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META-ANALYSIS

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Comparative Efficacy of Budesonide/Formoterol with Budesonide, Formoterol or Placebo for Stable Chronic Obstructive Pulmonary Disease: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1,2 Bin Tang
BF 2 Jun Wang
BF 2 Lin-lin Luo
AG 2,1 Qiu-gen Li
ABF 3 Dan Huang

1 School of Medicine, Nanchang University, Nanchang, Jiangxi, P.R. China
2 Department of Respiratory Medicine, Jiangxi Provincial People's Hospital, Nanchang, Jiangxi, P.R. China
3 Department of Anesthesiology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, P.R. China

Corresponding Author: Qiu-gen Li, e-mail: liqiugenjxyy@126.com, Dan Huang, e-mail: tanghuang05@163.com
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Background: The 2018 Global Initiative for Chronic Obstructive Lung Disease publication suggested that the combination of bronchodilator therapy of inhaled glucocorticoid/long-acting β_2 adrenoceptor agonist is more effective in improving pulmonary function and health status in the treatment of patients with acute exacerbations than the individual components; however, it is not known whether this also the case for stable chronic obstructive pulmonary disease (COPD). The purpose of this meta-analysis was to evaluate the effectiveness of budesonide/formoterol in the maintenance and relief therapy of patients with stable COPD.

Material/Methods: An electronic search of the literature in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials was undertaken to identify published randomized controlled trials (RCTs) of ≥12 weeks duration comparing the budesonide/formoterol, with budesonide, formoterol, or placebo in the treatment of patients with stable COPD. The identified RCTs were reviewed. The mean difference (MD) with corresponding 95% confidence interval (CI) was used to pool the results.

Results: Seven high quality studies with RCTs met the inclusion criteria for meta-analysis. Compared with budesonide alone, the combination therapy of budesonide/formoterol showed significant improvement in the following spirometric indices: pre-dose forced expiratory volume in 1 second (FEV_1) (SMD: 0.26, 95% CI: 0.18, 0.34; *P*=0.000). In addition, versus formoterol alone, budesonide/formoterol was associated with a significant increase in pre-dose FEV_1 (SMD: 0.12, 95% CI: 0.07, 0.17; *P*=0.000). A similar pattern was also evident in the comparison to placebo, where budesonide/formoterol yielded greater increase in pre-dose FEV_1 (SMD: 0.24, 95% CI: 0.18, 0.30; *P*=0.000). Moreover, compared with other controls, the combination of budesonide-formoterol significantly improved morning peak expiratory flow and evening peak expiratory flow, significantly reduced the total score of St. George's Respiratory Questionnaire.

Conclusions: For stable COPD patients, compared with controls (monocomponents or placebo), budesonide/formoterol improved pulmonary function and health status. Future larger long-term RCTs are warranted to assess the beneficial clinical efficacy of budesonide/formoterol in COPD patients.

MeSH Keywords: Budesonide • Meta-Analysis • Pulmonary Disease, Chronic Obstructive • Randomized Controlled Trial

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Background

Chronic obstructive pulmonary disease (COPD) is currently the leading prevalent public health problem, and the fourth major cause in the world of morbidity and mortality. By 2020, COPD is expected to become the third most common cause of death worldwide, and it results in huge health-care costs and a heavy social burden [1–4]. The main objectives in the treatment of COPD are to slow down or even improve the decline in pulmonary function, to control the symptoms, to ameliorate and prevent exacerbations, to improve health-related quality of life (HRQL), and to reduce the incidence and mortality of adverse events. Current COPD guidelines recommend treating with combination therapy if we are unable to control symptoms adequately by use of a single bronchodilator, such as inhaled corticosteroid (ICS), long-acting β_2 adrenoceptor agonist (LABA), long-acting muscarinic antagonist, anti-inflammatory drugs, etc. Because there are 2 different mechanism of actions of bronchodilators, combination therapy may strengthen treatment effect [5,6].

ICS/LABA combination bronchodilator therapy is the recommended treatment for COPD patients with a history of exacerbations [5], compared with placebo, and/or monotherapies, which have been proved effective in reducing the exacerbation of COPD [7–10]. Previous studies reported that LABA formoterol could improve pulmonary function, ameliorate symptoms, and reduce the need for rescue medication [11], as well as improve exercise tolerance and HRQL in COPD patients compared with other treatments [12]. Inhaled glucocorticoid budesonide therapy has been proven to have beneficial efficacy for exacerbations, symptoms, pulmonary function, and HRQL in COPD patients [13,14].

The combination of budesonide and formoterol, containing a fixed dose of ICS and LABA, was approved as first-line drug therapy for patients with COPD in Europe in 2003 for the first time and subsequently in the United States in 2009, and this combination shows remarkable clinical efficacy in the treatment of COPD patients. Previous research has mainly focused on western populations, and has reported that budesonide/formoterol could provide benefits by improving pulmonary function, COPD symptoms, HRQL, and reduced exacerbation rate in COPD patients [15–19].

To date, the 2018 Global Initiative for Chronic Obstructive Lung Disease publication [5] recommended that ICS/LABA treatment is more effective than monocomponents in improving pulmonary function and HRQL in patients with acute exacerbations, however, as for stable COPD patients, it is not known whether the combination drug has a similar efficacy. Moreover, many randomized controlled trials (RCTs) have reported that budesonide/formoterol is more clinically effective than monocomponents and placebo, and there is no significantly difference reported in the tolerance between combination therapy groups and controls. However, the statistical power of these findings represents borderline statistics. Therefore, to better understand the true clinical outcomes of this combination therapy, it is necessary to perform a meta-analysis of existing RCTs.

Material and Methods

Search strategy and eligibility criteria

The MEDLINE, Embase, and Cochrane Central Register were searched comprehensively for RCTs from inception to May 31, 2018, by using the following terms and strategy: ("budesonide" or "formoterol" or "Pulmicort" or "BD 40A" or "Foradil" or "Inhaled corticosteroids" or "long-acting β_2 adrenoceptor agonists") and ("COPD' or 'chronic obstructive pulmonary disease") AND ("randomized controlled trial" or "RCT" or "clinical trial"). The search had no language restrictions, and included unpublished studies. In order to avoid duplication, we only screened and enrolled the latest or most complete clinical trial reports. In addition, we manually searched the review list in the reference lists and retrieved each publication to find any other published papers.

Eligibility criteria for inclusion in our meta-analysis was: 1) research design of randomized, double-blind, parallel group design for at least 12 weeks; 2) study population of recruited stable COPD patients; 3) intervention of: inhaled budesonide/formoterol as the intervention drug compared with budesonide or formoterol or placebo; 4) outcome measures of the efficacy parameters of changes in pre-dose forced expiratory volume in 1 second (FEV_1), morning peak expiratory flow (PEF), evening PEF, and St. George's Respiratory Questionnaire (SGRQ) total score.

Data extraction

Two independent investigators reviewed the articles and accurately extracted the data. If there was any discrepancy on the inclusion of articles, it was resolved by consensus. For each publication, the following information was extracted: the last name of first author, year of publication, research design, participant number, target population, basic characteristics, treatment arms (dose of budesonide/formoterol and duration of treatment), duration of COPD, and outcome data.

Assessment of quality

The quality of the involved studies was evaluated by 2 reviewer in accordance with the modified Jadad scale by the risk assessment of bias of the Cochrane Collaboration's tool [20], and the following 4 aspects were evaluated: 1) methods for generating

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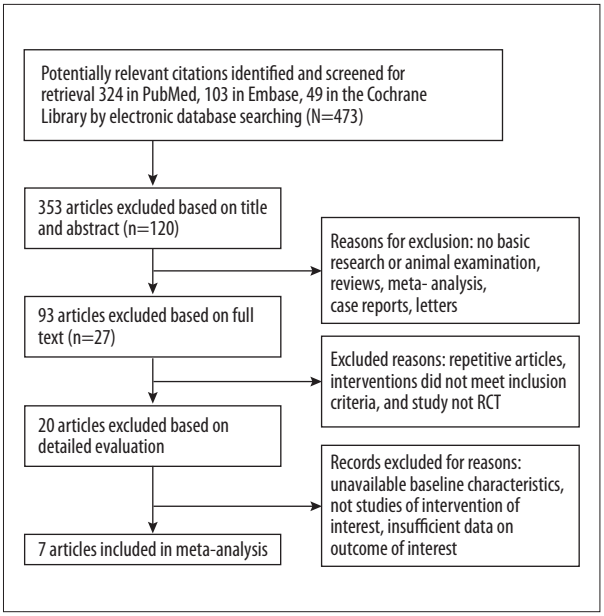

Figure 1. Flow chart showing study selection procedure.

random series; 2) randomization concealment; 3) blind method; 4) addressment of withdrawal and incomplete outcome data.

Data analysis

STATA version 14.0 (Stata Corporation, College Station, TX, USA) was used to perform all statistical analyses of the meta-analysis. For each study, mean difference (MD) with corresponding 95% CI was used to pool the continuous variable. The statistical heterogeneity involved in the studies was assessed using the chi-square Q and the I^2 tests; the results were pooled with a fixed-effect model if $P>0.1$ or I^2 <50% respectively, which indicates no obvious difference; otherwise, a random-effect model was employed. A Z test was used to evaluate the statistical significance of the pooled analysis, and $P<0.05$ was considered a statistically significant difference [21]. When there was an adequate number of RCTs included in the clinical outcome parameters evaluation, the funnel plot and Begg's test were employed to assess the publication bias [22].

Results

Search results and study descriptions

The study selection process is outlined in Figure 1. Initially, 473 published articles were found in databases and manual searches. Finally, only 7 articles [16–19,23–25] with 19 trials including 8035 participants were selected based on our inclusion/exclusion criteria. The detailed characteristics of studies included in the meta-analysis are shown in Table 1. We did not find significant statistical differences in baseline information between the experimental arms and the control arms. Each trial was multicenter, blinded, parallel, and controlled, scoring 5 on the Jadad scale.

Clinical outcomes and synthesis of result

Budesonide/formoterol versus budesonide alone

Pre-dose FEV_1

A total of 5 RCTs (budesonide/formoterol group: n=1176, budesonide group: n=1157) reported pre-dose FEV1, and

Table 1. Basic Characteristics of the studies included in the meta-analysis.

Study	Year	Design	Number	COPD severity	Mean age (years)	Duration of COPD (years)	Follow-up (weeks)	Jadad score
Fukuchi	2013	Multicenter, double-blind, parallel	1293	Moderate to severe	65.0	5.7	12	5
Ferguson	2017	Multicenter, double-blind, double-dummy, parallel	1219	Moderate to very severe	63.5	7.5	26	5
Tashkin	2008	Six studies, multicenter, double-blind, double-dummy, parallel	1417	Moderate to very severe	63.4	NA	26	5
Szafranski	2003	Three studies, multicenter, double-blind, parallel	812	Moderate to severe	64.0	NA	52	5
Zhong	2012	Multicenter, double-blind, double-dummy, parallel	308	Moderate to very severe	64.6	9.2	24	5
Rennard	2009	Four studies multicenter, double-blind, double-dummy parallel	1964	Moderate to very severe	63.2	10.8	52	5
Calverley	2003	Three studies, multicenter, double-blind, parallel	1022	Moderate to very severe	64.0	NA	52	5

COPD – chronic obstructive pulmonary disease; NA – not available.

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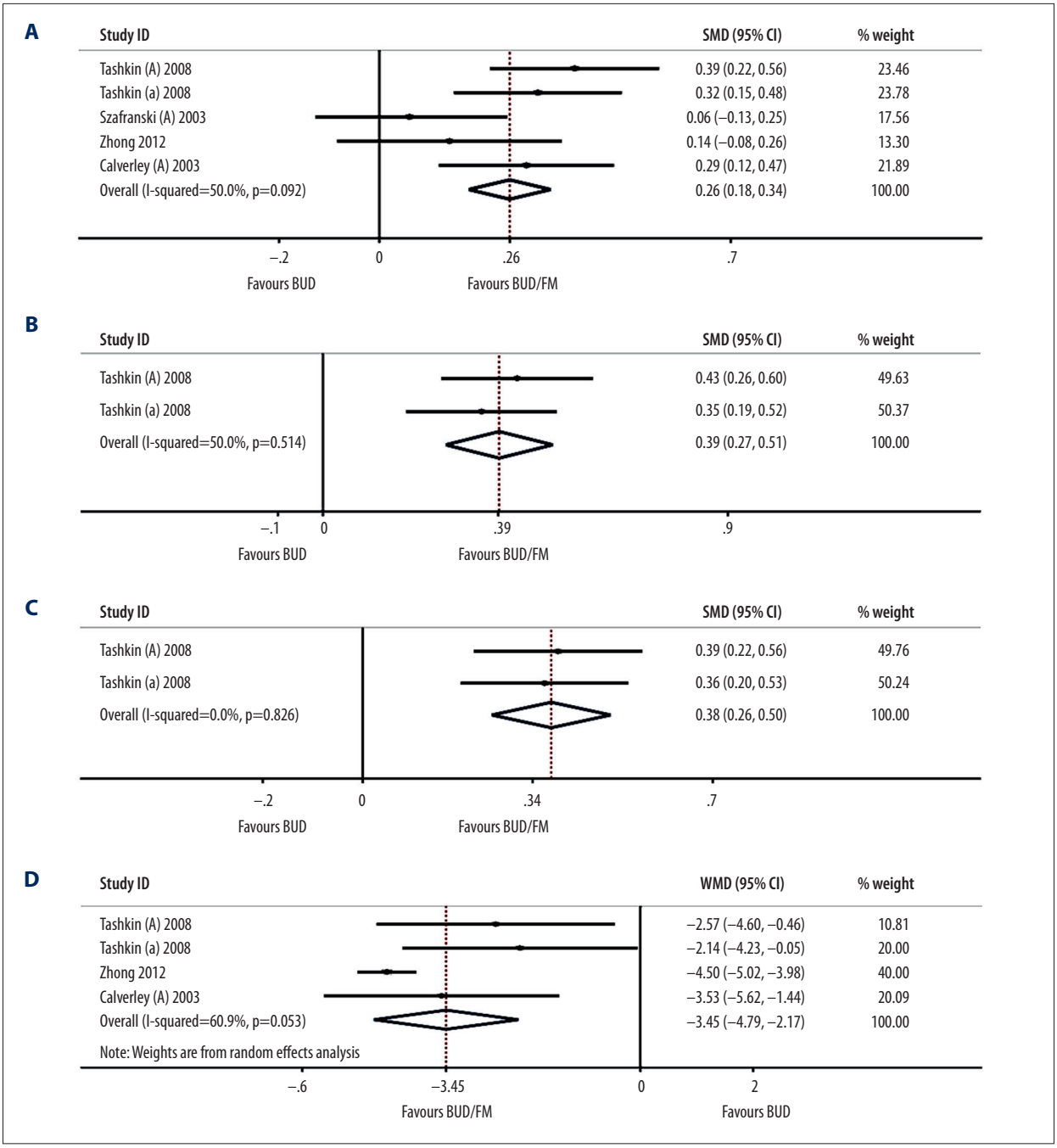

Figure 2. Forest plot for pre-dose FEV_1, morning PEF, evening PEF, and SGRQ comparison. (**A**) Pre-dose FEV_1 in BUD/FM versus BUD. (**B**) Morning PEF in BUD/FM versus BUD. (**C**) Evening PEF in BUD/FM versus BUD. (**D**) SGRQ in BUD/FM versus BUD. FEV_1 – forced expiratory volume in 1 second; BUD – budesonide; FM – formoterol; PEF – peak expiratory flow; SGRQ – St George's Respiratory Questionnaire.

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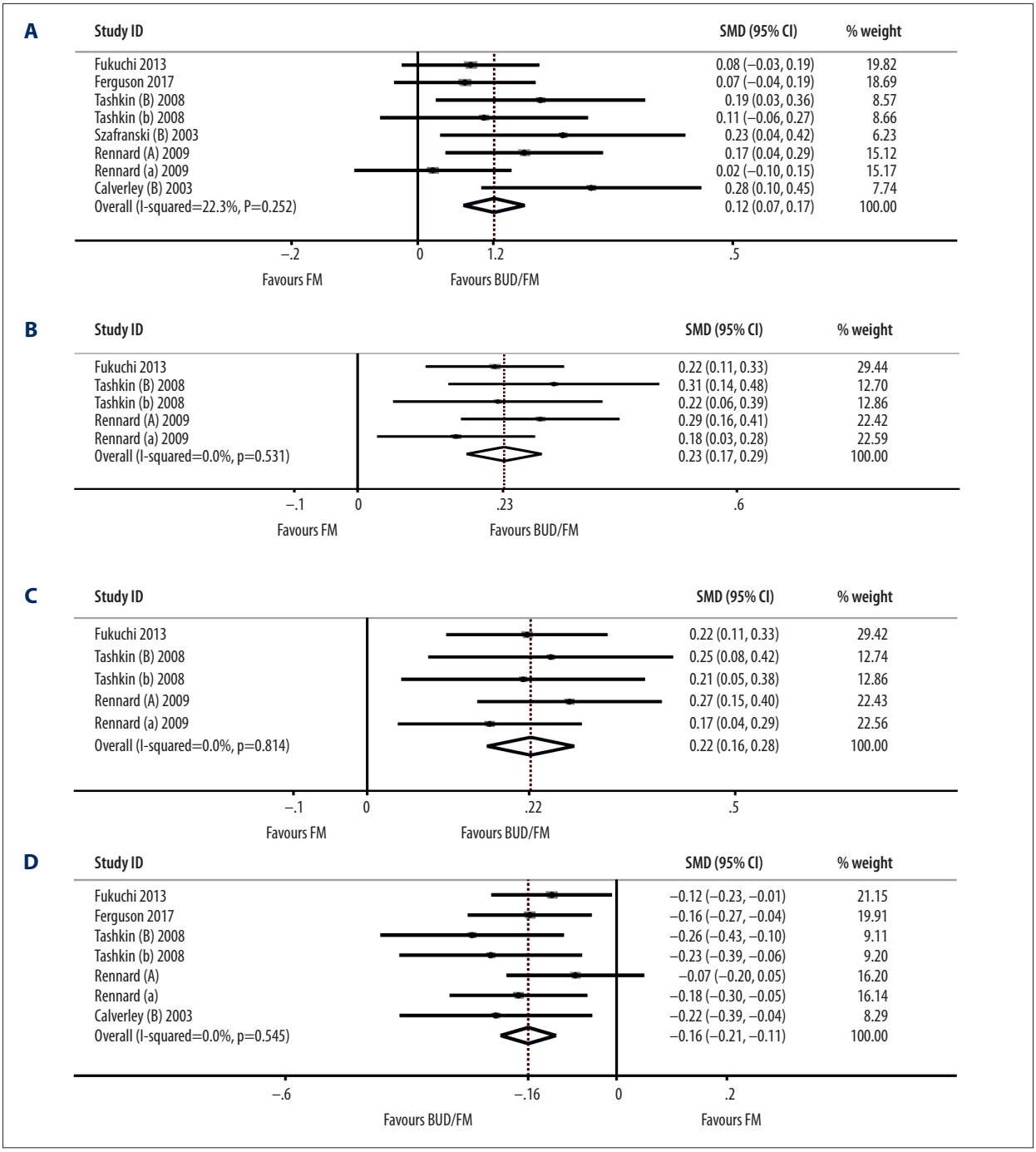

Figure 3. Forest plot for pre-dose FEV_1, morning PEF, evening PEF and SGRQ comparison. (**A**) Pre-dose FEV_1 in BUD/FM versus FM. (**B**) Morning PEF in BUD/FM versus FM. (**C**) Evening PEF in BUD/FM versus FM. (**D**) SGRQ in BUD/FM versus FM. FEV_1 – forced expiratory volume in 1 second; BUD – budesonide; FM – formoterol; PEF – peak expiratory flow; SGRQ – St George's Respiratory Questionnaire.

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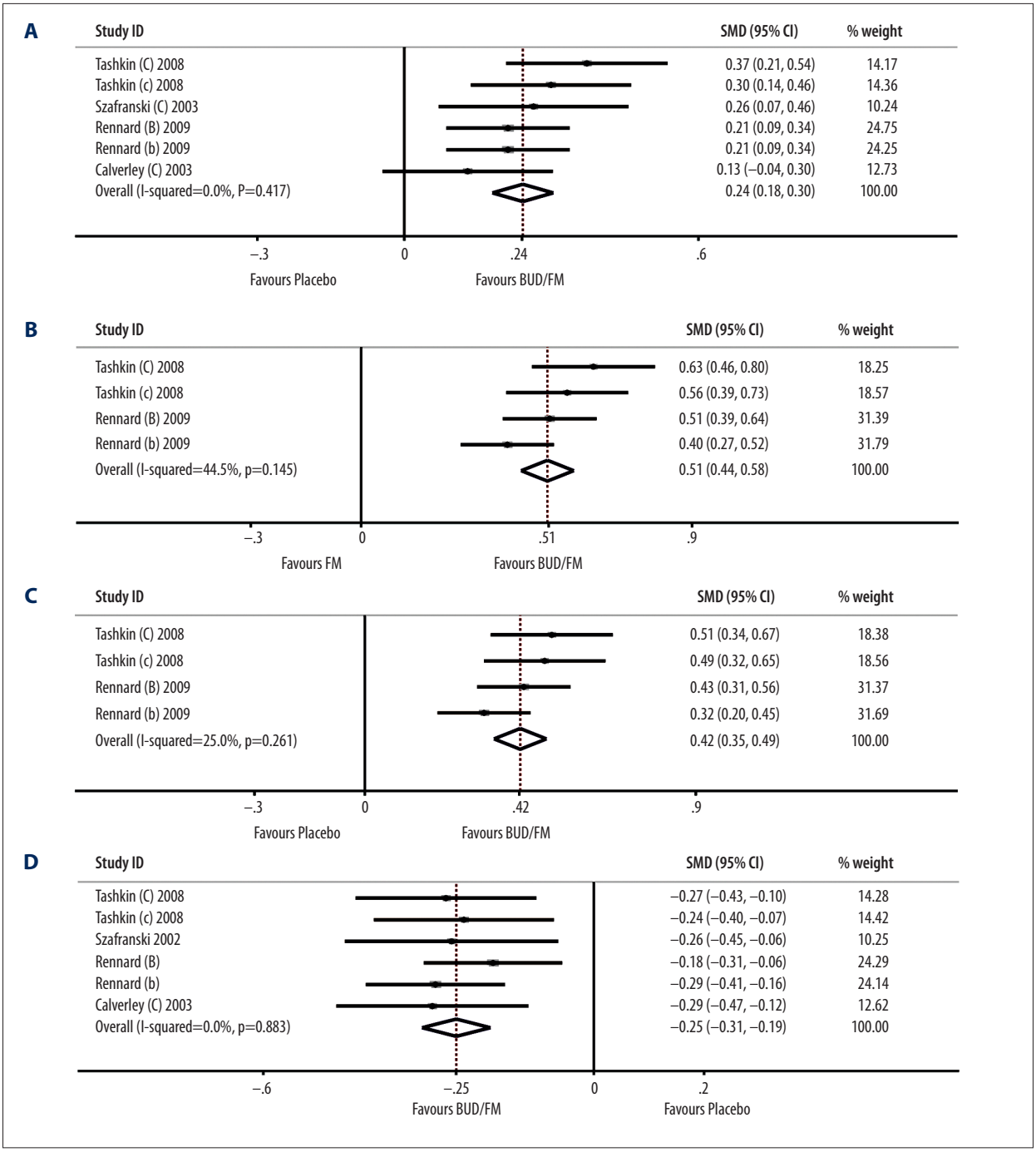

Figure 4. Forest plot for pre-dose FEV_1, morning PEF, evening PEF and SGRQ comparison. (**A**) Pre-dose FEV_1 in BUD/FM versus placebo. (**B**) Morning PEF in BUD/FM versus placebo. (**C**) Evening PEF in BUD/FM versus placebo. (**D**) SGRQ in BUD/FM versus placebo. FEV1 – forced expiratory volume in 1 second; BUD – budesonide; FM – formoterol; PEF – peak expiratory flow; SGRQ – St George's Respiratory Questionnaire.

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significant statistical difference was observed in the comparison between the 2 groups. The mean change of the pre-dose FEV1 in the budesonide/formoterol groups was significantly greater than that in the budesonide alone groups from the start of the trial to the end of the follow-up (SMD: 0.26, 95% CI: 0.18, 0.34, I^2=50.0%, *P*=0.092) (Figure 2A).

Morning PEF and evening PEF

Pooling data from Tashkin et al. [19], 2 trials (budesonide/formoterol group: n=558, budesonide group: n=550) showed that the use of budesonide/formoterol contributed to significantly improvements in morning PEF (SMD: 0.39, 95% CI: 0.27, 0.51; I^2=0.0%; *P*=0.514; Figure 2B) and evening PEF (SMD: 0.38, 95% CI: 0.26, 0.50; I^2=0.0%; *P*=0.826; Figure 2C) compared with budesonide alone.

SGRQ

Four trials (budesonide/formoterol group: n=968, budesonide group: n=959) used the SGRQ score to assess the clinical outcome; significant differences were observed between the 2 groups in changes from baseline (WMD: –3.45, 95% CI: –4.73, –2.17; I^2=60.9%; *P*=0.053; Figure 2D).

Budesonide/formoterol versus formoterol alone

Pre-dose FEV_1

Pre-dose FEV_1 was provided in 8 trials (budesonide/formoterol group: n=3250, formoterol group: n=3284), and the mean improvement was greater with budesonide/formoterol than with formoterol alone (SMD: 0.12, 95% CI: 0.07, 0.17; I^2=22.3%; *P*=0.252; Figure 3A).

Morning PEF and evening PEF

Five RCTs (budesonide/formoterol group: n=2182, formoterol group: n=2215) reported these clinical outcome parameters. The pooled analysis showed that in the improvements of morning PEF (SMD: 0.23, 95% CI: 0.17, 0.29: I^2=0.0%; *P*=0.531, Figure 3B) and evening PEF (SMD: 0.22, 95% CI: 0.16, 0.28; I^2=0.0%; *P*=0.814; Figure 3C) spirometric indices, the combination treatment groups was significantly higher than the monotherapy formoterol groups.

SGRQ

Data of SGRQ were shown in 7 RCTs (budesonide/formoterol group: n=3042, formoterol group: n=3083), and the pooled analysis showed that the decrease of SGRQ score was significantly greater in the combined treatment groups than in the control groups (SMD: –0.16, 95% CI: –0.21, –0.11; I^2=0.0%; *P*=0.545; Figure 3D).

Budesonide/formoterol versus placebo alone

Pre-dose FEV_1

Of the eligible studies, 6 RCTs (budesonide/formoterol group: n=2008, placebo group: n=2023) provided the pre-dose FEV_1 for the statistical analysis. Compared with the placebo alone groups, the combination bronchodilator treatment was associated with a significantly greater increase (SMD: 0.24, 95% CI: 0.18, 0.30; I^2=0.0%; *P*=0.417; Figure 4A).

Morning PEF and evening PEF

Four trials (budesonide/formoterol group: n=1546, placebo group: n=1562) provided the spirometric indices, and according to the pooled estimate, compared with the placebo groups, the combined drugs groups demonstrated significant improvements in morning PEF (SMD: 0.51, 95% CI: 0.44, 0.58; I^2=44.5%; *P*=0.145; Figure 4B) and evening PEF (SMD: 0.42,95% CI: 0.35, 0.49; I^2=25.0%, *P*=0.261; Figure 4C).

SGRQ

Six trials (budesonide/formoterol group: n=2008, placebo group: n=2023) required SGRQ score data, and according to the pooled analyses, the combined treatment groups caused a significant decline versus the placebo alone groups (SMD: –0.25, 95% CI: –0.31, –0.19; I^2=0.0%, *P*=0.883; Figure 4D).

Publication bias

Due to the insufficient number of studies included, we did not assess publication bias with a funnel plot and Begg's test in this meta-analysis.

Discussion

This meta-analysis was performed by pooled analyses of RCTs to evaluate the efficacy of budesonide/formoterol combination versus monotherapies or placebo in patients with stable COPD, and it proved that, compared with the monocomponent groups or placebo groups, the mean changes in spirometric indices such as FEV_1, morning PEF, and evening PEF, were significantly improved in the combination treatment groups, and the SGRQ score was significantly decreased. All these findings indicate that budesonide/formoterol has a positive effect on increasing pulmonary function and ameliorating quality of life (such as measured by SGRQ) versus budesonide, formoterol, and placebo.

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Consistent with results of our present review, a review by Calverley et al. [26] showed comparison among budesonide/formoterol, placebo, or tiotropium. It mainly described their outcomes with regard to exacerbation rates, FEV_1, morning PEF, total reliever use, and total symptom score from 3 papers. Similarly, of 2 studies available, Celli et al. [27] compared treatment with budesonide/formoterol to treatment with formoterol for FEV_1, forced vital capacity, and inspiratory capacity. In contrast, our meta-analysis included more relative effective parameters in comparing the clinical efficacy of budesonide/formoterol versus budesonide, formoterol monotherapies,or placebo for stable COPD patients. We assessed the efficacy outcomes not only using spirometric indices but also HRQL, which can better indicate the effectiveness of the budesonide/formoterol when compared with monotherapies or placebo. In addition, compared with other articles, we also evaluated clinical outcomes between budesonide/formoterol groups and budesonide groups.

The systematic evaluation of our paper has several advantages and limitations. In order to produce reliable results, we identified strict eligibility standards ahead of this meta-analysis, including only RCTs which clearly indicated stable COPD patients. This meta-analysis was based on a comprehensive and systematic search of medical databases by 2 independent reviewers, followed by extraction, analysis, and evaluation of the quality of the included studies, supervised by third-party assessor. Meanwhile, there were also some limitations such as the quality and number of the trials to influence the objectives of the conclusions.

The Global Initiative for Chronic Obstructive Lung Disease 2018 report advocates the use of ICS/LABA as a treatment regimen of group C (higher acute exacerbation risk/fewer clinical symptoms) or group D (higher acute exacerbation risk/more clinical symptoms) patients [5]. Due to the different mechanisms of budesonide and formoterol, there is a synergistic effect between them, and the 2-bronchodilator combination treatment may be more significant than the monodrug in clinical effectiveness outcomes. Combination therapy significantly increased lung function and HRQL compared to the same dose of placebo or monocomponents. Budesonide/formoterol is taken twice a daily with a pressurized metered-dose inhaler, and it is considered to be easy to use and therefore became the preferred choice for most patients [16,19,24], in addition, it is not only an economic and effective therapy for symptomatic COPD patients [28], but a better preferred remedy for patients with moderate to severe COPD.

Additional larger, more adequate and similar RCTs are needed to evaluate the clinical efficacy and safety outcomes of the combination of budesonide/formoterol more reliably and comprehensively in the future. These studies should include additional clinical efficacy and tolerability outcomes, which consist of COPD exacerbation, systemic steroid effects, cardiovascular complications, and all-cause mortality.

Conclusions

In summary, the present meta-analysis provides a useful and comprehensive assessment of the beneficial effects of budesonide/formoterol on outcomes in patients with stable COPD, and while it is not novel, it is of clinical importance or interest. Combination therapy had a greater positive effect compared with monotherapies or placebo.

Conflicts of interest

None.

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