COPD
Importance of Symptomatic Control

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Introduction

- Symptoms and outcomes in COPD
- Right drug, right patient – using LAMA/LABA

Drug Classes in COPD

LAMA

LABA

ICS/LABA

LAMA/LABA

Symbicort MDI
COPD only right now

PATIENT CHARACTERISTICS AND OUTCOMES IN COPD

Weak correlation between health status and FEV1 in COPD (ie. NOT FEV1)

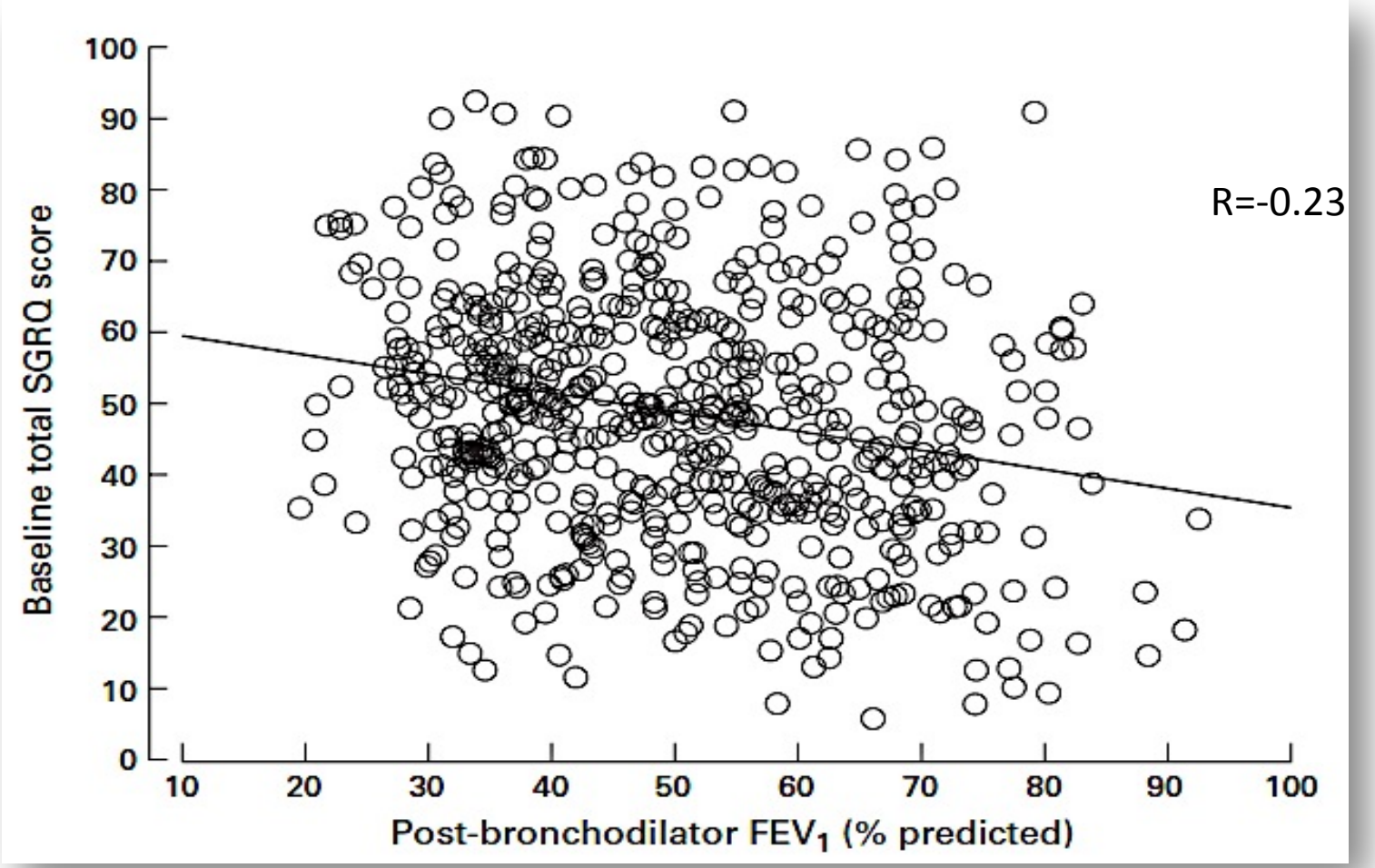
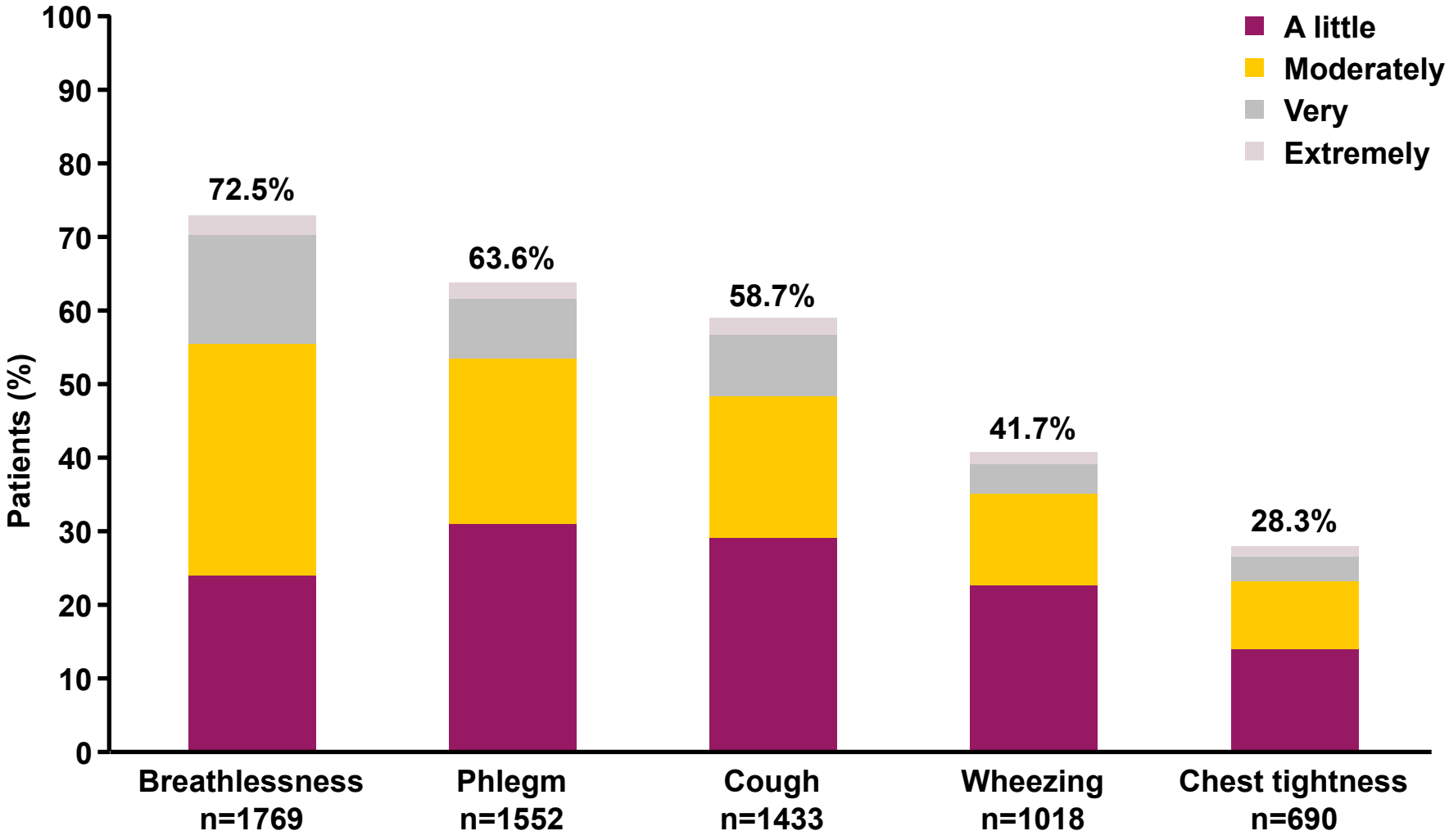


Figure adapted from Jones 2001: Correlation between SGRQ and post-bronchodilator FEV1 measured to ATS criteria, r=0.23, p<0.0001. SGRQ scores corresponding to the BTS criteria for COPD are: mild 43 (SD 18); moderate 48 (SD 17); severe 53 (SD 16), p<0.0001 (ANOVA). Data are from the baseline of the ISOLDE study of fluticasone in COPD.

Jones PW *Thorax* 2001;56:880–887

Patients with COPD symptoms



Patients were asked if they had experienced any symptoms (breathlessness, phlegm, cough, wheezing or chest tightness) in the 7 days prior to the telephone interview. Multiple answers were possible.

Van der Molen T et al. Int J Chron Obstruct Pulmon Dis, 2013;8:461-71
Kessler et al. Eur Respir J 2011;37:264-72

Higher levels of breathlessness are associated with higher mortality risk

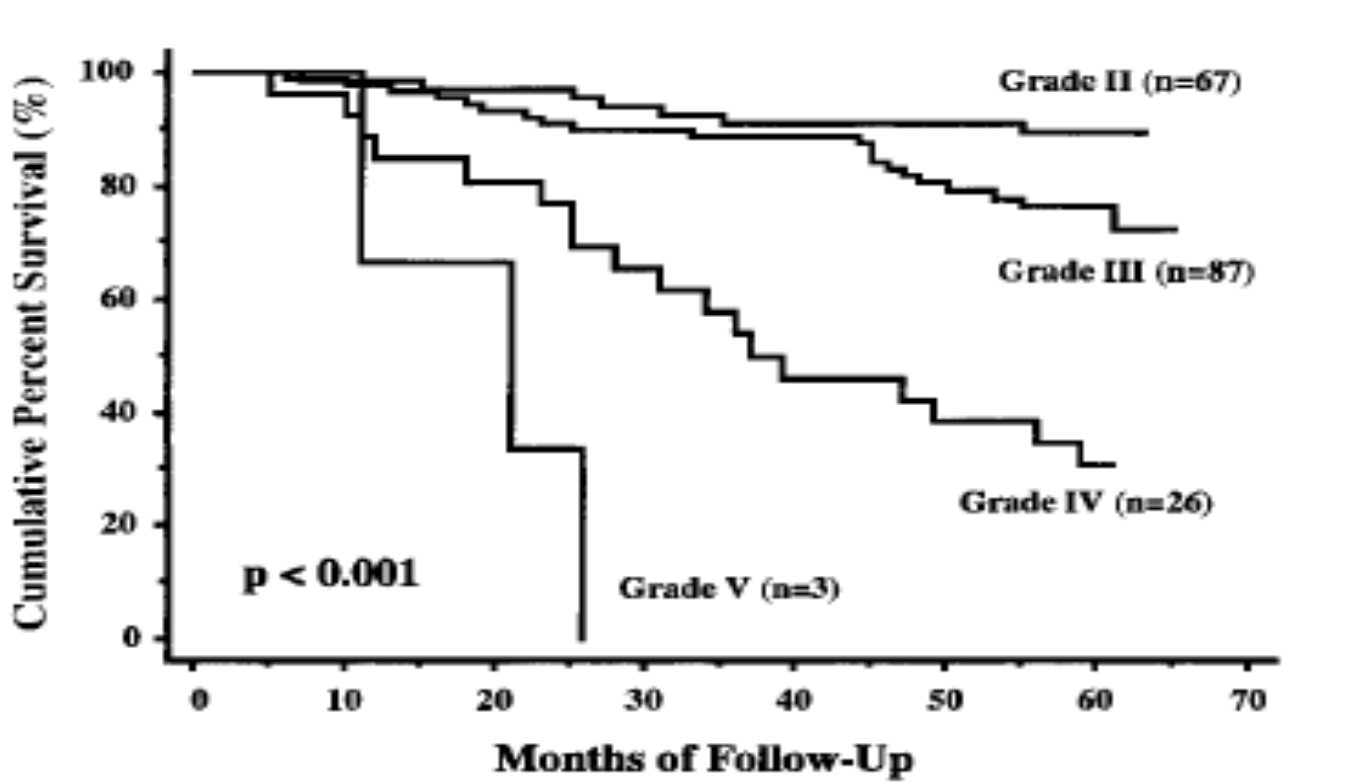


FIGURE 2. Five-year survival according to the level of dyspnea as evaluated by the modified 5-point grading system of Fletcher et al.[10]

N=227 patients. a 5-year, prospective, multicenter study in the Kansai area of Japan, involving 20 divisions of respiratory medicine from various university and city hospitals. The objective was to compare the effects of the level of dyspnea and disease severity, as evaluated by airway obstruction, on the 5-year survival rate of patients with COPD.

Nishimura K, Izumi T et al. CHEST 2002; 121:1434-1440

Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study

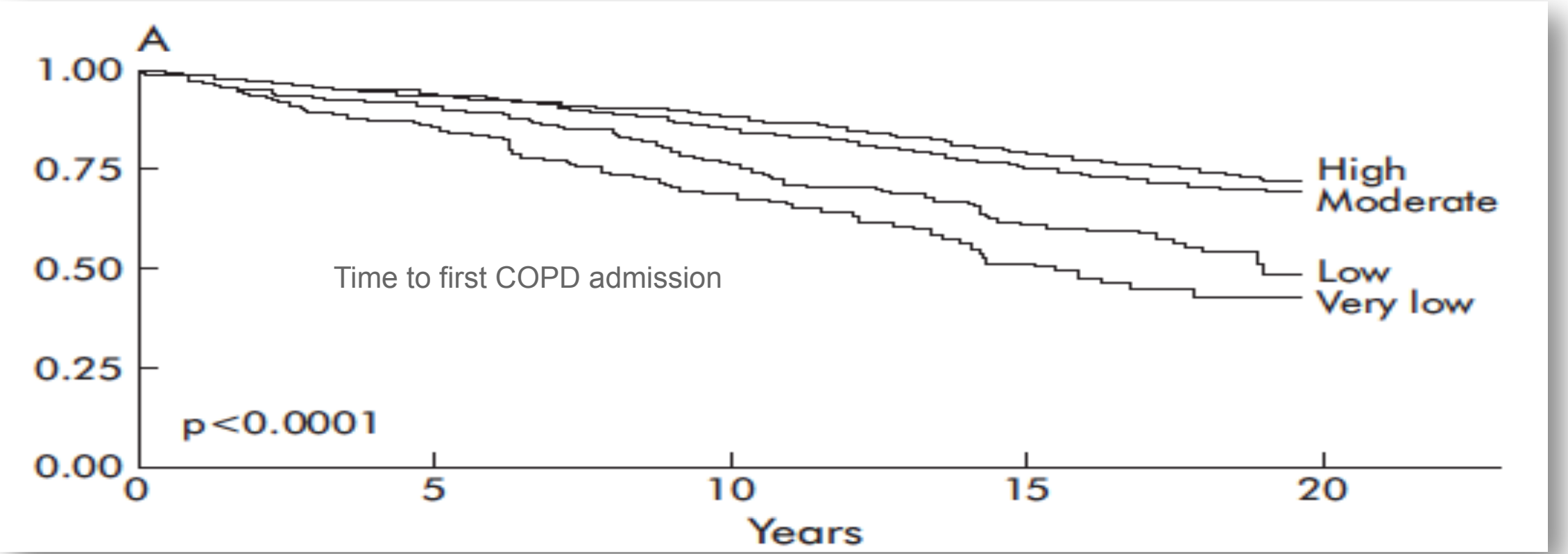
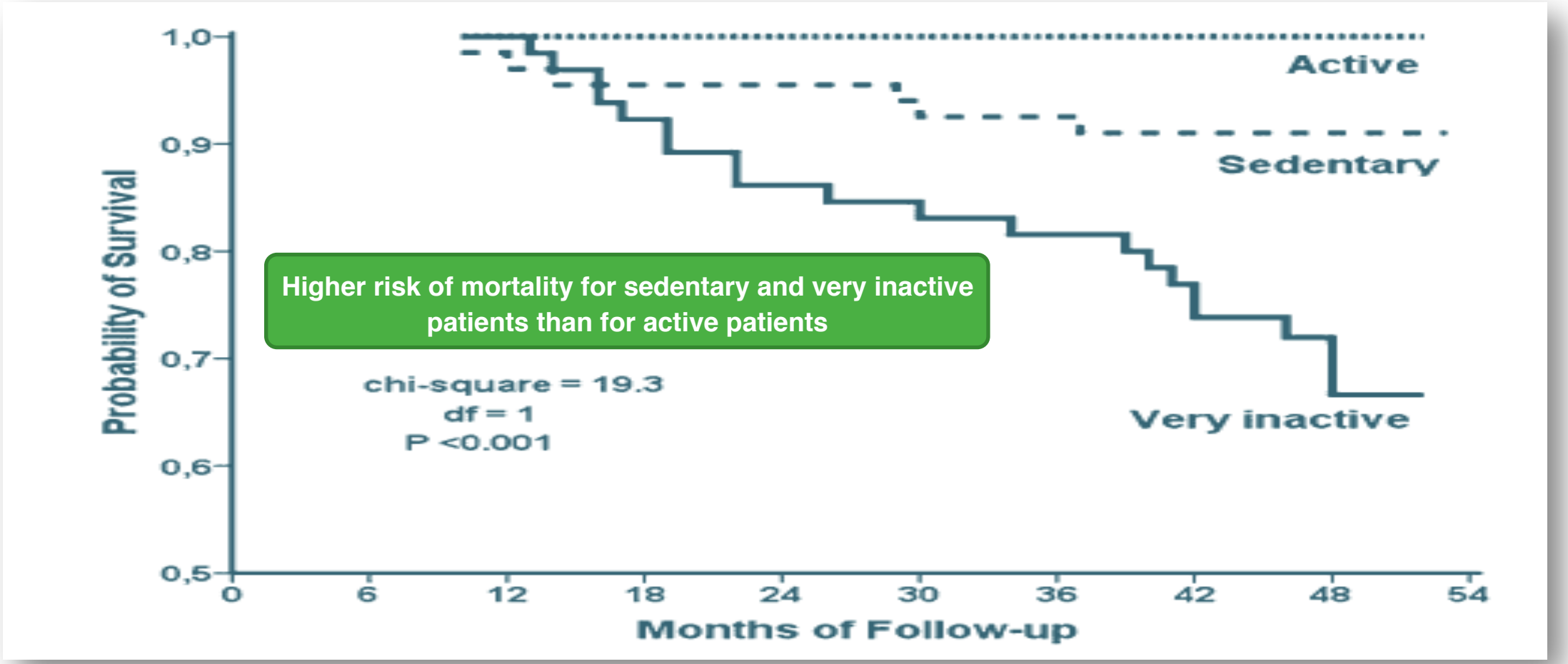


Figure adapted from Garcia-Aymerich et al. 2006: (A) Kaplan-Meier curve of time to first COPD admission
during follow up according to level of regular physical activity.

Thorax 2006;**61**:772–778.

Physical activity is a strong predictor of all-cause mortality in patients with COPD

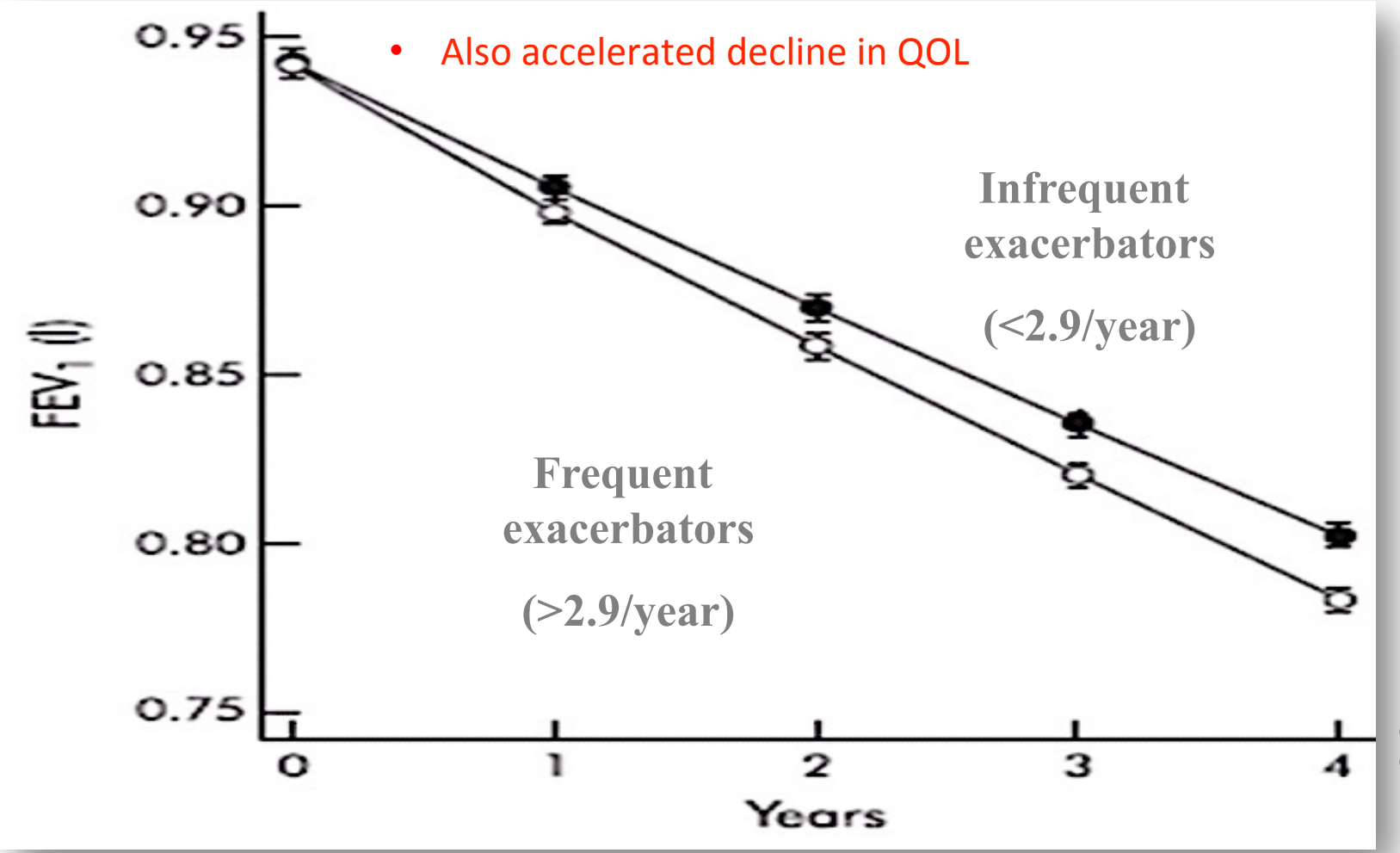


Prospective observational study with 170 COPD patients (GOLD 1–4) followed for 4 years for all-cause mortality. Physical activity was assessed by a multisensory armband according to World Health Organization categories of physical activity level.
df, degrees of freedom.

Reference: Waschki B, et al. CHEST 2011; 140: 331–342.

Accelerated lung function decline in frequent exacerbators

- Also accelerated decline in QOL



P<0.05

Figure adapted from Donaldson et al. 2002: Percentage change in FEV1 with standard errors over 4 years. Open circles represent infrequent exacerbators; closed circles represent frequent exacerbators.

Donaldson; Thorax 2002; 57; 847-852

ORIGINAL ARTICLE

Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality

Samy Suissa,[1,2] Sophie Dell'Aniello,[1] Pierre Ernst[1,3]

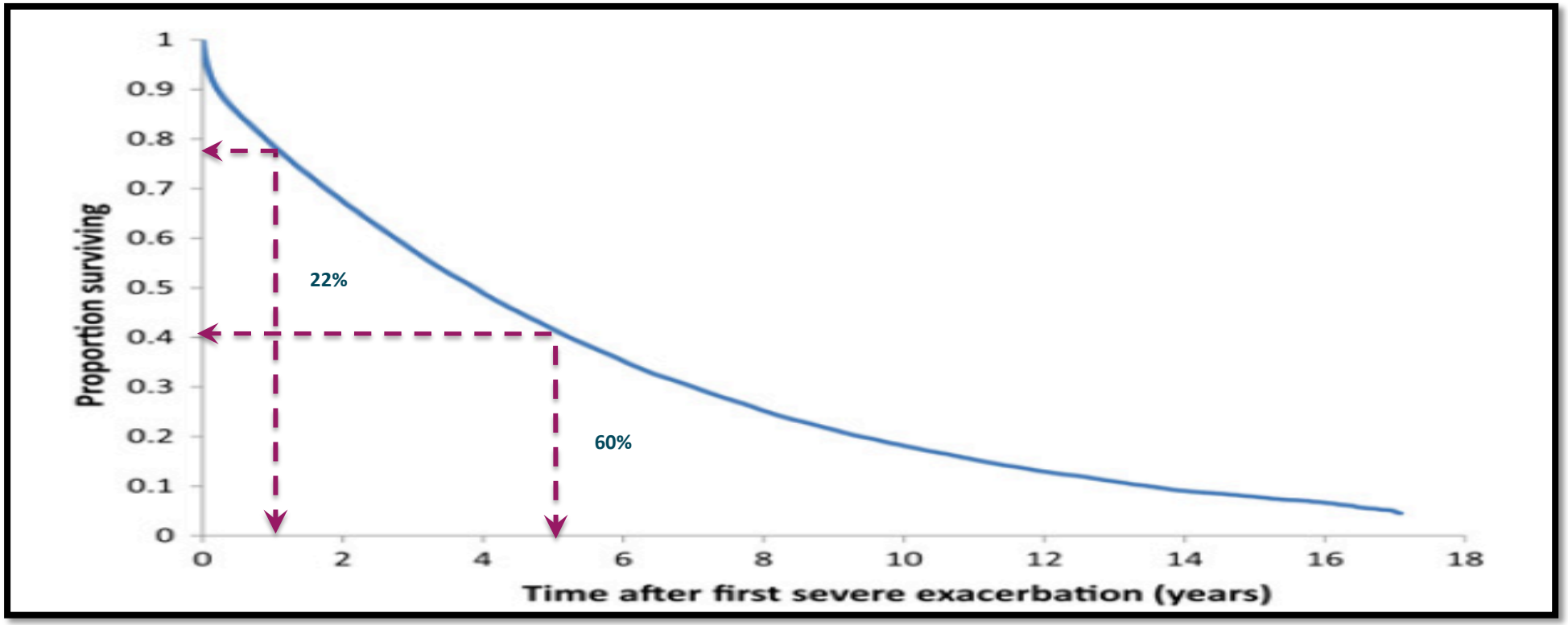
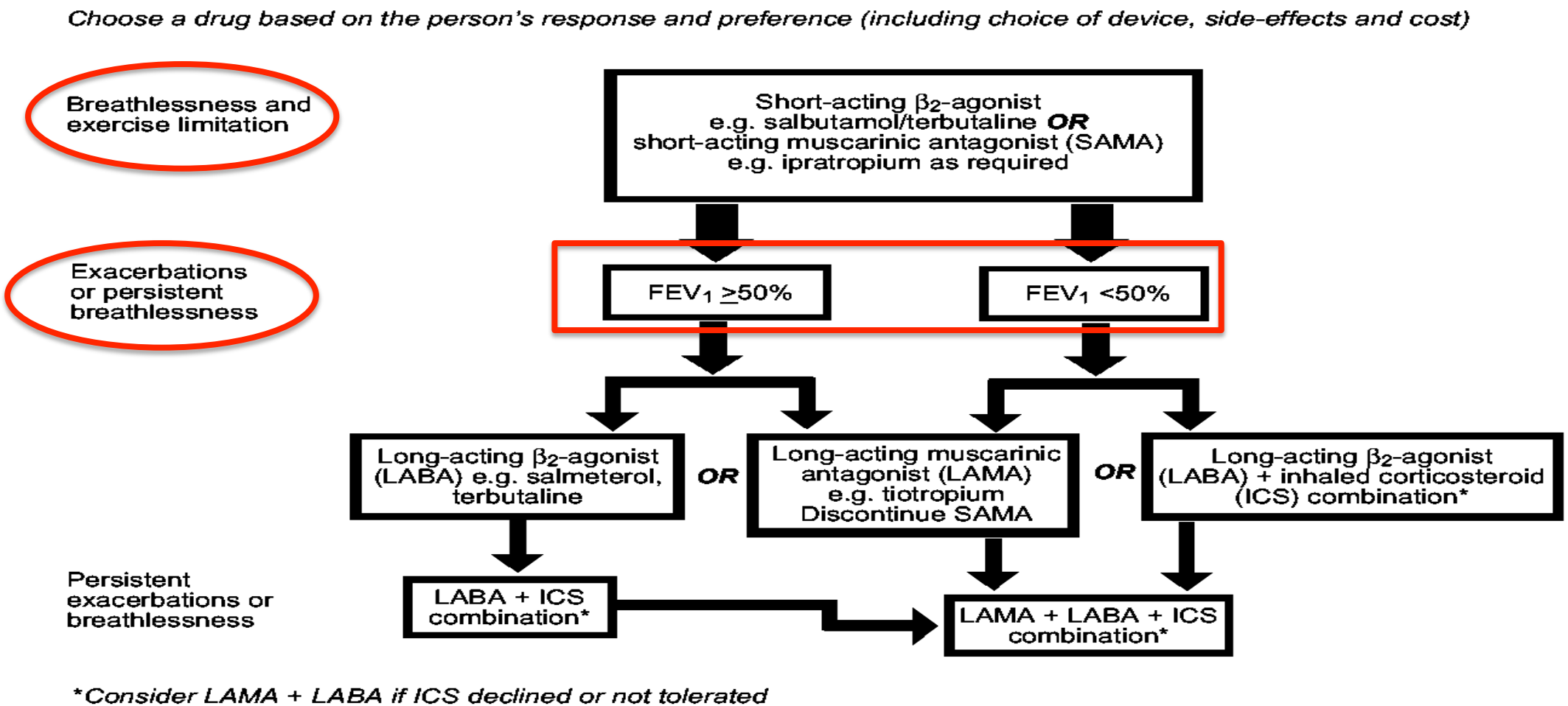


Figure adapted from Suissa et al. 2012: Kaplan-Meier survival function for the cohort of 73 106 patients from the time of their first ever hospitalisation for a chronic obstructive pulmonary disease exacerbation over the 17-year follow-up period.

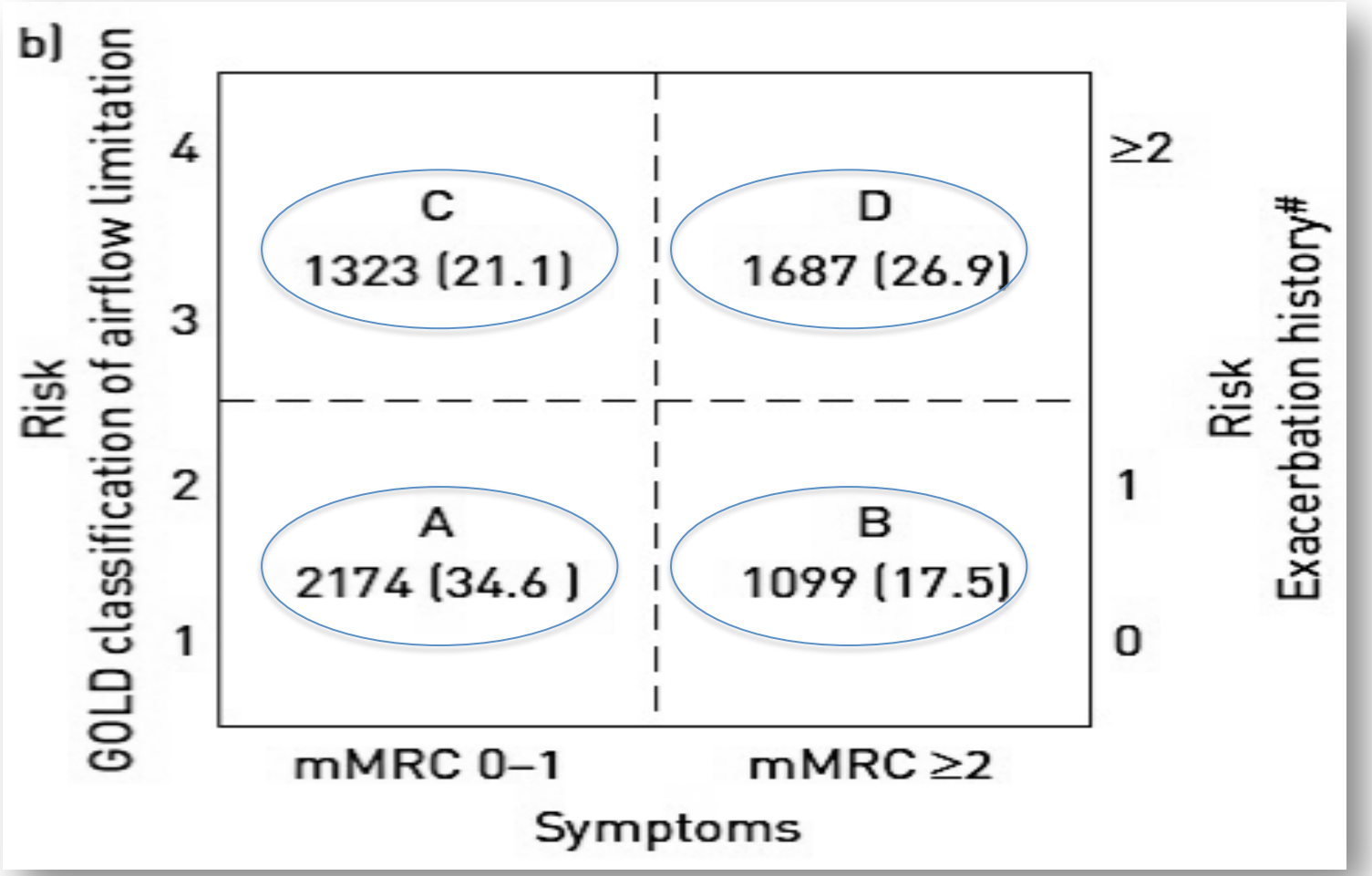
Thorax (2012). doi:10.1136/thoraxjnl-2011-201518

Pharmacotherapy– PCRS COPD Booklet

Figure 3: Inhaled pharmacotherapy algorithm.[1]
Adapted from NICE 2010 Guidelines



The distribution of COPD in UK general practice using the new GOLD classification

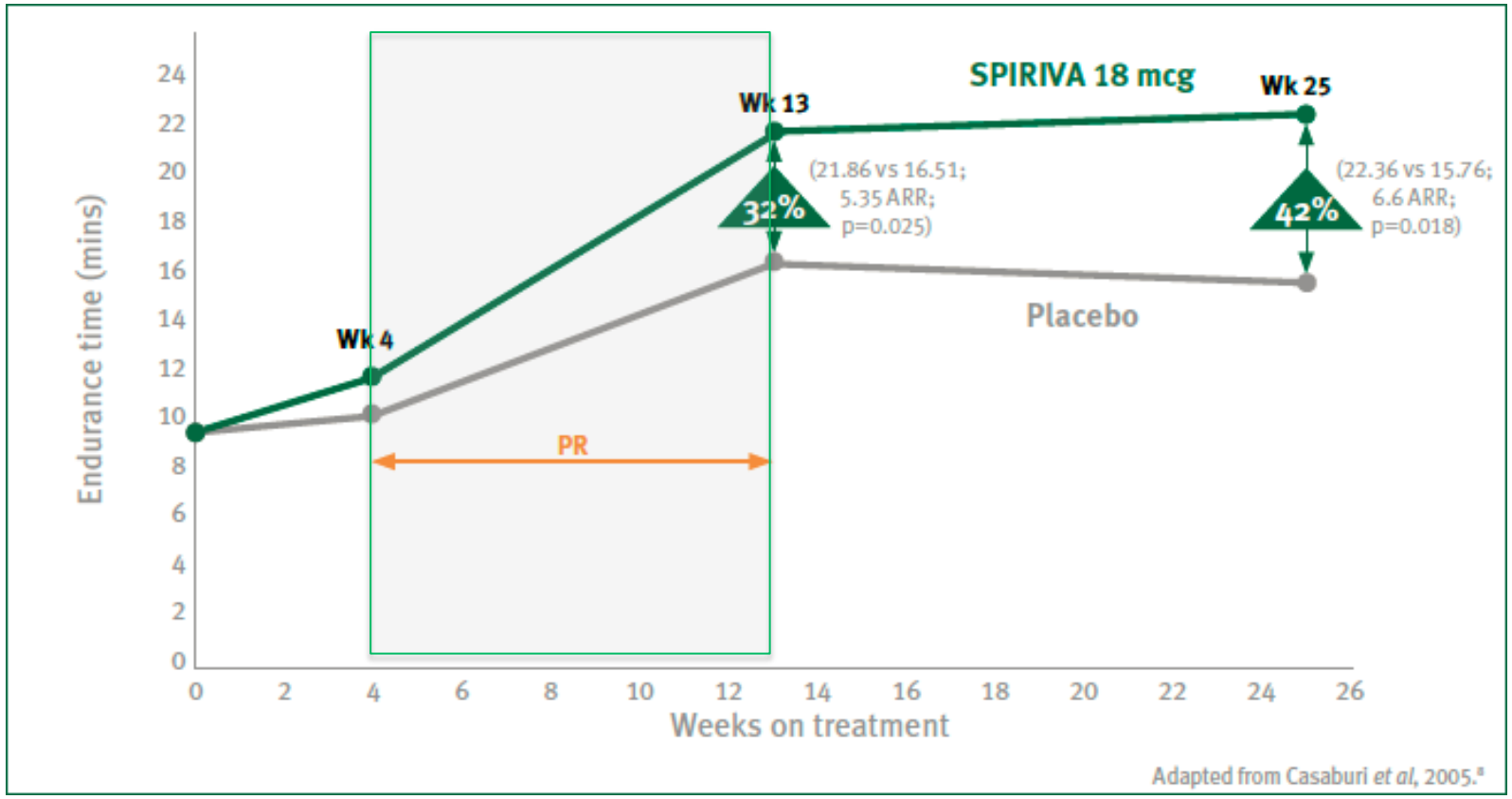


Eur Respir J 2014; 43: 993–1002

SINGLE BRONCHODILATORS

WHAT DO WE KNOW ALREADY?

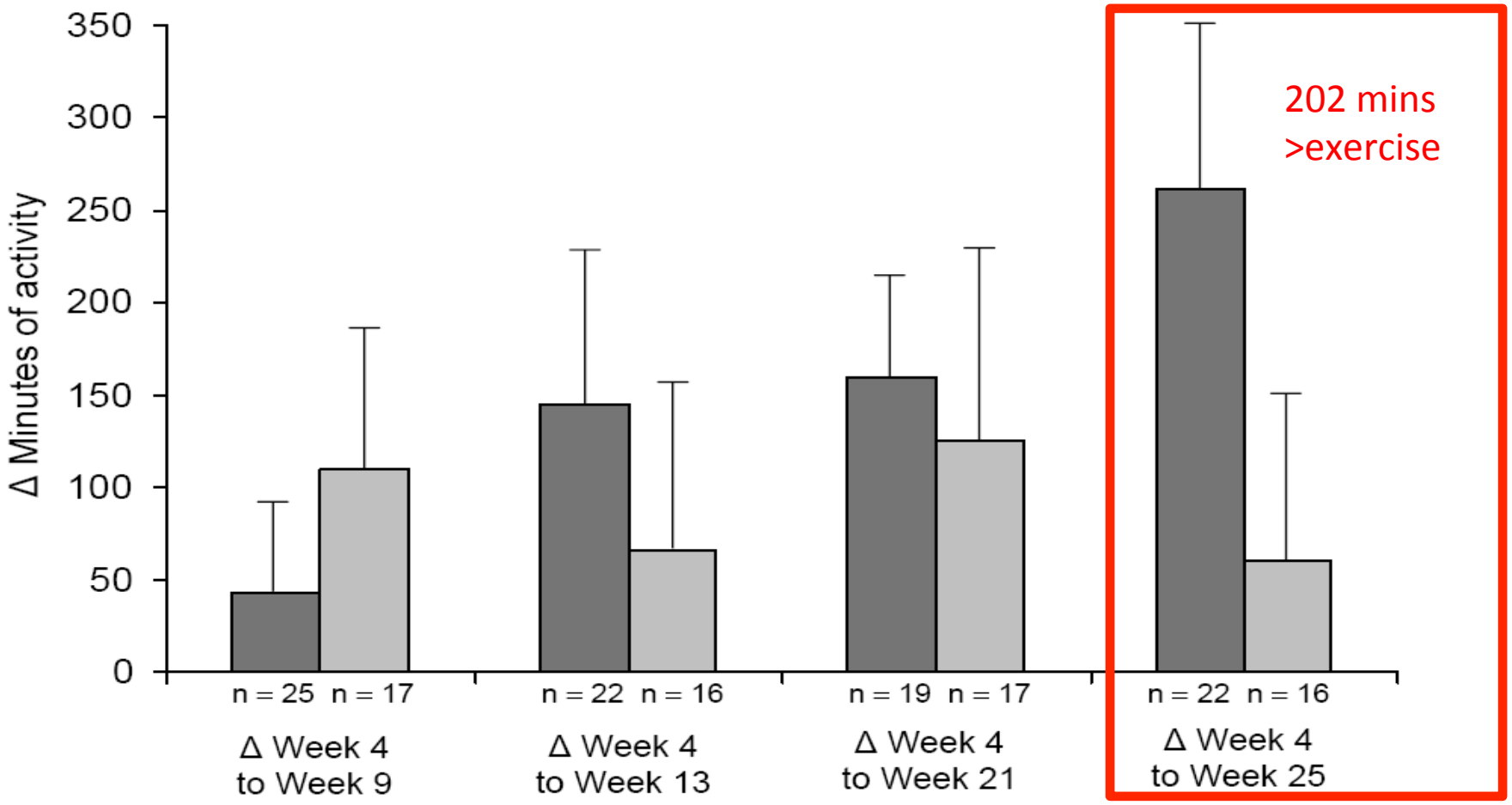
Treadmill endurance time. Tiotropium vs Placebo



Randomised, double blind study design

Casaburi: Chest : 2005; 127: pp809-817

Reported Exercise Post Rehab: Tiotropium vs Placebo

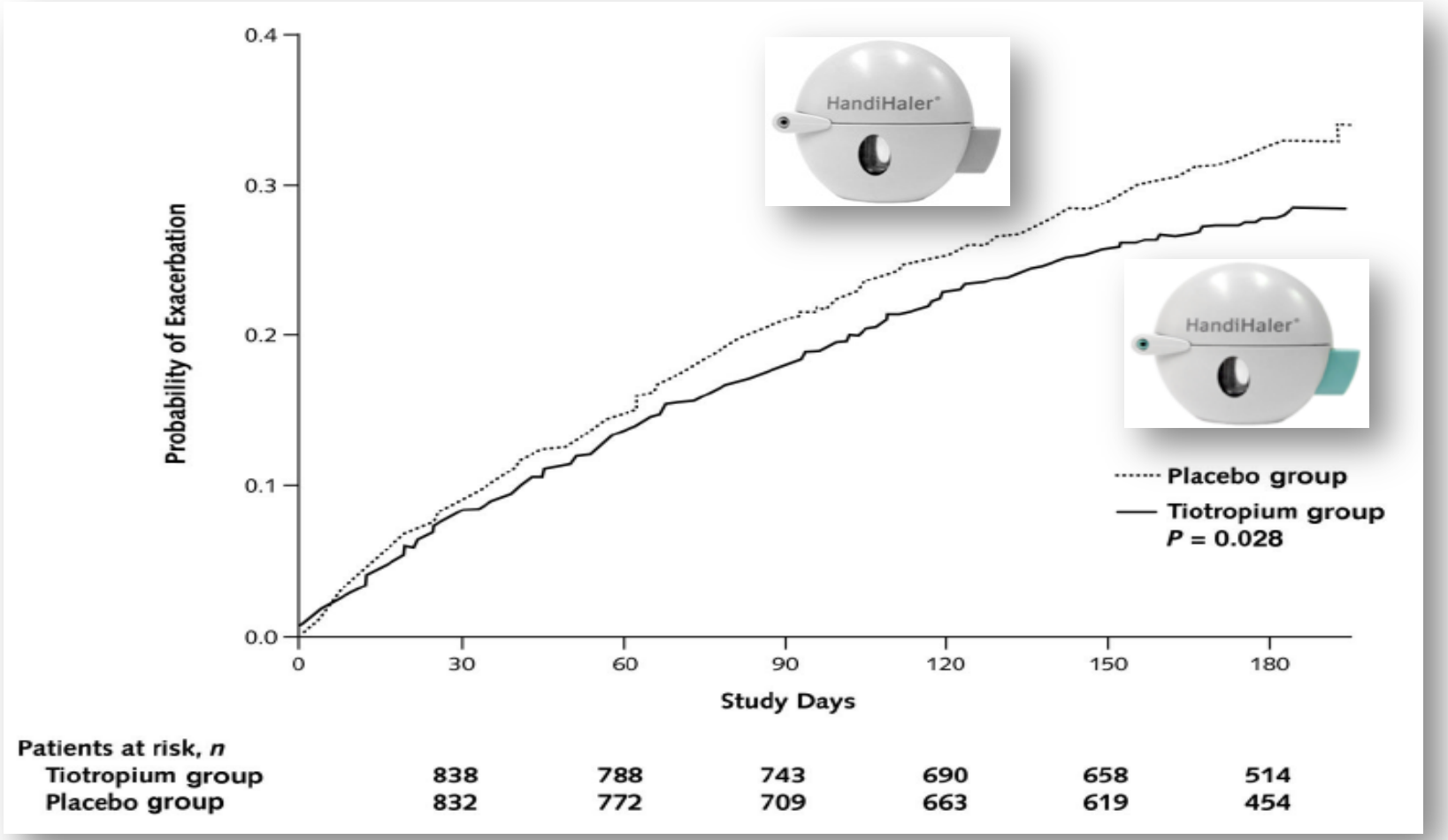


Randomised, double blind study design

Kesten: Internat J COPD: 2008

Prevention of Exacerbations of Chronic Obstructive Pulmonary Disease with Tiotropium, a Once-Daily Inhaled Anticholinergic Bronchodilator

A Randomized Trial

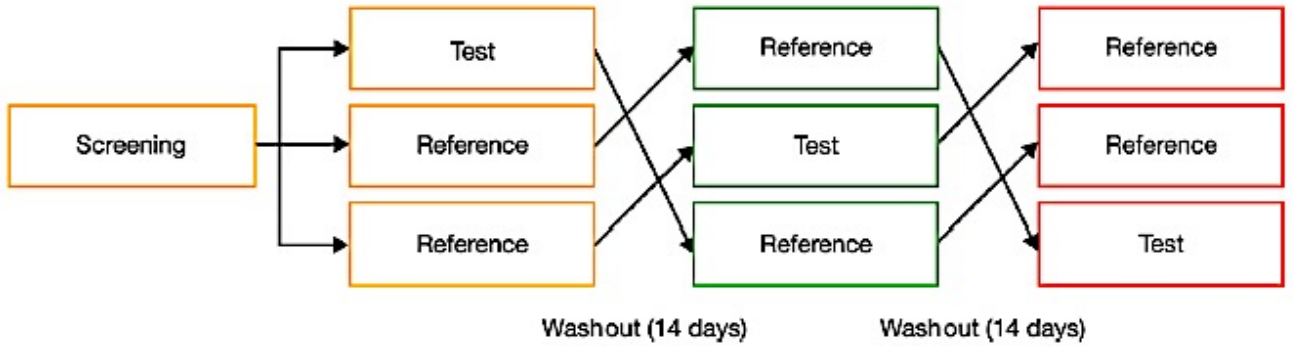


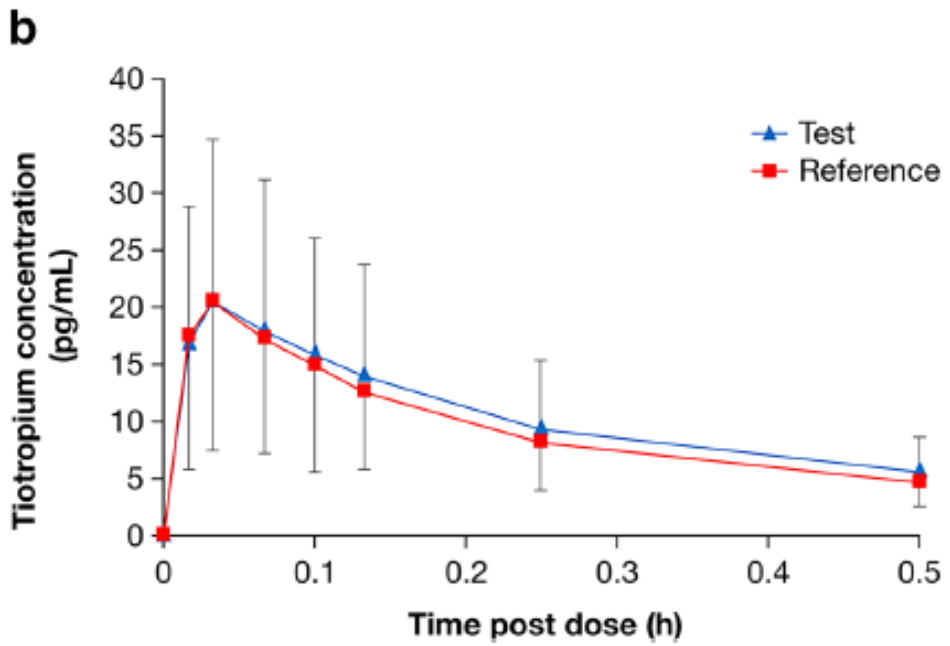
- Tiotropium reduced % experiencing ≥1 exacerbations vs. placebo (27.9% vs. 32.3%; p=0.037)
- Fewer tiotropium patients hospitalized because of COPD exacerbation (7.0% vs. 9.5%; p=0.056)

Figure adapted from Niewoeher et al. 2005. **Tiotropium is not licensed for the management of exacerbations in COPD patients**

Ann Intern Med. 2005;143:317-326.

Pharmacokinetic Bioequivalence of Two Inhaled Tiotropium Bromide Formulations in Healthy Volunteers





Clin Drug Investig (2016) 36:753–762

Pagani Zonda

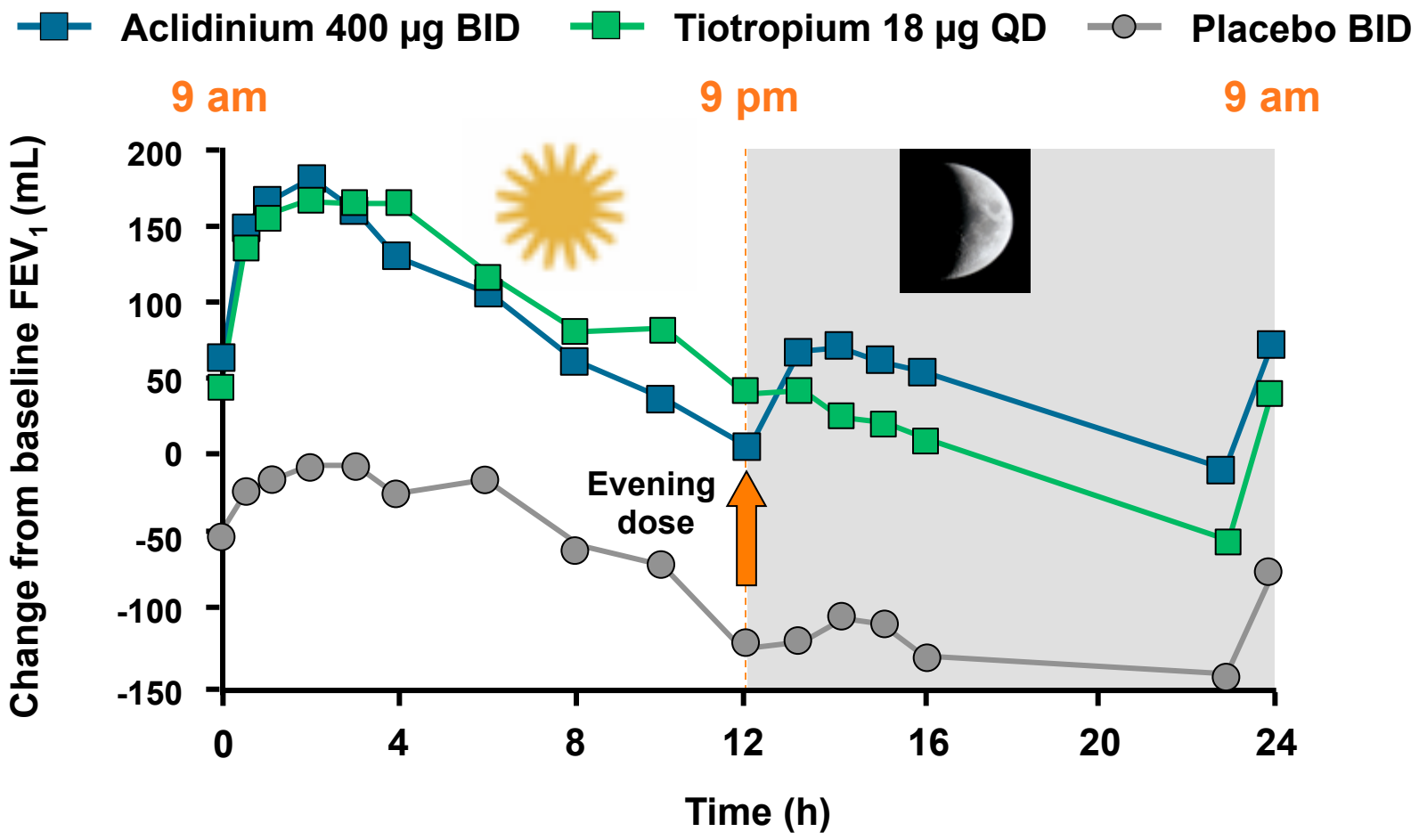
£2.8m

Braltus Zonda

£25.80

Twice a day bronchodilator treatment in COPD (Week 6)

Cf.



- Aclidinium provides effective bronchodilation vs placebo after 6 weeks

Both treatments statistically significantly higher than placebo at all time points

Beier et al, *COPD* 2013

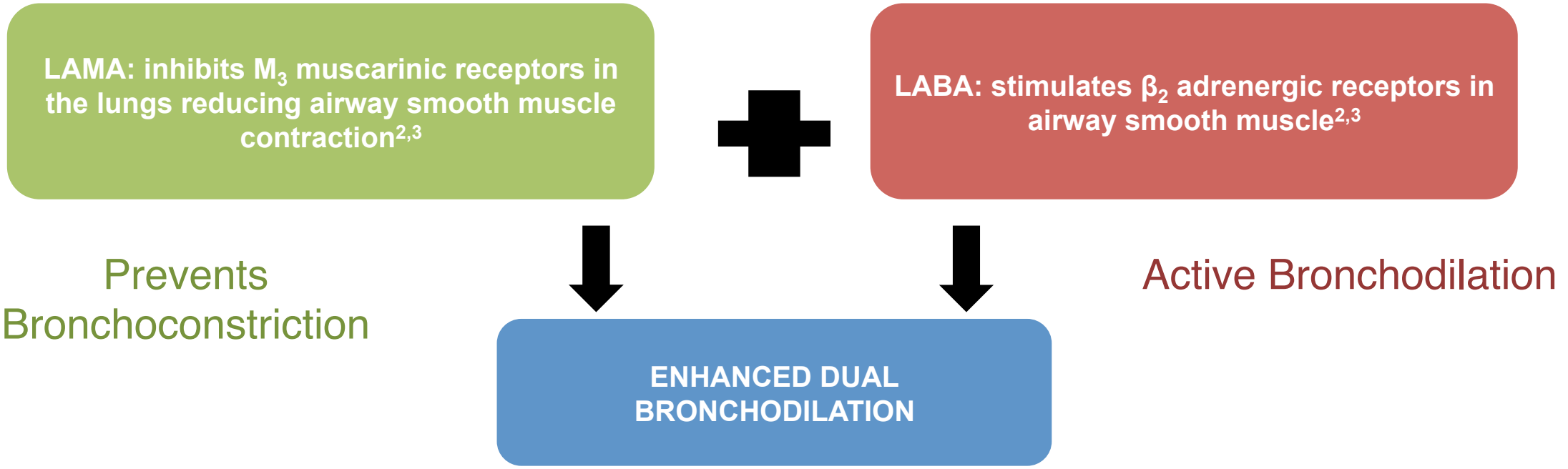
PHARMACOLOGICAL TREATMENT

DUAL BRONCHODILATORS

Dual bronchodilation may offer enhanced efficacy

*"Combining bronchodilators of different pharmacological classes may **improve efficacy** and **decrease the risk of adverse effects** compared to increasing the dose of a single bronchodilator."*

GOLD 2014[1]

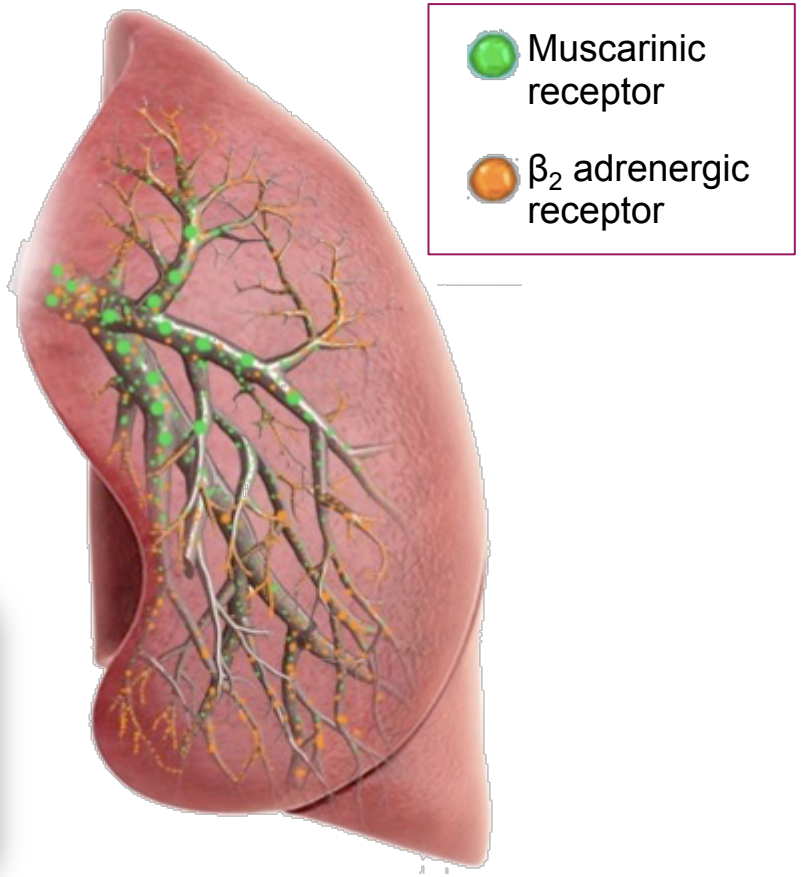


1. GOLD 2014. 2. Cazzola M & Molimard M. Pulm Pharmacol Ther 2010; 23:257–267. 3. Jones R & Østrem A. Prim Care Respir J 2011; 20:33–45.

Rationale for dual bronchodilator therapy in COPD: Distribution of receptor targets in the lung[1-4]

- Muscarinic antagonists are more effective in the proximal airways[1]
- β_2-agonists are relatively more effective in the distal airways[1]

This complementary distribution patterns of muscarinic and β_2-adrenergic receptors in the airways suggests that targeting both pathways may provide better coverage at all airway levels than either agent alone[2-4]

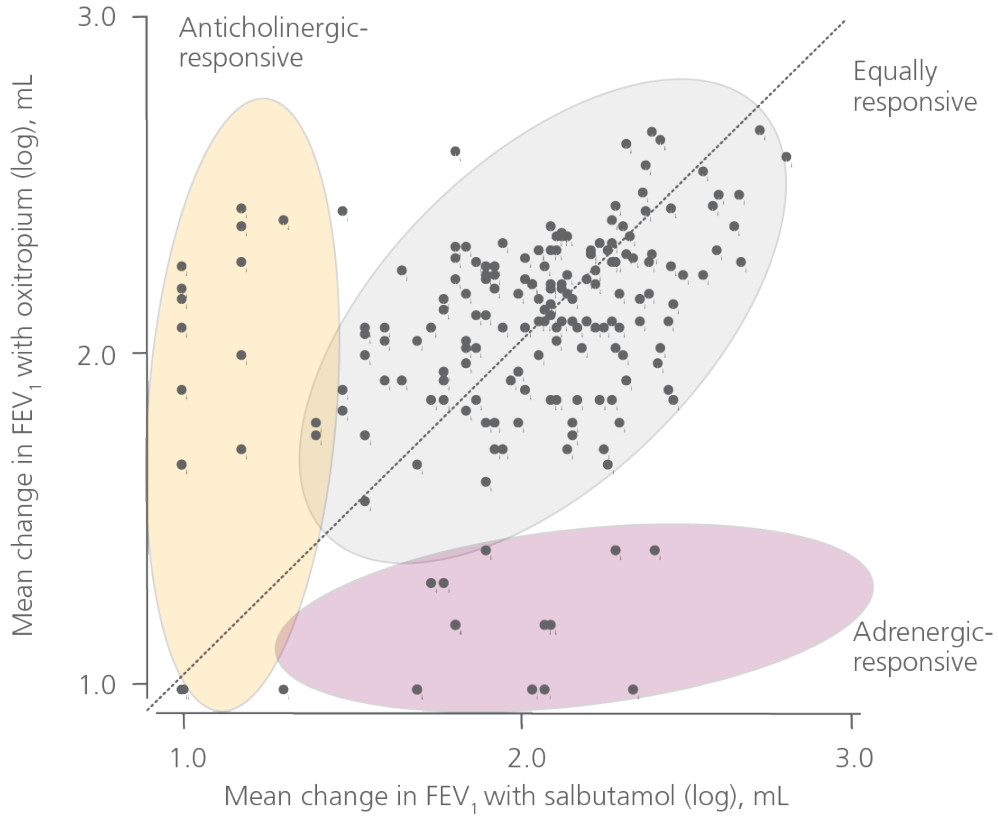


Adapted from Gardenhire, 2016 and Pelaia *et al*. 2014

1. Barnes, *Proc Am Thorac Soc* 2004;1:345-51
2. Nardini *et al*. Multidiscip Respir Med. 2014.
3. Gardenhire, Elsevier Mosby. 2016.
4. Pelaia *et al*. Multidiscip Respir Med. 2014.

Some individuals respond preferentially to anticholinergic than adrenergic agents and vice versa[1]

Intraindividual association between β2-adrenergic receptor gene of the prebronchodilator index (ΔFEV_1 salbutamol) and β2-adrenergic receptor gene to oxytropium bromide (ΔFEV_1 oxy)[1]



n=111

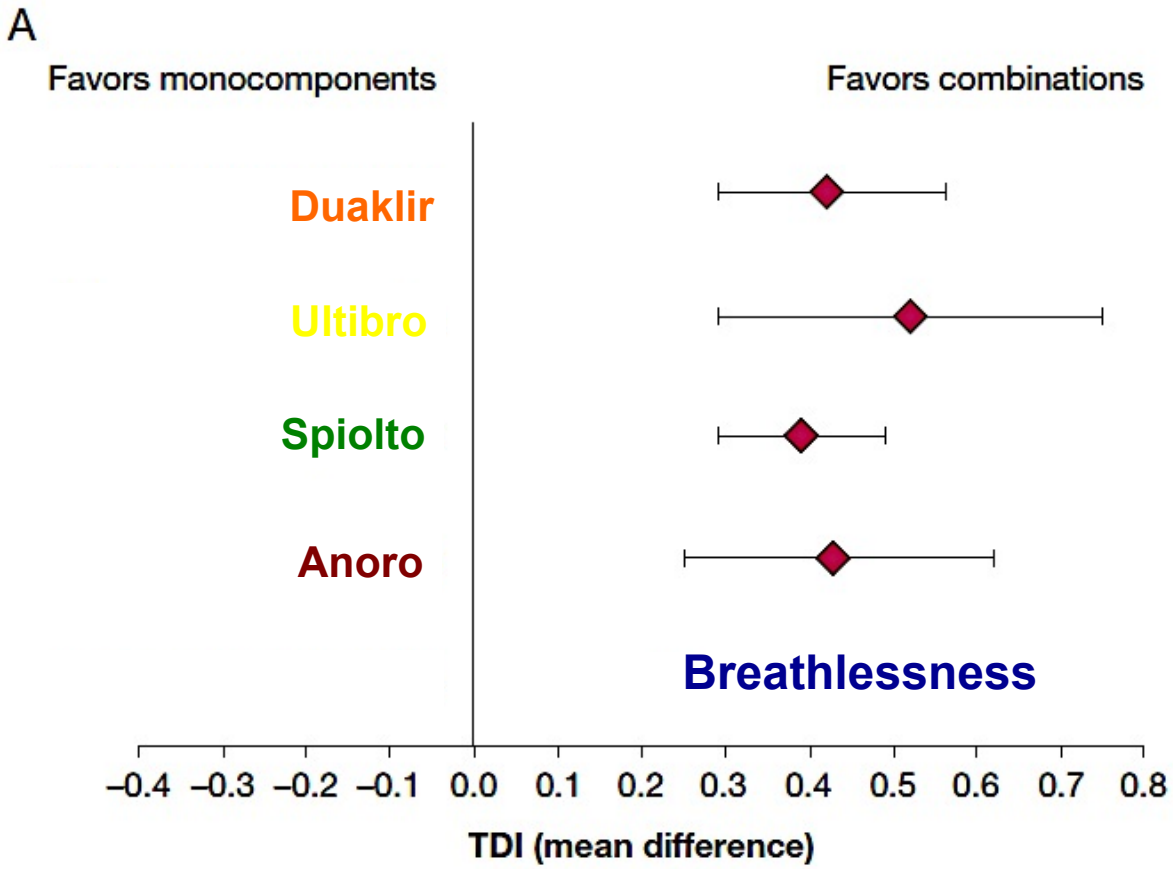
Dots on the line indicate equal ΔFEV_1 to the two agents.

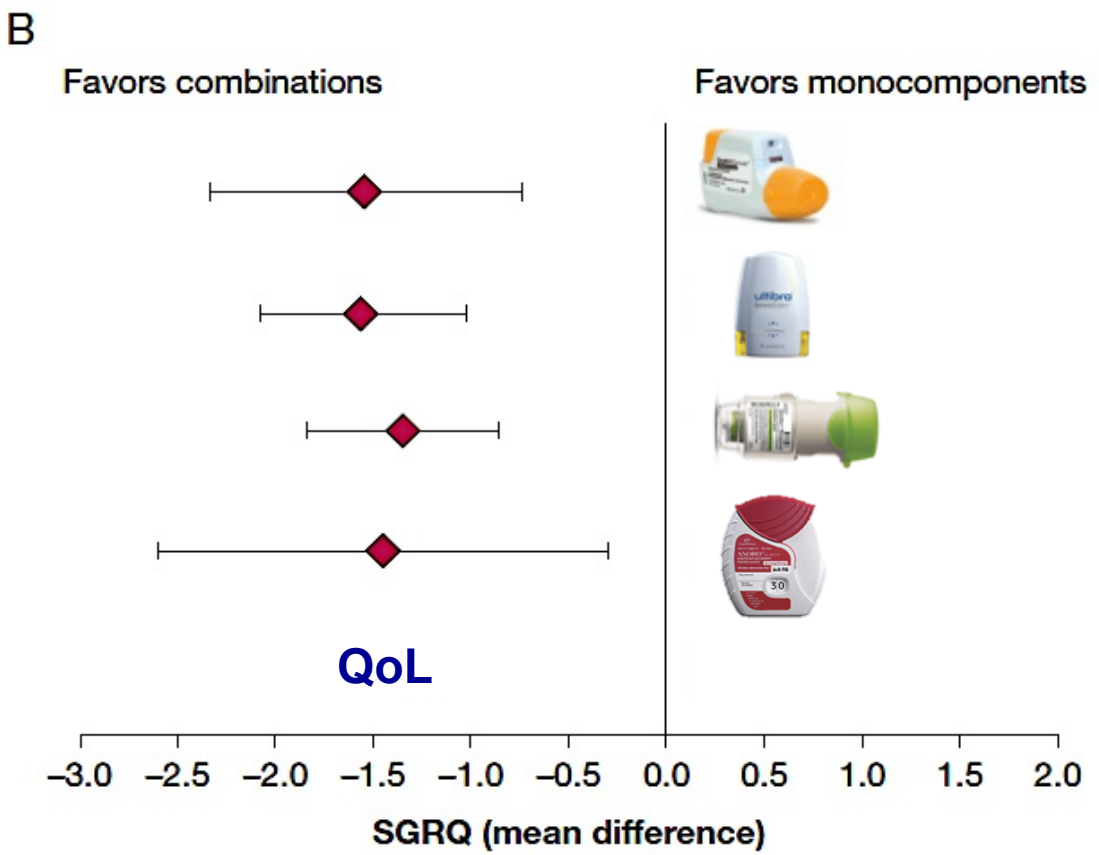
The objective of the study was to examine the association of ADRB2 polymorphisms and preferential BDR to β2-agonists and anticholinergics in patients with COPD. Participants were enrolled in the Hokkaido COPD cohort study. BDR to either class of bronchodilators (salbutamol or oxytropium, 0.4 mg) was measured every 6 months for 2 years. When patients were classified into two groups based on the bronchodilator causing better response (salbutamol -dominant group and oxytropium-dominant group) Arg allele was significantly more common in the oxytropium-dominant group the in salbutamol-dominant group ($0.001<p<0.05$).

1. Konno *et al*. Pharmacogenet Genomics.2011.

Dual bronchodilation is more effective than monobronchodilation[1]

Forest plot meta-analysis on trough TDI and SGRQ of LAMA/LABA combinations *vs* monocomponents [1]

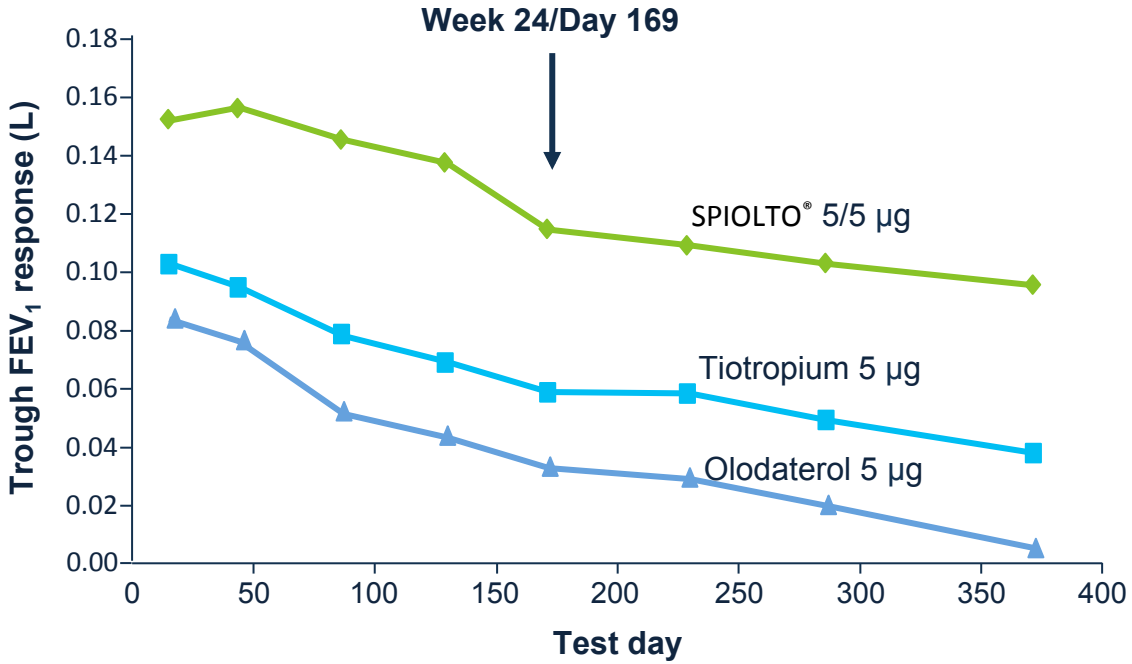




The objective of the study was to assess the influence of LABA/LAMA combinations on trough FEV_1, TDI SGRQ and cardiac safety vs monocomponents. The primary endpoint of this meta-analysis was to assess the effectiveness of LAMA/LABA combinations in modulating the change from baseline in trough FEV_1, *vs* monocomponents. Randomised clinical trials were identified searching from different databases of published and unpublished trials. Fourteen papers and 1 congress abstract with 23,168 COPD patients were included.

1. Calzetta *et al*. Chest. 2016.

Tiotropium and olodaterol (Spiolto) fixed dose combination versus mono-components in COPD (GOLD 2-4) Buhl et al ERJ 2015, 45; 969-979

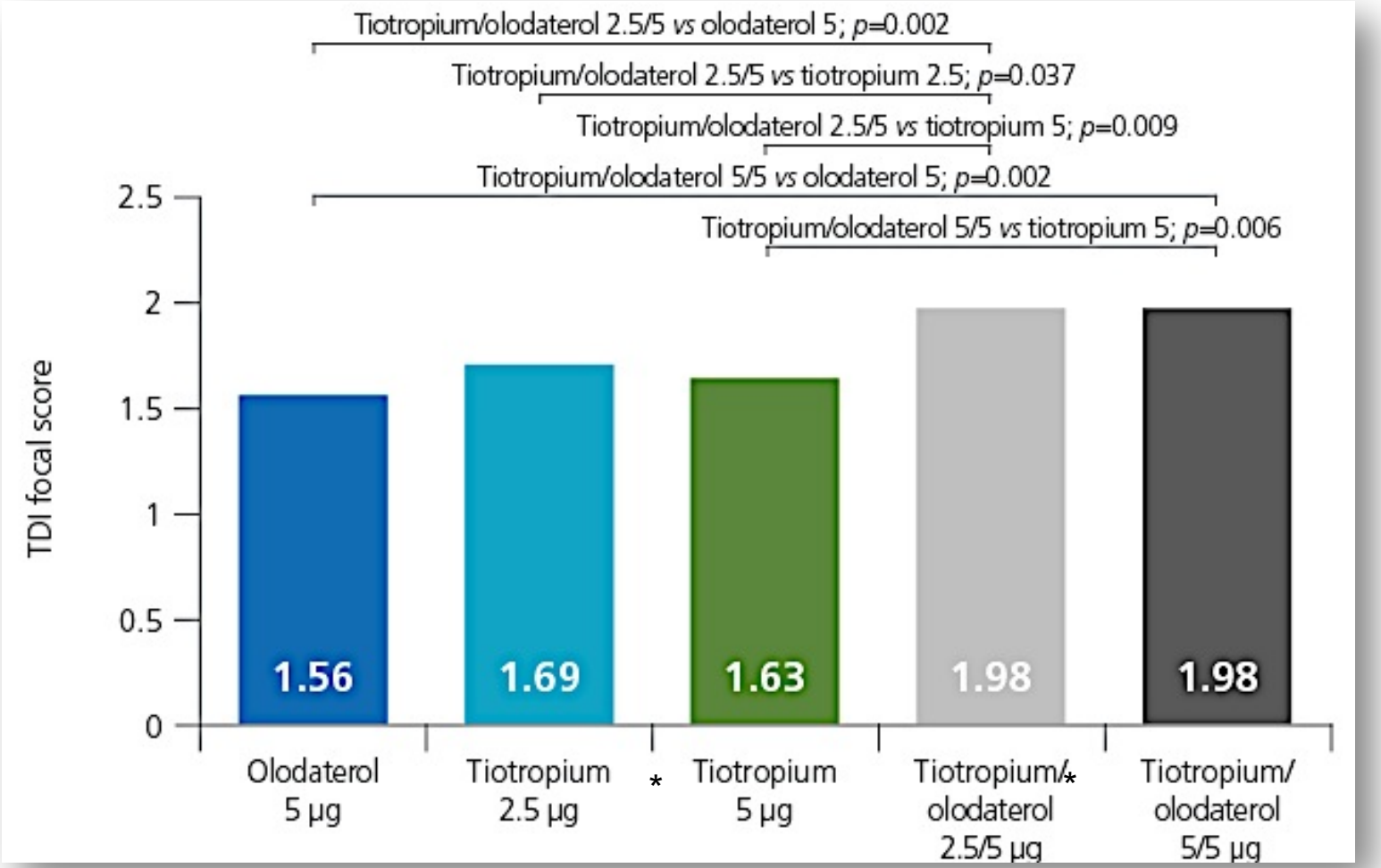


14% improved endurance during cycle ergometry vs placebo(difference of 63.9 sec p=0.021)

Treatment	SGRQ total score adjusted mean (SE) – full analysis set	Change from baseline, units	Adjusted mean (SE) change vs olodaterol 5 µg, units (p value)	Adjusted mean (SE) change vs tiotropium 5 µg, (p value)
Baseline	43.5 (0.26)			
Olodaterol 5 µg	38.4 (0.40)	-5.1		
Tiotropium 5 µg	37.9 (0.39)	-5.6		
Tiotropium + olodaterol 5/5 µg	36.7 (0.39)	-6.8	-1.693 (0.553) [p = 0.0022]	-1.233 (0.551) [p = 0.0252]

LAMA/LABA are effective in improving breathlessness *vs* monotherapies[1]

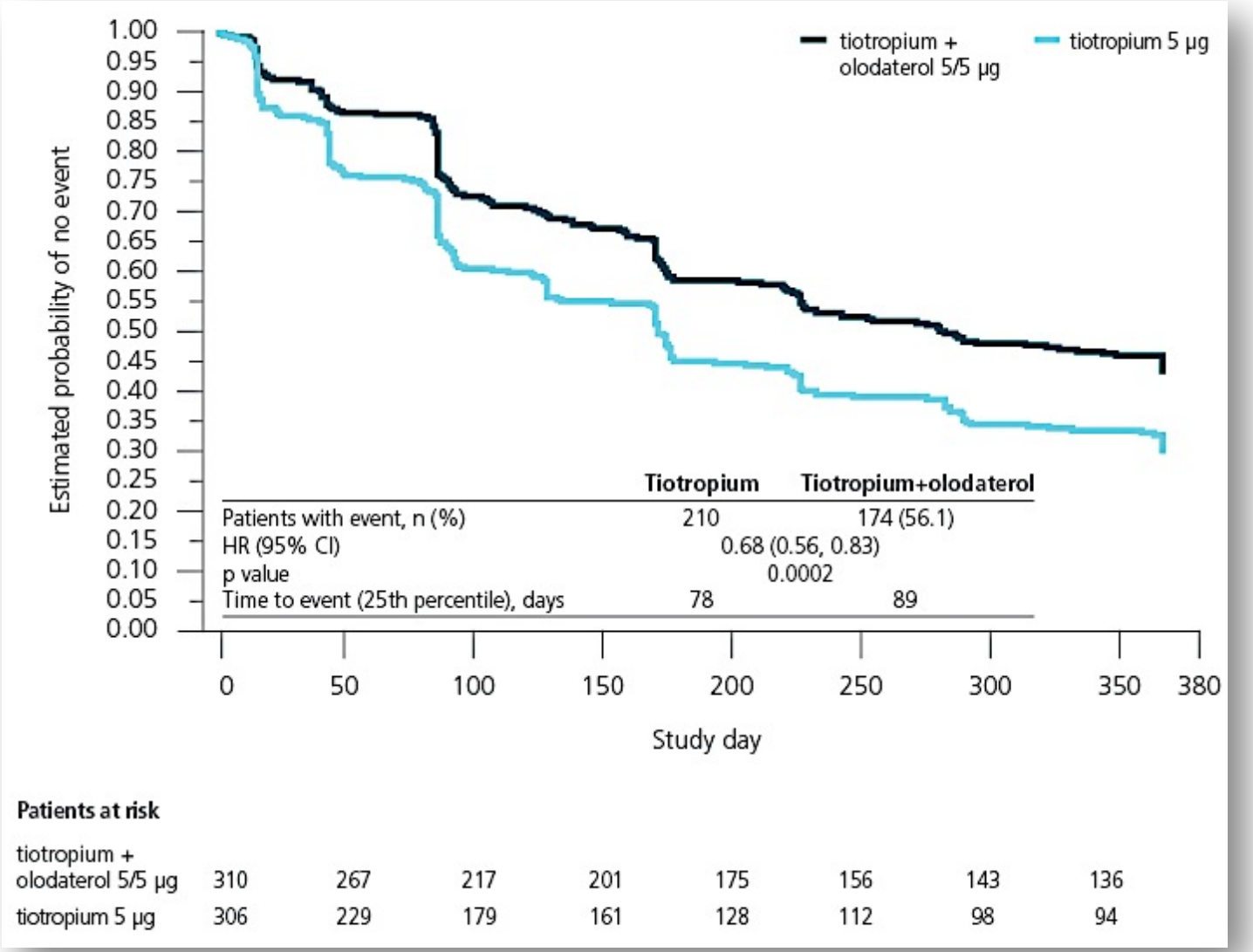
Adjusted mean Mahler TDI focal score at 24 weeks [1]



Two multinational, replicate, phase III, multicentre, randomised, double-blind, active-controlled, five-arm, parallel-group studies. Three primary endpoints were FEV_1 $AUC_{0–3}$ response in each individual trial, trough FEV_1 response in each individual trial and SGRQ total score. These endpoints were evaluated after 24 weeks of treatment. A total of 5163 patients (2624 Study 1237.5; 2539 Study 1237.6) were randomised.
*Unlicensed dose

1. Buhl *et al.* Eur Respir J. 2015
2. Maltais F et al: ERJ 2014;44 P283

LAMA/LABA are effective in reducing the risk of clinically important deterioration *vs* monotherapy[1]



	Tiotropium	Tiotropium+olodaterol
Patients with event, n (%)	210	174 (56.1)
HR (95% CI)	0.68 (0.56, 0.83)	
p value	0.0002	
Time to event (25th percentile), days	78	89

Patients at risk

tiotropium + olodaterol 5/5 µg	310	267	217	201	175	156	143	136
tiotropium 5 µg	306	229	179	161	128	112	98	94

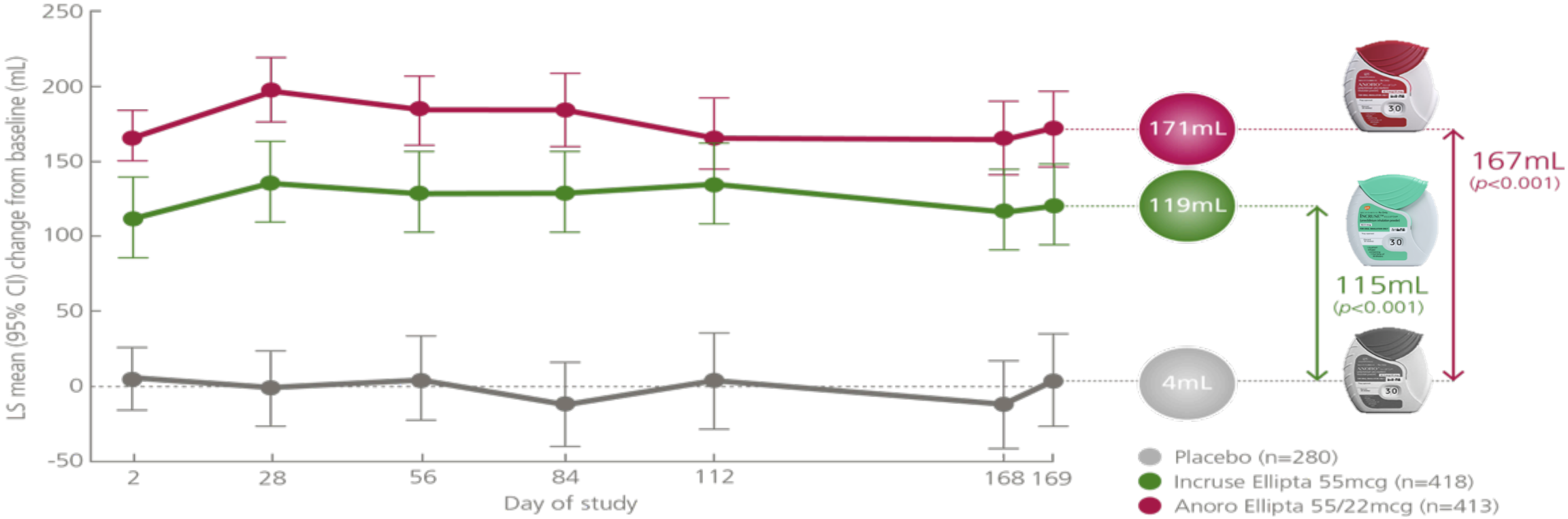
N= 5162. Post hoc analysis of the TONADO studies with the objective of investigate whether tiotropium/olodaterol is more effective than tiotropium at delaying clinically significant events in patients with GOLD stage B COPD (symptomatic COPD and a low risk of exacerbations).

1. Buhl *et al.* ATS. 2016.

Incruse Ellipta improves lung function vs placebo

Primary Endpoint: Trough FEV_1

Change from baseline in trough FEV_1 over 24 weeks[1]

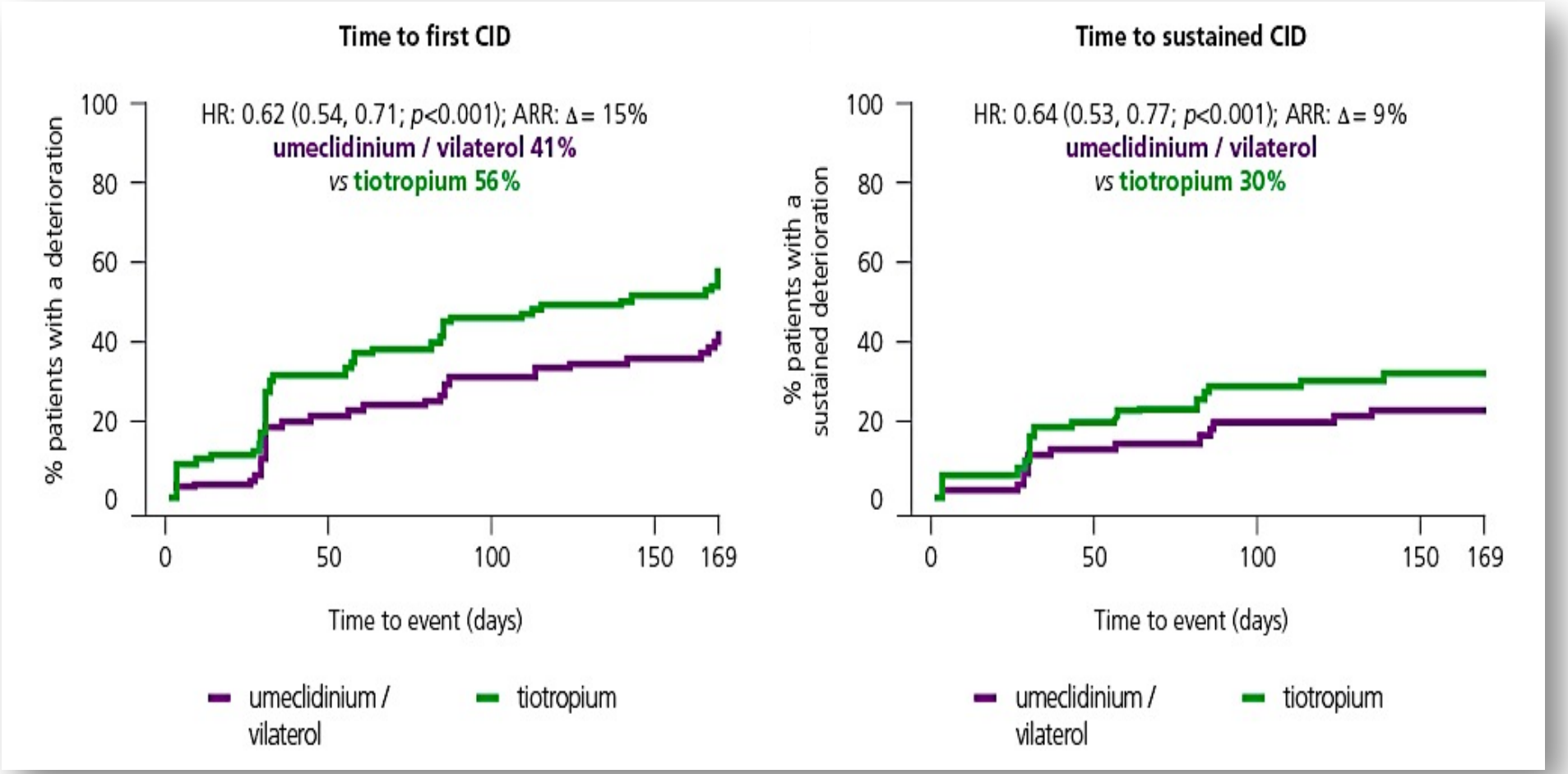


Adapted from Donohue JF *et al.* 2013.[2]

This was a pivotal study of Anoro Ellipta 55/22mcg (UMEC/vilanterol), in which Anoro Ellipta showed significantly greater improvements in trough FEV_1 compared with Incruse Ellipta (p=0.004)[1]

Reference: 1. Donohue JF *et al. Resp Med* 2013; 107:1538–1546.

LAMA/LABA are effective in reducing the risk of clinically important deterioration *vs* monotherapy[1]

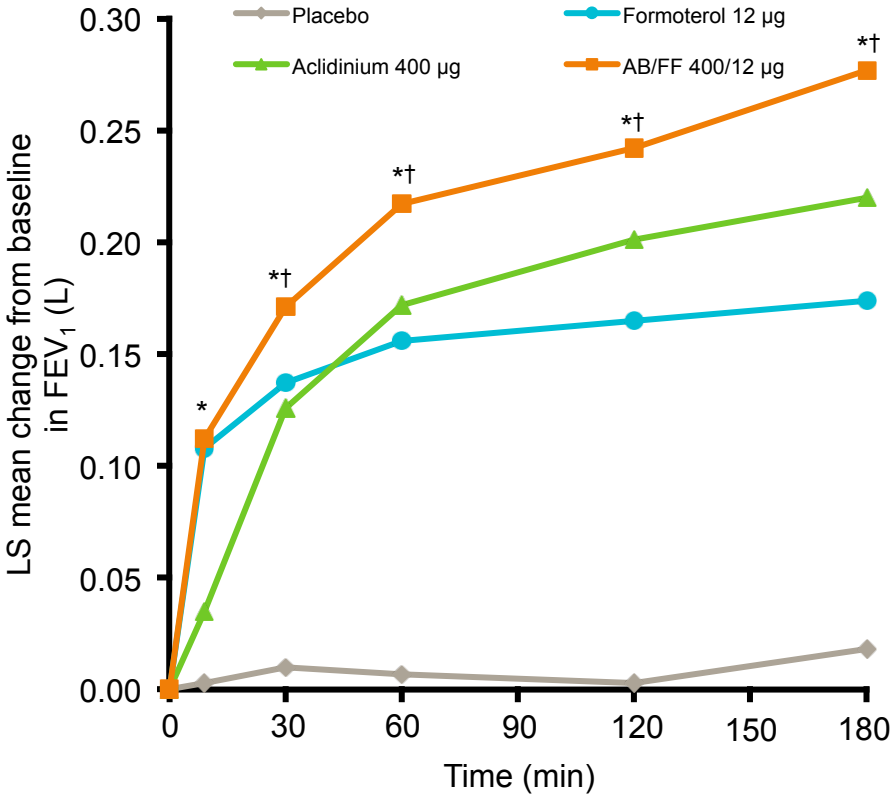


N= 1747. *Post hoc* analysis of data from three phase III multicentre, randomised, blinded, parallel-group, 24-week trials comparing once-daily inhaled umeclidinium/vilanterol 62.5/25 mcg* *vs* TIO 18 mcg.

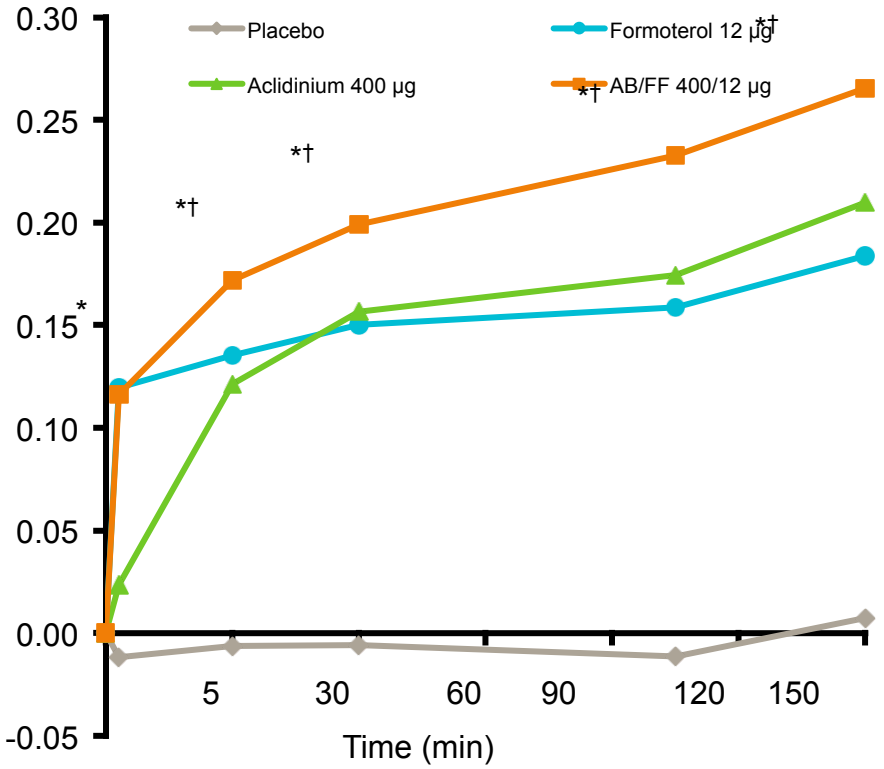
1. Singh *et al.* ERS. 2015.

ACLIFORM and AUGMENT: change from baseline in FEV_1 over 3 hours post-dose on Day 1

ACLIFORM[1]



AUGMENT[2]



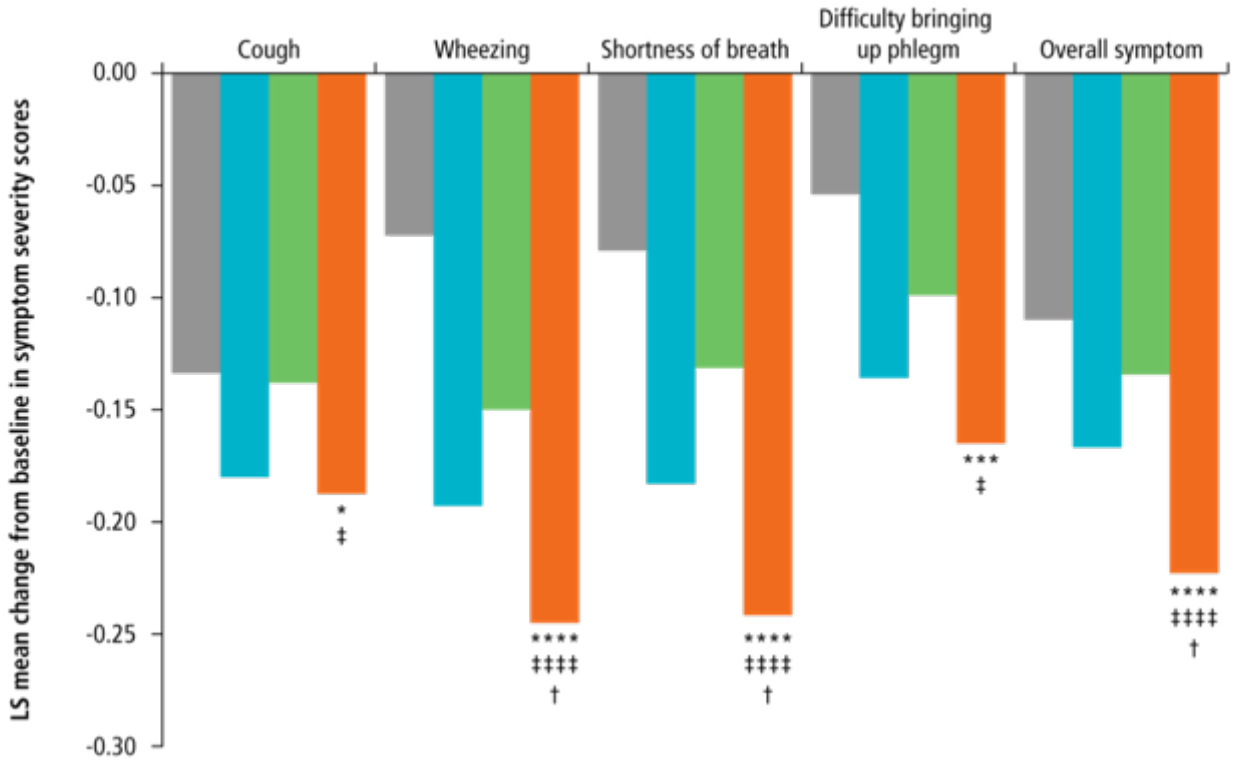
- AB/FF 400/12 µg demonstrates rapid bronchodilatory effects (within 5 minutes of the first inhalation) relative to placebo and to aclidinium ($p<0.05$) and comparable to formoterol

*$p<0.05$ vs placebo and aclidinium; †$p<0.05$ vs formoterol

[1]Singh et al. *BMC Pulm Med* 2014;
[2]D'Urzo et al. *Respir Res* 2014

Change in morning symptoms of COPD: pooled data

- Duaklir® was associated with an improvement in early-morning symptom control of COPD compared to its individual components[1,2]



Placebo

Formoterol fumarate 12 µg

Aclidinium bromide 322 µg

Aclidinium bromide/ Formoterol fumarate 340/12

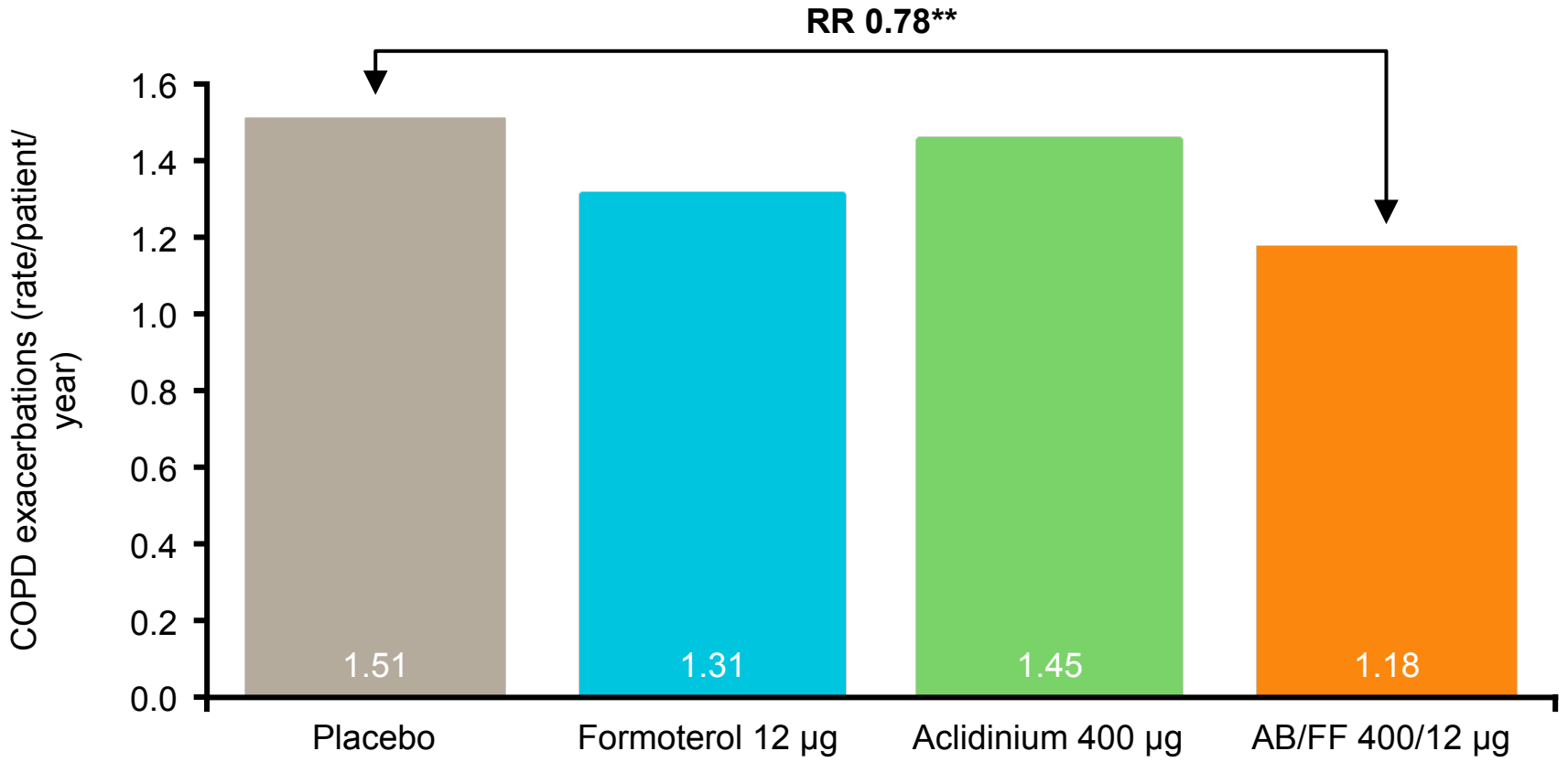
*p<0.05; ***p<0.001, ****p<0.0001 vs placebo; †p<0.05 vs formoterol fumarate, ‡p<0.05, ‡‡‡‡p<0.001 vs aclidinium bromide

LS = least squares
Note: The clinical trials investigated the 340/12 and 400/6 combinations, but only the 340/12 dose is licensed for use in patients with COPD and shown in this figure.

1. Bateman E *et al. Resp Res* 2015; 16: 92.
2. AstraZeneca. Data on File: ABF/011/Nov14.

Pooled ACLIFORM/AUGMENT: rate of any COPD exacerbations (EXACT questionnaire)

Analysis of the rate of exacerbations was assessed as a secondary outcome, based on the pooled data from ACLIFORM and AUGMENT (3,394 patients), as the studies were not powered to look at exacerbations, and as the study populations were not enriched for exacerbations, the rate of exacerbation was relatively low. As shown here, treatment with Duaklir® was associated with a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (based on healthcare resource utilisation [HCRU] criteria) compared with placebo ($p<0.05$) and a risk reduction of 24% for exacerbations of any severity, although this did not reach significance[1]



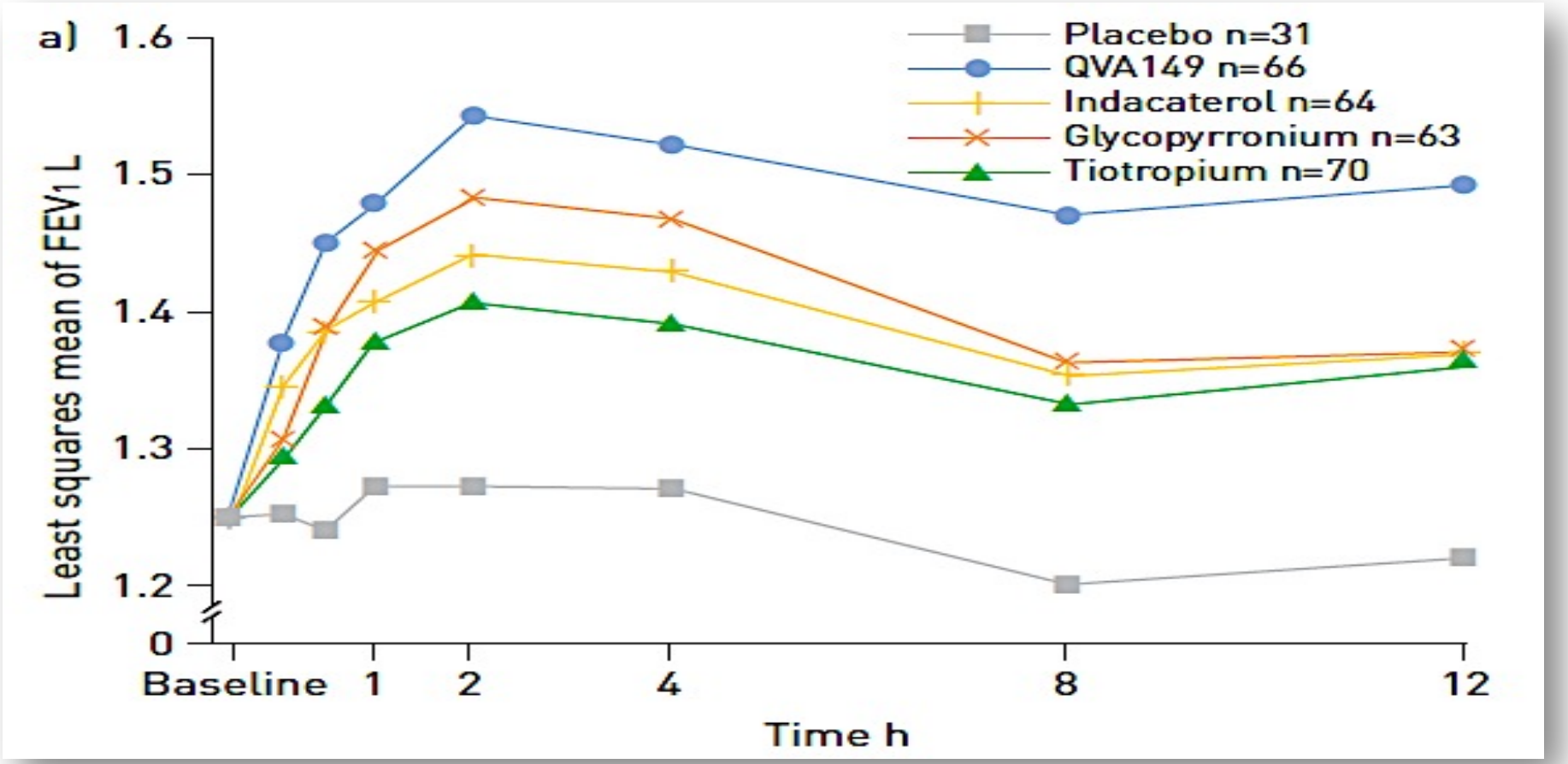
- AB/FF 400/12 µg demonstrates a statistically significant reduction of 22% in the rate of any exacerbations compared with placebo ($p<0.01$)

**$p<0.01$ vs placebo

An EXACT exacerbation was defined as a persistent increase from baseline in total EXACT score of ≥9 points for ≥3 days or ≥12 points for ≥2 days.

[1]Bateman et al. Respir Res 2015

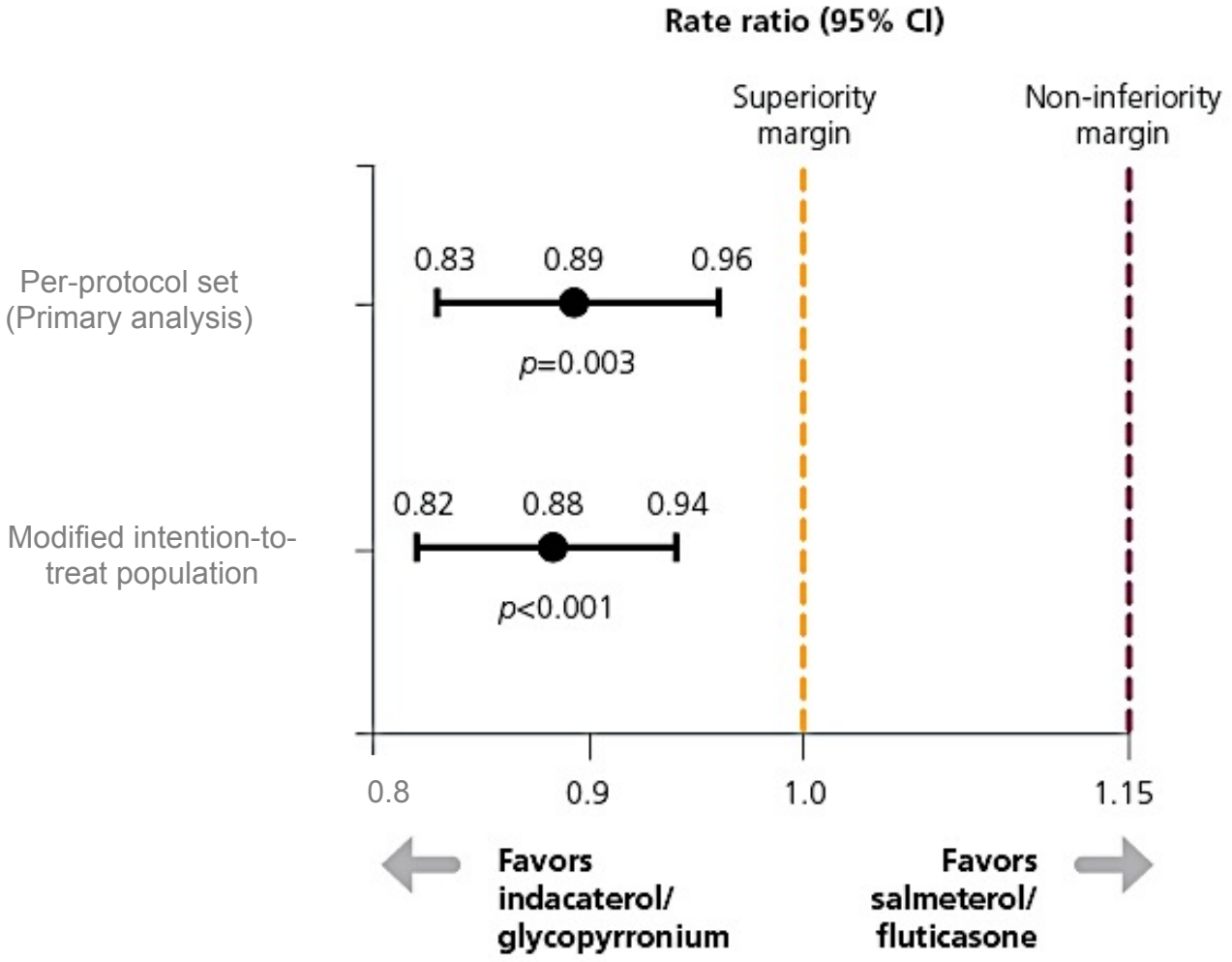
Dual bronchodilation with glycopyrronium/indacaterol (Ultibro Breezhaler ▼) versus single bronchodilator therapy: the SHINE study



Gly/ind still superior at 26 weeks

Eur Respir J 2013; 42: 1484–1494

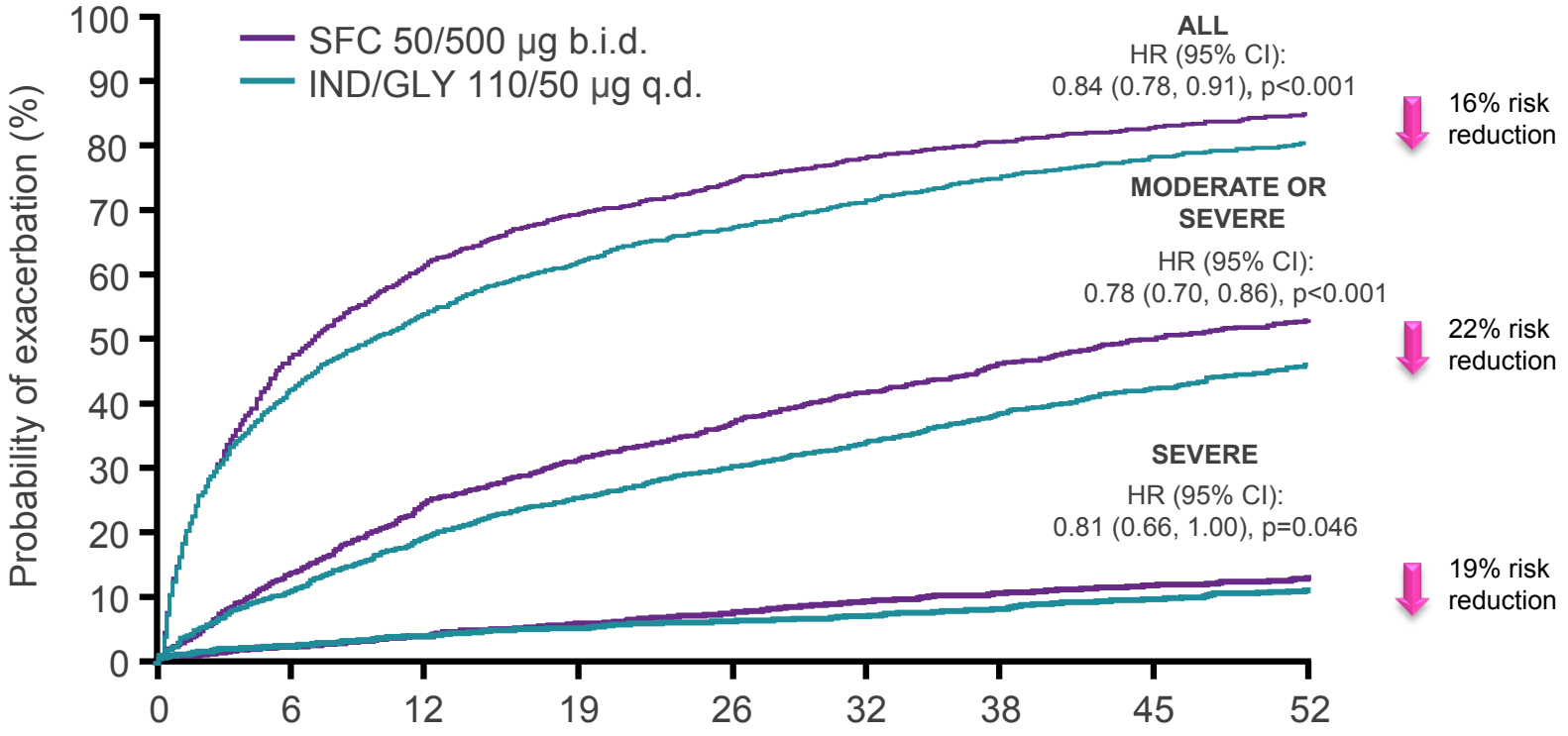
LAMA/LABA are effective in preventing all COPD exacerbations *vs* LABA/ICS over 52 weeks[1]



n = 1682
52-week trial in patients who had COPD with a history of at least one exacerbation during the previous year. The primary outcome was the annual rate of all COPD exacerbations.

1. Wedzicha *et al.* N Engl J Med. 2016.

LAMA/LABA are effective in reducing time to first COPD exacerbation *vs* LABA/ICS over 52 weeks[1]



Patients at risk						
ALL	IND/GLY	1675	763	535	409	281
	SFC	1679	642	415	313	217
MODERATE OR SEVERE	IND/GLY	1675	1299	1091	948	711
	SFC	1679	1210	975	820	608
SEVERE	IND/GLY	1675	1530	1434	1368	1138
	SFC	1679	1507	1389	1303	1071

1. Wedzicha *et al.* N Engl J Med. 2016.

STEROID/LABA COMBINATIONS

WHAT ARE THEY FOR?

Annual Exacerbation Rates from Other LABA/ICS Studies

- **Vivace (post-BD <50% predicted w/Hx exacerbations)** (p<0.0001)
  - Seretide(500) 0.92 vs 1.4 salmeterol (34% reduction)

- **Symbicort COPD Studies (≤ 50% predicted FEV_1 w/Hx exacerbations)**
  - Symbicort 1.3 vs 1.85 formoterol (30% reduction; Calverley et. al. p<0.05)
  - Symbicort 1.42 vs 1.84 formoterol (23% reduction; Szafranski et.al. p<0.043)

- **TRISTAN (25 to 75% predicted, Hx exacerbations)**
  - Seretide(500) 0.97 vs. 1.04 salmeterol (7% reduction)

- **TORCH (All patients, < 60% predicted)** (p<0.002)
  - Seretide (500) 0.85 vs. 0.97 salmeterol (12% reduction)

- **TORCH <50% Predicted**
  - Seretide 0.97 vs. 1.09 salmeterol (11% reduction)

  - *The primary end-point in the TORCH study (all cause mortality) was not met*

Risk of hospitalisation for pneumonia associated with current use, past use, and dose of ICS

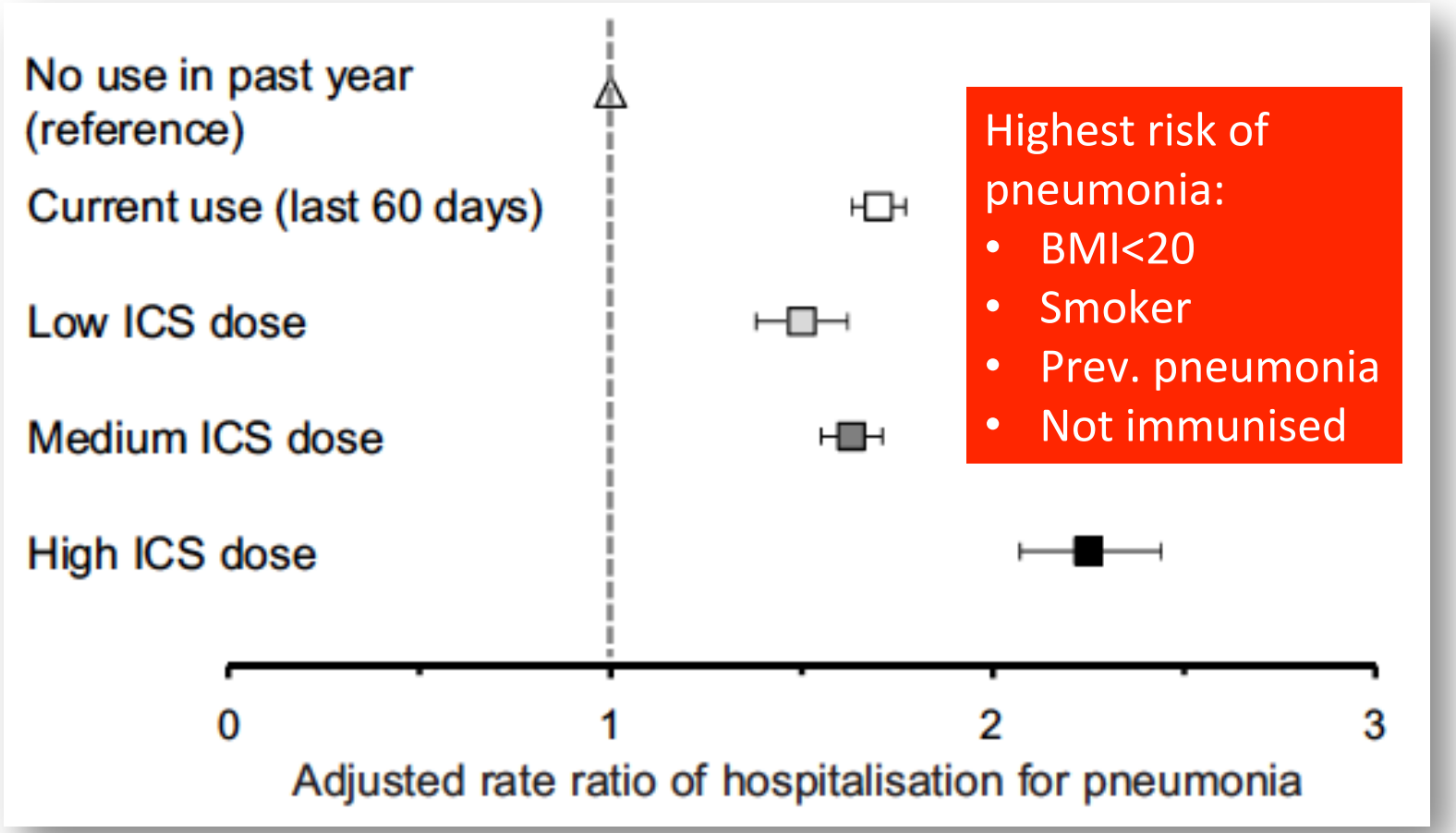
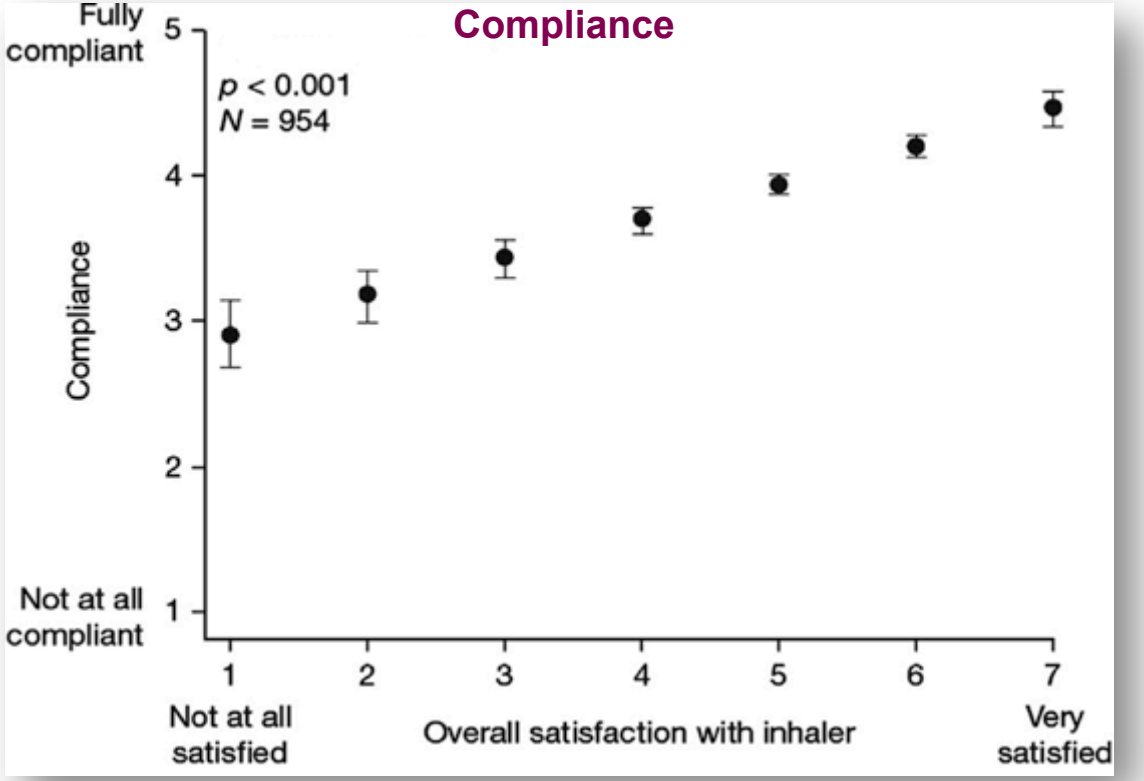
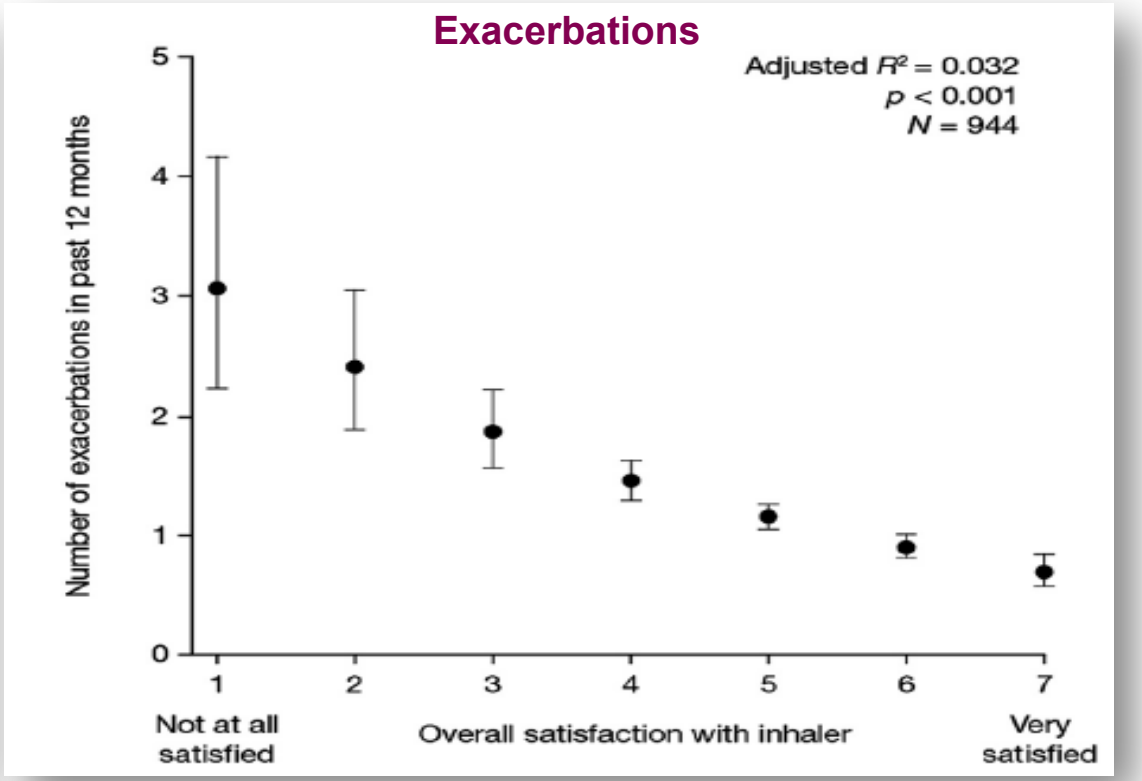


Figure adapted from data extracted from Price et al. 2013. **ICS monotherapy inhalers are not licensed for management of COPD in the UK.**

Prim Care Respir J 2013; 22(1): 92-100

Greater patient inhaler satisfaction is associated with higher compliance and better treatment outcomes





Relationship between patient-rated inhaler satisfaction and physician assessed treatment compliance in COPD patients.

Large, multinational, cross-sectional, real-world survey, respiratory specialists and primary care physicians provided information on six consecutive patients with COPD, who were then asked to complete a questionnaire. n: 1443 patients

Chrystyn H et al. Respir Med 2014;108

Comparing Devices

RISK	SYMPTOMS (choose highest score)	
Exacerbations per year	mMRC 0 - 1 or CAT < 10	mMRC ≥ 2 or CAT ≥ 10
≥ 2	HIGH RISK: LESS SYMPTOMS (C) / MORE SYMPTOMS (D) ICS/LABA (1st line) or LAMA/LABA (2nd line if high risk with ICS) ↓ (escalating) ICS/LABA + LAMA	
≤ 1	LOW RISK: LESS SYMPTOMS (A) SABA and/or SAMA ↓ (escalating) LAMA (stop SAMA) or LABA	LOW RISK: MORE SYMPTOMS (B) LAMA (stop SAMA) ↓ (escalating) LAMA/LABA

BNSSG Primary Care COPD Treatment Guidelines (Adults) July 2015

Device	Image*	LABA**	LAMA	LABA / LAMA	ICS / LABA
Breezhaler® - Dry powder inhaler re-quiring capsule ma-nipulation Hard/fast inhalation		Indacaterol 150 or 300 micrograms 1 puff daily (Onbrez®)	Glyco-pyrronium 1 puff daily (Seebri®)	Indacaterol/ Glyco-pyrronium 1 puff daily (UltiBro®)	X
Ellipta® - Dry powder inhaler Hard/fast inhalation		X	Umeclidinium 1 puff daily (Incruse®)	Umeclidinium/ Vilanterol 1 puff daily (Anoro®)	Fluticasone fu-roate / vilanterol 92/22 only 1 puff daily (Relvar®)
Genuair® - Dry pow-der inhaler Hard/fast inhalation		X	Aclidinium 1 puff twice day (Eklira®)	Formoterol / Aclidinium 1 puff twice day (Duaklir®)	X
pMDI - Pressurised metered dose inhaler co- ordinated actua-tion & inhalation Slow/long inhalation		Formoterol 1 -2 puffs twice daily (Atimos mod-ulite®)	X	X	Beclometasone/ Formoterol 2 puffs twice daily (Fostair®)
Easyhaler®- Dry pow-der inhaler Hard/fast inhalation		Formoterol 1 puff twice daily (Easyhaler®)	X	X	X
Respimat® - Soft Mist requires co-ordinated actuation inhalation Slow/long inhalation		Olodaterol 2 puffs once daily (Striverdi®)	Tiotropium 2 puffs once daily (Spiriva®)	Tiotropium/ olodaterol 2 puffs oncc daily (Spiolto®)	X
Spiromax® - Dry pow-der inhaler Hard/fast inhalation		X	X	X	Budesonide/ for-moterol 320/9 twice daily (DuoResp®)

Choose inhaler according to patient characteristics and preferences

Summary

- Bronchodilators are the cornerstone of COPD maintenance treatment
- Dual bronchodilation with LABA/LAMA may help avoid the inappropriate use of ICS in some patients
- Reserve LABA/ICS for those exacerbating regularly (licenced indication!) and those whose COPD may have an asthmatic component

Tapering to Dry Powder Inhalers (DPIs) - Breezhaler®, Ellipta® or Genuair®

NHS
Bristol
North Somerset
South Gloucestershire

1st visit

2nd visit

1st Month	2nd Month	3rd Month

(i) Planned end inhaler

LABA/LAMA or single agent LAMA or LABA (if contraindications to either)

Start and continue final bronchodilator / bronchodilator combination

(ii) Inhaled ICS/LABA Combination

Inhaled corticosteroid tapering to a stop

	1st Month	2nd Month	3rd Month
High dose ICS including; **Relvar® 92/22** one puff od **Seretide® 500 Accuhaler** one puff bd **Seretide® 250 Evohaler** two puffs bd	**Beclometasone Easyhaler® 100** Two puff BD ***OR*** **Pulmicort® Turbohaler® 100** Two puff BD	**Beclometasone Easyhaler® 100** One puff BD ***OR*** **Pulmicort® Turbohaler® 100** One puff BD	**Beclometasone Easyhaler® 100** One puff OD ***OR*** **Pulmicort® Turbohaler® 100** One puff OD
Intermediate dose ICS including; **Symbicort® 400/12** one puff bd or **200/6** two puffs bd **DuoResp® 320/9** one puff bd or **160/4.5** two puffs bd			
Low dose ICS including; **Fostair® 100/6** up to one puff BD (**Fostair® 100/6** 2 puff BD or **Fostair® 200/6** 1 – 2 puff BD treat as intermediate dose ICS)			

STOP INHALED STEROIDS

Designed by Dr James Calvert in conjunction with BNSSG Medicines Management Pharmacists July 2016
v1.0. Review July 2018

Tapering to Pressurised metered dose inhaler - (pMDI) or Respimat®

NHS Bristol North Somerset South Gloucestershire

1st visit

2nd visit

1st Month	2nd Month	3rd Month

(i) Planned end inhaler

LABA/LAMA or single agent LAMA or LABA (if contraindications to either)

Start and continue final bronchodilator / bronchodilator combination

(ii) Inhaled ICS/LABA Combination

High dose ICS including;
Relvar® 92/22 one puff od
Seretide® 500 Accuhaler one puff bd
Seretide® 250 Evohaler two puffs bd

Intermediate dose ICS including;
Symbicort® 400/12 one puff bd or **200/6** two puffs bd
DuoResp® 320/9 one puff bd or **160/4.5** two puffs bd

Low dose ICS including;
Fostair® 100/6 up to one puff BD
(**Fostair® 100/6** 2 puff BD or **Fostair® 200/6** 1 – 2 puff BD treat as intermediate dose ICS)

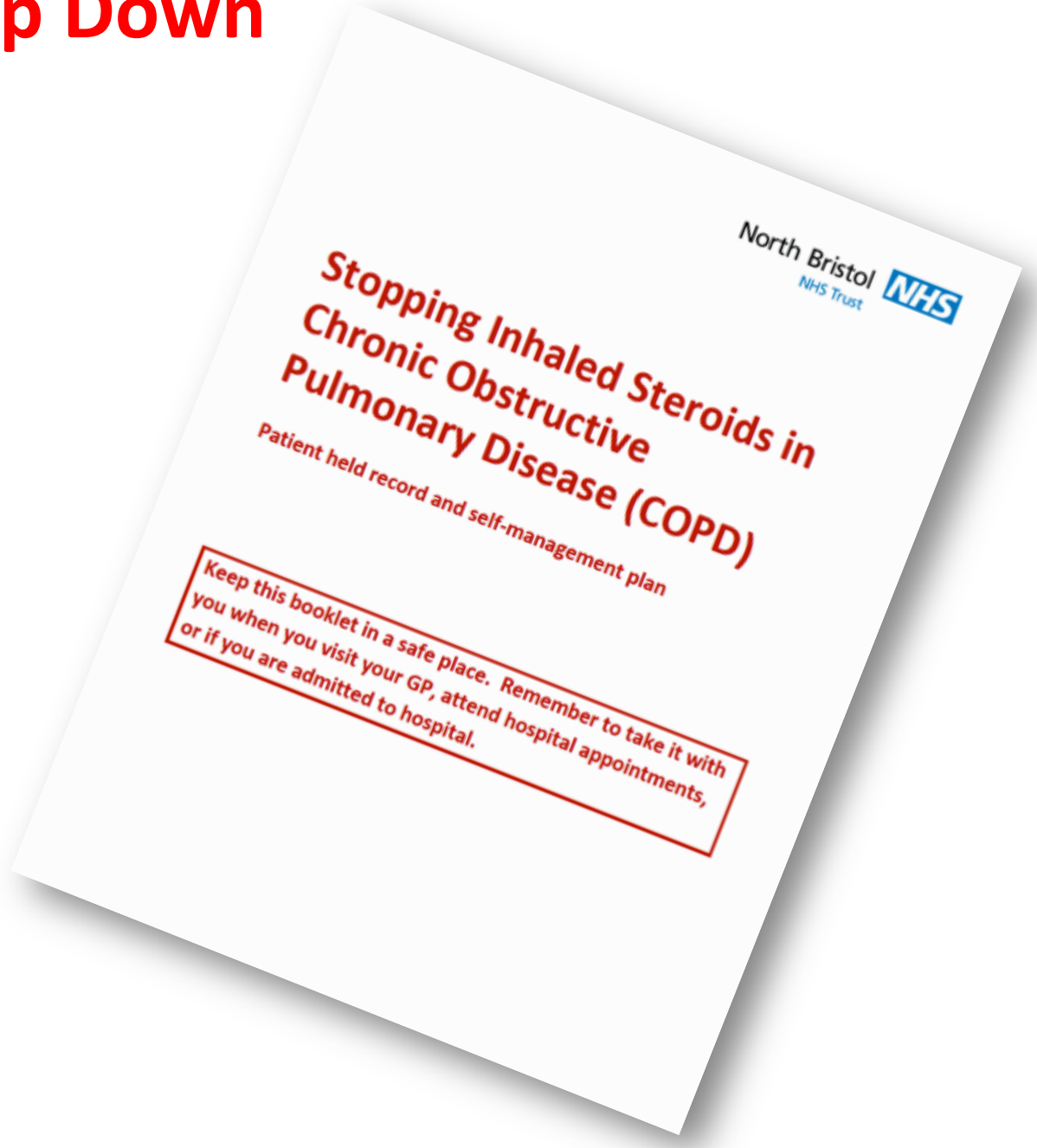
Inhaled corticosteroid tapering to a stop

Clenil® Easybreathe 100 Two puffs BD	**Clenil® Easybreathe 100** One puff BD	**Clenil® Easybreathe 100** One puff OD

STOP INHALED STEROIDS

Designed by Dr James Calvert in conjunction with BNSSG Medicines Management Pharmacists July 2016
v1.0. Review July 2018

BNSSG Step Down Protocol



November 2016