Evidence Profile # 1

Comparison: Mucolytics vs. placebo for patients with COPD to prevent COPD exacerbations

Bibliography: 9) Decramer M, Rutten-van Mölken M, Dekhuijzen PN, Fabbri L. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 2005; 365:1552-60; **10)** Malerba M, Ponticiello A, Radaeli A, Bensi G, Grassi V. Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD. Double-blind, randomized, multicenter, placebo-controlled study (the AMETHIST Trial). Pulm Pharmacol Ther 2004; 17(1):27-34; **11)** Schermer T, Chavannes N, Dekhuijzen R, Wouters E, Muris J, Akkermans R, van Schayck O, van, Weel C. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. Respir Med 2009; 103(4):542-551; **12)** Zheng JP, Kang J, Huang SG, Chen P, Yao WZ, Yang L, Bai CX, Wang CZ, Chen BY, Shi Y, Liu CT, Chen P, Li Q, Wang ZS, Huang YJ, Luo ZY, Chen FP, Yuan JZ, Yuan BT, Qian HP, Zhi RC, Zhong NS. Effect of carbocisteine on acute exacerbation of chronicobstructive pulmonary disease (PEACE Study): a randomisedplacebo-controlled study. Lancet 2008; 371(9629):2013-2018; **13)** Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, Loo CK, Chan MH. High dose N-acetylcysteine in stable COPD. The 1 year, double-blind, randomized, placebo-controlled HIACE study. Chest 2013; 144(1):106-118; **14)** Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, Yao WZ, Ma LJ, Li X, Raiteri L, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. Lancet Resp Med 2014; 2(3):187-94.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytics**	**Placebo**	**Relative (95% Confidence Interval)**	**Absolute (95% Confidence Interval)**		
Hospitalisations (proportion of patients hospitalized)												
All doses of mucolytics												
3 [1]	randomised trials	none	serious [2]	none	serious [3]	none	114/810 (14.1%)	150/827 (18.1%)	Risk Ratio 0.76 (0.59 to 0.97)	44 fewer per 1000 will be hospitalised (from 5 fewer to 74 fewer)	⊕⊕OO LOW	CRITICAL
High-dose mucolytics (N-acetylcysteine 600 mg PO BID)												
2 [4]	randomised trials	none	none	none	serious [3]	none	59/554 (10.6%)	81/560 (14.5%)	Risk Ratio 0.73 (0.0.49 to 1.11)	39 fewer per 1000 will be hospitalised (from 74 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Low-dose mucolytics (N-acetylcysteine 600 mg PO qD)												
1 [5]	randomised trials	none	none	none	serious [3]	none	55/256 (21.5%)	69/267 (25.8%)	Risk Ratio 0.83 (0.61 to 1.13)	44 fewer per 1000 will be hospitalised (from 101 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbation rate (exacerbations per patient-year)												
All doses of mucolytics												
4 [6]	randomised trials	none	serious [7]	none	serious [8]	none	1171	1185	Rate Ratio 0.79 (0.65 to 0.95)	Rate difference = 0.38 fewer exacerbations per patient-year (from 0.23 fewer to 0.54 fewer)[9]	⊕⊕OO LOW	CRITICAL
High-dose mucolytics (N-acetylcysteine 600 mg PO BID)												
2 [10]	randomised	none	serious [11]	none	serious [8]	none	562	564	Rate Ratio 0.69	Rate difference = 0.49 fewer	⊕⊕OO	CRITICAL

	trials								(0.50 to 0.94)	exacerbations per patient-year (from 0.09 fewer to 0.89 fewer)	LOW	
Low-dose mucolytics (N-acetylcysteine 600 mg PO qD, ambroxol 75 mg PO BID, and carbocisteine 500 mg PO TID)												
2 [12]	randomised trials	none	serious [13]	none	serious [8]	none			Rate Ratio 0.87 (0.66 to 1.14)	Rate difference = 0.34 fewer exacerbations per patient-year (from 0.17 fewer to 0.51 fewer)[14]	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (proportion of patients with no exacerbations)												
5 [15]	randomised trials	none	none	none	none	none	375/1098 (34.1%)	359/1107 (32.4%)	Risk Ratio 1.06 (0.95 to 1.19)	19 more per 1000 will be exacerbation-free (from 16 fewer to 62 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of Life (change in the St. George's Respiratory Questionnaire during treatment) (better quality of life indicated by lower values)												
4 [16]	randomised trials	none	very serious [17]	none	none	none	1165	1179	not estimable [18]	not estimable [18]	⊕⊕OO LOW	CRITICAL
Adverse events (proportion of patients experiencing an adverse event)												
4 [16]	randomised trials	none	none	none	none	none	149/553 (26.9%)	135/557 (24.2%)	Risk Ratio 1.11 (0.91 to 1.35) [19]	27 more per 1000 will have an adverse event (from 22 fewer to 85 more) [19]	⊕⊕⊕⊕ HIGH	IMPORTANT
Mortality (proportion of patients who died)												
5 [20]	randomised trials	none	none	none	serious [5]	none	16/1267 (1.3%)	14/1281 (1.1%)	Risk Ratio 1.15 (0.55 to 2.43)	2 more deaths per 1000 (from 5 fewer to 16 more)	⊕⊕⊕O MODERATE	IMPORTANT
Decrease in sputum production												
0												IMPORTANT

Notes :

PO BID: *per os bis in die* as oral route twice a day. PO qD: *per os quaque in die* as oral route once a day

[1] Decramer 2005, Tse 2013, and Zheng 2014.

[2] Large amount of heterogeneity across studies: for the mean difference, p- value (for heterogeneity) = 0.23 and I^2 = 33%.

[3] Wide confidence intervals: The ends of the confidence interval for the risk ratio will likely lead to different clinical decisions.

[4] Tse 2013 and Zheng 2014.

[5] Decramer 2005.

[6] Decramer 2005, Zheng 2008, Tse 2013, and Zheng 2014.

[7] Large amount of heterogeneity across studies. For the rate ratio: p- value (for heterogeneity) = 0.0004 and I^2 = 84%. For the rate difference: p- value (for heterogeneity) = 0.19 and I^2 = 39%.

[8] Wide confidence intervals: The ends of the confidence interval for the rate ratio will likely lead to different clinical decisions.

[9] Only three of the four trials contributed data toward the rate difference calculation: Zheng 2008, Tse 2013, and Zheng 2014.

[10] Tse 2013 and Zheng 2014.

[11] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.07 and I^2 = 69%.

[12] Decramer 2005 and Zheng 2008.

[13] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.002 and I^2 = 89%.

[14] Only one of the two trials contributed data toward the rate difference calculation: Zheng 2008.

[15] Malerba 2004, Zheng 2008, Schermer 2009, Tse 2013, and Zheng 2014.
[16] Decramer 2005, Zheng 2008, Tse 2013, and Zheng 2014.
[17] Large amount of heterogeneity across studies: for the mean difference, p- value (for heterogeneity) <0.00001 and I^2 = 97%.
[18] Decramer 2005 and Zheng 2014 did not report sufficient crude data to be included in the meta-analysis. When Zheng 2008 and Tse 2013 were pooled, the heterogeneity was very serious, indicating that these studies should not be pooled because doing so provides misleading results.
[19] Tse 2013 and Zheng 2014. Decramer 2005 and Zheng 2008 reported the number of adverse events in each arm of the trial, not the number of patients experiencing an adverse event; therefore these trials were not included in the meta-analysis.
[20] Decramer 2005, Schermer 2009, Tse 2013, Zheng 2008, and Zheng 2014.

Evidence Profile # 2

Comparison: Long-acting beta agonists versus long-acting muscarinic agents for patients with COPD to prevent COPD exacerbations
Bibliography: 19) Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-Van Molken MP, Beeh KM, Rabe KF, Fabbri LM, POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364(12):1093-103; **20)** Decramer ML, Chapman, KR, Dahl R, Frith P, Devouassoux G, Fritscher C, Cameron R, Shoaib M, Lawrence D, Young D, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med 2013; 1(7):524-533.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMAs	LABAs	Relative (95% Confidence interval)	Absolute (95% Confidence interval)		
Mortality (proportion of patients on treatment +30 days who died)												
2 [1]	randomised trials	none	none	none	serious [2]	none	92/5425 (1.7%)	106/5390 (2%)	Risk Ratio 0.86 (0.65 to 1.14)	3 fewer per 1000 (from 7 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
2 [1]	randomised trials	none	none	none	none	none	1624/5250 (30.9%)	1795/5189 (34.6%)	Risk Ratio 0.89 (0.85 to 0.94)	38 fewer per 1000 (from 21 fewer to 52 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
COPD exacerbations (proportion of patients having a severe exacerbation requiring hospitalisation)												
1 [3]	randomised trials	none	none	none	serious [2]	none	262/3707 (7.1%)	336/3669 (9.2%)	Risk Ratio 0.77 (0.66 to 0.9)	21 fewer per 1000 (from 9 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Severe adverse events (proportion of patients experiencing a severe adverse event)												
2 [1]	randomised trials	none	none	none	none	none	800/5425 (14.7%)	869/5390 (16.1%)	Risk Ratio 0.91 (0.84 to 1)	15 fewer per 1000 (from 26 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of Life (change in the St. George's Respiratory Questionnaire during treatment) (better quality of life indicated by lower values)												
1 [3]	randomised trials	none	none	none	none	none	1325	1281	-	Mean Difference 0.4 lower (1.56 lower to 0.76 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Forced expiratory volume in one second (mL)												
1 [3]	randomised trials	none	none	none	none	none	1362	1324	-	Mean Difference 19 greater (11.34 greater to 28.66 greater)	⊕⊕⊕⊕ HIGH	CRITICAL
Dyspnoea (change in the Transition Dyspnea Index [TDI] during treatment) (less dyspnea indicated by higher values)												
1 [3]	randomised	none	none	none	none	none	1332	1296	-	Mean Difference 0.3 lower (0.57	⊕⊕⊕⊕	IMPORTANT

	trials									to 0.03 lower)	HIGH	
Exercise tolerance												
0												IMPORTANT

[1] Vogelmeier C 2011 and Decramer ML 2013.
[2] Wide confidence intervals: The ends of the confidence interval for the risk ratio will likely lead to different clinical decisions.
[3] Decramer ML 2013.

Evidence Profile # 3

Comparison: Roflumilast versus placebo for patients with COPD to prevent COPD exacerbations
Bibliography: 23) M2-124 and M2-125, both reported by Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374(9691):685-94. **24)** Martinez FJ, Calverley PMA, Goehring UM. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT):a multicentre randomised controlled trial. Lancet 2015; 385(9971):857-866.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Roflumilast**	**Placebo**	**Relative (95% Confidence interval)**	**Absolute (95% Confidence interval)**		
COPD exacerbations (exacerbations per patient-year)												
3	randomised trials	none	none	none	serious[1]	none	2506	2520	Rate ratio 0.85 (0.78 to 0.92)	Rate difference = 0.14 fewer exacerbations per patient-year (from 0.25 fewer to 0.03 fewer)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
3	randomised trials	none	none	none	serious[1]	none	537/2506 (21.4%)	636/2520 (25.2%)	Risk ratio 0.85 (0.78 to 0.94)	38 fewer per 1000 (from 15 fewer to 56 fewer)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (time to first exacerbation, days)												
3	randomised trials	none	none	none	none	none	2506	2520	Hazard ratio 0.88 (0.81 to 0.96)	--	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality (%)												
3	randomised trials	none	none	none	serious[1]	none	59/2506 (2.4%)	60/2520 (2.4%)	Risk ratio 0.99 (0.70 to 1.42)	0 fewer per 1000 (from 7 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (%)												
3	randomised trials	none	none	none	none	none	1688/2505 (67.4%)	1535/2521 (60.9%)	Risk ratio 1.11 (1.06 to 1.15)	67 more per 1000 (from 37 more to 91 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiovascular events (%)												
3	randomised	none	none	none	none	none	136/2506	124/2520	Risk ratio 1.11	5 more per 1000 (from 6 fewer to	⊕⊕⊕⊕	CRITICAL

	trials						(5.4%)	(4.9%)	(0.88 to 1.40)	20 more)	HIGH	
Change in quality of life (assessed via the St. George's Respiratory Questionnaire) (Better indicated by lower values)												
0	--	--	--	--	--	--	--	--	--	--	--	IMPORTANT
Change in post-bronchodilator forced expiratory volume in one second, FEV1 (mL) (Better indicated by higher values)												
3	randomised trials	none	none	none	none	none	2381	2441	--	Mean difference 56.29 mL higher (45.45 mL higher to 67.14 mL higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in post-bronchodilator forced vital capacity, FVC (mL) (Better indicated by higher values)												
3	randomised trials	none	none	none	none	none	2381	2441	-	Mean difference 98.45 mL higher (79.35 mL higher to 117.55 mL higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Wide confidence interval: the ends of the confidence interval would lead to different clinical decisions

Evidence Profile # 4

Comparison: Fluroquinolones vs. placebo for patients with COPD to prevent COPD exacerbations
Bibliography: 26) Sethi S, Jones PW, Schmitt Terron M, Miravitlles M, Rubinstein E, Wedzicha JA, Wilson R, the PULSE Study Group. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respiratory Research 2010; 11:10.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluroquinolones	Placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)		
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
1	randomised trials	none	none	none	none	none	269/569[1] (47.3%)	295/580[1] (50.9%)	Risk ratio 0.93 (0.83 to 1.05)[1]		⊕⊕⊕⊕ HIGH	CRITICAL
Time to first COPD exacerbation (days)												
1	randomised trials	none	none	none	none	none	569[2]	580[2]	Not estimable[3]	Not estimable[3]	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisation (%)												
1	randomised trials	none	none	none	serious[4]	none	131/569[5] (23%)	136/580[5] (23.4%)	Risk ratio 0.98 (0.8 to 1.21)[5]	5 fewer per 1000 (from 47 fewer to 49 more)[5]	⊕⊕⊕O MODERATE	CRITICAL
Mortality (%)												
1	randomised trials	none	none	none	serious[1]	none	15/569[6] (2.6%)	17/580[6] (2.9%)	Risk ratio 0.901 (0.45 to 1.78)[6]	3 fewer per 1000 (from 16 fewer to 23 more)[6]	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (%)												
1	randomised trials	none	none	none	none	none	467/569 (82.1%)	493/580 (85.0%)	Risk ratio 0.97 (0.92 to 1.02)	25 fewer per 1000 (from 68 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in quality of life (Assessed via the St. George's Respiratory Questionnaire) (Better indicated by lower values)												
1	randomised trials	none	none	none	none	none	503[7]	526[7]	-	Mean difference 1.2 lower (3.01 lower to 0.61 higher)[7]	⊕⊕⊕⊕ HIGH	IMPORTANT
Reduction in airway bacterial load												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

[1] Derived by intention-to-treat analysis. Per-protocol analysis found 153/351 (43.6%) versus 190/387 (49.1%), Risk ratio 0.89 (95% CI 0.76- to 1.04).
[2] For the intention-to-treat analysis: fluroquinolone (n=569), placebo (n=580). For the per-protocol analysis: fluroquinolone (n=351), placebo (n=387).
[3] The trial did not provide estimates of the time to exacerbation in each arm in days; however, it reported a trend toward a longer duration to first exacerbation among patients who received fluroquinolones than placebo according to both intention-to-treat and per-protocol analyses.
[4] Wide confidence intervals: The ends of the confidence intervals lead to different clinical decisions.
[5] Derived by intention-to-treat analysis. Per-protocol analysis found 56/351 (16.0%) versus 54/387 (14.0%), Risk ratio 1.14 (95% CI 0.81 to 1.61).
[6] Derived by intention-to-treat analysis. Per-protocol analysis found 1/351 (0.3%) versus 3/387 (0.8%), Risk ratio 0.36 (95% CI 0.04 to 3.43).
[7] Derived by intention-to-treat analysis. Per-protocol analysis found fluroquinolone (n=569), placebo (n=580), mean difference -1.30 (95% CI -3.47 to 0.87).

Evidence Profile # 5

Comparison: Macrolides vs. placebo for patients with COPD to prevent COPD exacerbations.
Bibliography: 29) Suzuki T, Yanai M, Yamaya M, Satoh-Nakawaga T, Sekizawa K, Ishida S, Sasaki H. Erythromycin and common cold in COPD. Chest 2001;120(3):730-3; the time to exacerbation; **30)** Seemungal TAR, Wilkinson TMA, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations. Am J Respir Crit Care Med 2008; 178:1139-1147; **31)** Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365(8):689-98; and **32)** Uzun S, Djamin RS, Kluytmans JAJW et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014; 2: 361-368.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**macrolide**	**placebo**	**Relative (95% Confidence interval)**	**Absolute (95% Confidence interval)**		
COPD exacerbation rate (exacerbations per patient-year)												
3 [1]	randomised trials	none	serious [2]	none	serious [3]	none	658	660	Rate ratio 0.76 (0.68 to 0.86)	--	⊕⊕◯◯ LOW	CRITICAL
2 [4]	randomised trials	none	serious [5]	none	none	none	605	604	--	Rate difference 0.40 fewer (0.24 fewer to 0.55 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to first exacerbation (days)												
3 [1]	randomised trials	none	none	none	none	none	658	660	--	Mean difference 81.53 more (53.29 more to 109.77 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisation												
3 [1]	randomised trials	none	none	none	serious [3]	none	658	660	not estimable [6]	not estimable [6]	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**macrolide**	**placebo**	**Relative (95% Confidence interval)**	**Absolute (95% Confidence interval)**		
Serious adverse events												
3 [7]	randomised trials	none	none	none	serious [5]	none	187/660 (28.3%)	217/658 (33.0%)	Risk ratio 0.86 (0.74 to 1.01)	46 fewer per 1000 (from 86 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality												
3 [7]	randomised trials	none	none	none	serious [5]	none	18/660 (2.7%)	20/657 (3.0%)	Risk ratio 0.90 (0.48 to 1.69)	3 fewer per 1000 (from 17 fewer to 23 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Acquisition of macrolide-resistant bacteria												
2 [3]	randomised trials	none	serious [8]	none	none	none	605	604	not estimable [9]	not estimable [9]	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of Life (St. George's Respiratory Questionnaire score) (Lower values indicate a better quality of life)												
Total												
2 [3]	randomised trials	serious [10]	none	none	none	none	491	498	-	Mean difference 2.18 lower (1.53 lower to 2.82 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Symptoms												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**macrolide**	**placebo**	**Relative (95% Confidence interval)**	**Absolute (95% Confidence interval)**		
2 [3]	randomised trials	serious [10]	none	none	none	none	491	498	-	Mean difference 3.36 lower (2.42 lower to 4.29 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Activity												
2 [3]	randomised trials	serious [10]	not serious	none	none	none	491	498	-	Mean difference 1.82 lower (1.03 lower to 2.62 lower	⊕⊕⊕◯ MODERATE	IMPORTANT
Impacts												
2 [3]	randomised trials	serious [10]	serious [11]	none	none	none	491	498	-	Mean difference 2.04 lower (1.28 lower to 2.81 lower	⊕⊕◯◯ LOW	IMPORTANT

[1] Seemungal 2008, Albert 2011, and Uzun 2014.
[2] Inconsistency: $I^2 = 57\%$, $p_{het} = 0.10$.
[3] Wide 95% confidence intervals: the ends of the confidence interval would lead to different clinical decisions.
[4] Albert 2011 and Uzun 2014.
[5] Inconsistency: $I^2 = 85\%$, $p_{het} = 0.010$.
[6] The data could not be pooled because it was reported in different ways. Seemungal 2008 reported a non-significant decrease in the proportion of exacerbations that are severe enough to require hospitalization (7.4% versus 11.4%, risk ratio 0.66, 95% CI 0.27 to 1.65). Albert 2010 reported a non-significant reduction in the rate of hospitalization due to COPD (0.34 hospitalizations per patient-year versus 0.49 hospitalizations per patient-year, hazard ratio 0.82, 95% CI 0.64 to1.07). Uzun 2014 reported a non-significant increase in the time to first hospitalization (282 days versus 258 days, p=0.48) and a non-significant decrease in the proportion of exacerbations that are severe enough to require hospitalization (29.8% versus 24%, risk ratio 1.24, 95% CI 0.79 to 1.94.
[7] Suzuki 2001, Albert 2011, and Uzun 2014.
[8] One of the trials found an increase in the acquisition of macrolide-resistant organisms among patients who received macrolides, whereas the other trial found a decrease in the acquisition of macrolide-resistant organisms among patients who received macrolides.
[9] The data could not be pooled because one of the trials did not report the crude data. Albert 2011 reported the acquisition of macrolide-resistant organisms in 81% of patients who received macrolides and 41% of patients who received placebo; Uzun 2014 reported the acquisition of macrolide-resistant organisms in fewer patients who received macrolides than who received placebo (6% versus 24%, risk ratio 0.57, 95% CI 0.15 to 2.26).
[10] A large number of patients did not have quality of life assessed.
[11] Inconsistency: $I^2 = 38\%$, $p_{het} = 0.20$.