International Journal of COPD

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ORIGINAL RESEARCH

Risks of budesonide/formoterol for the treatment of stable COPD: a meta-analysis

This article was published in the following Dove Medical Press journal:
International Journal of COPD

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International Journal of Chronic Obstructive Pulmonary Disease downloaded from https://www.dovepress.com/
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Purpose: The aim of this study was to investigate the comparative risks of budesonide/formoterol, versus placebo or monotherapies, for the treatment of patients with stable COPD.

Materials and methods: We undertook a systematic search of the literature in PubMed, Embase, and the Cochrane Central Register of Controlled Trials, for randomized controlled trials (RCTs) comparing budesonide/formoterol with control regimens for the treatment of patients with stable COPD and at least 12 weeks of follow-up, meeting the inclusion criteria. Studies were reviewed, and OR with corresponding 95% CI was used to pool the results.

Results: A total of eight studies involving 9,254 patients met the inclusion criteria of this meta-analysis. Compared with placebo, combination therapy with budesonide/formoterol was associated with a significantly higher risk of adverse effects including oral candidiasis (OR: 3.09, 95% CI: 1.95–4.91) and dysphonia (OR: 2.76, 95% CI: 1.40–5.44), but not pneumonia (OR: 0.94, 95% CI: 0.64–1.37) or bronchitis (OR: 1.36, 95% CI: 0.95–1.95). A similar pattern was also evident for the comparison of formoterol with budesonide/formoterol, with increased occurrence of oral candidiasis (OR: 2.72, 95% CI: 1.33–5.58) and dysphonia (OR: 4.13, 95% CI: 1.95–8.76); however, there were no significant differences in pneumonia (OR: 1.31, 95% CI: 0.98–1.74) or bronchitis (OR: 1.05, 95% CI: 0.83–1.31). In contrast, compared with budesonide, combined budesonide/formoterol was associated with similar risks of adverse effects, including pneumonia (OR: 1.20, 95% CI: 0.60–2.39), bronchitis (OR: 0.95, 95% CI: 0.41–2.20), oral candidiasis (OR: 0.79, 95% CI: 0.41–1.53), and dysphonia (OR: 1.00, 95% CI: 0.40–2.47).

Conclusion: Combination therapy does not cause more adverse events, including pneumonia and bronchitis, than control (placebo, formoterol, or budesonide) treatment in patients with stable COPD, while there were higher risks of oral candidiasis and dysphonia compared with the non-inhaled corticosteroid group (placebo, formoterol).

Keywords: budesonide/formoterol, risk, COPD, meta-analysis, randomized controlled trial

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Introduction

COPD is a preventable and treatable disease, which is characterized by persistent respiratory symptoms and airflow limitation, and is a leading prevalent and public health issue associated with enormous social and economic burdens.[1–5] Inhaled corticosteroids (ICSs), combined with long-acting β_2 adrenoceptor agonists (LABAs), are a widely recommended treatment for patients with COPD who have a history of exacerbations.[6] Compared with placebo and/or monotherapies, ICS/LABA therapy is effective in reducing COPD flare-ups, improving health-related quality of life, and decreasing the incidence of, and mortality associated with, adverse events.[7–10] Furthermore, ICS/LABA, which is not a combination bronchodilator therapy like an LABA/long-acting muscarinic antagonist (LAMA), is associated with increased adverse events such as oral candidiasis and pneumonia,[11–13] while compared with ICS alone,

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http://dx.doi.org/10.2147/COPD.S192166

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the risk of pneumonia is similar.[14] Nevertheless, there have been many striking studies providing evidence of increased risks associated with ICS. Mapel et al[15] designed a nested case–control analysis, using data derived from three large regional managed-care organizations in the United States; the report found that there were similar risks among COPD patients using fluticasone propionate alone or in combination with salmeterol.

There are three brands of ICS/LABA combination agents available for the current clinical application: budesonide/formoterol, fluticasone propionate/salmeterol, and mometasone furoate/formoterol. Studies to determine whether the use of ICS increases the risk of pneumonia that are cited in the guidelines for its use are primarily focused on the randomized controlled trials (RCTs) of fluticasone. It is unknown whether budesonide/formoterol increases the risk of pneumonia or the risk of other ICS-related adverse events (bronchitis, oral candidiasis, and dysphonia). The combination of budesonide and formoterol, containing fixed doses of ICS and LABA, was approved as a mainstay drug therapy for patients with COPD in Europe in 2003 and subsequently in the United States in 2009 and shows remarkable clinical efficacy for the treatment of COPD. Previous studies have primarily focused on western populations, reporting that budesonide/formoterol provided benefits, in terms of improving pulmonary function, COPD symptoms, and health-related quality of life, and reduced flare-up rate in COPD patients and that it was generally well tolerated.[16–20]

The budesonide/formoterol combination exhibits a similar pattern of undesirable effects to its individual components; however, the results regarding the budesonide-related risk of pneumonia are more controversial. Ferguson et al[21] suggested that, compared with the formoterol group (pneumonia, 1.0%), there was a lower rate of adverse events in the budesonide/formoterol group (pneumonia, 0.5%). In contrast, Sharafkhaneh et al[16] found that the incidence of pneumonia in the combination therapy group (6.4%) was higher than that in the formoterol-alone group (2.7%). Two other studies reported similar rates of pneumonia for the two treatment regimens.[17,20]

The aim of this meta-analysis was to evaluate the current evidence regarding the risks of pneumonia, and other ICS-related adverse effects, associated with the systematic use of budesonide/formoterol in patients with stable COPD.

Materials and methods

Search strategy

Two reviewers independently and comprehensively searched the Cochrane Central Register, PubMed, and Embase for RCTs from inception to August 31, 2018, using the following terms: ("budesonide" or "formoterol" or "Pulmicort" or "BD 40A" or "Foradil" or "Inhaled corticosteroids" or "long-acting β2 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. To avoid duplication, we only included latest or most complete clinical trial reports. To identify additional publications, we manually searched for reviews in the reference lists of collected papers and retrieved all relevant, or potentially relevant, publications.

Eligibility criteria and exclusion criteria

We used the following criteria to select studies for inclusion in this meta-analysis: 1) methodological criteria: randomized, double-blind, parallel-group design, for at least 12 weeks; 2) study population: recruited patients with stable COPD, consistent with the GOLD 2018 criteria; 3) interventions: inhaled budesonide/formoterol as the intervention drug, compared with placebo or budesonide or formoterol; 4) outcome measures: the ICS-related adverse effects analyzed in this meta-analysis were as follows: pneumonia, bronchitis, oral candidiasis, and dysphonia. The following studies were excluded: repetitive articles, interventions that did not meet inclusion criteria, studies that were not RCTs, studies with unavailable baseline characteristics, not studies of intervention of interest, and studies with insufficient data on the outcome of interest.

Data extraction

Two independent investigators reviewed the articles and extracted the data. If there were any disagreements regarding the relevance of articles, they were resolved by consensus. For each publication, the following information was extracted: the last name of the 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 adverse effects data. In some cases, we extracted information from graphs and charts.

Quality assessment

The quality of included studies was independently evaluated by two reviewers, in accordance with the modified 7-point Jadad scale, using the risk assessment of bias tool from the Cochrane Collaboration's tool,[22] regarding the following four aspects: 1) methods for generating random series (0–2 points); 2) randomization concealment (0–2 points);

3) blind method (0–2 points); 4) assessment of withdrawal (0–1 points).

Data synthesis

Stata SE version 14.0 (StataCorp LP, College Station, TX, USA) was used to perform all statistical analyses. For each study, the OR and corresponding 95% CI values were used to pool dichotomous variable. The statistical heterogeneity of data included in this meta-analysis was assessed using chi-square Q and I^2 statistics. Results were pooled using a fixed-effect model if $p>0.1$ or $I^2<50\%$, respectively, indicating no substantial heterogeneity; otherwise, a random-effect model was employed. We estimated each of the safety parameters for each control group (placebo, formoterol, and budesonide). When there was an adequate number of RCTs included for evaluation of a clinical outcome parameter, funnel plots and Begg's test were employed to assess publication bias.[23]

Results

Search results and study descriptions

A flowchart outlining the study's screening process is presented in Figure 1. Initially, 491 published articles were found in databases and by manual searches. Finally, only eight articles, with 21 treatment arms, including 9,254 participants, were selected based on the inclusion/exclusion criteria.[16–21,24,25] The detailed characteristics of studies included in this meta-analysis are summarized in Table 1. No significant differences in baseline information were detected between experimental and control arms. Each trial was multicenter, blinded, parallel, and controlled and scored ≥5 on the Jadad scale.

Clinical outcomes and results synthesis

Budesonide/formoterol versus placebo alone

Pneumonia

Five treatment arms (budesonide/formoterol group: n=1,800, placebo group: n=1,818) of the eligible studies provided

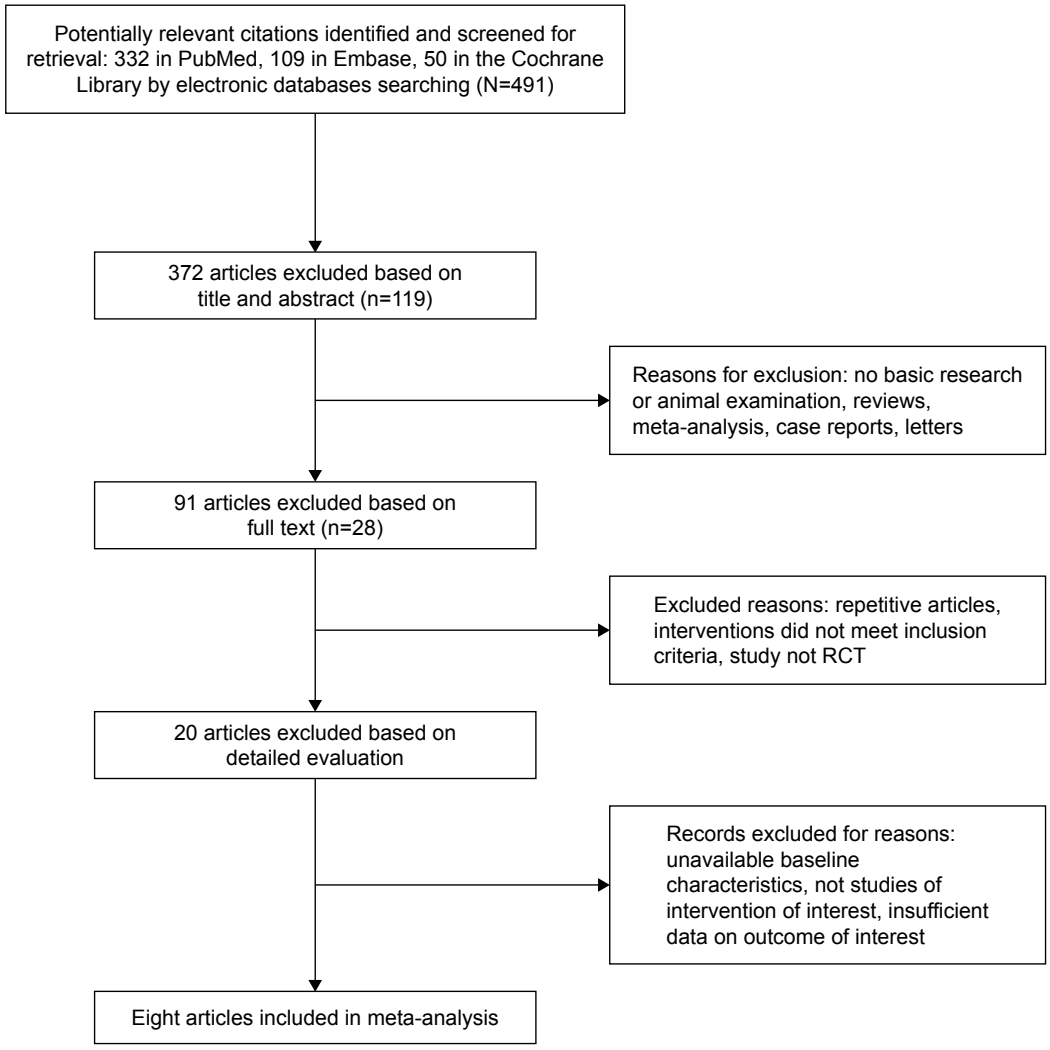


Figure 1 Flowchart of the study selection procedure.
Abbreviation: RCT, randomized controlled trial.

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
Ferguson et al[21]	2017	Multicenter, double-blind, double-dummy, parallel	1219	Moderate to very severe	63.5	7.5	26	5
Fukuchi et al[25]	2013	Multicenter, double-blind, parallel	1293	Moderate to severe	65.0	5.7	12	5
Sharafkhaneh et al[16]	2012	Two treatment arms, multicenter, double-blind, double-dummy, parallel	1219	Severe to very severe	63.0	10.2	52	6
Zhong et al[24]	2012	Multicenter, double-blind, double-dummy parallel	308	Moderate to very severe	64.6	9.2	24	5
Rennard et al[17]	2009	Four treatment arms, multicenter, double-blind, double-dummy parallel	1964	Moderate to very severe	63.2	10.8	52	5
Tashkin et al[20]	2008	Six treatment arms, multicenter, double-blind, double-dummy, parallel	1417	Moderate to very severe	63.4	NA	26	5
Calverley et al[18]	2003	Three treatment arms, multicenter, double-blind, parallel	1022	Moderate to very severe	64.0	NA	52	5
Szafranski et al[19]	2003	Three treatment arms, multicenter, double-blind, parallel	812	Moderate to severe	64.0	NA	52	5

Abbreviation: NA, not available.

pneumonia data for statistical analysis. Compared with the placebo-alone group, combination bronchodilator treatment showed no significant difference in terms of this adverse event (OR: 0.94, 95% CI: 0.64–1.37; I^2=33.2%; p=0.200; Figure 2A).

Bronchitis

Four treatment arms (budesonide/formoterol group: n=1,546, placebo group: n=1,562) provided bronchitis adverse event data. According to pooled estimates, compared with the placebo group, the combined drug group demonstrated a higher risk of bronchitis; however, the difference was not statistically significant (OR: 1.36, 95% CI: 0.95–1.95; I^2=0.0%; p=0.524; Figure 2B).

Oral candidiasis

Five treatment arms (budesonide/formoterol group: n=1,800, placebo group: n=1,818) contained oral candidiasis data. According to pooled analysis, combined treatment resulted in significantly higher odds versus placebo alone (OR: 3.09, 95% CI: 1.95–4.71; I^2=0.0%; p=0.428; Figure 2C).

Dysphonia

The five treatment arms (budesonide/formoterol group: n=1,800, placebo group: n=1,818) that reported dysphonia identified a significant higher risk with combined treatment than placebo alone (OR: 2.76, 95% CI: 1.40–5.44; I^2=0.0%; p=0.487; Figure 2D).

Budesonide/formoterol versus formoterol alone

Pneumonia

Pneumonia data were provided from nine treatment arms (budesonide/formoterol group: n=3,857, formoterol group: n=3,891). The rate of pneumonia was higher with budesonide/formoterol than with formoterol; however, the difference was well below that required for minimum clinical importance (OR: 1.31, 95% CI: 0.98–1.74; I^2=0.0%; p=0.525; Figure 3A).

Bronchitis

Eight treatment arms (budesonide/formoterol group: n=3,603, formoterol group: n=3,636) reported this clinical safety parameter. Pooled analysis showed that the incidence of bronchitis as an adverse effect was similar for the combination treatment and formoterol groups (OR: 1.05, 95% CI: 0.83–1.31; I^2=0.0%; p=0.524; Figure 3B).

Oral candidiasis

Data on this adverse event were included from eight treatment arms (budesonide/formoterol group: n=3,221, formoterol

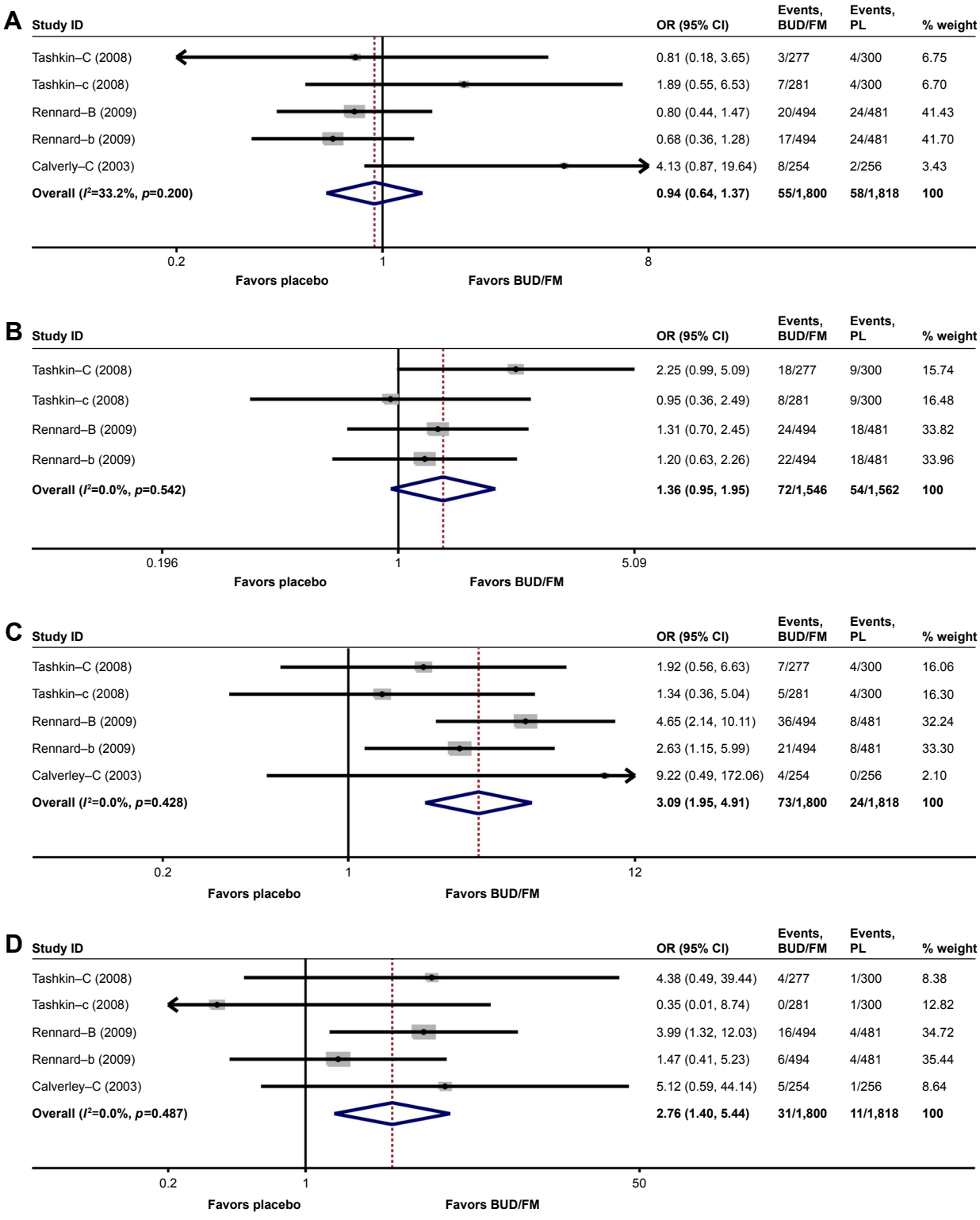
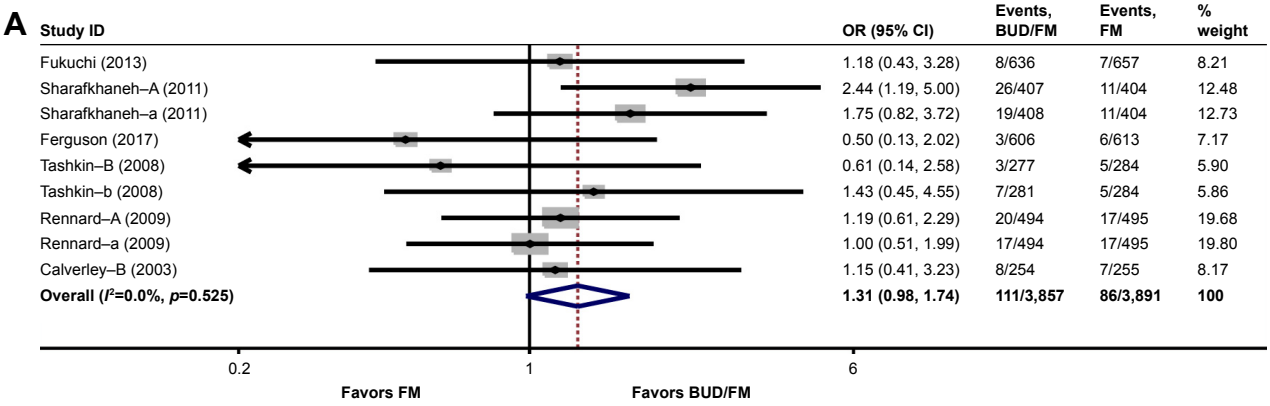


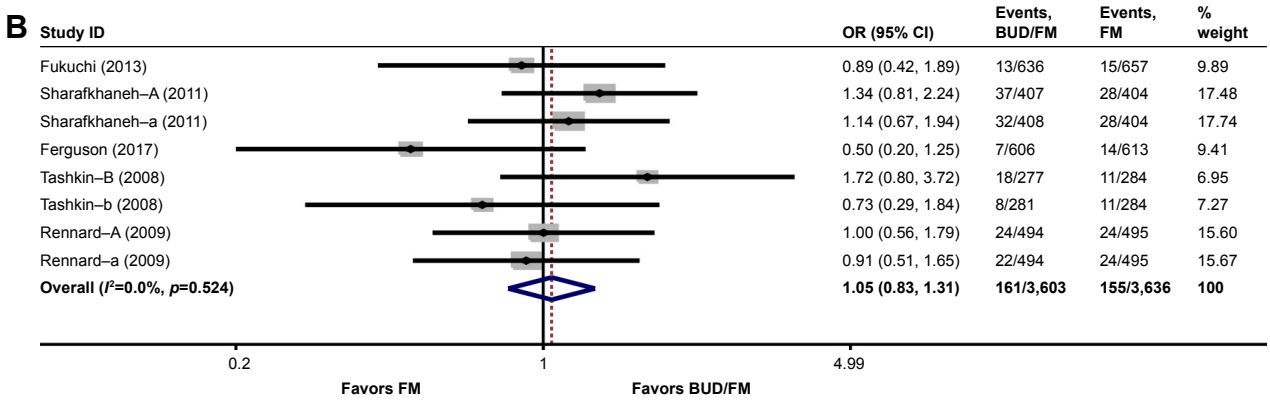
Figure 2 Forest plot of pneumonia, bronchitis, oral candidiasis, and dysphonia comparison. (**A**) Pneumonia in BUD/FM versus placebo. (**B**) Bronchitis in BUD/FM versus placebo. (**C**) Oral candidiasis in BUD/FM versus placebo. (**D**) Dysphonia in BUD/FM versus placebo.
Abbreviations: BUD, budesonide; FM, formoterol; PL, placebo.

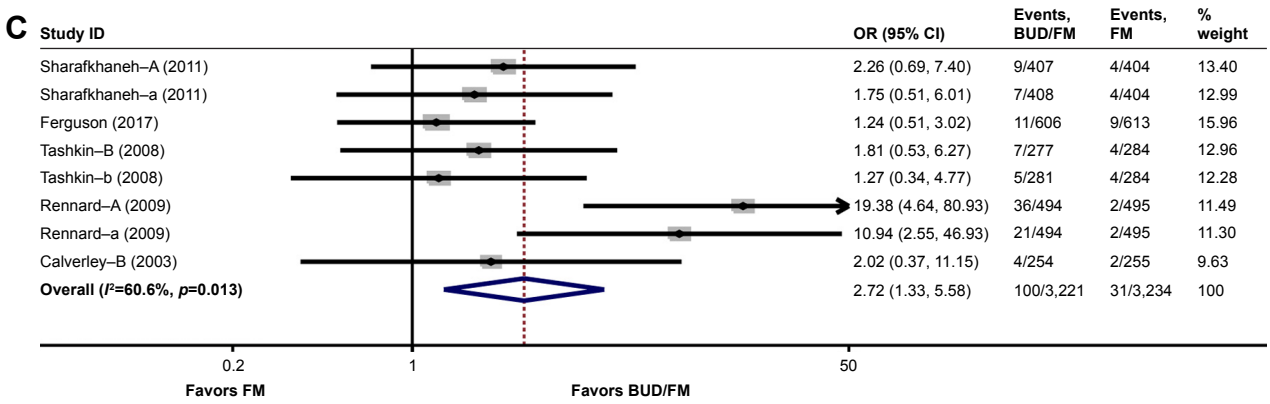
group: n=3,234). Pooled analysis showed that the rate of oral candidiasis was significantly higher in the combination treatment group than the formoterol-alone group (OR: 2.72, 95% CI: 1.35–5.58; I^2=60.6%; p=0.013; Figure 3C).

Dysphonia

Data regarding dysphonia were included from six treatment arms (budesonide/formoterol group: n=2,406, formoterol group: n=2,426), and pooled analysis showed that the risk







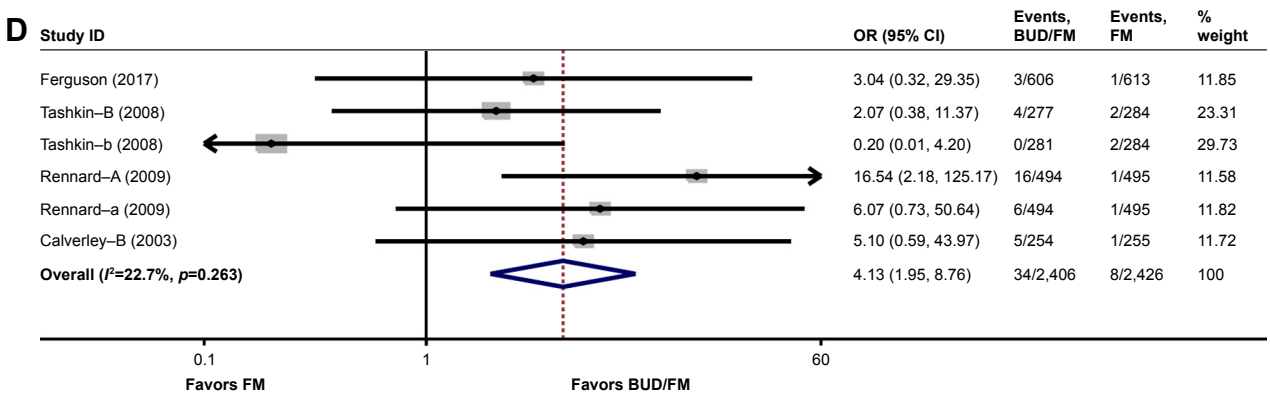


Figure 3 Forest plot of pneumonia, bronchitis, oral candidiasis, and dysphonia comparison. (**A**) Pneumonia in BUD/FM versus FM. (**B**) Bronchitis in BUD/FM versus FM. (**C**) Oral candidiasis versus FM. (**D**) Dysphonia in BUD/FM versus FM.
Note: Weights are from random-effects analysis.
Abbreviations: BUD, budesonide; FM, formoterol.

was significantly higher in the combined treatment group than in the control group (OR: 4.13, 95% CI: 1.95–8.76; I^2=22.7%; p=0.263; Figure 3D).

Budesonide/formoterol versus budesonide alone

Pneumonia

A total of four treatment arms (budesonide/formoterol group: n=968, budesonide group: n=959) reported pneumonia. The risk of pneumonia in the budesonide/formoterol group was not significantly higher than that in the budesonide-alone group (OR: 1.20, 95% CI: 0.60–2.39, I^2=0.0%, p=0.529; Figure 4A).

Bronchitis

Two treatment arms (budesonide/formoterol group: n=558, budesonide group: n=550) in the report of Tashkin et al[20] reported the risk of bronchitis; no difference was observed between the budesonide/formoterol combination and

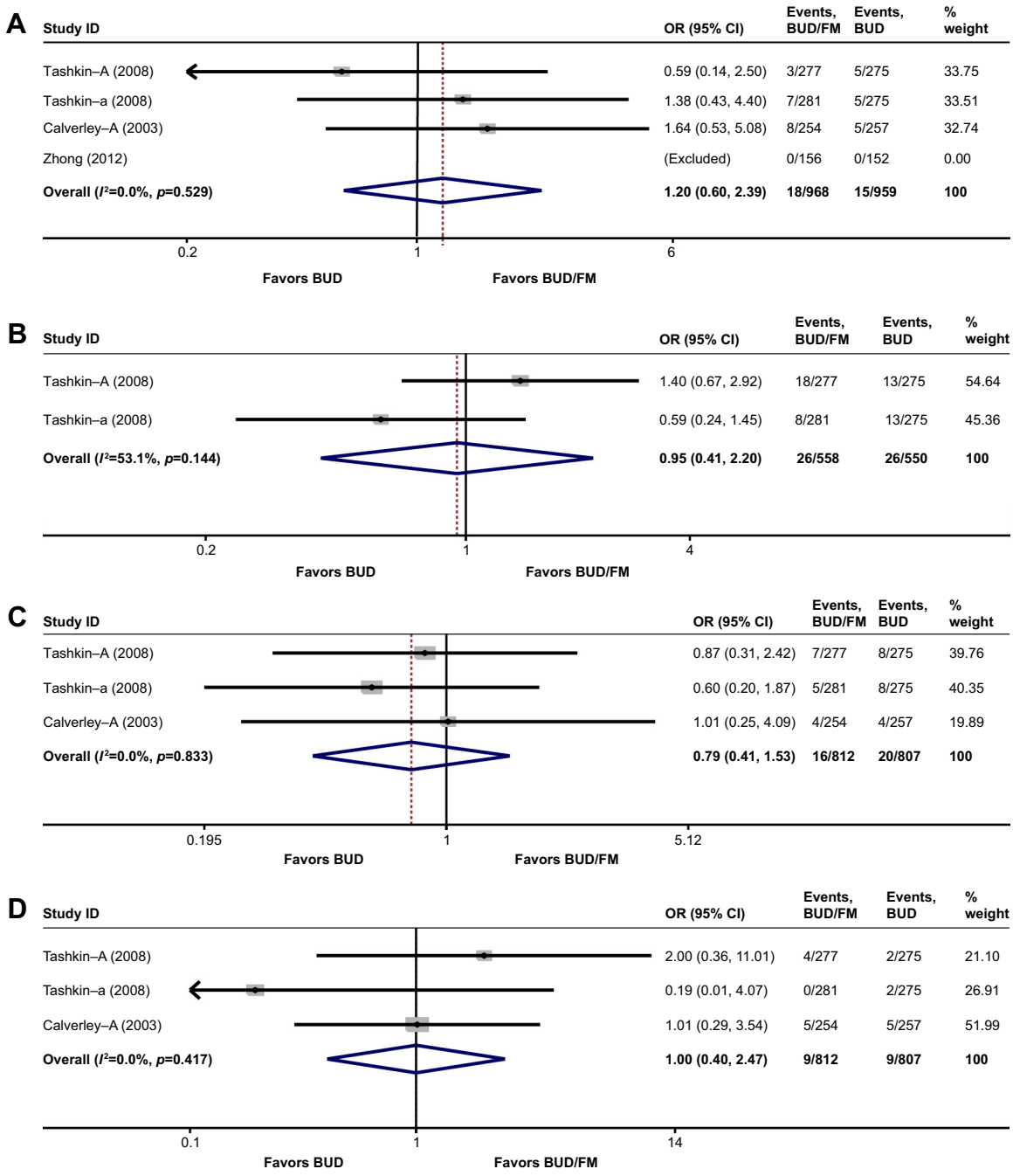


Figure 4 Forest plot of pneumonia, bronchitis, oral candidiasis, and dysphonia comparison. (**A**) Pneumonia in BUD/FM versus BUD. (**B**) Bronchitis in BUD/FM versus BUD. (**C**) Oral candidiasis in BUD/FM versus BUD. (**D**) Dysphonia in BUD/FM versus BUD.
Note: Weights are from random-effects analysis.
Abbreviations: BUD, budesonide; FM, formoterol.

budesonide-alone arms (OR: 0.95, 95% CI: 0.41–2.20, I^2=53.1%, p=0.144; Figure 4B).

Oral candidiasis

Pooling data from three treatment arms (budesonide/formoterol group: n=812, budesonide group: n=807) showed that the risk of oral candidiasis with budesonide/formoterol was similar to that with budesonide alone (OR: 0.79, 95% CI: 0.41–1.53, I^2=0.0%, p=0.833; Figure 4C).

Dysphonia

Three treatment arms (budesonide/formoterol group: n=812, budesonide group: n=807) used dysphonia to assess risk outcomes. Similar adverse rates were observed between combination therapy and budesonide regimens (OR: 1.00, 95% CI: 0.40–2.47, I^2=0.0%, p=0.417; Figure 4D).

Publication bias

Since there were too few trials available to make a meaningful assessment, no evaluation of the data for publication bias was conducted.

Discussion

Meta-analysis was performed by pooled analysis of data from RCTs to compare the risk of budesonide/formoterol with placebo or monotherapies in patients with stable COPD. The present study, comprising 9,254 patients, demonstrates that, as expected, there are significantly higher risks of local side effects (such as oral candidiasis and dysphonia) with combination treatment than with comparators (placebo or formoterol); nevertheless, no significant differences in adverse events (pneumonia and bronchitis) were noted between budesonide/formoterol and non-ICS (placebo or formoterol) arms. In contrast, compared with budesonide, budesonide/formoterol combination treatment did not contribute to significant risks of pneumonia, bronchitis, oral candidiasis, or dysphonia.

According to previous studies, the safety profile of budesonide/formoterol is similar to that of monotherapies, and no improvement in adverse events is observed by the administration of the combined drug. The results of our study are consistent with those of Nannini et al,[26] comparing the ICS/LABA combination with ICS alone, which found that the risk of pneumonia was similar between these two groups. The only described ICS-related adverse event was pneumonia. In contrast, our meta-analysis included more ICS-related parameters (pneumonia, bronchitis, oral candidiasis, and dysphonia) that can better indicate the safety of budesonide/formoterol relative to controls (placebo, formoterol, or budesonide) for the treatment of patients with stable COPD.

Traditionally, because ICS has good anti-inflammatory effect, it has been used as a mainstay drug for the treatment of patients with COPD. Nevertheless, it has various side effects, including the inhibition of host resistance; increasing the incidence of pneumonia, tuberculosis, and oropharyngeal candidiasis; and causing muscle lesions, leading to dysphonia. Our results differ from those of Nannini et al,[27,28] which showed an increased risk of pneumonia in patients with COPD receiving any dose of any type of ICS/LABA, compared with the control arm (LABA or placebo). Crim et al[12] found that, compared with vilanterol, combined fluticasone furoate and vilanterol significantly increased pneumonia risk. Halpin et al[29] observed that budesonide/formoterol was associated with a lower risk of pneumonia than fluticasone/salmeterol when used to treat patients with COPD. Although the exact reasons for the inconsistency of these findings are unclear, they may be related to the following factors. First, compared with fluticasone propionate, budesonide has a higher dissolution rate in lungs[30] and increased airway epithelial absorption[31] and leads to increased local immune effects[32] and reduced immunosuppressive efficacy.[33] Second, the COPD patients (ABCD classification) included in the study influence the study results; group D (higher acute exacerbation risk/more clinical symptoms) patients taking ICS (with or without LABA) have a greater risk of developing pneumonia.[12,13]

Budesonide/formoterol is taken twice daily, via a pressurized metered-dose inhaler, and is considered easy to use; therefore, it has become the primary choice for most patients.[17,20,24] This treatment is not only economic and effective for patients with symptomatic COPD,[34] but a preferable option, based on weighing the benefits and risks of ICS/LABA for the treatment of COPD.

Additional larger, more suitable similar RCTs are needed to evaluate the clinical safety outcomes of budesonide/formoterol more reliably and comprehensively in the future. These studies should be specifically designed to detect ICS-related adverse effects of combined budesonide/formoterol combination.

Limitations

The systematic evaluation approach used for our study has several limitations. To produce reliable results, we identified strict eligibility standards ahead of this meta-analysis,

incorporating only RCTs that clearly indicated the inclusion of patients with stable COPD. This meta-analysis was based on a comprehensive and systematic search of medical databases by two independent reviewers, followed by extraction, analysis, and evaluation of the quality of included studies, supervised by third-party assessor. The number of trials available was relatively small, and the total number of participants was also insufficient; hence, the results should be interpreted with a degree of caution. Consequently, we could not perform a subgroup analysis of variables such as drug dose, treatment time, duration of COPD, and sex. The subjects involved in the meta-analysis were mainly Asians and patients from western countries; none of the trials originally recruited Africans. Therefore, the results of this meta-analysis may be of limited suitability for application to the treatment of patients with COPD in the clinic. Finally, none of the included RCTs provided definite clinical, radiological, or microbiological criteria for all adverse events, and none were designed to assess ICS-related adverse effects.

Conclusion

This present meta-analysis provides a useful and comprehensive assessment of the ICS-related risks of budesonide/formoterol in patients with stable COPD. Although the study is not novel, it is of clinical importance, and the results could be used for reference in clinic. Compared with the no-ICS (placebo or formoterol) group, budesonide/formoterol significantly increased ICS-related risks of oral candidiasis and dysphonia, but not pneumonia and bronchitis. There were no significant differences in potential side effects (pneumonia, bronchitis, oral candidiasis, and dysphonia) between patients treated with budesonide/formoterol and budesonide alone. Future robust studies, including larger, long-term RCTs, are warranted to assess the risk of budesonide/formoterol in patients with stable COPD.

Acknowledgment

This work was supported by the Jiangxi Province Science and Technology Support Plan (grant number: 20141BBG70045).

Disclosure

The authors report no conflicts of interest in this work.

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