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보건의료전문가용

The University of Manchester

medicines evaluation unit

Advances in COPD; pharmacological treatment and early disease concepts

Professor Dave Singh

Professor of clinical pharmacology and respiratory medicine

University Of Manchester

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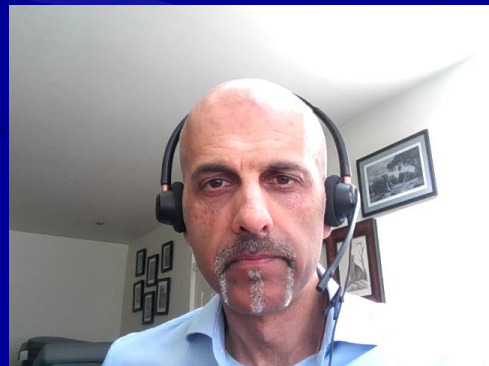
Disclosure of interest

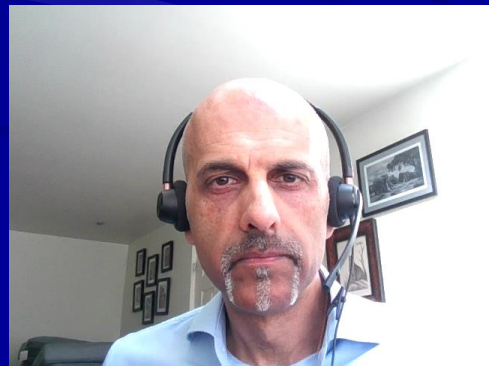
Received sponsorship to attend and speak at international meetings, honoraria for lecturing or attending advisory boards, and research grants from the following companies:

- Apellis, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Johnson & Johnson, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Skypharma, Teva, Therevance and Verona



Early disease; overview

- Terminology
- Pathology
- Clinical features
- Evidence for pharmacological intervention



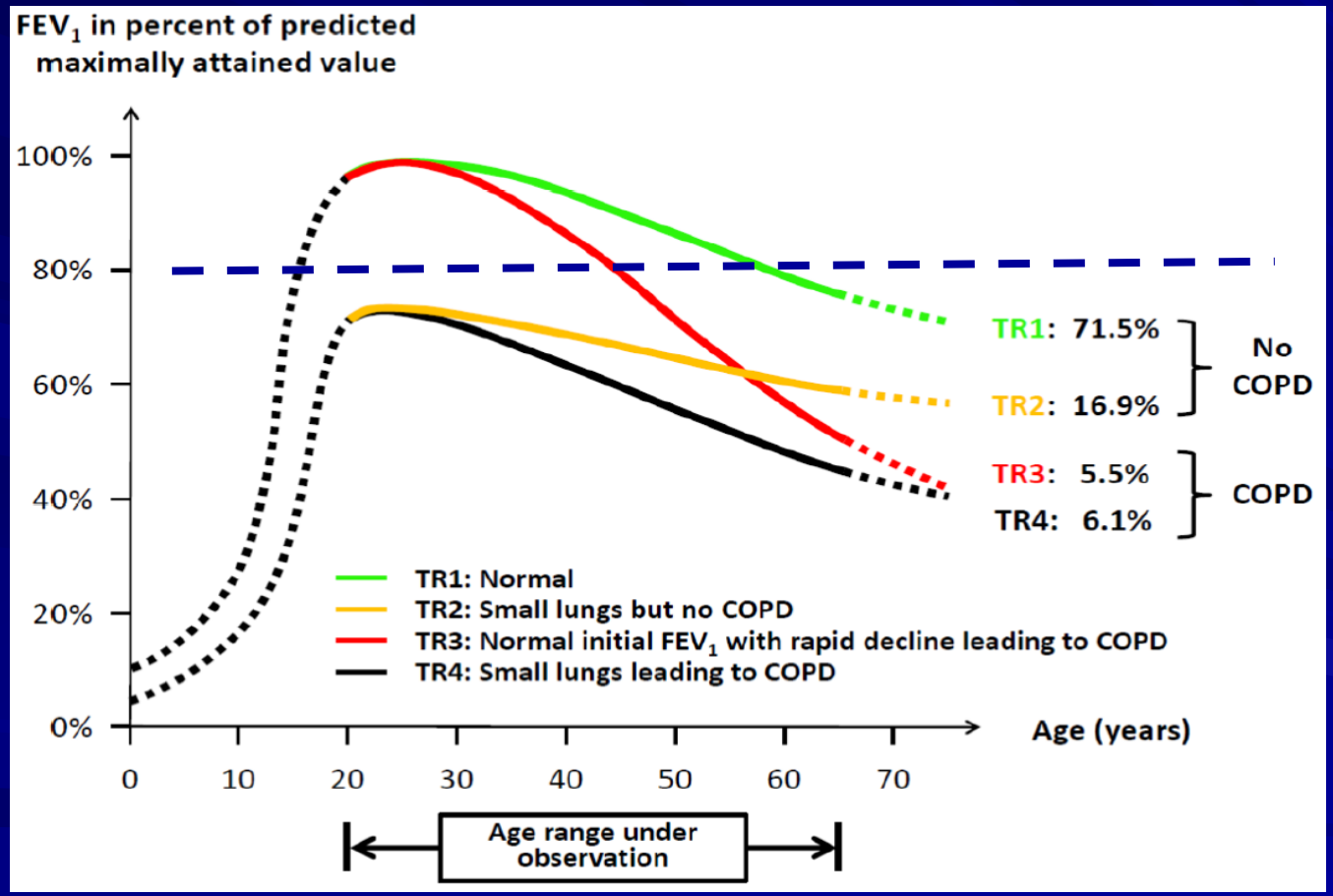
Early chronic obstructive pulmonary disease: definition, assessment, and prevention

Stephen I Rennard, M Bradley Drummond

"AN INTERVAL IN TIME AT THE BEGINNING OF THE DISEASE COURSE"

Rennard et al. Lancet 2015;385:1778-88

Lung growth and COPD development



MILD COPD

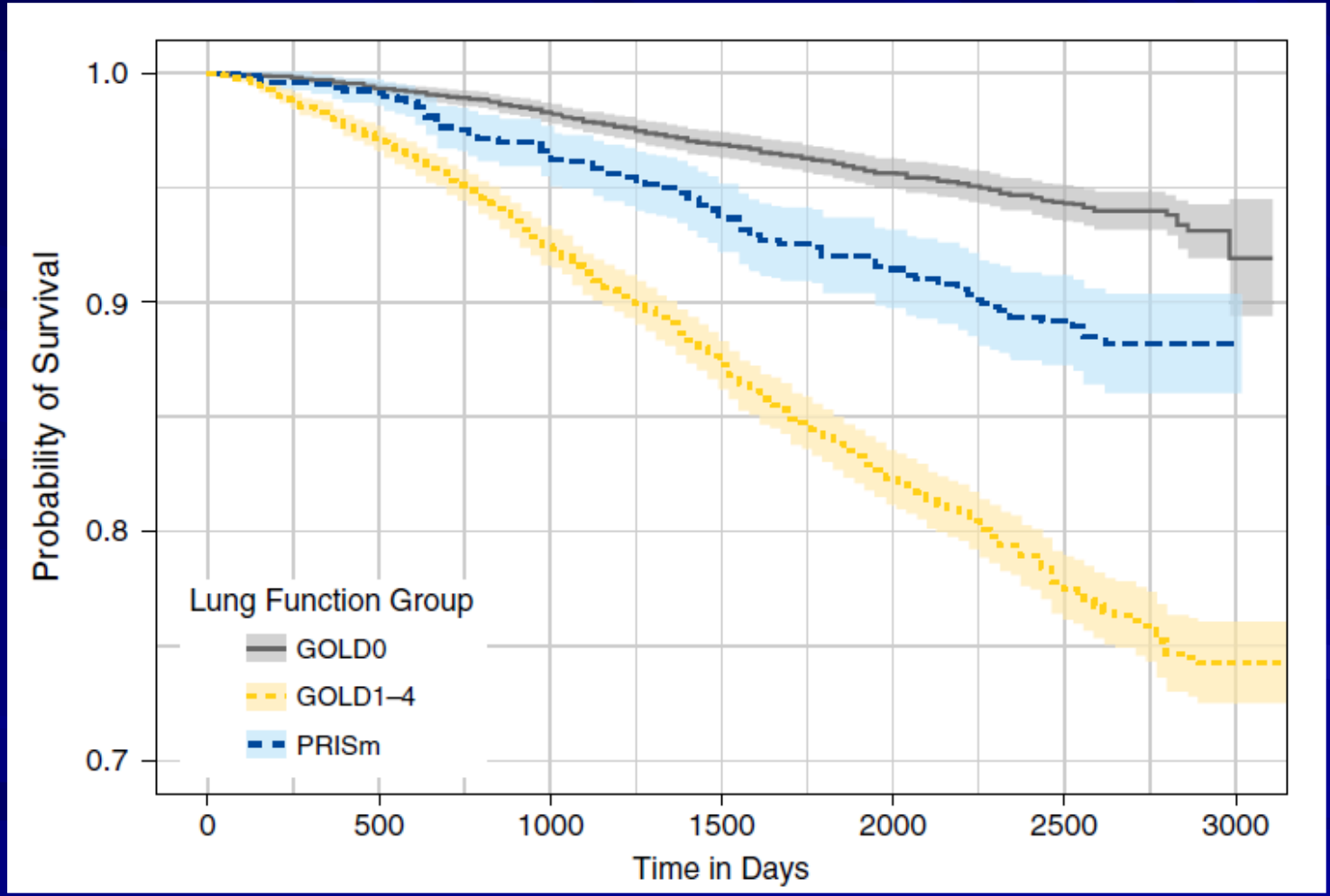
Lange et al. N Engl J Med 2015;373:111-22

COPD in young people. The term "COPD in young people" is straightforward because it directly relates to the chronological age of the subject. Given that lung function peaks at around 20-25 years,[82] we propose to operationally consider "COPD in young people" for those patients included in the 20–50 year age range.[83] Of

Pre-COPD. This term has been recently proposed to identify individuals (importantly, of any age) who have respiratory symptoms with or without detectable structural and/or functional abnormalities, in the absence

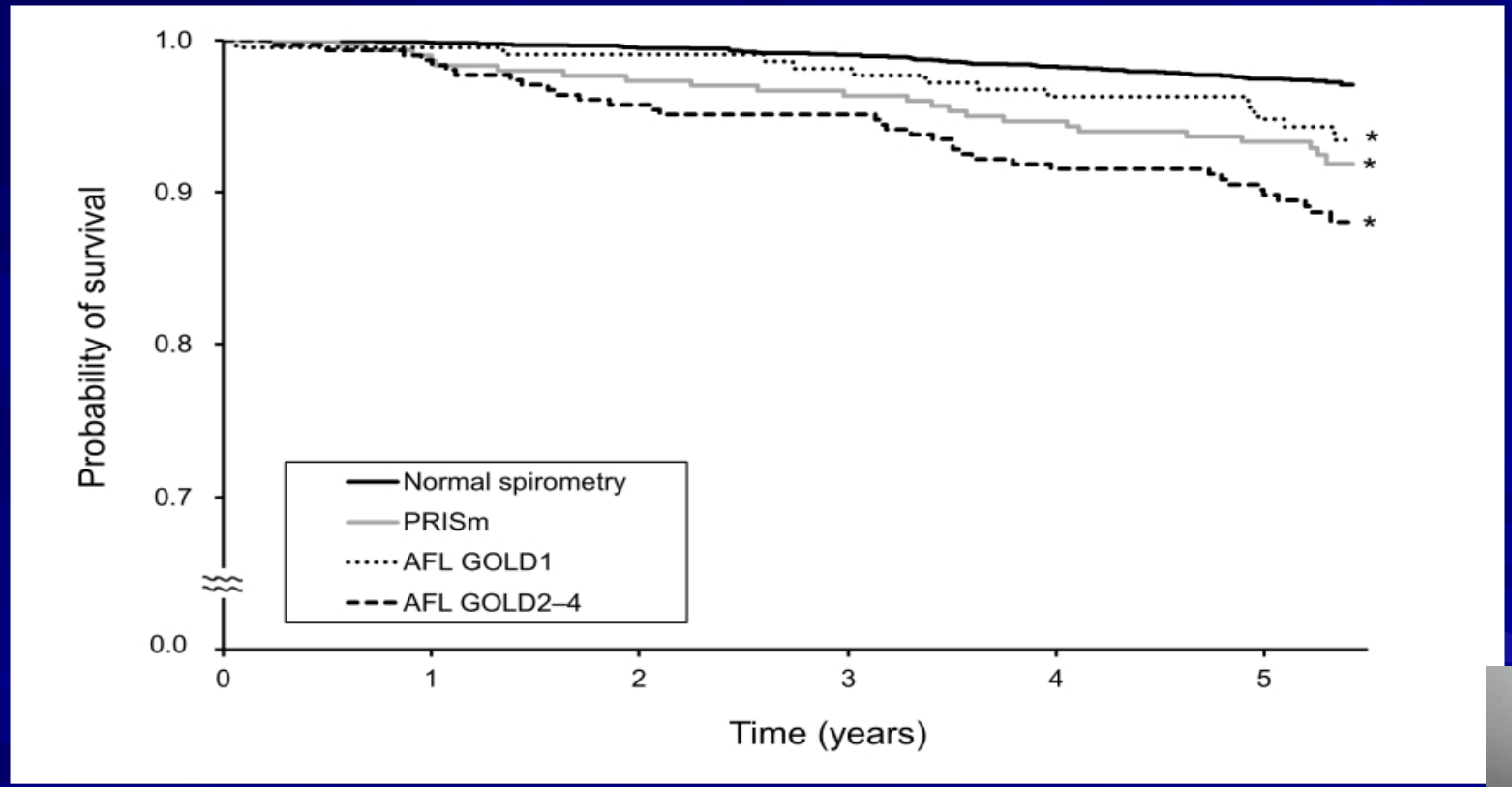
Global Initiative for Chronic Obstructive Lung Disease;GOLD;2022;1-177

Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study



Wan E et al. AJRCCM. 2018 Dec 1;198(11):1397-1405

Risks of Mortality and Airflow Limitation in Japanese with Preserved Ratio Impaired Spirometry

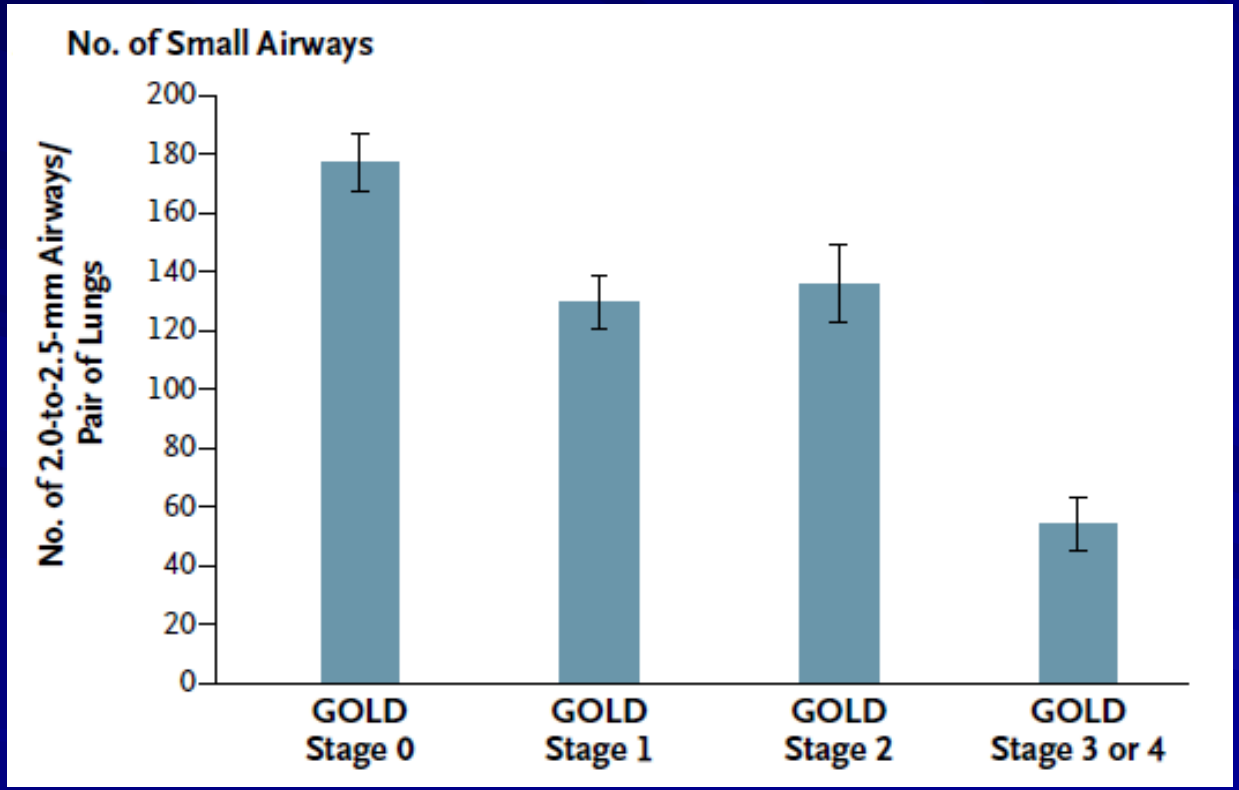


Washio et al, AJRCCM 2022, in press AJRCCM Articles in Press. Published May 12, 2022 as 10.1164

Early disease; overview

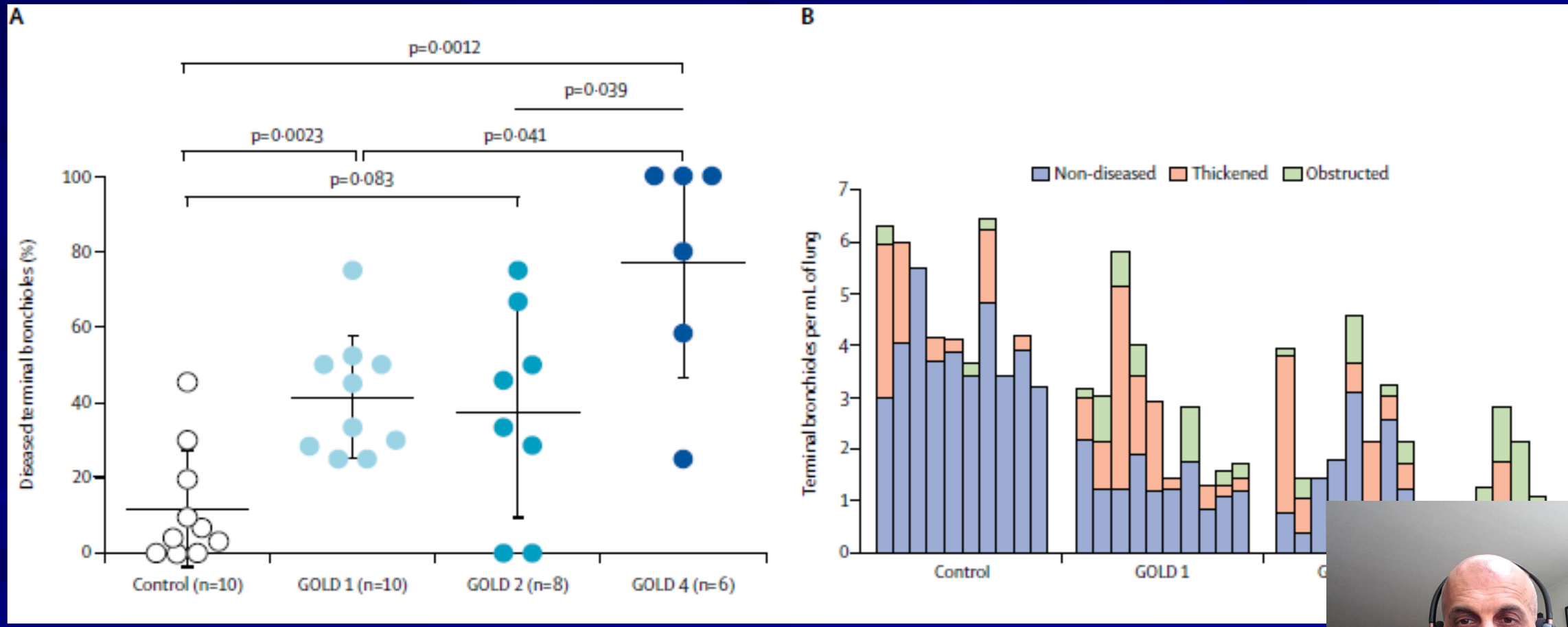
- Terminology
- Pathology
- Clinical features
- Evidence for pharmacological intervention

Small airway narrowing and destruction



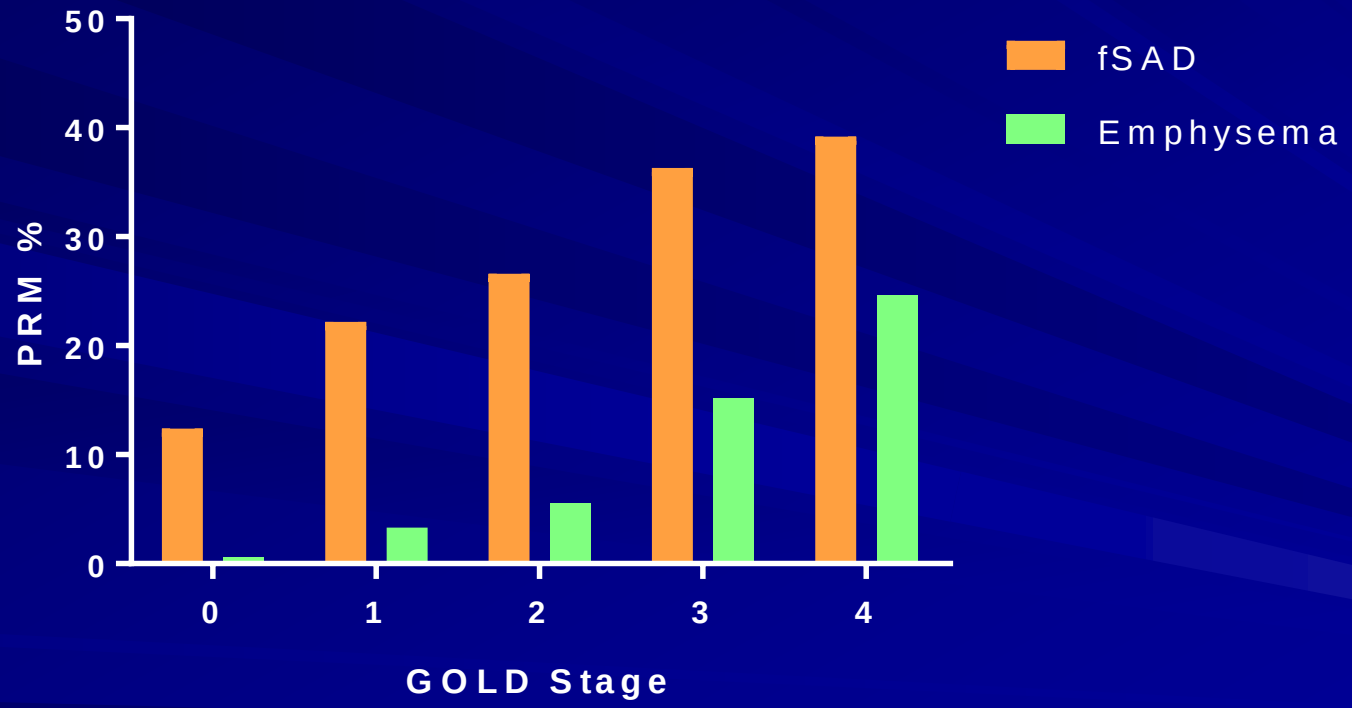
McDonough et al. *N Engl J Med* 2011; 365: 1567–75

Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study



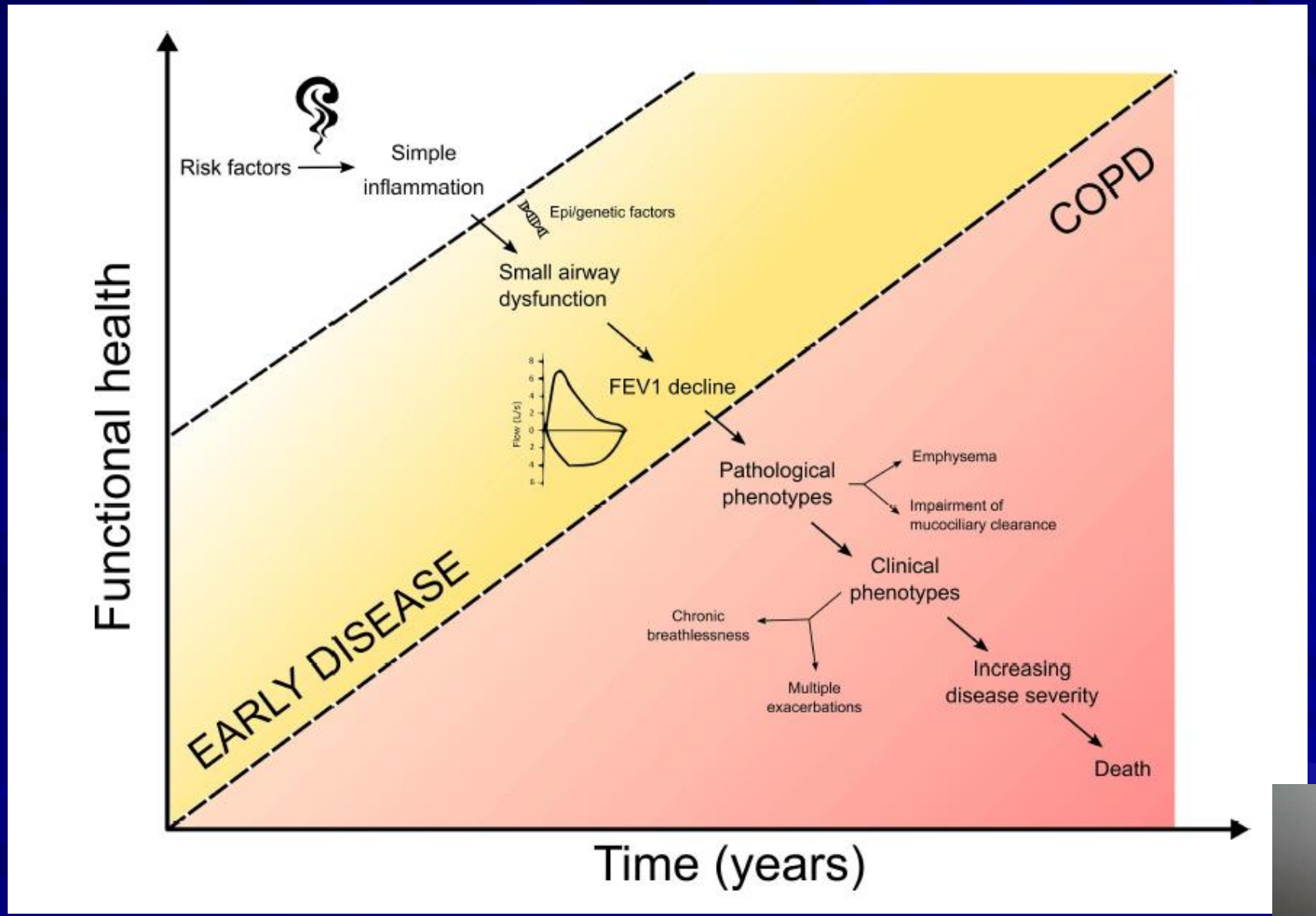
Koo et al Lancet Respir Med. 2018 Aug;6(8):591-602.

Small airway disease in COPD



fSAD: functional small airways disease;
PRM: parametric response mapping

Bhatt et al. *Am J Respir Crit Care Med.* 2016; 194: 178-184(supplement)



Yip et al. International Journal of Chronic Obstructive Pulmonary Disease 2021;16:957-968

Early disease; overview

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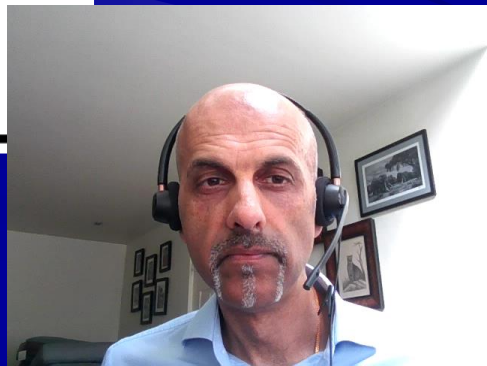
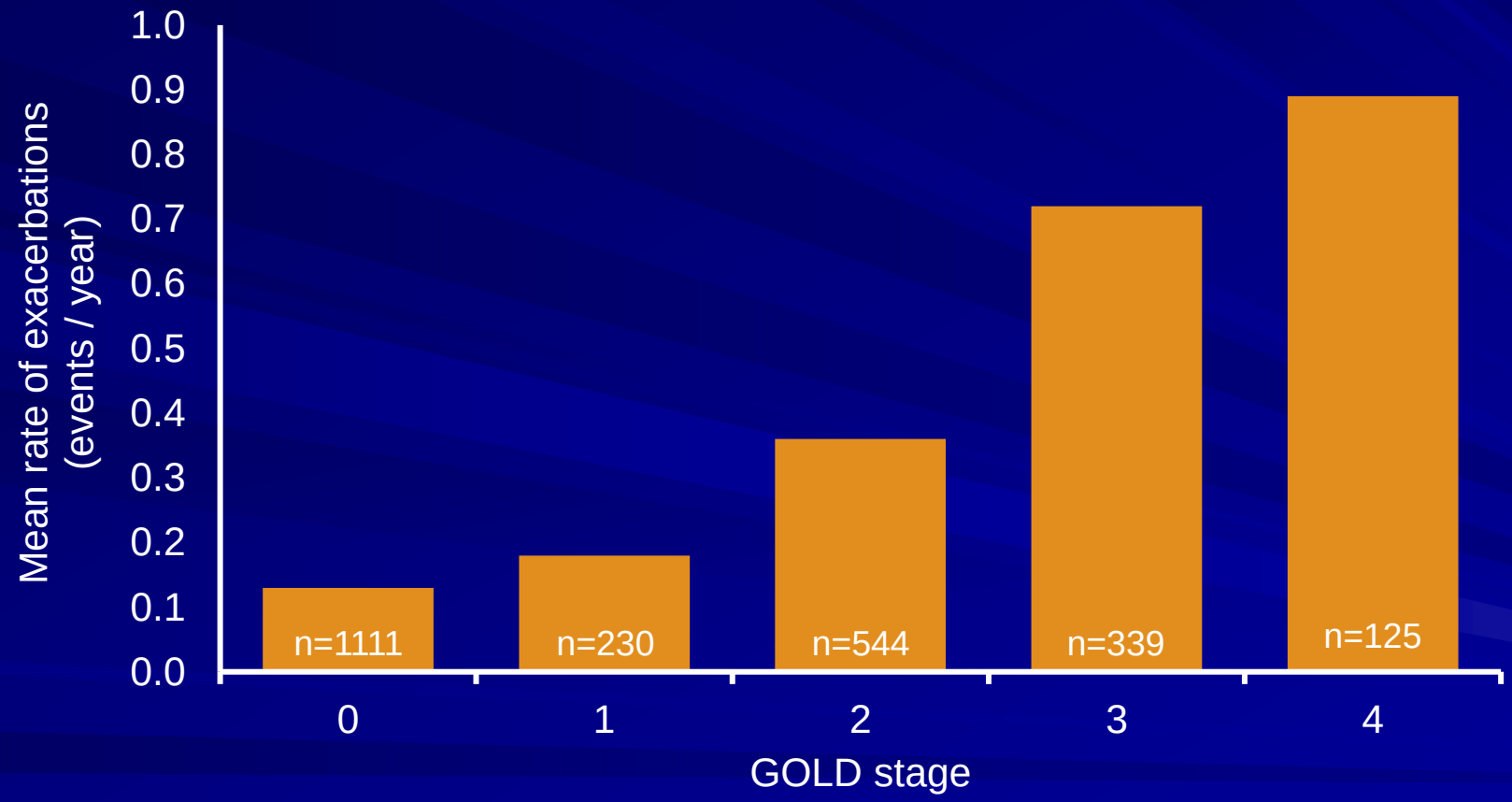
Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease

	Mild COPD	Healthy
Male:female, n	6:5	5:6
Age, yr	64.0 ± 11	64.1 ± 10
Height, cm	167 ± 11	169 ± 8
Body mass, kg	77.1 ± 15.9	78.9 ± 11.7
BMI, kg/m^2	27.2 ± 3.4	27.5 ± 3.3
Smoking history, pack-years	35.6 ± 14.9*	1.5 ± 3.2
Smoking status, % current smokers	45%*	0%
BDI focal score, 0–12	8.0 ± 1.2*	11.8 ± 0.6
Modified MRC dyspnea scale, 0–4	2.0 ± 0.4*	0.3 ± 0.5
CAT score, 0–40	15.6 ± 7.7*	2.9 ± 1.9
Oxygen cost diagram (0–100), mm	64 ± 11*	94 ± 10
SGRQ total score	29.6 ± 16.8*	2.5 ± 1.6
CHAMPS, kcal/wk for all activities	3,901 ± 2,753	5,100 ± 3,820
Medication use, % of patients:		
SABA	36	0
LAMA	27	0
ICS	9	0
Combined ICS/LABA	45*	0

Elbehairy et al. Am J Respir Crit Care Med. 2015 Jun 15;191(12):1384-94

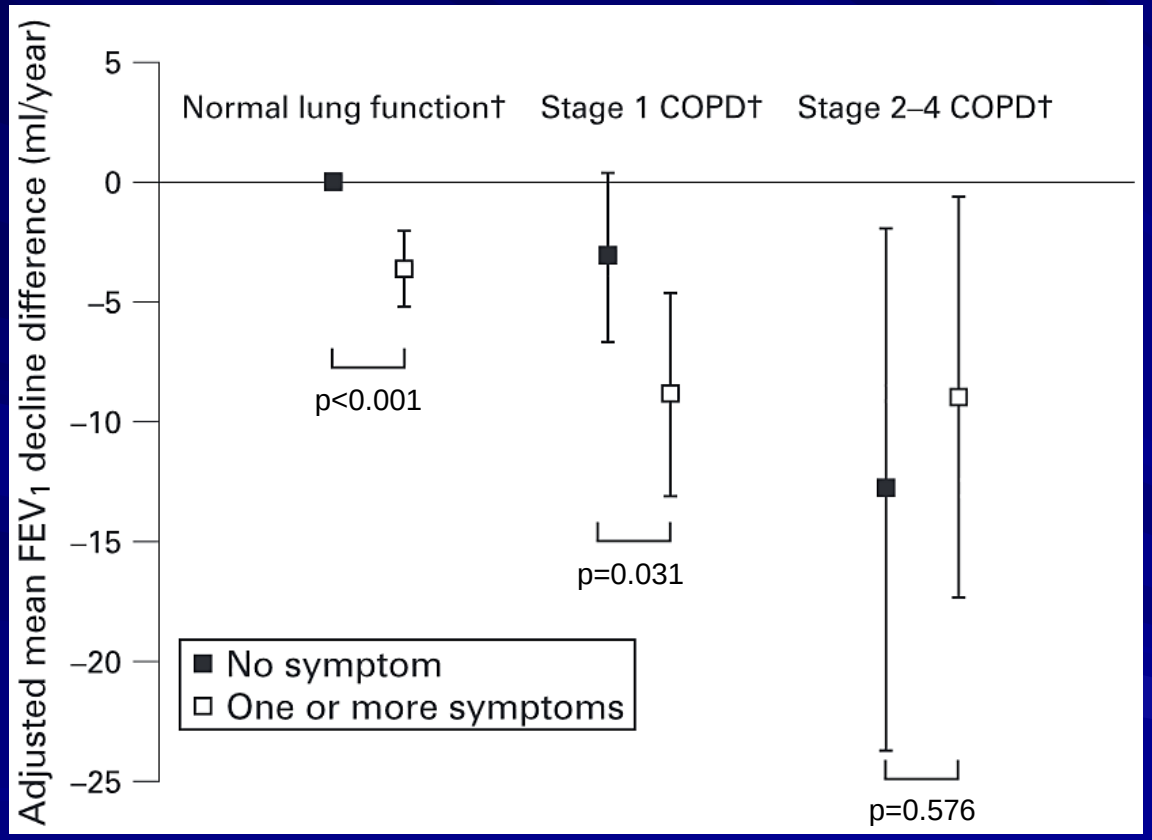


Exacerbations in smokers with COPD by GOLD stage



Dransfield et al. Am J Respir Crit Care Med 2017;195:324–330

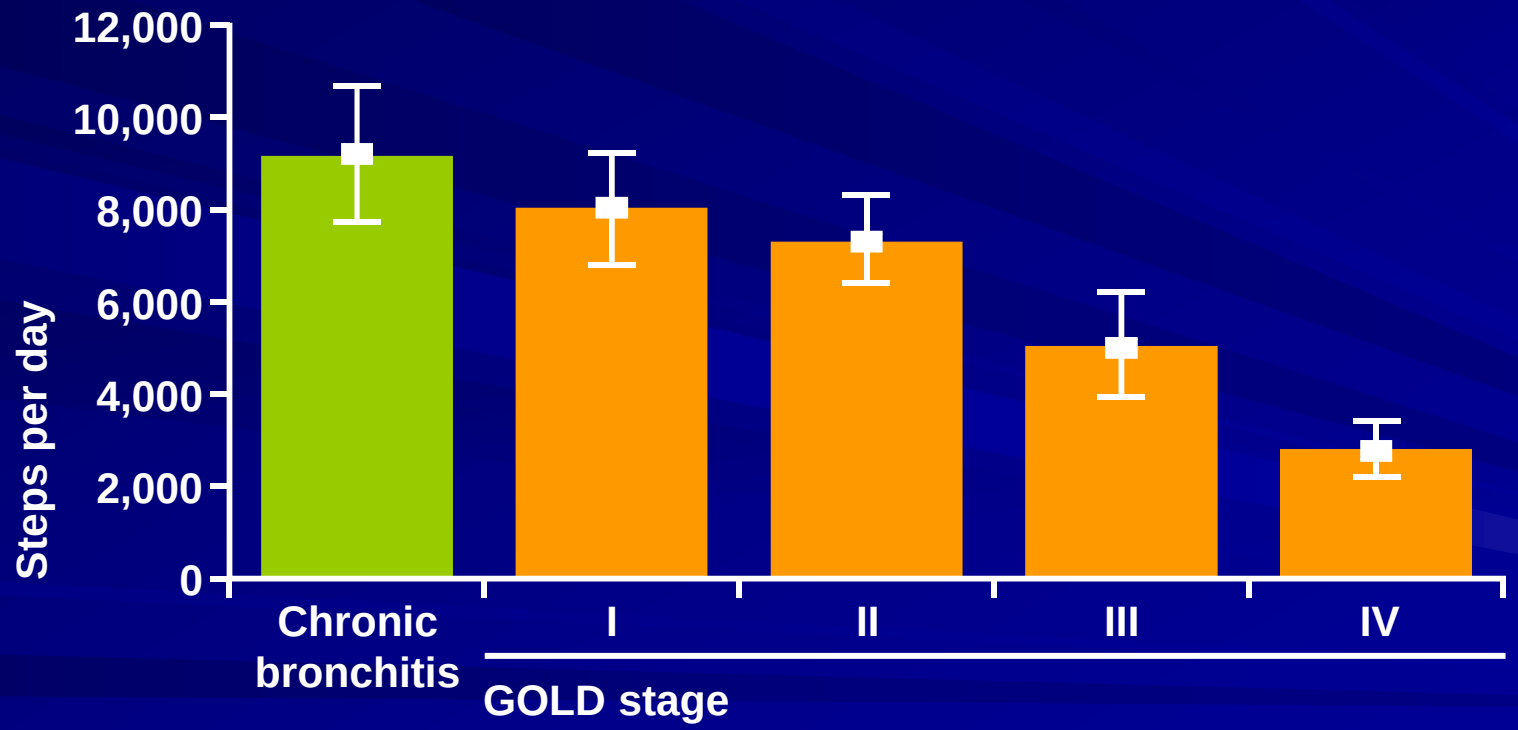
Adjusted decline in FEV_1



Adjusted difference in decline in FEV_1 over 11 years stratified by modified GOLD and symptom categories.
†Prebronchodilator spirometry. Error bars represent 95% confidence intervals

Bridevaux et al. Thorax 2008;63:768–774

COPD leads to a significant reduction in patients' ability to exercise



p<0.001 for linear relationship between steps per day and GOLD stage of severity

Watz, et al. Eur Respir J 200933: 262-272;

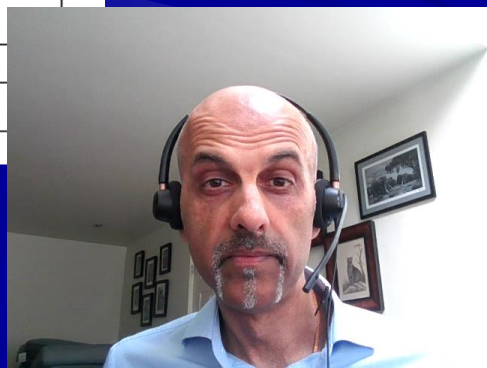
Improving Detection of Early Chronic Obstructive Pulmonary Disease

Wassim W. Labaki and MeiLan K. Han

Please answer each question	No	Yes
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	☐	☐
2. Does your breathing change with seasons, weather, or air quality?	☐	☐
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	☐	☐
4. Compared to others your age, do you tire easily?	☐	☐

	0	1	2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities due to a cold, bronchitis, or pneumonia?	☐	☐	☐

Ann Am Thorac Soc Vol 15, Supplement 4, pp S243–S248, Dec 2018



Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study

Data specific to COPD

Table S3. Multivariable-adjusted hazard ratios (95% confidence intervals) for the development of OLD by eosinophil count categories according to different criteria to identify incident OLD (lung function test, self-reported of a physician-diagnosis, or both)

	Eosinophil count category (cells/μL)				
	<100	100-199	200-299	300-499	≥ 500
Lung function test (pre-bronchodilator $FEV_1/FVC < 70\%$ & $FEV_1 < 80\%$ pred (a)	*Reference*	1.07 (1.00-1.15)	1.30 (1.20-1.42)	1.46 (1.33-1.60)	1.72 (1.51-1.95)
Self-reported of a physician-diagnosis of COPD (b)	*Reference*	1.13 (1.05-1.21)	1.11 (1.02-1.21)	1.25 (1.14-1.37)	1.30 (1.14-1.49)
(a) + (b)	*Reference*	1.11 (1.05-1.16)	1.20 (1.13-1.27)	1.33 (1.24-1.42)	1.49 (1.36-1.64)

Hazard ratios and 95% confidence intervals estimated from parametric proportional hazard models adjusted for age, sex, center, year of screening exam, BMI, smoking, alcohol intake, history of pulmonary tuberculosis, hsCRP and blood neutrophil counts.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; hsCRP, high sensitivity C-reactive protein; disease.

Park HY et al. ERJ 2021 DOI: 10.1183/13993003.03823-2020

Concept

- Active disease needs early treatment

Stop smoking

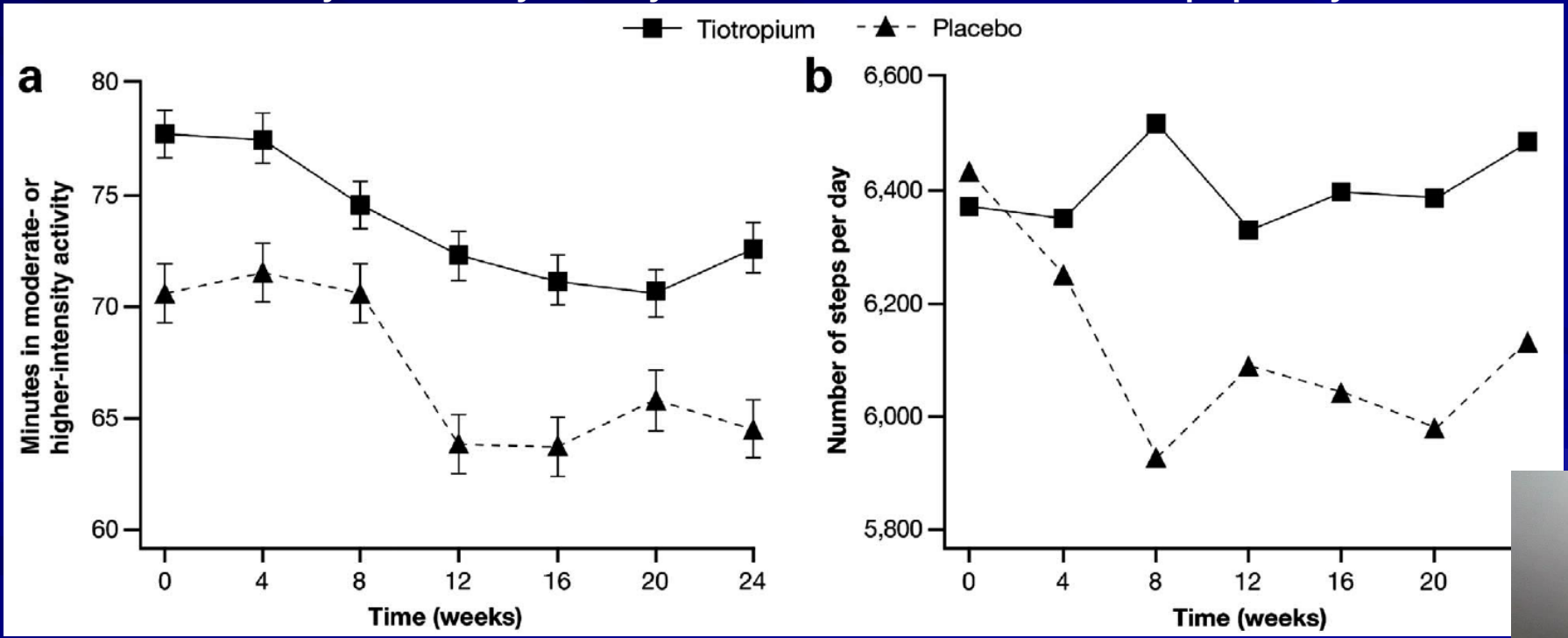
Physical activity

Pharmacotherapy

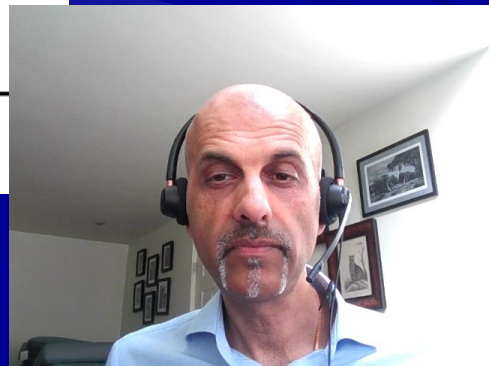
Physical activity in patients receiving tiotropium previously naïve to maintenance therapy

Overall physical activity levels

Physical activity min/day **Steps per day**



Troosters et al. NPJ Prim Care Respir Med. 2014;24:14003. doi: 10.1038/npjpcrm.2014.3



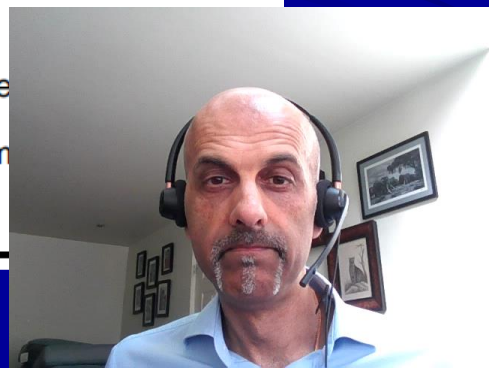
Treatment Trials in Young Patients with Chronic Obstructive Pulmonary Disease and Pre–Chronic Obstructive Pulmonary Disease Patients

Time to Move Forward

Table 5. Future Steps in the Design and Conduct of Intervention Studies of Young Patients with COPD or Those at Risk with Pre-COPD

	Young Patients with COPD	Pre-COPD
Potential outcomes to explore	• Rate of FEV_1 decline • Time to first COPD exacerbation	• Time to onset of COPD • Time to worsening in CAT (1 point) or SGRQ (4 points)
Study duration	• 3 yr	• 3–5 yr
Interim analysis at 6–12 mo (to assess dropping therapy arms and/or extending trial duration/ increase sample size)	• Rate of FEV_1 decline • Time to first COPD exacerbation • CAT change • Composite outcomes*	• Rate of FEV_1 decline • CAT change • E-RS: COPD • Others (impulse oscillometry and/or lung imaging: airways disease parameters; HCRU events; CompEx COPD) • Composite outcomes*
Potential intervention arms	Currently approved medications for COPD	Currently approved medications for COPD as well as novel agents capable of modifying disease progression
Placebo control	No (as these are currently approved medications for airflow limitation with no age limits)	Yes (as these medications are not approved for this indication)
Study population as per the definition in the text (plus some other potential characteristics to consider in the study design to enrich the population studied)	• CAT score >10 • A respiratory HCRU event in 2 of the past 3 yr • Biomarker enrichment†	• Individuals with NOCB symptoms as define CAT or SGRQ • A respiratory HCRU event in the past 24 m • Subjects with rapid FEV_1 decline • Biomarker enrichment†

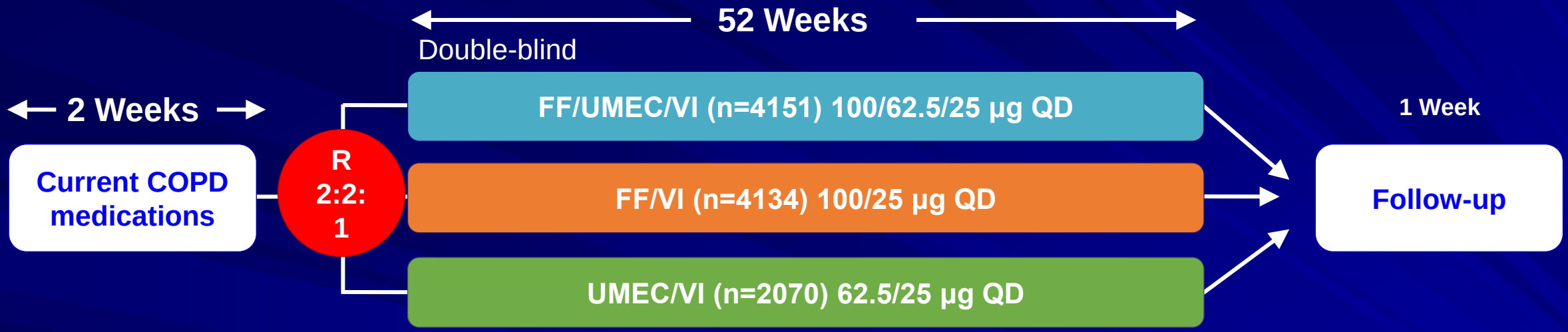
Martinez FJ et al. Am J Respir Crit Care Med. 2022;205(3):275-287.



Challenges

- Early diagnosis
- Lack of clinical trials
- Disease modifying medicines ?

IMPACT study schematic



- Age 40+ and COPD diagnosis (ATS/ERS definition)
- CAT ≥10
- FEV_1 <50% + ≥1 moderate/severe exacerbations in the past year

OR

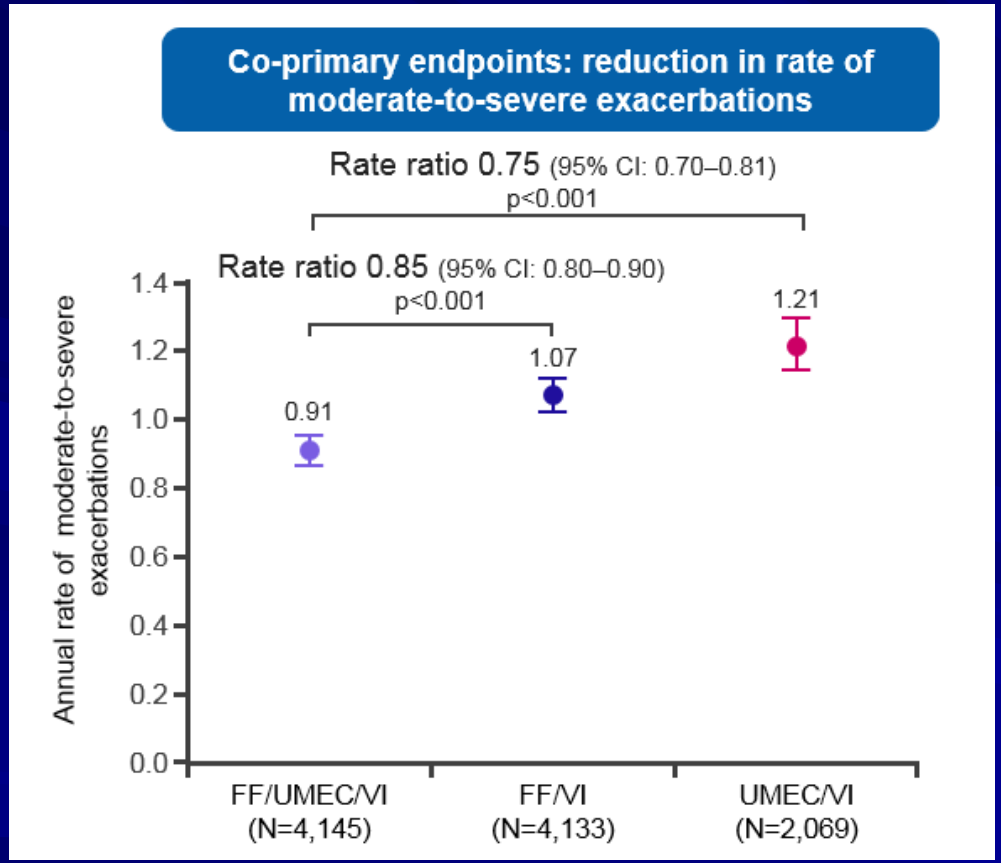
- FEV_1 ≥50% to <80% + ≥2 moderate exacerbations or ≥1 severe exacerbation in the past year

Co-primary treatment comparisons (ITT population)

- Annual rate of moderate/severe exacerbations comparing
  - FF/UMEC/VI with FF/VI
  - FF/UMEC/VI with UMEC/VI

Pascoe SJ, et al. Eur Resp J 2016;48:320–30; *Lipson DA, et al. N Engl J Med 2018;378:1671–80.*

IMPACT: FF/UMEC/VI versus FF/VI and UMEC/VI in patients at high risk of exacerbations



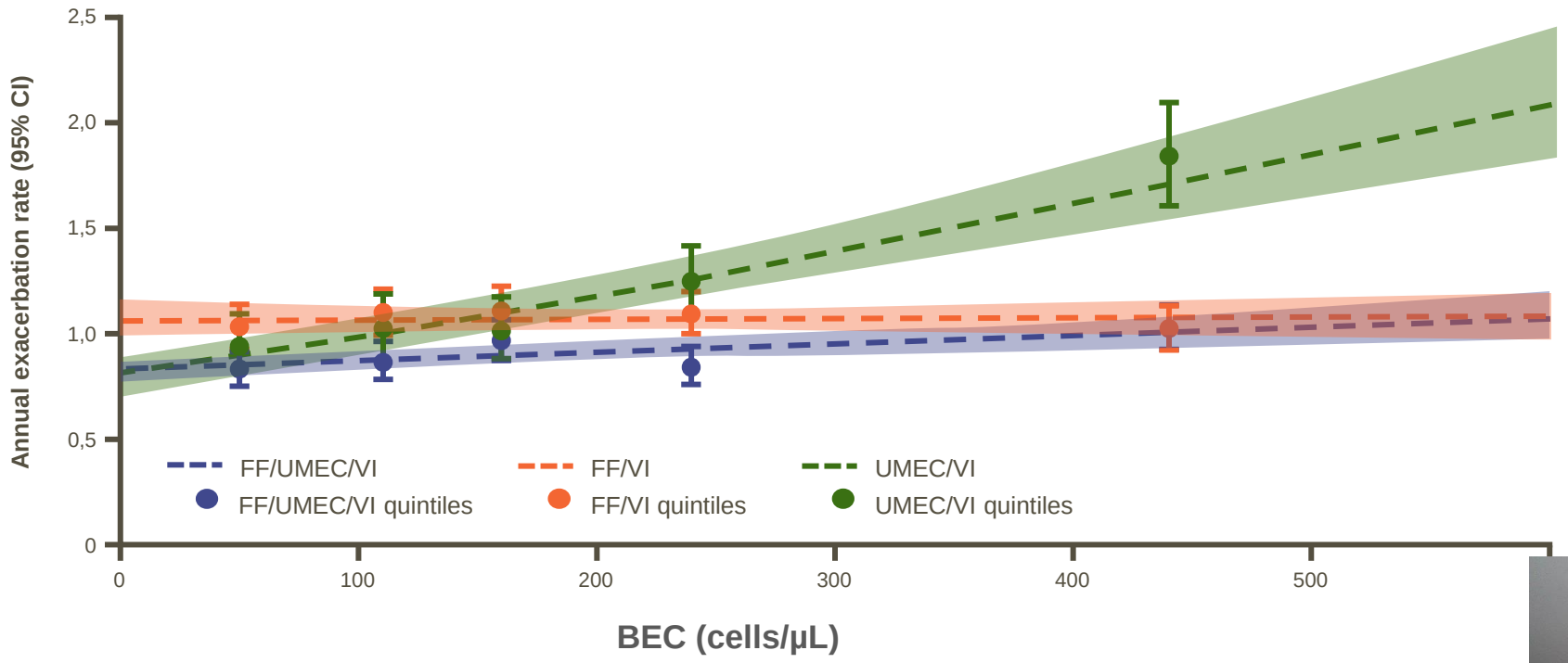
Patients with FEV_1 <50% predicted and ≥1 moderate or severe exacerbation in the previous year, or FEV_1 50–80% predicted and ≥2 moderate or ≥1 severe exacerbation in the previous year. Analysis was in the intention-to-treat population.

FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol

Lipson et al. N Engl J Med 2018; 378: 1671–80

Modelling eosinophil counts in the IMPACT study

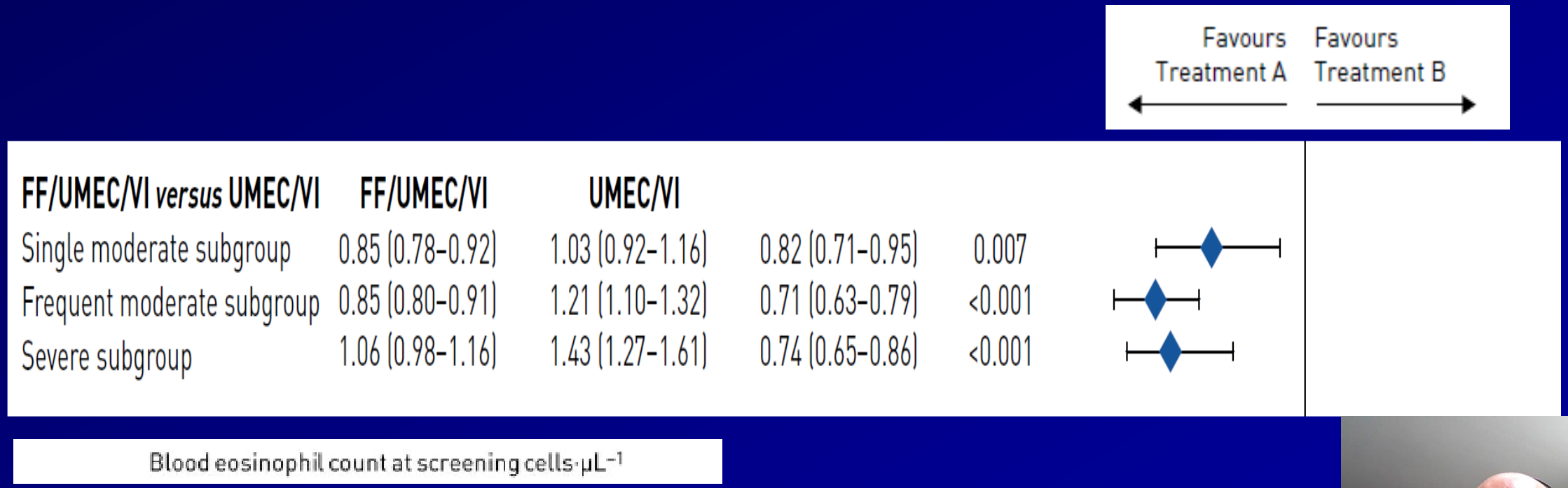
Prospective analysis of IMPACT



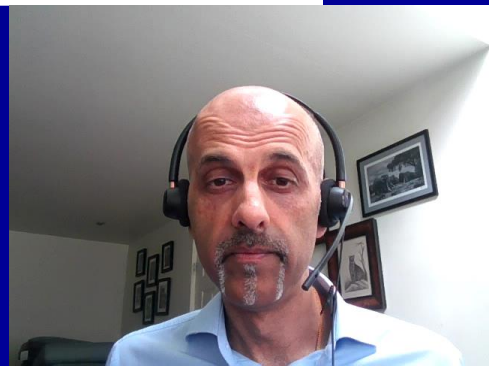
In patients on bronchodilators, exacerbation risk increases as the BEC increases.
In patients treated with ICS, the higher the BEC, the greater the exacerbation reduction.

Pascoe S, et al. Lancet Respir Med. 2019 Sep;7(9):745-756.

The effect of exacerbation history on outcomes on the IMPACT trial

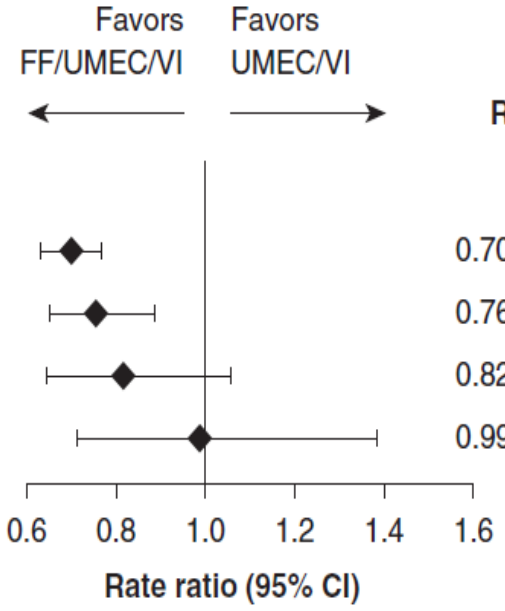


Halpin, D. et al. European Respiratory Journal Jan 2020 55 1901921;

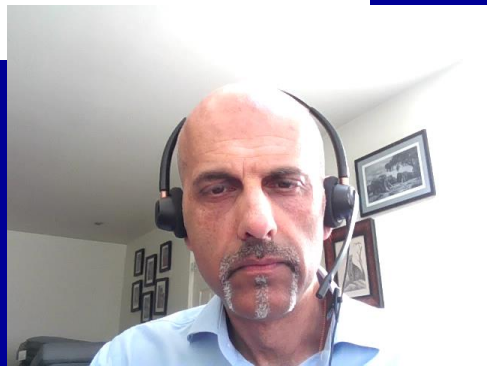


The Effect of Inhaled Corticosteroid Withdrawal and Baseline Inhaled Treatment on Exacerbations in the IMPACT Study

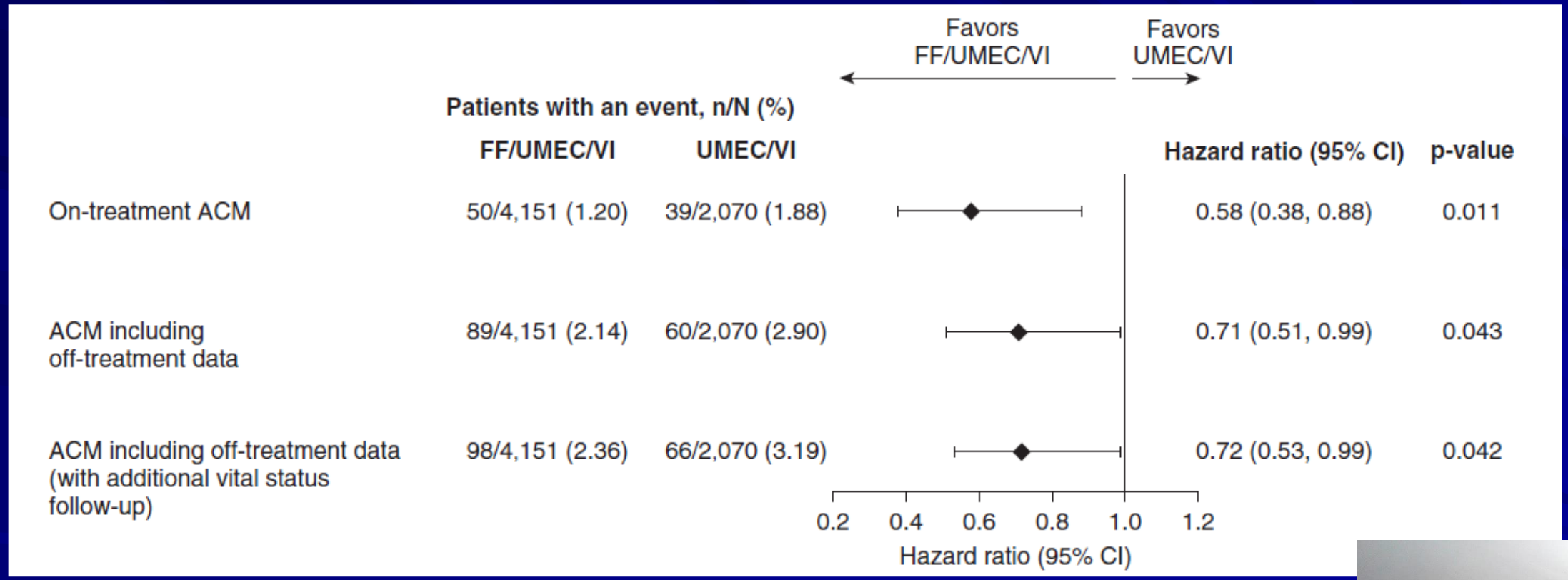
	n (FF/UMEC/VI, UMEC/VI)	Modelled annual rate (95% CI) FF/UMEC/VI	UMEC/VI	Rate ratio (95% CI); p-value	Annual rate reduction, % (95% CI)
ICS+LAMA+LABA	1,580, 826	1.22 (1.15, 1.30)	1.76 (1.61, 1.91)	0.70 (0.63, 0.77); p<0.001	30 (23, 37)
ICS+LABA	1,217, 576	0.71 (0.65, 0.78)	0.93 (0.82, 1.06)	0.76 (0.65, 0.89); p<0.001	24 (11, 35)
LAMA+LABA	359, 186	0.89 (0.77, 1.03)	1.08 (0.88, 1.32)	0.82 (0.64, 1.06); p=0.132	18 (–6, 36)
LAMA	288, 146	0.62 (0.51, 0.75)	0.62 (0.47, 0.82)	0.99 (0.71, 1.39); p=0.964	1 (–39, 29)



Han et al. Am J Respir Crit Care Med. Nov 1;202(9):1237-1243.

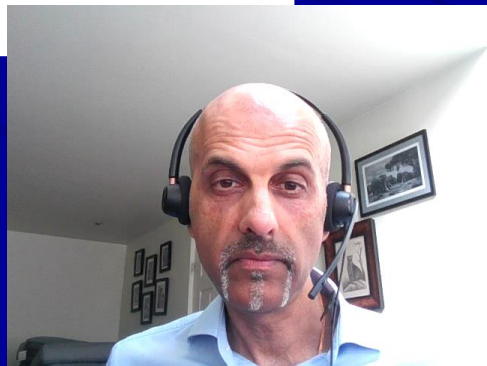


All cause mortality (ACM) in the IMPACT study

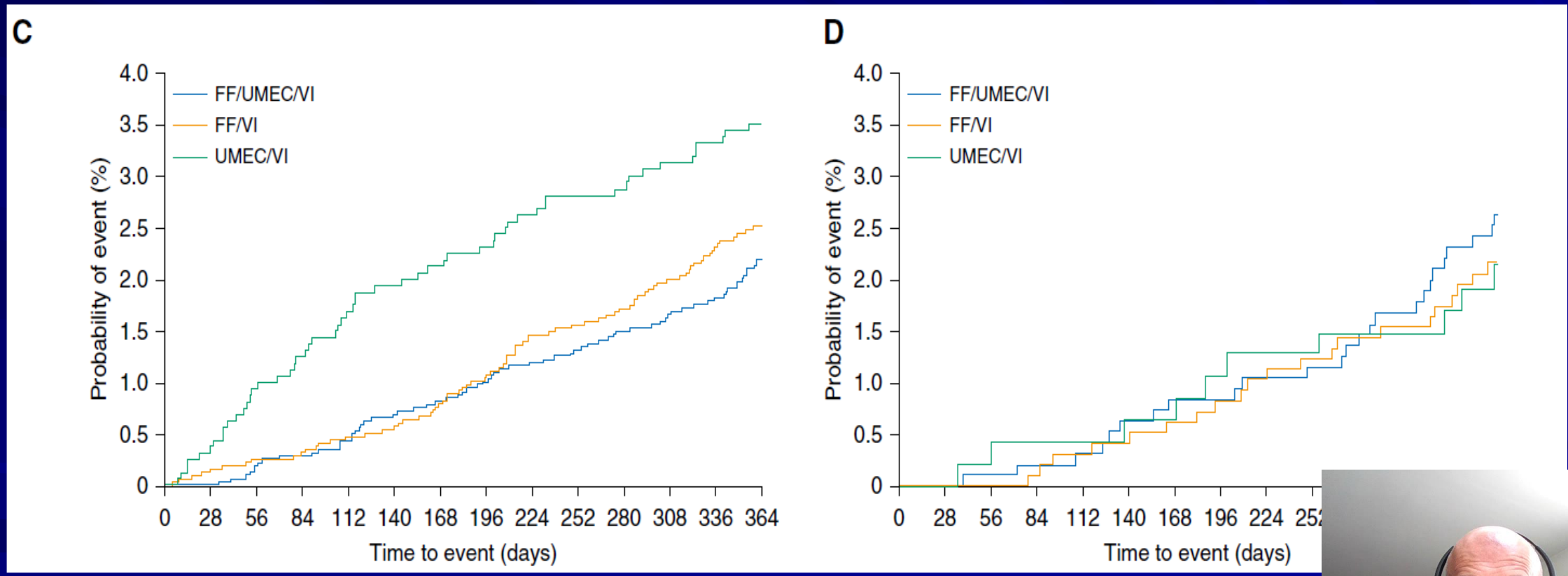


Forest plot of ACM analyses and hazard ratios FF/UMEC/VI versus UMEC/VI.
ACM: all-cause mortality; CI: confidence interval; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

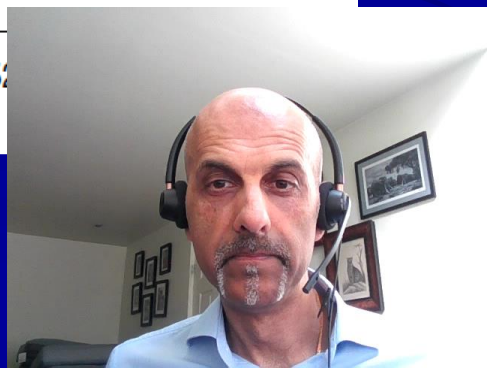
Lipson et al. Am J Respir Crit Care Med. 2020 Jun 15;201(12):1508-1516.



Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease

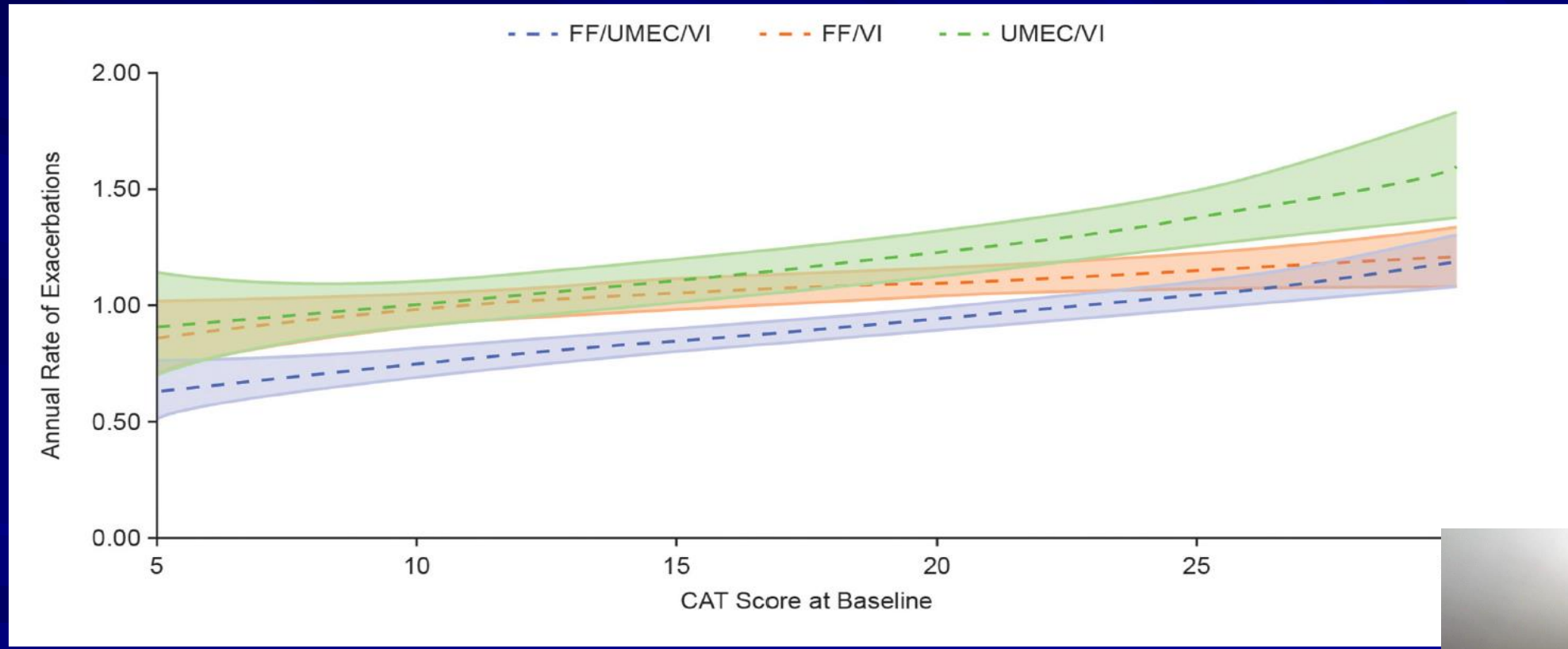


Lipson et al. Am J Respir Crit Care Med. 2020 Jun 15;201(12):1508-1516.

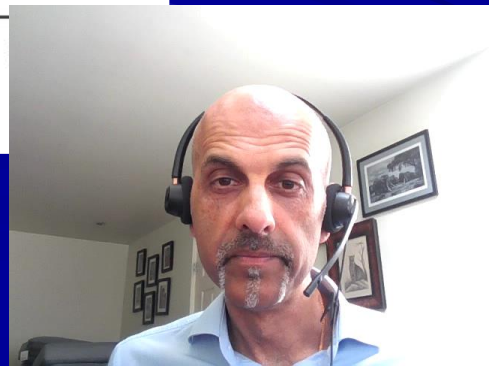


Higher COPD Assessment Test Score Associated With Greater Exacerbations Risk: A Post Hoc Analysis of the IMPACT Trial

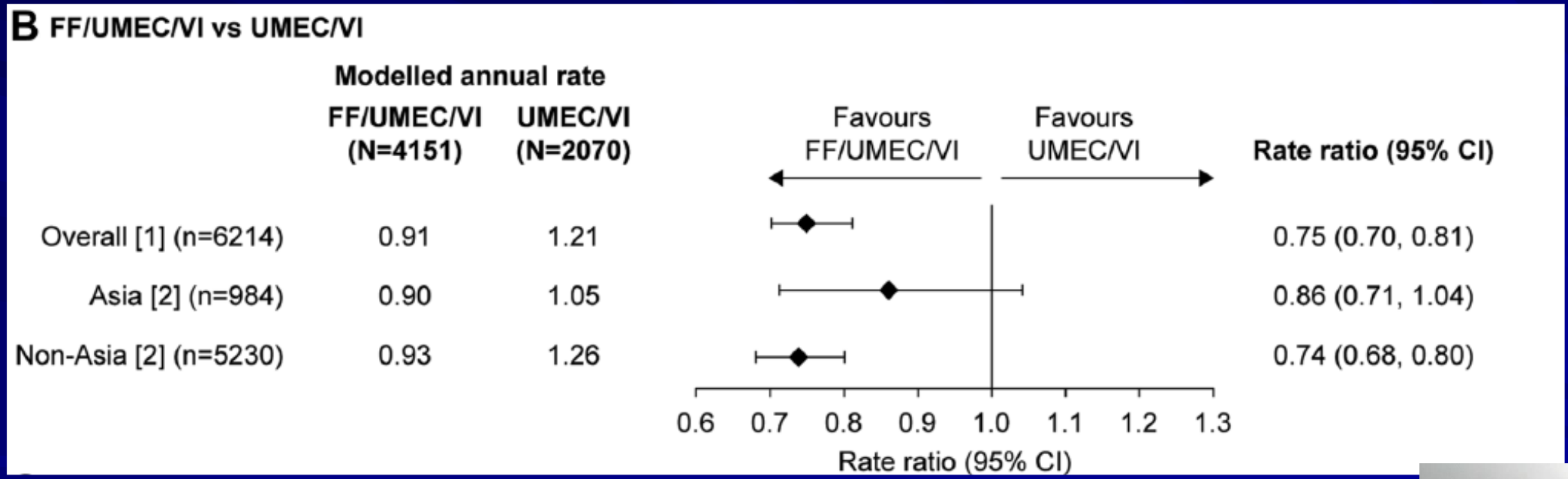
Journal of the COPD Foundation®



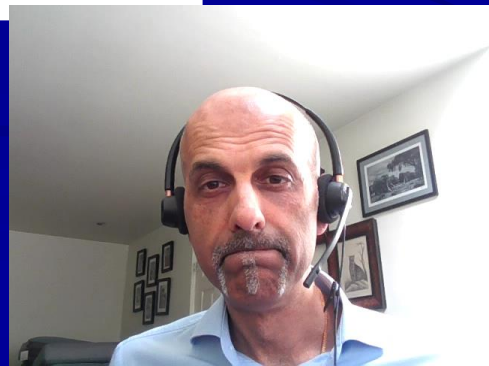
Thomashow et al, JCOPDF, 2022; 9: 68-79



Triple Versus Dual Combination Therapy in Chronic Obstructive Pulmonary Disease in Asian Countries: Analysis of the IMPACT Trial



Halpin D et al, Pulm Ther (2021) 7:101-118

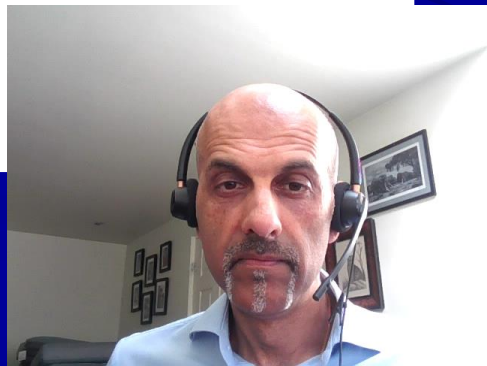


Triple Versus Dual Combination Therapy in Chronic Obstructive Pulmonary Disease in Asian Countries: Analysis of the IMPACT Trial

Table 2 Rates of radiological investigation and pneumonia in patients treated with FF/UMEC/VI, FF/VI and UMEC/VI in Asia and the non-Asia regions

	FF/UMEC/VI		FF/VI		UMEC/VI	
	Asia $N = 654$	Non-Asia $N = 3497$	Asia $N = 660$	Non-Asia $N = 3474$	Asia $N = 330$	Non-Asia $N = 1740$
Number of patients with investigator-reported pneumonia, *n* (%)	88 (13)	224 (6)	92 (14)	190 (5)	19 (6)	76 (4)
Number of patients with investigator-reported pneumonia supported by infiltrate on CXR/CT, *n* (%)	47 (7)	107 (3)	59 (9)	88 (3)	11 (3)	29 (2)

Halpin D et al, Pulm Ther (2021) 7:101-118



IMPACT summary

- Triple therapy reduces exacerbations and prevents mortality versus LAMA/LABA
- Clinical benefits in IMPACT were influenced by:
  - Exacerbation history
  - Previous inhaled treatment
  - Blood eosinophils
  - CAT score