

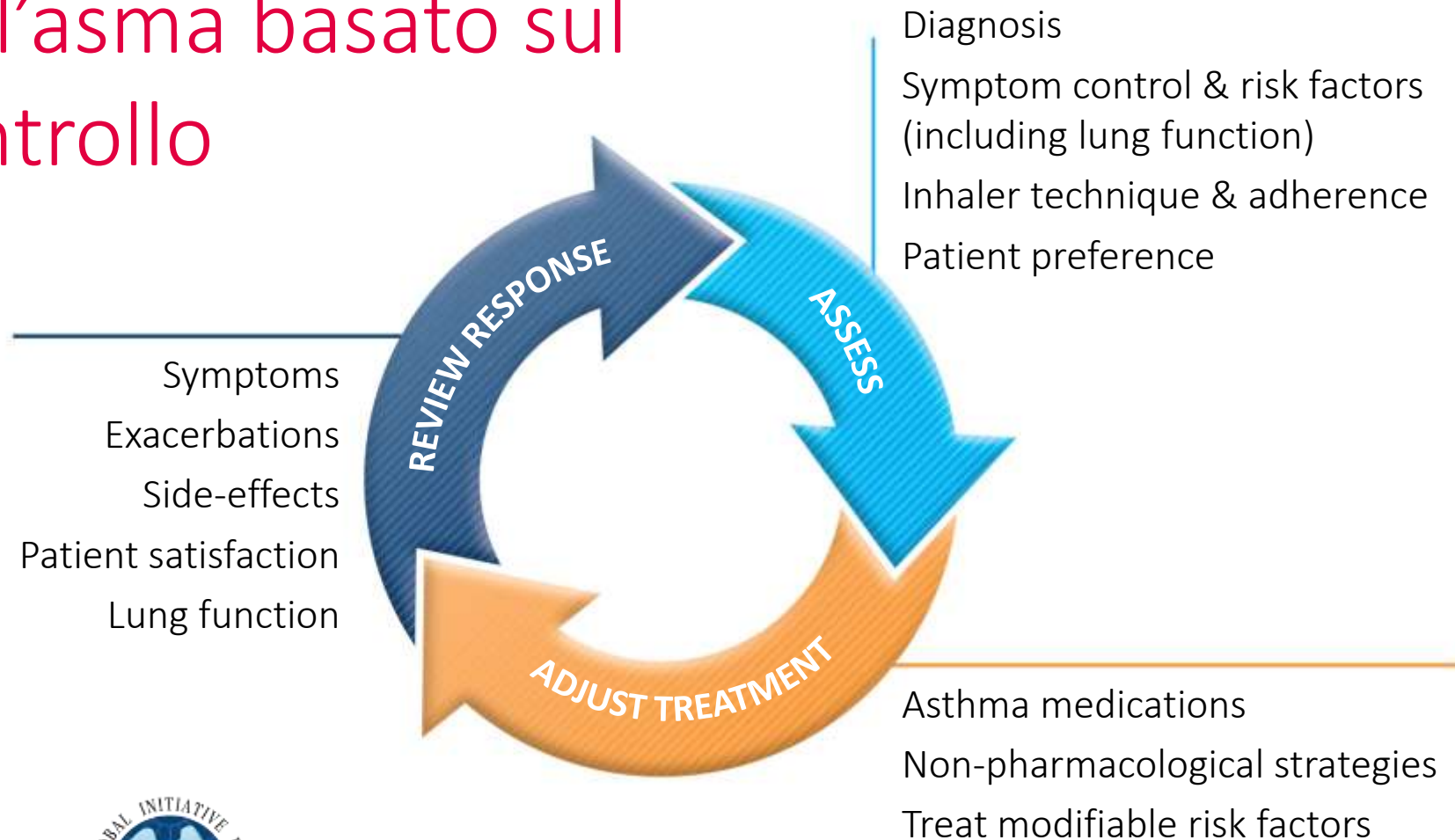


Up-to-date sulle terapie
di associazione nell'asma

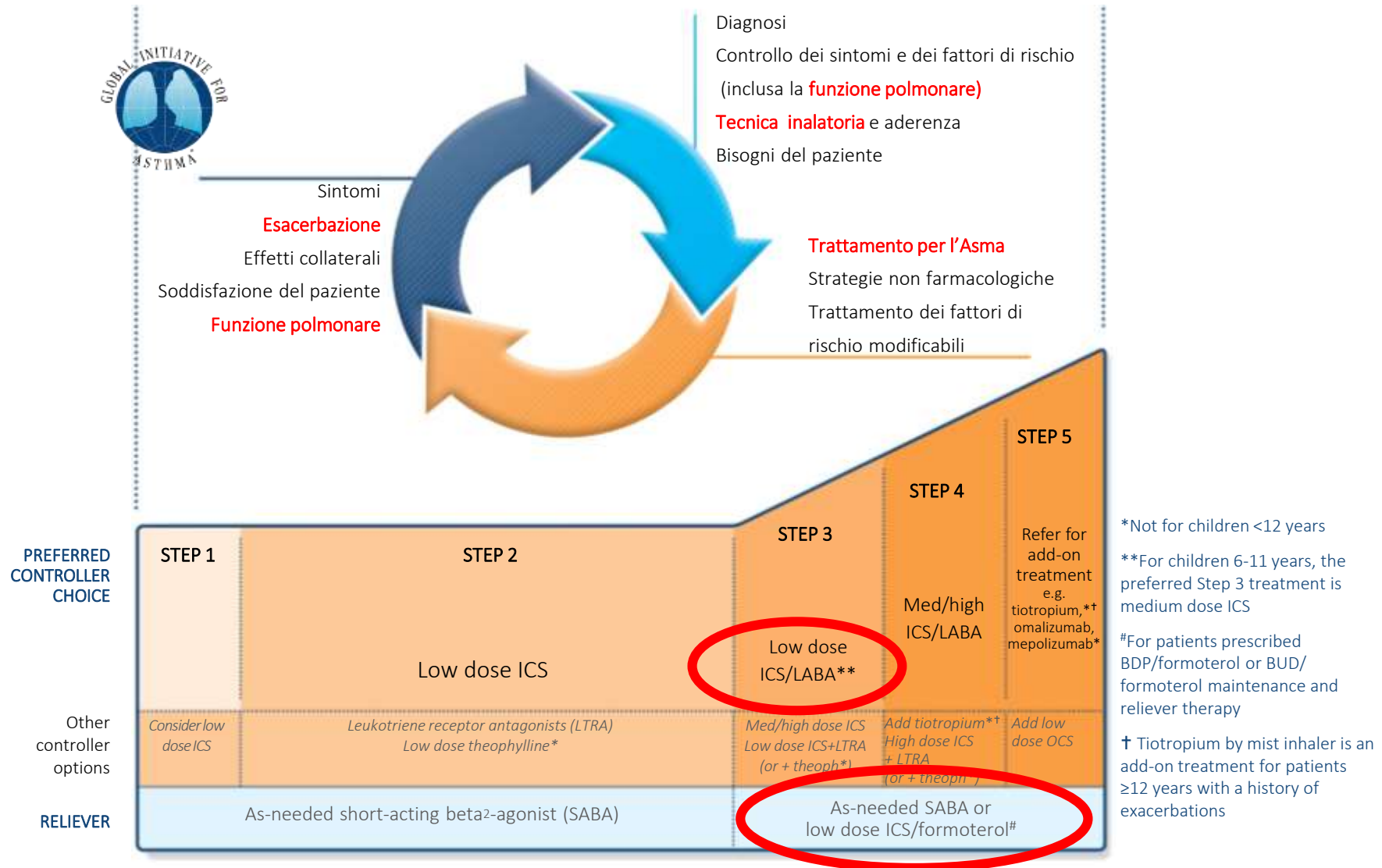
Paolo Solidoro

Responsabile Programma trapianto
e gestione avanzata vie aeree
S.C.D.U. Pneumologia
Presidio Molinette, Torino

Ciclo di gestione dell'asma basato sul controllo



Stepwise management - pharmacotherapy



Controllo dell'asma

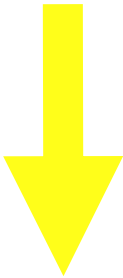
Possibili strategie

Controllo dell'asma

Tre domini

Sintomi

*(diurni e notturni,
limitazione delle
attività, necessità di
farmaco al bisogno)*



1. Valutare il quadro clinico

Funzione respiratoria

(PEF or FEV1)



2. Eseguire la spirometria

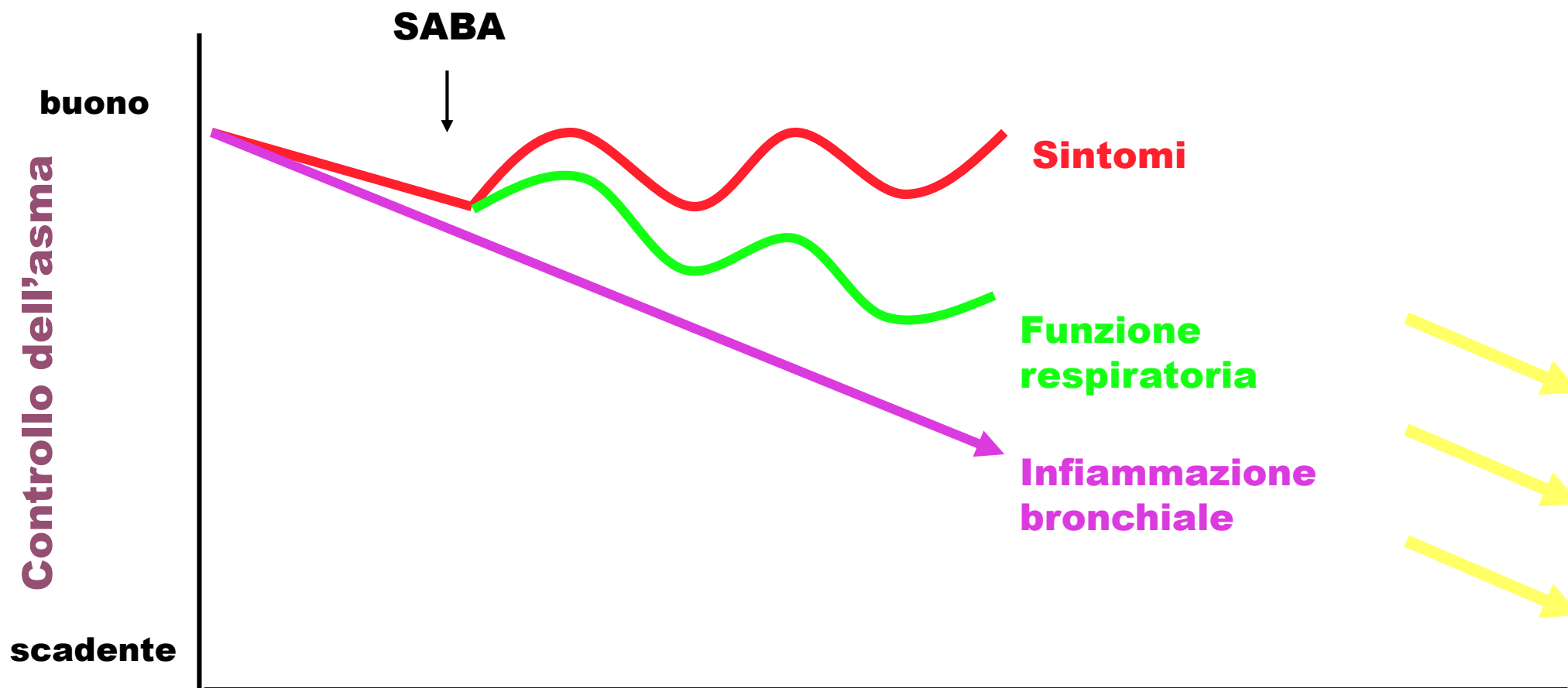
Riacutizzazioni

(frequenza e gravità)

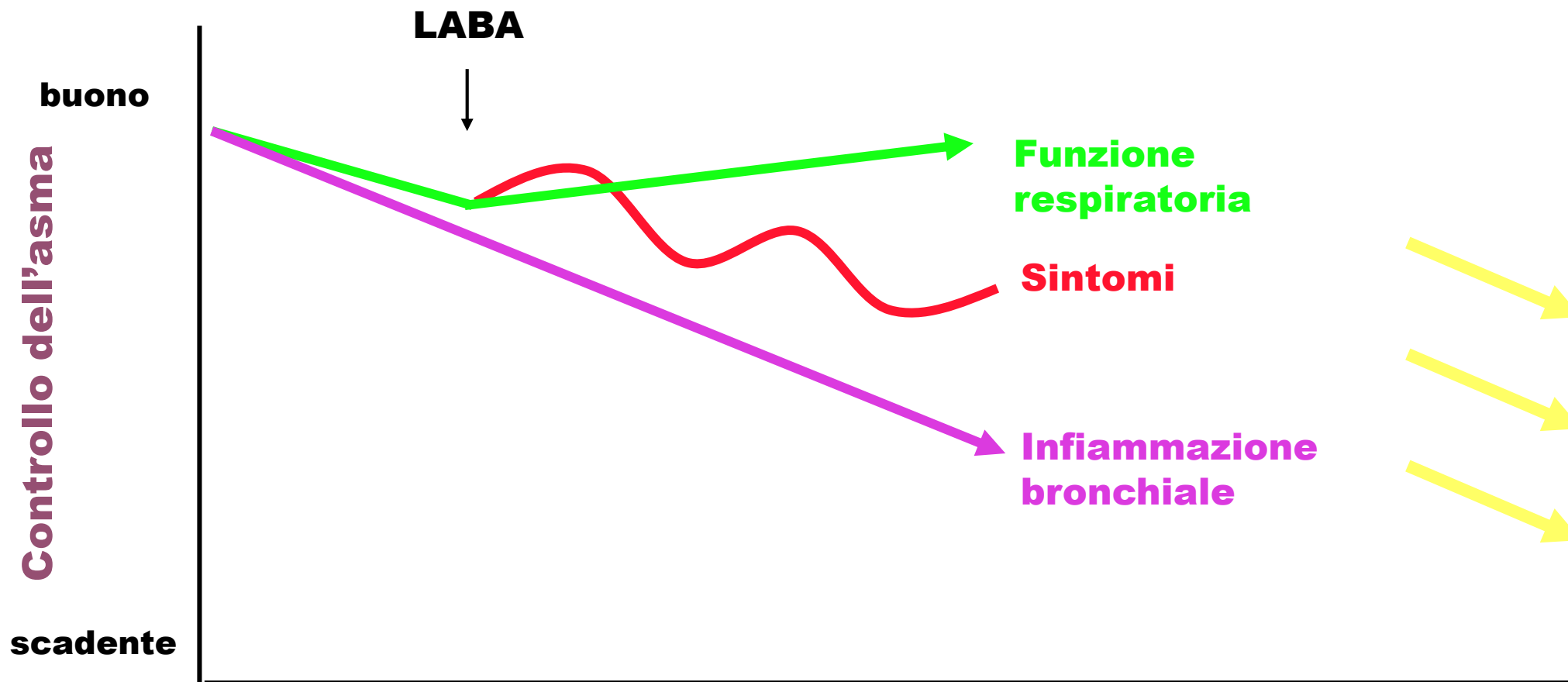


3. Rivedere la storia clinica

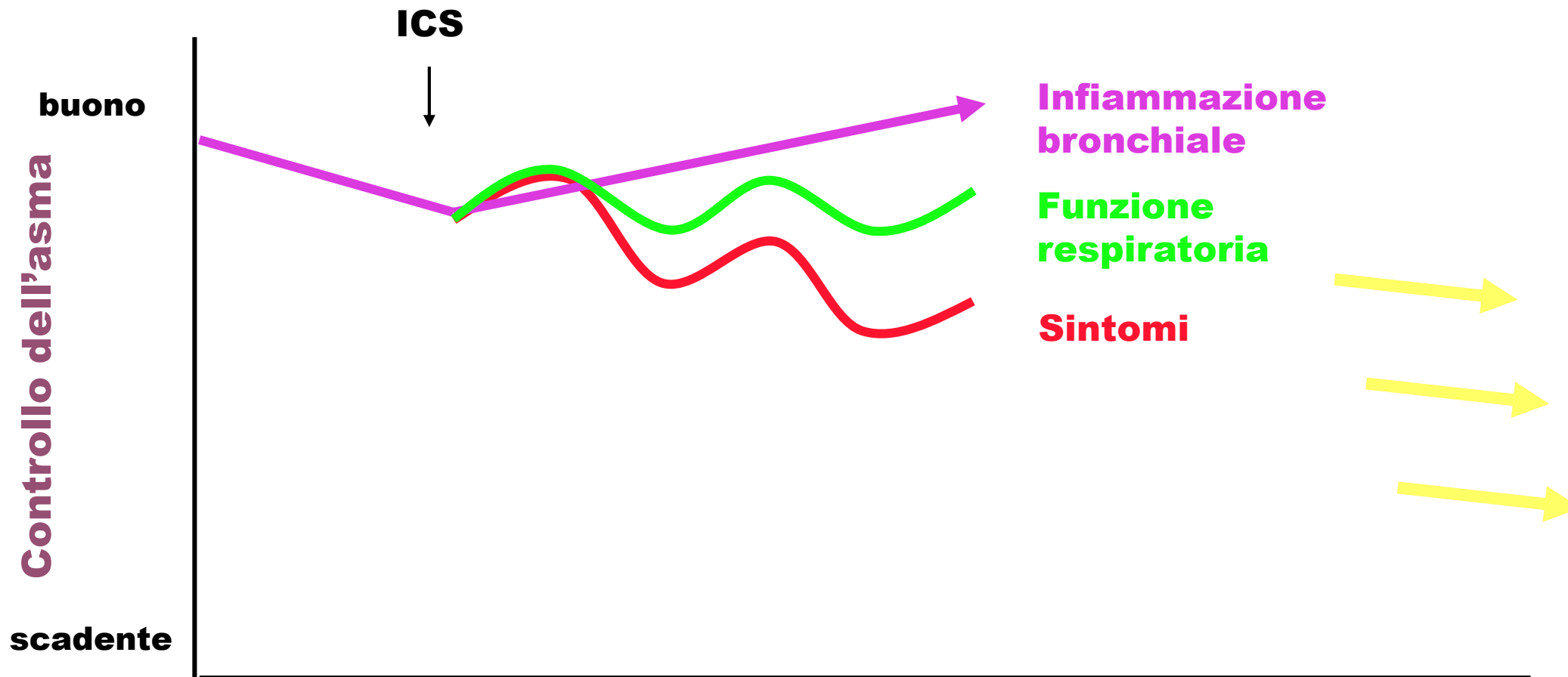
Scarso controllo dell'asma se solo basato sui sintomi



Scarso controllo dell'asma se solo basato sulla funzione respiratoria



Scarso controllo dell'asma se solo basato sulla flogosi bronchiale



Evoluzione delle strategie di trattamento dell'asma

<i>Farmaci controller</i>	<i>Farmaci reliever</i>
Steroidi inalatori a dosi crescenti	SABA

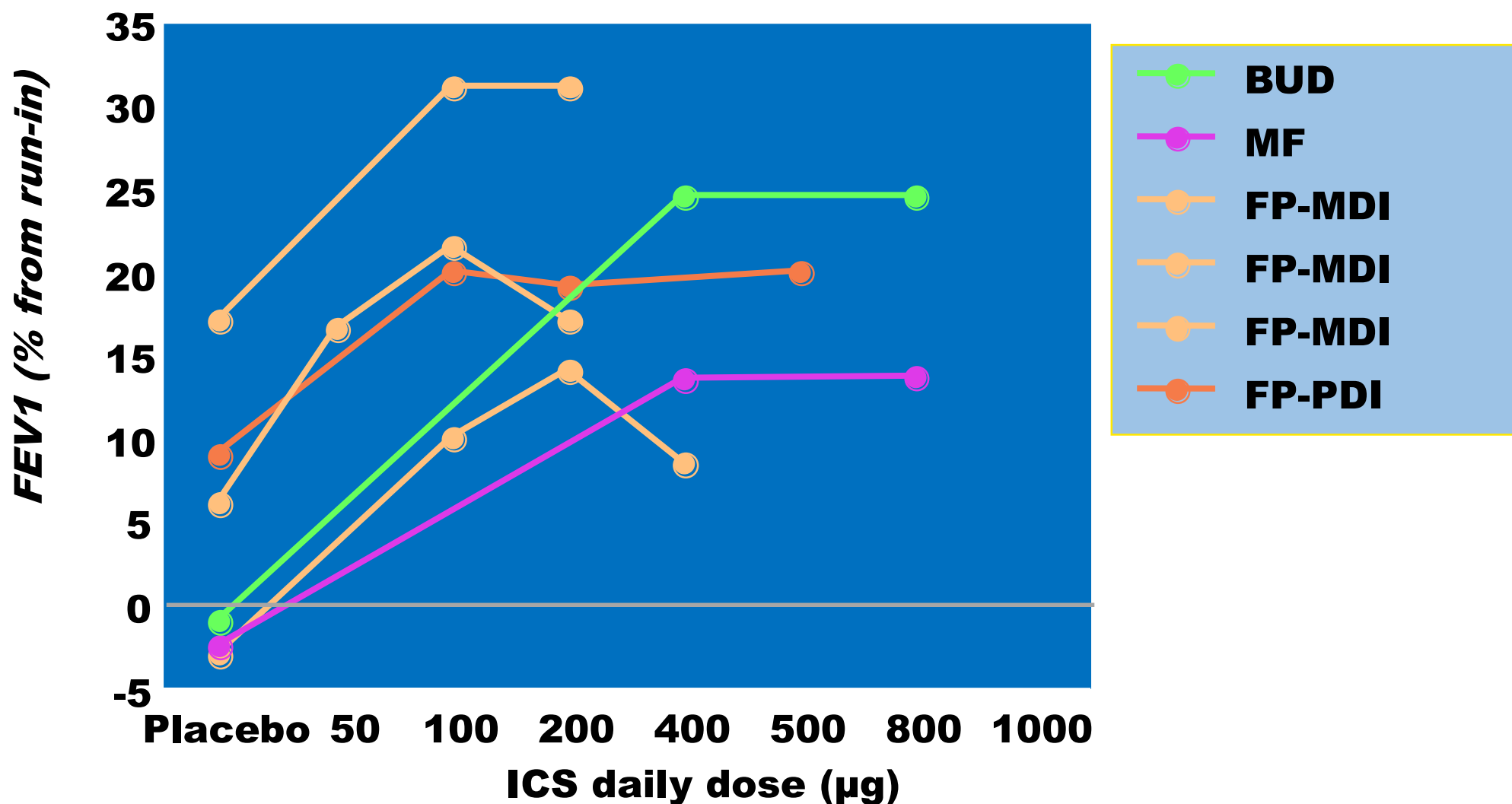


A Step toward Personalized Asthma Treatment

Jeffrey M. Drazen, M.D.

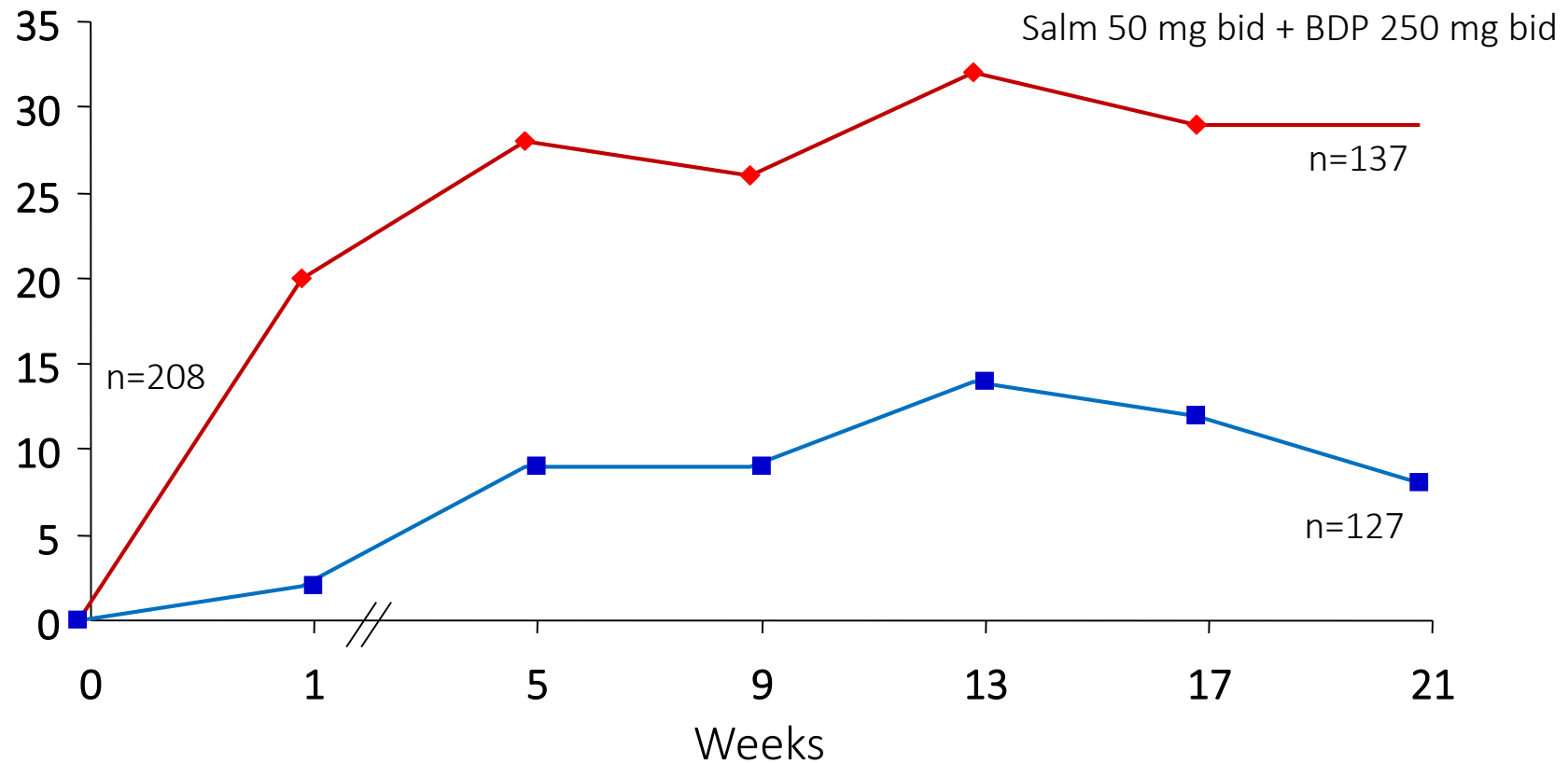
Inhaled glucocorticoids are used every day by millions of patients with asthma. As with all asthma-controller treatments, there is marked patient-to-patient variability in the therapeutic response; about one in three patients with asthma who use inhaled glucocorticoids may not benefit from this treatment.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

L'aumento della dose di corticosteroidi inalatorio non si accompagna ad aumento dell'efficacia

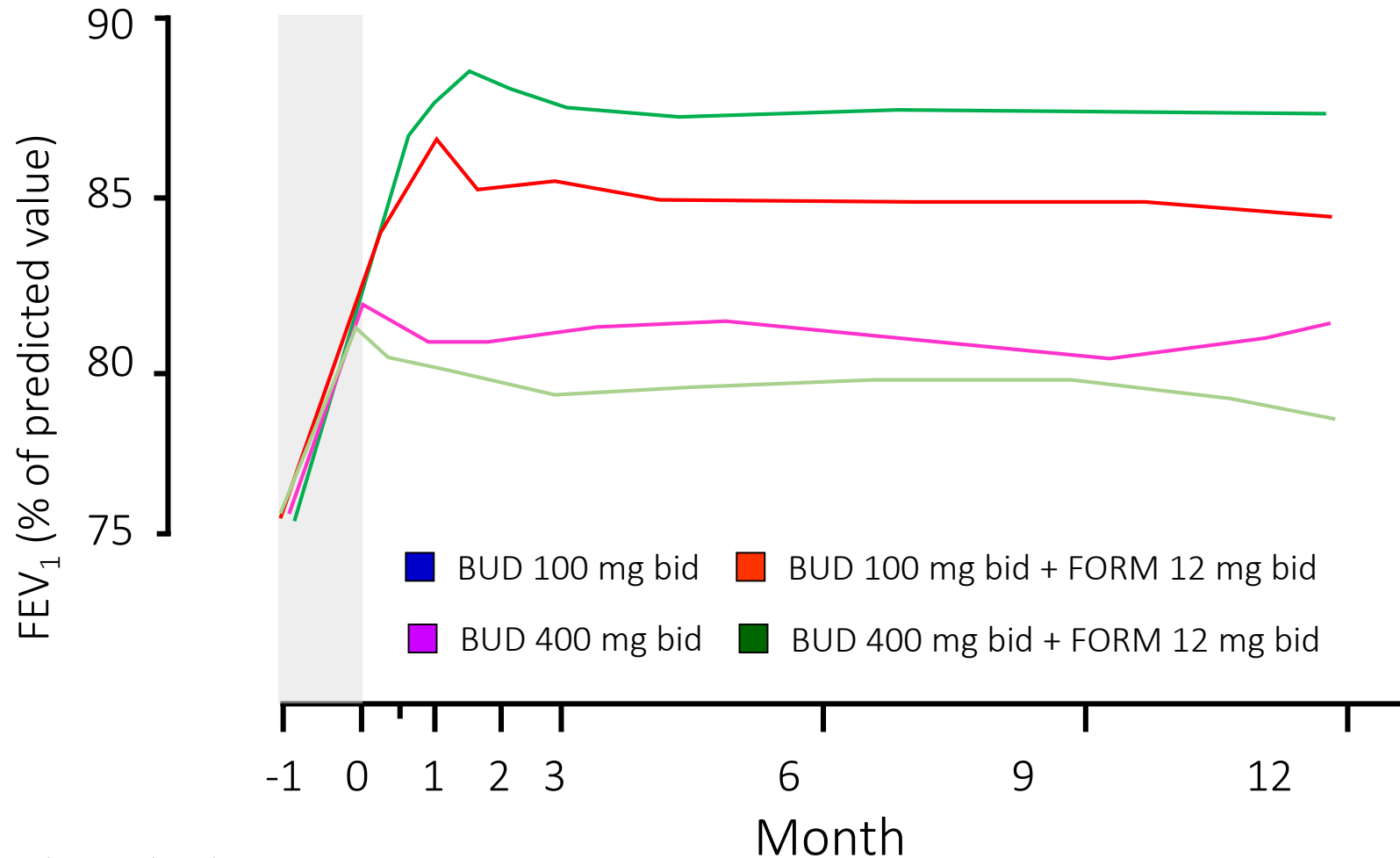


Aggiunta di salmeterolo vs steroidi ad alto dosaggio in pazienti con asma

Change in morning PEF (L/min)



Effetto di formoterolo inalatorio e budesonide sulla funzione polmonare nell'asma – Lo studio FACET



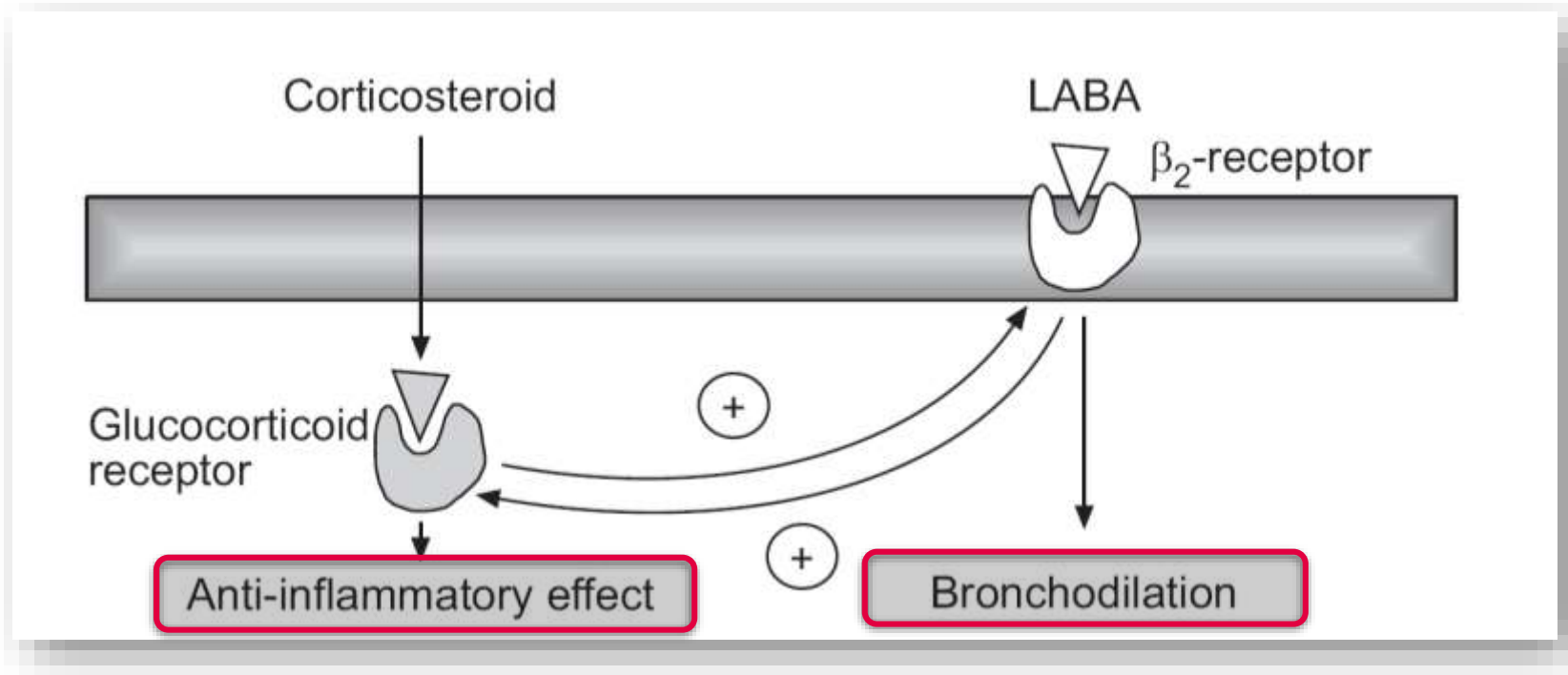
Evoluzione delle strategie di trattamento dell'asma

<i>Farmaci controller</i>	<i>Farmaci reliever</i>
Steroidi inalatori a dosi crescenti	SABA
	
Steroidi inalatori a dosi ridotte + LABA in associazione precostituita BID	SABA

Combinazione ICS-LABA

“Quando i sintomi persistono nonostante l’aderenza terapeutica e una corretta tecnica inalatoria, l’uso di un β beta2-agonista a lunga durata di azione in associazione con uno steroide inalatorio si è dimostrato lo step successivo più efficace, perché agisce su entrambi gli aspetti del restringimento delle vie aeree: broncocostrizione e infiammazione delle vie aeree.”

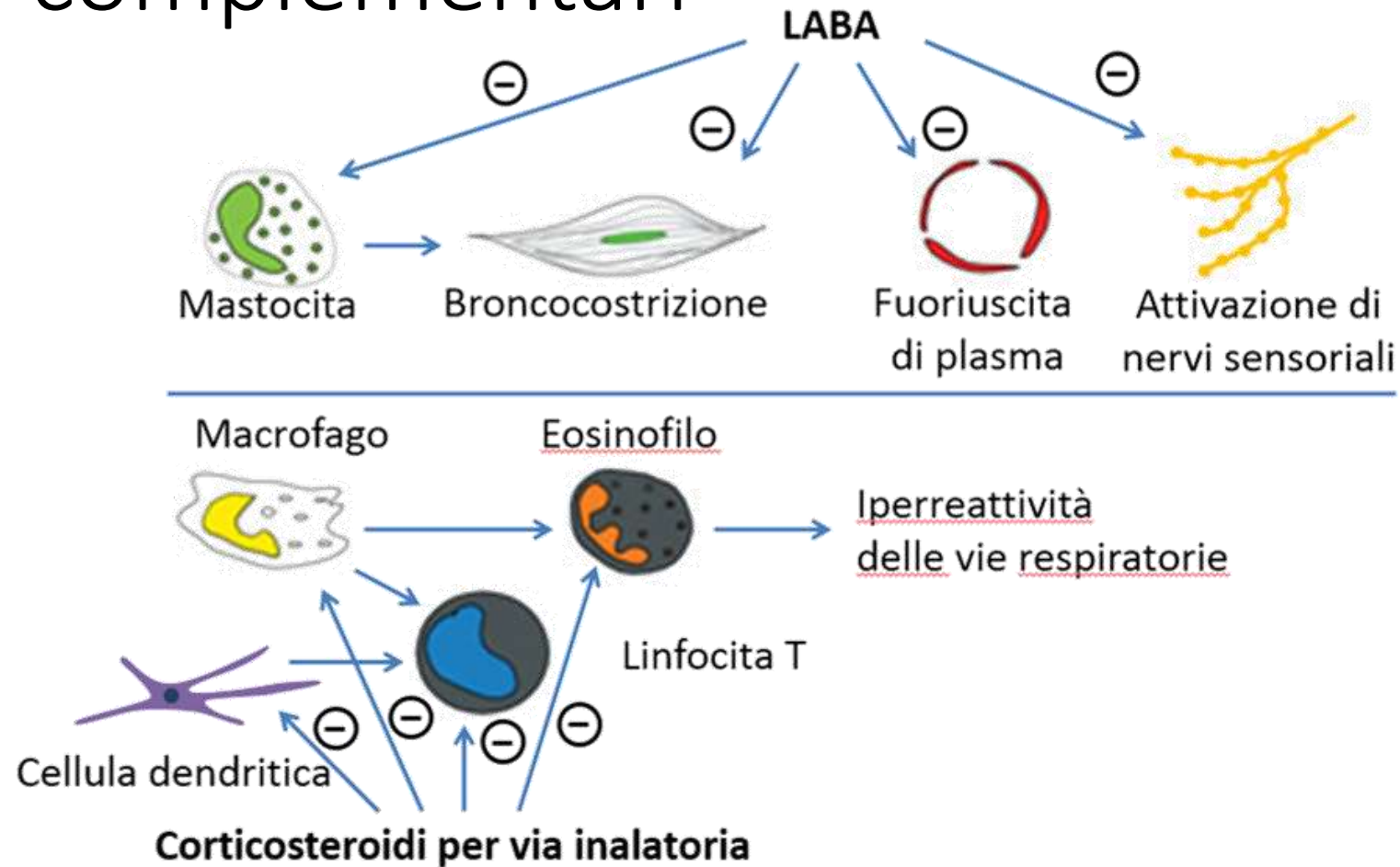
Interazione tra steroidi e beta2-agonisti a lunga durata di azione



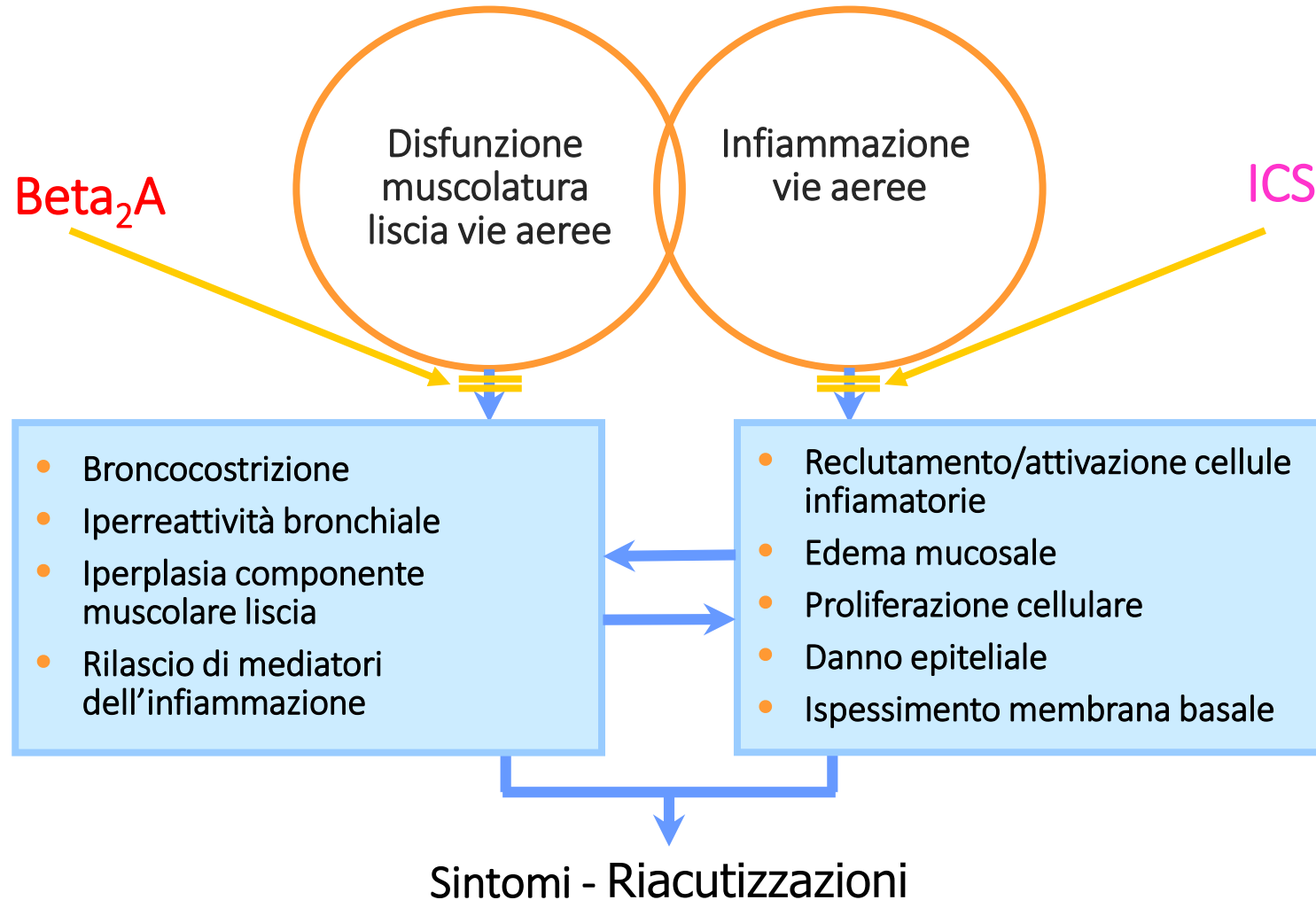
↑ β_2 -receptor expression
↑ β_2 -receptor coupling
↓ Downregulation of β_2 -receptors
Prevention of β -agonist tolerance

↑ GR translocation
↑ GRE binding
↑ Anti-inflammatory effect

I LABA e gli ICS affrontano aspetti complementari



Effetti antiasmatici complementari di steroidi inalatori e β_2 -agonisti



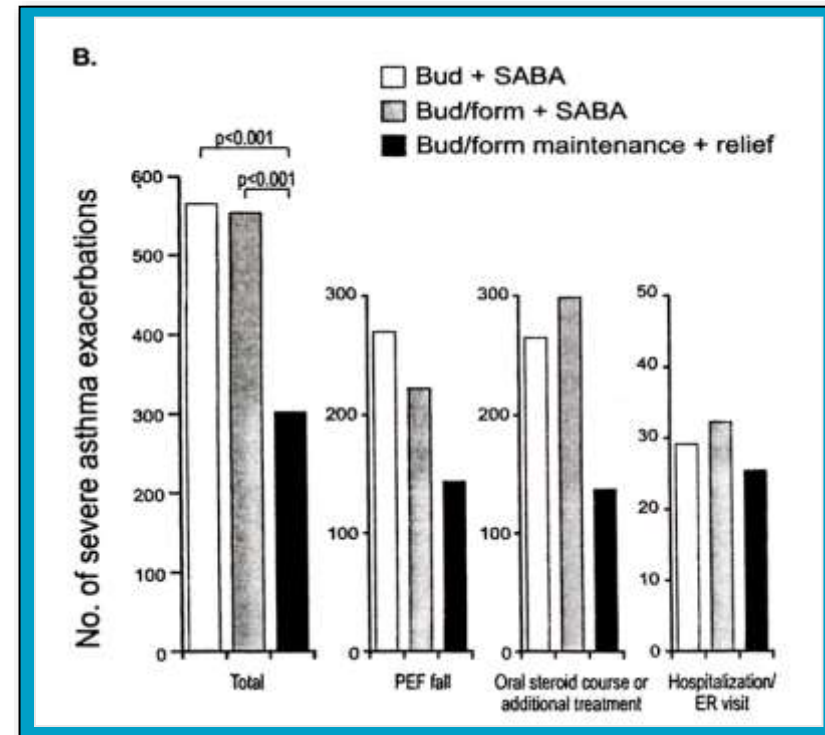
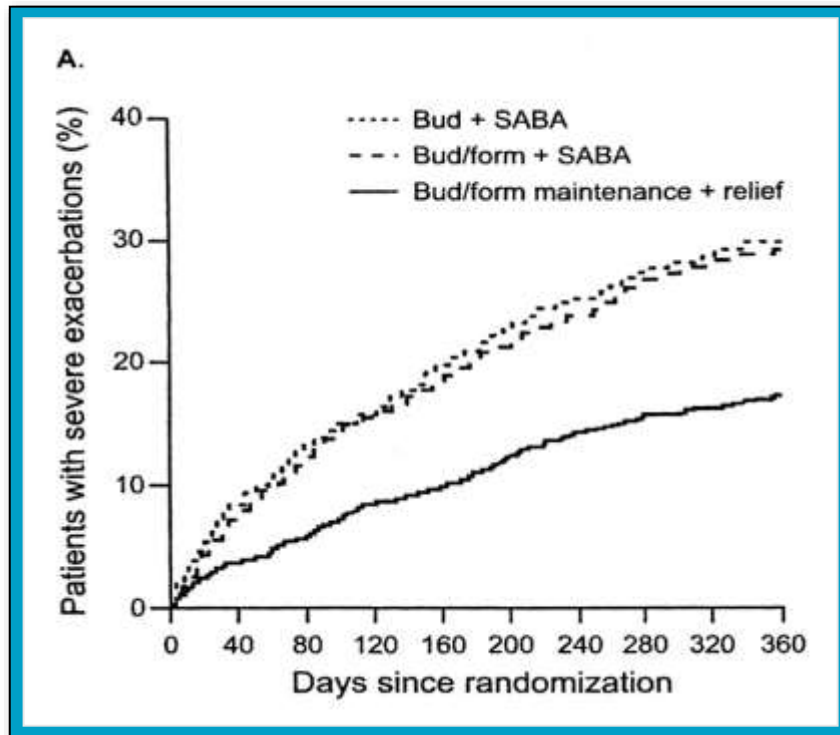
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Steroidi inalatori a dosi ridotte + LABA in associazione precostituita BID	SABA
	
Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita BID	Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita

Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma

Paul M. O'Byrne, Hans Bisgaard, Philippe P. Godard, Massimo Pistolesi, Mona Palmqvist, Yuanjue Zhu, Tommy Ekström, and Eric D. Bateman

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**

RESEARCH ARTICLE

Open Access

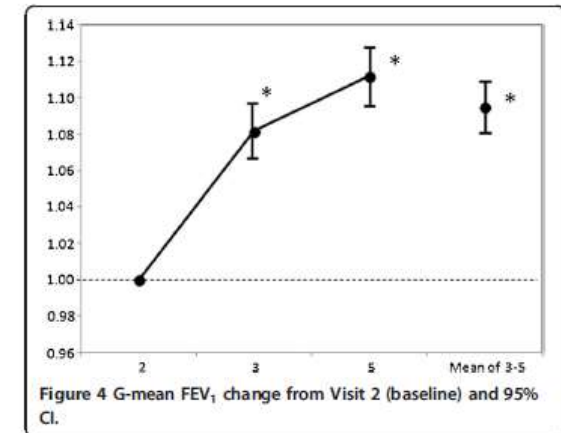
Real-life effectiveness of budesonide/formoterol maintenance and reliever therapy in asthma patients across Asia: SMARTASIA study

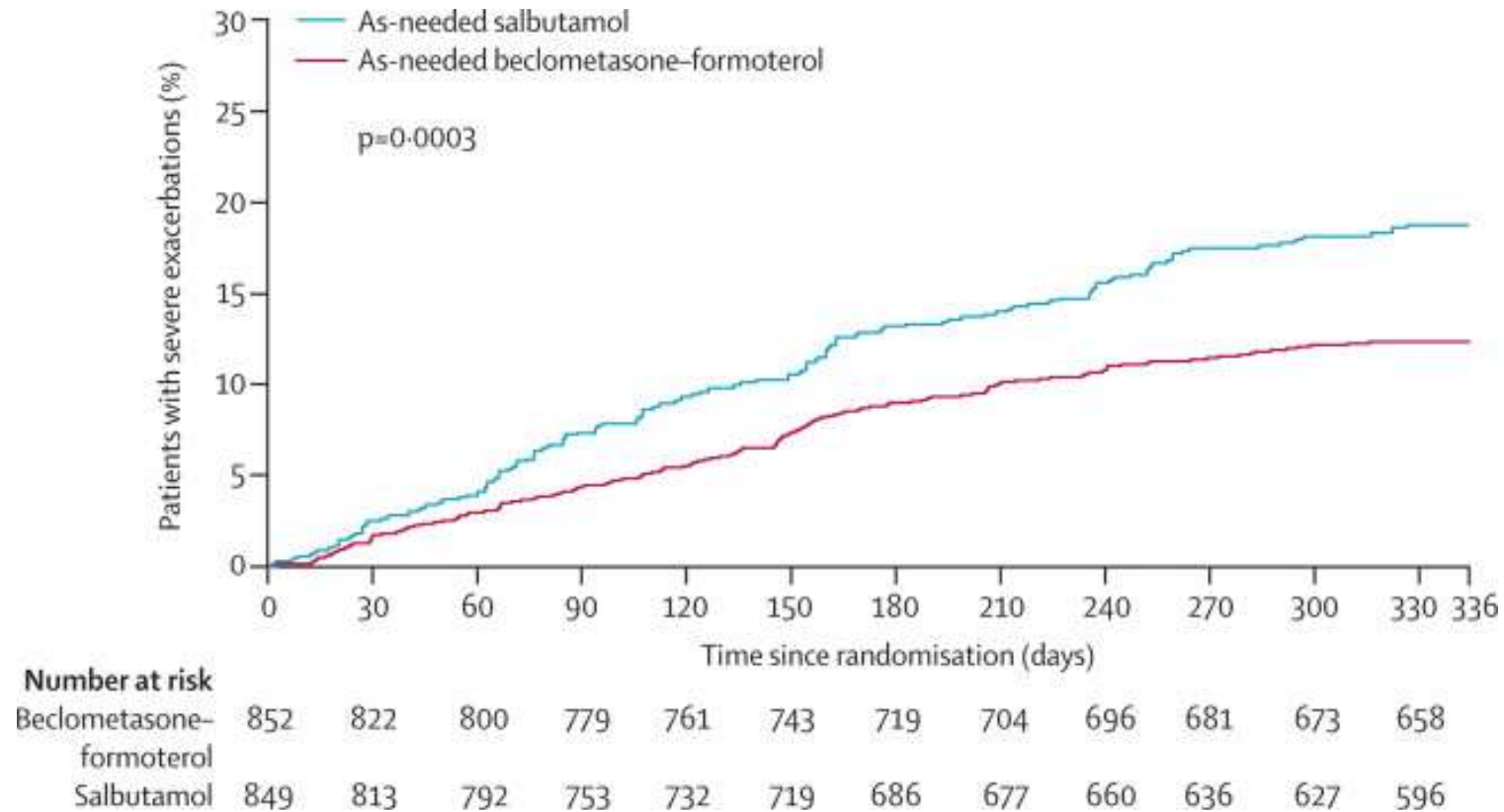
Nanshan Zhong^{1*}, Jiantao Lin^{2†}, Parthiv Mehta³, Pintip Ngamjanyapom^{4†}, Tzu-Chin Wu^{5†} and Faisal Yunus⁶

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 and
- as-needed medication use





Beclometasone-Formoterol as maintenance and reliever treatment in patients with asthma

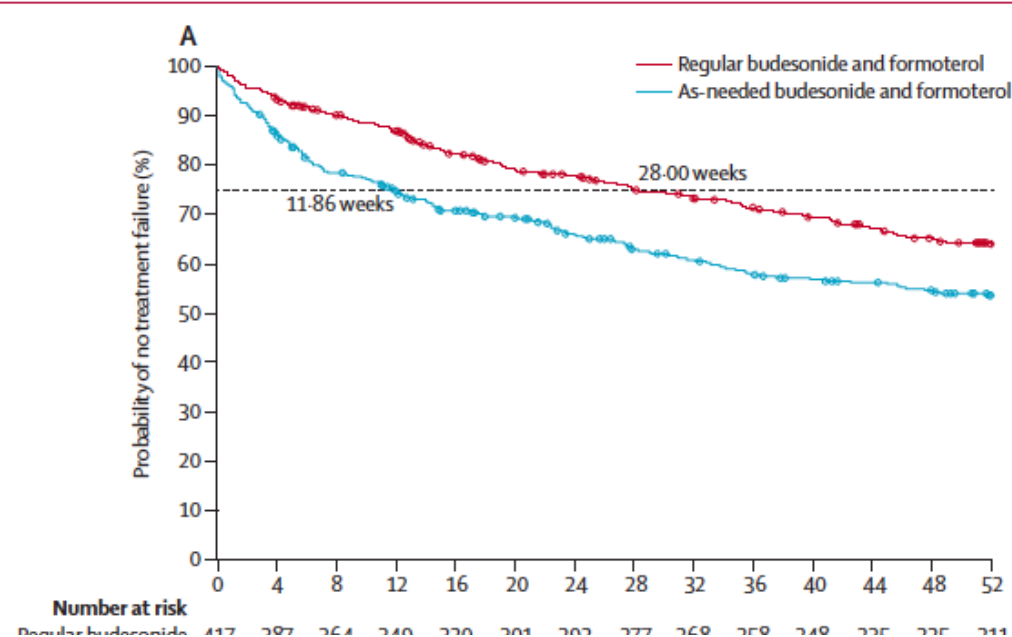
Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial



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 Pannacci, Paolo Morelli, Bianca Beghét, Leonardo M Fabbri†, for the AIFASMA Study Group‡

Summary

Background Treatment guidelines recommend a combination of an inhaled corticosteroid and a long-acting beta₂-agonist for moderate asthma. We investigated whether symptomatic treatment would be as effective as regular treatment in patients with moderate asthma.



with a
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line for

Lancet Respir Med 2015;
3: 109-19
Published Online
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)

Interpretation In patients with moderate stable asthma, as-needed budesonide and formoterol therapy is less effective than is the guideline-recommended regular budesonide and formoterol treatment, even though the differences are small.

Rapporto OSMED 2015

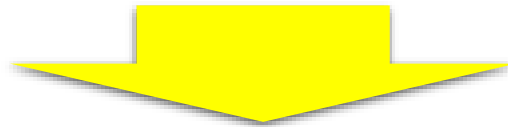
In Italia

Pazienti in trattamento con farmaci per le
sindromi ostruttive delle vie respiratorie
aderenti al trattamento



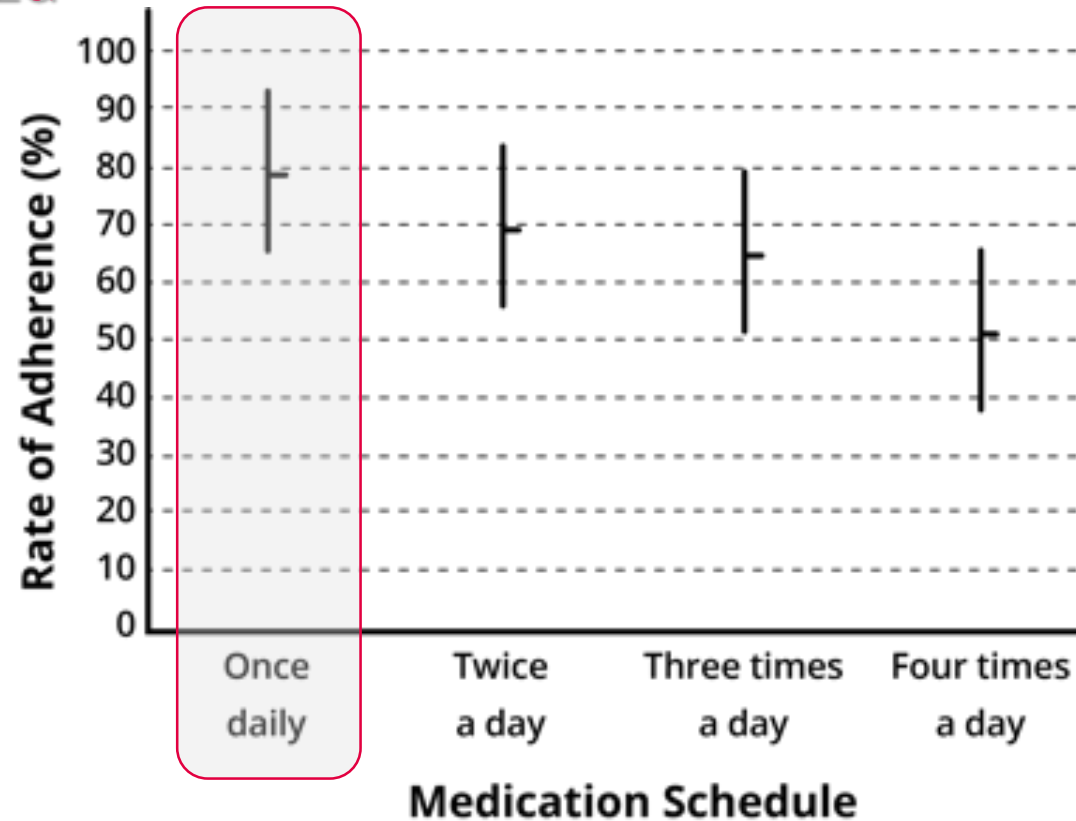
13,6%

SCARSA ADERENZA ALLA
TERAPIA INALATORIA



INSUCCESSO DELLA TERAPIA

Ridurre la frequenza delle somministrazioni migliora l'aderenza



La monosomministrazione giornaliera sia associa ad una percentuale di aderenza dell'80%

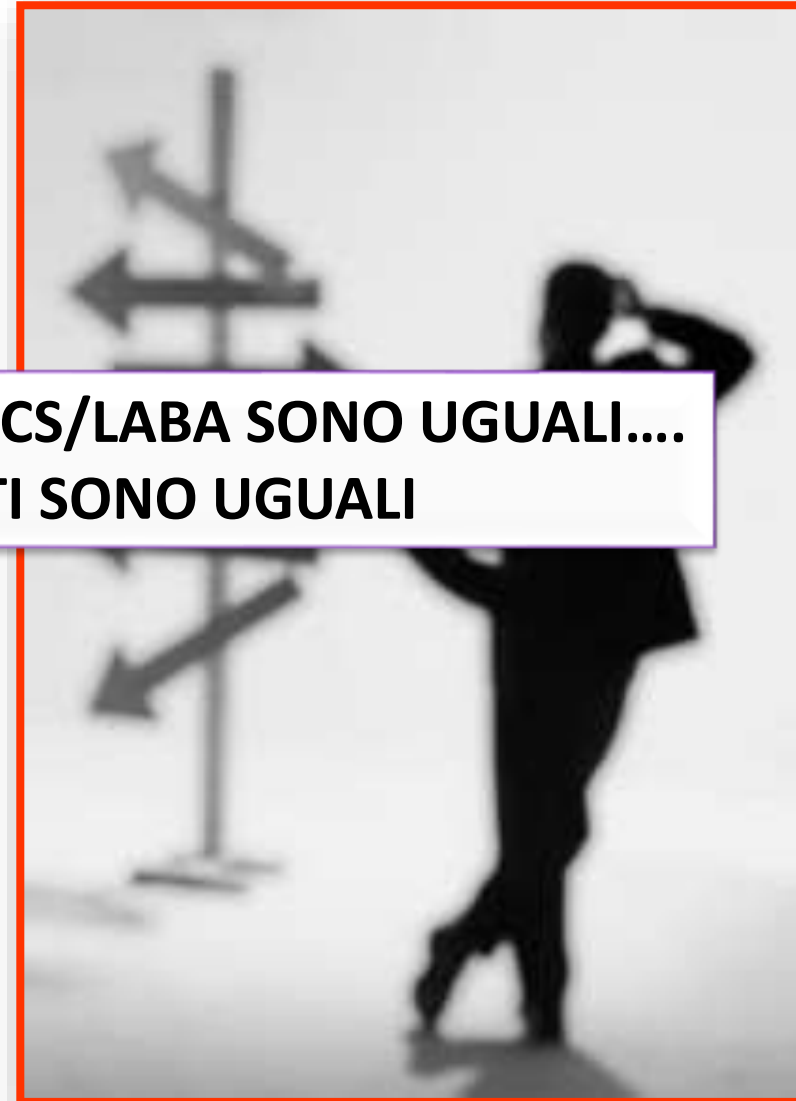
Evoluzione delle strategie di trattamento dell'asma

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Steroidi inalatori a dosi ridotte + LABA in associazione precostituita BID	SABA
Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita BID	Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita
CSI + LABA in associazione precostituita OD ? CSI + Formoterolo OD	SABA o CSI Low Dose + Formoterolo

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 $10^{(pK_{i\beta_2} - pK_{i\beta_1})}$

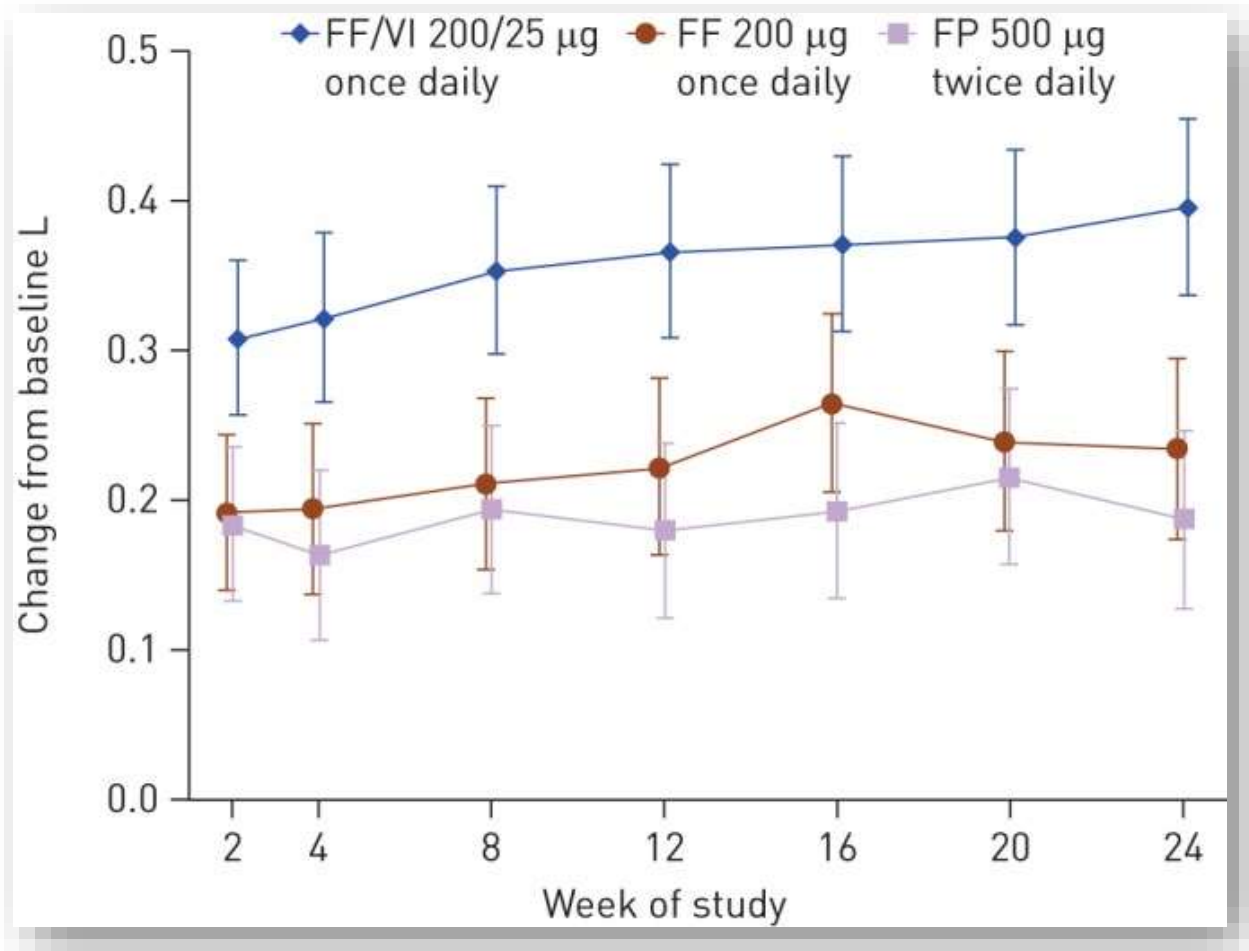
Associazioni precostituite ICS/LABA nel trattamento dell'asma

- Beclometasone propionato/formoterolo
- Budesonide/formoterolo
- Fluticasone propionato/formoterolo
- Fluticasone propionato/salmeterolo
- Fluticasone furoato/vilanterolo

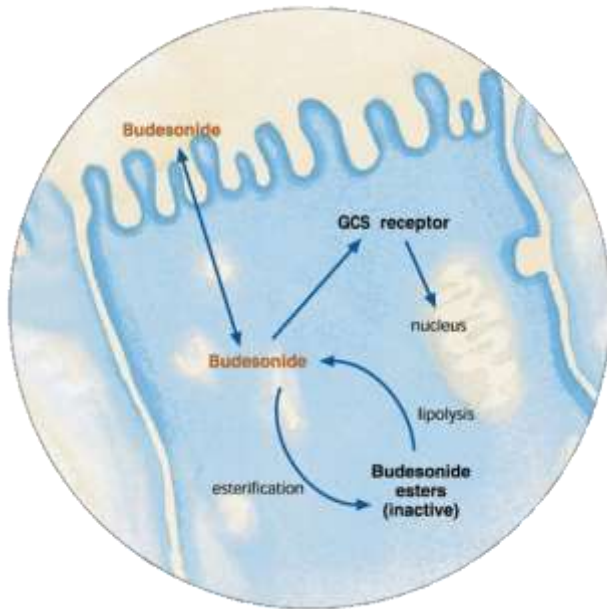
Combinazioni ICS/LABA: frequenza di somministrazione

Combination steroid/LABA	Available dosages ^a (microgram)	Frequency per day
Fluticasone propionate/salmeterol	100/50, 250/50, 500/50	Twice
Fluticasone propionate/salmeterol	45/21, 115/21, 230/21	Twice
Fluticasone furoate/vilanterol	100/25, 200/25	Once
Mometasone furoate/formoterol	50/5, 100/5, 200/5	Twice
Fluticasone propionate/formoterol	50/5, 125/5, 250/10	Twice
Beclometasone dipropionate/formoterol	100/6	Twice
Budesonide/formoterol	80/4.5, 160/4.5, 320/9	Twice

Effetti sul FEV1 del fluticasone furoato somministrato una volta al giorno da solo o in combinazione con vilanterolo

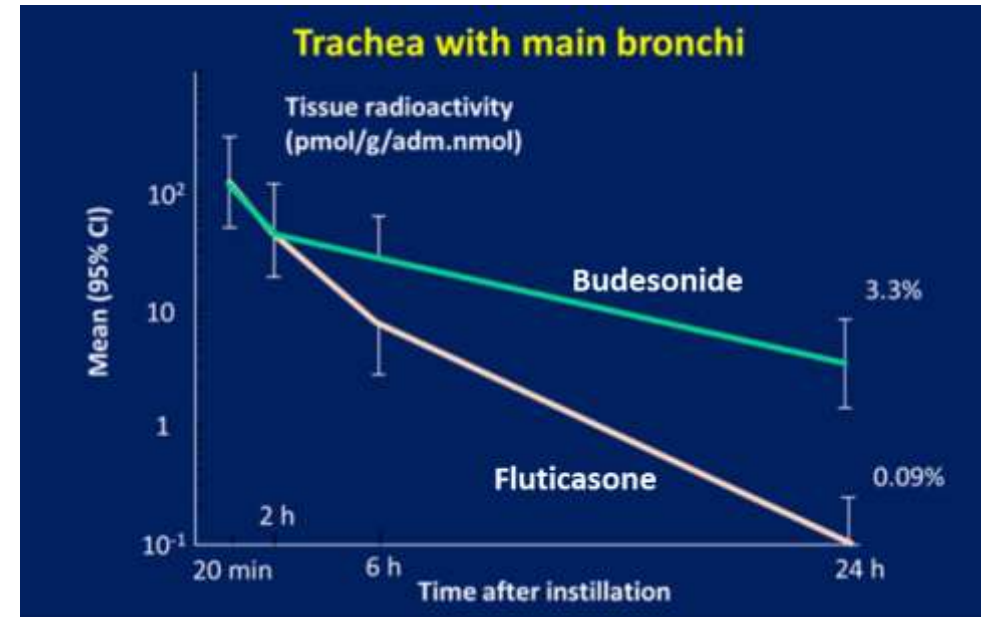


Farmacocinetica effetto prolungato di Budesonide



Wieslander et al. 1997

L'esterificazione di Budesonide nelle vie aeree forma un deposito locale dal quale viene rilasciato lentamente la budesonide libera prolungandone l'esposizione.



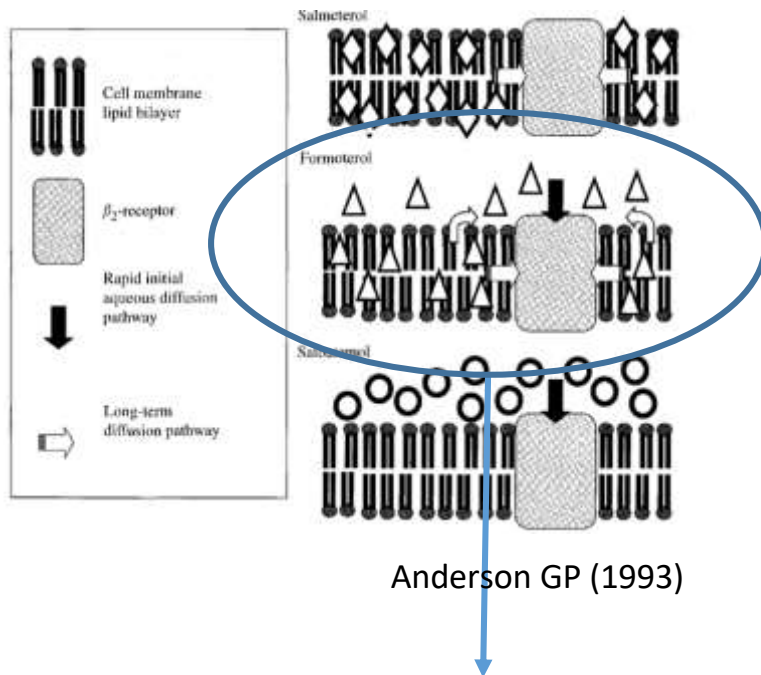
Miller-Larsson *et al.* 1998

Topical effect of budesonide is among the highest of available inhaled steroids.

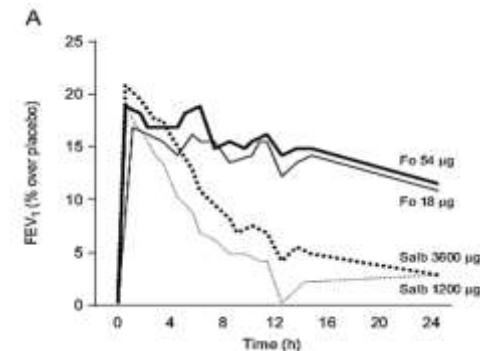
Budesonide is retained within airway cells in the form of inactive fatty acid esters.

This mechanism prolongs anti-inflammatory effect and increases the benefit/risk ratio.

Farmacocinetica effetto prolungato di Formoterolo



Il Formoterolo è l'unico LABA che se somministrato in dose più elevata (es. due inalazioni alla sera), in parte si lega ai recettori β_2 , in parte si accumula nella membrana cellulare costituendo un deposito a lungo rilascio che copre le 24h.



L'emivita terminale di Formoterolo= 17h (RCP Symbicort)

Dopo 17h dalla somministrazione Formoterolo è ancora al 50% della concentrazione iniziale

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

British Journal of General Practice, January 2008

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.

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

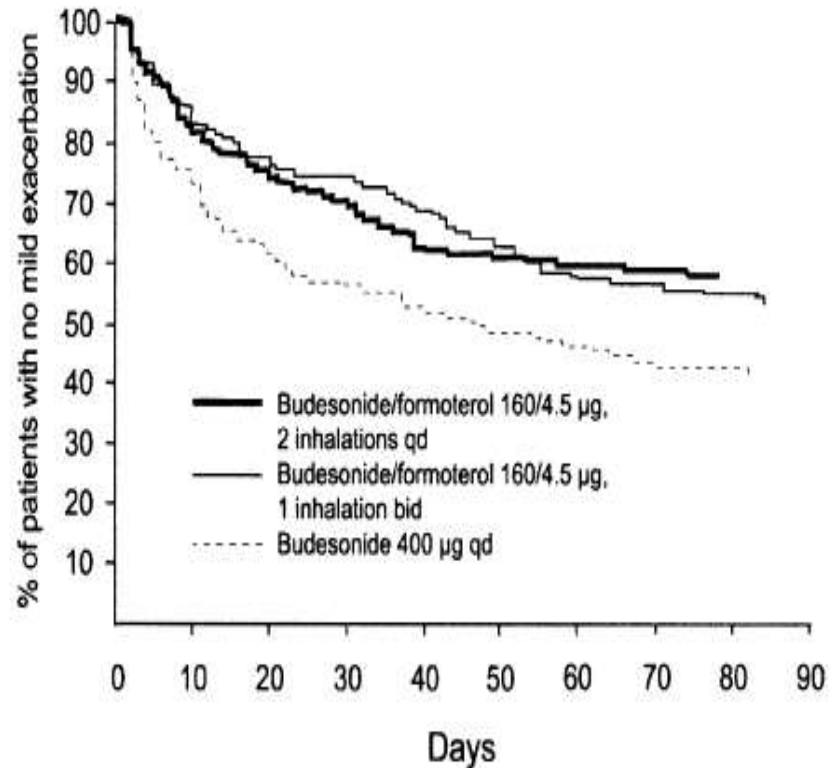
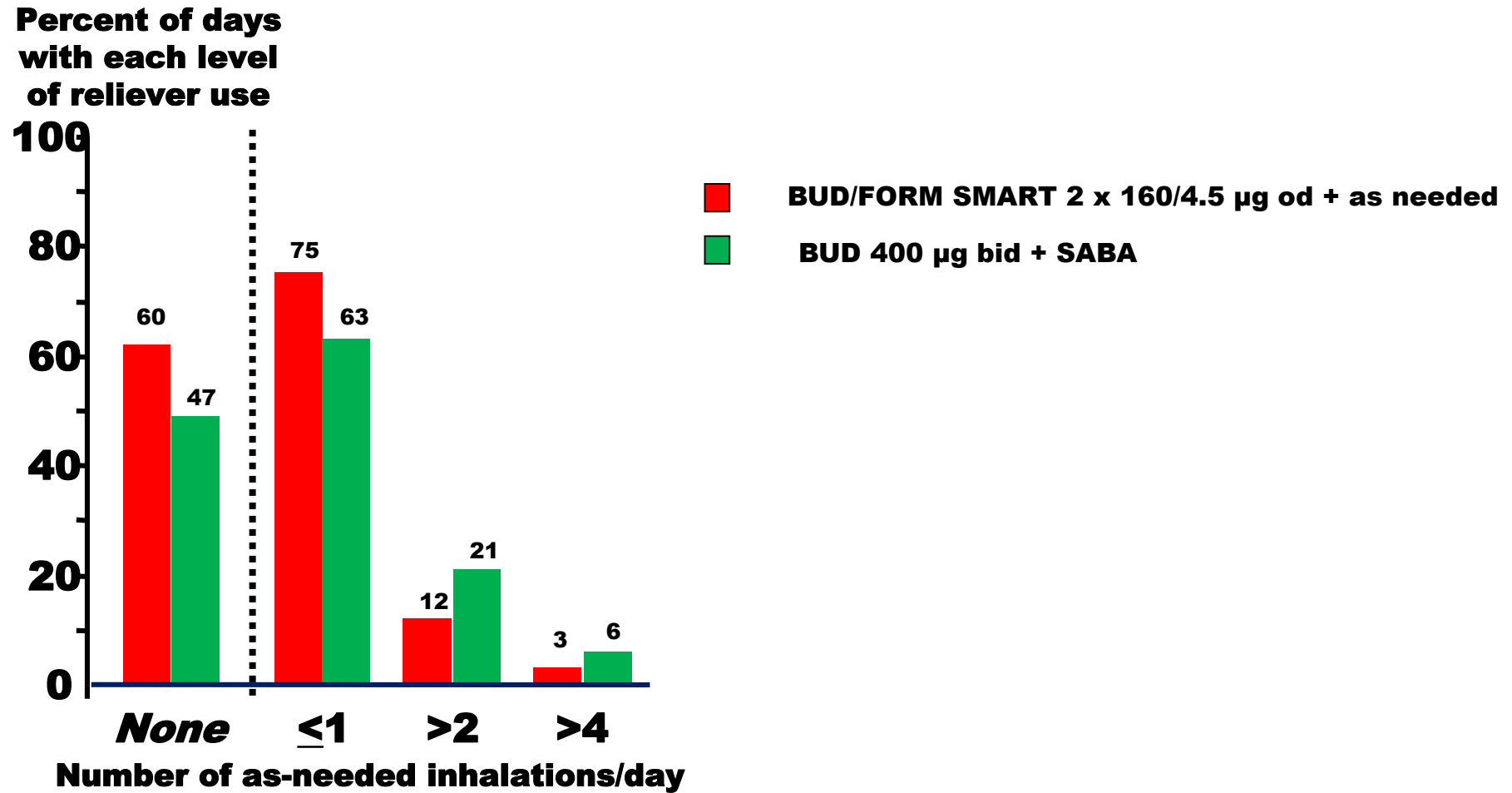


FIG 3. Kaplan–Meier survival curves of the time to first mild asthma exacerbation during 12 weeks' treatment with once-daily budesonide/formoterol (160/4.5 µg, two inhalations), twice-daily budesonide/formoterol (160/4.5 µg, one inhalation) or once-daily budesonide (400 µg) alone.

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

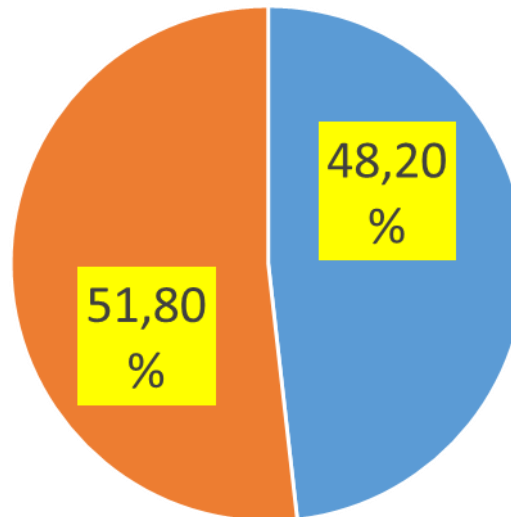
- **The decisions about dosage frequency (once versus twice a day) should be considered in the light of patients' beliefs about the prescription (e.g. necessity and concerns) and their preferences.**
- **For some patients, once-daily dosing might be helpful in achieving this.**
- **But once-daily dosing 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.**

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 Williams³

Pazienti che indicano la preferenza di una singola somministrazione giornaliera



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

Strategie per migliorare l'aderenza terapeutica nell'asma

- Solo alcuni interventi sono stati studiati e hanno dimostrato di essere efficaci nel migliorare l'aderenza terapeutica
 - Prendere decisioni condivise
 - Semplificare il regime terapeutico (uno vs due volte al giorno)
 - Informazioni comprensive sull'asma con visite domiciliari di personale sanitario
 - Inhalatore con promemoria in caso di dose non somministrata
 - Controllare quante dosi sono state erogate dall'inhalatore

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 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

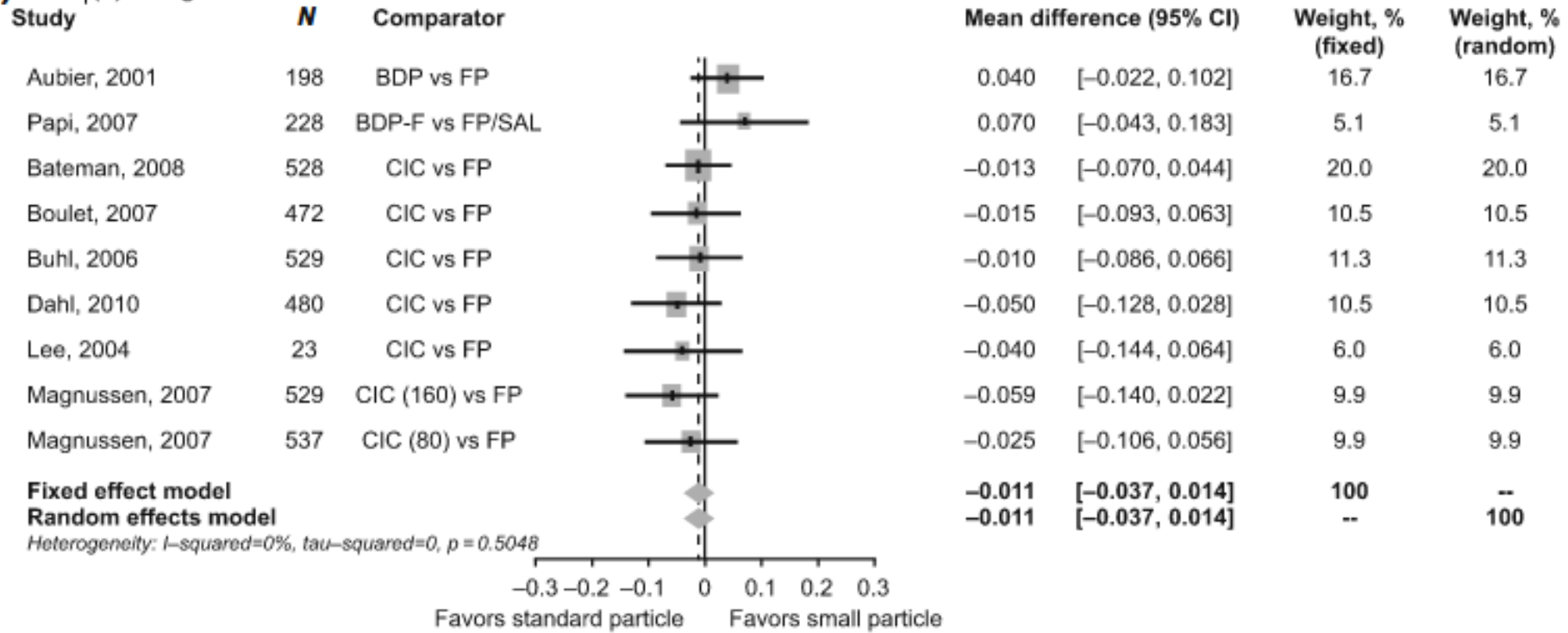


Effect of inhaled corticosteroid particle size on asthma efficacy and safety outcomes: a systematic literature review and meta-analysis

Céline El Baou^{1,11*}, Rachael L. Di Santostefano^{2,9}, Rafael Alfonso-Cristancho^{3,4}, Elizabeth A Suarez^{5,10}, David Stempel², Mark L Everard⁶ and Neil Barnes^{7,8}

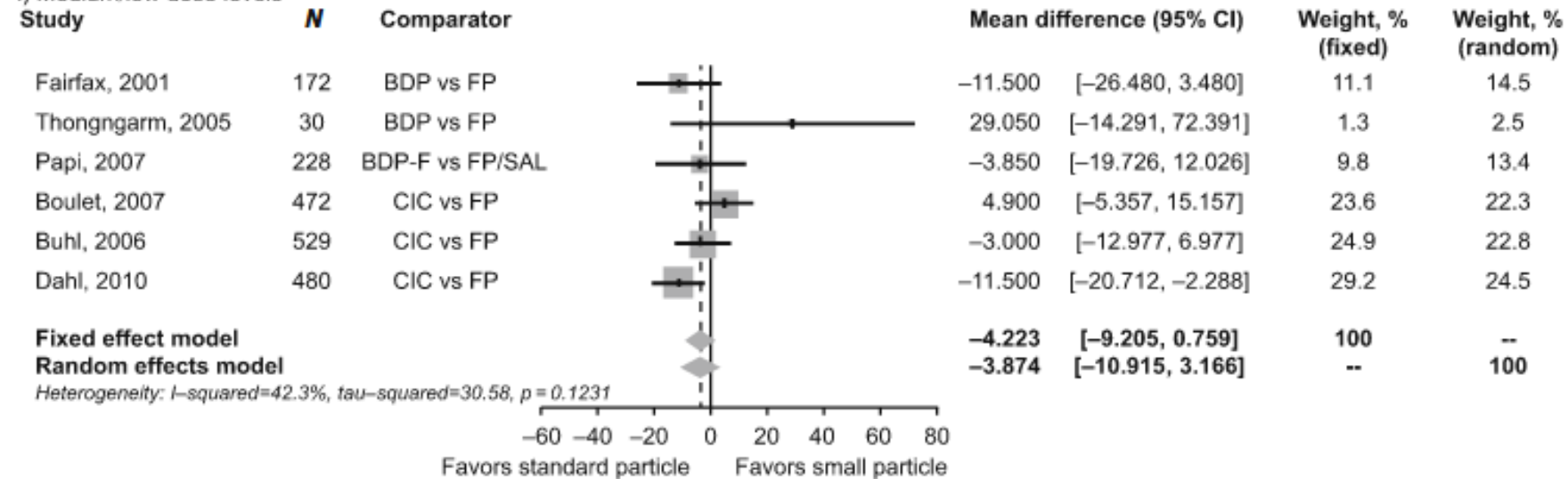
L'efficacia e la sicurezza del trattamento farmacologico non dipende dalla dimensione delle particelle

a) FEV₁ (L) change from baseline between treatments

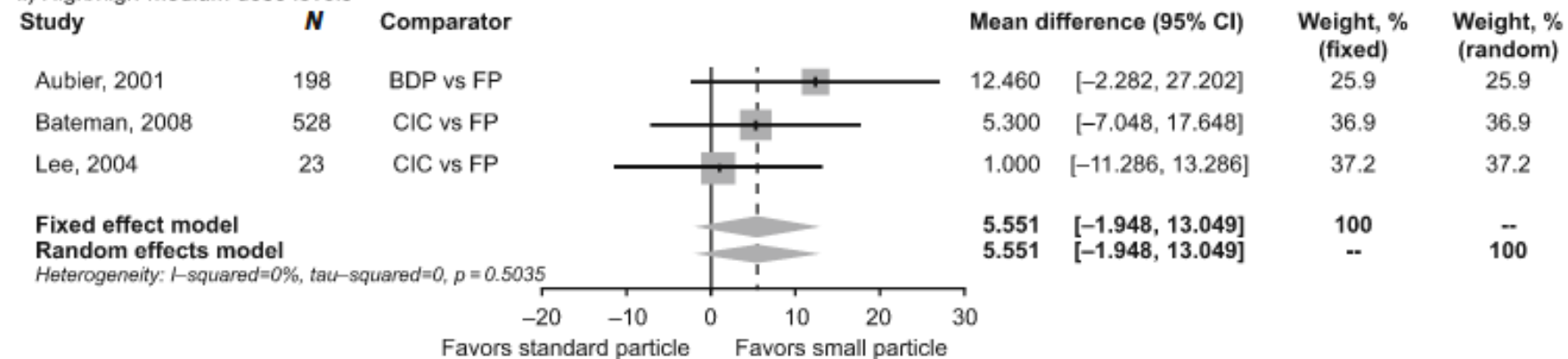


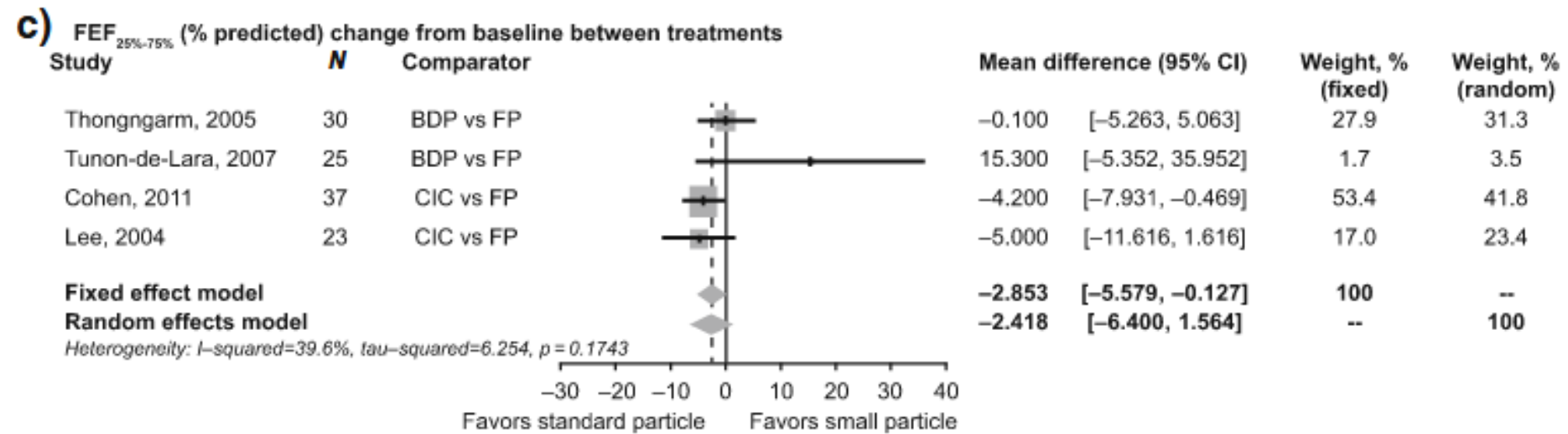
b) Morning PEF (L/min) change from baseline between treatments

i) Medium/low dose levels



ii) High/high-medium dose levels





Evoluzione delle strategie di trattamento dell'asma

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	SABA
Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita BID	Steroidi inalatori a dosi ridotte + formoterolo in associazione precostituita
CSI + LABA in associazione precostituita OD ? CSI + Formoterolo OD	SABA o CSI Low Dose + Formoterolo



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di associazione nell'asma

Paolo Solidoro

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e gestione avanzata vie aeree
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