Muhammad Ilyas *muhil.23il@gmail.com*

Education:

- *1992 : MD, Faculty of Medicine Hasanuddin University*
- *2004 : Internist, Faculty of Medicine Hasanuddin University*
- *2010 : Spesialist of Lung Diseases & Respirology Medicine, Faculty of Medicine University of Indonesia*
- *2012 : Consultant of Lung Diseases & Critical Respirology, PAPDI Collegium*
- *2014 : Consultant of Asthma & COPD, PDPI Collegium*

Occupation:

- *Head of Infection Centre Wahidin Sudirohusodo Hospitals*
- *Chairman of Pulmonology and Respiratology Unit, Faculty of Medicine, Hasanuddin University*
- *Academic staf of Internal Medicine Departmen, Faculty of Medicine, Hasanuddin University*

Patient with moderate COPD receiving ICS/LABA; concerned about pneumonia risk with ICS

MUHAMMAD ILYAS

Departement of Pulmonology and Respiratory Medicine
Faculty of Medicine University of Hasanuddin
Infection Center Dr. Wahidin Sudirohusodo Hospital

Mo: Moderate COPD receiving ICS/LABA; concerned about pneumonia risk with ICS

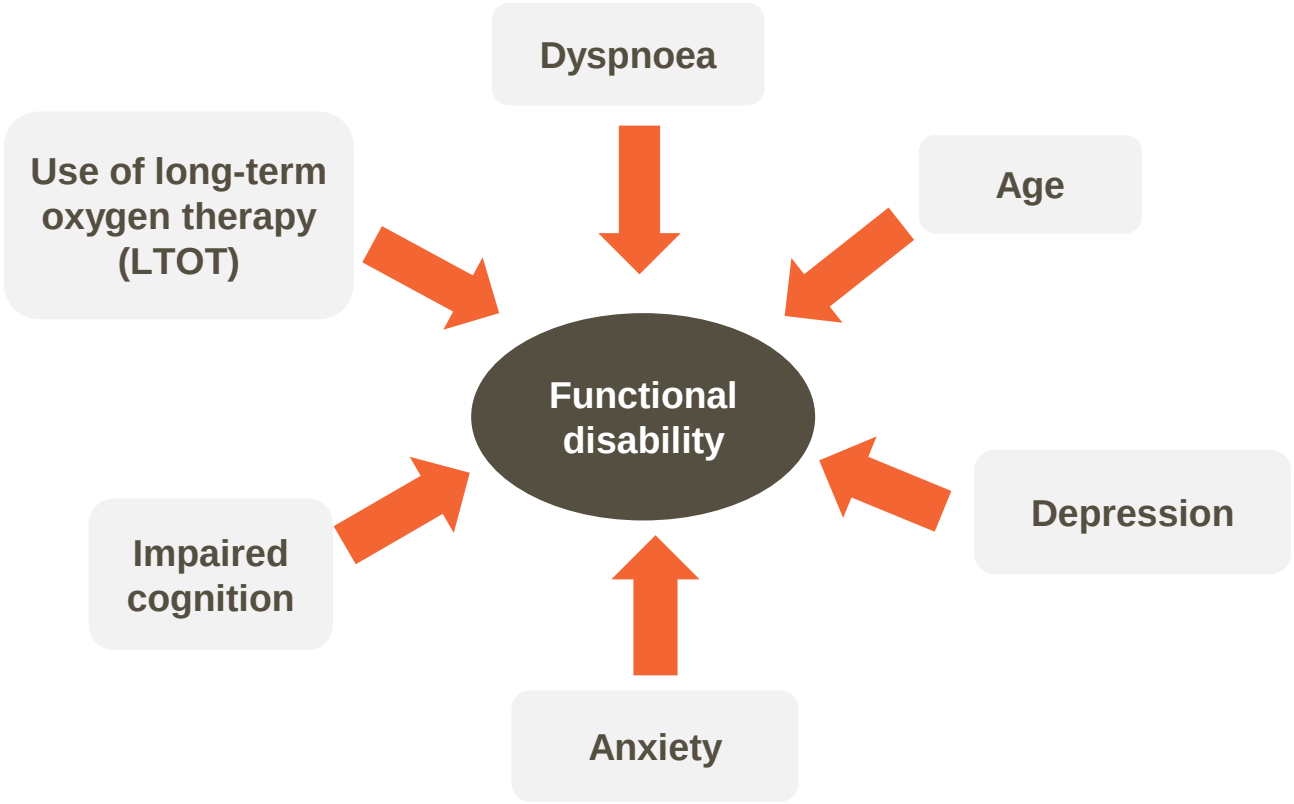
- Mo (70 years old) was diagnosed with moderate-to-severe COPD (GOLD category C) one year ago (received LAMA)
- He was hospitalised for one exacerbation (four months ago)
- As a result, his medication was changed to ICS/LABA (one puff twice daily) and he has had no exacerbations since
- Is trying to give up smoking
- Mo and his wife have recently moved to a shared care facility as his wife has mobility issues and early dementia
- Mo's wife also used to book their yearly flu vaccinations but as she has memory problems, he is unsure whether he has missed out on any vaccinations
- Mo wants to know if he can switch to another treatment that doesn't contain ICS (e.g. LABA/LAMA) but his doctor is concerned that this may increase Mo's exacerbation risk

ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist

Impact on functional performance

Patients with COPD frequently describe limitations in functional performance

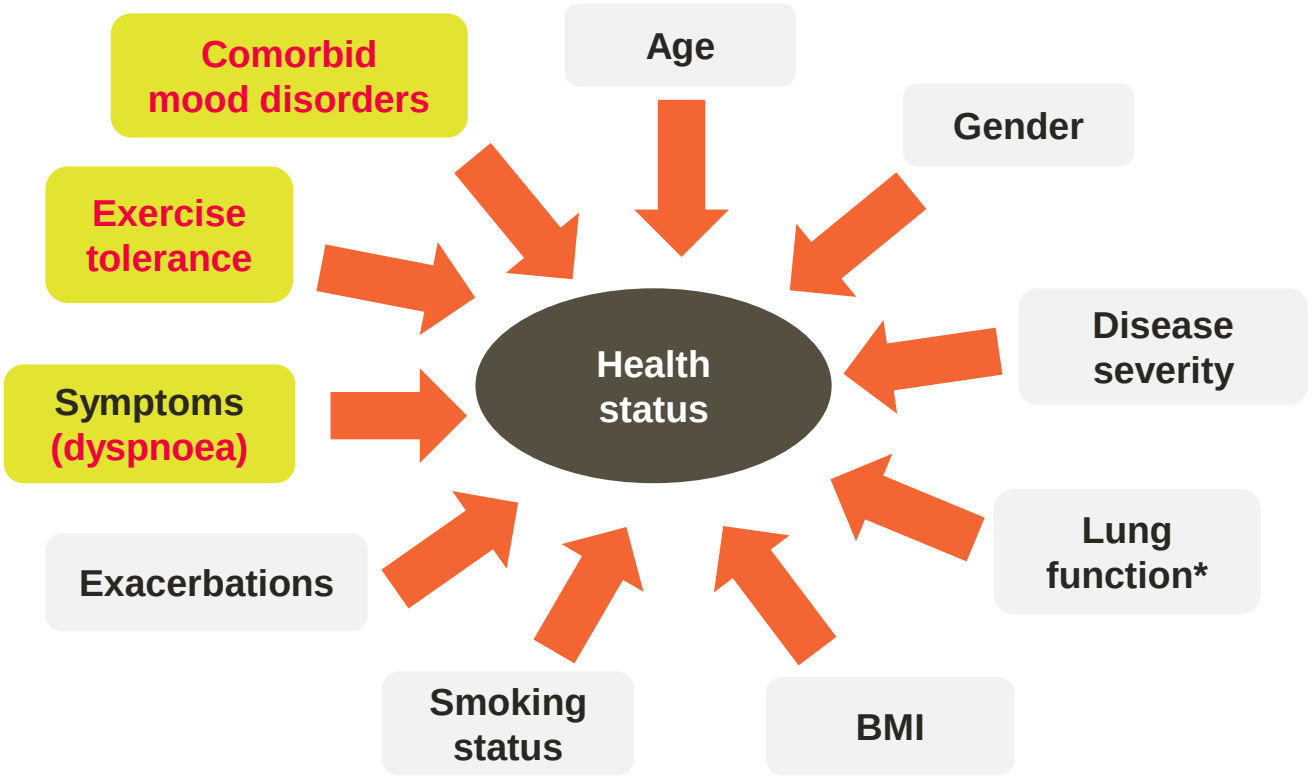
- These limitations predict **mortality** and adversely affect **health-care burden** and impair **health-related quality of life**
- Several factors contribute to limitations in functional performance in COPD



Impact on quality of life

Health status and quality of life in COPD is influenced by many different factors

Factors highlighted in red are most significant in COPD[1]



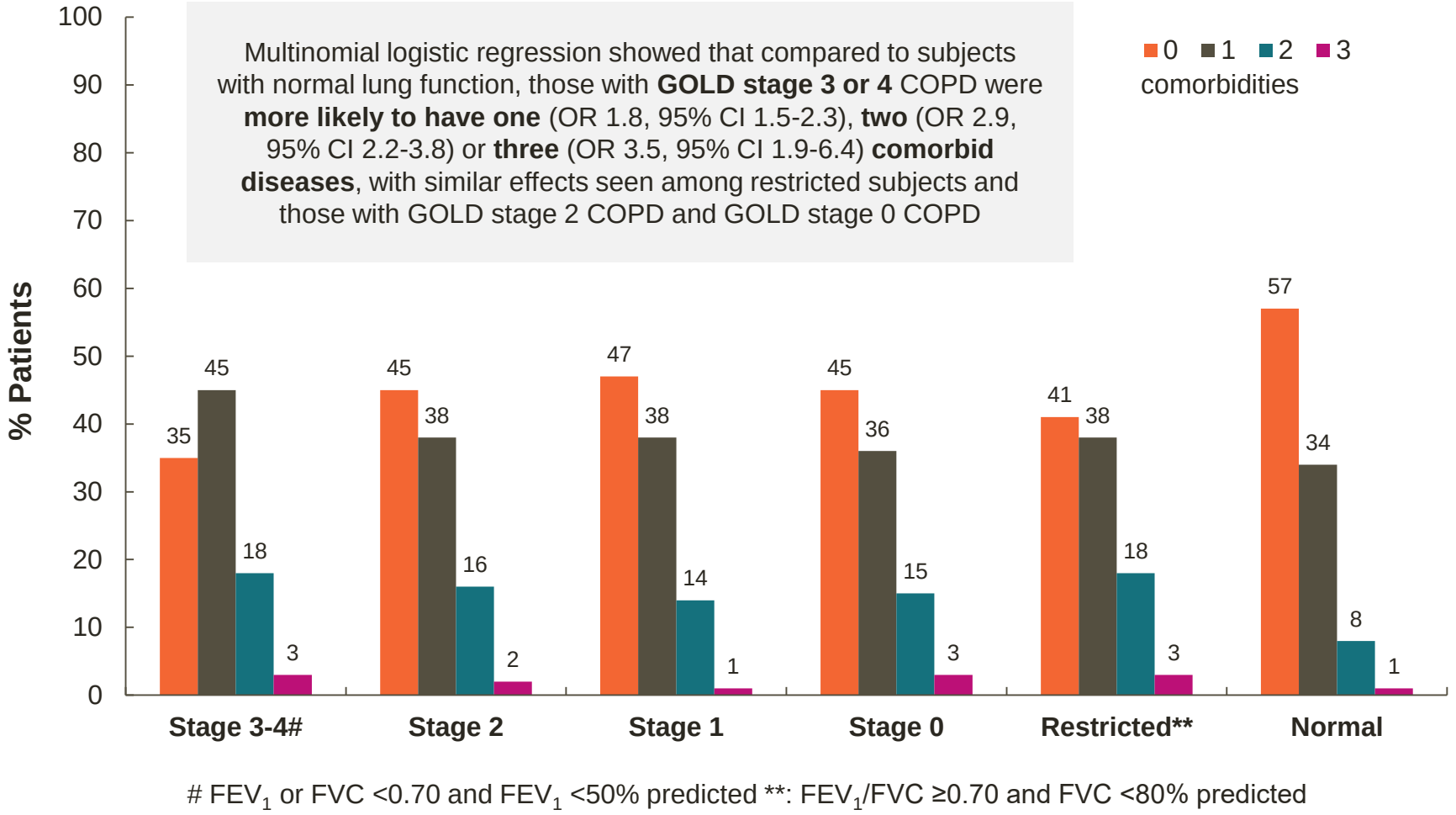
However, the level of influence each individual factor exerts is difficult to estimate due to differences in questionnaires used to assess health status[1]

*Spirometry values are only weakly associated with health status

1. Tsiligianni I et al. Prim Care Respir J 2011; 20(3):257-268.

Comorbidity burden of COPD

Comorbidities may be more common in later stages of the disease

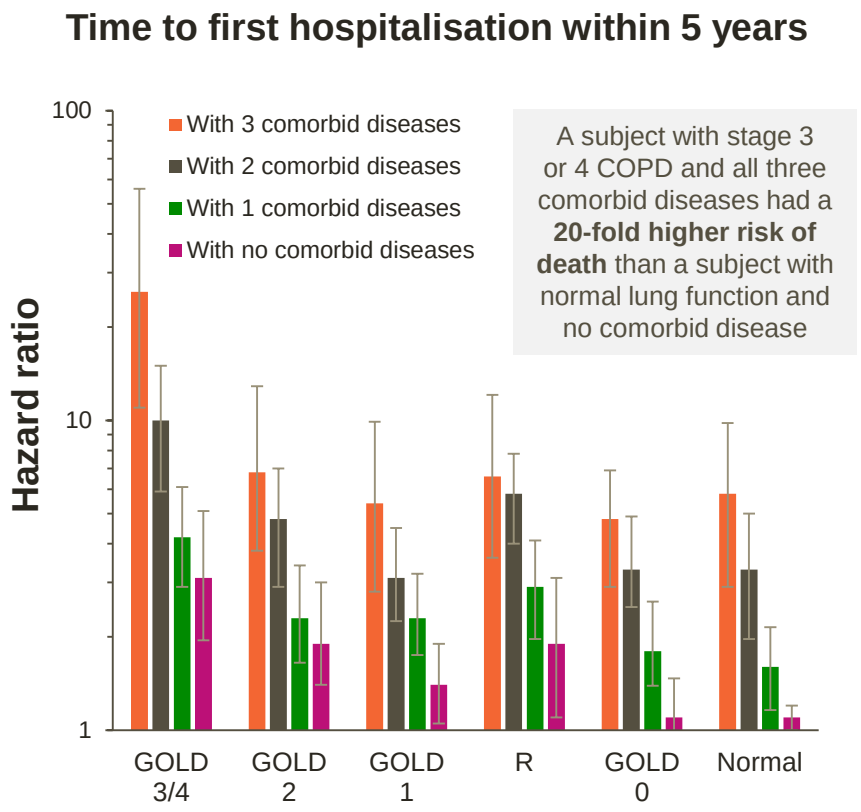


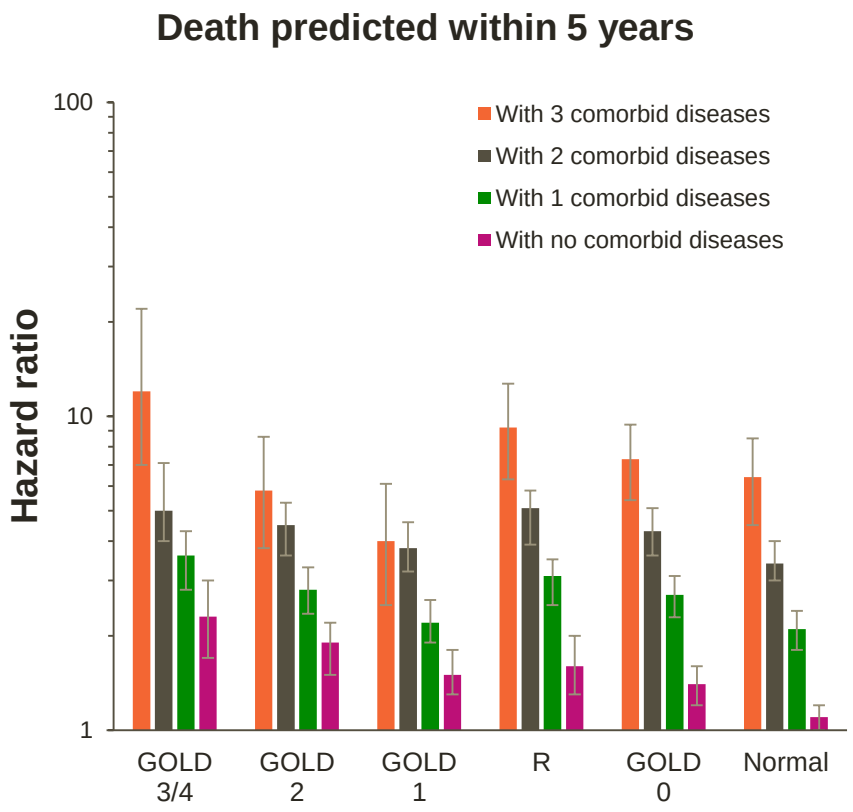
FEV_1 or FVC <0.70 and FEV_1 <50% predicted **: FEV_1/FVC ≥0.70 and FVC <80% predicted

Comorbidity data was analysed from 20,296 subjects aged over 45 yrs at baseline in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS).

The same results were first published in Mannino DM et al. Eur Respir J 2008;32:962–969. This graph has been independently created by GSK from the original.

Risk of hospitalisation and death increases with the number of COPD comorbidities





– There was a significant interaction between respiratory impairment, comorbid disease and hospitalisation ($p<0.05$ for all models).

Comorbidity data was analysed from 20,296 subjects aged over 45 yrs at baseline in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS).

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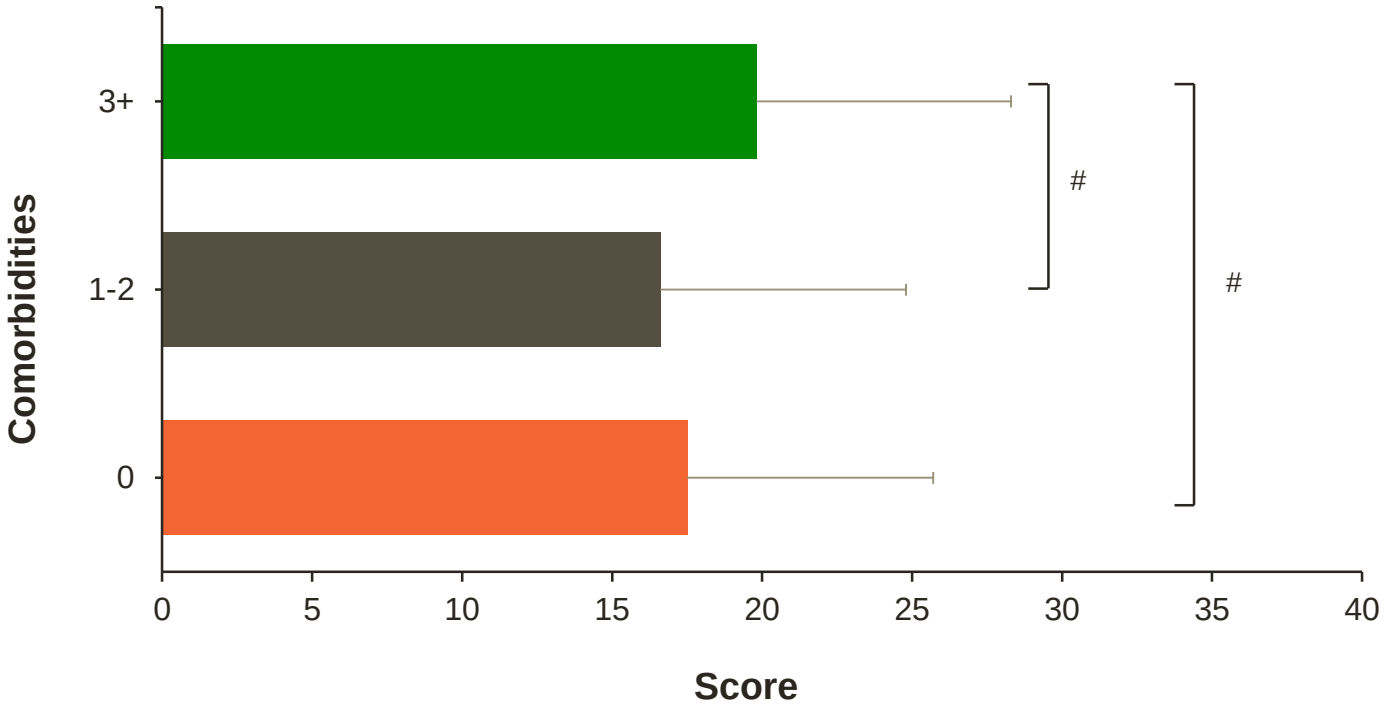
Increasing comorbidities significantly worsen health related quality of life

– The performance of the eight-item COPD Assessment Test (CAT) was analysed in 1,817 patients from primary care in seven European countries.



CAT score by number of comorbidities (mean+SD); none (n=350), one or two (n=870), or three or more (n=597)
# $p<0.0001$

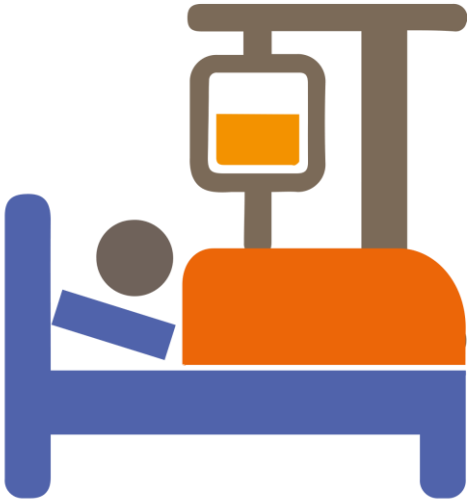
Assessment of COPD

What are the goals of assessing COPD?

The level of airflow limitation

The impact of disease on the health status of the patient

The risk of future events (such as exacerbations, hospital admissions, or death)

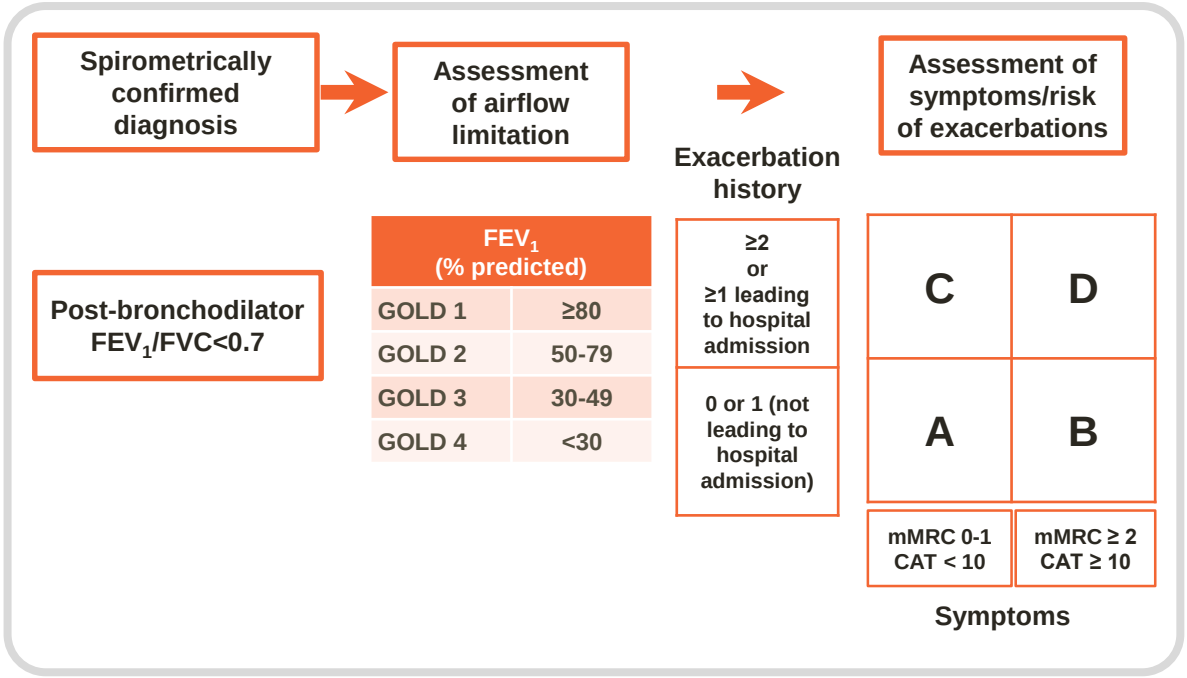


All of these are required to guide therapy.[1]

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/

Assessing COPD severity

- GOLD advocates a holistic approach to assess severity which includes:[1]
  - Symptomatic assessment
  - Spirometric classification of severity
  - Risk of exacerbations



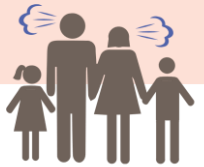
- This provides an overall understanding of the impact of COPD on an individual patient, and importantly helps to guide therapy.[1]
- Assessment of COPD severity should be carried out regularly (at least annually, and more frequently for severe disease) to monitor disease progression, help determine prognosis and inform management strategies[2]

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/; 2. Gruffydd-Jones K. (2016). Assessment of COPD in Primary Care. In: Primary Care Respiratory Academy. PCRS UK, pp. 17–9

COPD or something else?

– Many conditions can be confused with COPD. The principal differential diagnosis is asthma and this can usually be distinguished on clinical grounds[1]

	COPD[1]	ASTHMA[1]
Onset	Mid-life	Early in life (often in childhood)
Symptoms	Slowly progressive Dyspnea during exercise	Vary from day to day More common at night/early morning
Airflow limitations	Largely irreversible	Largely reversible
Main risk factors for development	Tobacco smoke and air bourne pollution	Exposure to allergens, infections, diet, tobacco smoke, socio economic status[2]
Additional features		Allergy, rhinitis and eczema also present Family history of asthma



– In some patients with chronic asthma, a clear distinction from COPD may be difficult and some patients could have co-existing COPD and asthma (Asthma COPD Overlap: ACO)[1]

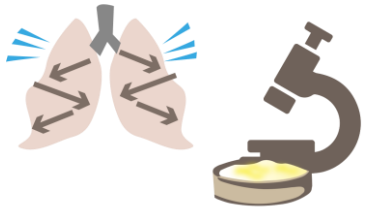
– Patients with ACO may have:[3,4]
  – Greater dyspnoea, wheezing and comorbidities
  – More frequent exacerbations
  – Worse health-related quality of life
  – More predominant eosinophilic inflammation

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/2; Subbarao P, *et al.* CMAJ 2009;181(9):e181–e191; 3. Hardin H. Respir Res. 2011; 12:127–34; 4 Miravitlles M. Respir Med. 2013;107:1053–60

Differential diagnosis of COPD

Diagnosis and suggestive features

Tuberculosis

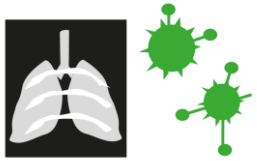


Onset all ages.
Chest X-ray shows lung infiltrate.
Microbiological confirmation.
High local prevalence of tuberculosis.

Congestive heart failure

Chest X-ray shows dilated heart, pulmonary oedema.
Pulmonary function test indicate volume restriction, not airflow limitation.

Bronchiectasis



Large volumes of purulent sputum.
Commonly associated with bacterial infection.
Chest X-ray/CT shows bronchial dilation, bronchial wall thickening.

Diffuse Panbronchiolitis

Predominantly seen in patients of Asian descent.
Most patients are male and non-smokers.
Almost all have chronic sinusitis.
Chest X-rays and HRCT show diffuse small centrilobular nodular opacities and hyperinflation.

Obliterative Bronchiolitis

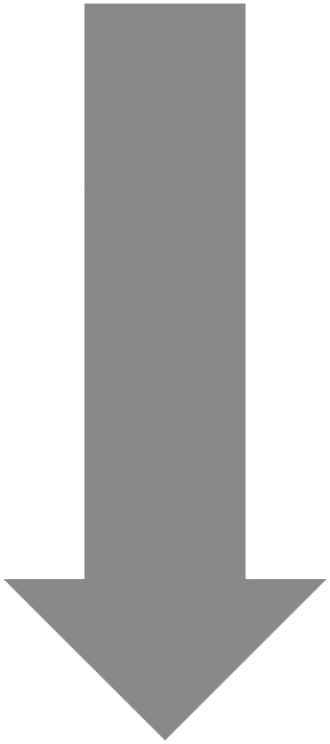
Onset at younger age, non-smokers.
May have history of rheumatoid arthritis or acute fume marrow transplantation.
CT on expiration shows hypodense areas.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/.

Management of symptomatic patients with stable COPD

Maintenance therapy for stable COPD: Where do we stand today?

We have clear treatment goals



Reduce symptoms

Relieve symptoms

Improve exercise tolerance

Improve health status

Reduce risk

Prevent & treat exacerbations

Prevent disease progression

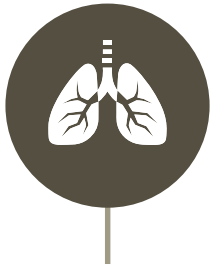
Reduce mortality

These goals should be achieved with minimal side effects

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd.

COPD treatment should be individualised based on symptoms and exacerbation risk

For Group B patients with persistent SYMPTOMS



Symptomatic despite as-needed SABA/SAMA

LAMA/LABA

Maximal bronchodilation

For SYMPTOMATIC patients on COPD maintenance therapy and AT RISK OF EXACERBATIONS

Symptomatic despite COPD maintenance therapy and history of COPD exacerbations

LAMA/LABA or **ICS/LABA** — **Group C or D patients**

LAMA + **ICS/LABA** — **Group D patients**

Triple Therapy

LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2018 Report. Available at: http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/.

GOLD guidelines advocate individualised therapy based on symptoms and exacerbation risk

≥ 2 moderate exacerbation or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA *or ICS + LABA** *Consider if highly symptomatic (e.g. CAT> 20 **Consider if eos ≥ 300
0 or 1 moderate exacerbation (not leading to hospitalization)	**Group A** A bronchodilator	**Group B** A long acting bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	**mMRC ≥ 2 CAT ≥ 10**

ICS LABA for patient with recurrent exacerbation

Key comparator studies for Seretide in COPD

Seretide vs SAL 50 vs FP 500 vs placebo

TRISTAN
Calverley[1]
1 year
N=1465

- Seretide vs. components – significant improvements in lung function, health status and reduced number of moderate-to-severe exacerbations

Seretide vs SAL 50 vs FP 500 vs placebo

TORCH
Calverley[2,3]
3 years
N=6112

- Improvements in following noted in Seretide group:
  - Reduction in rate of exacerbations
  - Health status
  - Lung function
  - Post-hoc analysis of cardiovascular AEs

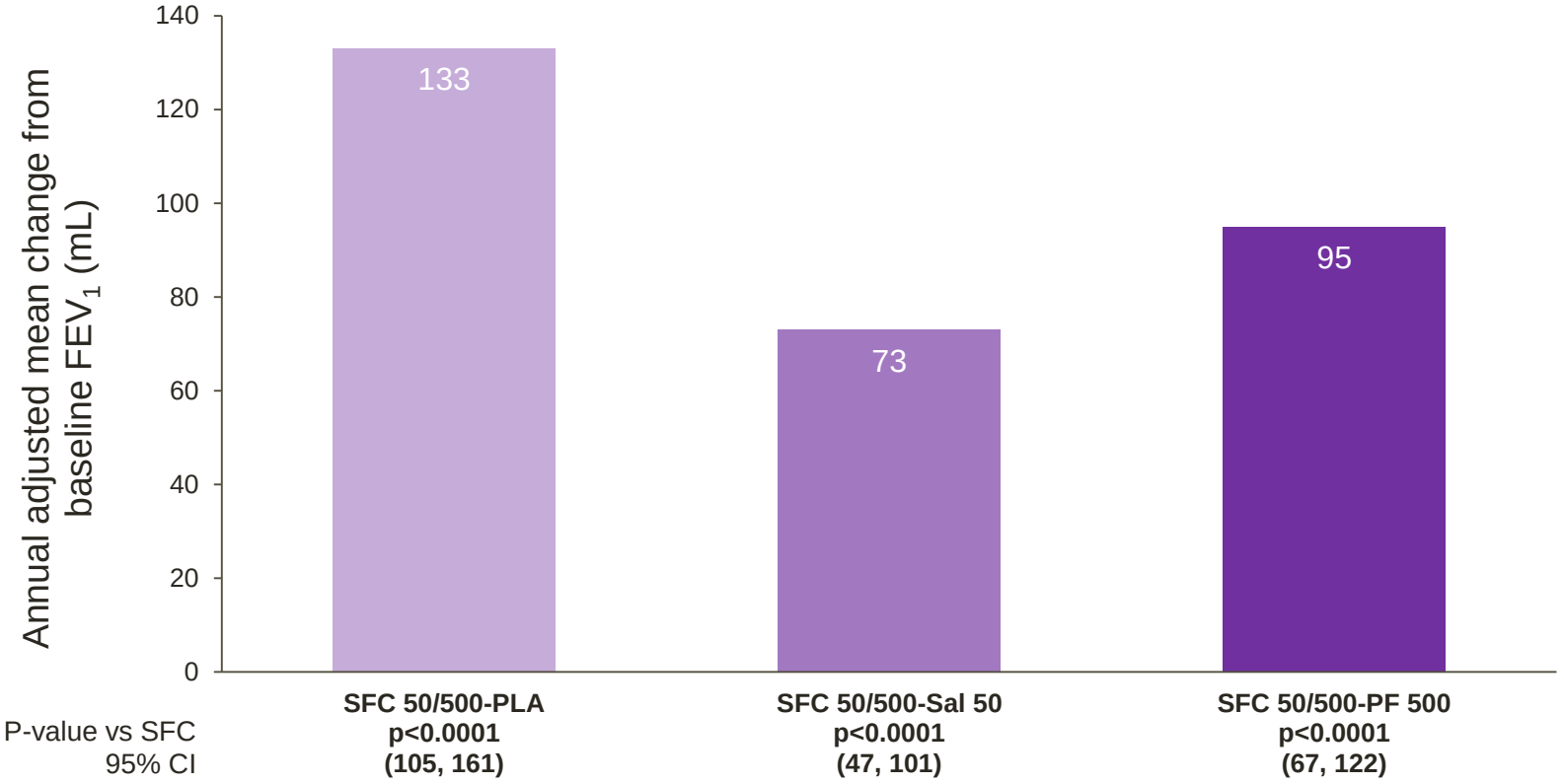
Seretide vs. tiotropium

INSPIRE
Wedzicha[4]
104 weeks
N=1291

- Rate of moderate to severe exacerbations similar
- Seretide associated with better health status, fewer patient withdrawals and a lower mortality rate

1. Calverley PM et al. Lancet 2003; 361: 449–56; 2.Calverley PM et al. N Engl J Med 2007; 356: 775–89; 3. Calverley PM et al. Thorax 2010;65:719-725; 4. Wedzicha et al. Am J Respir Crit Care Med 2008; 177: 19–26

SFC led to an increase in FEV_1 which was significantly greater than with either of its components separately



Patients with COPD (n=1465) were recruited from outpatient departments in 25 countries. They were treated in a randomised, double-blind, parallel-group, placebo-controlled study with either 50 µg salmeterol twice daily (n=372), 500 µg fluticasone twice daily (n=374), 50 µg salmeterol and 500 µg fluticasone twice daily (n=358), or placebo (n=361) for 12 months.

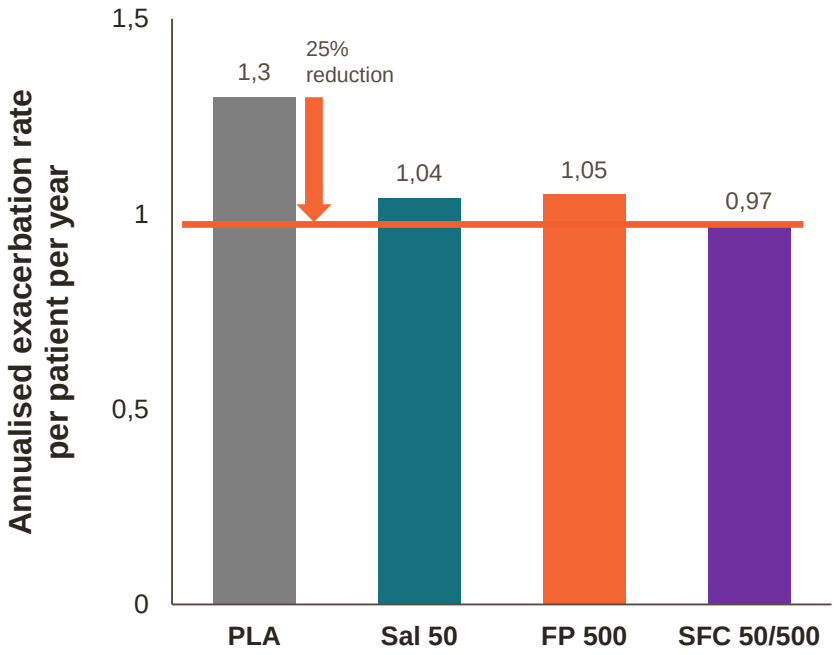
CI: Confidence interval; FEV_1: Forced Expiratory Volume in one second; SFC: Salmeterol/ Fluticasone propionate combination

The same results were first published in Calverley PM et al. Lancet 2003; 361: 449–56. This graph has been independently created by GSK from the original.

There was a trend for greater decreases in exacerbation rate with SFC vs. separate components

Overall rate of exacerbations per year

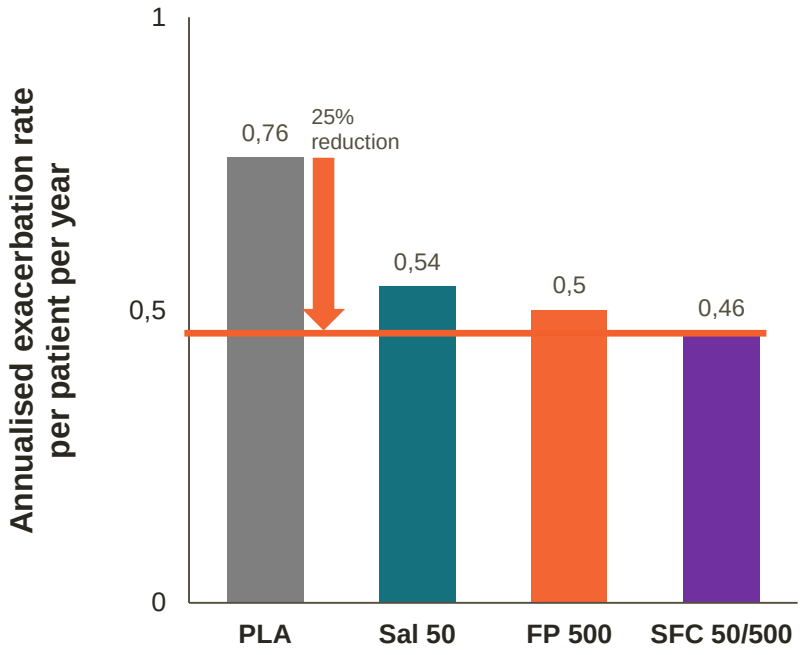
Exacerbations fell by 25% in the SFC group (p<0.001;95% CI: 0.643, 0.865) compared with placebo



P-value vs SFC	<0.0001	0.345	0.304
95% CI	(0.643, 0.865)	(0.801, 1.080)	(0.797, 1.073)
Rate ratio vs SFC	0.746	0.930	0.925

Overall rate of exacerbations requiring oral corticosteroids (per year)

The rate of exacerbations fell by 39% in the SFC group (p<0.001;95% CI: 0.500, 0.736) compared with placebo



P-value vs SFC	<0.0001	0.115	0.453
95% CI	(0.500, 0.763)	(0.699, 1.039)	(0.755, 1.133)
Rate ratio vs SFC	0.607	0.853	0.925

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CI: Confidence interval; FP: Fluticasone propionate; PLA: placebo; Sal: Salmerterol; SFC: Salmeterol/Fluticasone propionate combination

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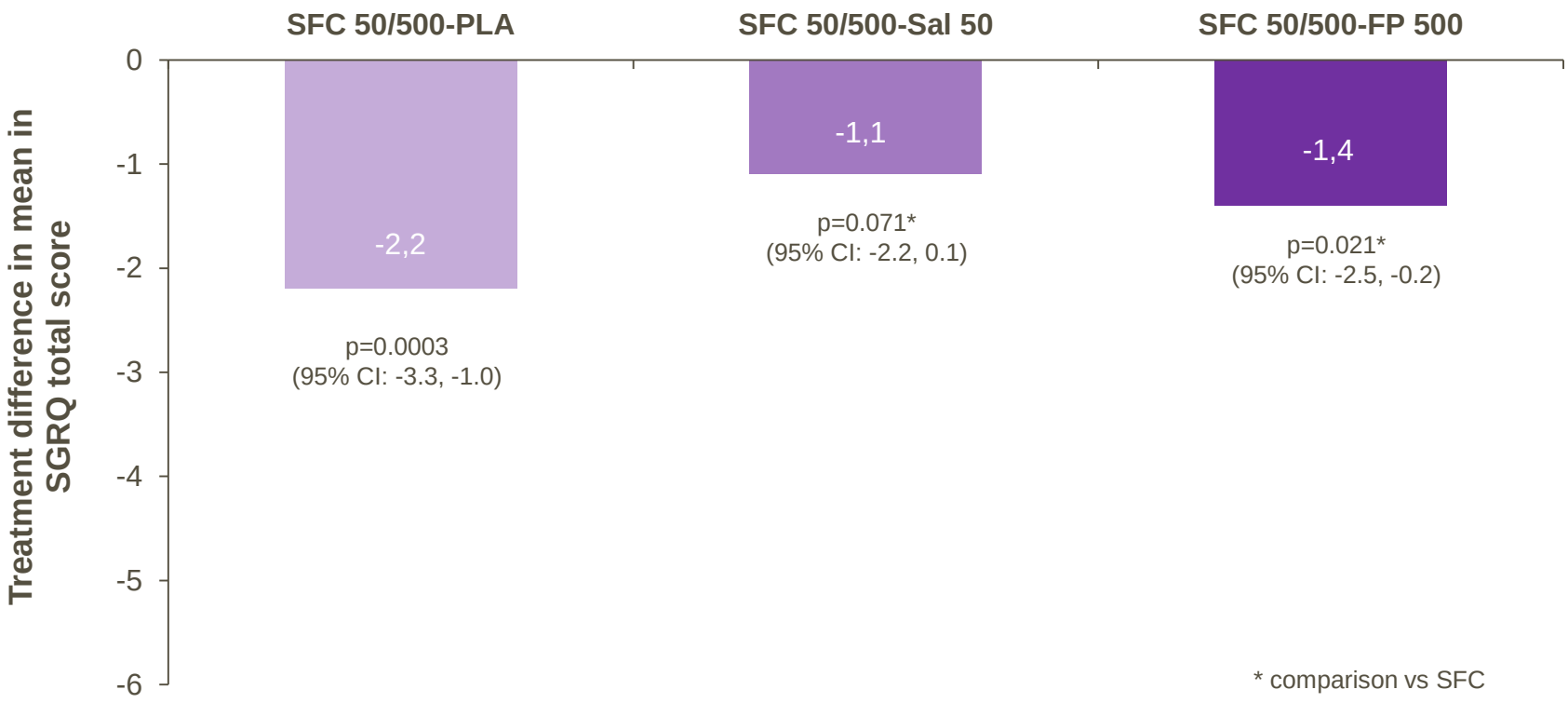
SFC led to a greater change in health status at the end of one year versus separate components



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SFC significantly reduced breathlessness and the use of relief medication vs. placebo or separate components

Efficacy measure	PLA (n=361)	Sal (n=372)	FP 500 (n=374)	SFC 50/500 (n=358)
Median % of days without use of relief medication p-value vs SFC	0 <0.001	3 0.004	2 <0.001	14
Breathlessness score (mean) p-value vs SFC	1.66 <0.001	1.59 0.006	1.58 0.010	1.47
No. night-time awakenings per week (mean) p-value vs SFC	3.01 0.006	2.94 0.011	2.45 0.591	2.31

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1 year
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TORCH
Calverley[2,3]
3 years
N=6112

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Seretide vs. tiotropium

INSPIRE
Wedzicha[4]
104 weeks
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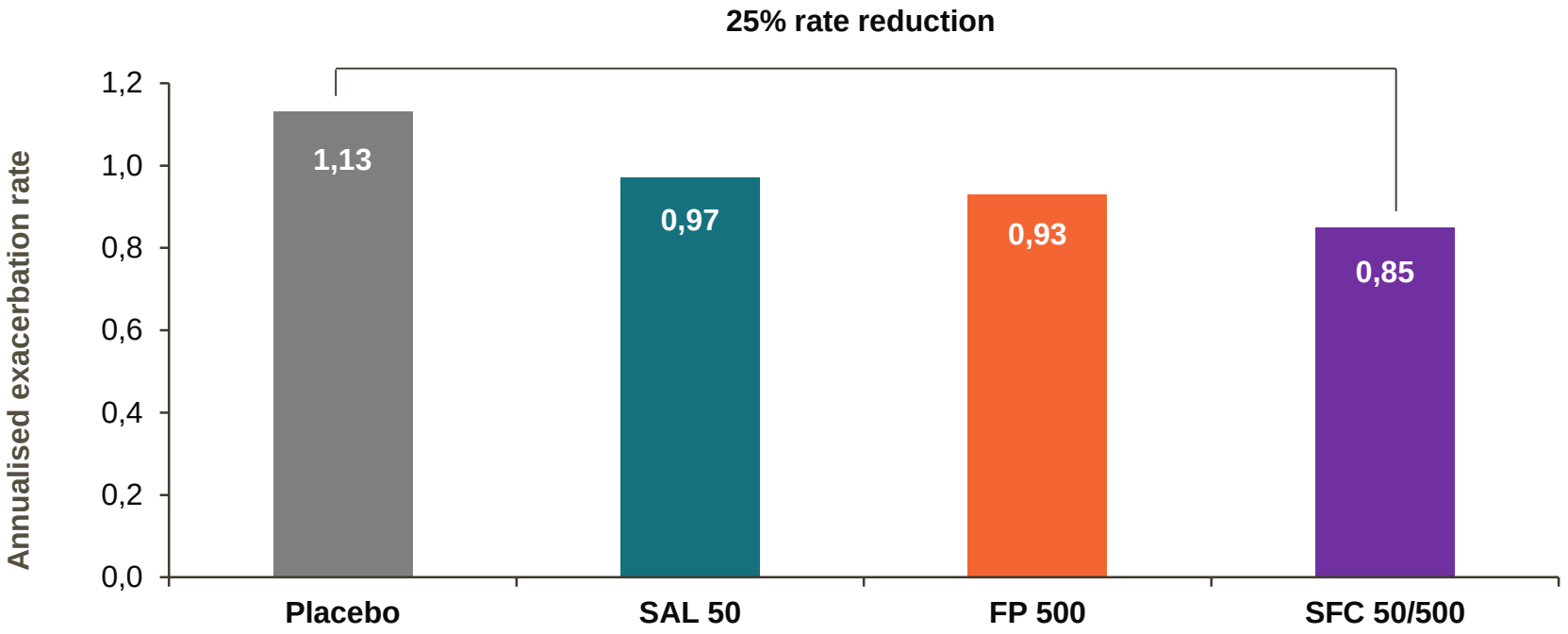
ICS/LABA significantly reduces exacerbations* over 3 years



	Treatment effect	P-value	95% CI
SFC vs. placebo	25%	<0.001	0.69–0.81
SFC vs. SAL	12%	0.002	0.81–0.95
SFC vs. FP	9%	0.02	0.84–0.99

The primary endpoint of the effect of SFC on mortality did not achieve statistical significance (P=0.052)

This study compared SFC 50/500 µg twice daily (combination regimen; n=1533), with placebo (n=1524), SAL alone (n=1521), or FP alone (n=1534) in patients with COPD for a period of 3 years

*Exacerbations were defined as a symptomatic deterioration requiring treatment with antibiotics, systemic corticosteroids, hospitalisation, or a combination of these

CI: Confidence interval; FP: Fluticasone propionate; SAL: Salmeterol; SFC: Salmeterol/Fluticasone propionate combination

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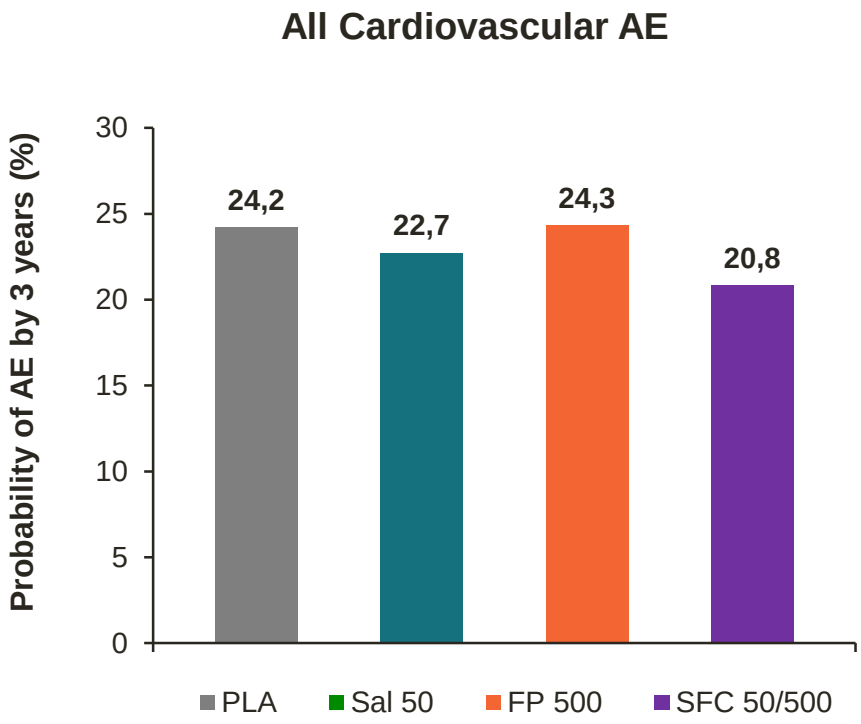
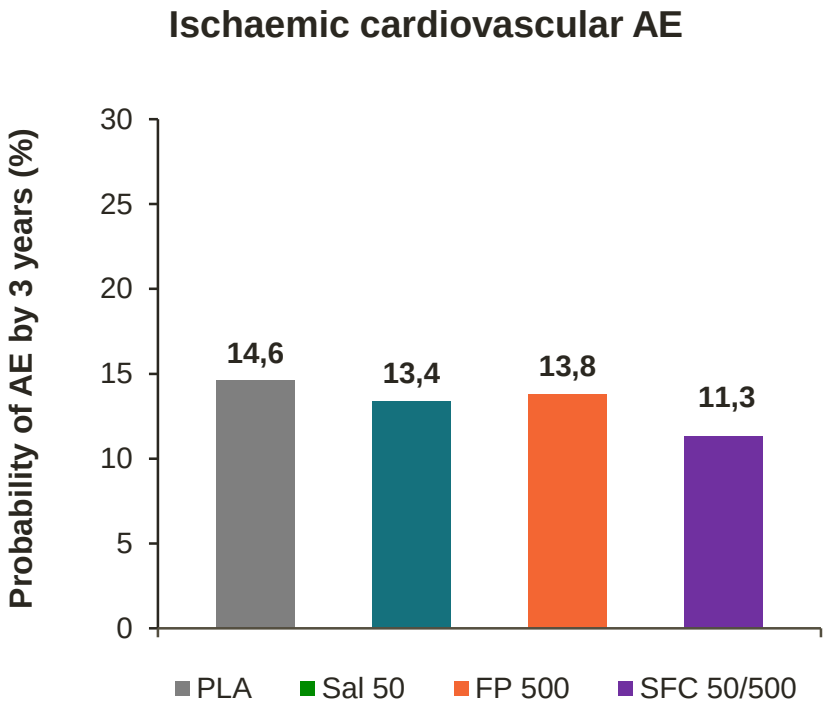
TORCH: Kaplan-Meier probability of AE over 3 years





	PLA	Sal 50	FP 500	SFC 50/500
Hazard ratio Active vs PLA:		0.96⁺	1.00⁺	0.83*
95% CI Active vs PLA:		(0.82, 1.13)	(0.85, 1.18)	(0.70, 0.98)

⁺p=non-significant; *p=0.031

	PLA	Sal 50	FP 500	SFC 50/500
Hazard ratio Active vs PLA:		0.93‡‡	0.93‡‡	0.76‡
95% CI Active vs PLA:		(0.75, 1.16)	(0.75, 1.15)	(0.61, 0.95)

‡‡p=non-significant; ‡ p=0.016

AE: Adverse event; CI: Confidence interval; FP: Fluticasone propionate; PLA: Placebo; SAL: Salmeterol; SFC: Salmeterol/fluticasone propionate combination

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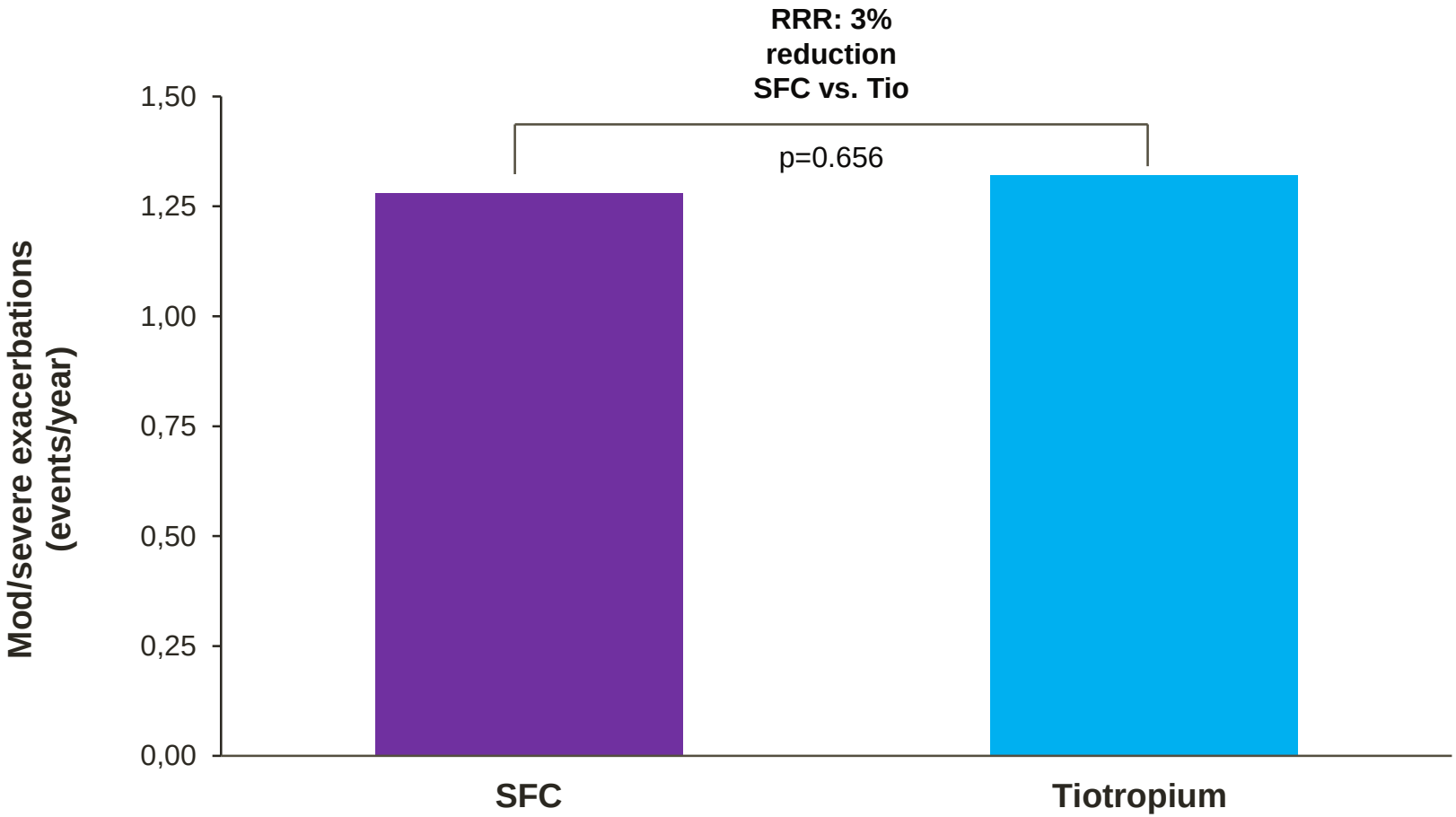
ICS/LABA and LAMA show similar reductions in the rate of moderate/severe exacerbations

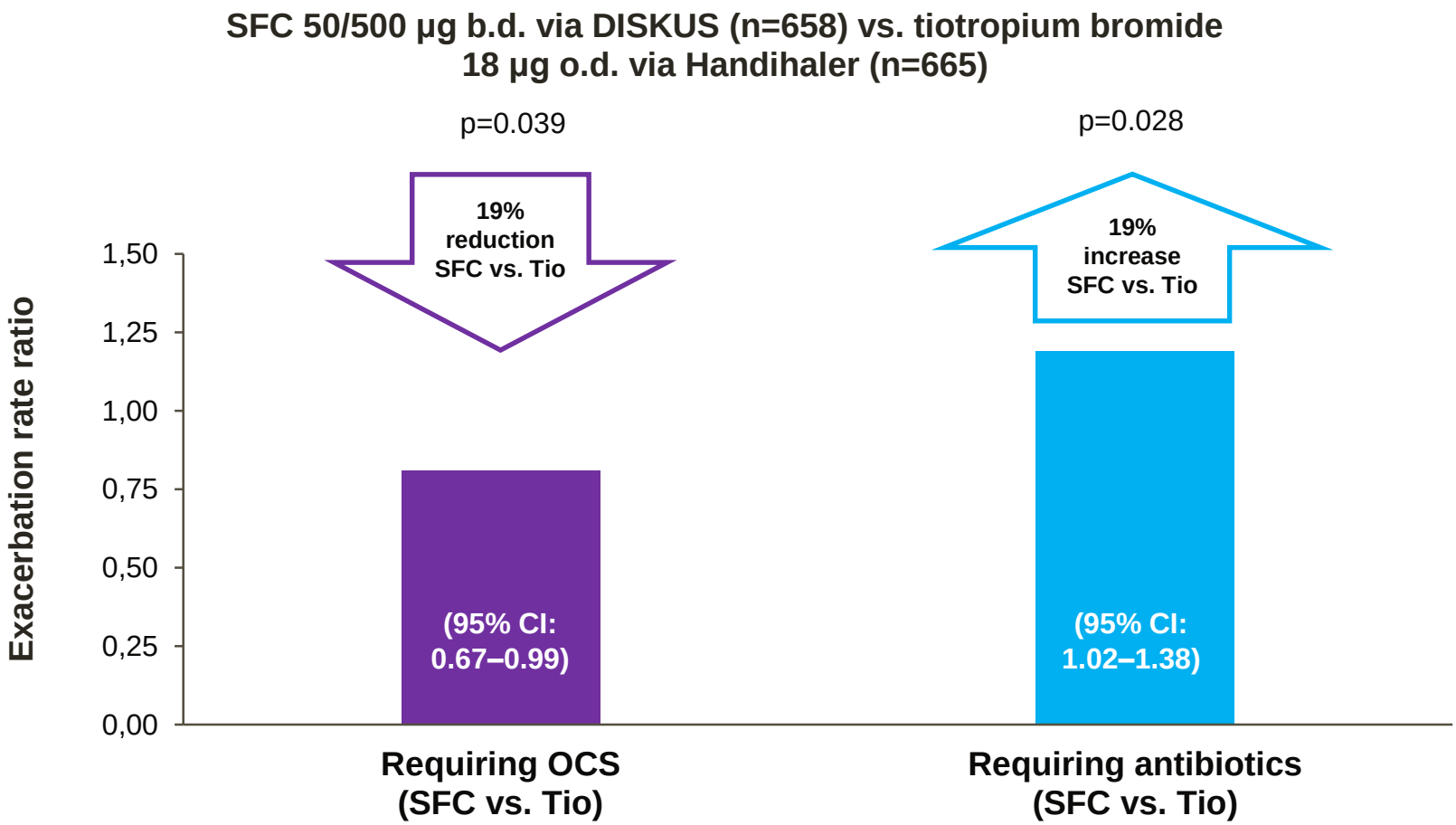


Data from the INSPIRE study: Patients (mean age 64 years, with post-bronchodilator FEV1 39% predicted) were randomised to receive salmeterol 50 µg plus fluticasone propionate 500 µg combination (SFC; n=658) twice daily or tiotropium bromide 18 µg once daily (Tio; n=665) for 2 years

FEV_1: Forced Expiratory Volume in one second; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; RRR: Relative Risk Reduction; SFC: Salmeterol/fluticasone propionate; Tio: Tiotropium bromide

The same results were first published in Wedzicha J, et.al. *Am J Respir Crit Care Med*. 2008;177:19–26. This graph has been independently created by GSK from the original.

SFC improves exacerbation rates in patients requiring OCS; tiotropium improves exacerbation rates in patients requiring antibiotics



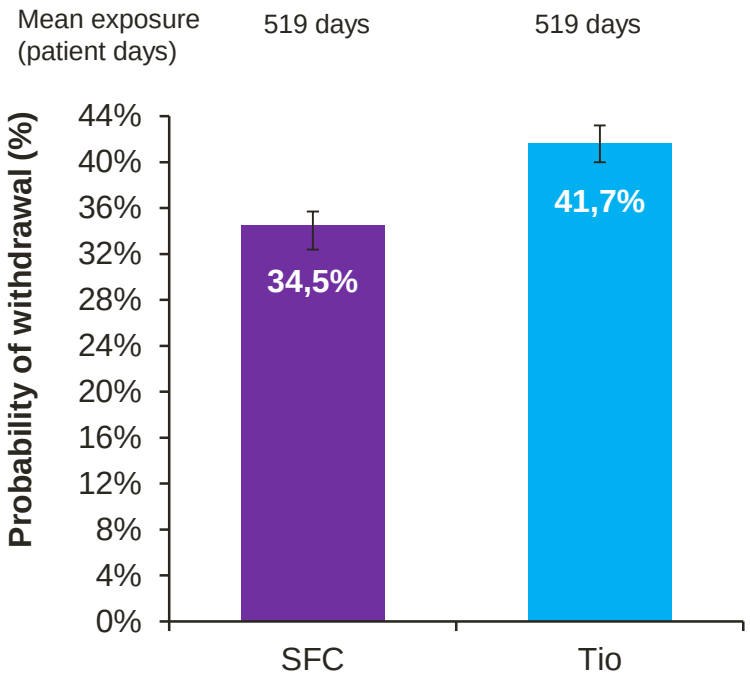
Data from the INSPIRE study: Patients (mean age 64 years, with post-bronchodilator FEV1 39% predicted) were randomised to receive salmeterol 50 µg plus fluticasone propionate 500 µg combination (SFC; n=658) twice daily or tiotropium bromide 18 µg once daily (Tio; n=665) for 2 years

CI: Confidence interval; FEV_1: Forced Expiratory Volume in one second; OCS: Oral corticosteroids; SFC: Salmeterol/fluticasone propionate; Tio: Tiotropium bromide

The same results were first published in Wedzicha J, et.al. *Am J Respir Crit Care Med*. 2008;177:19–26. This graph has been independently created by GSK from the original.

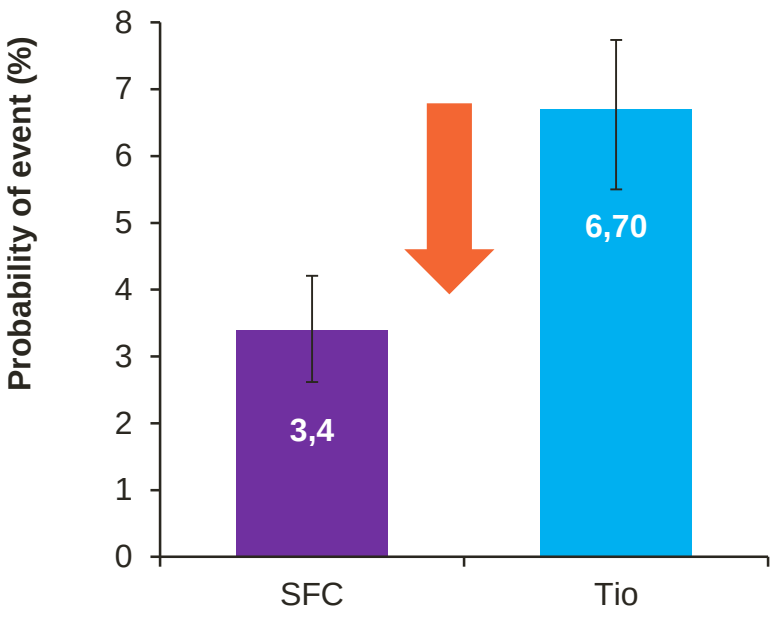
ICS/LABA vs. LAMA in severe COPD: fewer withdrawals and a lower mortality rate

Probability of withdrawal prior to Week 104



Probability of withdrawing from study: 29% greater with Tio. vs SFC
Absolute difference: 7.2%
Cox Hazard Ratio: 1.29
95% CI: 1.08–1.54
P=0.005

Probability of withdrawal prior to Week 104



Relative risk reduction SFC vs. Tio: 52%
Absolute risk difference 3%
Cox Hazard Ratio: 0.48
95% CI: 0.27–0.85
P=0.012

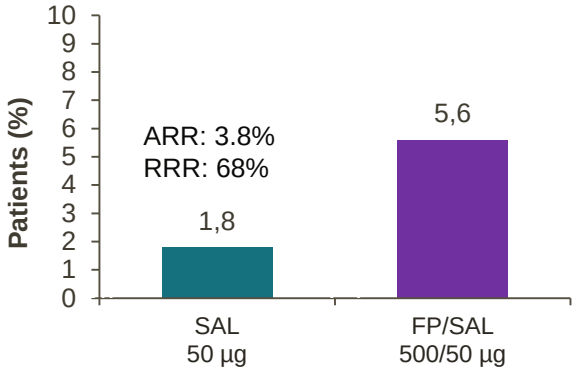
Data from the INSPIRE study: Patients (mean age 64 years, with post-bronchodilator FEV_1 39% predicted) were randomised to receive salmeterol 50 mg plus fluticasone propionate 500 mg combination (SFC; n=658) twice daily or tiotropium bromide 18 mg once daily (Tio; n=665) for 2 years

CI: Confidence interval; FEV_1: Forced Expiratory Volume in one second; SFC: Salmeterol/fluticasone propionate; Tio: Tiotropium bromide

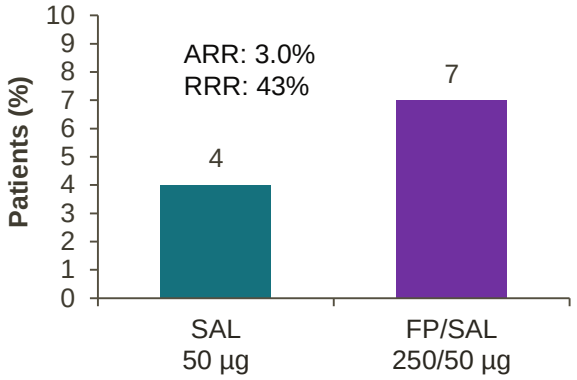
The same results were first published in Wedzicha J, et.al. *Am J Respir Crit Care Med*. 2008;177:19–26. This graph has been independently created by GSK from the original.

ICS/LABA in the management of COPD: understanding the risk of pneumonia

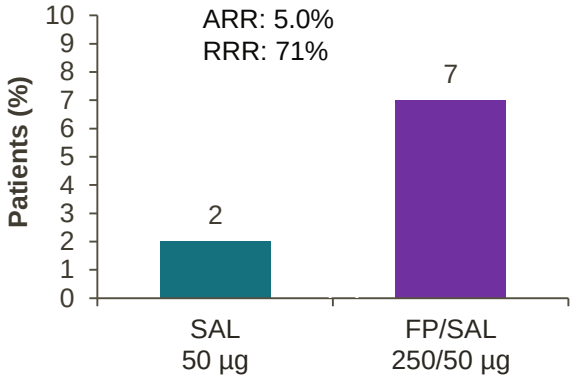
Increased risk of pneumonia has been reported with ICS-containing treatments



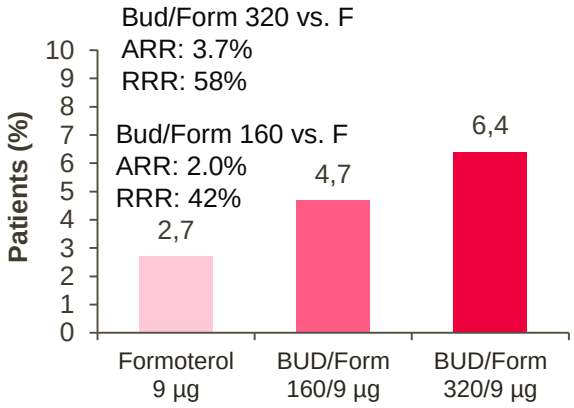
Kardos et al. 2007 (n=994)



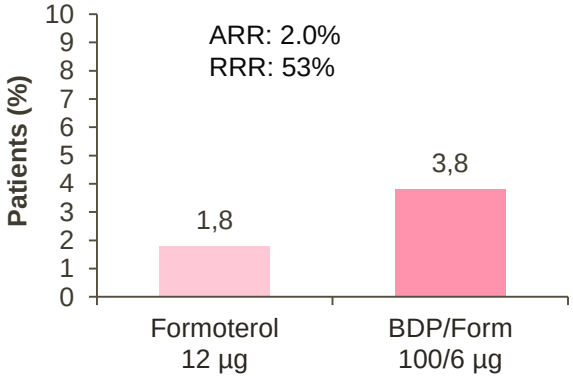
Ferguson et al. 2008 (n=782)



Anzueto et al. 2009 (n=797)



Sharafkhaneh et al. 2012 (n=1219)

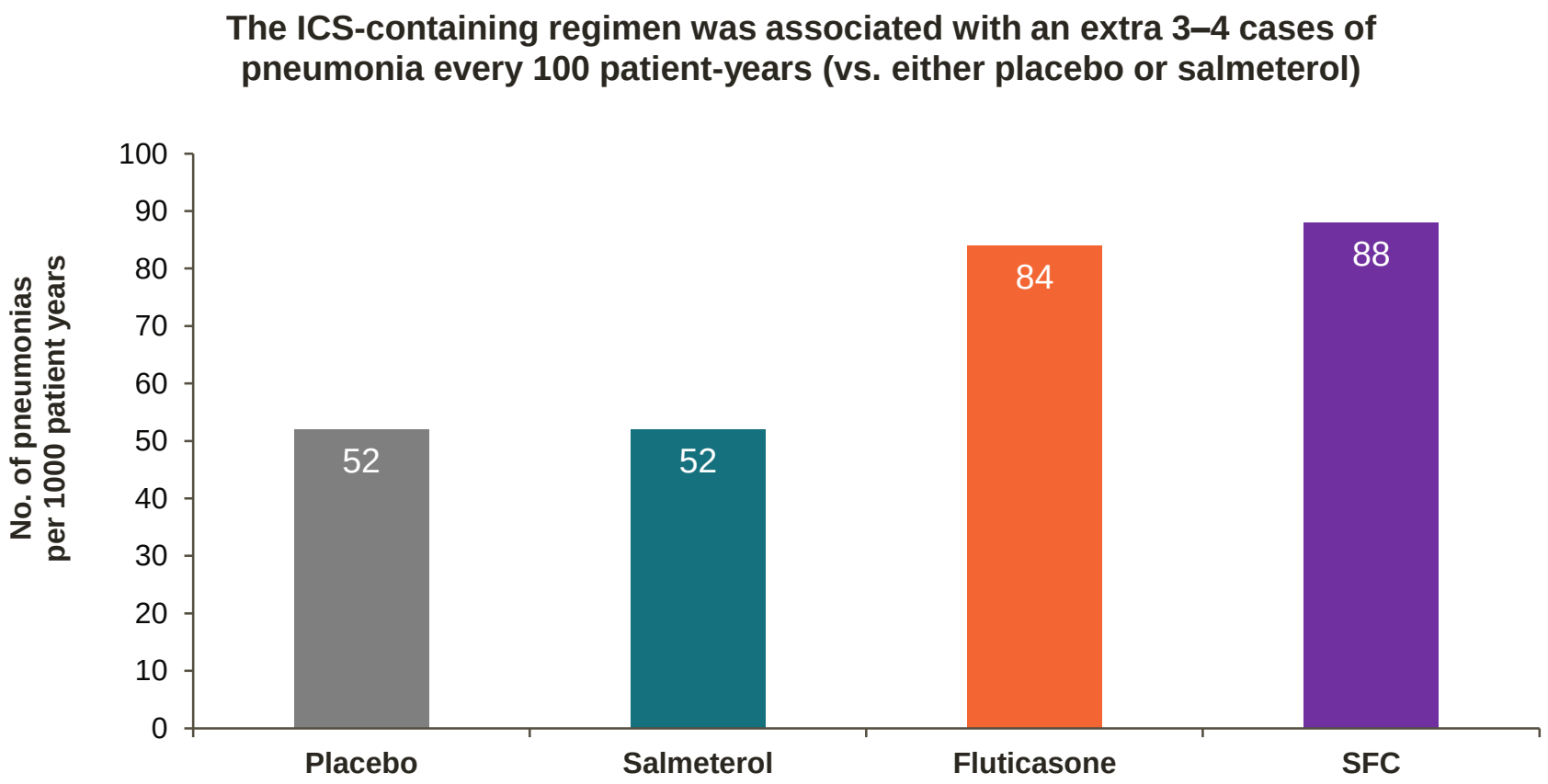


Wedzicha et al. 2014 (n=1197)

The same results were first published in Anzueto 2009, Dransfield 2013, Ferguson 2008, Kardos 2007, Sharafkhaneh 2012, and Wedzicha 2014.
These graphs have been independently created by GSK from the originals. ARR: Absolute Risk Reduction; Bud/Form: Budesonide/Formoterol; FF: Fluticasone furoate; FP: Fluticasone propionate; ICS: Inhaled corticosteroid; PLA: Placebo; Sal: Salmerterol; SFC: Salmeterol/Fluticasone propionate combination; RRR: Relative Risk Reduction; VI: Vilanterol

1. Anzueto A, et al. *COPD* 2009;6:320–9; 2. Dransfield MT, et al. *Lancet Respir Med* 2013;1:210–23; 3. Ferguson GT, et al. *Resp Med*. 2008;102:1099–108; 4. Kardos P, et al. *Am J Respir Crit Care Med.* 2007;175:144–9;5. Sharafkhaneh A, et al. *Respir Med*. 2012;106:257–68; 6. Wedzicha JA, et al. *Respir Med*. 2014;108:1153–62

Compared with placebo and LABA treatment, an ICS-containing regimen increased the risk of pneumonia in patients with COPD

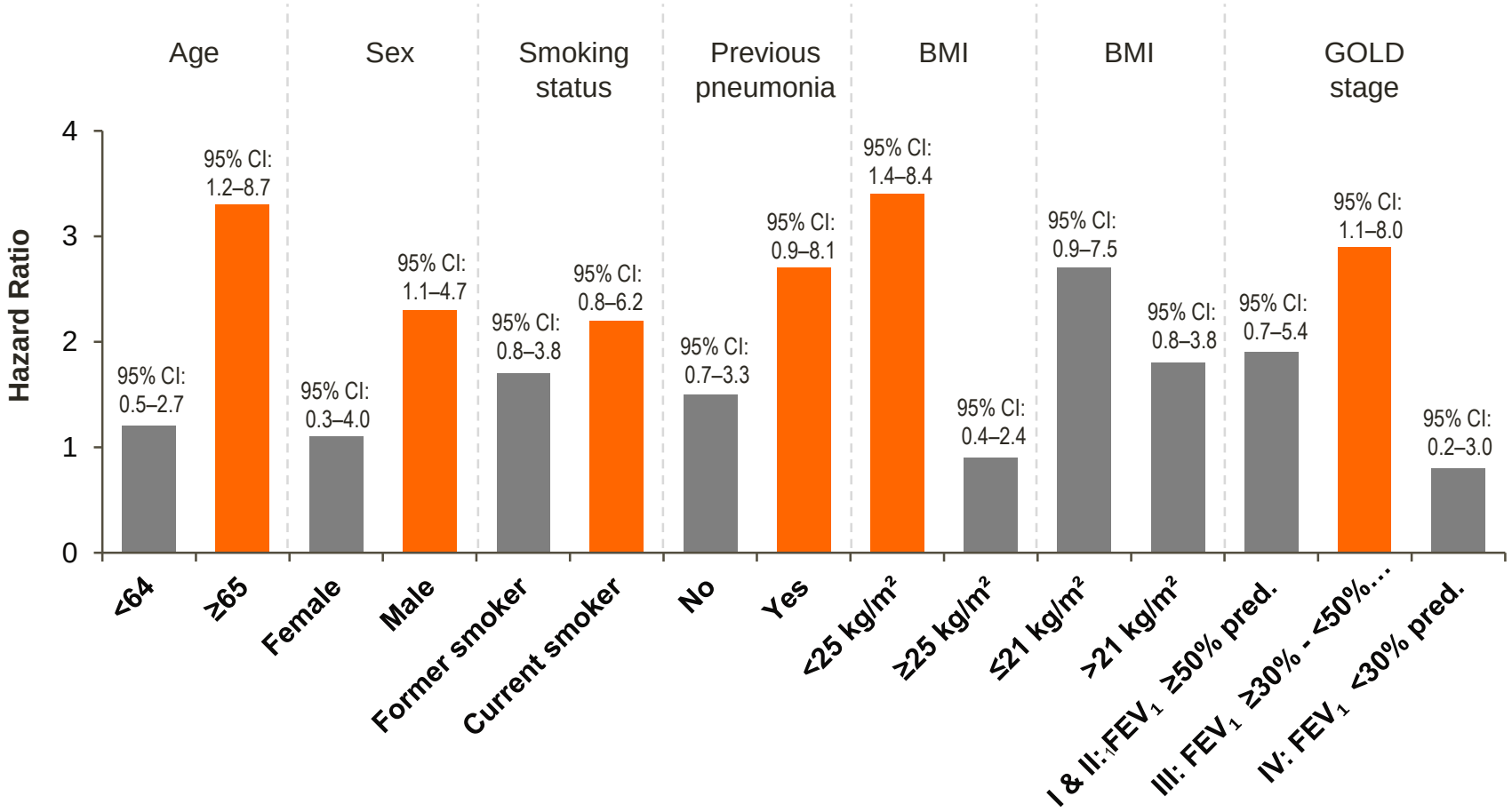


This was a post hoc analysis of the TORCH study designed to assess the risk factors for pneumonia in COPD patients receiving twice daily salmeterol 50 µg (n=1542), fluticasone propionate 500 µg (n=1552), and the combination (SFC) (n=1546) vs. placebo (n=1544)

ICS: Inhaled corticosteroid; SFC: Salmeterol/Fluticasone propionate combination

The same results were first published in Crim C, et al. *Eur Respir J.* 2009;34:641–7. This graph has been independently created by GSK from the original.

Factors associated with an increased pneumonia risk in COPD patients receiving ICS



Two replicate, 1-year, double-blind clinical trials in patients with moderate-to-severe COPD and at least one exacerbation within the prior year.

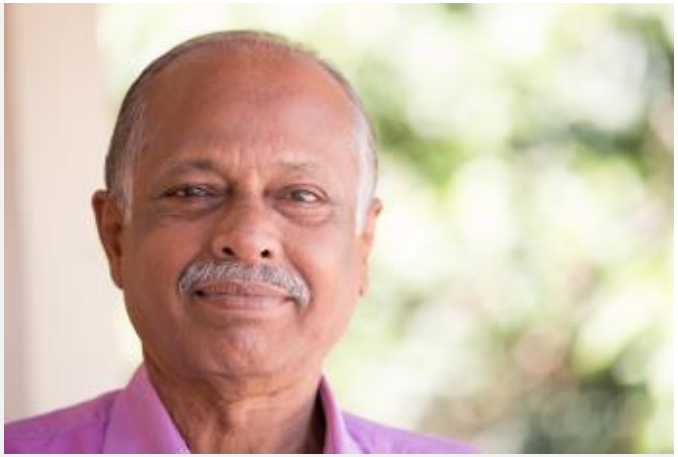
Patients received inhaled once-daily vilanterol (VI) 25 mg (n=818) or VI 25 mg combined with 50 (n=820), 100 (n=806), or 200 mg fluticasone furoate (n=811)

BMI: Body mass index; CI: Confidence interval; FEV_1: Forced Expiratory Volume in one second; ICS: Inhaled corticosteroid.

The same results were first published in Crim C, et al. *Ann Am Thorac Soc*. 2015;12:27–34. This graph has been independently created by GSK from the original.

Mo stays on ICS/LABA due to negative impact of exacerbation risk on his long-term prognosis

- Mo's doctor explains the long-term risk of recurrent exacerbations on his overall health
- Mo and his doctor decide to continue with ICS/LABA as he is at greater risk of recurrent exacerbations than pneumonia
- His doctor also books him in for his yearly flu vaccination and gives him a pneumococcal vaccination
- Mo also receives a written COPD action plan, which describes early symptoms of an exacerbation and what action to take
- Mo's doctor is also monitoring him for the potential pneumonia risk factors such as worsening lung function and dyspnoea



ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonist

This is a hypothetical case study reflective of real world experience.

Thank you

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