CON: De-escalation of Triple Therapy in COPD

Ki Uk Kim
Department of Internal Medicine
Pusan National University Hospital

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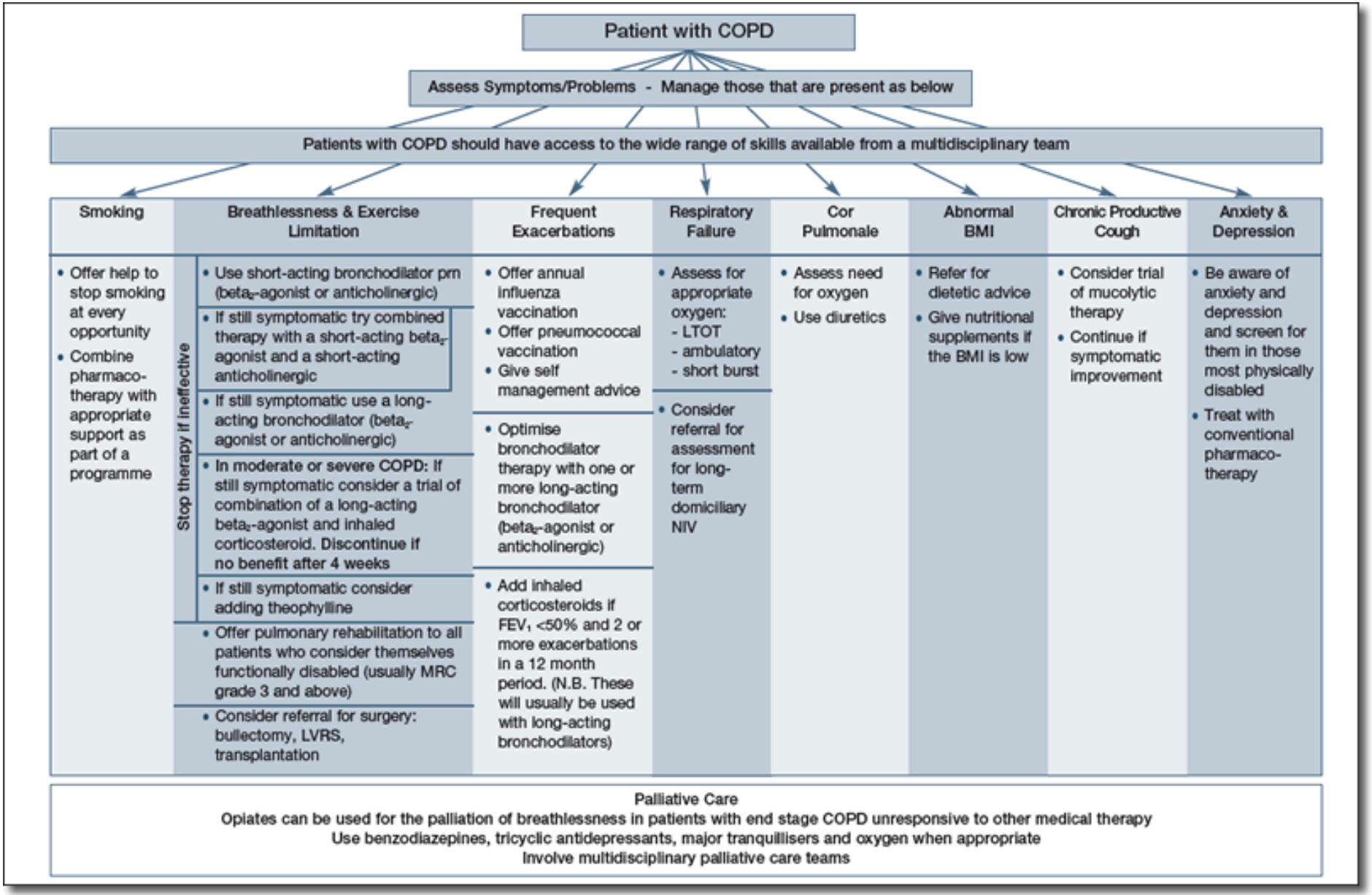
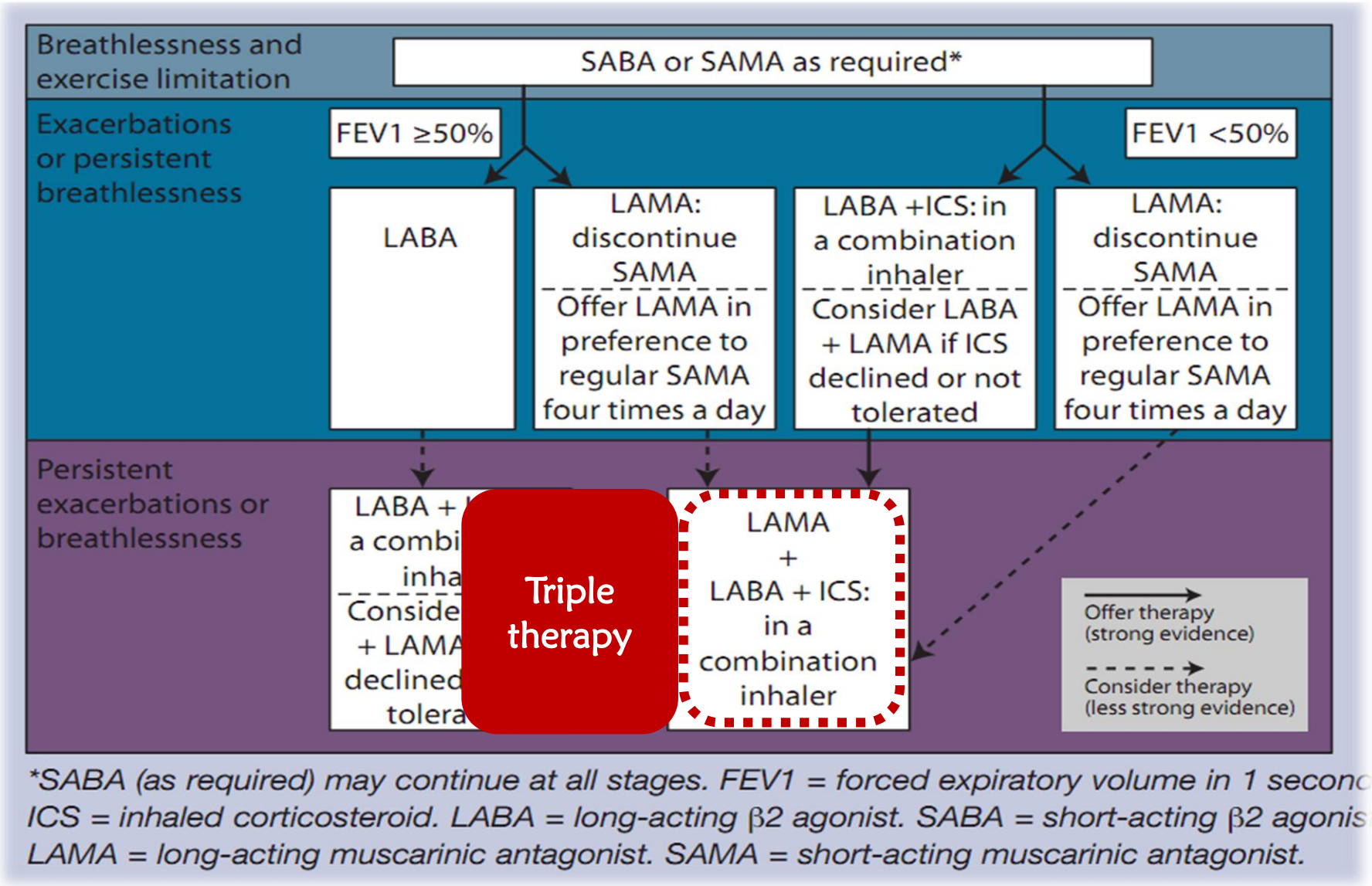
NICE 2004 guidelines



NICE 2010 guidelines



*SABA (as required) may continue at all stages. FEV1 = forced expiratory volume in 1 secon
ICS = inhaled corticosteroid. LABA = long-acting β2 agonist. SABA = short-acting β2 agonis
LAMA = long-acting muscarinic antagonist. SAMA = short-acting muscarinic antagonist.

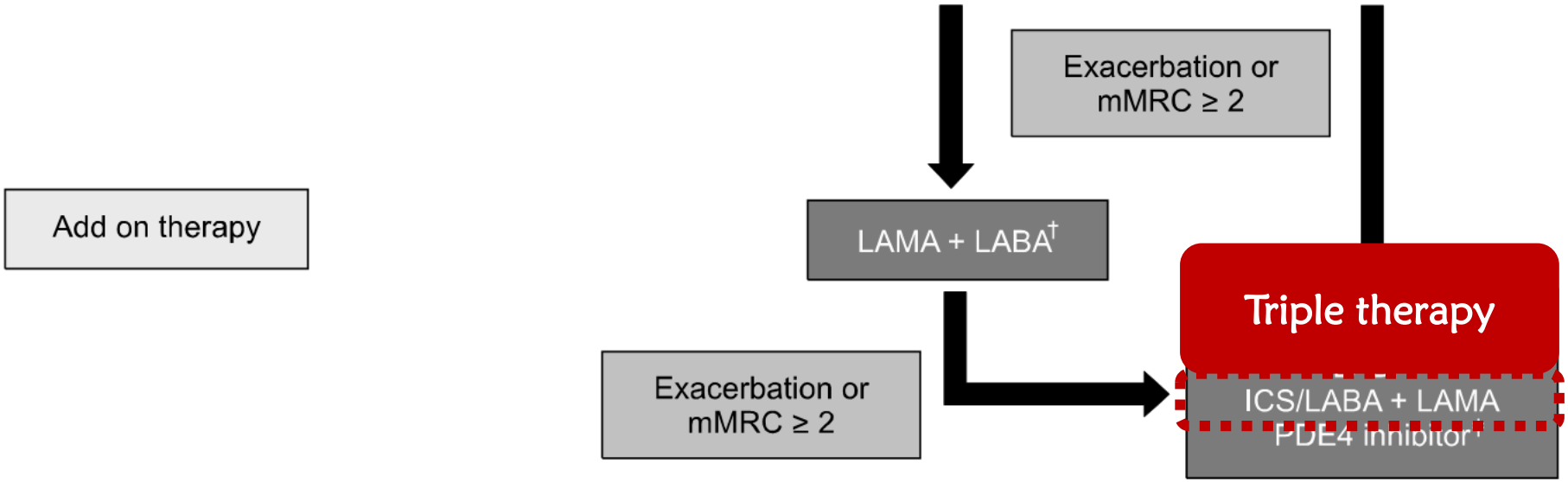
O'Reilly et al. BMJ 2010;340:c3134

Initial Pharmacologic Management GOLD 2016

Patient Group	First Choice	Alternative Choice	Other possible
A	SAMA or SABA prn	LAMA LABA SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS+LABA or LAMA	LAMA and LABA LAMA and PDE4 (-) LABA and PDE4 (-)	SAMA and/or SABA Theophylline
Triple therapy	ICS+LABA and/or LAMA	ICS+LABA and LAMA ICS+LABA and PDE4 (-) LAMA and LABA LAMA and PDE4 (-)	Carbocysteine N-acetylcysteine SAMA and/or SABA Theophylline

안정시 COPD 약물 단계치료 2014

	FEV_1 ≥ 60% pred. and 0~1 exacerbation/year		FEV_1 < 60% pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA



대한 결핵 및 호흡기학회, 2014

Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease

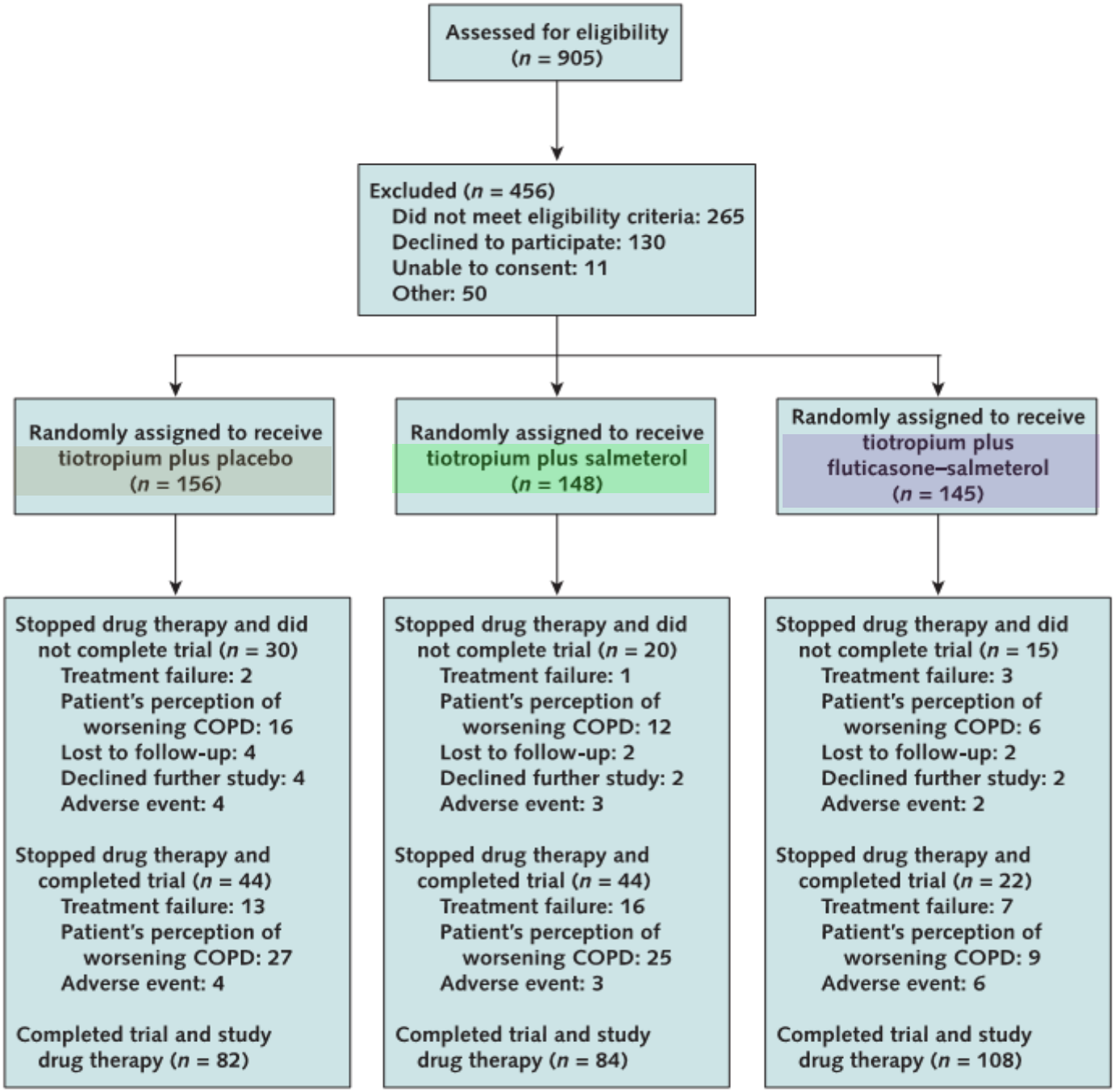
A Randomized Trial

Shawn D. Aaron, MD; Katherine L. Vandemheen, BScN; Dean Fergusson, PhD; François Maltais, MD; Jean Bourbeau, MD; Roger Goldstein, MD; Meyer Balter, MD; Denis O'Donnell, MD; Andrew McIvor, MD; Sat Sharma, MD; Graham Bishop, MD; John Anthony, MD; Robert Cowie, MD; Stephen Field, MD; Andrew Hirsch, MD; Paul Hernandez, MD; Robert Rivington, MD; Jeremy Road, MD; Victor Hoffstein, MD; Richard Hodder, MD; Darcy Marciniuk, MD; David McCormack, MD; George Fox, MD; Gerard Cox, MB; Henry B. Prins, MD; Gordon Ford, MD; Dominique Bleskie, BHScN; Steve Doucette, MSc; Irvin Mayers, MD; Kenneth Chapman, MD; Noe Zamel, MD; and Mark FitzGerald, MD, for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium

Ann Int Med 2007;146:545-55

- 1-yr randomized, double-blind, placebo-controlled trial
- Oct 2003 ~ Jan 2006 at 27 medical centers in Canada
- 449 subjects with moderate or severe COPD
  - FEV_1 < 65 % pred
  - ≥ 1 AE requiring systemic steroids and/or antibiotics/prev 1yr
- Primary end point

  : AECOPD requiring systemic steroids or antibiotics



Aaron et al. Ann Int Med 2007;146:545-55

Table 1. **Baseline Characteristics**

Characteristic	Tiotropium Plus Placebo (n = 156)	Tiotropium Plus Salmeterol (n = 148)	Tiotropium Plus Fluticasone–Salmeterol (n = 145)
Mean age (SD), *y*	68.1 (8.9)	67.6 (8.2)	67.5 (8.9)
Women, %	46.2	42.6	42.1
White, %	97.4	98.0	99.3
Body mass index (SD), kg/m^2	27.6 (6.0)	27.2 (5.8)	27.8 (6.2)
Smoking status			
Current smoker, %	26.9	24.3	32.4
Pack-year history (SD), *n*	51.8 (28.0)	48.7 (27.1)	50.3 (23.1)
Duration of reported dyspnea (SD), *y*	11.3 (8.8)	10.7 (8.7)	10.3 (8.1)
Medication use, %			
Ipratropium	34.4	44.5	42.9
Tiotropium	57.8	55.5	46.4
Short-acting β_2-agonists	77.9	82.2	80.0
Long-acting β_2-agonists	11.7	19.2	17.9
Combination of inhaled steroid and long-acting β_2-agonist	51.9	43.9	45.7
Inhaled corticosteroids	25.3	34.9	27.1
Antileukotrienes	2.0	2.7	2.9
Methylxanthines	7.1	11.6	5.7
Home oxygen	11.7	13.7	10.0
Influenza vaccine	74.8	74.0	77.3
Prebronchodilator lung function			
Mean FEV_1 (SD), *L*	1.01 (0.38)	1.00 (0.44)	1.05 (0.38)
Mean percent predicted FEV_1 (SD)	38.7 (12.9)	38.0 (13.1)	39.4 (11.9)
Mean FVC (SD), *L*	2.30 (0.69)	2.36 (0.80)	2.39 (0.75)
Mean FEV_1–FVC ratio (SD)	0.44 (0.11)	0.43 (0.12)	0.45 (0.12)
Postbronchodilator lung function			
Mean FEV_1 (SD), *L*	1.08 (0.40)	1.08 (0.43)	1.12 (0.41)
Mean percent predicted FEV_1 (SD)	42.1 (13.5)	41.2 (13.0)	42.2 (12.2)
Mean FVC (SD), *L*	2.50 (0.83)	2.51 (0.79)	2.51 (0.83)
Mean dyspnea index score (SD)	6.3 (1.8)	6.5 (1.9)	6.5 (2.0)
Comorbid conditions, %			
Hypertension	43.0	43.9	41.4
Coronary artery disease	16.0	21.0	22.8
Congestive heart failure	3.9	1.4	3.5
Cancer	5.8	9.5	6.9

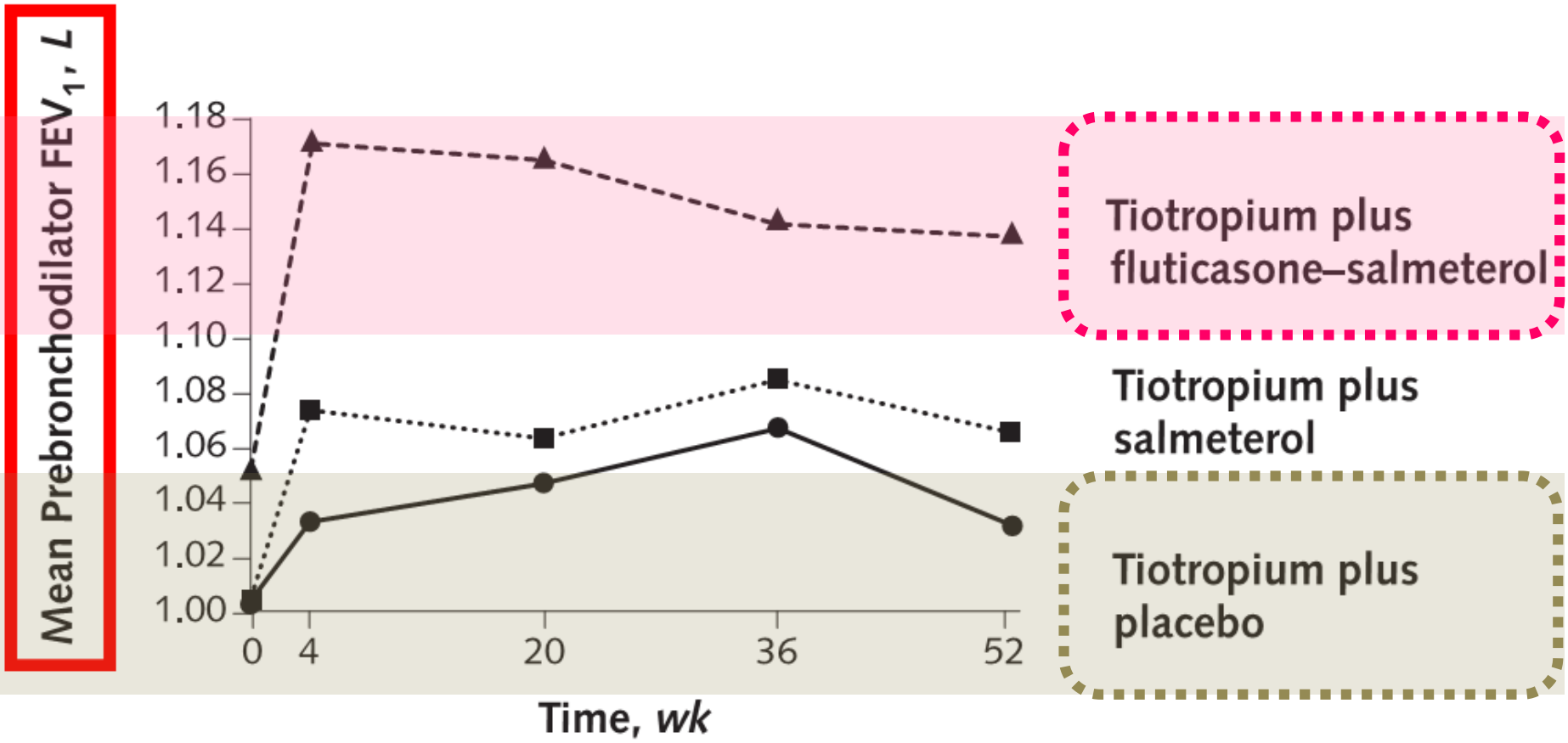
Aaron et al. Ann Int Med 2007;146:545-55

Table 2. **Exacerbations of Chronic Obstructive Pulmonary Disease and Health Care Utilization during 1 Year***

Outcome	Tiotropium plus Placebo (n = 156)	Tiotropium plus Salmeterol (n = 148)	Tiotropium plus Fluticasone–Salmeterol (n = 145)
Primary analysis†			
Patients with ≥1 acute exacerbation of COPD, *n (%)*	98 (62.8)	96 (64.8)	87 (60.0)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), *percentage points*		−2.0 (−12.8 to 8.8)	2.8 (−8.2 to 13.8)
Sensitivity analysis 1‡			
Patients with ≥1 acute exacerbation of COPD, *n (%)*	117 (75.0)	107 (72.3)	96 (66.2)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), *percentage points*		2.7 (−7.2 to 12.6)	8.8 (−1.5 to 19.0)
Sensitivity analysis 2§			
Patients with ≥1 acute exacerbation of COPD, *n (%)*	112 (71.8)	104 (70.3)	93 (64.1)
Absolute risk reduction compared with tiotropium plus placebo (95% CI), *percentage points*		1.5 (−8.7 to 11.7)	7.6 (−2.9 to 18.1)
Exacerbations of COPD			
All exacerbations, *n*	222	226	188
Duration of follow-up, *patient-years*	138.0	129.4	137.1
Mean exacerbations per patient-year, *n*	1.61	1.75	1.37
Incidence rate ratio compared with tiotropium plus placebo (95% CI)‖	–	1.09 (0.84 to 1.40)	0.85 (0.65 to 1.11)
Urgent physician or emergency department visits for COPD exacerbation			
Total, *n*	185	184	149
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		1.06 (0.87 to 1.30)	0.81 (0.65 to 1.01)
Hospitalizations for acute exacerbations of COPD			
Total, *n*	49	38	26
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		0.83 (0.54 to 1.27)	0.53 (0.33 to 0.86)
All-cause hospitalizations			
Total, *n*	62	48	41
Incidence rate ratio compared with tiotropium plus placebo (95% CI)		0.83 (0.57 to 1.21)	0.67 (0.45 to 0.99)

Aaron et al. Ann Int Med 2007;146:545-55

PreBD FEV_1



Aaron et al. Ann Int Med 2007;146:545-55

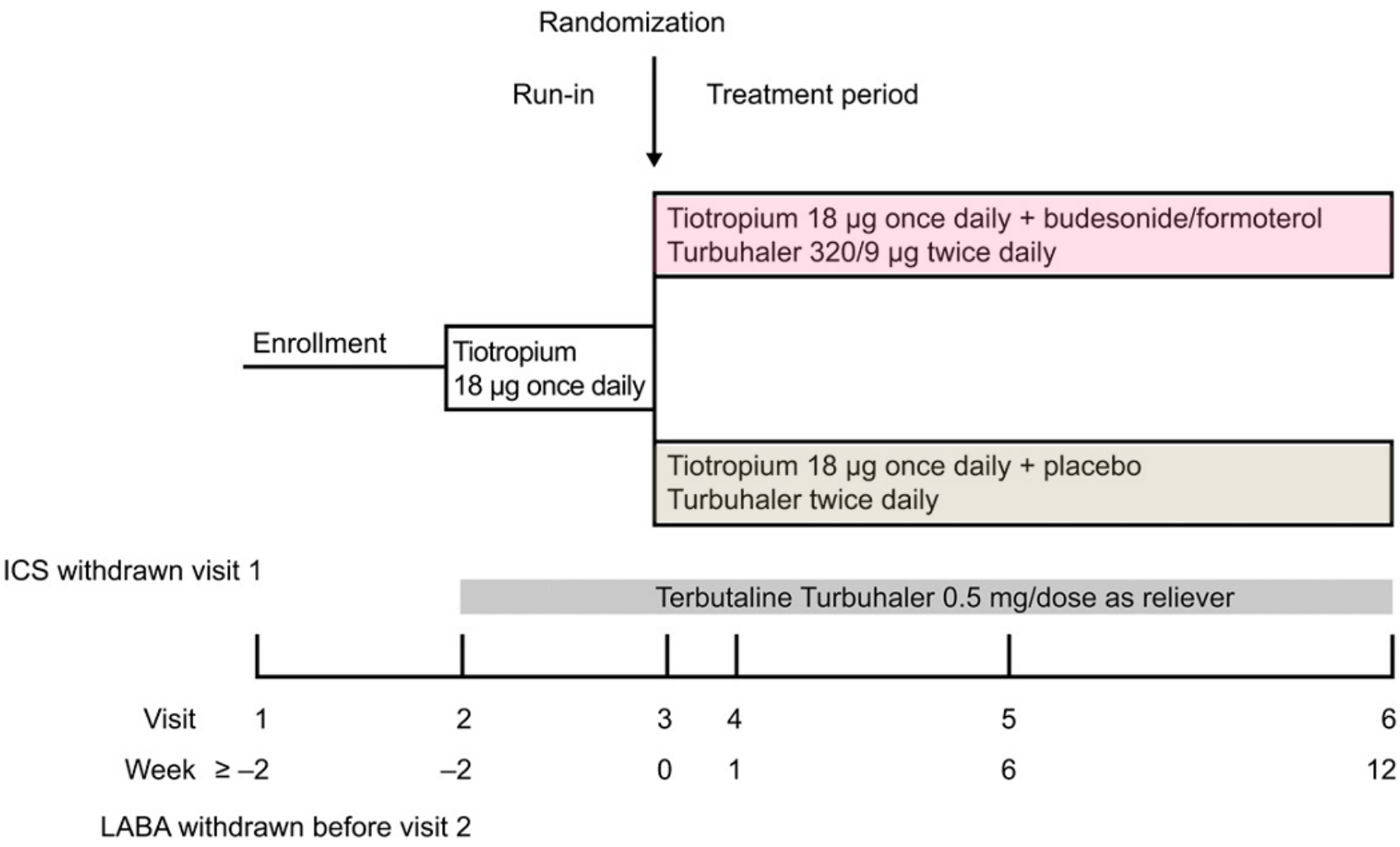
Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease

Tobias Welte[1], Marc Miravitlles[2], Paul Hernandez[3], Göran Eriksson[4,5], Stefan Peterson[5], Tomasz Polanowski[5], and Romain Kessler[6]

Am J Respir Crit Care Med 2009;180:741–50

- A 12-week, randomized, double-blind, parallel-group, multicenter study
- 102 centers in 9 countries
- 660 subjects
  - FEV_1 < 50 % pred
  - a history of AE requiring systemic steroids and/or antibiotics
- Primary outcome : morning predose FEV_1

Study protocol



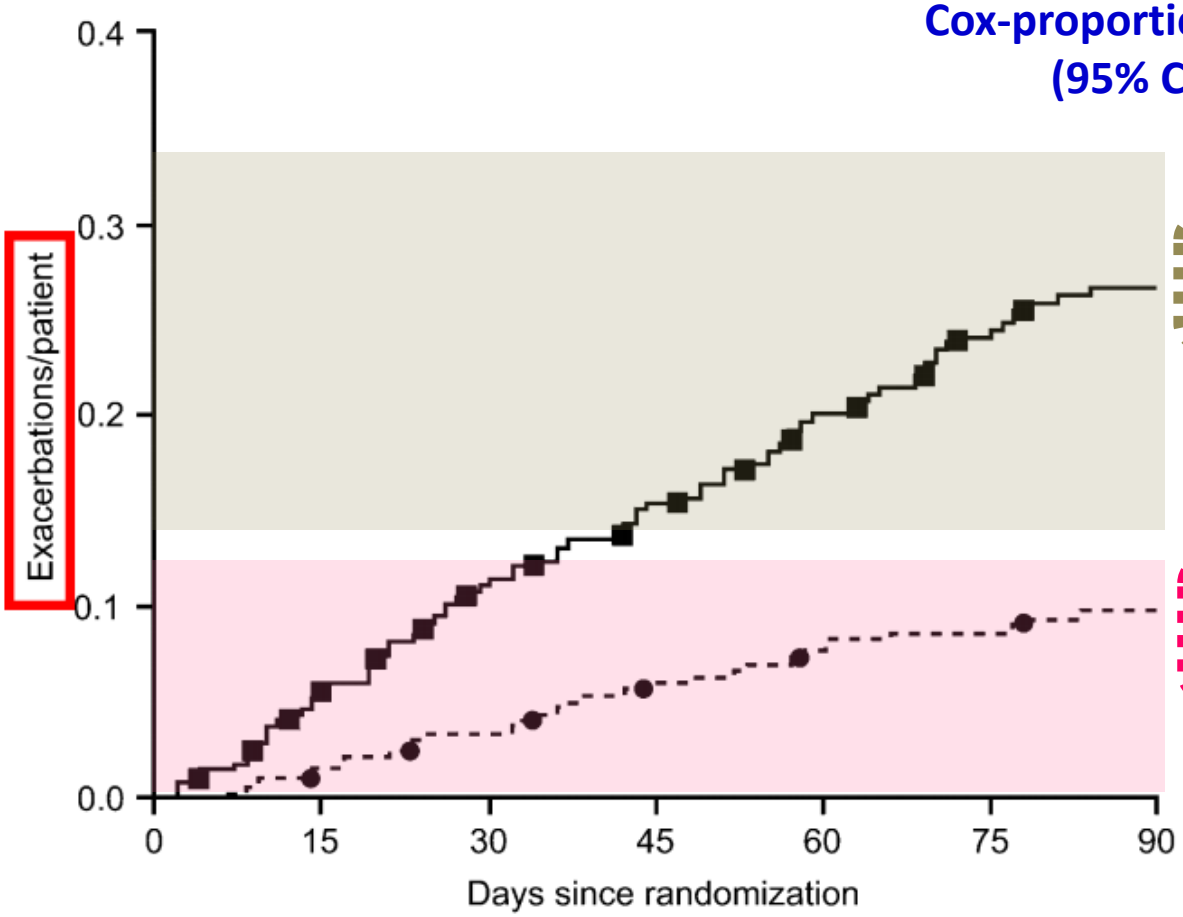
Welte et al. Am J Respir Crit Care Med 2009;180:741–50

TABLE 3. TREATMENT COMPARISONS FOR MORNING PEAK EXPIRATORY FLOW, RELIEVER USE, AND MORNING ACTIVITIES/SYMPTOMS FROM RUN-IN PERIOD TO LAST WEEK OF TREATMENT*

	Adjusted Mean Change		Mean Difference: BUD/FORM + TIO versus PBO + TIO (95% CI)	*P* Value
	PBO + TIO	BUD/FORM + TIO		
Morning FEV_1, L				
Predose	−0.074	0.054	0.128 (0.078–0.179)	<0.001
5 min postdose	−0.026	0.159	0.185 (0.134–0.237)	<0.001
15 min postdose	0.016	0.202	0.186 (0.126–0.246)	<0.001
Morning PEF, L/min				
Predose	−8.19	3.85	12.0 (6.08–18.0)	<0.001
5 min postdose	−2.39	15.3	17.7 (11.1–24.3)	<0.001
15 min postdose	2.53	20.5	18.0 (11.0–25.0)	<0.001
Reliever use, mean no. of inhalations				
Morning	−0.080	−0.480	−0.400 (−0.564, −0.236)	<0.001
Nighttime	0.075	−0.237	−0.313 (−0.456, −0.169)	<0.001
Daytime (including morning)	−0.141	−0.649	−0.508 (−0.772, −0.244)	<0.001
GCSQ (scale, 0–4)				
Predose				
Breathlessness	−0.036	−0.184	−0.148 (−0.238, −0.058)	0.001
Chest tightness	−0.029	−0.119	−0.090 (−0.181, 0.001)	0.051
5 min postdose				
Breathlessness	−0.222	−0.365	−0.144 (−0.244, −0.043)	0.005
Chest tightness	−0.169	−0.273	−0.104 (−0.204, −0.004)	0.042
15 min postdose				
Breathlessness	−0.310	−0.495	−0.185 (−0.286, −0.085)	<0.001
Chest tightness	−0.231	−0.352	−0.121 (−0.216, −0.025)	0.014
CDLM (scale, 0–5)†				
Total score	0.083	0.264	0.180 (0.090–0.270)	<0.001
Separate CDLM questions				
Wash yourself	0.125	0.298	0.174 (0.061–0.287)	0.003
Dry yourself	0.046	0.256	0.210 (0.097–0.322)	<0.001
Get dressed	0.108	0.298	0.189 (0.075–0.304)	0.001
Eat breakfast	0.034	0.173	0.140 (0.019–0.260)	0.023
Walk around early	0.128	0.261	0.133 (0.021–0.246)	0.020
Walk around later	0.140	0.278	0.138 (0.039–0.238)	0.006
Time to finish morning activities	0.945	1.01	1.07 (0.955–1.19)	0.258
COPD symptoms‡ (scale, 0–4)				
Breathlessness	−0.039	−0.181	−0.142 (−0.214, −0.069)	<0.001
Nighttime awakenings	−0.027	−0.184	−0.157 (−0.222, −0.092)	<0.001
Chest tightness	−0.053	−0.195	−0.142 (−0.212, −0.072)	<0.001
Cough	−0.088	−0.250	−0.161 (−0.238. −0.084)	<0.001

Severe AECOPD

Cox-proportional hazards: rate ratio 0.38
(95% CI 0.25- 0.57, p<0.001)



PBO+TIO

BUD/FORM+TIO

Welte et al. Am J Respir Crit Care Med 2009;180:741–50

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

N Engl J Med 2008;359:1543-54

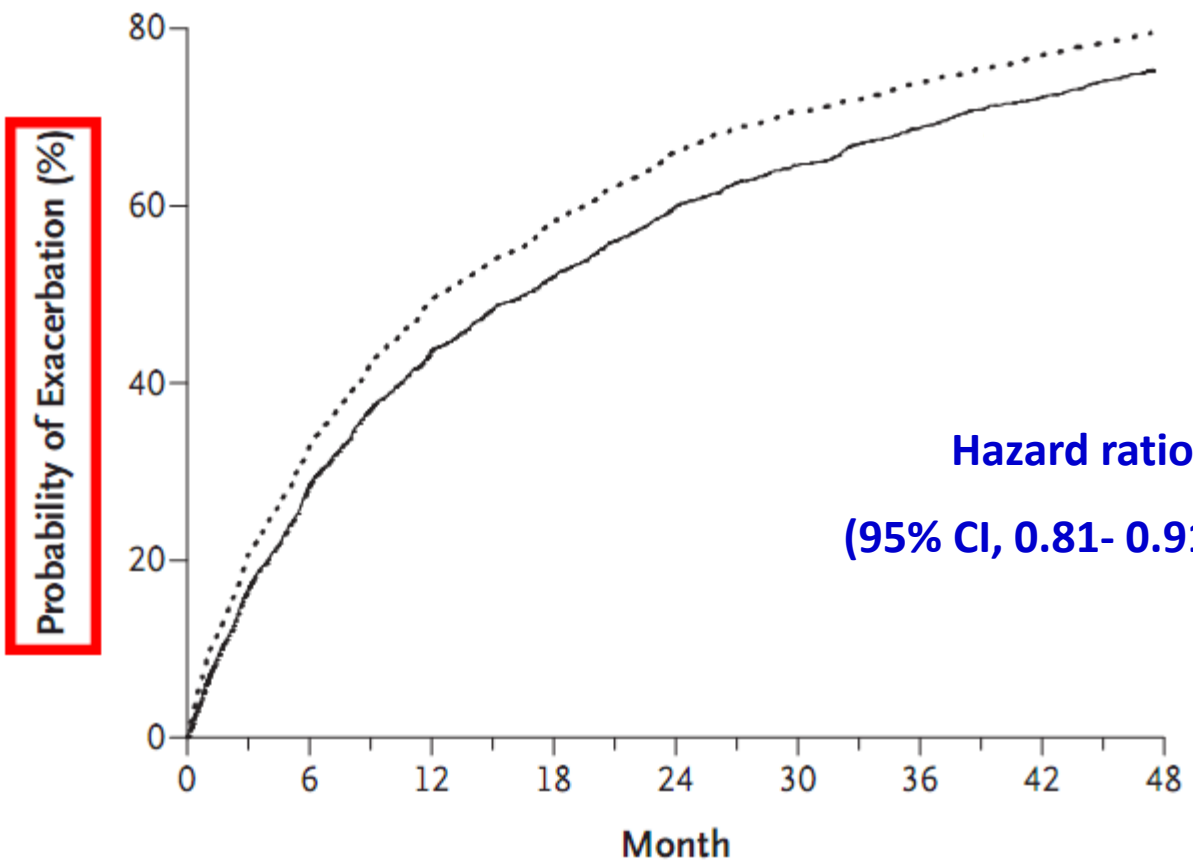
- Randomized, double-blind trial
- 490 centers in 37 countries
- 5993 subjects
- FEV_1 < 70 % pred , FEV_1/FVC < 70 %
- Coprimary end points
  : a rate of decline in the mean FEV_1
  before & after bronchodilation

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=2986)	Placebo (N=3006)
Male sex (%)	75.4	73.9
Age (yr)	64.5±8.4	64.5±8.5
Body-mass index	26.0±5.1	25.9±5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yr)	49.0±28.0	48.4±27.9
Duration of COPD (yr)	9.9±7.6	9.7±7.4
Baseline spirometry		
Before bronchodilation		
FEV_1 (liters)	1.10±0.40	1.09±0.40
FEV_1 (% of predicted value)	39.5±12.0	39.3±11.9
FVC (liters)	2.63±0.81	2.63±0.83
Ratio of FEV_1 to FVC	42.4±10.5	42.1±10.5
After bronchodilation		
FEV_1 (liters)	1.33±0.44	1.32±0.44
FEV_1 (% of predicted value)	47.7±12.7	47.4±12.6
FVC (liters)	3.09±0.86	3.09±0.90
Ratio of FEV_1 to FVC	43.6±10.8	43.3±10.7
GOLD stage (%)†		
II	46	45
III	44	44
IV	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β_2-agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	[illegible]	[illegible]

Tashkin et al. N Engl J Med 2008;359:1543-54

AECOPD



TIO

Hazard ratio, 0.86

(95% CI, 0.81- 0.91, p<0.001)

Tashkin et al. N Engl J Med 2008;359:1543-54

Contents

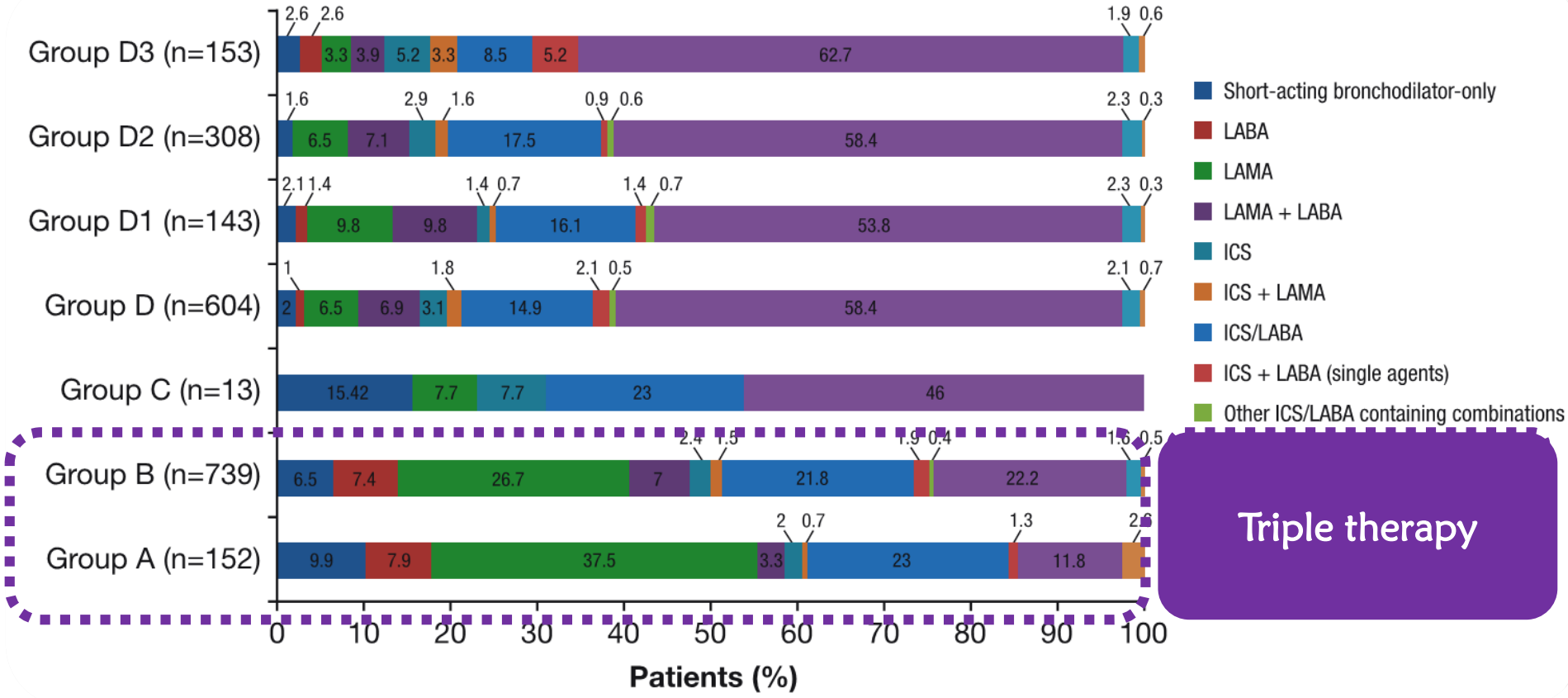
Understanding the GOLD 2011 Strategy as applied to a real-world COPD population

Jørgen Vestbo [a,b,*], Claus Vogelmeier [c], Mark Small [d], Victoria Higgins [d]

[a] *Department of Respiratory Medicine J, Odense University Hospital and University of Southern Denmark, Odense, Denmark*
[b] *The University of Manchester, Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, NIHR South Manchester Respiratory and Allergy Clinical Research Facility, Manchester, UK*
[c] *Universitätsklinikum Giessen und Marburg, Marburg, Germany*
[d] *Adelphi Real World, Macclesfield, Cheshire SK10 5JB, UK*

Respir Med 2014;108:729-36

- a real-world observational study
- in 5 European countries and in the US
- 3813 COPD patients



A considerable proportion of patients in **low risk** groups were receiving triple therapy

Global Initiative for Chronic Obstructive Lung Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
UPDATED 2016

SUMMARY OF RECOMMENDATIONS IN THE 2016 UPDATE

A. Additions to the text

Page 25, left column, paragraph 1, insert statement and reference: Withdrawal of inhaled corticosteroids, in COPD patients at low risk of exacerbation, can be safe provided that patients are left on maintenance treatment with long-acting bronchodilators[618].

Reference 618: Rossi A, Guerriero M, Corrado A; OPTIMO/AIPO Study Group. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res*. 2014 Jul 8;15:77.

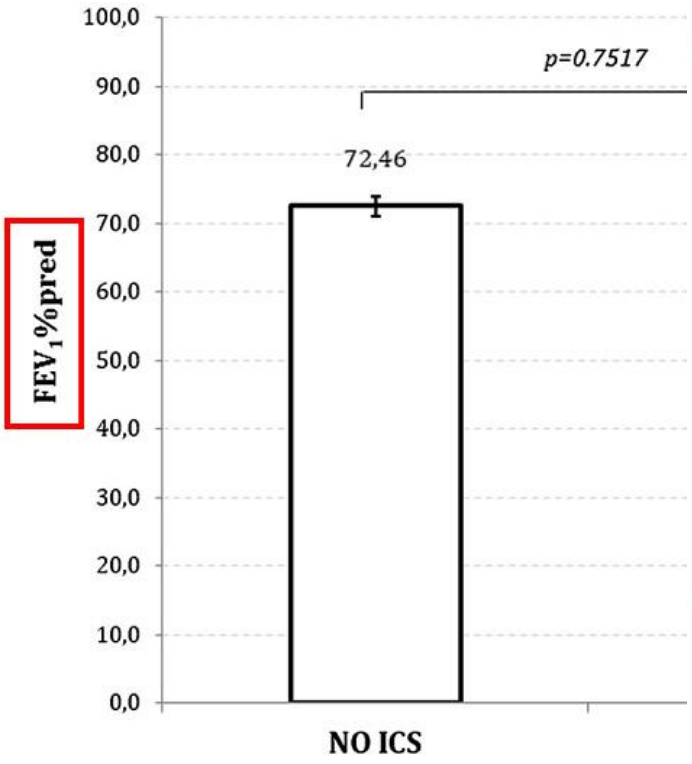
Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO)

Andrea Rossi[1*], Massimo Guerriero[2], Antonio Corrado[3], on behalf of OPTIMO/AIPO Study Group

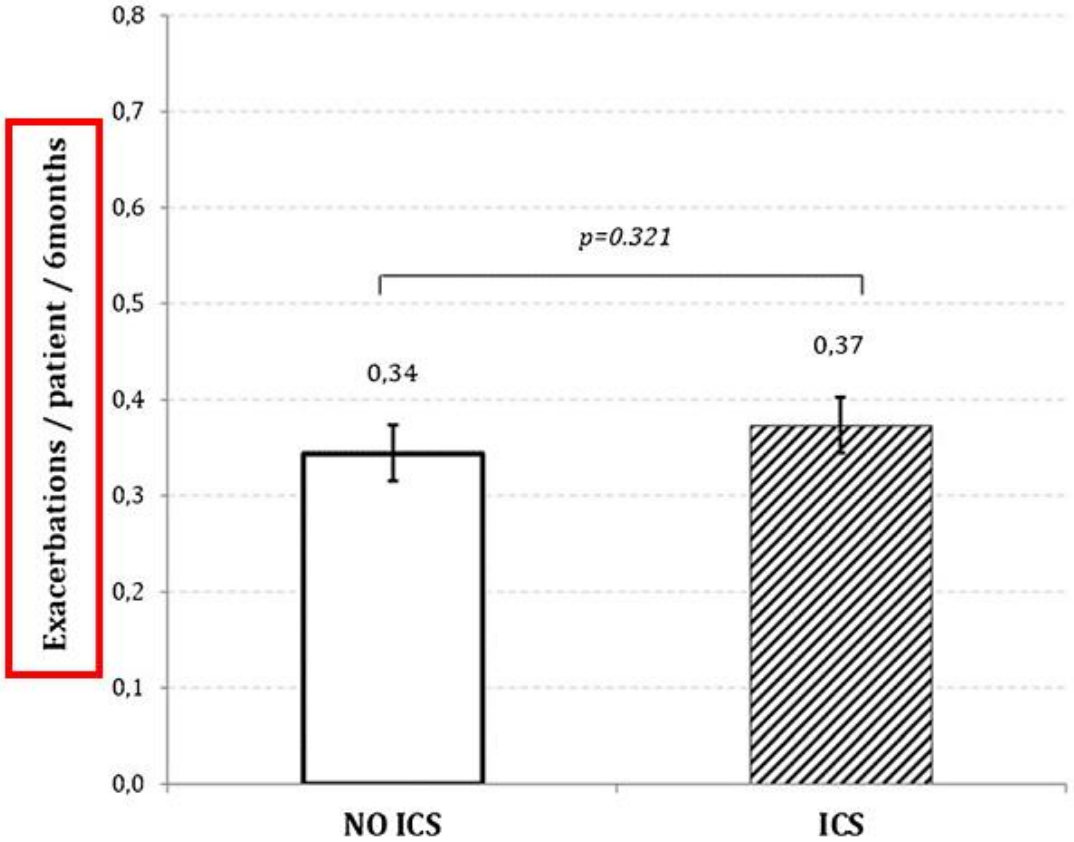
Respir Res 2014;15:77-88

- a multicenter, prospective, real-life study
- 914 COPD patients
  - on maintenance therapy with bronchodilators and ICS
  - FEV_1 > 50% pred
  - < 2 AE/yr
- 6 mo observational period

FEV_1



AECOPD *rate*



Rossi et al. Respir Res 2014;15:77-88

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Reasons FOR de-escalation

No effect on AECOPD

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

N Engl J Med 2014;371:1285-94

- 12-month, double-blind, parallel-group study
- 2485 pts
  - FEV_1 < 50% pred
  - ≥ 1 AE/yr
- tiotropium (TIO) + salmeterol (SM) +fluticasone propinate (FP) x 6 wks
  - continued triple therapy vs withdrawal of FP
- Primary end point

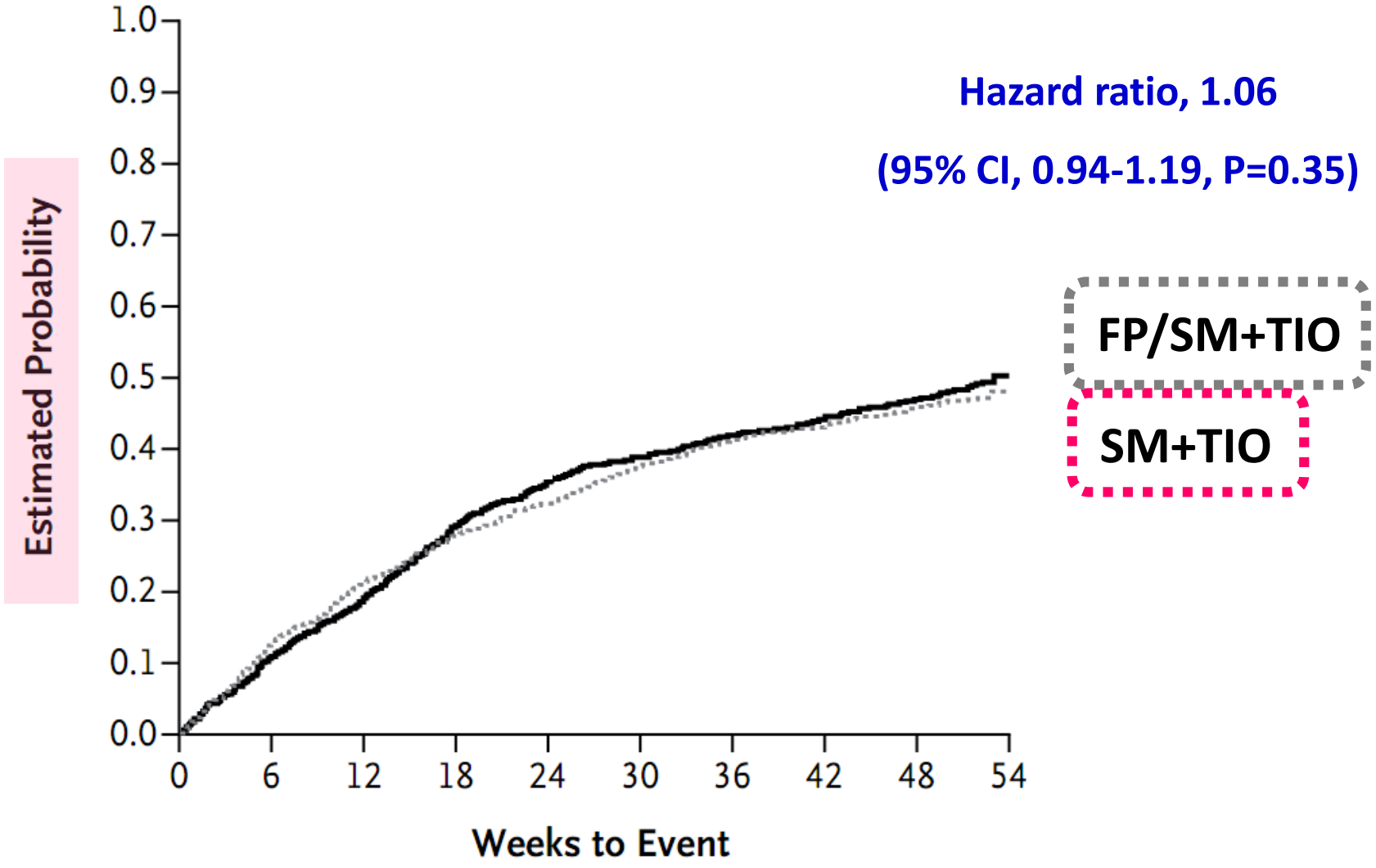
  : the time to the 1st moderate or severe AECOPD

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Glucocorticoid Continuation (N=1243)	Glucocorticoid Withdrawal (N=1242)	All Patients (N=2485)
Male sex — no. (%)	1013 (81.5)	1036 (83.4)	2049 (82.5)
Age — yr	63.6±8.6	64.0±8.4	63.8±8.5
Former smoker — no. (%)†	811 (65.2)	843 (67.9)	1654 (66.6)
Duration of COPD — yr	7.75±5.99	8.00±6.47	7.87±6.23
Percentage of predicted FEV_1 after bronchodilation — no. (%)			
30–49%: GOLD 3	760 (61.1)	761 (61.3)	1521 (61.2)
<30%: GOLD 4	473 (38.1)	474 (38.2)	947 (38.1)
Other category‡	10 (0.8)	7 (0.6)	17 (0.7)
Baseline lung function§			
Patients with available data — no.	1223	1218	2441
FEV_1			
Value — liters	0.97±0.36	0.98±0.36	0.98±0.36
Percentage of predicted value	34.2±11.2	34.3±10.8	34.2±11.0
Score on mMRC scale¶			
Patients with available data — no.	1238	1237	2475
Mean score	1.8±0.9	1.9±0.9	1.8±0.9
SGRQ score‖			
Patients with available data — no.	1136	1126	2262
Mean score	46.35±17.89	45.91±18.19	46.13±18.04
Medication use — no. (%)			
LAMA	588 (47.3)	578 (46.5)	1166 (46.9)
LABA	807 (64.9)	798 (64.3)	1605 (64.6)
Inhaled glucocorticoid	876 (70.5)	862 (69.4)	1738 (69.9)
Triple therapy with LAMA, LABA, and inhaled glucocorticoid, with or without other pulmonary medication — no. (%)**	479 (38.5)	491 (39.5)	970 (39.0)

Magnussen et al. N Engl J Med 2014;371:1285-94

Moderate or Severe AE



Magnussen et al. N Engl J Med 2014;371:1285-94

Reasons FOR de-escalation

No effect on AECOPD ?

Relative Effectiveness of Budesonide/Formoterol and Fluticasone Propionate/Salmeterol in a 1-Year, Population-Based, Matched Cohort Study of Patients With Chronic Obstructive Pulmonary Disease (COPD): Effect on COPD-Related Exacerbations, Emergency Department Visits and Hospitalizations, Medication Utilization, and Treatment Adherence

Clin Ther 2010;32:1320-8

Table III. Crude and adjusted measures of association of the outcomes under study comparing budesonide/formoterol (BUD/FM) and fluticasone propionate/salmeterol (FP/SM) in patients with chronic obstructive pulmonary disease (COPD).

Outcomes	Crude RR (95% CI)	Adjusted RR* (95% CI)
COPD exacerbations	0.88 (0.76 to 1.02)	0.88 (0.76 to 1.00)
ED visits for COPD	0.71 (0.53 to 0.96)	0.75 (0.58 to 0.97)
COPD hospitalizations	0.56 (0.41 to 0.76)	0.61 (0.47 to 0.81)
Claims for a short-course prescription of oral corticosteroids	0.83 (0.71 to 0.99)	0.85 (0.72 to 1.00)
Claims for a prescription of tiotropium	0.81 (0.61 to 1.08)	0.71 (0.57 to 0.89)
Ambulatory medical visits for COPD	1.10 (0.98 to 1.23)	1.08 (0.96 to 1.21)

Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study

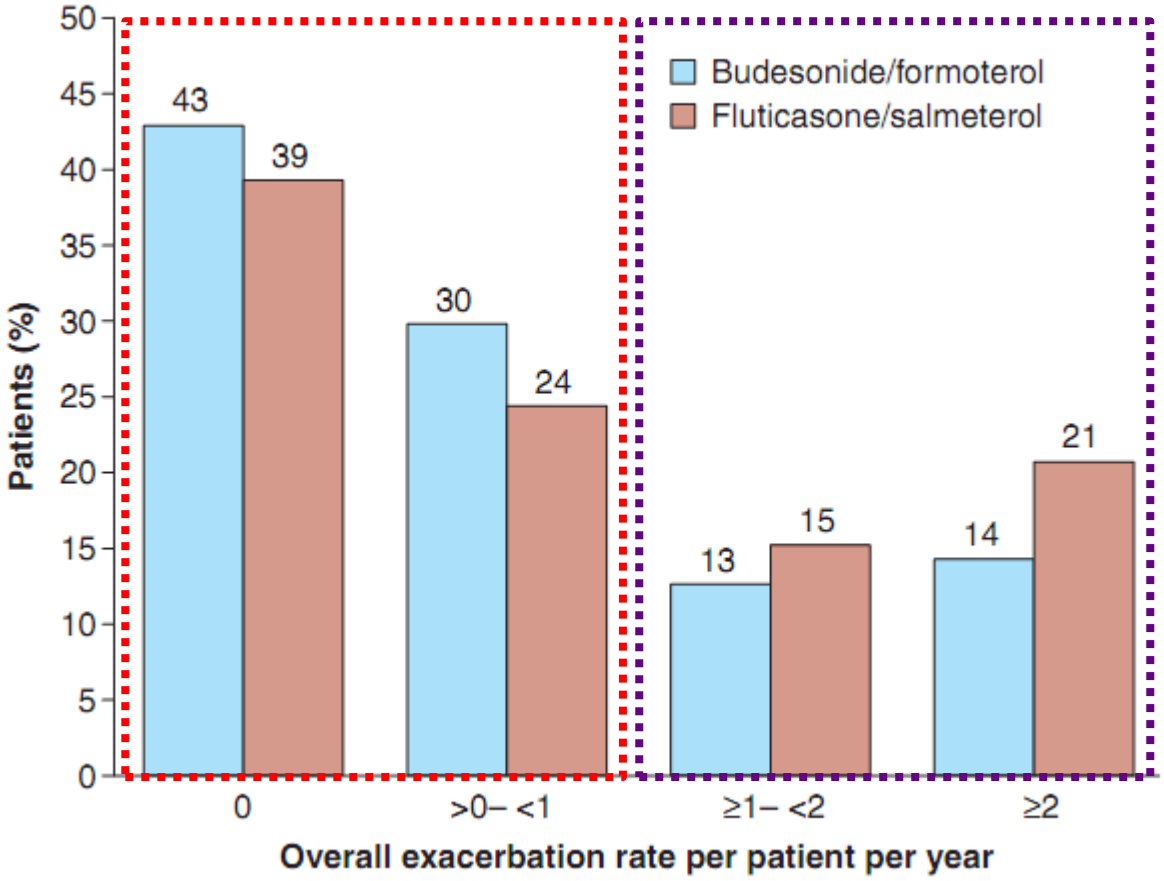
K. Larsson[1], C. Janson[2], K. Lisspers[3], L. Jørgensen[4], G. Stratelis[4], G. Telg[4], B. Ställberg[3] & G. Johansson[3]

J Intern Med 2013;273:584–94

Table 2 *Yearly occurrence of events among pairwise (1 : 1) propensity score-matched populations of COPD patients treated with budesonide/formoterol versus fluticasone/salmeterol*

Variable	Fluticasone/ salmeterol (n = 2734)	Budesonide/ formoterol (n = 2734)	Treatment contrast[a]	
Events, per patient-year	Mean (95% CI)	Mean (95% CI)	Rate ratio (95% CI)	*P*-value
All exacerbations	1.09 (1.05–1.14)	0.80 (0.77–0.84)	0.74 (0.69–0.79)	<0.0001
COPD hospitalizations	0.21 (0.20–0.23)	0.15 (0.142–0.163)	0.71 (0.65–0.78)	<0.0001
COPD-related hospital stay, days	0.95 (0.88–1.02)	0.63 (0.58–0.67)	0.66 (0.62–0.71)	<0.0001
Emergency visits	0.034 (0.031–0.037)	0.027 (0.025–0.030)	0.79 (0.71–0.89)	0.0003
Oral steroid use	0.85 (0.81–0.90)	0.63 (0.60–0.67)	0.74 (0.68–0.81)	<0.0001
Antibiotic use	0.54 (0.52–0.57)	0.38 (0.37–0.40)	0.70 (0.66–0.75)	<0.0001

AECOPD rate



Larsson et al. J Intern Med 2013;273:584-94

Reasons FOR de-escalation

Risk of pneumonia

Reasons FOR de-escalation

Risk of pneumonia ?

Budesonide and the risk of pneumonia: a meta-analysis of individual patient data

Don D Sin, Donald Tashkin, Xuekui Zhang, Finn Radner, Ulf Sjöbring, Anders Thorén, Peter M A Calverley, Stephen I Rennard

Lancet 2009; 374: 712–9

- 7042 patients from 7 large clinical trials
- inhaled budesonide (320–1280 µg/day), with or without formoterol, vs control regimen (placebo or formoterol alone)
- The primary analysis

  : the risk of pneumonia

  as an adverse event or serious adverse event

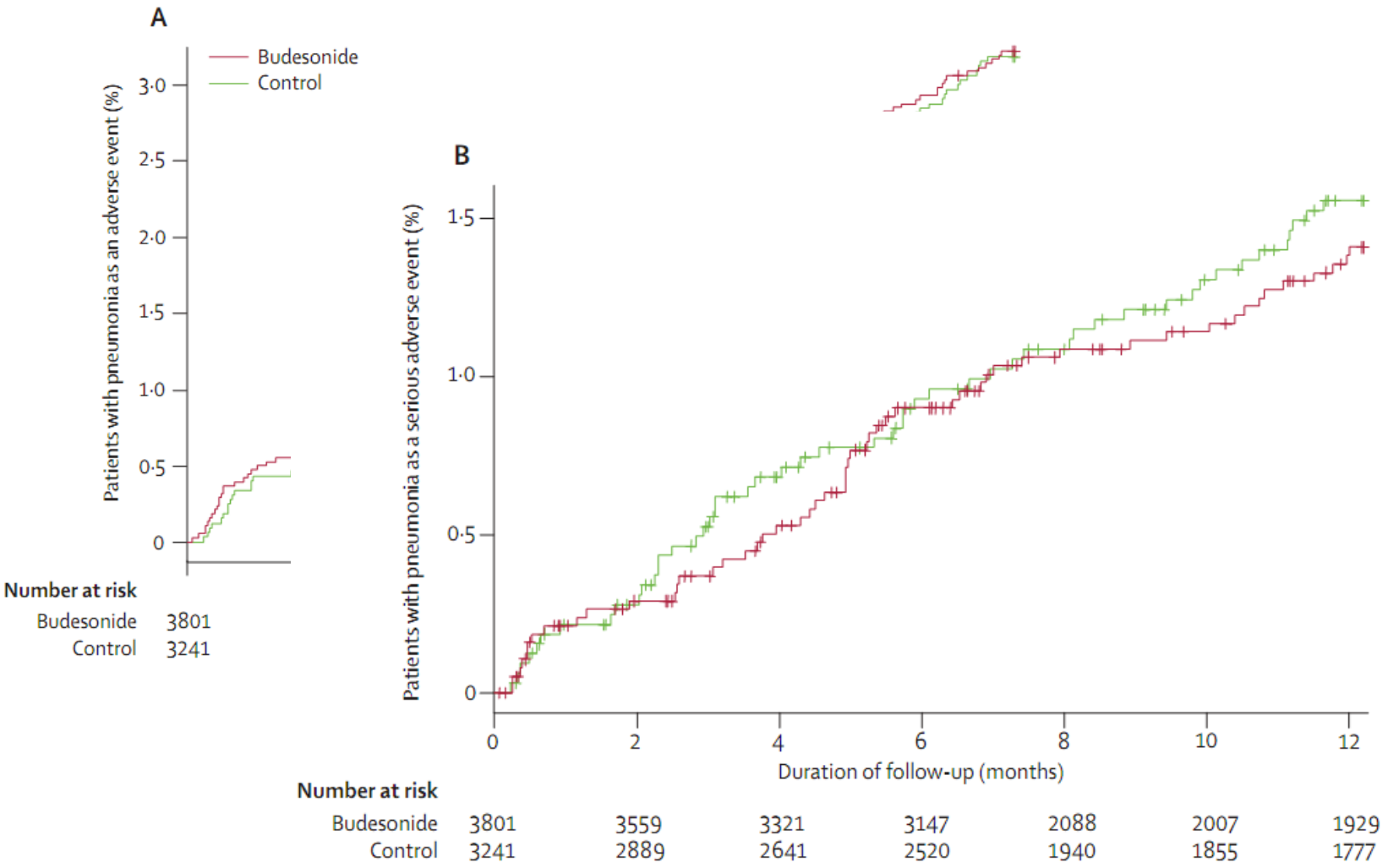
Occurrence of pneumonia

	Patients on inhaled budesonide	Patients on control	Adverse event		Serious adverse event		Duration of total exposure (person-years)	
			Inhaled budesonide	Control	Inhaled budesonide	Control	Inhaled budesonide	Control
Szafranski et al (2003)[12]	406	406	19 (5%)	15 (4%)	8 (2%)	10 (2%)	333	312
Calverley et al (2003)[13]	511	511	15 (3%)	9 (2%)	9 (2%)	7 (1%)	395	356
Rennard et al (2009)[14]	988	976	39 (4%)	43 (4%)	16 (2%)	21 (2%)	827	759
Tashkin et al (2008)[15]	1120	584	24 (2%)	11 (2%)	12 (1%)	6 (1%)	553	270
Bourbeau et al (1998)[16]	38	37	2 (5%)	4 (11%)	2 (5%)	4 (11%)	32	28
Pauwels et al (1999)[17]	593	582	15 (3%)	7 (1%)	6 (1%)	1 (<1%)	547	545
Vestbo et al (1999)[6]	145	145	8 (6%)	14 (10%)	0	1 (1%)	130	127
Total	3801	3241	122 (3%)	103 (3%)	53 (1%)	50 (2%)	2817	2397

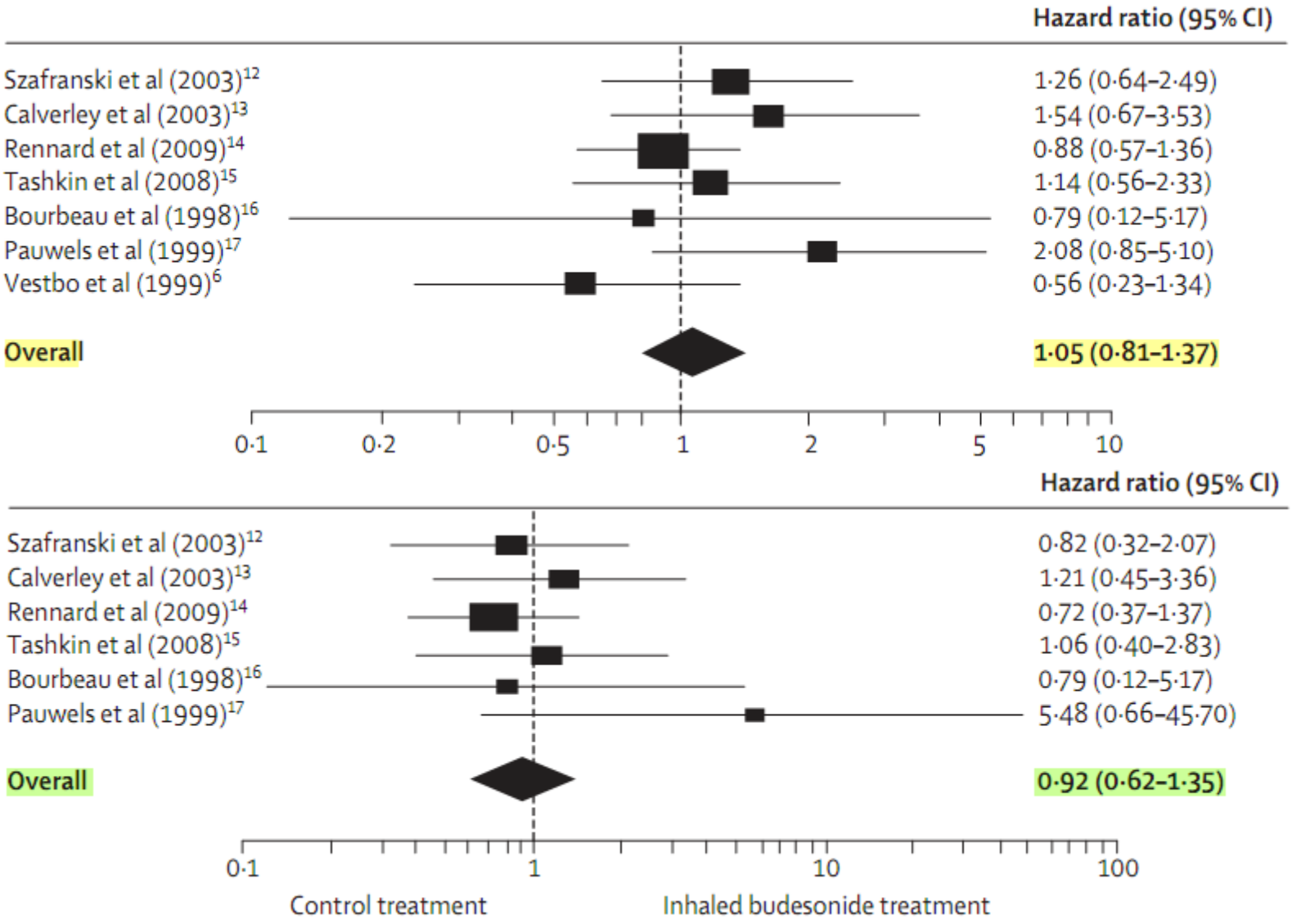
Data are number (%), unless otherwise indicated.

Table 3: Occurrence of pneumonia as an adverse event or serious adverse event

Time to pneumonia



Adjusted risk of pneumonia



Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update

Sonal Singh[a] and Yoon K. Loke[b]

Curr Opin Pulm Med 2010 ;16:118-22

Study or subgroup	Inhaled corticosteroid Events	Total	Control Events	Total	Weight	Risk ratio M.H, fixed, 95% CI
6.1.1 Fluticas-one exposure						
Aaron 2007	1	145	1	148	102%	1.02 [0.06, 16.16]
Burge 2000	18	372	8	370	1.7%	2.24 [0.99, 5.08]
Calve						
Calve						
Ferg						
FLTA						
Hanne						
Kardos 2007	23	507	7	487	1.5%	3.16 [1.37, 1.29]
Mahler 2002	4	333	0	341	0.1%	9.22 [0.50, 170.50]
Paggiaro 1998	2	142	2	139	0.4%	0.98 [0.14, 6.85]
6.1.2 Budesonide exposure						
Bourbeau 2001	3	38	4	37	0.9%	0.73 [0.18, 3.04]
Calverley (b) 2003	13	511	9	511	1.9%	1.44 [0.62, 3.35]
Pauwels 1999	33	593	16	582	3.4%	2.02 [1.13, 3.64]
Rennard 2009	37	988	17	495	4.8%	1.09 [0.62, 1.92]
Szafranski 2003	20	406	15	406	3.1%	1.33 [0.69, 2.57]
Tashkin 2008	18	1120	9	584	2.5%	1.04 [0.47, 2.31]
Vestbo 1999	16	145	24	145	5.0%	0.67 [0.37, 1.20]
Subtotal (95% CI)		3801		2760	21.5%	1.19 [0.92, 1.53]
Total events	140		94			

Heterogeneity: $Chi^2 = 7.83$, df = 6 ($P = 0.25$); $I^2 = 23\%$

Test for overall effect: $Z = 1.30$ ($P = 0.19$)

Risk ratio M.H, fixed, 95% CI

Fluticasone, but **not budesonide** are responsible for an increased risk of pneumonia.

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS)

Christer Janson *professor in respiratory medicine*[1], Kjell Larsson *professor in respiratory medicine*[2], Karin H Lisspers *general practitioner*[3], Björn Ställberg *general practitioner*[3], Georgios Stratelis *senior medical advisor*[4], Helena Goike *research scientist*[4], Leif Jörgensen *research statistician*[4], Gunnar Johansson *professor in public health sciences*[5]

BMJ 2013;346:f3306

- Observational retrospective pairwise cohort study
- Primary care medical records data, Sweden, 1999-2009
- Patients with COPD diagnosed by a physician and prescriptions of either BUD/FM or FP/SM
- Main outcome measures : yearly pneumonia event rates, admission to hospital related to pneumonia, mortality

Pneumonia events & Admissions

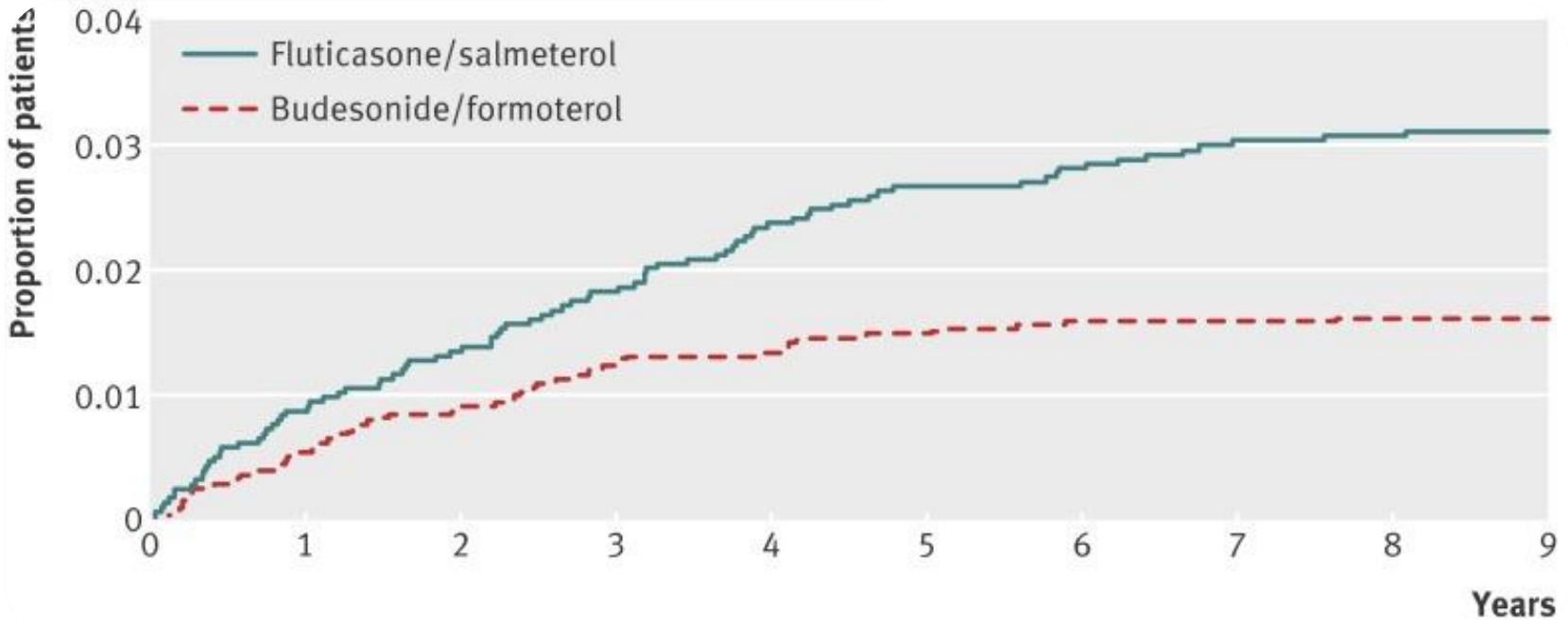
Measure	Event rate (95% CI)		Treatment contrast
	Fluticasone/salmeterol	Budesonide/formoterol	
Diagnosis of pneumonia overall†	11.0 (10.4 to 11.8)	6.4 (6.0 to 6.9)	1.73 (1.57 to 1.90)
Admission to hospital because of pneumonia†	7.4 (6.9 to 8.0)	4.3 (3.9 to 4.6)	1.74 (1.56 to 1.94)
Diagnosis of pneumonia in primary care†	4.2 (3.9 to 4.5)	2.7 (2.5 to 2.9)	1.56 (1.39 to 1.75)
Diagnosis of pneumonia in hospital outpatient care†	1.3 (1.2 to 1.4)	0.7 (0.7 to 0.8)	1.75 (1.53 to 2.00)
Days in hospital because of pneumonia‡	52.8 (48.9 to 57.0)	29.0 (26.5 to 31.7)	1.82 (1.62 to 2.05)

Janson et al. BMJ 2013;346:f3306

Mortality related to pneumonia

Hazard ratio, 1.76

(95% CI, 1.22-2.53, P=0.003)



Janson et al. BMJ 2013;346:f3306

Contents

Reasons AGAINST de-escalation

Asthma COPD Overlap Syndrome (ACOS)

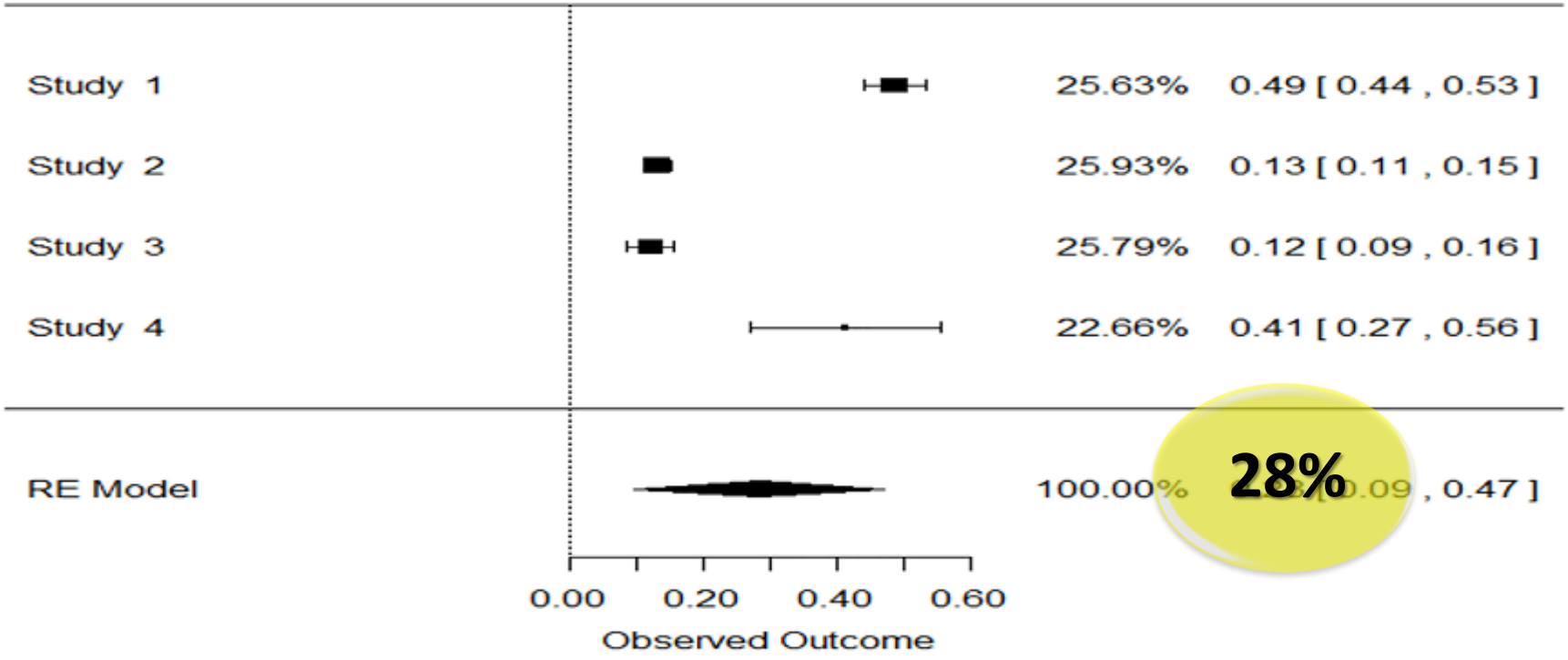
Asthma and COPD Overlap Syndrome

	Country	Prevalence (%)	Criteria
Database studies			
Soriano *et al.*, 2003 [28]	US and UK	52	Self-reported physician diagnosis of COPD and asthma
Rhee *et al.*, 2014 [31▪]	Korea	54.5	Diagnosis of COPD and asthma
Marsh *et al.*, 2008 [30]	US	55	Combinations of chronic bronchitis, emphysema and asthma, with and without incompletely reversible airflow obstruction
Clinical studies			
Miravitlles *et al.*, 2013 [22▪]	Spain	17.4	Previous diagnosis of asthma before the age of 40
Menezes *et al.*, 2014 [23▪]	Latin America (Brazil, Venezuela, Chile, Mexico, Uruguay)	11.6	Post-bronchodilator FEV1/FVC<0.7 and asthma (wheezing in the past 12 months + post-BD increase in FEV1 or FVC of 200 ml and 12% or 'Medical diagnosis of asthma')
Hardin *et al.*, 2011 [21]	US	13	Previous diagnosis of asthma before the age of 40
Louie *et al.*, 2013 [7]	US	15.8 in a pulmonary clinic 24.3 in an asthma clinic	Asthma with partially reversible airflow obstruction, with or without emphysema or DLCO<80%; or COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DCLO
Izquierdo-Alonso *et al.*, 2013 [34]	Spain	12	DLCO >80%, absence of pulmonary emphysema on CT or chest radiograph and personal history of asthma before the age of 40
Miravitlles *et al.*, 2014 [26]	Spain	5.8	Spanish consensus criteria[a]
Golpe *et al.*, 2014 [35▪]	Spain	21.3 in biomass-related COPD 5 in smoking-related COPD	Spanish consensus criteria[a]

Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis

A. Alshabanat[1¤‡*], Z. Zafari[2☯‡], O. Albanyan[3☯‡], M. Dairi[4☯‡], J. M. FitzGerald[2,5☯¤‡]

PLoS One 2015;10:e0136065



The clinical and genetic features of COPD-asthma overlap syndrome

TABLE 2 Clinical features of subjects with chronic obstructive pulmonary disease (COPD) and asthma compared to those with COPD alone

	COPD	COPD and asthma	Effect size	p-value
Females	1335 (42.8)	252 (56.0)	1.59 (1.29–1.95)	<0.001
African–American	627 (20.1)	167 (37.1)	1.74 (1.39–2.18)	<0.001
Bronchodilator responsiveness	1120 (36.1)	177 (39.4)	1.19 (0.97–1.47)	0.10
Absolute BDR L	0.09±0.16	0.11±0.16	0.02±0.08	0.03
BODE score	2.9±2.1	3.1±2.0	0.25±0.1	0.02
SGRQ score	39.7±21.5	47.4±22.7	6.81±1.1	<0.001
Exacerbations per year	0.7±1.2	1.2±1.6	0.56±0.06	<0.001
Severe exacerbations	646 (20.7)	153 (34.0)	1.70 (1.36–2.12)	<0.001
Hay fever	442 (17.8)	186 (50.3)	4.66 (3.68–5.90)	<0.001
High school graduates	1828 (58.6)	261 (58.0)	1.10 (-0.[illegible]0.39)	0.54
Maternal asthma	162 (7.0)	57 (19.0)	2.22 (1.59–3.12)	<0.001
Paternal asthma	123 (5.9)	47 (17.5)	2.64 (1.82–3.83)	<0.001

QoL

AE

Medical Utilization and Cost in Patients with Overlap Syndrome of Chronic Obstructive Pulmonary Disease and Asthma

Table 1. Patient characteristics

Characteristics	Overlap syndrome (n = 101,004)	COPD without asthma (n = 84,143)	*p*-value
Males (%)	68,025 (67.3%)	48,464 (57.6%)	<0.001
Mean age, years	69.7 ± 10.7	70.3 ± 10.5	<0.001
Number of patients in each age group (%)			
40–49 years	4,345 (4.3%)	3,784 (4.5%)	
50–59 years	12,498 (12.4%)	9,450 (11.2%)	
60–69 years	28,237 (28.0%)	22,376 (26.6%)	
70–79 years	39,405 (39.0%)	32,658 (38.8%)	
>80 years	16,519 (16.4%)	15,875 (18.9%)	
Medical aid[#]	17,643 (17.5%)	12,965 (15.4%)	<0.001
Type of hospital use			<0.001
Primary	44,379 (43.9%)	57,192 (68.0%)	
Secondary	9,676 (9.6%)	6,117 (7.3%)	
Tertiary	46,583 (46.1%)	20,834 (24.8%)	
Hospitalizations[†]	30,807 (30.5%)	11,884 (14.1%)	<0.001
ICU care[†]	477 (0.5%)	158 (0.2%)	<0.001
ER visits[†]	14,733 (14.6%)	4,222 (5.0%)	<0.001
Mean number of visits	1.5 ± 1.0	1.2 ± 0.5	<0.001

Admission

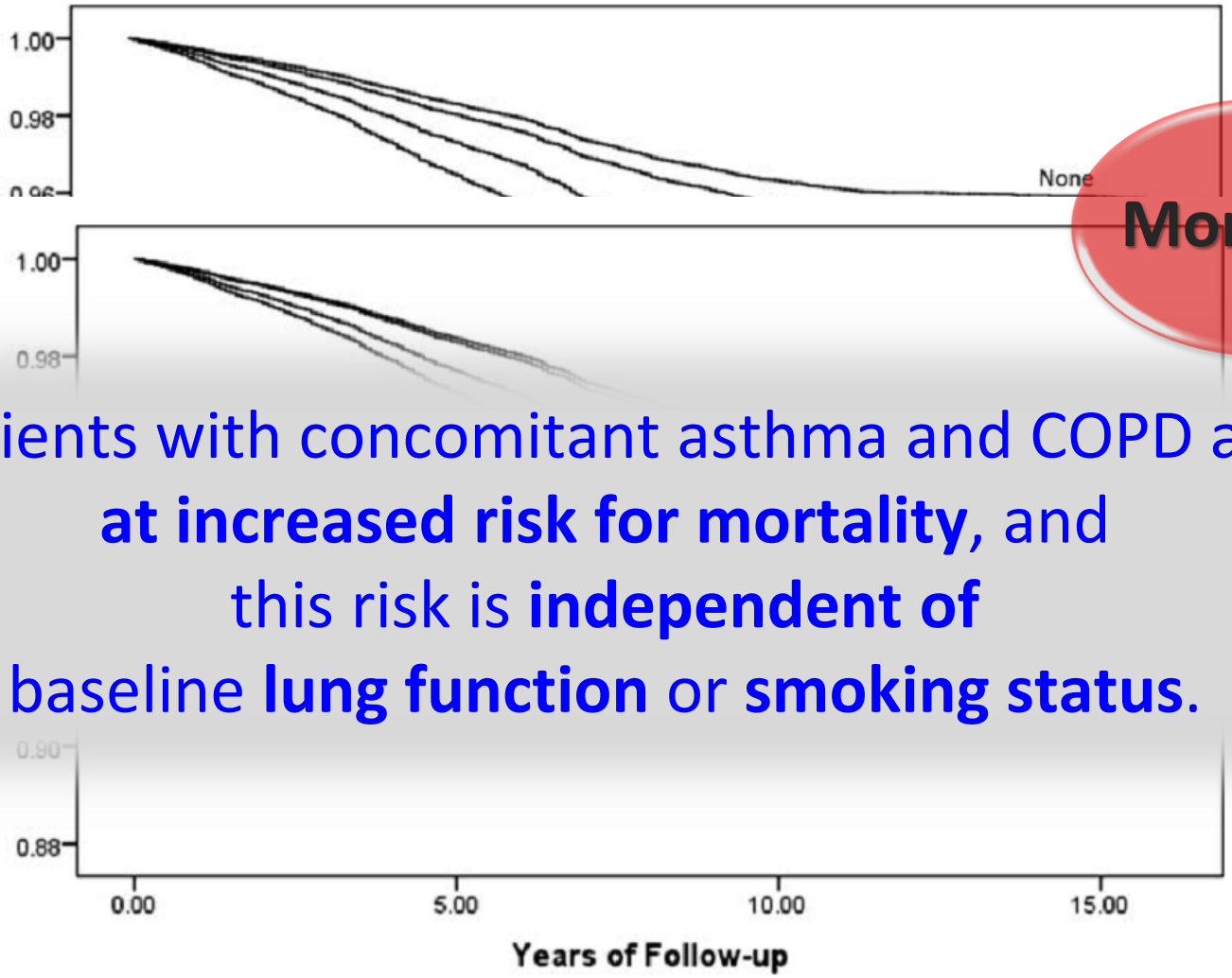
ER visit

Asthma, Chronic Obstructive Pulmonary Disease, and Mortality in the U.S. Population

Enrique Diaz-Guzman,[1] Mehdi Khosravi,[1] and David M. Mannino[1,2]

COPD 2011;8:400-7

- Baseline data from NHANES III (1988-1994) and the follow-up mortality data
- Subjects were asked “Has a doctor ever told you that you have asthma?” with similar questions asked about “chronic bronchitis” and “emphysema.”
- The sample consisted of 15,203 subjects, of whom 4,542 died during the follow-up period. Coexisting COPD and asthma was reported by 357 (2.7%), COPD by 815 (5.3%), and asthma by 709 (5.3%).

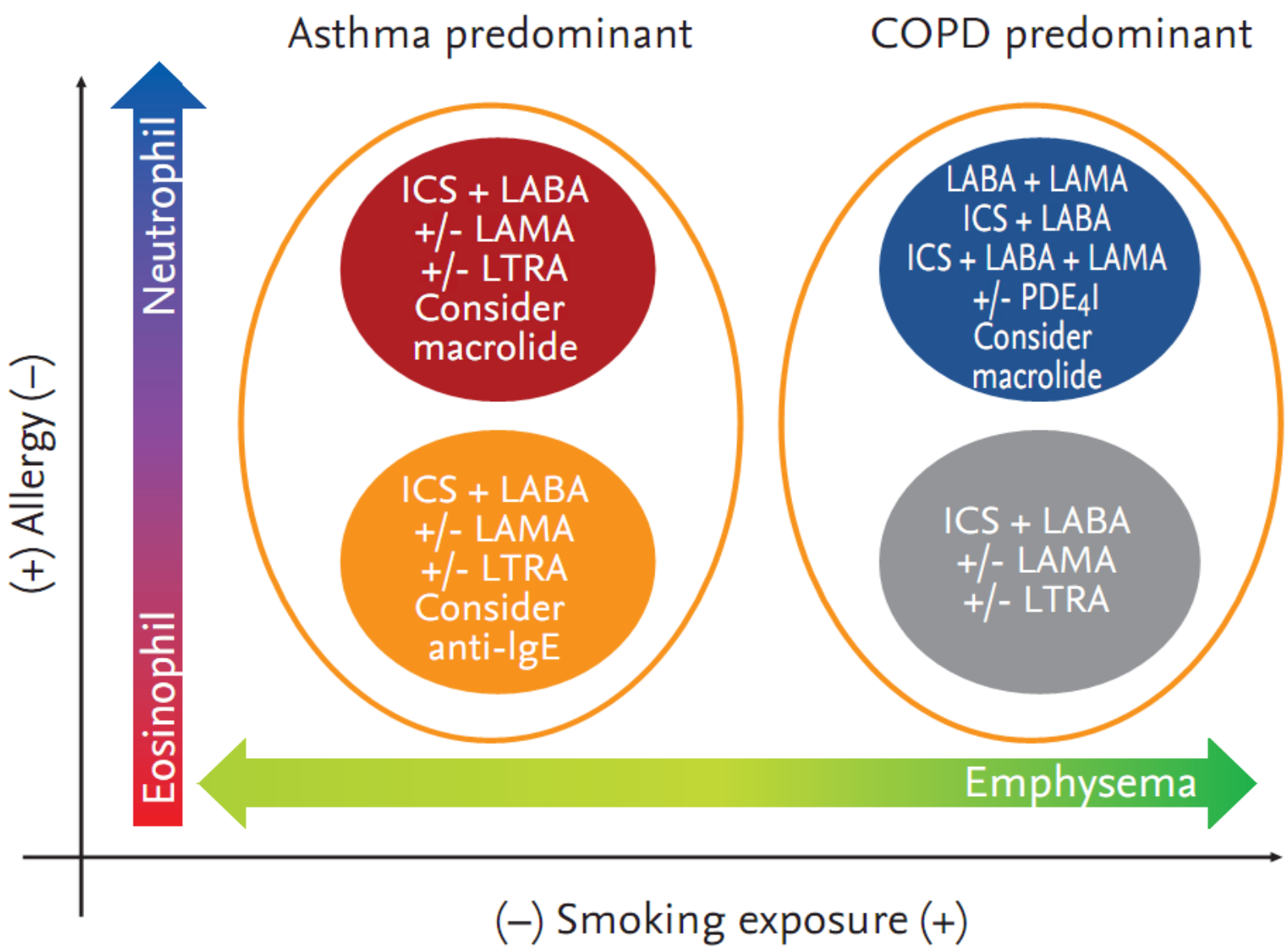


Mortality

Patients with concomitant asthma and COPD are **at increased risk for mortality**, and this risk is **independent of** baseline **lung function** or **smoking status**.

Figure 3. Results from Cox proportion hazard models. Curves are adjusted for sex, age, body mass index, education, race/ethnicity, smoking status and lung function status at baseline.

Díaz-Guzman et al. COPD 2011;8:400-7



Rhee Korean J Intern Med 2015;30:443-9

Reasons AGAINST de-escalation

Disease deterioration

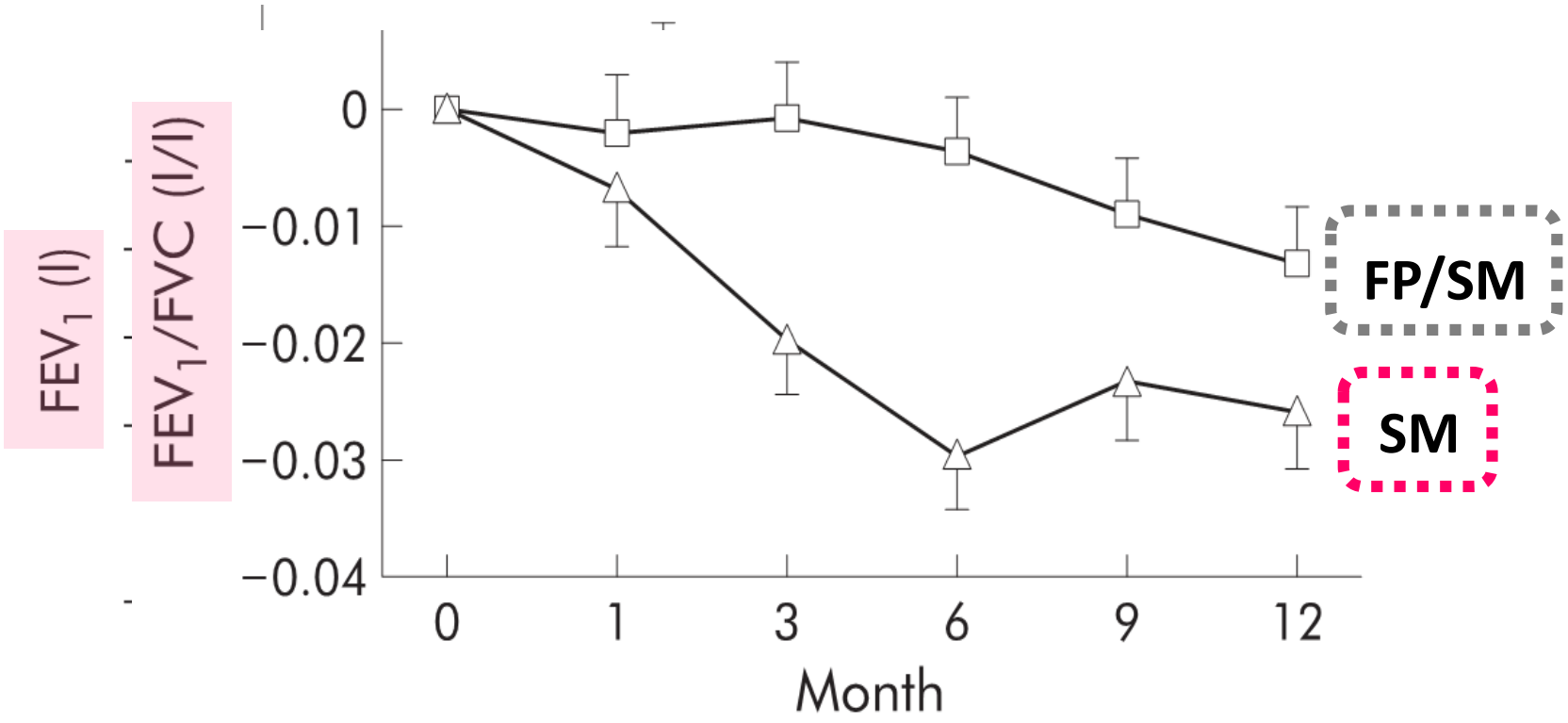
Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial

E F M Wouters, D S Postma, B Fokkens†, W C J Hop, J Prins, A F Kuipers, H R Pasma, C A J Hensing, E C Creutzberg, for the COSMIC (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group

Thorax 2005;60:480-7

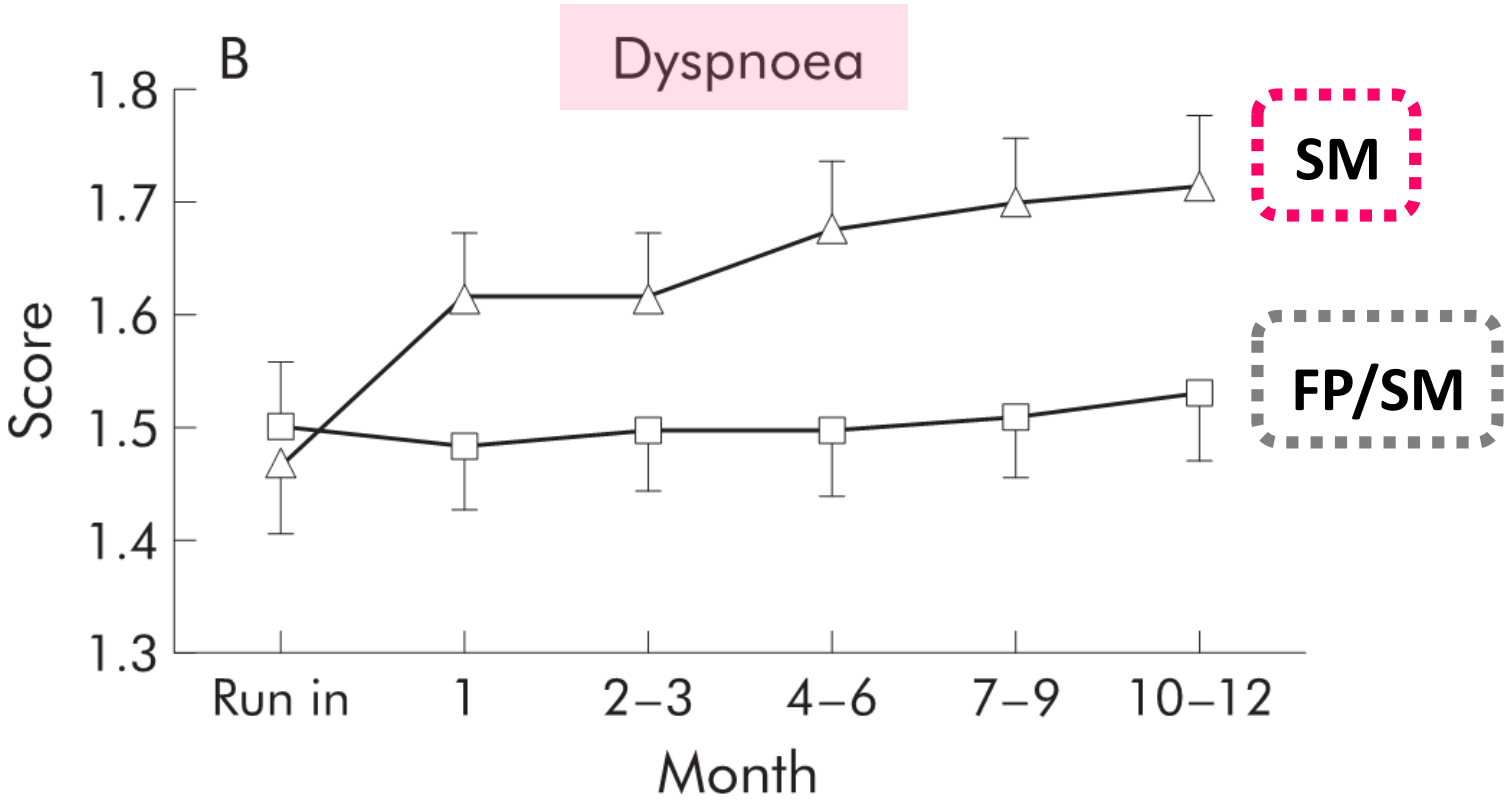
- a randomised, double blind study
- 39 centers in the Netherlands
- 373 pts
  - FEV_1 30-70% pred
  - ≥ 2 AE/yr requiring OCS and/or antibiotics
- FP/SM x 3 mo
  - continued FP/SM vs withdrawal of FP x 1 yr

Lung function



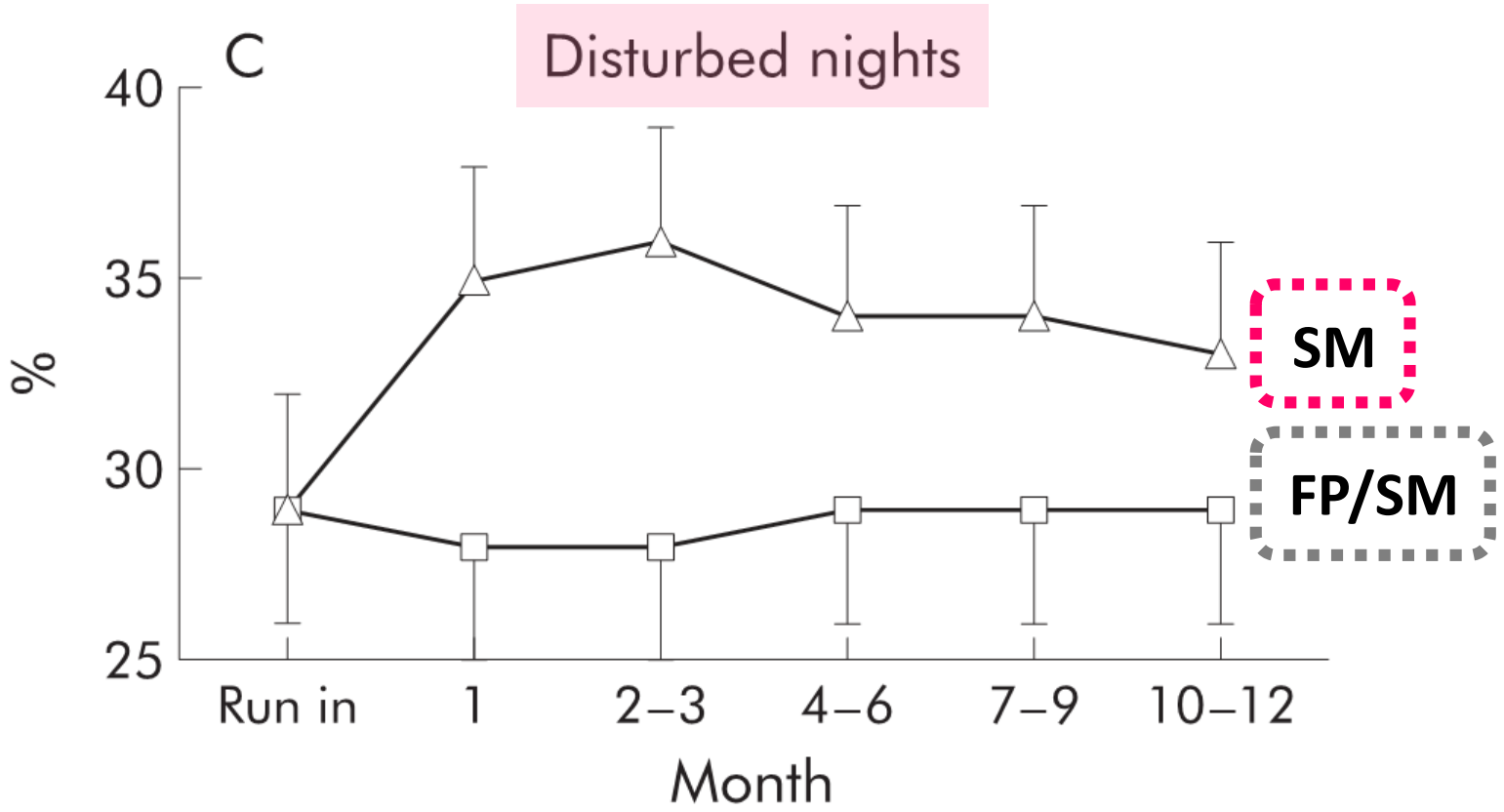
Wouters et al. Thorax 2005;60:480-7

Symptom



Wouters et al. Thorax 2005;60:480-7

Spleep



Wouters et al. Thorax 2005;60:480-7

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

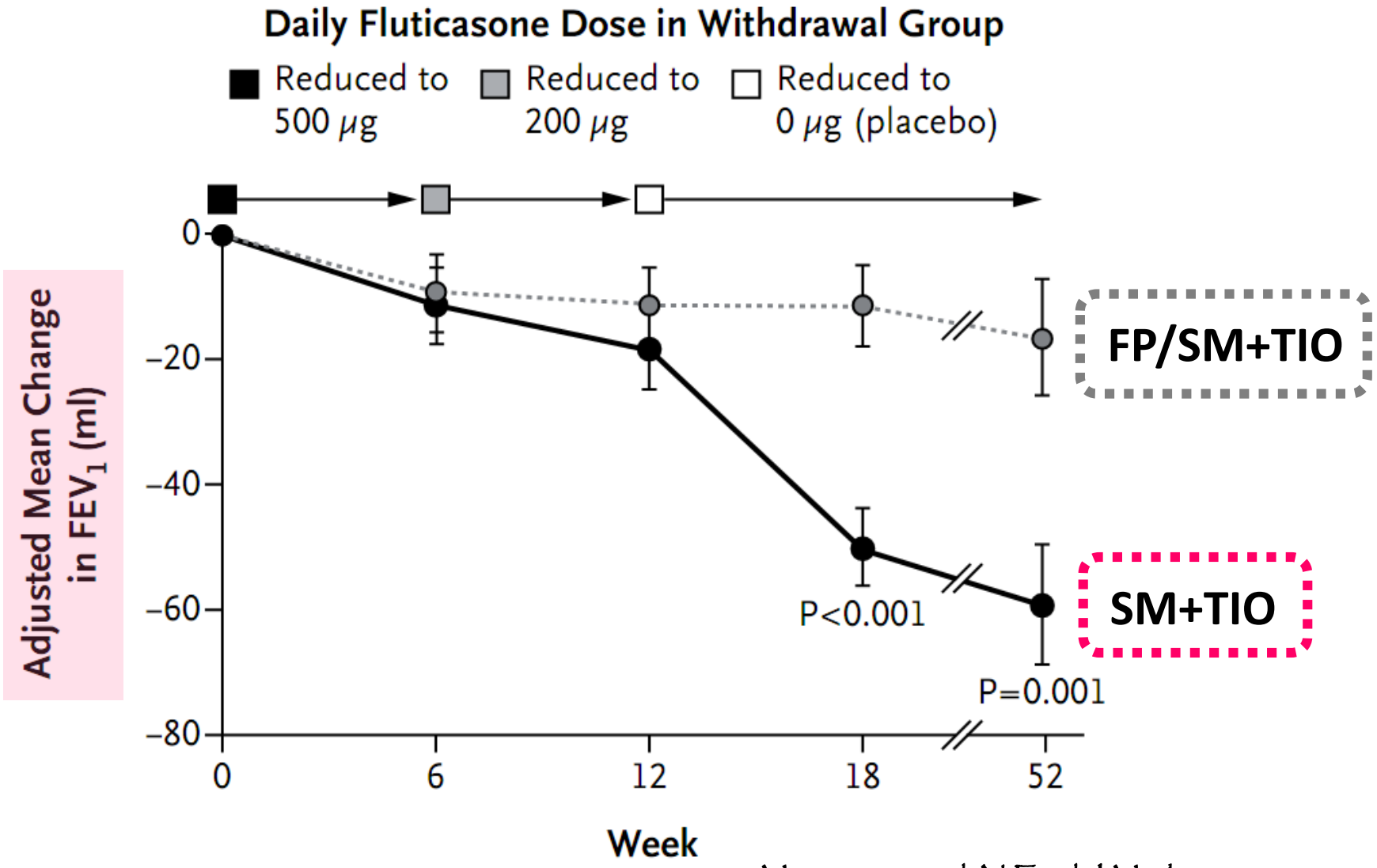
N Engl J Med 2014;371:1285-94

- 12-month, double-blind, parallel-group study
- 2485 pts
  - FEV_1 < 50% pred
  - ≥ 1 AE/yr
- tiotropium + salmeterol +fluticasone x 6 wks
  - continued triple therapy vs

    withdrawal of fluticasone three steps over 12 wks
- Primary end point

  : the time to the 1st mod/severe AECOPD

Lung function



Magnussen et al. N Engl J Med 2014;371:1285-94

Reasons AGAINST de-escalation

Cardiovascular Mortality

Impact of Long-Acting Bronchodilators and Exposure to Inhaled Corticosteroids on Mortality in COPD: A Real-Life Retrospective Cohort Study

Arvind Manoharan · Phillip M. Short ·
William J. Anderson · Brian J. Lipworth

Lung 2014;192:649-52

- A real-life retrospective analysis
- Scotland, 2001~2010
- 4,133 patients
- Mean FEV_1 of 59.5 %, mean follow-up of 4.6 years
- 1,372 patients (33 %) died during the study period.
- All-cause & cardiovascular mortality

Impact of Long-Acting Bronchodilators and Exposure to Inhaled Corticosteroids on Mortality in COPD: A Real-Life Retrospective Cohort Study

Arvind Manoharan · Phillip M. Short · William J. Anderson · Brian J. Lipworth

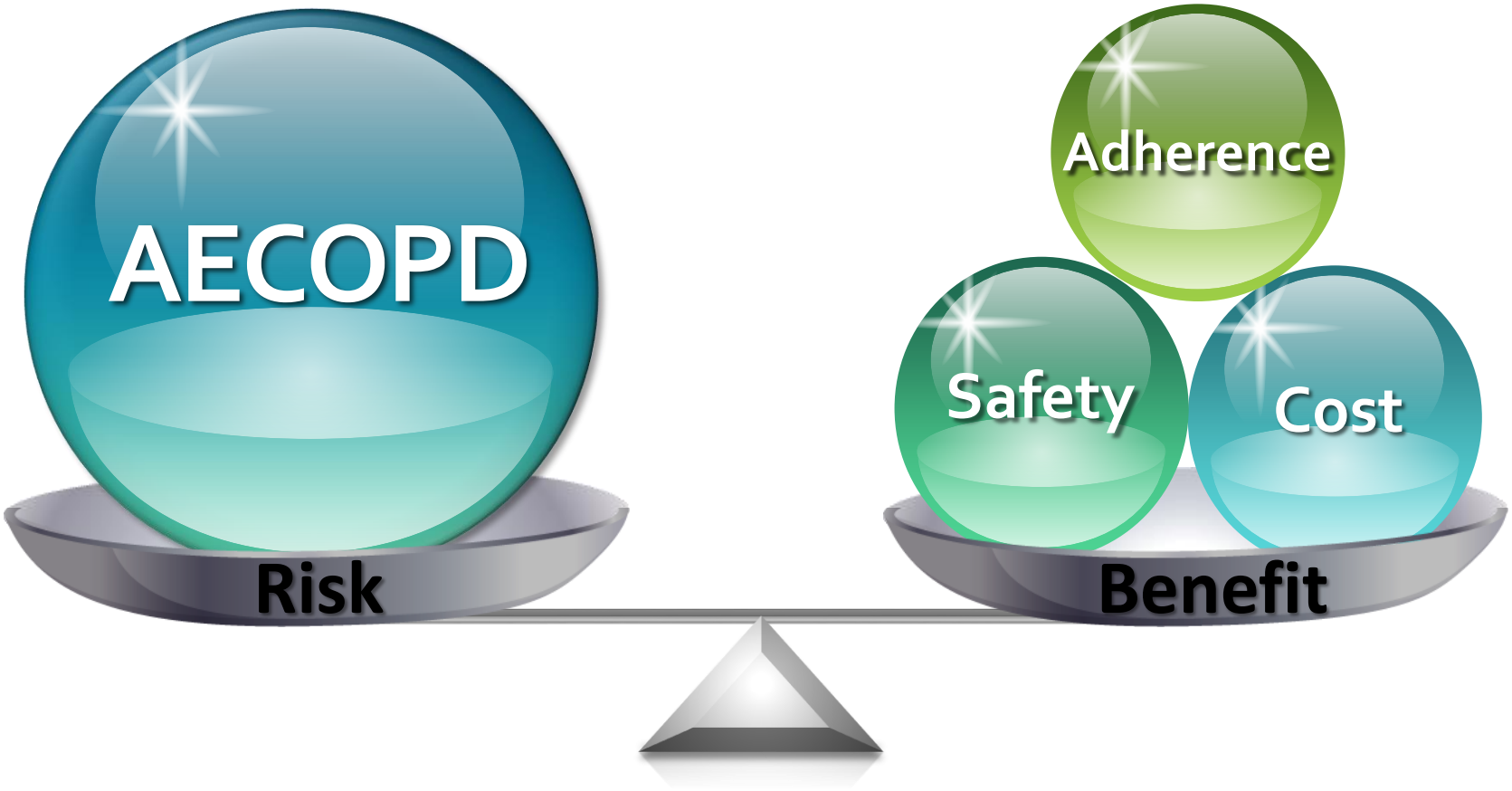
Lung 2014;192:649-52

Table 2 Crude and adjusted hazard ratio for all-cause and cardiovascular mortality for patients exposed to ICS using patients on long-acting bronchodilators only as the control group

Treatment group	Number of patients	FEV_1 mean (SD)[a]	SpO_2 mean (SD)[b]	All-cause mortality		Cardiovascular mortality	
				Crude hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)	Crude hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)
LABA or LAMA or LABA + LAMA (control group)	623	62 (17)	94 (6)	–	–	–	–
LABA + ICS	963	66 (19)	93 (13)	0.96 (0.80–1.14)	1.02 (0.80–1.31)	1.05 (0.74–1.49)	1.25 (0.78–2.01)
LAMA + ICS	328	57 (17)	93 (10)	0.81 (0.64–1.03)	0.62 (0.45–0.85)	0.75 (0.46–1.24)	0.58 (0.29–1.18)
LABA + LAMA + ICS	2,219	53 (17)	91 (12)	0.80 (0.69–0.94)	0.51 (0.41–0.64)	0.64 (0.46–0.89)	0.56 (0.35–0.90)
LABA + ICS or LAMA + ICS or LABA + LAMA + ICS	3,510	57 (19)	92 (12)	0.84 (0.73–0.98)	0.64 (0.52–0.80)	0.75 (0.55–1.03)	0.76 (0.49–1.16)

Contents

De-escalation of triple therapy



Mortality rate after hospitalization for exacerbation

TABLE 4 Mortality rates after hospitalisation for a chronic obstructive pulmonary disease exacerbation at different time-points for the six studies included and the 10 studies excluded from the meta-analysis fulfilling all inclusion criteria except follow-up >1.5 yrs

	Patients n	Mortality rate %					
		In-hospital	3 months	6 months	1 yr	2 yrs	5 yrs
Studies included in the meta-analysis							
Connors [15]	1016	11	NR	33	43	49	NR
Vestbo [16]	487	NR	NR	NR	NR	NR	44
Groenewegen [17]	171	8	16	18	23	NR	NR
Gunen [18]	205	8.3	NR	24	33	39	NR
McGhan [19]	54269	3.6	NR	NR	24	NR	57
Brekke [20]	996	9.9	22	27	32	41	NR
Studies excluded from the meta-analysis#							
Fuso [10]	590	14	NR	NR	NR	NR	NR
Cydulka [21]¶	131974	6	NR	NR	NR	NR	NR
Eriksen [22]	300	8.6	19	NR	36	NR	NR
Patil [9]	71130	2.5	NR	NR	NR	NR	NR
Yohannes [23]	104	3.8	NR	NR	38	NR	NR
Wang [24]	282	9.9	NR	NR	NR	NR	NR
Price [25]	7529	7.4	15	NR	NR	NR	NR
Bustamente [26]	763	6.4	NR	NR	NR	NR	NR
Kinnunen [27]	72896§	3.2	NR	NR	NR	NR	NR
Dransfield [28]	825	5.2	NR	NR	NR	NR	NR
Overall estimate based on all 16 studies % (95% CI)+		6.7 (5.7–7.7)	18 (14–22)	26 (20–32)	33 (25–40)	43 (37–50)	51 (38–63)

Hoogendoorn et al. Eur Respir J 2011;37:508–15

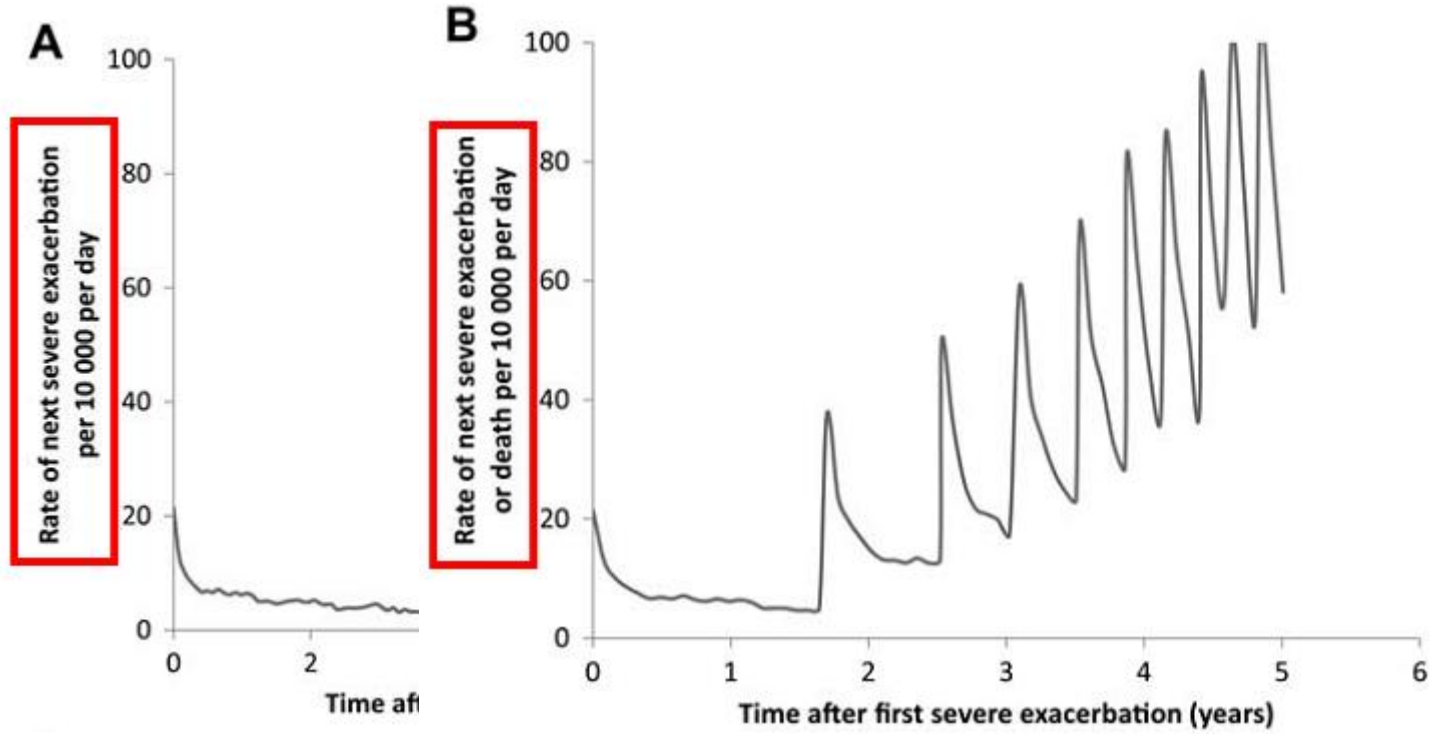
Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality

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

Thorax 2012;67:957-63

- Cohort of patients from their first ever hospitalization for COPD during 1990-2005
- Healthcare databases from Quebec, Canada
- 73,106 pts hospitalized for the first time for COPD
- 17-year follow-up
- 50,580 died during the follow-up

Hazard function of successive hospitalized AE from 1st hospitalization for AECOPD



Suissa et al. Thorax 2012;67:957-63

Hazard ratio of a subsequent AE

Exacerbation sequence number	Number with a subsequent exacerbation	Crude HR	Adjusted* HR (95% CI)
First (reference)	33 166	1.0	1.0 (reference)
Second	19 359	3.0	2.9 (2.8 to 2.9)
Third	12 413	5.1	4.9 (4.8 to 5.0)
Fourth	8374	7.3	6.9 (6.8 to 7.1)
Fifth	5903	9.8	9.2 (8.9 to 9.4)
Sixth	4316	11.9	11.2 (10.8 to 11.5)
Seventh	3190	13.9	13.0 (12.5 to 13.5)
Eighth	2404	16.6	15.2 (14.6 to 15.9)
Ninth	1823	18.1	16.6 (15.8 to 17.4)
Tenth or greater	1403	25.8	23.5 (22.8 to 24.2)

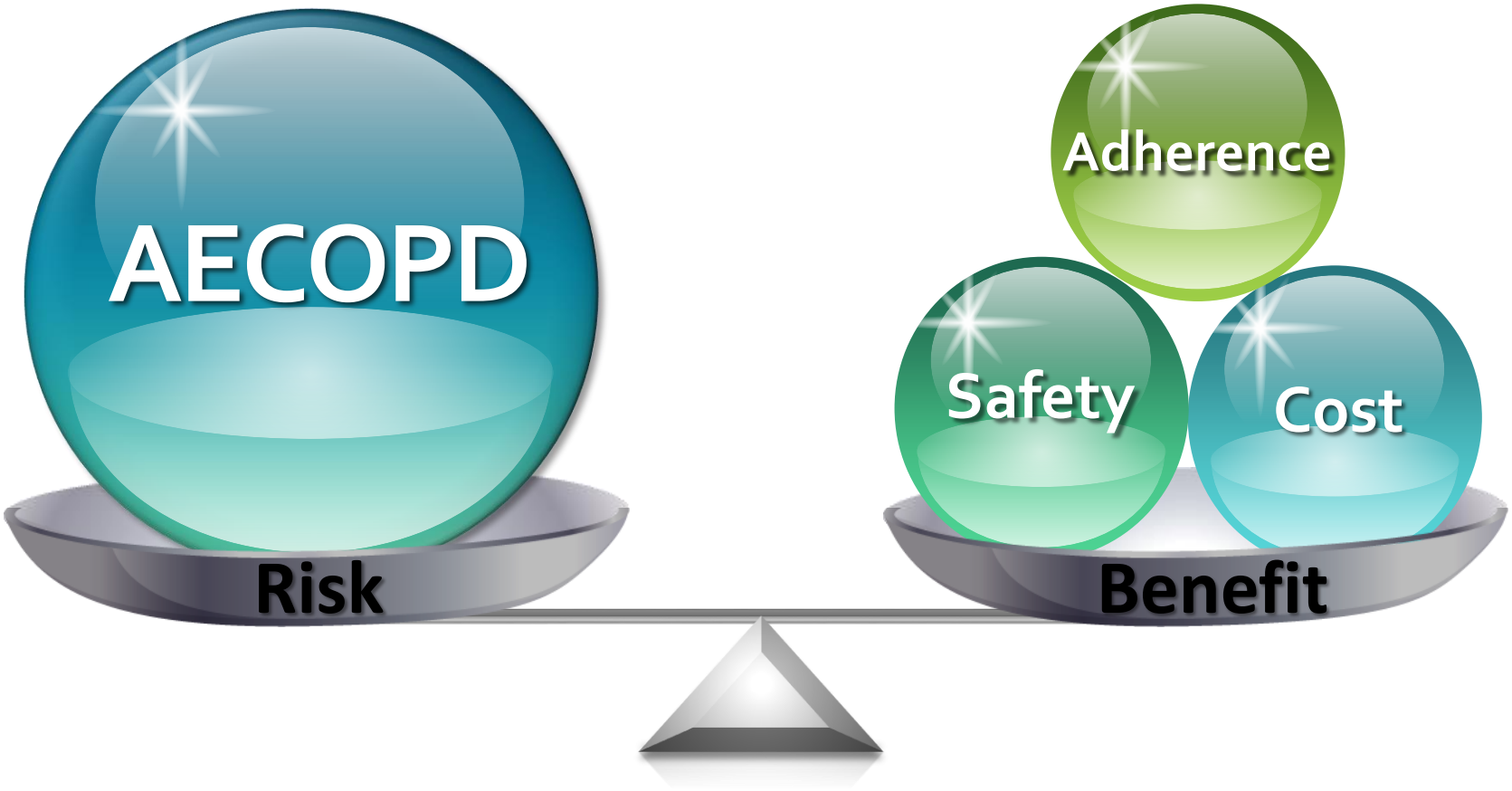
Suissa et al. Thorax 2012;67:957-63

Hazard ratio of death

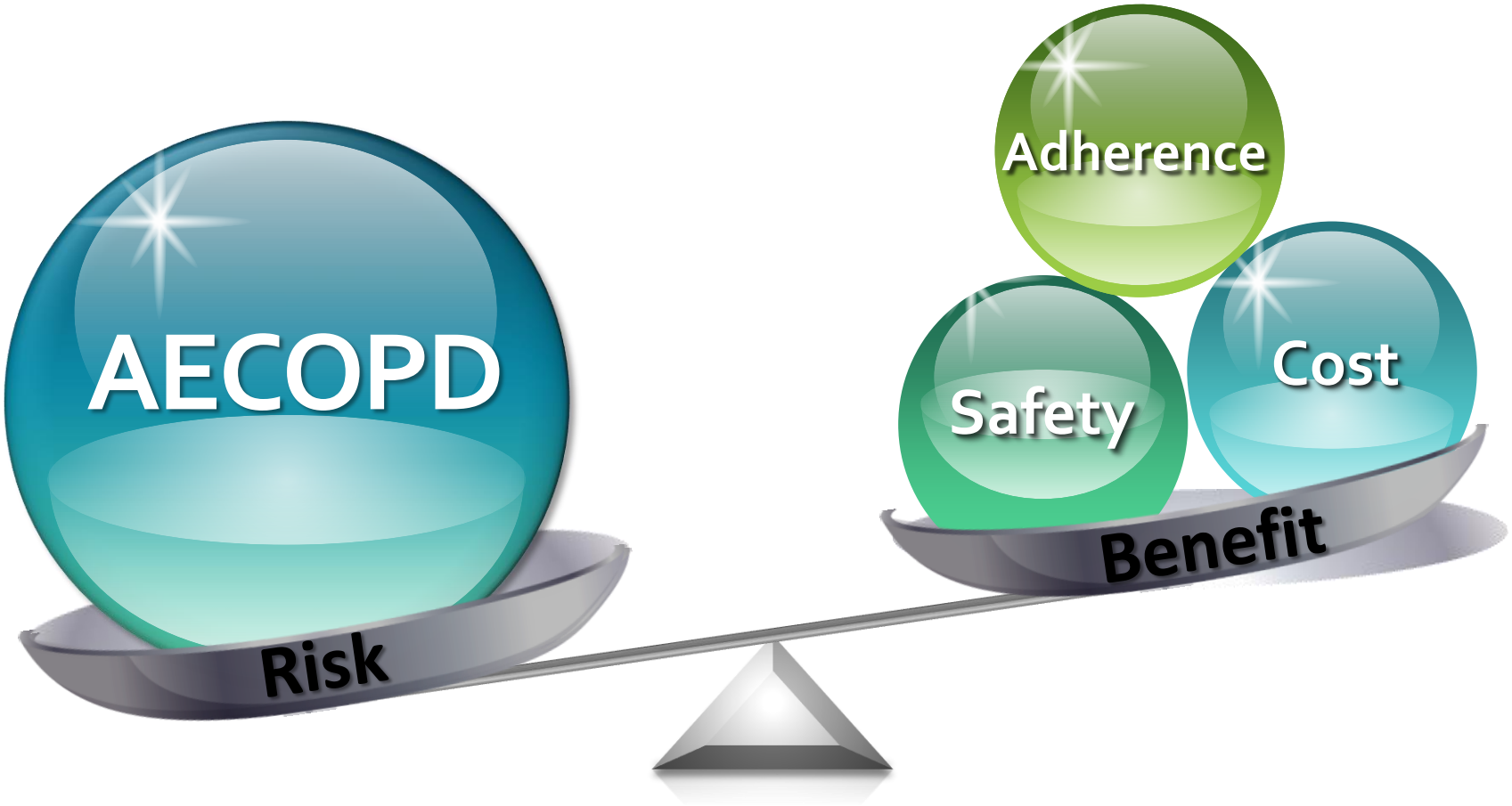
Exacerbation sequence number	Number of deaths	Crude HR	Adjusted* HR (95% CI)
First (reference)	25 953	1.0	1.0 (reference)
Second	9828	1.8	1.9 (1.8 to 1.9)
Third	5203	2.4	2.4 (2.3 to 2.5)
Fourth	3078	2.8	2.9 (2.8 to 3.0)
Fifth	1879	3.0	3.2 (3.0 to 3.4)
Sixth	1207	3.1	3.3 (3.1 to 3.5)
Seventh	872	3.4	3.6 (3.4 to 3.9)
Eighth	645	3.9	4.2 (3.9 to 4.5)
Ninth	470	3.8	4.3 (3.9 to 4.7)
Tenth or greater	1445	4.5	5.2 (4.9 to 5.5)

Suissa et al. Thorax 2012;67:957-63

De-escalation of triple therapy



De-escalation of triple therapy



Suggestions

- **All patients hospitalized due to an AECOPD should be discharged with the prescription of long-term triple therapy.**

- **It is always better to avoid a therapeutic step-up progression when it is not needed rather than being forced subsequently into a step-down approach in which the outcome is always unpredictable.**

감사합니다