



Voglio respirare  
meglio.  
I farmaci  
antiasmatici

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Alessandro Fiocchi

Presidente Società  
Italiana di Pediatria  
Sezione Lombarda

16 settembre 2011



# Ready?

At the end of this presentation you will be able to:

- Have a general idea of drugs for asthma
- Planning treatment of asthma episodes
- Planning prevention of asthma attacks



ARETAEI CAPPADOCIS

MEDICI INSIGNIS AC VETUSTISSIMI

LIBRI SEPTEM

Nunc primum e tenebris eruti

A IVNIO PAVLO CRASSO PATAVINO

*assuratore in latini sermone acce.*

R. VFFI EPHESII

MEDICI CLARISSIMI,

Decorporis huiusmodi appellationibus

LIBRI

AN EODEM IVNIO PAVLO

*Latine et Græce.*

Quin omnibus his libris fide ac memoris digna habetur.

INDEX LOCUPLETISS.

Operis ceteri appositus demonstrabit.



VENETIIS APUD IUNTAS.

M D L I I

Cum summi Pontificis Sereniss. Venerabilis  
Decretis et Annodis. 1712.

Oppressione toracica,  
lentezza nel lavoro  
consueto o nel fare  
qualunque altra cosa,  
difficile e cattiva  
respirazione nel correre,  
o nell'andare in salita;  
diventano rauchi e  
tossiscono;  
eruttano.

Adams F. The Extant Work of Aretaeus the  
Cappadocian. Sydenham Society,  
London, 1856



A  
TREATISE  
OF THE  
ASTHMA.

Divided into Four Parts.

In the First is given  
*A History of the Fits, and the Symptoms preceding them.*

In the Second,  
*The Cacochymia which disposes to the Fit, and the Rarefaction of the Spirits which produces it, are described.*

In the Third,  
*The Accidental Causes of the Fit, and the Symptomatic Asthmas are observed.*

In the Fourth,  
*The Cure of the Asthma Fit, and the Method of Preventing it is proposed. To which is annexed a Digression about the several Species of Acids distinguish'd by their Tastes. And 'tis observ'd how far they were thought Convenient or Injurious in general Practice by the Old Writers, and most particularly in relation to the Cure of the Asthma.*

Τὴν μὲν τετραχρὴν ἀρίστην ἢ βέλαν σποχαιὰ τῆς  
βέλ. Galen.

LONDON,

Printed for Richard Wilkin, at the King's-  
Head in St. Paul's Church-Yard. 1698.

Belladonna

Floyer J. A treatise of the asthma. R  
Wilkin & W Innis, London, 1698



Asthma cigarettes were used to deliver alkaloids with bronchodilator properties.



Chu EK. One Hundred Years of Treatment and Onward Am J Respir Crit Care Med 2005;171:1202–8



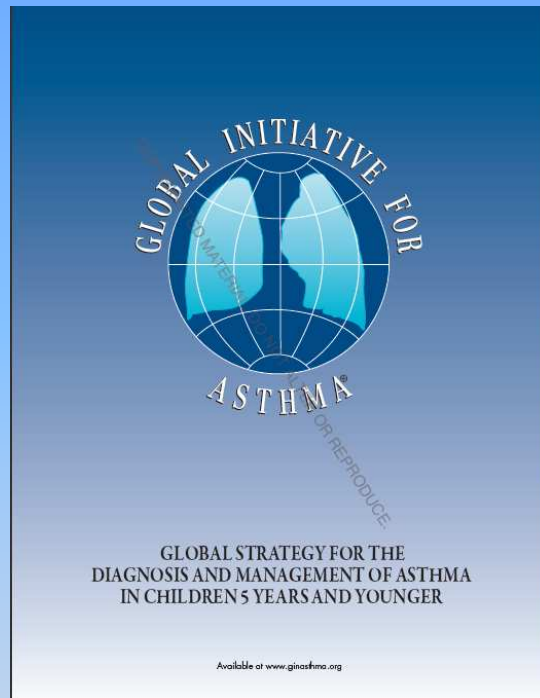
## Treating childhood asthma

1. **Asthma guidelines**
2. Controller medications
3. Reliever medications
4. Exercise-induced asthma
5. Conclusions



# The GINA approach (May 2009)

[www.ginasthma.org](http://www.ginasthma.org)



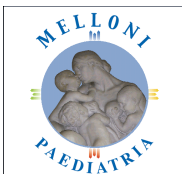
Making a diagnosis of asthma in children 5 years and younger may be difficult because episodic respiratory symptoms [...] are also common in children who do not have asthma.

**Table 1. Is It Asthma?**

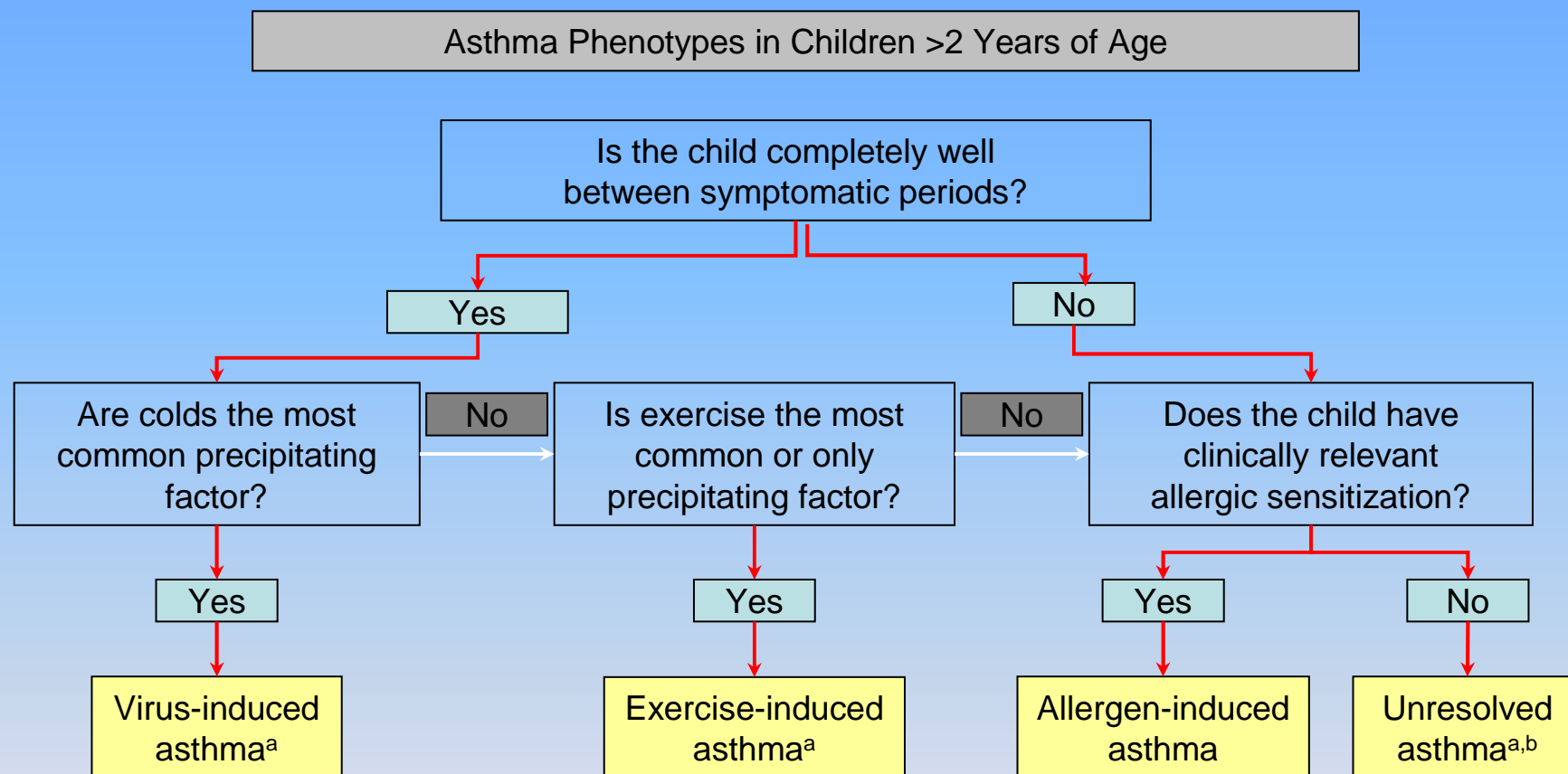
Consider asthma if any of the following signs or symptoms are present:

- Frequent episodes of wheezing—more than once a month.
- Activity-induced cough or wheeze.
- Cough particularly at night during periods without viral infections.
- Absence of seasonal variation in wheeze.
- Symptoms that persist after age 3.
- Symptoms occur or worsen in the presence of:
  - Aeroallergens (house dust mites, companion animals, cockroach, fungi)
  - Exercise
  - Pollen
  - Respiratory (viral) infections
  - Strong emotional expression
  - Tobacco smoke
- The child's colds repeatedly "go to the chest" or take more than 10 days to clear up.
- Symptoms improve when asthma medication is given.





# Identification of Asthma Phenotypes Is Critical



<sup>a</sup>Children may also be atopic.

<sup>b</sup>Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

Adapted from Bacharier LB, et al. *Allergy*. 2008;63(1):5–34.

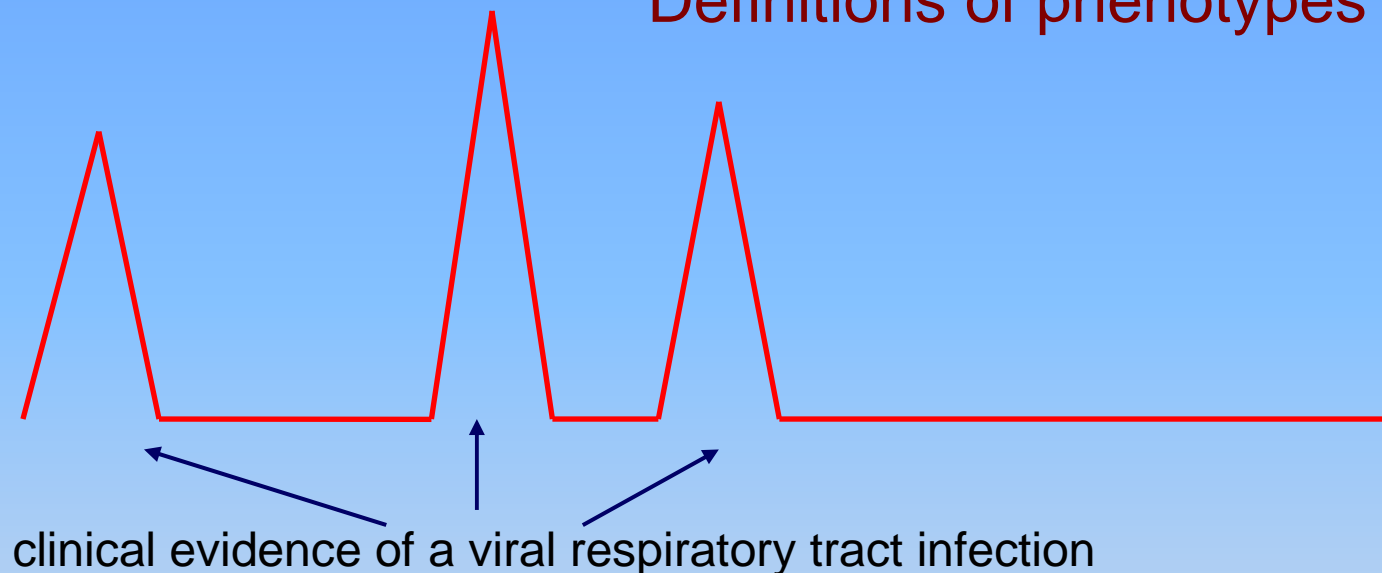




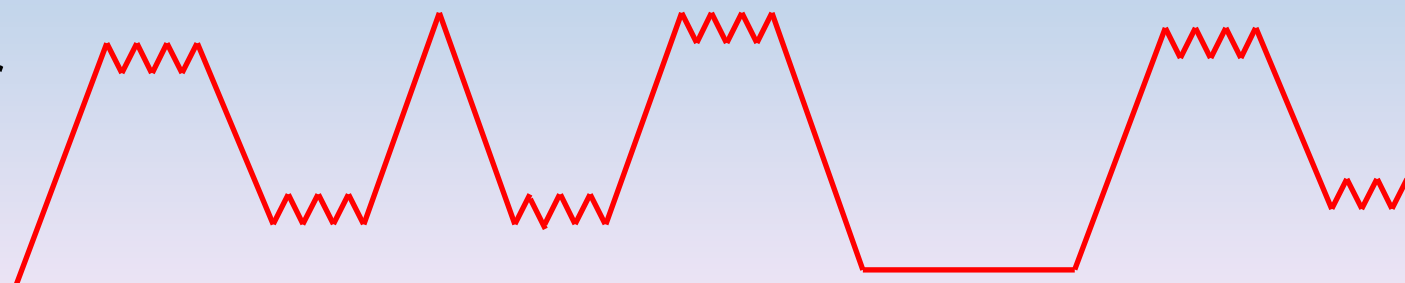
# Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach

## Definitions of phenotypes

Episodic  
(viral)  
wheeze



Multiple-trigger  
wheeze



Brand PL. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008; 32:1096-110.



## treating childhood asthma

1. Asthma guidelines
2. Asthma drugs
3. Controller medications
4. Reliever medications
5. Exercise-induced asthma
6. Conclusions

# Options for children < 5 years



Bacharier LB, Boner A, Carlsen K-H, Eigenmann, PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills TAE, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. The European Pediatric Asthma Group. Allergy 2008; 63:5–34



## treating childhood asthma

1. Asthma guidelines
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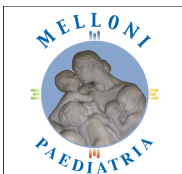
# Need for answers

## Figure 4.3-2: Management Approach Based on Control For Children 5 Years and Younger

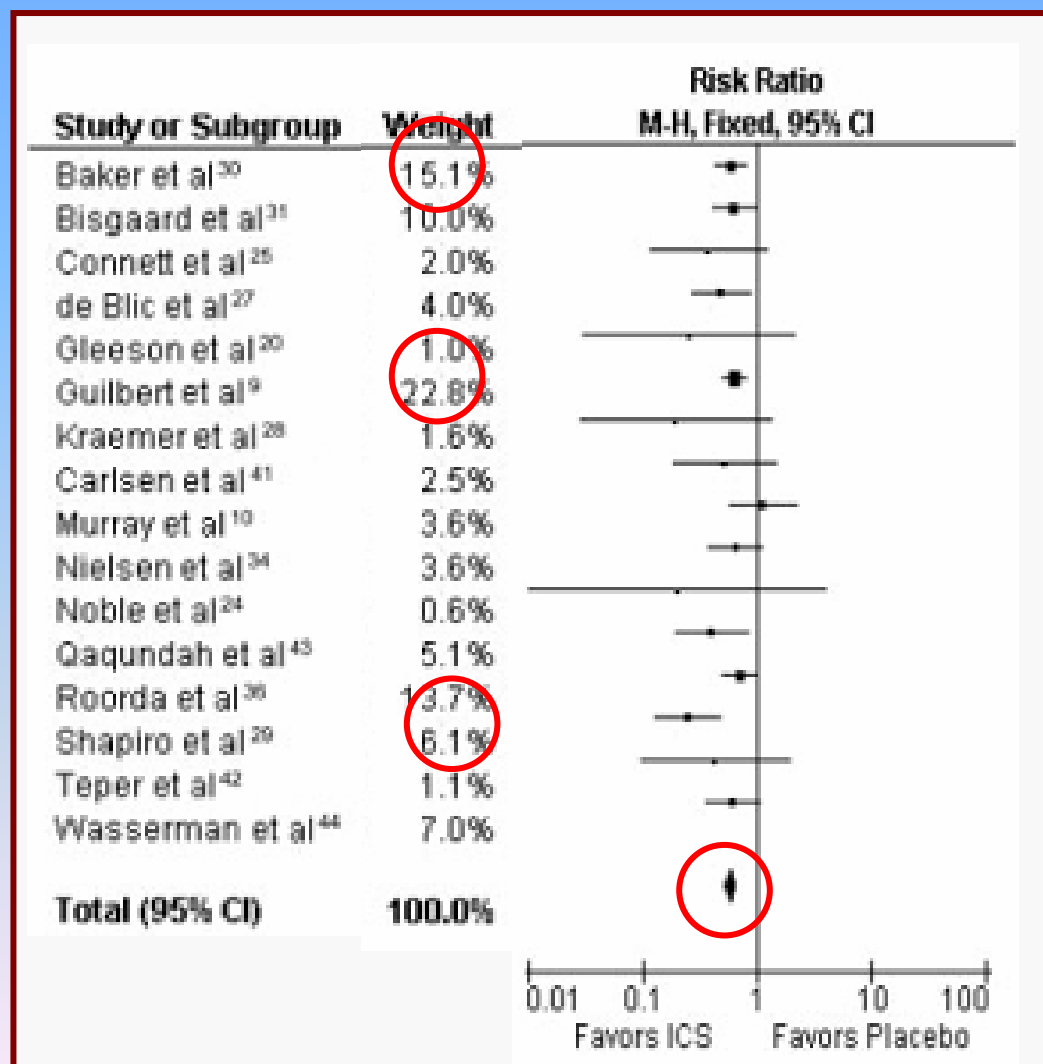
The available literature on treatment of asthma in children 5 years and younger precludes detailed treatment recommendations. The best documented treatment to control asthma in these age groups is inhaled glucocorticosteroids and at Step 2, a low-dose inhaled glucocorticosteroid is recommended as the initial controller treatment. Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in Chapter 3 (Figure 3-4).

The clinical benefits of intermittent systemic or inhaled glucocorticosteroids for children with intermittent, viral-induced wheeze remain controversial. While some studies in older children have found small benefits, a study in young children found no effects on wheezing symptoms. There is no evidence to support the use of maintenance low-dose inhaled glucocorticosteroids for preventing transient early wheezing.

**Leukotriene modifiers:** Clinical benefits of monotherapy with leukotriene modifiers have been shown in children older than age 2. Leukotriene modifiers reduce viral-induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma. No safety concerns have been demonstrated from the use of leukotriene modifiers in children.



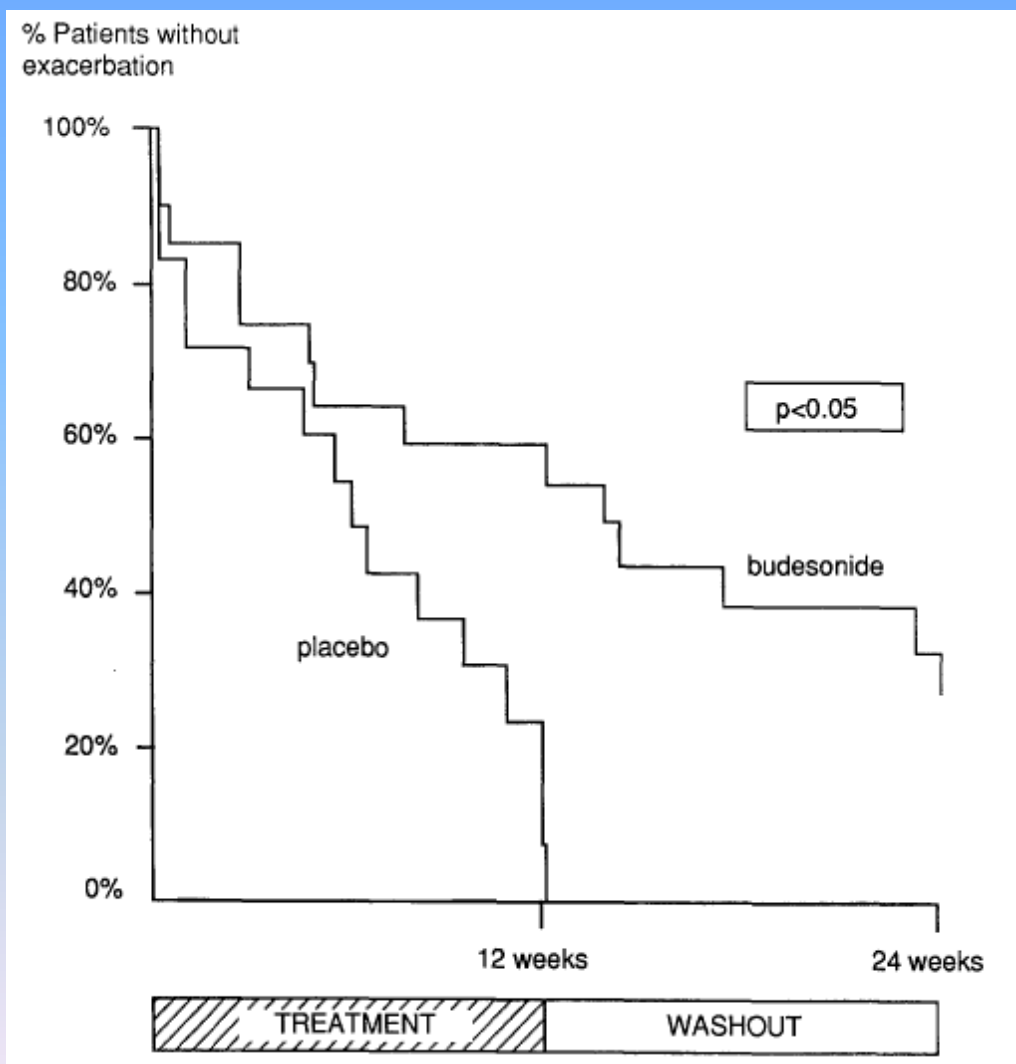
# Efficacy of Inhaled Corticosteroids in Infants and Preschoolers With Recurrent Wheezing and Asthma: A Systematic Review With Meta-analysis



This meta-analysis shows that ICSs are useful in infants and preschoolers with persistent wheeze/asthma in reducing exacerbations and withdrawals caused by exacerbations as compared with placebo.



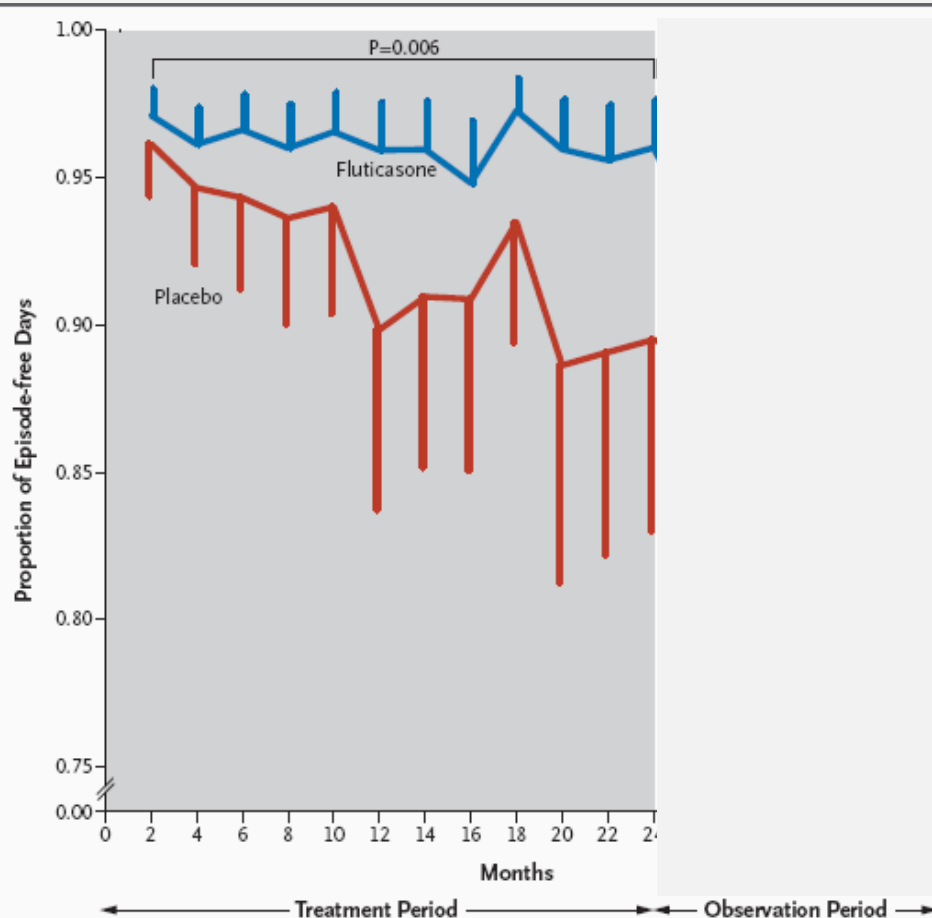
# Inhaled steroids in infants



de Blic J. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol. 1996; 98:14-20



# ICS control but do not cure the disease



285 preschool kids  
with wheeze and  
high asthma risk  
Index

Guilbert TW. Long-term  
inhaled corticosteroids in  
preschool children at  
high risk for asthma. N  
Engl J Med 2006;354:  
1985-97





## Does early use of inhaled corticosteroids prevent long term

- ICS influence

- Gupte S, Szekely A, et al. Intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life. *Arch Dis Child* 1997; 76:100-104

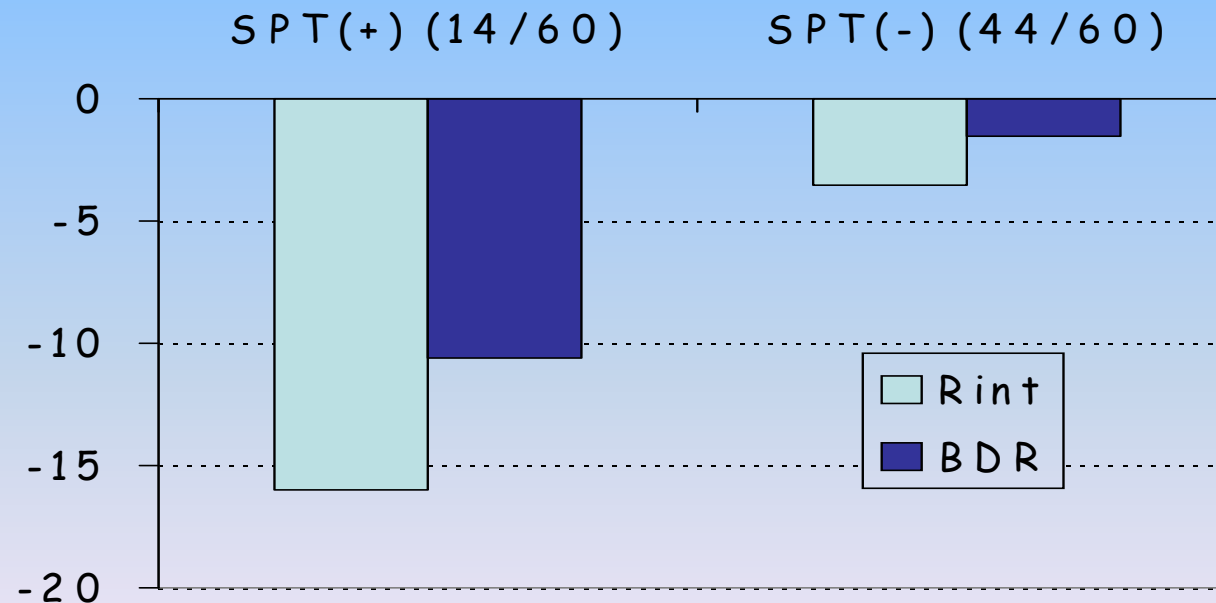
- Murray CS, von Steyern A, et al. Secondary prevention of wheezing with inhaled Fluticasone propionate in Wheezing Infants (WIFI): double-blind, randomised, controlled study. *Lancet* 2006; 368:754-62.

- Bisgaard H, Hermansen MN, Leand L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; 354:1998-2005



## Steroid improvement only in atopic children

- 61 children with intermittent wheeze
- Fluticasone or placebo for 16 weeks
- Measurement of airway resistance (Rint), bronchodilator responsiveness (BDR)



Pao CS, McKenzie SA. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med*. 2002; 166:945-9



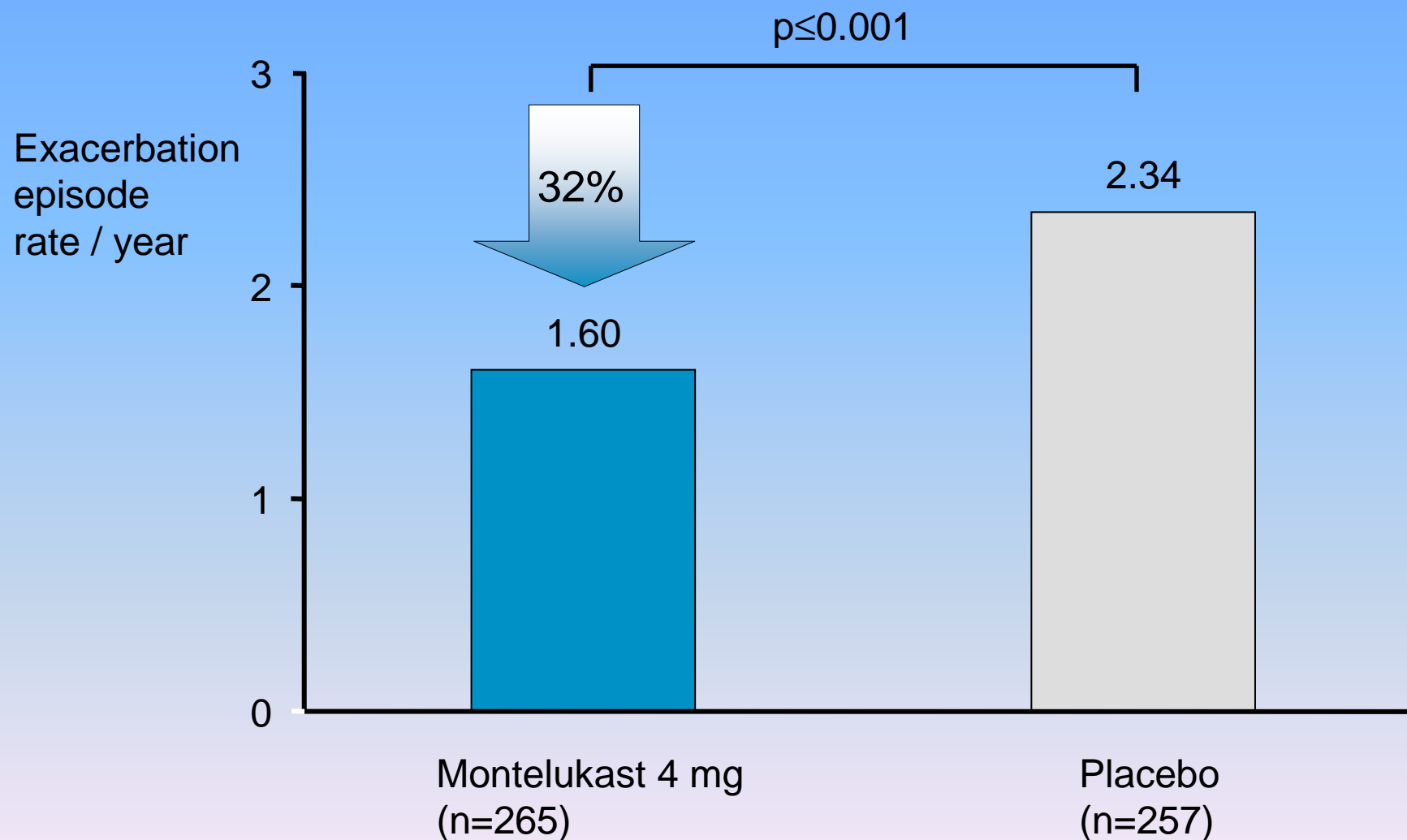
# PREventing Virus-Induced Asthma

- 549 children
- Aged 2 to 5 years
- Intermittent asthma symptoms from common cold
- 1-week screening period
- 2-week, single-blind, placebo run-in period
- 48-week, double-blind active treatment period
- Montelukast 4-mg chewable tablet or placebo

Bisgaard H. Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma. AJRCCM 2005; 171:315-22



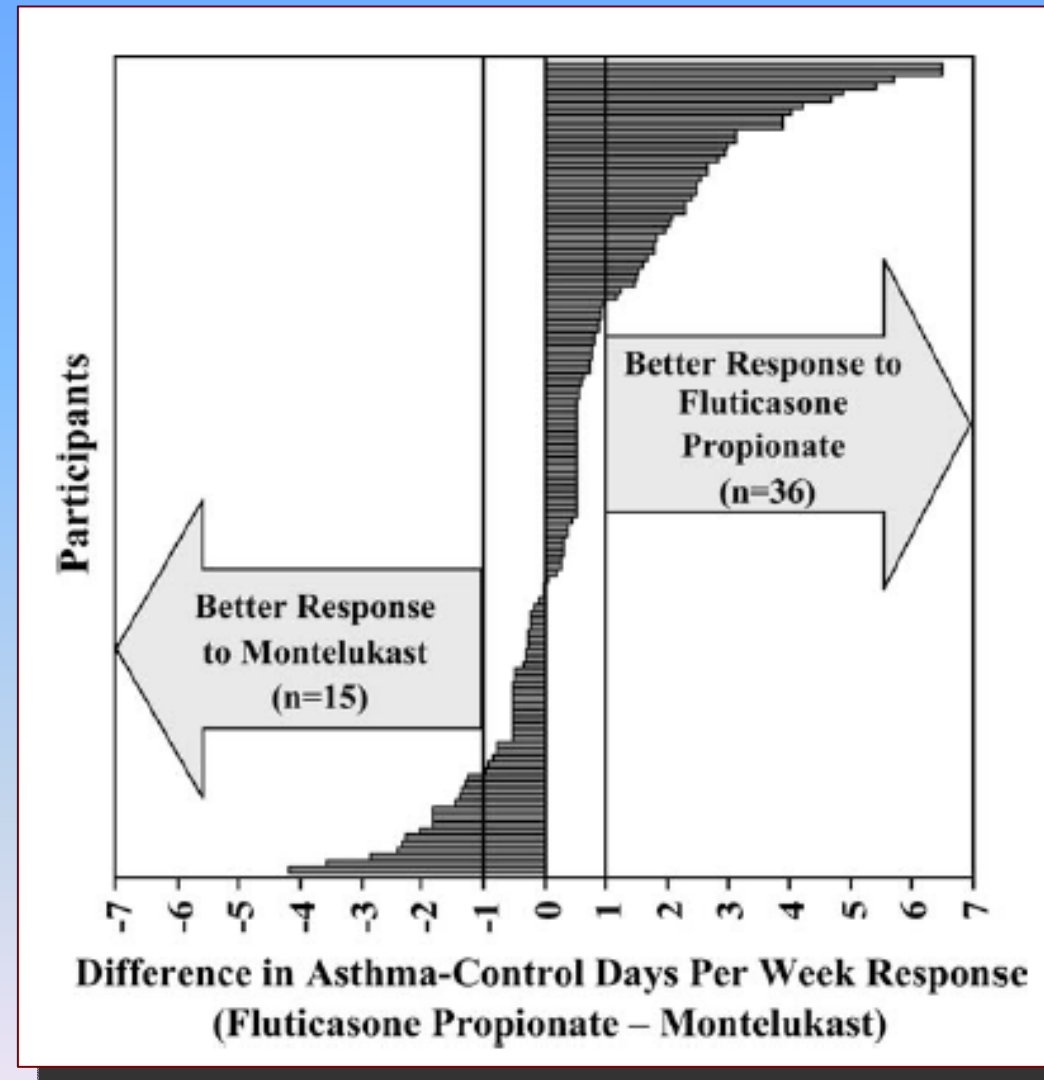
## Montelukast reduces asthma exacerbations in 2-to 5-year-old children with intermittent asthma



Bisgaard H. Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma. *AJRCCM* 2005;171:315-22



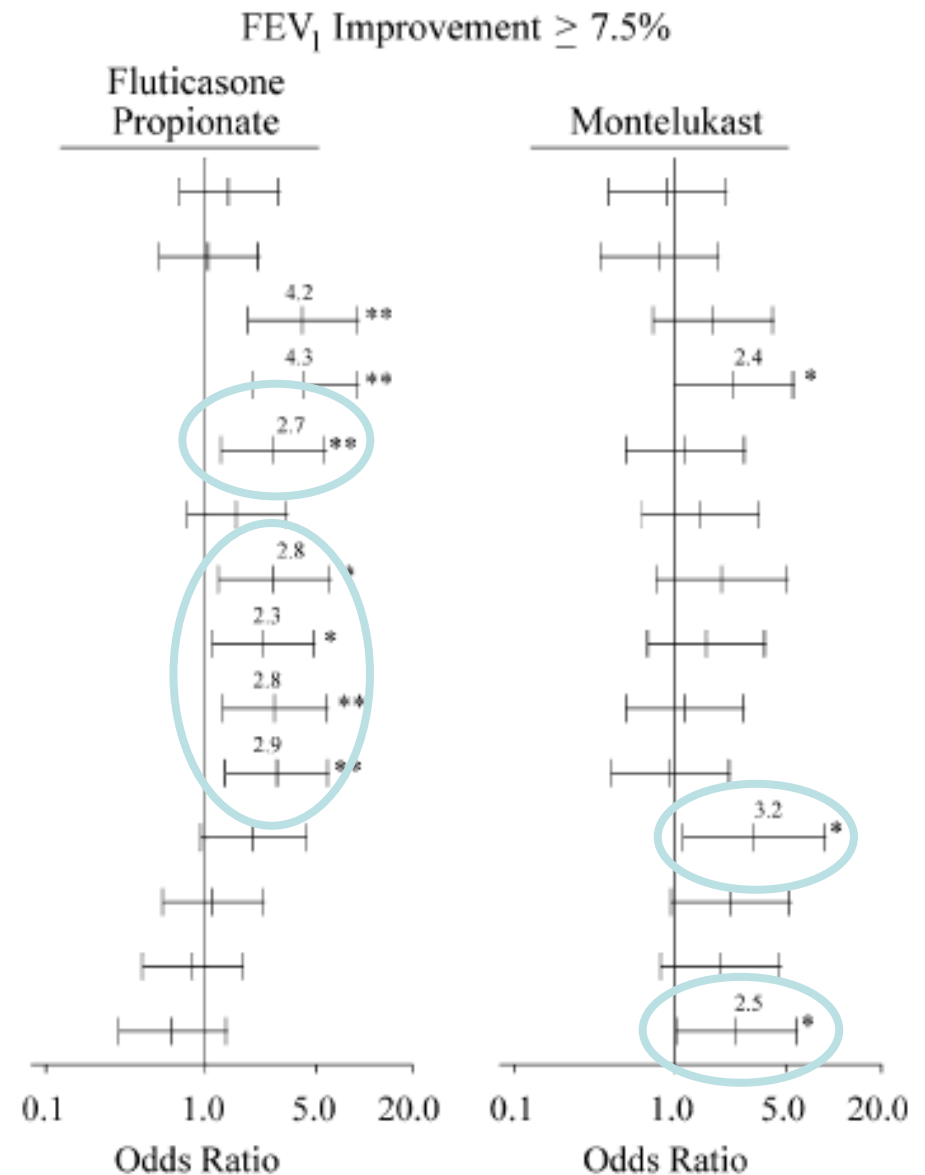
## Different response profiles



Zeiger RS. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol.* 2006;117:45-52



Baseline Characteristic (N, %)
Bronchodilator use > 4 puffs/week (65, 52%)
Asthma-free days $\leq$ 2 days/week (68, 54%)
Pre-bronchodilator FEV <sub>1</sub> % predicted < 90% (41, 33%)
Pre-bronchodilator FEV <sub>1</sub> /FVC < 80% (51, 40%)
Methacholine PC <sub>20</sub> $\leq$ 1 mg/ml (54, 45%)
Maximum bronchodilator response > 15% (58, 46%)
Exhaled nitric oxide > 25 ppb (61, 55%)
Blood total eosinophil count > 350 cells/mm <sup>3</sup> (51, 41%)
Serum eosinophilic cationic protein > 15 mcg/L (68, 54%)
Serum IgE > 200 kU/L (55, 44%)
Urinary leukotriene E4 > 100 pg/mg creatinine (59, 50%)
Female gender (52, 41%)
Minority (60, 48%)
Age < 10 (84, 67%)



Zeiger RS. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006;117:45-52



# Step-up Therapy for Children with Uncontrolled Asthma

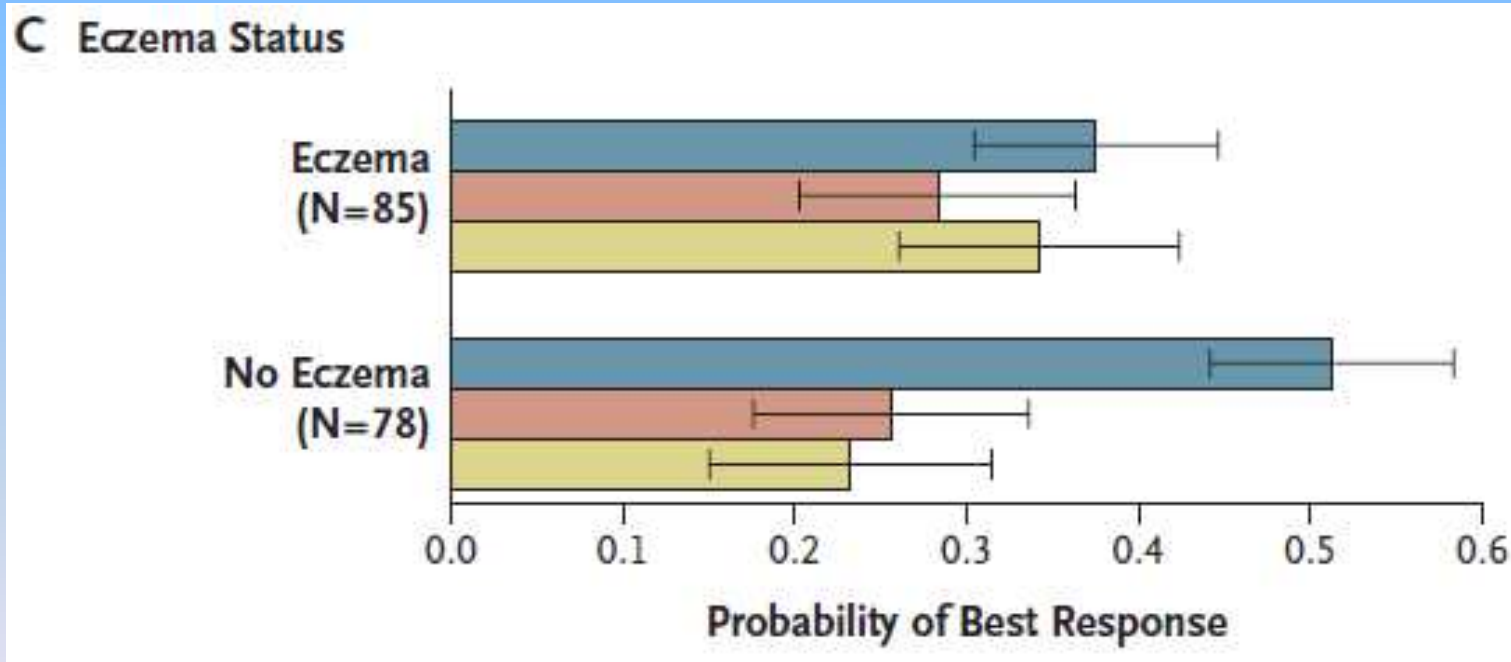
LABA ICS LTRA

ICS step-up, 250 µg fluticasone twice daily

LABA step-up, 100 µg fluticasone plus 50 µg LABA twice daily

LTRA step-up, 100 µg fluticasone twice daily plus 5 or 10 mg MK

157 children 6-12, asthma not controlled despite FP100 µg/die:



Lemanske RL. Step-up Therapy for Children with Uncontrolled Asthma while Receiving Inhaled Corticosteroids. NEJM 2010; 362:975-85



# Step-up Therapy for Children with Uncontrolled Asthma

ICS step-up, 250 µg fluticasone twice daily

LABA step-up, 100 µg fluticasone plus 50 µg LABA twice daily

LTRA step-up, 100 µg fluticasone twice daily plus 5 or 10 mg MK

157 children 6-12, asthma not controlled despite FP100 µg/die:

Although LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up, many children had a best response to ICS or LTRA step-up, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy within this level of care before further step-up.

Lemanske RL. Step-up Therapy for Children with Uncontrolled Asthma while Receiving Inhaled Corticosteroids. NEJM 2010; 362:975-85



# Options for children < 5 years



Bacharier LB, Boner A, Carlsen K-H, Eigenmann, PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills TAE, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. The European Pediatric Asthma Group. Allergy 2008; 63:5–34



# Options for children 0 to 2 Years

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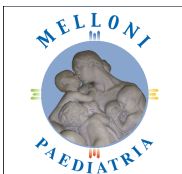
- Asthma ~ >3 episodes in the previous 6 months
  - Start with  $\beta_2$  agonists as first choice
- LTRA daily controller therapy for virus induced asthma symptoms
- Inhaled steroids for persistent wheezing, especially if severe or requiring frequent oral corticosteroid therapy
- Oral steroids (e.g. 1–2 mg/kg prednisone) for 3–5 days during acute and frequently recurrent obstructive episodes
- Evidence of atopy lowers the threshold for use of ICS and they may be used as first-line treatment in such cases

Bacharier LB, Boner A, Carlsen K-H, Eigenmann, PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills TAE, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. The European Pediatric Asthma Group. Allergy 2008; 63:5–34



## treating childhood asthma

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## Preemptive use of high-dose fluticasone for virus-induced wheezing in young children

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**In FP treated children:**

**-symptoms milder and of shorter duration;**

**-fewer days of albuterol use**

**-less negative effect on their parents' quality of life.**

Treatment with rescue systemic corticosteroids in upper respiratory infections

OR 0.49

8%

Placebo

Fluticasone

Ducharme FM. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med. 2009;360:339-53

AT AGE 6 YRS

Courtesy of Attilio Boner



## Preemptive use of high-dose fluticasone for virus-induced wheezing in young children

- 129

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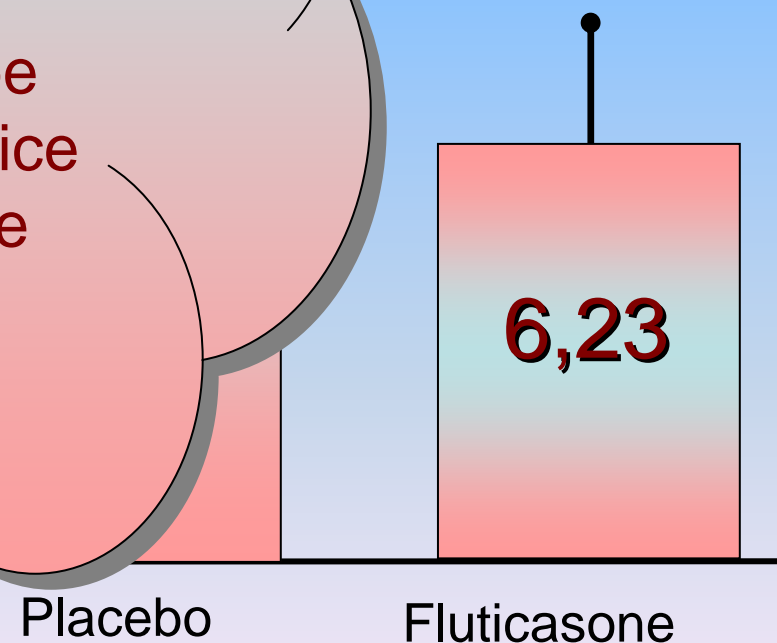
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Given the potential  
for overuse,  
this preventive  
approach should not be  
adopted in clinical practice  
until long-term adverse  
effects are clarified

gains from baseline in  
height in cm



Ducharme FM. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med. 2009;360:339-53

AT AGE 6 YRS

Courtesy of Attilio Boner

# Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma

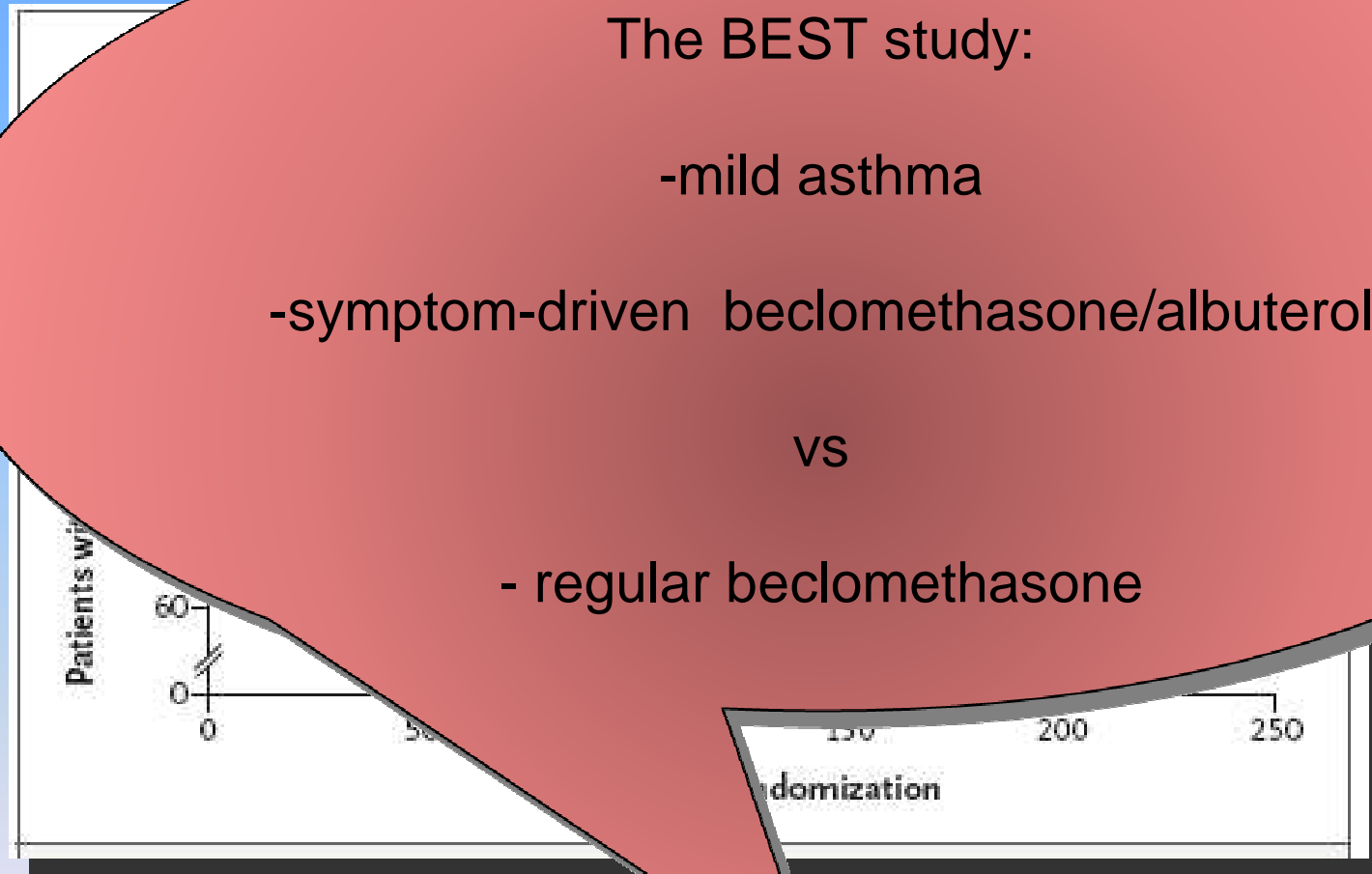
The BEST study:

-mild asthma

-symptom-driven beclomethasone/albuterol

VS

- regular beclomethasone



Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM; BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007;356:2040-52





## the best for children

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A word of caution for caregivers ready to apply this important research in children under eighteen years of age may not be unnecessary!

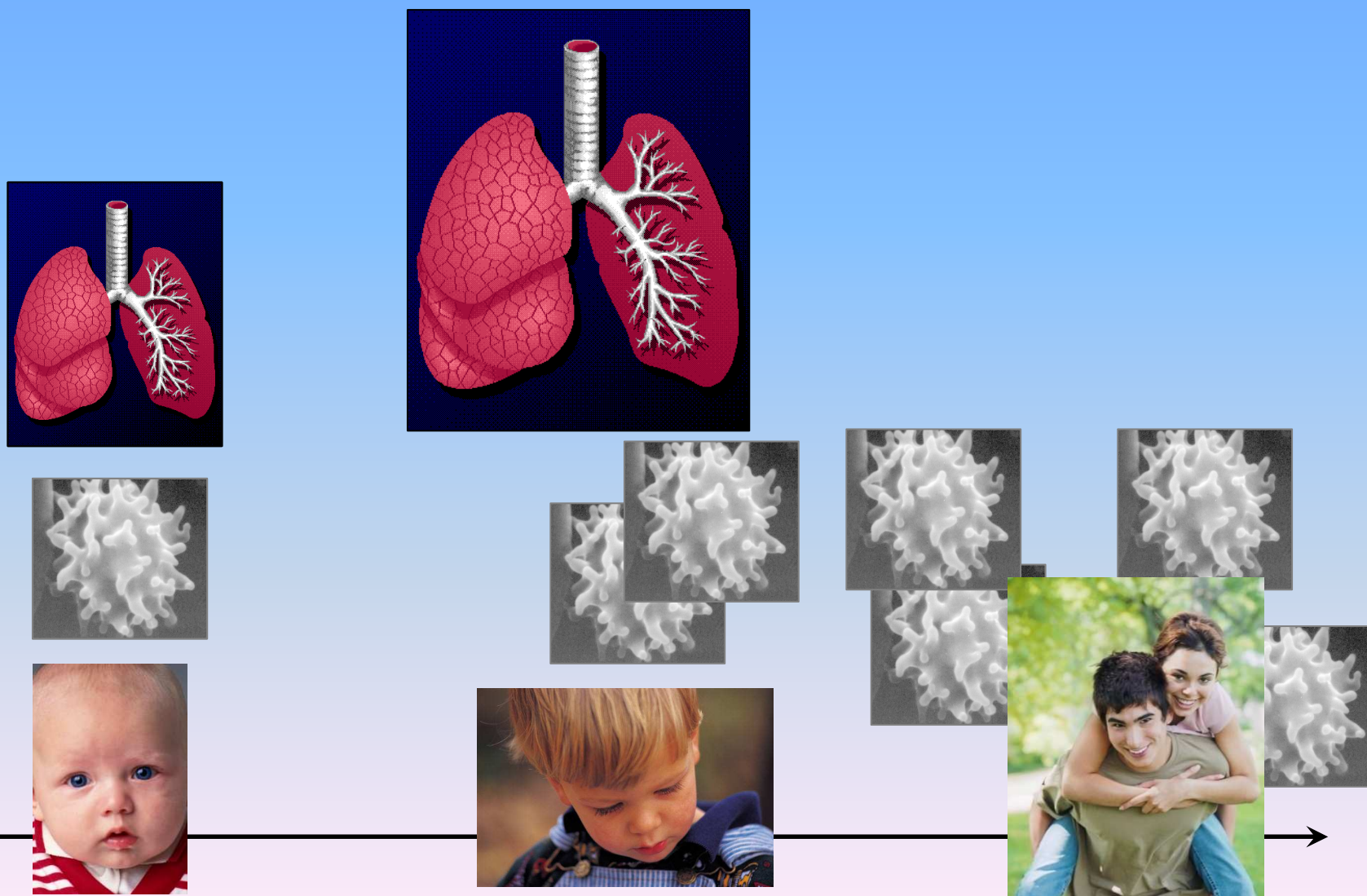
ate as primary outcome  
ong children with mild

which affects treatment  
be accounted for

of tissue thickening in  
be measured.

Terracciano L. Beclomethasone and albuterol in mild asthma (letter).  
N Engl J Med 2007; 357:506-7

# Lung growth



## Original article

# Regular vs prn nebulized treatment in wheeze preschool children

**Background:** International guidelines recommend regular treatment with inhaled glucocorticoids for children with frequent wheezing; however, prn inhaled bronchodilator alone or in combination with glucocorticoid is also often used in practice. We aimed to evaluate whether regular nebulized glucocorticoid plus a prn bronchodilator or a prn nebulized bronchodilator/glucocorticoid combination is more effective than prn bronchodilator alone in preschool children with frequent wheeze.

**Methods:** Double-blind, double-dummy, randomized, parallel-group trial. After a 2-week run-in period, 276 symptomatic children with frequent wheeze, aged 1–4 years, were randomly assigned to three groups for a 3-month nebulized treatment: (1) 400 µg beclomethasone bid plus 2500 µg salbutamol prn; (2) placebo bid plus 800 µg beclomethasone/1600 µg salbutamol combination prn; (3) placebo bid plus 2500 µg salbutamol prn. The percentage of symptom-free days was the primary outcome measure. Secondary outcomes included symptom scores, use of relief medication and exacerbation frequency.

**Results:** As compared with prn salbutamol ( $61.0 \pm 24.83$  [SD]), the percentage of symptom-free days was higher with regular beclomethasone (69.6%, SD 20.89;  $P = 0.034$ ) but not with prn combination (64.9%, SD 24.74). Results were no different in children with or without risk factors for developing persistent asthma. The effect of prn combination was no different from that of regular beclomethasone on the primary and on several important secondary outcomes.

**Conclusions:** Regular inhaled glucocorticoid is the most effective treatment for frequent wheezing in preschool children. However, prn bronchodilator/glucocorticoid combination might be an alternative option, but it requires further study.

**A. Papi<sup>1</sup>, G. Nicolini<sup>2</sup>, E. Baraldi<sup>3</sup>,  
A. L. Boner<sup>4</sup>, R. Cutrera<sup>5</sup>, G. A. Rossi<sup>6</sup>,  
L. M. Fabbri<sup>7</sup>, on behalf of the  
BEclomethasone and Salbutamol  
Treatment (BEST) for Children Study  
Group**

<sup>1</sup>Department of Respiratory Diseases, Research Center on Asthma and COPD, University of Ferrara, Ferrara, Italy; <sup>2</sup>Medical Department, Chiesi Farmaceutici, Parma, Italy; <sup>3</sup>Department of Pediatrics, Unit of Allergy and Respiratory Medicine, University of Padova, Padova, Italy; <sup>4</sup>Department of Pediatrics, University of Verona, Verona, Italy; <sup>5</sup>Respiratory Unit, Department of Pediatrics, Ospedale Pediatrico Bambino Gesù, Rome, Italy; <sup>6</sup>Department of Pediatrics, Ospedale Gaslini, Genova, Italy; <sup>7</sup>Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy

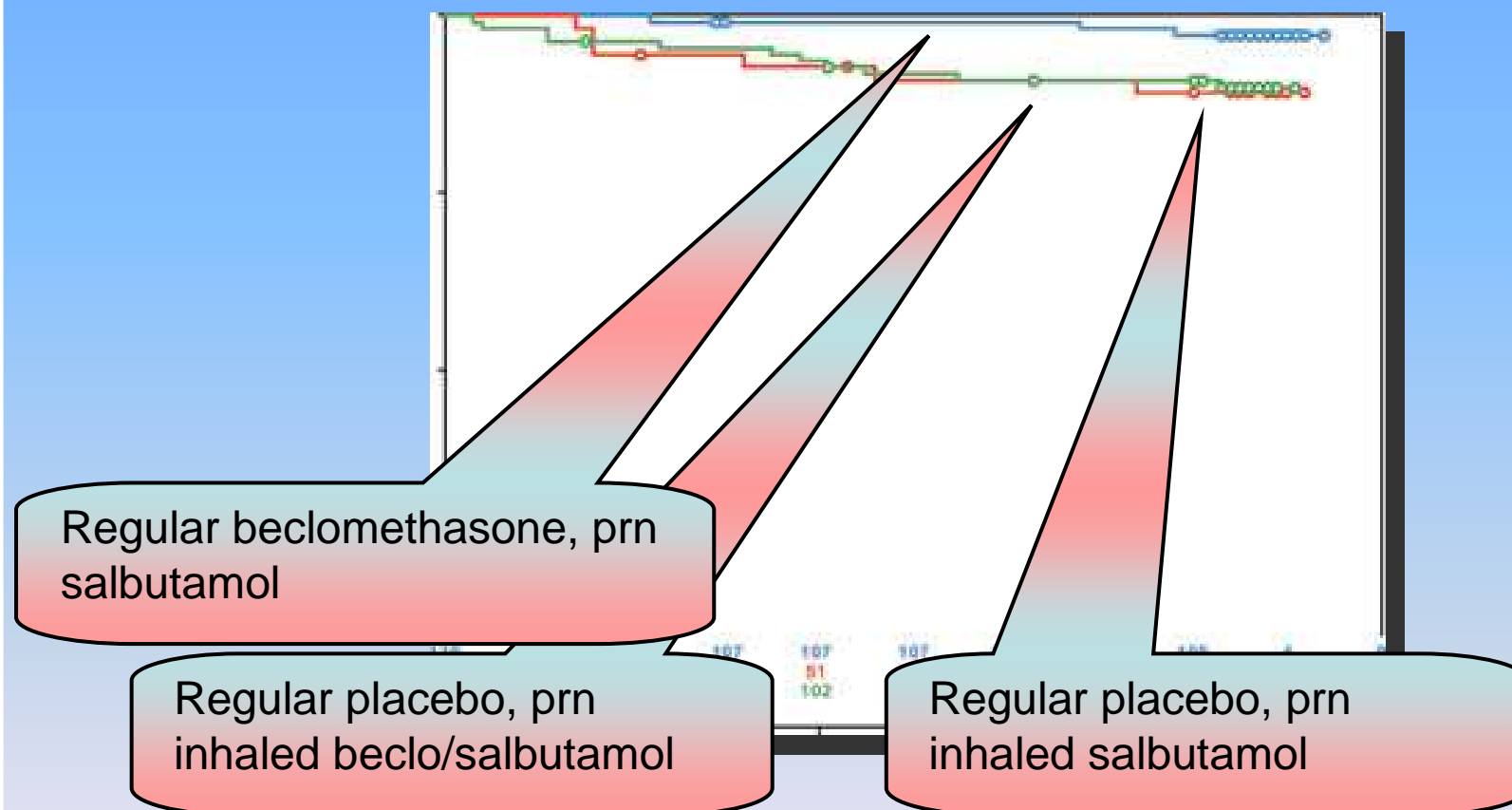
Key words: asthma; as needed; beclomethasone; salbutamol; wheezing.

L. M. Fabbri  
Department of Respiratory Diseases  
University of Modena and Reggio Emilia  
Via del Pozzo, 71  
41100 Modena  
Italy

Accepted for publication 28 May 2009



# Kaplan–Meier estimates of the time to first asthma exacerbation in the intention-to-treat population.



Papi A, BEST Study Group. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 2009; 64: 1463–1471





# Regular vs prn nebulized treatment in wheeze preschool children

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Papi A, BEST Study Group. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy* 2009; 64: 1463–1471



# Beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA)

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- A 44-week, randomised, double-blind, placebo-controlled trial
- 5-18 years, mild persistent asthma
- four groups:
  - a. Combined group: beclomethasone x 2; rescue beclomethasone + albuterol
  - b. Daily beclomethasone group: beclomethasone x 2; rescue albuterol
  - c. Rescue beclomethasone group: placebo x 2; rescue beclomethasone + albuterol
  - d. Placebo group: placebo x 2; rescue albuterol

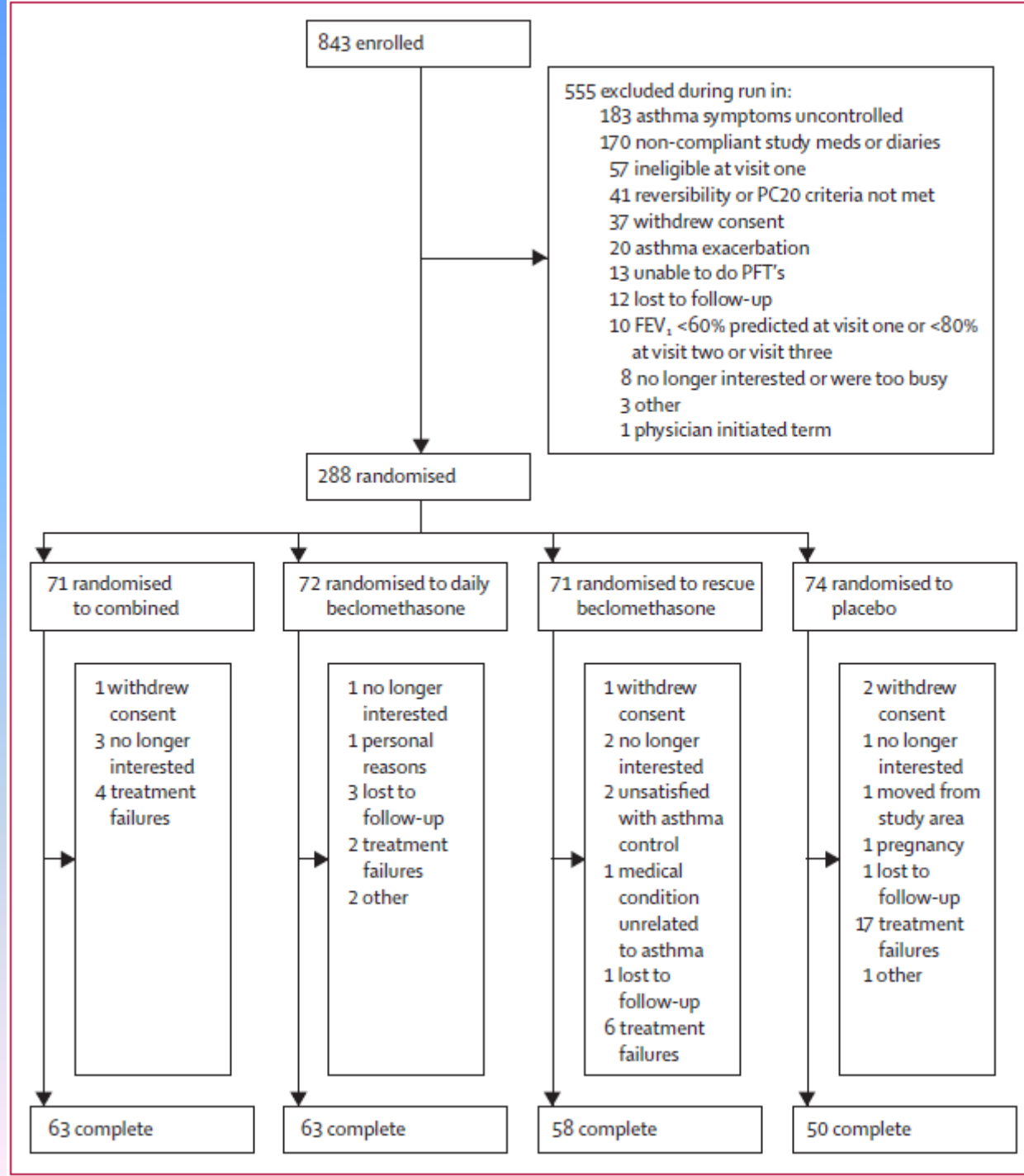
Primary outcome: time to first exacerbation requiring oral corticosteroids

Also measured: linear growth.

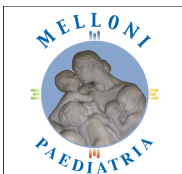
Martinez FD. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial Lancet 2011; 377: 650–57



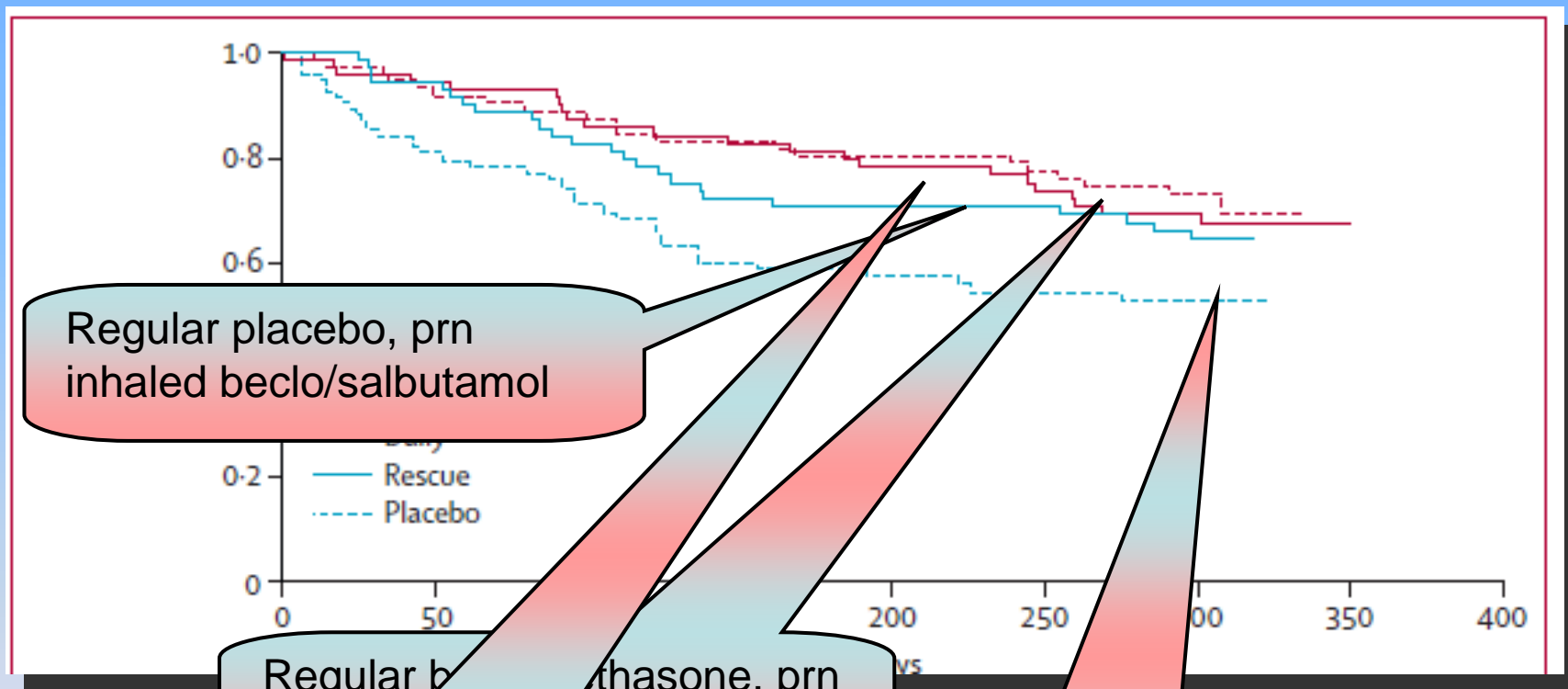
# Beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA)



Martinez FD. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial *Lancet* 2011; 377: 650–57



# Beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA)



Regular placebo, prn inhaled beclo/salbutamol

Regular beclomethasone, prn inhaled beclo/salbutamol

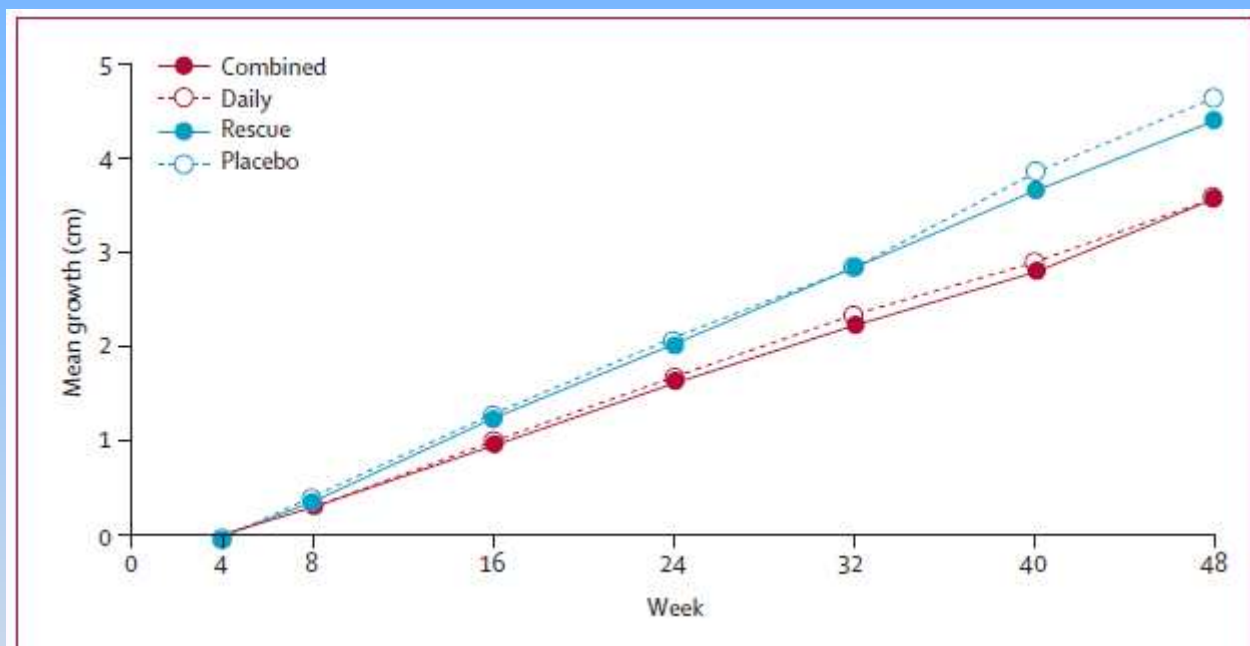
Regular beclomethasone, prn inhaled salbutamol

Regular placebo, prn inhaled salbutamol

for children with mild persistent asthma

blind, placebo-controlled, randomised trial, 2000-57

# TREXA: linear growth by treatment group



Martinez FD. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial *Lancet* 2011; 377: 650–57



# Beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA)

---

1. Children with mild persistent asthma should not be treated with rescue albuterol alone
2. The most effective treatment is daily inhaled corticosteroids
3. Inhaled corticosteroids as rescue medication with albuterol an effective step-down strategy for children with well controlled, mild asthma
4. Daily inhaled corticosteroid treatment can cause growth impairment

Martinez FD. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial Lancet 2011; 377: 650–57



## Oral steroids in acute virus-induced wheezing

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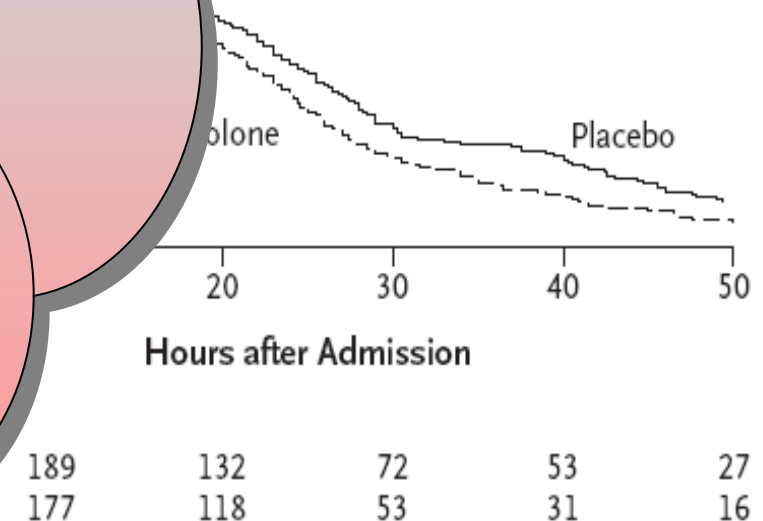
Sec  
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Assessme

albuterol use,  
symptom score

No justification for the administration of prednisolone to preschoolers without atopy who have episodic (viral) wheezing in either a community or hospital setting unless a severe clinical course is anticipated



Patel et al. J. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med. 2009;360:329-38



## What treatment can be recommended for acute episodic wheezing in preschool children?

$\beta$ 2-Agonists that are inhaled through an appropriate spacer, with a mask if age appropriate, should be given.

Intermittent use of leukotriene receptor antagonists may be beneficial, but comparisons with intermittent inhaled corticosteroids are needed.

Prednisolone should be administered to preschoolers only when they are severely ill in the hospital.

Intermittent, high-dose inhaled corticosteroids should not be used

Bush A. Practice imperfect--treatment for wheezing in preschoolers.  
N Engl J Med. 2009;360:409-10



## treating childhood asthma

1. Asthma guidelines
2. Asthma drugs
3. Controller medications
4. Reliever medications
5. Exercise-induced asthma
6. Conclusions









## EIA treatment: key questions

- T-1. do SABA or LABA develop tachyphylaxis to treatment?
- T-2. does LTRA reduce symptoms/prevent a 10% drop in FEV1?
- T-3. does pre-exercise treatment with ICS reduce symptoms/prevent a 10% drop in FEV1?
- T-4. does pre-exercise treatment with cromoglycate or nedocromil reduce symptoms/prevent a 10% drop in FEV1?
- T-5. does pre-exercise treatment with anticholinergic therapy reduce symptoms/prevent a 10% drop in FEV1?
- T-6. does a refractory period (10 to 15 minute warmup and/or cooldown) reduce symptoms/prevent a 10% drop in FEV1?



## EIA: Short-acting $\beta_2$ -agonists

- Inhaled  $\beta_2$  agonists:
- Protection in 80% to 90% of cases
- Short lived effect (usually about 2 hours)
- Oral  $\beta_2$  agonists:
- Despite the bronchodilator effect, are less efficacious than inhaled drugs in EIA



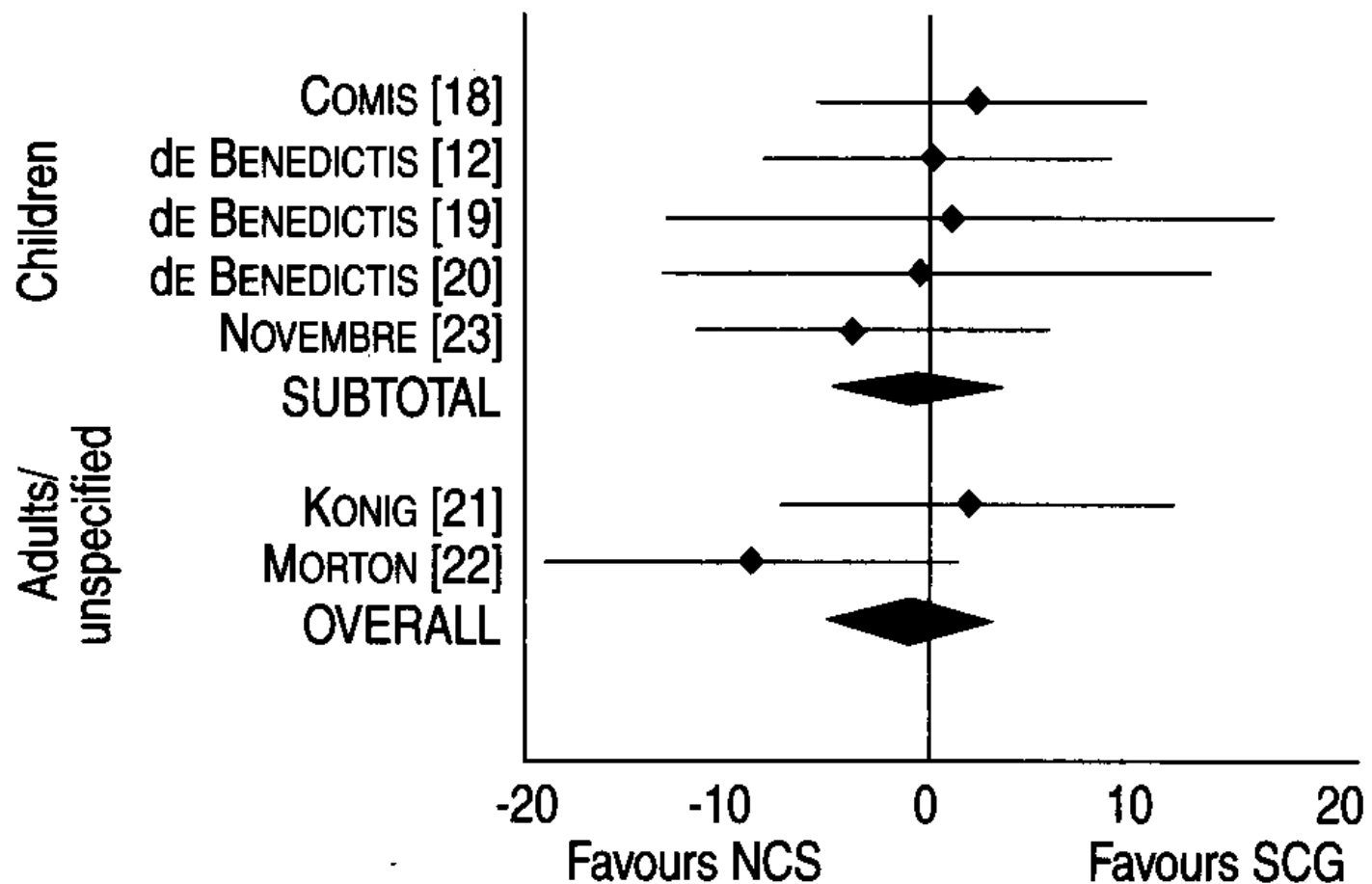
## EIA: Nedocromil vs Cromolyn

- Protective effect in about 60-70% of children
- No difference in the protection
- No difference when administered with or without a spacer
- Duration of the protective effect less than 2 hours

Kelly J. Nedocromil sodium vs sodium cromoglycate in the treatment of treating childhood bronchoconstriction in children. Eur Respir J 2001;17:39-44



## EIA: Nedocromil vs Cromolyn



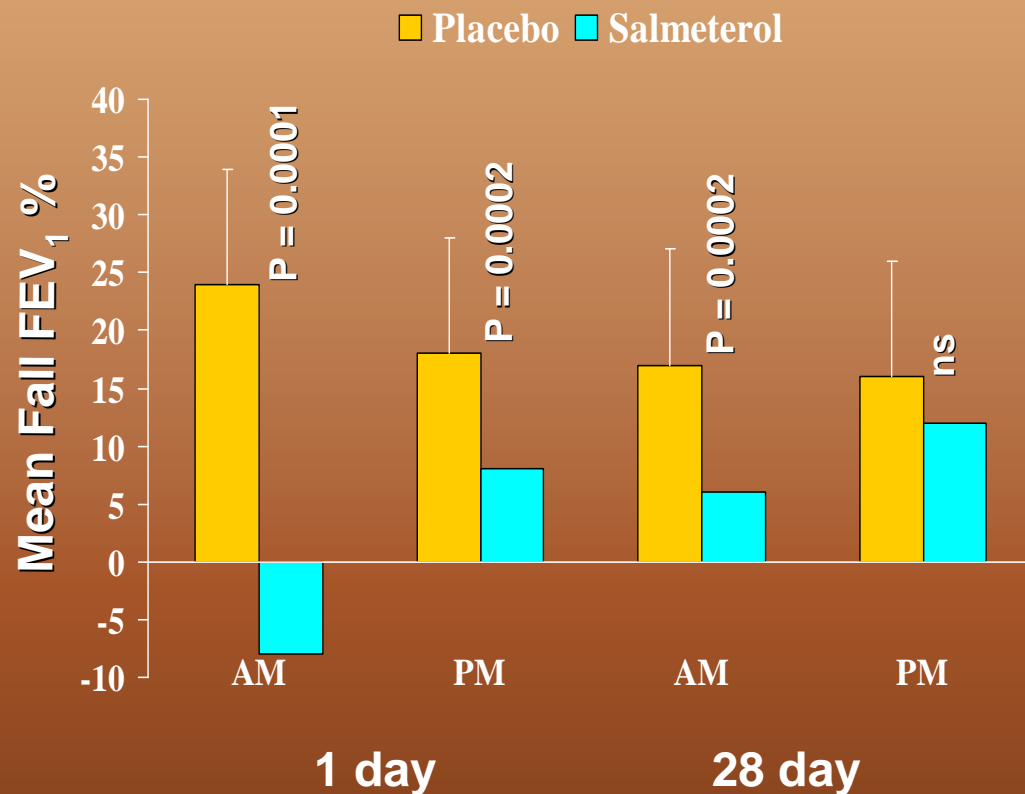
Kelly J. Nedocromil sodium vs sodium cromoglycate in the treatment of treating childhood bronchoconstriction in children. Eur Respir J 2001;17:39-44



## EIA treatment: key questions

1. SIm 50 mcg x 1 vs PI + daily ICS
2. Exercise at 1 and 12 hours after drug inhalation

The duration of the broncho-protective effect decreases during regular treatment with salmeterol despite concomitant use of inhaled steroids

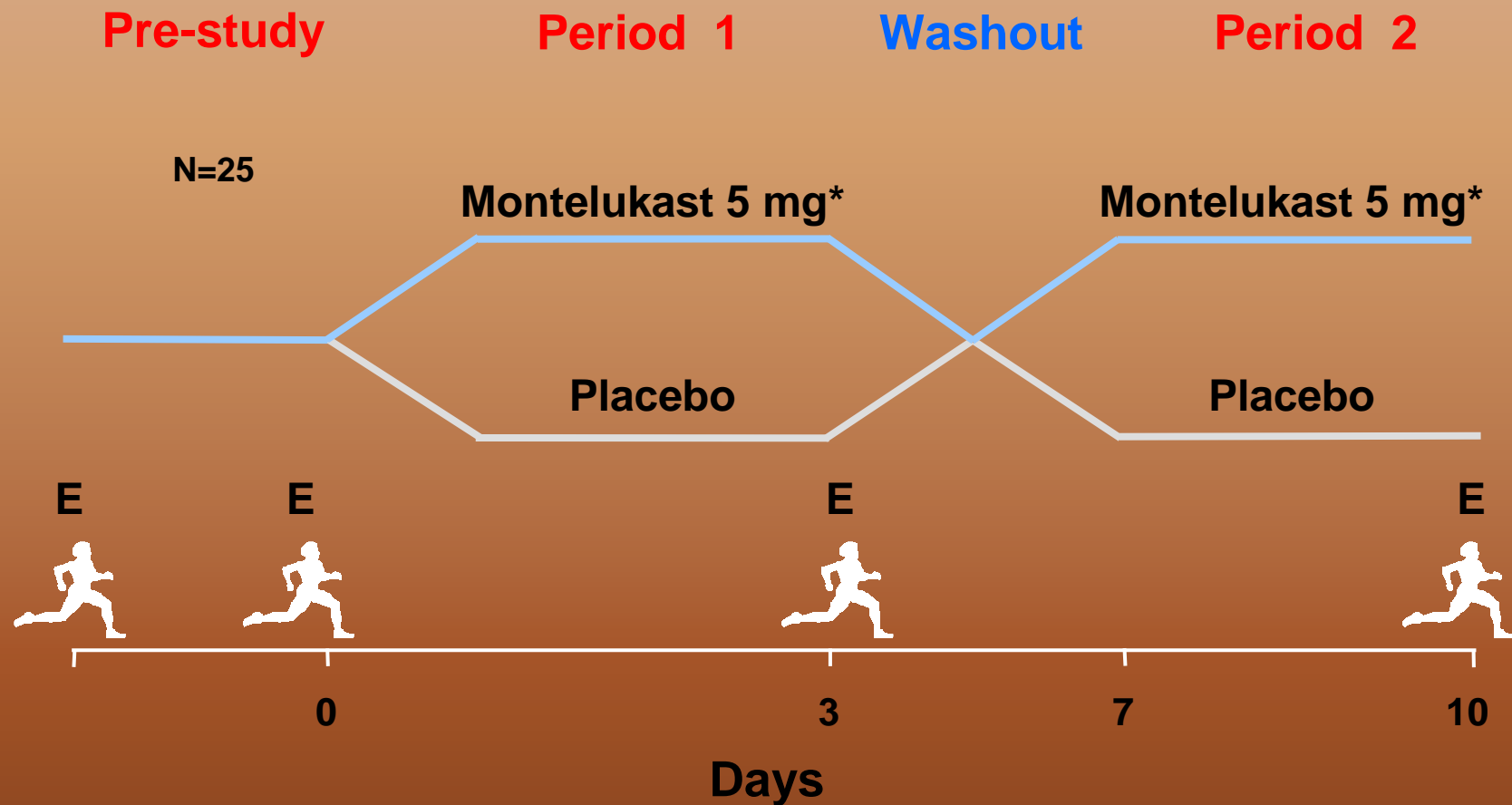


Simons FEM. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise induced asthma. *Pediatrics* 1997;99:665-70





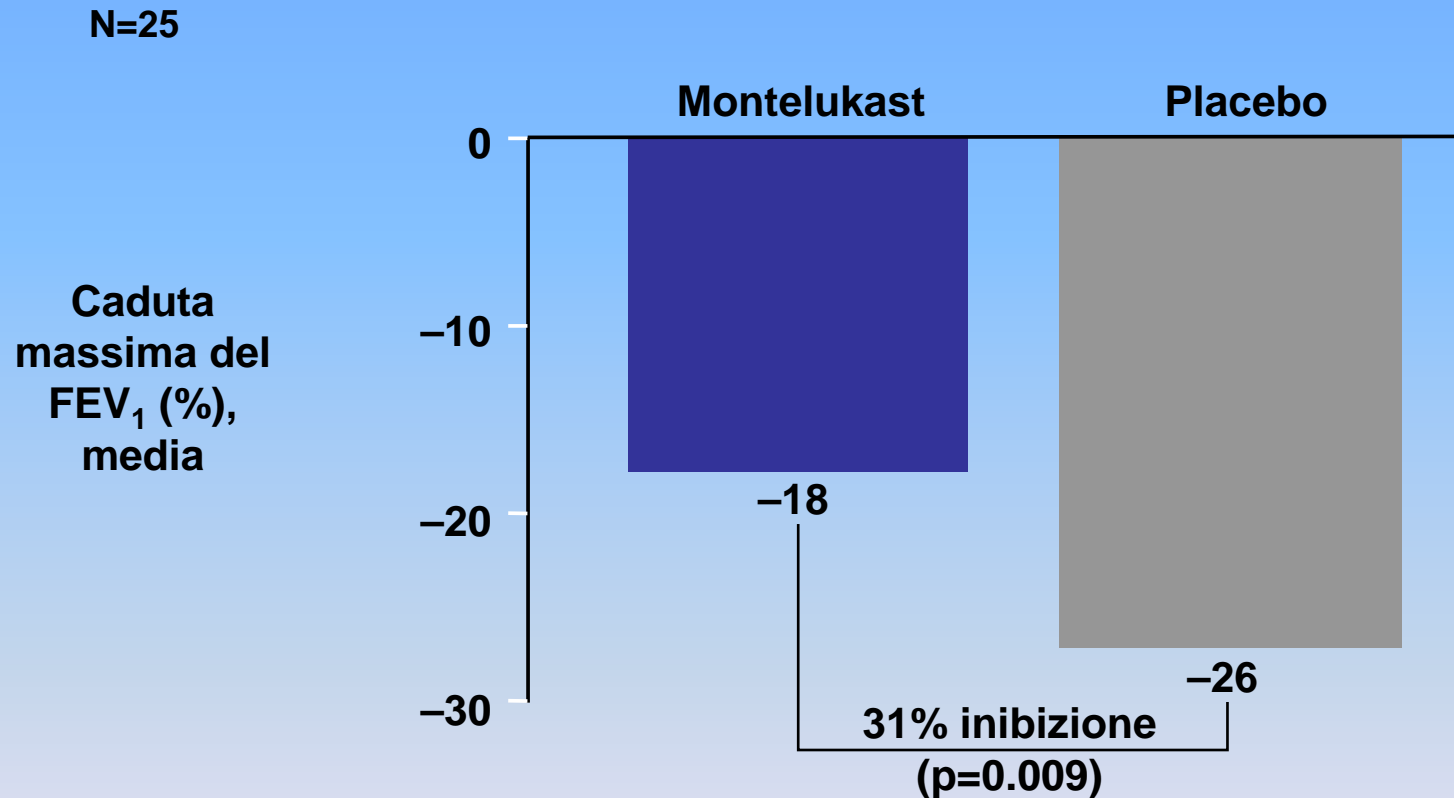
## Montelukast once daily inhibits treating childhood bronchoconstriction in 6- to 14-year-old children with asthma



Kemp JP. Montelukast once daily inhibits treating childhood bronchoconstriction in 6- to 14-year-old children with asthma. J Pediatr. 1998;133:424-8



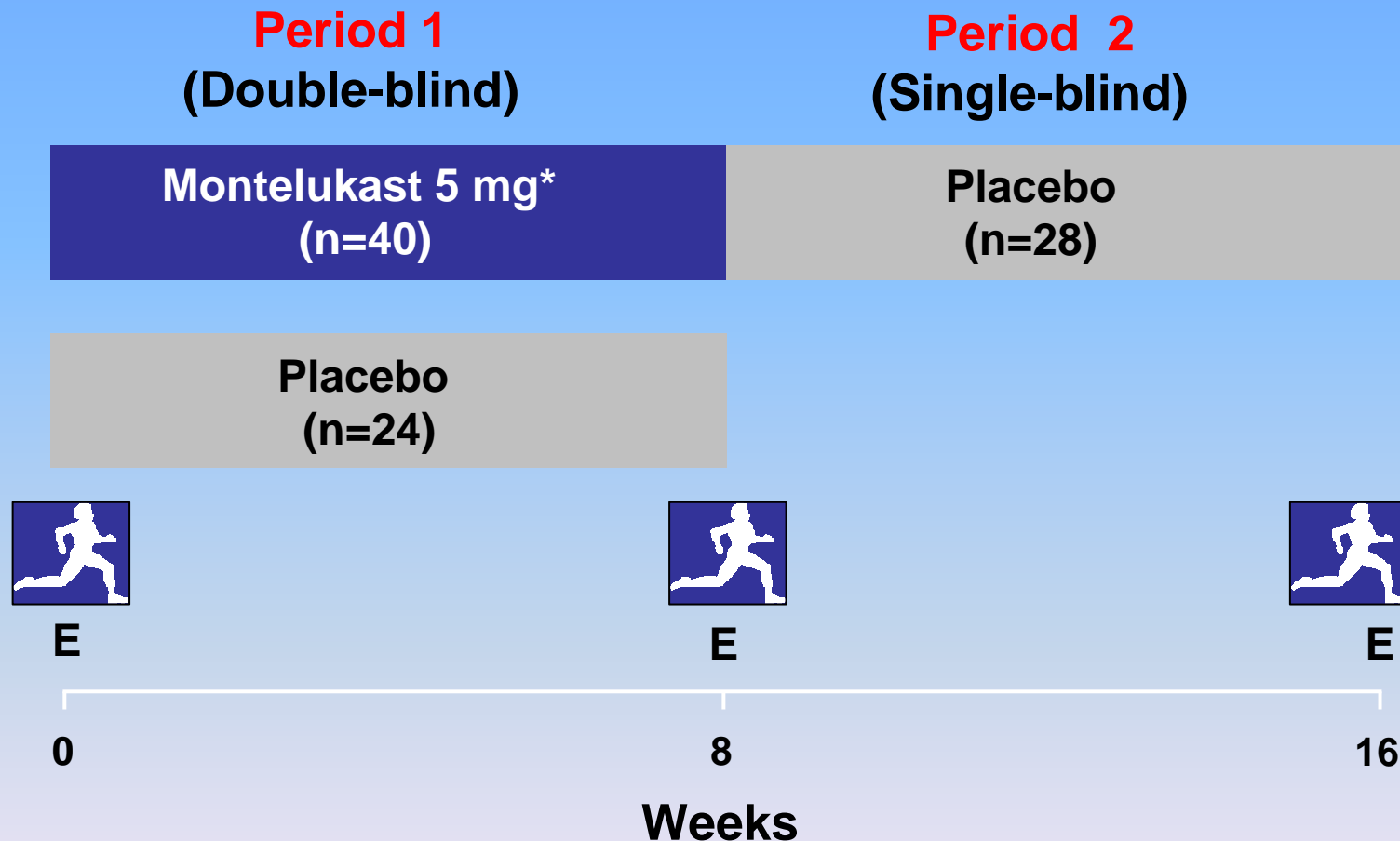
# Montelukast riduce la caduta massima percentuale del FEV<sub>1</sub>



Kemp JP. Montelukast once daily inhibits treating childhood bronchoconstriction in 6- to 14-year-old children with asthma. J Pediatr. 1998;133:424-8



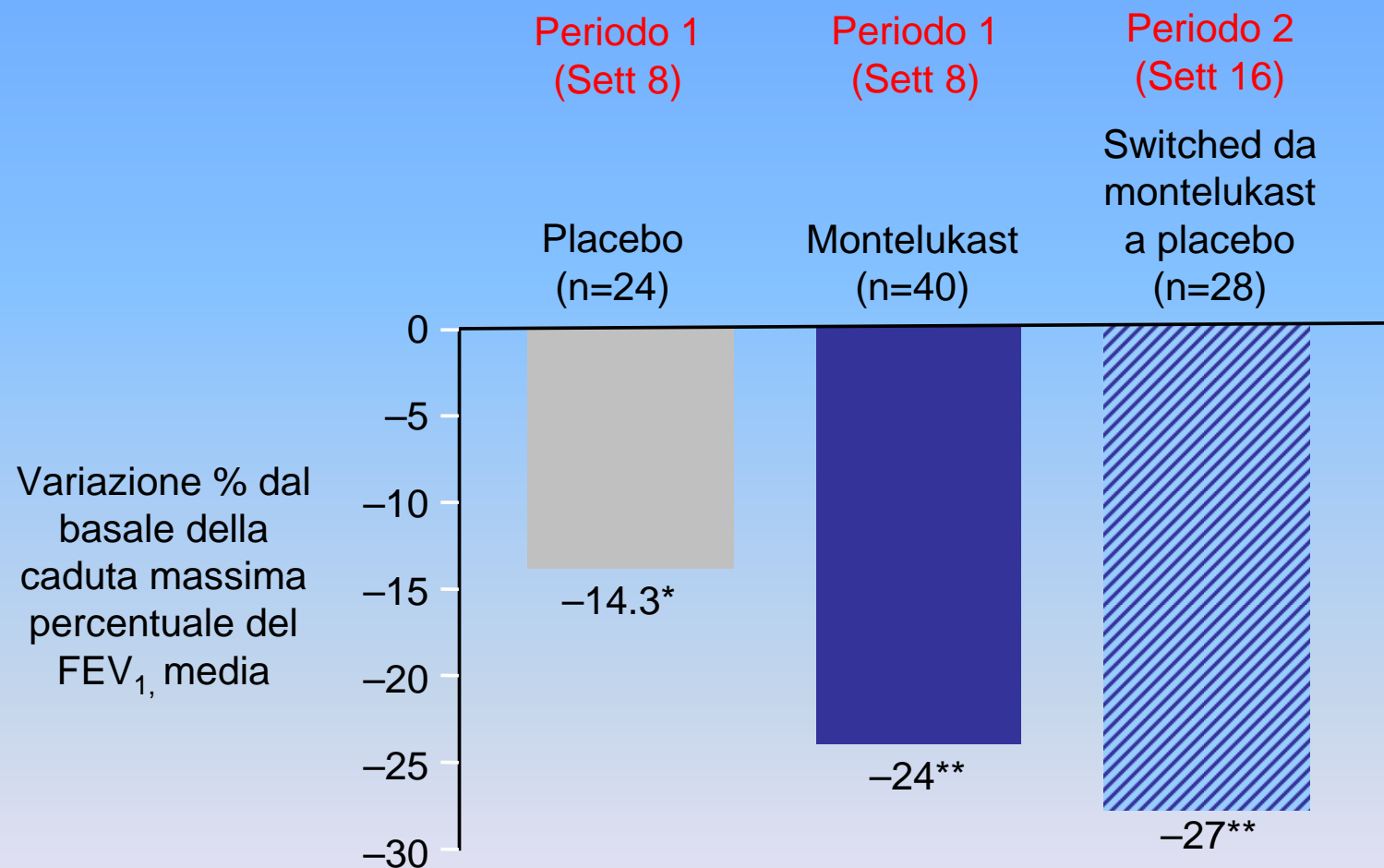
# Prolonged effect of montelukast in asthmatic children with treating childhood bronchoconstriction



Kim JH. Prolonged effect of montelukast in asthmatic children with treating childhood bronchoconstriction. *Pediatr Pulmonol.* 2005;39:162-6.



# Montelukast riduce la caduta massima percentuale del FEV<sub>1</sub>

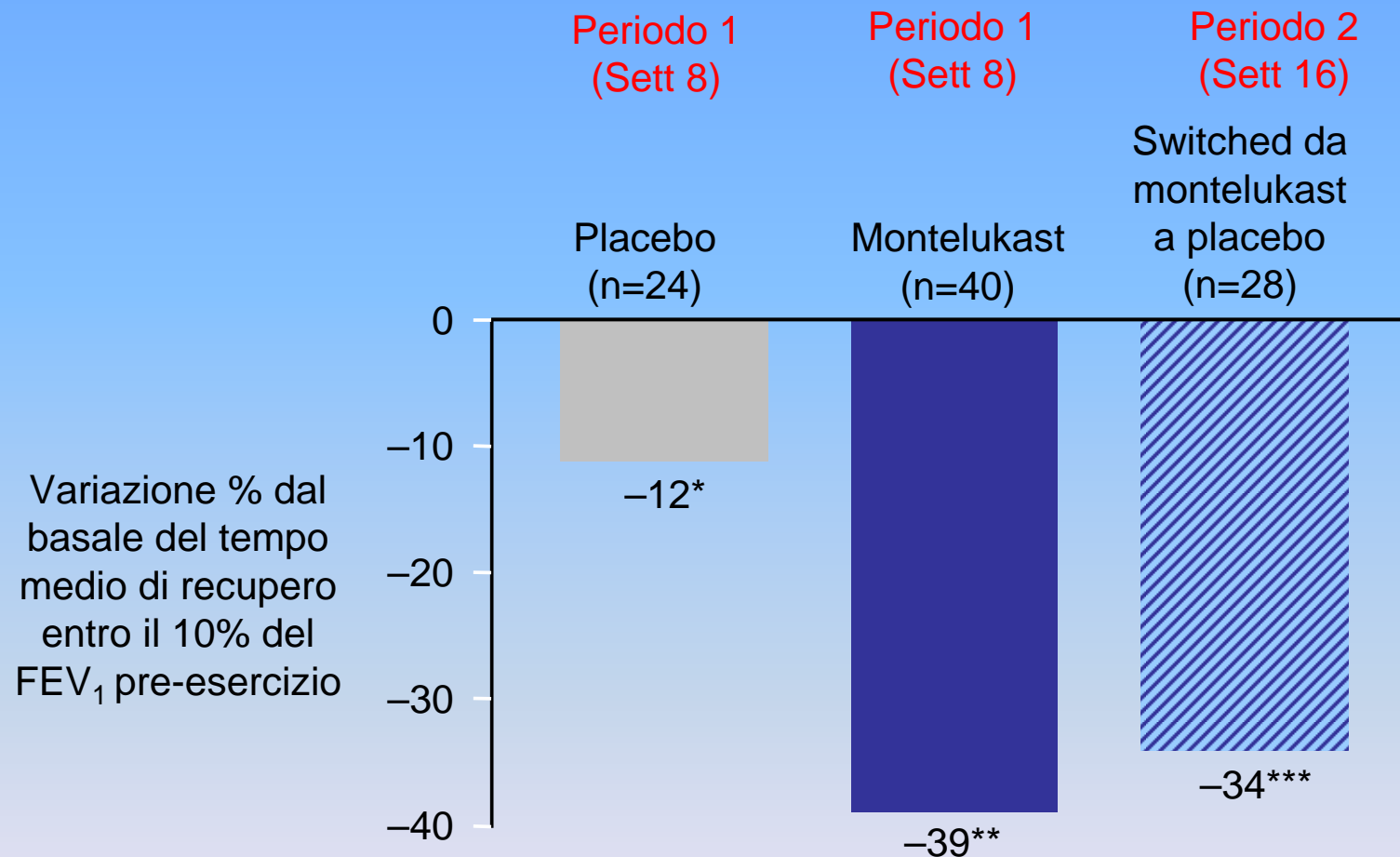


\*p = NS vs basale; \*\*p<0.01 vs basale

Kim JH. Prolonged effect of montelukast in asthmatic children with treating childhood bronchoconstriction. *Pediatr Pulmonol.* 2005;39:162-6.



# Montelukast riduce il tempo di recupero



\*p = NS vs basale; \*\*p<0.01 vs basale; \*\*\*p<0.05 vs basale

Kim JH. Prolonged effect of montelukast in asthmatic children with treating childhood bronchoconstriction. *Pediatr Pulmonol.* 2005;39:162-6.



## Lack of tolerance to the protective effect of montelukast in treating childhood bronchoconstriction in children

- Studio multicentrico, in doppio cieco, randomizzato, controllato con placebo, a gruppi paralleli, su 32 pazienti tra 6 e 12 anni affetti da asma di grado lieve-moderato, con FEV1 pari almeno al 75% di quello previsto e una riduzione del FEV1 di almeno il 12% rispetto al basale dopo un esercizio standardizzato.
- I pazienti sono stati randomizzati a Montelukast 5 mg o placebo, una volta al giorno, per 4 settimane.



# Obiettivo dello studio

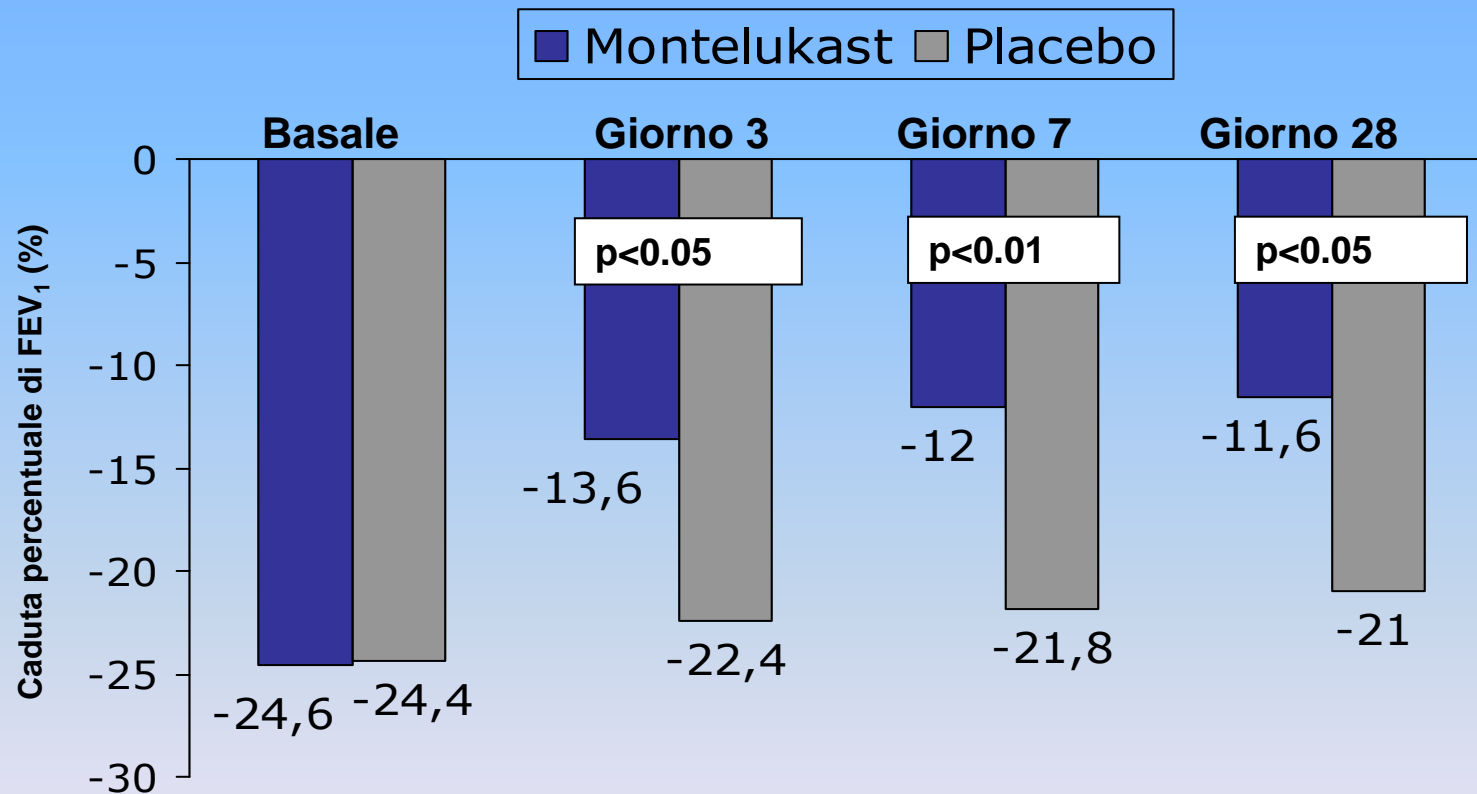
- Lo scopo dello studio era esaminare l'effetto preventivo del Montelukast nella broncocostrizione indotta dall'esercizio a diversi intervalli di tempo durante 4 settimane di trattamento

de Benedictis FM. Lack of tolerance to the protective effect of montelukast in treating childhood bronchoconstriction in children. Eur Respir J. 2006;28:291-5





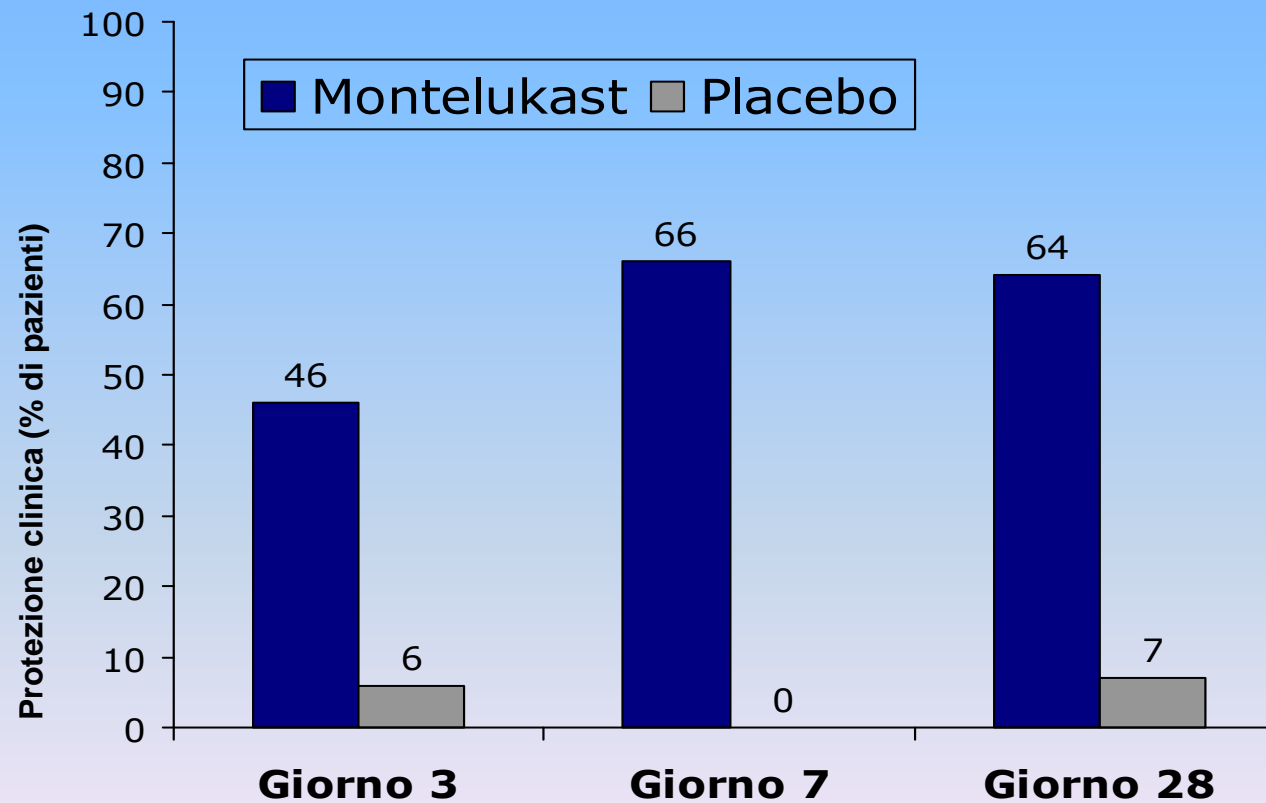
## Montelukast riduce la caduta percentuale di FEV<sub>1</sub> a diversi intervalli temporali



de Benedictis FM. Lack of tolerance to the protective effect of montelukast in treating childhood bronchoconstriction in children. Eur Respir J. 2006;28:291-5



## Percentuale di protezione clinica ottenuta nel tempo con MONTELUKAST



de Benedictis FM. Lack of tolerance to the protective effect of montelukast in treating childhood bronchoconstriction in children. Eur Respir J. 2006;28:291-5



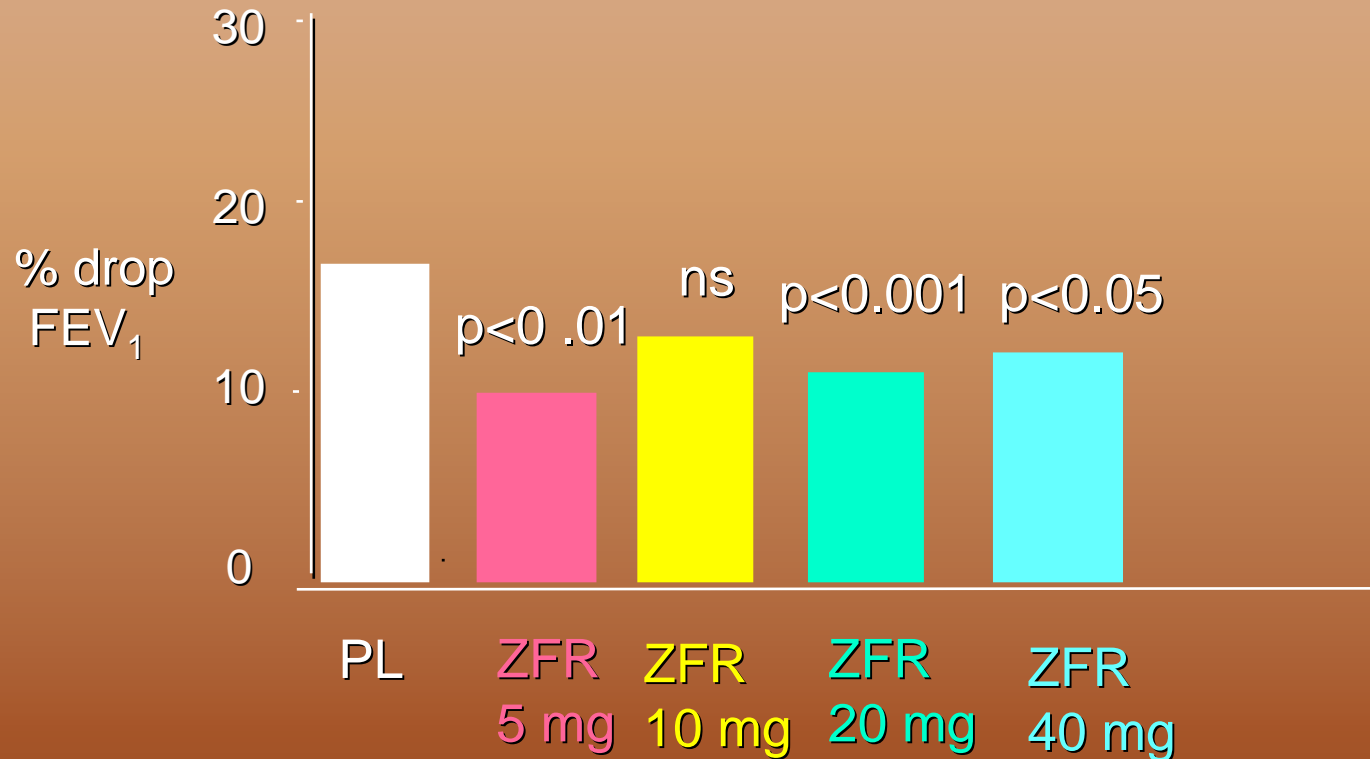
# Zafirlukast & EIB in children

- Studio in doppio cieco vs. placebo in 39 bambini (6-14 anni) con asma da sforzo
- Zafirlukast a 4 diversi dosaggi (5-10-20-40 mg) 4 ore prima dello sforzo
- Minor riduzione percentuale massima del FEV1
- Non identificazione della dose ottimale
- Breve durata della protezione (4 ore)

Pearlman DS. The leukotriene D4-receptor antagonist zafirlukast attenuates treating childhood bronchoconstriction in children. J Pediatr. 1999;134:273-9



# Zafirlukast & EIB in children



No significant difference between low and high doses

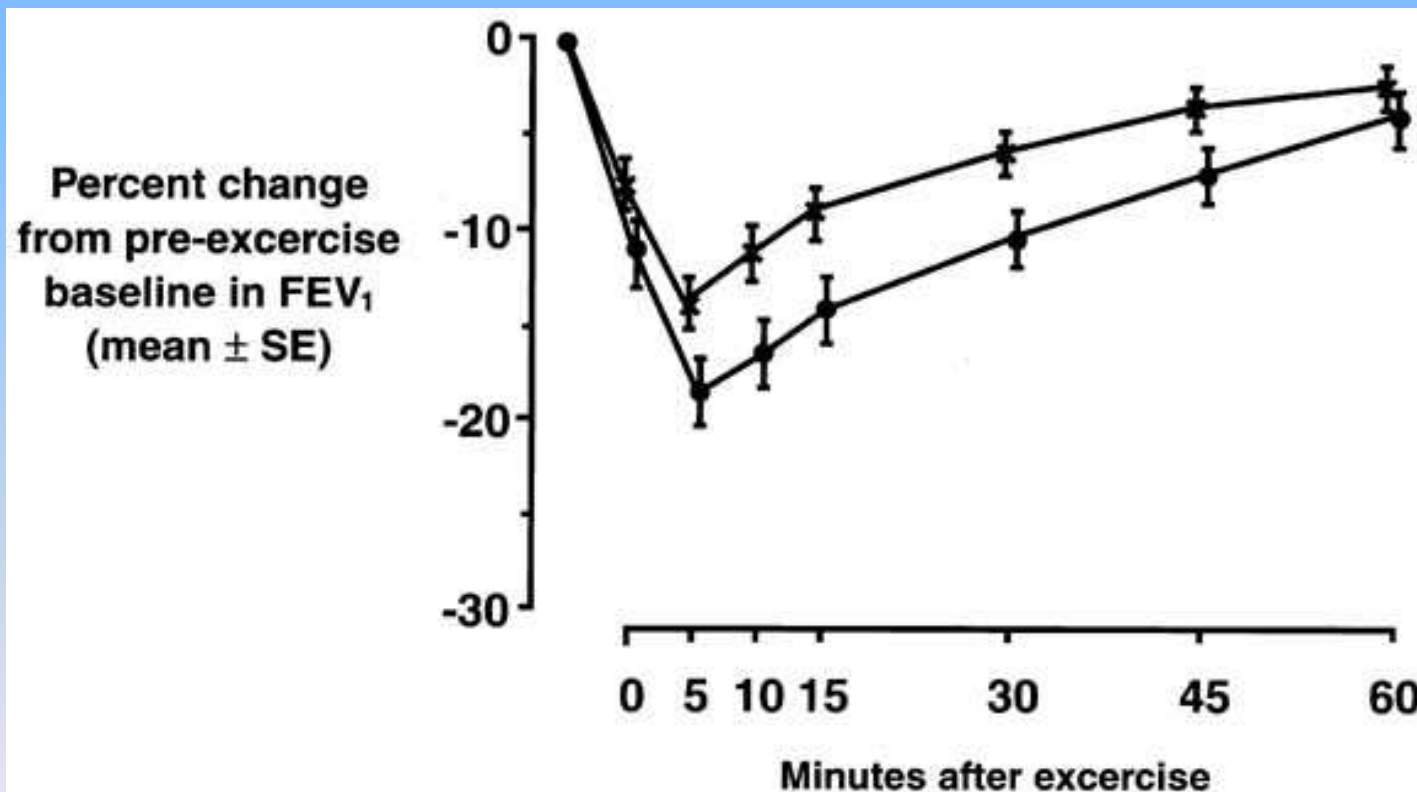
Pearlman DS. The leukotriene D<sub>4</sub>-receptor antagonist zafirlukast attenuates treating childhood bronchoconstriction in children. J Pediatr. 1999;134:273-9



# Montelukast vs. salmeterolo – asma da sforzo

117 pazienti con asma da sforzo

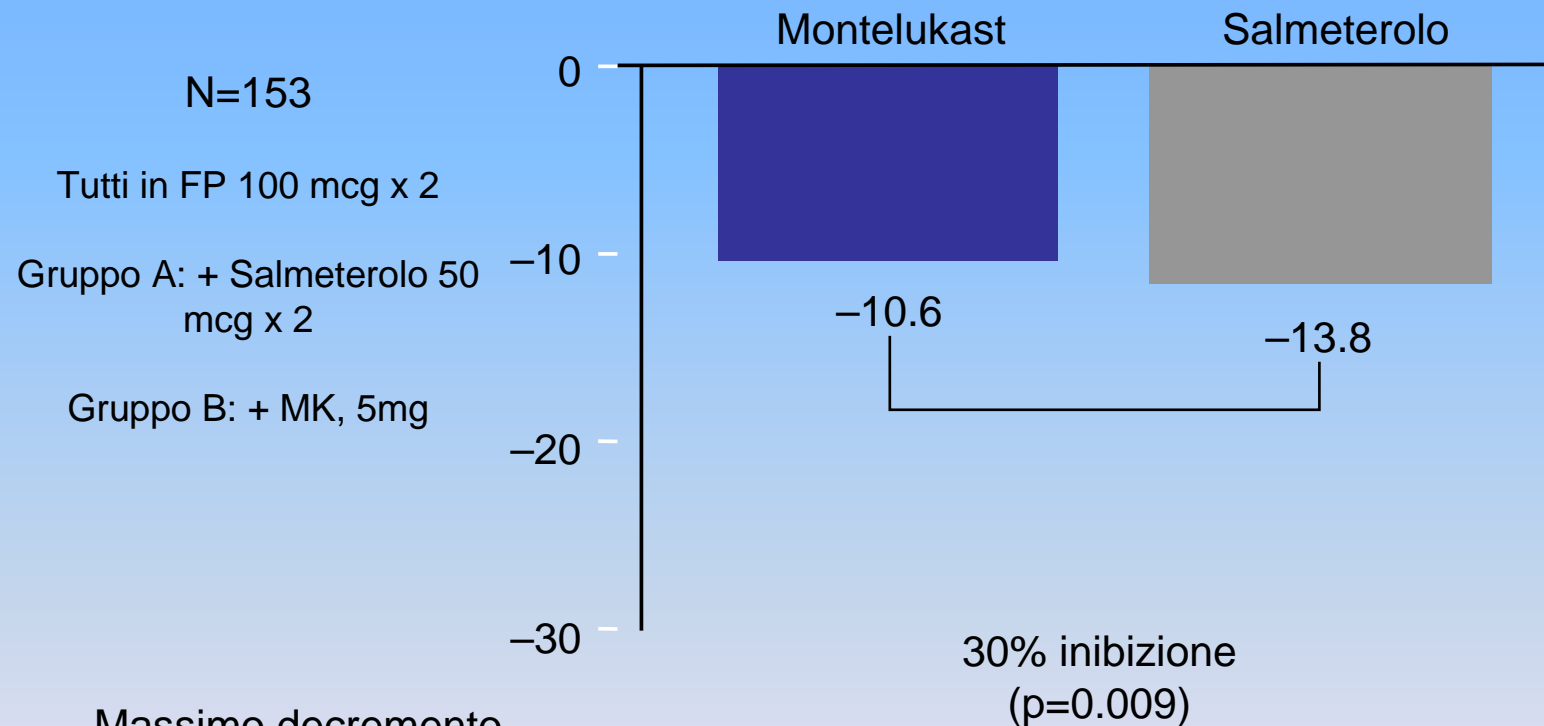
Montelukast > salmeterolo a 4 ed 8 settimane



Villaran C. Montelukast versus salmeterol in patients with asthma and treating childhood bronchoconstriction. J Allergy Clin Immunol 1999; 104:547-53



# Montelukast vs. salmeterolo – asma da sforzo



Massimo decremento percentuale del FEV1 dopo esercizio e prima della prima dose di SABA

Fogel RB. Effect of montelukast or salmeterol added to inhaled fluticasone on treating childhood bronchoconstriction in children Ann Allergy Asthma Immunol. 2010;104:511–7



# Montelukast vs. salmeterolo – asma da sforzo

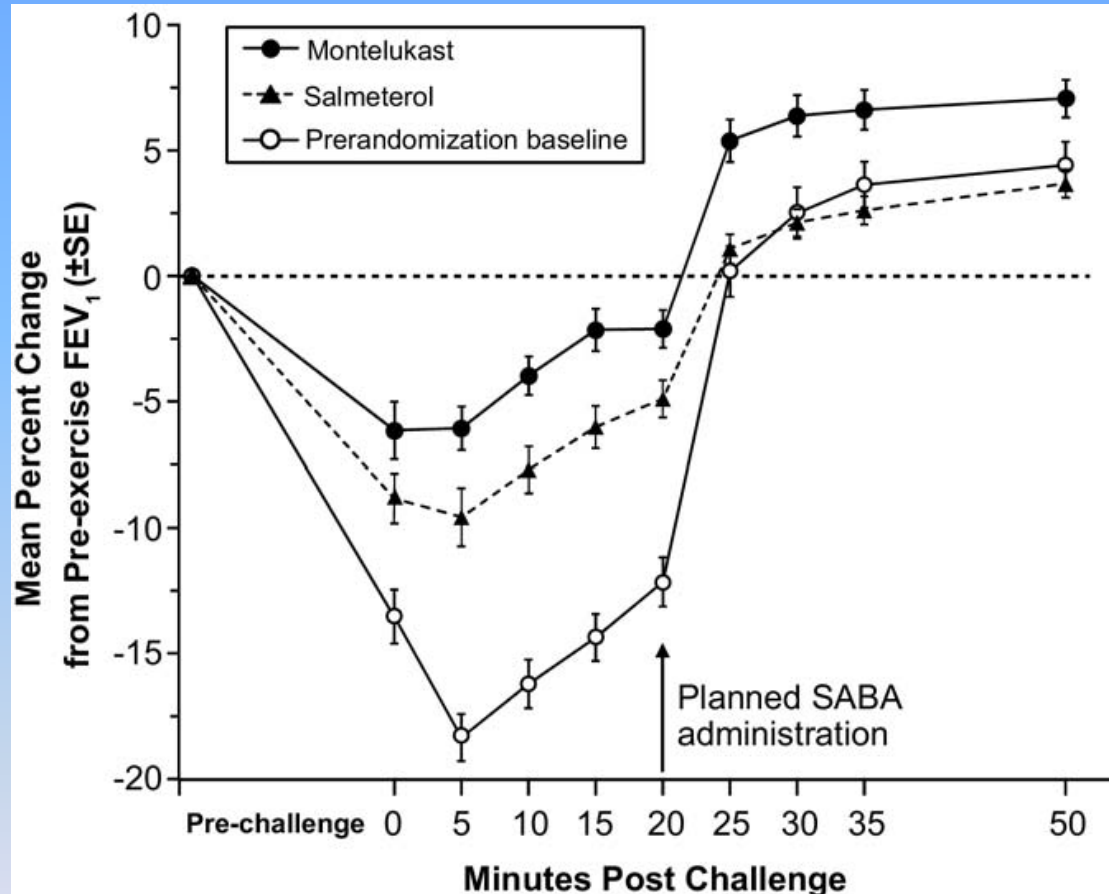
N=153

Tutti in FP 100 mcg x 2

Gruppo A: + Salmeterolo 50 mcg x 2

Gruppo B: + MK, 5mg

Massimo decremento percentuale del FEV1 dopo esercizio e prima della prima dose di SABA



Fogel RB. Effect of montelukast or salmeterol added to inhaled fluticasone on treating childhood bronchoconstriction in children Ann Allergy Asthma Immunol. 2010;104:511–7





## T-1. do SABA or LABA develop tachyphylaxis to treatment?

- Prophylactic use of SABA and LABA agents is safe and effective for episodic prophylaxis of EIA
- Tachyphylaxis develops if these agents are used daily.
- Evidence comparing SABA/LABA to placebo was graded as “moderate”
- Evidence comparing LABA to LTRA was graded as “low.”



## T-2. does LTRA reduce symptoms/prevent a 10% drop in FEV1?

From the available evidence, it appears that LTRAs are effective and safe as pre-exercise treatment for patients with mild to moderate stable asthma and EIA.

The strength of the body of evidence is “moderate.”



### T-3. does pre-exercise treatment with ICS reduce symptoms/prevent a 10% drop in FEV1?

From the available evidence, we cannot conclude that a pre-exercise single-dose of an ICS agent will attenuate EIA.

The strength of the body of evidence is “moderate.”



## T-4. does pre-exercise treatment with cromoglycate or nedocromil reduce symptoms/prevent a 10% drop in FEV1?

MCS agents are effective and safe as pre-exercise treatment for patients with stable asthma and EIA

No significant differences between NCS and SCG

MCS agents not as effective as SABA agents

The combination of SABA and MCS agents did not provide significant advantages over a SABA alone.

The strength of the body of evidence is “moderate”



## T-5. does pre-exercise treatment with anticholinergic therapy reduce symptoms/prevent a 10% drop in FEV1?

The evidence suggests that when used as a pre-treatment, SAAC agents are effective and safe for some patients with EIA

They can offer a clinically relevant protective effect to some people.

The strength of the body of evidence is “moderate”



## treating childhood asthma

1. Asthma guidelines
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6. Conclusions



## Conclusions

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1. **Control** of asthma in pre-schoolers is a realistic goal
2. Ban maternal & environmental **smoking**
3. A diagnosis of asthma in children 5 years and younger may be difficult – label as **wheezing**
4. It can be based on symptom patterns and on a careful clinical assessment of family history and physical findings.
5. Asthma **education** should be provided
6. For patients with asthma, the goal of treatment is to control the clinical manifestations of the disease for prolonged periods





## Conclusions

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7. The prolonged use of high doses of inhaled or systemic glucocorticosteroids must be avoided
8. Use a pressurized MDI with a valved spacer
9. **Inhaled steroids** in children 5 years and younger are effective
10. **Rapid-acting inhaled  $\beta$ 2-agonists** are the preferred reliever treatment
11. **Oral glucocorticosteroids only in acute severe exacerbations**
12. A low-dose inhaled glucocorticosteroid is recommended as the preferred initial treatment to control asthma
13. If it does not control symptoms (check technique & adherence!), double the initial dose of glucocorticosteroid
14. Asthma treatment should be **re-assessed** every 3–6 months.

Not everybody's cup of tea!

The 6<sup>th</sup> Milan International Meeting on Pediatric Allergy  
WAO, ACAAI, AAAAI, EAACI  
Milan, Thursday 9<sup>th</sup> – Sunday 12<sup>th</sup> February 2012

