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The efficacy and safety of different long-acting β 2-agonists combined with inhaled glucocorticoid regimens in patients with asthma: a network meta-analysis

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ABSTRACT

Objective: To determine the efficacy and safety of current maintenance therapies consisting of different regimens of long-acting β 2-agonists (LABA) with inhaled corticosteroids (ICS) in patients with asthma. **Methods:** A network meta-analysis (NMA) was conducted after a comprehensive search for relevant studies in the PubMed, Cochrane Library, and Embase databases up to January 1, 2017. Randomized clinical trials comparing LABA combined with ICS in patients with asthma were selected. **Results:** Seventeen trials were included in the analysis, comprising 10,961 patients and seven treatment regimens. Our NMA revealed that there were no statistically significant differences between agents regarding the frequency of moderate or severe exacerbations. For adverse effects, there were no significant differences between the included studies. Moreover, six of the results showed no statistically significant differences between agents regarding symptom-free days. The heterogeneity and inconsistency analysis of the outcomes showed that there were no differences between the regimens. **Conclusions:** Our findings have shown that there were no statistically significant differences between the different regimens of LABA + ICS regarding the frequency of moderate or severe exacerbations, adverse events, and symptom-free days.

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KEYWORDS

Asthma; long-acting β 2-agonists; inhaled corticosteroids; network meta-analysis

Introduction

Bronchial asthma is a chronic reactive airway disease characterized by recurrent episodes of wheezing, cough, and breathlessness, with reversible bronchoconstriction and remodeling of the airway [1]. World Health Organization estimates suggest that 300 million people are affected worldwide, with direct treatment costs and indirect costs related to lost productivity among the highest for non-communicable diseases [2].

According to the Global Initiative for Asthma (GINA), the combination of long-acting β 2-agonist (LABA) and an inhaled corticosteroid (ICS) is the main treatment modality for stage 3 or 4 asthma patients, and several meta-analyses have assessed the efficacy and safety of LABA in combination with ICS [3,4]. However, there are various LABAs (salmeterol, formoterol, vilanterol) and ICSs (beclomethasone propionate, mometasone furoate, ciclesonide, budesonide, fluticasone furoate, fluticasone propionate), as well as

different treatment regimens containing their combinations for physicians to choose, while evidence on the benefits of different treatment regimens for asthma has not been confirmed. The relative safety of different regimens is also unknown. Therefore, a large-scale analysis is needed to answer whether there are differences between the efficacy and safety of different LABA + ICS regimens.

A network meta-analysis (NMA) is an ideal method to compare different treatment regimens due to its good agreement with real-world scenarios [5,6]. NMA methods enable us to simultaneously compare more than two interventions in the same analysis of the same disease, to provide relative effect estimates for all intervention comparisons (even those for which there is no direct evidence available), to estimate the probability that an intervention is the best, and to reduce uncertainty in the intervention effect estimates [7–9].

Based on the above, the objective of this study was to perform an NMA to compare the efficacy and safety of LABA + ICS treatment regimens that will

provide assistance to the clinical decision-making process.

Methods

Protocol and registration

This protocol has been registered on PROSPERO (<http://www.Crd.York.Ac.uk/PROSPERO/>) with the registration number CRD42017060864 [10].

Search strategy

We systematically searched the PubMed, Embase, and Cochrane Library databases from their inception through January 1, 2017. To supplement the sources, we scanned through the reference lists of the included studies and relevant reviews. We tracked and searched those references to find additional studies. The specific search strategy used on PubMed is presented in [Frame 1](#).

Frame 1. PubMed search strategy

#1 long-acting[Title/Abstracts] AND beta2[Title/Abstracts] AND agonist[Title/Abstracts] OR LABA OR salmeterol[Title/Abstracts] OR formoterol[Title/Abstracts] OR vilanterol[Title/Abstracts]

#2 ("inhalation"[MeSH Terms] OR "inhalation"[Title/Abstracts] OR "inhaled"[Title/Abstracts]) AND ("adrenal cortex hormones"[Pharmacological Action] OR "adrenal cortex hormones"[MeSH Terms] OR "adrenal"[Title/Abstracts] AND "cortex"[Title/Abstracts] AND "hormones"[Title/Abstracts]) OR "adrenal cortex hormones"[Title/Abstracts] OR "corticosteroids"[Title/Abstracts] OR ICS[Title/Abstracts] OR beclomethasone propionate[Title/Abstracts] OR mometasone furoate[Title/Abstracts] OR ciclesonide[Title/Abstracts] OR Budesonide[Title/Abstracts] OR fluticasone furoate[Title/Abstracts] OR fluticasone propionate[Title/Abstracts]

Inclusion and exclusion criteria

We used the following inclusion criteria:

1. Type of study
All relevant randomized controlled trials were included. Studies published in languages other than English, duplicated studies, or conference abstracts were excluded.
2. Participants
The participants must have an established diagnosis of bronchial asthma of any age, who were taking LABA/ICS combination therapy. We excluded trials that contain participants with other chronic respiratory comorbidities (e.g. chronic obstructive pulmonary disease or bronchiectasis).

3. Type of intervention
Any regimens of a combination of LABA and ICS was included, such as budesonide/formoterol (BUD/F), fluticasone propionate/salmeterol (FP/S), beclomethasone dipropionate/formoterol (BDP/F), mometasone furoate/formoterol (MF/F), fluticasone propionate/formoterol (FP/F), fluticasone furoate/vilanterol (FF/VI), or ciclesonide/formoterol (CIC/F), regardless of publication status, duration of administration, or duration of follow-up. We did not include studies concerning short-acting β_2 -agonists combined with inhaled corticosteroids (ICS), or montelukast + LABA + ICS.
4. Outcomes of interest
 1. The frequency of moderate exacerbations, including decreasing in pulmonary functions, increased use of rescue medication, nighttime waking because of asthma symptoms (2 consecutive days) or unscheduled visits to or by a doctor, or severe exacerbations, including composite outcome of hospitalization/emergency room (ER) visit/oral steroid course.
 2. Adverse events, including rates of clinical and biochemical adverse events, mortality and life-threatening, requiring inpatient hospitalization or extension of existing hospitalization).
 3. Symptom-free days.

Data extraction and quality assessment

Two authors independently extracted data from each study using a standardized data extraction checklist, which includes study characteristics (e.g. first author's name, publication year, country where the study was conducted), characteristics of study subjects (e.g. mean age, baseline FEV₁, number of participants, study duration in weeks), treatment details (e.g. type, dosage, usage), and outcome variables (e.g. the frequency of moderate or severe exacerbations, adverse events, and the symptom-free days). Two authors independently evaluated the methodological quality of the included studies for potential major sources of bias using the Cochrane Collaboration's tool for assessing risk of bias [11], which includes a method of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting of incomplete outcome data, and other sources of bias. When evaluating the methodological quality of each study, we assigned, respectively, a low, high, and unclear risk of

bias to each criterion. Any disagreement was resolved, if needed, through discussion with another reviewer.

Statistical analyses

For the NMA of each outcome, we drew a network diagram using the “network plot” command of the Stata (V.13.0) program to ensure that the included studies forms a connected network. The lines between intervention nodes indicate the direct comparisons made within randomized trials. The width of the lines is proportional to the number of trials comparing each pair of interventions, and the size of each node is proportional to the number of randomly assigned participants. The missing links between active interventions reflect the scarcity of direct comparisons. Bayesian NMA was performed using the Markov Chain Monte Carlo (MCMC) method in the R (V.3.3.3) software package. The Bayesian approach has multiple advantages such as producing results for all comparisons of interest within a connected network, calculating the probability that a drug is the best treatment, and adjusting for correlations within multi-arm trials [12]. The MCMC chain achieves a stable and good overlap in the calculation process to determine whether the convergence degree of the model is satisfactory, where a satisfactory convergence depends on the number of pre-iterations and iterations [13]. When these numbers of pre-iterations and iterations are set to 5,000 and 20,000, respectively, the MCMC chains have reached the stable fusion from the initial part, the degree of convergence satisfaction. We assessed dichotomous outcomes and estimated the treatment effect for each pairwise comparison using the odds ratio (OR) and a 95% confidence interval (CI). Because of the feature of Bayesian statistical analysis, each outcome was a closed loop in the study, and the node-splitting analysis model was used to evaluate the degree of inconsistency. The inconsistency was caused by the clinical and methodological features of the studies included. Significant inconsistency was indicated if node-splitting analysis derived $p < .05$. Statistical heterogeneity was investigated with the I^2 statistics and predefined heterogeneity ($I^2 = 0$ indicates the inconsistency of the results makes no statistical difference, $I^2 < 50\%$ for low and $I^2 \geq 50\%$ for high). Statistical inconsistency and heterogeneity detection across studies was presented with a forest plot. The letters of A, B, C, etc. were used to replace the corresponding regimens for diagrams. The letter A is the regimens of the BDP/F, and B is the regimens of the FP/S. C represents BUD/F. D and E represent

FP/F and MF/F, respectively. FF/VI and CIC/F are denoted by F and G, respectively. We used the PRISMA extension [14] to report the results of the NMA.

Results

Study selection

Figure 1 presents a flow chart illustrating the selection process of the studies. The electronic searches identified 2,849 studies, of which 902 duplicates were excluded using the “Find duplicates” function of the Endnote software, and 1,842 articles were clearly not relevant after the first screening; 105 studies were retrieved in full text for in-depth consideration, of which 88 were excluded. The excluded studies were conference abstracts ($n = 52$) and non-RCTs ($n = 4$). There were other studies that did not meet the inclusion criteria ($n = 32$). Finally, 17 studies [15–31] were included in our analysis. The references cited in these studies were examined to find other related studies. However, we did not find any one from those references.

Characteristics of the included studies

The characteristics of the studies included in the NMA are presented in Table 1. The studies were published between 2005 and 2016, and nearly all were conducted in Europe. Of the included studies, four [17,18,20,22] were performed in Poland, two [15,23] in Italy, two [24,26] in Germany, two [25,31] in Brazil, one [16] in Argentina, one [19] in China, one [21] in the USA, one [27] in France, one [28] in Denmark, one [29] in Canada, and one [30] in England. The age of the patients was limited to ≥ 12 years old in more than 94% of the studies. The outcomes of the individual studies were concerned with the frequency of moderate or severe exacerbations, adverse events, and the symptom-free days, which were replaced by the abbreviations “a, b, c,” respectively. The combined sample size across the 17 included studies was 10,961 participants, with a total of seven treatment regimens: BUD/F, FP/S, BDP/F, MF/F, FP/F, FF/VI, and CIC/F.

Risk of bias in included studies

We initially assessed the included studies for quality using the Cochrane Collaboration tool. Figure 2 shows the methodological quality assessment of the included studies. Only 11 [15,18–22,25,28–31] studies have shown specific randomized methods, which was

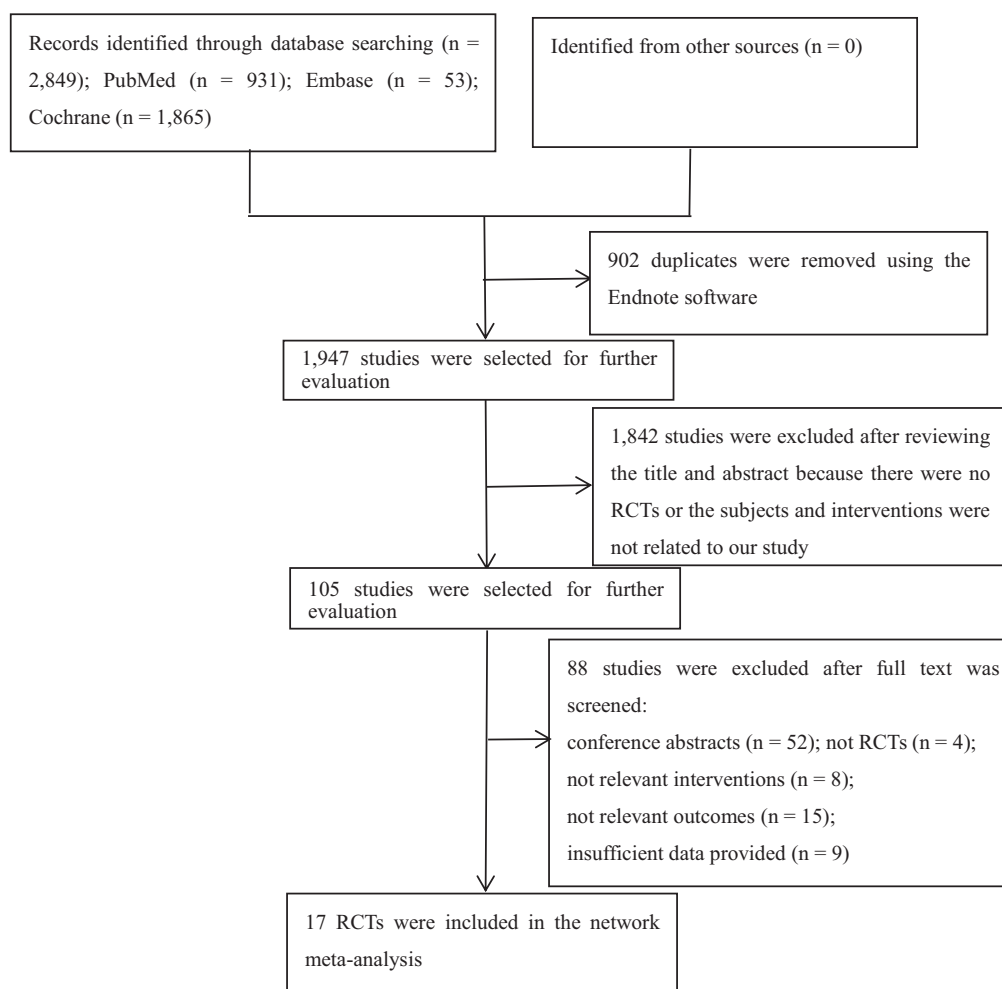


Figure 1. Flow chart of the selection process of the studies.

deemed low risk. The allocation of patients was concealed in all studies, which was deemed unclear risk. Twelve trials [15,17–19,21,22,24,26–30] featured blinded patients and personnel, two trials [16,21] had blinded outcome assessors, and four trials [20,24,25,31] were not blinded. About 5% of the studies were deemed high risk due to incomplete outcome data reports or selective reporting.

Results of network diagram

We performed an NMA to assess the relative outcomes of different LABA + ICS regimens using direct and indirect comparisons. Figure 3 shows the network diagram of the comparisons between the different treatment regimens regarding the outcomes. The first image I represents six treatment regimens in terms of the frequency of moderate or severe exacerbations. The second image II is seven treatment regimens in terms of the frequency of adverse events. The last one III concerns symptom-free days. The lines between treatment regimens nodes indicate the direct

comparisons made within randomized trials. The width of the lines is proportional to the number of trials comparing each pair of treatment regimens, and the size of each node is proportional to the number of randomly assigned participants. All these different LABA + ICS regimens form an FP/S and BUD/F-centric network diagram. The missing links between active treatment regimens reflect the scarcity of direct comparisons.

Effects on the frequency of moderate or severe exacerbations

The frequency of moderate or severe exacerbations was assessed in 14 studies [15–23,25,27–30]. The comparison of six regimens is presented in Figure 4. The all odds ratio (OR) ranges were 0.63–1.6 and 95% confidence interval (CI) 0.12–6.8. There was no difference in effects between six treatment regimens. Moderate or severe exacerbations were more frequent in the FF/VI group compared to other groups, but the difference did not reach statistical significance.

Table 1. The characteristics of included studies.

Study	Country	Mean age (years)	Baseline FEV ₁	Study duration (weeks)	Treatment I/C	Outcomes	Total no. of patients	Moderate or severe exacerbations	No. of patients (Exp/control)	Adverse events	No. of Patients (Exp/control)	Symptom free days	Total patient days (Exp/control)
Papi et al. [15]	Italy	18–65 years	50–80%	12	BDP/F; 100/6 µg pMDI; bid	a b	228	10	115	21	115		
Jorge et al. [16]	Argentina	≥12 years	≥50%	52	FP/S; 125/25 µg pMDI; bid MF/F; 100/5 µg; bid	a b	209	18 13	113 141	16 15	113 141		
Kuna et al. [17]	Poland	≥16 years	≥50%	24	FP/S; 125/25 µg; bid BUD/F; 640/18 µg per day + terbutaline	a b c	2854	736	947	387	941	81	186
Bodzenta-Lukaszyk et al. [18]	Poland	≥12 years	50–80%	12	FP/S; 100/500 µg per day + terbutaline FP/F; 250/10 µg; bid	a b c	279	710	966	381	962	84	186
Jiang-Tao et al. [19]	China	≥12 years	≥50%	24	BUD/F; 400/12 µg; bid BUD/F; 160/4.5 µg; two inhalation; twice daily	a b	222	2 61	139 111	26 31	139 111	70	186
Emeryk et al. [20]	Poland	4–12 years	≥60%	12	FP/S; 50/500 µg; one inhalation; twice daily FP/F; 100/10 µg; bid	a b	211	80	111	32	111		
Bernstein et al. [21]	the USA	≥12 years	60–90%	12	FP/S; 100/50 µg; bid MF/F; 200/10 µg; two inhalations of MF/FMDI; bid	a b	722	21	371	29	371		
Bodzenta-Lukaszyk et al. [22]	Poland	≥18 years	40–85%	12	FP/S; 250/50 µg; dry powder inhaler (DPI); bid FP/F; 50/5 µg; every 12 h; hydrofluoroalkane pressurized metered-dose inhaler FP/S; 50/25 µg; every 12 h; hydrofluoroalkane pressurized metered-dose inhaler	a b	202	14	101	16	101		
Papi et al. [23]	Italy	18–65 years	50–80%	12	BDP/F; 100/6 µg pMDI; in two inhalations; bid BUD/F; 200/6 µg DPI; in two inhalations; bid	a b c	219	15	109	15	109	29	84
Kirsten et al. [24]	Germany	18–65 years	≥65%	4	BDP/F; 100/6 µg; in a pressurized metered dose inhaler; bid BUD/F; 160/4.5 µg; dry powder inhaler; bid	b	22			5	11	25	84
Cukier et al. [25]	Brazil	12–65 years	≥60%	12	FP/F; 250/12 µg; bid BUD/F; 400/12 µg; bid	a b	196	6 6	96 100	44 32	96 100		
Korn et al. [26]	Germany	12–75 years	60–80%	6	CIC/F; 320/9 µg; bid FP/S; 250/50 µg; bid	b	160			37	81		

(Continued)

Table 1. Continued.

Study	Country	Mean age (years)	Baseline FEV1	Study duration (weeks)	Treatment I/C	Outcomes	Total no. of patients	Moderate or severe exacerbations	No. of patients (Exp/control)	Adverse events	No. of Patients (Exp/control)	Symptom free days	Total patient days (Exp/control)
Bousquet et al. [27]	France	≥12 years	≥50%	24	BUD/F; 160/4.5 µg; two inhalations/twice daily FP/S; 50/500 µg; inhalation of high-dose/twice daily	a b c	2309	108	1151	483	1151	79	168
Dahl et al. [28]	Denmark	≥18 years	≥12%	24	FP/S; 50/250 µg; one inhalation; bid BUD/F; 6/200 µg; two inhalations; bid	a b c	1391	436	694	384	694	106	168
FitzGerald et al. [29]	Canada	18–70 years	60–90%	52	FP/S; one inhalation; 50/250 µg; bid BUD/F; two inhalations; 6/200 µg; bid	a b c	688	50	344	31	344	269	364
Woodcock et al. [30]	England	≥12 years	40–85%	24	FF/Vi; 100/25 µg; once daily evening FP/S; 250/50 µg; bid (morning and evening)	a b	806	8	403	202	403	236	364
Antilla et al. [31]	Brazil	≥12 years	>40%		12 BUD/F; 400/12 µg; delivered via an Aerolizer®-type DPI FP/F; 250/12 µg; delivered via a CDM-Haler®DPI	b	243	12	403	175	403		
										14	82		
										13	76		

^aThe frequency of moderate to severe exacerbations.^bAdverse effects.^cSymptom-free days.

A. Cukier 2013	?	?	?	?	?	?
A. Papi 2007	+	?	+	?	+	+
A. Papi 2007 2	?	?	+	?	+	+
Andrzej Emeryk 2016	+	?	+	?	+	+
Anna Bodzenta-Lukaszyk 2011	+	?	+	?	+	+
Anna Bodzenta-Lukaszyk 2012	+	?	+	?	+	+
Anne-Marie Kirsten 2015	+	?	+	?	+	+
Ashley Woodcock 2013	+	?	+	?	+	+
David I Bernstein 2011	+	?	+	?	+	+
J. Mark Fitzgerald 2005	+	?	+	?	+	+
Jean Bousquet 2007	+	?	+	?	+	+
JORGE F2010	?	?	+	?	+	+
LIN Jiang-tao 2012	+	?	+	?	+	+
Mari Anttila 2014	?	?	+	?	+	+
Piotr Kuna 2010	?	?	+	?	+	+
Ronald Dahl 2006	+	?	+	?	+	+
Stephanie Korn 2012	?	?	+	?	+	+
	Random sequence generation (selection bias)					
	Allocation concealment (selection bias)					
	Blinding of participants and personnel (performance bias)					
	Blinding of outcome assessment (detection bias)					
	Incomplete outcome data (attrition bias)					
	Selective reporting (reporting bias)					
	Other bias					

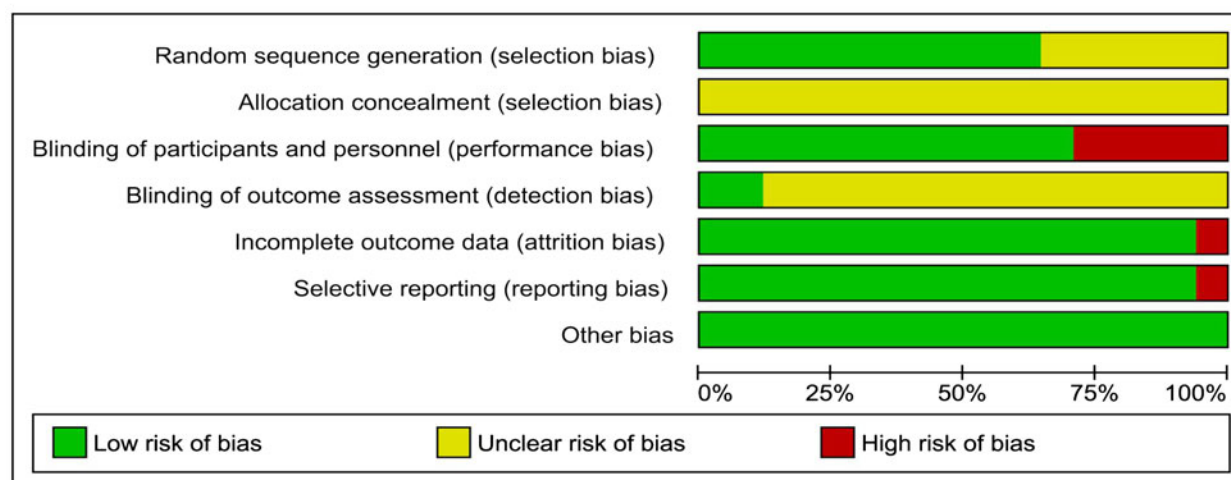


Figure 2. Risk of bias in included studies.

The inconsistency of the results makes no statistical differences ($p > 0.05$) between direct and indirect effects of the pair-wise comparisons (Appendix A). Heterogeneity was analyzed with pair wise meta-analyses, which found no significant heterogeneity ($I^2 = 0$, Appendix B).

Effects on adverse events

All trials [15–31] provided data for the analysis of the adverse events. The all odds ratio (OR) ranges were 0.63–1.6 and 95% confidence interval (CI) 0.28–3.6. The results showed that none of the treatment

regimens were found to be statistically significantly different when compared with each other (Figure 5).

The evaluation of inconsistency showed that there were no statistical differences ($p > 0.05$, Appendix C) between direct and indirect effects for many of the pair-wise comparisons. Heterogeneity was analyzed with pairwise meta-analyses, which found no significant heterogeneity ($I^2 = 0$, Appendix D).

Effects on symptom-free days

A total of six trials [15,17,18,27–29] including four different regimens provided an assessment of

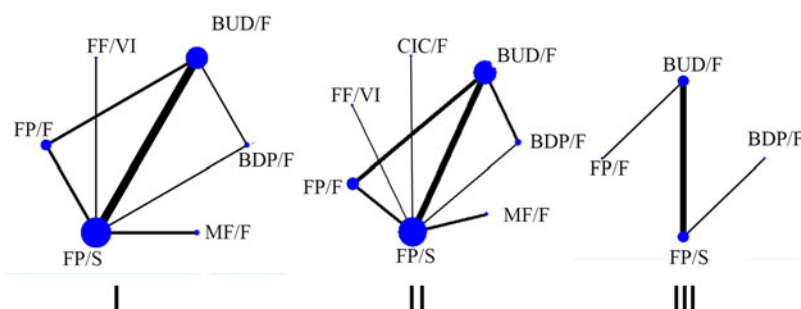


Figure 3. Network plot of evidence for moderate or severe exacerbations (I), adverse effects (II), symptom-free days (III).

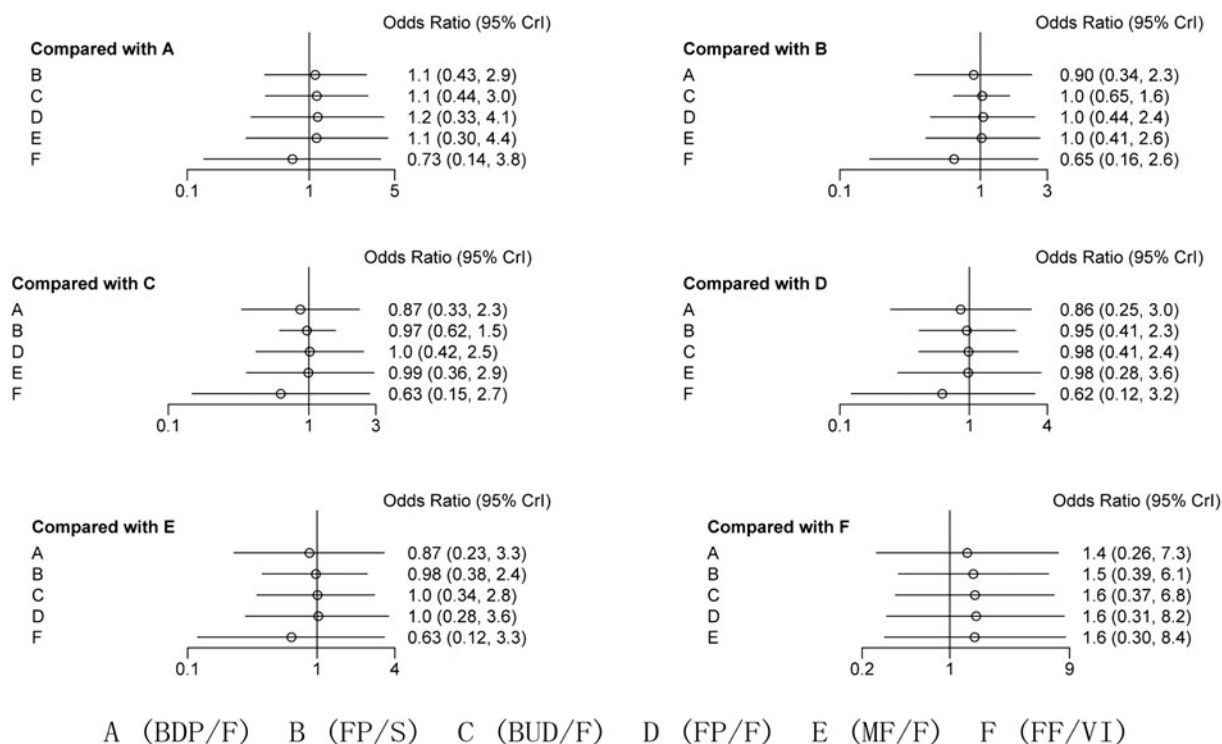


Figure 4. Effects on the frequency of moderate or severe exacerbations.

symptom-free days. Figure 6 summarizes the overall efficacy through symptom-free days. The results showed that none of the treatment regimens were found to be significantly different from each other. The results did not form a closed loop, and thus inconsistency had not been analyzed. The results of the evaluation of heterogeneity showed a low level ($I^2 < 50\%$) with no substantial heterogeneity for many of the pair-wise comparisons (Appendix E).

Discussion

This is the first systematic review of LABA + ICS combinations for patients with asthma, that has used an NMA method to assess different treatment

regimens and includes indirect comparisons. Over the past few years, several pair-wise meta-analyses have been published regarding the outcomes of these studies [3,4,32]. However, it is notable that these studies did not distinguish the types of LABA + ICS regimens. Every LABA + ICS regimen has different pharmacological profiles. Thus, it is unclear from these meta-analyses which regimens were responsible for the current treatment effects. To solve these problems, we would like to provide further evidence regarding the efficacy and safety of current LABA + ICS regimens for patients with asthma.

Fourteen studies [15–23,25,27–30] were included in the analysis of the frequency of moderate or severe exacerbations, and we found no statistically significant

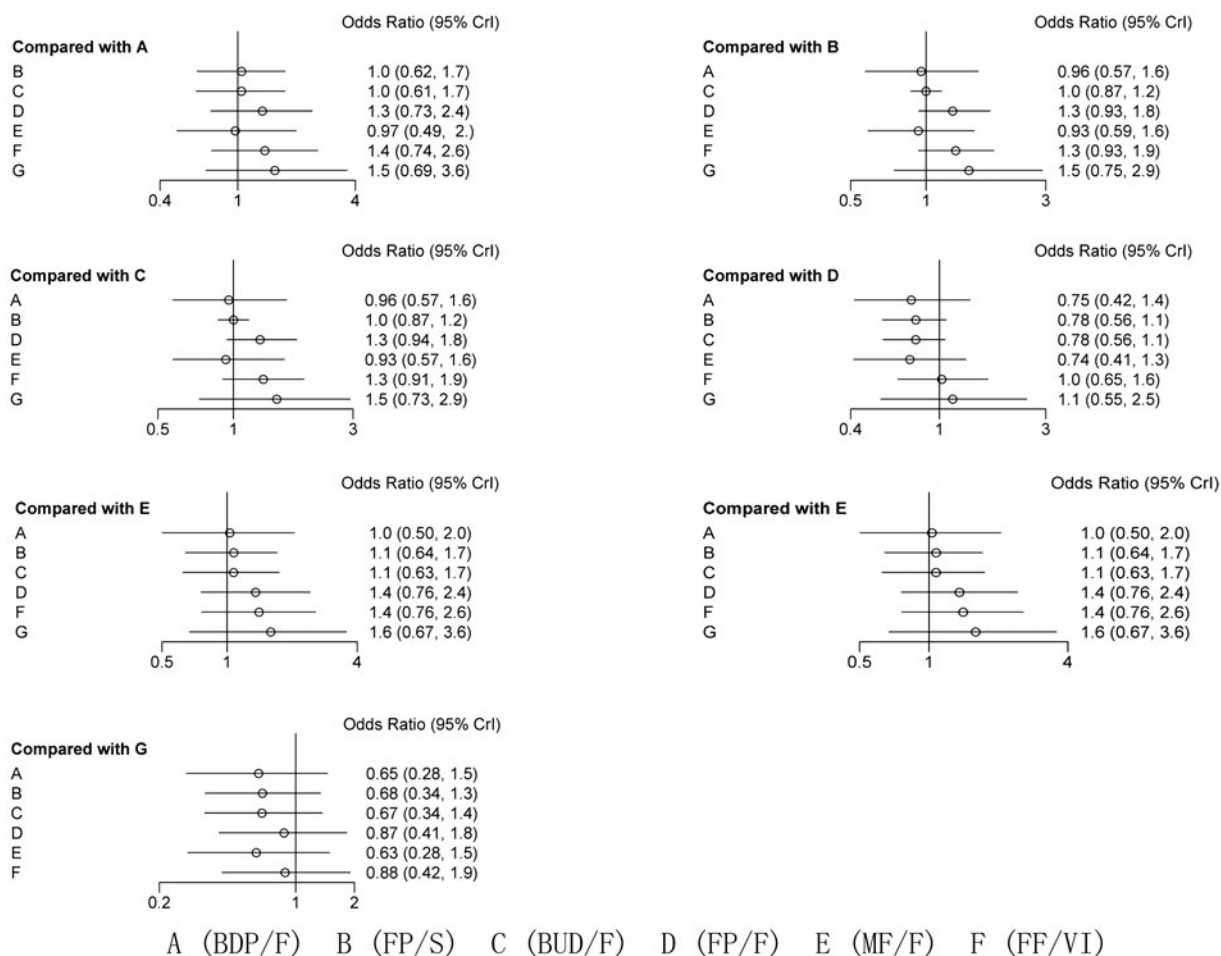


Figure 5. Effects on adverse events.

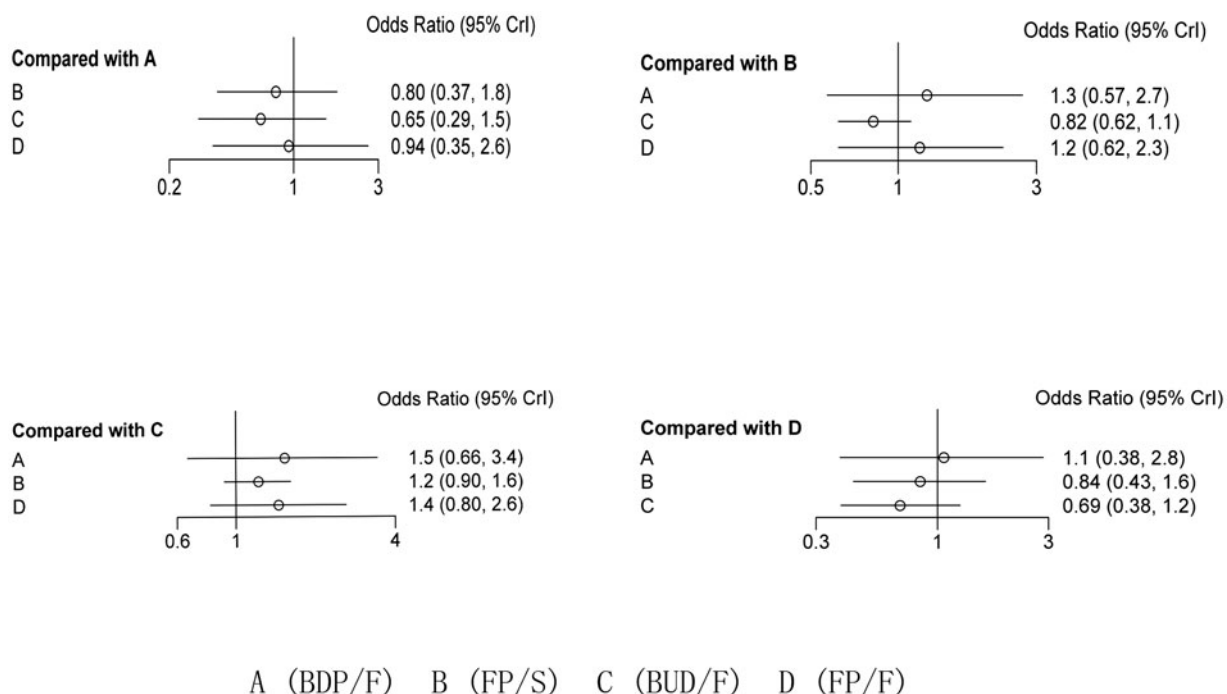


Figure 6. Effects on symptom-free days.

differences between six of the studied treatment regimens. Meanwhile, no significant difference in the treatment regimens effect was found with respect to either adverse events or symptom-free days for all included LABA + ICS regimens. The heterogeneity and inconsistency analyses of the outcomes showed that there was no significant difference between the regimens. The subgroup analysis was not performed on different doses and inhalation methods due to the small number of studies included.

There are several clinical studies on FF/VI and other regimens. Tamm et al. [33] mentioned four LABA + ICS combinations (FP/F, FP/S, BUD/F, BDP/F) that are commercially available for the treatment of asthma. However, FF/VI and M/F will be used in the future instead. A review of clinical trials showed that FF/VI could effectively reduce the risk and frequency of severe asthma exacerbations and improve lung function [34], but the number of randomized controlled studies (RCT) comparing the different regimens directly is insufficient.

Cates and Lasserson [35] have shown that over a period of 23 weeks, the rates of all-cause serious adverse events were 2.6% on BUD/F and 2.3% on FP/S, and for asthma-related serious adverse events those were 0.6% and 0.8%, respectively. However, the research of Dissanayake et al. [36] showed that FP/F has similar efficacy and tolerability profiles to BUD/F and FP/S.

We found only six RCTs in which symptom-free days were assessed, and no statistically significant differences were observed among them. Dissanayake et al. [36] demonstrated that both FP/F and BUD/F treatment regimens have a similar efficacy regarding symptom-free days and awakening-free nights. The tolerability profiles were similar in both treatment groups.

Limitations of the study

This study has some limitations. First, the sample size of the Kirsten [24] was small, only 22 cases. It can easily reduce the authenticity of the study. Second, some studies did not specify the methods of allocation hiding and blinding, which lead to methodological quality bias. Third, we were unable to include conference abstracts and report written in languages other than English. Besides, some treatment regimens were excluded because we cannot obtain the full articles or detailed data at the outcomes, such as olutetra/ICS, bambuterol/ICS, or indacaterol/mometasone furoate. Furthermore, we did not state different inhalers and recommended individualized regimens for patients. In

addition, there were fewer studies that met the inclusion criteria, and we did not carry out subgroup analysis. Finally, we did not identify which patients are being treated with advanced therapies, such as monoclonal antibodies for IgE or IL-5 therapies, and it did not include the type of asthma patients suffer from, such as allergic asthma. These will be the goal of future studies.

Conclusions

In summary, based on the results of NMA, the differences between the seven LABA + ICS regimens were not significant. However, evidence is scant, mostly indirect, and often derived from small trials with an unclear risk of bias. Therefore, a certain degree of caution should be taken when interpreting these results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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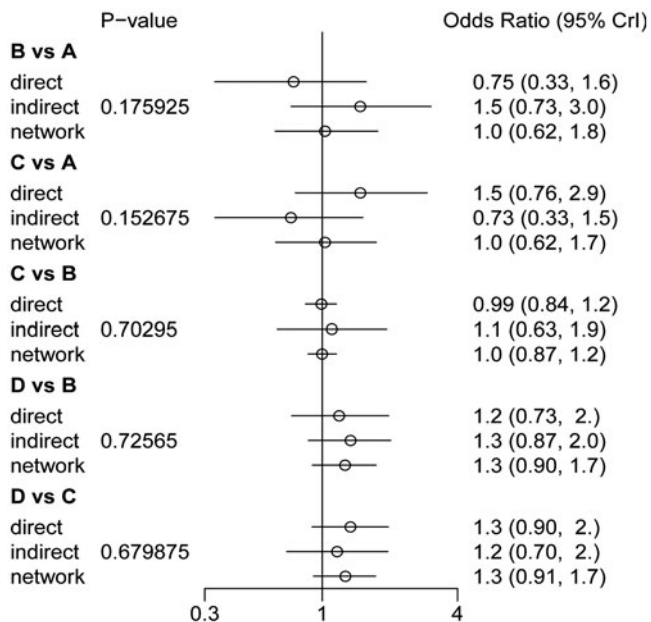
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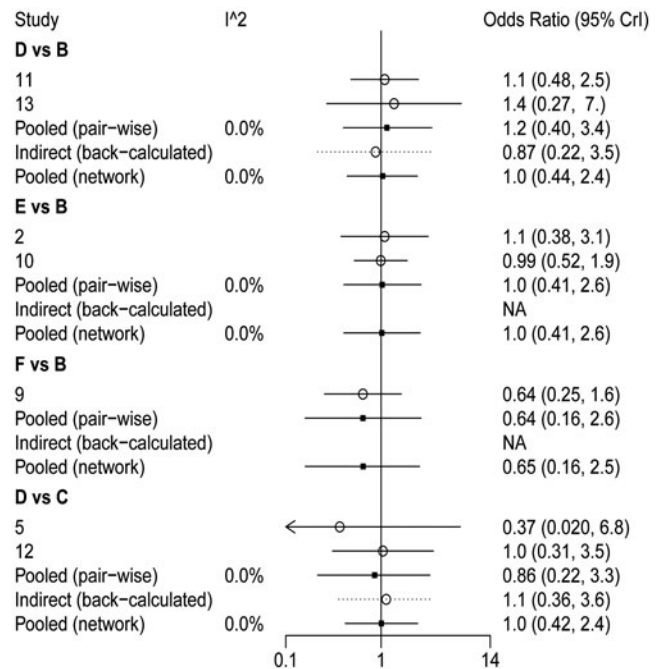
Appendix A

The inconsistency of the frequency of moderate or severe exacerbations.



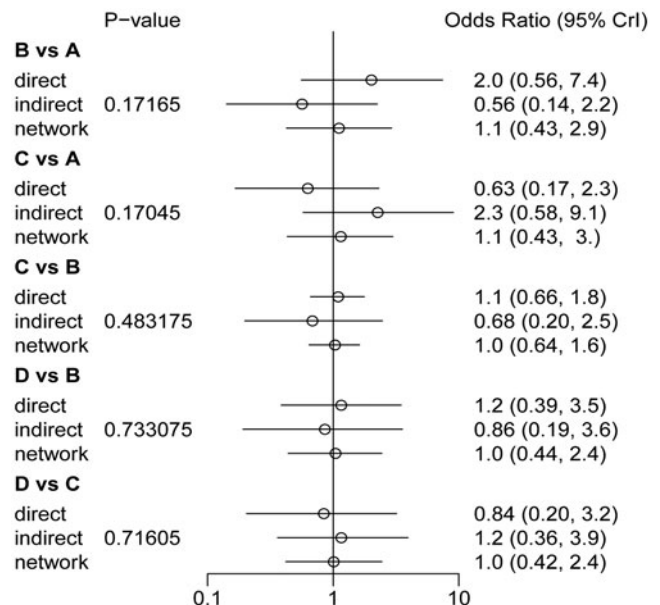
Appendix B

The heterogeneity of the frequency of moderate or severe exacerbations.



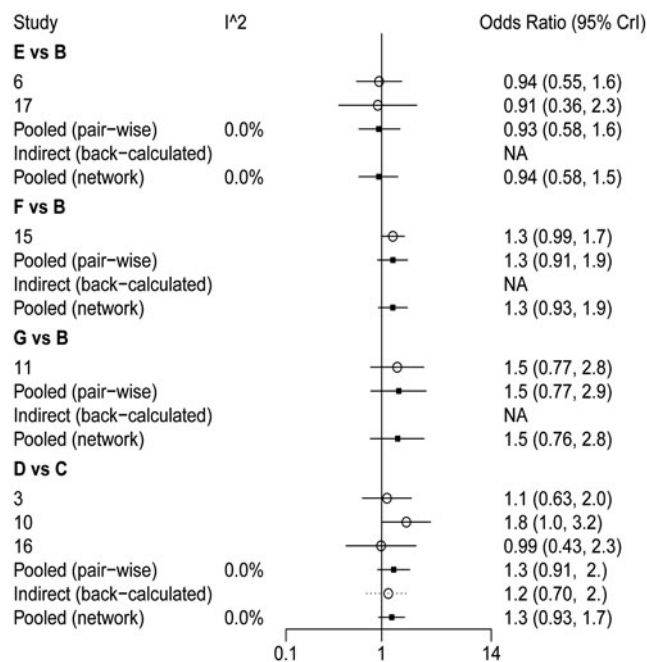
Appendix C

The inconsistency of the adverse events.



Appendix D

The heterogeneity of the adverse events.



Appendix E

The inconsistency of symptom-free days.

