Comparison of Regular, As-Needed, and Combined Use of Inhaled Corticosteroids and Other Asthma Treatments for Mild Asthma in Children and Adolescents/Adults: A Systematic Review and Meta-Analysis

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Abstract

Regular use of inhaled corticosteroids (ICS) is recommended in mild asthma. Efficacy of this approach in comparison with as-needed ICS with/without formoterol, long-acting beta-2 agonists (LABA), short-acting beta-2 agonists (SABA), leukotriene antagonists (LTRAs), or tiotropium is unclear. We aimed to compare the efficacy between regular ICS and other treatments in children (age ≥ 6) and adolescents/adults with mild asthma. A systematic review and meta-analysis of all randomized controlled trials (RCTs) was conducted. PubMed, Scopus, and ClinicalTrials.gov were searched up to August 2022. The outcomes of interest were number of exacerbations and symptom scores, for which the risk ratios (RR) and standardized mean differences (SMD) were estimated. Thirteen RCTs in children and 29 in adolescents/adults were included. The results revealed that in children (asthma step 2, 5 studies), regular ICS was similar to as-needed ICS in reducing exacerbations (RR [95% confidence interval]: 0.83 [0.63-1.25]), but better than LTRAs (RR: 0.82 [0.69-0.96]) and as-needed SABA (RR: 0.63 [0.49-0.82]). In adolescents/adults (asthma step 2, 12 studies), regular ICS reduced severe exacerbations compared to as-needed SABA (RR: 0.61 [0.46-0.80]), but inferior to as-needed ICS/formoterol (RR: 1.36 [1.03-1.80] and combination of ICS/LABA (RR: 1.54 [1.19-2.00]). In adults (N=7), symptom scores were better improved with regular ICS than as-needed SABA (SMD: -0.44 [-0.68 to -0.21]). In conclusion, to prevent exacerbation, regular and as-needed use of ICS are not different, and they are better than LTRAs and as-needed SABA in pediatric mild asthma, while as-needed ICS/formoterol and regular ICS/LABA are better than ICS-alone in adolescents/adults.

Keywords: *Mild Asthma, As-Needed Use, Regular Use, Inhaled Corticosteroid/Fast-Onset Bronchodilators, Inhaled Corticosteroids, Leukotriene Antagonists, Short-Acting Beta-2 Agonists, Meta-Analysis*

1. Introduction

1.1 Background

Anti-inflammatory drugs such as inhaled corticosteroid (ICS) is the main treatment of asthma in which symptoms and exacerbations are driven by inflammation. Historically, treatment with short-acting beta-2 agonist (SABA) whenever symptoms occur (as-needed use) was recommended in patients with mild asthma, based on the assumption that these patients would not benefit from ICS, because exacerbation was less likely (Reddel et al., 2022). Currently, regular use of ICS is recommended for mild asthma in order to achieve a better control of inflammation and reduction of asthma exacerbation (Reddel et al., 2022). Due to infrequent symptoms in mild asthma, poor adherence to regular use of ICS is a major problem. As-needed use of ICS whenever symptoms occur, with or without fast-onset long-acting bronchodilator (FABA) including formoterol or SABA, may be an alternative option.

1.2 Previous reviews of treatments of mild asthma

In adolescents and adults, regular use of low-dose ICS (<400 mcg/day of budesonide or equivalent) and leukotriene antagonists (LTRAs) have been used for treatment of mild asthma with better control of asthma symptom (Dusser et al., 2007). As-needed use of ICS with FABA was non-inferior to regular ICS in reduction of exacerbation and improvement of asthma symptom control (Bateman et al., 2018; O'Byrne et al., 2018). In other trials, as-needed ICS/ FABA were superior to regular ICS in reducing the risk of severe exacerbations (Beasley et al., 2019; Hardy et al., 2019). Tiotropium was not inferior to salmeterol in patients whose symptoms were not controlled by ICS alone (Peters et al., 2010). Tiotropium increased time to first exacerbation in patients whose symptom was poorly controlled with ICS/LABA (Kerstjens et al., 2012). Lazarus et al. (2019) reported that mild asthmatics with low sputum eosinophil level may not have favorable response to ICS. In children, Reddel et al. (2022) recommends as-needed SABA alone or as-needed ICS whenever SABA is taken in children with intermittent asthma symptoms. For those whose asthma symptoms occur > 2 times/month, regular use of low use ICS is the treatment of choice, but oral LTRA can be an alternative.

1.3 Why it is important to do this review

It is recognized that patients to whom inhalers are prescribed for daily use do not adhere to their inhalers if they do not have symptoms. Previous meta-analyses comparing the efficacy of combination of ICS/formoterol vs. regular ICS vs. as-needed SABA in children and adults with mild asthma (Crossingham et al., 2021; Hatter et al., 2021) reported a potential publication bias. Furthermore, based on the frequency of symptoms (mild asthma step 1 or step 2), there is an equipoise between treatments with ICS use when symptoms occur (as-needed) and regular use of ICS. A new treatment with tiotropium has been introduced for the treatment of mild asthma. Hence, an updated systematic review and meta-analysis to identify additional studies to improve the precision of the estimates of treatment effects in reduction of exacerbation and improvement of symptoms among the asthma medications in children and adults.

2. Objectives

To compare the efficacy on reduction of exacerbation and symptom control of treatments with regular ICS, as-needed ICS, as-needed combination of ICS/formoterol, regular combination ICS/LABA, LTRAs, and as-needed SABA in children (age $\geq$ 6) and adolescents/adults with mild asthma (in separate analyses)

3. Materials and Methods

This study was in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement published in 2020 (Page et al., 2021).

3.1 Search strategy and selection criteria

We electronically searched databases including PubMed and Scopus from its inception to August 2022 for randomized controlled trials (RCTs) using a comprehensive search strategy which included the following keywords based on the PICOS framework domains: “mild asthma”, “intermittent asthma”, “inhaled corticosteroids” OR “inhaled glucocorticoids”, “Budesonide, Formoterol Fumarate Drug Combination”, “Albuterol”, “Formoterol Fumarate”, “Leukotriene Antagonists”, “Tiotropium”, exacerbation”, “asthma attack”, and “symptom*”. The search terms were combined using “OR” within the same domain of PICOS and using “AND” between different domains. There was no language restriction for the search. We also searched for unpublished and ongoing studies from the ClinicalTrials.gov. with the following search terms: “mild asthma” and “treatment”. We included the trials if they met the following criteria: 1) RCTs of adults or children (age $\geq$ 6) with mild asthma, 2) trials comparing any of the asthma medications (SABA, ICS, LTRA, ICS/fast-onset bronchodilators (FABA) including formoterol and SABA, ICS/LABA, tiotropium) that were used as-needed or regularly, and 3) trials reporting at least one of the following outcomes (exacerbation, symptom score). We excluded the trials comparing the same intervention with different dosage or schedule or inhaler devices and trials with insufficient data for pooling. Following literature searches, two

reviewers independently selected articles based on screening of the title and abstract, then the full text that met the eligibility criteria were thoroughly checked.

3.2 Data extraction and quality assessment

Two reviewers independently extracted information from included studies for the following characteristics: authors, year of publication, sample size, age, sex, baseline lung function, asthma severity, treatment (name of drugs, dose, frequency of drug administration), and outcomes. The two reviewers independently assessed risk of bias to determine quality using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). Any disagreements were referred to the team consensus. Outcomes of interest were extracted for the number of exacerbations including all exacerbations and severe exacerbation as the primary outcomes. Severe exacerbation was defined as: 1) deteriorating asthma conditions leading to the use of systemic steroids for ≥ 3 days, hospitalization, or 2) emergency department visit leading to the use of systemic steroids). Secondary outcome included symptom scores.

3.3 Statistical analysis

Pairwise meta-analysis was performed on each pair of interventions from at least 3 studies. We prespecified separate analysis in children and adolescents/adults. To avoid repeating, exacerbation data were treated using patients as the unit of analysis instead of events. Where zero counts existed for an outcome in one arm of a trial, a value of 0.5 was added to permit meta-analysis. Comparative treatment effects on exacerbations were presented as risk ratios (RR) and on symptom scores as standardized mean differences (SMD), along with their 95% confidence interval (CI). RR and SMD from each study were pooled. Heterogeneity was assessed with the Q test and I^2 statistic. A random-effects model with the method of Der-Simonian and Laird was used to pool data if substantial heterogeneity was observed ($I^2 > 50\%$ or p-value of Q test < 0.1 for Q statistic), otherwise we used a fixed-effect model with inverse variance method. Data were analysed with Stata 17.0 software. (Stata Corp, College Station, Texas, USA). A two-sided p-value of < 0.05 was considered the threshold for statistical significance.

4. Results and Discussion

4.1 Result

The literature search returned 2869 results, of which 16 were unpublished and ongoing trials from ClinicalTrials.gov. (Figure 1) After removal of duplicates, 2211 studies were screened against the eligibility criteria. A total of 2169 studies were excluded. Forty-two RCTs were included in the review, see Table 1.

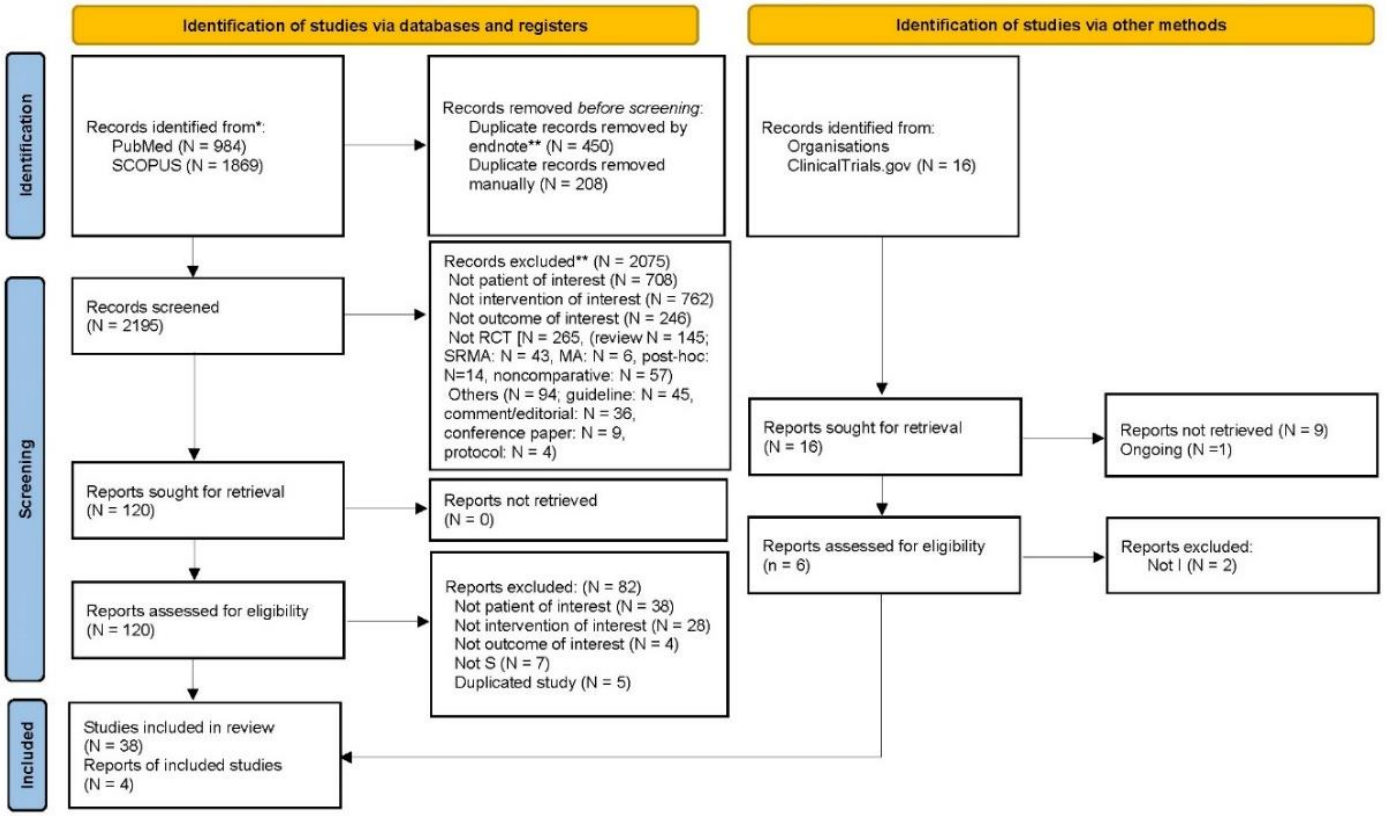


Figure 1 Flow diagram of literature search and screening process (PRISMA 2020)

4.1.1 Exacerbations in children

Three RCTs comparing regular ICS (340 participants) with as-needed ICS (268 participants), and three RCTs comparing regular ICS (648 participants) with LTRAs (645 participants) were included. Regular ICS showed no difference in reduction of exacerbation in comparison to as-needed ICS (RR 0.83, 95% CI 0.61-1.12, I^2=0%). Five studies comparing regular and as-needed ICS included participants with baseline FEV_1 or peak expiratory flow rate (PEF) > 80% predicted. Regular ICS was significantly better than LTRAs (RR of 0.82, 95% CI 0.69-0.96, I^2=0%) and as-needed SABA (RR of 0.63, 95% CI 0.49-0.82, I^2=0%), see Figure 2. There are no studies in children reporting outcome of symptom scores.

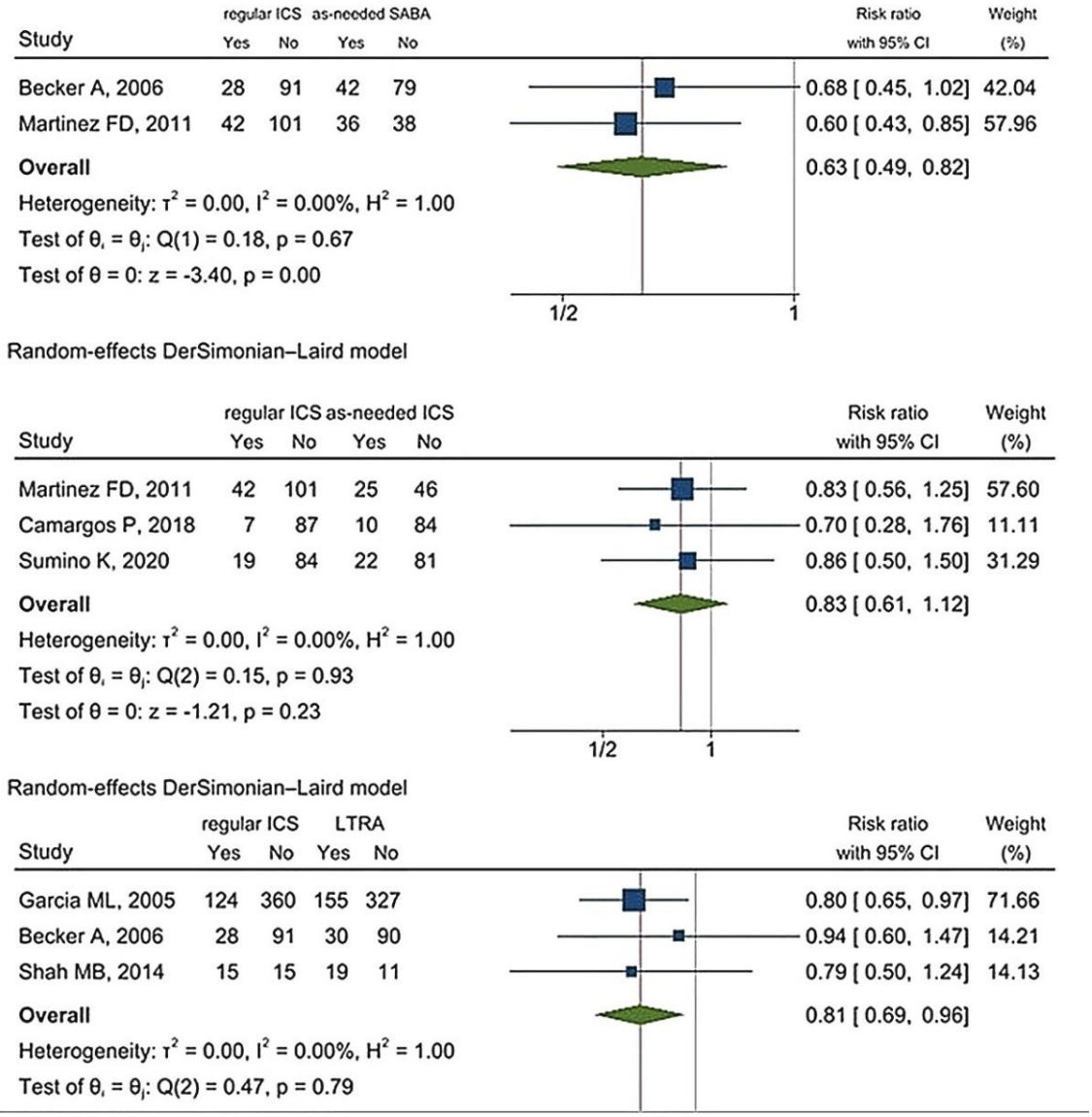


Figure 2 Comparison of the difference in exacerbations among the treatments in children

Table 1 Characteristics of included studies for outcomes of interest

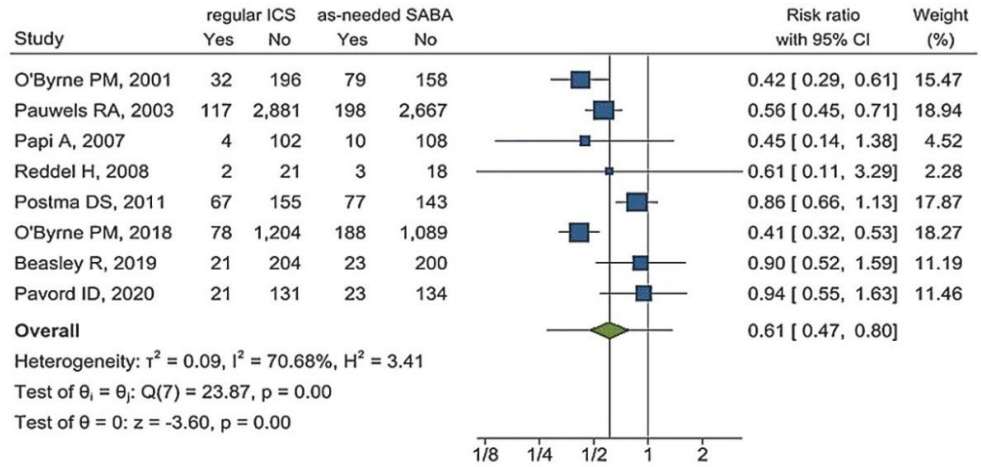
Study, author, year	Design	Wk	Participant (#I1, #I2 vs. #C)	Intervention-1 (I1)	Intervention-2 (I2)	Control (C)	Outcomes
Children							
Sumino et al., 2020	Parallel, assessor blinding	52	103/103	As-needed beclomethasone 80 mcg	-	Beclomethasone 40 mcg x2	exacerbation
Camargos et al., 2018	Parallel, open label	16	94/94	As-needed beclomethasone 250 mcg	-	Beclomethasone 250 x2	exacerbation
Shah et al., 2014	Parallel, open label	12	30/30	Montelukast 5 mg	-	Budesonide 200 mcg x2	
Martinez et al., 2011	Parallel, blinding	44	71/74/143	As-needed beclomethasone 80 mcg	As-needed albuterol 180 mcg	Beclomethasone 40 mcg x2	exacerbation
Becker et al., 2006	Parallel, blinding	56	120/121/119	Montelukast 5 mg	As-needed SABA	Beclomethasone 200 mcg x2	exacerbation
Garcia et al., 2005	Parallel, blinding	48	495/499	Montelukast 5 mg	-	Fluticasone 100 mcg x2	exacerbation
Adolescents and adults							
Pavord et al., 2020	Parallel, open label	52	72/49/62	As-needed budesonide/formoterol 200/6 mcg	As-needed salbutamol	Budesonide 200 mcg x2	severe exacerbation
Beasley et al., 2019	Parallel, open label	52	220/223/225	As-needed budesonide/formoterol 200/6 mcg	As-needed albuterol 100 mcg	Budesonide 200 mcg x2	exacerbation, severe exacerbation
Lazarus et al., 2019	Cross-over, blinding	12	221/221	Tiotropium Respimat 5 mcg x1	-	Mometasone 220 mcg x2	exacerbation
Hardy et al. 2019	Parallel, open label	52	437/448	As-needed budesonide/formoterol 200/6 mcg	-	Budesonide 200 mcg x2	severe exacerbation
O'Byrne et al., 2018	Parallel, blinding	52	1277/1277/	As-needed budesonide/formoterol 200/6 mcg	As-needed terbutaline 500 mcg	Budesonide 200 mcg x2	severe exacerbation
Bateman et al., 2018	Parallel, blinding	52	2089/2087	As-needed budesonide/formoterol 200/6 mcg	-	Budesonide 200 mcg x2	severe exacerbation
Postma et al., 2011	Parallel, blinding	52	222/220/210	Regular fluticasone/salmeterol 100/50 mcg x2	As-needed SABA	Ciclesonide 160 mcg x1	severe exacerbation, symptom score
Renzi et al., 2010	Parallel, blinding	24	253/263	Regular fluticasone/salmeterol 100/50 mcg twice daily	-	Fluticasone 100 mcg x2	exacerbation, severe exacerbation
Boulet et al., 2009	Parallel, blinding	52	33/24	As-needed SABA	-	Fluticasone 100 mcg x1	symptom score

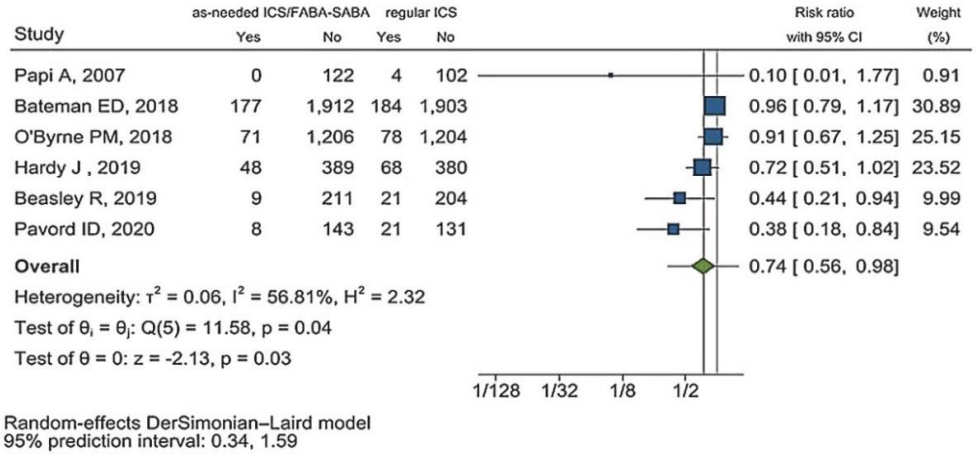
Study, author, year	Design	Wk	Participant (#I1, #I2 vs. #C)	Intervention-1 (I1)	Intervention-2 (I2)	Control (C)	Outcomes
Boonsawat et al., 2008	Parallel, blinding	12	149/155/154	Regular fluticasone/salmeterol 100/50 mcg x1	As-needed salbutamol	Fluticasone 100 mcg x1	exacerbation
Reddel et al., 2008	Parallel, blinding	48	21/23	As-needed SABA	-	Fluticasone 125 mcg x2	severe exacerbation
Chuchalin et al., 2008	Parallel, blinding	52	973/315/970	Regular fluticasone/salmeterol 100/50 mcg x1	As-needed SABA	Fluticasone 100 mcg x2	severe exacerbation, symptom score
Tamaoki et al., 2008	Parallel, open label	8	36/38	Pranukast 225 mg x2	-	Budesonide 100 mcg x2	symptom score
Stanković et al., 2007	Parallel, open label	24	40/45	As-needed salbutamol	-	Beclomethasone 250 mcg x1	symptom score
Papi et al., 2007	Parallel, blinding	24	109/122/118/106	Regular beclomethasone/albuterol 250/100 mcg twice daily	As-needed beclomethasone/albuterol 250/100 mcg	Beclomethasone 250 mcg x2	exacerbation, severe exacerbation and symptom score
Haahtela et al., 2006	Parallel, blinding	24	45/47	As-needed budesonide/formoterol 160/4.5 mcg	-	As-needed formoterol 4.5 mcg	symptom score
Boushey et al., 2005	Parallel, blinding	52	76/76/73	Zafirlukast 20 mg x2	As-needed albuterol	Budesonide 200 mcg x2	exacerbation, symptom score
Zeiger et al., 2005	Parallel, blinding	12	189/191	Montelukast 10 mg	-	Fluticasone 44 mcg x2	exacerbation, symptom score
Bousquet et al., 2005	Parallel, blinding	12	325/320	Montelukast 10 mg	-	Fluticasone 100 mcg x2	exacerbation
Strand et al., 2004	Parallel, blinding	24	78/72	Regular fluticasone/salmeterol 100/50 mcg x2	-	Fluticasone 100 mcg x2	severe exacerbation
Pauwels et al., 2003	Parallel, blinding	156	3568/3597	As-needed SABA	-	Budesonide 400 mcg x1	severe exacerbation
O'Byrne et al., 2001	Parallel, blinding	52	231/239/228	Regular budesonide/formoterol 100/6 mcg x2	As-needed SABA	Budesonide 100 mcg x2	severe exacerbation
Osterman et al., 1997	Parallel, blinding	52	37/38	As-needed salbutamol	-	Budesonide 200 mcg x2	symptom score

4.1.2 Exacerbations and severe exacerbations in adolescents/adults

A total of 9 RCTs reported outcome of exacerbations (see Table 1), 4 of which compared regular ICS (569 participants) and as-needed SABA (560 participants). Regular ICS was superior to as-needed SABA in reducing exacerbations (RR 0.44, 95% CI 0.32-0.61, I^2=0%). Two RCTs compared regular ICS (342 participants) and as-needed ICS/formoterol-SABA (334 participants). As-needed ICS/formoterol-SABA was

similar to regular ICS (RR 1.13, 95% CI 0.76-1.7, I^2=0%). Three RCTs compared regular ICS (500 participants) and regular ICS/LABA-SABA (476 participants). Regular ICS/LABA-SABA were not different from regular ICS (RR 0.81, 95% CI 0.40-1.6, I^2=54%). Three RCTs comparing regular ICS (548 participants) and LTRAs (543 participants) showed that LTRAs had higher exacerbation than regular ICS, but not reaching a statistical significance (RR 1.18, 95% CI0.82-1.69, I^2=0%). Only 2 RCTs compared regular ICS (564 participants) with tiotropium (413 participants), 1 study with low sputum eosinophil < 2%. Tiotropium was not different from regular ICS (RR 0.84, 95% CI 0.53-1.35, I^2=0%). For severe exacerbations, a total of 15 RCTs reported outcome of severe exacerbations, 8 of which compared regular ICS (6092 participants) and as-needed SABA (6205 participants). Regular ICS was superior to as-needed SABA in reducing severe exacerbations (RR 0.61, 95% CI 0.46-0.80, I^2=71%). Six RCTs compared regular ICS (4314 participants) and as-needed ICS/formoterol-SABA (4290 participants). As-needed ICS/formoterol-SABA was better than regular ICS (RR 0.74, 95% CI 0.56-0.976, I^2=57%). Seven RCTs compared regular ICS (1887 participants) and regular ICS/LABA-SABA (1870 participants). Regular ICS/LABA-SABA showed a significant greater reduction of severe exacerbations than regular ICS (RR 0.65, 95% CI 0.50-0.84, I^2=0%), see Figure 3.





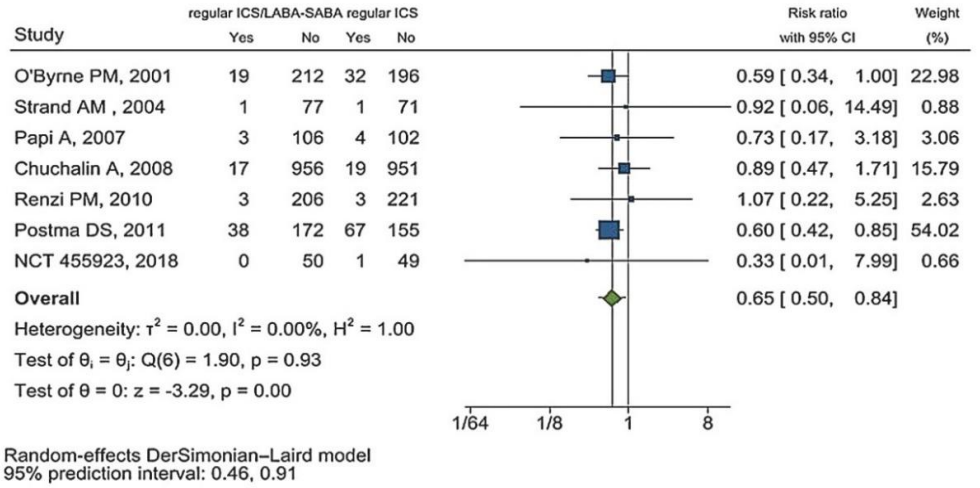


Figure 3 Comparison of the difference in severe exacerbations among the treatments in adolescents/adults

4.1.3 Symptom scores in adolescents/adults

A total of 12 RCTs reported the outcome of daily symptom scores, 7 of which compared regular ICS and as-needed SABA. Regular ICS was superior to as-needed SABA (N=2, step 1; N=5, step 2) in reducing symptom score (SMD -0.44, 95% CI -0.68 to -0.21, I^2=78%). Regular ICS/LABA-SABA was also better than as-needed SABA (N=3; step 2), (SMD -0.41, 95% CI -0.64 to -0.18, I^2=78%). In comparison of regular ICS with regular ICS/LABA-SABA (N=4; step 2) and with LTRAs (N=1; step 1, N=2; step 2), there were no differences in reduction of symptom score (SMD -0.02, 95% CI -0.18 to 0.13, I^2=55%, and SMD -0.83, 95% CI -2.18 to 0.52, I^2=97%, respectively). A sensitivity analysis was performed by excluding the study of Tamaoki et al. (2008) because this study compared lower dose of ICS (100 mcg of budesonide twice daily) and the study period was only 8 weeks (SMD 0.2, 95% CI -0.03 to 0.44, I^2=35%). There are no sufficient studies that reported the outcome of symptom scores comparing the treatments with as-needed ICS/formoterol-SABA and regular ICS, and as-needed SABA.

4.2 Discussion

This meta-analysis shows that in children, treatment with regular ICS yields a significant 37% reduction in the risk of exacerbations compared with as-need SABA, and a significant 18% reduction in the risk of exacerbations compared with LTRAs. Estimates of the treatment effect shows a 17% reduction in the risk of exacerbations with regular low-dose ICS when this approach is compared with as-needed ICS, but both treatments are not statistically different from each other. There was no evidence of heterogeneity in the finding for the exacerbation. From our findings, although regular ICS should be the first-line treatment of mild asthma step 2, low-dose ICS taken whenever symptoms occur (as-needed) in children also reveals a benefit in preventing exacerbations and may be an alternative to regular low-dose ICS. From our review, most children with mild asthma had baseline FEV_1 or PEF of $\geq$ 80%. There is no sufficient data to refer to this finding in those who had baseline FEV_1 or PEF of < 80%.

In adolescents and adults with mild asthma, treatment with regular low-dose ICS yields a statistically significant 56% reduction in the risk of exacerbations compared with as-need SABA without heterogeneity. No significant difference was found on a reduction of exacerbations between regular low-dose ICS and as-needed low-dose ICS/formoterol-SABA or regular low-dose ICS/LABA-SABA. Cautions to interpret these findings due to a limited number of studies for pooling this outcome for the former comparison, and a high heterogeneity for the latter comparison. For the comparison between regular low-dose ICS and LTRAs, we found no difference in reduction of exacerbation between the two treatments. It is likely that this finding was affected by the following contingencies: 1) short treatment duration for evaluation of exacerbation (12 weeks) in studies comparing LTRAs with other treatments, and 2) very low event rate.

Treatment with regular low-dose ICS yields a statistically significant 39% reduction in the risk of severe exacerbations compared with as-need SABA. Meanwhile, as-needed low-dose ICS/formoterol-SABA and regular low-dose ICS/LABA-SABA provide a significant 26% reduction and 35% reduction in the risk of severe exacerbations compared with regular low-dose ICS. All RCTs including for analysis of severe exacerbations are asthma step 2, with the exception of studies by O'Byrne et al. (2001) and Hardy et al. (2019) in which participants with asthma step 2 together with asthma step 3 were included. There was evidence of heterogeneity in the finding for severe exacerbations. This can be partly explained by the difference in study design, with the results of the two open-label studies having a greater treatment effect and favoring as-needed budesonide-formoterol (Beasley et al., 2019; Hardy et al., 2019). Regarding the reduction of the symptom scores, regular low-dose ICS with or without formoterol-LABA-SABA were superior to as-needed SABA alone. However, the symptom scores were not different when comparing regular low-dose ICS with regular low-dose ICS/LABA-SABA or with LTRAs. This implies that any asthma controller medications can improve symptom scores and this approach is preferred rather than using SABA-alone.

There are potential limitations to this review. First, it is unclear if these results can be applicable to other ICS/FABA or LABA combinations beyond formoterol and salmeterol. This review has insufficient data for pooling and analysis to draw clearer conclusions about other LABAs. Second, there is a limited number

of RCTs including mild asthma step 1, and there is a need for further updated review when there are additional studies sufficient for pooling.

5. Conclusion

This systematic review and meta-analysis provides evidence showing that in pediatric mild asthma step 2 (age ≥ 6), the initiation of regular low-dose ICS or as-needed ICS as an alternative can prevent exacerbations at a greater extent than as-needed SABA and LTRAs. Meanwhile, in adolescents and adults with mild asthma step 2, the option can be either low-dose ICS or combinations of as-needed low-dose ICS/FABA or regular ICS/LABA.

6. Acknowledgements

We would like to thank Ramathibodi Hospital's librarians for the support in the full-text literature search. No grants were applied for this work. The authors declare that they have no conflicts of interest.

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