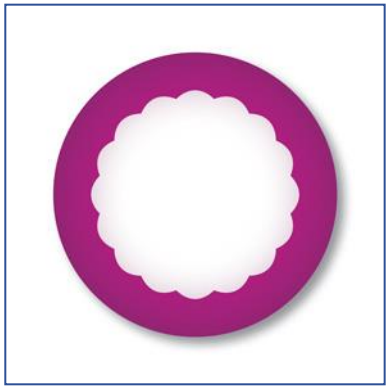
Pneumo Update Europe 2016

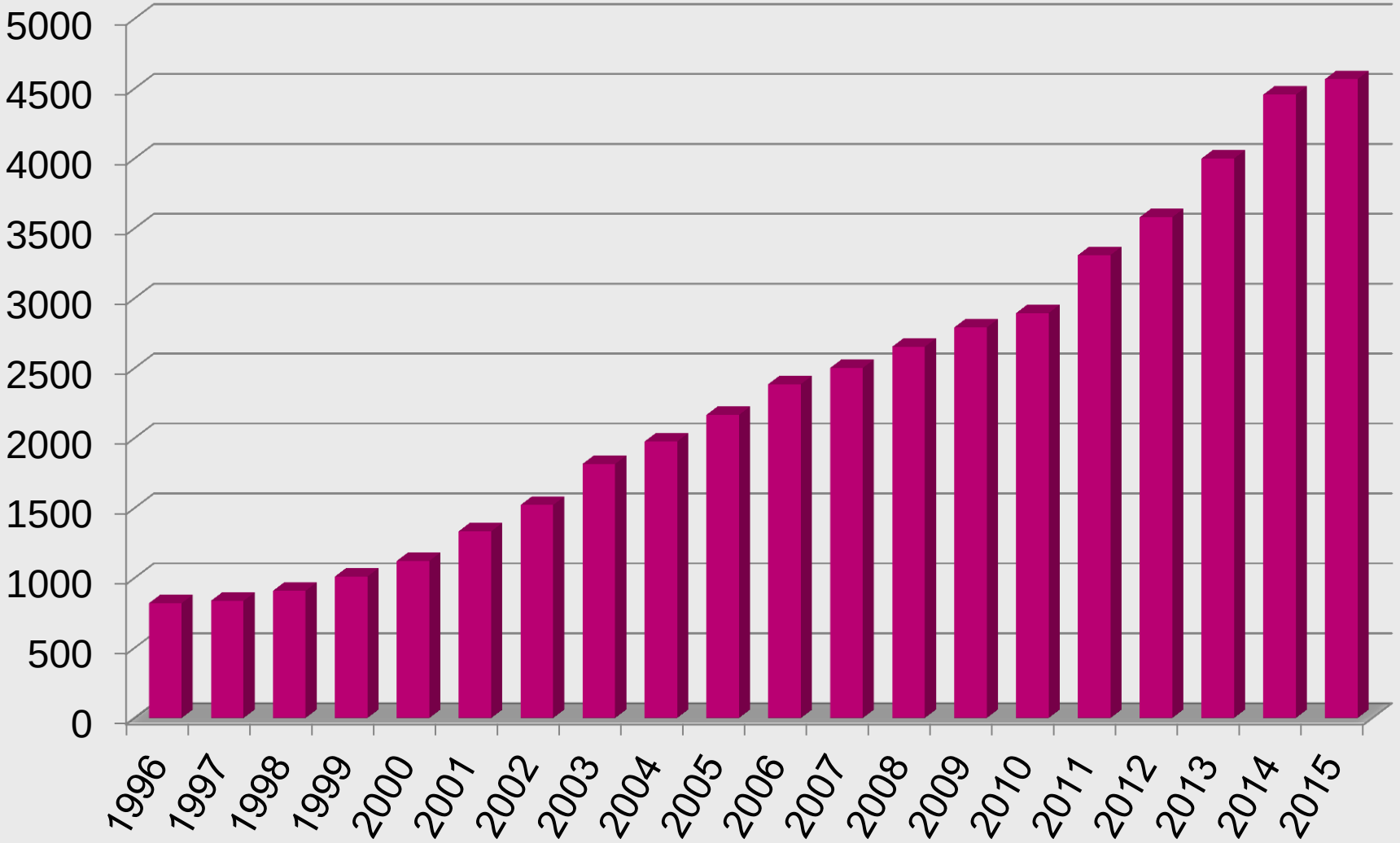
24-25 June, Prague

COPD



David M. G. Halpin, UK

PubMed Citations for COPD



Not Included

- Non-invasive ventilation
- Bronchoscopic Techniques

Outline

- Definitions & Diagnoses
- Early disease
- Biomarkers
- Exacerbations
- Telehealth
- Co-morbidities
- Pharmacotherapy

Definitions & Diagnoses

Treatable traits: toward precision medicine of chronic airway diseases

Alvar Agusti[1], Elisabeth Bel[2], Mike Thomas[3], Claus Vogelmeier[4], Guy Brusselle[5,6], Stephen Holgate[7], Marc Humbert[8], Paul Jones[9], Peter G. Gibson[10], Jørgen Vestbo[11], Richard Beasley[12] and Ian D. Pavord[13]

Precision medicine is defined as **"**treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations**"**.

- Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent chronic airway diseases
- They likely represent a continuum of different diseases that may
  - share biological mechanisms (i.e. endotypes),
  - present similar clinical, functional, imaging and/or biological features that can be observed (i.e. phenotypes)
  - require individualised treatment.
- Pulmonary Treatable Traits
- Extrapulmonary treatable traits of airway diseases
- Treatable behaviour/lifestyle risk factors of airway diseases

European Respiratory Journal. 2016;47(2):410-9

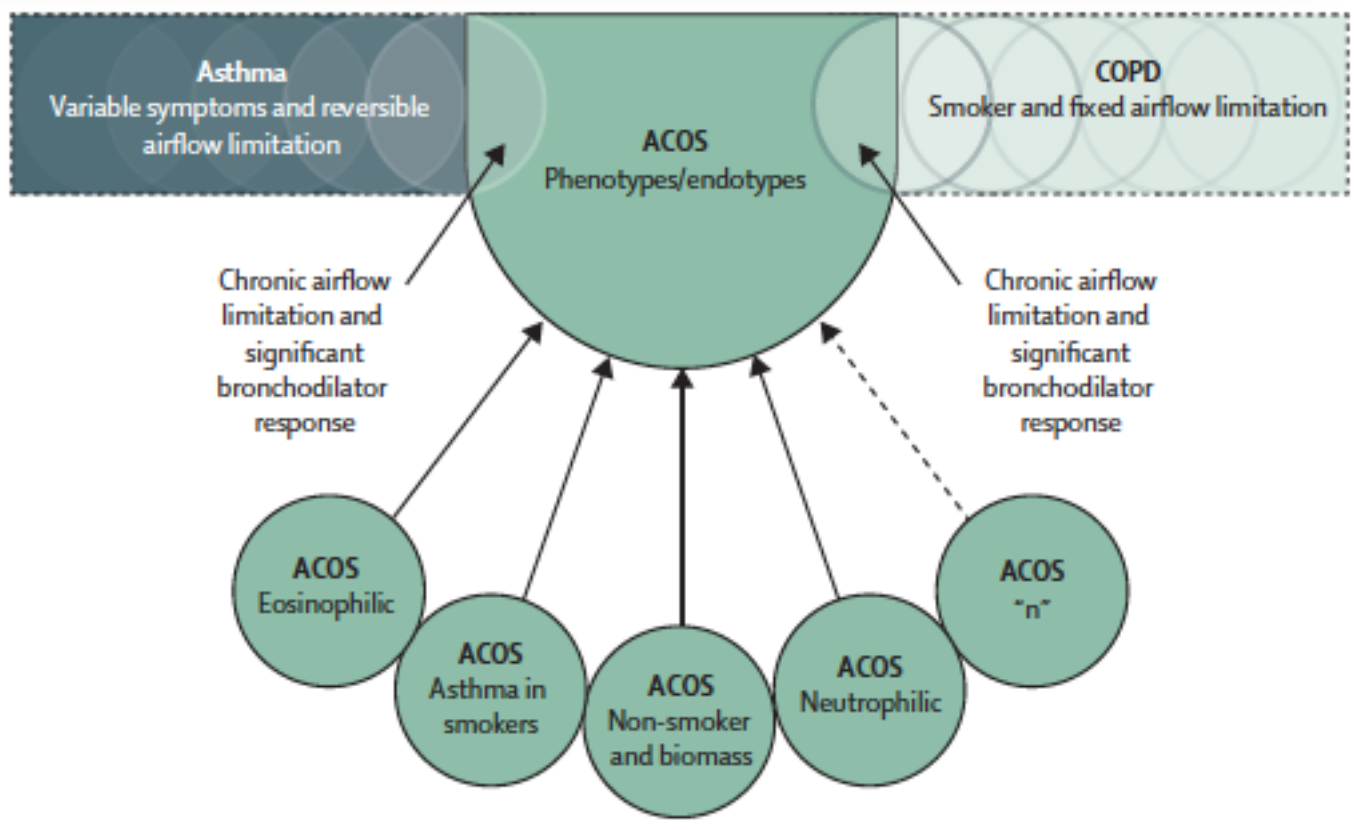
TABLE 1 Pulmonary treatable traits of airway diseases

Treatable traits (can coexist)	Imp.	Rec.	Diagnostic criteria	Treatment			Main expected benefit
				First choice	Efficacy	Second choice	
Airflow limitation [9]	+++	+++	FEV_1/FVC <0.7 (or lower limit of normal)				S
Airway smooth muscle contraction	++	+++	Bronchodilator reversibility, peak expiratory flow variability, positive PC20	Maintenance: long-acting β_2-adrenergic agonists/muscarinic antagonists; rescue: short-acting β_2-adrenergic agonists/muscarinic antagonists	+++	Inhaled corticosteroids, *bronchial thermoplasty*[#]	S
Loss of elastic recoil (emphysema)	+++	++	Chest computed tomography, *DLCO*, compliance	Smoking cessation	+	Lung volume reduction surgery, lung transplantation, α_1-anti-trypsin replacement if deficient, valves, *coils*	S, P
Airway mucosal oedema	++	+	*Chest computed tomography, spirometry-induced bronchoconstriction*	Inhaled corticosteroids	++	Oral corticosteroids, *anti-interleukin-5, -13, -4*	E
Eosinophilic airway inflammation [55, 56]	+++	+++	Sputum eosinophils, blood eosinophils, F_{ENO}, (*periostin*)	Inhaled corticosteroids	+++	Oral corticosteroids, leukotriene receptor antagonists, anti-IgE, *anti-interleukin-5, -13, -4*	E
Chronic bronchitis	++	+++	Cough and sputum 3 months×2 years (no eosinophilic airway inflammation)	Smoking cessation	+	Carbocysteine, macrolides, roflumilast	E
Airway bacterial colonisation[*]	++	++	Sputum culture, *quantitative PCR*	Antibiotics	++	*Long-term low-dose macrolides*, vaccination	E/S
Bronchiectasis[*]	++	++	Chest computed tomography	Drainage	+	Macrolides, nebulised antibiotics, surgery, vaccination	E/S
Cough reflex hypersensitivity [49, 57]	++	+++	Capsaicin challenge, cough counts, cough questionnaire	Speech and language treatment [58]	+	*Gabapentin* [56]	S
Pre-capillary pulmonary hypertension[*]	++	++	Doppler echocardiography, brain natriuretic peptide, right heart catheterisation	Long-term (domiciliary) oxygen therapy	++	Noninvasive ventilation, lung transplantation	S, E, P
Chronic respiratory failure[*]							
Arterial hypoxaemia	+++	+++	P_{aO_2} <55 mmHg	Long-term (domiciliary) oxygen therapy	++		P
Arterial hypercapnia	+++	+++	P_{aCO_2} >45 mmHg		+	Noninvasive ventilation, lung transplantation	

European Respiratory Journal. 2016;47(2):410-9

The asthma–COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases?

Eric D Bateman, Helen K Reddel, Richard N van Zyl-Smit, Alvar Agusti



Lancet Respir Med 2015; 3: 719–28

A comparison of COPD patients with and without ACOS in the ECLIPSE study

ACOS = Yes to question **“**Have you ever had asthma?**”** **(**493/1976 (25%))

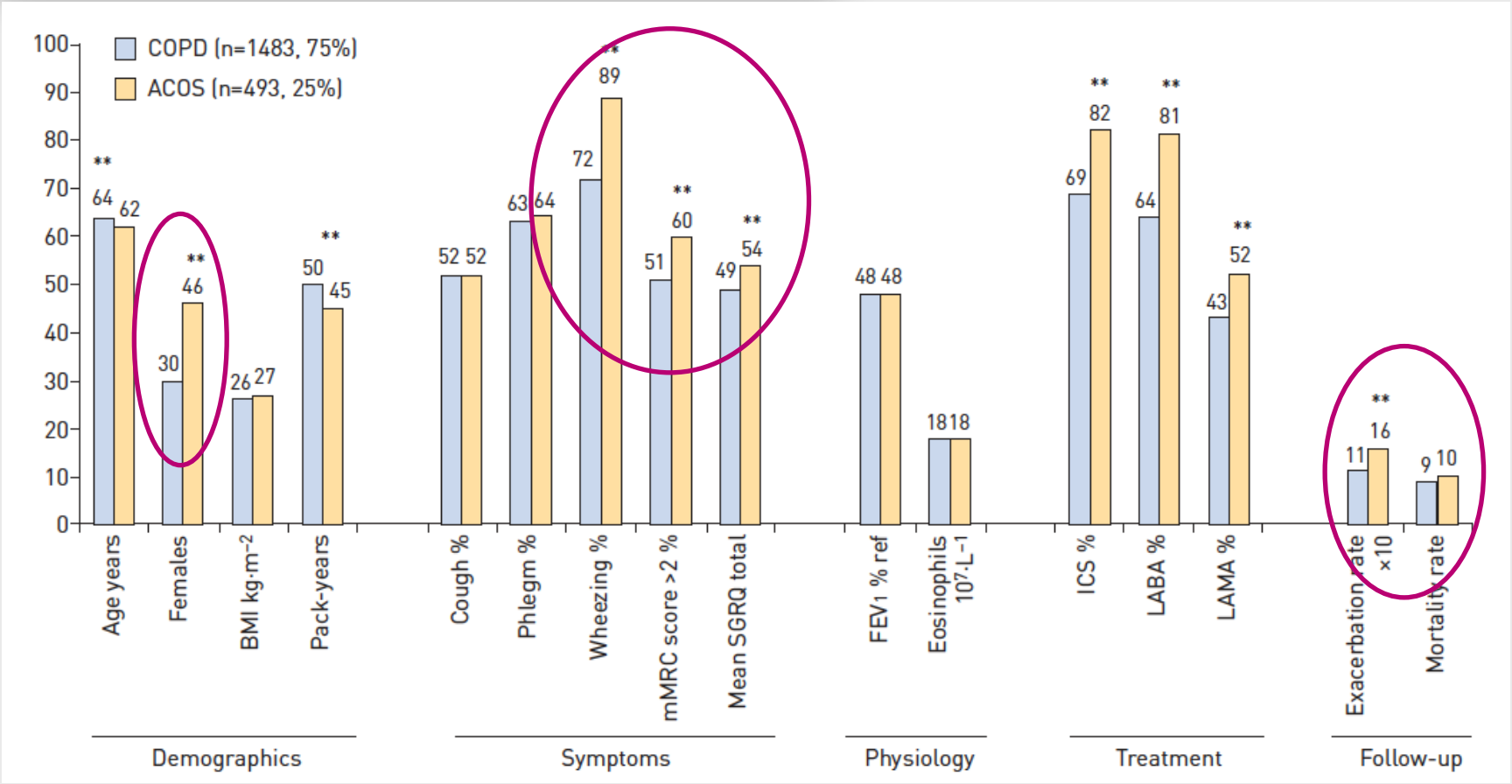
Five additional features of airways disease in conjunction to ACOS:

1. bronchodilator reversibility at recruitment (Δ FEV1 ⩾12% and ⩾200 mL)
2. presence of current asthma (affirmative answer to two questions: **“**Have you ever had asthma?**”** and **“**Do you still have it?**”**)
3. presence of wheeze (affirmative answer to the question **“**Does your chest ever sounds wheezy or whistling?**”**)
4. presence of atopy (affirmative answer to the question **“**Have you ever had hay fever?**”**);
5. presence of both wheeze and atopy.

Primary definition was not sensitive to the addition of specific clinical criteria related to asthma.

European Respiratory Journal. 2016. Epub 2016/03/19

A comparison of COPD patients with and without ACOS in the ECLIPSE study



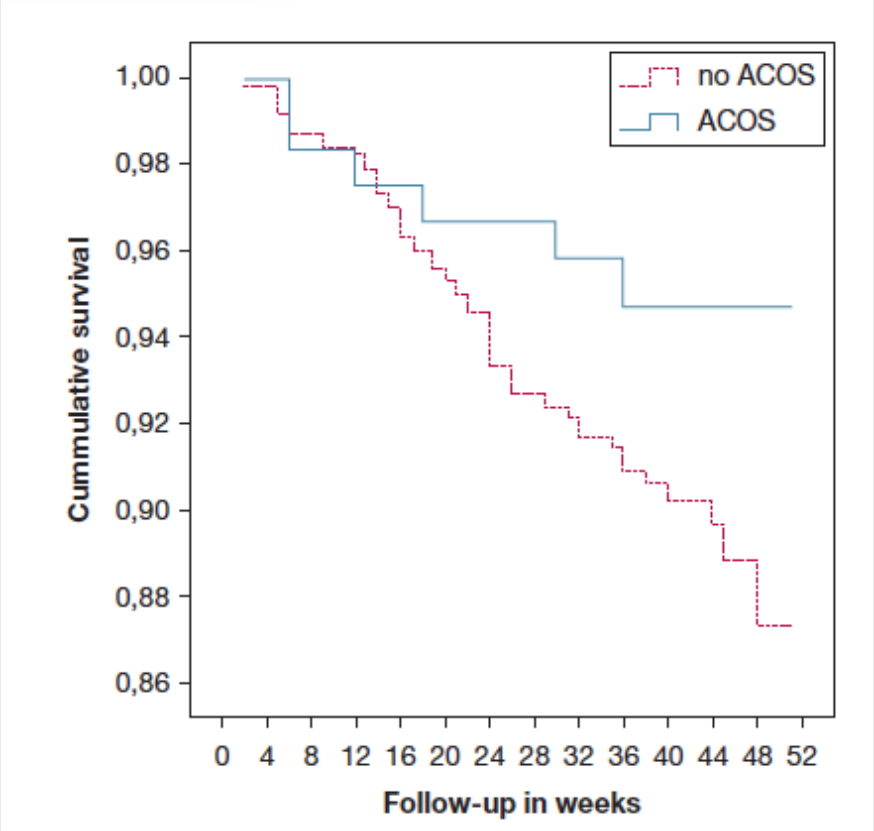
European Respiratory Journal. 2016. Epub 2016/03/19

Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort

Borja G. Cosio, MD; Joan B. Soriano, MD; Jose Luis López-Campos, MD; Myriam Calle-Rubio, MD; Juan José Soler-Cataluna, MD; Juan P. de-Torres, MD; Jose M. Marín, MD; Cristina Martínez-Gonzalez, MD; Pilar de Lucas, MD; Isabel Mir, MD; Germán Peces-Barba, MD; Nuria Feu-Collado, MD; Ingrid Solanes, MD; Inmaculada Alfageme, MD; and Ciro Casanova, MD; on behalf of the CHAIN Study

831 patients with COPD
125 (15%) met criteria for ACOS

Major Criteria	Minor Criteria
Previous history of asthma	IgE > 100 IU, or
Bronchodilator response to salbutamol > 15% and 400 mL	History of atopy,
	2 separated bronchodilator responses to salbutamol > 12% and 200 mL
	Blood eosinophils > 5%



Patients with ACOS:

- were mostly male (81.6%),
- had symptomatic mild to moderate disease (67%),
- were receiving ICS (63.2%)
- had better prognosis

CHEST 2016; 149(1):45-52

Asthma, COPD and overlap syndrome: a longitudinal study in young European adults

Roberto de Marco[1], Alessandro Marcon[1], Andrea Rossi[2], Josep M. Antó[3,4,5,6], Isa Cerveri[7], Thorarinn Gislason[8], Joachim Heinrich[9,10], Christer Janson[11], Deborah Jarvis[12], Nino Kuenzli[13,14], Bénédicte Leynaert[15], Nicole Probst-Hensch[13,14], Cecilie Svanes[16,17], Matthias Wjst[18,19] and Peter Burney[12]

Young adults in European Community Respiratory Health Survey
asthma = 941, COPD = 166, ACOS = 218, none of these = 5659

- Subjects with ACOS shared risk factors & clinical characteristics with subjects with asthma alone, but they had an earlier age of asthma onset.
- Asthmatics more likely to be female (61%) ACOS & COPD less likely (48%)
- Prevalence of lifetime and heavy smoking (>15 pack-years) was comparable in “healthy” (55 and 27%) and asthma (57 and 30%), a little higher in ACOS (64 and 35%) and highest in COPD (72 and 52%)
- FEV1 change in the ACOS group (−25.9 mL·year−1) was similar to that in the asthma group (−25.3 mL·year−1), and lower ($p<0.001$) than in the COPD group (−37.3 mL·year−1).
- ACOS was associated with the highest hospitalisation rate

European Respiratory Journal. 2015;46(3):671-9

Review

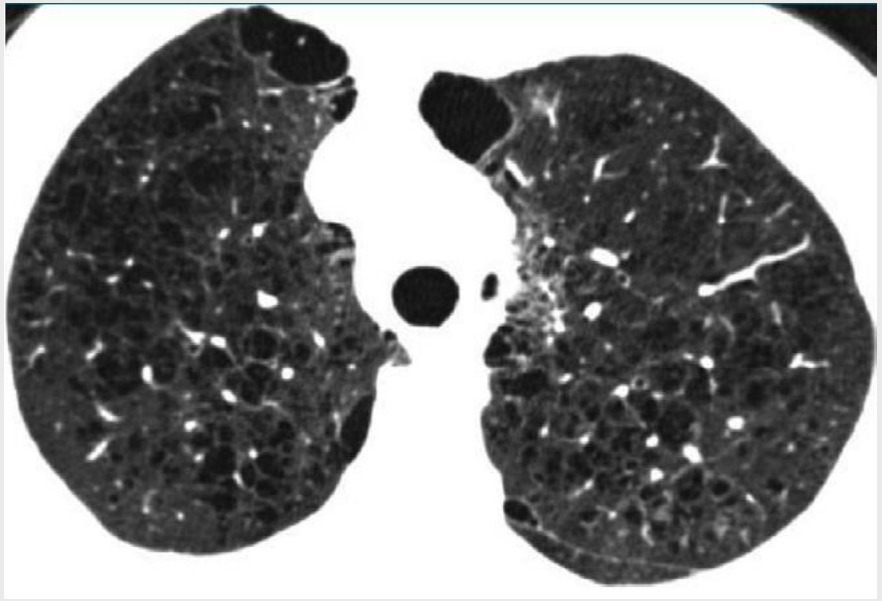
Asthma–COPD overlap 2015: *now we are six*

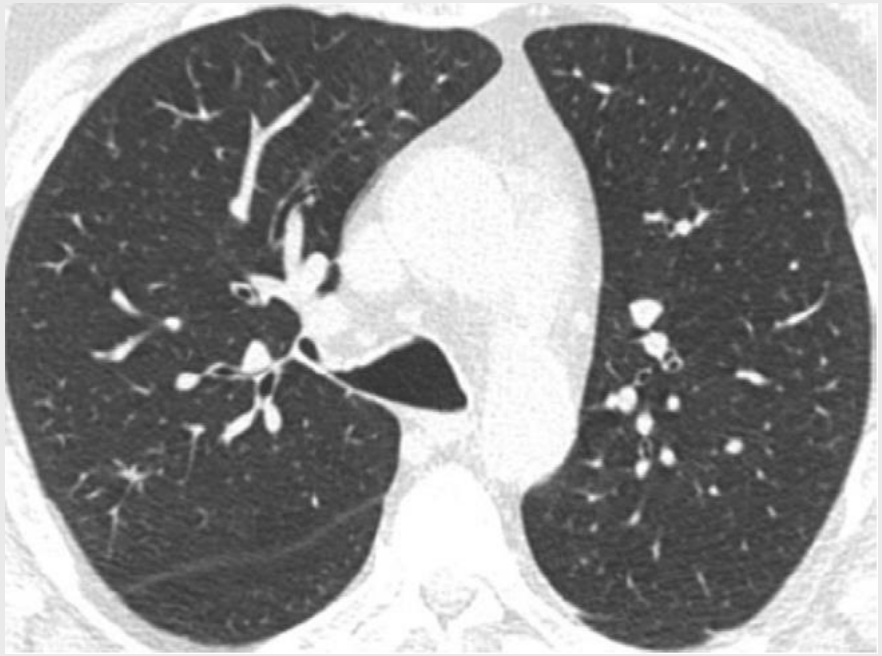
Peter G Gibson,[1,2] Vanessa M McDonald[1,2]

- Consistently recognised in studies using a variety of different study designs and sampling.
- Prevalence was approximately 20% in obstructive airways diseases.
- Increased morbidity & possibly an increased mortality & comorbidity.
- Heterogeneous pattern of airway inflammation
- Systemic inflammation was present and resembles COPD
- Evidence of different subgroups
- Can have its origins in childhood
- Using bronchodilator responsiveness does not separate ACOS & COPD
- Guidelines generally recommend a serial approach to assessment,
- Treatment recommendations dominated by an asthma paradigm.

Thorax 2015;70:683–691

CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society[1]





Radiology. 2015;277(1):192-205

Emphysema*

1. **Centrilobular Emphysema:** the dominant pattern should be scored
   a. **Trace Centrilobular Emphysema (CLE):** minimal centrilobular lucencies, occupying < 0.5% of a lung zone.
   b. **Mild CLE:** scattered centrilobular lucencies, usually separated by large regions of normal lung, involving an estimated 0.5-5% of a lung zone.
   c. **Moderate CLE:** many well-defined centrilobular lucencies, occupying more than 5% of any lung zone.
   d. **Confluent CLE:** coalescent centrilobular or lobular lucencies, including multiple regions of lucencies that span several secondary pulmonary lobules, but not involving extensive hyperexpansion of secondary pulmonary lobules or distortion of pulmonary architecture.
   e. **Advanced Destructive Emphysema (ADE):** panlobular lucencies, with hyperexpansion of secondary pulmonary lobules and distortion of pulmonary architecture.
2. **Panlobular Emphysema**
   Associated with A1AT Deficiency: most commonly, a lower lobe predominant pattern involving generalized destruction of all acini more or less equally.
3. **Paraseptal Emphysema**
   a. **Mild Paraseptal Emphysema (PSE):** small (≤1 cm), well-demarcated rounded juxtapleural lucencies, aligned in a row along a pleural margin, sometimes including along an interlobar fissure, and sometimes including a few small rounded lucencies immedi ately central to the juxtapleural lucencies.
   b. **Substantial Paraseptal Emphysema:** mainly large (>1 cm diameter) juxtapleural cyst-like lucencies or bullae, involving more than the lung apices, aligned in a row along a pleural margin, and sometimes including adjacent to an interlobar fissure.

Airway Disease

Airway disease is commonly found with all forms of emphysema, but also commonly occurs in the absence of emphysema as a predominant expression of COPD.

1. **Bronchial Disease:** Thickening of walls of segmental and subsegmental airways.
2. **Small Airway Disease (SAD):** Inflammatory SAD can be directly identified on CT scan by the presence of peripheral centrilobular micronodular opacities. Obstructive SAD is identified by gas trapping on expiratory CT, or FEV1/FVC ratio < 0.7, in the absence of significant emphysema.

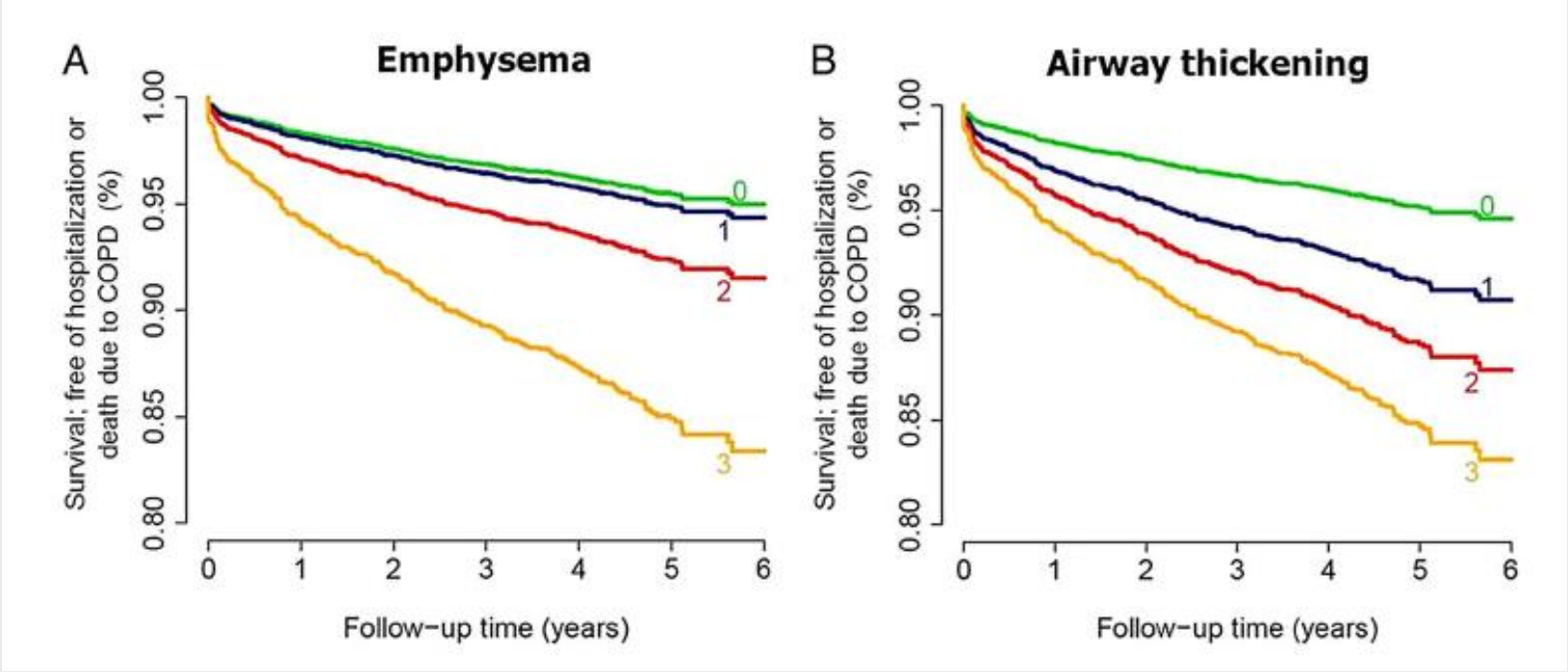
Associated Features

1. **Large Airway Disease:** Tracheobronchomalacia, saber sheath trachea, tracheobronchial outpouching/diverticula.
2. **Interstitial Lung Abnormality**: Patchy ground glass abnormality, mild subpleural reticular abnormality.
3. **Pulmonary Arterial Enlargement:** Enlargement of the pulmonary artery, suggesting pulmonary hypertension, occurs in advanced COPD, and a ratio of the pulmonary artery diameter to the aorta diameter >1 has been associated with increased risk of COPD exacerbation.
4. **Bronchiectasis**

Radiology. 2015;277(1):192-205

Incidental findings on chest CT imaging are associated with increased COPD exacerbations and mortality

Pushpa M Jairam,[1,2] Yolanda van der Graaf,[1] Jan-Willem J Lammers,[3] Willem P Th M Mali,[2] Pim A de Jong,[2] on behalf of the PROVIDI Study group



Thorax 2015;70:725–731

Take-Home Message

Treatable traits is a more useful concept than phenotypes

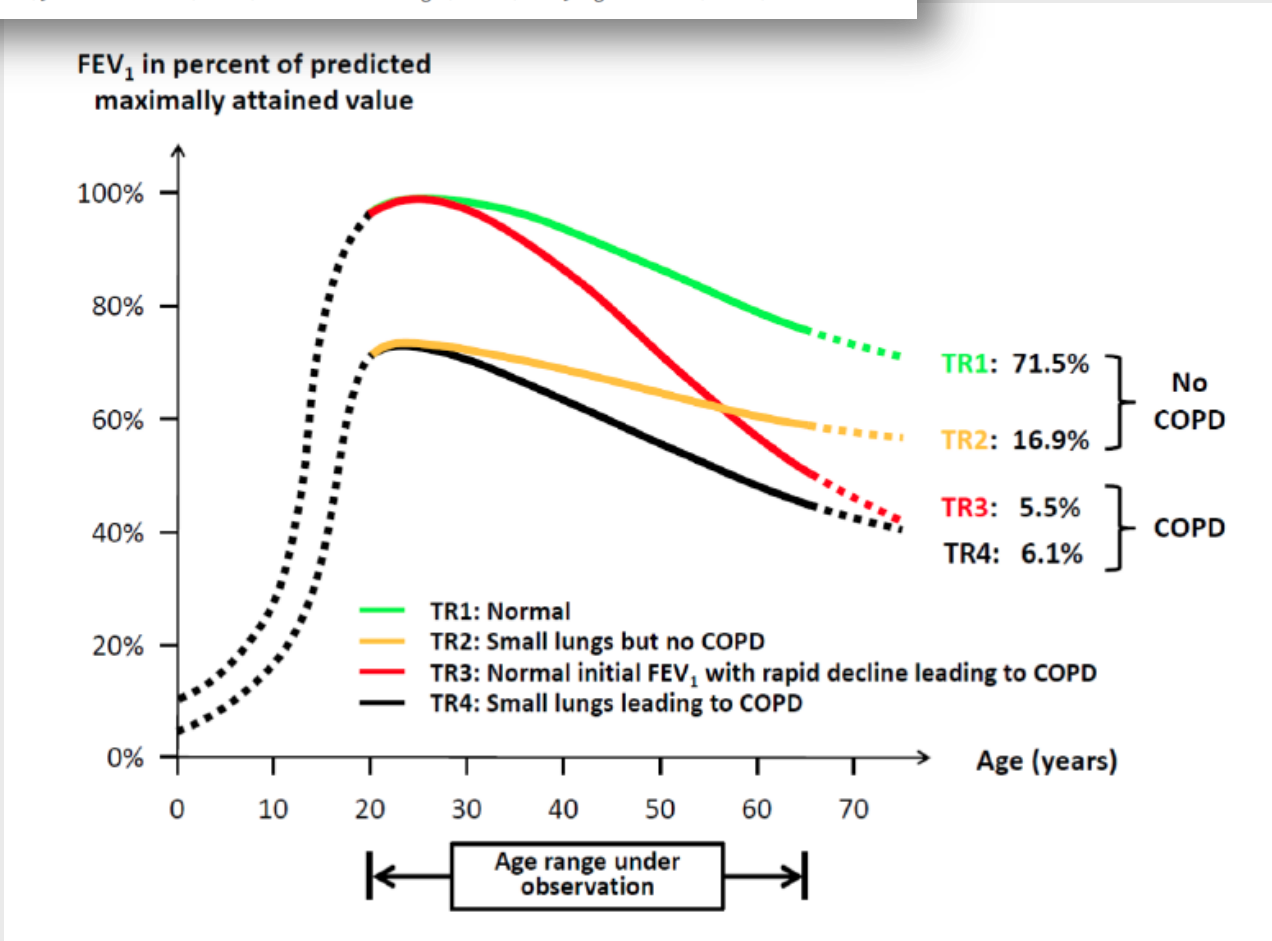
ACOS does exist but defintions vary making studies confusing

Incidental findings on CT matter

Origins, Early disease & Natural History

Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease

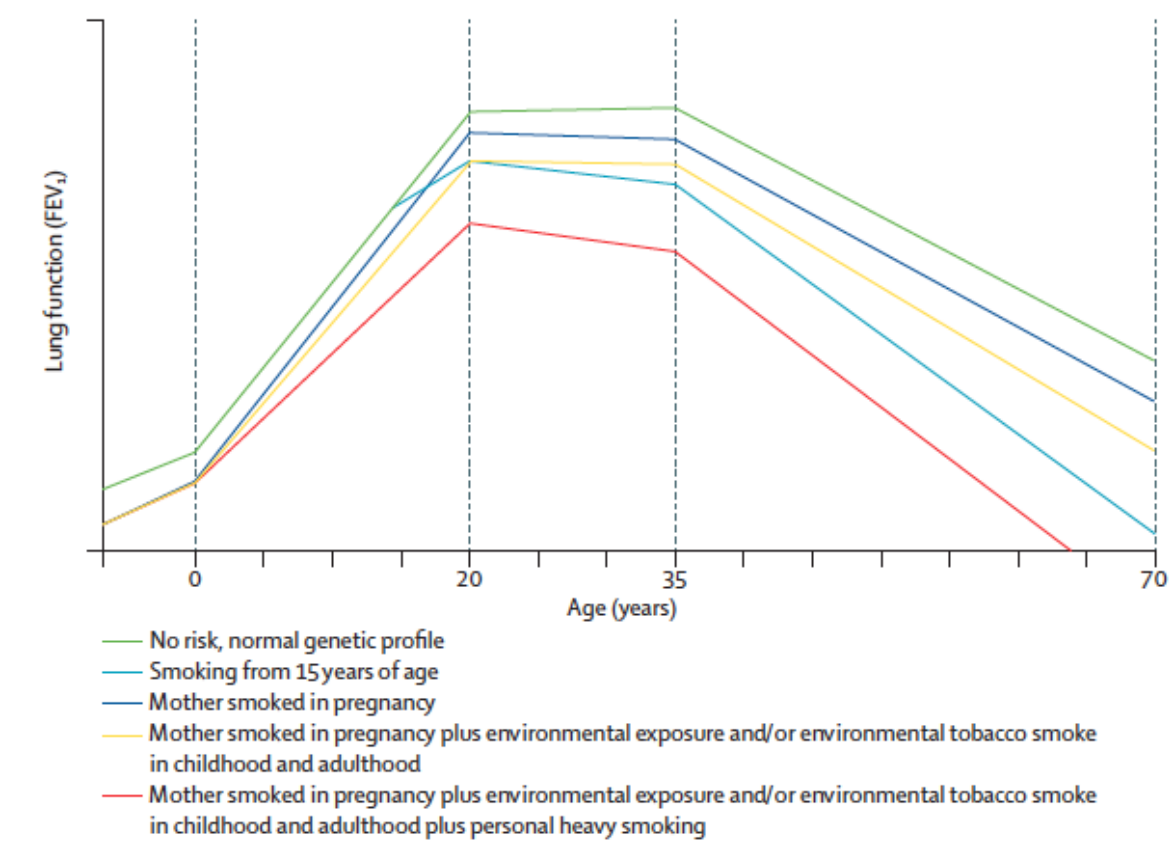
Peter Lange, M.D., Dr. Med. Sc., Bartolome Celli, M.D., Alvar Agustí, M.D., Ph.D., Gorm Boje Jensen, M.D., Dr. Med. Sc., Miguel Divo, M.D., Rosa Faner, Ph.D., Stefano Guerra, M.D., Ph.D., Jacob Louis Marott, M.Sc., Fernando D. Martinez, M.D., Pablo Martinez-Camblor, Ph.D., Paula Meek, R.N., Ph.D., Caroline A. Owen, M.D., Ph.D., Hans Petersen, Ph.D, Victor Pinto-Plata, M.D., Peter Schnohr, M.D., Dr. Med. Sc., Akshay Sood, M.D., M.P.H., Joan B. Soriano, M.D., Yohannes Tesfaigzi, Ph.D., and Jørgen Vestbo, M.D., Dr. Med. Sc.



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

Risk factors and early origins of chronic obstructive pulmonary disease

Dirkje S Postma, Andrew Bush, Maarten van den Berge



Lancet 2015; 385: 899–909

Risk factors and early origins of chronic obstructive pulmonary disease

Dirkje S Postma, Andrew Bush, Maarten van den Berge

Host factors

- Family history of chronic obstructive pulmonary disease
- Family history of asthma/atopy
- Genetic constitution
- Maternal exposure to air pollution
- Antibiotic use
- Mode of delivery
- Preterm birth

Childhood exposures

- Respiratory tract infections
- Maternal smoking
- Indoor and outdoor air pollution
- Indoor biomass exposure
- Cigarette smoking
- Outdoor air pollution
- Indoor air pollution

it is clearly no longer justifiable to state that COPD is a disease of old age. It has its origins before birth and in early childhood, where every effort must be made to ensure that lung health is preserved

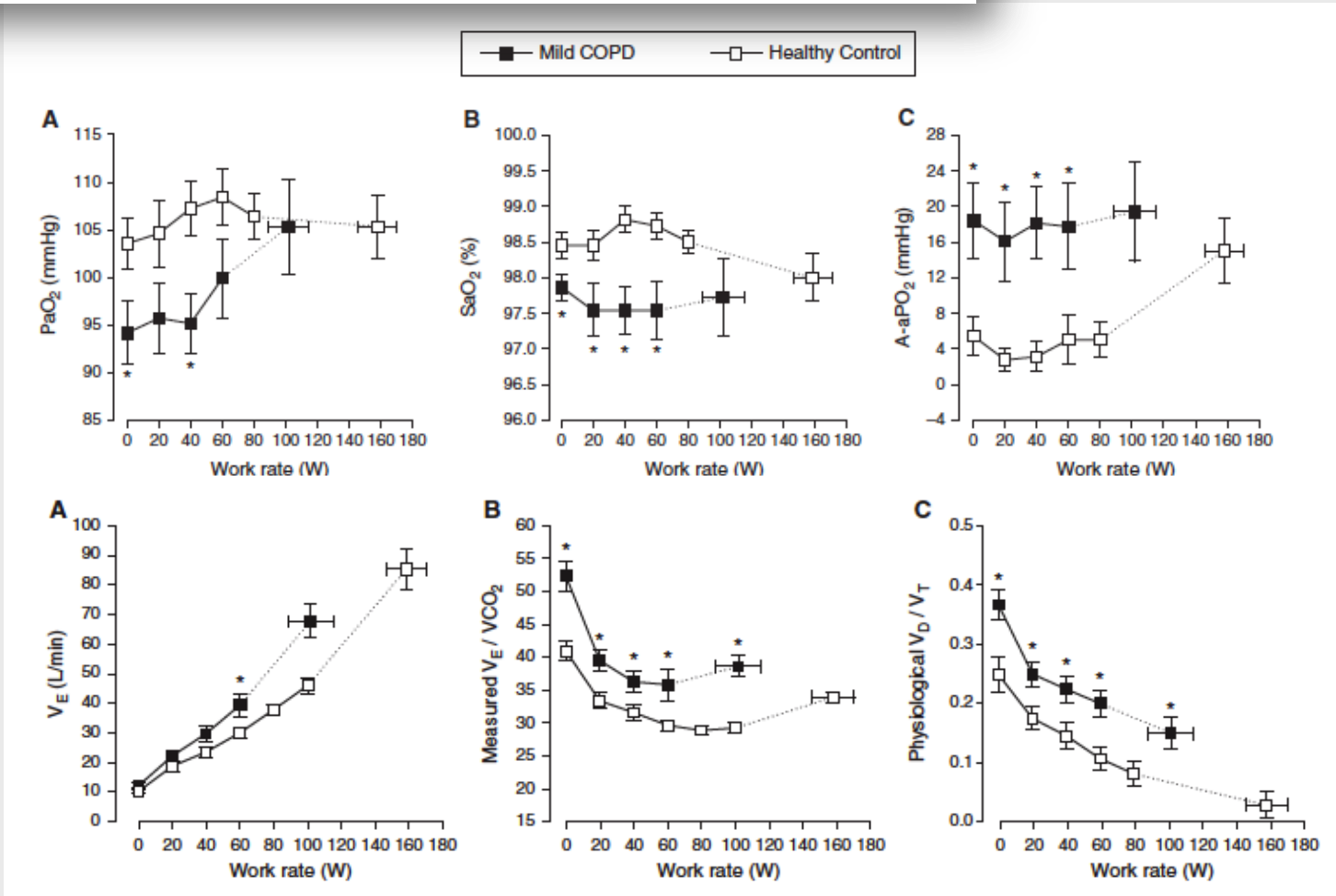
Lancet 2015; 385: 899–909

Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease

Implications for Dyspnea and Exercise Intolerance

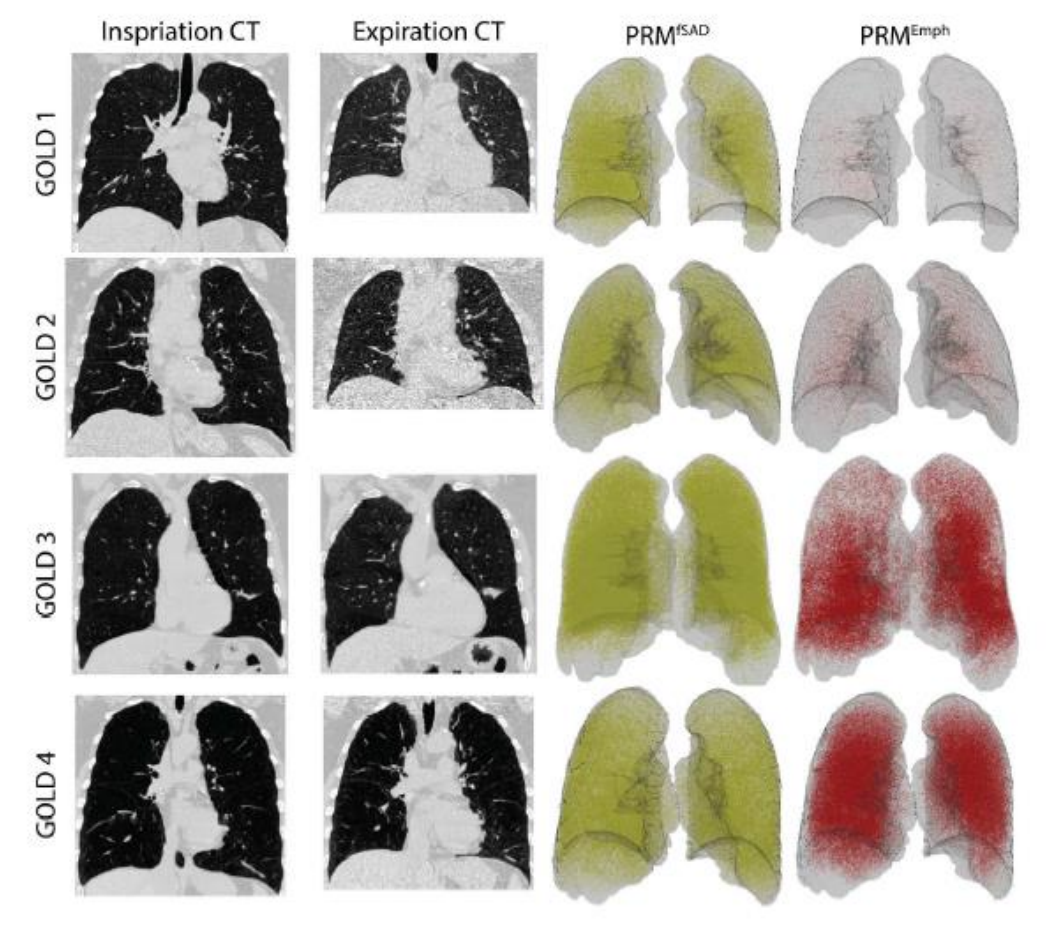
Amany F. Elbehairy[1,2], Casey E. Ciavaglia[1], Katherine A. Webb[1], Jordan A. Guenette[3], Dennis Jensen[4], Sahar M. Mourad[2], J. Alberto Neder[1], and Denis E. O'Donnell[1]; on behalf of the Canadian Respiratory Research Network

FEV1: 94±10% pred



Am J Respir Crit Care Med 2015;191:1384–1394

Association between functional small airways disease and FEV1 decline in COPD



"Both CT assessed functional small airways disease and emphysema are associated with FEV1 decline

the association with functional small airways disease has greatest importance in mild-to-moderate stage COPD where the rate of FEV1 decline is the greatest."

Am J Respir Crit Care Med 2016. Epub 2016/01/26

Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study

Raphaëlle Varraso,[1,2] Stephanie E Chiuve,[3,4] Teresa T Fung,[4,5] R Graham Barr,[6] Frank B Hu,[4,7,8] Walter C Willett,[4,7,8] Carlos A Camargo,[7,8,9]

	Women				Men		
AHEI-2010	No	Person years	Hazard ratio (95% CI)*	No	Person years	Hazard ratio (95% CI)*	No
Lowest fifth§	198	221 312	1.00 (referent)	53	103 567	1.00 (referent)	251
Second fifth	168	226 830	0.98 (0.80 to 1.21)	27	104 165	0.61 (0.38 to 0.97)	195
Third fifth	161	228 007	1.01 (0.81 to 1.25)	34	104 398	0.85 (0.55 to 1.33)	195
Fourth fifth	104	229 754	0.70 (0.54 to 0.89)	33	104 817	0.90 (0.57 to 1.43)	137
Highest fifth§	92	231 204	0.69 (0.53 to 0.90)	20	104 818	0.60 (0.34 to 1.03)	112
P for trend			<0.001			0.27	

Fish intake and risk of chronic obstructive pulmonary disease in 2 large US cohorts[1–4]

Raphaëlle Varraso, R Graham Barr, Walter C Willett, Frank E Speizer, and Carlos A Camargo Jr.

After adjustment for the dietary no significant associations were shown between PUFA intakes and risk of COPD.

BMJ 2015;350:h286
Am J Clin Nutr 2015;101:354–61

Take-Home Message

Some COPD has it‘s origins at an early age

„Mild“ airflow obstruction is associated with significant gas exchange abnormalities

Small airways dysfunction may contribute to development of emphysema

Diet influences risk of developing COPD

Exacerbations

Prevention of Acute Exacerbations of COPD

American College of Chest Physicians and Canadian Thoracic Society Guideline

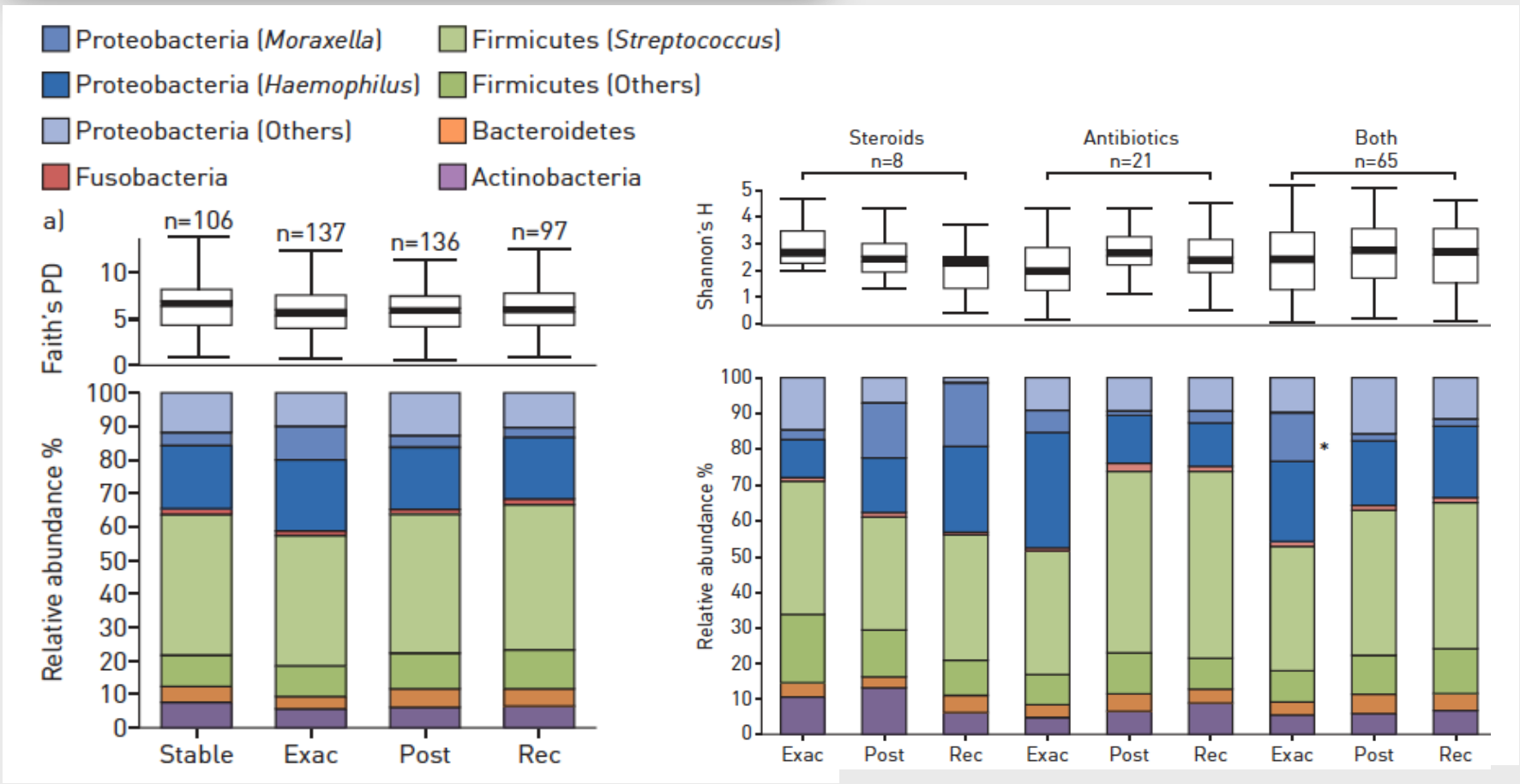
Gerard J. Criner, MD, FCCP; Jean Bourbeau, MD, FCCP; Rebecca L. Diekemper, MPH; Daniel R. Ouellette, MD, FCCP; Donna Goodridge, RN, PhD; Paul Hernandez, MDCM; Kristen Curren, MA; Meyer S. Balter, MD, FCCP; Mohit Bhutani, MD, FCCP; Pat G. Camp, PhD, PT; Bartolome R. Celli, MD, FCCP; Gail Dechman, PhD, PT; Mark T. Dransfield, MD; Stanley B. Fiel, MD, FCCP; Marilyn G. Foreman, MD, FCCP; Nicola A. Hanania, MD, FCCP; Belinda K. Ireland, MD; Nathaniel Marchetti, DO, FCCP; Darcy D. Marciniuk, MD, FCCP; Richard A. Mularski, MD, MSHS, MCR, FCCP; Joseph Ornelas, MS; Jeremy D. Road, MD; and Michael K. Stickland, PhD

PODCAST

Chest. 2015;147(4):883-93

Lung microbiome dynamics in COPD exacerbations

Zhang Wang[1,7], Mona Bafadhel[2,7], Koirobi Haldar[3,6], Aaron Spivak[1], David Mayhew[1], Bruce E. Miller[4], Ruth Tal-Singer[4], Sebastian L. Johnston[5], Mohammadali Yavari Ramsheh[3], Michael R. Barer[3], Christopher E. Brightling[3,6,8] and James R. Brown[1,8]



Eur Respir J 2016; 47: 1082–1092

Take-Home Message

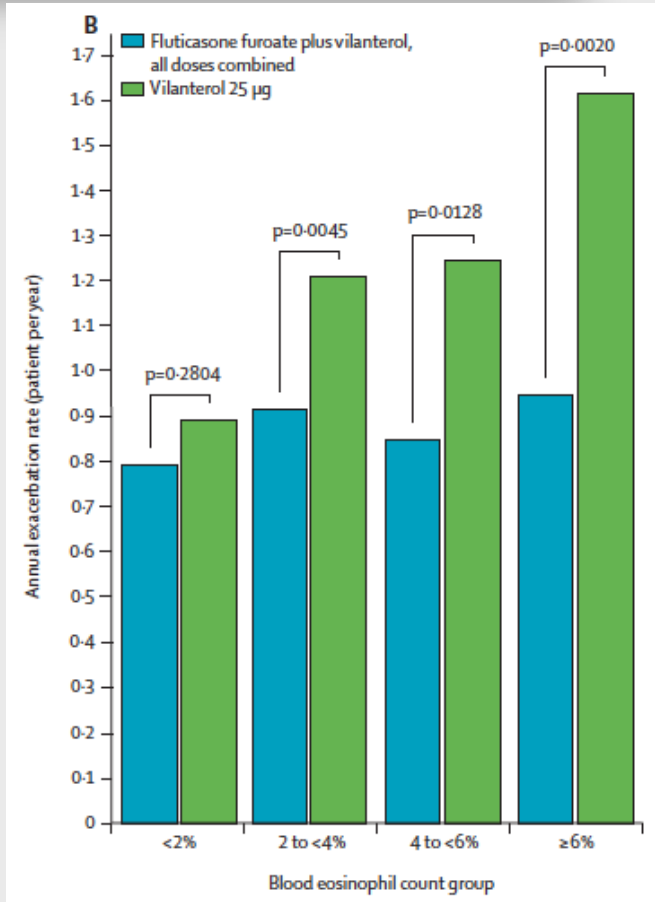
Exacerbations are significant events and prevention is important

Better understanding of the microbiome may lead to more effective treatments: precision medicine

Biomarkers

Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials

Steven Pascoe, Nicholas Locantore, Mark T Dransfield, Neil C Barnes, Ian D Pavord

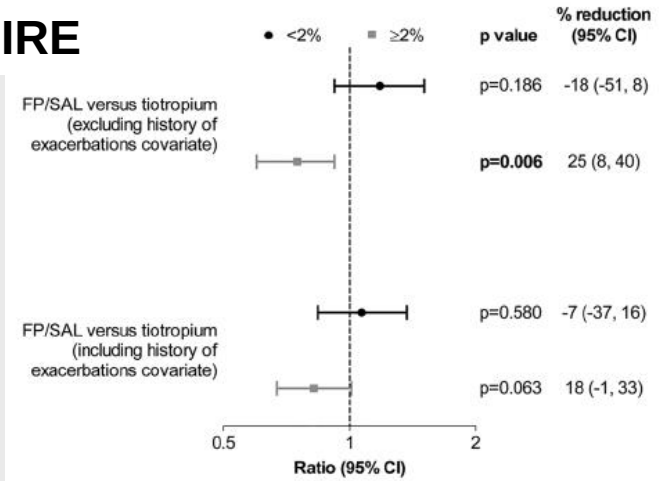


Lancet Respiratory Medicine. 2015;3(6):435-42.

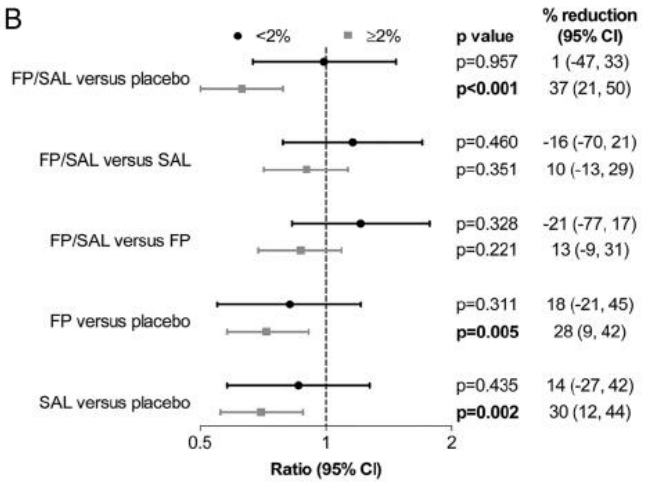
Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD

Ian D Pavord,[1] Sally Lettis,[2] Nicholas Locantore,[3] Steve Pascoe,[3] Paul W Jones,[4] Jadwiga A Wedzicha,[5] Neil C Barnes[6,7]

INSPIRE



TRISTAN



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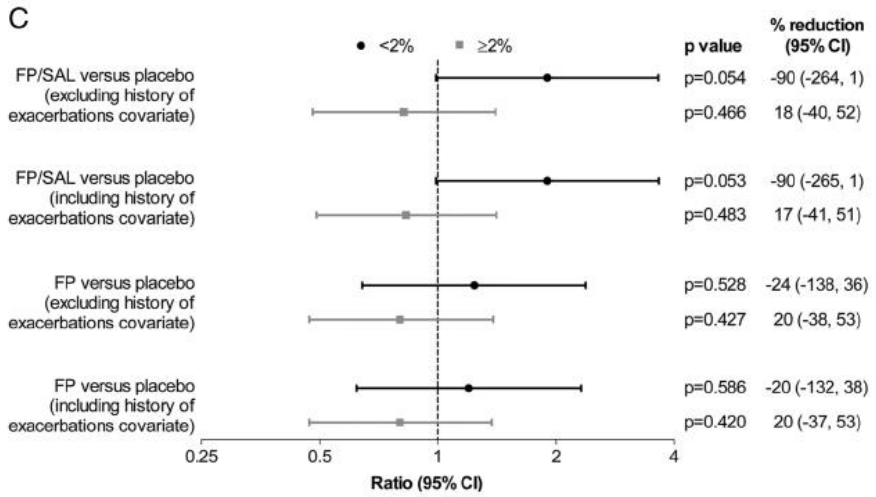
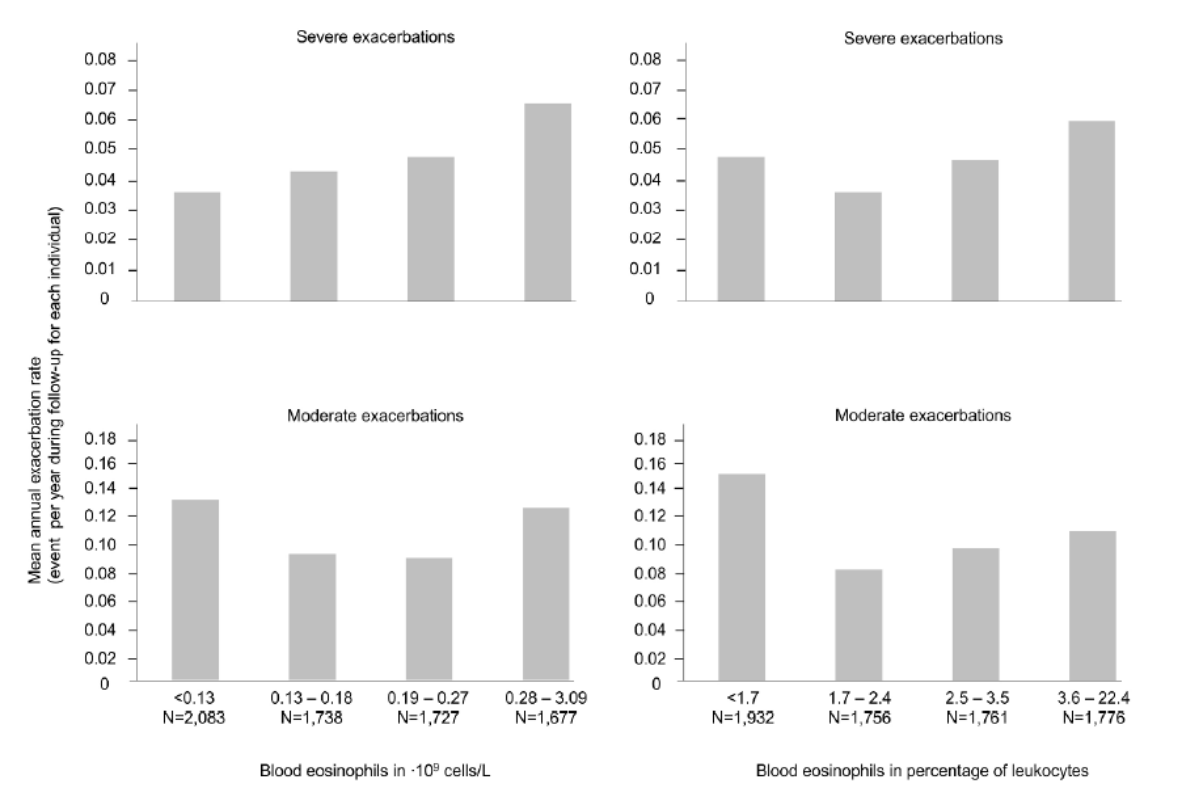


Thorax 2016;71:118–125.

Blood eosinophils and exacerbations in COPD: the Copenhagen General Population Study

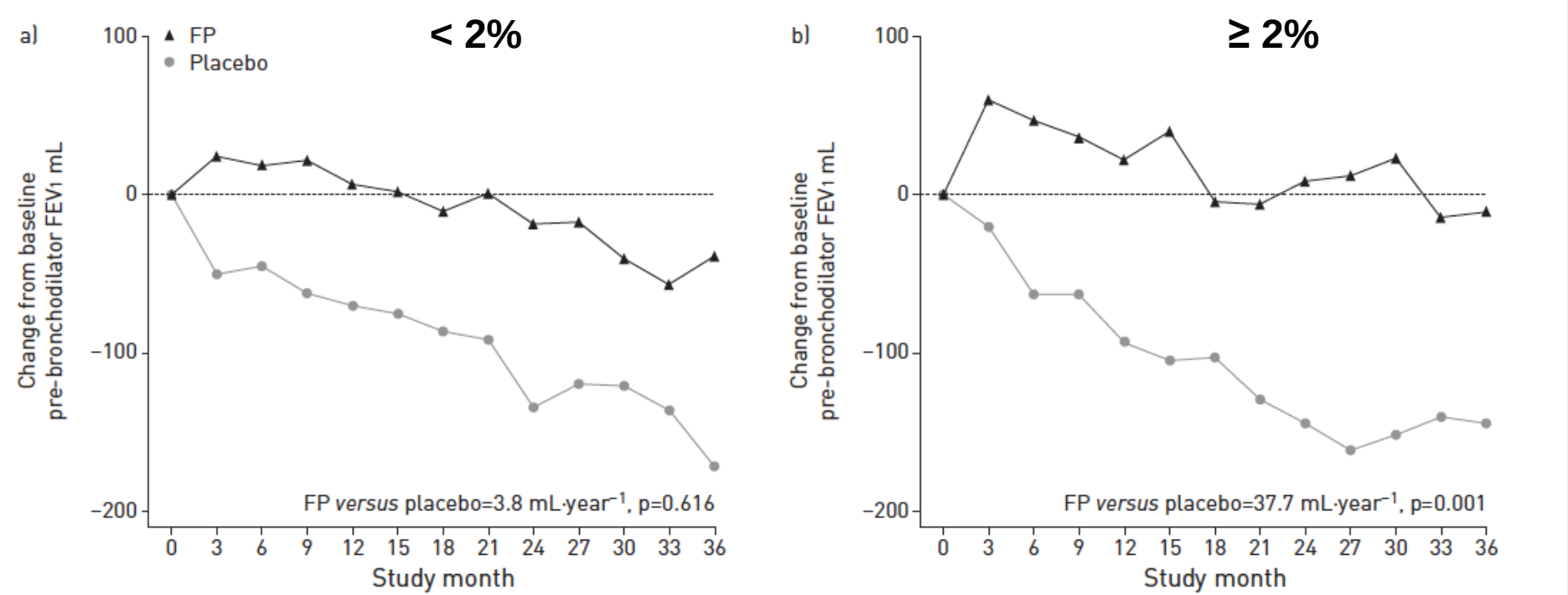


"In a general population setting among individuals with COPD, blood eosinophil levels above 0.34×10^9 cells/L are associated with increased risk of both moderate and severe exacerbations."

Am J Respir Crit Care Med 2016 May 1;193(9):965-74.

Blood eosinophils as a marker of response to inhaled corticosteroids in COPD

Neil C. Barnes[1,2], Raj Sharma[1], Sally Lettis[3] and Peter M.A. Calverley[4]



–54.2 v –51.3 mL·year−1; p=0.688

–40.6 v –74.5 mL·year−1; p=0.003

Eur Respir J 2016 May;47(5):1374-82.

Take-Home Message

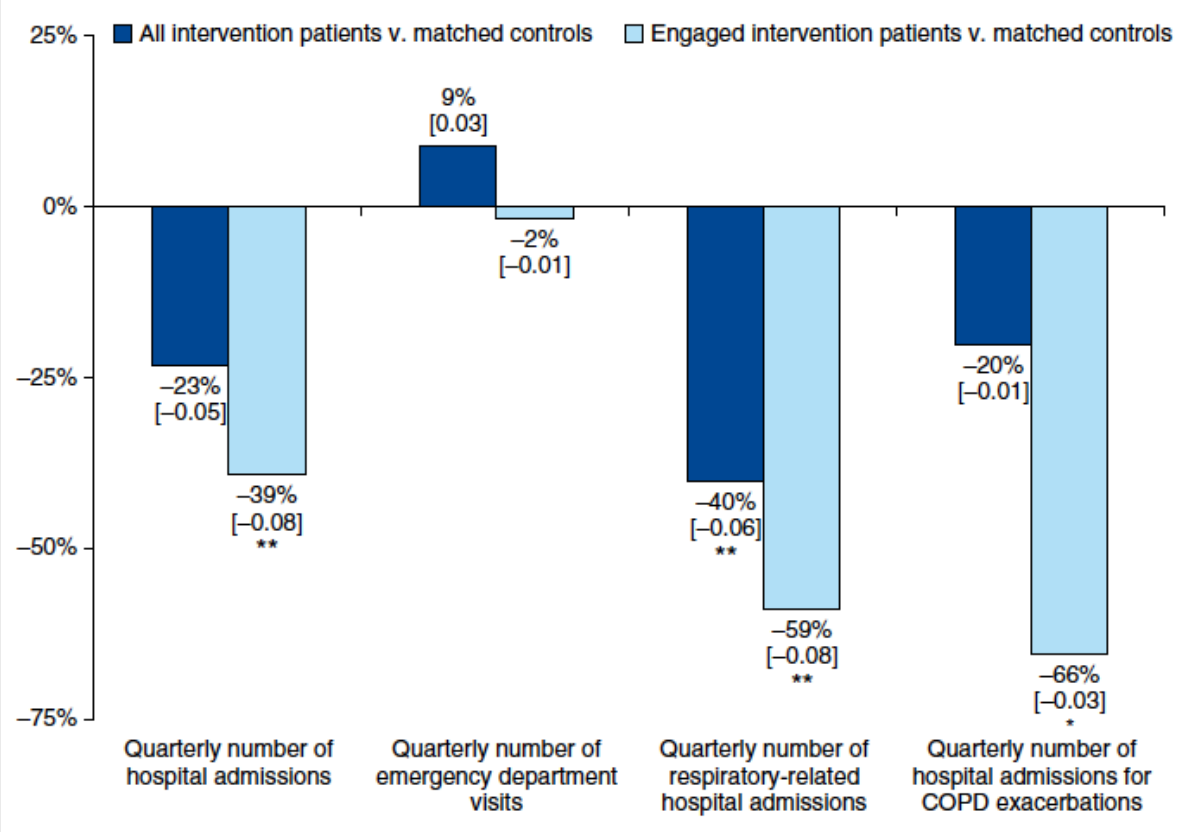
- Blood eosinophils look promising as a biomarker of exacerbations and response or non-response to treatment
- Blood eosinophils may also predict response to maintenance therapy with ICS
- Cut off values and absolute v % values still not clear

Telehealth

Impact of a Telehealth and Care Management Program for Patients with Chronic Obstructive Pulmonary Disease

David H. Au[1,2], Dendy S. Macaulay[3], John L. Jarvis[4], Urvi S. Desai[4], and Howard G. Birnbaum[4]

[1]Health Services Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; [2]Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; [3]Analysis Group, Inc., New York, New York; and [4]Analysis Group, Inc., Boston, Massachusetts



Health Buddy device collects data on vital signs and symptoms

Transmitted to central server

Risk Calculated

Registered nurse care managers and other provider staff (e.g., physical therapist, emergency medicine technician) monitor daily patient status and triage patient follow-up based on the categorized risk stratification

Ann Am Thorac Soc 2015; 12: 323–331

REVIEW

Telehealthcare in COPD: A systematic review and meta-analysis on physical outcomes and dyspnea☆

Sara Lundell [a,*], Åsa Holmner [b], Börje Rehn [a], Andre Nyberg [a], Karin Wadell [a]

Nine studies (982 patients).

Telehealthcare was promoted through phone calls, websites or mobile phones, often combined with education and/or exercise training

Significant effect on physical activity level favoring telehealthcare (MD, 64.7 min; 95% CI, 54.4-74.9).

No difference between groups was found for physical capacity (MD, 1.3 m; 95% CI, 8.1-5.5) and dyspnea (SMD, 0.088; 95% CI, 0.056-0.233).

Ann Am Thorac Soc 2015; 12: 323–331

A RCT of telehealth for COPD patient's quality of life: the whole system demonstrator evaluation

Lorna Rixon[1], Shashivadan P. Hirani[1], Martin Cartwright[1], Michelle Beynon[1], Helen Doll[2], Adam Steventon[3], Catherine Henderson[4] and Stanton P. Newman[1]

A randomised clinical trial of the effectiveness of home-based health care with telemonitoring in patients with COPD.

McDowell JE[1], McClean S[2], FitzGibbon F[3], Tate S[4].

The value of telehealth in the early detection of chronic obstructive pulmonary disease exacerbations: A prospective observational study.

Hamad GA[1], Crooks M[2], Morice AH[2].

Randomised crossover trial of telemonitoring in chronic respiratory patients (TeleCRAFT trial)

M Chatwin,[1] G Hawkins,[1] L Panicchia,[1] A Woods,[1] A Hanak,[1] R Lucas,[1] E Baker,[2] E Ramhamdany,[3] B Mann,[3] J Riley,[1] M R Cowie,[1] A K Simonds[1]

The Clinical Respiratory Journal. 2015. Epub 2015/08/12
J Telemed Telecare. 2015 ;21(2):80-7
Health informatics journal. 2015. Epub 2015/01/08
Thorax 2016;71:305–311

Take-Home Message

- Using telehealth to identify exacerbations early or reduce hospitalisation rates does not work
- Using telehealth to deliver or maintain exercise capacity may be of benefit
- Using telehealth to improve adherence with medication in COPD is untested

Co-morbidities

Chronic Obstructive Pulmonary Disease and the Risk of Stroke

The Rotterdam Study

Marileen L. P. Portegies[1,2*], Lies Lahousse[1,3*], Guy F. Joos[3], Albert Hofman[1], Peter J. Koudstaal[2], Bruno H. Stricker[1,4], Guy G. Brusselle[1,3,5], and M. Arfan Ikram[1,2,6]

Adjusted for age, age squared, and sex, COPD was significantly associated with:

all stroke (HR 1.20; 95%CI1.00–1.43)

ischemic stroke (HR 1.27; 1.02–1.59)

hemorrhagic stroke (HR 1.70; 1.01–2.84)

BUT

After adjusting for smoking no significant increased risk

Am J Respir Crit Care Med 2016; 193: 251–258

COPD and risk of venous thromboembolism and mortality in a general population

Trond Børvik[1,2,3], Sigrid K. Brækkan[1,2,3], Kristin Enga[1,2,3], Henrik Schirmer[4,5], Ellen E. Brodin[1,2,3], Hasse Melbye[6] and John-Bjarne Hansen[1,2,3]

	Person-years	VTE	Incidence rate (95% CI)#	HR (95% CI)¶	HR (95% CI)+
All VTE					
Normal	41744	137	3.3 (2.8–3.9)	1 (reference)	1 (reference)
Stage I	5912	26	4.4 (3.0–6.3)	0.98 (0.64–1.50)	1.02 (0.66–1.57)
Stage II	8008	40	5.0 (3.7–6.8)	1.09 (0.76–1.56)	1.12 (0.78–1.62)
Stage III/IV	1526	12	7.9 (4.5–13.8)	1.61 (0.90–2.93)	1.60 (0.88–2.92)
p-value for trend				0.2	0.2
PE					
Normal	41744	68	1.6 (1.3–2.1)	1 (reference)	1 (reference)
Stage I	5912	15	2.5 (1.5–4.2)	1.12 (0.64–1.96)	1.21 (0.68–2.14)
Stage II	8008	19	2.4 (1.5–3.7)	1.01 (0.60–1.69)	1.01 (0.60–1.72)
Stage III/IV	1526	7	4.6 (2.2–9.6)	1.83 (0.83–4.02)	1.80 (0.81–3.99)
p-value for trend				0.4	0.4
DVT					
Normal	41744	69	1.7 (1.3–2.1)	1 (reference)	1 (reference)
Stage I	5912	11	1.9 (1.0–3.4)	0.84 (0.44–1.60)	0.82 (0.41–1.61)
Stage II	8008	21	2.6 (1.7–4.0)	1.18 (0.72–1.93)	1.22 (0.73–2.04)
Stage III/IV	1526	5	3.3 (1.4–7.9)	1.38 (0.55–3.45)	1.39 (0.55–3.51)
p-value for trend				0.5	0.4

Eur Respir J. 2016 Feb;47(2):473-81

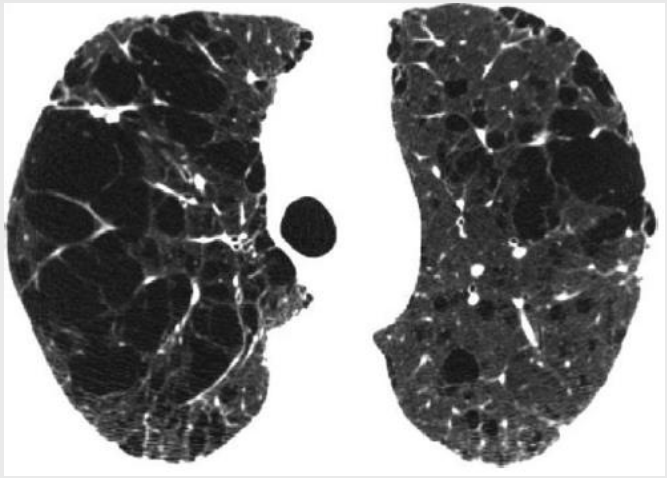
CT screening for lung cancer: Importance of emphysema for never smokers and smokers

Claudia I. Henschke[a,*], Rowena Yip[a,b], Paolo Boffetta[b], Steven Markowitz[c], Albert Miller[c], Takaomi Hanaoka[d], Ning Wu[e], Javier J. Zulueta[f], David F. Yankelevitz[a], for the I-ELCAP Investigators[1]

Improving Selection Criteria for Lung Cancer Screening

The Potential Role of Emphysema

Pablo Sanchez-Salcedo[1], David O. Wilson[2], Juan P. de-Torres[1], Joel L. Weissfeld[3], Juan Berto[1], Arantzazu Campo[1], Ana B. Alcaide[1], Jesús Pueyo[4], Gorka Bastarrika[4], Luis M. Seijo[5], Maria J. Pajares[6,7], Ruben Pio[6,8], Luis M. Montuenga[6,7], and Javier J. Zulueta[1]



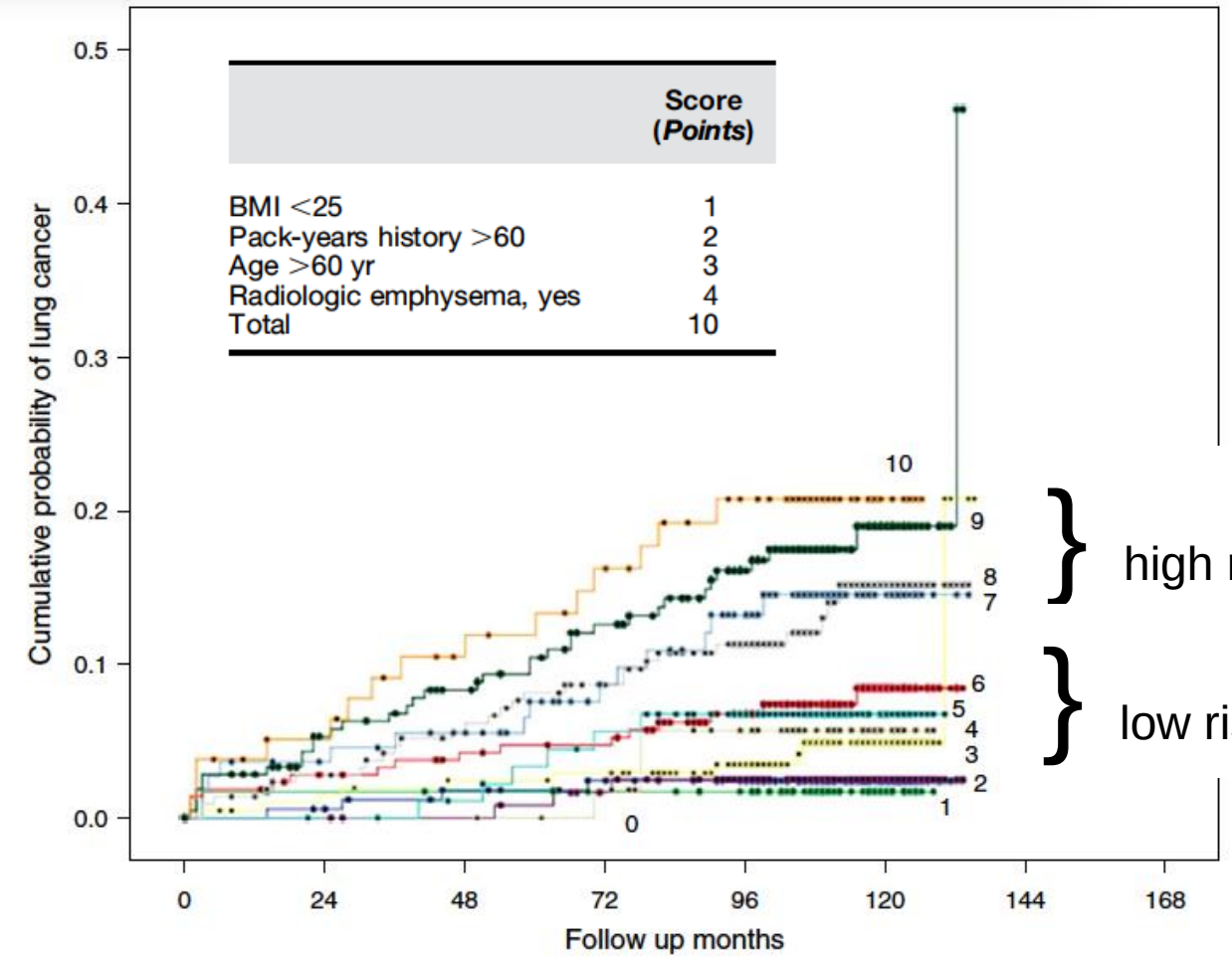
Lung Cancer 2015;88:42-47

Am J Respir Crit Care Med 2015; 191: 924–931

Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease

Development and Validation of the COPD Lung Cancer Screening Score

Juan P. de-Torres[1], David O. Wilson[2], Pablo Sanchez-Salcedo[1], Joel L. Weissfeld[3], Juan Berto[1], Arantzazu Campo[1], Ana B. Alcaide[1], Marta García-Granero[4], Bartolome R. Celli[5], and Javier J. Zulueta[1]



Am J Respir Crit Care Med 2015;191(3):285-91

Long-term Course of Depression Trajectories in Patients With COPD

A 3-Year Follow-up Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort

Abebaw M. Yohannes, PhD, FCCP; Hana Müllerová, PhD; Nicola A. Hanania, MD, FCCP; Kim Lavoie, PhD; Ruth Tal-Singer, PhD; Jorgen Vestbo, MD; Steven I. Rennard, MD; and Emil F. M. Wouters, MD

1,589 patients - baseline and 3-year CES-D* scores

- 55% (n = 869) never depressed,
- 24% (n = 377) persistently depressed,
- 14% (n = 226) developed new onset of depression
- 7% (n = 117) had depression that remitted.

- Female sex and history of stroke were associated with substantial increases in the odds of persistent depression

- Odds of new onset depression increased with worse health status and moderate to severe dyspnea

- patients with persistent or new-onset depression experienced more exacerbations and more pronounced loss in 6MWD

* Center for Epidemiologic Studies Depression Scale

CHEST 2016; 149(4):916-926

Erectile dysfunction in COPD patients

Onur Turan[1], Iyimser Ure[2] and Pakize Ayse Turan[3]

Varying degrees of ED were detected in 67.7% of COPD patients

The Risk of Erectile Dysfunction in Chronic Obstructive Pulmonary Disease

A Population-Based Cohort Study in Taiwan

Te-Chun Shen, MD, Wen-Chi Chen, MD, PhD, Cheng-Li Lin, MS, Chia-Hung Chen, MD, Chih-Yen Tu, MD, Te-Chun Hsia, MD, Chuen-Ming Shih, MD, PhD, Wu-Huei Hsu, MD, and Fung-Chang Sung, PhD, MPH

Incidence of ED was 1.88-fold greater in the COPD cohort than in the non-COPD cohort (24.9 vs 13.3/1000 person-years, 95%CI 1.61–2.18).

Chronic Respiratory Disease 2016; 13: 5–12
Medicine. 2015;94(14):e448

Take-Home Message

- Stroke does not appear to be a comorbity of COPD but VTE probably is
- Lung cancer is an important co-morbidity of COPD and COPD features identify people who get most benefit from CT screening

Pharmacotherapy

Article

Too many options, too little choice in COPD?

"At the last count there were five LABAs, four LAMAs and four ICS compounds licensed for use in COPD"

"There are an increasing number of combination products that contain a LAMA and LABA, or a LABA and ICS"

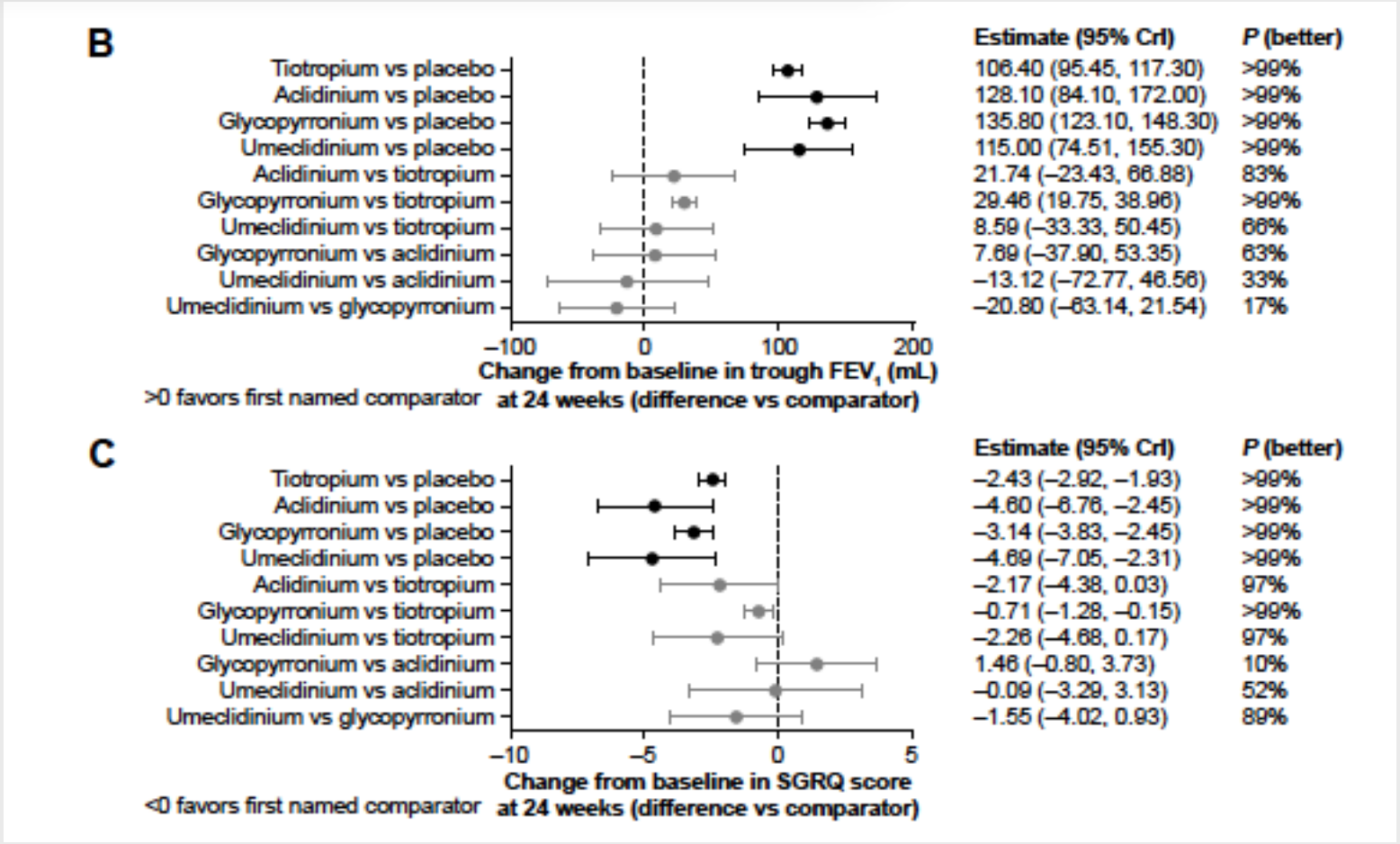
"The number of available options soon escalates when you add in the increasing number of generic inhalers and the arrival of several new inhaler devices (12 in total for COPD at the last count)"

DTB 2016;54:13 doi:10.1136/dtb.2016.2.0379

Open Access Full Text Article

ORIGINAL RESEARCH

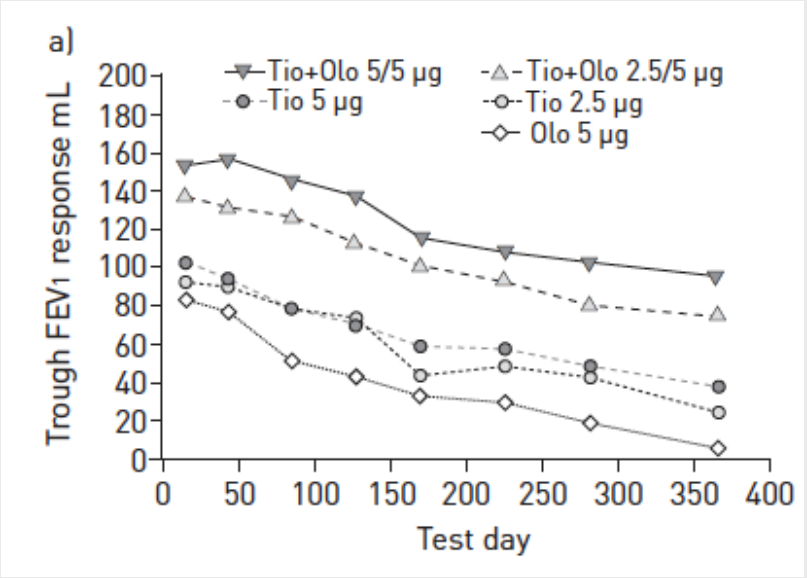
Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis



International Journal of COPD. 2015;10:2495-517

Tiotropium and olodaterol fixed-dose combination *versus* mono-components in COPD (GOLD 2–4)

Roland Buhl[1], François Maltais[2], Roger Abrahams[3], Leif Bjermer[4], Eric Derom[5], Gary Ferguson[6], Matjaž Fležar[7], Jacques Hébert[8], Lorcan McGarvey[9], Emilio Pizzichini[10], Jim Reid[11], Antony Veale[12], Lars Grönke[13], Alan Hamilton[14], Lawrence Korducki[15], Kay Tetzlaff[13,16], Stella Waitere-Wijker[17], Henrik Watz[18] and Eric Bateman[19]

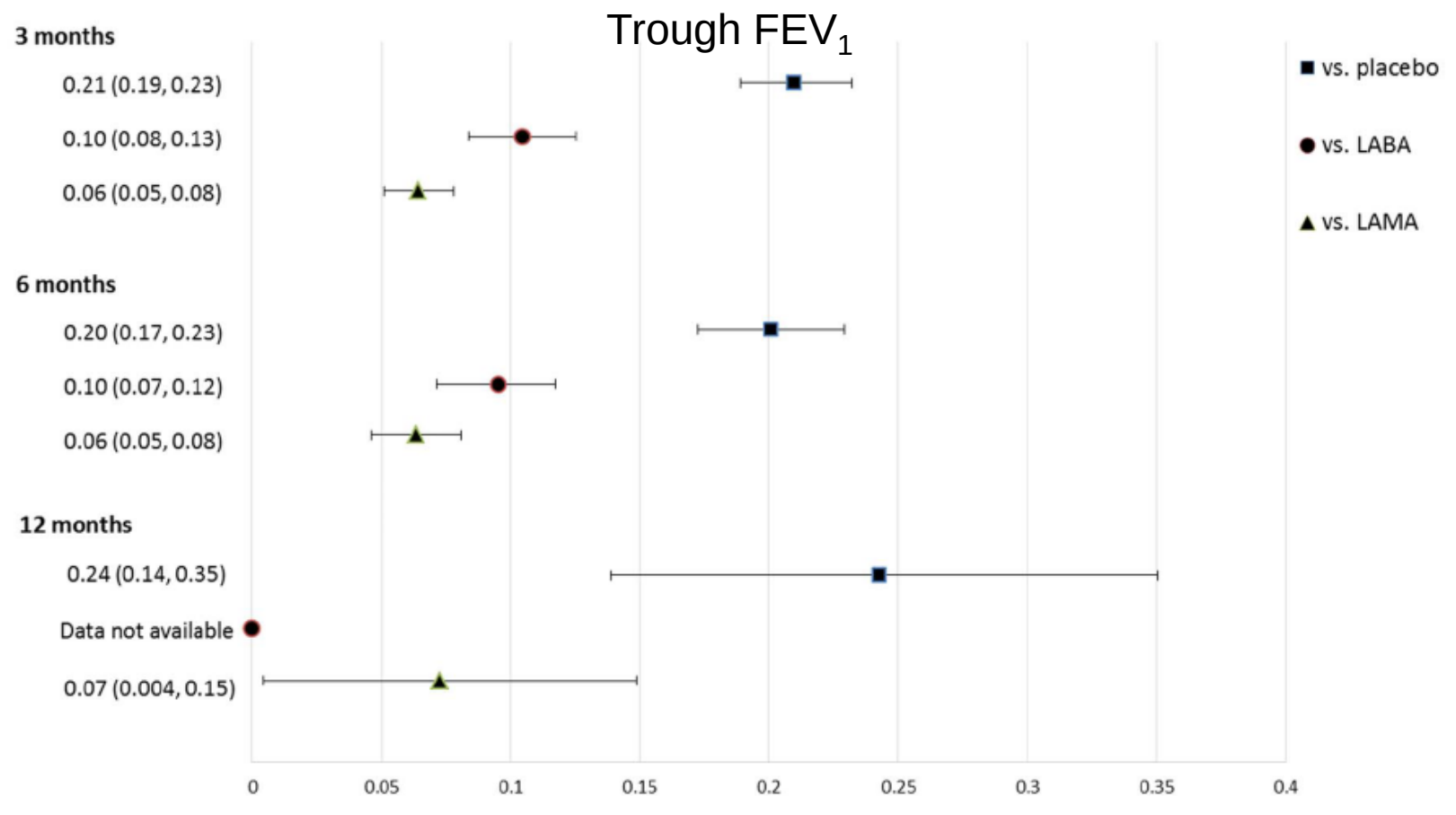


Treatment comparison	SGRQ total score[#]	p-value	Responder analysis[¶] odds ratio[§,f]	p-value
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	−1.693±0.553 (−2.778–−0.608)	0.0022	1.670±0.153 (1.395–1.999)	<0.0001
versus tiotropium 5 µg	−1.233±0.551 (−2.313–−0.153)	0.0252	1.426±0.131 (1.192–1.706)	0.0001

The European Respiratory Journal. 2015;45(4):969-79

Efficacy and safety of long-acting β-agonist/ long-acting muscarinic antagonist combinations in COPD: a network meta-analysis

Yuji Oba,[1] Siva T Sarva,[1] Sofia Dias[2]



Thorax. 2016;71(1):15-25

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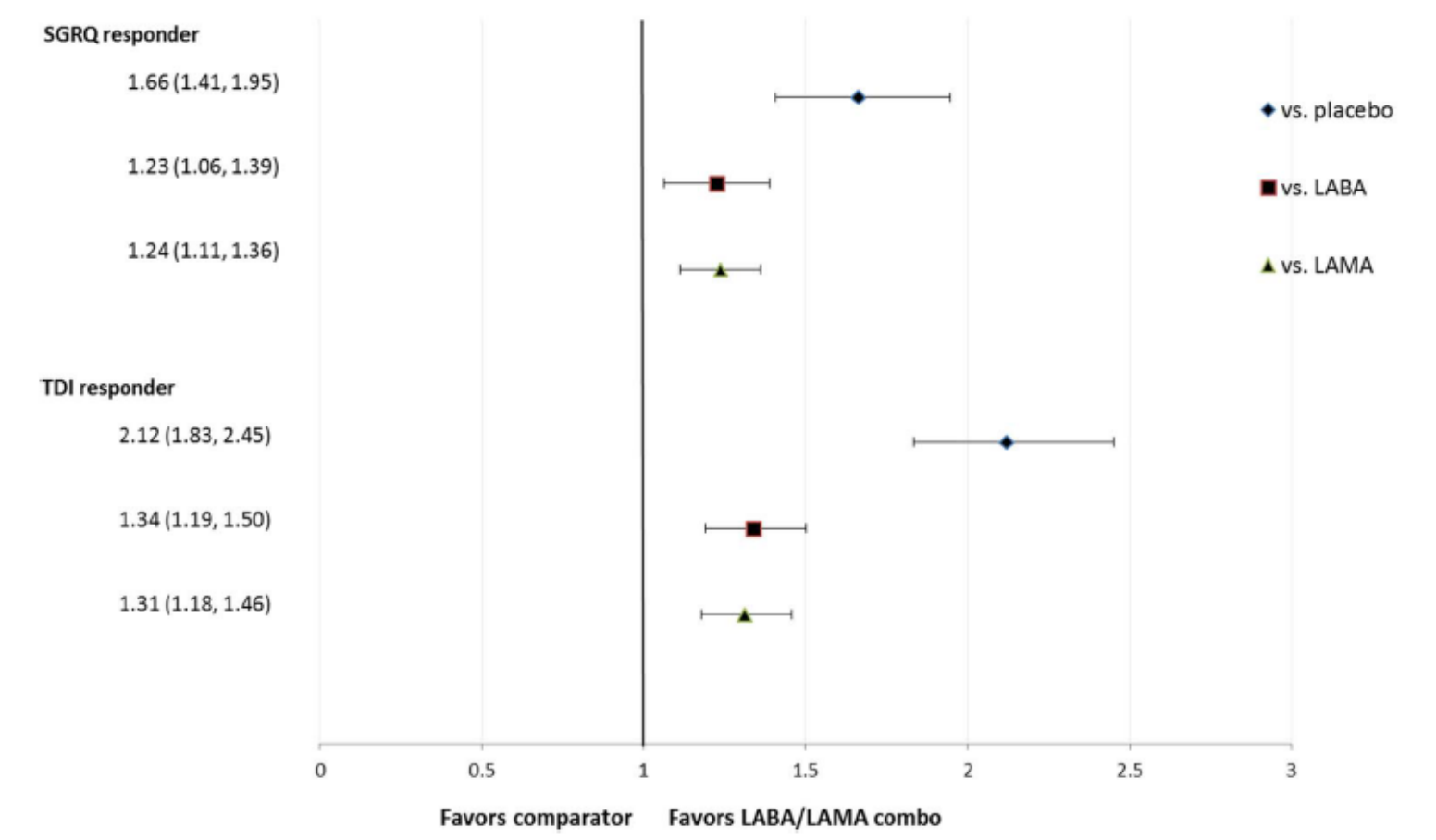

Thorax. 2016;71(1):15-25

Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis

Max Schlueter, N Gonzalez-Rojas, Michael Baldwin, Lars Groenke, Florian Voss and Tim Reason

Table 3. Change in $tFEV_1$ from baseline (24/26 weeks).

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		−0.042 [−0.077,−0.007]	−0.039 [−0.075,−0.002]	−0.064 [−0.099,−0.028]
QVA149 110/50 µg	0.042 [0.007,0.077]		0.003 [−0.024,0.031]	−0.022 [−0.050,0.007]
TIO/OLO 5/5 µg	0.039 [0.002,0.075]	−0.003 [−0.031,0.024]		−0.025 [−0.052,0.002]
UMEC/VI 62.5/25 µg	0.064 [0.028,0.099]	0.022 [−0.007,0.050]	0.025 [−0.002,0.052]	
Total residual deviance		35.24 [24.90,50.75]		
DIC		−177.79		

Table 7. SGRQ percentage of responders (24/26 weeks).

	ACL/FF 400/12 µg	QVA149 110/50 µg	TIO/OLO 5/5 µg	UMEC/VI 62.5/25 µg
Fixed effects*				
ACL/FF 400/12 µg		0.926 [0.680,1.257]	0.817 [0.588,1.138]	0.931 [0.692,1.252]
QVA149 110/50 µg	1.080 [0.795,1.470]		0.883 [0.696,1.120]	1.006 [0.804,1.258]
TIO/OLO 5/5 µg	1.224 [0.879,1.702]	1.132 [0.893,1.437]		1.139 [0.892,1.455]
UMEC/VI 62.5/25 µg	1.074 [0.799,1.446]	0.994 [0.795,1.244]	0.878 [0.687,1.121]	
Total residual deviance		39.89 [30.43,54.49]		
DIC		404.53		

Ther Adv Respir Dis 2016; 10: 89–104

Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis

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TIO/OLO 5/5 µg	0.039 [0.002,0.075]	−0.003 [−0.031,0.024]		−0.025 [−0.052,0.002]

Conclusion: All LAMA/LABA FDCs were found to have similar efficacy and safety. Definitive assessment of the relative efficacy of different treatments can only be performed through direct comparison in head-to-head RCTs. In the absence of such data, this indirect comparison may be of value in clinical and health economic decision-making.

Fixed effects*				
ACL/FF 400/12 µg		0.926 [0.680,1.257]	0.817 [0.588,1.138]	0.931 [0.692,1.252]
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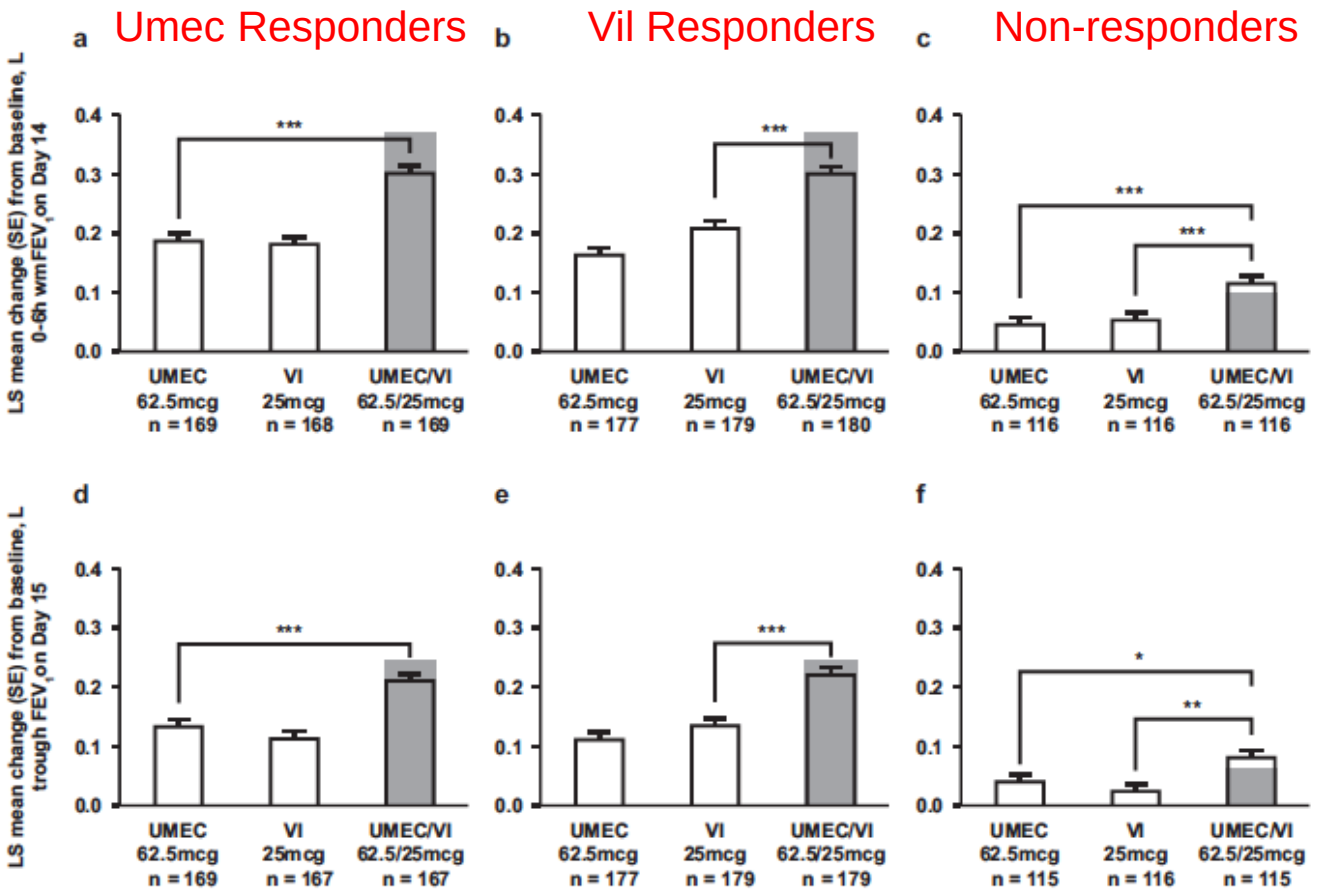
Total residual deviance		39.89 [30.43,54.49]		
DIC		404.53		

Ther Adv Respir Dis 2016; 10: 89–104

Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: Results from two randomised controlled trials

James F. Donohue [a,*], Dave Singh [b], Clara Munzu [c], Sally Kilbride [d], Alison Church [e]



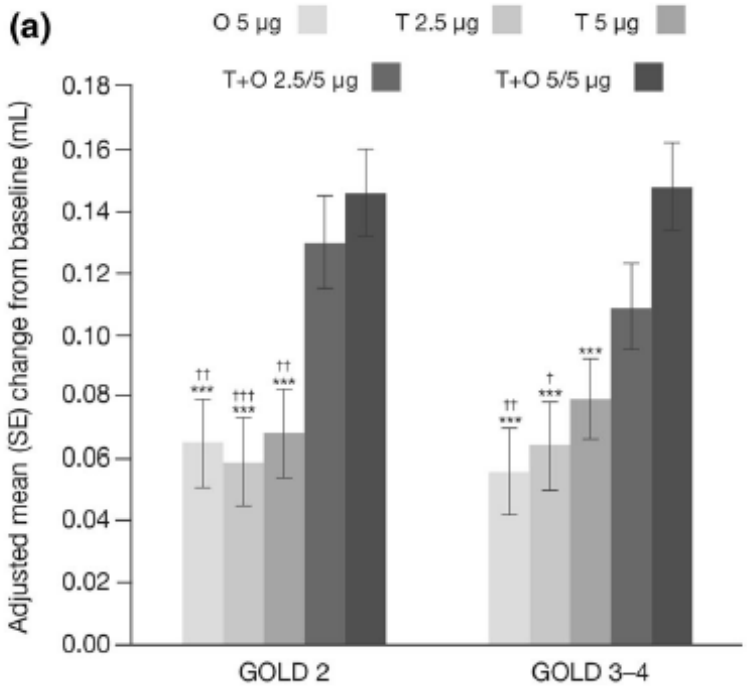
"responders" had an FEV_1 increase from baseline of ≥12% and ≥ 200 mL

Respiratory Medicine. 2016;112:65-74.

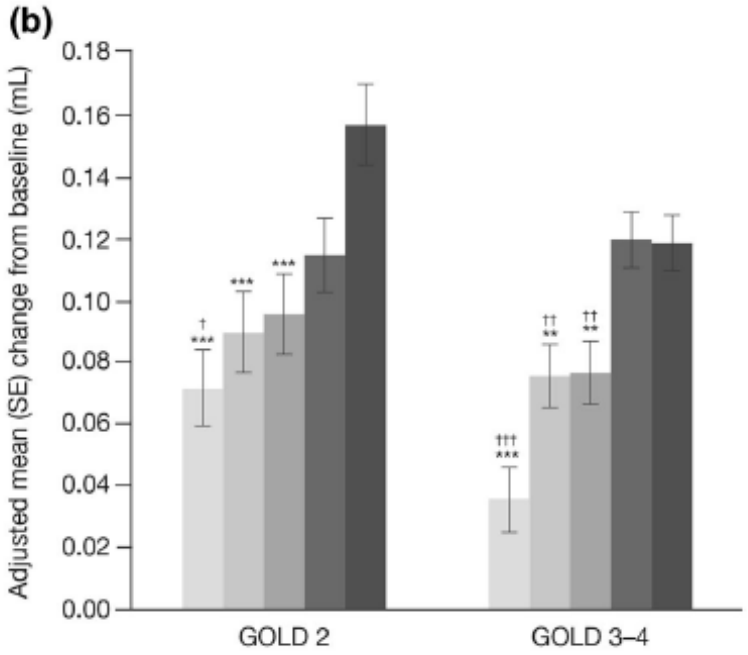
Efficacy of Tiotropium + Olodaterol in Patients with Chronic Obstructive Pulmonary Disease by Initial Disease Severity and Treatment Intensity: A Post Hoc Analysis

Gary T. Ferguson · Matjaž Fležar · Stephanie Korn · Lawrence Korducki · Lars Grönke · Roger Abrahams · Roland Buhl

without prior LAMA or LABA use

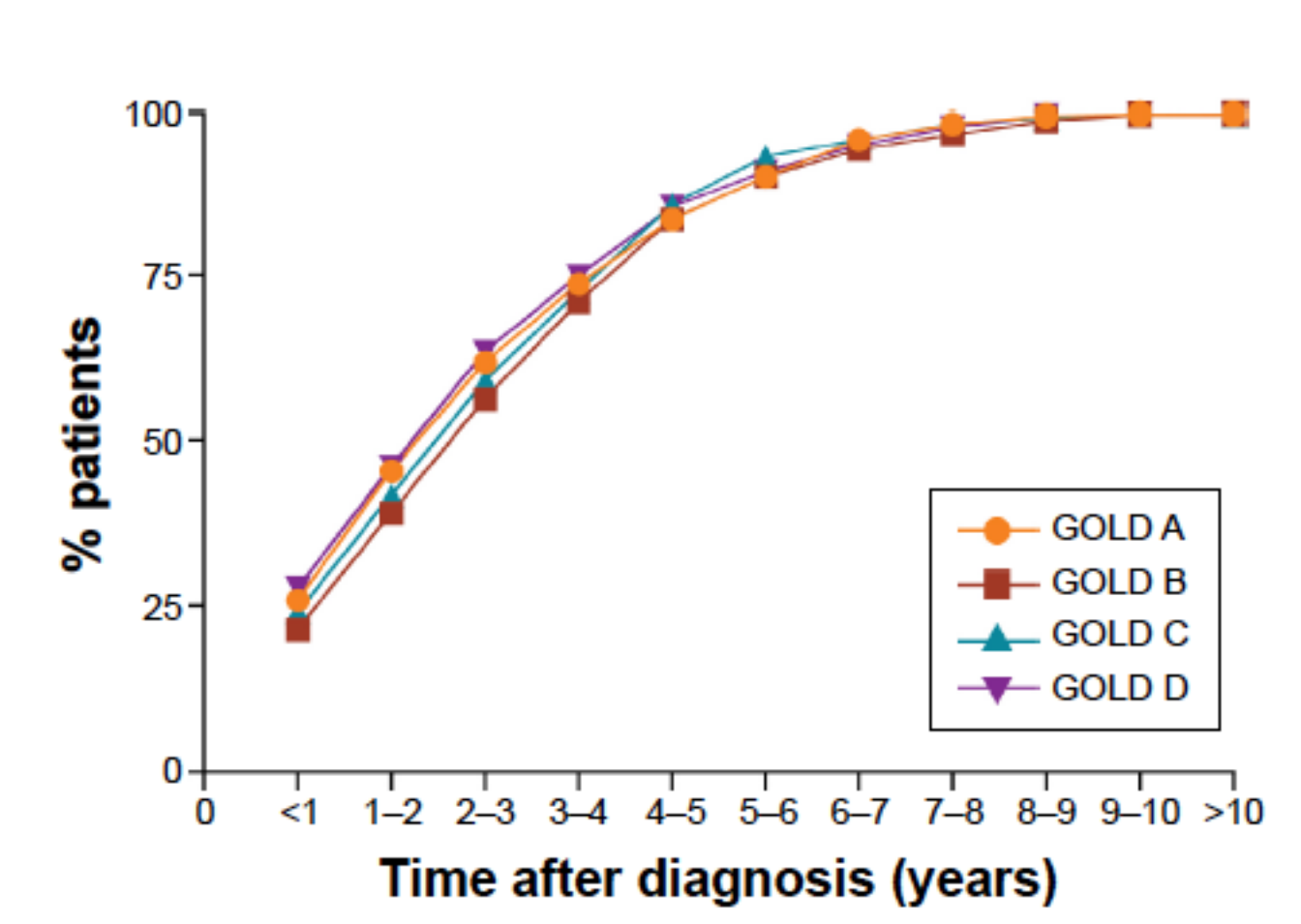


with prior LAMA or LABA use



Advances in Therapy. 2015;32(6):523-36

The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK



Int J COPD 2015; 10: 2207-2217

PULMONARY PERSPECTIVE

Incident Pneumonia and Mortality in Patients with Chronic Obstructive Pulmonary Disease

A Double Effect of Inhaled Corticosteroids?

Emir Festic[1] and Paul D. Scanlon[2]

[1]Pulmonary and Critical Care Medicine, Mayo Clinic, Jacksonville, Florida; and [2]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota

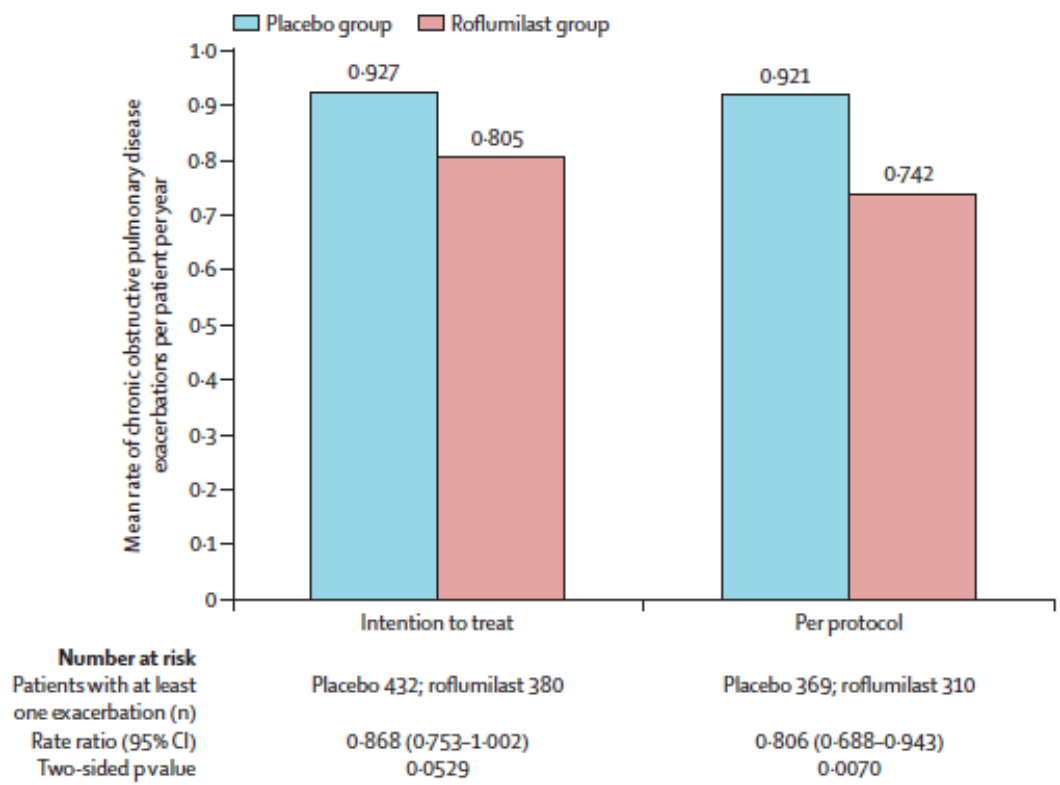
- The association of use of inhaled corticosteroids and incident pneumonia is substantial
- Present in the majority studies: both RCT and observational
- All of the studies have substantial risk of bias.
- Risk of pneumonia is associated with longer duration of use, more potent ICS compounds, and higher doses.
- All studies found either no difference or a reduction in pulmonary-related and overall mortality with ICS
- Suggest a double effect of ICS (i.e., an adverse effect plus an unexplained mitigating effect).

Am J Respir Crit Care Med 2015; 191:141–148

Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial

Fernando J Martinez*, Peter M A Calverley*, Udo-Michael Goehring, Manja Brose, Leonardo M Fabbri†, Klaus F Rabe†

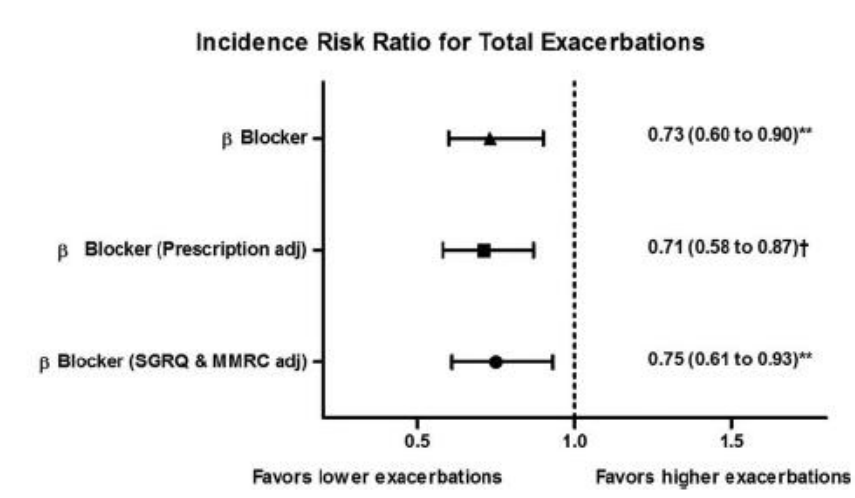
1495 patients with COPD
≥ 40 years of age
≥ 20 pack-years
FEV1 < 50% pred
chronic bronchitis,
≥ 2 exacerbations in 12/12

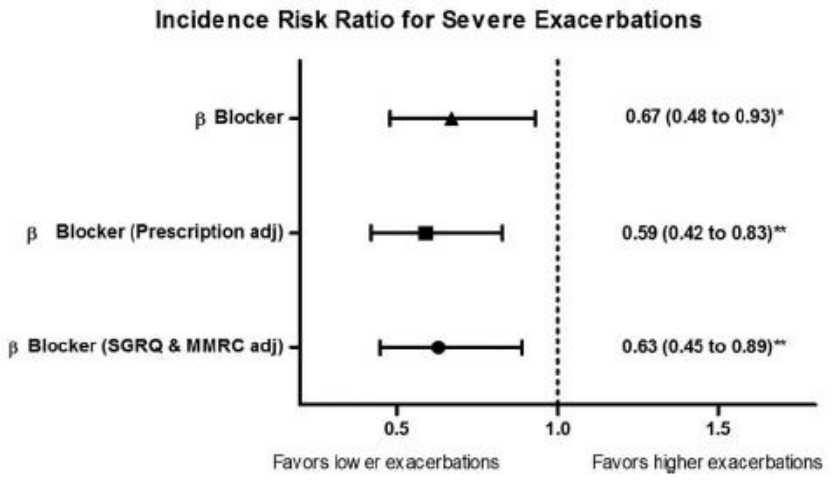


Lancet 2015; 385: 857–66

β-Blockers are associated with a reduction in COPD exacerbations

Surya P Bhatt,[1] James M Wells,[1] Gregory L Kinney,[2] George R Washko Jr,[3] Matthew Budoff,[4] Young-il Kim,[5] William C Bailey,[1] Hrudaya Nath,[6] John E Hokanson,[2] Edwin K Silverman,[7] James Crapo,[8] Mark T Dransfield,[1,9] For the COPDGene Investigators





Rates were adjusted for age, gender, race, smoking burden, body mass index, FEV1, %emphysema on CT, coronary artery calcification (CAC), presence of congestive heart failure and coronary artery disease, long-acting respiratory medications and for the propensity to prescribe **β**-blockers based on demographics, coronary artery disease, congestive heart failure and severity of airflow obstruction.

Thorax 2016;71:8–14

Original Research | April 2016

Oral Low-Dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients with Severe COPD: A Pilot Clinical Trial

Borja G. Cosío; Hanna Shafiek; Amanda Iglesias; Aina Yanez; Rocio Cordova; Alexandre Palou; Robert Rodriguez-Roisin; German Peces-Barba; Sergi Pascual; Joaquim Gea; Oriol Sibila; Peter J. Barnes; Alvar Agusti

70 patients (FEV1<50% predicted plus at least one hospitalization due to exacerbation in the previous year)

36 ICS plus theophylline 100 mg bid
34 matched placebo

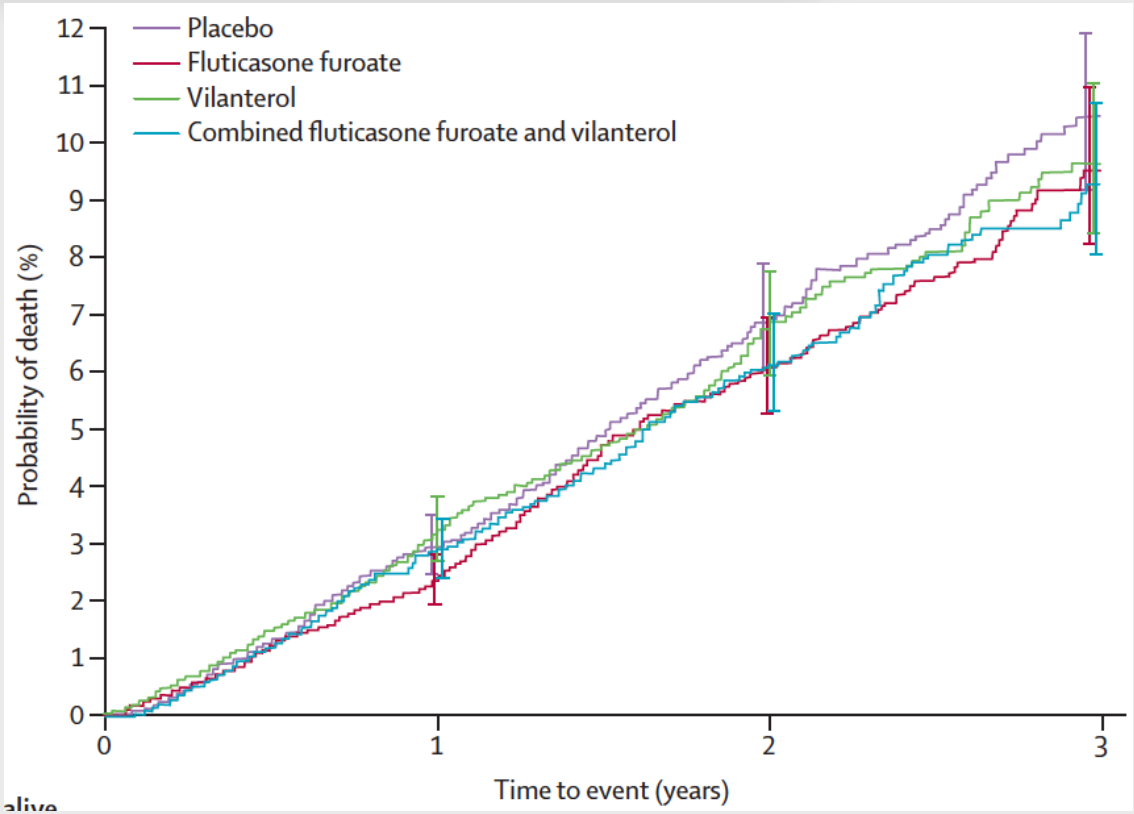
- HDAC activity and levels of the inflammatory markers were not different in both arms either at baseline or after 52 weeks.
- Rate of exacerbations during follow-up was similar in both groups.

“The combination of low dose oral theophylline and ICS does not enhance the anti-inflammatory properties of ICS in vivo nor influence exacerbation rate.”

Chest 2016. doi:10.1016

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators



Lancet 2016; 387: 1817–26

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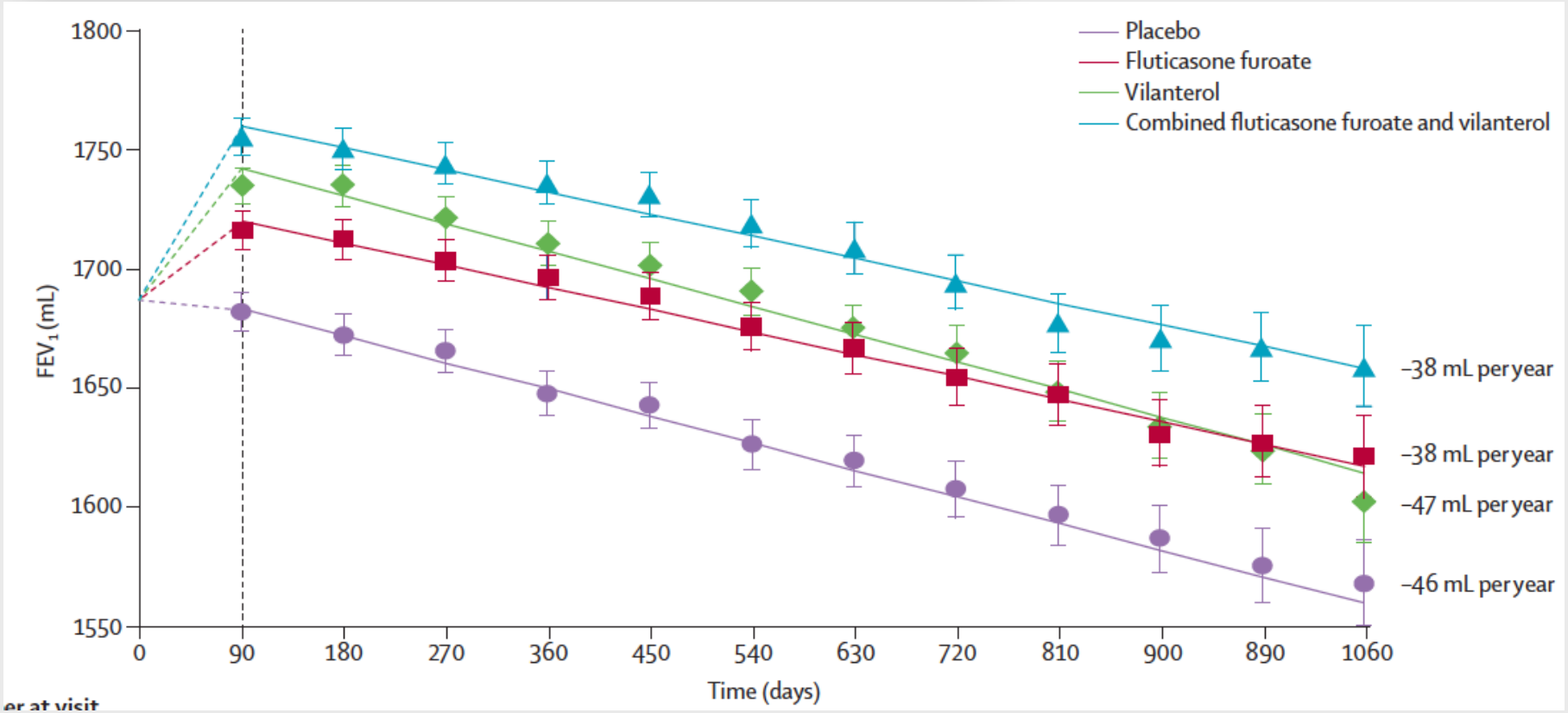

Lancet 2016; 387: 1817–26

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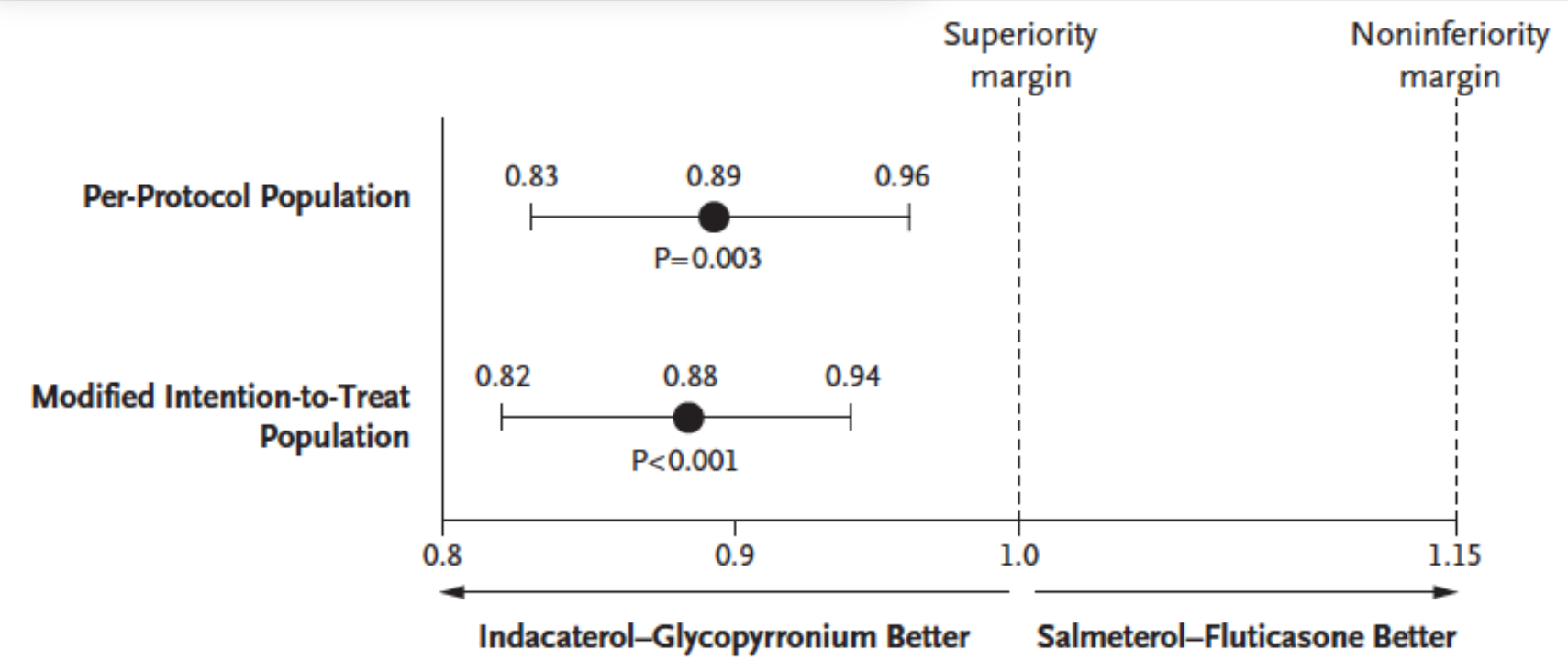
Late Breaking News

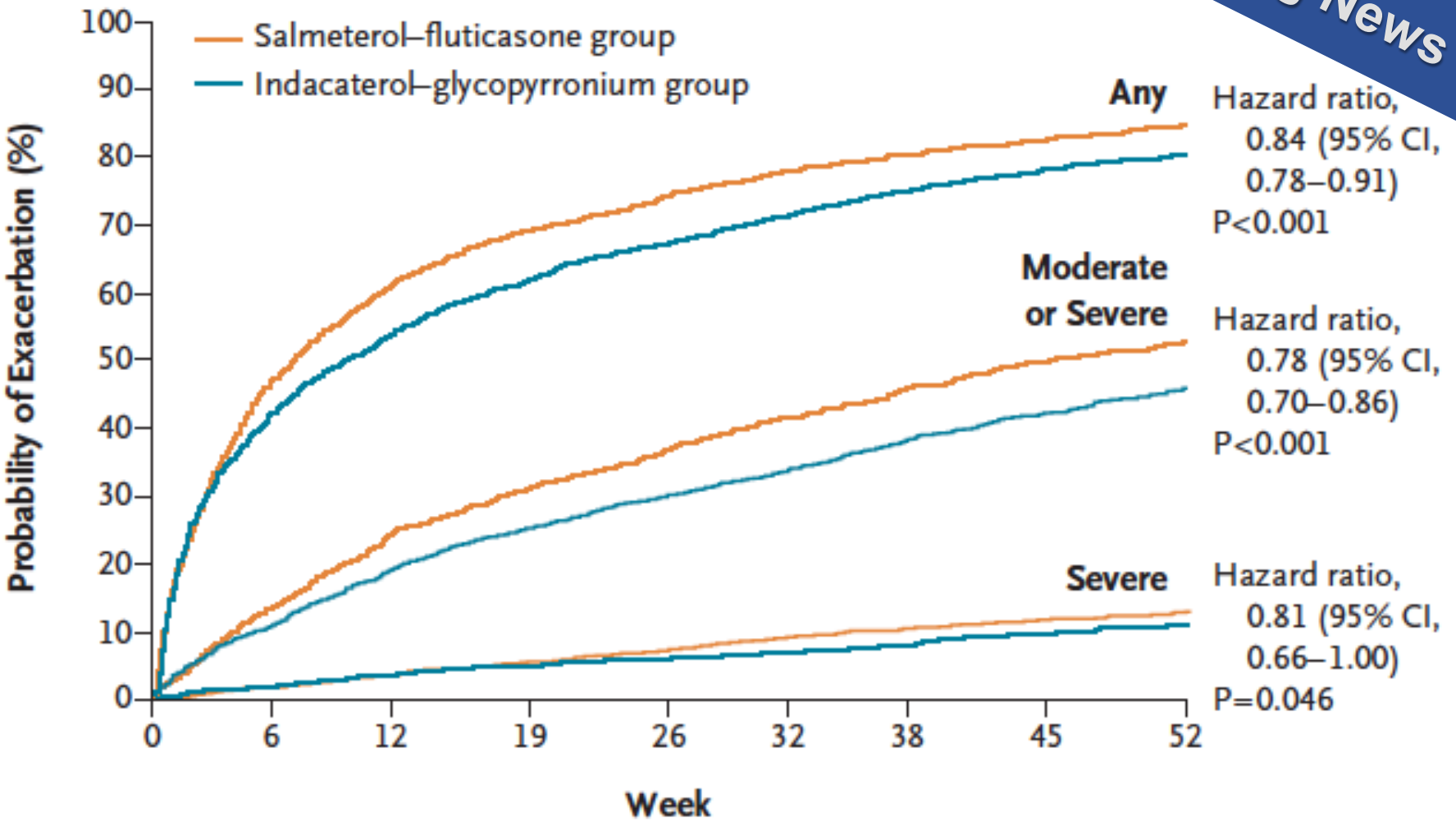
ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*



NEJM On line first 2016 DOI: 10.1056/NEJMoa1516385



NEJM On line first 2016 DOI: 10.1056/NEJMoa1516385

Take-Home Message

- Lots of options
- More evidence about LABA/LAMA combinations
  - Higher responder rates
  - Benefits in early disease
  - Response to monocomponents predicts benefit from combination
- PDE4 inhibitors may work in selected patients
- Beta blockers still look promising but theophylline was disappointing

Take-Home Messages

- The COPD literature grows unmanageably and it is incresingly difficult to keep up with all new studies
- We should approach management using treatable traits
- Prevention of exacerbations is a key priority
- Eosinophils may help chose best therapy but watch this space
- Remember co-morbidities & ACOS

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