The Lancet Commission: Taking action for the future of COPD

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Conflict of interest disclosure

- ❑ I have no real or perceived conflicts of interest that relate to this presentation.
- ❑x I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial company
Grants/research support:	OM Pharma
Honoraria or consultation fees:	Boehringer Ingelheim, Almirall, Novartis, GSK, Astra Zeneca, Vifor, MSD, Bayer, Sanofi, CSL Behring, Grifols, Roche, Chiesi, Chemie Menarini, OM-85
Participation in a company sponsored bureau:	
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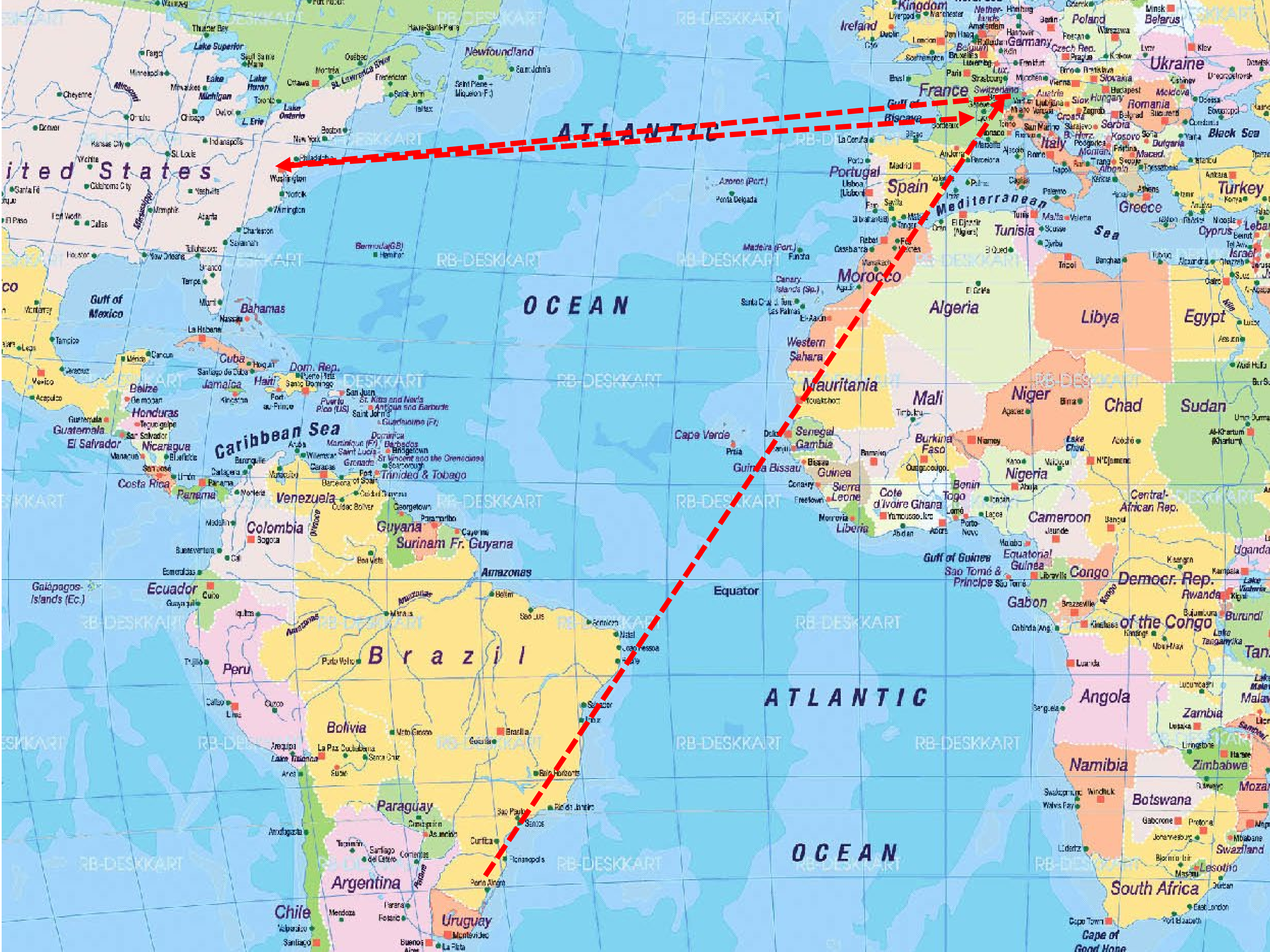
Spouse / partner:	
Other support / potential conflict of interests	GOLD Representative for Switzerland

Outline

- Importance of COPD
- COPD Subtypes 1-5
  - beyond cigarette smoking
  - the HISTORIC study
- New diagnostic criteria for COPD
  - beyond spirometric-defined obstruction
  - the CHRONOS study
- New definiton for exacerbation
  - beyond symptoms & need for medical therapy
  - the PREVENT study, the ProCOLD study
- Summary



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Costa Rica
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Colombia
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Galápagos-Islands (Ec.)
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Benin
Togo
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Equatorial Guinea
Gabon
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Sao Tomé & Principe
Angola
Namibia
Botswana
Zambia
Zimbabwe
South Africa
Cape of Good Hope
RB-DESKKART

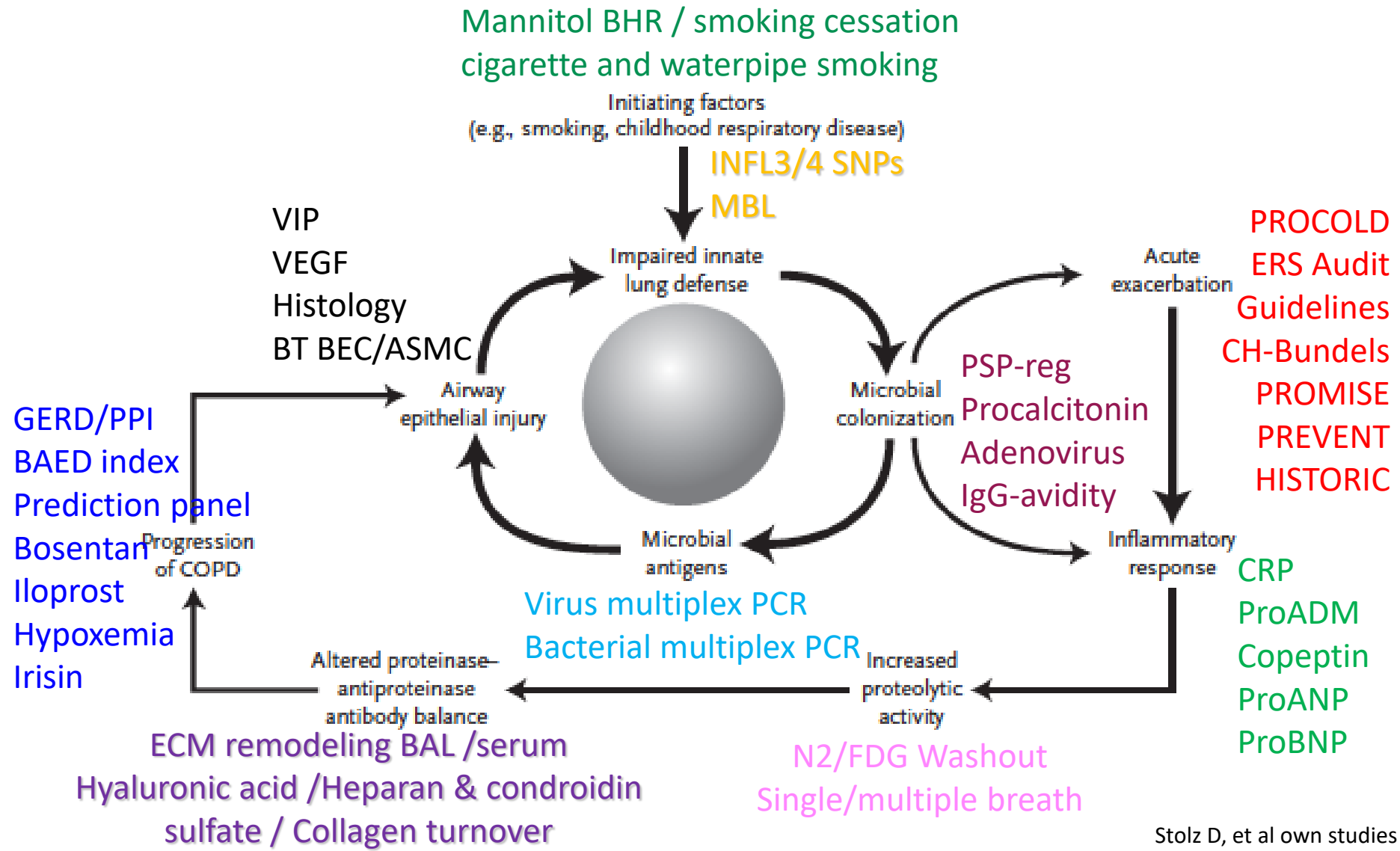
„Chronic obstructive pulmonary disease has ravaged my life“

Paul Joseph Brown, photojournalist and COPD patient

COPD: the vicious-circle at exacerbation

Spectrum of completed or on-going studies

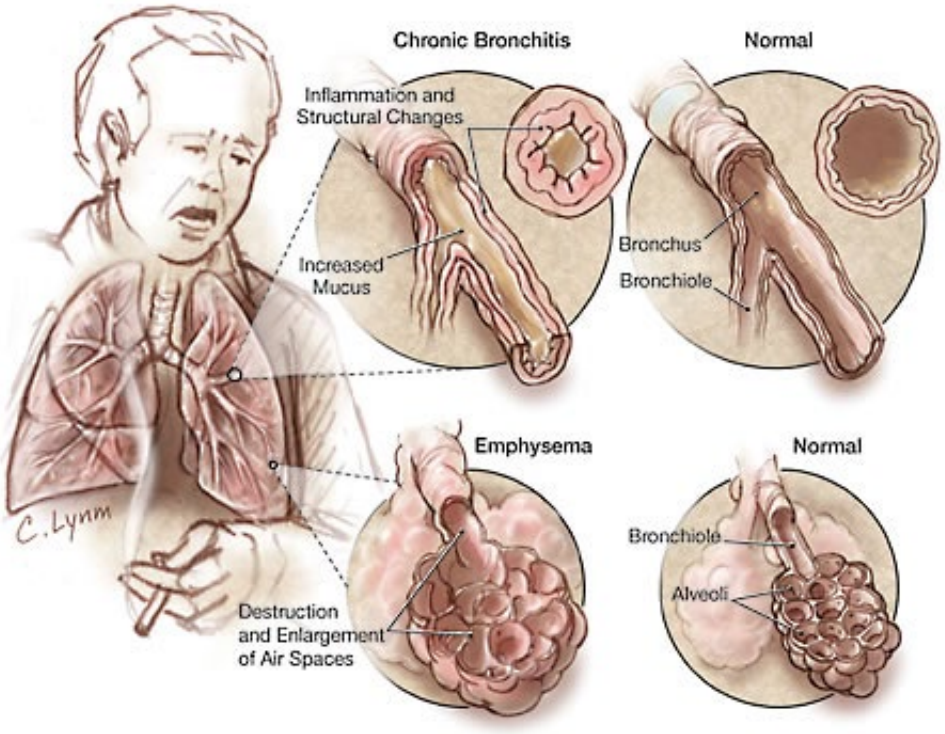
Modified from Sethi S. et al, NEJM



Stolz D, et al own studies

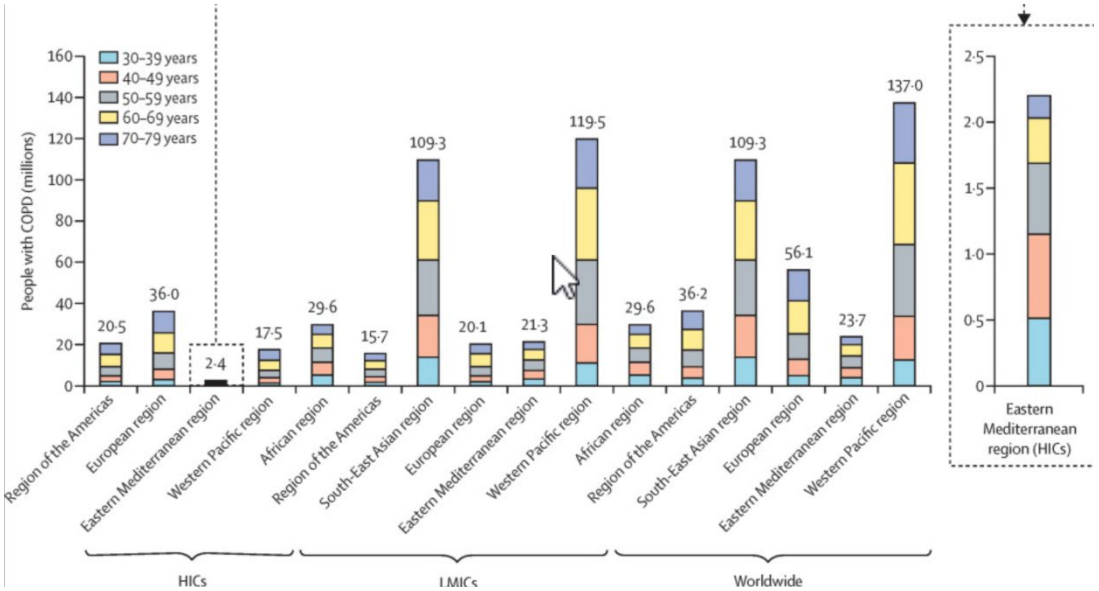
Chronic Obstructive Pulmonary Disease (COPD)

- Disease characterized by airflow limitation that is not fully reversible
- Usually progressive leading to physical impairment and extrapulmonary effects
- Highly heterogenous course
- Recurrent exacerbations



Adobe Stock | #228444876

Number of people with GOLD-COPD by region and age group in 2019



Prevalence:
11.7% in Western Pacific region
6.8% Americas

Germany among the ten countries with the most COPD cases (combined accounting for 65.2% or 255.4 million people)

Adeloye, D. et al, The Lancet Respir Med, 2022

Towards the elimination of chronic obstructive pulmonary disease: a *Lancet* Commission

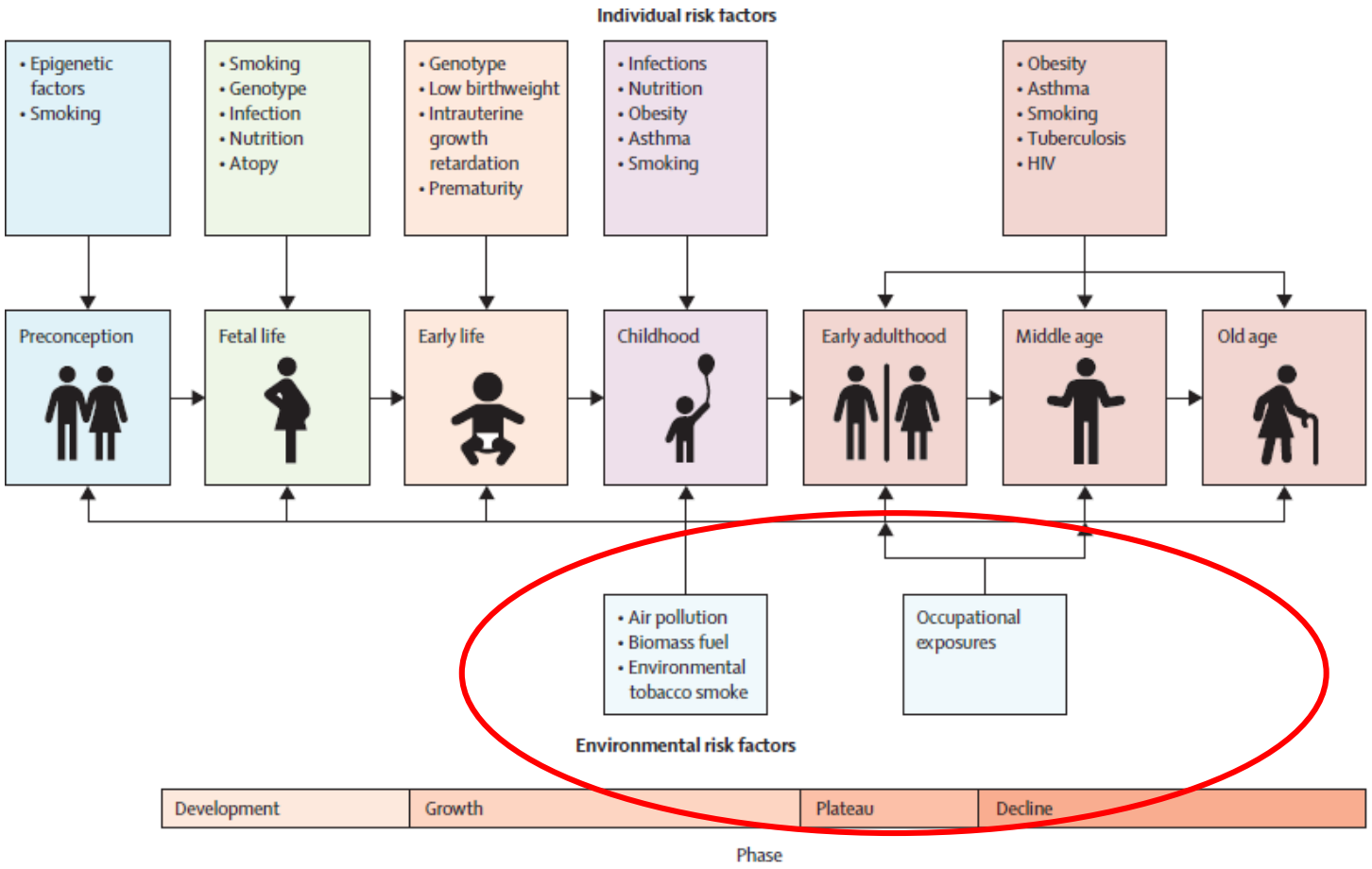
Daiana Stolz, Takudzwa Mkorombindo, Desiree M Schumann, Alvar Agusti, Samuel Y Ash, Mona Bafadhel, Chunxue Bai, James D Chalmers, Gerard R Criner, Shyamali Dharmage, Frits M E Franssen, Urs Frey, MeiLan Han, Nadia Hansel, Nathaniel Hawkins, Ravi Kalhan, Melanie Konigshoff, Fanny Ko, Trisha Parekh, Pippa Powell, Maureen Rutten-van Mölken, Jodie Simpson, Don D Sin, Yuanlin Song, Bela Suki, Thierry Troosters, George R Washko, Tobias Welte, Mark T Dransfield

Amsterdam, 11.02.2019

Proposal COPD Lancet Commission

- **COPD Subtypes 1-5** – beyond cigarette smoking
- **New diagnostic criteria for COPD** – beyond *spirometric*-defined obstruction
- **New definiton for exacerbation** – beyond symptoms & need for medical therapy

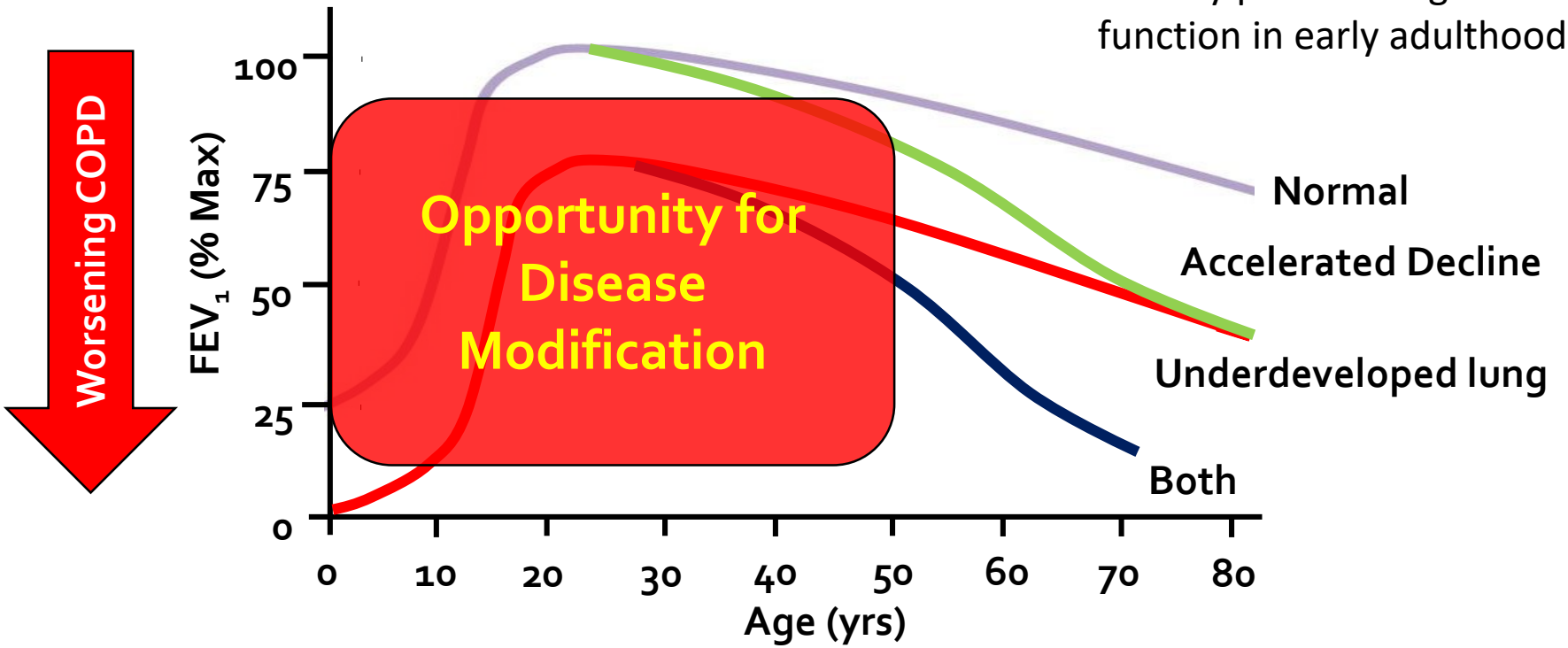
Early Life Events Impact COPD Development



Stolz et al, Lancet 2022

Different Pathways to COPD

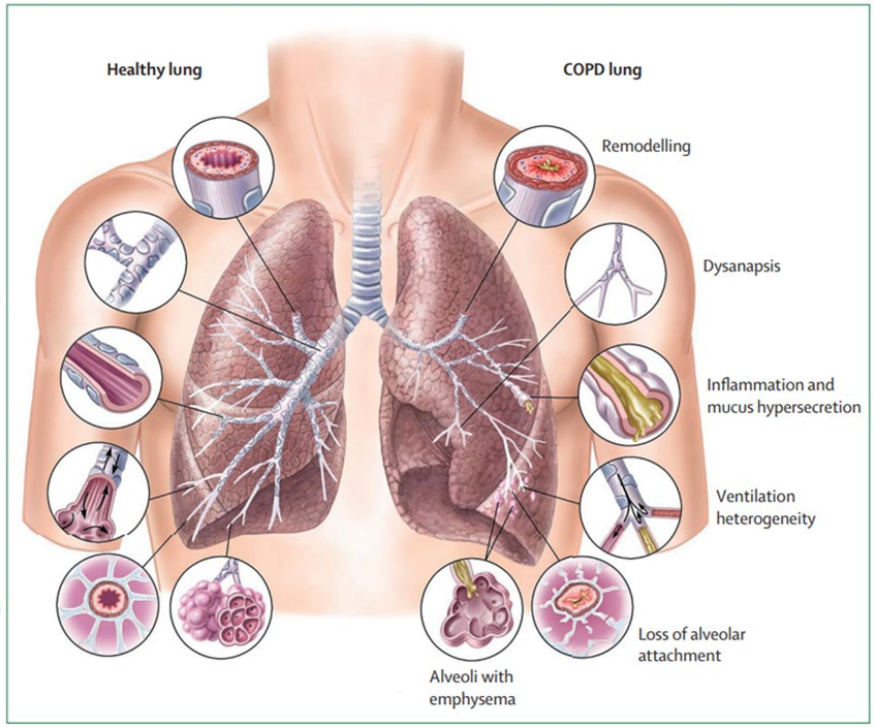
About 50% of patients with COPD have a normal rate of lung function decline, but never reached the expected healthy peak of lung function in early adulthood



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

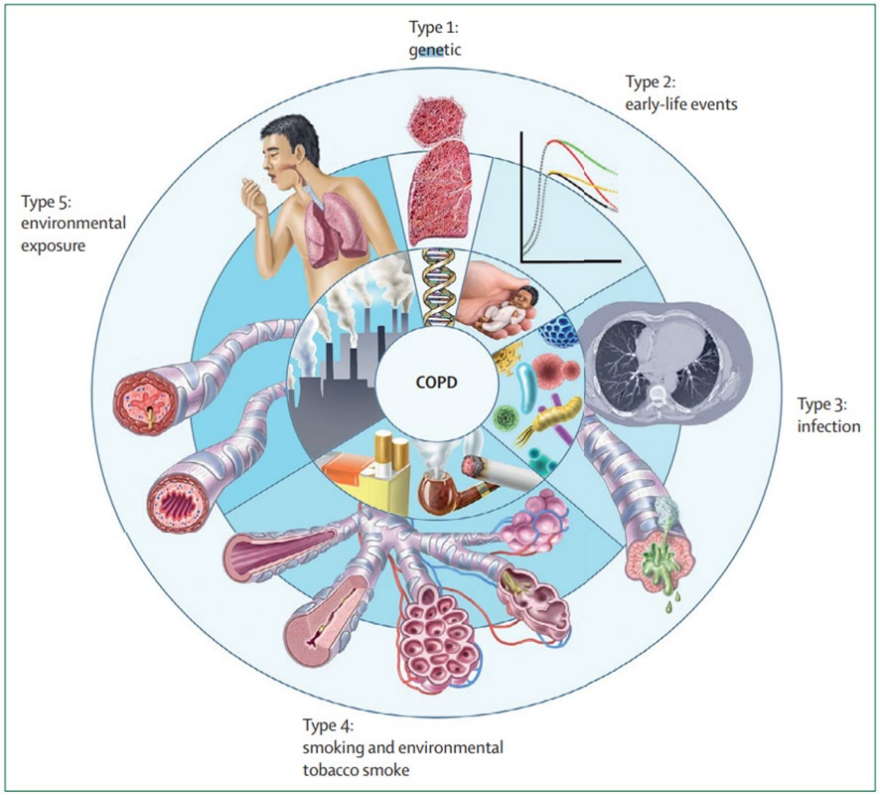
Chronic obstructive lung disease

- COPD is a complex and heterogeneous disease
- Heterogeneity manifests in the wide variations in respiratory symptoms, systemic consequences, and comorbid conditions
- Its pathophysiology implicates varying degrees of airway remodelling, inflammation, and tissue destruction



Stolz et al, Lancet 2022

A new classification of COPD based on risk factors



Why might this work?

- It reflects reality
- Different risks=different biology=different treatments
- It has worked before (pulmonary hypertension)
- It will galvanize support, advocacy, and funding

Stolz et al, Lancet 2022

Lancet commission COPD subtypes

- COPD should be classified into five types on the basis of the predominant risk factor driving the disease:
  - **Type 1 – genetically determined COPD**
  - **Type 2 - early-life events**
  - **Type 3 - respiratory infections**
  - **Type 4- related to smoking or vaping exposure**
  - **Type 5- environmental exposure-related**
- Individuals are prone to multiple exposures throughout life, which could cause additive or interactive damage to lung health

Panel: **Classification of COPD by the *Lancet* Commission on COPD**

Type 1: genetically determined COPD
- 1.1 α_1 antitrypsin deficiency
- 1.2 Telomerase reverse transcriptase mutations
- 1.3 Other genetic variants

Type 2: COPD related to early-life events
- 2.1 Prematurity (chronic lung disease of prematurity, bronchopulmonary dysplasia)
- 2.2 Childhood asthma

Type 3: infection-related COPD
- 3.1 Childhood respiratory infections
- 3.2 Tuberculosis-associated COPD
- 3.3 HIV-associated COPD

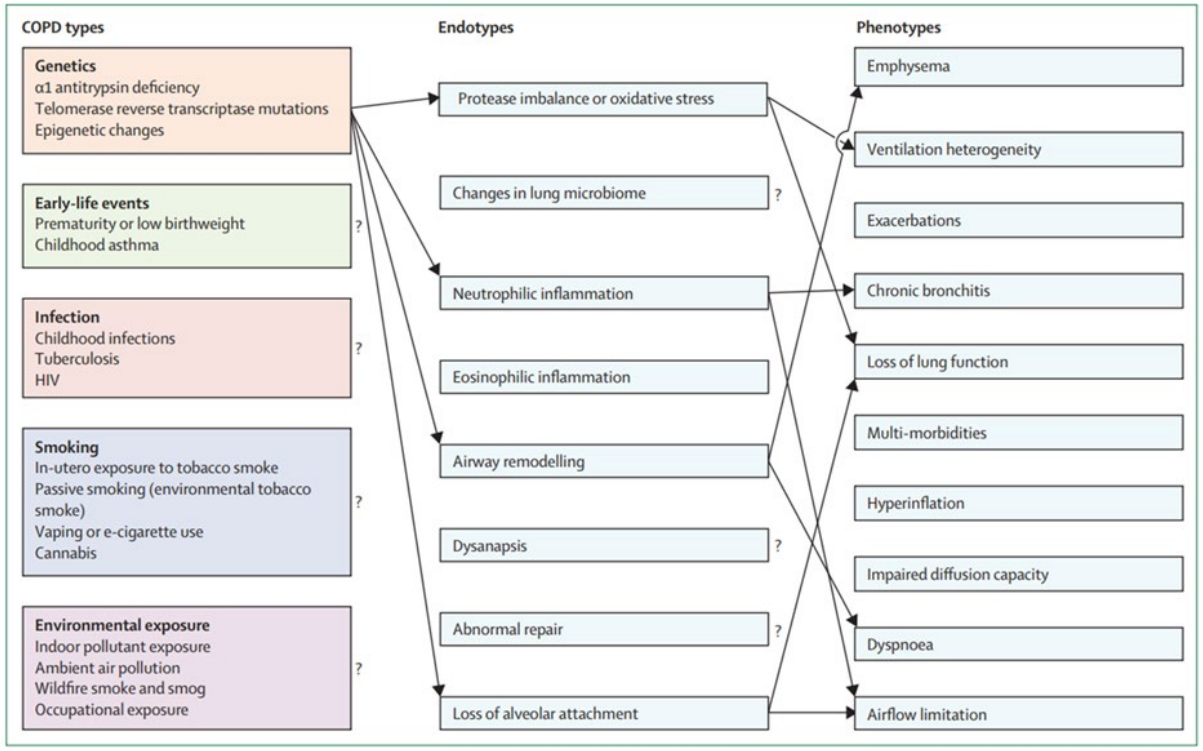
Type 4: COPD related to smoking or vaping
- 4.1 Tobacco smoking
- 4.2 In-utero exposure to tobacco smoke
- 4.3 Passive smoking (childhood and adult)
- 4.4 Vaping or e-cigarette smoking
- 4.5 Cannabis smoking

Type 5: environmental exposure-related COPD
- 5.1 Exposure to indoor air pollutants
- 5.2 Outdoor air pollution and smog
- 5.3 Wildfire smoke
- 5.4 Occupational exposures (to vapours, gases, dusts, or fumes)

COPD=chronic obstructive pulmonary disease.

Brusselle & Humbert, Editorial to Stolz et al, Lancet 2022

Association between proposed COPD subtypes, endotypes and phenotypes



Stolz et al, Lancet 2022

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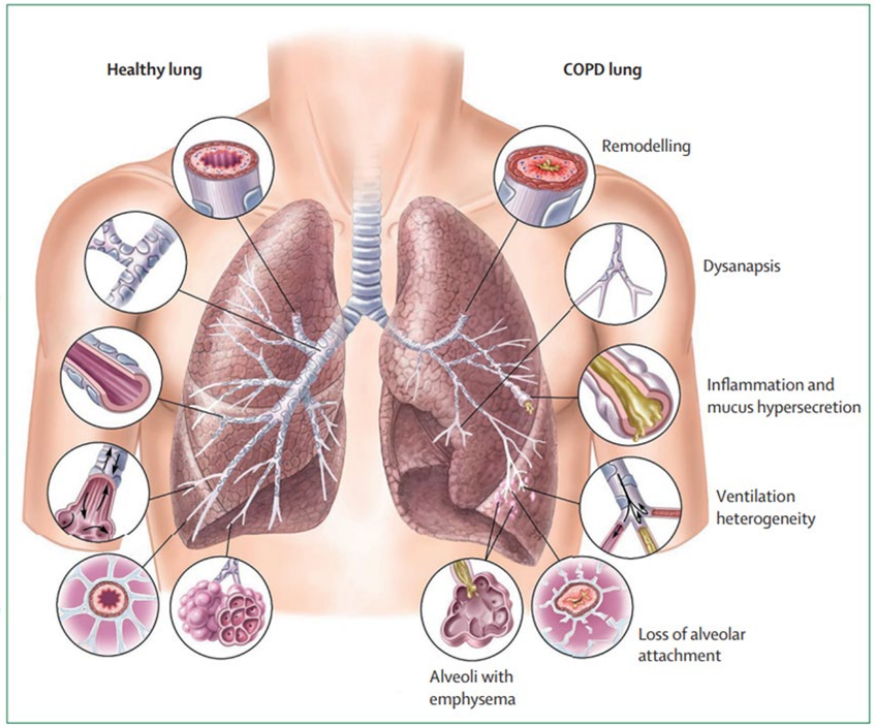
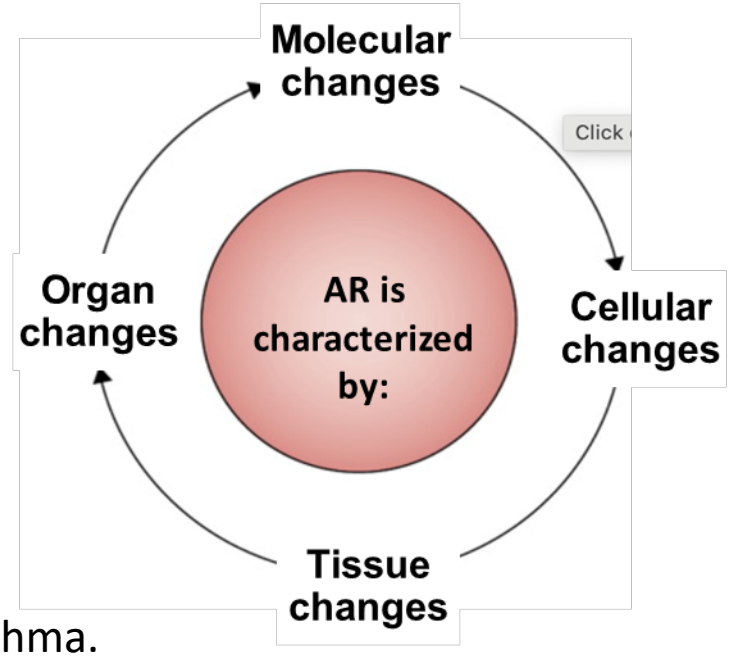


Stolz et al, Lancet 2022

Initial description of airway remodelling

- In a pioneering study in 1922 Huber and Koessler reviewed the necropsy findings of 21 patients who had died from severe asthma.
- “In addition to partial or total occlusion of the bronchial lumen by mucous plugs and extensive cellular infiltration of the bronchial wall, there was a prominent feature of thickening of the airway wall”

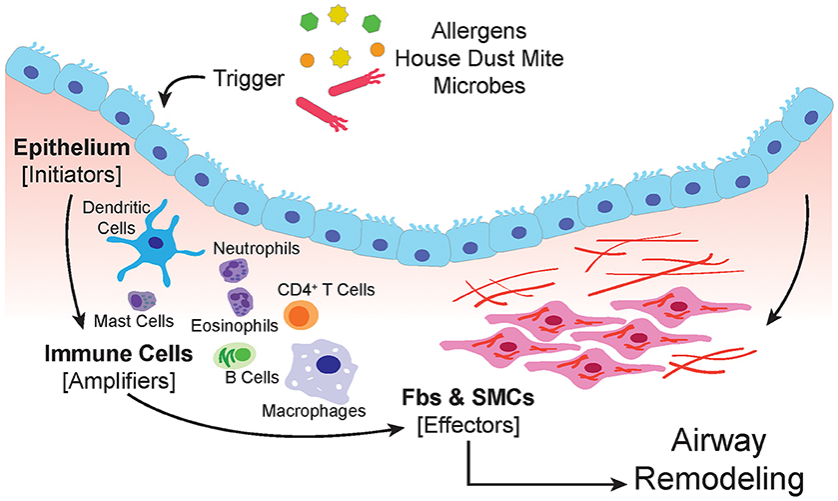
Airway remodeling comprises the structural changes of airway walls, induced by **repeated injury and repair processes**



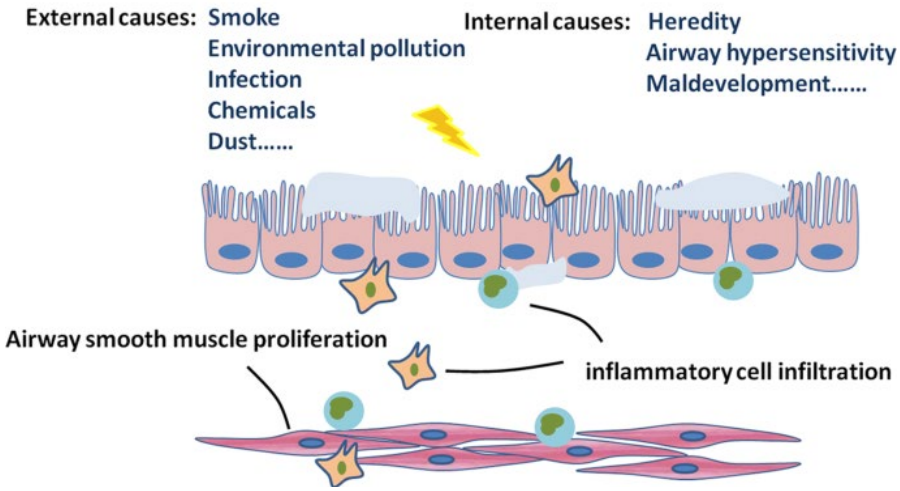
Huber HL, Koessler KK. The pathology of bronchial asthma. Arch Intern Med 1922

Causes of airway remodeling

Asthma



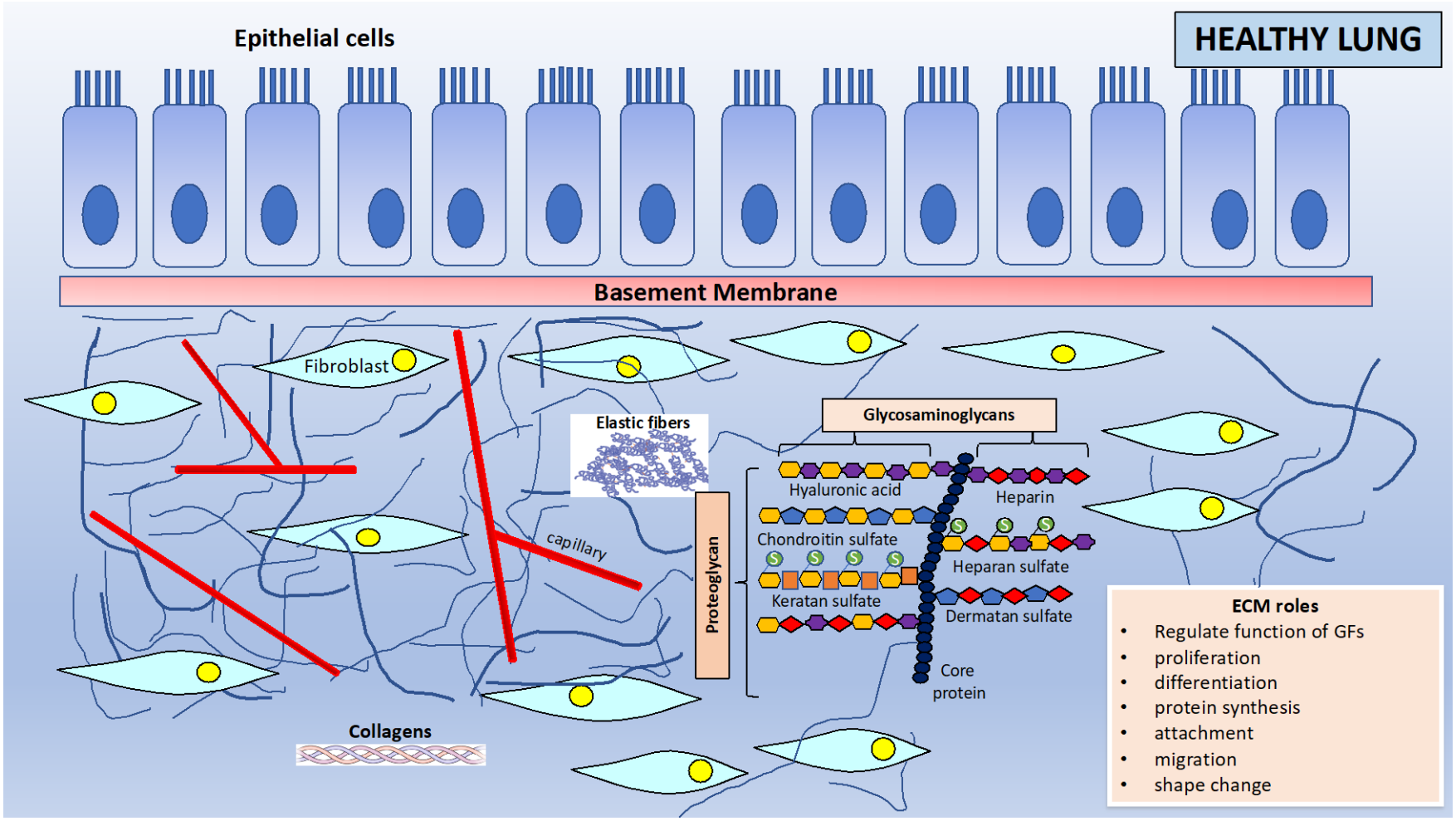
COPD



- increased ASM mass (hypertrophy and hyperplasia)
- epithelial cell hyperplasia
- squamous cell / goblet cell metaplasia and hyperplasia
- RBM thickening
- collagen deposition
- angiogenesis

Hough KP et al. (2020) *Front. Med, Yan F et al. J Transl Med 16, 262 2018 .*

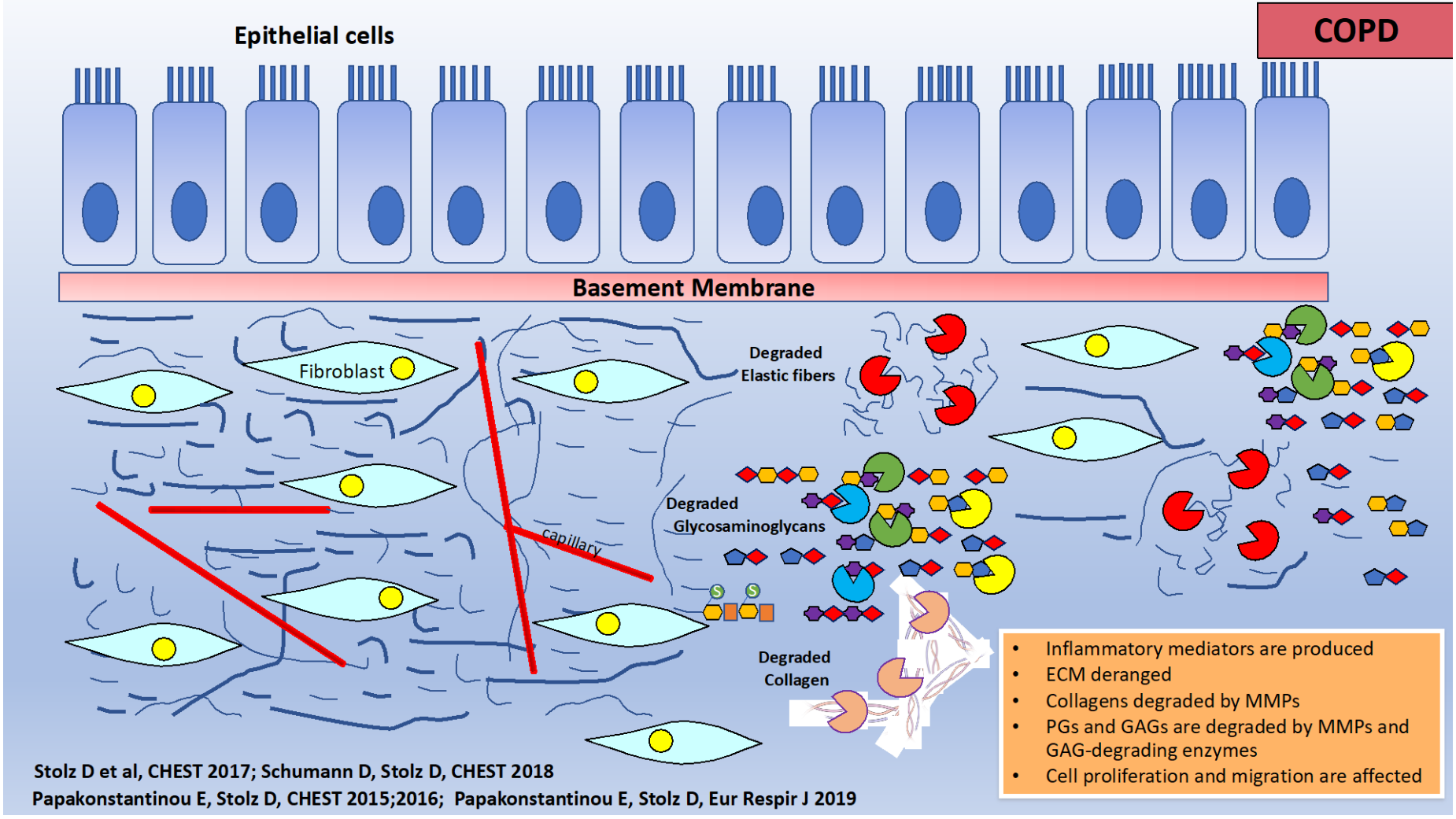
Extracellular matrix in the lung



Papakonstantinou E. & Stolz D, Eur Resp Review 2020

Extracellular matrix turnover is altered in COPD

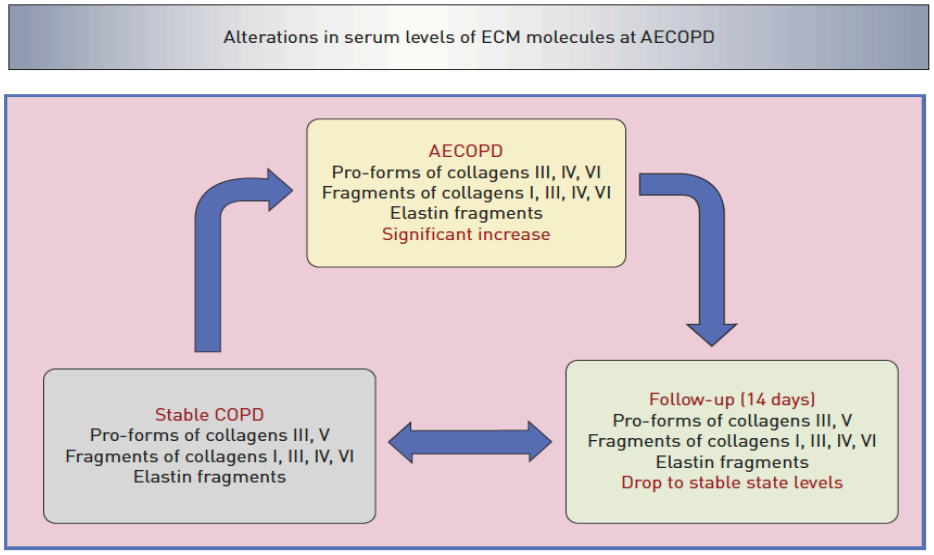
↑ MMP-9, TIMP-1, TIMP-2, heparan sulfate, chondroitin sulfate, hyaluronic acid

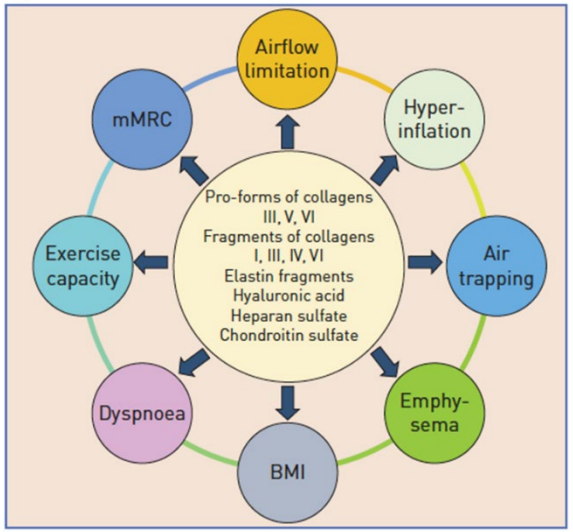


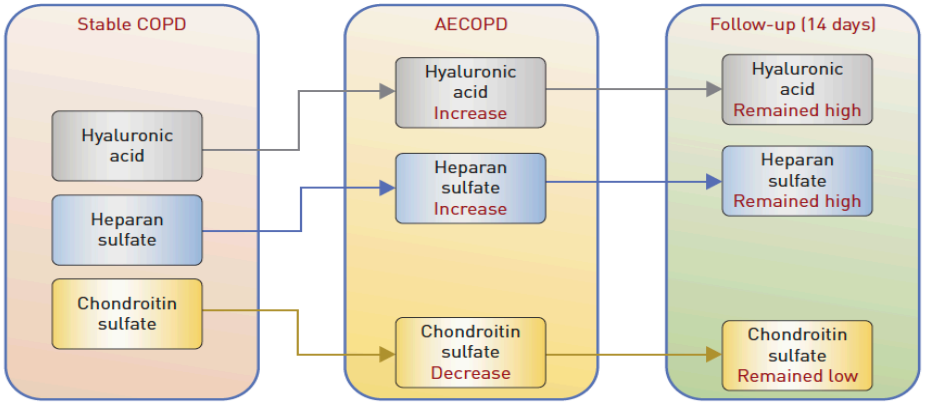
Stolz D et al, CHEST 2017; Schumann D, Stolz D, CHEST 2018

Papakonstantinou E, Stolz D, CHEST 2015;2016; Papakonstantinou E, Stolz D, Eur Respir J 2019

Circulating biomarkers of airway remodeling

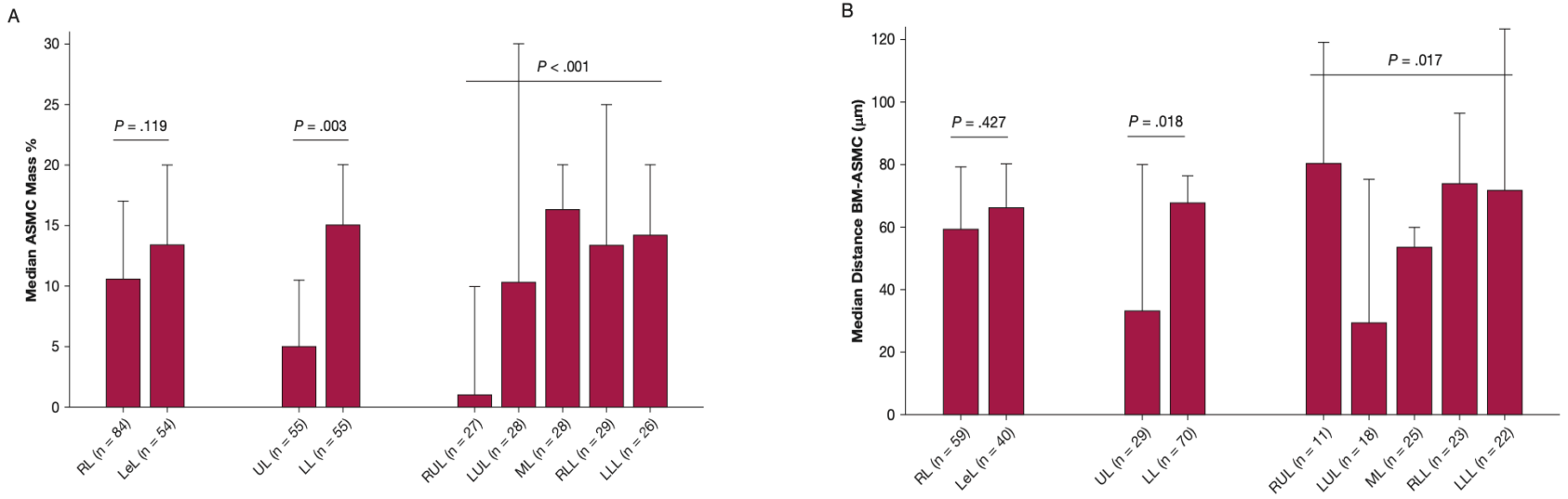






Stolz D et al. Chest 2017;
Papakonstantinou E..Stolz D. Chest 2015;
Papakonstantinou E...Stolz Dl. Eur Respir J 2019;
Schumann DM...Stolz D Chest 2018.
Papakonstantinou E...Stolz D. Respir Res 2015
Papakonstantinou E...Stolz D Chest 2016;
Papakonstantinou E...Stolz D. Eur Respir J 2017;
Karakioulaki M, Papakonstantinou E, Stolz D. Eur Respir Rev 2020

Assessment of airway remodeling



There are significant differences in features of airway remodeling between different lung lobes

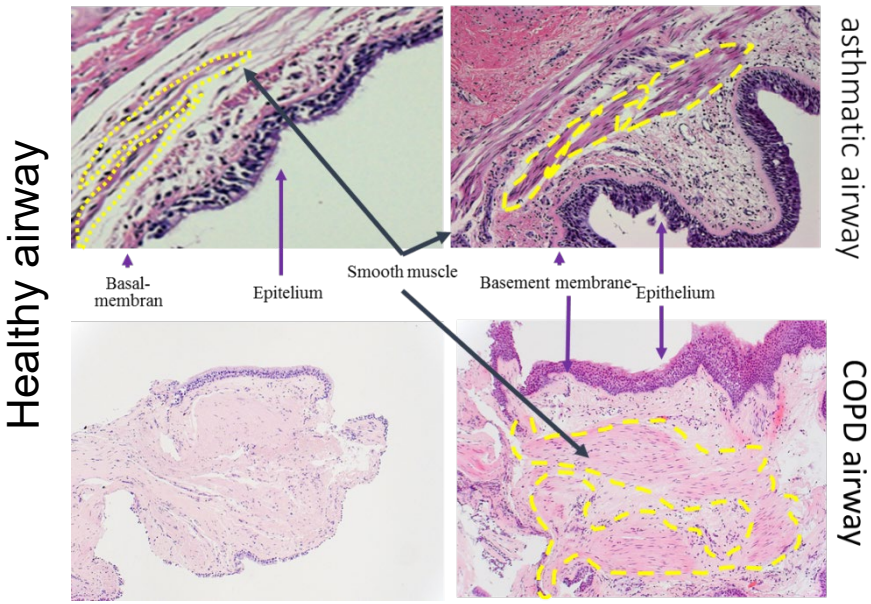
Karakioulaki M,…Stolz D, CHEST 2020

Airway remodeling can be used to differentiate COPD from ACO

Parameter	N=147 All COPD patients	N=19 All asthma patients	N=129 COPD patients without asthma features	N=12 Asthma patients <10 pack-years	N=7 Asthma patients >10 pack-years	N=18 COPD patients with asthma features[#]
Granulocytes in the epithelium[+]						
Absence	120 (81.6)	19 (100)	106 (82.2)	12 (100)	7 (100)	14 (77.8)
A few	27 (18.4)	0	23 (17.8)	0	0	4 (22.2)
Many	0	0	0	0	0	0
Goblet cells[+]						
Absence	45 (31.3)	2 (10.5)	38 (29.5)	1 (8.3)	1 (14.3)	7 (42.4)
A few	43 (24.5)	15 (73.7)	39 (24.8)	10 (83.3)	5 (71.4)	4 (22.2)
Many	47 (44.2)	2 (10.5)	41 (45.7)	1 (8.3)	1 (14.3)	6 (33.3)
Not detectable[§]	12 (8.2)		11 (8.5)			1 (5.5)
BM thickening[+]						
Normal	14 (9.3)	1 (5.3)	11 (8.5)	1 (8.3)		3 (16.7)
Mild–moderate	59 (40.1)	14 (73.7)	57 (44.2)	9 (75.0)	5 (71.4)	2 (11.1)
Severe	71 (48.2)	4 (21.1)	58 (45.0)	2 (16.7)	2 (28.6)	13 (72.2)
ASMC %	21.5±9.4	21.5±16.7	21.0±16.6	22.0±7.9	20.7±12.1	24.3±17.7
Distance BM–ASMC µm	80.5±55.5	62.6±21.1	80.4±55.9	62.8±23.8	62.1±23.8	81.3±55.2
Glands %	8.5±13.4	4.8±5.5	8.2±12.9	5.1±6.2	4.3±4.8	10.4±16.3
Eosinophils in BAL[f]	0.9±5.7	1.5±2.8	0.9±6.1	1.2±2.8	2.1±3.1	0.4±0.9
Leukocytes in BAL						
None	33 (22.4)	6 (31.6)	29 (22.4)	2 (16.7)	4 (57.1)	4 (22.2)
A few	69 (46.9)	13 (68.4)	59 (45.7)	10 (83.3)	3 (42.8)	10 (55.5)
Many	30 (20.4)		28 (21.7)			2 (11.1)
Excessive	10 (13.6)		8 (6.2)			2 (11.1)
Missing values	5 (3.4)		5 (3.8)			

Papakonstantinou E, … Stolz D. Eur Respir J 2019

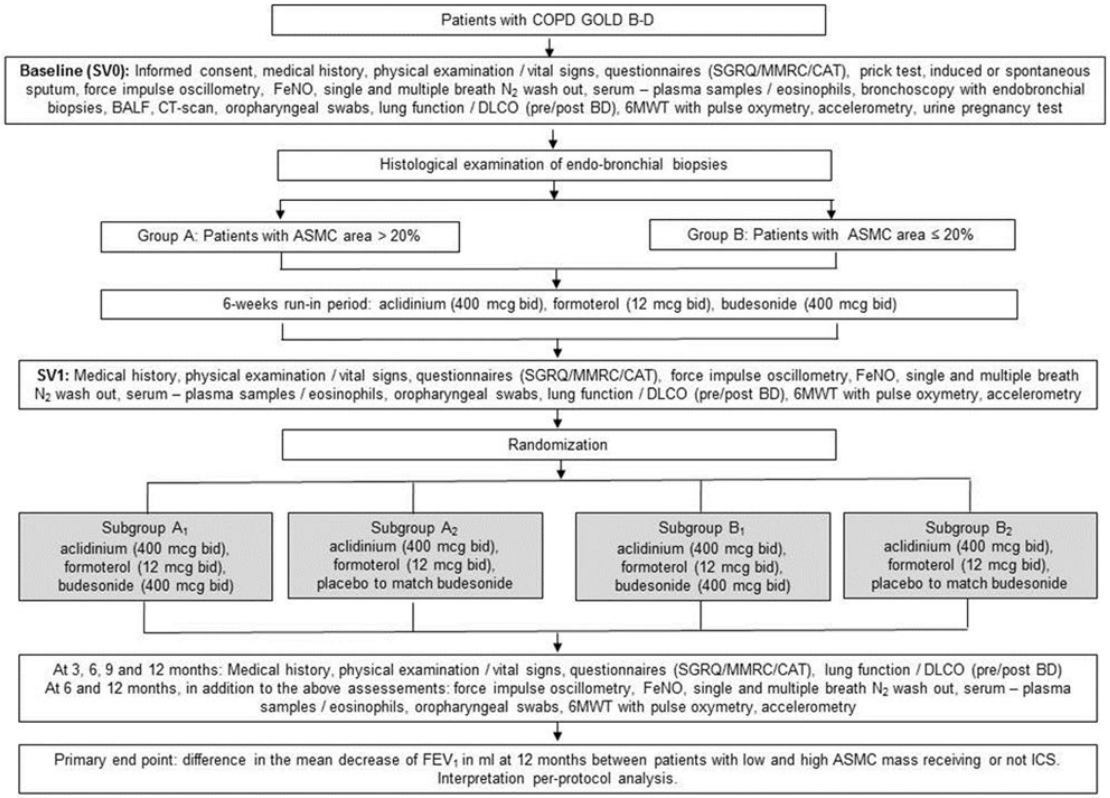
Can the endotype predict response to inhaled therapy?



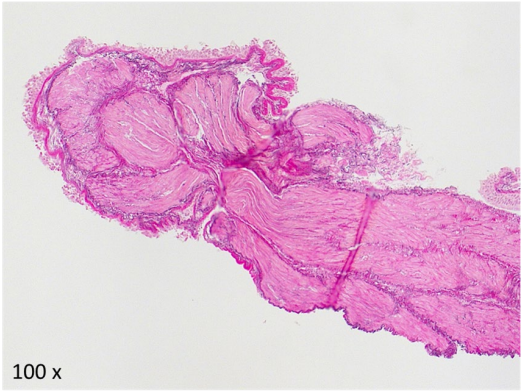
- Higher tissue eosinophilic infiltration (p=0.048) in asthma
- Asthma patients with <10PY had more severe inflammation in the stroma (p=0.008).
- ASMC and severe BM thickening was found in more COPD patients with asthma features versus without asthma features (p=0.021)

Papakonstantinou E. & Stolz, D., ERJ 2019

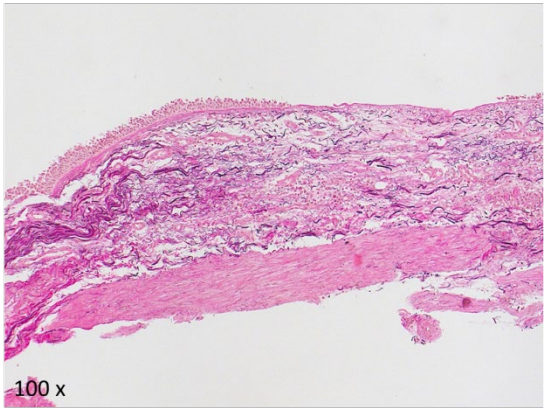
Prediction of response to triple therapy- the HISTORIC study



Airway smooth muscle cells (ASM): 90%



Airway smooth muscle cells (ASM): 25%

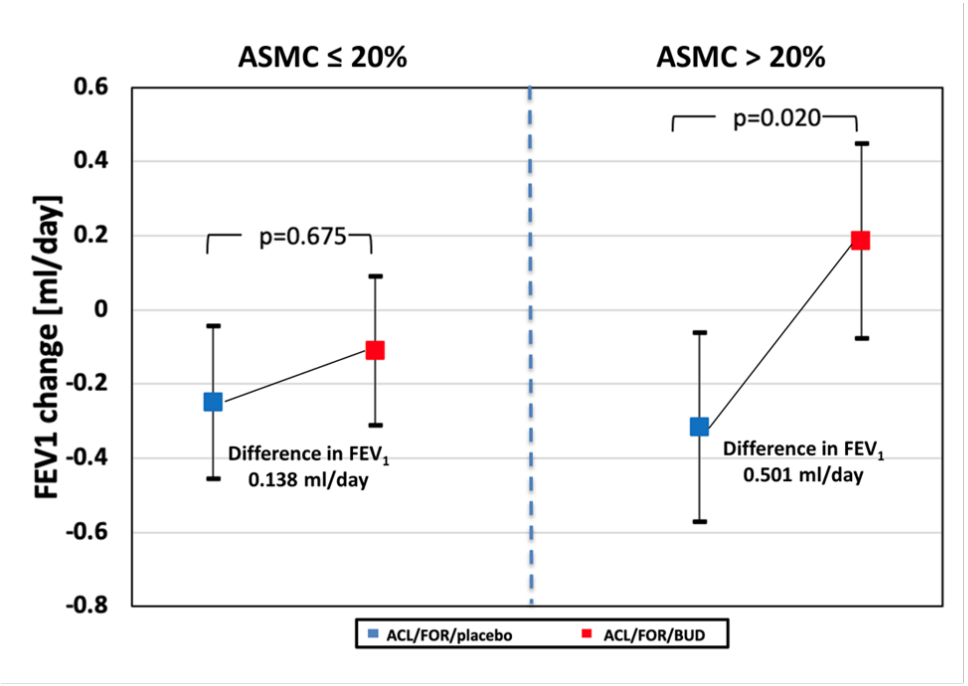


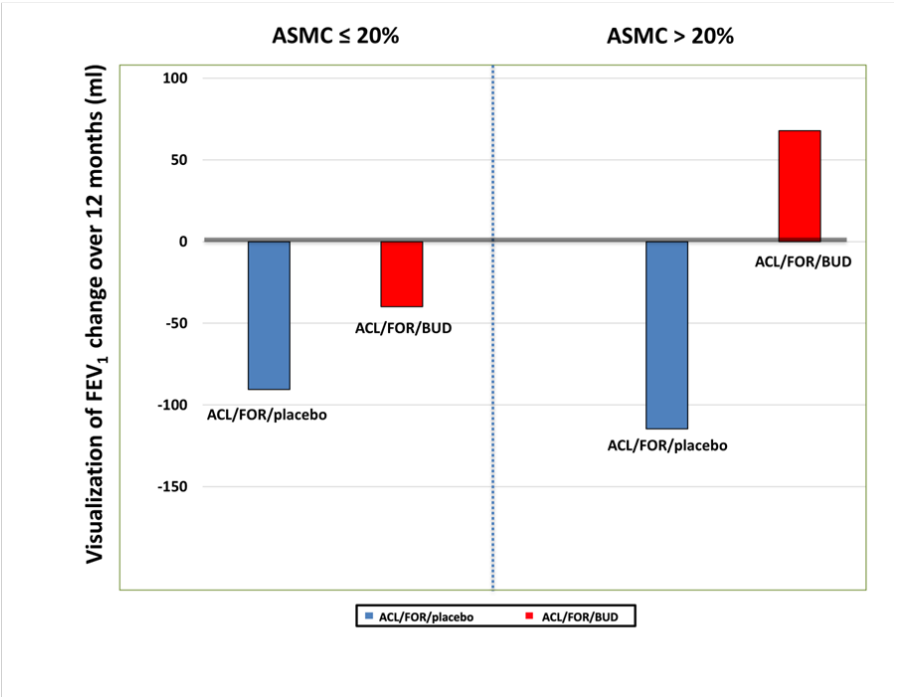
Stolz D. et al, ERJ 2019

The HISTORIC study

- Inclusion criteria: ≥40 years, current or ex-smokers with smoking history ≥10 pack-years, COPD, GOLD stage B-D and at least one exacerbation in the previous year
- Patients were divided in 2 groups A and B with high (>20%) and with low (≤20%) ASMC mass
- All patients followed a run-in period of 6 weeks on open-label triple inhaled therapy with aclidinium (ACL, 400 mcg, bid), formoterol (FOR, 12 mcg, bid) and budesonide (BUD, 400 mcg, bid)
- Subsequently, patients from each group were randomized (1:1) to receive either triple treatment with ACL/FOR/BUD (groups A1 and B1) or ACL/FOR/Placebo (groups A2 and B2)
- Patients, investigators and the funder were masked to treatment allocation and patients were followed for 12 months
- The primary end point of the study was the difference in post-bronchodilator FEV1 at 12 months between patients with ASMC ≤20% and ASMC >20% receiving or not ICS

Airway smooth muscle area to predict steroid responsiveness in COPD patients receiving triple therapy: a randomized, placebo-controlled, double-blind, investigator-initiated trial – the HISTORIC Study





Stolz D, Eur. Respir. J. 2023

Secondary outcomes

Change of secondary outcomes within 12 months

Outcome	Patients with ASMC ≤20%		Patients with ASMC >20%	
	ACL/FOR/Placebo 400/12 mcg (n=54)	ACL/FOR/BUD 400/12/400 mcg (n=56)	ACL/FOR/Placebo 400/12 mcg (n=34)	ACL/FOR/BUD 400/12/400 mcg (n=33)
	Adjusted mean change during 12 months (95% CI)			
MMRC Dyspnea Scale	0.30 (-0.02 to 0.75)	0.32 (-0.11 to 0.76)	0.47 (-0.07 to 1.02)	0.88 (0.30 to 1.45)
CAT (total score)	3.03 (0.46 to 5.61)	1.41 (-1.06 to 3.92)	0.90 (-2.26 to 4.08)	-1.94 (-5.22 to 1.33)
SF-36 (general health score)	-8.73 (-16.18 to -1.24)	-8.84 (-16.07 to -1.57)	-11.21 (-20.45 to -1.97)	-3.18 (-12.71 to 6.30)
SGRQ (total score)	2.09 (-3.87 to 8.07)	2.93 (-2.85 to 8.73)	8.58 (1.19 to 15.96)	0.67 (-6.90 to 8.28)
Fractional exhaled NO (ppb)	6.43 (-8.66 to 21.53)	-0.84 (-15.52 to 13.83)	26.18 (7.51 to 44.85)	1.06 (-18.15 to 20.31)
FEV1 % predicted/VC max PB	-2.56 (-4.64 to -0.44)	-0.66 (-2.67 to 1.38)	-2.26 (-4.86 to 0.31)	0.47 (-2.19 to 3.14)
RV (% predicted) Post bronchodilator	2.28 (-4.38 to 8.960)	0.14 (-6.31 to 6.63)	6.36 (-1.86 to 14.61)	-3.47 (-11.98 to 5.03)
FVC (% predicted) Post bronchodilator	0.04 (-4.38 to 4.49)	0.31 (-3.98 to 4.64)	-3.58 (-9.09 to 1.90)	2.69 (-2.96 to 8.36)
TLC (% predicted) Post bronchodilator	1.46 (-0.99 to 3.91)	-0.62 (-3.00 to 1.76)	1.57 (-1.42 to 4.61)	0.57 (-2.52 to 3.70)
DLCO SB/VA (% predicted) Post bronchodilator	-3.62 (-6.17 to -1.02)	-2.15 (-4.68 to 0.34)	0.34 (-2.85 to 3.54)	-5.84 (-9.13 to -2.56)
N_2-MBW: LCI 2,5 % normal	2.58 (-0.95 to 6.13)	1.41 (-2.01 to 4.86)	4.12 (-0.26 to 8.50)	5.86 (1.34 to 10.38)
N_2-SBW: % Predicted	-85.43 (-233.80 to 62.95)	122.60 (-21.66 to 266.89)	69.92 (-113.59 to 253.43)	-43.87 (-233.03 to 145.29)
Forced Impuls Oscillometry X5 [cmH2O.s]	-0.99 (-1.75 to -0.18)	-0.26 (-1.02 to 0.48)	-0.04 (-1.02 to 0.93)	0.26 (-0.73 to 1.27)

Stolz et al, ERJ 2023

Proposal COPD Lancet Commission

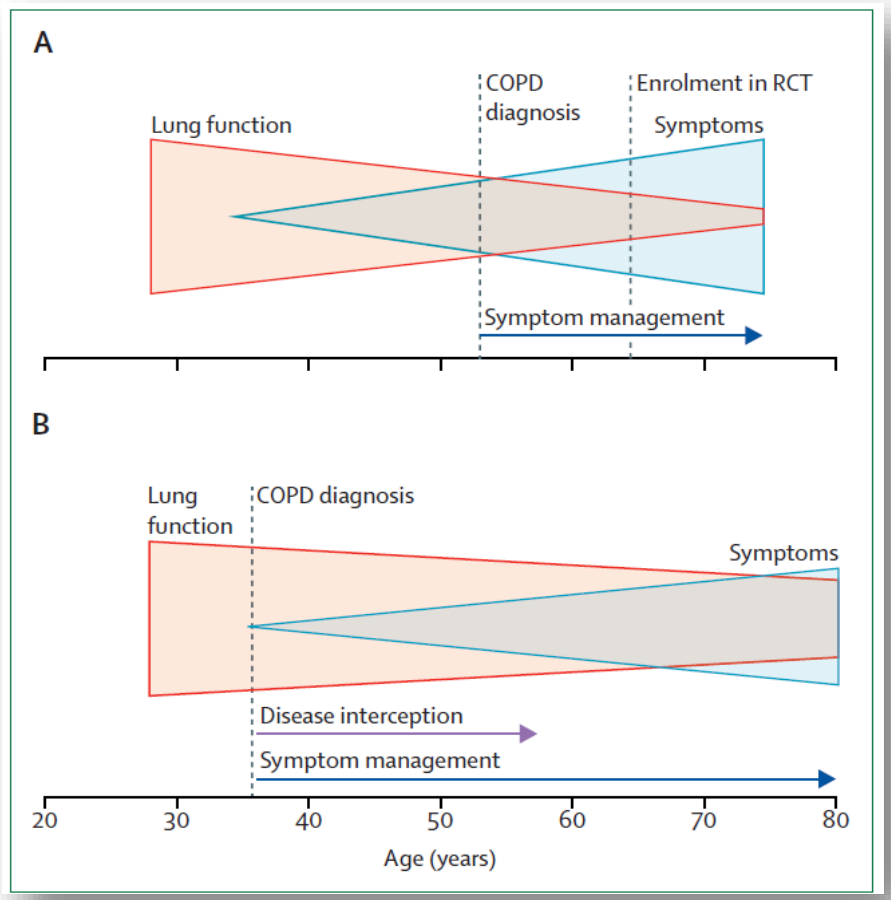
- **COPD Subtypes 1-5** – beyond cigarette smoking
- **New diagnostic criteria for COPD** – beyond *spirometric*-defined obstruction
- **New definiton for exacerbation** – beyond symptoms & need for medical therapy

Stolz et al, Lancet 2022

The importance of early diagnosis

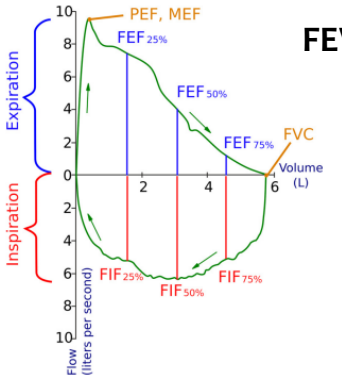
Status quo

Future?



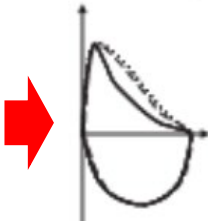
COPD – Chronic Obstructive Pulmonary Disease; RCT – Randomized Controlled Trial
Stolz D, *et al.* Lancet. 2022;400(10356):921-972.

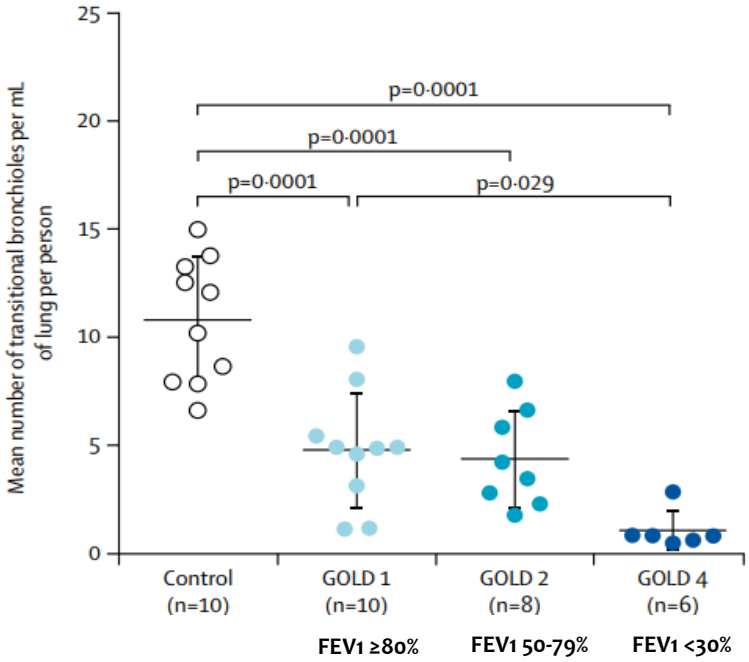
Lung function and lung destruction in COPD



FEV1

GOLD1 or 2

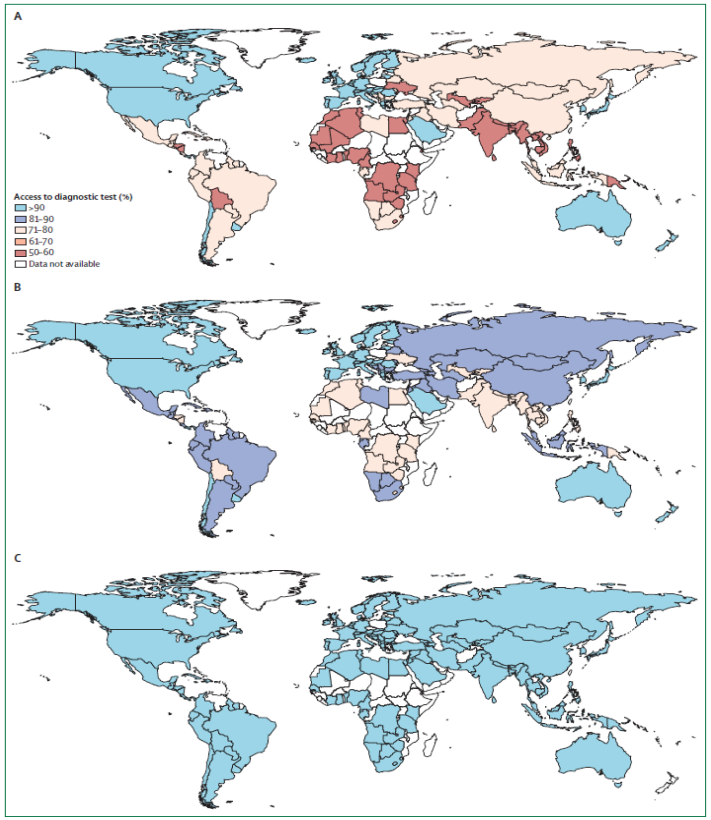




- Small airways rather than alveoli are the initial site of injury
- GOLD I has already lost 40% of the terminal bronchioles and 56% of the transitional bronchioles
- Independent to emphysema

Stolz et al. Lancet 2022 Hogg et al. Physiol Rev 2017;97:529-52 Koo et al. Lancet RM 2018;6:591-602

Spirometrie is not widely available



	Primary and specialist care	Primary care only	Specialist care only	Limited* availability in primary or specialist care, or both	Not available
Lower-middle-income countries (n=11)					
Spirometry	2 (18%)	0	4 (36%)	5 (45%)	0
Reversibility testing	1 (9%)	0	6 (55%)	4 (36%)	0
Whole body plethysmography	0	0	3 (27%)	5 (45%)	3 (27%)
Diffusion capacity measurement	0	0	3 (27%)	5 (45%)	3 (27%)
Arterial blood gas analysis	0	0	6 (55%)	5 (45%)	0
Chest radiography	6 (55%)	3 (27%)	0	2 (18%)	0
Chest CT	1 (9%)	0	7 (64%)	3 (27%)	0
Upper-middle-income countries (n=15)					
Spirometry	3 (20%)	2 (13%)	6 (40%)	4 (27%)	0
Reversibility testing	2 (13%)	1 (7%)	8 (53%)	4 (27%)	0
Whole body plethysmography	0	0	5 (33%)	9 (60%)	1 (7%)
Diffusion capacity measurement	0	0	6 (40%)	8 (53%)	1 (7%)
Arterial blood gas analysis	1 (7%)	2 (13%)	8 (53%)	4 (27%)	0
Chest radiography	8 (53%)	4 (27%)	3 (20%)	0	0
Chest CT	3 (20%)	0	10 (67%)	2 (13%)	0
High-income countries (n=17)					
Spirometry	12 (71%)	1 (6%)	3 (18%)	1 (6%)	0
Reversibility testing	8 (47%)	0	9 (53%)	0	0
Whole body plethysmography	0	0	16 (94%)	1 (6%)	0
Diffusion capacity measurement	1 (6%)	0	14 (82%)	2 (12%)	0
Arterial blood gas analysis	1 (6%)	0	15 (88%)	1 (6%)	0
Chest radiography	12 (71%)	0	4 (24%)	1 (6%)	0
Chest CT	4 (24%)	0	12 (71%)	1 (6%)	0

Stolz D, *et al.* Lancet. 2022;400(10356):921-972

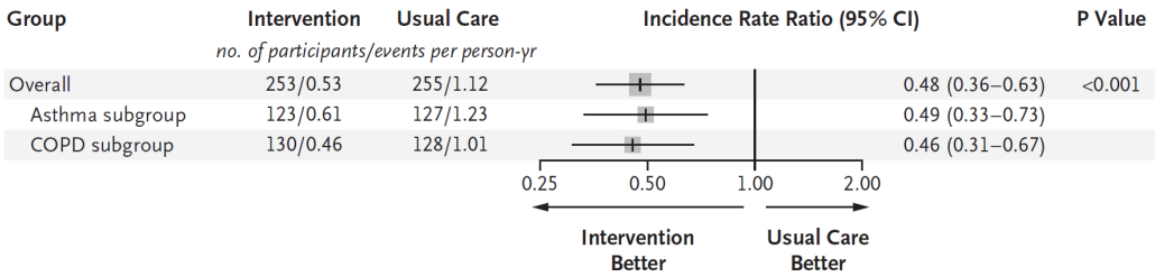
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Diagnosis and Treatment of COPD and Asthma — A Randomized, Controlled Trial

Authors: Shawn D. Aaron, M.D., Katherine L. Vandemheen, M.Sc.N., G. Alex Whitmore, Ph.D., Celine Bergeron, M.D., Louis-Philippe Boulet, M.D., Andréanne Côté, M.D., R. Andrew McIvor, M.D., +14, for the UCAP Investigators* Author Info & Affiliations

Published May 19, 2024 | DOI: 10.1056/NEJMoa2401389



- Patients with respiratory symptoms
- Pneumologist diagnosis of obstruction
- Therapy let to the discretion of the attending physician

We need to identify early disease

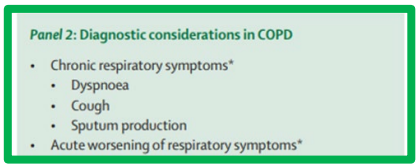
TABLE 1 Global Initiative for Chronic Obstructive Lung Disease update for 2023: key updates and potential missed opportunities

Updates	Missed opportunities
Revised definition based on biology	Continued requirement for post-bronchodilator spirometry for diagnosis
New taxonomy based on etiotypes	Continued requirement for spirometric airflow limitation to diagnose disease
Elimination of group C	Limited role for computed tomography and non-spirometric lung function testing
Definitive statement about triple therapy and mortality	Case finding as an option rather than routine
Objective evaluation of exacerbations	Potential undertreatment after severe exacerbations

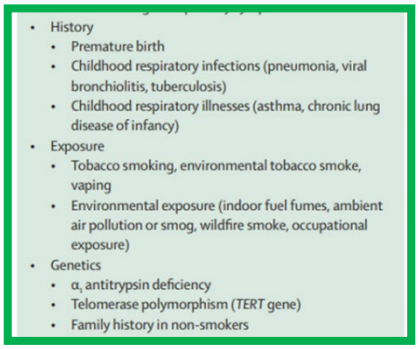
Stolz et al, ERJ 2023

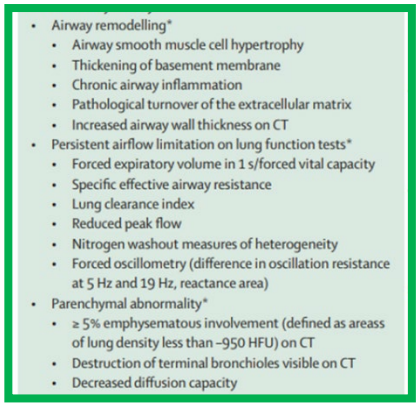
COPD defined by the Lancet commission

- Diagnosis criteria:
  - presence of respiratory symptoms AND
  - personal history of risk factors AND
  - persistent airflow limitation or ventilator heterogeneity as assessed by spirometry, other pulmonary function testing, histology or CT


***Panel 2*: Diagnostic considerations in COPD**

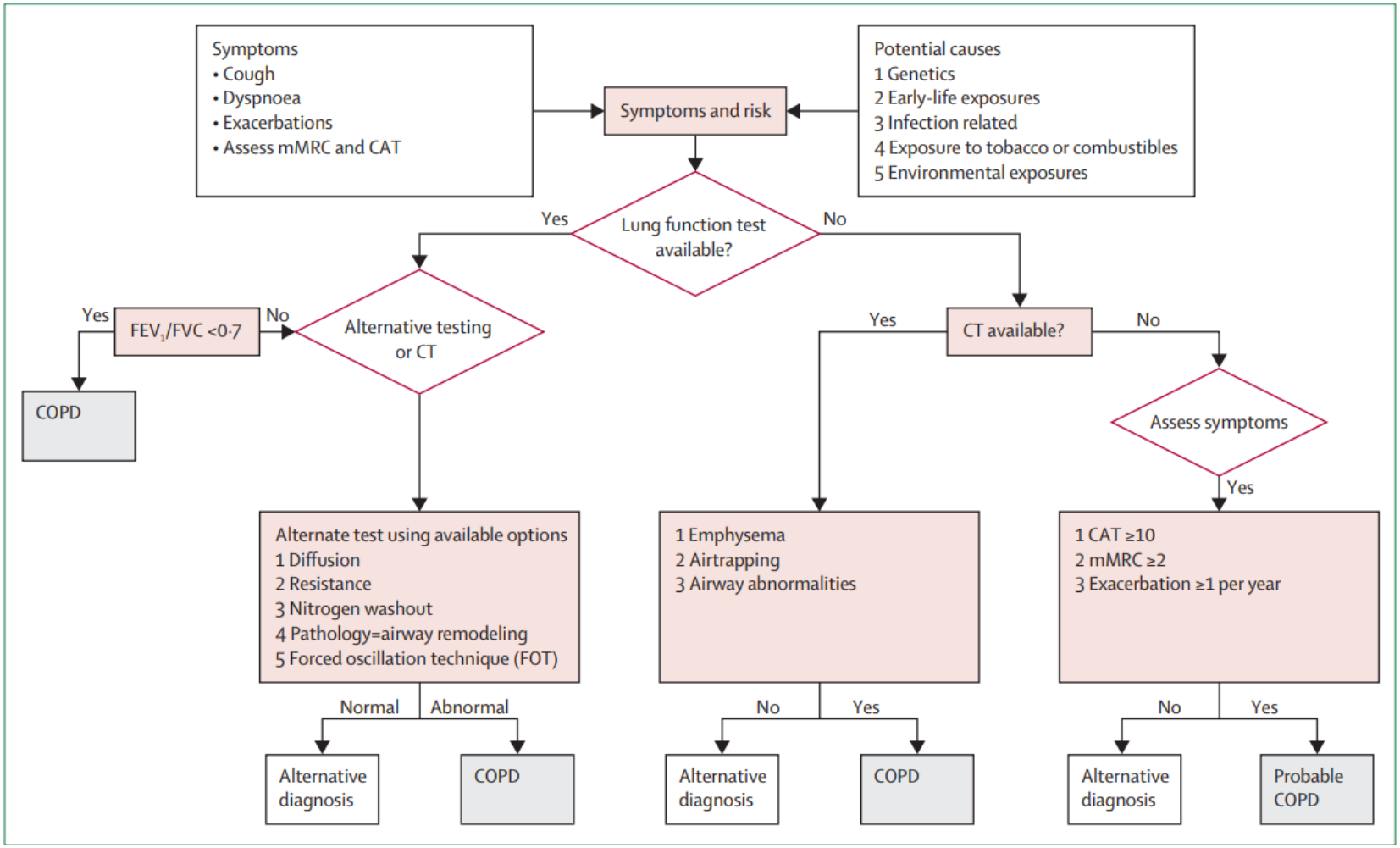
- Chronic respiratory symptoms*
  - Dyspnoea
  - Cough
  - Sputum production
- Acute worsening of respiratory symptoms*


- History
  - Premature birth
  - Childhood respiratory infections (pneumonia, viral bronchiolitis, tuberculosis)
  - Childhood respiratory illnesses (asthma, chronic lung disease of infancy)
- Exposure
  - Tobacco smoking, environmental tobacco smoke, vaping
  - Environmental exposure (indoor fuel fumes, ambient air pollution or smog, wildfire smoke, occupational exposure)
- Genetics
  - α$_1$ antitrypsin deficiency
  - Telomerase polymorphism (*TERT* gene)
  - Family history in non-smokers

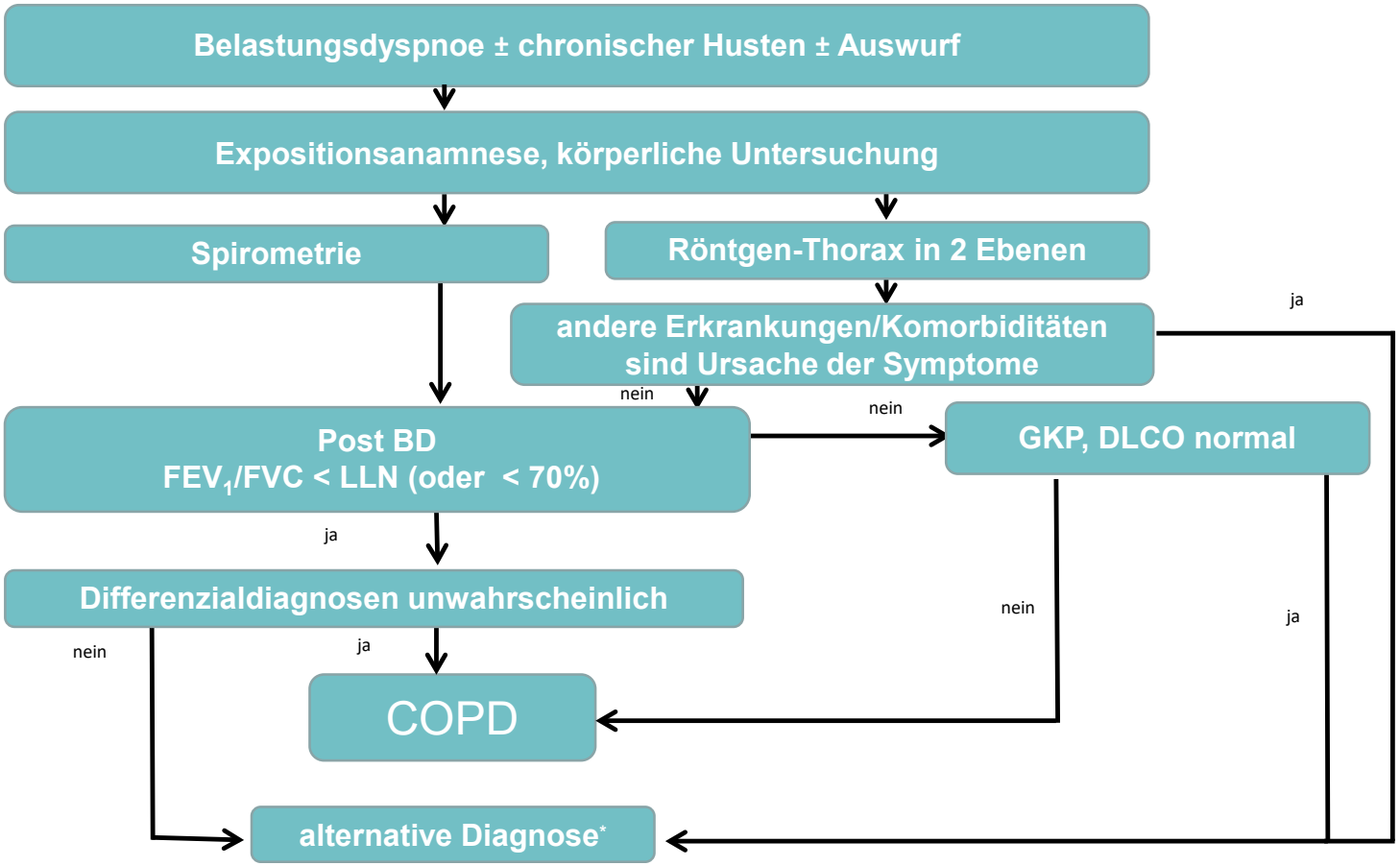

- Airway remodelling*
  - Airway smooth muscle cell hypertrophy
  - Thickening of basement membrane
  - Chronic airway inflammation
  - Pathological turnover of the extracellular matrix
  - Increased airway wall thickness on CT
- Persistent airflow limitation on lung function tests*
  - Forced expiratory volume in 1 s/forced vital capacity
  - Specific effective airway resistance
  - Lung clearance index
  - Reduced peak flow
  - Nitrogen washout measures of heterogeneity
  - Forced oscillometry (difference in oscillation resistance at 5 Hz and 19 Hz, reactance area)
- Parenchymal abnormality*
  - ≥ 5% emphysematous involvement (defined as areass of lung density less than –950 HFU) on CT
  - Destruction of terminal bronchioles visible on CT
  - Decreased diffusion capacity

Stolz et al, Lancet 2022

COPD Lancet Commission diagnostic algorithm



Diagnosis of COPD in Germany



NVL Germany, 2022

Triple therapy in Tobacco-Exposed Persons with symptoms and preserved FEV1/FVC ratio - an investigator initiated, interventional study

The CHRONOS study

Inclusion criteria

Both groups:

- Age ≥40
- FEV1/FVC ≥0.70
- FVC above the lower limit of the normal range

Intervention group:

- Current or past smokers ≥10 pack years
- Relevant respiratory symptoms

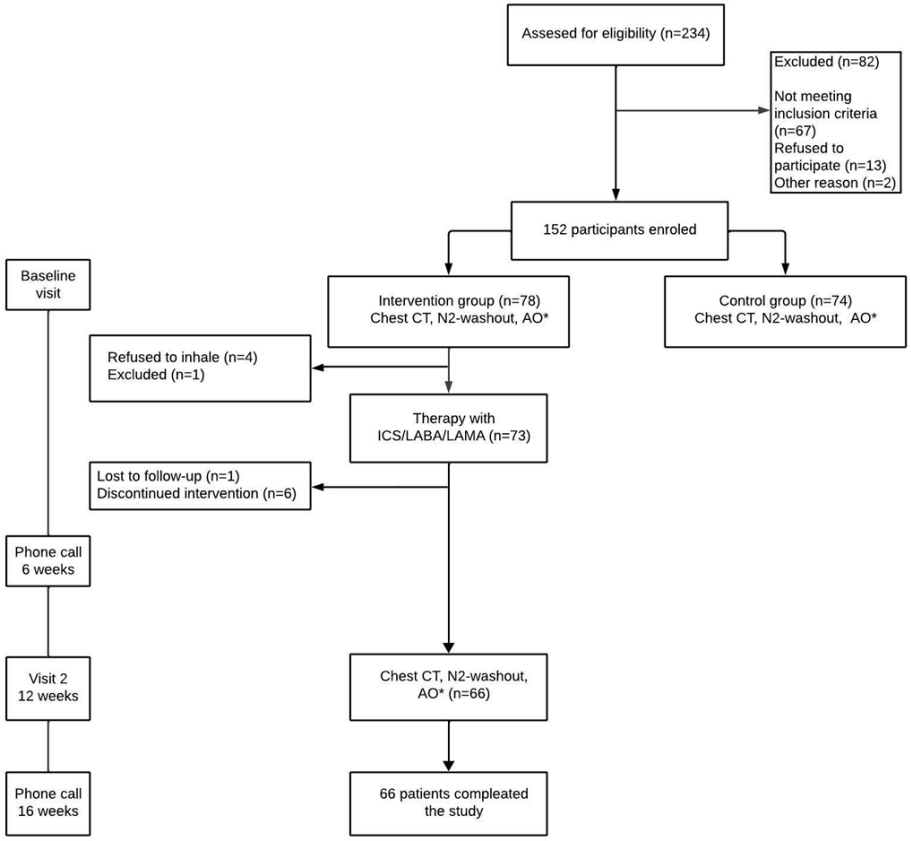
Control group:

- ≤1 pack year tobacco-smoking history

Exclusion criteria

Both groups:

- Currently diagnosed asthma
- Known concomitant respiratory disease or clinically significant bronchiectasis
- Active pulmonary infection or prior pulmonary infection where antibiotic and/or steroid treatment was completed ≤4 weeks prior to enrolment
- Chronic use of oral steroids (>10 mg per day)



Proposal COPD Lancet Commission

- **COPD Subtypes 1-5** – beyond cigarette smoking
- **New diagnostic criteria for COPD** – beyond *spirometric*-defined obstruction
- **New definiton for exacerbation** – beyond symptoms & need for medical therapy

Stolz et al, Lancet 2022

Exacerbation is a risk factor in COPD

- ↑ Morbidity
- ↑ Mortality
- ↑ Hospital admission
- ↑ Healthcare costs
- Long-term decline in lung function

Rate of next severe

Mortality risk increases with each new exacerbation: there is a fivefold greater risk of mortality after the 10th AECOPD

Stolz D. et al, Respiration 2018, Suissa S, et al, 2012

Why do we need a new definition for exacerbation? - we need objective measures -

- *"An exacerbation should be defined as an increase in* ***cough, dyspnoea, or sputum production*** *and* ***at least one of an increase in airflow limitation or ventilation heterogeneity, an increase in airway or systemic inflammation, or evidence of bacterial or viral infection****, in the absence of evidence of acute cardiac ischaemia, congestive heart failure, or pulmonary embolism"*

Stolz et al, Lancet 2022

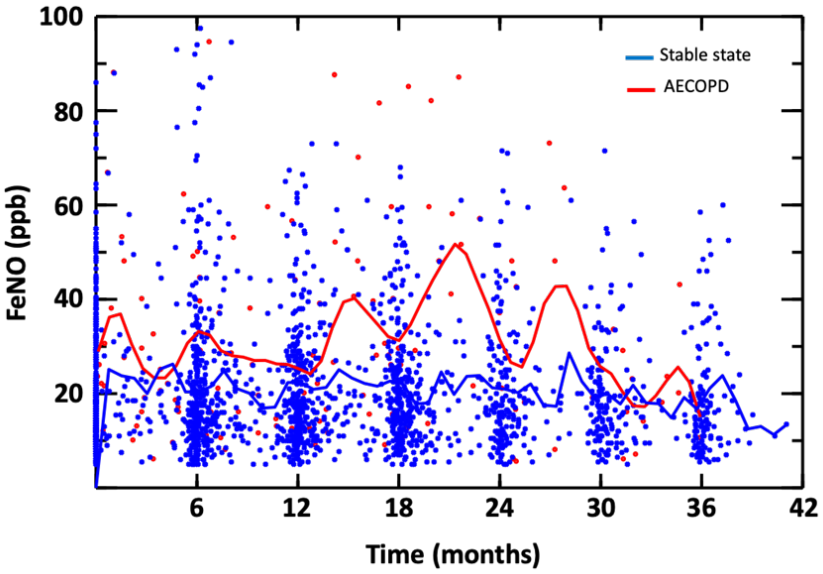
Standard investigations when patients with COPD seek medical attention for suspected disease exacerbation

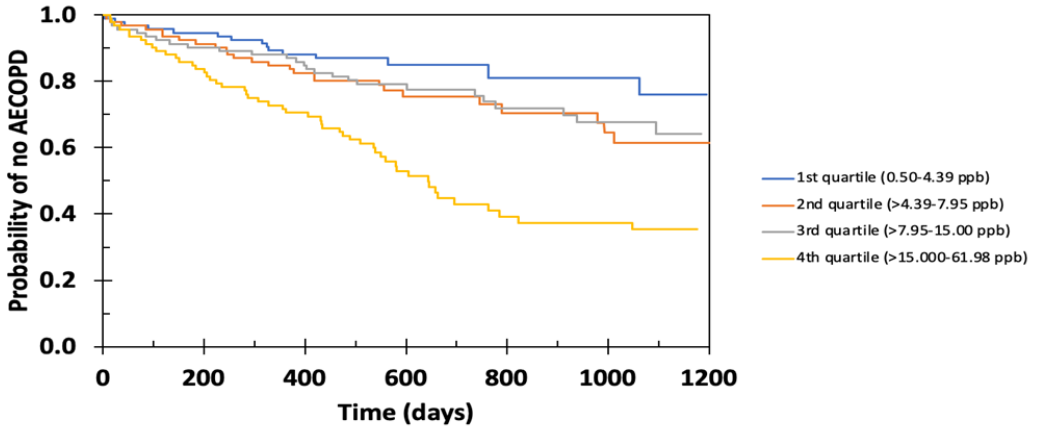
	Essential	Dependent on context or presentation
Inflammation and infection		
Full blood count	X	
C-reactive protein or procalcitonin	X	
Airway microscopy and culture		X
Airway cytology (eosinophils)		X
Airway molecular testing for pathogens		X
Fractional exhaled nitric oxide		X
Hypoxia, hypercapnia, and metabolic status		
pH of venous blood gas		X
Arterial oxygen saturation	X	
General physiology		
Breathing rate	X	
Electrocardiography	X	
Lung function		X
Imaging		
Chest radiography, ultrasonography, or CT	X	
Systemic measurements		
D-dimer	X	
Renal function		X
Troponin		X
B-type natriuretic peptide		X

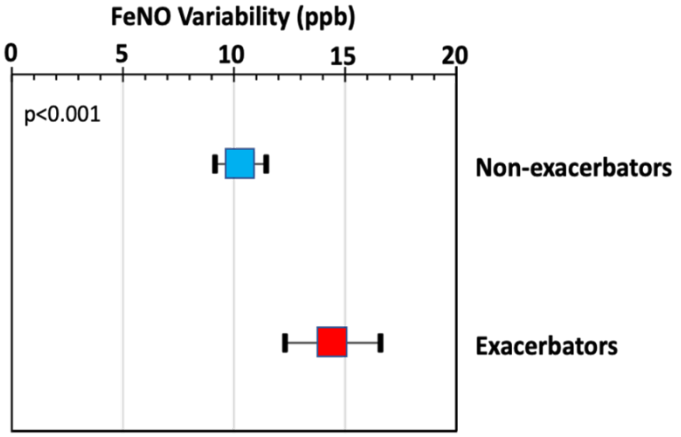
Stolz et al, Lancet 2022

Longitudinal FeNo variability

Exacerbators vs. non exacerbators

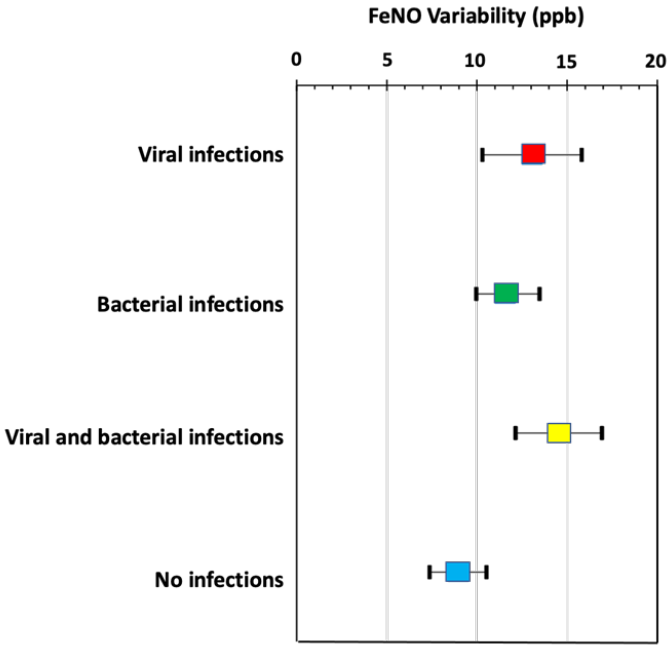


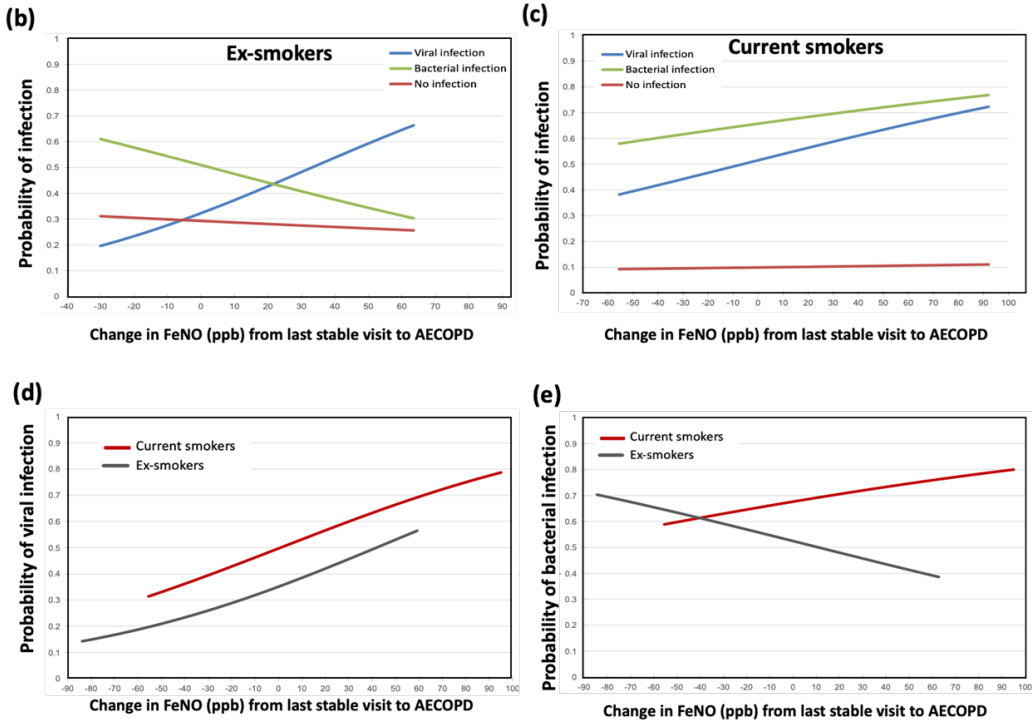




Schuhmann D, & Stolz D., Respirology 2023

FeNO variability and cause of exacerbation





Schumann D, & Stolz D., Respirology 2023

The BAED-C score

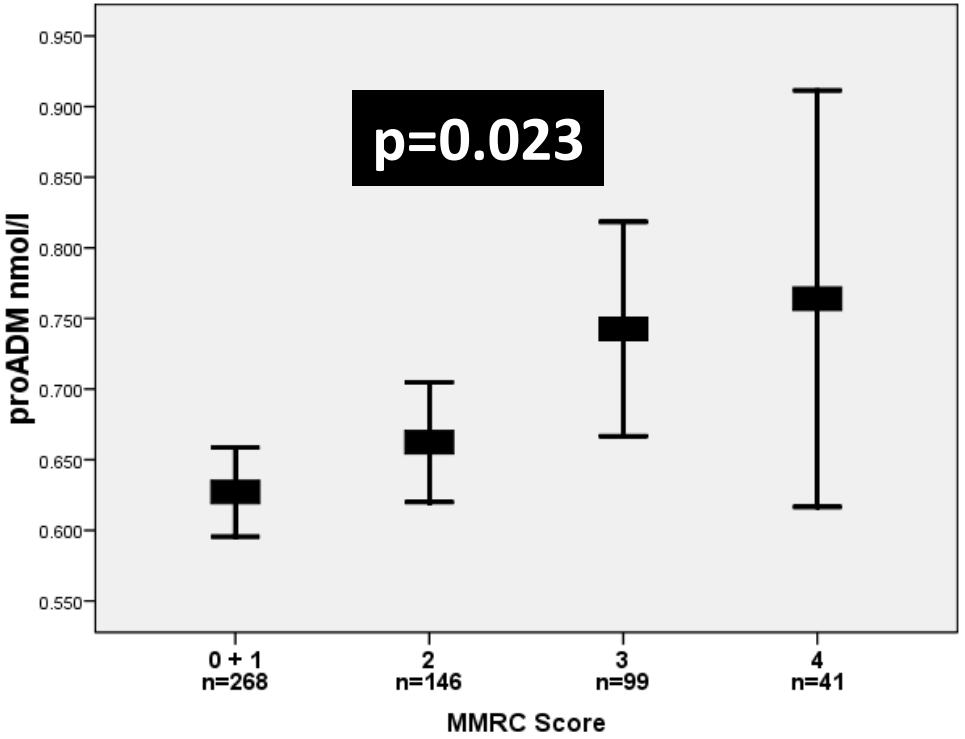
- BMI (B), severe AECOPD frequency (AE), dyspnea severity (D) and copeptin (ProVAP) (C)
- No added value of lung function if history of 1 severe AECOPD

	COPD-related 2-year mortality	**COPD-unrelated 2-year mortality**
Indices	C-statistic (95% CI)	C-statistic (95% CI)
BODE index[§]	0.86 (0.72-0.99)	0.55 (0.42-0.68)
Updated BODE index[§]	0.82 (0.68-0.96)	0.57 (0.44-0.71)
ADO index[¶]	0.84 (0.73-0.95)	0.65 (0.52-0.77)
DOSE index[¶]	0.78 (0.67-0.89)	0.52 (0.39-0.64)
Simplified B-AE-D index	0.87 (0.77-0.98)	0.60 (0.48-0.72)
Simplified B-AE-D-C index	0.89 (0.78-0.99)	0.64 (0.52-0.76)
Optimized B-AE-D index	0.88 (0.78-0.99)	0.61 (0.49-0.73)
Optimized B-AE-D-C index	0.90 (0.79-0.99)	0.65 (0.52-0.77)
Age	0.59 (0.47-0.70)	0.64 (0.52-0.77)
Adjusted Charlson comorbidity index	0.62 (0.50-0.73)	0.62 (0.50-0.74)

Boeck, L. & Stolz D. ERJ 2016

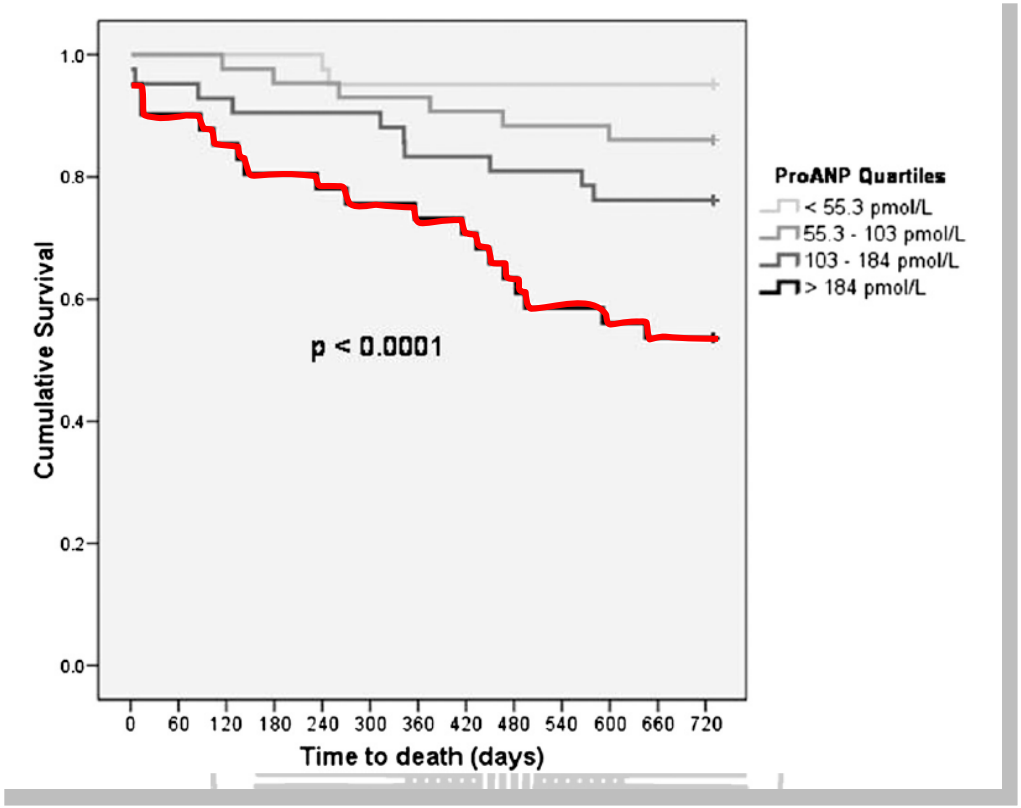
ProADM is associated with dypnoea and survival

- Stimulated by TNF-, IL-1ß and LPS
- Initiate the hyperdynamic response during bacterial infection
- ↓bronchoconstriction
- AM decreased Erk1/2 MAPK expression and activation in Ec but in ASMC, AM activated Erk1/2
- ↑ CxCL5 by Ec, IL-6 by ASMC
- Independently associated to survival at AECOPD



Stolz, D. et al, CHEST 2008, Citgez et al, CHEST 2018
Stolz, D. et al, CHEST 2014; Zuur-Telgen M et al, COPD 2017; Brusse-Keizer M. & Stolz D Respir Med 2015
Mandal J. & Stolz D. Pulm Pharmacol Ther 2019

ProANP and BNP and mortality



- ProANP levels are higher in non-survivors as compared to survivors
- MR-proANP is an independent predictor of mortality up to 2 years after AECOPD
- BNP was associated with the need for ICU but not mortality

Stolz D. et al., CHEST 2008; Bernasconi M. & Stolz, D CHEST 2011

Improvent of the BODE score by ProADM

Univariate Models

Model	N	Events	L.R. χ^2	DF	p-value	C Index
BODE	520	25	23.32	1	<0.00001	0.744
Pro-ADM	613	31	23.82	1	<0.00001	**0.7**11

Bivariate Models Biomarker + BODE Index

Model	N	Events	L.R. χ^2	DF	p-value	C Index
Pro-ADM	511	25	38.81	2	<0.00001	0.813

P<0.0001

Net reclassification improvement:

12% additional events end-up in higher category

14.6% additional survivors end-up in lower category

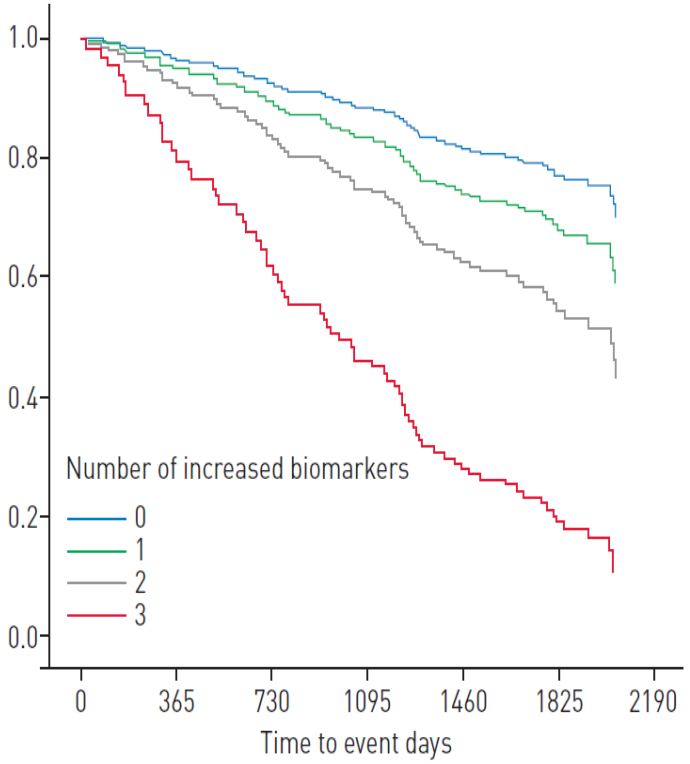
Overall reclassification improvement with ProADM: 26.6% p=0.015

Stolz, D. et al, CHEST 2008, Brusse-Keizer M & Stolz D Respir Med 2015, Stolz D et al, ERJ 2014

Mortality risk prediction in COPD by a prognostic biomarker panel

Daiana Stolz, Anja Meyer, Janko Rakic, Lucas Boeck, Andreas Scherr and Michael Tamm

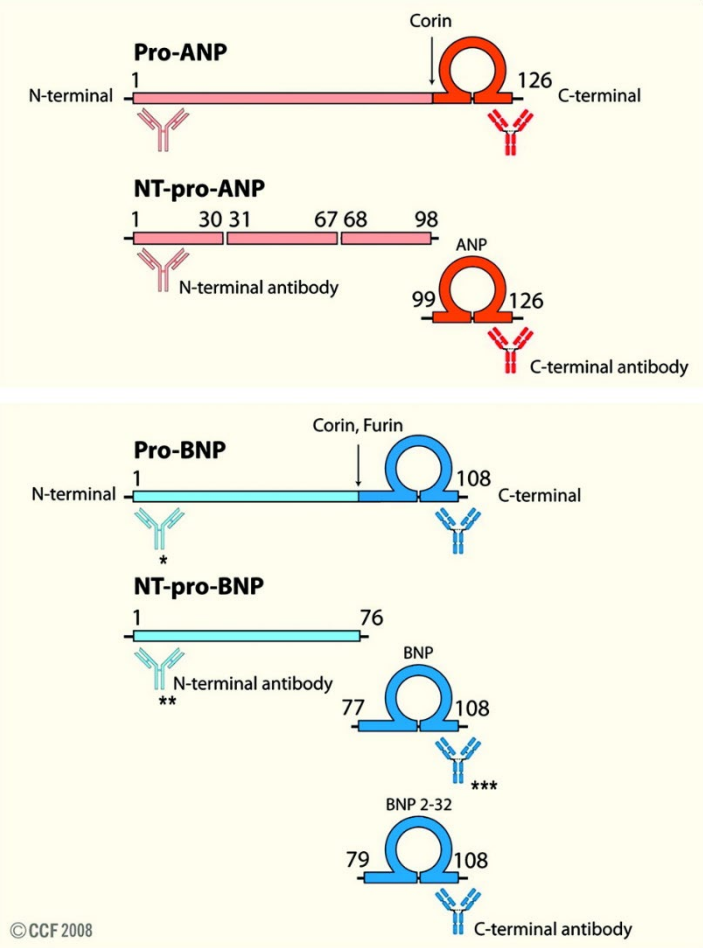
Characteristic	Hazard ratio (95% CI)#	p-value
1 increased biomarker *versus* 0	1.4 (0.8–2.4)	0.238
2 increased biomarkers *versus* 0	1.9 (1.01–3.4)	0.046
3 increased biomarkers *versus* 0	3.3 (1.5–7.3)	0.003
Smoking (current *versus* former)	1.4 (0.9–2.1)	0.184
Sex (female *versus* male)	0.98 (0.6–1.6)	0.923
Age-adjusted Charlson comorbidity score	1.2 (1.1–1.3)	<0.001
Post-bronchodilator FEV1 % predicted	0.970 (0.96–0.99)	<0.001



ProADM + ProANP + ProAVP

Stolz D et al, ERJ 2014

Cardiovascular-determined prognosis in COPD

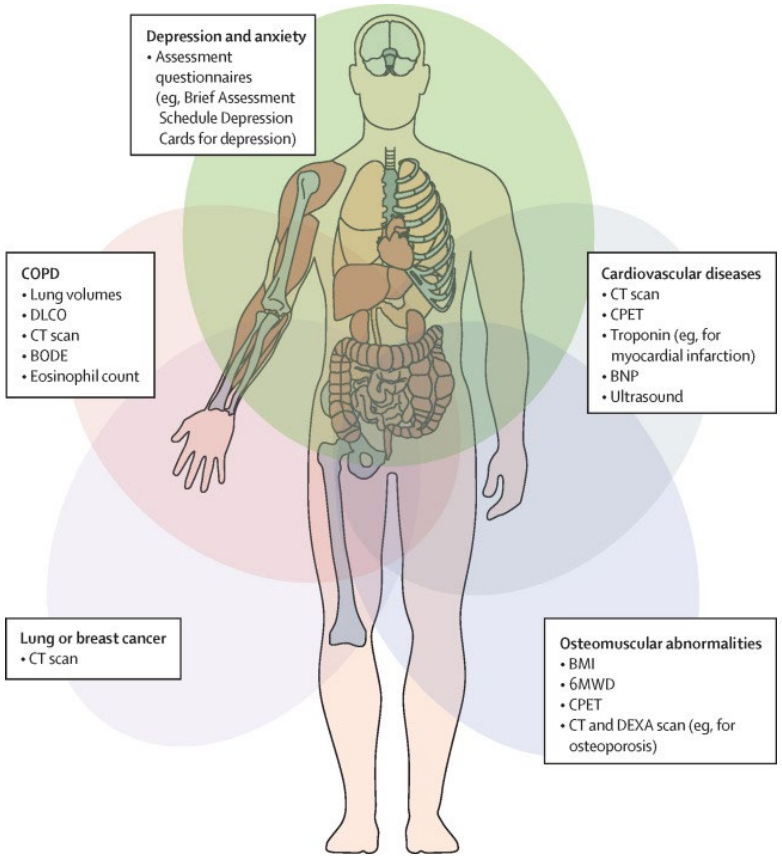


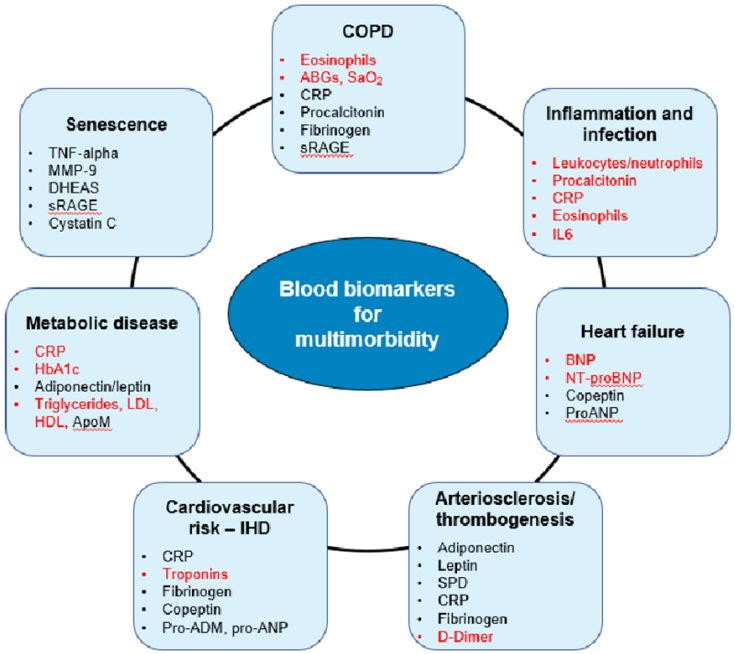
- 36% of patients with COPD die due to cardiovascular causes
- ANP blocks the pulmonary vasopressor response to acute hypoxia
- reduces pulmonary vascular resistance
- attenuates hypoxia-induced pulmonary hypertension

- Pulmonary hypertension is a main prognostic factor
- COPD-related PH does not respond to endothelin-antagonists or iloprost

Stolz, D. et al , Eur Resp J 2008
Boeck L & Stolz D, Plos One 2012

Identifying multimorbidity in patients with COPD

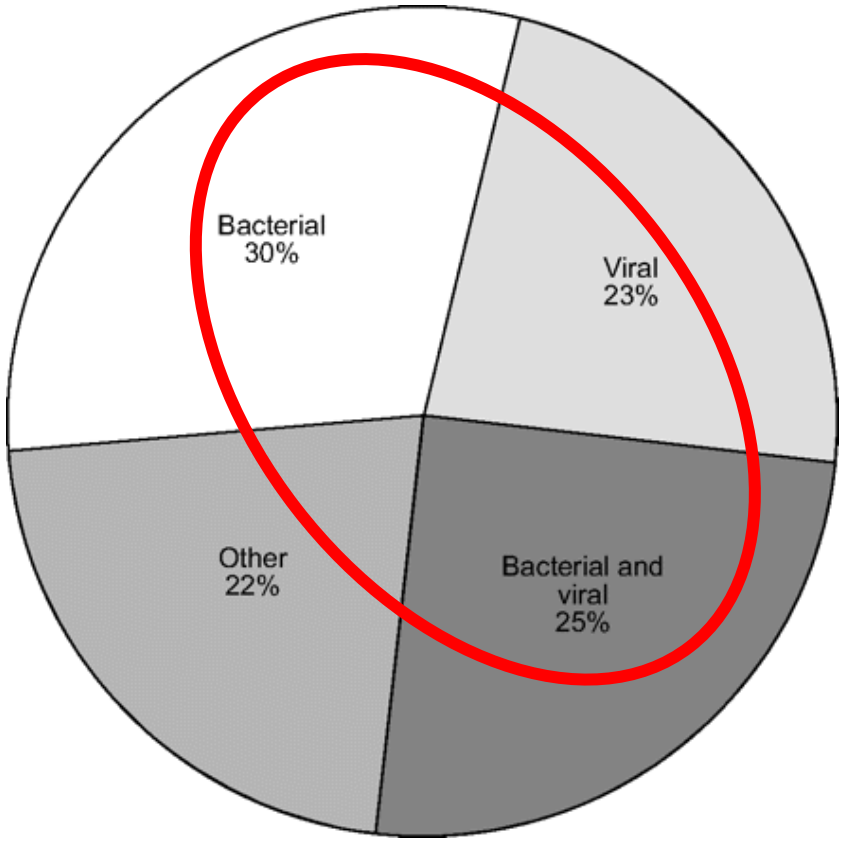




Fabbri, L…Stolz, D… et al. The Lancet Respiratory Medicine 2023

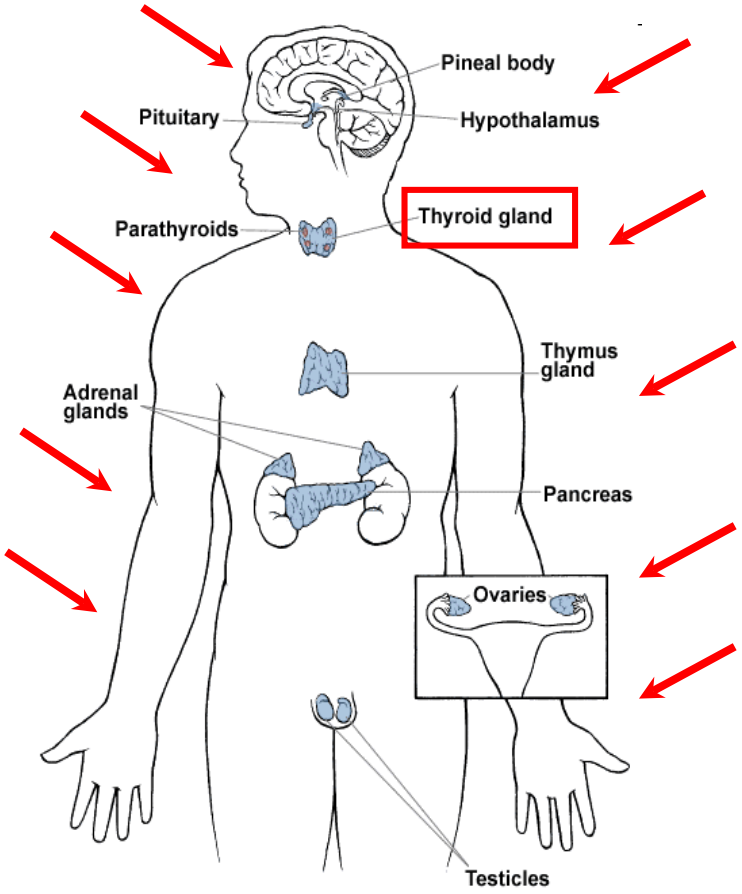
Cause of exacerbation

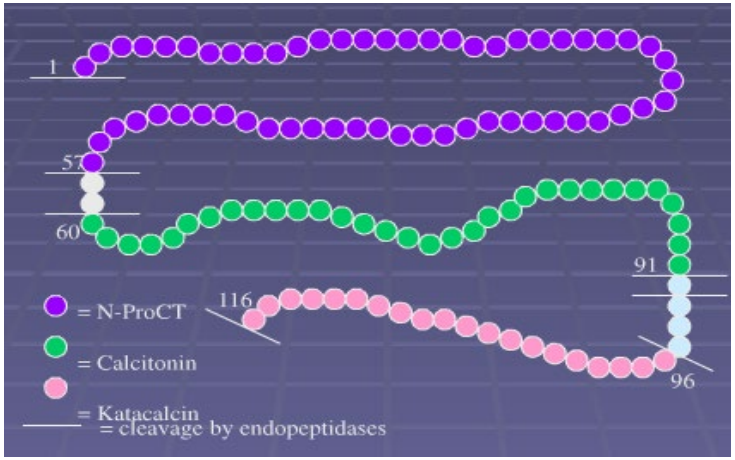
- Most exacerbations of COPD are triggered by either bacterial or viral infection or a combination of both



Stolz, D et al, Curr Opin Pulm Med 2009
Wilkinson, T et al, CHEST 2006

Overexpression of the CALC-1 gene in bacterial infection = Procalcitonin

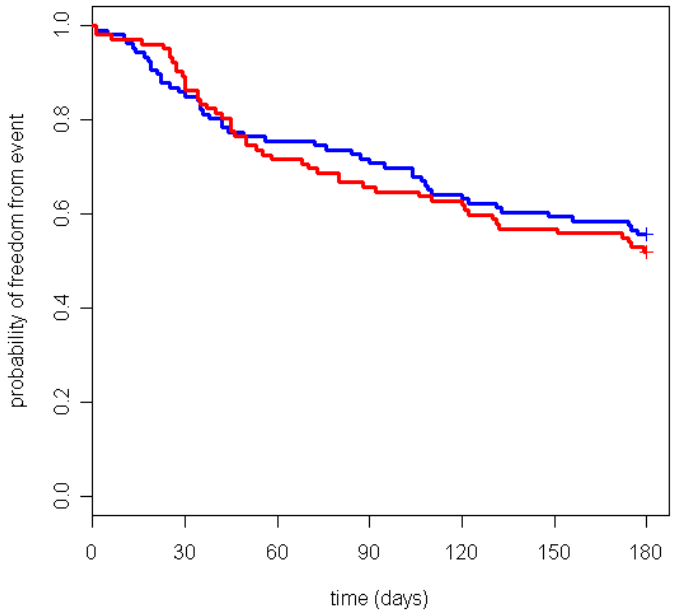


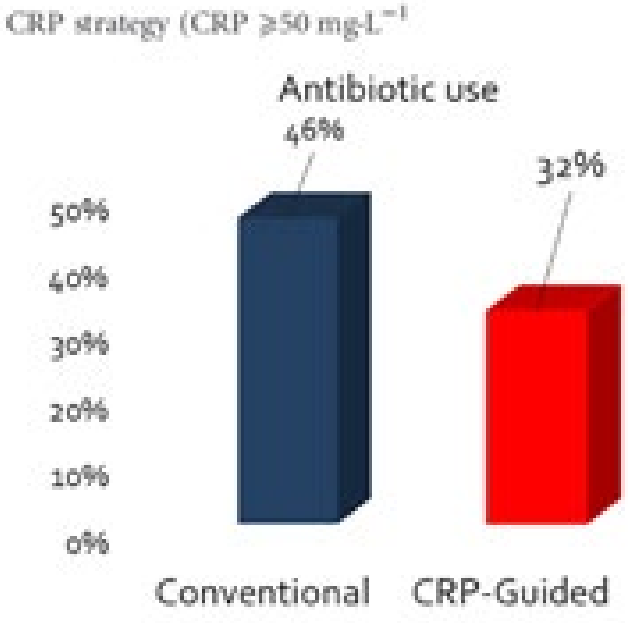


Müller et al. Stolz,D. JCE&M, 2001
Christ-Crain, Stolz D. et al, Lancet 2004
Christ-Crain, Stolz D. et al, AJRCCM 2006
Stolz et al, Swiss Med Week 2006
Stolz et al, CHEST 2007
Stolz et al, Eur Resp J 2009
Stolz et al Chest 2016
Schutz P et al. Cochrane 2017
Schutz P..Stolz D et al, Lancet Infect Dis 2018
Schuetz P & Stolz D. ERJ 2019
Karakioulaki M & Stolz D. Ann Thorac Med 2019

Procalcitonin-guided exacerbation therapy – the PROCOLD study

Recurrence of exacerbation





- PCT guided - 40% received antibiotics
- Controls - 72% received antibiotics

Stolz D et al, CHEST 2007

Prins H. et al ERJ 2019

FDA NEWS RELEASE

FDA clears test to help manage antibiotic treatment for lower respiratory tract infections and sepsis

For Immediate Release: February 23, 2017

The U.S. Food and Drug Administration today cleared the expanded use of the Vidas Brahms PCT Assay to help health care providers determine if antibiotic treatment should be started or stopped in patients with lower respiratory tract infections, such as community-acquired pneumonia, and stopped in patients with sepsis. This is the first test to use procalcitonin (PCT), a protein associated with the body's response to a bacterial infection, as a biomarker to help make antibiotic management decisions in patients with these conditions.

"Unnecessary antibiotic use may contribute to the rise in antibiotic-resistant infections," said Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostics and Radiological Health at the FDA's Center for Devices and Radiological Health. "This test may help clinicians make antibiotic treatment decisions."

The test works by measuring PCT. High levels of PCT suggest a bacterial infection, while low levels suggest a viral infection or non-infectious causes. Clinicians may be able to use PCT and other information to safely withhold or stop antibiotics. Because PCT may indicate the presence of a variety of bacterial infections, it does not detect the exact cause of a patient's symptoms.

Sepsis can be part of the body's response to an infection and can lead to tissue damage, organ failure, and death. Lower respiratory tract infections include community-acquired pneumonia, acute bronchitis, and acute exacerbations of chronic obstructive pulmonary disease (COPD). Bacteria often cause sepsis and lower respiratory tract infections, but

Content current as of:
03/28/2018

- *To aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock*
- *To aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time*
- *To aid in decision making on antibiotic therapy for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)*
- *To aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis*

THE LANCET
Respiratory Medicine

Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial

Andrei M Darie, Nina Khanna, Kathleen Jahn, Michael Osthoff, Stefano Bassetti, Mirjam Osthoff, Desiree M Schumann, Werner C Albrich, Hans Hirsch, Martin Brutsche, Leticia Grize, Michael Tamm, Daiana Stolz

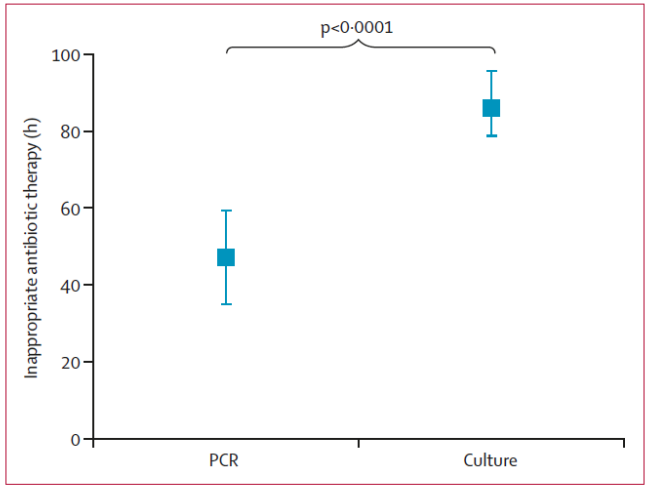


Figure 2: Duration of inappropriate antibiotic therapy
Bars indicate 95% CIs.

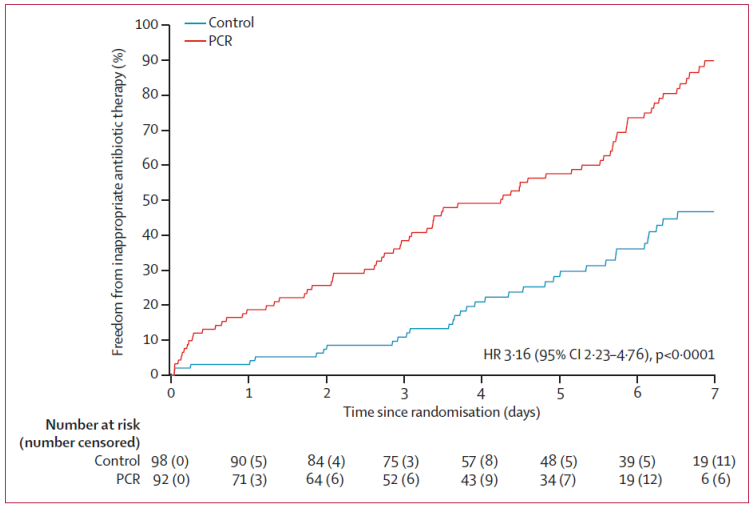
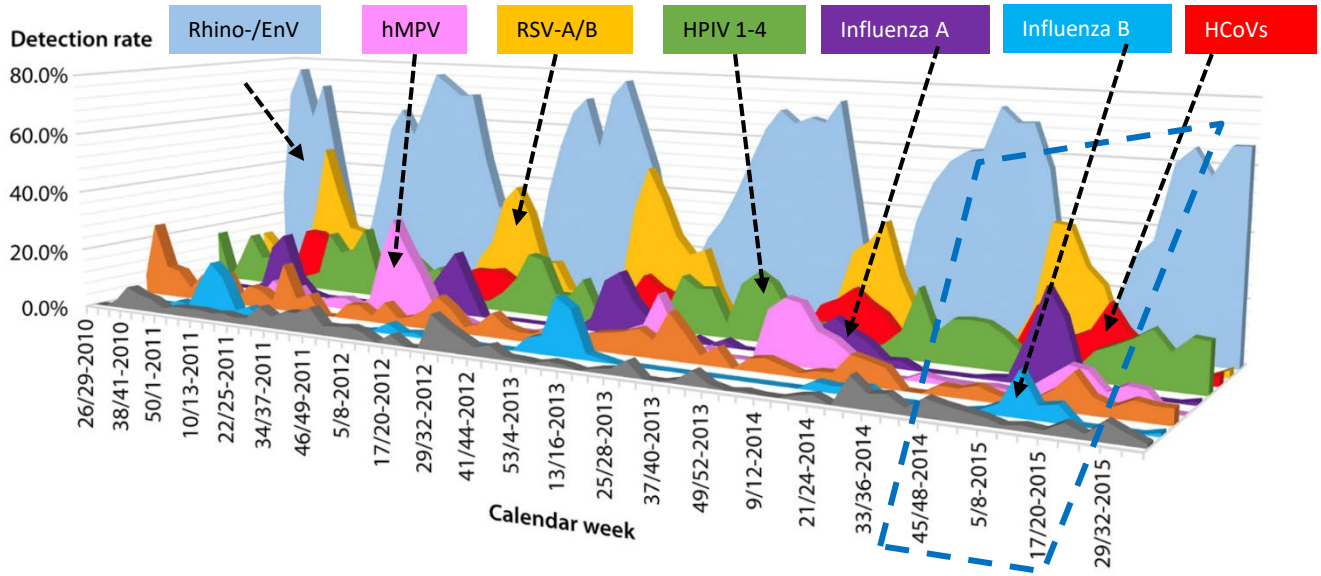


Figure 3: Freedom from inappropriate antibiotic therapy

Lancet Respir Med 2022; published online May 23. https://doi.org/10.1016/S2213-2600(22)00086-8.

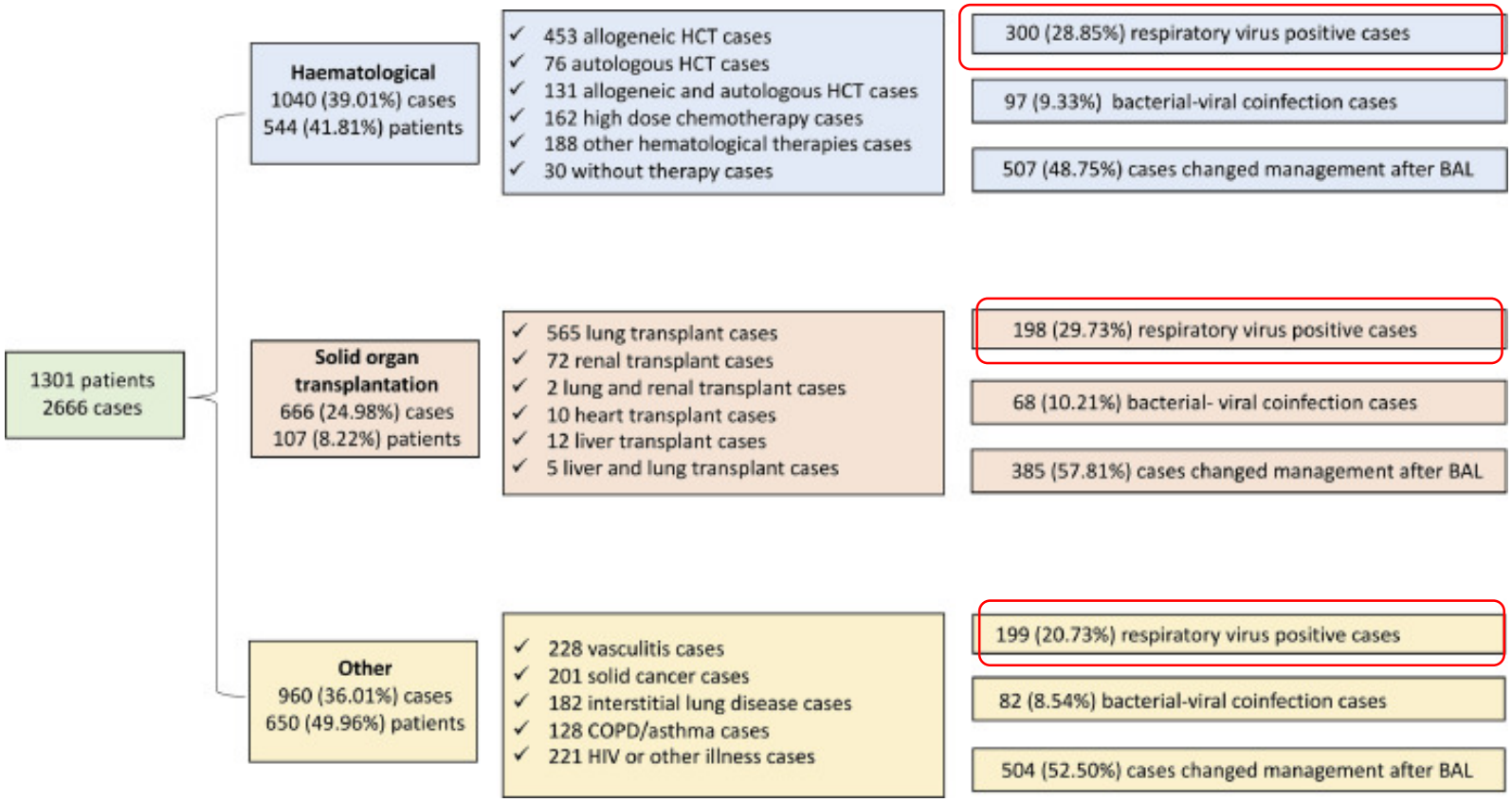
Epidemiology of community-acquired respiratory viruses

- CARVs by multiplexNAT results in *symptomatic* children and adults in Basel over 5 years
  - 255'670 results from 11'446 samples
  - Children positive 70% (no other dx); adults 30% (mostly risk factors)
  - Seasonal peaks, different in children and adults, dynamic changes



Compagno F, Braunacker-Mayer L, Khanna N, Stolz D, Battegay M, Frey U, Tamm M, Kouyos R, Hirsch HH (2017)
Comparing viral respiratory tract infections in symptomatic children and adults by mulitplex NAT from 2010 - 2015 (ePoster abstract ECCMID 2017 Vienna)

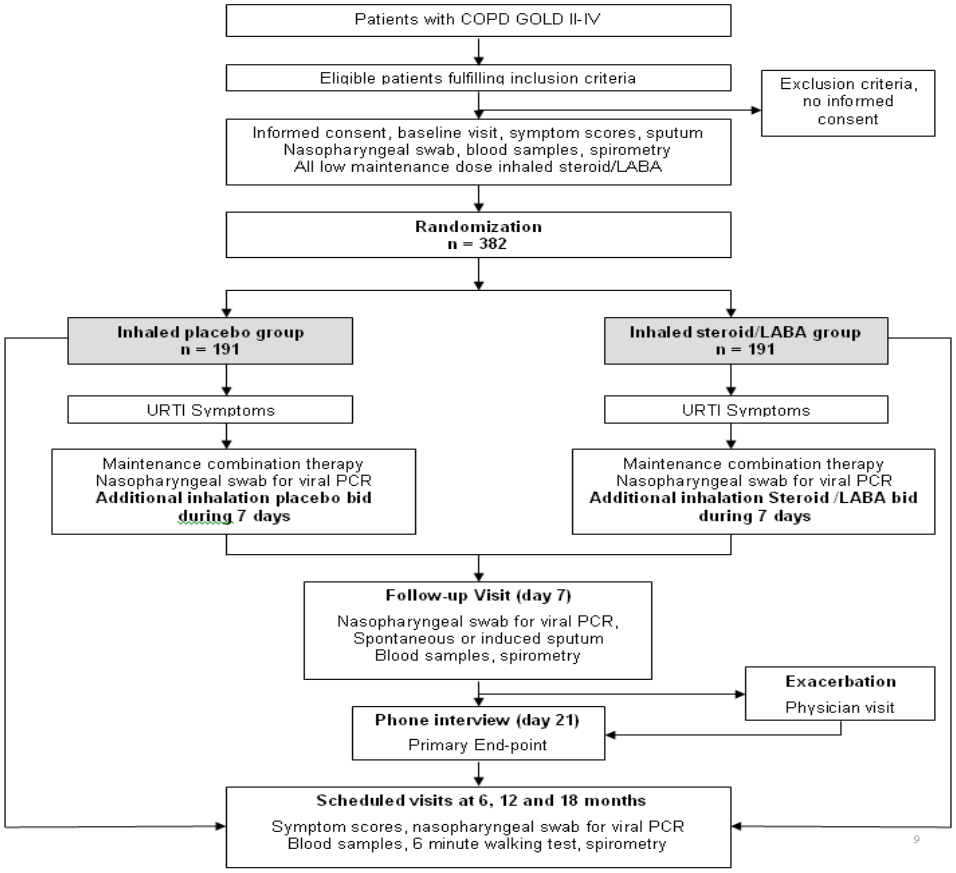
Aetiology of infection in BAL



Jahn K. ..& Stolz, D., European Journal of Internal Medicine, 2024

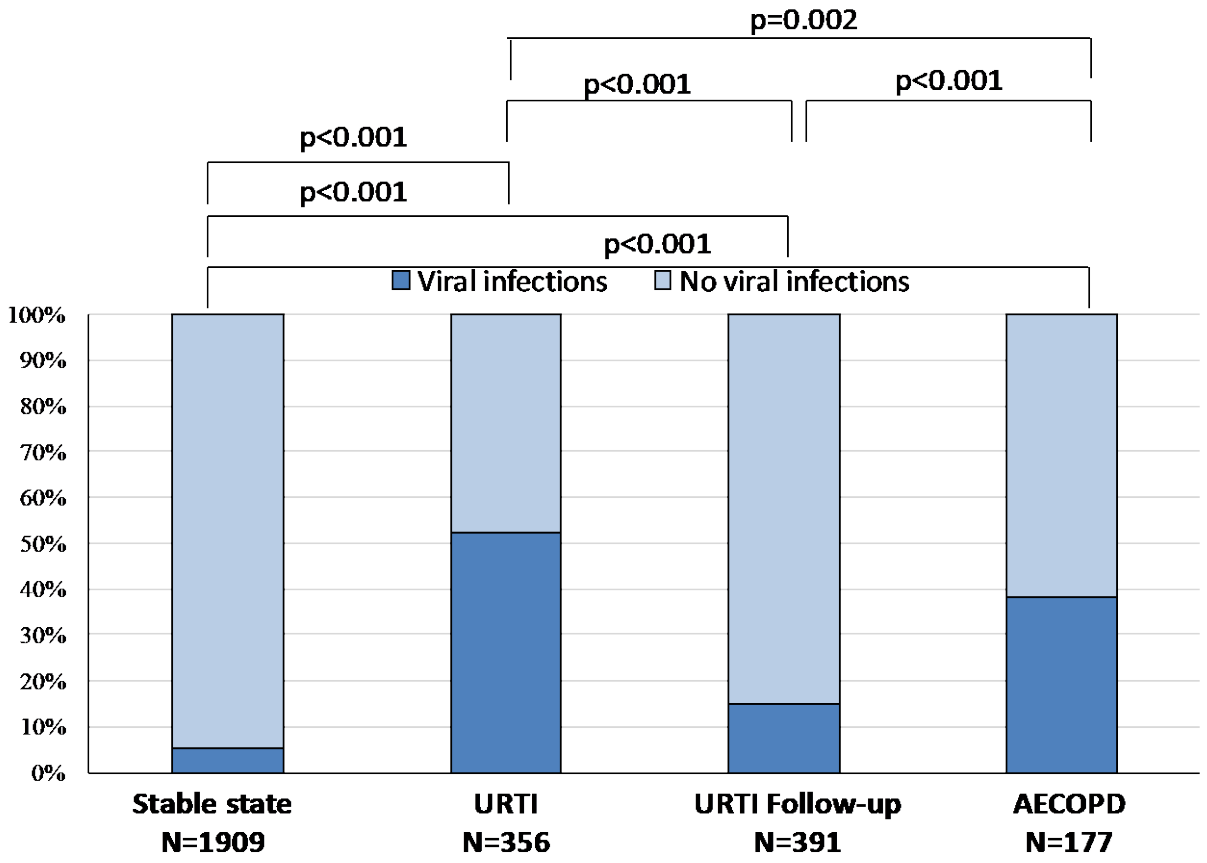
Preventing Viral Exacerbation of COPD in URTI – the PREVENT Study

- Multi-national, randomized, double-blind study
- Objectives:
  - Determine incidence of viral infection by multiplex PCR
  -Assess whether ↑ combination therapy at URTI ↓ incidence of AECOPD
  -Evaluate systemic repercussions



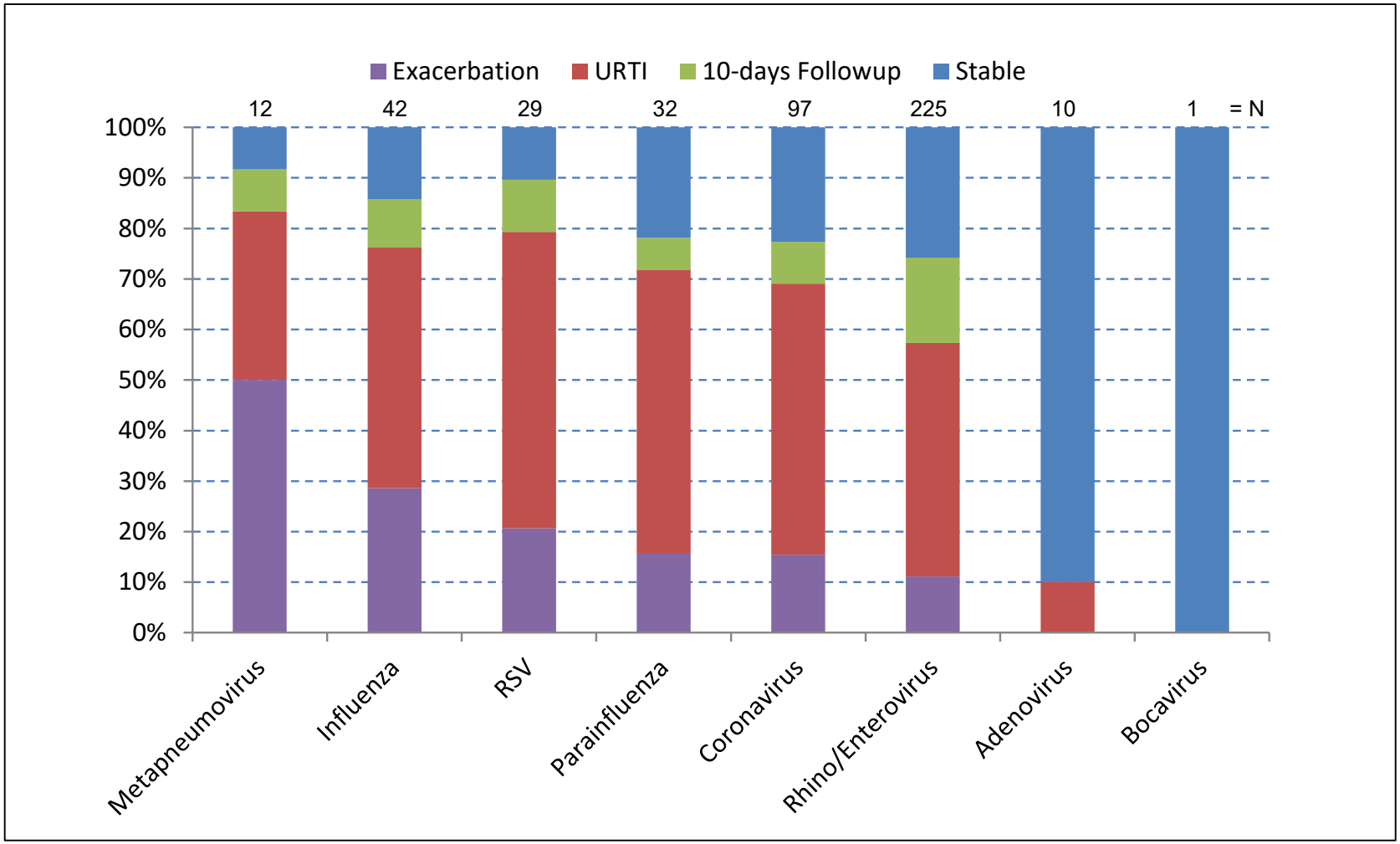
Stolz D, AJRCCM 2018

Exacerbations and upper respiratory airway infections in COPD



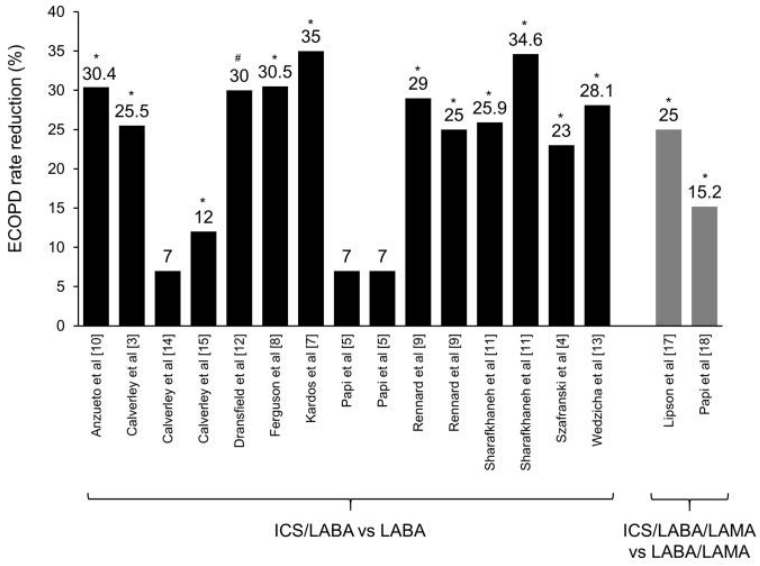
Stolz et al, ERJ 2019

Viruses at stable state, URTI and exacerbation – 50´000 PCRs

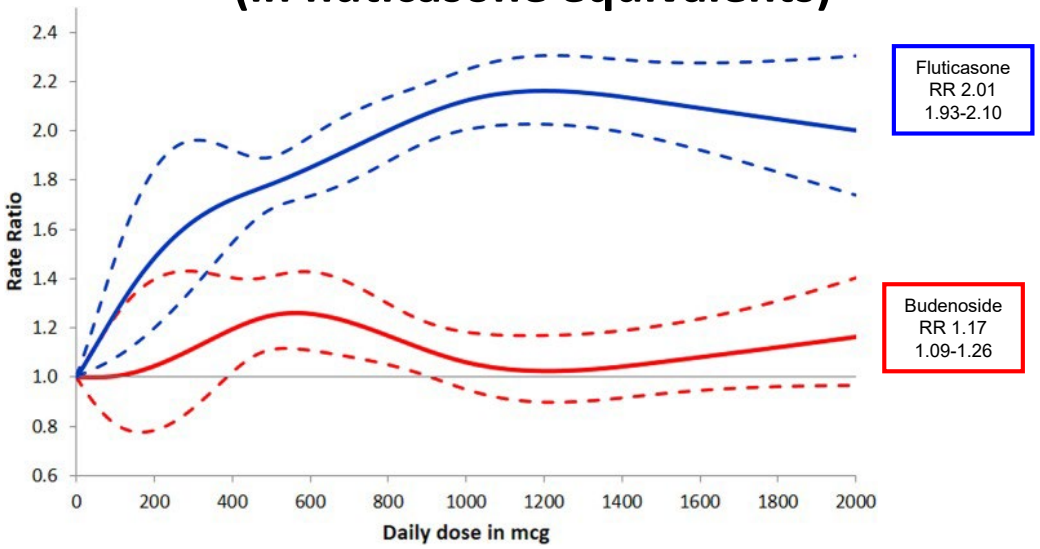


Stolz D et al, ERJ 2019

Prevent of exacerbation by ICS



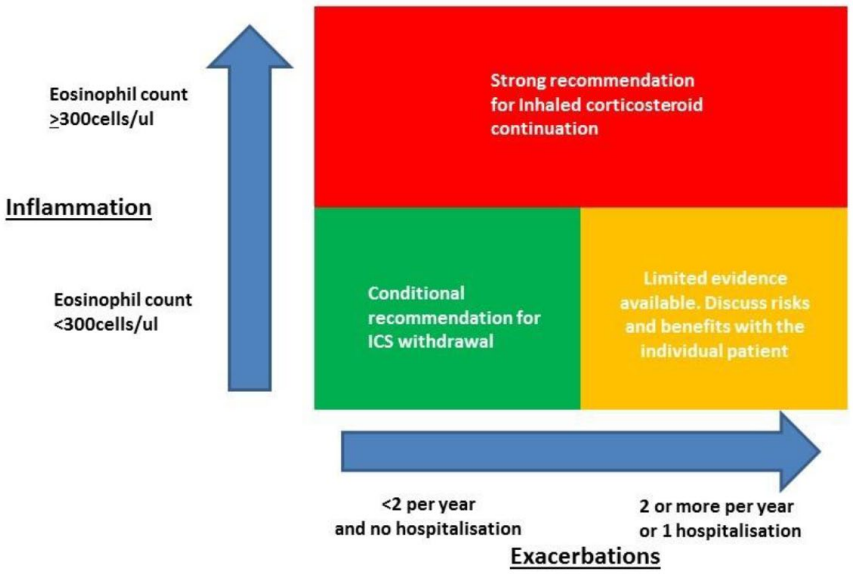
Dose-response curves for the rate-rate of pneumonia (in fluticasone equivalents)

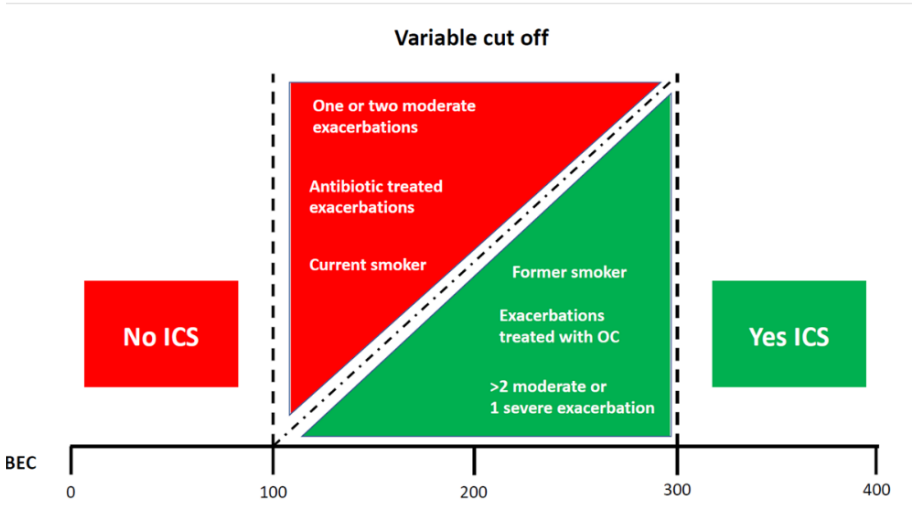


Agusti A. et al, ERJ 2018

Suissa S. et al, Thorax 2013

ICS discontinuation in COPD





Chalmers, J. .. Stolz, D et al, ERJ 2021; Stolz D. & Miravitlles M, ERJ 2021

Intensified Therapy with Inhaled Corticosteroids and Long-Acting β_2-Agonists at the Onset of Upper Respiratory Tract Infection to Prevent Chronic Obstructive Pulmonary Disease Exacerbations

A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial

Daiana Stolz[1,2,3], Hans H. Hirsch[2,3,4,5], Daniel Schilter[6], Renaud Louis[7], Janko Rakic[1,2,3], Lucas Boeck[1,2,3], Eleni Papakonstantinou[1,2,3], Christian Schindler[3,8], Leticia Grize[3,8], and Michael Tamm[1,2,3]

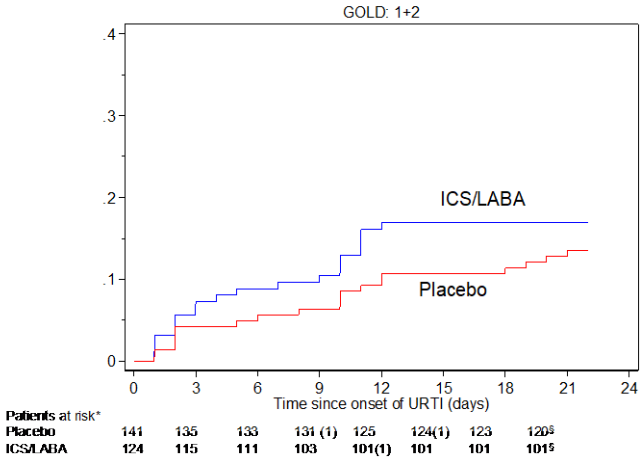
[1]Clinic of Respiratory Medicine and Pulmonary Cell Research, and [5]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland; [2]Department of Biomedicine, University of Basel, Basel, Switzerland; [3]University of Basel, Basel, Switzerland; [4]Transplantation and Clinical Virology, Department of Biomedicine, University of Basel, Basel, Switzerland; [6]Lindenhof Hospital, Bern, Switzerland; [7]Pneumology Department, GIGA I3 research group, University of Liege, CHU Liege, Belgium; and [8]Swiss Tropical and Public Health Institute, Basel, Switzerland

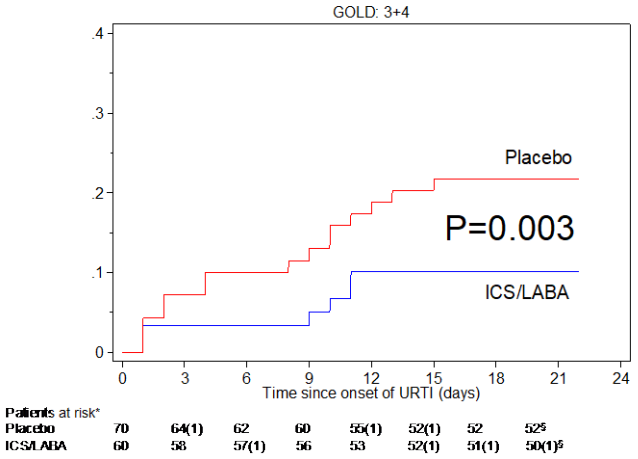
The PREVENT study

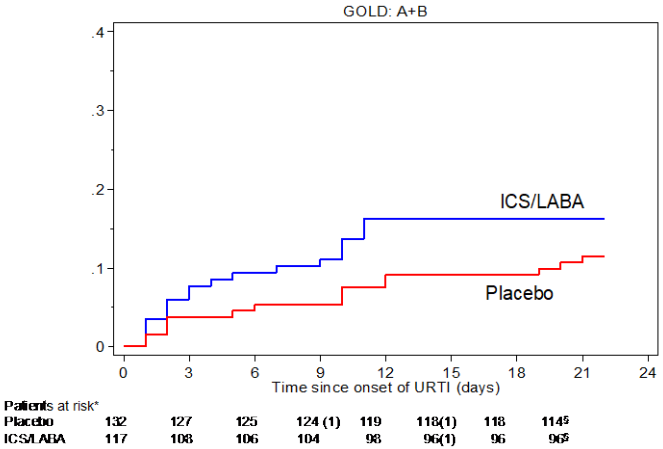
- 450 patients > 40 yo, > 10 PY, post BD FEV_1 < 80%; ≥ 1 exacerbation in the previous 12 months
- Started on maintainance low-dose ICS/LABA (200ug Budesonide/ 6ug Formoterol twice daily)
- At **URTI symptoms** – collect nasopharyngeal and oral swabs and **inhale 400ug Budesonide/12ug Formoterol or placebo twice daily, for 10 days**
- Primary end-point: number of exacerbations and severe exacerbations within 21 days of URTI

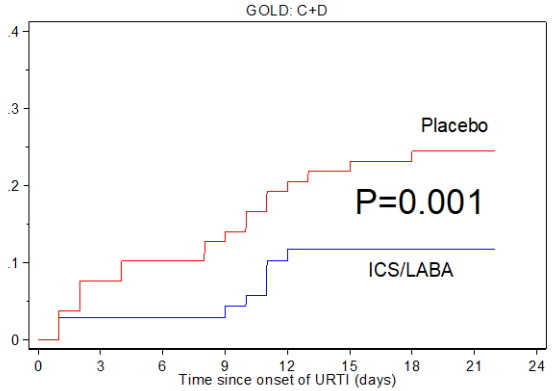
Stolz et al, AJRCCM 2018

Tripling of ICS at URTI decreases exacerbation of COPD





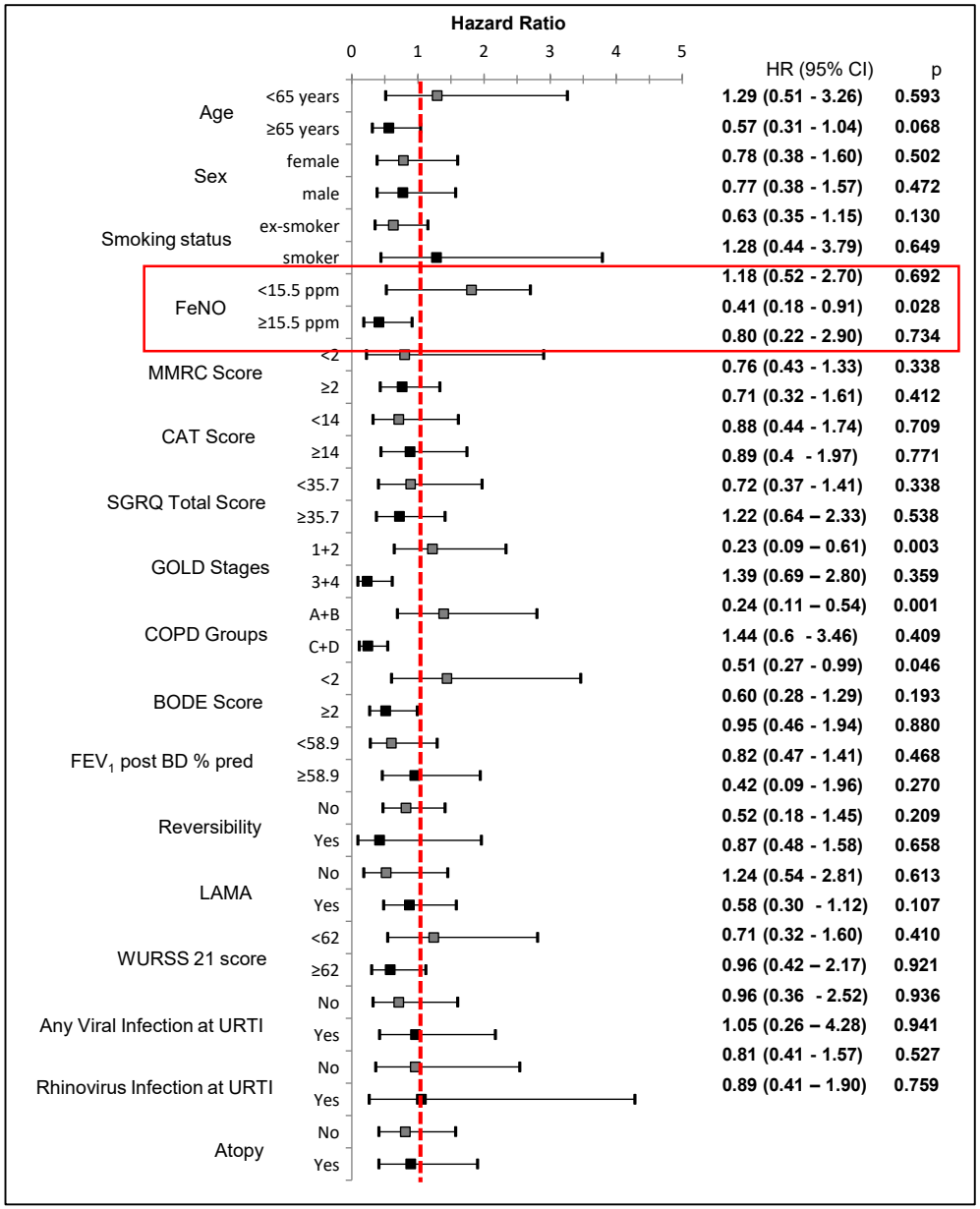




Stolz et al, AJRCCM 2018

Predictors of ICS Response

- FEV_1< 50%
- GOLD C and D
- BODE > 2
- FeNO > 15.5 ppm



Stolz et al, AJRCCM 2018

Take home messages

- COPD is a heterogenous disase
- We need to identify “early” COPD, wpirometry is not the (only) answer
- High ASMC mass appears to predict ICS response in COPD patients receiving triple therapy.
- Tobacco-Exposed Persons with symptoms and preserved FEV1/FVC ratio might benefit from triple therapy
- Objective assessments are necessary to evaluate and treat exacerbations
- Tripling of ICS at URTI decreases exacerbation of COPD

ERS President 2026-2027

UNIVERSITÄTS KLINIKUM FREIBURG

Thank you!