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Aclidinium bromide for stable chronic obstructive pulmonary disease (Review)

Ni H, Soe Z, Moe S

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[Intervention Review]

Aclidinium bromide for stable chronic obstructive pulmonary disease

Han Ni[1], Zay Soe[2], Soe Moe[3]

[1]Internal Medicine, SEGi University, Teluk Intan, Malaysia. [2]Internal Medicine, UCSI University, Terengganu, Malaysia. [3]Department of Community Medicine, Faculty of Medicine, Melaka-Manipal Medical College, Melaka, Malaysia

Contact: Han Ni, Internal Medicine, SEGi University, Hospital Teluk Intan, Jalan Changkat Jong, Teluk Intan, Perak Darul Ridzuan, 36000, Malaysia. hanni.dr@gmail.com.

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ABSTRACT

Background

Bronchodilators are the mainstay for symptom relief in the management of stable chronic obstructive pulmonary disease (COPD). Aclidinium bromide is a new long-acting muscarinic antagonist (LAMA) that differs from tiotropium by its higher selectivity for M3 muscarinic receptors with a faster onset of action. However, the duration of action of aclidinium is shorter than for tiotropium. It has been approved as maintenance therapy for stable, moderate to severe COPD, but its efficacy and safety in the management of COPD is uncertain compared to other bronchodilators.

Objectives

To assess the efficacy and safety of aclidinium bromide in stable COPD.

Search methods

We identified randomised controlled trials (RCT) from the Cochrane Airways Group Specialised Register of trials (CAGR), as well as www.clinicaltrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), US Food and Drug Administration (FDA) website and Almirall Clinical Trials Registry and Results. We contacted Forest Laboratories for any unpublished trials and checked the reference lists of identified articles for additional information. The last search was performed on 7 April 2014 for CAGR and 11 April 2014 for other sources.

Selection criteria

Parallel-group RCTs of aclidinium bromide compared with placebo, long-acting beta$_2$-agonists (LABA) or LAMA in adults with stable COPD.

Data collection and analysis

Two review authors independently selected studies, assessed the risk of bias, and extracted data. We sought missing data from the trial authors as well as manufacturers of aclidinium. We used odds ratios (OR) for dichotomous data and mean difference (MD) for continuous data, and reported both with their 95% confidence intervals (CI). We used standard methodological procedures expected by The Cochrane Collaboration. We applied the GRADE approach to summarise results and to assess the overall quality of evidence.

Main results

This review included 12 multicentre RCTs randomly assigning 9547 participants with stable COPD. All the studies were industry-sponsored and had similar inclusion criteria with relatively good methodological quality. All but one study included in the meta-analysis were double-blind and scored low risk of bias. The study duration ranged from four weeks to 52 weeks. Participants were more often males, mainly Caucasians, mean age ranging from 61.7 to 65.6 years, and with a smoking history of 10 or more pack years. They had moderate to severe

symptoms at randomisation; the mean post-bronchodilator forced expiratory volume in one second (FEV1) was between 46% and 57.6% of the predicted normal value, and the mean St George's Respiratory Questionnaire score (SGRQ) ranged from 45.1 to 50.4 when reported.

There was no difference between aclidinium and placebo in all-cause mortality (low quality) and number of patients with exacerbations requiring a short course of oral steroids or antibiotics, or both (moderate quality). Aclidinium improved quality of life by lowering the SGRQ total score with a mean difference of -2.34 (95% CI -3.18 to -1.51; I^2 = 48%, 7 trials, 4442 participants) when compared to placebo. More patients on aclidinium achieved a clinically meaningful improvement of at least four units decrease in SGRQ total score (OR 1.49; 95% CI 1.31 to 1.70; I^2 = 34%; number needed to treat (NNT) = 10, 95% CI 8 to 15, high quality evidence) over 12 to 52 weeks than on placebo. Aclidinium also resulted in a significantly greater improvement in pre-dose FEV1 than placebo with a mean difference of 0.09 L (95% CI 0.08 to 0.10; I^2 = 39%, 9 trials, 4963 participants). No trials assessed functional capacity. Aclidinium reduced the number of patients with exacerbations requiring hospitalisation by 4 to 20 fewer per 1000 over 4 to 52 weeks (OR 0.64; 95% CI 0.46 to 0.88; I^2 = 0%, 10 trials, 5624 people; NNT = 77, 95% CI 51 to 233, high quality evidence) compared to placebo. There was no difference in non-fatal serious adverse events (moderate quality evidence) between aclidinium and placebo.

Compared to tiotropium, aclidinium did not demonstrate significant differences for exacerbations requiring oral steroids or antibiotics, or both, exacerbation-related hospitalisations and non-fatal serious adverse events (very low quality evidence). Inadequate data prevented the comparison of aclidinium to formoterol or other LABAs.

Authors' conclusions

Aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable COPD compared to placebo. Overall, aclidinium did not significantly reduce mortality, serious adverse events or exacerbations requiring oral steroids or antibiotics, or both.

Currently, the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium. The efficacy of aclidinium versus LABAs cannot be assessed due to inaccurate data. Thus additional trials are recommended to assess the efficacy and safety of aclidinium compared to other LAMAs or LABAs.

PLAIN LANGUAGE SUMMARY

Effectiveness and safety of inhalers containing the drug aclidinium bromide for managing patients with stable COPD

Review question

We reviewed the evidence on the effectiveness and safety of aclidinium inhalers used by people with chronic obstructive pulmonary disease (COPD).

Background

COPD, also known as 'smoker's lung disease', includes conditions called emphysema and chronic bronchitis where there is airway narrowing that cannot be fully corrected. It is a progressive disease. COPD patients usually have breathing problems and a cough that produces a lot of phlegm. It is diagnosed by international guidelines set by the Global Initiative for Obstructive Lung Disease (GOLD). Symptoms may worsen during flare-ups. The main aims of treating COPD patients are to relieve symptoms, reduce flare-ups and improve quality of life. Aclidinium is a new inhaled drug that widens the airways (a bronchodilator). It is delivered by an inhaler called Genuair or Pressair. We wanted to discover whether aclidinium was better or worse than using other inhalers or a dummy inhaler.

Study characteristics

The evidence was current to 7 April 2014. We included 12 studies involving 9547 COPD patients over a period of four to 52 weeks. These studies were sponsored by drug companies and were well designed. Both patients and the people doing the research did not know which treatment the patients were getting; although in one study one treatment was known to both parties. More men than women took part, and they were mostly Caucasians. They were in their 60s and had smoked a lot in their lives. These people had moderate to severe symptoms when they started treatment.

Key results

Aclidinium did not reduce the number of people with flare-ups that need additional drugs. There was little or no difference in deaths or serious side effects between aclidinium and a dummy inhaler. Aclidinium inhalers improved quality of life more than the dummy inhalers.

People who took aclidinium had fewer hospital admissions due to serious flare-ups. Based on our results, among 1000 COPD patients using a dummy inhaler over four weeks to one year 37 would have severe flare-ups needing hospital admission. Only 17 to 33 patients out of 1000 would require hospital admission if they were using aclidinium inhalers. We also set out to compare this new medication with tiotropium, which is already used to treat COPD. There were only two studies for this comparison thus we could not be sure how aclidinium compared to tiotropium. We also could not compare aclidinium with another well known inhaler that contains the drug formoterol because of unreliable data.

Quality of the evidence

For the comparison of aclidinium inhalers and dummy inhalers, we are confident that there are benefits in terms of the number of hospitalisations and patients' quality of life; we are less certain about the numbers of flare-ups needing additional drugs and serious side effects. We do not have enough information to assess any effect on the number of deaths. We did not have enough information to reliably compare aclidinium with tiotropium or formoterol.

Summary of findings for the main comparison. Aclidinium bromide compared to placebo for stable chronic obstructive pulmonary disease

Aclidinium bromide compared to placebo for stable chronic obstructive pulmonary disease

Patient or population: patients with stable chronic obstructive pulmonary disease
Settings: community
Intervention: aclidinium bromide
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Aclidinium bromide				
Mortality (all-cause) Follow-up: 6-52 weeks	**5 per 1000**	**5 per 1000** (2 to 10)	**OR 0.92** (0.43 to 1.94)	5252 (9 studies)	⊕⊕⊖⊖ **low** [1]	
Exacerbations requiring steroids, antibiotics or both Follow-up: 4-52 weeks	**137 per 1000**	**122 per 1000** (105 to 141)	**OR 0.88** (0.74 to 1.04)	5624 (10 studies)	⊕⊕⊕⊖ **moderate** [2,3,4]	
Quality of life Number of patients who achieved at least 4 units improvement in SGRQ total score Follow-up: 12-52 weeks	**396 per 1000**	**494 per 1000** (462 to 527)	**OR 1.49** (1.31 to 1.7)	4420 (7 studies)	⊕⊕⊕⊕ **high**	The mean quality of life (SGRQ total score change from baseline) in the intervention groups was 2.34 lower (3.18 to 1.51 lower); (4442 participants; 7 studies)
Functional capacity Six-minute walking distance	See comment	See comment	Not estimable	0 (0)	See comment	No study assessed functional capacity
Hospital admissions due to exacerbations Follow-up: 4-52 weeks	**37 per 1000**	**24 per 1000** (17 to 33)	**OR 0.64** (0.46 to 0.88)	5624 (10 studies)	⊕⊕⊕⊕ **high** [2,3]	
Non-fatal serious adverse events Follow-up: 4-52 weeks	**56 per 1000**	**50 per 1000** (40 to 64)	**OR 0.89** (0.7 to 1.14)	5651 (10 studies)	⊕⊕⊕⊖ **moderate** [2,3,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] -2 for imprecision: the CI includes the possibility of both appreciable benefit and harm.
[2] Chanez 2010 failed to report some outcomes of lung function in the published full text but it is unlikely to affect this outcome.
[3] Chanez 2010 is double blinded for aclidinium and placebo arms though it is open label for tiotropium arm with no study limitation for this comparison.
[4] -1 for imprecision: the CI includes important benefit and potential harm.

Summary of findings 2. Aclidinium bromide compared to tiotropium for stable chronic obstructive pulmonary disease

Aclidinium bromide compared to tiotropium for stable chronic obstructive pulmonary disease

Patient or population: patients with stable chronic obstructive pulmonary disease
Settings: community
Intervention: aclidinium bromide
Comparison: tiotropium

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tiotropium	Aclidinium bromide				
Mortality (all-cause)	See comment	See comment	Not estimable	329 (1)	See comment	No deaths were reported
Exacerbations requiring steroids, antibiotics or both Follow-up: 4-6 weeks	**0 per 1000**	**11 per 1000** (0 to 26)[1]	**OR 2.64** (0.31 to 22.18)	729 (2 studies)	⊕⊝⊝⊝ **very low** [2,3,4]	
Quality of life St George's Respiratory Questionnaire (SGRQ) score	See comment	See comment	Not estimable	0 (0)	See comment	No studies measured and reported quality of

						life for aclidinium and tiotropium
Functional capacity Six-minute walk distance	See comment	See comment	Not estimable	0 (0)	See comment	No studies measured and reported functional capacity for aclidinium and tiotropium
Hospital admissions due to exacerbations Follow-up: 4-6 weeks	**4 per 1000**	**2 per 1000** (0 to 18)	**OR 0.54** (0.07 to 4.11)	729 (2 studies)	⊕⊝⊝⊝ **very low** [2,3,4]	
Non-fatal serious adverse events Follow-up: 4-6 weeks	**18 per 1000**	**12 per 1000** (3 to 46)	**OR 0.67** (0.17 to 2.65)	729 (2 studies)	⊕⊝⊝⊝ **very low** [2,3,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The corresponding risk for aclidinium bromide was calculated using the risk difference to avoid having zero in both columns.
[2] -1 for high risk of bias in Chanez 2010 because it was open label for tiotropium arm.
[3] Chanez 2010 failed to report some outcomes of lung function in the published full text but it is unlikely to affect this outcome.
[4] -2 for imprecision: the CI includes the possibility of both appreciable benefit or harm.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is "a common, preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases" (GOLD 2013). Tobacco smoke is the major risk factor in the pathogenesis of COPD; chemicals, occupational exposures, indoor and outdoor air pollution are also recognised risk factors (GOLD 2013; Hogg 2009; MacNee 2006; TSANZ 2012; WHO 2012).

COPD is the third leading cause of death after heart disease and malignancy in the United States (CDC 2011) and accounts for approximately 30,000 deaths each year in the UK (NICE 2010). It was the fourth leading cause of mortality in 2004, with three million deaths worldwide (WHO 2008). Ninety per cent of deaths from COPD occurred in low and middle-income countries in 2008 (WHO 2010). The World Health Organization (WHO) has estimated that COPD will become the third leading cause of death worldwide in 2030 due to a projected increase in smoking and environmental pollution (WHO 2012a). Exacerbations and co-morbidities contribute to the overall severity of COPD in patients (GOLD 2013). Currently available prevalence data do not reflect the actual total burden of COPD because of under reporting, with diagnosis only being made when the disease is clinically apparent (GOLD 2013).

COPD also has a significant economic impact, mainly due to exacerbations. The total annual cost of COPD to the National Health Service (NHS) in the UK is estimated to be over GBP 800 million, for direct healthcare costs (NICE 2011). It accounts for 56% (EUR 38.6 billion) of the total cost of respiratory diseases in the European Union, while the estimated cost in the United States (US) is USD 29.5 billion and USD 20.4 billion, for direct and indirect costs respectively (GOLD 2013).

Acute exacerbations are a major cause of morbidity and mortality in COPD patients and are defined as "an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum, that is beyond normal day-to-day variations, is acute in onset and may warrant a change in medication in a patient with underlying COPD" (GOLD 2013).

Currently there is no cure for COPD. Apart from smoking cessation and long-term oxygen therapy in severely hypoxic patients, other therapeutic options do not improve survival (GOLD 2013). Thus, the major goal of medication is to relieve symptoms, reduce the frequency and severity of exacerbations, and improve quality of life (ATS/ERS 2011; Chong 2012; GOLD 2013; Sutherland 2004; TSANZ 2012).

Management of stable COPD is multidisciplinary, with options such as smoking cessation (van der Meer 2012); education (Effing 2009); vaccination for influenza (Poole 2010) and pneumococcal infections (Walters 2010); breathing exercises (Holland 2012); pulmonary rehabilitation (Lacasse 2009); pharmacotherapy with inhaled bronchodilators, inhaled corticosteroids for severe COPD or frequent exacerbations (GOLD 2013; TSANZ 2012; Yang 2012), phosphodiesterase-4 inhibitors (Chong 2011); long-term domiciliary oxygen therapy (Cranston 2008); and lung volume reduction surgery (Tiong 2009). Regular long-term use of oral corticosteroids is not recommended for stable COPD and is associated with an increased risk of systemic side effects (GOLD 2013; Walters 2009). Oral theophylline has a modest bronchodilator effect (Ram 2009) but is less effective than inhaled long-acting bronchodilators (GOLD 2013). Mucolytic agents show a slight reduction in exacerbations but have no effect on the overall quality of life (Poole 2012). Neither of these medications are routinely recommended for stable COPD (GOLD 2013). Long-acting bronchodilators, either a long-acting beta$_2$-agonist (LABA) (Nannini 2012; Welsh 2011) or a long-acting muscarinic antagonist (LAMA) (Karner 2012), are the first-line maintenance therapy for moderate to severe, stable COPD (GOLD 2013; NICE 2010).

Description of the intervention

Aclidinium bromide is a new long-acting antimuscarinic agent that blocks the action of the neurotransmitter acetylcholine. It was approved by the US Food and Drug Administration (FDA) on 23 July 2012 for use in moderate to severe, stable COPD patients (FDA 2012). It is marketed as Tudorza Pressair by Forest Laboratories and Almirall in the US. It is a dry powder formulation (Sims 2011) and the FDA approved dosage is 400 µg inhaled twice daily. In Europe and the UK it has been launched as Eklira Genuair by Almirall.

It is delivered by a state of the art multidose dry powder inhaler (MDPI), termed Genuair or Pressair, which is preloaded with a one-month supply of medication. The MDPI is specially designed with a visible dose level indicator with an anti-double dosing mechanism, multiple feedback mechanisms to indicate successful inhalation, such as an audible click and a slightly sweet taste, as well as an end-of-dose lock-out system to prevent further use after the final dose (Maltais 2012; Sims 2011).

How the intervention might work

Airway obstruction mediated by vagal cholinergic tone is the major reversible contributor to COPD (Jones 2011). Currently there are five known subtypes of muscarinic cholinergic receptors (M1 to M5), of which three (M1, M2 and M3) are present in the bronchial airway smooth muscle (Karakiulakis 2012; Maltais 2012).

Acetylcholine acts on M1 receptors to facilitate further neurotransmission from parasympathetic ganglia, and binds to M3 receptors located on the airway smooth muscle cells to induce bronchoconstriction. M2 receptors mediate feedback inhibition of acetylcholine release at the cholinergic nerve endings (Karakiulakis 2012; Sims 2011; Vogelmeier 2011).

Aclidinium bromide is a LAMA which inhibits the action of acetylcholine at the muscarinic receptors with approximately a six-fold kinetic selectivity for M3 receptors compared to the M2 subtype, resulting in a more effective bronchodilator action with fewer M2 mediated cardiac side effects (Maltais 2012; Sims 2011). The onset of action of aclidinium bromide (30 minutes) is similar to ipratropium (30 minutes) but faster than tiotropium (80 minutes). The duration of action of aclidinium ($t_{1/2}$ = 29 hours) is shorter than for tiotropium ($t_{1/2}$ = 64 hours) but longer than for ipratropium ($t_{1/2}$ = 8 hours) (Maltais 2012).

These muscarinic receptors are also present in other parts of the body, such as M1 receptors in the central nervous system (CNS); M2 in the heart; M3 in the gastrointestinal tract (GIT), iris and sphincter; and M4 in the neostriatum, whereas the functional role

of M5 receptors is unclear (Gavaldà 2010). Thus, the non-selective blockade of muscarinic receptors has the potential for systemic side effects.

Aclidinium has been shown in preclinical and clinical studies to rapidly hydrolyse in the plasma into two inactive metabolites, with a very short plasma half life of 2.4 minutes, while the plasma half life for ipratropium is 96 minutes and for tiotropium it is more than six hours (Maltais 2012). This low and transient level in the plasma leads to less drug-drug interaction and contributes to a more favourable safety profile.

Why it is important to do this review

Although a long-lasting bronchodilator effect and favourable safety profile of aclidinium bromide has been shown in a number of clinical trials (Jones 2011; Jones 2012), the summarised safety and efficacy profile of this agent is lacking when compared to placebo or currently established treatment options such as LABAs or LAMAs. We aimed to fill this gap by performing a systematic review of the findings of all available randomised controlled trials to help clinicians provide evidence-based, long-term management of stable COPD.

OBJECTIVES

To assess the efficacy and safety of aclidinium bromide in stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a parallel-group design comparing aclidinium bromide with placebo or a LABA or LAMA, both open-label and blinded studies. Since COPD is a progressive disorder which deteriorates with time, we excluded cross-over trials. We also excluded cluster-randomised trials to avoid bias.

Types of participants

We included studies involving adults (over 18 years of age) diagnosed with moderate to severe COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2013), American Thoracic Society (ATS), European Respiratory Society (ERS) (ATS/ERS 2011), Thoracic Society of Australia and New Zealand (TSANZ 2012), UK National Institute for Health and Clinical Excellence (NICE 2010) or the WHO. Participants in the studies had evidence of airway obstruction (post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio of < 70% and FEV1 < 80% of predicted value) with clinical presentation of dyspnoea, chronic cough or sputum production with or without a history of smoking. We excluded studies which enrolled patients with bronchial asthma, bronchiectasis, cystic fibrosis or other lung diseases.

Types of interventions

1. Aclidinium bromide versus placebo
2. Aclidinium bromide versus long-acting beta$_2$-agonist (LABA)
3. Aclidinium bromide versus long-acting muscarinic antagonist (LAMA)

Types of outcome measures

Primary outcomes

1. Mortality (all-cause and respiratory)
2. Exacerbations requiring a short course of an oral steroid or antibiotic, or both
3. Quality of life measured by a validated scale, the St George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRQ)

Secondary outcomes

1. Change in lung function (FEV1, FEV1/FVC)
2. Functional capacity by six-minute walking distance
3. Hospital admissions due to exacerbations or from all causes
4. Improvement in symptoms measured by the Transitional Dyspnoea Index (TDI)
5. Adverse events
6. Non-fatal serious adverse events
7. Withdrawals due to lack of efficacy or adverse events

We assessed mortality and exacerbations as primary outcomes since exacerbations are the major cause of morbidity and mortality in COPD patients. We also classified quality of life as a primary outcome since it is one of the most important parameters that can measure both the subjective and objective well-being of COPD patients, who have to live with this chronic disease. We recorded change in lung function from the baseline, exercise capacity, hospital admissions and symptom improvement as secondary outcomes as these may not directly reflect mortality and morbidity in COPD. For the safety profile of this new intervention (aclidinium bromide), we studied adverse events, non-fatal serious adverse events and withdrawals from studies as secondary outcome measures.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from 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 (please see Appendix 1 for further details). We searched all records in the CAGR coded as 'COPD' using the following terms:

Aclidinium* or "LAS34273" or "Tudorza" or "Eklira" or "Genuair" or "Pressair" or "LAMA" or "Muscarinic Antagonist*".

We also conducted a search of ClinicalTrials.gov (Appendix 2) and the WHO International Clinical Trials Registry Platform (ICTRP) (WHO ICTRP) for additional trials. We searched all databases from their inception with no restrictions on language of publication. The initial search was conducted in March 2013 and it was updated in April 2014.

Searching other resources

We thoroughly checked the reference lists of all primary studies and review articles for additional references. We contacted corresponding authors of identified trials and asked them to

identify other published and unpublished studies. We also contacted manufacturers and experts in the field. We searched the US FDA website (FDA 2012) for details of the clinical trials. In addition, we searched the manufacturers' websites (Forest Pharmaceuticals and Almirall) for additional information on the studies identified through the electronic searches. We had planned to translate studies published in a language other than English.

Data collection and analysis

Selection of studies

Two review authors (HN and SM) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author (ZS) who is an expert in the field. We included the trials meeting the criteria regardless of language or publication status (published, unpublished, in press and in progress). We recorded the excluded studies together with the reasons for exclusion.

Data extraction and management

Two review authors (HN and SM) independently extracted and recorded the data from included studies using standard data extraction forms. The data were cross-checked. The data extraction included study characteristics: mainly study design, participants, interventions, primary and secondary outcome measures; and the analysis performed in the original studies. Where there were discrepancies, we consulted a third review author (ZS) to resolve the inconsistencies. In the case of insufficient or missing data, we contacted the corresponding authors of the studies for additional information. One of the review authors (HN) entered the data into Review Manager 5 software for analysis and the data were checked by another review author (SM).

Assessment of risk of bias in included studies

Two review authors (HN and SM) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor (ZS). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear. We recorded these judgements in the 'Risk of bias' tables accompanying the characteristics of each included study and summarised them in the 'Risk of bias' summary figure. We contacted the investigators of the RCTs for the details of procedures involved in the conduct of the trials and the replies were kept for evidence. We had planned to exclude trials with high risk of bias. We used the information from the assessment of risk of bias to carry out stratified analysis.

Measures of treatment effect

Dichotomous data

We analysed dichotomous outcome data (such as mortality, exacerbations and withdrawals) using the Mantel-Haenszel odds ratio (OR) with 95% confidence interval (CI). We had planned to apply the Peto odds ratio if events were rare.

We also calculated the number needed to treat (NNT) for dichotomous outcomes to reflect the number of patients necessary to obtain a beneficial or harmful outcome with the intervention.

Continuous data

We assessed continuous data variables (such as quality of life, symptoms, lung function and exercise capacity) as fixed-effect mean differences (MD) with 95% CIs when the same scale was used to measure the outcome in all the included studies. We planned to use the standardised mean difference (SMD) when all studies assessed the same outcome but measured it in different ways. We preferentially applied the MD based on change from baseline over the MD based on absolute values.

Unit of analysis issues

We analysed the participants as the unit of analysis for dichotomous data. For continuous data we used the MD, which was the average change from baseline and not the absolute mean. For outcomes that may occur more than once, such as exacerbations, hospital admissions and adverse events, we analysed the number of participants with one or more events.

Dealing with missing data

We contacted the investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data, where possible. In cases where missing data were not available despite attempts to obtain the data, we recorded this information in our review. We performed sensitivity analyses to assess the impact of unknown status or assumptions made about missing data on participants who withdrew from the trials on the overall pooled result of the meta-analysis. We followed the intention-to-treat (ITT) principle in the analysis of outcomes from the randomised trials, if appropriate.

Assessment of heterogeneity

We assessed heterogeneity between the trials by checking for poor overlap of the confidence intervals in the forest plot and by applying the Chi^2 test, with a 10% level of significance. in each analysis we used the I^2 statistic to measure the percentage of inconsistency in results due to inter-trial variability. When we identified substantial heterogeneity, we explored it by pre-specified subgroup analysis. The level of statistical variation between the trials was considered as high if the I^2 value was more than 50%.

Assessment of reporting biases

We minimised reporting bias as a result of non-publication of studies or selective outcome reporting by using a systematic search strategy, contacting study authors and manufacturers, and checking multiple references of the included studies. We also visually inspected funnel plots for asymmetry. If we suspected reporting bias because of the asymmetrical appearance of the funnel plot after exclusion of other reasons for funnel plot

asymmetry, we had planned to contact the study authors requesting them to provide any missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we had planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Data synthesis

We analysed the data using Review Manager 5. For pooling the outcomes of the studies, we used a fixed-effect model if the I^2 statistic was consistent with homogeneous results. We applied a random-effects model for data synthesis when heterogeneity was identified (I^2 > 50%) and it could not be explained by factors identified in the subgroup analyses. We combined dichotomous outcome variables using a Mantel-Haenszel OR with 95% CI. For continuous outcome data, we analysed the results as MD with 95% CI. Where treatment effects were reported as MD with 95% CI or exact P value, we had planned to calculate the standard error, enter it with the MD, and combine the results using a fixed-effect model generic inverse variance (GIV) analysis. We calculated the NNT from the pooled OR and assumed control risk (ACR) using the formula described in Section 12.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We created summary of findings tables using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using the GRADEpro software for overall grading of the quality of the evidence. We included the following outcomes.

1. Mortality (all-cause and respiratory).
2. Exacerbations requiring a short course of an oral steroid or antibiotic, or both.
3. Quality of life.
4. Functional capacity by the six-minute walking distance.
5. Hospital admissions due to exacerbations or all causes.
6. Non-fatal serious adverse events.

Subgroup analysis and investigation of heterogeneity

If there was significant heterogeneity, we had planned to perform subgroup analysis in order to explain it. We had planned to carry out the following subgroup analyses.

1. Dose of aclidinium bromide (e.g. 200 µg; 400 µg).
2. Frequency of aclidinium bromide (once daily; twice daily).
3. Duration of treatment period (short-term (12 weeks or less); long-term (more than 12 weeks)).
4. Disease severity at baseline (FEV1 < 50% predicted; FEV1 ≥ 50% predicted).
5. Concurrent therapy with theophylline (dichotomised as yes or no).

We had planned to include the following outcomes in subgroup analyses.

1. Exacerbations.
2. Quality of life.
3. Change in lung function.

Sensitivity analysis

We assessed the robustness of our analyses by repeating the meta-analysis after exclusion of studies with high risk of bias and those with unclear methodological data.

RESULTS

Description of studies

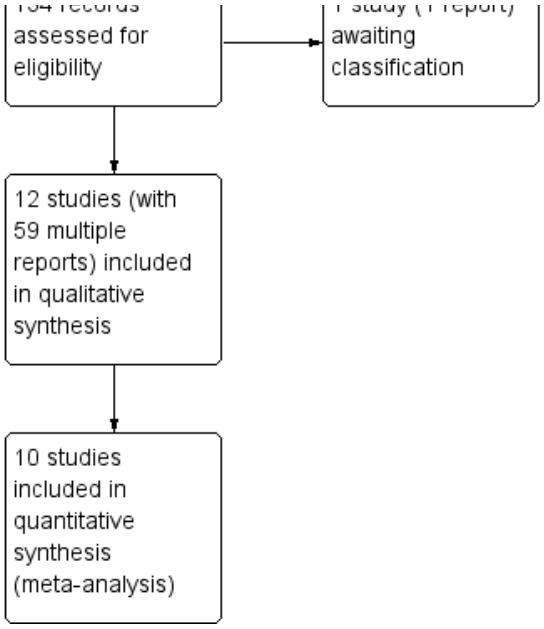
See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification and Characteristics of ongoing studies for complete details.

Results of the search

We conducted the initial search of the Cochrane Airways Group Specialised Register of trials (CAGR) on 14 March 2013 and the search of other sources (WHO ICTRP, Almirall, www.clinicaltrials.gov) on 28 June 2013 with no restriction on language. In January 2014, a second search was done for all resources. A third updated search was conducted on 7 April 2014 for the CAGR and on 11 April 2014 for other sources. We identified a total of 189 records from the CAGR (103 from the first search, 59 from the second, and 27 from the third search) and a total of 107 reports from other sources (40 from WHO ICTRP, 38 from www.clinicaltrials.gov, 24 from Almirall clinical trial registry, five from the reference lists of included studies). After removal of duplicates, we screened the titles and abstracts of 240 records for eligibility and excluded 106 reports. We thoroughly studied the remaining 134 references for further assessment, retrieving full text articles where applicable and contacting manufacturers about unpublished trials. From our search, we excluded a total of 73 references for 35 studies with complete agreement between the authors. Details of studies which failed to meet the inclusion criteria were recorded in 'Characteristics of excluded studies'. One study (NCT01636401) had been completed but the results were not available and it was awaiting classification. Another ongoing study (ASCENT COPD) is expected to be completed by January 2018. We identified a total of 12 studies reported in 59 references that were eligible for inclusion. For details of the search results please see Figure 1. We asked Forest Research Institute if there were any additional study reports or references to studies that they had sponsored, but there was no reply. Two of the included studies (AUGMENT COPD; Sliwinski 2010) were in abstract form and upon request we received the required information for AUGMENT COPD from Almirall. They also provided data for ACLIFORM and NCT01572792. From the correspondence, NCT01572792 data was in the public domain at the American Thoracic Society (ATS) conference in San Diego in May 2014.

Figure 1. Study flow diagram.

Figure 1. (Continued)



Included studies

See Table 1 for an overview of the included studies.

Study design and duration

All trials were randomised, double-blind, parallel group, multicentre studies. One trial (Chanez 2010) was open label for the tiotropium arm but double blind for the aclidinium and placebo arms. Six trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Maltais 2011) studied aclidinium bromide and placebo. In the two trials of Beier 2013 and Chanez 2010, aclidinium bromide was assessed in comparison to both placebo and tiotropium bromide. Four trials (ACLIFORM; AUGMENT COPD; NCT01572792; Sliwinski 2010) studied aclidinium bromide versus placebo and formoterol along with a fixed dose combination of aclidinium and formoterol. NCT01572792 was the 28-week extension study of AUGMENT COPD; the participants who agreed to participate in the extension study were kept on the same treatment and placebo arms as in the primary study.

The trials were of different study duration, ranging from four to 52 weeks, with a mean of 20.7 weeks. Six of the included studies were of short duration with two trials each having a duration of four weeks (Chanez 2010; Sliwinski 2010), six weeks (Beier 2013; Maltais 2011) and 12 weeks (ACCORD COPD I; ACCORD COPD II). The rest were long duration trials, with two studies of 52 weeks duration (ACCLAIM/COPD I; ACCLAIM/COPD II), one study of 28 weeks duration (NCT01572792) and three studies of 24 weeks duration (ACLIFORM; ATTAIN; AUGMENT COPD).

Setting

Most of the studies were based in the US and Canada (ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; AUGMENT COPD; Maltais 2011; NCT01572792). Other study locations were in Europe (ACCLAIM/COPD I; ACLIFORM; ATTAIN; Beier 2013; Chanez 2010), Australia and New Zealand (ACCLAIM/COPD II; ATTAIN; AUGMENT COPD; NCT01572792), South Africa (ACCLAIM/COPD II; ACLIFORM; ATTAIN) and Korea (ACLIFORM).

Participants

A total of 9547 participants were randomised in 12 eligible studies. The largest trial was ACLIFORM with 1729 participants, whilst Maltais 2011 had the fewest participants with a total of 181. The remaining trials had numbers of participants ranging from 414 to 1692. The participants were current or former cigarette smokers with a smoking history of ≥ 10 pack years who were diagnosed with stable COPD according to the GOLD criteria and with a post-bronchodilator FEV1/FVC ratio of < 70% and FEV1 < 80% of predicted value (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Maltais 2011; NCT01572792). American Thoracic Society (ATS) criteria were used for diagnosis of COPD in patients with a smoking history of ≥ 10 pack years in one other trial (Chanez 2010). No detailed information was available for COPD diagnosis for Sliwinski 2010.

The trials were conducted in adults ≥ 40 years of age, including both male and female patients (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011; NCT01572792). There was no specific description of age for the participants of Sliwinski 2010. The mean age of the participants ranged from 61.7 to 65.6 years and the majority were males. More than 90% of the participants were Causacians.

Participants had moderate to severe COPD according to the GOLD criteria with FEV1 ≥ 30% and < 80% in 10 studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Maltais 2011; NCT01572792) and moderate to severe COPD according to the ATS criteria in one trial (Chanez 2010). Moderate to severe COPD patients were also enrolled in Sliwinski 2010, however the specific criteria used for severity assessment were not mentioned. The participants' mean

post-bronchodilator FEV1 was between 46% and 57.6% predicted normal in the trials. Their baseline mean FEV1 was 1.21 L to 1.51 L and the mean St George's Respiratory Questionnaire score (SGRQ) score ranged from 45.1 to 50.4.

Interventions

The participants underwent a two-week run-in period to ensure disease stability and washout of disallowed medications in eight trials with full text publications (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011).

An aclidinium dose of 200 µg was studied in the only or one of the intervention arms in eight trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Chanez 2010; Maltais 2011; Sliwinski 2010). A higher dose of 400 µg was studied in eight trials in one of the treatment arms (ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; NCT01572792). Three studies (ACLIFORM; AUGMENT COPD; NCT01572792) and Sliwinski 2010 studied aclidinium 400 µg and 200 µg, respectively, in comparison to formoterol and placebo together with fixed dose combination arms of aclidinium plus various doses of formoterol. NCT01572792 was the extension study of AUGMENT COPD in which the patients who completed AUGMENT COPD and agreed to participate were kept on the same intervention in a double-blind fashion for another 28 weeks.

Aclidinium was given once daily in five trials (ACCLAIM/COPD I; ACCLAIM/COPD II; Chanez 2010; Maltais 2011; Sliwinski 2010) while a twice daily dosage was used in the other seven trials (ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; NCT01572792).

Administration of aclidinium was by inhalation via a novel, multidose dry powder inhaler (Genuair) in 10 trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACLIFORM; ATTAIN; AUGMENT COPD; Chanez 2010; Maltais 2011; NCT01572792; Sliwinski 2010), whereas either a Genuair or Pressair inhaler was used to deliver aclidinium in two studies (ACCORD COPD II; Beier 2013).

Tiotropium was delivered by the Handihaler in Beier 2013 and Chanez 2010; the latter was an open label study. Formoterol was studied as one of the interventions in ACLIFORM; AUGMENT COPD; NCT01572792 and Sliwinski 2010 where it was given via a Genuair inhaler, which was not an approved inhaler for formoterol.

Concomitant medications

The participants were permitted to continue inhaled corticosteroids (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011), systemic corticosteroids (oral or parenteral) at doses equivalent to prednisone ≤ 10 mg/day or 20 mg every other day (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Maltais 2011) and oral sustained-release theophylline (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010) provided the administration of these medications was stable for at least four weeks prior to screening; these medications had to be discontinued at least six hours before each study visit. Use of salbutamol or albuterol as rescue medication was also allowed (ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011). Oxygen therapy for less than 15 hours per day could be continued but not for two hours before study visits (ACCLAIM/COPD I; ACCLAIM/COPD II; ATTAIN; Beier 2013; Maltais 2011). In ACCORD COPD I inhaled anticholinergics and LABAs were specifically mentioned as not allowed during the study period.

Outcomes

The primary outcomes of the included studies were not identical with our review's primary outcomes because most of the individual trials assessed lung function as the primary outcome. Change from baseline in the morning pre-dose (trough) FEV1 was the primary outcome in eight individual trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Chanez 2010), which was analysed as a secondary outcome in this review. Quality of life measured by the SGRQ, one of the primary outcomes of our review, was studied in the same eight trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Chanez 2010) either as the change from baseline or as the percentage of participants who achieved the minimal clinically important difference (that is ≥ four unit decrease in SGRQ total score). Most of the data for the other primary outcomes of mortality and exacerbations were well reported in the trials and the authors also provided further necessary information regarding the number of patients with exacerbations who required a short course of oral steroids or antibiotics, or both.

None of the included studies assessed functional capacity by the six-minute walking distance, which was one of the secondary outcomes of our review. Specific data on hospital admissions due to exacerbations were also not mentioned in the published texts. However, the trial investigators provided the required data for this outcome. Other secondary outcomes of this review such as adverse events, non-fatal serious adverse events and withdrawals were well reported. Data in the format required for the meta-analysis of some of the secondary outcomes, especially lung function and TDI score, were kindly provided on request.

Funding

Studies were sponsored by Almirall, SA, Barcelona, Spain or Forest Laboratories, Inc, NY, USA.

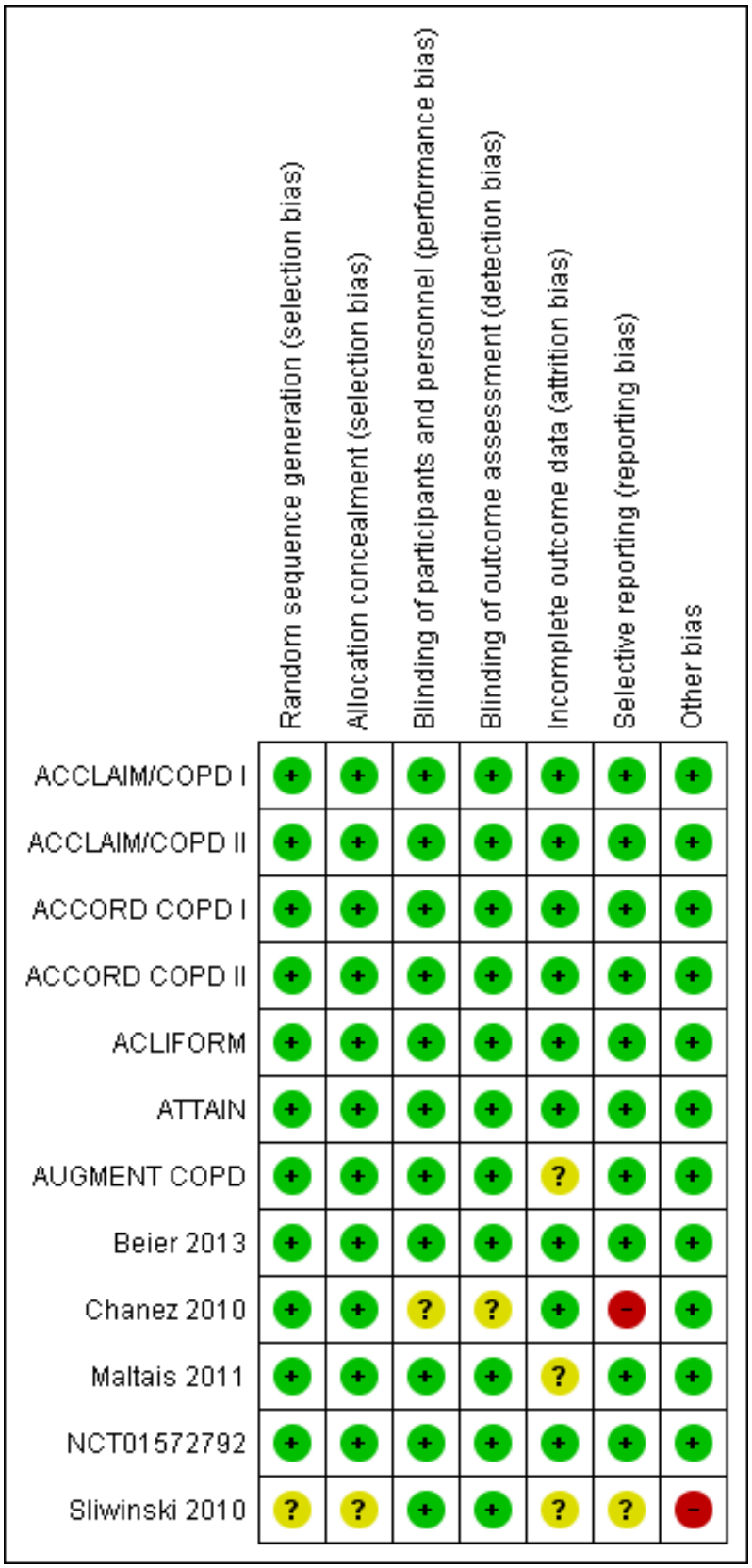
Excluded studies

We excluded a total of 35 studies with 73 references as they failed to meet the eligibility criteria of our review (see Characteristics of excluded studies for details). Thirteen had a cross-over study design; eight were phase one studies conducted in healthy participants; five lacked aclidinium as one of the treatment arms; four were reports of pooled data; three assessed the efficacy of and preferences for inhalers; and two studied aclidinium without a comparator.

Risk of bias in included studies

Generally the included studies had good methodological quality with low risk of bias in most of the domains. Detailed assessment of risk of bias across all studies is presented in Characteristics of included studies; and Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

One published study (Beier 2013) provided detailed information on random sequence generation by a computer generated schedule and allocation concealment via an interactive voice-response system (IVRS). Although not explicitly described in the trial reports, from correspondence all Almirall-sponsored trials applied a computer generated randomisation schedule which was prepared prior to initiating the trial. This was used to assign a treatment sequence to a randomisation number by the statistics and programming group within Almirall, according to the relevant standard operating procedures. The randomisation was performed in order to avoid any possible bias. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators. In all studies, the IVRS (and in some cases an interactive web-response system (IWRS)) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio defined in each study as well as the block size that was determined by the sponsor (Appendix 3). Since Sliwinski 2010 was available as an abstract only, the information was insufficient to accurately assess the selection bias.

Blinding

All of the included studies had a double-blind design with blinding of participants, caregivers and investigators. From correspondence, blinding was applicable for all study outcomes. In the placebo-controlled studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011; NCT01572792; Sliwinski 2010) matching placebo was prepared to have the same external appearance with the same composition except for the active ingredient so that the aclidinium bromide and placebo were indistinguishable. In Chanez 2010 the tiotropium arm was open label, though the trial was double-blinded for the aclidinium and placebo arms, causing a high risk of bias for the comparison with tiotropium but a low risk of bias for the comparison with placebo. For all trials, outcome assessors remained blinded with regard to the treatment assignments throughout the study period. Independent blinded experts and reviewers were assigned for analysing the spirometry data and dyspnoea scores (baseline dyspnoea index (BDI) and TDI). A double-dummy technique was applied in Beier 2013 to ensure the double-blinding of the trial in order to minimise bias.

Incomplete outcome data

All eight full text trials (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011) reported the number of dropouts, along with the reasons, for all the study arms. The number of and reasons for withdrawals for three trials (ACLIFORM; AUGMENT COPD; NCT01572792) were kindly provided on request by the investigators. However, Sliwinski 2010 did not report sufficient information to assess attrition bias. Nine of the included studies were rated as having a low risk of bias, either because the number of dropouts was considered low and was balanced between groups (ACCLAIM/COPD I; ACCORD COPD I; ACCORD COPD II; ACLIFORM; Beier 2013; Chanez 2010), because withdrawal rates were high but evenly distributed across study arms (NCT01572792), or because withdrawal rates were regarded as acceptable given the methods of imputation reported in the published articles (ACCLAIM/COPD II; ATTAIN). Efficacy analyses and safety outcomes were performed on the intention-to-treat population which consisted of all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline FEV1 assessment (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011). The last observation carried forward approach was used to impute missing data (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Chanez 2010). The remaining three trials were rated as unclear because of uneven dropouts and with no clear information on the methods of imputation (AUGMENT COPD; Maltais 2011) or because of unavailable data for dropouts (Sliwinski 2010).

Selective reporting

Seven published trials reported all the outcomes documented in the methodology section of the published manuscripts without any apparent bias (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ATTAIN; Beier 2013; Maltais 2011). The pre-specified outcomes of the three trials (ACLIFORM; AUGMENT COPD; NCT01572792) were supplied on request, with no detectable reporting bias. There were two unreported outcomes, namely trough FVC and peak expiratory flow rate (PEFR), in the Chanez 2010 trial though these outcome measures were specified in the methodology. Limited information prevented full assessment of reporting bias for Sliwinski 2010.

Other potential sources of bias

The studies were sponsored and funded by manufacturers of aclidinium, Almirall, SA, Barcelona, Spain and Forest Laboratories, Inc, NY, USA, and some of the authors received financial support from the same, all of which were declared with no potential source of bias. Sliwinski 2010 was published as an abstract in 2010 but as of 2014 has failed to be published as full text, thus publication bias could not be ruled out. In ACCORD COPD II the baseline mean FEV1 was 1.40 L for the aclidinium 200 µg arm, 1.25 L for the aclidinium 400 µg arm and 1.46 L for the placebo arm. This relative imbalance in baseline lung function was taken into consideration in performing the meta-analysis and judged as not causing a significant high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Aclidinium bromide compared to placebo for stable chronic obstructive pulmonary disease; **Summary of findings 2** Aclidinium bromide compared to tiotropium for stable chronic obstructive pulmonary disease

We included data from 10 studies for quantitative synthesis (meta-analysis) in the comparison of aclidinium bromide versus placebo (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011). Two studies (Beier 2013; Chanez 2010) assessed tiotropium as well and these data were pooled for the comparison of aclidinium bromide versus LAMA. Four trials (ACLIFORM; AUGMENT COPD; NCT01572792; Sliwinski 2010) included both aclidinium and formoterol as intervention arms, however formoterol was given via the Genuair inhaler in these studies thus the data were considered inappropriate for comparison of aclidinium bromide versus LABA.

1. Aclidinum bromide versus placebo

Primary outcomes

Mortality (all-cause)

The number of deaths was reported in nine studies involving a total of 5252 participants (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Maltais 2011). Overall, there was no statistically significant difference in the number of deaths between the aclidinium and placebo groups (OR 0.92; 95% CI 0.43 to 1.94, low quality evidence; Summary of findings for the main comparison). Five patients out of 1000 (95% CI 2 to 10) patients receiving aclidinium died over 6 to 52 weeks, which was similar to the placebo group. Subgroup analysis of aclidinium once daily and twice daily showed an OR of 0.63 (95% CI 0.25 to 1.60; 3 trials, 1828 participants) and an OR of 1.69 (95% CI 0.46 to 6.21; 6 trials, 3424 participants) respectively (Analysis 1.1). There was no significant difference between the subgroups.

Exacerbations requiring a short course of an oral steroid or antibiotic, or both

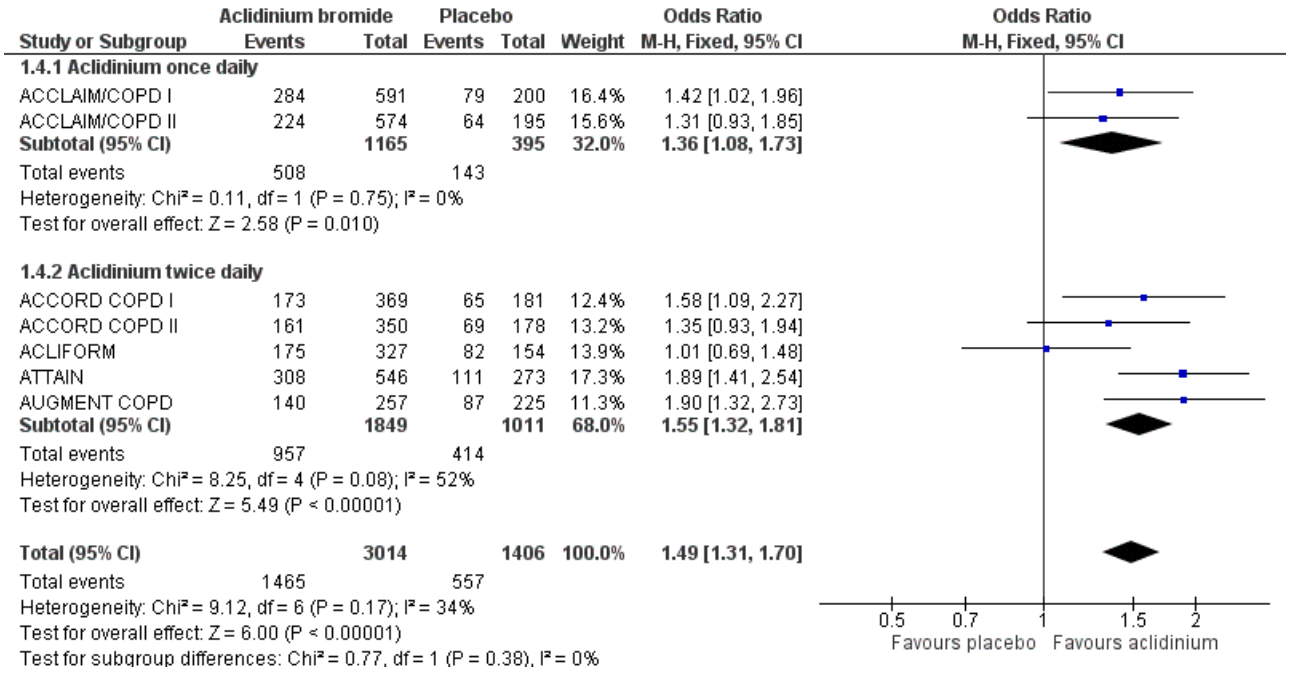
Overall, data from 10 trials involving 5624 participants were pooled for patients experiencing at least one COPD exacerbation requiring a short course of oral steroids or antibiotics, or both (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011). The exact data for the trials which did not specifically mention the number of moderate exacerbations requiring oral steroids, antibiotics or both were kindly supplied by the sponsors. Aclidinium demonstrated a non-significant reduction in moderate exacerbations compared to placebo (OR 0.88; 95% CI 0.74 to 1.04, moderate quality evidence). In patients on aclidinium, 122 people out of 1000 (95% CI 105 to 141) had exacerbations over 4 to 52 weeks, compared to 137 out of 1000 for patients on placebo (Summary of findings for the main comparison). In the subgroup analysis there was no significant difference between once daily (OR 0.93; 95% CI 0.73 to 1.20; 4 trials, 2201 participants) and twice daily aclidinium (OR 0.83; 95% CI 0.66 to 1.05; 6 trials, 3423 participants; test for subgroup differences: P = 0.51, Analysis 1.2).

Quality of life

Quality of life was assessed by the SGRQ in seven studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD), either as the change from the baseline mean value or as the percentage of patients who achieved the minimal clinically important difference in SGRQ total score of ≥ four units reduction. Some of the data, in the format necessary for pooling, were kindly provided by the sponsors. Meta-analysis of both measurements showed a statistically significant improvement with aclidinium bromide in comparison to placebo. Overall, aclidinium decreased the SGRQ total score by a mean difference of -2.34 units compared with placebo (95% CI -3.18 to -1.51; 7 trials, 4442 participants). A significant reduction in SGRQ total score was observed for both aclidinium once daily (MD -1.96; 95% CI -3.47 to -0.45; 2 trials, 1560 participants) and twice daily (MD -2.51; 95% CI -3.50 to -1.51; 5 trials, 2882 participants) with no significant difference between subgroups (test for subgroup differences: P = 0.55, Analysis 1.3).

More patients on aclidinium reported a clinically significant improvement (a fall of at least four units in SGRQ total score) in quality of life than in the placebo group, which was of statistical significance (OR 1.49; 95% CI 1.31 to 1.70; 7 trials, 4420 participants; Analysis 1.4). A total of 494 per 1000 patients on aclidinium (95% CI 462 to 527) compared to 396 out of 1000 patients on placebo achieved a clinically important improvement in SGRQ score, the quality of evidence being rated as high (Summary of findings for the main comparison). In absolute terms, 98 more per 1000 (from 66 more to 131 more) patients on aclidinium experienced clinically meaningful improvements in quality of life than on placebo over 12 to 52 weeks. For every 10 people treated with aclidinium instead of placebo, one additional person was estimated to achieve this clinically important improvement in quality of life (NNT = 10; 95% CI 8 to 15). Both twice daily (OR 1.55; 95% CI 1.32 to 1.81; 5 trials, 2860 participants) and once daily aclidinium (OR 1.36; 95% CI 1.08 to 1.73; 2 trials, 1560 participants) demonstrated significant improvement with no statistical difference in the subgroup analysis (test for subgroup differences: P = 0.38; Figure 3).

Figure 3. Forest plot of comparison: 1 Aclidinium bromide versus placebo, outcome: 1.4 Quality of life: Number of patients who achieved ≥ 4 units improvement in SGRQ total score.



Secondary outcomes

Lung function

Nine trials studied changes from baseline in trough and peak FEV1, and trough and peak FVC (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Maltais 2011) and seven studies reported the change from baseline in normalised FEV1 area under the curve in the first 12 hours (FEV1 $AUC_{0\text{-}12}$) (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD). Most of the trials reported the data for these outcomes as the difference in aclidinium versus placebo values, but the required data for each intervention arm and placebo arm for our meta-analysis were kindly provided by Almirall. These were pooled as the change from baseline to the end of the study.

The predose FEV1 for participants taking aclidinium was increased by 0.09 L (or 90 mL) at the end of the trials compared with participants using placebo inhalers (95% CI 0.08 to 0.10; 9 trials, 4963 participants). A greater improvement in the trough FEV1 was noted with twice daily dosing (MD 0.10; 95% CI 0.09 to 0.12; 6 trials, 3164 participants) compared to once daily (MD 0.07; 95% CI 0.05 to 0.09; 3 trials, 1799 participants; test for subgroup differences: P = 0.02, Analysis 1.5).

The meta-analysis for peak FEV1 change from baseline, using the random-effects model due to significant heterogeneity (I^2 = 56%), yielded an overall MD of 0.17 L (95% CI 0.15 to 0.20; 9 trials, 4962 participants). No difference in the pooled MD was observed between twice daily (MD 0.17; 95% CI 0.15 to 0.19; 6 trials, 3160 participants) and once daily aclidinium (MD 0.19; 95% CI 0.12 to 0.25; 3 trials, 1802 participants; test for subgroup differences: P = 0.62, Analysis 1.6).

Aclidinium resulted in a statistically significant improvement of normalised FEV1 $AUC_{0\text{-}12}$ from baseline with a pooled MD of 0.13 L, or 130 mL, compared to placebo (95% CI 0.10 to 0.16; 7 trials, 1237 participants). The pooled MD for twice daily (MD 0.13; 95% CI 0.10 to 0.17; 5 trials, 1106 participants) and once daily aclidinium (MD 0.13; 95% CI 0.08 to 0.19; 2 trials, 131 participants) were similar (Analysis 1.7).

The mean change in baseline trough FVC was 0.16 L greater with aclidinium than with placebo (95% CI 0.14 to 0.18; 9 trials, 4963 participants). There was no difference between twice daily (MD 0.17; 95% CI 0.14 to 0.20; 6 trials, 3164 participants) and once daily aclidinium (MD 0.14; 95% CI 0.10 to 0.18; 3 trials, 1799 participants; test for subgroup differences: P = 0.26, Analysis 1.8).

The improvement in peak FVC from baseline was also significantly greater in patients on aclidinium compared to placebo with a pooled MD of 0.27 L (95% CI 0.23 to 0.31; 9 trials, 4962 participants) in the meta-analysis using a random-effects model as the heterogeneity was high (I^2 = 56%). Subgroup analysis demonstrated no significant difference between twice daily (MD 0.25; 95% CI 0.22 to 0.28; 6 trials, 3160 participants) and once daily aclidinium (MD 0.33; 95% CI 0.23 to 0.42; 3 trials, 1802 participants; test for subgroup differences: P = 0.13, Analysis 1.9).

Functional capacity

None of the individual studies measured functional capacity.

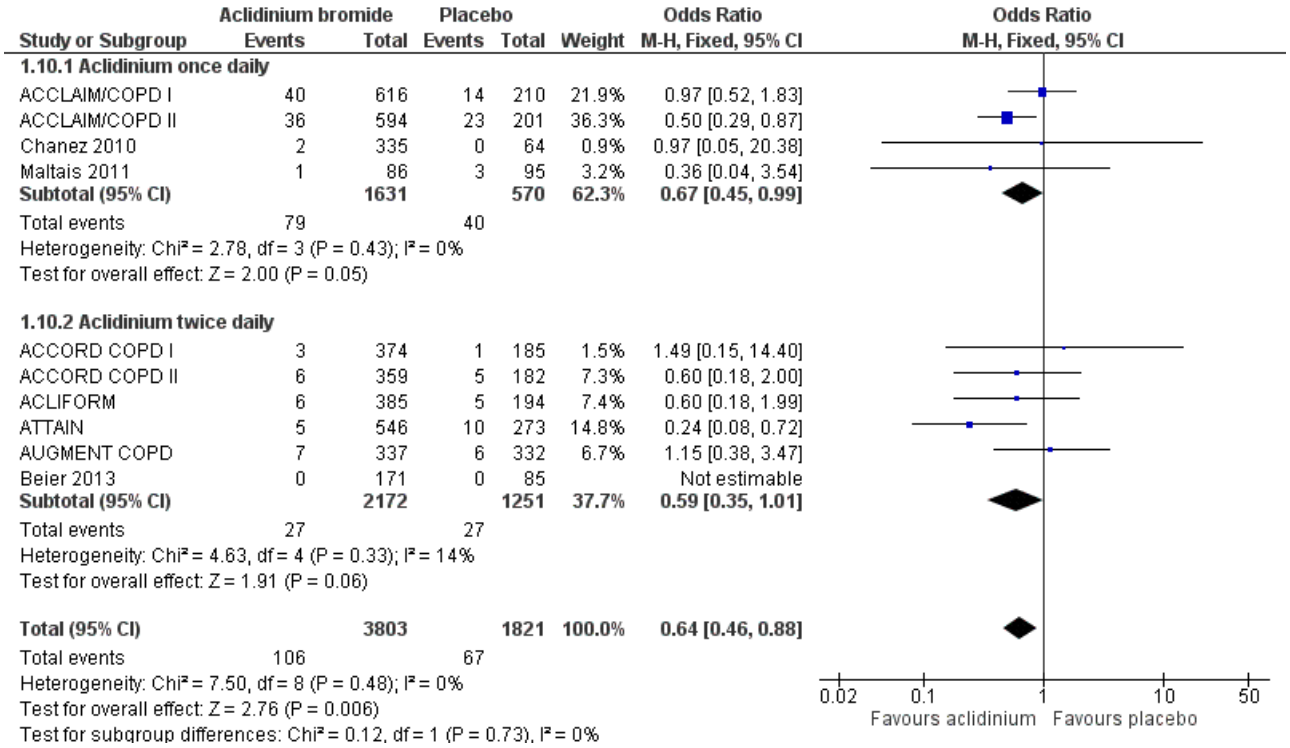
Hospital admissions due to exacerbations

The published reports of the included studies did not specifically mention hospital admissions due to either exacerbations or any cause. However, data for hospital admissions due to exacerbations, that is severe COPD exacerbations, were obtained for 10 studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD

COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011) from the study sponsors.

There were fewer patients on aclidinium who suffered one or more exacerbation(s) leading to hospitalisation than on placebo over 4 to 52 weeks (OR 0.64; 95% CI 0.46 to 0.88; 10 studies, 5624 participants) (Figure 4). Twenty four patients per 1000 (95% CI 17 to 33) on aclidinium suffered from at least one severe COPD exacerbation requiring hospital admission compared to 37 per 1000 on placebo, the quality of evidence being classified as high (Summary of findings for the main comparison). In absolute terms, aclidinium resulted in 13 fewer patients with exacerbation-related hospitalisations per 1000 (4 to 20 fewer) than placebo. It was estimated that for every 77 patients treated with aclidinium instead of placebo, one additional person was free from a severe COPD exacerbation necessitating hospitalisation (NNT = 77; 95% CI 51 to 233). Subgroup analysis showed that the difference between twice daily (OR 0.59; 95% CI 0.35 to 1.01; 6 trials, 3423 participants) and once daily aclidinium (OR 0.67; 95% CI 0.45 to 0.99; 4 trials, 2201 participants) was not statistically significant (test for subgroup differences: P = 0.73, Analysis 1.10).

Figure 4. Forest plot of comparison: 1 Aclidinium bromide versus placebo, outcome: 1.10 Number of patients with hospital admissions due to COPD exacerbation.



Improvement in symptoms

Changes in symptom of dyspnoea were assessed in eight studies using the transitional dyspnoea index (TDI) score (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Maltais 2011) and reported as either the change in mean value from baseline or as percentage of participants who achieved the minimal clinically important difference in TDI focal score of ≥ one unit increment.

Patients on aclidinium reported a MD of 0.84 units improvement in TDI compared with placebo (95% CI 0.50 to 1.18; 8 trials, 4490 participants) using a random-effects model as the heterogeneity was high (I^2 = 68%). This heterogeneity was caused by ACCORD COPD II in which the patients on aclidinium had a relatively lower baseline FEV1 with more severe disease (GOLD stage III) than in the placebo arm. Repeating the analysis with the exclusion of this particular study resulted in a MD of 0.95 units (95% CI 0.72 to 1.19) without heterogeneity (I^2 = 0%). Both once daily (MD 1.08; 95% CI 0.46 to 1.71; 3 trials, 1597 participants) and twice daily aclidinium (MD 0.72; 95% CI 0.33 to 1.11; 5 trials, 2893 participants) demonstrated an improvement in TDI focal score with no statistical difference in the subgroup analysis (test for subgroup differences: P = 0.33, Analysis 1.11).

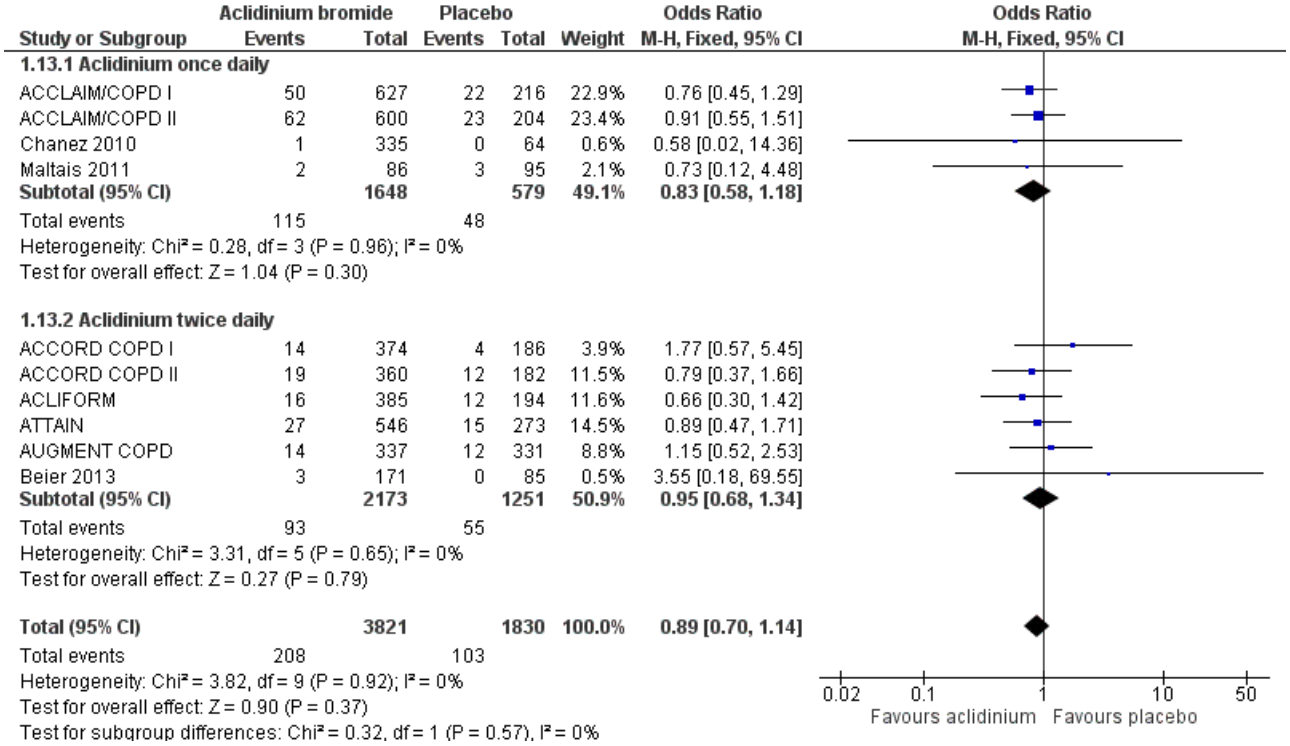
In terms of percentage of COPD patients achieving ≥ one unit improvement in TDI focal score for dyspnoea, more patients on aclidinium attained this minimal clinically important difference than for those on placebo (OR 1.73; 95% CI 1.52 to 1.98; 8 trials, 4289 participants; I^2 = 0%). A similar improvement was noted for both once daily (OR 1.75; 95% CI 1.39 to 2.20; 3 trials, 1589 participants) and twice daily aclidinium (OR 1.72; 95% CI 1.47 to 2.03; 5 trials, 2700 participants; test for subgroup differences: P = 0.92, Analysis 1.12).

Non-fatal serious adverse events

Ten studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011) reported this outcome with participants as the level of analysis (that is the number of people who had non-fatal serious adverse events as opposed to the number of adverse

events in total). When the findings of these studies were pooled, no difference was observed between aclidinium and placebo (OR 0.89; 95% CI 0.70 to 1.14; 10 trials, 5651 participants) (Figure 5). Among 1000 patients, 50 receiving aclidinium (95% CI 40 to 64) and 56 on placebo developed non-fatal serious adverse events, with moderate quality of evidence (Summary of findings for the main comparison). This result appeared to be independent of dosing (twice daily OR 0.95; 95% CI 0.68 to 1.34; 6 trials, 3424 participants; once daily OR 0.83; 95% CI 0.58 to 1.18; 4 trials, 2227 participants; test for subgroup differences: P = 0.57, Analysis 1.13).

Figure 5. Forest plot of comparison: 1 Aclidinium bromide versus placebo, outcome: 1.13 Non-fatal serious adverse events.



Withdrawals

Withdrawals due to either lack of efficacy or adverse events were provided in 10 studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; Beier 2013; Chanez 2010; Maltais 2011; NCT01572792).

There was a statistically and clinically significant reduction in withdrawals due to lack of efficacy with aclidinium compared to placebo (OR 0.31; 95% CI 0.23 to 0.43; 10 trials, 5672 participants). The effect estimates were similar for twice daily (OR 0.32; 95% CI 0.20 to 0.51; 6 trials, 3445 participants) and once daily aclidinium (OR 0.31; 95% CI 0.20 to 0.47; 4 trials, 2227 participants; test for subgroup differences: P = 0.91, Analysis 1.14).

Overall, aclidinium resulted in a non-significant reduction in withdrawals due to adverse events compared with placebo (OR 0.76; 95% CI 0.57 to 1.01; 10 trials, 5672 participants). No significant difference was observed for once daily dosing (OR 0.65; 95% CI 0.42 to 1.00; 4 trials, 2227 participants) and twice daily dosage regimens (OR 0.84; 95% CI 0.59 to 1.21; 6 trials, 3445 participants; test for subgroup differences: P = 0.36, Analysis 1.15).

2. Aclidinum bromide versus long-acting muscarinic antagonist

Primary outcomes

There were no deaths reported for both the aclidinium and tiotropium arms in a total of 329 patients in Beier 2013 (Analysis 2.1).

Two studies assessed exacerbations requiring a short course of oral steroids or antibiotics, or both, in 729 participants (Beier 2013 ; Chanez 2010). Aclidinium was associated with a higher number of exacerbations compared to tiotropium but this was not statistically significant (OR 2.64; 95% CI 0.31 to 22.18) (Analysis 2.2). There were no patients with moderate exacerbations in the tiotropium arm compared to five of 506 participants in the aclidinium arm. However, the quality of evidence was very low because of the high risk of bias in Chanez 2010, which was open label for the tiotropium arm and had very serious imprecision of the results (Summary of findings 2).

None of the studies measured quality of life for aclidinium and tiotropium.

Secondary outcomes

Only one trial provided data for aclidinium and tiotropium on lung function (Beier 2013). Aclidinium was associated with a greater

improvement in trough FEV1 (MD 0.04; 95% CI -0.01 to 0.09; 1 trial, 329 participants) (Analysis 2.3), peak FEV1 (MD 0.01; 95% CI -0.04 to 0.06; 1 trial, 329 participants) (Analysis 2.4), trough FVC (MD 0.08; 95% CI -0.01 to 0.17; 1 trial, 329 participants) (Analysis 2.5) and peak FVC (MD 0.04; 95% CI -0.05 to 0.13; 1 trial, 329 participants) (Analysis 2.6) than tiotropium, however none were statistically significant.

Functional capacity was not assessed in the two studies included in this comparison.

Aclidinium reduced the number of patients with hospitalisations due to COPD exacerbations compared to tiotropium but the difference was not statistically significant (OR 0.54; 95% CI 0.07 to 4.11; 2 trials, 729 participants) (Analysis 2.7). Two patients per 1000 (95% CI 0 to 18) on aclidinium versus four patients per 1000 on tiotropium were admitted to hospital for severe COPD exacerbations, but this was very low level evidence (Summary of findings 2). The wide CI included the possibility of no difference.

Data from the two trials (Beier 2013 ; Chanez 2010) were combined for non-fatal serious adverse events. Aclidinium demonstrated a non-significant reduction in non-fatal serious adverse events compared with tiotropium (OR 0.67; 95% CI 0.17 to 2.65; 2 trials, 729 participants) (Analysis 2.8). In a total of 1000 patients, 12 on aclidinium (95% CI 3 to 46) and 18 on tiotropium experienced non-fatal serious adverse events over a period of four to six weeks, with a very low quality of evidence as the CIs were wide.

Both Beier 2013 and Chanez 2010 reported withdrawals due to lack of efficacy or adverse events. There were no withdrawals due to lack of efficacy for both aclidinium and tiotropium in these two studies (Analysis 2.9). No significant difference existed between aclidinium and tiotropium for withdrawals due to adverse events (OR 0.94; 95% CI 0.26 to 3.42; 2 trials, 729 participants) (Analysis 2.10).

3. Aclidinum bromide versus long-acting beta$_2$-agonist

Inadequate and inaccurate data limited this comparison as formoterol was given via the Genuair inhaler in the trials, which was not an approved inhaler for formoterol (ACLIFORM; AUGMENT COPD; NCT01572792; Sliwinski 2010).

4. Adverse events

Adverse events with aclidinium were reported in a total of 10 studies (ACCLAIM/COPD I; ACCLAIM/COPD II; ACCORD COPD I; ACCORD COPD II; ACLIFORM; ATTAIN; AUGMENT COPD; Beier 2013; Chanez 2010; Maltais 2011). We have presented the adverse event data from both comparisons with placebo and tiotropium in section 4 of Data and analyses.

A lower incidence of cardiac events (Analysis 4.1) was more prominent with aclidinium compared to tiotropium and placebo, but both were statistically non-significant. There was no significant difference between aclidinium and placebo or tiotropium for the anticholinergic side effect of dry mouth (Analysis 4.2). Constipation was non-significantly more frequent with aclidinium compared to both placebo and tiotropium (Analysis 4.3). Aclidinium non-significantly decreased cerebrovascular events (Analysis 4.4) compared to placebo (OR 0.58; 95% CI 0.25 to 1.33; 9 trials, 5252 participants). However, in Beier 2013 cerebrovascular events were more frequent with aclidinium compared to tiotropium but the CIs were very wide and the difference was not statistically significant (OR 2.79; 95% CI 0.11 to 68.96; 1 trial, 329 participants).

Diarrhoea was found to be significantly increased with aclidinium (once daily therapy) compared to placebo (OR 2.32; 95% CI 1.14 to 4.74; 2 trials, 1647 participants). However, no statistical difference was observed between once daily and twice daily aclidinium (OR 1.06; 95% CI 0.63 to 1.78; 5 trials, 3168 participants; test for subgroup differences: P = 0.08, Analysis 4.5).

Other reported adverse events such as nasopharyngitis, headache, cough, hypertension, respiratory tract infections, urinary tract infections, fatigue, dizziness, dyspnoea, arthralgia, back pain and oropharyngeal pain showed no significant difference between aclidinium and placebo or tiotropium in the pooled analysis.

DISCUSSION

Summary of main results

We calculated summary estimates of the effects of aclidinium on clinical outcomes in comparison to placebo and tiotropium. Aclidinium improved quality of life and reduced exacerbation-related hospitalisations compared to placebo. Aclidinium significantly lowered the SGRQ total score by 2.34 units (from 3.18 to 1.51 lower), although this mean improvement did not reach the accepted threshold of four units for a clinically important difference. However, more patients on aclidinium achieved a minimal clinically important difference of at least four units decrease in the SGRQ total score (462 to 527 per 1000) than those on placebo (396 per 1000). A total of 10 patients need to be treated with aclidinium to attain one additional person with a four unit improvement in SGRQ total score. Similarly, aclidinium significantly reduced the number of patients with exacerbation-related hospital admissions compared to placebo (17 to 33 per 1000 versus 37 per 1000), which would correspond to approximately 77 patients having to be treated with aclidinium to prevent one additional exacerbation-related hospitalisation. However, aclidinium therapy failed to demonstrate a significant reduction in the number of patients experiencing an exacerbation that required an oral steroid or antibiotic, or both. In terms of safety, no significant difference between aclidinium and placebo was observed in all-cause mortality or non-fatal serious adverse events. All reported deaths in the trials were not related to aclidinium therapy.

For the secondary outcomes, improvements in symptom scales and spirometric indices appeared clinically significant with aclidinium compared to placebo. Patients treated with aclidinium experienced clinically significant improvements in dyspnoea with a TDI focal score change from baseline of 0.50 to 1.18 units. Exclusion of the data from ACCORD COPD II with its baseline imbalance in COPD severity resulted in a larger increase in the TDI focal score of 0.72 to 1.19 units, without significant heterogeneity. The proportion of patients on aclidinium who exceeded the minimum clinically important difference of one unit in TDI focal score was higher than with placebo. Lung function measurements of trough and peak FEV1, trough and peak FVC and normalised FEV1 area under the curve in the first 12 hours (FEV1 AUC$_{0\text{-}12}$) were significantly higher with aclidinium compared to placebo. A significantly lower number of participants withdrew from studies due to lack of efficacy in the aclidinium group compared to the placebo group. Similarly, fewer withdrawals due to adverse events were observed among patients on aclidinium than on placebo, but the differences were not statistically significant. We could not show a difference in most of the efficacy outcomes related to dosing of aclidinium, except for

trough FEV1 where the twice daily dosage demonstrated a relatively superior improvement compared with the once daily regimen.

Evaluation of the effects of aclidinium in relation to LABAs was unsuccessful due to a lack of trials of good design and inaccurate data.

For the comparison of aclidinium and LAMAs, we were able to pool the data from two studies (Beier 2013; Chanez 2010) which included tiotropium as one of the intervention arms. Based on the currently available, limited data, aclidinium did not differ significantly from tiotropium in terms of exacerbations requiring oral steroids or antibiotics, or both, exacerbation-related hospitalisations and non-fatal serious adverse events. There were no reported cases of deaths or withdrawals due to lack of efficacy for both aclidinium and tiotropium. Withdrawals due to adverse events were similar with aclidinium in comparison to tiotropium. Patients treated with aclidinium had greater improvements in the spirometric indices of trough FEV1, peak FEV1, trough FVC and peak FVC than with tiotropium. However, only Beier 2013 contributed to the lung function outcomes and the evidence for the other outcomes were of very low quality, thus reducing our confidence in the conclusions. Therefore, we strongly recommend future trials comparing the effects of aclidinium and tiotropium to strengthen our confidence in conclusions about the efficacy of this novel LAMA in relation to established LAMAs.

There was no statistically significant difference between the number of participants suffering from non-serious adverse events with aclidinium compared to placebo and tiotropium. Concern about a possible cardiovascular risk with aclidinium was not reinforced in our review as the risk did not differ from placebo or tiotropium. This was also in accordance with the greater kinetic selectivity of aclidinium on M3 over M2 receptors (Maltais 2012; Sims 2011). Interestingly, patients on once daily aclidinium developed diarrhoea more often than with placebo but this was not of clinical importance. However, further trials are needed in order to allow valid conclusions with regard to this. The numbers of anticholinergic side effects such as dry mouth and constipation were slightly higher with aclidinium than placebo but they were not of clinical or statistical significance. Other adverse events were comparable between aclidinium and placebo or tiotropium.

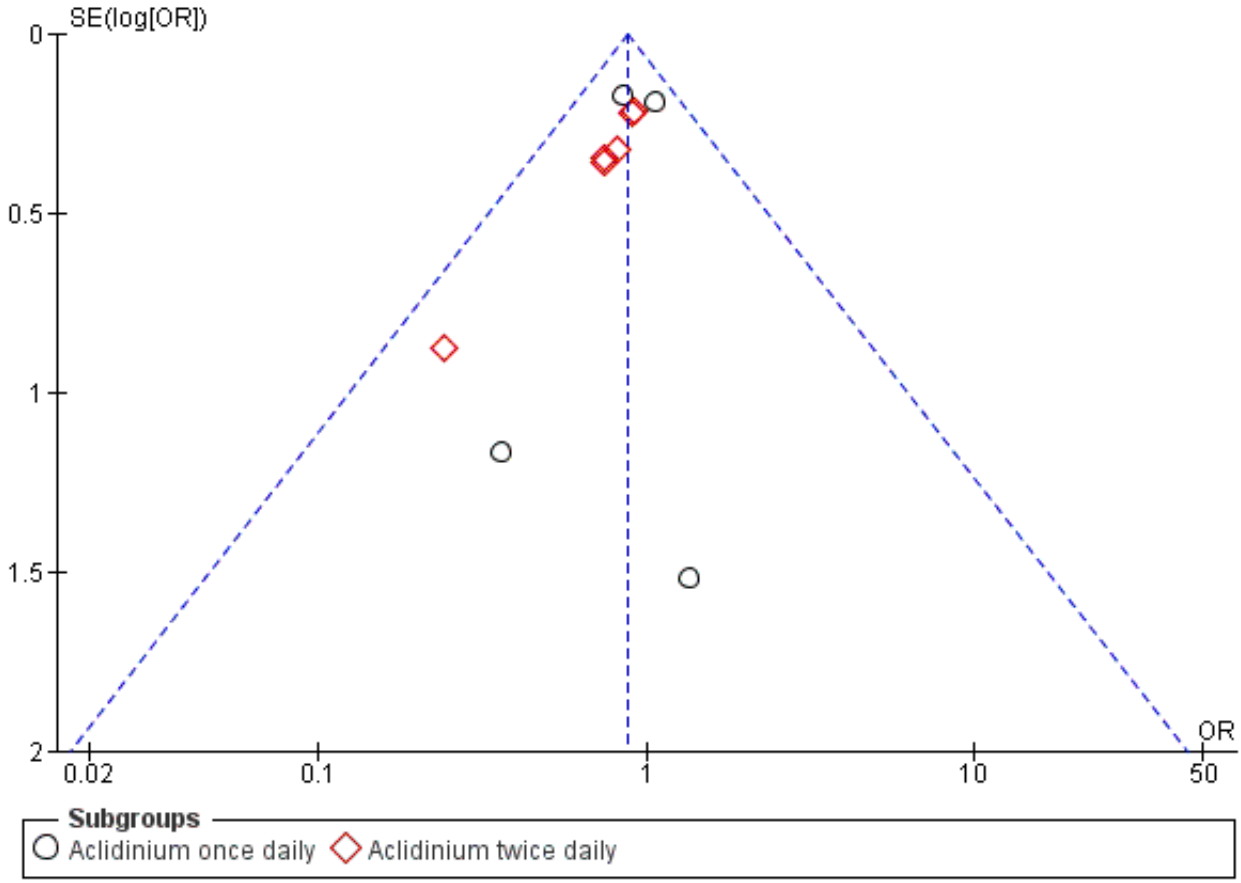
Overall completeness and applicability of evidence

There were substantial numbers of trials investigating aclidinium and placebo for this review, but the number of trials assessing aclidinium compared to tiotropium or formoterol were inadequate. Four of the included trials did investigate formoterol as one of the treatment arms (ACLIFORM; AUGMENT COPD; NCT01572792; Sliwinski 2010) yet, from discussion with the study sponsors, both aclidinium and formoterol were delivered in Genuair inhalers to maintain double-blindness. While aclidinium delivered in the Genuair is an approved drug, this is not the case for formoterol. Thus the data for formoterol were considered unsuitable to be included in our analysis. However, in two trials with tiotropium (Beier 2013; Chanez 2010) the tiotropium was administered in its approved HandiHaler. In Beier 2013, two Genuair inhalers loaded with either aclidinium or placebo and one HandiHaler loaded with either tiotropium or placebo were supplied. To maintain blinding, patients were instructed to use both inhalers each morning and the Genuair only each evening. However, tiotropium delivered via the HandiHaler was open label for Chanez 2010. This study limitation decreased the quality of evidence for the treatment effects of this comparison. In this review, subgroup analysis was performed for dosing of aclidinium, once daily versus twice daily. Most of the once daily trials studied aclidinium 200 µg whereas twice daily trials studied mainly aclidinium 400 µg; some of the twice daily trials investigated both aclidinium 200 µg and 400 µg. These differences in the total daily dose among the trials might have impacted on the summary estimates of subgroups but with minimal alterations in the overall effect estimates. The results from this review indicate an improvement in the mean health-related quality of life and a reduction in exacerbations requiring hospital admission for stable COPD patients on aclidinium compared to placebo. The mean improvement for these outcomes was statistically significant but was relatively small in relation to the minimum clinically important difference. However, there was a significant number of patients who had a clinically relevant improvement. The evidence that this review provides strengthens and supports the efficacy of aclidinium compared to placebo for use in patients with stable COPD. However, the lack of trials prevents a comprehensive assessment of the evidence on the efficacy of aclidinium compared to tiotropium or formoterol, or other LABAs or LAMAs. No significant increase in deaths, non-fatal serious adverse events and other adverse events compared with placebo make aclidinium a relatively safe medication for use as maintenance therapy by patients with moderate to severe stable COPD.

Quality of the evidence

The studies included in this review were generally of good to excellent methodological quality and the single conference abstract, which was of unknown quality, did not contribute any data to the analysis. The inclusion and exclusion criteria for the trials were almost identical. The results were unlikely to be compromised by performance (selection and allocation) or detection biases as all trials were industry-sponsored, in accordance with the pre-specified protocol, and double-blind; except for Chanez 2010 where the tiotropium arm was open label. Selective reporting was considered to be at low risk with the exception of Chanez 2010, where some of the lung function outcomes were not reported but none were outcomes of our review. The percentage of withdrawals in the included trials ranged from 6.3% to 42.2% for long-term studies of more than12 weeks, whereas short-term studies of 12 weeks or less had relatively lower withdrawal rates of 2.5% to 19.9%. However, most of the participants who completed treatment remained for follow-up, the percentage of participants lost to follow-up in the included trials being 0% to 3.4%. Missing data were imputed using the last observation carried forward approach in the individual studies. Several studies did not report on exacerbations requiring hospital admission or a short course of oral steroids or antibiotics, or both, and lung function data in a way that could be included in the review, however all these data were supplied by Almirall. All studies utilised intention-to-treat analysis. Visual inspection of the funnel plot for exacerbations with aclidinium and placebo did not suggest publication bias (Figure 6).

Figure 6. Funnel plot of comparison: 1 Aclidinium bromide versus placebo, outcome: 1.2 Number of patients with exacerbations requiring steroids, antibiotics or both.



In particular, the quality of the evidence ranged from very low to high for the outcomes of this review. High quality evidence reinforced the validity of findings on quality of life and hospitalisations due to exacerbations, for aclidinium in comparison to placebo, while the evidence for mortality was low quality; the evidence on exacerbations requiring a short course of oral steroids or antibiotics, or both, and non-fatal serious adverse events was rated as moderate. However, the evidence for the majority of outcomes for aclidinium versus tiotropium was of very low quality. We believe that additional information from future studies might change our confidence in these results and we will continue to update this review in an attempt to maximise the evidence to inform future clinical practice.

Potential biases in the review process

We made every effort to obtain grey literature in order to minimise the impact of publication bias. In addition to the Cochrane Airways Group's systematic electronic search, we performed a comprehensive search of other sources (for example searching drug company databases, clinical trial registration sites, and checking reference lists) for the identification of potentially relevant published and unpublished studies, with no language restrictions. The manufacturer was very helpful in providing additional information on completed published trials as well as completed but unpublished trials. Publication bias, therefore, was less likely, as supported by the funnel plot for the exacerbation data. Two review authors independently conducted trial selection and data extraction. We contacted authors for missing and incomplete data. To maximise the accuracy of our review, we requested the exact values of the data required in our meta-analysis directly from the drug companies. We did not use data from estimations based on figures or other available indirect data. The manufacturer (Almirall) was accommodating in supplying information about study designs, details of trials and missing data for several of the studies. Possible limitations of the meta-analysis include double-counting of patients from overlapping publications and trials. We avoided this potential concern of double counting by including only the results of the first period (24 weeks) of the primary study (AUGMENT COPD) instead of the data at the end (one year) of the extension study (NCT01572792) as the extension period was not a truly randomised comparison and had substantial withdrawals. Clinical characteristics of the patients recruited into the trials and the disease severity as measured by baseline spirometry were similar between trials except for one trial (ACCORD COPD II) in which there was a higher proportion of patients with lower baseline mean FEV1 in the aclidinium 400 µg arm (1.25 L) than in the placebo arm (1.46 L). Thus, we repeated our analysis of all outcome measures with the exclusion of this study to detect any alterations in the summary estimates of the effects of aclidinium. However, the clinical homogeneity of the majority of the trials yielded statistical homogeneity for

many outcome measures across the trials, except for symptom improvement measured by change from baseline in mean TDI focal score where the effect estimate was significantly altered by the data from this study. Another potential source of bias could be concomitant medications, however medications had to be used at a stable dose for at least four weeks and were stopped at least six hours before each study visit in the primary trials, making any possible interaction with aclidinium less likely.

Agreements and disagreements with other studies or reviews

There are a number of published reviews on aclidinium in the current literature.

Jones 2013 reported the efficacy of twice daily aclidinium and included the three studies ACCORD COPD I; ACCORD COPD II and ATTAIN. Pooled data from ACCORD COPD I and ATTAIN showed a statistically significant improvement in lung function (trough FEV1 and peak FEV1) and quality of life, which is in agreement with the results of our review. It, however, mentioned that aclidinium significantly reduced the frequency of exacerbations, which our review failed to prove. Pooled data from the two studies (ACCORD COPD I; ATTAIN) in that review showed a significant reduction in the rate of moderate to severe exacerbations for the aclidinium 400 µg dose when compared with placebo (0.31 versus 0.44; rate ratio 0.71; P = 0.01). Our review separately analysed moderate exacerbations that required a short course of oral steroids or antibiotics, or both, and severe exacerbations requiring hospital admissions. We also included trials of other doses of aclidinium, with a total of 10 studies in our meta-analysis. We found that aclidinium reduced severe exacerbations necessitating hospitalisation but not moderate exacerbations requiring oral steroids or antibiotics, or both.

A significant improvement in lung function with aclidinium over placebo in moderate to severe COPD was also reported in a meeting abstract by D'Urzo 2013a. This was derived from a pooled analysis of the ACCORD COPD I; ACCORD COPD II and ATTAIN trials. Aclidinium produced consistent improvements in both trough FEV1 (100 mL, P < 0.0001) and peak FEV1 (172 mL, P < 0.0001) from baseline to week 12 compared to placebo, which was in accordance with our findings.

Other available evidence comes from Karabis 2013, which analysed the comparative efficacy of aclidinium versus glycopyrronium and tiotropium using network meta-analysis. Twenty-one studies were included, with three studies on aclidinium (ACCORD COPD I; ACCORD COPD II; ATTAIN). The authors concluded that aclidinium was comparable to tiotropium and glycopyrronium regarding trough FEV1 and TDI score improvement. For the SGRQ score, aclidinium resulted in a larger improvement than tiotropium 5 µg but comparable improvement to tiotropium 18 µg and glycopyrronium. The quality of the evidence for these conclusions, which were based on indirect comparison by network meta-analysis through statistical inference, is questionable. We also determined that improvements in trough FEV1 with aclidinium were not statistically different from tiotropium. However, no trials in our review directly compared aclidinium to tiotropium in terms of SGRQ or TDI score.

In another review by Suppli 2012, 10 trials, both parallel-group and cross-over studies, were included after a systematic search. However, there was no meta-analysis and the conclusions drawn were based solely on the individual trial reports for a particular outcome. Thus, we did not consider the conclusions from that review to be suitable for comparison with our findings. Similarly, the other published reviews (Alagha 2011; Alagha 2014; Maltais 2012; Sims 2011; Woods 2013) were descriptive without pooling of the data making their findings inappropriate for comparison.

D'Urzo 2013b performed a pooled analysis of the anticholinergic adverse events from three trials. Gelb 2013 and D'Urzo 2013 had a duration of 52 weeks and the open label continuation phase of ACCORD COPD II was for 40 weeks. The highest incidence rates of adverse events with long-term aclidinium therapy were urinary tract infections (2.9%), oropharyngeal pain (1.8%) and constipation (1.5%). Our review also demonstrated that the anticholinergic adverse events associated with aclidinium were similar to those associated with placebo or tiotropium.

The major concern with the prolonged use of inhaled aclidinium bromide, a long-acting anticholinergic, is the possible cardiovascular risk. In our analysis cardiac events were not increased with aclidinium compared to placebo, and were even non-significantly fewer with aclidinium than with tiotropium. Donohue 2013 analysed the major adverse cardiovascular events (MACE) with aclidinium 400 µg of cardiovascular (CV) death, non-fatal myocardial infarction (MI) and non-fatal stroke by pooling the results of two double-blind trials with a duration of 52 weeks (D'Urzo 2013; Gelb 2013) and one open label study over 40 weeks (the continuation phase of ACCORD COPD II or LAS-MD-38 part B). The MACE composite scores with aclidinium for double-blind and open label studies were low (1.4% and 1.6% respectively). Similarly, Ferguson 2013 pooled the CV events from ACCORD COPD I; ACCORD COPD II and ATTAIN trials and reported that the MACE composite scores were equal for aclidinium and placebo (0.3%). A double-blind, randomised, placebo-controlled parallel-group phase IV trial (ASCENT COPD) that is ongoing is assessing the cardiovascular safety of long-term aclidinium therapy and is scheduled to be completed by January 2018.

AUTHORS' CONCLUSIONS

Implications for practice

Inhaled aclidinium bromide use in stable COPD is associated with better health-related quality of life and fewer hospitalisations due to severe exacerbations than with placebo. The results from this review indicate a larger percentage of patients attaining the minimal clinically important difference of at least four units change and a small mean improvement in health-related quality of life for patients on aclidinium therapy compared to placebo. Aclidinium does not significantly lower the number of patients with exacerbations requiring a short course of oral steroids or antibiotics or both compared to placebo. Significant improvements in spirometric indices of trough and peak FEV1, and trough and peak FVC were seen with aclidinium compared with placebo. Adverse events, non-fatal serious adverse events and mortality did not differ significantly between aclidinium and placebo. Currently available data for aclidinium in comparison to tiotropium were insufficient for coming to a valid conclusion. Inappropriate drug delivery of formoterol limits our effort to determine the relative efficacy and safety of aclidinium compared to LABAs. We did not conduct a cost-effectiveness analysis so we cannot comment on implications for resource allocations.

Implications for research

Additional long-term studies are required to establish the risks and benefits of aclidinium compared to LAMAs and LABAs. Pharmacoeconomic analyses would be helpful to assist healthcare providers in making decisions about the cost-effectiveness of aclidinium compared to other long-acting bronchodilators such as LABA and LAMA. In future COPD trials, strategies using specific approved inhalers for formoterol, tiotropium and aclidinium while maintaining the procedure of blinding should be implemented to have accurate data for the individual interventions.

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Ian Yang was the Editor for this review and commented critically on the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACCLAIM/COPD I

Methods	Study design: double-blind, randomised, placebo-controlled, parallel-group, phase III study Study duration: 52 weeks Run-in: 14 days Setting: multicentre trial Number of study centres and location: 132 centres in 16 European countries (one in Andorra, five in Austria, four in Belgium, 10 in Bulgaria, eight in the Czech Republic, three in Denmark, nine in France, 10 in Germany, eight in Hungary, six in Italy, four in Netherlands, nine in Poland, nine in Romania, 25 in Russia, eight in Spain, 13 in the UK)

ACCLAIM/COPD I *(Continued)*

	Date of study: August 2006 to May 2008 Randomisation: yes Blinding: double-blind (subject, investigator) Withdrawals: stated
Participants	Number screened: 1313 Number randomised: 843 Number in treatment group: 627 (inhaled aclidinium 200 µg once daily) Number in control group: 216 Number of withdrawals (treatment/control): 89/47 Number completing trial (treatment/control): 538/169 Mean age (years) (treatment/control): 62.6/61.9 Gender (male/female): 488/139 (treatment), 175/41 (control) Caucasian (%) (treatment/control): 100/99.5 **Inclusion criteria**: male and non-pregnant, non-lactating female patients aged ≥ 40 years with a diagnosis of COPD according to GOLD criteria, with a post-bronchodilator FEV1/FVC ratio of ≤ 70% and FEV1 < 80% of the predicted value. The predose FEV1 at randomisation was within 80-120% of the pre-bronchodilator FEV1 at screening. Current or previous cigarette smokers with a smoking history of ≥ 10 pack-years **Exclusion criteria**: history or current diagnosis of asthma, allergic rhinitis or atopy; blood eosinophil count > 600 cell/mm^3; respiratory tract infection or COPD exacerbation within six weeks prior to screening or during the run-in period; hospitalisation for an acute COPD exacerbation within three months prior to screening; use of long-term oxygen therapy; clinically significant respiratory diseases other than COPD; unstable cardiac conditions Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: aclidinium 200 µg once daily via the Genuair inhaler Comparison: matching placebo once daily via the Genuair inhaler As-needed therapy: inhaled salbutamol was permitted on as-needed basis, but had to be discontinued six hours prior to and during a study visit Concomitant medications: inhaled corticosteroids or oral sustained-release theophyllines; oral or parenteral corticosteroids at maximal doses equivalent to 10 mg/day of prednisone or 20 mg every other day; oxygen therapy (less than 15 hours per day) were allowed if the dosage had been stable for at least four weeks prior to screening Definition of COPD exacerbations: an increase in COPD symptoms over at least two consecutive days, associated with increased use of bronchodilators (mild exacerbation), treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation) or leading to hospitalisation (severe exacerbation)
Outcomes	**Primary outcomes**: trough FEV1 at weeks 12 and 28 **Secondary outcomes**: number of patients who achieved a clinically relevant improvement in health-related quality of life at 52 weeks, as measured by a ≥ four units decrease from baseline on the SGRQ total score; and time to first moderate or severe COPD exacerbation Time points: spirometry was conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations at one hour pre-dose and immediately before dosing during study visits on day one (baseline); day two; week one; every month up to week 20; and thereafter every two months until week 52. Measurements were also performed at 0.25, 0.5, 1, 2 and 3 hours post-dose on day one; and at 0.5, 1, 2 and 3 hours post-dose at weeks 1, 4, 8, 12, 28, 44 and 52. Health status and dyspnoea were evaluated pre-dose on day one (baseline) and at weeks 12, 28, 44 and 52 using the St George's Respiratory Questionnaire (SGRQ; self administered) and Baseline/Transitional Dyspnoea Index (BDI/TDI; administered by an independent reviewer)
Notes	Full text publication

ACCLAIM/COPD I *(Continued)*

Source of funding: Almirall, SA, Barcelona, Spain, and Forest Laboratories, Inc, NY, USA

Study number: ClinicalTrials.gov NCT00363896

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (participant and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from report): "spirometry data were electronically transmitted to a data-management centre where an independent, blinded, spirometric expert reviewed the acceptability and repeatability of the data. Dyspnoea was evaluated using baseline/transitional dyspnoea index (BDI/TDI) administered by an independent reviewer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number of withdrawals and reasons were clearly mentioned for both intervention and placebo arms. Withdrawal rates were relatively similar between groups (aclidinium 14.2% and placebo 21.8%). All efficacy analyses and safety summaries were performed on the intent-to-treat population, comprising all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline trough FEV1 measurement Quote (from report): "missing data were imputed using a last observation carried forward approach"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

ACCLAIM/COPD II

Methods	Study design: double-blind, randomised, placebo-controlled, parallel-group, phase III study Study duration: 52 weeks Run-in: 14 days Setting: multicentre trial Number of study centres and location:119 sites in seven countries (72 sites in the United States, 13 sites in Argentina, 13 sites in Australia, seven sites in Canada, two sites in Mexico, three sites in New Zealand and nine sites in South Africa)

ACCLAIM/COPD II *(Continued)*

	Date of study: August 2006 to June 2008 Randomisation: yes Blinding: double-blind (subject, investigator) Withdrawals: stated
Participants	Number screened: 1456 Number randomised: 804 Number in treatment group: 600 (inhaled aclidinium 200 µg once daily) Number in control group: 204 Number of withdrawals (treatment/control): 154/86 Number completing trial (treatment/control): 446/118 Mean age (years) (treatment/control): 65.1/65.2 Gender (male/female): 383/217 (treatment), 124/80 (control) Caucasian (%) (treatment/control): 92/92.7 **Inclusion criteria**: male and non-pregnant, non-lactating female patients aged ≥ 40 years with a diagnosis of COPD according to GOLD criteria, with a post-bronchodilator FEV1/FVC ratio of ≤ 70% and FEV1 < 80% of the predicted value. The pre-dose FEV1 at randomisation within 80-120% of the pre-bronchodilator FEV1 at screening. Current or previous cigarette smokers with a smoking history of ≥ 10 pack-years **Exclusion criteria**: history or current diagnosis of asthma, allergic rhinitis or atopy; blood eosinophil count > 600 cell/mm3; respiratory tract infection or COPD exacerbation within six weeks prior to screening or during the run-in period; hospitalisation for an acute COPD exacerbation within three months prior to screening; use of long-term oxygen therapy; clinically significant respiratory diseases other than COPD; unstable cardiac conditions Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: aclidinium 200 µg once daily via the Genuair inhaler Comparison: matching placebo once daily via the Genuair inhaler As-needed therapy: inhaled salbutamol was permitted on as-needed basis, but had to be discontinued six hours prior to and during a study visit Concomitant medications: inhaled corticosteroids or oral sustained-release theophyllines; oral or parenteral corticosteroids at maximal doses equivalent to 10 mg/day of prednisone or 20 mg every other day; oxygen therapy (less than 15 hours per day) were allowed if the dosage had been stable for at least four weeks prior to screening Definition of COPD exacerbations: an increase in COPD symptoms over at least two consecutive days, associated with increased use of bronchodilators (mild exacerbation), treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation) or leading to hospitalisation (severe exacerbation)
Outcomes	**Primary outcomes**: trough FEV1 at weeks 12 and 28 **Secondary outcomes**: number of patients who achieved a clinically relevant improvement in health-related quality of life at 52 weeks, as measured by a ≥ four units decrease from baseline on the SGRQ total score; and time to first moderate or severe COPD exacerbation Time points: spirometry was conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations at one hour pre-dose and immediately before dosing during study visits on day one (baseline); day two; week one; every month up to week 20; and thereafter every two months until week 52. Measurements were also performed at 0.25, 0.5, 1, 2 and 3 hours post-dose on day one; and at 0.5, 1, 2 and 3 hours post-dose at weeks 1, 4, 8, 12, 28, 44 and 52. Health status and dyspnoea were evaluated pre-dose on day one (baseline) and at weeks 12, 28, 44 and 52 using the St George's Respiratory Questionnaire (SGRQ; self administered) and Baseline/Transitional Dyspnoea Index (BDI/TDI; administered by an independent reviewer)
Notes	Full text publication

ACCLAIM/COPD II *(Continued)*

Source of funding: Almirall, SA, Barcelona, Spain, and Forest Laboratories, Inc, NY, USA

Study number: ClinicalTrials.gov NCT00358436

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from report): "spirometry data were electronically transmitted to a data-management centre where an independent, blinded, spirometric expert reviewed the acceptability and repeatability of the data. Dyspnoea was evaluated using baseline/transitional dyspnoea index (BDI/TDI) administered by an independent reviewer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout was higher in the placebo group (aclidinium 25.7% and placebo 42.2%) but efficacy analyses and safety summaries were performed on the intent-to-treat population, comprising all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline trough FEV1 measurement Quote (from report): "missing data were imputed using a last observation carried forward approach"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

ACCORD COPD I

Methods	Study design: double-blind, randomised, placebo-controlled, parallel-group, phase III study Study duration: 12 weeks Run-in: two weeks Follow-up: two weeks by phone contact/study visit Setting: multicentre trial Number of study centres and location: 106 study sites (100 in the United States and six additional sites in Canada) Date of study: April 2009 to July 2009

ACCORD COPD I *(Continued)*

	Randomisation: yes Blinding: double-blind (subject, caregiver, investigator, outcomes assessor) Withdrawals: stated
Participants	Number screened: 1062 Number randomised: 561 Number in treatment group: 185 (Inhaled aclidinium 200 µg twice daily), 190 (Inhaled aclidinium 400 µg twice daily) Number in control group: 186 Number of withdrawals (treatment/control): 33 (200 µg), 24 (400 µg)/37 Number completing trial (treatment/control): 152 (200 µg), 166 (400 µg)/149 Mean age (years): 63.1 (200 µg), 64.9 (400 µg), 65.1 (control) Gender (male/female): 101/83 (200 µg), 100/90 (400 µg), 96/90 (control) Caucasian (%): 91.8 (200 µg), 95.3 (400 µg), 94.1 (control) **Inclusion criteria**: male and female patients ≥ 40 years of age, current or former cigarette smokers with a smoking history of ≥ 10 pack-years and diagnosed with moderate-to-severe COPD (post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 30% but < 80% of predicted) **Exclusion criteria**: other significant respiratory conditions (including asthma), respiratory infection or COPD exacerbation ≤ six weeks prescreening (≤ three months if it resulted in hospitalisation), clinically significant cardiovascular conditions including myocardial infarction during the previous six months, unstable arrhythmia, Bazett-corrected QTc > 470 msec and medical conditions where anticholinergic drugs are contraindicated Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: inhaled aclidinium 200 µg twice daily, inhaled aclidinium 400 µg twice daily at the same time in the morning (between 8:00 and 10:00 AM) and evening (between 8:00 and 10:00 PM) via a multiple-dose dry powder inhaler (Genuair) Comparison: inhaled placebo twice daily via Genuair inhaler As-needed therapy: albuterol as rescue medication but had to be discontinued ≥ six hours before each study visit Concomitant medications: inhaled corticosteroids (ICS), systemic corticosteroids equivalent to ≤ 10mg/day of prednisone or 20 mg every other day, and theophylline if treatment was stable for ≥ four weeks prior to screening. Theophylline and ICS were discontinued the morning before each study visit. Inhaled anticholinergics and LABAs were prohibited throughout the study Definition of COPD exacerbation: an increase in COPD symptoms ≥ two consecutive days resulting in medical intervention and categorised as mild (increased use of rescue medication), moderate (treatment with antibiotics and/or systemic corticosteroids), or severe (hospitalisation)
Outcomes	**Primary outcomes**: change in morning pre-dose (trough) FEV1 (the average of two pre-dose FEV1 values) from baseline to week 12 **Secondary outcomes**: change in peak FEV1 (the highest value observed within three hours post-morning dose) from baseline to week 12 Other outcomes: changes from baseline on day one (peak FEV1 only), weeks 1, 4, and 8 (trough and peak FEV1) and week 12 ($AUC_{0\text{-}3/3h}$ FEV1, trough, peak, and $AUC_{0\text{-}3/3h}$ FVC, and trough IC), changes from baseline at weeks 4, 8 and 12 in SGRQ and TDI (including percentage of subjects with a clinically meaningful improvement (decrease of ≥ four points for SGRQ or increase of ≥ one unit for TDI)), changes from baseline at week 12 in COPD Nighttime Symptoms Questionnaire and Daily Sleep Diary scores, rescue medication use over 12 weeks, and COPD exacerbation rate
Notes	Full text publication Source of funding: Forest Research Institute, Inc.

ACCORD COPD I *(Continued)*

Study number: ClinicalTrials.gov NCT00891462

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject, caregiver and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind including blinding of outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawals were relatively low and balanced across the groups with similar reasons (aclidinium 200 µg 17.8%, aclidinium 400 µg 12.6% and placebo 19.9%). All efficacy analyses and safety outcomes were performed on the intent-to-treat population, comprising all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline trough FEV1 measurement Quote (from report): "missing values were imputed using the last-observation-carried-forward approach"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

ACCORD COPD II

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III study Study duration: 12 weeks Run-in: two weeks Follow-up: phone call or visit two weeks after the last study treatment dose Setting: multicentre trial Number of study centres and location: 103 study centres (101 in the United States and two in Canada) Date of study: December 2009 to September 2010 Randomisation: yes Blinding: double blind (subject, caregiver, investigator, outcomes assessor)

ACCORD COPD II *(Continued)*

	Withdrawals: stated
Participants	Number screened: 1236 Number randomised: 544 Number in treatment group: 184 (Inhaled aclidinium 200 µg twice daily), 178 (Inhaled aclidinium 400 µg twice daily) Number in control group:182 Number of withdrawals (treatment/control): 29 (200 µg), 30 (400 µg)/31 Number completing trial (treatment/control): 155 (200 µg), 148 (400 µg)/151 Mean age (years): 63.4 (200 µg), 63.2 (400 µg), 61.7 (control) Gender (male/female): 100/82 (200 µg), 99/84 (400 µg), 89/88 (control) Caucasian (%): 89.1 (200 µg), 90.4 (400 µg), 92.3 (control) **Inclusion criteria**: male and female patients ≥ 40 years old, current or former cigarette smokers with a smoking history of ≥ 10 pack-years and diagnosed with stable moderate-to-severe COPD according to GOLD guidelines (post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 30% and < 80% of predicted) **Exclusion criteria**: COPD exacerbation requiring hospitalisation ≤ three months before screening, respiratory tract infection or COPD exacerbation ≤ six weeks before screening, other clinically significant respiratory condition including asthma, clinically significant cardiovascular conditions including myocardial infarction ≤ six months or newly diagnosed arrhythmia ≤ three months before screening, history of hypersensitivity reaction or contraindications to inhaled anticholinergics Baseline characteristics of treatment/control groups: percentage of severe (GOLD stage III) patients: 46.4% (aclidinium 200 µg), 54.2% (aclidinium 400 µg), 36.8% (placebo) baseline mean FEV1 (L): 1.40 (aclidinium 200 µg), 1.25 (aclidinium 400 µg), 1.46 (placebo)
Interventions	Intervention: inhaled aclidinium 200 µg twice daily, inhaled aclidinium 400 µg twice daily via a multiple-dose dry powder inhaler (Genuair/Pressair) Comparison: inhaled placebo twice daily As-needed therapy: albuterol (salbutamol) was permitted as rescue medication but was discontinued ≥ six hours before study visits Concomitant medications: theophylline, inhaled corticosteroids (ICS), oral or parenteral corticosteroids equivalent to ≤ 10mg/day of prednisone or 20 mg every other day were allowed if treatment was stable for ≥ four weeks before screening. These medications were discontinued ≥ six hours before each study visit Other short/long acting anticholinergics and LABAs were prohibited throughout the study
Outcomes	**Primary outcomes**: change in morning pre-dose (trough) FEV1 from baseline to week 12 **Secondary outcomes**: change in peak FEV1 (maximum FEV1 reading observed ≤ three hours post-morning dose) from baseline to week 12 Other outcomes: changes from baseline in morning trough and peak FEV1 at day one (peak FEV1 only) and weeks 1, 4, and 8. Changes from baseline in FEV1 at 0.5-3 hour post-dose and area under the concentration-time curve from 0 to 3 hour normalized over 3 hour ($AUC_{0\text{-}3/3h}$), FVC (trough, peak), and IC (trough, three hours post-dose) at day one (except for trough) and weeks 1, 4, 8 and 12. Changes from baseline in SGRQ score at weeks 4, 8 and 12 and TDI at week 12, percentage of patients with a minimal clinically important differences from baseline in SGRQ (decrease of ≥ four points) or TDI (increase of ≥ one unit) at study end
Notes	Full text publication Source of funding: Almirall, SA, Barcelona, Spain, and Forest Laboratories, Inc, NY, USA Study number: ClinicalTrials.gov NCT01045161

ACCORD COPD II *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject, caregiver and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind including blinding of outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number of withdrawals were low and even across the groups with similar reasons (aclidinium 200 µg 15.8%, aclidinium 400 µg 16.9% and placebo 17%). Efficacy analyses and safety summaries were based on the intent-to-treat population, defined as all randomised patients who received at least one dose of double blind study medication and who had a baseline and at least one post-baseline trough FEV1 assessment. Quote (from report): "missing data were imputed by the last-observation-carried-forward approach"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published report included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed Relatively higher percentage of severe COPD patients were recruited in aclidinium 400 µg arm than placebo, however sensitivity analysis by exclusion of this study data had no significant change on the overall effect estimates

ACLIFORM

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III study Study duration: 24 weeks Setting: multicentre trial Number of study centres and location: 197 study sites in 22 countries (two sites in Austria, two in Belgium, five in Bulgaria, two in Croatia, 12 in Czech Republic, four in Denmark, five in Finland, seven in France, 28 in Germany, 15 in Hungary, four in Italy, eight in Repulbic of Korea, seven in Netherlands, 21 in Poland, 12 in Romania, five in Russia, seven in Slovakia, nine in South Africa, seven in Spain, five in Sweden, 14 in Ukraine, 16 in the United Kingdom) Date of study: October 2011 to January 2013

ACLIFORM *(Continued)*

	Randomisation: yes Blinding: double-blind (subject, investigator)
Participants	Number randomised: 1729 Number in treatment group: 381 (aclidinium 400 µg plus formoterol 6 µg), 385 (aclidinium 400 µg plus formoterol 12 µg), 385 (aclidinium 400 µg monotherapy) Number in control group: 384 (formoterol 12 µg) or 194 (placebo) Number of withdrawals : 40 (aclidinium 400 µg plus formoterol 6 µg), 34 (aclidinium 400 µg plus formoterol 12 µg), 50 (aclidinium 400 µg monotherapy), 45 (formoterol 12 µg) or 34 (placebo) Number completing trial : 341 (aclidinium 400 µg plus formoterol 6 µg), 351 (aclidinium 400 µg plus formoterol 12 µg), 335 (aclidinium 400 µg monotherapy), 339 (formoterol 12 µg) or 160 (placebo) Mean age (years): 62.9 (aclidinium 400 µg plus formoterol 6 µg), 62.7 (aclidinium 400 µg plus formoterol 12 µg), 63.1 (aclidinium 400 µg monotherapy), 63.4 (formoterol 12 µg) or 64.2 (placebo) Gender (male/female): 259/122 (aclidinium 400 µg plus formoterol 6 µg), 261/124 (aclidinium 400 µg plus formoterol 12 µg), 256/129 (aclidinium 400 µg monotherapy), 255/129 (formoterol 12 µg) or 138/56 (placebo) Caucasian (%): 96.1 (aclidinium 400 µg plus formoterol 6 µg), 95.3 (aclidinium 400 µg plus formoterol 12 µg), 94.3 (aclidinium 400 µg monotherapy), 94.3 (formoterol 12 µg) or 94.3 (placebo) **Inclusion criteria**: male or non-pregnant, non-lactating female ≥ 40 years, current or ex-smokers with a cigarette smoking history of at least 10 pack-years, diagnosed with stable moderate to severe COPD as defined by the GOLD at the screening visit, able to perform repeatable pulmonary function testing for FEV1 according to "ATS/ERS" 2005 criteria at screening visit **Exclusion criteria**: asthma, any respiratory tract infection or COPD exacerbation in the six weeks before screening visit, hospitalisation for an acute COPD exacerbation within three months prior to the screening visit, clinically significant respiratory conditions including active tuberculosis, interstitial lung disease or massive pulmonary thromboembolic disease, pulmonary resection or lung volume reduction surgery within 12 months prior to screening visit, history of lung transplantation, bronchiectasis, alpha1-antitrypsin deficiency, chronic use of oxygen therapy greater than or equal to 15 hours/day, clinically significant cardiovascular conditions, hospitalisation within 12 months prior to screening visit for heart failure functional classes III according to the New York Heart Association, corrected QT interval "QTc" > 470 msec at screening visit
Interventions	Intervention: inhaled aclidinium/formoterol fixed dose combination (FDC) high dose twice daily, inhaled aclidinium/formoterol FDC low dose twice daily, inhaled aclidinium 400 µg twice daily Comparison: inhaled formoterol 12 µg twice daily, inhaled dose-matched placebo twice daily
Outcomes	**Primary outcomes**: change from baseline in morning pre-dose (trough) FEV1 and one hour post-morning dose FEV1 at week 24 **Secondary outcomes**: change from baseline in Transition Dyspnoea Index (TDI) score and St. George's Respiratory Questionnaire (SGRQ) total score at week 24
Notes	Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"

ACLIFORM *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawal rates were somewhat higher in the placebo group but overall low in all groups (aclidinium 13%, placebo 17.5%, formoterol 11.7%, fixed dose combination with formoterol 6 µg 10.5%, fixed dose combination with formoterol 12 µg 8.8%) and the reasons were provided upon request
Selective reporting (reporting bias)	Low risk	Comment: no published report available, but results for all specified outcomes were supplied on request
Other bias	Low risk	Comment: no apparent source of bias was observed

ATTAIN

Methods	Study design: double-blind, randomised, placebo-controlled, parallel-group, phase III study Study duration: 24 weeks Run-in: two weeks Setting: multicentre trial Number of study centres and location: 103 sites in 11 countries (10 sites in the Czech Republic, five in France, 17 in Germany, 13 in Hungary, three in Italy, one in Peru, 21 in Poland, 10 in the Russian Federation, five in Spain, 13 in South Africa and five in the Ukraine) Date of study: October 2009 to November 2010 Randomisation: yes Blinding: double-blind (subject, investigator) Withdrawals: stated
Participants	Number screened: 1061 Number randomised: 828 Numer included in statistical analysis: 819 Number in treatment group: 280 (Inhaled aclidinium 200 µg twice daily), 272 (Inhaled aclidinium 400 µg twice daily) Number in control group: 276 Number of withdrawals (treatment/control): 24 (200 µg), 17 (400 µg)/41 Number completing trial (treatment/control): 253 (200 µg), 252 (400 µg)/232 Mean age (years): 62.3 (200 µg), 62.9 (400 µg), 62.0 (control) Gender (male/female): 181/96 (200 µg), 182/87 (400 µg), 189/84 (control) Caucasian (%): 95.0 (200 µg), 95.5 (400 µg), 95.2 (control)

ATTAIN *(Continued)*

	Inclusion criteria: male and female patients aged ≥ 40 yrs, current or former cigarette smokers with a smoking history of ≥ 10 pack-years with a diagnosis of COPD according to GOLD criteria (post-bronchodilator FEV1/FVC ratio of < 70% and FEV1 < 80% of the predicted value) **Exclusion criteria**: history or current diagnosis of asthma; respiratory tract infection or COPD exacerbation within six weeks (three months if hospitalisation) before screening or during the run-in period; clinically relevant respiratory conditions other than COPD; unstable cardiac conditions, including myocardial infarction, within the previous six months; and contraindications to the use of anticholinergic drugs Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: inhaled aclidinium 200 µg twice daily or 400 µg twice daily via a multiple-dose dry powder inhaler (Genuair) Comparison: placebo twice daily via Genuair inhaler As-needed therapy: inhaled salbutamol was permitted but was discontinued six hours before and during study visits Concomitant medications: inhaled corticosteroids or oral sustained-release theophyllines; systemic corticosteroids at doses equivalent to 10 mg per day of prednisone or 20 mg every other day; and oxygen therapy (< 15 hours per day) if their administration had been stable for ≥ four weeks before screening Definition of COPD exacerbation: increase in COPD symptoms over at least two consecutive days, resulting in the increased use of short-acting bronchodilators and/or inhaled corticosteroids (mild exacerbation), treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation), or hospitalisation (severe exacerbation)
Outcomes	**Primary outcomes**: change from baseline in morning pre-dose (trough) FEV1 at week 12 and 24 **Secondary outcomes**: change from baseline in peak FEV1 (highest FEV1 value observed within three hours of morning dosing) at week 12 and 24, percentages of patients achieving clinically significant improvements in SGRQ total score and TDI focal score at week 24 Time points: standardised spirometric measurements (FEV1, FVC and inspiratory capacity) before the morning dose on day one (baseline) and during visits at weeks 1, 4, 8, 12, 18 and 24. FEV1 and FVC measurements were obtained at 0.5, 1, 2 and 3 hour post-dose and inspiratory capacity measurements at three hour post-dose on day one and weeks 1, 4, 12 and 24. Health status was evaluated pre-dose at baseline and weeks 4, 12 and 24 using the St George's Respiratory Questionnaire (SGRQ). Dyspnoea was assessed at baseline using the Baseline Dyspnoea Index (BDI) and changes were measured using the Transitional Dyspnoea Index (TDI) at weeks 4, 12 and 24
Notes	Full text publication Source of funding: Almirall, SA, Barcelona, Spain, and Forest Laboratories, Inc, NY, USA Study number: ClinicalTrials.gov NCT01001494

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"

ATTAIN *(Continued)*

Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject and investigator) Quote (from report): "all study centres had identical spirometry equipment, detailed study manual and training" Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind Quote (from report): "dyspnoea was assessed at baseline using the Baseline Dyspnoea Index (BDI) and changes were measured using the Transitional Dyspnoea Index (TDI) at weeks 4, 12 and 24. The BDI and TDI were administered by an independent reviewer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall dropout was low in all groups though the number of withdrawals were slightly higher in the placebo group (aclidinium 200 µg 8.6%, aclidinium 400 µg 6.3% and placebo 14.9%). Efficacy analyses and safety outcomes were performed on the intention-to-treat (ITT) population, defined as all randomised patients who took one or more dose of study medication and had a baseline and one or more post-baseline FEV1 assessment Quote (from report): "missing data were imputed using last observation carried forward (LOCF). For spirometry data, linear interpolation and time-matched LOCF were applied"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

AUGMENT COPD

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III study Study duration: 24 weeks Run-in: present, duration not mentioned Follow-up: two weeks Setting: multicentre trial Number of study centres and location: 222 study sites (193 sites in the United States, 11 in Australia, 10 in Canada and eight in New Zealand) Date of study: September 2011 to March 2013 Randomisation: yes Blinding: double-blind (subject, caregiver, investigator, outcomes assessor) Withdrawals: available on request (though published only as abstract)
Participants	Number randomised: 1692 Number in treatment group: 338 (aclidinium 400 µg plus formoterol 6 µg), 338 (aclidinium 400 µg plus formoterol 12 µg), 340 (aclidinium 400 µg monotherapy) Number in control group: 339 (formoterol 12 µg) or 337 (placebo)

AUGMENT COPD *(Continued)*

	Number of withdrawals : 62 (aclidinium 400 µg plus formoterol 6 µg), 66 (aclidinium 400 µg plus formoterol 12 µg), 72 (aclidinium 400 µg monotherapy), 69 (formoterol 12 µg) or 101 (placebo) Number completing trial : 276 (aclidinium 400 µg plus formoterol 6 µg), 272 (aclidinium 400 µg plus formoterol 12 µg), 268 (aclidinium 400 µg monotherapy), 270 (formoterol 12 µg) or 236 (placebo) Mean age (years): 63.9 (aclidinium 400 µg plus formoterol 6 µg), 64.2 (aclidinium 400 µg plus formoterol 12 µg), 64.4 (aclidinium 400 µg monotherapy), 63.7 (formoterol 12 µg) or 63.5 (placebo) Gender (male/female): 187/151 (aclidinium 400 µg plus formoterol 6 µg), 168/170 (aclidinium 400 µg plus formoterol 12 µg), 188/152 (aclidinium 400 µg monotherapy), 169/170 (formoterol 12 µg) or 175/162 (placebo) Caucasian (%): 92.8 (aclidinium 400 µg plus formoterol 6 µg), 91 (aclidinium 400 µg plus formoterol 12 µg), 93.2 (aclidinium 400 µg monotherapy), 93.7 (formoterol 12 µg) or 95.5 (placebo) **Inclusion criteria**: male and female patients aged ≥ 40 yrs diagnosed with stable, moderate to severe COPD as defined by the GOLD criteria and stable airway obstruction, current or former cigarette smokers with a smoking history of at least 10 pack-years **Exclusion criteria**: hospitalisation for acute COPD exacerbation within three months prior to the first visit, any respiratory tract infection or COPD exacerbation in the six weeks before first visit, respiratory conditions other than COPD, asthma, chronic use of oxygen therapy greater than or equal to 15 hours/day, clinically significant cardiovascular conditions, history of hypersensitivity reaction to inhaled anticholinergics
Interventions	Intervention: inhaled fixed dose combination of aclidinium 400 µg plus formoterol 6 µg or 12 µg twice daily, inhaled aclidinium 400 µg twice daily Comparison: inhaled formoterol 12 µg twice daily, inhaled dose-matched placebo twice daily
Outcomes	**Primary outcomes**: change from baseline in morning pre-dose (trough) FEV1 and one hour post-dose FEV1 at week 24 **Secondary outcomes**: change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score and improvement in Transition Dyspnoea Index (TDI) score at week 24
Notes	This trial was available as abstract only Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA Study number: ClinicalTrials.gov NCT01437397

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Double-blind

AUGMENT COPD *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: number of withdrawals and the reasons were provided upon request. Dropout was relatively higher for placebo group (aclidinium 21.2%; placebo 30%, formoterol 20.4%, fixed dose combination with formoterol 6 µg 18.3%; fixed dose combination with formoterol 12 µg 19.5%). No clear information on what method of imputation was used for each outcome
Selective reporting (reporting bias)	Low risk	Comment: no published report available, but results for all specified outcomes were supplied on request
Other bias	Low risk	Comment: no apparent source of bias was observed

Beier 2013

Methods	Study design: randomised, double-blind, double-dummy, placebo- and active comparator-controlled, parallel-group, phase IIIb study Study duration: six weeks Run-in: two to three weeks Setting: multicentre trial Number of study centres and location: 49 study sites in four countries (three sites in the Czech Republic, 23 in Germany, eight in Hungary and 15 in Poland) Date of study: October 2011 to March 2012 Randomisation: yes Blinding: double-blind (subject, investigator) Withdrawals: stated
Participants	Number screened: 485 Number randomised: 414 Number in treatment group: 171 (aclidinium 400 µg twice daily), 158 (tiotropium 18 µg once daily) Number in control group: 85 Number of withdrawals (treatment/control): 5 (aclidinium 400 µg twice daily), 4 (tiotropium 18 µg once daily)/5 Number completing trial (treatment/control): 166 (aclidinium 400 µg twice daily), 154 (tiotropium 18 µg once daily)/80 Mean age (years): 61.8 (aclidinium 400 µg twice daily), 62.8 (tiotropium 18 µg once daily), 62.2 (placebo) Gender (male/female): 114/57(aclidinium 400 µg twice daily), 116/42 (tiotropium 18 µg once daily), 48/37 (placebo) Caucasian (%): 100 (aclidinium 400 µg twice daily), 100 (tiotropium 18 µg once daily), 98.8 (placebo) **Inclusion criteria**: patients aged ≥ 40 years with a clinical diagnosis of stable moderate-to-severe COPD (post-bronchodilator FEV1/FVC < 70%, and FEV1 ≥ 30% and < 80%), either current or former cigarette smokers (smoking history of ≥ 10 pack-years) **Exclusion criteria**: history or current diagnosis of asthma or other clinically significant respiratory or cardiovascular conditions, any respiratory tract infection or COPD exacerbation ≤ six weeks before screening (≤ three months if hospitalisation), contraindications and hypersensitivity to muscarinic antagonists and inability to use the study inhalers properly Baseline characteristics of treatment/control groups: comparable

Beier 2013 *(Continued)*

Interventions	Intervention: aclidinium bromide 400 µg twice daily in the morning (9:00 ± 1 hour) and evening (21:00 ± 1 hour) via the Genuair/Pressair multidose dry powder inhaler, tiotropium 18 µg once daily in the morning (9:00 ± 1 hour) via the HandiHaler Comparison: matched placebo As-needed therapy: inhaled salbutamol 100 µg/puff was permitted except ≤ six hours before each visit Concomitant medications: stable use of oral sustained-release theophylline (not other methylxanthines), inhaled corticosteroids and oral or parenteral corticosteroids (prednisone ≤ 10 mg/day or 20 mg/every other day, or equivalent) were permitted except ≤ six hours before each visit. Oxygen therapy (except ≤ two hours before each visit) was also allowed
Outcomes	**Primary outcomes**: change from baseline in normalized FEV1 area under the curve over the 24-hour period post-morning dose (AUC_{0-24}) at week six **Secondary outcomes**: change from baseline in normalized FEV1 AUC over the nighttime period (AUC_{12-24}) at week six Other outcomes: changes from baseline in normalized FEV1 AUC for the 12-hour period post-morning treatment (AUC_{0-12}), morning predose (trough) and peak FEV1 and FVC Time points: spirometry was conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations over 24 hours following morning treatment on day one and at week six. Three manoeuvres were performed at each time point. Additional measurements (up to a total of eight tests) were made if the first three were not acceptable
Notes	Full text publication Source of funding: Almirall, SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA Study number: ClinicalTrials.gov NCT01462929

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from report): "random sequence generation was by computer-generated schedule" Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from report): "allocation via an interactive voice-response system" Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject and investigator), double-dummy Quote (from report): "patients and study personnel remained blinded to treatment allocation throughout the study" Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"

Beier 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number of withdrawals and reasons were clearly mentioned for intervention and placebo arms Withdrawals were low and balanced across the groups (aclidinium 2.9%, tiotropium 2.5%, placebo 5.9%). Efficacy analyses and safety summaries were based on the intent-to-treat population, which included all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline trough FEV1 value Quote (from report): "no patients were lost to follow-up"
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

Chanez 2010

Methods	Study design: randomised, parallel-group, double-blind (open-label for patients randomised to tiotropium), phase IIb study Study duration: four weeks Run-in: two weeks Setting: multicentre trial Number of study centres and location: 42 centres in Europe and Russia Randomisation: yes Blinding: double-blind (open label for patients randomised to tiotropium) Withdrawals: stated
Participants	Number screened: 694 Number randomised: 464 Number in treatment group: 66 (aclidinium 25 µg), 65 (aclidinium 50 µg), 70 (aclidinium 100 µg), 67 (aclidinium 200 µg), 67 (aclidinium 400 µg), 65 (tiotropium 18 µg) Number in control group: 64 Number of withdrawals (treatment/control): 4 (aclidinium 25 µg), 3 (aclidinium 50 µg), 3 (aclidinium 100 µg), 3 (aclidinium 200 µg), 3 (aclidinium 400 µg), 4 (tiotropium 18 µg)/3 Number completing trial (treatment/control): 62 (aclidinium 25 µg), 62 (aclidinium 50 µg), 67 (aclidinium 100 µg), 64 (aclidinium 200 µg), or 64 (aclidinium 400 µg), 61 (tiotropium 18 µg)/61 Mean age (years): 60.4 (aclidinium 25 µg), 61.1 (aclidinium 50 µg), 61.6 (aclidinium 100 µg), 62.1 (aclidinium 200 µg), 62.0 (aclidinium 400 µg), 62.2 (tiotropium 18 µg), 61.2 (placebo) Gender (male/female): 49/16 (aclidinium 25 µg), 47/18 (aclidinium 50 µg), 54/15 (aclidinium 100 µg), 57/9 (aclidinium 200 µg), 53/14 (aclidinium 400 µg), 56/8 (tiotropium 18 µg), 55/9 (placebo) Ethnicity: not stated **Inclusion criteria**: male and female patients ≥ 40 years with a diagnosis of stable moderate to severe COPD according to American Thoracic Society criteria with a smoking history of ≥ 10 pack-years, and FEV1 in the range of 30–65% of predicted normal (Quanjer predicted normal value) at the screening visit; pre-dose FEV1 at the randomisation visit within 20% of the screening visit value. The ratio between FEV1 and FVC was required to be ≤ 70% at both the screening visit and randomisation visit

Chanez 2010 *(Continued)*

	Exclusion criteria: history of or current asthma, allergic rhinitis, or atopy; reversibility to inhaled salbutamol 400 mg > 20% of pre-dose value; blood eosinophil count > 400 cells/mm3; respiratory tract infection or COPD exacerbation within one month (or hospitalisation within three months) of the screening visit; clinically significant or relevant cardiovascular conditions, laboratory tests, or electrocardiogram (ECG) parameters; QTc interval > 450 ms; history of narrow-angle glaucoma, symptomatic prostatic hypertrophy, or bladder neck obstruction Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: inhaled aclidinium 25 µg, 50 µg, 100 µg, 200 µg, or 400 µg (via multidose dry-powder inhaler, Genuair) or tiotropium 18 µg (via Handi-Haler) once daily in the morning between 08.00 and 12.00 Comparison: matching placebo once daily As-needed therapy: salbutamol 100 mg/puff was allowed as rescue medication, and was discontinued for eight hours prior to any visit Concomitant medications: inhaled corticosteroids, oral sustained release theophyllines (suspended at least 48 hours before each study visit), antihistamines, nedocromil, and ketotifen was permitted, provided the stable dose was administered prior to randomisation. The morning dose of these medications was delayed until the completion of spirometry measurements at each visit. Any other medication used for the treatment of COPD was withdrawn prior to the start of the study, and medications with pro-arrhythmic effects or that affect heart rate or QTc were not permitted
Outcomes	**Primary outcomes**: trough FEV1 (the mean value of the three highest readings assessed at 22, 23, and 24 hour following the trial drug administration) on day 29 for aclidinium (all doses) versus placebo **Secondary outcomes**: trough FEV1 on days 2, 8, and 15; trough FVC (the mean value of the three highest readings assessed at 22, 23, and 24 hour following the trial drug administration) on days 2, 8, 15, and 29; change from baseline in trough and peak FEV1 and FVC; change from baseline in total and component (symptoms, activity, and impact) scores of the St. George's Respiratory Questionnaire (SGRQ); improvement in Transition Dyspnoea Index (TDI); number of days with COPD symptoms; change from baseline in average morning and evening peak expiratory flow rate (PEFR); and use of rescue medication Time points: Two spirometry measurements at one hour interval at the screening visit and before randomisation on day one, and the averaged values provided the screening and baseline values. Efficacy spirometry measurements were taken at 0.5, 1, 2, 3, 4, 5, and 6 hours after the first and last dose (days 1 and 29 respectively) in addition to 22, 23, and 24 hours after the first dose and at each study visit (i.e. after the 7th, 14th, and 28th day of drug administration). Three acceptable readings were taken for each measurement at each time point according to the ATS/ERS recommendations on spirometric assessments
Notes	Full text publication Source of funding: Almirall, Barcelona, Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"

Chanez 2010 *(Continued)*

Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Unclear risk	Quote: "double blind for aclidinium and placebo arms but open label for patients randomised to tiotropium arm" Comment: high risk of bias for comparison with tiotropium but low risk of bias for comparison with placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind for aclidinium and placebo arms but open label for patients randomised to tiotropium arm" Comment: high risk of bias for comparison with tiotropium but low risk of bias for comparison with placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number of withdrawals were low and comparable across the study arms (aclidinium 25 µg 6.1%, aclidinium 50 µg 4.6%, aclidinium 100 µg 4.3%, aclidinium 200 µg 4.5%, aclidinium 400 µg 4.5%, tiotropium 6.2%, placebo 4.7%). Efficacy data are reported for the intention-to-treat (ITT) population, defined as all randomised patients who received at least one dose of study medication and who had a baseline and at least one post-baseline efficacy assessment. The safety population comprised of all randomised patients who received at least one dose of study medication. Quote (from report): "missing spirometry data were handled as follows: for discontinuations because of lack of efficacy, the least favourable value prior to discontinuation was imputed; for other discontinuations, the last value carried forward approach was used. When only some values were missing from a test day, linear interpolation was used to estimate a value missing between two valid measurements. If values were missing for an entire visit or at the beginning or the end of an assessment period (i.e. 0.5, 6, 22, or 24 hour), time-matched values of the previous available visit were used"
Selective reporting (reporting bias)	High risk	Comment: trough FVC on days 2,8,15 and 29; and change from baseline in average morning and evening peak expiratory flow rate (PEFR) were mentioned as secondary end points of the trial, but no data on these outcomes was reported in the published results
Other bias	Low risk	Comment: no apparent source of bias was observed

Maltais 2011

Methods	Study design: randomised, double-blind, parallel group, phase III study Study duration: six weeks Run-in: two weeks Setting: multicentre trial Number of study centres and location: 52 study sites (42 sites in the United States and 10 additional sites in Canada) Date of study: July 2007 to October 2007 Randomisation: yes Blinding: double-blind (subject, investigator, outcomes assessor) Withdrawals: stated
Participants	Number screened: 587

Maltais 2011 *(Continued)*

	Number randomised: 181 Number in treatment group: 86 Number in control group: 95 Number of withdrawals (treatment/control): 5/17 Number completing trial (treatment/control): 81/78 Mean age (years) (treatment/control): 64.0/65.6 Gender (male/female): 52/34 (treatment), 53/42 (control) Caucasian (%) (treatment/control): 96.5/96.8 **Inclusion criteria**: males and females ≥ 40 years, current and ex-smokers with a smoking history ≥ 10 pack-years, clinical diagnosis of moderate to severe stable COPD (post-bronchodilator FEV1/FVC < 70% and FEV1 ≥ 30% and < 80% predicted), functional residual capacity (FRC) ≥ 120% predicted at screening, and Baseline Dyspnoea Index (BDI) focal score ≤ seven **Exclusion criteria**: previous hospitalisation for an acute COPD exacerbation ≤ three months pre-screening, or respiratory tract infection or COPD exacerbation six weeks pre-screening, history of asthma, allergic rhinitis or atopy, contraindications to clinical exercise testing according to the American Thoracic Society (2003), cycled ≥ 20 min during constant work-rate exercise tests during run-in or participated in current or previous COPD rehabilitation programs ≤ six weeks pre-randomisation Baseline characteristics of treatment/control groups: comparable
Interventions	Intervention: inhaled aclidinium 200 µg once-daily via a multidose dry powder inhaler (Genuair) Comparison: placebo once-daily As-needed therapy: levalbuterol (US) or salbutamol (Canada) was allowed ≥ six hours before each visit Concomitant medications: inhaled, oral or parenteral corticosteroids at doses ≤ 10 mg/day or 20 mg every other day were allowed if use was stable ≥ four weeks before screening. No other COPD medications were allowed. Oxygen therapy was allowed ≤ 15 hours/day but not within two hours of study visits
Outcomes	**Primary outcomes**: change in exercise tolerance from baseline to week six **Secondary outcomes**: changes in exercise tolerance from baseline to day one (randomisation) and week three, and changes in trough FEV1, IC, FRC, IC/TLC from baseline to day one, week three and week six Other outcomes: changes from baseline in exercise measures of Inspiratory capacity (IC) and breathing pattern, dyspnoea and leg discomfort Time points: pulmonary function tests and cycle ergometry performed at study visits (screening, run-in, randomisation, weeks three and six)
Notes	Full text publication Source of funding: Forest Laboratories, Inc. and Almirall, SA Study number: ClinicalTrials.gov NCT00500318

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"

Maltais 2011 *(Continued)*

Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind (subject and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind including blinding of outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: dropout was three times higher for placebo arm (aclidinium 5.8%, placebo 17.9%). Analyses of efficacy endpoints and safety outcomes were performed on the intent-to-treat (ITT) population, defined as patients who received one dose of study drug and with a baseline value and one post-baseline assessment of exercise tolerance. However, no clear information on the method of imputation for the missing data
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the published reports included all pre-specified outcomes
Other bias	Low risk	Comment: no apparent source of bias was observed

NCT01572792

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group, phase III, extension study of AUGMENT COPD (NCT01437397) Study duration: 28 weeks Follow-up: four weeks Setting: multicentre trial Number of study centres and location: 208 study sites (179 sites in the United States, 11 in Australia, 10 in Canada and eight in New Zealand) Date of study: April 2012 to June 2013 Randomisation: yes Blinding: double-blind (subject, caregiver, investigator, outcomes assessor)
Participants	Number randomised: 921 Number in treatment group: 205 (aclidinium 400 µg plus formoterol 6 µg), 184 (aclidinium 400 µg plus formoterol 12 µg), 194 (aclidinium 400 µg monotherapy) Number in control group: 192 (formoterol 12 µg) or 146 (placebo) Number of withdrawals: 26 (aclidinium 400 µg plus formoterol 6 µg), 29 (aclidinium 400 µg plus formoterol 12 µg), 29 (aclidinium 400 µg monotherapy), 32 (formoterol 12 µg) or 25 (placebo) Number completing trial: 179 (aclidinium 400 µg plus formoterol 6 µg), 155 (aclidinium 400 µg plus formoterol 12 µg), 165 (aclidinium 400 µg monotherapy), 160 (formoterol 12 µg) or 121 (placebo) The demographics remain the same as AUGMENT COPD, patients were kept on the same treatment arm **Inclusion criteria**: patients who completed the treatment phase of the lead-in study, LAC-MD-31 (AUGMENT COPD) with no medical contraindication; compliance with LAC-MD-31 study procedures and IP dosing; agreed to participate in this six-month extension study

NCT01572792 *(Continued)*

	Exclusion criteria: no specific exclusion criteria
Interventions	Intervention: inhaled aclidinium/formoterol FDC high dose twice daily, inhaled aclidinium/formoterol FDC low dose twice daily, inhaled aclidinium 400 µg twice daily, Comparison: inhaled formoterol 12 µg twice daily, inhaled dose-matched placebo twice daily
Outcomes	**Primary outcomes**: safety and tolerability, adverse events, clinical laboratory parameters, vital sign measurement, and electrocardiogram parameters at week 28
Notes	Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number. The block size was determined in agreement with the clinical trial manager and the statistician and was not to be communicated to the investigators"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "IVRS (or IWRS in some cases) was used to sequentially randomise patients to the intervention arms according to the randomisation ratio and the block size determined as mentioned above"
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double blind (subject, caregiver and investigator) Quote (from correspondence): "matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. Blinding was applicable for all study outcomes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind including blinding of outcomes assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropouts and the reasons were provided upon request. Withdrawal rates at the end of one year were high but relatively even across the groups (aclidinium 29.7%; placebo 37.4%, formoterol 29.8%, fixed dose combination with formoterol 6 µg 26.0%; fixed dose combination with formoterol 12 µg 28.1%)
Selective reporting (reporting bias)	Low risk	Comment: no published report available, but results for all specified outcomes were supplied on request
Other bias	Low risk	Comment: no apparent source of bias was observed

Sliwinski 2010

Methods	Study design: randomised, double-blind, placebo-controlled, parallel group study Study duration: four weeks Randomisation: yes, method not stated Blinding: double-blind
Participants	Number randomised: 566

Sliwinski 2010 *(Continued)*

	Number in treatment group: 121 (aclidinium 200 µg plus formoterol 6 µg), 120 (aclidinium 200 µg plus formoterol 12 µg), 125 (aclidinium 200 µg plus formoterol 18 µg), 76 (aclidinium 200 µg monotherapy) Number in control group: 65 (formoterol 12 µg) or 59 (placebo) **Inclusion criteria**: moderate to severe COPD **Exclusion criteria**: not stated
Interventions	Intervention: aclidinium 200 µg plus formoterol 6 µg, 12 µg or 18 µg or monotherapy with aclidinium 200 µg once daily via the Genuair, multidose dry powder inhaler Comparison: formoterol 12 µg or placebo once daily via the Genuair inhaler
Outcomes	**Primary outcome**: change from baseline in normalised FEV1 area under the curve over 12 hours ($AUC_{0\text{-}12h}$) at week four Other outcomes: safety (outcomes were not mentioned specifically)
Notes	This trial was available as abstract only Source of support: Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc, New York, USA Study number: EUCTR2007-004435-30-CZ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information on methods of randomisation though it is a randomised trial
Allocation concealment (selection bias)	Unclear risk	Comment: no details were provided on allocation concealment
Blinding of participants and personnel (performance bias) Aclidinium versus placebo	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information on withdrawals and the reasons in the abstract
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information regarding study end points and pre-specified outcomes
Other bias	High risk	Comment: incomplete information for proper assessment. Publication bias cannot be ruled out as no published full text article was available though the abstract had been published since 2010

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
D'Urzo 2013	Extension study of ACCORD COPD I, which assessed two doses of aclidinium without comparator
D'Urzo 2013a	Pooled subgroup analysis of three trials
D'Urzo 2013b	Pooled analysis of three trials
de Miquel 2008	Healthy subjects
Donohue 2013	Pooled analysis of three trials
EUCTR2007-000010-36-DE	Cross-over trial
EUCTR2007-003648-31-DE	Cross-over trial
Ferguson 2013	Pooled analysis of ACCORD COPD I, ACCORD COPD II and ATTAIN trials
Flach 2010	Healthy subjects
Fuhr 2012	Cross-over trial
Gelb 2013	Study of two doses of aclidinium without comparator
Jansat 2009	Healthy subjects
Jansat 2009a	Healthy subjects
Joos 2010	Cross-over trial
Kerwin 2013	Cross-over trial
Lasseter 2008	Healthy subjects
Lasseter 2012	Healthy subjects
Magnussen 2009	Assess the efficacy of Genuair inhaler
Magnussen 2010	Cross-over trial
NCT00435760	Cross-over trial
NCT00626522	Study of three different doses of aclidinium bromide/formoterol combination versus placebo
NCT00706914	Study of aclidinium bromide and formoterol fumarate fixed-dose combination (FDC) versus formoterol fumarate
NCT01078623	Cross-over trial
NCT01437540	Study of aclidinium bromide/formoterol fumarate combination versus formoterol fumarate
NCT01551888	Study of aclidinium/formoterol fixed dose combination versus formoterol
NCT01908140	Study of aclidinium bromide/formoterol fumarate combination versus salmeterol/fluticasone
NCT01915784	Study on preference of inhalers

Study	Reason for exclusion
NCT02038829	Cross-over trial
NCT02039050	Cross-over trial
Ortiz 2010	Healthy subjects
Schelfhout 2010	Healthy subjects
Singh 2012	Cross-over trial
van der Palen 2013	Preference study of Genuair versus HandiHaler inhalers
Vestbo 2010	Cross-over trial
Watz 2013	Cross-over trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01636401

Methods	Study design: placebo controlled, phase III study Study duration: 12 weeks Study centre and location: Seoul National University Hospital, Republic of Korea Date of study: August 2012 to May 2013
Participants	**Inclusion criteria**: male or female ≥ 40 years, current or former smokers with a cigarette smoking history of at least 10 pack-years, diagnosed with stable, moderate to severe COPD as defined by the GOLD (post-bronchodilator FEV1/FVC ratio < 70% and FEV1 ≥ 30% to < 80% of the predicted value) **Exclusion criteria**: history of or current asthma, hospitalisation for an acute COPD exacerbation within three months prior to the first visit, any respiratory tract infection or COPD exacerbation in the six weeks before first visit, clinically significant respiratory conditions other than COPD
Interventions	Intervention: inhaled aclidinium bromide 400 µg twice daily Comparison: matching placebo twice daily
Outcomes	**Primary outcome**: change from baseline in morning predose (trough) FEV1 at week 12 **Secondary outcome**: change from baseline in peak FEV1 at week 12
Notes	Source of support: Daewoong Pharmaceutical Co Ltd

Characteristics of ongoing studies *[ordered by study ID]*

ASCENT COPD

Trial name or title	Double-blind, randomised, placebo-controlled, parallel-group, phase IV study to evaluate the effect of aclidinium bromide on long-term cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD (ASCENT COPD)
Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, phase IV study

ASCENT COPD *(Continued)*

	Study duration: 36 months Setting: multicentre trial Number of study centres and locations: 158 centres (152 in the United States and six in Canada)
Participants	Estimated enrolment: 4000 **Inclusion criteria**: male and females of ≥ 40 years of age; current or former smokers with at least 10 pack years of smoking; diagnosed with stable, moderate to very severe COPD according to GOLD criteria 2011 (post-bronchodilator FEV1 < 70% predicted and FEV1/FVC ratio < 70% at first visit with at least one of the following criteria: a. documented cerebrovascular disease b. documented coronary artery disease c. documented peripheral vascular disease or history of claudication d. at least two artherothrombotic risk factors **Exclusion criteria**: significant diseases other than COPD or cardiovascular disease; unstable or life threatening cardiovascular disease or COPD; co-morbid lung diseases; current treatment with a combination of LAMA and LABA/ICS therapy; planned lung transplant or lung volume reduction surgery; malignancies (except treated basal cell and squamous cell (skin) carcinoma); respiratory infection or COPD exacerbation within four weeks prior to screening; Uncontrolled infection from human immunodeficiency virus (HIV) and/or active hepatitis; drug or alcohol abuse within the past 12 months
Interventions	Intervention: inhaled aclidinium bromide 400 µg twice daily via a multi-dose dry-powder inhaler Comparison: dose matched placebo twice daily via a multi-dose dry-powder inhaler
Outcomes	**Primary outcomes**: Time to first major adverse cardiovascular event (up to 36 months) Rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment **Secondary outcomes**: Rate of hospitalisations due to COPD exacerbation per patient per year during the first year of treatment Time to first major adverse cardiovascular event (MACE) or other serious cardiovascular events of interest (up to 36 months)
Starting date	October 2013
Contact information	Sandra Beaird, 1-800-678-1605 ext 66297, FRXClinTrials@frx.com
Notes	Estimated primary completion date: January 2018 Source of support: Forest Laboratories, Inc, New York, USA

DATA AND ANALYSES

Comparison 1. Aclidinium bromide versus placebo

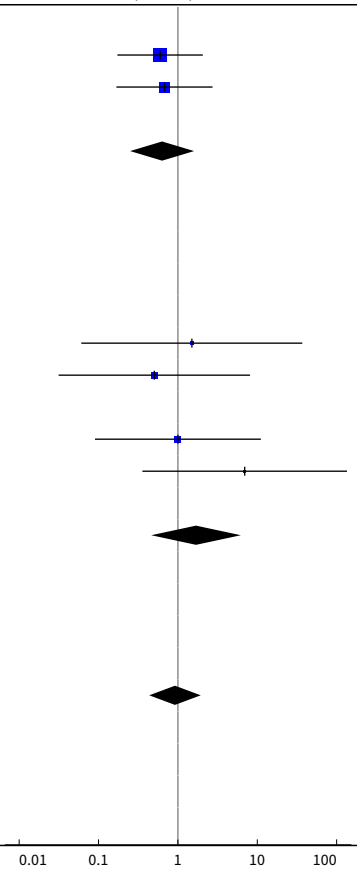
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total number of deaths	9	5252	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.43, 1.94]
1.1 Aclidinium once daily	3	1828	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.60]
1.2 Aclidinium twice daily	6	3424	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [0.46, 6.21]
2 Number of patients with exacerbations requiring steroids, antibiotics or both	10	5624	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.04]
2.1 Aclidinium once daily	4	2201	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.20]
2.2 Aclidinium twice daily	6	3423	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.66, 1.05]
3 Quality of life: change from baseline in SGRQ total score	7	4442	Mean Difference (IV, Fixed, 95% CI)	-2.34 [-3.18, -1.51]
3.1 Aclidinium once daily	2	1560	Mean Difference (IV, Fixed, 95% CI)	-1.96 [-3.47, -0.45]
3.2 Aclidinium twice daily	5	2882	Mean Difference (IV, Fixed, 95% CI)	-2.51 [-3.50, -1.51]
4 Quality of life: Number of patients who achieved ≥ 4 units improvement in SGRQ total score	7	4420	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [1.31, 1.70]
4.1 Aclidinium once daily	2	1560	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [1.08, 1.73]
4.2 Aclidinium twice daily	5	2860	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [1.32, 1.81]
5 Lung function: Change from baseline in trough FEV1 (L)	9	4963	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.08, 0.10]
5.1 Aclidinium once daily	3	1799	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.05, 0.09]
5.2 Aclidinium twice daily	6	3164	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.09, 0.12]
6 Lung function: Change from baseline in peak FEV1 (L)	9	4962	Mean Difference (IV, Random, 95% CI)	0.17 [0.15, 0.20]
6.1 Aclidinium once daily	3	1802	Mean Difference (IV, Random, 95% CI)	0.19 [0.12, 0.25]
6.2 Aclidinium twice daily	6	3160	Mean Difference (IV, Random, 95% CI)	0.17 [0.15, 0.19]
7 Lung function: Change from baseline in normalised FEV1 AUC 0-12 hour	7	1237	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.10, 0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Aclidinium once daily	2	131	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.08, 0.19]
7.2 Aclidinium twice daily	5	1106	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.10, 0.17]
8 Lung function: Change from baseline in trough FVC (L)	9	4963	Mean Difference (IV, Fixed, 95% CI)	0.16 [0.14, 0.18]
8.1 Aclidinium once daily	3	1799	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.10, 0.18]
8.2 Aclidinium twice daily	6	3164	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.14, 0.20]
9 Lung function: Change from baseline in peak FVC (L)	9	4962	Mean Difference (IV, Random, 95% CI)	0.27 [0.23, 0.31]
9.1 Aclidinium once daily	3	1802	Mean Difference (IV, Random, 95% CI)	0.33 [0.23, 0.42]
9.2 Aclidinium twice daily	6	3160	Mean Difference (IV, Random, 95% CI)	0.25 [0.22, 0.28]
10 Number of patients with hospital admissions due to COPD exacerbation	10	5624	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.88]
10.1 Aclidinium once daily	4	2201	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 0.99]
10.2 Aclidinium twice daily	6	3423	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 1.01]
11 Improvement in symptoms: Change from baseline in TDI focal score	8	4490	Mean Difference (IV, Random, 95% CI)	0.84 [0.50, 1.18]
11.1 Aclidinium once daily	3	1597	Mean Difference (IV, Random, 95% CI)	1.08 [0.46, 1.71]
11.2 Aclidinium twice daily	5	2893	Mean Difference (IV, Random, 95% CI)	0.72 [0.33, 1.11]
12 Number of patients who achieved ≥ 1 unit improvement in TDI focal score	8	4289	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [1.52, 1.98]
12.1 Aclidinium once daily	3	1589	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.39, 2.20]
12.2 Aclidinium twice daily	5	2700	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [1.47, 2.03]
13 Non-fatal serious adverse events	10	5651	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.14]
13.1 Aclidinium once daily	4	2227	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Aclidinium twice daily	6	3424	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.68, 1.34]
14 Withdrawals due to lack of efficacy	10	5672	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.23, 0.43]
14.1 Aclidinium once daily	4	2227	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.20, 0.47]
14.2 Aclidinium twice daily	6	3445	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.20, 0.51]
15 Withdrawals due to adverse events	10	5672	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.57, 1.01]
15.1 Aclidinium once daily	4	2227	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 1.00]
15.2 Aclidinium twice daily	6	3445	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.21]

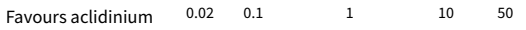
Analysis 1.1. Comparison 1 Aclidinium bromide versus placebo, Outcome 1 Total number of deaths.

Study or subgroup	Aclidinium bromide n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Aclidinium once daily					
ACCLAIM/COPD I	7/627	4/216		41.63%	0.6[0.17,2.06]
ACCLAIM/COPD II	6/600	3/204		31.36%	0.68[0.17,2.73]
Maltais 2011	0/86	0/95			Not estimable
Subtotal (95% CI)	**1313**	**515**		**72.99%**	**0.63[0.25,1.6]**
Total events: 13 (Aclidinium bromide), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
1.1.2 Aclidinium twice daily					
ACCORD COPD I	1/374	0/186		4.7%	1.5[0.06,36.95]
ACCORD COPD II	1/360	1/182		9.37%	0.5[0.03,8.11]
ACLIFORM	0/385	0/194			Not estimable
ATTAIN	2/546	1/273		9.4%	1[0.09,11.08]
AUGMENT COPD	3/337	0/331		3.53%	6.94[0.36,134.83]
Beier 2013	0/171	0/85			Not estimable
Subtotal (95% CI)	**2173**	**1251**		**27.01%**	**1.69[0.46,6.21]**
Total events: 7 (Aclidinium bromide), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.79, df=3(P=0.62); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**3486**	**1766**		**100%**	**0.92[0.43,1.94]**
Total events: 20 (Aclidinium bromide), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.7, df=5(P=0.75); I^2=0%					
Test for overall effect: Z=0.22(P=0.82)					
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.5%					



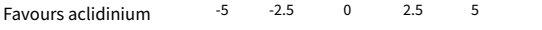
Analysis 1.2. Comparison 1 Aclidinium bromide versus placebo, Outcome 2 Number of patients with exacerbations requiring steroids, antibiotics or both.

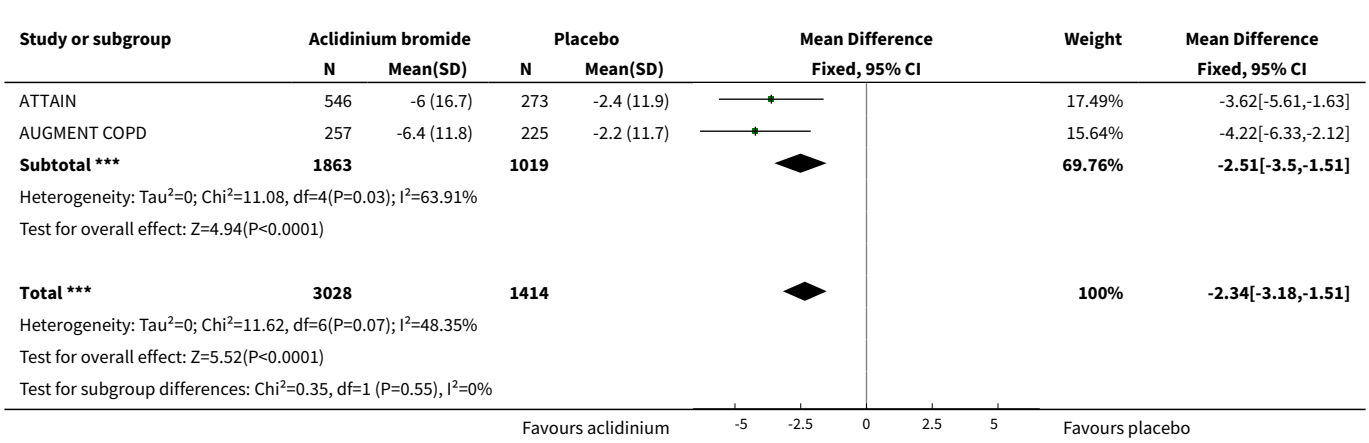
Study or subgroup	Aclidinium bromide n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Aclidinium once daily					
ACCLAIM/COPD I	136/616	44/210		18.79%	1.07[0.73,1.57]
ACCLAIM/COPD II	175/594	66/201		25.56%	0.85[0.61,1.2]
Chanez 2010	3/335	0/64		0.3%	1.36[0.07,26.6]
Maltais 2011	1/86	3/95		1.04%	0.36[0.04,3.54]
Subtotal (95% CI)	**1631**	**570**		**45.69%**	**0.93[0.73,1.2]**
Total events: 315 (Aclidinium bromide), 113 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=3(P=0.69); I^2=0%					
Test for overall effect: Z=0.53(P=0.6)					
1.2.2 Aclidinium twice daily					
ACCORD COPD I	23/374	15/185		6.92%	0.74[0.38,1.46]
ACCORD COPD II	21/359	14/182		6.43%	0.75[0.37,1.5]
ACLIFORM	28/385	17/194		7.7%	0.82[0.44,1.53]
ATTAIN	64/546	35/273		15.14%	0.9[0.58,1.4]
AUGMENT COPD	48/337	51/332		16.19%	0.92[0.6,1.4]
Beier 2013	2/171	4/85		1.94%	0.24[0.04,1.34]
Subtotal (95% CI)	**2172**	**1251**		**54.31%**	**0.83[0.66,1.05]**
Total events: 186 (Aclidinium bromide), 136 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.55, df=5(P=0.77); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					
Total (95% CI)	**3803**	**1821**		**100%**	**0.88[0.74,1.04]**
Total events: 501 (Aclidinium bromide), 249 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.45, df=9(P=0.88); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					
Test for subgroup differences: Chi^2=0.44, df=1 (P=0.51), I^2=0%					



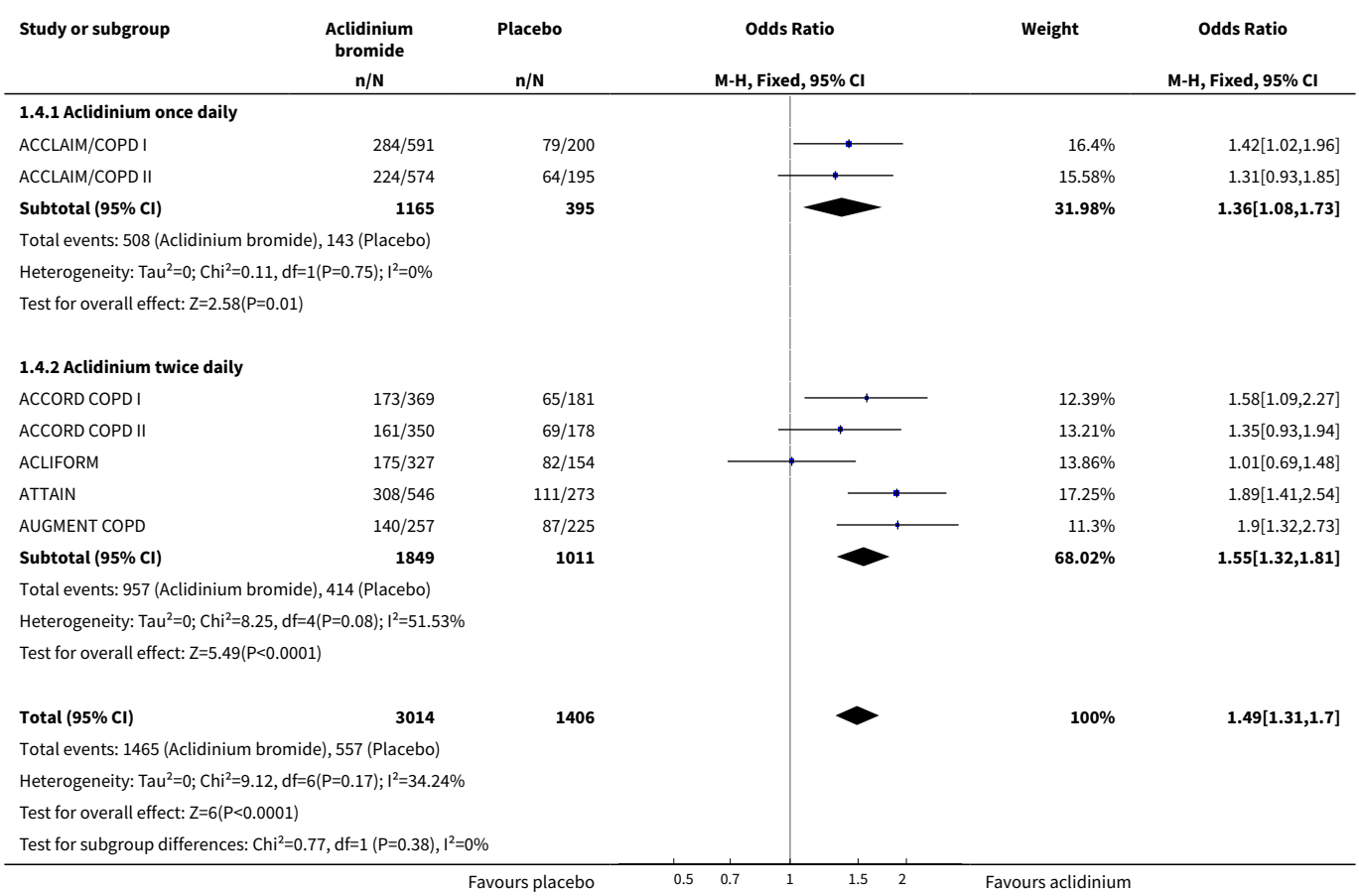
Analysis 1.3. Comparison 1 Aclidinium bromide versus placebo, Outcome 3 Quality of life: change from baseline in SGRQ total score.

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.3.1 Aclidinium once daily							
ACCLAIM/COPD I	591	-4.6 (16.4)	200	-3.1 (15.3)		11.13%	-1.53[-4.02,0.96]
ACCLAIM/COPD II	574	-3.5 (11.9)	195	-1.3 (11.6)		19.11%	-2.21[-4.12,-0.31]
Subtotal ***	**1165**		**395**			**30.24%**	**-1.96[-3.47,-0.45]**
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%							
Test for overall effect: Z=2.54(P=0.01)							
1.3.2 Aclidinium twice daily							
ACCORD COPD I	374	-4.7 (14.7)	185	-2 (10.5)		15.39%	-2.63[-4.75,-0.51]
ACCORD COPD II	359	-5.7 (18.3)	182	-4.3 (13)		9.72%	-1.37[-4.04,1.29]
ACLIFORM	327	-5.8 (12.8)	154	-6.5 (12.8)		11.52%	0.71[-1.74,3.16]





Analysis 1.4. Comparison 1 Aclidinium bromide versus placebo, Outcome 4 Quality of life: Number of patients who achieved ≥ 4 units improvement in SGRQ total score.



Analysis 1.5. Comparison 1 Aclidinium bromide versus placebo, Outcome 5 Lung function: Change from baseline in trough FEV1 (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Aclidinium once daily							
ACCLAIM/COPD I	616	-0 (0.3)	210	-0.1 (0.3)		11.02%	0.07[0.03,0.11]
ACCLAIM/COPD II	594	0 (0.2)	201	-0 (0.2)		18.85%	0.06[0.03,0.09]
Maltais 2011	86	0.1 (0.2)	92	-0 (0.2)		7.57%	0.1[0.05,0.15]
Subtotal ***	**1296**		**503**			**37.43%**	**0.07[0.05,0.09]**
Heterogeneity: Tau^2=0; Chi^2=1.79, df=2(P=0.41); I^2=0%							
Test for overall effect: Z=6.13(P<0.0001)							
1.5.2 Aclidinium twice daily							
ACCORD COPD I	374	0.1 (0.3)	185	-0 (0.2)		10.89%	0.11[0.06,0.15]
ACCORD COPD II	359	0.1 (0.3)	182	-0 (0.2)		10.53%	0.06[0.02,0.1]
ACLIFORM	332	0.1 (0.2)	159	-0.1 (0.2)		10.47%	0.12[0.07,0.16]
ATTAIN	546	0 (0.4)	273	-0.1 (0.3)		9.57%	0.11[0.07,0.16]
AUGMENT COPD	266	0.1 (0.2)	232	-0 (0.2)		15.66%	0.1[0.07,0.14]
Beier 2013	171	0 (0.2)	85	-0.1 (0.2)		5.44%	0.14[0.08,0.2]
Subtotal ***	**2048**		**1116**			**62.57%**	**0.1[0.09,0.12]**
Heterogeneity: Tau^2=0; Chi^2=6.04, df=5(P=0.3); I^2=17.23%							
Test for overall effect: Z=11.65(P<0.0001)							
Total ***	**3344**		**1619**			**100%**	**0.09[0.08,0.1]**
Heterogeneity: Tau^2=0; Chi^2=13.03, df=8(P=0.11); I^2=38.62%							
Test for overall effect: Z=12.97(P<0.0001)							
Test for subgroup differences: Chi^2=5.2, df=1 (P=0.02), I^2=80.76%							

Analysis 1.6. Comparison 1 Aclidinium bromide versus placebo, Outcome 6 Lung function: Change from baseline in peak FEV1 (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Aclidinium once daily							
ACCLAIM/COPD I	616	0.2 (0.3)	210	0 (0.3)		11.19%	0.16[0.12,0.21]
ACCLAIM/COPD II	594	0.2 (0.2)	201	0 (0.2)		13.9%	0.15[0.11,0.18]
Maltais 2011	86	0.3 (0.2)	95	-0 (0.2)		9.55%	0.26[0.21,0.31]
Subtotal ***	**1296**		**506**			**34.65%**	**0.19[0.12,0.25]**
Heterogeneity: Tau^2=0; Chi^2=12.88, df=2(P=0); I^2=84.47%							
Test for overall effect: Z=5.68(P<0.0001)							
1.6.2 Aclidinium twice daily							
ACCORD COPD I	374	0.2 (0.3)	185	0.1 (0.2)		11.49%	0.17[0.12,0.21]
ACCORD COPD II	359	0.2 (0.3)	182	0.1 (0.2)		10.31%	0.12[0.07,0.17]
ACLIFORM	330	0.2 (0.2)	157	0 (0.2)		11.32%	0.18[0.13,0.22]
ATTAIN	546	0.2 (0.4)	273	0 (0.3)		10.89%	0.2[0.15,0.24]
AUGMENT COPD	266	0.2 (0.2)	232	0 (0.2)		13.12%	0.17[0.14,0.21]
Beier 2013	171	0.2 (0.2)	85	0.1 (0.2)		8.21%	0.18[0.12,0.24]
Subtotal ***	**2046**		**1114**			**65.35%**	**0.17[0.15,0.19]**
Heterogeneity: Tau^2=0; Chi^2=5.3, df=5(P=0.38); I^2=5.57%							

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=17.19(P<0.0001)							
Total ***	**3342**		**1620**			**100%**	**0.17[0.15,0.2]**
Heterogeneity: Tau²=0; Chi²=18.24, df=8(P=0.02); I²=56.14%							
Test for overall effect: Z=14.92(P<0.0001)							
Test for subgroup differences: Chi²=0.24, df=1 (P=0.62), I²=0%							

Favours placebo -0.2 -0.1 0 0.1 0.2 Favours aclidinium

Analysis 1.7. Comparison 1 Aclidinium bromide versus placebo, Outcome 7 Lung function: Change from baseline in normalised FEV1 AUC 0-12 hour.

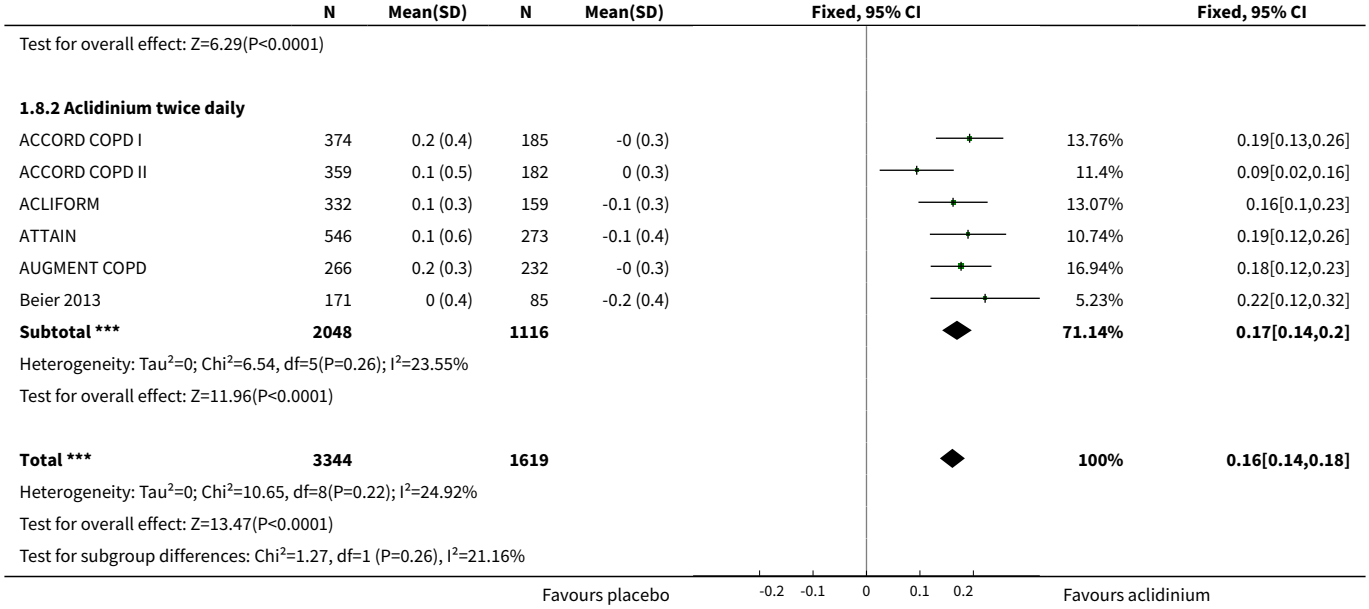
Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 Aclidinium once daily							
ACCLAIM/COPD I	28	0.1 (0.2)	9	-0.1 (0.3)		2.59%	0.18[-0.02,0.37]
ACCLAIM/COPD II	67	0.1 (0.2)	27	-0 (0.1)		29.42%	0.13[0.07,0.18]
Subtotal ***	**95**		**36**			**32%**	**0.13[0.08,0.19]**
Heterogeneity: Tau²=0; Chi²=0.22, df=1(P=0.64); I²=0%							
Test for overall effect: Z=4.73(P<0.0001)							
1.7.2 Aclidinium twice daily							
ACCORD COPD I	147	0.1 (0.3)	73	-0 (0.2)		19.88%	0.13[0.06,0.2]
ACCORD COPD II	359	0.1 (0.6)	182	-0 (0.4)		12.33%	0.11[0.03,0.2]
ACLIFORM	73	0.1 (0.2)	37	-0.1 (0.2)		12.15%	0.16[0.07,0.25]
ATTAIN	117	0.1 (0.3)	46	-0 (0.2)		10.71%	0.12[0.03,0.21]
AUGMENT COPD	36	0.1 (0.2)	36	-0.1 (0.2)		12.93%	0.14[0.06,0.23]
Subtotal ***	**732**		**374**			**68%**	**0.13[0.1,0.17]**
Heterogeneity: Tau²=0; Chi²=0.61, df=4(P=0.96); I²=0%							
Test for overall effect: Z=6.94(P<0.0001)							
Total ***	**827**		**410**			**100%**	**0.13[0.1,0.16]**
Heterogeneity: Tau²=0; Chi²=0.83, df=6(P=0.99); I²=0%							
Test for overall effect: Z=8.4(P<0.0001)							
Test for subgroup differences: Chi²=0, df=1 (P=0.98), I²=0%							

Favours placebo -0.2 -0.1 0 0.1 0.2 Favours aclidinium

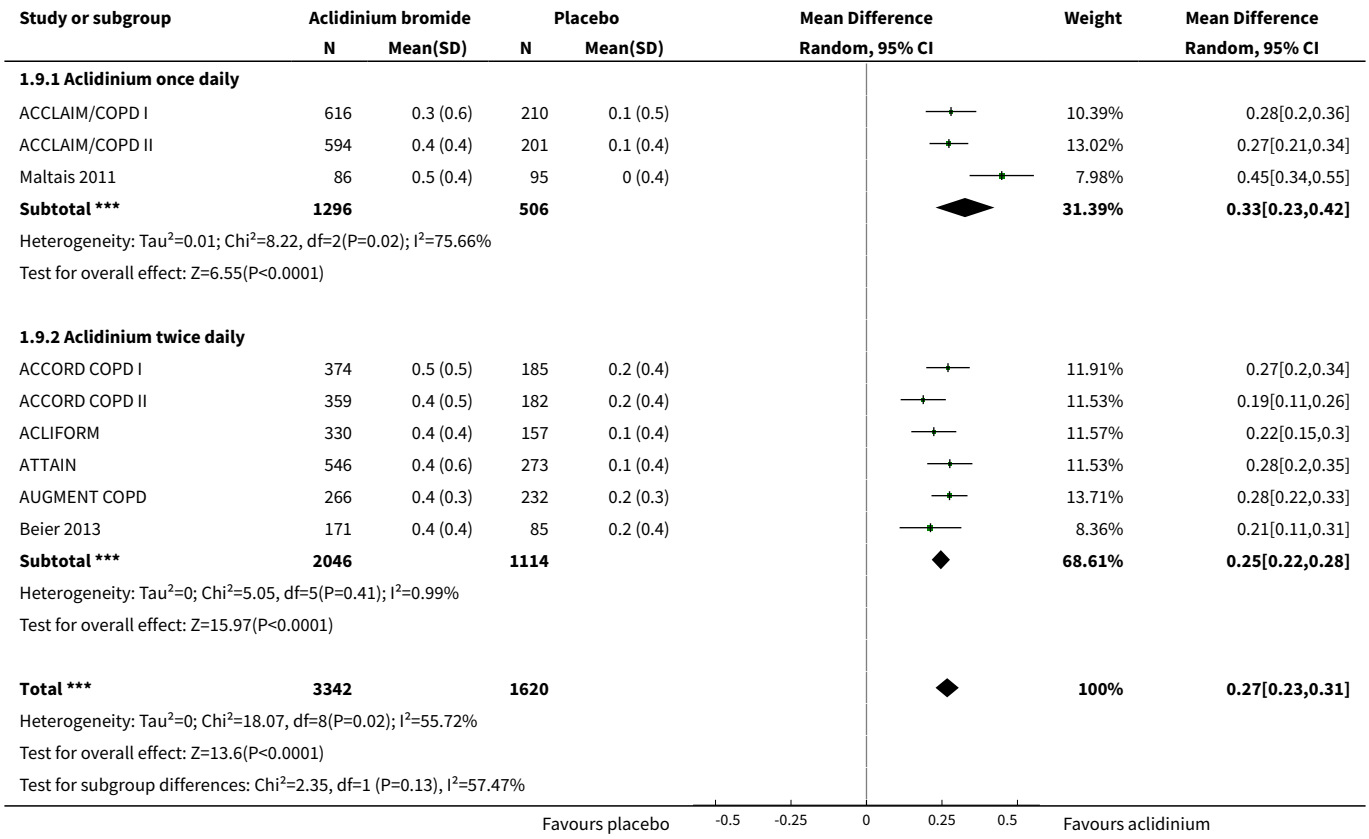
Analysis 1.8. Comparison 1 Aclidinium bromide versus placebo, Outcome 8 Lung function: Change from baseline in trough FVC (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 Aclidinium once daily							
ACCLAIM/COPD I	616	0 (0.5)	210	-0.1 (0.5)		9.31%	0.13[0.06,0.21]
ACCLAIM/COPD II	594	0.1 (0.4)	201	-0 (0.4)		14.46%	0.12[0.05,0.18]
Maltais 2011	86	0.2 (0.3)	92	-0 (0.4)		5.09%	0.22[0.12,0.32]
Subtotal ***	**1296**		**503**			**28.86%**	**0.14[0.1,0.18]**
Heterogeneity: Tau²=0; Chi²=2.85, df=2(P=0.24); I²=29.74%							

Favours placebo -0.2 -0.1 0 0.1 0.2 Favours aclidinium

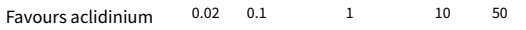


Analysis 1.9. Comparison 1 Aclidinium bromide versus placebo, Outcome 9 Lung function: Change from baseline in peak FVC (L).



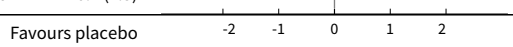
Analysis 1.10. Comparison 1 Aclidinium bromide versus placebo, Outcome 10 Number of patients with hospital admissions due to COPD exacerbation.

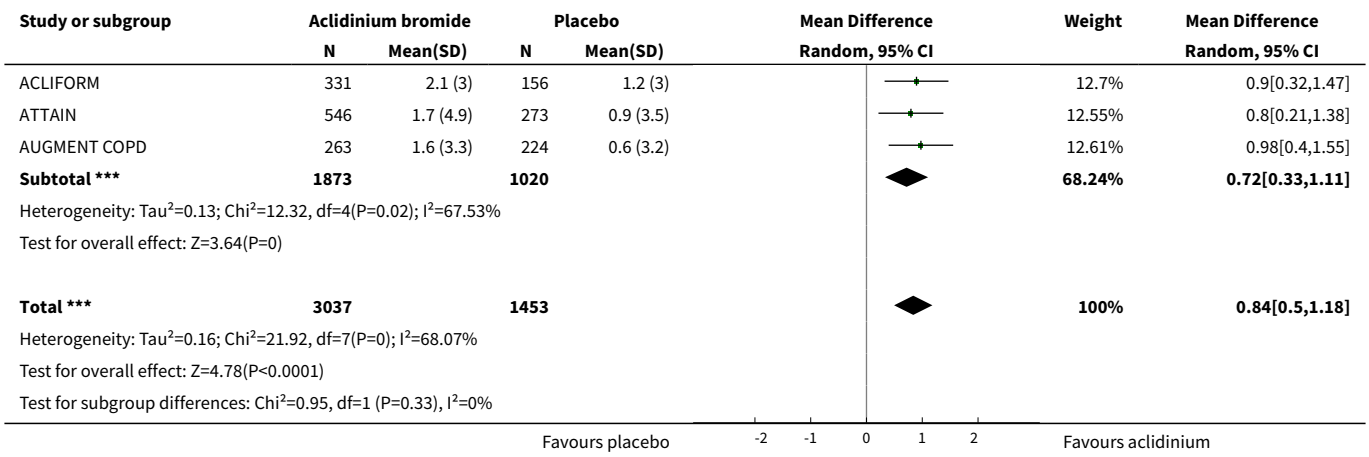
Study or subgroup	Aclidinium bromide n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.10.1 Aclidinium once daily					
ACCLAIM/COPD I	40/616	14/210		21.94%	0.97[0.52,1.83]
ACCLAIM/COPD II	36/594	23/201		36.28%	0.5[0.29,0.87]
Chanez 2010	2/335	0/64		0.93%	0.97[0.05,20.38]
Maltais 2011	1/86	3/95		3.17%	0.36[0.04,3.54]
Subtotal (95% CI)	**1631**	**570**		**62.32%**	**0.67[0.45,0.99]**
Total events: 79 (Aclidinium bromide), 40 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=3(P=0.43); I^2=0%					
Test for overall effect: Z=2(P=0.05)					
1.10.2 Aclidinium twice daily					
ACCORD COPD I	3/374	1/185		1.49%	1.49[0.15,14.4]
ACCORD COPD II	6/359	5/182		7.33%	0.6[0.18,2]
ACLIFORM	6/385	5/194		7.36%	0.6[0.18,1.99]
ATTAIN	5/546	10/273		14.85%	0.24[0.08,0.72]
AUGMENT COPD	7/337	6/332		6.65%	1.15[0.38,3.47]
Beier 2013	0/171	0/85			Not estimable
Subtotal (95% CI)	**2172**	**1251**		**37.68%**	**0.59[0.35,1.01]**
Total events: 27 (Aclidinium bromide), 27 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.63, df=4(P=0.33); I^2=13.66%					
Test for overall effect: Z=1.91(P=0.06)					
Total (95% CI)	**3803**	**1821**		**100%**	**0.64[0.46,0.88]**
Total events: 106 (Aclidinium bromide), 67 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.5, df=8(P=0.48); I^2=0%					
Test for overall effect: Z=2.76(P=0.01)					
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%					



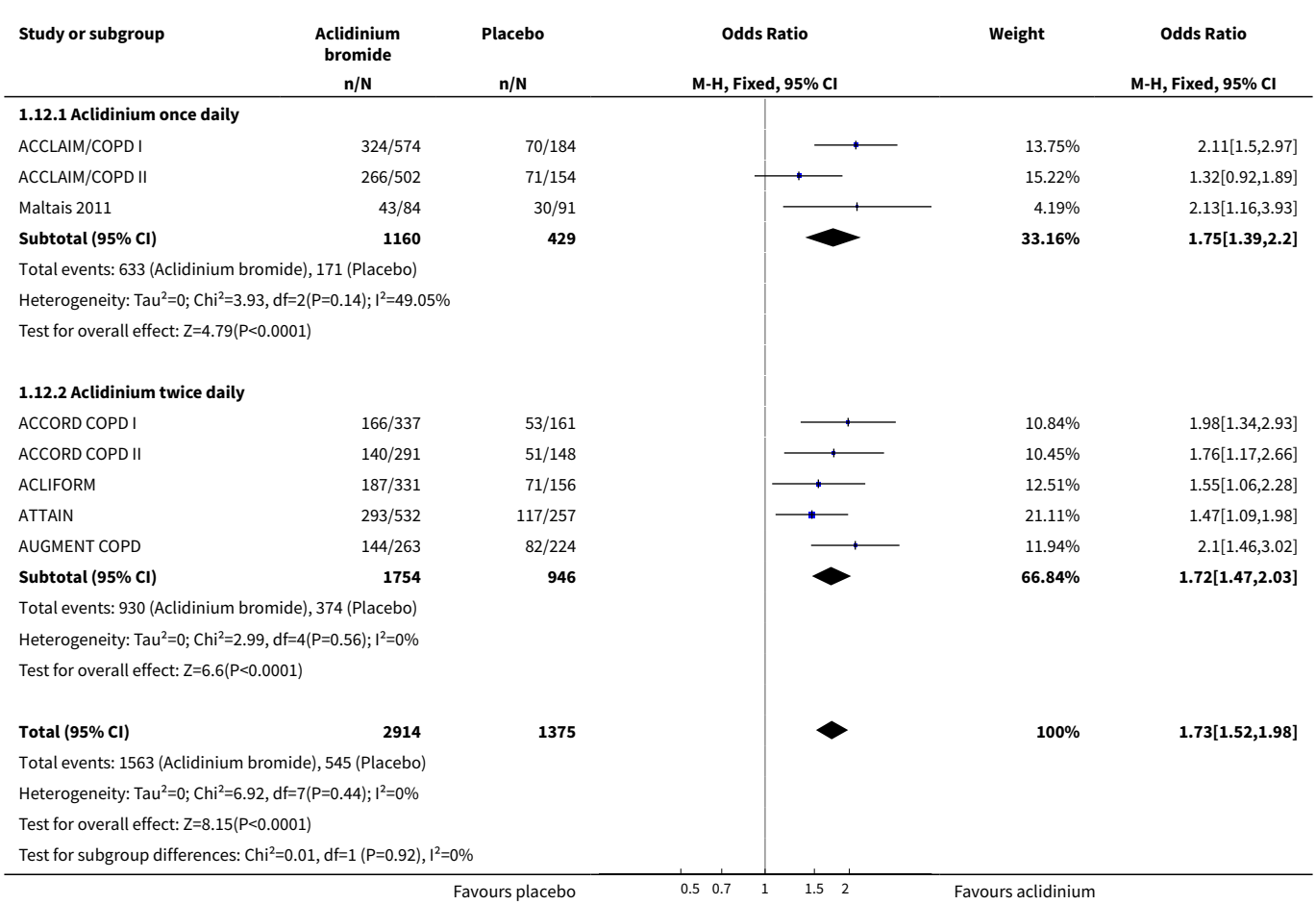
Analysis 1.11. Comparison 1 Aclidinium bromide versus placebo, Outcome 11 Improvement in symptoms: Change from baseline in TDI focal score.

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Aclidinium once daily							
ACCLAIM/COPD I	575	1.8 (3.4)	187	0.6 (3.4)		12.92%	1.22[0.66,1.78]
ACCLAIM/COPD II	505	1.6 (3.6)	155	1.1 (3.6)		11.49%	0.52[-0.13,1.17]
Maltais 2011	84	1.4 (3.3)	91	-0.3 (3.4)		7.35%	1.71[0.71,2.72]
Subtotal ***	**1164**		**433**			**31.76%**	**1.08[0.46,1.71]**
Heterogeneity: Tau^2=0.17; Chi^2=4.57, df=2(P=0.1); I^2=56.28%							
Test for overall effect: Z=3.41(P=0)							
1.11.2 Aclidinium twice daily							
ACCORD COPD I	374	1.5 (3.9)	185	0.5 (2.7)		12.99%	0.95[0.4,1.51]
ACCORD COPD II	359	0.3 (1.9)	182	0.1 (1.3)		17.39%	0.2[-0.08,0.48]



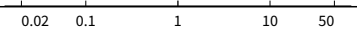


Analysis 1.12. Comparison 1 Aclidinium bromide versus placebo, Outcome 12 Number of patients who achieved ≥ 1 unit improvement in TDI focal score.



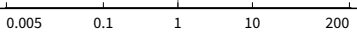
Analysis 1.13. Comparison 1 Aclidinium bromide versus placebo, Outcome 13 Non-fatal serious adverse events.

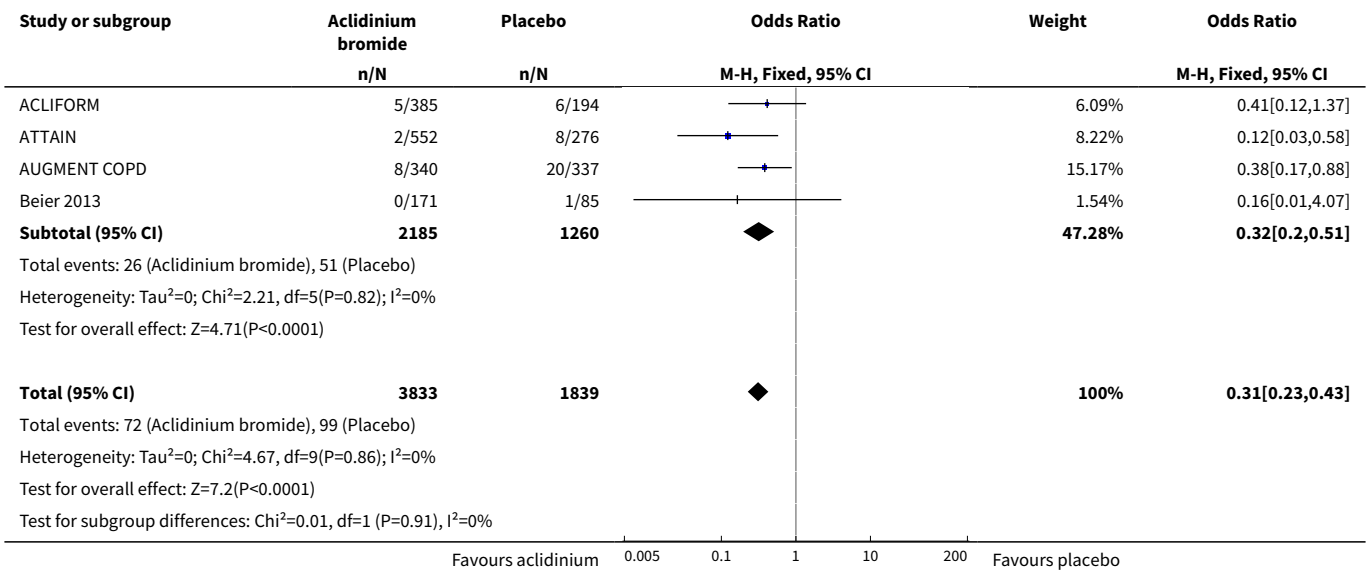
Study or subgroup	Aclidinium bromide n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.13.1 Aclidinium once daily					
ACCLAIM/COPD I	50/627	22/216		22.93%	0.76[0.45,1.29]
ACCLAIM/COPD II	62/600	23/204		23.44%	0.91[0.55,1.51]
Chanez 2010	1/335	0/64		0.64%	0.58[0.02,14.36]
Maltais 2011	2/86	3/95		2.12%	0.73[0.12,4.48]
Subtotal (95% CI)	**1648**	**579**		**49.13%**	**0.83[0.58,1.18]**
Total events: 115 (Aclidinium bromide), 48 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=3(P=0.96); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					
1.13.2 Aclidinium twice daily					
ACCORD COPD I	14/374	4/186		3.92%	1.77[0.57,5.45]
ACCORD COPD II	19/360	12/182		11.5%	0.79[0.37,1.66]
ACLIFORM	16/385	12/194		11.65%	0.66[0.3,1.42]
ATTAIN	27/546	15/273		14.48%	0.89[0.47,1.71]
AUGMENT COPD	14/337	12/331		8.84%	1.15[0.52,2.53]
Beier 2013	3/171	0/85		0.5%	3.55[0.18,69.55]
Subtotal (95% CI)	**2173**	**1251**		**50.87%**	**0.95[0.68,1.34]**
Total events: 93 (Aclidinium bromide), 55 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.31, df=5(P=0.65); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					
Total (95% CI)	**3821**	**1830**		**100%**	**0.89[0.7,1.14]**
Total events: 208 (Aclidinium bromide), 103 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.82, df=9(P=0.92); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Chi^2=0.32, df=1 (P=0.57), I^2=0%					



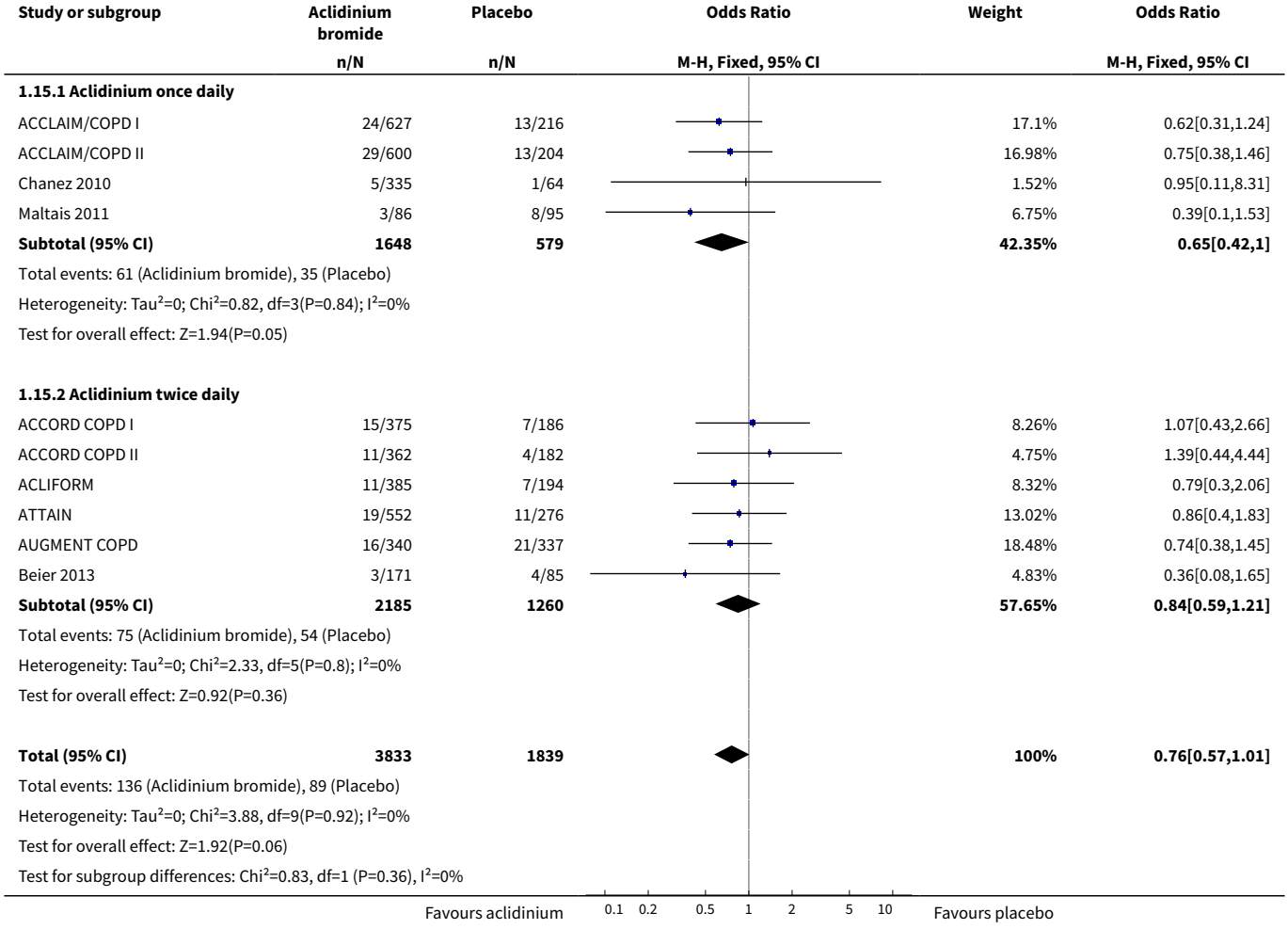
Analysis 1.14. Comparison 1 Aclidinium bromide versus placebo, Outcome 14 Withdrawals due to lack of efficacy.

Study or subgroup	Aclidinium bromide n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.14.1 Aclidinium once daily					
ACCLAIM/COPD I	12/627	8/216		9.03%	0.51[0.2,1.26]
ACCLAIM/COPD II	34/600	36/204		39.19%	0.28[0.17,0.46]
Chanez 2010	0/335	1/64		1.94%	0.06[0,1.57]
Maltais 2011	0/86	3/95		2.56%	0.15[0.01,3]
Subtotal (95% CI)	**1648**	**579**		**52.72%**	**0.31[0.2,0.47]**
Total events: 46 (Aclidinium bromide), 48 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.45, df=3(P=0.48); I^2=0%					
Test for overall effect: Z=5.49(P<0.0001)					
1.14.2 Aclidinium twice daily					
ACCORD COPD I	6/375	10/186		10.17%	0.29[0.1,0.8]
ACCORD COPD II	5/362	6/182		6.09%	0.41[0.12,1.36]





Analysis 1.15. Comparison 1 Aclidinium bromide versus placebo, Outcome 15 Withdrawals due to adverse events.



Comparison 2. Aclidinium bromide versus long-acting muscarinic antagonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total number of deaths	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of patients with exacerbations requiring steroids, antibiotics or both	2	729	Odds Ratio (M-H, Fixed, 95% CI)	2.64 [0.31, 22.18]
3 Lung function: Change from baseline in trough FEV1 (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Lung function: Change from baseline in peak FEV1 (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Lung function: Change from baseline in trough FVC (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Lung function: Change from baseline in peak FVC (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Number of patients with hospital admissions due to COPD exacerbation	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.07, 4.11]
8 Non-fatal serious adverse events	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.17, 2.65]
9 Withdrawals due to lack of efficacy	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Withdrawals due to adverse events	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.26, 3.42]

Analysis 2.1. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 1 Total number of deaths.

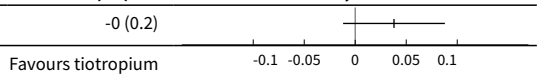
Study or subgroup	Aclidinium bromide n/N	Tiotropium bromide n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Beier 2013	0/171	0/158		Not estimable

Analysis 2.2. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 2 Number of patients with exacerbations requiring steroids, antibiotics or both.

Study or subgroup	Aclidinium bromide n/N	Tiotropium bromide n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Beier 2013	2/171	0/158		38.24%	4.68[0.22,98.14]
Chanez 2010	3/335	0/65		61.76%	1.38[0.07,27.01]
Total (95% CI)	**506**	**223**		**100%**	**2.64[0.31,22.18]**
Total events: 5 (Aclidinium bromide), 0 (Tiotropium bromide)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=0.89(P=0.37)					

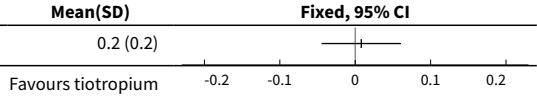
Analysis 2.3. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 3 Lung function: Change from baseline in trough FEV1 (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Tiotropium bromide N	Tiotropium bromide Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Beier 2013	171	0 (0.2)	158	-0 (0.2)		0.04[-0.01,0.09]



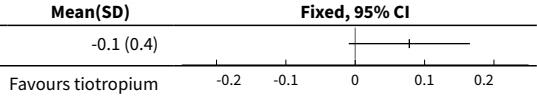
Analysis 2.4. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 4 Lung function: Change from baseline in peak FEV1 (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Tiotropium bromide N	Tiotropium bromide Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Beier 2013	171	0.2 (0.2)	158	0.2 (0.2)		0.01[-0.04,0.06]



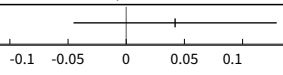
Analysis 2.5. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 5 Lung function: Change from baseline in trough FVC (L).

Study or subgroup	Aclidinium bromide N	Aclidinium bromide Mean(SD)	Tiotropium bromide N	Tiotropium bromide Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Beier 2013	171	0 (0.4)	158	-0.1 (0.4)		0.08[-0.01,0.17]



Analysis 2.6. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 6 Lung function: Change from baseline in peak FVC (L).

Study or subgroup	Aclidinium bromide		Tiotropium bromide		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Beier 2013	171	0.4 (0.4)	158	0.3 (0.4)		0.04[-0.05,0.13]

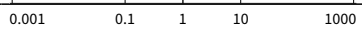


Analysis 2.7. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 7 Number of patients with hospital admissions due to COPD exacerbation.

Study or subgroup	Aclidinium bromide	Tiotropium bromide	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Beier 2013	0/171	1/158		65.2%	0.31[0.01,7.57]
Chanez 2010	2/335	0/65		34.8%	0.98[0.05,20.69]
Total (95% CI)	**506**	**223**		**100%**	**0.54[0.07,4.11]**
Total events: 2 (Aclidinium bromide), 1 (Tiotropium bromide)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.59(P=0.55)					

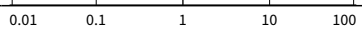
Analysis 2.8. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 8 Non-fatal serious adverse events.

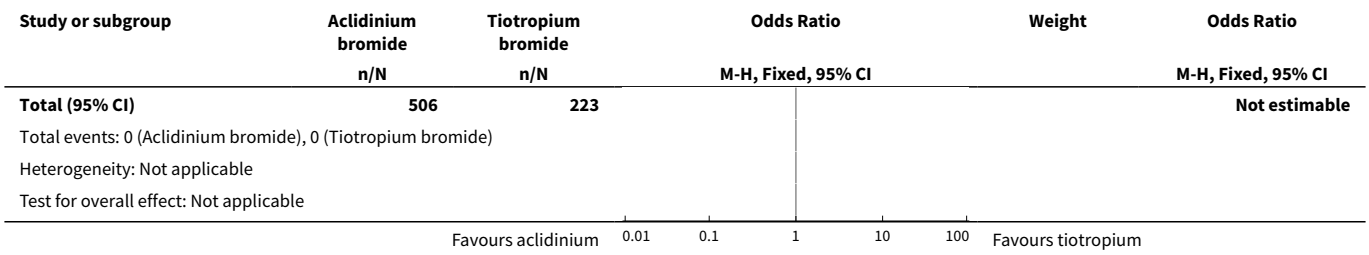
Study or subgroup	Aclidinium bromide	Tiotropium bromide	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Beier 2013	3/171	4/158		83.08%	0.69[0.15,3.12]
Chanez 2010	1/335	0/65		16.92%	0.59[0.02,14.58]
Total (95% CI)	**506**	**223**		**100%**	**0.67[0.17,2.65]**
Total events: 4 (Aclidinium bromide), 4 (Tiotropium bromide)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					



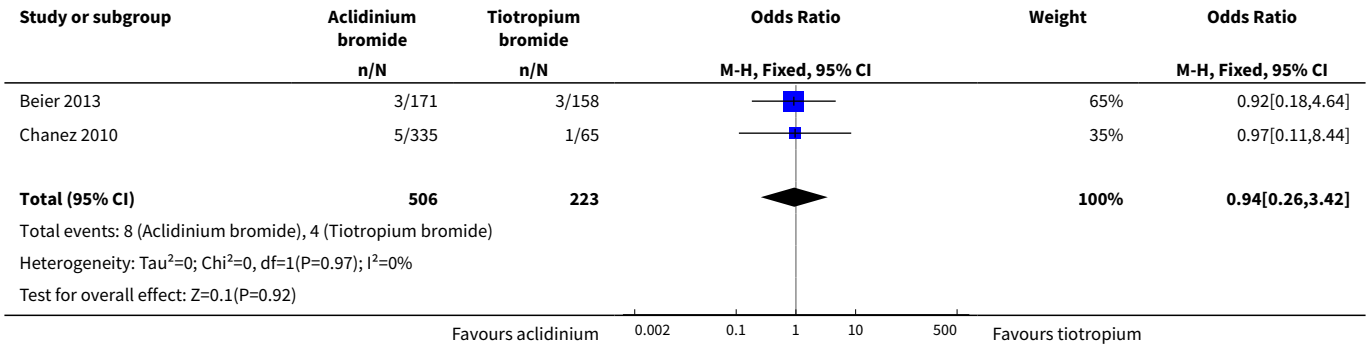
Analysis 2.9. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 9 Withdrawals due to lack of efficacy.

Study or subgroup	Aclidinium bromide	Tiotropium bromide	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Beier 2013	0/171	0/158			Not estimable
Chanez 2010	0/335	0/65			Not estimable





Analysis 2.10. Comparison 2 Aclidinium bromide versus long-acting muscarinic antagonist, Outcome 10 Withdrawals due to adverse events.



Comparison 4. Adverse events

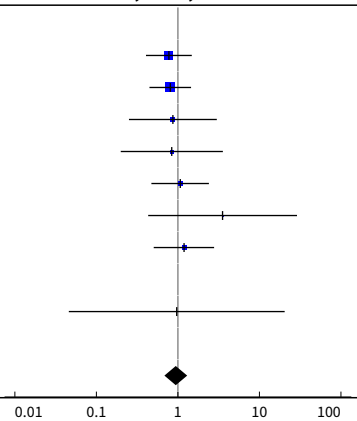
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiac events	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 vs placebo	10	5651	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.30]
1.2 vs tiotropium bromide	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.06, 2.45]
2 Dry mouth	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 vs placebo	10	5651	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.55, 1.95]
2.2 vs tiotropium bromide	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.13, 1.20]
3 Constipation	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 vs placebo	7	4252	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.59, 1.99]
3.2 vs tiotropium bromide	1	329	Odds Ratio (M-H, Fixed, 95% CI)	2.79 [0.11, 68.96]
4 Cerebrovascular events	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

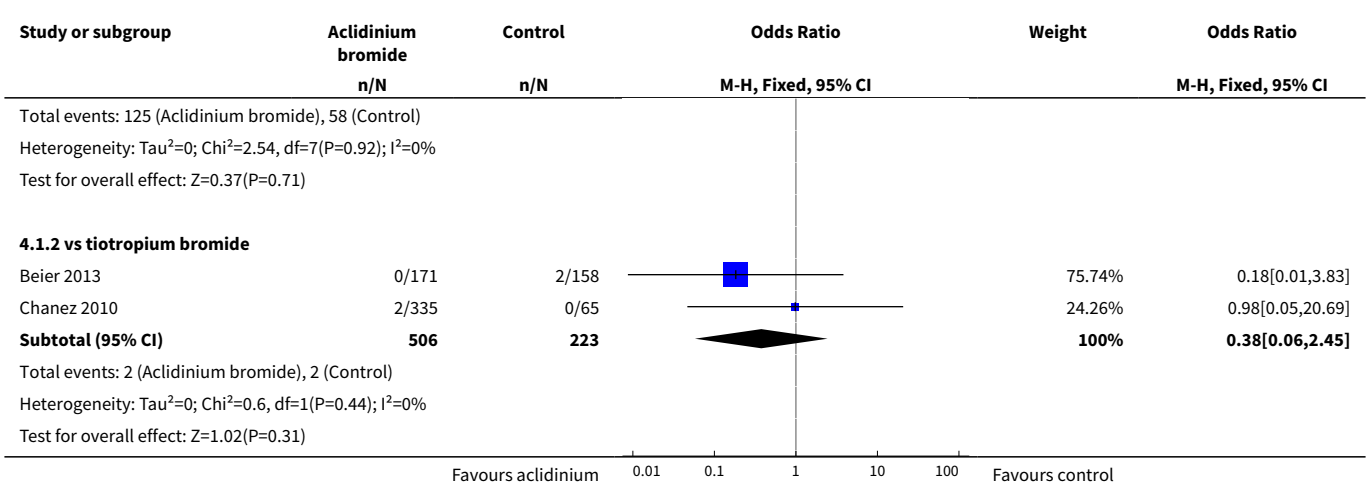
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 vs placebo	9	5252	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.33]
4.2 vs tiotropium bromide	1	329	Odds Ratio (M-H, Fixed, 95% CI)	2.79 [0.11, 68.96]
5 Diarrhoea	7	4815	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.96, 2.20]
5.1 vs placebo once daily	2	1647	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [1.14, 4.74]
5.2 vs placebo twice daily	5	3168	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.63, 1.78]
6 Nasopharyngitis	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 vs placebo	8	4710	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.95, 1.52]
6.2 vs tiotropium bromide	1	329	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.50, 3.29]
7 Headache	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 vs placebo	10	5651	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.98, 1.50]
7.2 vs tiotropium bromide	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.33, 1.60]
8 Cough	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 vs placebo	10	5651	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.55]
8.2 vs tiotropium bromide	2	729	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.16, 1.56]
9 Hypertension	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 vs placebo	7	4654	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.22]
9.2 vs tiotropium bromide	1	400	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.07, 27.01]
10 Respiratory tract infections	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 vs placebo	6	3474	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.77, 1.34]
10.2 vs tiotropium bromide	1	400	Odds Ratio (M-H, Fixed, 95% CI)	2.58 [0.14, 46.44]
11 Urinary tract infections	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 vs placebo	9	5395	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 vs tiotropium bromide	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.05, 20.69]
12 Fatigue	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 vs placebo	7	4395	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.03]
12.2 vs tiotropium bromide	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.06]
13 Dizziness	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 vs placebo	6	3853	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.49]
13.2 vs tiotropium bromide	1	400	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.06, 5.65]
14 Dyspnoea	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 vs placebo	7	4177	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.44, 1.10]
15 Arthralgia	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 vs placebo	6	4273	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [0.98, 2.78]
16 Back pain	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 vs placebo	7	4454	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.74, 1.39]
17 Oropharyngeal pain	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 vs placebo	6	3635	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.66, 1.64]

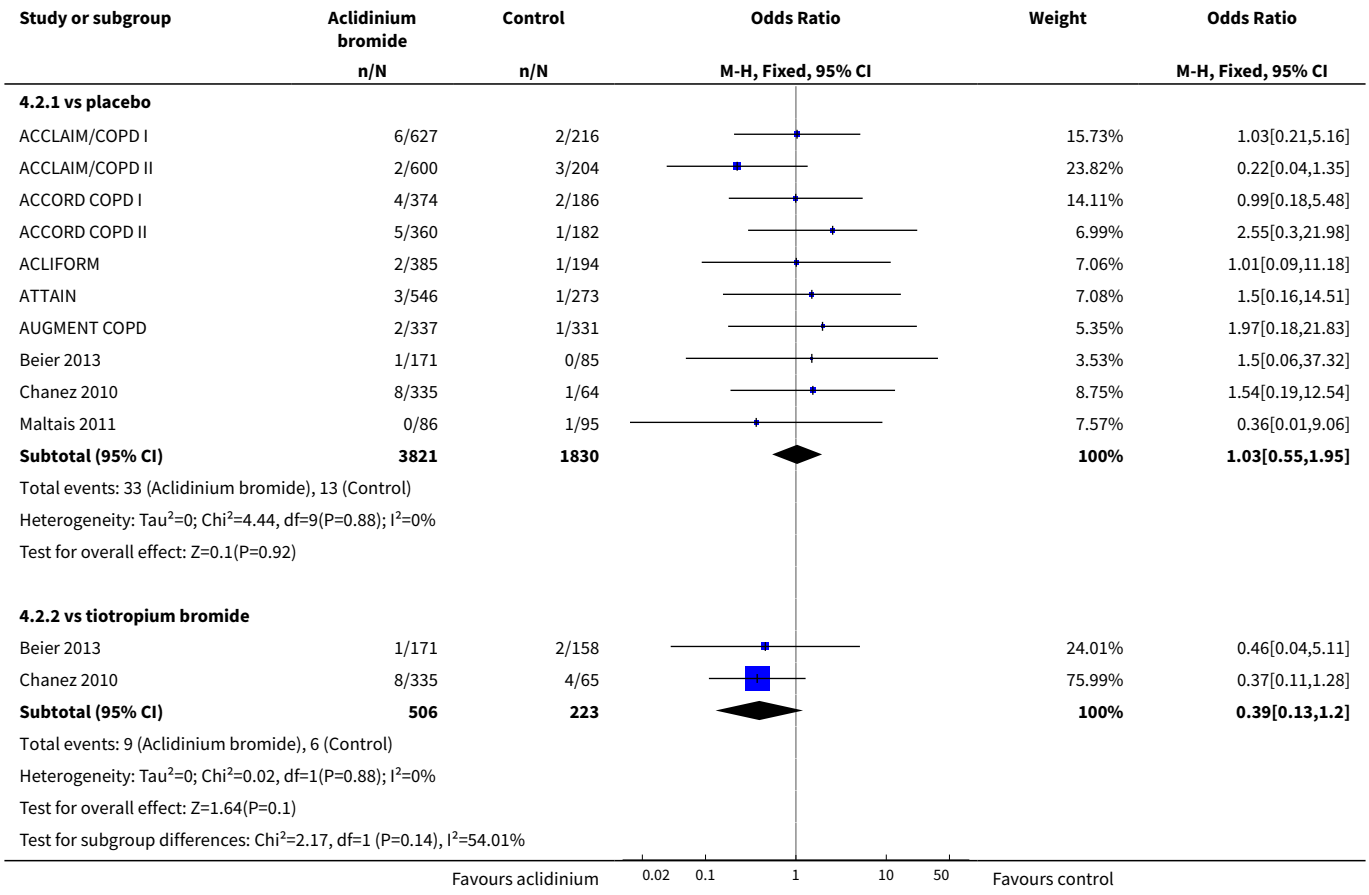
Analysis 4.1. Comparison 4 Adverse events, Outcome 1 Cardiac events.

Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 vs placebo					
ACCLAIM/COPD I	32/627	14/216		26.06%	0.78[0.41,1.48]
ACCLAIM/COPD II	41/600	17/204		31.17%	0.81[0.45,1.45]
ACCORD COPD I	7/374	4/186		6.91%	0.87[0.25,3]
ACCORD COPD II	5/360	3/182		5.18%	0.84[0.2,3.56]
ACLIFORM	19/385	9/194		15%	1.07[0.47,2.4]
ATTAIN	7/546	1/273		1.74%	3.53[0.43,28.86]
AUGMENT COPD	12/337	10/331		12.83%	1.19[0.5,2.78]
Beier 2013	0/171	0/85			Not estimable
Chanez 2010	2/335	0/64		1.1%	0.97[0.05,20.38]
Maltais 2011	0/86	0/95			Not estimable
Subtotal (95% CI)	**3821**	**1830**		**100%**	**0.94[0.68,1.3]**





Analysis 4.2. Comparison 4 Adverse events, Outcome 2 Dry mouth.

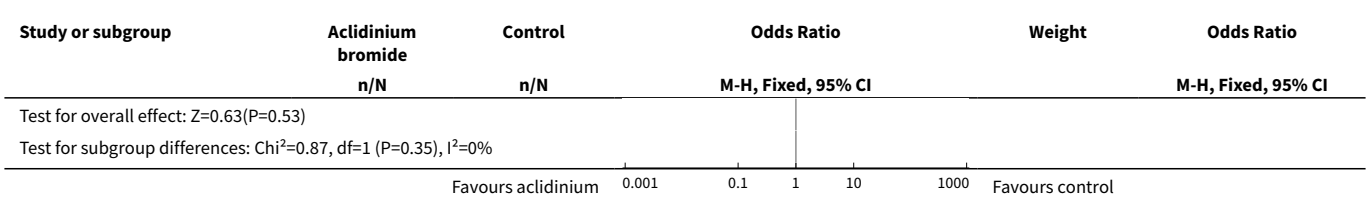


Analysis 4.3. Comparison 4 Adverse events, Outcome 3 Constipation.

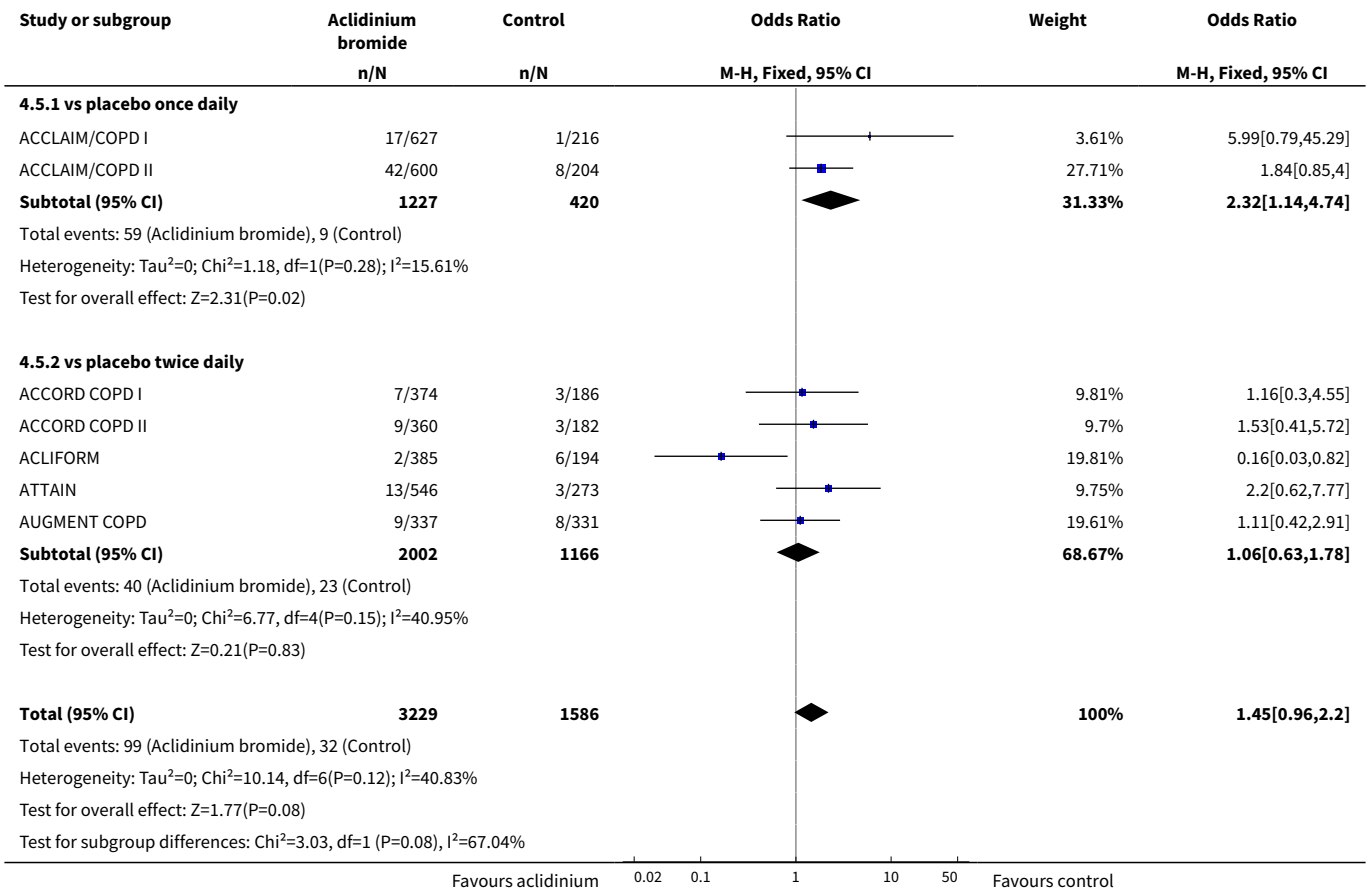
Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.1 vs placebo					
ACCLAIM/COPD I	4/627	0/216		3.61%	3.13[0.17,58.28]
ACCLAIM/COPD II	13/600	4/204		28.57%	1.11[0.36,3.44]
ACCORD COPD I	2/374	1/186		6.5%	0.99[0.09,11.04]
ACCORD COPD II	1/360	3/182		19.44%	0.17[0.02,1.61]
ACLIFORM	6/385	1/194		6.4%	3.06[0.37,25.56]
AUGMENT COPD	7/337	6/331		28.99%	1.15[0.38,3.46]
Beier 2013	1/171	1/85		6.5%	0.49[0.03,8]
Subtotal (95% CI)	**2854**	**1398**		**100%**	**1.09[0.59,1.99]**
Total events: 34 (Aclidinium bromide), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.36, df=6(P=0.63); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					
4.3.2 vs tiotropium bromide					
Beier 2013	1/171	0/158		100%	2.79[0.11,68.96]
Subtotal (95% CI)	**171**	**158**		**100%**	**2.79[0.11,68.96]**
Total events: 1 (Aclidinium bromide), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi^2=0.32, df=1 (P=0.57), I^2=0%					

Analysis 4.4. Comparison 4 Adverse events, Outcome 4 Cerebrovascular events.

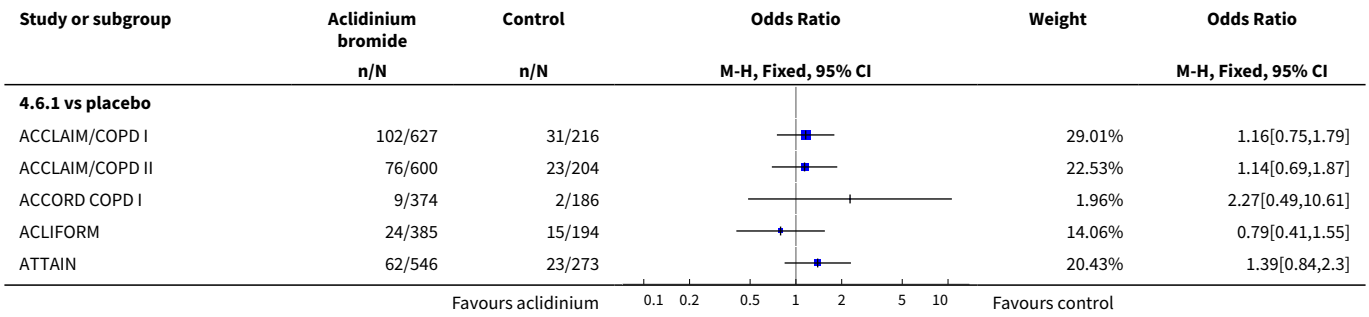
Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.4.1 vs placebo					
ACCLAIM/COPD I	1/627	1/216		10.93%	0.34[0.02,5.51]
ACCLAIM/COPD II	7/600	2/204		21.7%	1.19[0.25,5.79]
ACCORD COPD I	0/374	1/186		14.71%	0.17[0.01,4.07]
ACCORD COPD II	1/360	1/182		9.75%	0.5[0.03,8.11]
ACLIFORM	0/385	1/194		14.64%	0.17[0.01,4.13]
ATTAIN	1/546	0/273		4.89%	1.5[0.06,37.04]
AUGMENT COPD	0/337	2/331		18.53%	0.2[0.01,4.08]
Beier 2013	1/171	0/85		4.86%	1.5[0.06,37.32]
Maltais 2011	0/86	0/95			Not estimable
Subtotal (95% CI)	**3486**	**1766**		**100%**	**0.58[0.25,1.33]**
Total events: 11 (Aclidinium bromide), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.29, df=7(P=0.86); I^2=0%					
Test for overall effect: Z=1.29(P=0.2)					
4.4.2 vs tiotropium bromide					
Beier 2013	1/171	0/158		100%	2.79[0.11,68.96]
Subtotal (95% CI)	**171**	**158**		**100%**	**2.79[0.11,68.96]**
Total events: 1 (Aclidinium bromide), 0 (Control)					
Heterogeneity: Not applicable					

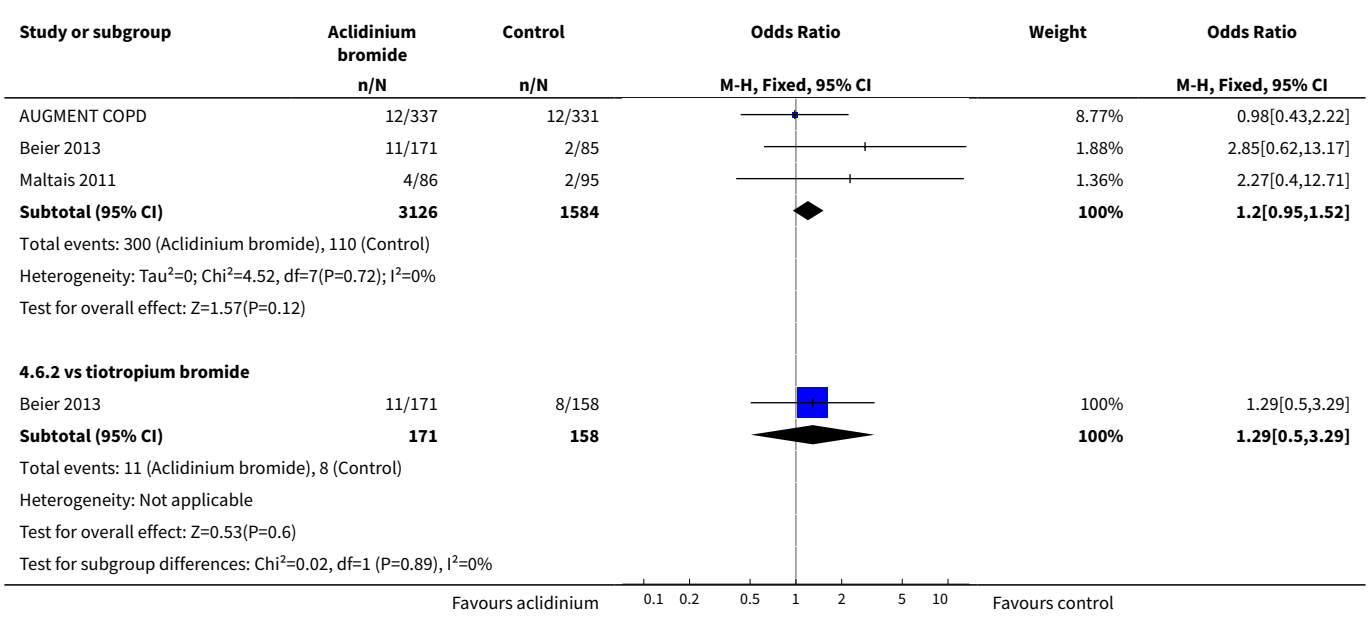


Analysis 4.5. Comparison 4 Adverse events, Outcome 5 Diarrhoea.

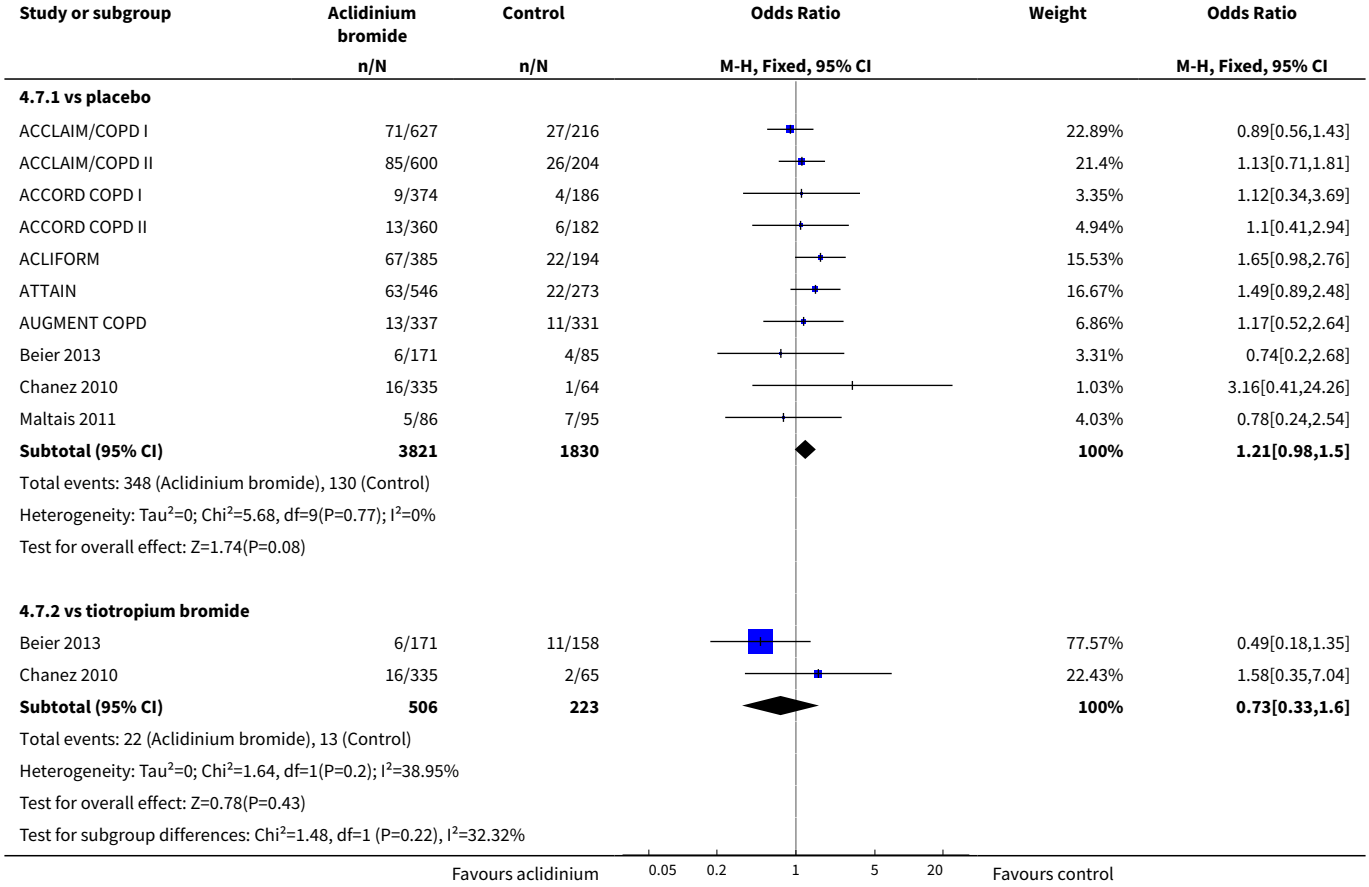


Analysis 4.6. Comparison 4 Adverse events, Outcome 6 Nasopharyngitis.



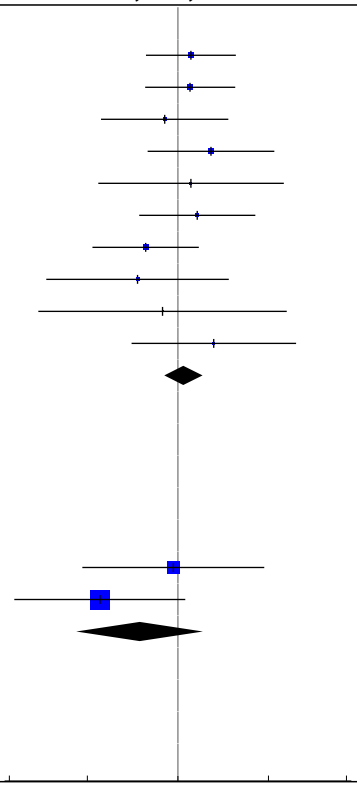


Analysis 4.7. Comparison 4 Adverse events, Outcome 7 Headache.



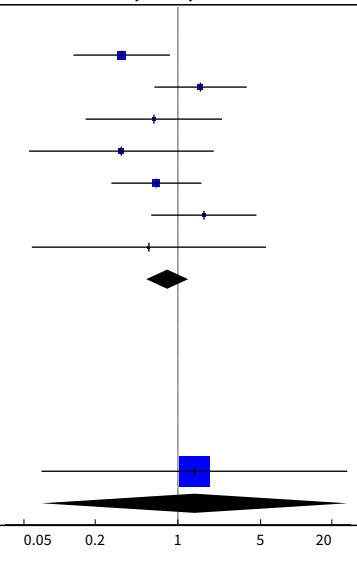
Analysis 4.8. Comparison 4 Adverse events, Outcome 8 Cough.

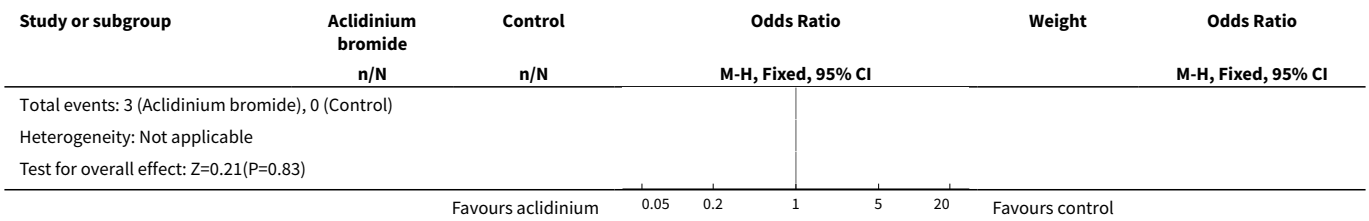
Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.8.1 vs placebo					
ACCLAIM/COPD I	29/627	8/216		17.84%	1.26[0.57,2.8]
ACCLAIM/COPD II	29/600	8/204		17.86%	1.24[0.56,2.77]
ACCORD COPD I	8/374	5/186		10.27%	0.79[0.26,2.45]
ACCORD COPD II	14/360	4/182		8.03%	1.8[0.58,5.55]
ACLIFORM	5/385	2/194		4.13%	1.26[0.24,6.57]
ATTAIN	14/546	5/273		10.21%	1.41[0.5,3.96]
AUGMENT COPD	7/337	12/331		18.64%	0.56[0.22,1.45]
Beier 2013	3/171	3/85		6.19%	0.49[0.1,2.47]
Chanez 2010	4/335	1/64		2.61%	0.76[0.08,6.92]
Maltais 2011	5/86	3/95		4.22%	1.89[0.44,8.17]
Subtotal (95% CI)	**3821**	**1830**		**100%**	**1.1[0.78,1.55]**
Total events: 118 (Aclidinium bromide), 51 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.04, df=9(P=0.83); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					
4.8.2 vs tiotropium bromide					
Beier 2013	3/171	3/158		38.16%	0.92[0.18,4.64]
Chanez 2010	4/335	3/65		61.84%	0.25[0.05,1.14]
Subtotal (95% CI)	**506**	**223**		**100%**	**0.51[0.16,1.56]**
Total events: 7 (Aclidinium bromide), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=1(P=0.24); I^2=26.44%					
Test for overall effect: Z=1.18(P=0.24)					
Test for subgroup differences: Chi^2=1.68, df=1 (P=0.19), I^2=40.61%					



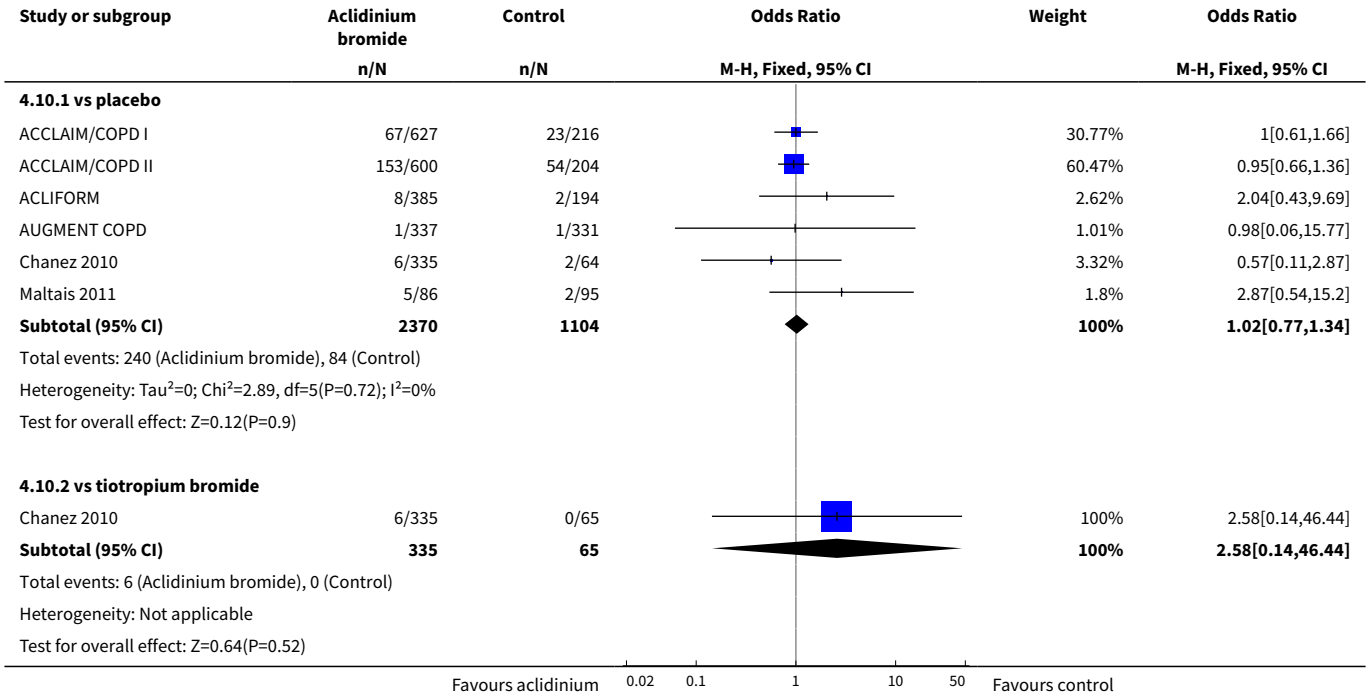
Analysis 4.9. Comparison 4 Adverse events, Outcome 9 Hypertension.

Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.9.1 vs placebo					
ACCLAIM/COPD I	9/627	9/216		26.27%	0.33[0.13,0.86]
ACCLAIM/COPD II	27/600	6/204		17.03%	1.55[0.63,3.82]
ACCORD COPD II	5/360	4/182		10.43%	0.63[0.17,2.36]
ACLIFORM	2/385	3/194		7.9%	0.33[0.06,2.01]
ATTAIN	12/546	9/273		23.36%	0.66[0.27,1.58]
AUGMENT COPD	10/337	6/331		11.69%	1.66[0.6,4.61]
Chanez 2010	3/335	1/64		3.31%	0.57[0.06,5.56]
Subtotal (95% CI)	**3190**	**1464**		**100%**	**0.81[0.54,1.22]**
Total events: 68 (Aclidinium bromide), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.7, df=6(P=0.19); I^2=31.03%					
Test for overall effect: Z=1.01(P=0.31)					
4.9.2 vs tiotropium bromide					
Chanez 2010	3/335	0/65		100%	1.38[0.07,27.01]
Subtotal (95% CI)	**335**	**65**		**100%**	**1.38[0.07,27.01]**

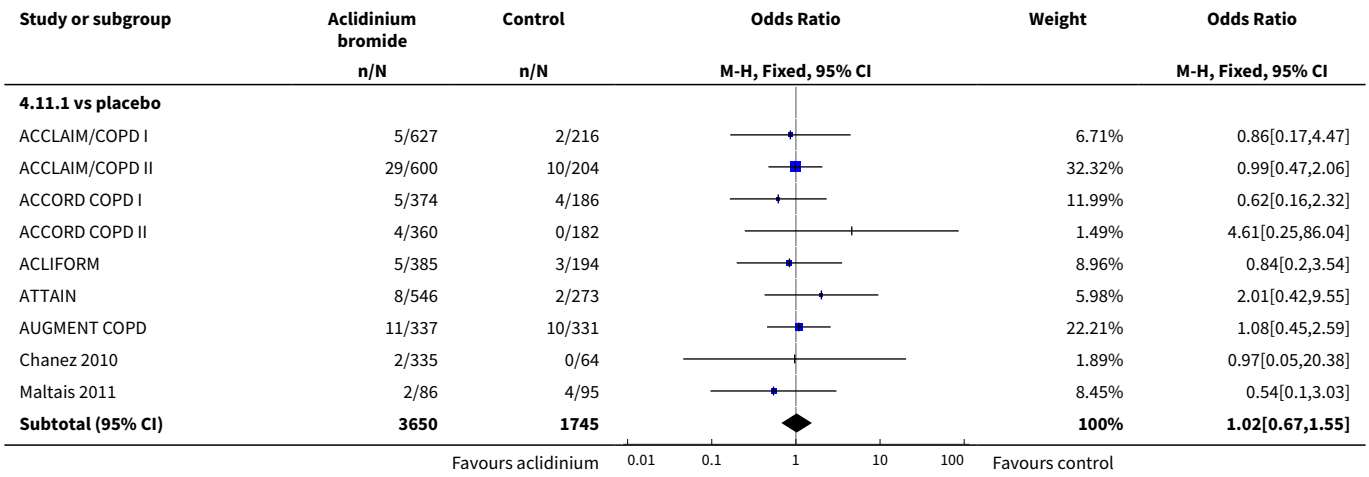


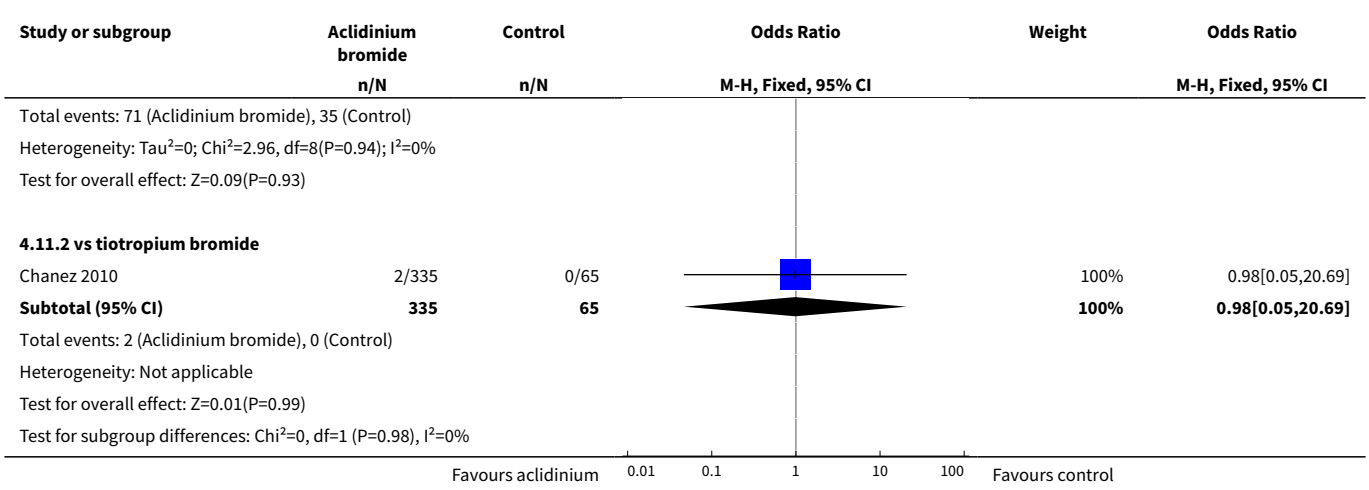


Analysis 4.10. Comparison 4 Adverse events, Outcome 10 Respiratory tract infections.

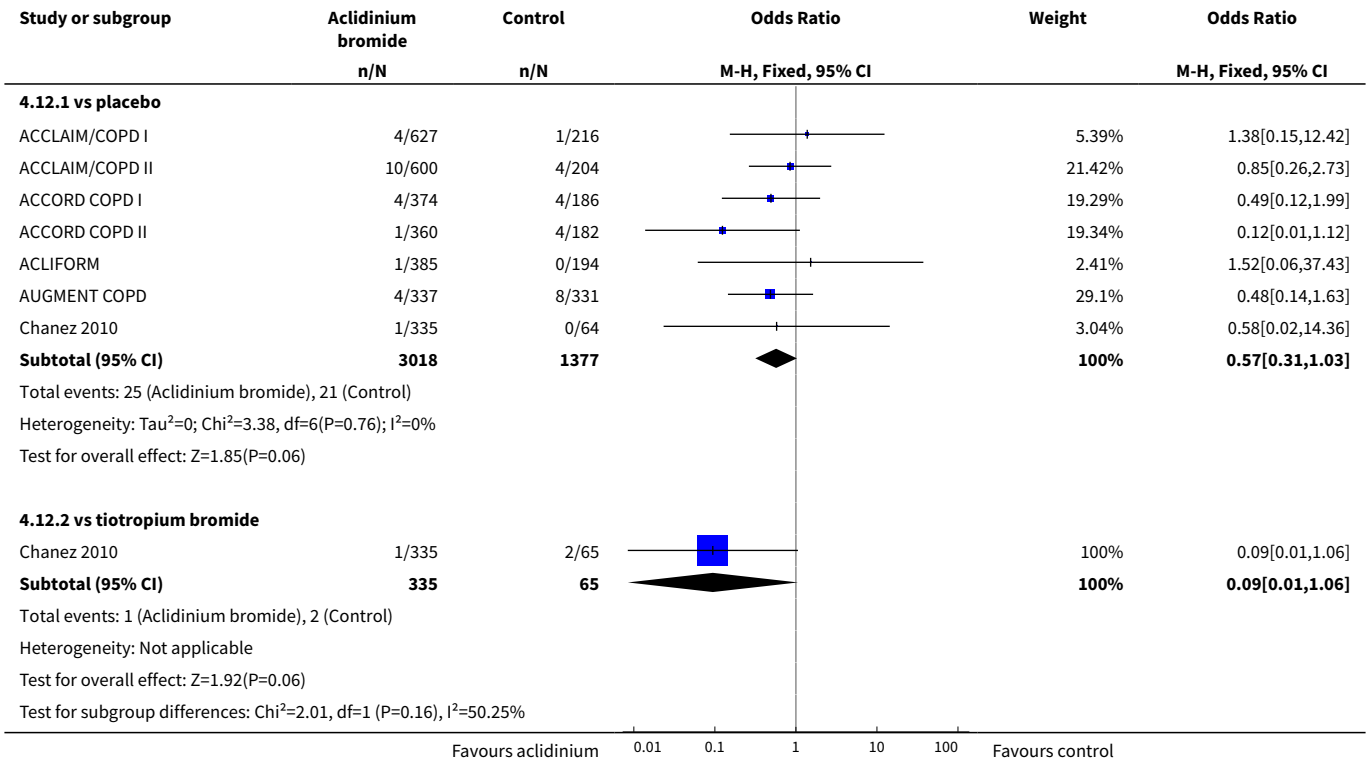


Analysis 4.11. Comparison 4 Adverse events, Outcome 11 Urinary tract infections.

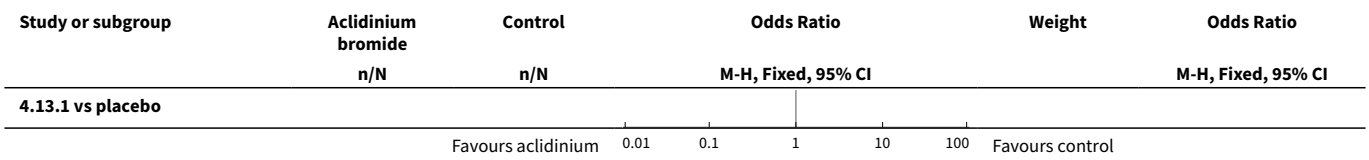


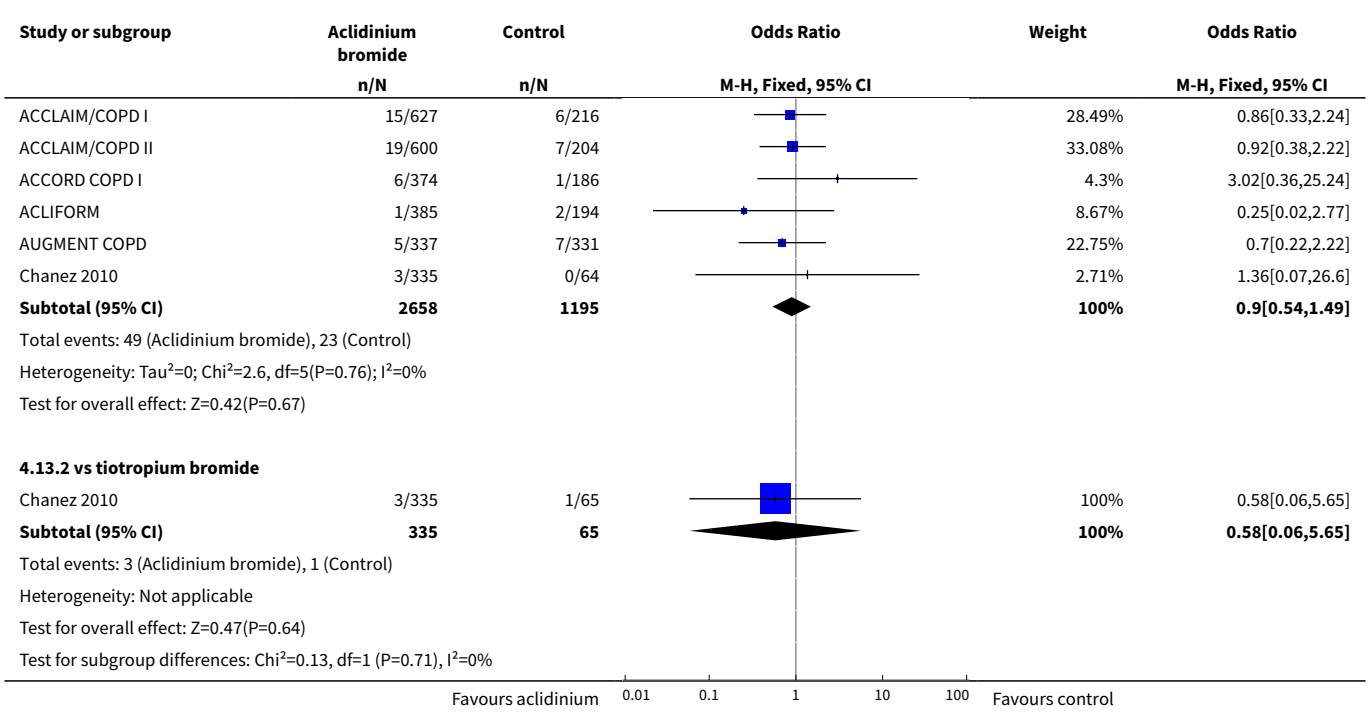


Analysis 4.12. Comparison 4 Adverse events, Outcome 12 Fatigue.

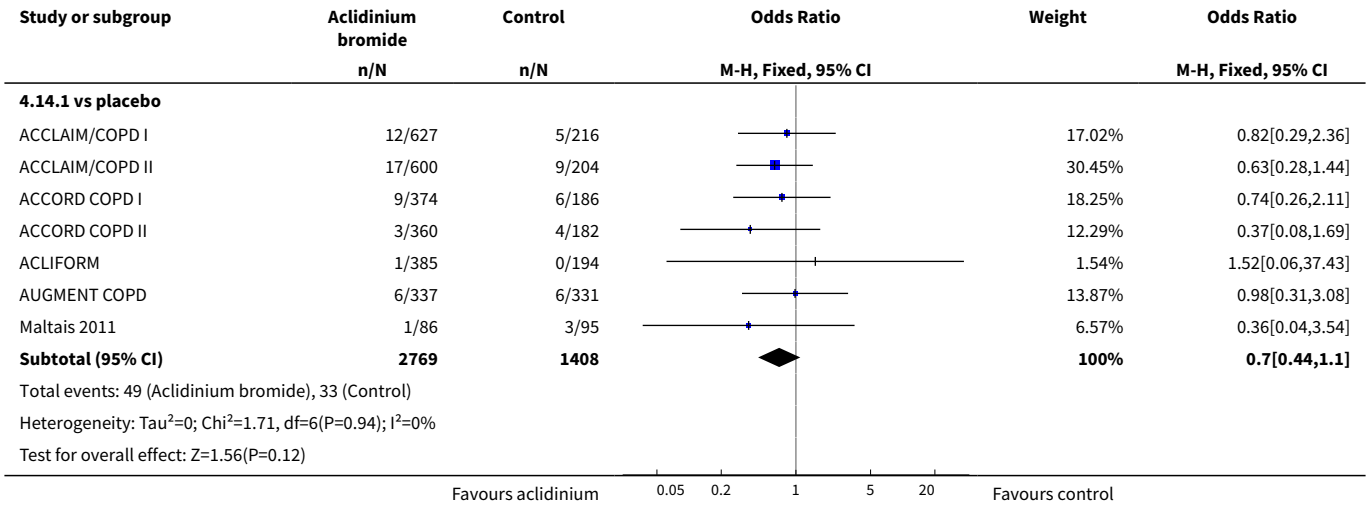


Analysis 4.13. Comparison 4 Adverse events, Outcome 13 Dizziness.

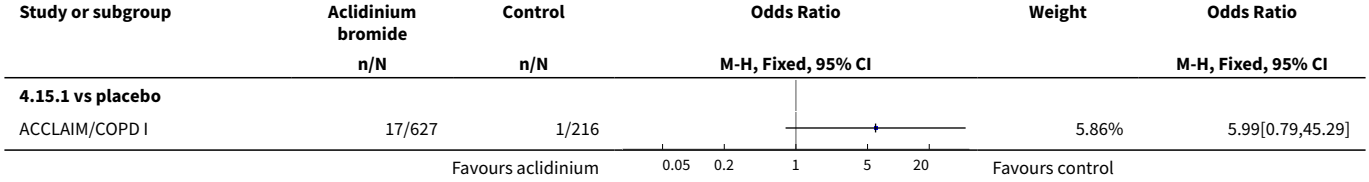




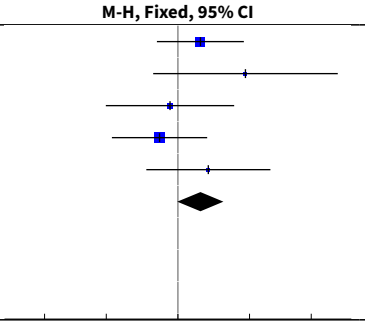
Analysis 4.14. Comparison 4 Adverse events, Outcome 14 Dyspnoea.



Analysis 4.15. Comparison 4 Adverse events, Outcome 15 Arthralgia.

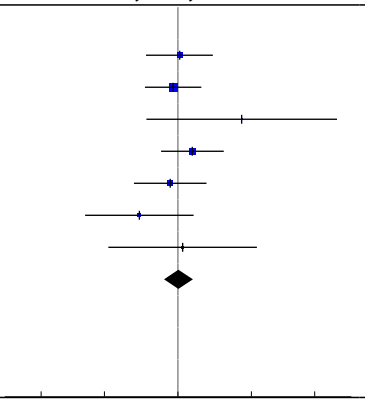


Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ACCLAIM/COPD II	24/600	5/204		28.99%	1.66[0.62,4.4]
ACCORD COPD I	9/374	1/186		5.28%	4.56[0.57,36.28]
ACLIFORM	5/385	3/194		15.94%	0.84[0.2,3.54]
ATTAIN	8/546	6/273		31.9%	0.66[0.23,1.93]
AUGMENT COPD	6/337	3/331		12.03%	1.98[0.49,7.99]
Subtotal (95% CI)	**2869**	**1404**		**100%**	**1.66[0.98,2.78]**
Total events: 69 (Aclidinium bromide), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.22, df=5(P=0.29); I^2=19.63%					
Test for overall effect: Z=1.9(P=0.06)					



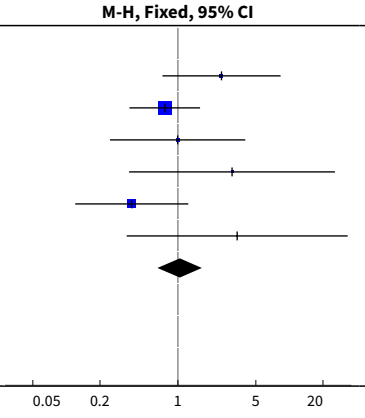
Analysis 4.16. Comparison 4 Adverse events, Outcome 16 Back pain.

Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.16.1 vs placebo					
ACCLAIM/COPD I	30/627	10/216		18.72%	1.04[0.5,2.15]
ACCLAIM/COPD II	40/600	15/204		27.62%	0.9[0.49,1.67]
ACCORD COPD I	8/374	1/186		1.73%	4.04[0.5,32.57]
ACLIFORM	32/385	12/194		19.34%	1.37[0.69,2.73]
ATTAIN	17/546	10/273		17.08%	0.85[0.38,1.87]
AUGMENT COPD	4/337	9/331		11.86%	0.43[0.13,1.41]
Maltais 2011	3/86	3/95		3.64%	1.11[0.22,5.64]
Subtotal (95% CI)	**2955**	**1499**		**100%**	**1.01[0.74,1.39]**
Total events: 134 (Aclidinium bromide), 60 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.81, df=6(P=0.57); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					



Analysis 4.17. Comparison 4 Adverse events, Outcome 17 Oropharyngeal pain.

Study or subgroup	Aclidinium bromide n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.17.1 vs placebo					
ACCLAIM/COPD I	21/627	3/216		11.92%	2.46[0.73,8.33]
ACCLAIM/COPD II	25/600	11/204		43.48%	0.76[0.37,1.58]
ACCORD COPD I	6/374	3/186		10.9%	0.99[0.25,4.02]
ACLIFORM	6/385	1/194		3.62%	3.06[0.37,25.56]
AUGMENT COPD	4/337	10/331		27.55%	0.39[0.12,1.24]
Maltais 2011	3/86	1/95		2.53%	3.4[0.35,33.3]
Subtotal (95% CI)	**2409**	**1226**		**100%**	**1.04[0.66,1.64]**
Total events: 65 (Aclidinium bromide), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.39, df=5(P=0.19); I^2=32.38%					
Test for overall effect: Z=0.15(P=0.88)					



ADDITIONAL TABLES

Table 1. Overview of included studies

	Duration of study	Number randomised	Severity of participants	Dose of aclidinium	Frequency of aclidinium
ACCLAIM/COPD I	52 weeks	843	Moderate to severe (GOLD)	200 µg	Once daily
ACCLAIM/COPD II	52 weeks	804	Moderate to severe (GOLD)	200 µg	Once daily
ACCORD COPD I	12 weeks	561	Moderate to severe (GOLD)	200, 400 µg	Twice daily
ACCORD COPD II	12 weeks	544	Moderate to severe (GOLD)	200, 400 µg	Twice daily
ACLIFORM	24 weeks	1729	Moderate to severe (GOLD)	400 µg	Twice daily
ATTAIN	24 weeks	828	Moderate to severe (GOLD)	200, 400 µg	Twice daily
AUGMENT COPD	24 weeks	1692	Moderate to severe (GOLD)	400 µg	Twice daily
Beier 2013	6 weeks	414	Moderate to severe (GOLD)	400 µg	Twice daily
Chanez 2010	4 weeks	464	Moderate to severe (ATS)	25, 50, 100, 200, 400 µg	Once daily
Maltais 2011	6 weeks	181	Moderate to severe (GOLD)	200 µg	Once daily
NCT01572792	28 weeks	921	Moderate to severe (GOLD)	400 µg	Twice daily
Sliwinski 2010	4 weeks	566	Moderate to severe	200 µg	Once daily

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for ClinicalTrials.gov

Search terms: "aclidinium" OR "aclidinium bromide" OR "LAMA" OR "muscarinic antagonists" OR "LAS34273"

Condition: COPD or Chronic Obstructive Pulmonary Disease

Study type: interventional studies

Appendix 3. Details of Almirall randomisation processes

The procedures for randomising Almirall sponsored studies have been detailed in correspondence between Esther Garcia Gil, Head of Late Stage Development Respiratory ,and HN, the details of which are given below.

Responses to your specific questions:

1. Randomisation process: prior to initiating the trial, a computer generated randomisation schedule was prepared to assign a treatment sequence to a randomisation number by the Statistics/Programming group within Almirall, according to the relevant Standard Operating Procedure (SOP). The randomisation was performed in order to avoid any possible bias due to the order of the IMP administrations. The block size was determined in agreement with the Clinical Trial Manager and the Statistician and was not to be communicated to the investigators.

In all studies, we used IVRS (and in some cases IWRS) to sequentially randomise patients to the intervention arms according to the randomisation ratio defined in each study as well as the block size determined by the sponsor as mentioned above.

2. Blinding: in all our studies, blinding was applicable for all study outcomes. In the placebo-controlled studies, matching placebo of aclidinium bromide had the same external appearance with the same composition, except for the active ingredient. In regards to the study that included tiotropium, in order to minimise bias, a double-dummy technique to ensure the double blind of the trial was applied.

FEEDBACK

Approriateness of decision to pool exacerbation and hospitalization outcomes, 13 March 2015

Summary

We agree with the review authors' statement regarding lack of information to reliably compare aclidinium and tiotropium, but we have some concerns regarding whether it was appropriate to meta-analyze pooled data for COPD exacerbation and hospitalisation outcomes for aclidinium vs tiotropium.

1) The short duration (4 to 6 weeks) of the two included studies (Chanez 2010 and Beier 2013) may not reflect an adequate time period for assessment of COPD exacerbation or hospitalisation rates and we cannot project how the patients in Chanez 2010 and Beier 2013 would have fared in terms of exacerbations beyond the 4 to 6 week study periods. Of note, Cochrane Reviews of tiotropium vs placebo [1] tiotropium vs ipratropium [2] and tiotropium vs long-acting beta-agonists [3] included only studies of at least 12 weeks duration. We do not believe the short study periods in this review captures enough COPD exacerbations to perform clinically meaningful comparisons, and that the meta-analyses should not have been done.

2) In Chanez 2010, a total of eight COPD exacerbations were reported in the published paper across the five different aclidinium dosage arms. However, only three exacerbations were included in Analysis 2.2 and two hospitalizations in the aclidinium arms were included in Analysis 2.7. The published study reported only total COPD exacerbations, and the events were not categorized according to the definitions in this review and we are unable to replicate the meta-analyses. To help readers interpret the findings, we would have liked clarification regarding how the events were categorized and which dosage arms these events occurred in.

3) In Beier 2013, the published paper describes COPD exacerbations occurring in 2.4% of patients, suggesting approximately 10 events in total. The study also describes two COPD exacerbations resulting in withdrawal in each of the treatment groups, but it is unclear whether these events were included in final analysis of the study or in either Analysis 2.2 or 2.7, leading to difficulties interpreting this analysis. Given the short study duration, the quality of the data (assessed as "very low" in the review) and the lack of clarity regarding data extraction, we feel that the included meta-analyses do not provide appropriate context for clinical decision making. While the odds ratios and confidence intervals are reported as not clinically significant, including them in this review may lead readers to inappropriately hypothesize that there is no difference between aclidinium and tiotropium, or that aclidinium may be associated with more moderate COPD exacerbations and fewer hospitalizations than tiotropium. However, the current pooled estimates have such wide confidence intervals that it could include a clinically meaningful increase or decrease in COPD exacerbations or hospitalizations with aclidinium compared to tiotropium.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

References:

1. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009285. DOI: 10.1002/14651858.CD009285.pub3

2. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD009552. DOI: 10.1002/14651858.CD009552.pub2

3. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD009157. DOI: 10.1002/14651858.CD009157.pub2.

Reply

Thank you very much for your interest and comments regarding our Cochrane review on “Aclidinium bromide for stable chronic obstructive pulmonary disease”.

1) For comparison of aclidinium and tiotropium we only found two short trials (Chanez 2010 and Beier 2013). According to the published protocol, both studies met our inclusion criteria, in which there was no predefined minimum trial duration. As practicing physicians, we have also seen cases of exacerbations occurring very frequently in our practice even within a short period after discharge from hospital. We do agree with your statement regarding the clinical meaningfulness of analyses 2.2 and 2.7, the results of which are not reliable for projection beyond 4 to 6 weeks. The readers might also inappropriately infer that aclidinium may be associated with more moderate exacerbations (analysis 2.2) but fewer hospitalizations (analysis 2.7) than tiotropium as you mentioned, based on the direction of the treatment effect, but both of these are non-significant. The aim of Cochrane Reviews is to provide unbiased evidence to the readers; therefore we could not omit these analyses solely due to statistical imprecision. Due to imprecision and lack of blinding in the tiotropium arm in Chanez 2010, the quality of evidence for these comparisons was rated as "very low" meaning we are very uncertain about the estimate. We have included our reasons for down-grading the quality of evidence for these analyses in the summary of findings table 2 and also in the discussion under the "overall completeness and applicability of evidence" section. We will be updating this review at regular intervals and if new trials comparing aclidinium with tiotropium become available in the future, we will update these analyses and hope to provide better evidence.

2 and 3)

Regarding the discrepancies of the number of events used for meta-analyses and those in the published papers, most trials did not report mild, moderate or severe exacerbations separately. We specified in our protocol that we would analyse moderate exacerbations requiring short course of oral steroids and/or antibiotics and severe exacerbations needing hospitalisation separately. Dr Esther Garcia Gil (head of late stage development respiratory) and Christina Serra and Rosa Segarra (clinical trial managers) from Almirall helped us in providing the necessary data. Thus, the values you found in the review are provided by Almirall as the data from published articles are not appropriate for inclusion in the analyses. We describe how we obtained this information under the “effects of intervention” section. The data was checked by two review authors, the Almirall personnel and by the statistical editor of the Airways group. Thus, we hope readers will be able to appreciate why the data entered for analyses cannot be identified in the published articles.

We do hope that these will clarify your doubts and if you have further queries and comments, we are happy to respond.

Best regards,

Han Ni

MBBS, MMedSc (Internal Medicine), MRCP, FCCP

Contact author

Contributors

Julian Lee, BSc. (Pharm), Lower Mainland Pharmacy Services, Vancouver, Canada (julian.lee1@fraserhealth.ca)

Erin Ready, BSc. (Pharm), Lower Mainland Pharmacy Services, Vancouver, Canada

Aaron Tejani, PharmD, Therapeutics Initiative (UBC), Vancouver, Canada (aaron.tejani@ti.ubc.ca)

WHAT'S NEW

Date	Event	Description
1 April 2015	Feedback has been incorporated	Feedback and rebuttal added.

CONTRIBUTIONS OF AUTHORS

HN and ZS wrote the protocol with suggestions and input on the methods from SM. HN and SM performed the search of additional resources, screened the search results and retrieved full text articles. HN and SM selected studies for inclusion. HN contacted the trial authors and manufacturer of aclidinium (Almirall) for unpublished data. HN and SM independently performed risk of bias assessment of included studies and extracted data. When any difference arose between HN and SM, ZS was consulted. HN performed data entry, which was checked by SM. HN performed data analysis with statistical expertise and advice from SM. HN drafted the manuscript with statistical input from SM and clinical input from ZS. All authors revised and agreed on the full review manuscript prior to submission for editorial review.

DECLARATIONS OF INTEREST

The authors have no connection with any organisations which could have caused a conflict of interest. We are doing this systematic review for academic purposes.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cochrane Airways Group, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

All the references that were identified were in the English language and we did not require translations. We did not perform analyses using the Peto odds ratio because there were no rare events. We did not calculate standardised mean difference as no data from differing metric scales were combined. We analysed the outcome data for quality of life by the SGRQ total score and improvement in symptoms by the TDI focal score as mean changes from baseline (continuous data) as well as the percentage of patients who achieved a minimal clinically important difference in these scores (dichotomous data). Subgroup analysis for the dose of aclidinium, duration of therapy, baseline severity of COPD and concurrent therapy with theophylline were not conducted as planned.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [therapeutic use]; Bronchodilator Agents [*therapeutic use]; Disease Progression; Muscarinic Antagonists [*therapeutic use]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic; Scopolamine Derivatives [therapeutic use]; Tiotropium Bromide; Tropanes [*therapeutic use]

MeSH check words

Aged; Female; Humans; Male; Middle Aged