

Potential Drawbacks of ICS/LABA/LAMA Triple Fixed-Dose Combination Therapy in the Treatment of Asthma: A Quantitative Synthesis of Safety Profile

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Introduction: Inhaled corticosteroid/long-acting β_2 -adrenoceptor agonist/long-acting muscarinic antagonist (ICS/LABA/LAMA) fixed-dose combination (FDC) is currently recommended as controller option at asthma Step 4 and as preferred treatment at asthma Step 5, but no research investigated the potential drawbacks of this therapeutic option in a large asthmatic population. Thus, the aim of this study was to quantify the potential drawbacks of triple FDC therapy in asthma.

Methods: A pairwise meta-analysis was performed according to PRISMA-P guidelines to assess the risk of overall serious adverse events (SAEs), cardiovascular SAEs, and pneumonia reported as SAE in asthmatic patients treated with ICS/LABA/LAMA FDC vs ICS/LABA FDC. A pooled analysis was performed to calculate the frequency of SAEs.

Results: Data from 7204 asthmatic patients were extracted from the CAPTAIN, IRIDIUM, TRIMARAN, and TRIGGER studies. Triple FDC vs ICS/LABA FDC did not increase the risk of total SAEs (RR 0.99 95% CI 0.83–1.18) and cardiac SAEs (RR 0.74 95% CI 0.39–1.40), whereas the sensitivity analysis performed to resolve heterogeneity resulted in increased risk of vascular SAEs (RR 3.23 95% CI 1.05–9.90, $P < 0.05$). The level of ICS dose did not modulate the risk of pneumonia, in any case pneumonia was the most frequent SAE (0.57%). These results were not affected by significant risk of bias.

Conclusion: Triple FDC is a safe pharmacological therapy in severe asthmatic patients; it is characterized by a favourable safety profile and few potential drawbacks, namely, the increased risk of vascular SAEs, that certainly are worthy of future investigations.

Keywords: asthma, cardiovascular, meta-analysis, pneumonia, safety, triple combination

Introduction

The current Global Initiative for Asthma (GINA, 2021)¹ recommendations suggest to administer as-needed low dose inhaled corticosteroid (ICS)/formoterol fixed-dose combination (FDC) as preferred controller treatment at asthma Step 1 and 2, and low dose maintenance ICS/formoterol FDC as preferred controller treatment at asthma Step 3 in adults and adolescents.² The GINA document also recommends to administer ICS/long-acting β_2 -adrenoceptor agonist (LABA)/long-acting muscarinic antagonist (LAMA) FDC as controller option at asthma Step 4 and as preferred treatment at add on asthma Step 5 in adults and adolescents.² Effectively, the co-primary endpoints of a large quantitative synthesis of data from randomized controlled trials (RCTs) indicated that triple FDC was significantly effective in preventing the risk of moderate to severe exacerbation and improving lung function.³ These data were confirmed also by the clinical interpretation of efficacy outcomes in pharmacological studies on triple FDC for uncontrolled asthma, reporting that ICS/LABA/LAMA FDC reached the minimal clinically important difference for the risk of exacerbation, lung function, asthma control, and quality of life not only when compared to ICS/LABA FDC, but often also vs the free triple combination of fluticasone/salmeterol plus tiotropium where the ICS was administered at high dose.⁴

Despite the proved therapeutic efficacy of triple FDC in severe asthma, to date only few evidence originated from research specifically performed to assess the safety profile of ICS/LABA/LAMA FDC in a large asthmatic population.⁵ Therefore, the aim

of this study was to investigate the potential drawbacks of triple FDC therapy in asthma via quantitative synthesis assessing the risk of overall serious adverse events (SAEs), and more specifically the risk of cardiovascular SAEs and pneumonia reported as SAE.

Materials and Methods

Search Strategy and Study Eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO registration ID: CRD42022298742, available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=298742), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).⁶ The relative flow diagram is shown in Figure 1. This study satisfied all the recommended items reported by the PRISMA-P checklist (Table S1).⁶

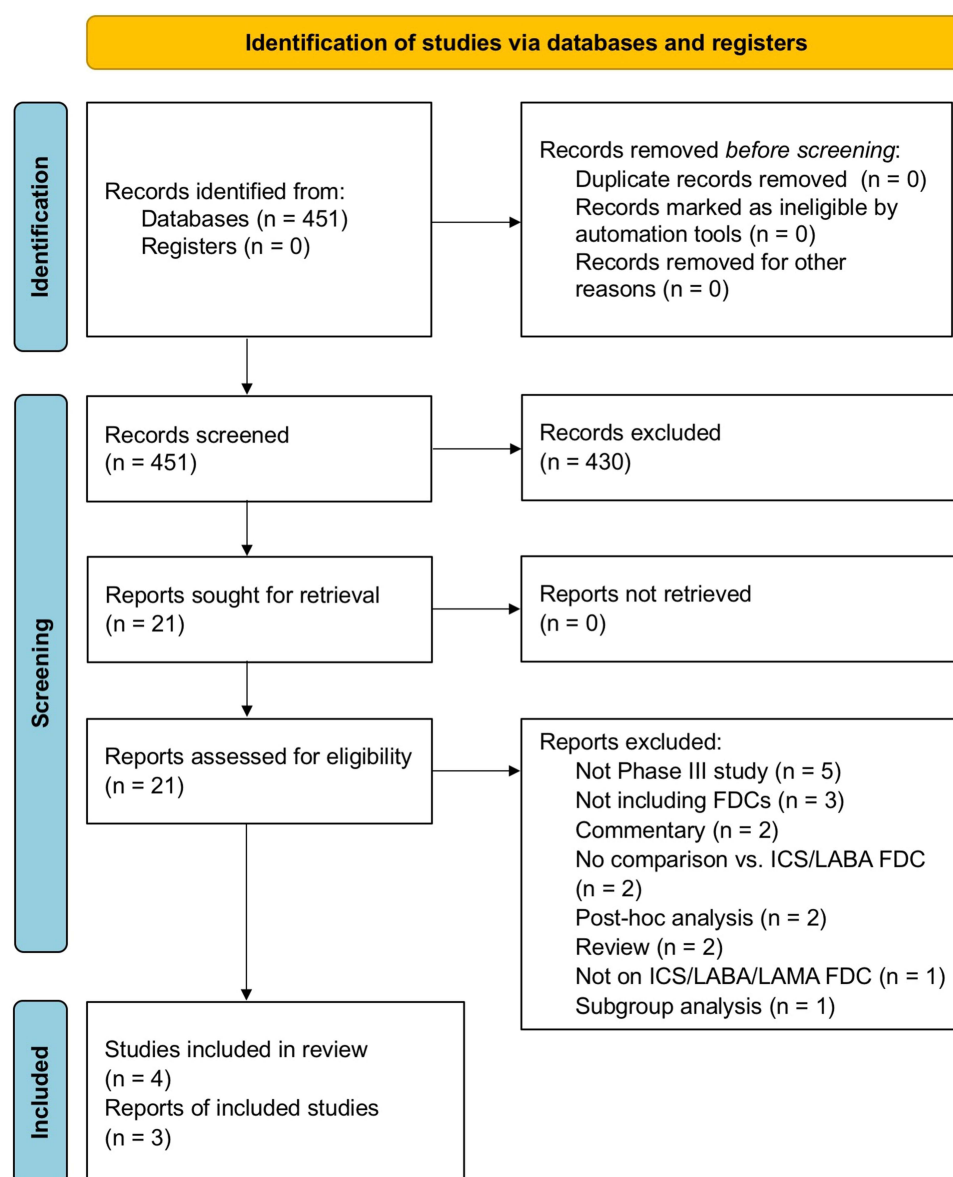


Figure 1 PRISMA 2020 flow diagram for the identification of Phase III RCTs included in the meta-analysis concerning the safety profile of triple FDC in asthma.

Note: Adapted from Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.⁶

Abbreviations: FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2 -adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

A comprehensive literature search was performed for Phase III RCTs written in English and evaluating the impact of FDC 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.

The PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported.⁷ Namely, the “Patient problem” included patients suffering from asthma; the “Intervention” regarded the administration of triple FDC; the “Comparison” was performed with respect to the same ICS/LABA FDC as in the triple FDC and administered via the same inhaler device; the assessed “Outcome” was the risk of SAEs, and more specifically the risk of cardiovascular SAEs and pneumonia reported as SAE.

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 December 14th, 2021.

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.

Literature search results were uploaded to Eppi-Reviewer 4 (EPPI-Centre Software. London, UK), a web-based software program for managing and analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

Study Selection Funnel

Phase III RCTs that enrolled asthmatic patients, lasting ≥ 24 weeks, and that included at least one arm assessing the safety of any triple FDC vs the same ICS/LABA FDC included in the triple therapy were included in the meta-analysis. Two 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 Phase III RCTs included in this quantitative synthesis were extracted from published papers, and/or supplementary files, and/or the public database ClinicalTrials.gov.

Data were checked for study characteristics and duration, number of analysed patients, treatments with doses of medications, regimen of administration and inhaler device, asthma severity and main inclusion criteria, age, gender, asthma duration, forced expiratory volume in the 1st second (FEV₁), level of FEV₁ reversibility, exacerbations, blood eosinophil count at baseline, smoking habit, Asthma Control Questionnaire (ACQ), Jadad Score,⁸ and the Cochrane risk of bias.⁹

The level of ICS doses (medium-dose and high-dose) included in the FDC was ranked in agreement with the current GINA recommendations¹⁰ and the National Institute for Health and Care Excellence (NICE) guidelines.¹¹

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations.¹² The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described.¹³ Briefly, Cohen's Kappa ≥ 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.

Endpoint

The primary endpoint of this meta-analysis was the safety profile of triple FDC vs ICS/LABA FDC expressed as the risk of SAEs, with specific focus on cardiovascular SAEs and pneumonia reported as SAE.

Data Synthesis and Analysis

A pairwise meta-analysis was performed to quantify the risk of SAEs of triple FDC vs ICS/LABA FDC in asthmatic patients. Results were expressed as relative risk (RR) and 95% confidence interval (95% CI).

Since data were selected from a series of studies performed by researchers operating independently and a common effect size cannot be assumed, binary random-effects method (derSimonian and Laird model) was used to balance the

study weights and adequately estimate the 95% CI of the mean distribution of drugs effect on the investigated variables.

Subgroup analyses were performed in agreement with the level of ICSs doses included in the FDC.

A pooled analysis was performed to calculate the frequency of SAEs, ranked in agreement with the European Medicine Agency (EMA) document undesirable effect, as follows: very common $\geq 1/10$, common $\geq 1/100$ to $<1/10$, uncommon $\geq 1/1000$ to $<1/100$, rare $\geq 1/10,000$ to $<1/1000$, frequency not known if not calculable from the available data.¹⁴

Quality of the Studies, Risk of 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)¹⁵ and Jadad score.⁸ 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 2.¹⁵

The test for heterogeneity (I^2) was performed to quantify the between-study dissimilarity, as previously reported.¹⁶ Sensitivity analysis was carried out if studies introduced significant and/or substantial ($I^2 > 50\%$) level of heterogeneity in the quantitative synthesis.¹⁷ In sensitivity analysis, after significant and/or substantial heterogeneity was resolved, fixed-effect (Mantel Haenszel) method was used if sparse data were reported.¹⁸

Funnel plot and Egger's test were carried out to assess the origin and risk of publication bias if more than 10 studies were included in the meta-analysis.^{19–22}

The quality of the evidence was assessed 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.⁹

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

Software and Statistical Significance

Open-MetaAnalyst was used to perform the pairwise meta-analysis,¹⁶ GRADEpro GDT to assess the quality of evidence,⁹ and the robvis visualization software to perform the RoB 2 tool.^{23,24} The statistical significance was assessed for $P < 0.05$.

Results

Study Characteristics

Data obtained from 7204 asthmatic patients (medium-dose ICS/LABA/LAMA FDC: 27.86%; high-dose ICS/LABA/LAMA FDC: 27.79%; high-dose ICS/LABA FDC: 22.18%; medium-dose ICS/LABA FDC: 22.17%) were extracted from 4 Phase III RCTs,^{25–27} published between 2019 and 2020 as full-text papers, and with a period of treatment of 52 weeks (Table S3). All the four studies were performed in patients suffering from inadequately controlled asthma.^{25–27}

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), mometasone furoate (MOM)/indacaterol (IND)/GLY, and fluticasone furoate (FF)/vilanterol (VI)/umeclidinium (UMEC).^{25–27} The active comparators were the ICS/LABA FDCs BDP/FOR, FF/VI, and MOM/IND.

The level of ICS doses in the FDC is shown in Table 1. The inter- and intra-rater reliability for data abstraction was generally excellent (Cohen's Kappa > 0.90).

Safety Profile

Risk of Total SAEs

Triple FDC did not significantly increase the risk of total SAEs compared to ICS/LABA FDC (RR 0.99 95% CI 0.83–1.18, $P > 0.05$; GRADE +++); the subgroup analysis did not show significant ($P > 0.05$) difference between medium-dose ICS and high-dose ICS (Figure 2).

Table I Level of ICS Doses in Agreement with the Daily Doses of Medications in Adults in the Phase III RCTs Included in the Meta-Analysis as Reported by Current GINA Recommendations¹⁰ and NICE Guidelines.¹¹

Treatment	Regimen of Administration	Daily Dose	Level of ICS Dose
BDP	200 µg b.i.d.	400 µg	Medium-dose
	400 µg b.i.d.	800 µg	High-dose
FF	100 µg q.d.	100 µg	Medium-dose ^a
	200 µg q.d.	200 µg	High-dose ^a
MOM	80 µg q.d.	80 µg	Medium-dose ^b
	160 µg q.d.	160 µg	High-dose ^b
	320 µg q.d.	320 µg	High-dose ^b

Notes: ^aThe dose levels refer to those reported in the NICE guidelines.¹¹ ^bThe medium-dose 80 µg and the high-dose 160 µg of MOM delivered via Breezhaler® device correspond to the medium-dose 400 µg and the high-dose 800 µg of MOM delivered via the approved Twisthaler® formulation.²⁶

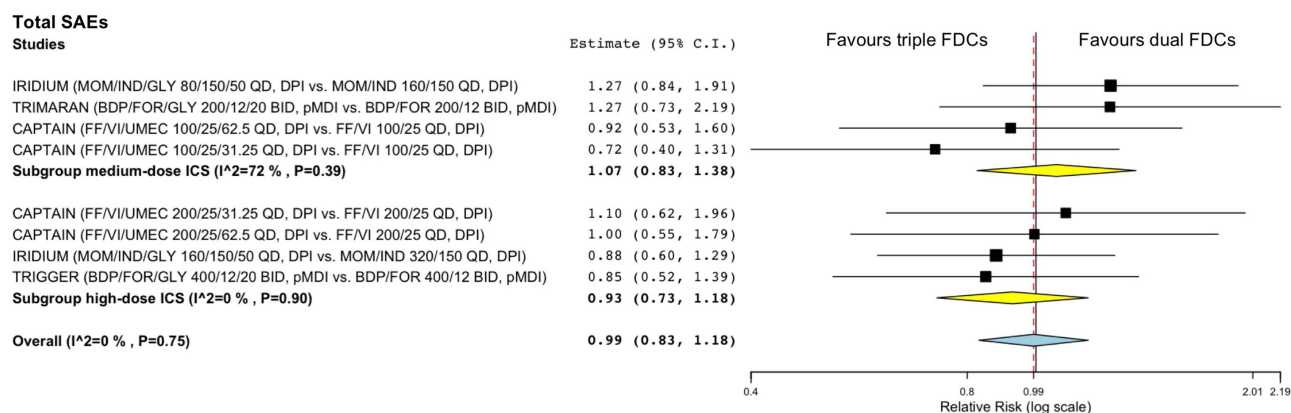
Abbreviations: b.i.d., bis in die (twice-daily); BDP, beclomethasone dipropionate; FF, fluticasone furoate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; MOM, mometasone furoate; NICE, National Institute for Health and Care Excellence; q.d., quaque die (once-daily); RCT, randomized controlled trial.

Neither significant ($P>0.05$) nor substantial heterogeneity was reported for triple FDC vs ICS/LABA FDC in the subgroup high-dose ICS (GRADE +++). Conversely, in the subgroup medium-dose ICS heterogeneity was substantial ($I^2=72\%$), although not significant ($P>0.05$; GRADE ++).

The sensitivity analysis indicated that FF/VI/UMEC 100/25/31.25 vs FF/VI 100/25 was the comparison in the CAPTAIN²⁵ study that introduced substantial heterogeneity when comparing triple FDC vs ICS/LABA FDC in the subgroup medium-dose ICS ($I^2=0\%$ after sensitivity analysis). When substantial heterogeneity was resolved by sensitivity analysis, no significant differences were detected for the risk of total SAEs between triple FDC and ICS/LABA FDC (RR 1.02 95% CI 0.85–1.23, $P>0.05$; GRADE ++++), regardless of the ICS doses.

Risk of Cardiovascular SAEs

The overall analysis of cardiovascular SAEs reported no significant increased risk when comparing triple FDC with ICS/LABA FDC (RR 1.03 95% CI 0.61–1.73, $P>0.05$; GRADE +++), regardless of the ICS doses.

**Figure 2** Forest plot of meta-analysis concerning the impact of triple FDC vs ICS/LABA FDC on the risk of total SAEs. The effect estimates resulting from the meta-analysis are reported in bold.

Abbreviations: BDP, beclomethasone dipropionate; BID, bis in die (twice daily); DPI, dry powder inhaler; FDC, fixed-dose combination; FF, fluticasone furoate; FOR, formoterol fumarate; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2 -adrenoceptor agonist; MOM, mometasone furoate; pMDI, pressurized metered dose inhaler; QD, quaque die (once daily); SAE, serious adverse event; UMEC, umecidinium bromide; VI, vilanterol.

The specific analysis of cardiac SAEs showed no significant difference between triple FDC and ICS/LABA FDC (RR 0.74 95% CI 0.39–1.40, $P>0.05$; GRADE +++), regardless of the ICS doses, with neither significant ($P>0.05$) nor substantial heterogeneity (Figure 3A).

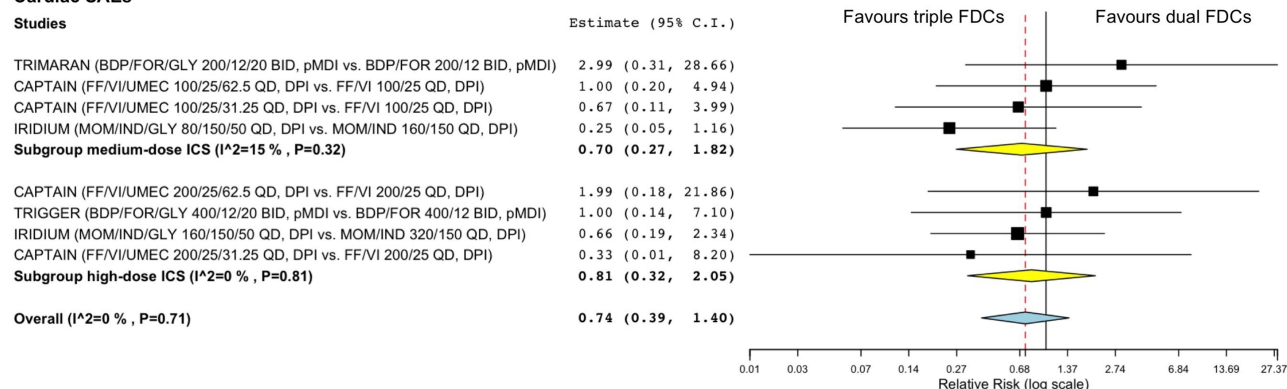
Triple FDC did not apparently modulate the risk of vascular SAEs compared to ICS/LABA FDC (RR 1.91 95% CI 0.71–5.17, $P>0.05$; GRADE +++). While neither significant ($P>0.05$) nor substantial heterogeneity resulted in the subgroup medium-dose ICS (GRADE +++), when triple FDC was compared to ICS/LABA FDC in the subgroup high-dose ICS substantial, although not significant ($P>0.05$), heterogeneity was detected ($I^2=52\%$; GRADE ++). The sensitivity analysis revealed that the comparison between FF/VI/UMEC 200/25/31.25 and FF/VI 200/25 in the CAPTAIN²⁵ study caused substantial heterogeneity in the subgroup high-dose ICS ($I^2=0\%$ after sensitivity analysis). When substantial heterogeneity was resolved by sensitivity analysis, triple FDC vs ICS/LABA FDC resulted in significant ($P<0.05$) greater risk of vascular SAEs (RR 3.23 95% CI 1.05–9.90; GRADE +++) (Figure 3B' and S1).

Risk of Pneumonia

Triple FDC did not significantly enhance the risk of pneumonia compared to ICS/LABA FDC (RR 0.79 95% CI 0.40–1.55, $P>0.05$; GRADE +++), regardless of the ICS doses, with neither significant ($P>0.05$) nor substantial heterogeneity (Figure 4).

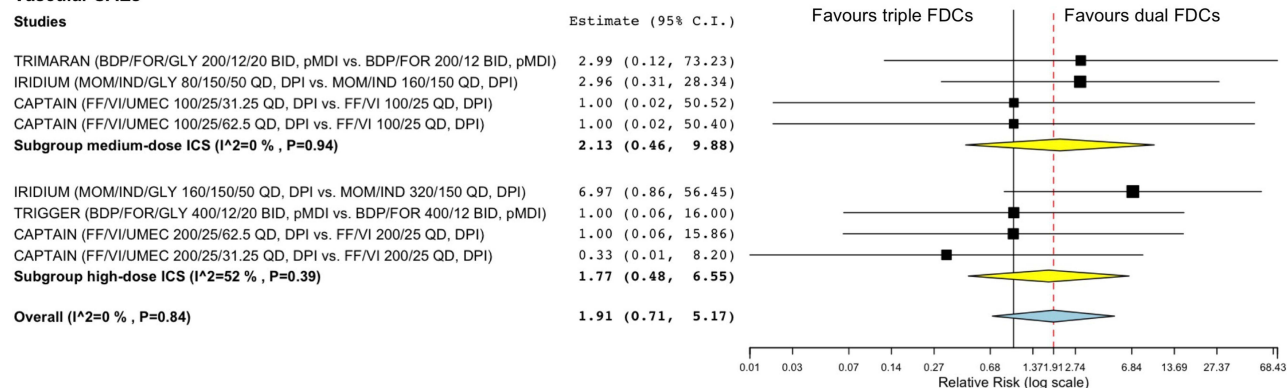
A

Cardiac SAEs



B

Vascular SAEs



B'

Vascular SAEs (sensitivity analysis)

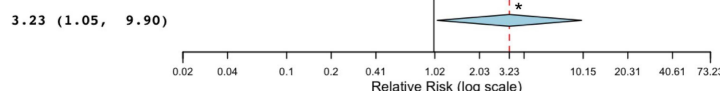


Figure 3 Forest plots of meta-analysis concerning the impact of triple FDC vs ICS/LABA FDC on the risk of cardiac SAEs (A) and vascular SAEs (B). (B') reports the overall sensitivity meta-analysis by excluding the comparison (FF/VI/UMEC 200/25/31.25 vs FF/VI 200/25) that introduced substantial heterogeneity in the subgroup high-dose ICS. The effect estimates resulting from the meta-analysis are reported in bold.

Abbreviations: BDP, beclomethasone dipropionate; BID, bis in die (twice daily); DPI, dry powder inhaler; FDC, fixed-dose combination; FF, fluticasone furoate; FOR, formoterol fumarate; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2 -adrenoceptor agonist; MOM, mometasone furoate; pMDI, pressurized metered dose inhaler; QD, quaque die (once daily); SAE, serious adverse event; UMEC, umeclidinium bromide; VI, vilanterol.

Pneumonia reported as SAE

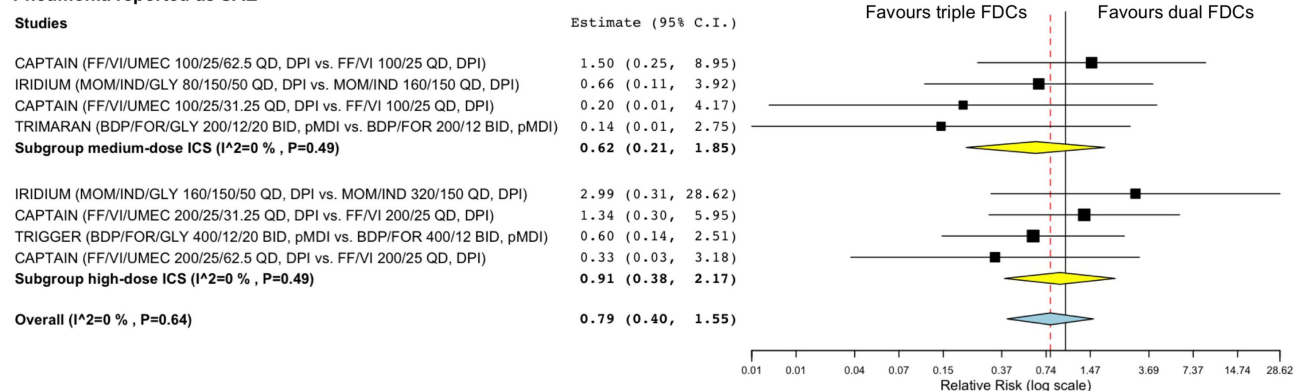


Figure 4 Forest plots of meta-analysis concerning the impact of triple FDC vs ICS/LABA FDC on the risk of pneumonia reported as SAE. The effect estimates resulting from the meta-analysis are reported in bold.

Abbreviations: BDP, beclomethasone dipropionate; BID, bis in die (twice daily); DPI, dry powder inhaler; FDC, fixed-dose combination; FF, fluticasone furoate; FOR, formoterol fumarate; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2 -adrenoceptor agonist; MOM, mometasone furoate; pMDI, pressurized metered dose inhaler; QD, quaque die (once daily); SAE, serious adverse events; UMEC, umeclidinium bromide; VI, vilanterol.

High-dose triple FDC vs medium-dose ICS/LABA FDC and medium-dose triple FDC vs high-dose ICS/LABA FDC did not significantly ($P>0.05$) modulate the risk of pneumonia (RR 1.14 95% CI 0.40–3.24 and RR 0.86 95% CI 0.26–2.23, respectively; GRADE +++).

Pooled Analysis of SAEs Frequency

The pooled analysis reported consistency in the frequency of SAEs across medium- and high-dose ICS/LABA/LAMA FDC and medium- and high-dose ICS/LABA FDC. The total SAEs were common, whereas the cardiovascular SAEs and pneumonia were uncommon. Overall, the most frequent SAEs were pneumonia (0.57%), followed by angina unstable and myocardial infarction (0.13%), and by acute coronary syndrome, atrial fibrillation, deep vein thrombosis, hypertension, hypertensive crisis, and varicose vein (0.10%); other SAEs were ranked as rare ($<0.10\%$). Detailed information on the frequency of SAEs are shown in [Table 2](#).

Risk of Bias and Quality of Evidence

The traffic light plot for the assessment of each included RCT is reported in [Figure 5A](#) and the weighted plot for the assessment of the overall risk of bias by domains is shown in [Figure 5B](#). All the Phase III RCTs had a low risk of bias for the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcomes, and selection of the reported results (4 [100.0%]). All four studies (100.0%) included in this meta-analysis were ranked as being of high quality in agreement with the Jadad score ([Table S3](#)). Funnel plot and Egger's test were not performed since less than 10 studies were included in the meta-analysis.

Discussion

This meta-analysis provides the moderate to high quality evidence that ICS/LABA/LAMA triple FDC is characterized by an favourable safety profile when compared to ICS/LABA FDC with respect to the risk of total SAEs, regardless of ICS dose. The safety profile was also confirmed for the risk of cardiac SAEs and pneumonia reported as SAEs. However, the sensitivity analysis reported significant increased risk of vascular SAEs related to triple FDC vs ICS/LABA FDC.

The treatment comparison that introduced a bias leading to reduced risk of vascular SAEs included FF/VI/UMEC 200/25/31.25, a triple FDC in which the LABA was administered at lower dose. Evidently, the dose of LABA in the FDC may modulate the risk of vascular SAEs. This finding originates from results obtained by specific meta-analysis technique pertinent to conditions in which very little heterogeneity exists and, above all, data are sparse.¹⁸ In this regard, the frequency of cardiovascular SAEs and pneumonia reported as SAEs were rare to uncommon across all the meta-analysis, and often no events were reported for some treatments.

Table 2 Pooled Analysis of Total SAEs, Cardiovascular SAEs, and Pneumonia with Number of Events, Frequency, and Rank According to EMA Guidelines.¹⁴

	Medium-Dose ICS/LABA/LAMA FDC (N=2004; CAPTAIN, IRIDIUM, TRIMARAN)			High-Dose ICS/LABA/LAMA FDC (N=1999; CAPTAIN, IRIDIUM, TRIGGER)			Medium-Dose ICS/LABA FDC (N=1589; CAPTAIN, IRIDIUM, TRIMARAN)			High-Dose ICS/LABA FDC (N=1592; CAPTAIN, IRIDIUM, TRIGGER)		
	Events	Frequency	Rank	Events	Frequency	Rank	Events	Frequency	Rank	Events	Frequency	Rank
Total SAEs	118	5.89	Common	118	5.90	Common	85	5.35	Common	106	6.66	Common
Cardiovascular SAEs	14	0.70	Uncommon	17	0.85	Uncommon	13	0.82	Uncommon	12	0.75	Uncommon
Cardiac SAEs	10	0.50	Uncommon	8	0.40	Uncommon	12	0.76	Uncommon	9	0.57	Uncommon
Angina unstable	1	0.05	Rare	1	0.05	Rare	2	0.13	Uncommon	0	0.00	FNK
Myocardial infarction	2	0.10	Uncommon	1	0.05	Rare	2	0.13	Uncommon	1	0.06	Rare
Acute coronary syndrome	2	0.10	Uncommon	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK
Acute myocardial infarction	2	0.10	Uncommon	2	0.10	Uncommon	0	0.00	FNK	1	0.06	Rare
Angina pectoris	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Atrial fibrillation	2	0.10	Uncommon	1	0.05	Rare	1	0.06	Rare	1	0.06	Rare
Atrial flutter	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Acute cardiac event	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Arrhythmia	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Atrioventricular block complete	0	0.00	FNK	1	0.05	Rare	1	0.06	Rare	0	0.00	FNK
Cardiac failure	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Cardiac failure congestive	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Cardiac tamponade	0	0.00	FNK	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK
Myocardial ischaemia	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Palpitations	0	0.00	FNK	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK
Supraventricular tachycardia	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Ventricular extrasystoles	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare

Cardiovascular death due to heart failure	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK
Heart failure due to left ventricular dysfunction	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare	0	0.00	FNK
Sudden cardiac death	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Worsening of heart failure	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Vascular SAEs	4	0.20	Uncommon	9	0.45	Uncommon	1	0.06	Rare	3	0.19	Uncommon
Circulatory collapse	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Hypertensive crisis	0	0.00	FNK	2	0.10	Uncommon	0	0.00	FNK	0	0.00	FNK
Angiopathy	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Aortic dissection	0	0.00	FNK	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK
Aortic dissection rupture	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK
Deep vein thrombosis	0	0.00	FNK	2	0.10	Uncommon	1	0.06	Rare	0	0.00	FNK
Hypertension	2	0.10	Uncommon	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK
Thrombophlebitis	0	0.00	FNK	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK
Varicose vein	0	0.00	FNK	2	0.10	Uncommon	0	0.00	FNK	0	0.00	FNK
Acute ischaemic stroke	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK	1	0.06	Rare
Death due to haemorrhagic stroke	0	0.00	FNK	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK
Ischaemic stroke	1	0.05	Rare	0	0.00	FNK	0	0.00	FNK	0	0.00	FNK
Pneumonia	5	0.25	Uncommon	11	0.55	Uncommon	8	0.50	Uncommon	9	0.57	Uncommon

Notes: Rank: common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1000$ to $< 1/100$, rare $\geq 1/10,000$ to $< 1/1000$. Treatments and high-level categories used to group adverse events are reported in bold.

Abbreviations: EMA, European Medicine Agency; FDC, fixed-dose combination; FNK, frequency not known; ICS, inhaled corticosteroid; LABA, long-acting β_2 -adrenoceptor agonist; LAMA, long-acting muscarinic antagonist, SAEs, serious adverse events.

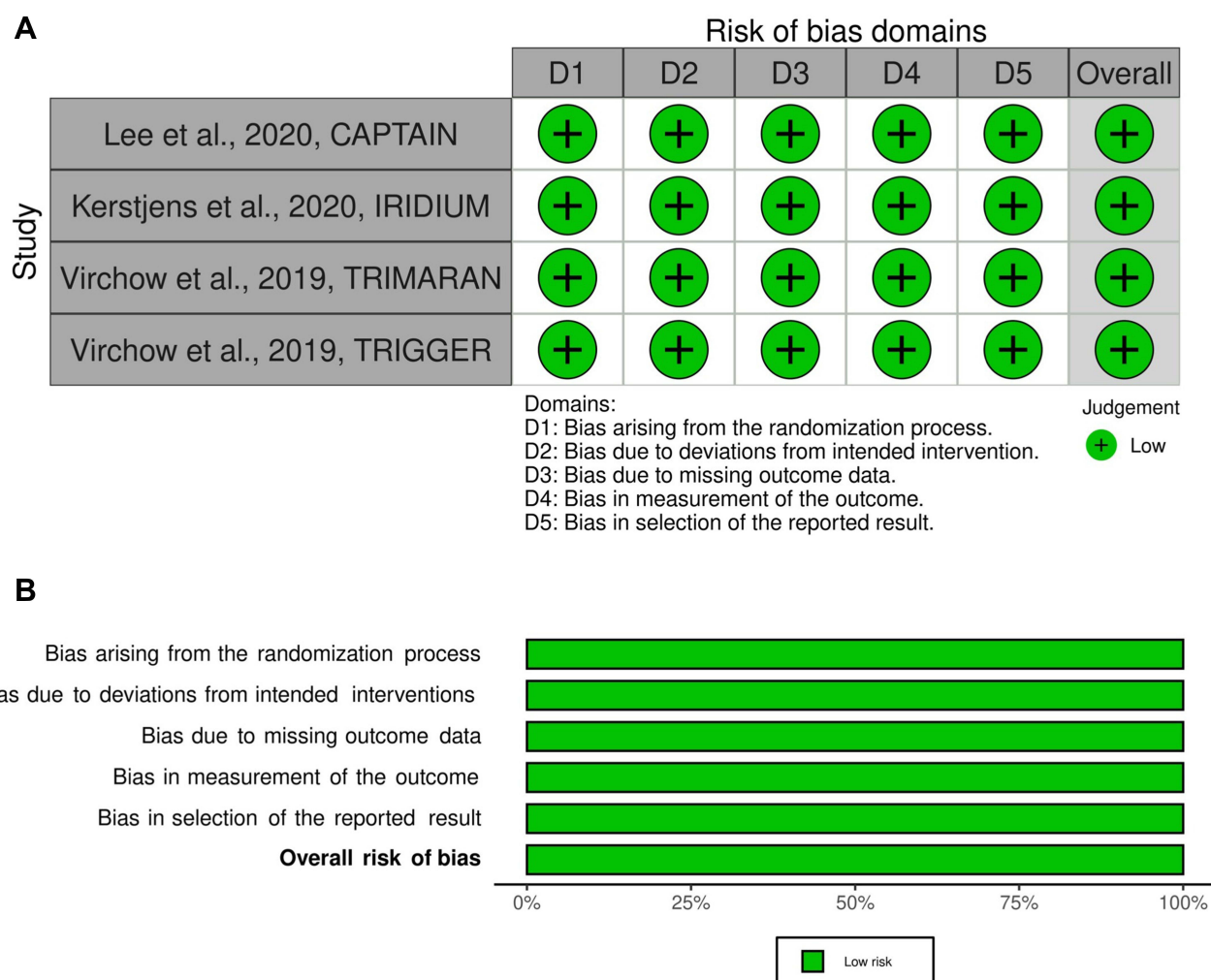


Figure 5 Traffic light plot for assessment of the risk of bias of each included Phase III RCT (A) and weighted plot for the assessment of the overall risk of bias (B) via the Cochrane RoB 2 tool (n=4 Phase III RCTs). The overall risk of bias resulting from the Cochrane RoB 2 tool is reported in bold.

Abbreviations: 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. Green circle represents low risk of bias.

Indeed, the sparsity of data poses the question whether this meta-analysis based on RCTs lasting only one year may be strong enough to quantify the real potential drawbacks of triple FDC in the treatment of asthma. Unfortunately, neither longer RCTs nor larger observational studies are currently available on this topic. In any case, the number of patients per treatment ($N > 1000$) included in the pooled analysis of CAPTAIN, IRIDIUM, TRIMARAN, and TRIGGER^{25–27} studies allowed intercepting rare SAEs, a condition characterized by a level of frequency of less than 0.1% according to EMA guidelines.¹⁴ This evidence confirms that, in some specific areas of healthcare such as the study of sparse data, meta-analysis may be a suitable way to quantify the impact of interventions on rare events, by giving more precise answer to a research question than a single RCT and detecting an effect with greater statistical power.²⁸

This study generally supports the safety profile resulting from a previous network meta-analysis on triple therapy in uncontrolled asthma³ that, however, considered the cardiovascular risk as pooled data and not differentiated as cardiac SAEs and vascular SAEs. This is the reason why in the present meta-analysis, specifically focused on the safety profile, we were able to detect a significant increased risk associated with triple FDC specifically for vascular SAEs.

However, since meta-analytical methods are based on large sample approximations, it is possible that they may provide misleading results on rare but important outcomes such as the risk of SAEs. This may happen according to the underlying event rate, likely size of the treatment effect, and balance in the numbers of treated and control participants in the RCTs.^{28,29}

The discrepancy between the selected patients fitting the criteria of RCTs and real-life asthmatic patients^{3,30} may limit the possible application of results of this meta-analysis in daily clinical practice. Therefore, further well-permed real-life studies are needed to assess if the treatment of asthmatic patients with triple FDC is really associated to increased vascular risk.

Another drawback of adding a LAMA to ICS/LABA FDC in asthma is related to the risk of prescribing triple therapy on “one size fits all” basis, whereas the trend should be towards a personalized medicine approach even in severe asthma.^{31,32} In this respect, the response to triple FDCs should be at least assessed according to the sex and body mass index (BMI), even before considering the difference in asthma phenotypes.^{31,32} In fact, in women with chronic obstructive pulmonary disease the bronchorelaxant effect of inhaled antimuscarinic agents resulted inversely correlated to BMI, whereas in men the impact of BMI was of little extent.³³ Moreover, lower expression of M₂ muscarinic acetylcholine receptor (mAChR) was found in women than in men, leading to a greater M₃/M₂ mAChR receptor ratio.³³ Indeed, the inhibition of M₂ mAChR expressed at the level of cardiovascular system is related to adverse events such as tachycardia and prolonged QT,³⁴ thus administering a triple FDC including a LAMA should be well assessed in those asthmatic patients that may have an altered response to muscarinic antagonists.

Although the safety profile of ICS is markedly better than that of oral corticosteroids, ICS are however absorbed from the lungs into the systemic circulation, leading to osteoporosis and increase the risk of cataracts, glaucoma, skin atrophy, and vascular alterations.³⁵ The possibility of modulating the dose of ICS in the triple FDC and the evidence that medium-dose triple FDC may be effective even when compared to high-dose ICS/LABA³ opens new perspectives of asthma treatment. We should consider the opportunity of shifting from high-dose ICS/LABA to medium-dose ICS/LABA/LAMA in patients with airflow obstruction and few exacerbations, as well as the option of de-escalating the ICS dose in the triple FDC according to the patient's clinical response to therapy.²

Conclusion

Triple FDC is a pharmacological therapy to treat severe asthma characterized by a favourable safety profile and few potential drawbacks that, however, are worthy of future investigations. The possibility of adding a LAMA to ICS/LABA FDC along with the option of modulating the dose of ICS in the triple FDC make ICS/LABA/LAMA therapy a flexible pharmacological tool suitable not only for difficult-to-treat asthma, but also for patients suffering from moderate forms of the disease. Finally, but not less important, FDC including a LAMA at lower dose such as UMEC at 31.25 µg instead of 62.25 µg may improve the safety profile of the combination and further improve the possible therapeutic options in asthma. However, EMA did not approve asthma label expansion for FF/VI/UMEC since the CAPTAIN²⁵ study did not clearly show that the medicine was effective at reducing asthma attacks or controlling symptoms,³⁶ a missing opportunity to optimize the benefit-risk ratio of ICS/LABA/LAMA FDC in the treatment of asthma.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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