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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\textbf{A B S T R A C T}

Despite several long-acting β\textsubscript{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 5/5μg (area 66.83%) \textgreater{} glycopyrronium/indacaterol 15.6/27.5μg (area 40.43%) \textgreater{} umeclidinium/vilanterol 62.5/25μg (area 30.48%) \textapprox{} aclidinium/formoterol 400/12μg (area 28.44%) > glycopyrronium/indacaterol 50/110μg (area 19.95%) > glycopyrronium/formoterol 14.4/9.6μg (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\textsubscript{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\textsubscript{1}), umeclidinium/vilanterol 62.5/25μg (U/V 62.5/25) resulted superior to both glycopyrronium/indacaterol 50/110μg (G/I 50/110) and tiotropium/olodaterol 5/5μg (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...
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 Implemented Bi-dimensional SURCA 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 FEV1, 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 14.9/9.6) 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 obtained from the already mentioned 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. mono-components 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>
<thead>
<tr>
<th>Author, study and year</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Study design</th>
<th>Duration of treatment (weeks)</th>
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<th>Drugs (doses)</th>
<th>Comparator</th>
<th>Inhaler device</th>
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<tbody>
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<td>AERISTO, 2019 [2], NCT03162055</td>
<td>Multicentre, randomized, double-blind, double-dummy, parallel group, active-controlled</td>
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Table 1 (continued)

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<th>Author, study and year</th>
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<th>Main inclusion criteria</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Current smokers (%)</th>
<th>Smoking history (pack-years)</th>
<th>Post bronchodilator FEV₁ (% predicted)</th>
<th>Jadad score</th>
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<td>AERSTO, 2019 [2]</td>
<td>Glycopyrronium/formoterol 14.4/9.6μg: twice-daily; umeclidinium/vilanterol 62.5/25μg: once daily</td>
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<td>Glycopyrronium/vilanterol 62.5/25μg: once daily; tiotropium/olodaterol 5/5μg: once daily</td>
<td>COPD (pre- and post-bronchodilator FEV₁/FVC &lt; 0.7; post-bronchodilator FEV₁ &gt;50% and ≤70% predicted)</td>
<td>64.4</td>
<td>60</td>
<td>53</td>
<td>50.2</td>
<td>59.6</td>
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<td>Kerwin et al., 2017 [4]</td>
<td>Glycopyrronium/indacaterol 15.6/27.5μg: once daily; umeclidinium/vilanterol 62.5/25μg: twice daily</td>
<td>Moderate to very severe COPD (post-bronchodilator FEV₁/FVC &lt; 70%; post-bronchodilator FEV₁ ≥ 30% and &lt; 80% predicted; modified Medical Research Council Dyspnea Scale of grade ≥2)</td>
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<td>51.4</td>
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<td>Singh et al., ACLIFORM-COPD, 2014 [30]</td>
<td>Twice-daily</td>
<td>Moderate to severe COPD (post-bronchodilator FEV₁/FVC &lt; 0.7; FEV₁ ≥30% and &lt; 80% predicted)</td>
<td>63.5</td>
<td>69.5</td>
<td>47.8</td>
<td>&gt; 10</td>
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<td>Lipworth et al., PINNACLE 4, 2018 [31]</td>
<td>Twice-daily</td>
<td>Moderate to very severe COPD (post-bronchodilator FEV₁/FVC &lt; 0.7; &lt; 80% predicted and ≥750 ml if FEV₁ &lt; 30% of predicted normal value)</td>
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<td>53.2</td>
<td>51.4</td>
<td>51.7</td>
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<td>Twice-daily</td>
<td>Stable COPD (post-bronchodilator FEV₁/FVC &lt; 0.7; FEV₁ ≥30% and &lt; 80% predicted)</td>
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<td>61.8</td>
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<td>63.1</td>
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<td>Beeh et al., 2015 [41]</td>
<td>Once-daily</td>
<td>COPD (post-bronchodilator FEV₁/FVC &lt; 0.7; FEV₁ ≥30% and &lt; 80% predicted)</td>
<td>61.1</td>
<td>58.9</td>
<td>62.6</td>
<td>NA</td>
<td>54.0</td>
<td>3</td>
</tr>
<tr>
<td>Singh et al., OTEMTO, 2015 [42]</td>
<td>Once-daily</td>
<td>Moderate to severe COPD (post-bronchodilator FEV₁/FVC &lt; 0.7; FEV₁ ≥30% and &lt; 80% predicted)</td>
<td>64.8</td>
<td>60.6</td>
<td>47.6</td>
<td>&gt; 10</td>
<td>55.1</td>
<td>3</td>
</tr>
<tr>
<td>Siler et al., 2016 [43]</td>
<td>Once-daily</td>
<td>COPD (pre- and post-albuterol (salbutamol) FEV₁/FVC &lt; 0.7; post-albuterol FEV₁ ≤70% predicted)</td>
<td>63.4</td>
<td>59</td>
<td>53.5</td>
<td>38.6</td>
<td>47.5</td>
<td>4</td>
</tr>
<tr>
<td>Zheng et al., 2015 [44]</td>
<td>Once-daily</td>
<td>COPD (postalbuterol FEV₁/FVC &lt; 0.7; postalbuterol FEV₁ ≤70% predicted; dyspnea score ≥2)</td>
<td>64.2</td>
<td>93</td>
<td>31.5</td>
<td>37.4</td>
<td>NA</td>
<td>4</td>
</tr>
</tbody>
</table>

(continued on next page)
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 FEV1, 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, FEV1, 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 FEV1, TDI, SGRQ, and risk of 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].

2.6. 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>
<thead>
<tr>
<th>Author, study and year</th>
<th>Main inclusion criteria</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Current smokers (%)</th>
<th>Smoking history (pack-years)</th>
<th>Post-bronchodilator FEV1 (% predicted)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltais et al., 2014 [45]</td>
<td>Moderate to severe stable COPD (post-bronchodilator FEV1/FVC &lt;0.7; FEV1 ≥35% and ≤70% predicted)</td>
<td>62.0</td>
<td>62.0</td>
<td>48.1</td>
<td>51.3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Donohue et al., 2013 [46]</td>
<td>Once-daily moderate to severe COPD (post-bronchodilator FEV1/FVC &lt;0.7; FEV1 &lt;70% predicted)</td>
<td>55.4</td>
<td>62.7</td>
<td>72.0</td>
<td>51.5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>° Equivalent to glycopyrrolate 18μg. DPI: Dry Powder Inhaler; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; NA: not available; RCT: randomized controlled trial; PMDI: Pressurized Metered Dose Inhaler; SMI: Soft Mist Inhaler.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

" In German sites only, FEV1 ≥30%.
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 was: A/F 400/12 ≈ G/I 15.6/27.5 ≈ G/F 14.4/9.6 > T/O 5/5 > G/I 50/110 > G/F 14.4/9.6 ≈ G/I 50/110 > U/V 62.5/25. Concerning the improvement in trough FEV1 (T/O 5/5 > U/V 62.5/25 ≈ G/I 50/110 > G/F 14.4/9.6 > A/F 400/12) and 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%CI resulting from the network meta-analysis are reported in Table 2.

The SUCRA indicated a specific rank of effectiveness with respect to the efficacy variables (change from baseline in FEV1, 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 (97.5ml, 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%CI 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 FEV1 (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.
The combined efficacy/safety profile resulting from the IBiS score provided the following rank:

\[
T/O \ 5/5 \ (\text{area} \ 66.83\%) \succ G/I \ 15.6/27.5 \ (\text{area} \ 40.43\%) \succ U/V \ 62.5/25 \ (\text{area} \ 30.48\%) \approx A/F \ 400/12 \ (\text{area} \ 28.44\%) \succ G/I \ 50/110 \ (\text{area} \ 19.95\%) \succ G/F \ 14.4/9.6 \ (\text{area} \ 11.50\%).
\]

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 were 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:

\[
T/O \ 5/5 \ (G/I \ 15.6/27.5 \succ U/V \ 62.5/25 \approx A/F \ 400/12 \succ G/I \ 50/110 \succ G/F \ 14.4/9.6).
\]

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 synthesis 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...
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 FEV₁) 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

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**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 FEV₁ (A), TDI (B), SGRQ (C), and cardiovascular SAEs (D). COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 s; FDC: fixed-dose combination; LABA: long-acting β₂-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; SAEs: serious adverse events; SGRQ: St’ George Respiratory Questionnaire; TDI: transitional dyspnea index.
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 [2,21,31,32], 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 EXACerations of Chronic obstructive pulmonary disease Tool Respiratory Symptoms (EXACT-RS) score [29,30]. 

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, and personal fees from Chiesi Farmaceutici, grants and personal fees from Almirall, grants from Zambon, personal fees from Biofuture, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees from Mundipharma, outside the submitted work.

MG M 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

MC reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, personal fees from AstraZeneca, personal fees from Chiesi Farmaceutici, grants and personal fees from Almirall, personal fees from ABC Farmaceutici, personal fees from Edmond Pharma, personal fees from Mundipharma, personal fees from Pfizer, outside the submitted work.

LC reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, non-financial support from AstraZeneca, grants from Chiesi 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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