Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis

Luigino Calzetta, Josuel Ora, Francesco Cavalli, Paola Rogliani, Denis E. O'Donnell, Mario Cazzola

PII: S0954-6111(17)30187-7
DOI: 10.1016/j.rmed.2017.06.020
Reference: YRMED 5196

To appear in: Respiratory Medicine

Received Date: 8 May 2017
Revised Date: 26 June 2017
Accepted Date: 28 June 2017


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: a pair-wise and network meta-analysis

Authors

Luigino Calzetta¹, Josuel Ora², Francesco Cavalli¹, Paola Rogliani¹,², Denis E. O'Donnell³, Mario Cazzola¹,*

¹Chair of Respiratory Medicine and Unit of Respiratory Clinical Pharmacology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
²Division of Respiratory Medicine, University Hospital Tor Vergata, Rome, Italy
³Division of Respiratory Medicine, Department of Medicine, Queen's University, Kingston, ON, Canada

Contact

*Correspondence: Mario Cazzola, Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133, Roma, Italy; e-mail: mario.cazzola@uniroma2.it
Abbreviations list
COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise test; ET: endurance time; ESWT: endurance shuttle walking test; FDC: fixed-dose combinations; FEV$_1$: forced expiratory volume in one second; HRQoL: health-related quality of life; IC: inspiratory capacity; ISWT: incremental shuttle walking test; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonists; MCID: minimal clinical important difference; MD: mean difference; OIS: optimal information size; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomised clinical trial; RE: relative effect; SE: standard error; SMD: standardized mean difference; SGRQ: St. George’s Respiratory Questionnaire; SUCRA: surface under the cumulative ranking curve; TDI: transition dyspnea index; Tlim: limit of tolerance; 95%CI: 95% confidence interval; 95%Crl: 95% credible level.
Abstract

Background
The ability to exercise is an important clinical outcome in COPD, and the improvement in exercise capacity is recognized to be an important goal in the management of COPD. Therefore, since the current interest in the use of bronchodilators in COPD is gradually shifting towards the dual bronchodilation, we carried out a meta-analysis to evaluate the impact of LABA/LAMA combination on exercise capacity and lung hyperinflation in COPD.

Methods
RCTs were identified after a search in different databases of published and unpublished trials. The aim of this study was to assess the influence of LABA/LAMA combinations on endurance time (ET) and inspiratory capacity (IC), vs. monocomponents.

Results
Eight RCTs including 1,632 COPD patients were meta-analysed. LABA/LAMA combinations were significantly (P<0.05) more effective than the LABA or LAMA alone in terms of the improvement in ET (+43 sec and +22 sec, respectively) and IC (+107 ml and +87ml, respectively). LABA/LAMA combinations showed the highest probability of being the best therapy with regard of both ET and IC (100% and 100%, respectively), followed by LAMA (66% and 64%, respectively) and LABA (32% and 36%, respectively), as indicated by the analysis of surface under the cumulative ranking curve (SUCRA). No publication bias was detected in this meta-analysis.

Conclusions
This meta-analysis clearly demonstrates that if the goal of the therapy is to enhance exercise capacity in patients with COPD, LABA/LAMA combination consistently met the putative clinically meaningful differences for both ET and IC and, in this respect, was superior to the monocomponents.

Keywords
COPD, exercise, LABA, LAMA, combination, meta-analysis.
Introduction

Exercise limitation, driven predominantly by activity-related breathlessness, is an important feature of chronic obstructive pulmonary disease (COPD) that compromises activities of daily living, leading to physical deconditioning and reduced quality of life [1]. This is the reason why improving dyspnoea and exercise tolerance are now recognised as important goals in the treatment of stable COPD and, consequently, direct assessment of the effects of interventions on exercise performance is relevant for COPD [2].

Although activity limitation in COPD is multifactorial, there is now compelling evidence that the intensity and quality of dyspnea during exercise in patients with COPD is influenced by the time to onset of critical mechanical volume constraints that are ultimately dictated by the magnitude of resting inspiratory capacity (IC) [3]. Lung hyperinflation is thought to represent a mechanical link between the characteristic expiratory airflow impairment, dyspnea, and exercise capacity [3]. Accordingly, therapies aimed at partially reversing pulmonary hyperinflation represent the first step in improving dyspnea and exercise capacity. There has recently been interest in measuring increases in IC as a surrogate measure of lung deflation during exercise in response to bronchodilator treatment in COPD. In general, long-acting bronchodilators have been proven to be able to reduce hyperinflation and therefore to improve dyspnea and tolerance to physical activity [4], and recently studies have demonstrated their effectiveness in improving both IC and exercise endurance time (ET) [5, 6]. Nevertheless, it has been suggested that further data on the benefits of long-acting bronchodilators on exercise tolerance are needed [5].

In these last years, the interest in the use of bronchodilators in COPD is gradually shifting towards the dual bronchodilation, i.e. the simultaneous use of two bronchodilators with different mechanisms of action. Several once- or twice-daily long-acting muscarinic antagonist (LAMA)/long-acting $\beta_2$-agonist (LABA) fixed-dose combinations (FDCs) have been developed because of the solid documentation that dual bronchodilation is superior to monotherapy with regards to classical markers of airflow limitation [7-9]. The impact of almost all LAMA/LABA FDCs on exercise endurance and lung function has also been assessed. Apparently, LABA/LAMA FDCs extend the improvements seen with single agents.
However, we still do not know if dual bronchodilation is consistently better than monocomponents in positively influencing exercise endurance and IC and, consequently, if it is more appropriate to treat patients with dual bronchodilation instead of single components when the aim of treatment is to improve dyspnea and exercise tolerance in COPD. In order to give an answer to these questions, we have carried out a pair-wise and network meta-analysis to evaluate the impact of LABA/LAMA combination on exercise capacity and lung hyperinflation in COPD. Actually, the meta-analytic method permits to derive estimates of effect across studies, to measure and investigate differences among interventions, and to interpret the obtained findings [10].

**Materials and methods**

**Searching strategy**

This pair-wise and network meta-analysis has been registered in PROSPERO (registration number: PROSPERO 2016:CRD42016048655, available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048655), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure 1) [11]. Furthermore, this synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist [12].

We undertook a comprehensive literature search for RCTs on exercise capacity lasting at least 2 weeks that examined the influence of treatment with LABAs and LAMAs administered in combination in patients suffering from COPD, diagnosed by pulmonary function testing.

The terms "exercise test", AND “COPD”, AND/OR “combination”, AND/OR “therapy” were searched. Published and unpublished randomised clinical trials (RCTs) were searched in PubMed, Scopus, Embase and Google Scholar through March 2017, and citations of recent published meta-analyses were examined in order to identify further pertinent studies, if any [13].

RCTs reported in English, carried out in COPD patients, and comparing the effects of LABA/LAMA combination therapy vs. at least one of the monocomponents contained into the combination were included in this meta-analysis. Furthermore, only studies involving constant work rate exercise testing as the measure of exercise tolerance
entered into the synthesis. Two reviewers 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.

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

The Jadad score, with a scale of 1 to 5 (score of 5 being the best quality), was used to assess the quality of the RCTs concerning the likelihood of biases related to randomisation, double blinding, withdrawals and dropouts [9].

Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of publication bias was assessed by applying the funnel plot and Egger test through the following regression equation: \( \text{SND} = a + b \times \text{precision} \), where \( \text{SND} \) represents the standard normal deviation (treatment effect divided by its standard error [SE]), and precision represents the reciprocal of the standard error. Evidence of asymmetry from Egger’s test was considered to be significant at \( P<0.1 \), and the graphical representation of 90% confidence bands have been presented [9].

The quality of the evidence has been assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [14] either overall for all the studies included in the synthesis, and for the subset meta-analyses.

**Data extraction**

Data from included studies were extracted and checked for study characteristics and duration, doses of medication, patient characteristics, age, gender, smoking habits, \( \text{FEV}_1 \), IC, exercise tests characteristics and Jadad score [9].

**End points**

The endpoint of this meta-analysis was to assess the influence of LABA/LAMA combination vs. monocomponents (pair-wise and network meta-analysis) and placebo (network meta-analysis) in the change of endurance time (ET), also defined as limit of tolerance (Tlim), assessed by cardiopulmonary exercise test (CPET) via cycle ergometer and treadmill tests, endurance shuttle walking test (ESWT), incremental
shuttle walking test (ISWT), and IC assessed via integrated volume measured by pneumotachograph.

**Data analysis**

We performed both a pair-wise and network meta-analysis to evaluate the impact of LABA/LAMA combination on exercise capacity and lung hyperinflation in COPD.

Since data have been selected from a series of studies performed by researchers operating independently, and a common effect size cannot be assumed, we used the random-effects model to perform the pair-wise meta-analysis in order to balance the study weights and to adequately estimate the 95% confidence interval (95%CI) of the mean distribution of drugs effect on the investigated variable.

Considering that ET was investigated via different exercise tests and, consequently, the resulting outcomes were not standardized, we standardized ET results before combining them in the meta-analysis by using the following formula: 

\[ SMD = \frac{(difference \ in \ mean \ outcome \ between \ groups)}{(standard \ deviation \ of \ outcome \ among \ participants)} \]

where SMD was the standardized mean difference, vs. monocomponents and/or placebo. On the other hand, since the change in IC was analysed at exercise isotime by using the same methods, this variable was expressed as mean difference (MD) vs. monocomponents [15]. A subset analysis concerning the different exercise tests, such as cycle ergometer test, shuttle walking test, and treadmill test has been performed. A sensitivity analysis has been carried out by the studies with no calculable Jadad score.

The network meta-analysis was performed by using a full Bayesian evidence network (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 by using the Brooks-Gelman-Rubin method [16]. Results of network meta-analysis have been expressed as relative effect (RE) and 95% credible level (95%Crl). Due to the complex evidence structure, the inconsistency of evidence has been assessed in addition to heterogeneity obtained from the pair-wise meta-analysis. While heterogeneity represents between-study variation in the measured relative effect of a pair of treatments, inconsistency can only occur when one of the treatment has a different effect when it is compared with the others [17]. 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 surface under the cumulative ranking curve (SUCRA), representing the summary of these probabilities, was also calculated. The SUCRA is 100% when a treatment is certain to be the best, and 0% when a treatment is certain to be the worst [18]. Subset analysis has been performed via SUCRA according with the airflow limitation.

The optimal information size (OIS) was calculated [19, 20], and the statistical significance was assessed for P<0.05.

The OpenMetaAnalyst and GeMTC [21] software were used for performing the meta-analysis, GraphPad Prism (CA, USA) software to graph the data, and GRADEpro to assess the quality of evidence [14]. The statistical significance was assessed for P<0.05, and moderate to high levels of heterogeneity were considered for $I^2>50%$.

Results

Study characteristics

Results obtained from 1,632 COPD patients were selected from 6 published and unpublished studies [22-27] including 8 RCTs (Table 1, Figure 2). The studies of Maltais et al. [24] and O’Donnell et al. [27] reported the data of two replicate RCTs each.

The period of treatment ranged from 2 to 12 weeks. Four studies [22-24, 27] had a Jadad score ≥3, whereas for two RTCs [25, 26] the Jadad score was not calculable because data were extracted from abstracts presented at International Congresses.

Pair-wise meta-analysis

The treatment with LABA/LAMA combination significantly improved both the ET (SMD, units of standard deviation: 0.15, 95%CI 0.07 – 0.23; P<0.001) and IC (MD, ml: 92.73, 95%CI 73.69 – 111.77; P<0.001), vs. monocomponents (Figure 3A and B). The sensitivity analysis of both ET and IC performed by excluding the studies with no calculable Jadad score (SMD, units of standard deviation: 0.14, 95%CI 0.06 – 0.23; IC MD, ml: 92.92, 95%CI 73.94 – 112.04) did not show any significant difference compared to the overall analysis (P>0.05 compared with data reported in Figure 3A and B).

The subset analysis concerning the different exercise tests indicated that the treatment with LABA/LAMA combination significantly improved the ET during both the cycle
ergometer test (MD, sec: 36.23, 95% CI 6.52 – 65.94; P<0.05) and shuttle-walking test (MD, sec: 26.59, 95% CI 11.21 – 41.97; P<0.001), vs. monocomponents. LABA/LAMA combinations were also significantly effective in improving the IC when patients performed cycle ergometer test (MD, ml: 93.80, 95% CI 68.62 – 118.98; P<0.001) and shuttle walking test (MD, ml: 89.85, 95% CI 51.46 – 128.25; P<0.001). The subset analysis for treadmill test was not performed because it was carried out in only one RCT assessing IC [22].

**Network meta-analysis**

The network meta-analysis showed that LABA/LAMA combinations significantly increased the ET vs. LABA (RE, sec: 43.38, CrI95% 24.24 - 63.83; P<0.05), LAMA (RE, sec: 21.96, CrI95% 2.48 - 41.93; P<0.05) and placebo (RE, sec: 60.26, CrI95% 42.55 - 78.60; P<0.05) (Figure 4A). The LABA/LAMA combinations also significantly improved the IC vs. LABAs (RE, ml: 107.40, CrI95% 84.55 - 132.47; P<0.05), LAMAs (RE, ml: 86.79, CrI95% 59.83 - 112.51; P<0.05), and placebo (RE, ml: 229.47, CrI95% 204.41 - 250.90; P<0.05) (Figure 4B).

LABA/LAMA combinations showed the highest probability of being the best therapy with regard of both ET and IC (100% and 100%, respectively), as confirmed by SUCRA analysis that indicated the following rank of effectiveness: LABA/LAMA combination >> LAMA > LABA > placebo (Table 2).

Subset analysis demonstrated that combining a LABA with a LAMA was always the best therapeutic option regardless of the level of airflow limitation. The analysis of RCTs that enrolled mostly GOLD II patients did not show difference between LABAs and LAMAs administered as monocomponents on both EC and IC. On the other hand, the benefit induced by LAMAs on both EC and IC was considerably greater than that induced by LABAs in patients with larger airflow limitation (mostly GOLD II-III) (Table 3).

**Bias and quality of evidence**

Substantial level of heterogeneity was detected by pair-wise meta-analysis for the impact of LABA/LAMA combination vs. monocomponents on ET (I² 47.71%, P<0.001) but not on IC (I² 0.00%, P=0.48), whereas no significant (P>0.05) inconsistency factors were found by network meta-analysis for both ET and IC. The subset meta-analysis did not show any substantial level of heterogeneity (P>0.05). The analysis performed via
Funnel plot and Egger’s tests indicate that smaller studies have not distorted the results of this meta-analysis, and that no publication bias exists in this quantitative synthesis (Figure 5).

Overall, all the RCTs included in this meta-analysis were characterized by high quality concerning the likelihood of bias related with randomisation, double blinding, withdrawals and dropouts. The results of only one RCT [23] were inconsistent when compared with those of the other studies, by eliciting the so called “small study effect” and inducing the tendency for treatment effect estimates to be greater than those in larger studies.

The cumulative number of enrolled COPD patients in the studies reached the OIS for a binary outcome meta-analysis for both ET (OIS: 1,182; delta: +421) and IC (OIS: 455; delta: +1,030).

The GRADE approach indicated high quality of evidence for the impact of LABA/LAMA combinations vs. monocomponents on both ET and IC (Table 4).

Taken together, these findings indicate that the results of this pair-wise and network meta-analysis are robust and reliable.

**Discussion**

The results of this meta-analysis demonstrate that LABA/LAMA combination is consistently superior to monocomponents, and LAMAs are more effective than LABAs in improving ET and IC. Since studies with no calculable Jadad score may affect the results of a meta-analysis, we have performed a sensitivity analysis by including exclusively studies that had a Jadad score ≥3. The sensitivity analysis confirmed the overall results obtained for both ET and IC.

Our data also show that LABA/LAMA combination increased the ET of ≃60 sec vs. placebo, with lower 95%CI of ≃43 sec, values that fit with the minimal clinical important difference (MCID) estimates of submaximal exercise ET on a cycle ergometer and endurance shuttle walking test ranging between 45 sec and 105 sec [1, 28]. Furthermore, LABA/LAMA combination increased the IC of ≃229 ml vs. placebo. Unfortunately, the MCID for IC has yet to be determined and, thus, no accepted MCID
for this variable is currently available [29, 30], although the European Respiratory Society exercise endurance task force has recently suggested that changes in IC between 140 ml and 200 ml after the administration of bronchodilators may be associated with significantly increased exercise endurance time in moderate-to-severe COPD patients [31].

We did not find heterogeneity for IC, a variable that was assessed in a homogeneous manner across the analysed studies. However, a substantial level of heterogeneity was detected for ET that was most likely related with the intrinsic characteristics of the analysis carried out on this variable. In fact, since ET was investigated via different exercise tests throughout the studies included in this meta-analysis (i.e. CPET, E SWT, and ISWT), it was not possible to standardize the resulting outcomes. Therefore, we applied the SMD approach instead of the MD analysis. In any case, the overall analysis of bias and quality of evidence indicate that the results of this meta-analysis are robust and reliable with regard of both ET and IC.

The MCID values are usually identified in the context of placebo-controlled RCTs, in which the measured treatment effects may be large, but for trials comparing active treatments, the differences between treatments may be smaller [28]. Our data indicate that there is an interesting signal of a likely clinically important change induced by dual bronchodilation when compared with LABAs, with an increase of ET of ≃43 sec and IC of ≃107 ml, whereas a lower and perhaps not clinically relevant improvement was detected versus LAMAs (≃22 sec and ≃87 ml, respectively). Nevertheless, our figures suggest that LABA/LAMA combinations have the highest probability of being the best therapy with regard of both ET and IC, with the following rank of effectiveness: LABA/LAMA combination >> LAMA > LABA > placebo.

The superior impact of LABA/LAMA combination than monocomponents on hyperinflation was to be expected considering the results of in vitro studies documenting the greater effectiveness of the LABA/LAMA combination on human small airways, compared with the partial effect of LAMA or LABA alone [32, 33]. We believe that this finding is of particular clinical relevance for improving air-trapping related to the obstruction of bronchioles. In fact, as airway patency over time increases with longer duration of a more potent bronchodilator action, emptying of peripheral airways with trapped air is facilitated, thus reducing hyperinflation and improving breathing.
mechanics ("pharmacological lung volume reduction") [34] and, consequently, enhancing the exercise capacity.

The results of our study are a significant step forward compared to the review of Liesker and colleagues published in 2002 [35]. In particular, we have provided a pragmatic synthesis of the most recent available data concerning the effects of the so-called "dual bronchodilator therapy" on exercise capacity and lung hyperinflation in patients with COPD. We must point out that evidences generated by our meta-analysis are of high quality, as indicated by the GRADE analysis. We must also highlight that we have not used a network approach that included studies of a single LABA or LAMA vs. placebo because we strongly believe that, regardless of the LAMA/LABA combination examined, dual bronchodilation is always more effective than the LAMA or LABA alone in terms of the improvement in lung function [9].

In this context, we must dutifully remark that, as already stressed in the past, we also strongly believe that the effectiveness of dual bronchodilation should always be compared with at least one of the monocomponents included in the FDCs, and not with different LABAs or LAMAs [36]. In fact, it should be obvious that comparing LABA/LAMA combinations with monocomponents characterised by different pharmacokinetics and pharmacodynamics represents a strict pharmacological matter, and not a merely statistical problem that may be solved by performing a subgroup analysis [36]. This is the reason why our meta-analysis did not take into account two FDCs, glycopyrronium/indacaterol and aclidinium/formoterol, already on the market. The effects of glycopyrronium/indacaterol on lung hyperinflation and physical activity in patients with moderate to severe COPD have been successfully evaluated in two studies [37, 38], but a study compared this FDC vs. placebo [37] and the other glycopyrronium/indacaterol vs. placebo and tiotropium [38], a LAMA not present in the tested combination. A study has evaluated the effect of the aclidinium/formoterol FDC on the hyperinflation, exercise endurance and physical activity in patients with moderate to severe COPD (ref ClinicalTrials.gov Identifier: NCT02424344). It has been completed but its results have not been posted yet and, in any case, it compared aclidinium/formoterol only vs. placebo.

Finally, although the results of this quantitative synthesis indicate that LABA/LAMA combination represents the best first line treatment for troublesome dyspnea, it is also possible that some patients would benefit more from dual than single bronchodilation,
while others may not. Pooling data from several RCTs could increase the power in order to adequately detect subgroups of responders, but this approach would require to use individual rather than global data that, unfortunately, are not currently accessible to independent researchers. However, in order to assess whether patients with different stages of COPD severity may have a different response to bronchodilators with regard to exercise capacity and lung hyperinflation, we have performed a subset analysis according with the GOLD stage. Intriguingly, the subset analysis confirms that LABA/LAMA combination is always the best therapeutic option regardless of airflow limitation. However, while LABAs were as effective as LAMAs in less severe patients, in more severe COPD patients the impact of LAMAs on both ET and IC was considerably greater than that of LABAs. These findings suggest that, although lung hyperinflation and exercise capacity are different issues, these variables are related with the specific response to pharmacological treatments not only in subjects with more severe airflow limitation, but also in less severe COPD patients in whom leg fatigue could overwhelm the improvement in lung function.

Conclusion

This quantitative synthesis has clearly demonstrated that if the goal of the therapy is to enhance exercise capacity in patients with COPD, only dual LABA/LAMA combination consistently met the putative MCIDs for both ET and IC and in this respect, was superior to the monocomponents. It follows that for patients with persistent troublesome dyspnea and exercise intolerance initiation of dual bronchodilator therapy would seem to be a reasonable first step in management. However, the optimal test for assessment of the impact of a therapeutic intervention on exercise capacity remains to be determined.
Acknowledgments

Study Registration
PROSPERO 2016:CRD42016048655

Contributions

MC and DOD contributed to study conception and design; contributed to interpretation of data; drafted the submitted article and revised it critically for important intellectual content and provided final approval of the version to be published.

LC contributed to study conception and design; contributed to acquisition, analysis, and interpretation of data; drafted the submitted article and revised it critically for important intellectual content and provided final approval of the version to be published.

PR contributed to interpretation of data; revised the submitted article critically for important intellectual content and provided final approval of the version to be published.

JO contributed to acquisition and interpretation of data; revised the submitted article critically for important intellectual content and provided final approval of the version to be published.

FC contributed to acquisition of data and provided final approval of the version to be published.

Guarantor
LC has the responsibility for the content of the manuscript, including the data and analysis.

Sources
This study was supported by institutional funds (University of Rome “Tor Vergata”, Rome, Italy).

Sponsor
Not applicable

Role of sponsor/funder
No sponsor/funder had a role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Prior abstract publication/presentation
Not applicable
Financial/non-financial disclosures

L.C. has participated as advisor in scientific meetings under the sponsorship of Boehringer Ingelheim, received non-financial support by AstraZeneca, received a research grant partially funded by Boehringer Ingelheim, Novartis and Almirall, and is or has been a consultant to Zambon and Verona Pharma.

J.O. has no conflict of interest to declare.

F.C. has no conflict of interest to declare.

P.R. participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis.

D.O’D. reports previous research grants, support and consultancy fees from Boehringer Ingelheim, advisory committee fees from Novartis, GlaxoSmithKline and Almirall, speaker fees from Boehringer Ingelheim, Novartis, GlaxoSmithKline, AstraZeneca and Almirall, and research support from GlaxoSmithKline and Nycomed.

M.C. has participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Lallemand, Mundipharma, Novartis, Pfizer, Verona Pharma, and Zambon, and is or has been a consultant to Chiesi Farmaceutici, Lallemand, Novartis, Verona Pharma, and Zambon.

The Department of Systems Medicine of the University of Rome "Tor Vergata" was funded by Almirall, Boehringer Ingelheim, Novartis, and Zambon to conduct research in the respiratory field.

References


38. Watz H, Mailänder C, Baier M, Kirsten A. Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to
## Tables

**Table 1.** Patient demographics, baseline and study characteristics.

<table>
<thead>
<tr>
<th>Study, year and reference</th>
<th>Trial Number Identifier</th>
<th>Study characteristics</th>
<th>Study duration (weeks)</th>
<th>Number of analyzed patients</th>
<th>Drugs</th>
<th>Doses and administration regimen</th>
<th>Patients characteristics</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Current smoker (%)</th>
<th>Smoking history (pack-years)</th>
<th>Post-bronchodilator FEV₁ (% predicted)</th>
<th>IC (L)</th>
<th>Exercise tests performed</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troosters, 2016 [25]</td>
<td>NCT02085161, PHYSACTO®</td>
<td>Randomized, partially double-blind, placebo-controlled, parallel-group trial</td>
<td>12</td>
<td>303</td>
<td>TIO/OLO vs. TIO</td>
<td>TIO/OLO 5/5 mcg q.d. + BM vs. TIO + BM 5/5 mcg q.d.</td>
<td>Moderate-to-severe COPD</td>
<td>≥40, ≤75</td>
<td>66.0</td>
<td>NA</td>
<td>&gt;10</td>
<td>56.7</td>
<td>NA</td>
<td>ISWT and ESWT</td>
<td>#</td>
</tr>
<tr>
<td>O'Donnel, 2015 [27]</td>
<td>NCT01533922, MORACTO™</td>
<td>Randomized, double-blind, placebo-controlled, and incomplete cross-over trial</td>
<td>6</td>
<td>295</td>
<td>TIO/OLO vs. TIO vs. OLO</td>
<td>TIO/OLO 0.5 mcg q.d. vs. TIO/OLO 2.5 mcg q.d. vs. TIO 5 mcg q.d. vs. OLO 5 mcg q.d.</td>
<td>Moderate-to-severe COPD</td>
<td>62.2</td>
<td>72.2</td>
<td>NA</td>
<td>&gt;10</td>
<td>58.6</td>
<td>1.71</td>
<td>CPET performed on a cycle ergometer</td>
<td>3</td>
</tr>
<tr>
<td>O'Donnel, 2015 [27]</td>
<td>NCT01533935, MORACTO™</td>
<td>Randomized, double-blind, placebo-controlled, and incomplete cross-over trial</td>
<td>6</td>
<td>291</td>
<td>TIO/OLO vs. TIO vs. OLO</td>
<td>TIO/OLO 0.5 mcg q.d. vs. TIO/OLO 2.5 mcg q.d. vs. TIO 5 mcg q.d. vs. OLO 5 mcg q.d.</td>
<td>Moderate-to-severe COPD</td>
<td>61.2</td>
<td>70.1</td>
<td>NA</td>
<td>&gt;10</td>
<td>57.7</td>
<td>1.73</td>
<td>CPET performed on a cycle ergometer</td>
<td>3</td>
</tr>
<tr>
<td>Webb, 2015 [26]</td>
<td>NCT01491802</td>
<td>Randomized, double-blind, placebo-controlled, and cross-over trial</td>
<td>4</td>
<td>17</td>
<td>UMEC/VI vs. UMEC</td>
<td>UMEC/VI 125/25 mcg q.d. vs. UMEC 125 mcg q.d.</td>
<td>Moderate COPD</td>
<td>66.0</td>
<td>47</td>
<td>NA</td>
<td>&gt;20</td>
<td>69.0</td>
<td>2.15</td>
<td>CPET performed on a cycle ergometer</td>
<td>#</td>
</tr>
<tr>
<td>Maltais, 2014 [24]</td>
<td>NCT01328444</td>
<td>Randomized, double-blind, placebo-controlled, and cross-over trial</td>
<td>12</td>
<td>348</td>
<td>UMEC/VI vs. VI vs. PBO</td>
<td>UMEC/VI 125/25 mcg q.d. vs. UMEC 125 mcg q.d. vs. VI 25 mcg q.d. vs. PBO</td>
<td>Moderate-to-severe COPD</td>
<td>61.6</td>
<td>56.1</td>
<td>NA</td>
<td>&gt;10</td>
<td>51.3</td>
<td>2.27</td>
<td>ISWT and ESWT</td>
<td>4</td>
</tr>
<tr>
<td>Study</td>
<td>NCT Number</td>
<td>Design</td>
<td>Duration</td>
<td>Treatment Comparison</td>
<td>COPD Severity</td>
<td>Follow-up</td>
<td>Exercise Test</td>
<td>Notes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td>-------------------------------</td>
<td>----------</td>
<td>-----------------------</td>
<td>----------------</td>
<td>-----------</td>
<td>---------------</td>
<td>--------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maltais, 2014</td>
<td>NCT01323660</td>
<td>Randomized, double-blind, placebo-controlled, and cross-over trial</td>
<td>12</td>
<td>UMEC/VI vs. UMEC vs. VI vs. PBO</td>
<td>Moderate-to-severe COPD</td>
<td>62.6 54.7 NA</td>
<td>ISWT and ESWT</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canto, 2012</td>
<td>NA</td>
<td>Randomized, double-blind, placebo-controlled, and cross-over trial</td>
<td>2</td>
<td>FOR + TIO vs. FOR</td>
<td>Moderate-to-severe COPD</td>
<td>56.0 NA NA</td>
<td>CPET performed on a cycle ergometer</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton, 2010</td>
<td>NCT00680056</td>
<td>Randomized, double-blind, placebo-controlled, and cross-over trial</td>
<td>2</td>
<td>FOR + TIO vs. FOR</td>
<td>Moderate-to-severe COPD</td>
<td>64.9 78.8 0</td>
<td>CPET performed on a treadmill</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#: not calculable because data have been extracted from abstracts presented at International Congresses
b.i.d.: bis in die, twice daily
BM: standardized physical activity self-management behaviour-modification
CPET: cardiopulmonary exercise test
ESWT: endurance shuttle walking test
ExT: exercise training
FEV₁: forced expiratory volume in one second
FOR: formoterol
ISWT: incremental shuttle walking test
mcg: microgram
OLO: olodaterol
PBO: placebo
q.d.: quaque die, once daily
TIO: tiotropium
UMEC: umeclidinium bromide
VI: vilanterol
Table 2. Probability of best therapy and SUCRA values for LABA/LAMA combination, monocomponents and placebo in COPD patients.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probability of being the best therapy (%)</th>
<th>SUCRA value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET</td>
<td>IC</td>
</tr>
<tr>
<td>LABA/LAMA combination</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>LABA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LAMA</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ET: endurance time  
IC: inspiratory capacity  
LABA: long-acting β₂-agonist  
LAMA: long-acting muscarinic antagonist  
SUCRA: surface under the cumulative ranking curve
Table 3. Subset analysis performed via SUCRA to assess the impact of LABA/LAMA combination, monocomponents and placebo on ET and IC according with the airflow limitation (GOLD II FEV$_1$ 59-79% predicted; GOLD III FEV$_1$ 30-49% predicted).

<table>
<thead>
<tr>
<th>Characteristics of patients enrolled in the RCTs</th>
<th>Mostly GOLD II patients</th>
<th>Mostly GOLD II-III patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>ET</td>
<td>IC</td>
</tr>
<tr>
<td>LABA/LAMA combination</td>
<td>97.0</td>
<td>100.00</td>
</tr>
<tr>
<td>LABA</td>
<td>47.7</td>
<td>50.7</td>
</tr>
<tr>
<td>LAMA</td>
<td>55.7</td>
<td>49.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

ET: endurance time  
FEV$_1$: forced expiratory volume in one second  
GOLD: Global Initiative for Chronic Obstructive Lung Disease  
IC: inspiratory capacity  
LABA: long-acting β$_2$-agonist  
LAMA: long-acting muscarinic antagonist  
RCTs: randomized clinical trials  
SUCRA: surface under the cumulative ranking curve
Table 4. GRADE evidence profile: impact of LABA/LAMA combinations vs. monocomponents on exercise capacity and lung hyperinflation in COPD patients.

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: endurance time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Randomised trials</td>
<td>Not serious</td>
<td>Serious *</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Strong association</td>
<td>HIGH</td>
</tr>
<tr>
<td>Outcome: inspiratory capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Randomised trials</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Strong association</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
Low quality: our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect)
Very low quality: we have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)

* I² 47.7%; P<0.01
LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist.
Figures legends

**Figure 1.** PRISMA flow diagram for the identification of studies included in the meta-analysis concerning the impact of LABA/LAMA combination on exercise capacity and lung hyperinflation in COPD patients. LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist.

**Figure 2.** Diagram displaying the network of four arms involved in the Bayesian analysis. The links between nodes indicate the direct comparisons between pairs of treatments. The numbers shown along the link lines indicate the number of COPD patients comparing pairs of treatments head-to-head. LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist.

**Figure 3.** Forest plot of pair-wise meta-analysis on the impact of the LABA/LAMA combinations vs. monocomponents on ET expressed as units of standard deviation (A), and IC expressed in ml (B). ET: endurance time; IC: inspiratory capacity; LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist.

**Figure 4.** Network meta-analysis on the influence of the LABA/LAMA combinations vs. monocomponents and placebo on the ET (A) and IC (B). ET: endurance time; IC: inspiratory capacity; LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist.

**Figure 5.** Publication bias assessment via Funnel plots (left panels) and Egger's test (right panels) for the impact of LABA/LAMA combinations vs. monocomponents on ET (A and B) and IC (C and D). ET: endurance time; IC: inspiratory capacity; LABA: long-acting $\beta_2$-agonist; LAMA: long-acting muscarinic antagonist; SND: standard normal deviate.
9,230 of records identified through database searching

1 of additional records identified through other sources

7,830 of records after duplicates removed

7,830 of records screened

7,566 of records excluded

264 of full-text articles assessed for eligibility

258 of full-text articles excluded, with reasons:
- Reviews (96)
- Inadequate inclusion criteria (82)
- Other languages (47)
- Systematic reviews (24)
- Meta analysis (3)
- Guidelines (2)
- Comments (1)
- Editorials (1)
- Lecturers (1)
- Letters (1)

6 of studies included in qualitative synthesis

6 of studies included in quantitative synthesis (meta-analysis)
### A

<table>
<thead>
<tr>
<th>Studies</th>
<th>estimate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosbrer (NCT02085161; TOSOLO05 vs. TOS5; group A) 2015</td>
<td>0.27 (-0.97, 0.61)</td>
</tr>
<tr>
<td>Tosbrer (NCT02085161; TOSOLO05 vs. TOS5; group B) 2015</td>
<td>0.25 (-0.94, 0.57)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.41 (-0.21, 0.05)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.46 (0.19, 0.18)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.48 (0.39, 0.27)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.46 (0.29, 0.29)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.45 (0.29, 0.29)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.25 (-0.06, 0.64)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.07 (-0.12, 0.27)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>0.02 (-0.93, 0.42)</td>
</tr>
<tr>
<td>Webb (NCT01481682; UMEC125/VI/25 vs. UMEC125) 2015</td>
<td>-0.16 (-0.80, 0.58)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.06 (-0.29, 0.46)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.02 (-0.37, 0.22)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.20 (-0.10, 0.50)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.12 (-0.22, 0.46)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-0.06 (-0.32, 0.20)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-0.06 (-0.34, 0.17)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-0.08 (-0.38, 0.25)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-0.04 (-0.12, 0.04)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.22 (-0.15, 0.44)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>0.19 (-0.13, 0.52)</td>
</tr>
<tr>
<td>Canto (NA; FOR127010 vs. FOR12) 2012</td>
<td>1.05 (0.02, 2.06)</td>
</tr>
</tbody>
</table>

**Overall** [P*<.001, P*<.001]**

### B

<table>
<thead>
<tr>
<th>Studies</th>
<th>estimate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>114.00 (29.50, 188.50)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>119.00 (44.59, 183.41)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>87.00 (10.02, 164.98)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>92.00 (18.15, 145.99)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>88.00 (16.68, 152.12)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>85.00 (16.68, 149.22)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>97.00 (28.14, 163.44)</td>
</tr>
<tr>
<td>O’Donnel (NCT10133322; TOSOLO05 vs. TOS5) 2015</td>
<td>99.00 (28.16, 171.34)</td>
</tr>
<tr>
<td>Webb (NCT01481682; UMEC125/VI/25 vs. UMEC125) 2015</td>
<td>93.00 (92.72, 73.22)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>9.00 (-9.12, 11.22)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>171.00 (66.89, 275.26)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>129.00 (28.38, 218.46)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-19.00 (-122.22, 84.22)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>143.00 (38.39, 248.19)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>101.00 (15.65, 191.55)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>129.00 (21.26, 246.74)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>135.00 (41.65, 228.46)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>-10.00 (-125.65, 105.65)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>127.00 (39.72, 234.78)</td>
</tr>
<tr>
<td>Maitais (NCT10132444; UMEC125/VI/25 vs. UMEC125) 2014</td>
<td>122.00 (28.75, 217.25)</td>
</tr>
<tr>
<td>Canto (NA; FOR127010 vs. FOR12) 2012</td>
<td>-119.00 (-430.73, 192.13)</td>
</tr>
<tr>
<td>Berton (NCT00860864; FOR127010 vs. FOR12) 2010</td>
<td>99.00 (-298.12, 327.72)</td>
</tr>
</tbody>
</table>

**Overall** [P*<0.001, P*<0.001]**
A

Favours monocomponents

Favours combination

LABA/LAMA combination vs. LABA
43 (24, 64)

LABA/LAMA combination vs. LAMA
22 (3, 42)

LABA/LAMA combination vs. placebo
60 (43, 79)

Relative Effect (95% CrI, Tlim, sec)

B

Favours monocomponents

Favours combination

LABA/LAMA combination vs. LABA
107 (85, 133)

LABA/LAMA combination vs. LAMA
87 (60, 113)

LABA/LAMA combination vs. placebo
229 (204, 251)

Relative Effect (95% CrI, IC, ml)
**Highlights**

- LABA/LAMA combinations consistently meet the putative minimal clinical difference for both endurance time and inspiratory capacity, being always superior to the monocomponents.
- For patients with persistent troublesome dyspnea and exercise intolerance initiation of dual bronchodilator therapy would seem to be a reasonable first step in management of COPD.
- However, the optimal test for assessment of the impact of a therapeutic intervention on exercise capacity remains to be determined.