

Con il patrocinio di



Associazione Italiana Pneumologi Ospedalieri



PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

La terapia dell'asma oggi



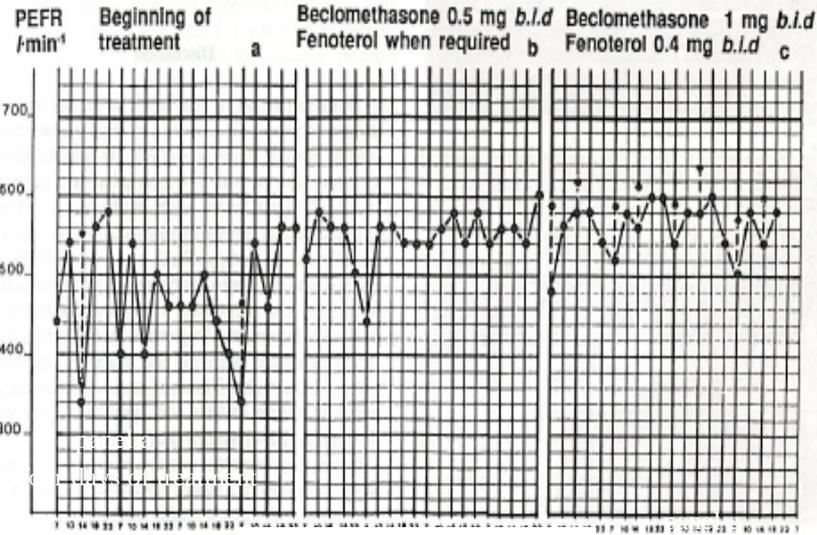
Antonio Spanevello

**Università degli Studi dell'Insubria, Varese
Dipartimento di Medicina Clinica e Sperimentale
Malattie dell'Apparato Respiratorio**

**Fondazione Salvatore Maugeri, IRCCS, Tradate
Dipartimento di Medicina e Riabilitazione Cardiorespiratoria
U.O. C. Pneumologia Riabilitativa**

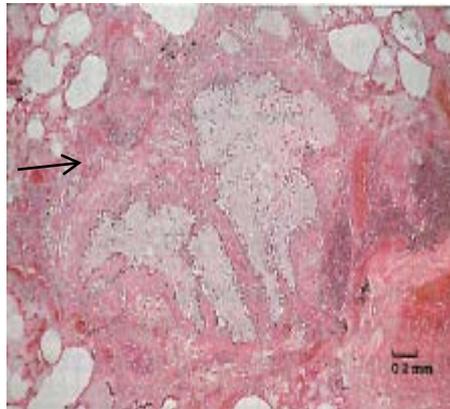


Fatal asthma in a young patient with severe bronchial hyperresponsiveness but stable peak flow records



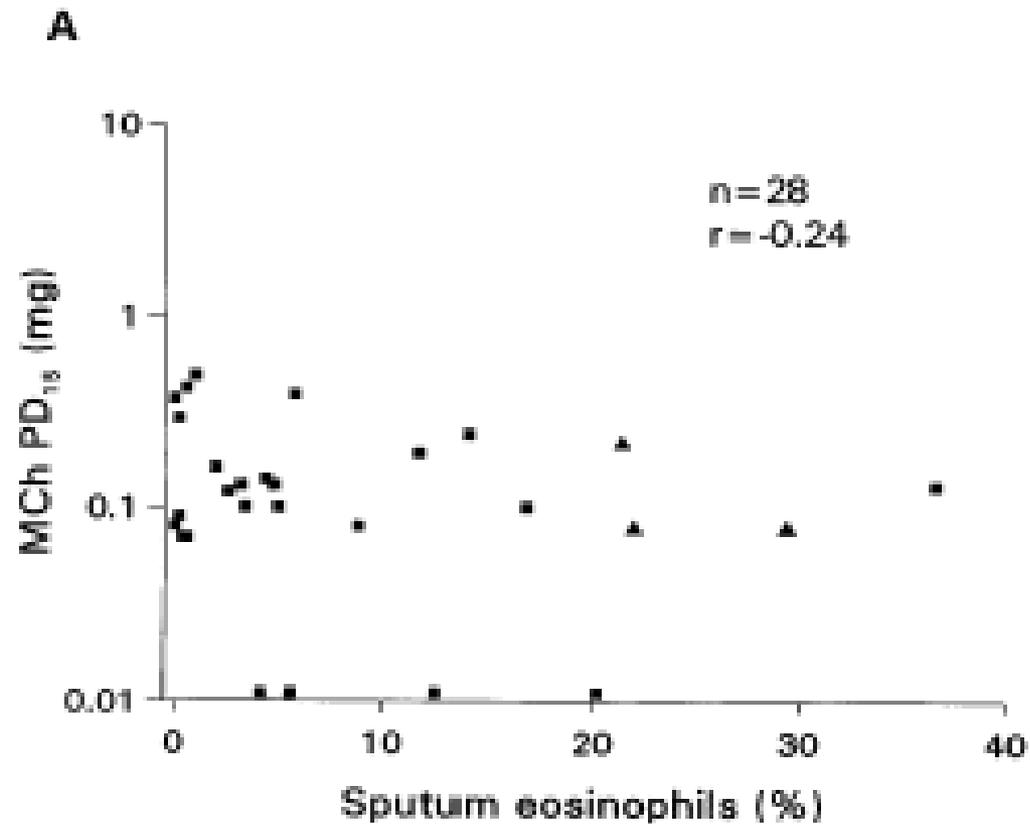
panel b last four days
four days of the following week before the fatal attack

thickening of the
basement membrane



Dissociation between Airway Inflammation and Airway hyperresponsiveness in Allergic Asthma

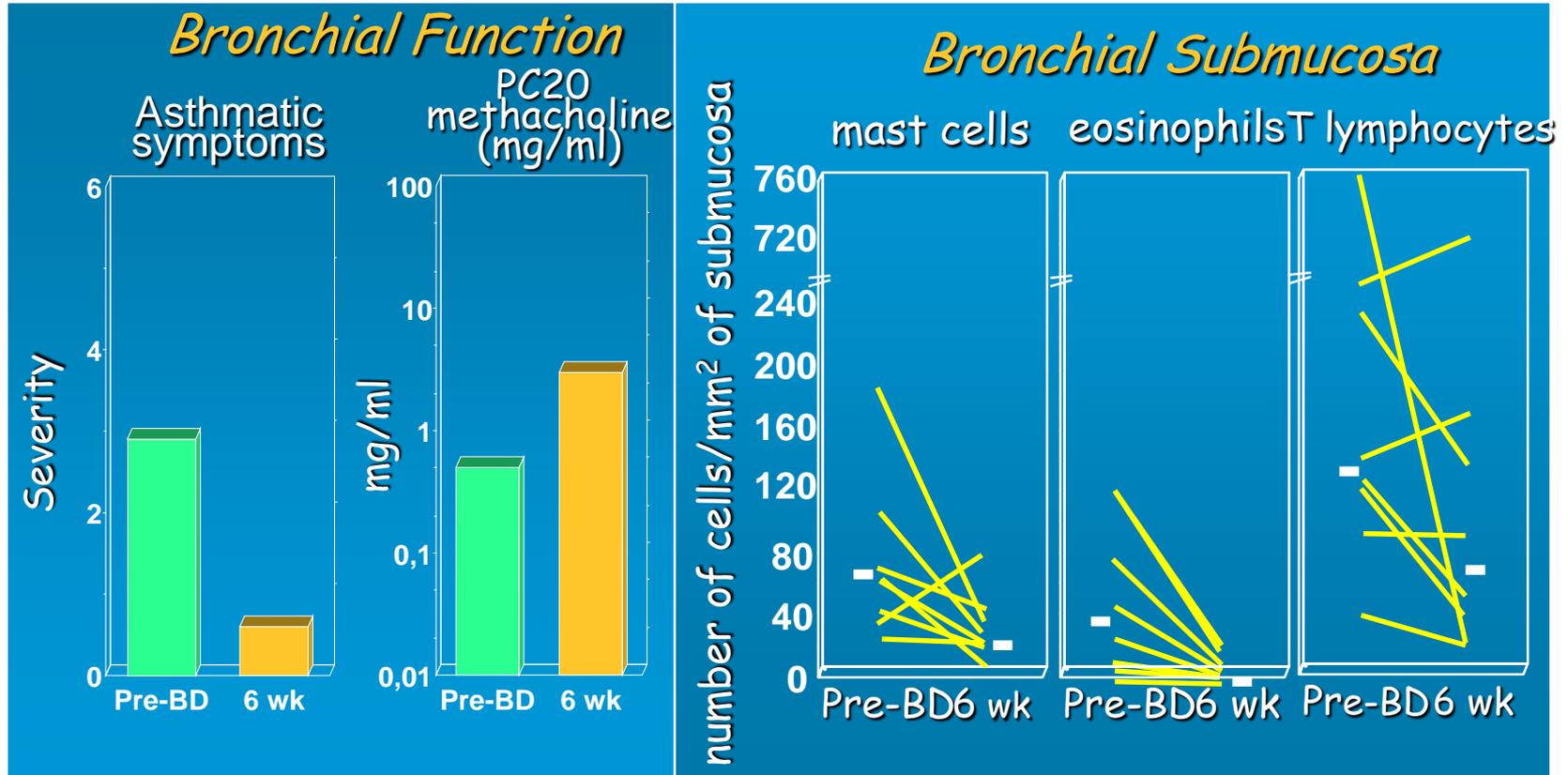
Crimi E, Spanevello A et al. Am J Respir Crit Care Med 1998; 157:4-9



Effect of an Inhaled Corticosteroid on Airway Inflammation and Symptoms in Asthma

Ratko Djukanović, John W. Wilson, Karen M. Britten, Susan J. Wilson, Andrew F. Walls, William R. Roche, Peter H. Howarth, and Stephen T. Holgate

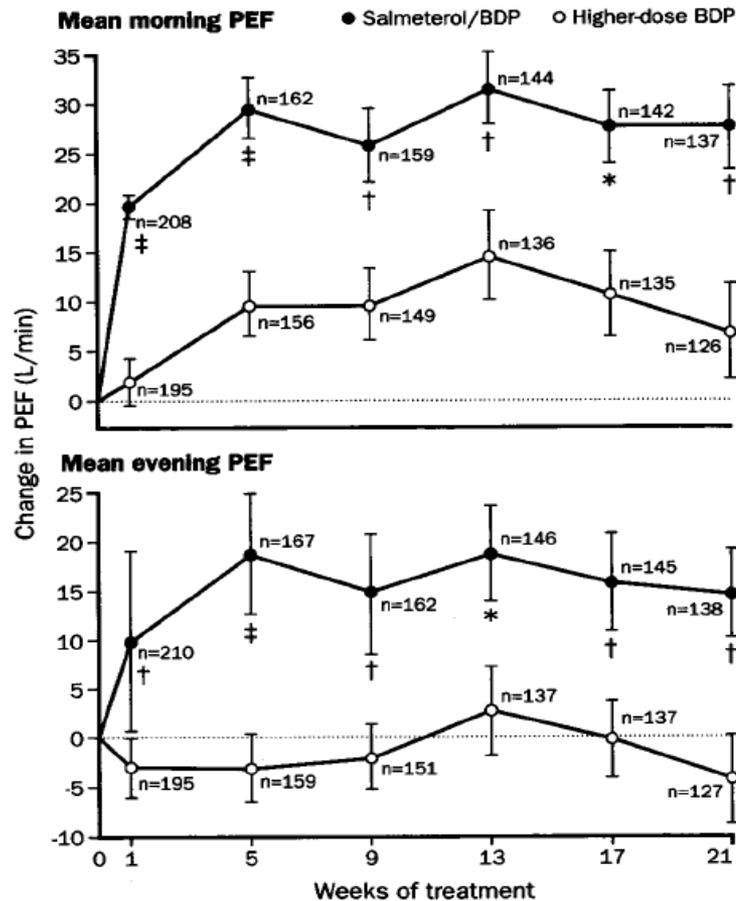
Am Rev Respir Dis 1992;145:669-74



Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroids

AP Greening, PW Ind, M Northfield, G Shaw

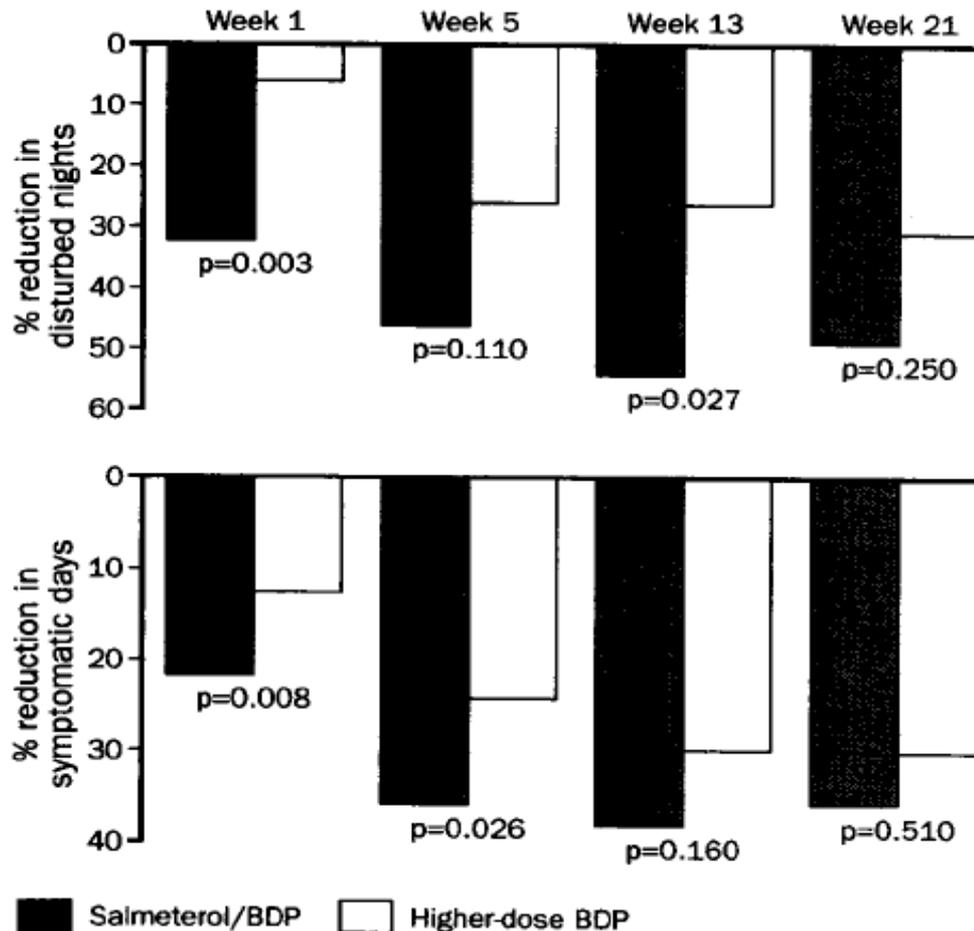
Lancet 1994; 344:219-224



Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroids

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Lancet 1994; 344:219-224



Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroids

AP Greening, PW Ind, M Northfield, G Shaw

Lancet 1994; 344:219-224

Exacerbations per patient	Number of patients			
	Salmeterol/BDP (n = 220)		Higher-dose BDP (n = 206)	
	Mild	Moderate	Mild	Moderate
One	36	12	28	16
Two	14	5	18	1
Three	4	0	4	1
Four	6	0	3	1
Five	3	0	0	0
Six	1	0	3	0
Seven	1	0	0	0
Fifteen	1	1	1	0

Includes all exacerbations during the study, except the 2-week baseline period.

Table 5: Asthma exacerbations per patient

Exacerbations / patient / 28 days (Salmeterol/BPD 0.21 vs 0.29 for higher dose BPD)

Il controllo dell'asma

LIVELLI DI CONTROLLO DELL'ASMA			
CARATTERISTICHE	CONTROLLATO	PARZIALMENTE CONTROLLATO	NON CONTROLLATO
<i>Sintomi giornalieri</i>	Nessuno (<2/settimana)	>2/settimana	3 o più aspetti presenti nell'asma parzialmente controllato
<i>Limitazione delle attività</i>	Nessuna	Qualche	
<i>Sintomi notturni / risvegli</i>	Nessuno	Qualche	
<i>Necessità di farmaco al bisogno</i>	Nessuna (<2/settimana)	>2/settimana	
<i>Funzione polmonare (PEF o FEV₁) §</i>	Normale	<80% del predetto o del personal best (se noto)	
<i>Esacerbazioni</i>	Nessuna	1 o più per anno *	1 in qualsiasi settimana §

* Qualsiasi esacerbazione dovrebbe essere prontamente seguita da una revisione del trattamento di mantenimento per assicurarsi che esso sia adeguato

§ Per definizione, 1 esacerbazione in una qualsiasi delle settimane di monitoraggio rende l'intera settimana non controllata

§ La funzione polmonare è valutabile solo in individui con età superiore a 5 anni

Can Guideline-defined Asthma Control Be Achieved?

The Gaining Optimal Asthma Control Study

Eric D. Bateman, Homer A. Boushey, Jean Bousquet, William W. Busse, Tim J. H. Clark, Romain A. Pauwels, and Søren E. Pedersen for the GOAL Investigators Group

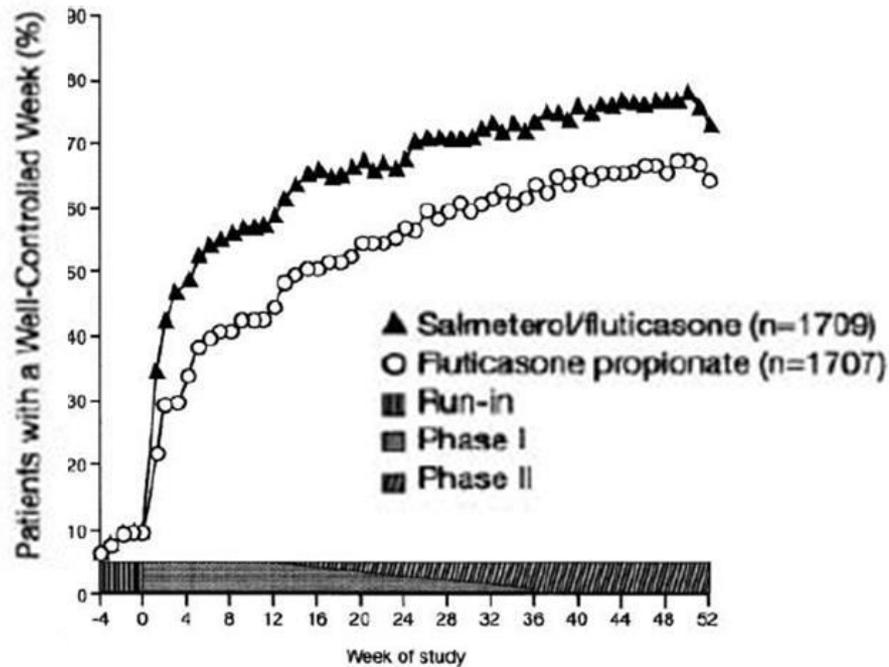
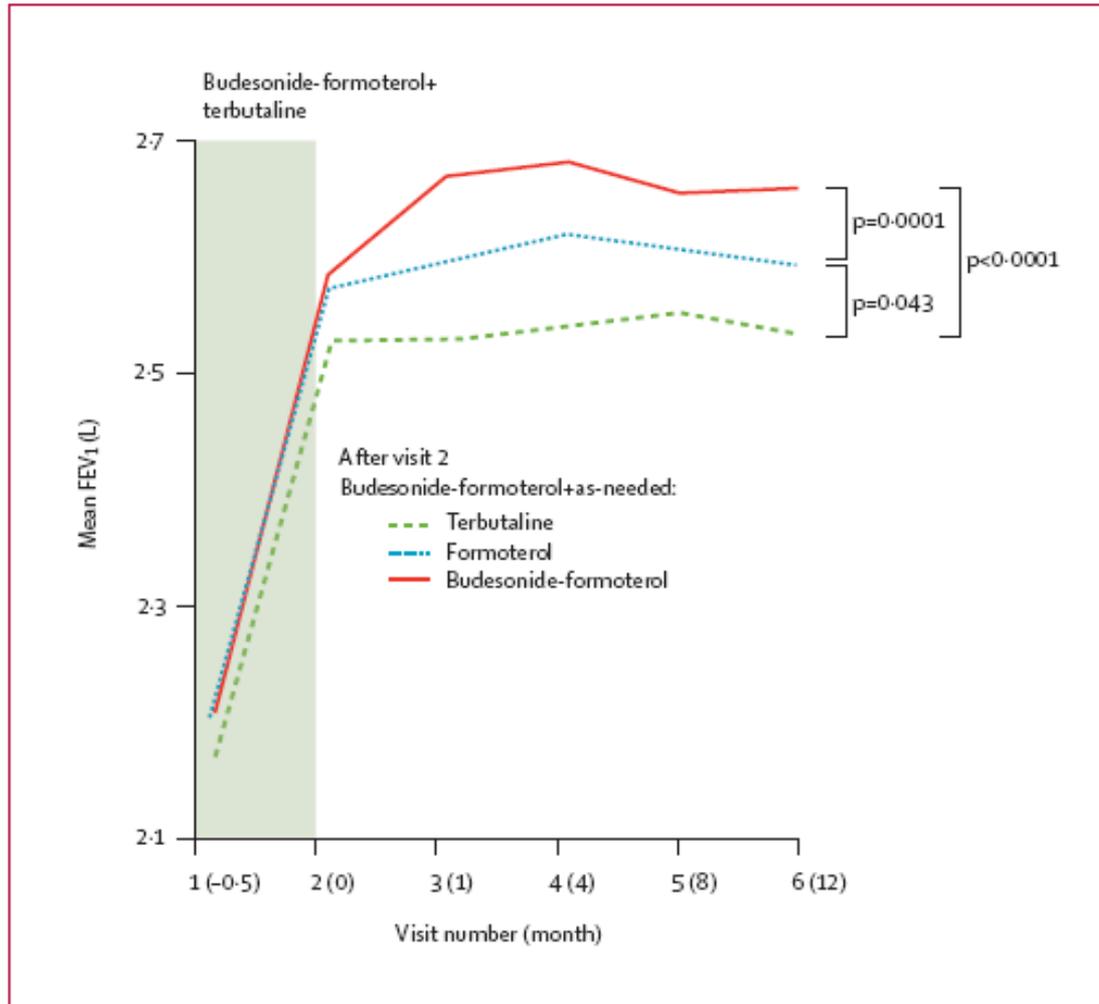


Figure 2. Proportion of patients achieving a well-controlled week (non-cumulative) over Weeks -4 to 52 for all strata combined on treatment with salmeterol/fluticasone or fluticasone propionate.

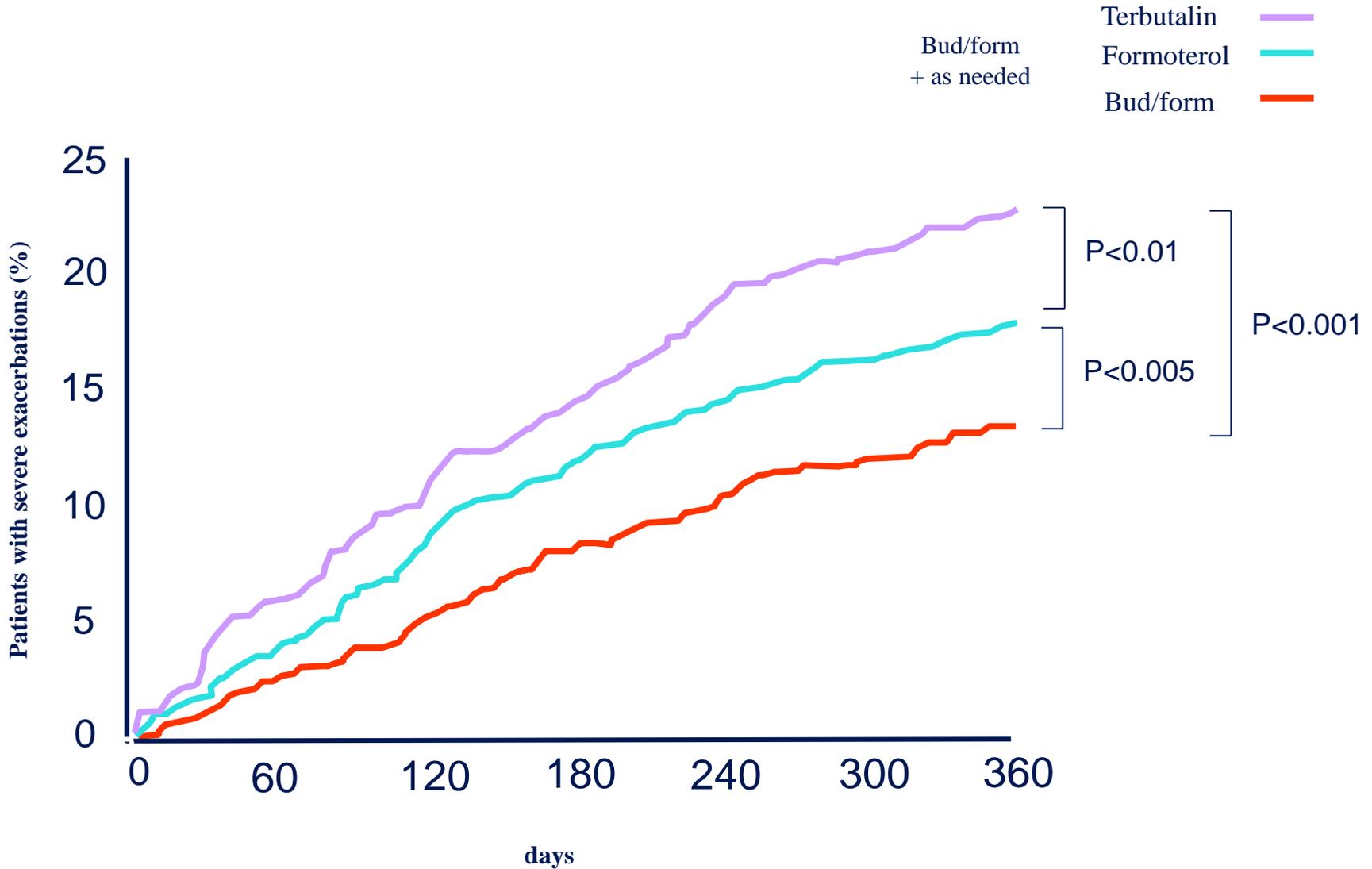
Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.

Rabe KF¹, Atienza T, Magyar P, Larsson P, Jorup C, Laloo UG.



Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.

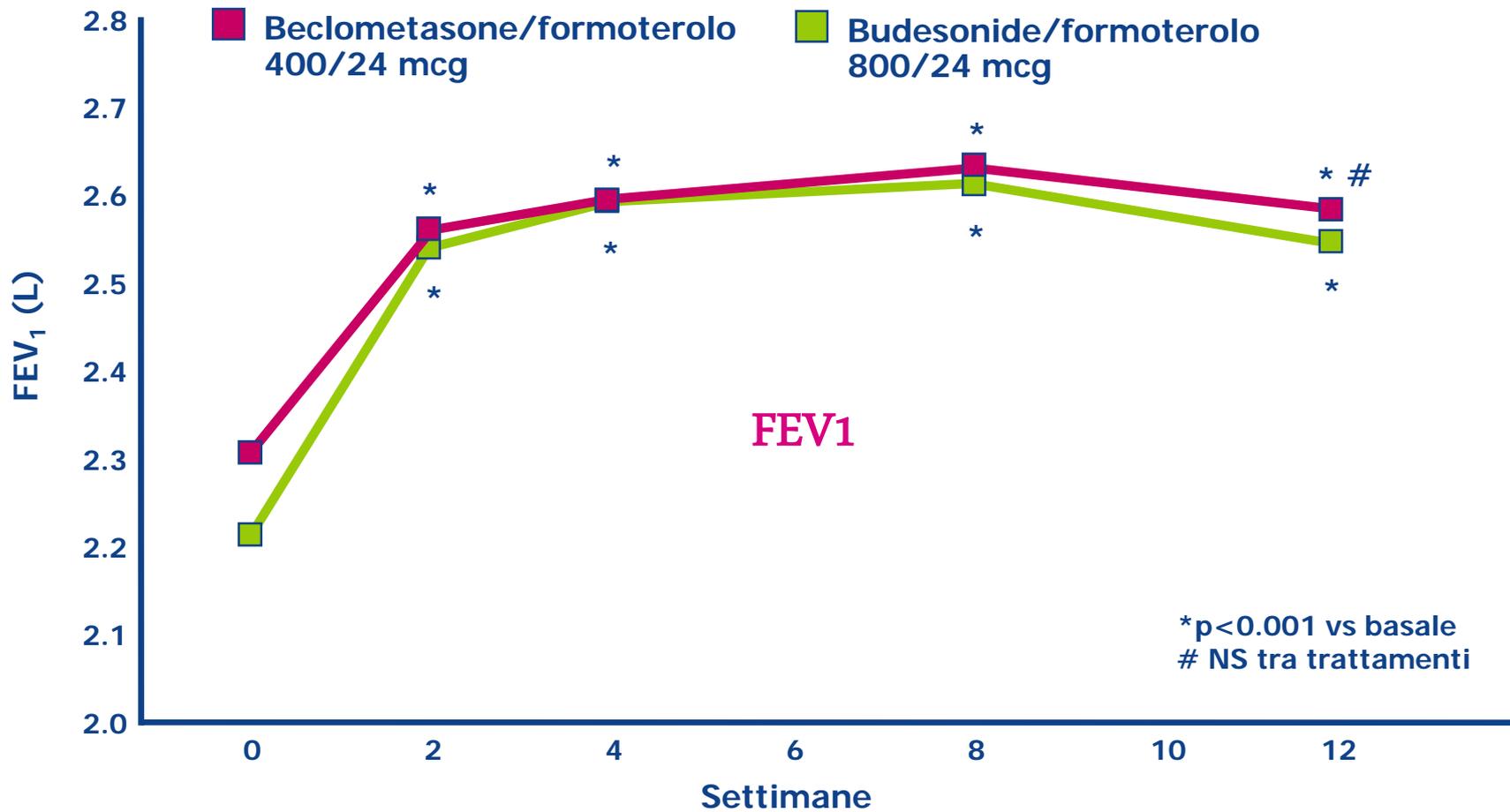
Rabe KF¹, Atienza T, Magyar P, Larsson P, Jorup C, Laloo UG.





Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma

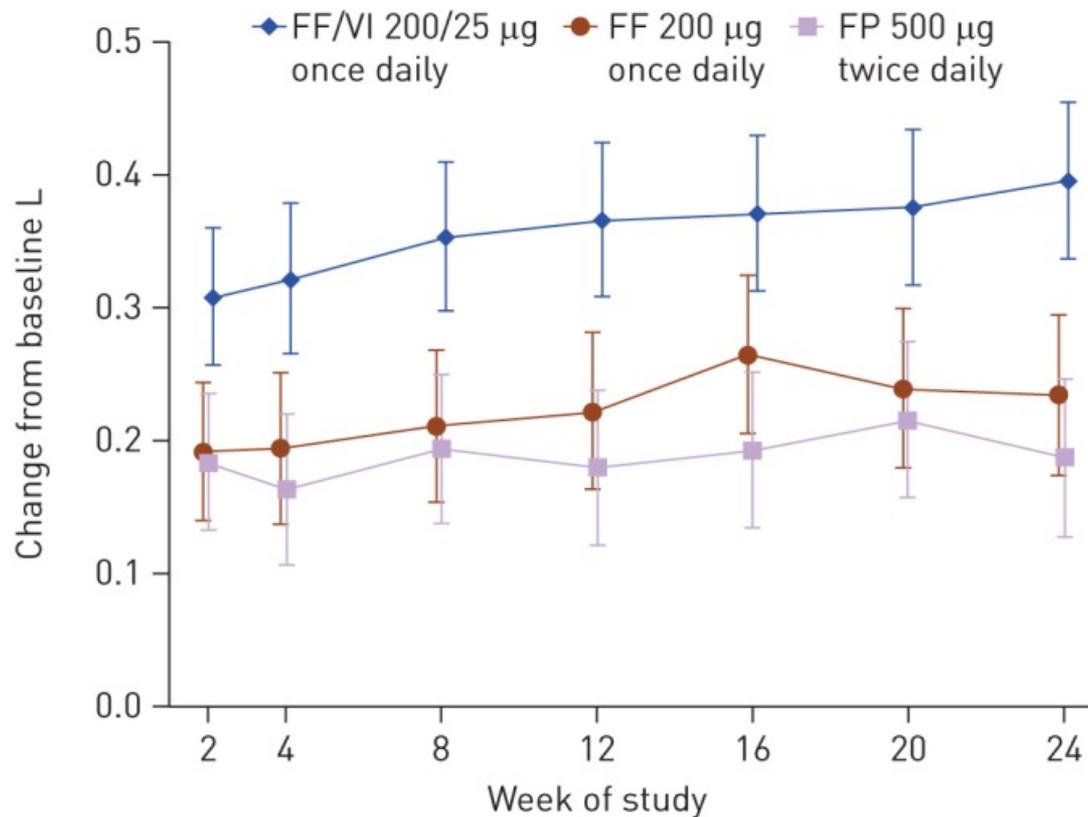
A. Papi^{*}, P.L. Paggiaro[®], G. Nicolini[†], A.M. Vignola^{†*}, L.M. Fabbri[‡] and on behalf of
the Inhaled Combination Asthma Treatment versus SYmbicort (ICAT SY) study
group[†]



Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma

Paul M. O'Byrne¹, Eugene R. Bleecker², Eric D. Bateman³, William W. Busse⁴, Ashley Woodcock⁵, Richard Forth⁶, William T. Toler⁷, Loretta Jacques⁸ and Jan Lötvall⁹

Eur Respir J 2014; 43: 773–782

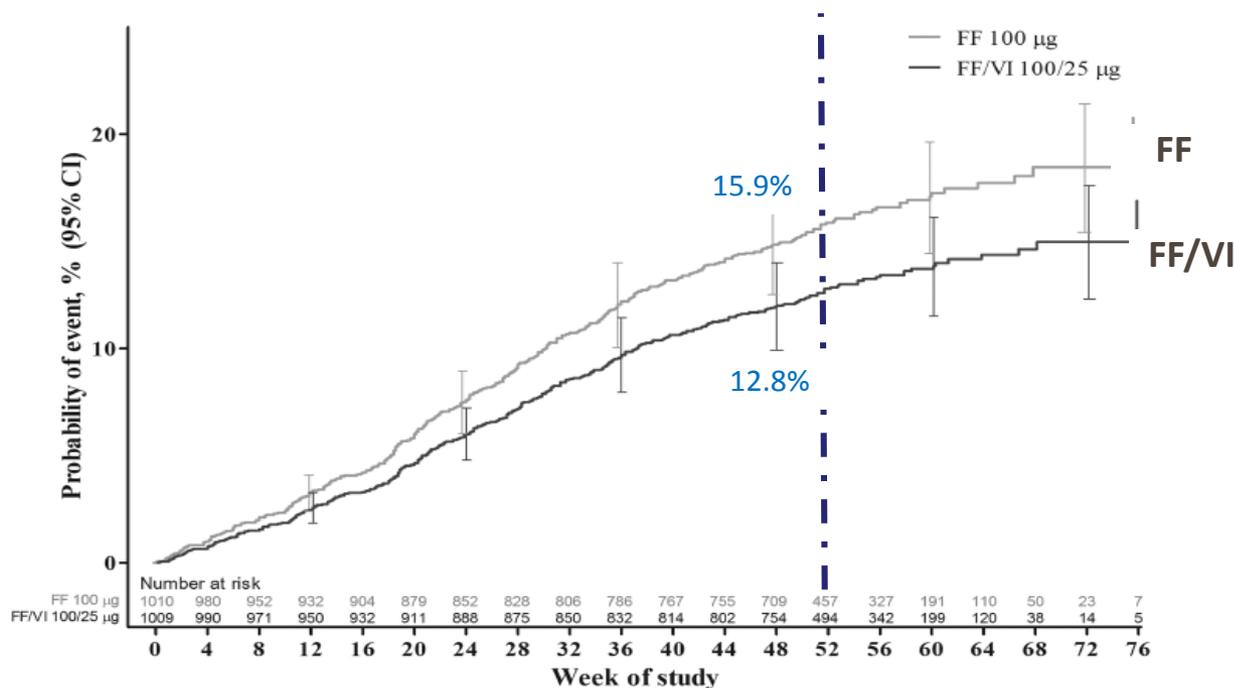


Il trattamento con FF/ VI per 24 settimane è stato associato ad un miglioramento statisticamente significativo della funzione polmonare

Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone

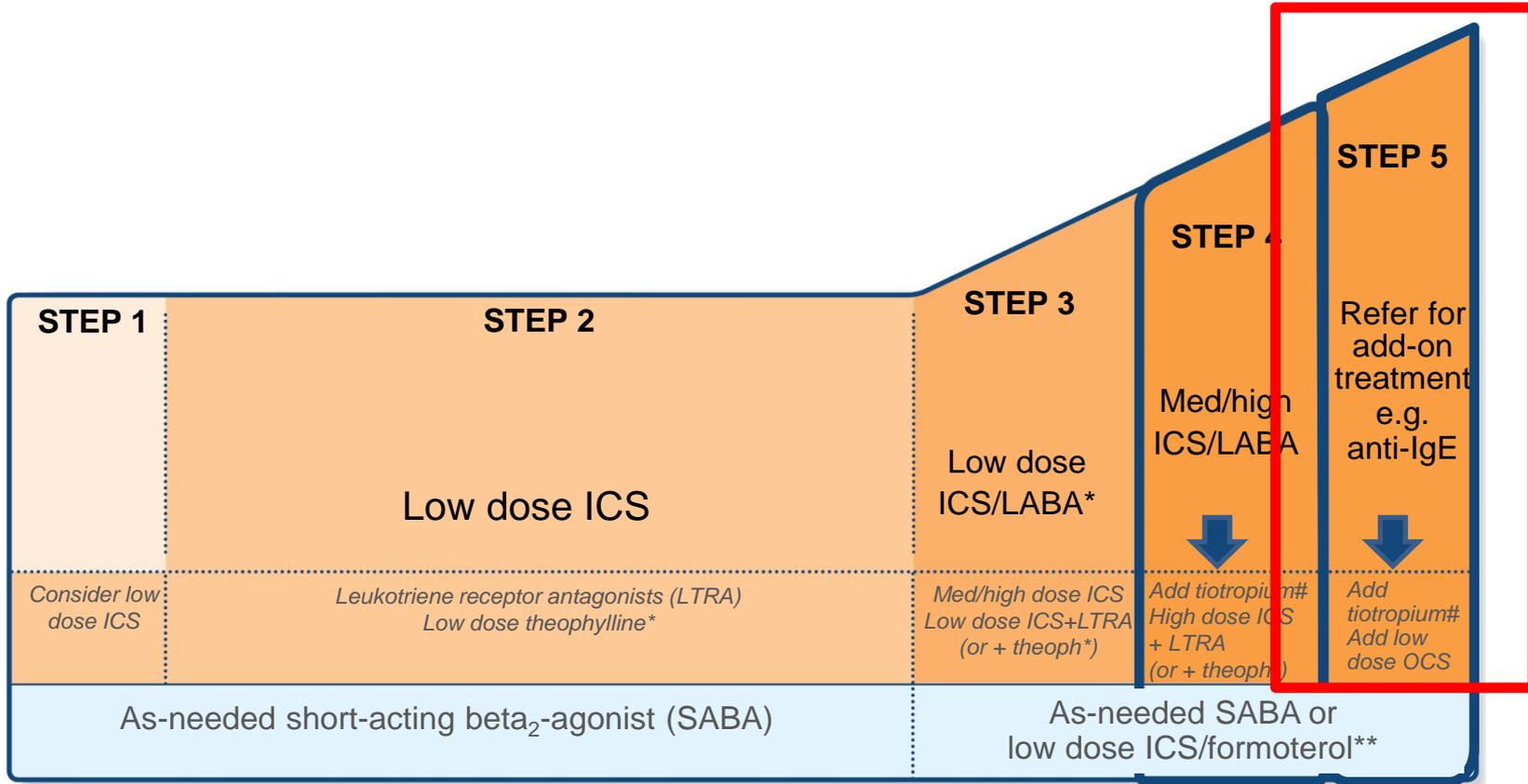
Eric D Bateman,¹ Paul M O'Byrne,² William W Busse,³ Jan Lötvall,⁴ Eugene R Bleecker,⁵ Leslie Andersen,⁶ Loretta Jacques,⁷ Lucy Frith,⁸ Jessica Lim,⁸ Ashley Woodcock⁹

Thorax 2014;69: 312–319



La combinazione VI/FF, rispetto al solo FF, ha ridotto significativamente, del 20%, il rischio di riacutizzazioni gravi in pazienti non controllati con soli ICS e con storia recente di riacutizzazioni gravi.

GINA 2015 – changes to Steps 4 and 5

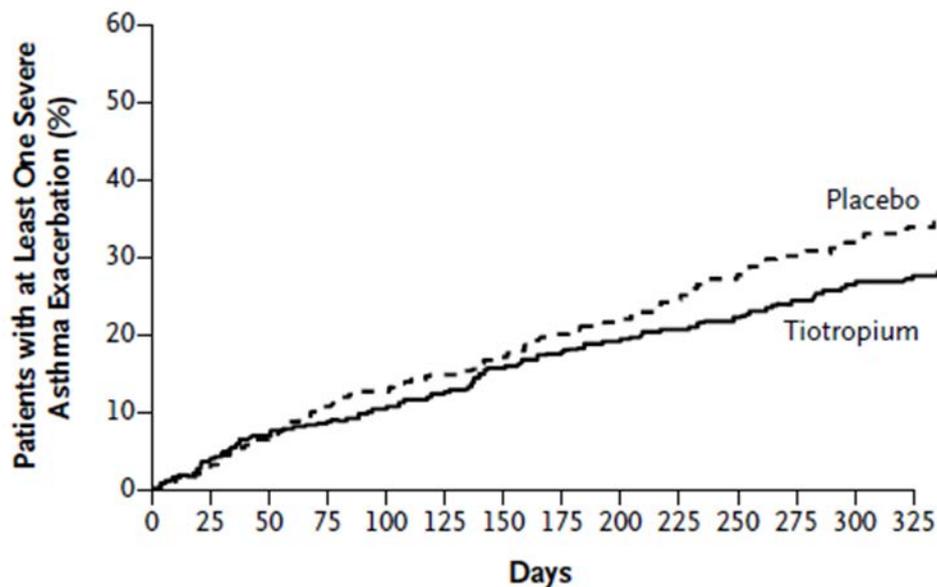


Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

N Engl J Med 2012.

C Severe Exacerbation



No. at Risk

Placebo	454	435	412	338	379	367	356	339	332	319	303	290	282	272
Tiotropium	453	430	409	401	389	378	363	353	348	339	331	319	308	298

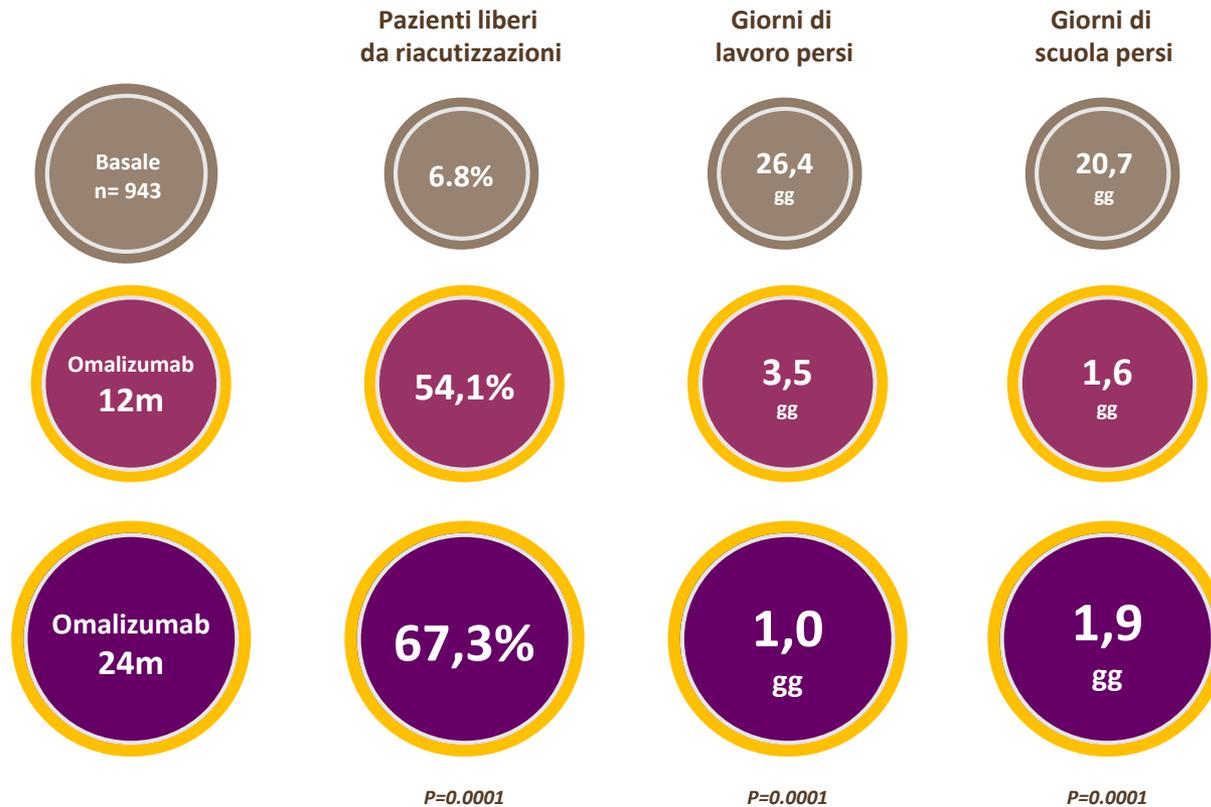


ELSEVIER



The eXpeRience registry: The 'real-world' effectiveness of omalizumab in allergic asthma

G.-J. Braunstahl ^{a,*}, C.-W. Chen ^b, R. Maykut ^c, P. Georgiou ^d,
G. Peachey ^d, J. Bruce ^c



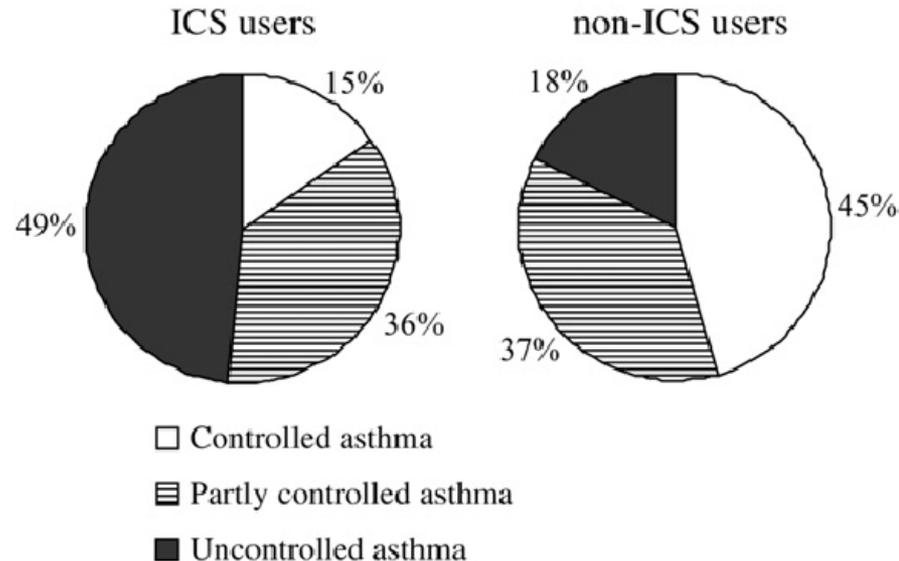
Future biologic drugs in asthma

Name	Target	Phase	Biomarkers
Mepolizumab	IL-5	Phase III – EMA+	Blood eos
Benralizumab	IL-5 R	Phase III	Blood eos
Reslizumab	IL-5	Phase III	Blood eos
Lebrikizumab	IL-13	Phase III	Periostin
Tralokinumab	IL-13	Phase II-III	DPP-4, periostin (?)
Dupilumab	IL-4	Phase III	??
Brodalumab	IL-17	Phase II	??
??			



Asthma control in Europe: A real-world evaluation based on an international population-based study

Lucia Cazzoletti, MSc,^a Alessandro Marcon, MSc,^a Christer Janson, MD,^b Angelo Corsico, MD, PhD,^c Deborah Jarvis, FFPHM,^d Isabelle Pin, MD,^e Simone Accordini, MSc,^a Enrique Almar, MD,^f Massimiliano Bugiani, MD,^g Adriana Carolei, MSc,^h Isa Cerveri, MD,^c Eric Duran-Tauleria, BS, MB,ⁱ David Gislason, MD,^j Amund Gulsvik, MD, PhD,^k Rain Jõgi, PhD,^l Alessandra Marinoni, PhD,^h Jesús Martínez-Moratalla, MD,^f Paul Vermeire, MD,^{m†} and Roberto de Marco, PhD,^a for the Therapy and Health Economics Group of the European Community Respiratory Health Survey *Verona, Pavia, and Turin, Italy, Uppsala, Sweden, London, United Kingdom, Grenoble, France, Albacete and Barcelona, Spain, Reykjavik, Iceland, Bergen, Norway, Tartu, Estonia, and Antwerp, Belgium*



WHY ?

Different Phenotypes

Low Adherence

Asthma: defining of the persistent adult phenotypes

Sally E Wenzel

Lancet 2006; 368: 804-13

Clinical or physiological phenotypes

Severity- defined

Exacerbation-prone

Defined by chronic restriction

Treatment-resistant

Defined by age at onset

Phenotypes related to the following triggers

Aspirin or on-steroidal anti-inflammatory drugs

Environmental allergens

Occupational allergens or irritants

Menses

Exercise

Inflammatory phenotypes

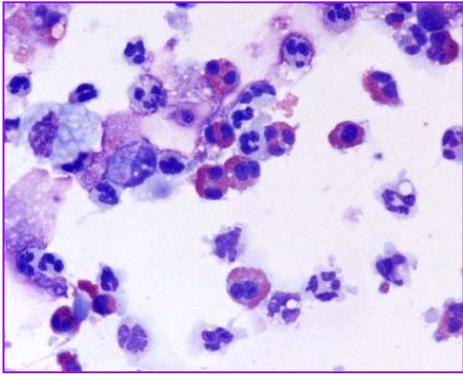
Eosinophilic

Neutrophilic

Pauci-granulocytic

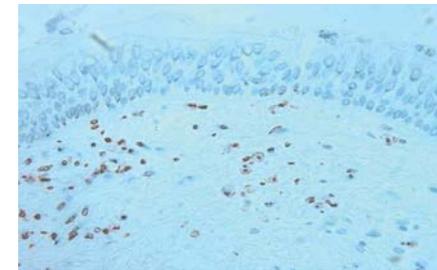
Inflammatory Phenotypes

Eosinophilic asthma



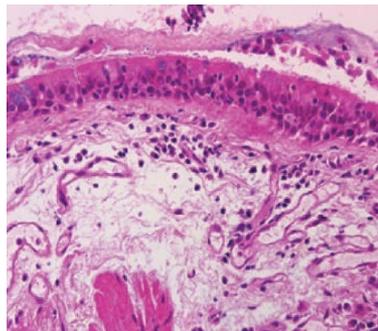
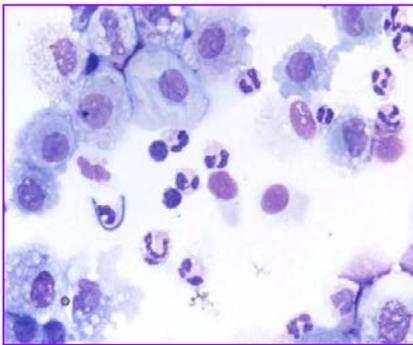
EG2 +

Neutrophilic asthma



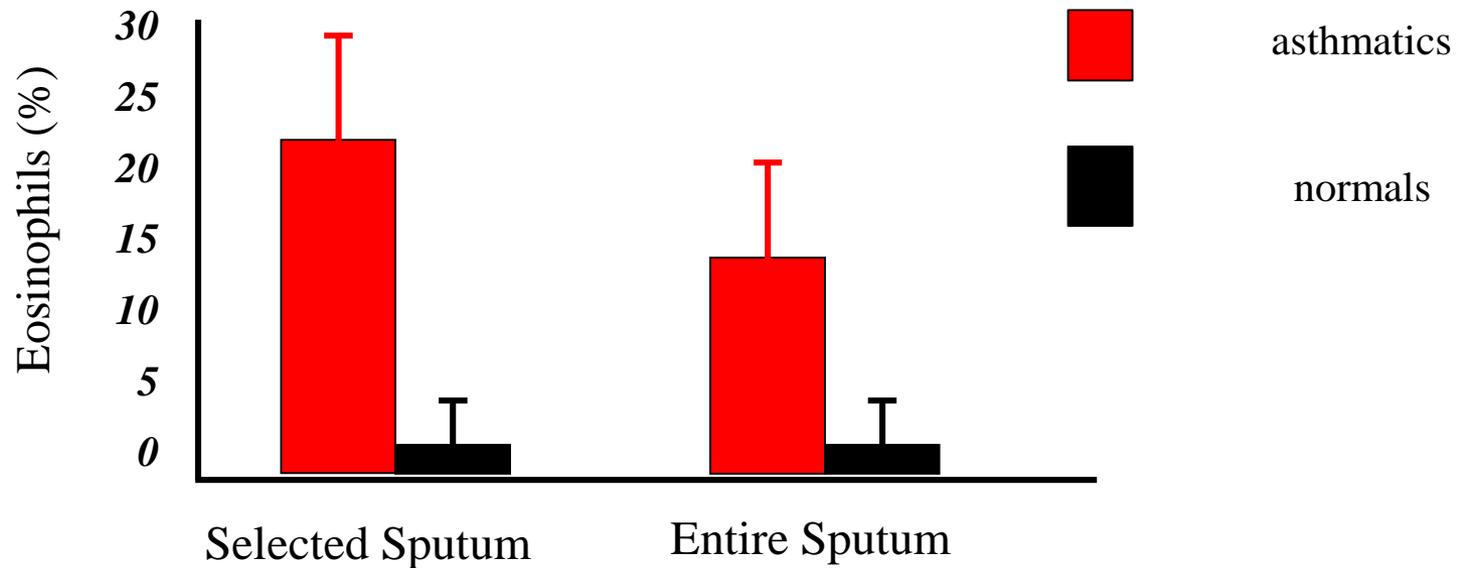
Neutrophil elastase +

Paucigranulocytic asthma



Comparison of two methods of processing induced sputum: selected versus entire sputum

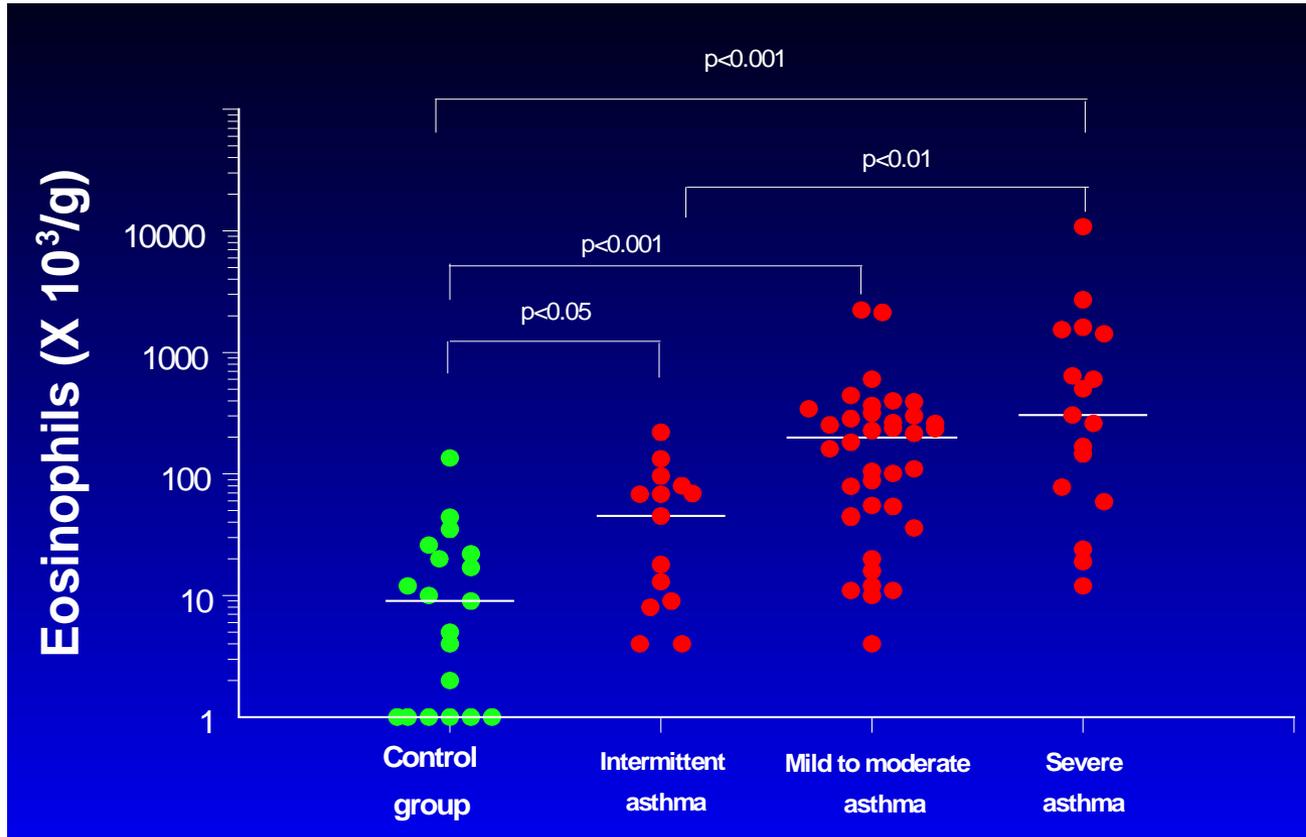
A Spanevello et al. AJRCCM 1998; 157: 665-668



The Relationship between Airways Inflammation and Asthma Severity

RENAUD LOUIS, LAURIE C. K. LAU, ADRIAAN O. BRON, ALBERT C. ROLDAAN, MAURICE RADERMECKER, and RATKO DJUKANOVIĆ

AM J RESPIR CRIT CARE MED 2000;161:9-16.

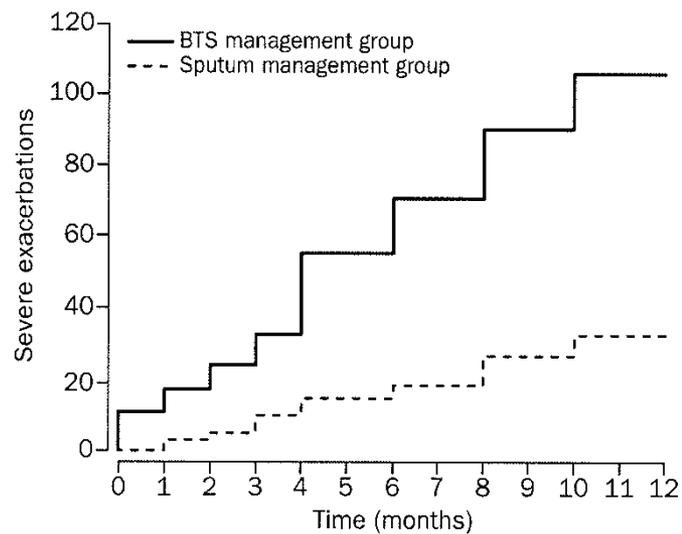
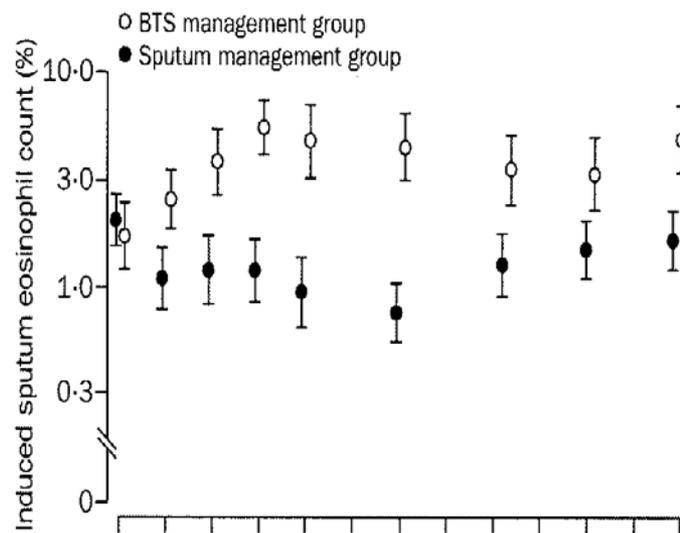


Sputum eosinophils are higher in asthmatics than in controls and their amount in sputum increases with the severity of the disease

Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial

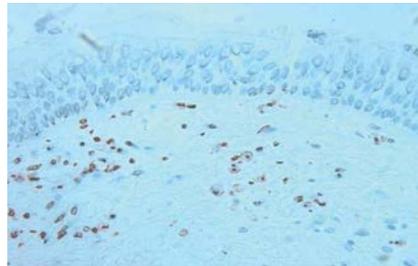
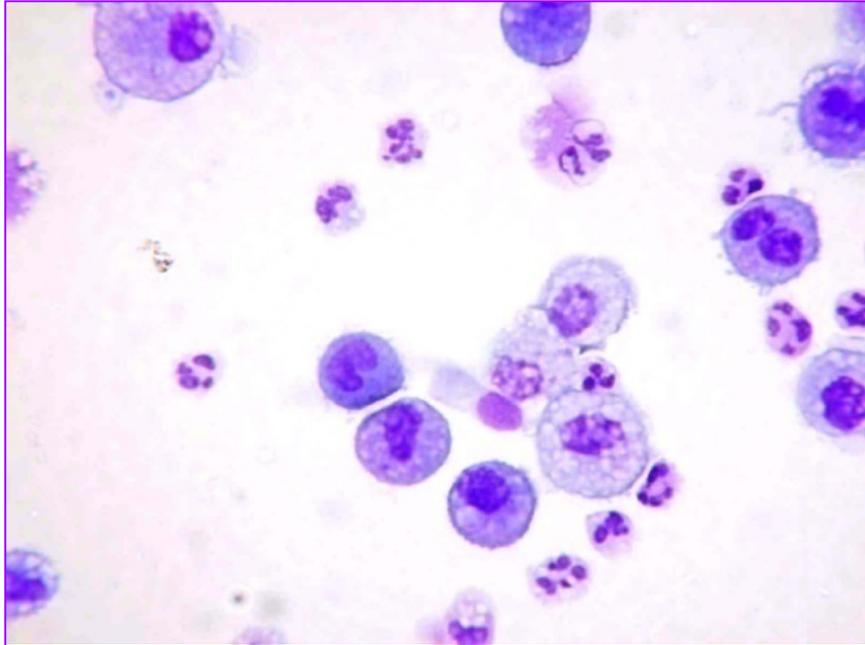
Ruth H Green, Christopher E Brightling, Susan McKenna, Beverley Hargadon, Debbie Parker, Peter Bradding, Andrew J Wardlaw, Ian D Pavord

Lancet 2002;360: 1715-21



Inflammatory Phenotypes

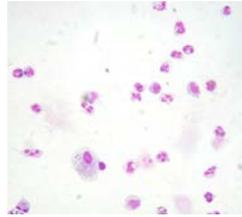
Neutrophilic asthma



Neutrophil elastase +

The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma

The ENFUMOSA Study Group*



AIRWAY
INFLAMMATION

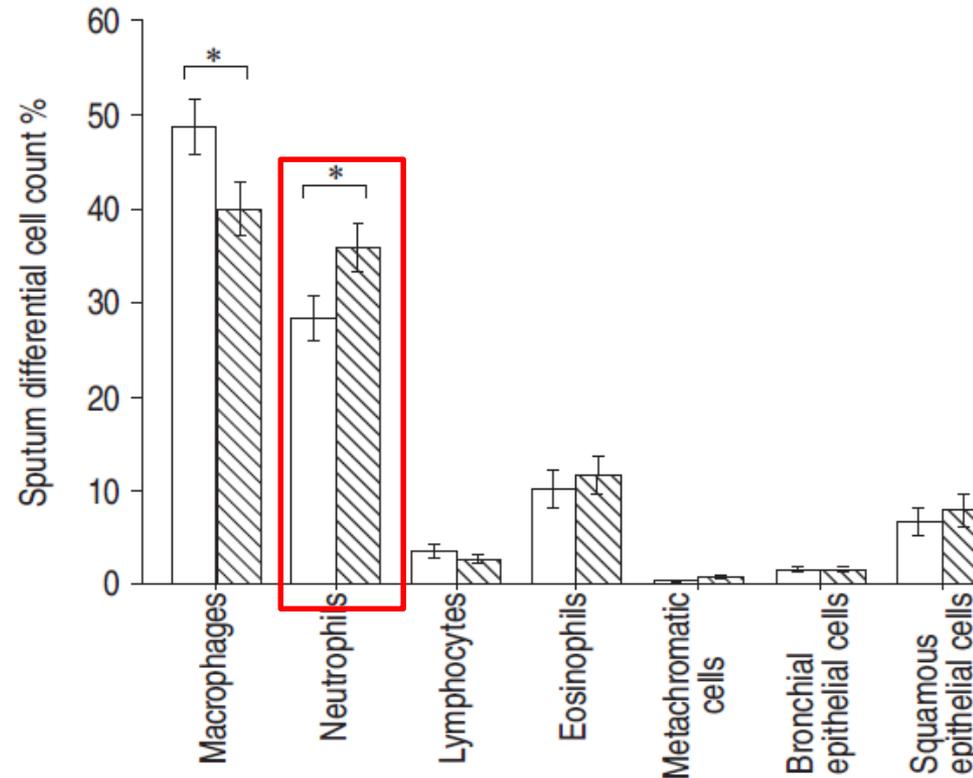


Fig. 2. – Sputum differential cell count in subjects with severe asthma (▨; n=99) compared with subjects with well-controlled asthma (□; n=89). Data expressed as %±SEM. There were no difference in total sputum cell counts between the groups (controlled asthma 4.6 ± 0.5 million cells per gram *versus* 5.6 ± 0.6 million cells per gram in the subjects with severe asthma). *: $p<0.05$.

Asthma and cigarette smoking

N.C. Thomson, R. Chaudhuri, E. Livingston

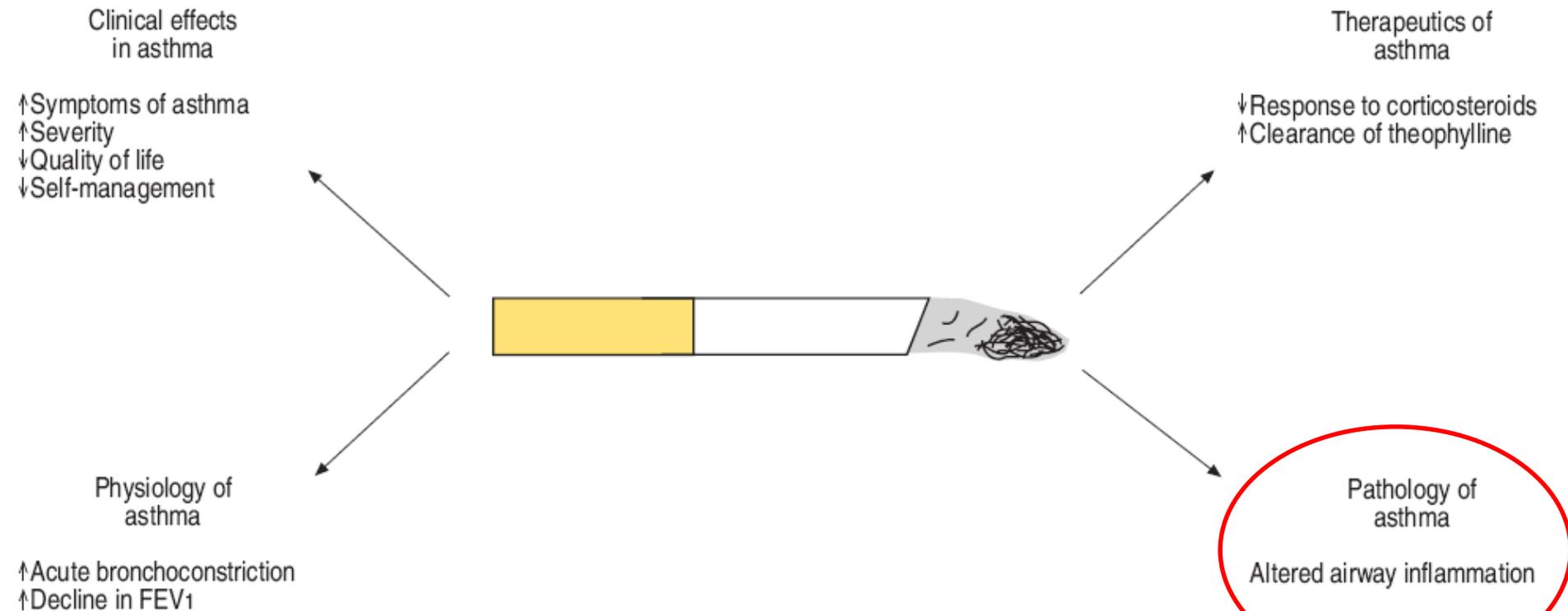


Fig. 1.— Interactions between asthma and cigarette smoking. FEV₁: forced expiratory volume in one second; ↑ : increase; ↓ : decrease.

Airway inflammation in patients affected by obstructive sleep apnea syndrome

F.G. Salerno^a, E. Carpagnano^b, P. Guido^a, M.R. Bonsignore^c, A. Roberti^a, M. Aliani^a, A.M. Vignola^{b,c}, A. Spanevello^{a,*}

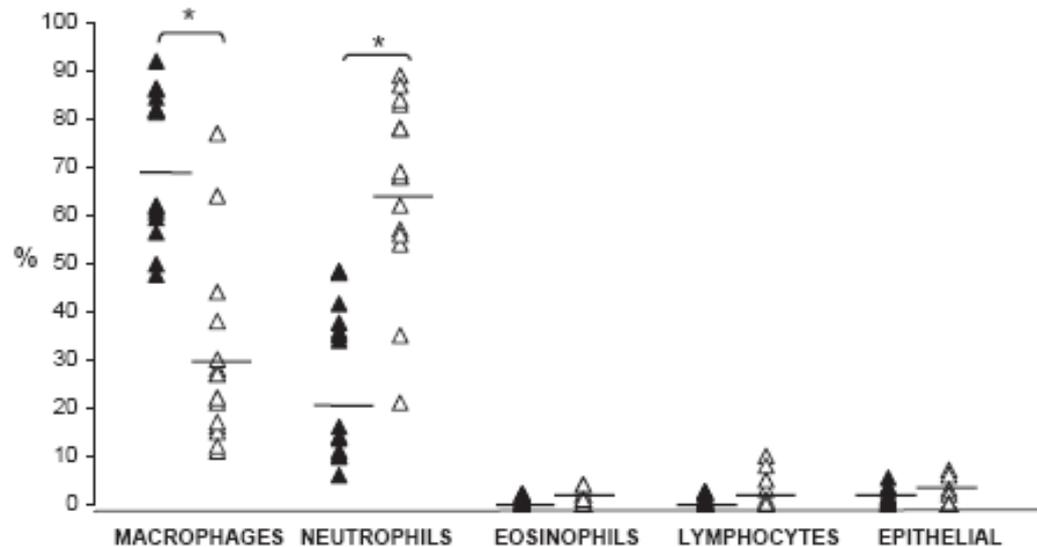


Figure 1 Induced sputum cellular profile in the OSAS group (empty triangles) and in the control group (filled triangles) as % of the total cell count. *, $P < 0.001$ vs. control.

Short communication

Sputum induced cellularity in a group of traffic policemen

Silvano Dragonieri ^a, Marina Musti ^b, Carmelina Izzo ^c, Luisa Maria Esposito ^c,
Maria Pia Foschino Barbaro ^d, Onofrio Resta ^a, Antonio Spanevello ^{c,d,*}

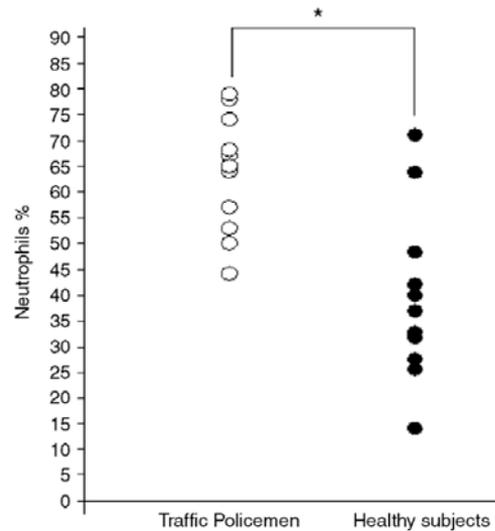
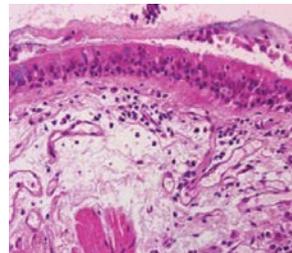
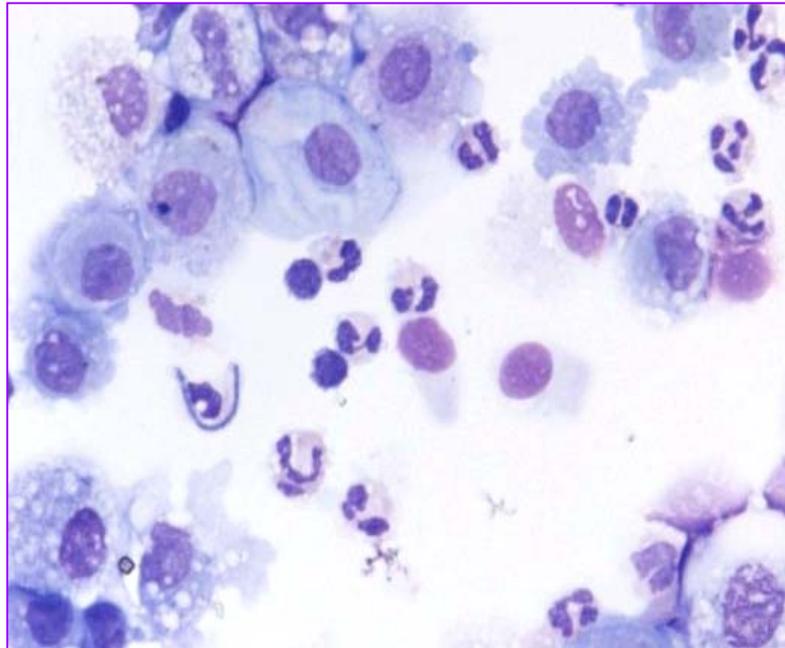


Fig. 1. Neutrophil cell count of induced sputum. The group of traffic policemen (open circles) shows a statistically significant increase of the neutrophils compared to the control group (closed circles) ($p < 0.01$). The open circles and the closed circles are 11 (instead of 12) because two subjects present the same value of neutrophils (65% for open circles and 42% for closed circles).

Inflammatory Phenotypes

Paucigranulocytic asthma



Noneosinophilic asthma: A distinct clinical and pathologic phenotype

JACI 2007

Pranab Haldar, MA, MRCP, and Ian D. Pavord, DM, FRCP *Leicester, United Kingdom*

	Noneosinophilic asthma	Eosinophilic asthma
	Normal eosinophil count (<1.9%)	Raised eosinophil count
Normal neutrophil count (< 61%)	Paucigranulocytic <ul style="list-style-type: none"> - Well controlled or intermittent asthma - Consider alternative diagnosis 	Eosinophilic <ul style="list-style-type: none"> - Typical asthma, frequently associated with atopic disease - May indicate inadequate corticosteroid therapy
Raised neutrophil count	Neutrophilic <ul style="list-style-type: none"> - Acute infection (viral or bacterial) - Chronic infection (chlamydia, adenovirus) - Smoking - Environmental pollutants (ozone, NO₂) - Occupational antigens - Endotoxin exposure - Obesity 	Mixed granulocytic <ul style="list-style-type: none"> - (Severe) asthma exacerbations - Refractory asthma

FIG 2. Classification based on induced sputum patterns of cellular inflammation in asthma.

Different Phenotypes

Low Adherence

Asthma medication adherence: the role of God and other health locus of control factors

Brian K. Ahmedani, PhD^{*}; Edward L. Peterson, PhD[†]; Karen E. Wells, MPH[†]; Cynthia S. Rand, PhD[‡]; and L. Keoki Williams, MD, MPH^{*,§}

Ann Allergy Asthma Immunol 110 (2013) 75–79

Table 1
Baseline characteristics of study sample stratified by race/ethnicity

Characteristic	Total sample (n = 1,025)	White individuals (n = 702)	African American individuals (n = 323)	P value ^a
Age, mean (SD), y	37.59 (14.77)	38.41 (14.65)	35.81 (14.90)	.004
Female sex, No. (%)	675 (65.9)	464 (66.2)	211 (65.3)	.79
Health locus of control, mean (SD) ^b				
God/higher power	1.92 (1.18)	1.71 (1.05)	2.38 (1.31)	.001
Internal	3.90 (1.00)	3.96 (0.97)	3.77 (1.05)	.008
Chance	2.09 (0.87)	2.09 (0.83)	2.09 (0.95)	.35
Physicians (powerful others)	4.94 (0.92)	4.95 (0.93)	4.94 (0.90)	.64
Other people (powerful others)	2.65 (1.09)	2.69 (1.06)	2.57 (1.15)	.06
Medical history, mean (SD) ^c				
No. of ED visits for asthma	0.04 (0.23)	0.02 (0.16)	0.08 (0.32)	.001
No. of oral corticosteroid fills	0.57 (1.17)	0.61 (1.27)	0.50 (0.91)	.41
ICS adherence, mean (SD), % ^d	36 (40) (n = 1,004)	39 (41) (n = 687)	28 (36) (n = 317)	.001

Adherence 36%

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don't work in patients who don't take them.

— C. Everett Koop, M.D.



opinions/hypotheses

What Does It Mean When a Patient Says, “My Asthma Medication Is Not Working?”*

Bruce K. Rubin, MEng, MD, FCCP



In the office of a busy practice, it is often easier to respond to the patient who tells you that their medications are not working by simply writing a prescription for a different medication or for additional medications. In many cases, the problem is not the medication at all...

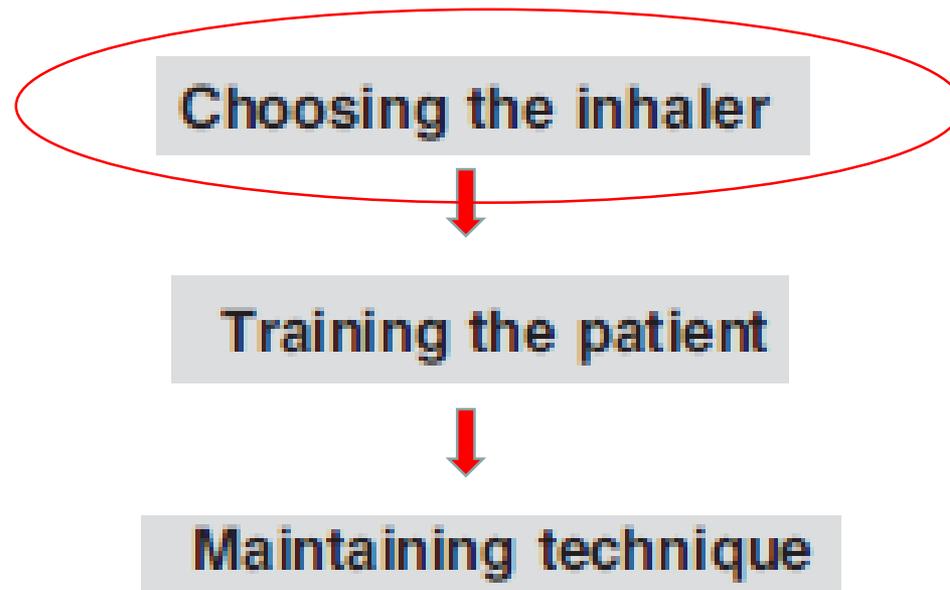
- Patient Who Does Not Want To Take Medication
- **The Patient Who Does Not Understand How or When To Use Medication**
 - The Patient Who Is Concerned About Medication Side Effects
 - The Patient Who Cannot Feel the Medication Working
 - The Patient With Unrealistic Expectations
- The Patient Who Incorrectly Thinks That They Are Inhaling Medication
 - The Patient Who Does Not Have Asthma
 - The Patient Who Really Needs More Medicine

EDITORIAL

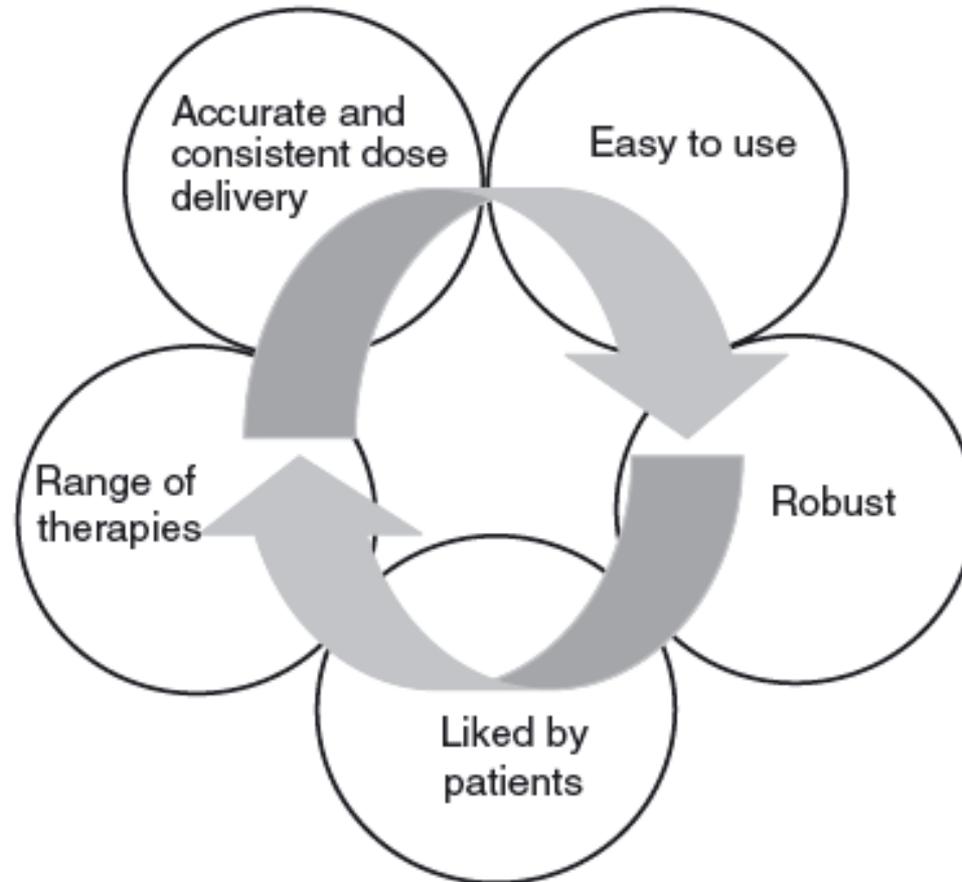
Inhaler devices for asthma: a call for action in a neglected field

A. Papi*, **J. Haughney[#]**, **J.C. Virchow[†]**, **N. Roche⁺**, **S. Palkonen[§]** and **D. Price[#]**

Summary of proposals and needs to improve inhaler prescribing, patient training, and monitoring



Criteria for ideal inhaler



Chrystyn H et al.,

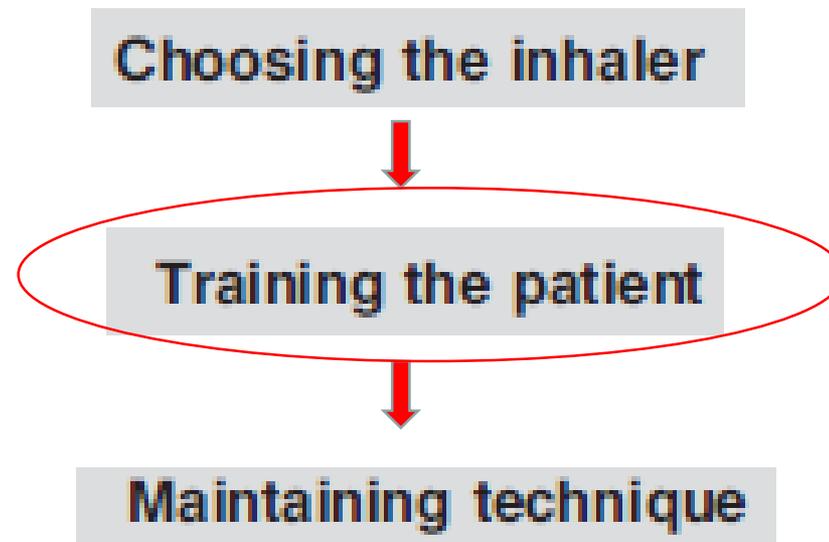
Int J Clin Pract, June 2007, 61, 6, 1022–1036

EDITORIAL

Inhaler devices for asthma: a call for action in a neglected field

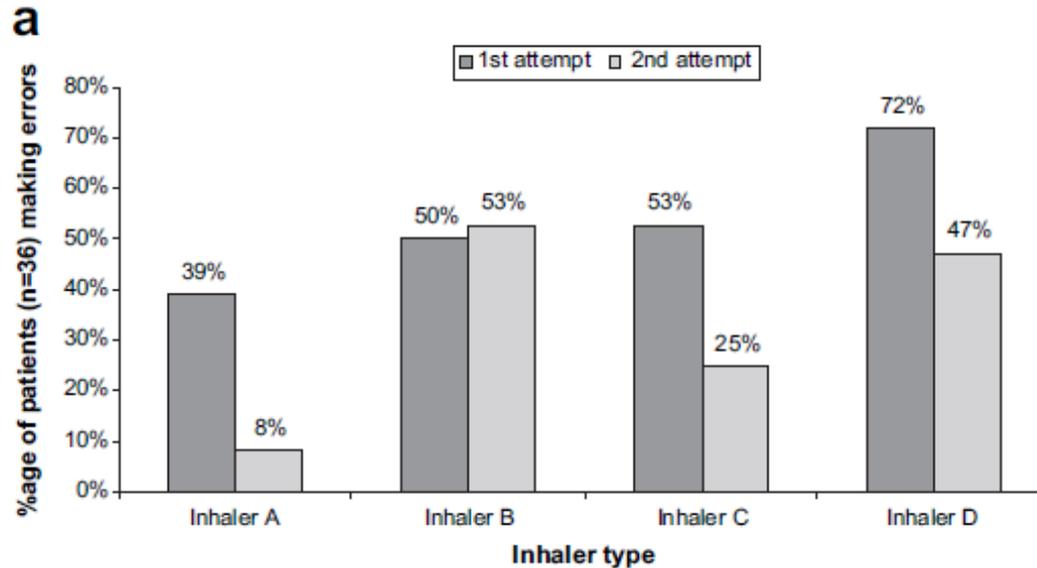
A. Papi*, J. Haughney[#], J.C. Virchow[†], N. Roche⁺, S. Palkonen[§] and D. Price[#]

Summary of proposals and needs to improve inhaler prescribing, patient training, and monitoring



Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs[☆]

John Haughney^{a,*}, David Price^a, Neil C. Barnes^b, J. Christian Virchow^c, Nicolas Roche^d, Henry Chrystyn^e



Patients with asthma or COPD

1° attempt= after reading instructions
2° attempt= after investigator explained device handling

Adapted from: Schulte M, et al. J Aerosol Med Pulm Drug Deliv 2008;21:321e8.

EDITORIAL

Inhaler devices for asthma: a call for action in a neglected field

A. Papi*, **J. Haughney[#]**, **J.C. Virchow[†]**, **N. Roche⁺**, **S. Palkonen[§]** and **D. Price[#]**

Summary of proposals and needs to improve inhaler prescribing, patient training, and monitoring

Choosing the inhaler



Training the patient



Maintaining technique



Economic analysis of two structured treatment and teaching programs on asthma

Neri M, Migliori GB, Spanevello A

Allergy 1996; 51: 313-319

Program	Complete		Reduced	
	Mean	Median	Mean	Median
Year before				
No. of asthma attacks	8.40	7.5	7.84	5
No. of urgent medical examinations	1.66	0.5	1.87	1
No. of admission days	6.59	0	7.24	8
No. of working days lost	9.4	0	10.4	7
Year after				
No. of asthma attacks	4.72	3	7.91	5
No. of urgent medical examinations	0.72	0	2.18	1
No. of admission days	0.12	0	0.12	0
No. of working days lost	2.1	0	5.1	0

Economic analysis of two structured treatment and teaching programs on asthma

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Allergy 1996; 51: 313-319

Program	Complete	Reduced	
	\$	\$	P value
Year before	254.8 ± 294.8	206.3 ± 182.1	>0.05
Year after	528.6 ± 355.4	631.8 ± 470.9	>0.05
P value	<0.001	<0.001	

Cost of drugs used by patients attending complete and reduced programme in years before and after enrolment

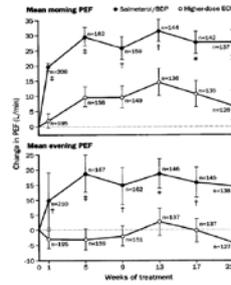
Economic analysis of two structured treatment and teaching programs on asthma

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Allergy 1996; 51: 313-319

Program	Complete	Reduced
	\$	\$
Year before		
Urgent medical examinations	$1.66 \times 44 = 73$	$1.87 \times 44 = 82.3$
Admission days	$6.59 \times 244.5 = 1611.3$	$7.24 \times 244.5 = 1770.2$
Working days lost	$9.37 \times 75 = 702.7$	$10.38 \times 75 = 778.5$
Drug cost	254.8	206.3
Total	2641.8	2837.3
Year after		
Urgent medical examinations	$0.72 \times 44 = 31.7$	$2.18 \pm 44 = 95.9$
Admission days	$0.12 \times 244.5 = 29.3$	$0.12 \pm 244.5 = 29.3$
Working days lost	$2.1 \times 75 = 257.5$	$5.1 \pm 75 = 382.5$
Drug cost	528.6	631.8
Total	747.1	1139.5

Take home messages



Past

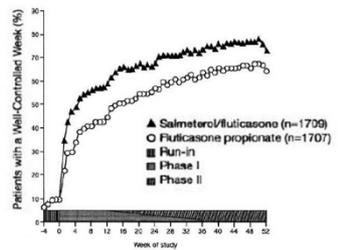
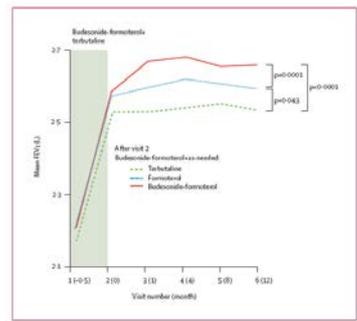


Figure 2. Proportion of patients achieving a well-controlled week (non-cumulative) over Weeks -4 to 52 for all strata combined on treatment with salmeterol/fluticasone or fluticasone propionate.

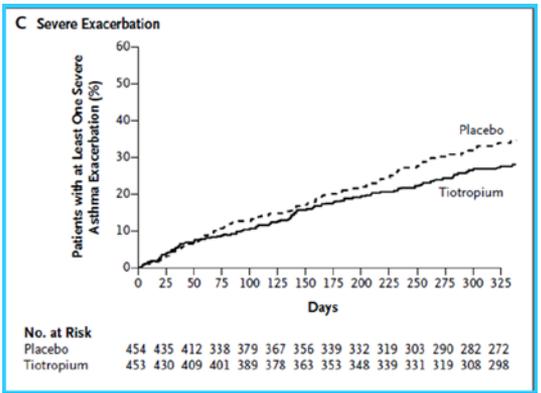


Present

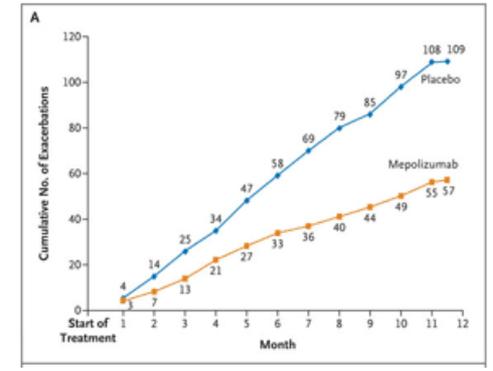


The eXpeRience registry: The 'real-world' effectiveness of omalizumab in allergic asthma

G.-J. Braunstahl^{a,*}, C.-W. Chen^b, R. Maykut^c, P. Georgiou^d, G. Peachey^d, J. Bruce^c



Future



Cluster Analysis and Clinical Asthma Phenotypes

Pranab Haldar^{1*}, Ian D. Pavord^{1*}, Dominic E. Shaw¹, Michael A. Berry¹, Michael Thomas², Christopher E. Brightling¹, Andrew J. Wardlaw¹, and Ruth H. Green^{1*}

