Supplementary data

Dual bronchodilation in COPD: a simple pharmacological-based approach to meta-analysis

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Tables

Table S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3, 4**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**4**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**NA**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4, 5**

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**5**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5, 6**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**6**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**6**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**6, 7**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**7 supplemental data file**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**21, 22**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**9**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**8 - 16 supplemental data file**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**7 - 9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**9**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**9**

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**10, 11**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**10, 11**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**12**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table S2. Results from the network meta-analysis on the 14 studies [1-14] included in the quantitative synthesis: summary effects of LABA/LAMA combinations vs. LABAs and LAMAs administered as monocomponents on changes in trough FEV_1, SGRQ and TDI at 3 months, 6 months and 12 months. Data expressed as mean or median and 95% credible level (Crl). NC: not calculable.

		Consistency model			Inconsistency model		
		Relative effects (difference, mean and 95%Crl)		Variance (median and 95% Crl)	Inconsistency factors (median and 95% Crl)	Variance (median and 95% Crl)	
		LABA/LAMA combinations		Random effects standard deviation	LABA/LAMA combinations, LABAs, LAMAs	Random effects standard deviation	Inconsistency standard deviation
		vs. LABAs	vs. LAMAs				
Trough FEV_1 (ml)	**3 months**	103.53 (73.40, 134.74)	62.82 (38.10, 87.09)	32.39 (15.46, 57.00)	-38.32 (-124.26, 25.03)	30.99 (14.46, 56.09)	76.73 (3.75, 167.26)
	6 months	66.70 (41.45, 90.87)	38.00 (13.04, 62.19)	29.18 (16.92, 49.74)	10.23 (-30.62, 68.61)	28.81 (16.15, 50.21)	41.26 (1.67, 108.94)
	12 months	81.21 (67.22, 95.77)	55.78 (45.90, 65.91)	4.77 (0.07, 18.73	NC	6.51 (0.47, 19.23	48.94 (2.23, 96.67)
SGRQ (units)	**3 months**	-1.90 (-3.21, -0.65)	-1.99 (-2.80, -1.14)	0.40 (0.03, 1.49)	-0.12 (-2.34, 1.26)	0.38 (0.01, 1.63)	1.00 (0.05, 2.51)
	6 months	-1.57 (-2.28, -0.72)	-1.33 (-2.08, -0.59)	0.36 (0.01, 1.39)	-0.04 (-1.51, 1.54)	0.48 (0.04, 1.47)	1.13 (0.06, 3.12)
	12 months	-1.84 (-3.63, -0.20)	-0.62 (-1.99, 0.41)	0.69 (0.04, 2.63)	NC	0.74 (0.01, 2.65)	1.77 (0.08, 3.48)
TDI (units)	**3 months**	0.68 (0.20, 1.17)	0.64 (0.21, 1.09)	0.60 (0.11, 0.86	-0.27 (-1.51, 0.24)	0.58 (0.30, 0.87)	0.62 (0.11, 0.98)
	6 months	0.42 (0.29, 0.57)	0.37 (0.23, 0.52)	0.05 (0.00, 0.19)	-0.02 (-0.36, 0.33)	0.04 (0.00, 0.19)	0.29 (0.02, 0.76)
	12 months	0.59 (0.20, 1.01)	0.33 (0.01, 0.67)	0.19 (0,03,	NC	0.20 (0.03,	0.32 (0.02, 0.63)

0.55) 0.56)

Table S3. Optimal information size (OIS) for all outcomes and at each time point.

		OIS	
		LABA/LAMA combinations	
	Months	vs. LABAs	vs. LAMAs
Trough FEV_1	3	335	390
	6	472	462
	12	362	404
SGRQ	3	281	220
	6	398	386
	12	320	371
TDI	3	362	293
	6	259	276
	12	310	311

Figures

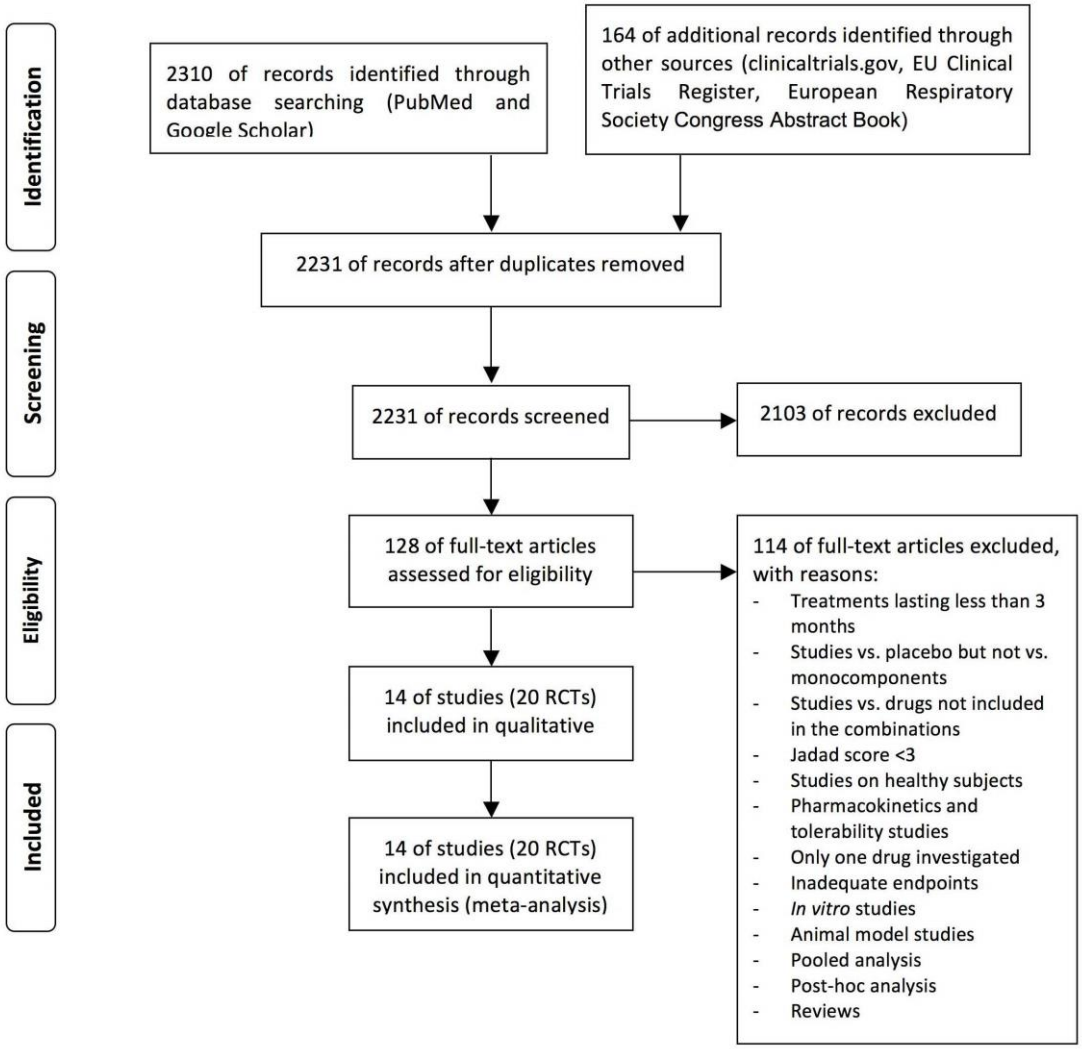

Figure S1. PRISMA flow diagram (updated April 15, 2016) for the identification of studies lasting at least 3 months and included in the meta-analysis concerning the influence of LABA/LAMA combinations, vs. at least one monocomponent, on trough FEV_1, SGRQ and TDI in COPD patients. RCTs: randomized clinical trials; SGRQ: St. George's Respiratory Questionnaire; TDI: transition dyspnoea index.

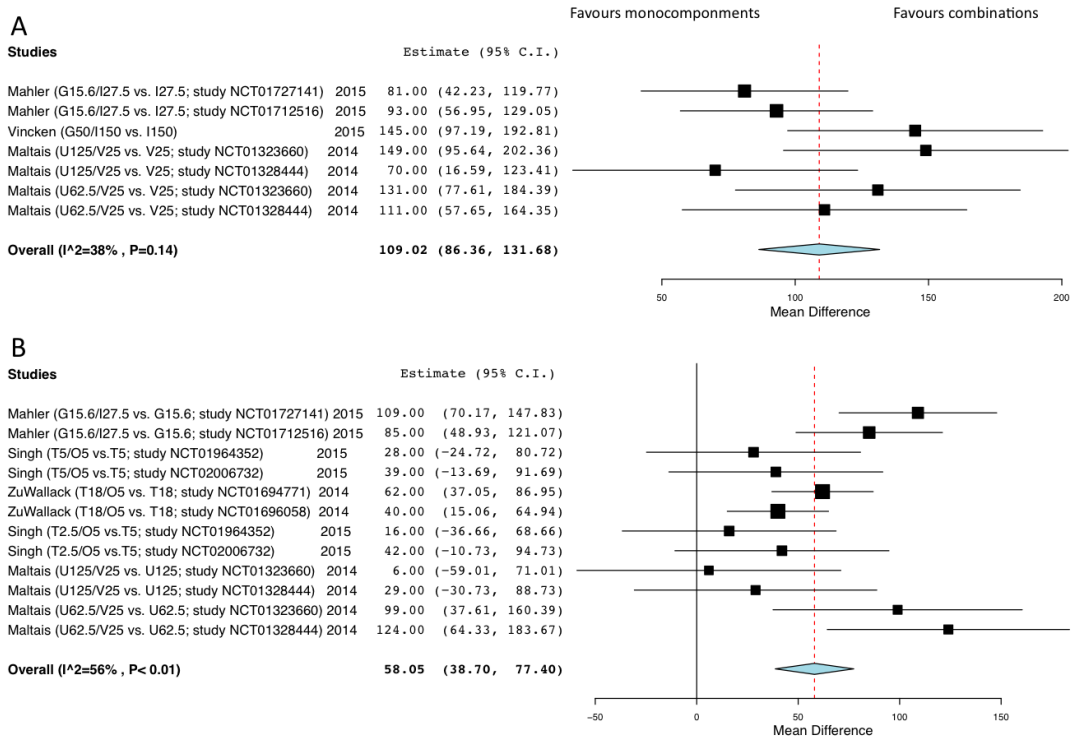

Figure S2. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in trough FEV_1 at 3 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as µg and results as the mean difference (ml). G: glycopyrronium, I: indacaterol, O: olodaterol, T: tiotropium, U: umeclidinium, and V: vilanterol.

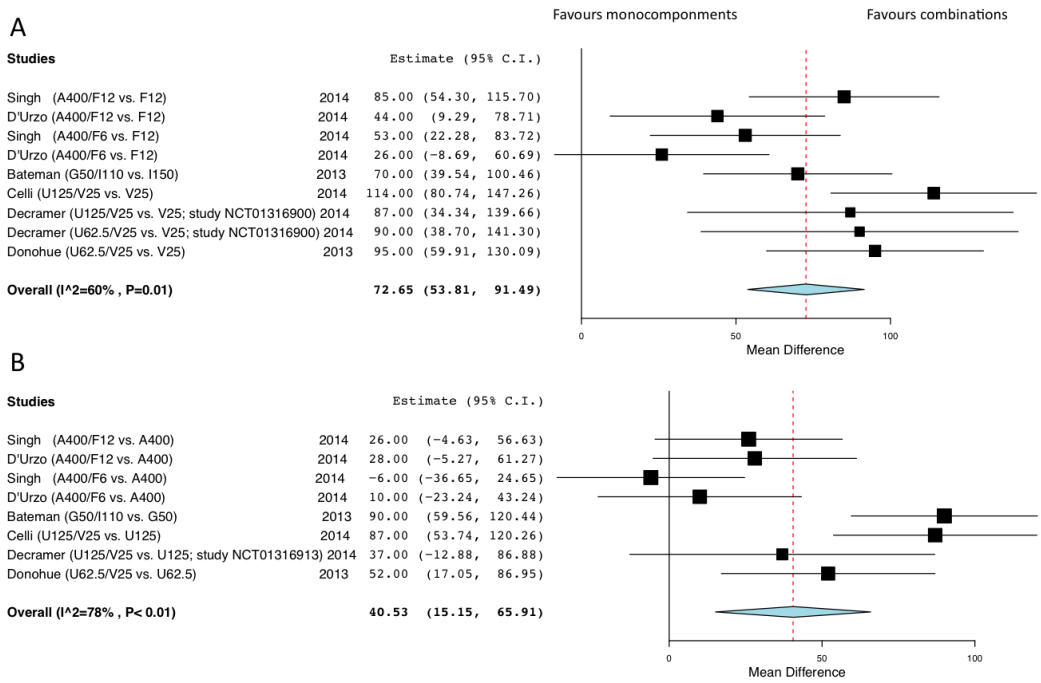

Figure S3. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in trough FEV_1 at 6 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (ml). A: aclidinium, F: formoterol, G: glycopyrronium, I: indacaterol, U: umeclidinium, and V: vilanterol.

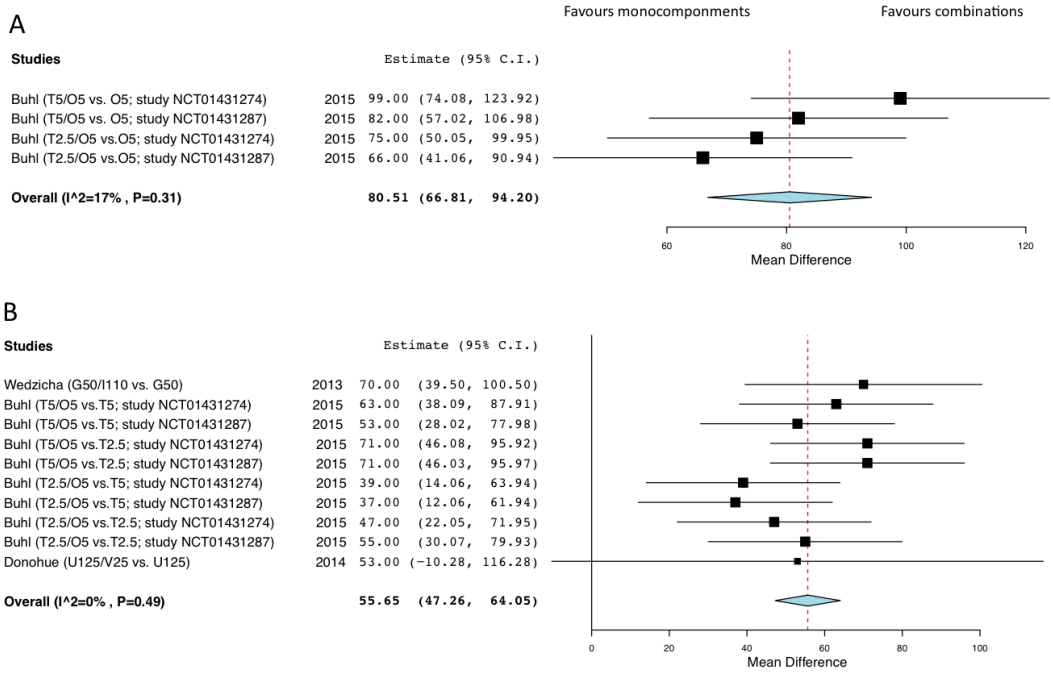

Figure S4. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in trough FEV_1 at 12 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (ml). G: glycopyrronium, I: indacaterol, O: olodaterol, T: tiotropium, U: umeclidinium, and V: vilanterol.

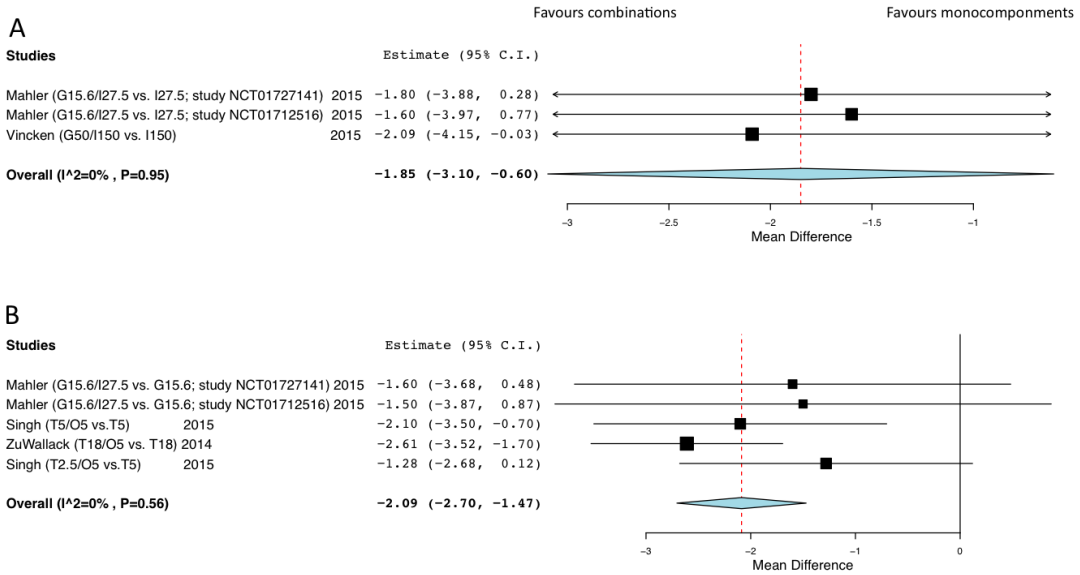

Figure S5. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in SGRQ at 3 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as µg and results as the mean difference (units). G: glycopyrronium, I: indacaterol, O: olodaterol, and T: tiotropium.

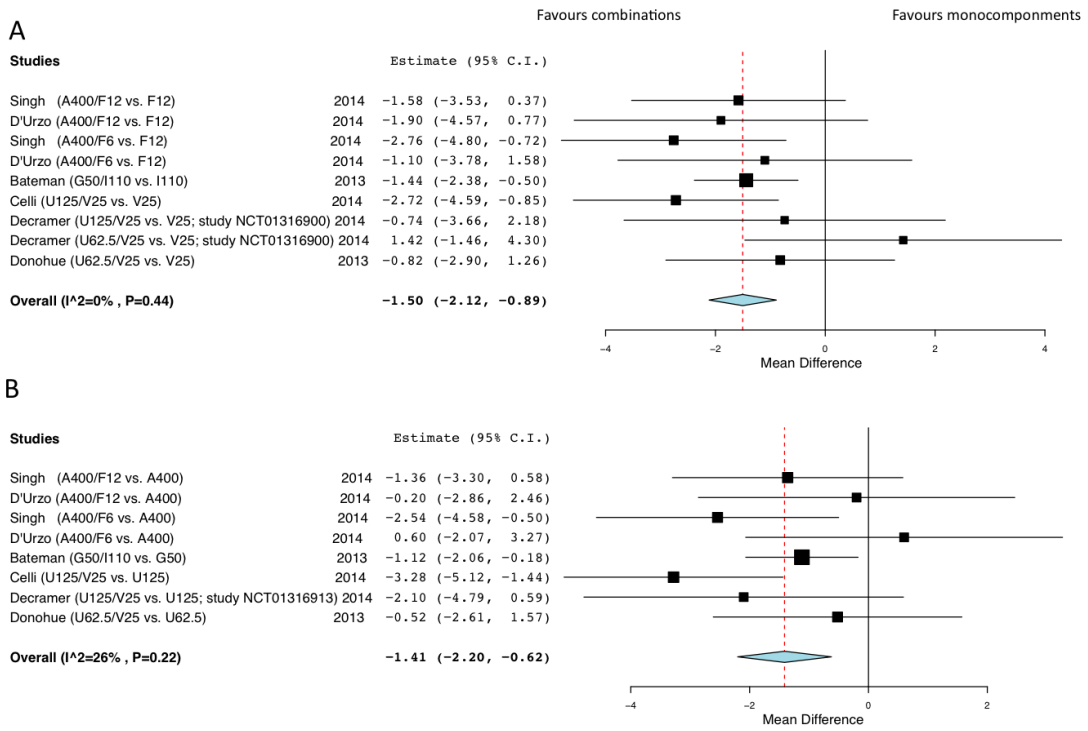

Figure S6. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in SGRQ at 6 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (units). A: aclidinium, F: formoterol, G: glycopyrronium, I: indacaterol, U: umeclidinium, and V: vilanterol.

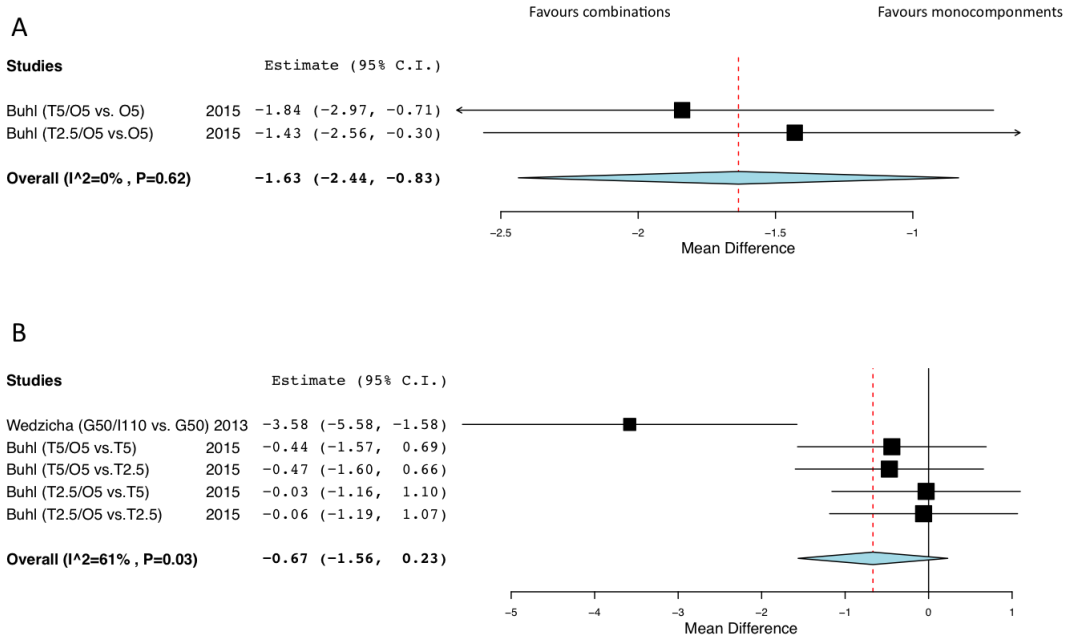

Figure S7. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations in SGRQ at 12 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (units). G: glycopyrronium, I: indacaterol, O: olodaterol, and T: tiotropium.

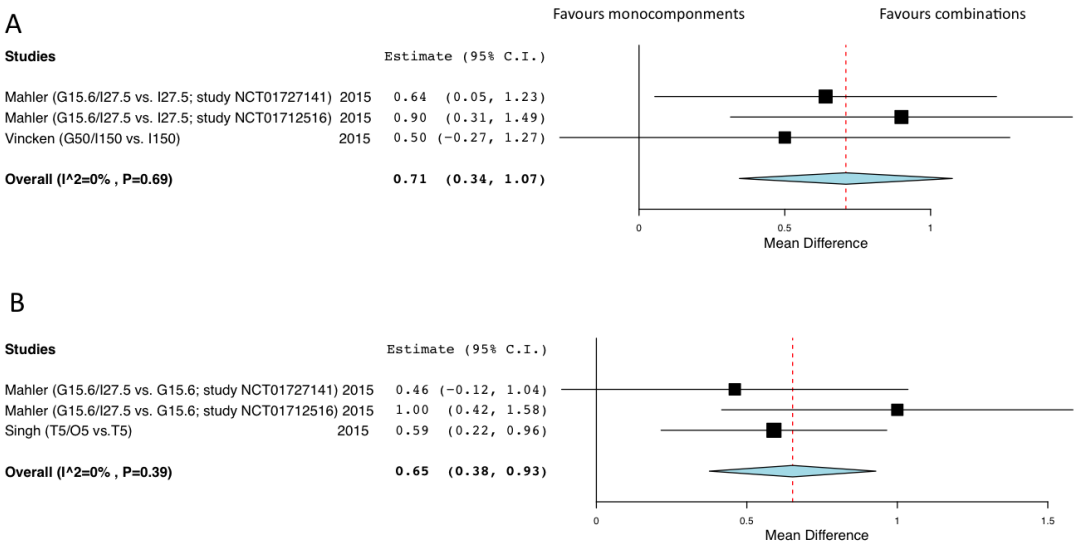

Figure S8. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in TDI at 3 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as µg and results as the mean difference (units). G: glycopyrronium, I: indacaterol, O: olodaterol, and T: tiotropium.

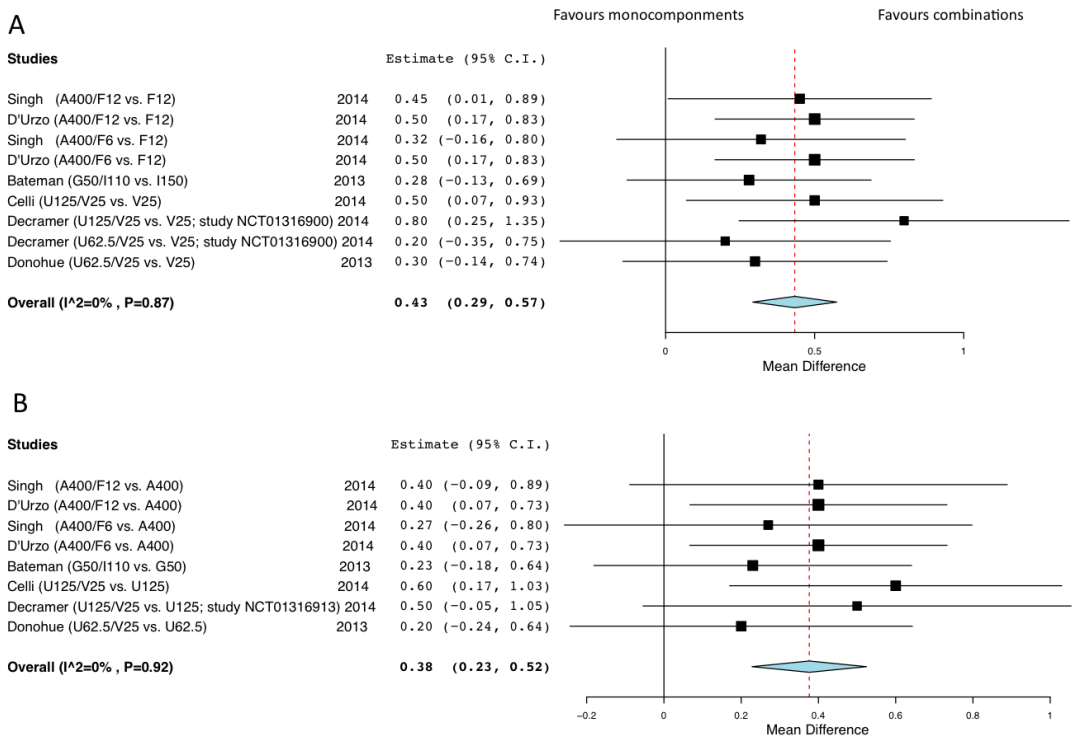

Figure S9. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in TDI at 6 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (units). A: aclidinium, F: formoterol, G: glycopyrronium, I: indacaterol, U: umeclidinium, and V: vilanterol.

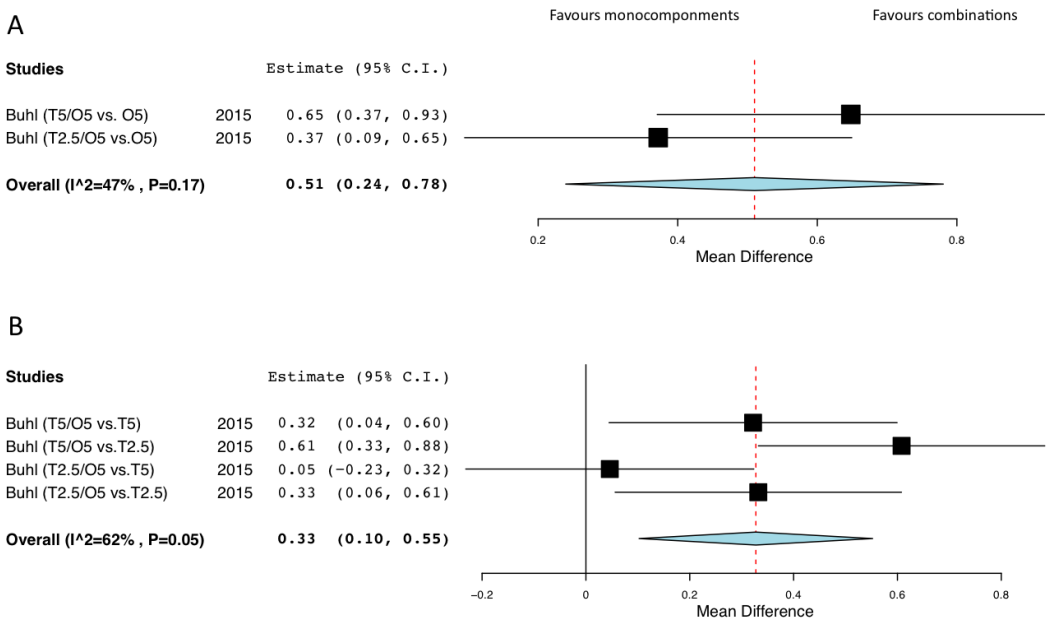

Figure S10. Forest plot from the pair-wise meta-analysis of the impact of LABA/LAMA combinations on changes in TDI at 12 months vs. LABAs (upper panel) and LAMAs (lower panel) administered as monocomponents. The doses of medications are expressed as μg and results as the mean difference (units). O: olodaterol and T: tiotropium.

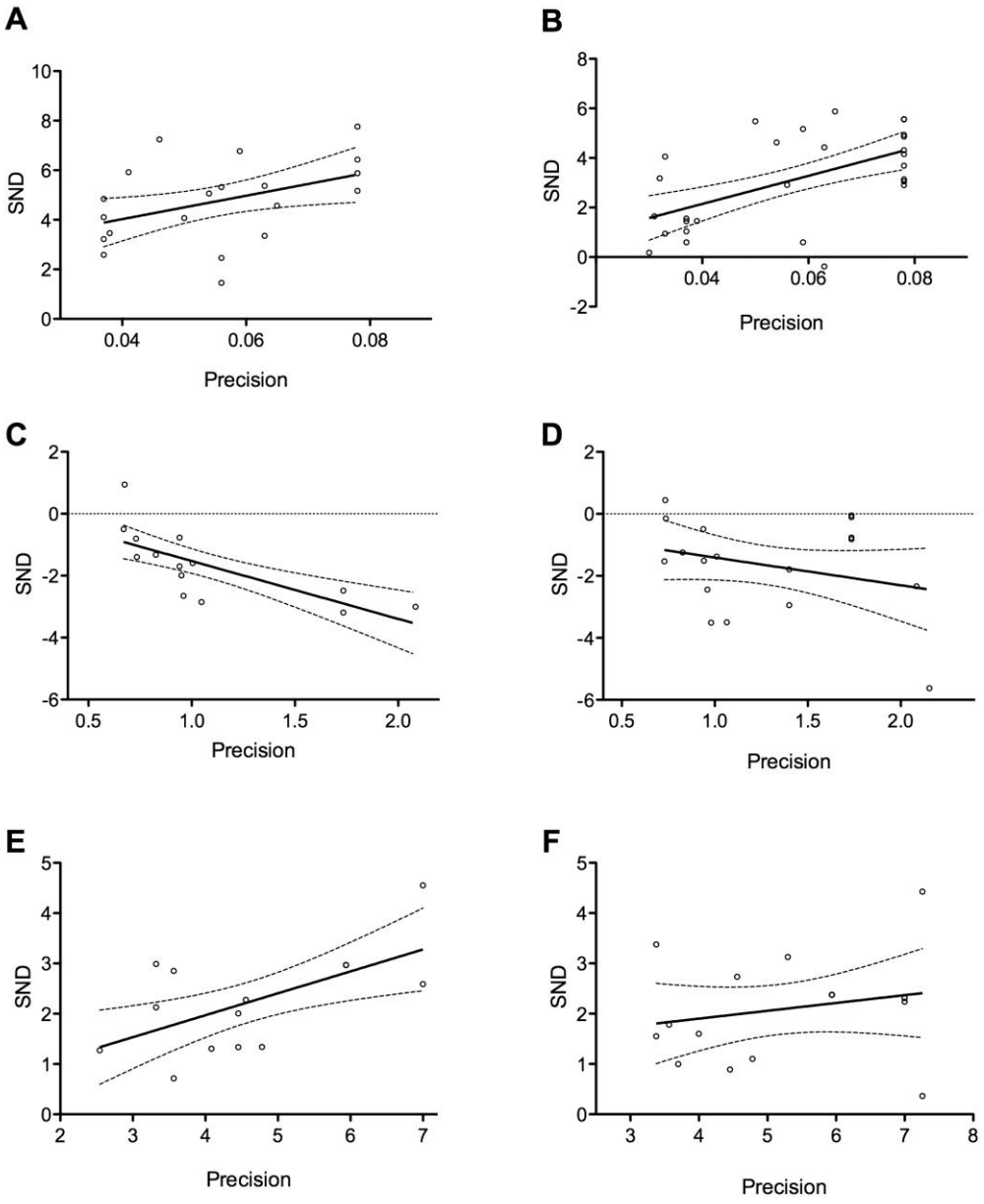

Figure S11. Graphical representations of Egger's test for the impact of LABA/LAMA combinations on changes in trough FEV_1 (A, B), SGRQ (C, D) and TDI (E, F), vs. LABAs (left panels) and LAMAs (right panels) administered as monocomponents. SND: standard normal deviate.

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