FENOTIPIZZAZIONE E TAILORING TERAPEUTICO DEL PAZIENTE ANZIANO CON BPCO

I corticosteroidi inalatori

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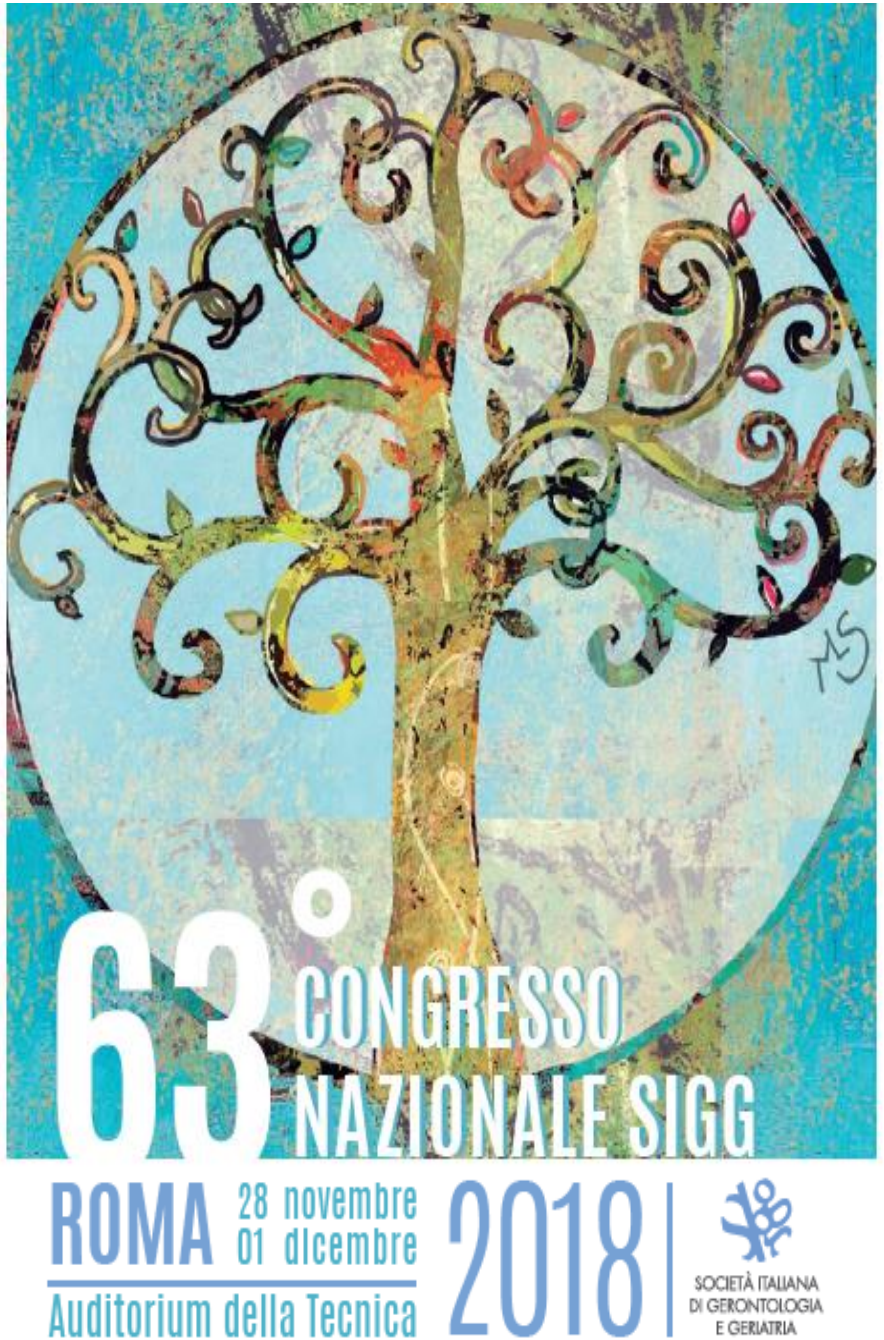
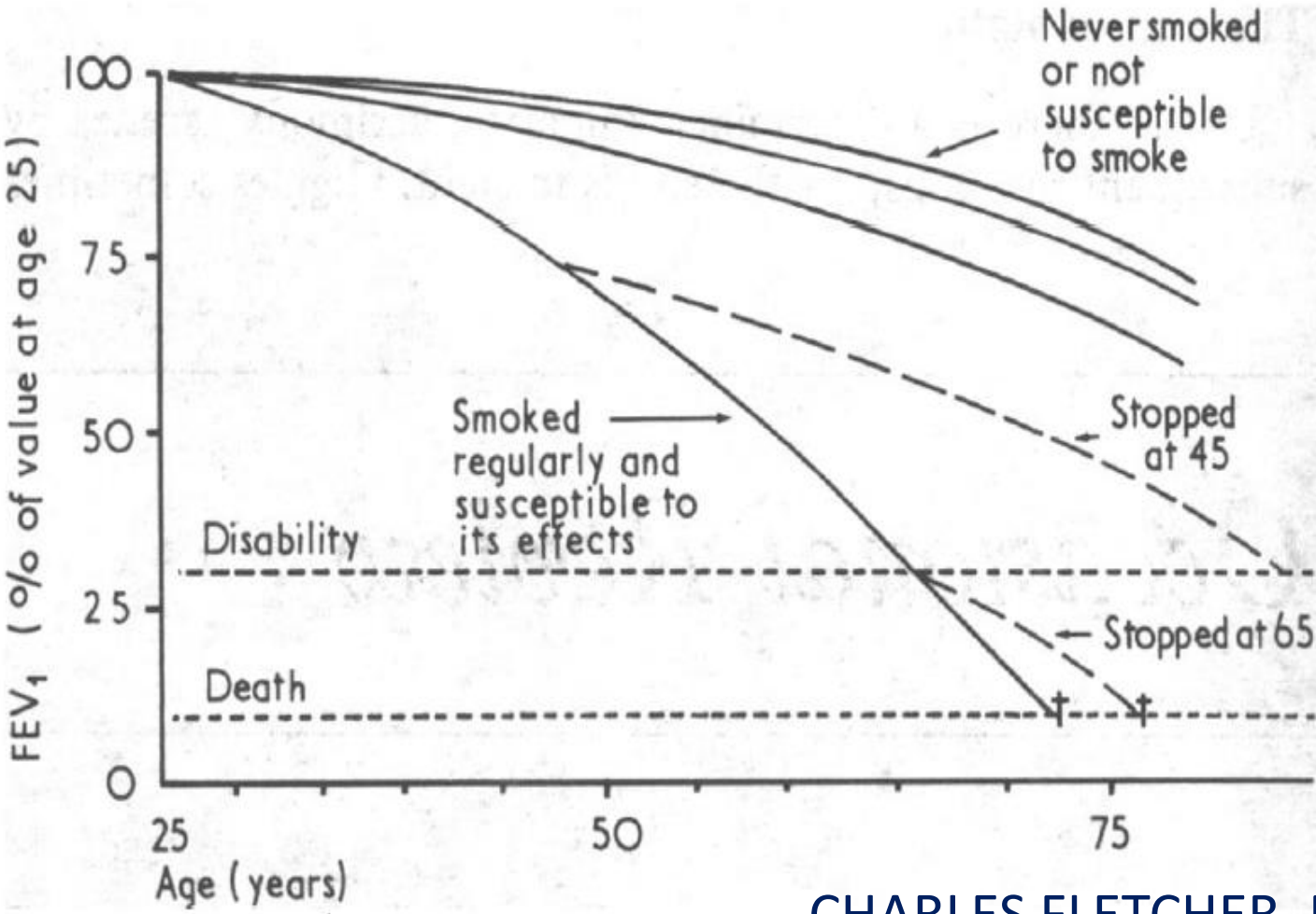
30/11/2018



The natural history of chronic airflow obstruction



CHARLES FLETCHER, RICHARD PETO
British Medical Journal, 1977, 1, 1645-1648

I primi grandi RCT sulla BPCO
Fine scorso secolo

- Tre RCT di dimensioni che oggi considereremmo medio-piccole, ma grandi per il periodo in cui furono concepiti ed eseguiti:

- **Copenhagen City Heart Study**

Acta Med Scand; suppl 682 Thesis; 1984
Scand J Soc Med. 1989;170(suppl 41):1–160
Eur Heart J. 2001;3(suppl H)

- **EUROSCOP**

Respir Med. 1998 Mar;92(3):467-72
Eur Respir J. 1992 Nov;5(10):1254-61
Eur Respir J. 1992 Nov;5(10):1169-70

- **ISOLDE**

Respir Med. 1999 Mar;93(3):161-6
BMJ. 2000 May 13;320(7245):1297-303

- Tutti RCT per valutare se una terapia con ICS può ridurre la velocità di declino del FEV1.

- Tutti studi in cui **ICS non è associato** ad una **sistematica broncodilatazione** e tutti studi con **esito negativo**.

Gratitude is due to AstraZeneca and GlaxoWellcome for sponsoring these huge expensive trials.

I believe, however, that both companies should now admit that the value of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease of any severity has not yet been established.

This form of treatment is not inexpensive, and on the present evidence the NHS should not be expected to fund the long term use of inhaled corticosteroids in patients with chronic obstructive pulmonary disease.

Graham K Crompton, *recently retired consultant physician, Respiratory Unit, Western General Hospital, Edinburgh.*

BMJ, Nov 25, 2000

Oltre il FEV1

Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial.

Conclusions:

Fluticasone propionate 500 µg twice daily did not affect the rate of decline in FEV1 but did produce a small increase in FEV1.

Patients on fluticasone propionate had fewer exacerbations and a slower decline in health status.

These improvements in clinical outcomes support the use of this treatment in patients with moderate to severe chronic obstructive pulmonary disease.

Burge PS. *BMJ* 2000;320:1297–303

Eur Respir J 2003; 22: 912–919
DOI: 10.1183/09031936.03.00027003
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European Respiratory Journal
ISSN 0903-1936

Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease

P.M. Calverley*, W. Boonsawat#, Z. Cseke¶, N. Zhong+, S. Peterson§, H. Olsson§

Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. P.M. Calverley, W. Boonsawat, Z. Cseke, N. Zhong, S. Peterson, H. Olsson. ©ERS Journals Ltd 2003.

ABSTRACT: Lung function in chronic obstructive pulmonary disease (COPD) can be improved acutely by oral corticosteroids and bronchodilators. Whether clinical improvement can be maintained by subsequent inhaled therapy is unknown.

COPD patients (n=1,022, mean prebronchodilator forced expiratory volume in one second (FEV_1) 36% predicted) initially received formoterol (9 µg *b.i.d.*) and oral prednisolone (30 mg *o.d.*) for 2 weeks. After this time, patients were randomised to *b.i.d.* inhaled budesonide/formoterol 320/9 µg, budesonide 400 µg, formoterol 9 µg or placebo for 12 months.

Postmedication FEV_1 improved by 0.21 L and health-related quality of life using the St George's Respiratory Questionnaire (SGRQ) by 4.5 units after run-in. Fewer patients receiving budesonide/formoterol withdrew from the study than those receiving budesonide, formoterol or placebo. Budesonide/formoterol patients had a prolonged time to first exacerbation (254 *versus* 96 days) and maintained higher FEV_1 (99% *versus* 87% of baseline), both primary variables *versus* placebo. They had fewer exacerbations (1.38 *versus* 1.80 exacerbations per patient per year), had higher prebronchodilator peak expiratory flow, and showed clinically relevant improvements in SGRQ *versus* placebo (-7.5 units). Budesonide/formoterol was more effective than either monocomponent in both primary variables.

Budesonide/formoterol in a single inhaler (Symbicort®) maintains the benefit of treatment optimisation, stabilising lung function and delaying exacerbations more effectively than either component drug alone or placebo.

Eur Respir J 2003; 22: 912–919.

*University Hospital Aintree, Liverpool, UK. #Srinagarind Hospital, Khon Kaen University, Thailand. ¶Vas Megyei Markusovszky Kórház, Szombathely, Hungary. +Guangzhou Institute of Respiratory Disease, Guangzhou, China. §AstraZeneca R&D Lund, Lund, Sweden.

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Keywords: Exacerbations
health-related quality of life
health status
inhaled corticosteroids
long-acting β_2-agonists

Received: March 11 2003
Accepted after revision: July 4 2003

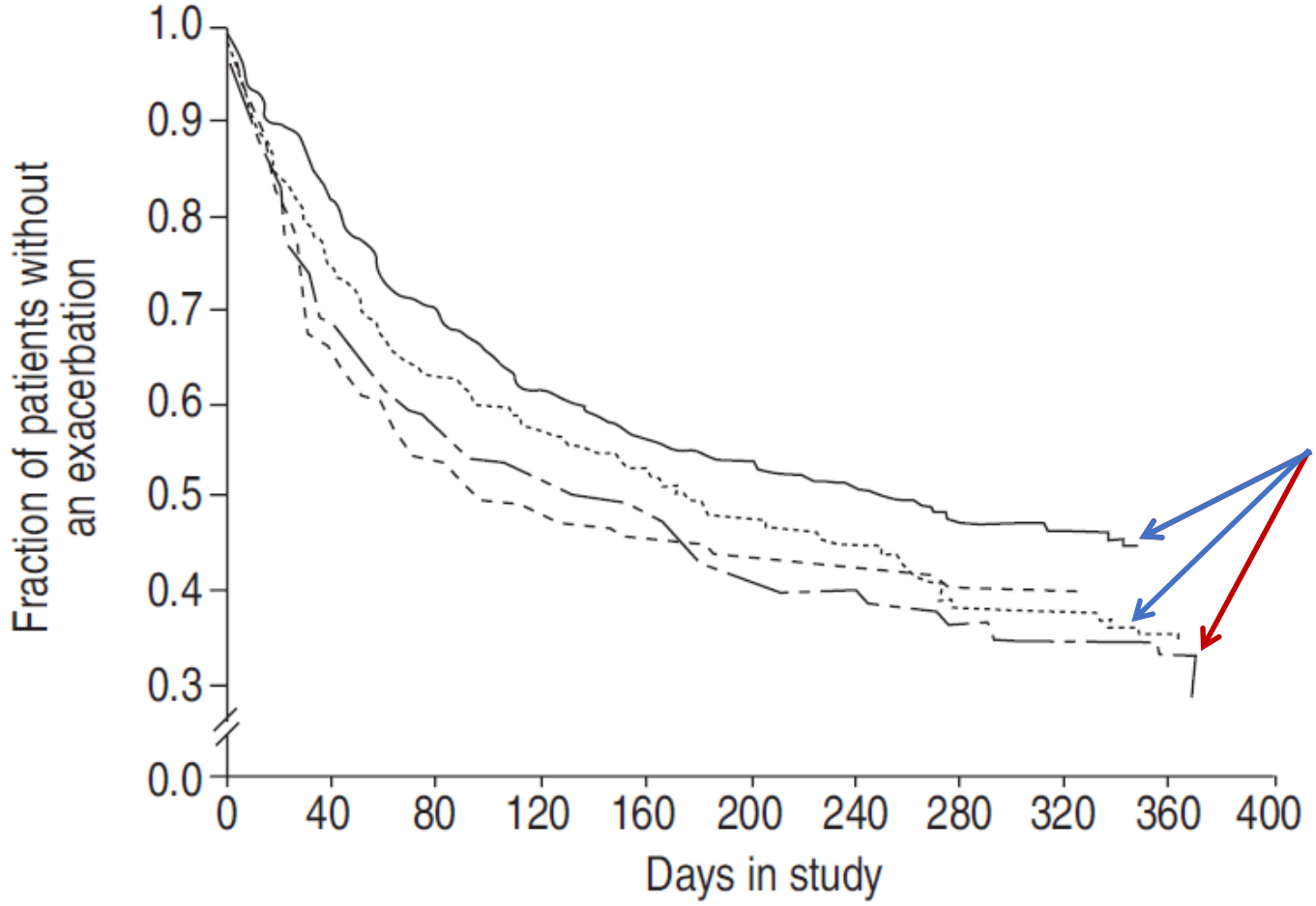

Fig. 1.–Kaplan-Meier plot of time to first exacerbation by treatment group. Log-rank tests of budesonide/formoterol (——) *versus* budesonide (·····), p=0.037; budesonide/formoterol *versus* formoterol (— -), p=0.002; budesonide *versus* placebo (- - -), p=0.796; formoterol *versus* placebo, p=0.490; and budesonide/formoterol *versus* placebo, p<0.05.

Eur Respir J 2003; 22: 912–919
DOI: 10.1183/09031936.03.00027003

Il contributo del LAMA

E’ tuttavia vero che, utilizzando **le riacutizzazioni** come **esito principale**, una terapia con un **broncodilatatore a lunga durata d’azione** di tipo **colinergico** è in grado di migliorare significativamente la storia dei pazienti riducendo significativamente l’incidenza di tale esito rispetto ad un beta adrenergico.

ABSTRACT

BACKGROUND

Treatment guidelines recommend the use of inhaled long-acting bronchodilators to alleviate symptoms and reduce the risk of exacerbations in patients with moderate-to-very-severe chronic obstructive pulmonary disease (COPD) but do not specify whether a long-acting anticholinergic drug or a β_2-agonist is the preferred agent. We investigated whether the anticholinergic drug tiotropium is superior to the β_2-agonist salmeterol in preventing exacerbations of COPD.

METHODS

In a 1-year, randomized, double-blind, double-dummy, parallel-group trial, we compared the effect of treatment with 18 μg of tiotropium once daily with that of 50 μg of salmeterol twice daily on the incidence of moderate or severe exacerbations in patients with moderate-to-very-severe COPD and a history of exacerbations in the preceding year.

RESULTS

A total of 7376 patients were randomly assigned to and treated with tiotropium (3707 patients) or salmeterol (3669 patients). Tiotropium, as compared with salmeterol, increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). Tiotropium also increased the time to the first severe exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduced the annual number of moderate or severe exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001). Overall, the incidence of serious adverse events and of adverse events leading to the discontinuation of treatment was similar in the two study groups. There were 64 deaths (1.7%) in the tiotropium group and 78 (2.1%) in the salmeterol group.

CONCLUSIONS

These results show that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov number, NCT00563381.)

From the Hospital of the Universities of Giessen and Marburg, Marburg (C.V.); Boehringer Ingelheim, Ingelheim (B.H., T.G., H.S.); and insaf Respiratory Research Institute, Wiesbaden (K.M.B.) — all in Germany; the Institute for Medical Technology Assessment (IMTA), Erasmus University, Rotterdam (M.P.M.H.R.-M.); and Leiden University Medical Center, Leiden (K.F.R.) — both in the Netherlands; and the University of Modena and Reggio Emilia, Modena, Italy (L.M.F.). Address reprint requests to Dr. Fabbri at the Section of Respiratory Diseases, Department of Oncology, Hematology, and Pulmonary Diseases, University of Modena and Reggio Emilia, Policlinico di Modena, Largo del Pozzo 71, I-41124 Modena, Italy, or at leonardo.fabbri@unimore.it.

*The investigators in the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;364:1093-103.

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ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

Claus Vogelmeier, M.D., Bettina Hederer, M.D., Thomas Glaab, M.D., Hendrik Schmidt, Ph.D., Maureen P.M.H. Rutten-van Mölken, Ph.D., Kai M. Beeh, M.D., Klaus F. Rabe, M.D., and Leonardo M. Fabbri, M.D., for the POET-COPD Investigators*

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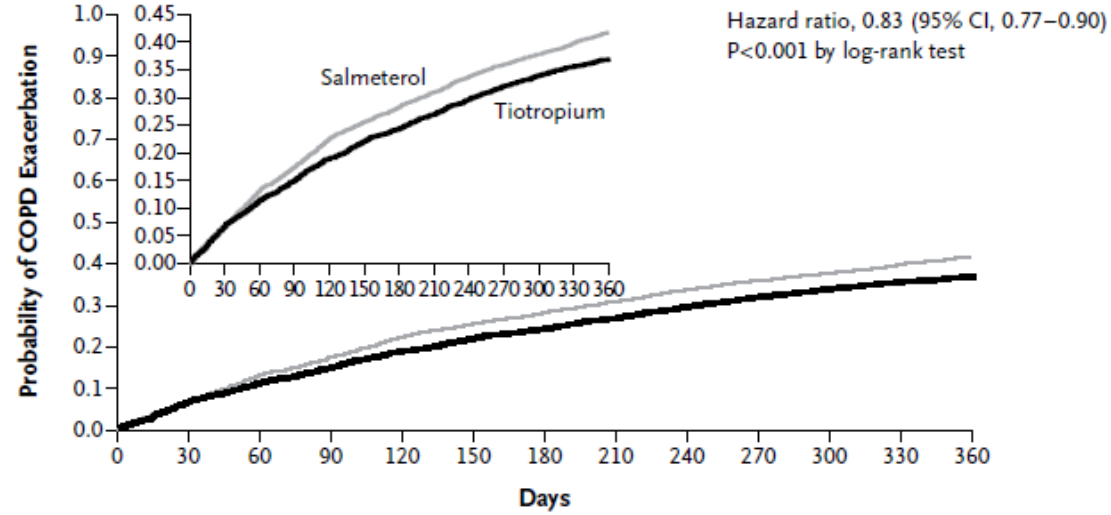
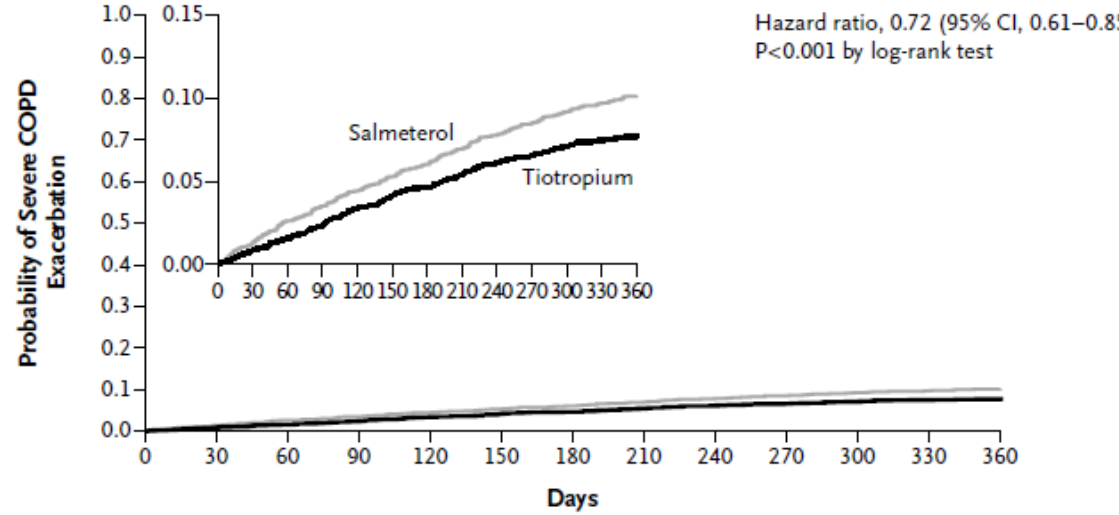


No. at Risk													
Tiotropium	3707	3369	3136	2955	2787	2647	2561	2455	2343	2242	2169	2107	1869
Salmeterol	3669	3328	3028	2802	2605	2457	2351	2251	2137	2050	1982	1915	1657



No. at Risk													
Tiotropium	3707	3564	3453	3359	3285	3217	3177	3125	3066	3017	2977	2948	2663
Salmeterol	3669	3502	3362	3244	3172	3080	3032	2982	2921	2870	2834	2806	2489

L’impatto della doppia broncodilatazione

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

This article was published on May 15, 2016, at NEJM.org.

N Engl J Med 2016;374:2222-34.
DOI: 10.1056/NEJMoa1516385

From the National Heart and Lung Institute, Imperial College London, London (J.A.W.), and the Centre for Respiratory Medicine and Allergy, University of Manchester and University Hospital South Manchester NHS Foundation Trust, Manchester (J.V.) — all in the United Kingdom; Novartis Pharmaceuticals, East Hanover, NJ (D.B., R.T.A., C.T., R.F.); Asthma and Airway Centre, University Health Network and University of Toronto, Toronto (K.R.C.); Service de Pneumologie Assistance Publique–Hôpitaux de Paris, University Paris Descartes (EA2511), Paris (N.R.); Novartis Pharma AG, Basel, Switzerland (F.P.); and the Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-Universität Marburg, Marburg, Germany (C.F.V.). Address reprint requests to Dr. Wedzicha at the COPD Research Group, Airways Disease Section, National Heart and Lung Institute, Imperial College London, Dovehouse St., London SW3 6LY, United Kingdom, or at j.wedzicha@imperial.ac.uk.

*A complete list of investigators in the FLAME trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 15, 2016, at NEJM.org.

N Engl J Med 2016;374:2222-34.
DOI: 10.1056/NEJMoa1516385

ABSTRACT

BACKGROUND

Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA–LAMA regimen in these patients is unclear.

METHODS

We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS

A total of 1680 patients were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Indacaterol–glycopyrronium showed not only noninferiority but also superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol–glycopyrronium group had a longer time to the first exacerbation than did the salmeterol–fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001). The annual rate of moderate or severe exacerbations was lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001), and the time to the first moderate or severe exacerbation was longer in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; P<0.001), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046). The effect of indacaterol–glycopyrronium versus salmeterol–fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol–glycopyrronium group and 4.8% in the salmeterol–fluticasone group (P=0.02).

CONCLUSIONS

Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.)

Cope et al. Respiratory Research 2013, 14:100
http://respiratory-research.com/content/14/1/100

RESPIRATORY RESEARCH

RESEARCH Open Access

Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis

Shannon Cope[1], James F Donohue[2], Jeroen P Jansen[3], Matthias Kraemer[4], Gorana Capkun-Niggli[4], Michael Baldwin[5], Felicity Buckley[3], Alexandra Ellis[3] and Paul Jones[6*]

Abstract

Background: Clinicians are faced with an increasingly difficult choice regarding the optimal bronchodilator for patients with chronic obstructive pulmonary disease (COPD) given the number of new treatments. The objective of this study is to evaluate the comparative efficacy of indacaterol 75/150/300 μg once daily (OD), glycopyrronium bromide 50 μg OD, tiotropium bromide 18 μg/5 μg OD, salmeterol 50 μg twice daily (BID), formoterol 12 μg BID, and placebo for moderate to severe COPD.

Methods: Forty randomized controlled trials were combined in a Bayesian network meta-analysis. Outcomes of interest were trough and post-dose forced expiratory volume in 1 second (FEV_1), St. George's Respiratory Questionnaire (SGRQ) score and responders (≥4 points), and Transition Dyspnea Index (TDI) score and responders (≥1 point) at 6 months.

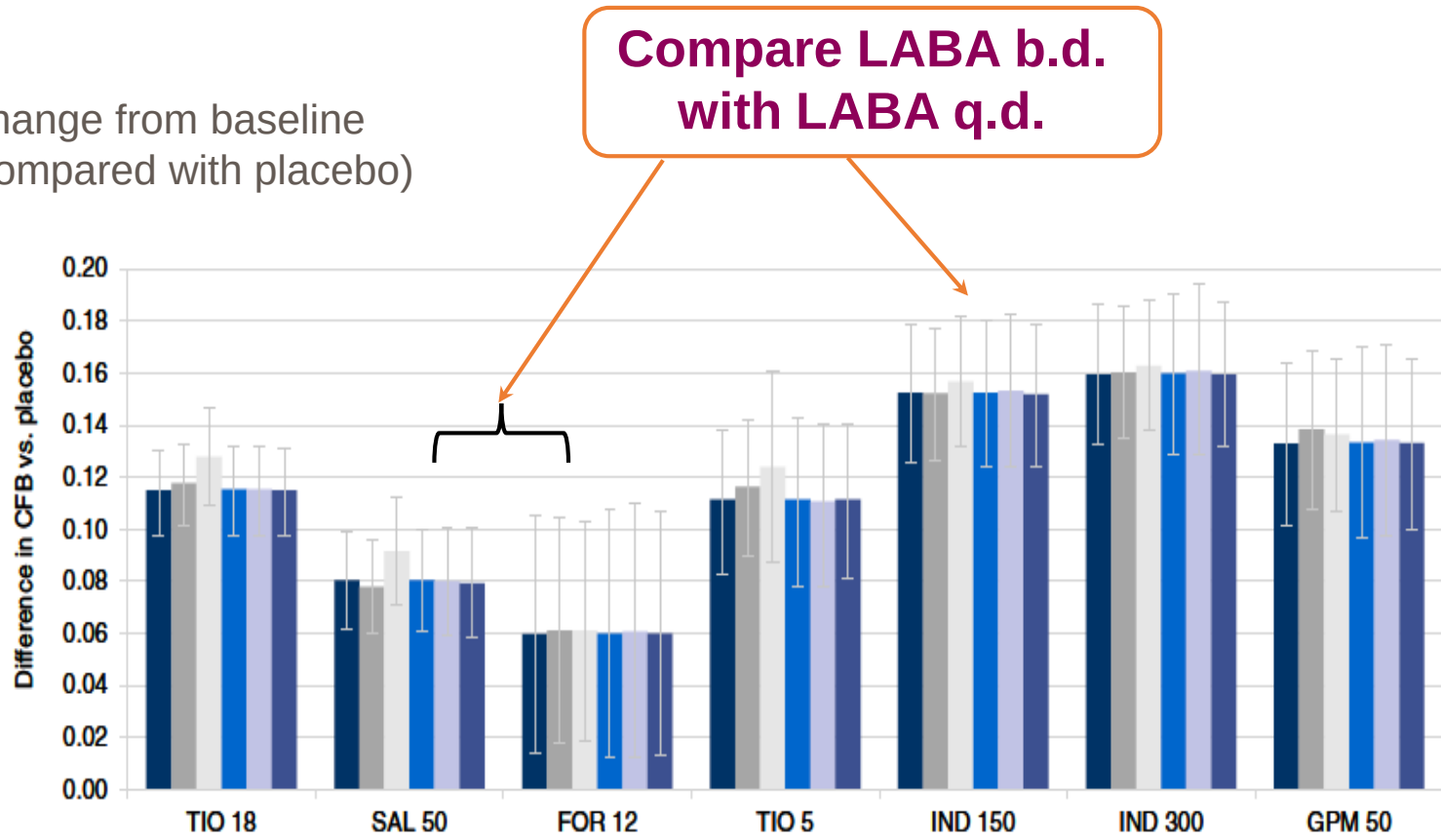
Results: Indacaterol was associated with a higher trough FEV_1 than other active treatments (difference for indacaterol 150 μg and 300 μg versus placebo: 152 mL (95% credible interval (CrI): 126, 179); 160 mL (95% CrI: 133, 187)) and the greatest improvement in SGRQ score (difference for indacaterol 150 μg and 300 μg versus placebo: -3.9 (95% CrI -5.2, -2.6); -3.6 (95% CrI -4.8, -2.3)). Glycopyrronium and tiotropium 18 μg resulted in the next best estimates for both outcomes with minor differences (difference for glycopyrronium versus tiotropium for trough FEV_1 and SGRQ: 18 mL (95% CrI: -16, 51); -0.55 (95% CrI: -2.04, 0.92).

Conclusion: In terms of trough FEV_1 and SGRQ score indacaterol, glycopyrronium, and tiotropium are expected to be the most effective bronchodilators.

Keywords: COPD, Bronchodilator, Systematic review, Meta-analysis, Mixed treatment comparison

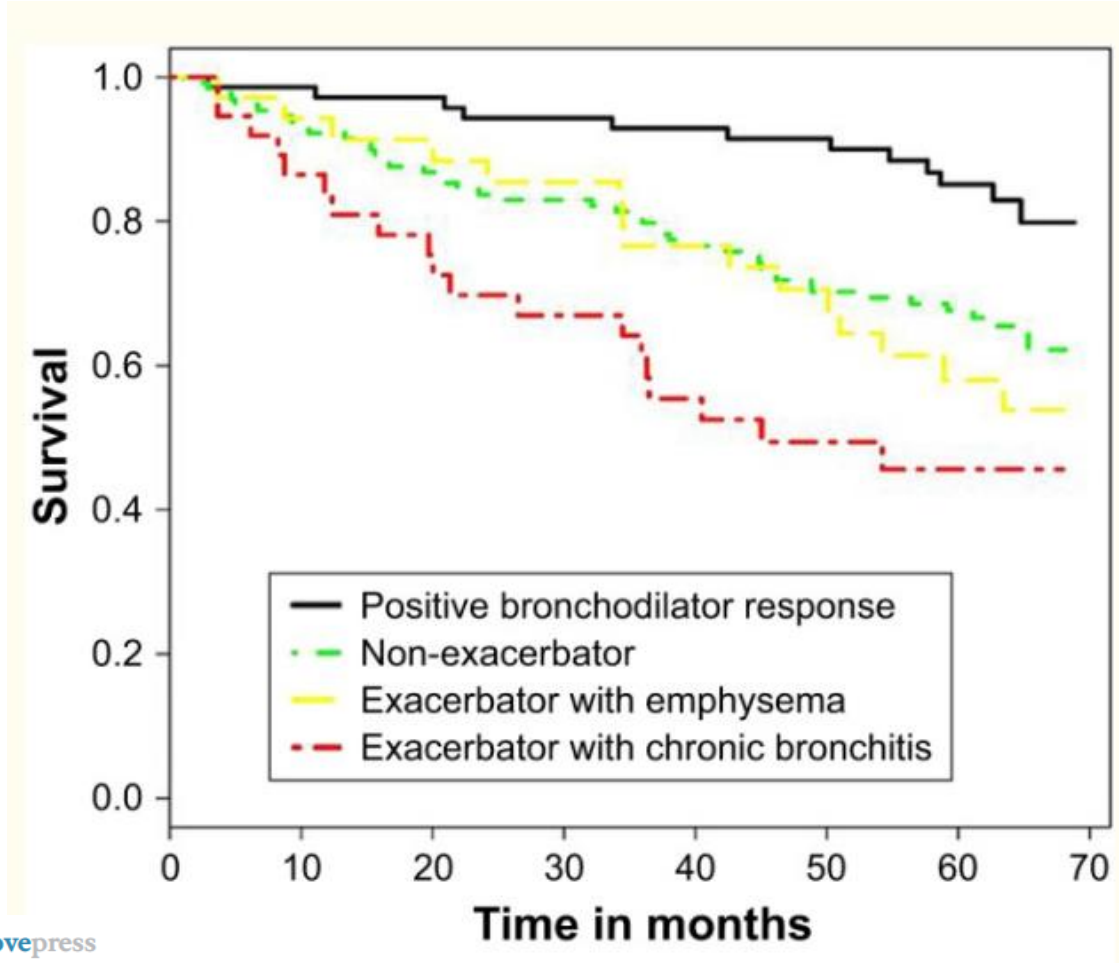
Network meta-analysis of long-acting bronchodilator: trough FEV_1

Change from baseline
(compared with placebo)



Cope et al Respiratory Research 2013, 14:100

L’importanza del fenotipo COPD



International Journal of COPD

Dovepress
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ORIGINAL RESEARCH

COPD phenotypes: differences in survival

This article was published in the following Dove Press journal:
International Journal of COPD

L'importanza del fenotipo COPD

Table 1. COPD phenotypes.

Classical: [Clinico-histological Criteria]	Chronic Bronchitic Emphysematous Mixed
Historical (pathophysiological criteria)	Blue Bloater – Pink Puffer
One Criteria	Frequent Exacerbator Inflammatory phenotype Fast decliner (FEV^1) Co-morbidities Current smokers
Multi Criteria	• Chronic bronchitis with frequent exacerbations • Emphysema with frequent exacerbations • Younger with severe disease, few co-morbidities, poor nutritional status, and poor health status • Older with moderate disease, obesity, cardiovascular and metabolic co-morbidities • ACOS: Asthma-COPD – Overlap Syndrome

COPD: Journal of Chronic Obstructive Pulmonary Disease

Taylor & Francis

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: http://www.tandfonline.com/loi/icop20

Phenotyping Before Starting Treatment in COPD?

Nikolaos Siafakas, Alexandru Corlateanu & Evangelia Fouka

To cite this article: Nikolaos Siafakas, Alexandru Corlateanu & Evangelia Fouka (2017): Phenotyping Before Starting Treatment in COPD?, COPD: Journal of Chronic Obstructive Pulmonary Disease, DOI: 10.1080/15412555.2017.1303041

To link to this article: http://dx.doi.org/10.1080/15412555.2017.1303041

Published online: 07 Apr 2017.

Hanno un ruolo gli eosinofili?

Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials

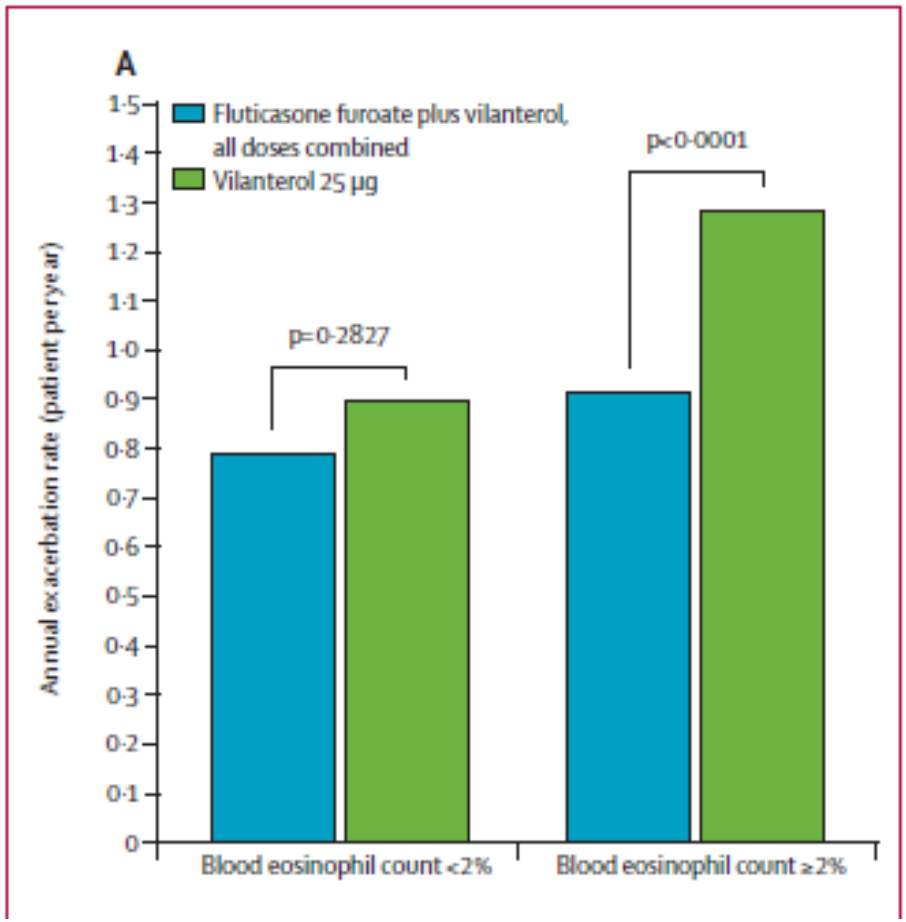
Steven Pascoe, Nicholas Locantore, Mark T Dransfield, Neil C Barnes, Ian D Pavord

Lancet Respir Med 2015

Published Online

April 13, 2015

http://dx.doi.org/10.1016/S2213-2600(15)00106-X



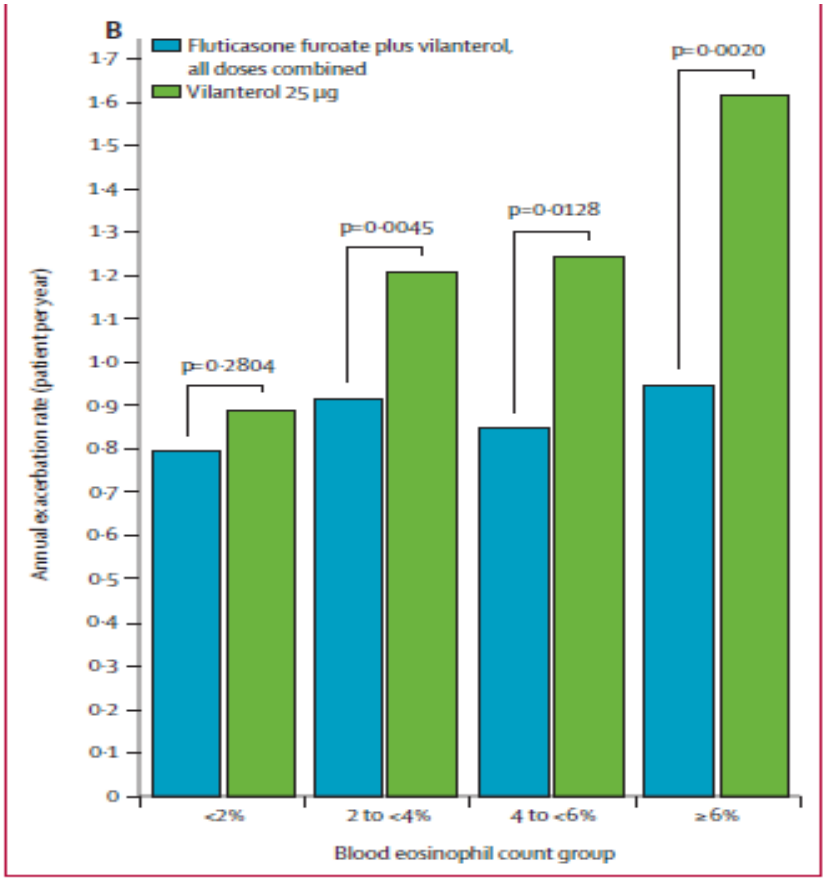


Figure: **Moderate or severe exacerbation rates (per patient per year) by eosinophil count strata (A) and by four groups of patients by eosinophil count (B)**

Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials

Mona Bafadhel, Stefan Peterson, Miguel A De Blas, Peter M Calverley, Stephen I Rennard, Kai Richter, Malin Fagerås

Summary

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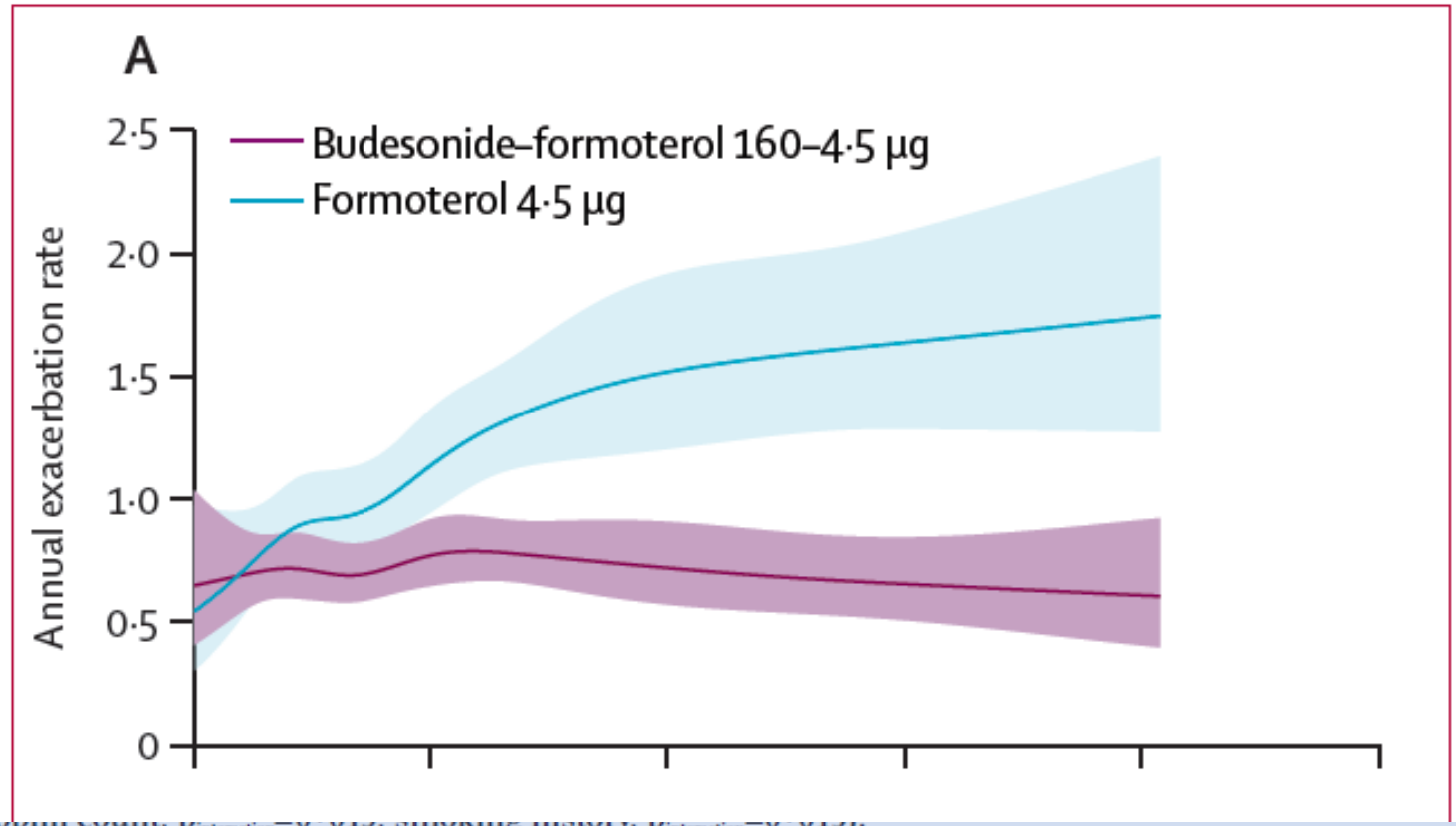

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Interpretation In patients with COPD treated with formoterol, blood eosinophil count predicts exacerbation risk and the clinical response to ICS.

Lancet Respir Med 2018

Published Online
January 10, 2018
http://dx.doi.org/10.1016/S2213-2600(18)30006-7

Lancet Respir Med. 2016 May;4(5):390-8. doi: 10.1016/S2213-2600(16)00100-4. Epub 2016 Apr 7.

Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial.

Watz H[1], Tetzlaff K[2], Wouters EF[3], Kirsten A[4], Magnussen H[4], Rodriguez-Roisin R[5], Vogelmeier C[6], Fabbri LM[7], Chanez P[8], Dahl R[9], Disse B[10], Finnigan H[11], Calverley PM[12].

Author information

Abstract

BACKGROUND: Blood eosinophil counts might predict response to inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations. We used data from the WISDOM trial to assess whether patients with COPD with higher blood eosinophil counts would be more likely to have exacerbations if ICS treatment was withdrawn.

METHODS: WISDOM was a 12-month, randomised, parallel-group trial in which patients received 18 µg tiotropium, 100 µg salmeterol, and 1000 µg fluticasone propionate daily for 6 weeks and were then randomly assigned (1:1) electronically to receive either continued or reduced ICS over 12 weeks. We did a post-hoc analysis after complete ICS withdrawal (months 3-12) to compare rate of exacerbations and time to exacerbation outcomes on the basis of blood eosinophil subgroups of increasing cutoff levels. The WISDOM trial is registered at ClinicalTrials.gov, number NCT00975195.

FINDINGS: In the 2296 patients receiving treatment after ICS withdrawal, moderate or severe exacerbation rate was higher in the ICS-withdrawal group versus the ICS-continuation group in patients with eosinophil counts (out of total white blood cell count) of 2% or greater (rate ratio 1·22 [95% CI 1·02-1·48]), 4% or greater (1·63 [1·19-2·24]), and 5% or greater (1·82 [1·20-2·76]). The increase in exacerbation rate became more pronounced as the eosinophil cutoff level rose, with significant treatment-by-subgroup interaction reached for 4% and 5% only. Similar results were seen with eosinophil cutoffs of 300 cells per µL and 400 cells per µL, and mutually exclusive subgroups.

INTERPRETATION: Blood eosinophil counts at screening were related to the exacerbation rate after complete ICS withdrawal in patients with severe to very severe COPD and a history of exacerbations. Our data suggest that counts of 4% or greater or 300 cells per µL or more might identify a deleterious effect of ICS withdrawal, an effect not seen in most patients with eosinophil counts below these thresholds.

Lancet Respir Med. 2018 Nov;6(11):855-862. doi: 10.1016/S2213-2600(18)30368-0. Epub 2018 Oct 18.

Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study.

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Author information

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Abstract

BACKGROUND: Long-acting β_2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the recommended initial maintenance treatment for chronic obstructive pulmonary disease (COPD), with almost all LABAs dispensed in fixed combination with inhaled corticosteroids (LABA-ICS). We compared the effectiveness and safety of LABA-ICS versus LAMA treatment initiation as a function of blood eosinophilia, a potential biomarker of ICS effectiveness, in a real-world setting.

METHODS: In this population-based cohort study, we identified a cohort of patients with COPD initiating treatment with a LAMA or LABA-ICS during 2002-15, age 55 years or older, from the UK's Clinical Practice Research Datalink. We excluded patients who initiated treatment with both bronchodilators on the same date. All patients required at least 1 year of medical history and a measure of blood eosinophil concentration before cohort entry, defined by the date of the first cohort-defining bronchodilator prescription. Patients initiating a LAMA were matched on high-dimensional propensity scores with patients initiating a LABA-ICS. They were followed up for 1 year for the occurrence of a moderate or severe COPD exacerbation and for severe pneumonia. Sensitivity analyses included, among others, repeating the analysis among patients with two blood eosinophil concentration measures and stratification by concurrent asthma and previous exacerbations.

FINDINGS: The base cohort included 539 643 patients with a prescription for LABAs or LAMAs from Jan 1, 2002, to Dec 31, 2015, of whom 18 500 were initiated on LABA-ICS and 13 870 on LAMAs. Propensity score analysis resulted in 12 366 initiators of LAMAs (mainly tiotropium) matched to 12 366 initiators of LABA-ICS. The hazard ratio (HR) of COPD exacerbation associated with LABA-ICS initiation, relative to LAMA initiation, was 0·95 (95% CI 0·90-1·01). In patients with blood eosinophil concentrations of less than 2% of white blood cell count, the HR was 1·03 (95% CI 0·93-1·13) and for those with eosinophil concentrations of 2-4%, the HR was 1·00 (0·91-1·10). For patients with eosinophil concentrations of more than 4%, the HR was 0·79 (0·70-0·88). The incidence of pneumonia increased with LABA-ICS initiation (HR 1·37 [95% CI 1·17-1·60]) and was similar across all eosinophil concentrations. Sensitivity analyses were consistent with these findings, but the incidence of exacerbation with LABA-ICS among the 2766 (11%) of all 24 732 patients with two or more COPD exacerbations during the baseline year was marginally lower (HR 0·87 [95% CI 0·79-0·97]).

INTERPRETATION: In this real-world, clinical practice, observational study, initial COPD treatment with LABA-ICS inhalers was only more effective than with LAMAs in patients with high blood eosinophil concentrations (>4%) or counts (>300 cells per μL) and possibly in frequent exacerbators. Because of the increased risk of pneumonia associated with the ICS component, initiation with a LAMA should be preferred in patients with blood eosinophil concentrations of less than 4%.

Treatment of stable COPD

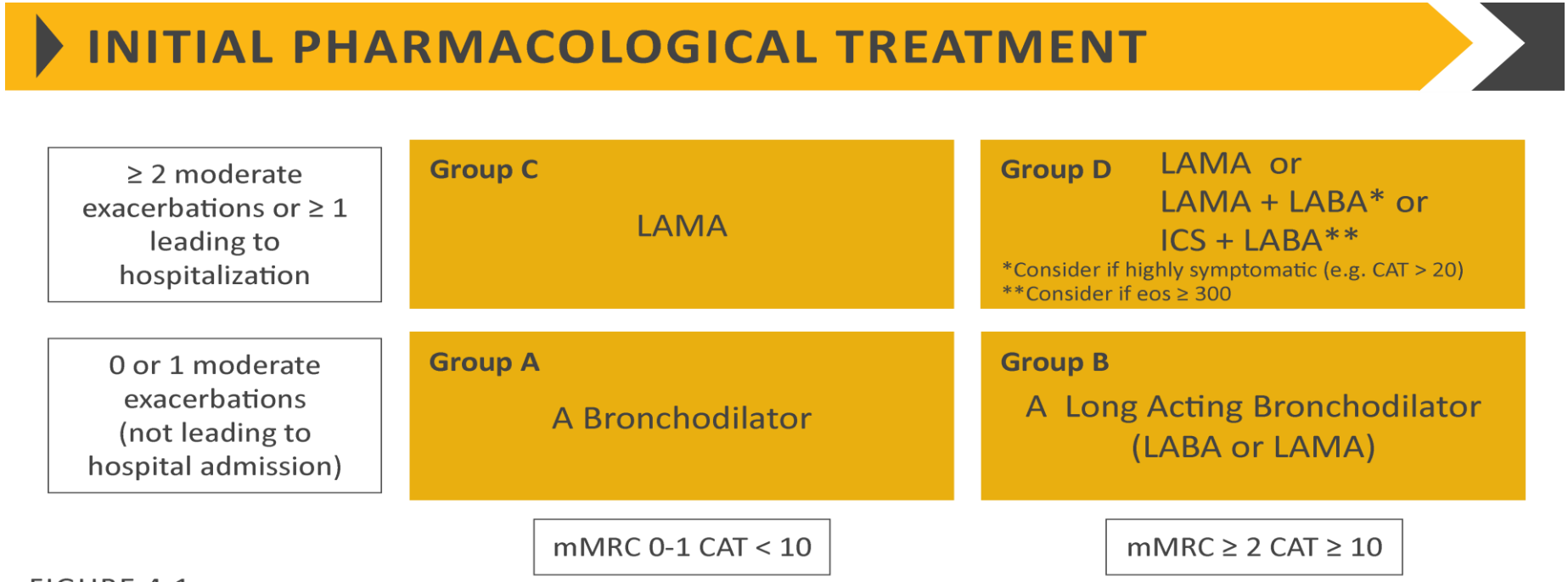
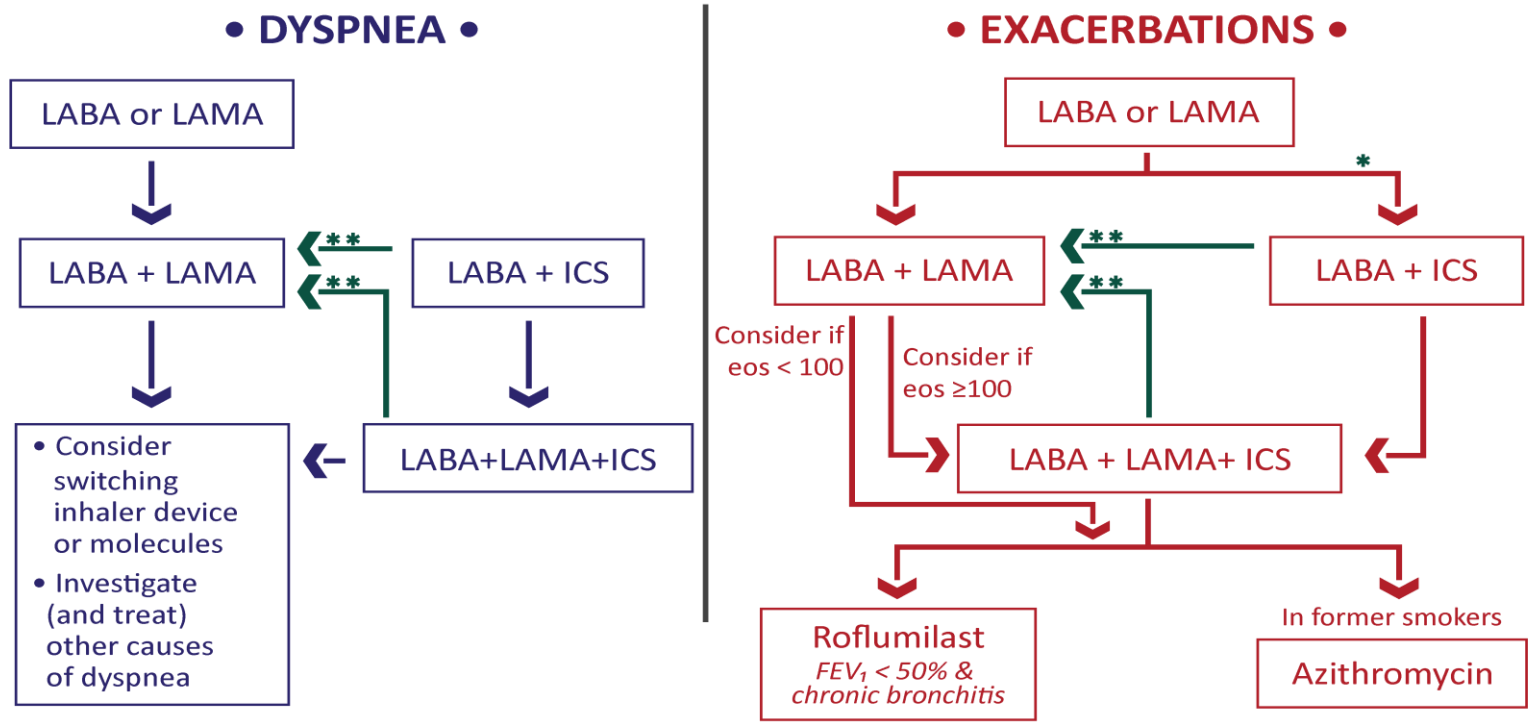


FIGURE 4.1

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

?

Il punto aperto attualmente è se si debba considerare fin dall'inizio una terapia triplice, individuando il paziente che abbia una chiara indicazione a tale terapia.

A quale paziente la terapia triplice?

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Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

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ABSTRACT

BACKGROUND

The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid–LABA or LAMA–LABA), are uncertain.

METHODS

In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 μg, umeclidinium (a LAMA) at a dose of 62.5 μg, and vilanterol (a LABA) at a dose of 25 μg (triple therapy) with fluticasone furoate–vilanterol (at doses of 100 μg and 25 μg, respectively) and umeclidinium–vilanterol (at doses of 62.5 μg and 25 μg, respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

RESULTS

The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium–vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; P<0.001).

CONCLUSIONS

Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol or umeclidinium–vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium–vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513.)

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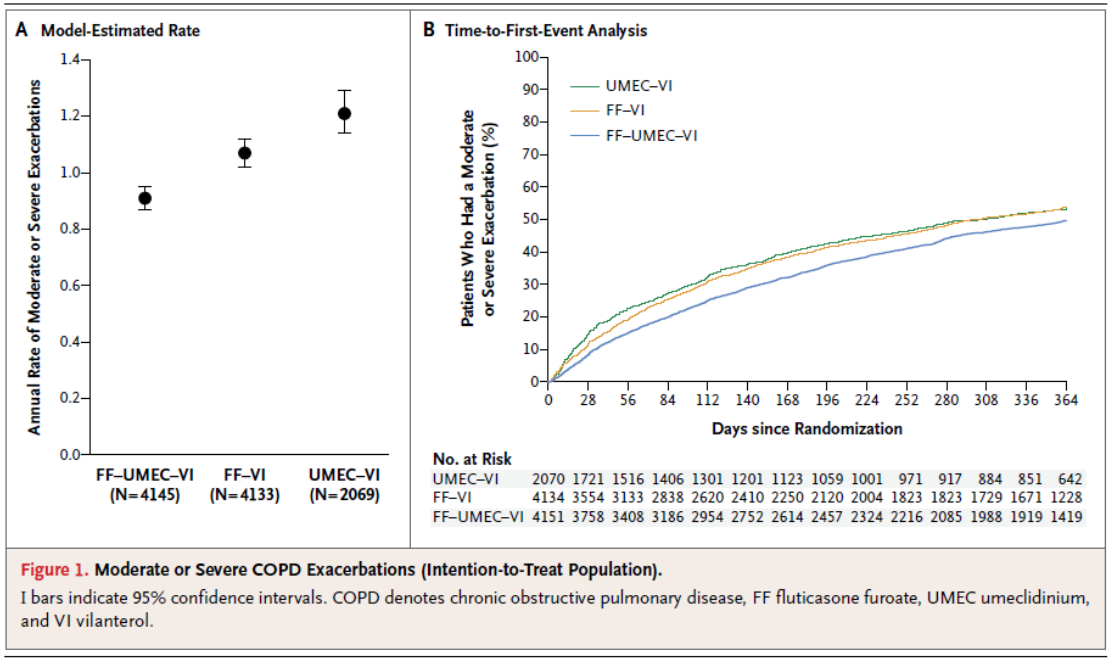

Figure 1. Moderate or Severe COPD Exacerbations (Intention-to-Treat Population).
I bars indicate 95% confidence intervals. COPD denotes chronic obstructive pulmonary disease, FF fluticasone furoate, UMEC umeclidinium, and VI vilanterol.

Gli argomenti contro ciò che è nuovo evolvono solitamente attraverso tre fasi distinte:

Da "*Non è vero*" a

"*Forse è vero, ma non è importante*" sino a

"*È vero ed è importante, ma non è una novità: l'abbiamo sempre saputo!*"

Saggezza impopolare

Grazie dell'attenzione