Prevention for acute infectious exacerbations in chronic lung disease

순천향대 호흡기알레르기내과
이지혜

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Introduction

- Acute exacerbations are major clinical problem in chronic respiratory diseases
- Each exacerbation accelerates lung-function decline, leading to increased hospitalization rates and mortality.
- **Mortality** ↑: The 90-day mortality following hospitalization for COPD exacerbations is reported at 10–15%, and exceeds 30% when ICU care is required.
- **Re-admission** ↑: Approximately 20–30% of patients with COPD or asthma are readmitted within 30 days after discharge.
- **Healthcare burden** ↑: Exacerbations not only impair QOL but also account for a substantial proportion of healthcare expenditures.

- Infection is the leading cause of acute exacerbations
- COPD
  - 50–70% due to bacterial or viral infections
  - Associated with ↑ severity and hospitalization
- Asthma
  - 80% triggered by viral infections
  - Enhance airway hyper-responsiveness and eosinophilic inflammation
- Bronchiectasis
  - Chronic bacterial colonization, especially Pseudomonas aeruginosa
  - Frequent exacerbations, lung function decline, ↑ mortality
- Interstitial Lung Disease
  - Acute exacerbations often linked to infections
  - High mortality (>50% in hospitalized AE-IPF)
  - Infection may accelerate lung injury and diffuse alveolar damage

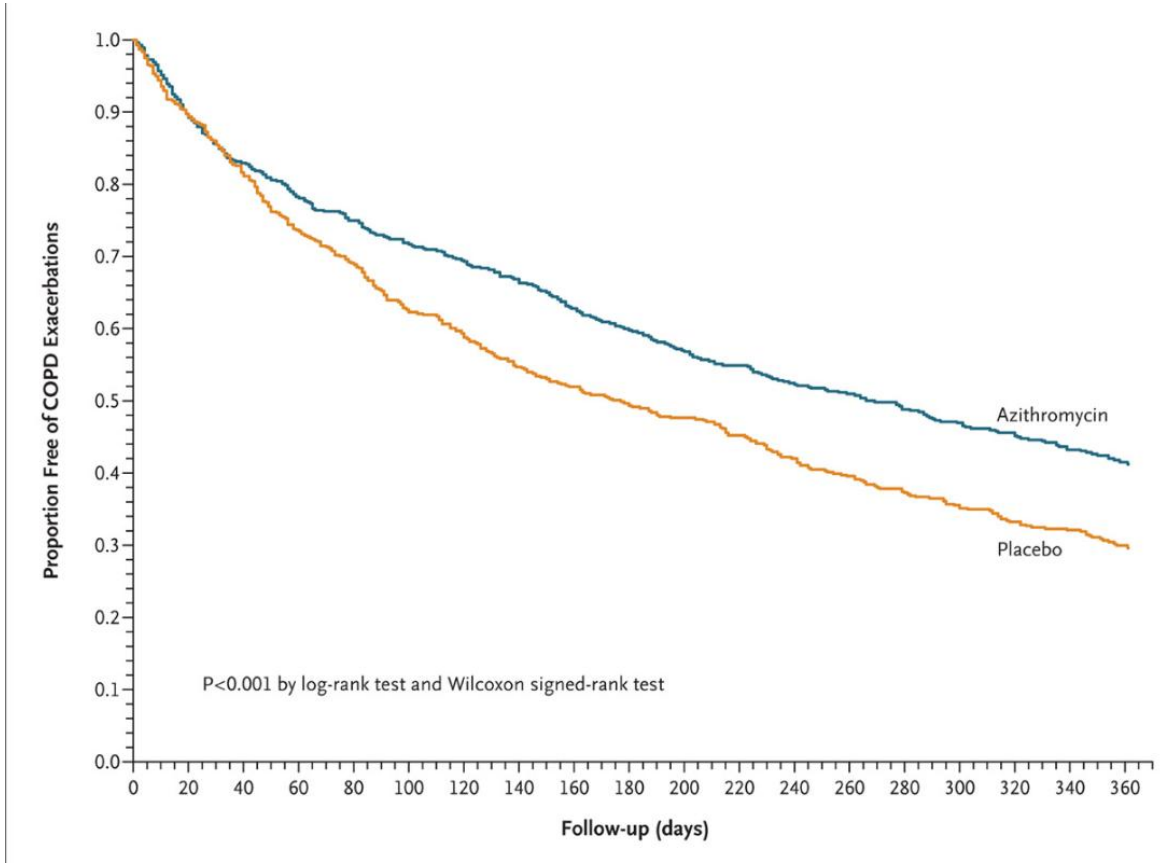
1. Prophylactic Antibiotics

Macrolide

- Mechanisms of Macrolides
  - Antibacterial effect
    - Suppress common airway pathogens (H. influenzae, M. catarrhalis, S. pneumoniae)
    - Reduce bacterial load and prevent colonization during stable phase
  - Anti-inflammatory
    - Decrease neutrophil influx into the airway
    - Suppress pro-inflammatory cytokines (IL-8, TNF-α, IL-6) and oxidative stress
    - Reduce mucus hypersecretion and airway wall damage
  - Immunomodulatory
    - Enhance macrophage phagocytosis and bacterial clearance
    - Improve epithelial barrier integrity and repair processes
    - Modulate T-cell responses, reducing exaggerated immune activation
  - Anti-biofilm
    - Inhibit formation of biofilms by Pseudomonas and other pathogens
    - Disrupt existing biofilm structure, enhancing antibiotic penetration
    - Prevent chronic colonization and recurrent exacerbations

COPD-Macrolide

- **Azithromycin for Prevention of Exacerbations of COPD – MACRO study**
  - Azithromycin 250 mg daily for 1 year reduced COPD exacerbations by 27%, prolonged time to first exacerbation (266 vs. 174 days)



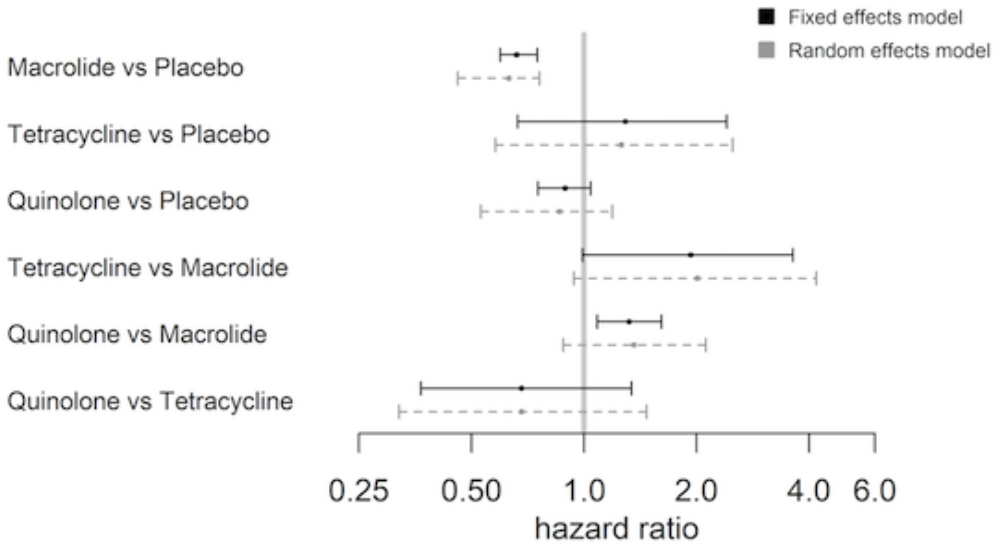
N Engl J Med 2011;365:689-698

COPD-Macrolide

- **Prophylactic antibiotics for adults with chronic obstructive pulmonary disease: a network meta-analysis (Review)**
  - Macrolides reduced the risk of COPD exacerbations by 33% (HR 0.67, 95% CI 0.60–0.75) compared with placebo, and ranked as the most effective antibiotic class. Quinolones showed uncertain benefit (HR 0.89), and tetracyclines showed no clear effect (HR 1.29)

Table 7. Exacerbations: number of trials, number of participants, and relative effect estimates for all class comparisons

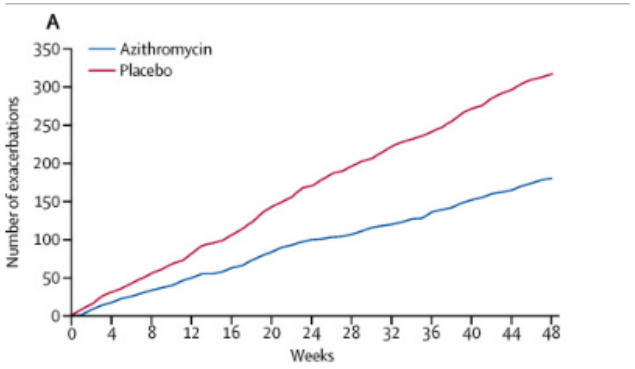
Comparison		Hazard ratios		Number of trials	N
Intervention	Comparator	Median	95% CrI		
Macrolide	Placebo	0.67	0.60 to 0.75	9	1509
Tetracycline	Placebo	1.29	0.66 to 2.41	1	49
Quinolone	Placebo	0.89	0.75 to 1.04	2	1198
Tetracycline	Macrolide	1.93	0.99 to 3.62	1	50
Quinolone	Macrolide	1.32	1.08 to 1.61	1	50

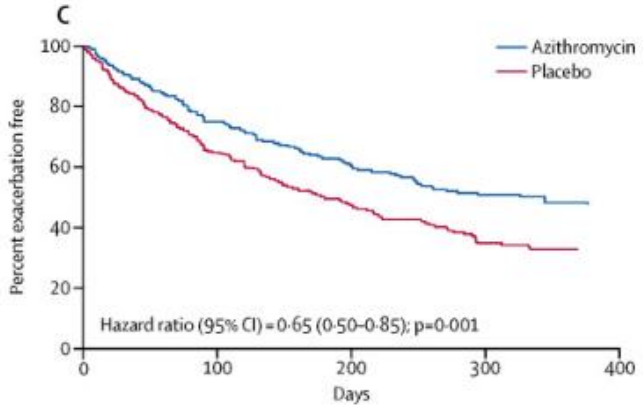


Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013198.

Asthma-Macrolide

- **Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial**
  - 420 adults with persistent uncontrolled asthma on ICS + LABA
  - Azithromycin 500 mg, 3 times/week for 48 weeks
  - ↓ Exacerbation rate by 41%
  - Prolonged time to first exacerbation (HR 0.65)

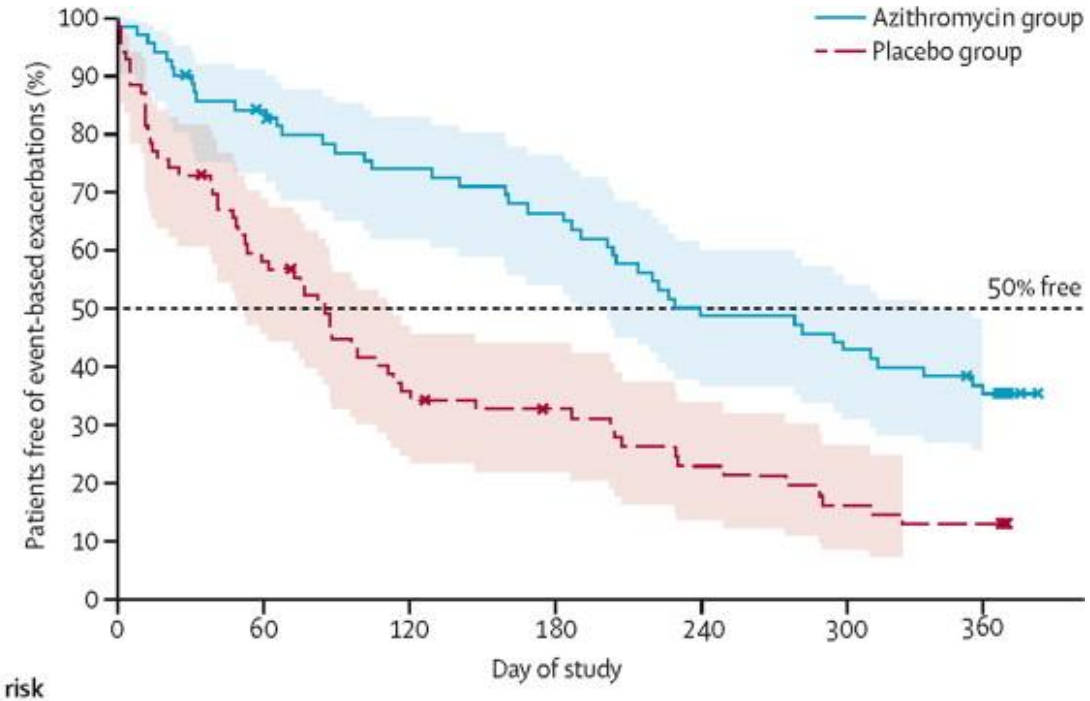




Lancet 2017; 390: 659–668.

Bronchiectasis-Macrolide

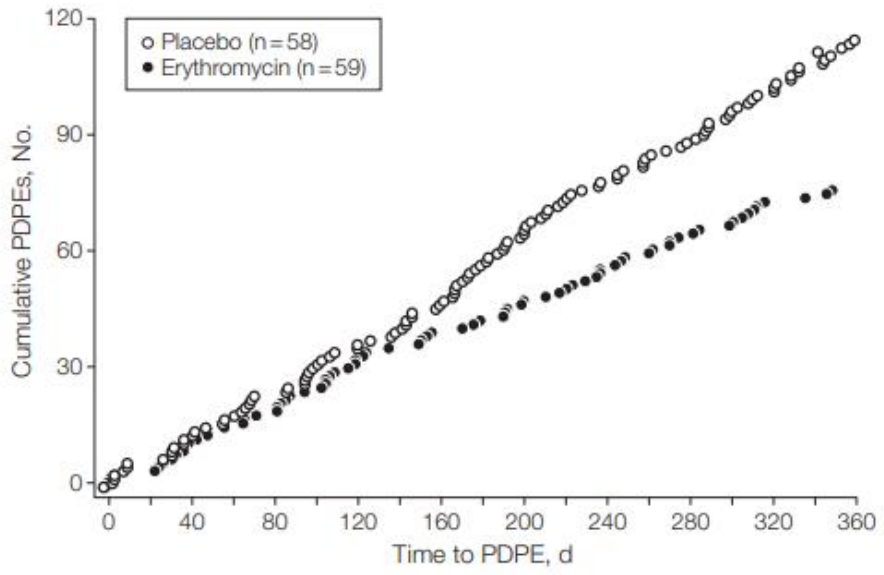
- **Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial**
  - 141 adults with non-CF bronchiectasis, ≥1 exacerbation in past year
  - Azithromycin 500 mg, 3 times/week for 6 months
  - ↓ Exacerbation rate by 62% (0.59 vs 1.57 per patient; RR 0.38, p<0.0001)
  - ↑ Median time to first exacerbation (104 vs 21 days; HR 0.34, p<0.0001)



Lancet 2012; 380: 660–67

Bronchiectasis-Macrolide

- **Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis - The BLESS Randomized Controlled Trial**
  - 117 adults with non-CF bronchiectasis, ≥2 exacerbations in prior year
  - Erythromycin 400 mg BID for 12 months
  - ↓ Exacerbation rate by 43% (1.29 vs 1.97 per patient/year; IRR 0.57, p=0.003)
  - Benefit also seen in Pseudomonas-infected subgroup

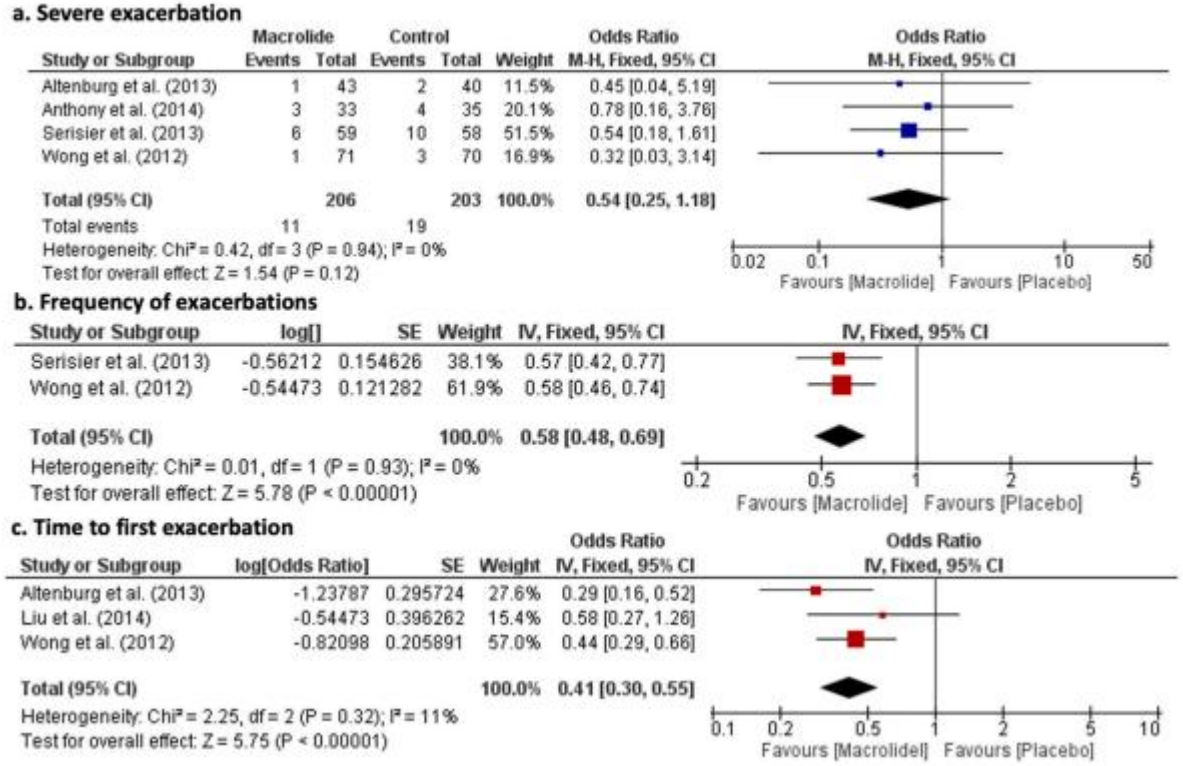


Each point represents a separate protocol-defined pulmonary exacerbation (PDPE). Individual participants could account for more than 1 event each. *P*=.003 for the comparison with placebo for the rate of pulmonary exacerbations per patient per year.

JAMA. 2013;309(12):1260-1267

Bronchiectasis-Macrolide

- **Efficacy and safety of long-term macrolide therapy for non-cystic fibrosis bronchiectasis: A systematic review and meta-analysis**
  - Macrolides significantly reduced overall exacerbation frequency (42%↓) and prolonged time to first exacerbation, while the reduction in severe exacerbations was not statistically significant.



Respiratory Investigation 62 (2024) 1079–1087

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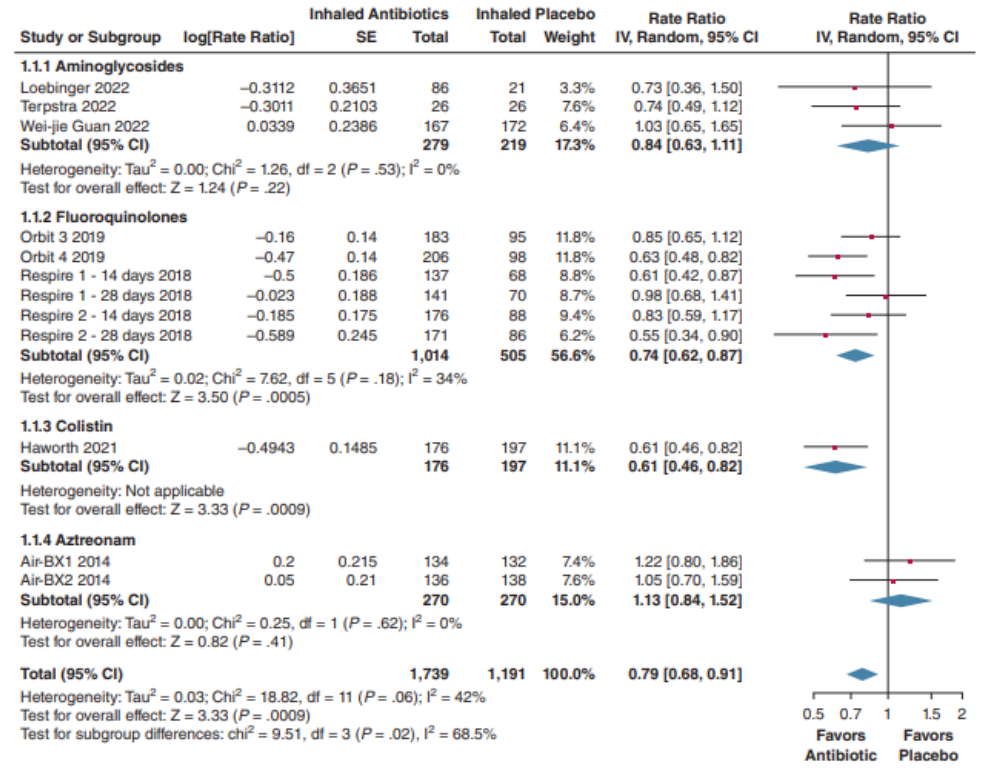
Bronchiectasis-Inhaled Antibiotics

- **The Efficacy and Safety of Inhaled Antibiotics for the Treatment of Bronchiectasis in Adults: Updated Systematic Review and Meta-Analysis**
  - 20 RCTs, 3,468 patients
  - ↓Exacerbation frequency (RR 0.78, 95% CI 0.68-0.91)
  - ↓Severe exacerbations (RR 0.48, 95% CI 0.31-0.74)

A



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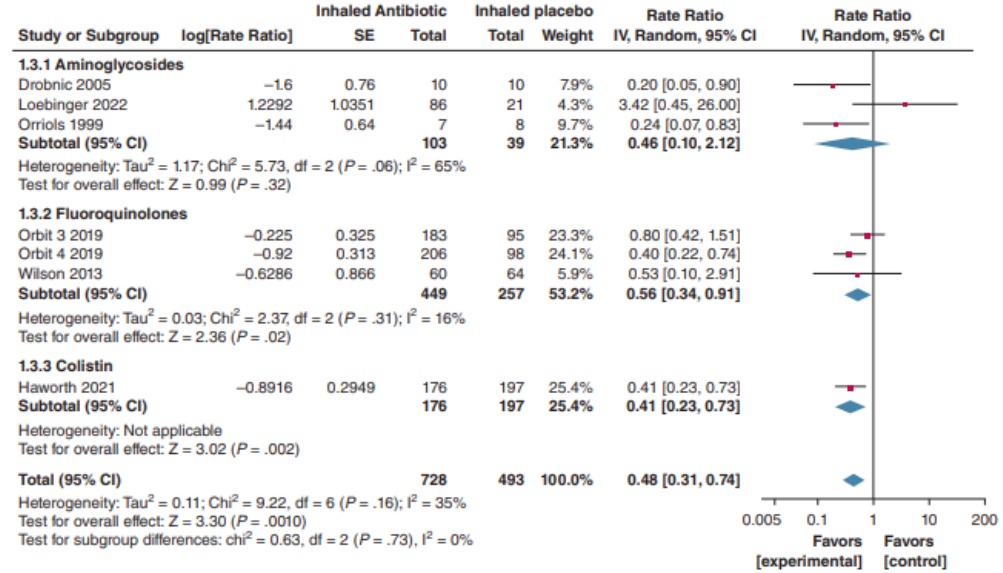
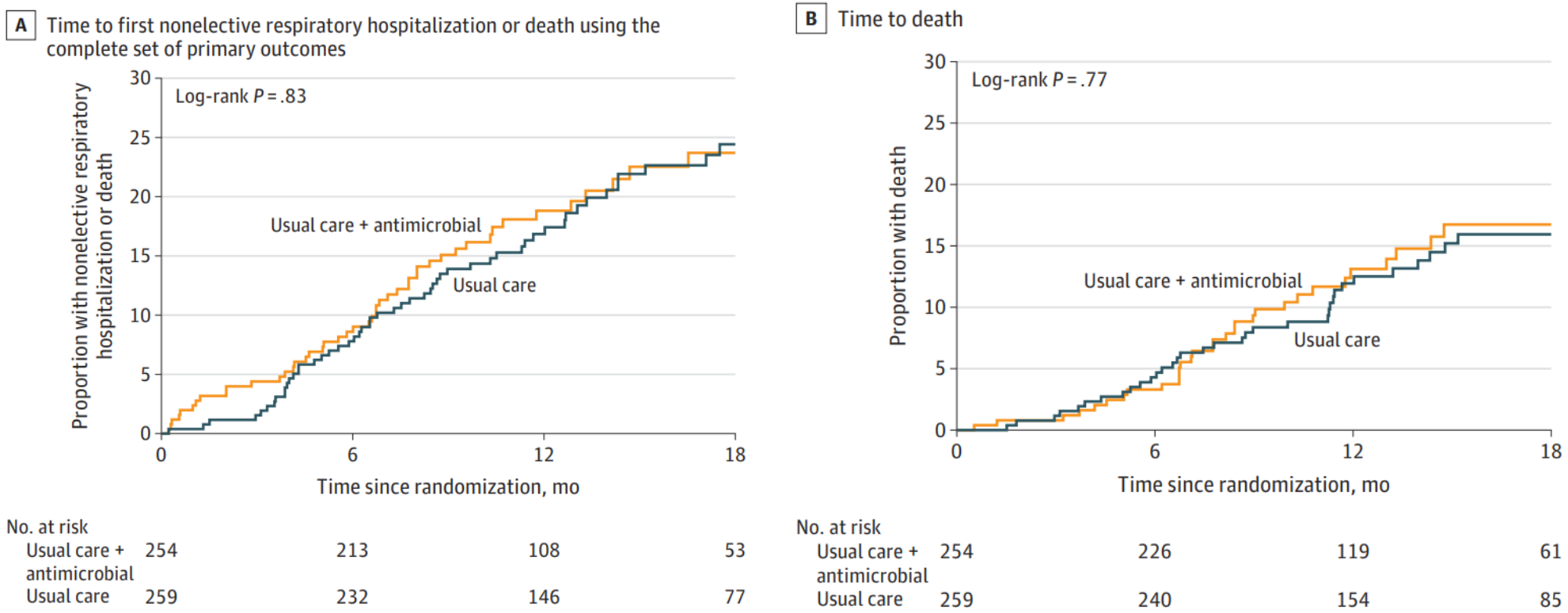


CHEST 2024; 166(1):61-80

순천향대학교 천안병원

ILD-Antimicrobial therapy

- **Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis: The CleanUP-IPF Randomized Clinical Trial**
  - 513 patients with IPF (91% on antifibrotics)
  - Co-trimoxazole or doxycycline + usual care vs usual care alone
  - No reduction in respiratory hospitalizations (HR 1.34) or mortality (HR 1.11)

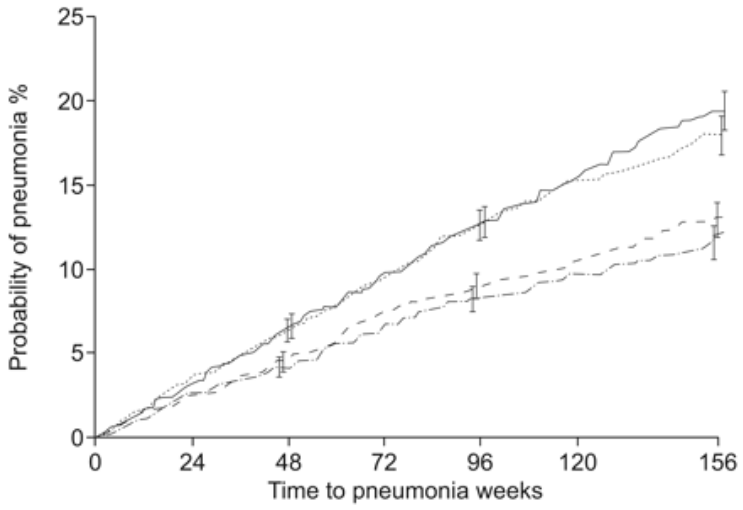


JAMA. 2021;325(18):1841-1851.

2. Optimal disease control

COPD-inhaled therapy

- Appropriate inhaled therapy is important
  - In TORCH study, Regular ICS treatment increases the risk of pneumonia
    - Higher pneumonia incidence with FP & SFC vs SAL & placebo
    - FP 14%, SFC 16% vs SAL 11%, placebo 9%
    - SFC vs placebo: 1.64 (95% CI 1.33–2.02) → 64% ↑ risk

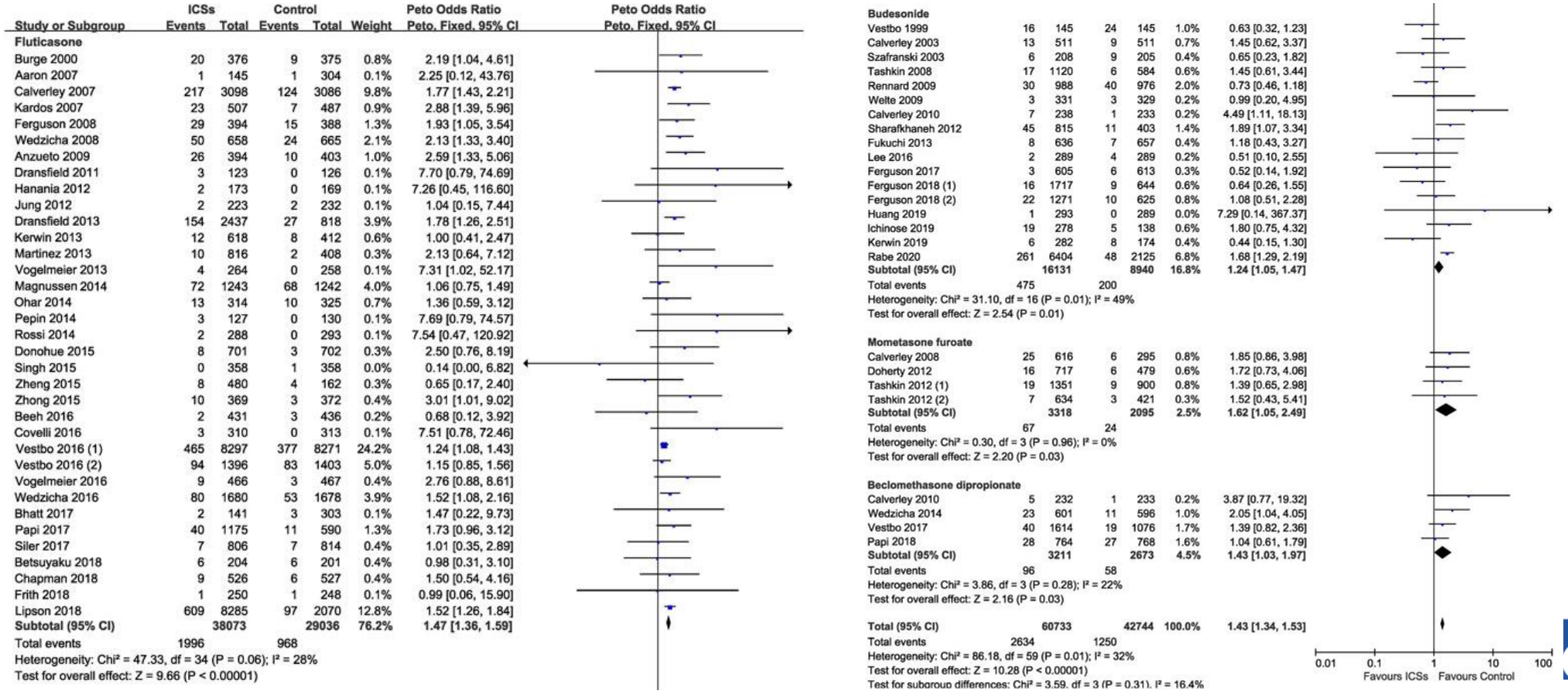


	Placebo	SAL 50 µg	FP 500 µg	SFC 50 µg/500 µg	ICS overall
Patients n	1544	1542	1552	1546	
Patients with pneumonia n	139	162	224	248	
Probability[#] of pneumonia by 3 yrs %	12.3	13.3	18.3	19.6	
Hazard ratio[¶]		1.09	1.53	1.64	1.52[+]
95% CI[¶]		0.87–1.37	1.24–1.89	1.33–2.02	1.32–1.76[+]
p-value[¶]		0.465	<0.001	<0.001	<0.001[+]

European Respiratory Journal 2009 34(3): 641-647

COPD-inhaled therapy

- **Inhaled Corticosteroids and the Pneumonia Risk in Patients With Chronic Obstructive Pulmonary Disease: A Meta-analysis of Randomized Controlled Trials**
  - 59 RCTs, 103,477 patients
  - All ICS types ↑ pneumonia risk (OR 1.43, 95% CI 1.34–1.53)



Study or Subgroup	ICSs Events	ICSs Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fluticasone						
Burge 2000	20	376	9	375	0.8%	2.19 [1.04, 4.61]
Aaron 2007	1	145	1	304	0.1%	2.25 [0.12, 43.76]
Calverley 2007	217	3098	124	3086	9.8%	1.77 [1.43, 2.21]
Kardos 2007	23	507	7	487	0.9%	2.88 [1.39, 5.96]
Ferguson 2008	29	394	15	388	1.3%	1.93 [1.05, 3.54]
Wedzicha 2008	50	658	24	665	2.1%	2.13 [1.33, 3.40]
Anzueto 2009	26	394	10	403	1.0%	2.59 [1.33, 5.06]
Dransfield 2011	3	123	0	126	0.1%	7.70 [0.79, 74.69]
Hanania 2012	2	173	0	169	0.1%	7.26 [0.45, 116.60]
Jung 2012	2	223	2	232	0.1%	1.04 [0.15, 7.44]
Dransfield 2013	154	2437	27	818	3.9%	1.78 [1.26, 2.51]
Kerwin 2013	12	618	8	412	0.6%	1.00 [0.41, 2.47]
Martinez 2013	10	816	2	408	0.3%	2.13 [0.64, 7.12]
Vogelmeier 2013	4	264	0	258	0.1%	7.31 [1.02, 52.17]
Magnussen 2014	72	1243	68	1242	4.0%	1.06 [0.75, 1.49]
Ohar 2014	13	314	10	325	0.7%	1.36 [0.59, 3.12]
Pepin 2014	3	127	0	130	0.1%	7.69 [0.79, 74.57]
Rossi 2014	2	288	0	293	0.1%	7.54 [0.47, 120.92]
Donohue 2015	8	701	3	702	0.3%	2.50 [0.76, 8.19]
Singh 2015	0	358	1	358	0.0%	0.14 [0.00, 6.82]
Zheng 2015	8	480	4	162	0.3%	0.65 [0.17, 2.40]
Zhong 2015	10	369	3	372	0.4%	3.01 [1.01, 9.02]
Beeh 2016	2	431	3	436	0.2%	0.68 [0.12, 3.92]
Covelli 2016	3	310	0	313	0.1%	7.51 [0.78, 72.46]
Vestbo 2016 (1)	465	8297	377	8271	24.2%	1.24 [1.08, 1.43]
Vestbo 2016 (2)	94	1396	83	1403	5.0%	1.15 [0.85, 1.56]
Vogelmeier 2016	9	466	3	467	0.4%	2.76 [0.88, 8.61]
Wedzicha 2016	80	1680	53	1678	3.9%	1.52 [1.08, 2.16]
Bhatt 2017	2	141	3	303	0.1%	1.47 [0.22, 9.73]
Papi 2017	40	1175	11	590	1.3%	1.73 [0.96, 3.12]
Siler 2017	7	806	7	814	0.4%	1.01 [0.35, 2.89]
Betsuyaku 2018	6	204	6	201	0.4%	0.98 [0.31, 3.10]
Chapman 2018	9	526	6	527	0.4%	1.50 [0.54, 4.16]
Frith 2018	1	250	1	248	0.1%	0.99 [0.06, 15.90]
Lipson 2018	609	8285	97	2070	12.8%	1.52 [1.26, 1.84]
Subtotal (95% CI)		**38073**		**29036**	**76.2%**	**1.47 [1.36, 1.59]**
Total events	1996		968			
Heterogeneity: Chi² = 47.33, df = 34 (P = 0.06); I² = 28%						
Test for overall effect: Z = 9.66 (P < 0.00001)						
Budesonide						
Vestbo 1999	16	145	24	145	1.0%	0.63 [0.32, 1.23]
Calverley 2003	13	511	9	511	0.7%	1.45 [0.62, 3.37]
Szafranski 2003	6	208	9	205	0.4%	0.65 [0.23, 1.82]
Tashkin 2008	17	1120	6	584	0.6%	1.45 [0.61, 3.44]
Rennard 2009	30	988	40	976	2.0%	0.73 [0.46, 1.18]
Welte 2009	3	331	3	329	0.2%	0.99 [0.20, 4.95]
Calverley 2010	7	238	1	233	0.2%	4.49 [1.11, 18.13]
Sharafkhaneh 2012	45	815	11	403	1.4%	1.89 [1.07, 3.34]
Fukuchi 2013	8	636	7	657	0.4%	1.18 [0.43, 3.27]
Lee 2016	2	289	4	289	0.2%	0.51 [0.10, 2.55]
Ferguson 2017	3	605	6	613	0.3%	0.52 [0.14, 1.92]
Ferguson 2018 (1)	16	1717	9	644	0.6%	0.64 [0.26, 1.55]
Ferguson 2018 (2)	22	1271	10	625	0.8%	1.08 [0.51, 2.28]
Huang 2019	1	293	0	289	0.0%	7.29 [0.14, 367.37]
Ichinose 2019	19	278	5	138	0.6%	1.80 [0.75, 4.32]
Kerwin 2019	6	282	8	174	0.4%	0.44 [0.15, 1.30]
Rabe 2020	261	6404	48	2125	6.8%	1.68 [1.29, 2.19]
Subtotal (95% CI)		**16131**		**8940**	**16.8%**	**1.24 [1.05, 1.47]**
Total events	475		200			
Heterogeneity: Chi² = 31.10, df = 16 (P = 0.01); I² = 49%						
Test for overall effect: Z = 2.54 (P = 0.01)						
Mometasone furoate						
Calverley 2008	25	616	6	295	0.8%	1.85 [0.86, 3.98]
Doherty 2012	16	717	6	479	0.6%	1.72 [0.73, 4.06]
Tashkin 2012 (1)	19	1351	9	900	0.8%	1.39 [0.65, 2.98]
Tashkin 2012 (2)	7	634	3	421	0.3%	1.52 [0.43, 5.41]
Subtotal (95% CI)		**3318**		**2095**	**2.5%**	**1.62 [1.05, 2.49]**
Total events	67		24			
Heterogeneity: Chi² = 0.30, df = 3 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Beclomethasone dipropionate						
Calverley 2010	5	232	1	233	0.2%	3.87 [0.77, 19.32]
Wedzicha 2014	23	601	11	596	1.0%	2.05 [1.04, 4.05]
Vestbo 2017	40	1614	19	1076	1.7%	1.39 [0.82, 2.36]
Papi 2018	28	764	27	768	1.6%	1.04 [0.61, 1.79]
Subtotal (95% CI)		**3211**		**2673**	**4.5%**	**1.43 [1.03, 1.97]**
Total events	96		58			
Heterogeneity: Chi² = 3.86, df = 3 (P = 0.28); I² = 22%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Total (95% CI)		**60733**		**42744**	**100.0%**	**1.43 [1.34, 1.53]**
Total events	2634		1250			
Heterogeneity: Chi² = 86.18, df = 59 (P = 0.01); I² = 32%						
Test for overall effect: Z = 10.28 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.59, df = 3 (P = 0.31), I² = 16.4%						

Peto Odds Ratio Peto, Fixed, 95% CI

0.01 0.1 1 10 100

Favours ICSs Favours Control

- GOLD guideline 2025
  - Patients at Higher Risk of Pneumonia
    - Current smokers
    - Age ≥55 years
    - History of prior exacerbations or pneumonia
    - BMI <25
    - High mMRC grade and/or severe airflow obstruction

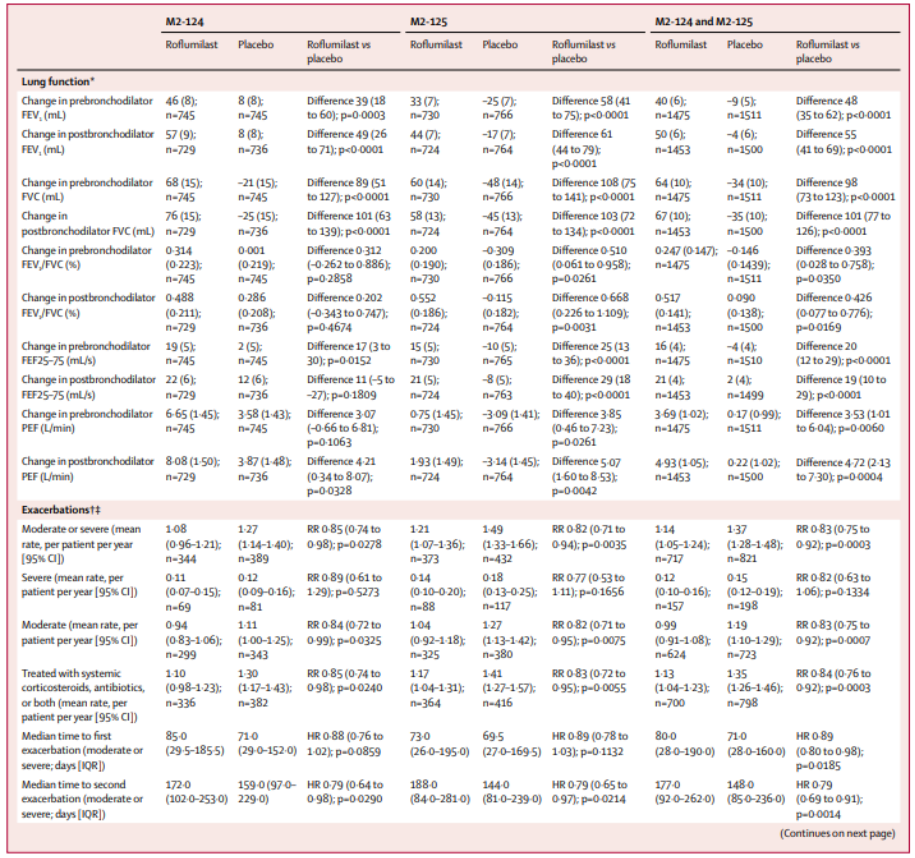
Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/μL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/μL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/μL
	History of mycobacterial infection

COPD-Roflumilast

- **Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials**
  - Two large RCTs (M2-124, M2-125), >3,000 patients with severe COPD & chronic bronchitis
  - Roflumilast 500 μg daily vs placebo for 52 weeks
  - ↓ Moderate–severe exacerbation rate by 17% (RR 0.83, 95% CI 0.75–0.92, p=0.0003)



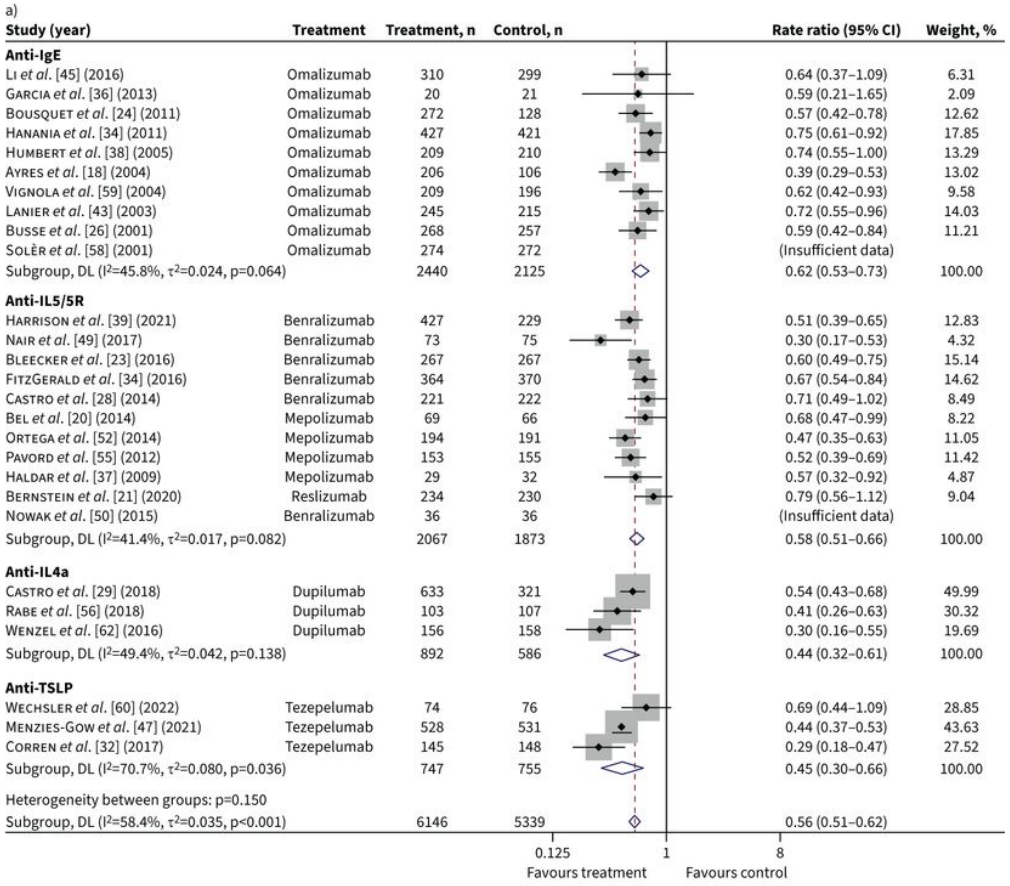
	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo
Lung function*									
Change in prebronchodilator FEV_1 (mL)	46 (8); n=745	8 (8); n=745	Difference 39 (18 to 60); p=0·0003	33 (7); n=730	−25 (7); n=766	Difference 58 (41 to 75); p<0·0001	40 (6); n=1475	−9 (5); n=1511	Difference 48 (35 to 62); p<0·0001
Change in postbronchodilator FEV_1 (mL)	57 (9); n=729	8 (8); n=736	Difference 49 (26 to 71); p<0·0001	44 (7); n=724	−17 (7); n=764	Difference 61 (44 to 79); p<0·0001	50 (6); n=1453	−4 (6); n=1500	Difference 55 (41 to 69); p<0·0001
Change in prebronchodilator FVC (mL)	68 (15); n=745	−21 (15); n=745	Difference 89 (51 to 127); p<0·0001	60 (14); n=730	−48 (14); n=766	Difference 108 (75 to 141); p<0·0001	64 (10); n=1475	−34 (10); n=1511	Difference 98 (73 to 123); p<0·0001
Change in postbronchodilator FVC (mL)	76 (15); n=729	−25 (15); n=736	Difference 101 (63 to 139); p<0·0001	58 (13); n=724	−45 (13); n=764	Difference 103 (72 to 134); p<0·0001	67 (10); n=1453	−35 (10); n=1500	Difference 101 (77 to 126); p<0·0001
Change in prebronchodilator FEV_1/FVC (%)	0·314 (0·223); n=745	0·001 (0·219); n=745	Difference 0·312 (−0·262 to 0·886); p=0·2858	0·200 (0·190); n=730	−0·309 (0·186); n=766	Difference 0·510 (0·061 to 0·958); p=0·0261	0·247 (0·147); n=1475	−0·146 (0·1439); n=1511	Difference 0·393 (0·028 to 0·758); p=0·0350
Change in postbronchodilator FEV_1/FVC (%)	0·488 (0·211); n=729	0·286 (0·208); n=736	Difference 0·202 (−0·343 to 0·747); p=0·4674	0·552 (0·186); n=724	−0·115 (0·182); n=764	Difference 0·668 (0·226 to 1·109); p=0·0031	0·517 (0·141); n=1453	0·090 (0·138); n=1500	Difference 0·426 (0·077 to 0·776); p=0·0169
Change in prebronchodilator FEF25–75 (mL/s)	19 (5); n=745	2 (5); n=745	Difference 17 (3 to 30); p=0·0152	15 (5); n=730	−10 (5); n=765	Difference 25 (13 to 36); p<0·0001	16 (4); n=1475	−4 (4); n=1510	Difference 20 (12 to 29); p<0·0001
Change in postbronchodilator FEF25–75 (mL/s)	22 (6); n=729	12 (6); n=736	Difference 11 (−5 to −27); p=0·1809	21 (5); n=724	−8 (5); n=763	Difference 29 (18 to 40); p<0·0001	21 (4); n=1453	2 (4); n=1499	Difference 19 (10 to 29); p<0·0001
Change in prebronchodilator PEF (L/min)	6·65 (1·45); n=745	3·58 (1·43); n=745	Difference 3·07 (−0·66 to 6·81); p=0·1063	0·75 (1·45); n=730	−3·09 (1·41); n=766	Difference 3·85 (0·46 to 7·23); p=0·0261	3·69 (1·02); n=1475	0·17 (0·99); n=1511	Difference 3·53 (1·01 to 6·04); p=0·0060
Change in postbronchodilator PEF (L/min)	8·08 (1·50); n=729	3·87 (1·48); n=736	Difference 4·21 (0·34 to 8·07); p=0·0328	1·93 (1·49); n=724	−3·14 (1·45); n=764	Difference 5·07 (1·60 to 8·53); p=0·0042	4·93 (1·05); n=1453	0·22 (1·02); n=1500	Difference 4·72 (2·13 to 7·30); p=0·0004
Exacerbations†‡									
Moderate or severe (mean rate, per patient per year [95% CI])	1·08 (0·96–1·21); n=344	1·27 (1·14–1·40); n=389	RR 0·85 (0·74 to 0·98); p=0·0278	1·21 (1·07–1·36); n=373	1·49 (1·33–1·66); n=432	RR 0·82 (0·71 to 0·94); p=0·0035	1·14 (1·05–1·24); n=717	1·37 (1·28–1·48); n=821	RR 0·83 (0·75 to 0·92); p=0·0003
Severe (mean rate, per patient per year [95% CI])	0·11 (0·07–0·15); n=69	0·12 (0·09–0·16); n=81	RR 0·89 (0·61 to 1·29); p=0·5273	0·14 (0·10–0·20); n=88	0·18 (0·13–0·25); n=117	RR 0·77 (0·53 to 1·11); p=0·1656	0·12 (0·10–0·16); n=157	0·15 (0·12–0·19); n=198	RR 0·82 (0·63 to 1·06); p=0·1334
Moderate (mean rate, per patient per year [95% CI])	0·94 (0·83–1·06); n=299	1·11 (1·00–1·25); n=343	RR 0·84 (0·72 to 0·99); p=0·0325	1·04 (0·92–1·18); n=325	1·27 (1·13–1·42); n=380	RR 0·82 (0·71 to 0·95); p=0·0075	0·99 (0·91–1·08); n=624	1·19 (1·10–1·29); n=723	RR 0·83 (0·75 to 0·92); p=0·0007
Treated with systemic corticosteroids, antibiotics, or both (mean rate, per patient per year [95% CI])	1·10 (0·98–1·23); n=336	1·30 (1·17–1·43); n=382	RR 0·85 (0·74 to 0·98); p=0·0240	1·17 (1·04–1·31); n=364	1·41 (1·27–1·57); n=416	RR 0·83 (0·72 to 0·95); p=0·0055	1·13 (1·04–1·23); n=700	1·35 (1·26–1·46); n=798	RR 0·84 (0·76 to 0·92); p=0·0003
Median time to first exacerbation (moderate or severe; days [IQR])	85·0 (29·5–185·5)	71·0 (29·0–152·0)	HR 0·88 (0·76 to 1·02); p=0·0859	73·0 (26·0–195·0)	69·5 (27·0–169·5)	HR 0·89 (0·78 to 1·03); p=0·1132	80·0 (28·0–190·0)	71·0 (28·0–160·0)	HR 0·89 (0·80 to 0·98); p=0·0185
Median time to second exacerbation (moderate or severe; days [IQR])	172·0 (102·0–253·0)	159·0 (97·0–229·0)	HR 0·79 (0·64 to 0·98); p=0·0290	188·0 (84·0–281·0)	144·0 (81·0–239·0)	HR 0·79 (0·65 to 0·97); p=0·0214	177·0 (92·0–262·0)	148·0 (85·0–236·0)	HR 0·79 (0·69 to 0·91); p=0·0014

(Continues on next page)

Lancet 2009; 374: 685–94

Asthma-biologics

- **Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials**
  - 48 RCTs, n=16,350
  - Exacerbations ↓ 44% (rate ratio 0.56, 95% CI 0.51–0.62)



European Respiratory Review 2024 33(172): 230238

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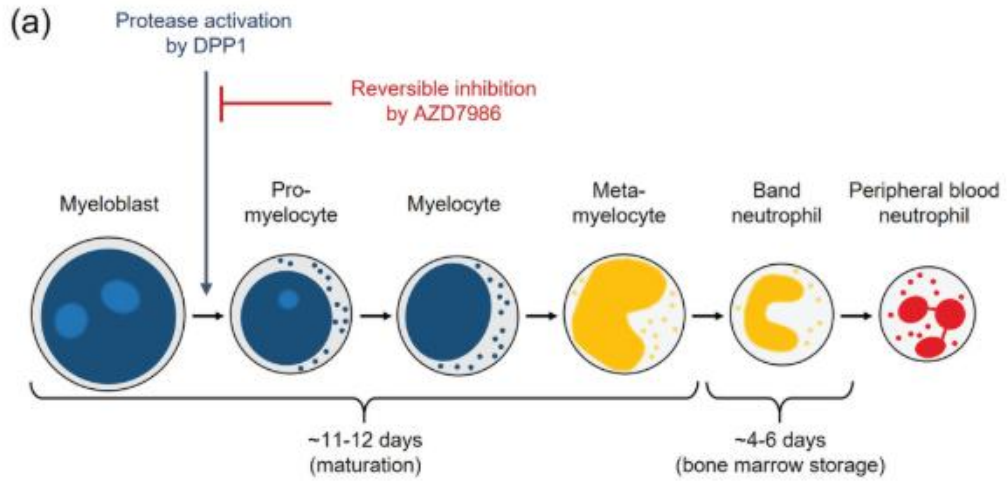
3. New strategies

Bronchiectasis – DPP1 inhibitor

- Neutrophils -> Exacerbations
  - Excess neutrophil influx during infection
  - Release of neutrophil proteases (elastase, cathepsin G, proteinase 3)

  → airway inflammation & mucus hypersecretion, Tissue damage, More frequent AE

- Brensocatib (AZD7986)
  - DPP1 activates neutrophil proteases during maturation in bone marrow
  - Brensocatib = reversible DPP1 inhibitor
  - Blocks premature protease activation → ↓ airway inflammation → ↓ exacerbations



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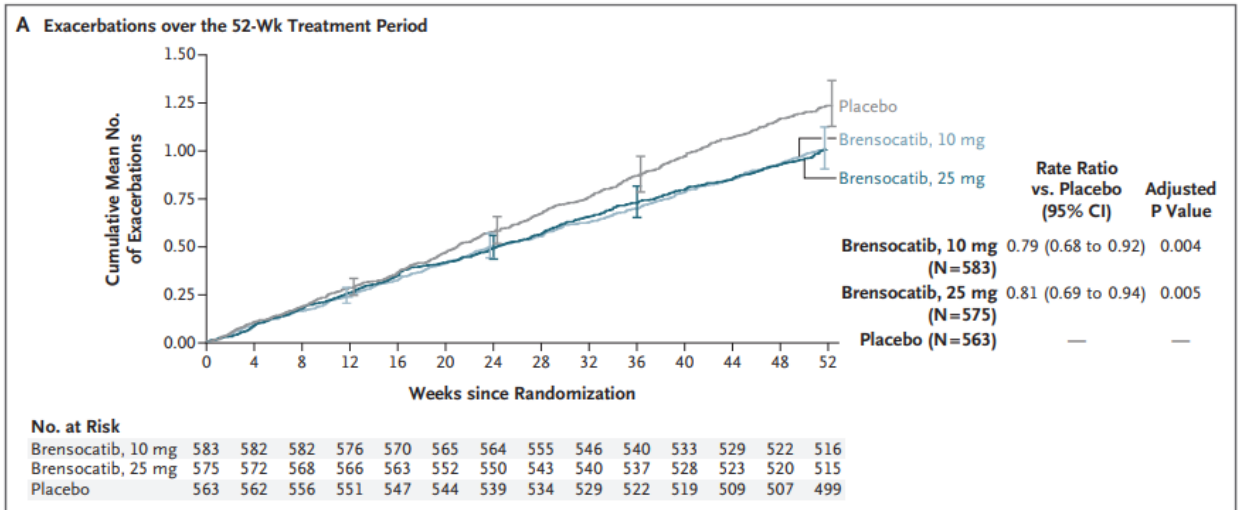
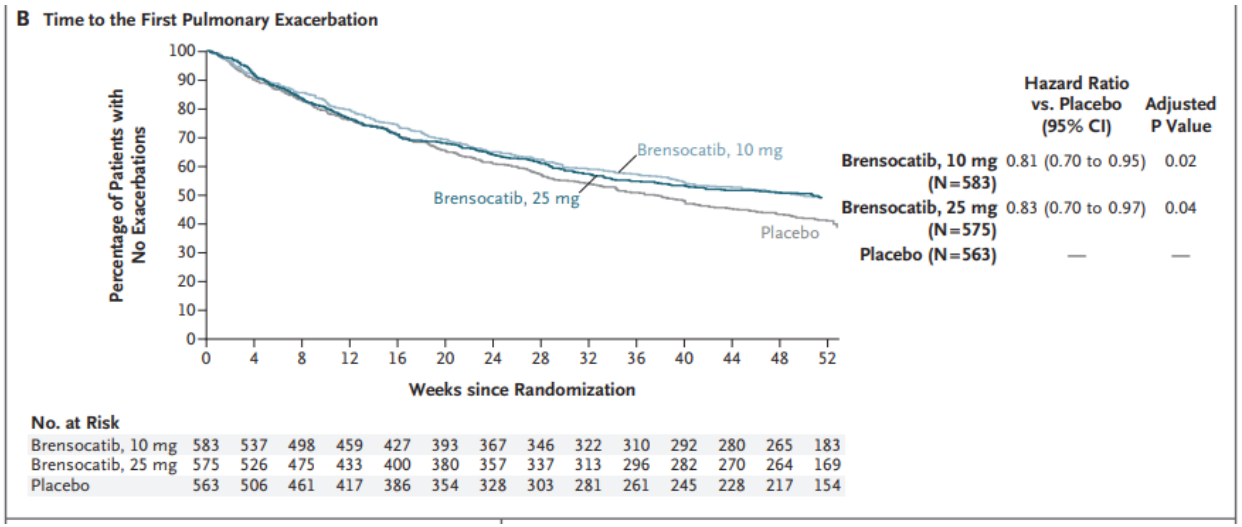
Brochiectasis-Brensocatib

- **Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis**
  - 1,721 patients with bronchiectasis
  - Brensocatib 10 mg: 1.02 events/yr (RR 0.79, p=0.004)
  - Brensocatib 25 mg: 1.04 events/yr (RR 0.81, p=0.005)
  - Time to first exacerbation: HR 0.81–0.83 vs placebo (significant)
  - Exacerbation-free at 52 wks: 48.5% with brensocatib vs 40.3% placebo





N Engl J Med 2025;392:1569-81

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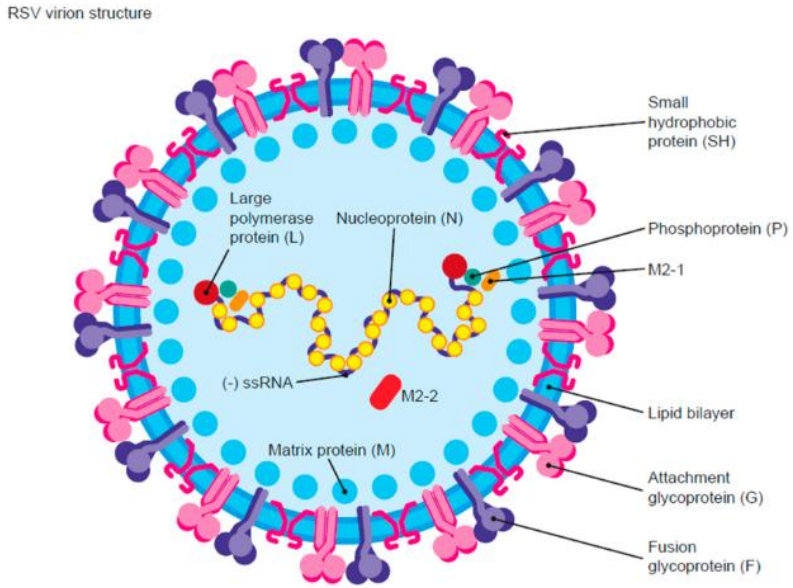
Vaccination

- Influenza
  - Routine annual influenza vaccination is recommended as the most effective strategy for preventing seasonal influenza

- Pneumococcal
  - Adults 19–64 years with chronic respiratory disease or ≥65 years
  - One dose of PCV20 or
  - PCV15 followed by PPSV23 (≥8 weeks later)
  - If previously received PPSV23 only → administer PCV15 or PCV20 as a supplemental dose.

- RSV

RSV

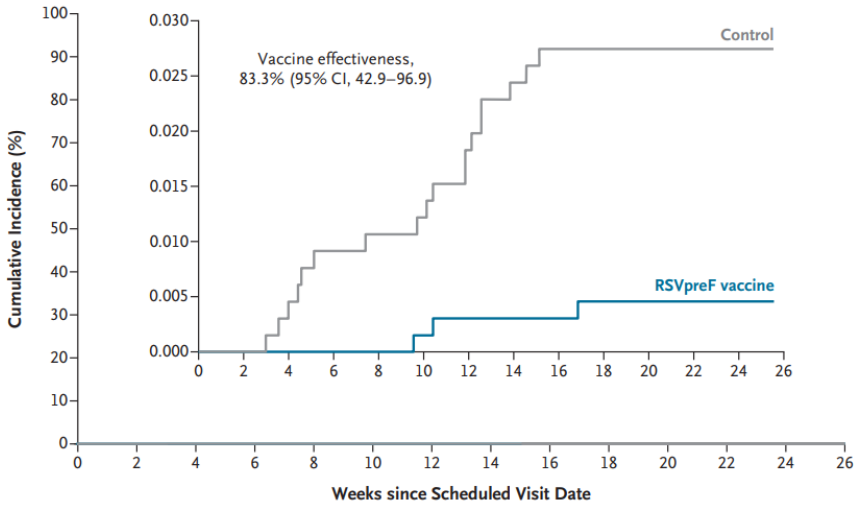


- RSV burden
  - 8.7% of outpatient AE-COPD
  - 336,000 patients hospitalizations
  - 14,000 patients in-hospital deaths annually worldwide
- High-risk groups: Infants, older adults, COPD & chronic lung disease patients

- RSV
  - G glycoprotein (attachment protein): facilitates binding to host cells
  - **F glycoprotein** (fusion protein): Enables fusion of RSV with host cells, allowing viral entry.
  - prefusion and postfusion forms
  - Prefusion F protein is the most potent target for neutralizing antibodies
  - RSV vaccines (e.g., Arexvy) use a stabilized prefusion F protein as the antigen

RSV vaccine

- **RSV Prefusion F Vaccine for Prevention of Hospitalization in Older Adult**
  - 131,276 adults ≥60, Denmark, 2024–2025 winter
  - Primary endpoint: Hospitalization for RSV-related respiratory tract disease
    - RSVpreF: 0.11 / 1000 pt-yrs (3 cases)
    - Control: 0.66 / 1000 pt-yrs (18 cases)
    - Vaccine effectiveness: 83.3% (95% CI 42.9–96.9, p=0.007)
  - Secondary endpoints:
    - RSV-related LRTD hospitalization: 91.7% VE (1 vs 12 cases)
    - Any respiratory hospitalization: 15.2% VE (284 vs 335 cases)



Subgroup	RSVpreF Vaccine	Control	Vaccine Effectiveness (95% CI)
	no. of events/total no. of participants		
Overall	3/65,642	18/65,634	83.3 (42.9 to 96.9)
Age			
60–74 yr	1/51,803	10/51,781	90.0 (29.7 to 99.8)
≥75 yr	2/13,839	8/13,853	75.0 (−25.0 to 97.4)
<Median	0/32,890	4/32,751	—
≥Median	3/32,752	14/32,883	78.5 (23.6 to 96.1)
Sex			
Male	2/32,931	9/33,082	77.7 (−6.8 to 97.7)
Female	1/32,711	9/32,552	88.9 (19.4 to 99.8)
Presence of at least 1 chronic disease			
No	0/38,080	5/38,080	—
Yes	3/27,562	13/27,554	76.9 (16.0 to 95.8)
Chronic lung disease			
No	3/60,834	13/60,832	76.9 (16.1 to 95.8)
Yes	0/4808	5/4802	—

10.1056/NEJMoa2509810

RSV vaccine

- Arexvy is Korea’s first RSV vaccine, authorized in December 2024 for adults 60 years and older.

- Route: Intramuscular injection (preferably deltoid muscle)
- Dose: Single dose, 0.5 mL

- One-time administration (no series required)

Take home message

- Acute infectious exacerbations are a major driver of morbidity and mortality in chronic lung diseases.
- Prophylactic macrolides consistently reduce exacerbations in COPD, asthma, and bronchiectasis.
- Optimal disease control with inhaled therapy, biologics, and roflumilast prevents infection-triggered events.
- New strategies such as brensocatib and RSV vaccines show promising efficacy.

Thank you!

icujh@schmc.ac.kr