Prophylactic antibiotics for prevention of chronic obstructive pulmonary disease exacerbation: Pro

한림대학교 강남성심병원

호흡기내과

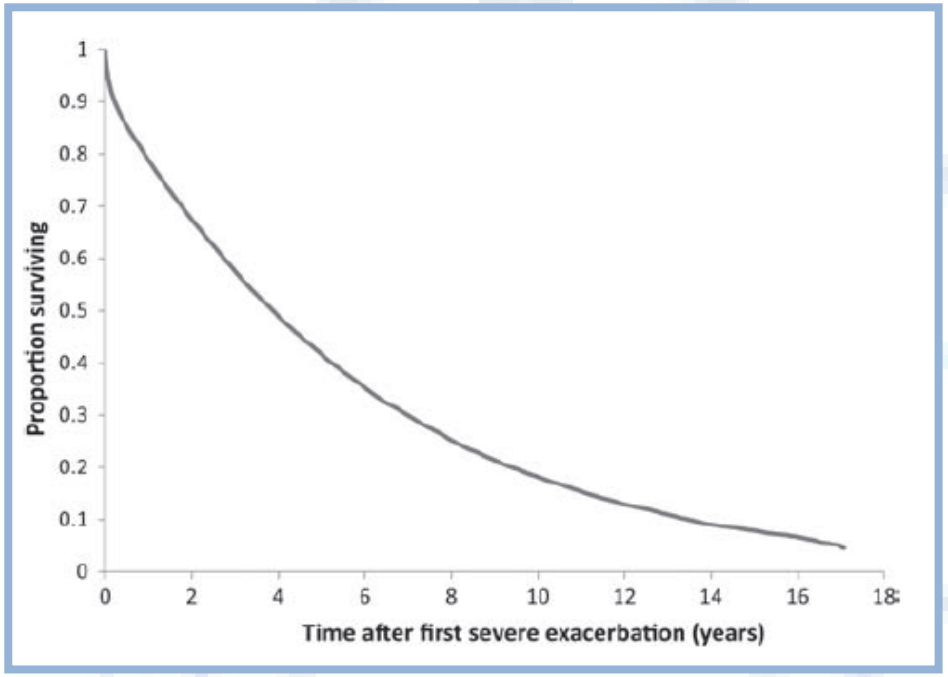
심윤수

Acute exacerbation of COPD

- Acceleration of disease progression
  - FEV_1 fall by 33mL/year in COPD
  - Each acute exacerbation additional 2mL/year
- Quality of life ↓
- Cost of healthcare ↑
  - 35-84% of total cost of COPD treatment
- Mortality ↑

Mortality of AECOPD

- 73,106 patients hospitalized for the first time for COPD during 1990-2005
  - 17 years follow up
- Mortality
  - 50% at 3.6 years
  - 75% at 7.7 years



Suissa S. Thorax. 2011

Risk of the subsequent AECOPD

- Duration for subsequent exacerbation
  - 5.4 years from first
  - 1.6 years from second
  - 0.9 years from third

Exacerbation sequence number	Median time to subsequent exacerbation (years)	Number with a subsequent exacerbation	Crude HR	Adjusted* HR (95% CI)
First (reference)	5.4	33 166	1.0	1.0 (reference)
Second	1.6	19 359	3.0	2.9 (2.8 to 2.9)
Third	0.9	12 413	5.1	4.9 (4.8 to 5.0)
Fourth	0.7	8374	7.3	6.9 (6.8 to 7.1)
Fifth	0.5	5903	9.8	9.2 (8.9 to 9.4)
Sixth	0.4	4316	11.9	11.2 (10.8 to 11.5)
Seventh	0.3	3190	13.9	13.0 (12.5 to 13.5)
Eighth	0.3	2404	16.6	15.2 (14.6 to 15.9)
Ninth	0.3	1823	18.1	16.6 (15.8 to 17.4)
Tenth or greater	0.2	1403	25.8	23.5 (22.8 to 24.2)

Suissa S. Thorax. 2011

Prevention of AECOPD

Pharmacologic intervention	Nonpharmacologic Intervention
ICS	LVRS
LABA	Pulmonary rehabilitation
ICS/LABA combination	Disease-management programs
LAMA	Vaccination
ICS/LABA+LAMA	
PDE4 inhibitor	

Prevention of AECOPD

- 40-50 % of exacerbations are related to bacterial infection : *S. pneumoniae, H.influenza, M.catarrhalis*

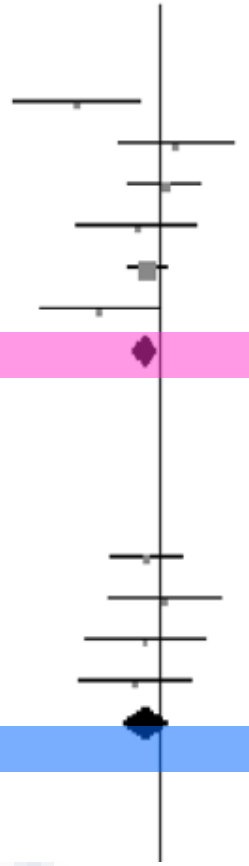
- Prophylactic antibiotics
  - The reduction of airway bacterial load
  - Prevention of new strain acquisition

- Before 1970
  - Small numbers of patients included
  - Low doses of narrow-spectrum antibiotics

Tetracyclin, penicillin

- Number of exacerbations per study

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight %	IV, fixed SMD (95%CI)	Year	IV, fixed SMD 95%CI
Tetracyclines										
Moyes and Kershaw[29]	1.93	0.0	27	2.19	0.0	31		Not estimable	1957	
Buchanan et al.[28]	0.33	0.48	21	1.13	1.19	15	3.0	−0.92 (−1.62–−0.22)	1958	
Francis and Spicer,[25] arm 1	1.07	0.51	79	1.04	0.7	37	9.7	0.05 (−0.34–0.44)	1960	
Pridie et al.,[26] arm 1	1.12	1.26	25	0.91	0.93	16	3.7	0.18 (−0.45–0.81)	1960	
Djajadiningrat et al.,[23] arm 1	0.86	1.13	29	1.15	1.07	13	3.4	−0.26 (−0.91–0.40)	1964	
Fletcher and Oldham[22]	3.04	3.09	181	3.45	3.08	192	35.8	−0.13 (−0.34–0.07)	1966	
Johnston et al.[24]	2.1	2.17	21	5.1	6.14	17	3.4	−0.67 (−1.33–−0.01)	1969	
Subtotal (95%CI)			**383**			**321**	**59.1**	**−0.16 (−0.32–−0.00)**		
Heterogeneity: $\chi^2 = 9.24$, df = 5 ($P = 0.10$); $I^2 = 46\%$										
Test for overall effect: $Z = 1.99$ ($P = 0.05$)										
Penicillins										
Francis and Spicer,[25] arm 2	0.92	0.84	73	1.04	0.7	37	9.4	−0.15 (−0.55–0.25)	1960	
Pridie et al.,[26] arm 2	0.96	1.14	25	0.91	0.93	16	3.8	0.05 (−0.58–0.67)	1960	
Johnston et al.[20]	0.5	0.62	18	0.61	0.7	18	3.5	−0.16 (−0.82–0.49)	1961	
Djajadiningrat et al.,[23] arm 2	1.1	1.11	31	1.4	1.06	15	3.9	−0.27 (−0.89–0.35)	1964	
Subtotal (95%CI)			**147**			**86**	**20.5**	**−0.14 (−0.41–0.13)**		
Heterogeneity: $\chi^2 = 0.51$, df = 3 ($P = 0.92$); $I^2 = 0\%$										
Test for overall effect: $Z = 1.01$ ($P = 0.31$)										



Lee JS. Int J Tuberc lung dis. 2013

Choice of antibiotics

- Antibacterial effects
  - The reduction of airway bacterial load
  - Prevention of new strain acquisition
- Anti-inflammatory effects
- Immunomodulatory effects

Macrolide

Quinolone

Sethi *et al. Respiratory Research* 2010, **11**:10
http://respiratory-research.com/content/11/1/10

RESPIRATORY RESEARCH

RESEARCH Open Access

Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial

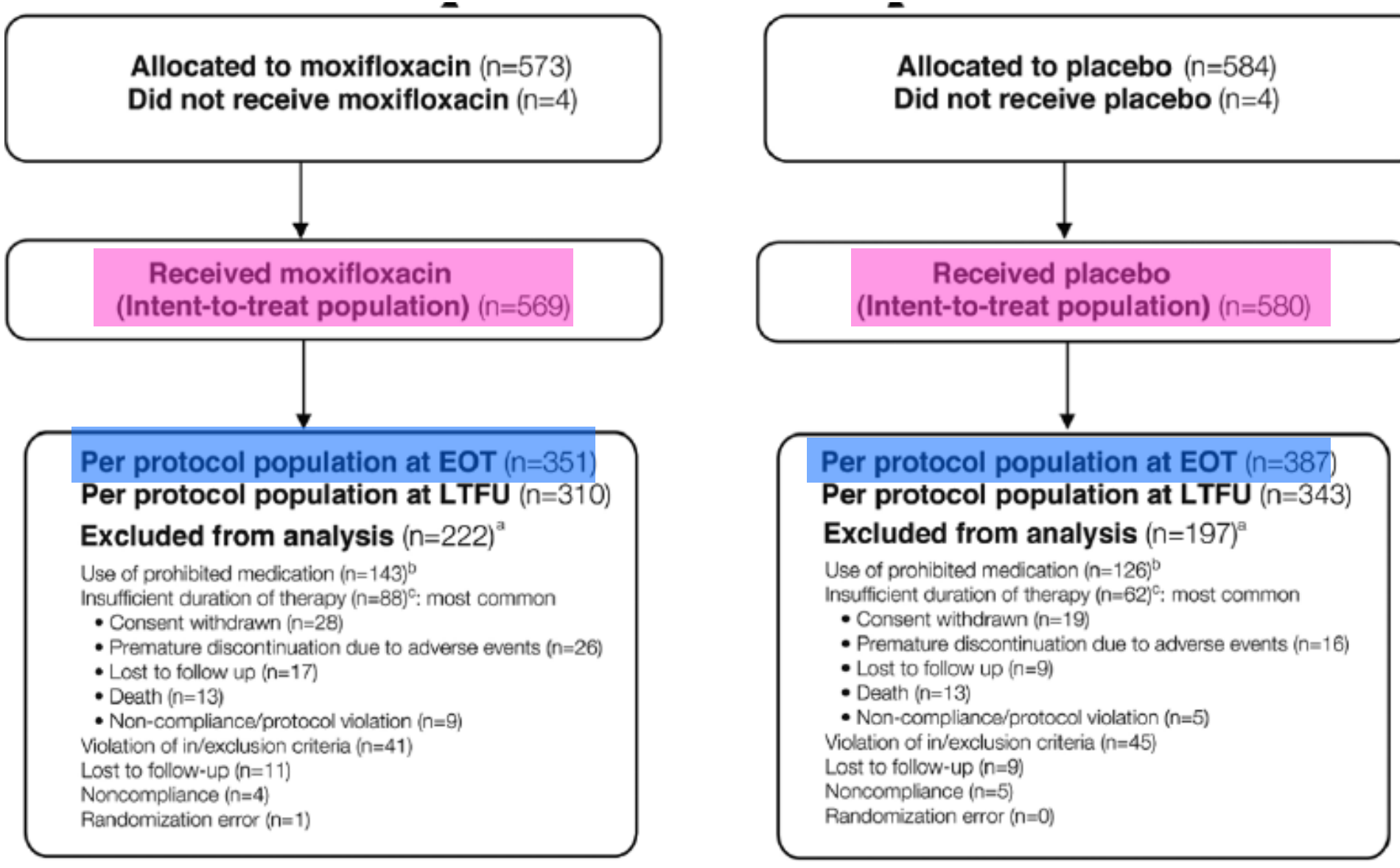
Sanjay Sethi[1*], Paul W Jones[2], Marlize Schmitt Theron[3], Marc Miravitlles[4], Ethan Rubinstein[5], Jadwiga A Wedzicha[6], Robert Wilson[7], the PULSE Study group

- Excellent penetration into respiratory tissues
- High oral bioavailability

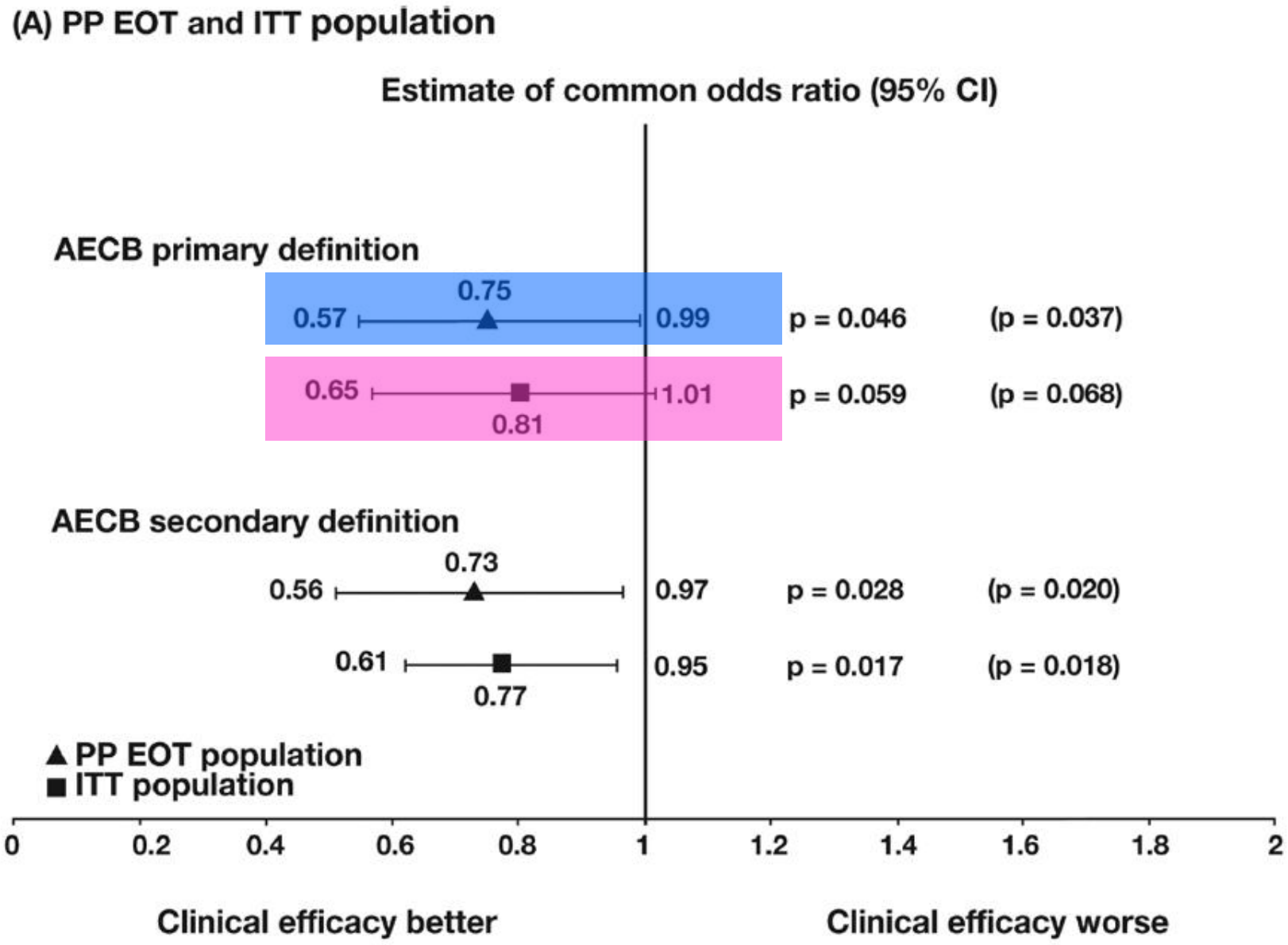
Moxifloxacin

- Patients
  - 45 years of age with 20 pack years
  - At least two exacerbations with antibiotics or steroid in the 12 months prior to enroll.
- Moxifloxacin 400mg orally once daily for 5 days every 8 weeks for a total of 6 course
- Total 72 weeks: three additional follow up every 8 weeks

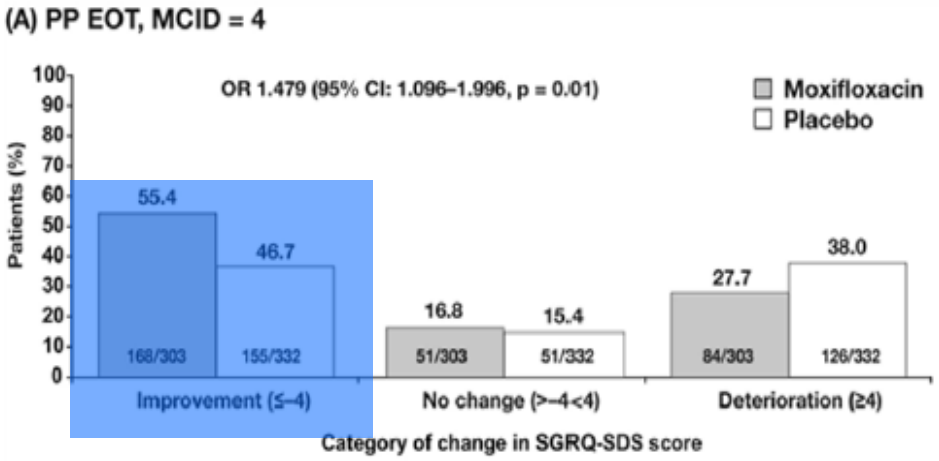
Moxifloxacin

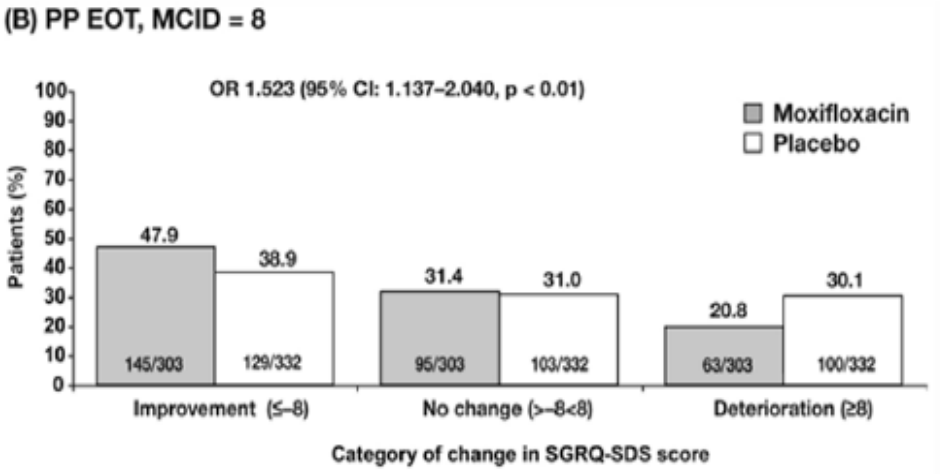


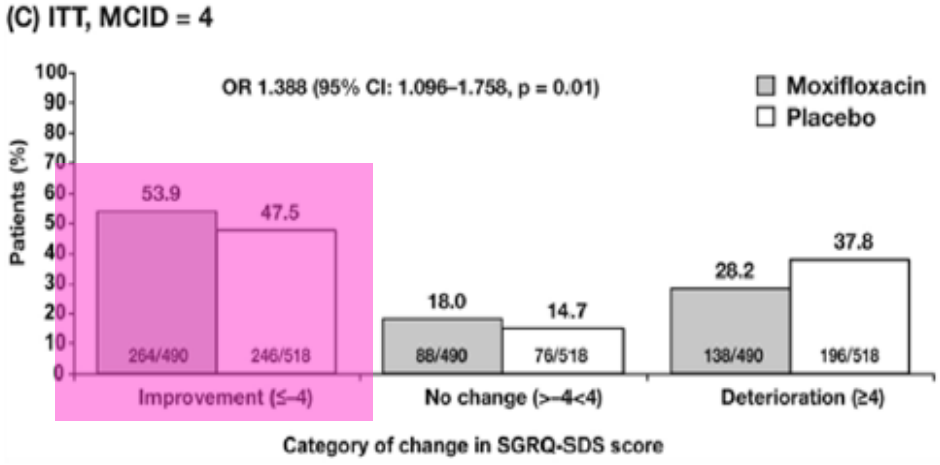
Moxifloxacin-AECOPD

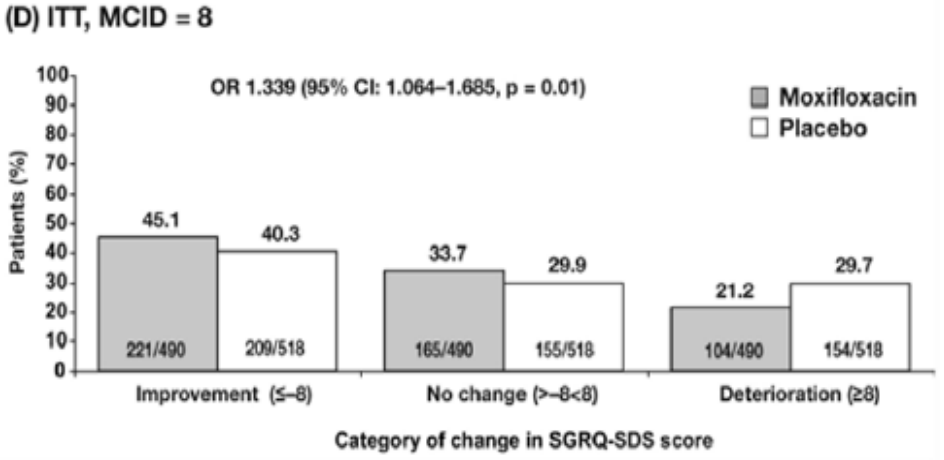


Moxifloxacin-SGRQ







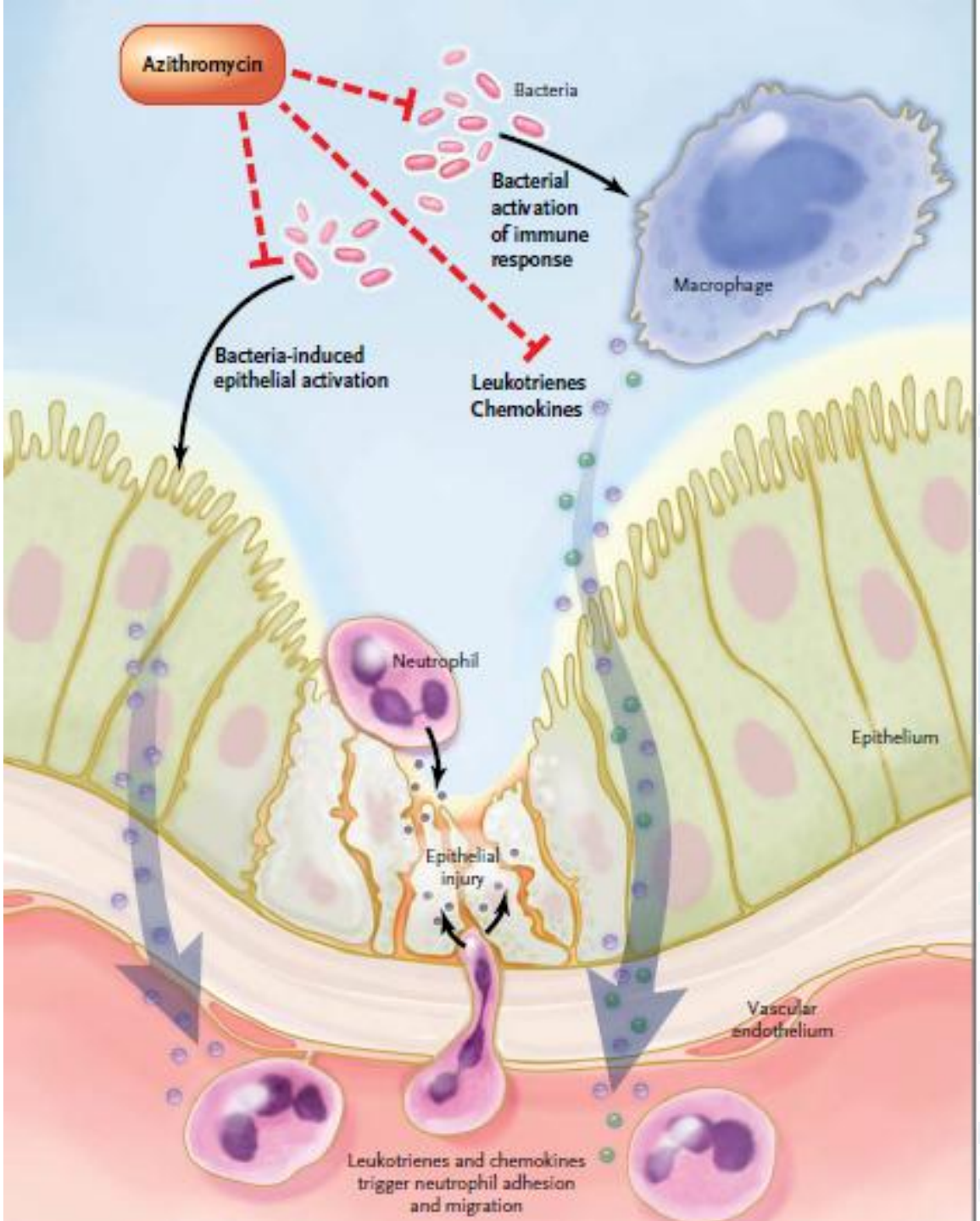


Macrolide

- Azithromycin

  compared with erythromycin or clarithromycin

  – Superior activity against Gram-negative bacteria
  – Better uptake in peripheral blood polymorphonuclear neutorphils
  – Better tissue uptake


Azithromycin
Bacteria
Bacterial activation of immune response
Macrophage
Bacteria-induced epithelial activation
Leukotrienes Chemokines
Neutrophil
Epithelium
Epithelial injury
Vascular endothelium
Leukotrienes and chemokines trigger neutrophil adhesion and migration

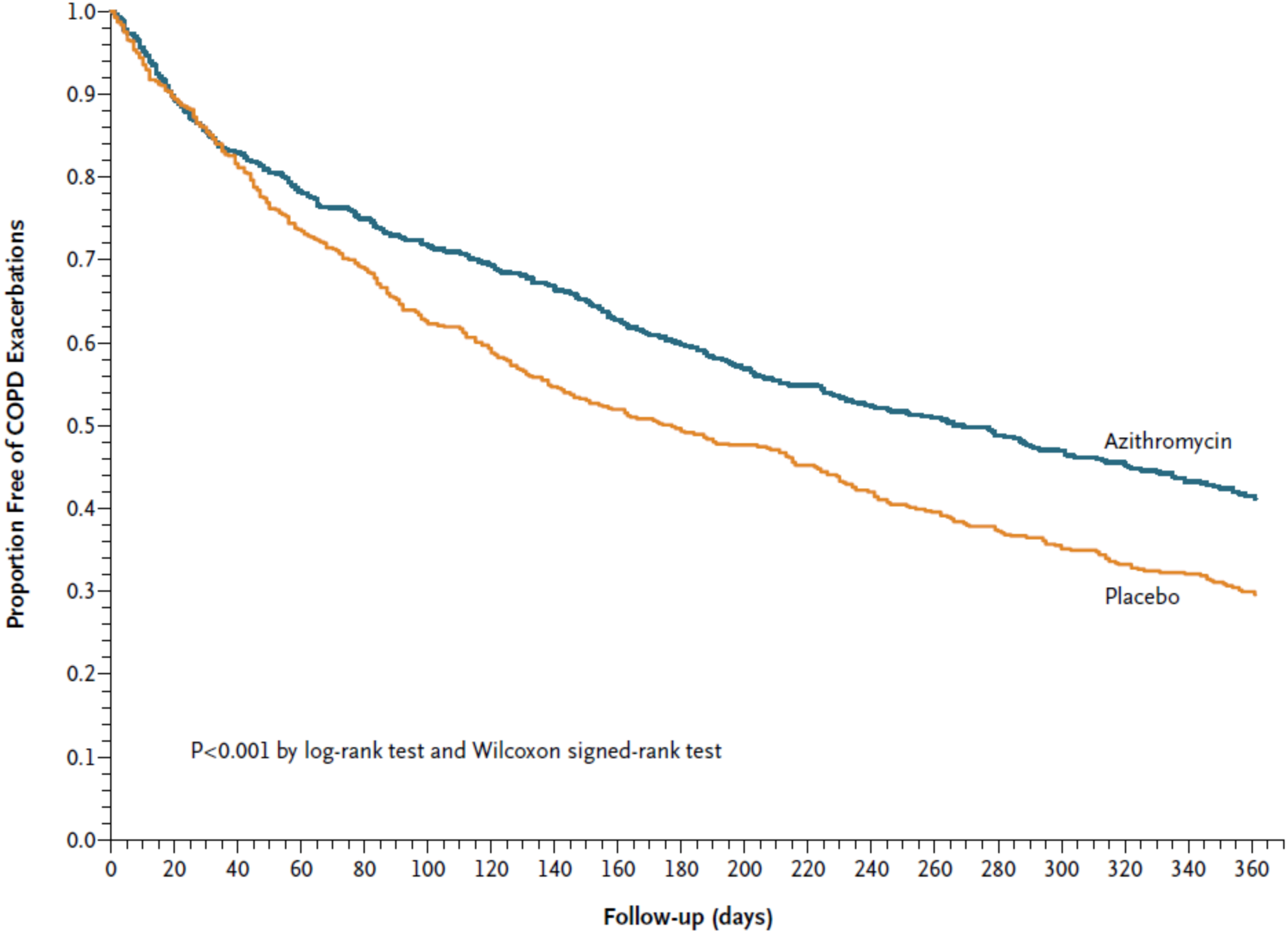
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

- Patients
  - 40 years of age with 10 pack years
  - Continuous oxygen or systemic steroid within previous year or AECOPD
  - No AECOPD at least 4 weeks before enrollment
  - Exclusion: tachycardia, prolonged QT(450 msec), hearing impairement
  - 250mg azithromycin daily for 1 years

Characteristic	Azithromycin (N = 558)	Placebo (N = 559)
Age — yr	65±9	66±8
Female sex — no. (%)	229 (41)	227 (41)
Race or ethnic group — no. (%)†		
White	456 (82)	449 (80)
Black	75 (13)	86 (15)
Other	19 (3)	22 (4)
Multiethnic	19 (3)	16 (3)
Postbronchodilator FEV_1		
Liters	1.10±0.50	1.12±0.52
% of predicted value	39±16	40±16
Ratio of FEV_1 to FVC — %	42±13	43±13


Proportion Free of COPD Exacerbations
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Azithromycin
Placebo
P<0.001 by log-rank test and Wilcoxon signed-rank test
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
Follow-up (days)

Azithromycin - daily

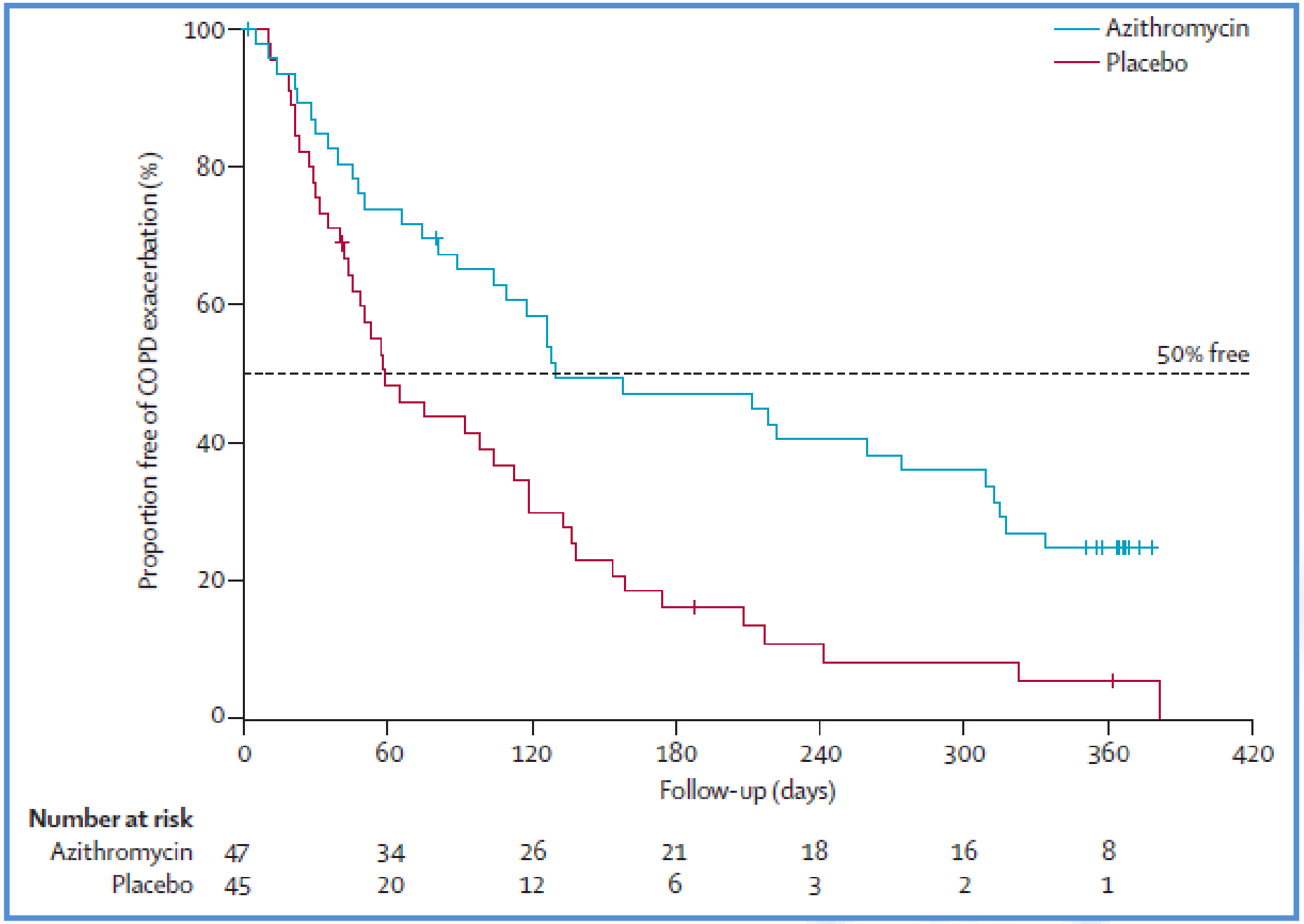
- The median time to the first exacerbation
  - Azithromycin: 266 days
  - Control: 174 days
- The frequency of exacerbation
  - Azithromycin: 1.48/year
  - Control: 1.83/year
- SGRQ
  - Azithromycin: 2.8±12.1
  - Control: 0.6±11.4

Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial

Sevim Uzun, Remco S Djamin, Jan A J W Kluytmans, Paul G H Mulder, Nils E van't Veer, Anton A M Ermens, Aline J Pelle, Henk C Hoogsteden, Joachim G J V Aerts, Menno M van der Eerden**

- Three or more exacerbations in the previous year
- Exlusion
  - other clinically significant respiratory disease (asthma, cystic fibrosis, bronchiectasis)
  - Maintenance antibiotics
  - More than 10mg prednisolone
- 500mg azithromycin three times a week for 12 months

	Azithromycin (n=47)	Placebo (n=45)
Men	22 (47%)	18 (40%)
Age (years)	64·7 (10·2)	64·9 (10·2)
Present smoker	20 (43%)	9 (20%)
Body-mass index (kg/m^2)	25·9 (4·6)	26·3 (5·7)
Acute exacerbations of COPD in the past year	4·0 (1·2)	4·0 (1·1)
Hospital admissions due to acute exacerbations of COPD	1·0 (1·1)	0·7 (0·8)
Symptoms		
Cough	28 (60%)	34 (76%)
Sputum production	29 (62%)	32 (71%)
Spirometry after bronchodilation		
FEV_1 (L)	1·1 (0·47)	1·1 (0·43)
FEV_1 (% of predicted)	44·2 (19·3)	45·0 (19·5)
FVC (L)	2·9 (0·8)	2·7 (0·92)
FVC (% of predicted)	92·5 (22·2)	88·9 (20·3)
FEV_1/FVC (%)	38·0 (11·7)	40·3 (12·4)


Azithromycin
Placebo
100
80
60
40
20
0
Proportion free of COPD exacerbation (%)
50% free
0
60
120
180
240
300
360
420
Follow-up (days)
Number at risk
Azithromycin 47 34 26 21 18 16 8
Placebo 45 20 12 6 3 2 1

Azithromcyin – three/week

- The median time to the first exacerbation
  - Azithromycin: 130 days
  - Control: 59 days
- The frequency of exacerbation
  - Azithromycin: 1.94/year
  - Control: 3.22/year
- SGRQ
  - No difference in total score
  - Symptoms score ↓ in azithromycin

[Intervention Review]

Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Samantha C Herath[1], Phillippa Poole[2]

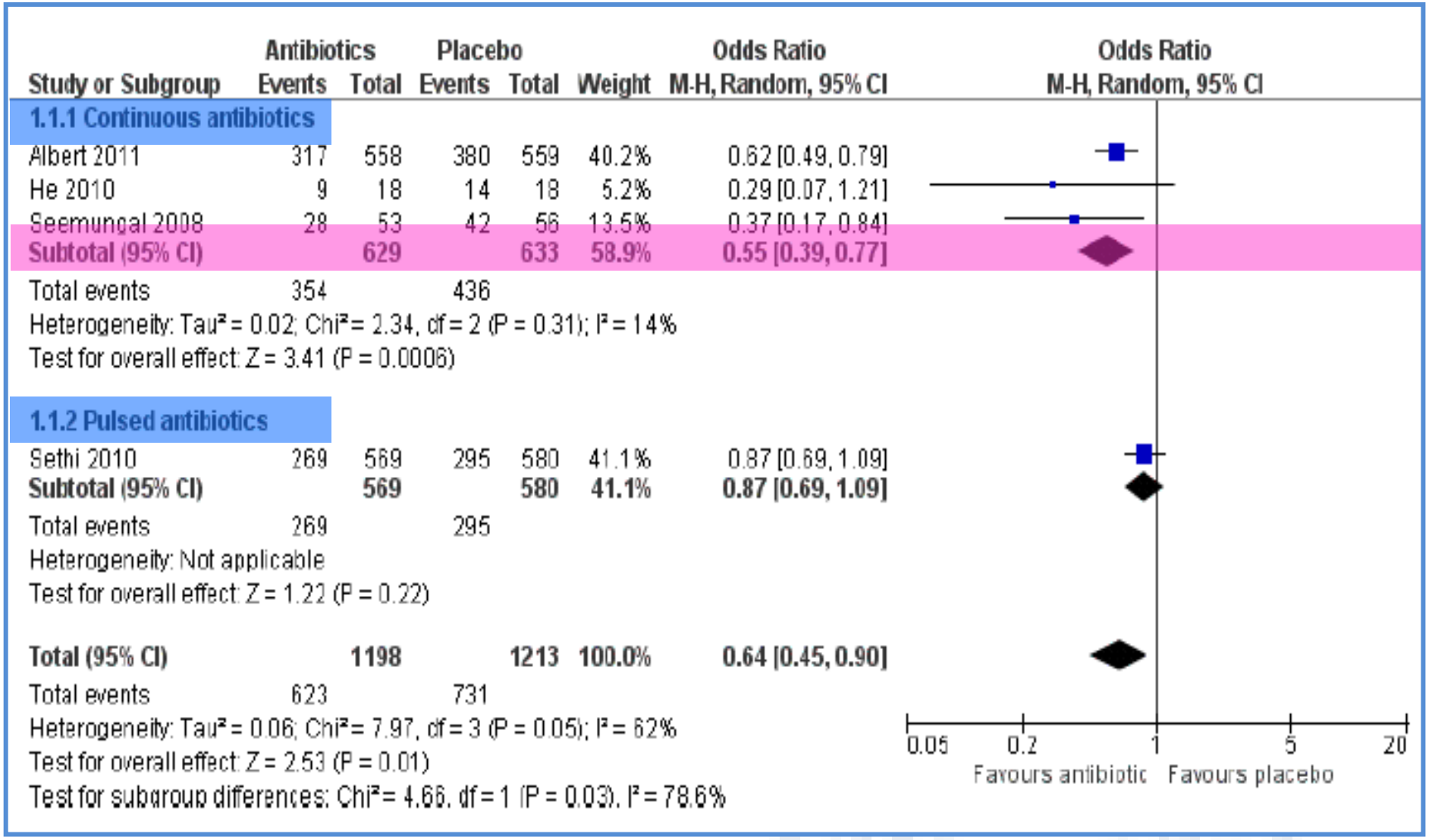
[1]Woolcock Institute of Medical Research, 431 Glebe Point Road, Sydney, Australia. [2]Department of Medicine, University of Auckland, Auckland, New Zealand

Contact address: Samantha C Herath, Woolcock Institute of Medical Research, 431 Glebe Point Road, Sydney, New South Wales, 2037, Australia. scherath@yahoo.com.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 11, 2013.
Review content assessed as up-to-date: 29 August 2013.

Citation: Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews* 2013, Issue 11. Art. No.: CD009764. DOI: 10.1002/14651858.CD009764.pub2.

Number of people with one or more exacerbation

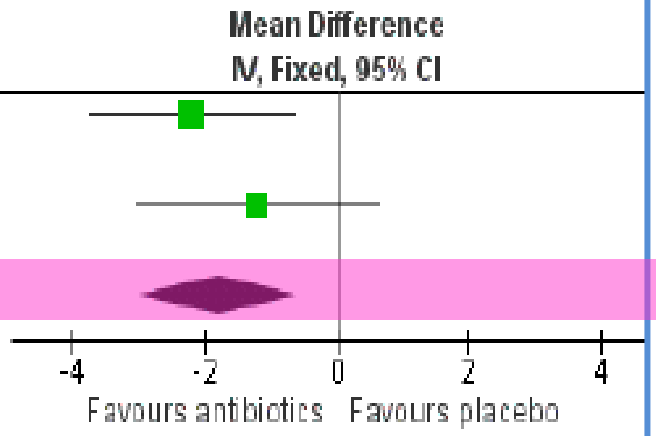


SGRQ score

Study or Subgroup	Antibiotics Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Albert 2011	-2.8	12.1	444	-0.6	11.4	453	58.0%	-2.20 [-3.74, -0.66]
He 2010	-2	0	18	0.4	0	18		Not estimable
Sethi 2010	-4	14.9	503	-2.8	14.7	526	42.0%	-1.20 [-3.01, 0.61]
Total (95% CI)			965			997	100.0%	-1.78 [-2.95, -0.61]

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%

Test for overall effect: Z = 2.98 (P = 0.003)

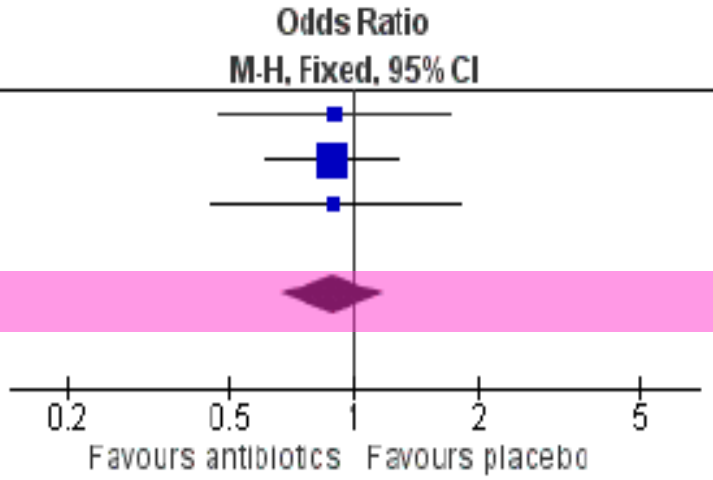


All cause mortality

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Albert 2011	18	558	20	559	20.2%	0.90 [0.47, 1.72]
Mygind 2010	74	287	81	288	62.7%	0.89 [0.61, 1.28]
Sethi 2010	15	569	17	580	17.1%	0.90 [0.44, 1.81]
Total (95% CI)		**1414**		**1427**	**100.0%**	**0.89 [0.67, 1.19]**
Total events	107		118			

Heterogeneity: $Chi^2 = 0.00$, $df = 2$ ($P = 1.00$); $I^2 = 0\%$

Test for overall effect: $Z = 0.77$ ($P = 0.44$)

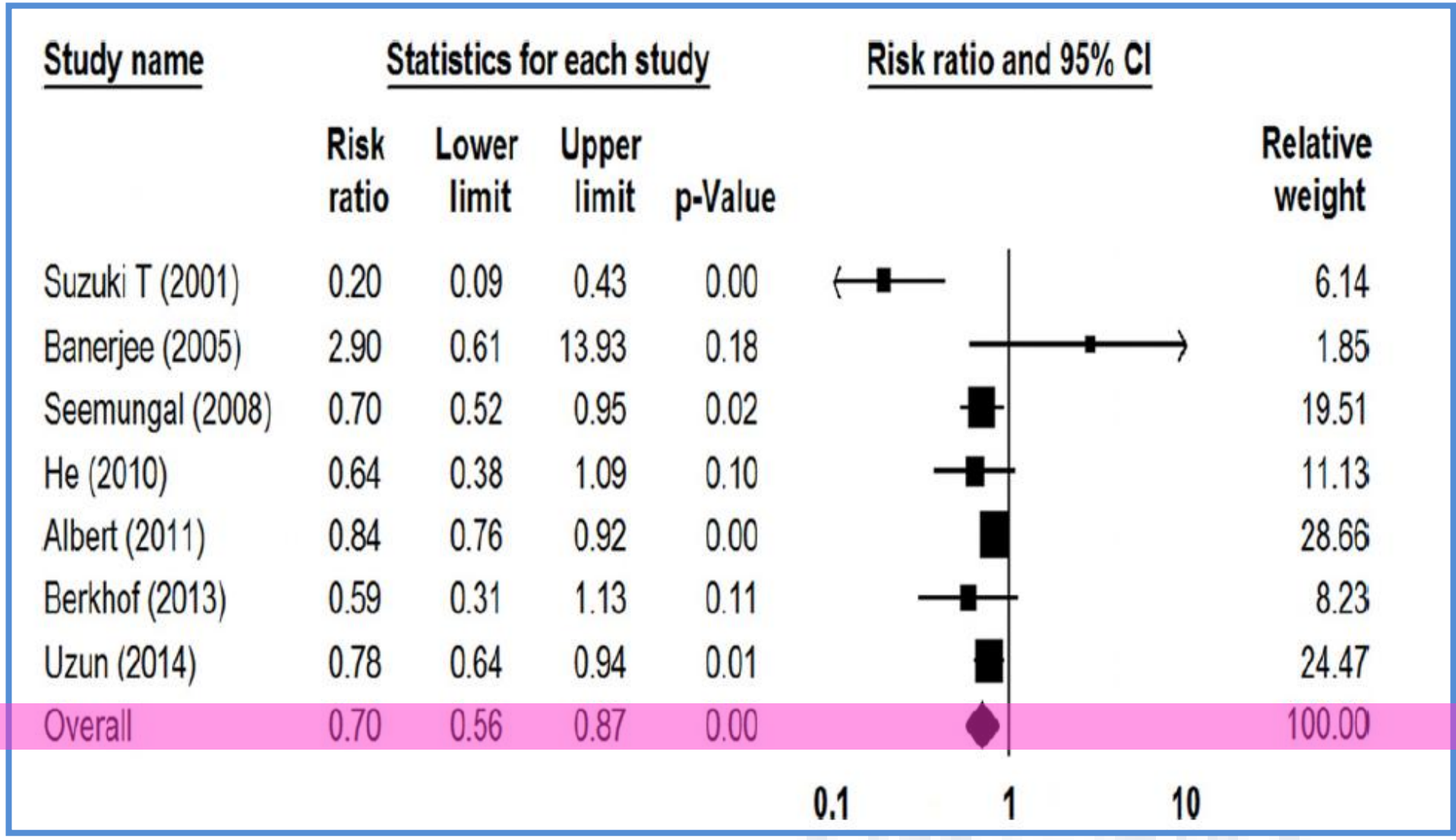


PLOS ONE

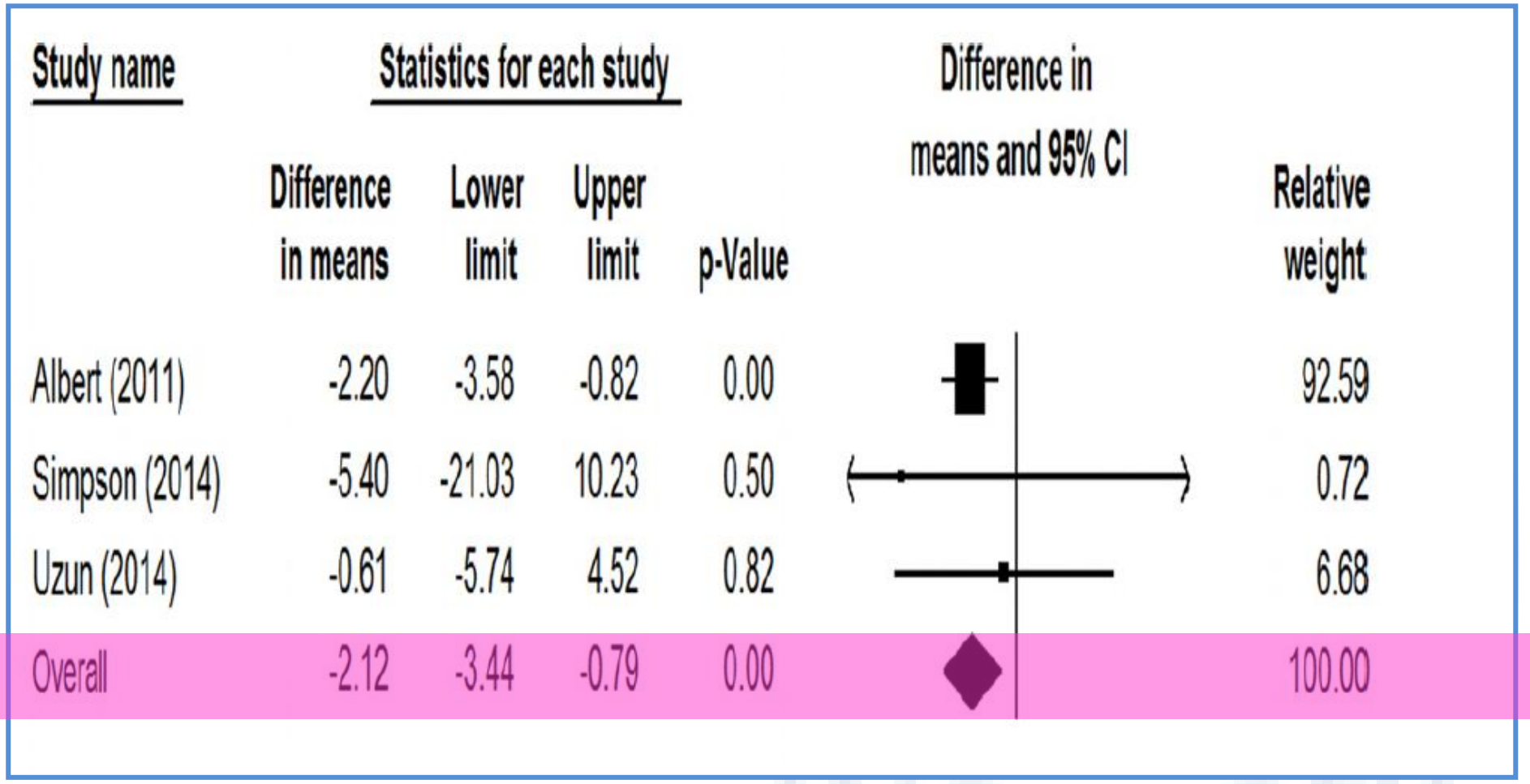
RESEARCH ARTICLE

Prophylactic Use of Macrolide Antibiotics for the Prevention of Chronic Obstructive Pulmonary Disease Exacerbation: A Meta-Analysis

Number of people with one or more exacerbation



SGRQ score

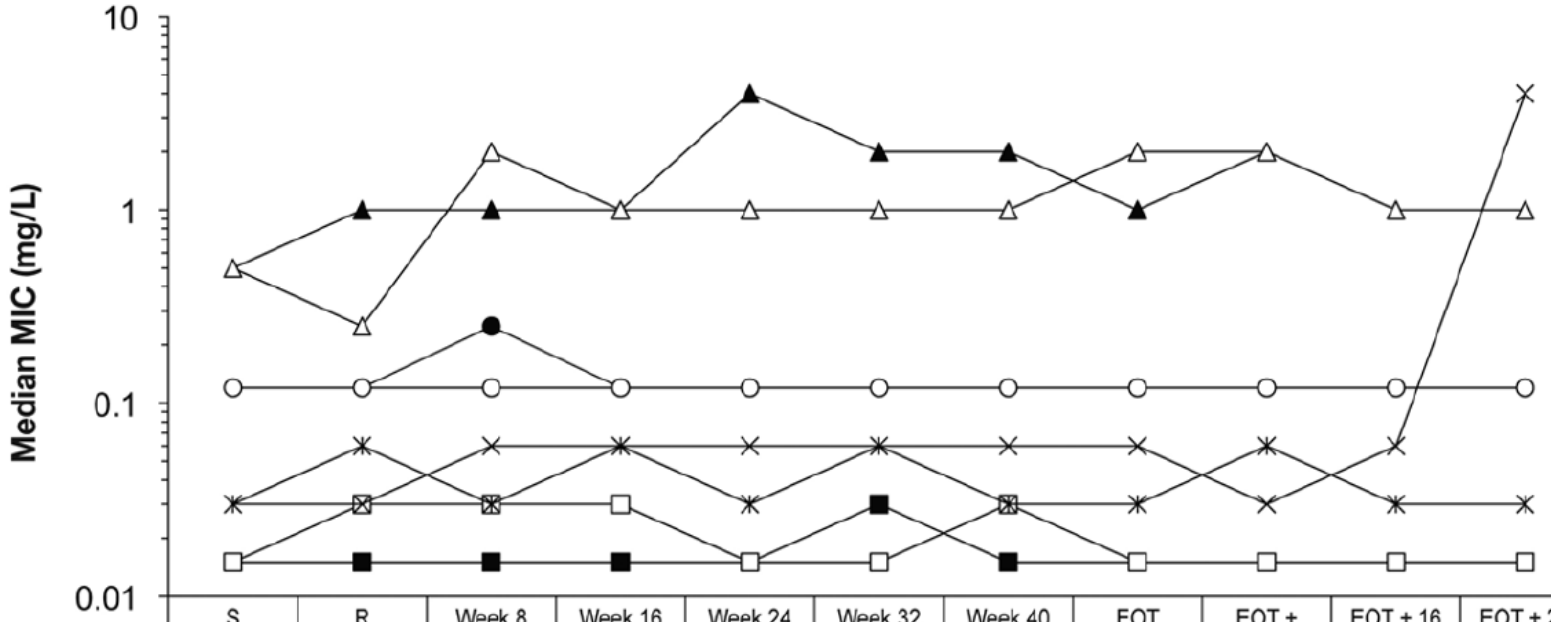

Study name
Statistics for each study
Difference in means and 95% CI
Difference in means
Lower limit
Upper limit
p-Value
Relative weight
Albert (2011) -2.20 -3.58 -0.82 0.00 92.59
Simpson (2014) -5.40 -21.03 10.23 0.50 0.72
Uzun (2014) -0.61 -5.74 4.52 0.82 6.68
Overall -2.12 -3.44 -0.79 0.00 100.00

Prophylactic antibiotics for AECOPD

- Survival ?
- Acute exacerbations of COPD ↓
- Quality of life ↑

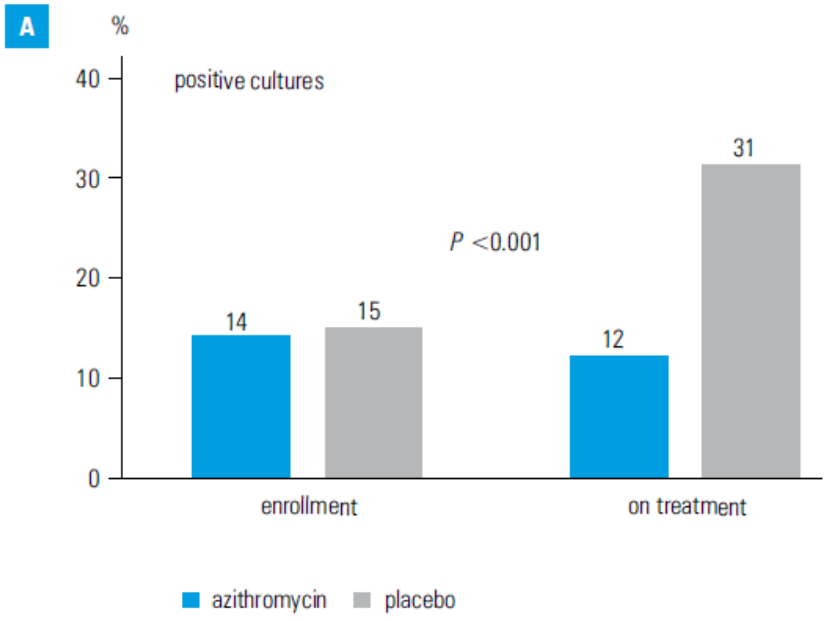
- Resistance for antibiotics
- Adverse events

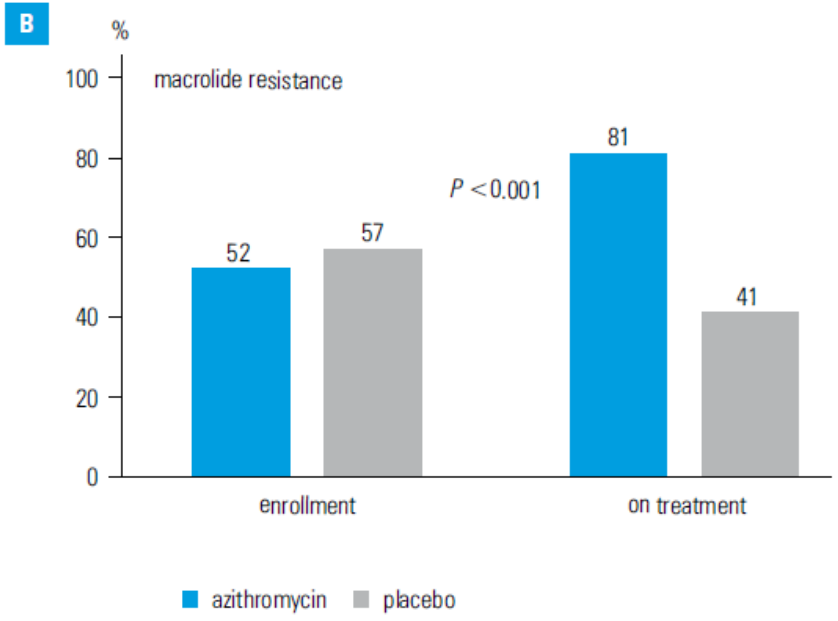
Moxifloxacin MIC



	S visit	R visit	Week 8	Week 16	Week 24	Week 32	Week 40	EOT	EOT + 8 weeks	EOT + 16 weeks	EOT + 24 weeks
H. influenzae, moxifloxacin	22	24	7	5	5	5	9	4	10	14	8
H. influenzae, placebo	25	37	31	25	18	21	23	28	25	19	19
S. pneumoniae, moxifloxacin	12	15	9	9	3	2	7	6	6	8	5
S. pneumoniae, placebo	8	17	12	6	9	10	11	12	9	8	5
S. aureus, moxifloxacin	10	8	4	8	7	3	6	5	3	2	2
S. aureus, placebo	10	11	8	9	5	5	1	2	5	3	2
P. aeruginosa, moxifloxacin	9	10	11	10	9	7	11	8	10	7	10
P. aeruginosa, placebo	10	8	12	13	9	10	8	12	11	8	12

Azithromycin daily – nasopharyngeal culture





	Azithromycin		Placebo	
	Patients Colonized N (%)	Macrolide Resistant N resistant/ N tested (%)	Patients Colonized (N, %)	Macrolide Resistant N resistant/ N tested (%)
On enrollment				
S. aureus	60 (10.7)	16/35 (46)	71 (12.7)	23/37 (62)
S. pneumoniae	6 (1.1)	1/2 (50)	6 (1.1)	3/7 (43)
Hemophilus spp	0 (0)	3/4 (75)	0 (0)	2/3 (67)
Moraxella spp	13 (2.3)	3/3 (100)	6 (1.0)	0/2 (0)
Total	79 (14.1)	23/44 (52)	83 (14.8)	28/49 (57)
During course of study				
S. aureus	59 (10.6)	34/41 (83)	127 (22.7)	30/87 (34)
S. pneumoniae	6 (1.1)	2/2 (100)	15 (1.8)	2/4 (50)
Hemophilus spp.	1 (0.2)	2/3 (67)	3 (0.5)	5/7 (71)
Moraxella spp	0 (0)	0/1 (0)	27 (5.8)	7/10 (70)
Total	66 (11.9)	38/47 (81)	172 (30.8)	44/108 (41)

Azithromycin daily – respiratory culture

- Decreased the prevalence of colonization with respiratory flora
  - 66 (azithromycin) *vs.* 172 (control)

- Actual number of patients who colonized with resistant organism
  - 38 (azithromycin) *vs.* 41 (control)

Azithromycin three/week – respiratory culture

- 42 samples at baseline
  - azithromycin: 22 *vs.* control: 20
- 108 samples during 1 years
  - azithromycin: 51 *vs.* control: 57

- *H. influenza, s. pneumoniae, p.aerusinosa*

- New respiratory pathogen
  - azithromycin: 4 *vs.* control: 12, p=0.044
- Acquisition of macrolide resistant bacteria
  - azithromycin: 6% *vs.* control: 24%, p=0.036

Macrolide resistance

- Mycoplasma infection

  : Quinolone

- Non-tuberculous mycobacterial infection

  : Screening (Sputum culture, Radiologic evaluation)

Macrolide resistance

- COPD population >> DPB or CF population
- Public health level is the development of microbial resistance from long-term azithromycin exposure.
- Indication criteria is narrow

Adverse events - moxifloxacin

	Moxifloxacin (N = 569) n (%)	Placebo (N = 580) n (%)	p-value*
Any adverse event	467 (82.1)	493 (85.0)	0.181
Any treatment-emergent[a] adverse event	258 (45.3)	265 (45.7)	0.906
Any treatment-emergent[a] drug-related adverse events[b]	53 (9.3)	22 (3.8)	< 0.001
Cardiac disorders	3 (0.5)	1 (0.2)	
Gastrointestinal disorders	27 (4.7)	4 (0.7)	
Diarrhea	17 (3.0)	9 (1.6)	
Nausea	6 (1.1)	0 (-)	
Vomiting	5 (0.9)	1 (0.2)	
General disorders and administration site conditions	4 (0.7)	2 (0.3)	
Asthenia	3 (0.5)	0 (-)	
Immune system disorders	4 (0.7)	0 (-)	
Hypersensitivity	3 (0.5)	0 (-)	
Infections and infestations	5 (0.9)	3 (0.5)	
Musculoskeletal and connective tissue disorders	3 (0.5)	1 (0.2)	
Nervous system disorders	6 (1.1)	4 (0.7)	
Dizziness	3 (0.5)	1 (0.2)	
Respiratory, thoracic and mediastinal disorders	8 (1.4)	0 (-)	
Dyspnea	4 (0.7)	0 (-)	
Skin and subcutaneous tissue disorders	5 (0.9)	5 (0.9)	
Deaths	15 (2.6)	17 (2.9)	
Any treatment-emergent[a] serious adverse event	94 (16.5)	97 (16.7)	0.926
Any treatment-emergent[a] drug-related serious adverse event	9 (1.6)	3 (0.3)	0.076
Any adverse event leading to premature discontinuation	26 (4.6)	16 (2.8)	0.102
Any deaths	19 (3.3)	26 (4.5)	0.318

Adverse events - Azithromycin three/week

	Azithromycin (n=47)	Placebo (n=45)
Any adverse events	68	
Serious adverse events	3 (6%)	
Most frequent adverse events*		
Gastrointestinal		
Diarrhoea	9 (19%)	1 (2%)
Nausea or vomiting	3 (6%)	2 (4%)
Other	4 (9%)	7 (16%)
Laboratory investigations		
Creatinine increase	7 (15%)	3 (7%)
Elevated blood urea nitrogen	4 (9%)	10 (22%)
Hyperchloraemia	6 (13%)	5 (11%)
Alkaline phosphatase increase	4 (9%)	1 (2%)
ALT increase	5 (11%)	4 (9%)
AST increase	3 (6%)	3 (7%)
Gamma-glutamyltransferase increase	6 (13%)	1 (2%)
LDH increase	3 (6%)	4 (9%)
Other	9 (19%)	17 (38%)

2 lung cancer
1 acute coronary syndrome

Adverse events - Azithromycin daily

- Hearing decrements
  - azithromycin: 25% *vs.* control: 20%, p=0.04

- 32% reversal of hearing decrements on subsequent test in azithromycin participants despite continuing medication

- Old age or insensitivity of audiogram test

10년 전 COPD 진단

10년 전 금연 – 30 PY

LAMA+ICS/LABA

PDE4-inhibitor

작년에 4차례 AECOPD

QT interval normal

NTM x

Survival?

Frequency of AECOPD ↓

Quality of life ↑

Macrolide !