LEUKOTRIENE RECEPTOR ANTAGONISTS VERSUS PLACEBO IN ADULTS AND ADOLESCENTS WITH ASTHMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

A thesis submitted by

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Abstract

Background: Leukotriene receptor antagonists (LTRAs) are recommended as alternative treatment in patients with mild asthma, but their relative effect compared with placebo is unknown. **Objective:** To determine the benefits and harms of LTRAs compared with placebo in adults and adolescents with asthma. **Data sources:** MEDLINE and the Cochrane Central Register of Controlled Trials from inception through December 2012. **Study selection:** Peer-reviewed, English-language, randomized controlled trials ($\geq$ 4 weeks in duration) in patients with asthma that reported the effect of LTRAs versus placebo on measures of asthma control. **Data extraction:** Data on the study population, interventions, outcome measures, adverse events, and study methodology were extracted by three authors. **Data synthesis:** Forty seven trials satisfied our eligibility criteria. Random-effects model meta-analyses, random-effects meta-regression, and subgroup analyses were performed. In 9 trials, LTRAs reduced the risk of an exacerbation by 35% (summary risk ratio = 0.65, 95% CI 0.50, 0.84). The effect was more pronounced in studies of shorter duration ($p < 0.01$). LTRAs significantly increased FEV_1 (summary mean difference [MD] from 13 trials= 0.11 liters, 95% CI 0.08, 0.15; summary MD in percent change from 11 trials = 5.95, 95% CI 3.3, 8.6) and FEV_1 % predicted (summary MD from 8 trials = 4.2%, 95% CI 1.5, 1.9). Daytime symptoms (summary standardized MD from 14 trials = -0.21, 95% CI -0.37, -0.04), short-acting β_2-agonist use (summary MD from 11 trials = -0.65 puffs/day, 95% CI -0.82, -0.49; summary MD in percent change from 8 trials = -16.4, 95% CI -22.4, -10.4), nocturnal awakenings (summary MD from 7 trials= -0.66, 95% CI -1,-0.3), and asthma-specific quality of life (summary standardized MD from 5 trials = 0.13, 95% CI 0.02, 0.2) were also significantly improved compared to placebo. The

proportions of patients with adverse events were similar between intervention and comparator groups. **Limitations:** Variation in definitions and reporting of outcomes, large heterogeneity, and possible selective outcome reporting bias. **Conclusion:** LTRAs improved asthma control compared to placebo. It remains unclear however, which patients with asthma are more likely to respond to treatment with LTRAs.

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List of abbreviations

AE: Adverse Events
AIA: Aspirin Induced Asthma
ALT: Alanine Aminotransferase
AQLQ: Asthma Quality of Life Questionnaire
AR: Allergic Rhinitis
ASQL: Asthma Specific Quality of Life
AST: Aspartate Aminotransferase
BEC: Beclomethasone
BUD: Budesonide
CI: Confidence Interval
ER: Emergency Room
FEV_1: Forced Expiratory Volume in one second
FCS: Fluticasone
ICS: Inhaled Corticosteroids
ITT: Intention To Treat analysis
LABA: Long Acting β_2 Agonist
LTRA: Leukotriene Receptor Antagonist
MD: Mean Difference
PEFR: Peak Expiratory Flow Rate
RCT: Randomized Controlled Trial
RR: Risk Ratio
SABA: Short Acting β_2 Agonist
SD: Standard Deviation
SMD: Standardized Mean Difference
SRDR: Systematic Review Data Repository
URTI: Upper Respiratory Tract Infection

Introduction

Asthma is one of the most common chronic diseases with considerable social and economic burden, involving both high direct costs related to healthcare utilization and indirect costs related to time lost from work or school. In the US the annual cost is estimated around $18 billion.[1] Approximately 300 million people worldwide, and 25 million Americans, are affected by asthma. These numbers are expected to rise to 400 million by 2025.[2]

The successful long-term management of asthma includes the use of medications that target the underlying inflammatory process. Although inhaled corticosteroids (ICS) constitute the current gold standard of maintenance treatment, leukotriene receptor antagonists (LTRAs) have the advantage of being administered orally in a single or twice daily dose; importantly, these agents appear to lack the adverse effects associated with long-term corticosteroid therapy.[3] In addition, their mechanism of action theoretically predicts a good response in patients with specific asthma 'phenotypes'. Allergic rhinitis (AR) is present in many patients with asthma and LTRAs might improve asthma-related outcomes by treating both conditions concurrently.[4] Moreover, aspirin-induced asthma (AIA), which is clinically characterized by chronic eosinophilic rhinosinusitis, nasal polyposis, aspirin hypersensitivity, and development of persistent asthma, is associated with increased airway leukotrienes and is frequently poorly responsive to ICS.[5] Current guidelines recommend the use of LTRAs as monotherapy in patients with mild persistent asthma, as an alternative, or as add-on therapy to ICS, and as an alternative to either increasing the ICS dose or adding a long-acting β_2-agonist.[6] However, the relative benefits and harms of LTRAs compared with placebo have not been established.

We conducted a systematic review of randomized controlled trials (RCTs) that compared the efficacy and safety of LTRAs with placebo in adults and adolescents with asthma for both objective and patient-reported outcome measures used to assess asthma control.

Materials and Methods

Data sources and search

We searched MEDLINE and the Cochrane Central Register of Controlled trials from inception through December 2012. We developed a search strategy with a combination of Medical Subject Headings terms and free text keywords relevant to study design ("randomized controlled trial"), disease of interest ("asthma"), and intervention of interest ("leukotriene receptor antagonists") [Table 1].

Eligibility criteria and study selection

We included peer-reviewed publications of RCTs if they fulfilled the following criteria: comparison of a LTRA either as monotherapy or as add-on therapy to ICS with placebo in adults and adolescents (≥12 years) with asthma; oral administration of usual licensed doses of a LTRA on a daily basis (montelukast 10 mg once daily for individuals 15 years and older, zafirlukast 20 mg twice daily for individuals 12 years and older, pranlukast 225 mg twice daily for individuals 12 years and older); minimum treatment duration of 4 weeks; inclusion of at least one pre-specified outcome measure that reflects asthma control (asthma exacerbations, pulmonary function tests, daytime asthma symptom scores, asthma-specific quality of life, nocturnal awakenings, short acting β_2-agonist use, adverse events); and English language publication. The primary outcome measure was the number of

exacerbations requiring systemic corticosteroids, an unscheduled visit to a doctor, or a visit to an emergency department. Asthma-specific quality of life is assessed using the asthma-specific quality of life and mini asthma quality of life questionnaires.[7-8] The scales range from 1 to 7 (or 0 to 6), with higher values indicating better quality of life. The minimally important difference considered clinically important is 0.5.[7-8] Due to the inclusion of children and adolescents in some studies of montelukast, we included studies in which at least some children and adolescents received 10 mg daily and excluded those in which none of the participants received 10 mg. Two investigators independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr;[9] the full text publications of potentially relevant articles were retrieved and rescreened by the same two investigators. Disagreements were resolved by consensus.

Data extraction

Each eligible study was independently data extracted by two of three investigators; any disagreements were resolved by consensus. We extracted data on study design and methodology, patient characteristics, interventions, comparators, outcome measures, and adverse events using a standardized electronic form in the Systematic Review Data Repository (SRDR), which is an open-access, collaborative, Web-based repository of systematic review data.[10]

Assessment of risk of bias

We assessed the methodological quality of the eligible studies using the Cochrane Collaboration's 'Risk of bias' tool.[11] This tool includes 13 'risk of bias' items (Table 2). A judgment of 'low', 'high', or 'unclear' risk of bias was assigned for the first seven items (sequence generation, allocation concealment, patients' blinding, caregivers' blinding,

outcome assessors' blinding, attrition, selective outcome reporting), whereas a judgment of 'yes', 'no', or 'unsure' was assigned for the remainder (intention-to-treat analysis, baseline balance, co-interventions similarity, compliance, presence of other biases). Reviewing across all risk of bias items, we assigned an overall quality grade of good, fair, or poor to each RCT. We considered a study of poor quality if any of the following was observed: a) absence of blinding, b) differential loss-to-follow up, c) baseline imbalances, d) absence of a washout period in the case of crossover trials. Studies that reported sufficient details about the implementation of blinding (e.g., double-blind and use of identical capsules) were considered as having low risk of bias for this specific item, whereas studies with insufficient reporting (e.g., double-blind) were considered as having unclear risk of bias. Blinding of the outcome assessors with regard to patient-reported outcomes was considered adequate if patients were reported to be blinded. We compared the proportions of withdrawals in each group using the Chi-square test and a p-value less than 0.1 was indicative of differential loss-to-follow up. An analysis was considered as intention-to-treat (ITT) if the number of participants who were randomized was equal to the number of participants who were analyzed. The assessments were completed by one author.

Data synthesis and analysis

Study treatment effects for binary outcomes were estimated using the risk ratio (RR) with corresponding 95% confidence intervals (CI). For the continuous outcome measures, the difference in mean changes from baseline between LTRAs and placebo was calculated for each study. The 95% CI was calculated based on the pooled standard deviation (SD) of calculated differences. Study treatment effects for daytime symptom scores and asthma-specific quality of life scores were computed using Hedges' g statistic corrected for small

samples.[12] When only the baseline and final SDs were reported, we calculated SDs of change from baseline in each group assuming a correlation coefficient of 0.5.[13] When means and measures of dispersion were not reported in the text, they were approximated from figures using Engauge Digitizer Qt4.[14] We imputed missing group SDs in one study using the median of all available SDs from other studies.

In the meta-analyses, the summary treatment effects were estimated using the random-effects model estimated by restricted maximum likelihood.[15] Random-effects modeling assumes a genuine diversity in the results of various studies and incorporates a between-study variance in the calculations. We calculated a summary RR, a summary mean difference, and a summary standardized mean difference (SMD) between LTRAs and placebo, where appropriate. Statistical heterogeneity was quantified by the I^2 statistic.[16] Values around 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.[16] The overall analysis included only the reported endpoint values at the longest follow-up within each trial. Subgroup analyses and random effects meta-regression were employed to explore the effect of pre-specified factors on the effect estimates, when an outcome of interest was reported by at least three RCTs in each subgroup. The pre-specified factors were: type of LTRA, use of ICS, dose of ICS, treatment duration, asthma severity, presence of comorbid allergic rhinitis, aspirin-induced asthma. The RCTs were classified into three categories based on the concomitant use of ICS in the intervention groups; no use of ICS, equal use of ICS, or unequal use of ICS. Wherever possible, doses of ICS were converted to microfine hydrofluoroalkane-beclometasone dipropionate (HFA-BDP) equivalent based on 1 μg of microfine HFA-propelled beclomethasone = 2 μg of chlorofluorocarbon (CFC) – propelled beclomethasone = 1 μg of fluticasone = 2 μg of

budesonide = 1 μg of ciclesonide = 1 μg of mometasone = 4 μg of triamcinolone = 4 μg of flunisolide.[17] Since the treatment duration varied among the trials, we grouped the time points of outcome assessments in the individual trials into six intervals: 4-7, 8-11, 12-15, 16-23, 24-30, and more than 30 weeks. This grouping was designed to best capture all available data in the trials, but also reflects periodic monitoring of asthma control used in clinical practice. Crossover trials were not included in the primary meta-analyses. All analyses were performed with OpenMetaAnalyst.[18]

Sensitivity analyses

Additional analyses addressed: 1) trials in which all participants were 12 years and older in order to investigate the impact of including RCTs with overlapping populations of children and adolescents; 2) trials with an unclear definition of exacerbation; and 3) inclusion of two crossover trials that assessed the outcomes FEV_1, short-acting β_2-agonist use, and nocturnal awakenings in paired analyses.

Table 1. Search strategy

1. Leukotriene antagonists.sh.
2. Leukotriene receptor antagonist*.af.
3. (leukotriene and receptor antagonist*.af.
4. Leukotriene modifier*.af.
5. (leukotriene receptor and antagonist*).af.
6. Montelukast.af.
7. Zafirlukast.af.
8. Pranlukast.af.
9. Singulair.af.
10. Accolate.af.
11. Onon.af.
12. Azlaire.af.
13. Or/1-12
14. Exp Asthma/
15. Asthma*.af.
16. Samter* syndrome.af.
17. Aspirin intolerance.af.
18. Aspirin sensitivity.af.
19. Aspirin hypersensitivity.af.
20. Exercise induced broncho*.af.
21. (Exercise induced and broncho*).af.
22. Nasal polyp*.af.
23. Or/14-22
24. Randomized controlled trial.pt.
25. Controlled clinical trial.pt.
26. Randomized controlled trials/
27. Random Allocation/
28. Double-blind method/
29. Single-blind method/
30. Clinical trial.pt.
31. Clinical Trials.mp. or exp Clinical Trials/
32. (clinic$ adj25 trial$).tw.
33. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
34. Placebos/
35. Placebo$.tw.
36. Random$.tw.
37. Trial$.tw.
38. (randomized control trial or clinical control trial).sd.
39. Latin adj square.tw.
40. Comparative Study.tw. or Comparative Study.pt.
41. Exp Evaluation studies/
42. Follow-up Studies/
43. Prospective Studies/
44. (control$ or prospective$ or volunteer$).tw.
45. Cross-over Studies/
46. Or/24-45
47. And/13, 23, 46

Table 2. Risk of bias items assessed for randomized controlled trials

1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence? [Low, Unclear, High]

2. What is the risk of selection bias (biased allocation of interventions) due to inadequate concealment of allocations before assignment? [Low, Unclear, High]

3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)? [Low, Unclear, High]

4. Was the care provider blinded to the intervention? [Low, Unclear, High]

5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)? [Low, Unclear, High]

6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data? [Low, Unclear, High]

7. What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]

8. Were all randomized participants analyzed in the group to which they were allocated? [Yes, No, Unsure].

9. Were the groups similar at baseline regarding the most important prognostic indicators? [Yes, No, Unsure]

10. Were co-interventions avoided or similar? [Yes, No, Unsure]

11. Was the compliance acceptable in all groups? [Yes, No, Unsure]

12. Was the timing of the outcome assessment similar in all groups?* [Yes, No, Unsure]

13. Are there other risks of bias? [Yes, No]

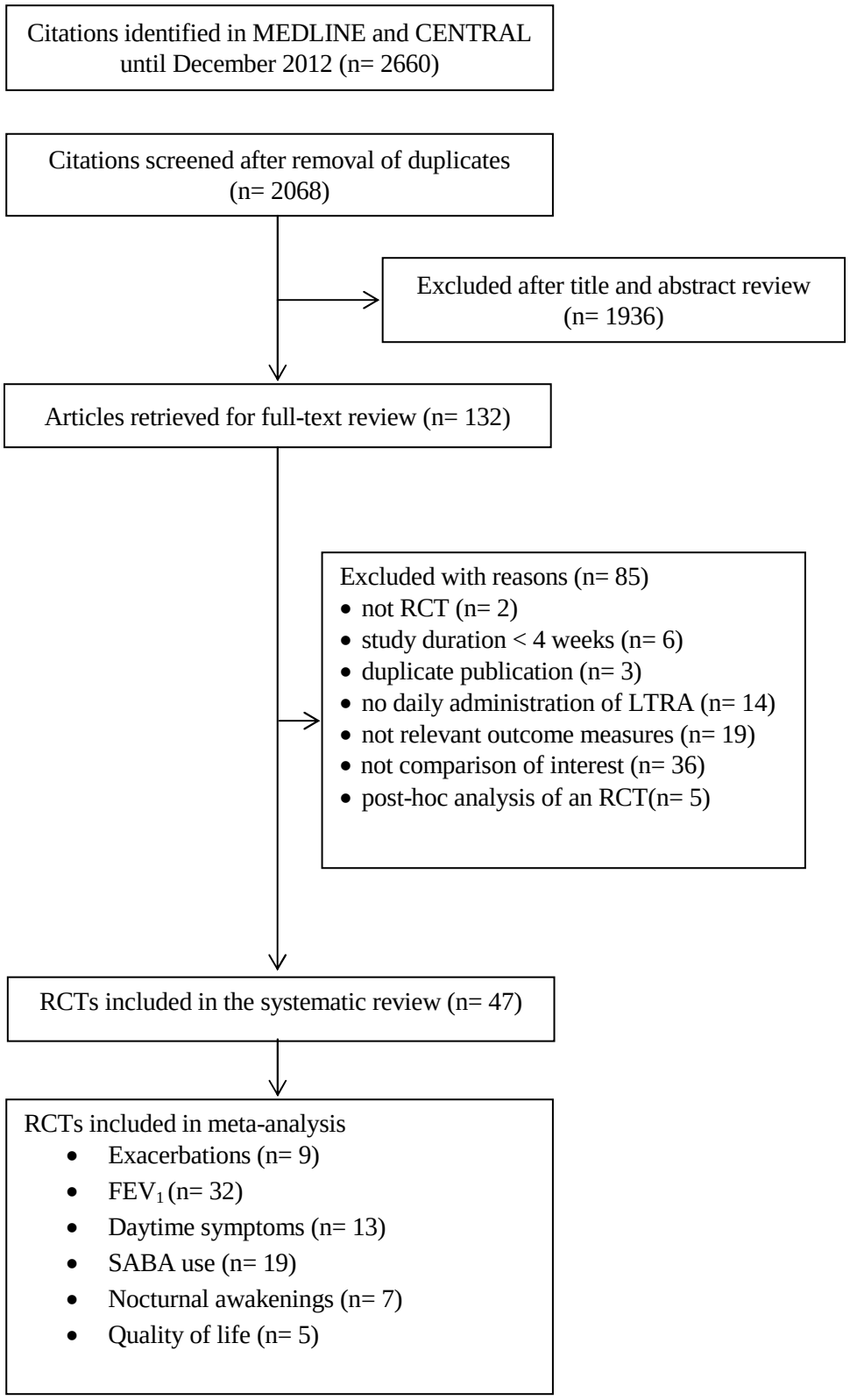
* Question 12 was incorporated into question 13 for the purpose of the current study

Results

Literature search

Figure 1 summarizes our search yield. We screened 2068 citations. A total of 224 articles were retrieved for full-text review, and 47 RCTs[19-65] met our inclusion criteria.

Figure 1. Flow diagram



Trial characteristics

Table 3 summarizes the characteristics of the included RCTs, which were published between 1994 and 2011. Five RCTs included both children and adolescents.[51,54-56,58] Asthma was generally diagnosed by the demonstration of reversibility of airway obstruction after administration of short-acting β_2-agonists. The main exclusion criteria within trials were active upper respiratory tract infection, recent use of oral corticosteroids, and recent ER visit or hospitalization due to worsening asthma. Smokers were excluded in 28 trials.

Overall, 9057 patients were randomized to receive either a LTRA or placebo. Montelukast was administered in 33 RCTs, zafirlukast in 9, and pranlukast in 5. ICS were used as concomitant treatments by all patients in 15 trials, whereas in 8 trials ICS were used only by a proportion of participants. In 4 RCTs the dose of ICS was gradually reduced during follow-up according to specific criteria described in the trials. Short-acting β_2-agonists were permitted on an "as needed" basis in every trial. Mean FEV_1 at baseline was between 59% and 102% of predicted values. Sixteen RCTs reported inclusion of patients with a history of atopy, 9 reported presence of concomitant allergic rhinitis, and 2 RCTs reported inclusion of patients with aspirin-induced asthma. Patients with exercise induced bronchoconstriction were included in 5 trials. There were 38 parallel and 9 crossover RCTs. Twenty eight RCTs were multicenter. Treatment duration ranged from 4 to 30 weeks.

Table 3. Characteristics of included trials

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years	Sex, %Male	FEV_1 % predicted at baseline (SD)	FEV_1 % predicted range of inclusion
Altman 1998[19]	USA	Montelukast Placebo	Theophylline, ICS*, SABA	6	57 58	33 median 36 median	79 78	62 (13) 59 (13)	40-80
American Lung Association 2007[20]	USA	Montelukast Placebo	ICS*, LABA, SABA	24	164 164	40 40	28 26	77 (17) 80 (16)	> 50
Awad 2002[21]	India	Zafirlukast Placebo	SABA	12	116 99	35 35.	47 50	62 (11) 64 (12)	45-80
Baena-Cagnani 2003[22]	USA	Montelukast Placebo	SABA	4	311 302	34 32	39 33	86 86	> 70
Barnes 1997[23]	Europe	Pranlukast Placebo	BEC* (≤ 1000 µg/d), SABA	4	46 44	39 38	59 66	68 (12) 67 (11)	50-80
Baumgartner 2003[24]	North & South America	Montelukast Placebo	SABA	6	313 103	36 36	34 overall	69 (12) 68 (12)	50-85
Busse 2001[25]	USA	Zafirlukast Placebo	SABA	12	111 114	12-75 overall	50 overall	66-67 overall	50-80
Cakmak 2004[26]	Turkey	Zafirlukast/ BUD (400 µg/d) Placebo/ BUD (400µg/d)	SABA	6	11 10	30 28	55 20	88 (14) 89 (14)	≥ 70
Dahlén 2002[27]	USA, Europe	Montelukast Placebo	Theophylline, ICS*, SABA	4	40 40	49 median 47 median	38 28	70 70	ND
Fish 1997[28]	USA	Zafirlukast Placebo	SABA	13	514 248	18-55 (80%)	57 59	78 (16) 79 (17)	≥ 55
Green 2006[29]	UK	Montelukas/BUD (200µg/d) Placebo / BUD (200 µg/d)	SABA	4	49	42 median	51	75 (3)	ND
Helenius 2004[30]	Finland	Montelukast Placebo	SABA	4	16	18	100	101 (12)	ND
Huang 2003[31]	Taiwan	Zafirlukast Placebo	BUD (800-1600 µg/d), SABA	4	20 18	59 57	53 50	68 (1) 69 (1)	60-80
Israel 2002[32]	USA	Montelukast Placebo	SABA, antihistamines	6	339 111	34 33	48 47	67 (11) 67 (12)	50-80
Jayaram 2005[33]	Canada	Montelukast Placebo	BUD (1857 µg/d), SABA	4	14	61	57	62 (15)	ND
Jayaram 2005[34]	Canada, Brazil	Montelukast Placebo	SABA	8	19 13	31 39	58 71	77 (16) 80 (23)	ND
Kanazawa 2004[35]	Japan	Pranlukast/ BEC (800 µg/d) Placebo/ BEC (800 µg/d)	SABA	4	10	28	60	87	ND
Kanniess 2002[36]	Germany	Montelukast Placebo	BEC (tapered doses), SABA	12	26 24	38 43	50 46	95 (10) 92.3 (9)	> 80
Kraft 2006[37]	USA	Montelukast Placebo	SABA	4	19	38	32	83 (3)	ND

Table 3. (continued)

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years	Sex, %Male	FEV_1 % predicted at baseline (SD)	FEV_1 % predicted range of inclusion
Laviolette 1999[38]	North America, Europe, Africa, Australia, Asia	Montelukast/ BEC (400 µg/d) Placebo/ BEC (400 µg/d) Montelukast Placebo	SABA	16	193 200 201 48	40 median 39 median 38 41	56 52 49 40	72 (12) 71 (12) 72 (12) 71 (11)	50-85
Leff 1998[39]	USA	Montelukast Placebo	SABA, antihistamines	12	54 56	25 25	52 52	83 (11) 84 (11)	ND
Löfdahl 1999[40]	USA,Canada, Europe	Montelukast Placebo	ICS (various doses), SABA	12	113 113	40 41	42 54	85 (11) 82 (13)	> 70
Malmstrom 1999[41]	Europe, Africa, Australia, Central and South America	Montelukast Placebo	theophylline, SABA	12	387 257	35 median 36 median	40 43	65 (10) 66 (11)	50-85
Minoguchi 2002[42]	Japan	Montelukast Placebo	Theophylline, SABA	4	26	37	50	83 (16)	ND
Nakamura 1998[43]	Japan	Pranlukast Placebo	SABA	4	10 7	35 median 32 median	80 43	71 median 80 median	≥ 50
Nathan 1998[44]	USA	Zafirlukast Placebo	SABA, nasal corticosteroids	13	231 223	33 32	45 41	66.6 overall	45-80
Nathan 1999[45]	USA	Zafirlukast Placebo	SABA	13	96 95	32 30	55 53	77 (15) 78 (17)	> 55
Nathan 2005[46]	USA	Montelukast Placebo	FCS/LABA (100/50 µg/d), SABA	4	282 290	34 36	33 28	81 (10) 81 (10)	ND
Pizzichini 1999[47]	USA, Canada	Montelukast Placebo	SABA	4	19 21	31 28	63 57	69 (11) 69 (15)	ND
Reid (A) 2008[48]	Australia	Zafirlukast Placebo	SABA	12	14 7	42 median 29 median	57 43	85 median 80	≥ 60
Reid (B)		Zafirlukast/ BUD (1600 µg/d) Placebo/ BUD (1600 µg/d)			16 8	37 median 45 median	56 25	77 76	
Reiss 1998[49]	USA	Montelukat Placebo	ICS*, SABA	12	408 273	31 median 31 median	43 47	67 (11) 69 (11)	50-85
Schäper 2011[50]	Germany	Montelukast Placebo	ICS*, SABA	6	24	56 median	71	88	ND
Spahn 2006[51]	USA	Montelukast Placebo	SABA	8	11 10	13 14	64 36	88 (10) 83 (10)	60-90

Table 3. (continued)

Source	Region	Treatment arms	Concomitant treatments	Treatment duration, weeks	Patients, n	Age, years	Sex, %Male	FEV_1 % predicted at baseline (SD)	FEV_1 % predicted range of inclusion
Spector 1994[52]	USA	Zafirlukast	SABA	6	70	37	74	66	40-75
		Placebo			70	36	71	69	
Spector 2004[53]	USA	Montelukast	SABA, nasal corticosteroids	4	8	42	50	> 50	50-85
		Placebo			6	36	67		
Stelmach (A) 2007[54]	Poland	Montelukast/ BUD (200µg/d)	SABA	4	29	11	69	95 (11)	ND
		Placebo/ BUD (200µg/d)			29	12	69	94 (10)	
Stelmach (B)		Montelukast			29	10	62	96 (11)	
		Placebo			29	11	70	95 (10)	
Stelmach 2002[55]	Poland	Montelukast	SABA	4	18	12	60	77 (4)	ND
		Placebo			36	12	44	75 (5)	
Stelmach 2002[56]	Poland	Montelukast	SABA	6	16	14	67	85.(9)	ND
		Placebo			19	13	59	81 (7)	
Storms 2004[57]	USA	Montelukast/ FCS (200µg/d)	SABA	4	39	33	28	88 (10)	≥ 70
		Placebo/ FCS (200µg/d)			44	31	45	88 (11)	
Strunk 2008[58]	USA	Montelukast	BUD (800-1600µg/d), LABA, SABA	30	19	11	58	102 (14)	ND
		Placebo			19				
Tohda 2002[59]	Japan	Montelukast	BEC (various doses), SABA	24	93	16-70 range	58	87 (18)	ND
		Placebo			98		58	86 (25)	
Ulrik 2009[60]	Denmark	Montelukast	SABA	12	16	34	44	79 (14)	> 70
		Placebo			15	33	40	83 (10)	
Vaquerizo 2003[62]	Spain	Montelukast / BUD (400 -1600µg/d)	SABA	16	326	42	62	81 (19)	≥ 55
		Placebo/ BUD (400 -1600µg/d)			313	44	61	81 (21)	
Wise (A) 2009[63]	USA	Montelukast	ICS*, SABA	4	120	37	19	87 (12)	> 75
		Placebo			121	39	27	87 (15)	
Wise (B)		Montelukast			119	37	29	86 (13)	
		Placebo			120	39	32	87 (13)	
Yoo 2001[63]	South Korea	Pranlukast	ICS*, SABA	4	98	45	61	73	60-80
		Placebo			99	45	54	73	
Yoshida 2002[64]	Japan	Pranlukast	Theophylline, SABA	4	32	41	44	77 (7)	ND
		Placebo							
Zeidler 2006[65]	USA	Montelukast	SABA	4	20	36	56	86 (12)	≥ 60
		Placebo							

Abbreviations: BEC: Beclomethasone; BUD: Budesonide; FCS: Fluticasone; ICS: Inhaled corticosteroids; ND: No data; SABA: Short acting β_2-agonists; SD: Standard deviation.
* ICS used only by a proportion of participants (20%-90%) [a] Data are shown as means, unless otherwise specified.

Assessment of risk of bias

Among the 47 RCTs, 20 were assessed to be of good quality, 13 of fair quality, and 14 of poor quality (Table 4). Generation of a randomized sequence and allocation concealment were not clearly reported in the majority of trials. All but one RCT reported double-blinding; the other RCT was single-blind. Six RCTs had differential loss-to-follow-up. Intention-to-treat analyses were not widely used. RCTs were generally balanced with regard to baseline characteristics and co-interventions. Among the nine crossover trials, six had at least a 1-week wash-out period which was considered adequate; one had no wash-out period and two did not clarify whether a wash-out period was implemented.

Table 5 comprises all included trials and shows which studies contributed data to the meta-analysis of each outcome.

Table 4. Risk of bias in included trials

Source	Sequence generation	Allocation concealment	Blinding/ Patients	Blinding/ Caregivers	Blinding/ Assessors	Attrition	Selective outcome reporting	Intention-to-treat analysis	Baseline balance	Co-interventions similarity	Compliance	Other biases	Overall grade
Altman 1998	Unclear	Unclear	Low	Low	Low	Unclear	Low	Yes	Yes	Yes	Unsure	No	Fair
American Lung Association 2007	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Yes	No	Good
Awad 2002	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Yes	Yes	Unsure	Unsure	No	Fair
Baegna-Cagnani 2003	Low	Unclear	Low	Low	Low	High	Unclear	Yes	Yes	Yes	Unsure	No	Poor
Barnes 1997	Unclear	Unclear	Low	Low	Low	Low	Low	Yes	Yes	Yes	Unsure	No	Good
Baumgartner 2003	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Yes	No	Good
Busse 2001	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unsure	No	Good
Cakmak 2004	High	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	No	Unsure	Unsure	No	Poor
Dahlén 2002	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unsure	No	Good
Fish 1997	Unclear	Unclear	Low	Low	Low	High	Unclear	Yes	Yes	Yes	Unsure	No	Poor
Green 2006	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	NA	Yes	Yes	No	Fair
Helenius 2003	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	NA	Unsure	Yes	No	Fair
Huang 2003	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Israel 2002	Low	Low	Low	Low	Low	Low	Low	No	Yes	Yes	Unsure	No	Good
Jayaram 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	No	NA	Yes	Yes	No wash-out period	Poor
Jayaram 2005	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Unsure	Yes	Yes	No	Good
Kanazawa 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unsure	NA	Yes	Unsure	No	Fair
Kanniess 2002	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	Yes	Yes	Yes	Unsure	Fair

Table 4. (continued)

Source	Sequence generation	Allocation concealment	Blinding/ Patients	Blinding/ Caregivers	Blinding/ Assessors	Attrition	Selective outcome reporting	Intention-to-treat analysis	Baseline balance	Co-interventions similarity	Compliance	Other biases	Overall grade
Kraft 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unsure	NA	Yes	Unsure	No	Fair
Laviolette 1999	Low	Unclear	Low	Low	Low	Low	Low	No	Yes	Yes	Yes	No	Good
Leff 1998	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Löfdahl 1999	Low	Unclear	Unclear	Unclear	Unclear	High	Low	Unsure	Yes	No	Unsure	No	Poor
Malmstrom 1999	Low	Unclear	Low	Low	Low	High	Low	No	Yes	Yes	Yes	No	Poor
Minoguchi 2002	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	NA	Yes	Unsure	No	Good
Nakamura 1998	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	No	Yes	Unsure	No	Poor
Nathan 1998	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Nathan 1999	Unclear	Unclear	Low	Low	Low	High	Unclear	No	Yes	Yes	Unsure	No	Poor
Nathan 2005	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Poor
Pizzichini 1999	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unsure	No	Good
Reid 2008	Low	Low	Low	Low	Low	Low	Unclear	Unsure	No	Yes	Yes	No	Poor
Reiss 1998	Low	Unclear	Low	Low	Low	High	Low	No	Yes	Yes	Unsure	No	Poor
Schäper 2011	Unclear	Unclear	Unclear	High	High	Low	Unclear	Yes	NA	Unsure	Unsure	No wash-out period reported, differential duration of treatment periods	Poor
Spahn 2006	Unclear	Unclear	Low	Low	Low	Low	Unclear	Yes	Unsure	Yes	Unsure	No	Fair
Spector 1994	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	Unsure	No	Fair

Table 4. (continued)

Source	Sequence generation	Allocation concealment	Blinding/ Patients	Blinding/ Caregivers	Blinding/ Assessors	Attrition	Selective outcome reporting	Intention-to-treat analysis	Baseline balance	Co-interventions similarity	Compliance	Other biases	Overall grade
Spector 2004	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unsure	No	Yes	Unsure	No	Fair
Stelmach 2007	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Stelmach 2002	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Stelmach 2002	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear	No	Yes	Yes	Unsure	No	Fair
Storms 2004	Low	Low	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Strunk 2008	Unclear	Unclear	Low	Low	Low	High	Unclear	Yes	Unsure	No	Yes	Stopped early	Poor
Tohda 2002	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	No	Unsure	No	Good
Ulrik 2009	Unclear	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Yes	No	Good
Vaquerizo 2003	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Wise 2009	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unsure	No	Good
Yoo 2001	Low	Unclear	Low	Low	Low	Unclear	Unclear	No	Yes	Yes	Unsure	No	Fair
Yoshida 2002	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Unsure	NA	Unsure	Unsure	No	Fair
Zeidler 2006	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	No	NA	Yes	Unsure	No wash-out period reported	Poor

Abbreviations: NA: Non applicable

Table 5. List of included trials and contribution to meta-analysis of each outcome

Source	Exacerbations	FEV_1	Daytime symptoms	SABA use	Nocturnal awakenings	Asthma specific quality of life
Altman 1998		**X** (% change from baseline)	**X**	**X** (change from baseline)		
American Lung Association 2007	**X**	**X** (change from baseline in liters)				**X**
Awad 2002		**X** (change from baseline in liters) **X** (change from baseline in FEV_1 predicted)	**X**			
Baena-Cagnani 2003				**X** (% change from baseline)		
Barnes 1997		**X** (change from baseline in liters)	**X**	**X** (change from baseline)		
Baumgartner 2003	**X**	**X** (% change from baseline)		**X** (% change from baseline)		
Busse 2001	**X**	**X** (% change from baseline)	**X**	**X** (change from baseline)	**X**	
Cakmak 2004						
Dahlén 2002		**X** (% change from baseline)	**X**	**X** (change from baseline)		**X**
Fish 1997		**X** (change from baseline in liters) **X** (change from baseline in FEV_1 % predicted)		**X** (change from baseline)	**X**	
Green 2006						
Helenius 2004						
Huang 2003						
Israel 2002	**X**	**X** (change from baseline)		**X** (% change from baseline)		
Jayaram 2005						
Jayaram 2005		**X** (change from baseline)	**X**	**X** (change from baseline)		
Kanazawa 2004						
Kanniess 2002		**X** (change from baseline)	**X**	**X** (change from baseline)		
Kraft 2006		X (sensitivity analysis)				
Laviolette 1999	**X**	**X** (% change from baseline)	**X**	**X** (% change from baseline)	**X**	
Leff 1998		**X** (change from baseline)				
Löfdahl 1999		**X** (% change from baseline)				
Malmstrom 1999	**X**	**X** (% change from baseline)	**X**	**X** (% change from baseline)	**X**	**X**
Minoguchi 2002						
Nakamura 1998						
Nathan 1998	X (sensitivity analysis)	**X** (change from baseline) **X** (change from baseline in FEV_1 % predicted)		**X** (change from baseline)	**X**	
Nathan 1999						
Nathan 2005						
Pizzichini 1999		**X** (% change from baseline)	**X**	**X** (% change from baseline)		
Reid (A) 2008		**X** (change from baseline)		**X** (change from baseline)		
Reid (B)						
Reiss 1998	**X**	**X** (% change from baseline)	**X**	**X** (% change from baseline)	**X**	
Schäper 2011						

Table 5. (continued)

Source	Exacerbations	FEV_1	Daytime symptoms	SABA use	Nocturnal awakenings	Asthma specific quality of life
Spahn 2006	**X**	**X** (change from baseline in FEV_1 % predicted)	**X**	**X** (change from baseline)		
Spector 1994		**X** (% change from baseline)		**X** (change from baseline)	**X**	
Spector 2004						
Stelmach (A) 2007		**X** (change from baseline in FEV_1 % predicted)				
Stelmach (B)						
Stelmach 2002		**X** (change from baseline in FEV_1 % predicted)				
Stelmach 2002		**X** (change from baseline in FEV_1 % predicted)				
Storms 2004		**X** (change from baseline in FEV_1 % predicted)				
Strunk 2008						
Tohda 2002						
Ulrik 2009						
Vaquerizo 2003		**X** (% change from baseline)	**X**	**X** (% change from baseline)		**X**
Wise (A) 2009	**X**	**X** (change from baseline)				**X**
Wise (B)						
Yoo 2001		**X** (change from baseline)	**X**			
Yoshida 2002						
Zeidler 2006		X (sensitivity analysis)		X (sensitivity analysis)	X (sensitivity analysis)	

Studies not included in the meta-analyses

A summary of the results from the trials included in the systematic review, but not meta-analyzed, is presented in Table 6. The reasons for exclusion are also provided. Seven crossover trials were not included in the meta-analyses due to inadequate reporting or missing data.

Table 6. Effect of LTRAs versus placebo in trials not included in the meta-analyses

Outcome measure	Study	LTRA, (95% CI)	Placebo (95% CI)	Reported p-value (difference in effects)	Reason for exclusion
FEV_1(L) change from baseline					
	Baena-Cagnani 2003	0.18	0.05	p< 0.01	data provided only for patients with FEV_1 % predicted less than 80%
	Cakmak 2004	ND	ND	NS	no effect estimates reported
	Green 2006	-0.05 (-0.13, 0.03)	-0.07 (-0.20, 0.05)	NS	crossover trial
	Helenius 2004	-0.01	0.02	NS	crossover trial
	Jayaram 2005	0.09	0.02	NS	crossover trial
	Nathan 1999	0.23	0.04	p < 0.05	patients with PEF ≥ 10%
		0.15	0.07	NS	patients with PEF < 10%
	Schäper 2011‡	0.2	-0.5	NS overall	1st period of crossover
		0.2	-0.2		2nd period of crossover
	Spector 2004	ND	ND	NS	no effect estimates reported
	Tohda 2002	ND	ND	NS	no effect estimates reported
	Ulrik 2009	ND	ND	NS	no effect estimates reported
	Yoshida 2002	9.8	-0.2	p < 0.05	crossover trial
FEV_1 % predicted change from baseline					
	Helenius 2004	-1.5	-1.3	NS	crossover trial
	Jayaram 2005	3.6	1.5	p = 0.4	crossover trial
	Nakamura 1998	-3.5 median	1.1 median	NS	data reported as medians
	Schäper 2011‡	3.6	-0.3	NS overall	1st period of crossover
		5	-1.7		2nd period of crossover
Daytime symptoms change from baseline					
scale: 0-3 (more symptoms)	Fish 1997†	-	-	p < 0.01 (-1.4)	expressed as weekly totals
scale: 0-3 (more symptoms)	Green 2006	-0.09 (-0.27, 0.10)	-0.07 (-0.20, 0.06)	NS	crossover trial
scale: 5-35 (fewer symptoms)	Jayaram 2005	-0.3	0.6	p =0.6	crossover trial
scale: 0-6 (more symptoms)	Löfdahl 1999	0.07	0.12	NS	inadequate reporting
scale: 0.5-10 (more symptoms)	Minoguchi 2002	-1.6	0	-	crossover trial
scale: 0-3 (more symptoms)	Nathan 1998 †	-	-	p < 0.01 (-0.14)	'adjusted' treatment effect scale: 0-3 (more symptoms)
scale: 0-3 (more symptoms)	Spector 1994	-27%	-13%	p ≤ 0.01	reported as percentages
scale: 0-4 (more symptoms)	Zeidler 2006 *	-0.2	0.2	NS	crossover trial

Table 6. (continued)

Outcome measure	Study	LTRA, (95% CI)	Placebo, (95% CI)	Reported p-value (difference in effects)	Reason for exclusion
SABA use (puffs/day) change from baseline					
	Awad 2002	-14.3	-0.6	NS	number of SABA tablets
	Cakmak 2004	ND	ND	NS	no effect estimates reported
	Green 2006□	-0.6 (-1.14, 0.06)	0.9 (-0.07, 2.5)	NS	crossover trial
	Jayaram 2005□	-16	-9.4	NS	µg/day
	Nakamura 1998	1.4 median	0.3 median	p < 0.01 (-1.4 median)	data reported as medians
	Nathan 1999	-1.79	0.1	p < 0.05	patients with PEF ≥ 10%
		-0.75	-0.31	NS	patients with PEF < 10%
	Schäper 2011‡	ND	ND	p < 0.05	crossover trial
	Yoo 2001	-5.36	0.28	-	puffs/2 weeks
Nocturnal awakenings (per week) change from baseline					
	Altman 1998	-1.4 (-2.1,-0.8)	0.8 (-1.4,-0.1)	-	N analyzed missing
	Dahlén 2002	-0.18	-0.04	-	N analyzed missing
	Nathan 1999	-1	-0.23	p < 0.05	patients with PEF ≥ 10%
		-0.7	-0.37	NS	patients with PEF < 10%
	Nathan 2005	ND	ND	NS	no effect estimates reported
	Reid (A) 2008	0.2	0.7	-	change in total awakenings
	Reid (B) 2008	-1.6	-1.1	-	change in total awakenings
	Wise (A) 2009	-	-	NS	patients with at least 1 awakening
	Wise (B) 2009	-	-	NS	patients with at least 1 awakening
	Zeidler 2006*	-0.1	0	NS	
ASQL change from baseline					
scale: 0-6 (better)	Altman 2002	-	-	-	pooled effect for all doses used in the trial (scale 0-6)
scale: 1-7 (better)	Busse 2001	ND	ND	-	no clinically meaningful difference for any AQLQ domain
scale: 1-7 (better)	Green 2006□	0.2 (0,0.2)	0 (-0.2,0.3)	NS	crossover trial
scale: ND	Spector 2004	ND	ND	-	significant improvement
scale: 1-7 (better)	Zeidler 2006*	0.5	0.1	p = 0.04	

Abbreviations: ASQL: Asthma-specific quality of life; AQLQ: Asthma quality of life questionnaire; CI: Confidence interval; FEV_1: Forced expiratory volume in one second; ND: No data; NS: Not statistically significant; PEF: Peak Expiratory Flow; SABA: Short acting β_2-agonist use.

* Included in sensitivity analyses for FEV_1, SABA use, and nocturnal awakenings.

† Not meta-analyzed because final values and changes from baseline should not be combined together as standardized mean differences[74]

‡ Not meta-analyzed because timing of assessment of endpoints differed between comparator groups (6 weeks vs. 4 weeks)

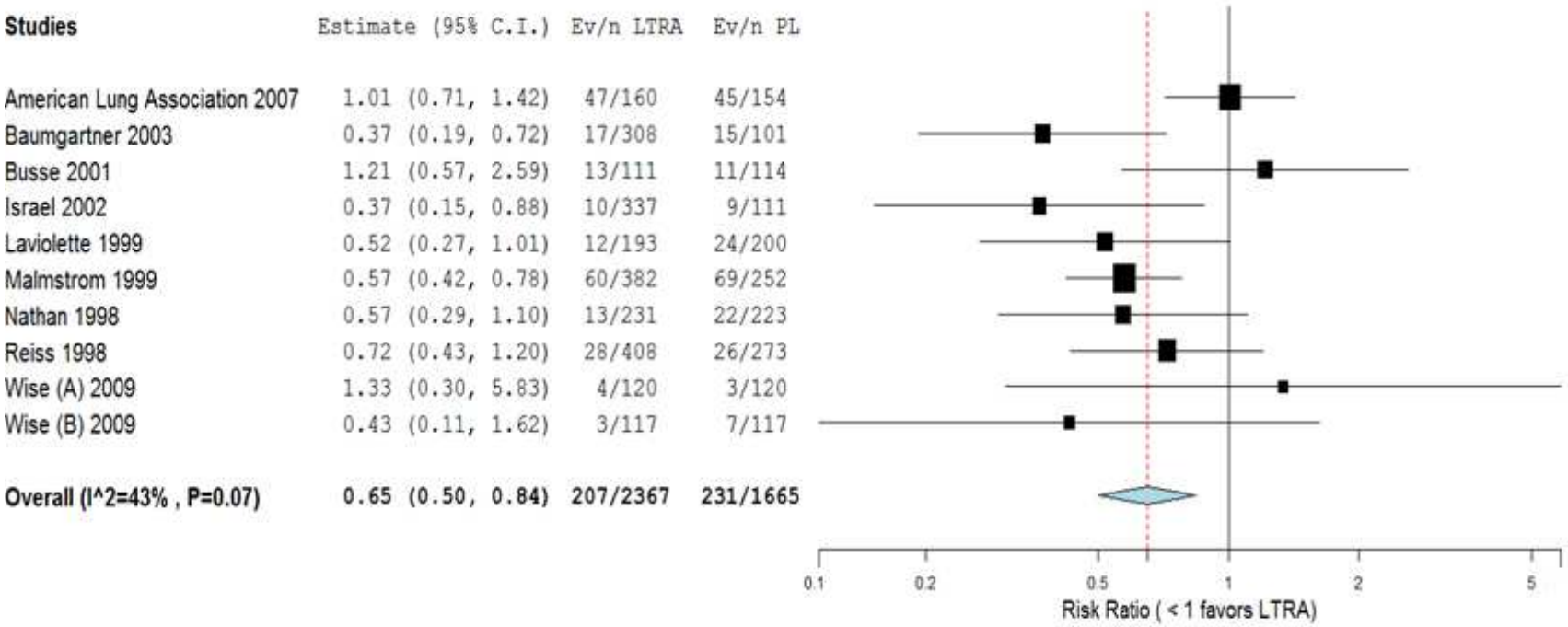
□ Not meta-analyzed due to missing correlation

Asthma exacerbations

The definition of an exacerbation reported in nine RCTs was consistent with our definition and, therefore, these trials were included in our main analysis (one RCT included two separate comparisons of LTRA vs. placebo in different patients). All definitions of exacerbations reported in the included RCTs are presented in Table 7. The main analysis included 2367 patients who received a LTRA and 1665 patients who received placebo.

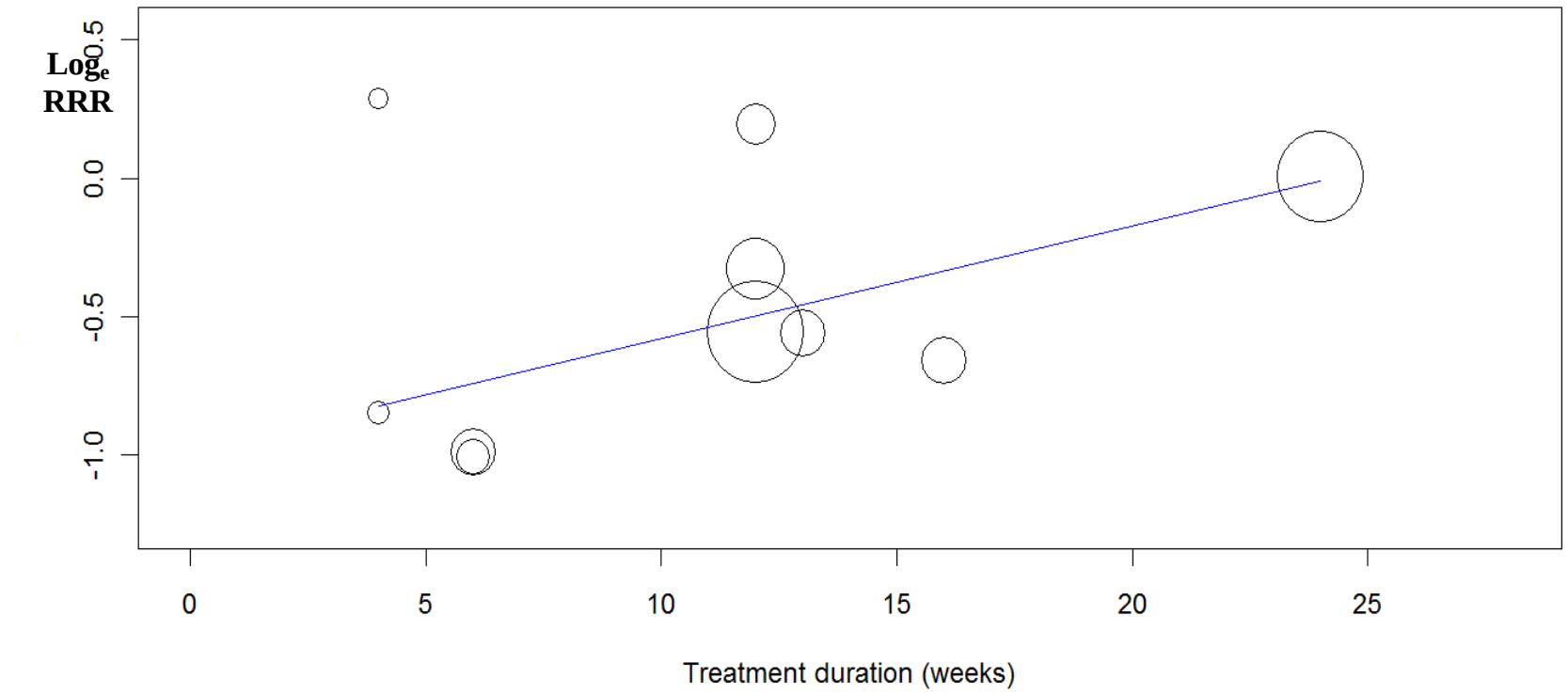
Overall, patients treated with LTRAs displayed a 35% decreased risk of experiencing an exacerbation compared to those treated with placebo (summary RR = 0.65, 95% CI: 0.5, 0.84) (Figure 2). The observed statistical heterogeneity was moderate (I^2 = 43%). The addition of the one RCT with an unclear definition of an exacerbation did not change the results (summary RR = 0.65, 95% CI: 0.51, 0.84, I^2 = 37%). The results of the univariate meta-regressions that we used in order to explore the effect of study-level characteristics on the pooled treatment effect are presented in Table 8. Across studies, the magnitude of the effect appeared to weaken as the study duration increased; the summary RR increased by 4% with every additional week of treatment duration (Relative Risk Ratio = 1.04, 95% CI: 1.01, 1.07) [Figure 3]. The limited number of studies in which all patients used ICS precluded meta-regression of this factor. Similarly, we could not assess the impact of the type of LTRA on the summary estimate because montelukast was administered in seven RCTs and zafirlukast in two. We could not examine the effect of allergic rhinitis or aspirin-induced asthma on the summary estimate due to incomplete reporting in the RCTs included.

Figure 2. Summary forest plot for asthma exacerbation



The center of the diamond (red dotted line) represents the pooled Risk Ratio and its size the length of the 95% Confidence Interval. Risk Ratios (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis.

Figure 3. Meta-regression plot of $\log_e$ relative risk ratio for exacerbation by treatment duration



Blue line represents the change in $\log_e$ relative risk ratio. The relative risk ratio is defined as the ratio of Risk Ratios for exacerbation for each 1 week change in treatment duration. Circles represent studies included in the analysis and their size is proportional to the weight assigned in the meta-regression.

Table 7. Definitions of exacerbations in included trials

Source	Reported definitions
Altman 1998	more than 20% decrease in PEFR compared to baseline, more than 70% increase in SABA use, more than 50% increase in symptom score, "awake all night", or unscheduled visit to a doctor or hospital (reported as percent of days with exacerbations)
American Lung Association 1997	required use of oral corticosteroids or unscheduled health care (included in main analysis)
Awad 2002	treated with ICS
Baumgartner 2003	required use of oral corticosteroids or unscheduled medical care (included in main analysis)
Busse 2001	required use of oral corticosteroids (included in main analysis)
Dahlen 2002	more than 20% decrease in PEFR compared to baseline, more than 70% increase in SABA use, more than 50% increase in symptom score, "awake all night", or unscheduled visit to a doctor or hospital (reported as percent of days with exacerbations) [4 exacerbations occurred in each group]
Green 2006	required use of oral corticosteroids (Not included in main analysis because only number of events were reported)
Israel 2002	required unscheduled visit to the doctor's office or emergency department, hospitalization, or treatment with oral corticosteroids (included in main analysis)
Jayaram 2005	treated with ICS
Kanniess 2002	more than 50% decrease in PEFR compared to values at entry, or an increase in daytime symptoms of 3 or more, or in night-time symptoms of 2 or more on at least 3 consecutive days
Laviolette 1999	required unscheduled visit, hospitalization, or treatment with oral corticosteroids (included in main analysis)
Leff 1998	treated with ICS
Malmstrom 1999	required unscheduled visit, hospitalization, or treatment with oral corticosteroids (included in main analysis)
Nathan 2005	required treatment with asthma medications beyond study medications (included in sensitivity analysis)
Reiss 1998	required oral corticosteroids (included in main analysis)
Spahn 2006	required oral corticosteroids (included in main analysis)
Spector 1994	no specific treatment protocol
Vaquerizo 2003	more than 20% decrease in PEFR compared to baseline, more than 70% increase in SABA use, more than 50% increase in symptom score, "awake all night", or unscheduled visit to a doctor or hospital (reported as percent of days with exacerbations)
Wise 2009	required urgent asthma care or oral corticosteroids (included in main analysis)
Zeidler 2006	required oral corticosteroids (not included in analysis because it is was not specified in which group of patients 2 exacerbations occurred)

Abbreviations: ICS: Inhaled corticosteroids; PEFR: Peak expiratory flow rate; SABA: Short-acting β_2-agonist.

Table 8. Meta-regression analyses examining the association of pre-specified covariates with the pooled treatment effect for exacerbation

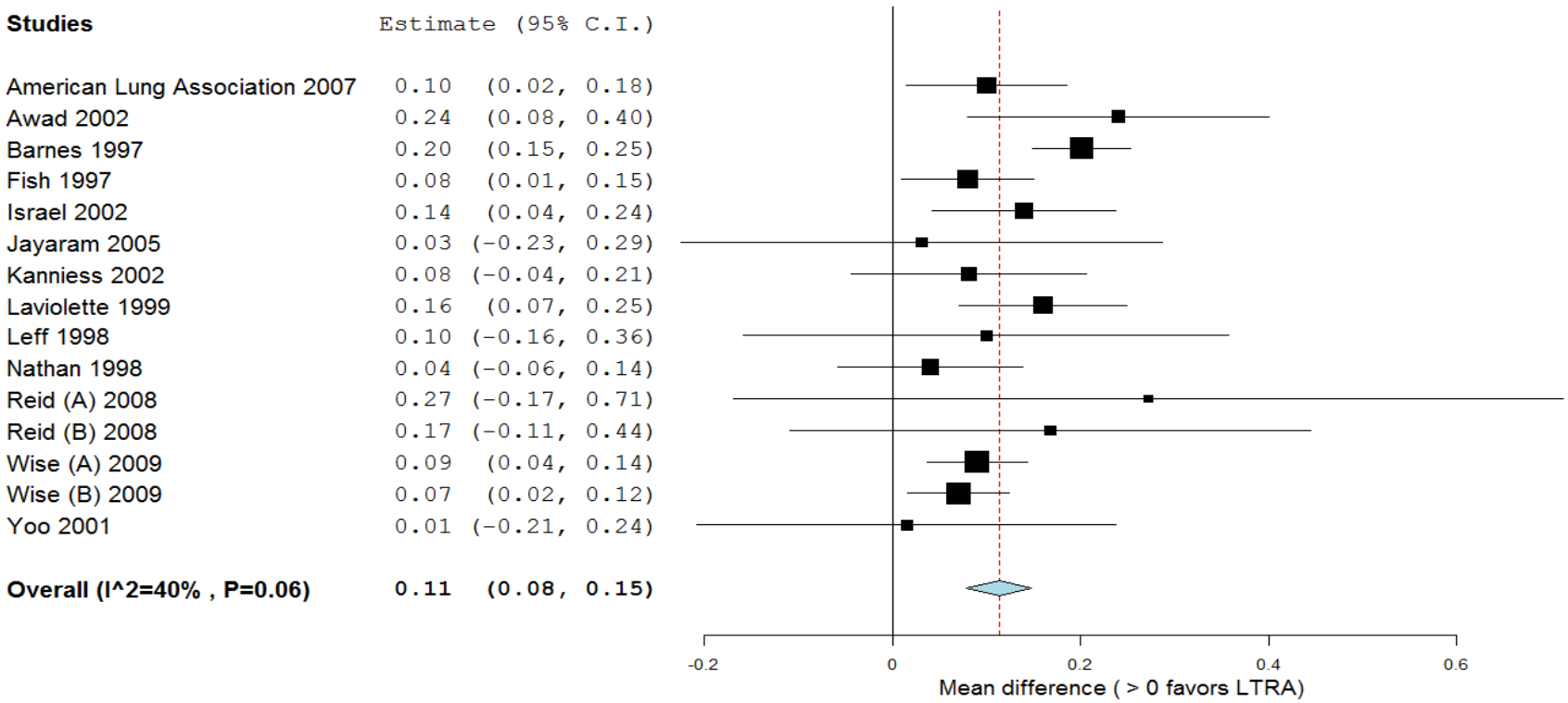
Covariate	Relative risk	95% CI
Treatment duration	1.04	1.01-1.07
Equal ICS use*	Not performed†	
ICS dose	Not performed†	
Type of LTRA	Not performed†	
Allergic rhinitis	Not performed‡	
Aspirin-induced asthma	Not performed‡	

* No use of ICS was used as the reference group
† Analyses were not performed due to insufficient number of RCTs in each subgroup
‡ Analyses were not performed due to inadequate reporting in the RCTs

Forced Expiratory Volume in one second

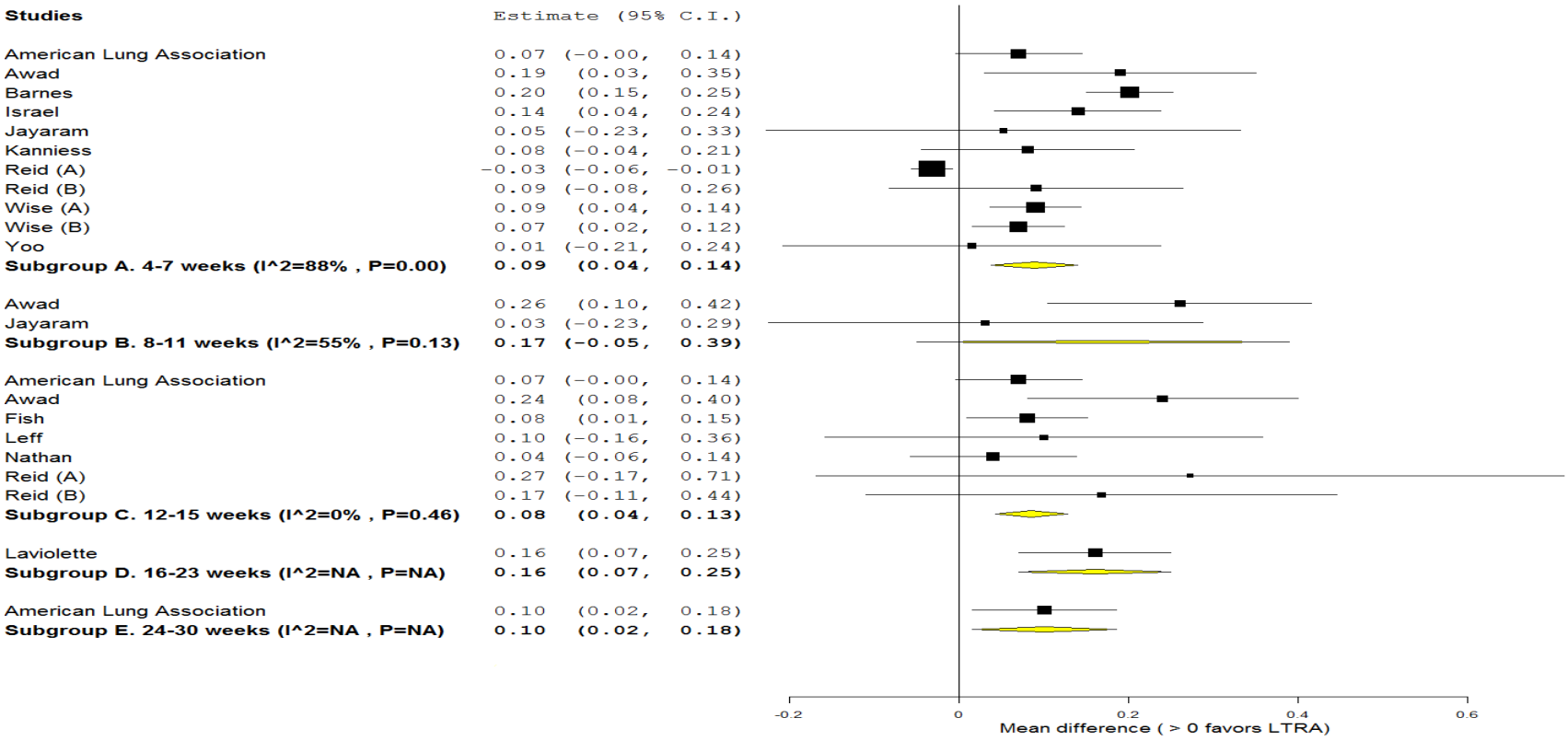
Forty-three trials reported the effect of LTRAs compared with placebo on FEV_1. Thirty-five trials reported FEV_1 in liters (L) and 15 as percent of predicted values (FEV_1 % predicted). A mean difference in change from baseline in FEV_1 (L) was computed for 13 trials, a mean difference in percent change from baseline was computed for 11 trials, and a mean difference in FEV_1 % predicted was computed for 8 trials. Overall, LTRAs significantly improved FEV_1 (L) compared to placebo (summary MD = 0.11, 95% CI: 0.08, 0.15) (Fig 4). The observed statistical heterogeneity was moderate (I^2 = 48%). Using meta-regression, there was no association between treatment duration and the effect (p-value = 0.93) [Fig 5 and 6]. No association was observed between concomitant ICS use and the pooled effect (p-value = 0.39) [Fig 7]. There was no significant difference in the effect of zafirlukast compared to montelukast on the summary effect (p-value = 0.88) [Fig 8]. Results did not change with the inclusion of one crossover study (summary MD = 0.12, 95% CI: 0.08, 0.15).

Figure 4. Summary forest plot of mean difference for FEV_1 (L)



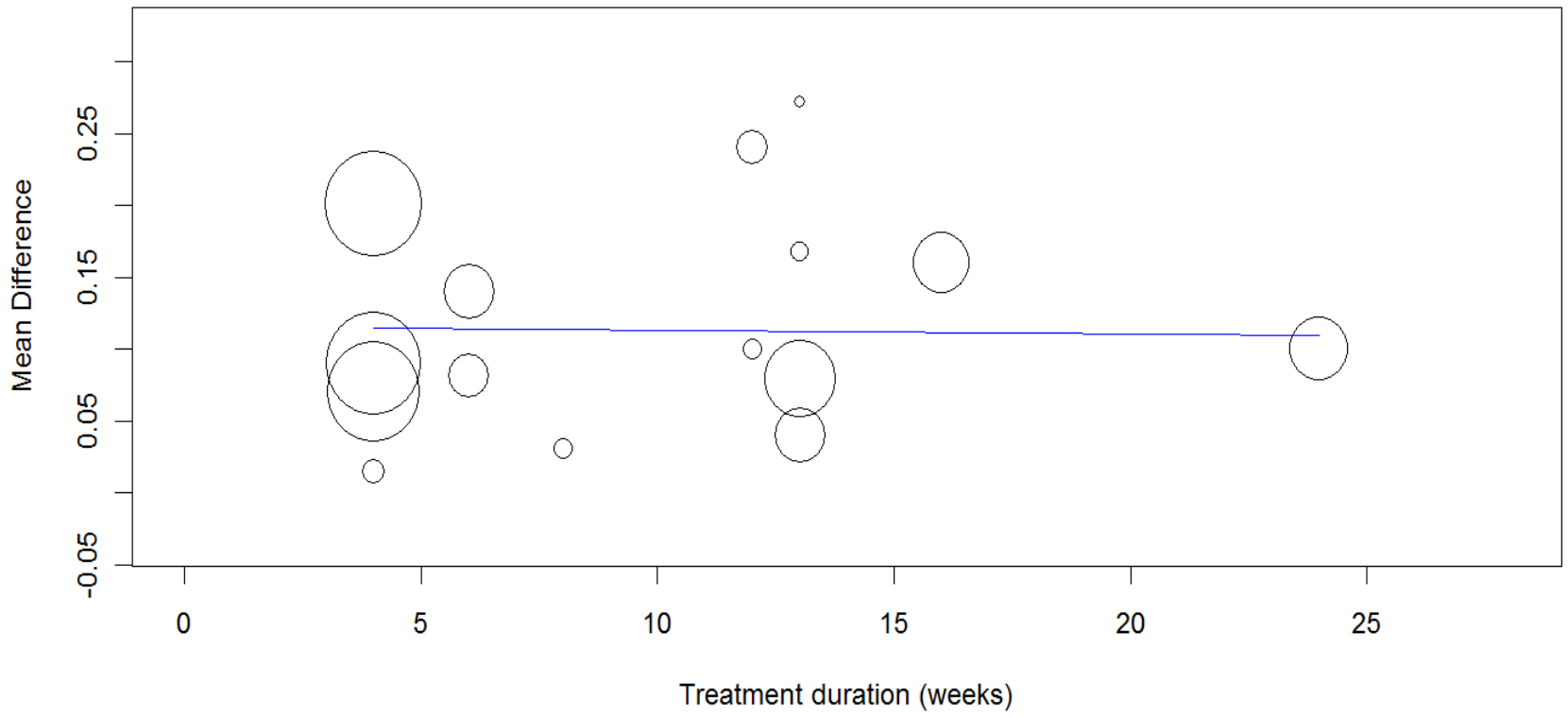
The center of the diamond (red dotted line) represents the pooled mean difference and its size the length of the 95% Confidence Interval. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis.

Figure 5. Summary forest plot of mean difference by subgroups of treatment duration for FEV_1 (L)



The center of the yellow diamonds represents the pooled mean difference and its size the length of the 95% Confidence Interval in each subgroup. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. Some studies may contribute data to more than one subgroup.

Figure 6. Meta-regression plot of mean difference in FEV_1 by treatment duration



Blue line represents the change in mean difference. Circles represent studies included in the analysis and their size is proportional to the weights assigned in meta-regression.

Figure 7. Summary forest plot of mean difference by subgroups of ICS use for FEV_1 (L)

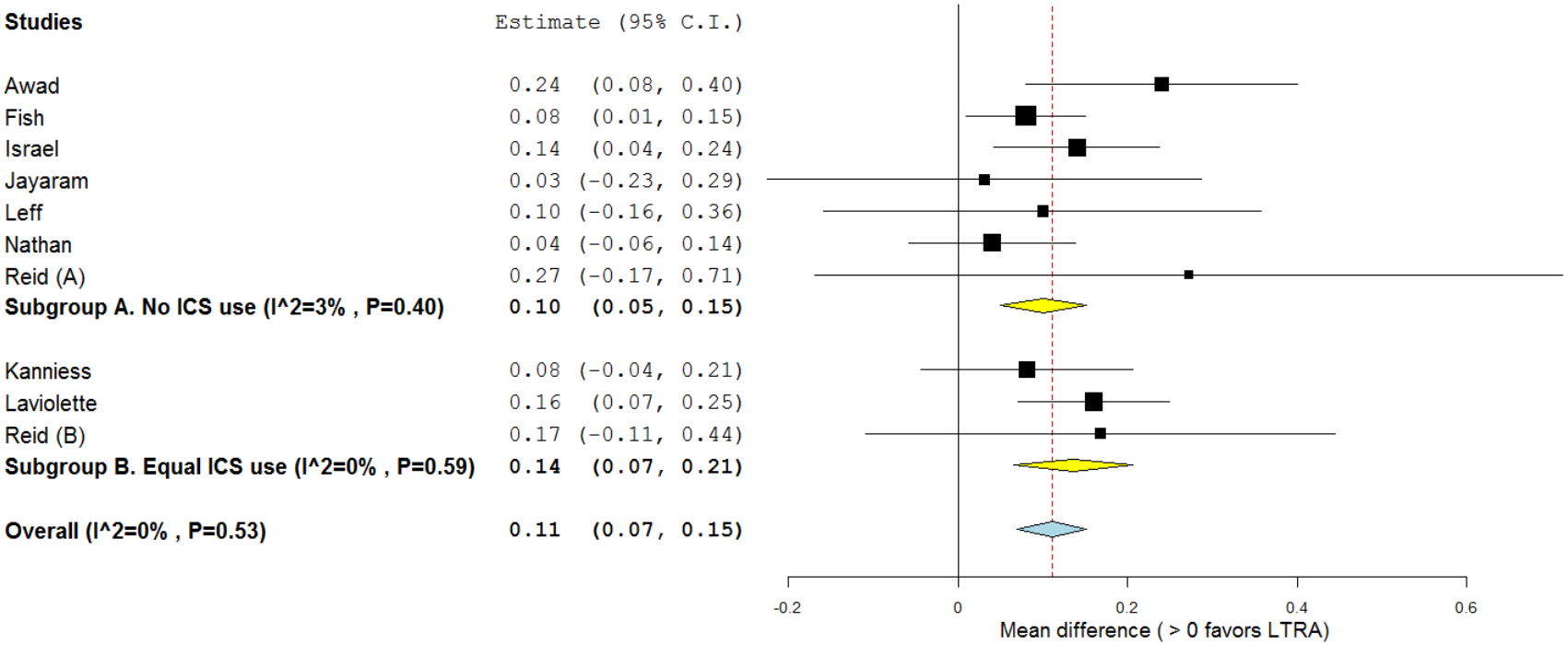
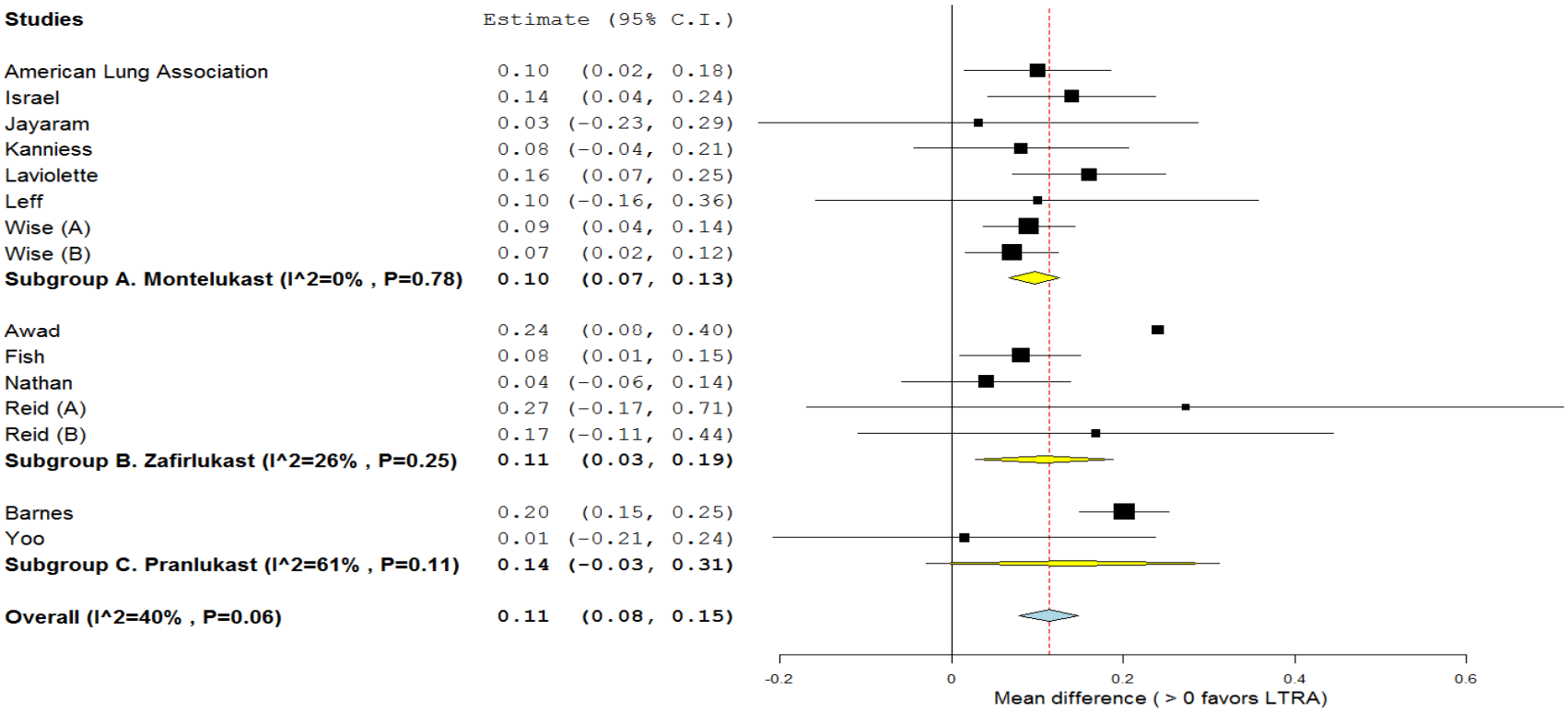


Figure 8. Summary forest plot of mean difference by subgroups of LTRA for FEV_1 (L)



The mean difference in percent change from baseline between LTRAs and placebo was statistically significant (summary MD = 5.95, 95% CI: 3.30, 8.60). Trials were heterogeneous (I^2 = 69%) [Fig 9]. The treatment effect was larger in studies of shorter duration (MD = -0.62, 95% CI: -1.16, -0.08) [Fig 10 and 11]. The limited number of studies precluded meta-regression of other pre-specified factors (Fig 12 and 13).

LTRAs significantly improved FEV_1 % predicted (summary MD = 4.16, 95 % CI: 1.47, 6.85) [Fig 14]. Studies were significantly heterogeneous (I^2 = 63%). No significant association was observed between treatment duration, concomitant ICS use, or type of LTRA with the pooled effect (p-value = 0.8, 0.4, 0.6, respectively) [Fig 15-18]. The summary estimate increased when two crossover trials were included in the meta-analysis (summary MD = 5.07, 95% CI: 2.46, 7.69).

Figure 9. Summary forest plot of mean difference in percent change from baseline

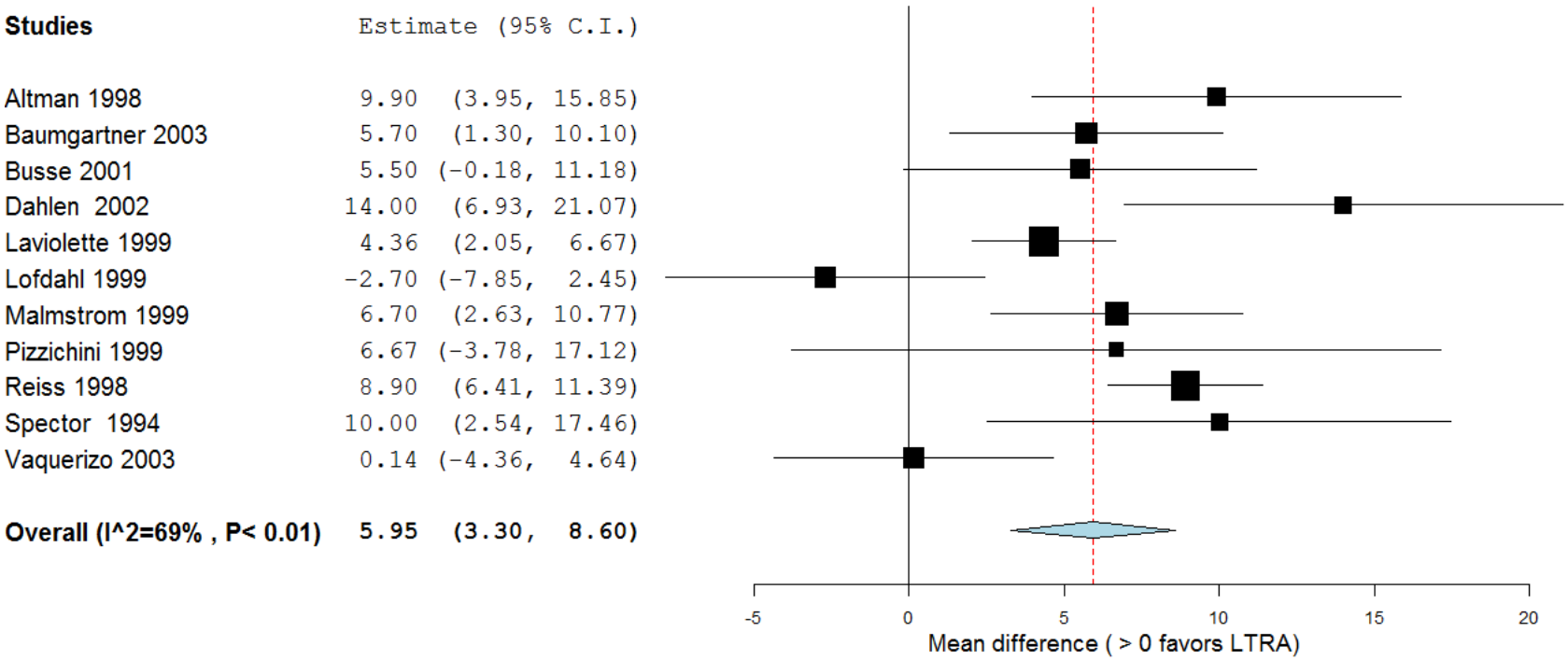


Figure 10. Meta-regression plot of mean difference in percent change from baseline for FEV_1 by treatment duration

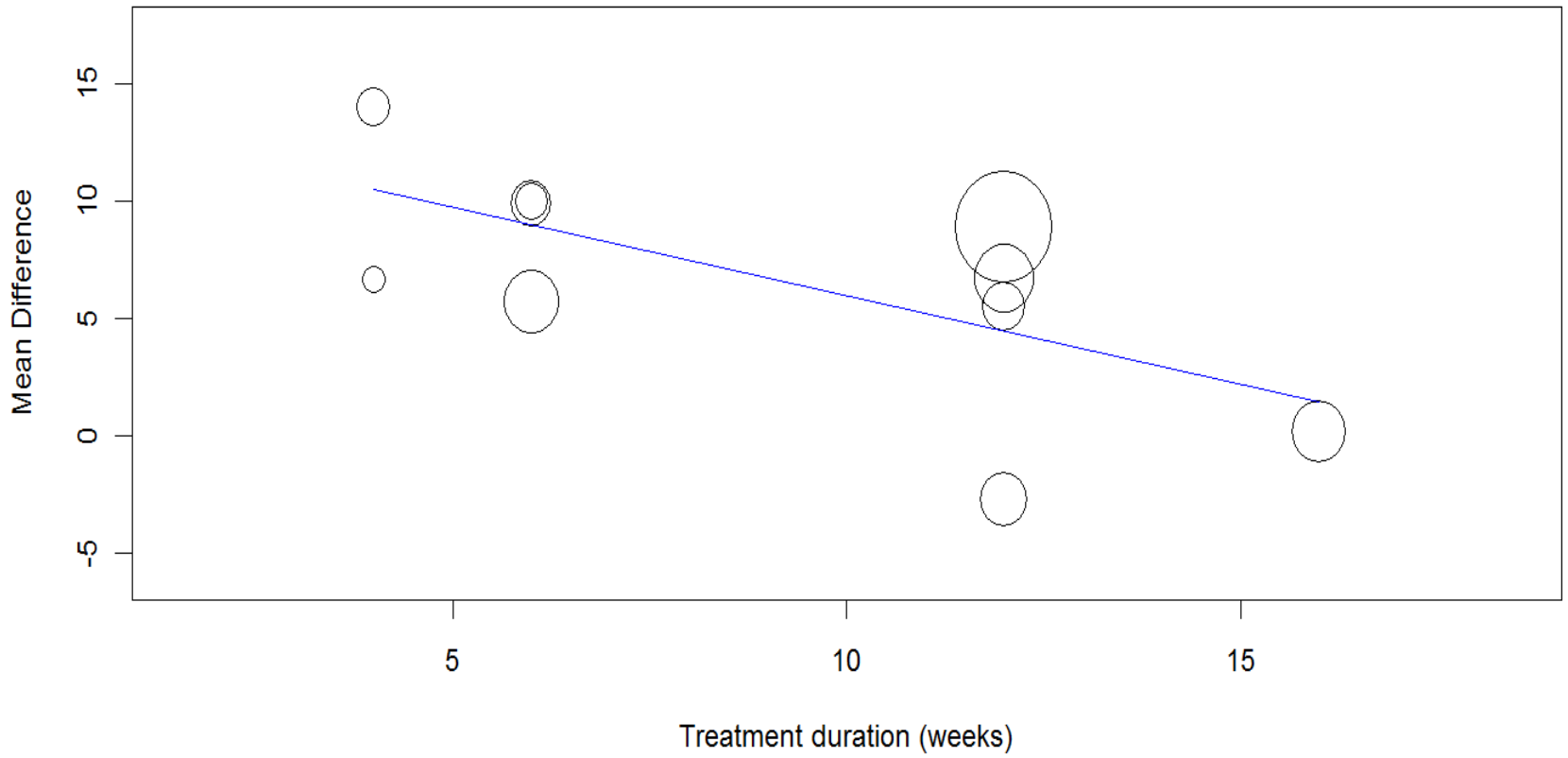


Figure 11. Summary forest plot of mean difference in percent change from baseline by subgroups of treatment duration for FEV_1

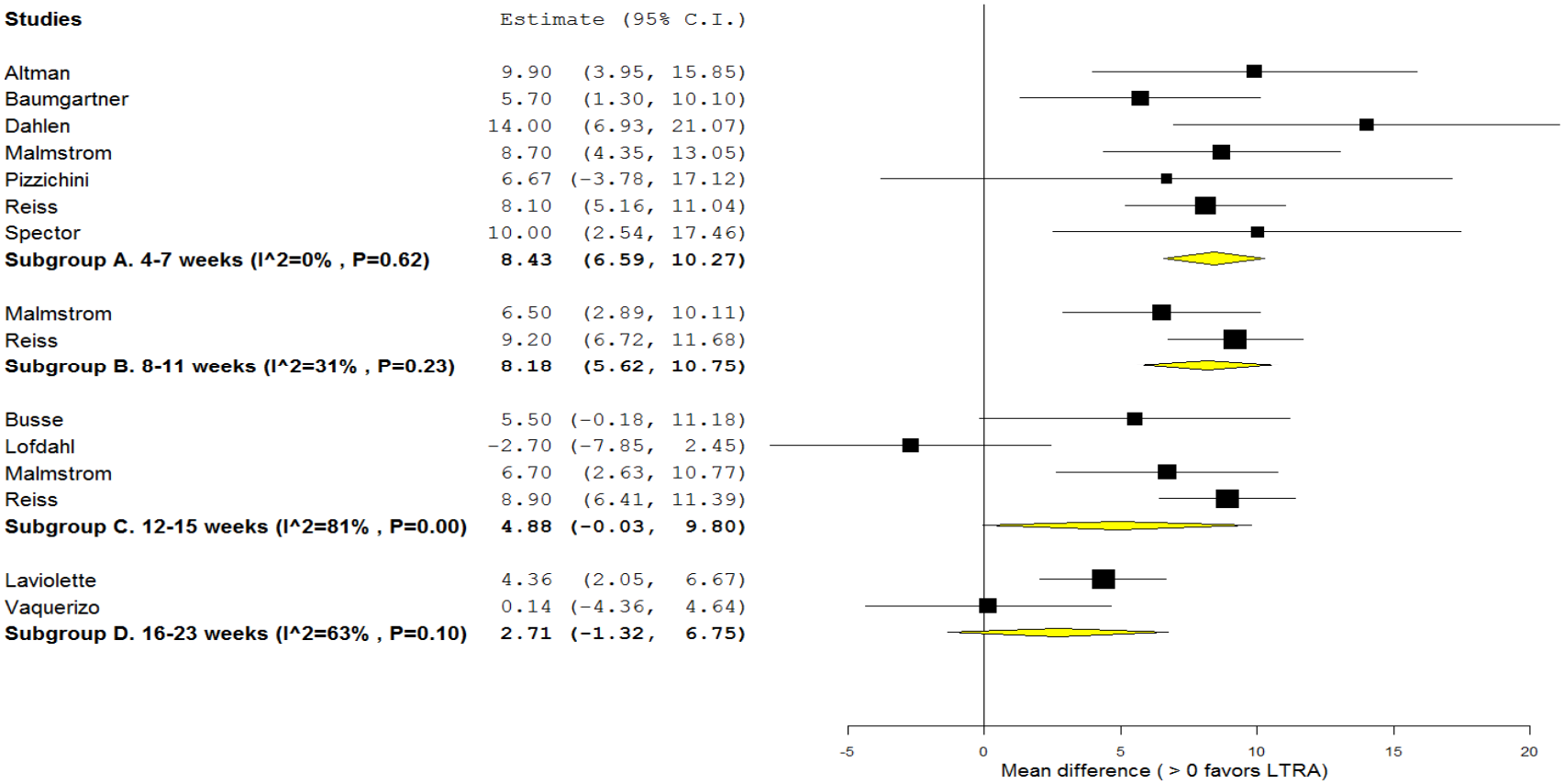


Figure 12. Summary forest plot of mean difference in percent change from baseline by subgroups of ICS use for FEV_1

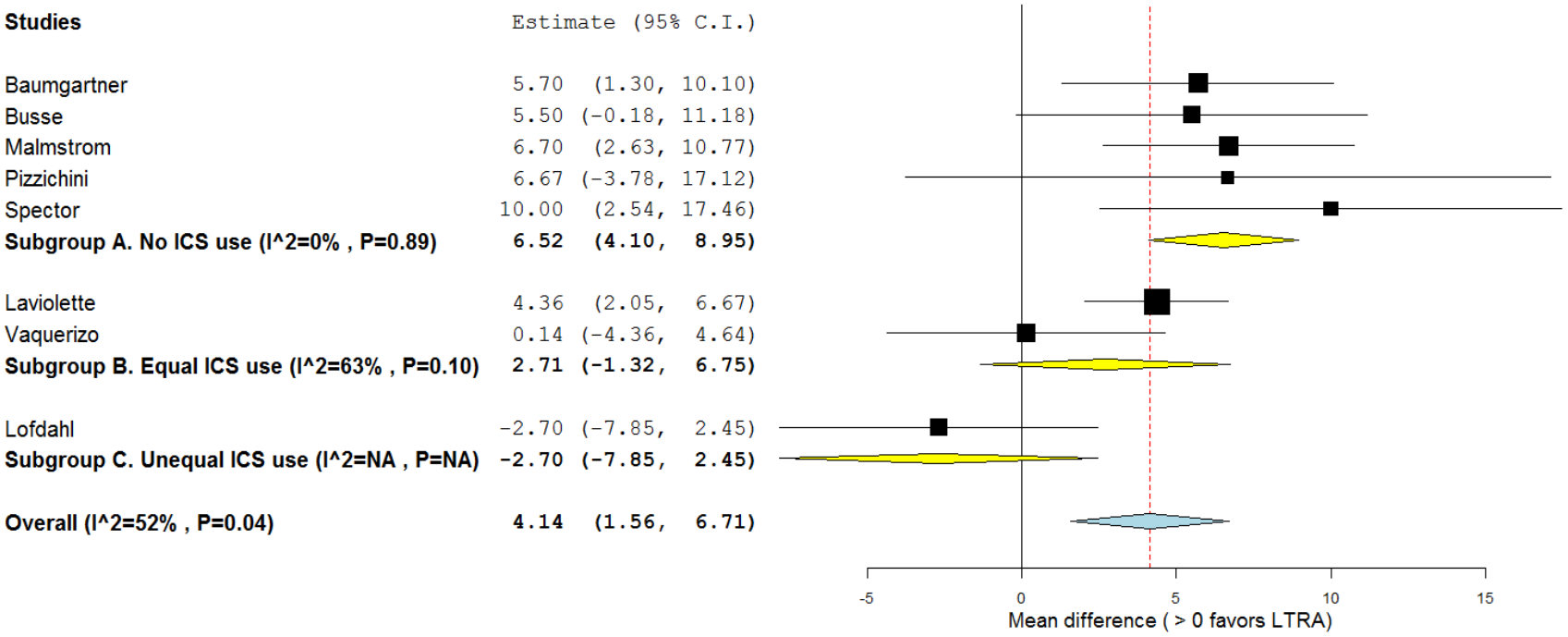


Figure 13. Summary forest plot of mean difference in percent change from baseline by subgroups of LTRAs for FEV_1

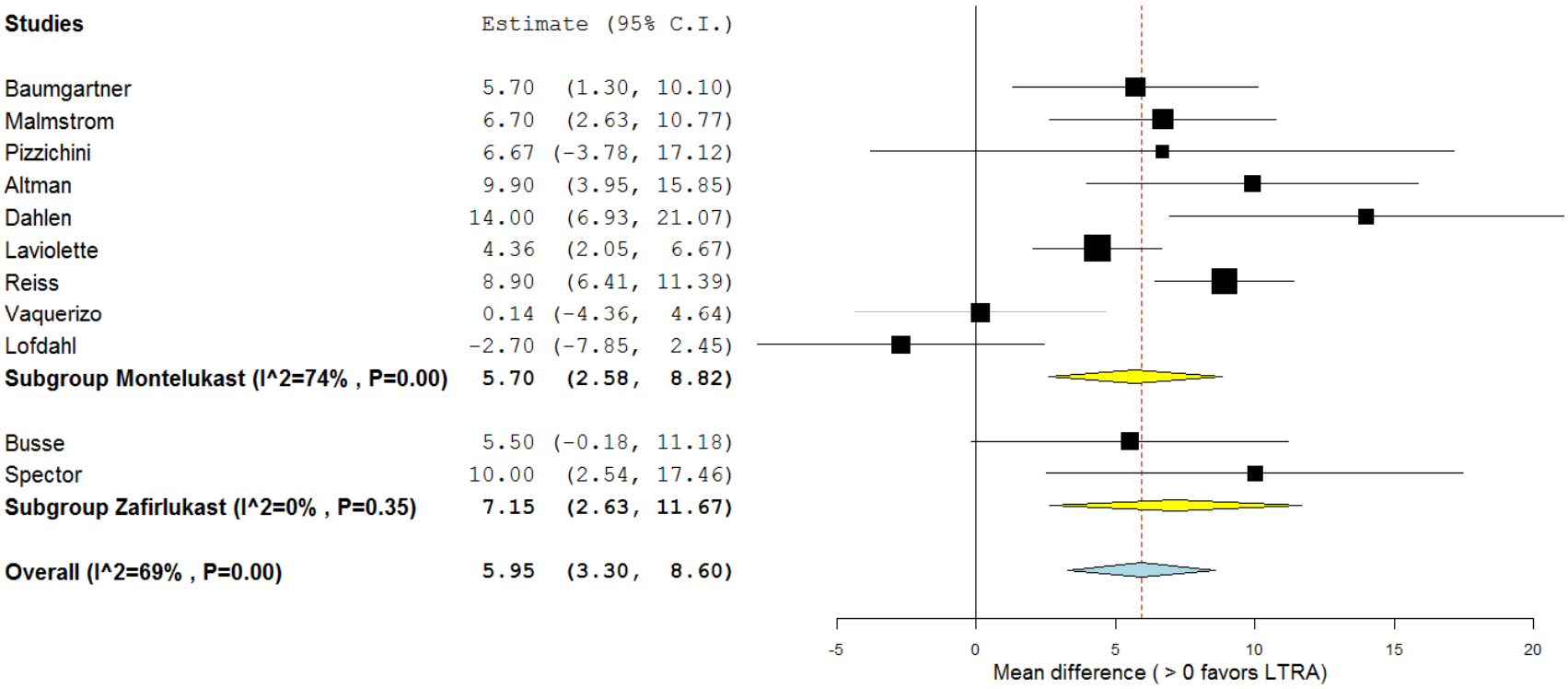


Figure 14. Summary forest plot of mean difference for FEV_1 % predicted

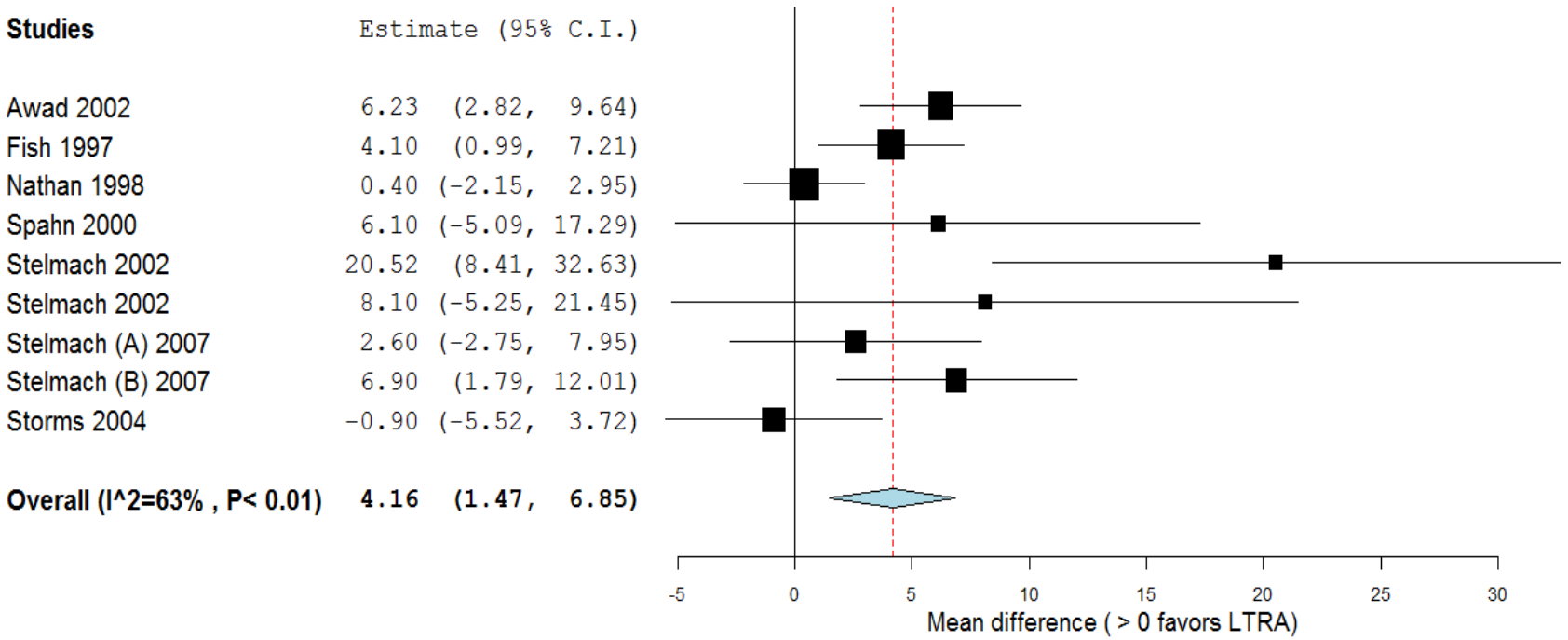


Figure 15. Meta-regression plot of mean difference for FEV_1 % predicted by treatment duration

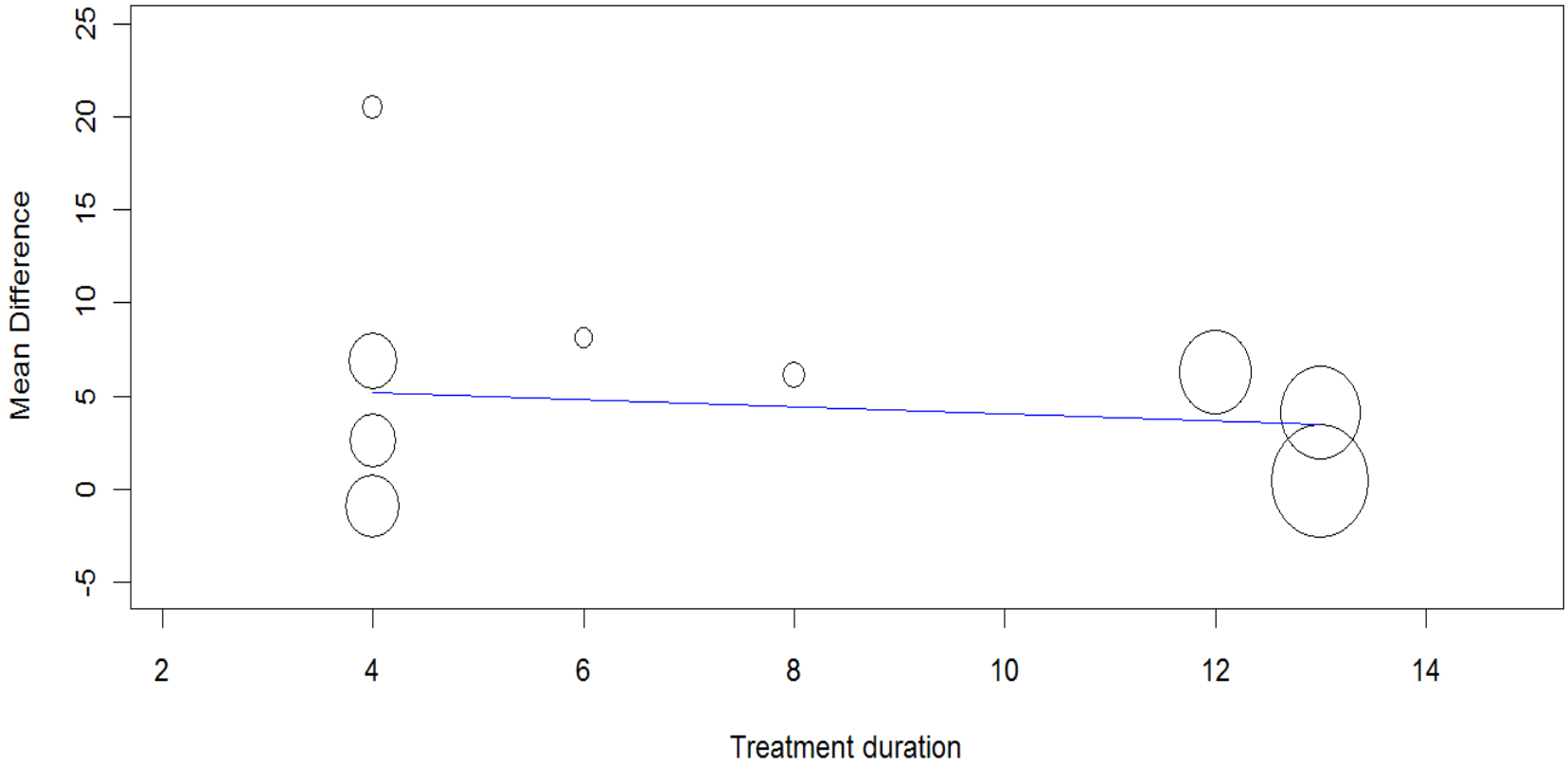


Figure 16. Summary forest plot of mean difference by subgroups of treatment duration for FEV_1 % predicted

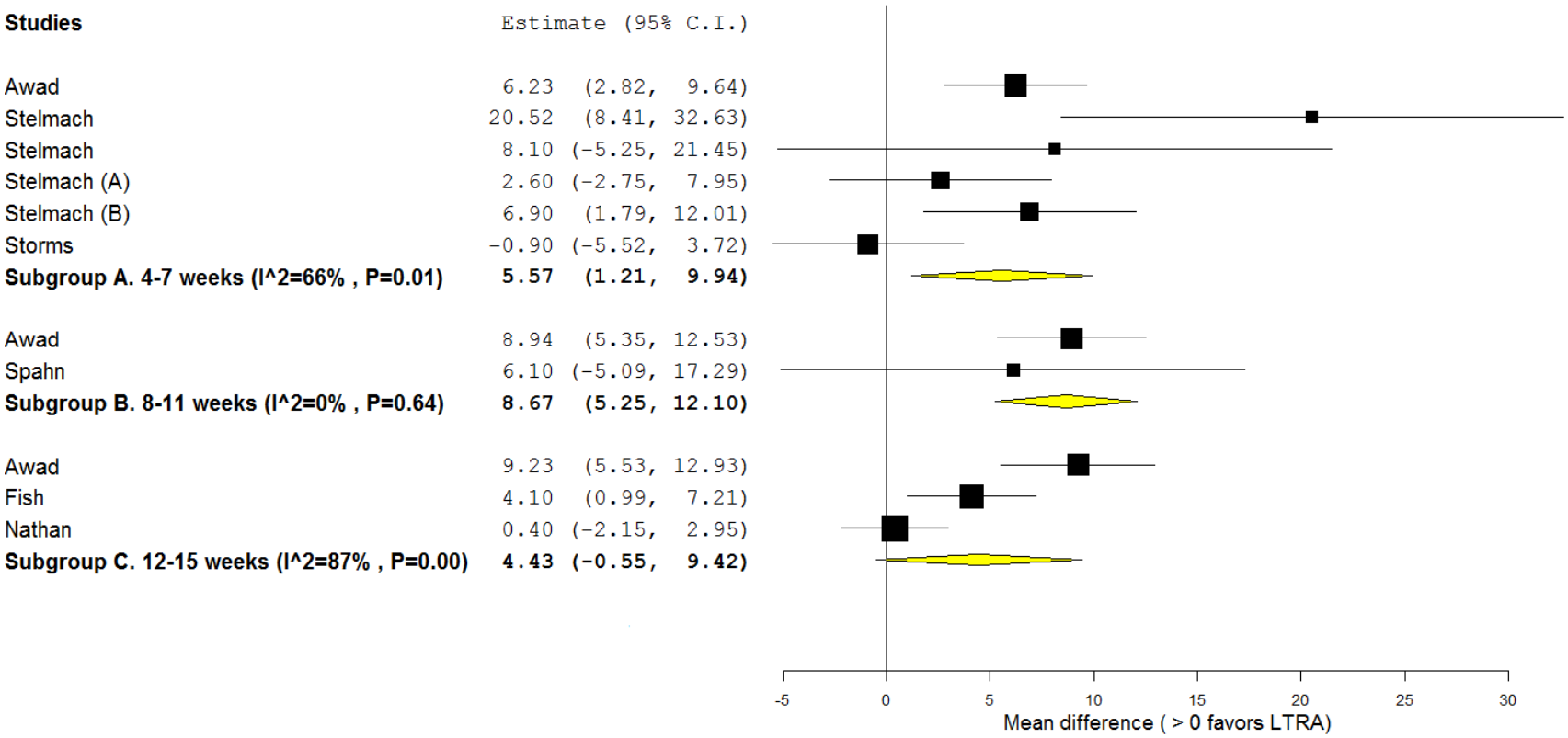


Figure 17. Summary forest plot of mean difference by subgroups of ICS use for FEV_1 % predicted

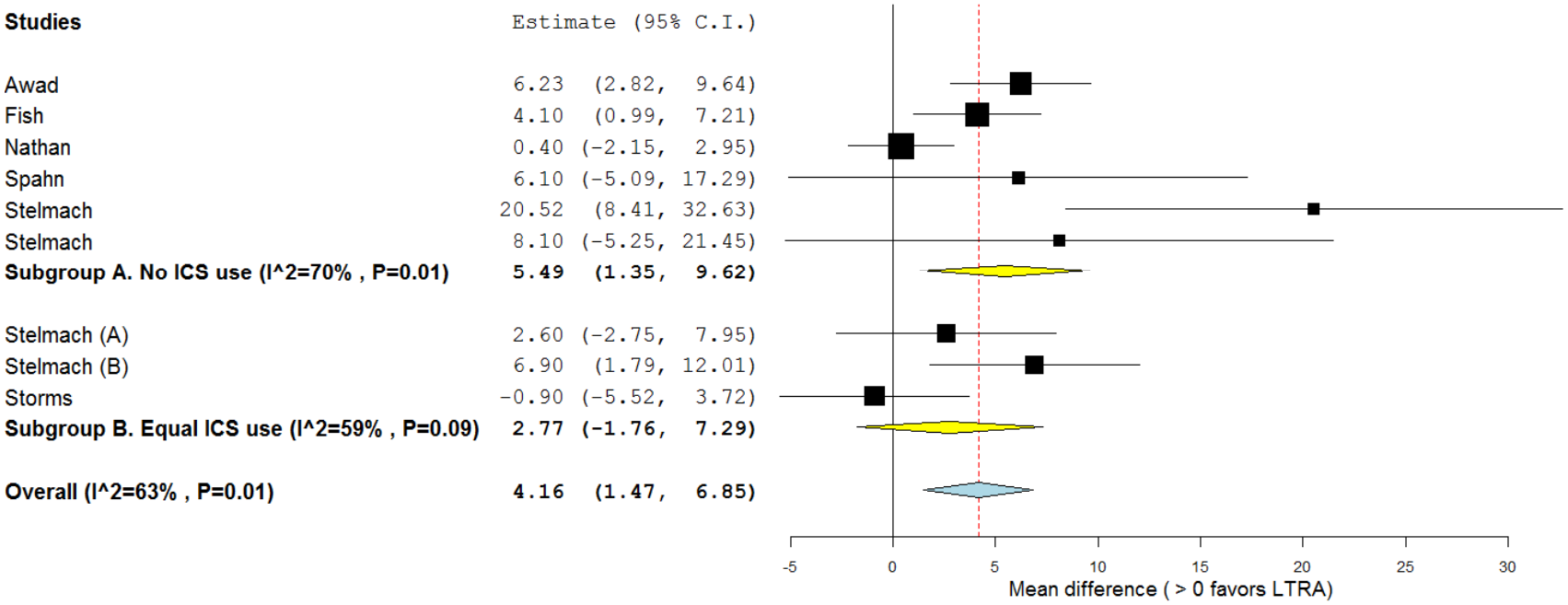
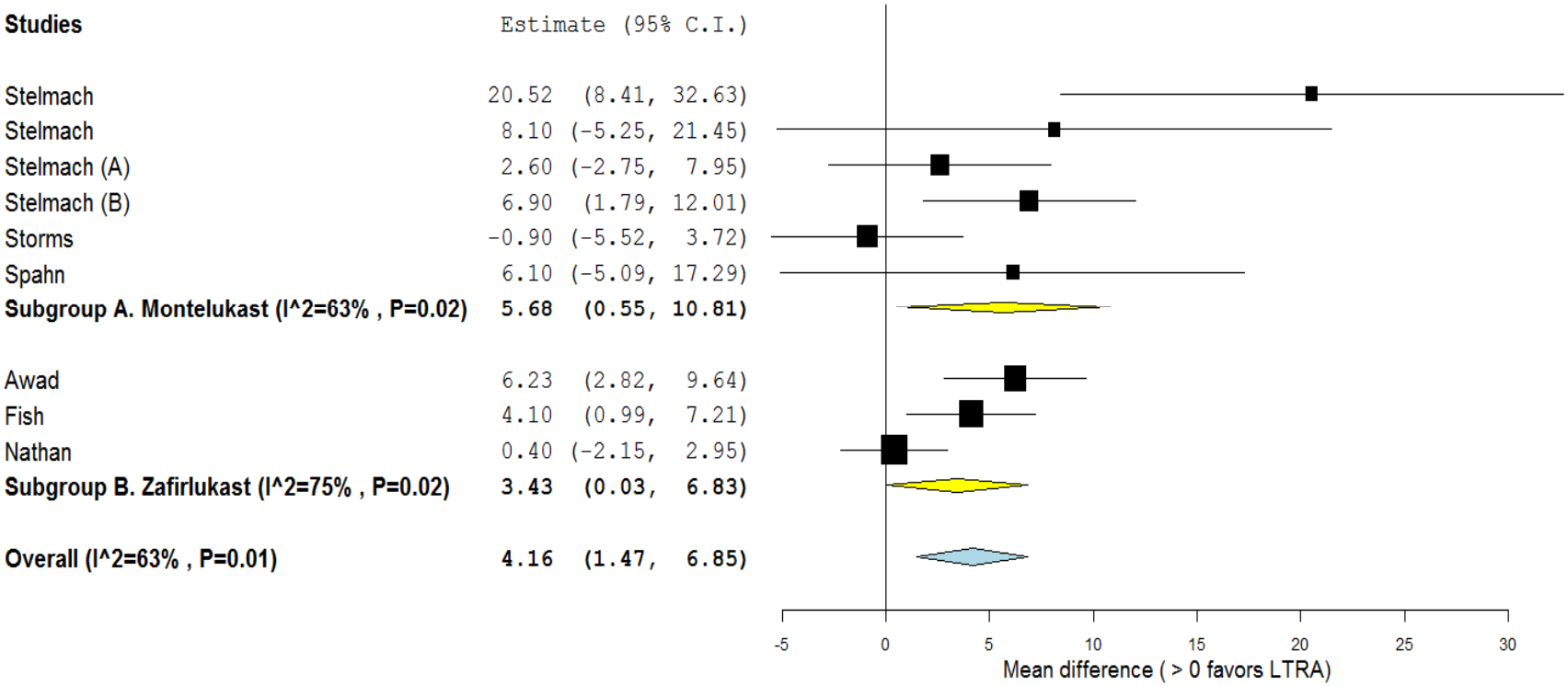


Figure 18. Summary forest plot of mean difference by subgroups of LTRA for FEV_1 % predicted



Daytime symptoms

Daytime symptom scores were reported in 22 RCTs. Fourteen trials contributed data to the meta-analysis. A variety of scales were used with lower values indicating fewer symptoms. LTRAs significantly reduced daytime symptoms (summary SMD = -0.21, 95%: -0.37, -0.04) [Fig 19]. The level of statistical heterogeneity was high (I^2 = 70%). Treatment duration and concomitant ICS use were not associated with the pooled effect (p-value = 0.8, p-value = 0.43, respectively) [Fig 20-22].

Short acting β_2-agonist use

The effect of LTRAs on SABA use compared to placebo was examined in 29 RCTs. We could compute a mean difference in change from baseline in SABA use for 11 trials and a mean difference in percent change from baseline for 8 trials. LTRAs decreased the number of inhalations per day by 0.35 (summary MD = -0.65, 95% CI: -0.82, -0.49). The level of statistical heterogeneity observed was low (I^2 = 7%). [Fig 23]. The effect was consistent across time-points (p-value = 0.99) and types of LTRA [Fig 24-26]. Results did not change when one crossover trial was included (summary MD = -0.66, 95% CI: -0.82,-0.49).

The mean difference in percent change from baseline was statistically significant (summary MD = -16.39, 95% CI: -22.37, -10.41). High statistical heterogeneity was observed (I^2 = 74%). No association with treatment duration was observed (p-value = 0.78) [Fig 27-28].

Nocturnal awakenings

Nocturnal awakenings were reported in 15 RCTs. Only seven RCTs could be meta-analyzed due to missing data in the original trials (primarily, missing number of participants analyzed). Overall, LTRAs reduced nocturnal awakenings per week (summary MD = -0.66, 95% CI: -1.01, -0.32). The statistical heterogeneity detected was high (I^2 = 85%). [Fig 29]. Inclusion of one crossover trial did not affect the results (summary MD = -0.65, 95% CI: -0.89,-0.30). We did not use meta-regression due to the limited number of studies.

Asthma-specific quality of life

Eleven trials examined the effect of LTRAs compared to placebo on asthma-specific quality of life. However, only five trials contributed data to our meta-analysis. The main reason for missing data was reporting of either non-significant results or results were presented per quality domain. LTRAs improved quality of life (summary SMD = 0.13, 95% CI: 0.02, 0.23). Statistical heterogeneity was low (I^2 = 23%) [Fig 30]. We did not use meta-regression due to the small number of studies.

Figure 19. Summary forest plot of standardized mean difference for daytime symptoms

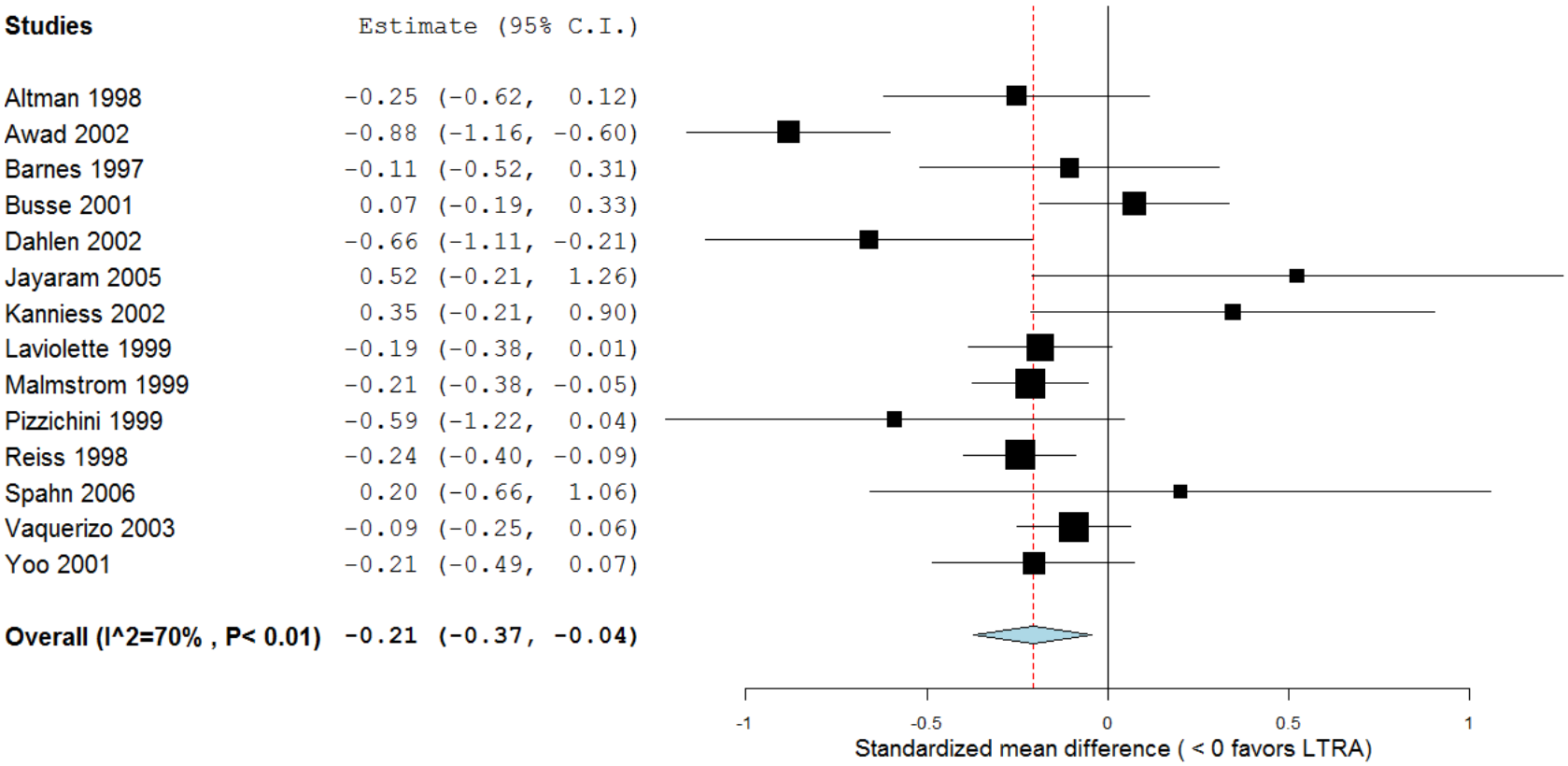


Figure 20. Meta-regression plot of standardized mean difference for daytime symptoms by treatment duration

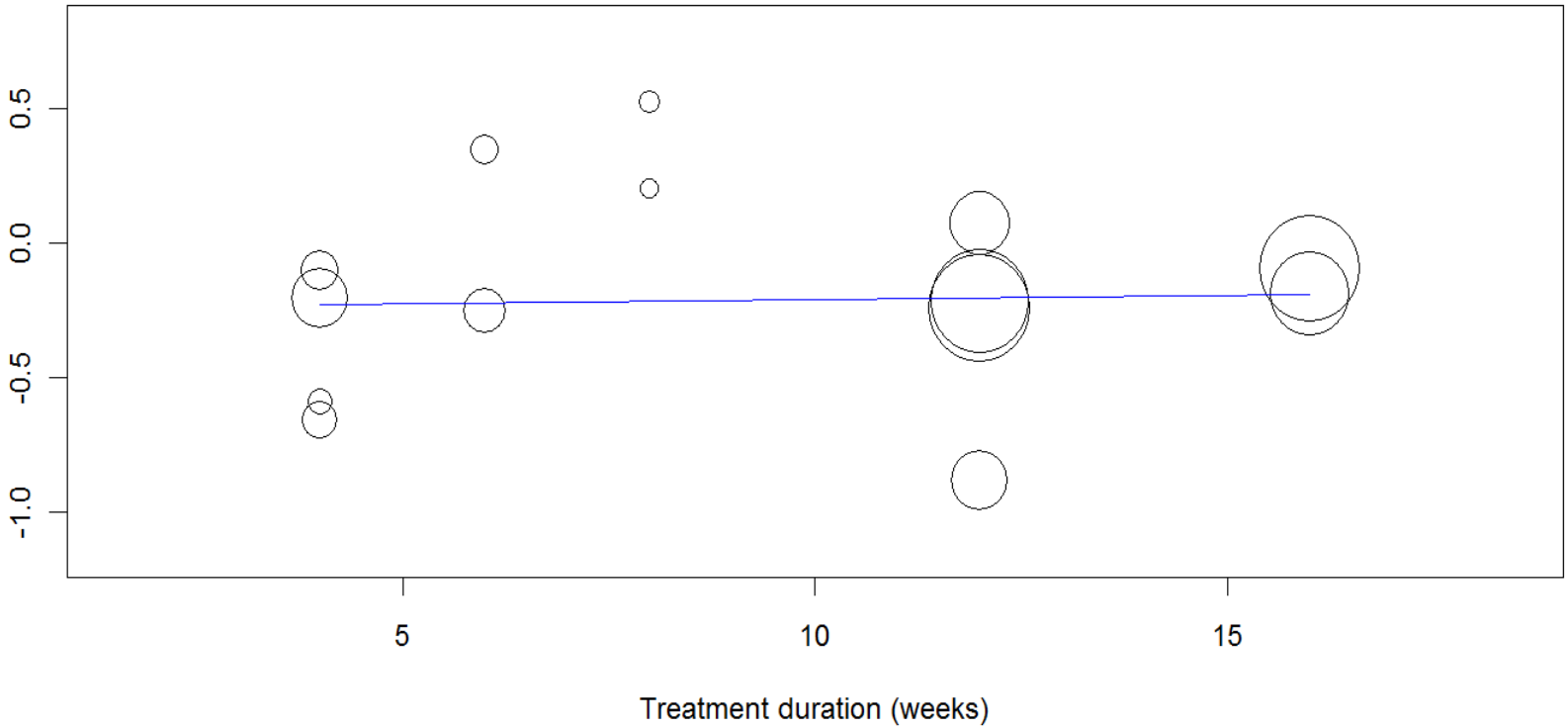


Figure 21. Summary forest plot of standardized mean difference by subgroups of treatment duration for daytime symptoms

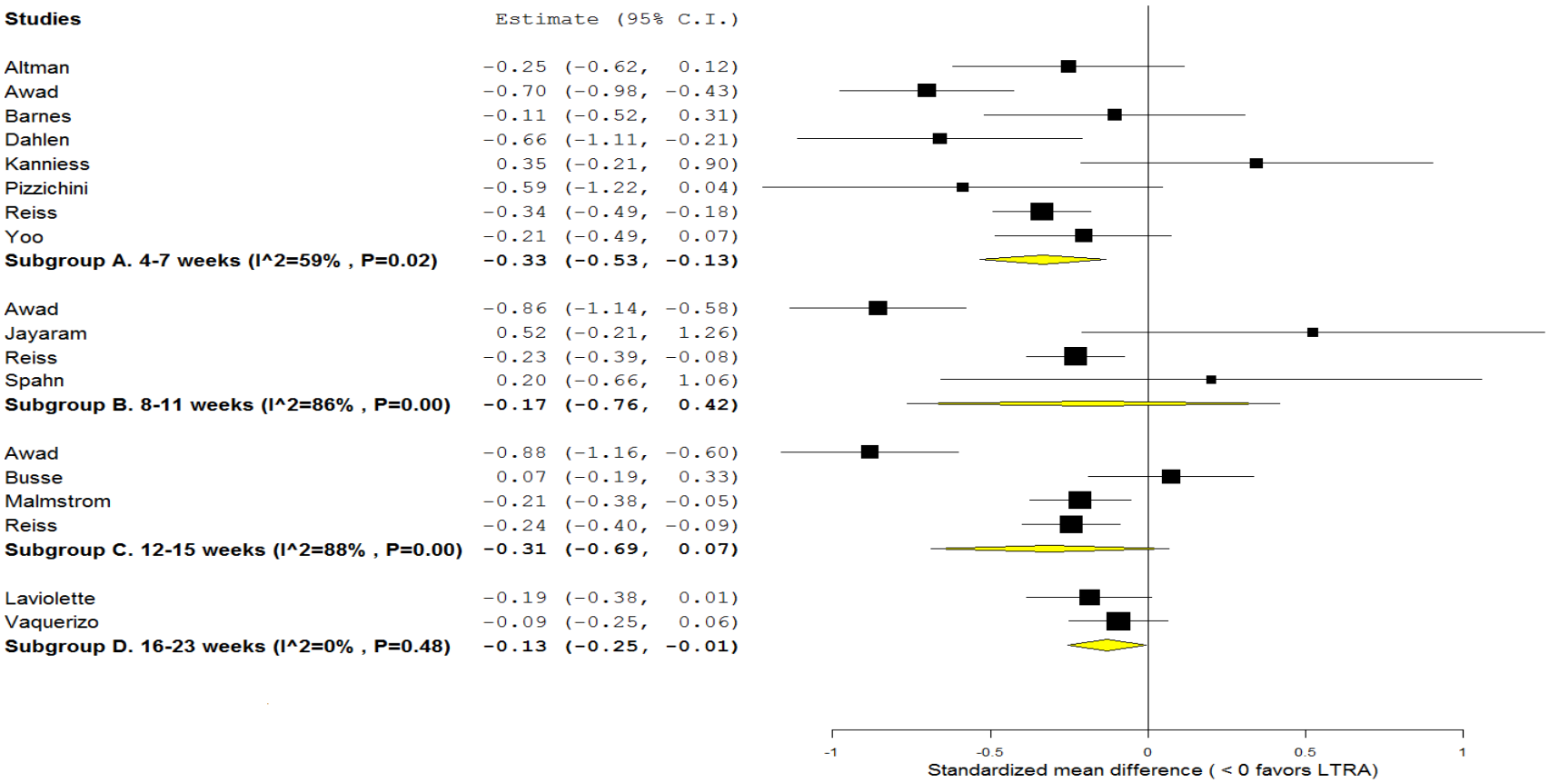


Figure 22. Summary forest plot of standardized mean difference by subgroups of ICS use for daytime symptoms

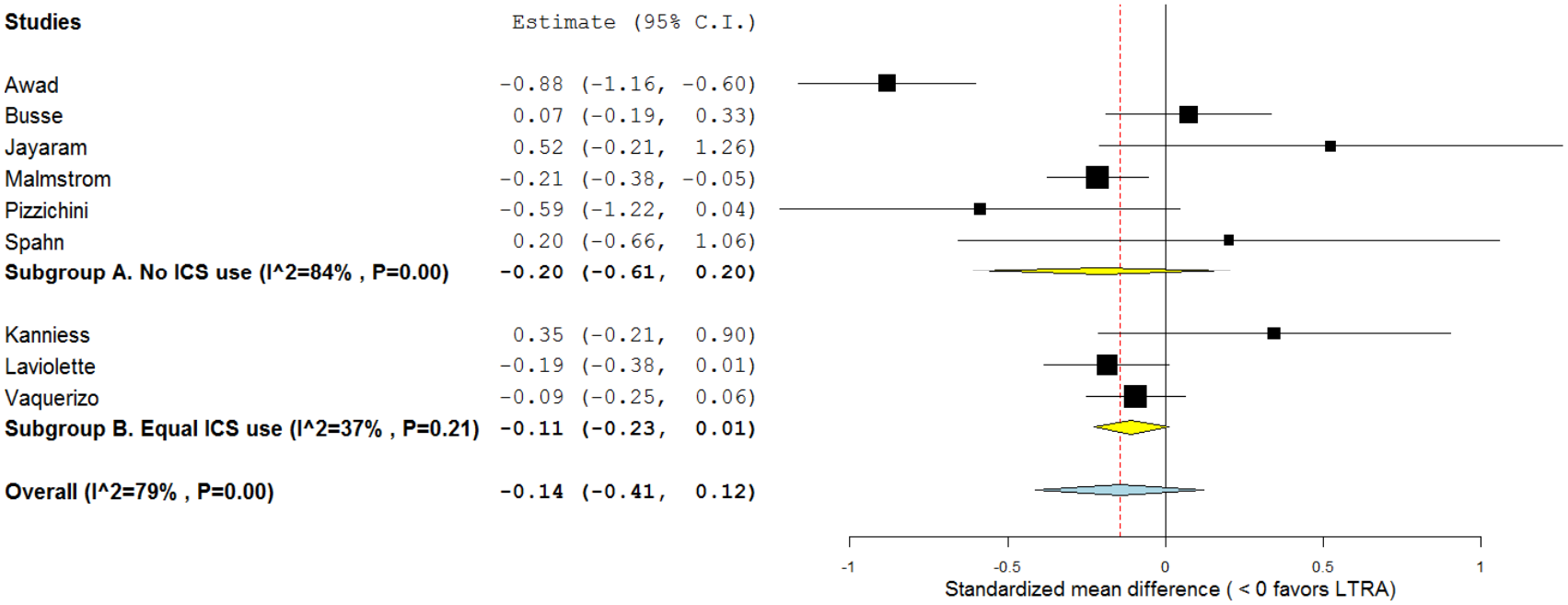


Figure 23. Summary forest plot of mean difference for SABA use

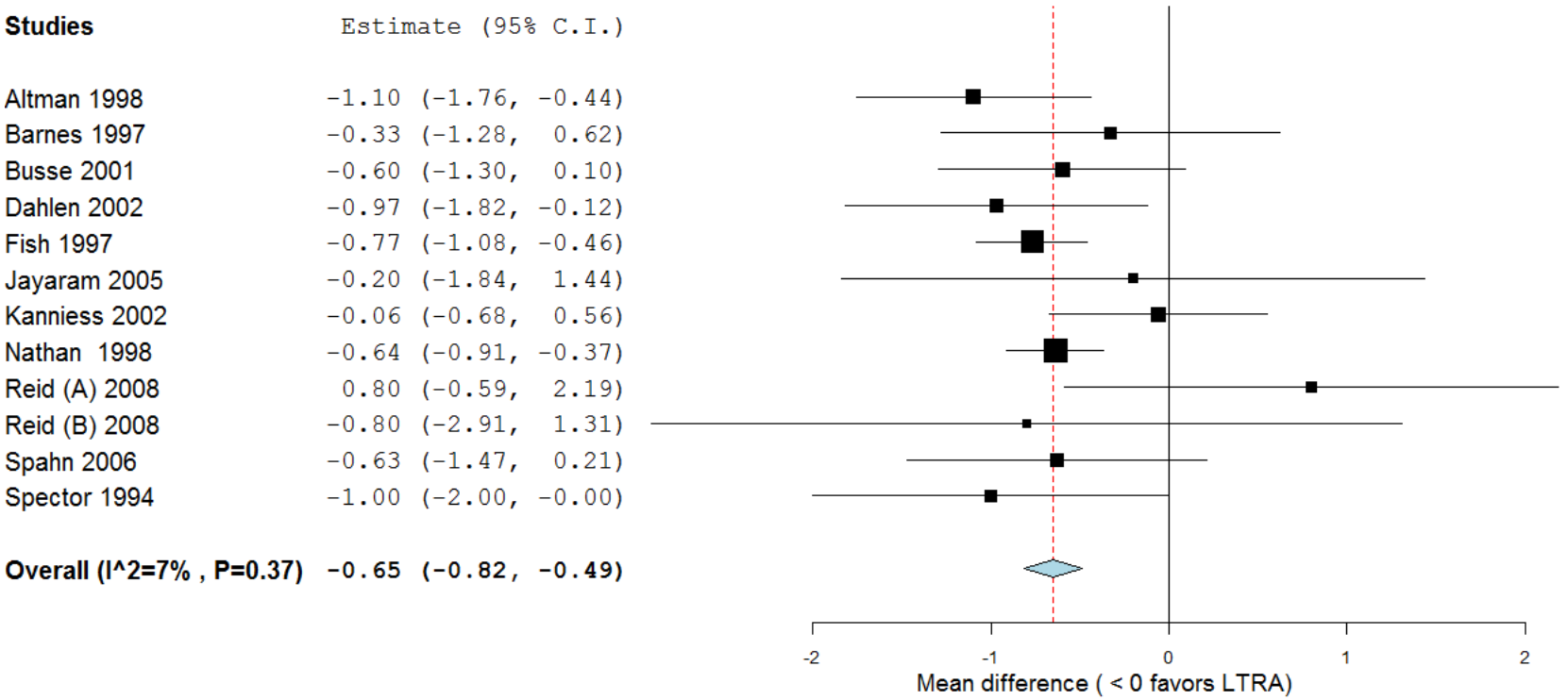


Figure 24. Meta-regression plot of mean difference for SABA by treatment duration

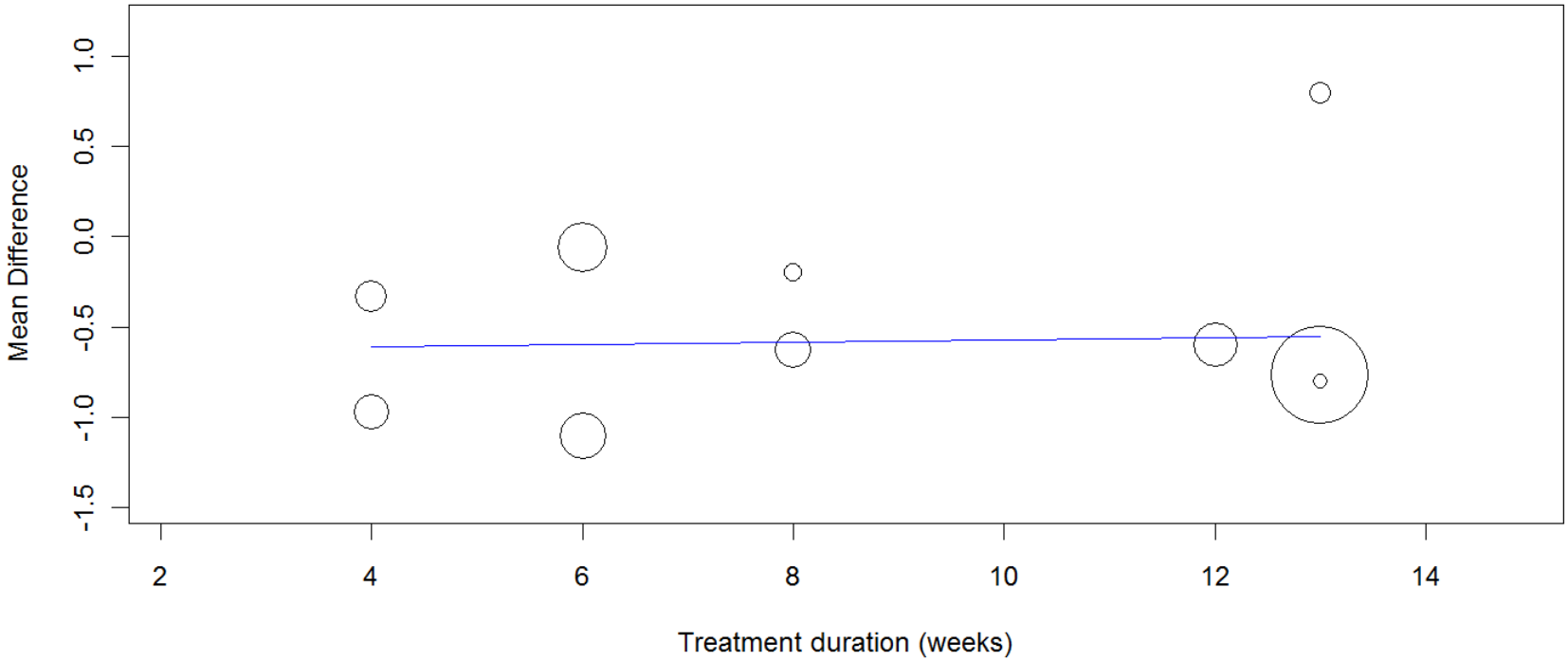


Figure 25. Summary forest plot of mean difference by subgroups of treatment duration for SABA use

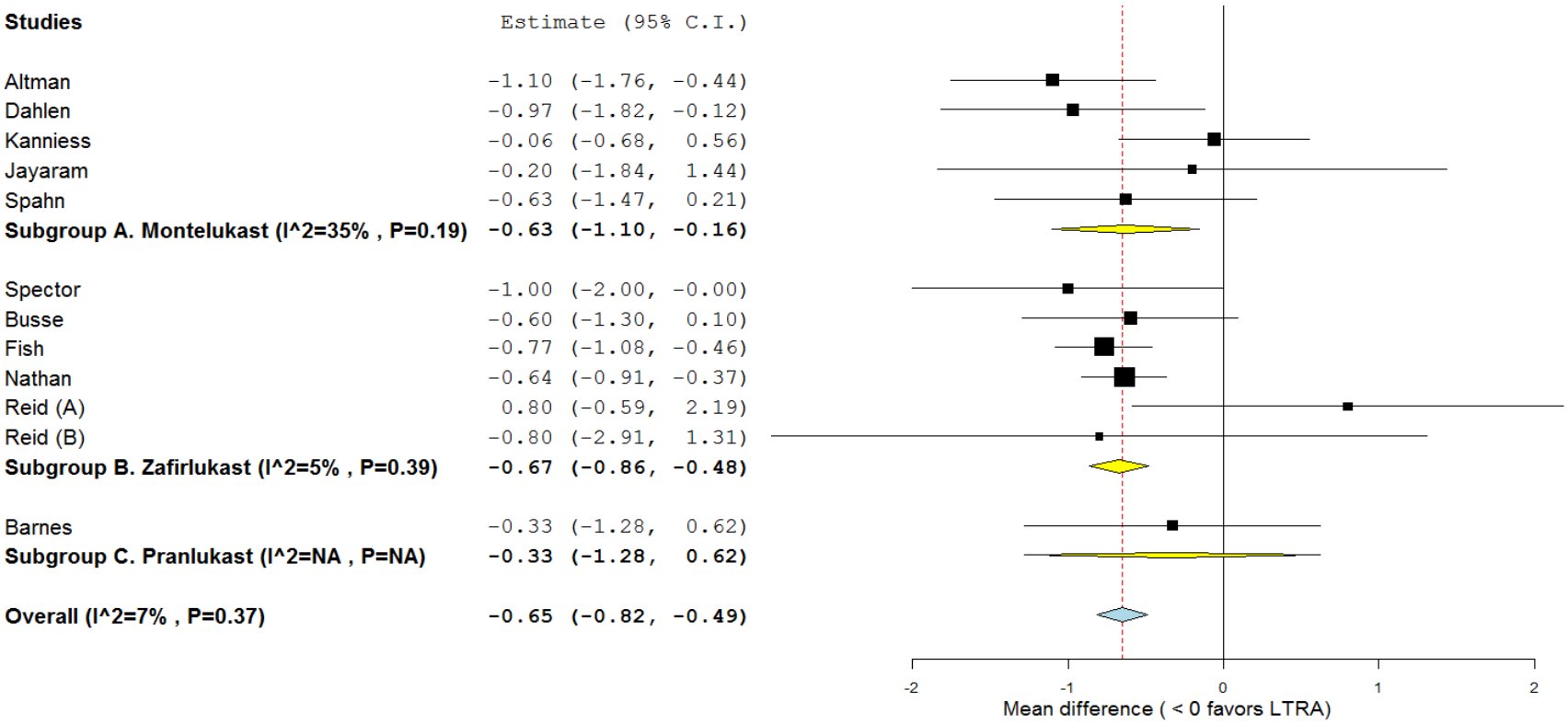


Figure 26. Summary forest plot of mean difference by subgroups of LTRA for SABA use

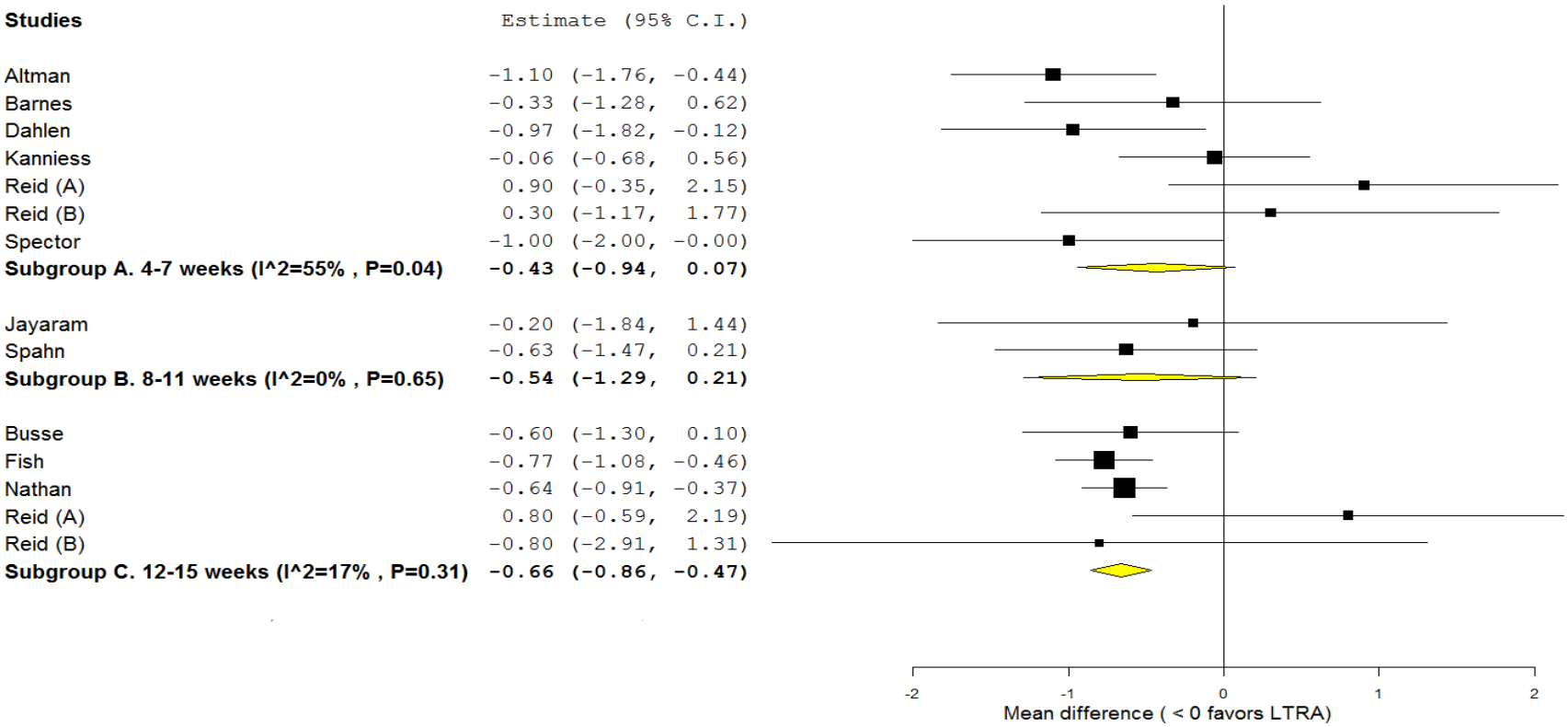


Figure 27. Summary forest plot of mean difference in percent change from baseline for SABA use

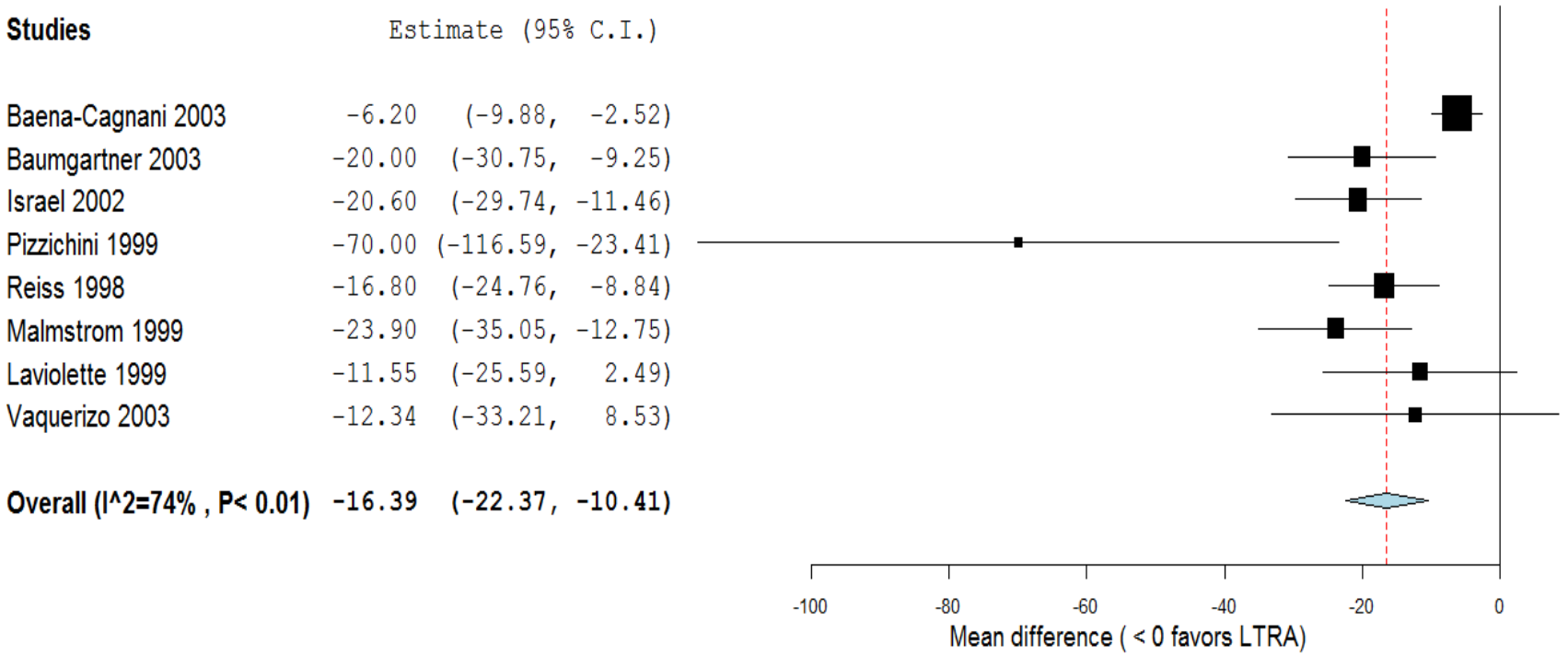


Figure 28. Summary forest plot of mean difference in % change from baseline by subgroups of treatment duration for SABA

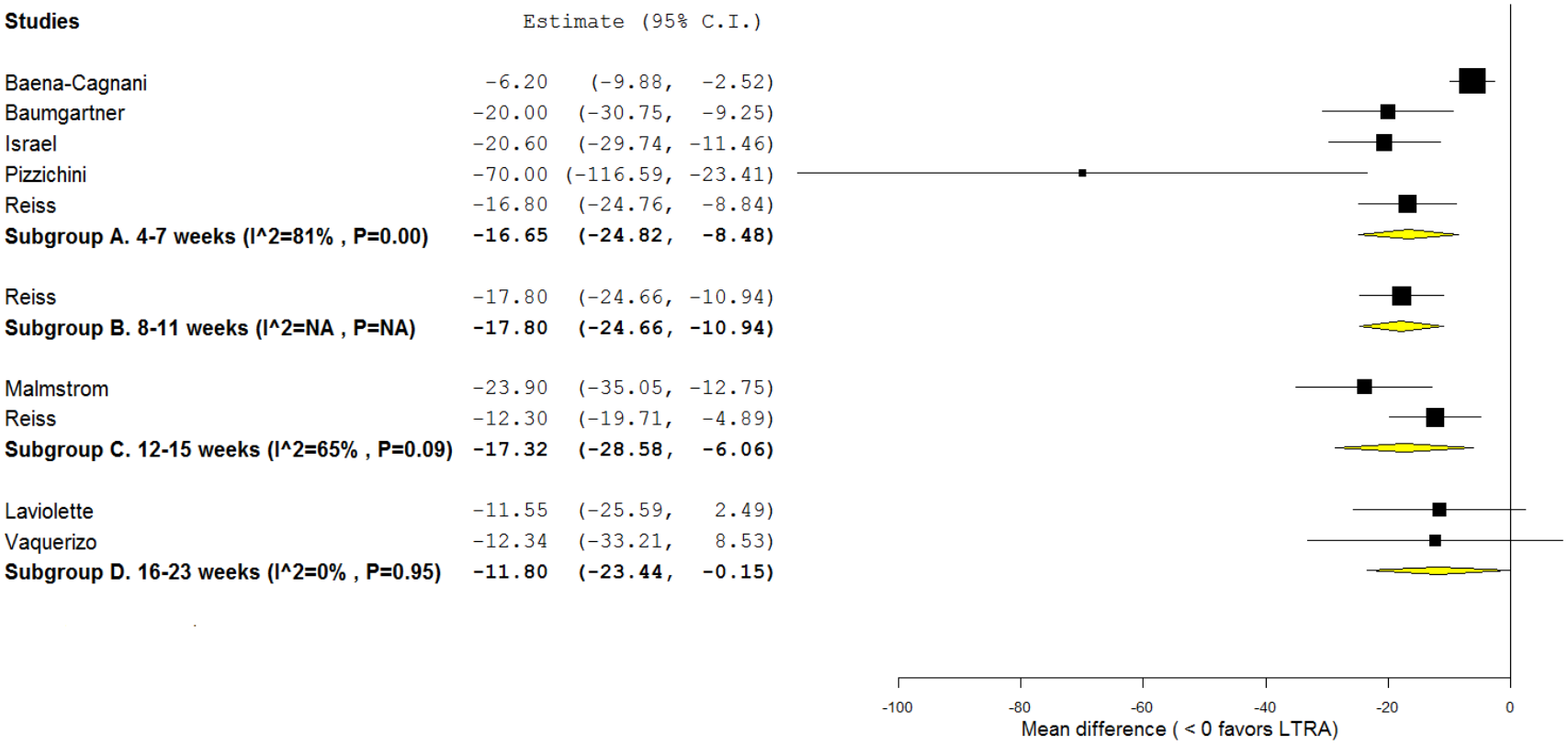


Figure 29. Summary forest plot for mean difference for nocturnal awakenings

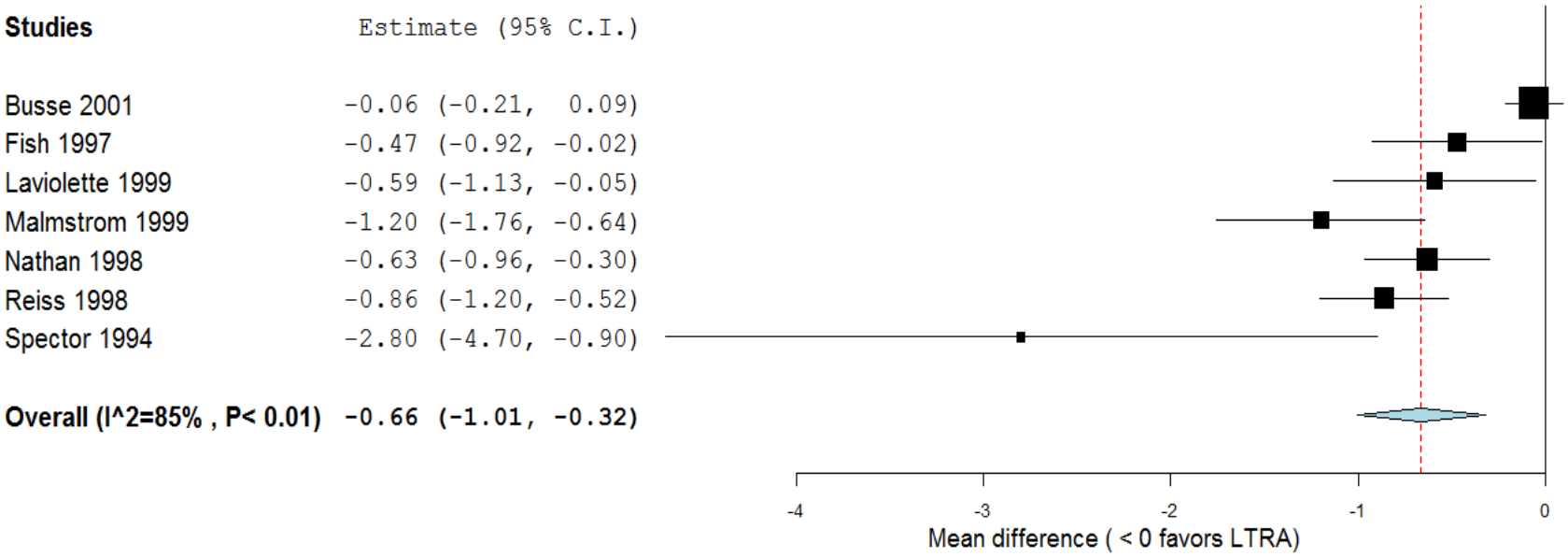
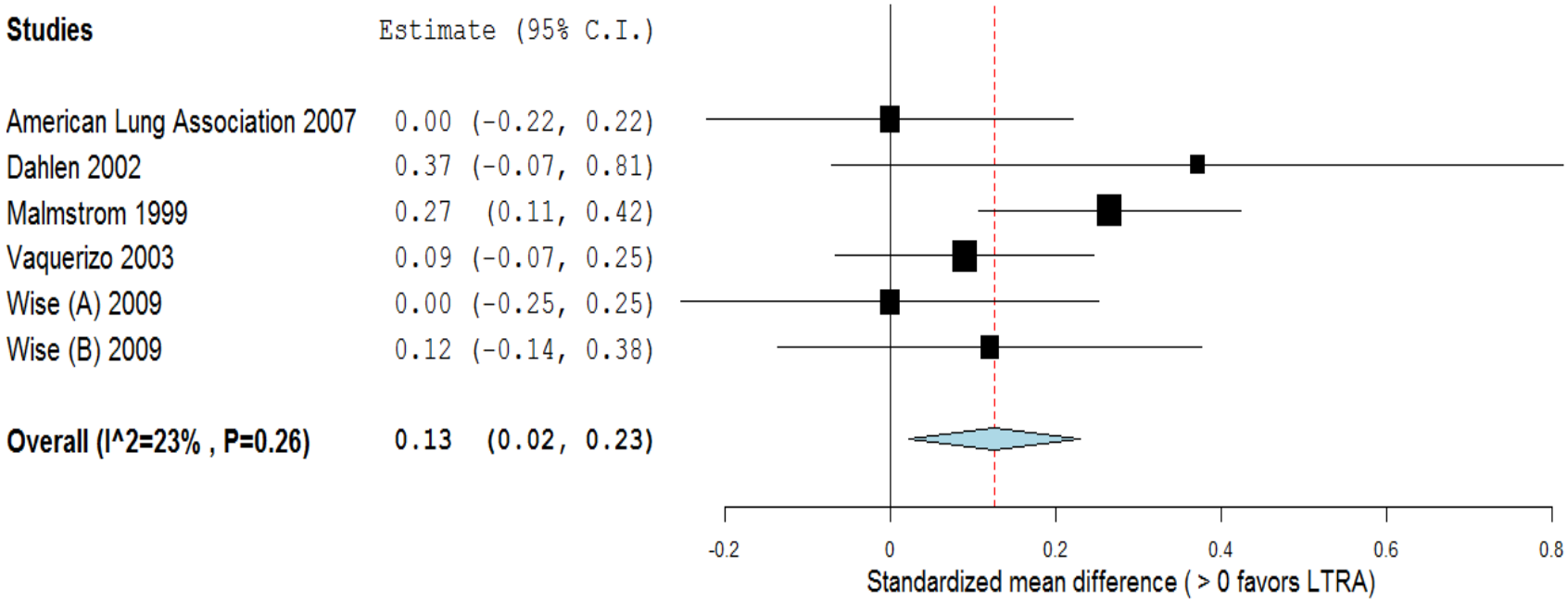


Figure 30. Summary forest plot of standardized mean difference for ASQL



Adverse events and tolerability

The proportions of patients with adverse events were generally similar between intervention and comparator groups (Table 9). Overall, no serious adverse events were reported. Five trials reported no adverse events. Withdrawals from adverse events or worsening asthma were generally similar across our comparator groups (Table 10). The definitions of exacerbations that led to withdrawals are also presented in this table.

Table 9. Adverse events reported in included trials

Adverse event / Source	Treatment arms	Number of events	Number of patients with ≥ 1 event	Total number of patients	Reported p-value	Comments in original studies
Abdominal pain						
Barnes 1997	Pranlukast Placebo		2 0	46 44		
Nathan 1998	Zafirlukast Placebo		1 0	125 132		Led to withdrawal
Vaquerizo	Montelukast/ICS Placebo/ICS		8 6	317 308	0.6	
Yoo 2001	Pranlukast Placebo	0 1		98 99		
Back pain						
Fish 1997	Zafirlukast Placebo		15	514		
Nathan 2005	Montelukast Placebo		8	248		
Bronchitis						
Barnes 1997	Pranlukast Placebo		1 2	46 44		
Laviolette 1999	Montelukast/ICS Placebo/ICS Montelukast Placebo		5 4 7 4	193 200 201 48		
Vaquerizo 2003	Montelukast/ICS Placebo/ICS		5 3	317 308	0.2	
Chest congestion						
Busse 2001	Zafirlukast Placebo		6 0	111 114		
Clinical AE						
Altman 1998	Montelukast Placebo			57 58	NS	Headache, URTI most commonly observed
Israel 2002	Montelukast Placebo			339 111		Similar frequency, URTI, headache, sinusitis
Löfdahl 1999	Montelukast Placebo					No significant differences between groups
Minoguchi 2002	Montelukast Placebo	26 30	13 15	27 28	NS	Respiratory events most commonly observed
Nathan 1999	Zafirlukast Placebo		64 72	96 95	p <0.05 for pharyngitis	Pharyngitis and headache were common
Pizzichini 1999	Montelukast Placebo			19 21		few AE and similar frequencies
Tohda 2002	Montelukast Placebo		6 6	89 92	0.6	headache, stomach ache, heartburn, diarrhea, constipation
Cough						
Barnes 1997	Pranlukast Placebo		0 1	46 44		
Fish 1997	Zafirlukast Placebo		16 11	514 248		

Table 9. (continued)

Adverse event / Source	Treatment arms	Number of events	Number of patients with ≥ 1 event	Total number of patients	Reported p-value	Comments in original studies
Laviolette 1999	Montelukast/ICS		8	193		
	Placebo/ICS		42	200		
	Montelukast		11	201		
	Placebo		3	48		
Diarrhea						
Barnes 1997	Pranlukast		2	46		
	Placebo		0	44		
Fish 1997	Zafirlukast		14	514		
	Placebo		11	248		
Dyspepsia						
Nathan 2005	Montelukast		11	282		
	Placebo		6	290		
Yoo 2001	Pranlukast	1		98		
	Placebo	8		99		
Dyspnea						
Barnes 1997	Pranlukast		2	46		
	Placebo		0	44		
Elevated ALT or AST						
Baumgartner 2003	Montelukast		1	313		
	Placebo		0	103		
Dahlen 2002	Montelukast		5	40		
	Placebo		7	40		
Fish 1997	Zafirlukast		17	514	NS	
	Placebo		10	248		
Leff 1998	Montelukast		1	54		More than 3 times the upper limit of normal
	Placebo		1	56		
Malmstrom 1999	Montelukast		85	382		4 patients in each arm had levels more than 3 times the upper limit of normal
	Placebo		56	254		
Nathan 1998	Zafirlukast		2	231		
	Placebo		8	223		
Spector 1994	Zafirlukast		3	67		
	Placebo		3	66		
Tohda 2002	Montelukast		10 (	89		
	Placebo		8	92		
Yoo 2001	Pranlukast	1		98		
	Placebo	2		99		
Epistaxis						
Nathan 2005	Montelukast		6	282		
	Placebo		12	290		
Gastritis						
Awad 2002	Zafirlukast	6		116		
	Placebo	2		99		
Spector 1994	Zafirlukast		1	67		
	Placebo		4	66		
Headache						
Baena-Cagnani 2003	Montelukast		11	311		
	Placebo		11	302		
Barnes 1997	Pranlukast		1	42		
	Placebo		2	43		
Baumgartner 2003	Montelukast		31	313		
	Placebo		18	103		

Table 9. (continued)

Adverse event / Source	Treatment arms	Number of events	Number of patients with ≥ 1 event	Total number of patients	Reported p-value	Comments in original studies
Busse 2001	Zafirlukast		2	111		
	Placebo		3	114		
Dahlen 2002	Montelukast		0	40		Severe that led to withdrawal
	Placebo		1	40		
Fish 1997	Zafirlukast		71	514		
	Placebo		28	248		
Laviolette 1999	Montelukast/ICS		50	193		
	Placebo/ICS		42	200		
	Montelukast		52	201		
	Placebo		3	48		
Leff 1998	Montelukast		11	54		
	Placebo		16	56		
Malmstrom 1999	Montelukast		68	387		
	Placebo		40	257		
Nathan 2005	Montelukast		40	282		
	Placebo		38	290		
Reiss 1998	Montelukast		73	408		
	Placebo		57	273		
Spector 1994	Zafirlukast		5	68		
	Placebo		8	70		
Vaquerizo 2003	Montelukast		34	317	0.6	
	Placebo		29	308		
Wise (A) 2009	Montelukast		44	120		
	Placebo		34	121		
Wise (B)	Montelukast		35	119		
	Placebo		23	120		
Yoo 2001	Pranlukast	1		98		
	Placebo	4		99		
Hepatitis						
Jayaram 2005	Montelukast	1		14		Drug induced
	Placebo	0				
Jayaram 2005	Montelukast	1		19		Drug induced
	Placebo	0		22		
Hypertonia						
Fish 1997	Zafirlukast		15	514		
	Placebo		8	248		
Nathan 1998	Zafirlukast		1	125		Led to withdrawal
	Placebo		0	132		
Influenza						
Fish 1997	Zafirlukast		17	514		
	Placebo		11	248		
Laviolette 1999	Montelukast/ICS		11	193		
	Placebo/ICS		11	200		
	Montelukast		15	201		
	Placebo		3	48		
Malmstrom 1999	Montelukast		25	387		
	Placebo		10	257		
Vaquerizo 2003	Montelukast		38	317	0.7	
	Placebo		34	308		
Laboratory AE						
Altman 1998	Montelukast					More frequent in the placebo group
	Placebo					
Israel 2002	Montelukast		13	339	NS	
	Placebo		5	111		

Table 9. (continued)

Adverse event / Source	Treatment arms	Number of events (%)	Number of patients with ≥ 1 event (%)	Total number of patients	Reported p-value	Comments in original studies
Löfdahl1999	Montelukast Placebo			113 113		No significant differences between groups
Minoguchi 2002	Montelukast Placebo	5 6	4 5	27 28	NS	
Nathan 1998	Montelukast Placebo		5 1	125 132		Increased bilirubin or alkaline phosphatase
Pizzichini 1999	Montelukast Placebo					Infrequent and similar frequencies
Tohda 2002	Montelukast Placebo		12 7	89 92	NS	leukocytosis, increased levels of liver enzymes, glycosuria
Yoo 2001	Pranlukast Placebo	2 1		98 99		Increased bilirubin
Myalgia						
Fish 1997	Zafirlukast Placebo		19 9	514 248		
Nausea						
American Lung Association 2007	Montelukast Placebo		44 52	164 164		
Awad 2002	Zafirlukast Placebo	5 1		116 99		
Laviolette 1999	Montelukast/ICS Placebo/ICS Montelukast Placebo		5 11 12 0	193 200 201 48		
Yoo 2001	Pranlukast Placebo	1 1		98 99		
Nervousness						
American Lung Association 2007	Montelukast Placebo		62 57	164 164		
Oropharyngeal candidiasis						
Busse 2001	Zafirlukast Placebo		0 2	111 114		
Pharyngitis						
Awad 2002	Zafirlukast Placebo	2 2		116 99		
Barnes 1997	Pranlukast Placebo		1 0	46 44		
Fish 1997	Zafirlukast Placebo		127 53	514 248		
Laviolette 1999	Montelukast/ICS Placebo/ICS Montelukast Placebo		10 16 12 2	193 200 201 48		
Malmstrom 1999	Montelukast Placebo		25 11	387 257		
Nathan 1998	Zafirlukast Placebo		43 42	231 223		
Reiss 1998	Montelukast Placebo		22 29	408 273		
Spector 1994	Zafirlukast Placebo		14 16	68 70		

Table 9. (continued)

Adverse event / Source	Treatment arms	Number of events (%)	Number of patients with ≥ 1 event (%)	Total number of patients	Reported p-value	Comments in original studies
Vaquerizo 2003	Montelukast		5	317	0.8	
	Placebo		4	308		
Rash/Itching						
Barnes 1997	Pranlukast		1	46		
	Placebo		1	44		
Fish 1997	Zafirlukast		16	514		
	Placebo		9	248		
Laviolette 1999	Montelukast/ICS		1	193		
	Placebo/ICS		3	200		
	Montelukast		7	201		
	Placebo		3	48		
Yoo 2001	Pranlukast	7		98		
	Placebo	4		99		
Respiratory disorder						
Barnes 1997	Pranlukast		3	46		
	Placebo		1	44		
Rhinitis						
Awad 2002	Zafirlukast	1		116		
	Placebo	6		99		
Fish 1997	Zafirlukast		16	514		
	Placebo		8	248		
Nathan 1998	Zafirlukast		5	231		
	Placebo		8	223		
Spector 1994	Zafirlukast		5	68		
	Placebo		1	70		
Vaquerizo 2003	Montelukast		5	317	0.7	
	Placebo		6	308		
Sinusitis						
Busse 2001	Zafirlukast		4	111		
	Placebo		4	114		
Fish 1997	Zafirlukast		18	514		
	Placebo		12	248		
Laviolette 1999	Montelukast/ICS		8	193		
	Placebo/ICS		9	200		
	Montelukast		12	201		
	Placebo		2	48		
Nathan 1998	Zafirlukast		8	231		
	Placebo		13	223		
Reiss 1998	Montelukast		31	408		
	Placebo		22	273		
Sore throat						
Busse 2001	Zafirlukast		3	111		
	Placebo		3	114		
Nathan 2005	Montelukast		11	282		
	Placebo		9	290		
Upper respiratory tract infection						
Baumgartner 2003	Montelukast		22	313		
	Placebo		7	103		
Laviolette 1999	Montelukast/ICS		70	193		
	Placebo/ICS		79	200		
	Montelukast		72	201		
	Placebo		20	48		
Leff 1998	Montelukast		12	54		
	Placebo		16	56		

Table 9. (continued)

Adverse event / Source	Treatment arms	Number of events	Number of patients with ≥ 1 event (%)	Total number of patients	Reported p-value	Comments in original studies
Malmstrom 1999	Montelukast		48	387		
	Placebo		28	357		
Reiss 1999	Montelukast		129	408		
	Placebo		96	273		
Vaquerizo 2003	Montelukast		17	317	0.5	
	Placebo		21	308		
Urinary Tract infection						
Vaquerizo 2003	Montelukast		6	317	0.7	
	Placebo		7	308		
Vomiting						
Awad 2002	Zafirlukast	1		116		
	Placebo	0		99		

Abbreviations: AE: Adverse events; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; NS: Not statistically significant; URTI: Upper Respiratory Tract Infection.

Table 10. Withdrawals in included trials

Source	Treatment arms	Number of withdrawals due to adverse events	Number of withdrawals due to worsening asthma / exacerbation	Total number of patients	Comments about exacerbations
American Lung Association 2007	Montelukast Placebo	7 5		164 164	
Barnes 1997	Pranlukast Placebo		2 1	46 44	No definition of an exacerbation reported
Baumgartner 2003	Montelukast Placebo	1 3		313 103	
Busse 2001	Zafirlukast Placebo	1 1		111 114	
Dahlén 2002	Montelukast Placebo	0 1		40 40	
Fish 1997	Zafirlukast Placebo	12 7	16 16	514 248	No definition of an exacerbation reported
Huang 2003	Zafirlukast Placebo		3 4	20 18	Exacerbation that required emergency room visit
Kanniess 2002	Montelukast Placebo		3 2	26 24	An exacerbation was defined as a decrease in PEF of >50% compared to values at entry, or an increase in daytime symptoms of three or more or in night-time symptoms of two or more on >3 consecutive days
Laviolette 1999	Montelukast/ICS Placebo/ICS Montelukast Placebo		2 8 23 7	193 200 201 48	
Leff 1998	Montelukast Placebo	2 4		54 56	
Löfdahl 1999	Montelukast Placebo	0 9	4 0	112 113	Exacerbation that required oral corticosteroids
Malmstrom 1999	Montelukast Placebo	8 11			
Minoguchi 2002	Montelukast Placebo		1 2	27 28	During wash-out period
Nakamura 1998	Pranlukast Placebo	0 2		11 10	
Nathan 1998	Zafirlukast Placebo	3 0	2 6	231 223	
Nathan 1999	Zafirlukast Placebo		3 8	96 95	No definition of an exacerbation reported
Nathan 2005	Montelukast Placebo		1 2	282 290	Exacerbation defined as any event that required treatment with asthma medications beyond study medications
Pizzichini 1999	Montelukast Placebo	1 1	1 0	19 21	
Reiss 1998	Montelukast Placebo		6 10	408 273	
Spahn 2006	Montelukast Placebo		1 1	11 10	Required rescue prednisone
Spector 1994	Zafirlukast Placebo		0 8	70 70	Treated with no specific treatment protocol

Table 10. (continued)

Source	Treatment arms	Number of withdrawals due to adverse events	Number of withdrawals due to worsening asthma / exacerbation	Total number of patients	Comments about exacerbations
Stelmach (A) 2007	Montelukast		0	29	
	Placebo		0	29	
Stelmach (B)	Montelukast		0	29	No definition of an exacerbation reported
	Placebo		2	29	
Strunk 2008	Montelukast		0	19	Exacerbations required oral corticosteroids
	Placebo		3	19	
Vaquerizo 2003	Montelukast	3	3	317	
	Placebo	5	3	308	
Wise (A) 2009	Montelukast	2		120	
	Placebo	2		121	
Wise (B)	Montelukast	2		120	
	Placebo	2		121	

Discussion

Administration of a LTRA to adults and adolescents with asthma significantly reduced the risk of an exacerbation and improved both lung function and patient-reported outcomes compared to placebo. This effect was consistent across all types of LTRAs. The effect on the risk of exacerbations was more evident in studies of shorter duration. The incidence of adverse events and withdrawals due to adverse events and worsening asthma was similar for LTRAs and placebo reflecting a favorable safety and tolerability profile for LTRAs.

Several systematic reviews have examined the state of evidence regarding the use of LTRAs in adults and adolescents with asthma, but only a few have included RCTs that have compared a LTRA with placebo. Joos et al.[66] included RCTs of at least 12 weeks duration that examined the benefits and harms of montelukast as add-on therapy to ICS compared to ICS with or without placebo and concluded that the addition of montelukast to ICS improved control of mild to moderate asthma compared to ICS monotherapy; no meta-analytic technique was employed in this study, however, due to the inclusion of a limited number of RCTs. Ducharme et al.[67] included RCTs of at least 4 weeks duration that compared LTRAs with placebo as add-on to ICS, but only two out of six included RCTs reported use of usual licensed doses. Currie et al.[68] examined the bronchoprotective effects of LTRAs compared to placebo after administration of bronchial stimuli. These provocative challenges, though, are mainly used in order to establish the diagnosis of asthma. In contrast, our systematic review was more expansive and more applicable to current clinical practice in a number of ways. Our study included outcome measures that correspond to the components proposed by international guidelines to periodically assess

and monitor asthma control in patients with an established diagnosis of asthma.[69] More specifically, we included RCTs of at least 4 weeks duration because the level of asthma control is assessed over a 4 week period at the minimum.[6] We also excluded RCTs where LTRAs were not administered on a daily basis because we intended to examine their effect as long-term controller medications.[6] Therefore, RCTs that only assessed the pharmacodynamic profile of single doses of LTRAs after provocative challenges or exercise were excluded. In a systematic review of LTRA safety data that included both RCTs and their extension studies, Storms et al.[70] concluded that there was no significant difference in the incidence of adverse events between patients who were treated with montelukast and those who received placebo. Although our systematic review included only RCTs with a relatively short length of follow-up, the reported adverse events and their relative frequencies were similar to those reported in the meta-analysis by Storms et al.

Despite the broader scope and improved generalizability of our study to previous reviews, our systematic review had several limitations both at the individual-study level and the systematic review level that need to be kept in mind in interpreting our study results. Different definitions of asthma exacerbation were used in the trials reviewed and some studies did not explicitly define this important clinical endpoint. Therefore, the severity of the exacerbations could not be fully assessed across studies. Importantly, in 12 studies only withdrawals due to an exacerbation were reported. Taking the conservative approach of meta-analyzing asthma exacerbations only from studies that clearly defined and reported the outcome, we assumed that no events occurred in studies that did not mention any exacerbation and we did not quantitatively summarize those studies which

reported only withdrawals because the number of patients at risk could not be determined. In addition, the definitions of asthma severity in the individual trials were not consistent and it was not possible to assess the impact of baseline asthma severity on summary treatment effects. Our conclusions about the magnitude of the treatment effect are limited due to the small number of RCTs included in each analysis compared to the total number of RCTs included in the systematic review. Part of this difference arises because studies used different analytic scales for the same outcome measure, which prevented combination of all available data. For instance, change from baseline in FEV_1 was provided as an absolute number in some trials and as a percentage in others. Another set of studies reported a non-significant difference, without providing the actual numbers, for clinical outcomes. These studies were generally either not primarily designed to assess outcome measures relevant to clinical practice or had a relatively small sample size. In either case, this leads to outcome reporting bias and so the summary effect sizes from the meta-analyses may be overstated.

The large amount of between-study statistical heterogeneity found for most outcomes could be sometimes be partly explained by subgroup analyses and meta-regression, but such analyses can only be hypothesis generating by the retrospective nature of meta-analysis. For other outcomes, however, the observed statistical heterogeneity remained largely unexplained. Potential association between allergic rhinitis and the magnitude of the summary treatment effect remains unclear due to insufficient reporting in the individual studies. Similarly, only two trials reported inclusion of patients with aspirin-induced asthma. Another limitation of the study is the inclusion of only peer-reviewed and English-language publications. Finally, we cannot exclude publication bias.

To our knowledge, this is the first systematic review to investigate the use of all marketed LTRAs in usual licensed doses as asthma controller medications compared with placebo. Our findings suggest that LTRAs might be an efficacious and safe alternative treatment, in adult and adolescent patients who cannot or prefer not to take ICS. However, which patients are more likely to respond to LTRAs administered as monotherapy remains unclear. Asthma is a complex disease with various clinical, inflammatory, and trigger-related "phenotypes" that may overlap.[71] It is hypothesized that proper identification of these phenotypes would lead to better management of the disease. Moreover, since not all patients respond well to ICS, the need for alternative treatments that would benefit specific subpopulations increases. Therefore, professional organizations or expert panels should recommend standardized study-protocols, definitions of phenotypes, and outcome measures (e.g., asthma control test, asthma control questionnaire)[72-73] for the purpose of research and encourage future researchers to implement these standards.

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