

Reduced COPD Exacerbation Risk Correlates With Improved FEV₁

A Meta-Regression Analysis

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e-Appendix 1.

Details of methods: search terms, full inclusion/exclusion criteria, details of statistics

Identification and selection of trials

On August 5th, 2015, we conducted a search of MEDLINE, clinicaltrials.gov, the Cochrane library of controlled trials (CENTRAL), and the Cochrane database of systematic reviews (CDSR), and the Cochrane database of abstracts of reviews of effects (DARE). For MEDLINE, we utilized the Cochrane randomized trial search strategy (specific and precise) to identify RCTs. For each database, our specific search strategy is outlined below:

MEDLINE:

1. Search randomized controlled trial [pt]
2. Search controlled clinical trial [pt]
3. Search randomized [tiab]
4. Search placebo [tiab]
5. Search clinical trials as topic [mesh: noexp]
6. Search randomly [tiab]
7. Search trial [ti]
8. Search #1 or #2 or #2 or #4 or #5 or #6 or #7
9. Search animals [mh] not humans [mh]
10. Search #8 not #9
11. Search (((COPD[Title/Abstract]) OR Chronic obstructive pulmonary disease[Title/Abstract]) OR Chronic bronchitis[Title/Abstract]) OR emphysema[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]
12. Search pulmonary disease, chronic obstructive[MeSH Terms]
13. Search chronic bronchitis[MeSH terms]
14. Search emphysema[MeSH terms]
15. Search #11 or #12 or #13 or #14
16. Search #10 and #15

Clinicaltrials.gov

- Search string: COPD OR chronic obstructive pulmonary disease OR chronic bronchitis OR emphysema
- Limited to trials with results.

CENTRAL, DARE, and CDSR

- MeSH: Pulmonary Disease, Chronic Obstructive [exploded]
- MeSH: Chronic Bronchitis [exploded]
- MeSH: Emphysema [exploded]
- A search of each database was done for each of the above subject headings

We limited our results to those published in 1990 or later; we did not have any language restrictions. This search yielded 6,896 results after 2,397 duplicates were removed (Figure 1). We included prospective randomized trials of pharmacologic interventions at least 24 weeks in length that reported 1) at least one of the following: number of exacerbations, exacerbation rates, or hazard ratio and 2) changes in FEV₁ from the beginning to end of the study. All patients were reported to have stable COPD at baseline (>30 days since prior exacerbation). Exacerbations and grading of their severity had to be clearly defined, otherwise the trial was excluded. We excluded trials that tested non-pharmacologic interventions, including but not limited to: alternative and complementary medicine, vaccines, oxygen therapy, pulmonary rehabilitation, surgical interventions, educational interventions, and case management interventions. Single-arm trials were excluded due to the lack of comparison group. Cross-over trials were excluded due to potential confounding of treatment effect. Two authors (A.Z. and R.B.) assessed the citations for eligibility in our analysis. We retrieved 621 full text articles, of which 94 articles were included in the meta-analysis.

Data abstraction

For FEV₁ data, we extracted trough FEV₁ as this variable is consistently reported across studies, and likely represents a longer-term effect of therapy on airway patency. Pre-bronchodilator FEV₁ was preferred over post-bronchodilator FEV₁. The same measures were always compared between the baseline and final assessments.

As we sought to explore the effects of therapeutic changes on exacerbations, we defined our moderator variable, dFEV₁ as the between group change from baseline in trough FEV₁. Thus, for a trial with an intervention arm (a) and a control arm (b), $dFEV_1 = dTrial(a) - dTrial(b)$, where dTrial(x) represents the change from baseline for the respective arm (eFigure 1). Often, dFEV₁ was directly reported by the trial, but frequently it was not. When possible, we either used the reported change in baseline for each arm (dTrial) (preferred), or the FEV₁ at the beginning (dRand) and end of the trial (dEnd) to calculate the dFEV₁. If dEnd and dRand are reported, then $dFEV_1 = dEnd - dRand$. If trials had more than one treatment arm, we used only the comparisons to the control

arm (preferably placebo). To examine the effects of multiple comparisons to the same control, we also performed a subgroup analysis of two arm studies.

For exacerbation data, we examined moderate to severe exacerbation rates and risk. We defined moderate exacerbations as those requiring oral corticosteroids, antibiotics, or both, and severe exacerbations as those requiring hospitalizations. We did not include mild exacerbations in our analysis, due to the wide variability in definition and approaches to measurement. If reported, we used exacerbation rates based on Poisson or negative binomial analysis. If only numbers of exacerbations (E) were reported, we calculated a mean exacerbation rate (e-rate), using the arithmetic mean number of patients observed as follows: total exacerbations / [(patients at entry + patients at completion)/2 * duration of study in years].

Absolute differences in exacerbation rate (rate difference, or RD) were defined as the exacerbation rate in treatment A less the exacerbation rate in treatment B. Thus, $RD = e\text{-rate}(A) - e\text{-rate}(B)$. Exacerbation rate ratios were calculated as $RR(A)/RR(B)$. The hazard ratios extracted were based on survival analyses of time to first moderate or severe exacerbation.

If trials had more than one treatment arm, we used only the comparisons to the control arm (preferably placebo). To examine the effects of multiple comparisons to the same control, we also performed a subgroup analysis of two arm studies.

Statistical analysis

Mixed-effect meta regression models were used to examine the impact of the moderator variable $dFEV_1$ on the heterogeneity in the study effect estimates such as absolute difference in exacerbation rate (RD), ratio of exacerbation rates (RR), or hazard ratio (HR), respectively.¹ A pseudo- R^2 statistic, which was the proportion of variance among the effect sizes that can be accounted for by the moderator, was computed for each regression model.² Bubble scatterplots were used to represent predictions for RD, RR and HR as a function of $dFEV_1$ observed at the study level.³ The bubbles were drawn with sizes proportional to the contribution of individual studies towards the linear prediction, which was the inverse of the standard error. In addition to the bubbles, the predicted average effects based on the mixed-effects meta-regression model were added to the plot, with the corresponding 95% confidence interval bounds.

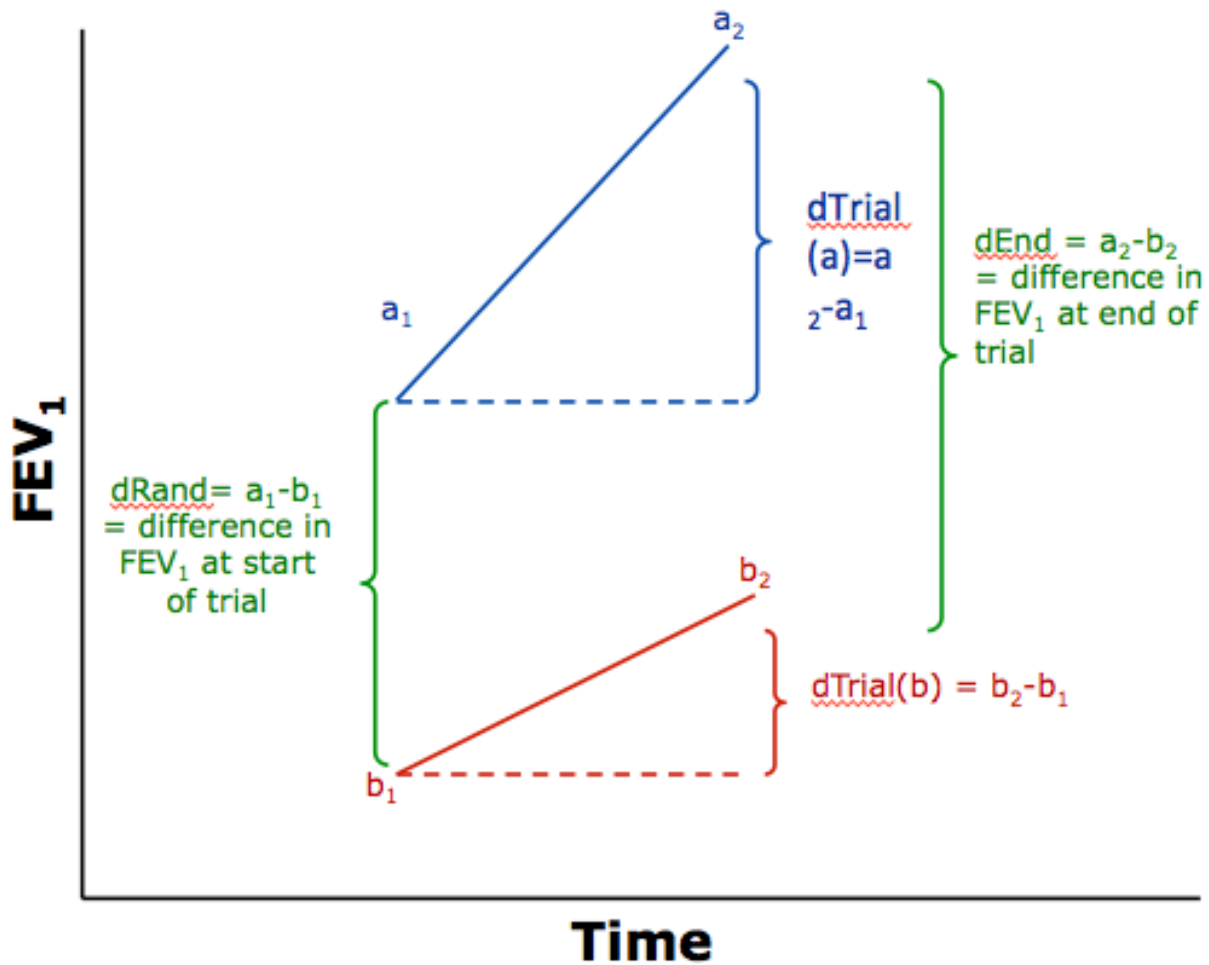
For each clinical outcome, we performed multiple subgroup meta-regression analyses. We examined subgroups based on trial characteristics: whether an exacerbation history was required, or if a study had only two arms. We also examined subgroups of similar drug classes. For this, LAMAs and LABAs were grouped as bronchodilators (BD), and all other medications were considered "non-bronchodilators" (non-BD).

For all statistical investigations, hypothesis testings were two-sided, and p-values less than 0.05 were deemed statistically significant. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary NC) and R Version 3.2.2.⁴

Our study has been registered on The Research Registry (www.researchregistry.com), with unique identifier number reviewregistry180.

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If trial reports $dTrial$:
 $dFEV_1 = dTrial(a) - dTrial(b)$

If trial reports $dEnd$:
 $dFEV_1 = dEnd - dRand$

e-Figure 1. Calculation of $dFEV_1$. Shown is the graphical and mathematical relationship between $dFEV_1$, $dTrial$, $dEnd$, and $dRand$.

e-Table 1. Trial demographics and characteristics.

	<u>RD/RR</u>	<u>HR</u>	<u>Total</u>
Trials (N)	94	39	100
Patients (N)	119,227	73,475	126,293
Per trial (median, range)	905(79-17,116)	1050 (182-17,116)	905 (79-17,116)
Demographics			
Age (median, range)	64 (58-72)	64 (60-68)	64 (58-72)
% Male patients (median, range)	73% (40-99%)	70% (48-92%)	73% (40-99%)
% Current smokers (median, range)	42% (14-65%)	41% (14-65%)	42% (14-65%)
Baseline spirometry			
FEV1 (median, range)	1.25 (0.81-1.72)	1.32 (0.93-1.78)	1.26 (0.81-1.78)
FEV1/FVC (median, range)	47% (35-60%)	48% (40-59%)	48% (35-60%)
COPD severity			
Included mild (N, %)	2 (2%)	0 (0%)	2(2%)
Included moderate (N, %)	76 (81%)	30 (77%)	81 (81%)
Included severe (N, %)	92 (98%)	38 (97%)	98 (98%)
Included very severe (N, %)	65 (69%)	23 (59%)	66 (66%)
Characteristics			
Required ≥ 1 exacerbation (N, %)	26 (28%)	12 (31%)	27 (27%)
Placebo controlled (N, %)	73 (78%)	28 (72%)	76 (76%)
Industry funded (N, %)	85 (90%)	34 (87%)	91 (91%)

The median values represent the medians of the mean demographics for the trials used in each analysis.

e-Table 2. Characteristics of included studies

First Author	Publication Year	Study ID	Arms	Total patients	RD & RR	HR
Bateman, ED (1-3)	2015	NCT01462942	Aclidinium/Formoterol 400/12	2,680	RD, RR	HR
		NCT01437397	Aclicnidinum 400 Formoterol 12 Placebo			
Buhl, R (4)	2015	NCT01574651	Indacaterol/Glycopyrronium Tiotropium/Formoterol	934	RD, RR	
Martinez, FJ (5)	2015	NCT01329029	Roflumilast Placebo	1,935	RD, RR	HR
Rennard, SI (6)	2015	NCT01006616	MK-7123 10mg	614	RD, RR	HR
			MK-7123 30mg			
			MK-7123 50mg			
			Placebo			
Wang, C (7)	2015	NCT01566604	Glycopyrronium Placebo	459	RD, RR	HR
Zheng, J (8)	2015	NCT01376245	Fluticasone/Vilanterol 200/25	643	RD, RR	
			Fluticasone/Vilanterol 100/25			
			Fluticasone/Vilanterol 150/25			
			Placebo			
Zhong, N (9)	2015	NCT01709903	Indacaterol/Glycopyrronium Salmeterol/Fluticasone	741	RD, RR	HR
Celli, B (10)	2014	NCT01313637	Umeclidinium/Vilanterol	1,489	RD, RR	HR
			Umeclidinium			
			Vilanterol			
			Placebo			
Donohue, JF (11)	2014	NCT00909779	Arformoterol Placebo	841	RD, RR	
Donohue, JF (12)	2014	NCT01316887	Umeclidinium/Vilanterol	562	RD, RR	HR
			Umeclidinium			
			Placebo			
Ferguson, GT (13)	2014	NCT00782210	Olodaterol 10mcg	624	RD, RR	
			Olodaterol 5mcg			
			Placebo			
		NCT00782509	Olodaterol 10mcg			
			Olodaterol 5mcg			
			Placebo			
Koch, A (14)	2014	NCT00793624	Formoterol	904	RD, RR	
			Olodaterol 10mcg			

			Olodaterol 5mcg Placebo			
		NCT00796653	Formoterol Olodaterol 10mcg Olodaterol 5mcg Placebo	934	RD, RR	
Magnussen, H (15)	2014	NCT00975195	Tiotropium + Salmeterol/Fluticasone Tiotropium + Salmeterol	2,485	RD, RR	HR
Maleki-Yazdi, MR (16)	2014	NCT01777334	Umeclidinium/Vilanterol Tiotropium	905	RD, RR	HR
Rossi, A (17)	2014	NCT01555138	Indacaterol Salmeterol/Fluticasone	581	RD, RR	HR
Uzun, S (18)	2014	NCT00985244	Azithromycin Placebo	92	RD, RR	
Watz, H (19)	2014	NCT01218126	Losmapimod 15 Losmapimod 7.5 Losmapimod 2.5 Placebo	602	RD, RR	
Wedzicha, JA (20)	2014	FORWARD	Beclomethasone/Formoterol Formoterol	1,190	RD, RR	
Zheng, J (21)	2014	NCT01313494	Roflumilast Placebo	626	RD, RR	
Bateman, ED (22)	2013	NCT01202188	Tiotropium Glycopyrronium Indacaterol QVA149 Placebo	2,135	RD, RR	
Cooper, CB (23)	2013	NCT00525512	Tiotropium Placebo	519	RD, RR	HR
Dransfield, MT (24)	2013	NCT01009463	Fluticasone/Vilanterol 200/25 Fluticasone/Vilanterol 100/25 Fluticasone/Vilanterol 50/25 Vilanterol	1,622	RD, RR	HR
		NCT01017952	Fluticasone/Vilanterol 200/25 Fluticasone/Vilanterol 100/25 Fluticasone/Vilanterol 50/25 Vilanterol	1,633	RD, RR	HR
Decramer, ML (25)	2013	NCT00845728	Indacaterol Tiotropium	3,439	RD, RR	HR
Donohue, JF (26)	2013	NCT01313650	Umeclidinium/Vilanterol	1,532	RD, RR	HR

			Vilanterol Umeclidinium Placebo			
Hagedorn, C (27)	2013	NCT00527826	Salmeterol/Fluticasone Salmeterol + Fluticasone	212	RD, RR	
Kerwin, EM (28)	2013	NCT01053988	Fluticasone/Vilanterol 100/25 Fluticasone/Vilanterol 50/25 Vilanterol Fluticasone Placebo	1,030	RD, RR	
Martinez, FJ (29)	2013	NCT01054885	Fluticasone/Vilanterol 200/25 Fluticasone/Vilanterol 100/25 Vilanterol Fluticasone 200 Fluticasone 100 Placebo	1,224	RD, RR	
Wedzicha, JA (30)	2013	NCT01120691	Indacaterol/Glycopyrronium Glycopyrronium Tiotropium	2,206	RD, RR	
Wise, RA (31)	2013	NCT01126437	Tiotropium Respimat 2.5 Tiotropium Respimat 5 Tiotropium HandiHaler 18	17,116	RD, RR	HR
Doherty, DE (32)	2012	NCT00383721	Mometasone/Formoterol 400/10 Mometasone/Formoterol 200/10 Mometasone 400 Formoterol 10 Placebo	1,196	RD, RR	
Jones, PW (33)	2012	NCT01001494	Aclidinium 400 Aclidinium 200 Placebo	819	RD, RR	
Jung, KS (34)	2012	SUPER	Salmeterol/Fluticasone + Tiotropium Tiotropium	455	RD, RR	
Kerwin, E (35)	2012	NCT00929110	Glycopyrronium Tiotropium Placebo	1,060	RD, RR	HR
Lehouck, A (36)	2012	NCT00666367	Vitamin D Placebo	182	RD, RR	HR
Sharafkhaneh, A (37)	2012	NCT00419744	Budesonide/Formoterol 320/9 Budesonide/Formoterol 160/9 Placebo	1,218	RD, RR	HR

Tashkin, DP (38)	2012	NCT00383435	Mometasone/Formoterol 400/10 Mometasone/Formoterol 200/10 Mometasone 400 Formoterol 10 Placebo	1,055	RD, RR	
Zhong, N (39)	2012	NCT00421122	Budesonide/Formoterol 320/9 Budesonide 400	308	RD, RR	
D'Urzo, A (40)	2011	NCT01005901	Glycopyrronium Placebo	817	RD, RR	HR
Jones, PW (41)	2011	NCT00363896	Acclidinium Placebo	843	RD, RR	HR
		NCT00363896	Acclidinium Placebo	804	RD, RR	HR
Kornmann, O (42)	2011	NCT00567996	Indacaterol 150 Salmeterol Placebo	998	RD, RR	
Rennard, SI (43)	2011	NCT00076089	Roflumilast Placebo	1,173	RD, RR	
Bateman, ED (44)	2010	NCT00387088	Tiotropium Respimat Placebo	3,917	RD, RR	HR
Bateman, ED (45)	2010	NCT00168844	Tiotropium 5	1,990	RD, RR	
		NCT00168831	Tiotropium 10 Placebo			
Calverley, PM (46)	2010	NA	Beclomethasone/Formoterol Budesonide/formoterol Formoterol	703	RD, RR	
Dahl, R (47)	2010	NCT00393458	Indacaterol 300 Indacaterol 600 Formoterol 12 Placebo	1,728	RD, RR	HR
Donohue, JF (48)	2010	NCT00463567	Indacaterol 150 Indacaterol 300 Tiotropium Placebo	1,665	RD, RR	HR
Hanania, NA (49)	2010	NCT00250679	Arformoterol 25 Arformoterol 15 Formoterol	443	RD, RR	
Sethi, S (50)	2010	NCT00473460	Moxifloxacin Placebo	1,149	RD, RR	
Anzueto, A (51)	2009	NCT00115492	Salmeterol/Fluticasone Salmeterol	797	RD, RR	HR
Calverley, PM (52)	2009	NCT00297102	Roflumilast	1,523	RD, RR	HR

			Placebo			
		NCT00297115	Roflumilast	1,568	RD, RR	HR
			Placebo			
Fabbri, LM (53)	2009	NCT00313209	Salmeterol + Roflumilast	933		HR
			Salmeterol + Placebo			
		NCT00424268	Tiotropium + Roflumilast	743		HR
			Tiotropium + Placebo			
Rennard, SI (54)	2009	NCT00206167	Budesonide/Formoterol 320/9	1,964	RD, RR	
			Budesonide/formoterol 160/9			
			Formoterol			
			Placebo			
Ambrosino, N (55)	2008	NA	Tiotropium	234	RD, RR	
			Placebo			
Calverley, PM (56)	2008	NA	Mometasone 800	911	RD, RR	
			Mometasone 400			
			Placebo			
Donohue, JF (57)	2008	NA	Arformoterol	793	RD, RR	
			Salmeterol			
Ferguson, GT (58)	2008	NCT00144911	Salmeterol/Fluticasone	782	RD, RR	HR
			Salmeterol			
Rennard, SI (59)	2008	207499/157	Cilomilast	907	RD, RR	
			Placebo			
Rennard, SI (59)	2008	207499/156	Cilomilast	825	RD, RR	
			Placebo			
Rennard, SI (59)	2008	207499/042	Cilomilast	700	RD, RR	
			Placebo			
Rennard, SI (59)	2008	207499/091	Cilomilast	711	RD, RR	
			Placebo			
Rennard, SI (59)	2008	CIL103657	Cilomilast	613	RD, RR	
			Placebo			
Rennard, SI (59)	2008	207499/121	Cilomilast	1,018	RD, RR	
			Placebo			
Seemungal, TA (60)	2008	NCT00147667	Erythromycin	109	RD, RR	
			Placebo			
Tashkin, DP (61)	2008	NCT00206154	Budesonide/Formoterol 320/9	1,704	RD, RR	
			Budesonide/Formoterol 160/9			
			Budesonide 320 + Formoterol 9			
			Budesonide			
			Formoterol			
			Placebo			
Tashkin, DP (62)	2008	NCT00144339	Tiotropium	5,992	RD, RR	HR

			Placebo			
Wedzicha, JA (63)	2008	NCT00361959	Salmeterol/Fluticasone Tiotropium	1,323	RD, RR	
Aaron, SD (64)	2007	ISRCTN-29870041	Salmeterol/Fluticasone + Tiotropium Tiotriopum + Salmeterol Tiotropium	449	RD, RR	
Calverley, PM (65)	2007	NCT00268216	Salmeterol/Fluticasone Fluticasone Salmeterol Placebo	6,112	RD, RR	HR
Calverley, PM (66)	2007	NCT00430729	Roflumilast Placebo	1,513	RD, RR	
Chan, CK (67)	2007	SAFE	Tiotropium Placebo	913	RD, RR	
Choudhury, AB (68)	2007	NCT00440687	Placebo Fluticasone	260	RD, RR	HR
Kardos, P (69)	2007	NA	Salmeterol/Fluticasone Salmeterol	994	RD, RR	
Powrie, DJ (70)	2007	NCT00405236	Tiotropium Placebo	142	RD, RR	
Zheng, JP (71)	2007	SCO100540	Salmeterol/Fluticasone Placebo	445	RD, RR	
Dusser, D (72)	2006	BI: 0205.214	Tiotropium Placebo	1,010	RD, RR	
Rennard, SI (73)	2006	NA	Cilomilast Placebo	647		HR
Campbell, M (74)	2005	NA	Formoterol + terbutaline Formoterol Placebo	657	RD, RR	HR
Niewoehner, DE (75)	2005	NA	Tiotropium Placebo	1,829	RD, RR	HR
Rabe, KF (76)	2005	NA	Roflumilast 500 Roflumilast 250 Placebo	1,411	RD, RR	
Brusasco, V (77)	2003	NA	Tiotropium Salmeterol Placebo	1,207	RD, RR	
Calverley, PM (78)	2003	TRISTAN	Salmeterol/Fluticasone Fluticasone Salmeterol Placebo	1,465	RD, RR	
Calverley, PM (79)	2003	NA	Budesonide/Formoterol	1,022	RD, RR	HR

			320/9 Budesonide Formoterol Placebo			
Hanania, NA (80)	2003	SFCA3007	Salmeterol/Fluticasone Fluticasone Salmeterol Placebo	723	RD, RR	
Hiller, FC (81)	2003	NA	Sibenaadet Placebo	435	RD, RR	
Szafranski, W (82)	2003	NA	Budesonide/Formoterol 320/9 Budesonide Formoterol Placebo	812	RD, RR	
Casaburi, R(83)	2002	NA	Tiotropium Placebo	921	RD, RR	
Mahler, DA (84)	2002	SFCA3006	Salmeterol/Fluticasone Fluticasone Salmeterol Placebo	674	RD, RR	
van der Valk, P (85)	2002	COPE	Placebo Fluticasone	244		HR
Burge, PS (86)	2000	ISOLDE	Fluticasone Placebo	751	RD, RR	
Bourbeau, J (87)	1998	NA	Budesonide Placebo	79	RD, RR	
Paggiaro, PL (88)	1998	NA	Fluticasone Placebo	281	RD, RR	
AstraZeneca	Unpublished	D589DC00008	Budesonide/Formoterol 320/9 Standard of Care	260	RD, RR	
GlaxoSmithKline	Unpublished	SCO100470	Salmeterol/Fluticasone Salmeterol	1,050	RD, RR	HR
Novartis	Unpublished	GLOW4	Glycopyrronium Tiotropium	163	RD, RR	
				126,293		

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