

Impact of dosage timing of once-daily inhaled corticosteroids in asthma: A systematic review and meta-analysis

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ABSTRACT

Background: Once-daily inhaled corticosteroids (ICSs) are widely used as first-line therapy in patients with asthma.

Objective: To compare the efficacy of ICSs administered once daily in the morning or evening as determined by lung function.

Methods: Medline, Embase, and the Cochrane Central Register were searched for relevant clinical trials. The primary outcome was lung function assessed as trough forced expiratory volume in 1 second and peak expiratory flow at end point.

Results: Eight randomized clinical trials involving 1,234 patients were analyzed. The total number of patients treated with once-daily ICS in the morning and evening was 628 and 606, respectively. Pooled estimates showed that ICS administered once daily in the evening resulted in mild improvements in trough forced expiratory volume in 1 second (mean difference 0.05 L; 95% confidence interval 0.01–0.09; $P = .026$; $I^2 = 22.5\%$) and morning peak expiratory flow (mean difference 13.92 L/min; 95% confidence interval 5.77–22.06; $P = .001$; $I^2 = 13\%$) at end point compared with morning dosing. The change in use of rescue medicine and the incidence of adverse events with once-daily ICS were not significantly different between the 2 dosing times.

Conclusion: Compared with morning dosing, ICSs administered once daily in the evening seemed to provide some benefits in lung function for patients with asthma. However, because of methodologic limitations, further large-scale randomized clinical trials for dosing time of once-daily ICSs are needed.

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Introduction

Asthma is a crucial global health problem affecting all age groups and is usually characterized by chronic airway inflammation.^{1,2} Airway inflammation is considered the main factor of asthma symptoms, and inhaled corticosteroids (ICSs) have proved the most effective and essential therapy for the treatment of asthma.^{1,2} As a reflection of this, the current Global Initiative for Asthma guidelines recommend an ICS as first-choice control therapy for all patients with asthma that is not controlled by a rapid-acting β_2 -agonist as needed.¹

Lack of adherence and suboptimal use of ICS therapy are associated with poor control of asthma.^{3,4} Among the many reasons for poor compliance, complicated regimens and treatment dosing frequency should be considered. One of the current strategies to improve compliance with ICS therapy is a decrease in dosing frequency to once daily. Budesonide, ciclesonide, mometasone furoate (MF), and fluticasone furoate (FF) are currently used as once-daily maintenance ICSs for asthma control.^{1,5} Once-daily dosing of these ICSs has been shown to be an efficacious and well-tolerated treatment for asthma control and not inferior to the same total dose given twice daily.^{6,7} A recent systematic literature review also found that once-daily ICS and long-acting β_2 -agonist (LABA) combination therapy (FF + vilanterol) showed comparable efficacy to twice-daily combination therapies in improving lung function and health status.⁸

Patients with asthma frequently experience nocturnal symptoms including cough, wheezing, and dyspnea.⁹ These symptoms can lead to sleep disruption.⁹ Also, lung function shows a circadian rhythm, with lung functionality being lowest in the early morning.¹⁰ These factors suggest that evening dosing with ICSs would provide an improved benefit compared with morning dosing. To date,

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several randomized controlled trials (RCTs) for time of dosing of once-daily ICSs in patients with asthma have been published^{11–18}; however, it is unclear whether the efficacy of once-daily ICSs is different between morning and evening dosing. Therefore, the aim of this study was to investigate the differences in clinical efficacy of ICSs administered once daily in the morning vs evening in patients with asthma based on a systematic review of clinical trial data.

Methods

Data Sources and Search Strategy

To identify potentially relevant articles, a comprehensive search was performed through electronic databases (Medline, Embase, and Cochrane Central Register). The cutoff date for publication was December 31, 2016. The search filters provided by SIGN (<http://www.sign.ac.uk/search-filters.html>) were used. The search was without language restriction and was limited to human studies. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. In addition, we performed a manual search of the references listed in relevant review articles. Because this study was a systematic review of published articles, neither informed consent nor ethics approval was required.

Inclusion Criteria

A systematic review and meta-analysis was performed of studies that met the following criteria: (1) RCTs for patients with asthma and documented use of once-daily ICS (budesonide, ciclesonide, MF, and FF) with or without a LABA; (2) comparison of morning vs evening for dosing time of inhalation; and (3) available clinical outcomes of pulmonary function testing (forced expiratory volume in 1 second [FEV₁] or peak expiratory flow [PEF]) as a primary outcome, rescue medication use, and adverse events (AEs).

Study Selection and Data Extraction

Two pulmonologists independently retrieved potentially relevant studies, reviewed each study according to predefined criteria for eligibility, and extracted data. Any disagreement in the process of study selection or data extraction was resolved through consensus. For each study a predefined form was used to extract data including authors, year of publication, patient sex, sample size, standard treatments, interventions, outcomes, and AEs. We used only published data in our analysis. The primary outcome was change in lung function assessed as FEV₁ and PEF to estimate the efficacy of dosing. Other outcomes included changes in the use of rescue medicine and the incidence of AEs for morning or evening dosing.

Quality Assessment

The quality of RCTs was assessed using the Cochrane Handbook for Systemic Reviews of Interventions “risk of bias” tool.¹⁹ A “low,” “high,” or “unclear” risk of bias was assigned to the following domains: sequence generation or allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Agreement between reviewers was achieved through consensus.

Statistical Analysis

We analyzed data in Review Manager Software 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and STATA 14.2 (StataCorp LP, College Station, Texas). Statistical

significance was evaluated using a raw mean difference (MD) for continuous variables and risk ratios with 95% confidence intervals (CIs) for dichotomous variables. We performed a χ^2 test for heterogeneity based on a fixed effect and the I^2 statistic to quantify the degree of heterogeneity between studies. Heterogeneity was assessed using I^2 statistics on a scale of 0% to 100%. We considered an I^2 of 30% to 60% as an indication of moderate heterogeneity and a value higher than 60% as significant between-study heterogeneity.²⁰ If significant heterogeneity existed, then a random-effects model was used for analysis; otherwise, a fixed-effects model was used. We performed the subgroup analysis according to treatment duration (≤ 4 vs ≥ 8 weeks). Publication bias was examined using funnel plots when at least 10 studies reported a given outcome. A P value less than .05 was considered statistically significant.

Results

Study Search

A total of 4,482 published articles were initially identified through database searches. After removing duplicate articles, we screened 3,927 potentially eligible articles from database searches and added 1 potentially eligible article from the reference lists. Of these articles, 3,819 were excluded based on the title and abstract, and the remaining 109 articles underwent a full-text review. One hundred one articles were excluded for the reasons presented in Figure 1. Eight articles were included in the present analysis.^{11–18} All included articles were published from 1994 through 2016. The characteristics of the selected studies are presented in Table 1. The number of patients in the trials ranged from 26 to 646. The total number of patients in our systematic review and meta-analysis was 1,234, of whom 628 were treated with ICSs in the morning and 606 were treated in the evening. Assessment of quality for the RCTs is presented in Table 2.

Primary and Secondary Outcomes

A forest plot of the primary outcome, effect of morning or evening administration of once-daily dosing of ICSs on trough FEV₁ at end point, is shown in Figure 2.^{11–16} Overall, a fixed-effects model showed that ICS administered once daily in the evening resulted in mild improvements compared with ICS once daily in the morning with respect to trough FEV₁ at end point (MD 0.05 L; 95% CI 0.01–0.09; $P = .026$).^{11–16} There was little evidence of statistical heterogeneity (Higgins and Green $I^2 = 22.5\%$; $P = .257$, $Q = 7.75$, $df = 6$).^{11–16} In subgroup analysis for patients treated with FF, the MD in trough FEV₁ at end point was not significantly different between morning and evening dosing (MD 0.04 L; 95% CI –0.01 to 0.08; $P = .113$; $I^2 = 0\%$; Fig 2).^{11–14} We also performed a subgroup analysis according to treatment duration (≤ 4 vs ≥ 8 weeks). The MD in trough FEV₁ at end point was not significantly different between the 2 dosing times (MD 0.04 L; 95% CI –0.01 to 0.10; $P = .138$; $I^2 = 0\%$ for ≤ 4 weeks; MD 0.06 L; 95% CI –0.01 to 0.12; $P = .190$; $I^2 = 59.7\%$ for ≥ 8 weeks).

We retrieved data concerning changes in PEF according to the dosing time of once-daily ICSs from 6 RCTs.^{12,13,15–18} Compared with morning dosing, once-daily ICS in the evening produced statistically significant increases in morning PEF at end point (MD 13.92 L/min; 95% CI 5.77–22.06; $P = .001$; $I^2 = 13\%$; Fig 3A).^{12,15–18} Evening PEF and mean daily PEF at end point showed no significant difference between morning and evening dosing (MD 6.06 L/min; 95% CI –1.81 to 13.93; $P = .131$; $I^2 = 0\%$; MD 7.53 L/min; 95% CI –0.29 to 15.35; $P = .059$; $I^2 = 0\%$, respectively; Fig 3B, C).^{12,13,16–18}

The change in use of rescue medication at end point was not statistically significant between the 2 groups (MD –0.14; 95% CI –0.41 to 0.12; $P = .291$; $I^2 = 38.2\%$; Fig 4A).^{16–18} Also, as shown in Figure 4B,

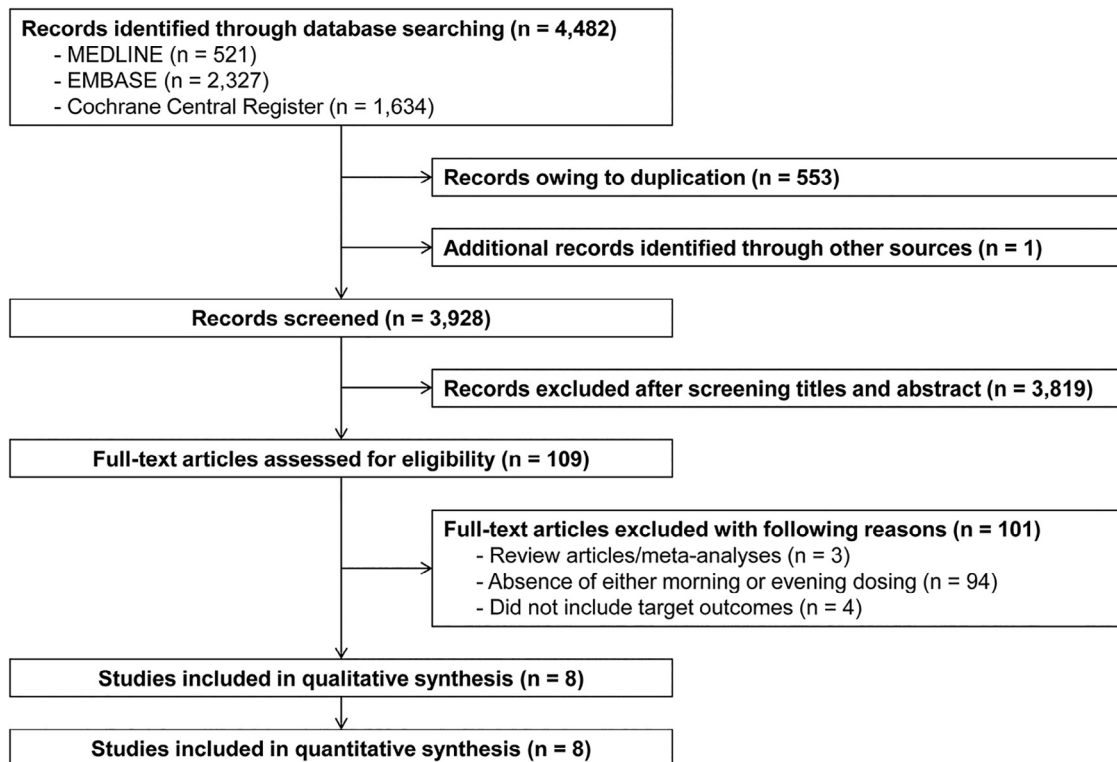


Figure 1. Flowchart of study selection.

the incidence of any AE for once-daily ICS was not significantly different between morning and evening dosing (34.8% vs 31.9%; risk ratio 0.92; 95% CI 0.76–1.11; $P = .382$; $I^2 = 0\%$).^{11,13,14}

Discussion

In the present study, we found that, compared with morning dosing, once-daily ICS administered in the evening produced mild increases in trough FEV₁ and morning PEF at end point. In addition, the change in use of rescue medicine at end point and the incidence of AEs with once-daily ICS were not significantly different between the 2 groups.

Adherence to treatment has an important influence on the control of asthma.³ A recent meta-analysis of 31 parallel-group RCTs found that once-daily ICS and LABA combination therapies demonstrated a probability of noninferiority in lung function, as assessed by change from baseline morning PEF and FEV₁ compared with twice-daily therapies.⁸ One recent study reported that a once-daily dosing regimen of MF showed higher adherence rates than a twice-daily dosing regimen.⁶ Based on these results, once-daily treatment could offer greater convenience and tolerability for the patients. Next, we questioned whether the dosing time of once-daily ICS affected clinical outcomes in patients with asthma. When selecting the optimal timing of ICS administration for an individual patient, circadian changes in asthma would be the most relevant aspect to consider for effective asthma control. In this regard, it is noteworthy that the present study provides a clinically relevant answer to the question regarding the most effective time of dosing of once-daily ICS.

The effectiveness of ICS on lung function is one of the most important parameters to consider in clinical studies of asthma. Asthma is characterized by variable expiratory airflow limitation. Because variation in airflow limitation is generally evaluated from variation in FEV₁ or PEF in clinical practice, we selected these parameters

to represent the primary efficacy in the present study.¹ Morning PEF, evening PEF, and mean daily PEF at end point were considered representative of diurnal effect on lung function after treatment with ICSs. Pooled estimates demonstrated that evening dosing with once-daily ICSs statistically increased trough FEV₁ and morning PEF at end point compared with morning dosing. However, the difference in improvement of mean PEF and evening PEF between the 2 dosing regimens was not significant.

Possible explanations for the present findings could be circadian changes such as night-time worsening of asthma symptoms and lung function.²¹ This variability is associated with recruitment of inflammatory cells into the airway during sleep.²² Serum cortisol also follows a circadian rhythm, with peak concentrations seen in the morning between 6 and 10 AM and trough concentrations seen at night between 8 PM and 2 AM.²³ In consequence, the administration time of ICS affects the diurnal variation in cortisol suppression, with the most distinct cortisol suppression being observed when corticosteroids are administered in the morning compared with the evening.²⁴ Thus, evening dosing of ICS might be the optimal time of administration.^{23,24} Consistent with these findings, our results suggest that evening dosing time of once-daily ICSs might provide mild improvement in trough FEV₁ and morning PEF. In addition, this strategy can decrease side effects related to cortisol suppression.²³

Fluticasone furoate is the newer ICS with greater glucocorticoid receptor binding affinity compared with other ICSs.⁷ FF also has higher cellular accumulation and slower efflux than other ICSs, resulting in prolonged retention in the lung tissue and long-lasting improvement in lung function for 24 hours after once-daily dosing.^{25,26} Previous studies reported that FF was not inferior to fluticasone propionate administered twice daily with regard to lung function.^{7,27} In the present study, FF was the most common of once-daily ICSs in the included studies. Our pooled estimates demonstrated that the change of lung function was not significantly

Table 1
Main Characteristics of Randomized Controlled Trials Included in Meta-Analysis

Study, year	Design	Patients (N)	Age (y), mean	Men, %	Treatment duration (wk)	Baseline pre-bronchodilator FEV ₁ % predicted, mean	Intervention protocol	Primary end point	Main conclusion
Kempsford et al, 2016 ¹¹	single-center, repeat-dose, double-blinded, double-dummy, placebo-controlled, 3-way crossover RCT	28	31.7	46	2	86.9	FF 100 µg in morning, FF 100 µg in evening, or placebo once daily	24-hour weighted mean FEV ₁ on day 14	once-daily administration of FF 100 µg resulted in increased weighted mean FEV ₁ vs placebo, with no appreciable difference between morning or evening dosing
Kempsford et al, 2013 ¹²	single-center, double-blinded, placebo-controlled, 3-way crossover RCT	26	38.1	69	2	80.25	FF/vilanterol 100/25 µg (morning or evening) or matching placebo once daily	24-hour weighted mean FEV ₁ on day 14	FF/vilanterol 100/25 µg produced comparable improvements in lung function whether dosed in morning or evening
Medley et al, 2012 ¹³	multicenter, phase IIa, double-blinded, double-dummy, placebo-controlled, parallel-group RCT	575	36.6	56.9	4	not available	FF 100 µg in morning, FF 100 µg in evening, FF 250 µg in evening, or placebo once daily	mean change from baseline to end point in PEF	once-daily treatment with FF dosed in morning or evening was well tolerated and associated with improvements in lung function and measurements of asthma symptoms, rescue medication use, and night-time awakenings
Woodcock et al, 2011 ¹⁴	multicenter, phase IIa, double-blinded, parallel-group, placebo-controlled RCT	646	45.1	35.1	8	67.38	FF 200 or 400 µg in morning, FF 200 or 400 µg in evening, FF 200 µg twice daily, or placebo twice daily	mean change from baseline to end point in FEV ₁	FF 400 µg once daily in evening had similar efficacy to FF 200 µg twice daily and all FF regimens had safety tolerability profile generally similar to placebo
Noonan et al, 2001 ¹⁵	multicenter, double-blinded, 5-arm, parallel-group RCT	286	39.4	39.8	12	78.6	MF 200 µg twice daily, MF 200 or 400 µg in morning, MF 200 µg in evening, or placebo once daily	mean change from baseline to end point in FEV ₁	once-daily MF 400 µg in morning was as effective as MF 200 µg twice daily, whereas once-daily MF 200 µg was more effective when administered in evening vs morning
Postma et al, 2001 ¹⁶	single-center, double-blinded, parallel-group RCT	209	38.5	54.5	8	77	ciclesonide 200 µg in morning, ciclesonide 200 µg in evening	weekly average of morning PEF	ciclesonide can be given in the morning or evening so that patient preference and individual medical needs can be addressed
Pincus et al, 1997 ¹⁷	single-center RCT	59	34.2	54.2	4	not available	TA 800 µg in morning, TA 800 µg in evening, TA 800 µg 4 times daily	FEV ₁ , PEF rates, bronchial hyperresponsiveness, use of β ₂ -agonist, nocturnal awakenings, and responses to quality-of-life questionnaire	once-daily TA 800 µg administered in evening had no increased systemic effects and produced efficacy similar to once-daily dosing
Jones et al, 1994 ¹⁸	single-center, double-blinded, parallel-group RCT	340	37	52.3	12	not available	budesonide 400 µg in morning, budesonide 400 µg in evening, budesonide 200 µg twice daily, or placebo twice daily	PEF rates (best of 3 always taken) and asthma symptoms on diary card	once-daily budesonide 400 µg administered in morning or evening was as effective as twice-daily budesonide 200 µg

Abbreviations: FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; MF, mometasone furoate; PEF, peak expiratory flow; RCT, randomized controlled trial; TA, triamcinolone acetate.

Table 2
Risk of Bias of the Studies Included in the Meta-Analysis

Study, year	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting
Kempsford et al, 2016 ¹¹	low risk	low risk	low risk	low risk	low risk	low risk
Kempsford et al, 2013 ¹²	low risk	low risk	low risk	low risk	low risk	low risk
Medley et al, 2012 ¹³	unclear	low risk	low risk	low risk	low risk	low risk
Woodcock et al, 2011 ¹⁴	unclear	low risk	low risk	low risk	low risk	low risk
Noonan et al, 2001 ¹⁵	unclear	low risk	low risk	low risk	low risk	low risk
Postma et al, 2001 ¹⁶	unclear	low risk	low risk	low risk	low risk	low risk
Pincus et al, 1997 ¹⁷	unclear	high risk	high risk	high risk	high risk	high risk
Jones et al, 1994 ¹⁸	unclear	low risk	low risk	low risk	low risk	low risk

different between the 2 dosing strategies, when subgroup analysis for FF studies was conducted.

Changes in symptoms can be regarded an important parameter when evaluating ICS efficacy in asthma treatment. Several studies found that evening administration of MF lessened asthma symptoms in patients previously dependent on twice-daily ICS therapy.^{15,28} A prospective study using MF reported that evening and morning dosing times provided the same level of 24-hour symptom control, as shown by similar decreases from baseline in daytime and nighttime symptoms.²⁹ We tried to examine the change in asthma symptoms but could not perform pooled estimates because of insufficient data; therefore, we investigated the change in daily use of rescue medications. With respect to the change in use of rescue medication at end point, there was no significant difference between morning and evening dosing. However, these pooled estimates included small data from relatively old ICSs. Instead, a recent RCT

reported that the percentage of changes in asthma symptom-related parameters for FF once daily in the morning was similar to that for FF once daily in the evening.¹³ In addition, our results showed no differences in the reported frequency of AEs after morning or evening dosing.

There are some limitations to this study. First, because our meta-analysis was performed with a small number of trials, it might be insufficient to allow generalizations of efficacy and safety of once-daily dosing strategies in the morning or evening. In addition, we could not construct funnel plots to examine the effects of publication bias because of limited data. Additional large-scale RCTs should be performed. Second, our results were based on findings from RCTs using various ICSs and a heterogeneous patient population. In particular, 1 study allowed the use of LABAs, and the effect of concomitant LABA treatment could not be evaluated.¹² Third, lung function was estimated within 2 to 12 weeks of treatment with ICSs.

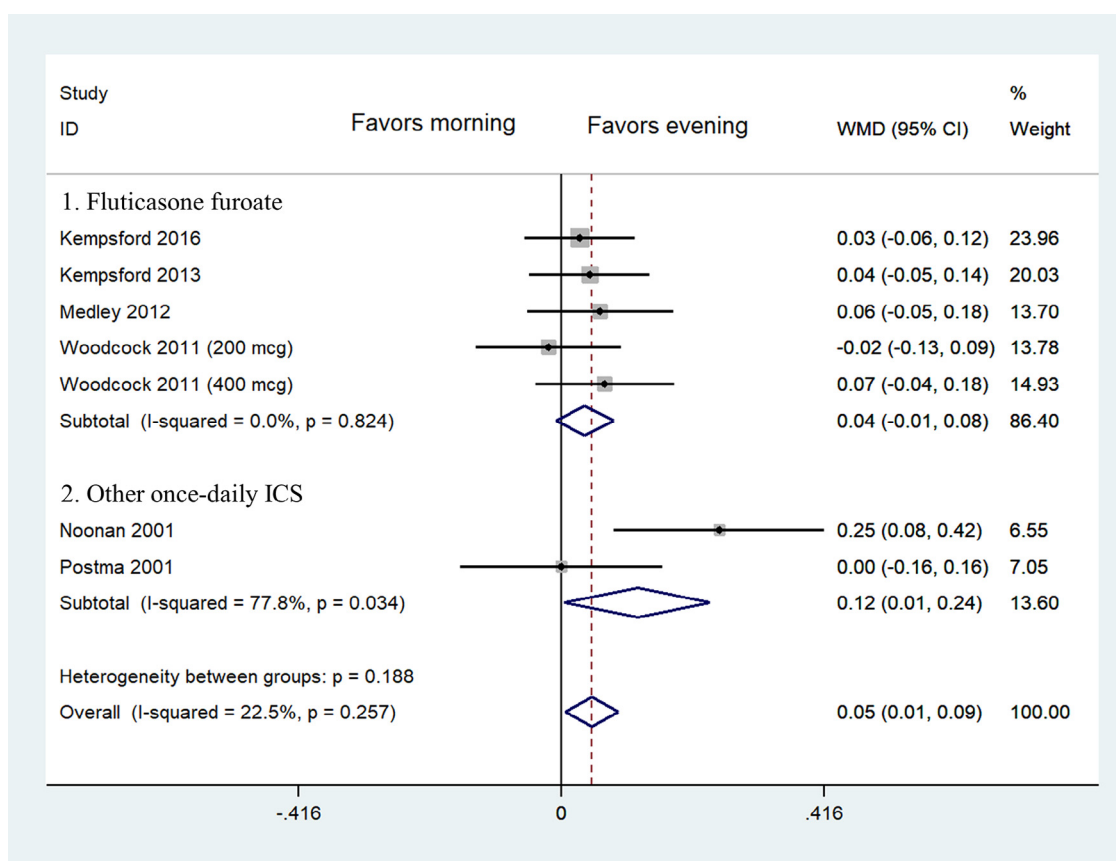


Figure 2. Pooled results of the mean differences (liters) in forced expiratory volume in 1 second for treatment with inhaled corticosteroids administered in the morning vs evening in patients with asthma. CI, confidence interval; ICS, inhaled corticosteroid; WMD, weighted mean difference.

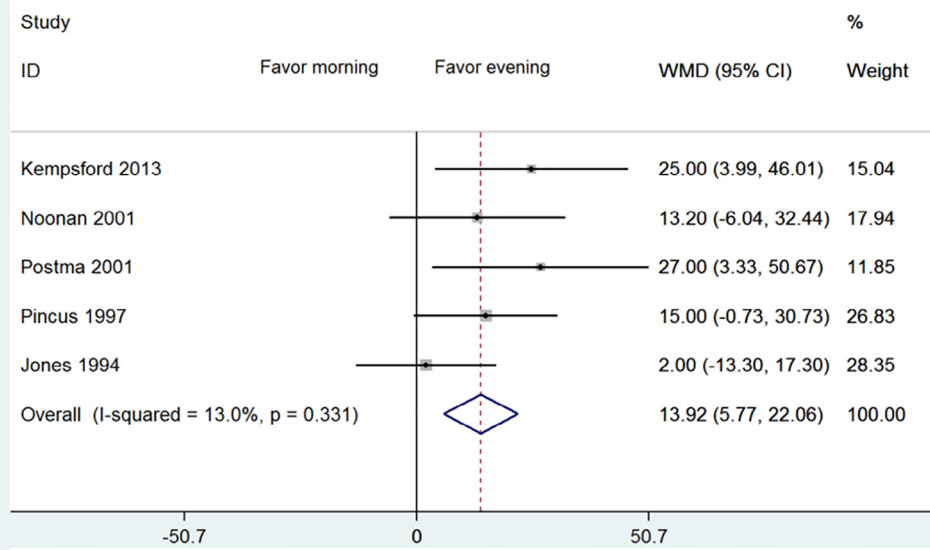
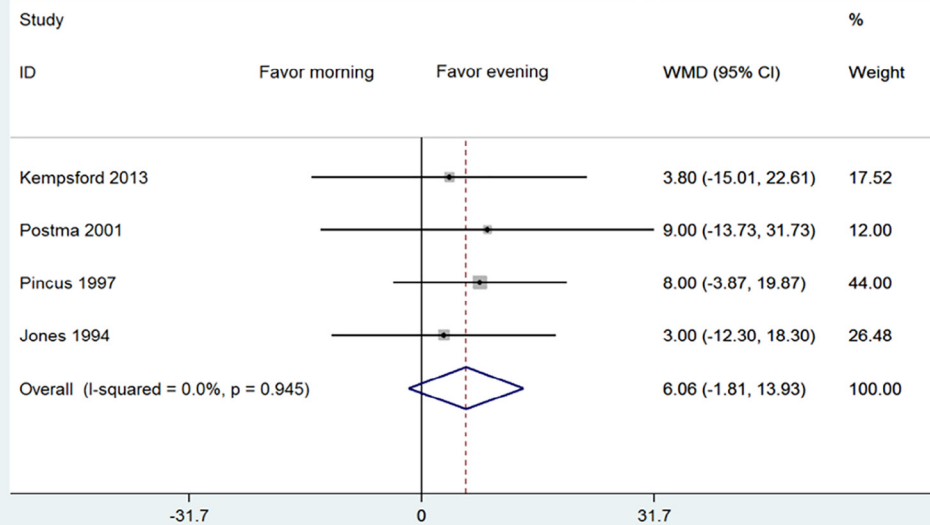
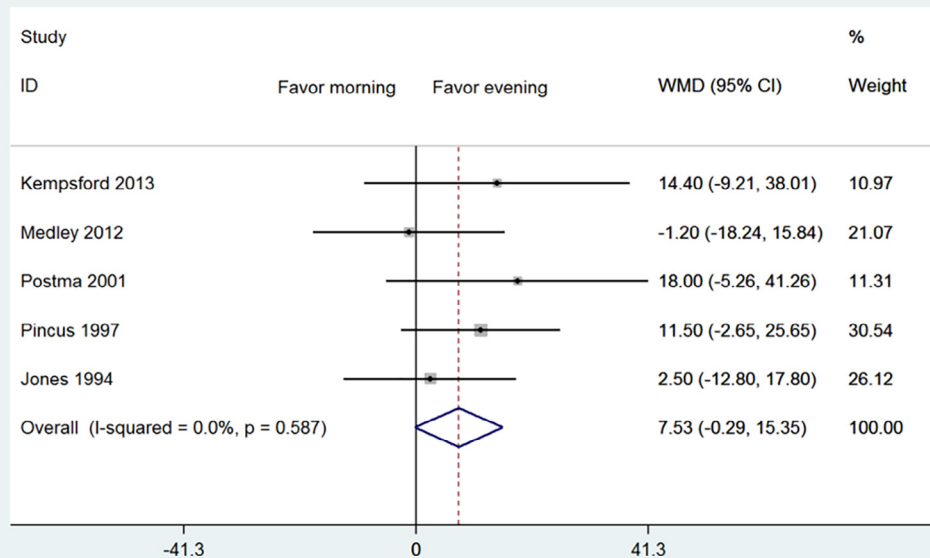
A**B****C**

Figure 3. Pooled results of mean differences (liters per minute) in peak expiratory flow measured in the (A) morning and (B) evening and (C) mean daily value for treatment of inhaled corticosteroids administered in the morning vs evening in patients with asthma. CI, confidence interval; WMD, weighted mean difference.

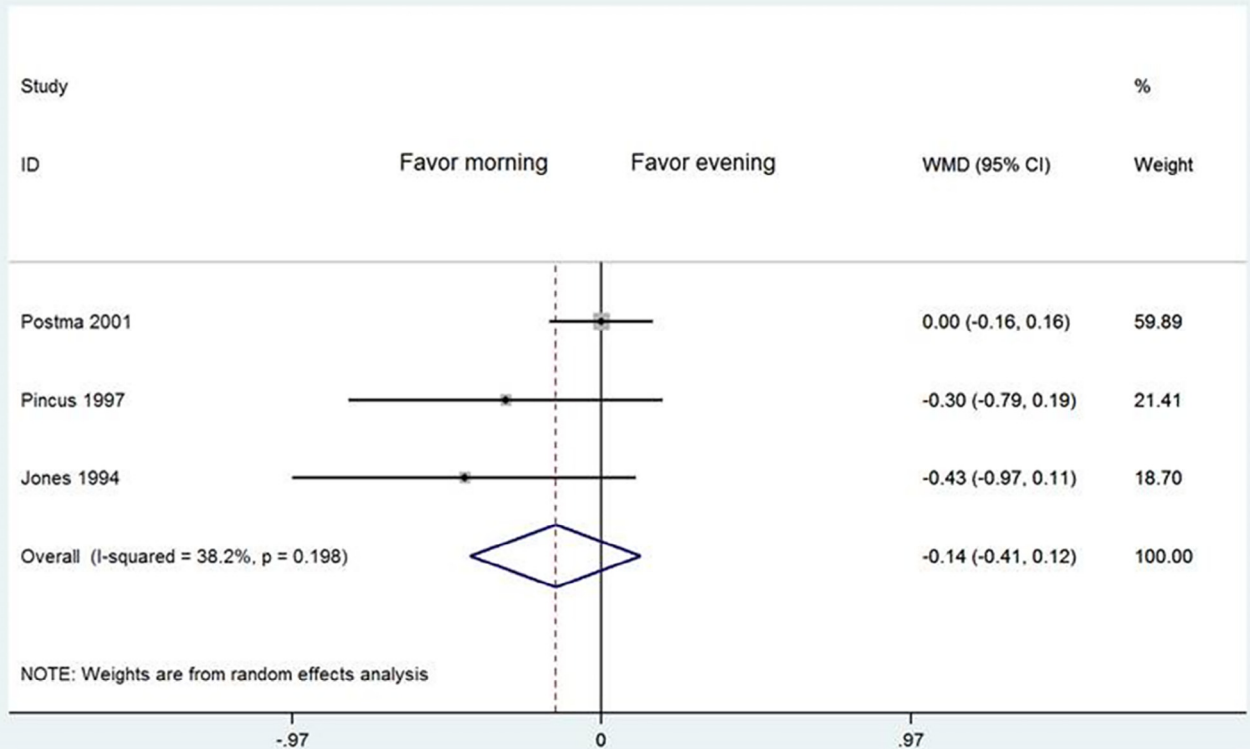
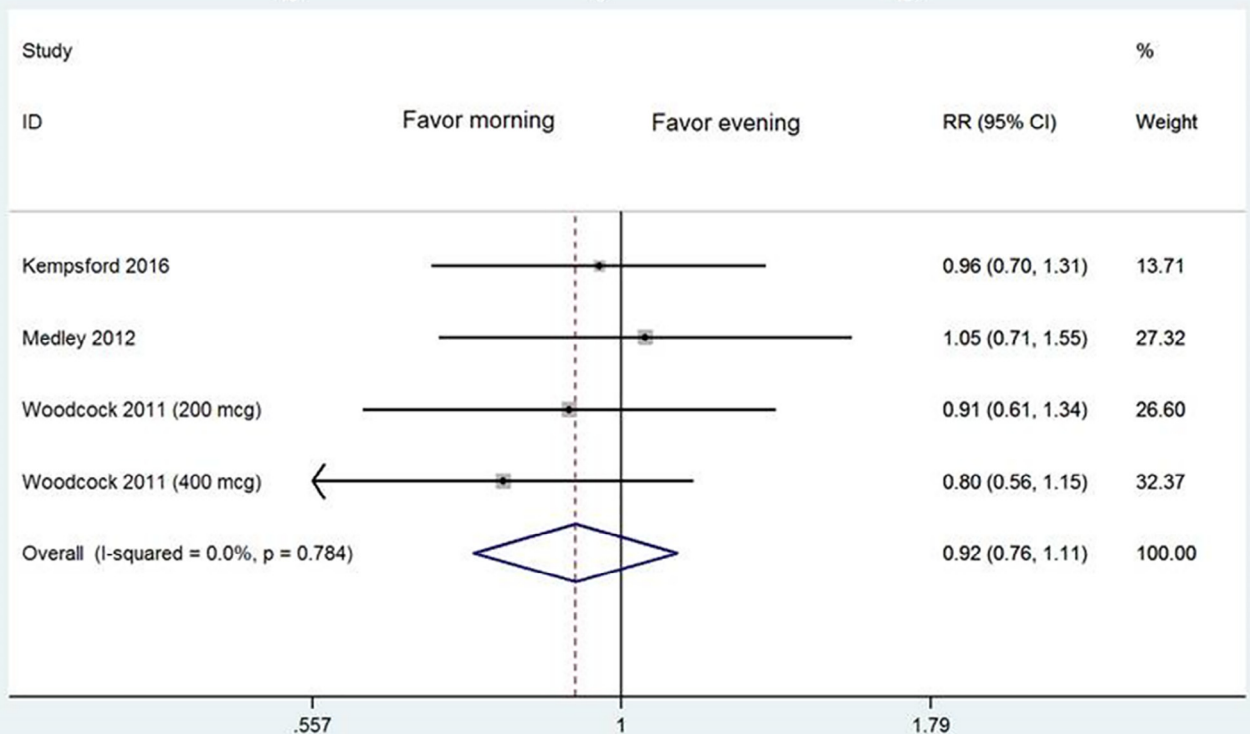
A**B**

Figure 4. Pooled results of (A) change in the use of rescue medications and (B) incidence of any adverse events in patients with asthma treated with inhaled corticosteroids in the morning vs evening. CI, confidence interval; RR, risk ratio; WMD, weighted mean difference.

Specifically, 2 studies included in our analysis investigated outcomes after 2 weeks of treatment with FF.^{11,12} This short study duration might be insufficient to characterize the long-term clinical efficacy of ICSs. Although the pooled estimates in the present study showed that differences in the duration of ICS treatment did

not contribute to effects on the trough FEV₁ as an end point, further large-scale studies are necessary to determine the impact of treatment duration.

In conclusion, our systemic review and meta-analysis showed that ICS administered once daily in the evening was associated with

mild improvements in lung function for trough FEV₁ and morning PEF at end point compared with morning dosing. Because the change in use of rescue medicine at end point and the incidence of AEs with once-daily ICS were not significantly different between the 2 dosing times, it would be not harmful to advise once-daily administration of an ICS in the evening. To confirm the present results, further large-scale RCTs are needed for the evaluation of chronotherapeutic effects of once-daily ICSs because of the methodologic limitations of the included trials and a scarcity of trials for analysis.

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