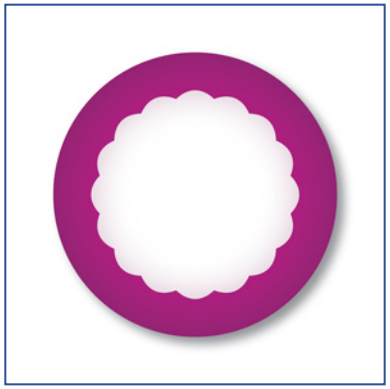
Pneumo Update Europe 2018

15 - 16 June, Budapest

COPD



David M. G. Halpin, UK

Topics Not Covered

- ☐ NIV & CPAP
- ☐ Rehabilitation
- ☐ Interventional Bronchoscopy
- ☐ Radiology

GOLD 2018

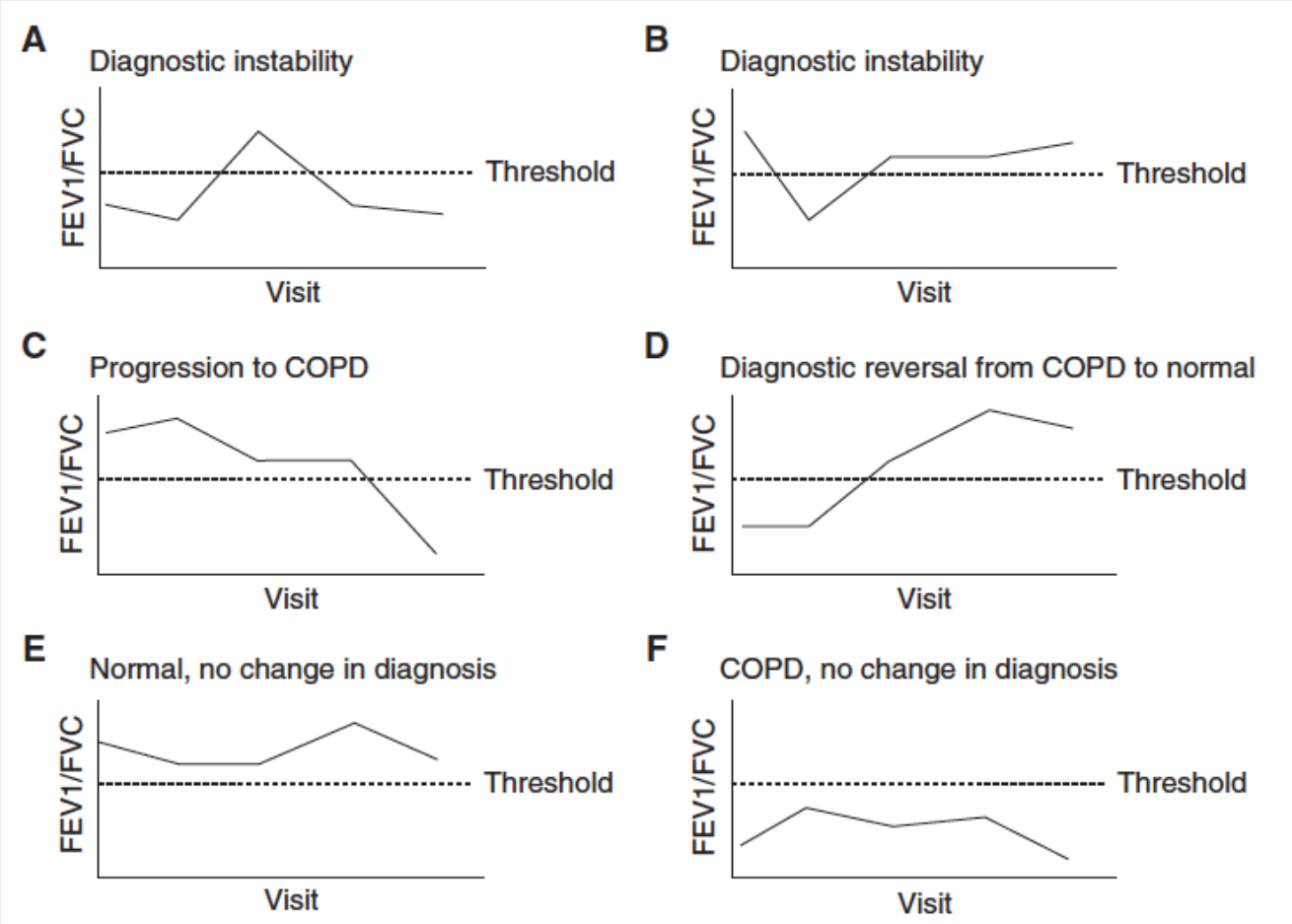
Confirming Presence of Airflow Obstruction

Assessment of the presence or absence of airflow obstruction based on a single measurement of the post-bronchodilator FEV1/FVC ratio should be confirmed by repeat spirometry on a separate occasion if the value is between 0.6 and 0.8, as in some cases the ratio may change as a result of biological variation when measured at a later interval (Aaron et al., 2017; Schermer et al., 2016)

If the initial post-bronchodilator FEV1/FVC ratio is less than 0.6 it is very unlikely to rise above 0.7 spontaneously.(Aaron et al., 2017)

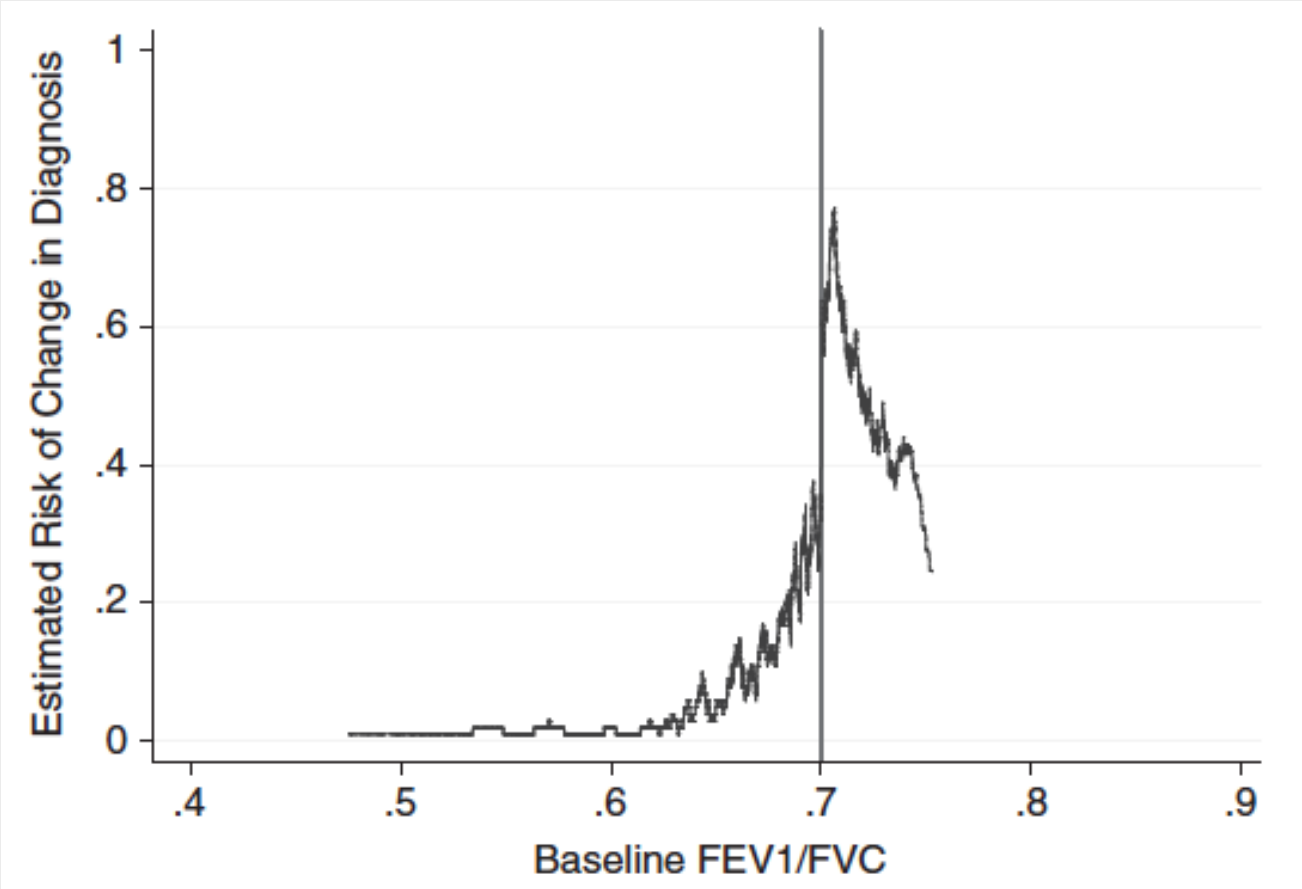
goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf
Aaron et al. Am J Respir Crit Care Med 2017;196:306-314
Schermer et al. NPJ Prim Care Respir Med. 2016;26:1605

Confirming Presence of Airflow Obstruction



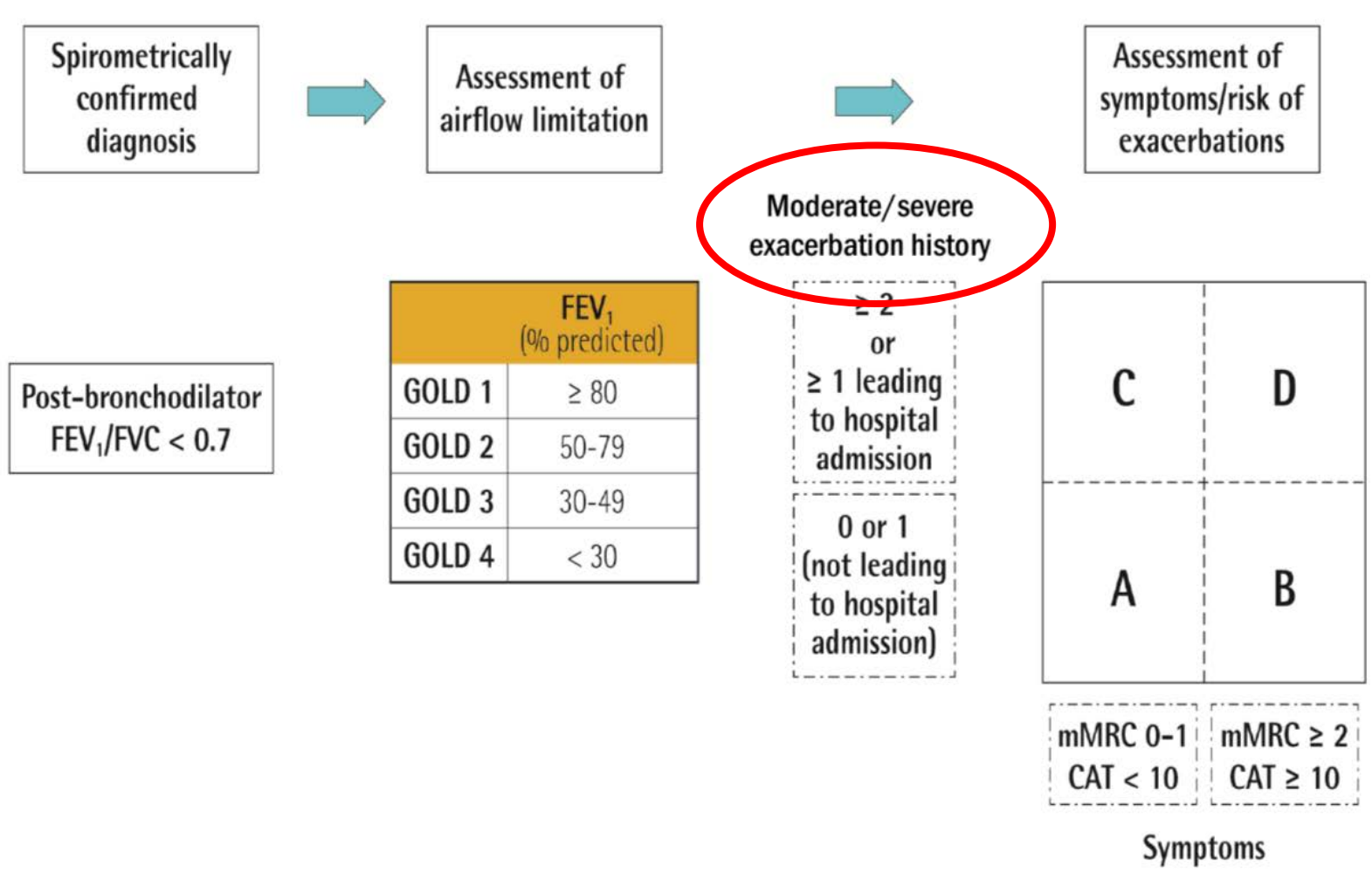
Aaron et al. Am J Respir Crit Care Med 2017;196:306-314

Confirming Presence of Airflow Obstruction



Aaron et al. Am J Respir Crit Care Med 2017;196:306-314

Assessing Exacerbation Risk



goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf

Other GOLD Updates

- Early influences & pollution
- Effectiveness of legislative smoking bans
- Dual & Triple inhaled therapy
- PDE4 inhibitors and hospitalisation
- Different models of pulmonary rehabilitation
- Oxygen including hi-flow
- CPAP for co-existent OSA
- NIV
- Exacerbations – risk factors and management

goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf

Take-Home Message

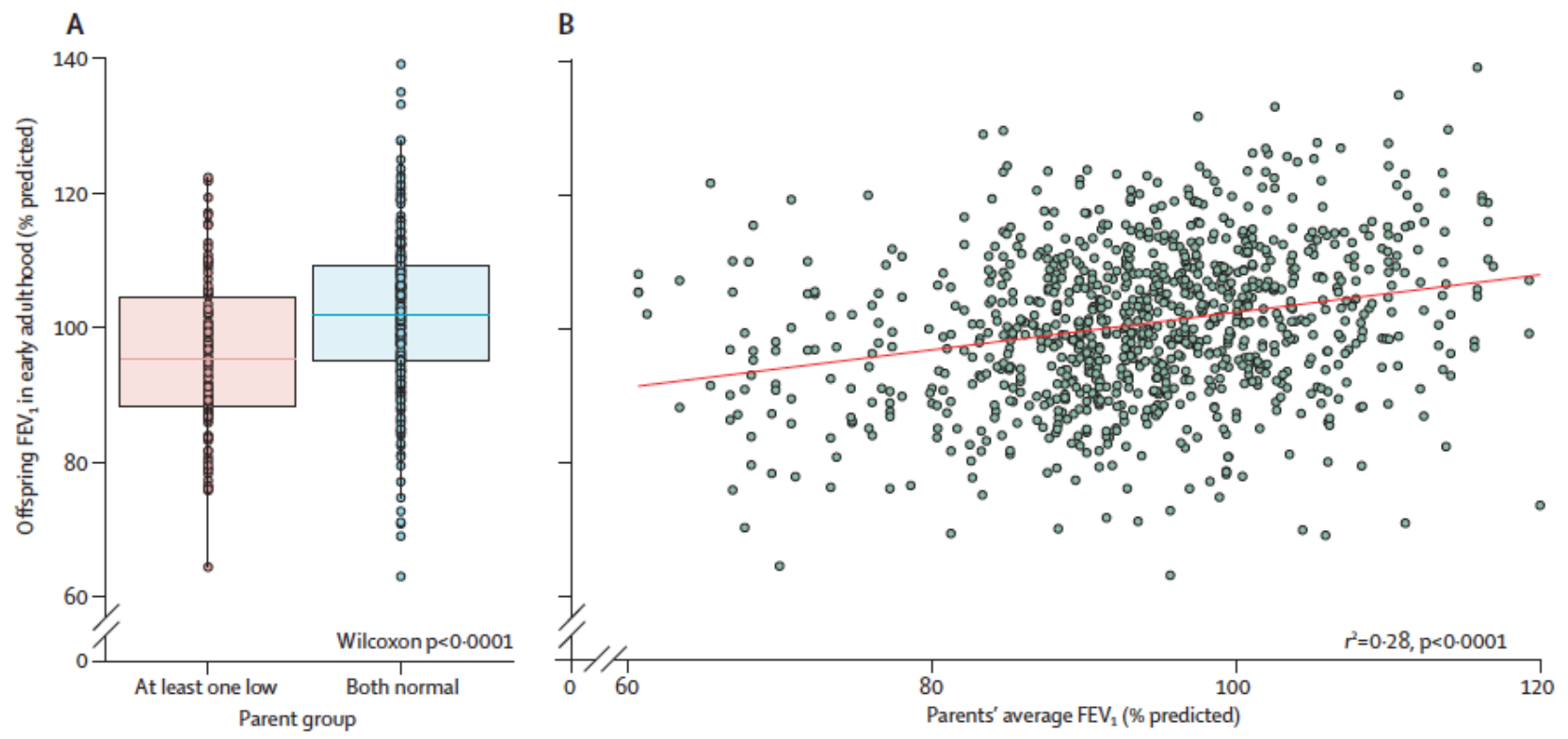
- Do not rely on single spirometric measurements to diagnose or exclude airflow obstruction if the FEV1:FVC ratio is close to 0.7

Developing COPD

Developing COPD

Parental Lung Function

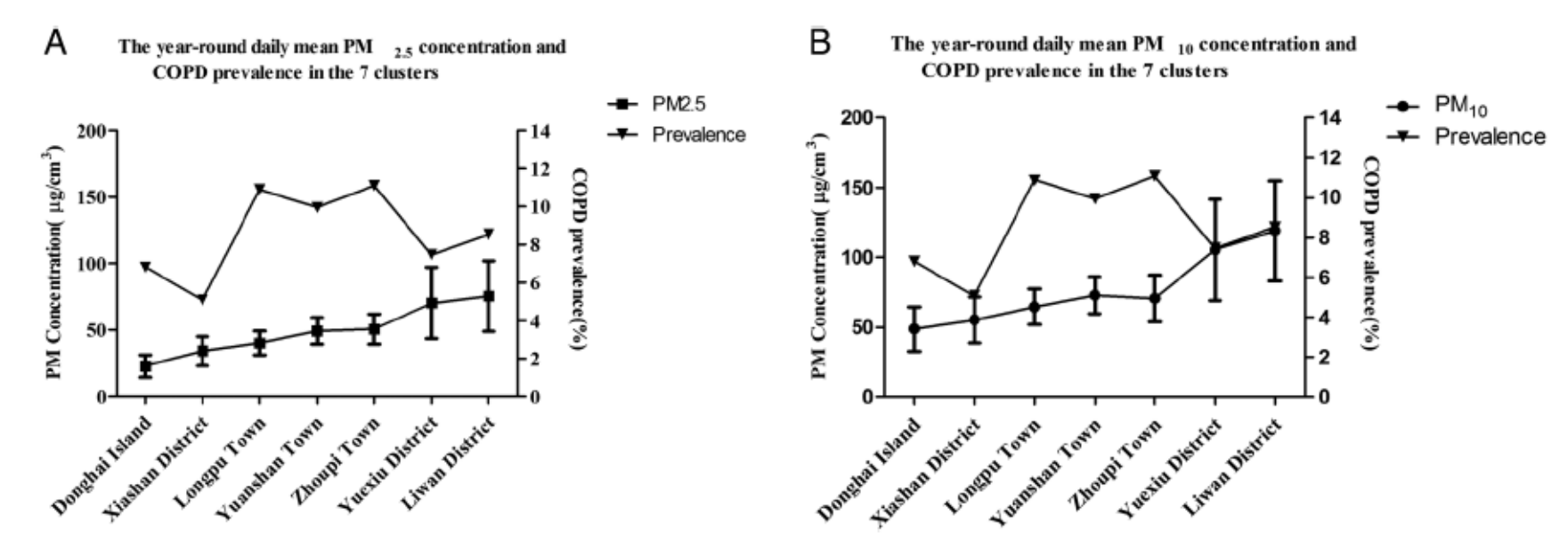
In GenIII, individuals with at least one parent stratified as having low lung function in early and early adulthood FEV1 of GenIII participants was to FOC parents' average FEV1 in early adulthood.



Agusti et al. Lancet Respir Med 2017;5:935-945

Developing COPD
Air Pollution (PM_{10} & $PM_{2.5}$)

Higher PM concentrations were strongly associated with COPD development and decreased respiratory function.

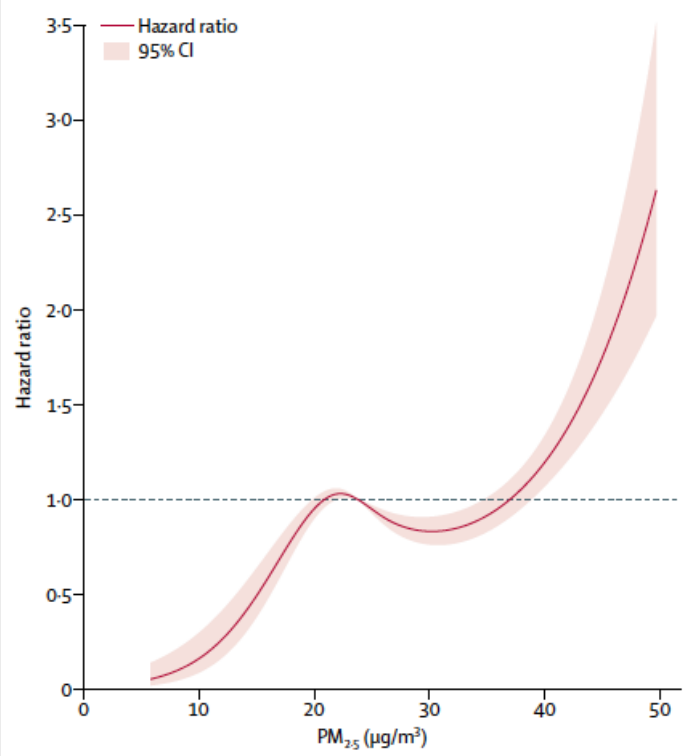


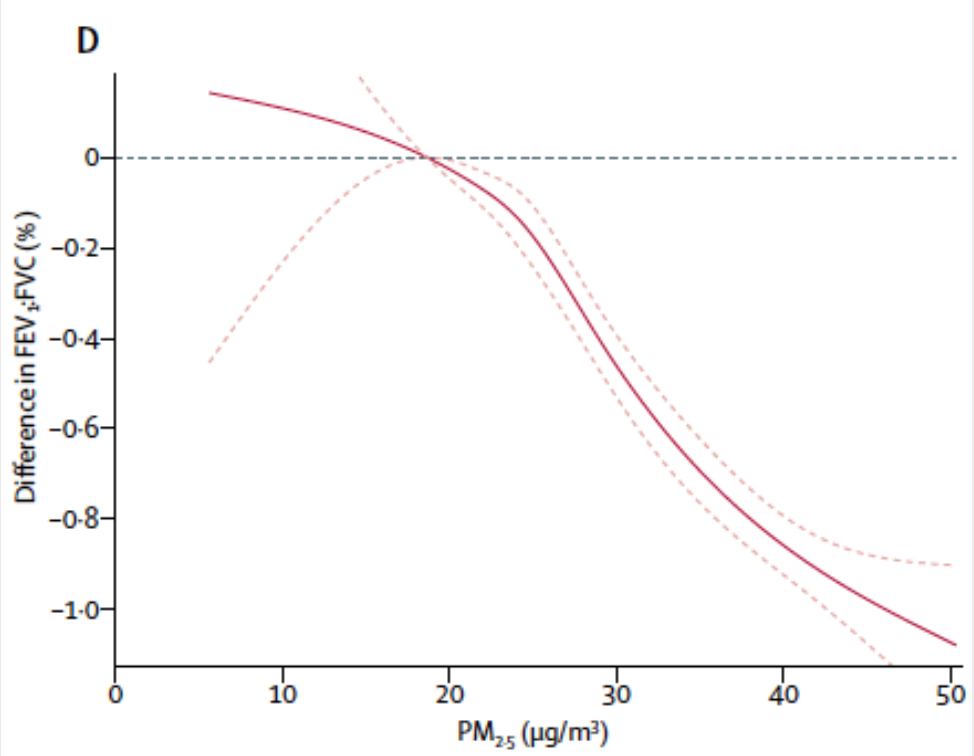
Liu et al. Thorax 2017;72:788-795

Developing COPD

Air Pollution in Taiwan ($PM_{2.5}$)

Long-term exposure to ambient PM2.5 is associated with reduced, and faster declines in, lung function and an increased risk of the incidence of COPD.





Guo et al. Lancet Planet Health 2018;2:e114-e125

Developing COPD: Occupation

ECRHS

Participants exposed to biological dust had a higher incidence of COPD compared with those unexposed, as did those exposed to gases and fumes and pesticides.. The combined population attributable fraction for these exposures was 21.0%.

	Cases in unexposed (%)	Cases in exposed (%)	Relative risk (95% CI)	Population attributable fraction (%)
Biological dust	55/2264 (2.4)	41/1079 (3.8)	1.6 (1.1 to 2.3)	16.0
Mineral dust	65/2501 (2.6)	31/842 (3.7)	1.1 (0.7 to 1.7)	3.9
Gases and fumes	41/1888 (2.2)	55/1455 (3.8)	1.5 (1.0 to 2.2)	19.4
Vapours, gases, dusts and fumes	40/1725 (2.3)	56/1618 (3.5)	1.3 (0.9 to 2.0)	14.1
Herbicides	91/3269 (2.8)	5/74 (6.8)	2.0 (0.7 to 4.1)	2.6
Insecticides	88/3229 (2.7)	8/114 (7.0)	2.3 (1.1 to 4.2)	4.7
Fungicides	88/3211 (2.7)	8/132 (6.1)	1.9 (0.9 to 3.6)	3.9
All pesticides	86/3179 (2.7)	10/164 (6.1)	2.2 (1.1 to 3.8)	5.6
Aromatic solvents	80/2796 (2.9)	16/547 (2.9)	0.9 (0.5 to 1.5)	–
Chlorinated solvents	83/2904 (2.9)	13/439 (3.0)	0.8 (0.5 to 1.4)	–
Other solvents	71/2391 (3.0)	25/952 (2.6)	0.8 (0.5 to 1.3)	–
Metals	82/2922 (2.8)	14/421 (3.3)	1.0 (0.5 to 1.6)	–

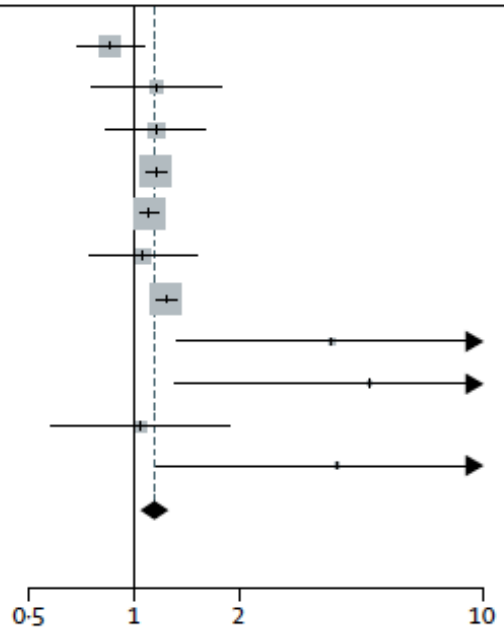
Lytras et al. Thorax 2018 (in press)

Developing COPD
HIV Infection

There is a “high prevalence of COPD in the global population with HIV, and an association with HIV”

	HIV-positive		HIV-negative		OR (95% CI)	Weight (%)
	Events	Total	Events	Total		
Akgun (2016)[57]	154	3538	182	3606	0·86 (0·69–1·07)	10·3
Crothers (2013)[61]	54	300	46	289	1·16 (0·75–1·79)	3·8
Crothers (2006)[59]	104	1014	64	713	1·16 (0·84–1·61)	5·9
Crothers (2011)[60]	1537	33420	2677	66840	1·16 (1·08–1·23)	23·5
Depp (2016)[63]	1919	43618	3461	86492	1·10 (1·04–1·17)	24·1
Drummond (2013)[64]	52	316	117	748	1·06 (0·74–1·52)	5·2
Kendall (2014)[71]	1106	14005	4621	71410	1·24 (1·16–1·33)	23·2
Madeddu (2013)[74]	26	111	5	65	3·67 (1·33–10·10)	0·8
Nakamura (2014)[79]	5	48	5	208	4·72 (1·31–17·02)	0·5
Pefura-Yone (2015)[47]	24	461	23	461	1·05 (0·58–1·88)	2·2
Vos (2017)[85]	10	84	4	117	3·82 (1·15–12·62)	0·6
Random-effects model	**4991**	**96915**	**11205**	**230949**	**1·14 (1·05–1·25)**	**100**

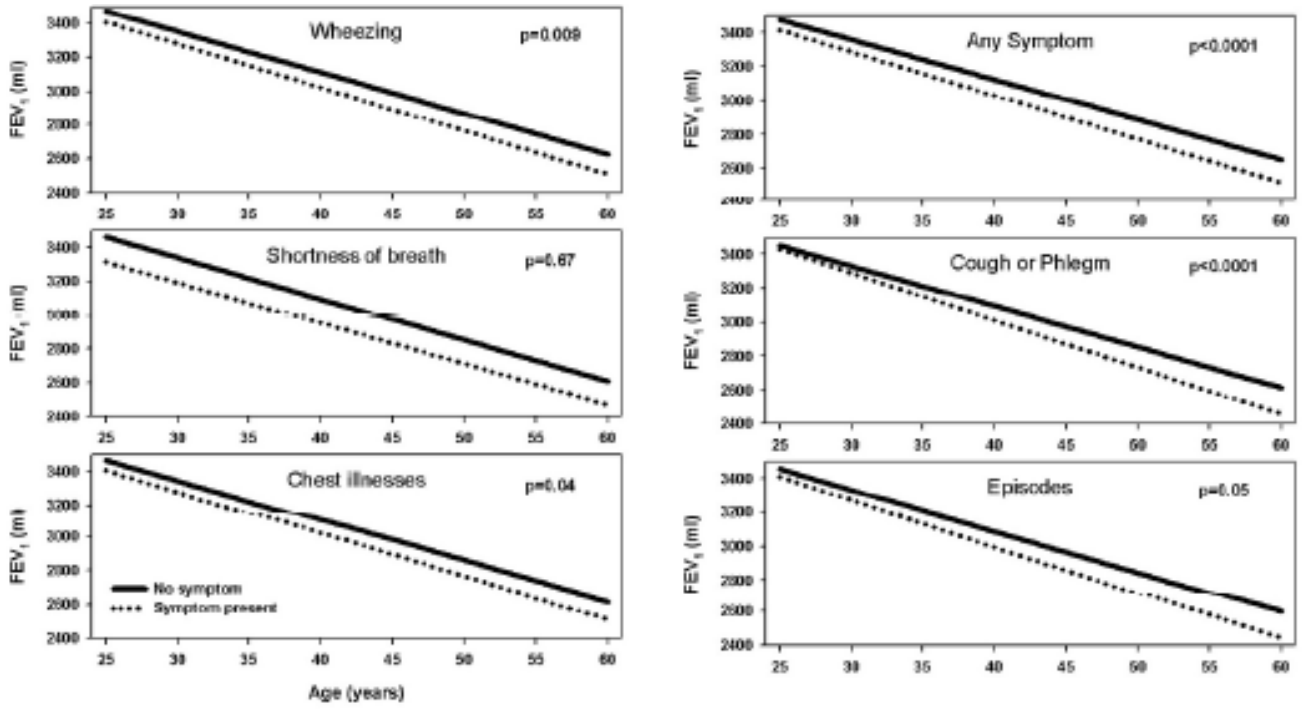
Heterogeneity: I^2=63·5% (95% CI 30·1–80·9), τ^2=0·008; p=0·0023



Bigna et al. Lancet Glob Health 2018;6:e193-e202

“Pre COPD”

Symptoms in Young Adults & Airflow Obstruction



2749 participants in Coronary Artery Risk Development in Young Adults (CARDIA) study

Respiratory symptom questionnaires at baseline & 2 yr later

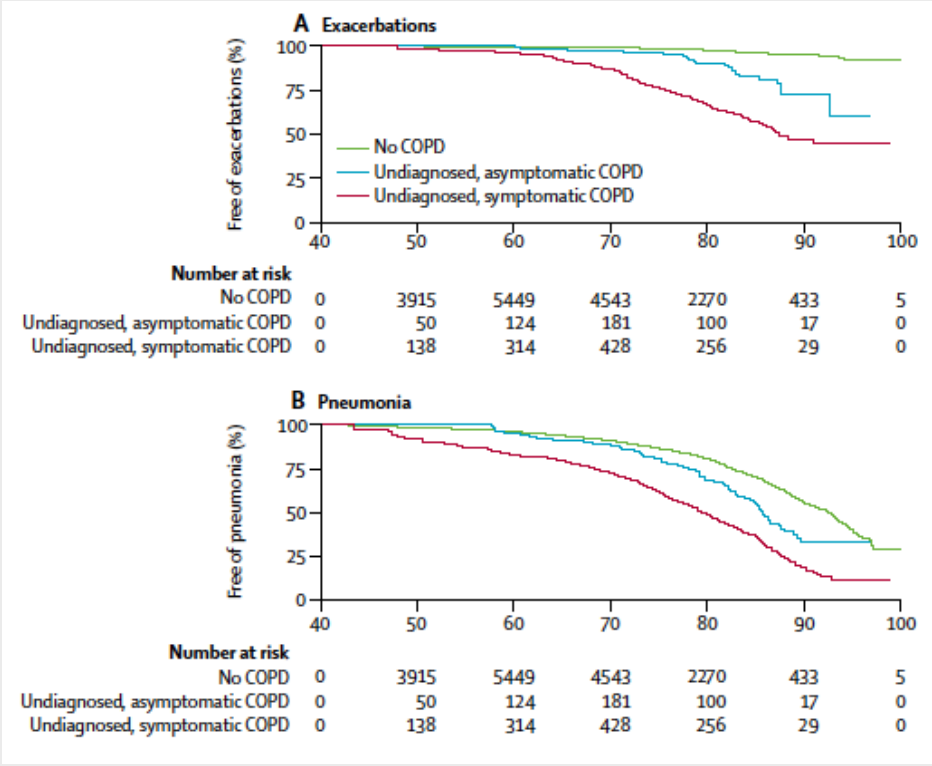
Repeated spirometry over 30 yr

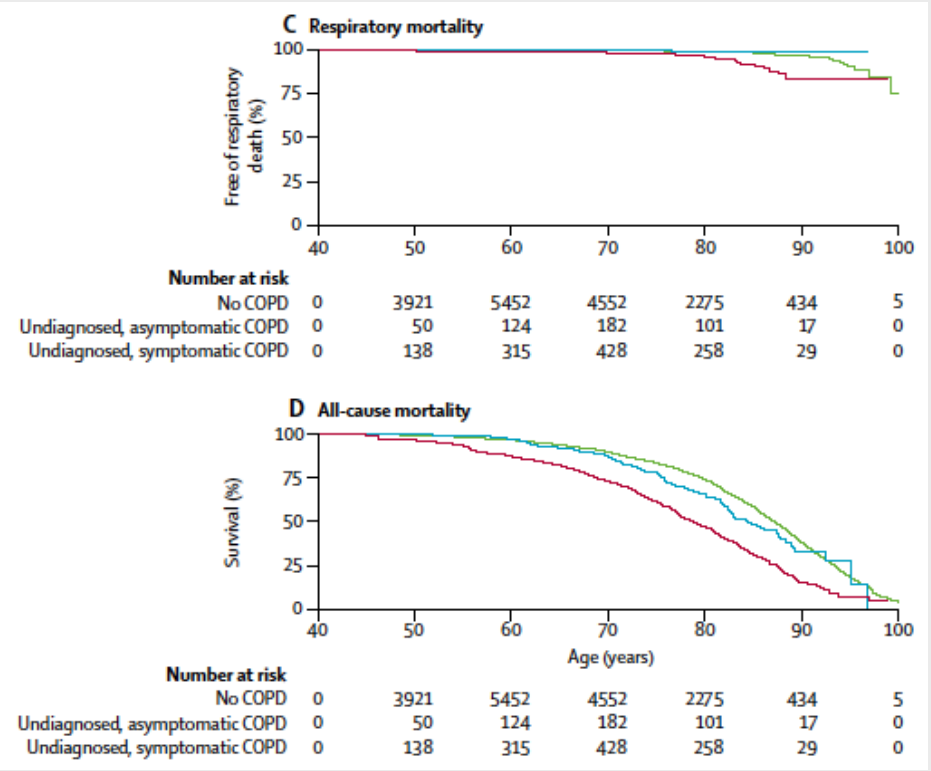
Kalhan et al. Am J Respir Crit Care Med 2018 on line first

Undiagnosed COPD

Copenhagen General Population Study

Individuals with undiagnosed, asymptomatic COPD had an increased risk of exacerbations and pneumonia.





Colak et al. Lancet Respir Med 2017;5:426-434

Developing COPD
Additional References

Childhood Lung Function Predicts Adult Chronic Obstructive Pulmonary Disease and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome
Bui et al. Am J Respir Crit Care Med 2017;196:39-46

Airflow Obstruction and Use of Solid Fuels for Cooking or Heating: BOLD Results
Amaral et al. Am J Respir Crit Care Med 2017;197:595-610

Association between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low- and Middle-Income Country Settings
Siddharthan et al. Am J Respir Crit Care Med 2018;197:611-620

Smoking, telomere length and lung function decline: a longitudinal population-based study
Andujar et al. Thorax 2018;73:283-285

Take-Home Messages

- Parental lung function influences lung function in offspring
- Particulate air pollution, Occupational dust exposures and HIV are risk factors for COPD
- Respiratory symptoms is young adults indicate an increased risk of COPD in later life
- Undiagnosed COPD causes morbidity and mortality

Pharmacotherapy

LABA/LAMA & Exercise

Once-daily tiotropium/olodaterol yielded improvements in lung hyperinflation versus placebo and statistically significant improvements versus monotherapies.

O'Donnell et al. Eur Respir J 2017;49:1601348

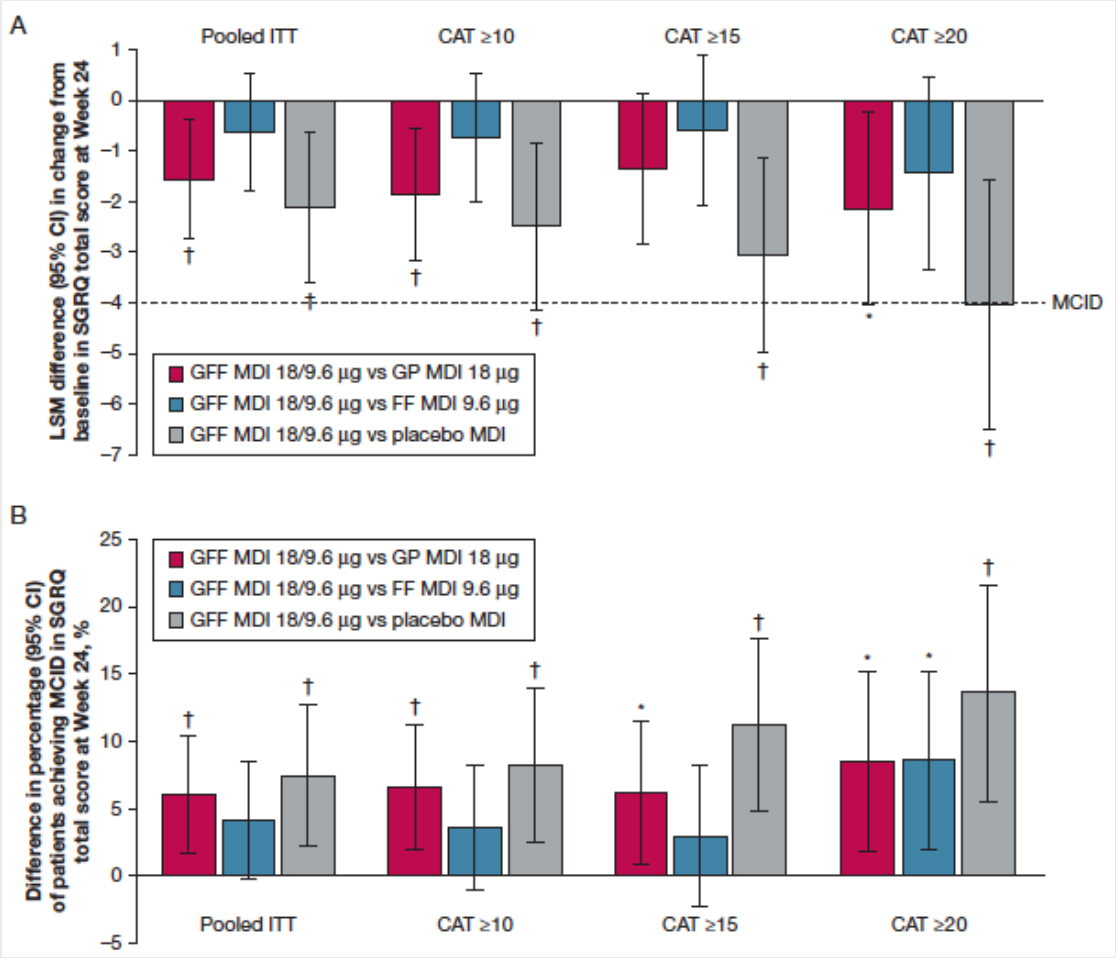
Aclidinium/formoterol significantly improved exercise endurance time and IC at isotime versus placebo at Week 4 and Week 8

Watz et al. Int J Chron Obstruct Pulmon Dis 2017;12:2545-2558

UMEC/VI did not result in improvements in EET at week 12 versus placebo, despite improvements in measures of lung function, hyperinflation and health status

Riley et al. ERJ Open Res 2018;4:00073-2017

LABA/LAMA
Baseline Symptom Score & Benefit



Martinez et al. CHEST 2017;152:1169-1178

LABA/LAMA CV Safety

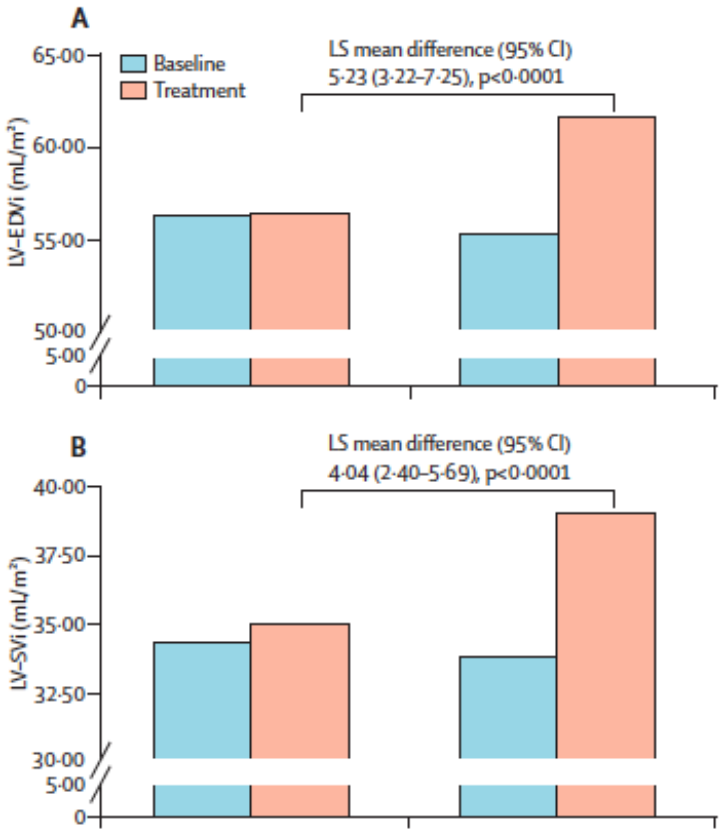
Adding a second long-acting bronchodilator in the real-world-setting treatment of COPD does not increase the risk of most cardiovascular events.

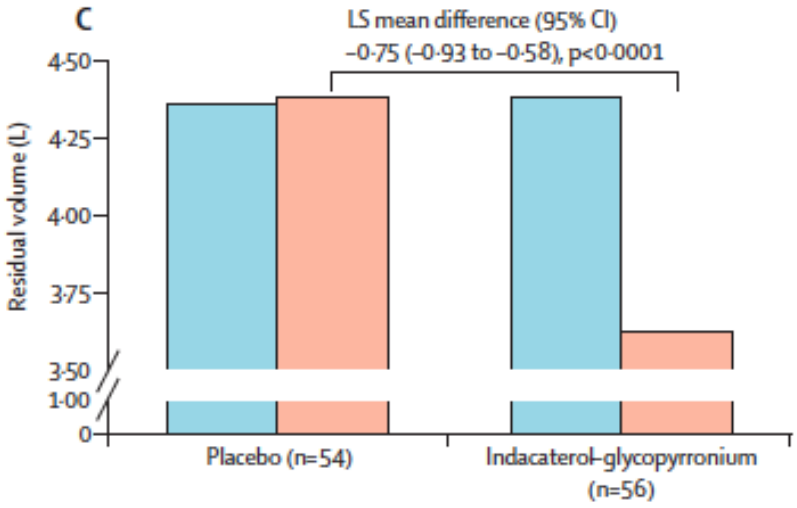
	Patients n	Events n	Person-years	Rate per 1000 per year	Crude[#] HR	Adjusted[¶] HR (95% CI)
Acute myocardial infarction						
Monotherapy	31 138	251	23 253	10.8	1.00	1.00 (reference)
Combination	31 138	318	27 956	11.4	1.07	1.06 (0.89–1.25)
Stroke						
Monotherapy	31 123	194	23 267	8.3	1.00	1.00 (reference)
Combination	31 123	213	27 980	7.6	0.92	0.94 (0.77–1.15)
Heart failure						
Monotherapy	31 174	697	23 192	30.0	1.00	1.00 (reference)
Combination	31 174	928	27 660	33.5	1.15	1.14 (1.03–1.26)
Arrhythmia						
Monotherapy	18 861	149	14 076	10.6	1.00	1.00 (reference)
Combination	18 861	184	16 919	10.9	1.04	1.01 (0.81–1.26)

Suissa et al. Eur Respir J 2017;49:1602245

LABA/LAMA & Cardiac Effects

Dual bronchodilation with indacaterol–glycopyrronium significantly improved cardiac function as measured by left-ventricular end-diastolic volume





Hohlfeld et al. Lancet Respir Med 2018;6: 368–78

LABA/LAMA
Additional References

Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study
Feldman et al. Adv Ther 2017;34:2518-2533

Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel Co-Suspension Delivery Technology in patients with chronic obstructive pulmonary disease
Hanania et al. Respir Med 2017;126:105-115

How Do Dual Long-Acting Bronchodilators Prevent Exacerbations of Chronic Obstructive Pulmonary Disease?
Beeh et al. Am J Respir Crit Care Med 2017;196:139-149

Maximal bronchodilation: a therapeutic target in COPD?
Agusti et al. Lancet Respir Med 2017;5:540-542

Reduction in clinically important deterioration in chronic obstructive pulmonary disease with aclidinium/formoterol
Singh et al. Respir Res 2017;18:106

The effect of indacaterol/glycopyrronium versus tiotropium or salmeterol/fluticasone on the prevention of clinically important deterioration in COPD
Anzueto et al. Int J Chron Obstruct Pulmon Dis 2017;12:1325-1337

Take-Home Messages

- LABA/LAMA improve exercise capacity but there may be differences between molecules
- LABA/LAMA offer greatest benefit compared to monotherapy in the more symptomatic patients
- LABA/LAMA are safe and may improve cardiac function

LABA/LAMA/ICS
TRIBUTE

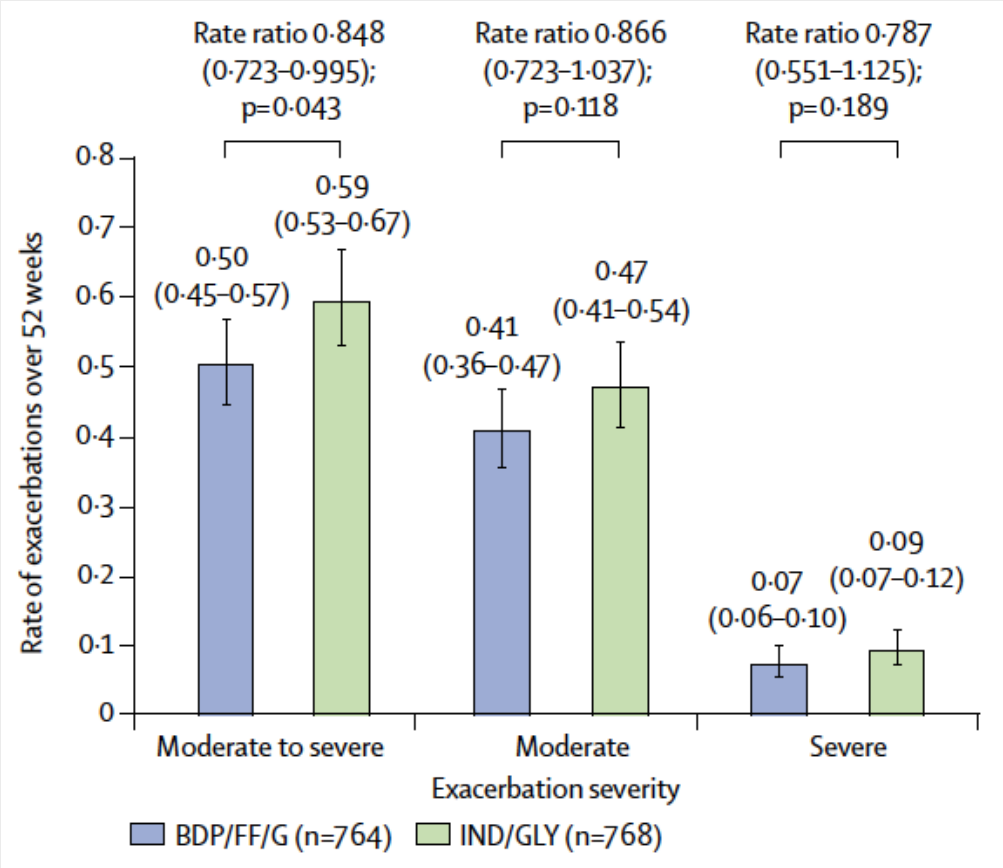
Eligible patients:

- 40 years or older
- current or ex-smokers
- diagnosis of COPD:
  - post-bronchodilator (salbutamol 400 µg) FEV1/FVC < 0.7
  - severe or very severe airflow limitation (FEV1 <50%)
- at least one documented moderate or severe COPD exacerbation in the previous 12 months
- symptomatic at screening, CAT ≥ 10
- for at least 2 months before screening had used:
  - ICS/LABA
  - ICS/LAMA
  - LAMA/LABA
  - LAMA
  - but not triple therapy.

Papi et al. Lancet 2018;391:1076-1084

LABA/LAMA/ICS
TRIBUTE

1532 patients received BDP/FF/G (n=764) or IND/GLY (n=768).



Papi et al. Lancet 2018;391:1076-1084

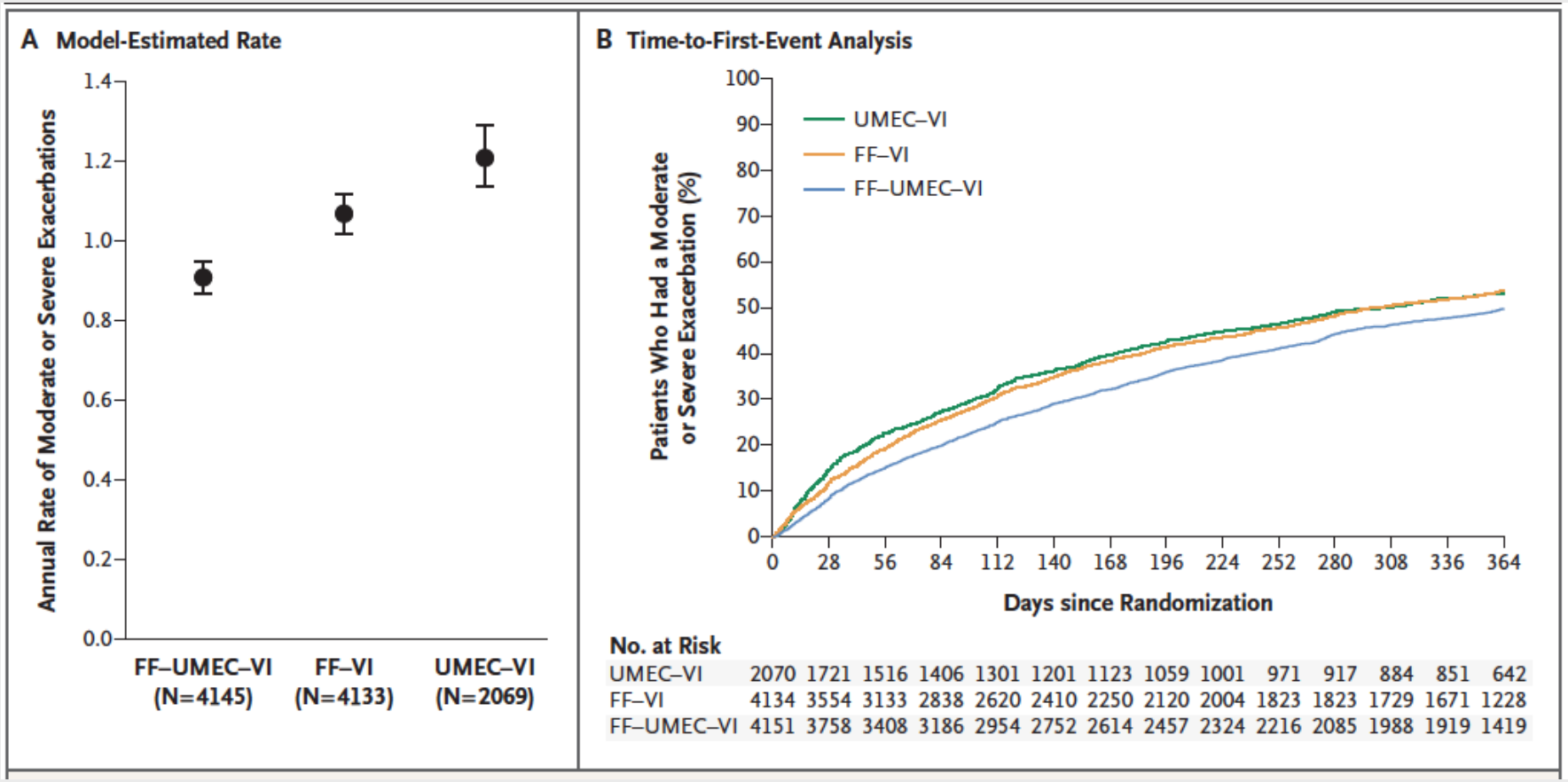
LABA/LAMA/ICS
IMPACT

Eligible patients:

- 40 years or older
- current or ex-smokers
- symptomatic at screening, CAT ≥ 10
- Either
  - FEV1 < 50% predicted and a history of at least one moderate or severe exacerbationin the previous year,
  - or FEV1 50-80% predicted and at least two moderate exacerbations or one severe exacerbation in the previous year.
- Patients continued on their own medication, which could include a LAMA, a LABA, or an inhaled glucocorticoid alone or in combination, during a 2-week run-in period before randomization.

Lipson et al. NEJM 2018 (on line first)

LABA/LAMA/ICS
IMPACT



Lipson et al. NEJM 2018 (on line first)

LABA/LAMA/ICS
IMPACT

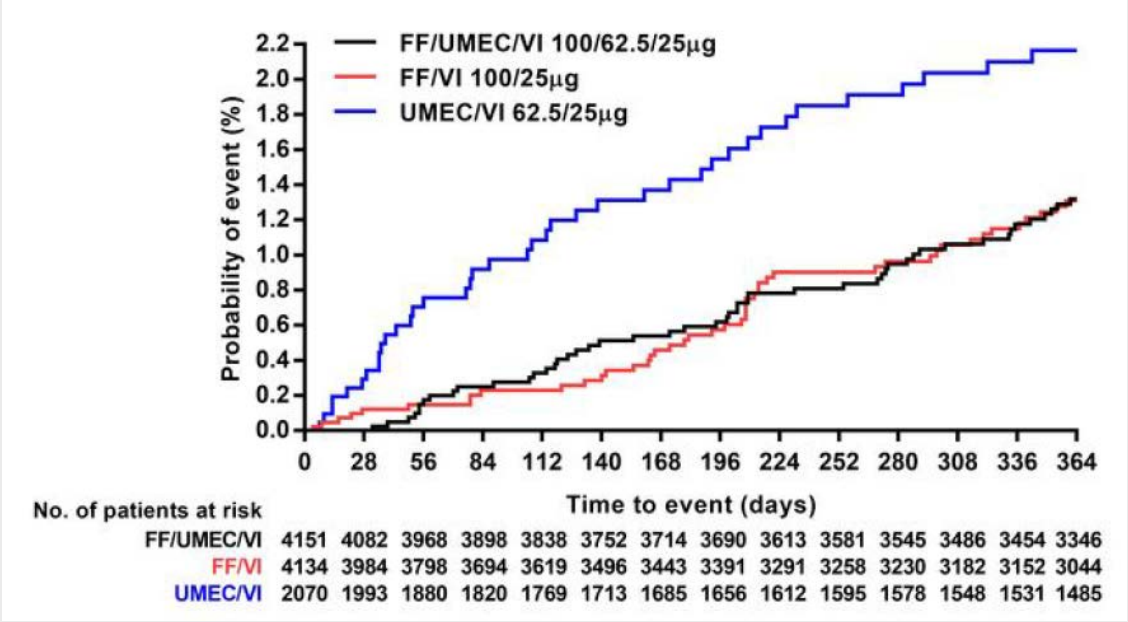
Outcome	Triple Therapy (N=4151)	Fluticasone Furoate–Vilanterol (N=4134)	Umeclidinium–Vilanterol (N=2070)
Trough FEV_1			
No. of patients evaluated	3366	3060	1490
Mean at wk 52 (95% CI) — ml	1274 (1265 to 1282)	1177 (1168 to 1185)	1220 (1208 to 1232)
Mean change from baseline (95% CI) — ml	94 (86 to 102)	–3 (–12 to 6)	40 (28 to 52)
Difference between triple therapy and dual-therapy comparator (95% CI) — ml	—	97 (85 to 109)†	54 (39 to 69)†
SGRQ total score‡			
No. of patients evaluated	3318	3026	1470
Mean at wk 52 (95% CI)	45.0 (44.5 to 45.4)	46.8 (46.3 to 47.2)	46.8 (46.1 to 47.4)
Mean change from baseline (95% CI)	–5.5 (–5.9 to –5.0)	–3.7 (–4.2 to –3.2)	–3.7 (–4.4 to –3.0)
Difference between triple therapy and dual-therapy comparator (95% CI)	—	–1.8 (–2.4 to –1.1)†	–1.8 (–2.6 to –1.0)†
Response according to SGRQ total score at wk 52 — no. (%)§	1723 (42)	1390 (34)	696 (34)
Odds ratio for triple therapy vs. dual-therapy comparator (95% CI)	—	1.41 (1.29 to 1.55)†	1.41 (1.26 to 1.57)†

Lipson et al. NEJM 2018 (on line first)

LABA/LAMA/ICS
IMPACT

FF/UMEC/VI and FF/VI demonstrated a signal in reduction of on-treatment all-cause mortality compared with UMEC/VI.

- FF/UMEC/VI compared with UMEC/VI: HR 0.58 (95% CI, 0.38 to 0.88; 42.1% reduction; unadjusted p=0.011)
- FF/VI compared with UMEC/VI: HR 0.61 (95% CI, 0.40 to 0.93; 38.7% reduction; unadjusted p=0.022)



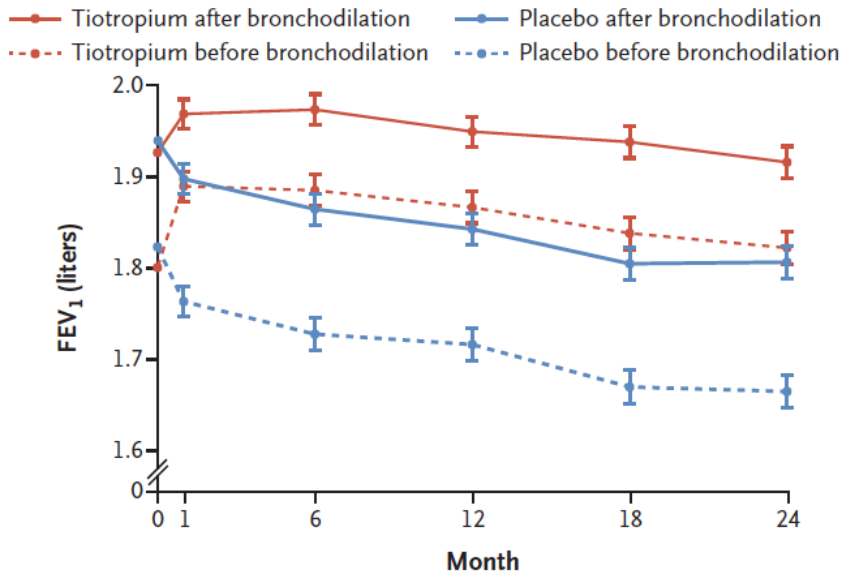
Lipson et al. NEJM 2018 (on line first)
Lipson et al. ATS 2018 Abstract AJRCCM 2018;197:A1015

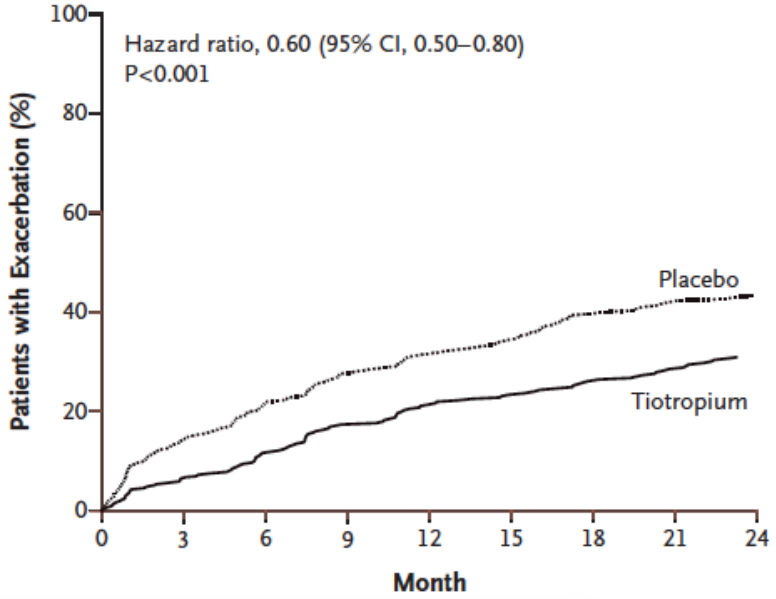
Take-Home Messages

- Triple therapy reduces exacerbation rates compared to LABA/LAMA or LABA/ICS
- In IMPACT triple therapy also improved lung function and health status compared to LABA/LAMA or LABA/ICS
- In IMPACT triple therapy and LABA/ICS reduced all cause mortality
- Differences in the enrolled populations and trial design may explain differences between recent and previous studies
- The results of subgroup analyses will be very informative

Tiotropium in Early Disease

mean post-bronchodilator 1.94 L (78.1% predicted)





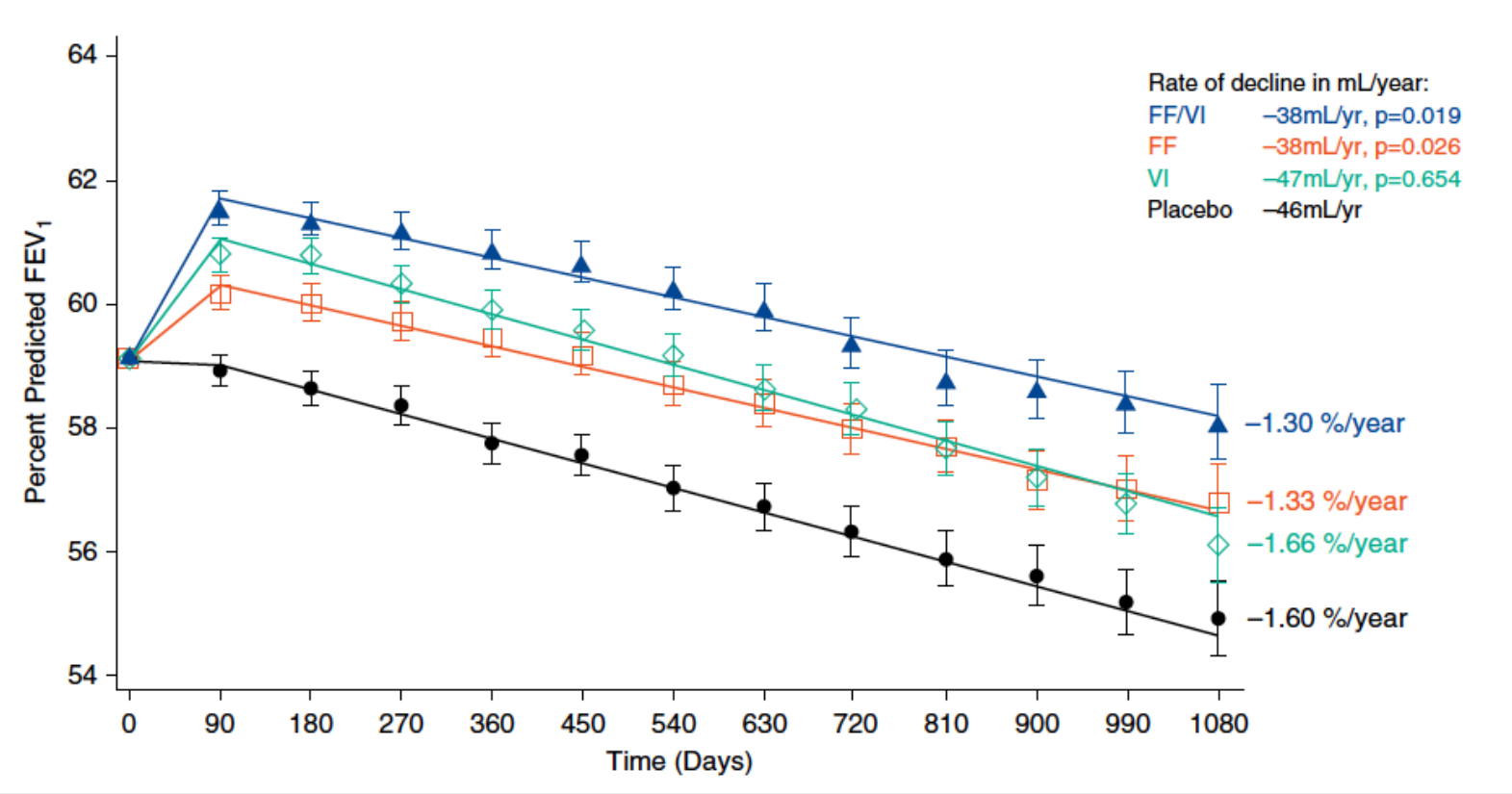
Variable	Decline per Year		
	Placebo Group (N=383)	Tiotropium Group (N=388)	Difference (95% CI)†
Total			
FEV_1 (ml)			
Before bronchodilator use	53±6	38±6	15 (–1 to 31)
After bronchodilator use	51±6	29±5	22 (6 to 37)

Zhou et al. NEJM 2017;377:923-35

LABA/ICS

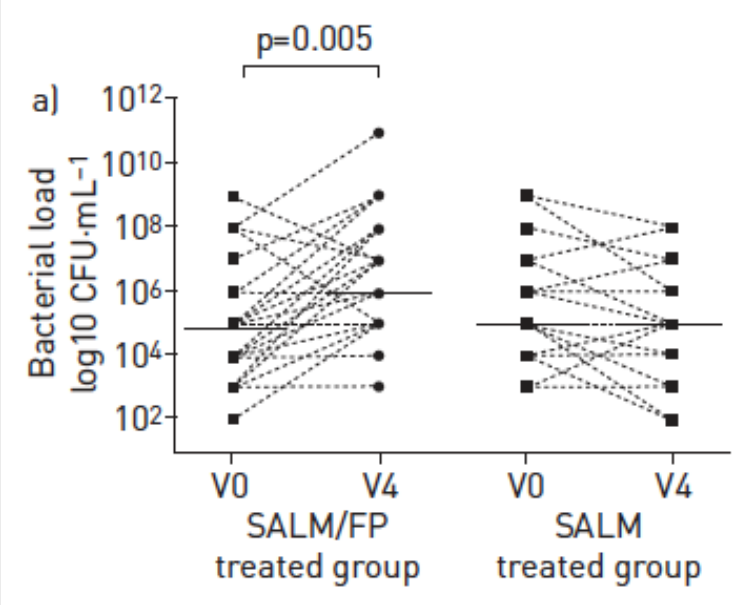
FF, VI & Lung Function Decline in SUMMIT

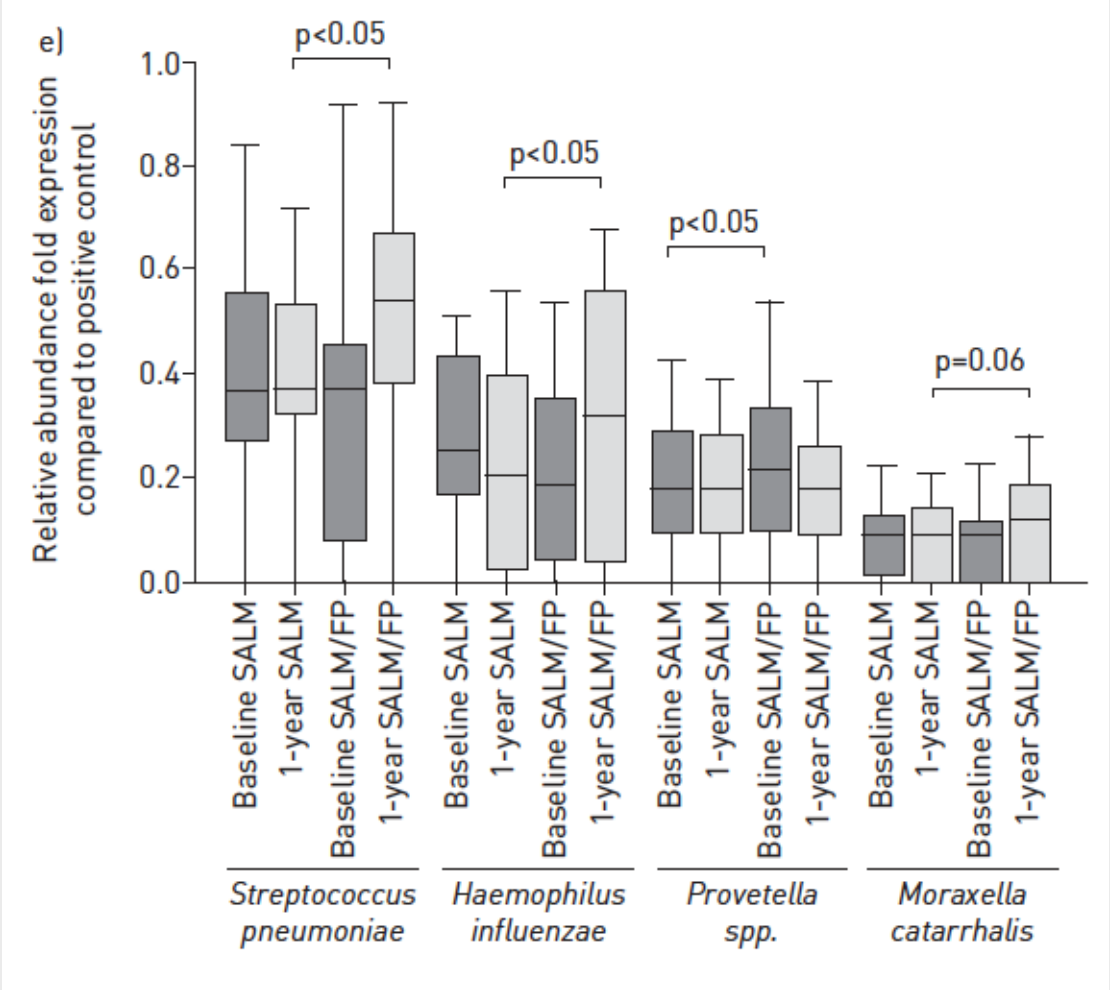
Rate of FEV_1 decline, was slower in patients randomized to the fluticasone-containing treatments than in those in the vilanterol and placebo arms.



Calverley et al. Am J Respir Crit Care Med 2018;197:47-55

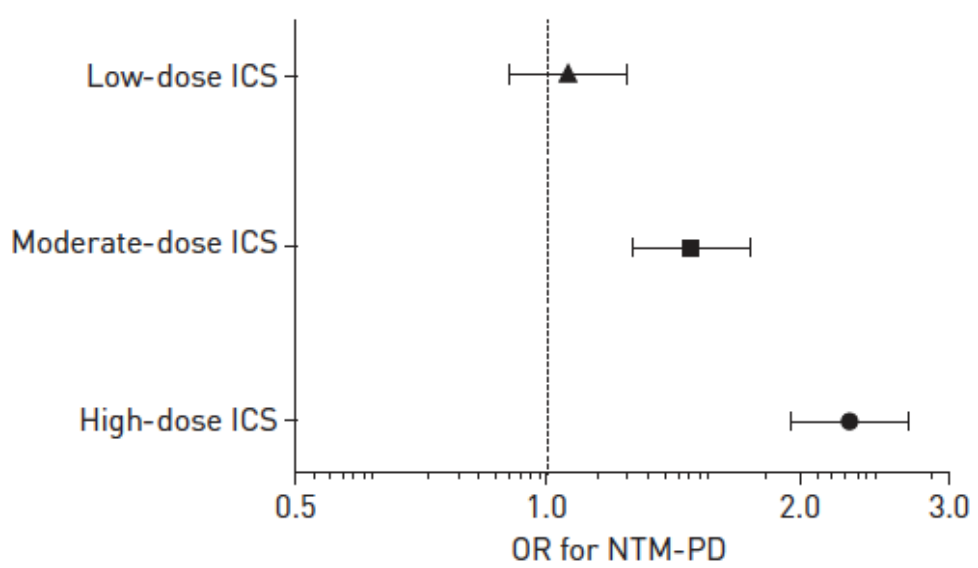
ICS Adverse Effects





Contoli et al. Eur Respir J 2017;50: 1700451

ICS Adverse Effects
Mycobacterial Infection

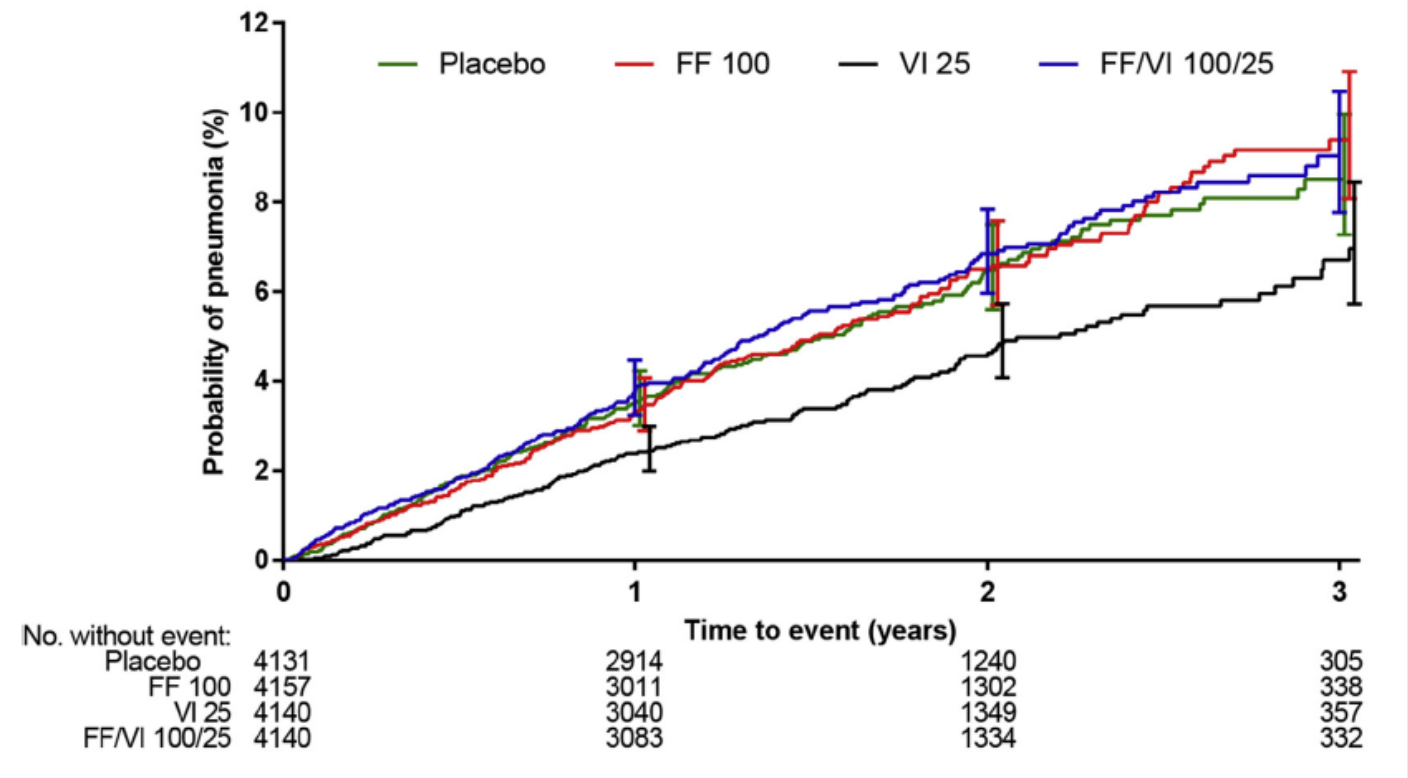


Current ICS use was associated with NTM-PD compared with nonuse (adjusted OR (aOR) 1.86, 95% CI 1.60–2.15) and was statistically significant for fluticasone (aOR 2.09, 95% CI 1.80–2.43), but not for budesonide (aOR 1.19, 95% CI 0.97–1.45). There was a strong dose–response relationship between incident NTM-PD and cumulative ICS dose over 1 year. There was no significant association between current ICS use and TB (aOR 1.43, 95% CI 0.95–2.16).

Brode et al. Eur Respir J 2017;50: 1700037

ICS Adverse Effects
SUMMIT

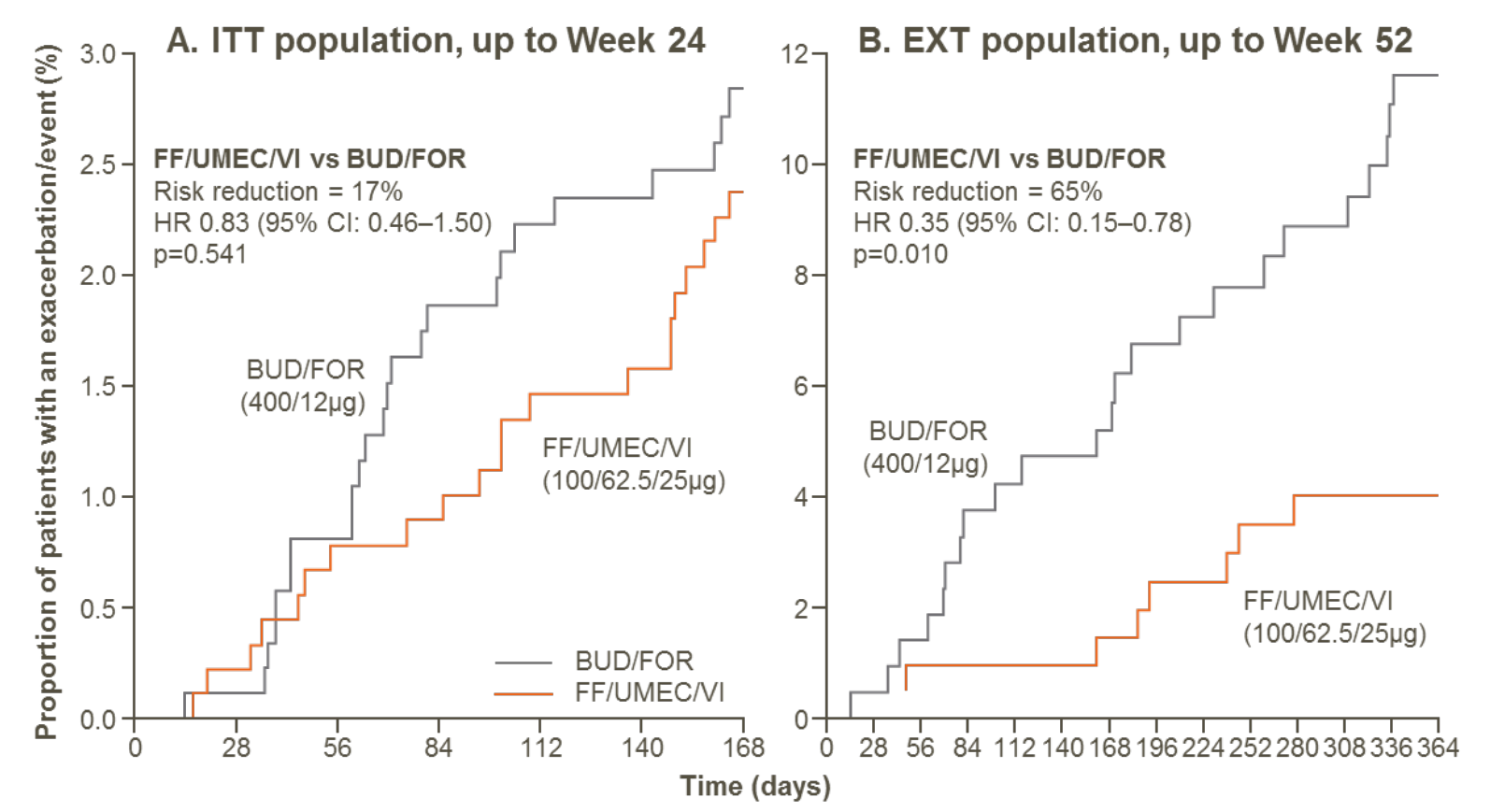
In contrast to previous studies in patients with severe disease, increased pneumonia risk with inhaled corticosteroid use was not evident in COPD subjects with moderate airflow limitation and heightened cardiovascular risk



Crim et al. Respir Med 2017;131:27-34

ICS Adverse Effects
FULFIL

Time to first serious exacerbation or serious pneumonia



Dransfield, Halpin, Barnacle et al. ERS Congress 2017, Abstract #PA1069

ICS Step Down

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2017, VOL. 14, NO. 5, 465–468
https://doi.org/10.1080/15412555.2017.1342233

PERSPECTIVE

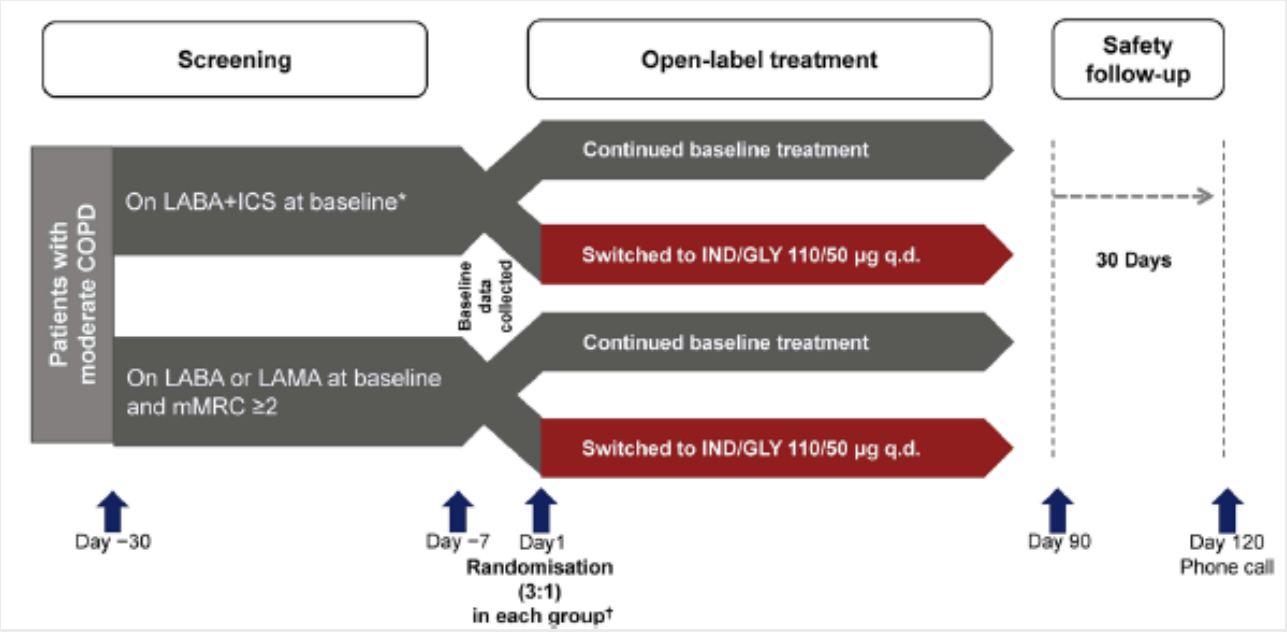
Should Patients Switched from D to B in the GOLD 2017 Classification be Discontinued from Inhaled Corticosteroids?

Matevz Harlander[a], Miriam Barrecheguren[b], Matjaz Turel[a], and Marc Miravitlles[b]

[a]Department of Pulmonary Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia; [b]Pneumology Department, Hospital Universitari Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

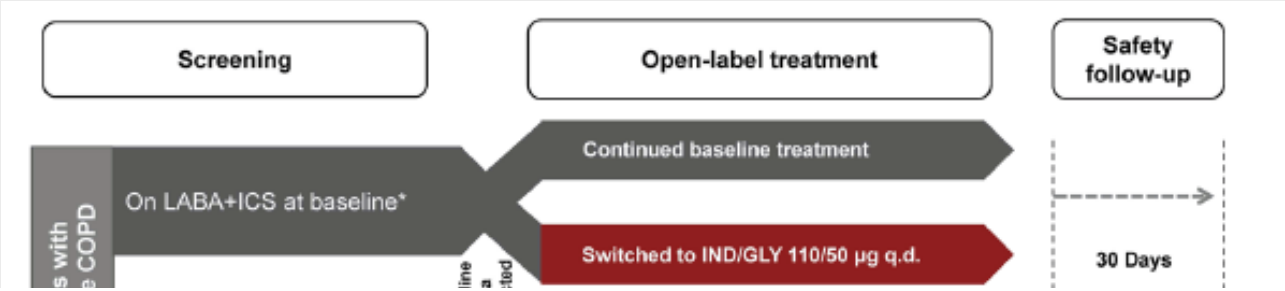
Harlander et al. COPD 2017;14:465-468

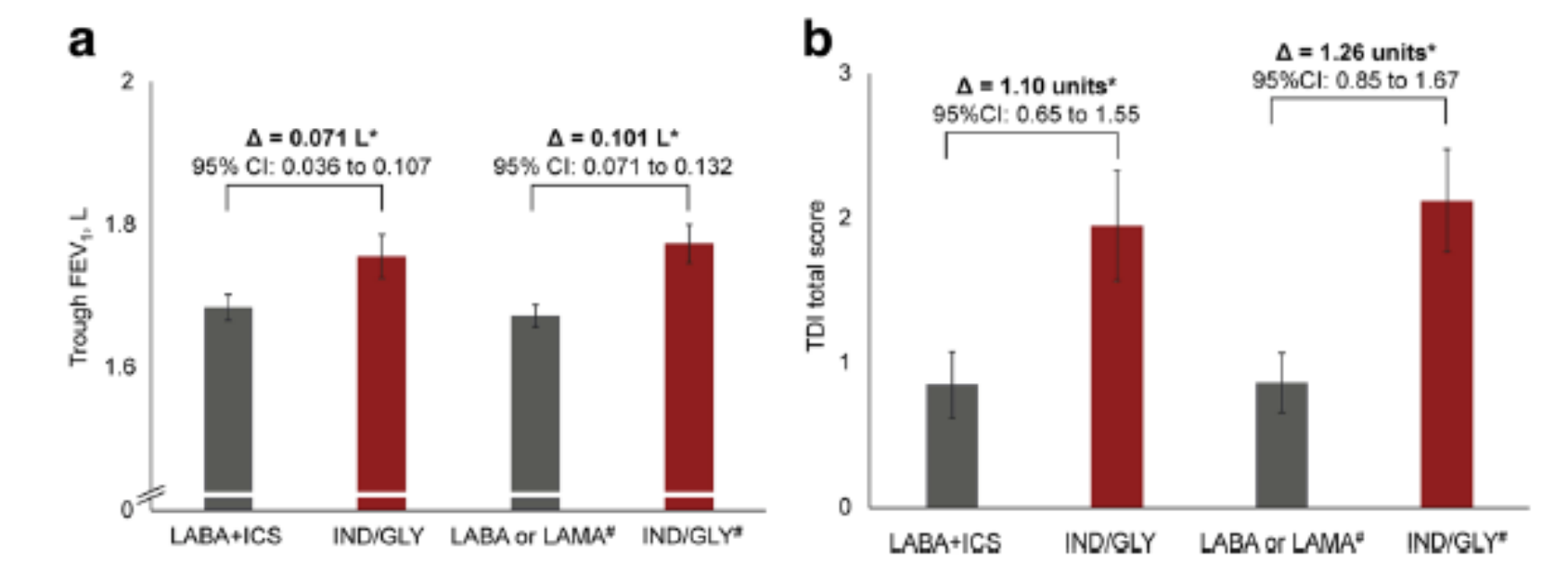
Treatment Switch
CRYSTAL



Vogelmeier et al. Respir Res 2017;18:140

Treatment Switch
CRYSTAL





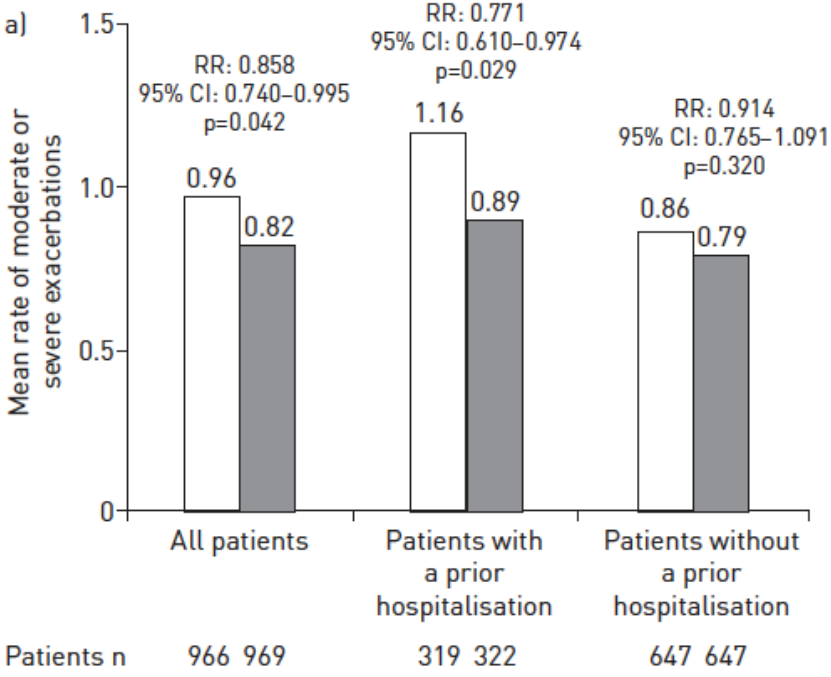
Vogelmeier et al. Respir Res 2017;18:140

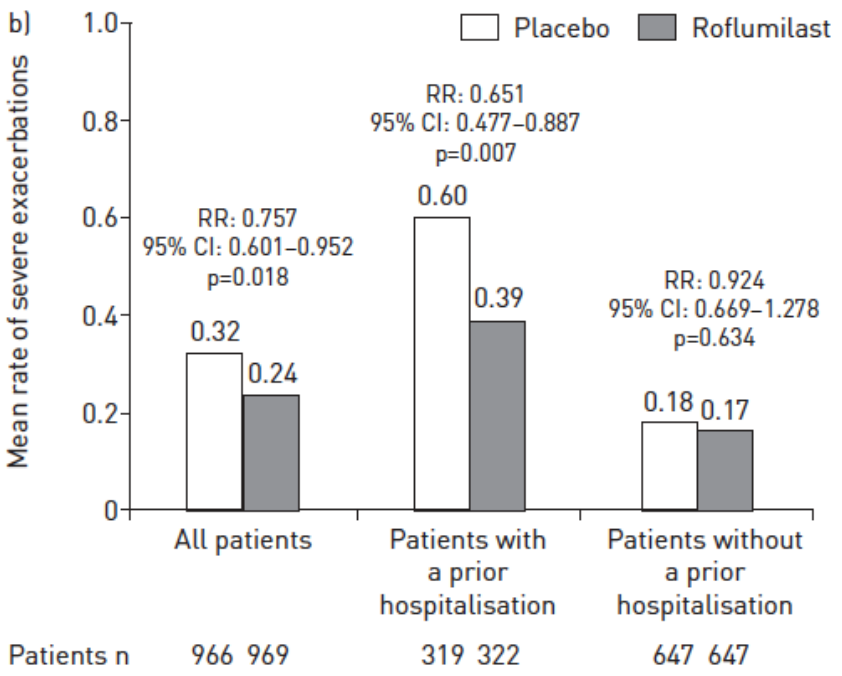
Take-Home Messages

- Early intervention with tiotropium and FF/VI appears to slow loss of lung function
- ICS use changes the lung microbiome
- In milder disease ICS may not increase the risk of pneumonia
- Overall ICS use reduces risk of hospitalization from either an exacerbation or pneumonia
- In well controlled patients switching from ICS/LABA to LABA/LAMA appears safe

Roflumilast
Post-hoc analysis of REACT

"The results from REACT and RE^{2}SPOND indicate that roflumilast is most effective at reducing the rate of moderate or severe exacerbations in a subgroup of patients with a hospitalisation for a COPD exacerbation in the previous year"





Rabe et al. Eur Respir J 2017;50: 1700158

Mepolizumab in COPD

METREX & METREO

Entry Criteria

Both trials:

- Age ≥ 40; documented diagnosis of COPD for at least 1 year
- Pre and post bronchodilator FEV1:FVC <0.7
- Post-bronchodilator FEV1 >20% & ≤ 80% predicted
- Documented history of ≥2 moderate or ≥ 1 severe exacerbations in the previous year
- For 12 months before screening, patients had to have been receiving:
  - high dose ICS (≥500 µg per day of fluticasone propionate or equivalent)
  - a long-acting bronchodilator (LABA or LAMA)
  - a third class of regularly prescribed COPD medication (e.g. LABA, LAMA PDE4)
- For ≥3 months immediately before screening, patients had to have been receiving triple inhaled therapy

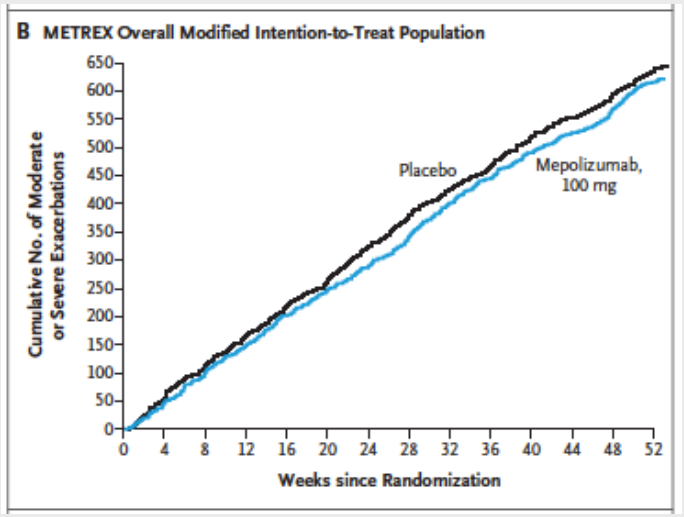
In METREX, patients were stratified on the basis of blood Eos (<150, 150-300, >300)

In METREO, only patients who had an eosinophilic phenotype were eligible for inclusion.

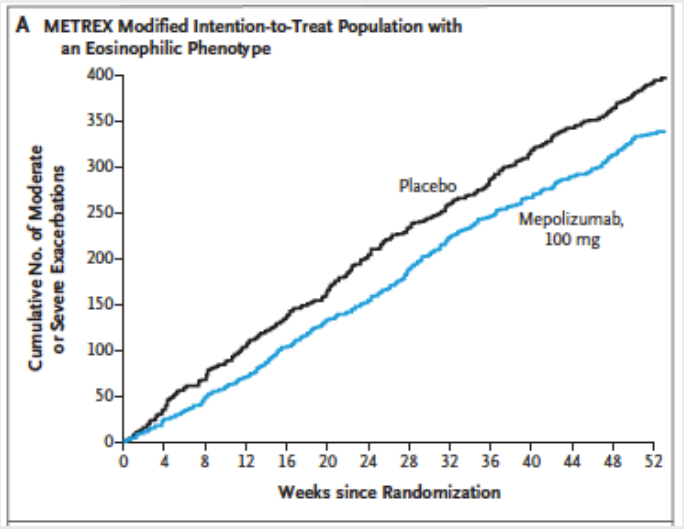
Pavord et al. N Engl J Med 2017;377:1613-1629

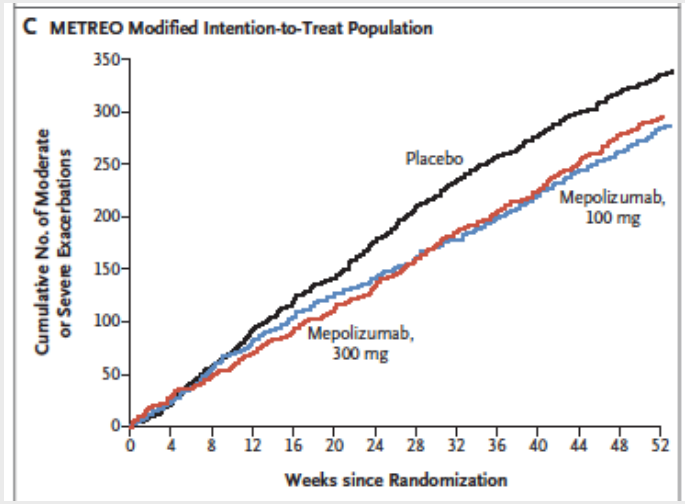
Mepolizumab in COPD

METREX & METREO



Mepolizumab at a dose of 100 mg was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and an eosinophilic phenotype.





Pavord et al. N Engl J Med 2017;377:1613-1629

Pharmacotherapy
Additional References

How Do Dual Long-Acting Bronchodilators Prevent Exacerbations of Chronic Obstructive Pulmonary Disease?
Beeh et al. Am J Respir Crit Care Med 2017;196:139-149

Factors associated with appropriate inhaler use in patients with COPD - lessons from the REAL survey
Price et al. Int J Chron Obstruct Pulmon Dis 2018;13:695-702

Maximal bronchodilation: a therapeutic target in COPD?
Agusti et al. Lancet Respir Med 2017;5:540-542

Reduction in clinically important deterioration in chronic obstructive pulmonary disease with aclidinium/formoterol
Singh et al. Respir Res 2017;18:106

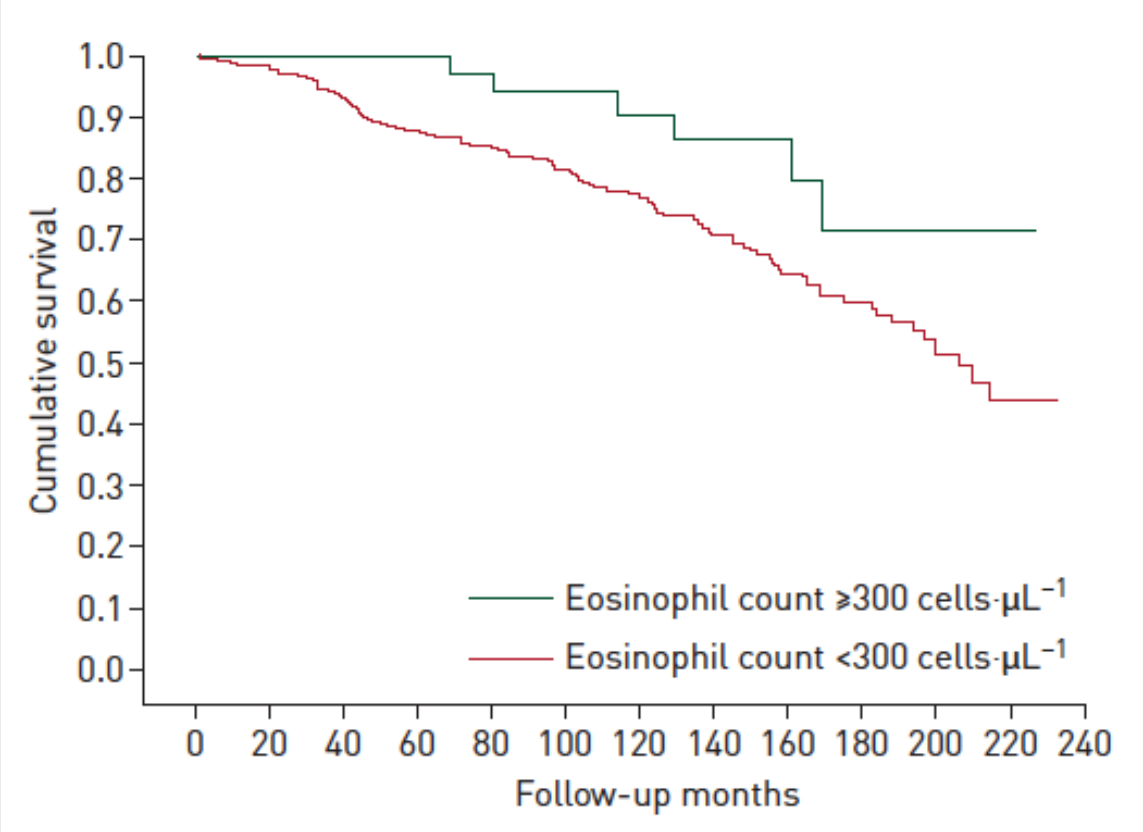
Eosinophils

Stability of Eosinophil Counts

	Proportion with Stable Eosinophil Counts at Time Point (%)						
	6 mo	9 mo	1 yr	2 yr	4 yr	6 yr	8 yr
Patients with COPD	85	82	75	62	49	42	35
Absolute blood eosinophil count							
$<0.34 \times 10^9$, cells/L	95	93	90	86	80	77	75
$\geq 0.34 \times 10^9$, cells/L	80	70	63	45	30	23	18
Age							
40–59 yr	95	93	85	83	76	71	67
60–79 yr	93	90	80	79	70	65	60
≥80 yr	91	89	77	73	66	61	58
Sex							
Female	94	92	89	81	75	70	68
Male	92	89	85	75	65	61	57
Smoking status							
Yes	95	90	88	81	72	69	62
No	95	90	88	79	72	69	62

Oshagbemi et al. Am J Respir Crit Care Med 2017;195:1402-1404

Eosinophils & Outcomes
Survival



"In patients with COPD, blood eosinophils ⩾300 cells·μL^{-1} persisting over 2 years was not a risk factor for COPD exacerbations.
High eosinophil count was associated with better survival."

Casanova et al. Eur Respir J 2017;50:1701162

Eosinophils & Outcomes
SPIROMICS

	Blood eosinophils <200 cells per µL (n=1262)	Blood eosinophils ≥200 cells per µL (n=1237)	p value*	Sputum eosinophils <1·25% (n=656)	Sputum eosinophils ≥1·25% (n=171)	p value*
Lung function before bronchodilator						
FEV_1, L	1·86 (1·22–2·54)	1·81 (1·16–2·55)	0·38	2·15 (1·57–2·77)	1·83 (1·38–2·32)	<0·0001
FEV_1 percentage predicted	70·5 (46·6–88·2)	66·3 (42·0–85·6)	0·006	75·7 (59·3–90·2)	65·7 (51·8–81·3)	<0·0001
FVC percentage predicted	87·2 (74·1–99·3)	84·4 (70·1–96·7)	0·0002	90·9 (78·9–100·0)	87·1 (76·9–97·1)	0·06
FEV_1:FVC	0·64 (0·49–0·73)	0·61 (0·47–0·72)	0·016	0·66 (0·58–0·74)	0·61 (0·52–0·69)	<0·0001
Lung function after bronchodilator						
FEV_1, L	2·05 (1·43–2·72)	2·03 (1·39–2·75)	0·62	2·34 (1·78–2·59)	2·11 (1·69–2·59)	0·003
FEV_1 percentage predicted	77·7 (53·9–94·4)	74·2 (51·6–91·4)	0·008	82·9 (67·8–95·9)	77·3 (63·1–88·5)	0·001
FVC percentage predicted	92·9 (81·3–103·8)	90·5 (78·8–101·6)	0·001	94·5 (85·1–105·2)	94·2 (85·9–104·1)	0·84
FEV_1:FVC	0·66 (0·50–0·76)	0·63 (0·49–0·74)	0·004	0·68 (0·59–0·76)	0·64 (0·55–0·72)	0·0002
Percentage FEV_1 reversibility	9·3 (4·2–17·7)	9·8 (4·5–19·0)	0·46	8·0 (3·7–15·4)	11·6 (6·0–21·8)	<0·0001
Total	311 (25%)	309 (25%)	0·35	125 (19%)	44 (26%)	0·05
Requiring health-care use	294 (23%)	291 (24%)	0·36	125 (19%)	43 (25%)	0·07
Antibiotic treatment	232 (18%)	240 (19%)	0·29	92 (14%)	34 (20%)	0·09
Corticosteroid treatment	199 (16%)	209 (17%)	0·27	66 (10%)	32 (19%)	0·002
Any drug treatment	265 (21%)	273 (22%)	0·29	105 (16%)	39 (23%)	0·033
Severe†	137 (11%)	162 (13%)	0·15	52 (8%)	22 (13%)	0·044

"high concentrations of sputum eosinophils were a better biomarker than high concentrations of blood eosinophils to identify a patient subgroup with more severe disease, more frequent exacerbations, and increased emphysema by QCT. Blood eosinophils alone were not a reliable biomarker for COPD severity or exacerbations, or for sputum eosinophils.."

Hastie et al. Lancet Respir Med 2017;5:956-967

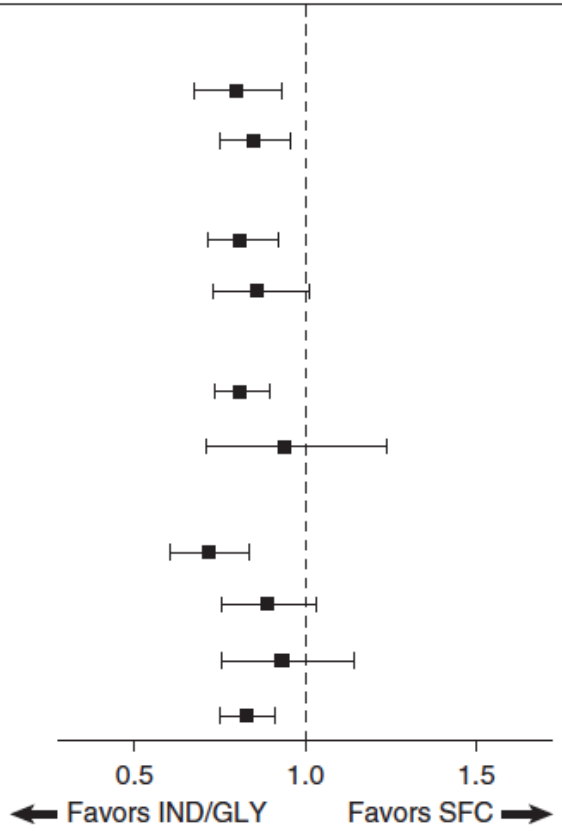
Eosinophils & Outcomes

- The percentage of COPD subjects with at least one exacerbation, either moderate or severe, was similar in those with persistently low (57%), high (49%) and variable eosinophils (54%).
- Even subjects with more than 300 eosinophils/μL did not have excess severe exacerbations.
- There was no difference in the median number of eosinophils/mm^2 in central airways, peripheral airways and lung parenchyma in smokers with and without COPD, and tissue eosinophils did not change with disease severity
- The use of blood eosinophils as a biomarker in COPD is based in the premise that they reflect and correlate with tissue eosinophilic inflammation in pulmonary airways and parenchyma.
- In the present study tissue eosinophilia was not different in smokers with and without COPD and, more importantly, it was not related to blood eosinophilia

Turato et al. Am J Respir Crit Care Med 2017 (on line first)

Eosinophils & Therapy
FLAME

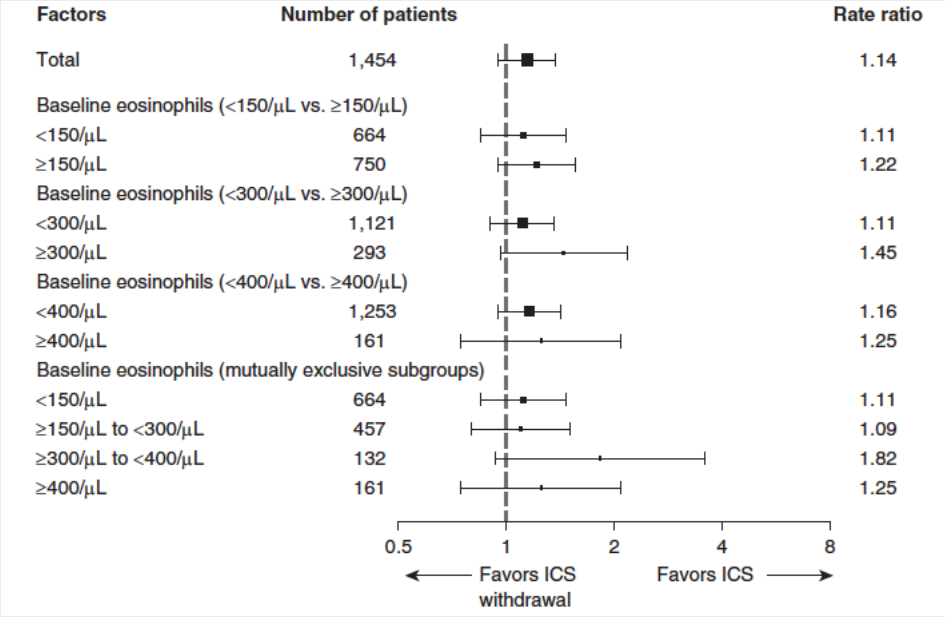
Subgroup	No. of patients IND/GLY	No. of patients SFC	Annualized rate IND/GLY	Annualized rate SFC	Rate ratio (95% CI)
Blood eosinophils count					
< 2 %	620	659	0.99	1.24	0.80 (0.68, 0.93)
≥ 2%	1,026	993	0.98	1.15	0.85 (0.75, 0.96)
Blood eosinophils count					
< 3 %	1,041	1,037	0.99	1.22	0.81 (0.72, 0.92)
≥ 3 %	605	615	0.98	1.14	0.86 (0.73, 1.01)
Blood eosinophils count					
< 5 %	1,442	1,444	0.98	1.20	0.81 (0.74, 0.90)
≥ 5 %	204	208	1.01	1.08	0.94 (0.71, 1.24)
Blood eosinophils count					
< 150 cells/µl	623	654	0.90	1.26	0.72 (0.61, 0.84)
150 to < 300 cells/µl	655	631	1.04	1.17	0.89 (0.76, 1.03)
≥ 300 cells/µl	368	367	1.03	1.11	0.93 (0.76, 1.14)
Overall	1,651	1,656	0.98	1.19	0.83 (0.75, 0.91)



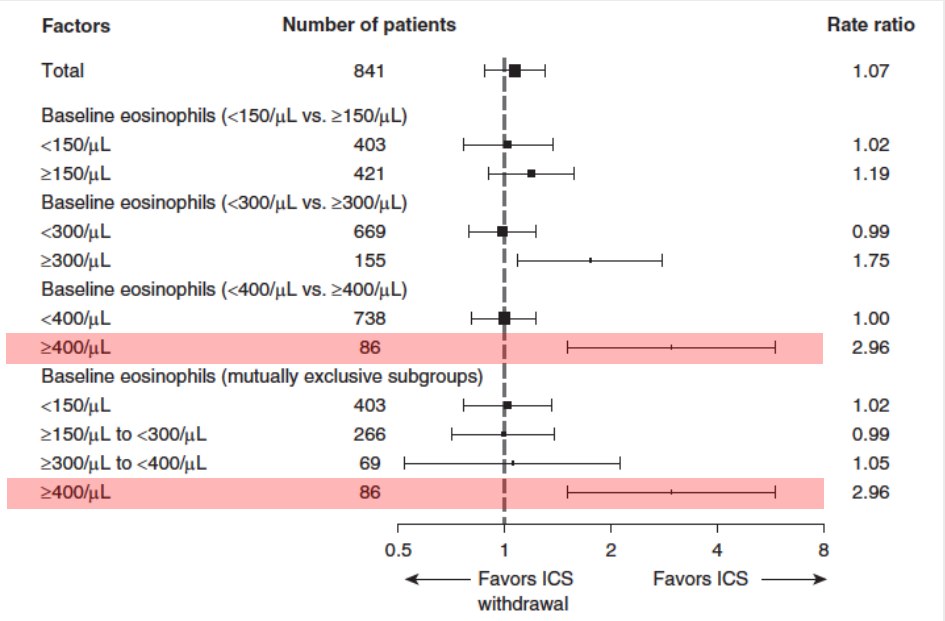
Roche et al. Am J Respir Crit Care Med 2017;195:1189-1197

Eosinophils & Therapy
WISDOM

1 exacerbation per year

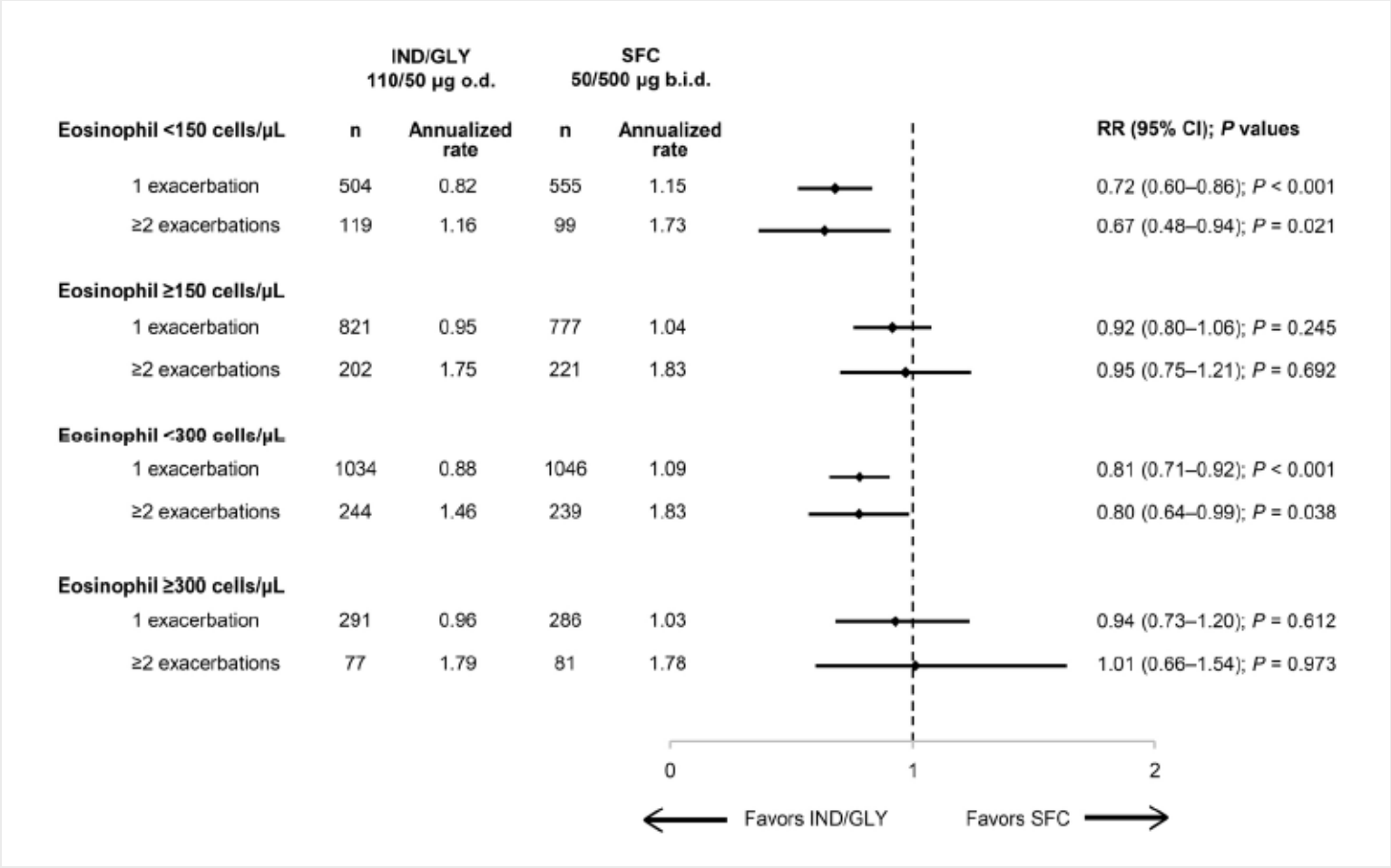


≥2 exacerbations per year



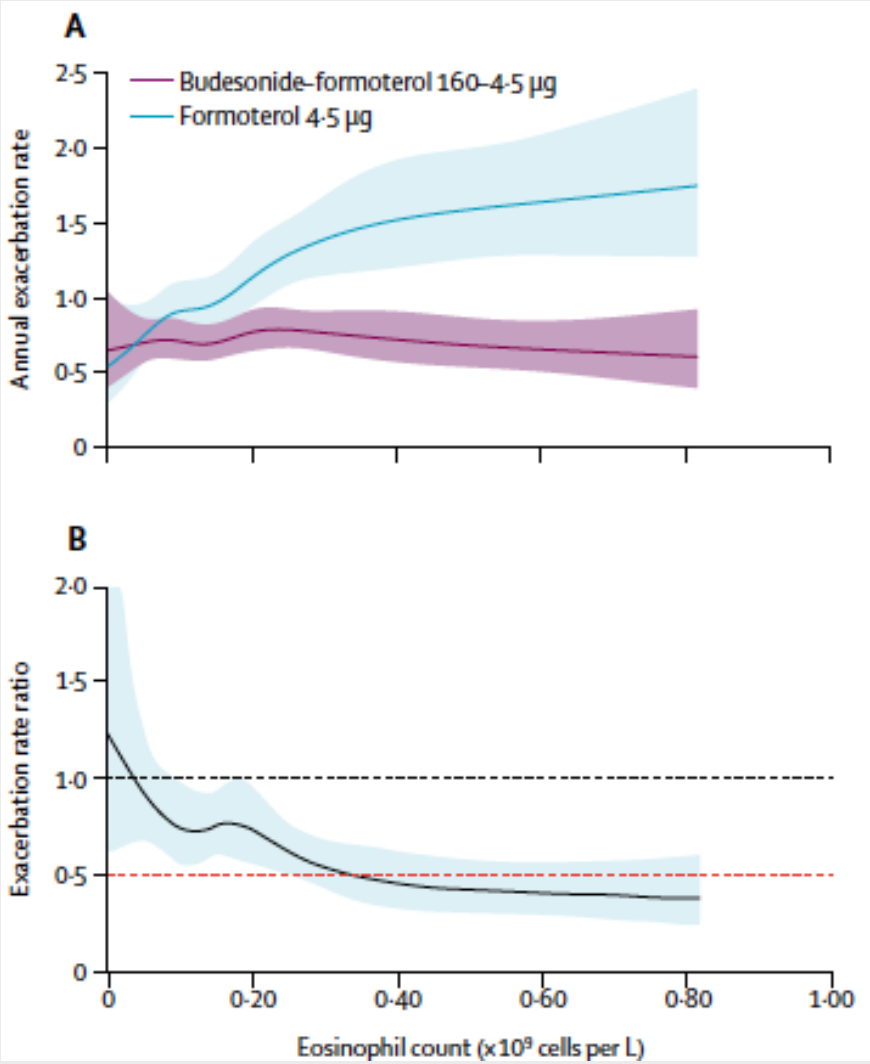
Calverley et al. Am J Respir Crit Care Med 2017;196:1219-1221

Eosinophils & Therapy
FLAME



Papi et al. Am J Respir Crit Care Med 2017 (on line first)

Eosinophils & ICS Response

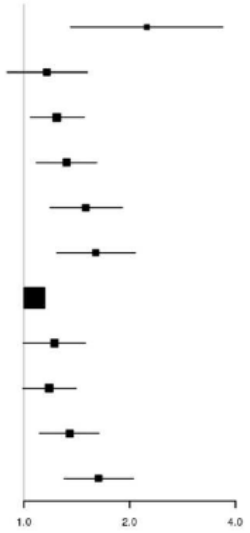


Bafadhel et al. Lancet Respir Med 2018;6:117-26

Eosinophils & ICS Response

COPD Gene

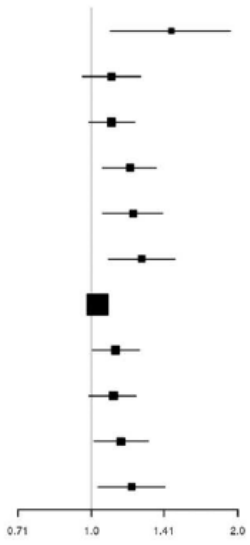
Eosinophil Cutoff	n	n	IRR	95% CI
cell/uL continuous	NA	1540	2.24	1.35-3.68
100 cells/uL	223	1330	1.16	0.90-1.52
200 cells/uL	814	739	1.24	1.04-1.48
300 cells/uL	1187	366	1.32	1.08-1.61
340 cells/uL	1350	203	1.5	1.18-1.91
400 cells/uL	1398	155	1.6	1.24-2.08
% continuous	NA	1540	1.07	1.02-1.11
2 %	408	1145	1.22	0.99-1.50
3 %	859	694	1.18	0.99-1.40
4 %	1166	387	1.35	1.11-1.63
5 %	1334	219	1.63	1.30-2.05



ECLIPSE

C

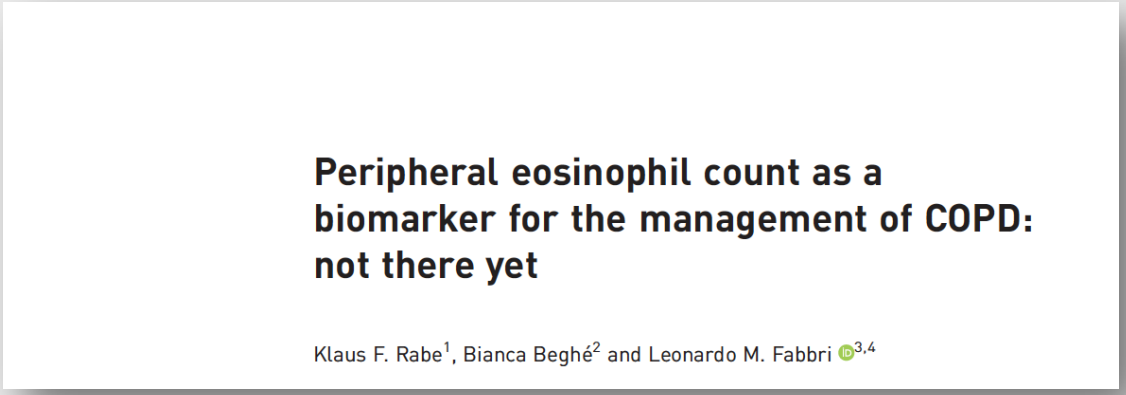
Eosinophil Cutoff	< n	≥ n	IRR	95% CI
continuous cells/uL	NA	1895	1.46	1.09-1.93
100 cells/uL	368	1527	1.1	0.96-1.26
200 cells/uL	1032	863	1.1	0.99-1.23
300 cells/uL	1477	418	1.2	1.05-1.36
340 cells/uL	1584	311	1.22	1.06-1.40
400 cells/uL	1668	227	1.27	1.08-1.48
continuous %	NA	1895	1.03	1.01-1.06
2 %	720	1175	1.12	1.00-1.25
3 %	1178	717	1.11	0.99-1.24
4 %	1476	419	1.15	1.01-1.31
5 %	1660	235	1.21	1.03-1.42



Adjusted incidence rate ratios for COPD exacerbations with different eosinophil cutoff values

Yun et al. J Allergy Clin Immunol. 2018 (on line first)

Eosinophils



1. at the present time, blood eosinophil counts cannot be recommended as biomarkers for the management of individual patients with COPD, particularly because of their poor reproducibility over time;
2. ICS probably should be maintained and not withdrawn in patients with high blood eosinophil counts and a history of frequent exacerbations, irrespective of powerful bronchodilator combinations;
3. ICS should be used with caution in COPD patients with persistent eosinopenia, and, if given, they should be carefully monitored for the increased risk of pneumonia.

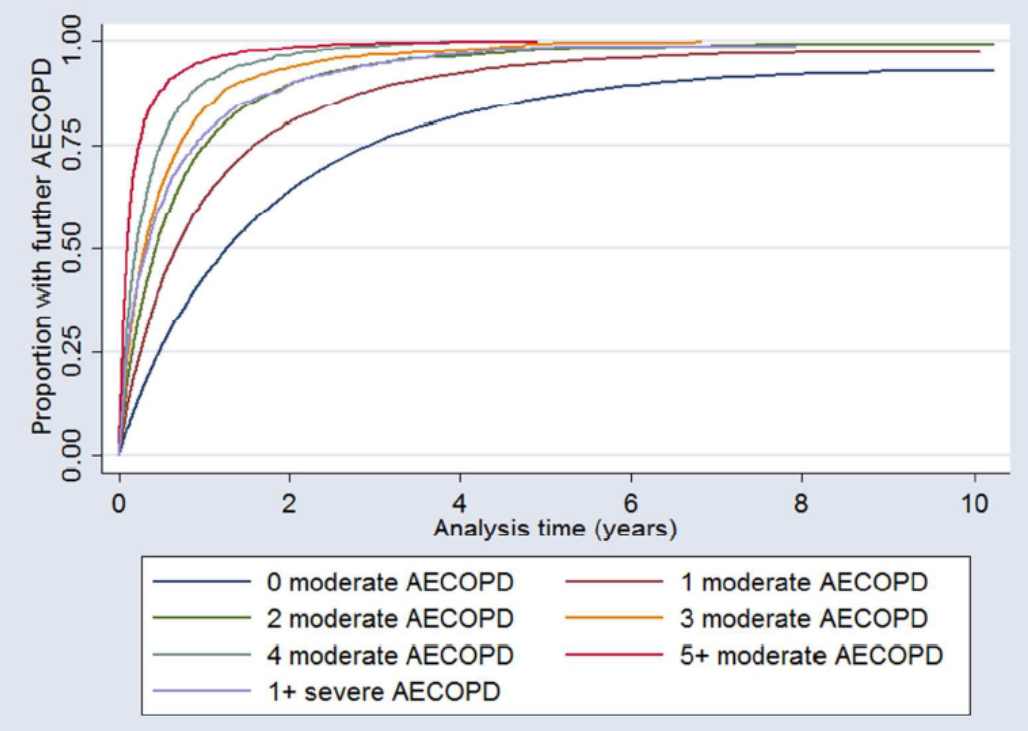
Rabe et al. Eur Respir J 2017;50:1702165

Take-Home Messages

- Eosinophil counts vary over time
- There may be differences in the predictive value of blood and sputum eosinophils and between the percentage and absolute number of eosinophils
- The relationship between eosinophils and outcomes is affected by ICS use
- ICS prevent some exacerbations in patients with higher blood eosinophils in some studies but not all
- The relationship between eosinophils and ICS response is a continuum but there is probably also a threshold for the effect
- ICS should not be withdrawn in patients with high eosinophil counts who have had exacerbations

Exacerbations

Natural History of Exacerbations in a Primary Care Population



A large proportion of COPD patients do not exacerbate over a maximum 10 years of follow-up.

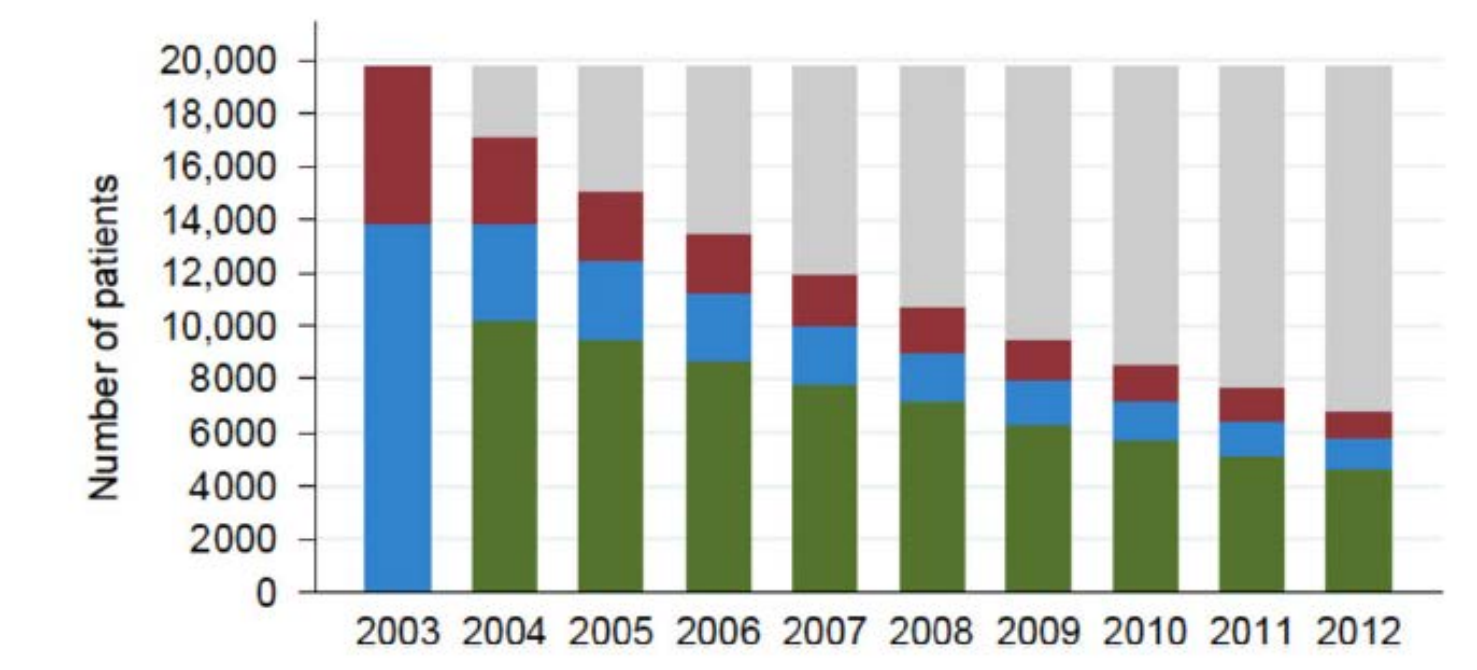
AECOPD frequency in a single year predicts long-term AECOPD rate.

Increasing frequency and severity of AECOPD is associated with risk of death, and highlights the importance of preventing AECOPD.

Rothnie et al. Am J Respir Crit Care Med 2018 (on line first)

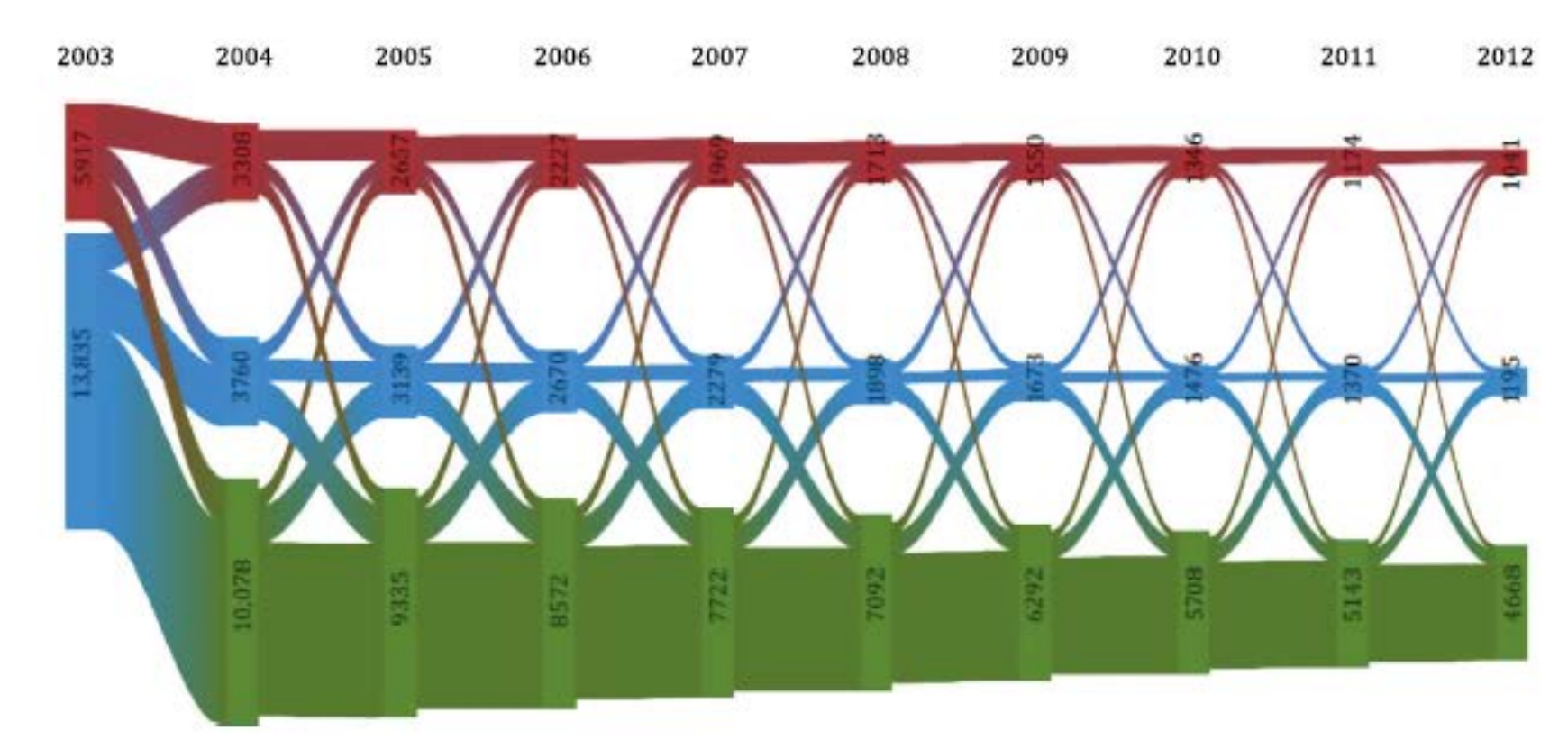
Natural History of Exacerbations in a Primary Care Population

Danish nationwide register-based descriptive study
Among all Danish citizens who were 55 years or older (1.5 million) 19,752 patients had at least one COPD exacerbation in 2003.
Follow-up over 10 years



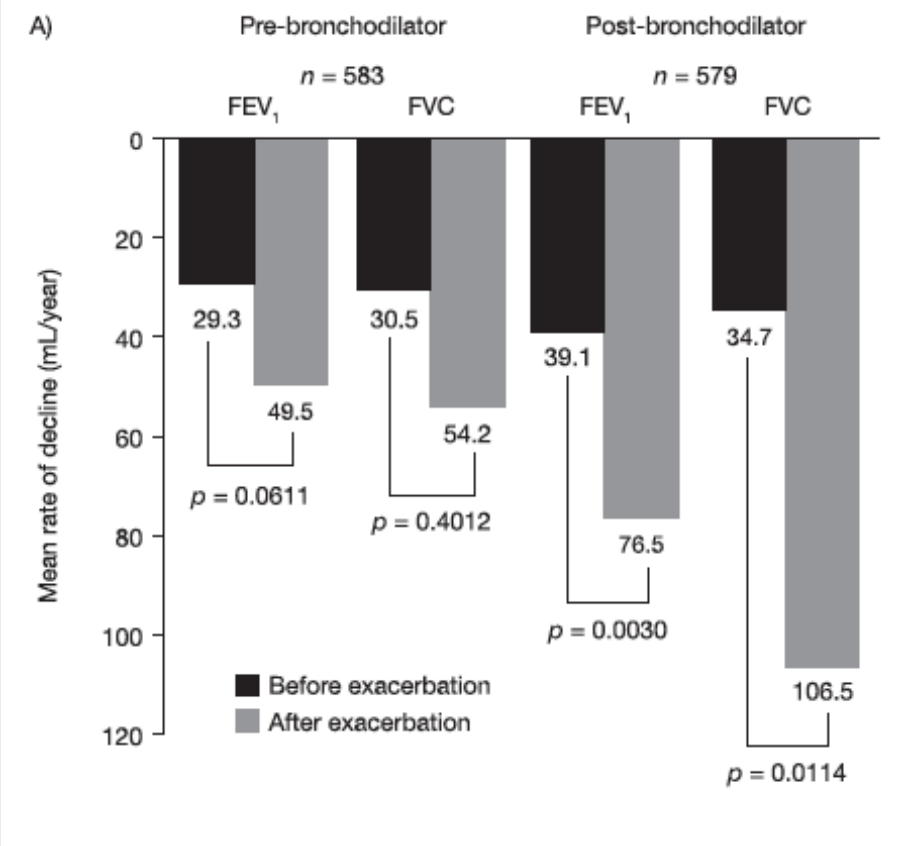
Reilev et al. NPJ Prim Care Respir Med 2017;27:25

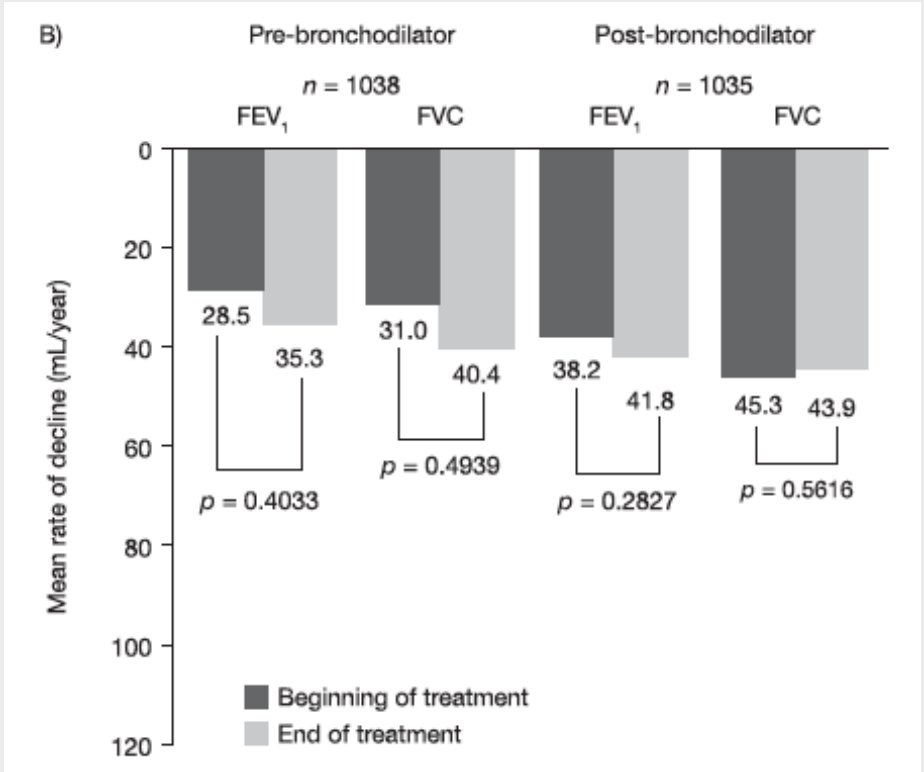
Natural History of Exacerbations in a Primary Care Population



Reilev et al. NPJ Prim Care Respir Med 2017;27:25

Impact of a Single Exacerbation



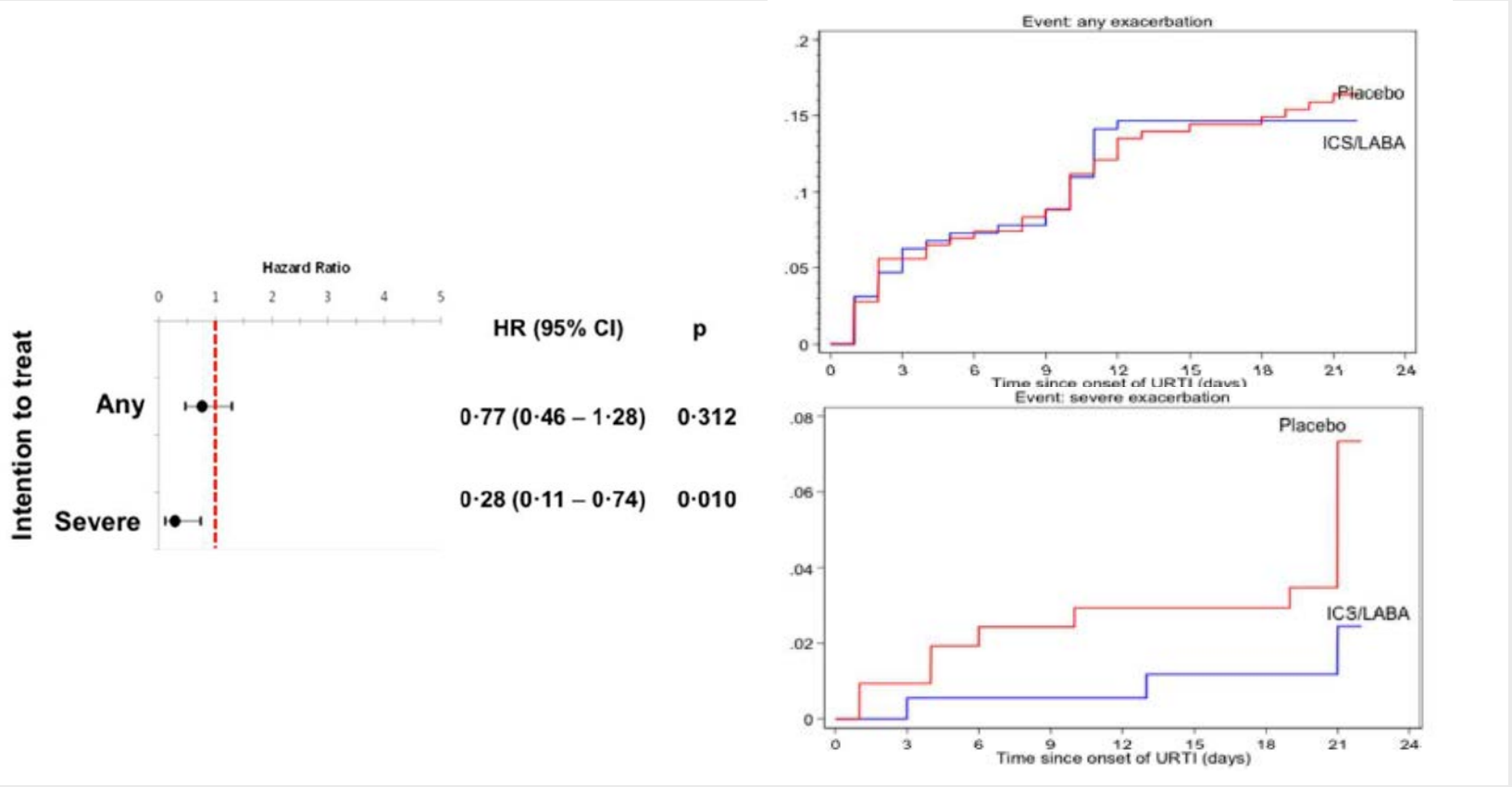


Halpin et al. Respir Med 2017;128:85-91

LABA/ICS

Managing Exacerbations

Intensified combination therapy with ICS/LABA for 10 days at URTI onset did not decrease the incidence of any COPD exacerbation but prevented severe exacerbation



Stolz et al. Am J Respir Crit Care Med 2018 (on line first)

ERS/ATS Statements

Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline

Jadwiga A. Wedzicha (ERS co-chair)[1], Marc Miravitlles[2], John R. Hurst[3], Peter M.A. Calverley[4], Richard K. Albert[5], Antonio Anzueto[6], Gerard J. Criner[7], Alberto Papi[8], Klaus F. Rabe[9], David Rigau[10], Pawel Sliwinski[11], Thomy Tonia[12], Jørgen Vestbo[13], Kevin C. Wilson[14] and Jerry A. Krishnan (ATS co-chair)[15]

Prevention of COPD exacerbations: a European Respiratory Society/ American Thoracic Society guideline

Jadwiga A. Wedzicha (ERS co-chair)[1], Peter M.A. Calverley[2], Richard K. Albert[3], Antonio Anzueto[4], Gerard J. Criner[5], John R. Hurst[6], Marc Miravitlles[7], Alberto Papi[8], Klaus F. Rabe[9], David Rigau[10], Pawel Sliwinski[11], Thomy Tonia[12], Jørgen Vestbo[13], Kevin C. Wilson[14] and Jerry A. Krishnan (ATS co-chair)[15]

Wedzicha et al. Eur Respir J 2017;49:1600791
Wedzicha et al. Eur Respir J 2017;50:1602265

Exacerbations
Additional References

Predictors of one-year mortality after hospitalization for an exacerbation of COPD
Esteban et al. BMC Pulm Med 2018;18:18

Risk Factors of Poor Outcomes after Admission for a COPD Exacerbation: Multivariate Logistic Predictive Models
Garcia-Rivero et al. COPD 2017;14:164-169

Early Hospital Readmissions Following an Acute Exacerbation of COPD in the Nationwide Readmissions Database
Jacobs et al. Ann Am Thorac Soc 2018;:

Determinants of exacerbation risk in patients with COPD in the TIOSPIR study
Calverley et al. Int J Chron Obstruct Pulmon Dis 2017;12:3391-3405

Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort
Han et al. Lancet Respir Med 2017;5:619-626

Take-Home Messages

- Exacerbations in the previous year remain the best predictor of future exacerbation rates
- Most patients are not frequent exacerbators
- A single exacerbation leads to an acceleration in the rate of loss of lung function
- Stepping up ICS/LABA at URTI onset may reduce risk of hospitalization

Co-Morbidities

COPD & Cardiovascular Disease

Patients with COPD had higher adjusted inpatient mortality and more likely to develop AF post STEMI and less likely to undergo diagnostic angiographies and any revascularization procedures.

Agarwal et al. Am J Cardiol 2017;119:1555-1559

Patients with COPD had worse survival from COPD and non-COPD causes after PCI

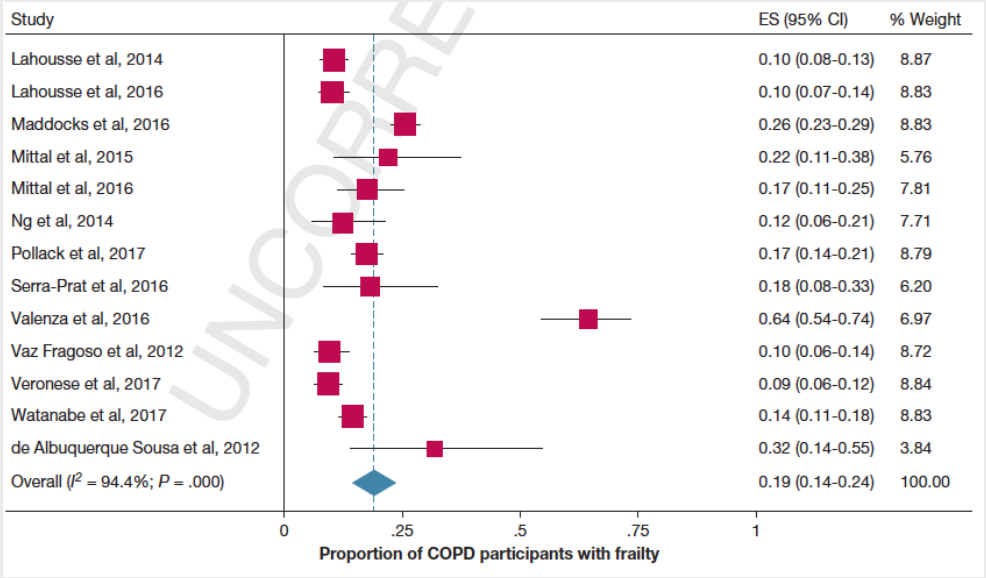
Almagro et al. Am J Respir Crit Care Med 2018;197:824-826

Patients with COPD had increased risk of CV events after an exacerbation, particularly if hospitalised

Kunisaki et al. Am J Respir Crit Care Med 2018 (on line first)

COPD & Frailty

Frailty is a clinical syndrome that reflects a state of decreased physiological reserves and vulnerability to stressors
Frail patients are at risk of adverse outcomes such as adverse drug reactions, prolonged hospitalization, mobility decline, disability onset, and mortality

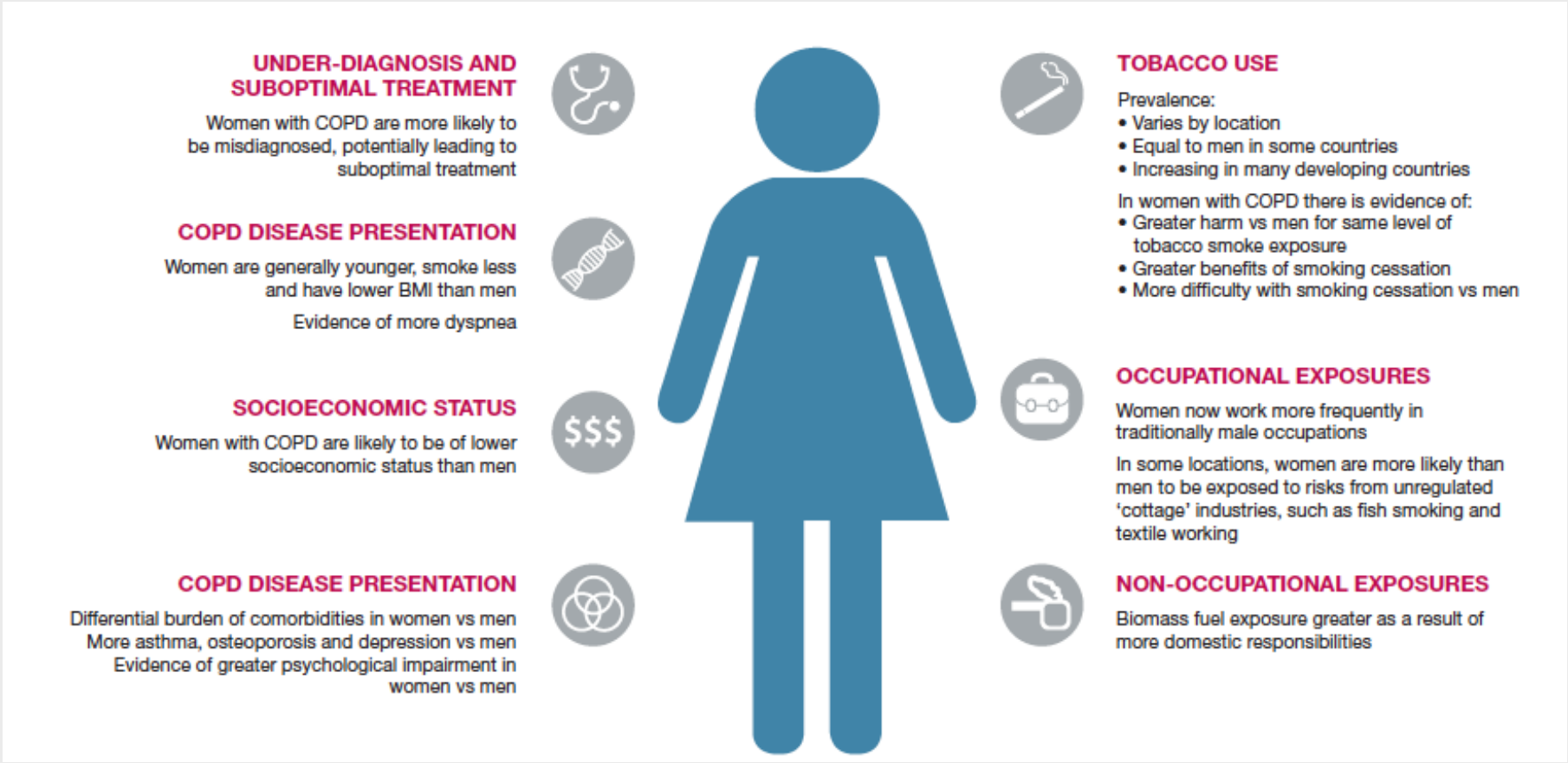


" …data are needed to understand if treating COPD (eg, with pulmonary rehabilitation) may slow the frailty process and if patients with both COPD and frailty should be treated differently from those with COPD alone."

Marengoni et al. Chest 2018 (on line first)

Other Issues

COPD in Women



Also:

Chronic obstructive pulmonary disease in Women. Is it Different?
Alonso et al. Arch Bronconeumol 2017;53:222-227

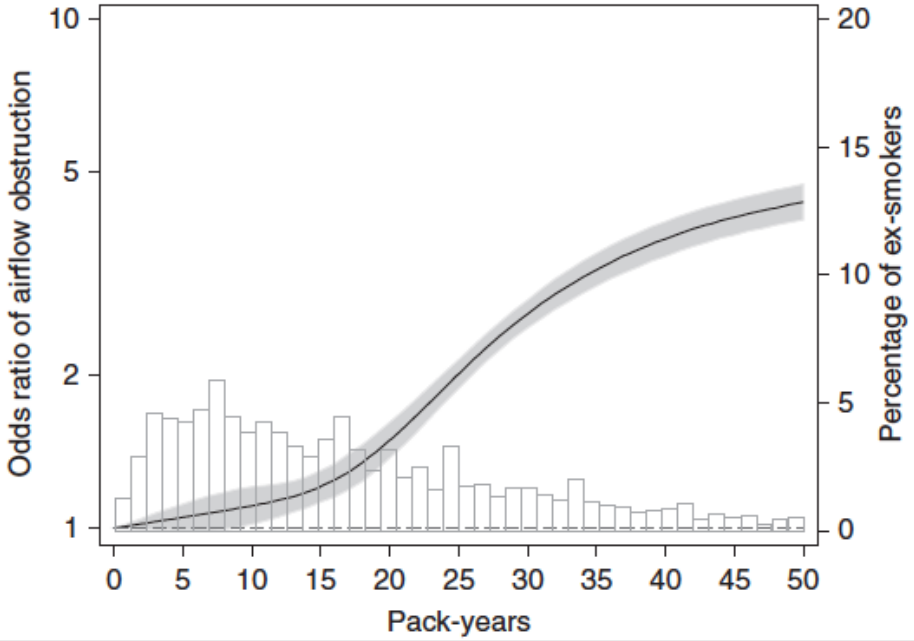
Jenkins et al. Chest 2017;151:686-696

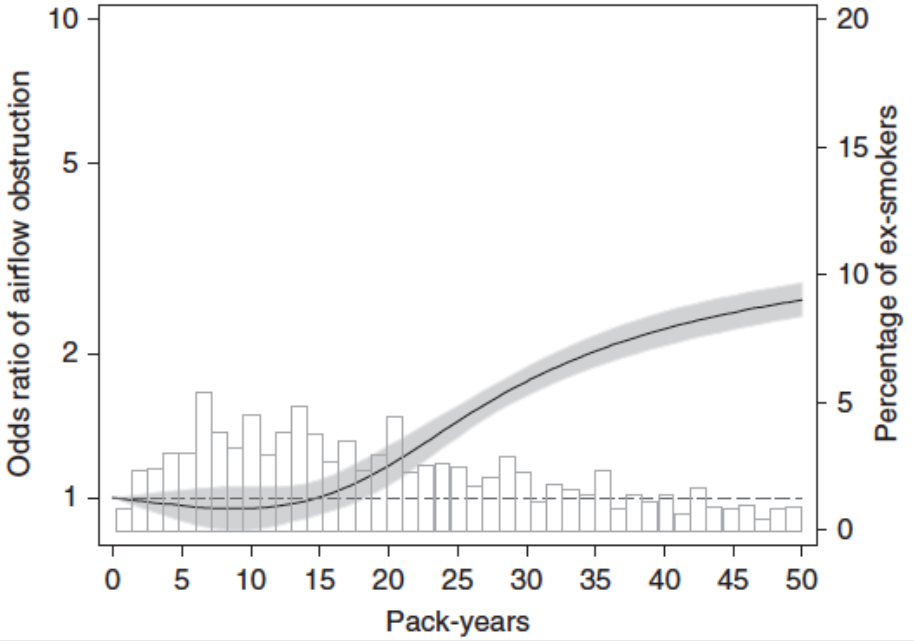
Developing COPD in Women

UK Biobank

149,075 women and 100,252 men

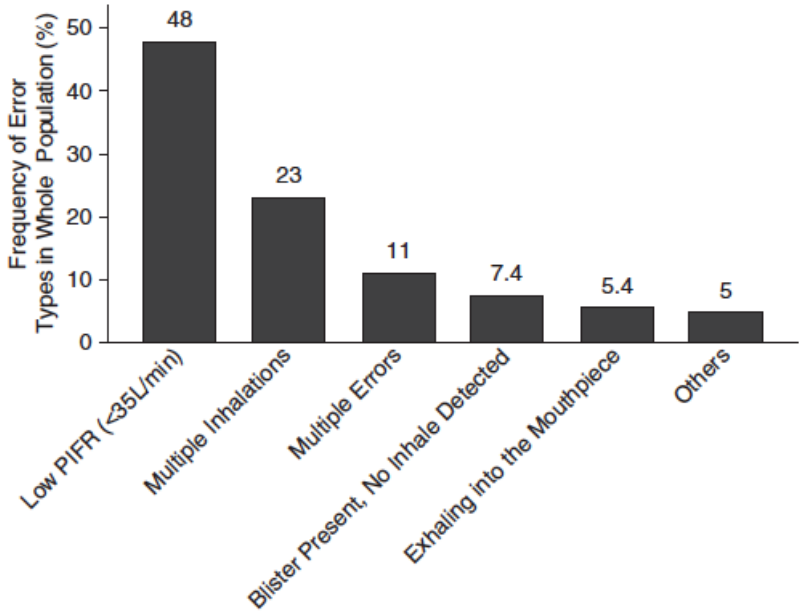
“women who have ever smoked are at a greater risk of airflow obstruction than men who ever smoked in a similar fashion in terms of duration, cigarettes per day, and packyears.

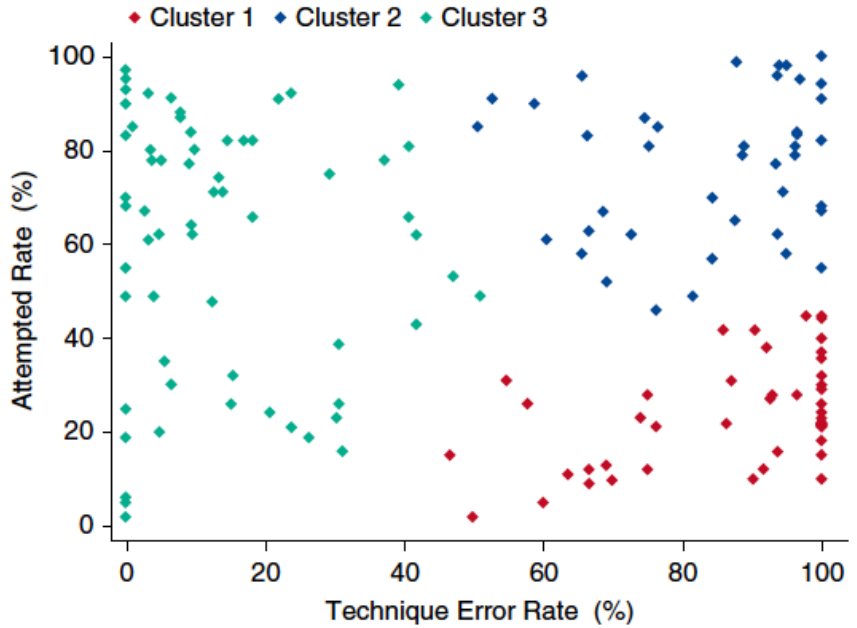




Amaral et al. Am J Respir Crit Care Med 2017;195:1226-1235

Inhaler Technique





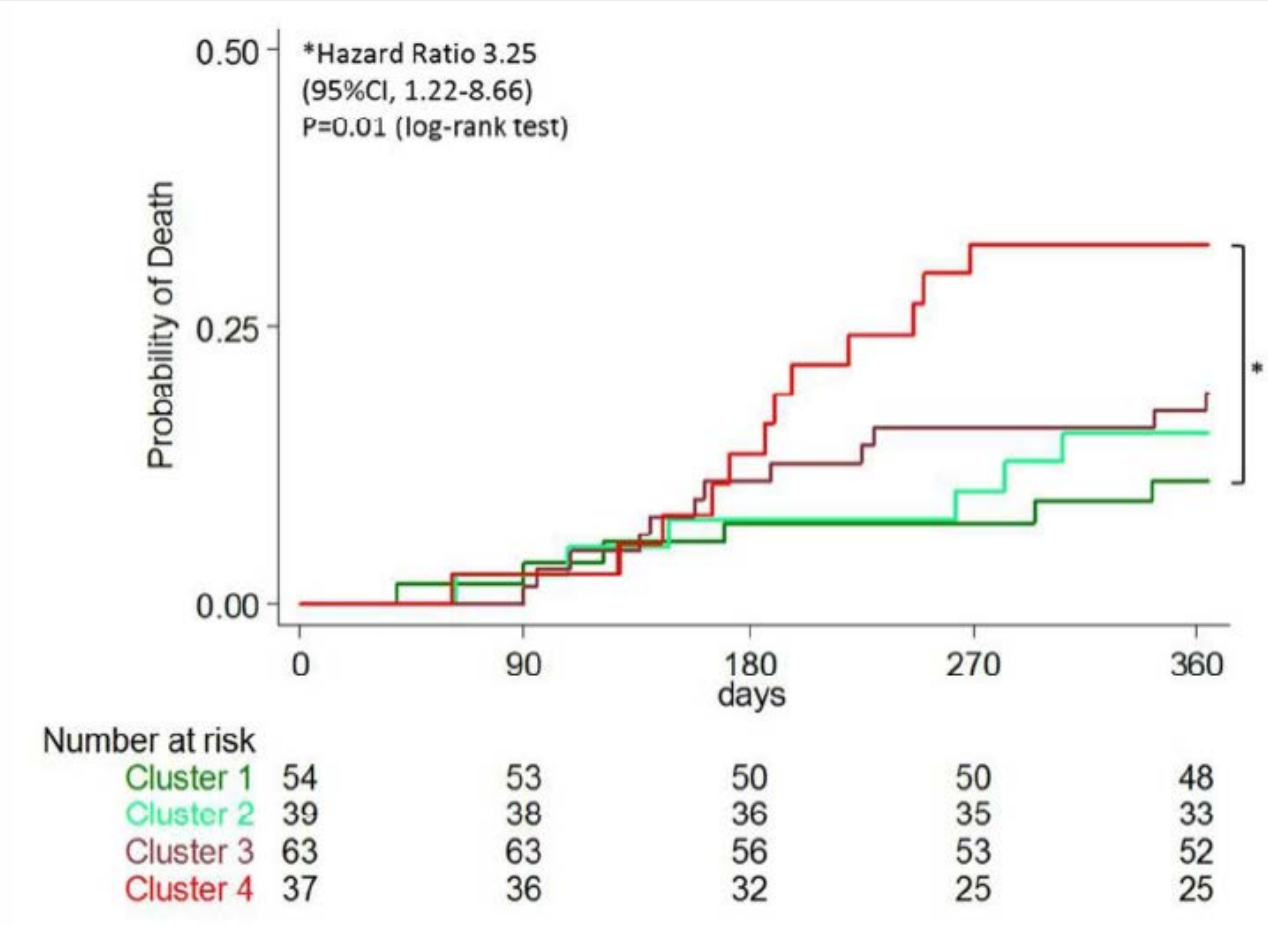
Used an acoustic-based system to quantify when and how a Diskus inhaler used

Actual adherence over the study was 22.6% of what would be expected

Only 6% of the study population had an actual adherence greater than 80%.

Sulaiman et al. Am J Respir Crit Care Med 2017;195:1333-1343

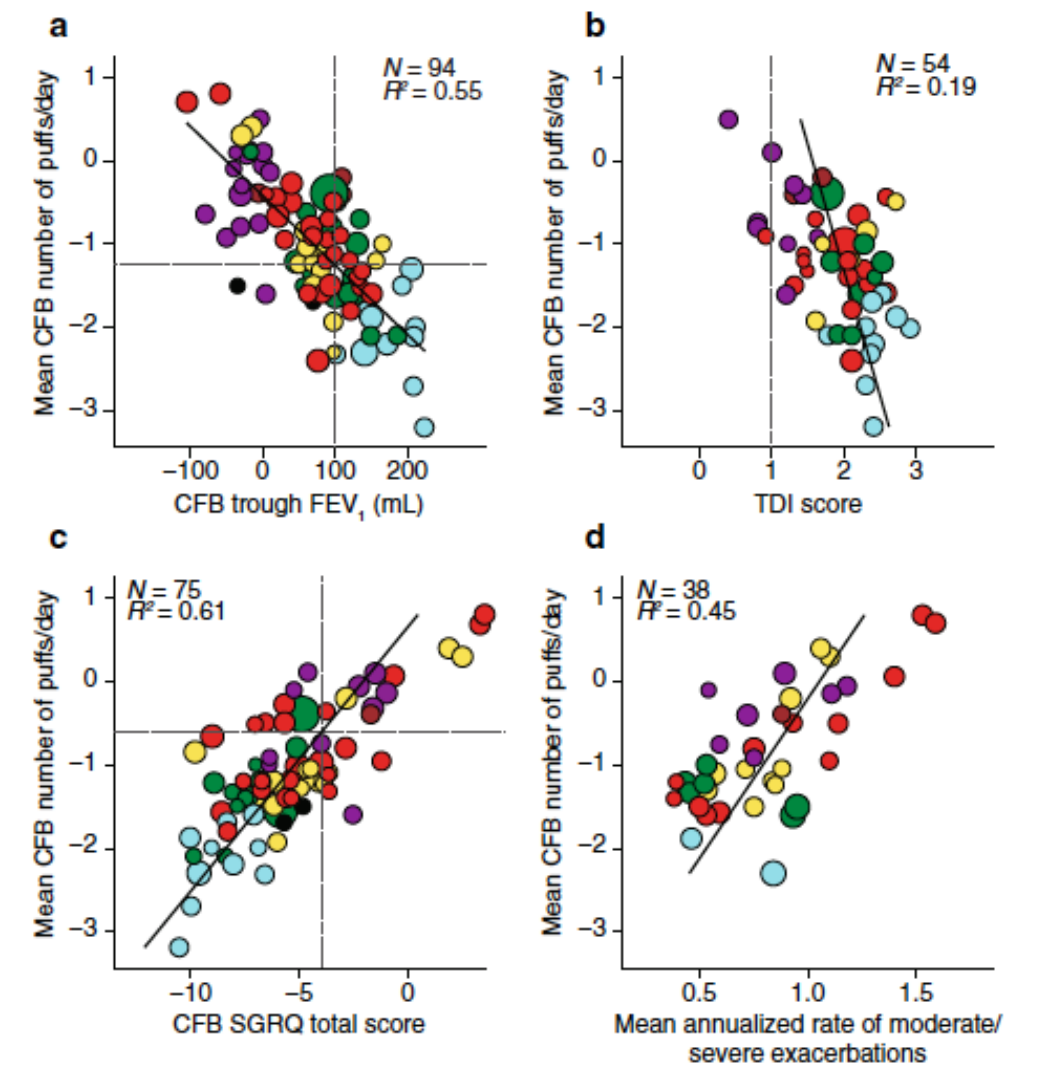
Adherence & Outcomes



Cluster 1 Regular & Good
Cluster 2 Regular & Poor
Cluster 3 Irregular & Good
Cluster 4 Irregular & Poor

Cushen et al. Am J Respir Crit Care Med 2018 (on line first)

Rescue Medication Use as a PRO



Punekar et al. Respir Res 2017;18:86

Telehealth

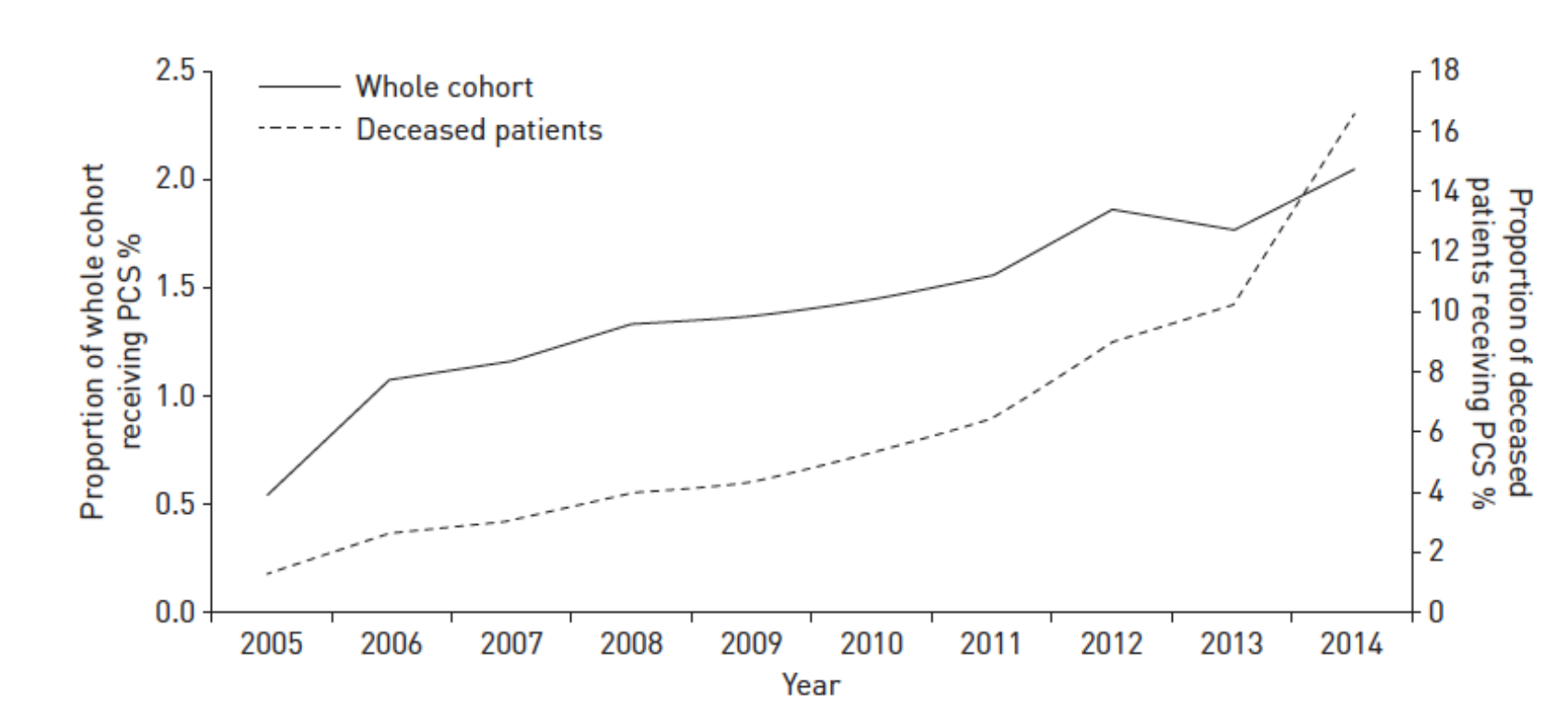
Telemonitoring in COPD: The CHROMED Study, a Randomized Clinical Trial
Walker et al. Am J Respir Crit Care Med 2018 (on line first)
Monitoring using FOT

Telehealthcare for patients suffering from chronic obstructive pulmonary disease: effects on health-related quality of life: results from the Danish 'TeleCare North' cluster-randomised trial
Lilholt et al. BMJ Open 2017;7:e014587
“The overall sample and all subgroups demonstrated no statistically significant differences in HRQoL between telehealthcare and usual practice”

Effectiveness of Smartphone Devices in Promoting Physical Activity and Exercise in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review
Martinez-Garcia et al. COPD 2017;14:543-551
No benefit

Palliative & End of Life

Use of Specialist Palliative Care
UK

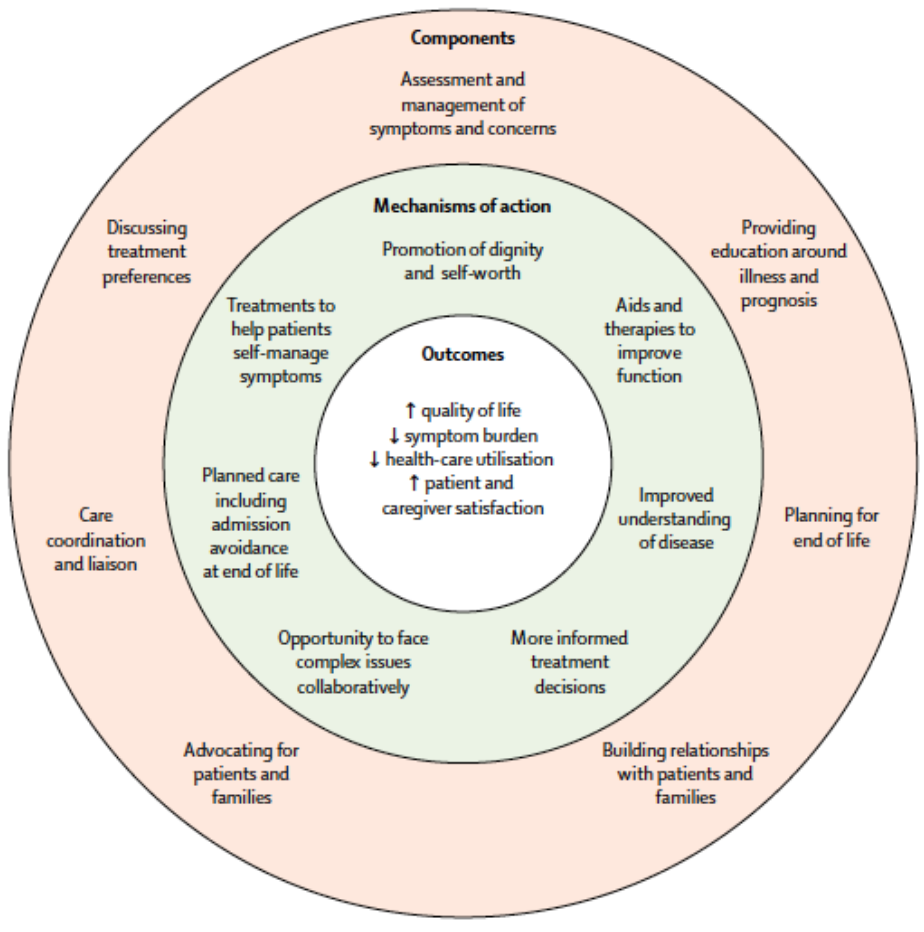


Also:

Chronic obstructive pulmonary disease in Women. Is it Different?
Alonso et al. Arch Bronconeumol 2017;53:222-227

Bloom et al. Eur Respir J 2018;51:1701879

Palliative & End of Life Care



Interventions for Breathlessness; Fatigue; Anxiety; Depression; Anorexia; Cough; Somonlence & Insomnia

PR
Multiprofessional integrated
breathlessness
services
Breathing techniques
Self-management education programmes
Hand-held fan
Cognitive behavioural therapy
Tai Chi
Yoga
Low-dose oral or parenteral opioids
Benzodiazepines
Oxygen
Activity pacing and good sleep hygiene
Psychological therapies
Antidepressant drugs

Maddocks et al. Lancet 2017;390:988-1002

COPD
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Fletcher and Peto 40 Years On. A Tribute and Reflection
Vestbo et al. Am J Respir Crit Care Med 2017;195:1420-1422

AJRCCM: 100-Year Anniversary. Physiology and Chronic Obstructive Pulmonary Disease in the Blue Journals
Calverley et al. Am J Respir Crit Care Med 2017;195:1088-1090

Functional Tests in Chronic Obstructive Pulmonary Disease, Part 1: Clinical Relevance and Links to the International Classification of Functioning, Disability, and Health
Bui et al. Ann Am Thorac Soc 2017;14:778-784

Functional Tests in Chronic Obstructive Pulmonary Disease, Part 2: Measurement Properties
Bui et al. Ann Am Thorac Soc 2017;14:785-794

Mechanisms of lung aging
Brandenberger et al. Cell Tissue Res 2017;367:469-480

Chronic obstructive pulmonary disease
Rabe et al. Lancet 2017;389:1931-1940

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