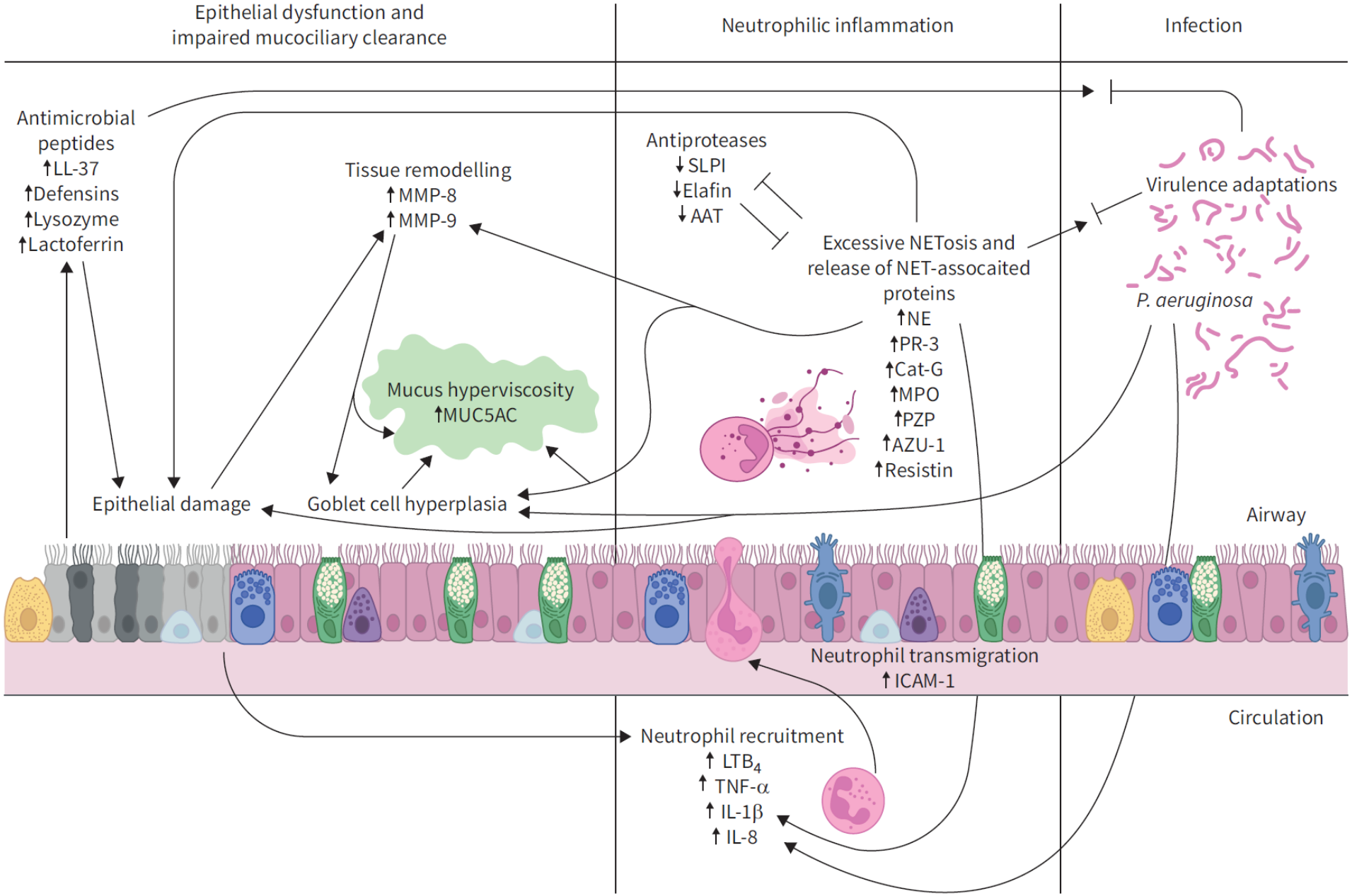
Inflammation in Bronchiectasis: Clinical Implications and Novel Therapies

한림의대 호흡기내과
최하영

Agenda

- Role of inflammation in bronchiectasis
- Long-term macrolides – efficacy and safety
- Novel anti-inflammatory therapies



Johnson E et al. *Eur Respir Rev* 2024;33:230234

Renewed understanding of bronchiectasis

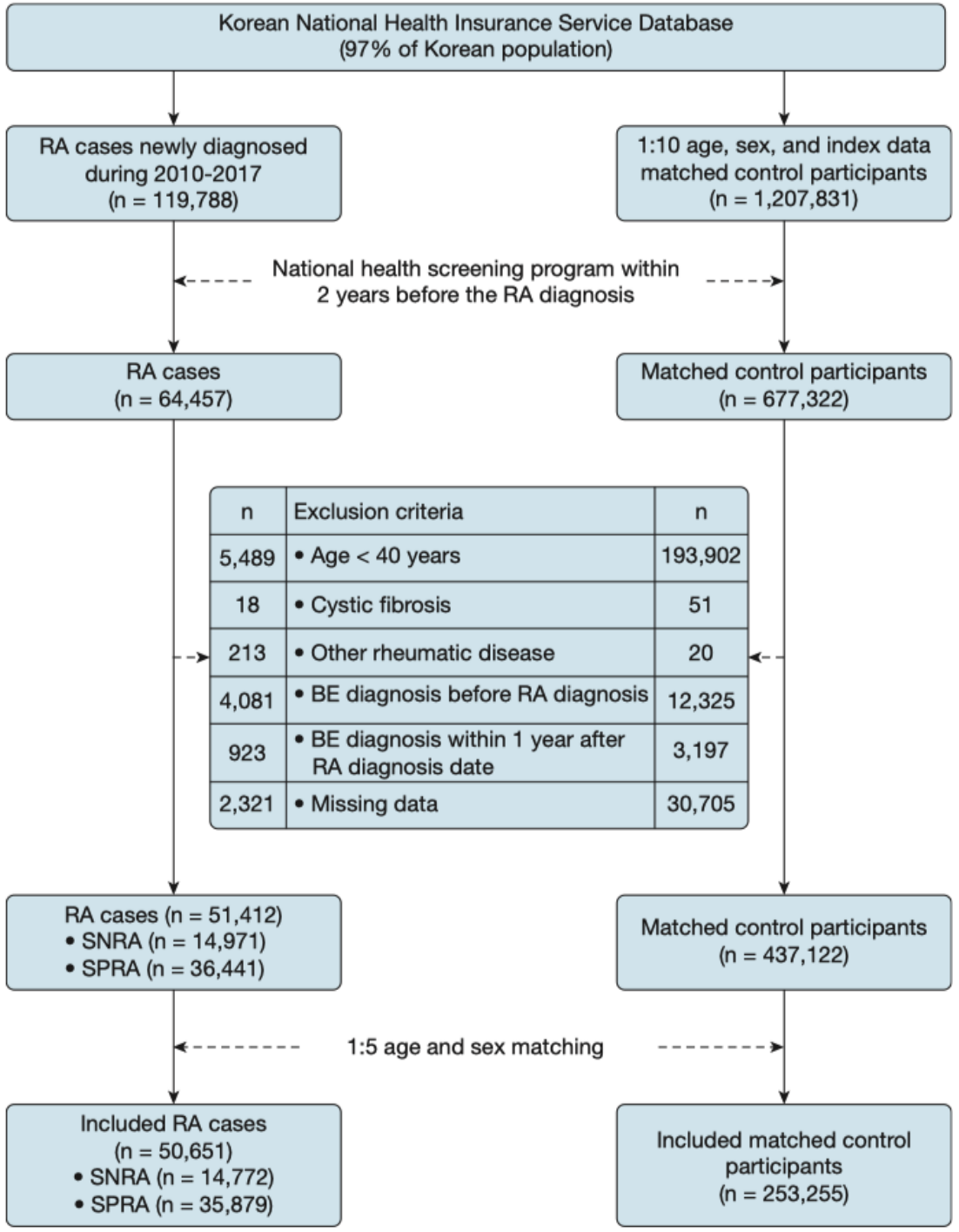
Mucus clearance failure

Infection

Inflammation

Choi H et al. *Eur Respir J* 2024;63:2400518

Impact of Rheumatoid Arthritis and Seropositivity on the Risk of Non-Cystic Fibrosis Bronchiectasis



Choi H and Lee H et al. *Chest* 2024;165:1330

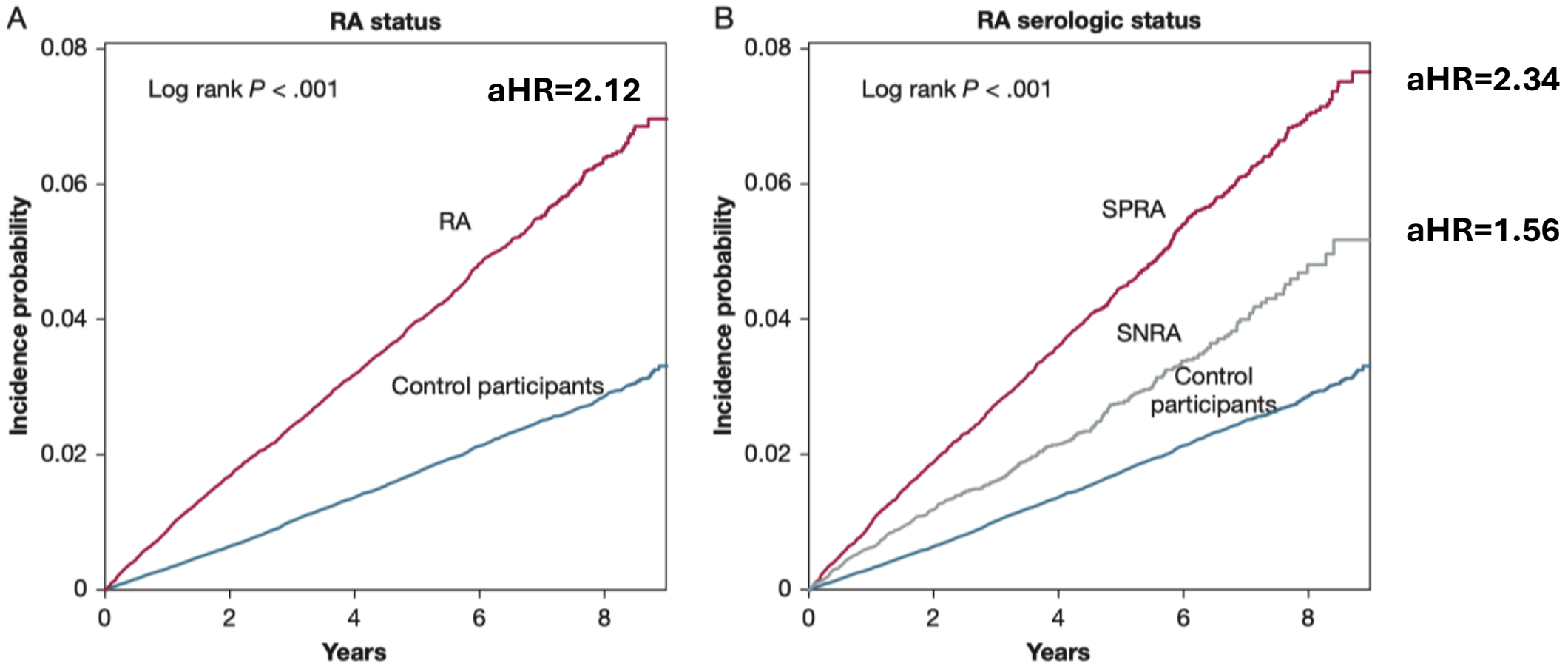


Figure 2 – *A, B, Cumulative incidence of bronchiectasis according to (A) RA status and (B) serologic status of RA. Year 0 indicates 1 year after RA diagnosis in participants with RA and 1 year after the time of being matched in matched control patients. RA = rheumatoid arthritis; SNRA = seronegative rheumatoid arthritis; SPRA = seropositive rheumatoid arthritis.*

Choi H and Lee H et al. *Chest* 2024;165:1330

Original Research Article | Open access

Mucus plugging, disease severity, and sputum myeloperoxidase concentration in bronchiectasis

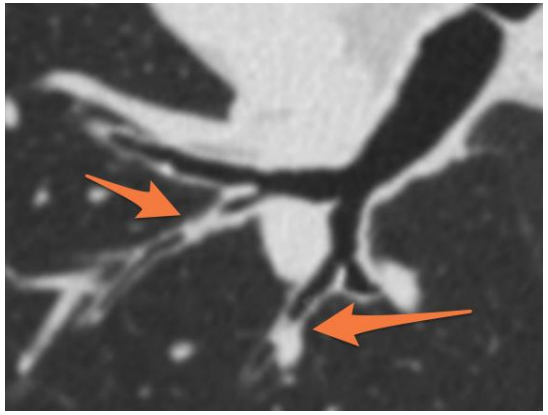
Sun-Hyung Kim | Ki Man Lee | Jin Young Yoo Show More

ERJ Open Research 2024 00279-2024; DOI: https://doi.org/10.1183/23120541.00279-2024

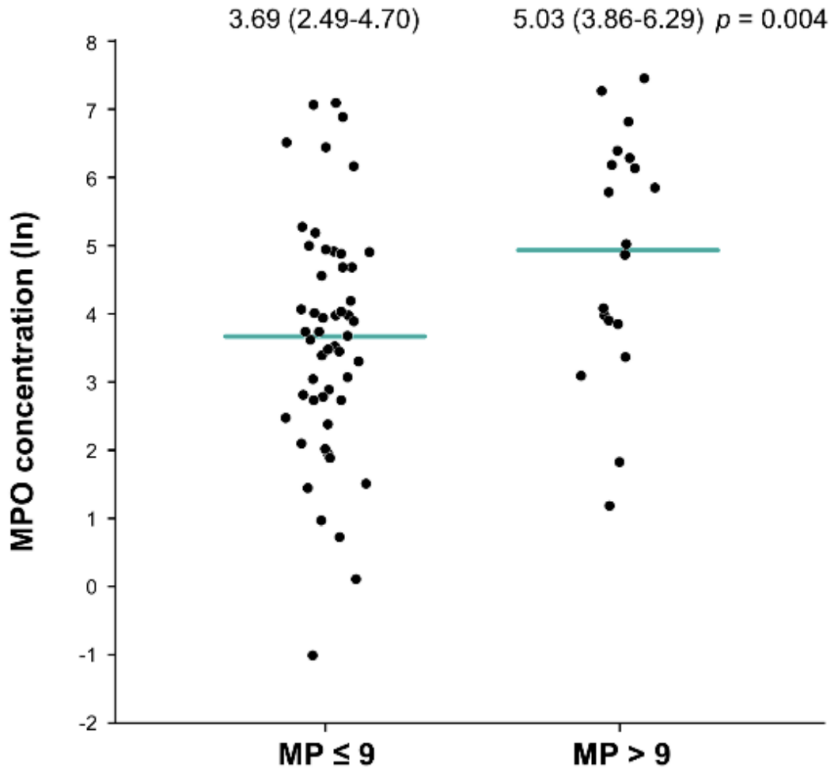
This article appears in:

ERJ Open Research

Early View

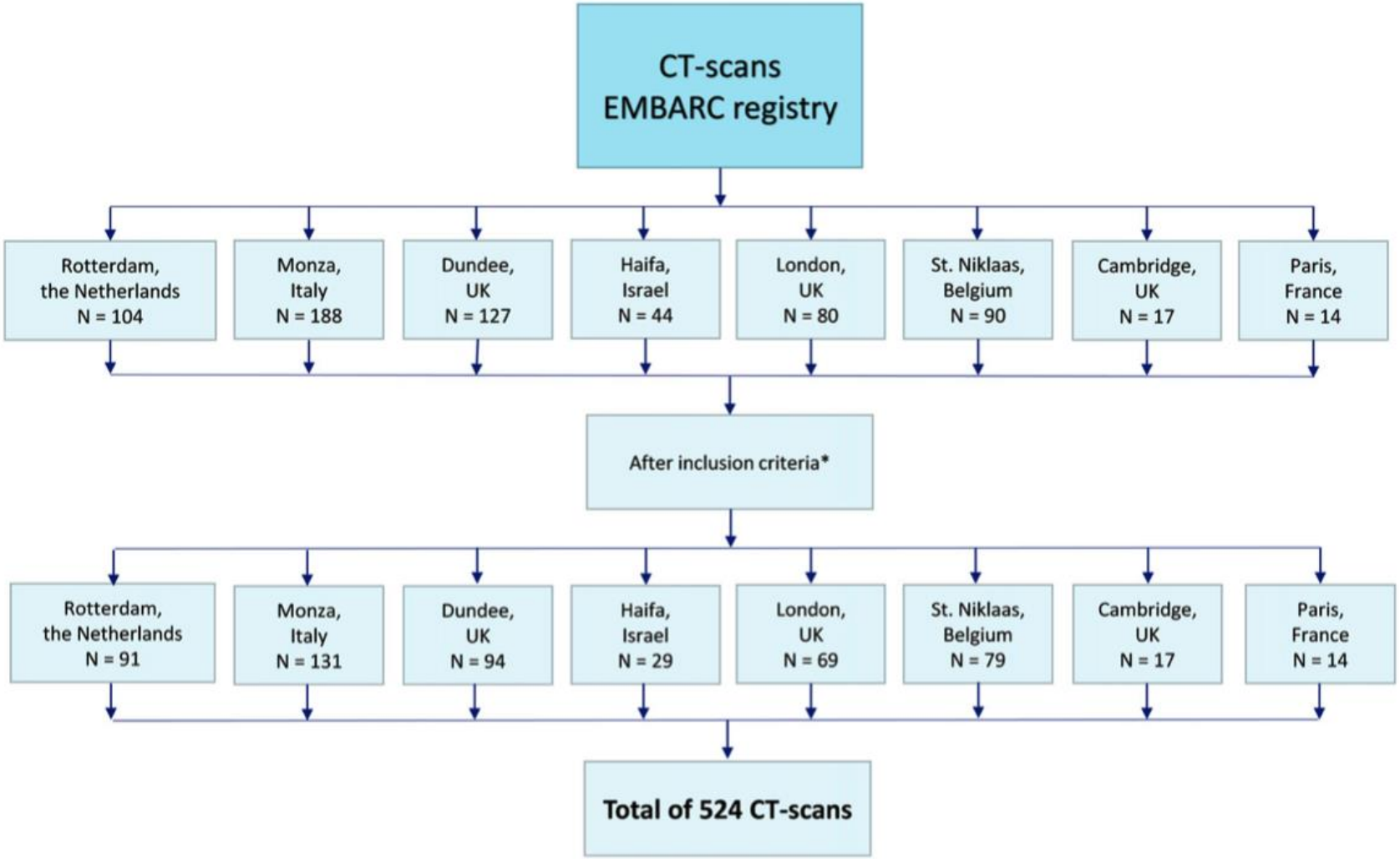


Mucus plugging

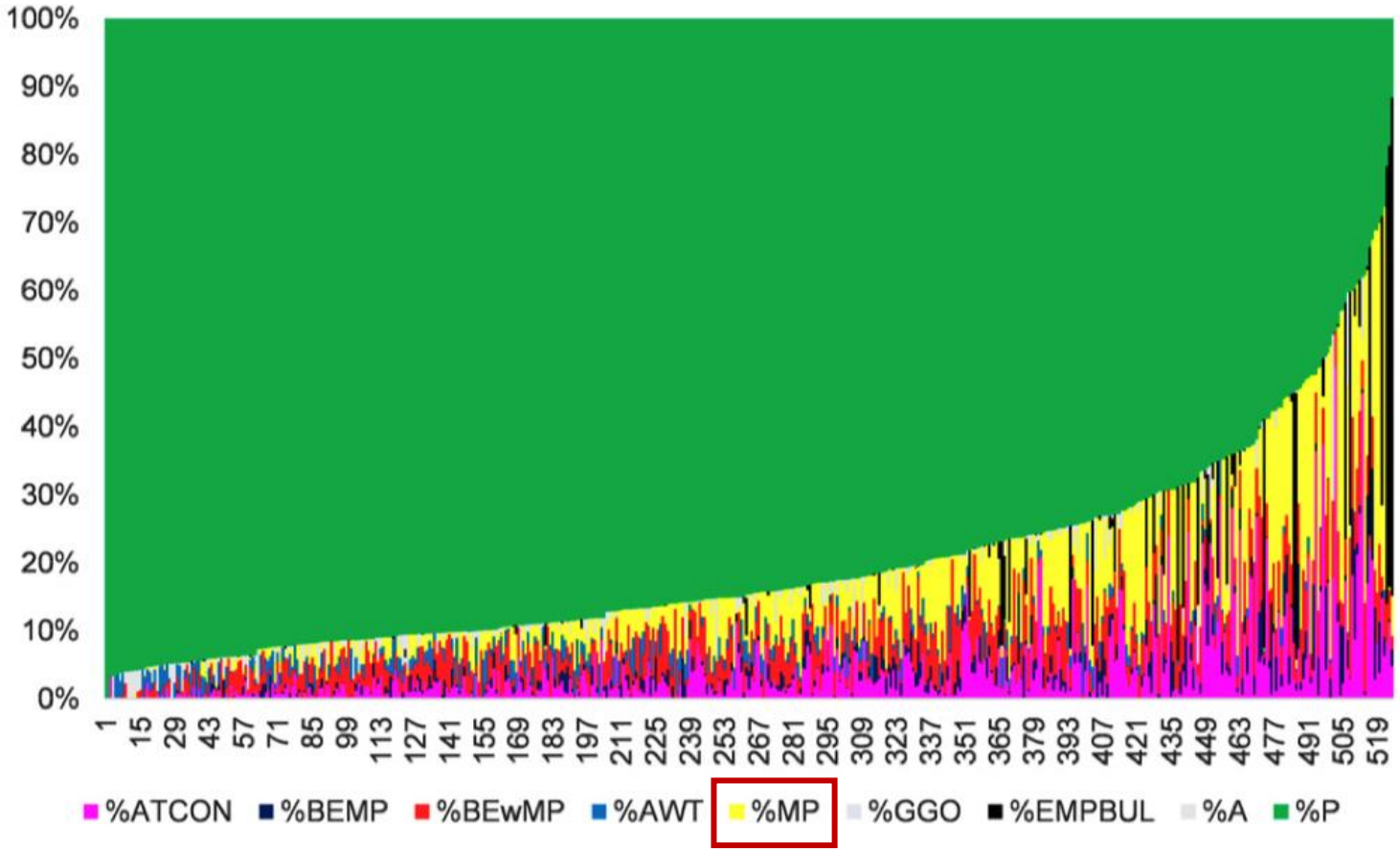


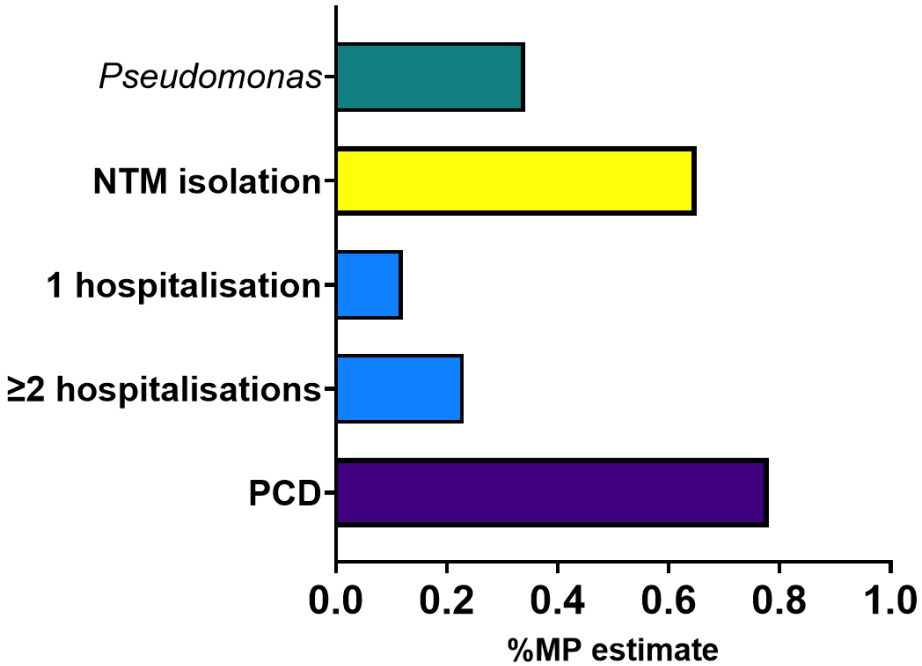
Kim SH and Yang B et al. *ERJ Open Res* 2024 (in press)

Visualising inflammation in bronchiectasis



Pieters ALP et al. *Am J Respir Crit Care Med* 2024;210:87





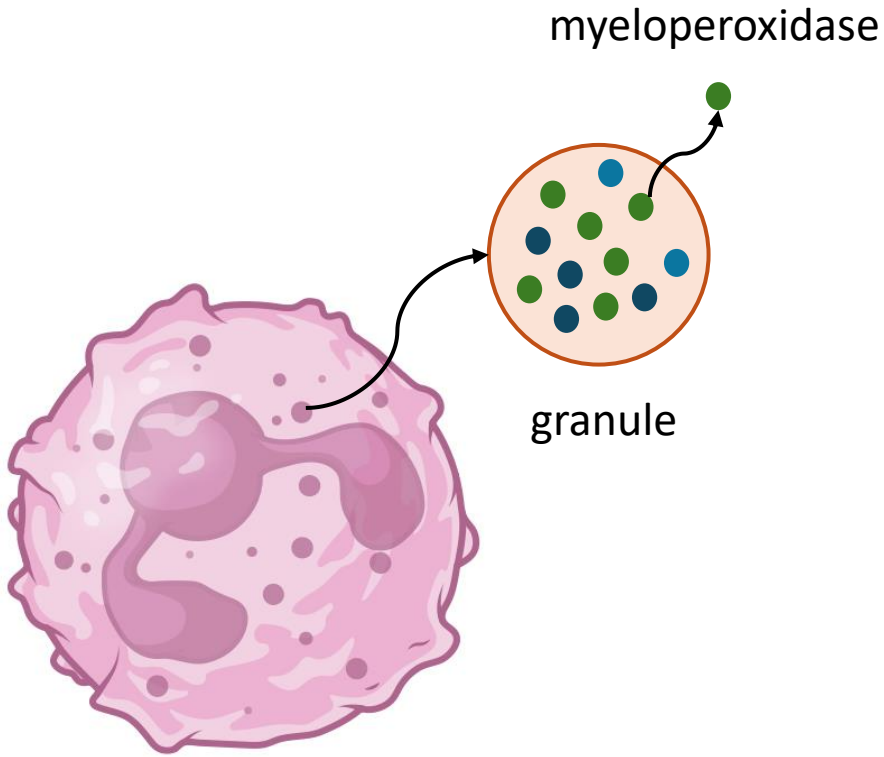
Pieters ALP et al. *Am J Respir Crit Care Med* 2024;210:87

Thorax 2001;**56**:366–372

Assessment of airway neutrophils by sputum colour: correlation with airways inflammation

R A Stockley, D Bayley, S L Hill, A T Hill, S Crooks, E J Campbell

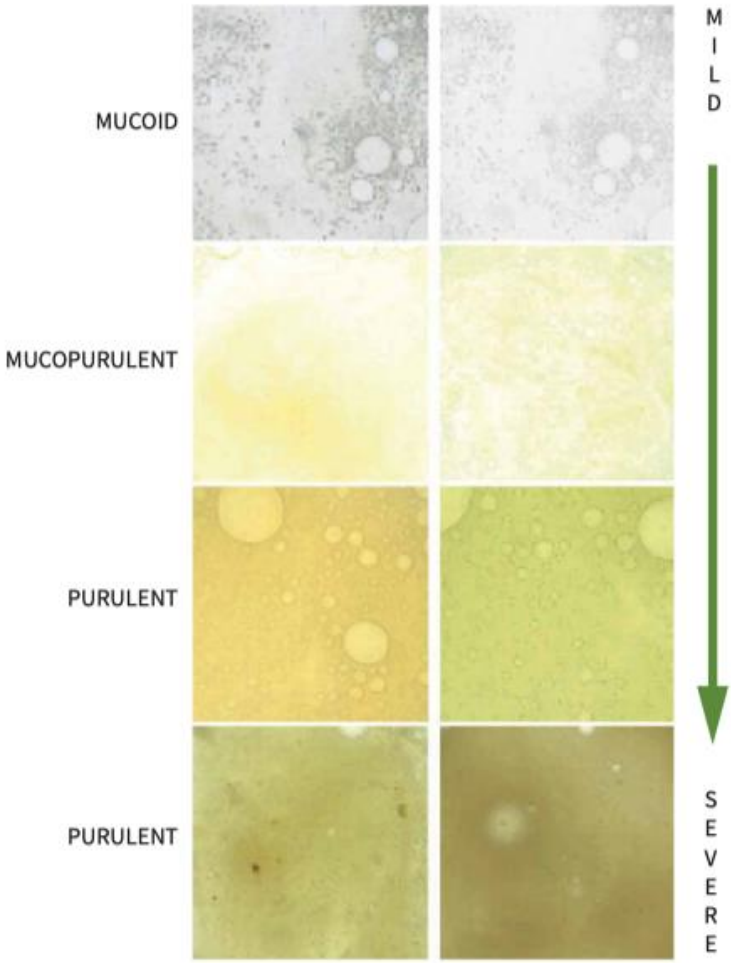
purulent sputum



neutrophil

Stockley et al. *Thorax* 2001;56:366

Sputum colour representing airway inflammation



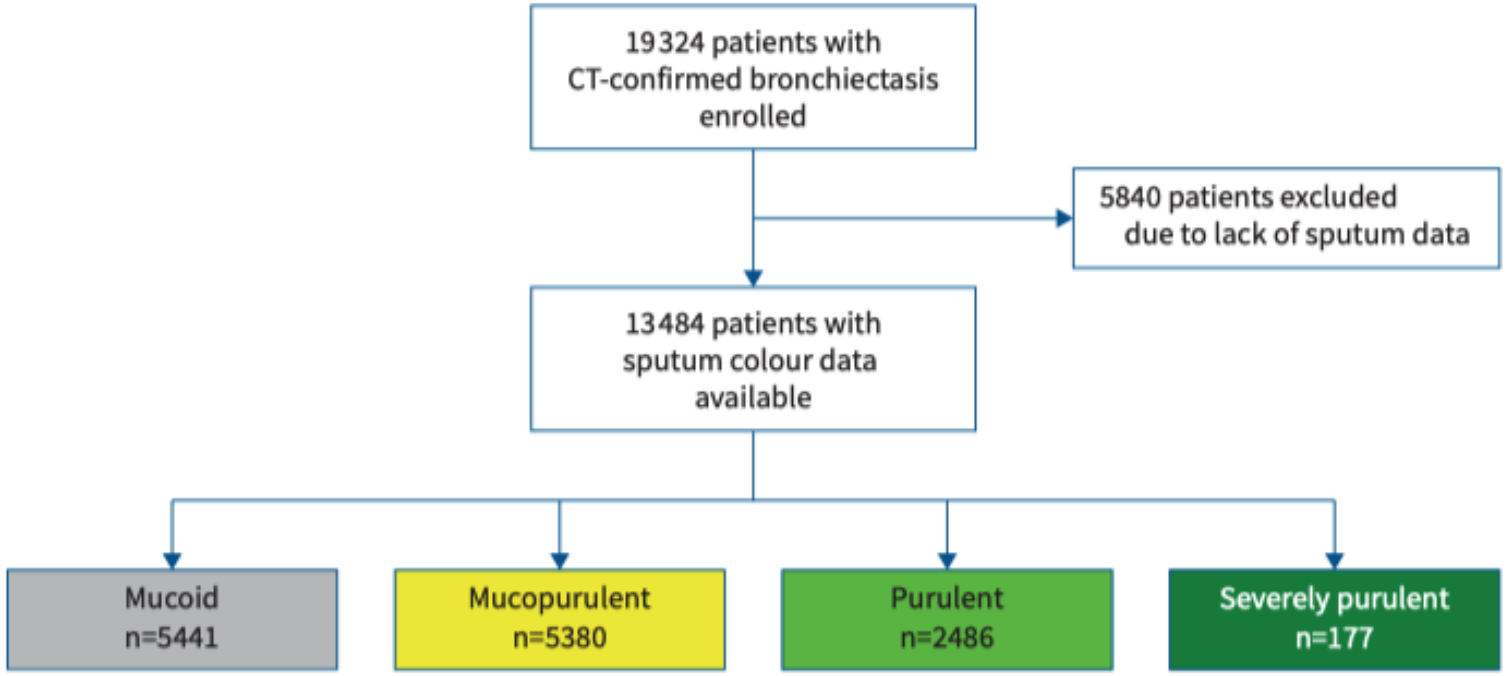
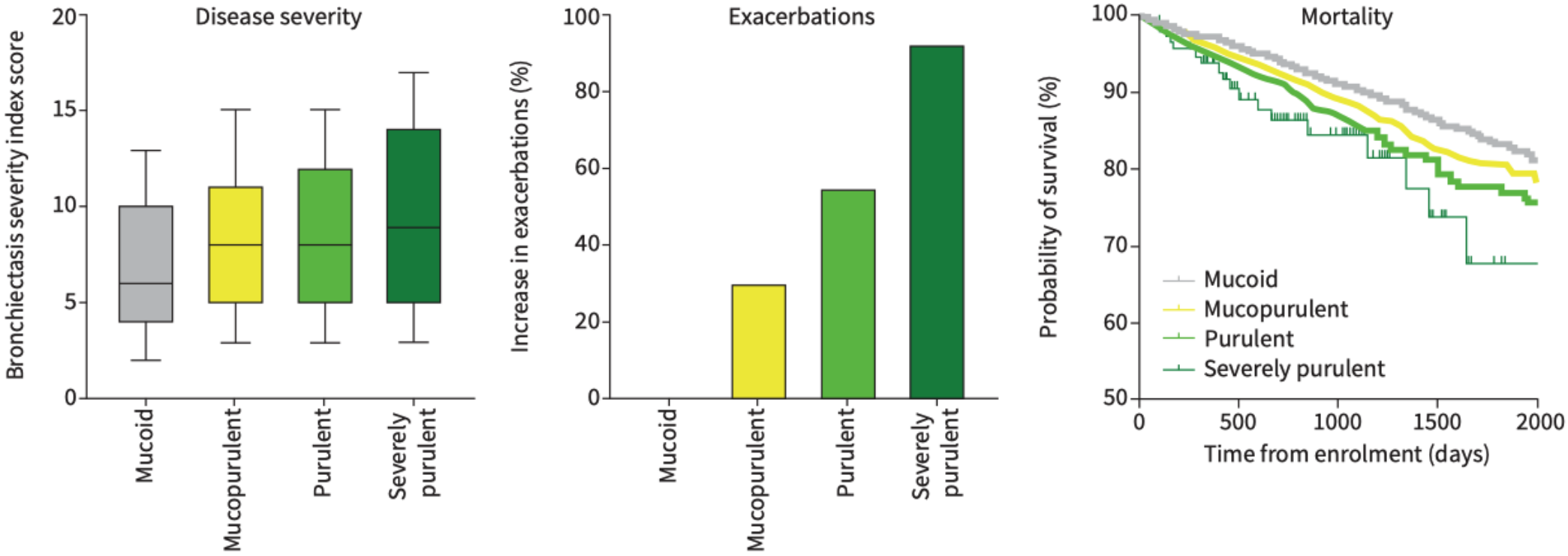


FIGURE 2 Flow of patients through the study. CT: computed tomography.

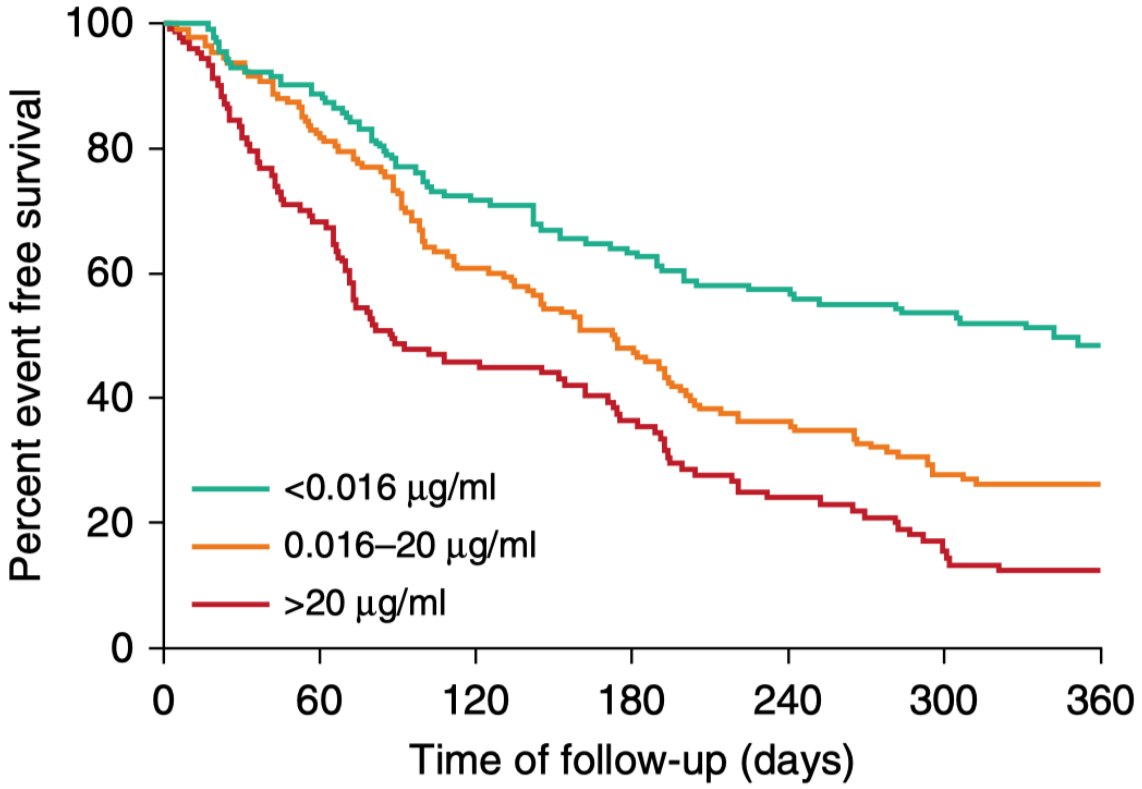
Aliberti S et al. *Eur Respir J* 2024;63:2301554



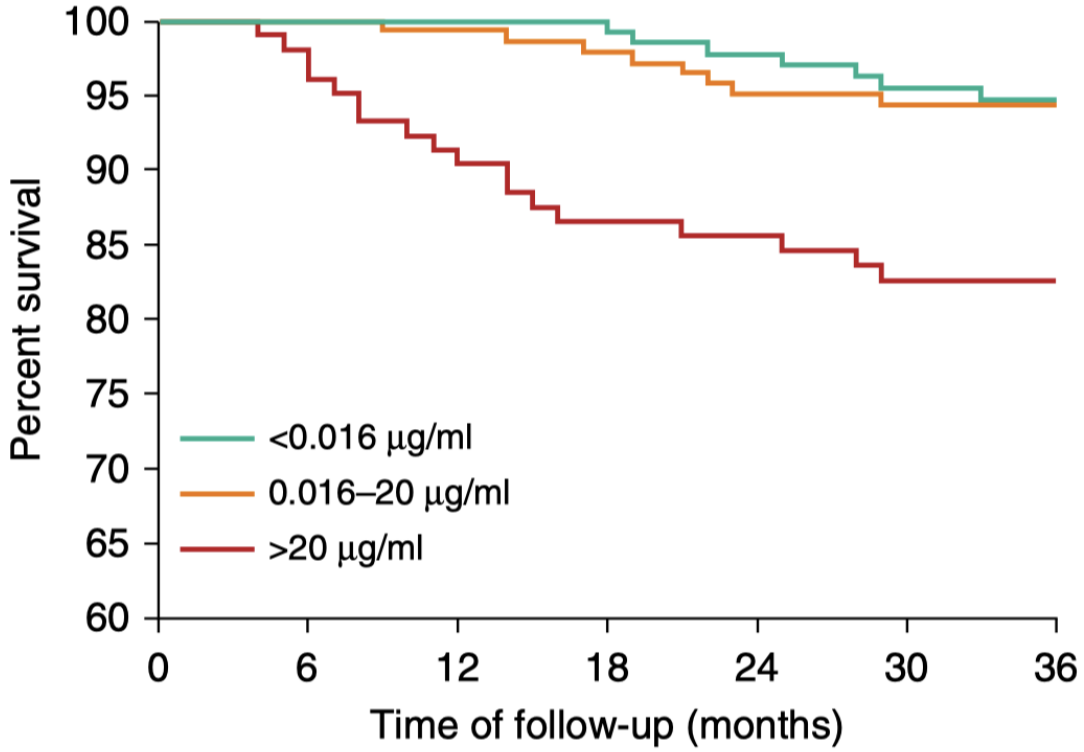
Aliberti S et al. *Eur Respir J* 2024;63:2301554

Sputum neutrophil elastase activity in bronchiectasis

Time to the next exacerbation



Mortality



(FEV1 decline: coefficient, –0.139; *P*=0.001)

Chalmers JD et al. *Am J Respir Crit Care Med* 2017

ORIGINAL ARTICLE

Endotypes of Exacerbation in Bronchiectasis
An Observational Cohort Study

Yonghua Gao[1], Hollian Richardson[2], Alison J. Dicker[2], Alun Barton[2], Elena Kuzmanova[2], Michal Shteinberg[3], Lidia Perea[4], Pieter C. Goeminne[5], Erin Cant[2], Chandani Hennayake[2], Jennifer Pollock[2], Hani Abo Leyah[6], Hayoung Choi[7], Eva Polverino[8], Francesco Blasi[9], Tobias Welte[10†], Stefano Aliberti[11], Merete Long[2], Amelia Shoemark[2], Oriol Sibila[4], Jeffrey T. J. Huang[2], and James D. Chalmers[2]

- 120 patients with bronchiectasis
- Characterization of exacerbation
  - Microbiome
  - Viral PCR
  - Sputum proteomics

Virus	Proportion (%)
≥1 Virus detected	**46%**
2 Viruses detected	13%
Rhinovirus	**31%**
Parainfluenza virus	8%
RSV	7%
Coronavirus	7%
Influenza A	4%

Gao et al. *Am J Respir Crit Care Med* 2024;210:77

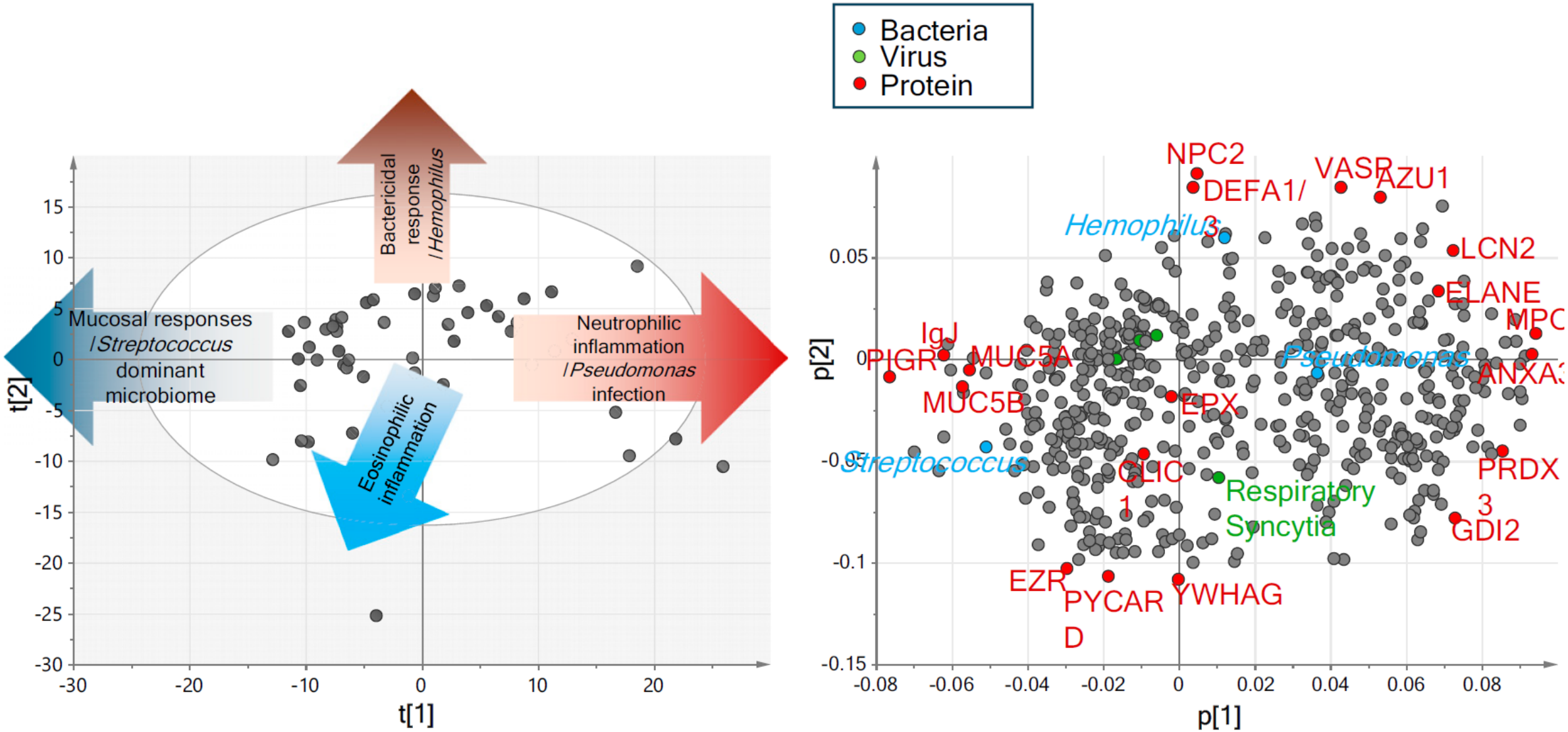
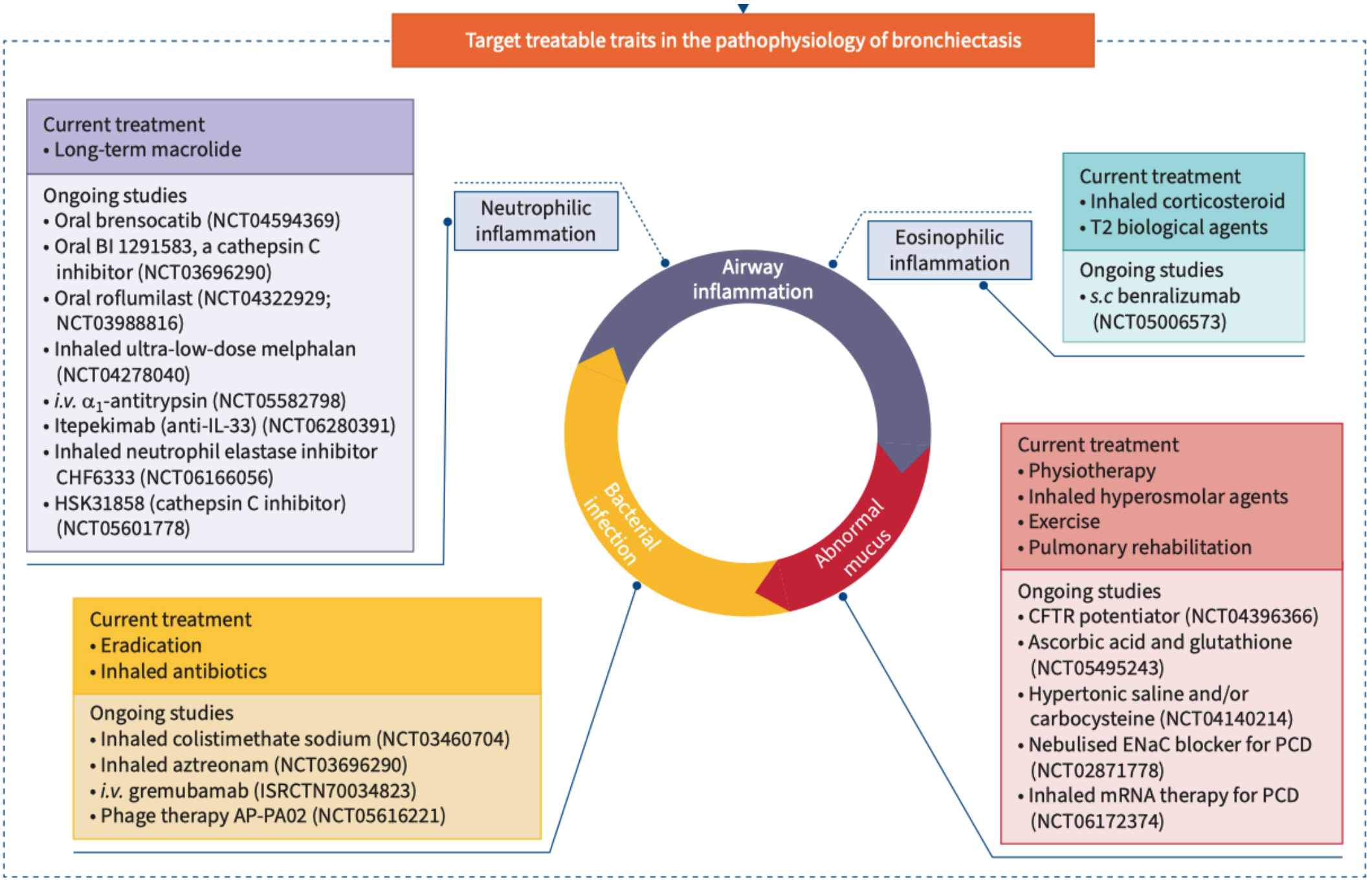


Figure 5. (*A*) Clusters of exacerbation based on 52 exacerbation samples. Principal component analysis. (*B*) Loadings plot illustrating the protein and microbiome parameters associated with distinct microbiome clusters.

Gao et al. *Am J Respir Crit Care Med* 2024;210:77



Choi H et al. *Eur Respir J* 2024;63:2400518

Agenda

- Role of inflammation in bronchiectasis
- Long-term macrolides – efficacy and safety
- Novel anti-inflammatory therapies

Long-term macrolide RTCs in bronchiectasis

	EMBRACE New Zealand	**BLESS Australia**	**BAT Netherlands**
Publication	Lancet 2012	JAMA 2013	JAMA 2013
Subjects	AZIT 500mg TIW (n=71) vs. Placebo (n=70)	EM 400mg BID (n=59) vs. Placebo (n=58)	AZIT 250mg QD (n=43) vs. Placebo (n=40)
Treatment duration	6 months	12 months	12 months
Mean exacerbation rate	**1.5** vs. **2.5** (*P*<0.001)	**1.3** vs. **2.0** (*P*<0.05)	**0.9** vs. **2.0** (*P*<0.001)

Choi H et al. *Eur Respir J* 2024;63:2400518

Individual patient data meta-analysis: macrolides

Pooled effect shows macrolides reduce exacerbation frequency by

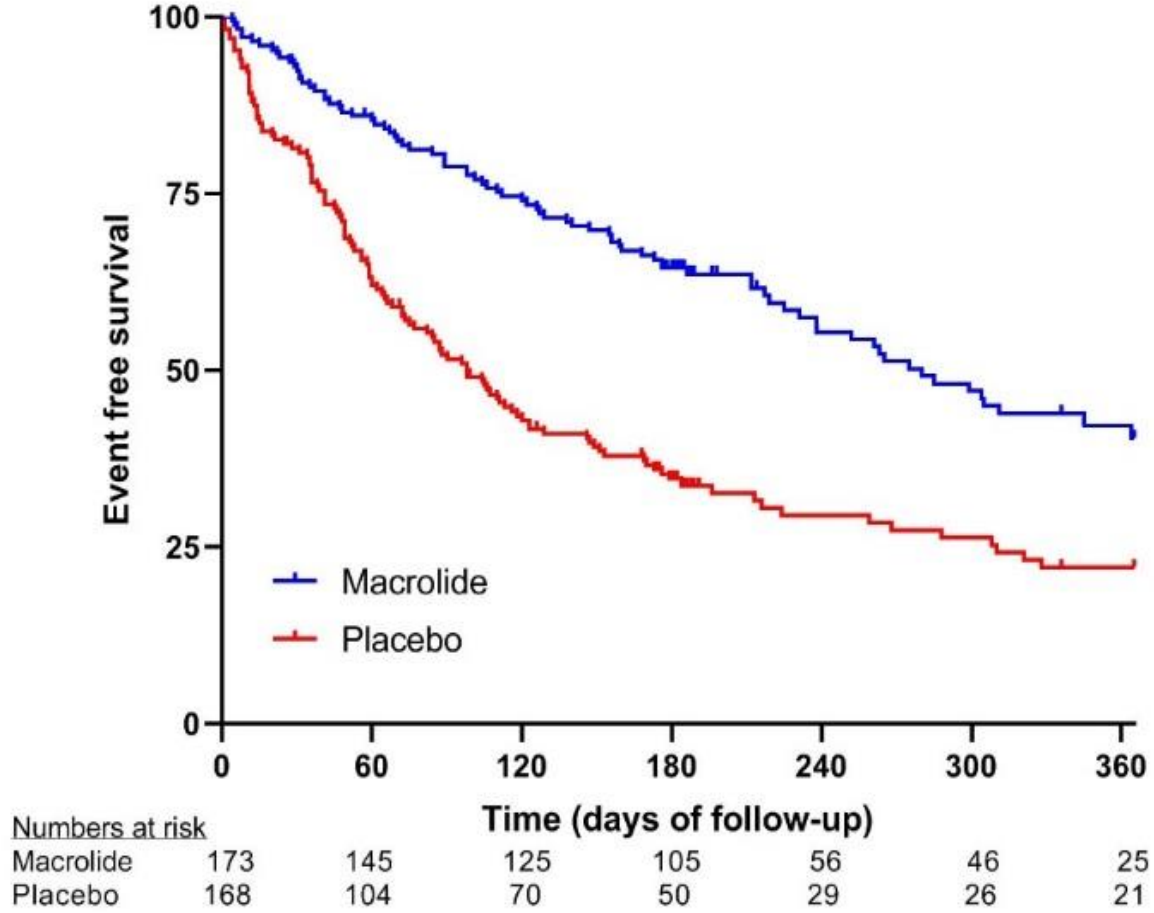
51% (IRR 0.49 95% CI 0.36-0.66,p<0.0001)

BUT

Largest effect (**66%** reduction in exacs)

in patients with ***P. aeruginosa*** infection

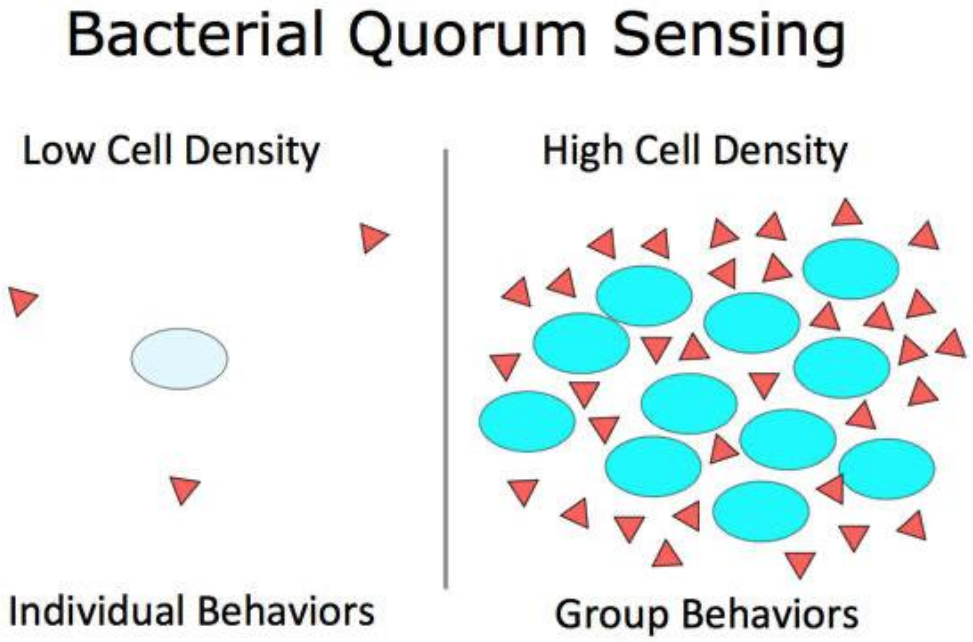
- Anti-inflammatory effect

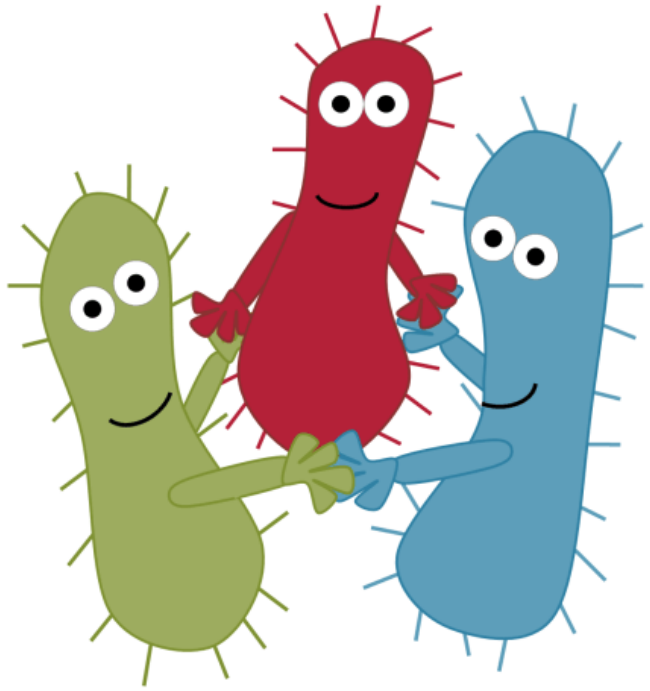


Chalmers JD et al. *Lancet Respir Med* 2019

Courtesy of Prof. James D. Chalmers

Quorum sensing = a cell-to-cell communication system

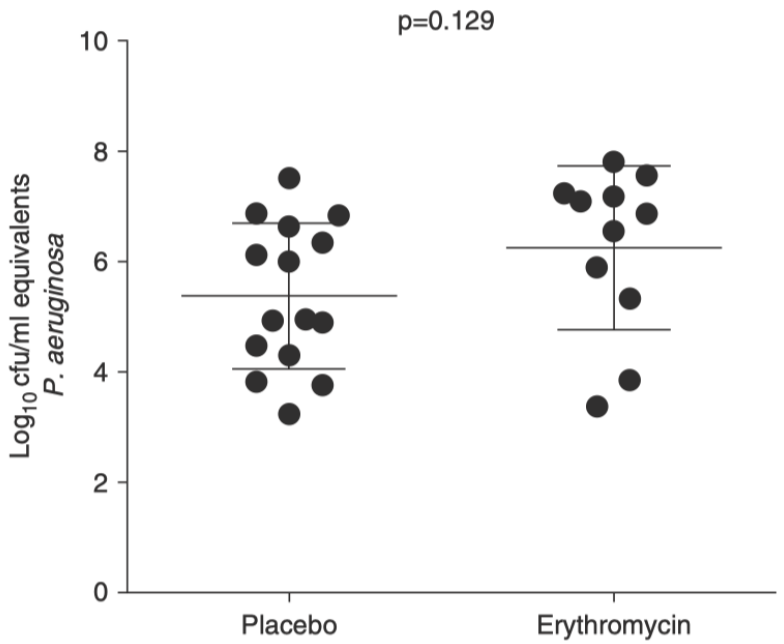




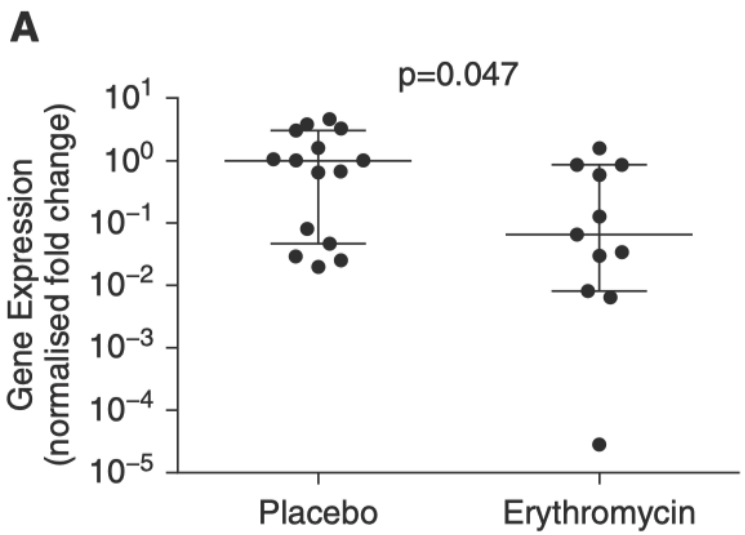
Burr LD et al. *Ann Am Thorac Soc* 2016;13:1697
basslerlab.scholar.princeton.edu

Macrolide Treatment Inhibits *Pseudomonas aeruginosa* Quorum Sensing in Non–Cystic Fibrosis Bronchiectasis

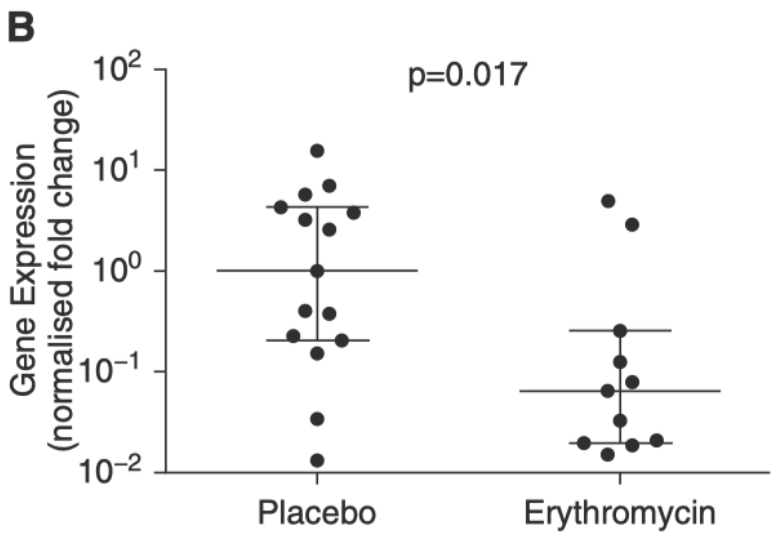
An Analysis from the Bronchiectasis and Low-Dose Erythromycin Study Trial



LasR expression



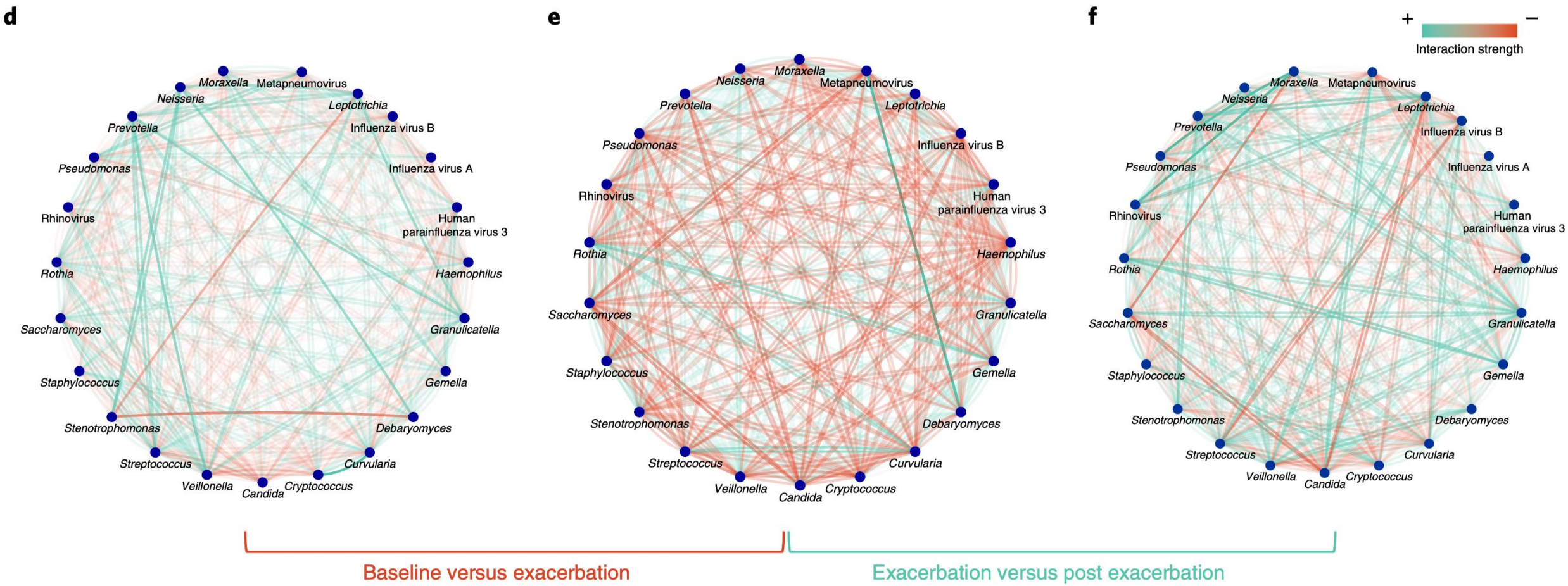
PqsA expression



Burr LD et al. *Ann Am Thorac Soc* 2016;13:1697

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01289-7

Integrative microbiomics in bronchiectasis exacerbations



Aogain MM et al. *Nat Med* 2021;27:688

Safety concerns on long-term macrolide

- Macrolide-resistant NTM infections

- GI side effects
- Ototoxicity
- **Cardiovascular adverse events**
  - Historical studies reported an incidence of sudden cardiac death or ventricular tachycardia
  - RCT duration (6–12 months)

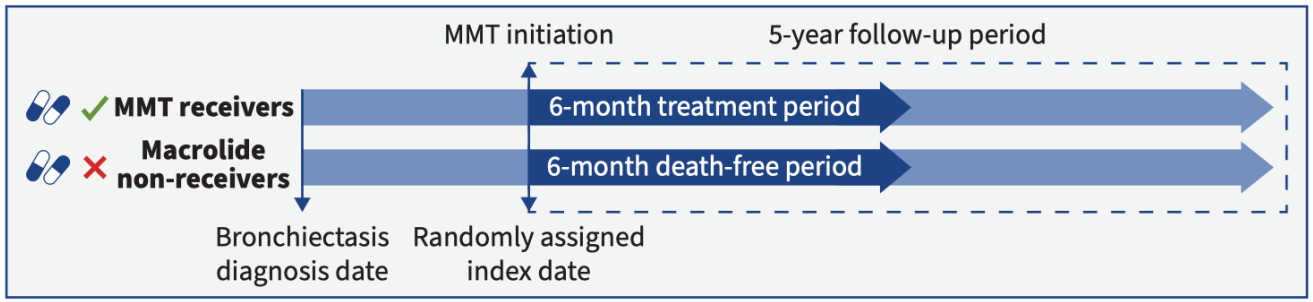
Choi H et al. *Eur Respir J* 2024;63:2400518

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
R. GUO ET AL.

Cardiovascular benefits and safety profile of macrolide maintenance therapy in patients with bronchiectasis

Study aim: 1) Evaluate the relationship between MMT administration and the incidence of cardiovascular adverse events
2) Evaluate the cardiovascular safety profile of MMT

Population: Adults with ICD-9 code 494 (Bronchiectasis) between 1 January 2001 and 30 September 2018



1236 MMT receivers

12453 macrolide non-receivers

1:2 PSM

1123 MMT receivers

2014 macrolide non-receivers

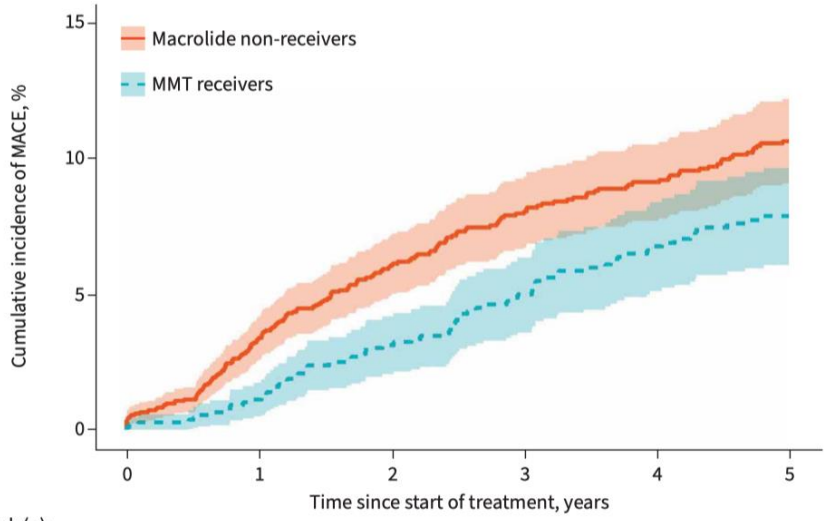
Primary outcome:
- Major adverse cardiovascular events (MACE)

(cardiovascular death, AMI and stroke)

Safety outcome:
- Composite of ventricular arrhythmias and sudden cardiac death

Guo R et al. *Eur Respir J* 2025;65:2401574

Macrolide and MACE in bronchiectasis



At risk (n):						
Macrolide non-receivers	2014	1721	1407	1230	1104	1031
MMT receivers	1123	1034	889	781	690	628

FIGURE 2 Cumulative incidence of major adverse cardiovascular events (MACE) in the propensity score-matched cohort. MMT: macrolide maintenance therapy.

	Events, n (incidence rate per 1000 person-years)		Hazard ratio (95% CI)	p-value
	MMT receivers	Macrolide non-receivers		
Primary outcome				
MACE	70 (16.38)	169 (24.11)	0.68 (0.52–0.90)	0.007
Secondary outcomes				
All-cause mortality	476 (109.95)	948 (132.04)	0.83 (0.74–0.93)	<0.001
Cardiovascular death	28 (6.47)	54 (7.52)	0.86 (0.54–1.35)	0.51
AMI	23 (5.33)	73 (10.28)	0.52 (0.33–0.83)	0.006
Stroke	32 (7.46)	79 (11.15)	0.61 (0.45–1.01)	0.059
Safety outcome				
Ventricular dysrhythmia or sudden cardiac death	31 (7.17)	55 (7.67)	0.93 (0.60–1.44)	0.746
Negative control outcome				
Hip fracture hospitalisation	27 (6.31)	53 (7.46)	0.85 (0.54–1.35)	0.496

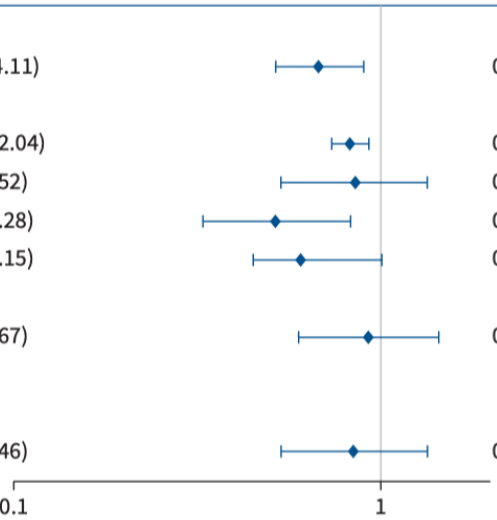


FIGURE 1 Outcomes in the 1:2 propensity score-matched macrolide maintenance therapy (MMT) receivers *versus* macrolide non-receivers. MACE: major adverse cardiovascular events; AMI: acute myocardial infarction.

- MACE = composite outcomes (cardiovascular death, AMI and stroke)
- Safety outcomes = ventricular dysrhythmia or sudden cardiac death
- Negative control outcome

Guo R et al. *Eur Respir J* 2025;65:2401574

CHEST

Cardiovascular Events During and After Bronchiectasis Exacerbations and Long-term Mortality

250 patients with bronchiectasis exacerbation

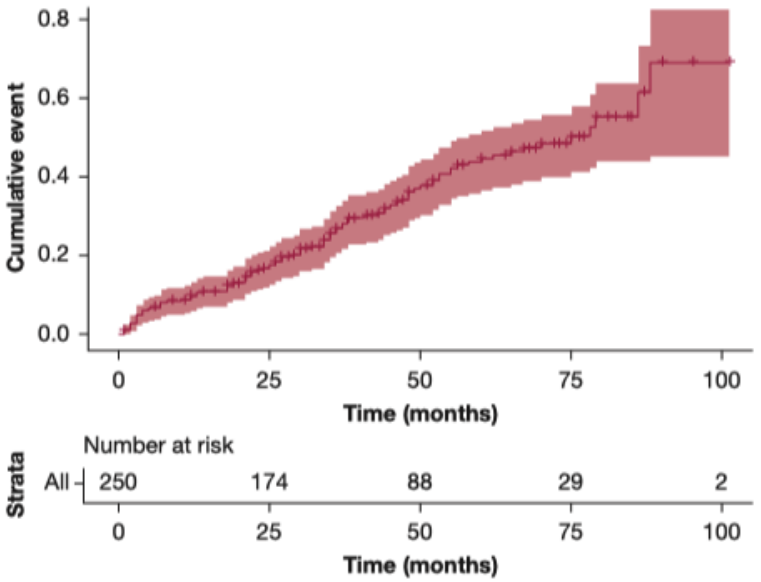


Figure 1 – *Cumulative frequency of cardiovascular events during follow-up.*

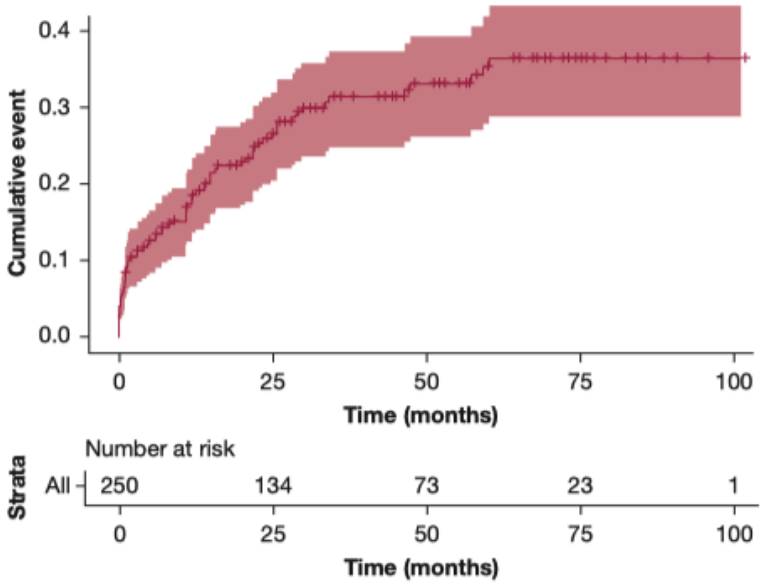


Figure 2 – *Cumulative mortality rate during follow-up.*

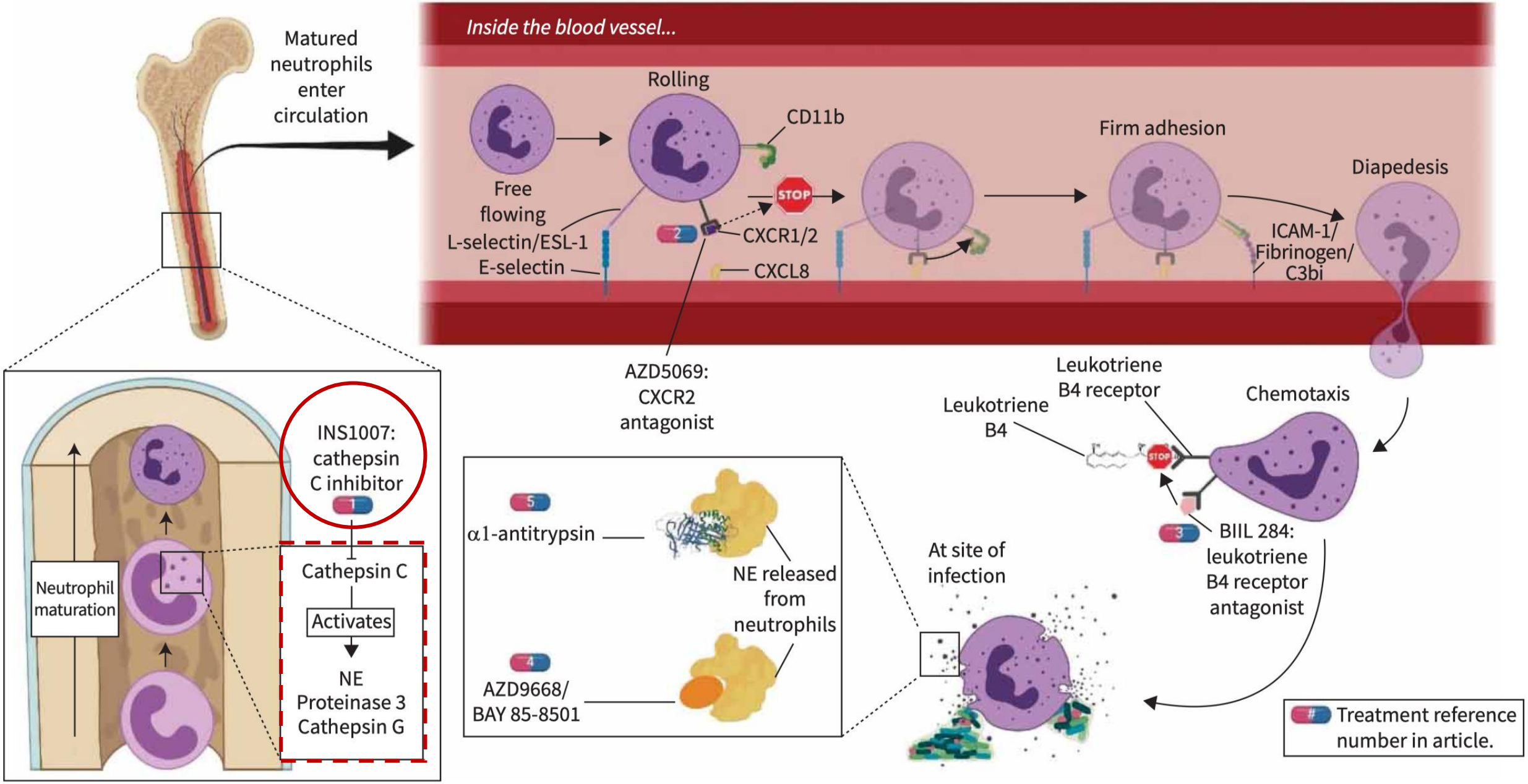
Cardiovascular events

Mortality

Mendez R et al. *Chest* 2022;161:629

Agenda

- Role of inflammation in bronchiectasis
- Long-term macrolides – efficacy and safety
- Novel anti-inflammatory therapies



Cathepsin C inhibitor

Giam YH et al. *Eur Respir J* 2021

Cathepsin C/DPP1 inhibitors in clinical development

Drug	Current development status
Brensocatib (INS1007)	Phase II Willow trial (international) (published in 2020) Phase III Aspen trial (international) (completed)
BI 1291583	Phase II AIRLEAF trial (international) (published in 2025) Phase III AIRTIVITY trial (international) (start in 2025)
HSK31858	Phase II SAVE-BE trial (China) (published in 2025) Phase III trial (NCT06660992) (China)

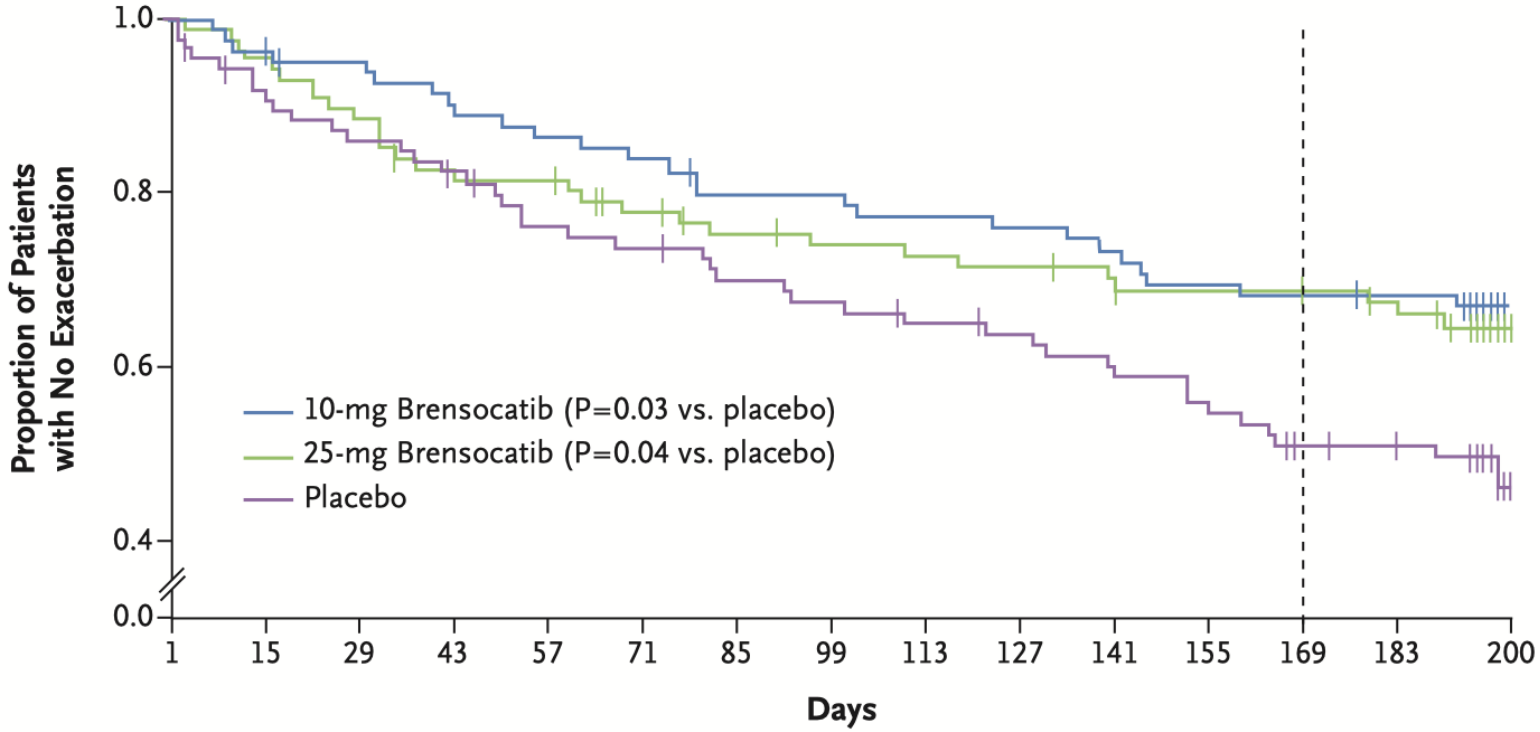
ORIGINAL ARTICLE

Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Primary endpoint: time to first exacerbation

- Brensocatib 10mg: **HR 0.58** (95% CI, 0.35–0.95), *P* = 0.03
- Brensocatib 25mg: **HR 0.62** (95% CI, 0.38–0.99), *P* = 0.046

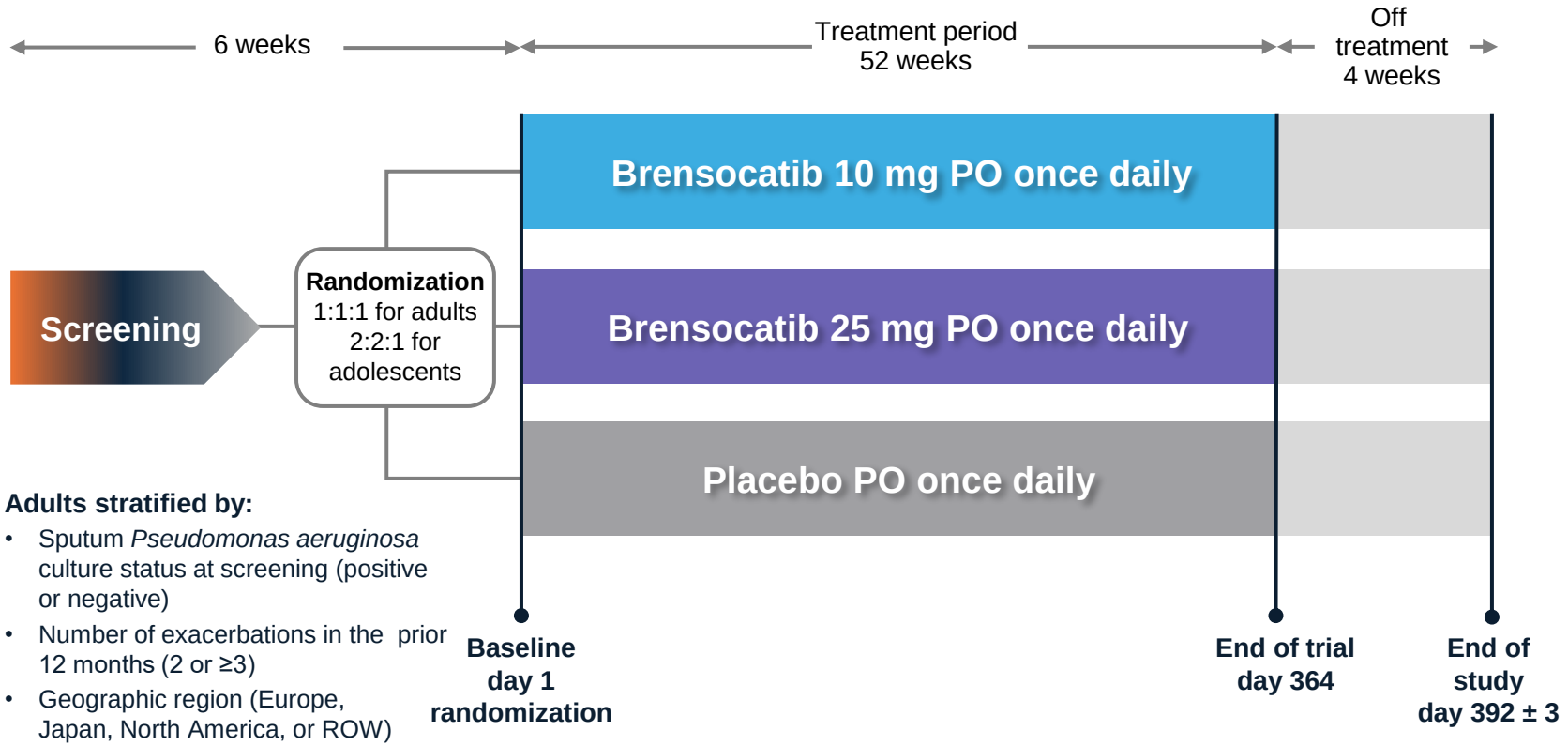
A



Chalmers JD et al. *N Engl J Med* 2020;383:2127

ASPEN Study Design

A phase 3, randomized, double-blind, placebo-controlled 52-week study of 2 doses of brensocatib vs placebo in patients with bronchiectasis[a]



Primary endpoint:
Annualized rate of adjudicated pulmonary exacerbations[b] over 52 weeks

Secondary endpoints (hierarchical):

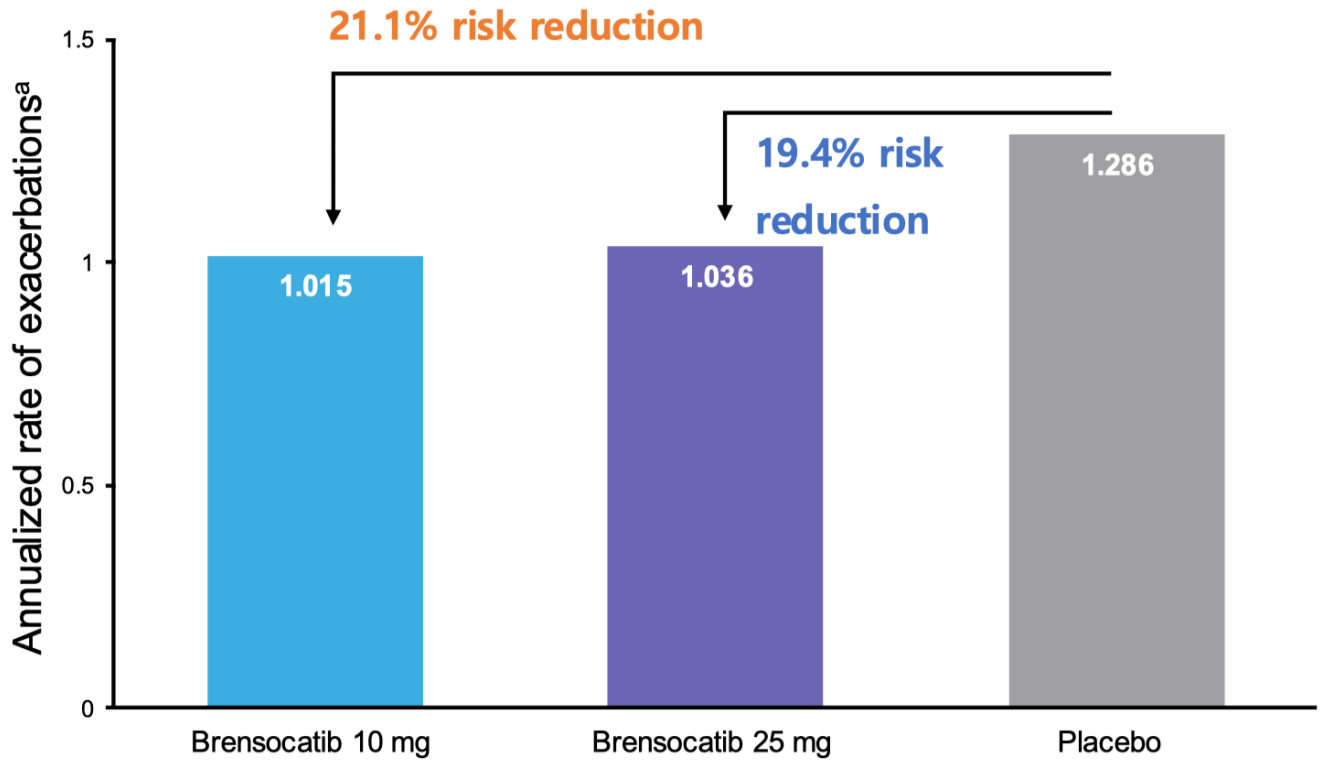
- Time to first exacerbation
- Proportion of patients who remained exacerbation-free
- Change from baseline in post-bronchodilator FEV_1 at week 52
- Annualized rate of severe exacerbations
- Change from baseline in QOL-B Respiratory Symptoms Domain score at week 52

[a]ASPEN trial (NCT04594369). [b]Defined as the presence of ≥3 of the following symptoms for at least 48 hours, resulting in a physician's decision to prescribe systemic antibiotics: (1) increased cough, (2) increased sputum production or change in sputum consistency, (3) increased sputum purulence, (4) increased breathlessness and/or decreased exercise tolerance, (5) fatigue and/or malaise, or (6) hemoptysis.
FEV_1, forced expiratory volume in 1 second; PO, orally; QOL-B, Quality of Life-Bronchiectasis questionnaire; ROW, rest of world.

Courtesy of Prof. James D. Chalmers

Annualized Rate of Adjudicated Pulmonary Exacerbations Over 52 Weeks

Primary endpoint



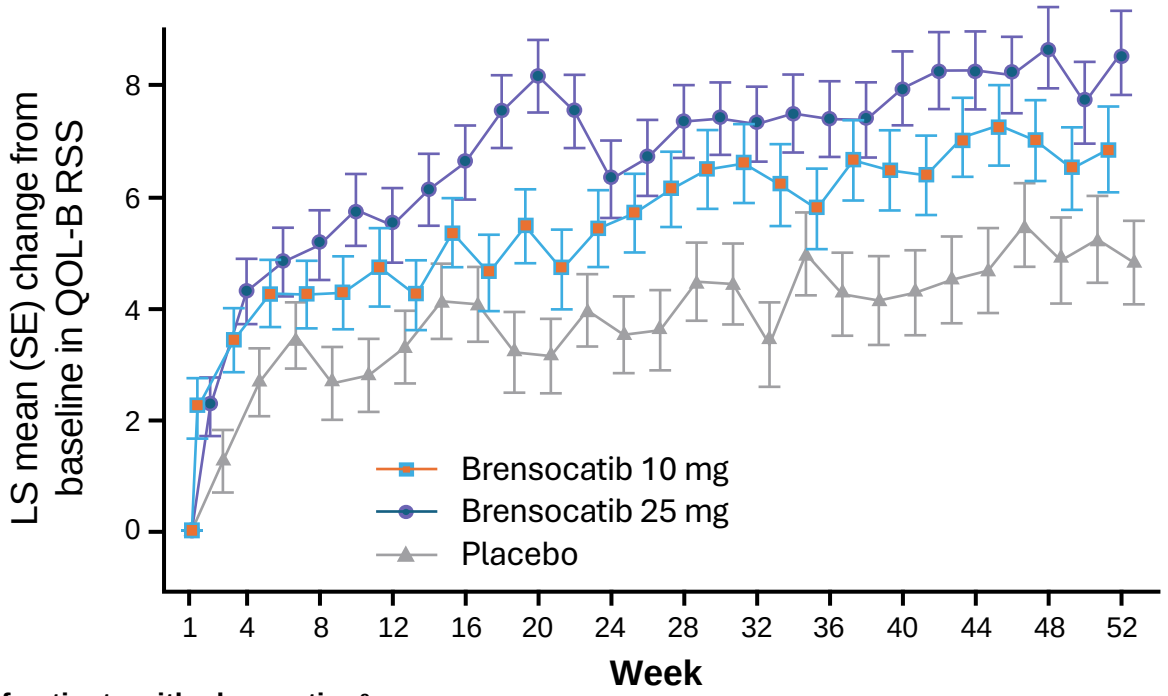
	Brensocatib 10 mg n=583	Brensocatib 25 mg n=575
Rate ratio vs placebo (95% CI)	0.789 (0.680–0.916)	0.806 (0.694–0.936)
P value	0.0019[b]	0.0046[b]

[a]Exacerbations were adjudicated events in the ITT analysis set analyzed using a negative binomial model. [b]*P* value is statistically significant when adjusted for multiplicity control.
ITT, intention-to-treat.

Courtesy of Prof. James D. Chalmers

Change From Baseline in QOL-B Respiratory Symptoms Domain Score at Week 52

Secondary endpoint



Number of patients with observation[a]

Brensocatib 10 mg	488	473	463	456	453	450	446	443	418	418	435	423	416	381
Brensocatib 25 mg	497	476	464	459	454	456	442	446	434	438	432	426	423	394
Placebo	487	457	459	452	448	437	421	434	428	411	408	405	399	366

Brensocatib 25 mg showed a nominally significant improvement in QOL-B RSS of 3.8 points vs placebo

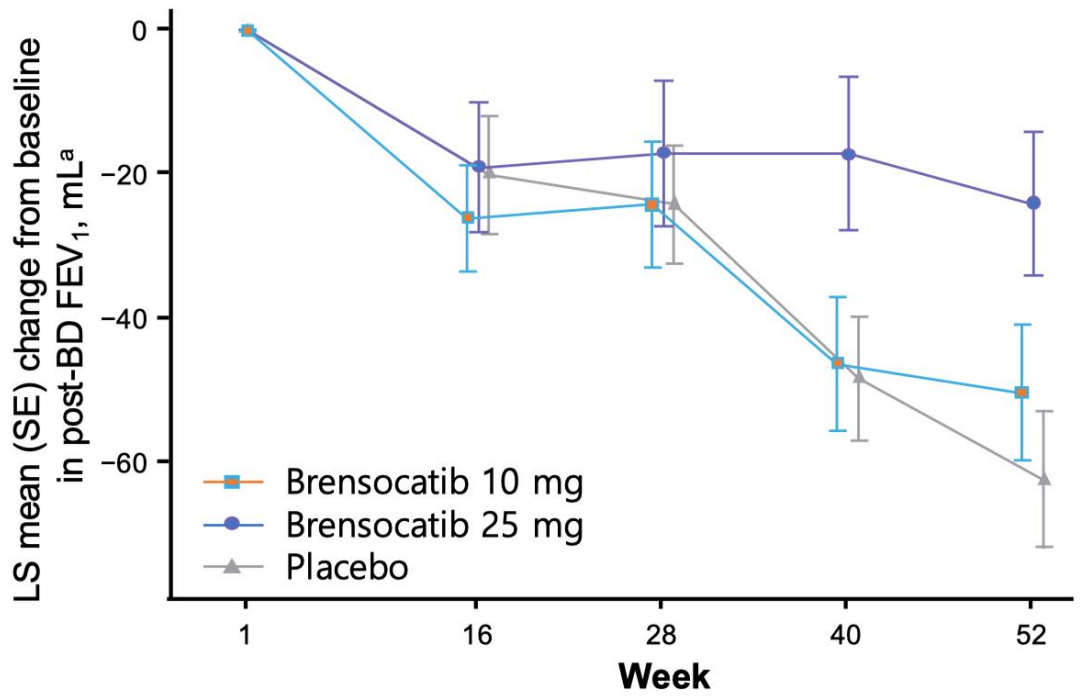
	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
LS mean change from baseline in QOL-B RSS at week 52	**6.841**	**8.575**	**4.809**
LS mean difference vs placebo in QOL-B RSS	**2.031**	**3.766**	**–**
***P* value vs placebo[b]**	**0.0594**	**0.0004[c]**	**–**

[a]Adult patients only. [b]*P* value vs placebo calculated using a linear repeated measures model in the ITT analysis set. [c]Nominally significant *P* value.
LS, least squares; QOL-B RSS, Quality of Life-Bronchiectasis questionnaire Respiratory Symptoms Domain score.

Courtesy of Prof. James D. Chalmers

Change From Baseline in Post-Bronchodilator FEV_1 at Week 52

Secondary endpoint



Number of patients with observation					
Brensocatib 10 mg	579	545	529	513	475
Brensocatib 25 mg	571	529	523	494	487
Placebo	563	522	513	494	468

Brensocatib 25 mg showed a **38 mL less** FEV_1 decline vs placebo

	Brensocatib 10 mg	Brensocatib 25 mg	Placebo
LS mean change from baseline in post-BD FEV_1 at week 52, mL	−50	−24	−62
LS mean difference vs placebo in post-BD FEV_1, mL	11	38	–
P value vs place bo	0.3841	0.0054[b]	–

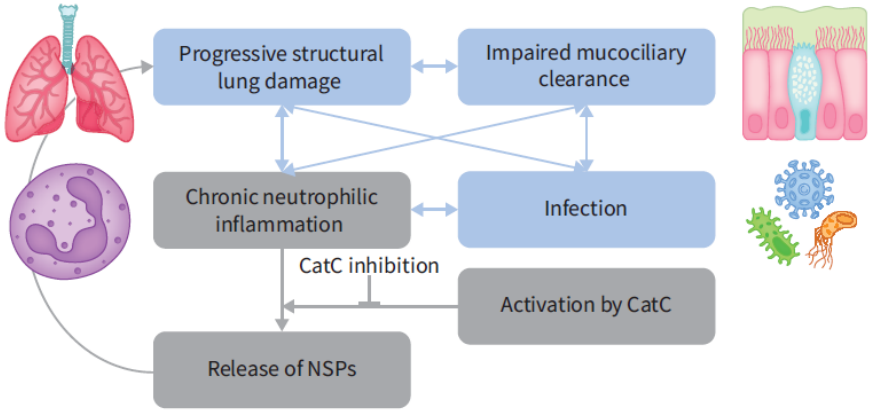
[a]% predicted FEV_1 analyzed using a linear repeated measures model in the ITT analysis set. [b]*P* value is statistically significant when adjusted for multiplicity control.
BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; LS, least squares.

Courtesy of Prof. James D. Chalmers

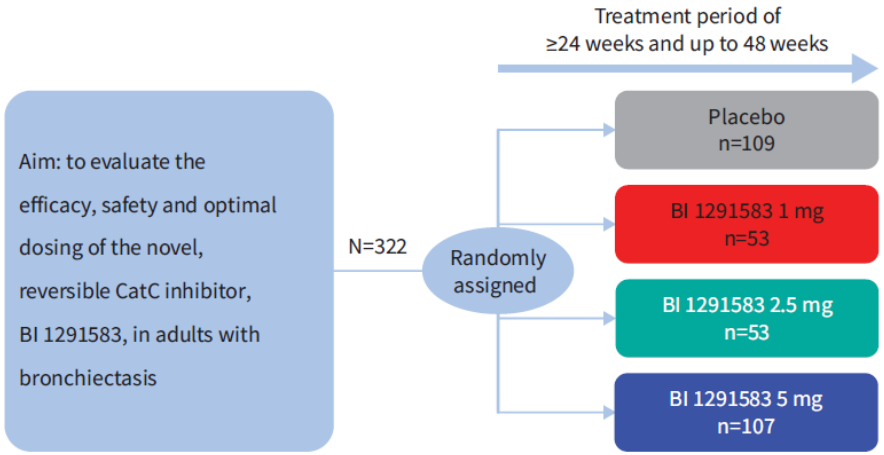
EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
J.D. CHALMERS ET AL.

Cathepsin C (dipeptidyl peptidase 1) inhibition in adults with bronchiectasis: AIRLEAF, a phase II randomised, double-blind, placebo-controlled, dose-finding study

Bronchiectasis: the vicious vortex

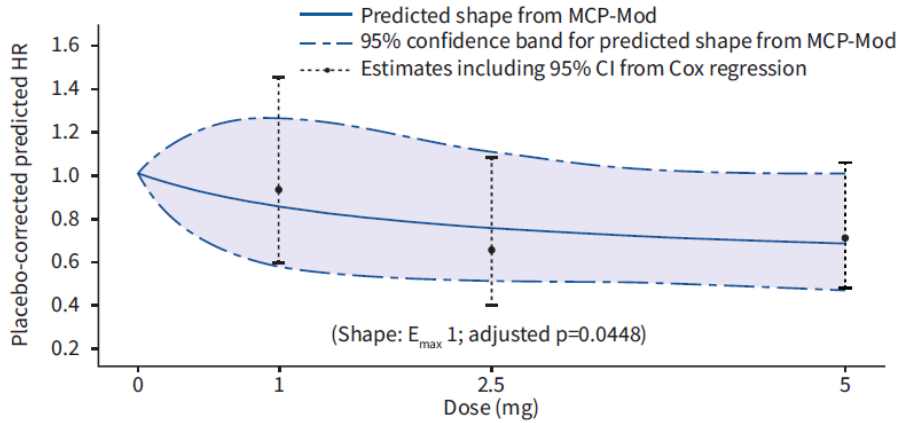


AIRLEAF phase II trial design

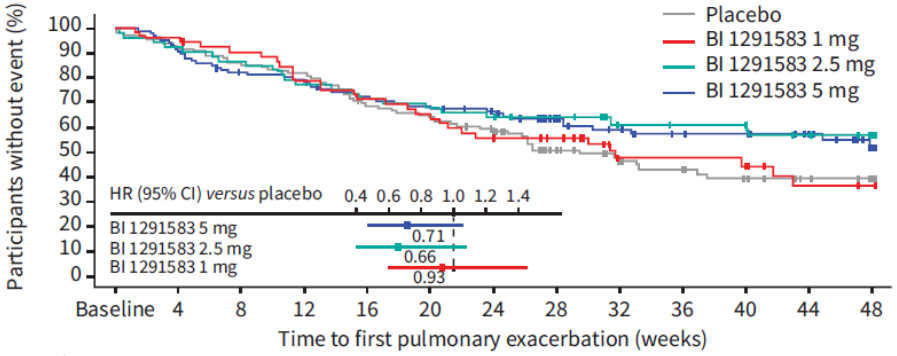


AIRLEAF results

1



2



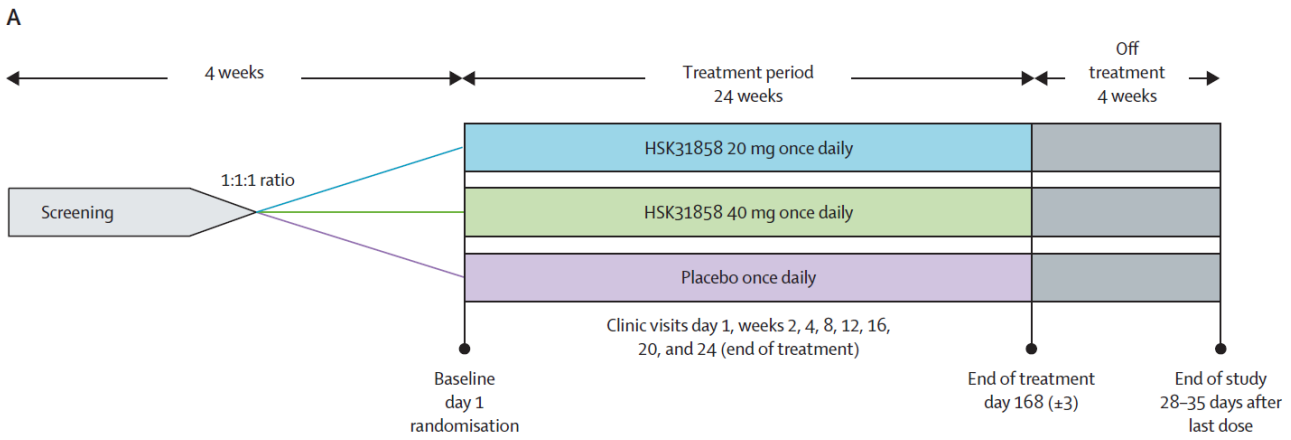
The safety profile of BI 1291583 was similar to placebo

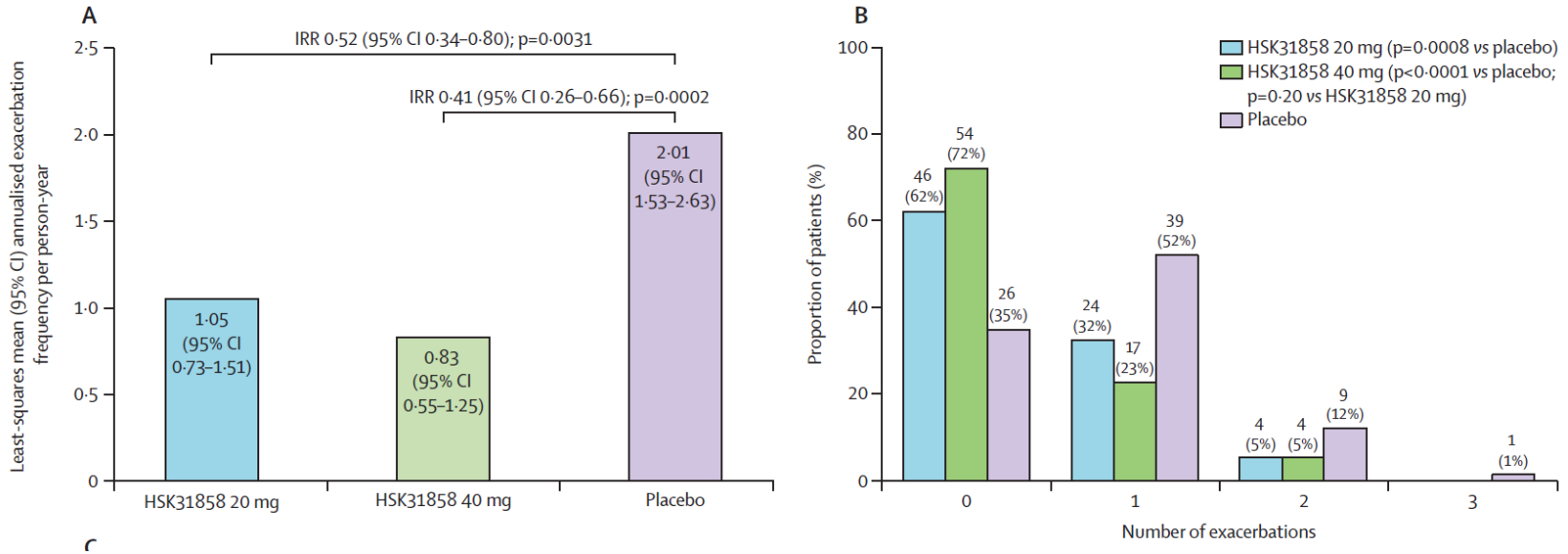
The AIRTIVITY phase III trial is planned to begin in 2025

- 2.5 mg (HR 0.66)
- 5 mg (HR 0.71)

Chalmers JD et al. *Eur Respir J* 2025;65:2401551

Effects of the DPP-1 inhibitor HSK31858 in adults with bronchiectasis in China (SAVE-BE): a phase 2, multicentre, double-blind, randomised, placebo-controlled trial





Zhong NS et al. *Lancet Respir Med* 2025 (in press)

Highly symptomatic patients benefit from long-term macrolide therapy

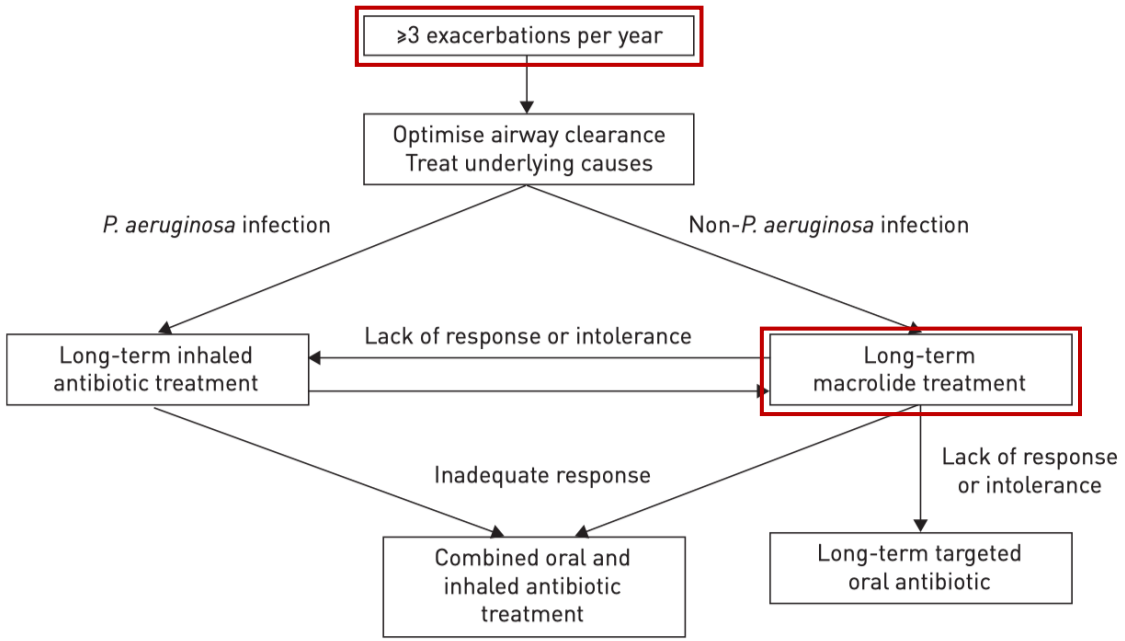


FIGURE 4 Summary of recommendations for long-term antibiotic treatment.

Conference Abstract Free

Highly symptomatic patients have an increased risk of exacerbations and benefit from long-term macrolide treatment in Bronchiectasis

Oriol Sibila Vidal | Jamie Stobo | Lidia Perea Show More

European Respiratory Journal 2024 64(suppl 68): PA2375; DOI: https://doi.org/10.1183/13993003.congress-2024.PA2375

Abstract

Introduction: Prior exacerbations are the main risk factor for exacerbations in bronchiectasis. Guidelines recommend macrolide only in frequent exacerbators. Other studies suggest that symptoms are related to increased exacerbation risk. We aimed to investigate if symptoms could independently predict future exacerbations and identify responders to long-term macrolide therapy.

Methods: Prospective observational study including 8328 patients from EMBARC registry with symptoms (Quality-of-life questionnaire Bronchiectasis (QoL-B) at baseline) and follow-up for at least one year, and posthoc analysis of 3 randomized clinical trials (RCTs) of macrolides in 341 bronchiectasis patients.

Results: Prior exacerbations (RR for every exacerbation=1.10, 95%CI 1.09-1.11, p<0.001) and symptoms (RR for every 10 points lower QoL-B=1.10, 95%CI 1.08-1.11, p<0.001) were identified as independent risk factors for future exacerbations in the EMBARC registry. The expected number of exacerbations in 1-year was similar between the group with 3 prior exacerbations and average symptom scores (1.49, 95% CI 1.38-1.60) and the group with no prior exacerbations but high symptom scores (1.47, 95% CI 1.34-1.60). The same pattern was observed in the post-hoc analysis of RCTs, both in macrolide and placebo arms. The number needed to treat to prevent exacerbations with macrolides was similar among patients selected based on frequent exacerbations and in those with no prior/few exacerbations but high symptom scores.

Conclusion: Symptoms are an independent risk factor for exacerbations in bronchiectasis, and highly symptomatic patients may benefit from long-term macrolides.

- number needed to treat to prevent exacerbation

Sibila O et al. *Lancet Respir Med* 2025 (in revision)

Conclusions

- Bronchiectasis is an inflammatory disease
- Inflammation is a key driver of bronchiectasis symptoms and exacerbations
- New RCT data support the efficacy of anti-inflammatory treatment with DPP1 inhibitors and suggest the potential for disease modification

감사합니다

Thank you~!