Original Article

The optimal dose of indacaterol for treatment of chronic obstructive pulmonary disease: a systematic review and Bayesian network meta-analysis

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Background: The optimal dose of indacaterol for treatment of chronic obstructive pulmonary disease (COPD) was in debate. We did this network meta-analysis to assess the efficacy and safety of three dosages (75, 150, and 300 μg) of indacaterol in patients with moderate-to-severe COPD.

Methods: We searched studies from inception until January 20, 2023 on PubMed, Embase, Cochrane Library, and Web of Science database. All studies comparing different doses of indacaterol for COPD were included in this network meta-analysis. Outcomes were forced expiratory volume in 1 second (FEV1), exacerbation rate, St. George respiratory questionnaire (SGRQ), transitional dyspnea index (TDI), and adverse events. Weighted mean difference (WMD) and odds ratio (OR) with 95% credible interval (CrI) was calculated by R software with gemtc package.

Results: Finally, a total of 10 studies (4,991 patients) were finally included in this network meta-analysis. Indacaterol 75 μg (WMD: 0.07; 95% CrI: 0.05–0.08), indacaterol 150 μg (WMD: 0.13; 95% CrI: 0.12–0.14), and indacaterol 300 μg (WMD: 0.22; 95% CrI: 0.22–0.23) were all more effective than the placebo, and the difference was statistically significant. Indacaterol 75 μg (OR: 0.80; 95% CrI: 0.53–1.21), indacaterol 150 μg (OR: 0.59; 95% CrI: 0.45–0.78), indacaterol 300 μg (OR: 0.35; 95% CrI: 0.26–0.46) were more effective than the placebo in terms of exacerbation rate, and the difference was statistically significant. The surface under the cumulative ranking (SUCRA) showed that indacaterol 300 μg ranked first, indacaterol 150 μg ranked second, indacaterol 75 μg ranked third, and placebo ranked the last for FEV1, SGRQ, TDI, exacerbation rate. There was no significant difference among the adverse events (P>0.05).

Conclusions: Considering the network meta-analysis and rankings, 300 μg indacaterol is superior to the other two dosages in treating patients with moderate-to-severe COPD. However, the quality of available evidence limits the formation of powerful conclusions regarding the comparative efficacy or safety of different doses of indacaterol used to treat COPD. Higher-quality randomized controlled trials (RCTs) are required for further research in the future.

Keywords: Chronic obstructive pulmonary disease (COPD); indacaterol; meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable common disease characterized by persistent respiratory symptoms and airflow limitation, typically associated with exposure to harmful particles or gases causing abnormalities in the airways and/or alveoli (1,2). Research shows that the prevalence of COPD in the Chinese population aged 40 years and above was 8.2% in 2007 and increased significantly to 13.7% in 2018, making it the third most common chronic disease in China after hypertension and diabetes (3,4). The persistent airflow limitation severely affects the patient's work capacity and quality of life. Bronchodilators can improve airflow limitation and are the mainstay of COPD treatment. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2019 recommends selecting a long-acting bronchodilator monotherapy for initial treatment of COPD and that is considered as GOLD group B (5). Currently, long-acting beta2-agonists (LABA) or long-acting anticholinergic drugs remain the preferred treatment to improve symptoms and reduce acute exacerbations.

Indacaterol is a new generation LABA that can be taken once daily, and its bronchodilating effect can last for 24 hours. This drug can improve the symptoms of dyspnea and quality of life in COPD patients and reduce acute exacerbations (6,7). Indacaterol is as effective as salmeterol and formoterol in improving lung function and dyspnea symptoms during stable periods, as well as in improving quality of life and reducing acute exacerbations in COPD patients (8). Indacaterol comes in three strengths: 75, 150, and 300 μg. The recommended dose of indacaterol according to the 2017 GOLD guidelines ranges from 75 to 300 μg (9). Although there are already studies that have evaluated the efficacy and safety of the three doses of indacaterol (75, 150, and 300 μg) compared to placebo in treating stable COPD, there are few direct comparisons among the three doses (10,11). Furthermore, it is not clear which dose has a better advantage in terms of efficacy and safety.

Therefore, this study used a network meta-analysis method to evaluate the efficacy and safety of the three doses of indacaterol (75, 150, and 300 μg) for treating moderate to severe COPD and to rank them based on current evidence, in order to provide a basis for clinical medication. There was no registered protocol. We present this article in accordance with the PRISMA-NMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1044/rc).

Highlight box

Key findings

- Three hundred μg indacaterol is superior to the other two dosages in treating patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

What is known and what is new?

- Indacaterol is an effective non-drug treatment for COPD that has been suggested to be a component of the standard treatment for COPD.
- We first identify the optimal dose of indacaterol for COPD.

What is the implication, and what should change now?

- Considering the network meta-analysis and rankings, 300 μg indacaterol is superior to the other two dosages in treating patients with moderate-to-severe COPD. Higher-quality randomized controlled trials are required for further research in the future.

Methods

Search strategy

A search was conducted for potentially relevant randomized controlled trials (RCTs) about different doses of indacaterol (75, 150, and 300 μg) versus placebo for treatment of COPD on PubMed, Embase, Cochrane Library, and Web of Science database up to January 15, 2023. Additional records were also identified through other sources, especially references from the retrieved records. ClinicalTrials.gov was also manually searched. A structured search was performed using the following search strings: "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "COAD" OR "COPD" OR "chronic airflow obstruction" OR "pulmonary disease", "chronic obstructive" [MeSH] AND "indacaterol". Two independent reviewers screened the titles, abstracts, and full publications according to pre-established criteria. In cases of disagreement, a consensus was reached through discussion or with the intervention of a third reviewer. In conducting this systematic review and meta-analysis, reference lists, related citations, and grey literature from websites were manually searched. Since no direct contact with patients was involved, ethics approval was not required.

Inclusion criteria and exclusion criteria

To be included in the meta-analysis, studies had to fulfill the

PICOS (population, intervention, comparator, outcome, study design) criteria as follows: population (P)—patients with COPD; intervention (I)—the intervention group received different doses of indacaterol (75, 150, and 300 μg), or placebo; outcomes (O)—forced expiratory volume in 1 second (FEV1), exacerbation rate, St. George respiratory questionnaire (SGRQ), transitional dyspnea index (TDI), and adverse events; study design (S)—RCTs retrospective studies, cadaver studies, comments, letters, editorials, protocols, guidelines, surgical registries, and review papers were excluded.

Literature selection

All pertinent studies were first gathered and imported into Endnote X7 (EndNote X7, Thomson Reuters, NY, USA), and any duplicate literature was eliminated. Next, two researchers independently evaluated the titles and abstracts to exclude any studies that did not meet the PICOS criteria, any remaining irrelevant studies were removed. If there was any disagreement about which literature to include, a senior reviewer was consulted.

Data extraction

The available data from the included studies, including author, study design, publishing year, age, sample size, gender, intervention, and control procedure, were extracted by two independent reviewers. The primary outcomes assessed were FEV1, SGRQ, TDI, exacerbation rate, and adverse events. Primary outcome: trough FEV1 (change in mL from baseline). If any data were missing, the corresponding author of the study was contacted to obtain the necessary information.

Quality assessment

The risk of bias in RCTs was assessed by two reviewers using the Cochrane Collaboration's risk of bias tool as depictive in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0), which comprised items such as random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, reporting bias, and other bias. Each domain was assessed as low, unclear and high according to the instruction. In case of any discrepancies in the evaluations between the two reviewers, a third reviewer was consulted to resolve them.

Data analysis and statistical methods

For the network meta-analyses of efficacy outcomes, we utilized Bayesian methods, specifically JAGS via R with the R package gemtc (https://cran.r-project.org/web/packages/gemtc/gemtc.pdf). To ensure the reliability of our findings, we conducted sampling simulations and Markov chain Monte Carlo (MCMC) calculations utilizing a random effects model. We evaluated the convergence diagnostic outcomes using diagnostic plots like trajectory plots and density plots. We determined the means under the random effects model and fixed effects model and inspected homogeneity in the literature using the BlandAltmanLeh package. Homogeneity was deemed good if the distances between all points were within 95% of the limits of agreement (LoA). To assess consistency between direct and indirect comparisons, we utilized the node-splitting approach and considered P values greater than 0.05 to be favorable. If heterogeneity was detected (with I^2 values over 50%), we investigated further heterogeneity and considered the total I^2.pair and I^2.cons for the overall results. We also conducted sensitivity analyses by excluding one study at a time and combining the remaining studies for analysis to assess the potential impact on the outcomes. We calculated the mean surface under the cumulative ranking (SUCRA) curve for each intervention, where a higher SUCRA indicated a higher rank of the protocol.

Results

Search results

A total of 258 studies were retrieved from the preliminary literature search (PubMed =132, Embase =56, Cochrane Library =50, and Web of Science =20), and an additional ten studies were identified from a review of citations. After the EndNote software (Thomson Reuters, Philadelphia, PA, USA; version X7) automatically removed 50 duplicate studies. Finally, a total of 10 studies (12-21) were included in this network meta-analysis (*Figure 1*). General characteristics of the included studies can be seen in *Table 1*. The sample size of the included studies varied from 51 to 476 cases between the years of 2010 to 2014. The age range of patients was from 62.9 to 66.5 years. Doses of indacaterol including 75, 150, and 300 μg. Follow-up duration ranged from 2 to 52 weeks.

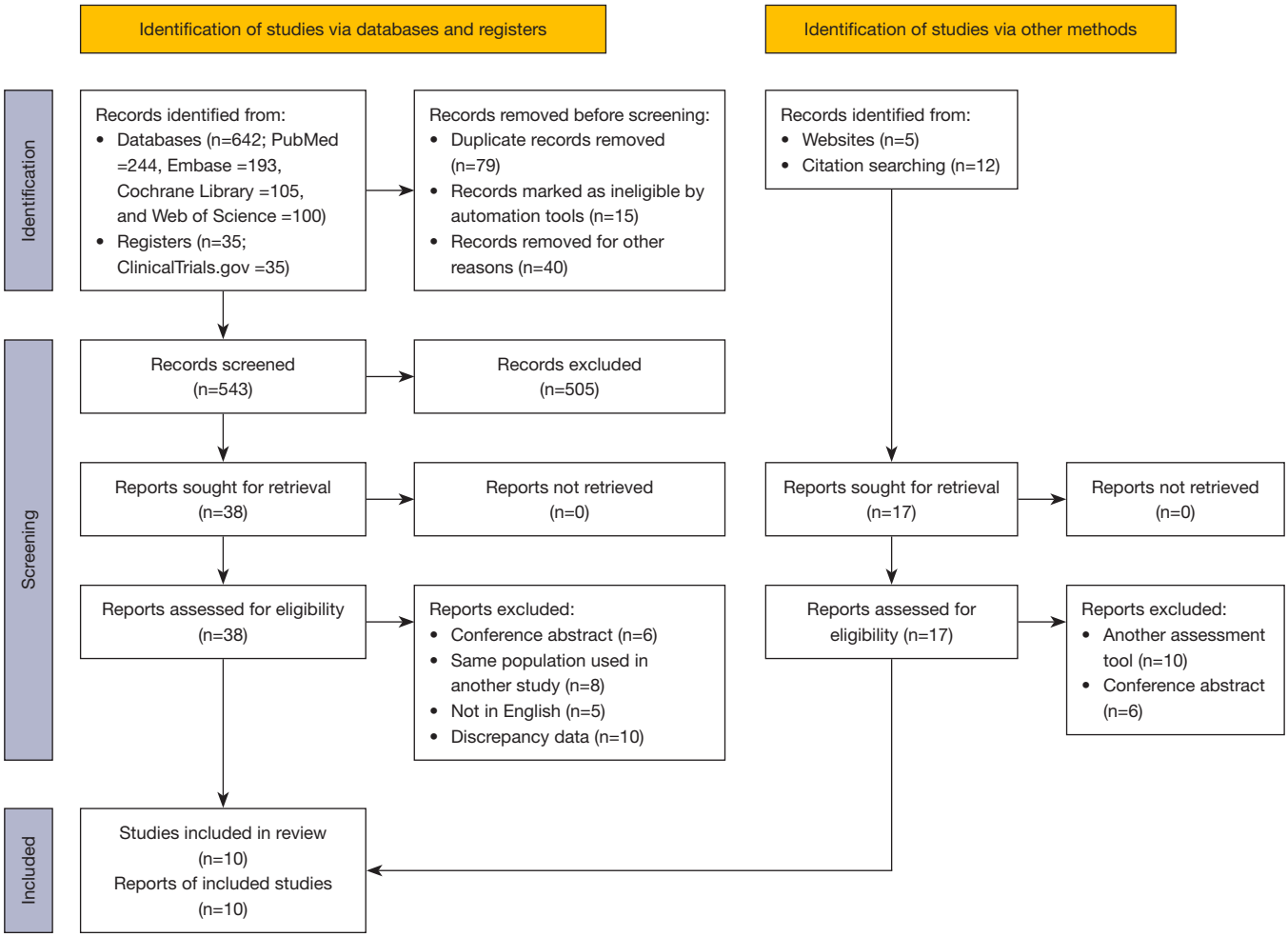

Figure 1 PRISMA flow diagram of the literature selection process.

Quality of the included studies

The risk of bias summary and risk of bias graph for the included trials is shown in *Figures 2,3*, respectively. Five trials were graded as having a low risk of bias, five trials were at an unclear risk of bias. Five trials reported an appropriate randomization, and eight trials described the methods of allocation concealment.

Outcomes

FEV1

A total of 10 studies involving 5,314 patients, including four treatments (indacaterol 75 μg, indacaterol 150 μg, indacaterol 300 μg, and placebo) contributed to the clinical outcome of the FEV1. As displayed in *Figure 4A*, the network structure diagrams detailed the direct comparisons among different treatment options in the FEV1. In head-to-head comparison, indacaterol 75 μg [weighted mean difference (WMD): 0.07; 95% credible interval (CrI): 0.05–0.08; *Figure 4B*], indacaterol 150 μg (WMD: 0.13; 95% CrI: 0.12–0.14; *Figure 4B*), and indacaterol 300 μg (WMD: 0.22; 95% CrI: 0.22–0.23; *Figure 4B*) were all more effective than the placebo, and the difference was statistically significant.

The SUCRA showed that indacaterol 300 μg ranked first (SUCRA, 100%), indacaterol 150 μg ranked second (SUCRA, 66.7%), indacaterol 75 μg ranked third (SUCRA, 33.0%), and placebo ranked the last (SUCRA, 0.4%; *Figure 4C*).

Exacerbation rate

A total of six studies, including four treatments (indacaterol 75 μg, indacaterol 150 μg, indacaterol 300 μg, and placebo)

Table 1 General characteristic of the included studies

Author, year	Number of patients			Mean age (years)			Intervention			Duration (weeks)	Severity	Outcomes
	T1	T2	C	T1	T2	C	T1	T2	C			
Bateman, 2013	476	–	232	63.6	–	64.4	IND 150 μg	–	Placebo	26	Moderate-to-severe COPD	1, 2, 3, 4, 5
Chapman, 2011	144	146	124	62.5	62.5	62.8	IND 150 μg	IND 300 μg	Placebo	52	Moderate-to-severe COPD	1, 2, 3, 5
Dahl, 2010	437	–	432	64.0	–	63.0	IND 300 μg	–	Placebo	52	Moderate-to-severe COPD	1, 2, 3, 4, 5
Donohue, 2010	416	416	418	63.4	63.3	63.6	IND 150 μg	IND 300 μg	Placebo	26	Moderate-to-severe COPD	1, 2, 3, 4, 5
Feldman, 2010	211	–	205	62.9	–	63.1	IND 150 μg	–	Placebo	12	Moderate-to-severe COPD	1, 5
Gotfried, 2012	163	–	160	64.0	–	64.0	IND 75 μg	–	Placebo	12	Moderate-to-severe COPD	1, 2, 3, 4, 5
Kerwin, 2011	163	–	159	64.0	–	62.0	IND 75 μg	–	Placebo	12	Moderate-to-severe COPD	1, 2, 3, 4, 5
Kinoshita, 2012	114	116	117	66.4	67.1	66.5	IND 150 μg	IND 300 μg	Placebo	12	Moderate-to-severe COPD	1, 3, 4, 5
Van De Maele, 2010	51	–	53	64.5	–	64.3	IND 300 μg	–	Placebo	2	Moderate-to-severe COPD	1, 5
Yao, 2014	187	188	186	66.2	65.5	64.6	IND 150 μg	IND 300 μg	Placebo	26	Moderate-to-severe COPD	1, 3, 4, 5

T1, treatment 1, T2, treatment 2, C, control. Outcomes: 1, FEV1; 2, exacerbation rate, 3, SGRQ, 4, TDI; 5, adverse events. IND, indacaterol; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; SGRQ, St. George respiratory questionnaire; TDI, transitional dyspnea index.

contributed to the clinical outcome of the exacerbation rate. As displayed in *Figure 5A*, the network structure diagrams detailed the direct comparisons among different treatments in the exacerbation rate.

In head-to-head comparison, indacaterol 75 μg [odds ratio (OR): 0.80; 95% CrI: 0.53–1.21; *Figure 5B*], indacaterol 150 μg (OR: 0.59; 95% CrI: 0.45–0.78; *Figure 5B*), indacaterol 300 μg (OR: 0.35; 95% CrI: 0.26–0.46; *Figure 5B*) were more effective than the placebo in terms of exacerbation rate, and the difference was statistically significant. Indacaterol 300 μg (OR: 0.43; 95% CrI: 0.26–0.71) was more effective than the indacaterol 75 μg in terms of exacerbation rate, and the difference was statistically significant. However, there was no statistically significance between indacaterol 150 μg and indacaterol 75 μg in terms of exacerbation rate (OR: 0.74; 95% CrI: 0.45–1.21).

The SUCRA showed that indacaterol 300 μg ranked first (SUCRA, 99.8%), indacaterol 150 μg ranked second (SUCRA, 63.3%), indacaterol 75 μg ranked third (SUCRA, 32.2%), and placebo ranked the last (SUCRA, 4.7%; *Figure 5C*).

SGRQ

A total of eight studies involving 4,794 patients, including four treatments (indacaterol 75 μg, indacaterol 150 μg, indacaterol 300 μg, and placebo) contributed to the clinical outcome of the SGRQ (*Figure 6A*). As displayed in *Figure 6A*, the network structure diagrams detailed the direct comparisons among different treatments in the SGRQ. In head-to-head comparison, indacaterol 75 μg (WMD: −2.5; 95% CrI: −3.3 to −1.6; *Figure 6B*), indacaterol 150 μg (WMD: −6.9; 95% CrI: −7.4 to −6.5; *Figure 6B*), indacaterol 300 μg (WMD: −10.0; 95% CrI: −11.0 to −9.7; *Figure 6B*) were more effective than the placebo in terms of SGRQ and the difference was statistically significant. Indacaterol 300 μg (WMD: −7.64; 95% CrI: −8.63 to −6.65) and indacaterol 150 μg (WMD: −4.45; 95% CrI: −5.45 to −3.45) were more effective than the indacaterol 75 μg in terms of SGRQ, and

the difference was statistically significant.

The SUCRA showed that indacaterol 300 μg ranked first (SUCRA, 97.3%), indacaterol 150 μg ranked second (SUCRA, 73.2%), indacaterol 75 μg ranked third (SUCRA, 36.2%), and placebo ranked the last (SUCRA, 5.5%; *Figure 6C*).

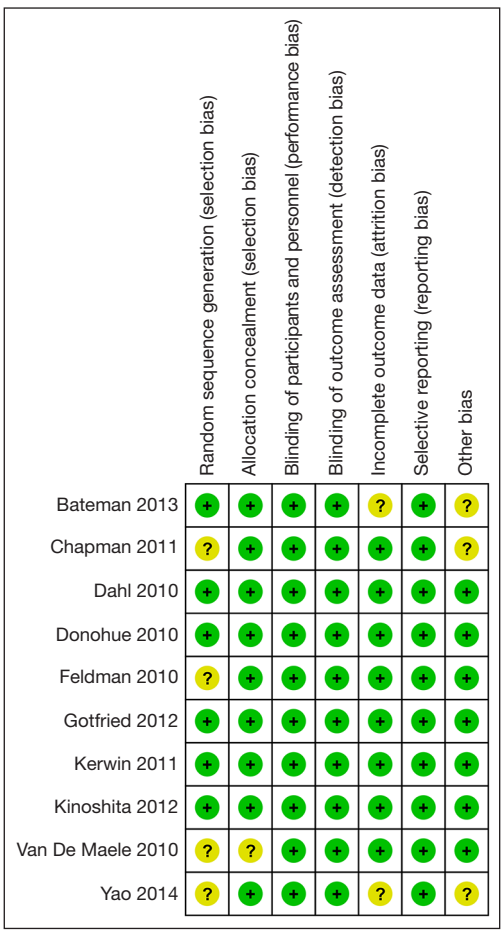

Figure 2 Risk of bias summary of the included studies.

TDI

A total of eight studies involving 4,380 patients, including four treatments (indacaterol 75 μg, indacaterol 150 μg, indacaterol 300 μg, and placebo) contributed to the clinical outcome of the TDI (*Figure 7A*). As displayed in *Figure 7A*, the network structure diagrams detailed the direct comparisons among different treatments in the TDI. In head-to-head comparison, indacaterol 75 μg (WMD: 0.49; 95% CrI: 0.19 to 0.79; *Figure 7B*), indacaterol 150 μg (WMD: 0.69; 95% CrI: 0.48 to 0.90; *Figure 7B*), indacaterol 300 μg (WMD: 1.25; 95% CrI: 1.04 to 1.46; *Figure 7B*) were more effective than the placebo in terms of TDI and the difference was statistically significant. Indacaterol 300 μg (WMD: 0.76; 95% CrI: 0.39 to 1.13) was more effective than the indacaterol 75 μg in terms of TDI, and the difference was statistically significant. However, there was no significant difference between indacaterol 150 μg and indacaterol 75 μg in terms of TDI (WMD: 0.2; 95% CrI: −0.16 to 0.57).

The SUCRA showed that indacaterol 300 μg ranked first (SUCRA, 99.9%), indacaterol 150 μg ranked second (SUCRA, 62.9%), indacaterol 75 μg ranked third (SUCRA, 37.0%), and placebo ranked the last (SUCRA, 0.1%; *Figure 7C*).

Adverse events

A total of 10 studies involving 5,314 patients, including four treatments (indacaterol 75 μg, indacaterol 150 μg, indacaterol 300 μg, and placebo) contributed to the clinical

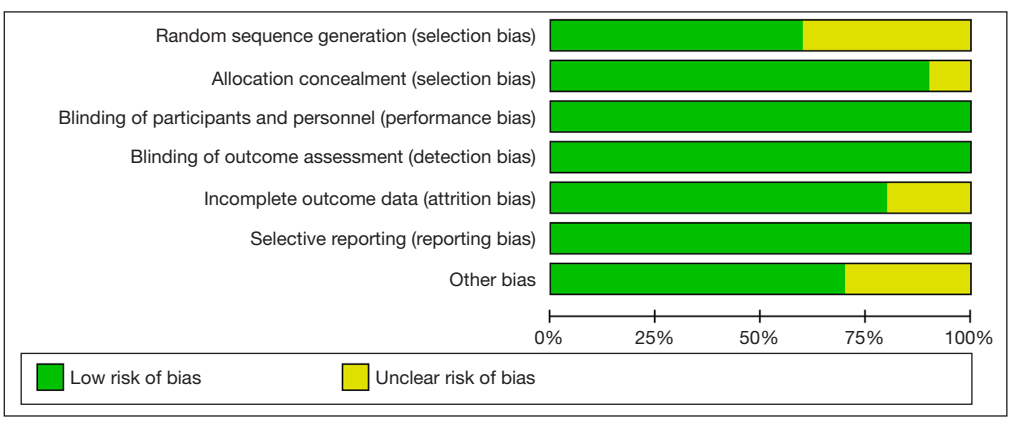

Figure 3 Risk of bias graph of the included studies.

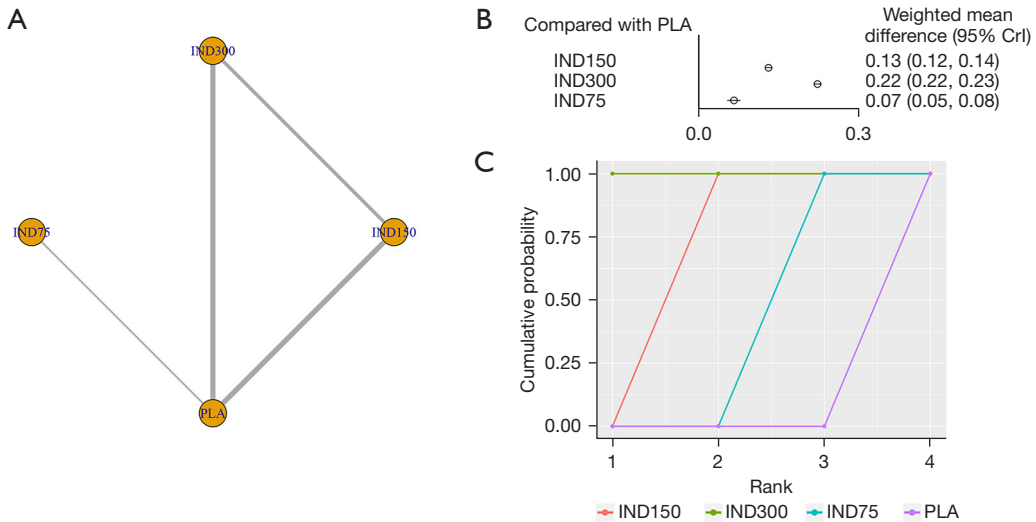

Figure 4 Network meta-analysis results of FEV1. (A) Network structure diagrams of FEV1; (B) forest plot of the FEV1 as compared with placebo; (C) SUCRA probabilities of different drugs for FEV1. IND, indacaterol; PLA, placebo; CrI, credible interval; FEV1, forced expiratory volume in 1 second; SUCRA, surface under the cumulative ranking curve.

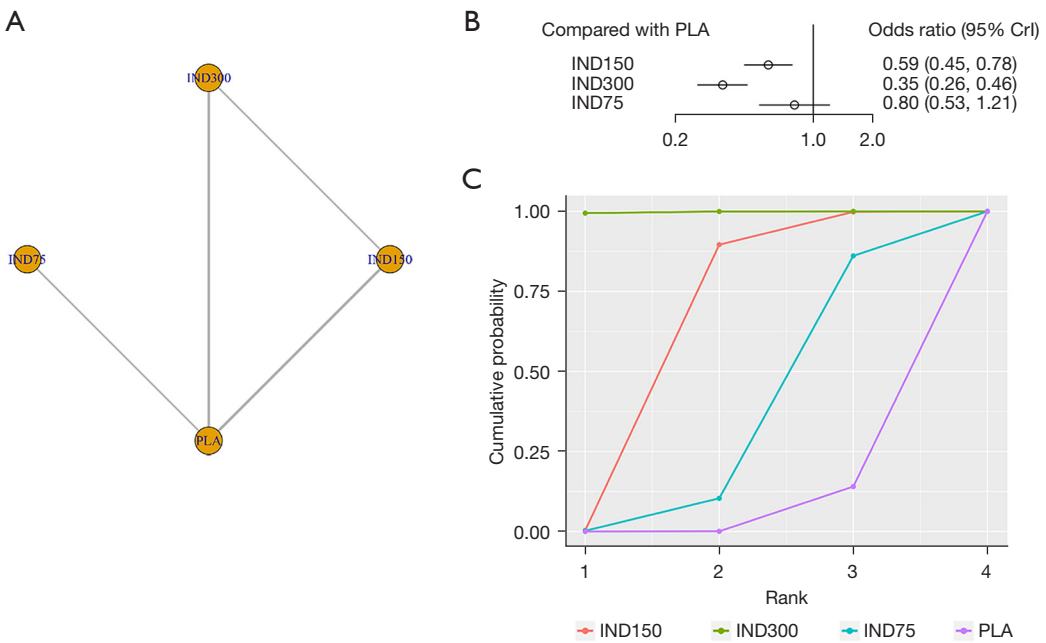

Figure 5 Network meta-analysis results of exacerbation rate. (A) Network structure diagrams of exacerbation rate; (B) forest plot of the exacerbation rate as compared with placebo; (C) SUCRA probabilities of different drugs for exacerbation rate. IND, indacaterol; PLA, placebo; CrI, credible interval; SUCRA, surface under the cumulative ranking curve.

outcome of the adverse events (*Figure 8A*). As displayed in *Figure 8A*, the network structure diagrams detailed the direct comparisons among different treatments in the adverse events. In head-to-head comparison, indacaterol 75 μg (OR: 1.1; 95% CrI: 0.73 to 1.5; *Figure 8B*), indacaterol 150 μg (OR: 1.0; 95% CrI: 0.84 to 1.2; *Figure 8B*), indacaterol 300 μg (OR: 1.0; 95% CrI: 0.85 to 1.2; *Figure 8B*) were not associated with more adverse events, the difference was not

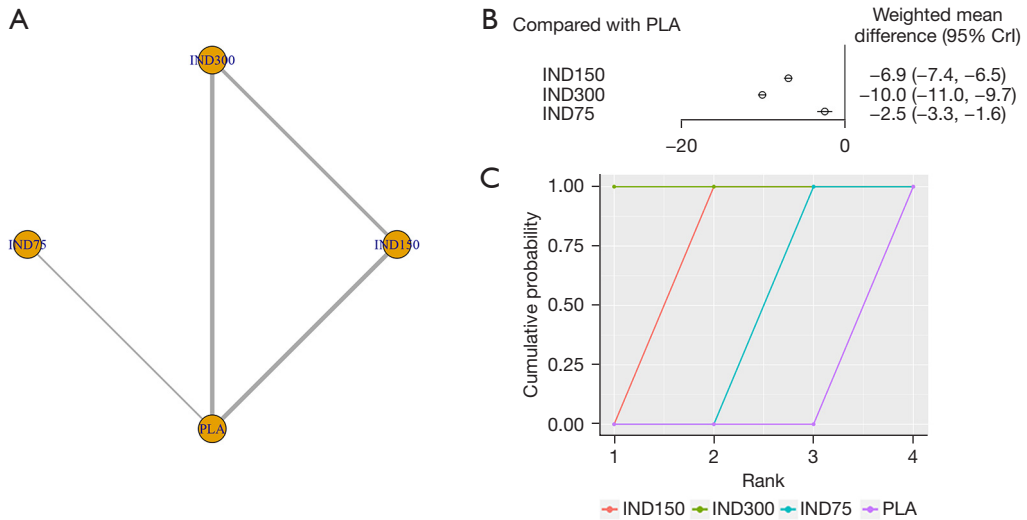

Figure 6 Network meta-analysis results of SGRQ. (A) Network structure diagrams of SGRQ; (B) forest plot of the SGRQ as compared with placebo; (C) SUCRA probabilities of different drugs for SGRQ. IND, indacaterol; PLA, placebo; CrI, credible interval; SGRQ, St. George respiratory questionnaire; SUCRA, surface under the cumulative ranking curve.

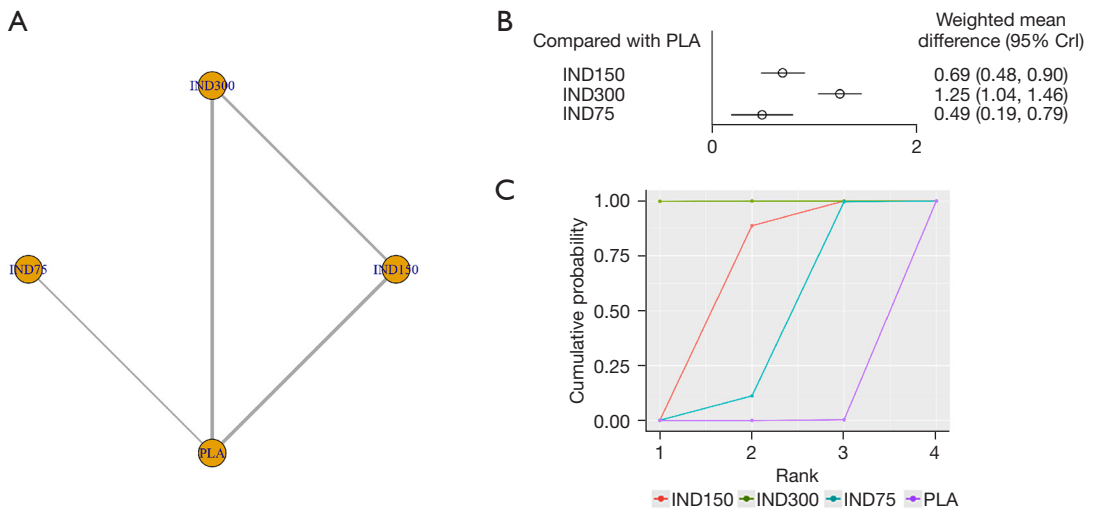

Figure 7 Network meta-analysis results of TDI. (A) Network structure diagrams of TDI; (B) forest plot of the TDI as compared with placebo; (C) SUCRA probabilities of different drugs for TDI. IND, indacaterol; PLA, placebo; CrI, credible interval; TDI, transitional dyspnea index; SUCRA, surface under the cumulative ranking curve.

statistically significant.

The SUCRA showed that placebo ranked first (SUCRA, 57.0%), indacaterol 150 μg ranked second (SUCRA,52.9%), indacaterol 300 μg ranked third (SUCRA, 49.7%), and placebo ranked the last (SUCRA, 57.0%; *Figure 8C*).

Node-split results

No significant difference between direct and indirect evidence was observed in FEV1 (*Figure 9A*), SGRQ (*Figure 9B*), and TDI (*Figure 9C*).

Discussion

This network meta-analysis comprehensively assessed and ranked the effects of different doses of indacaterol for COPD patients tested in 10 RCTs. The currently

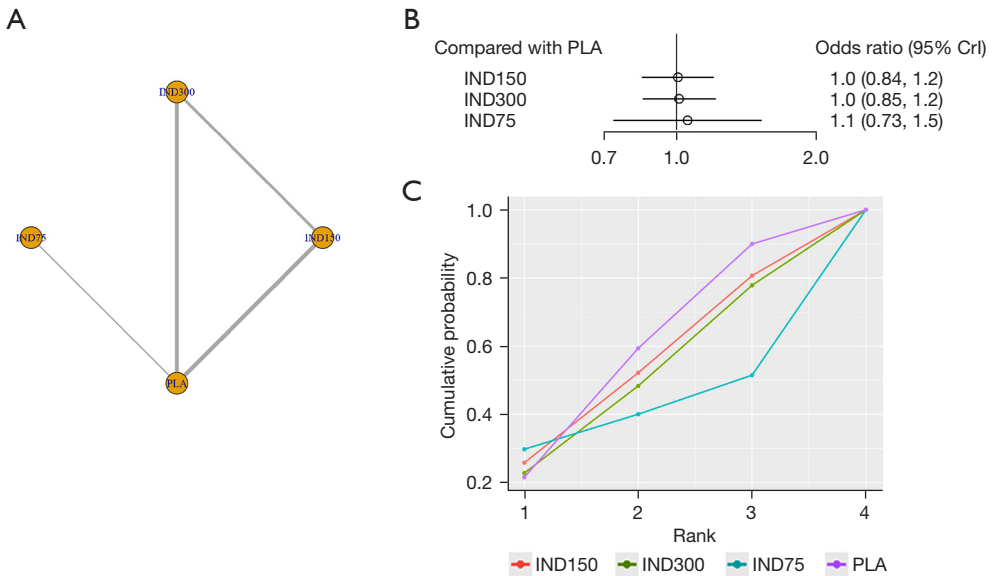

Figure 8 Network meta-analysis results of adverse events. (A) Network structure diagrams of adverse events; (B) forest plot of the adverse events as compared with placebo; (C) SUCRA probabilities of different drugs for adverse events. IND, indacaterol; PLA, placebo; CrI, credible interval; SUCRA, surface under the cumulative ranking curve.

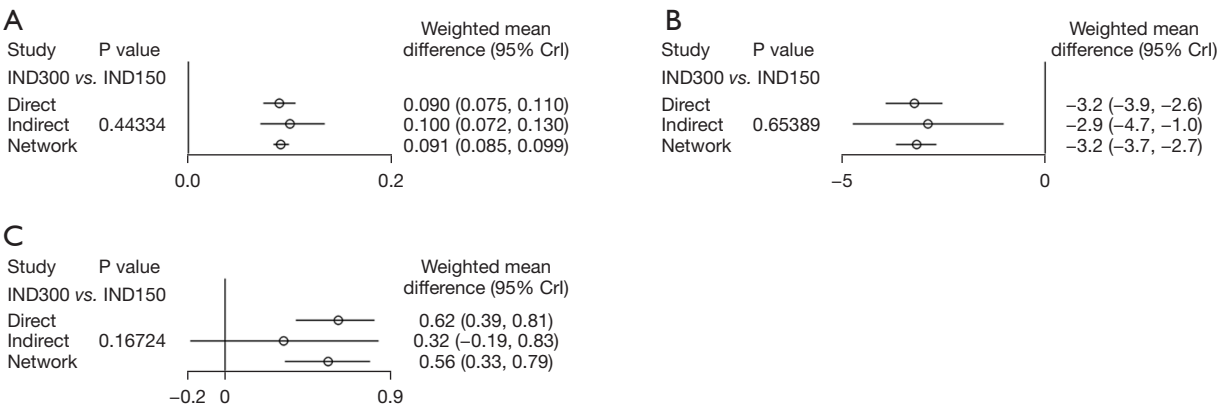

Figure 9 Inconsistency analysis of this network meta-analysis. Comparison between direct and indirect evidence for FEV1 (A), SGRQ (B), and TDI (C). IND, indacaterol; CrI, credible interval; FEV1, forced expiratory volume in 1 second; SGRQ, St. George respiratory questionnaire; TDI, transitional dyspnea index.

available doses of indacaterol on the market include 75, 150, and 300 μg, but it is still unclear which dose has the advantage in terms of efficacy and safety. This study used a network meta-analysis method to explore this issue, not only addressing the limitations of traditional meta-analysis but also incorporating the latest relevant research. Five outcome indicators were compared to evaluate the efficacy and safety of indacaterol treatment in severe COPD during the stable phase among the three doses. This provides more reference basis for the selection of clinical treatment plans and has certain clinical guiding significance.

The results of the network meta-analysis showed that in terms of improving FEV1 trough values, all three doses of indacaterol were superior to placebo, and the improvement in FEV1 trough values gradually increased with increasing doses of indacaterol. The results of our study are consistent with these two prior meta-analyses (10). Donohue *et al.* (10)

conducted a meta-analysis that compared the efficacy of LABA as monotherapy for COPD. They concluded that indacaterol 300 µg, followed by 150 and 75 µg, were the most effective LABA monotherapies for moderate to severe COPD. Chung *et al.* (11) concluded that indacaterol is safe and beneficial for patients with COPD at dosage ≤150 µg. While our meta-analysis consistently aligns with and extends the findings of previous research, it contributes to the existing knowledge in several significant ways. Our study builds upon earlier results by incorporating three recently published RCTs (12,13,21), all of which were characterized by high quality and collectively involved an additional 560 patients. Furthermore, this network meta-analysis offers valuable insights by providing rank probabilities for various doses of indacaterol.

In terms of reducing the frequency of COPD exacerbations, 150 and 300 µg of indacaterol were superior to the placebo group, while there was no statistically significant difference between the 75 µg dose of indacaterol and the placebo. In terms of reducing SGRQ scores, all three doses of indacaterol were superior to placebo, and the 300 µg dose of indacaterol reduced SGRQ scores beyond minimum clinically important difference (MCID). In terms of improving TDI, all three doses of indacaterol were superior to placebo, and the 300 µg dose of indacaterol improved TDI beyond MCID. In terms of the incidence of adverse events, all three doses of indacaterol did not increase the incidence of adverse events. Although there was no statistical difference among the three doses of indacaterol in improving FEV1 trough values, reducing the frequency of COPD exacerbations, reducing SGRQ scores, and improving TDI, the ranking probability table results showed that the 300 µg dose of indacaterol had the highest probability of being the most effective in improving FEV1 trough values, reducing SGRQ scores, and improving TDI, and was second only to the 150 µg dose of indacaterol in reducing the frequency of COPD exacerbations. After a comprehensive comparison of the above results, it was found that the 300 µg dose of indacaterol had better efficacy than the other two doses in the treatment of severe COPD during the stable phase.

COPD patients are mostly elderly and often have comorbidities, including cardiovascular disease, hypertension, and diabetes (22). Clinical studies have shown that LABA can increase hospitalization and mortality rates due to asthma exacerbations (23). For these reasons, the safety of indacaterol must be fully considered when selecting doses for COPD treatment. Donohue *et al.* (10) conducted a network meta-analysis of 33 RCTs on the treatment of severe COPD during stable periods with different LABAs for COPD. Indacaterol 300 µg, followed by 150 and 75 µg, were the most effective LABA monotherapies for moderate to severe COPD. None of the three doses of indacaterol (150, 300, and 600 µg) increased the mortality rate of COPD patients. Geake *et al.* (24) conducted a meta-analysis comparing four doses of indacaterol (75, 150, 300, and 600 µg) with placebo and other LABAs, but did not evaluate the efficacy and safety of the four doses of indacaterol for COPD treatment using indirect comparisons or network meta-analyses. The results showed that all four doses of indacaterol did not increase the incidence of serious adverse reactions or mortality rates in COPD patients compared with placebo. This study obtained similar results, indicating that indacaterol 150 and 300 µg can not only reduce the frequency of COPD exacerbations, but also do not increase the overall incidence of adverse reactions in COPD patients compared with placebo.

Our systematic review and network meta-analysis have some limitations: (I) two studies included in the analysis did not use proper allocation concealment, which may result in selection bias; (II) only two studies investigating the use of 75 µg indacaterol were included in the analysis, both from the same research institution, with similar basic characteristics and methodology, which may lead to publication bias and may also contribute to the high heterogeneity observed between 75 µg indacaterol and placebo in terms of TDI improvement; (III) the duration of the included studies varied from 2 to 52 weeks, and we were unable to conduct detailed subgroup analysis based on treatment duration, which may affect the reliability of the meta-analysis results; and (IV) economic evaluation indicators were not included in the search, and therefore cost-effectiveness analysis was not conducted. Future research could further analyze this aspect.

Conclusions

In summary, based on the network meta-analysis and ranking of five outcome measures, it is recommended to prioritize the use of 300 µg of indacaterol in the treatment of moderate to severe COPD patients. Due to limitations in the number and quality of included studies, further high-quality research is needed to validate these conclusions. Direct comparison RCTs comparing the three doses of indacaterol in the treatment of moderate to severe COPD patients can be conducted to address the limitations of

indirect comparisons.

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Footnote

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