Early View

Original article

**Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies**

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Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies

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Take home message

Triple combination therapy by adding either a LAMA to ICS/LABA FDC or escalating ICS on a background of ICS/LABA/LAMA FDC may reduce severe exacerbations and improve lung function; adding a LAMA along with escalating ICS provides incremental effects.
Abstract
Conflicting evidence is currently available concerning the impact on asthma exacerbation of triple inhaled corticosteroid (ICS), long-acting $\beta_2$-adrenoceptor agonist (LABA), and long-acting muscarinic receptor antagonist (LAMA) fixed-dose combination (FDC). Since meta-analyses allow settling controversies of apparently inconsistent results, we performed a network meta-analysis of Phase III randomized controlled trials including 9535 patients to assess the effect of ICS/LABA/LAMA combinations in uncontrolled asthma. Triple combination therapies with an ICS administered at high dose (HD) were more effective (P<0.05) than medium dose (MD) ICS/LABA/LAMA FDC and both MD and HD ICS/LABA FDCs against moderate to severe exacerbation (relative risk [RR] from 0.61 to 0.80) and increasing trough forced expiratory volume in the 1st second (mL from +33 to +114). Triple combination therapies including HD ICS were superior (P<0.05) than MD ICS/LABA/LAMA FDC in preventing severe exacerbation (RR from 0.46 to 0.65), but not with respect to moderate exacerbation (P>0.05). Triple combination therapies were equally effective on asthma control, with no safety concerns. This quantitative synthesis suggests that ICS/LABA/LAMA FDCs are effective and safe in uncontrolled asthma, and that the dose of ICS in the combination represents the discriminating factor to treat patients with a history of moderate or severe exacerbation.

Keywords
Asthma; exacerbation; network meta-analysis; triple combination.
**Introduction**

Adding tiotropium bromide (TIO) to dual inhaled corticosteroid (ICS)/long-acting $\beta_2$-agonist (LABA) fixed-dose combination (FDC) is currently recommended to treat asthmatic patients suffering from the most severe forms of disease [1]. Nevertheless, conflicting data are currently available concerning the real efficacy of triple ICS/LABA/long-acting muscarinic receptor antagonist (LAMA) FDCs in asthma, especially with respect to their effect against the risk of exacerbation in symptomatic patients with uncontrolled asthma [2-4].

Data from well performed meta-analyses of pivotal studies may reach the greater level of evidence [5] and, along with other numerous recognized advantages, meta-analyses may give the opportunity to settle controversies arising from apparently conflicting studies [6]. Moreover, the Bayesian network approach, the so-called network meta-analysis, not only permits to compare the effect estimates of specific outcomes resulting from different medications, but it offers also suitable information for clinicians in the form of treatment rankings, that can be graphically summarized by the surface under the cumulative ranking curve analysis (SUCRA) [7, 8].

Therefore, we have performed an unbiased network meta-analysis of Phase III randomized controlled trials (RCTs) in order to compare and rank the efficacy and safety profile of triple ICS/LABA/LAMA combination therapies in patients with uncontrolled asthma with respect to the risk of exacerbation and lung function. We also investigated the impact of triple therapies on asthma control and serious adverse events (SAEs).

**Materials and methods**

Detailed methods are reported in the Supplementary Data.

**Search strategy and study eligibility**

This meta-analysis was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P,
Protocol ID: CRD42020211870) [9]. The flow diagram and network nodes are shown in Figure 1A and B, and Table S1 reports the PRISMA-P checklist [9].

A comprehensive literature search was performed for Phase III RCTs evaluating the impact of triple combination therapy for the treatment of asthma. As an example, Table S2 reports the literature search terms used for OVID MEDLINE and Appendix 1 shows the summary text of the identified records.

**Study selection**

Phase III RCTs that enrolled asthmatic patients, lasting $\geq 24$ weeks, and that included at least one arm assessing the effect of any triple combination therapy in asthma were selected.

**Data extraction**

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [10]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen’s Kappa score, as previously described [11].

**Endpoints**

The co-primary endpoints were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe asthma exacerbation and the change from baseline in trough forced expiratory volume in the 1st second (FEV$_1$).

The secondary efficacy endpoint included the comparison across the triple combination therapies and comparators with respect to the change from baseline in asthma control questionnaire (ACQ) score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular (CV) adverse events (AEs).

**Quality of studies, risk bias, and evidence profile**

The summary of the risk of bias for each included RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [12] and Jadad score [13]. The weighted assessment of the overall risk of bias was analyzed via the Cochrane RoB 2 [12], along with the normalized consistency/inconsistency analysis [14]. The
quality of evidence was assessed for the primary endpoint via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [15].

**Data synthesis and analysis**

A network meta-analysis was performed via full Bayesian random-effect model to compare the impact of the different triple combination therapies and comparators in asthmatic patients. Subset and sensitivity analyses were performed in agreement with average patients’ characteristics at baseline. Results are expressed as relative effect (RE) and 95% credible interval (95%CrI) or 95% confidence interval (95%CI). The SUCRA was calculated for both the co-primary and secondary endpoints [16]; the SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [14]. The statistical significance was assessed for P<0.05.

**Results**

**Study characteristics**

Data obtained from 9535 asthmatic patients were selected from 5 Phase III RCTs (Table S3). All five studies were performed in symptomatic patients suffering from uncontrolled asthma [17-20].

In agreement with the search strategy and study selection criteria, the investigated ICS/LABA/LAMA FDCs included beclomethasone dipropionate (BDP)/formoterol fumarate (FOR)/glycopyrronium bromide (GLY) in 2 studies [20], momethasone furoate (MF)/indacaterol (IND)/glycopyrronium bromide (GLY) in 2 studies, and fluticasone furoate (FF)/vilanterol (VI)/umeclidinium (UMEC) in 1 study [17]. The investigated free combination ICS/LABA FDC + TIO included BDP/FOR + TIO in 1 study [20] and FP/SAL + TIO in 1 study [19].

The active comparators were the ICS/LABA FDCs BDP/FOR, FF/VI, MF/IND, and FP/SAL.

The definition of moderate to severe asthma exacerbation and the level of ICS doses are shown in Table S4 and S5 of the supplement, respectively. The
inter- and intra-rater reliability for data abstraction was generally excellent (Cohen’s Kappa >0.90).

Further study characteristics are reported in the Supplementary Data.

**Co-primary endpoints**

**Risk of exacerbation**

High dose (HD) ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO were equally effective (P>0.05) in preventing the risk of moderate to severe asthma exacerbation. HD ICS/LABA/LAMA FDC significantly (P<0.05) reduced the risk of exacerbation compared to medium dose (MD) ICS/LABA/LAMA FDC and MD ICS/LABA FDC, whereas a trend toward significance (P=0.05) was detected vs. HD ICS/LABA FDC. Detailed RR and 95%CI values across the investigated combinations are reported in Table 1, with data graphically reported in Figure 2A as forest plot.

The SUCRA analysis indicated that both HD ICS/LABA FDC + TIO and HD ICS/LABA/LAMA FDC were the most effective treatments in reducing the risk of moderate or severe asthma exacerbation (first quartile), followed by HD ICS/LABA FDC (borderline second/third quartile), MD ICS/LABA/LAMA FDC (third quartile), and MD ICS/LABA FDC (fourth quartile) (Figure 3A).

The person-based NNT per year concerning the prevention of moderate to severe asthma exacerbation was 40.29 for HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC, 32.90 vs. HD ICS/LABA FDC, and 12.08 vs. MD ICS/LABA FDC. Considering MD ICS/LABA/LAMA FDC, the person-based NNT per year was 179.29 vs. HD ICS/LABA FDC and 17.25 vs. MD ICS/LABA FDC. The person-based NNT analysis was performed only for FDCs because the data concerning HD ICS/LABA FDC + TIO were spurious since the ARGON study [19] did not provide data suitable to be included in the NNT analysis. Details on the person-based NNT per year on moderate to severe asthma exacerbation are shown in Table 2.

The subset analysis performed in agreement with the severity of exacerbation reported an overall superiority of both HD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO over both MD ICS/LABA/LAMA FDC, HD ICS/LABA FDC, and MD ICS/LABA FDC with respect to the protection against the risk of
severe asthma exacerbation. Conversely, MD and HD ICS/LABA/LAMA FDC were superior only to MD ICS/LABA FDC, and not to HD ICS/LABA FDC, in reducing the risk of moderate asthma exacerbation. No significant difference (P>0.05) was recorded across all the triple combination therapies in preventing the risk of moderate asthma exacerbation (Table 3). Another subset analysis performed in agreement with the different doses of UMEC included in the FDCs of the CAPTAIN RCT [17] did not result in significant (P>0.05) differences in the risk of moderate to severe asthma exacerbation, compared to the overall network meta-analysis (data not shown).

A sensitivity analysis was carried out by excluding the CAPTAIN RCT [17] from the Bayesian network, since this was the only study that included a population of asthmatic patients reporting less than 1 exacerbation in the previous year (average rate =0.8). Conversely, all the other investigated RCTs [18-20] enrolled asthmatic patients reporting more than 1 exacerbation in the previous year (average rate ≥1.2). Results of the sensitivity analysis (Table S6) were not significantly (P>0.05) different when compared with those of the overall analysis, although the level of significance between some triple combination therapies and some comparators changed (i.e. HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO vs. HD ICS/LABA FDC). In any case, the sensitivity analysis carried out specifically on either moderate or severe exacerbation produced results generally consistent (P>0.05) with those of the overall subset analysis (Table S7).

Trough FEV₁

The improvement in trough FEV₁ was not different between HD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO, with both the treatments being significantly (P<0.05) more effective than MD and HD ICS/LABA FDCs. HD ICS/LABA/LAMA FDC was also significantly more effective than MD ICS/LABA/LAMA FDC on trough FEV₁, and in turn MD ICS/LABA/LAMA FDC was significantly (P<0.05) superior than both HD and MD ICS/LABA FDCs. Detailed comparisons across the investigated combinations on trough FEV₁ are reported in Table 1 and Figure 2B.
The SUCRA analysis showed that HD ICS/LABA/LAMA FDC was the most effective treatment improving trough FEV₁, followed by HD ICS/LABA FDC + TIO (borderline first/second quartile), MD ICS/LABA/LAMA FDC (second quartile), HD ICS/LABA FDC (borderline third/fourth quartile), and MD ICS/LABA FDC (fourth quartile) (Figure 3B).

The subset analysis performed in agreement with the different doses of UMEC included in the FDCs of the CAPTAIN RCT [17] did not result in significant (P>0.05) differences in trough FEV₁, compared to the overall network meta-analysis (data not shown).

The sensitivity analysis (Table S6) carried out by excluding the CAPTAIN RCT [17] provided results not significantly (P>0.05) different compared with those of the overall Bayesian network. Only the level of significance between HD ICS/LABA/LAMA FDC and MD ICS/LABA/LAMA FDC changed compared with the overall analysis.

**Adding a LAMA and/or escalate ICS in FDC**

Adding a LAMA to either MD or HD ICS/LABA FDC reduced the risk of moderate to severe asthma exacerbation (risk difference [RD]: -0.21 95%CrI -0.35 - -0.06 and -0.17 95%CrI -0.31 – 0, respectively; Figure 4A) and increased trough FEV₁ (delta effect, mL: +81 95%CrI 53 – 111 and +91 95%CrI 63 - 121, respectively; Figure 4B), as well as escalating the dose of ICS on a background of MD ICS/LABA/LAMA FDC (RD: -0.20 95%CrI -0.34 - -0.05, Figure 4A; delta effect, mL: +33 95%CrI 5 – 62, Figure 4B). Adding a LAMA along with escalating the dose of ICS further prevented the risk of moderate to severe asthma exacerbation (RD -0.25 95%CrI -0.38 - -0.09, Figure 4A) and improved trough FEV₁ (delta effect, mL: +114 95%CrI 85 – 145, Figure 4B).

**Secondary endpoints**

Detailed comparisons across the investigated combinations with respect to the secondary endpoints are reported in Table 1.

**ACQ**
Both MD and HD ICS/LABA/LAMA FDCs and HD ICS/LABA FDC + TIO were equally (P>0.05) effective in improving ACQ, although a trend toward significance (P=0.05) was detected for HD ICS/LABA/LAMA vs. MD ICS/LABA/LAMA FDC (Table 1).

Safety

No significant (P>0.05) difference was detected across the investigated combinations concerning the risk of SAEs, pneumonia, and serious CV AEs (Table 1).

Risk of bias and quality of evidence

The weighted plot for the assessment of the overall risk of bias by domains is shown in Figure S1, and the traffic light plot for the assessment of each included RCT is reported in Figure S2. All Phase III RCTs had a low risk of bias for the randomization process (5 [100.0%]), missing outcome data (5 [100.0%]), and selection of the reported results (5 [100.0%]). Three RCTs (60.0%) had some concerns in the domain of deviations from intended intervention and measurement of the outcomes.

All the studies (100.0%) included in this network meta-analysis were ranked as being of medium- to high-quality in agreement with Jadad score (Table S3).

The normalized consistency/inconsistency analysis showed that all points fit adequately with the line of equality (overall goodness of fit: R² 0.961; slope 0.993, 95%CI 0.927 – 1.058), indicating that this network meta-analysis was not affected by significant bias with respect to co-primary endpoints (Figure S3A and B). The lack of bias in the overall Bayesian network was further confirmed by the absence of significant (P>0.05) inconsistency factors when the investigated triple combination therapies and active treatments were compared directly or indirectly.

However, a potential source of bias can be related with the fact that the definition of moderate and severe asthma exacerbation was not uniform among the investigated studies [17-20]. The impact of exacerbation frequency in the previous year on the co-primary outcomes was investigated via sensitivity analysis, whose results are shown in Table S6 and S7.
Overall, the assessment of the quality of evidence carried out via the GRADE system reported a general high-quality of evidence (++++) for the results concerning the comparison across the investigated triple combination therapies with respect to the risk of moderate to severe asthma exacerbation and trough FEV₁. Details on the quality of evidence for each specific comparison are shown in Table 1.

**Discussion**

The overall results of this network meta-analysis provide the high-quality evidence that triple combination therapies including an ICS administered at HD have greater beneficial impact than MD ICS/LABA/LAMA FDC and both MD and HD ICS/LABA FDCs in reducing the risk of moderate to severe exacerbation and improving trough FEV₁ in patients suffering from uncontrolled asthma, regardless of whether the monocomponents were combined in the formulation as FDC or free combination.

Such a superiority on the risk of exacerbation of triple combinations including an ICS at HD was further confirmed by the NNT analysis. In fact, while ≈40 patients had to be treated for one year with HD ICS/LABA/LAMA FDC to prevent one moderate or severe asthma exacerbation compared to MD ICS/LABA/LAMA FDC, the NNT was ≈33 and only ≈12 when compared to HD and MD ICS/LABA FDCs, respectively. Unexpectedly, the treatment with MD ICS/LABA/LAMA FDC resulted in a clinically appreciable NNT value of ≈17 when compared to MD ICS/LABA FDC, but not vs. HD ICS/LABA FDC as the NNT value was ≈179. Since Kaplan-Meyer curves were not available for all the studies that included free combinations of HD ICS/LABA FDC + TIO [19], the available data were spurious and not suitable to adequately assess the NNT of this triple combination. In any case, looking at the specific RR of triple combinations including HD ICS, we can postulate that the NNT values of HD ICS/LABA FDC + TIO could be similar to that of HD ICS/LABA/LAMA FDC.

Overall, the superiority of triple combination therapies with an ICS at HD over MD ICS/LABA/LAMA FDC, and of MD ICS/LABA/LAMA FDC over MD and HD ICS/LABA FDC, was confirmed in the subset analysis on severe asthma.
exacerbations. Conversely, all the combinations, excluded MD ICS/LABA FDC, were equally effective in reducing the risk of moderate asthma exacerbation. These findings suggest that triple combinations including an ICS administered at HD may represent the first treatment choice in patients with a history of severe asthma exacerbation, whereas in those patients with a history of moderate asthma exacerbation either MD ICS/LABA/LAMA FDC or HD ICS/LABA FDC, but not MD ICS/LABA FDC, may be used as first line treatment.

Despite the unpredictable nature of asthma exacerbations regardless of disease severity, recent evidence indicates that the past history and severity of exacerbations in the year prior may predict the risk and severity of future asthma exacerbations [21]. In this respect, the results of the subset analysis on exacerbation severity may provide the rationale for a tailored therapy based on the severity of exacerbation that each patient experienced in the previous year, thus leading to the optimization of the dose of ICS and the number of bronchodilators included in the FDC.

Concerning the secondary endpoints investigated in this network meta-analysis, triple combination therapies were equally effective in improving ACQ, and no safety concerns resulted with respect of the risk of SAEs, pneumonia, and serious CV AEs.

Indeed, the studies included in this network meta-analysis enrolled symptomatic patients with uncontrolled asthma [17-20], for which the current Global Initiative for Asthma (GINA) document [1] suggests using MD ICS/LABA FDC at Step 4 and HD ICS/LABA plus either TIO or biologic therapy depending on the phenotypic assessment at Step 5 as preferred controller therapies to control symptoms and prevent exacerbations. Furthermore, GINA [1] recommends HD ICS or add-on TIO at Step 4 as alternative controller option.

Clearly, the evidence raised by this quantitative synthesis provides new horizon for the treatment of severe asthma, in which poorly controlled symptomatic patients could be effectively treated with triple combination therapies including different doses of an ICS according with the severity of
previous exacerbations. The recent approval of the first once-daily single inhaler triple therapy for the treatment of asthma by the Food and Drug Administration (FDA) [22] and the current data resulting from the studies included in this network meta-analysis [17-20] support the clinical benefit of adding a LAMA to ICS/LABA, an effect of class not related with a specific antimuscarinic agent. In the light of this evidence, it is expected that the next iteration of asthma recommendations and guidelines will include also ICS/LABA/LAMA FDCs as effective pharmacological strategies for symptom control and risk reduction. Moreover, and not less important, this meta-analysis allows us to clear the assumption that in the treatment of uncontrolled asthma a LAMA should be combined only with an ICS administered at HD, as well as a LABA, because MD ICS/LABA/LAMA FDC was effective on both symptoms and moderate asthma exacerbations.

The limitations of this study are related with the intrinsic characteristics of the Bayesian network approach [23-25], mainly due to the indirect comparison across treatments and to the fact that only 5 studies [17-20] were included in the quantitative synthesis. However, as shown in Figure 1B, the resulting network included several direct comparisons across the investigated treatments, leading to solid network loops also in the subset analyses carried out in more homogenous asthmatic populations. Therefore, also considering that data from a large number of patients (>9500 subjects) were analysed, the resulting effect estimates were free from any within- and across-studies risk of bias, at least for the co-primary endpoints.

Furthermore, as correctly stated by Mauger and Apter [26], while some degree of variation across study populations could be acceptable in a pairwise meta-analysis, this can lead to biased results in a network meta-analysis. Thus, considering that four [18-20] of the five studies included in the Bayesian network enrolled frequent exacerbators, whereas only the CAPTAIN study [17] enrolled patients reporting less than 1 exacerbation in the previous year, we performed a sensitivity analysis by considering exclusively those studies in which populations of asthmatic patients with frequent exacerbations were investigated. Considering also the severity of exacerbation, the sensitivity analysis basically confirmed the main findings of the overall analysis,
indicating that the results are robust. The small changes in the level of significance detected in the sensitivity analysis could be due by the fact that in the overall analysis some of the 95%CrIs were lying close to the line of equality, thus the reduction in the study population due to the exclusion of the CAPTAIN study [17] changed the 95%CrIs with no relevant modification of the effect estimates. Interestingly, in the sensitivity analysis we found greater consistency in the level of statistical significance between the risk of moderate to severe exacerbation and trough FEV1 than in the overall analysis. This evidence corroborates the hypothesis that exacerbation-prone asthma may be a specific phenotype with implications for the targeting of exacerbation prevention strategies along with lung function improvement [27].

Certainly, the CAPTAIN study [17] also provided further important information concerning the potential confounder of disparate study populations. Specifically, Lee and colleagues [17] demonstrated that increasing the ICS dose resulted in improved outcomes among the patients with high type 2 inflammatory biomarkers. On the other hand, in patients with low type 2 inflammatory biomarkers the increase in ICS dose provided no further disease improvement, while adding a LAMA was efficacious. This is an important finding supporting an alternative approach by adding a LAMA instead of escalating the dose of ICS in type 2 low asthma.

International recommendations and guidelines [1, 28] provide general definitions of asthma exacerbation, however, despite the attempt to uniform the definition of asthma exacerbation [29, 30], to date there is no consensus on a standardized definition of moderate and severe asthma exacerbation [31-33]. Such a clinical unmet need led to the last intrinsic limitation of this network meta-analysis: apart from the TRIMARAN and TRIGGER RCTs [20], there was not consistence among the investigated studies in the definition of either moderate or severe asthma exacerbation. Unfortunately, this is a limitation that cannot be solved by a sensitivity analysis and that may potentially introduce some unquantifiable bias in the exacerbation outcome.

Concluding, both ICS/LABA/LAMA FDC and free combination of TIO added to ICS/LABA FDC are effective and safe therapeutic strategies in patients suffering from uncontrolled asthma, with the level of the ICS dose...
representing the discriminating factor to treat patients with a history of moderate or severe exacerbation. Furthermore, here we provide the clinical evidence that triple FDCs by adding either a LAMA or increase ICS dose on a background of ICS/LABA/LAMA FDC may reduce the risk of severe exacerbation and improve lung function, and that adding a LAMA along with escalating ICS provides incremental effects. Indeed, the evidence raised by this quantitative synthesis may help to solve the inconsistencies across the primary publications [17-20] with respect to the beneficial impact of triple combination therapy against asthma exacerbation. However, there remains the question concerning the correct positioning of triple combination therapy in the GINA stepwise approach for adjusting treatment for individual patient needs [1]. In this respect, MD and HD ICS/LABA/LAMA FDCs should be tested in well-designed Phase III RCTs enrolling separately asthmatic patients at Step 4 and 5 in order to guide clinicians to correctly practice personalized medicine. In any case, the decision of whether or not to first add a LAMA or escalate the dose of ICS, or both, in a poorly controlled patient on MD ICS/LABA FDC remains a clinical matter that may be driven by the overall level of disease control, available biomarkers, or concerns over potential AEs.

**Contributors**

PR, BLR, and LC had full access to all of the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. PR, BLR, and LC designed the statistical analyses. PR and LC wrote the first draft of the Article, in consultation with BLR for data interpretations. All authors revised the Article critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the Article in ensuring that questions related to the accuracy or integrity of any part of the Article were appropriately investigated and resolved.
Guarantor of the review

PR and LC are the guarantors of this review and meta-analysis.

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Not applicable.

Declaration of interests

PR participated as a lecturer and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis, and her department was funded by Almirall, Boehringer Ingelheim, Chiesi Farmaceutici Novartis, and Zambon. BLR has no conflict of interest to declare. LC has participated as advisor in scientific meetings under the sponsorship of Boehringer Ingelheim and Novartis; received nonfinancial support from AstraZeneca; a research grant partially funded by Chiesi Farmaceutici, Boehringer Ingelheim, Novartis, and Almirall; is or has been a consultant to ABC Farmaceutici, Edmond Pharma, Zambon, Verona Pharma, and Ockham Biotech; and his department was funded by Almirall, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, and Zambon.

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Not applicable.
References


Table 1. Relative effects with 95%CrI resulting from the overall network meta-analysis. Treatments comparisons have been sorted in agreement with SUCRA\textsuperscript{§} findings for the co-primary endpoints reported in Figure 3.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>References for direct comparisons</th>
<th>Co-primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate to severe asthma exacerbation (RR)</td>
<td>Trough FEV\textsubscript{1} (mL)</td>
</tr>
<tr>
<td>HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>[17-19]</td>
<td>0.80 (0.66 - 0.95) *</td>
<td>3.72 (2.99 - 4.10) *</td>
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<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[17, 18, 20]</td>
<td>0.83 (0.69 - 1.00) *</td>
<td>91.18 (62.85 - 120.94) *</td>
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<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[17, 18]</td>
<td>0.63 (0.52 - 0.76) *</td>
<td>114.18 (85.03 - 146.44) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>[19]</td>
<td>0.78 (0.68 - 0.95) *</td>
<td>32.7 (5.29 - 61.89) *</td>
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<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[17, 18, 20]</td>
<td>0.61 (0.45 - 0.82)</td>
<td>95.71 (41.18 - 152.30)</td>
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<td>HD ICS/LABA FDC vs. HD ICS/LABA FDC</td>
<td>[17, 18]</td>
<td>0.79 (0.65 - 0.94)</td>
<td>58.45 (27.45 - 88.78) *</td>
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<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[17, 18]</td>
<td>0.79 (0.65 - 0.94) *</td>
<td>81.49 (52.75 - 110.76) *</td>
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<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>IC</td>
<td>0.75 (0.62 - 0.91)</td>
<td>23.00 (-7.30 - 54.06)</td>
</tr>
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\textsuperscript{*}The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst.

\textsuperscript{#} P=0.05

Bold text with asterisk indicates statistical significance (*P<0.05). ACQ: asthma control questionnaire; AE: adverse event; CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV\textsubscript{1}: forced expiratory volume in the 1\textsuperscript{st} second; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting \(\beta_2\)-adrenoceptor agonist; MD: medium-dose; RR: relative risk; SAE: serious adverse event; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.
**Table 2.** Person-based NNT and 95%CI over 52 weeks of treatment concerning the prevention of moderate to severe asthma exacerbation inpatients treated with triple combination therapies vs. active comparators. All data were calculated as weighted average.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>NNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD ICS/LABA/LAMA FDC (rate: 0.41) vs. MD ICS/LABA/LAMA FDC (rate: 0.44)</td>
<td>40.29 (19.27 - ∞)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC (rate: 0.44) vs. MD ICS/LABA FDC (rate: 0.49)</td>
<td>32.90 (17.81 - 215.88)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC (rate: 0.44) vs. MD ICS/LABA FDC (rate: 0.49)</td>
<td>12.08 (8.85 - 19.02)</td>
</tr>
<tr>
<td>MD ICS/LABA/LAMA FDC (rate: 0.44) vs. HD ICS/LABA FDC (rate: 0.44)</td>
<td>179.29 (31.15 - ∞)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC (rate: 0.49) vs. MD ICS/LABA FDC (rate: 0.49)</td>
<td>17.25 (11.26 - 36.88)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC (rate: 0.44) vs. MD ICS/LABA FDC (rate: 0.49)</td>
<td>19.09 (12.08 - 45.53)</td>
</tr>
</tbody>
</table>

*aThe NNT was calculated by using the weighted rates of the arms reported in each study. 95%CI: 95% confidence interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting \( \beta_2 \)-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; NNT: number needed to treat.*
Table 3. Relative effects with 95%CrI resulting from the subset network meta-analysis with respect to the moderate or severe asthma exacerbations. Treatments comparisons have been sorted in agreement with SUCRA§ findings for the co-primary endpoints reported in Figure 3.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Moderate asthma exacerbation (RR)</th>
<th>Severe asthma exacerbation (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD ICS/LABA/LAMA FDC + TIO vs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.87 (0.65 - 1.15)</td>
<td>1.41 (0.92 - 2.21)</td>
</tr>
<tr>
<td>MD ICS/LABA/LAMA FDC</td>
<td>0.91 (0.75 - 1.10)</td>
<td>0.65 (0.49 - 0.87) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.88 (0.73 - 1.06)</td>
<td>0.75 (0.57 - 1.00) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.67 (0.55 - 0.82) *</td>
<td>0.57 (0.42 - 0.78) *</td>
</tr>
<tr>
<td>HD ICS/LABA/LAMA FDC + TIO vs. MD ICS/LABA/LAMA FDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>1.04 (0.78 - 1.44)</td>
<td>0.46 (0.29 - 0.72) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>1.00 (0.76 - 1.39)</td>
<td>0.53 (0.33 - 0.85) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.77 (0.56 - 1.07)</td>
<td>0.40 (0.24 - 0.66) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.96 (0.79 - 1.18)</td>
<td>1.16 (0.87 - 1.58)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.74 (0.61 - 0.89) *</td>
<td>0.88 (0.66 - 1.16)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.76 (0.62 - 0.94) *</td>
<td>0.76 (0.55 - 1.02)</td>
</tr>
</tbody>
</table>

§The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst. Bold text with asterisk indicates statistical significance (*P<0.05).
#P=0.05.
CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β₂-adrenoceptor agonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.
Figures and legends

Figure 1. PRISMA-P flow diagram (A) and diagram displaying the network across the treatments (B). The links between the nodes indicate the direct comparisons between pairs of treatments, the thickness of lines is proportional with the number of the patients comparing pairs of treatment head-to-head, and the area of the boxes is proportional with the number of patients receiving the same treatment. BDP: beclomethasone dipropionate; BID: *bis in die*, twice daily; FDC: fixed-dose combination; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; HD: high-dose; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β₂-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; MF: momethasone furoate; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; QD: *quaque die*, once daily; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium; VI: vilanterol.

Figure 2. Overall forest plot of the comparisons across different triple combination therapies and active comparators on the risk of moderate to severe asthma exacerbation (A) and on the change from baseline in trough FEV₁ (B). Treatment comparisons have been sorted in agreement with level of efficacy. CrI: credible interval; FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; HD: high-dose; ICS: inhaled corticosteroid; LABA, long-acting β₂-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.

Figure 3. Overall ranking plot of the efficacy of triple combination therapies in preventing the risk of moderate to severe exacerbation (A) and in improving the change from baseline in trough FEV₁ (B) in asthmatic patients. Therapeutic strategies were plotted on X-axis according to the surface under the cumulative ranking curve analysis (SUCRA), where 1 results for a treatment considered to be the best, and 0 for a treatment considered to be the worst. The treatments were plotted on Y-axis according to the rank probability of best therapy, where a score of 1 is assigned to the best therapeutic strategy. FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; HD: high-dose; ICS: inhaled corticosteroid; LABA, long-acting β₂-adrenoceptor agonist; MD: medium-dose; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

Figure 4. RD of moderate to severe exacerbation (A) and delta effect of trough FEV₁ (B) when adding a LAMA to either MD or HD ICS/LABA FDC, escalating the dose of ICS on a background of MD ICS/LABA/LAMA FDC, or both adding a LABA and escalating the dose of ICS in asthmatic patients. *P<0.05. FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β₂-adrenoceptor agonist; MD: medium-dose; RD: risk difference.
A

B

SUCRA for reduction in risk of moderate to severe asthma exacerbation

SUCRA for change in trough FEV₁

Probability of being the best treatment

HD ICS/LABA FDC

HD ICS/LABA/LAMA FDC

MD ICS/LABA FDC

MD ICS/LABA/LAMA FDC
Supplementary data

Materials and methods

Search strategy and study eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO, Protocol ID: CRD42020211870), and performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [1]. The relative flow diagram and network nodes are shown in Figure 1A and B. This study satisfied all the recommended items reported by the PRISMA-P checklist (Table S1) [1].

A comprehensive literature search was performed for Phase III randomized controlled trials (RCTs) written in English and evaluating the efficacy and safety of triple combination therapies for the treatment of asthma. In this regard, the PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported [2]. Namely, the "Patient problem" included patients suffering from asthma; the “Intervention” regarded the administration of different triple combination therapies; the “Comparison” was performed across active combination treatments; the assessed “Outcomes” were the risk of moderate to severe asthma exacerbation, lung function, level of asthma control, and risk of serious adverse events (SAEs), specifically with respect to pneumonia and serious cardiovascular adverse events (AEs).

The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science, in order to provide for relevant studies lasting ≥24 weeks, and published up to September 23rd, 2020. The research string was as follows: (((Beclomethasone formoterol glycopyrronium) OR (CHF 5993) OR (CHF5993)) OR (fluticasone furoate vilanterol umeclidinium) OR (mometasone indacaterol glycopyrronium OR (QVM149) OR (QVM 149)) OR ((fluticasone propionate salmeterol tiotropium) OR (ICS LABA tiotropium)) OR triple) AND asthma. Citations of previous published reviews were checked to select further pertinent RCTs, if any.

Literature search results were uploaded to Epi-Reviewer 4 (EPPI-Centre Software. London, UK), a web-based software program for managing and
Supplementary data

analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting $\geq 24$ weeks, and that included at least one arm assessing the impact of any triple combination therapy in asthma were included in the network meta-analysis. Three reviewers independently examined the studies, and any difference in opinion concerning the selection of relevant Phase III RCTs from literature searches and databases was resolved by consensus.

Data extraction

Data from the RCTs included in this quantitative synthesis were extracted from published papers, and/or supplementary files, and/or the public database ClinicalTrials.gov and/or publically available pharmaceutical companies’ clinical databases. Data were checked for study characteristics and duration, number of analysed patients, treatments with doses of medications and regimen of administration, asthma severity and main inclusion criteria, age, gender, asthma duration; forced expiratory volume in the 1st second (FEV$_1$); level of FEV$_1$ reversibility; blood eosinophil count at baseline; smoking habit, Asthma Control Questionnaire (ACQ), primary outcomes analysed in every study, Jadad Score [3], and the Cochrane risk of bias [4].

The level of inhaled corticosteroid (ICS) doses (medium-dose [MD] and high-dose [HD]) included in the combinations was ranked in agreement with the current Global Initiative for asthma (GINA) recommendations [5] and the National Institute for Health and Care Excellence (NICE) guidelines [6]. Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [7]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen’s Kappa score, as previously described [8]. Briefly, Cohen’s Kappa $\geq 0.80$ indicated excellent agreement, coefficients between 0.61 and 0.80 represented substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and $<0.41$ fair to poor agreement.

Endpoints
Supplementary data

The co-primary endpoints of this network meta-analysis were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe exacerbation in asthmatic patients and the change from baseline in trough FEV₁.

The secondary efficacy endpoint was the comparison across the different triple combination therapies and comparators with respect to the change from baseline in ACQ score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular AEs.

Quality of studies, risk bias, and evidence profile

The summary of the risk of bias for each included Phase III RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [4] and Jadad score [3]. The Jadad score ranges from 1 to 5 (score of 5 being the best score), and the quality of studies was ranked as follows: score ≤2, low quality; score =3, medium quality; score ≥4 high quality. The weighted assessment of the risk of bias was analyzed via the Cochrane RoB 2 [4].

The risk of bias was performed for the co-primary endpoints and it was checked via the normalized consistency/inconsistency analysis, a procedure that allows assessing whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [9]. The inconsistency of evidence was also investigated by quantifying the inconsistency factor, that indicates whether one of the treatments had a different effect when it was compared with the others.

The quality of the evidence was assessed for the co-primary endpoints in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, indicating ++++ for high-quality of evidence, +++ for moderate-quality of evidence, ++ for low-quality of evidence, and + for very low-quality of evidence [10].

Three reviewers independently assessed the quality of studies, risk bias, and evidence profile, and any difference in opinion was resolved by consensus.

Data synthesis and analysis

A network meta-analysis was performed to indirectly compare the impact of the different triple combination therapies and active comparators in asthmatic patients.
A full Bayesian evidence network was used in the network meta-analysis (chains: 4; initial values scaling: 2.5; tuning iterations: 20,000; simulation iterations: 50,000; tuning interval: 10). The convergence diagnostics for consistency and inconsistency were assessed via the Brooks-Gelman-Rubin method, as previously described [11]. Due to the characteristics of parameters besides the available data, the just proper non-informative distributions specified the prior densities, in agreement with the Bayesian Approaches to Clinical Trials and Health-Care Evaluation [12, 13]. Since the distributions were sufficiently vague, the reference treatment, study baseline effects, and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, via heuristically determining a value for the outcome scale parameter (i.e. outcome scale S) [14, 15]. The posterior mean deviance of data points in the unrelated mean effects model was plotted against their posterior mean deviance in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent [16]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI).

The analysis of the number needed to treat (NNT) was performed on the risk of moderate to severe exacerbations. NNT is the reciprocal of the absolute risk reduction associated with an intervention over a fixed period of time [17-19]. The values of NNT are reported in this study as person-based per year and calculated by analysing the Kaplan-Meyer curves or the Cox proportional hazards model, as previously described [20, 21]. The relative weight of each study resulting from the network meta-analysis was used to calculate the weighted average rate of the investigated treatment arms and to correctly provide NNT values.

Sensitivity analysis was performed in agreement with the patients’ characteristics at baseline of each study.

Subset analyses were performed on both moderate or severe exacerbations, and with respect to the different doses of umeclidinium included in the fixed-dose combination (FDC).
Supplementary data

The probability that each intervention arm was the most effective/safe was calculated by counting the proportion of iterations of the chain in which each intervention arm had the best relative effect, and the surface under the cumulative ranking curve analysis (SUCRA), representing the summary of these probabilities [22]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [9].

Software and statistical significance

ImageJ was used to extract data from the figures, when necessary [23], GeMTC [24] software was used to perform the network meta-analysis, GraphPad Prism (CA, US) software to graph the data, GRADEpro GDT to assess the quality of evidence [10], and the robvis visualization software to perform the RoB 2 tool [25, 26]. The statistical significance of the effect estimates resulting from the network meta-analysis was assessed for P<0.05.

Results

Study characteristics

Data obtained from 9535 asthmatic patients (MD ICS/LABA/LAMA FDC: 26.02%; HD ICS/LABA/LAMA FDC: 25.99%; HD ICS/LABA FDC: 23.23%; MD ICS/LABA FDC: 16.76%; HD ICS/LABA FDC + TIO: 8.00%) were selected from 5 Phase III RCTs published between 2019 and 2020.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen’s Kappa >0.90). The intra-rater reliability produced a Cohen’s Kappa of 1.00 after the learning process.

All the studies included in the network meta-analysis were Phase III RCTs published as full-text papers, with a period of treatment between 24 weeks and 52 weeks.
## Supplementary data

### Supplementary Tables

**Table S1.** PRISMA-P Checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1 main MS</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>2 main MS</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3 main MS</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>3 main MS</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>3-4 main MS; 1 suppl. file</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>3-4 main MS; 1 suppl. file</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>1 suppl. file</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>1 suppl. File; Table S2; Appendix 1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>4 main MS; 2 suppl. file</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>4 main MS; 2 suppl. file</td>
</tr>
</tbody>
</table>
**Supplementary data**

<table>
<thead>
<tr>
<th>Data items</th>
<th>11</th>
<th>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
</tr>
</tbody>
</table>

**RESULTS**

| Study selection                     | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| Study characteristics               | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| Risk of bias within studies         | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| Results of individual studies       | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| Synthesis of results                | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| Risk of bias across studies         | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| Additional analysis                 | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |
**DISCUSSION**

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>24</th>
<th>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
</tr>
</tbody>
</table>

**FUNDING**

| Funding         | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this network meta-analysis is reported at step #30. The summary text of the identified records is shown in Appendix 1.

<table>
<thead>
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<th>Search strategy</th>
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<tbody>
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<tr>
<td>5</td>
<td>CHF 5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>1 and 2 and 3</td>
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<td>21</td>
<td>4 or 5</td>
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<tr>
<td>22</td>
<td>6 and 7 and 8</td>
</tr>
<tr>
<td>23</td>
<td>3 and 9 and 10</td>
</tr>
<tr>
<td>24</td>
<td>11 or 12</td>
</tr>
<tr>
<td>25</td>
<td>13 and 14 and 15</td>
</tr>
<tr>
<td>26</td>
<td>15 and 16 and 17</td>
</tr>
<tr>
<td>27</td>
<td>20 or 21</td>
</tr>
<tr>
<td>28</td>
<td>23 or 24</td>
</tr>
<tr>
<td>29</td>
<td>18 or 22 or 25 or 27 or 28</td>
</tr>
<tr>
<td>30</td>
<td>19 and 29</td>
</tr>
</tbody>
</table>
### Supplementary data

**Table S3.** Patient demographics, baseline, study characteristics, and Jadad score.

<table>
<thead>
<tr>
<th>Study and year and reference</th>
<th>Trial number identifier</th>
<th>Study characteristics</th>
<th>Study duration (months)</th>
<th>Number of analyzed patients</th>
<th>Number of patients</th>
<th>Comparator (doses and regimen of administration)</th>
<th>Inhailer device (brand)</th>
<th>Patients characteristics</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Duration of asthma (years)</th>
<th>Pred. bronchodilator FEV₁ (% predicted)</th>
<th>Reversibility (% FEV₁)</th>
<th>Rate of exacerbation in the previous year</th>
<th>Blood eosinophil count (cells per µL)</th>
<th>Current smokers (%)</th>
<th>ACQ at baseline (score)</th>
<th>Primary outcome</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2020, CAPTAIN [27]</td>
<td>NCT02504688</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>2436</td>
<td></td>
<td>FFV/UMEC (100/25/25 25 µg q.d.), FFV/UMEC (100/25/25 25 µg q.d.), FFV/UMEC (200/25/25 25 µg q.d.), FFV/UMEC (200/25/25 25 µg q.d.)</td>
<td>FFV/VI (100/25 µg q.d.), FFV/VI (200/25 µg q.d.)</td>
<td>Improvability controlled asthma (pre-bronchodilator FEV₁ 2300% and ≥10% predicted; airway reversibility at screening defined as an increase in FEV₁ ≥12% and ≥200 mL after four inhalations of salbutamol; ICS stable use ≥250 µg per day for 26 weeks prior to pre-screening)</td>
<td>53.2</td>
<td>38.0</td>
<td>21.2</td>
<td>58.5</td>
<td>29.9</td>
<td>0.8</td>
<td>228</td>
<td>0.0</td>
<td>2.8</td>
<td>Change in trough FEV₁ at week 26</td>
<td>5</td>
</tr>
<tr>
<td>Keviljans et al., 2020 IRIDIUM [28]</td>
<td>NCT0257177</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>3092</td>
<td></td>
<td>MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>MF/IND/GLY (80/150 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>Symptomatic asthma (pre-bronchodilator FEV₁ ≥80% predicted; ≤1 asthma exacerbation requiring medical care from a physician, ER visit, hospitalization, and systemic corticosteroid treatment for at least 3 days in the year prior to screening; airway reversibility defined as an increase in FEV₁ ≥12% and ≥200 mL after inhalation of salbutamol; use of ICS/LABA medium- or high-dose for ≥3 months and at stable dose for ≥1 month prior to screening)</td>
<td>52.2</td>
<td>38.0</td>
<td>18.1</td>
<td>54.8</td>
<td>27.7</td>
<td>1.3</td>
<td>NA</td>
<td>NA</td>
<td>2.5</td>
<td>Change in trough FEV₁ at week 26</td>
<td>5</td>
</tr>
<tr>
<td>Quenan et al., 2020 ORION [29]</td>
<td>NCT03158311</td>
<td>Phase III, multicentre, randomized, non-inferiority, partially-blinded, open-label, active-controlled, parallel-group</td>
<td>5.5</td>
<td>1426</td>
<td></td>
<td>MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>Symptomatic asthma (pre-bronchodilator FEV₁ ≥80% predicted; ≤1 severe asthma exacerbation requiring medical care from a physician, ER visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the year prior to study entry; airway reversibility defined as an increase in FEV₁ ≥85% predicted and ≥200 mL or historical evidence within the past 5 years of reversibility or positive bronchial provocation test; use of ICS/LABA stable medium- or high-dose prior to screening)</td>
<td>52.5</td>
<td>36.7</td>
<td>20.7</td>
<td>62.9</td>
<td>28.1</td>
<td>1.2</td>
<td>NA</td>
<td>2.2</td>
<td>2.6</td>
<td>Change in AQOL total score</td>
<td>3</td>
</tr>
<tr>
<td>Vincenzi et al., 2019 TRIMARAN [30]</td>
<td>NCT02676076</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>1150</td>
<td></td>
<td>BD/POR/GLY (200/125/25 µg b.i.d.)</td>
<td>BD/POR/GLY (200/125/25 µg b.i.d.)</td>
<td>Uncontrolled asthma (pre-bronchodilator FEV₁ ≥80% predicted; ≤1 asthma exacerbation requiring an ER visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the year prior to study entry; airway reversibility defined as an increase in FEV₁ ≥12% and ≥200 mL at ≥10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA medium-dose for ≥1 month prior to study entry)</td>
<td>52.6</td>
<td>38.5</td>
<td>25.0</td>
<td>55.5</td>
<td>31.7</td>
<td>1.2</td>
<td>NA</td>
<td>0.0</td>
<td>2.3</td>
<td>Change in trough FEV₁ at week 26, rate of moderate and severe exacerbations</td>
<td>5</td>
</tr>
</tbody>
</table>
**Supplementary data**

| Virchow et al., 2019 TRIGGER [20] | NCT02676089 | Phase III, multicentre, randomized, double-blind (BDP/FOR + TIO group was open-label), active-controlled, parallel group | 12.0 | 1431 | BDP/FOR/GLY (400/12/20 µg b.i.d.) | BDP/FOR (400/12 µg b.i.d.) + TIO (5 µg q.d.) | BDP/FOR/GLY: pMDI (NA); BDP/FOR: pMDI (NA); TIO: soft mist inhaler (Respimat®) | Uncontrolled asthma (pre-bronchodilator FEV₁<80% predicted); ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV₁≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA high-dose for ≥1 month prior to study entry | 52.9 | 38.7 | 25.2 | 51.9 | 34.6 | 1.2 | NA | 0.0 | 2.4 | Change in trough FEV₁ at week 26, rate of moderate and severe exacerbations | 5 |

ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BDP: beclomethasone dipropionate; b.i.d.: *bis in die*, twice daily; DPI: dry powder inhaler; ER: emergency room; FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1ˢᵗ second; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β₂-adrenoceptor agonist; q.d.: *quaque die*, once daily; MF: mometasone furoate; NA: not available; pMDI: pressurized metered dose inhaler; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.
## Table S4. Definition of moderate and severe asthma exacerbations as reported by the studies included in the network meta-analysis.

<table>
<thead>
<tr>
<th>Study, year and reference</th>
<th>Study identifier</th>
<th>Definition of asthma exacerbation</th>
</tr>
</thead>
</table>
| Lee et al., 2020, CAPTAIN [27] | NCT02924688 | Moderate asthma exacerbation: “deterioration in either asthma symptoms or lung function, or increased rescue bronchodilator use, that required a physician-directed temporary change in maintenance treatment to prevent the exacerbation from becoming a severe exacerbation”. Severe asthma exacerbation: “an exacerbation requiring admission to hospital or a visit to an emergency department due to the need for SCSs, or asthma deterioration requiring SCS use (or doubling of the current maintenance SCS dose) for at least 3 days”.
| Kerstjens et al., 2020 IRIDIUM [28] | NCT02571777 | Moderate asthma exacerbation: “the occurrence of two or more of the following: progressive increase of at least one asthma symptom; increased use of rescue medication; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant SCSs for more than 2 days or hospitalization”. Severe asthma exacerbation: “an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that requires SCSs for at least 3 consecutive days or a need for an ER visit, hospitalisation owing to asthma, or death due to asthma”.
| Gessner et al., 2020 ARGON [29] | NCT03158311 | Moderate asthma exacerbation: “the occurrence of two or more of the following: 1. progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms were outside the patient’s usual range of day-to-day asthma and lasted at least two consecutive days. 2. increased use of "rescue" inhaled bronchodilators defined by: ≥50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured or night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights. 3. deterioration in lung function, which lasted for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalisation. This deterioration was defined by: ≥20% decrease in FEV1 from baseline value or ≥20% decrease in morning or evening PEF from baseline on 2 out of any 3 consecutive days compared to baseline or <60% of predicted PEF compared to baseline”. Severe asthma exacerbation: “an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that required SCS for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalisation due to asthma or death due to asthma”.
| Virchow et al., 2019 TRIMARAN [30] | NCT02676076 | Moderate asthma exacerbation: “nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV1 from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs” (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: “worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)”.
| Virchow et al., 2019 TRIGGER [30] | NCT02676089 | Moderate asthma exacerbation: “nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV1 from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs” (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: “worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)”.

**Supplementary data**

**Table S5.** Level of ICS doses in agreement with the daily doses of medications in adults in the Phase III RCTs included in the network meta-analysis as reported by current GINA recommendations [5] and NICE guidelines [6].

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen of administration</th>
<th>Daily dose</th>
<th>Level of ICS dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP</td>
<td>200 µg b.i.d.</td>
<td>400 µg</td>
<td>MD</td>
</tr>
<tr>
<td></td>
<td>400 µg b.i.d.</td>
<td>800 µg</td>
<td>HD</td>
</tr>
<tr>
<td>FF</td>
<td>100 µg q.d.</td>
<td>100 µg</td>
<td>MD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>200 µg q.d.</td>
<td>200 µg</td>
<td>HD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FP</td>
<td>500 µg b.i.d.</td>
<td>1000 µg</td>
<td>HD</td>
</tr>
<tr>
<td>MF</td>
<td>80 µg q.d.</td>
<td>80 µg</td>
<td>MD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>160 µg q.d.</td>
<td>160 µg</td>
<td>HD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>320 µg q.d.</td>
<td>320 µg</td>
<td>HD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The dose levels refer to those reported in the NICE guidelines [32].

<sup>b</sup>The MD 80 µg and the HD 160 µg of MF delivered via Breezhaler® device correspond to the MD 400 µg and the HD 800 µg of MF delivered via the approved Twisthaler® formulation [28, 29].

**Supplementary data**

**Table S6.** Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network concerning the relative effects with 95%CrI of the co-primary endpoints.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>References for direct comparisons</th>
<th>Moderate to severe asthma exacerbation (RR)</th>
<th>Trough FEV$_1$ (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD ICS/LABA FDC + TIO vs. MD ICS/LABA/LAMA FDC</td>
<td>[29, 30]</td>
<td>1.01 (0.76 - 1.31)</td>
<td>20.11 (-45.84 - 86.08)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>[28, 30]</td>
<td>0.74 (0.59 - 0.92) *</td>
<td>97.13 (43.71 - 150.47) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[28]</td>
<td>0.66 (0.51 - 0.84) *</td>
<td>98.80 (43.55 - 82.46) *</td>
</tr>
<tr>
<td>MD ICS/LABA/LAMA FDC vs. MD ICS/LABA/FDC</td>
<td>[29]</td>
<td>0.83 (0.62 - 1.11)</td>
<td>10.20 (-61.15 - 83.76)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[30]</td>
<td>0.73 (0.54 - 0.98) *</td>
<td>76.38 (2.87 – 151.51) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC IC</td>
<td></td>
<td>0.65 (0.47 - 0.91) *</td>
<td>80.42 (1.44 - 160.14) *</td>
</tr>
<tr>
<td>HD ICS/LABA/FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>[28]</td>
<td>0.89 (0.69 - 1.12)</td>
<td>65.15 (9.29 – 120.94) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[27, 28, 30]</td>
<td>0.79 (0.63 - 0.99) *</td>
<td>67.55 (16.00 - 118.41) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC IC</td>
<td></td>
<td>0.89 (0.69 – 1.15)</td>
<td>1.52 (-56.02 – 62.01)</td>
</tr>
</tbody>
</table>

*P<0.05.

CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV$_1$: forced expiratory volume in the 1st second; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting $\beta_2$-adrenoceptor agonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.
Supplementary data

Table S7. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network with respect to the moderate or severe asthma exacerbations.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Moderate asthma exacerbation (RR)</th>
<th>Severe asthma exacerbation (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>0.95 (0.73 - 1.23)</td>
<td>0.72 (0.48 - 1.09)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>0.79 (0.60 - 1.01)</td>
<td>0.65 (0.42 - 0.98)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC vs. HD ICS/LABA FDC</td>
<td>0.74 (0.55 - 0.98) *</td>
<td>0.57 (0.36 - 0.90) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>1.10 (0.80 - 1.58)</td>
<td>0.52 (0.29 - 0.89) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>0.92 (0.67 - 1.32)</td>
<td>0.46 (0.26 - 0.80) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>0.85 (0.60 - 1.28)</td>
<td>0.41 (0.22 - 0.75) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA/FDC</td>
<td>0.83 (0.63 - 1.10)</td>
<td>0.89 (0.57 - 1.40)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>0.77 (0.60 - 1.00) *</td>
<td>0.79 (0.52 - 1.20)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>0.93 (0.69 - 1.26)</td>
<td>0.88 (0.55 - 1.42)</td>
</tr>
</tbody>
</table>

*P<0.05, *P=0.05.

CrI: credible interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β₂-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.
Figure S1. Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=5 Phase III RCTs). RCT: randomized controlled trial; RoB 2: Risk of Bias 2.
**Supplementary data**

**Figure S2.** Traffic light plot for assessment of the risk of bias of each included Phase III RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; RCT: randomized controlled trial; RoB: risk of bias; robvis: risk of bias visualization tool. Yellow circle indicates some concerns on the risk of bias and green circle represents low risk of bias.
Figure S3. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% prediction bands) of different triple combination therapies and active comparators with respect to the risk of moderate to severe asthma exacerbation (A) and change from baseline in trough FEV₁ (B). FEV₁: forced expiratory volume in the 1st second.
References


Appendix

Appendix 1. Summary text of the identified records.


14: Virchow JC. Assessing the benefits of triple versus dual fixed-dose
Supplementary data


Supplementary data

32302698.


Supplementary data

PMID: 31931792; PMCID: PMC6958672.


50: FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new


109: Mesonzhnik NV, Moskaleva NE, Shestakova RM, Kurymina KO, Baranov PA, Gretskaya NM, Serkov IV, Lyubimov II, Bezuglov VV, Appolonova SA. LC-MS/MS


print. PMID: 29108533.


Supplementary data


166: Lichtveld M, Kennedy S, Krouse RZ, Grimsley F, El-Dahr J, Bordelon K,


Supplementary data


Supplementary data


220: Suikkerbuijk AW, de Wit GA, Wijga AH, Heijmans M, Hoogendoorn M, Rutten-van Molken M, Maurits EK, Hoogenveen RT, Feenstra TL. Maatschappelijke kosten van astma, COPD en respiratoire allergie [Societal costs of asthma, COPD and


Supplementary data


