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

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Shareable abstract (@ERSpublications)
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 https://bit.ly/39NuNKb

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Abstract

Conflicting evidence is currently available concerning the impact on asthma exacerbation of triple inhaled corticosteroid (ICS)/long-acting β_2-adrenoceptor agonist (LABA)/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 randomised 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 0.61–0.80) and increasing trough forced expiratory volume in 1 s (from +33 to +114 mL). Triple combination therapies including HD ICS were superior ($p<0.05$) to MD ICS/LABA/LAMA FDC in preventing severe exacerbation (relative risk 0.46–0.65), 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.

Introduction

Adding tiotropium bromide (TIO) to dual inhaled corticosteroid (ICS)/long-acting β_2-adrenoceptor 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 recognised advantages, meta-analyses may provide the opportunity to settle controversies arising from apparently conflicting studies [6]. Moreover, the Bayesian network approach, so-called network meta-analysis, not only allows the effect estimates of specific outcomes resulting from different medications to be compared, but it also offers suitable information for clinicians in the form of treatment rankings that can be graphically summarised by surface under the cumulative ranking curve analysis (SUCRA) [7, 8].

Therefore, we performed an unbiased network meta-analysis of phase III randomised 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 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 material.

Search strategy and study eligibility

This meta-analysis was performed in agreement with PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) [9] and is registered at PROSPERO with identifier number CRD42020211870. The flow diagram and network nodes are shown in figures 1 and 2, and supplementary 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, supplementary table S2 reports the literature search terms used for Ovid MEDLINE and appendix S1 in the supplementary material shows the summary text of the identified records.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ⩾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 DECiMAL (Data Extraction for Complex Meta-anALysis) recommendations [10]. The inter- and intra-rater reliability for data abstraction was assessed *via* Cohen's κ, as previously described [11].

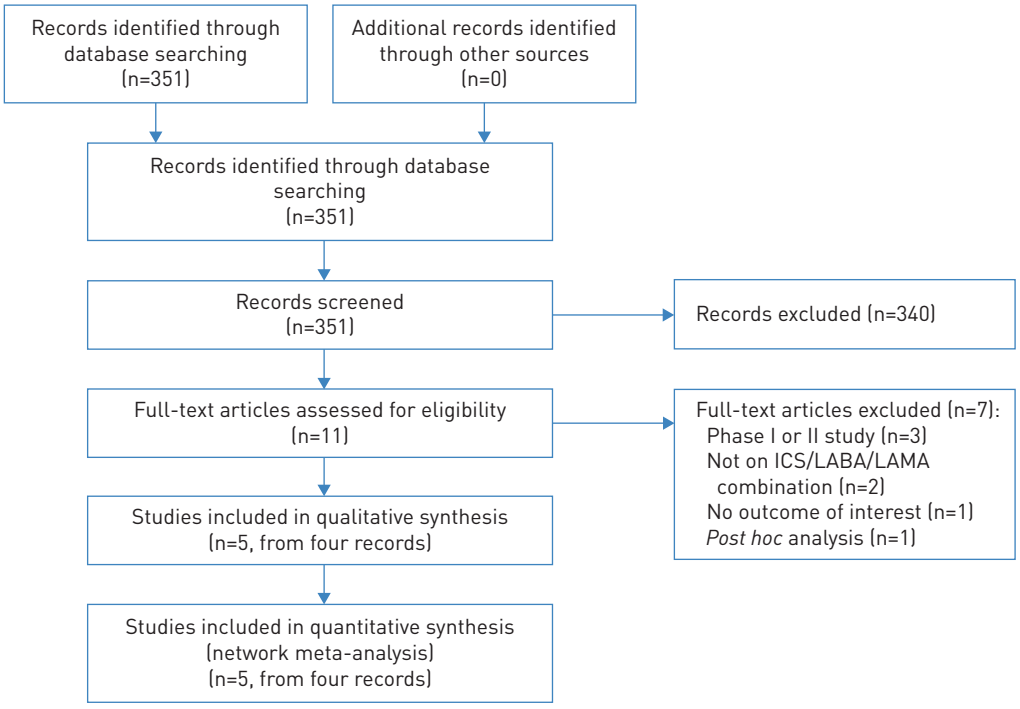

FIGURE 1 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) flow diagram. ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist.

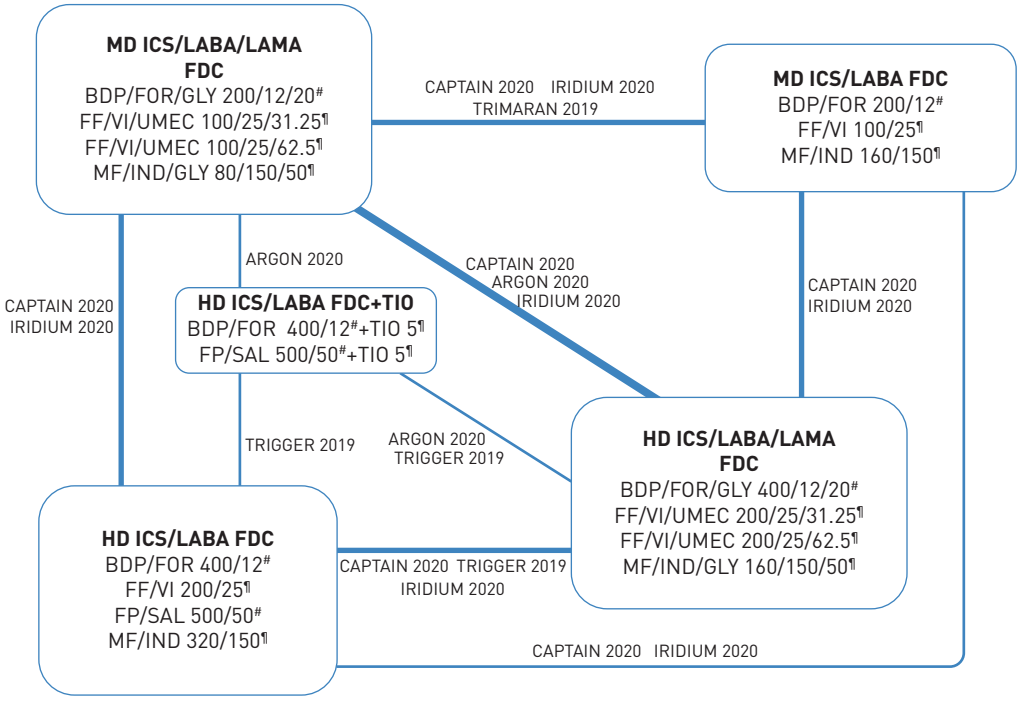

FIGURE 2 Diagram displaying the network across the treatments. MD: medium dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; BDP: beclomethasone dipropionate; FOR: formoterol fumarate; GLY: glycopyrronium; FF: fluticasone furoate; VI: vilanterol; UMEC: umeclidinium; MF: mometasone furoate; IND: indacaterol; HD: high dose; TIO: tiotropium bromide; FP: fluticasone propionate; SAL: salmeterol. Doses are in µg. #: twice daily; ¶: once daily. The links between the nodes indicate the direct comparisons between pairs of treatments, the thickness of lines is proportional to the number of the patients comparing pairs of treatment head-to-head and the area of the boxes is proportional to the number of patients receiving the same treatment. CAPTAIN [17], IRIDIUM [18], ARGON [19], TRIMARAN [20] and TRIGGER [20].

End-points

The co-primary end-points 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 1 s (FEV_1).

The secondary efficacy end-point 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 end-point was the risk of SAEs, specifically with respect to 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 analysed *via* the Cochrane Risk of Bias 2 (RoB 2) tool [12] and Jadad score [13]. The weighted assessment of the overall risk of bias was analysed *via* the Cochrane RoB 2 tool [12], along with the normalised consistency/inconsistency analysis [14]. The quality of evidence was assessed for the primary end-point *via* the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [15].

Data synthesis and analysis

A network meta-analysis was performed *via* a full Bayesian random effects 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 and 95% credible interval (95% CrI) or 95% confidence interval (95% CI). SUCRA was calculated for both the co-primary and secondary end-points [16]; SUCRA=1 when a treatment is considered to be the best and SUCRA=0 when a treatment is considered to be the worst [14]. Statistical significance was assessed for $p<0.05$.

Results

Study characteristics

Data obtained from 9535 asthmatic patients were selected from five phase III RCTs (supplementary 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 two studies [20], mometasone furoate (MF)/indacaterol (IND)/GLY in two studies and fluticasone furoate (FF)/vilanterol (VI)/umeclidinium (UMEC) in one study [17]. The investigated free combination ICS/LABA FDC+TIO included BDP/FOR+TIO in one study [20] and FP/SAL+TIO in one 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 supplementary tables S4 and S5, respectively. The inter- and intra-rater reliability for data abstraction was generally excellent (κ>0.90).

Further study characteristics are reported in the supplementary material.

Co-primary end-points

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 with medium-dose (MD) ICS/LABA/LAMA FDC and MD ICS/LABA FDC, whereas a trend toward significance ($p=0.05$) was detected *versus* HD ICS/LABA FDC. Detailed relative risk and 95% credible interval values across the investigated combinations are reported in table 1, with data graphically reported in figure 3a as a 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 4a).

The person-based number needed to treat (NNT) per year concerning the prevention of moderate to severe asthma exacerbation was 40.29 for HD ICS/LABA/LAMA FDC *versus* MD ICS/LABA/LAMA FDC, 32.90 *versus* HD ICS/LABA FDC and 12.08 *versus* MD ICS/LABA FDC. Considering MD ICS/LABA/LAMA FDC, the person-based NNT per year was 179.29 *versus* HD ICS/LABA FDC and 17.25 *versus* 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 MD ICS/LABA/LAMA FDC, HD ICS/LABA FDC and MD ICS/LABA FDC with respect to 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 with 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 one exacerbation in the previous year (average rate 0.8). Conversely, all the other investigated RCTs [18–20] enrolled asthmatic patients reporting more than one exacerbation in the previous year (average rate $\geqslant$1.2). Results of the sensitivity analysis (supplementary table S6) were not significantly ($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 *versus* MD ICS/

TABLE 1 Relative effects with 95% credible interval resulting from the overall network meta-analysis

Comparisons	References for direct comparisons	Co-primary end-points			Secondary end-points			
		Moderate to severe asthma exacerbation relative risk	Trough FEV_1 mL	GRADE	ACQ points	SAEs relative risk	Pneumonia relative risk	Serious CV AEs relative risk
HD ICS/LABA/LAMA FDC *versus*								
HD ICS/LABA FDC+TIO	[19, 20]	1.02 (0.79–1.34)	18.97 (−30.62–68.99)	++++	−0.07 (−0.15–0.02)	0.92 (0.60–1.41)	3.80 (0.68–23.45)	0.67 (0.16–3.61)
MD ICS/LABA/LAMA FDC	[17–19]	0.80 (0.66–0.95)#	32.72 (5.29–61.89)#	++++	−0.05 (−0.10–−0.00)¶	0.98 (0.78–1.25)	2.13 (0.91–5.73)	1.31 (0.53–2.69)
HD ICS/LABA FDC	[17, 18, 20]	0.83 (0.69–1.00)¶	91.18 (62.85–120.94)#	++++	−0.08 (−0.12–−0.03)#	0.99 (0.78–1.28)	1.03 (0.47–2.48)	1.36 (0.57–2.84)
MD ICS/LABA FDC	[17, 18]	0.63 (0.52–0.76)#	114.18 (85.03–146.44)#	++++	−0.11 (−0.16–−0.06)#	1.08 (0.84–1.39)	1.16 (0.47–2.89)	1.01 (0.41–2.10)
HD ICS/LABA FDC+TIO *versus*								
MD ICS/LABA/LAMA FDC	[19]	0.78 (0.58–1.03)	13.94 (−36.86–67.92)	++++	0.02 (−0.07–0.11)	1.08 (0.65–1.67)	0.56 (0.08–4.12)	1.92 (0.32–8.31)
HD ICS/LABA FDC	[20]	0.81 (0.61–1.07)	72.60 (19.86–126.45)#	++++	−0.01 (−0.10–0.08)	1.09 (0.68–1.69)	0.29 (0.04–1.52)	1.93 (0.34–9.73)
MD ICS/LABA FDC	IC	0.61 (0.45–0.82)#	95.71 (41.18–152.30)#	++++	−0.05 (−0.14–0.05)	1.18 (0.75–1.85)	0.32 (0.04–1.68)	1.50 (0.24–6.83)
MD ICS/LABA/LAMA FDC *versus*								
HD ICS/LABA FDC	[17, 18]	1.04 (0.87–1.26)	58.45 (27.45–88.78)#	++++	−0.03 (−0.07–0.02)	1.02 (0.79–1.29)	0.52 (0.17–1.31)	1.04 (0.47–2.44)
MD ICS/LABA FDC	[17, 18, 20]	0.79 (0.65–0.94)#	81.49 (52.75–110.76)#	++++	−0.06 (−0.12–−0.02)#	1.10 (0.86–1.39)	0.52 (0.19–1.43)	0.76 (0.35–1.78)
HD ICS/LABA FDC *versus*								
MD ICS/LABA FDC	IC	0.75 (0.62–0.91)#	23.00 (−7.30–54.06)	+++	−0.04 (−0.09–0.01)	1.11 (0.83–1.40)	1.06 (0.43–2.70)	0.75 (0.32–1.75)

Treatment comparisons have been sorted in agreement with surface under the cumulative ranking curve analysis (SUCRA) findings for the co-primary end-points reported in figure 4 (SUCRA=1 when a treatment is considered to be the best and SUCRA=0 when a treatment is considered to be the worst). FEV_1: forced expiratory volume in 1 s; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ACQ: Asthma Control Questionnaire; SAE: serious adverse event; CV: cardiovascular; AE: adverse event; HD: high dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; TIO: tiotropium bromide; MD: medium dose; IC: indirect comparison. #: $p<0.05$ (statistical significance); ¶: $p=0.05$.

LABA/LAMA FDC and HD ICS/LABA FDC+TIO *versus* 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 (supplementary table S7).

Trough FEV_1

The improvement in trough FEV_1 was not different between HD ICS/LABA/LAMA FDC and HD ICS/LABA FDC+TIO, with both 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 FEV_1, and in turn MD ICS/LABA/LAMA FDC was significantly ($p<0.05$) superior to both HD and MD ICS/LABA FDCs. Detailed comparisons across the investigated combinations on trough FEV_1 are reported in table 1 and figure 3b.

The SUCRA analysis showed that HD ICS/LABA/LAMA FDC was the most effective treatment in improving trough FEV_1, 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 4b).

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 FEV_1 compared with the overall network meta-analysis (data not shown).

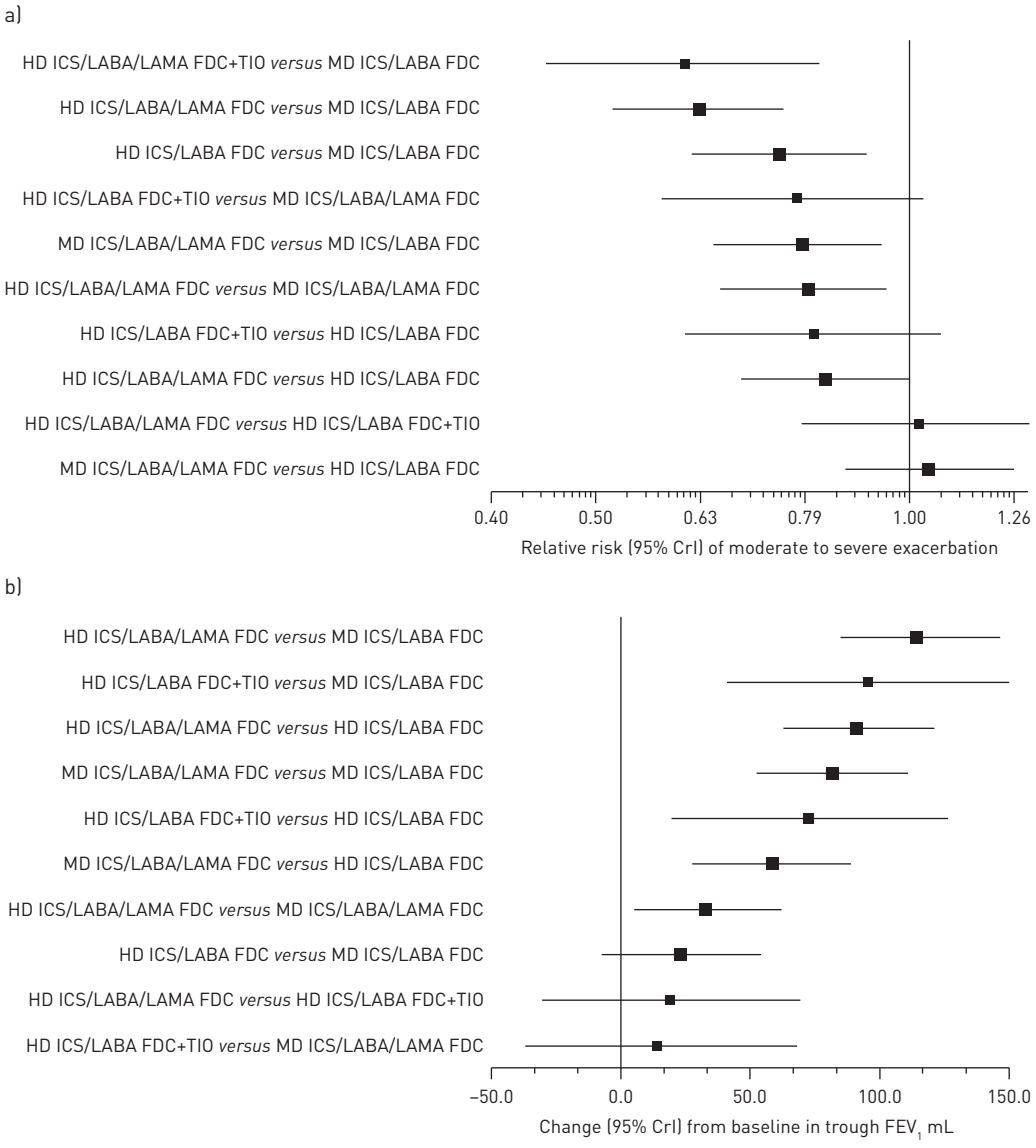

FIGURE 3 Overall forest plots of the comparisons across different triple combination therapies and active comparators on a) relative risk of moderate to severe asthma exacerbation and b) change from baseline in trough forced expiratory volume in 1 s (FEV_1). Treatment comparisons have been sorted according to level of efficacy. HD: high dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; TIO: tiotropium bromide; MD: medium dose; CrI: credible interval.

The sensitivity analysis (supplementary 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 escalating 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 −0.21 (95% CrI −0.35–−0.06) and −0.17 (95% CrI −0.31–0.00), respectively) (figure 5a) and increased trough FEV_1 (Δ effect +81 (95% CrI 53–111) mL and +91 (95% CrI 63–121) mL, respectively) (figure 5b), as well as escalating the dose of ICS on a background of MD ICS/LABA/LAMA FDC (risk difference −0.20 (95% CrI −0.34–−0.05) (figure 5a); Δ effect +33 (95% CrI 5–62) mL (figure 5b)). Adding a LAMA along with escalating the dose of ICS further prevented the

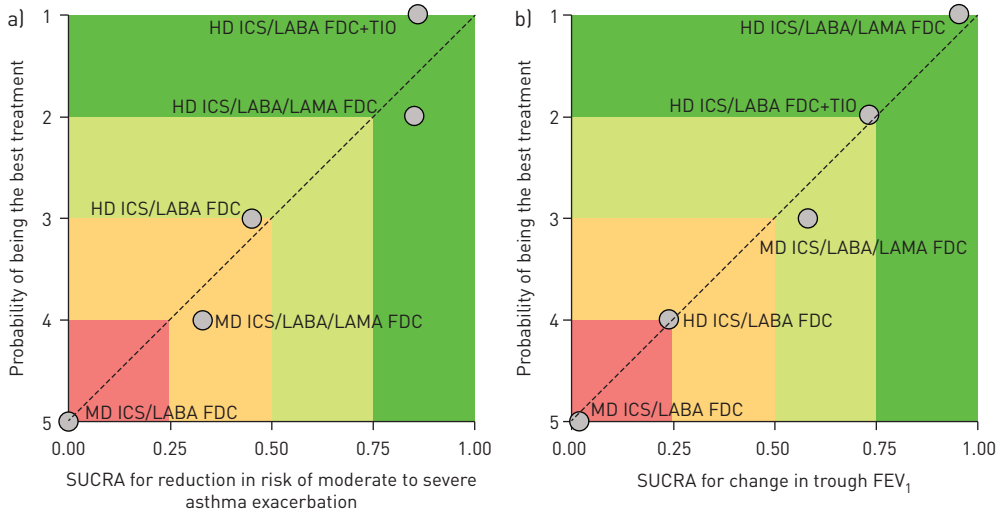

FIGURE 4 Overall ranking plots of the efficacy of triple combination therapies in a) preventing the risk of moderate to severe exacerbation and b) improving the change from baseline in trough forced expiratory volume in 1 s (FEV_1) in asthmatic patients. HD: high dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; TIO: tiotropium bromide; MD: medium dose; SUCRA: surface under the cumulative ranking curve analysis. Therapeutic strategies were plotted on the *x*-axis according to SUCRA, where SUCRA=1 for a treatment considered to be the best and SUCRA=0 for a treatment considered to be the worst. The treatments were plotted on the *y*-axis according to the rank probability of best therapy, where a score of 1 is assigned to the best therapeutic strategy.

risk of moderate to severe asthma exacerbation (risk difference −0.25 (95% CrI −0.38–−0.09)) (figure 5a) and improved trough FEV_1 (Δ effect +114 (95% CrI 85–145) mL) (figure 5b).

Secondary end-points

Detailed comparisons across the investigated combinations with respect to the secondary end-points are reported in table 1.

Asthma Control Questionnaire

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

TABLE 2 Person-based number needed to treat (NNT) with 95% confidence interval over 52 weeks of treatment concerning the prevention of moderate to severe asthma exacerbation in patients treated with triple combination therapies *versus* active comparators

Comparisons	NNT[#]
HD ICS/LABA/LAMA FDC (rate: 0.41) ***versus***	
MD ICS/LABA/LAMA FDC (rate: 0.44)	40.29 (19.27–∞)
HD ICS/LABA FDC (rate: 0.44)	32.90 (17.81–215.88)
MD ICS/LABA FDC (rate: 0.49)	12.08 (8.85–19.02)
MD ICS/LABA/LAMA FDC (rate: 0.44) ***versus***	
HD ICS/LABA FDC (rate: 0.44)	179.29 (31.15–∞)
MD ICS/LABA FDC (rate: 0.49)	17.25 (11.26–36.88)
HD ICS/LABA FDC (rate: 0.44) ***versus***	
MD ICS/LABA FDC (rate: 0.49)	19.09 (12.08–45.53)

All data were calculated as weighted average. HD: high dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; MD: medium dose. [#]: NNT was calculated by using the weighted rates of the arms reported in each study.

TABLE 3 Relative effects with 95% credible interval resulting from the subset network meta-analysis with respect to the moderate or severe asthma exacerbations

Comparisons	Moderate asthma exacerbation relative risk	Severe asthma exacerbation relative risk
HD ICS/LABA/LAMA FDC *versus*		
HD ICS/LABA FDC+TIO	0.87 (0.65–1.15)	1.41 (0.92–2.21)
MD ICS/LABA/LAMA FDC	0.91 (0.75–1.10)	0.65 (0.49–0.87)[#]
HD ICS/LABA FDC	0.88 (0.73–1.06)	0.75 (0.57–1.00)[¶]
MD ICS/LABA FDC	0.67 (0.55–0.82)[#]	0.57 (0.42–0.78)[#]
HD ICS/LABA FDC+TIO *versus*		
MD ICS/LABA/LAMA FDC	1.04 (0.78–1.44)	0.46 (0.29–0.72)[#]
HD ICS/LABA FDC	1.00 (0.76–1.39)	0.53 (0.33–0.85)[#]
MD ICS/LABA FDC	0.77 (0.56–1.07)	0.40 (0.24–0.66)[#]
MD ICS/LABA/LAMA FDC *versus*		
HD ICS/LABA FDC	0.96 (0.79–1.18)	1.16 (0.87–1.58)
MD ICS/LABA FDC	0.74 (0.61–0.89)[#]	0.88 (0.66–1.16)
HD ICS/LABA FDC *versus*		
MD ICS/LABA FDC	0.76 (0.62–0.94)[#]	0.76 (0.55–1.02)

Treatment comparisons have been sorted according to surface under the cumulative ranking curve analysis (SUCRA) findings for the co-primary end-points reported in figure 4 (SUCRA=1 when a treatment is considered to be the best and SUCRA=0 when a treatment is considered to be the worst). HD: high dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic receptor antagonist; FDC: fixed-dose combination; TIO: tiotropium bromide; MD: medium dose. [#]: $p<0.05$ (statistical significance); [¶]: $p=0.05$.

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 supplementary figure S1 and the traffic light plot for the assessment of each included RCT is reported in supplementary figure S2. All five (100%) of the phase III RCTs had a low risk of bias for the randomisation process, missing outcome data and selection of the reported results. Three of the RCTs (60.0%) had some concerns in the domain of deviations from intended intervention and measurement of the outcomes.

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

The normalised consistency/inconsistency analysis showed that all points fit adequately with the line of equality (overall goodness of fit $R^2=0.961$; 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 end-points (supplementary 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 to 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, and the results are shown in supplementary tables 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 FEV_1. 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

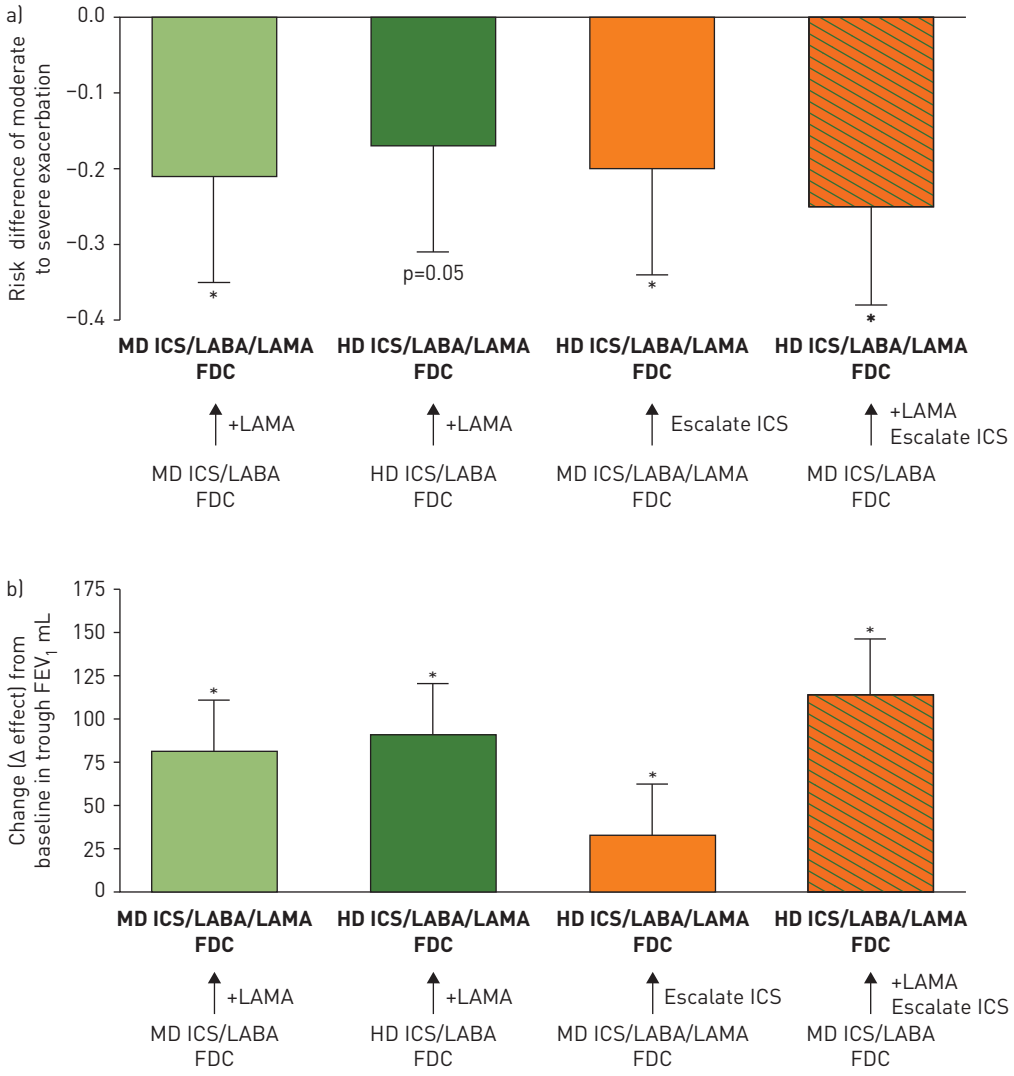

FIGURE 5 a) Risk difference of moderate to severe exacerbation and b) change (Δ effect) of trough forced expiratory volume in 1 s (FEV_1) when adding a long-acting muscarinic receptor antagonist (LAMA) to either medium-dose (MD) or high-dose (HD) inhaled corticosteroid (ICS)/long-acting β_2-adrenoceptor agonist (LABA) fixed-dose combination (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. Error bars indicate upper 95% credible interval. *: p<0.05 (statistical significance).

FDC and both MD and HD ICS/LABA FDCs in reducing the risk of moderate to severe exacerbation and improving trough FEV_1 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 1 year with HD ICS/LABA/LAMA FDC to prevent one moderate or severe asthma exacerbation compared with MD ICS/LABA/LAMA FDC, the NNT was ∼33 and only ∼12 when compared with 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 with MD ICS/LABA FDC, but not *versus* 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 relative risks of triple combinations including HD ICS, we can postulate that the NNT 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, excluding 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 optimisation of the dose of ICS and the number of bronchodilators included in the FDC.

Concerning the secondary end-points investigated in this network meta-analysis, triple combination therapies were equally effective in improving ACQ score, and no safety concerns resulted with respect to 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 biological 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 an alternative controller option.

Clearly, the evidence raised by this quantitative synthesis provides new horizons 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 to the severity of previous exacerbations. The recent approval of the first once-daily single inhaler triple therapy for the treatment of asthma by the US 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 to a specific antimuscarinic agent. In the light of this evidence, it is expected that the next iteration of asthma recommendations and guidelines will also include ICS/LABA/LAMA FDCs as effective pharmacological strategies for symptom control and risk reduction. Moreover, and no 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 to the intrinsic characteristics of the Bayesian network approach [23–25], mainly due to the indirect comparison across treatments and to the fact that only five studies [17–20] were included in the quantitative synthesis. However, as shown in figure 2, 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 (more than 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 end-points.

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 one 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% credible intervals 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% credible intervals 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 FEV_1 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 *et al.* [17] demonstrated that increasing the ICS dose resulted in improved outcomes among 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 make the definition of asthma exacerbation uniform [29, 30], to date there is no consensus on a standardised 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 consistency 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.

In conclusion, 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 adding either a LAMA or increasing ICS dose on a background of ICS/LABA/LAMA FDC triple FDCs 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 personalised 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.

This study is registered at PROSPERO with identifier number CRD42020211870.

Author contributions: P. Rogliani, B.L. Ritondo and L. Calzetta had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. P. Rogliani, B.L. Ritondo and L. Calzetta designed the statistical analyses. P. Rogliani and L. Calzetta wrote the first draft of the article, in consultation with B.L. Ritondo 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. P. Rogliani and L. Calzetta are the guarantors of this review and meta-analysis.

Conflict of interest: P. Rogliani 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. B.L. Ritondo has nothing to disclose. L. Calzetta 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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