and hypokalemia at high doses.[2]
- Evidence of bronchospasm and excess mortality through the use of long-acting β2-mimetics in asthma, when they are not used in association with inhaled corticosteroids. [2]

11.1.2 LAMA

- Dry mouth, especially at the beginning of the treatment; dysgeusia, dysphagia, oral candidiasis. [2]
- Palpitations; constipation; difficult urination, urinary retention.
- Rare: increased intraocular pressure, nose bleeding, gastroesophageal reflux, bronchospasm, hypersensitivity.
- Suspicion of serious cardiovascular adverse events with tiotropium in metered dose inhaler. Recent studies found no difference in risk between metered dose inhaler and powder inhalation [see Folia January 2012 and March 2014]. For aclidinium, glycopyrronium and umeclidinium, the risk of cardiovascular adverse effects are not known.

11.1.3 ICS

- Systemic adverse effects (by inhibition of the hypothalamic-pituitary-adrenal axis) especially with prolonged use of high doses. [2]
- Oral, pharyngeal and esophageal candidiasis, often asymptomatic. This risk can be reduced by using a spacer and by gargling with water after inhalation.[2]
- Hoarseness.[2]
- Suspicion of increased risk of pneumonia in long-term use in COPD.[2]

11.1.4 Combinations

For adverse effects of combinations, bcfi/cbip refers to the individual components.

11.2 Monoclonal antibodies

- Reactions at the injection site.[2]
- Headache, joint pain.[2]
- Rare: local and systemic allergic reactions that can occur up to 24 hours (or even more) after injection, idiopathic thrombocytopenia, allergic granulomatous vasculitis, serum sickness.[2]

[2] *Belgisch Centrum voor Farmacotherapeutische Information www.bcfi.be (consulted 16/02/2017)*

- The FDA estimates an incidence of (possibly delayed) anaphylactic reactions with omalizumab of at least 1 in 1,000 patients treated.[3]

11.3 Macrolides

1.1.1 Erythromycin

- Dyspepsia, abdominal pain.[2]
- Allergic reactions: rare .[2]
- Reversible elevated liver function tests ; rarely cholestatic hepatitis.[2]
- Ototoxicity in high doses .[2]
- Effects on central nervous system (psychotic reactions ,nightmares). [2]
- QT prolongation with risk of torsades de pointes , particularly when erythromycin is too rapidly injected intravenously.[2]

1.1.2 Neomacrolides (azithromycin, clarithromycin, roxithromycin)

- The adverse effects of the neo-macrolides resemble those of erythromycin, but the gastrointestinal adverse effects are less pronounced.[2]
- Azithromycin and clarithromycin, cannot be excluded for roxithromycin: QT-interval elongation and torsades de pointes.[2]

  A cohort study evaluated the risk of cardiovascular mortality of clarithromycin and roxithromycin . Relative to penicillin V (2.5 deaths in 1,000 patients per year), there was a significantly increased risk of cardiovascular mortality with clarithromycin (5.3 deaths in 1,000 patients per year), but not with roxithromycin (2.5 deaths in 1,000 patients per year). Given the small number of cardiac deaths in this study these results are difficult to interpret.[4]

[3] *Folia Pharmacotherapeutica, June 2007*
[4] *Folia Pharmacotherapeutica, October 2014.*

12 Appendix 1 - Search strategy

12.1 Pubmed systematic search for RCTs, SRs, MAs

12.1.1 Inhalation medication in COPD

(((((((("Emphysema"[Mesh] OR emphysema[all fields] OR "pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields]))))) OR (("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "lung"[All Fields] AND "disease"[All Fields]) OR "obstructive lung disease"[All Fields]))) OR (("bronchitis, chronic"[MeSH Terms] OR ("bronchitis"[All Fields] AND "chronic"[All Fields]) OR "chronic bronchitis"[All Fields] OR ("chronic"[All Fields] AND "bronchitis"[All Fields]))))) AND ((((((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND ("muscarinic 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("adrenal"[Title/Abstract] AND "cortex"[Title/Abstract] AND "hormones"[Title/Abstract]) OR "adrenal cortex hormones"[Title/Abstract] OR "corticosteroids"[Title/Abstract]))) OR (("budesonide"[MeSH Terms] OR "budesonide"[Title/Abstract]) OR ("fluticasone"[MeSH Terms] OR "fluticasone"[Title/Abstract] OR "fluticasone furoate"[Supplementary Concept] OR "fluticasone furoate"[Title/Abstract])) OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract] OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract]) AND ("propionates"[MeSH Terms] OR "propionates"[Title/Abstract] OR "propionate"[Title/Abstract])))))) OR ((((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND ("beta"[Title/Abstract] AND agonist*[Title/Abstract]) OR beta 2 adrenoceptor agonist*[Title/Abstract]OR “beta 2 receptor agonist*”[Title/Abstract] OR beta 1 Receptor Agonist*[Title/Abstract] OR beta 1 adrenoceptor Agonist* [Title/Abstract])) OR 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12.1.2 Inhalation medication in asthma

(((((((("asthma"[MeSH Terms] OR "asthma"[All Fields])) OR ("Respiratory Sounds"[Mesh] OR “respiratory sounds”[All Fields])) OR ("Bronchial Hyperreactivity"[Mesh] OR “Bronchial Hyperreactivity”[All Fields]))) AND (((((((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND ("muscarinic antagonists"[Pharmacological Action] OR "muscarinic antagonists"[MeSH Terms] OR ("muscarinic"[Title/Abstract] AND "antagonists"[Title/Abstract]) OR "muscarinic antagonists"[Title/Abstract] OR ("muscarinic"[Title/Abstract] AND "antagonist"[Title/Abstract]) OR "muscarinic antagonist"[Title/Abstract]))) OR (((((("glycopyrrolate"[MeSH Terms] OR "glycopyrrolate"[Title/Abstract] OR "glycopyrronium"[Title/Abstract])) OR ("GSK573719"[Supplementary Concept] OR "GSK573719"[Title/Abstract] OR "umeclidinium"[Title/Abstract])) OR ("tiotropium bromide"[MeSH Terms] OR ("tiotropium"[Title/Abstract] AND "bromide"[Title/Abstract]) OR "tiotropium bromide"[Title/Abstract] OR "tiotropium"[Title/Abstract])) OR ("aclidinium bromide" [Supplementary Concept] OR “aclidinium”[Title/Abstract] OR (“aclinidium”[Title/Abstract] AND “bromide”[Title/Abstract])))))) AND ((((("inhalation"[MeSH Terms] OR "inhalation"[Title/Abstract] OR "inhaled"[Title/Abstract]) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[Title/Abstract] AND "cortex"[Title/Abstract] AND "hormones"[Title/Abstract]) OR "adrenal cortex hormones"[Title/Abstract] OR "corticosteroids"[Title/Abstract]))) OR (("budesonide"[MeSH Terms] OR "budesonide"[Title/Abstract]) OR ("fluticasone"[MeSH Terms] OR "fluticasone"[Title/Abstract] OR "fluticasone furoate"[Supplementary Concept] OR "fluticasone furoate"[Title/Abstract])) OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract] OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract]) AND ("propionates"[MeSH Terms] OR "propionates"[Title/Abstract] OR "propionate"[Title/Abstract])))))) OR (((((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND ("beta"[Title/Abstract] AND agonist*[Title/Abstract]) OR beta 2 adrenoceptor agonist*[Title/Abstract]OR “beta 2 receptor agonist*”[Title/Abstract] OR beta 1 Receptor Agonist*[Title/Abstract] OR beta 1 adrenoceptor Agonist* [Title/Abstract])) OR ((((((("indacaterol"[Supplementary Concept] OR "indacaterol"[Title/Abstract])) OR ("vilanterol"[Supplementary Concept] OR "vilanterol"[Title/Abstract])) OR ("olodaterol"[Supplementary Concept] OR "olodaterol"[Title/Abstract])) OR ("formoterol fumarate"[MeSH Terms] OR ("formoterol"[Title/Abstract] AND "fumarate"[Title/Abstract]) OR "formoterol fumarate"[Title/Abstract] OR "formoterol"[Title/Abstract])) OR ("Salmeterol Xinafoate"[Mesh] OR ("salmeterol"[Title/Abstract] AND "xinafoate"[Title/Abstract]) OR "salmeterol xinafoate"[Title/Abstract] OR "salmeterol"[Title/Abstract]))))) AND ((((("inhalation"[MeSH Terms] OR "inhalation"[Title/Abstract] OR "inhaled"[Title/Abstract]) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[Title/Abstract] AND "cortex"[Title/Abstract] AND "hormones"[Title/Abstract]) OR "adrenal cortex hormones"[Title/Abstract] OR "corticosteroids"[Title/Abstract]))) OR (("budesonide"[MeSH Terms] OR "budesonide"[Title/Abstract]) OR ("fluticasone"[MeSH Terms] OR "fluticasone"[Title/Abstract] OR "fluticasone furoate"[Supplementary Concept] OR "fluticasone furoate"[Title/Abstract])) OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract] OR ("beclomethasone"[MeSH Terms] OR "beclomethasone"[Title/Abstract]) AND ("propionates"[MeSH Terms] OR "propionates"[Title/Abstract] OR "propionate"[Title/Abstract])))))) OR (((((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND ("beta"[Title/Abstract] AND agonist*[Title/Abstract]) OR beta 2 adrenoceptor agonist*[Title/Abstract]OR “beta 2 receptor agonist*”[Title/Abstract] OR beta 1 Receptor Agonist*[Title/Abstract] OR beta 1 adrenoceptor Agonist* [Title/Abstract])) OR ((((((("indacaterol"[Supplementary Concept] OR "indacaterol"[Title/Abstract])) OR ("vilanterol"[Supplementary Concept] OR "vilanterol"[Title/Abstract])) OR ("olodaterol"[Supplementary Concept] OR "olodaterol"[Title/Abstract])) OR ("formoterol fumarate"[MeSH Terms] OR ("formoterol"[Title/Abstract] AND "fumarate"[Title/Abstract]) OR "formoterol fumarate"[Title/Abstract] OR "formoterol"[Title/Abstract])) OR ("Salmeterol Xinafoate"[Mesh] OR ("salmeterol"[Title/Abstract] AND "xinafoate"[Title/Abstract]) OR "salmeterol xinafoate"[Title/Abstract] OR "salmeterol"[Title/Abstract]))))) AND ((((long-acting[Title/Abstract] OR (long[Title/Abstract] AND acting[Title/Abstract])) AND

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12.1.3 Monoclonal antibodies

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12.1.4 Macrolides

COPD

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ASTHMA

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12.1.5 Adherence

COPD

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Fields] AND "disease"[All Fields]))))) OR (("lung diseases, obstructive"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields] AND "obstructive"[All Fields]) OR "obstructive lung diseases"[All Fields] OR ("obstructive"[All Fields] AND "lung"[All Fields] AND "disease"[All Fields]) OR "obstructive lung disease"[All Fields])) OR (("bronchitis, chronic"[MeSH Terms] OR ("bronchitis"[All Fields] AND "chronic"[All Fields]) OR "chronic bronchitis"[All Fields] OR ("chronic"[All Fields] AND "bronchitis"[All Fields]))))) AND ((“Patient Compliance"[Mesh] OR ((patient[TIAB] OR medication[TIAB] OR medicine[TIAB] OR drug[TIAB] OR regimen[TIAB] OR treatment[TIAB] OR therap*[TIAB]) AND (Complian*[TIAB] OR non-complian* OR non complian* OR noncomplian* [TIAB] OR adheren*[TIAB] OR non-adheren*[TIAB] OR nonadheren*[TIAB] OR non adheren*[TIAB] OR concordan*[TIAB])))))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))) AND ("2012/01/01 "[PDAT] : "2016/12/31"[PDAT])

ASTHMA

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13 Appendix 2-List of excluded publications

The following publications were excluded after reviewing the full text. The reason for exclusion is stated in **bold.**

13.1 COPD: inhalation medication

1. Breo Ellipta: An Inhaled Fluticasone/ Vilanterol Combination for COPD. Med Lett Drugs Ther 2013;55:69-71, 45-8.**n, not a study**
2. Glycopyrronium + indacaterol. A fixed-dose combination with no advantages in COPD. Prescrire Int 2014;23:288.**n, narrative reviews**
3. [Inhaled corticosteroids. Essential in asthma, problematic in COPD]. MMW Fortschr Med 2014;156:26.**n, no access**
4. Anoro Ellipta: an inhaled umeclidinium/vilanterol combination for COPD. Med Lett Drugs Ther 2014;56:30-1.**n, no access through UGent, KUL or ULB**
5. Tiotropium/olodaterol (Stiolto Respimat) for COPD. Med Lett Drugs Ther 2015;57:161-2.**n, no access**
6. Hot topics from the Assemblies. Breathe (Sheff) 2015;11:81-2.**n, type of work**
7. Albrecht JS, Park Y, Hur P, et al. Adherence to Maintenance Medications among Older Adults with Chronic Obstructive Pulmonary Disease. The Role of Depression. Ann Am Thorac Soc 2016;13:1497-504.**n, adherence**
8. Anzueto A, Jenkins CR, Make BJ, et al. Efficacy of an inhaled corticosteroid/long-acting beta2-agonist combination in symptomatic COPD patients in GOLD groups B and D. Eur Respir J 2015;46:255-8.**n, post hoc analysis not according to COPD classification**
9. Ayazpoor U. [Therapy with new LAMA / LABA combination]. Pneumologie 2015;69:244.**n, narrative review**
10. Bakerly ND, Woodcock A, New JP, et al. The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease. Respir Res 2015;16:101.**n, protocol, no study results**
11. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res 2015;16:92.**n, not pre-specified pooled analysis of individual studies (which we have included), is a MA but not a SR so correctness of method debatable**
12. Beeh KM, Derom E, Echave-Sustaeta J, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat((R)) is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler((R)) (ENERGITO((R)) study). Int J Chron Obstruct Pulmon Dis 2016;11:193-205.**n, trough FEV1 endpoints measured after 6 weeks, duration insufficient**
13. Beeh KM, Korn S, Beier J, et al. Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. Respir Med 2014;108:584-92.**n, duration only 3 weeks per treatment**
14. Beeh KM, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2015;32:53-9.**n, each treatment option was received for only 6 weeks**
15. Bender BG, Hernandez Vecino RA, McGrath K, et al. Comparative Analysis of Persistence to Treatment among Patients with Asthma or COPD Receiving AirFluSal Forspiro or Seretide Diskus Salmeterol/Fluticasone Propionate Combination Therapy. J Allergy Clin Immunol Pract 2016;4:884-9.**n, adherence between two devices, not a research question**
16. Betsuyaku T, Kato M, Fujimoto K, et al. A study to assess COPD Symptom-based Management and to Optimise treatment Strategy in Japan (COSMOS-J) based on GOLD 2011. Int J Chron Obstruct Pulmon Dis 2013;8:453-9.**n, is a protocol**
17. Bodzenta-Lukaszyk A, van Noord J, Schroder-Babo W, et al. Efficacy and safety profile of fluticasone/formoterol combination therapy compared to its individual components administered concurrently in asthma: a randomised controlled trial. Curr Med Res Opin 2013;29:579-88.**n, asthma, devices**
18. Bollmeier SG, Prosser TR. Combination of fluticasone furoate and vilanterol for the treatment of chronic obstructive pulmonary disease. Ann Pharmacother 2014;48:250-7.**n, narrative review**
19. Boscia JA, Pudi KK, Zvarich MT, et al. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. Clin Ther 2012;34:1655-66.e5.**n, duration for each molecule is only 28 days**

20. Bourbeau J, Lavoie KL, Sedeno M, et al. Behaviour-change intervention in a multicentre, randomised, placebo-controlled COPD study: methodological considerations and implementation. BMJ Open 2016;6:e010109.**n, protocol**
21. Bousquet J. Inhaled corticosteroids in severe COPD. Lancet Respir Med 2013;1:177-8.**n, no access**
22. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015;45:969-79.**n, included in source document**
23. Calverley PM, Postma DS, Anzueto AR, et al. Early response to inhaled bronchodilators and corticosteroids as a predictor of 12-month treatment responder status and COPD exacerbations. Int J Chron Obstruct Pulmon Dis 2016;11:381-90.**n, is a post-hoc analysis**
24. Cazzola M, Segreti A, Rogliani P. Comparative effectiveness of drugs for chronic obstructive pulmonary disease. Drugs Today (Barc) 2012;48:785-94.**n, narrative review**
25. Cecere LM, Slatore CG, Uman JE, et al. Adherence to long-acting inhaled therapies among patients with chronic obstructive pulmonary disease (COPD). Copd 2012;9:251-8.**n, adherence**
26. Chung VC, Ma PH, Hui DS, et al. Indacaterol for chronic obstructive pulmonary disease: systematic review and meta-analysis. PLoS One 2013;8:e70784.**n, mono vs mono or mono vs placebo**
27. Dahl R, Jadayel D, Alagappan VK, et al. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. Int J Chron Obstruct Pulmon Dis 2013;8:501-8.**n, duration: only 4 weeks**
28. Dalal AA, Shah MB, D'Souza AO, et al. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respir Res 2012;13:41.**n, observational, costs**
29. Dhar R, Salvi S, Rajan S, et al. Salmeterol/fluticasone through breath-actuated inhaler versus pMDI: a randomized, double-blind, 12 weeks study. J Asthma 2015;52:1065-72.**n, asthma**
30. Dhillon S. Tiotropium/Olodaterol: A Review in COPD. Drugs 2016;76:135-46.**n, narrative review**
31. DiSantostefano RL, Li H, Hinds D, et al. Risk of pneumonia with inhaled corticosteroid/long-acting beta2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis. Int J Chron Obstruct Pulmon Dis 2014;9:457-68.**n, type of analysis**
32. Donohue JF, Niewoehner D, Brooks J, et al. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. Respir Res 2014;15:78.**n, interventions are only compared with placebo**
33. Einecke D. [Dual bronchodilators becomes the first choice combination]. MMW Fortschr Med 2016;158:18.**n, opinion**
34. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. Eur Respir J 2015;45:525-37.**n, narrative review**
35. Hagedorn C, Kassner F, Banik N, et al. Influence of salmeterol/fluticasone via single versus separate inhalers on exacerbations in severe/very severe COPD. Respir Med 2013;107:542-9.**n, one inhaler vs two separate inhalers**
36. Horita N, Kaneko T. Role of combined indacaterol and glycopyrronium bromide (QVA149) for the treatment of COPD in Japan. Int J Chron Obstruct Pulmon Dis 2015;10:813-22.**n, no systematic search described**
37. Hoshino M, Ohtawa J. Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. Respiration 2013;86:280-7.**n, population too small**
38. Hoshino M, Ohtawa J. Computed tomography assessment of airway dimensions with combined tiotropium and indacaterol therapy in COPD patients. Respirology 2014;19:403-10.**n, included in source document farne 2015**
39. Hubert M. [LAMA/LABA or LABA/ICS?]. MMW Fortschr Med 2015;157:76.**n, no access**
40. Hubert M. [LAMA/LABA supports physical activity in COPD patients]. MMW Fortschr Med 2016;158:71.**n, short narrative article**
41. Incorvaia C, Montagni M, Makri E, et al. New combinations in the treatment of COPD: rationale for aclidinium-formoterol. Ther Clin Risk Manag 2016;12:209-15.**n, not an SR**
42. Incorvaia C, Ridolo E, Riario-Sforza E, et al. Indacaterol in the Treatment of Chronic Obstructive Pulmonary Disease: From Clinical Trials to Daily Practice. Rev Recent Clin Trials 2014;9:96-101.**n, no access**
43. Institute for Q, Efficiency in Health C. IQWiG Dossier Assessment Extracts. Umeclidinium/Vilanterol -- Benefit Assessment According to section sign35a Social Code Book V 2014.**n, language**
44. Jiang FM, Liang ZA, Zheng QL, et al. Safety and efficacy of 12-week or longer indacaterol treatment in moderate-to-severe COPD patients: a systematic review. Lung 2013;191:135-46.**n, comparison: indacaterol vs several interventions, not relevant for our research questions**

45. Jones PW, Barnes N, Vogelmeier C, et al. Efficacy of indacaterol in the treatment of patients with COPD. Prim Care Respir J 2011;20:380-8.**n, vs placebo**
46. Karner C, Cates CJ. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012:Cd008989.**n, is verouderder versie, huidige zie Farne 2015**
47. Keating GM. Tiotropium bromide inhalation powder: a review of its use in the management of chronic obstructive pulmonary disease. Drugs 2012;72:273-300.**n, is a SR but studies tiotropium vs placebo or vs monotherapy**
48. Kim JS, Park J, Lim SY, et al. Comparison of clinical efficacy and safety between indacaterol and tiotropium in COPD: meta-analysis of randomized controlled trials. PLoS One 2015;10:e0119948.**n, monotherapy vs monotherapy**
49. Koczorek M. [LAMA / LABA fixed combination 2 times daily]. Pneumologie 2015;69:242.**n, no access**
50. Liapikou A, Toumbis M, Torres A. Managing the safety of inhaled corticosteroids in COPD and the risk of pneumonia. Expert Opin Drug Saf 2015;14:1237-47.**n, expert opinion**
51. Liu Y, Shi H, Sun X, et al. Benefits of adding fluticasone propionate/salmeterol to tiotropium in COPD: a meta-analysis. Eur J Intern Med 2014;25:491-5.**n, SR Rojas Reyes more recent**
52. Magnussen H, Paggiaro P, Schmidt H, et al. Effect of combination treatment on lung volumes and exercise endurance time in COPD. Respir Med 2012;106:1413-20.**n, duration**
53. Magnussen H, Tetzlaff K, Bateman ED, et al. Lung function changes over time following withdrawal of inhaled corticosteroids in patients with severe COPD. Eur Respir J 2016;47:651-4.**n, letter to the editor**
54. Magnussen H, Watz H, Kirsten A, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. Respir Med 2014;108:593-9.**n, protocol wisdom trial**
55. Mahler DA, Decramer M, D'Urzo A, et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. Eur Respir J 2014;43:1599-609.**n, duration under each treatment only 8 weeks**
56. Mahler DA, Gifford AH, Satti A, et al. Long-term safety of glycopyrrolate: A randomized study in patients with moderate-to-severe COPD (GEM3). Respir Med 2016;115:39-45.**n, monotherapy vs monotherapy**
57. Malerba M, Radaeli A, Montuschi P, et al. Vilanterol trifenatate for the treatment of COPD. Expert Rev Respir Med 2016;10:719-31.**n, not an SR**
58. Maltais F, Singh S, Donald AC, et al. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. Ther Adv Respir Dis 2014;8:169-81.**n, only umec/vi comparisons vs placebo are reported**
59. Maspero J, Cherrez I, Doherty DE, et al. Appraisal of lens opacity with mometasone furoate/formoterol fumarate combination in patients with COPD or asthma. Respir Med 2014;108:1355-62.**n, AE that is not an outcome of interest**
60. Matera MG, Rogliani P, Rinaldi B, et al. Umeclidinium bromide + vilanterol for the treatment of chronic obstructive pulmonary disease. Expert Rev Clin Pharmacol 2015;8:35-41.**n, no access**
61. McKeage K. Indacaterol: a review of its use as maintenance therapy in patients with chronic obstructive pulmonary disease. Drugs 2012;72:543-63.**n, not an SR**
62. Metzger NL, Lundquist LM. A review of the advances in chronic obstructive pulmonary disease treatment. J Pharm Pract 2012;25:576-82.**n, not an SR**
63. Meyer KC. COPD 2013: an update on treatment and newly approved medications for pharmacists. J Am Pharm Assoc (2003) 2013;53:e219-29; quiz e30-1.**n, guideline**
64. Oba Y, Chandran AV, Devasahayam JV. Long-acting Muscarinic Antagonist Versus Inhaled Corticosteroid when Added to Long-acting beta-agonist for COPD: A Meta-analysis. Copd 2016:1-9.**n, no access**
65. O'Byrne PM, Rennard S, Gerstein H, et al. Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids. Respir Med 2012;106:1487-93.**n, AE not part of our research questions**
66. Papi A, Jones PW, Dalvi PS, et al. The EFFECT trial: evaluating exacerbations, biomarkers, and safety outcomes with two dose levels of fluticasone propionate/formoterol in COPD. Int J Chron Obstruct Pulmon Dis 2015;10:2431-8.**n, protocol**
67. Pascoe SJ, Lipson DA, Locantore N, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. Eur Respir J 2016;48:320-30.**n, protocol**
68. Ramadan WH, Kabbara WK, El Khoury GM, et al. Combined bronchodilators (tiotropium plus olodaterol) for patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:2347-56.**n, narrative**

69. Restrepo RD, Tate A, Coquat J. Evaluation of salmeterol xinafoate plus fluticasone propionate for the treatment of chronic obstructive pulmonary disease. Expert Opin Pharmacother 2013;14:1993-2002.**n, expert opinion**
70. Ribeiro M, Chapman KR. Comparative efficacy of indacaterol in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2012;7:145-52.**n, not an SR**
71. Ridolo E, Montagni M, Riario-Sforza GG, et al. Combination therapy with indacaterol and glycopyrronium bromide in the management of COPD: an update on the evidence for efficacy and safety. Ther Adv Respir Dis 2015;9:49-55.**n, search not well described**
72. Rodrigo GJ, Plaza V, Castro-Rodriguez JA. Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review. Pulm Pharmacol Ther 2012;25:40-7.**n, other MA selected with later search date**
73. Scott LJ. Budesonide/formoterol Turbuhaler(R): a review of its use in chronic obstructive pulmonary disease. Drugs 2012;72:395-414.**n, systematic search not described**
74. Spencer S, Karner C, Cates CJ, et al. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011:Cd007033.**n, other more recent source documents**
75. Suppli Ulrik C. Aclidinium Bromide: Clinical Benefit in Patients with Moderate to Severe COPD. Open Respir Med J 2012;6:150-4.**n, systematic search but no MA, narrative reporting of results**
76. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res 2013;14:49.**n, not an SR**
77. Ulrik CS. Clinical benefit of fixed-dose dual bronchodilation with glycopyrronium and indacaterol once daily in patients with chronic obstructive pulmonary disease: a systematic review. Int J Chron Obstruct Pulmon Dis 2014;9:331-8.**n, comparisons cannot be isolated**
78. Vestbo J, Leather D, Diar Bakerly N, et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. N Engl J Med 2016;375:1253-60.**n, what constitutes "usual care" not defined precisely enough for our research questions**
79. Wang L, Zhai CJ, Liu Y, et al. Umeclidinium Plus Vilanterol Versus Placebo, Umeclidinium, or Vilanterol Monotherapies for Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Randomized Controlled Trials. Clin Drug Investig 2016;36:865-75.**n, vilanterol alone not on belgian market**
80. Wedzicha JA, Dahl R, Buhl R, et al. Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. Respir Med 2014;108:1498-507.**n, comparisons cannot be isolated properly**
81. Zhong N, Wang C, Zhou X, et al. Efficacy and Safety of Indacaterol/Glycopyrronium (IND/GLY) Versus Salmeterol/Fluticasone in Chinese Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease: The Chinese Cohort from the LANTERN Study. Copd 2016:1-7.**n, only results from the chinese cohort of the LANTERN study, not the entire population**
82. Zou Y, Xiao J, Lu XX, et al. Tiotropium plus formoterol versus tiotropium alone for stable moderate-to-severe chronic obstructive pulmonary disease: A meta-analysis. Clin Respir J 2016.**n, inclusion criteria too liberal**

13.2 Asthma: inhalation medication

1. Adams KS, Lowe DK. Tiotropium for adults with inadequately controlled persistent asthma. Ann Pharmacother 2013;47:117-23.**n, other SRs are more complete**
2. Allen A. The relationship between fluticasone furoate systemic exposure and cortisol suppression. Clin Pharmacokinet 2013;52:885-96.**n, outcomes related to HPA axis suppression**
3. Antoniu SA, Antohe I. Evaluation of inhaled tiotropium in asthma, uncontrolled with standard combination therapy. Expert Opin Pharmacother 2013;14:967-9.**n, expert opinion**
4. Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. J Allergy Clin Immunol 2015;136:914-22.**n, studies ACQ and AQLQ, not a research question**
5. Beeh KM, Moroni-Zentgraf P, Ablinger O, et al. Tiotropium Respimat(R) in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respir Res 2014;15:61.**n, study duration**
6. Bollmeier SG, Lee SY. The emerging role of tiotropium for patients with asthma. Ann Pharmacother 2013;47:704-13.**n, systematic search not well described, selection criteria not well described, narrative retelling of results**

7. Lee SW, Kim HJ, Yoo KH, et al. Long-acting anticholinergic agents in patients with uncontrolled asthma: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2014;18:1421-30.**n, other SR with better analyses**
8. Maspero J, Cherrez I, Doherty DE, et al. Appraisal of lens opacity with mometasone furoate/formoterol fumarate combination in patients with COPD or asthma. Respir Med 2014;108:1355-62.**n, cataract side effect, not a research question**
9. Pizzichini MM, Kerstjens HA, Pizzichini E. Current role of anticholinergic drugs in the treatment of asthma - key messages for clinical practice. Pol Arch Med Wewn 2015;125:859-66.**n, no systematic search reported**
10. Rajanandh MG, Nageswari AD, Ilango K. Pulmonary function assessment in mild to moderate persistent asthma patients receiving montelukast, doxofylline, and tiotropium with budesonide: a randomized controlled study. Clin Ther 2014;36:526-33.**n, no outcomes of interest reported**
11. Rajanandh MG, Nageswari AD, Ilango K. Assessment of montelukast, doxofylline, and tiotropium with budesonide for the treatment of asthma: which is the best among the second-line treatment? A randomized trial. Clin Ther 2015;37:418-26.**n, no outcomes of interest reported**
12. Rajanandh MG, Nageswari AD, Ilango K. Assessment of various second-line medications in addition to inhaled corticosteroid in asthma patients: a randomized controlled trial. Clin Exp Pharmacol Physiol 2014;41:509-13.**n, other publication of ref 112 (Rajanandh 2015)**
13. Rashid Q, Klein R. Tiotropium in the treatment of patients with asthma. South Med J 2014;107:330-7.**n, no acces through KUL, Ugent nor ULB**
14. Rodrigo GJ, Castro-Rodriguez JA. Tiotropium for the treatment of adolescents with moderate to severe symptomatic asthma: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2015;115:211-6.**n, population between 12 and 18**
15. Rodrigo GJ, Castro-Rodriguez JA. What is the role of tiotropium in asthma?: a systematic review with meta-analysis. Chest 2015;147:388-96.**n, other SRs with better analyses**
16. Schwartz RH, Neacsu O, Ascher DP, et al. Moderate dose inhaled corticosteroid-induced symptomatic adrenal suppression: case report and review of the literature. Clin Pediatr (Phila) 2012;51:1184-90.**n, effect on HPA axis, not a research question**
17. Suissa S, Ariel A. US Food and Drug Administration-mandated trials of long-acting beta-agonists safety in asthma: will we know the answer? Chest 2013;143:1208-13.**n, methodological analyses and concerns, narrative / opinion article**

13.3 Monoclonal antibodies

1. Abraham I, Alhossan A, Lee CS, et al. 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. Allergy 2016;71:593-610.**n, pragmatic studies also found by source doc**
2. Bergrath E, Hwa Ong S, Bousquet J, et al. Systematic Review of Observational Studies and Rcts of Omalizumab in Severe Persistent Allergic Asthma and Meta-Analysis Feasibility Assessment. Value Health 2014;17:A589.**n, pharmacoeconomics**
3. CADTH CADTH Rapid Response Reports: Omalizumab Treatment for Adults and Children with Allergic Asthma: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2015.**n, methodology insufficiently described**
4. Caminati M, Senna G, Stefanizzi G, et al. Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience. BMC Pulm Med 2016;16:128.**n, not a research question**
5. de Roos EW, In 't Veen JC, Braunstahl GJ, et al. Targeted Therapy for Older Patients with Uncontrolled Severe Asthma: Current and Future Prospects. Drugs Aging 2016;33:619-28.**n, not a research question**
6. Hambly N, Nair P. Monoclonal antibodies for the treatment of refractory asthma. Curr Opin Pulm Med 2014;20:87-94.**n, other mabs than those on market in belgium**
7. Hendeles L, Khan YR, Shuster JJ, et al. Omalizumab therapy for asthma patients with poor adherence to inhaled corticosteroid therapy. Ann Allergy Asthma Immunol 2015;114:58-62.e2.**n, not enough patients**
8. Lai T, Wang S, Xu Z, et al. Corrigendum: Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep 2015;5:9548.**n, corrigendum, original article not selected either**
9. Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep 2015;5:8191.**n, comparison not well defined**

10. Ledford D, Busse W, Trzaskoma B, et al. A Randomized, Multicenter Study Evaluating Xolair(R) Persistency Of Response After Long-Term Therapy (XPORT). J Allergy Clin Immunol 2016.**n, not a research question**
11. Menzella F, Lusuardi M, Montanari G, et al. Clinical usefulness of mepolizumab in severe eosinophilic asthma. Ther Clin Risk Manag 2016;12:907-16.**n, not an sr**
12. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess 2013;17:1-342.**n, narrative synthesis**
13. Reinhardt D. [Mepolizumab can reduce oral steroids]. MMW Fortschr Med 2015;157:38.**n, no access to full text**
14. Wang FP, Liu T, Lan Z, et al. Efficacy and Safety of Anti-Interleukin-5 Therapy in Patients with Asthma: A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0166833.**n, SR Powell selected**
15. Yancey SW, Ortega HG, Keene ON, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. J Allergy Clin Immunol 2016.**n, only analyses one endpoint and more stringent selection criteria's than us**

13.4 Macrolides

1. Albert RK, Schuller JL. Macrolide antibiotics and the risk of cardiac arrhythmias. Am J Respir Crit Care Med 2014;189:1173-80.**n, not a research question**
2. de Roos EW, In 't Veen JC, Braunstahl GJ, et al. Targeted Therapy for Older Patients with Uncontrolled Severe Asthma: Current and Future Prospects. Drugs Aging 2016;33:619-28.**n, no access to full text through Ugent, KUL or ULB**
3. Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. Am J Respir Crit Care Med 2014;189:1503-8.**n, not a research question for macrolides**
4. Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 2013:Cd009764.**n, SR Ni selected (more recent)**
5. Johnston SL, Szigeti M, Cross M, et al. Efficacy and Mechanism Evaluation. A randomised, double-blind, placebo-controlled study to evaluate the efficacy of oral azithromycin as a supplement to standard care for adult patients with acute exacerbations of asthma (the AZALEA trial) 2016.**n, not for prevention of exacerbations but use during acute exac.**
6. Johnston SL, Szigeti M, Cross M, et al. Azithromycin for Acute Exacerbations of Asthma : The AZALEA Randomized Clinical Trial. JAMA Intern Med 2016;176:1630-7.**n, acute exacerbations, not preventive treatment**
7. Narsingam S, Bozarth AL, Abdeljalil A. Updates in the management of stable chronic obstructive pulmonary disease. Postgrad Med 2015;127:758-70.**n, narrative review**
8. Nicholson TT, Franciosi A, Landers S, et al. Assessing potential risks of treatment with long-term azithromycin in COPD patients: long-term oxygen users beware? Ir J Med Sci 2016;185:993-7.**n, sample size too small**

13.5 Adherence

1. [Inhaled corticosteroids. Essential in asthma, problematic in COPD]. MMW Fortschr Med 2014;156:26.**n, no access**
2. Agh T, Domotor P, Bartfai Z, et al. Relationship Between Medication Adherence and Health-Related Quality of Life in Subjects With COPD: A Systematic Review. Respir Care 2015;60:297-303.**n, SR of observational studies**
3. Alexopoulos GS, Kiosses DN, Sirey JA, et al. Personalised intervention for people with depression and severe COPD. Br J Psychiatry 2013;202:235-6.**n, is a short report of the original study (which is included)**
4. Apter AJ, Wan F, Reisine S, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. J Allergy Clin Immunol 2013;132:321-7.**n, patient factors, does not answer the question how to measure adherence**
5. Boise E, Rotella M. ABCs of asthma inhaler and device training. Int Forum Allergy Rhinol 2015;5 Suppl 1:S71-5.**n, specifically about device training**
6. Bonini M. Electronic health (e-Health): emerging role in asthma. Curr Opin Pulm Med 2017;23:21-6.**n, opinion article**
7. Bourbeau J, Saad N, Joubert A, et al. Making collaborative self-management successful in COPD patients with high disease burden. Respir Med 2013;107:1061-5.**n, subject**

8. Cecere LM, Slatore CG, Uman JE, et al. Adherence to long-acting inhaled therapies among patients with chronic obstructive pulmonary disease (COPD). Copd 2012;9:251-8.**n, identify factors linked with adherence in copd patients is not a research question**
9. Cruz J, Brooks D, Marques A. Home telemonitoring in COPD: a systematic review of methodologies and patients' adherence. Int J Med Inform 2014;83:249-63.**n, other documents with later search date already included**
10. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, et al. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev 2012;12:Cd007459.**n, we have included another study specifically about COPD and other references specifically on asthma**
11. Ershad Sarabi R, Sadoughi F, Jamshidi Orak R, et al. The Effectiveness of Mobile Phone Text Messaging in Improving Medication Adherence for Patients with Chronic Diseases: A Systematic Review. Iran Red Crescent Med J 2016;18:e25183.**n, other SRs more specific**
12. Fairbrother P, Pinnock H, Hanley J, et al. Exploring telemonitoring and self-management by patients with chronic obstructive pulmonary disease: a qualitative study embedded in a randomized controlled trial. Patient Educ Couns 2013;93:403-10.**n, sample size too small**
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14 Appendix 3 – AGREE scores

14.1 Detailed scoring

ASTHMA			
ERS/ATS 2014	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	7	search for SR"s; when no recent valid SR systematically searched for relevant studies; MEDLINE, time periods and search strings in supplementary material
The criteria for selecting the evidence are clearly described	8	4	target population, study design mentioned; not in detail
The strengths and limitations of the body of evidence are clearly described	9	7	Evidence symmaries were made; using GRADE; in suppl materials; summarized in main body of tekst
The methods for formulating the recommendations are clearly described	10	2	probably informal consensus, not described
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	discussed in values and preferences/remarks
There is an explicit link between the recommendations and the supporting evidence.	12	7	yes, table 1 and discussion below
The guideline has been externally reviewed by experts prior to its publication	13	1	not done or not described
A procedure for updating the guideline is provided	14	5	"the committee intends to regularly update the document up until 2015"
NHG ASTMA 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	5	full search for some questions in appendix; not for others
The criteria for selecting the evidence are clearly described	8	4	described in general; not specifically for this guideline
The strengths and limitations of the body of evidence are clearly described	9	4	described in general; not specifically for this guideline; sometimes in footnotes
The methods for formulating the recommendations are clearly described	10	1	no description
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	described in general; and in footnotes
There is an explicit link between the recommendations and the supporting evidence.	12	6	in footnotes
The guideline has been externally reviewed by experts prior to its publication	13	5	described in general; experts named; no description or summary of comments
A procedure for updating the guideline is provided	14	3	none described; but guidelines have been regularly updated
GINA 2016	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	6	pubmed, search terms, previous years, exact time period not known
The criteria for selecting the evidence are clearly described	8	6	publication should potentially impact the GINA report; english language
The strengths and limitations of the body of evidence are clearly described	9	5	levels of evidence are assigned; not clear how methodology is evaluated
The methods for formulating the recommendations are clearly described	10	5	discussion, if necessary: open vote; no description of the outcomes of this process
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	in discussion of the recommendations
There is an explicit link between the recommendations and the supporting evidence.	12	6	LoE are provided + references
The guideline has been externally reviewed by experts prior to its publication	13	5	Not described. The 2015 update was externally reviewed,
A procedure for updating the guideline is	14	7	twice-yearly update of evidence base; yearly update guideline

provided			
BTS/SIGN 2016	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	7	medline, embase, cinahl, psycinfo, cochrane library, full search in appendix
The criteria for selecting the evidence are clearly described	8	7	using standard SIGN methodological checklists; PICOs for each question
The strengths and limitations of the body of evidence are clearly described	9	7	yes, loE, in discussion
The methods for formulating the recommendations are clearly described	10	2	not described in this guideline; guideline handbook describes several possibilities, including informal consensus
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	yes, in discussion
There is an explicit link between the recommendations and the supporting evidence.	12	7	yes, loE, discussion and references
The guideline has been externally reviewed by experts prior to its publication	13	7	yes, external expert review, + open review of draft. Comments in appendix.
A procedure for updating the guideline is provided	14	5	every two years; procedure not explicitly described for next update
COPD			
VA/DoD 2014	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	7	yes; but not all aspects of 2007 guideline were updated; up to feb 2014; 6 databases searched; grey literature; jan 2005-feb 2014; search terms listed
The criteria for selecting the evidence are clearly described	8	7	yes, clearly defined PICOTS + criteria for study inclusion and exclusion given
The strengths and limitations of the body of evidence are clearly described	9	7	GRADE, evidence tables
The methods for formulating the recommendations are clearly described	10	5	experts gathered; work group members asked to review: retain, revise or reject; informal, no report of outcomes
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	strength of recommendations based on balance of desirable and undesirable outcomes; in discussion
There is an explicit link between the recommendations and the supporting evidence.	12	7	LoE/GoR; discussion with references
The guideline has been externally reviewed by experts prior to its publication	13	1	unclear, probably not
A procedure for updating the guideline is provided	14	1	not explicitely stated
AECOPD 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	6	yes, PICO defined, full search available, dates available in appendix; search for systematic reviews 2007-2013
The criteria for selecting the evidence are clearly described	8	7	yes, clearly defined PICO, study type
The strengths and limitations of the body of evidence are clearly described	9	7	AGREE was used for guidelines, GRADE for evidence base; discussed after each recommendation
The methods for formulating the recommendations are clearly described	10	6	well described process (review, controversial statements discussed via webinar, voting; 75% participation and 80% consensus required); no outcomes of discussions reported
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	benefit/risk balance is discussed underneath each recommendation
There is an explicit link between the recommendations and the supporting evidence.	12	6	Yes, GRADE, and discussion underneath recommendation; however no references (except in evidence tables in appendix, but this is difficult to access)
The guideline has been externally reviewed by experts prior to its publication	13	1	Unclear; it seems only CHEST and CTS reviewed the guideline; no report of outcomes
A procedure for updating the guideline is provided	14	7	annual reviews; procedure according to established criteria of CHEST GOC and CTS CRGC
NHG COPD 2015	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	5	full search for some questions in appendix; not for others
The criteria for selecting the evidence are clearly described	8	4	described in general; not specifically for this guideline
The strengths and limitations of the body of evidence are clearly described	9	4	described in general; not specifically for this guideline; sometimes in footnotes

The methods for formulating the recommendations are clearly described	10	1	no description
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	described in general; and in footnotes
There is an explicit link between the recommendations and the supporting evidence.	12	6	in footnotes
The guideline has been externally reviewed by experts prior to its publication	13	5	described in general; experts named; no description or summary of comments
A procedure for updating the guideline is provided	14	3	none described; but guidelines have been regularly updated
GOLD 2016	**Item**	**Rating**	**Comment**
Systematic methods were used to search for evidence	7	6	yearly update: this time from july 2014 to june 2015; pubmed; search terms
The criteria for selecting the evidence are clearly described	8	5	each abstract is evaluated according to questionnaire (what qs?); not clearly described
The strengths and limitations of the body of evidence are clearly described	9	6	loE, in discussion
The methods for formulating the recommendations are clearly described	10	6	committee; consensus on what publications to include; open vote; report of outcomes (but not discussions)
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	in discussion: risks and side effects are discussed
There is an explicit link between the recommendations and the supporting evidence.	12	7	discussion; LoE, references
The guideline has been externally reviewed by experts prior to its publication	13	1	not reported
A procedure for updating the guideline is provided	14	7	yearly updates
GOLD 2017	**Item**		
Systematic methods were used to search for evidence	7	5	yearly update: this time from 2015 to 2016 (exact dates not provided); pubmed; search terms
The criteria for selecting the evidence are clearly described	8	5	each abstract is evaluated according to questionnaire (what qs?); not clearly described
The strengths and limitations of the body of evidence are clearly described	9	6	loE, in discussion
The methods for formulating the recommendations are clearly described	10	6	committee; consensus on what publications to include; open vote; report of outcomes (but not discussions)
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	7	in discussion: risks and side effects are discussed
There is an explicit link between the recommendations and the supporting evidence.	12	7	discussion; LoE, references
The guideline has been externally reviewed by experts prior to its publication	13	5	sent to 10 experts outside of GOLD; the document was revised based on their comments; no reporting of comments
A procedure for updating the guideline is provided	14	7	yearly updates

Table 337

14.2 Summary

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
ERS/ATS 2014	7	4	7	2	7	7	1	5	**40**	**71**
NHG ASTMA 2015	5	4	4	1	6	6	5	3	**34**	**61**
GINA 2016	6	6	5	5	6	6	5	7	**46**	**82**
BTS/SIGN 2016	7	7	7	2	7	7	7	5	**49**	**88**
VA/DoD 2014	7	7	7	5	7	7	1	1	**42**	**75**
AECOPD 2015	6	7	7	6	7	6	1	7	**47**	**84**
NHG COPD 2015	5	4	4	1	6	6	5	3	**34**	**61**
GOLD 2016	6	5	6	6	7	7	1	7	**45**	**80**
GOLD 2017	5	5	6	6	7	7	5	7	**48**	**86**

Table 338

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.

15 References

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