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Efficacy and cardiovascular safety profile of dual bronchodilation therapy in chronic obstructive pulmonary disease: A bidimensional comparative analysis across fixed-dose combinations

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A B S T R A C T

Despite several long-acting β_2-adrenoceptor agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) are currently approved for the treatment of chronic obstructive pulmonary disease (COPD), there are limited findings concerning the direct comparison across the different LABA/LAMA FDCs. The aim of this study was to compare the efficacy/safety profile of approved LABA/LAMA FDCs in COPD. A network meta-analysis was performed by linking the efficacy (forced expiratory volume in 1 s, St' George Respiratory Questionnaire, transitional dyspnea index) and safety (cardiovascular serious adverse events) outcomes resulting from randomized controlled trials that directly compared LABA/LAMA FDCs with placebo and/or each other. The Surface Under the Cumulative Ranking Curve Analysis (SUCRA) was performed for each single outcome (SUCRA: 1 = best, 0 = worst). The combined efficacy/safety profile was reported via the novel Improved Bidimensional SUCRA score (IBiS: the higher the value the better the treatment). Data obtained from 12,136 COPD patients (79.50% LABA/LAMA FDCs vs. placebo; 20.50% direct comparison between different LABA/LAMA FDCs) were extracted from 22 studies published between 2013 and 2019. The IBiS score showed the following rank of efficacy/safety profile: tiotropium/olodaterol 5/5 μg (area 66.83%) » glycopyrronium/indacaterol 15.6/27.5 μg (area 40.43%) > umeclidinium/vilanterol 62.5/25 μg (area 30.48%) ≈ aclidinium/formoterol 400/12 μg (area 28.44%) > glycopyrronium/indacaterol 50/110 μg (area 19.95%) > glycopyrronium/formoterol 14.4/9.6 μg (area 11.50%). Each available LABA/LAMA FDC has a specific efficacy/safety profile that needs to be considered for personalized therapy in COPD. Head-to-head studies aimed to assess the impact of different LABA/LAMA FDCs on the risk of COPD exacerbation are needed to further improve the information provided by this quantitative synthesis.

1. Introduction

Despite dual bronchodilation therapy still represents the cornerstone therapy for most patients with chronic obstructive pulmonary disease (COPD) [1], to date only few randomized controlled trials (RCTs) [2–4] have directly compared two different long-acting β_2-adrenoceptor agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs). Considering the change from baseline in trough forced expiratory volume in 1 s (FEV_1), umeclidinium/vilanterol 62.5/25 μg (U/V 62.5/25) resulted superior to both glycopyrronium/indacaterol 50/110 μg (G/I 50/110) and tiotropium/olodaterol 5/5 μg (T/O 5/5), whereas no difference was found between U/V 62.5/25 and G/I 50/110 [2–4].

However, there is the possibility that the primary outcomes resulting from some of these studies were affected by certain limitations, such as the short duration of treatment [3,4], the number of enrolled patients that did not permit to detect differences between the treatments [4], the potential differences in severity of the disease and baseline characteristics of COPD patients [2–4]. Further bias could have been introduced in the results also by the study design, as two RCTs [3,4] were designed as cross-over studies.

Therefore, to date there is the need of bridging the gap of knowledge regarding the unbiased comparison across the currently approved LABA/LAMA FDCs in COPD with respect to their efficacy and cardiovascular safety profile.

As recently reported by Gershon et al. [5], a well conducted meta-analysis of RCTs provides the highest level of evidence, even greater than that obtained by single RCTs. Moreover, along with the effect estimates, network meta-analyses may produce supporting information of considerable interest for clinicians in the form of treatment rankings, generally summarized by a parameter called the surface under the cumulative ranking curve (SUCRA) [6]. Indeed SUCRA facilitates the interpretation of the results from multiple comparisons, but the resulting rankings are specific for each single outcome.

Therefore, the aim of this study was to perform a high-quality systematic review with meta-analysis by including in the network the RCTs

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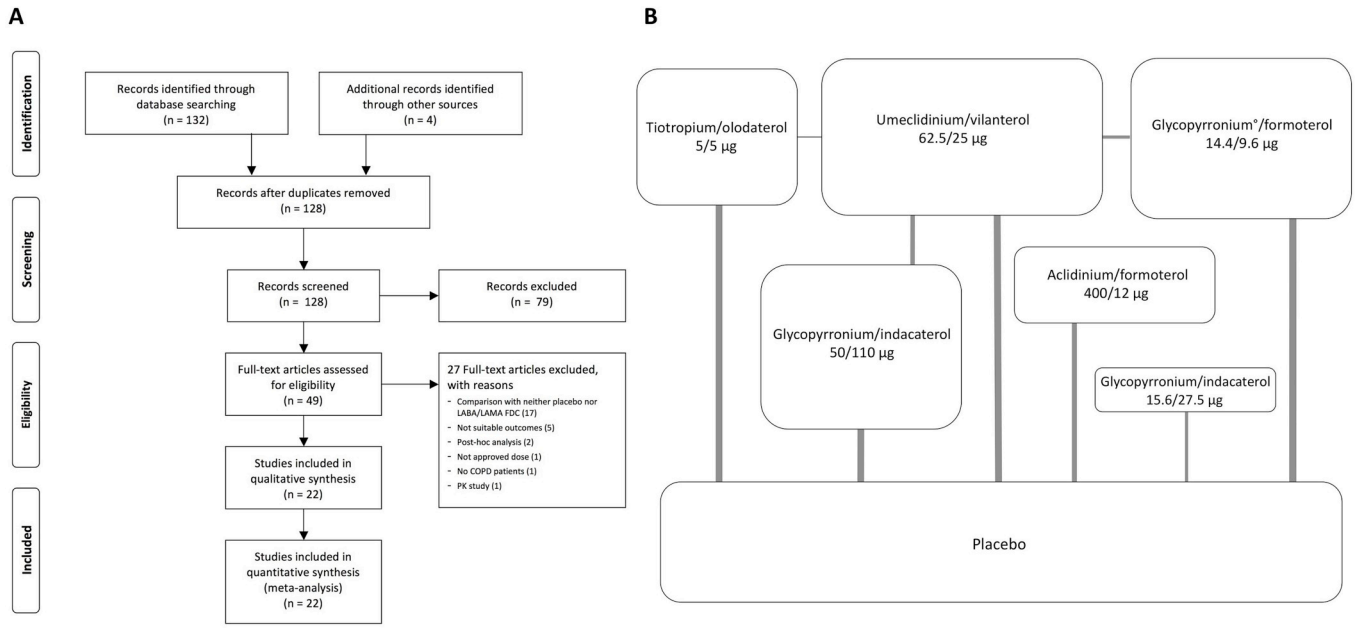

Fig. 1. PRISMA flow diagram for the identification of studies included in the network meta-analysis (A) and diagram displaying the network across the treatments (B): the links between nodes indicate the direct comparisons between pairs of treatments, the thickness of lines is proportional with the number of patients comparing pairs of treatments head-to-head. °Equivalent to glycopyrrolate 18 µg.

that directly compared the currently approved LABA/LAMA FDCs with placebo, along with the RCTs that have directly compared at least two different LABA/LAMA FDCs. The primary outcome of this study was the IBiS score, an **I**mplemented **Bi**dimensional **S**UCRA score that permits to assess in a single outcome measure the overall efficacy and cardiovascular safety profile of the investigated medications.

2. Materials and methods

2.1. Search strategy

This network meta-analysis has been registered in PROSPERO (registration number: CRD42017070100; available at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017070100), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [7]. The PRISMA-P flow diagram and network nodes are shown in Fig. 1. This quantitative synthesis satisfied all the recommended items reported by the PRISMA-P checklist [7].

Two reviewers (PR and LC) performed a comprehensive literature search from May 25th 2019 to May 30th 2019 for RCTs evaluating the impact of dual bronchodilation therapy in COPD patients. The PICO (Patient problem, Intervention, Comparison, and Outcome) framework was used to develop the literature search strategy, as previously described [8]. Namely, the "Patient problem" included subjects affected by COPD; the "Intervention" regarded the administration of LABA/LAMA FDC therapy; the "Comparison" was performed with regard to other LABA/LAMA FDCs or placebo; the "Outcomes" were lung function via the assessment of the change in FEV_1, dyspnea via the assessment of the change in transitional dyspnea index (TDI), health-related quality of life (HRQoL) via the assessment of the change in St' George Respiratory Questionnaire (SGRQ), and cardiovascular safety profile via the assessment of the risk of cardiovascular serious adverse events (SAEs).

RCTs on LABA/LAMA FDCs currently approved in COPD by the European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA) were searched. Specifically, aclidinium/formoterol 400/12 µg (A/F 400/12) AND/OR glycopyrronium/formoterol 14.9/9.6 µg (G/F 14.4/9.6) AND/OR glycopyrronium/indacaterol 15.6/27.5 µg (G/I 15.6/27.5) AND/OR G/I 50/110 AND/OR T/O 5/5 AND/OR U/V 62.5/25 were searched for the FDCs, and the terms "chronic obstructive pulmonary disease" AND/OR "COPD" were searched for the disease in Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Scopus, Web of Science, ClinicalTrials.gov and EU Clinical Trials Register databases in order to provide for relevant studies lasting ≥2 weeks reported in English and published up to May 30th 2019. Citations of recently published meta-analyses and reviews were checked to select further pertinent studies, if any [9–11].

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 [12].

Two reviewers (PR and LC) independently checked the relevant RCTs identified from literature searches and databases. RCTs were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

2.2. Study selection

The criteria to include the studies in the network meta-analysis were high-quality RCTs with a Jadad score ≥3 that lasted ≥2 weeks in which moderate-to-very severe COPD patients were enrolled, that compared LABA/LAMA FDCs vs. placebo or that compared different LABA/LAMA FDCs each other.

Exclusion criteria were: Jadad score < 3, study duration < 2 weeks, mild COPD patients, no comparison between LABA/LAMA FDCs and placebo, no comparison between different LABA/LAMA FDCs each other. RCTs that compared LABA/LAMA FDCs exclusively vs. monocomponents included or not included in the FDC, that compared LABA/LAMA FDCs vs. open LABA/LAMA combinations, or that compared LABA/LAMA FDCs exclusively vs. FDCs including inhaled corticosteroids (ICSs) were also excluded from the network meta-analysis.

Two reviewers (PR and LC) independently checked the relevant studies identified from literature searches obtained from the already mentioned databases. The studies were selected in agreement with the above-mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Table 1
Patient demographics, baseline and study characteristics as reported by the RCTs included in the network meta-analysis.

Author, study and year	ClinicalTrials.gov Identifier	Study design	Duration of treatment (weeks)	Number of analyzed patients	Drugs (doses)	Comparator	Inhaler device
AERISTO, 2019 [2],	NCT03162055	Multicentre, randomized, double-blind, double-dummy, parallel group, active-controlled	24	1016	Glycopyrronium°/formoterol 14.4/9.6 μg	Umeclidinium/vilanterol 62.5/25 μg	PMDI (Co-Suspension™ Delivery Technology); umeclidinium/vilanterol 62.5/25 μg: DPI (Ellipta®)
Feldman et al., 2017 [3]	NCT02799784	Randomized, open-label, cross-over	8	236	Umeclidinium/vilanterol 62.5/25 μg	Tiotropium/olodaterol 5/5 μg	Umeclidinium/vilanterol 62.5/25 μg: DPI (Ellipta®); tiotropium/olodaterol 5/5 μg: SMI (Respimat®)
Kerwin et al., 2017 [4]	NCT02487446, NCT02487498	Multicentre, randomized, double-blind, active-controlled, cross-over, double-dummy	12	712	Glycopyrronium/indacaterol 15.6/27.5 μg	Umeclidinium/vilanterol 62.5/25 μg	NA
D'Urzo et al., 2017 [28]	NCT01572792	Randomized, double-blind, parallel-group, placebo- and active-controlled	28	328	Aclidinium/formoterol 400/12 μg	Placebo	DPI (Genuair®/Pressair®)
D'Urzo et al., AUGMENT-COPD, 2014 [29]	NCT01437397	Multicentre, randomized, double-blind, placebo-controlled	24	667	Aclidinium/formoterol 400/12 μg	Placebo	DPI (Genuair®/Pressair®)
Singh et al., ACLIFORM-COPD, 2014 [30]	NCT01462942	Multicentre, randomized, double-blind, parallel-group, active- and placebo-controlled	24	579	Aclidinium/formoterol 400/12 μg	Placebo	DPI (Genuair®/Pressair®)
Lipworth et al., PINNACLE 4, 2018 [31]	NCT02343458	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	24	786	Glycopyrronium°/formoterol 14.4/9.6 μg	Placebo	PMDI (Co-Suspension™ Delivery Technology)
Martinez et al., PINNACLE 1 and 2, 2017 [32]	NCT01854645, NCT01854658	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	24	1478	Glycopyrronium°/formoterol 14.4/9.6 μg	Placebo	PMDI (Co-Suspension™ Delivery Technology)
Mahler et al., FLIGHT, 2015 [33]	NCT01727141, NCT01712516	Multicentre, randomized, double-blind, parallel-group, placebo- and active-controlled	12	1016	Glycopyrronium/indacaterol 15.6/27.5 μg	Placebo	DPI (Neohaler®)
Watz et al., MOVE, 2016 [34]	NCT01996319	Multicentre, randomized, double-blind, placebo-controlled, crossover	3	194	Glycopyrronium/indacaterol 50/110 μg	Placebo	NA
Beeh et al., BRIGHT, 2014 [35]	NCT01294787	Multicentre, randomized, double-blind, placebo-controlled, three-period crossover, double-dummy	3	84	Glycopyrronium/indacaterol 50/110 μg	Placebo	DPI (Breezhaler®)
Mahler et al., BLAZE, 2014 [36]	NCT01490125	Multicentre, randomized, blinded, placebo-controlled, three-period crossover, double-dummy	6	246	Glycopyrronium/indacaterol 50/110 μg	Placebo	DPI (Breezhaler®)
Bateman et al., SHINE, 2013 [37]	NCT01202188	Multicentre, randomized, double-blind, parallel-group, placebo- and active-controlled	26	706	Glycopyrronium/indacaterol 50/110 μg	Placebo	DPI (Breezhaler®)
Dahl et al., ENLIGHTEN, 2013 [38]	NCT01120717	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, dummy	52	338	Glycopyrronium/indacaterol 50/110 μg	Placebo	DPI (NA)
O′ Donnell et al., MORACTO, 2017 [39]	NCT01533922, NCT01533935	Replicate, randomized, double-blind, placebo-controlled, incomplete-crossover	6	450	Tiotropium/olodaterol 5/5 μg	Placebo	SMI (Respimat®)
Troosters et al., PHYSACTO, 2016 [40]	NCT02085161	Randomized, partially double-blind, placebo-controlled, parallel-group	12	151	Tiotropium/olodaterol 5/5 μg	Placebo	SMI (Respimat®)

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Table 1 (*continued*)

Author, study and year	ClinicalTrials.gov Identifier	Study design	Duration of treatment (weeks)	Number of analyzed patients	Drugs (doses)	Comparator	Inhaler device
Beeh et al., 2015 [41]	NCT01559116	Multicentre randomized, double-blind, placebo-controlled, incomplete-crossover	6	139	Tiotropium/olodaterol 5/5 μg	Placebo	SMI (Respimat®)
Singh et al., OTEMTO, 2015 [42]	NCT01964352, NCT02006732	Multinational, replicate, randomized, double-blind, placebo-controlled, parallel group	12	811	Tiotropium/olodaterol 5/5 μg	Placebo	SMI (Respimat®)
Siler et al., 2016 [43]	NCT02152605	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	12	496	Umeclidinium/vilanterol 62.5/25 μg	Placebo	DPI (Ellipta®)
Zheng et al., 2015 [44]	NCT01636713	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	24	387	Umeclidinium/vilanterol 62.5/25 μg	Placebo	DPI (NA)
Maltais et al., 2014 [45]	NCT01323660, NCT01328444	Multicentre, randomized, placebo-controlled, parallel-group	12	603	Umeclidinium/vilanterol 62.5/25 μg	Placebo	DPI (Ellipta®)
Donohue et al., 2013 [46]	NCT01313650	Multicentre, randomized, double-blind, parallel-group, placebo-controlled	24	693	Umeclidinium/vilanterol 62.5/25 μg	Placebo	DPI (NA)

Author, study and year	Regimen of administration	Main inclusion criteria	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post bronchodilator FEV_1 (% predicted)	Jadad score
AERISTO, 2019 [2],	Glycopyrronium°/formoterol 14.4/9.6 μg: twice-daily; umeclidinium/vilanterol 62.5/25 μg: once daily	COPD (pre- and post-bronchodilator $FEV_1/FVC < 0.7$; post-bronchodilator $FEV_1 < 80\%$ predicted)	40–95	NA	NA	> 10	NA	4
Feldman et al., 2017 [3]	Umeclidinium/vilanterol 62.5/25 μg: once daily; tiotropium/olodaterol 5/5 μg: once daily	COPD (pre- and post-bronchodilator $FEV_1/FVC < 0.7$; post-bronchodilator $FEV_1 \geqslant 50\%$ and $\leq 70\%$ predicted)	64.4	60	53	50.2	59.6	3
Kerwin et al., 2017 [4]	Glycopyrronium/indacaterol 15.6/27.5 μg: once daily; umeclidinium/vilanterol 62.5/25 μg: twice daily	Moderate to very severe COPD (post-bronchodilator $FEV_1/FVC < 70\%$; post-bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ predicted; modified Medical Research Council Dyspnea Scale of grade ≥ 2)	64	53.1	57.1	53.3	54.3	5
D'Urzo et al., 2017 [28]	Twice-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; $FEV_1 \geq 30\%$ and $< 80\%$ predicted)	63.5	52	53.3	53.9	52.7	5
D'Urzo et al., AUGMENT-COPD, 2014 [29]	Twice-daily	Moderate to severe stable COPD (post-bronchodilator $FEV_1/FVC < 0.7$; $FEV_1 \geq 30\%$ and $< 80\%$ predicted)	63.9	51.4	51.3	53.3	52.9	3
Singh et al., ACLIFORM-COPD, 2014 [30]	Twice-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; $FEV_1 \geq 30\%$ and $< 80\%$ predicted)	63.5	69.5	47.8	> 10	54.8	4

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Table 1 (*continued*)

Author, study and year	Regimen of administration	Main inclusion criteria	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post bronchodilator FEV_1 (% predicted)	Jadad score
Lipworth et al., PINNACLE 4, 2018 [31]	Twice-daily	Moderate to very severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; < 80% predicted and ≥750 ml if FEV_1 < 30% of predicted normal value)	64.3	73.4	46.9	45.8	54.2	4
Martinez et al., PINNACLE 1 and 2, 2017 [32]	Twice-daily	Moderate to very severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; < 80% predicted and ≥750 ml if FEV_1 < 30% of predicted normal value)	63.0	55.1	53.2	51.4	51.7	4
Mahler et al., FLIGHT, 2015 [33]	Twice-daily	Stable COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	63.3	61.8	51.0	> 10	54.7	5
Watz et al., MOVE, 2016 [34]	Once-daily	Moderate to severe stable COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 40–80% predicted)	62.8	65.5	56.7	47.5	61.6	4
Beeh et al., BRIGHT, 2014 [35]	Once-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥40% and < 80% predicted)	62.1	63.1	53.6	≥10	55.9	4
Mahler et al., BLAZE, 2014 [36]	Once-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	< 65 years: 57.7%; ≥65: 42.23	70.3	56.1	45.5	46.0	3
Bateman et al., SHINE, 2013 [37]	Once-daily	Moderate to severe stable COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	64.2	74.6	40.3	> 10	55.5	4
Dahl et al., ENLIGHTEN, 2013 [38]	Once-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	62.7	76.7	45.2	37.2	57.9	5
O′ Donnell et al., MORACTO, 2017 [39]	Once-daily	COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	61.7	71.2	39.1	45.8	52.0	3
Troosters et al., PHYSACTO, 2016 [40]	Once-daily	COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	64.7	66.3	NA	> 10	NA	4
Beeh et al., 2015 [41]	Once-daily	COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 < 80% predicted)[a]	61.1	58.9	62.6	NA	54.0	3
Singh et al., OTEMTO, 2015 [42]	Once-daily	Moderate to severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$; FEV_1 ≥30% and < 80% predicted)	64.8	60.6	47.6	> 10	55.1	3
Siler et al., 2016 [43]	Once-daily	COPD (pre- and post-albuterol (salbutamol) $FEV_1/FVC < 0.7$; post-albuterol FEV_1 ≤70% predicted)	63.4	59	53.5	38.6	47.5	4
Zheng et al., 2015 [44]	Once-daily	COPD (postalbuterol $FEV_1/FVC < 0.7$; postalbuterol FEV_1 ≤70% predicted; dyspnea score ⩾2)	64.2	93	31.5	37.4	NA	4

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Table 1 (*continued*)

Author, study and year	Regimen of administration	Main inclusion criteria	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post bronchodilator FEV_1 (% predicted)	Jadad score
Maltais et al., 2014 [45]	Once-daily	Moderate to severe stable COPD (post-bronchodilator FEV_1/FVC < 0.7; $FEV_1 \geqslant 35\%$ and $\leqslant 70\%$ predicted)	62.0	55.4	62.0	48.1	51.3	4
Donohue et al., 2013 [46]	Once-daily	COPD (post-bronchodilator FEV_1/FVC < 0.7; $FEV_1 \leq 70\%$ predicted)	62.7	72.0	51.5	46.9	47.3	4

° Equivalent to glycopyrrolate 18 μg.
DPI: Dry Powder Inhaler; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; NA: not available; RCT: randomized controlled trial; PMDI: Pressurised Metered Dose Inhaler; SMI: Soft Mist Inhaler.
[a] In German sites only, $FEV_1 \geq 30\%$.

2.3. Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of the RCTs concerning the likelihood of bias related to randomization, double blinding, withdrawals and dropouts [13]. A Jadad score ≥ 3 was defined to identify high-quality studies. Two reviewers (PR and LC) independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of bias was assessed via the normalized consistency/inconsistency analysis to check whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [14]. The inconsistency of evidence was also assessed by quantifying the inconsistency factor, indicating whether one of the treatments had a different effect when it was compared with the others directly or indirectly in the loop [15].

Meta-regression analysis was performed to identify potential effect modifiers (i.e. duration of treatment, inhaler device, regimen of administration, age, sex, smoking habit, pack-years, post-bronchodilation FEV_1, Jadad score) that could have altered the comparison across LABA/LAMA FDCs with respect to the investigated outcomes. Meta-regression coefficient (slope) values ≤ 0.02 were considered very small and, thus, not relevant also in the presence of statistical significance [16].

The quality of the evidence was assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [17].

2.4. Data extraction

Data from included RCTs were extracted and checked for study design and duration, doses of medications, main inclusion criteria of each RCT, age, gender, smoking habits, FEV_1, TDI, SGRQ, cardiovascular SAEs, and Jadad score. Two reviewers (PR and LC) independently extracted the data, and then checked for accuracy; any inconsistency was resolved by consensus. Due to the complexity of this meta-analysis, data were extracted in agreement with DECiMAL recommendations [18].

2.5. Endpoints

The primary endpoint of this network meta-analysis was a novel index, the IBiS score, based on the change from baseline in trough FEV_1, TDI, SGRQ, and risk of cardiocascular SAEs, aimed to concomitantly rank the efficacy/safety profile of LABA/LAMA FDCs.

2.6. Data analysis

A network meta-analysis was performed to quantify and compare the efficacy/safety profile of LABA/LAMA FDCs included in the study.

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 was assessed via the Brooks-Gelman-Rubin method, as previously described [19].

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 [20,21]. 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) [22,23]. The posterior mean deviance of data points in the unrelated mean

Table 2
Relative effects with 95%CrI and overall GRADE score resulting from the network meta-analysis across LABA/LAMA FDCs on the main functional, clinical, and cardiovascular safety outcomes in COPD patients.

	FEV_1	TDI	SGRQ	Cardiovascular SAEs	GRADE
A/F 400/12 vs. G/F 14.4/9.6	3.37 (−95.31–102.45)	0.57 (−0.25–1.37)	0.44 (−2.70–3.74)	0.29 (0.05–1.76)	+ +
A/F 400/12 vs. G/I 15.6/27.5	−64.73 (−171.53–42.21)	−0.29 (−1.16–0.53)	2.57 (−0.80–6.26)	0.20 (0.01–2.89)	+ + +
A/F 400/12 vs. G/I 50/110	−66.57 (−167.24–37.04)	0.07 (−0.82–0.85)	0.61 (−3.91–5.24)	0.08 (0.01–0.61) *	+ + + +
A/F 400/12 vs. T/O 5/5	−97.47 (−189.96 −10.93) *	−0.31 (−1.13–0.45)	2.55 (−1.87–6.95)	0.53 (0.08–3.60)	+ + +
A/F 400/12 vs. U/V 62.5/25	−68.04 (−157.19–19.26)	0.25 (−0.56–1.04)	1.37 (−2.09–4.57)	0.29 (0.06–1.97)	+ +
G/F 14.4/9.6 vs. G/I 15.6/27.5	−68.07 (−166.07–31.00)	−0.89 (−1.80–0.02)	2.10 (−1.28–5.69)	0.67 (0.06–7.90)	+ + +
G/F 14.4/9.6 vs. G/I 50/110	−69.61 (−161.05–22.87)	−0.54 (−1.41–0.39)	0.14 (−4.26–4.59)	0.27 (0.03–1.84)	+ + +
G/F 14.4/9.6 vs. T/O 5/5	−101.04 (−180.49 −23.95) *	−0.91 (−1.78 −0.02) *	2.11 (−2.36–6.42)	1.76 (0.35–10.91)	+ + +
G/F 14.4/9.6 vs. U/V 62.5/25	−71.48 (−142.15 −0.39) *	−0.33 (−0.91–0.31)	0.91 (−2.49–3.99)	1.00 (0.31–4.53)	+ + + +
G/I 15.6/27.5 vs. G/I 50/110	−2.16 (−102.35–100.55)	0.33 (−0.54–1.26)	−1.94 (−6.68–2.63)	0.43 (0.02–5.97)	+ + +
G/I 15.6/27.5 vs. T/O 5/5	−33.34 (−121.19–54.41)	−0.07 (−0.91–0.86)	−0.01 (−4.85–4.57)	2.65 (0.20–40.89)	+ + +
G/I 15.6/27.5 vs. U/V 62.5/25	−3.35 (−84.13–75.34)	0.58 (−0.36–1.46)	−1.21 (−5.01–2.35)	1.53 (0.14–18.36)	+ + +
G/I 50/110 vs. T/O 5/5	−31.13 (−117.57–49.32)	−0.39 (−1.23–0.46)	1.99 (−3.54–7.33)	6.65 (0.93–61.41)	+ + + +
G/I 50/110 vs. U/V 62.5/25	−2.24 (−85.99–77.38)	0.22 (−0.70–1.08)	0.78 (−3.92–5.15)	3.59 (0.58–38.43)	+ + + +
T/O 5/5 vs. U/V 62.5/25	29.57 (−26.83–87.16)	0.59 (−0.25–1.45)	−1.20 (−5.76–3.22)	0.57 (0.11–2.88)	+ + + +

A/F 400/12: aclidinium/formoterol 400/12 μg; CrI: credible interval; FDCs: fixed-dose combinations; FEV_1: forced expiratory volume in 1 s; G/F 14.4/9.6; glycopyrronium/formoterol 14.9/9.6 μg; G/I 15.6/27.5: glycopyrronium/indacaterol 15.6/27.5 μg; G/I 50/110: glycopyrronium/indacaterol 50/110 μg; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; LABA: β_2-adrenoceptors agonist; LAMA: long-acting muscarinic antagonist; SAEs: serious adverse events; SGRQ: St' George Respiratory Questionnaire; TDI: transitional dyspnea index; T/O 5/5: tiotropium/olodaterol 5/5 μg; U/V 62.5/25: umeclidinium/vilanterol 62.5/25 μg *P < 0.05; + +: low quality of evidence; + + +: moderate quality of evidence; + + + +: high quality of evidence.

Table 3
Probability of best therapy in agreement with SUCRA values for LABA/LAMA FDCs in COPD patients with respect to efficacy and cardiovascular safety outcomes.

LABA/LAMA FDC	Specific SUCRA values			
	FEV_1	TDI	SGRQ	Cardiovascular SAEs
A/F 400/12	0.31	0.60	0.34	0.90
G/F 14.4/9.6	0.28	0.20	0.43	0.45
G/I 15.6/27.5	0.66	0.82	0.83	0.32
G/I 50/110	0.67	0.57	0.48	0.09
T/O 5/5	0.90	0.85	0.79	0.73
U/V 62.5/25	0.69	0.43	0.63	0.46

COPD chronic obstructive pulmonary disease; FDC: fixed-dose combination; FEV_1: forced expiratory volume in 1 s; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; SAEs: serious adverse events; SGRQ: St' George Respiratory Questionnaire; SUCRA: surface under the cumulative ranking curve; TDI: transitional dyspnea index.

effects model were 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 [24].

Results of the network meta-analysis were expressed as relative effect (RE) and 95% credible interval (95%CrI). The probability that each intervention arm was the most effective was calculated by counting the proportion of iterations of the chain in which each intervention arm had the highest mean difference, and the SUCRA, representing the summary of these probabilities, was also calculated [25]. The SUCRA is 1 when a treatment is certain to be the best, and 0 when a treatment is certain to be the worst [26].

In this study the rank resulting from SUCRA with respect to the efficacy variables (change from baseline in FEV_1, TDI, and SGRQ) and safety variable (risk of cardiovascular SAEs) were combined and plotted on different axes to produce radar charts [27], thus providing the IBiS score, in which the greater the percentage of area covered by the radar chart the greater the efficacy/safety profile of each LABA/LAMA FDC.

GeMTC [22] software was used for performing the meta-analysis, Microsoft Excel (Washington US) and GraphPad Prism (CA, US) software to graph the data, and GRADEpro GDT software to assess the quality of evidence [17]. The statistical significance was assessed for $P < 0.05$.

3. Results

3.1. Studies characteristics

Results obtained from 12,136 COPD patients (A/F 400/12: 6.33%; G/F 14.4/9.6: 14.73%; G/I 15.6/27.5: 3.58%; G/I 50/110: 13.76%; U/V 62.5/25: 18.27%; T/O 5/5: 9.20%; placebo: 34.13%) were selected from 22 studies including 28 RCTs [2–4,28–46] and published between 2013 and 2019. All the RCTs included in the network meta-analysis were randomized and blinded, with a period of treatment between 3 and 52 weeks. Patient demographics, baseline and study characteristics (Table 1) were homogeneous across the studies included in this meta-analysis and did not influence the effect of specific LABA/LAMA FDCs (meta-regression analysis: $P > 0.05$).

3.2. Network meta-analysis

Data resulting from the network meta-analysis across LABA/LAMA FDCs with respect to the main functional, clinical, and cardiovascular safety outcomes in COPD patients indicated that T/O 5/5 was significantly ($P < 0.05$) more effective than both A/F 400/12 (97.5 ml, 95%CrI 10.9–190.0) and G/F 14.4/9.6 (101.0 ml, 95%CrI 24.0–180.5) in improving trough FEV_1, and significantly ($P < 0.05$) more effective than G/F 14.4/9.6 in improving TDI (0.91 points, 95%CrI 0.02–1.78). Also U/V 62.5/25 significantly improved FEV_1 when compared to G/F 14.4/9.6 (71.5 ml, 95%CrI 0.5–142.2). The risk of cardiocascular SAEs was significantly ($P < 0.05$) greater in patients treated with G/I 50/110 than in those treated with A/F 400/12. Further effect estimates and 95%CrI resulting from the network meta-analysis are reported in Table 2.

The SUCRA indicated a specific rank of effectiveness with respect to the improvement in trough FEV_1 (T/O 5/5 > U/V 62.5/25 ≈ G/I 50/110 ≈ G/I 15.6/27.5 > A/F 400/12 ≈ G/F 14.4/9.6), TDI (T/O 5/5 ≈ G/I 15.6/27.5 > A/F 400/12 ≈ G/I 50/110 > U/V 62.5/25 > G/F 14.4/9.6), and SGRQ (G/I 15.6/27.5 ≈ T/O 5/5 > U/V 62.5/25 > G/I 50/110 > G/F 14.4/9.6 > A/F 400/12). Concerning the cardiovascular safety profile, the rank resulting from SUCRA was: A/F 400/12 > T/O 5/5 > U/V 62.5/25 ≈ G/F 14.4/9.6 > G/I 15.6/27.5 » G/I 50/110. Detailed SUCRA values are reported in Table 3.

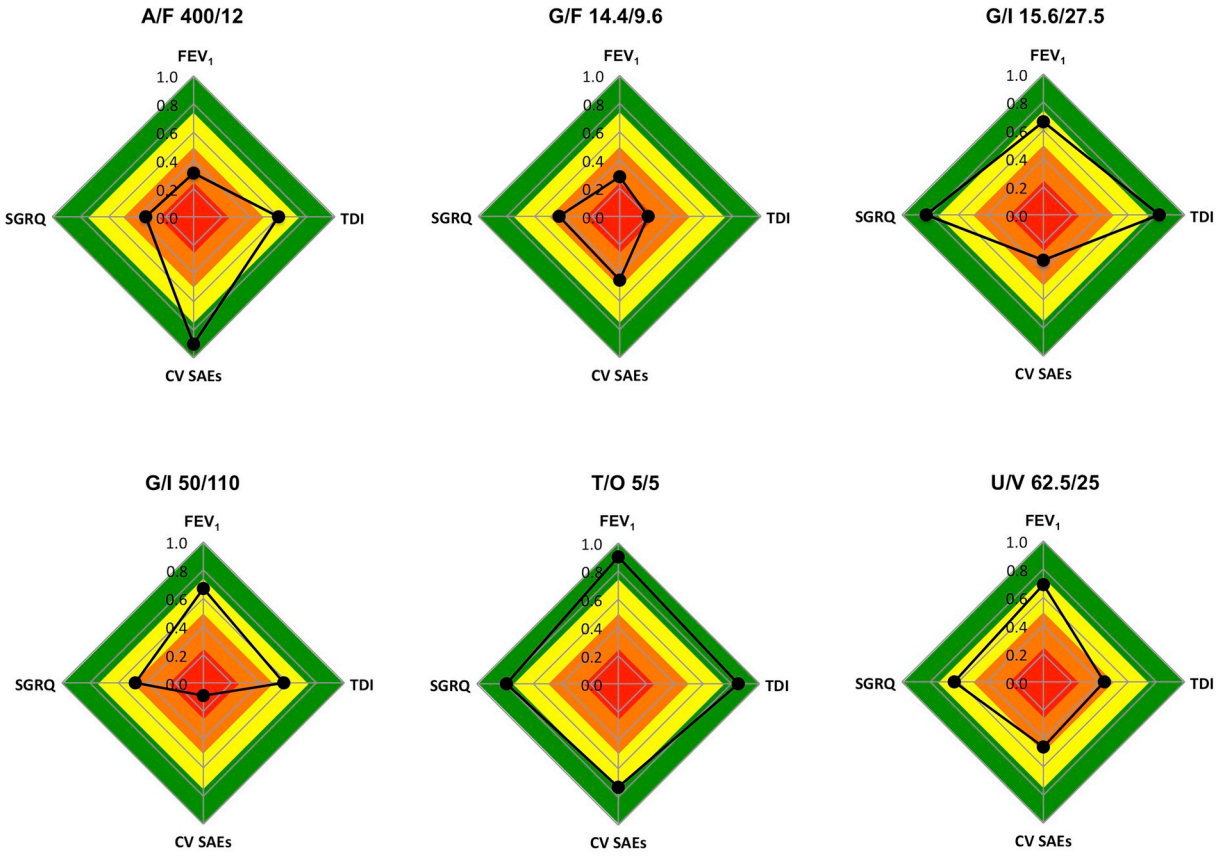

Fig. 2. Graphical representation of combined efficacy/safety profile of LABA/LAMA FDCs in COPD patients in agreement with the IBiS score: the greater the area, the better the efficacy/safety profile. COPD chronic obstructive pulmonary disease; CV: cardiovascular; FDC: fixed-dose combination; FEV_1: forced expiratory volume in 1 s; IBiS: Implemented Bidimensional SUCRA; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; SAEs: serious adverse events; SGRQ: St' George Respiratory Questionnaire; SUCRA: surface under the cumulative ranking curve; TDI: transitional dyspnea index. Red: first quartile; orange: second quartile; yellow: third quartile; green: fourth quartile. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The combined efficacy/safety profile resulting from the IBiS score provided the following rank: T/O 5/5 (area 66.83%) » G/I 15.6/27.5 (area 40.43%) > U/V 62.5/25 (area 30.48%) ≈ A/F 400/12 (area 28.44%) > G/I 50/110 (area 19.95%) > G/F 14.4/9.6 (area 11.50%). Detailed data resulting from IBiS analysis are shown in Fig. 2.

3.3. Quality score, risk of bias and evidence profile

All the RCTs included in the network meta-analysis where high-quality studies (Jadad score ≥3).

The normalized consistency/inconsistency analysis showed that all the points fit adequately with the line of equality (overall goodness of fit: R^2 0.99; slope 0.96, 95%CI 0.95–1.00), indicating that this network meta-analysis was not affected by significant bias (Fig. 3A–D).

The lack of bias in the Bayesian network was further confirmed by the absence of significant ($P > 0.05$) inconsistency factor when the investigated FDCs were compared directly or indirectly. The meta-regression analysis indicated that no effect modifiers altered the comparison across the LABA/LAMA FDCs with respect to the investigated outcomes.

The GRADE system showed that the overall quality of evidence was moderate-to-high for most the FDCs comparisons, excluding A/F 400/12 vs. G/F 14.4/9.6 and A/F 400/12 vs. U/V 62.5/25 for which the quality of evidence was low.

4. Discussion

The results of this network meta-analysis demonstrate that T/O 5/5 was significantly more effective than A/F 400/12 and G/F 14.4/9.6 in improving trough FEV_1 ≈95 ml in COPD patients, and that U/V 62.5/25 significantly improved FEV_1 when compared to G/F 14.4/9.6, with effect estimate values that overcame the minimal clinically important difference (MCID) calculated vs. active comparators (MCID: > 60 ml) [47]. T/O 5/5 was also significantly more effective than G/F 14.4/9.6 in improving TDI, showing effect estimate values that were borderline the MCID (1 unit) [48]. Moreover, G/I 50/110 was significantly less safe than A/F 400/12 with respect to the risk of cardiovascular SAEs, with a relative risk of ≈11 that extensively exceeded the MCID when compared with active treatments (MCID: relative risk ≈1.2) [48–51].

Although no further significant differences were found across LABA/LAMA FDCs with respect to the investigated outcomes, the SUCRA analysis indicates that the currently available LABA/LAMA FDCs may have a different impact on FEV_1, TDI, SGRQ, and risk of cardiovascular SAEs. Specifically, T/O 5/5 was generally the most effective FDC characterized by a good safety profile, and A/F 400/12 was the safest FDC.

Thus, considering the combined analysis of the efficacy and cardiovascular safety profile of each FDC, the IBiS score provides the following rank: T/O 5/5 » G/I 15.6/27.5 > U/V 62.5/25 ≈ A/F 400/12 > G/I 50/110 > G/F 14.4/9.6. Indeed the IBiS analysis represents a simple graphical summary to display the combined efficacy/safety profile of the different LABA/LAMA FDCs investigated in this meta-analysis.

Paradoxically, in this quantitative sinthesys we have found that G/I 15.6/27.5 reached an IBiS score greater than G/I 50/110. This finding confirms previous evidence that administering G/I twice daily at lower

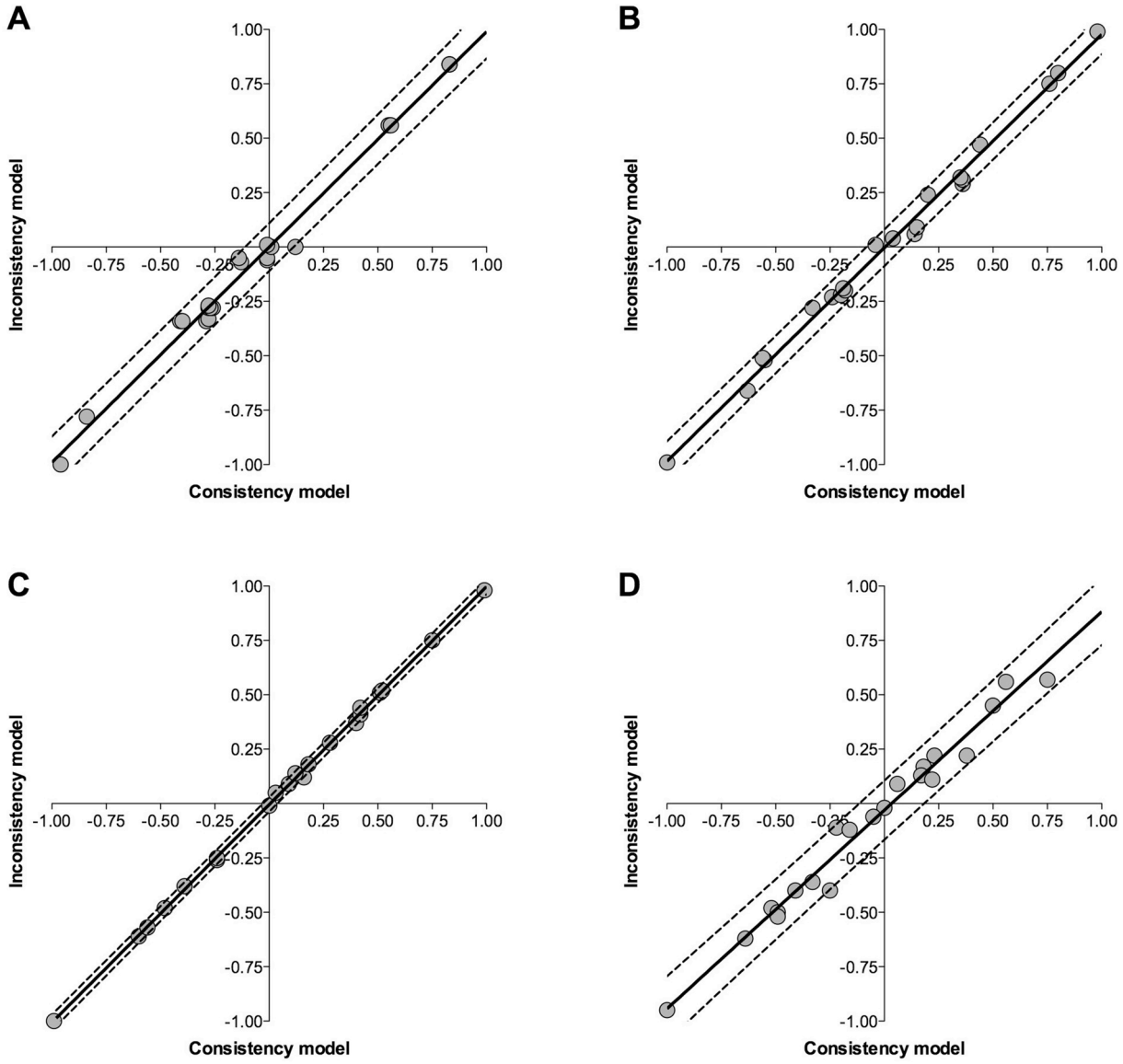

Fig. 3. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% confidence bands) of the combined efficacy/safety profile of LABA/LAMA FDCs in COPD patients with respect to the change from baseline in FEV_1 (A), TDI (B), SGRQ (C), and cardiovascular SAEs (D). COPD chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FDC: fixed-dose combination; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; SAEs: serious adverse events; SGRQ: St' George Respiratory Questionnaire; TDI: transitional dyspnea index.

dose works better than administering G/I once daily at higher dose [13].

The results of this network meta-analysis seem to be not affected by significant publication bias and, interestingly, no effect modifiers influenced the comparison across the investigated LABA/LAMA FDCs. The main inclusion criteria of the studies included in the network meta-analysis were heterogeneous, however the characteristics of patients (i.e. age, sex, smoking habit, pack-years, post-bronchodilation FEV_1) that were enrolled in each study were generally homogeneous across the RCTs. This finding may explain why no significant effect modifiers resulted from the meta-regression analysis.

The overall quality of evidence of this meta-analysis is moderate-to-high for most the LABA/LAMA FDCs comparisons, excluding A/F 400/12 vs. G/F 14.4/9.6 or U/V 62.5/25 for which the quality of evidence was low. In particular, the GRADE analysis of T/O 5/5 vs. G/I 50/110 or U/V 62.5/25, G/I 50/110 vs. U/V 62.5/25 or A/F 400/12, and U/V 62.5/25 vs. G/F 14.4/9.6 indicates that we can be very confident that the true effect lies close to the results of this meta-analysis, and that further research is very unlikely to change our confidence in the obtained findings [52].

IBiS may help clinicians in interpreting the data obtained from complex multiple-treatment meta-analysis, as it simplifies the information about the efficacy and safety of each FDC. Another advantage of IBiS is that the radar charts can be divided into quartiles. This permits to assess whether difference in preference between successive ranks remains the same across the entire ranking scale [53], thus providing suitable clinical information to identify the specific characteristics of each LABA/LAMA FDC. Although few statistical differences were found in this network meta-analysis, the ranking provided by IBiS score allows identifying what is the best LABA/LAMA FDC in agreement with the multifaceted functional, clinical, and cardiovascular safety needs of each COPD patient.

IBiS derives from SUCRA, and thus it could be affected by the same limitations of SUCRA itself, such as the level of accuracy that is related with the robustness of Bayesian network. Considering that in this meta-analysis the structure of network can be considered strong as it included four RCTs [2–4] that directly compared different LABA/LAMA FDCs, the studies were well-powered, and no risk of bias was detected, the

data resulting from IBiS can be considered reliable.

The main limitation of this study is that no comparison has been performed with respect to the risk of COPD exacerbation. In fact, across the 10 out of the 22 RCTs included in the network meta-analysis that lasted ≥6 months [2,28–32,37,38,44,46], only three studies reported the frequency of exacerbation as an efficacy endpoint [28,44,46]. The remaining RCTs did not report the frequency of exacerbation [2,31,32], or reported the events of exacerbation as safety endpoint [37,38]. In further studies the impact on exacerbations of LABA/LAMA FDCs was indirectly investigated via the EXAcerbations of Chronic obstructive pulmonary disease Tool Respiratory Symptoms (EXACT-RS) score [29,30]. Certainly this background does not permit to close the loop in the Bayesian network to include in the IBiS score the impact of the investigated LABA/LAMA FDCs on the risk of COPD exacerbation.

Concluding, this network meta-analysis suggests that each currently available LABA/LAMA FDC has a specific efficacy/safety profile that needs to be considered for personalized therapy in COPD. Future head-to-head RCTs focused on the impact of different LABA/LAMA FDCs on the risk of COPD exacerbation are needed to further improve the information provided by the IBiS score.

Conflicts of interest

PR reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, personal fees from AstraZeneca, grants and personal fees from Chiesi Farmaceutici, grants and personal fees from Almirall, grants from Zambon, personal fees from Biofutura, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees from Mundipharma, outside the submitted work.

MGM reports personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, personal fees from AstraZeneca, personal fees from Chiesi Farmaceutici, personal fees from Almirall, personal fees from ABC Farmaceutici, personal fees from GlaxoSmithKline, outside the submitted work.

BLR reports no conflict of interest

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LC reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, non-financial support from AstraZeneca, grants from Chiesi Farmaceutici, grants from Almirall, personal fees from ABC Farmaceutici, personal fees from Edmond Pharma, grants and personal fees from Zambon, personal fees from Verona Pharma, personal fees from Ockham Biotech, outside the submitted work.

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References

[1] GOLD. Global Initiative for Chronic Obstructive Lung Disease, Global strategy for diagnosis, management, and prevention of COPD – 2019 Report, Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.5-FINAL-04Nov2018_WMS.pdf, (2019) , Accessed date: 11 March 2019.

[2] AERISTO, Efficacy and safety of glycopyrronium/formoterol fumarate fixed-dose combination relative to umeclidinium/vilanterol fixed-dose combination over 24 Weeks in patients with moderate to very severe chronic obstructive pulmonary disease (AERISTO), NCT03162055 (available at: https://clinicaltrials.gov/ct2/show/results/NCT03162055, (2019) last access June 27, 2019). ClinicalTrialsgov.

[3] G.J. Feldman, A.R. Sousa, D.A. Lipson, L. Tombs, N. Barnes, J.H. Riley, et al., Comparative efficacy of once-daily umeclidinium/vilanterol and tiotropium/olodaterol therapy in symptomatic chronic obstructive pulmonary disease: a randomized study, Adv. Ther. (2017) 1–16.

[4] E. Kerwin, G.T. Ferguson, S. Sanjar, T. Goodin, A. Yadao, R. Fogel, et al., Dual bronchodilation with indacaterol maleate/glycopyrronium bromide compared with umeclidinium bromide/vilanterol in patients with moderate-to-severe COPD: results from two randomized, controlled, cross-over studies, Lung 195 (2017) 739–747.

[5] A.S. Gershon, S.R. Jafarzadeh, K.C. Wilson, A.J. Walkey, Clinical knowledge from observational studies. Everything you wanted to know but were afraid to ask, Am. J. Respir. Crit. Care Med. 198 (2018) 859–867.

[6] F. Catalá-López, A. Tobías, C. Cameron, D. Moher, B. Hutton, Network meta-analysis for comparing treatment effects of multiple interventions: an introduction, Rheumatol. Int. 34 (2014) 1489–1496.

[7] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst. Rev. 4 (2015) 1.

[8] C. Schardt, M.B. Adams, T. Owens, S. Keitz, P. Fontelo, Utilization of the PICO framework to improve searching PubMed for clinical questions, BMC Med. Inf. Decis. Mak. 7 (2007) 16.

[9] P. Rogliani, L. Calzetta, M.G. Matera, N. di Daniele, A. Girolami, M. Cazzola, et al., Inhaled therapies and cardiovascular risk in patients with chronic obstructive pulmonary disease, Expert Opin. Pharmacother. 20 (2019) 737–750.

[10] P. Rogliani, M.G. Matera, J. Ora, M. Cazzola, L. Calzetta, The impact of dual bronchodilation on cardiovascular serious adverse events and mortality in COPD: a quantitative synthesis, Int. J. COPD 12 (2017) 3469–3485.

[11] P. Rogliani, J. Ora, M.G. Matera, M. Cazzola, L. Calzetta, The safety of dual bronchodilation on cardiovascular serious adverse events in COPD, Expert Opin. Drug Saf. 17 (2018) 589–596.

[12] L. Calzetta, M. Cazzola, M.G. Matera, P. Rogliani, Adding a LAMA to ICS/LABA therapy: a meta-analysis of triple combination therapy in COPD, Chest 155 (2019) 758–770.

[13] L. Calzetta, P. Rogliani, M.G. Matera, M. Cazzola, A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD, Chest 149 (2016) 1181–1196.

[14] M. Cazzola, P. Rogliani, L. Calzetta, N.A. Hanania, M.G. Matera, Impact of mucolytic agents on COPD exacerbations: a pair-wise and network meta-analysis, COPD 14 (2017) 552–563.

[15] M. Cazzola, L. Calzetta, P.J. Barnes, G.J. Criner, F.J. Martinez, A. Papi, et al., Efficacy and safety profile of xanthines in COPD: a network meta-analysis, Eur. Respir. Rev. 27 (2018).

[16] L. Calzetta, M. Cazzola, M.G. Matera, P. Rogliani, Adding a LAMA to ICS/LABA therapy: a meta-analysis of triple combination therapy in COPD, Chest 155 (2019) 758–770.

[17] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, et al., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, J. Clin. Epidemiol. 64 (2011) 383–394.

[18] H. Pedder, G. Sarri, E. Keeney, V. Nunes, S. Dias, Data extraction for complex meta-analysis (DECiMAL) guide, Syst. Rev. 5 (2016) 212.

[19] L. Calzetta, P. Rogliani, J. Ora, E. Puxeddu, M. Cazzola, M. Gabriella Matera, LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment, Eur. Respir. Rev. 0 (2016) 1–11, https://doi.org/10.1183/16000617.0043-2016.

[20] G. Lu, A.E. Ades, Assessing evidence inconsistency in mixed treatment comparisons, J. Am. Stat. Assoc. 101 (2006) 447–459.

[21] D.J. Spiegelhalter, K.R. Abrams, J.P. Myles, Bayesian Approaches to Clinical Trials and Health-Care Evaluation, John Wiley & Sons, 2004.

[22] G. van Valkenhoef, G. Lu, B. de Brock, H. Hillege, A.E. Ades, N.J. Welton, Automating network meta-analysis, Res. Synth. Methods 3 (2012) 285–299.

[23] G. Valkenhoef, S. Dias, A.E. Ades, N.J. Welton, Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis, Res. Synth. Methods 7 (2016) 80–93.

[24] S. Dias, N.J. Welton, A.J. Sutton, D.M. Caldwell, G. Lu, A.E. Ades, Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials, Med. Decis. Mak. 33 (2013) 641–656.

[25] C.C. Dobler, M.E. Wilson, M.H. Murad, A pulmonologist's guide to understanding network meta-analysis, Eur. Respir. J. 52 (2018).

[26] M. Cazzola, L. Calzetta, P. Rogliani, M.G. Matera, Tiotropium Formulations and Safety: a Network Meta-Analysis, Therapeutic Advances in Drug Safety (2016), https://doi.org/10.1177/2042098616667304 2042098616667304.

[27] G. Gordon, The cost-effectiveness of public higher education: integrating accounting and quality to assess value, J. Account. Financ. 18 (2018).

[28] A. D'Urzo, S. Rennard, E. Kerwin, J.F. Donohue, A. Lei, E. Molins, et al., A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease, Respir. Med. 125 (2017) 39–48.

[29] A.D. D'Urzo, S.I. Rennard, E.M. Kerwin, V. Mergel, A.R. Leselbaum, C.F. Caracta, et al., Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study, Respir. Res. 15 (2014) 123.

[30] D. Singh, P.W. Jones, E.D. Bateman, S. Korn, C. Serra, E. Molins, et al., Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations

compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study, BMC Pulm. Med. 14 (2014) 178.
[31] B.J. Lipworth, D.J. Collier, Y. Gon, N. Zhong, K. Nishi, R. Chen, et al., Improved lung function and patient-reported outcomes with co-suspension delivery technology glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a randomized Phase III study conducted in Asia, Europe, and the USA, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 2969–2984.
[32] F.J. Martinez, K.F. Rabe, G.T. Ferguson, L.M. Fabbri, S. Rennard, G.J. Feldman, et al., Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using Co-suspension delivery technology in patients with COPD, Chest 151 (2017) 340–357.
[33] D.A. Mahler, E. Kerwin, T. Ayers, A. FowlerTaylor, S. Maitra, C. Thach, et al., FLIGHT: efficacy and safety of QVA149 (Indacaterol/Glycopyrrolate) versus its monocomponents and placebo in patients with COPD, Am. J. Respir. Crit. Care Med. 192 (2015) 1068–1079.
[34] H. Watz, C. Mailander, M. Baier, A. Kirsten, Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomised, placebo-controlled, crossover study (The MOVE Study), BMC Pulm. Med. 16 (2016) 95.
[35] K.-M. Beeh, S. Korn, J. Beier, D. Jadayel, M. Henley, P. D'Andrea, et al., Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study, Respir. Med. 108 (2014) 584–592.
[36] D.A. Mahler, M. Decramer, A. D'Urzo, H. Worth, T. White, V.K. Alagappan, et al., Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study, Eur. Respir. J. 43 (2014) 1599–1609.
[37] E.D. Bateman, G.T. Ferguson, N. Barnes, N. Gallagher, Y. Green, M. Henley, et al., Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study, Eur. Respir. J. 42 (2013) 1484–1494.
[38] R. Dahl, K.R. Chapman, M. Rudolf, R. Mehta, P. Kho, V.K. Alagappan, et al., Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study, Respir. Med. 107 (2013) 1558–1567.
[39] D.E. O'Donnell, R. Casaburi, P. Frith, A. Kirsten, D. De Sousa, A. Hamilton, et al., Effects of combined tiotropium/olodaterol on inspiratory capacity and exercise endurance in COPD, Eur. Respir. J. 49 (2017).
[40] T. Troosters, F. Maltais, N. Leidy, K.L. Lavoie, M. Sedeno, W. Janssens, et al., Effect of bronchodilation, exercise training, and behavior modification on Symptoms and physical activity in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 198 (2018) 1021–1032.
[41] K.M. Beeh, J. Westerman, A.M. Kirsten, J. Hebert, L. Gronke, A. Hamilton, et al., The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease, Pulm. Pharmacol. Ther. 32 (2015) 53–59.
[42] D. Singh, G.T. Ferguson, J. Bolitschek, L. Gronke, C. Hallmann, N. Bennett, et al., Tiotropium + olodaterol shows clinically meaningful improvements in quality of life, Respir. Med. 109 (2015) 1312–1319.
[43] T.M. Siler, A.C. Donald, D. O'Dell, A. Church, W.A. Fahy, A randomized, parallel-group study to evaluate the efficacy of umeclidinium/vilanterol 62.5/25 μg on health-related quality of life in patients with COPD, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 971–979.
[44] J. Zheng, N. Zhong, A. Newlands, A. Church, A.H. Goh, Efficacy and safety of once-daily inhaled umeclidinium/vilanterol in Asian patients with COPD: results from a randomized, placebo-controlled study, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 1753–1767.
[45] F. Maltais, S. Singh, A.C. Donald, G. Crater, A. Church, A.H. Goh, et al., Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials, Ther. Adv. Respir. Dis. 8 (2014) 169–181.
[46] J.F. Donohue, M.R. Maleki-Yazdi, S. Kilbride, R. Mehta, C. Kalberg, A. Church, Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD, Respir. Med. 107 (2013) 1538–1546.
[47] M. Cazzola, P. Rogliani, L. Calzetta, M.G. Matera, Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis, Eur. Respir. J. 52 (2018).
[48] M. Cazzola, W. MacNee, F.J. Martinez, K.F. Rabe, L.G. Franciosi, P.J. Barnes, et al., Outcomes for COPD pharmacological trials: from lung function to biomarkers, Eur. Respir. J. 31 (2008) 416–469.
[49] H. Magnussen, B. Disse, R. Rodriguez-Roisin, A. Kirsten, H. Watz, K. Tetzlaff, et al., Withdrawal of inhaled glucocorticoids and exacerbations of COPD, N. Engl. J. Med. 371 (2014) 1285–1294.
[50] L. Calzetta, M.G. Matera, F. Braido, M. Contoli, A. Corsico, F. Di Marco, et al., Withdrawal of inhaled corticosteroids in COPD: a meta-analysis, Pulm. Pharmacol. Ther. 45 (2017) 148–158.
[51] G.H. Guyatt, A.D. Oxman, R. Kunz, J. Brozek, P. Alonso-Coello, D. Rind, et al., GRADE guidelines 6. Rating the quality of evidence–imprecision, J. Clin. Epidemiol. 64 (2011) 1283–1293.
[52] H. Balshem, M. Helfand, H.J. Schunemann, A.D. Oxman, R. Kunz, J. Brozek, et al., GRADE guidelines: 3. Rating the quality of evidence, J. Clin. Epidemiol. 64 (2011) 401–406.
[53] G. Salanti, A.E. Ades, J.P. Ioannidis, Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial, J. Clin. Epidemiol. 64 (2011) 163–171.