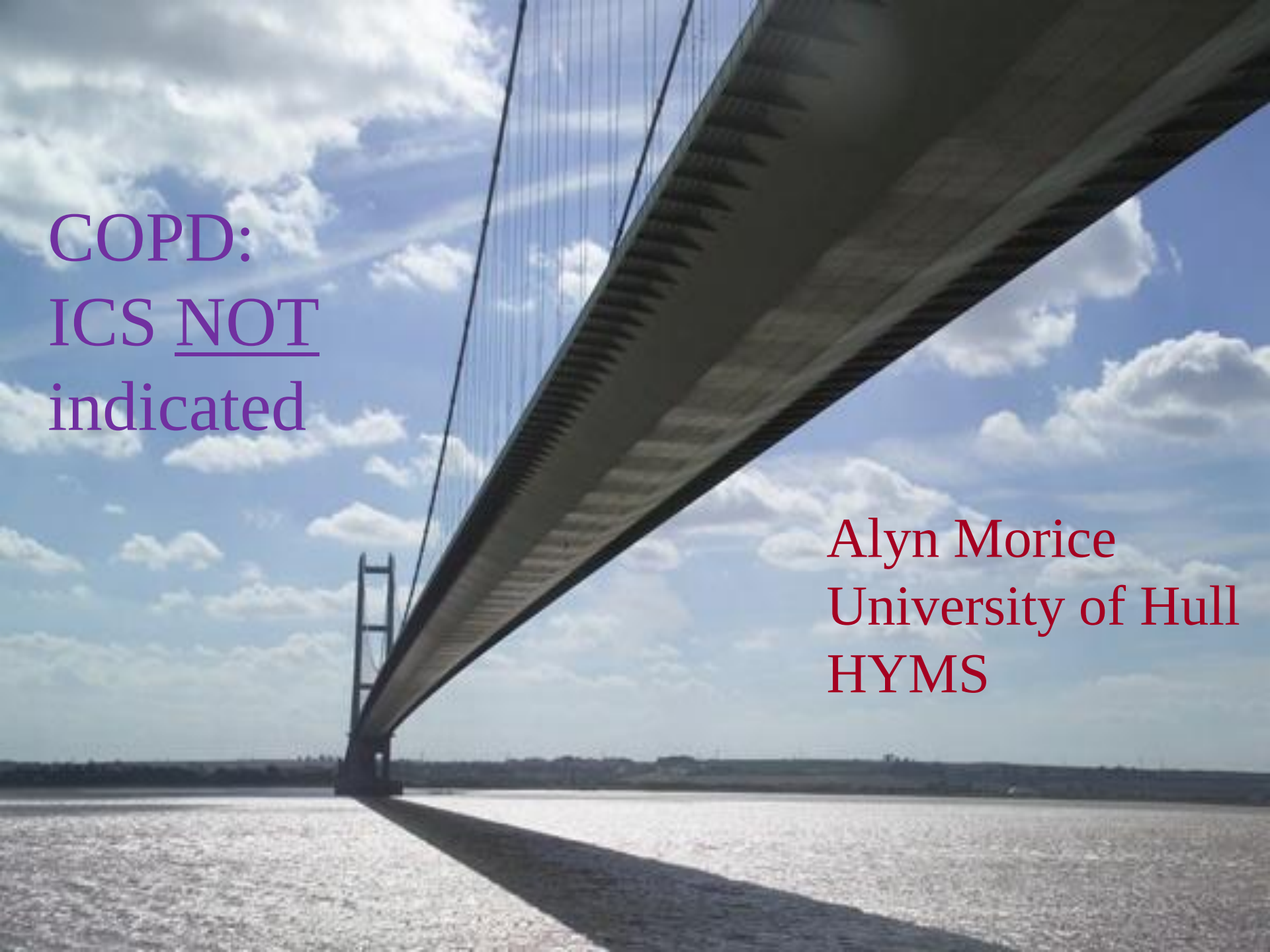


COPD: ICS NOT indicated

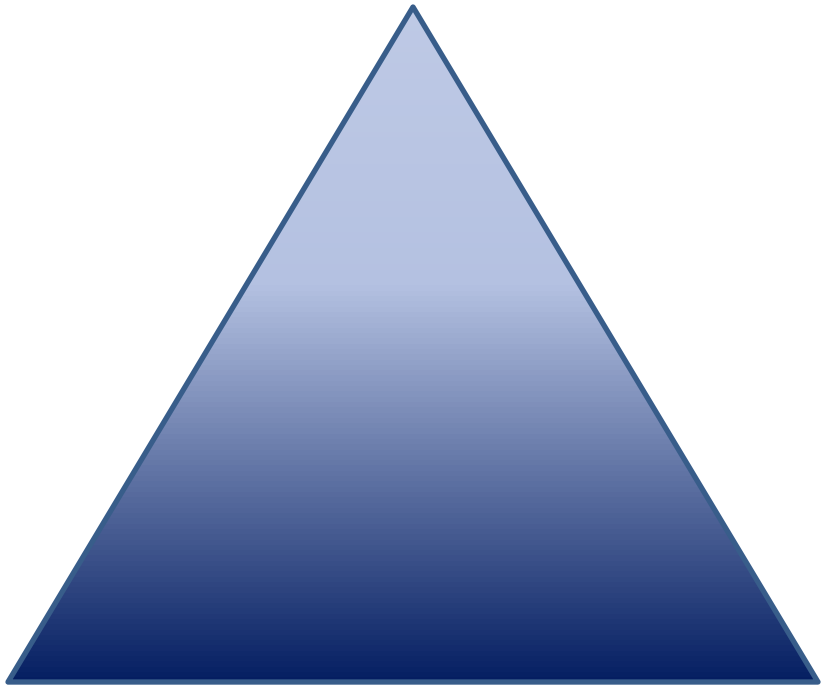
Alyn Morice
University of Hull
HYMS

Prof P Calverley

Gerald the Gnome

What is COPD?

Asthma (eosinophilic bronchitis)



Emphysema

Chronic Bronchitis
(neutrophilic bronchitis)

National Clinical Guideline Centre

Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care

Update guideline

All update work added to the original guideline is highlighted in pink

Note to stakeholders:

The Guideline Development Group wish to point out that this is a partial update of an existing guideline, with the integration of new sections into the old publication. This has inevitably led to inconsistencies in style, particularly where new tables and forest plots have been inserted alongside old-style evidence statements, and also where new recommendations (without any gradings) have been added to, or replaced, existing recommendations which do have gradings.

The expanded section on Inhaled Therapy (which now incorporates the previous separate sections on Inhaled Bronchodilators, Inhaled Corticosteroids and Inhaled Combination Therapy) now concludes with a number of new recommendations which have all been grouped together for ease of reference, although this has necessitated their being somewhat removed from their supporting evidence.

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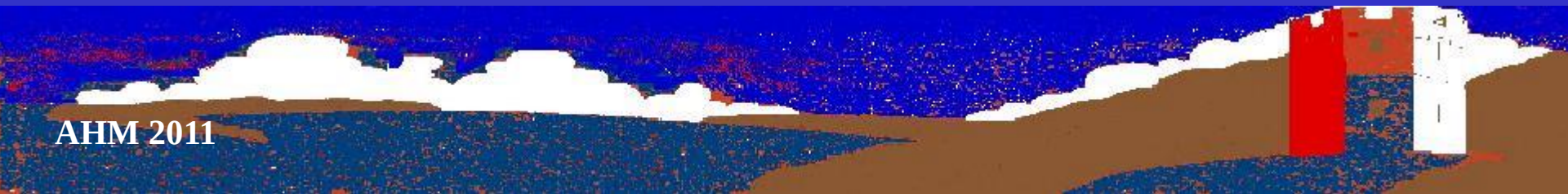
Page 1 of 673!

The New Asthma and COPD Guidelines

Hull & E Yorkshire APC

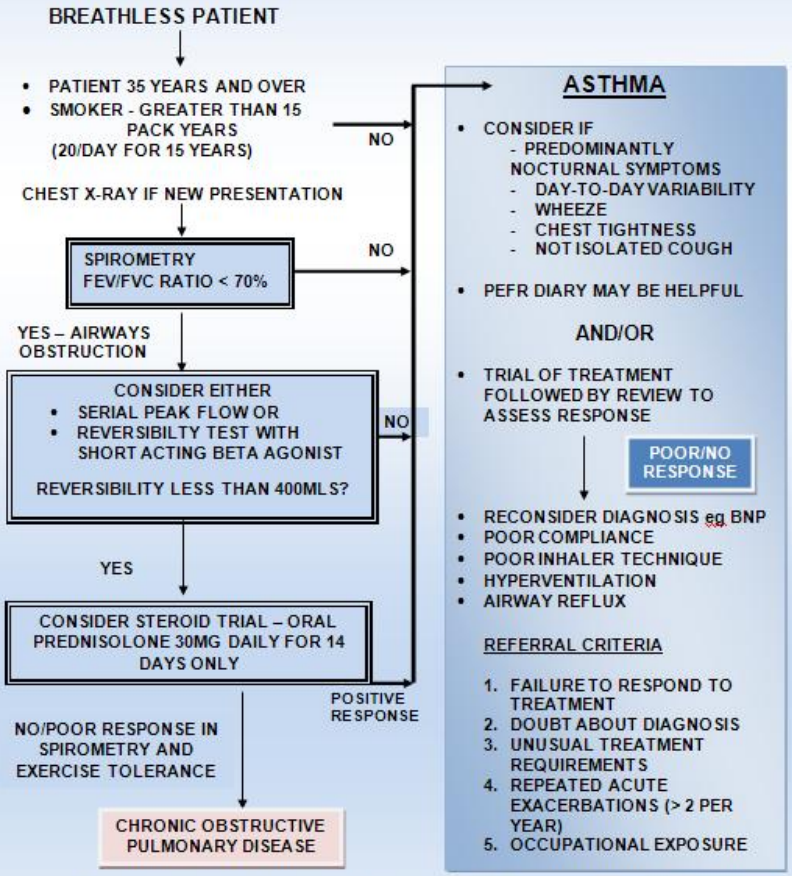


AHM 2011

EAST RIDING AND HULL TRUSTS
JOINT RESPIRATORY GUIDELINES FOR ADULTS

DIAGNOSIS OF AIRWAYS DISEASE

"Long term treatment of airways disease should not be contemplated without a firm diagnosis"



Approved By: Hull and East Riding Prescribing Committee Review date: May 2015

COPD Treatment Pathway

Establish diagnosis of COPD in at risk population with history, examination and spirometry (FEV^1/FVC ratio <70%)
Establish severity of disease by FEV^1 as % predicted

Management of RISK FACTORS plus EDUCATION plus IMMUNISATION

SMOKING CESSATION Lifestyle Advice Diet/Exercise Influenza vacc (annual) Pneumococcal vacc. Psychological Issues

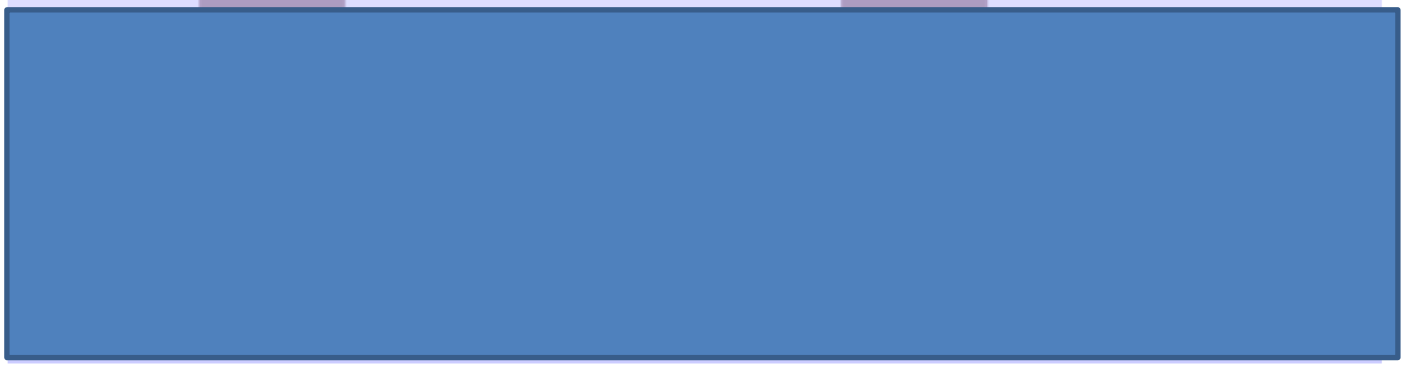
Pulmonary rehabilitation if functionally disabled – (Ensure treatment is optimised)

PHARMACOLOGICAL TREATMENT
Review at each step after one month before escalating treatment

SHORTNESS OF BREATH

prn short acting β^2 agonist

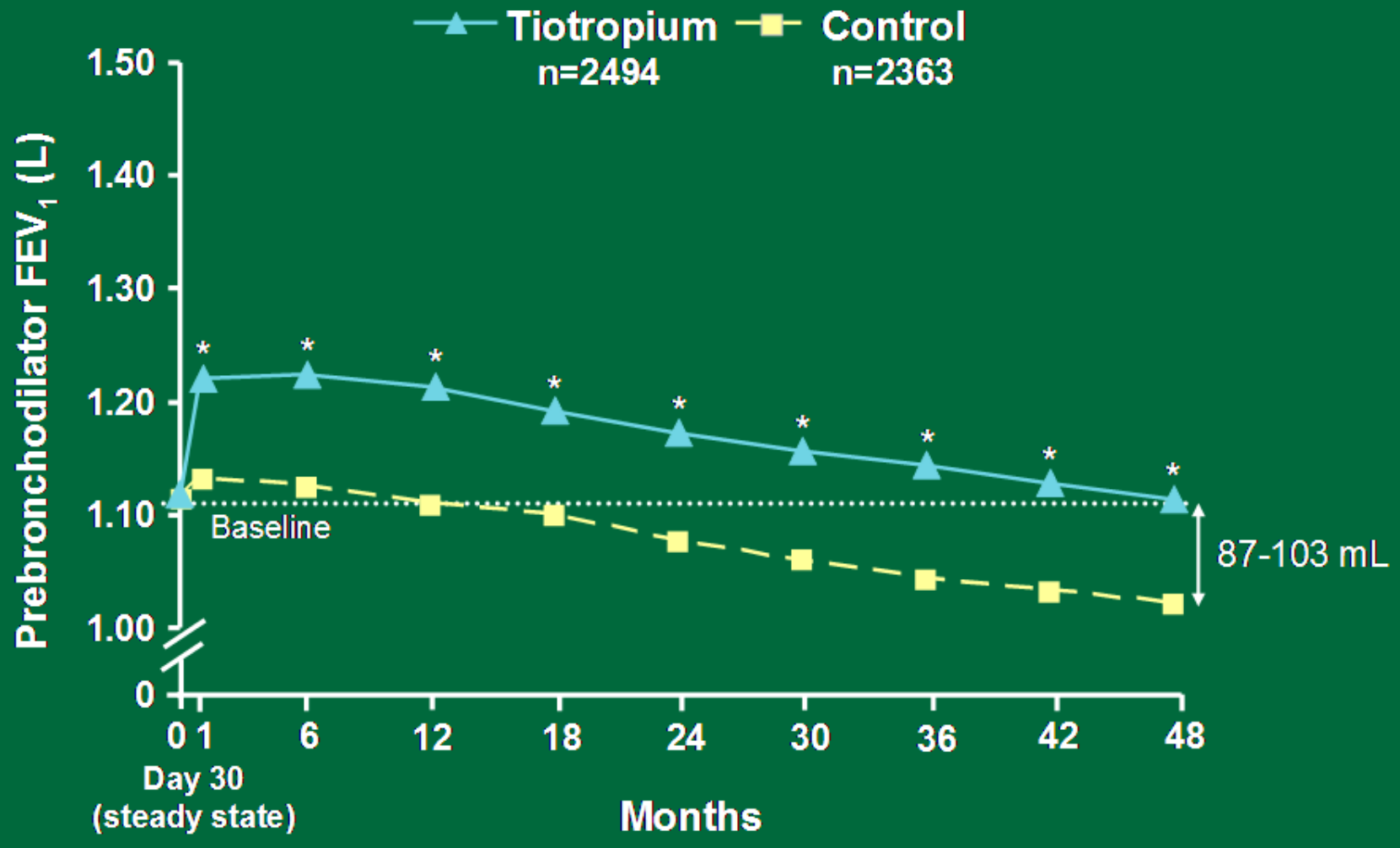
FREQUENT (>2/YEAR) EXACERBATIONS



Approved By: Hull & East Riding Prescribing Committee

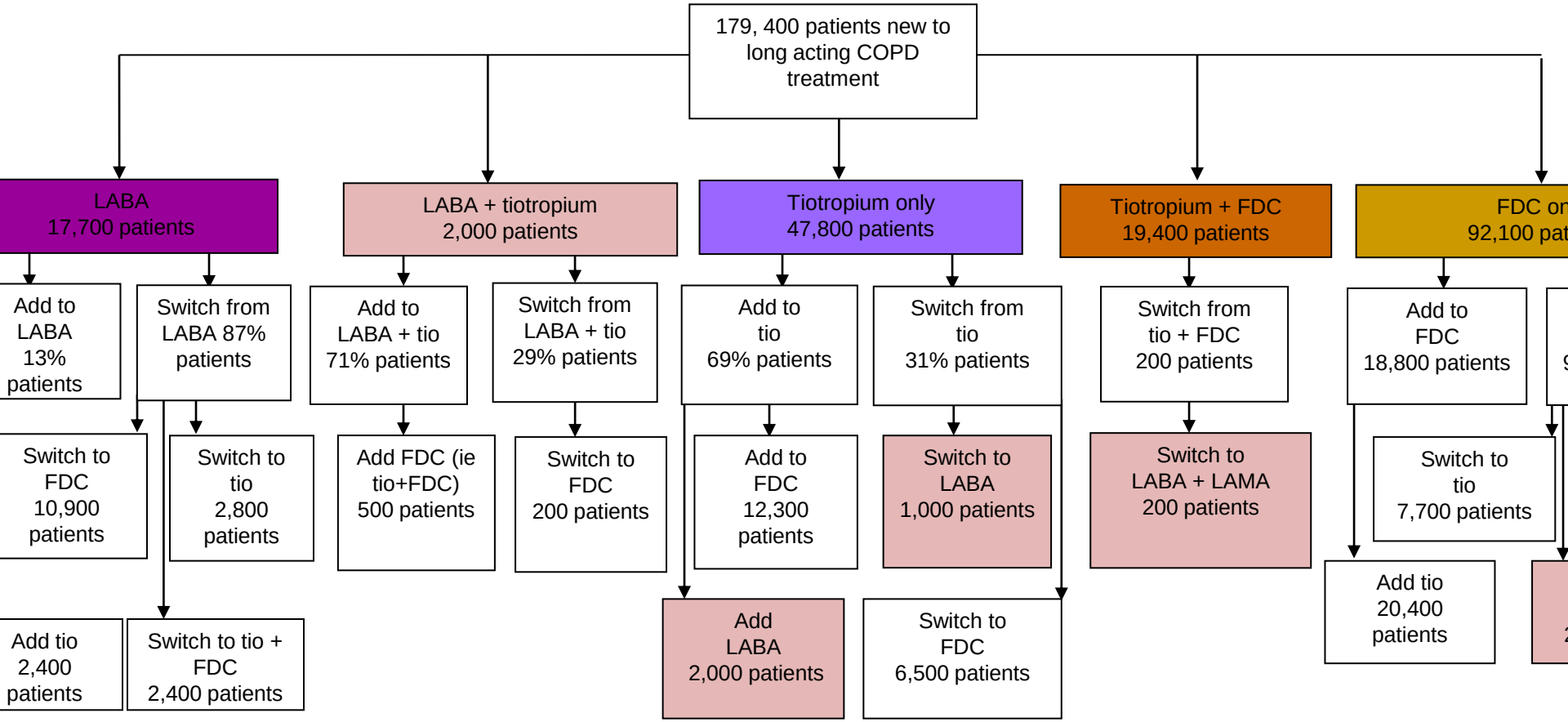
Review Date: May 2015

Tiotropium Provides Significant and Sustained Improvements in Prebronchodilator FEV_1

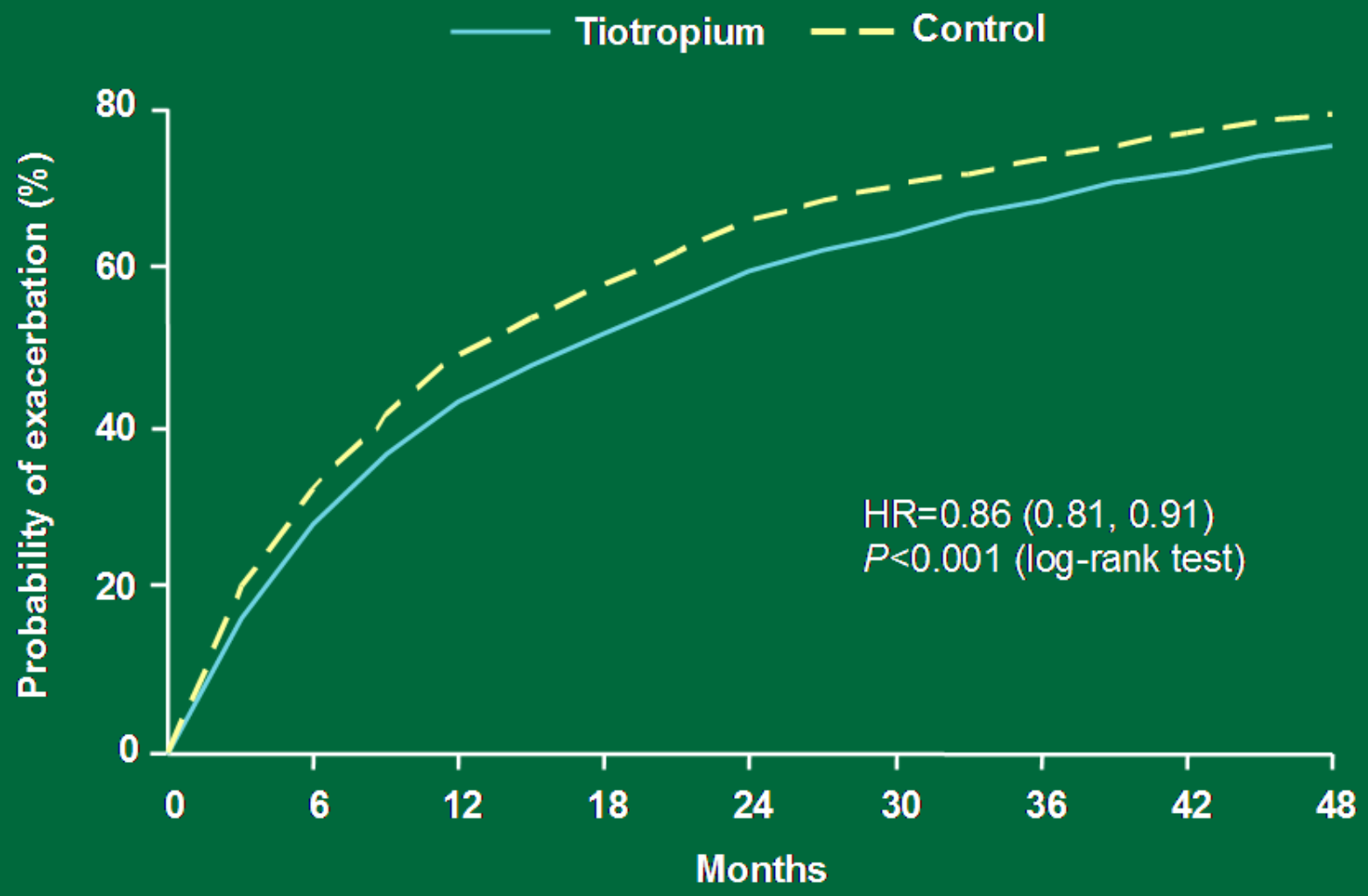


*P<0.001 versus control

Tashkin DP et al. UPLIFT Study Investigators. N Engl J Med 2008;359:1543-54


179, 400 patients new to long acting COPD treatment
LABA 17,700 patients
LABA + tiotropium 2,000 patients
Tiotropium only 47,800 patients
Tiotropium + FDC 19,400 patients
FDC on 92,100 pat
Add to LABA 13% patients
Switch from LABA 87% patients
Add to LABA + tio 71% patients
Switch from LABA + tio 29% patients
Add to tio 69% patients
Switch from tio 31% patients
Switch from tio + FDC 200 patients
Add to FDC 18,800 patients
Switch to FDC 10,900 patients
Switch to tio 2,800 patients
Add FDC (ie tio+FDC) 500 patients
Switch to FDC 200 patients
Add to FDC 12,300 patients
Switch to LABA 1,000 patients
Switch to LABA + LAMA 200 patients
Switch to tio 7,700 patients
Add tio 2,400 patients
Switch to tio + FDC 2,400 patients
Add LABA 2,000 patients
Switch to FDC 6,500 patients
Add tio 20,400 patients

Tiotropium Significantly Reduces the Risk of Exacerbations in UPLIFT®



HR = Hazard ratio (95% confidence intervals)

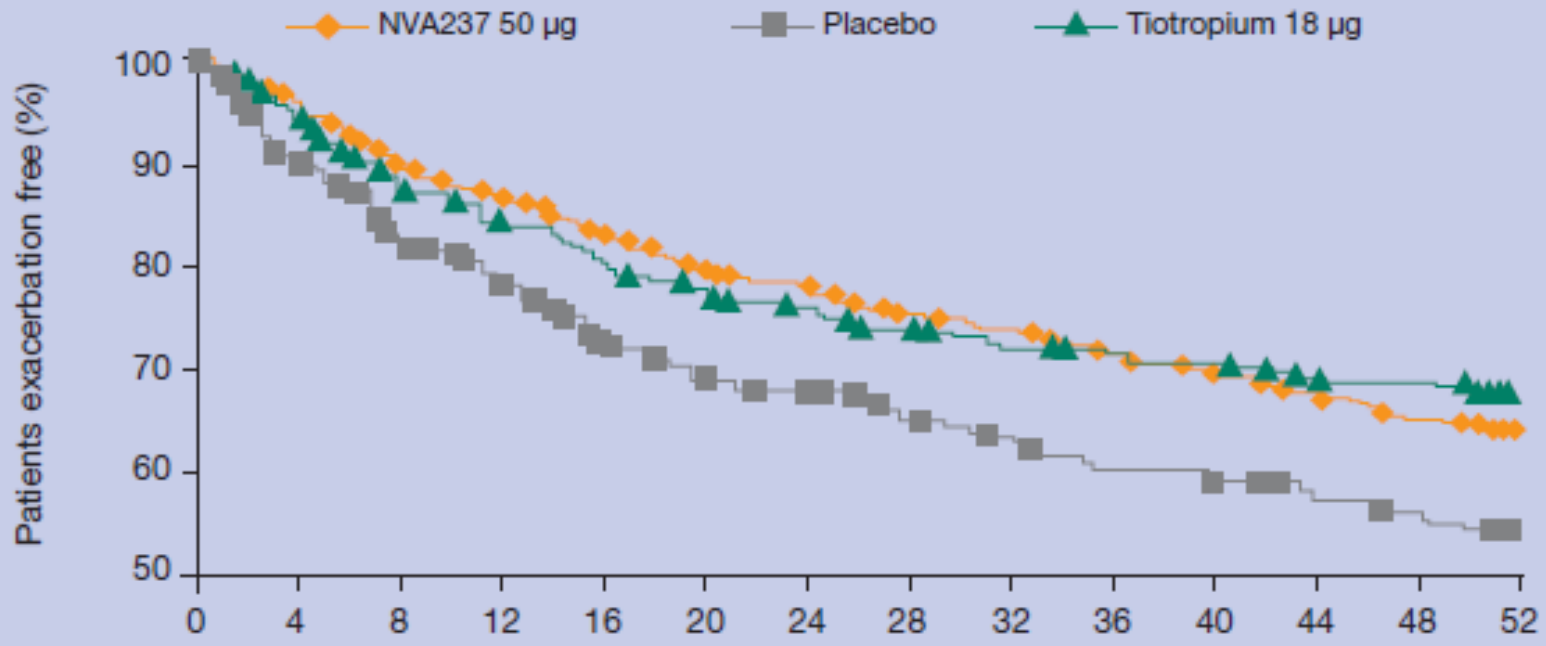
Tashkin DP et al. UPLIFT Study Investigators. N Engl J Med 2008;359:1543-54

NVA237 once daily reduces COPD exacerbations with similar rates to tiotropium: the GLOW2 trial

E.M. Kerwin[1], A. Pedinoff[2], T.B. Casale[3], N. Gallagher[4], C. Martin[4], D. Banerji[5], Y. Lu[5], T. Overend[4]

[1]Clinical Research Institute of Southern Oregon, Medford, OR, USA; [2]Princeton Center For Clinical Research, Princeton, NJ, USA;
[3]Division of Allergy & Immunology, Creighton University, Omaha, NE, USA; [4]Novartis Horsham Research Centre, Horsham, UK; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Figure 2. Kaplan-Meier plot of time to first moderate or severe exacerbation



Number at Risk

NVA237	495	451	426	394	370	360	341	335	318	310	296	282	239
Placebo	229	202	188	168	159	153	142	137	129	129	122	116	98
Tiotropium	245	222	209	200	190	184	176	169	166	163	157	155	129

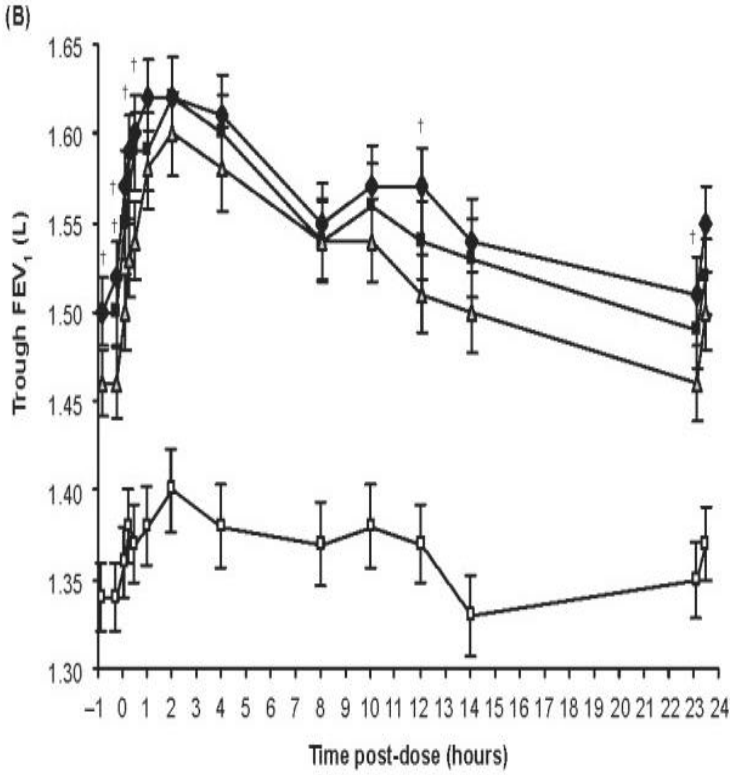
Ultra-LABAs

- Once-daily beta2-agonists or ultra long-acting beta2-agonists (LABAs) are under development for asthma and COPD.

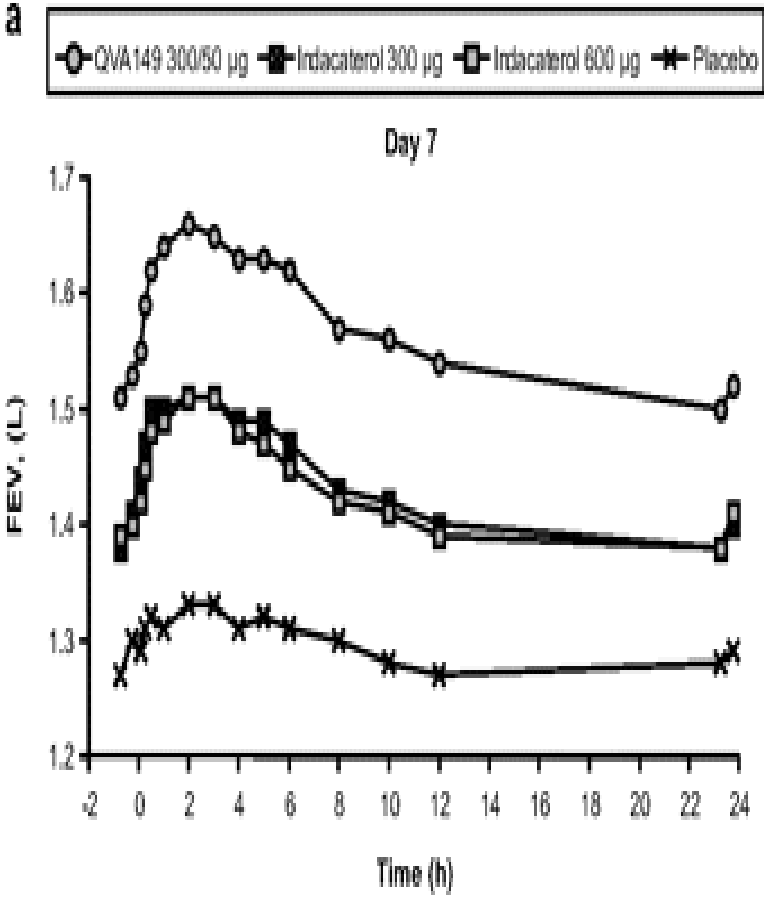
- **Ultra-LABAs** under development for treatment of asthma and COPD include:
  - carmoterol
  - indacaterol
  - vilanterol

- Indacaterol is the only once-daily ultra-LABA approved for COPD maintenance.

INDACETEROL ALONE AND COMBINED WITH GLYCOPYRRONIUM -14 DAY DATA



Vogelmeier et al. Respir Res 2010



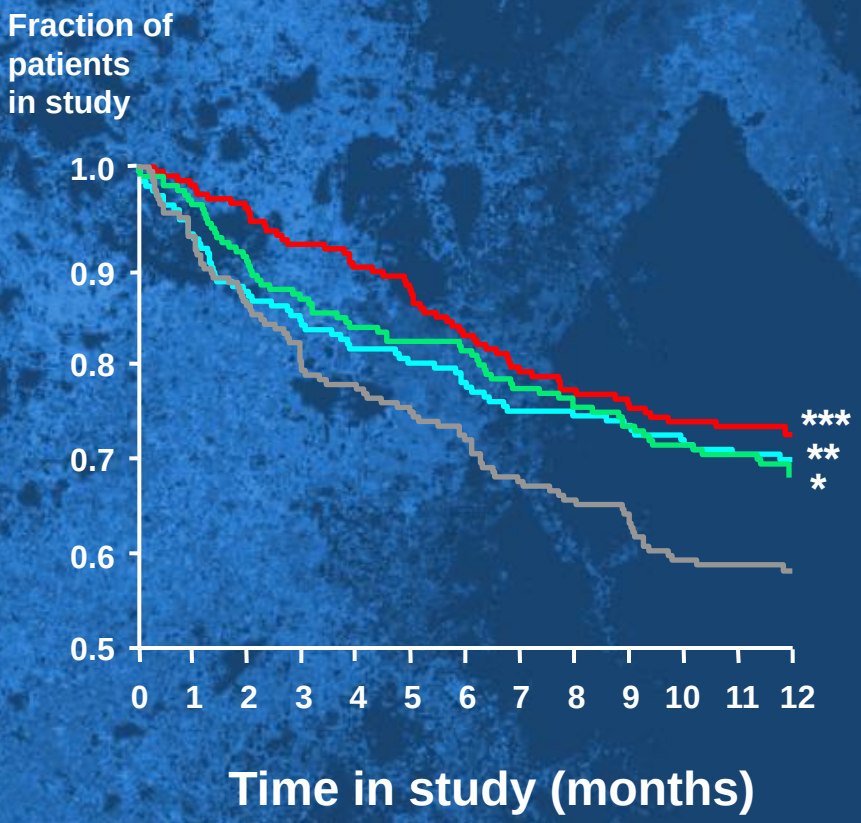
Van Noord et al. Thorax 2010

Kaplan–Meier plot of discontinuations

Ref:

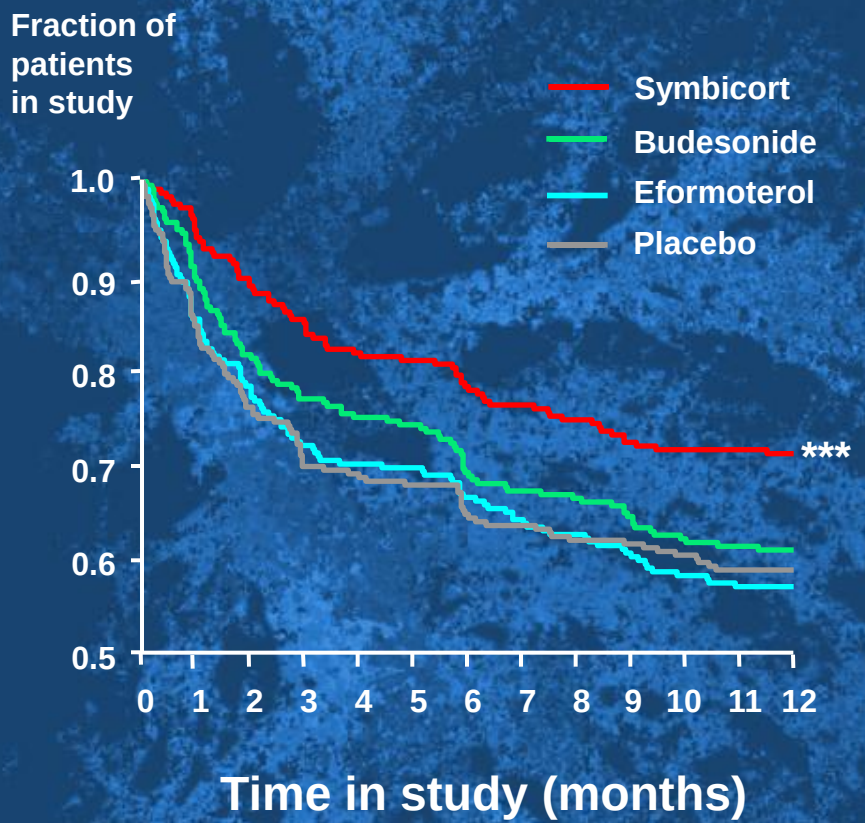
1. Szafranski W, European Respiratory Journal 2003
2. Calverley P, Thorax 2002
3. AstraZeneca UK Ltd Data on File SYM\037\APR2003

Withdrawal – Szafranski[1]



***p<0.001 Symbicort vs placebo
*p<0.05 budesonide vs placebo
**p=0.01 eformoterol vs placebo

Optimisation – Calverley[2,3]



***p=0.001 Symbicort vs placebo
p=0.037 Symbicort vs budesonide
p<0.001 Symbicort vs eformoterol

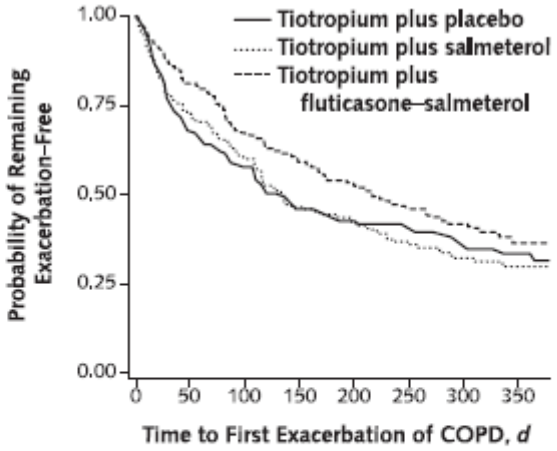
Annals of Internal Medicine | ARTICLE

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 Intern Med. 2007;146:545-555.



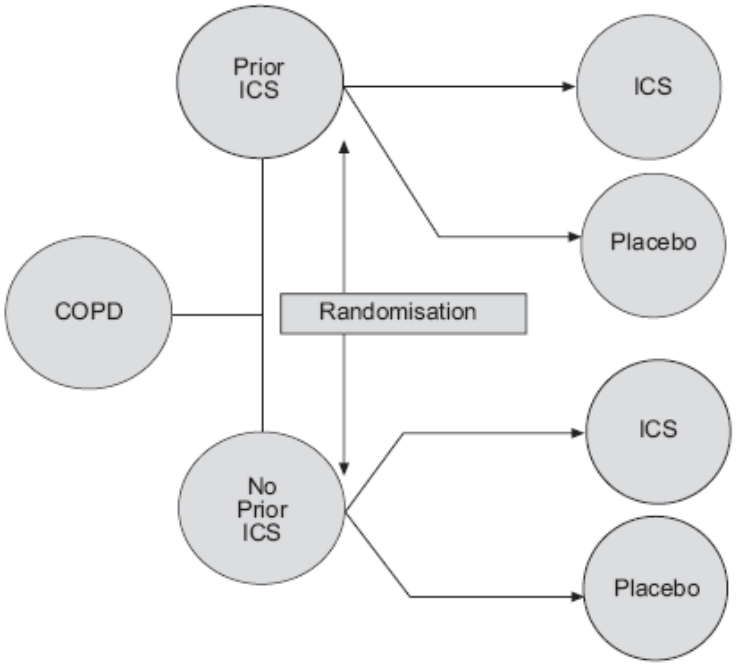
Patients at risk, *n*								
Tiotropium plus placebo	156	102	84	65	59	57	50	45
Tiotropium plus salmeterol	148	100	81	61	55	48	41	38
Tiotropium plus fluticasone–salmeterol	145	116	94	82	72	62	55	48

Eur Respir J 2008; 31: 927–933
DOI: 10.1183/09031936.00098307

PERSPECTIVE

Methodological issues in therapeutic trials of COPD

S. Suissa*,#, P. Ernst*,#, K.L. Vandemheen¶ and S.D. Aaron¶



Effect of pre-treatment with ICS in Optimal

Tiotropium

+ placebo
+ Tiotropium
+ Tiotropium and FP

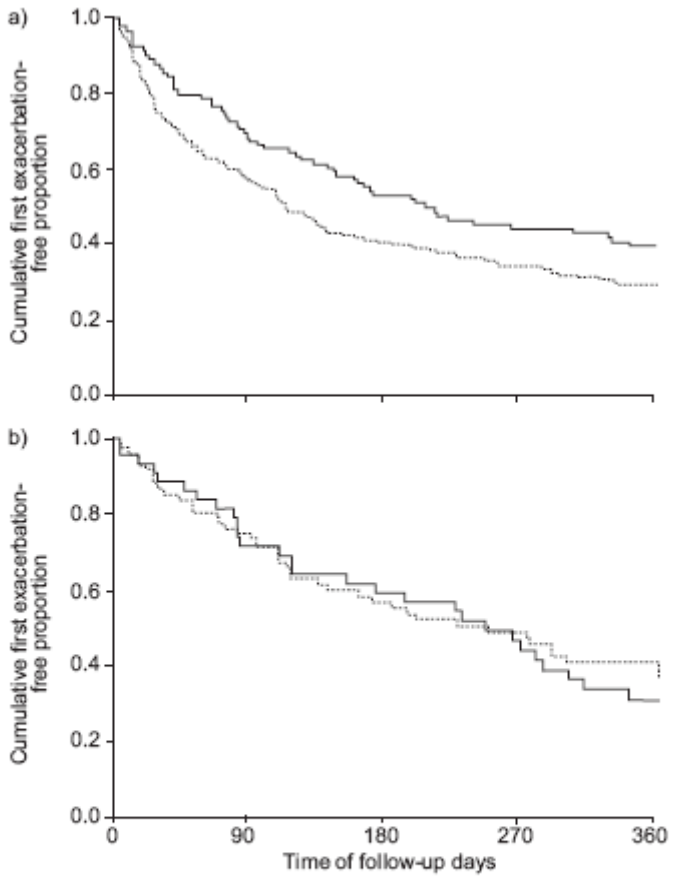
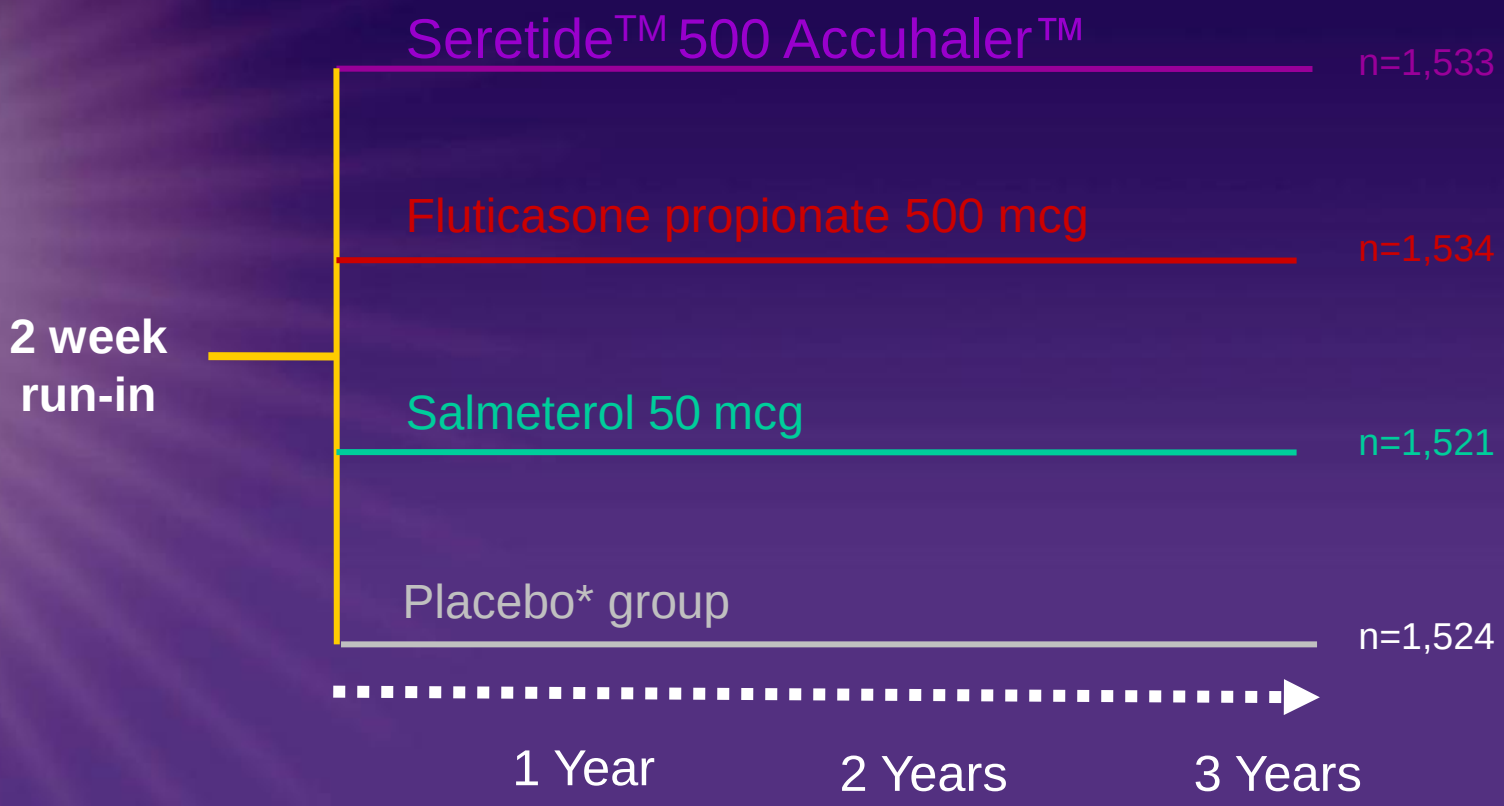


FIGURE 2. Kaplan–Meier curves for the time to the first exacerbation comparing the patients randomised to either inhaled corticosteroids (ICS) or bronchodilators among a) the 335 patients who were previous users of ICS at the time of randomisation, and b) the 114 patients who were naive to ICS at the time of randomisation (data from the Canadian Optimal Therapy of COPD Trial). ——: inhaled ICS users; ----: bronchodilator users.

TORCH: study design

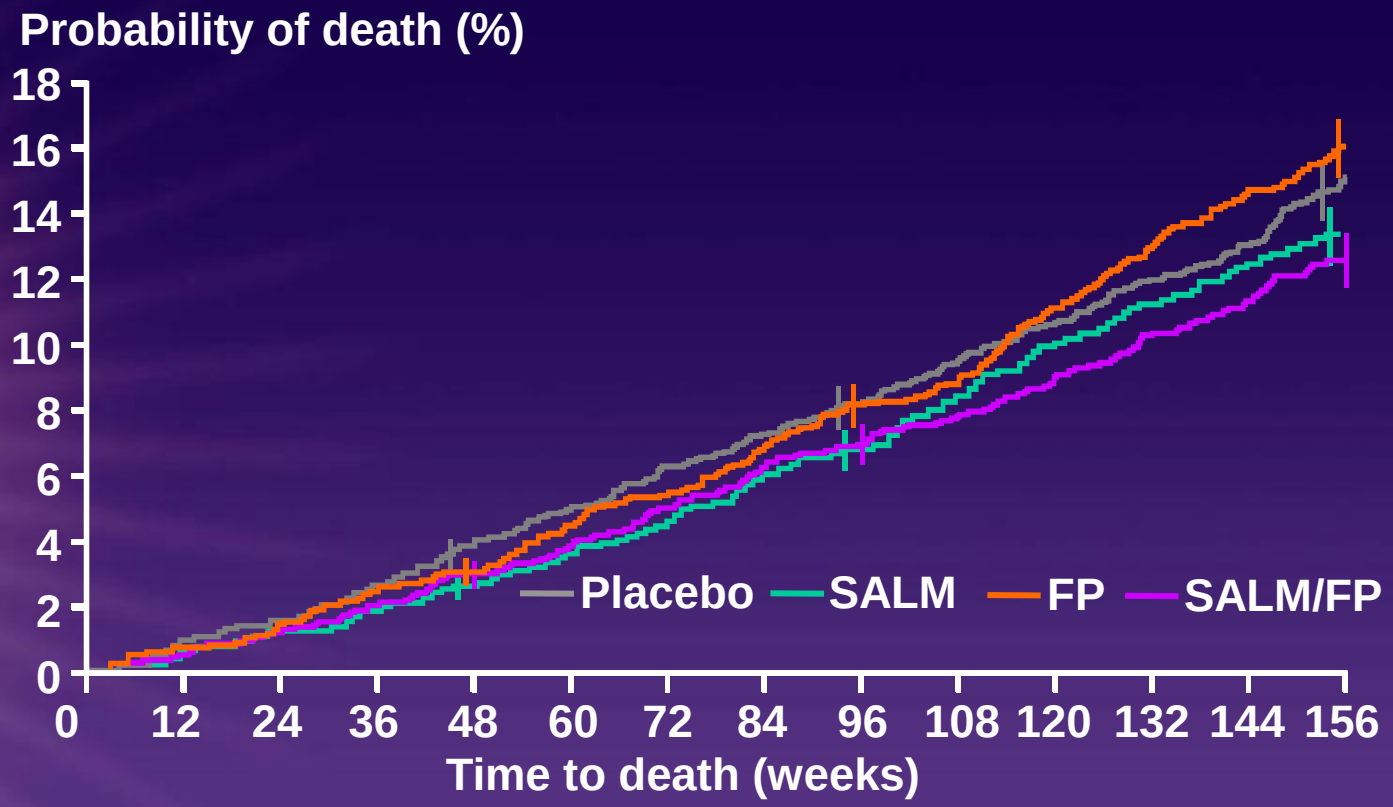
3-year study duration (6,112 patients)



*The control group received usual medications other than ICS or long-acting bronchodilators

Vestbo et al. *Eur Respir J* 2004

All-cause mortality at 3 years



Number alive				
Placebo	1524	1464	1399	1293
FP	1533	1487	1426	1339
SALM	1521	1481	1417	1316
SALM/FP	1534	1487	1409	1288

Vertical bars are standard errors

The addition of fluticasone has no effect on mortality

TABLE 4 Factorial analysis of Towards a Revolution in COPD Health (TORCH) data of the independent effects of fluticasone and salmeterol on the 3-yr incidence of all-cause mortality

	Medication allocated		Crude RR	Adjusted RR (95% CI)
	Yes deaths/total n	No deaths/total n		
Medication				
Fluticasone	439/3067	436/3045	1.00	1.00 (0.89–1.13)
Salmeterol	398/3054	477/3058	0.83	0.83 (0.74–0.95)

RR: relative rate ratio; CI: confidence interval.

	Yes	No	
Salmeterol	13%	16%	RR 0.83
Fluticasone	14%	14%	RR 1.0

Most common reported AEs which started during treatment: Rate per treatment year

	Placebo (N = 1544)	SALM (N = 1542)	FP (N = 1552)	SFC (N = 1546)
COPD exacerbations	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02

Calverley *et al.* NEJM 2007

What is known on the comparative effectiveness of ICS/LABAs in COPD?

- **Both fluticasone propionate/salmeterol (FPS) and budesonide/formoterol (BF) are perceived to reduce exacerbations similarly in COPD patients.**
- **No double-blind prospective RCTs have compared exacerbation rates between FPS vs. BF in COPD patients**
- **One propensity matched Canadian COPD cohort study of 1 year duration, suggested that efficacy differences may exist between the ICS/LABAs in favour of BF.[1]**
- **FPS use has been shown to increase pneumonia in COPD patients[2-6] and also increases exacerbations requiring antibiotic use vs. tiotropium.[5] The pneumonia risk with FPS also increases with disease severity.[3]**
- **No similar increase in pneumonia risk has been reported in COPD patients using BF at 1 year [6,7,8]**

1. Blais L *et al* Clinical Therapeutics 2010; 32: 1320
2. Crim et al Eur Respir J 2009, 34: 641
3. Jenkins et al Respir. Research 2009 10:59
4. Calverley et al. Chest 2011;139:505
5. Wedzicha JA, *et al*. AJRCCM *2008*
6. Singh S *et al* Curr Opin Pulm Med. 2010; 16: 118
7. Halpin D *et al*., Int J Clin Pract. 2011, 65, 764
8. Sin DD et al. Lancet 2009; 374:712

Pneumonia Risk in COPD Patients (Stratified by ICS Type)

Meta-analysis of ICS use for ≤3 years duration

Corticosteroid type (No. of studies)	ICS containing regimen n/N (%)	Non ICS control n/N (%)	Adjusted Pneumonia Odd Ratio (95% CI)
Fluticasone (16)*	612 / 7,919 (7.7)	364 / 7,705 (4.7)	1.67 (1.47, 1.89) **
Budesonide (6)*	124 / 3,656 (3.3)	70 / 2,615 (2.7)	1.34 (1.01, 1.79)
Mometasone (1)	25 / 616 (4.1)	6 / 295 (2.0)	2.00 (0.83, 4.81) [ns]

** data inclusive of combinations with exposure lasting up to 3 years with fluticasone and budesonide*
*** statistically significant increase with fluticasone p<0.0001*
[ns] = no statistically significant increase in risk detected

- Up to 3 years exposure with fluticasone was associated with a significant 67% increase in risk.
- 1 of the 24 trials focused on mometasone for ≤1 year, i.e. long-term risk with this ICS is unclear

Singh S *et al* Curr Opin Pulm Med. 2010; 16: 118

Abstracts presented at ERS 2012

Effectiveness of fixed ICS/LABA combinations in COPD – A population based register linkage study

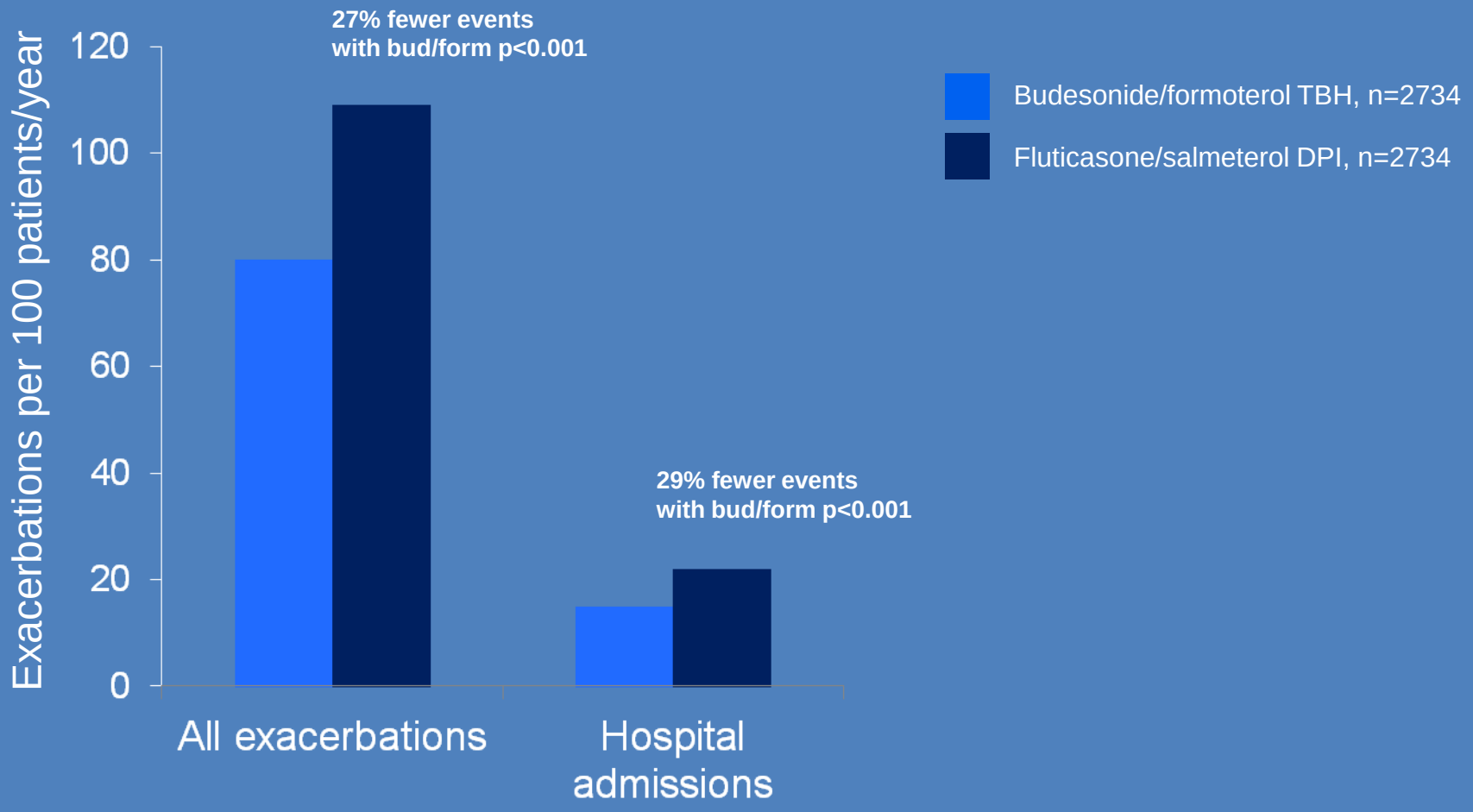
B. Stallberg, C. Janson, K. Lisspers, G. Johansson, L. Jörgensen, G. Stratelis, G. Telg, K. Larsson (Uppsala,
Södertälje, Stockholm, Sweden)

Pneumonia in COPD patients treated with fixed ICS/LABA combinations

C. Janson, K. Larsson, K. Lisspers, B. Ställberg, G. Stratelis, G. Telg, L. Jörgensen, G. Johansson (Uppsala,
Stockholm, Södertälje, Sweden)

ERS Abstract: Exacerbation rate in the matched cohort with censoring for 14 days to avoid double counting events

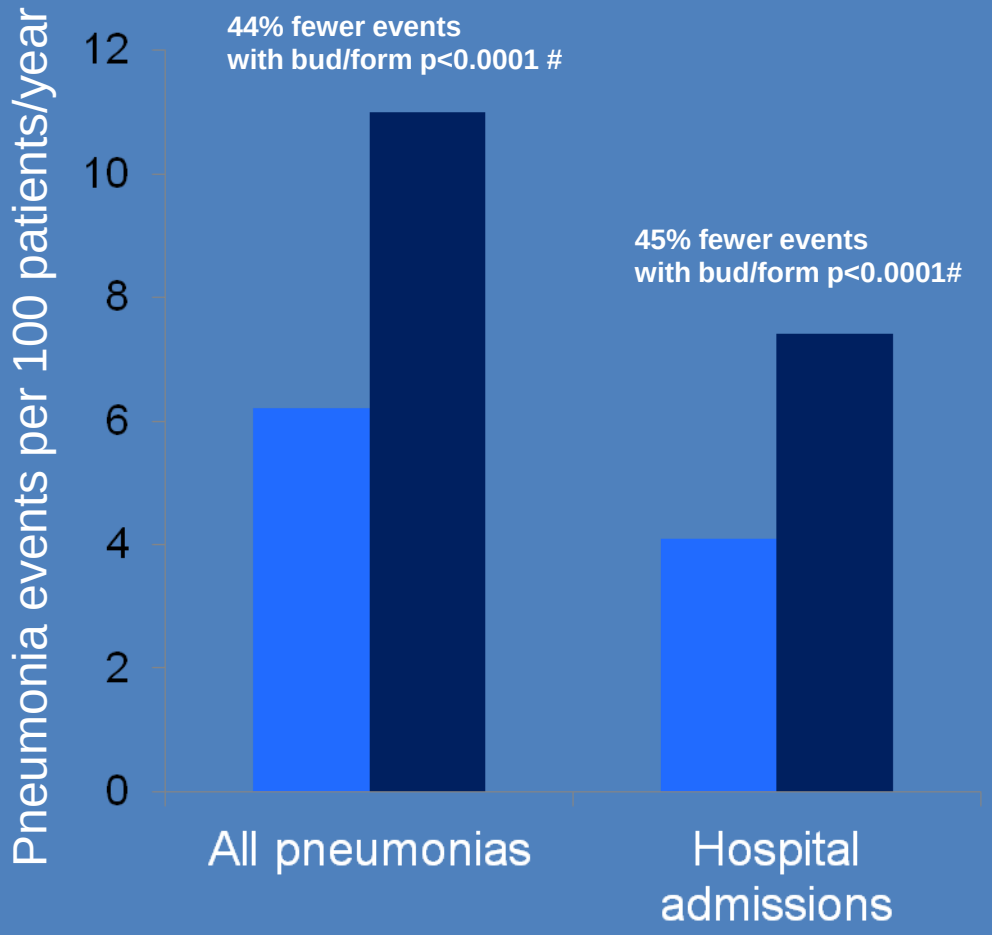
Stallberg B et al ERJ 2012 ERS Abstract #4339



Exacerbations defined as a script of oral steroids alone or antibiotics alone or ER visits for COPD were all significantly fewer in the budesonide/formoterol group (p<0.001)

ERS Abstract : Pneumonia rate in the matched cohort with censoring for 14 days to avoid double counting events

Janson C et al ERJ 2012 ERS Abstract #2897



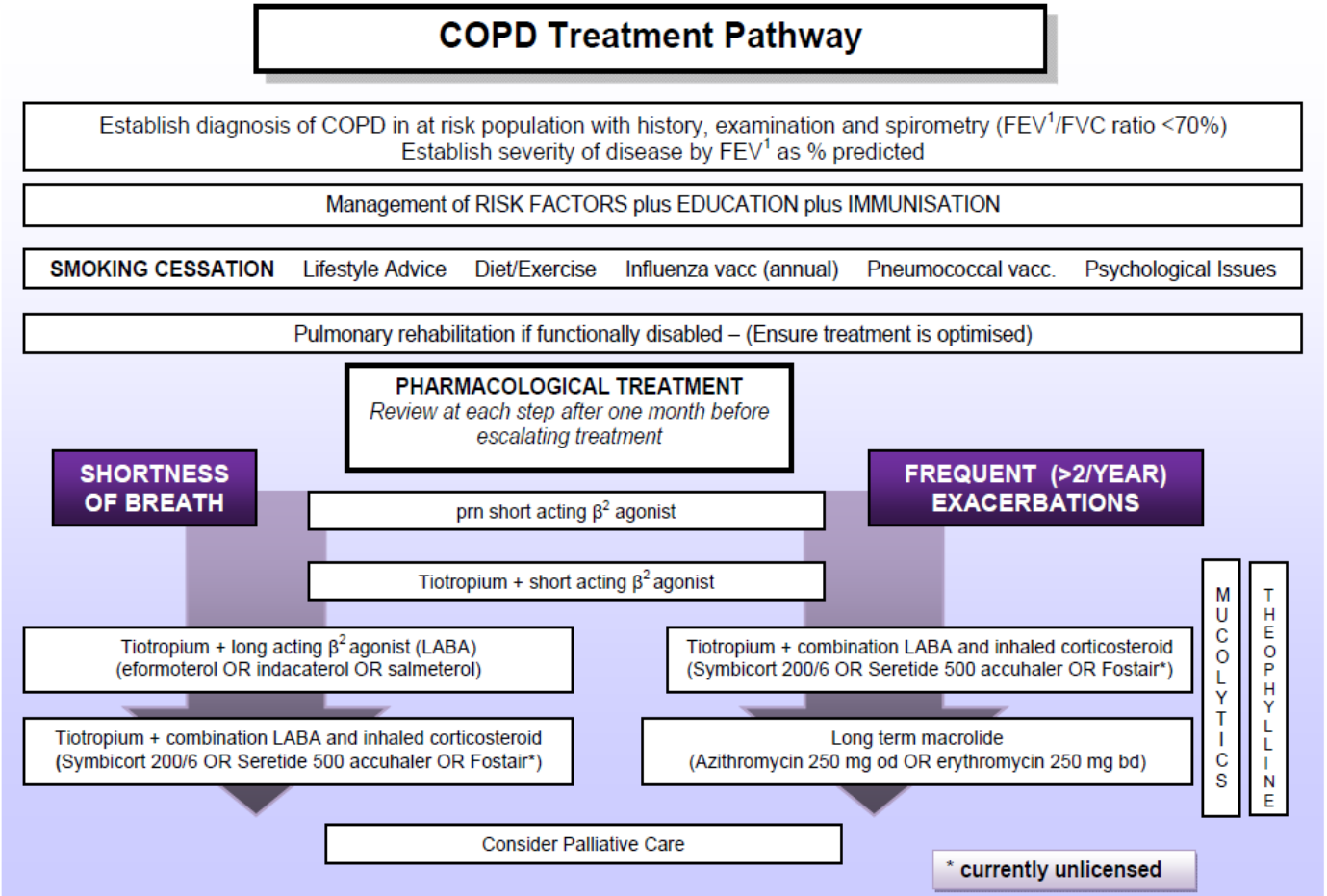
Budesonide/formoterol TBH, n=2734

Fluticasone/salmeterol DPI, n=2734

 # NB: 44-45% reductions in rate with bud/form correspond to an ~ 1.79 to 1.82 fold increase in event rate with fluticasone/salmeterol

Pneumonia hospital days per 100 patient-treatment years were on budesonide/formoterol (34 days) vs fluticasone/salmeterol (63 days), i.e. a 46% reduction with Budesonide/formoterol (p<0.0001)

COPD Treatment Pathway



Approved By: Hull & East Riding Prescribing Committee

Review Date: May 2015