

Terapia dell'asma. Uno per tutti o è possibile un approccio personalizzato?



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XXX CONGRESSO NAZIONALE

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Società Italiana di Allergologia,
Asma ed Immunologia Clinica



FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG



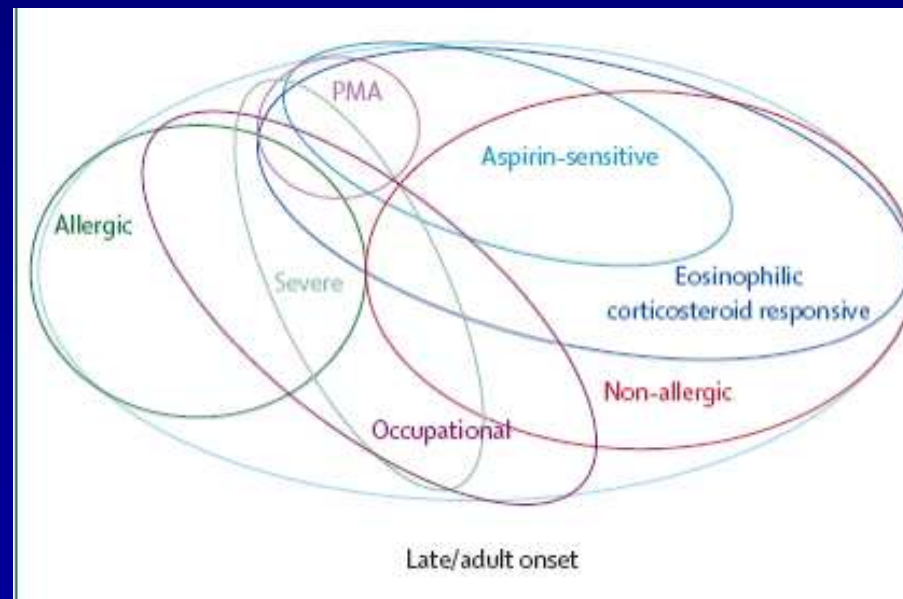
Italian Society for Allergy, Asthma & Clinical Immunology



Asthma: defining of the persistent adult phenotypes

Sally E Wenzel

The common disease asthma is probably not a single disease, but rather a complex of multiple, separate syndromes that overlap. Although clinicians have recognised these different phenotypes for many years, they have remained poorly characterised, with little known about the underlying pathobiology contributing to them. Development of targeted therapies for asthma, and phenotype-specific clinical trials have raised interest in these phenotypes. Improved understanding of these phenotypes in complex diseases such as asthma will also improve our ability to link specific genotypes to their associated disease, which should help development of biomarkers. However, there is no standardised method to define asthma phenotypes. This Review analyses some of the methods that have been used to define asthma phenotypes and proposes an integrated method of classification to improve our understanding of these phenotypes.



Wenzel, Lancet 2006

Personalized Respiratory Medicine: Exploring the Horizon, Addressing the Issues

Summary of a BRN-AJRCCM Workshop Held in Barcelona on June 12, 2014

Alvar Agusti^{1,2}, Josep Maria Antó³, Charles Auffray⁴, Ferran Barbé^{2,5}, Esther Barreiro^{2,6}, Jordi Dorca^{2,7}, Joan Escarrabill¹, Rosa Faner^{1,2}, Laura I. Furlong⁸, Judith Garcia-Aymerich³, Joaquim Gea^{2,6}, Bertil Lindmark⁹, Eduard Monsó^{2,10}, Vicente Plaza¹¹, Milo A. Puhan¹², Josep Roca^{1,2}, Juan Ruiz-Manzano^{2,13}, Laura Sampietro-Colom¹, Ferran Sanz⁸, Luis Serrano^{14,15}, James Sharpe^{14,15}, Oriol Sibila¹¹, Edwin K. Silverman¹⁶, Peter J. Sterk¹⁷, and Jacob I. Sznajder¹⁸

YESTERDAY

Traditional Medicine

All patients with a
given disease



A Step toward Personalized Asthma Treatment

Jeffrey M. Drazen, M.D.

Inhaled glucocorticoids are used every day by millions of patients with asthma. As with all asthma-controller treatments, there is marked patient-to-patient variability in the therapeutic response; about one in three patients with asthma who use inhaled glucocorticoids may not benefit from this treatment. It would be advantageous if we could identify, in advance, patients who would respond to such treatment, but we have not been

DEFINIZIONE DI ASMA: CRITICITA'

L'asma è una malattia **episodica, caratterizzata dal punto di vista clinico, da episodi recidivanti di dispnea parossistica con sibili e tosse, le cui fasi acute possono intervallarsi a periodi sintomatologicamente silenti.**

Harrison, 14^a Ediz, 1999, cap 252, p 1625

L'identificazione dell'asma con il sintomo può portare ad un comportamento terapeutico scorretto

Original Research

ASTHMA

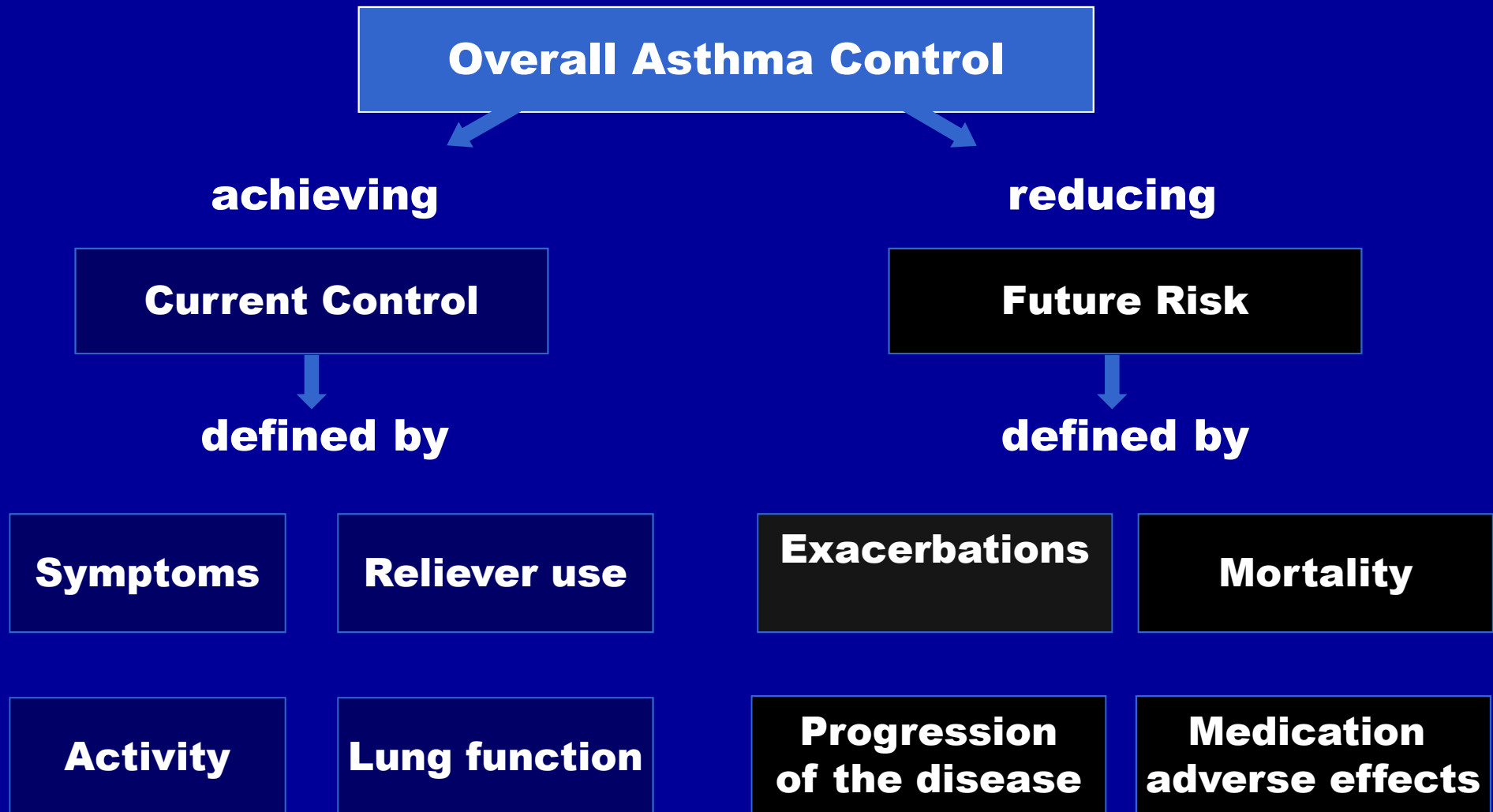
No Symptoms, No Asthma*

The Acute Episodic Disease Belief Is Associated With Poor Self-Management Among Inner-City Adults With Persistent Asthma

Ethan A. Halm, MD, MPH; Pablo Mora, PhD; and Howard Leventhal, PhD

Chest 2006

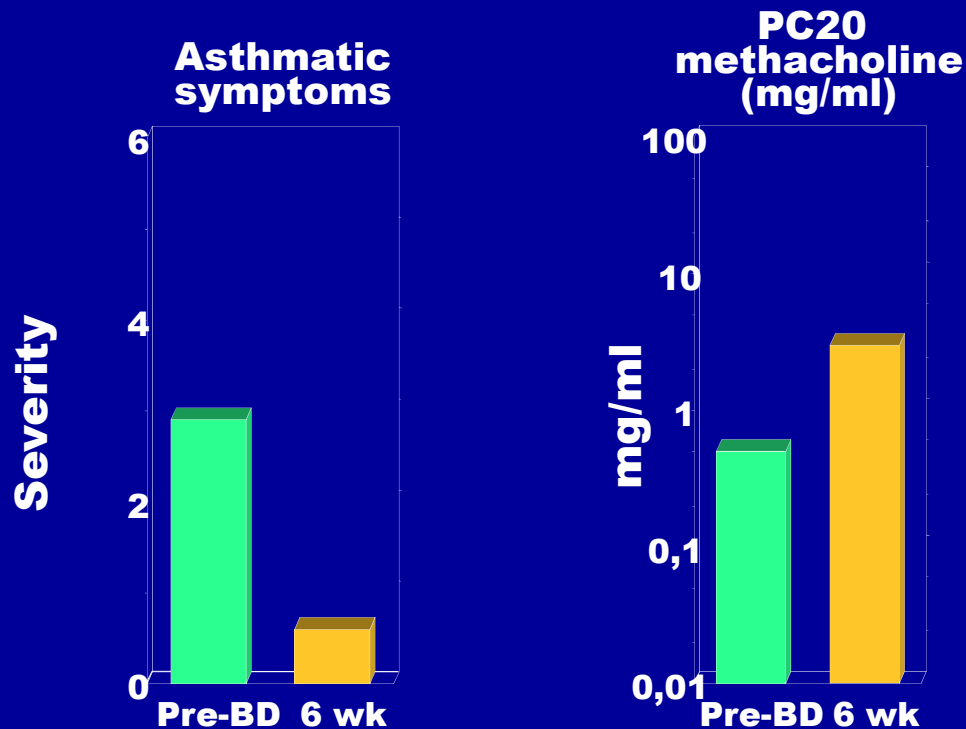
Obiettivi del trattamento dell'asma



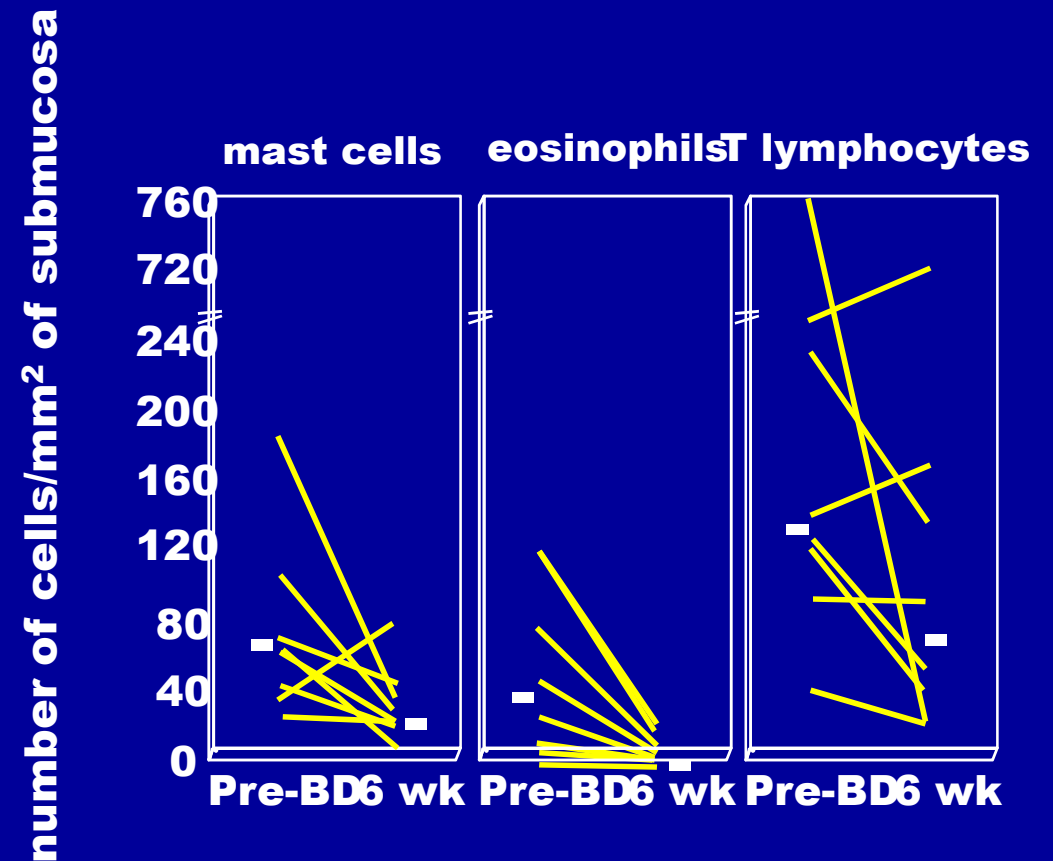
Approccio terapeutico all'asma persistente

Corticosteroidi inalatori

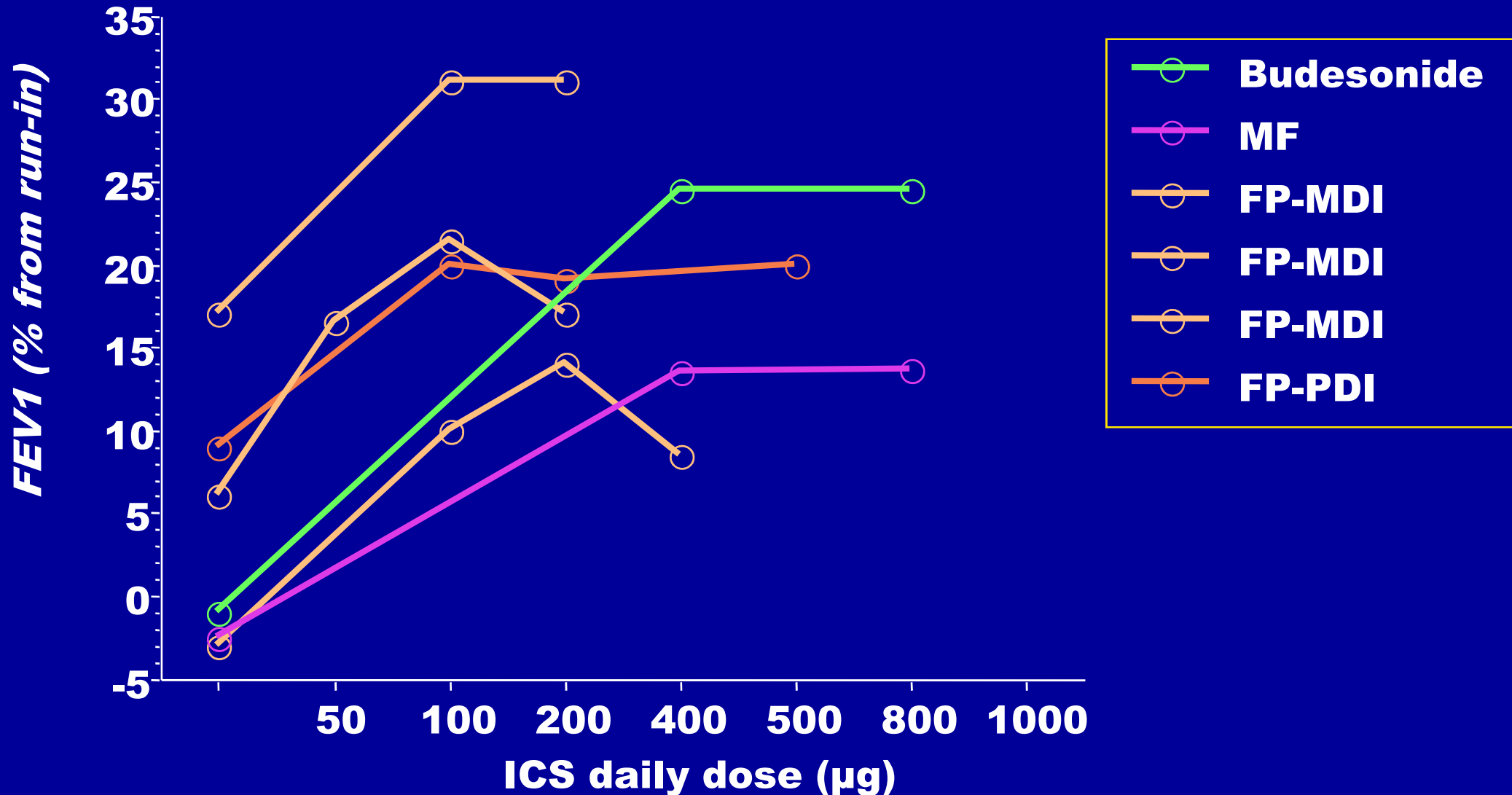
Bronchial Function



Bronchial Submucosa



Assenza di effetto dose-risposta dei corticosteroidi inalatori sulla funzione respiratoria nell' asma moderato

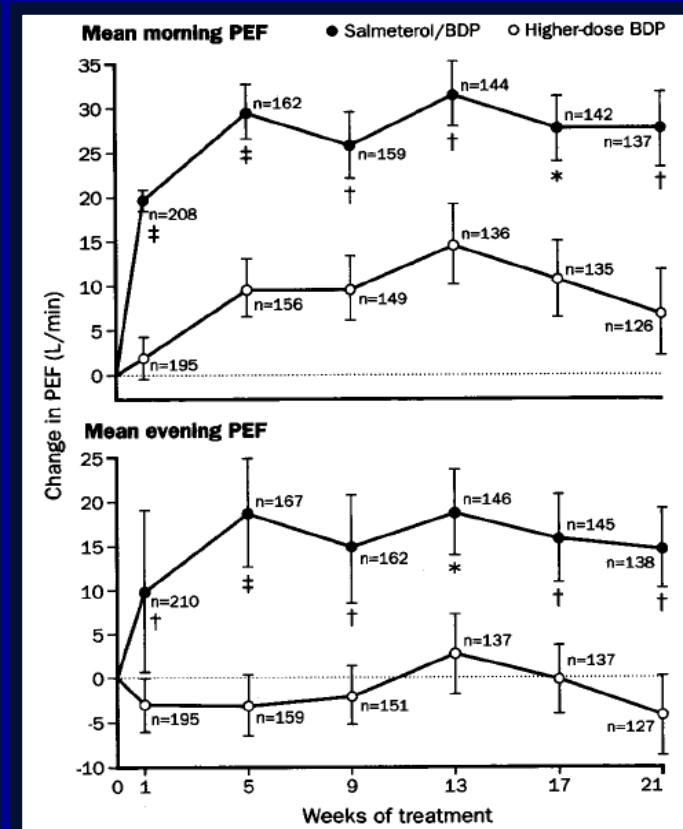
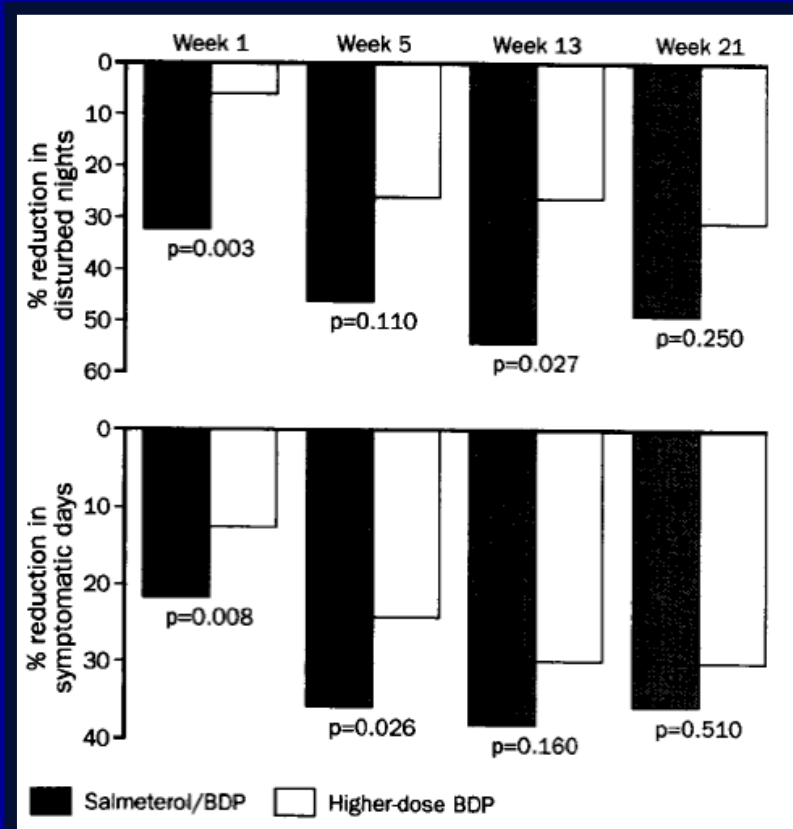


Aggiunta di broncodilatatore long-acting vs. aumento di corticosteroidi inalatorio

Sintomi

Funzione respiratoria

Riacutizzazioni



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.

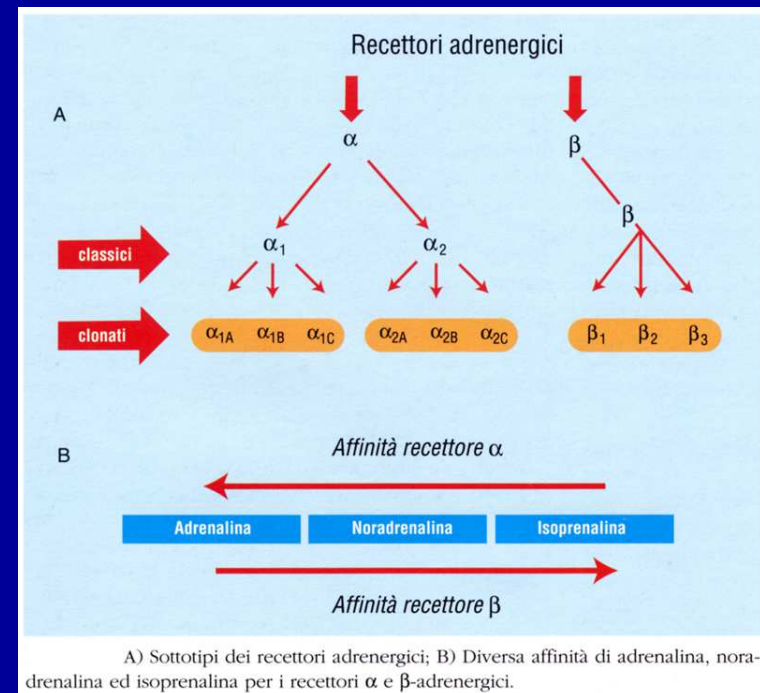
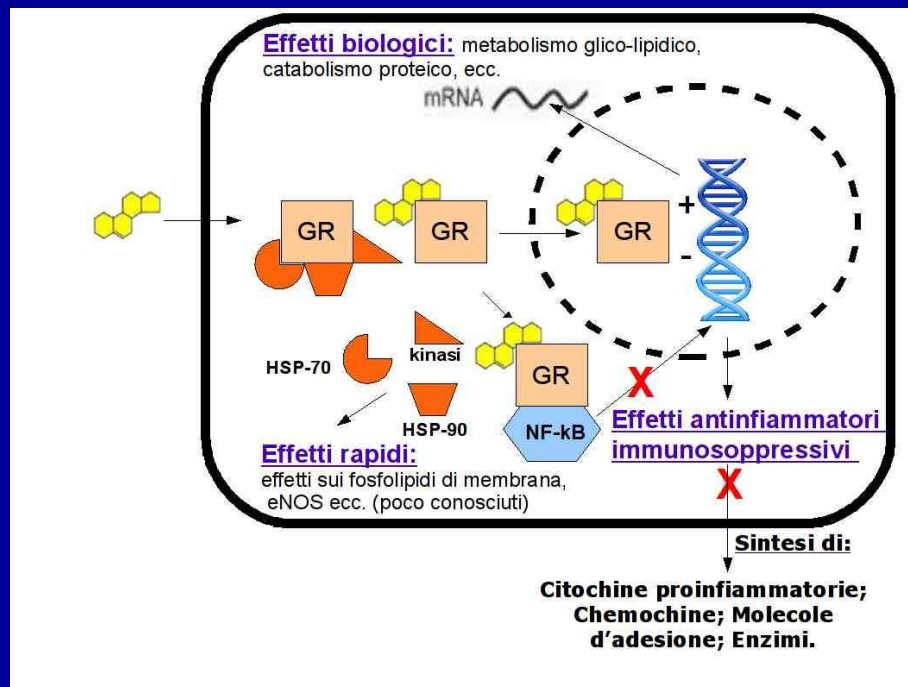
Table 5: Asthma exacerbations per patient

Meccanismo d'azione sinergico di ICS e LABA

Agiscono sinergicamente per attivare fattori di trascrizione, riducono la proliferazione della muscolatura liscia e l'adesione degli eosinofili

I LABA incrementano la traslocazione del recettore per i corticosteroidi, dal citoplasma al nucleo, dopo attivazione da parte dei ICS

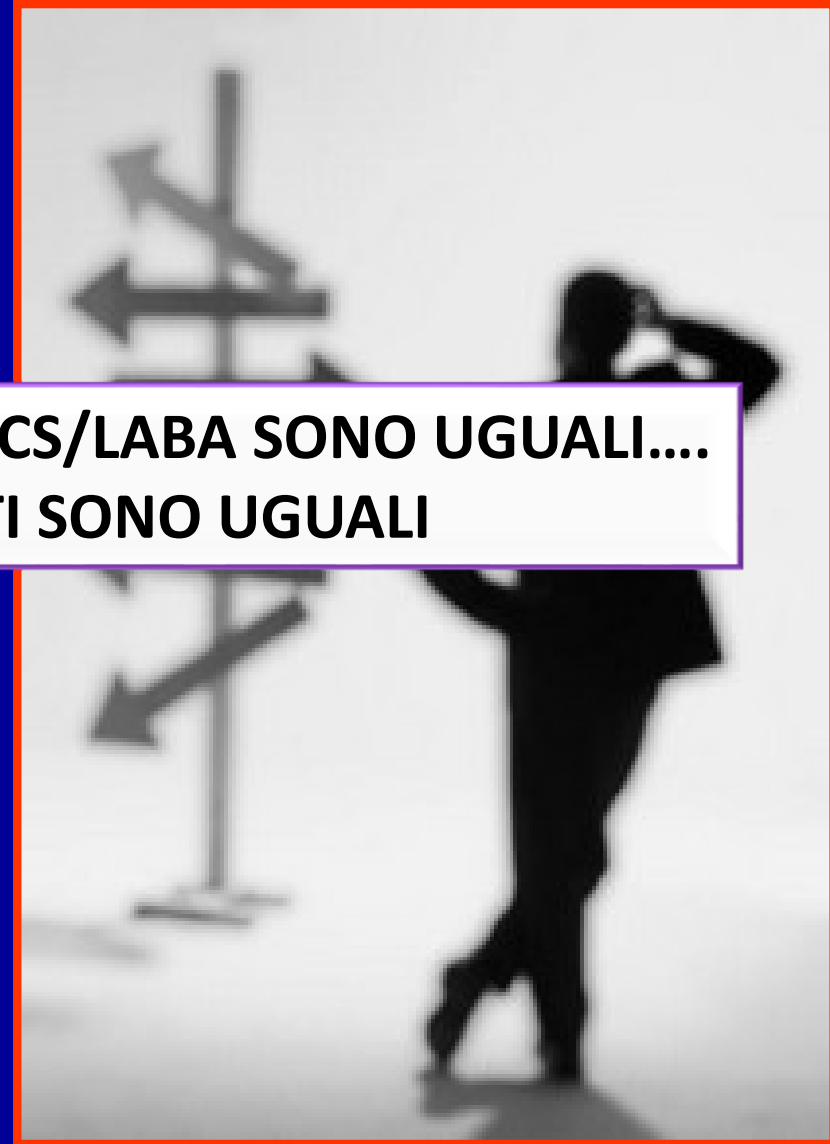
Gli ICS incrementano l'espressione dei recettori beta₂ adrenergici



Le combinazioni ICS/LABA: come orientarsi?



**NON TUTTE LE ASSOCIAZIONI ICS/LABA SONO UGUALI....
NON TUTTI I PAZIENTI SONO UGUALI**



Affinità e selettività dei beta₂-agonisti

Competing agonist	pK _i (affinity)		Selectivity β ₂ /β ₁
	β ₁ receptor	β ₂ receptor	
Isoprenaline	6.1	6.3	1
Salmeterol	5.7	8.0	190
Formoterol	6.3	8.1	60
Fenoterol	5.7	6.3	5
Salbutamol	4.7	5.8	13

Selectivity is the ratio of the inhibition constants $10^{(pK_{i\beta_2} - pK_{i\beta_1})}$

Proprietà farmacocinetiche e farmacodinamiche degli ICS

TABLE 1. PHARMACODYNAMIC/PHARMACOKINETIC PROPERTIES OF CURRENTLY AVAILABLE INHALED CORTICOSTEROIDS*

ICS/Dosage	Determinants of Efficacy			Determinants of Therapeutic Index		
	Binding Affinity [†]	Lung Delivery [‡] (%)	Relative Equivalency (μg) [§]	Oral Bioavailability (%)	Systemic Clearance (L/h)	Volumes of Distribution (L)
BDP MDI/40 and 80 μg	0.4	50–60	80	20	150	424
BUD DPI/90 and 180 μg nebulas/250, 500, and 1,000 μg	9.4	15–30	180	11	84	280
CIC MDI/80 or 160 μg	0.12	5–8	500	<1	152	897
FLU/80 μg	1.8	50	80	20	58	96
FP MDI/44, 110, and 220 μg DPI/ 50, 100, and 250 μg	18	68	160	\leq 1	66	602
MF/110 and 220 μg	23	20	88	<1	53	332
		15	100			
		11	110			

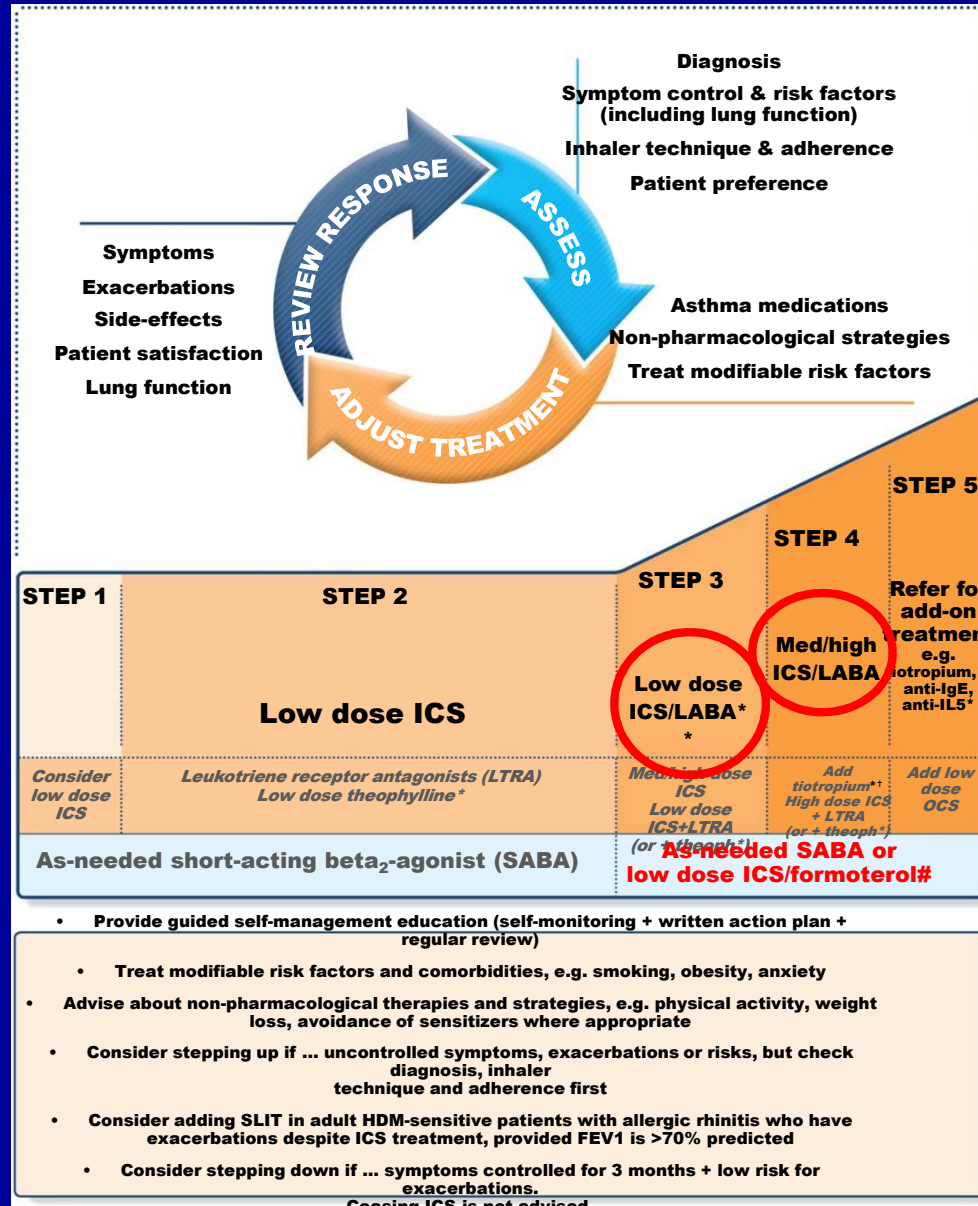
Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; DPI = dry-powder inhaler; FLU = flunisolide; FP = fluticasone propionate; ICS = inhaled corticosteroid; MDI = metered-dose inhaler; MF = mometasone furoate.

**Terapia dell'asma.
Uno per tutti o è possibile un approccio personalizzato?**

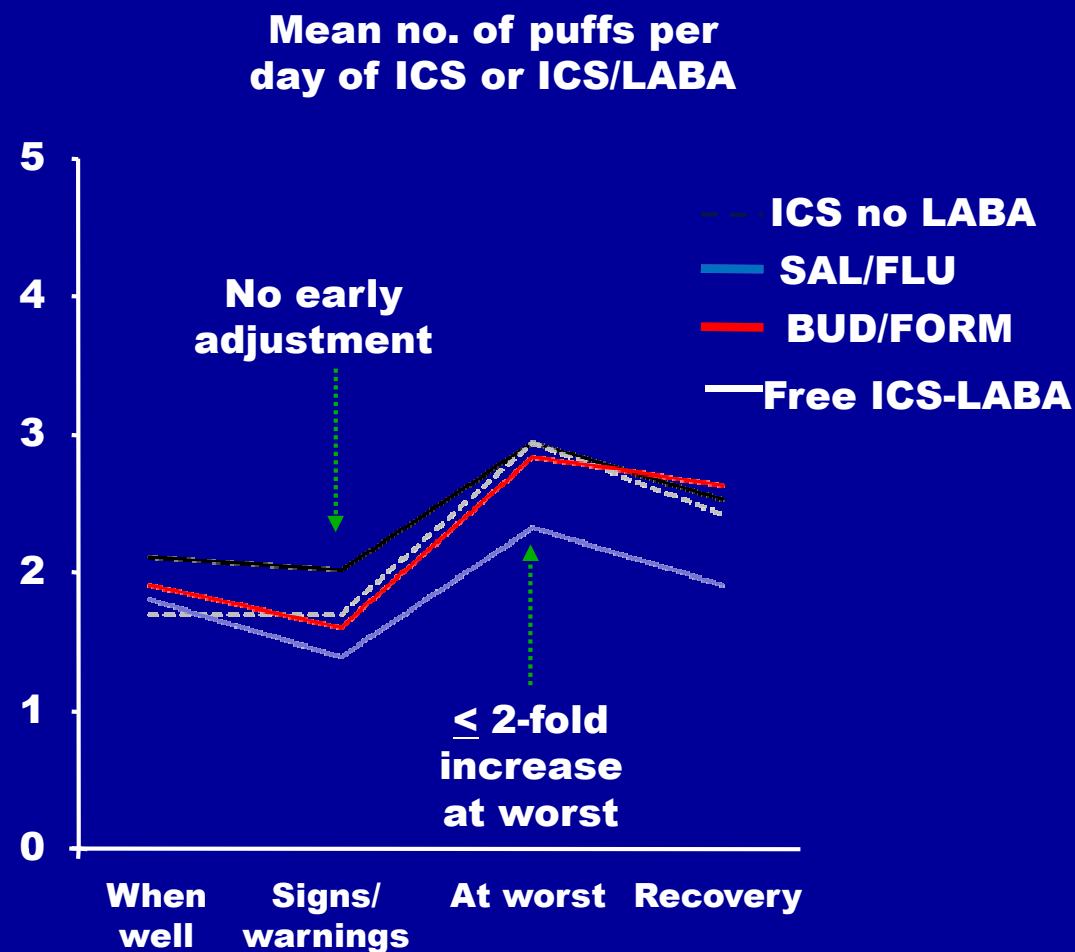
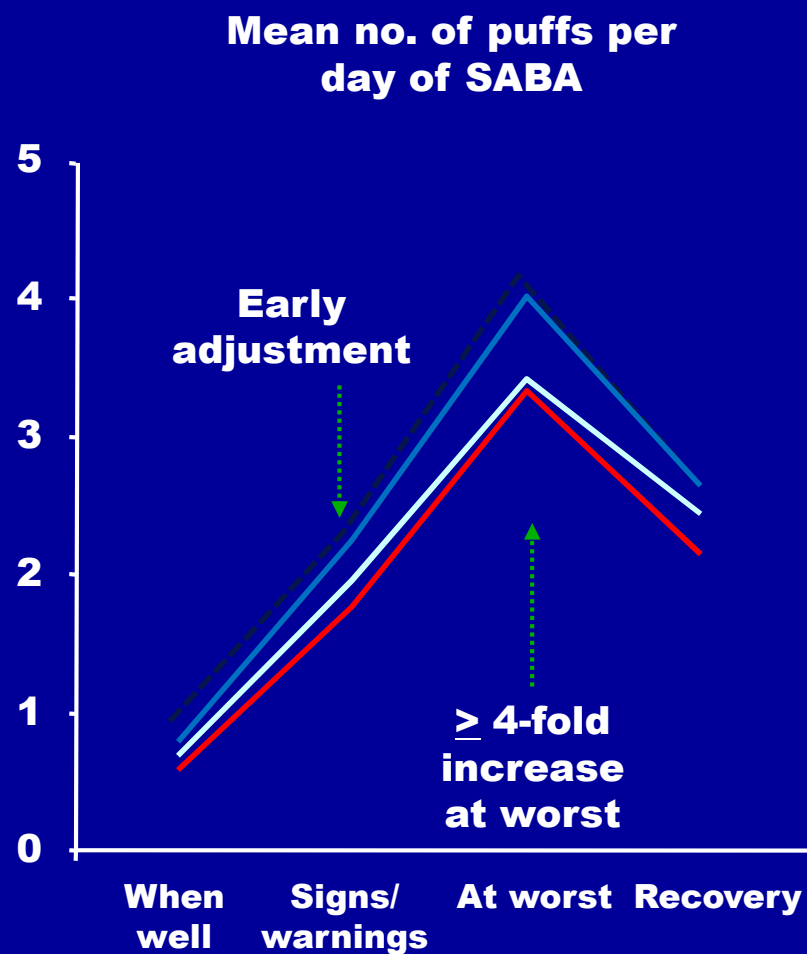


***GD Tiepolo. La processione del cavallo di Troia
1773. Londra. National Gallery***

Stepwise approach to control asthma symptoms and reduce risk



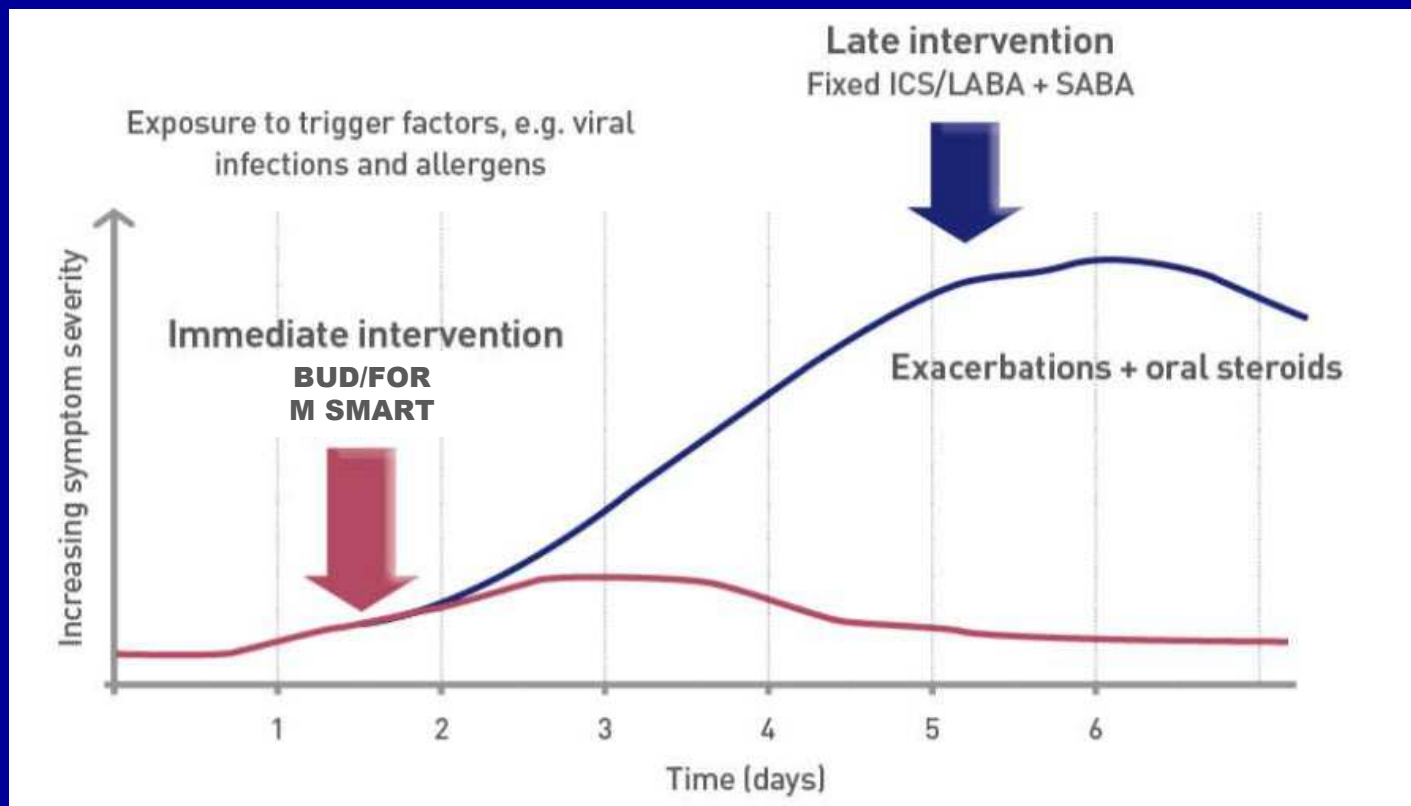
INSPIRE study: During symptom worsening, patients adjust their SABA early but ICS late



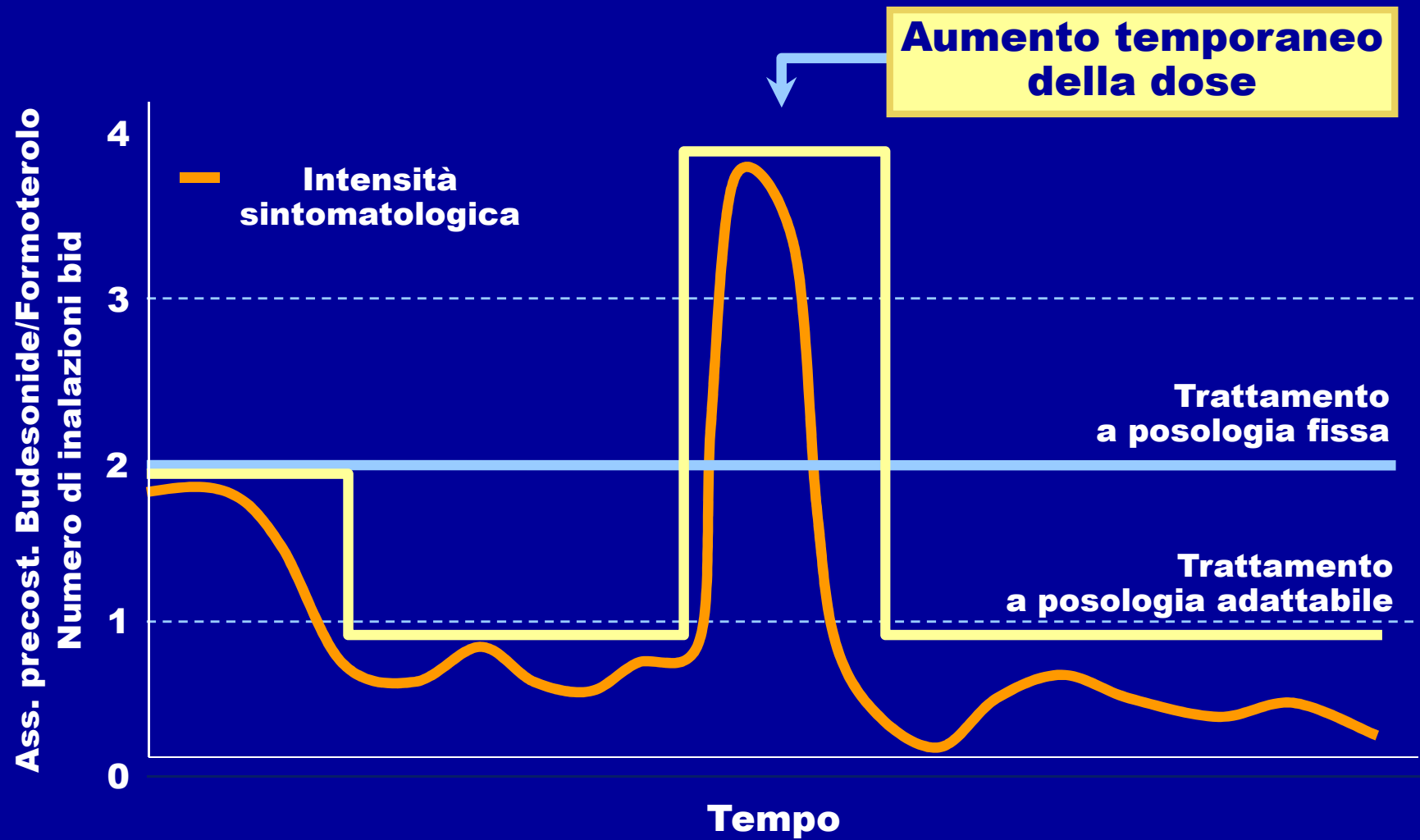
Stages of symptom worsening

Perchè intervenire precocemente con la terapia di mantenimento e bisogno?

- Early intervention with ICS as part of a reliever regimen can prevent exacerbations^{1,2}

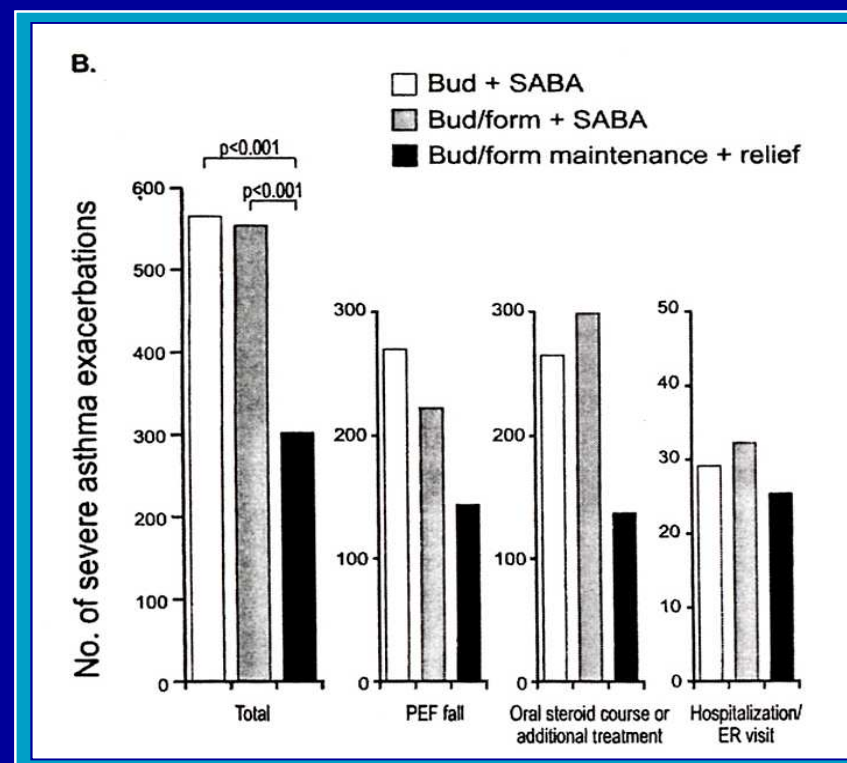
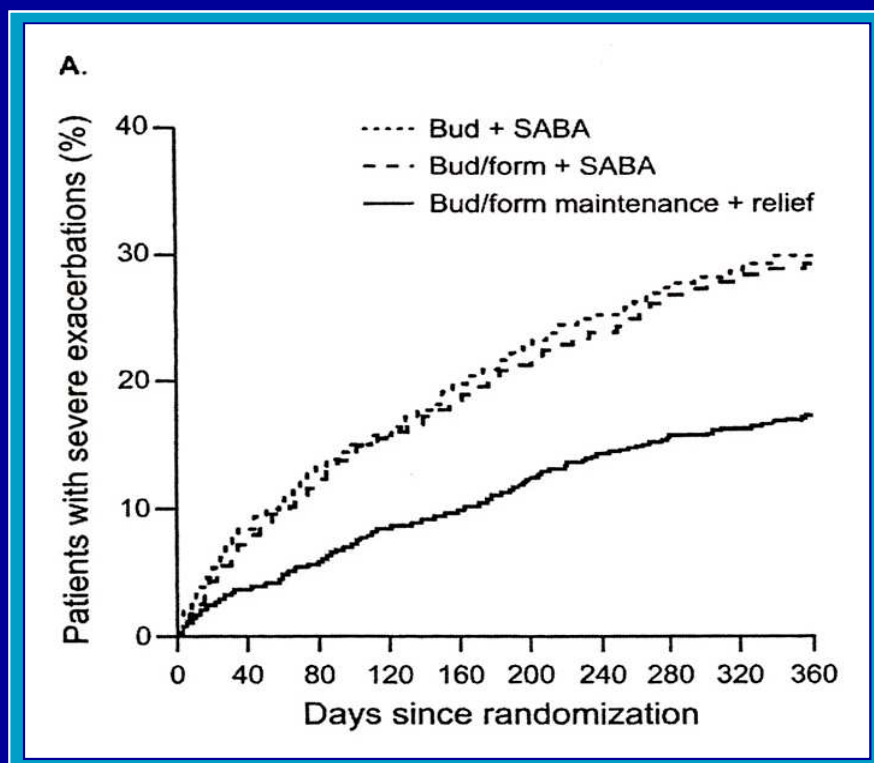


Schemi di trattamento a posologia fissa e a posologia adattabile



La strategia SMART (Bud/Form mantenimento e bisogno)

La SMART riduce la frequenza di gravi riacutizzazioni rispetto alle strategie tradizionali



Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children (Review)

Kew KM, Karner C, Mindus SM, Ferrara G

The Cochrane Library

2013, Issue 12

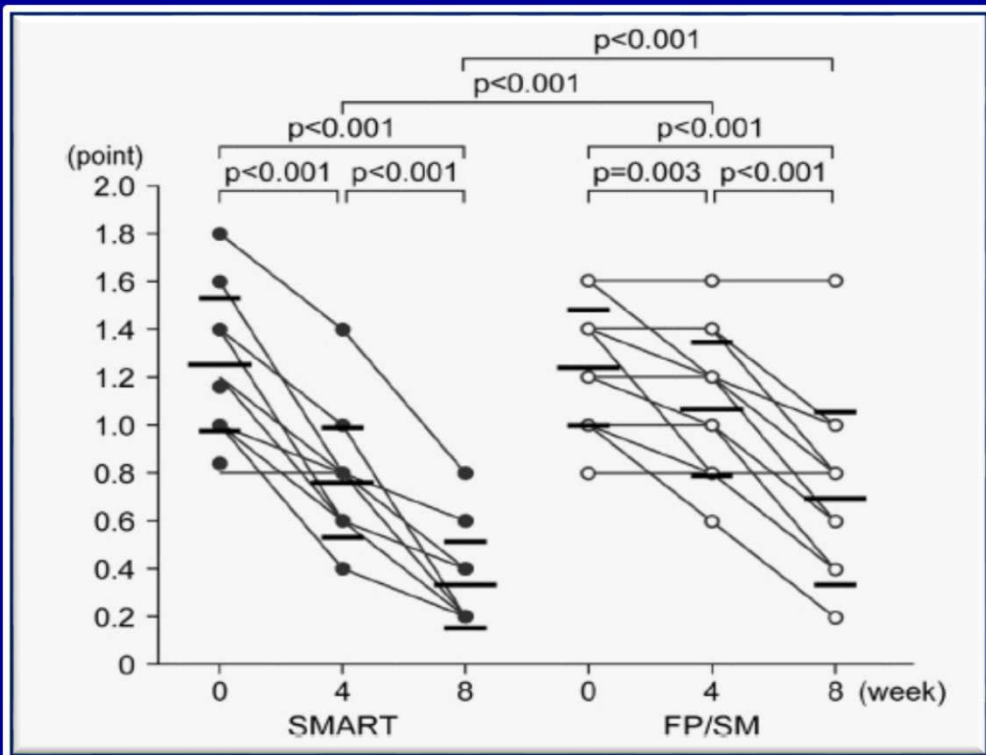
AUTHORS' CONCLUSIONS:

SMART reduces:

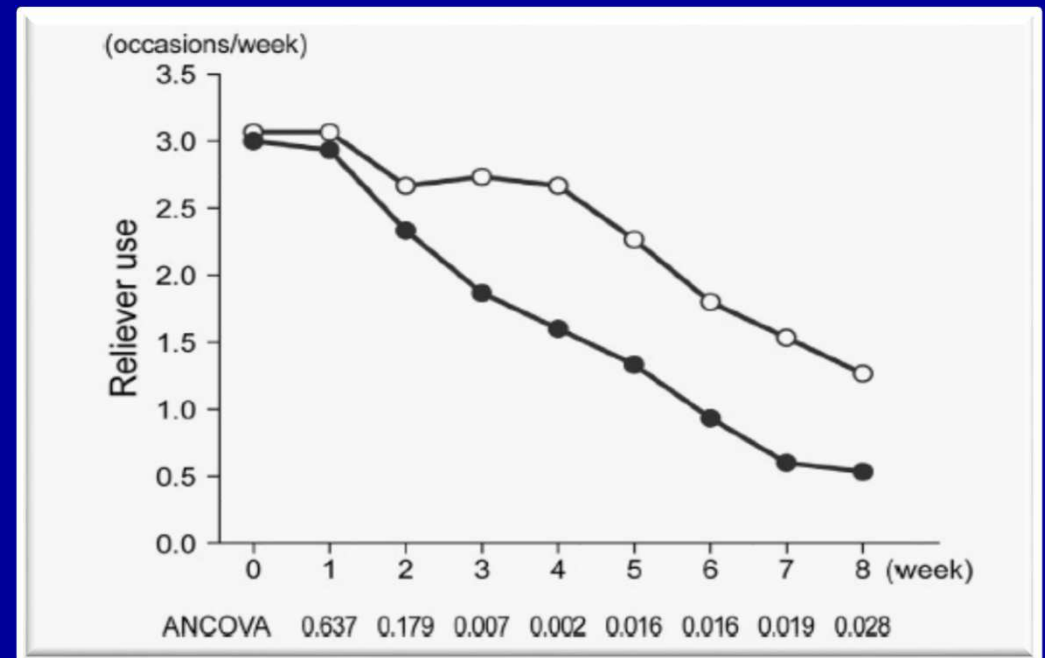
- **number of people having asthma exacerbations**
 - **requiring oral steroids**
 - **number requiring hospitalisation or ER visit**
- compared with fixed-dose combination inhalers**

Approccio SMART vs ICS/LABA+SABA

ACQ5



Rescue Medication



RESEARCH ARTICLE

Open Access

Real-life effectiveness of budesonide/formoterol maintenance and reliever therapy in asthma patients across Asia: SMARTASIA study

Nanshan Zhong^{1*}, Jiangtao Lin^{2†}, Parthiv Mehta³, Pintip Ngamjanyapom^{4†}, Tzu-Chin Wu^{5†} and Faisal Yunus⁶

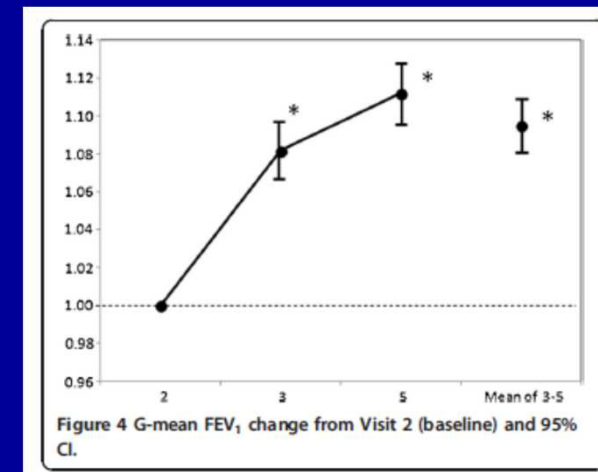
Conclusion:

During treatment of inadequately controlled asthmatic patients with budesonide/formoterol maintenance and reliever therapy, significant **improvement in patients**

- asthma control
- quality of life

reductions

- asthma symptoms
- as-needed medication use





P.R.N. BUDESONIDE/FORMOTEROL COMBINATION VERSUS REGULAR BUDESONIDE/FORMOTEROL COMBINATION PLUS PRN TERBUTALINE IN MILD- MODERATE PERSISTENT ASTHMA

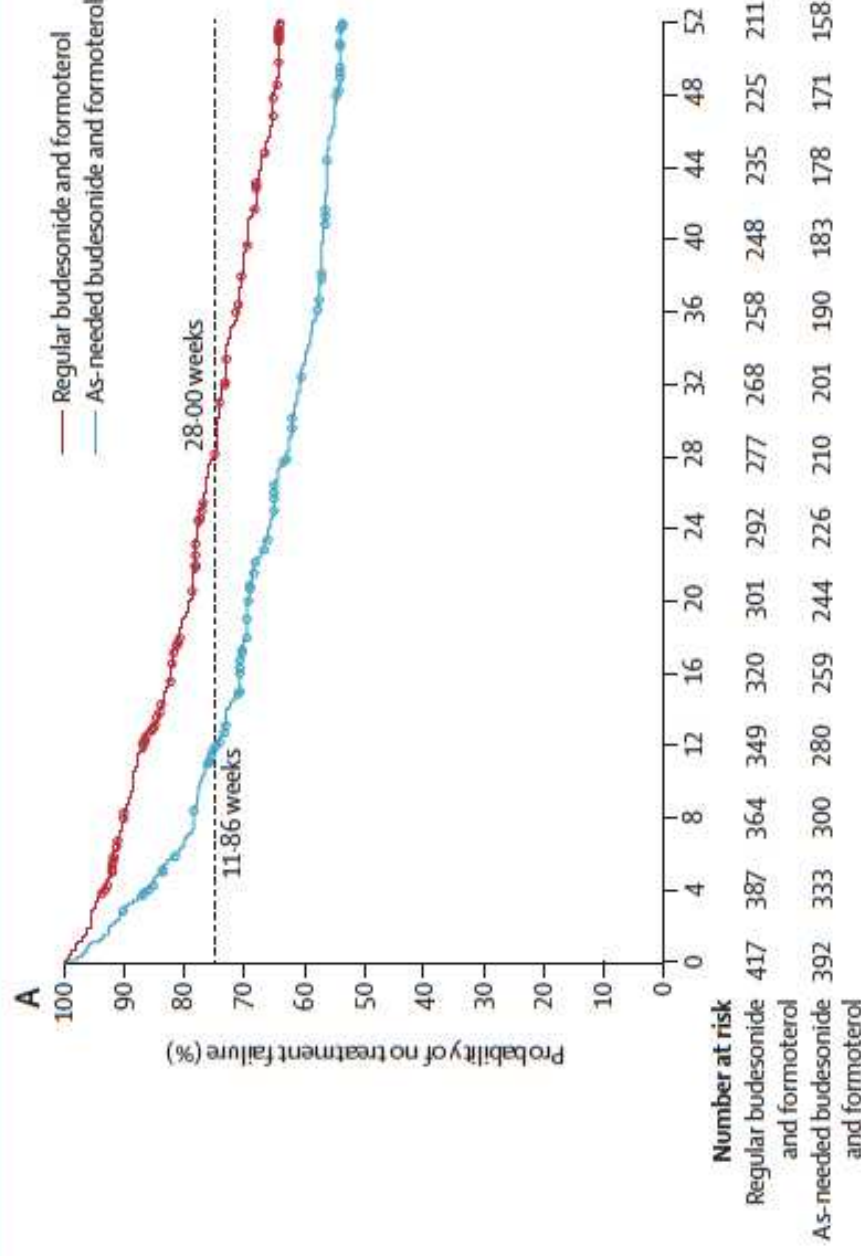


Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial

Alberto Papi*, Brunilda Marku*, Nicola Scichilone, Piero Maestrelli, Pierluigi Paggiaro, Marina Saetta, Stefano Nava, Ilenia Folletti, Giuseppina Bertorelli, Stefano Bertacco, Marco Contoli, Mario Plebani, Maria Pia Foschino Barbaro, Antonio Spanevello, Maria Aliani, Marco Pannaccà, Paolo Morelli, Bianca Beghét, Leonardo M Fabbri†, for the ALFASMA Study Group‡

Summary

Background Treatment combination of an inhaled corticosteroid and a long-acting beta₂-agonist is investigated whether it would be as effective as patients with moderate



a *Lancet Respir Med* 2015;
e 3: 109-19
d Published Online
r December 4, 2014
[http://dx.doi.org/10.1016/S2213-2600\(14\)70266-8](http://dx.doi.org/10.1016/S2213-2600(14)70266-8)



**Terapia dell'asma.
Uno per tutti o è possibile un approccio personalizzato?**

Problems With Inhaler Use:
A Call for Improved Clinician and Patient Education

James B Fink MSc RRT FAARC and Bruce K Rubin MEngr MD MBA FAARC

***“Management of chronic airway disease is
10% medication and 90% education”***



Respir Care 2005;50(10):1360–1374.

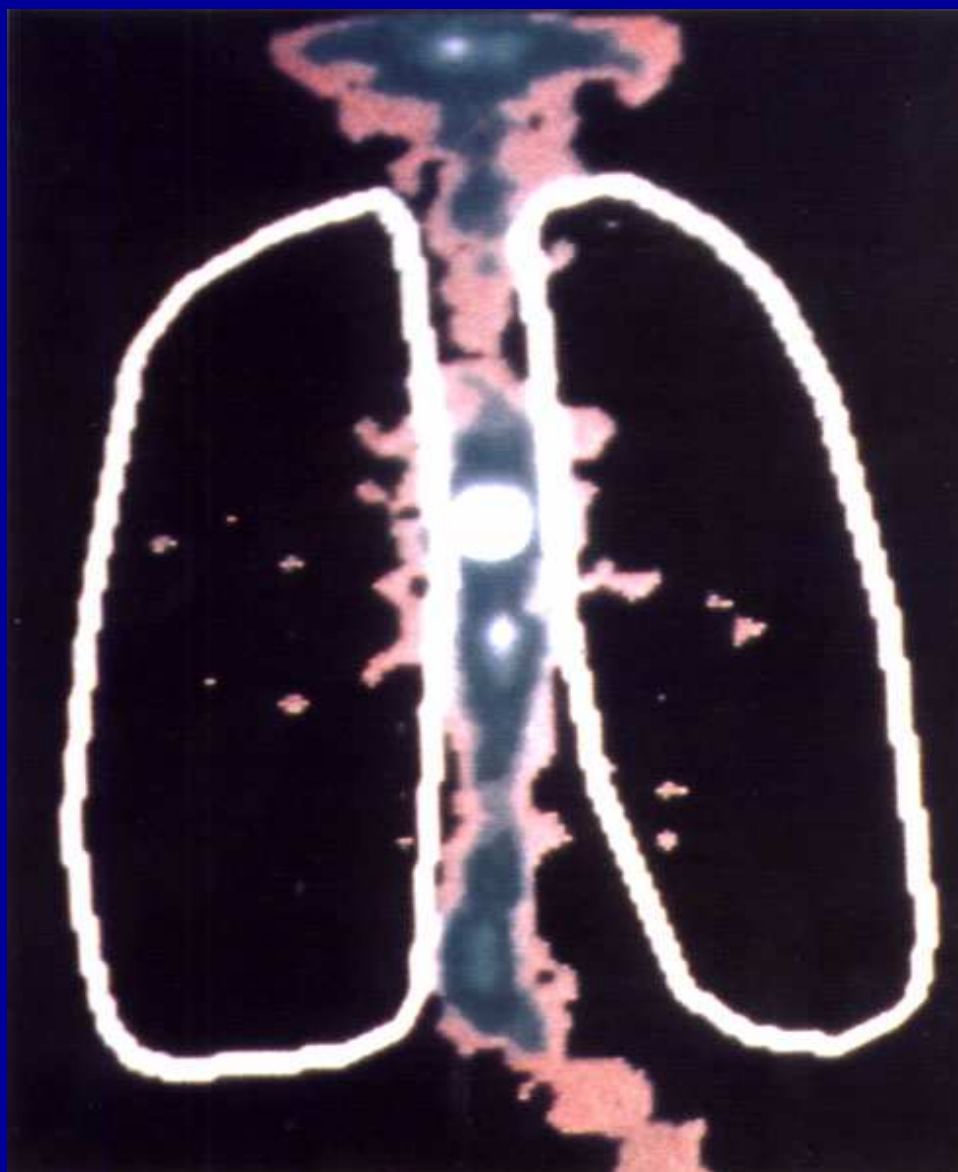
Cosa si chiede al *device*?

Consentire il raggiungimento da parte del farmaco della zona bersaglio

Migliorare l'aderenza alla terapia



Deposizione di radiomarcato in soggetto con tecnica inalatoria scorretta



Cosa ricercano i pazienti in un inalatore?

Device factors

Perceived device efficacy

Ease of use of device

- Need for actuation/inhalation coordination
- Ability to actuate device (strength, arthritis issues)
- Ability to generate sufficient inspiratory flows (dry powder inhalers)

Convenience of device

- Dose and refill frequency
- Dose counter
- Availability of combination inhalers

Feelings of stigmatization due to need for device use in public

Physician device preference

Availability of drug/device preparations

“Brand loyalty”

Cost

Time to learn; clear instructions

Size, weight, taste, device appearance

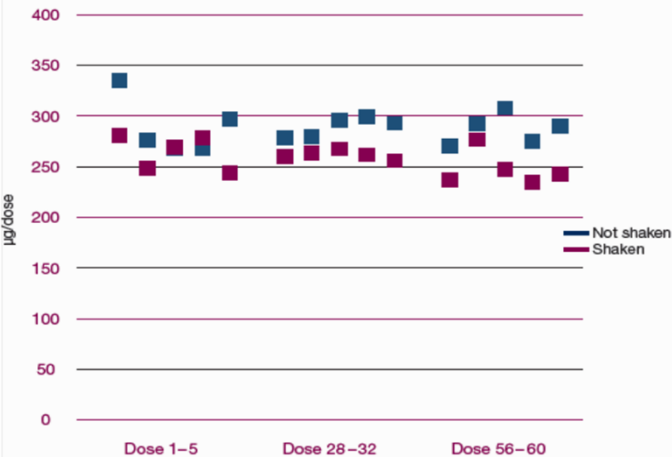
Cleaning issues

Disposability/environmental issues

Turbohaler non risente dello scuotimento: la DD è costante, al contrario di Spiromax ed Easyhaler

Figure 1

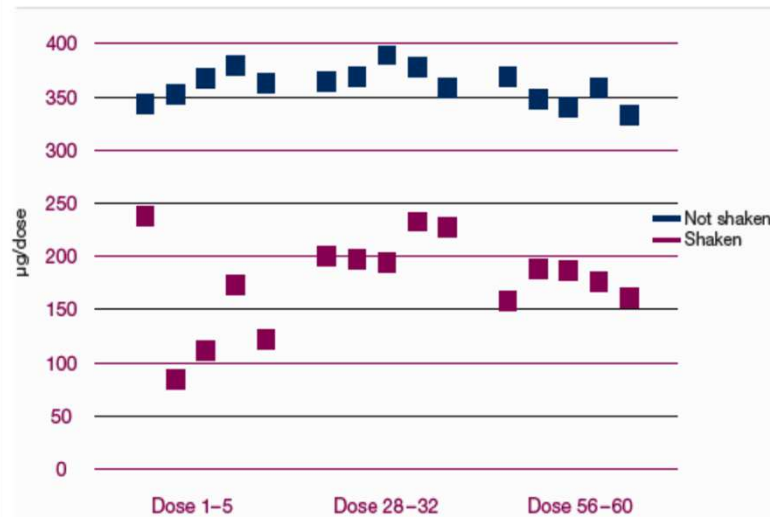
Turbohaler budesonide, delivered dose 320/9 µg/dose strength, average



Shaken -50% DD

Figure 2

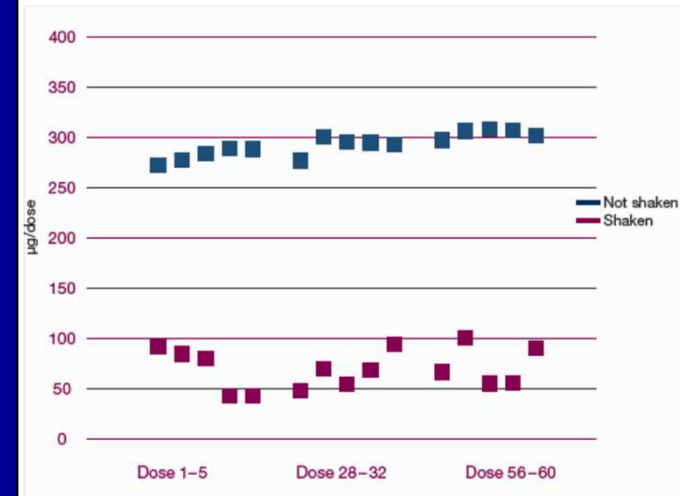
Easyhaler budesonide, delivered dose 320/9 µg/dose strength, average.



Shaken -80% DD

Figure 3

Spiromax budesonide, delivered dose 320/9 µg/dose strength, average



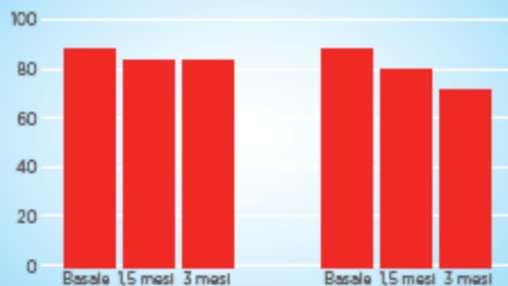
ARTICLE OPEN

Difference in resistance to humidity between commonly used dry powder inhalers: an *in vitro* study

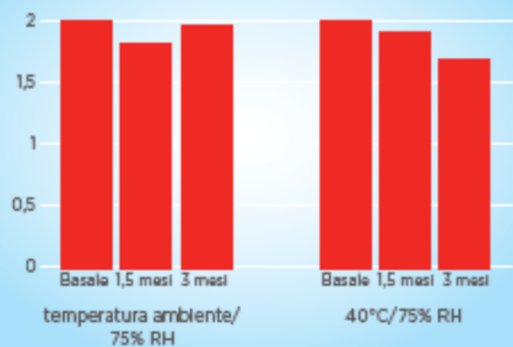
Christer Janson¹, Thomas Löf², Gunilla Telg³, Georgios Stratelis^{1,3} and Folke Nilsson⁴

Turbohaler

Variatione della Fine Particle Dose di **Budesonide Turbohaler M3** conservata a temperatura ambiente/75% RH e 40°C/75 RH



Variatione della Fine Particle Dose di **Formoterolo Turbohaler M3** conservata a temperatura ambiente/75% RH e 40°C/75 RH 1,5 e 3 mesi

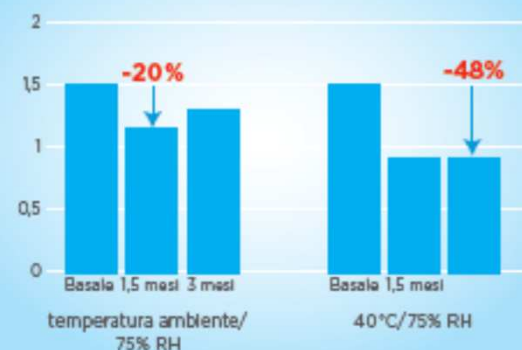


Easyhaler

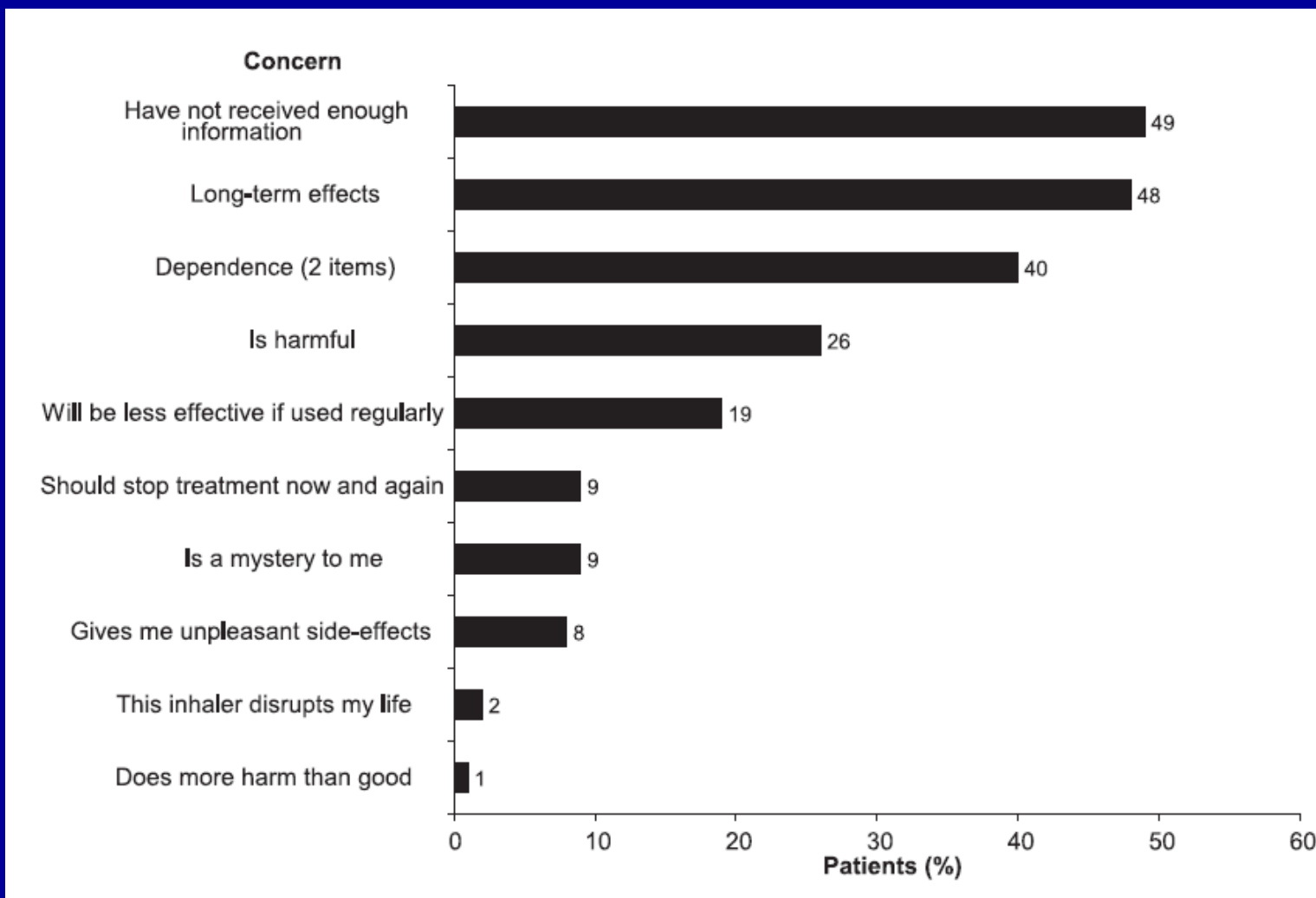
Variatione della Fine Particle Dose di **Budesonide Easyhaler** conservata a temperatura ambiente/75% RH e 40°C/75 RH



Variatione della Fine Particle Dose di **Formoterolo Easyhaler** conservata a temperatura ambiente/75% RH e 40°C/75 RH



I motivi per i quali i pazienti non assumono con continuità i farmaci inalatori

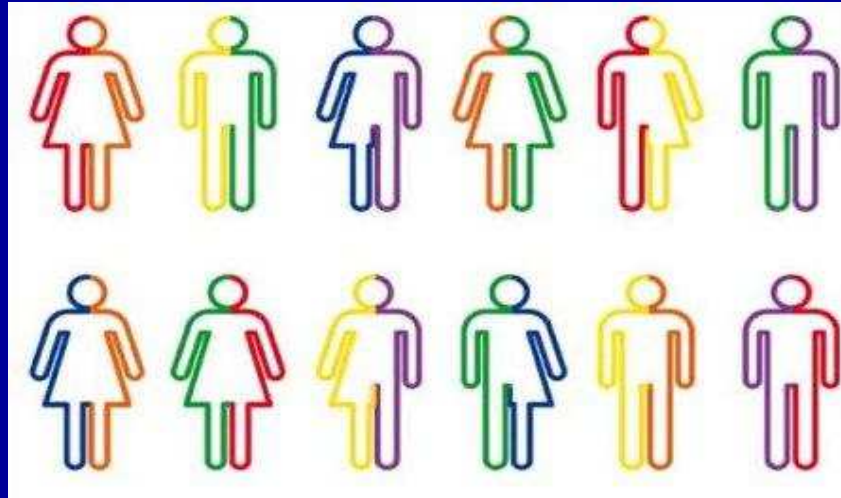


Studio condotto su 100 pazienti asmatici seguiti dal medico di medicina generale

Horne H. Chest 2006

STRATEGIE TERAPEUTICHE : NON TUTTI I PAZIENTI SONO UGUALI

« UNA VALUTAZIONE PERSONALIZZATA DEL PAZIENTE ASMATICO »



- **ASMA CON COMORBIDITA'**
 - **TERAPIE CONCOMITANTI**
 - **DURATA ED ENTITA' DEI SINTOMI**
- **ALLERGIA (SINGOLA O POLISENSIBILE ?!)**
 - **ETA'**
 - **ATTIVITA' LAVORATIVA**
 - **ATTIVITA' SPORTIVA**
 - **GENERE**
- **FUMATORE O ESPOSTO AL FUMO**
 - **PESO CORPOREO**
- **ESPOSIZIONE ALLERGENICA AMBIENTALE**
- **CARATTERISTICHE PSICOLOGICHE DEL PAZIENTE**

Aderenza al trattamento regolare nella vita reale

Reference	Title	Adherence
Partridge <i>Pulm Med</i> 2006	Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study	45% used maintenance medication as prescribed
De Marco <i>et al.</i> <i>Int Arch Allergy Immunol</i> 2005	Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma	34% had used maintenance medication as prescribed
Janson <i>et al.</i> <i>Eur Respir J</i> 2001	The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II	Adherence ranged from 17% in Italy to 49% in the UK
Breekveldt-Postma <i>et al. Pharmacoe- pidemiol Drug Saf</i> 2008	Treatment with inhaled corticosteroids in asthma is too often discontinued	14.1% of the patients with fixed combined and 8.3% of patients with single ICS treatment still continued treatment at 1 year
Stallberg <i>et al.</i> <i>Resp Med</i> 2003	Living with asthma in Sweden. The ALMA study	34% regularly followed the prescriptions
Adam <i>et al.</i> <i>J Allergy Clin Immunol</i> 2002	Inadequate use of asthma medication in the USA: results of the asthma in national population survey	21% had used maintenance medication as prescribed
Currigan <i>et al.</i> <i>Prim Care Resp J</i> 2011	Asthma therapy: there are guidelines, and then there is real life	Even compliant patients take only 30–50% of prescribed medication at the correct time

Poor adherence with inhaled corticosteroids for asthma:

can using a single inhaler containing budesonide and formoterol help?

Milind P Sovani, Christopher I Whale, Janet Osborne, Sue Cooper, Kevin Mortimer, Tommy Ekström, Anne E Tattersfield, and Timothy W Harrison

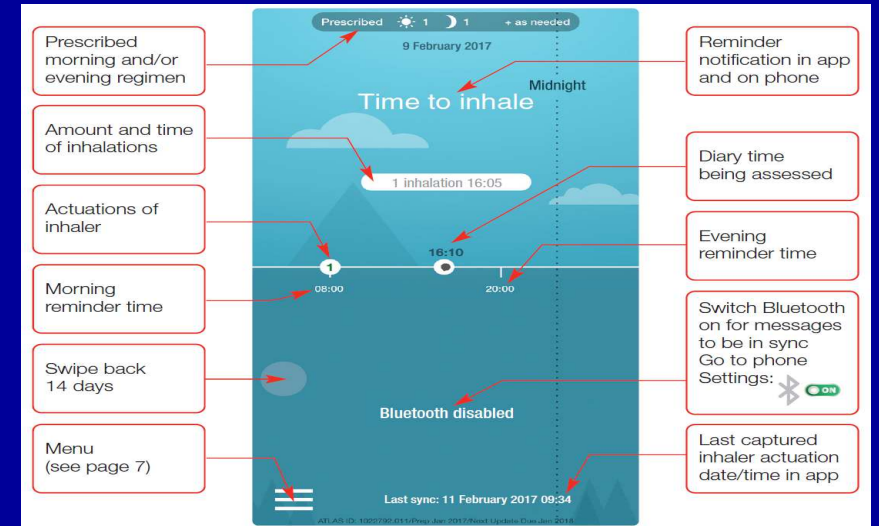
Conclusion

Using a single inhaler for both maintenance treatment and symptom relief approximately doubled the dose of inhaled corticosteroid taken, suggesting this could be a useful strategy to overcome the problems related to poor adherence with inhaled corticosteroids.

Il corretto utilizzo del *device* è cruciale per il controllo della malattia

- **Incorrect device use leads to uncontrolled disease and increased costs**
- **The reasons for incorrect use are multifactorial and include:**
 - **Features of the device (e.g. how medication is dispensed, the formulation)**
 - **Level of physical skill, strength, dexterity, lung capacity and co-ordination required to operate the device correctly**
 - **Patient beliefs and preferences**
 - **Knowledge of the healthcare professional about specific devices and their features and benefits**
 - **Education provided to the patient**
 - **Cultural barriers (e.g. some CFC-free inhalers contain alcohol)**

Cosa è il Turbo+?



Il turbo+ è uno strumento elettronico che si monta alla base del Turbohaler e dotato di un microfono che permette di *sentire* quando il paziente fa l'inalazione.

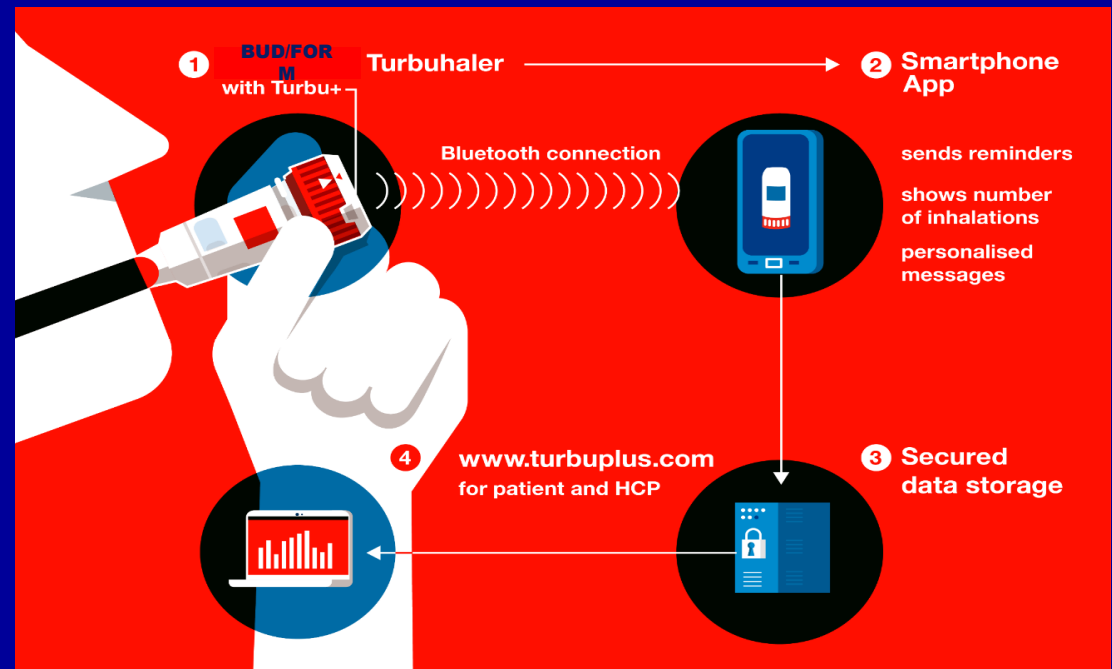
Il turbo+ è collegato ad una App che il paziente dovrà installare nel suo smartphone, le inalazioni verranno inviate in automatico alla App ed il paziente potrà verificare se e quando ha fatto le inalazioni.

In sostanza è l'evoluzione tecnologica del buon vecchio *diario delle somministrazioni*

Il medico a sua volta avrà un accesso riservato in un portale in cui potrà seguire il proprio paziente.

E-health: Turbu+

- Empowering patients by providing them insight into their treatment pattern
 - Reminding patients to take the number of inhalations as prescribed
- Supporting patients in their self management based on their condition and individual behaviours
- Supporting the interaction between HCP and patient

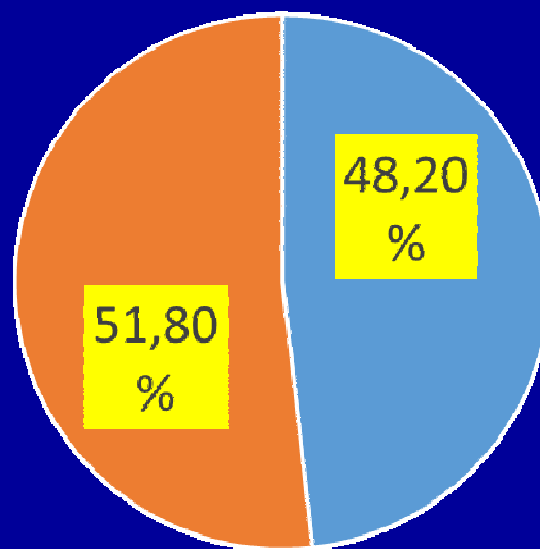


RESEARCH PAPER

Characteristics of patients preferring once-daily controller therapy for asthma and COPD: a retrospective cohort study

*David Price^{1,2}, Amanda J Lee³, Erika J Sims^{2,4}, Linda Kemp², Elizabeth V Hillyer², Alison Chisholm², Julie von Ziegenweidt², Angela Williams⁵

Pazienti che indicano la preferenza di una singola somministrazione giornaliera



Pazienti che non indicano la preferenza di una singola somministrazione e giornaliera

ORIGINAL ARTICLE

Once-daily budesonide/formoterol in a single inhaler
in adults with moderate persistent asthma

R. BUHL*, J.P.H.M. CREEMERS[†], V. VONDRA[‡], N.A. MARTELLI[§], I.P. NAYA^{||} AND T. EKSTRÖM^{||}

A randomized, double-blind study on 512 asthmatic patients, comparing two budesonide/formoterol regimens:

- **2 inhalations once-daily in the evening (+ as needed)**
 - **1 inhalation BID (+ as needed)**

BUD/FORM once nocte and twice daily on mild and severe exacerbations vs BUD alone

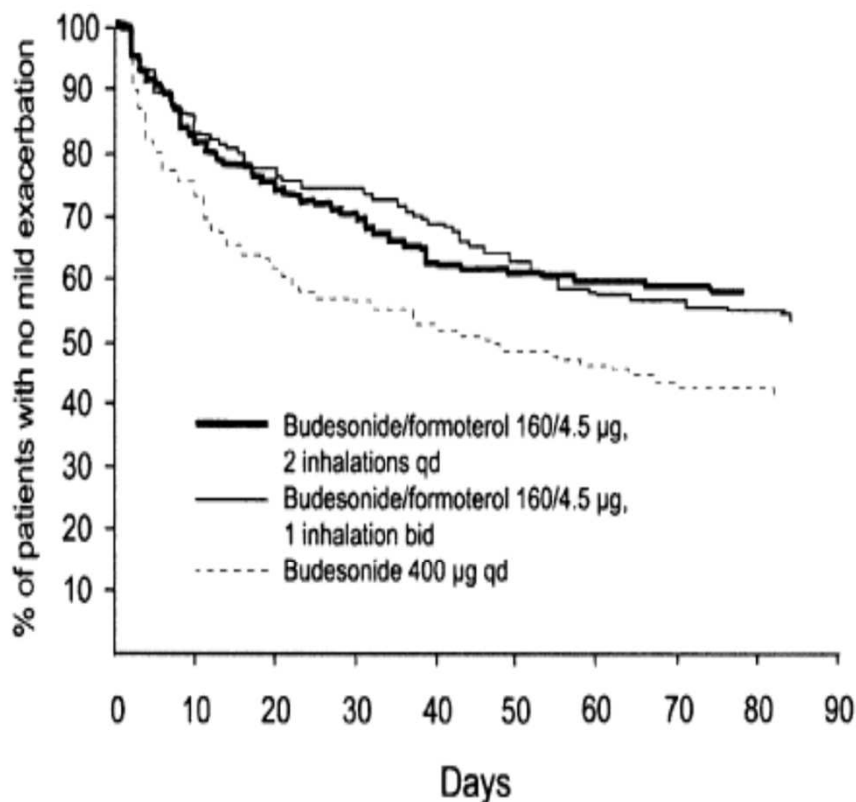
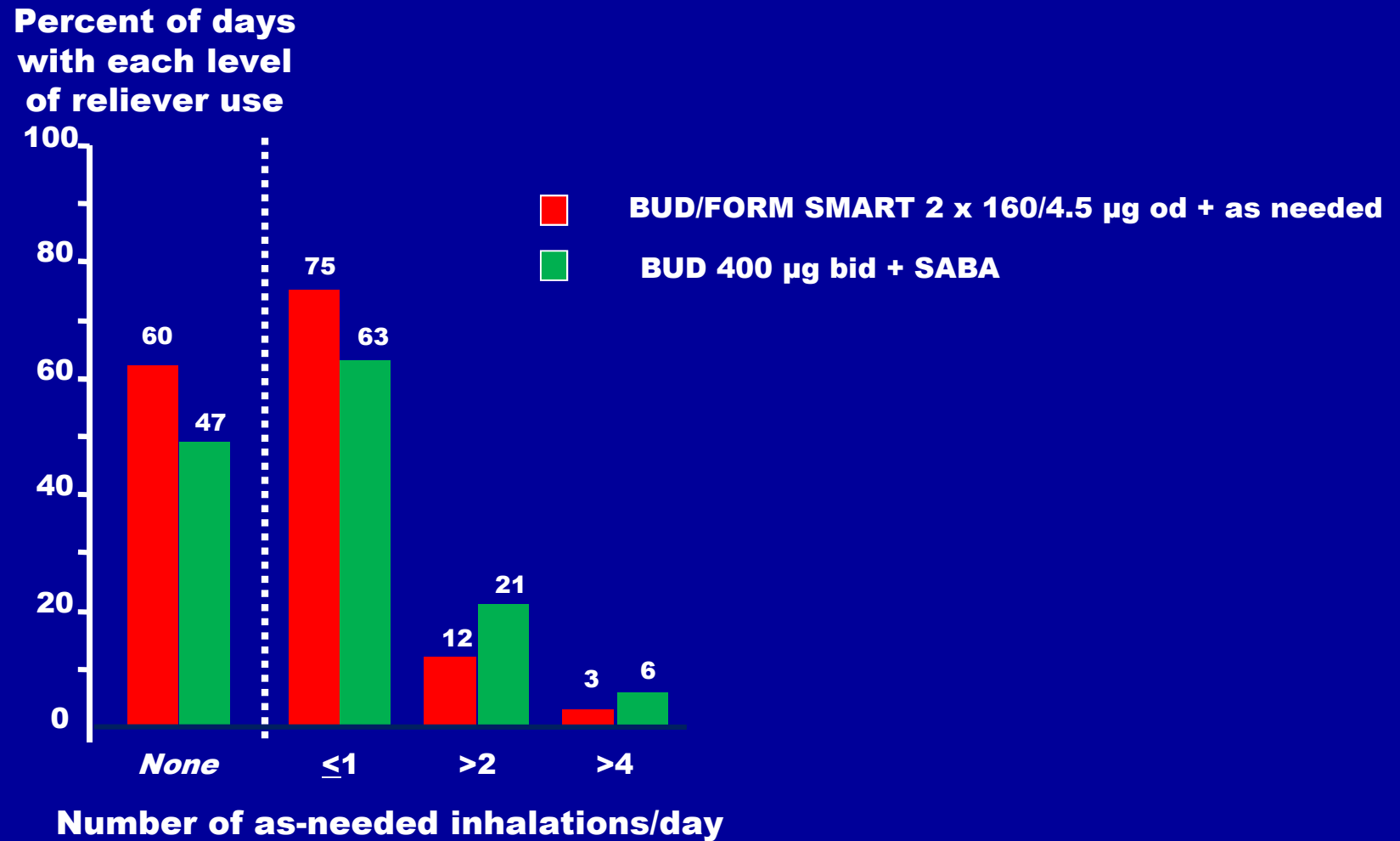


FIG 3. Kaplan–Meier survival curves of the time to first mild asthma exacerbation during 12 weeks' treatment with once-daily budesonide/formoterol (160/4.5 µg, two inhalations), twice-daily budesonide/formoterol (160/4.5 µg, one inhalation) or once-daily budesonide (400 µg) alone.

The incidence of severe exacerbations was comparable across the treatment groups, with a pattern similar to that observed for mild exacerbations. A total of 8% of patients in the once-daily budesonide/formoterol group and 9% of patients in the twice-daily budesonide/formoterol group experienced a severe exacerbation compared with 11% of patients in the budesonide-alone group. Overall, the incidences of mild and severe asthma exacerbations were numerically lower in the once-daily budesonide/formoterol group (42% and 8%, respectively) than those observed in the twice-daily budesonide/formoterol group (45% and 9%, respectively) with no significant difference between the groups.

STEP: No reliever needed on 60% of days when using SMART once-daily in moderate-severe asthma





Is once enough? Understanding the preferences of COPD and asthma patients for once- versus twice-daily treatment

- **The decisions about dosage frequency (once versus twice a day) should be considered in the light of patients' beliefs about the prescription (e.g. necessity and concerns) and their preferences.**
- **For some patients, once-daily dosing might be helpful in achieving this.**
- **But once-daily dosing is not a panacea for non-adherence, and we need to identify those patients who will benefit most from once-daily versus twice-daily treatment.**