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[Intervention Review]

Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma

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ABSTRACT

Background

Anti-leukotriene (AL) agents are being considered as 'add-on' therapy to inhaled corticosteroids (ICS), in chronic asthma.

Objectives

To examine the safety and efficacy of daily AL plus ICS compared to ICS alone, and determine the corticosteroid-sparing effect of AL when added to ICS in chronic asthma.

Search methods

We searched MEDLINE, EMBASE, CINAHL (until August 2003), reference lists of review articles and trials, contacted international headquarters of AL manufacturers and looked at American Thoracic Society and European Respiratory Society meeting abstracts (1998 to 2003).

Selection criteria

Randomised placebo-controlled trials of asthmatics aged two years and older with at least one month intervention.

Data collection and analysis

Two reviewers assessed quality and extracted data independently. Trials were grouped by asthma control at baseline (symptomatic or well-controlled) and dose of ICS in the control group (same or double).

Main results

Of 587 citations, 27 (25 adult and 2 paediatric) trials met inclusion criteria. Sixteen trials were published in full-text and 16 trials reported data in a way that allowed meta-analysis. In symptomatic patients, addition of licensed doses of anti-leukotrienes to ICS resulted in a non-significant reduction in the risk of exacerbations requiring systemic steroids: Relative Risk (RR) 0.64; 95% Confidence Interval (CI) 0.38 to 1.07). A modest improvement group difference in PEF was seen (Weighted Mean Difference (WMD) 7.7 L/min; 95% CI 3.6 to 11.8 L/min) together with decrease in use of rescue short-acting beta2-agonist use (WMD 1 puff/week; 95%CI 0.5 to 2). With only 3 trials comparing the use of licensed doses of anti-leukotrienes with increasing the dose of inhaled glucocorticoids, no firm conclusion can be drawn about the equivalence of both treatment options. In ICS-sparing studies of patients who were well controlled at baseline, addition of anti-leukotrienes produced no overall difference in dose of inhaled glucocorticoids (WMD -21 mcg/d, 95%CI -65, 23 mcg/d), but it was associated with fewer withdrawals due to poor asthma control (RR 0.63, 95% CI 0.42 to 0.95).

Authors' conclusions

The addition of licensed doses of anti-leukotrienes to add-on therapy to inhaled glucocorticoids brings modest improvement in lung function. Although addition of anti-leukotrienes to inhaled glucocorticoids appears comparable to increasing the dose of inhaled steroids, the power of the review is insufficient to confirm the equivalence of both treatment options. Addition of anti-leukotrienes is associated with superior asthma control after glucocorticoid tapering; although the glucocorticoid-sparing effect cannot be quantified at present, it appears modest.

PLAIN LANGUAGE SUMMARY**The addition of anti-leukotriene agents to inhaled corticosteroids versus placebo for chronic asthma**

Inhaled steroids remain the cornerstone of asthma treatment. Anti-leukotrienes constitute a new class of drugs that can be taken by mouth and do not have the side effects associated with steroids. We looked to see how effective these drugs were when they were added to the treatment of patients who needed steroid inhalers to control their asthma. In asthmatics that are not well controlled on inhaled steroids, the addition of anti-leukotrienes brings modest improvement in asthma control but it remains unclear whether they are as effective as increasing the dose of inhaled steroids. Higher doses of anti-leukotrienes are more effective, but associated with an increased risk of side effect that occurs with these particular drugs. In asthmatics that are well controlled on inhaled steroids, the addition of anti-leukotrienes did not allow a reduction in the amount of inhaled steroid used but they seemed to have a beneficial effect on the asthma control. There are only two studies that have looked at these issues in children; this is insufficient to firmly conclude whether anti-leukotrienes are useful in children.

BACKGROUND

Since the mid 1980's, the understanding of the primarily inflammatory nature of asthma has tremendously changed its management (Murphy 1993). Infiltration of bronchial airways with eosinophils and neutrophils with production of inflammatory mediators is characteristic of asthma. The most potent inflammatory mediators may be the cysteinyl leukotrienes which are produced by the 5-lipoxygenase pathway of the arachidonic acid metabolism. These mediators stimulate the production of airway secretions, cause microvascular leakage and enhance eosinophilic migration in the airways; thus, leukotrienes are believed to play a major role in mediating bronchoconstriction and inflammatory changes pivotal in the pathophysiology of asthma (Piper 1989). Treatment of airway inflammation is now advocated by all recent consensus statements on asthma (GINA 2002; BTS 2003; Australia 2002; Boulet 2001; CTS 1999). Although several drugs such as ketotifen, sodium cromoglycate and sodium nedocromil have anti-inflammatory properties, inhaled glucocorticoids remain the cornerstone of asthma management because of their efficacy, tolerance, and rapid onset of action (CTS 1999; Spahn 1996). The administration of inhaled glucocorticoids is generally considered safe, unless the daily dose required for control of symptoms remains large for a prolonged period. In these conditions, adverse effects such as growth stunting in children (Wolthers 1996; Lipworth 1999; Kamada 1995), suppression of the adrenal axis (Wolthers 1998) and bone osteopenia may be observed (Efthimiou 1998; Bootsma 1997). To reduce the dose of glucocorticoids required for symptom control, other drugs may be added. Long-acting beta-2-agonists, which have only mild anti-inflammatory effect, are being used for this purpose (Bisgaard 2000; CTS 1999). Anti-leukotrienes form a new class of anti-inflammatory drugs which may have important glucocorticoids-sparing effects. These drugs interfere either with leukotriene production (5-lipoxygenase inhibitors) or with leukotriene receptors (leukotriene receptors antagonists). Anti-leukotrienes have the advantage of being administered orally in a single or twice daily dose and, importantly, seem to lack the adverse effects associated with long-term systemic glucocorticoid therapy. However, safety remains an important issue particularly with elevation of hepatic enzymes and Churg-Strauss syndrome reported in some patients treated with anti-leukotrienes (Price 2000).

As relatively new therapeutic agents, it is important to determine the proper place of anti-leukotrienes in the management of asthma. While the 2002 Global Initiative for Asthma guidelines classifies the role of anti-leukotrienes as still under investigation, (GINA 2002) several national guidelines advocate its use as adjunct therapy to inhaled glucocorticoids in moderate to severe persistent asthma or as alternative single-agent management in mild asthma (BTS 2003; CTS 1999; Australia 2002). Randomised controlled trials have provided evidence of the efficacy of anti-leukotrienes as add-on therapy to inhaled glucocorticoids in persistent asthma (Laviolette 1999; Lofdahl 1999; Tamaoki 1997; Virchow 2000); the evidence was summarized in a Cochrane review last updated in September 2001. With the publication of new trials, an update of the systematic review of the randomised controlled trials was indicated to review the potential benefit of anti-leukotrienes as add-on therapy to inhaled glucocorticoids and to provide better insight in the influence of study characteristics on results.

OBJECTIVES

1. In patients who were symptomatic, despite use of maintenance inhaled corticosteroids, we wished to determine whether the addition of anti-leukotriene agents reduced the frequency and severity of exacerbations and improved chronic asthma control while maintaining a good safety profile. The addition of anti-leukotriene agents to inhaled corticosteroids was compared to either the use of the same or double dose of inhaled corticosteroids.
2. In patients who were well controlled on their baseline dose of inhaled corticosteroids, we wished to quantify the magnitude of dose reduction in inhaled glucocorticoids (glucocorticoid-sparing effect) that could be achieved with the addition of anti-leukotrienes.

Secondary objectives were to determine whether patients' characteristics, such as dose and type of anti-leukotrienes, dose of inhaled glucocorticoids required to control symptoms, age (adult versus child), severity of airway obstruction on baseline (% predicted FEV1), duration of intervention, and asthma triggers (allergens, viral infection, aspirin, or others), influenced the magnitude of effect attributable to anti-leukotrienes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised placebo controlled trials in adults and children in which anti-leukotriene agents were added to inhaled glucocorticoid were considered for inclusion. Sensitivity analyses were performed based on the reported quality of randomisation, concealment of allocation, blind assessment of outcomes, and description of withdrawals and dropouts.

Types of participants

Children aged two to 17 years and adults with recurrent or chronic asthma, symptomatic or well-controlled on daily maintenance inhaled glucocorticoids.

Types of interventions

Combination of daily oral anti-leukotriene agents, including leukotriene synthesis inhibitors and leukotriene receptor antagonists, with inhaled glucocorticoids (treatment group) compared to inhaled glucocorticoids alone (control group).

Types of outcome measures

Primary outcomes

The primary outcome was the number of patients with exacerbations requiring use of systemic glucocorticoids when the intervention was compared to the same or increased dose of inhaled glucocorticoids. The change from the baseline dose of inhaled glucocorticoids required to maintain control was the main outcome when the intervention was aimed at establishing the steroid-sparing effect.

Secondary outcomes

The following secondary outcomes were considered after various lengths of treatment:

1. Change in clinical or physiologic outcomes reflecting chronic asthma control (such as symptom score, night-time awakenings, days without symptoms, quality of life, rescue short-acting beta-2-agonist use, and pulmonary function tests)
2. Clinical or physiologic outcomes reflecting the frequency and severity of asthma exacerbations (such as hospital admissions)
3. Inflammatory markers (such as serum and sputum eosinophils, serum eosinophilic cationic protein (ECP), expired nitric oxide, etc)
4. Clinical and biochemical adverse effects (i.e. elevation of liver enzymes) as well as withdrawal rates were also examined.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group Asthma trials register on all fields for:

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[leukotriene* OR anti-leukotriene* OR *lukast* ] AND [[inhaled* AND [steroid* OR corticosteroid* OR fluticasone * OR triamcinolone* OR dexamethasone* OR dexamethasone* OR glucocorticoid* OR flovent OR beclomethasone* OR beclomethasone* OR beclomethasone* OR beclomethasone* OR budesonide* OR pulmicort OR flunisolide OR aerobid OR bronalide OR azmacort OR vancericil OR becotide OR flixotide OR aerobec]].
```

We also completed an advanced search of CENTRAL, the Cochrane Central Register of Controlled Trials using the above search strategy.

Searching other resources

We then reviewed all abstracts and citations and annotated as a RCT, clearly not an RCT or unclear. We obtained and reviewed the publications of references identified as RCTs or unclear and identified trials as clearly or potentially relevant. Secondly, we checked reference lists of all identified RCTs to identify potentially relevant citations. Thirdly, we contacted the international headquarters of pharmaceutical companies producing anti-leukotrienes and inhaled steroids. We also made enquiries regarding other published or unpublished studies known and/or supported by these companies or their subsidiaries. Finally, we searched the abstract books of the American Thoracic Society and the European Respiratory Society Meetings from 1998-2003. The search was last updated in August 2003.

Data collection and analysis

Selection of studies

Two authors independently assessed the search results (FD or ZS). Studies were retrieved selected on the basis of relevance, and were selected for inclusion by the agreement of two authors.

Data extraction and management

Data were extracted independently by two reviewers (FMD and ZS, GH or RK), blinded as above, and disagreement was dealt with by consensus.

Assessment of risk of bias in included studies

The methodological quality of the eligible controlled trials was assessed with a 5-point scoring instrument (Jadad 1995). This instrument evaluates the reported quality of randomisation, blinding, and description of withdrawals and dropouts. The quality

assessment was done independently by two reviewers (FMD and ZS, GH or RK). We dealt with disagreement by consensus. We sought confirmation of methodology for all included trials directly from the authors and/or the funding pharmaceutical companies.

Dealing with missing data

Confirmation of data extraction for all included trials was sought directly from the authors and/or the funding pharmaceutical companies.

Assessment of heterogeneity

Homogeneity of effect sizes between studies being pooled was tested with the DerSimonian & Laird method, with $p < 0.05$ being used as the cut-off level for significance. If heterogeneity was suggested, the DerSimonian & Laird random-effects model was applied to the summary estimates. Due to low power for detecting heterogeneity with few trials, any difference in the conclusions related to the choice of the (fixed or random) model were reported, when observed for the main outcomes. To detect possible biases, funnel plot symmetry was examined for trials contributing data to the main outcomes (Egger 1997). All estimates were reported with their 95% confidence interval.

Data synthesis

Treatment effects for dichotomous outcomes were reported as pooled relative risks with the fixed-effect model (Greenland 1985) or, in case of heterogeneity, the random-effects model (DerSimonian 1986). We summarised differences between groups in event rates, such as the number of participants with exacerbations in a specific period of time, using the Relative Risk of the event occurring. Equivalence was assumed if the relative risk estimate and its confidence interval were between 0.9 and 1.1. For continuous outcomes, such as pulmonary function tests or quality of life scores, we used a Weighted Mean Difference (WMD) or Standardised Mean Difference (SMD), where appropriate, to estimate individual and pooled effect sizes. Numbers Needed to Treat (NNT) were derived from the pooled Odds Ratios using Visual Rx (an online calculator at www.nntonline.net) as the results are not affected by the way in which the events are recorded (Cates 2002).

Trials were divided into three protocols, according to the relative dose of inhaled glucocorticoids used by the control group (same, double, tapered).

(1) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus SAME dose of ICS.

(2) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus DOUBLE dose of ICS.

(3) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus ICS (TAPERING protocol).

In all comparisons, the dose and type of anti-leukotriene agents served as the primary stratifying variable.

Subgroup analysis and investigation of heterogeneity

The magnitude or direction of treatment response: (1) dose and anti-leukotrienes used, (2) baseline dose of inhaled glucocorticoids, (3) age, (4) severity of baseline airway obstruction, (5) duration of intervention and (6) asthma triggers. Whenever possible, these factors were examined as possible source of

heterogeneity. The mean baseline dose of inhaled glucocorticoids in the intervention group was recorded as 'User defined order' in mcg/day of chlorofluorocarbon (CFC)-propelled beclomethasone dipropionate or equivalent $\times 0.1$; where, irrespective of delivery system used, 1 mcg of beclomethasone = 1 mcg of budesonide = 0.5 mcg of fluticasone = 2 mcg of triamcinolone = 2 mcg of flunisolide (USA 2002). Usual licensed doses of leukotriene receptor antagonists are: montelukast 10 mg daily, pranlukast 450 mg daily, and zafirlukast 20 mg twice daily. For the primary outcome, sensitivity analyses were performed to determine the effect of publication status and methodological quality on results. We performed the meta-analysis using RevMan software

RESULTS

Description of studies

Results of the search

The search strategy last updated in August 2003 yielded additional 211 citations for a total of 587 citations.

A total of 27 (2 paediatric and 25 adult) trials, 16 of which were published in full text at the time of this report (Kanniess 2002; Laviolette 1999; O'Sullivan 2003; Price 2003; Riccioni 2001; Riccioni 2002; Shingo 2001; Simons 2001; Tamaoki 1997; Tohda 2002; Tomari 2001; Tomita 1999; Vaquerizo 2003; Virchow 2000; Wada 1999), met the inclusion criteria for this review. We grouped these 27 trials according to one of three protocols defining their specific objective and design.

Included studies

Anti-leukotrienes + ICS versus SAME dose of inhaled corticosteroids (ICS)

DESIGN

Thirteen trials, including 10 full-text publications (Laviolette 1999; O'Sullivan 2003; Riccioni 2001; Riccioni 2002; Simons 2001; Tamaoki 1997; Tomita 1999; Vaquerizo 2003; Virchow 2000; Wada 1999) and two abstracts (Finn 2000; Nishimura 1999) and an unpublished report (Hultquist 2000) evaluated the degree of asthma control achieved by the addition of anti-leukotrienes to inhaled corticosteroids compared to the same dose of inhaled corticosteroids in the control group. All but three trials (Nishimura 1999; O'Sullivan 2003; Simons 2001) were parallel-group randomised controlled trials. Eight trials (Finn 2000; Hultquist 2000; Laviolette 1999; Nishimura 1999; Simons 2001; Vaquerizo 2003; Virchow 2000; Wada 1999) enrolled participants who were clearly symptomatic at baseline; two trials enrolled well controlled adults (Riccioni 2001; Riccioni 2002); two trials (Tamaoki 1997; Tomita 1999) recruited well controlled participants in whom their usual dose of ICS required to maintain control was suddenly reduced by half on randomisation in an attempt to render them symptomatic; and the last trial (O'Sullivan 2003) enrolled well controlled mild asthmatics in a cross-sectional study to determine the impact on inflammatory markers and lung function of the addition of leukotriene receptor antagonists. Finn 2000 randomised 479 children of whom only 98 received co-treatment with inhaled glucocorticoids which were analysed separately (although it is unclear if the randomisation was stratified on the presence/absence of co-treatment with inhaled glucocorticoids). Two trials (Tomita 1999; Wada 1999) were open label studies (no blinding) with no placebo use in the control group, while two other trials

reported their study (Riccioni 2001; Riccioni 2001) as double-blind for the patients and assessor but with no use of placebo.

PARTICIPANTS

All but two trials, (Finn 2000; Simons 2001), focused on adults; the mean age of participants varied between 38 to 50 years; the pediatric trials enrolled children with a mean age of 10 years for Simons 2001 and an age range of 5-11 years in Finn 2000. There was relatively similar representation of genders. In adult trials, the average duration of asthma was greater than 10 years. The severity of airway obstruction on baseline was mild to moderate. In the trials that enrolled participants who were symptomatic on maintenance inhaled glucocorticoids, the baseline FEV1 varied between 63% to 81% of predicted (Virchow 2000; Finn 2000; Hultquist 2000; Laviolette 1999; Simons 2001; Vaquerizo 2003) while it was unreported in Wada 1999. In the trials that enrolled asthmatics who were well controlled prior to sudden decrease of the inhaled glucocorticoids dose, the FEV1 was 80% predicted in Tamaoki 1997 and 88% predicted in Tomita 1999. O'Sullivan 2003, Riccioni 2001 and Riccioni 2002 enrolled well controlled mild asthmatics with an average of 90% predicted FEV1. Allergic triggers were reported in over 45% to 100% of participants, when reported (Laviolette 1999; O'Sullivan 2003, Simons 2001; Tomita 1999; Virchow 2000; Wada 1999); allergic rhinitis was seldom mentioned.

INTERVENTION

The duration of trials was short, varying between four weeks (Nishimura 1999; Simons 2001; Wada 1999), six weeks (Finn 2000; Tamaoki 1997; Virchow 2000), eight weeks (Hultquist 2000; O'Sullivan 2003; Riccioni 2001; Tomita 1999), to 16 weeks (Laviolette 1999; Riccioni 2002; Vaquerizo 2003). The tested intervention drugs were all leukotriene receptor antagonists, namely pranlukast (Nishimura 1999; Tamaoki 1997; Tomita 1999; Wada 1999) at a daily dose of 450 mg/day (double dose in Tamaoki 1997), montelukast 5 mg (Simons 2001), montelukast 10 mg die (Laviolette 1999; O'Sullivan 2003; Riccioni 2002; Vaquerizo 2003), zafirlukast 10 mg bid (Finn 2000), zafirlukast 20 mg bid (Hultquist 2000; Riccioni 2001), and zafirlukast 80 mg bid (Virchow 2000). In all trials, the inhaled glucocorticoids was administered at the same daily dose in both the control and intervention groups. Most trials used beclomethasone dipropionate (BDP). Five trials added leukotriene receptor antagonists to low doses of inhaled glucocorticoids (≤ 400 mcg/day of BDP or equivalent) (Hultquist 2000; Laviolette 1999; O'Sullivan 2003; Simons 2001; Tomita 1999), four trials pertained to moderate doses of inhaled steroids (i.e., 401-800 mcg/day of BDP or equivalent) (Tamaoki 1997; Riccioni 2001; Riccioni 2002; Vaquerizo 2003); three trials pertained high doses of inhaled steroids (i.e., > 800 mcg/day of BDP or equivalent) (Nishimura 1999; Virchow 2000; Wada 1999); while it remained unspecified in one trial (Finn 2000)

In five trials, Hultquist 2000, Laviolette 1999, Riccioni 2001, Riccioni 2002 and Vaquerizo 2003, no additional co-treatment was permitted other than rescue inhaled beta-2 agonists and systemic corticosteroids. In other trials, the following co-treatments were permitted if maintained constant throughout the trial: oral beta-2 agonists, theophylline and inhaled anticholinergics (Tamaoki 1997), maintenance oral corticosteroid therapy was permitted in five participants in Tomita 1999 and slow-release theophylline in Wada 1999. No information regarding co-intervention was provided for Simons 2001, Finn 2000, Nishimura 1999, and O'Sullivan 2003.

OUTCOMES

The pre-designated primary outcome (the number of participants with exacerbations requiring systemic corticosteroids) was documented in only four trials (Lavolette 1999; Simons 2001; Tamaoki 1997; Virchow 2000). Six trials (Hultquist 2000; Lavolette 1999; Simons 2001; Tamaoki 1997; Virchow 2000; Vaquerizo 2003) reported other measures of asthma control (pulmonary function tests, symptoms scores, or functional status indices) as change from baseline. Five trials (Hultquist 2000; Lavolette 1999; Simons 2001; Virchow 2000; Vaquerizo 2003) performed intention-to-treat analyses. Five trials (Finn 2000; Nishimura 1999; O'Sullivan 2003; Tomita 1999; Wada 1999) contributed no data in the format required for the meta-analysis.

Anti-leukotrienes + ICS versus INCREASED dose of ICS

DESIGN

Seven trials, (Green 2002a; Nayak 1998; Nsouli 2000; Price 2003; Ringdal 1999; Tomari 2001; Yildirim 2001), compared the addition of anti-leukotrienes to inhaled corticosteroids to increasing the dose of inhaled corticosteroids in symptomatic patients. All but one trial (Green 2002a) were parallel-group, randomised trials, placebo-controlled. In two trials (Nayak 1998; Ringdal 1999), various doses of anti-leukotrienes were considered in a three-arm trial design (see below). Only two trials are currently full text publications (Price 2003; Tomari 2001), while data for two additional trials (Nayak 1998; Ringdal 1999) were derived from abstracts and unpublished reports kindly provided by Astra-Zeneca, the manufacturer of zafirlukast.

PARTICIPANTS

All trials focused on adults with a mean age of about 40 years, with balanced representation of genders (except in Nayak 1998 with 38% of males). The severity of airway obstruction on baseline was mild to moderate, with mean % FEV1 of 67% to 71% of predicted in 3 trials (Nayak 1998; Price 2003; Tomari 2001) and 85% predicted (Ringdal 1999) while on maintenance inhaled glucocorticoids dose (described below). Allergic triggers were not reported, although 94.2% of patients enrolled in Nayak 1998 had allergic rhinitis.

INTERVENTION

The duration of each trial was: 4 weeks (Green 2002a), 12-13 weeks (Nayak 1998; Nsouli 2000; Price 2003; Ringdal 1999; Yildirim 2001) and 16 weeks (Tomari 2001). Licensed doses of leukotriene receptor antagonists were tested in 6 trials, namely montelukast 10 mg die (Green 2002a; Nsouli 2000; Price 2003; Yildirim 2001), pranlukast 450 mg die (Tomari 2001) and zafirlukast 20 mg bid (Ringdal 1999). Two trials also used higher than licensed doses of zafirlukast of 40 mg bid (Nayak 1998) and 80 bid (Nayak 1998, Ringdal 1999). In the intervention group, BDP or BUD was given at a dose of 200 mcg/day (Green 2002a), 400-500 mcg/day (Nayak 1998; Ringdal 1999; Yildirim 2001) and 600-800 mcg/day in the remaining 3 trials (Nsouli 2000; Price 2003; Tomari 2001). While the control groups all received double-dose of inhaled glucocorticoids, the magnitude of the increased dose was of 400 mcg/day of beclomethasone or equivalent in 3 trials (Nayak 1998; Ringdal 1999; Yildirim 2001) and of 600 to 800 mcg/day in the remaining 4 trials (Green 2002a; Nsouli 2000; Price 2003; Tomari 2001). No additional co-treatment was described other than rescue inhaled beta2-agonists and systemic corticosteroids.

OUTCOMES

The primary outcome was the number of participants with exacerbations requiring systemic corticosteroids: this was documented in only three trials (Nayak 1998; Price 2003; Ringdal 1999). Other measures of asthma control (pulmonary function tests, symptoms scores, functional status indices), withdrawals and adverse effects were also considered. Intention-to-treat analyses were reported in 2 trials (Price 2003; Tomari 2001). Three trials (Green 2002a; Nsouli 2000; Yildirim 2001), all published in abstract form, contributed no data in the format required for the meta-analysis.

Anti-leukotrienes + ICS versus SAME dose of ICS (TAPERING ICS dose)

DESIGN

Seven trials included participants who were well controlled at baseline (Baba 1999; Bateman 1995; Kanness 2002; Laitinen 1995; Lofdahl 1999; Shingo 2001; Tohda 2002), and assessed the magnitude of reduction in inhaled corticosteroids following the addition of anti-leukotrienes. At the time of publication, four trials (Kanness 2002; Lofdahl 1999; Shingo 2001; Tohda 2002) were published in full-text; the data for Bateman 1995 and Laitinen 1995 were derived from abstracts and unpublished reports provided by Astra-Zeneca; the data provided in one abstract (Baba 1999) was insufficient to be used in this review. All but one trial (Kanness 2002) were parallel-group trials; Kanness 2002 described a cross-over study where tapering (from 800 to 400 mcg/day of beclomethasone or equivalent) was initiated in the first period then, without a washout period, patients crossed-over to the alternate treatment strategy in the second period where the dose of inhaled steroids was tapered (from 400 to 200 mcg/day of beclomethasone or equivalent). Because this unusual design did not allow merging of the two periods and because no significant change in asthma control occurred in the first period suggesting of over-treatment at baseline, the second period was chosen for analysis. Use of an identical placebo was described in all but one trial (Baba 1999).

PARTICIPANTS

All trials focused on adults with a mean age of 40 years, with relatively balanced representation of genders and an asthma duration of 13 to 18 years. Participants were well controlled and no evidence of airway obstruction with mean baseline FEV1 of 2.5 to 2.6 L (Bateman 1995; Laitinen 1995) or 83 to 93% predicted FEV1 (Kanness 2002; Lofdahl 1999; Shingo 2002; Tohda 2002). Allergic triggers were reported in 43 to 48% of enrolled participants, when reported (Bateman 1995; Laitinen 1995); the proportion of participants afflicted with allergic rhinitis was not mentioned. No participants' description was provided for one trial (Baba 1999)

INTERVENTION

Only two of the seven trials, (Laitinen 1995; Lofdahl 1999), had a dose optimisation period prior to randomisation during which the maintenance dose of inhaled corticosteroids was tapered according to a standard procedure over a period of two weeks to three months. The intervention period varied from six (Kanness 2002), eight (Shingo 2002), 12 (Laitinen 1995; Lofdahl 1999), 20 weeks (Bateman 1995), and 24 weeks (Tohda 2002) during which the tapering of inhaled corticosteroids to the minimum effective

dose was continued. [Baba 1999](#) failed to describe the intervention duration.

The intervention drugs were: zafirlukast 20 mg bid ([Bateman 1995](#); [Laitinen 1995](#)), montelukast 10 mg die ([Kanniess 2002](#); [Lofdahl 1999](#); [Shingo 2002](#); [Tohda 2002](#)) and pranlukast at an unspecified dose ([Baba 1999](#)). The reported dose of inhaled corticosteroids at randomisation varied widely within and between trials: 400 mcg ([Kanniess 2002](#)), 300 to 3000 mcg ([Lofdahl 1999](#)), 400 to 750 mcg ([Bateman 1995](#)), 945 mcg on average ([Tohda 2002](#)), 800 to 2000 mcg ([Laitinen 1995](#)), 1600 mcg ([Shingo 2002](#)) while it was unreported in one trial ([Baba 1999](#)). [Lofdahl 1999](#) and [Shingo 2002](#) reported the use of several types of inhaled corticosteroids; [Lofdahl 1999](#) reported use of 16% beclomethasone, 22% budesonide, 15% flunisolide, 7% fluticasone, and 40% triamcinolone, but the corticosteroid dose reduction could not be provided in 'beclomethasone-equivalent' dose (TR Reiss, Personal communication, June 2000); [Shingo 2002](#) reported the use of triamcinolone in 72%, flunisolide in 18% and beclomethasone in 10%. [Baba 1999](#), [Bateman 1995](#), [Kanniess 2002](#), [Laitinen 1995](#), and [Tohda 2002](#) reported the use of beclomethasone and/or budesonide.

OUTCOMES

The primary outcome with the tapering-steroid studies was the change from baseline in the dose of inhaled corticosteroids needed to maintain asthma control. This was documented in sufficient detail to permit aggregation of data in four trials after 12 to 24 weeks of tapering ([Bateman 1995](#); [Laitinen 1995](#); [Lofdahl 1999](#); [Tohda 2002](#)). In the study by [Kanniess 2002](#), the tapering from 400 mcg to 200 mcg was forced and thus, could not served to document the minimal effective dose; instead the data was used to document maintenance of asthma control. The lowest tolerated dose reported by [Lofdahl 1999](#) was assumed to have been observed after 12 ±4 weeks. Intention-to-treat analyses were used in four trials ([Bateman 1995](#); [Kanniess 2002](#); [Lofdahl 1999](#); [Shingo 2002](#)). To confirm the stability of participants, [Bateman 1995](#), [Laitinen 1995](#) and [Shingo 2002](#) reported the other measures of asthma control as final values measured at the endpoint (or end of study). [Kanniess 2002](#), [Lofdahl 1999](#), and [Tohda 2002](#) reported change from baseline at the lowest tolerated ICS dose, irrespective of when this was achieved. One study ([Baba 1999](#)) published in abstract form contributed insufficient data to include in the meta-analysis.

Excluded studies

Of these 560 citations were excluded for the following mutually exclusive reasons: (1) duplicate references (N = 115), (2) not a randomised controlled trial (N = 231), ongoing trials (N = 3), or awaiting assessment (N = 3) (3) subjects were not asthmatics (N = 16), (4) the tested intervention was not anti-leukotrienes (N = 15), (5) no consistent co-treatment with inhaled glucocorticoids (N = 138), (6) the control intervention was not inhaled corticosteroids (N = 19), (7) use of non permitted drugs (N = 5), (8) the tested intervention was administered for less than 4 weeks (N = 7), (9) outcomes measures did not reflect asthma control (N = 7) and (10) acute care setting (N = 1). Due to the large number of citations considered, the references and reasons for exclusion are provided only for full-text randomised controlled trials.

Risk of bias in included studies

Fifteen of the 27 trials had high reported methodological quality with a Jadad score ≥ 4 ([Bateman 1995](#); [Hultquist 2000](#); [Kanniess 2002](#); [Laitinen 1995](#); [Laviolette 1999](#); [Lofdahl 1999](#); [Nayak 1998](#); [Price 2003](#); [Ringdal 1999](#); [Shingo 2002](#); [Simons 2001](#); [Tamaoki 1997](#); [Tohda 2002](#); [Vaquerizo 2003](#); [Virchow 2000](#)); confirmation of methodology was confirmed in 15 trials ([Bateman 1995](#); [Hultquist 2000](#); [Kanniess 2002](#); [Laitinen 1995](#); [Laviolette 1999](#); [Lofdahl 1999](#); [Nayak 1998](#); [Price 2003](#); [Ringdal 1999](#); [Riccioni 2001](#); [Riccioni 2002](#); [Shingo 2001](#); [Simons 2001](#); [Tohda 2002](#); [Virchow 2000](#)).

Blinding of allocation: all but 7 trials ([Baba 1999](#); [Riccioni 2001](#); [Riccioni 2002](#); [Tomita 1999](#); [Wada 1999](#); [Nsouli 2000](#); [Tomari 2001](#); [Yildirim 2001](#)) clearly reported convincing blinding of treatment. Poor reported methodological quality were often associated with abstract report.

Randomisation was clearly described and appropriate in 16 trials ([Hultquist 2000](#); [Bateman 1995](#); [Kanniess 2002](#); [Laitinen 1995](#); [Laviolette 1999](#); [Lofdahl 1999](#); [Nayak 1998](#); [Price 2003](#); [Riccioni 2001](#); [Riccioni 2002](#); [Riccioni 2002](#); [Ringdal 1999](#); [Simons 2001](#); [Shingo 2001](#); [Tohda 2002](#); [Vaquerizo 2003](#); [Virchow 2000](#)); reporting of methods of randomisation and mode of allocation not insufficiently described in the remaining trials.

Withdrawal rate was described in all but seven trials ([Baba 1999](#); [Finn 2000](#); [Green 2002a](#); [Nishimura 1999](#); [Nsouli 2000](#); [Tomita 1999](#); [Yildirim 2001](#)). Withdrawal rates varied from 2% ([Simons 2001](#)) to 27% ([Lofdahl 1999](#)) in the control group and from 2% ([Tamaoki 1997](#)) to 20% ([Bateman 1995](#)) in the intervention group.

Effects of interventions

The results are stratified within each study protocol on the use of usual, versus higher than licensed, doses of anti-leukotrienes and anti-leukotriene used.

(1) Anti-leukotrienes + ICS vs. SAME dose of ICS

Of the thirteen trials using this protocol, five trials (2 abstracts [Finn 2000](#); [Nishimura 1999](#); and 3 full-text publications [O'Sullivan 2003](#), [Tomita 1999](#), [Wada 1999](#)) reported data in a way that could not be used in this review. The meta-analysis therefore pertains to 8 trials contributing data to the following outcomes.

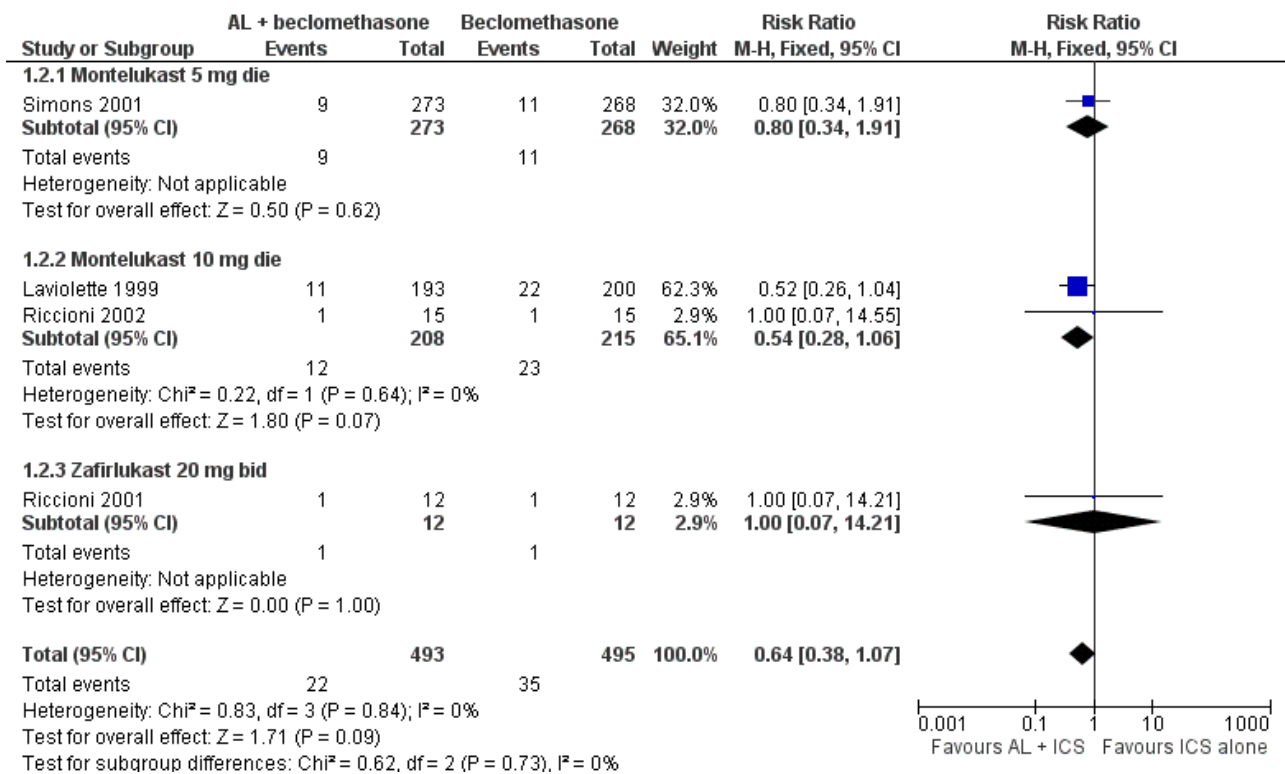
Primary outcome: requirement for oral steroids

Although 6 trials ([Laviolette 1999](#); [Riccioni 2001](#); [Riccioni 2002](#); [Simons 2001](#); [Tamaoki 1997](#); [Virchow 2000](#)) contributed data to the primary outcome, only four trials tested anti-leukotrienes at licensed doses, namely zafirlukast ([Riccioni 2001](#)) and montelukast at adult ([Laviolette 1999](#); [Riccioni 2002](#)) and paediatric ([Simons 2001](#)) doses. The addition of licensed doses of anti-leukotrienes to 400 to 800 mcg/day of beclomethasone or equivalent resulted in a non-significant reduction in the risk of exacerbations requiring systemic steroids (RR 0.64, 95% CI 0.38 to 1.07, [Figure 1](#)). When higher than licensed doses were examined, the addition of pranlukast or zafirlukast to high doses of inhaled corticosteroids clearly reduced by 66% the risk of exacerbations requiring systemic steroids (RR 0.34, 95% CI 0.13 to 0.88, [Analysis 1.1](#)). The number of patients needed to be treated with higher than licensed doses of anti-leukotrienes to prevent one patient with exacerbation(s) requiring systemic corticosteroids is 22 (95% CI 17 to 117). Between

and within each stratum (licensed versus higher than licensed doses of anti-leukotrienes), the results were homogeneous despite the different doses and anti-leukotrienes tested, age, baseline dose of inhaled glucocorticoids and duration of intervention. The individual effect of the type of anti-leukotrienes, dose of beclomethasone (400 to 1600 mcg/day), duration of treatment (4 to 16 weeks), asthma triggers, and intention-to-treat (not reported

for Tamaoki 1997) on this outcome could not be examined due to insufficient trials and/or inadequate reporting. Removal of the two trials with no convincing blinding (Riccioni 2001; Riccioni 2002) did not affect the results (RR 0.61, 95% CI 0.36 to 1.05). Due to the published status of all six contributing trials, no additional sensitivity analyses were performed.

Figure 1. Forest plot of comparison: 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, outcome: 1.2 Patients with exacerbations requiring systemic steroids with licensed AL doses at 4 to 16 weeks.



Secondary outcomes

Pooling of the four trials testing the use of licensed doses of montelukast or zafirlukast for 4 (Simons 2001), 8 (Hultquist 2000), and 16 weeks (Laviolette 1999, Vaquerizo 2003) revealed significant, but modest, group differences in favour of anti-leukotrienes in the change from baseline in morning peak expiratory flow rate (4 trials, WMD 7.65 L/min, 95% CI 3.55 to 11.75), β_2 -agonists use (4 trials, SMD -0.15, 95% CI -0.24 to -0.05) or (3 trials, WMD -1, 95% CI: -0.5 to -2 puffs/week), and eosinophil counts (N=2 trials, WMD -0.07 x 10e9/L, 95% CI -0.14 to 0.00, random effects model). No significant group difference was observed in the change in FEV1 (3 trials, WMD 0.06 L, 95% CI -0.01 to 0.14; random effects model), symptom score (2 trials, WMD = -0.10, 95% CI -0.24 to 0.03), nocturnal awakenings (2 trials, WMD -6.25, 95% CI -12.72 to 0.23) or quality of life (2 trials, WMD 0.08, 95% CI -0.03 to 0.20). No significant group differences were observed in the risk of overall withdrawals (3 trials, RR 0.97, 95% CI 0.69 to 1.37), withdrawal due to poor asthma control (3 trials, RR 0.46, 95% CI 0.16 to 1.31), withdrawals due to adverse effects (3 trials, RR 0.63, 95% CI 0.29 to 1.37), overall adverse effects (2 trials, RR 1.01, 95% CI 0.88 to 1.15), elevated liver enzymes (2 trials, RR 1.02, 95% CI 0.36 to 2.88), headache (3 trials,

RR 1.15, 95% CI 0.89 to 1.49), and nausea (2 trials, RR 0.45, 95% CI 0.19 to 1.07). There was no death. Insufficient number of trials prevented the pooling of data for nocturnal waking, markers of inflammation, and hospital admissions.

Pooling of the two trials using higher than licensed doses of pranlukast (Tamaoki 1997) or zafirlukast (Virchow 2000) for six weeks of treatment, revealed a significant group difference favouring the addition of anti-leukotrienes to inhaled corticosteroids in the magnitude of improvement from baseline in FEV1 (WMD= 0.10 L, 95% CI 0.01 to 0.20), PEFR (WMD= 27.2 L/min, 95% CI: 18.6 to 35.8); asthma symptom scores (SMD= -0.46, 95% CI -0.25 to -0.66); use of rescue beta2-agonists (SMD -0.43, 95% CI -0.22 to -0.63). No significant group difference was observed the change from baseline in night awakenings (WMD -0.52 episodes/week, 95% CI -1.35 to 0.32).

There was no significant group difference in the risk of overall withdrawals (2 trials, RR 0.74 95% CI 0.39 to 1.39), withdrawals due to adverse effects (RR 0.73, 95% CI: 0.28 to 1.88), overall adverse effects (RR 1.02, 95% CI: 0.81 to 1.27) and nausea (RR 1.48, 95% CI 0.45 to 4.87). Insufficient data prevented pooling of trials for

withdrawals due to poor asthma control, inflammatory markers, headache, elevated liver enzymes and death.

while two trials (Nayak 1998; Ringdal 1999) also tested higher than licensed doses.

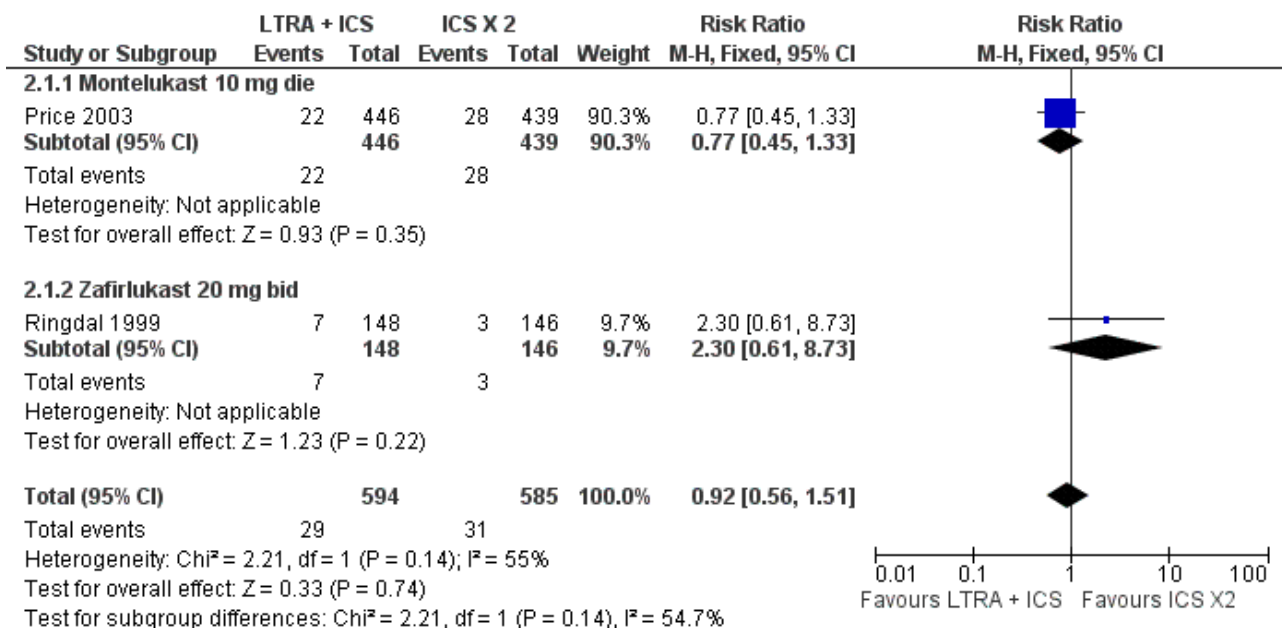
(2) Anti-leukotrienes + ICS vs. INCREASED dose of ICS

Of the seven trials using this protocol, three trials (Green 2002a; Nsouli 2000; Yildirim 2001) all published in abstract form, reported data in a way that could not be used in this review. The meta-analysis therefore pertains to 4 trials contributing data to the following outcomes. Three trials (Price 2003; Ringdal 1999; Tomari 2001) tested licensed doses of leukotriene receptor antagonist

Primary outcome: requirement for oral steroids

When comparing the combination of licensed doses of leukotriene receptor antagonist with 400 - 800 mcg/day of BDP or equivalent to doubling the dose of inhaled steroids, there was no significant group difference in the risk of experiencing an asthma exacerbation requiring systemic steroids (2 trials, RR 0.92, 95% CI 0.56 to 1.51, Figure 2); this finding did not meet our criteria of equivalence.

Figure 2. Forest plot of comparison: 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, outcome: 2.1 Patients with 1 or more exacerbations requiring systemic steroids at LICENSED DOSES.



When comparing the combination of two to four-fold the licensed doses of leukotriene receptor antagonists with 400-500 mcg/day of BDP or equivalent as opposed to doubling the dose of inhaled steroids, there was no significant group difference in the risk of experiencing an asthma exacerbation requiring systemic steroids (2 trials, RR 1.05 95% CI 0.55 to 2.00, Analysis 2.2); this finding did not meet our criteria of equivalence.

Secondary outcomes

There was also no significant group difference in the change from baseline in AM peak expiratory flow rate (2 trials, WMD 1.56, 95% CI -5.77 to 8.89; random effect model), in symptoms score (2 trials, WMD 0.01, 95% CI -0.09 to 0.10), in use of rescue B2-agonists (2 trials, WMD -0.03 95% CI -0.24 to 0.18), withdrawals due to poor asthma control (2 trials, RR 0.49, 95% CI 0.15 to 1.63). Safety measures also show no significant group difference for overall withdrawals (2 trials, RR 0.99, 95% CI 0.63 to 1.55), withdrawals due to side effects (2 trials, RR 1.14, 95% CI 0.55 to 2.37), overall adverse effects (2 trials, RR 0.95, 95% CI 0.84 to 1.06), elevated liver enzymes (2 trials, RR 0.8 95% CI 0.34 to 1.92), headache (2 trials, RR 1.07, 95% CI 0.76 to 1.52), and nausea (2 trials, RR 0.63 95% CI 0.25 to 1.60). There was no death. The width of all these confidence interval exceeded our definition of equivalence. Insufficient data

preventing pooling of trials for FEV1, diurnal variation in PEF, night waking, admission and moniliasis. The small number of trials prevented subgroup and sensitivity analyses.

The change from baseline in FEV1 in favour of anti-leukotrienes reached our definition of equivalence (2 trials, RR 0.01, 95% CI -0.05 to 0.07). With regards to other outcomes, no significant group difference were observed in the change from baseline in AM peak expiratory flow rate (3 trials, WMD 6.05, 95% CI -1.26 to 13.36), in change in diurnal variation in peak expiratory flow rate (3 trials, SMD -0.11%, 95% CI -0.23 to 0.03), in change in symptoms (3 trials, WMD -0.06, 95% CI -0.16 to 0.03), in use of rescue B2-agonists (3 trials, WMD 0.00 95% CI -0.37 to 0.37), and in withdrawals due to poor asthma control (3 trials, RR 0.72 95% CI 0.29 to 1.76); the width of all these confidence intervals exceeded our definition of equivalence.

With regards to safety, use of higher than licensed doses of leukotriene receptor antagonist was associated with a five-fold increased risk of liver enzyme elevation (3 trials, RR 4.97 95% CI 1.45 to 17), but has a marked protective effect on oral moniliasis (3 trials, RR 0.29 95% CI 0.10 to 0.81). Other safety measures show no significant group difference, namely for overall withdrawals (3 trials, RR 1.05 95% CI 0.73 to 1.50), withdrawals due to side effects

(3 trials, RR 2.27 95% CI 0.95 to 5.45), overall adverse effects (3 trials, RR 0.98 95% CI 0.89 to 1.07), headache (3 trials, RR 1.14 95% CI 1.14 to 1.63), and nausea (3 trials, RR 1.77 95% CI 0.79 to 3.95). There was no death. The small number of trials prevented subgroup and sensitivity analyses.

(3) Anti-leukotrienes + ICS vs. SAME dose of ICS (TAPERING ICS dose)

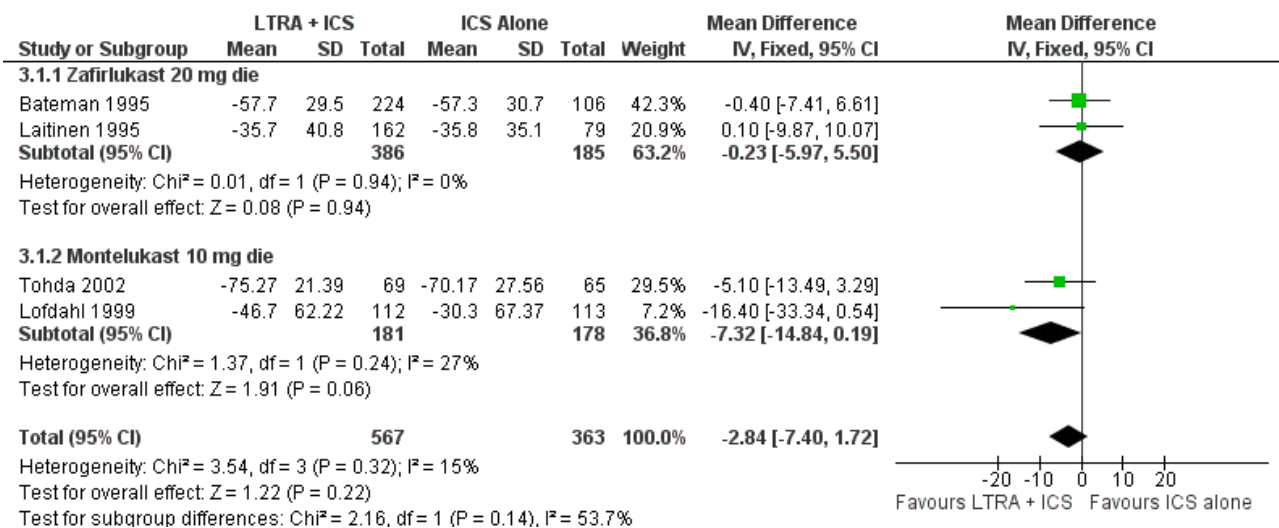
The data from six of the seven identified trials, all testing licensed doses of anti-leukotrienes, were provided in sufficient details to be analysed. (Bateman 1995; Kanniss 2002; Laitinen 1995; Lofdahl 1999; Shingo 2001; Tohda 2002).

Assessment of the glucocorticoid-sparing effect of anti-leukotrienes rests on the demonstration that asthma control was adequate after tapering and comparable between the treatment and control groups.

Primary outcome: maintenance dose of inhaled corticosteroids

After 6 to 24 weeks of treatment, there was no significant group difference in the % change from baseline in the inhaled corticosteroid dose required to maintain asthma control (4 trials; WMD -3%, 95% CI: -7 to 2; Figure 3). When the lowest tolerated dose of inhaled glucocorticoids was considered, no significant group difference was observed either (4 trials, WMD -21 mcg/day, 95% CI: -65 to 23; Analysis 3.2). There was no heterogeneity between the four trials contributing data to the glucocorticoids dose reduction although the trials differed not only in the dose and anti-leukotriene used, but also in the baseline dose and inhaled glucocorticoid used, dose optimisation period, weaning protocol, and intention-to-treat analysis. When the two trials not analysed by intention-to-treat were excluded, the lowest tolerated dose of glucocorticoids remained not significantly different between groups (WMD -71, 95% CI -284 to 141). The rate of complete glucocorticoid weaning was similar between groups (3 trials, RR 1.18, 95% CI 0.95 to 1.47; Analysis 3.4).

Figure 3. Forest plot of comparison: 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, outcome: 3.1 % Change from baseline ICS dose at 12 -24 weeks.



Secondary outcomes

After 12 to 20 weeks of treatment, two trials using zafirlukast (Bateman 1995; Laitinen 1995), reported no significant group difference in final FEV1 (WMD 0.13 L, 95% CI -0.02 to 0.27), final PEFr (WMD 17.98.0 L/min, 95% -1.68 to 37.64), final symptom scores (WMD -0.06, 95% CI -0.17 to 0.05), final β2-agonists use (WMD -0.2 puffs/day, 95% CI -0.7 to 0.3). More sensitive outcomes for insuring similar asthma control are the changes from baseline. When the lowest tolerated dose of inhaled glucocorticoids was reached, there was no significant group difference in the change from baseline in FEV1 (2 trials, WMD 0 L, 95% CI -0.10 to 0.09), in PEFr (2 trials, WMD 7.9 L/min, 95% CI: -1.61 to 17.4) and in β2-agonists use (2 trials, WMD -0.15 puffs/week; 95% CI -0.91, 0.61). Yet, pooling of the five trials revealed a marked reduction (RR 0.63, 95% CI 0.42 to 0.95) in the rate of withdrawals due to poor asthma control in the group treated with leukotriene receptor antagonists, suggesting better asthma control with the combination therapy. When only the trials using intention-to-treat analysis were considered, the rate of withdrawals due to poor asthma control was unaffected (RR 0.63, 95% CI 0.42 to 0.95). A trend favouring leukotriene receptor antagonists was also

observed in the number of patients with exacerbations requiring systemic steroids (RR 0.47, 95% CI 0.20, 1.09).

Markers of inflammation such as serum eosinophils showed no group difference (WMD 0.18, 95% CI -1.13 to 1.50); nitric oxide concentration was only reported for one study, preventing pooling of data.

Less withdrawals due to any cause were observed in the leukotriene receptor antagonists group (6 trials, RR 0.77, 95% CI: 0.60 to 0.98), probably influenced by the marked reduction in withdrawals due to poor asthma control in the anti-leukotriene group.

With regard to side effects, there was no group difference in the number of withdrawals due to adverse effects (RR 0.88; 95% CI 0.52 to 1.51) overall adverse effects (RR 0.95; 95% CI 0.83 to 1.08, random effect model), elevated liver enzymes (RR 1.67, 95% CI 0.86 to 3.21), headache (RR 0.79, 95% CI 0.58 to 1.08), nausea (RR 1.49, 95% CI 0.70 to 3.19). In contrast, there was a significant increased risk of serious adverse events defined in accordance to the U.S. Food and Drug Administration (FDA) criteria (Anonymous 2001),

associated with zafirlukast (RR 2.47, 95% CI 1.53 to 3.97) (Bateman 1995; Laitinen 1995). Only one death, not related to asthma, was reported.

DISCUSSION

In patients who were symptomatic on inhaled corticosteroids (ICS), two treatment alternatives were addressed in these studies: adding an anti-leukotriene agent or increasing the dose of inhaled corticosteroids.

When compared to an unchanged dose of ICS, the addition of LICENSED doses of anti-leukotrienes resulted in a non-significant reduction in the risk of exacerbations requiring systemic glucocorticoids with modest group differences in peak expiratory flow (+8 L/min), β_2 -agonist use (-0.3 puffs/day), and eosinophils counts (-0.07×10^9) in favour of anti-leukotrienes. The beneficial effect of anti-leukotrienes was clearly apparent with HIGHER THAN LICENSED doses of pranlukast or zafirlukast where a 66% reduction in exacerbations requiring rescue glucocorticoids was firmly documented. Twenty two (95% Confidence interval: 17 to 117) patients would need to receive anti-leukotrienes at unlicensed doses to prevent one patient having an exacerbation that required systemic corticosteroids during the six weeks of treatment. Group differences in the improvement from baseline in FEV1 (+100 mL), PEF (+27 L/min), symptoms (-0.5 SD) and β_2 -agonist use (-0.4 SD) in favour of the combination of anti-leukotrienes and ICS are consistent with the reduction in exacerbations. When licensed and unlicensed doses of anti-leukotrienes were combined, no statistical heterogeneity was observed despite variation in the dose and anti-leukotrienes used, dose (750-2000 mcg/day) of beclomethasone, age, duration of treatment and intention-to-treat analysis. The risk of side effects from anti-leukotrienes was comparable to that of placebo. The available evidence thus suggests a modest effect of licensed doses of montelukast in symptomatic children and adults, but a clear beneficial effect of higher than licensed doses of pranlukast and zafirlukast, as add-on therapy to inhaled glucocorticoids in adults.

In symptomatic patients, however, most physicians would be uncomfortable with status quo; the majority would increase the dose of inhaled glucocorticoids or consider additional therapy. Only three trials compared the combination of licensed doses of leukotriene receptor antagonists with 400 to 800 mcg/day of BDP (or equivalent) to increasing the dose of inhaled steroids by 400-800 mcg/day. There was no significant group difference in the risk of experiencing a moderate exacerbations or any other outcomes, but due to the paucity of trials, equivalency could not be established. Both two options appears comparably safe.

When the combination of leukotriene receptor antagonists at higher than licensed doses with 400-500 mcg/day of BDP (or equivalent) was compared to doubling the dose of inhaled steroids, the improvement in FEV1 was equivalent between the two treatment options, with a modest benefit in the diurnal variation of peak flow rates in favour of anti-leukotrienes. However, no other group differences in exacerbations requiring systemic steroids, peak flow, symptoms, and use of rescue beta2-agonists were observed: again, there was insufficient power to conclude to equivalency. The use of higher doses of zafirlukast was associated with a five-fold increase in the risk of liver enzyme elevation, but was clearly protective for oral moniliasis, raising serious doubt about the safety of this strategy.

Also of interest is whether the addition of anti-leukotrienes will allow a meaningful reduction in the dose of inhaled glucocorticoids required to maintain control. Data from six trials (Bateman 1995; Kanness 2002; Laitinen 1995; Lofdahl 1999; Shingo 2001; Tohda 2002) all using licensed doses of anti-leukotrienes, tested the inhaled corticosteroid sparing properties of anti-leukotrienes.

In adults well controlled on various doses (300 to 3000 mcg/day) of inhaled glucocorticoids, a 6 to 24-week treatment combining daily oral anti-leukotrienes with inhaled steroids did not result in a reduction in the dose of inhaled steroids any more than placebo (Bateman 1995; Laitinen 1995; Lofdahl 1999; Tohda 2002). No significant group differences were observed in the lowest tolerated dose of inhaled steroids or in the rate of patients with complete steroid withdrawal. Pooling of trials did not result any statistical heterogeneity.

To establish the overall or relative efficacy of anti-leukotrienes, the level of asthma control achieved after glucocorticoid tapering must be similar among groups. In fact, patients treated with anti-leukotrienes appeared to have better control than the placebo group, with a significant 37% reduction in withdrawals due to poor asthma control; yet there was no group difference in the change from baseline in FEV1 and PEF after the minimal tolerated dose was achieved. The apparent discordant findings may be explained by the small number of trials (N=2) reporting change from baseline in FEV1 compared to the 5 trials reporting withdrawals and by the inconsistent use of intention-to-treat analyses. These observations may suggest that various factors such as trial-specific designs may influence the level of asthma control after tapering. Possible explanations include differences in the dose optimisation period prior to randomisation, tapering protocols, baseline dose of inhaled glucocorticoids, anti-leukotriene used, and intention-to-treat analysis. A longer tapering period for example, may have permitted greater reduction in the dose of inhaled corticosteroids or demonstrated better asthma control in favour of anti-leukotriene agents. Although there are insufficient data to make a firm conclusion, based on the upper confidence limit for each anti-leukotrienes, the maximal glucocorticoid-sparing effect of anti-leukotrienes would probably be less than 300 mcg/day. This is concordant with a previous systematic review demonstrating that the use of anti-leukotrienes as single agent is less effective than 400 mcg/day of beclomethasone (Ducharme 2001).

Although, there are insufficient data to make firm conclusions about the magnitude of the corticosteroid-sparing effect of anti-leukotriene agents, it is important to note that during the pre-randomisation run-in period of Lofdahl 1999, it was possible to taper the dose of inhaled corticosteroids by 500-600 mcg, a third of the original dose. A reduction of similar magnitude was observed in the placebo group after randomisation. Similarly Kanness 2002 reduced by 400 mcg the baseline dose of beclomethasone with no difference in asthma control. This attests to a general overdosing of enrolled patients. If the patients recruited to this study were typical of patients on moderate-high dose inhaled corticosteroids, the level of dose reduction achievable, without any additional treatment, appears to far outweigh that achieved with anti-leukotriene agents. The importance of repeated attempts at tapering the dose of inhaled corticosteroids in well-controlled patients is clear.

With only one paediatric trial contributing data and showing little benefit, extrapolation of data from any of the above protocols to children remains speculative.

There is insufficient data to determine whether patients' characteristics such as age, severity of airway obstruction on baseline, asthma triggers, and baseline dose of inhaled glucocorticoids required to achieve control have any influence of the magnitude of response. With the lack of heterogeneity between trials, there is no evidence to suggest that the anti-leukotriene used and duration of intervention affect the findings.

Like all systematic reviews, this meta-analysis is limited by the quantity and quality of existing data (Khan 1996). Despite the abundance of literature on anti-leukotrienes, few randomised controlled trials were designed to assess the role of anti-leukotrienes as add-on therapy to inhaled glucocorticoids; 67% of trials compared anti-leukotrienes to placebo in groups of patients comprised of, or including, steroid naive patients. Most included trials (15/16) contributing data to the meta-analysis were of high methodological quality (Jadad score ≥ 4). Data from 9 of the 11 trials with lower reported methodological quality (Jadad score ≤ 3) were not used in this review because they were not reported in a way that permitted aggregation and thus, could not bias the conclusions (Baba 1999; Finn 2000; Green 2002a; Nishimura 1999; Nsouli 2000; O'Sullivan 2003; Tomari 2001; Tomita 1999; Wada 1999; Yildirim 2001). Sensitivity analyses excluding the remaining 2 trials with Jadad score of 0 (Riccioni 2001; Riccioni 2002) failed to alter the findings. A thorough systematic search resulted in the identification of methodologically strong, unpublished trials, increasing the power and scope of the review (Cook 1993; Thornton 2000). The value of this review is strengthened by the direct confirmation of methodology and extracted data from the authors or sponsors of 15 of 27 trials, and the voluntary disclosure of data for five unpublished trials (Hultquist 2000; Nayak 1998; Ringdal 1999; Bateman 1995; Laitinen 1995). Because the number and size of studies pooled under each protocol was small, the robustness of the analyses could not be assessed. Furthermore, the influence on study results of different types of inhaled glucocorticoids and anti-leukotrienes, doses, age, duration of intervention, severity of airway obstruction on baseline, and asthma triggers remain speculative. No trials have documented the known adverse effects associated with prolonged use of inhaled glucocorticoids such as osteopenia, adrenal suppression, and growth suppression in children, which would permit a fairer comparison between the safety profile of treatment options. Clearly, these preliminary conclusions may be modified with accumulating data from future well-designed trials.

This review summarises the best evidence available until August 2003 and emphasises the ongoing shortage of relevant trials testing the role of licensed doses of anti-leukotrienes as add-on to inhaled glucocorticoids.

AUTHORS' CONCLUSIONS

Implications for practice

The small number and short duration of trials pooled under each protocol preclude firm conclusions. However, the data currently available suggest that:

(1) In patients with chronic asthma who are symptomatic on ≥ 400 mcg/day of inhaled beclomethasone, the addition of licensed doses of montelukast to inhaled glucocorticoids may improve lung function, symptoms, and use of relief beta2-agonists by a modest amount. High dose of anti-leukotrienes (2 to 4 times the licensed dose of pranlukast or zafirlukast) reduces the rate of exacerbations that require systemic corticosteroids; approximately 22 patients would have to be treated to achieve this effect. Use of higher than licensed doses of anti-leukotrienes are also associated with significant improvement in lung function, symptoms, and use of relief beta-2 agonists.

(2) In patients treated with 400 to 800 mcg/day of beclomethasone-equivalent of inhaled corticosteroids, use of licensed doses of leukotriene receptor antagonists are associated with improvement similar to that of dose doubling of inhaled glucocorticoids but there is insufficient power to conclude to equivalency. Use of higher than the licensed dose of zafirlukast also appears to have a similar, but not equivalent, effect to that of doubling the dose of inhaled steroids. However, this is associated with increased risk of liver enzyme elevation. With only three trials, there is still insufficient evidence to firmly recommend the use of licensed doses of anti-leukotrienes as a substitute to increasing the dose of inhaled glucocorticoids.

(3) In well-controlled patients, the addition of anti-leukotrienes as compared to placebo is possibly associated with superior asthma control after glucocorticoids tapering. There is insufficient evidence to firmly quantify the corticosteroids-sparing effect, which would appear to be less than 300 mcg/day of beclomethasone or equivalent.

To date, there is no evidence to suggest that the anti-leukotriene used (montelukast, zafirlukast, or pranlukast) influenced the response to treatment: the findings appear similar irrespective of the leukotriene receptor antagonists.

Implications for research

Future studies should focus on children in whom few trials have been published. Two main protocols should be examined:

- the addition of anti-leukotriene agents to inhaled corticosteroids versus dose-doubling of inhaled corticosteroids in symptomatic children and adults (grouped separately)
- the corticosteroid-sparing effect of anti-leukotriene agents, after ensuring similar asthma control between the treatment and control groups, in well-controlled children and adults (grouped separately).

In addition, the following issues should be considered:

The best way to assess corticosteroids-sparing effect of anti-leukotrienes as 'add-on' therapy to inhaled corticosteroids is to design trials with a prolonged run-in period prior to randomisation, during which inhaled corticosteroids are tapered to the minimum effective dose. The run-in period may need to be as long as 16 weeks as evidenced by the large reduction in maintenance dose of inhaled corticosteroids in the placebo groups both pre- and post-randomisation. Documentation of comparable asthma control after tapering must be demonstrated, preferably with exacerbations requiring systemic steroids and change from baseline in lung function, asthma symptoms, and use of rescue beta-2 agonists. The corticosteroids-sparing effect should be

reported at the lowest tolerated dose in an intention-to-treat analysis.

The trials should :

- be double-blind, randomised, with complete reporting of withdrawals and drop-outs and intention-to-treat analysis
- be parallel-group
- involve relatively homogeneous asthmatics in terms of severity of airway obstruction on baseline as evidenced by their lung function on a given dose of inhaled glucocorticoids.
- have a minimal intervention period of ≥ 24 -52 weeks for assessing the corticosteroid-sparing effect and long-term side effects of both interventions (anti-leukotrienes and inhaled corticosteroids)
- provide complete reporting of continuous (N, mean change and mean standard deviation of change) and dichotomous (denominators and event rate) data.
- report specifically the number of patients with exacerbations requiring systemic corticosteroids and those requiring hospital admissions
- report specifically change from baseline (rather than final values at the end of the intervention period) in lung function, symptoms, functional status, use of rescue beta2- agonist.
- systematically document reasons for withdrawals and adverse effects, including those associated with inhaled corticosteroids

such as oral candidiasis, osteopenia, adrenal suppression, growth suppression, etc.

- test anti-leukotriene agents (synthesis inhibitor and receptor antagonists) at LICENSED DOSES
- use more uniform doses and type of inhaled corticosteroids (reported in mcg/day of CFC-beclomethasone- equivalent), whenever possible, within the same trial.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Baba 1999

Methods	DESIGN: -parallel-group -3 arm study: a. pranlukast b. seratrodast c. placebo ALLOCATION -random (means of allocation un-specified) BLINDING -not specified -placebo-controlled WITHDRAWAL/DROPOUTS -not described JADAD's Quality Score = 1 Confirmation of methodology not obtained
Participants	WELL-CONTROLLED PARTICIPANTS -RANDOMISED = 24 Pranlukast = 8/ Control = 9/ Seratrodast = 7 -WITHDRAWALS: not described -AGE: not described -GENDER: not described -SEVERITY: not described

Baba 1999 (Continued)

-Baseline FEV1(L)
not described

-ALLERGEN TRIGGERS:
not described

-ASTHMA DURATION: not described

ELIGIBILITY CRITERIA
-AGE: not described

-well-controlled on non-described dose of beclomethasone

Interventions

PROTOCOL:
AL + ICS vs same dose
ICS (TAPERING ICS dose)

DURATION
-Dose optimisation period: not described

-Intervention Period: not described

TEST GROUP
-Pranlukast (dose not specified)
+ beclomethasone (dose not specified)

CONTROL GROUP
-Placebo + beclomethasone (dose not specified)

DEVICE
-not specified

-CO-TREATMENT: not specified

CRITERIA FOR TAPERING every 4 weeks by 50% the beclomethasone dose

MINIMAL DOSE OF ICS ALLOWED: 1/3 to 1/4 of baseline dose

Outcomes

INTENTION-TO-TREAT ANALYSES
-not specified

PULMONARY FUNCTION TESTS
-PEF rates

-SYMPTOM SCORES
not reported

FUNCTIONAL STATUS
-not reported
-exacerbations

ICS DOSE REDUCTION:
-not reported
-successful tapering

INFLAMMATORY MARKERS:
not reported

ADVERSE EFFECTS
-not reported

WITHDRAWALS
-not reported

Baba 1999 (Continued)

Notes

- Abs (1999)
- funding source (not specified)
- No contact information provided in abstract. Unable to request confirmation of methodology and data extraction until publication in full-text of the report
- User-defined order: unable to be determined (re: un-specified mean daily ICS dose)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Bateman 1995

Methods

DESIGN: -parallel-group
 -multicentre trial

ALLOCATION
 -Random: 2:1 ratio intervention:control -Computer-generated

BLINDING
 -double-blind
 -placebo-controlled
 -identical placebo

WITHDRAWAL/DROPOUTS
 -described

JADAD's Quality Score = 5

Confirmation of methodology obtained

Participants

WELL-CONTROLLED PARTICIPANTS

- RANDOMISED = 359
 Zafirlukast = 242/
 Control = 117
- WITHDRAWALS:
 Zafirlukast: 20%
 Control: 22%
- AGE: Zafirlukast: 42.2 ± 14.8 (SD) years Control: 41.6 ± 14.2 years
- GENDER: Zafirlukast: 45% male
 Control: 44% male
- SEVERITY: mild asthma
- Baseline FEV1(L)
 Zafirlukast: 2.64 ± 0.86 (SD) L Control: 2.63 ± 0.85 (SD)
- ALLERGEN TRIGGERS:
 Zafirlukast: 48%
 Control: 49%
- ASTHMA DURATION: Zafirlukast: 13.1 ± 12.3 (SD) years

Bateman 1995 (Continued)

Control: 14.1±13.0 years

ELIGIBILITY CRITERIA

- AGE: 12 to 70 years
- reversibility >= 15% after inhaled beta2-agonists
- well-controlled on ICS 400 to 750 mcg daily (Beclomethasone or BUDesonide)

Interventions

PROTOCOL:

AL + ICS vs same dose ICS (TAPERING ICS dose)

DURATION

- Run-in Period: 1 week to confirm asthma control -Dose optimisation period: NONE
- Intervention Period: 20 weeks

TEST GROUP

-ICI 204,219 = Zafirlukast 20 mg bid p.o. + ICS 400 to 750 ug/day (beclomethasone or BUDesonide)

CONTROL GROUP

-Placebo + ICS 400 to 750 ug/day (beclomethasone or BUDesonide)

DEVICE

-various devices used

-CO-TREATMENT: none reported

CRITERIA FOR TAPERING ICS every 2 weeks:

- FEV1 >= 80% of predicted
- B2-use <= 800 ug/day of salbutamol

MINIMAL DOSE OF ICS ALLOWED: None

Outcomes

PER-PROTOCOL (PP) ANALYSES

- some intention-to-treat (ITT) analysis
- outcomes used at 6, 12, and 20 weeks

PULMONARY FUNCTION TESTS (reported as cross-sectional values not as change from baseline)

- FEV1 (L) - ITT
- Am PEFR -PP (L/min)

SYMPTOM SCORES (PP)

-Mean daytime symptom scores (range 0 to 3)

FUNCTIONAL STATUS (PP)

- Mean daily use of B2-agonists at (puffs/day) averaged over a week

ICS DOSE REDUCTION (PP)

- **ICS dose reduction (%)
- % complete ICS withdrawal

INFLAMMATORY MARKERS

-not reported

ADVERSE EFFECTS

-elevated liver enzymes, headache, nausea, death, etc.

WITHDRAWALS

-reported

(** denotes primary outcomes)

Notes

-Abs (1995) and unpublished data graciously provided by Christopher Miller and Susan Shaffer from Astra-Zeneca, USA (Oct 2000)

-funded by Zeneca

Bateman 1995 (Continued)

-Confirmation of methodology and data extraction graciously received from M. Christopher Miller and Ms. Susan Shaffer, Astra-Zeneca, Oct 2000

-User-defined order: 54
(mean ICS dose of 540 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Finn 2000

Methods	<p>DESIGN -parallel-group -multicentre trial -Analysed by co-treatment with ICS</p> <p>ALLOCATION -Random -Methods of randomisation: not described -Means of treatment assignment: not described</p> <p>BLINDING -double-blind -Means of concealment: not described</p> <p>WITHDRAWAL/DROPOUT -not described</p> <p>JADAD's Quality Score =2</p> <p>-Confirmation of methodology: not obtained</p>
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED N = 479 of which only 98 were co-treated with inhaled glucocorticoids Zafirlukast + ICS = 56 ICS alone = 42</p> <p>WITHDRAWALS AMONG CHILDREN WITH CO-TX WITH ICS not described Zafirlukast: % Control: %</p> <p>AGE: 5-11 years old Zafirlukast: years Control: years</p> <p>GENDER (% male) not described</p> <p>SEVERITY: mild-moderate asthma</p> <p>BASELINE % predicted FEV1 Zafirlukast: 72 ± 12 (SD)</p>

Finn 2000 (Continued)

Control: 71 ± 12

ALLERGIC RHINITIS:

Zafirlukast: 76%

Control: 74%

EXERCISE-INDUCED ASTHMA:

Zafirlukast: 88%

Control: 83%

ASTHMA DURATION: Zafirlukast: 19 (0.5 to 62) years

Control: 18 (0.5 to 59) years

ELIGIBILITY CRITERIA

-Age: > 15 years old

-healthy, non-smoking

-history of >= one year of intermittent or persistent asthma symptoms

-ICS treatment >= 6 wks prior to pre-study visit (ICS dose comparable to beclomethasone 400 to 500 mcg)

-50 to 85% FEV1 Pred

-improvement > 15% FEV1 after B2-agonist

- >= 1 puff/day of B2-agonist

EXCLUSION CRITERIA:

-Upper respiratory tract infection < 3 weeks

Interventions

PROTOCOL:

AL + ICS vs SAME dose ICS

DURATION:

-Run-in Period: 7-14 days

-Intervention Period: 10 weeks

TEST GROUP

Accolate 10 mg bid +/- ICS (dose not specified)

CONTROL GROUP

Placebo +/- ICS (dose not specified)

DEVICE

-not specified

-CO-TREATMENT: not described

Outcomes

INTENTION-TO-TREAT ANALYSES: not described

PULMONARY FUNCTION TESTS

-*change in AM PEF (L/min)

SYMPTOM SCORES (PP)

-not reported

FUNCTIONAL STATUS (PP)

-change in mean daily use of B2-agonist (puffs/day)

-change in nocturnal awakenings/week

INFLAMMATORY MARKERS

-not described

ADVERSE EFFECTS

-not reported

WITHDRAWALS

-not reported

Finn 2000 (Continued)

* primary outcome

Notes

- Abstract 2000
- Funded by Astra-Zenece
- Confirmation of methodology and data extraction: not obtained.
- User-defined order: not specified
(mean intervention ICS dose in mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Green 2002a

Methods

DESIGN

- cross-over trial
- 4 weeks for each of the 4 periods
- 1-month wash-out between periods

ALLOCATION

- Random
- Means of randomisation: not specified
- Mode of allocation: not specified

BLINDING

- double-blind
- mode of blinding: not specified

WITHDRAWAL/DROPOUTS

- not described

JADAD's Quality score = 2

Confirmation of methodology

- not obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED

N = 49 for each of 4 periods

WITHDRAWALS

not reported

AGE:

not reported

GENDER (% male)

not reported

SEVERITY:

?mild-moderate asthma

BASELINE % predicted FEV1 ± (SD)

not reported

Green 2002a (Continued)

BUD 800:
 BUD 200 + Montelukast:
 BUD 200 + Formoterol:
 BUD 200 + Placebo:

ALLERGIC RHINITIS:
 -not reported

ASTHMA DURATION:
 -not reported

ELIGIBILITY CRITERIA
 -not reported

EXCLUSION CRITERIA
 -not reported

Interventions

PROTOCOL:
 AL + ICS vs HIGHER dose ICS

DURATION:
 -Run-in Period: not described
 -Intervention Period: 4 weeks
 -Wash-out period: 4 weeks

TEST GROUP 1
 BUD 100 mcg bid + Montelukast 10 mg die

TEST GROUP 2 (not used in this review)
 BUD 100 mcg bid + formoterol

CONTROL GROUP 1
 4 x ICS: BUD 400 mcg bid

CONTROL GROUP 2 (not used in this review)
 BUD 100 mcg bid

DEVICE
 -not specified

CO-TREATMENT:
 -not reported

Outcomes

INTENTION-TO-TREAT ANALYSES

PULMONARY FUNCTION TESTS
 -change in FEV1 (L)
 -*change in AM PEF (L/min)

SYMPTOM SCORES (PP)
 -change in symptom score (scale 0 to 6)

FUNCTIONAL STATUS (PP)
 -change in mean daily use of B2-agonist (puffs/day)
 -change in quality of life score (range 1-7)
 -change in nocturnal awakenings

INFLAMMATORY MARKERS
 -change in peripheral blood eosinophil count

ADVERSE EFFECTS
 -not reported

WITHDRAWALS

Green 2002a (Continued)

-not reported
 * primary outcome

Notes
 -Abstract 2002
 -Funding: not specified
 -Confirmation of methodology and data extraction: not obtained.
 User-defined order: 20
 (mean intervention BUD dose in mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Hultquist 2000

Methods

DESIGN
 -parallel-group study
 -multicentre trial (49 centres in 6 countries)

ALLOCATION
 -Random
 -Methods of randomisation: computer generated
 -means of assignment by opaque consecutive numbered envelopes containing assignment

BLINDING
 -double-blind
 -double-dummy

WITHDRAWAL/DROPOUT
 - described by treatment groups
 JADAD's Quality Score = 5

Confirmation of methodology: received

Participants

INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
 400-1000 ug of ICS (not specified)/day

RANDOMISED
 -Anti-leukotriene= 118
 -Long-acting beta2-agonist = 118
 -Bud=116

WITHDRAWALS:
 -Anti-leukotriene= 19/118 (16%)
 -Long-acting beta2-agonist = 12/118 (10%)
 -BUD= 9/116 (8%)

AGE in years: mean ± SD
 -Anti-leukotriene= 38.3 ± NS
 -Long-acting beta2-agonist = 38.1 ± NS
 -BUD=38.1 ± NS

Hultquist 2000 (Continued)

GENDER (% male)

- Anti-leukotriene= 47 %
- Long-acting beta2-agonist = 49%
- BUD=53%

SEVERITY:

Not described

BASELINE FEV1 (% pred)

- Anti-leukotriene= 72.03 ± SD
- Long-acting beta2-agonist = 69.71 ± SD
- BUD=72.12 ± SD

ALLERGEN TRIGGERS:

-Not reported

ALLERGIC RHINITIS:

-Not reported

ASTHMA DURATION in years

- Anti-leukotriene= 10.1 ± SD
- Long-acting beta2-agonist = 12.1 ± SD
- BUD=10.6 ± SD

ELIGIBILITY CRITERIA

- male or female outpatient
- age 12-70 years
- treated for at least 3 mo with 400-1000 mcg of inhaled glucocorticoids
- asthma diagnosis
- FEV1 50-80% predicted
- >=12 % reversibility in FEV1 and at least 200 mL after inhalation of 1 mg of terbutaline
- smoking history of <=10 pack years

In the 7 days prior to randomisation one or more of the following:

- an symptom score of >=1 on 4 days
- awakening on >= 1 night due to asthma symptoms
- use of B2-agonists >=10 puffs as weekly mean

EXCLUSION CRITERIA:

- Respiratory infection
- clinical obstructive pulmonary disease, or pulmonary dysfunction other than asthma
- pregnant or lactating women
- use of long-acting beta2-agonist within 1 month prior to visit 1
- previous use ever of a leukotriene antagonist
- known intolerance to study drugs or inhaled lactose

SETTING: not described

Interventions

PROTOCOL:

AL + ICS vs SAME dose ICS
(Stable dose of ICS)

DURATION:

- Run-in Period: not reported
- Intervention Period: 8 weeks

INTERVENTION GROUP 1

-AL = Zafirlukast 20 mg bid
+
Budesonide 200 mcg bid
via Turbuhaler

INTERVENTION GROUP 2 (not used)

Hultquist 2000 (Continued)

-LAB2 = Formoterol 9 ug bid, via Turbuhalor
+
Budesonide 200 mcg bid
via Turbuhaler

CONTROL:
Budesonide 200 mcg bid
via Turbuhaler

-CO-TREATMENT:
None allow other than rescue LAB2

Outcomes

Modified INTENTION-TO-TREAT ANALYSES
(on all patients who receive at least 1 dose of study medication)

-outcomes used at endpoint or 8 weeks

PULMONARY FUNCTION TESTS

-**Change from baseline in AM PEFr
-Change from baseline in PM PEFr ?

SYMPTOM SCORES

-Change from baseline OVERALL symptom scores?
-Change from baseline DAYTIME symptom scores?
-Change in symptom-free days?
- Patient satisfaction?

EXACERBATIONS

Definition: Any worsening of asthma symptoms requiring treatment beyond the use of blinded study drug &/or supplemental albuterol. Patients who experienced an asthma exacerbation were withdrawn from the study ??

FUNCTIONAL STATUS

-Change from baseline in mean OVERALL use of B2-agonists (puffs/DAY)?
-Change from baseline in mean DAYTIME use of B2-agonists (puffs/DAY)?
-Change from baseline in mean NIGHT-TIME use of B2-agonists (puffs/DAY)?
-Change in rescue-free days?
-Change in night-time awakenings ?

INFLAMMATORY MARKERS:

Not reported

ADVERSE EFFECTS

-drug related & non-drug related ?

WITHDRAWALS

-due to adverse effects reported ?

(** denotes primary outcome)

Notes

- Unpublished data

-Received full disclosure of unpublished data provided by Ian Naya and Roger Metcalf, AstraZeneca, Sept 2003

-Funded by Astra Zeneca
Report #SD-004CR-0216

Confirmation with supportive documents received for methodology and data extraction (Sept 2003)

User-defined order: 40
(mean intervention BUD dose in mcg/day X 0.1)

Hultquist 2000 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Kanniess 2002

Methods	DESIGN -cross-over trial -6 weeks for each period -no wash-out between periods -dose reduction of 50% at beginning of each period ALLOCATION -Random: Computer-generated random number -means of assignment: opaque consecutive numbered envelopes BLINDING -double-blind -placebo-controlled -identical placebo WITHDRAWAL/DROPOUTS -described JADAD's Quality score = 5 Confirmation of methodology - obtained
Participants	WELL-CONTROLLED PARTICIPANTS RANDOMISED N = 50 -Montelukast = 26 -Control = 24 WITHDRAWALS: -Montelukast = 3 (11.54%) -Control = 2 (8.33%) AGE: -Montelukast: 38 ± 12 (SEM) years -Control: 43± 11 (SEM) years GENDER (% male): -Montelukast: 50% -Control: 46% SEVERITY: -moderate bronchial asthma BASELINE % PREDICTED FEV1: -Montelukast: 95.0 ± 2 (SEM) -Control: 92.3 ± 1.8 (SEM) ATOPY: not reported

Kanniess 2002 (Continued)

ASTHMA DURATION:
not reported

ELIGIBILITY CRITERIA

- taking a dose of ICS (Beclomethasone or equivalent) 800 ug/day for more than 8 weeks prior to randomisation
- FEV1 > 80% predicted
- no oral corticosteroids within 6 months of entry to study
- no oral antihistamines within 4 weeks of entry to study
- provocation concentration of methacholine causing a 20% fall in FEV1 (PC20) <8mg/mL
- FEV1 and PC20 be reproducible within 15% and 1.5 doubling concentrations, respectively, between visits one and two
- no smokers
- no signs of an acute exacerbation or respiratory tract infection within 4 weeks prior to screening

EXCLUSION CRITERIA

- none mentioned

Interventions

PROTOCOL

- AL + ICS vs same dose ICS (TAPERING ICS)

DURATION

- Run-in Period: 1-3 weeks
- Dose optimisation period: none
- Intervention Period: 6 weeks (X 2 periods)

TEST GROUP

Period 1

- Montelukast 10 mg once daily +
- BDP 800 mcg/day or equivalent

Period 2:

- Placebo +
- BDP-eq 400 mcg/day

CONTROL GROUP

Period 1

- Placebo + BDP 800 mcg/day or equivalent

Period 2

- Montelukast 10 mg die +
- BDP-eq 400 mcg/day

DEVICE

- not reported

CO-TREATMENT:

- none reported (need confirmation)

CRITERIA FOR TAPERING

- 1st treatment period ICS reduced to 50% baseline (400 ug/day)
- 2nd treatment period ICS reduced to 50% of 1st treatment (25% of baseline or 200ug/day)

* For purpose of the analysis, because this unusual design did not allow merging of the two periods and because no significant change in asthma control occurred in the first period suggesting of over-treatment at baseline, the second period was arbitrarily chosen for analysis.

Outcomes

INTENTION-TO-TREAT ANALYSES

- yes

PULMONARY FUNCTION TESTS

- data are given as changes relative to baseline (1st period) and relative to each other (2nd period)
- change in FEV1 (L)

Kanniess 2002 (Continued)

- change in PEF daytime
- change in PEF night-time
- change in PC20

SYMPTOM SCORES

- change in daytime symptoms score (range 0 - 4)
- change in night-time symptoms score (range 0 - 4)

FUNCTIONAL STATUS

- Use of rescue B2-agonists (puffs/day)

ICS DOSE REDUCTION:

- fixed by protocol

INFLAMMATORY MARKERS:

- data are given as changes relative to baseline (1st period) and relative to each other (2nd period)
- exhaled NO ppb
- % sputum eosinophils

ADVERSE EFFECTS

- reported (personal communication)

WITHDRAWALS

- reported

Notes	<ul style="list-style-type: none"> -Full-text (2002) publication and unpublished data -Funds by an educational grant from MSD, Munich, Germany -Confirmation of data extraction and methodology graciously obtained from Dr Frank Kanniess, from the Pulmonary Research Institute, Germany, August 2003. -User defined number = 40 (mcg of beclomethasone-equivalent at baseline of the 2nd period) (mean ICS dose of 400 mcg/ day X 0.1)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Laitinen 1995

Methods	<p>DESIGN</p> <ul style="list-style-type: none"> -parallel-group -multicentre trial (83 centres) <p>ALLOCATION</p> <ul style="list-style-type: none"> -Random: 2:1 ratio intervention:control -Computer-generated <p>BLINDING</p> <ul style="list-style-type: none"> -double-blind -placebo-controlled -identical placebo <p>WITHDRAWAL/DROPOUT</p> <ul style="list-style-type: none"> -described
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Laitinen 1995 (Continued)

JADAD's Quality Score = 5

Confirmation of methodology obtained

Participants

WELL-CONTROLLED PARTICIPANTS

-RANDOMISED N = 262

Zafirlukast:175

Control:87

WITHDRAWALS

Zafirlukast:15%

Control:14%

AGE:

Zafirlukast: 45.5 ±13.6 (SD) years

Control: 43.5 ± 13.4 years

GENDER (% male)

Zafirlukast:46%

Control:34%

SEVERITY:

moderate asthma

BASELINE FEV1 (L)

Zafirlukast: 2.58 ± 0.89 (SD)

Control: 2.42 ± 0.78

ALLERGEN TRIGGERS:

Zafirlukast: 45%

Control:40%

ASTHMA DURATION:

Zafirlukast: 14.1 ± 13.1 (SD) years

Control: 14.3 ± 12.5years

ELIGIBILITY CRITERIA

-taking a dose of ICS (BUD or BDP) between 800 and 2000 ug/day

-stable in the preceding month

Interventions

PROTOCOL:

AL + ICS vs same dose ICS

(TAPERING ICS dose)

DURATION:

-Run-in Period: 1 week to confirm asthma control

-Dose optimisation period:

2 weeks to 3 months

Zafirlukast: 7.7 ± 4.0 weeks (SD)

Control: 7.9 ± 4.0 weeks

-Intervention Period: 12 weeks

TEST GROUP

-ICI 204219 = Zafirlukast 20 mg bid p.o. + ICS (BUD or BDP) 800 to 2000 ug/day

CONTROL GROUP

Placebo + ICS (BUD or BDP) 800 to 2000 ug/day

DEVICE

-various devices used

-CO-TREATMENT: none reported

Laitinen 1995 (Continued)

CRITERIA FOR TAPERING every 2 weeks by 200 to 250 mcg/day
 -FEV1 \geq 80% predicted
 -B2-agonist use \leq 800 ug/day of salbutamol

MINIMAL DOSE OF ICS ALLOWED: 400 mcg/day

CRITERIA TO INCREASE CORTICOSTEROIDS:
 -FEV1 $<$ 60% of predicted

Outcomes

PER-PROTOCOL (PP) ANALYSES

- some intention-to-treat (ITT) analysis

-outcomes used at 6 and 12 weeks

PULMONARY FUNCTION TESTS (reported as cross-sectional values not as change from baseline)

-FEV1 (L)- ITT

-Mean Am PEFR (L/min) -PP

SYMPTOM SCORES - PP

-Mean daytime symptom scores

FUNCTIONAL STATUS - PP

-Mean daily use of beta2-agonist (puffs/day) averaged over a week

ICS DOSE REDUCTION:

(PP)

-**ICS dose reduction (% change from baseline)

INFLAMMATORY MARKERS

-not reported

ADVERSE EFFECTS

-elevated liver enzymes, headache, nausea, death, etc.

WITHDRAWALS

-reported

(** denotes primary outcomes)

Notes

-Abs (1995) and unpublished data graciously provided by Christopher Miller and Susan Shaffer from Astra-Zeneca, USA (Oct 2000)

-funded by Zeneca

-Confirmation of methodology and data extraction received from M. Christopher Miller and Ms. Susan Shaffer, Astra-Zeneca, Oct 2000

-User-defined order: 114

(mean intervention ICS dose of 1137 mcg/ day X 0.1)

Risk of bias
Bias
Authors' judgement
Support for judgement

Allocation concealment
(selection bias)

Low risk

Study investigators unaware as to order of treatment group assignment
(Cochrane Grade A)

Laviolette 1999
Methods

DESIGN

-parallel-group

Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma (Review)

Laviolette 1999 (Continued)

- Multicentre trial (70 centres)
- 4-arm study of which two are considered in this review

- ALLOCATION
- Random
- computer-generated allocation
- opaque consecutive-numbered envelopes containing assignment

- BLINDING
- double-blind
- double-dummy
- identical placebo

- WITHDRAWAL/DROPOUT
- described

- JADAD's Quality Score = 5

- Confirmation of methodology obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED

N = 393
Montelukast = 193
Control = 200

WITHDRAWALS

Montelukast: 8%
Control: 21%

AGE: 15 to 78 years old

Montelukast: 40 (range: 15 to 76) years Control:39(15 to 78) years

GENDER (% male)

Montelukast: 56% Control: 52%

SEVERITY:

mild-moderate asthma

BASELINE % predicted FEV1

Montelukast: 72 ± 12 (SD)
Control: 71 ± 12

ALLERGIC RHINITIS:

Montelukast: 76%
Control: 74%

EXERCISE-INDUCED ASTHMA:

Montelukast: 88%
Control: 83%

ASTHMA DURATION: Montelukast: 19 (0.5 to 62) years

Control: 18 (0.5 to 59) years

ELIGIBILITY CRITERIA

- Age: > 15 years old
- healthy, non-smoking
- history of >= one year of intermittent or persistent asthma symptoms
- ICS treatment >= 6 wks prior to prestudy visit (ICS dose comparable to beclomethasone 400 to 500 mcg)
- 50 to 85% FEV1 Pred
- improvement > 15% FEV1 after B2-agonist
- >= 1 puff/day of B2-agonist

Laviolette 1999 (Continued)

EXCLUSION CRITERIA:
-Upper respiratory tract infection < 3 weeks

Interventions

PROTOCOL
AL + ICS vs SAME dose ICS

DURATION
-Run-in Period: 4 weeks
-Dose optimisation period: none
-Intervention Period: 16 weeks

TEST GROUP 1
-Montelukast 10 mg die + Inhaled Beclomethasone 200 ug bid

TEST GROUP 2
-Montelukast 10 mg die + Placebo (not used in this review)

CONTROL GROUP 1
-Placebo + Inhaled Beclomethasone 200 ug bid

CONTROL GROUP 2
-Placebo + Placebo (not used in this review)

DEVICE
-metered-dose aerosol inhalers

-CO-TREATMENT: none permitted (other than anti-histaminic)

Outcomes

INTENTION-TO-TREAT ANALYSIS
-outcomes used at 16 weeks

PULMONARY FUNCTION TESTS
-**Change from baseline FEV1
-Change from baseline AM PEFR

SYMPTOM SCORES
-**Change from baseline daytime symptom scores
-Change from baseline nocturnal awakenings (nights/wk)

FUNCTIONAL STATUS
-Change from baseline mean daily B2-agonist use (puffs/day)

INFLAMMATORY MARKERS
-Change from baseline in blood serum eosinophils

ADVERSE EFFECTS
-elevated liver enzymes, headache, nausea, death, etc.

WITHDRAWALS
-reported

(** denotes primary outcomes)

Notes

-Full Text 1999 and unpublished data graciously provided by Theodore F Reiss and GP Noonan from Merck Frosst, USA

-Funded by Merck

-Confirmation of methodology received June 1999

-Confirmation of data extraction graciously provided by T.F Reiss and G.P. Noonan, Merck Frosst, USA, June 2000 and June 2001.

-User-defined order: 40

Laviolette 1999 (Continued)

(mean intervention ICS dose of 400 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Lofdahl 1999

Methods	DESIGN -parallel-group -multicentre trial ALLOCATION -Random -computer-generated allocation -opaque consecutive-numbered envelopes containing assignment BLINDING -triple-blind -placebo-controlled -identical placebo WITHDRAWAL/DROPOUTS - described JADAD's Quality Score = 5 Confirmation of methodology obtained
Participants	WELL-CONTROLLED PARTICIPANTS RANDOMISED N = 226 Montelukast = 113 Placebo = 113 WITHDRAWALS Montelukast: 16% Control: 27% AGE: 16 to 70 years old Montelukast: 40 years (mean) Control: 41 years GENDER:(% male) Montelukast: 42% Control: 45% SEVERITY: not described BASELINE FEV1 (% predicted): Montelukast: 84.4 ± 11.1 % (SD) Control: 82.3 ± 12.9 % ALLERGEN TRIGGERS: not reported ASTHMA DURATION: Montelukast: 18 ± 13.3 (SD) years Control: 19 ± 14 years ELIGIBILITY CRITERIA -non-smoking adults

Lofdahl 1999 (Continued)

- clinical history of asthma for at least one year
- treatment with stable, ICS bid for at least 3 weeks prior to pre-study visit
- >= 70% FEV1 % Pred
- >= 15% reversibility after inhaled B2-agonist

- after two ICS dose reductions:
 - FEV1 >= 90% of baseline value,
 - levels < baseline level in asthma symptoms and B2-agonist use,
 - >= 65% of maximum peak flow, and
 - a required prespecified minimum ICS dose was met

- EXCLUSION:
 - emergency treatment in past 1 month
 - hospitalised in past 3 months
 - upper respiratory tract infection within 3 weeks

Interventions

- PROTOCOL:
AL + ICS vs same dose
ICS (TAPERING ICS dose)
- DURATION
-Dose optimisation period: <=7 weeks (ICS dose reduced to minimum dose necessary to maintain stability before randomisation)
-Intervention Period: 12 weeks
- TEST GROUP
-Montelukast 10 mg die p.o. + ICS 300 to 3000 ug/day
- CONTROL GROUP
-Placebo + ICS 300 to 3000 ug/day
(Various ICS including fluticasone 7%, beclomethasone 16%, BUDesonide 22%, flunisolide 15%, triamcinolone 40%)
- DEVICE
-variety used
- CO-TREATMENT: none reported
- CRITERIA FOR TAPERING every 2 weeks by 25% of their ICS dose
- FEV1 >= 90% of value at randomisation
 - B2-agonist use <= 135% of pre-allocation
 - Daytime symptoms score <= 120% of pre-allocation baseline
- MINIMAL DOSE OF ICS ALLOWED: None

Outcomes

- INTENTION-TO-TREAT ANALYSES
-outcomes used at last tolerated dose or 12 weeks
- PULMONARY FUNCTION TESTS
-Change from baseline FEV1 at visit of lowest tolerated ICS dose
- SYMPTOM SCORES
-Change from baseline daily symptom scores at visit of lowest tolerated ICS dose
- FUNCTIONAL STATUS
-Change from baseline mean daily use of B2-agonists at visit of lowest tolerated ICS dose
- ICS DOSE REDUCTION:
-**Mean % change from baseline ICS dose reduction -**Change from baseline ICS dose (mcg)
- INFLAMMATORY MARKERS:
not reported

Lofdahl 1999 (Continued)

ADVERSE EFFECTS
 -elevated liver enzymes, headache, nausea, death

WITHDRAWALS
 -reported

(** denotes primary outcomes)

Notes

- Full Text 1999 and unpublished data
- Funded by Merck Frosst
- Confirmation of methodology received June 1999
- Confirmation of data extraction graciously received from T.F Reiss and G.P. Noonan, June 2000.
- User-defined order: 98
 (mean intervention ICS dose of 976 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Nayak 1998

Methods

DESIGN
 -parallel-group
 -multicentre trial (41 centres)
 -3 arms study:
 (1) Z80+ICS
 (2) Z160+ICS
 (c) 2 x ICS

ALLOCATION
 -Random
 -Computer generated random numbers,
 -number coded solutions supplied by pharmacy

BLINDING
 -triple-blind
 -double-dummy
 -identical placebo-controlled

WITHDRAWAL/DROPOUT
 -described

JADAD's Quality Score = 5
 -Confirmation of methodology obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED
 N = 394
 Z80+ICS = 130
 Z160+ICS = 134
 2 x ICS = 130

Nayak 1998 (Continued)

WITHDRAWALS:Z40+ICS = 16%
Z160+ICS = 12%
2 x ICS = 16%

AGE MEAN (range)
(1) Z80+ICS = 39.2 (12 to 78) years
(2) Z160+ICS = 39.3 (12 to 79) years
(3) 2 x ICS = 39.5 (12 to 74) years

GENDER (% male)
(1) Z80+ICS = 40%
(2) Z160+ICS=37%
(3) 2 x ICS=38%

SEVERITY: mild to moderate

BASELINE FEV1 (% predicted):
(1) Z80+ICS = 68.3%
(2) Z160+ICS=67.3%
(3) 2 x ICS = 67.2%

-ALLERGIC RHINITIS:
94.2%

ELIGIBILITY CRITERIA

- Age: >= 12 years old
- symptomatic on low-dose ICS
- non-smoker for at least 6 months preceding screening
- FEV1 of 45 to 80% of predicted at least 6 hours after short-acting inhaled beta2-agonist and at least 48 hours after salmeterol or antihistamines
- reversibility >= 15% after inhaled beta2-agonists within 6 months of screening or non-specific bronchial hyperreactivity to histamine or methacholine challenge between 0.25-8.0 mg/ml within 12 months of screening
- 85% compliance with placebo tablets
- no chronic diseases
- no drug/alcohol abuse
- has not taken other steroids besides BDP
- no use of salmeterol 48 hours prior to, or astemizole 3 months prior screening
- no recent upper respiratory tract infection
- no seasonal asthma

Interventions

PROTOCOL:
AL + ICS vs DOUBLE dose ICS

DURATION
-Run-in Period: 7-14 days
-Dose optimisation period: NONE
-Intervention Period: 13 weeks

TEST GROUP (Z80+ICS)
-Zafirlukast 40 mg bid p.o. + Beclomethasone 400 ug/day

TEST GROUP Z160+ICS
-Zafirlukast 80 mg bid p.o. + Beclomethasone 400 ug/day

CONTROL GROUP (2 X ICS)
-Beclomethasone 800 ug/day

DEVICE
-metered-dose aerosol inhaler

-CO-TREATMENT: none

Outcomes

PER-PROTOCOL (PP) ANALYSES

Nayak 1998 (Continued)

- outcomes used at 6-8 and 13 weeks

- PULMONARY FUNCTION TESTS
- Change from baseline FEV1
- **Change from baseline Am PEFR

- SYMPTOM SCORES
- **Change from baseline daytime symptom scores (scale 0-3)
- Change from baseline nocturnal awakenings
- Change from baseline mornings with asthma

- FUNCTIONAL STATUS
- Change from baseline mean daily use of B2-agonists

- INFLAMMATORY MARKERS:
- not reported

- ADVERSE EFFECTS
- elevated liver enzymes, oral moniliasis, headache, nausea, death

- WITHDRAWALS
- reported

- (** denotes primary outcomes)

- Notes
- Abs (1998) and unpublished report provided by Astra-Zeneca (Oct 2000)
 - Funded by Astra-Zeneca
 - Confirmation of methodology and data extraction graciously received from M. Christopher Miller and Ms. Susan Shaffer, Astra-Zeneca, Oct 2000
 - User-defined order: 40
(mean intervention ICS dose of 400 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Nishimura 1999

- Methods
- DESIGN
 - Cross-over trial

 - ALLOCATION
 - Random
 - Mode of randomisation: not described
 - Means of assignment: not described

 - BLINDING
 - double-blind
 - means of blinding: not described

 - WITHDRAWAL/DROPOUT
 - not described

 - JADAD's Quality Score =

Nishimura 1999 (Continued)

-Confirmation of methodology obtained/not obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED
N = 27

WITHDRAWALS
not described

AGE:
not described

GENDER (% male)
56% male

SEVERITY:
moderate to severe persistent asthma

BASELINE % predicted FEV1
not described

ALLERGIC RHINITIS:
not described

EXERCISE-INDUCED ASTHMA:
not described

ASTHMA DURATION:
not described

ELIGIBILITY CRITERIA
-Adults: age not specified
-asthma: not defined
-improperly controlled on BDP 800-1200 mcg/day for 3 months.

EXCLUSION CRITERIA:
-not described

Interventions

PROTOCOL
AL + ICS vs SAME dose ICS

DURATION
-Run-in Period: 4 not described
-Intervention period: 4 weeks
-Wash-out period: not described

TEST GROUP
-Pranlukast 225 mg twice daily + Inhaled BDP 800-1200 mcg /day

CONTROL GROUP
-Placebo + Inhaled BDP 800-1200 mcg /day

DEVICE
-not described

-CO-TREATMENT:
-not described

Outcomes

INTENTION-TO-TREAT ANALYSIS
-not described
-outcomes reported at 4 weeks

PULMONARY FUNCTION TESTS

Nishimura 1999 (Continued)

- *Change from baseline AM PEFR
- Change from baseline in FEV1

- SYMPTOM SCORES
- Change from baseline daytime symptom scores
- Change from baseline nighttime symptoms

- FUNCTIONAL STATUS
- Change from baseline mean daily B2-agonist use
- Change from baseline in health-related quality of life (Living with Asthma Questionnaire)

- INFLAMMATORY MARKERS
- not reported

- ADVERSE EFFECTS
- not reported

- WITHDRAWALS
- not reported

- (* denotes primary outcomes)

- Notes
- Abstract 1999
 - Funding source: not reported
 - Confirmation of methodology and data extraction: not obtained.
 - User-defined order: not specified
(mean intervention ICS dose in mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Nsouli 2000

- Methods
- DESIGN
 - parallel-group

 - ALLOCATION
 - Random
 - Methods of randomisation: not reported -means of assignment: not reported

 - BLINDING
 - no blinding (open label)

 - WITHDRAWAL/DROPOUT
 - not described

 - JADAD's Quality Score = 1
 - Confirmation of methodology not obtained
-
- Participants
- SYMPTOMATIC PARTICIPANTS

 - RANDOMISED
 - N= 30

Nsouli 2000 (Continued)

-M10 + ICS = NR
-2 X ICS= NR

WITHDRAWALS
-M10 + ICS =NR
-2 X ICS= NR

GENDER (% male)
-M10 + ICS = NR
-2 X ICS =NR

AGE (SD) years
-M10 + ICS = NR
-2 X ICS= NR

SEVERITY
-not specified

BASELINE PREDICTED FEV1 % (SD)
-M10 + ICS = NR
-2 X ICS = NR

ALLERGEN TRIGGERS
-not described

ASTHMA DURATION (SD) years
- M10 + ICS = NR
-2 X ICS = NR

ELIGIBILITY CRITERIA
-symptomatic on low dose of ICS (FP 100-300 mcg; BDP 200 - 1200 mcg; BUD 200-400 mcg; flunisolide:
500-1000 mcg; TAA:400-1000 mcg)

EXCLUSION CRITERIA
-not reported

Interventions

PROTOCOL:
AL + ICS vs DOUBLE dose ICS

DURATION
-Run-in Period: not described
-Intervention period: 12 weeks

TEST GROUP
-Montelukast 10 mg die p.o. + Beclomethasone 200-500/day or equivalent

CONTROL GROUP (2 X ICS)
-Beclomethasone 400-1200 ug/day or equivalent

DEVICE
-not described

-CO-TREATMENT:
not described

Outcomes

INTENTION-TO-TREAT ANALYSIS
-not described
-outcomes reported at 12weeks

PULMONARY FUNCTION TESTS
-Change from baseline AM PEFR
-Change from baseline in FEV1

SYMPTOM SCORES

Nsouli 2000 (Continued)

- Change from baseline daytime symptom scores
- Change from baseline nighttime symptoms

FUNCTIONAL STATUS

- Change from baseline mean daily B2-agonist use

INFLAMMATORY MARKERS

- not reported

ADVERSE EFFECTS

- not reported

WITHDRAWALS

- not reported

(* denotes primary outcomes)

Notes

- Abstract 2000
- Funding source: not reported
- Confirmation of methodology and data extraction: not obtained.
- User-defined order: 35
(mean intervention (350) dose in mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

O'Sullivan 2003

Methods

- DESIGN
- Cross-over trial
- ALLOCATION
- Random
 - Mode of randomisation: not described
 - Means of assignment: not described
- BLINDING
- ?triple-blind
 - ?double-dummy
 - ?identical placebo-controlled
- WITHDRAWAL/DROPOUT
- ? described
- JADAD's Quality Score =
- Confirmation of methodology obtained/not obtained

Participants

- SYMPTOMATIC PARTICIPANTS
- RANDOMISED:
N = 34 adults
- WITHDRAWALS:

O'Sullivan 2003 (Continued)

Montelukast: 3 (9%)
Placebo: 2 (6%)
+ 1 no group specified

AGE (Mean, SEM):
-27.7 ± 1.1 years (range: 19 to 55)

GENDER(% male):
-53%

Baseline mean FEV1 % Pred (± SD)
-90.7± 3.4 % predicted

ASTHMA SEVERITY:
-mild

ATOPY:
-100 % atopic (one positive skin prick test to house dust mites or two other commonly inhaled allergens)

ASTHMA DURATION:
-not described

ELIGIBILITY CRITERIA
-Age: >=19 years
-mild persistent asthma
-FEV1 >=60% of predicted
-change in FEV1 of 12% or more after salbutamol
-provocative PD20% of 4 mg/mL or less
-use of rescue B2-agonists as needed
-no inhaled steroids in previous 6 weeks
-pre-existing history of asthma

Exclusion criteria:
-not described

Interventions

PROTOCOL
AL + ICS vs ICS (same dose)

Duration
-Run-in Period: 2 weeks
-Intervention Period 2: 8 weeks
-Washout period: not reported

TEST GROUP
-Montelukast 10 mg qd p.o.
-FP 100 mcg bid

CONTROL GROUP
-FP 100 mcg bid
-Placebo montelukast capsule die

DEVICE
-Diskus

CO-INTERVENTION:
-not described

Outcomes

ANALYSES not detailed (ITT vs per protocol)

PULMONARY FUNCTION TESTS
-change in FEV1 (L)
-*change in AM PEF (L/min)

O'Sullivan 2003 (Continued)

- change in PM PEF (L/min)
- methacholine PC20

- SYMPTOM SCORES (PP)
- change in symptom score (on a visual analogue scale)

- FUNCTIONAL STATUS (PP)
- change in mean daily use of B2-agonist (puffs/day)
- change in quality of life score (range 1-7)
- change in Juniper Asthma Quality of Life

- INFLAMMATORY MARKERS
- change in induced sputum
- exhaled nitric oxide

- ADVERSE EFFECTS
- not reported

- WITHDRAWALS
- not reported

- * primary outcome

- | | |
|-------|--|
| Notes | -Full text 2003

-Funding: GlaxoSmithKline R & D, UK

-Confirmation of methodology and data extraction:
not obtained

-User-defined order: 40
(intervention FP dose of 200 mcg/ day X 2) |
|-------|--|

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Price 2003

- | | |
|---------|--|
| Methods | DESIGN
-multicentre

ALLOCATION
-random
-computer generated random numbers
-assignment by numbered coded Rx supplied by pharmacy

BLINDING
-triple blind
-identical placebo
-double -dummy

WITHDRAWALS/ DROPOUT
-described

JADAD's Quality Score = 5 |
|---------|--|

Price 2003 (Continued)

Confirmation of methodology confirmed

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED

- N= 889
- M10 + BUD = 448
- 2 X ICS= 441

WITHDRAWALS

- M10 + BUD 800 = 20 (4.5%)
- 2 X ICS= 26 (6%)

GENDER (% male)

- M10 + BUD= 41%
- 2 X ICS =39%

AGE (SD) years

- M10 + BUD = 43 ± 14
- 2 X ICS= 43 ± 14 (SD)

SEVERITY

- not specified

BASELINE PREDICTED FEV1 % (SD)

- M10 + BUD = 69.0 ± 13.3
- 2 X ICS = 68.3 ± 13.4

ALLERGEN TRIGGERS

- not described

ASTHMA DURATION (SD) years

- M10 + BUD = 18 ±14
- 2 X ICS = 17 ± 15

ELIGIBILITY CRITERIA

- non-smokers or ex-smokers
- diagnosis of asthma > 1 year
- age 15 to 75
- not optimally controlled on ICS 600 to 1200 mcg/day of BUD, BDP, triamcinolone, flunisolide, or 300-800 mcg FP
- FEV1 >= 50% predicted
- >=12% improvement in FEV1 after B2-agonist use
- symptoms requiring at least 1 puff/day of B2-agonist during the last 2 weeks of the run-in

EXCLUSION CRITERIA

- other active pulmonary disorders
- respiratory infection within 3 weeks of visit 1 or during the run-in period
- ER visit for asthma in past 2 months of visit 1
- systemic corticosteroid treatment within 1 month
- cromones or leukotriene receptor antagonists within 2 weeks
- long-acting antihistamine within 1 week (astemizole 3 months)
- long acting B2 agonist or anticholinergic agents within 24 hours

Interventions

PROTOCOL

- AL + ICS vs. DOUBLE dose ICS

DURATION

- run-in period = 4 weeks
- treatment period = 12 weeks

TEST GROUP

- ICS (BUD 800mcg/day) + 10 mg/day montelukast

Price 2003 (Continued)

CONTROL GROUP
-ICS (BUD 1600mcg/day) + placebo

DEVICE
-Turbohaler

CO-TREATMENT
- none reported

Outcomes

INTENTION-TO-TREAT ANALYSES

PULMONARY FUNCTION TESTS
-change in FEV1 (L)
-*change in AM PEF (L/min)

SYMPTOM SCORES (PP)
-change in symptom score (scale 0 to 6)

FUNCTIONAL STATUS (PP)
-change in mean daily use of B2-agonist (puffs/day)
-change in quality of life score (range 1-7)
-change in nocturnal awakenings

INFLAMMATORY MARKERS
-change in peripheral blood eosinophil count

ADVERSE EFFECTS
-reported

WITHDRAWALS
-reported

* primary outcome

Notes

-Full text 2003

-Funding: Merck & Co

-Confirmation of methodology and data extraction obtained by DB Price, August 2003

-User-defined order: 80
(mean intervention ICS dose of 800 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Riccioni 2001

Methods

DESIGN
-parallel group

ALLOCATION
-Random
-method of randomization: computer generated
-method of assessment: not mentioned

BLINDING

Riccioni 2001 (Continued)

-reported as double-blind (patient and assessor) but without placebo

WITHDRAWAL/DROPOUT

-described

JADAD's Quality Score = 2

-Confirmation of methodology: received (Oct 2003)

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED:

N = 48

Z= 12

BUD= 12

Z+BUD= 12

Control= 12

WITHDRAWALS;

Z=2 (16%)

BUD= 1 (8%)

Z+BUD= 2 (16%)

AGE: mean (\pm SD) years

Z:

33.75 (\pm 11.24)

BUD:

32.15 (\pm 10.27)

Z+BUD:

33.44 (\pm 11.12)

Control:

29.15 (\pm 10.34)

GENDER (% male):

Z: 6 (50)

BUD: 6 (50)

Z+BUD: 6 (50)

Control: 6 (50)

BASELINE SEVERITY:

-mild persistent

% Predicted FEV1 (Mean \pm SD)

Z:

94.75 \pm 7.68

BUD:

92.75 \pm 9.87

Z+BUD:

92.16 \pm 5.06

Control:

95.75 \pm 5.84

ATOPY/ALLERGEN TRIGGERS:

-not reported

ASTHMA DURATION (years)

-1 year

ELIGIBILITY CRITERIA

-1 year of mild persistent bronchial asthma

-PEF >80% pred. and PEF daily variability in 20-30% range with positive salbutamol reversibility test

EXCLUSION:

Riccioni 2001 (Continued)

- URTI in last 3 weeks
- hospitalization for asthma in the last 3 months
- treatment with antihistamines, anticholinergics, theophylline drugs
- presence of autoimmune, hepatic, or renal disorders
- malabsorption, drug or alcohol addiction
- pregnancy or lactation

Interventions

PROTOCOL

Duration

- run-in Period: 2 weeks
- Intervention: 8 weeks

TEST GROUP:

- Zafirlukast 20 mg bid

TEST GROUP 2

- Zafirlukast 20 mg bid + Budesonide 400 g bid

CONTROL GROUP

- Budesonide 400 g bid

CONTROL GROUP 2

- Placebo

DEVICE:

- not reported

CO-INTERVENTION:

- not reported

Outcomes

ANALYSIS PER PROTOCOL
(not by ITT)

OUTCOMES

- reported at 8 weeks

PULMONARY FUNCTION TEST

- pre- and post FVC values
- pre- and post FEV1
- pre- and post PC20

SYMPTOM SCORES

- not reported

FUNCTIONAL STATUS

- not reported

INFLAMMATORY MEDIATORS

- not reported

ADVERSE EVENTS

- not mentioned

WITHDRAWALS

- not reported

Primary outcome not specified

Notes

- Full-text publication (2001)

Funded by University

Riccioni 2001 (Continued)

-confirmation of methodology and data extraction: obtained from Graziano Riccioni, Oct 2003
 USER-DEFINED ORDER: 800 (daily dose of BDP-equivalent=800 mcg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Study investigators aware as to treatment group assignment (Cochrane Grade C)

Riccioni 2002

Methods	DESIGN -parallel-group ALLOCATION -random -method of randomization: computer generated -method of assessment: not described BLINDING -reported as double-blind (patient and assessor) but without placebo WITHDRAWAL/DROPOUT -described JADAD = 3 CONFIRMATION OF METHODOLOGY: obtained (Oct 2003)
Participants	SYMPTOMATIC PARTICIPANTS RANDOMISED (N=45) M=15 BUD=15 M+BUD=15 WITHDRAWALS: M=1 (7%) BUD=1 (7%) M+BUD=1 (7%) AGE (\pm SD) M= 26.7 \pm 8.6 BUD=26.9 \pm 12.3 M+BUD=28.2 \pm 10 GENDER (% male) M= 9 (60) BUD=8 (53.3) M+BUD=5(33.7) ASTHMA SEVERITY: -mild ASTHMA DURATION: -1 year % Pred. FEV1

Riccioni 2002 (Continued)

M=97 (85-123)
BUD=97 (76-123)
M+BUD=99 (84-131)

Mean (+-SD) beta2agonist use (puffs per day)
-not described

ATOPY:
-100% (Definition not mentioned)

ELIGIBILITY

CRITERIA

- asthma as per ATS criteria
- confirmation of the presence of BHR by methacholine on the initial visit
- regular attendance of the outpatient clinic over 4 months from the initial visit
- PEF >= 80% of predicted
- PEF variability <=20% as per NIH criteria

EXCLUSION:

- ER visit for asthma exacerbation within 1 month
- URTI in the past 4 weeks
- hospitalization for asthma in past 6 months
- treatment with antihistamines, anticholinergics, theophylline and cromones, LABA, inhaled and oral corticosteroids
- bronchiectasis
- gastroesophageal reflux
- poor knowledge of the Italian language

Interventions

PROTOCOL

Duration
-Run-in: 4 weeks
-Intervention: 16 weeks

TEST GROUP 1
-10 mg montelukast once daily

TEST GROUP 2
10 mg Montelukast once daily +
400 ug budesonide bid

CONTROL GROUP
-400 Budesonide bid

DEVICE
-turbohaler

CRITERIA FOR WITHDRAWAL
-not described

CO-INTERVENTION:
-none permitted

Outcomes

ANALYSIS PER PROTOCOL
(not by ITT)

OUTCOMES
-reported at 16 weeks

PULMONARY FUNCTION TEST
-change from baseline in FVC
-change from baseline in FEV1
-change from baseline in PC20

Riccioni 2002 (Continued)

SYMPTOM SCORES

-not reported

FUNCTIONAL STATUS

-Change in AQOL (Asthma Quality of Life Questionnaire - Juniper) in each of 4 domains

-Asthma exacerbations (defined as requiring systemic steroids or hospital admission or ED treatment for worsening asthma or decrease in morning PEF >25%)

INFLAMMATORY MEDIATORS

-not reported

ADVERSE EVENTS

-not mentioned

WITHDRAWALS

-reported

Primary outcome not specified

Notes

-Full-text publication

Funded by University

-confirmation of methodology and data extraction: obtained by Graziono Riccioni, Oct 2003

-confirmation of methodology and data obtained

USER-DEFINED ORDER: 800 (daily dose of BDP-equivalent=800 mcg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Study investigators aware as to treatment group assignment (Cochrane Grade C)

Ringdal 1999

Methods

DESIGN

-parallel-group

-multicentre

-3-arm study

(1) Z40 + ICS

(2) Z160 + ICS

(3) 2 x ICS

ALLOCATION

-Random

-Computer generated random numbers

-sealed envelopes containing allocation

BLINDING

-double-blind

-double-dummy

-identical placebo

WITHDRAWAL/DROPOUT

-described

JADAD's Quality Score = 5

Ringdal 1999 (Continued)

-Confirmation of methodology obtained

Participants

SYMPTOMATIC PARTICIPANTS

Randomised

N = 440

Z40+ICS = 148

Z160+ICS = 146

2 x ICS = 146

WITHDRAWALS

Z40+ICS = 10%

Z160+ICS = 12%

2 x ICS = 6%

AGE: 12 to 70 years old

Z40+ICS: 41.3 ± 14.36 years

Z160 + ICS: 40.1 ± 13.46 years

2 x ICS: 42.2 ± 14.54 years

GENDER (% male):

Z40 + ICS: 49%

Z160 + ICS: 48%

2 x ICS: 50%

SEVERITY: mild- moderate

BASELINE FEV1 (% Pred)

Z40 + ICS: 84.1 ± 12.53 %

Z160 + ICS: 85.0 ± 14.25 %

2 x ICS: 85.1 ± 15.02 %

ALLERGEN TRIGGERS:

not described

ASTHMA DURATION

-not described

MEAN ICS DOSE AT ENTRY (mcg/day)

Z40 + ICS:432 ± 63 Z160 + ICS:424 ± 63

2 x ICS:426 ± 54

ELIGIBILITY CRITERIA

-treated with either BDP, BUD or FP and beta2-agonist prn

-FEV1 >= 60 at screening

- >= 15% improvement in clinic FEV1 or PEF in response to dose =< 400ug albuterol at screening

-total asthma symptom score >= 10 (0 to 3 scale recorded daily) in the last 7days of screening period

Interventions

PROTOCOL:

AL + ICS vs DOUBLE dose ICS

DURATION:

-Run-in Period: 2 week (fixed)

-Dose optimisation period: none

Intervention Period: 12 weeks

TEST GROUP

Z40 + ICS:

Zafirlukast 20 mg bid + BDP 400 to 500 ug/day

TEST GROUP

-Z160 + ICS:

Zafirlukast 80 mg bid + BDP 400 to 500 ug/day

Ringdal 1999 (Continued)

CONTROL GROUP
2 x ICS: BDP 800 to 1000 ug/day

DEVICE
-metered-dose aerosol inhaler

-CO-TREATMENT: none reported

Outcomes

PER PROTOCOL
(PP) ANALYSES- -some Intention -to- treat (ITT) analyses available
-outcomes used at 6 and 12 weeks

PULMONARY FUNCTION TESTS (PP)
-**Change in morning PEFR (L/min)
-Change in evening PEFR

SYMPTOM SCORES (PP)
-Change in mean symptom scores
-Change in night-time awakenings per week

FUNCTIONAL STATUS
-Change in mean daily use of beta2- agonists (PP)
-St-Georges' QOL questionnaire (ITT)

INFLAMMATORY MARKERS:
-not reported

ADVERSE EFFECTS
-elevated liver enzymes, headache, nausea, death

WITHDRAWALS
-reported

(** denotes primary outcomes)

Notes

-Abs (1999) and poster and unpublished report provided by Astra-Zeneca (Oct 2000)

-Funded by Astra-Zeneca

-Confirmation of methodology and data extraction graciously received from M. Christopher Miller and Ms. Susan Shaffer, Astra-Zeneca, Oct 2000

-User-defined order: 45
(mean intervention ICS dose of 450 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Shingo 2001

Methods

DESIGN
-parallel-group study
-multicentre

ALLOCATION
-Random

Shingo 2001 (Continued)

-computer-generated
-assignment by numbered coded solutions supplied by Merck

BLINDING
-double-blind
-identical placebo

WITHDRAWAL/DROPOUT
-described

JADAD's Quality Score =5

Methodology confirmed

Participants

WELL-CONTROLLED PARTICIPANTS

N = 22 patients
montelukast: 10
placebo: 12

WITHDRAWALS:
Montelukast: 10%
Placebo: 8%

AGE (Mean, SD):
Montelukast: 41.0 ± 11.03 years
Placebo: 37.00 ±
8.64 years

GENDER(% male):
Montelukast: 60% Placebo: 25%

BASELINE % PRED FEV1 mean (SD):
Montelukast:84.48± 8.68 %
Placebo: 84.68 ± 8.4 %

ATOPY: not described

BASELINE DOSE OF ICS: 793 beclo-equivalent:1523 (536) mcg/day or 761 mcg/day of BPD-equivalent
montelukast: 1600 mcg/day or 800 mcg/day of BDP-equivalent
placebo: 1350 mcg/day or 675 mcg/day of BDP equivalent

ELIGIBILITY CRITERIA
-non-smoking patients
-age 15 to 70 years
-Stable asthma
-Baseline FEV1>= 75% of predicted
-improvement in FEV1>= 15% after inhaled beta2-agonist
-daytime symptom score <= 7 averaged over the run-in period
-stable doses of inhaled glucocorticoids for >= 21 days, namely BDP (600 to 1600 mcg/day), flunisolide (1000 to 2000 mcg/day), or triamcinolone (1200 to 3200 mcg/day)

Exclusion criteria: not described

Interventions

PROTOCOL
AL + ICS vs same dose
ICS (TAPERING ICS dose)

Duration
-Run-in Period: 7 to 10 days
-Intervention Period : 8 weeks

TEST GROUP
-Montelukast 10 mg qd p.o.

Shingo 2001 (Continued)

-Inhaled glucocorticoids: dose (median: 761 mcg/day of BDP equivalent)

CONTROL GROUP
-Placebo die -Inhaled glucocorticoids: dose (median: 675 mcg/day of BDP equivalent)

DEVICE
-not specified

CO-INTERVENTION: theophylline (? %) of patients

Outcomes

INTENTION-TO-TREAT ANALYSIS

OUTCOMES REPORTED AT 8 WEEKS

PULMONARY FUNCTION TESTS (measured but not reported)
-% Change from baseline FEV1
-Change in am and pm PEFR (L/min) averaged over ? weeks
- diurnal PEFR variation

FUNCTIONAL STATUS (measured but not reported)
-Use of rescue beta2-agonist (puffs/days)
-Change in daytime symptom score (0-6)
-night-time awakening
-exacerbations requiring systemic steroids or hospital admission (reported upon request)

ICS DOSE REDUCTION:
-Number of patients tapered off ICS (mcg)

INFLAMMATORY MARKERS:
-not reported

ADVERSE EVENTS:
reported upon request

WITHDRAWALS: reported upon request

Primary outcome: change in baseline dose of ICS

Notes

-Full-text publication and unpublished data

-Funded by Merck

-Confirmation of methodology and data extraction graciously received from T.F Reiss and G.P. Noonan, Merck Frosst, USA, June 2001

user-defined order: 80
(mean intervention ICS dose of 800 mcg/day of BDP-equivalent X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Simons 2001

Methods

DESIGN
-Cross-over study

ALLOCATION

Simons 2001 (Continued)

- Random
 - Computer-generated random number
 - Assignment by numbered coded solutions supplied by Merck
- BLINDING
- triple-blind
 - identical placebo
- WITHDRAWAL/DROPOUT
- described but not by group/period
- JADAD's Quality Score =5
- Methodology confirmed

Participants

SYMPTOMATIC PARTICIPANTS

N = 279 children

RANDOMISED:

PERIOD 2:

Montelukast: 146

Placebo: 133

PERIOD 3:

Montelukast: 129

Placebo: 137

WITHDRAWALS:

Montelukast: 3%

Placebo: 2%

AGE (Mean, SD):10.4 ± 2.2 years (range: 5 to 15 years)

GENDER(% male): 67

Baseline mean FEV1 % Pred (SD) = 77.7 (10.6)

ATOPY: 72% allergic rhinitis

ELIGIBILITY CRITERIA

-Age: 6 to 14 years

-persistent asthma

-treatment with inhaled glucocorticoid for at least 6 weeks at 200 to 800 mcg/day of BUDesonide, beclomethasone, triamcinolone, flunisolide or 100 to 500 mcg/day of fluticasone

-during run-in on 200 mcg bid of BUDesonide: FEV1 between 60% to 85% of predicted; >= 12% improvement in FEV1 after beta2-agonist, beta2-agonist use >= 2 puffs/day

Exclusion criteria: not described

Interventions

PROTOCOL

AL + ICS vs ICS (same dose)

Duration

-Run-in Period 1: 2 weeks

-Intervention Period 2: 4 weeks

Period 3: 4 weeks

No washout period

TEST GROUP

-Montelukast 5 mg qd p.o.

-BUDesonide 200 mcg bid

CONTROL GROUP

Simons 2001 (Continued)

-BUDesonide 200 mcg bid
-Placebo die

DEVICE
-Turbuhaler

CO-INTERVENTION: not reported

Outcomes

INTENTION-TO-TREAT ANALYSIS
(adjusted for period effect)

PULMONARY FUNCTION TESTS
-% Change from baseline FEV1 at 4 weeks
-Change in am and pm PEFR (L/min) averaged over 2 weeks
-diurnal PEFR variation?

FUNCTIONAL STATUS
-Use of rescue beta2-agonist (puffs/days)
-Change in quality of life
-Physician and parents global assessments
-exacerbations days
-Asthma exacerbations and attack rates (unscheduled visit to a physician, or Ed or admission to hospital or treatment with oral glucocorticoids)
-Patients with exacerbations requiring systemic steroids (provided upon request)

ADVERSE EVENTS:
reported

WITHDRAWALS: not reported

Notes

-Full Text 2001 and unpublished data

-Funded by Merck

-Confirmation of methodology and data extraction (published and unpublished data) graciously obtained from T.F Reiss and G.P. Noonan, Merck Frosst, USA, June 2001

User-defined order = 40
(mean intervention ICS dose of 400 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Tamaoki 1997

Methods

DESIGN
-parallel-group
-multicentre

ALLOCATION
-Random
-blocks of four at each center

BLINDING
-double-blind
-placebo-controlled

Tamaoki 1997 (Continued)

-identical placebo

WITHDRAWAL/DROPOUTS
-described

JADAD's Quality Score = 4

Confirmation of methodology not obtained

Participants

WELL CONTROLLED PARTICIPANTS- SUDDEN ICS DOSE REDUCTION

-RANDOMISED
N = 79
Pranlukast = 43
Control = 40

WITHDRAWALS:
Pranlukast = 2%
Control = 8%

GENDER: 43 % male

AGE
Pranlukast: 49 ± 3 years (SEM)
Control: 47 ± 3 years

SEVERITY: not described

BASELINE FEV1 (% Pred)
Pranlukast: 79.1 ± 2.6 (SEM)
Control: 81.6 ± 2.3 (SEM)

ALLERGEN TRIGGERS: not described

ASTHMA DURATION: Pranlukast: 11.3 ± 4.5 years (SEM) years
Control: 10.6 ± 3.9 years

ELIGIBILITY CRITERIA

-Age ≥ 21 years old
-Am PEF > 70%, or FEV1 > 70% Pred
-< 10 asthma symptom score during previous 2 weeks
-no systemic steroid course during previous 8 weeks,
or < 4 short courses during past year
-symptoms well controlled on daily dose of inhaled beclomethasone ≥ 1500 mcg for at least 6 weeks

Interventions

PROTOCOL:
AL + ICS vs SAME dose ICS

DURATION:
-Run-in Period: 2 weeks
-Dose Optimisation period: none
(sudden decrease in ICS at study onset)
-Intervention Period: 6 weeks

TEST GROUP
-Pranlukast 450 mg bid p.o. + Beclomethasone dipropionate 1/2 of usual dose
(? 750 ug/day)

CONTROL GROUP
-Placebo + Beclomethasone dipropionate 1/2 of usual dose(? 750 ug/day)

DEVICE
-metered-dose aerosol inhaler

Tamaoki 1997 (Continued)

-CO-TREATMENT:
-Oral beta2-agonist
(Pranlukast: 93%/Control:97%)
-Oral theophylline:
(Pranlukast:93%/Control:91%)
-Inhaled anticholinergics
(Pranlukast:50%/control:51%)

Outcomes

ANALYSES (intention-to- treat not specified)
-used at 6 weeks

-PULMONARY FUNCTION TESTS
-**Change from baseline FEV1
-Change from baseline Am PEF
-Change from baseline Pm PEF
-Change from baseline mean diurnal variation of PEF

SYMPTOM SCORES
-Change from baseline daytime asthma symptoms (episodes/week)
-Change from baseline nighttime asthma symptoms (episodes/week)

FUNCTIONAL STATUS
-Change from baseline daytime use of B2-agonists (puffs/weeks)
-Change from baseline nighttime use of B2-agonists (puffs/week)
-Change in night wakings (episodes/week)
-Number of patients experiencing exacerbations requiring systemic steroids

INFLAMMATORY MARKERS
-Change from baseline serum ECP (ug/L)
-Change from baseline exhaled NO (ppb)

ADVERSE EFFECTS
-not reported

WITHDRAWALS
-reported

(** denotes primary outcomes)

Notes

-Full Text (1997)

-Funded by Japanese Ministry of Educ, Sci, & Culture and Glaxo/ONO?

-Request for confirmation of methodology and data extraction (sent to Tamaoki 28 May 1999)

-No reply as of Sept 2001

-User-defined order: 75
(mean intervention ICS dose of 750 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Tohda 2002

Methods DESIGN

Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma (Review)

Tohda 2002 (Continued)

-parallel-group
-multicentre (16 study sites)

ALLOCATION
-Computer generated random allocation
-Mode of allocation (not described)

BLINDING
-double-blind
-placebo-controlled
-identical placebo

WITHDRAWAL/DROPOUTS
-described

JADAD's Quality score = 5

Confirmation of methodology confirmed

Participants

WELL-CONTROLLED PARTICIPANTS

RANDOMISED N = 191
-Montelukast = 93
-Control = 98

WITHDRAWALS:
-Montelukast = 14 (15%)
-Control = 20 (20%)

AGE (years):
-Montelukast: 50.1 ± 14.5 (SD)
-Control: 53.0 ± 13.2 (SD)

GENDER (% male):
-Montelukast: 58.3%
-Control: 58.3%

SEVERITY:
-moderate-to-severe bronchial asthma

BASELINE PREDICTED FEV1 (%):
-Montelukast: 87.4 ± 18.4 (SD)
-Control: 85.6 ± 24.8 (SD)

ALLERGEN TRIGGERS
-not reported

ASTHMA DURATION
-montelukast: < 10 years = 57 (67.9); >10 years = 27 (32.1)
- control: < 10 years = 56 (66.7); > 10 years = 28 (33.3)

ELIGIBILITY CRITERIA
-taking a dose of ICS 800-1600 ug/day
-PEFR ≥ 80% of patients best or predicted
-diurnal variation PEFR of no more than 20%
-asthma symptom score of no more than 5 points/week

EXCLUSION CRITERIA
- use of following medication one month prior to run-in period
- anti-allergic drugs (disodium cromoglycate, ketotifen or pranlukast)
- oral corticosteroids at the start of the run-in period
-long-acting corticosteroids (methylprednisolone acetate or triamcinolone acetonide)

Interventions

PROTOCOL:

Tohda 2002 (Continued)

AL + ICS vs same dose
ICS (TAPERING ICS dose)

DURATION

-4 week run-in period
-24 week treatment period with ICS titrated at weeks 8 and 16

TEST GROUP

-Montelukast 10 mg film-coated tablet once daily + BDP 800-1600 mcg daily

CONTROL GROUP

-Placebo +
+ BDP 800-1600 mcg daily

DEVICE

- not reported

CO-TREATMENT:

- bronchodilators : xanthine derivatives, anticholinergics
-antibiotics, antitussive and expectorants, chinese medicine, desensitization therapy

CRITERIA FOR TAPERING

- mean PEFr observed during previous 2 weeks in not less than 90% of value in run-in
- weekly mean symptom score during the previous 2 weeks is not 3 points or more higher than score at run-in period
- mean inhaled B-agonist use during the previous 2 weeks is less than twice use at run-in period

CRITERIA FOR MAINTAINING ICS DOSE

- 2 out of the 3 criteria for dose tapering mentioned above

CRITERIA FOR INCREASING ICS DOSE

- 1 or none of the criteria for dose tapering mentioned above

MINIMAL DOSE OF ICS ALLOWED:

- no minimal dose required

Outcomes

EFFICACY ANALYSIS - NO INTENTION TO TREAT ANALYSIS

-outcomes available at 4, 8, 16 and 24 weeks

PULMONARY FUNCTION TESTS

-% change in PEFr
-% change in FVC
-% change in FEV1

SYMPTOM SCORES

-% change in breathlessness and wheezing (range 0-9)
- % change in therapy score (range not reported, based on Japanese Society of Allergology)
- % change in asthmatic score (combining symptom score with therapy score)

FUNCTIONAL STATUS

- not reported

ICS DOSE REDUCTION

-

INFLAMMATORY MARKERS

- not reported

ADVERSE EFFECTS

- alopecia areata, headache, bitter taste, stomach ache, heartburn and asthma in the montelukast group, and toxicoderma, papules, headache, diarrhoea, constipation, retching, palpitations and nocturia in the placebo group
****data not reported****

Tohda 2002 (Continued)

 WITHDRAWALS
 - reported

Notes

-Full text (2002) and unpublished data

-Funded by Banyu Pharmaceutical Limited (makers of montelukast)

-Confirmation of methodology and data extraction graciously obtained from Takaaki Ishine, PhD, Banyu Pharmaceutical Co, LTD, August 2003

-user-defined order: 92.mcg/day
 (mean ICS dose of 925 mcg/ day x 0.1

Risk of bias
Bias
Authors' judgement
Support for judgement

 Allocation concealment
 (selection bias)

Low risk

 Study investigators unaware as to order of treatment group assignment
 (Cochrane Grade A)

Tomari 2001

Methods

DESIGN
 -parallel-group

ALLOCATION
 -random: not specified
 -Mode of allocation (not described)

BLINDING
 -not described

WITHDRAWALS/ DROPOUTS
 -described

JADAD's Quality Score = 2

Confirmation of methodology not obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED
 -N=41
 -BDP + pranlukast = 21
 -2 X BDP = 20

WITHDRAWALS
 -none

AGE years (SEM)
 -BDP + pranlukast = 53.7 (3.1) (SEM)
 -2 X BDP = 56.1 (3.2) (SEM)

GENDER (% male)
 -BDP + pranlukast = 38%
 -2 X BDP = 45%

SEVERITY
 - moderate asthma

BASELINE % PREDICTED FEV1

Tomari 2001 (Continued)

-not documented

BASELINE % PREDICTED PEF
-BDP + pranlukast = 72.1 ± 2.8 (SEM)
-2 X BDP = 69.5 ± 3.1 (SEM)

ALLERGEN TRIGGERS
-not reported

ASTHMA DURATION years (SEM)
-BDP + pranlukast = 14.8 (2.7) (SEM)
-2 X BDP = 14.1 (2.7) (SEM)

ELIGIBILITY CRITERIA
-diagnosis of asthma
-treated with 800 mcg/day of BDP
-PEFR < 80% predicted

EXCLUSION CRITERIA
-pulmonary or bronchial diseases for 2 weeks before study

Interventions

PROTOCOL:
AL + ICS vs DOUBLE dose ICS

DURATION
-2 week run-in period
-16 week treatment period

TEST GROUP
-BDP 800 mcg/day + 450 mg/day pranlukast

CONTROL GROUP
-2 X BDP (1600 mcg/day)

DEVICE
-not specified

CO-TREATMENT
-theophylline and B2-agonists if previously in use

Outcomes

INTENTION-TO-TREAT ANALYSES
-outcome reported at 16 weeks

PULMONARY TESTS
-pre and post treatment am PEFR (%)
-pre and post treatment in daily variability of PEFR (%)

SYMPTOM SCORES
-pre and post treatment symptom score
(sum of 7 symptoms scored from 0-3)

FUNCTIONAL STATUS
-pre and post treatment B2-agonists use/week

INFLAMMATORY MARKERS
-not reported

ADVERSE EFFECTS
-reported

WITHDRAWALS
-no withdrawals

Tomari 2001 (Continued)

* Primary outcome not mentioned

Notes

- Full text 2001
- Funding not specified (information requested)
- Confirmation of methodology and data extraction not obtained.
- User-defined order: 80
(mean intervention ICS dose of 800 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Tomita 1999

Methods

DESIGN
-parallel-group

ALLOCATION
-Random (method of randomisation not described)
-Mode of allocation (not described)

BLINDING
-none
-no placebo

WITHDRAWALS/DROP-OUTS
-not reported

JADAD's Quality score = 1

Confirmation of methodology not obtained

Participants

WELL-CONTROLLED PARTICIPANTS- SUDDEN DECREASE OF ICS DOSE

RANDOMISED
N = 41
pranlukast = 24 control = 17

WITHDRAWALS
Pranlukast:?
Placebo:?

AGE
Pranlukast: 56.7 ± 18.0 years (SD)
Control: 42.2 ± 16.9 years

GENDER (% male): Pranlukast: 62%
Control: 59%

SEVERITY:
mild-moderate asthma

BASELINE FEV1 (% predicted FEV1/HT):
Pranlukast: 90.3 ± 13.4 (SD)
Control: 86.3 ± 19.0

Tomita 1999 (Continued)

ALLERGEN TRIGGERS (% atopic):
Pranlukast: 67%/ Control: 65%

ASTHMA DURATION: not specified

ELIGIBILITY CRITERIA:

Adults with stable asthma well controlled on 800 mcg/day of beclomethasone for 3 months

EXCLUSION CRITERIA:

-non described

Interventions

PROTOCOL:

AL + ICS vs SAME dose ICS

DURATION

-Run-in Period (4 weeks)

-Dose Optimisation Period: NONE

-Intervention period (8 weeks)

TEST GROUP:

-Pranlukast 450 mg die p.o.

+ ICS 400 mcg/day of beclomethasone

CONTROL GROUP:

-400 mcg/day of beclomethasone

-no placebo

DEVICE:

not described

-CO-TREATMENT: ? 2 patients on oral steroids (to be confirmed)

Outcomes

NO INTENTION-TO-TREAT ANALYSES

-outcome used at 8 weeks

PULMONARY FUNCTION TESTS

(reported as cross-sectional values not as change from baseline)

-FEV1

-V50

-V25

-morning % PEF

-evening % PEF

-diurnal PEF variation

SYMPTOM SCORES

(reported as cross-sectional values not as change from baseline)

-symptom score

-therapeutic score

(both defined by the Japanese Society of Allergology)

FUNCTIONAL STATUS

-not reported (?)

INFLAMMATORY MARKERS

-not reported (?)

ADVERSE EFFECTS

-not reported (?)

WITHDRAWALS

-not reported (?)

(unclear primary outcome)

Tomita 1999 (Continued)

- Notes
- Full-text (1999) Japanese paper with English abstract
 - Partial translation obtained from Cochrane Collaborator
 - Funding status (unknown)
 - Confirmation of methodology and data extraction (requested Jan 2001: pending)
 - User-defined order: 40
(mean intervention ICS dose of 400 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Vaquerizo 2003

- Methods
- DESIGN
- parallel-group
 - multi-centre (80 sites in Spain)
- ALLOCATION
- random
 - central computer generated schedule
 - treatment assignments (1:1) stratified according to site and 3 BUD dose levels (400-800 mcg/day ; 801-1200 mcg/day ; and 1201-1600 mcg/day)
 - Mode of treatment allocation not described
- WITHDRAWALS/ DROPOUTS
- described
- JADAD's quality score = 5
- Confirmation of methodology: requested but not obtained

- Participants
- WELL-CONTROLLED PARTICIPANTS
- RANDOMISED
- N = 639
 - BUD + M = 326
 - BUD + placebo = 313
- WITHDRAWALS
- BUD + M = 34 (10%)
 - BUD + placebo = 32 (10%)
- AGE years (SD)
- range 18-79
 - BUD + M = 42 (15) years
 - BUD + placebo = 44 (16) years
- GENDER (% male)
- BUD + M = 62%
 - BUD + placebo = 61%
- SEVERITY
- mild to moderate asthma

Vaquerizo 2003 (Continued)

BASELINE % PREDICTED FEV1 (SD)

- BUD + M = 81 (19)
- BUD + placebo = 81 (21)

ALLERGEN TRIGGERS

- not described

ELIGIBILITY CRITERIA

- non-smokers
- aged 18-70 (*age of participants outside of range*)
- treated with 400-1600mcg/day BUD for at least 8 weeks
- FEV1 \geq 55% predicted
- reversible airway obstruction (increase \geq 12% of baseline FEV1)
- minimum total daytime asthma symptom score of 64 during the 2 week run-in period
- using a mean of at least 1 puff/day of B2-agonist during run-in period
- negative pregnancy test (urine B-human chorionic gonadotropin)
- use of contraceptive 2 weeks prior to treatment and 2 weeks after study

EXCLUSION:

- not described

Interventions

PROTOCOL

- AL + ICS vs. SAME dose ICS + placebo

DURATION

- 2 week run-in period
- 16 week treatment period

TEST GROUP

- montelukast (10mg/day) + BUD (400-1600 mcg/day)

CONTROL GROUP

- placebo + BUD (400-1600 mcg/day)

DEVICE

- Turbuhaler

CO-TREATMENT

- use of B2-agonist as needed

Outcomes

INTENTION-TO-TREAT ANALYSES

PULMONARY FUNCTION TESTS

- % change from baseline at end point
- % change in am and pm PEFr (L/min)
- % change in FEV1 (L)

SYMPTOM SCORE

- % change from baseline in daily daytime symptom score (range not specified)

FUNCTIONAL STATUS

- *% of asthma exacerbation days
- % change in mean daily use of B2-agonist (puffs/day)
- change in nocturnal awakenings
- change in asthma specific quality of life (32 questions, range 0-6)

INFLAMMATORY MARKERS

- none documented

ADVERSE EFFECTS

- described
- influenza, headache, URI, worsening asthma, epigastric pain, urinary tract infections, rhinitis, pharyngitis, bronchitis

Vaquerizo 2003 (Continued)

WITHDRAWALS
 -reported
 * Primary outcome

Notes
 -Full text (2003)
 -Funded by Merck Sharp and Dohme Spain
 -Confirmation of methodology and data extraction requested: not obtained
 -user-defined order: 80 mcg/day
 (mean ICS dose about 800 mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Virchow 2000

Methods

DESIGN
 -parallel-group
 -multicentre (82 centres)

-ALLOCATION
 -Random
 -Computer-generated

BLINDING
 -double-blind
 -placebo controlled
 -identical placebo
 -number coded solutions/boxes

WITHDRAWAL/DROPOUT
 -described

JADAD's Quality Score = 5
 -Confirmation of methodology obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED
 N = 368
 Zafirlukast = 180
 Control = 188

WITHDRAWALS:
 Zafirlukast = 18%
 Control = 18%

AGE:
 Zafirlukast: 49.2 ± 12.9 (SD) years
 Control: 47.4 ± 12.6 years

GENDER (% male)
 Zafirlukast : 48%

Virchow 2000 (Continued)

Control: 53%

SEVERITY:
moderate/severe asthma

BASELINE FEV1 (% pred):
Zafirlukast: 64.3 ± 7.5 (SD)
Control: 63.5 ± 8.0

ALLERGEN TRIGGERS (%)
Zafirlukast: 41%
Control: 51%

DURATION OF ASTHMA:
Zafirlukast: 15.7 ± 12.61(SD) years
Control: 17.5 ± 13.63 years

ICS DOSE:
Zafirlukast: 1598 ± 381 mcg/day (SD)
Control: 1650 ± 456 mcg/day of beclomethasone-equivalent

ELIGIBILITY CRITERIA
-50 to 75% FEV1 Pred
-ICS dose >= 1200 mcg/day beclomethasone-equivalent
-mean FEV1/PEF reversibility >= 15% after salbutamol
-symptomatic asthma
-no smoking in preceding 6 months

Interventions

PROTOCOL:
AL + ICS vs SAME dose ICS

DURATION:
-Run-in Period: not described
-Dose optimisation period: NONE
-Intervention Period: 6 weeks

TEST GROUP
-Zafirlukast 80 mg bid p.o. + Beclomethasone >= 1200 ug/day

CONTROL GROUP
-Placebo + Beclomethasone >= 1200 ug/day

DEVICE
-various devices used

-CO-TREATMENT: none reported

Outcomes

INTENTION-TO-TREAT (ITT) ANALYSIS
(some per-protocol (PP) analyses)
-results used at 6 weeks

PULMONARY FUNCTION TESTS - ITT
-Change from baseline FEV1
-**Change from baseline Am PEF

FUNCTIONAL STATUS -ITT
-Change in night wakings (episodes/week)-Number of patients with exacerbations requiring additional treatment
-Number of days off work
-Change in use of rescue beta2-agonist (puffs/day)

INFLAMMATORY MARKERS
-not reported

Virchow 2000 (Continued)

ADVERSE EFFECTS
 -elevated liver enzymes, headache, nausea, death, etc.

WITHDRAWALS
 -reported

(** denotes primary outcomes)

Notes

- Full Text (2000)
- Funded by Astra-Zeneca
- Confirmation of methodology and data extraction received from M. Christopher Miller and Ms. Susan Shaffer, Astra-Zeneca, Oct 2000
- User-defined order: 165
 (mean intervention ICS dose of 1650 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Wada 1999

Methods

DESIGN:
 -parallel group

ALLOCATION
 -Random
 -Method of randomisation not described
 -Mode of treatment allocation not described

BLINDING
 -none

WITHDRAWALS/DROPOUTS
 -Described

JADAD's Quality Score=1

CONFIRMATION OF METHODOLOGY: -not obtained

Participants

SYMPTOMATIC PARTICIPANTS

RANDOMISED
 N = 80
 Pranlukast = 40 Control = 40

WITHDRAWAL
 Pranlukast: 8%
 Control: 18%

AGE:
 pranlukast 50.8 years ±2.4 (SEM)
 Control: 48.4 years ± 2.2 (SEM)

GENDER (% male):
 Pranlukast: 59%

Wada 1999 (Continued)

Control: 40%

SEVERITY: moderate asthma

BASELINE FEV1 (L):
Pranlukast: 1.83 L
Control: not reported

ALLERGEN TRIGGERS:
Pranlukast: 54%
Control: 51%

BASELINE BDP DOSE: Pranlukast: 1048.6 ± 39.1 mcg/day
Control: 1127.3 ± 53.5 mcg/day

ELIGIBILITY CRITERIA
Adults not well controlled on:
- 800 mcg/day of beclomethasone ± slow-release theophylline for 3 months
- FEV1 > 50% of predicted
- Reversibility in FEV1 > 15% post B2-agonists
on 800 mcg/day of beclomethasone for 3 months

EXCLUSION CRITERIA:
- no systemic steroids and no upper respiratory tract infection in past 4 weeks

Interventions

PROTOCOL:
AL + ICS vs SAME dose ICS

DURATION:
- Run-in period: 2 weeks to establish baseline
- Dose optimisation period: NONE
- Intervention period: 4 weeks

TEST GROUP:
- Pranlukast 225 mg bid po + 800-1200 mcg/day of beclomethasone

CONTROL GROUP:
- 800-1200 mcg/day of beclomethasone
- no placebo

DEVICE:
- not described

CO-TREATMENT:
unspecified % on slow-release theophylline

Outcomes

ANALYSIS (intention-to-treat not specified)
- outcomes used at 4 weeks

PULMONARY FUNCTION TESTS
- FEV1 (L)
- morning PEF (L/min)
- V25/HT (L/min)

SYMPTOMS SCORES
(reported as cross-sectional values, not change from baseline)
- symptom scores averaged over 2 weeks
(scale 0-9)

FUNCTIONAL STATUS
(reported as cross-sectional values, not change from baseline)
- use of rescue Beta2-agonist (puffs/week)
- exacerbations requiring systemic steroids

Wada 1999 (Continued)

INFLAMMATORY MARKERS
 (reported as cross-sectional values, not change from baseline)
 -sputum eosinophils(%)
 -serum eosinophils (/uL)
 -serum ECP(ng/uL)
 -serum total IgE
 -serum Der f-specific IgE

ADVERSE EFFECTS
 -not reported

WITHDRAWALS
 -reported

Primary outcome
 not specified

Notes
 -Full-text (2000) paper
 -funding status (not reported)
 -confirmation of methodology and data extraction (pending)
 -User-defined order: 100
 (mean intervention ICS dose of 1000 mcg/ day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Yildirim 2001

Methods
DESIGN
 -parallel-group

ALLOCATION
 -Random
 -Methods of randomisation: not reported
 -means of assignment: not reported

BLINDING
 -not reported

WITHDRAWAL/DROPOUT
 -not described

JADAD's Quality Score = 1
 -Confirmation of methodology not obtained

Participants
SYMPTOMATIC PARTICIPANTS
RANDOMISED
 - N= 30
 -M10 + ICS = NR
 -2 X ICS= NR

Yildirim 2001 (Continued)

WITHDRAWALS
-M10 + ICS =NR
-2 X ICS= NR

GENDER (% male)
-M10 + ICS = NR
-2 X ICS =NR

AGE (SD) years
-M10 + ICS = NR
-2 X ICS= NR

SEVERITY
-not specified

BASELINE PREDICTED FEV1 % (SD)
-M10 + ICS = NR
-2 X ICS = NR

ALLERGEN TRIGGERS
-not described

ASTHMA DURATION (SD) years
- M10 + ICS = NR
-2 X ICS = NR

ELIGIBILITY CRITERIA
-not reported

EXCLUSION CRITERIA
-not reported

Interventions

PROTOCOL:
AL + ICS vs DOUBLE dose ICS

DURATION
-Run-in Period: not described
-Intervention period: 12 weeks

TEST GROUP
-Montelukast 10 mg die p.o. + BUD 400 mcg/day

CONTROL GROUP (2 X ICS)
-BDP 800 mcg/day

DEVICE
-not described

-CO-TREATMENT:
none allowed

Outcomes

INTENTION-TO-TREAT ANALYSIS
-not described
-outcomes reported at 12 weeks

PULMONARY FUNCTION TESTS
-Change from baseline AM PEFR
-Change from baseline in FEV1

SYMPTOM SCORES
-Change from baseline daytime symptom scores
-Change from baseline nighttime symptoms

FUNCTIONAL STATUS

Yildirim 2001 (Continued)

-Change from baseline mean daily B2-agonist use

INFLAMMATORY MARKERS

-serum eosinophil counts

ADVERSE EFFECTS

-not reported

WITHDRAWALS

-not reported

(* denotes primary outcomes)

Notes

-Abstract 2001

-Funding source: not reported

-Confirmation of methodology and data extraction: not obtained.

User-defined order: 40

(mean intervention (400) dose in mcg/day X 0.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available (Cochrane Grade B)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Altman 1998	No co-treatment with inhaled corticosteroids
Barnes 1996	Inconsistent co-treatment with inhaled corticosteroids, and no tapering attempt Outcomes solely the result of provocation
Barnes 1997	No co-treatment with inhaled corticosteroids
Basyigit 2001	No co-treatment with inhaled corticosteroids
Baumgartner 1999	No co-treatment with inhaled corticosteroids
Becker 2000	No co-treatment with inhaled corticosteroids
Bisgaard 1999	No systematic co-treatment with inhaled corticosteroids Intervention administered for < 4 weeks Outcomes were solely the results of provocation tests
Bisgaard 2000	No co-treatment with inhaled corticosteroids Outcomes did not reflect chronic asthma control Intervention administered for < 4 weeks
Bjermer 2000	Planned (ongoing) trial Control intervention was not placebo (long-acting beta2-agonist)

Study	Reason for exclusion
Bjermer 2002	Use of other non permitted drug
Brabson 2002	No co-treatment with inhaled corticosteroids
Brannan 2001	No co-treatment with inhaled corticosteroids Intervention < 4 weeks Control intervention is not placebo (it is an anti-histamine)
Brocks 1996	Subjects were not asthmatic
Bronsky 1997	Subjects were not asthmatic
Bruce 2002	Outcome measures did not reflect asthma control
Busse 1999	No systematic co-treatment with inhaled corticosteroids Control intervention was not placebo (it's a long-acting beta2-agonist)
Cakmak 2000	Outcome measures did not reflect asthma control
Calhoun 1997	No co-treatment with inhaled corticosteroids
Calhoun 2001	Use of other non permitted drug
Camargo 2002	Acute asthma setting
Capella 2001	Subjects not asthmatic
Chuchalin 2002	Intervention was not anti-leukotrienes
Clifford 2000	Duplicate reference
Cloud 1989	No co-treatment with inhaled corticosteroids
Currie 2003	Duplicate reference
Currie 2003 (B)	Use of other non permitted drug
Cylly 2003	Ongoing trial
Dahlen 2002	No consistent co-treatment with inhaled corticosteroids. Merck Frosts unable to provide subgroup analysis.
Daikh 2003	Subjects were not asthmatics
Dempsey 1999	Intervention administered for < 4 weeks. No consistent co-treatment with inhaled glucocorticoids
Dempsey 2000	Intervention administered for < 4 weeks (single dose study)
Dempsey 2000b	Control intervention was not placebo
Dempsey 2001	No co-treatment with inhaled glucocorticoids
Dempsey 2002	Control intervention was not placebo
Dessanges 1999	Intervention administered for < 4 weeks (single dose study)

Study	Reason for exclusion
	Outcomes did not reflect control of chronic or acute asthma (solely the results of exercise challenge) No consistent co-treatment with inhaled corticosteroids
Diamant 1999	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes solely the result of provocation
Dicpinigaitis 2002	Outcome measures did not reflect asthma control
Dockhorn 2000	Intervention administered for < 4 weeks (single dose study) No co-treatment with inhaled corticosteroids
Eliraz 2001	Tested intervention is not anti-leukotrienes
Faul 2002	Outcome measures did not reflect asthma control
Findlay 1992	No co-treatment of inhaled corticosteroids Intervention was administered for less than a four-week period
Fischer 1995	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes were solely the result of provocation
Fischer 1997	No co-treatment with inhaled corticosteroids
Fish 1997	No co-treatment with inhaled corticosteroids
Flynn 2001	Duplicate Reference
Fujimura 1993	No co-treatment with inhaled corticosteroids
Gaddy 1990	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period, intravenously
Galant 2001	Duplicate reference
Geha 2001	Tested intervention is not anti-leukotrienes
Georgiou 1997	No co-treatment with inhaled corticosteroids Subjects were not asthmatic Intervention was administered for less than a four-week period
Ghiro 2002	Outcome measures did not reflect asthma control
Gold 2001	Control intervention was not placebo
Green 2002b	Intervention was not anti-leukotrien
Grossman 1995	No co-treatment with inhaled corticosteroids
Grossman 1997	No co-treatment with inhaled corticosteroids
Hahtela 1994	Intervention was not anti-leukotrienes
Hamilton 1998	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period

Study	Reason for exclusion
	Outcomes were solely the result of provocation
Hassall 1998	No co-treatment with inhaled corticosteroids
Hood 1999	Control subjects not asthmatics (normal subjects)
Howland 1994	No co-treatment with inhaled corticosteroids
Hsieh 1996	Intervention was not anti-leukotrienes
Hughes 1999	No co-treatment with inhaled corticosteroids
Hui 1991	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Israel 1990	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes were solely the result of provocation
Israel 1992	No co-treatment with inhaled corticosteroids
Israel 1993	No co-treatment with inhaled corticosteroids
Israel 1996	No co-treatment with inhaled corticosteroids
Israel 2002	No co-treatment with inhaled corticosteroids
Jayaram 2002	No co-treatment with inhaled corticosteroids
Johnson 1999	No co-treatment with inhaled corticosteroids
Juniper 1995	No co-treatment with inhaled corticosteroids
Kalberg 1999	No co-treatment with inhaled corticosteroids
Kanniess 2002 (B)	No co-treatment with inhaled corticosteroids
Kemp 1995	No co-treatment with inhaled corticosteroids
Kemp 1997	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes were solely the result of provocation
Kemp 1998	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Kemp 1999	Not a randomised controlled trial (meta-analysis of RCTs) Subjects not all treated with inhaled corticosteroids
Kim 2000	No co-treatment with inhaled corticosteroids
Kips 1991	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period, intravenously
Knorr 1997	Inconsistent co-treatment with inhaled corticosteroids, and no tapering attempt

Study	Reason for exclusion
Knorr 1998	Inconsistent co-treatment with inhaled corticosteroids, and no tapering attempt
Knorr 1999	Control intervention were not placebo
Korenblat 1998	No co-treatment with inhaled corticosteroids
Kuna 1997	Inconsistent co-treatment with inhaled corticosteroids, and no tapering attempt
Kylstra 1998	No co-treatment with inhaled corticosteroids
Laitinen 1997	No co-treatment with inhaled corticosteroids
Leff 1998	No co-treatment with inhaled corticosteroids Outcomes solely the result of provocation
Leigh 2002	Tested intervention administrated for less than 4 weeks
Leigh 2002 (B)	Use of other non permitted drug
Lipworth 1999	Ongoing trial No co-treatment with inhaled corticosteroids
Lipworth 2000	Planned (or ongoing) trial Control intervention is not placebo (anti-histamine)
Liu 1996	No co-treatment with inhaled corticosteroids
Lockey 1995	No co-treatment with inhaled corticosteroids
Malerba 2002	No co-treatment with inhaled corticosteroids
Malmstrom 1999	No co-treatment with inhaled corticosteroids
Margolskee 1991	No co-treatment with inhaled corticosteroids
Meltzer 2002	No co-treatment with inhaled corticosteroids
Micheletto 1997	Interim report of an included eligible trial : Laitinen LA, Zetterstrom O, Holgate ST, Binks SM, Whitney JG. Effects of Accolate (zafirlukast: 20 mg bd) in permitting reduced therapy with inhaled steroids: a multicentre trial in patients with doses of inhaled steroids optimised between 800 and 2000 mcg per day. Allergy 1995; 50 suppl 26:320 (Abs)
Minkwitz 1998	No co-treatment with inhaled corticosteroids
Miyamoto 1999	No co-treatment with inhaled corticosteroids
Nathan 1998	No co-treatment with inhaled corticosteroids
Nathan 2001	No co-treatment with inhaled corticosteroids
Nelson 2001	Control intervention were not placebo
Nishizawa 2002	Intervention was not anti-leukotrien

Study	Reason for exclusion
Noonan 1998	No co-treatment with inhaled corticosteroids
Nsouli 2001	Control group were not placebo
O'Shaughnessy 1996	Subjects were not asthmatic Outcomes were solely the result of provocation
Obase 2001	Subjects received additional non-permitted drugs (maintenance systemic steroids)
Overbeek 2002	No co-treatment with inhaled corticosteroids
Paterson 1999	Tested intervention administered for less than 4 weeks
Pearlman 1999	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes solely the result of provocation
Pearlman 2002	No co-treatment with inhaled corticosteroids
Pizzichini 1999	No co-treatment with inhaled corticosteroids
Pullerits 1999	Subjects non asthmatics (allergic rhinitis)
Pullerits 2001	Subjects were not asthmatics
Pullerits 2002	Subjects were not asthmatics
Ramsay 1997	No co-treatment with inhaled corticosteroids
Ramsay 1998	No co-treatment with inhaled corticosteroids
Reiss 1996	Inconsistent co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Reiss 1997a	Inconsistent co-treatment with inhaled corticosteroids, and no tapering attempt
Reiss 1997b	Inconsistent co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Reiss 1998a	No co-treatment with inhaled corticosteroids
Reiss 1998b	No co-treatment with inhaled corticosteroids
Reiss 1998c	No co-treatment with inhaled corticosteroids (Phase II) Not blinded (Phase IV)
Riccioni 2002 (B)	No co-treatment with inhaled corticosteroids
Riccioni 2002 (c)	No co-treatment with inhaled corticosteroids
Ringdal 1997	No co-treatment with inhaled corticosteroids
Robinson 2001	Treatment for < 4 weeks
Rosenhall 2003	Intervention was not anti-leukotrienes

Study	Reason for exclusion
Sahn 1997	No co-treatment with inhaled corticosteroids No measure of efficacy or inflammatory markers.
Schwartz 1998	No co-treatment with inhaled corticosteroids
Sheth 2002	No co-treatment with inhaled corticosteroids
Skalky 1999	No co-treatment with inhaled corticosteroids
Smith 1993	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Smith 1998	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes solely the result of provocation
Spector 1992	No co-treatment with inhaled corticosteroids
Spector 1994	No co-treatment with inhaled corticosteroids
Spector 1995	No co-treatment with inhaled corticosteroids
Stanford 2002	No co-treatment with inhaled corticosteroids
Stelmach 2002	No co-treatment with inhaled corticosteroids
Stelmach 2002 (b)	No co-treatment with inhaled corticosteroids
Storms 2001	Duplicate reference
Suissa 1997	No co-treatment with inhaled corticosteroids
Svensson 1994	No co-treatment with inhaled corticosteroids
Tashkin 1998	No co-treatment with inhaled corticosteroids
Terzano 2001	Intervention was not anti-leukotrien
Townley 1995	No co-treatment with inhaled corticosteroids
Tukiainen 2002	Intervention was not anti-leukotrien
Verhoeven 2001	Subjects non-asthmatics
Vethanayagam 2002	Tested intervention administrated for less than 4 weeks
Vidal 2001	No consistent co-treatment with inhaled corticosteroids Intervention administered for < 4 weeks
Volovitz 1999	Subjects not all treated with inhaled corticosteroids
Von Berg 2002	Intervention was not anti-leukotrien
Wahedna 1991	Intervention was administered for less than a four-week period Outcomes solely the result of provocation challenge

Study	Reason for exclusion
Weinberg 1998	No co-treatment with inhaled corticosteroids
Welch 1994	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period
Wenzel 1994	No co-treatment with inhaled corticosteroids
Wenzel 1995	Control subjects were not asthmatic Intervention was administered for less than a four-week period
Wenzel 1997	No co-treatment with inhaled corticosteroids
Westbroek 1998	No co-treatment with inhaled corticosteroids
Westbroek 2000	Intervention administered for < 4 weeks Subjects not all treated with inhaled corticosteroids
Williams 2000	3 studies: Study A :No co-treatment with inhaled corticosteroids Study B: No consistent co-treatment with inhaled corticosteroids Study C: No consistent co-treatment with inhaled corticosteroids
Wilson 1999	Ongoing trial Subjects not asthmatics (allergic rhinitis)
Wilson 1999 (b)	Control intervention were not placebo
Wilson 2001	Outcome measures did not reflect asthma control
Wilson 2001 (c)	Subjects were not asthmatics
Wilson 2001a	No co-treatment with inhaled corticosteroids control intervention is not placebo treatment < 4 weeks
Wilson 2001b	Control intervention is not placebo (it's a long-acting beta2-agonist)
Xiang 2001	Use of other non permitted drug
Yamamoto 1994	No co-treatment with inhaled corticosteroids Intervention was administered for less than a four-week period Outcomes solely the result of provocation
Yamauchi 2001	No co-treatment with inhaled corticosteroids
Yoo 2001	Inconsistent co-treatment with inhaled corticosteroids
Yoshida 2000	Tested intervention asministrated for less than 4 weeks
Yoshida 2002	Tested intervention asministrated for less than 4 weeks
Zhang 1999	No co-treatment with inhaled corticosteroids
Zorc 2003	Intervention was not anti-leukotrienes

DATA AND ANALYSES

Comparison 1. Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with exacerbations requiring systemic steroids with higher than licensed AL doses at 4 to 16 weeks	2	451	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.13, 0.88]
1.1 Pranlukast 450 mg bid	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.77]
1.2 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 1.01]
2 Patients with exacerbations requiring systemic steroids with licensed AL doses at 4 to 16 weeks	4	988	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.07]
2.1 Montelukast 5 mg die	1	541	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.34, 1.91]
2.2 Montelukast 10 mg die	2	423	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.28, 1.06]
2.3 Zafirlukast 20 mg bid	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.21]
3 Patients with exacerbations requiring hospital admission using licensed AL doses	2	934	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.43]
3.1 Montelukast 5 mg die	1	541	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Montelukast 10 mg die	1	393	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.43]
4 Change from baseline FEV1 (L) using higher than licensed LTRA doses at 6 weeks	2	343	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.01, 0.20]
4.1 Pranlukast 450 mg bid	1	79	Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.65, 1.47]
4.2 Zafirlukast 80 mg bid	1	264	Mean Difference (IV, Fixed, 95% CI)	0.1 [0.01, 0.19]
5 Change from baseline FEV1 using licensed doses of LTRA (at 4 to 16 weeks)	3	1123	Mean Difference (IV, Random, 95% CI)	0.06 [-0.01, 0.14]
5.1 Montelukast 5 mg die	1	502	Mean Difference (IV, Random, 95% CI)	0.03 [-0.01, 0.07]
5.2 Montelukast 10 mg die	1	389	Mean Difference (IV, Random, 95% CI)	0.12 [0.07, 0.17]

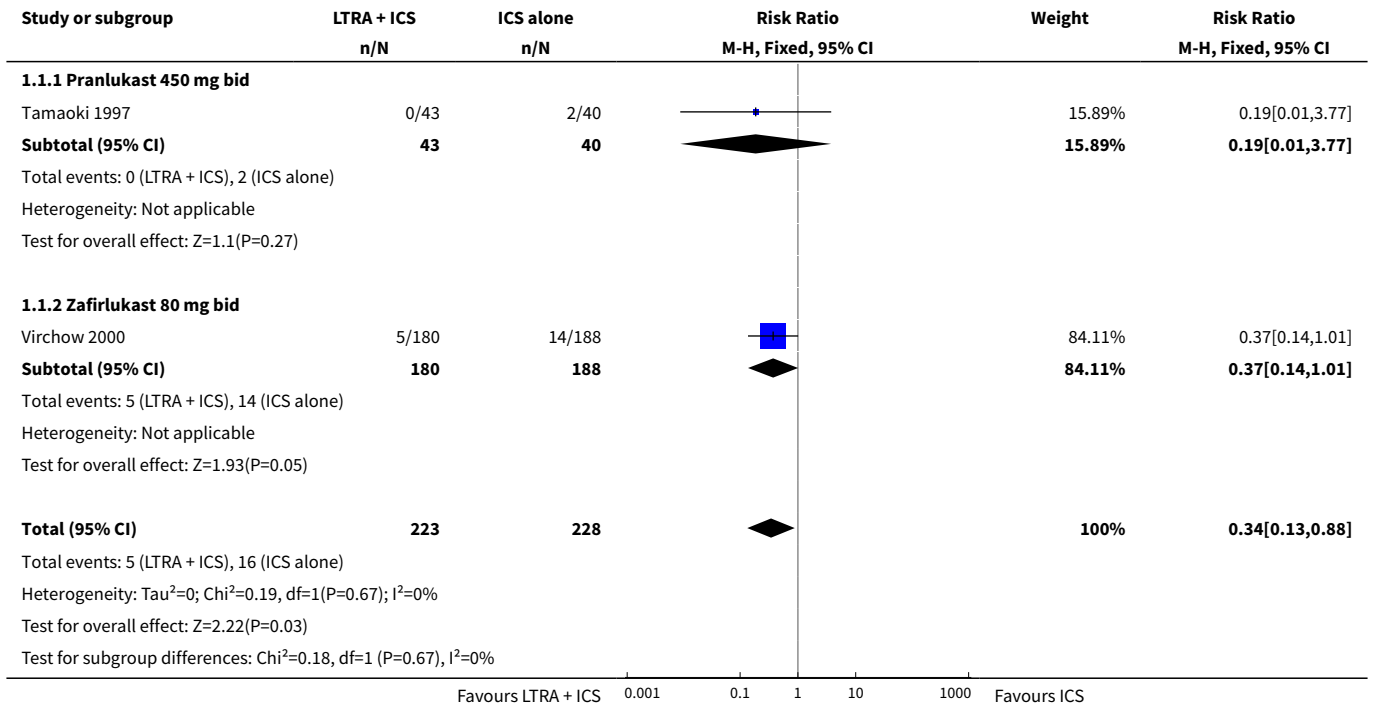
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Zafirlukast 20 mg bid	1	232	Mean Difference (IV, Random, 95% CI)	0.01 [-0.13, 0.15]
6 Change from baseline Am PEFR (L/min) using higher than licensed AL doses at 6 weeks	2	382	Mean Difference (IV, Fixed, 95% CI)	27.19 [18.60, 35.78]
6.1 Pranlukast 450 mg bid	1	79	Mean Difference (IV, Fixed, 95% CI)	51.0 [35.20, 66.80]
6.2 Zafirlukast 80 mg bid	1	303	Mean Difference (IV, Fixed, 95% CI)	17.2 [6.96, 27.44]
7 Change from baseline AM PEFR using licensed doses of LTRA at 4-16 weeks	4	1681	Mean Difference (IV, Fixed, 95% CI)	7.65 [3.55, 11.75]
7.1 Montelukast 5 mg die	1	436	Mean Difference (IV, Fixed, 95% CI)	9.40 [-4.61, 23.41]
7.2 Montelukast 10 mg die	2	1013	Mean Difference (IV, Fixed, 95% CI)	7.07 [2.63, 11.51]
7.3 Zafirlukast 20 mg bid	1	232	Mean Difference (IV, Fixed, 95% CI)	13.14 [-3.22, 29.50]
8 Change from baseline in mean asthma symptom using higher than licensed AL doses at 6 weeks	2	381	Std. Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.66, -0.25]
8.1 Pranlukast 450 mg bid	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.93, -0.03]
8.2 Zafirlukast 80 mg bid	1	302	Std. Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.68, -0.22]
9 Change from baseline mean asthma symptom score using licensed doses using licensed doses of AL at 4 - 16 wks	2	1018	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.24, 0.03]
9.1 Montelukast 5 mg die	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Montelukast 10 mg die	2	1018	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.24, 0.03]
10 Change from baseline mean daily use of B2-agonists (puffs) using higher than licensed AL doses at 6 weeks	2	382	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.63, -0.22]
10.1 Pranlukast 450 mg bid	1	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.19, -0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Zafirlukast 80 mg bid	1	303	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.58, -0.12]
11 Change from baseline mean daily use of B2-agonists (puffs/day or %) using licensed doses of AL at 4 to 16 wee	4	1699	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.24, -0.05]
11.1 Montelukast 5 mg die	1	450	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.33, 0.04]
11.2 Montelukast 10 mg die	2	1018	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.26, -0.01]
11.3 Zafirlukast 20 mg bid	1	231	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.47, 0.05]
12 Change in night-time awakenings(episodes/week) using higher than licensed AL doses at 6 weeks	2	382	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.35, 0.32]
12.1 Pranlukast 450 mg bid	1	79	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-4.94, 3.14]
12.2 Zafirlukast 80 mg bid	1	303	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.35, 0.35]
13 Change from baseline in night-time awakenings(episodes/week) using licensed doses of LTRA	1	393	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.68, 0.50]
13.1 Montelukast 5 mg die	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Montelukast 10 mg die	1	393	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.68, 0.50]
14 Change in quality of life using licensed doses of AL	2	921	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.03, 0.20]
14.1 Montelukast 5 mg die	1	296	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.13, 0.31]
14.2 Montelukast 10 mg die	1	625	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.06, 0.22]
15 Change in mean serum ECP concentration (ug/L) using higher than licensed AL doses at 6 +/- 4 weeks	1	79	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Pranlukast 450 mg bid	1	79	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

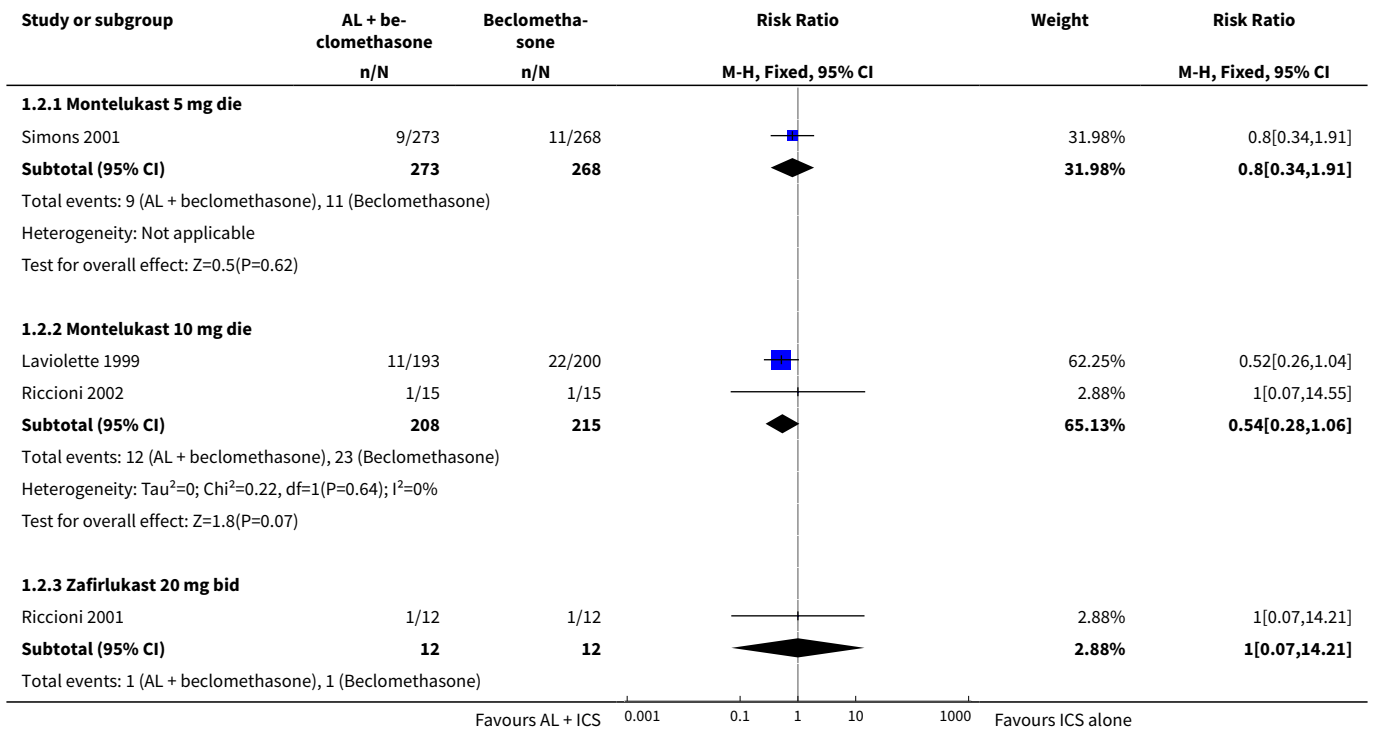
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Change from baseline NO concentration (ppb) using higher than licensed AL doses at 6 +/- 4 weeks	1	79	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 Pranlukast 450 mg bid	1	79	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Change from baseline eosinophil counts using licensed AL doses at 4 to 16 weeks	2	849	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.14, -0.00]
17.1 Montelukast 5 mg die	1	464	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.17, -0.05]
17.2 Montelukast 10 mg die	1	385	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.06, -0.02]
18 Withdrawals due to poor asthma control/exacerbations	5	1975	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.29, 1.39]
18.1 Montelukast 5 mg die	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Montelukast 10 mg die	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.16, 1.31]
18.3 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.27, 4.11]
18.4 Zafirlukast 20 mg bid	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
19 Overall withdrawals	7	2082	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.24]
19.1 Montelukast 5 mg die	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.53, 4.08]
19.2 Montelukast 10 mg die	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.32]
19.3 Pranlukast 450 mg bid	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.03, 2.86]
19.4 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.42, 1.58]
19.5 Zafirlukast 20 mg bid	2	54	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.24]
20 Withdrawals due to adverse effects	6	2030	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.37, 1.22]
20.1 Montelukast 5 mg die	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.38]
20.2 Montelukast 10 mg die	3	1034	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.28, 1.48]
20.3 Pranlukast 450 mg bid	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.28, 1.88]
21 Headache	4	1933	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.92, 1.50]
21.1 Montelukast 5 mg die	1	547	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.58, 1.78]

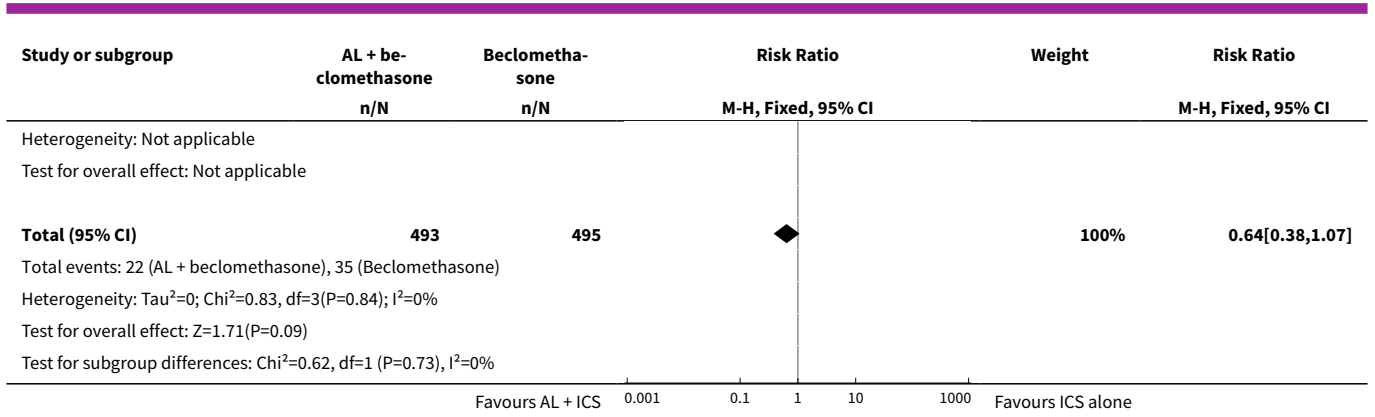
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 Montelukast 10 mg die	2	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.90, 1.59]
21.3 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.59, 3.49]
22 Overall adverse effects	4	1623	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.13]
22.1 Montelukast 5 mg die	1	547	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.12]
22.2 Montelukast 10 mg die	1	625	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.31]
22.3 Pranlukast 450 mg bid	1	83	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.12, 66.70]
22.4 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
23 Elevated liver enzymes	3	1301	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.50, 3.35]
23.1 Montelukast 5 mg die	1	547	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 21.37]
23.2 Montelukast 10 mg die	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.27, 2.77]
23.3 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	5.22 [0.25, 108.01]
24 Nausea	4	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.32]
24.1 Montelukast 5 mg die	1	547	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.99]
24.2 Montelukast 10 mg die	1	393	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.17, 1.33]
24.3 Pranlukast 450 bid	1	83	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.12, 66.70]
24.4 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.36, 4.78]
25 Death	3	1308	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
25.1 Montelukast 5 mg die	1	547	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Montelukast 10 mg die	1	393	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Zafirlukast 80 mg bid	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.49]
26 % nocturnal awakenings	2	856	Mean Difference (IV, Fixed, 95% CI)	-6.25 [-12.72, 0.23]
26.1 Montelukast 10 mg die	1	625	Mean Difference (IV, Fixed, 95% CI)	-6.60 [-15.51, 2.31]
26.2 Zafirlukast 20 mg bid	1	231	Mean Difference (IV, Fixed, 95% CI)	-5.85 [-15.26, 3.56]

Analysis 1.1. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 1 Patients with exacerbations requiring systemic steroids with higher than licensed AL doses at 4 to 16 weeks.

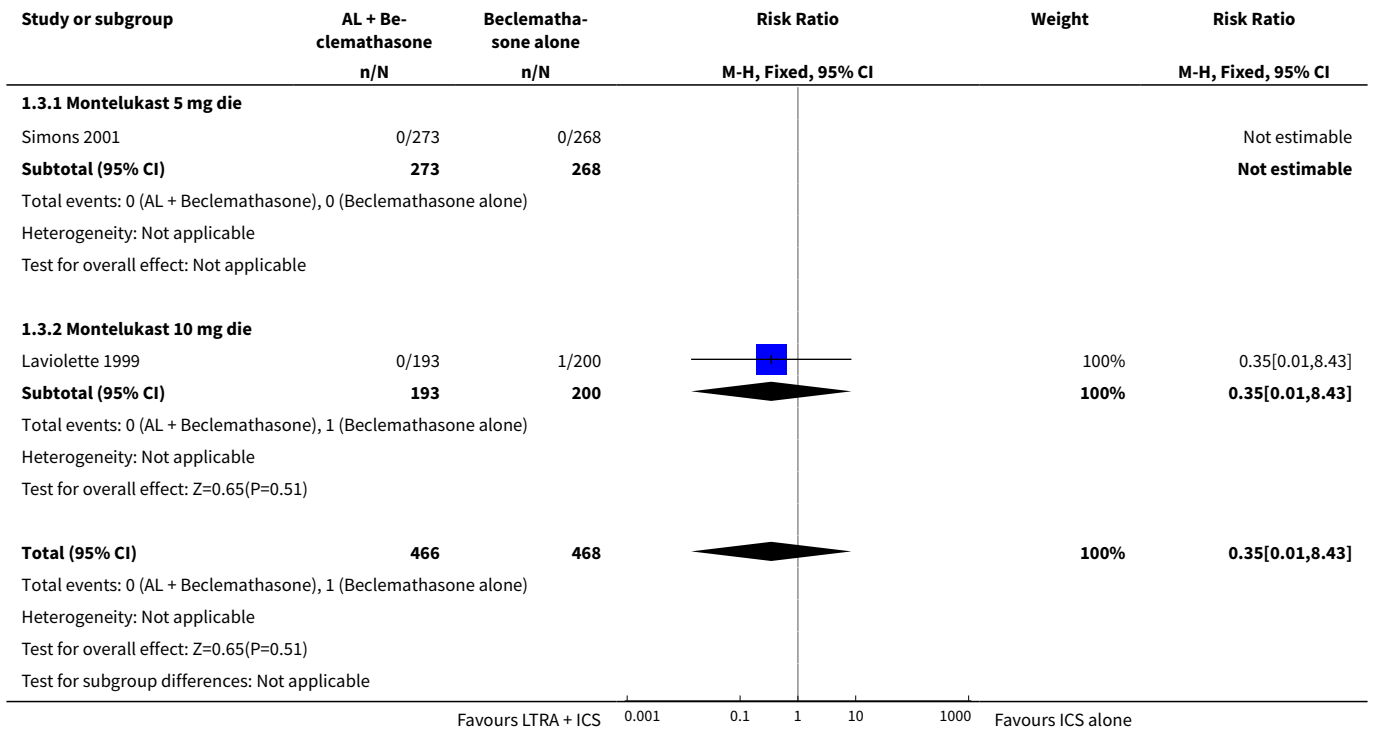


Analysis 1.2. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 2 Patients with exacerbations requiring systemic steroids with licensed AL doses at 4 to 16 weeks.

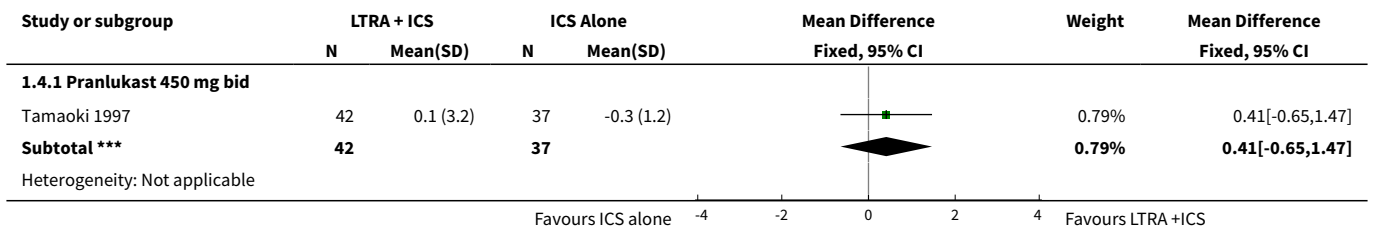


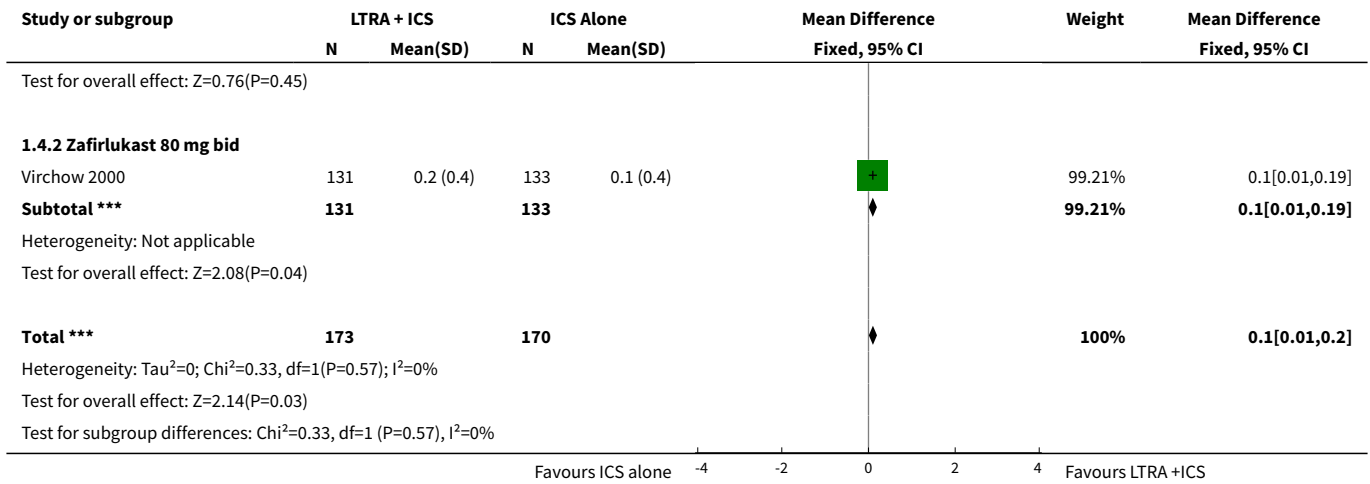


Analysis 1.3. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 3 Patients with exacerbations requiring hospital admission using licensed AL doses.

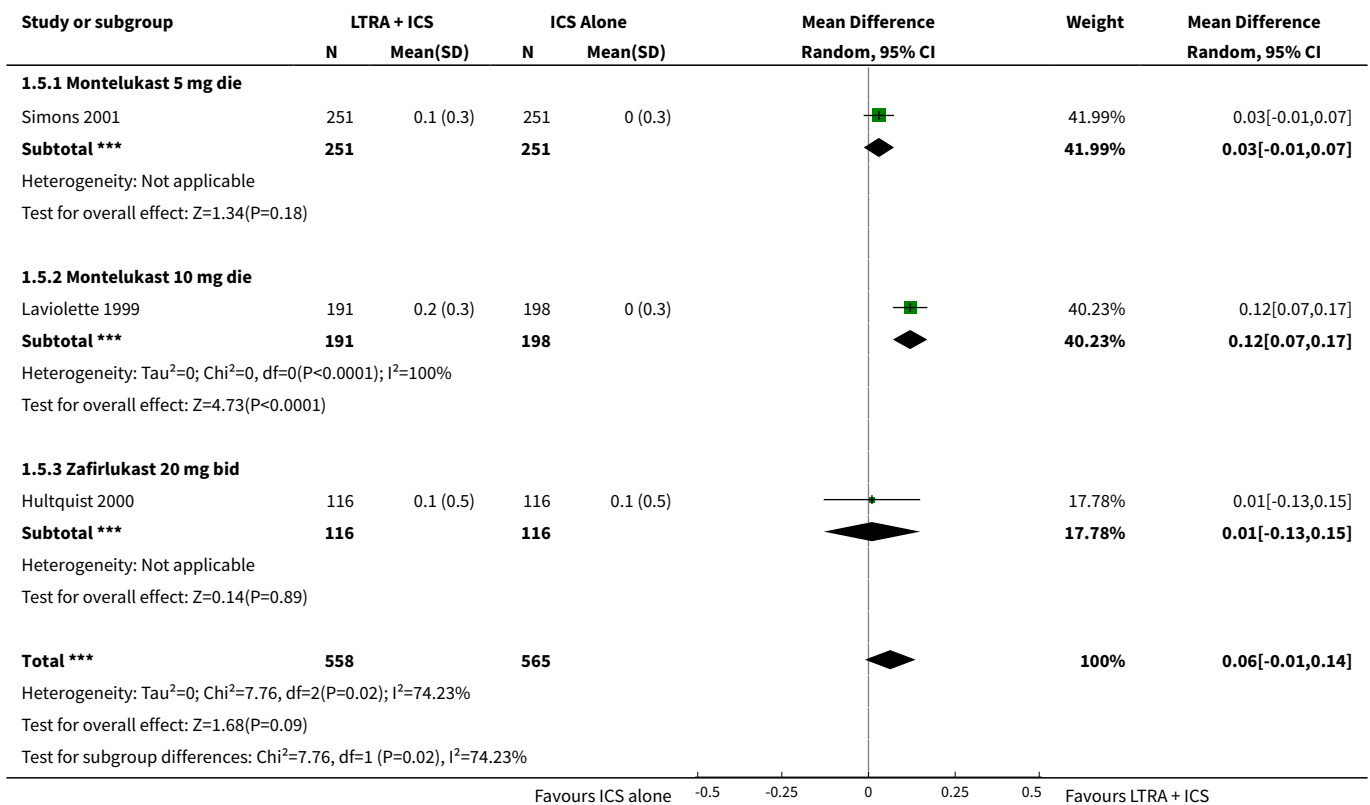


Analysis 1.4. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 4 Change from baseline FEV1 (L) using higher than licensed LTRA doses at 6 weeks.

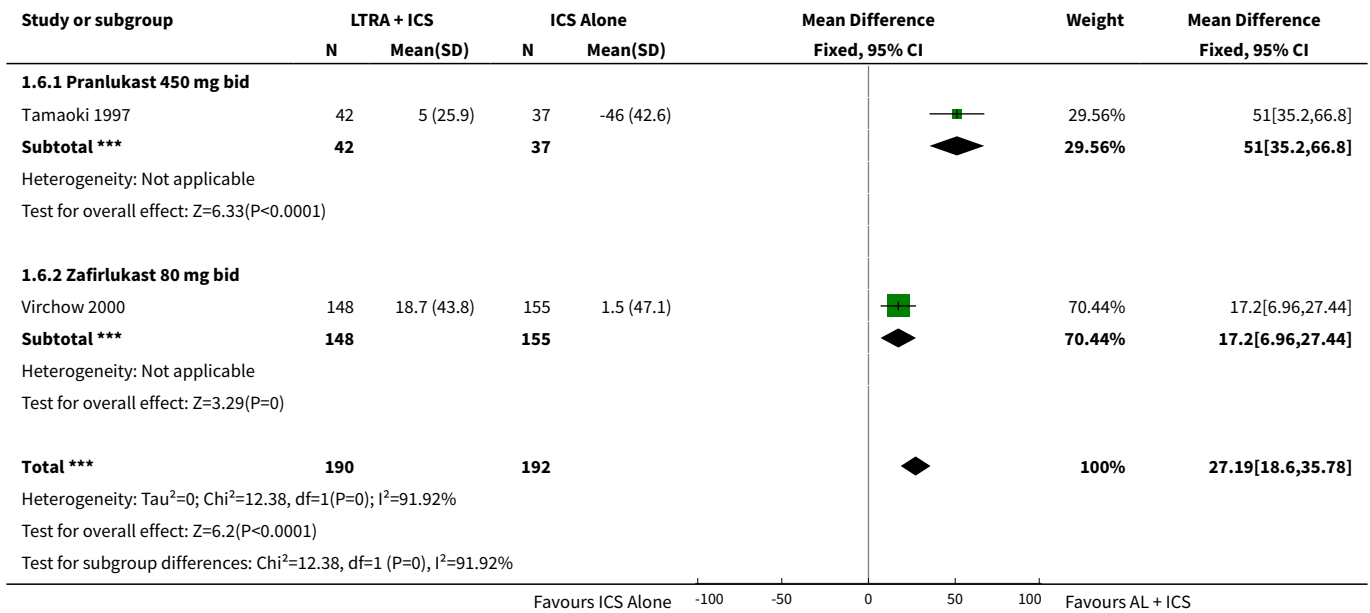




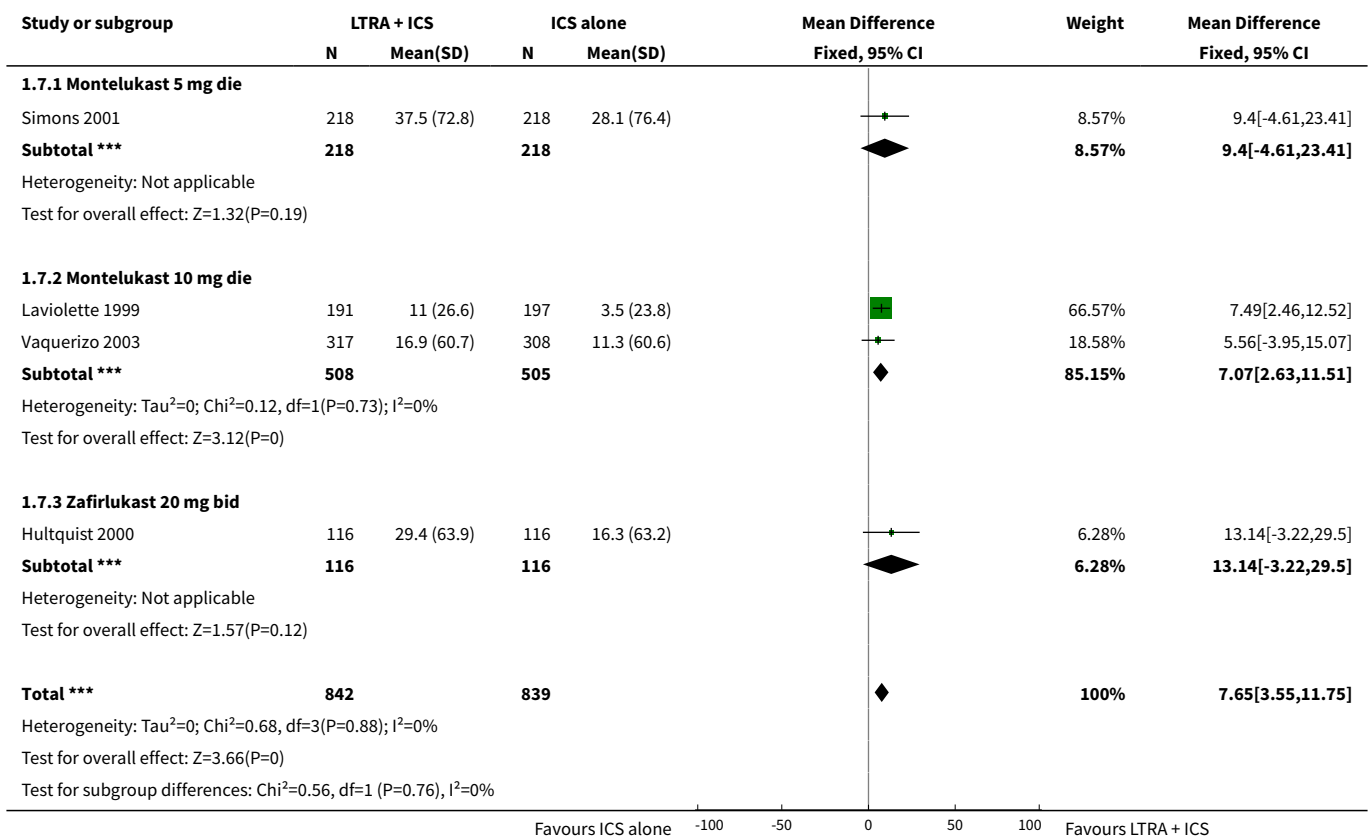
Analysis 1.5. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 5 Change from baseline FEV1 using licensed doses of LTRA (at 4 to 16 weeks).



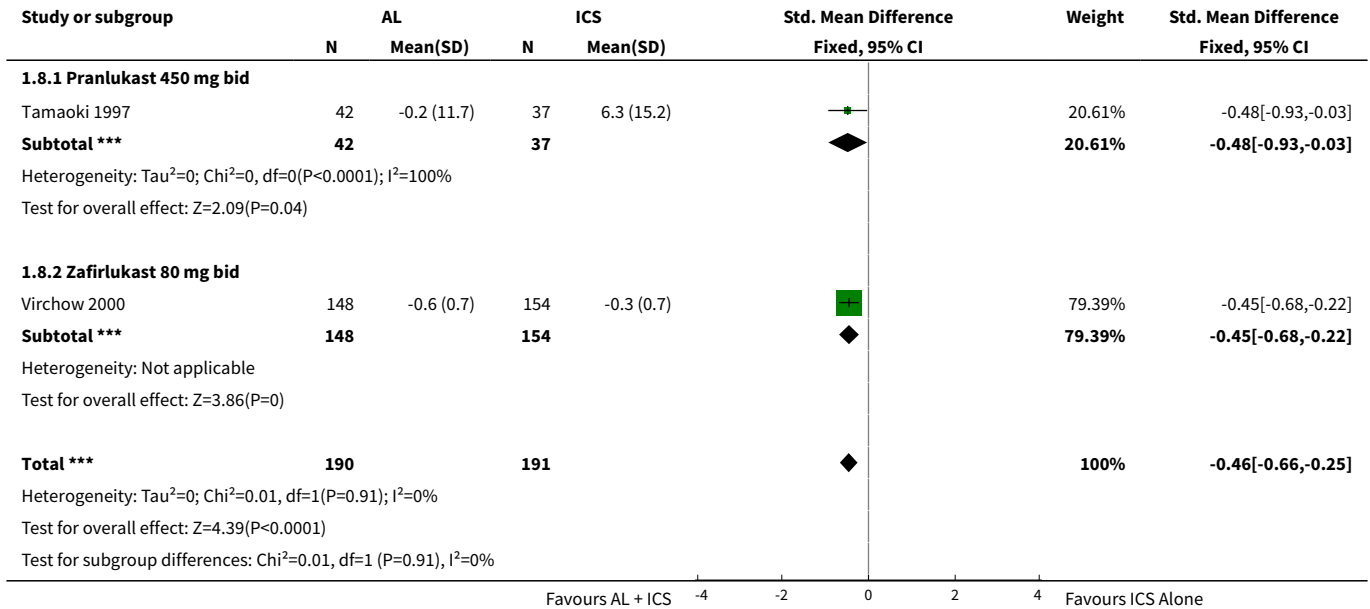
Analysis 1.6. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 6 Change from baseline Am PEFR (L/min) using higher than licensed AL doses at 6 weeks.



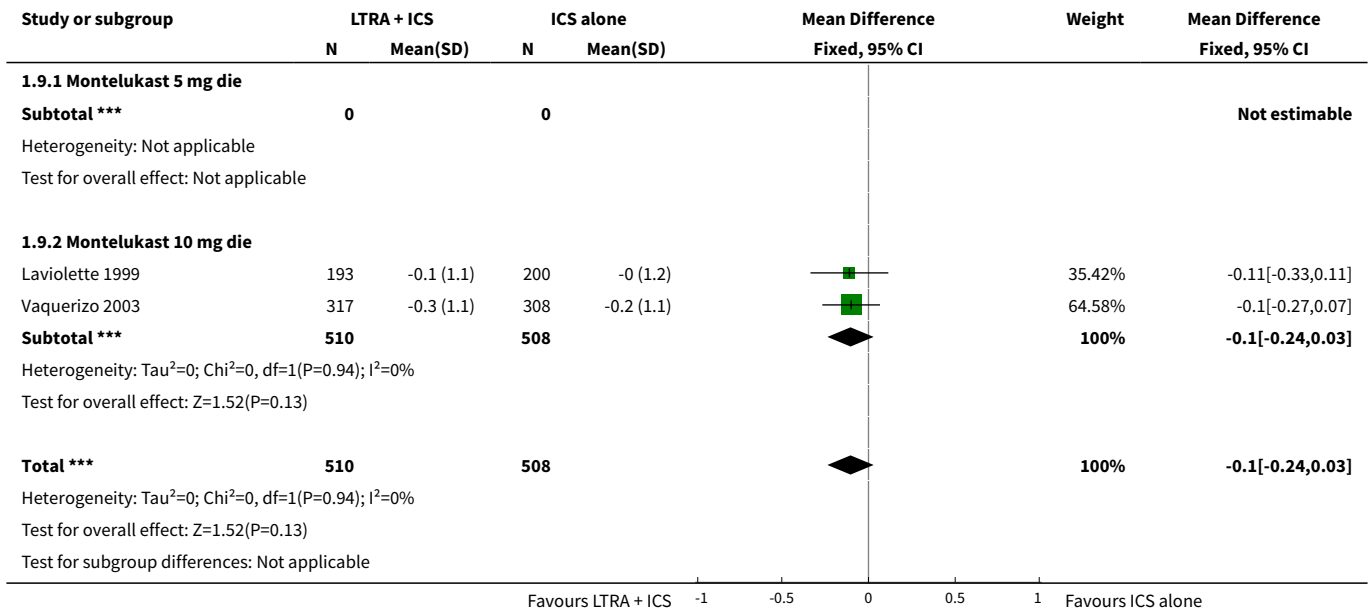
Analysis 1.7. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 7 Change from baseline AM PEFR using licensed doses of LTRA at 4-16 weeks.



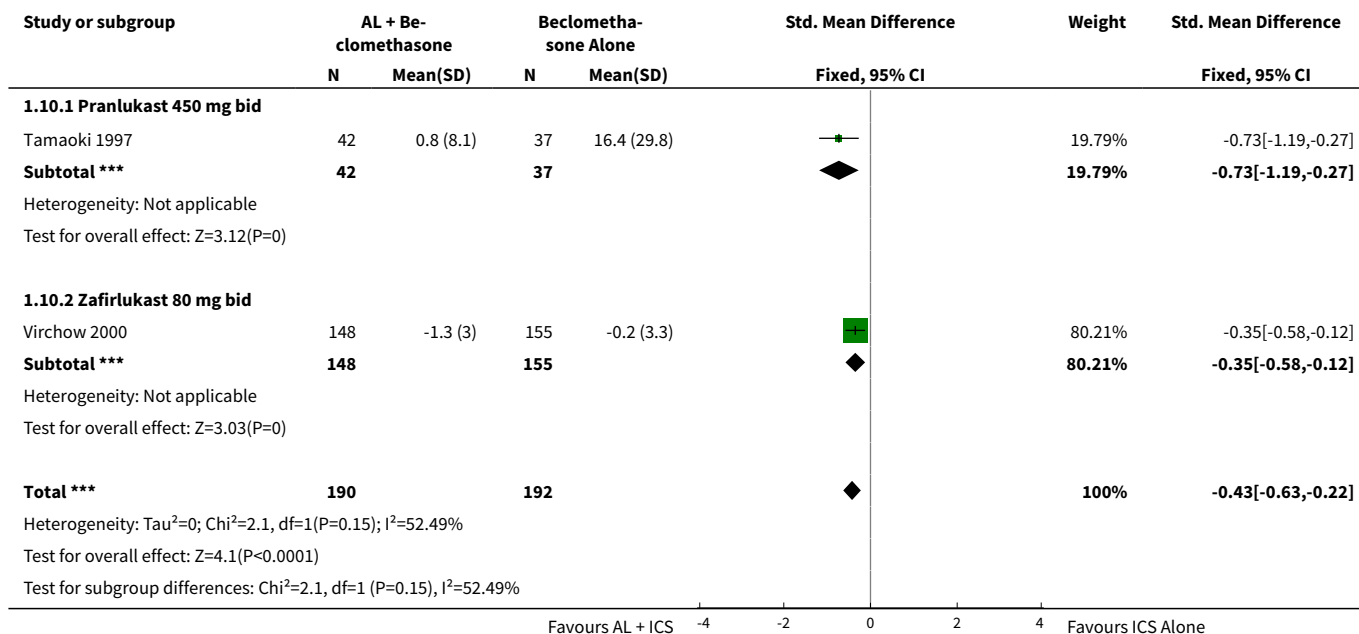
Analysis 1.8. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 8 Change from baseline in mean asthma symptom using higher than licensed AL doses at 6 weeks.



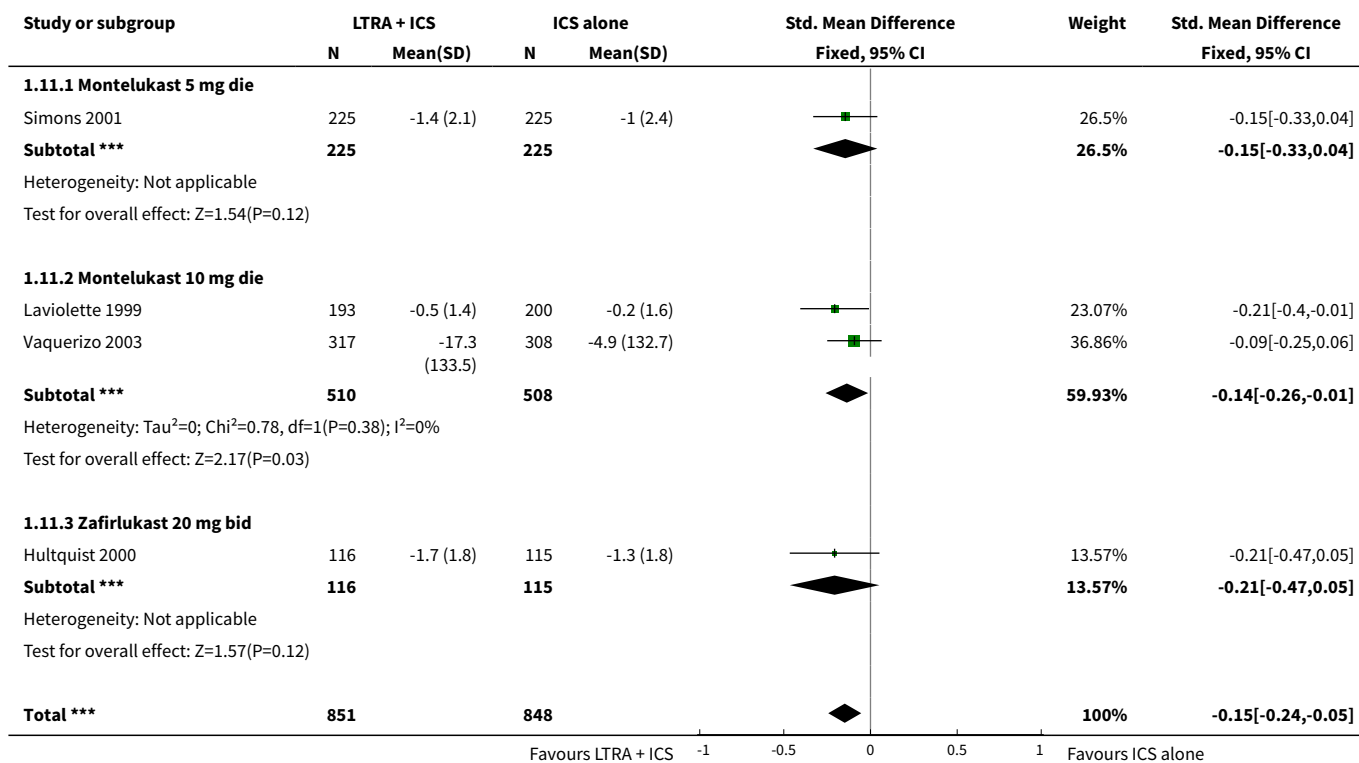
Analysis 1.9. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 9 Change from baseline mean asthma symptom score using licensed doses using licensed doses of AL at 4 - 16 wks.

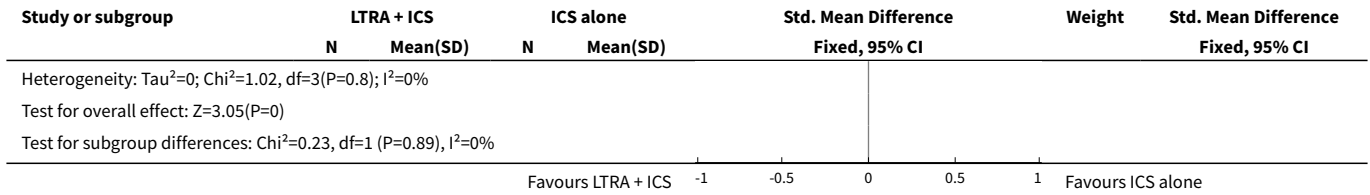


Analysis 1.10. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 10 Change from baseline mean daily use of B2-agonists (puffs) using higher than licensed AL doses at 6 weeks.

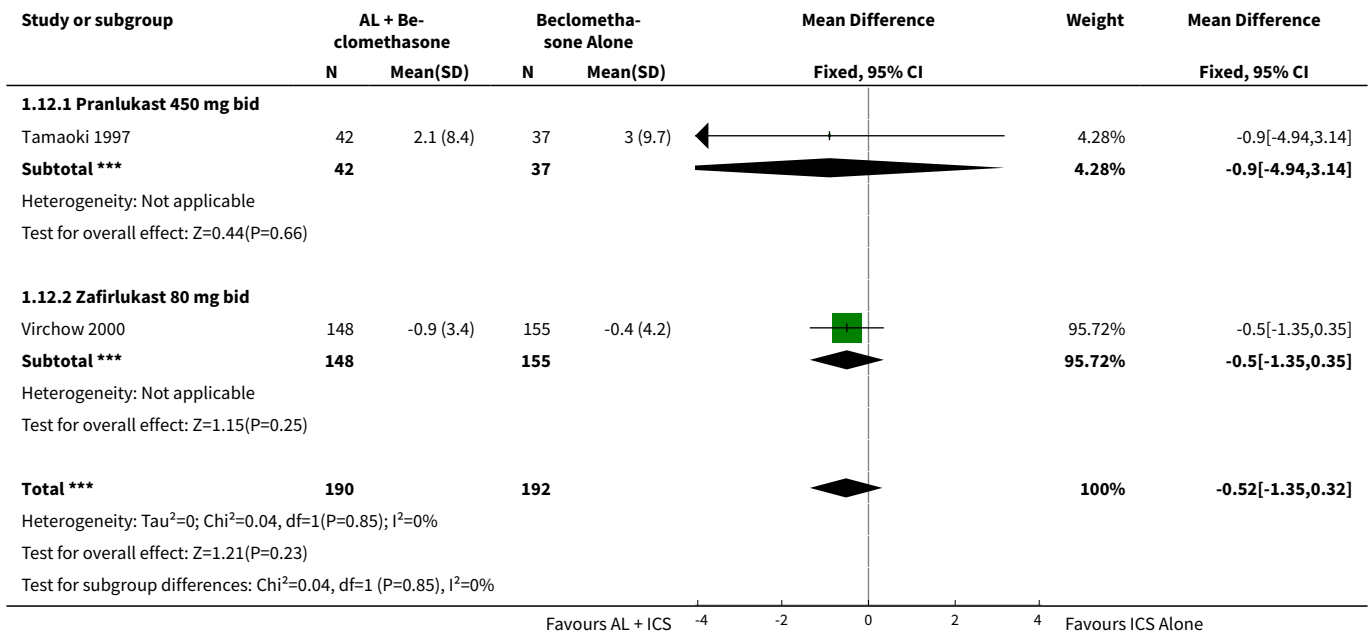


Analysis 1.11. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 11 Change from baseline mean daily use of B2-agonists (puffs/day or %) using licensed doses of AL at 4 to 16 wee.

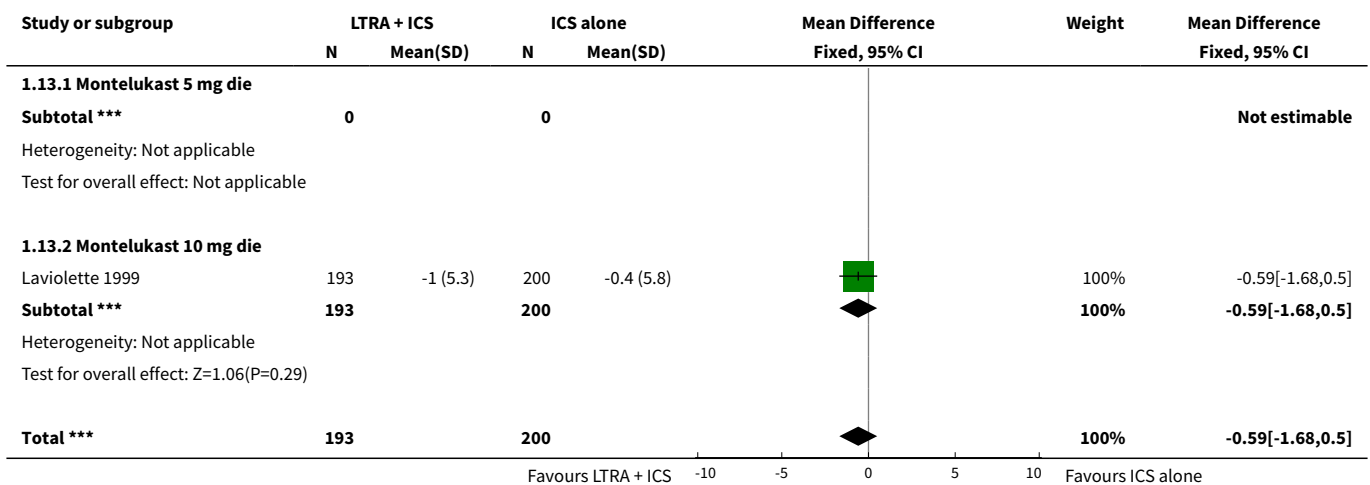




Analysis 1.12. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 12 Change in night-time awakenings(episodes/week) using higher than licensed AL doses at 6 weeks.



Analysis 1.13. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 13 Change from baseline in night-time awakenings(episodes/week) using licensed doses of LTRA.



Study or subgroup	LTRA + ICS		ICS alone		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							
Test for subgroup differences: Not applicable							
Favours LTRA + ICS -10 -5 0 5 10 Favours ICS alone							

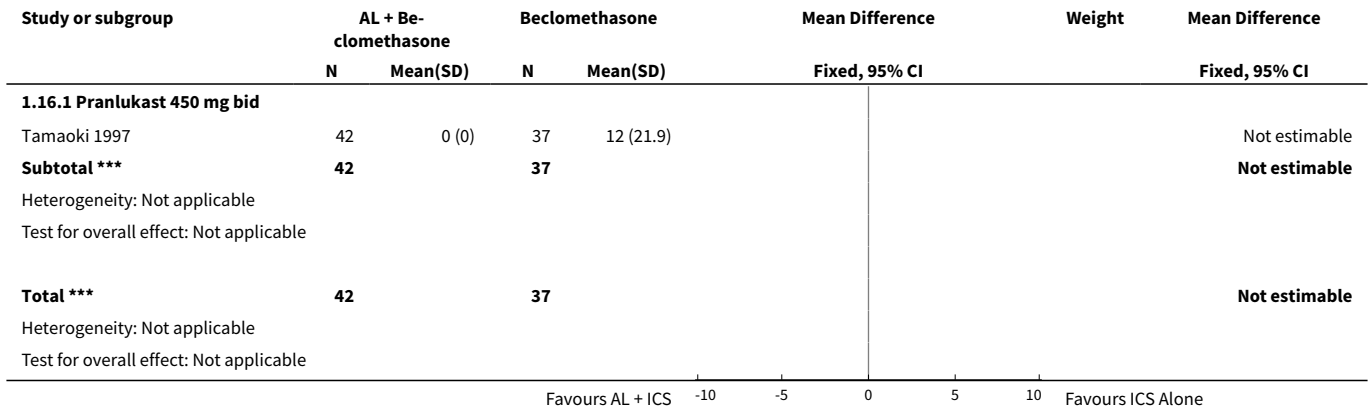
Analysis 1.14. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 14 Change in quality of life using licensed doses of AL.

Study or subgroup	LTRA + ICS		ICS alone		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.14.1 Montelukast 5 mg die							
Simons 2001	148	0.5 (1)	148	0.5 (0.9)		29.35%	0.09[-0.13,0.31]
Subtotal ***	148		148			29.35%	0.09[-0.13,0.31]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.82(P=0.41)							
1.14.2 Montelukast 10 mg die							
Vaquerizo 2003	317	0.6 (0.9)	308	0.5 (0.9)		70.65%	0.08[-0.06,0.22]
Subtotal ***	317		308			70.65%	0.08[-0.06,0.22]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
Total ***	465		456			100%	0.08[-0.03,0.2]
Heterogeneity: Tau ² =0; Chi ² =0.01, df=1(P=0.94); I ² =0%							
Test for overall effect: Z=1.39(P=0.16)							
Test for subgroup differences: Chi ² =0.01, df=1 (P=0.94), I ² =0%							
Favours ICS alone -1 -0.5 0 0.5 1 Favours LTRA + ICS							

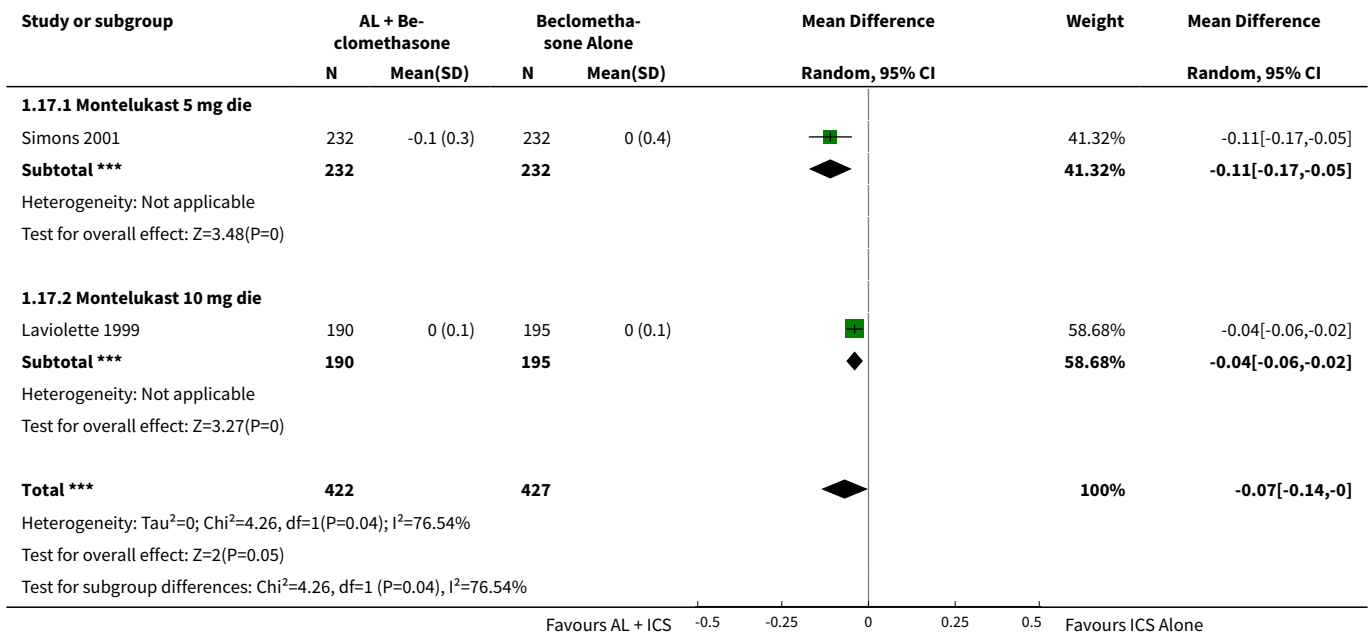
Analysis 1.15. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 15 Change in mean serum ECP concentration (ug/L) using higher than licensed AL doses at 6 +/- 4 weeks.

Study or subgroup	AL + Be-clomethasone		Beclomethasone Alone		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.15.1 Pranlukast 450 mg bid							
Tamaoki 1997	42	0 (0)	37	11.5 (32.2)			Not estimable
Subtotal ***	42		37				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	42		37				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Favours AL + ICS -10 -5 0 5 10 Favours ICS Alone							

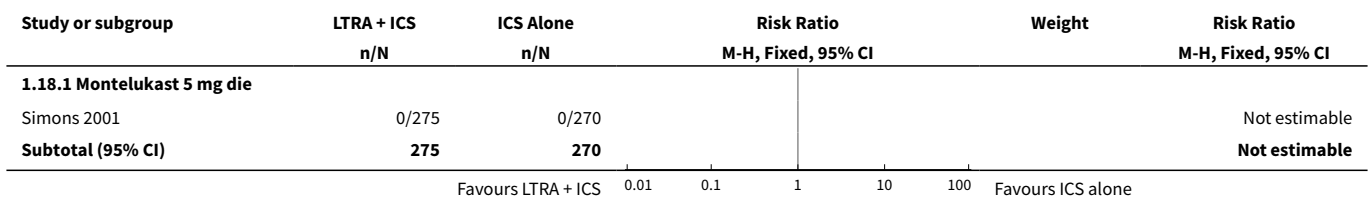
Analysis 1.16. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 16 Change from baseline NO concentration (ppb) using higher than licensed AL doses at 6 +/- 4 weeks.

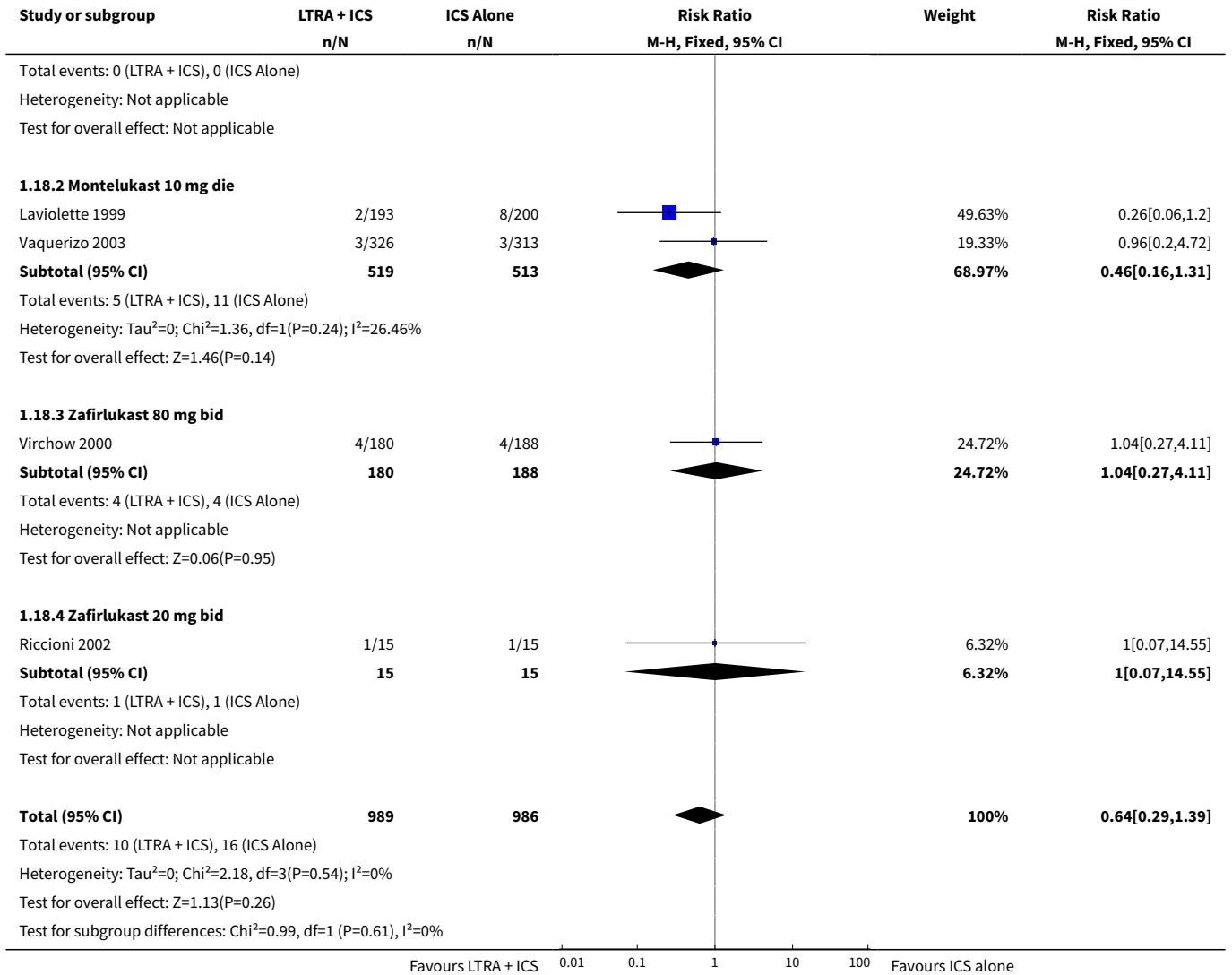


Analysis 1.17. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 17 Change from baseline eosinophil counts using licensed AL doses at 4 to 16 weeks.

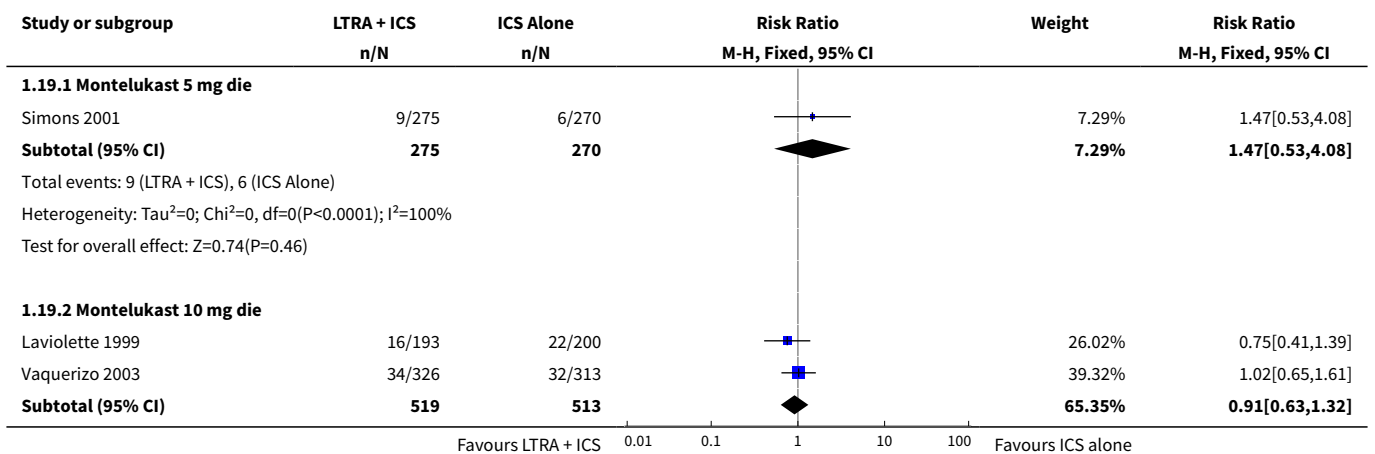


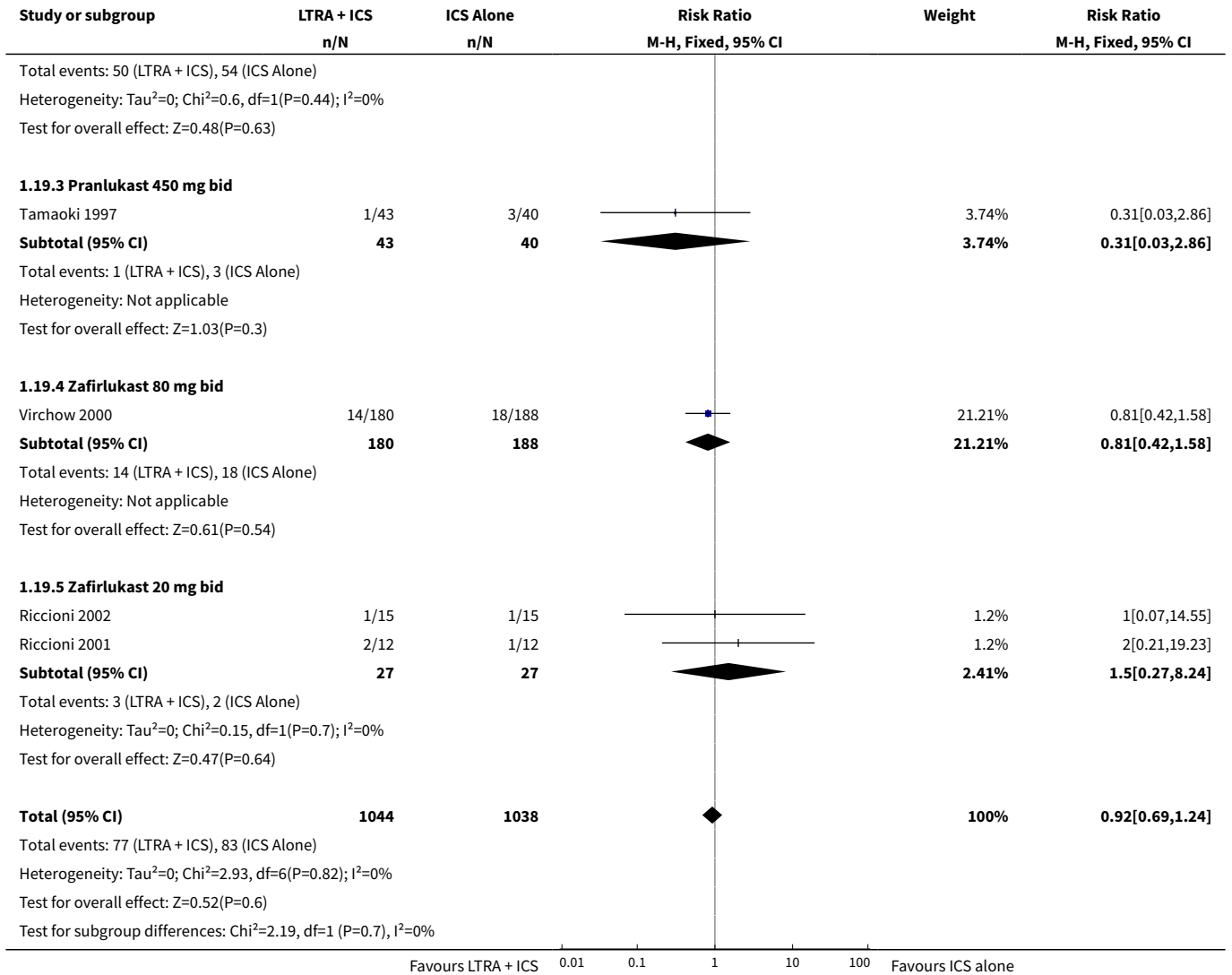
Analysis 1.18. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 18 Withdrawals due to poor asthma control/exacerbations.



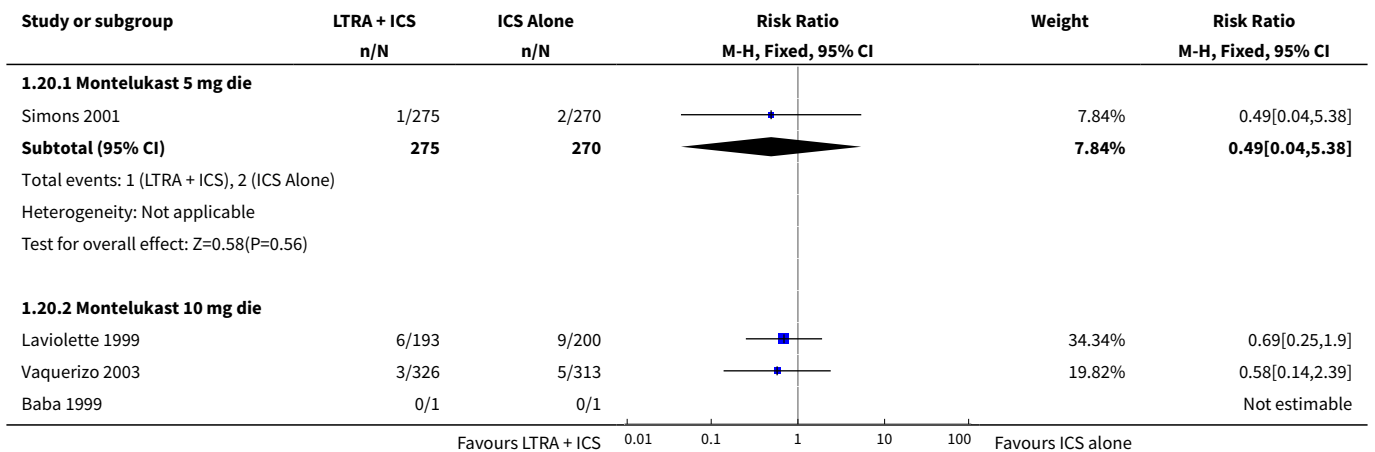


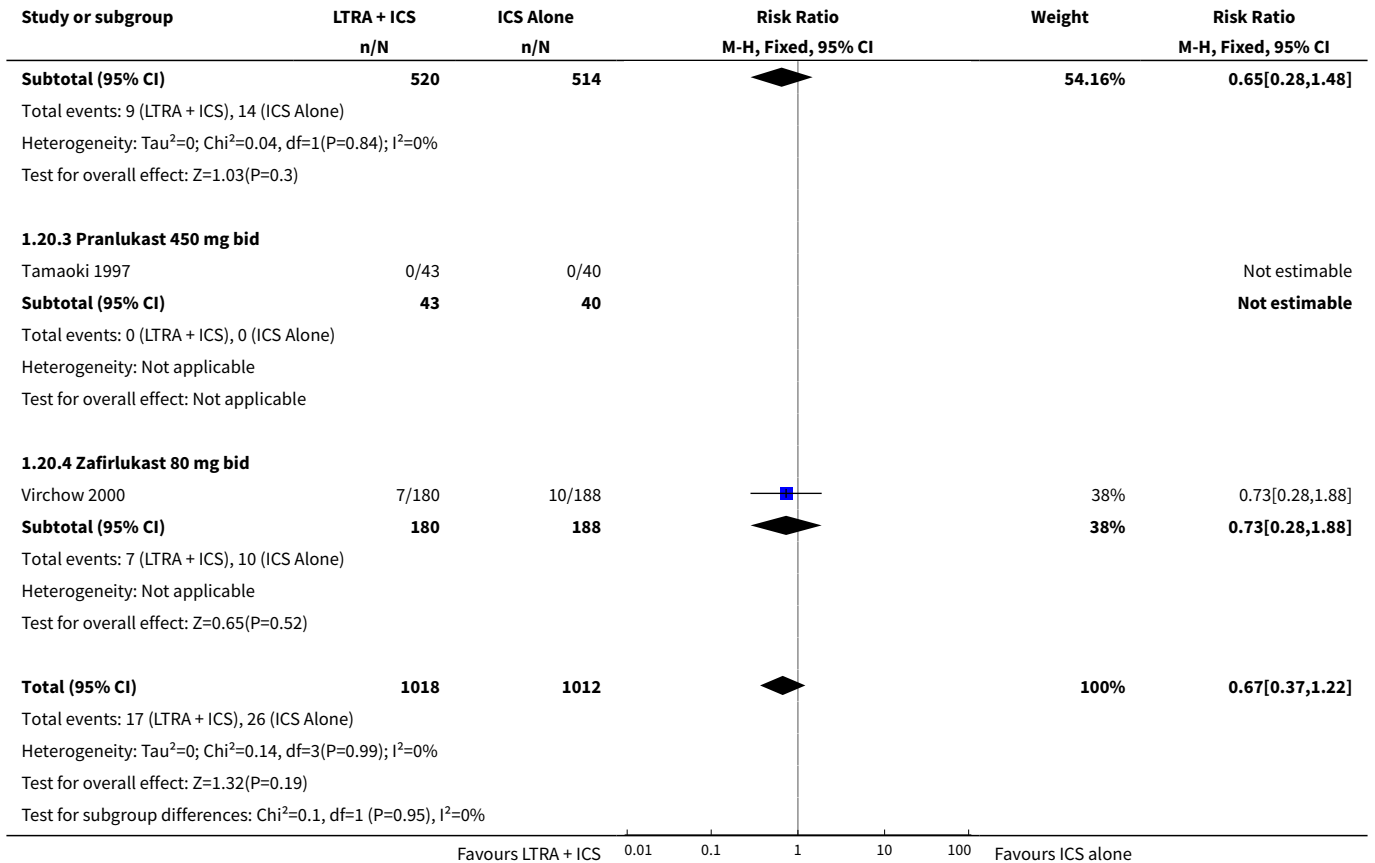
Analysis 1.19. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 19 Overall withdrawals.



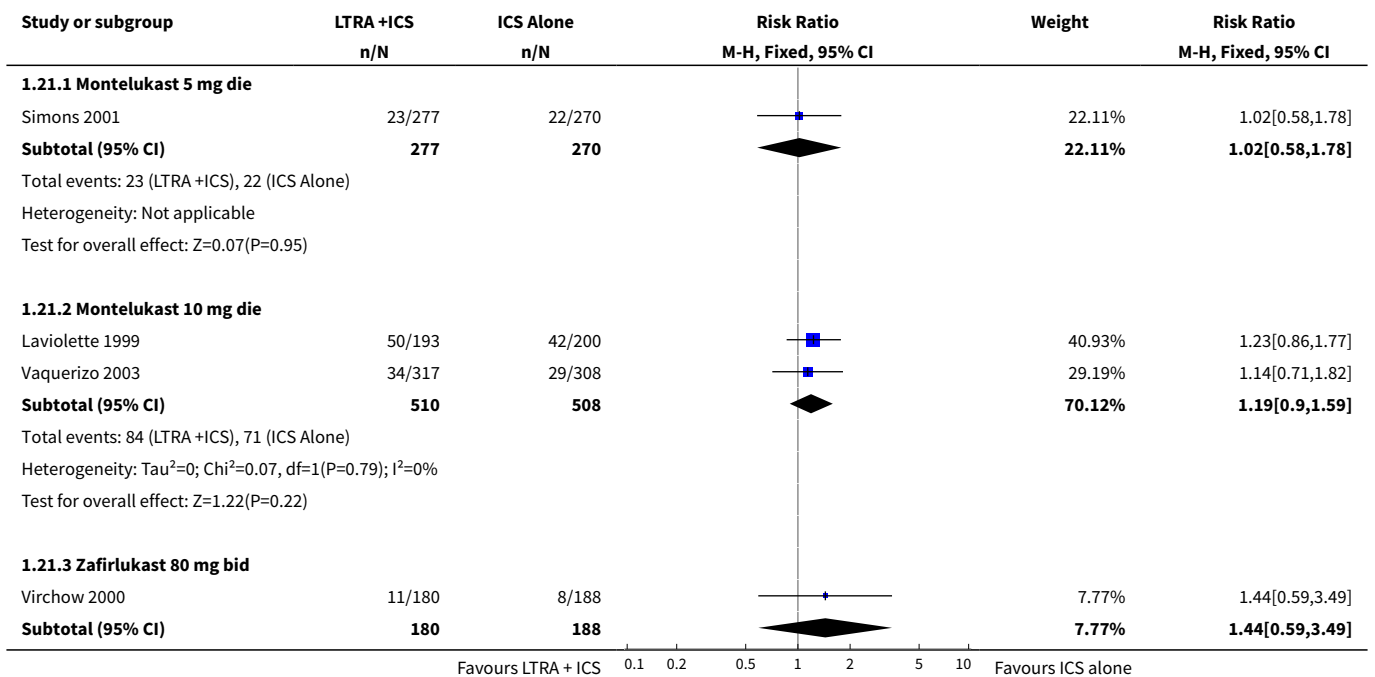


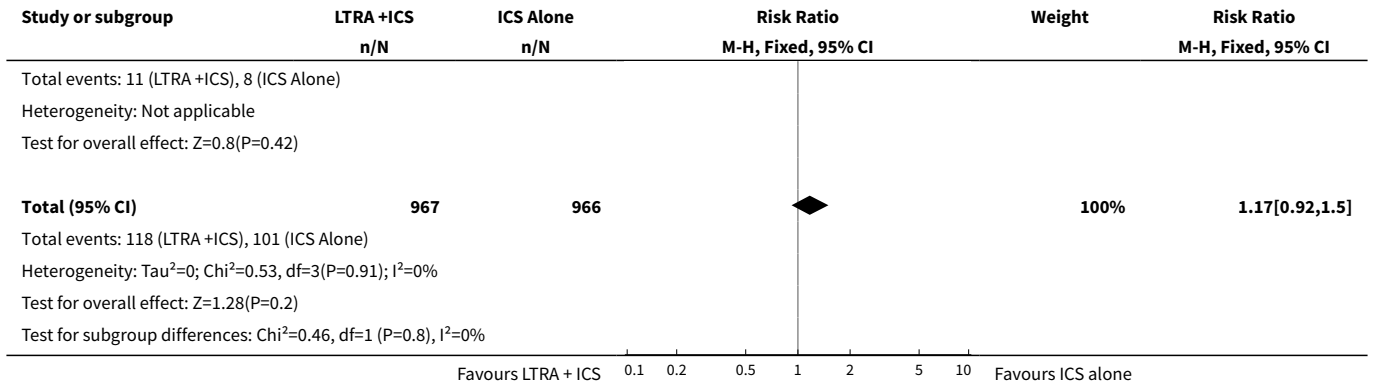
Analysis 1.20. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 20 Withdrawals due to adverse effects.



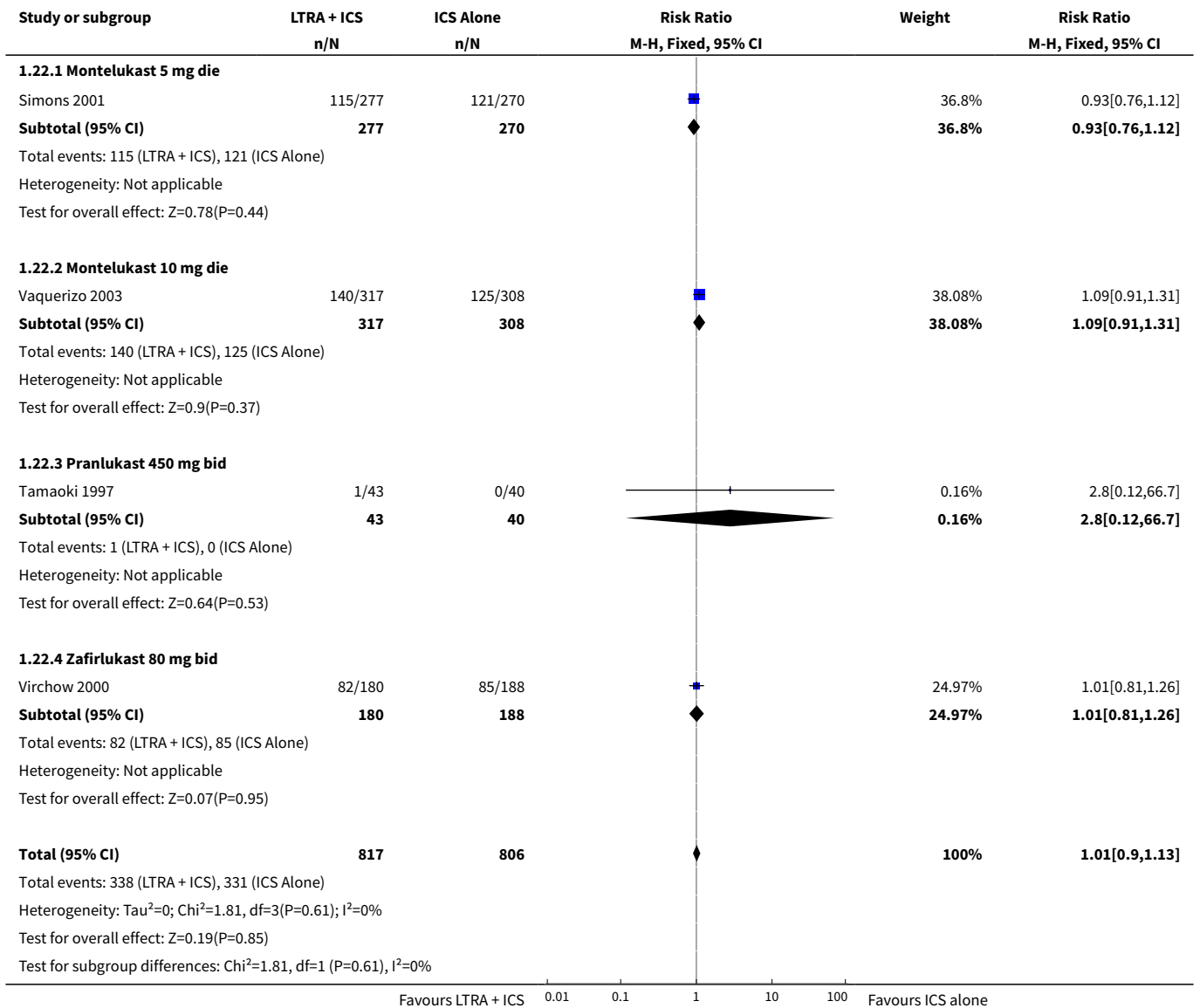


Analysis 1.21. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 21 Headache.

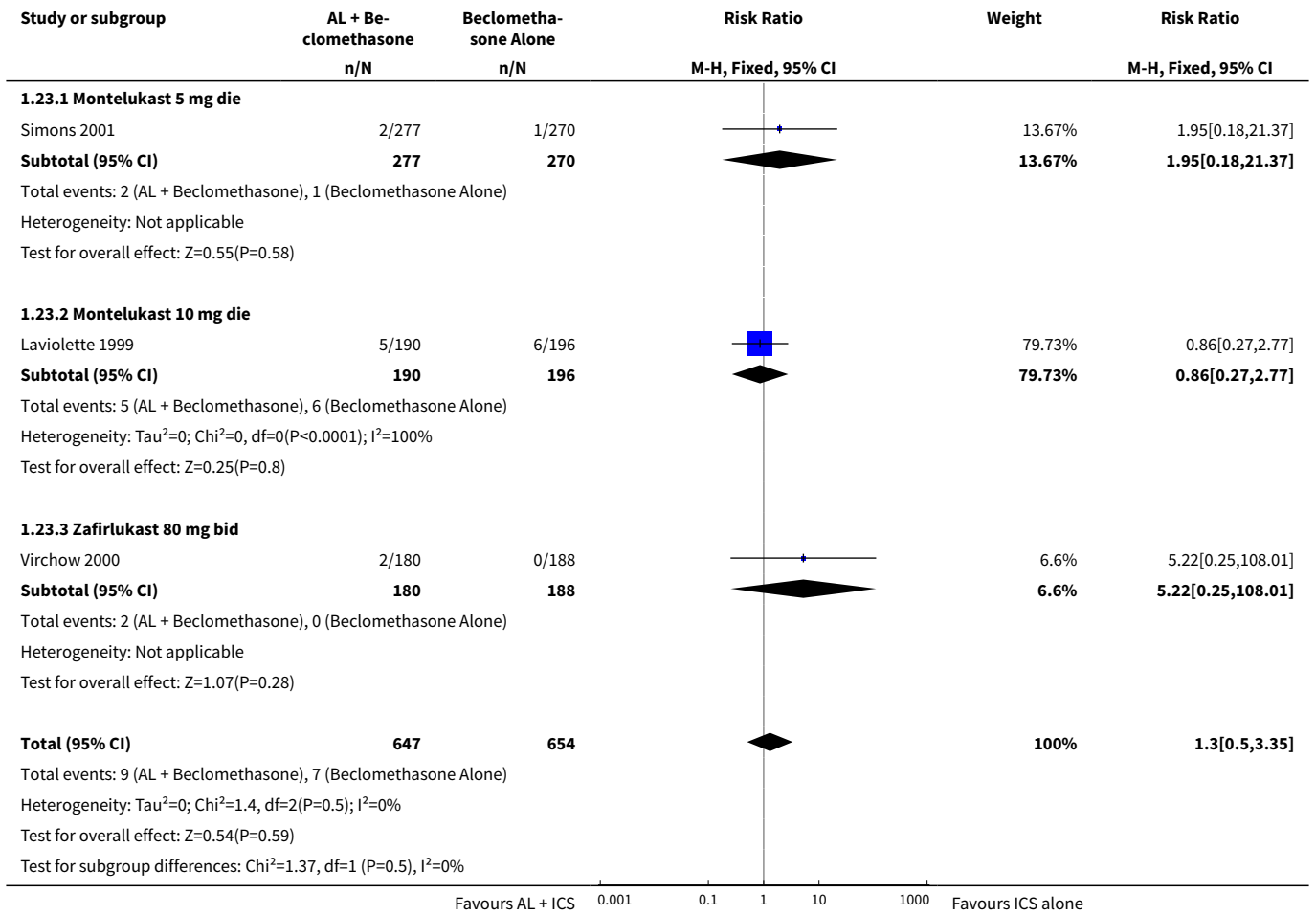




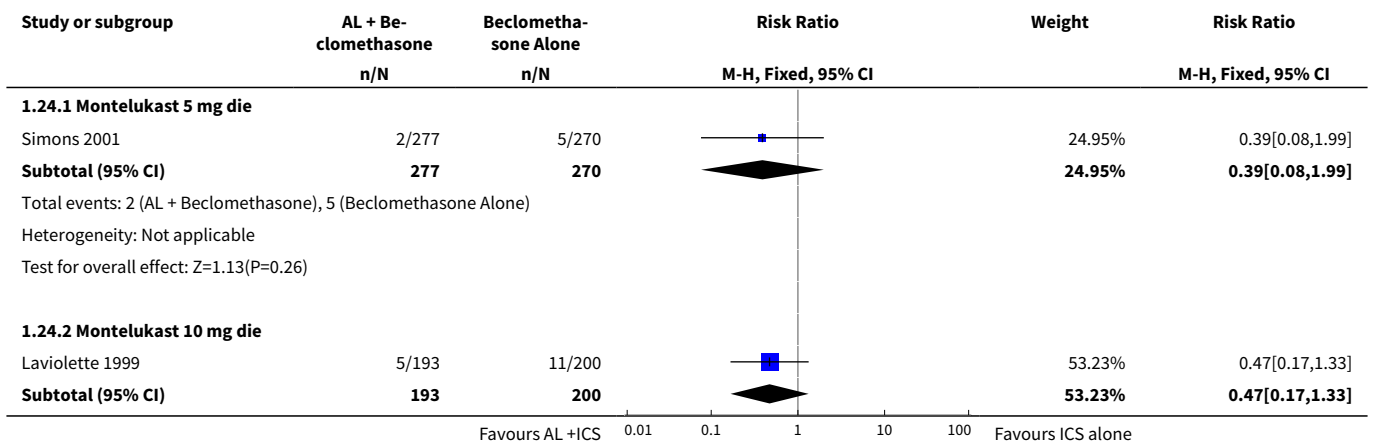
Analysis 1.22. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 22 Overall adverse effects.

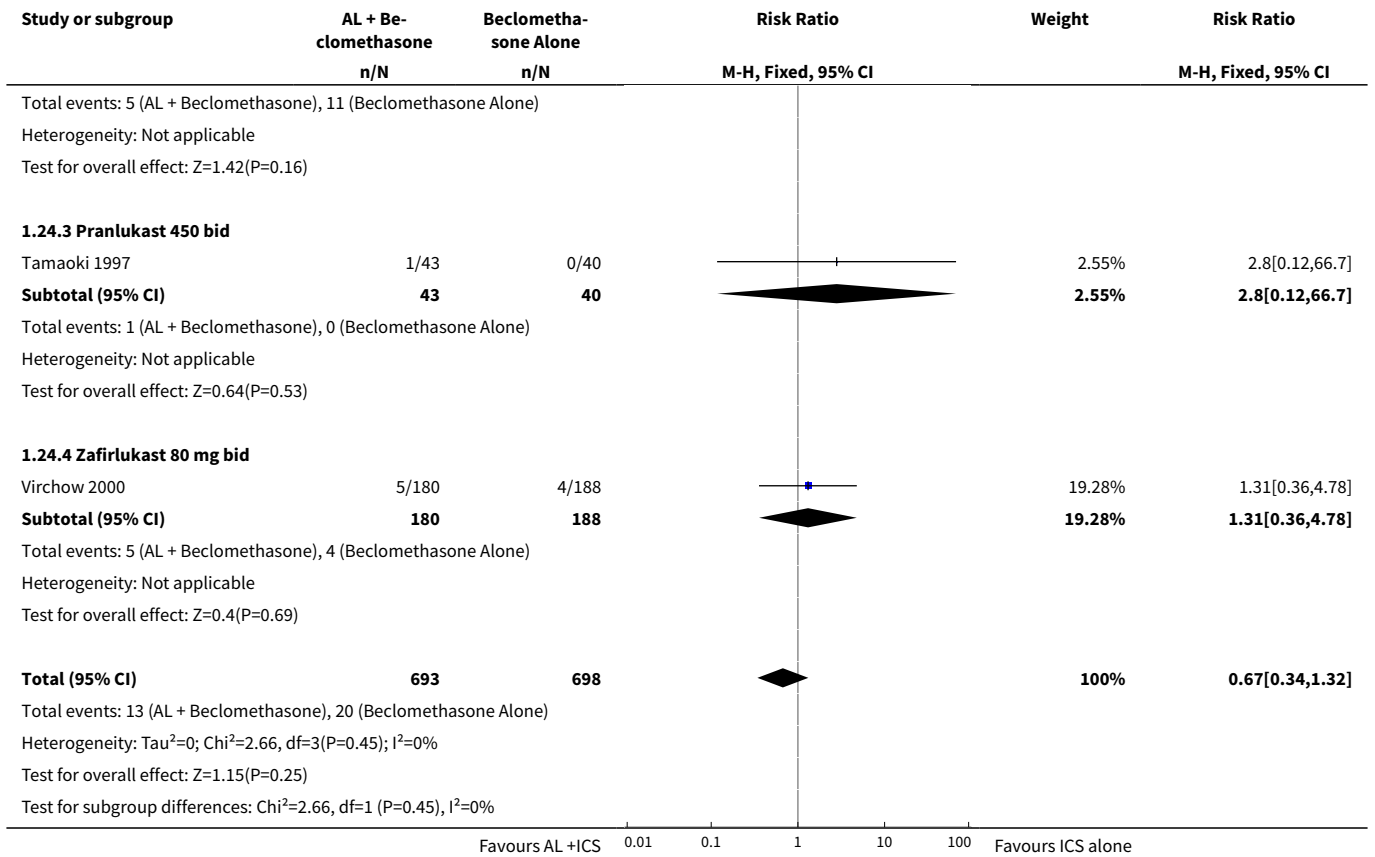


Analysis 1.23. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 23 Elevated liver enzymes.

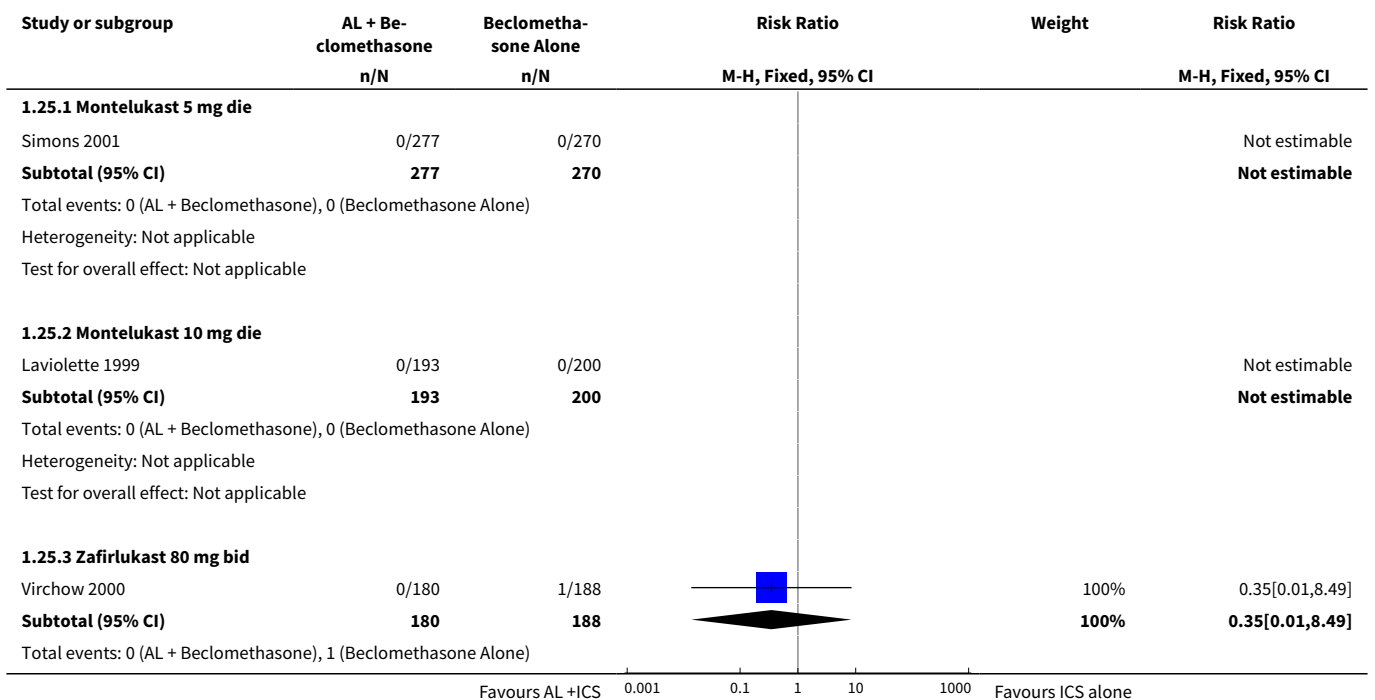


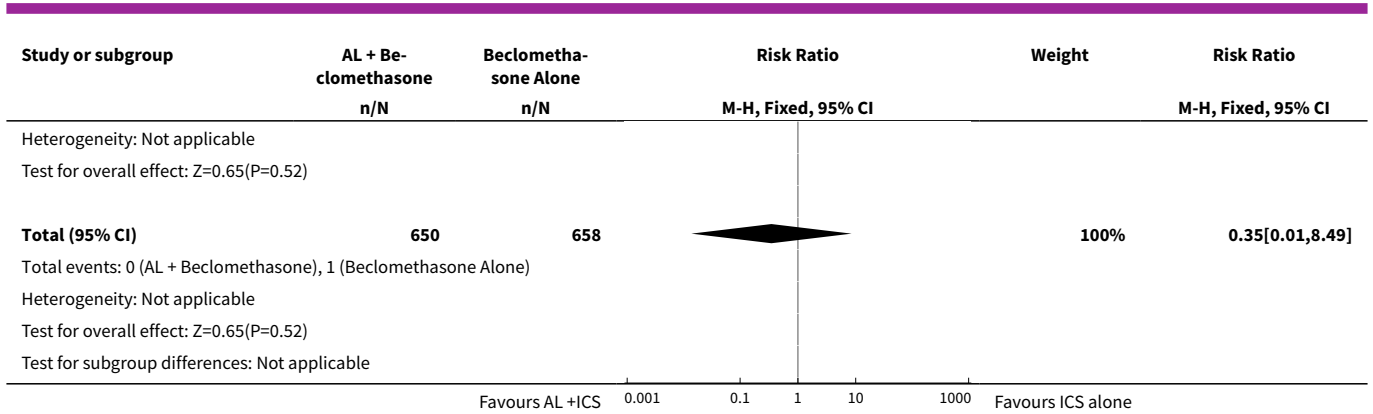
Analysis 1.24. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 24 Nausea.



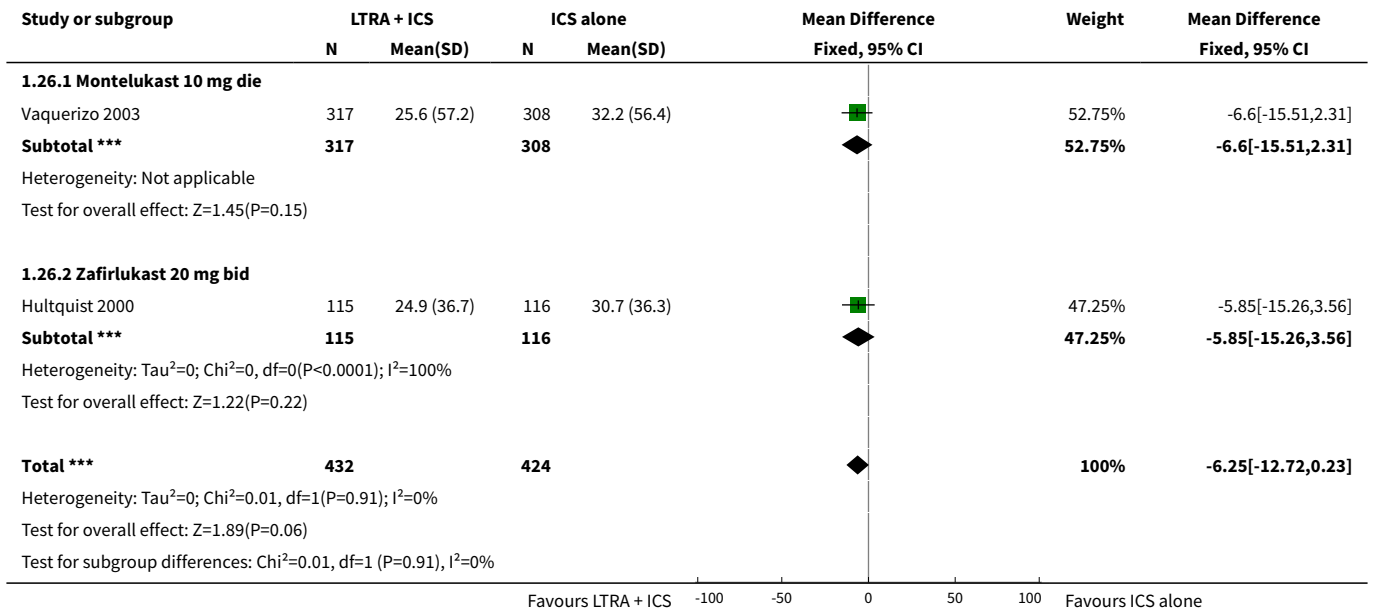


Analysis 1.25. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 25 Death.





Analysis 1.26. Comparison 1 Leukotriene Receptor Antagonists (LTRA) + ICS vs. same dose of ICS in SYMPTOMATIC patients, Outcome 26 % nocturnal awakenings.



Comparison 2. Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with 1 or more exacerbations requiring systemic steroids at LICENSED DOSES	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.56, 1.51]
1.1 Montelukast 10 mg die	1	885	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.45, 1.33]
1.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.61, 8.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Patients with 1 or more exacerbations requiring systemic steroids at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.55, 2.00]
2.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.77]
2.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.47, 2.50]
3 Patients with 1 or more exacerbations requiring hospital admission at LICENSED DOSES	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Montelukast 10 mg die	1	885	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change from baseline FEV1(L) at LICENSED DOSES at 12 weeks	2	225	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.12, 0.06]
4.1 Montelukast 10 mg die	1	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Zafirlukast 20 mg bid	1	223	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.12, 0.06]
5 Change from baseline FEV1 (L) at HIGHER THAN LICENSED doses at 12 +/- 4 weeks	2	638	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.07]
5.1 Zafirlukast 40 mg bid	1	206	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.12, 0.10]
5.2 Zafirlukast 80 mg bid	2	432	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]
6 Change from baseline Am PEFr (L/min) at LICENSED DOSES at 12 weeks weeks	2	1130	Mean Difference (IV, Random, 95% CI)	1.56 [-5.77, 8.89]
6.1 Montelukast 10 mg die	1	889	Mean Difference (IV, Random, 95% CI)	3.40 [-5.19, 11.99]
6.2 Zafirlukast 20 mg bid	1	241	Mean Difference (IV, Random, 95% CI)	-3.40 [-17.49, 10.69]
7 Change from baseline Am PEFr (L/min) at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks	2	663	Mean Difference (IV, Fixed, 95% CI)	6.05 [-1.26, 13.36]
7.1 Zafirlukast 40 mg bid	1	208	Mean Difference (IV, Fixed, 95% CI)	7.60 [-4.70, 19.90]
7.2 Zafirlukast 80 mg bid	2	455	Mean Difference (IV, Fixed, 95% CI)	5.21 [-3.89, 14.30]

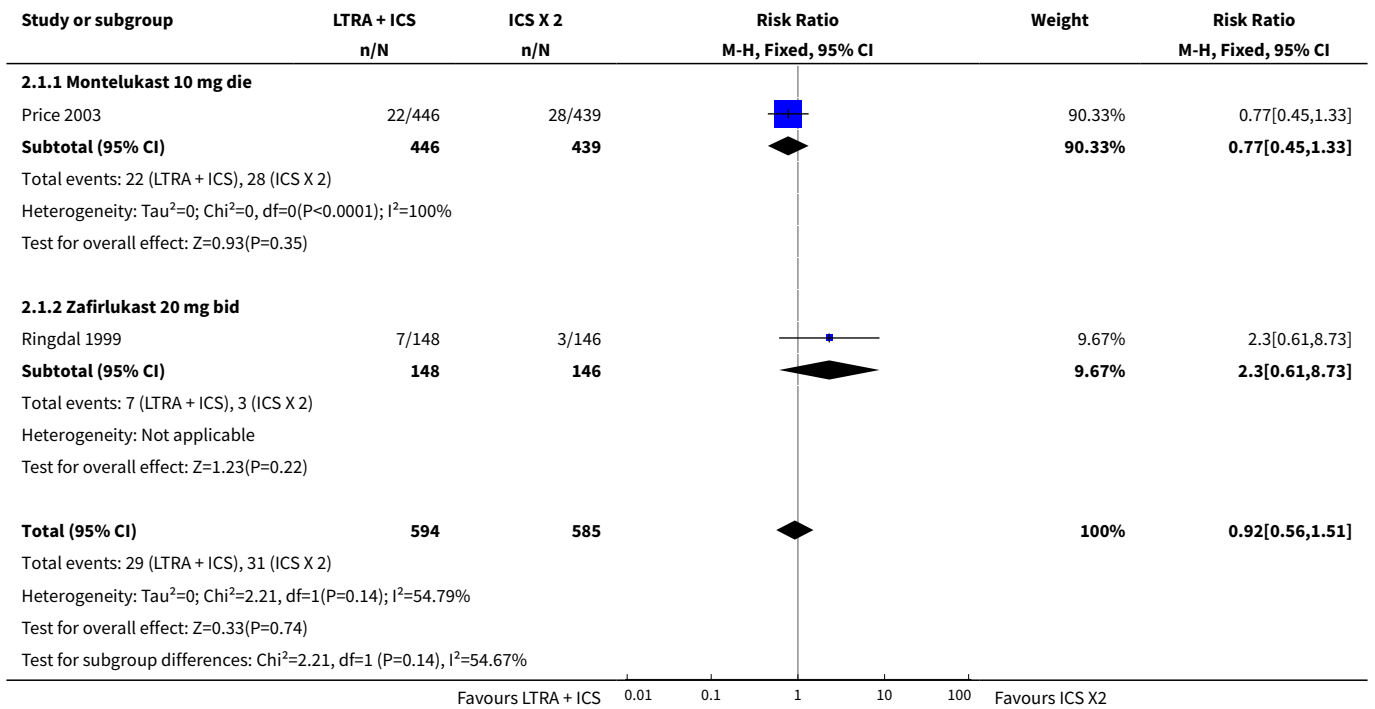
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 % Change from baseline mean diurnal variation in PEF at LICENSED DOSES at 12 +/- 4 weeks	1	241	Mean Difference (IV, Random, 95% CI)	-6.40 [-15.63, 2.83]
8.1 Zafirlukast 20 mg bid	1	241	Mean Difference (IV, Random, 95% CI)	-6.40 [-15.63, 2.83]
9 Change (% or L/min) from baseline mean diurnal variation in PEF at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks	2	746	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.25, 0.03]
9.1 Zafirlukast 40 mg bid	1	251	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.37, 0.13]
9.2 Zafirlukast 80 mg bid	2	495	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.28, 0.07]
10 Change from baseline mean symptom scores at LICENSED DOSES at 12 +/- 4 weeks	2	1101	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.09, 0.10]
10.1 Montelukast 10 mg die	1	860	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.10, 0.12]
10.2 Zafirlukast 20 mg bid	1	241	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.18, 0.18]
11 Change from baseline mean symptom scores at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks	2	664	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.16, 0.03]
11.1 Zafirlukast 40 mg bid	1	208	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.17, 0.15]
11.2 Zafirlukast 80 mg bid	2	456	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.21, 0.03]
12 Change from baseline mean daily use of B2-agonists at LICENSED DOSES at 12 +/- 4 weeks	2	1015	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.24, 0.18]
12.1 Montelukast 10 mg die	1	774	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.25, 0.19]
12.2 Zafirlukast 20 mg bid	1	241	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.74, 0.74]
13 Change from baseline mean daily use of B2-agonists at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks	2	663	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.37, 0.37]
13.1 Zafirlukast 40 mg bid	1	208	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.34, 0.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Zafirlukast 80 mg bid	2	455	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.62, 0.31]
14 Change in night-time awakenings per week at LICENSED DOSES at 12 +4 weeks	1	241	Mean Difference (IV, Fixed, 95% CI)	0.4 [-0.60, 1.40]
14.1 Zafirlukast 20 mg bid	1	241	Mean Difference (IV, Fixed, 95% CI)	0.4 [-0.60, 1.40]
15 Change in night-time awakenings per week at HIGHER THAN LICENSED DOSES at 12 +4 weeks	1	236	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.73, 1.13]
15.1 Zafirlukast 80 mg bid	1	236	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.73, 1.13]
16 Overall withdrawals at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.63, 1.55]
16.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.43, 1.34]
16.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.74, 3.64]
17 Withdrawals due to adverse effects at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.55, 2.37]
17.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.31, 1.98]
17.2 Zafirlukast 20mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.61, 8.73]
18 Withdrawals due to poor asthma control/exacerbations at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.15, 1.63]
18.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.06, 1.35]
18.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.18, 21.52]
19 Overall adverse effects at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.06]
19.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
19.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.19]
20 Elevated liver enzymes at LICENSED DOSES	2	1147	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.34, 1.92]
20.1 Montelukast 10 mg die	1	853	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.18, 1.61]
20.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.37, 10.61]
21 Headache at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.76, 1.52]

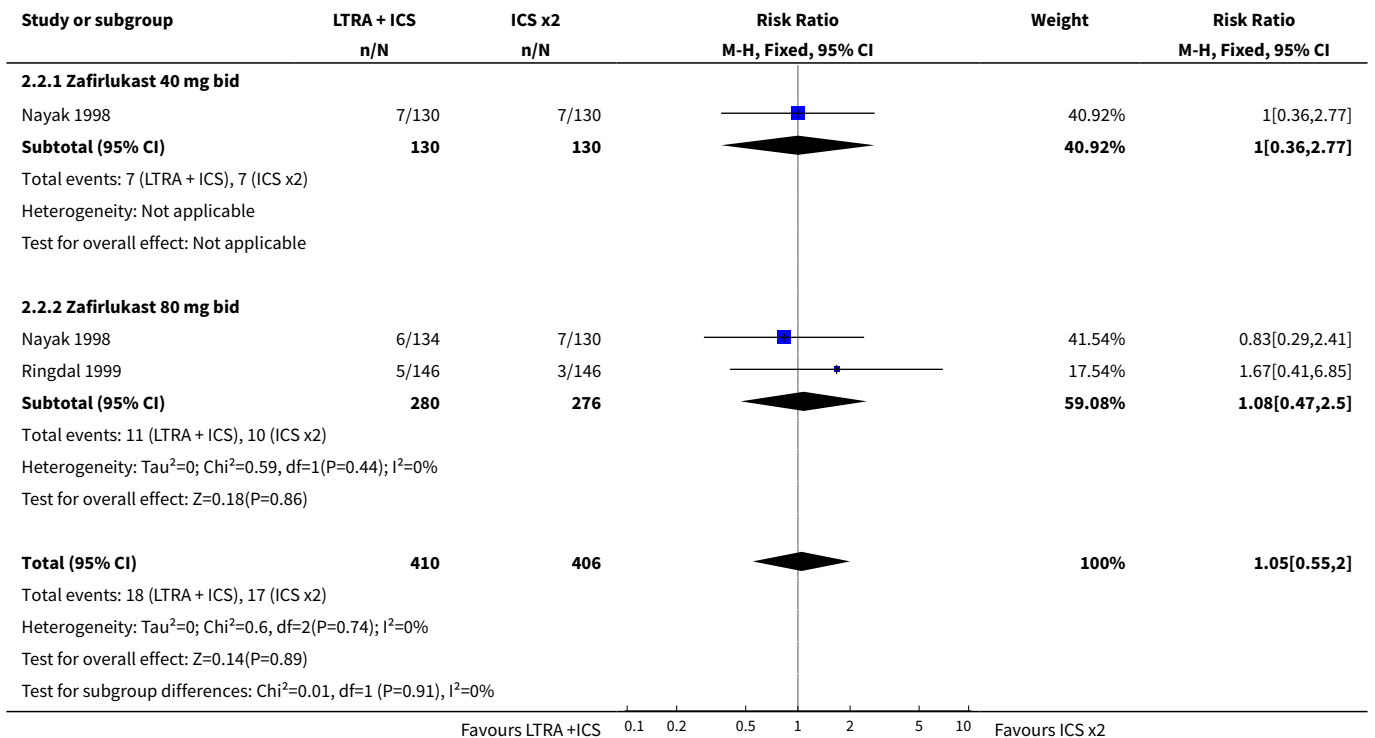
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.72, 1.86]
21.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.62]
22 Nausea at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.60]
22.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.19, 2.31]
22.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.43]
23 Oral Moniliasis at LICENSED DOSES	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 2.00]
23.1 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 2.00]
24 Death at LICENSED DOSES	2	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.1 Montelukast 10 mg die	1	889	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Zafirlukast 20 mg bid	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Patients with 1 or more exacerbations requiring hospital admission at HIGHER THAN LICENSED DOSES	2	699	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.04]
25.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Zafirlukast 80 mg bid	2	439	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 73.04]
26 Nighttime awakenings/week at USUAL LICENSED DOSES at 12 weeks	1	820	Mean Difference (IV, Fixed, 95% CI)	1.0 [-2.69, 4.69]
26.1 Montelukast 10 mg die	1	820	Mean Difference (IV, Fixed, 95% CI)	1.0 [-2.69, 4.69]
27 Overall withdrawals at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.73, 1.50]
27.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.57, 1.74]
27.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.72]
28 Withdrawals due to adverse effects at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.95, 5.45]
28.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 6.99]
28.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [1.02, 7.58]
29 Withdrawals due to poor asthma control/exacerbations at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.29, 1.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.46]
29.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.25, 2.62]
30 Overall adverse effects at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.07]
30.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
30.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.12]
31 Elevated liver enzymes at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [1.45, 17.00]
31.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.97]
31.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	5.36 [1.40, 20.44]
32 Headache at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.79, 1.63]
32.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.65, 2.86]
32.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.71, 1.62]
33 Nausea at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.79, 3.95]
33.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.62, 14.59]
33.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.55, 3.66]
34 Oral moniliasis at HIGHER THAN LICENSED DOSES	2	816	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.81]
34.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.46]
34.2 Zafirlukast 80 mg bid	2	556	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.77]
35 Death at HIGHER THAN LICENSED DOSES	2	820	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.1 Zafirlukast 40 mg bid	1	260	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Zafirlukast 80 mg bid	2	560	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

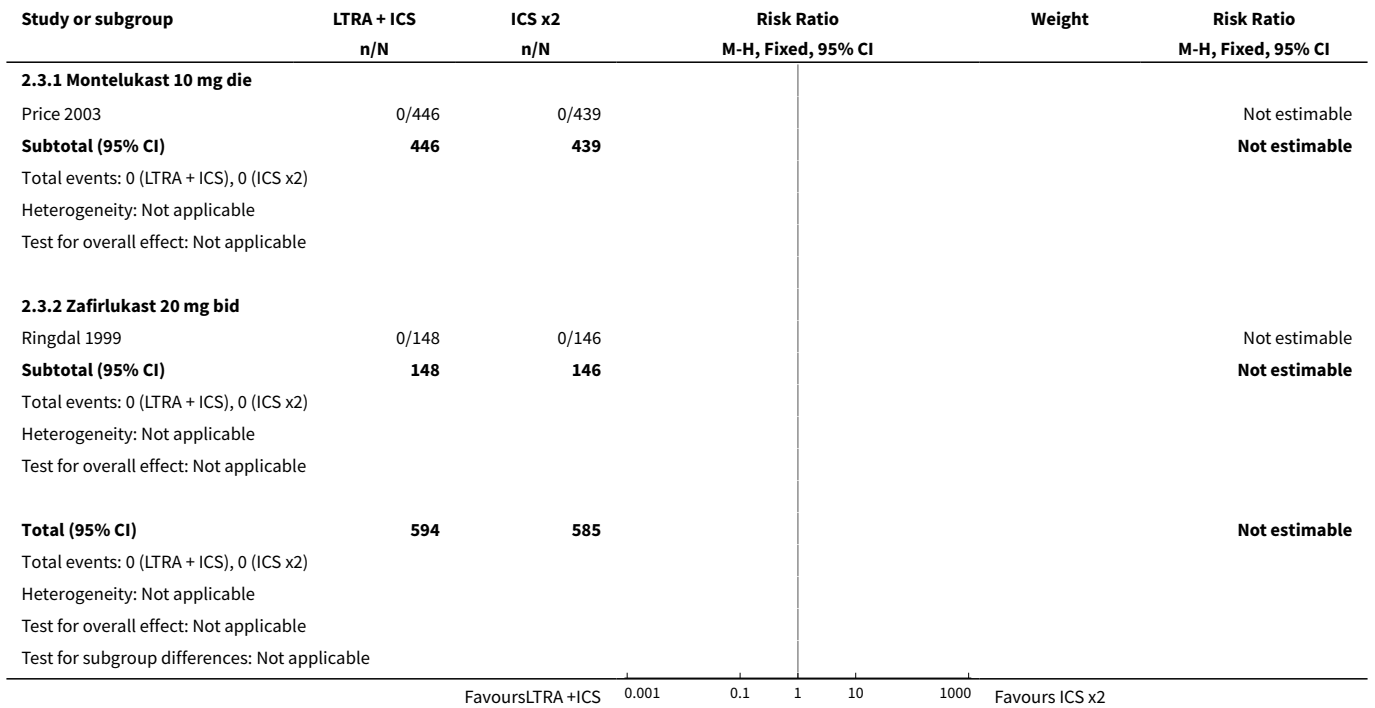
Analysis 2.1. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 1 Patients with 1 or more exacerbations requiring systemic steroids at LICENSED DOSES.



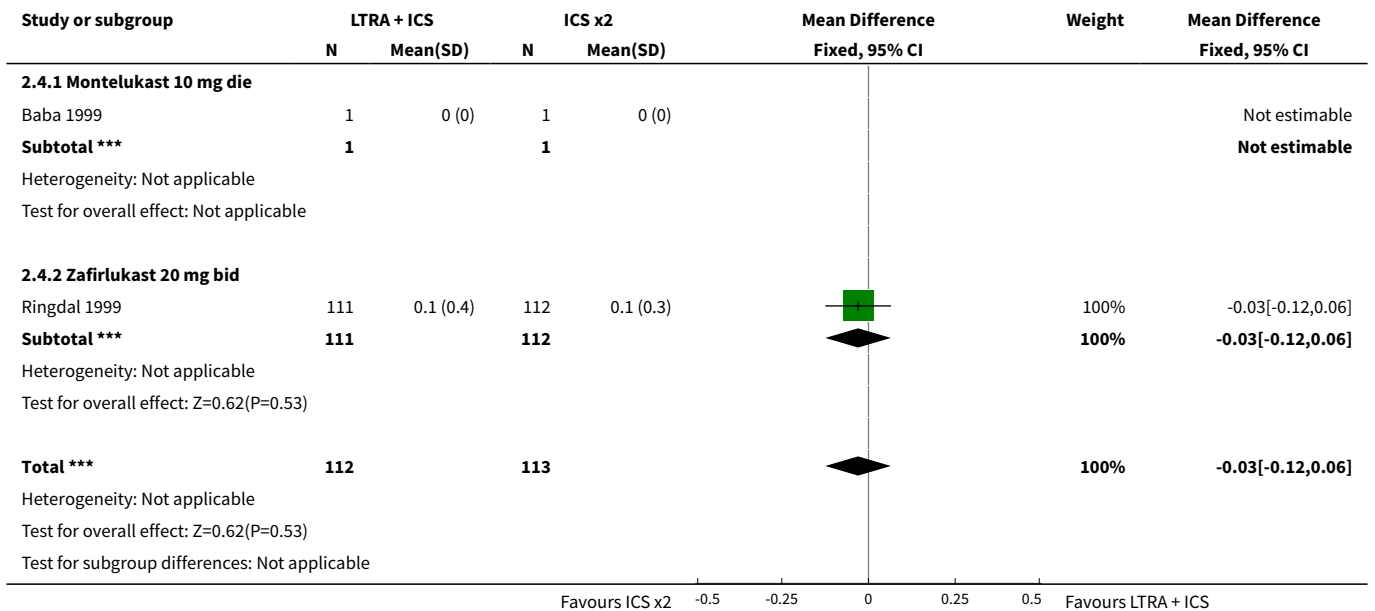
Analysis 2.2. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 2 Patients with 1 or more exacerbations requiring systemic steroids at HIGHER THAN LICENSED DOSES.



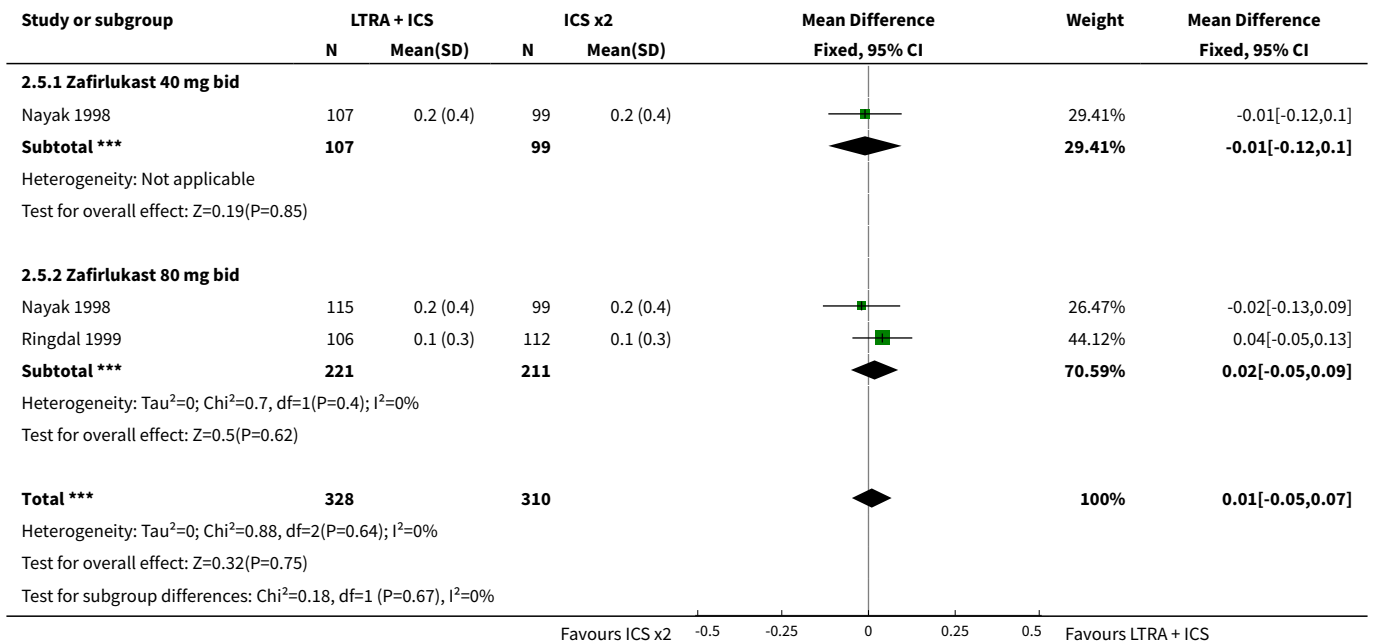
Analysis 2.3. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 3 Patients with 1 or more exacerbations requiring hospital admission at LICENSED DOSES.



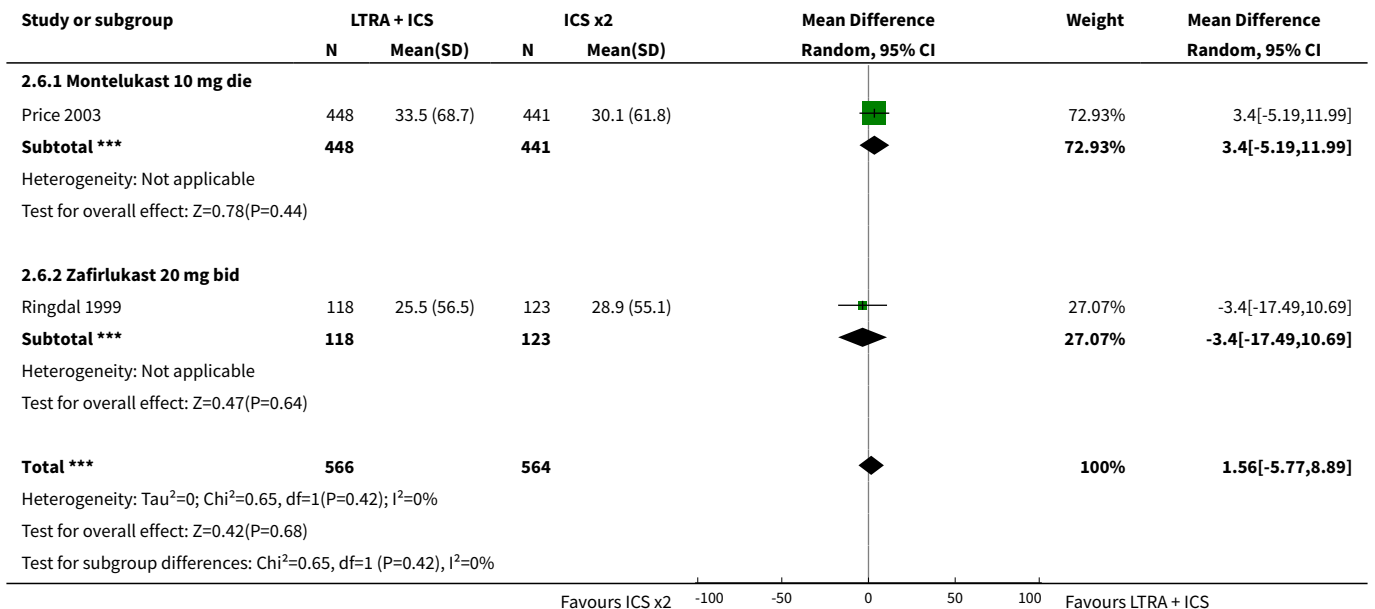
Analysis 2.4. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 4 Change from baseline FEV1(L) at LICENSED DOSES at 12 weeks.



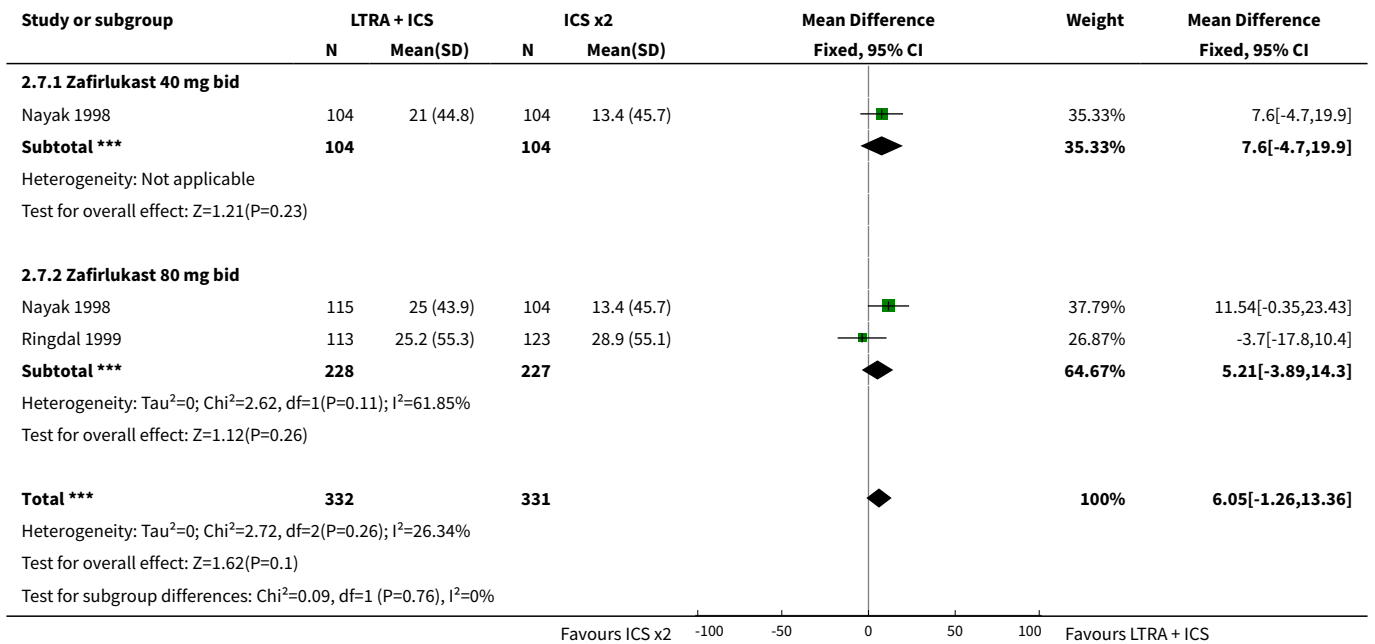
Analysis 2.5. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 5 Change from baseline FEV1 (L) at HIGHER THAN LICENSED doses at 12 +/- 4 weeks.



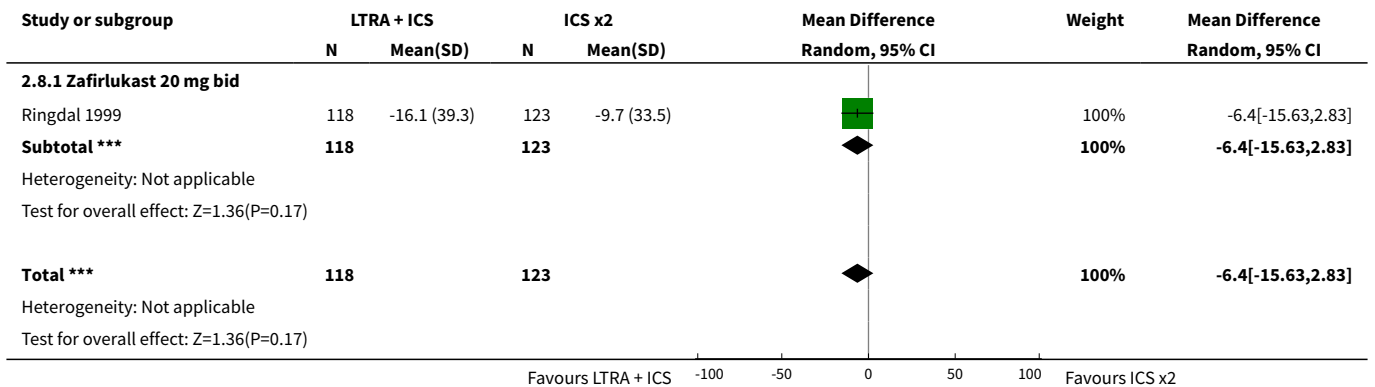
Analysis 2.6. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 6 Change from baseline Am PEFR (L/min) at LICENSED DOSES at 12 weeks weeks.



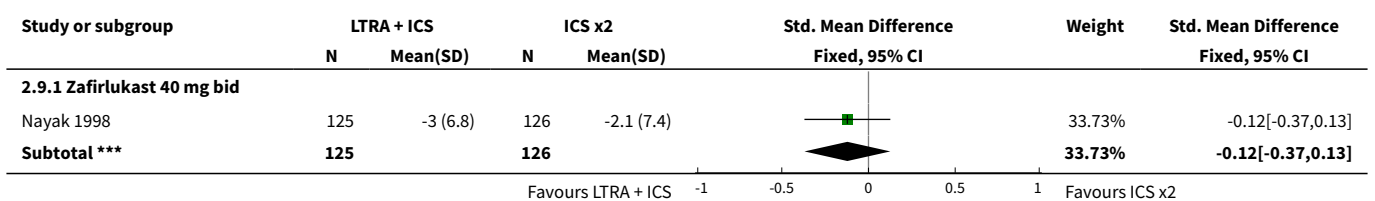
Analysis 2.7. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 7 Change from baseline Am PEFR (L/min) at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks.

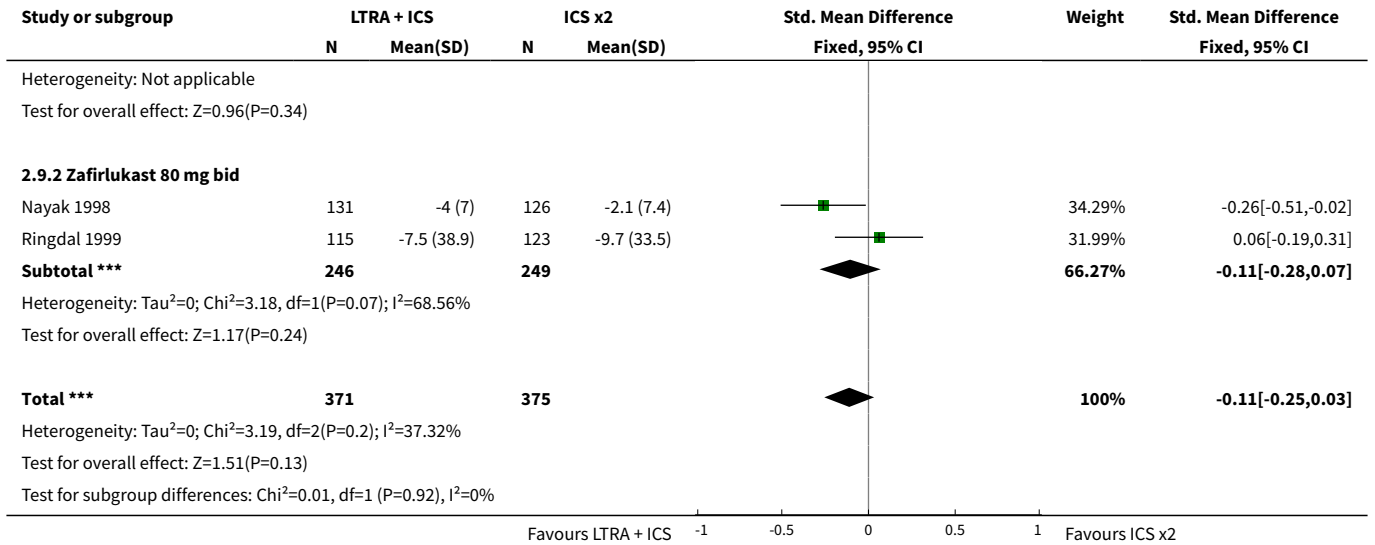


Analysis 2.8. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 8 % Change from baseline mean diurnal variation in PEF at LICENSED DOSES at 12 +/- 4 weeks.

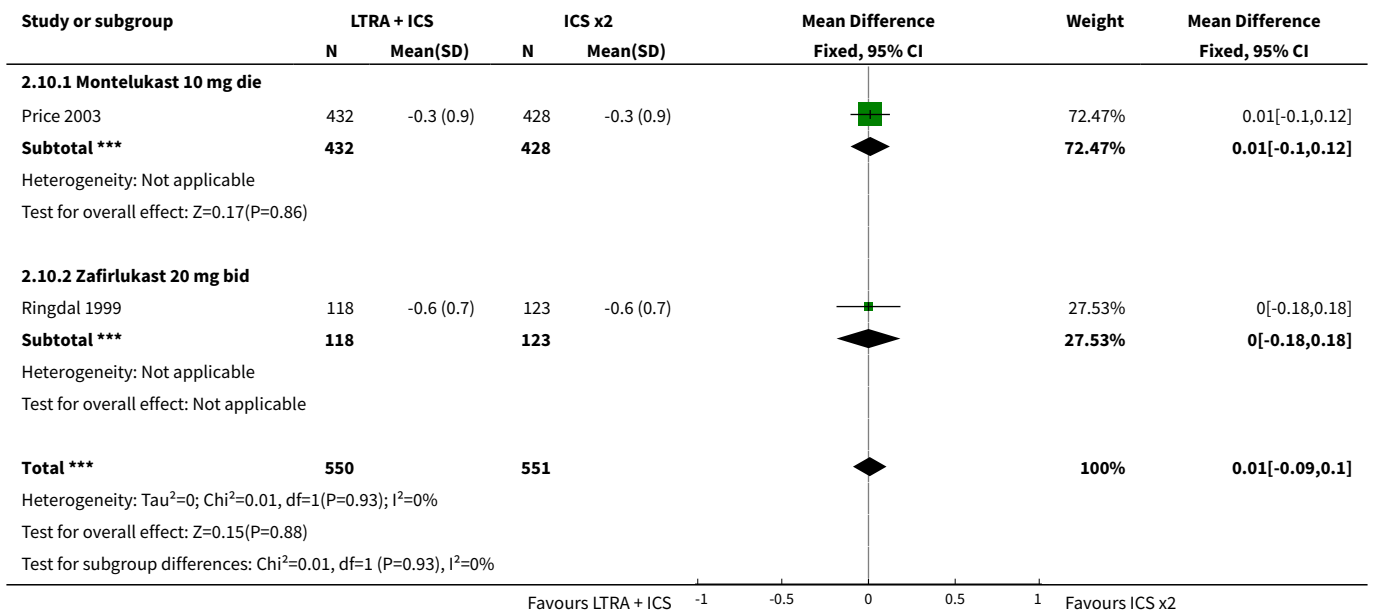


Analysis 2.9. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 9 Change (% or L/min) from baseline mean diurnal variation in PEF at HIGHER THAN LICENSED DOSES at 12 +/- 4 wee.

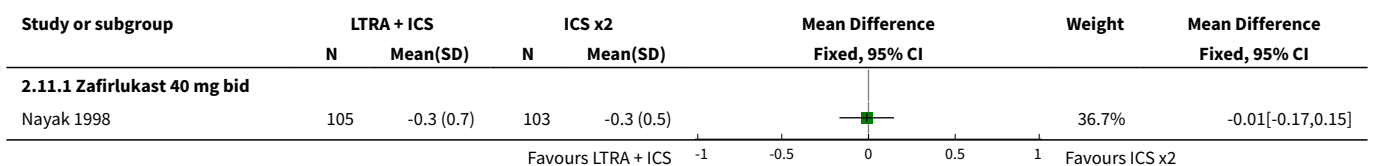


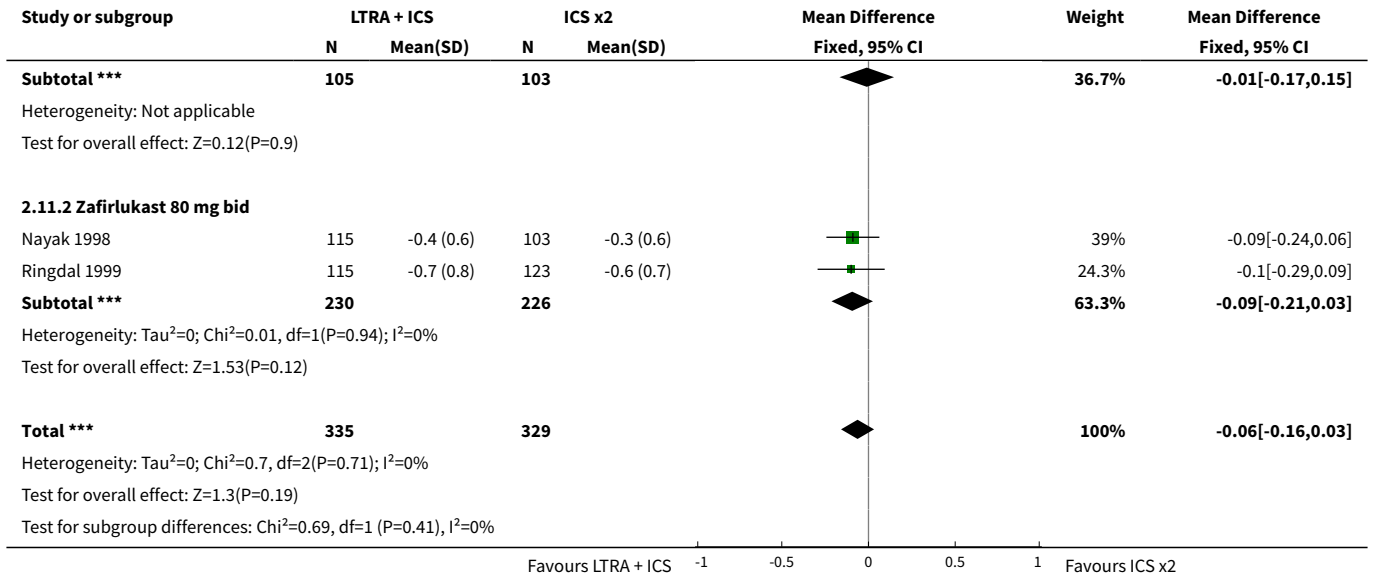


Analysis 2.10. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 10 Change from baseline mean symptom scores at LICENSED DOSES at 12 +/- 4 weeks.

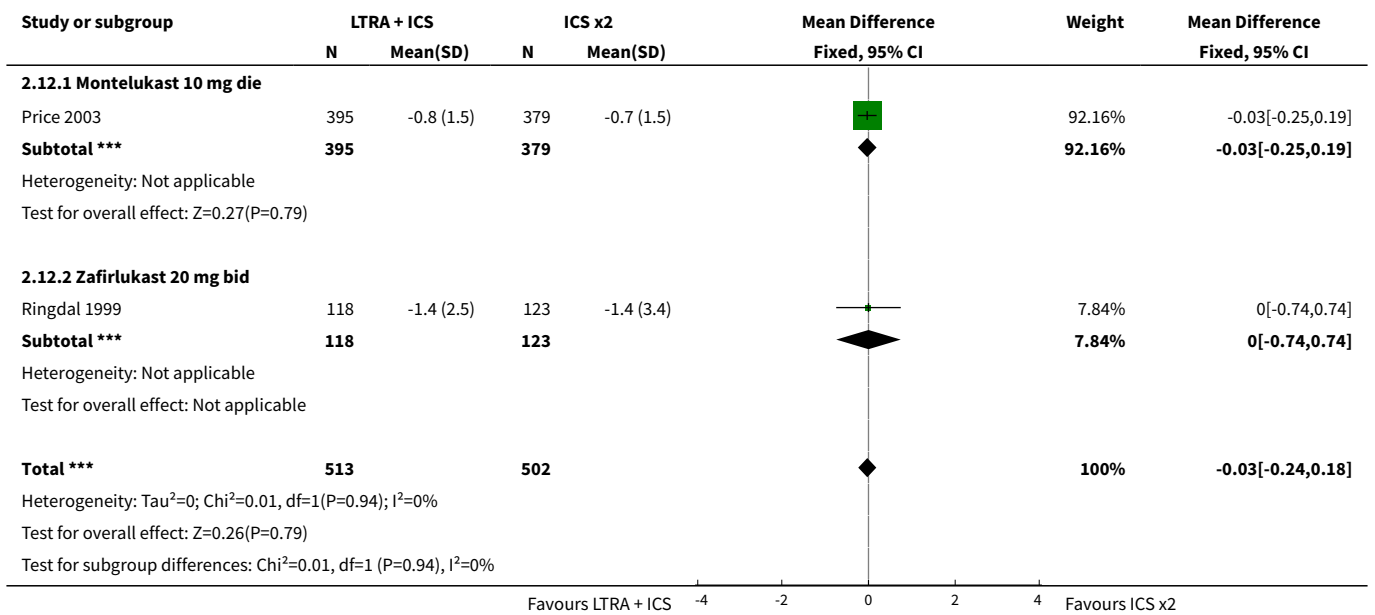


Analysis 2.11. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 11 Change from baseline mean symptom scores at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks.

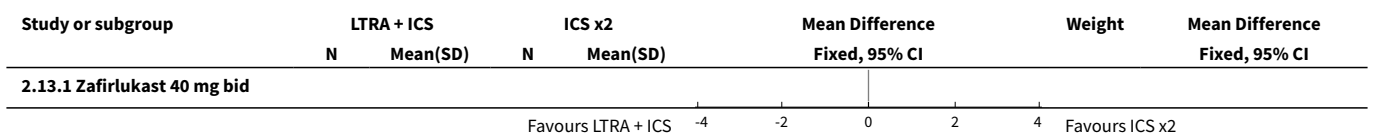


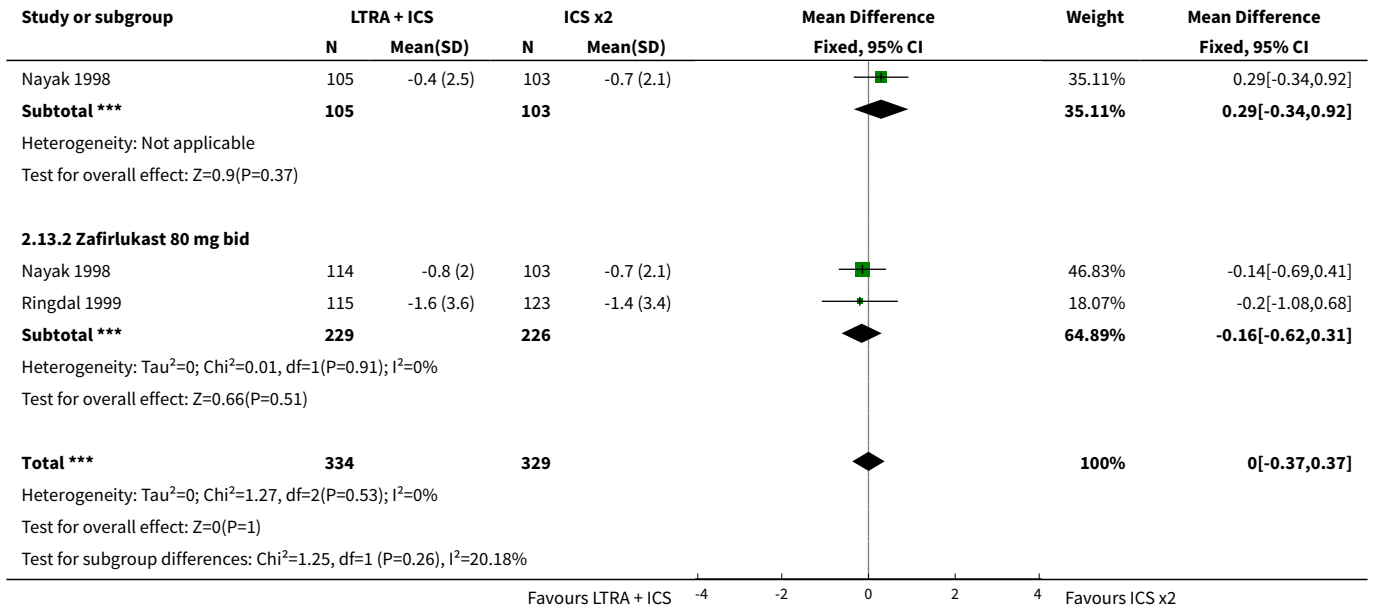


Analysis 2.12. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 12 Change from baseline mean daily use of B2-agonists at LICENSED DOSES at 12 +/- 4 weeks.

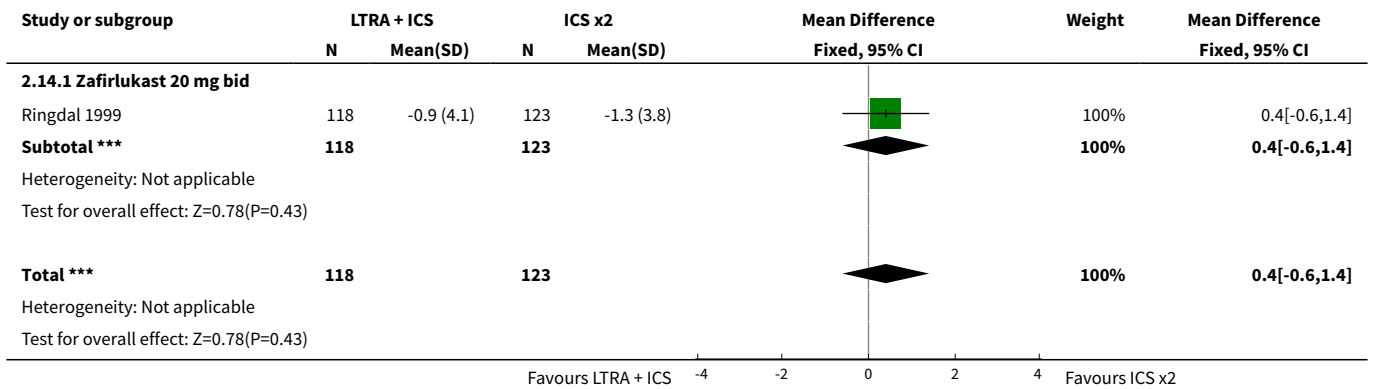


Analysis 2.13. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 13 Change from baseline mean daily use of B2-agonists at HIGHER THAN LICENSED DOSES at 12 +/- 4 weeks.

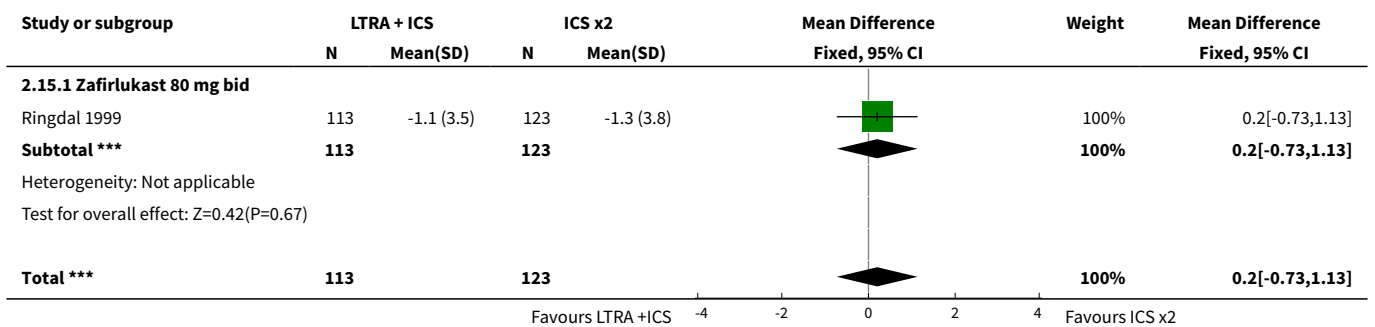




Analysis 2.14. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 14 Change in night-time awakenings per week at LICENSED DOSES at 12 +-4 weeks.



Analysis 2.15. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 15 Change in night-time awakenings per week at HIGHER THAN LICENSED DOSES at 12 +-4 weeks.



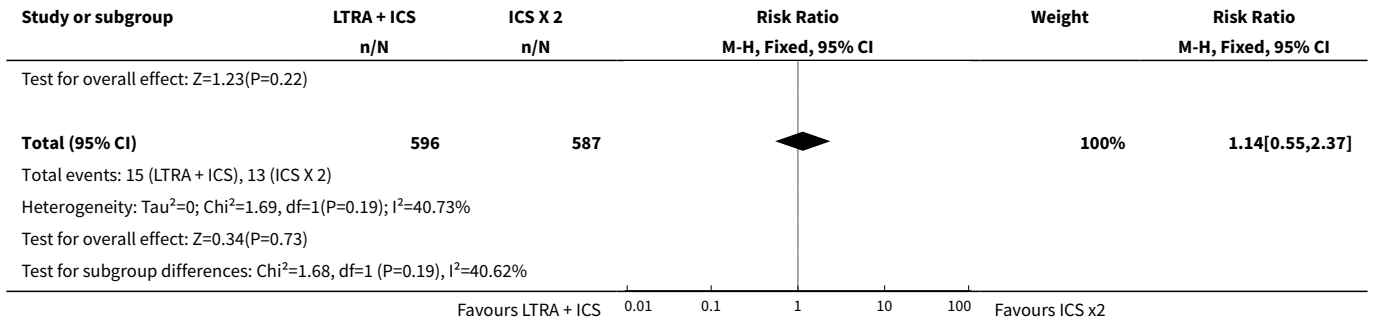
Study or subgroup	LTRA + ICS		ICS x2		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Heterogeneity: Not applicable Test for overall effect: Z=0.42(P=0.67)							
Favours LTRA + ICS -4 -2 0 2 4 Favours ICS x2							

Analysis 2.16. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 16 Overall withdrawals at LICENSED DOSES.

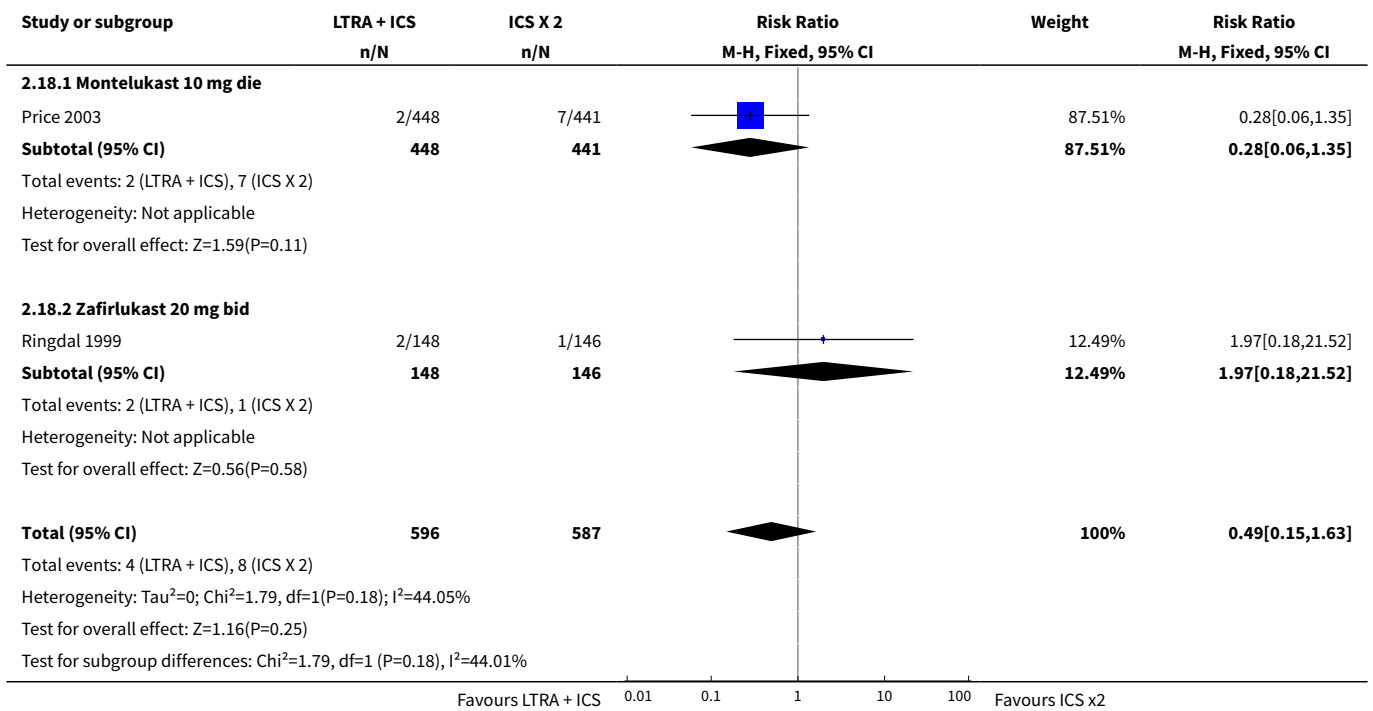
Study or subgroup	LTRA + ICS		ICS X 2		Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
	n/N	n/N	n/N	n/N			
2.16.1 Montelukast 10 mg die							
Price 2003	20/448	26/441				74.31%	0.76[0.43,1.34]
Subtotal (95% CI)	448	441				74.31%	0.76[0.43,1.34]
Total events: 20 (LTRA + ICS), 26 (ICS X 2) Heterogeneity: Not applicable Test for overall effect: Z=0.96(P=0.34)							
2.16.2 Zafirlukast 20 mg bid							
Ringdal 1999	15/148	9/146				25.69%	1.64[0.74,3.64]
Subtotal (95% CI)	148	146				25.69%	1.64[0.74,3.64]
Total events: 15 (LTRA + ICS), 9 (ICS X 2) Heterogeneity: Not applicable Test for overall effect: Z=1.23(P=0.22)							
Total (95% CI)	596	587				100%	0.99[0.63,1.55]
Total events: 35 (LTRA + ICS), 35 (ICS X 2) Heterogeneity: Tau ² =0; Chi ² =2.42, df=1(P=0.12); I ² =58.72% Test for overall effect: Z=0.06(P=0.95) Test for subgroup differences: Chi ² =2.42, df=1 (P=0.12), I ² =58.72%							
Favours LTRA + ICS 0.1 0.2 0.5 1 2 5 10 Favours ICS x2							

Analysis 2.17. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 17 Withdrawals due to adverse effects at LICENSED DOSES.

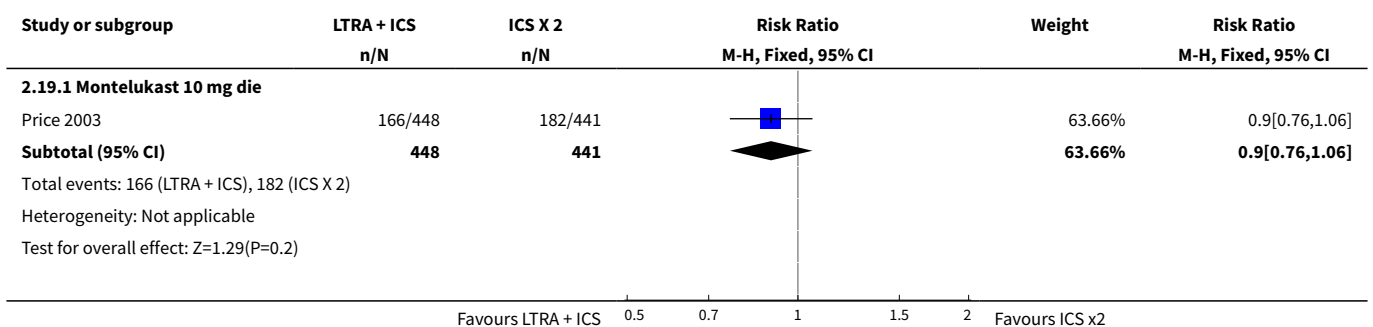
Study or subgroup	LTRA + ICS		ICS X 2		Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
	n/N	n/N	n/N	n/N			
2.17.1 Montelukast 10 mg die							
Price 2003	8/448	10/441				76.94%	0.79[0.31,1.98]
Subtotal (95% CI)	448	441				76.94%	0.79[0.31,1.98]
Total events: 8 (LTRA + ICS), 10 (ICS X 2) Heterogeneity: Not applicable Test for overall effect: Z=0.51(P=0.61)							
2.17.2 Zafirlukast 20mg bid							
Ringdal 1999	7/148	3/146				23.06%	2.3[0.61,8.73]
Subtotal (95% CI)	148	146				23.06%	2.3[0.61,8.73]
Total events: 7 (LTRA + ICS), 3 (ICS X 2) Heterogeneity: Not applicable							
Favours LTRA + ICS 0.01 0.1 1 10 100 Favours ICS x2							

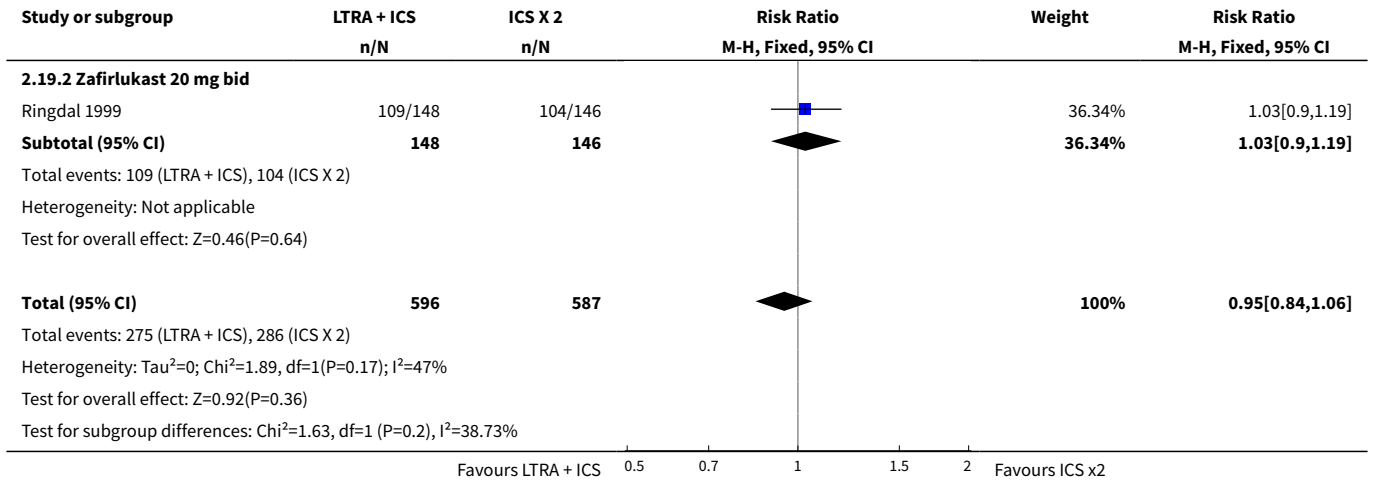


Analysis 2.18. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 18 Withdrawals due to poor asthma control/exacerbations at LICENSED DOSES.

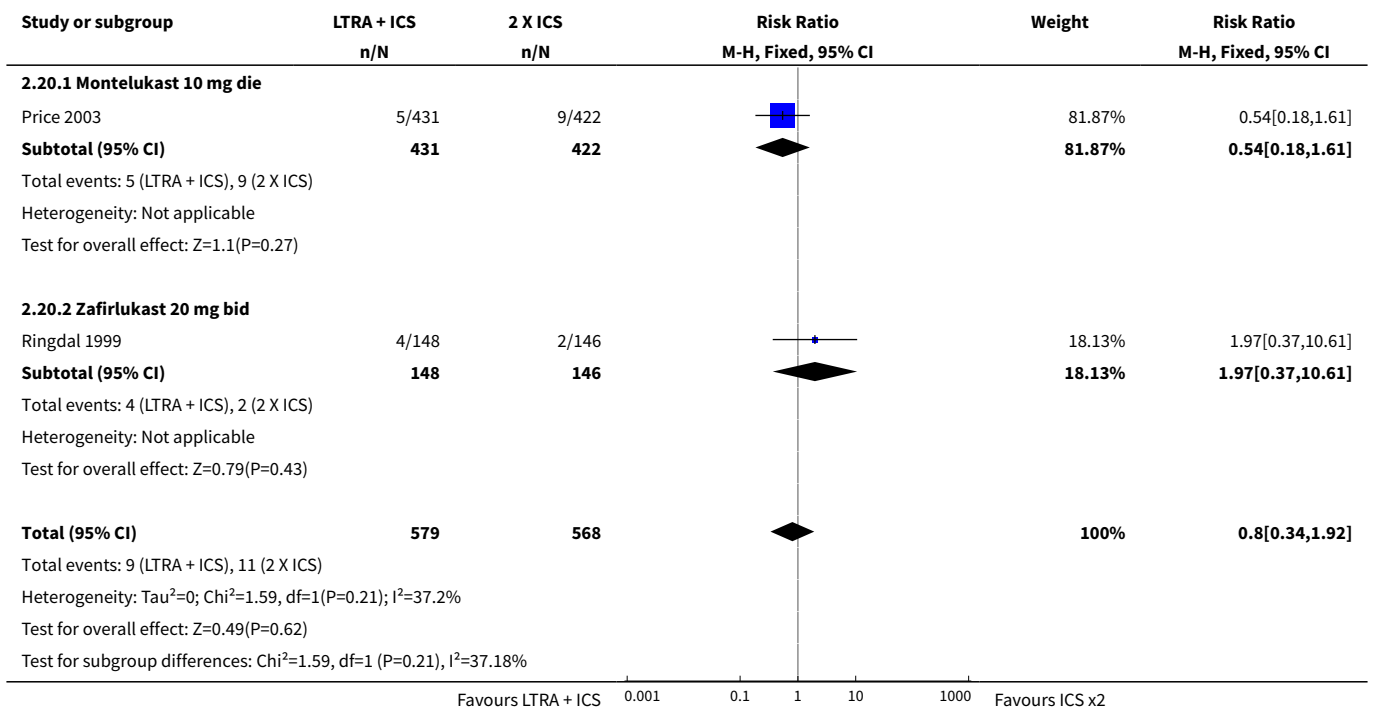


Analysis 2.19. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 19 Overall adverse effects at LICENSED DOSES.

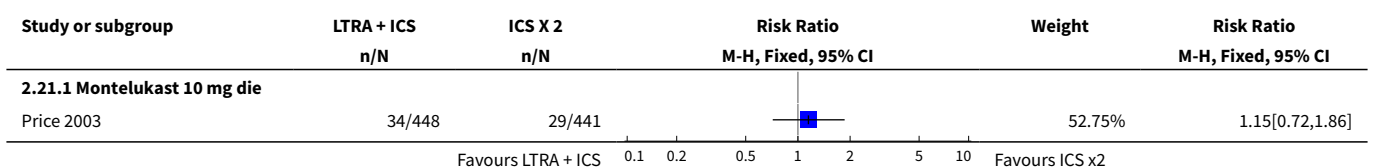


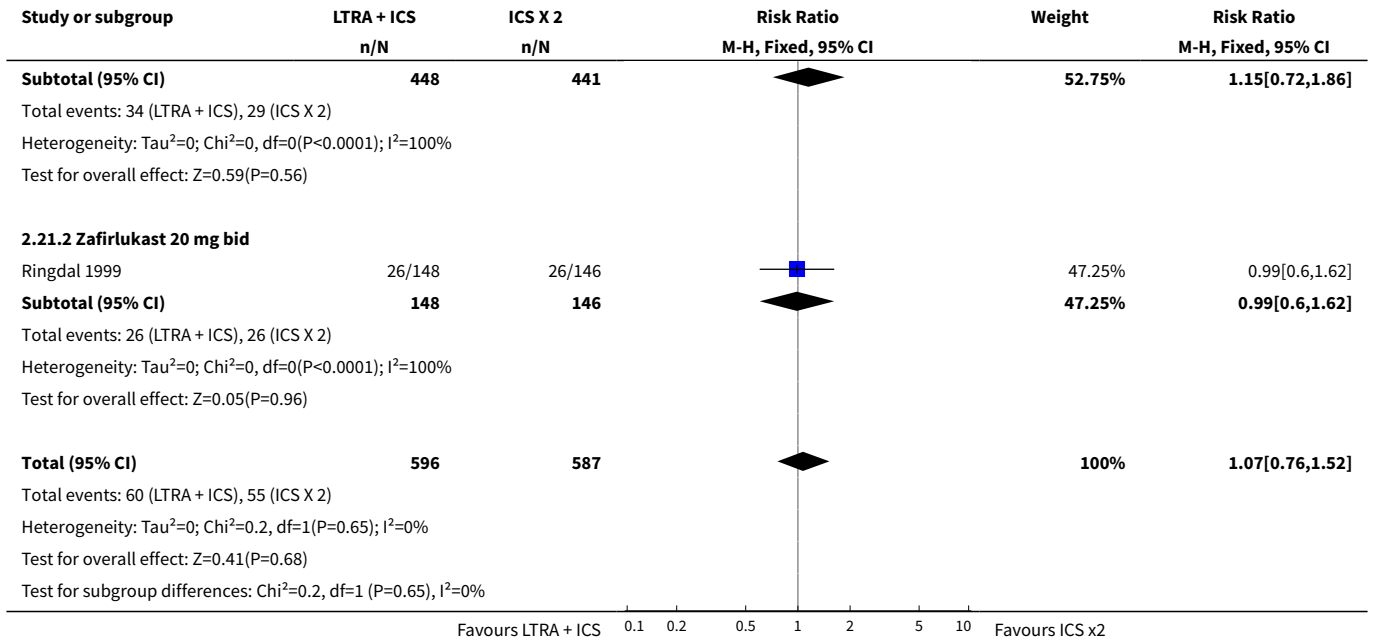


Analysis 2.20. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 20 Elevated liver enzymes at LICENSED DOSES.

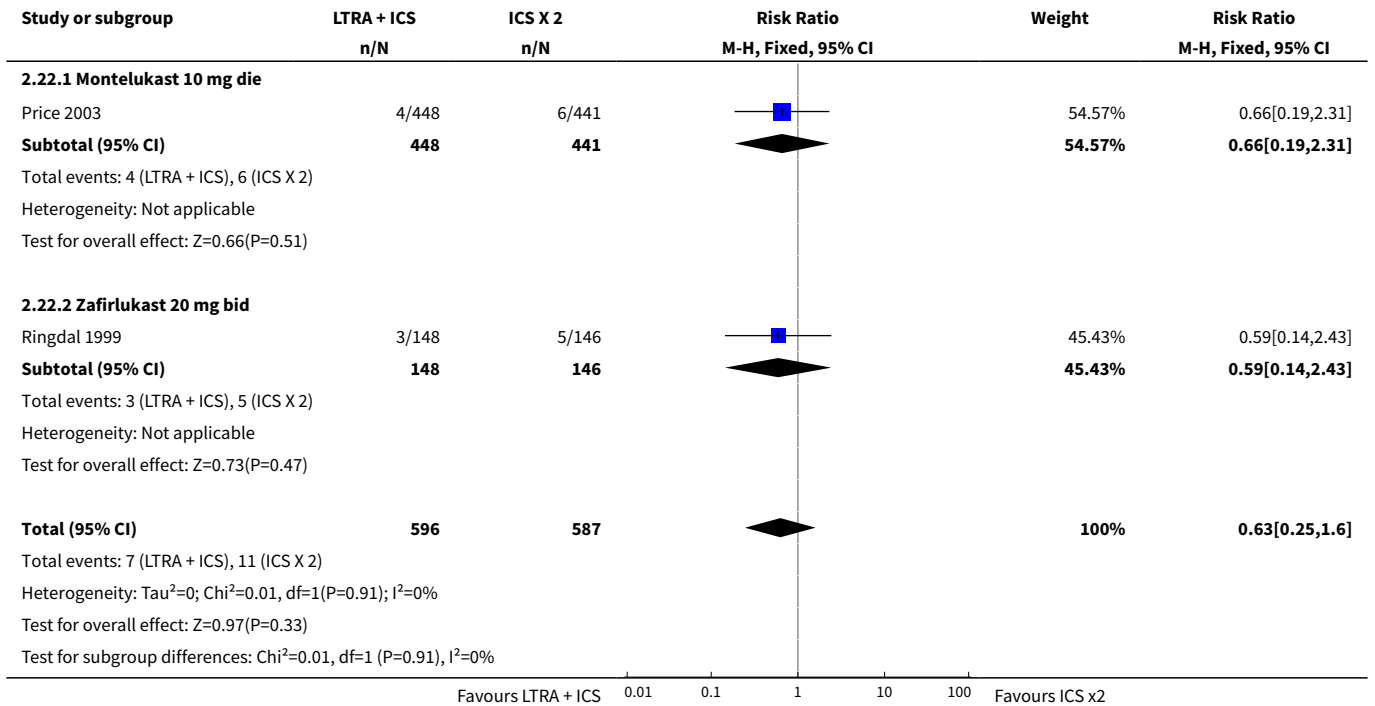


Analysis 2.21. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 21 Headache at LICENSED DOSES.

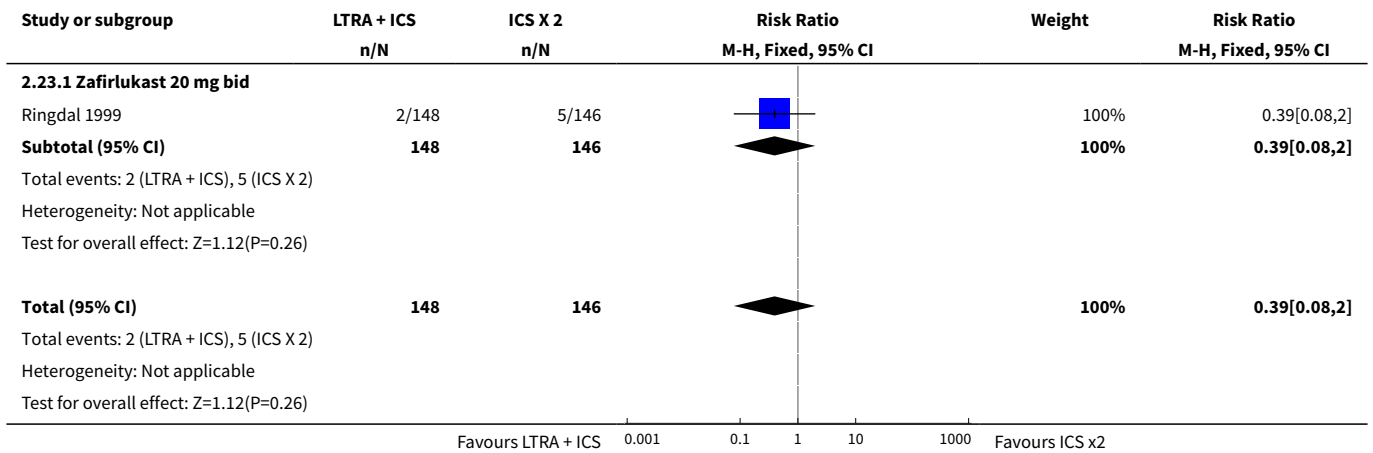




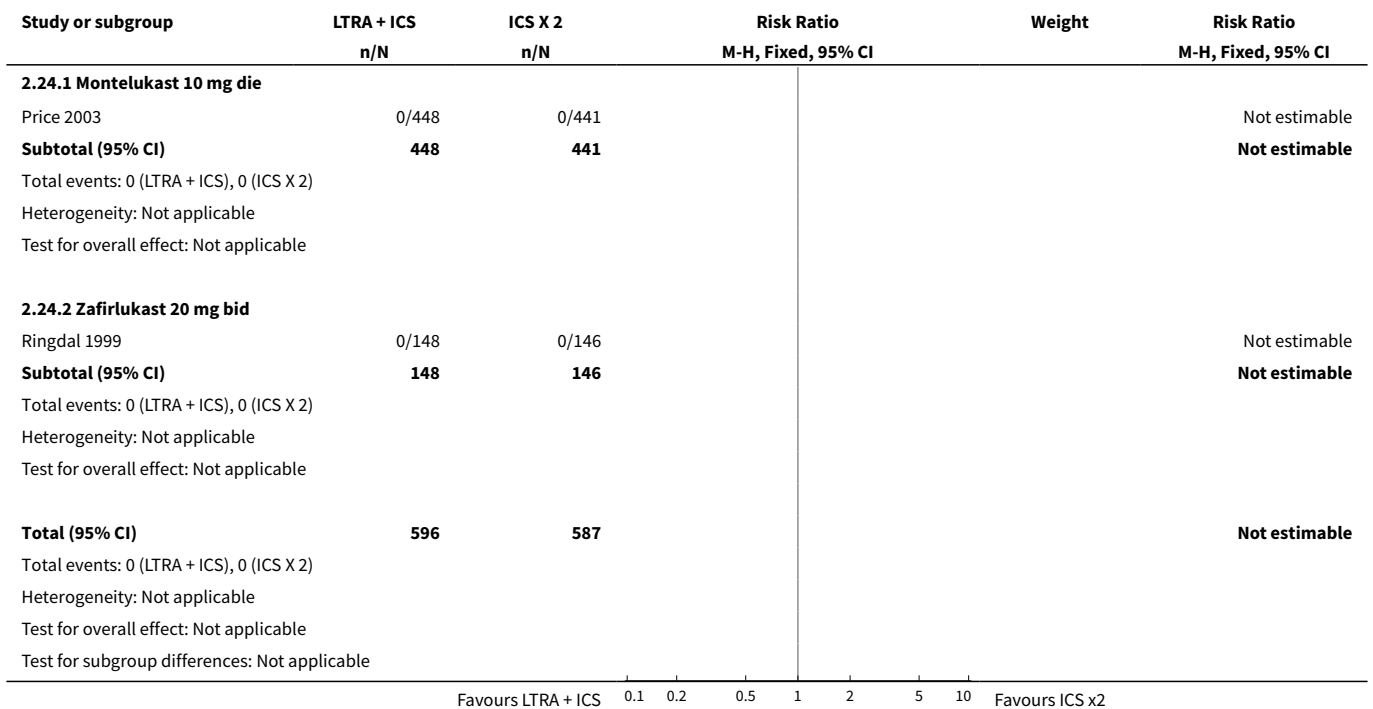
Analysis 2.22. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 22 Nausea at LICENSED DOSES.



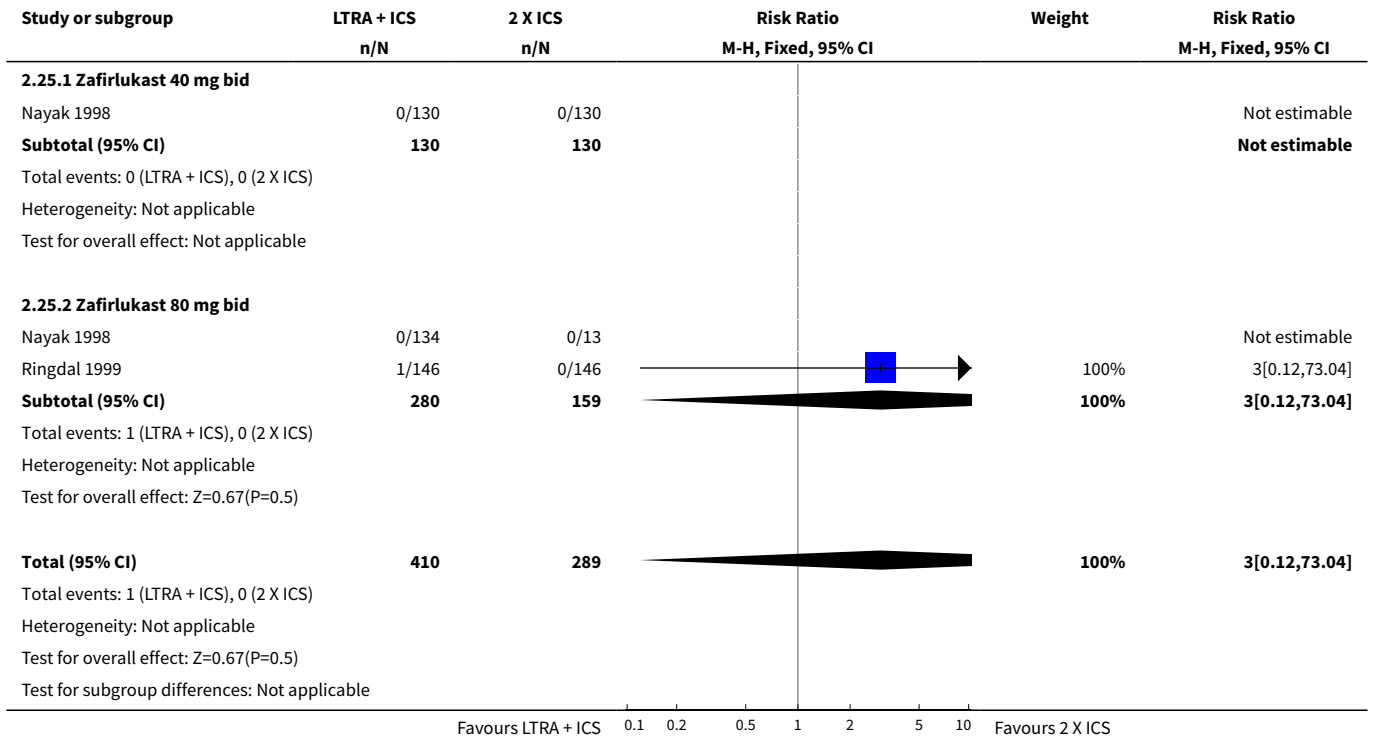
Analysis 2.23. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 23 Oral Moniliasis at LICENSED DOSES.



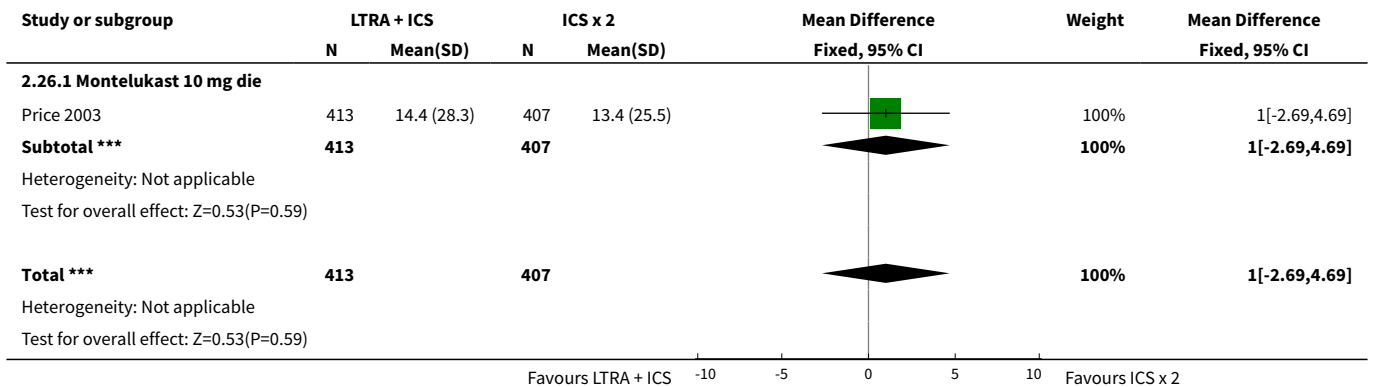
Analysis 2.24. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 24 Death at LICENSED DOSES.



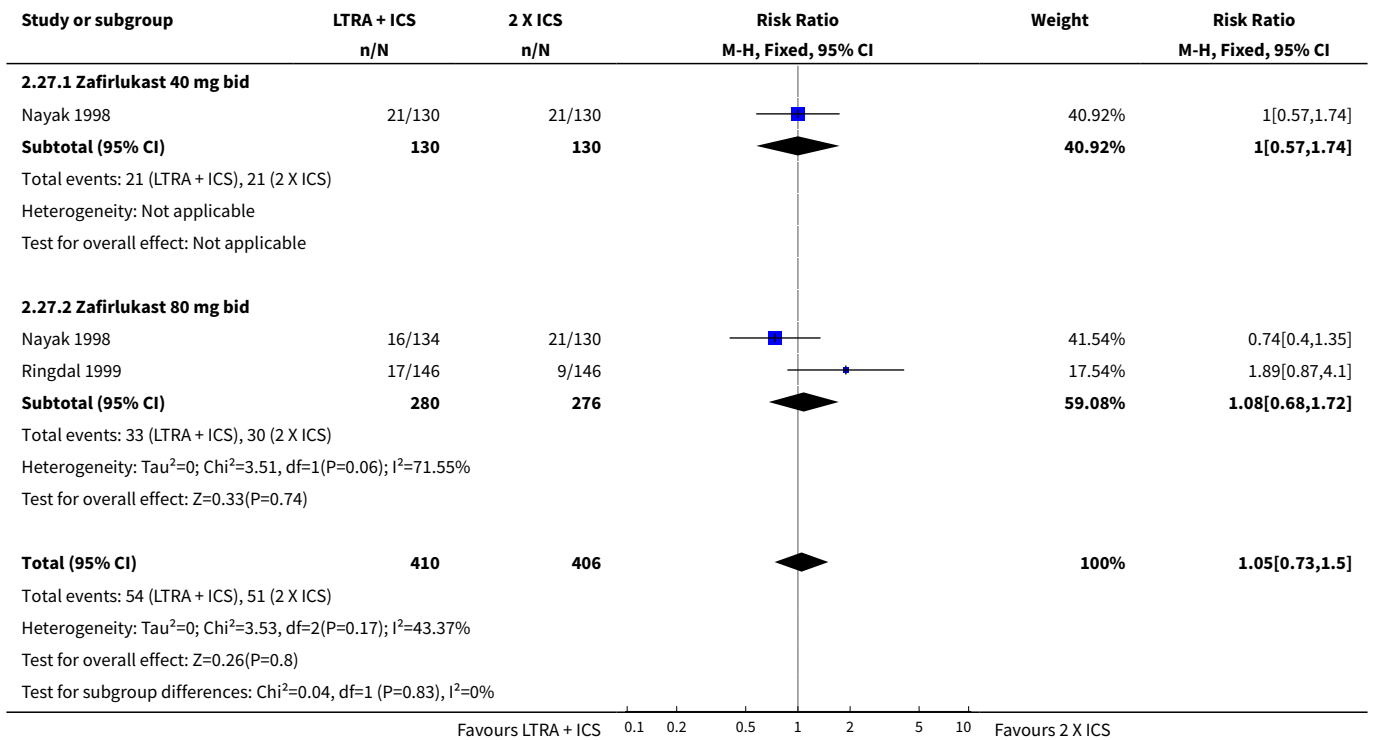
Analysis 2.25. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 25 Patients with 1 or more exacerbations requiring hospital admission at HIGHER THAN LICENSED DOSES.



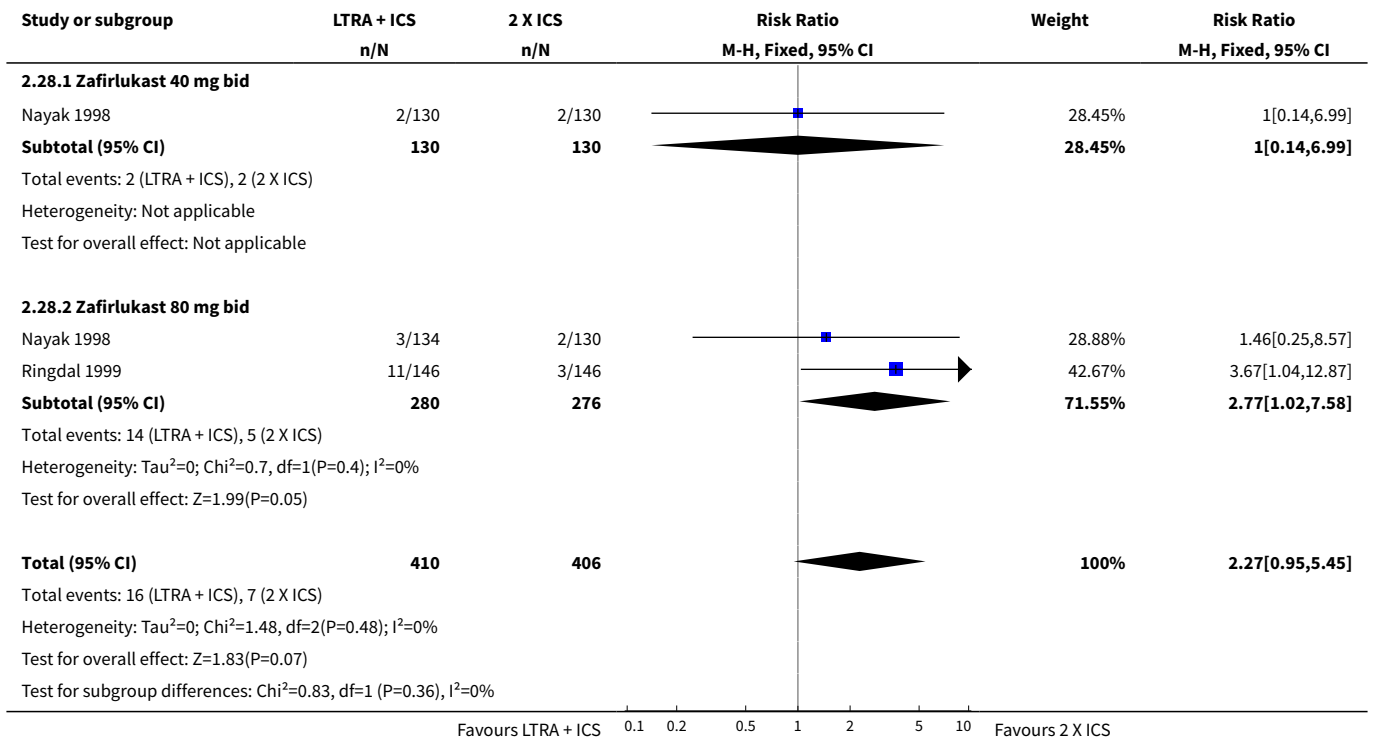
Analysis 2.26. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 26 Nighttime awakenings/week at USUAL LICENSED DOSES at 12 weeks.



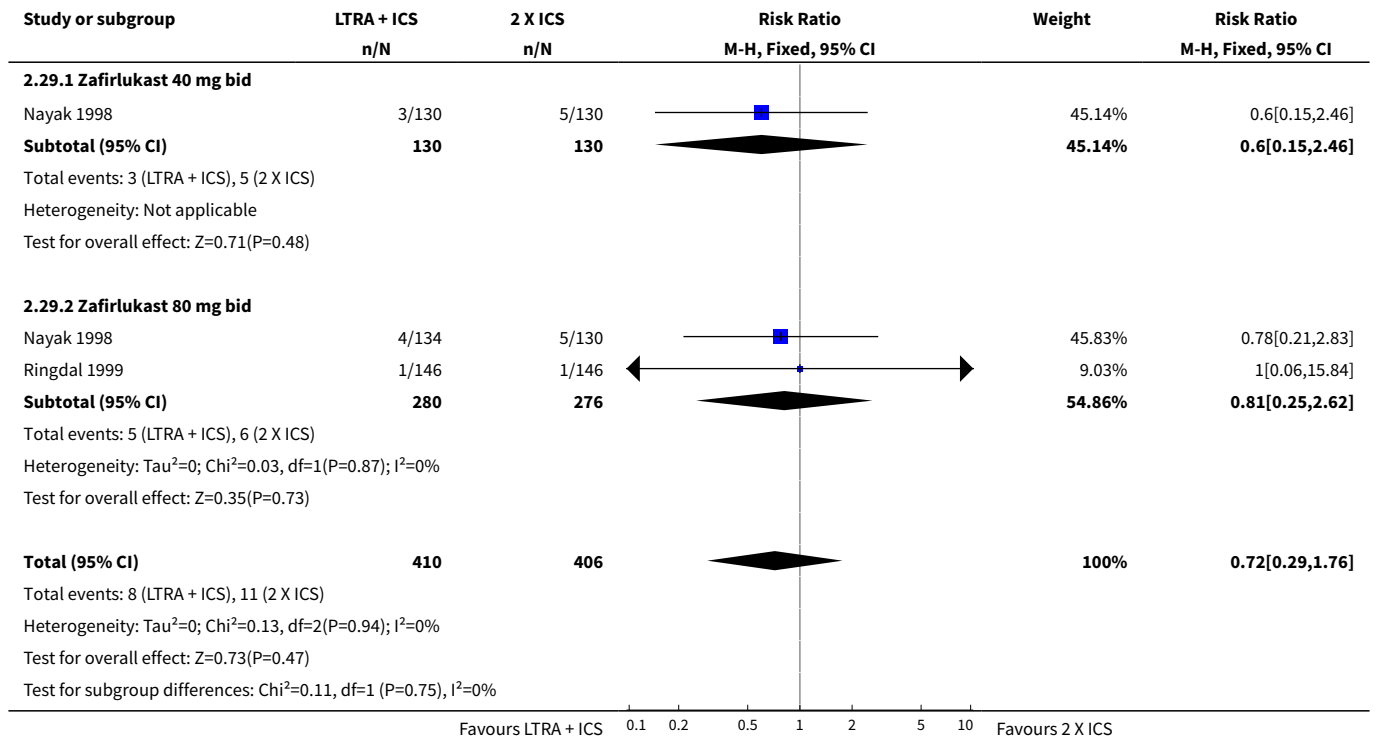
Analysis 2.27. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 27 Overall withdrawals at HIGHER THAN LICENSED DOSES.



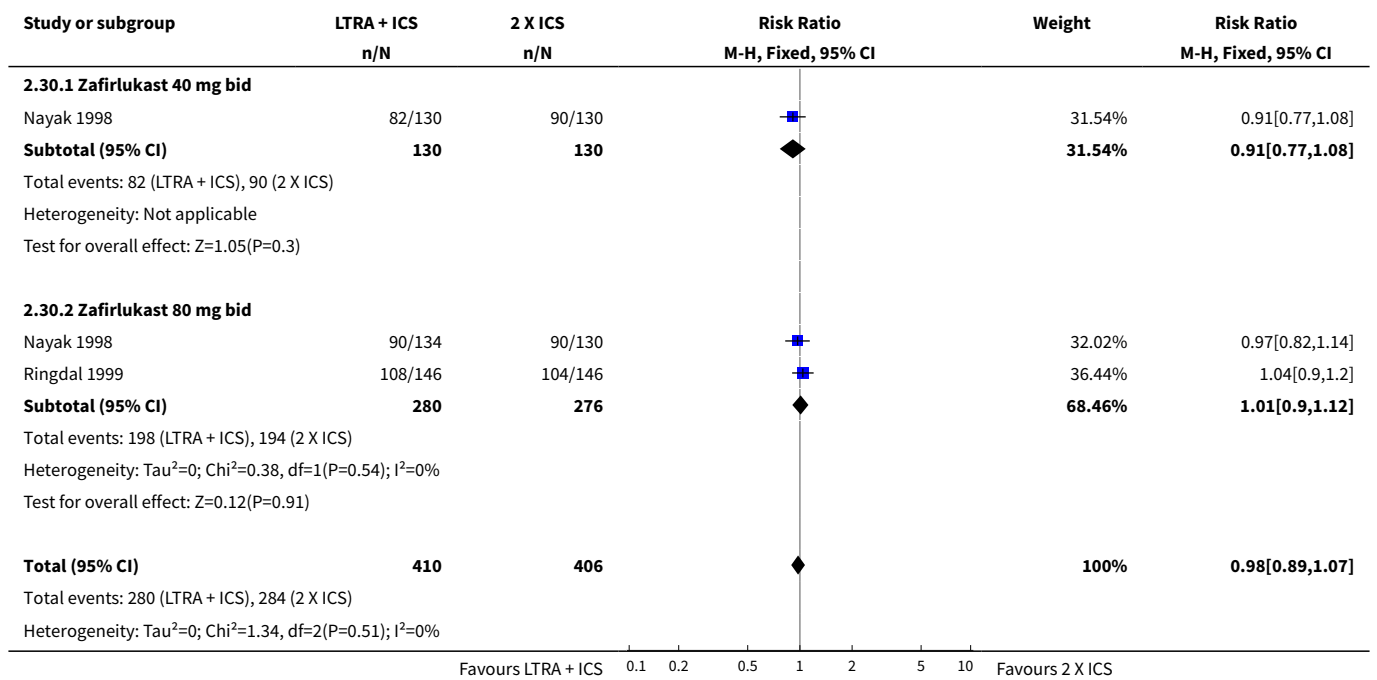
Analysis 2.28. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 28 Withdrawals due to adverse effects at HIGHER THAN LICENSED DOSES.



Analysis 2.29. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 29 Withdrawals due to poor asthma control/exacerbations at HIGHER THAN LICENSED DOSES.



Analysis 2.30. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 30 Overall adverse effects at HIGHER THAN LICENSED DOSES.



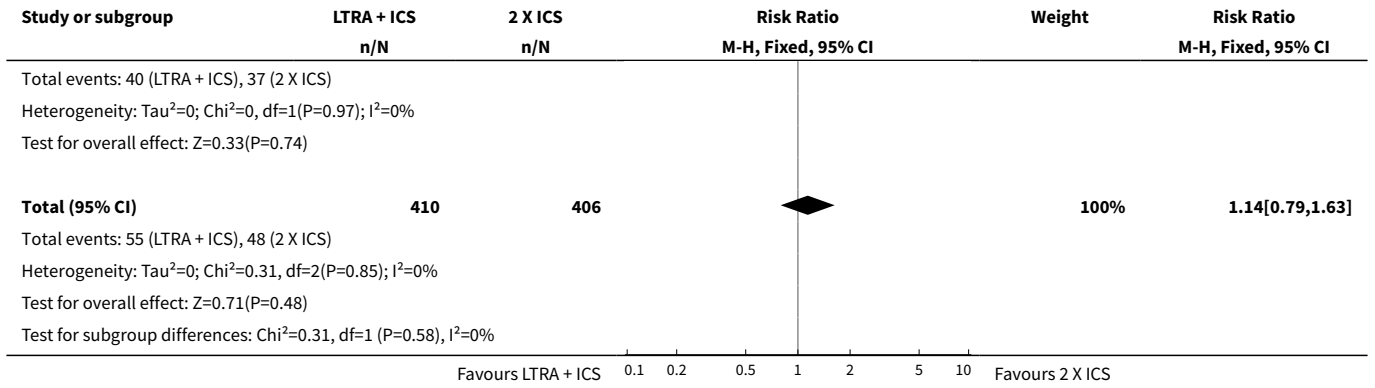
Study or subgroup	LTRA + ICS n/N	2 X ICS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi ² =0.91, df=1 (P=0.34), I ² =0%					
Favours LTRA + ICS 0.1 0.2 0.5 1 2 5 10 Favours 2 X ICS					

Analysis 2.31. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 31 Elevated liver enzymes at HIGHER THAN LICENSED DOSES.

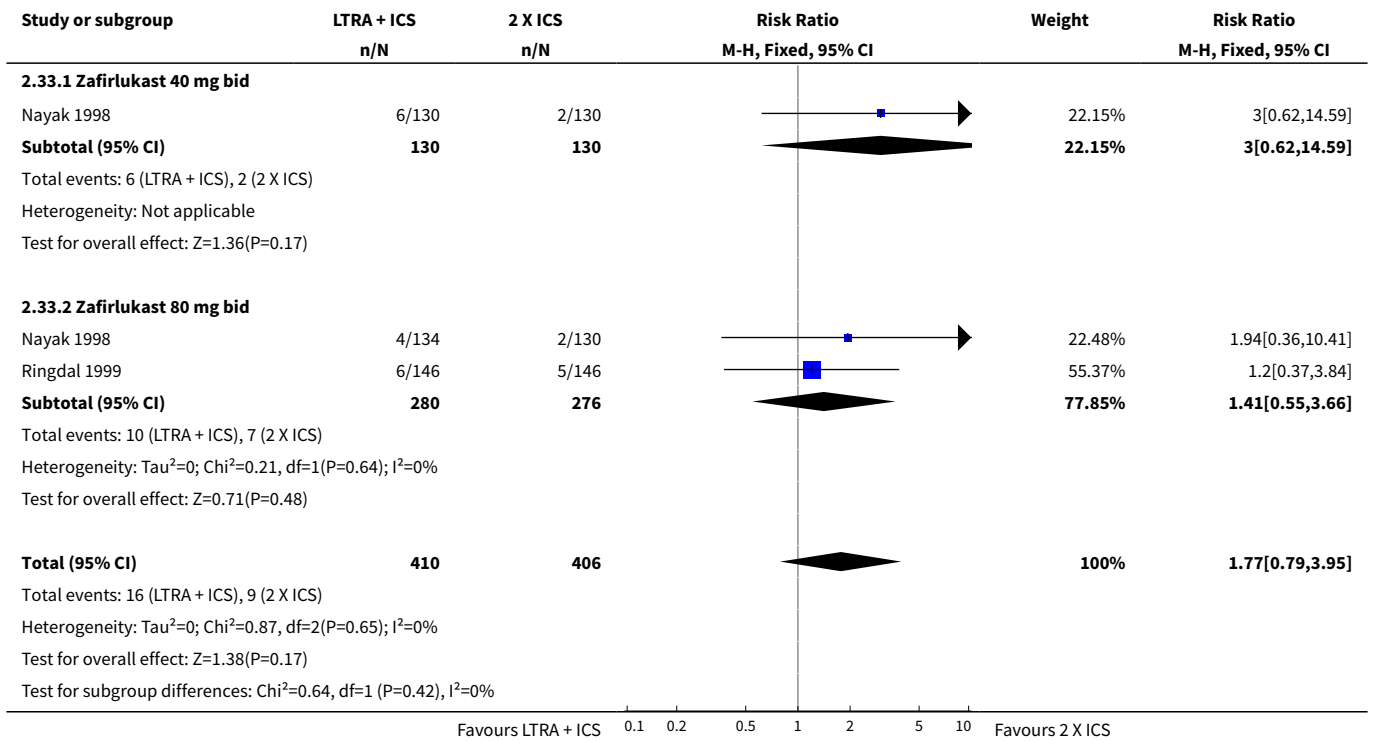
Study or subgroup	LTRA + ICS n/N	2 X ICS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.31.1 Zafirlukast 40 mg bid					
Nayak 1998	1/130	0/130		16.63%	3[0.12,72.97]
Subtotal (95% CI)	130	130		16.63%	3[0.12,72.97]
Total events: 1 (LTRA + ICS), 0 (2 X ICS)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
2.31.2 Zafirlukast 80 mg bid					
Nayak 1998	4/134	0/130		16.88%	8.73[0.47,160.61]
Ringdal 1999	9/146	2/146		66.5%	4.5[0.99,20.47]
Subtotal (95% CI)	280	276		83.38%	5.36[1.4,20.44]
Total events: 13 (LTRA + ICS), 2 (2 X ICS)					
Heterogeneity: Tau ² =0; Chi ² =0.16, df=1(P=0.69); I ² =0%					
Test for overall effect: Z=2.46(P=0.01)					
Total (95% CI)	410	406		100%	4.97[1.45,17]
Total events: 14 (LTRA + ICS), 2 (2 X ICS)					
Heterogeneity: Tau ² =0; Chi ² =0.26, df=2(P=0.88); I ² =0%					
Test for overall effect: Z=2.55(P=0.01)					
Test for subgroup differences: Chi ² =0.11, df=1 (P=0.74), I ² =0%					
Favours LTRA + ICS 0.1 0.2 0.5 1 2 5 10 Favours 2 X ICS					

Analysis 2.32. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 32 Headache at HIGHER THAN LICENSED DOSES.

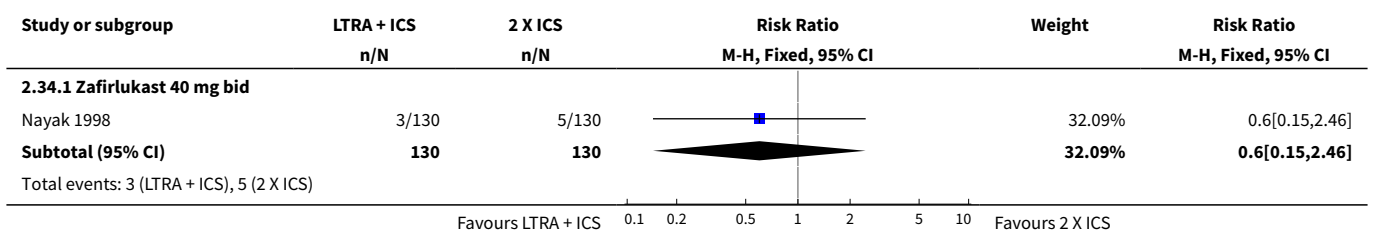
Study or subgroup	LTRA + ICS n/N	2 X ICS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.32.1 Zafirlukast 40 mg bid					
Nayak 1998	15/130	11/130		22.84%	1.36[0.65,2.86]
Subtotal (95% CI)	130	130		22.84%	1.36[0.65,2.86]
Total events: 15 (LTRA + ICS), 11 (2 X ICS)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
2.32.2 Zafirlukast 80 mg bid					
Nayak 1998	12/134	11/130		23.18%	1.06[0.48,2.31]
Ringdal 1999	28/146	26/146		53.98%	1.08[0.67,1.74]
Subtotal (95% CI)	280	276		77.16%	1.07[0.71,1.62]
Favours LTRA + ICS 0.1 0.2 0.5 1 2 5 10 Favours 2 X ICS					

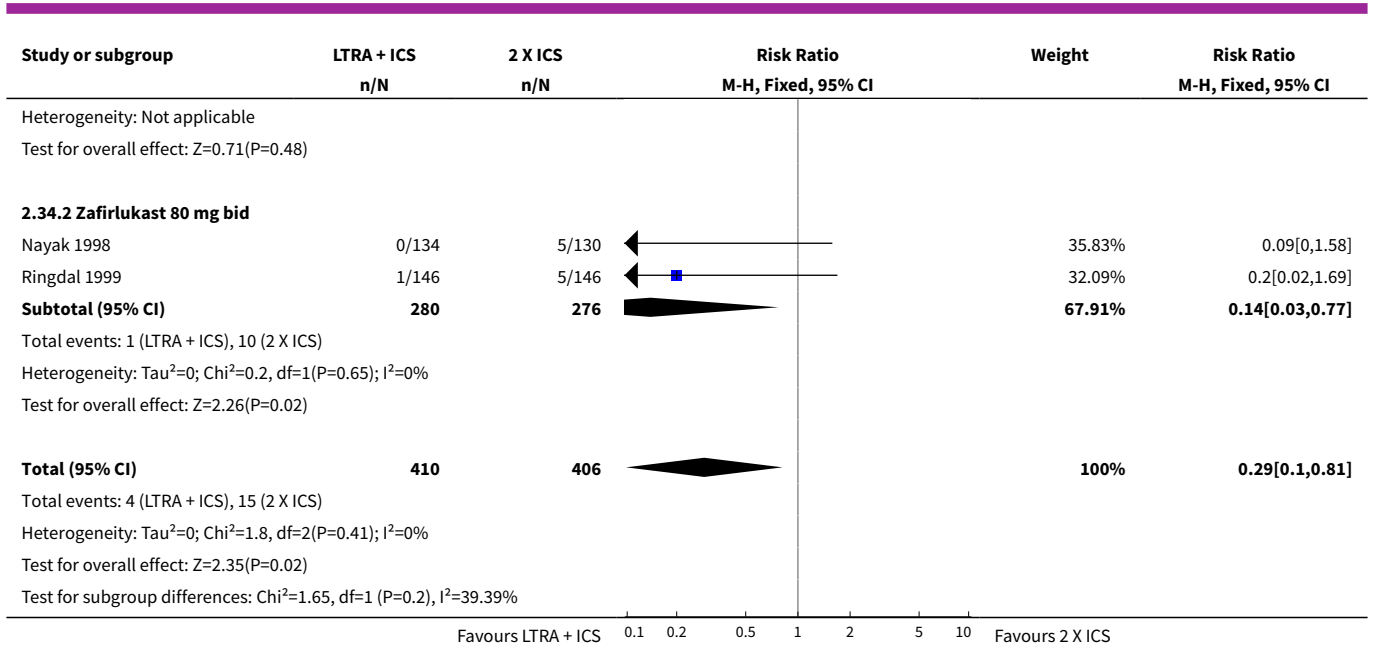


Analysis 2.33. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 33 Nausea at HIGHER THAN LICENSED DOSES.

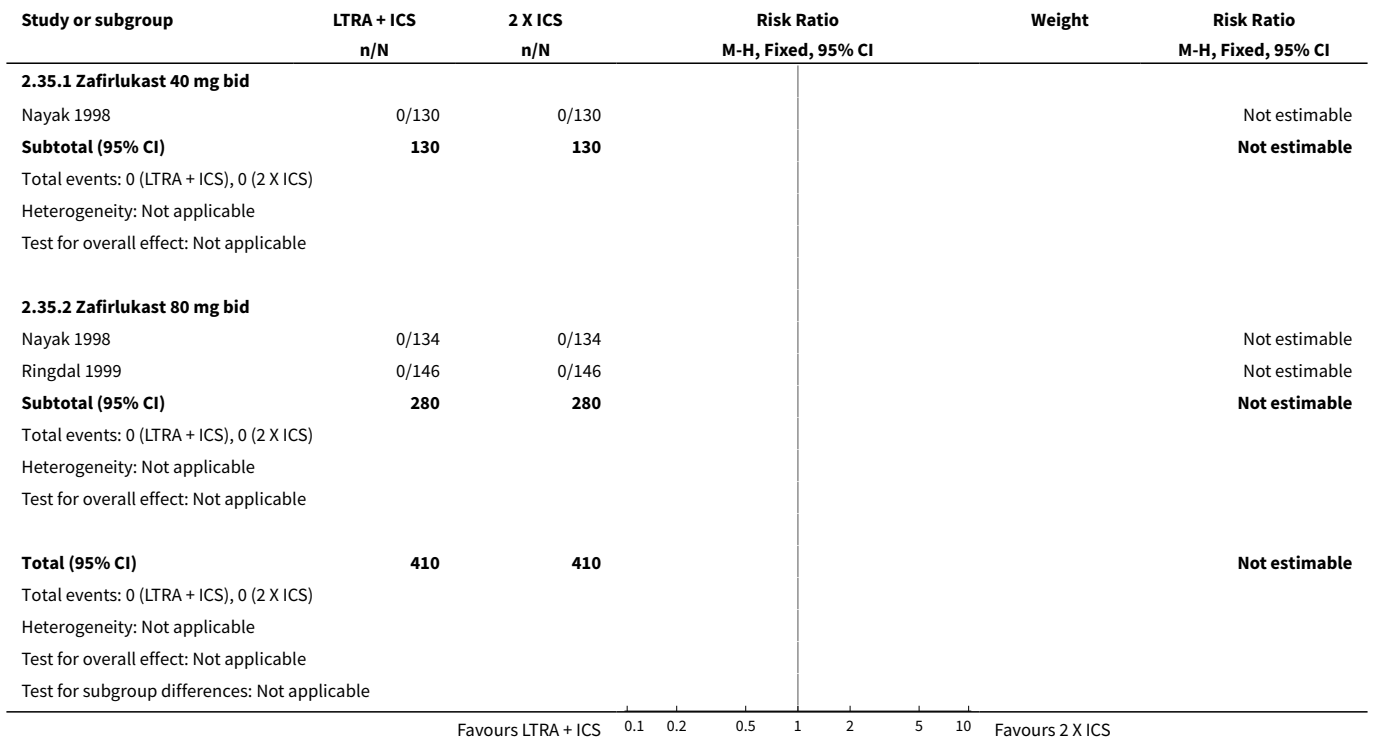


Analysis 2.34. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 34 Oral moniliasis at HIGHER THAN LICENSED DOSES.





Analysis 2.35. Comparison 2 Leukotriene Receptor Antagonists (LTRA) + ICS vs. DOUBLE dose of ICS in SYMPTOMATIC PATIENTS, Outcome 35 Death at HIGHER THAN LICENSED DOSES.



Comparison 3. Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients

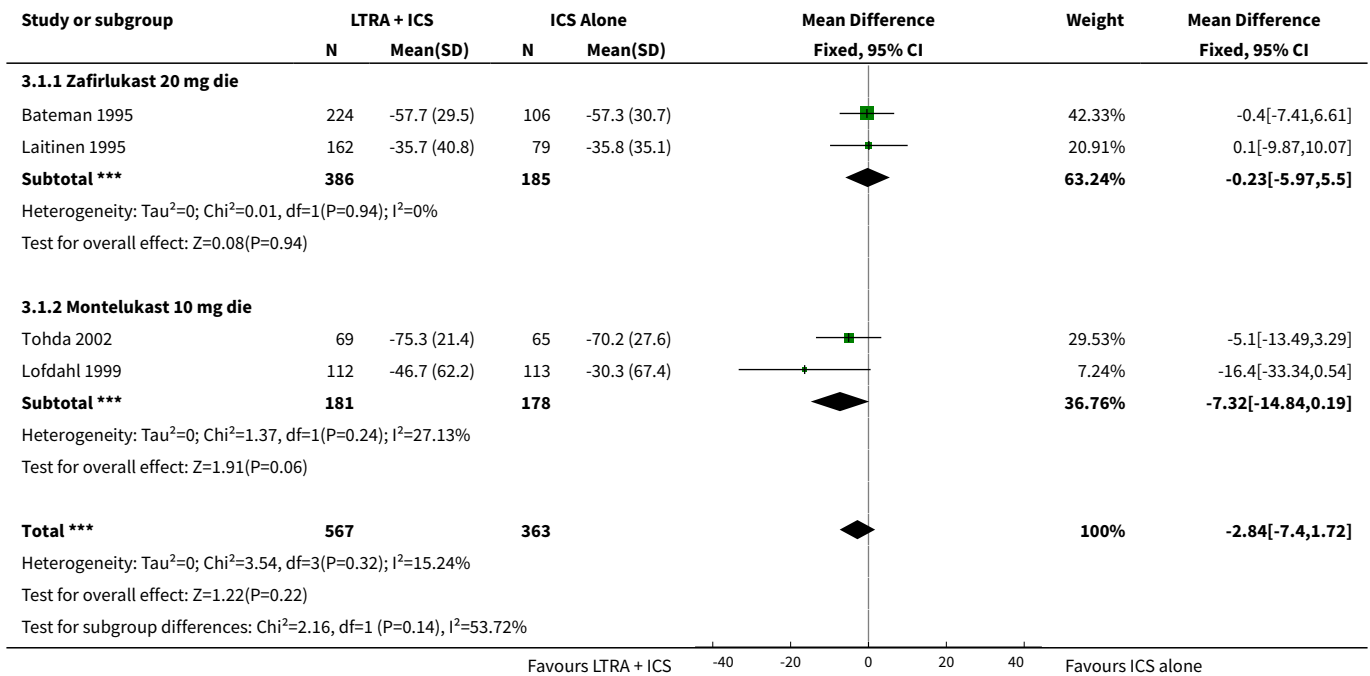
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % Change from baseline ICS dose at 12 -24 weeks	4	930	Mean Difference (IV, Fixed, 95% CI)	-2.84 [-7.40, 1.72]
1.1 Zafirlukast 20 mg die	2	571	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-5.97, 5.50]
1.2 Montelukast 10 mg die	2	359	Mean Difference (IV, Fixed, 95% CI)	-7.32 [-14.84, 0.19]
2 Last ICS dose tolerated (mcg) at 12 -24 weeks	4	932	Mean Difference (IV, Random, 95% CI)	-40.65 [-111.22, 29.93]
2.1 Zafirlukast 20 mg die	2	573	Mean Difference (IV, Random, 95% CI)	5.60 [-47.22, 58.43]
2.2 Montelukast 10 mg die	2	359	Mean Difference (IV, Random, 95% CI)	-103.32 [-235.02, 28.37]
3 Change from baseline in ICS dose (mcg)	1	134	Mean Difference (IV, Fixed, 95% CI)	66.95 [-25.41, 159.31]
3.1 Montelukast 10 mg die	1	134	Mean Difference (IV, Fixed, 95% CI)	66.95 [-25.41, 159.31]
4 Complete withdrawal from ICS	3	607	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.95, 1.47]
4.1 Zafirlukast 20 mg bid	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]
4.2 Montelukast 10 mg	2	248	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.97, 1.96]
5 Final FEV1 (L) at lowest tolerated dose (at 12 -20 weeks)	2	621	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.02, 0.27]
5.1 Zafirlukast 20 mg bid	2	621	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.02, 0.27]
6 Change from baseline in FEV1 (L) at lowest tolerated dose (at 6-24 weeks)	2	164	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.10, 0.09]
6.1 Montelukast 10 mg die	2	164	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.10, 0.09]
7 Final Am PEFR (L/min) at 12 -20 weeks	2	500	Mean Difference (IV, Fixed, 95% CI)	17.98 [-1.68, 37.64]
7.1 Zafirlukast 20 mg bid	2	500	Mean Difference (IV, Fixed, 95% CI)	17.98 [-1.68, 37.64]
8 Change from baseline in morning PEFR (L/min) at lowest tolerated dose	2	183	Mean Difference (IV, Fixed, 95% CI)	7.90 [-1.61, 17.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Montelukast 10 mg die	2	183	Mean Difference (IV, Fixed, 95% CI)	7.90 [-1.61, 17.40]
9 Final mean symptom scores (episodes/week) at 12 -20 weeks	2	487	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.17, 0.05]
9.1 Zafirlukast 20 mg bid	2	487	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.17, 0.05]
10 Change in symptom scores at 6-24 weeks	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-0.79, -0.21]
10.1 Montelukast 10 mg bid	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-0.79, -0.21]
11 Final mean daily use of B2-agonists (puffs/day) at lowest tolerated dose (at 12-20 weeks)	2	496	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.73, 0.32]
11.1 Zafirlukast 20 mg bid	2	496	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.73, 0.32]
12 Absolute change in mean daily use of B2-agonists (puffs/week) at lowest tolerated dose (at 6-24 weeks)	3	409	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.76, 0.52]
12.1 Montelukast 10 mg die	3	409	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.76, 0.52]
13 Change in serum eosinophils at lowest tolerated dose (at 6- 24 weeks)	2	167	Mean Difference (IV, Fixed, 95% CI)	0.18 [-1.13, 1.50]
13.1 Montelukast 10 mg die	2	167	Mean Difference (IV, Fixed, 95% CI)	0.18 [-1.13, 1.50]
14 Patients with 1 or more exacerbations requiring systemic steroids	4	502	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.09]
14.1 Zafirlukast 20 mg bid	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.41]
14.2 Montelukast 10 mg die	3	240	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.17, 1.25]
15 Patients with 1 or more exacerbations requiring hospital admission	2	231	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Montelukast 10 mg die	2	231	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Overall withdrawals	6	1110	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.98]
16.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.34]

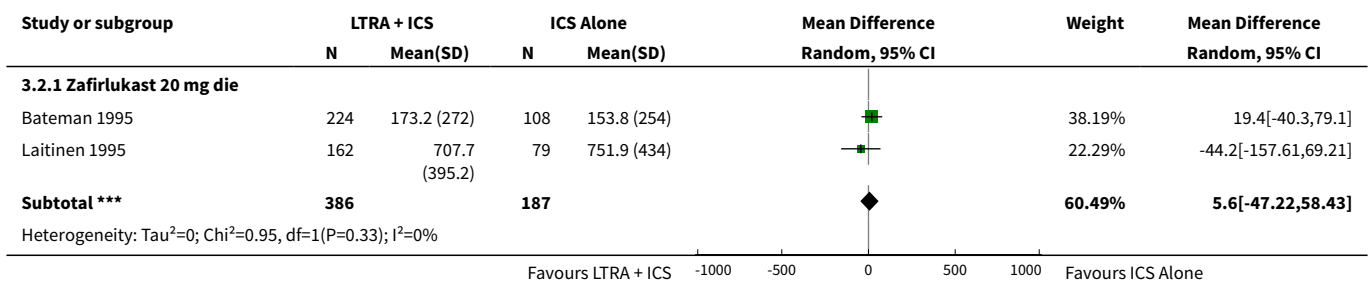
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Montelukast 10 mg die	4	489	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.89]
17 Withdrawals due to adverse effects	6	1110	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.51]
17.1 Zafirlukast 20mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.73, 3.82]
17.2 Montelukast 10 mg die	4	489	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.23, 1.05]
18 Withdrawals due to poor asthma control/exacerbations	6	1110	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.42, 0.95]
18.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.21, 2.59]
18.2 Montelukast 10 mg die	4	489	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.95]
19 Overall adverse effects	6	1100	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.08]
19.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.09]
19.2 Montelukast 10 mg die	4	479	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.25]
20 Serious adverse events	2	621	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.53, 3.97]
20.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.53, 3.97]
21 Elevated liver enzymes	6	1099	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.86, 3.21]
21.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [0.75, 10.68]
21.2 Montelukast 10 mg die	4	478	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.79]
22 Headache	6	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.08]
22.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.56, 1.28]
22.2 Montelukast 10 mg die	4	479	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.16]
23 Nausea	6	1100	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.70, 3.19]
23.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.52, 3.27]
23.2 Montelukast 10 mg die	4	479	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.50, 7.86]
24 Death	6	1100	Risk Ratio (M-H, Fixed, 95% CI)	3.1 [0.13, 75.10]
24.1 Zafirlukast 20 mg bid	2	621	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Montelukast 10 mg die	4	479	Risk Ratio (M-H, Fixed, 95% CI)	3.1 [0.13, 75.10]

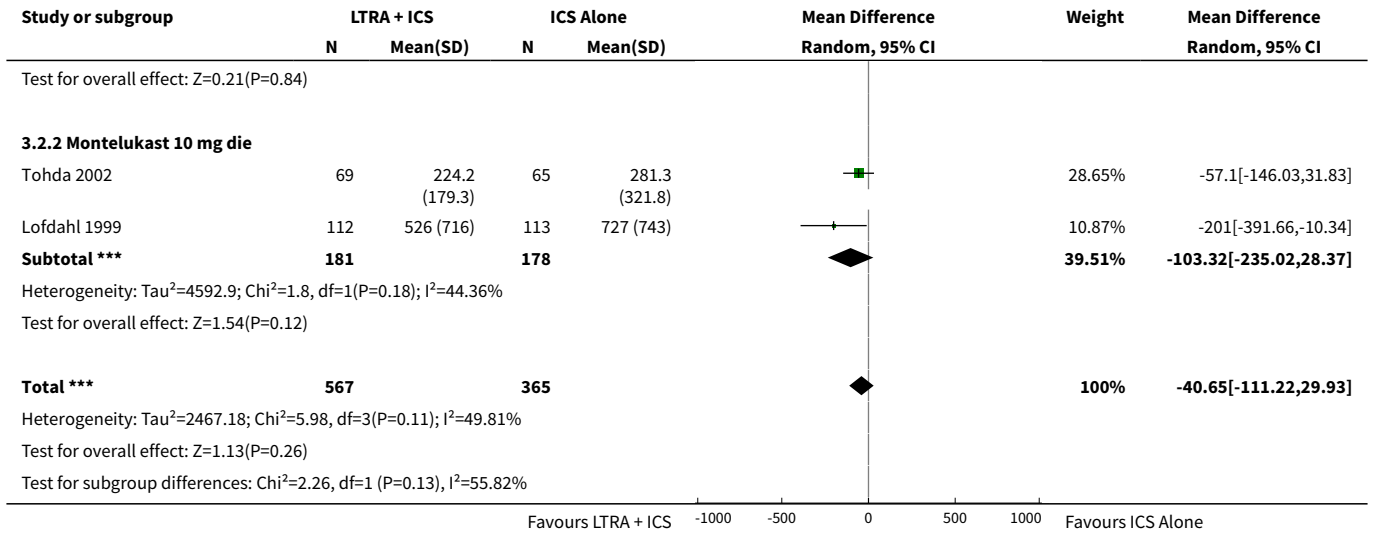
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Patients unable to taper inhaled corticosteroids	1	226	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.11]
25.1 Montelukast 10 mg	1	226	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.11]
26 Change in expired NO concentration (ppb) at 6 weeks	1	50	Mean Difference (IV, Fixed, 95% CI)	0.03 [-3.45, 3.51]
26.1 Montelukast 10 mg die	1	50	Mean Difference (IV, Fixed, 95% CI)	0.03 [-3.45, 3.51]

Analysis 3.1. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 1 % Change from baseline ICS dose at 12 -24 weeks.

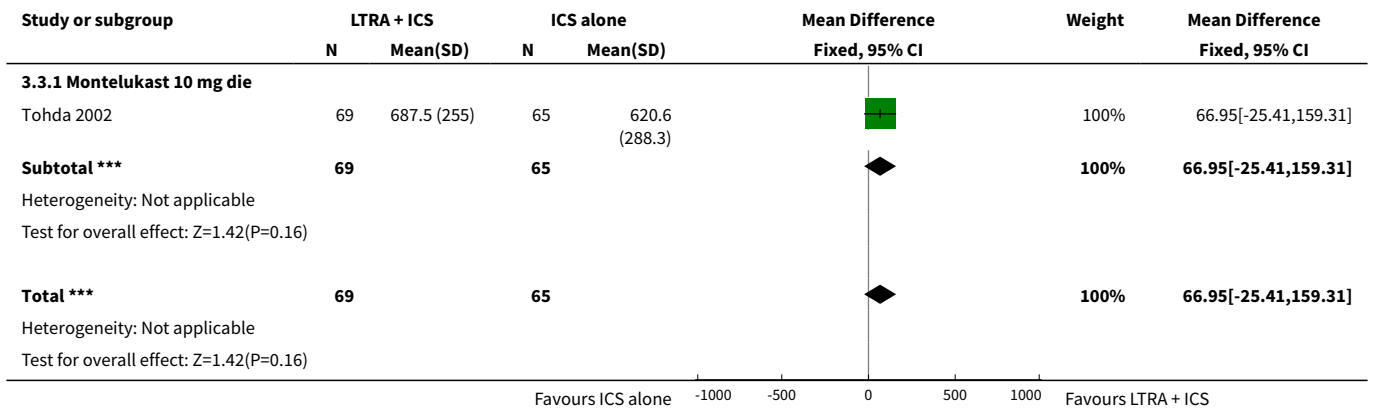


Analysis 3.2. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 2 Last ICS dose tolerated (mcg) at 12 -24 weeks.

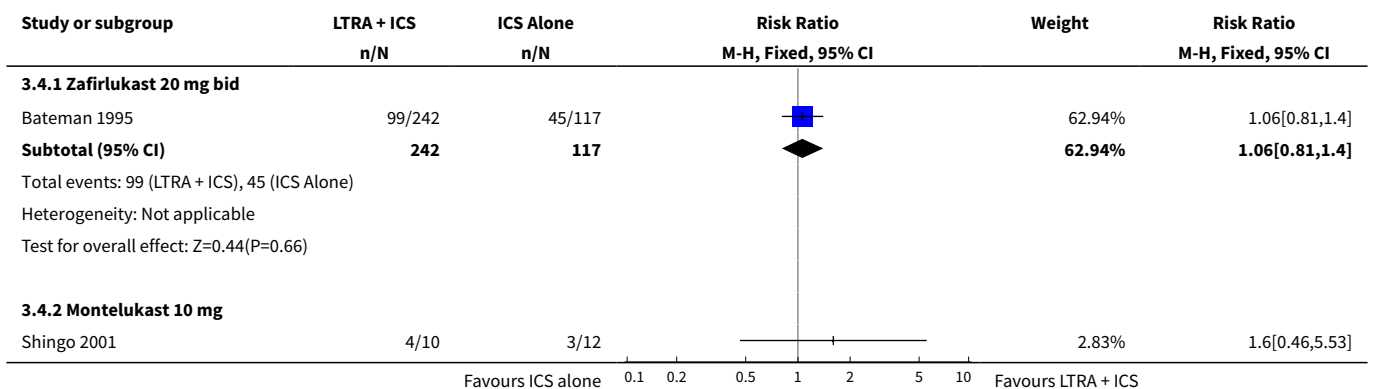


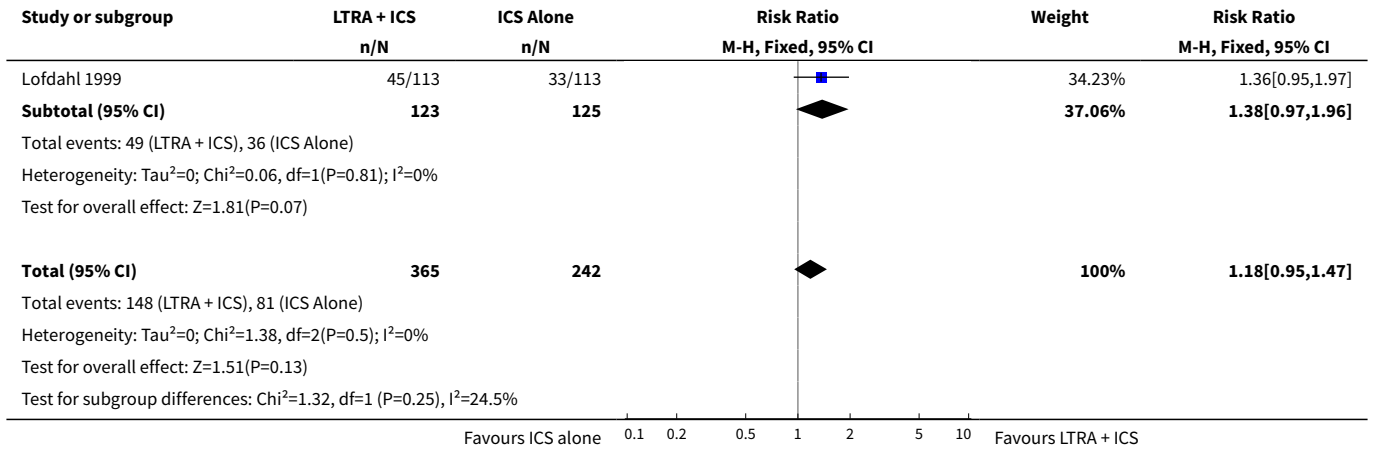


Analysis 3.3. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 3 Change from baseline in ICS dose (mcg).

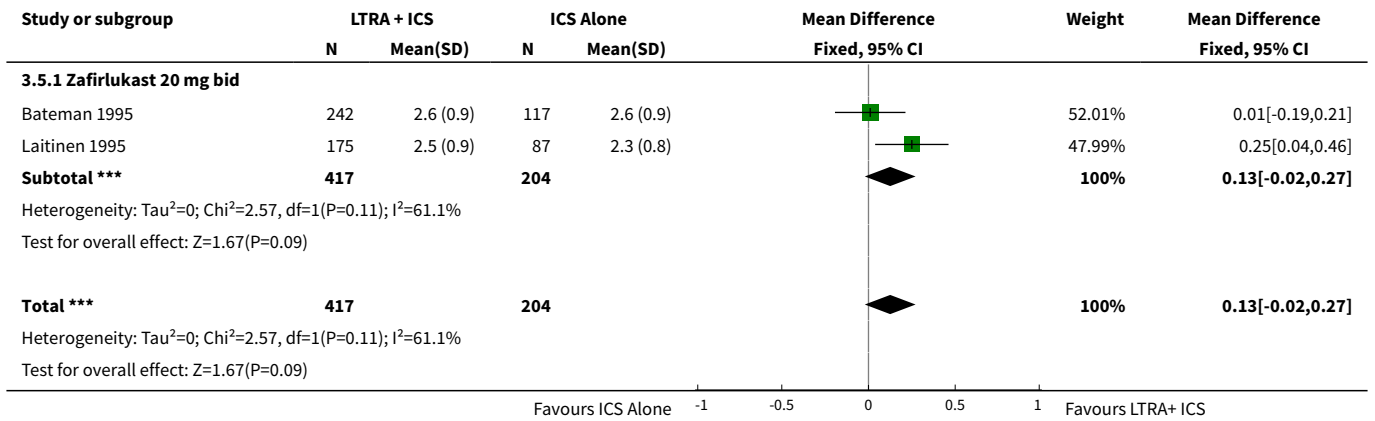


Analysis 3.4. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 4 Complete withdrawal from ICS.

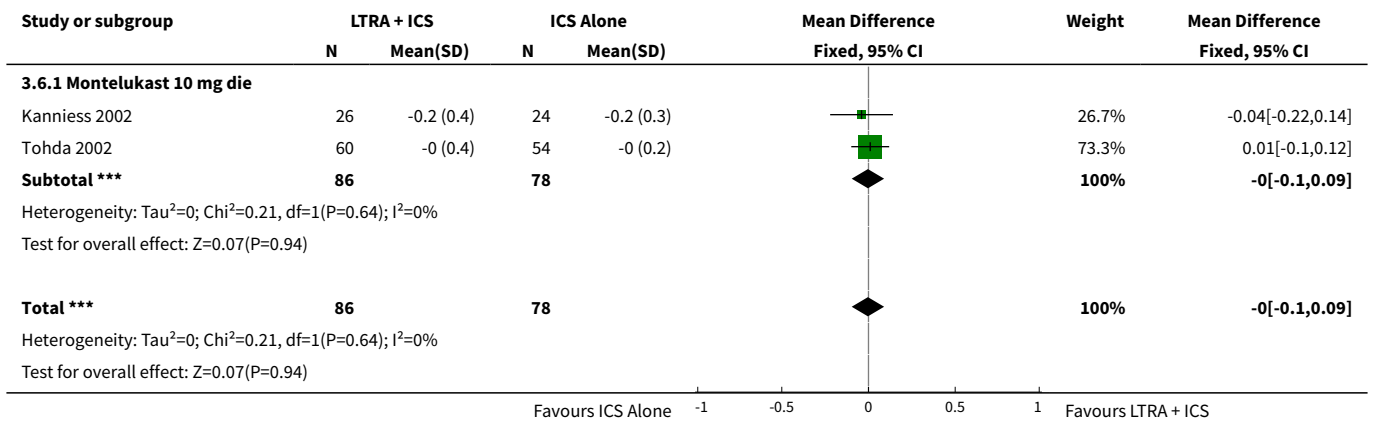




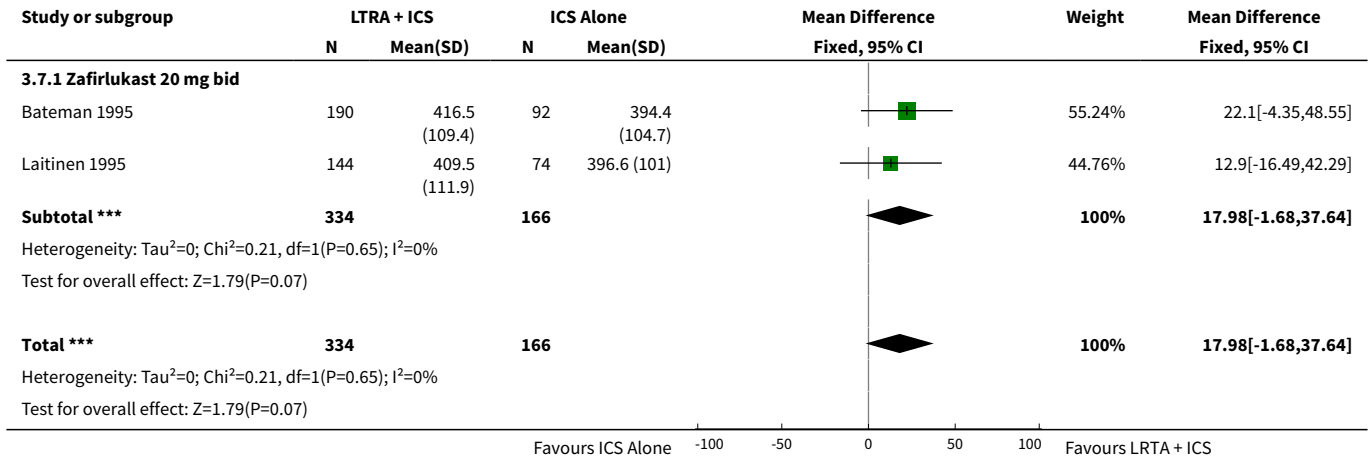
Analysis 3.5. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 5 Final FEV1 (L) at lowest tolerated dose (at 12 -20 weeks).



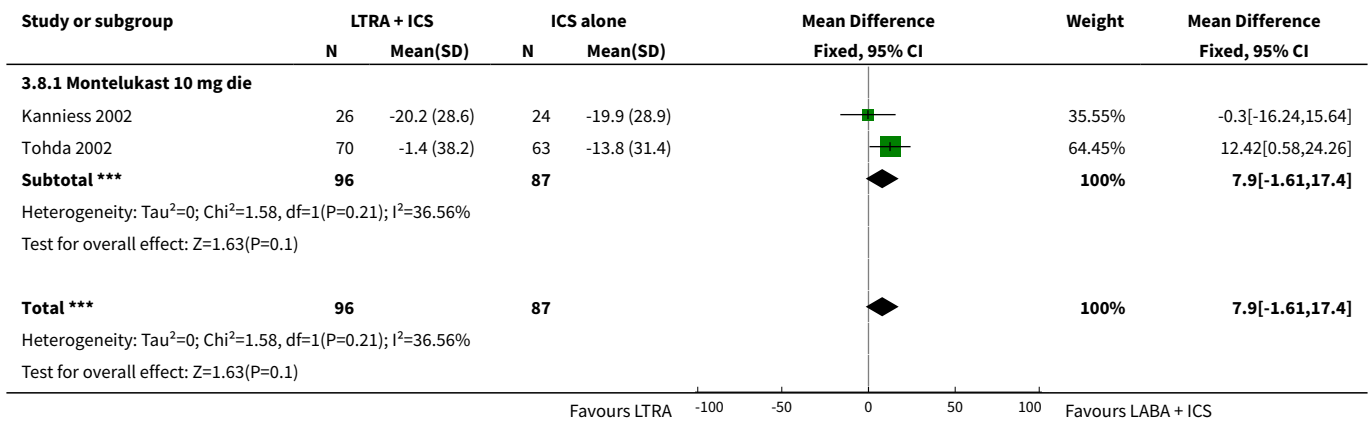
Analysis 3.6. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 6 Change from baseline in FEV1 (L) at lowest tolerated dose (at 6-24 weeks).



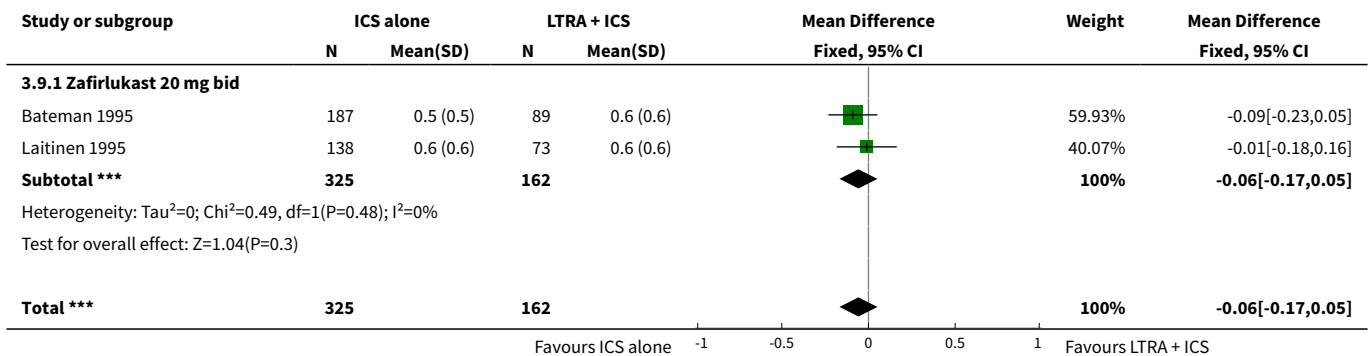
Analysis 3.7. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 7 Final Am PEFR (L/min) at 12 -20 weeks.

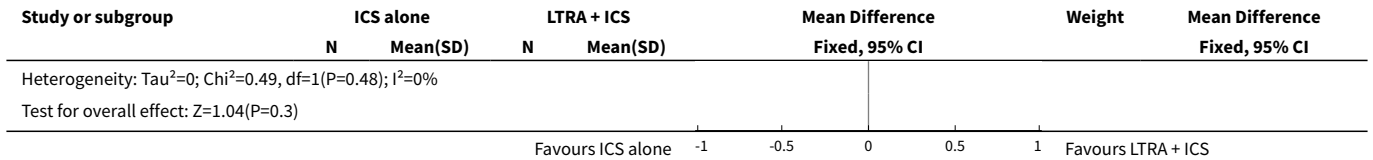


Analysis 3.8. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 8 Change from baseline in morning PEFR (L/min) at lowest tolerated dose.

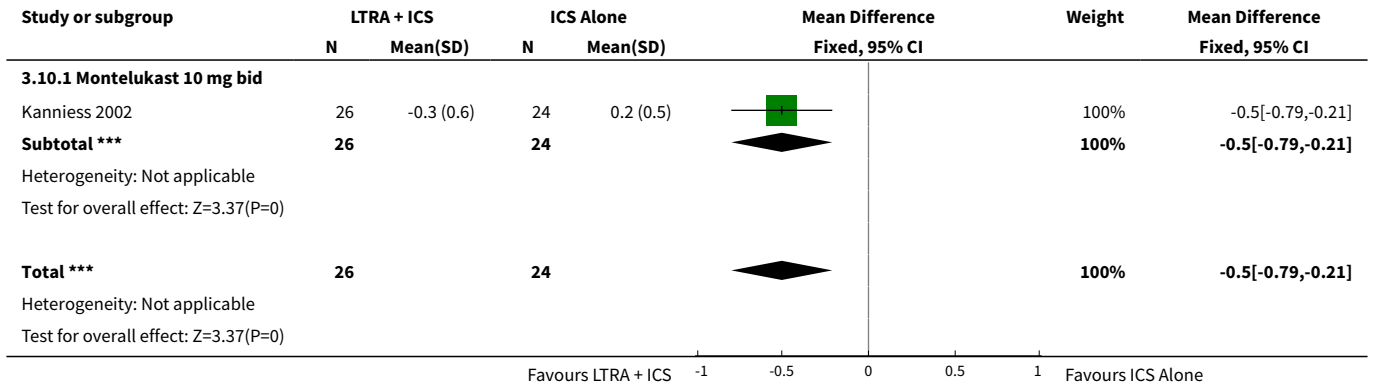


Analysis 3.9. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 9 Final mean symptom scores (episodes/week) at 12 -20 weeks.

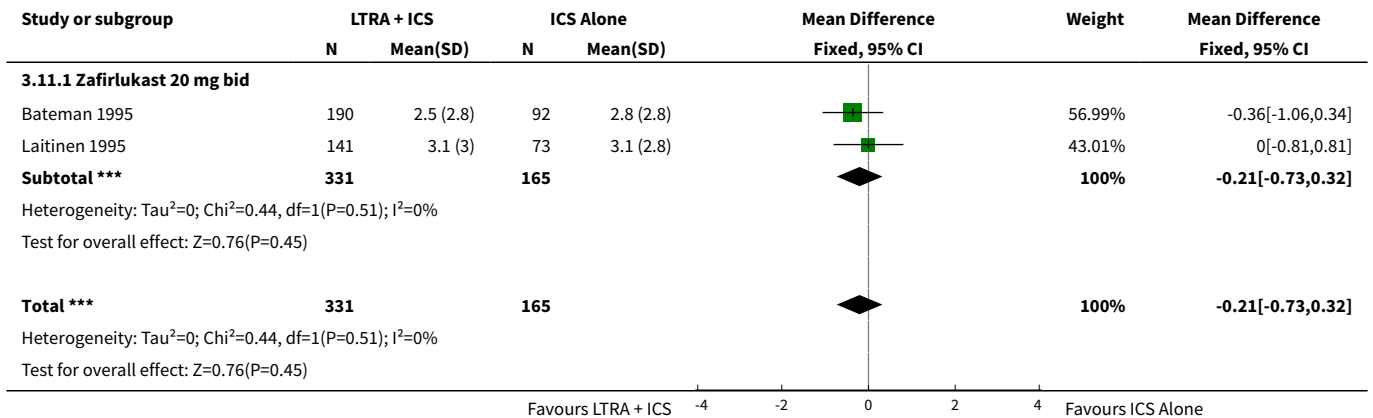




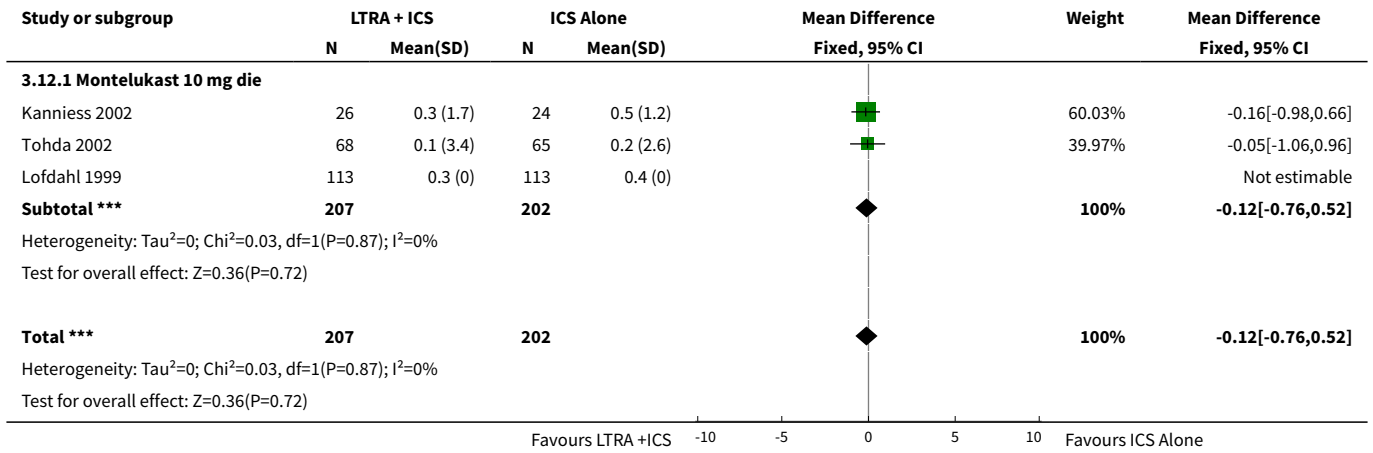
Analysis 3.10. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 10 Change in symptom scores at 6-24 weeks.



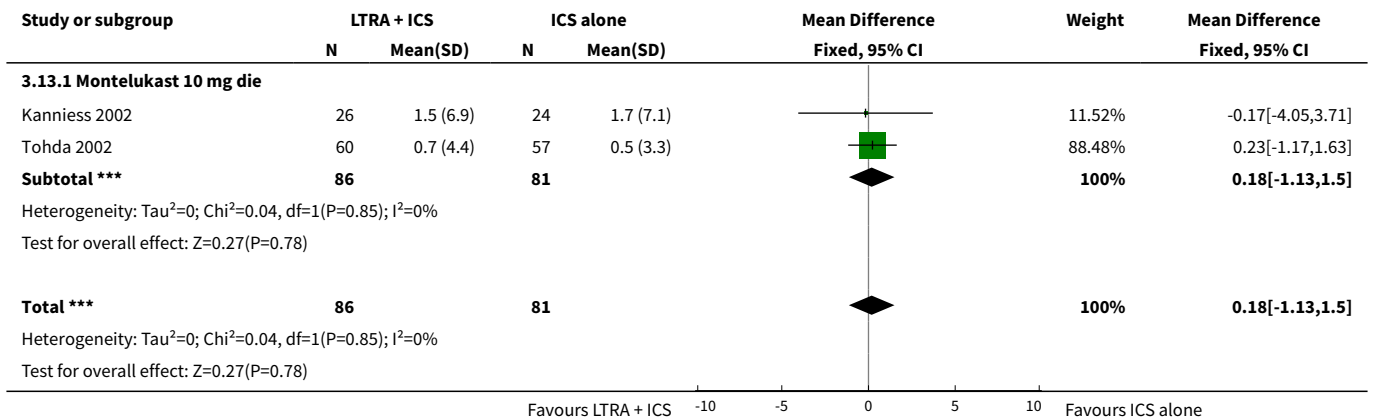
Analysis 3.11. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 11 Final mean daily use of B2-agonists (puffs/day) at lowest tolerated dose (at 12-20 weeks).



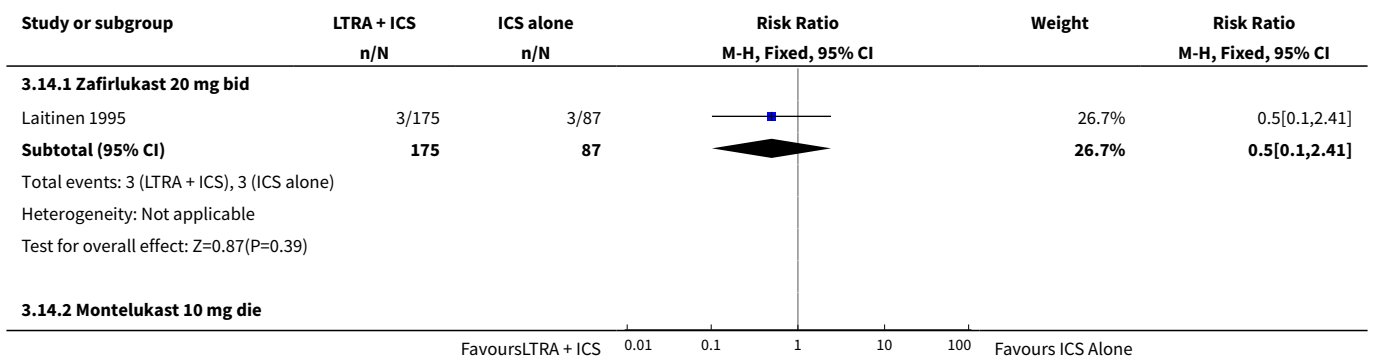
Analysis 3.12. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 12 Absolute change in mean daily use of B2-agonists (puffs/week) at lowest tolerated dose (at 6-24 weeks).

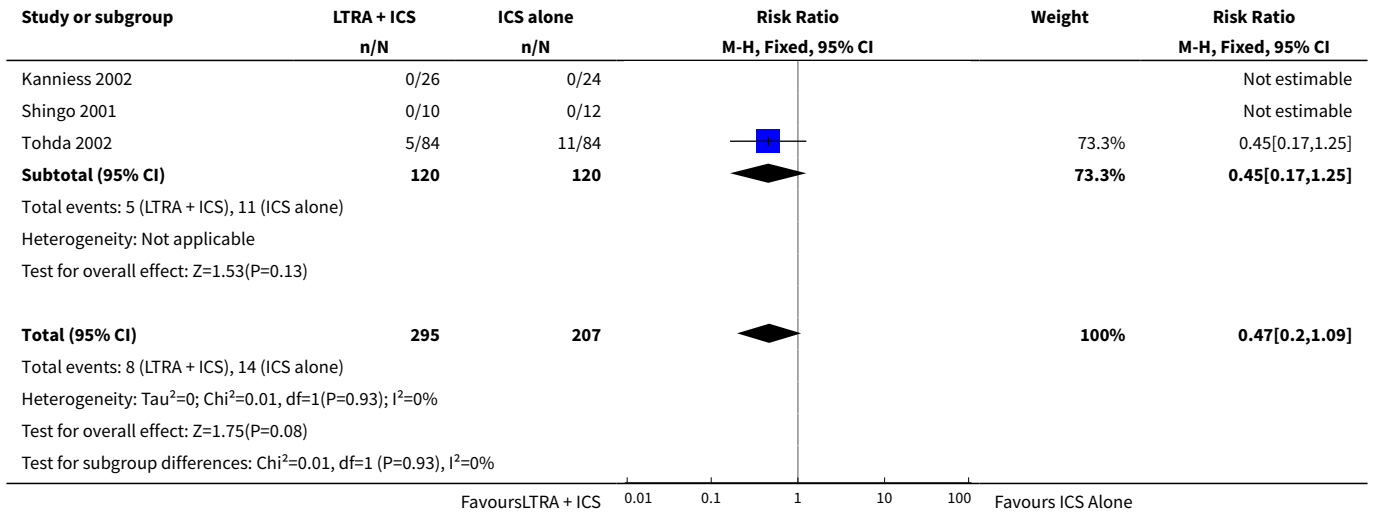


Analysis 3.13. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 13 Change in serum eosinophils at lowest tolerated dose (at 6- 24 weeks).

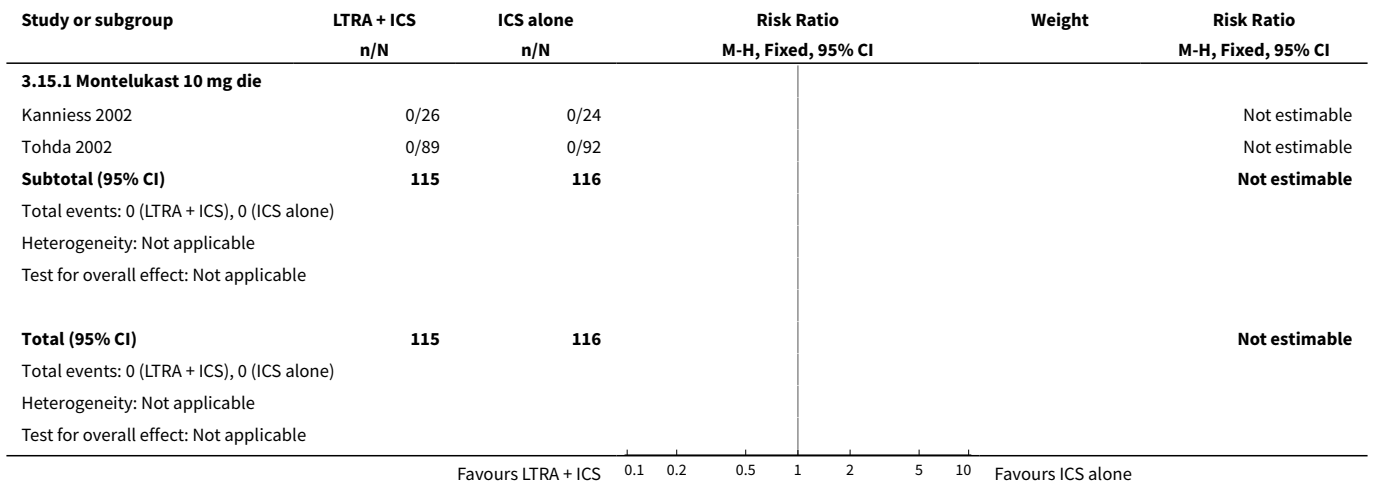


Analysis 3.14. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 14 Patients with 1 or more exacerbations requiring systemic steroids.

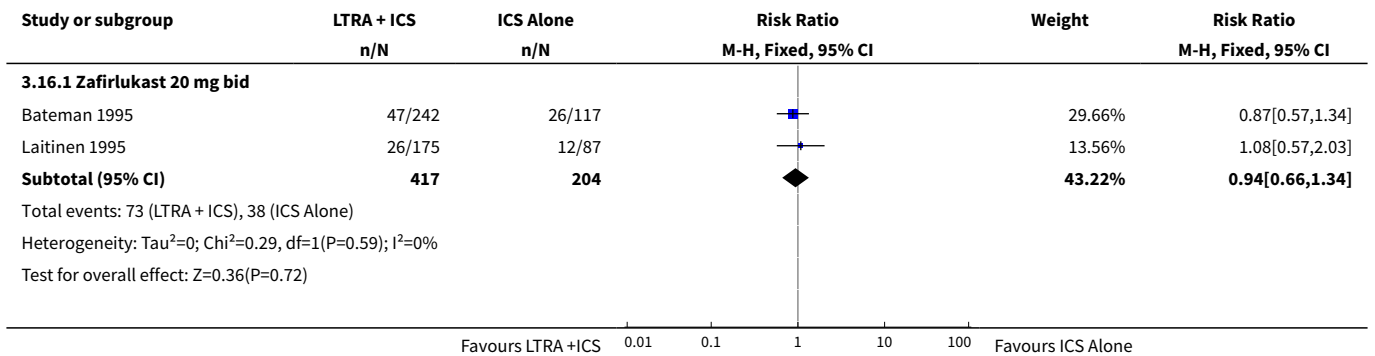


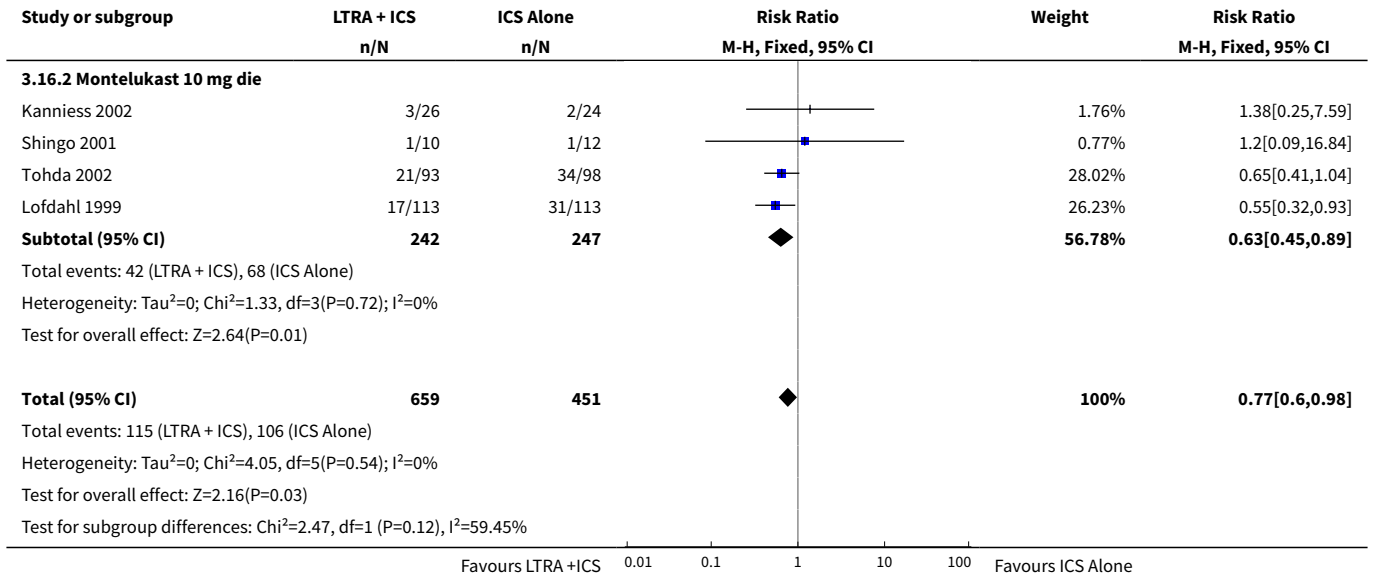


Analysis 3.15. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 15 Patients with 1 or more exacerbations requiring hospital admission.

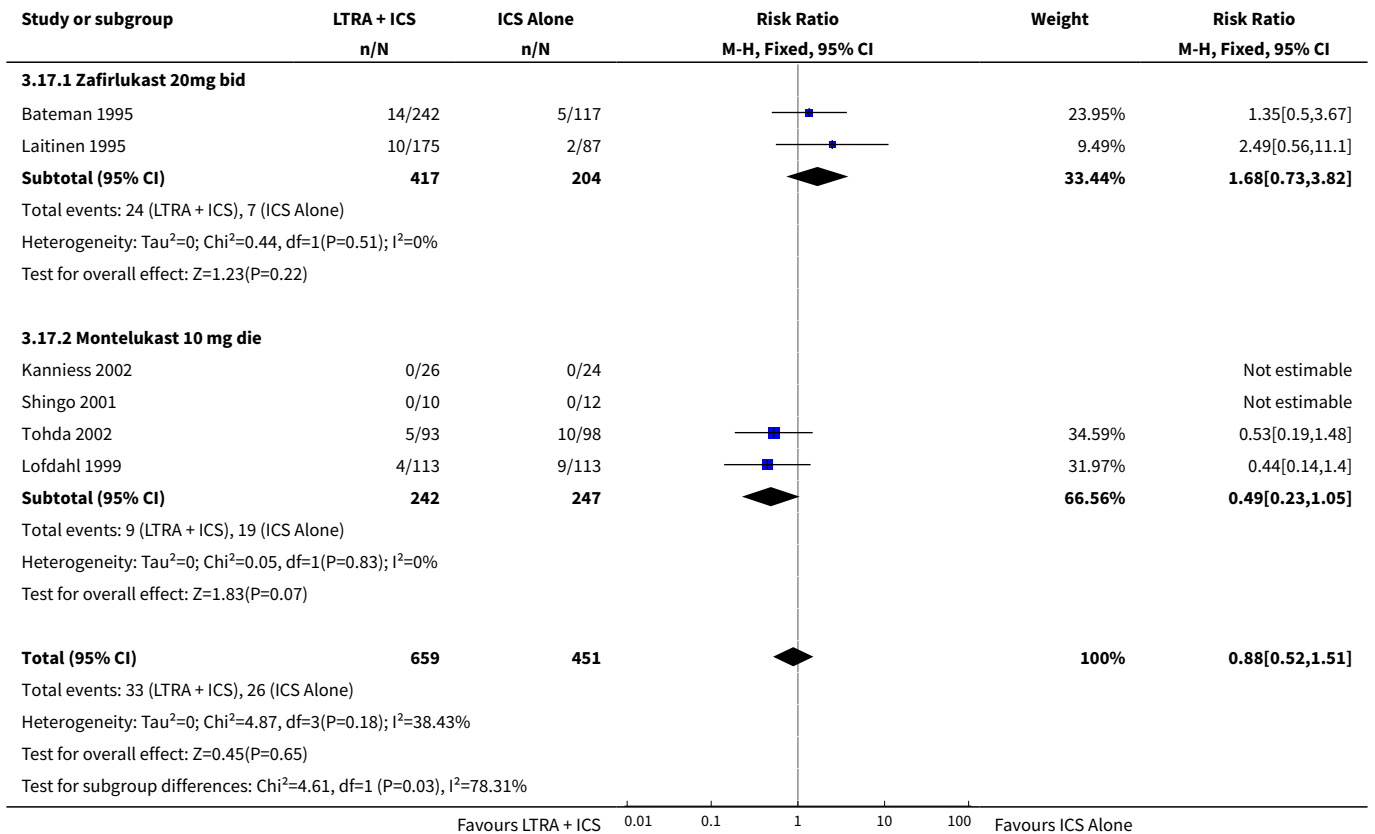


Analysis 3.16. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 16 Overall withdrawals.

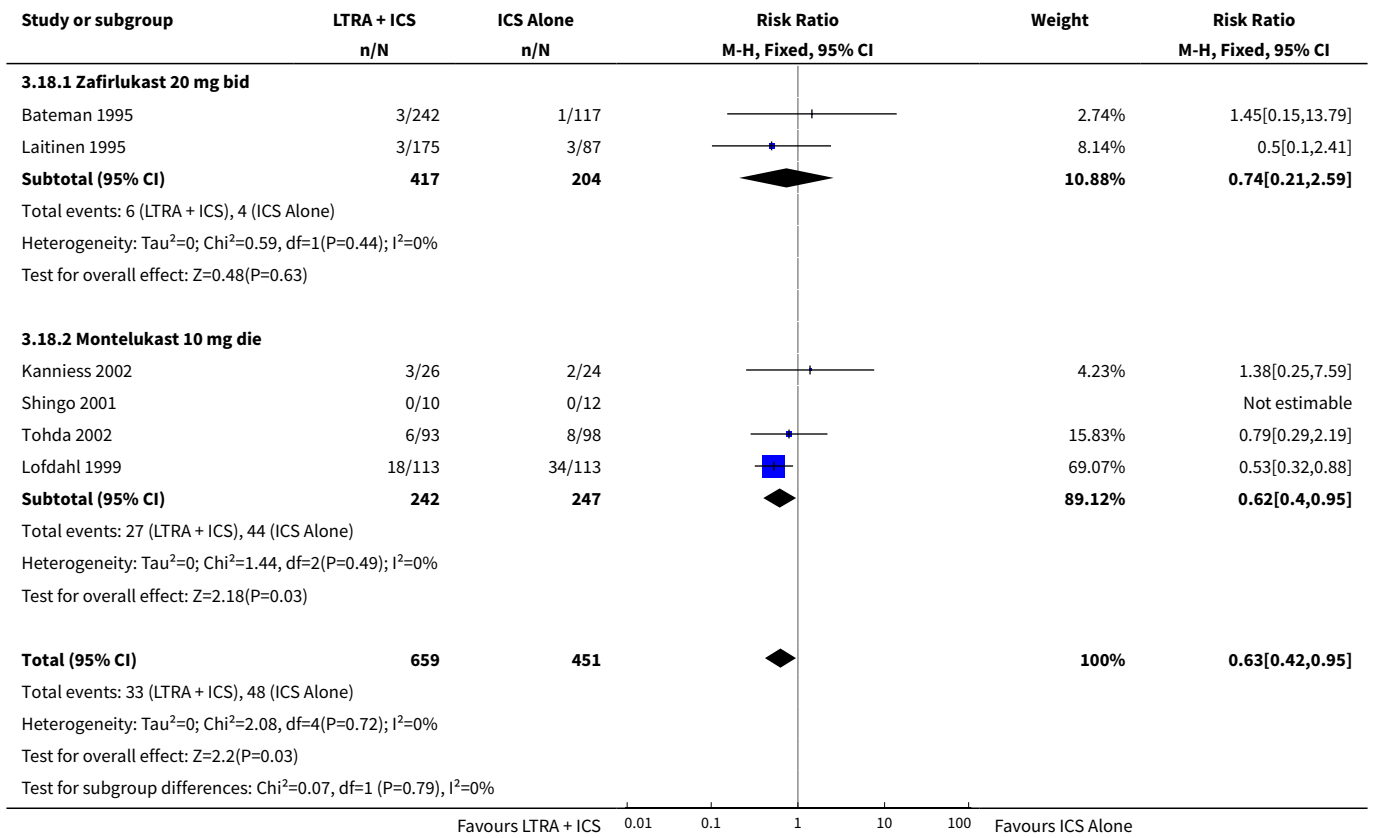




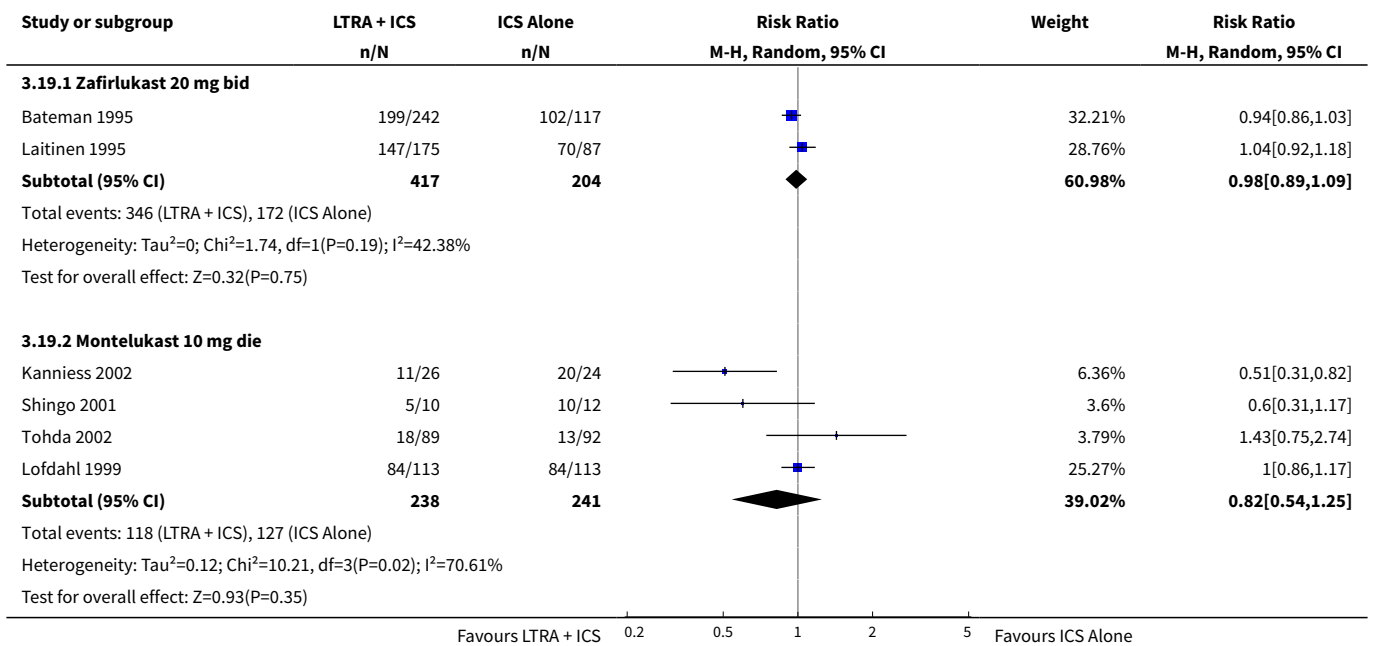
Analysis 3.17. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 17 Withdrawals due to adverse effects.

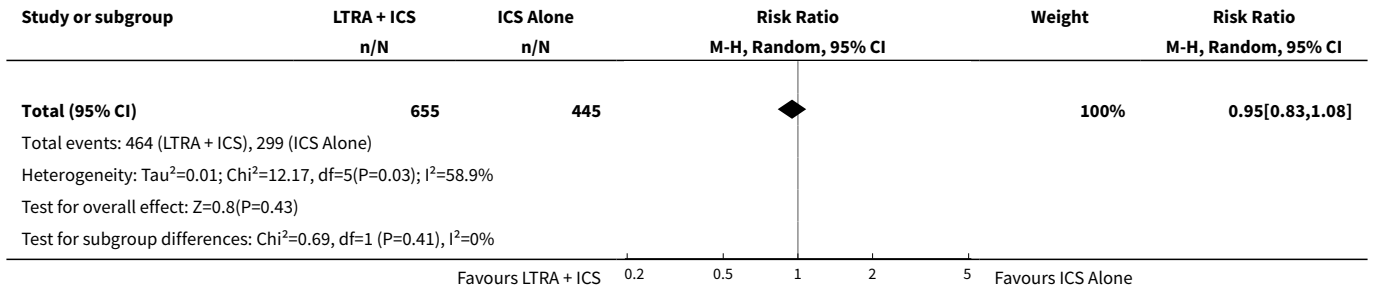


Analysis 3.18. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 18 Withdrawals due to poor asthma control/exacerbations.

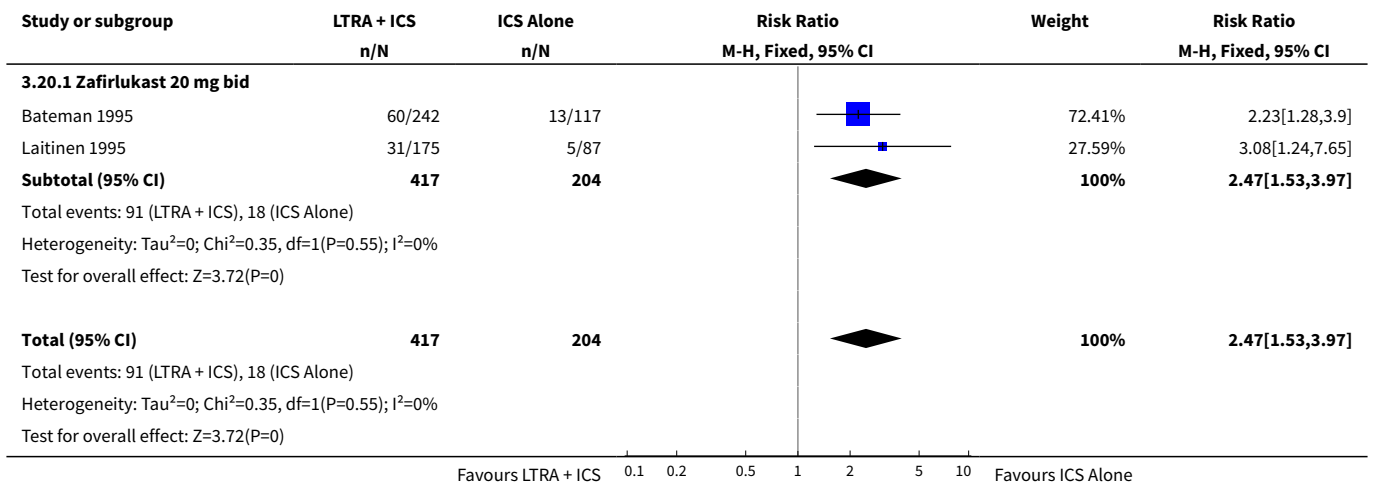


Analysis 3.19. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 19 Overall adverse effects.

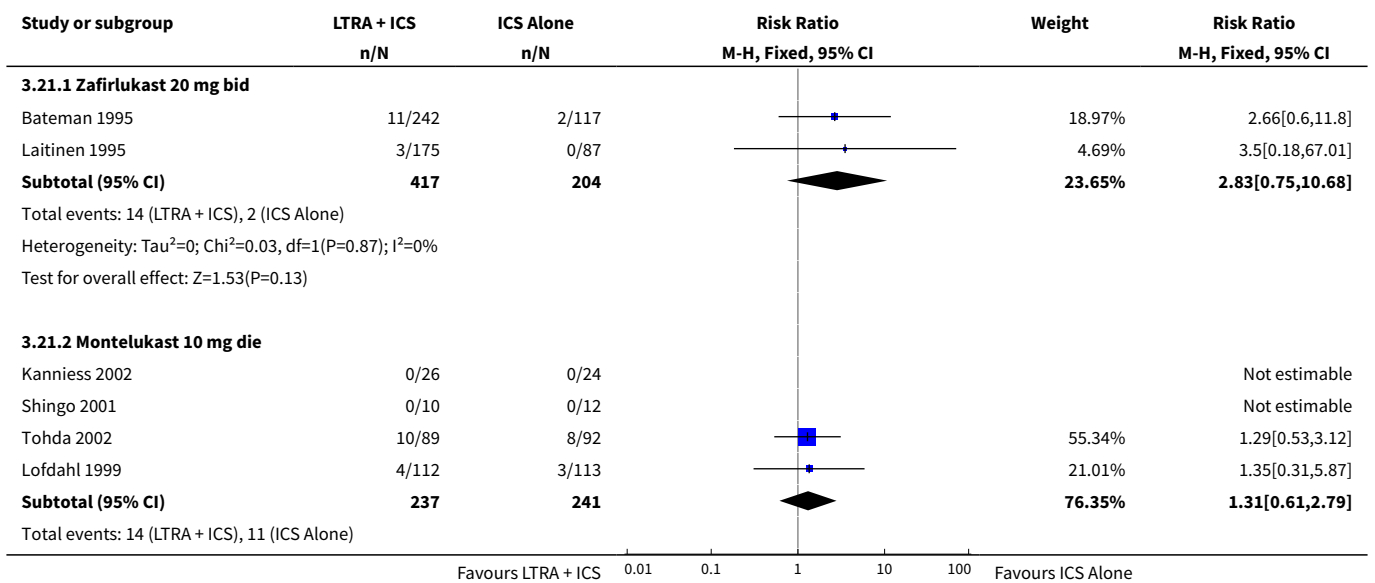


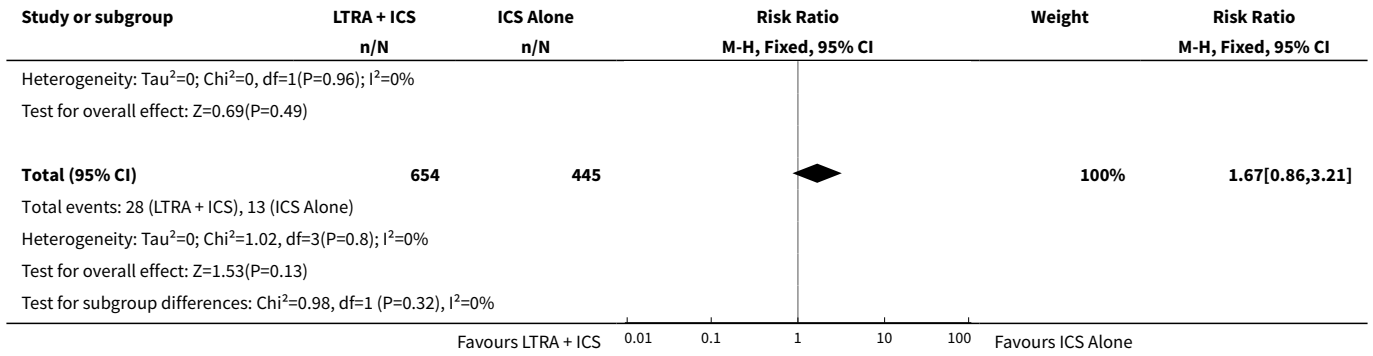


Analysis 3.20. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 20 Serious adverse events.

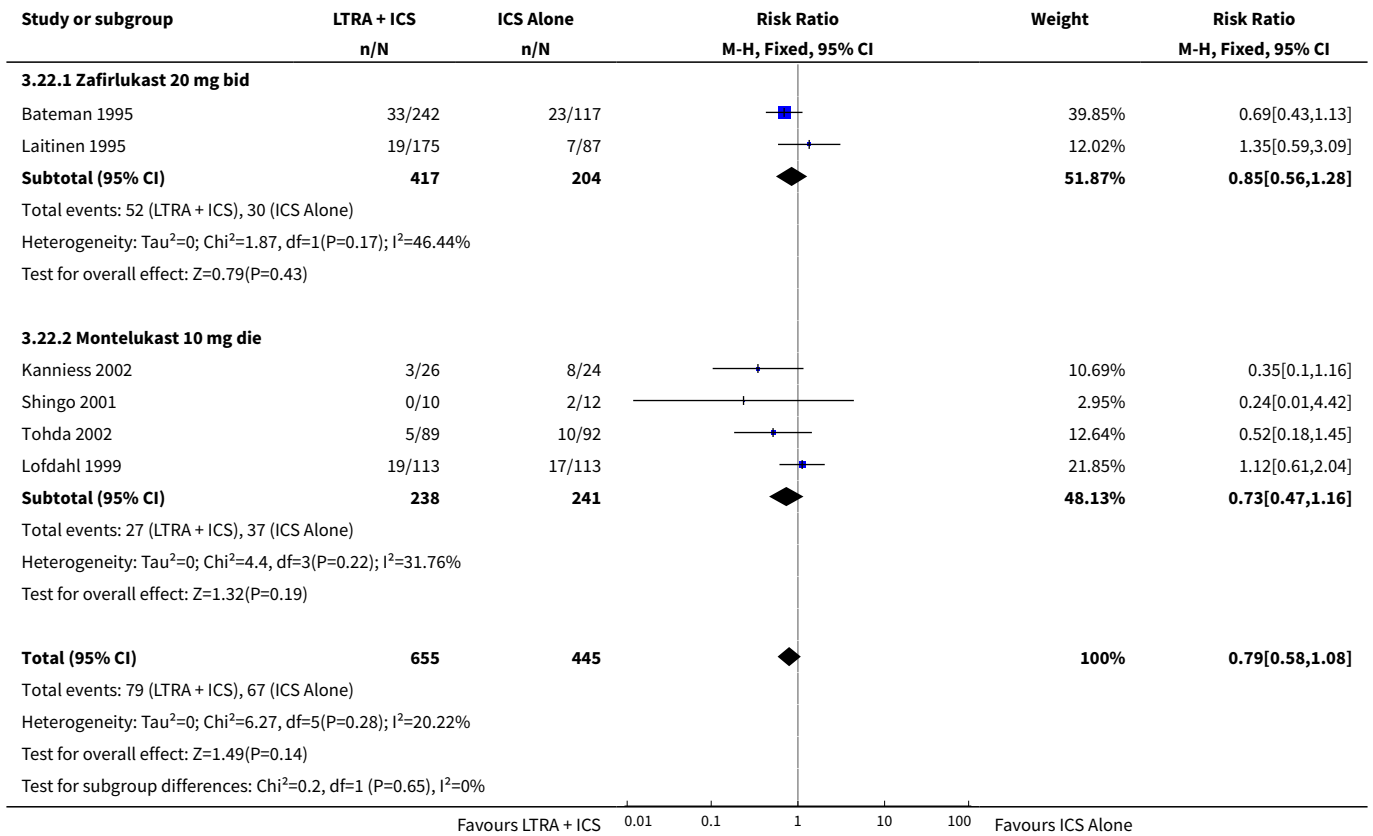


Analysis 3.21. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 21 Elevated liver enzymes.

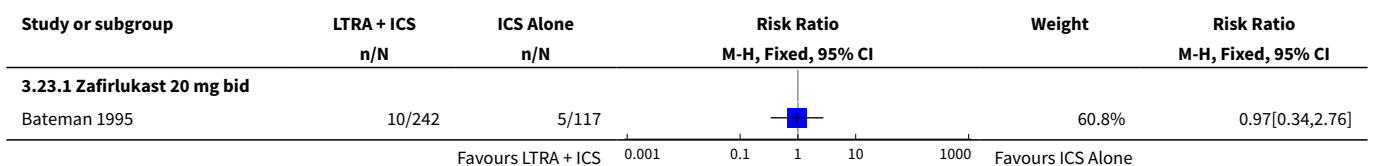


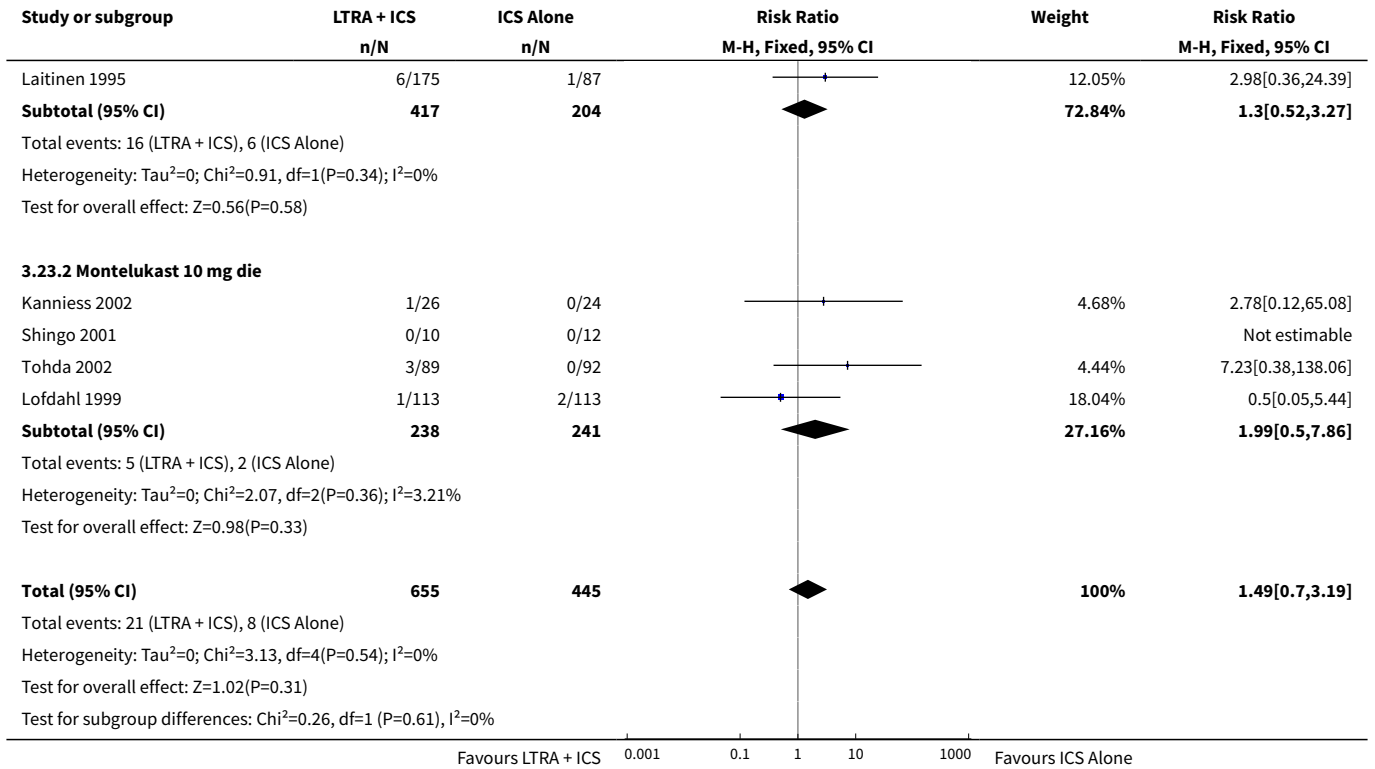


Analysis 3.22. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 22 Headache.

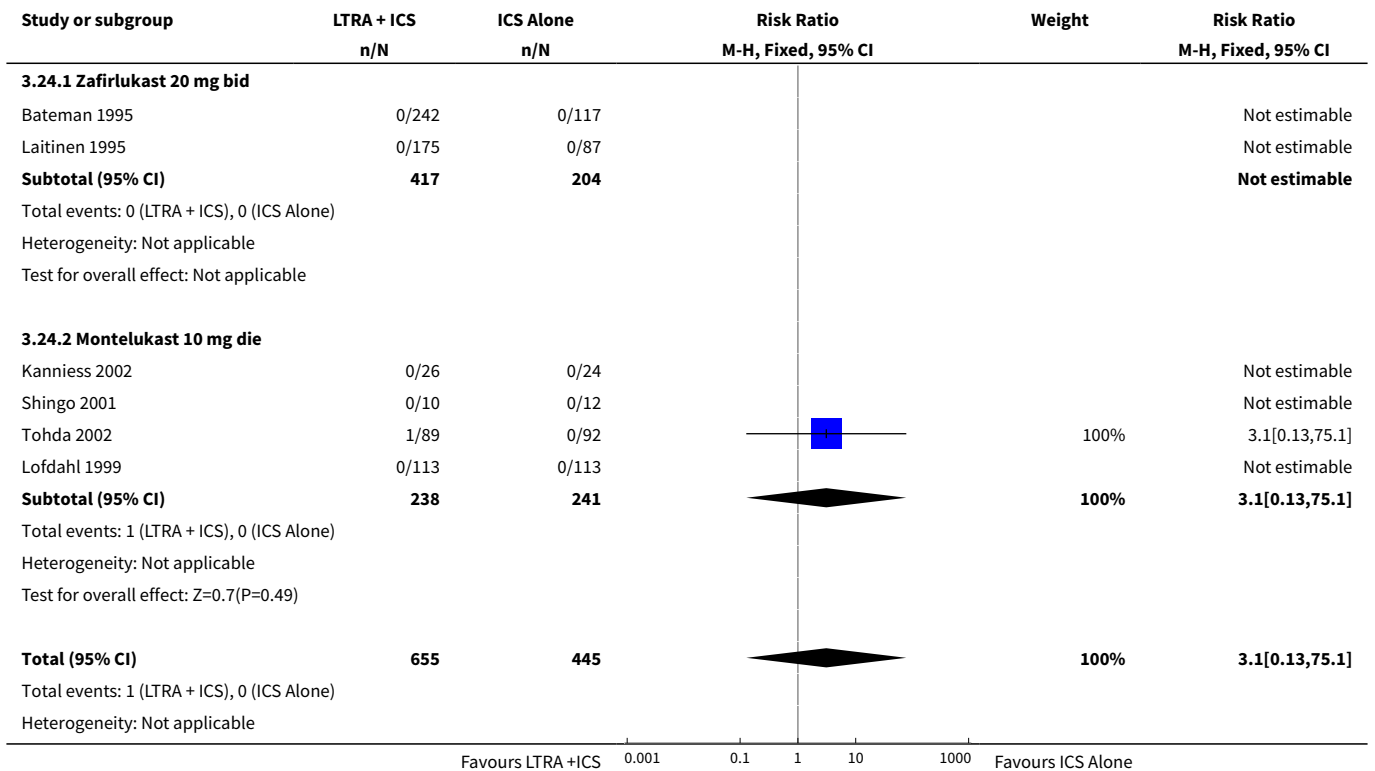


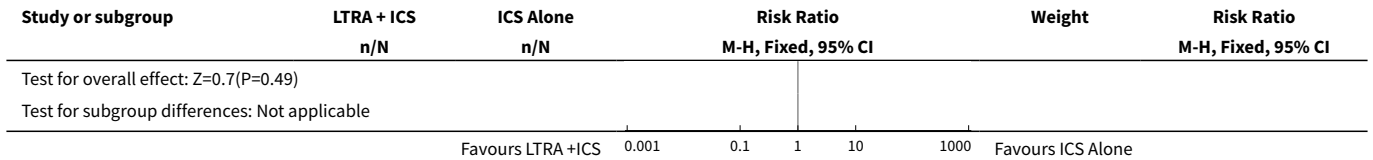
Analysis 3.23. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 23 Nausea.



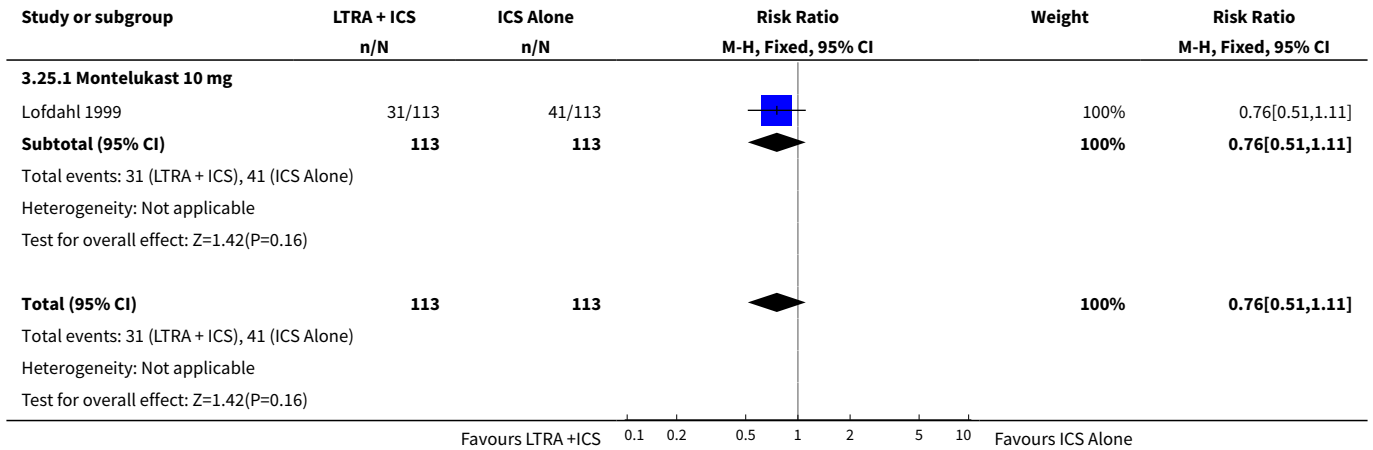


Analysis 3.24. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 24 Death.

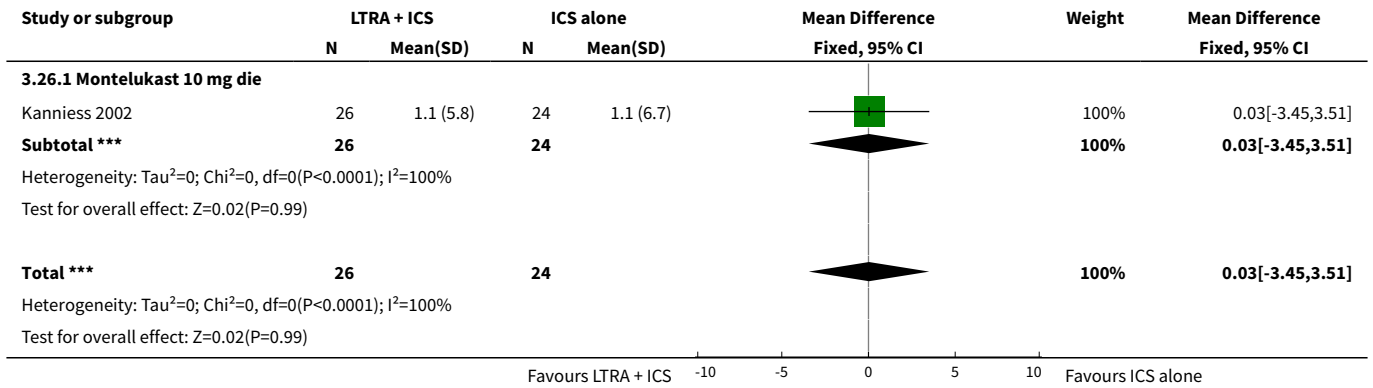




Analysis 3.25. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 25 Patients unable to taper inhaled corticosteroids.



Analysis 3.26. Comparison 3 Leukotriene Receptor Antagonists (LTRA) + ICS vs. ICS (TAPERING protocol) in WELL CONTROLLED patients, Outcome 26 Change in expired NO concentration (ppb) at 6 weeks.



APPENDICES

Appendix 1. Protocol for update of the review: Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma

Methods

Types of studies

Randomised placebo controlled trials in adults and children in which anti-leukotriene agents are added to inhaled glucocorticoid were considered for inclusion. We will restrict the eligible studies to those of 4 weeks duration and longer.

Types of participants

Children aged two to 17 years and adults with recurrent or chronic asthma, symptomatic or well-controlled on daily maintenance inhaled glucocorticoids. We will include studies where participants have to have been taking their inhaled steroids for a minimum of 4 weeks prior to study entry (inclusive of any run-in period).

Types of interventions

Combination of daily oral anti-leukotriene agents, including leukotriene synthesis inhibitors and leukotriene receptor antagonists, with inhaled glucocorticoids (treatment group) compared to inhaled glucocorticoids alone (control group). This review will consider three comparisons:

1. Anti-leukotrienes versus placebo in addition to a stable dose of ICS with equal doses of ICS between treatment groups: Anti-leukotrienes can be added to any dose of inhaled steroids which must be fixed. The dose of ICS in both groups must either be the same, or can be maintained from pre-study entry. Details of the type, dose and delivery of inhaled steroid will be recorded. We will record whether the ICS and dose were maintained from pre-study treatment, titrated during a run-in period, or whether a standard ICS and dose were introduced.
2. Anti-leukotrienes versus placebo in addition to a stable dose of ICS versus a higher dose of ICS in the control group: Anti-leukotrienes can be added to any dose of inhaled steroids which must be fixed. The dose of ICS in the control must be higher than that of the ICS in the treatment group. Details of the type, dose and delivery of inhaled steroid will be recorded. We will record whether the ICS and dose were maintained from pre-study treatment, titrated during a run-in period, or whether a standard ICS and dose were introduced.
3. Studies assessing anti-leukotrienes as an inhaled steroid sparing agent: Anti-leukotrienes can be added to ICS and then the dose of ICS in both groups will be permitted to vary according to a pre-specified protocol (such as symptoms, lung function, exacerbation history or a combination).

Types of outcome measures

Primary outcomes

Number of participants with exacerbations requiring use of systemic glucocorticoids for comparisons 1 and 2. For comparison 3, our primary endpoint will be the change from the baseline dose of inhaled glucocorticoids required to maintain control.

Secondary outcomes

The following secondary outcomes were considered after various lengths of treatment:

1. Change in clinical or physiologic outcomes reflecting chronic asthma control (such as symptom score, night-time awakenings, days without symptoms, quality of life, rescue short-acting beta-2-agonist use, and pulmonary function tests)
2. Clinical or physiologic outcomes reflecting the frequency and severity of asthma exacerbations (such as hospital admissions)
3. Inflammatory markers (such as serum and sputum eosinophils, serum eosinophilic cationic protein (ECP), expired nitric oxide, etc)
4. Clinical and biochemical adverse effects (i.e. elevation of liver enzymes) as well as withdrawal rates were also examined.

Data collection and analysis

Two authors will independently assess the search results (FD or TL). Studies will be retrieved selected on the basis of relevance, and will be selected for inclusion by the agreement of two authors.

Data extraction and management

Data will be extracted independently by two reviewers (FD and TL), and disagreement will be resolved by discussion.

Assessment of risk of bias in included studies

We will assess the risk of bias for each study according to the Risk of Bias tool outlined in Chapter 8 of the [Cochrane Handbook](#). The domains we will assess for the risk of bias will be:

1. Allocation generation. The method used to allocate participants to treatment group (e.g. computer-generated random number sequences)
2. Allocation concealment. The method used to conceal the sequence of treatment group assignment from study investigators and participants (e.g. assignment by date of birth, opaque sealed envelopes)
3. Blinding. The method by which knowledge of treatment group assignment was concealed from study investigators and participants after the study began (double-blind, single-blind).
4. Completeness of outcome data. The method for handling data from participants who withdrew from the study (e.g. intention to treat analysis, available case).
5. Selective reporting. Whether there is evidence that outcomes measured in the study are unreported (e.g. unreported harms, relevant efficacy data that are not available due for reporting and not statistical reasons).
6. Other sources of bias. Any other aspect of the study design which may be a source of bias.

We will collect and report information for each domain of bias and provide a judgment based on this information as high, low or unclear risk of bias.

We will seek confirmation of methodology for all included trials directly from the authors and/or the funding pharmaceutical companies.

Dealing with missing data

Confirmation of data extraction for all included trials will be sought directly from the authors and/or the funding pharmaceutical companies.

Assessment of heterogeneity

Homogeneity of effect sizes between studies being pooled will be assessed with the I square measurement. This estimates the amount of statistical variation between the studies above what would be expected with the play of chance ([Cochrane Handbook](#)).

Data synthesis

Treatment effects for dichotomous outcomes were reported as pooled Risk Ratios with a fixed-effect model (RR). Equivalence was assumed if the RR estimate and its confidence interval were between 0.9 and 1.1.

For continuous outcomes, such as pulmonary function tests or quality of life scores, we used a Weighted Mean Difference (WMD) or Standardised Mean Difference (SMD), where appropriate, to estimate individual and pooled effect sizes. Numbers Needed to Treat (NNT) were derived from the pooled Odds Ratios using Visual Rx (an online calculator at www.nntonline.net) as the results are not affected by the way in which the events are recorded ([Cates 2002](#)).

Trials were divided into three protocols, according to the relative dose of inhaled glucocorticoids used by the control group (same, double, tapered).

- (1) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus SAME dose of ICS.
- (2) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus DOUBLE dose of ICS.
- (3) Anti-leukotrienes (AL) + inhaled glucocorticoids (ICS) versus ICS (TAPERING protocol).

In all comparisons, the dose and type of anti-leukotriene agents served as the primary stratifying variable.

To detect possible biases, funnel plot symmetry was examined for trials contributing data to the main outcomes ([Egger 1997](#)). All estimates were reported with their 95% confidence interval.

We will complete a Summary of Findings (SoF) table using GRADEpro software. Our assessments of the overall quality of evidence will be made according to the recommendations of the [GRADE working group](#). We will include outcome data for the primary outcomes of OCS-treated exacerbations (comparisons 1 and 2), change from baseline in ICS dose (comparison 3), hospital admission and serious adverse events.

Subgroup analysis and investigation of heterogeneity

If the I square measurement exceeds 25% we will consider its possible causes and assess whether this affected the results of the analysis by incorporating the variation in a random effects model. Subgroup analysis is also planned based on the following aspects of the studies:

1. dose and anti-leukotrienes used,
2. baseline dose of inhaled glucocorticoids,
3. age,
4. severity of baseline airway obstruction,

5. duration of intervention,
6. asthma triggers.

The mean baseline dose of inhaled glucocorticoids in the intervention group will be recorded in mcg/day of chlorofluorocarbon (CFC)-propelled beclomethasone dipropionate or equivalent x 0.1; where, irrespective of delivery system used, 1 mcg of beclomethasone = 1 mcg of budesonide = 0.5 mcg of fluticasone = 2 mcg of triamcinolone = 2 mcg of flunisolide (USA 2002).

Usual licensed doses of leukotriene receptor antagonists are: montelukast 10 mg daily, pranlukast 450 mg daily, and zafirlukast 20 mg twice daily. For the primary outcome, sensitivity analyses will be performed to determine the effect of publication status and risk of bias on results. We will perform the meta-analysis using RevMan 5.

WHAT'S NEW

Date	Event	Description
18 July 2011	Review declared as stable	This review is no longer being updated. It is being replaced by two new protocols/reviews. The review question will be split into adults and children.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2001

Date	Event	Description
30 September 2009	Amended	Change in contact details for Francine Ducharme
16 May 2008	Amended	Converted to new review format.
13 October 2003	New citation required and conclusions have changed	<p>This review represents the second update since its initial publication in The Cochrane Library 2001, Issue 1, May 2001; the first update being in September 2001.</p> <p>The search strategy updated in August 2003 yielded 211 additional citations; 197 citations were excluded for the following mutually exclusive reasons:</p> <ol style="list-style-type: none"> (1) Duplicate references (N = 91) (2) Not a randomised controlled trial (N = 44), ongoing trial (N=1), or awaiting assessment (N=3) (3) Subjects were not asthmatics (N=4) (4) The tested intervention was not anti-leukotrienes (N=9) (5) No consistent co-treatment with inhaled glucocorticoids (N=20) (6) The control intervention was not inhaled corticosteroids (N=8) (7) Use of non permitted drugs (N=5) (8) The tested intervention was administered for less than 4 weeks (N=5) (8) Outcomes not reflective of asthma control (N=6) (9) Acute care setting (N=1). <p>Fourteen new trials were included in the updated review;</p> <p>-7 new trials (2 abstracts contributing little data, 4 full-text publications and 1 full disclosure of unpublished trial) comparing anti-leukotrienes versus placebo as add-on to inhaled glucocor-</p>

Date	Event	Description
		<p>ticoids for a total of 13 trials, of which 8 trials contributed data with sufficient details to be aggregated;</p> <p>-5 new trials (3 abstracts contributing little data and 2 full-text publications) comparing anti-leukotrienes as add-on to inhaled glucocorticoids versus double-dose of inhaled steroids for a total of 7 trials, of which 4 trials could be aggregated;</p> <p>-2 new trials (both full-text publications) comparing anti-leukotrienes versus placebo as add-on to tapering doses of inhaled glucocorticoids for a total of 7 trials, with 6 trials contributing data that were aggregated.</p> <p>The updated review now comprised 27 trials comparing anti-leukotrienes versus placebo as add-on to inhaled glucocorticoids.</p> <p>The systematic review was re-structured to clearly distinguish trials that use licensed, from those that used higher than licensed, doses of anti-leukotrienes.</p> <p>The results of the review have not changed markedly as result of the 14 additional trials. The main new feature is the addition of 2 new trials for a total of 3 trials comparing the addition of leukotriene receptor antagonists at LICENSED dose to inhaled glucocorticoids as compared to double-dose of inhaled glucocorticoids. The two options appear to provide similar benefit although the power is insufficient to assume equivalency.</p>

CONTRIBUTIONS OF AUTHORS

Dr Francine Ducharme conceived the protocol, requested the literature search, identified and contacted the corresponding authors and/or the pharmaceutical companies to solicit their collaboration in this review and in the identification of other possibly relevant trials, created the methodology and data extraction forms, reviewed all citations for relevance with research assistants, reviewed all included trials for methodology and data extraction, corresponded with authors or pharmaceutical companies to verify methodology and data extraction, verified all references, description of studies and data entry, analysed and interpreted results of the meta-analysis.

Three research assistants participated in some aspects of the review.

From November 1999 to February 2000, Giselle Hicks reviewed many citations for relevance, extracted the methodology and data and entered data for several trials.

Miss Ritz Kakuma, supported by The Canadian Cochrane Network, participated in the review from June 2000 to November 2001. She reviewed several included trials for methodology and data extraction, and entered data.

Mr Zachary Schwartz assisted in the August 2003 update. He extracted the methodology and data for the new identified trials, identified missing information for, and completed the table of characteristics of, included studies, and entered the references for all excluded studies with their reason for exclusion. Justin Grondines, data manager, tallied the reasons for exclusion for the literature search.

DECLARATIONS OF INTEREST

Francine Ducharme has received travel support, research funds and fees for speaking from Zeneca Pharma Inc. producer of zafirlukast and Merck Frosst Inc, producer of montelukast. She has received some travel support for meeting attendance, research grant and consulting fee from Glaxo Wellcome Inc, producer of some inhaled corticosteroids preparation to which anti-leukotriene agents have been compared. Zachary Schwartz, Giselle Hicks, and Ritz Kakuma: None declared.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Received research assistant support from the Canadian Cochrane Network, Canada.
- Francine Ducharme was supported by a senior clinical scientist award from the Fonds de la Santé du Québec, Canada.

NOTES

Several comments were made about an earlier version of this systematic review. They have been removed from this version of the review but remain listed on the comments and criticisms website. To read them and the author's response in full, please refer to: <http://www.update.co.uk/feedback/introduction.htm>.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Anti-Asthmatic Agents [*therapeutic use]; Anti-Inflammatory Agents [*therapeutic use]; Asthma [*drug therapy]; Chronic Disease; Drug Therapy, Combination; Leukotriene Antagonists [*therapeutic use]; Steroids [therapeutic use]

MeSH check words

Humans