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Single inhaler with beclometasone, formoterol, and glycopyrronium versus triple therapies in adults with uncontrolled asthma: a systematic review and meta-analysis

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Recent literature has shown that triple therapy is more effective than dual therapy for individuals with uncontrolled asthma. However, the comparative efficacy between different triple therapies remains unclear. The objective of this study was to determine the comparative efficacy of extra-fine single-inhaler medium-dose (MD) or high-dose (HD) of beclometasone/formoterol/glycopyrronium bromide (BDP/FOR/GLY) compared to other triple therapies in patients whose asthma remains uncontrolled with MD or HD inhaled corticosteroids and long-acting β2-agonists. A systematic literature review identified randomized control trials on adult patients with uncontrolled asthma. Two separate networks were constructed according to patients' previous inhaled-corticosteroid dosage. Network meta-analyses evaluated severe and moderate-to-severe exacerbations, pre-dose forced expiratory volume, and asthma control questionnaire responses at 52 (± 3) weeks. Among single-inhaler triple therapies, MD BDP/FOR/GLY significantly reduced the risk of severe exacerbations (RR [95% CrI] compared to MD fluticasone/umeclidinium/vilanterol: 0.65 [0.49, 0.89]), while HD BDP/FOR/GLY demonstrated an improved trend in reducing severe and moderate-to-severe exacerbations versus HD indacaterol acetate/glycopyrronium bromide/mometasone, fluticasone/umeclidinium/vilanterol, and salmeterol/fluticasone + tiotropium. HD BDP/FOR/GLY and HD BDP/FOR + tiotropium did not differ significantly. Compared to relevant single-inhaler triple therapies, MD and HD BDP/FOR/GLY are associated with a significant benefit or trend for improvement in terms of reducing the rate of severe and moderate-to-severe exacerbations.

Keywords Asthma, Triple therapy, Network meta-analysis, Exacerbation

Abbreviations

ACQ-7	Asthma control questionnaire
AE	Adverse event
BDP/FOR/GLY	Beclometasone/formoterol/glycopyrronium bromide
BDP/FOR + TIO	Beclometasone/formoterol + tiotropium
CrI	Credible interval
DIC	Deviance information criterion
FEV1	Forced expiratory volume in one second
FF/UMEC/VI	Fluticasone/umeclidinium/vilanterol

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HD	High-dose
ICS	Inhaled corticosteroids
IND/GLY/MF	Indacaterol acetate/glycopyrronium bromide/mometasone
LABA	Long-acting β2-agonist
MD	Medium-dose
NMA	Network meta-analysis
PICOS	Population, intervention, comparators, outcomes and study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SLR	Systematic literature review
SUCRA	Surface under the cumulative ranking curve

Asthma is a major chronic respiratory disease affecting 1–18% of population worldwide, characterized by airway inflammation leading to airflow limitation[1]. In 2019, over 260 million people were affected by poorly controlled asthma globally[2]. Common symptoms include wheezing, chest tightness, cough, and shortness of breath that may vary in intensity. Persistent respiratory symptoms and exacerbations can lead to hospitalization or even death, representing a significant burden on quality of life and health care systems[1]. The long-term treatment goal is to reduce exacerbations and improve symptoms by re-establishing adequate airflow, and preventively lowering the risk of future exacerbations[1,3].

Treatment choice follows an escalating, stepwise approach and depends on the level of on asthma symptom control[1,4]. The Global Initiative for Asthma guidelines for asthma management recommend two alternative therapy tracks for adults with asthma. For maintenance treatment, track 1 suggests low-dose inhaled corticosteroid (ICS) plus formoterol for steps 1–3, and medium-dose (MD) ICS plus formoterol for step 4. Track 2 advises using ICS with short-acting β2-agonist for step 1, low-dose ICS maintenance for step 2, low-dose ICS plus long-acting β2-agonist (LABA) for step 3, and increasing ICS to MD or high-dose (HD) at step 4. However, for step 5, both tracks recommend add-on long-acting muscarinic antagonist (LAMA) and biologics[1].

The addition of LAMA and increase to HD ICS in patients who still experience persistent symptoms or exacerbations with dual therapy is in line with the recent National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group report[5] and the British Thoracic Society/Scottish Intercollegiate Guideline Network guidelines[6]. The use of LAMA offers an additional bronchodilating effect[7] that could control symptoms without the need for an increased ICS dose (which is associated with adverse effects [AEs])[8–10] or resource-intensive biologics[11]. Further, phenotyping and biomarkers are vital in asthma management for personalizing treatment. Phenotyping classifies asthma into subtypes based on characteristics like symptoms and triggers, enabling tailored therapies. Biomarkers, such as FeNO, blood eosinophils, IgE, and periostin, help identify specific asthma types and guide treatment decisions. These tools allow for a targeted approach, improving outcomes and reducing exacerbations, particularly in severe asthma cases[12].

Recently, single-inhaler triple therapies (SITTs) such as indacaterol acetate/glycopyrronium bromide/mometasone (IND/GLY/MF), fluticasone/umeclidinium/vilanterol (FF/UMEC/VI), and extra-fine beclometasone/formoterol/glycopyrronium bromide (BDP/FOR/GLY) have been introduced for patients uncontrolled on ICS/LABA. Their phase III clinical trials (ARGON, CAPTAIN, IRIDIUM, TRIGGER, TRIMARAN) have proved significantly higher efficacy over dual therapies in terms of pulmonary function[13–16], and mostly favorable trends over dual therapies were observed on moderate-to-severe exacerbations[17]. Quantitative synthesis studies consistently concluded the superiority of triple over dual therapies in terms of several clinical outcomes, including severe and moderate-to-severe exacerbations, and across a range of patients with uncontrolled asthma[18–20]. The improved efficacy of triple therapies could be attributed to the synergistic relationship between ICS/LABA/LAMA[17]. In addition, economic studies have concluded that triple therapies are likely to be cost-effective[21,22]. However, it is pertinent to mention that FF/UMEC/VI should not be prescribed for patients with asthma since it has not been studied in this patient population[23].

To date, despite the established superiority of triple over dual therapies in patients with uncontrolled asthma, evidence on the comparative efficacy of SITTs remains limited. Oba et al.[20] estimated the relative efficacy between several triple therapies, but only the MD arm of the TRIMARAN study was included in the analysis of moderate-to-severe exacerbations, and the TRIGGER study was excluded from the analysis of severe exacerbations due to a lack of granularity of published evidence. More importantly, previous network meta-analyses (NMAs) did not account for whether patients at baseline were receiving treatments with MD or HD ICS/LABA, despite the differences in ICS dose potentially indicating varying severity among patients. Similarly, prior NMAs included studies where patients had received ICS monotherapy, which may also suggest less severe patients at an earlier treatment stage.

This paper presents a NMA evaluating the relative efficacy of BPD/FOR/GLY versus triple therapies in uncontrolled adult asthma patients. The NMA is based on findings from a systematic literature review (SLR) of studies assessing the efficacy of triple or double therapies containing ICS, LABA, and LAMA.

Materials and methods

Search strategy

An SLR was conducted in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[24,25]. Searches were run using the OVID SP platform[26] and considered the following databases: Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment database. The SLR was originally conducted in November 2019 and later updated in October 2022. Abstracts from key conferences identified through EMBASE and MEDLINE were also reviewed. Conference abstracts that met the PICOS criteria were included for data extraction. The detailed search strategy is available in Supplementary Material S1.

Selection criteria

We included all randomized clinical trials (RCTs) in patients with uncontrolled asthma. Uncontrolled asthma is characterized by frequent daytime symptoms, nighttime waking, and the need for reliever medication more than twice per week. It also involves significant activity limitations, reduced lung function (forced expiratory volume in one second [FEV1], or peak expiratory flow less than 80% of predicted), and one or more severe exacerbations in the past year requiring oral corticosteroids or hospitalization. These criteria help determine the severity of asthma and the effectiveness of treatment strategies. Patients were restricted to adults only, and no restrictions were imposed on language, race, sex, or year. Journal publications with unavailable full texts or involving animals were excluded. Two independent reviewers assessed studies for inclusion against the predetermined population, intervention and comparators, outcomes, and study design (PICOS) inclusion and exclusion criteria (Supplementary Material S1). Conflicts were resolved by a third reviewer with considerable research experience in asthma. Among papers reporting on the same trial, the studies providing the most extensive level of detail were retained.

Data extraction

For each study meeting the eligibility criteria, the following data were extracted: year of publication, country of origin, total number of participants in the trial, study and treatment duration, and inclusion and exclusion criteria. Extracted participant demographics included age, sex, weight, race, previous exacerbations, disease duration, smoking status, medication at study entry, and data regarding lung function parameters at the time of screening. All information was extracted by two independent reviewers, and conflicts were resolved by a third experienced reviewer. A Microsoft Excel template was used for data extraction.

Quality assessment

Both reviewers independently validated the methodological quality of each selected study using the Cochrane Collaboration risk-of-bias tool[27]. The risk-of-bias assessment considered selection bias, performance bias, detection bias, attrition bias, reporting bias, or any other possible type of bias identified. Studies were rated as "high," "low," or "unclear" risk-of-bias. Disagreements were resolved by discussion, and a third experienced reviewer was consulted where necessary.

Outcomes and interventions

The NMA considered clinically relevant efficacy outcomes, including exacerbation outcomes (severe, and moderate or severe), pre-dose FEV1, and asthma control questionnaire (ACQ-7) response rates, broadly in line with efficacy outcomes included in previous NMAs in this area[18–20]. Although the focus of the NMA was the comparison between BDP/FF/GLY and other triple therapies, to ensure network connectivity, the scope of the SLR and NMA included both triple and double therapies for patients with uncontrolled asthma (Table S1.1).

Assessment of between-study heterogeneity

Following the evidence identification and extraction, an NMA feasibility assessment was undertaken in line with Cope et al.[28] to assess whether a connected network can be produced for each outcome and evaluate whether the transitivity assumption is likely to hold. Specifically, studies were compared in terms of differences in effect-modifying PICOS characteristics such as the baseline characteristics of the enrolled populations (e.g., age, weight, baseline treatment proportion of smokers) and study designs (Table 1).

Statistical methods

NMA extends pairwise meta-analytic methods to enable the simultaneous comparison of multiple treatments and comparators that have been investigated across several studies in a single, coherent, analytic framework. Nowadays, NMA is routinely used to establish the relative efficacy of competing interventions and to inform treatment choices in health technology assessment and economic analyses[29].

Our modeling approach aligned with The National Institute for Health and Clinical Excellence Method guide[30]. A Poisson likelihood with log link was used for exacerbation rate outcomes, a normal likelihood with identity link for pre-dose FEV1 (L) at 52 (±3) weeks, and a binomial likelihood with logit link for ACQ-7 response at 52 (±3) weeks[30]. Both fixed-effects and random-effects models were fit to the data, with the latter accounting for heterogeneity, but not explaining it. Within-study correlations across relative effects pertaining to multiple arms were corrected for using multi-arm adjustments.

Analyses were conducted under a Bayesian framework adopting a Hamiltonian Monte Carlo approach, which was fitted using the *multinma* package v0.5.0[31] that implements Stan[32] through R (version 4.2.1 or higher)[33] via RStudio[34]. We ran four Markov chain Monte Carlo chains with different starting values. The initial 20,000 iterations (burn-in) were discarded, and inference was based on the subsequent 50,000 iterations. Uninformative priors were used throughout[30]. Model convergence was based on visual inspection of chain mixing, autocorrelation plots, inspection of divergent iterations, effective sample size, and the *R-hat* convergence diagnostic, which assesses Markov chain Monte Carlo chain mixing by comparing between- and within-chain estimates for the monitored parameters of interest[35]. Model selection was based on the posterior mean residual deviance and the deviance information criterion (DIC), with differences in DIC of three or more considered important[36].

Whenever the network comprised closed loops, the consistency of the direct and indirect evidence was assessed. Consistency and inconsistency models were compared based on DIC, and the posterior mean deviance contributions of the two models were plotted to identify loops where inconsistency may be present[37].

Results were provided as posterior estimates of the median relative treatment effects and associated 95% credible intervals. The probability of each treatment being ranked at each position was also calculated and

Study	Interventions/comparators (daily dose in µg)[a]	Study phase	Blinding	Treatment duration (weeks)	Baseline treatment	Included (observation)
Dahl et al., [71]	SALM/FF (100/500) FOR/BUD (24/800)	Not reported	Double-blind	24	1000–2000 µg/day of BDP or equivalent. Combination therapy was discontinued and replaced with ICS alone at least 4 weeks prior to study start.	Reported moderate-to-severe asthma exacerbations
Gessner et al.,[13]	IND/GLY/MF (150/50/80) IND/GLY/MF (150/50/160) SALM/FF + TIO (100/1000 + 5)	Phase III	Open-label	24	Medium or high doses of ICS/LABA	Reported change from baseline in pre-dose FEV1 (L) at 52 (± 3) weeks and asthma exacerbations
Kerstjens et al.,[14]	IND/GLY/MF (150/50/80) IND/GLY/MF (150/50/160) IND/MF (150/160) IND/MF (150/320) SALM/FF (100/1000)	Phase III	Double-blind	52	Medium or high doses of ICS/LABA	Reported all outcomes of interest
Lee et al.,[15]	FF/VI (100/25) FF/VI (200/25) FF/UMEC/VI (100/31.25/25) FF/UMEC/VI (100/62.5/25) FF/UMEC/VI (200/31.25/25) FF/UMEC/VI (200/62.5/25)	Phase III	Double-blind	52	ICS/LABA (> 250 µg/day FF propionate or equivalent)	Reported asthma exacerbations only
TRIGGER [16]	BDP/FOR/GLY (800/24/50) BDP/FOR (800/24) BDP/FOR + TIO (800/24 + 5)	Phase III	Double-blind	52	Double therapy only on high doses of ICS (> 1000 µg daily dose BDP non-extra-fine) in combination with LABA	Reported all outcomes of interest
TRIMARAN[16]	BDP/FOR/GLY (400/24/50) BDP/FOR (400/24)	Phase III	Double-blind	52	Medium doses of ICS in combination with LABA	Reported all outcomes of interest

Table 1. Characteristics of studies included in the network meta-analysis following feasibility assessment ($n = 6$). For each therapy combination, the daily dose in µg is provided in parenthesis. BDP, beclometasone dipropionate or beclometasone; BUD, budesonide; FEV1, forced expiratory volume in one second; FF, fluticasone; FOR, formoterol fumarate or formoterol; GLY, glycopyrronium bromide; ICS, inhaled corticosteroids; IND, indacaterol acetate; LABA, long-acting β2-agonist; MF, mometasone furoate or mometasone; SALM, salmeterol xinafoate or salmeterol; TIO, tiotropium; VI, vilanterol trifenatate or vilanterol; UMEC, umeclidinium.

visualized using rankograms. Surface under the cumulative ranking curve (SUCRA) values were reported, illustrating the overall ranking of each intervention with a higher SUCRA value indicating that a treatment is overall more likely to be better[38].

Results

Search results

A total of 5,110 records (3,799 during the 2019 initial SLR and 1,311 during the 2022 update) were identified (Fig. 1). We excluded 459 duplicate papers. Following title and abstract screening based on the inclusion and exclusion criteria, 326 articles qualified for full-text review. Of those, 269 full texts did not meet the inclusion criteria (Supplementary Material S1). Overall, among the 37 unique clinical studies (reported in 57 published articles) that were considered relevant and extracted in the SLR, four studies were precluded from the NMA feasibility assessment due to unclear dosing regimen.

Study and patient characteristics

The study characteristics of the 33 RCTs considered in the NMA feasibility assessment are provided in Supplementary Material S2.1. Among the relevant studies most were double-blind phase III, and no study allowed crossover. The duration of the studies ranged between two[39] and 52 weeks[14–16,40,41]. A total of 21,262 patients were reported in the included studies. Demographic variables demonstrated low heterogeneity between studies. Some differences were observed in terms of disease duration, the proportion of smokers, FEV1 reversibility, and use of asthma controller medications. Overall, the risk-of-bias was considered low across studies (Supplementary Material S3).

Feasibility assessment

The 33 studies considered in the feasibility assessment (Table S2.1) were assessed in terms of their comparability on effect-modifying characteristics and their potential to form connected treatment networks. The baseline exacerbation rate, an important effect modifier according to clinical experts and the literature[42], was generally balanced across studies. Also, studies were, in general, of good quality (Table S3.1).

Of the 33 studies included in the NMA feasibility assessment, one study did not report outcomes of interest[43], and 26 studies included patients receiving single ICS at baseline[39–41,44–66] (Table S2.1). However, single ICS is typically prescribed for patients at the earlier disease stages[1], which are associated with higher baseline exacerbation rates[67], and therefore clinical experts suggested that these studies should not be considered in the

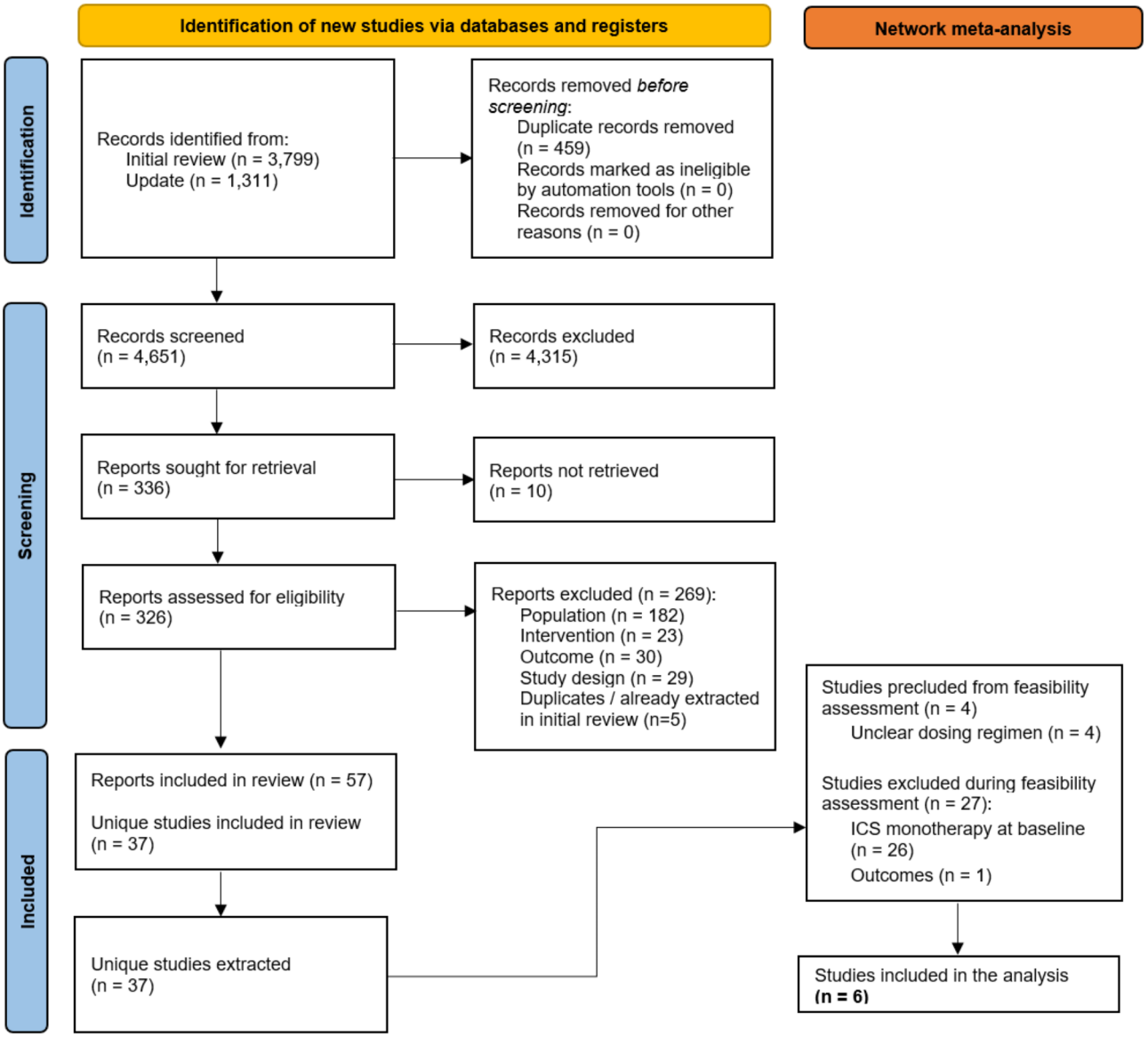

Fig. 1. Adapted PRISMA flow diagram of studies included in the systematic literature review and network meta-analysis.

NMA. To assist network connectivity and avoid unnecessarily uncertain estimates, no distinction was made among ICS/LABA treatments, and this assumption was validated by clinical experts. Where trials included a comparison of a triple therapy against its backbone double, other trial arms (that were used as the sole licensed therapy at the time of the trial conduct to establish meaningful comparisons) were excluded. The patient characteristics and key outcome definitions of the six studies included in the NMA are presented in Table S2.2.

Clinical feedback also indicated that patients on MD ICS/LABA may be at an earlier point in the treatment pathway because ICS dose escalation may be associated with an increased rate of AEs[68,69]. Hence, escalation to HD ICS should be carefully considered, as increasing the ICS dose often results in limited, non-proportional additional benefit, while it increases the risk of AEs, such as adrenal suppression[70]. The BDP/FOR/GLY clinical development program aligned with this practice and conducted separate trials for patients with inadequately controlled asthma on MD ICS/LABA (TRIMARAN) and patients with inadequately controlled asthma on high-dose ICS/LABA (TRIGGER). Therefore, we constructed two separate treatment networks based on whether patients were previously uncontrolled with MD dual therapy or HD dual therapy.

The judgments applied to construct the treatment networks for this analysis are presented in Supplementary Material S4, and the full list of studies included in each network, conditional on outcome availability, is provided in Table 1. Note that "/" denotes a closed combination, while "+" an open combination (i.e., separate inhalers).

Network meta-analysis results

Although both fixed and random effects models were run, only fixed effects are presented because no network included more than four studies, and therefore the between-study heterogeneity is unlikely to be properly estimated without the use of informative priors. The results of the meta-analysis between BDP/FF/GLY and other triple therapies are presented in the form of forest plots in Figs. 2 and 3, while the full results are available in Supplementary Material S5. Network plots for the MD and HD networks are provided, respectively, in Fig. S5.1 and Fig. S5.2, league tables in Table S5.1 and Table S5.2, absolute rate estimates for severe exacerbation and moderate-to-severe exacerbations in Table S5.3 and Table S5.4, SUCRA values in Table S5.5, rankograms in Figs. S5.3 –S5.10, and deviance contribution plots in Fig. S5.11 and Fig. S5.12, along with DIC values in Table S5.6. No evidence of inconsistency was detected in any network.

Patients with inadequately controlled asthma on MD ICS/LABA

Severe exacerbations

The treatment network included three studies evaluating five treatments (three triple therapies). MD BDP/FOR/GLY was associated with statistically significant improvement over MD FF/UMEC/VI (RR [95% CrI]: 0.65 [0.49, 0.89]), and a similar effect to MD IND/GLY/MF.

Moderate or severe asthma exacerbations

Four studies evaluated five treatments (three triple therapies), where a similar effect was estimated in the comparison of MD BDP/FOR/GLY over MD FF/UMEC/VI, and MD IND/GLY/MF.

Pre-dose FEV1 (L) at 52 (± 3) weeks

Two studies assessed four treatments overall (two triple therapies). No statistically significant difference was estimated for MD BDP/FOR/GLY against MD IND/GLY/MF.

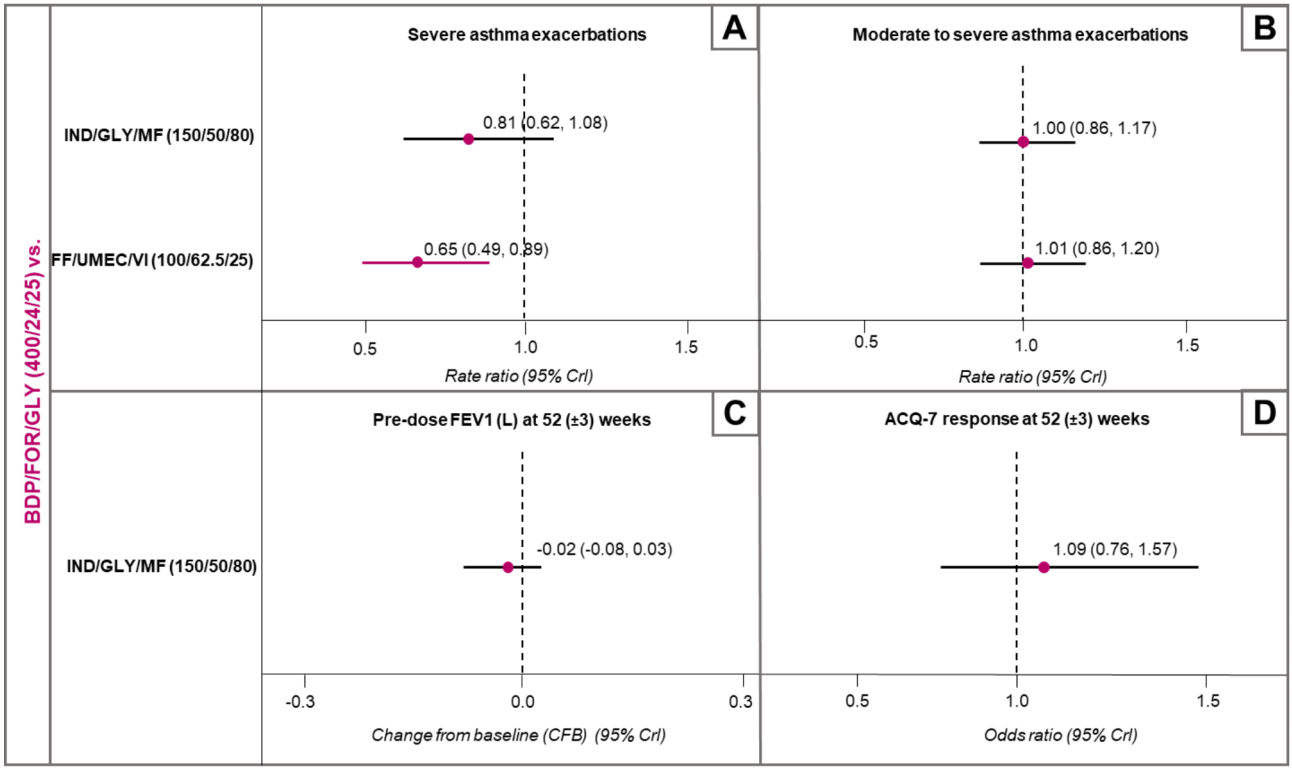

Fig. 2. Forest plots of patients with inadequately controlled asthma on HD ICS/LABA. Forest plots of relative efficacy of BDP/FOR/GLY (400/24/25; daily dose in µg) in patients with inadequately controlled asthma on MD ICS/LABA in the analysis. (**A**) severe asthma exacerbation rates (**B**) moderate-to-severe asthma exacerbation rates (**C**) pre-dose FEV1 (L) at 52 (± 3) weeks (**D**) ACQ-7 response at 52 (± 3) weeks BDP, beclometasone dipropionate or beclometasone; CFB, change from baseline; CrI, credible interval; FEV1, forced expiratory volume in one second; FF, fluticasone; FOR, formoterol fumarate or formoterol; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol acetate; LABA, long-acting β2-agonist; MD, medium-dose; MF, mometasone furoate or mometasone; UMEC, umeclidinium; VI, vilanterol trifenatate or vilanterol.

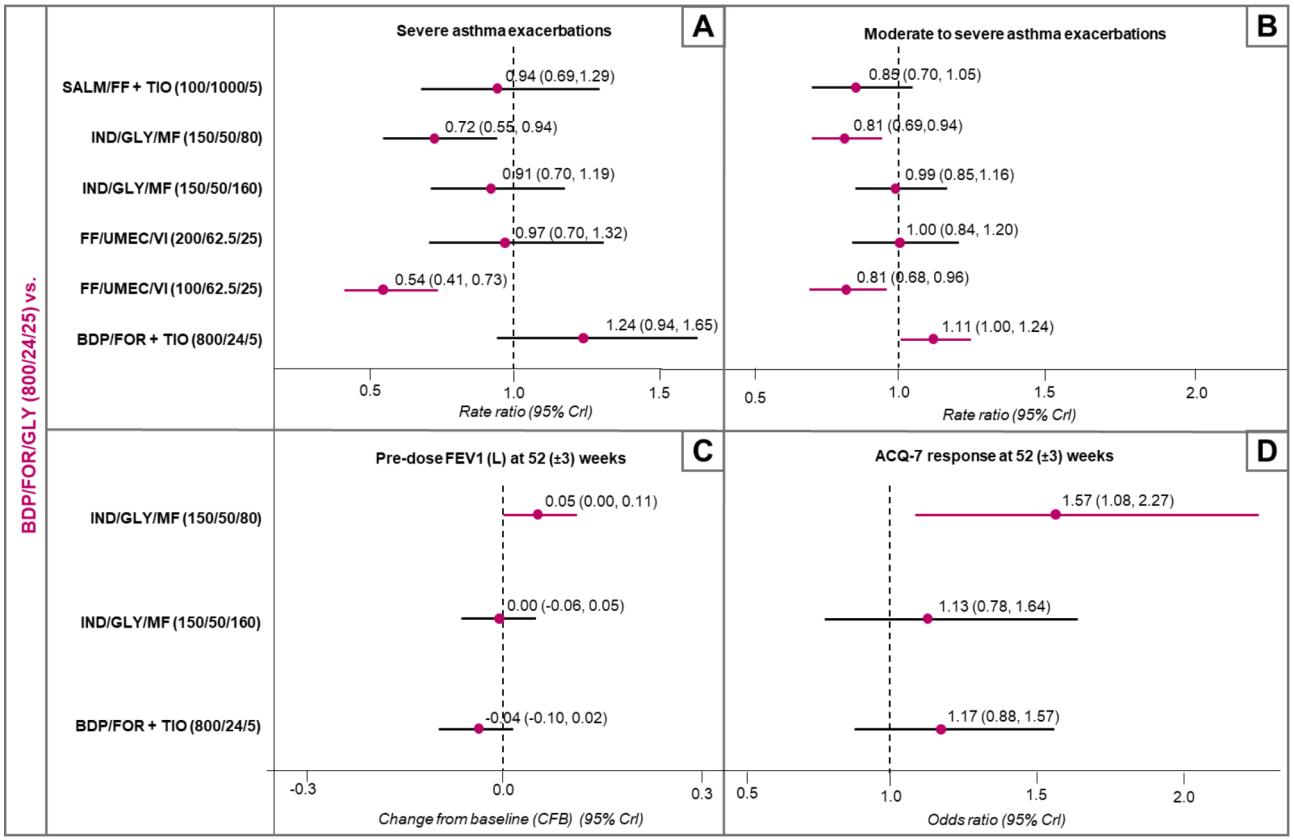

Fig. 3. Forest plots of patients with inadequately controlled asthma on HD ICS/LABA. Forest plots of relative efficacy of BDP/FOR/GLY (800/24/25; daily dose in μg) in patients with inadequately controlled asthma on HD ICS/LABA in the analysis of: (**A**) severe asthma exacerbation rates (**B**) moderate-to-severe asthma exacerbation rates (**C**) pre-dose FEV1 (L) at 52 (± 3) weeks (**D**) ACQ-7 response at 52 (± 3) weeks BDP, beclometasone dipropionate or beclometasone; CFB, change from baseline; CrI, credible interval; FEV1, forced expiratory volume in one second; FF, fluticasone; FOR, formoterol fumarate or formoterol; GLY, glycopyrronium bromide; HD, high-dose; ICS, inhaled corticosteroid; IND, indacaterol acetate; LABA, long-acting β2-agonist; MF, mometasone furoate or mometasone; SALM, salmeterol xinafoate or salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol trifenatate or vilanterol.

ACQ-7 response at 52 (± 3) weeks

Two studies evaluated four treatments (two triple therapies), and no statistically significant differences were observed. However, the results numerically favored MD BDP/FOR/GLY over MD IND/GLY/MF.

Patients with inadequately controlled asthma on HD ICS/LABA

Severe exacerbations

The treatment network consisted of four multi-arm studies evaluating nine treatments (seven triple therapies). HD BDP/FOR/GLY was significantly better than MD IND/GLY/MF (RR [95% CrI]: 0.72 [0.55, 0.94]), and MD FF/UMEC/VI (RR [95% CrI]: 0.54 [0.41, 0.73]). HD BDP/FOR/GLY was associated with a numerical benefit against HD IND/GLY/MF, salmeterol/fluticasone + tiotropium (SALM/FF + TIO), and HD FF/UMEC/VI and numerical inferiority against HD beclometasone/formoterol + tiotropium (BDP/FOR + TIO).

Moderate or severe asthma exacerbations

Four studies assessing nine treatments were synthesized, of which seven were triple therapies. The results indicated a significantly reduced risk of moderate or severe asthma exacerbations for HD BDP/FOR/GLY over MD IND/GLY/MF (RR [95% CrI]: 0.81 [0.69, 0.94]), and MD FF/UMEC/VI (RR [95% CrI]: 0.81 [0.68, 0.96]), and a similar effect compared to HD IND/GLY/MF and SALM/FF + TIO. HD BDP/FOR/GLY was similar to HD FF/UMEC/VI, and numerically less effective than HD BDP/FOR + TIO.

Pre-dose FEV1 (L) at 52 (± 3) weeks

Two studies evaluating six treatments (four triple therapies) were analyzed. HD BDP/FOR/GLY was associated with a similar effect to MD IND/GLY/MF and HD IND/GLY/MF, while the results were numerically less effective than HD BDP/FOR + TIO.

ACQ-7 response at 52 (± 3) weeks
The network included two multi-arm studies evaluating six treatments (four triple therapies). HD BDP/FOR/GLY was more effective than MD IND/GLY/MF (OR [95% CrI]: 1.57 [1.08, 2.27]), and similar to HD IND/GLY/MF, and HD BDP/FOR + TIO.

Discussion

Despite the breadth of existing therapeutic options, patients with moderate or severe asthma often remain uncontrolled. Current asthma guidelines suggest treatment combinations and dose escalations based on the severity of the disease and control of symptoms[1]. However, ICS dose escalation may be associated with an increased rate of systemic AEs[68]. Hence, ICS dose escalation should be thoroughly considered, as maintaining the same ICS dose and adding a controller inhaler (e.g., LAMA) to the treatment plan might be more beneficial to the patient[72,73]. Recent evidence suggests that SITTs (ICS/LABA/LAMA) may be more effective than dual therapies for patients on MD and/or HD ICS/LABA whose asthma remains uncontrolled with MD or HD ICS/LABA[13–16]. This is particularly true in certain phenotypes, where adding LAMA to the ICS/LABA treatment appears more advantageous than an increase in the ICS dose[72,73].

This study aimed to identify existing evidence on the efficacy of triple versus triple or double combination therapies in adult patients with uncontrolled asthma and to produce comparative efficacy evidence for extra-fine BDP/FOR/GLY versus other triple therapies, particularly SITTs. A total of 37 relevant RCTs were identified, 6 of which were included in the NMA. In line with the BDP/FOR/GLY clinical trial programs, separate networks were constructed for patients whose asthma remained uncontrolled with MD and HD ICS. However, RCTs of other triple therapies beyond BDP/FOR/GLY did not separate patients according to baseline ICS dosage, and, thus, randomized patients were mixed in terms of baseline ICS/LABA dosage.

In patients with uncontrolled asthma on MD ICS/LABA at baseline, MD BDP/FOR/GLY was superior to MD FF/UMEC/VI in terms of severe exacerbations. No statistically significant results were obtained for pre-dose FEV1 or ACQ-7. In patients with uncontrolled asthma on HD ICS/LABA, HD BDP/FOR/GLY was superior to both HD FF/UMEC/VI and MD IND/GLY/MF across all outcomes reported in the corresponding RCTs. HD BDP/FOR/GLY showed favorable trends compared to other HD triple therapies, apart from the open triple based on HD BDP/FOR + TIO, which was numerically better than HD BDP/FOR/GLY. However, this comparison has limitations, as it was informed only by TRIGGER, in which the HD BDP/FOR + TIO comparator arm was open-label and enrolled half of the sample size of the other two double-blind arms. Hence, the results should be interpreted carefully. Nevertheless, the use of a SITT ensures the consistent delivery of all three components of treatment (ICS/LABA/LAMA) via one device and could potentially optimize both adherence to and persistence of treatment[16,74,75], the lack of which may lead to worsening of asthma symptoms[76].

Our study aimed to shed light on the comparative efficacy of extra-fine BDP/GLY/FOR versus other triple therapies, and our results, where comparable, were largely consistent with previous NMAs[19,20]. While earlier analyses considered a single network of evidence[18–20], our analysis refined the evidence base to avoid introducing heterogeneity due to differences in patients' clinical characteristics. Two separate networks were constructed to account for differences between studies on the baseline dosage of ICS/LABA, which may signal different asthma severity and disease phenotypes. Moreover, differently from Oba et al.[20], our analysis only included studies where patients at baseline received ICS/LABA, because treatment with ICS alone may relate to less severe patients and an earlier treatment step[1]. Finally, we did not limit our search to studies assessing SITT[19] or to a specific year range[18,20].

Our study has some limitations. First, no study assessed SITTs head-to-head, and therefore, for most outcomes, comparative efficacy estimates between SITT are based on indirect comparisons. In addition, most SITTs were only assessed in a single trial, and no network included more than four studies in total, potentially resulting in increased uncertainty around relative effects and in some cases inability to produce statistically significant conclusions. Second, some differences were detected across studies in terms of study design, disease duration, smoker percentage, FEV1 reversibility, prior exacerbation rates, and asthma controller medication prior screening. The lack of a uniform definition across trials for asthma severity and criteria for classification into moderate and severe exacerbations (Table S2.2) might have resulted in additional between-study heterogeneity and bias of unclear magnitude or direction. Even so, due to pragmatic considerations, random effects models were not preferred as the small number of studies in the networks would prevent the appropriate estimation of heterogeneity. Where closed loops were identified, no evidence of inconsistency was detected. Finally, no subgroup analyses were conducted because trials generally did not consistently report results for all the endpoints included in this NMA, and therefore no conclusions could be drawn for populations that stand to benefit more from particular triple therapies.

Overall, this analysis showed either superiority or a trend for improvement associated with extra-fine HD BDP/FOR/GLY (i.e., statistically significant and non-statistically significant improvements), in terms of reducing the rate of severe, and moderate and severe exacerbations, while a similar trend was observed for extra-fine MD BDP/FOR/GLY, in terms of reducing severe exacerbations. This might be attributed to the extra-fine formulation, resulting in improved distribution into both large and small airways[77], and is likely critical because patients with considerable dysfunction of the small airways tend to be at an increased risk of exacerbations and poorer asthma control[78]. However, further research is required to evaluate this hypothesis.

Conclusion

Overall, MD and HD BDP/FOR/GLY are associated with either statistically significant benefit or a trend for improvement in terms of reducing the rate of severe, and moderate to severe exacerbations compared to relevant

SITT comparators. Further research and sub-group analyses are required to identify the phenotypes of patients that stand to benefit more from the various treatment options.

Data availability

All data generated or analyzed during this study are included in this published article (and its Supplementary information files).

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Author contributions
IV, GFN, DT, IB, and AM contributed to the conception of the study and the methodology. GFN, DT, and IB curated the data extracted from the literature. IB performed the data analysis. GFN, DT, and IB constructed and designed the manuscript. IV, NS, FB, GFN, DT, IB, AP, and AM interpreted the results. NS, FB, IV, AP, and AM critically reviewed the manuscript and provided constructive feedback to its design and layout. All the authors agreed to the manuscript's final version. IV submitted the study and has taken responsibility for the overall content as guarantor.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
Ethics approval was not obtained because this study did not involve human or animal subjects.

Consent to publish
Not applicable.

Human and animal rights
Patients and members of the public were not specifically involved in the design, conduct, and reporting of this research. Nevertheless, the research questions answered in this study is of broad public health and decision-making interest, and results will be disseminated to the general public through websites, public engagement events, and conferences.

Additional information
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