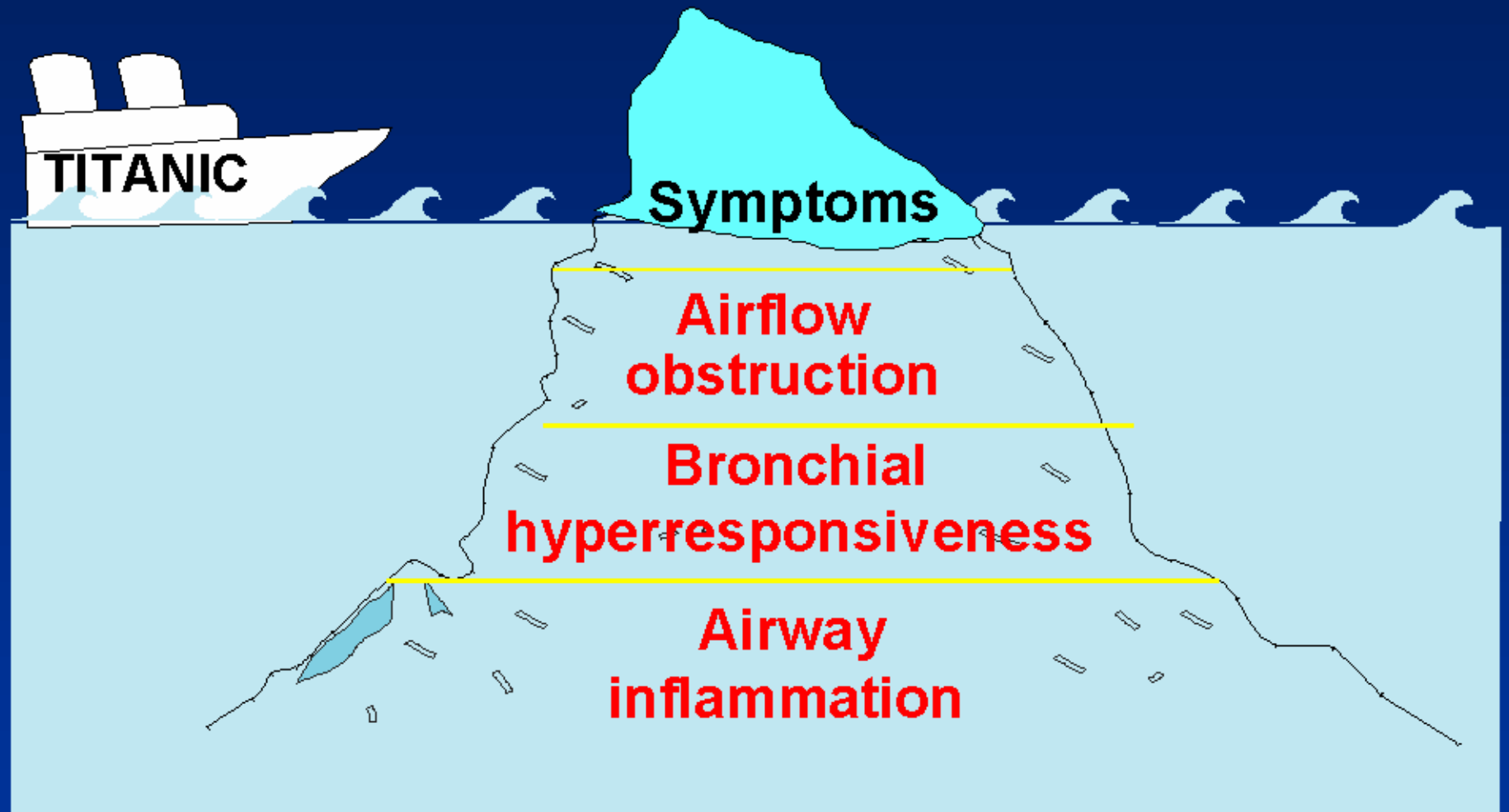


I NUOVI FARMACI DELLA FLOGOSI ASMATICA LA COLLOCAZIONE DEGLI ANTILEUCOTRIENI

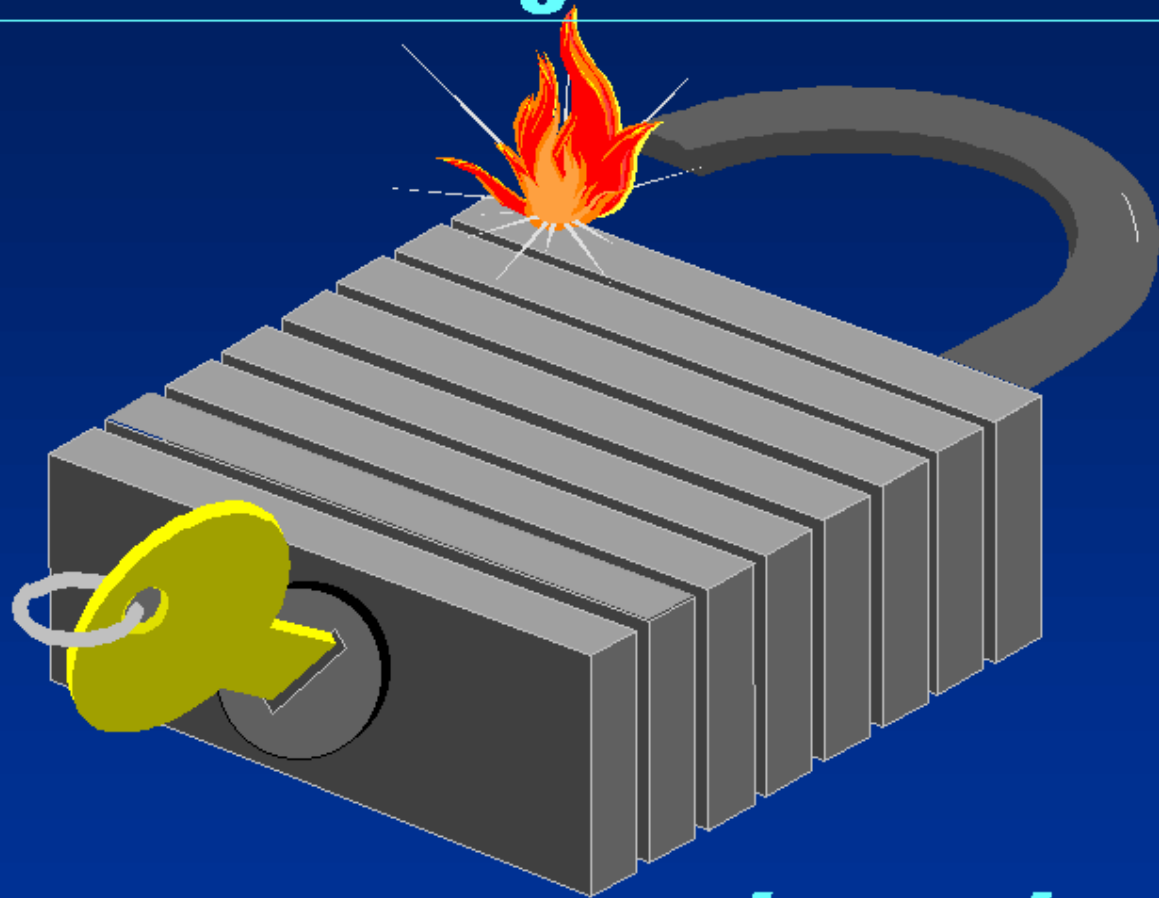


Dott. Michele Miraglia del Giudice

The “Tip” of the Iceberg



The Key
to understanding inflammation...

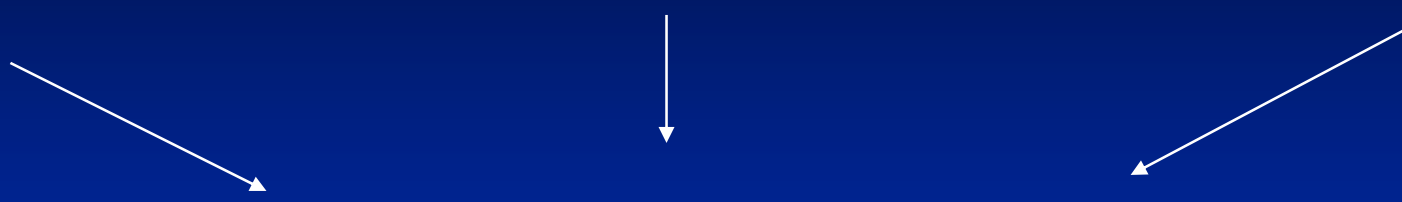


is understanding
Inflammatory Mediators

Esercizio

Aria fredda

Allergeni



Cellule infiammatorie

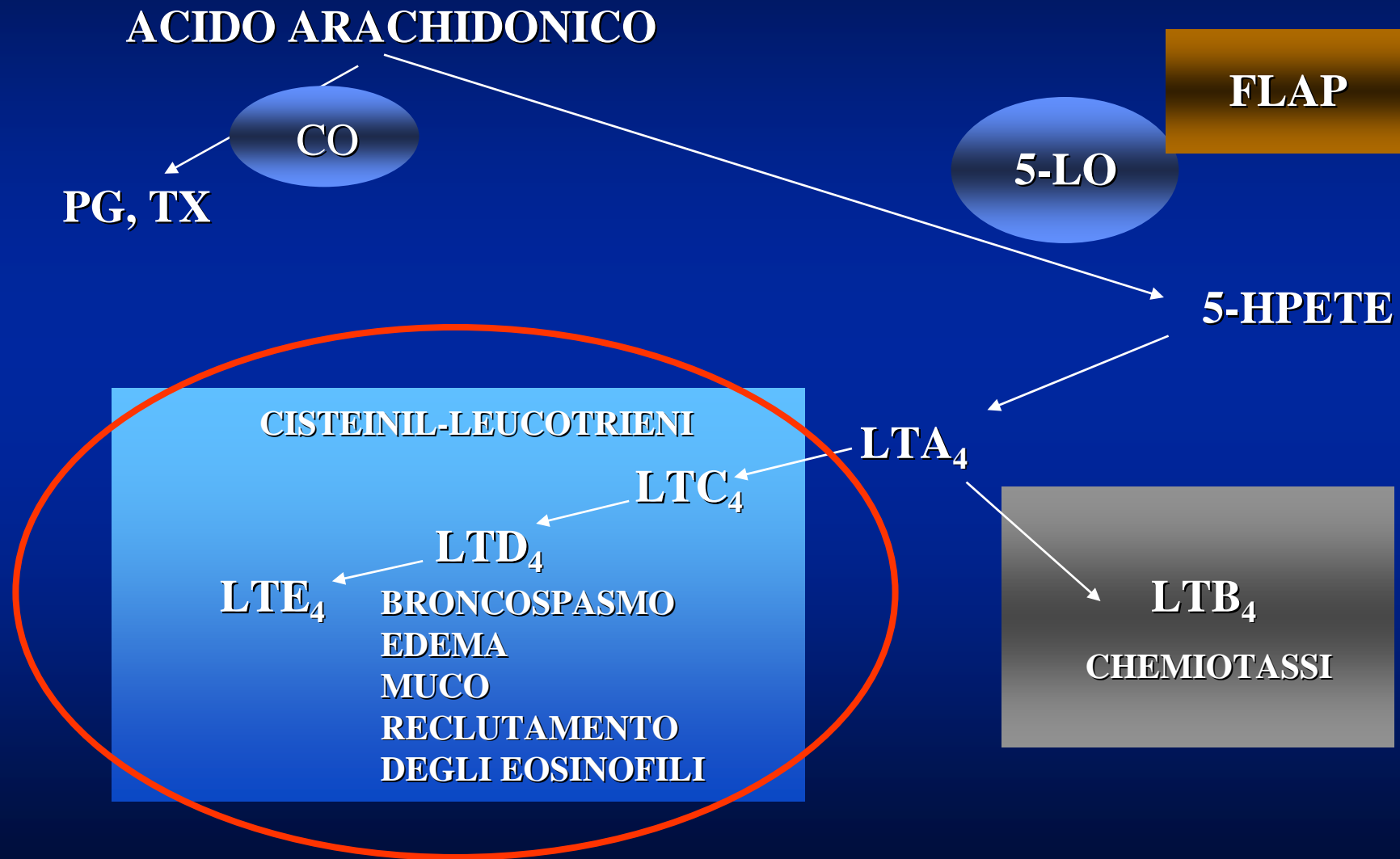


LTC₄, LTD₄, LTE₄

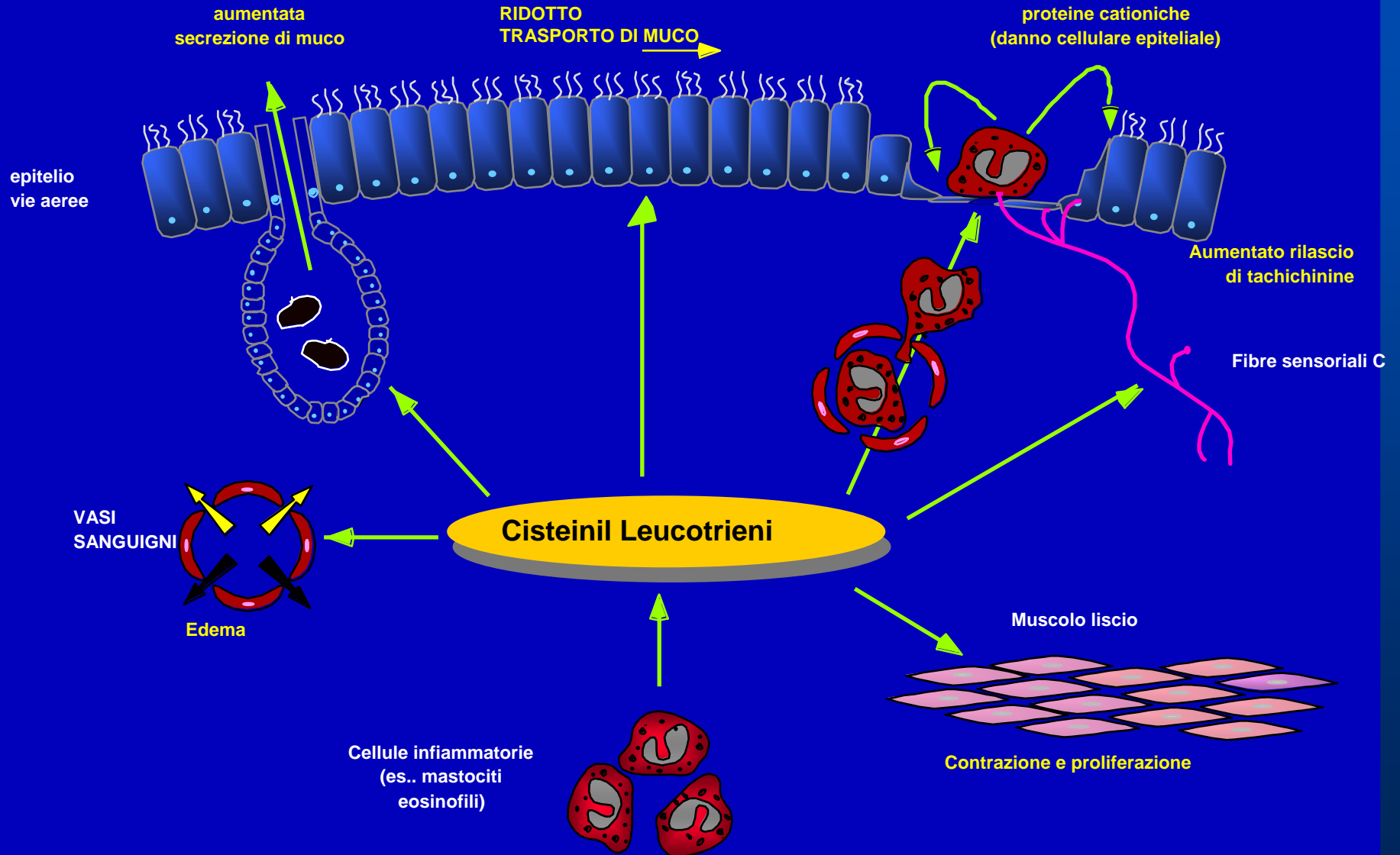


INFIAMMAZIONE VIE AEREE

VIA METABOLICA DEI LEUCOTRIENI



Potenziali siti d'azione dei leucotrieni nella fisiopatologia dell'asma



I CYS-LT NEL BAMBINO

☆ La produzione di Cys-LT e' aumentata negli asmatici

Wenzel et al. AJRCCM 1995

☆ I livelli di Cys-LT correlano con la gravita' dell'asma

Chavis et al. Allergy 1997

☆ I livelli di Cys-LT aumentano durante la crisi asmatica, il challenge allergenico e l'EIA

Sampson Arch.Dis.Child 1995; Kumlin ARRD 1992; Kikawa JACI 1992

I CYS-LT NEL BAMBINO

La produzione di Cys-LT e' aumentata nel "wheezing infant"

☆ I macrofagi alveolari rilasciano maggior quantita' di LTB4

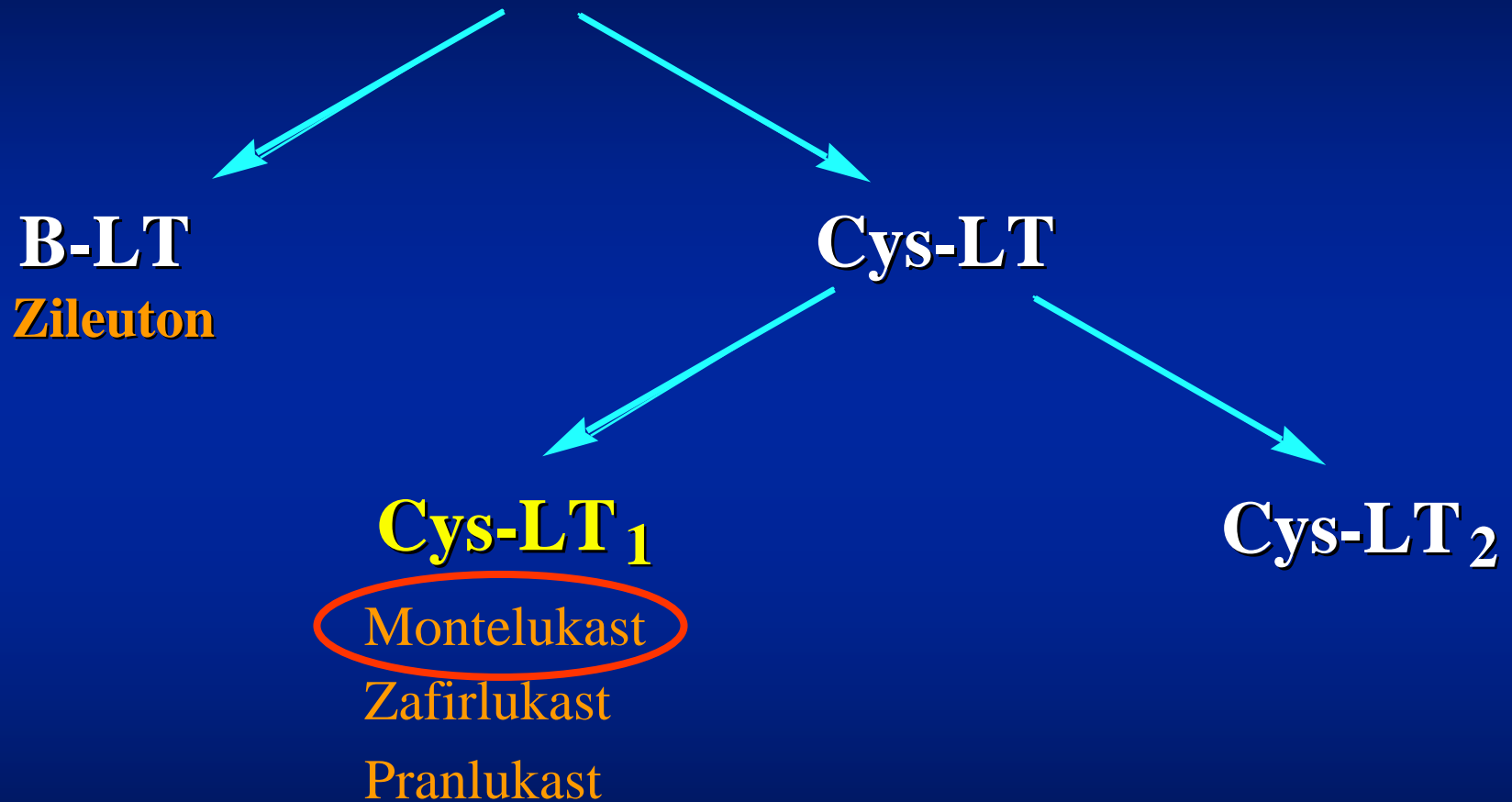
Azevedo et al. AJRCCM 1995

☆ Maggior secrezione nasofaringea di LTC4 rispetto ai controlli e nei "wheezing infant" in cui e' stata dimostrata un'eziologia virale

Volovitz et al. J Pediatr 1988

La produzione di Cys-LT e' aumentata nella displasia broncopolmonare e nella fibrosi cistica

Recettori dei Leucotrieni



Hay DWP et al. Trends Pharmacol Sci 1995;16:304-9

STUDI CON MONTELUKAST SULL'ASMA DA SFORZO NEGLI ADULTI E NEI BAMBINI

Kemp et al. J of Pediatrics 133 (3): 424-8, 1998.

Villaran et al., J Allergy Clin Immunol, 1999

Leff et al. NEJM 339: 147-152, 1998.

Strategie attuali del trattamento dell'asma da sforzo

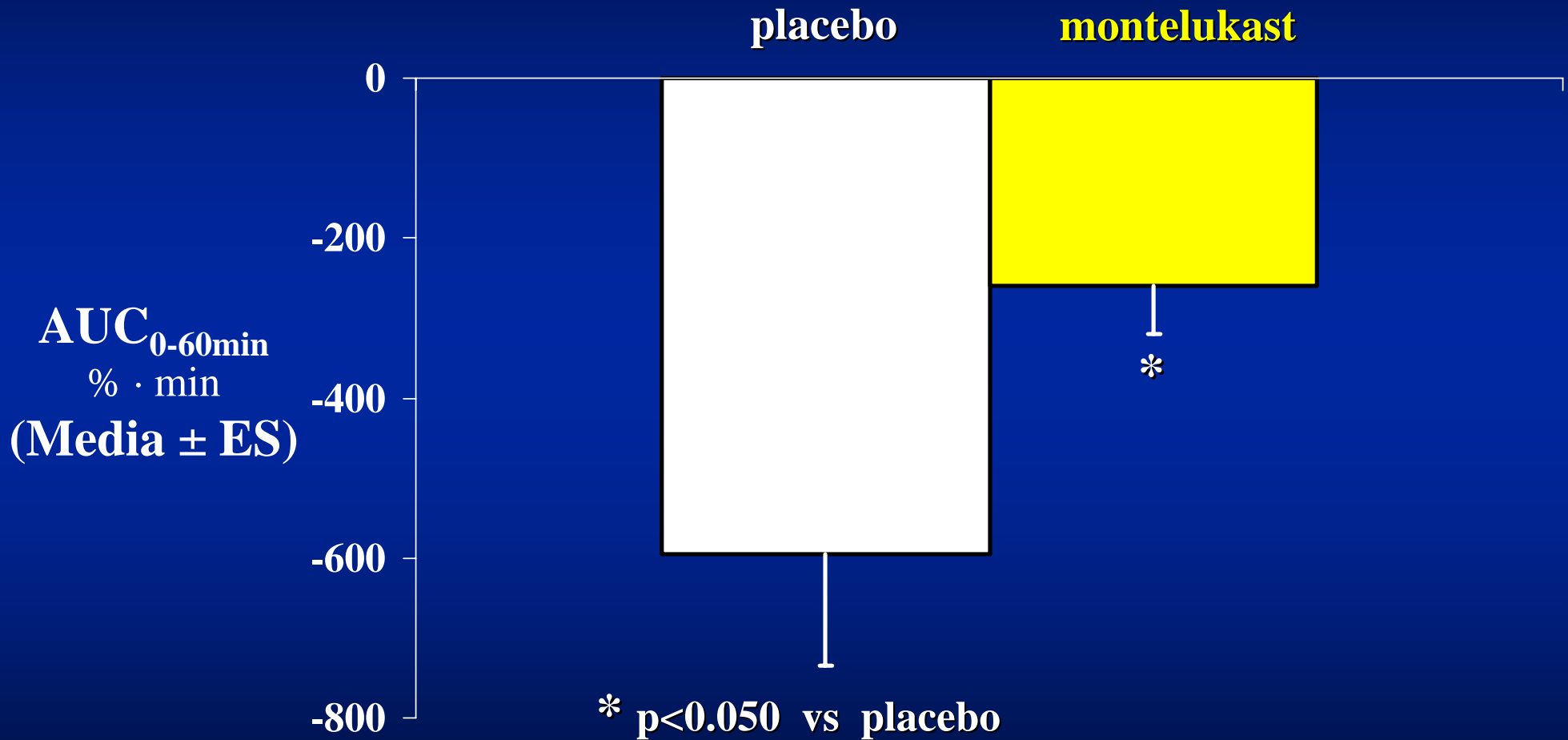
☆ **Pretrattamento con:**

- ◆ **β -agonisti a breve o lunga durata d'azione**
- ◆ **Inibitori della degranulazione (DSCG o nedocromil)**

☆ **Le limitazioni della terapia includono:**

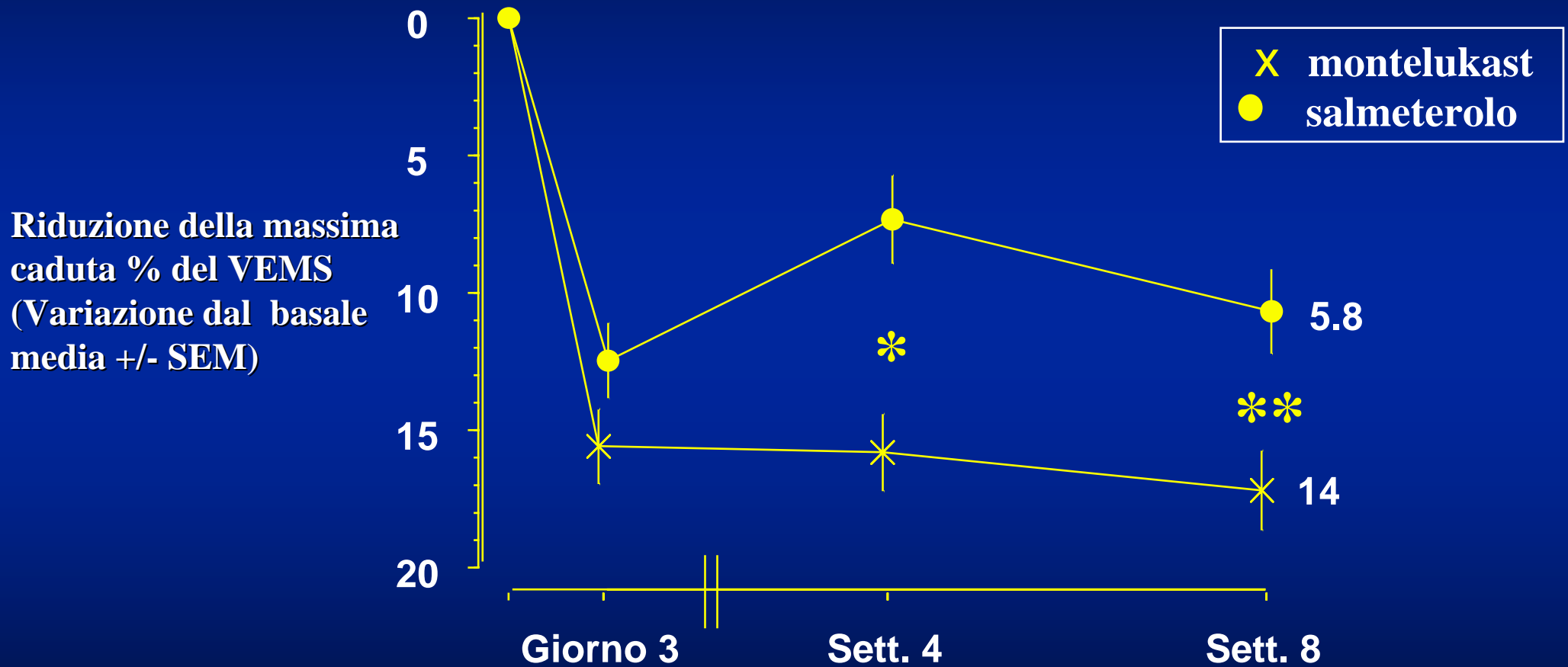
- ◆ **Frequenti somministrazioni**
- ◆ **Sviluppo di tolleranza (ai β -agonisti)**

Studio con Montelukast vs placebo sull'Asma da Sforzo nel Bambino



Montelukast vs Salmeterolo nell'asma da sforzo

Massima caduta % del VEMS

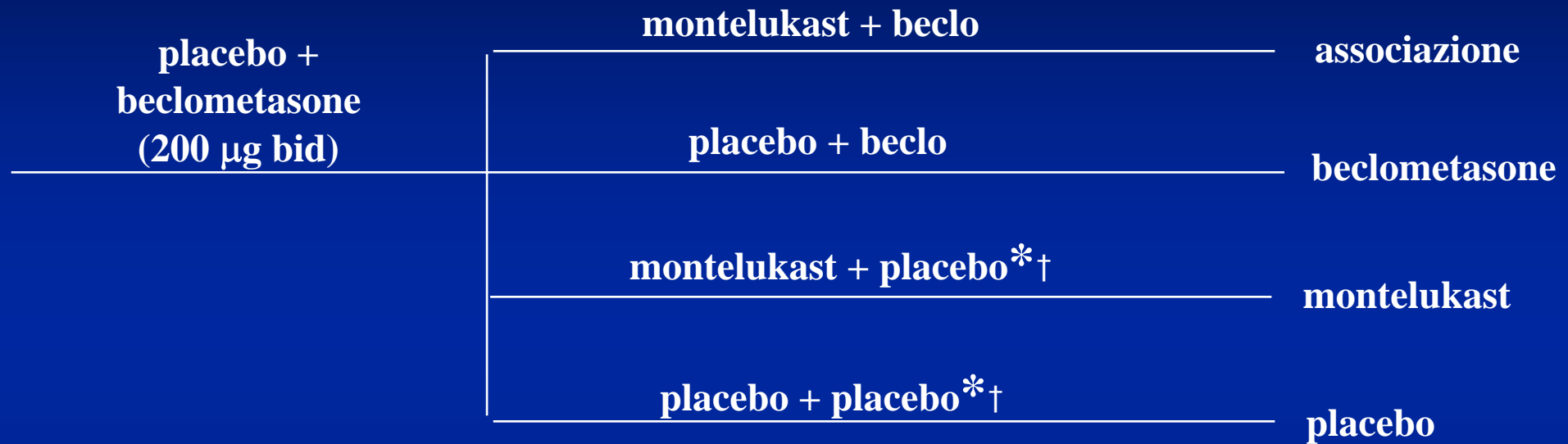


* $p < 0.001$ ** $p = 0.001$ montelukast vs salmeterolo

**STUDIO CON MONTELUKAST IN
PAZIENTI NON ADEGUATAMENTE
CONTROLLATI DALLA TERAPIA
STANDARD CON STEROIDI
INALATORI**

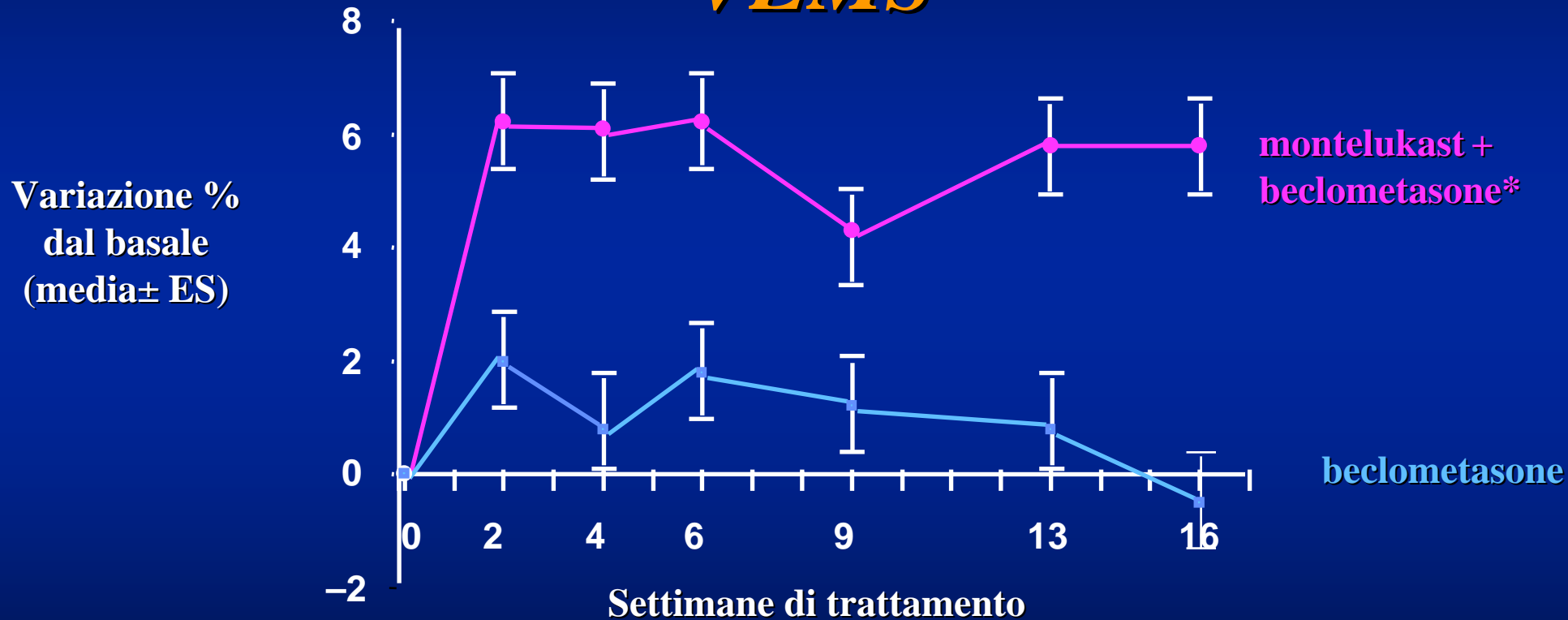
Laviolette et al. Am J Resp Crit Care Med, Dic. 99

Studio con Montelukast su pazienti non controllati dalla terapia steroidea inalatoria



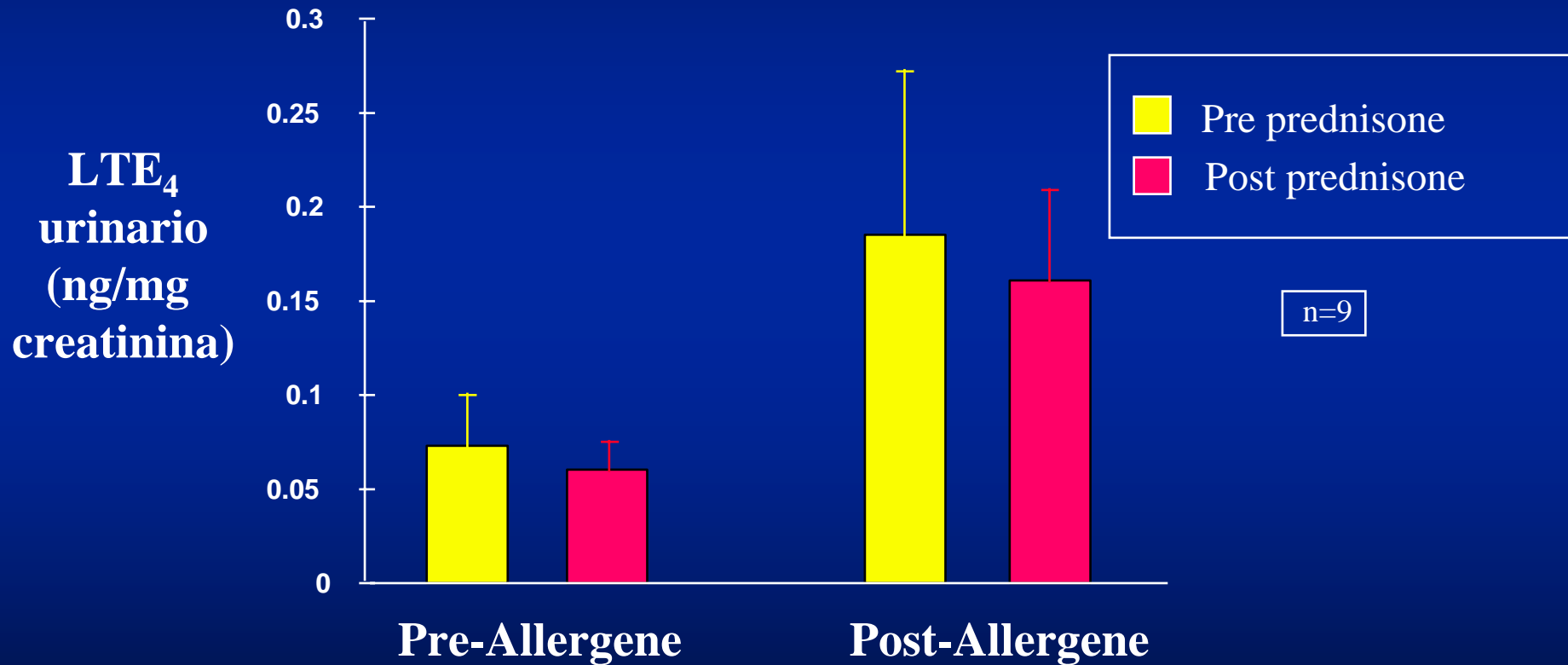
Studio con Montelukast su pazienti non controllati dalla terapia steroidea inalatoria

VEMS



* $p < 0.001$ vs beclometasone in monoterapia

Il trattamento steroideo non ha soppresso i livelli di leucotrieni nelle urine dopo esposizione all'antigene

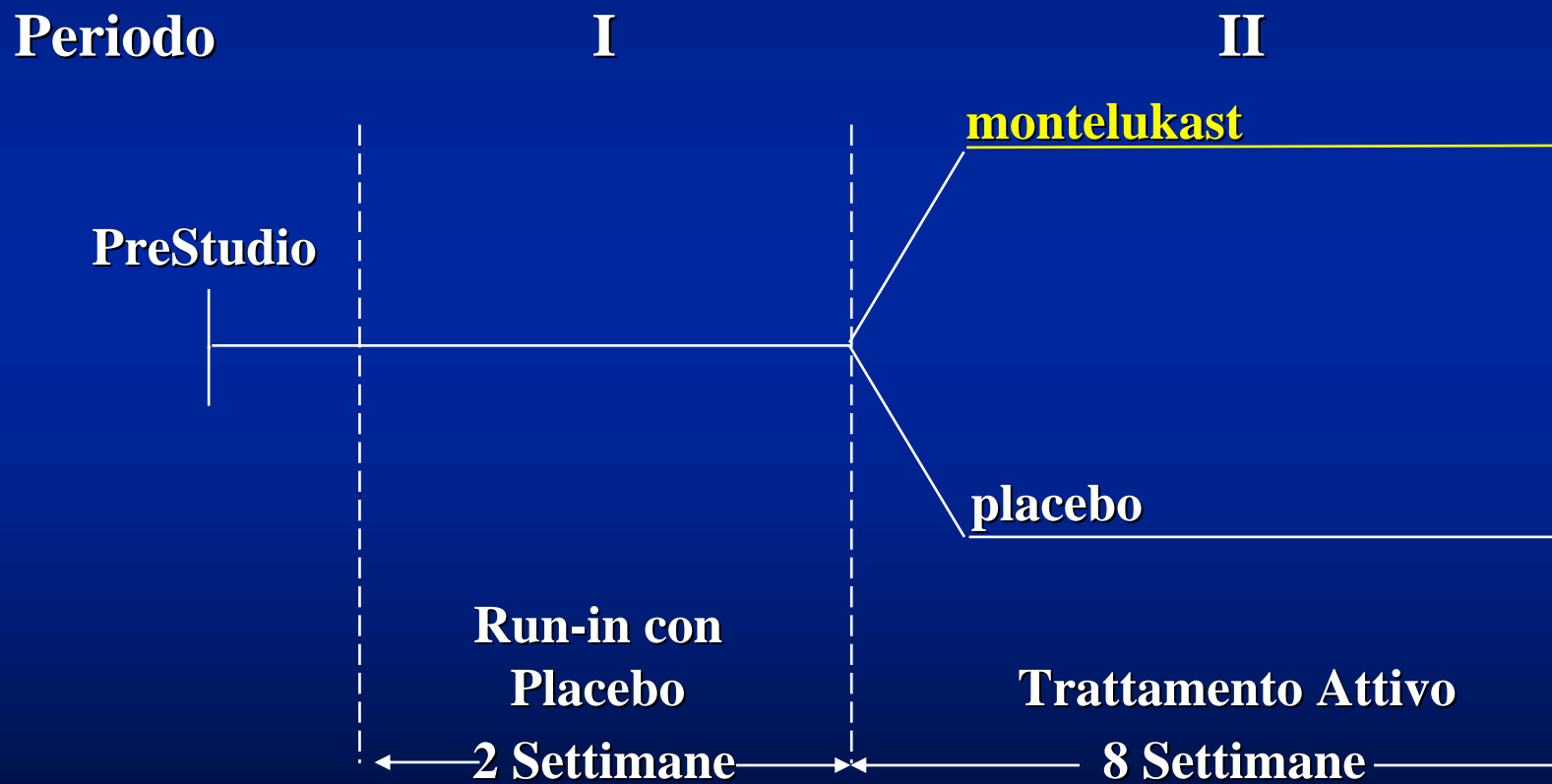


STUDIO CON MONTELUKAST NEI BAMBINI CON ASMA CRONICO

Knorr et al JAMA 279 (15): 1181-1186, 1998.

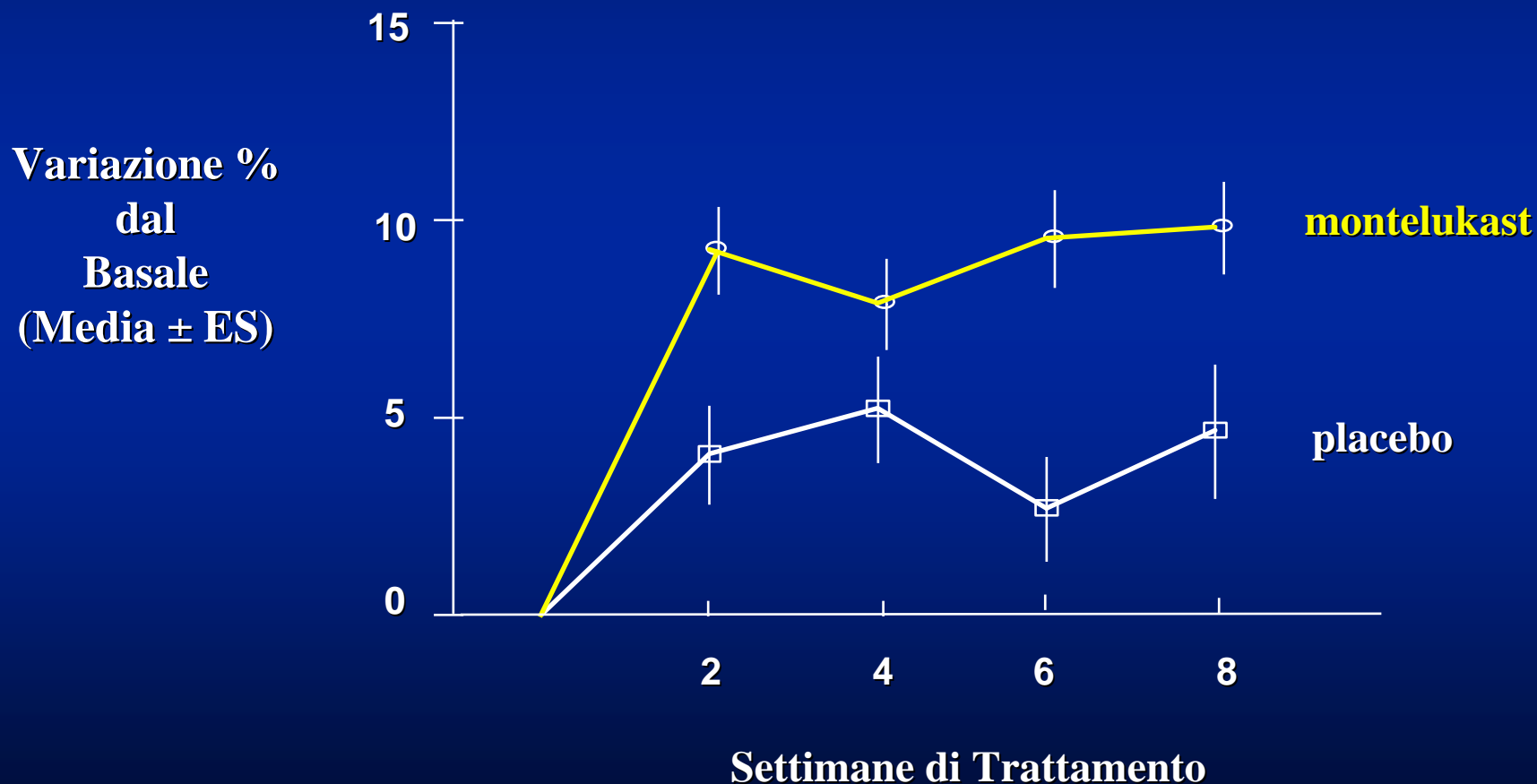
Studio Controllato con Placebo sui bambini affetti da asma cronico

Disegno



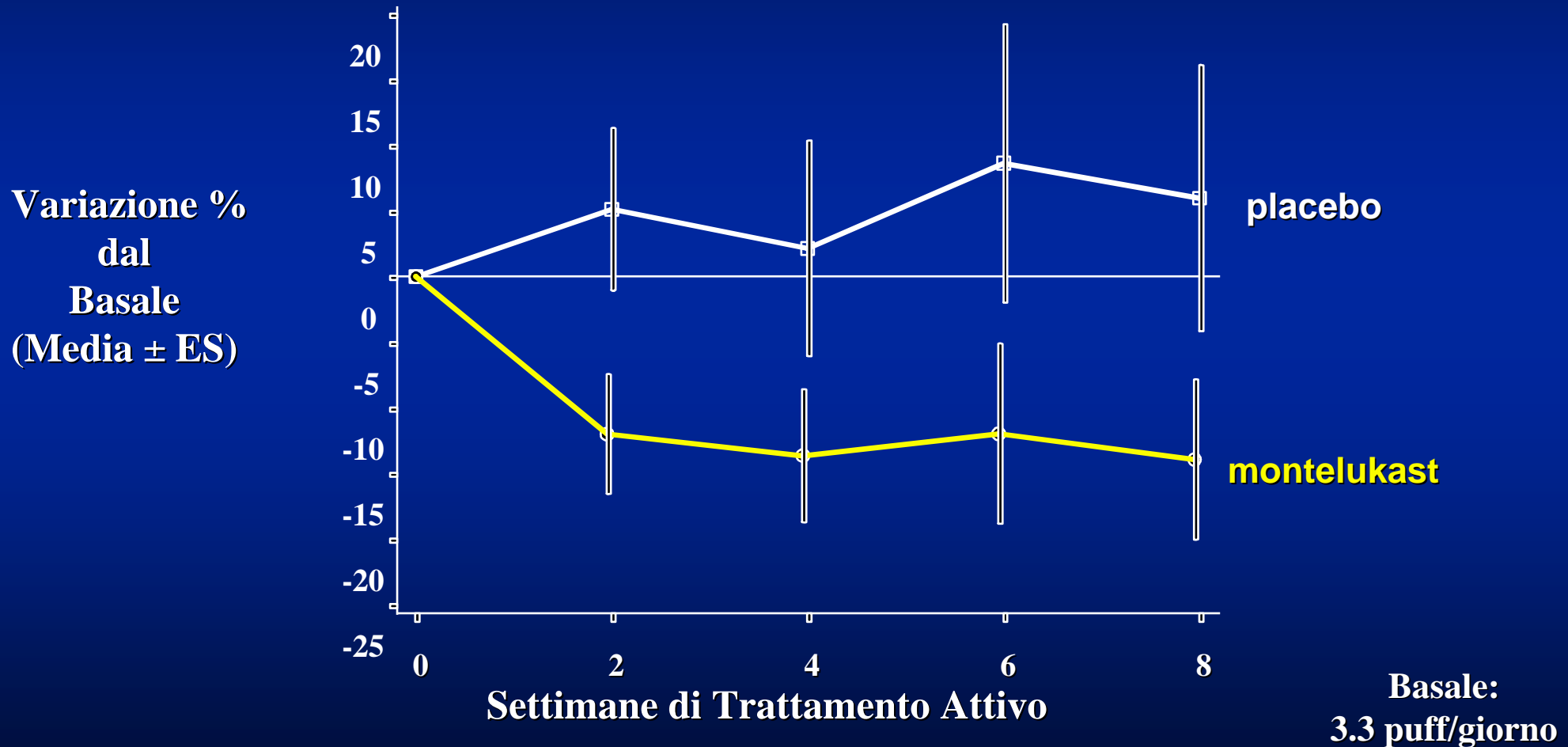
Studio Controllato con Placebo sui bambini affetti da asma cronico

VEMS



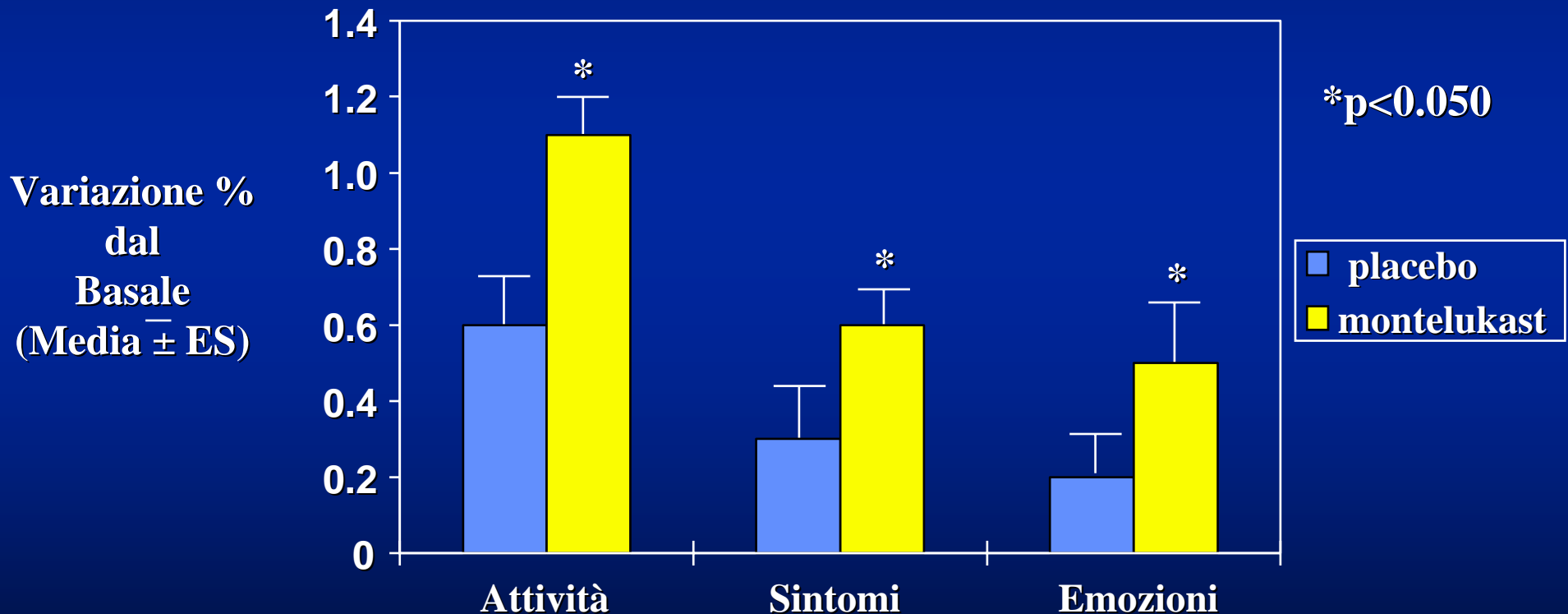
Studio Controllato con Placebo sui bambini affetti da asma cronico

Utilizzo Totale di β -Agonisti



Studio Controllato con Placebo sui bambini affetti da asma cronico

Qualità della Vita del paziente asmatico

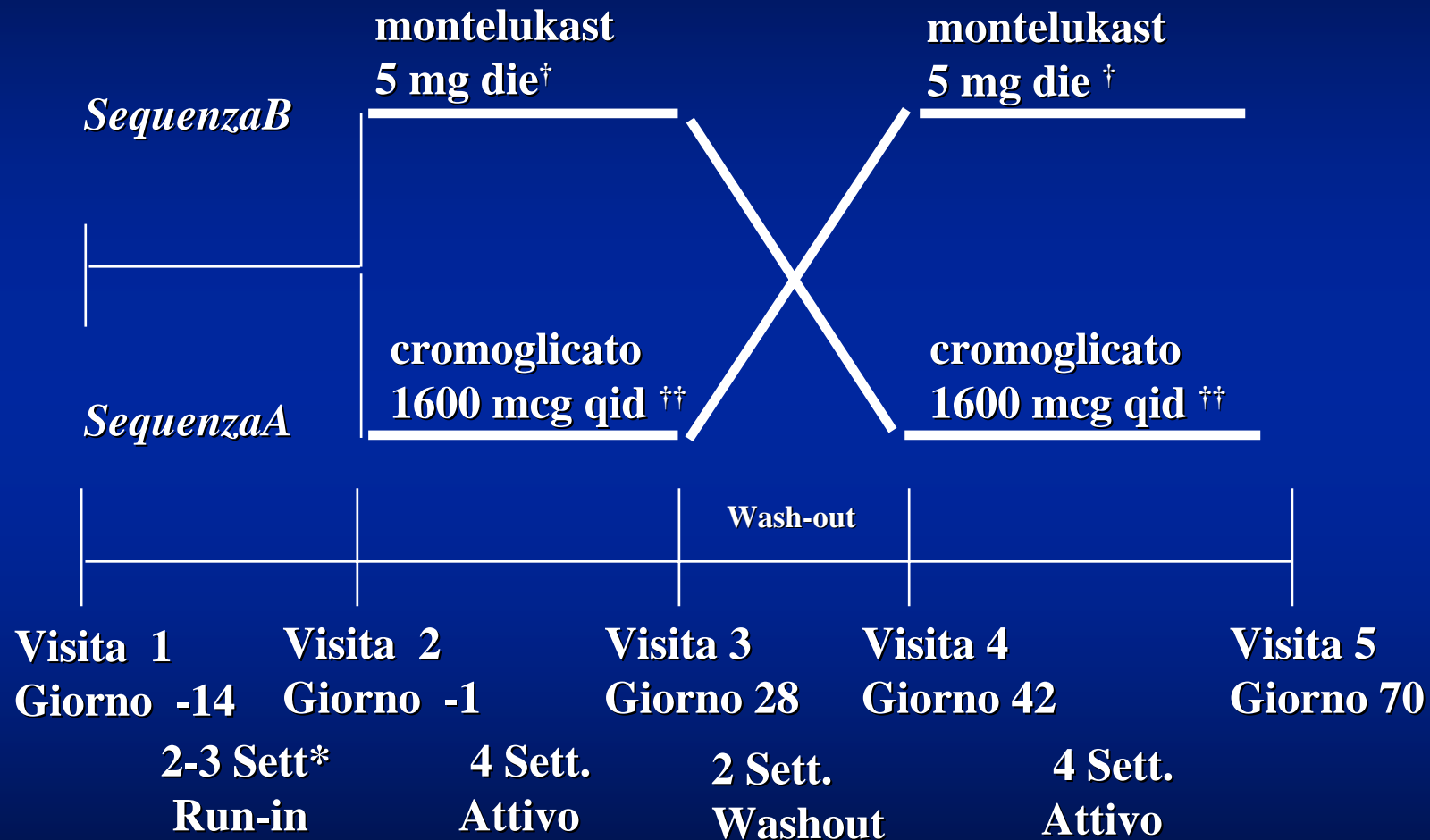


STUDIO PEDIATRICO DI PREFERENZA MONTELUKAST VS CROMOGLICATO

Edelman et al. JACI 1999; 103 (1): part 2 S134 A510

Studio di Preferenza Montelukast vs Cromoglicato

Schema dello studio



*Vi era la possibilità di 1 settimana di estensione durante il basale dopo la visita 2 (visita 2A)

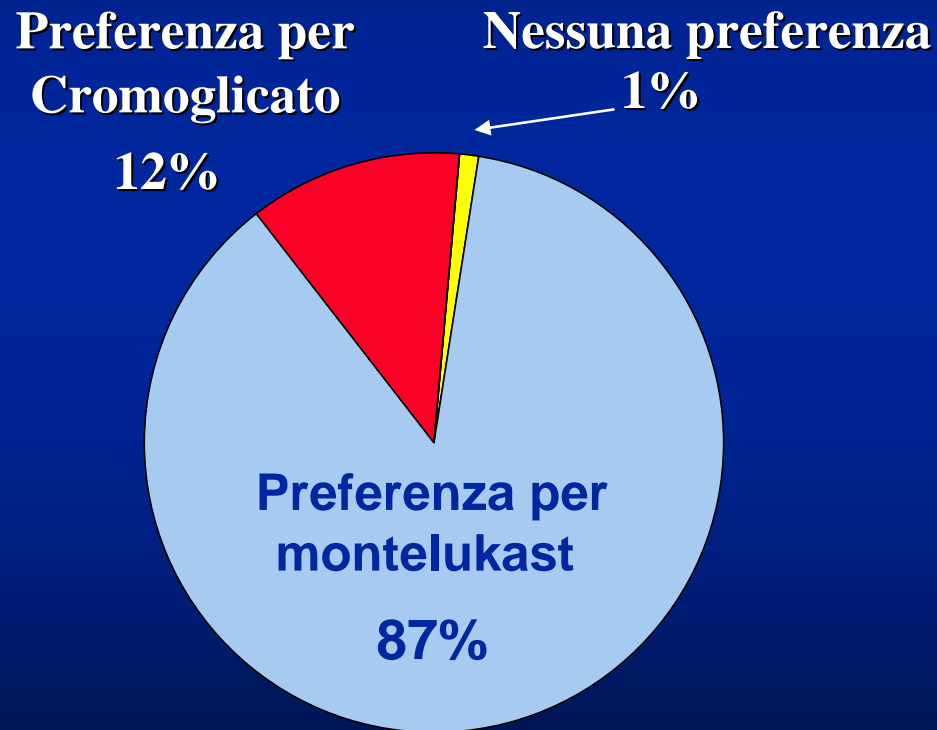
[†] die = una volta al giorno prima di coricarsi

^{††} q.i.d. = 4 volte al giorno

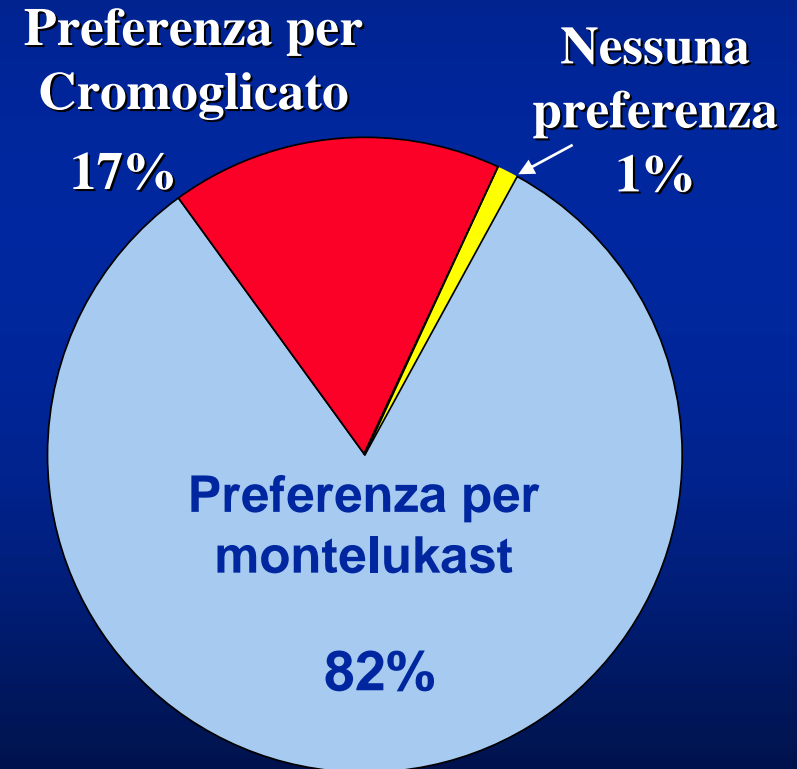
Studio di Preferenza Montelukast vs Cromoglicato

Genitori ed i Bambini hanno preferito montelukast

Genitore/Tutore* (n=295)



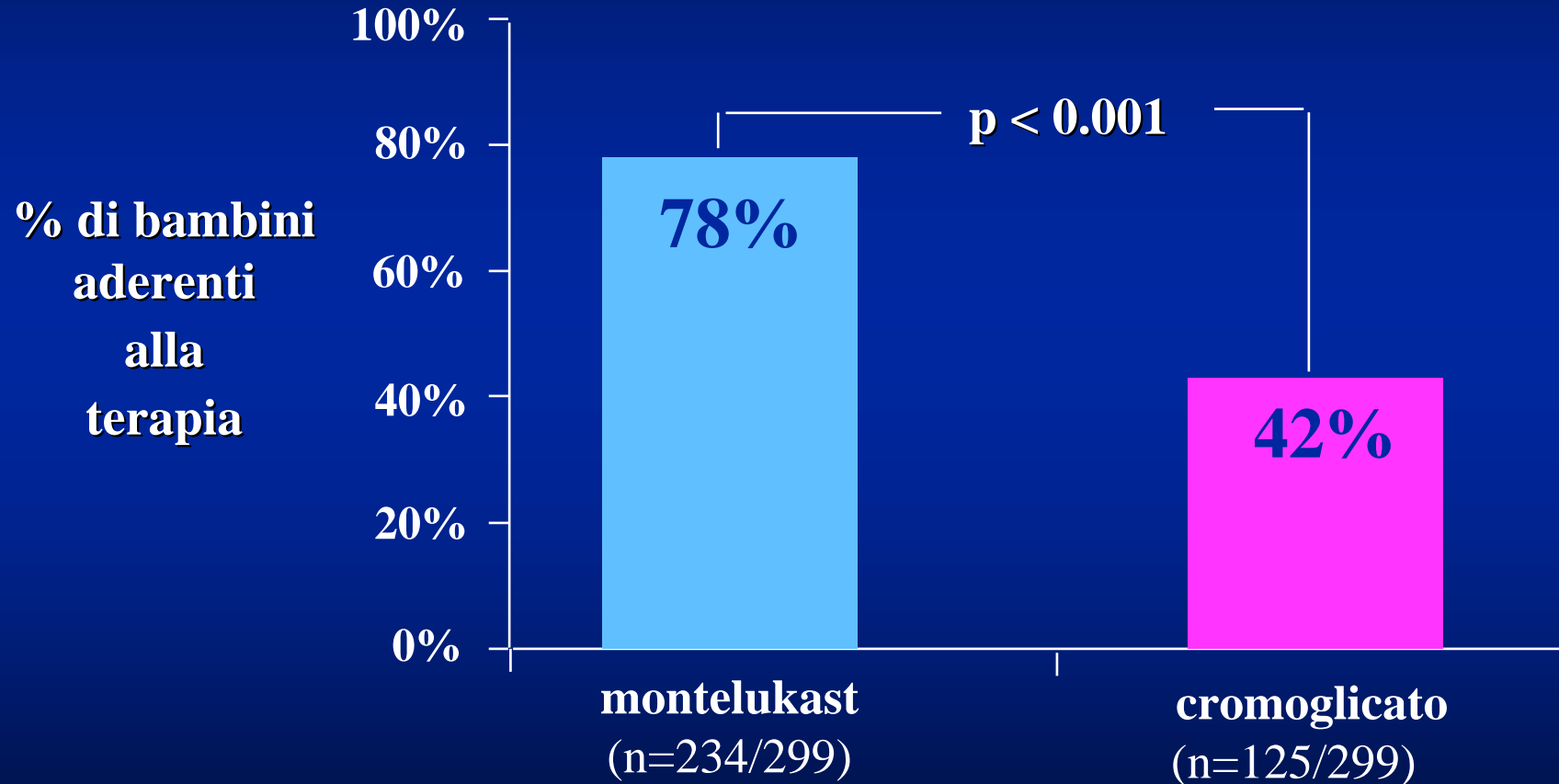
Bambino*(n=296)



***p < 0.001 montelukast vs cromoglicato**

Studio di Preferenza Montelukast vs Cromoglicato

L'aderenza alla terapia con montelukast ha superato quella al cromoglicato



Aderenza definita come assunzione di tutta la terapia prescritta giornaliera per un numero di giorni > 95% dei giorni totali di terapia

Montelukast Dose Selection: 2- to 5-Year-Olds
4 mg dose: Clinical safety confirmed

**Evaluation of the Safety Profile of Montelukast
(MK-0476) in Pediatric Patients Aged 2 to 5 Years.**

Knorr B, Noonan G, Nguyen H, et al.

J Allergy Clin Immunol. Jan 2000;105(1, pt 2) [abstract].

Once the 4 mg dose was selected
for 2- to 5-year-olds, it was taken
into a large clinical trial

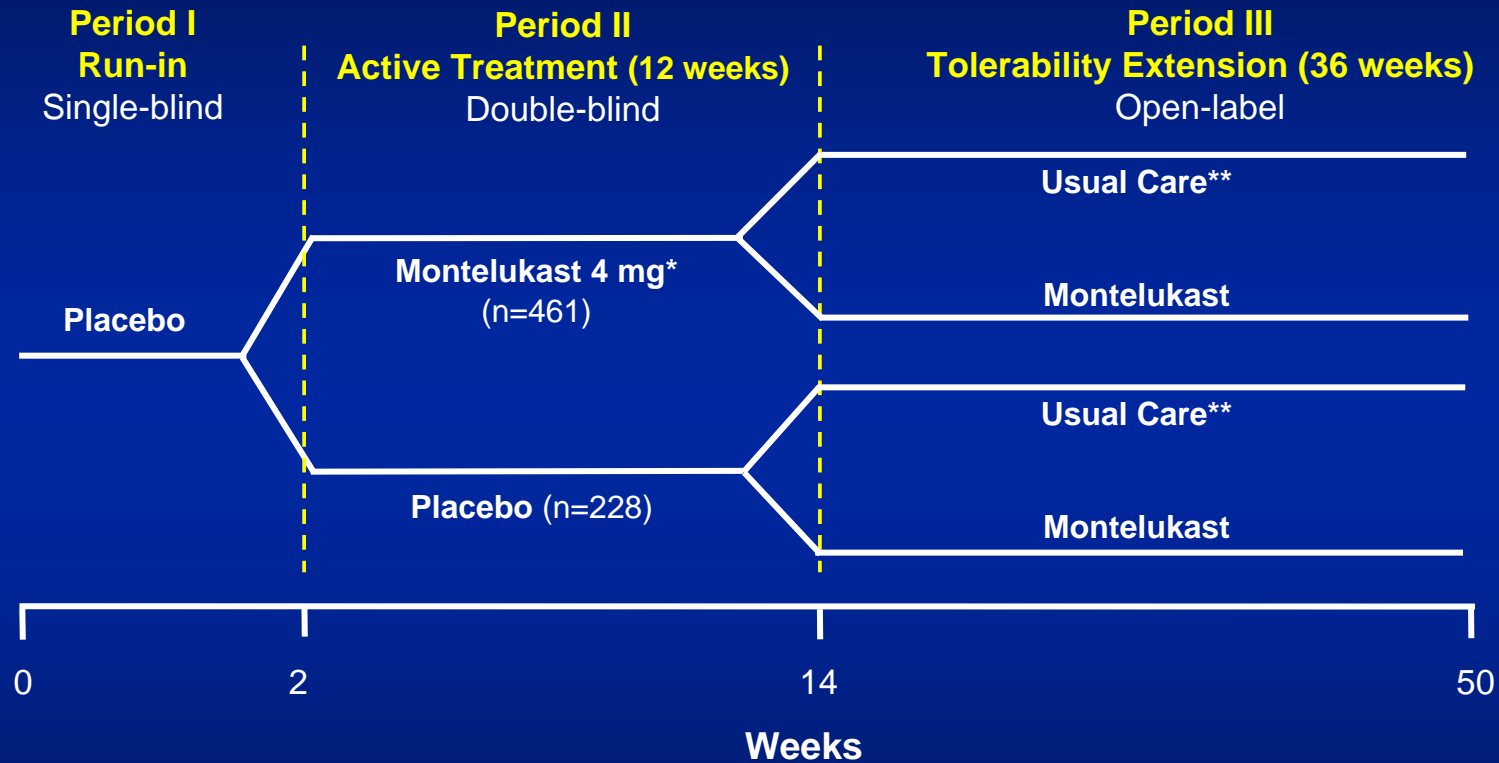
Montelukast in Children Aged 2 to 5 years

Study description

- Objective:** To evaluate the safety profile of montelukast compared to placebo in children with asthma aged 2 to 5 years
- Design:** Multinational, randomized, double-blind, placebo-controlled, parallel-group study of 689 patients
- Population:** History of physician-diagnosed asthma
-- at least 3 episodes of typical asthma symptoms within 1 year prior to the study

Montelukast in Children 2–5 Years of Age

Study Design



Numbers represent patients entering each period. In Period III: montelukast (n=288); usual care (n=119)
Short-acting beta₂ agonists were used as needed in both groups.

*One chewable tablet once daily at bedtime; patients in the extension study who became six years of age were switched to montelukast 5 mg (one chewable tablet once daily at bedtime).

**Inhaled/nebulized corticosteroids or cromolyn according to the usual clinical practice of the investigator

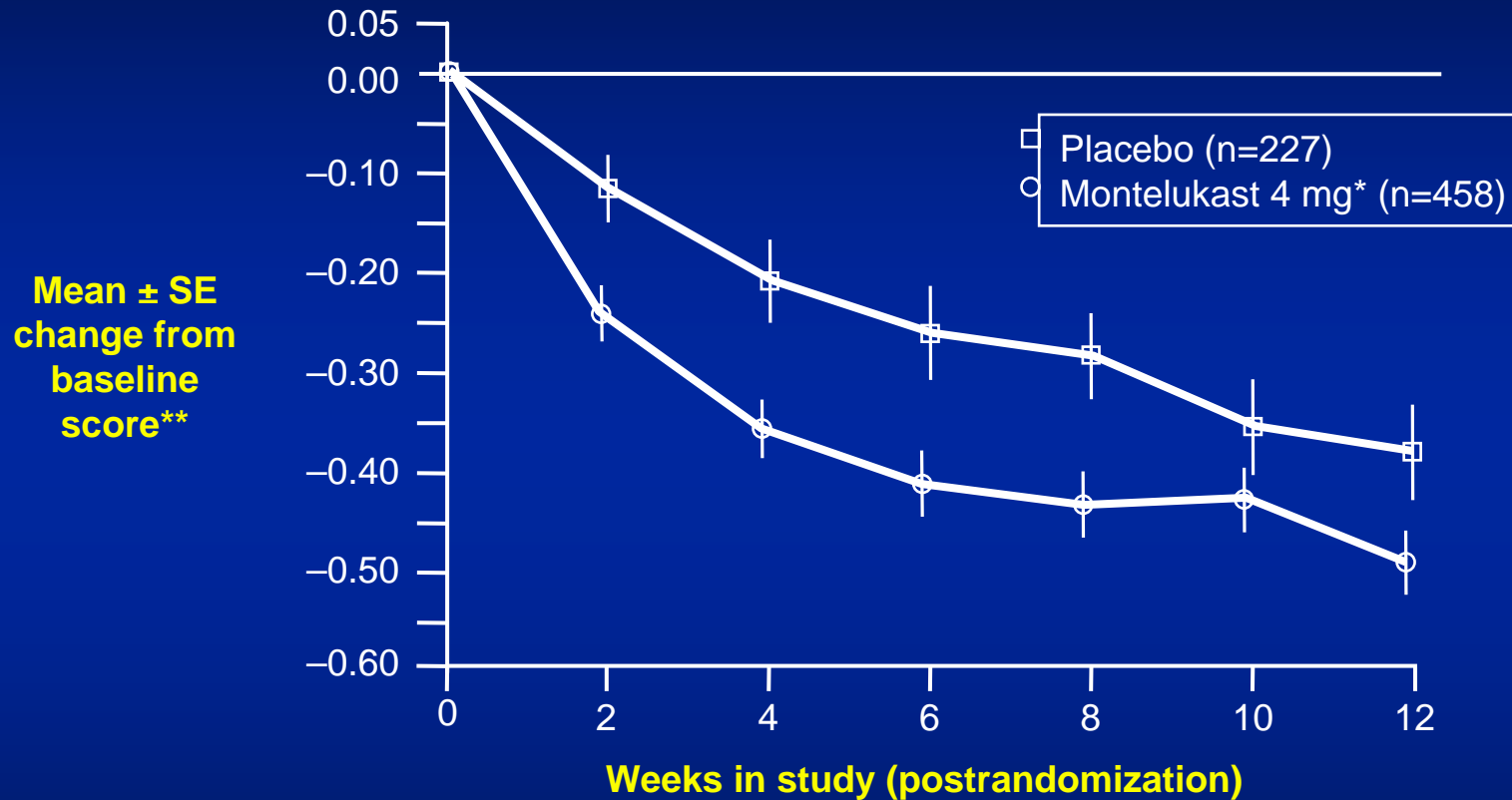
Baseline Characteristics of Patients

	Montelukast 4 mg (n=461)	Placebo (n=228)
Patient numbers		
Randomized (n=689)	461	228
Completed (n=618)	416	202
Gender (% of patients)		
Male	59	57
Female	41	43
Mean age (% of patients)*		
2 years	22	21
3 years	25	22
4 years	29	31
5 years	23	25
Concomitant medication use (% of patients)		
Corticosteroids	27	29
Cromolyn	14	11
Normal RAST (% of patients)**	53	49
Mean duration of asthma (years)	2.4	2.4
Mean daytime asthma symptom score (scale of 0 = no symptoms to 5 = very severe)	0.98	0.95

*Percentages total <100 because 7/461 (1.5%) montelukast patients and 2/228 (0.9%) placebo patients became 6 years old during the study

**RAST = radioallergosorbent tests (serum IgE excluded)

Montelukast Improved Daytime Symptom Score



$p=0.003$ montelukast vs. placebo averaged over 12 weeks of treatment

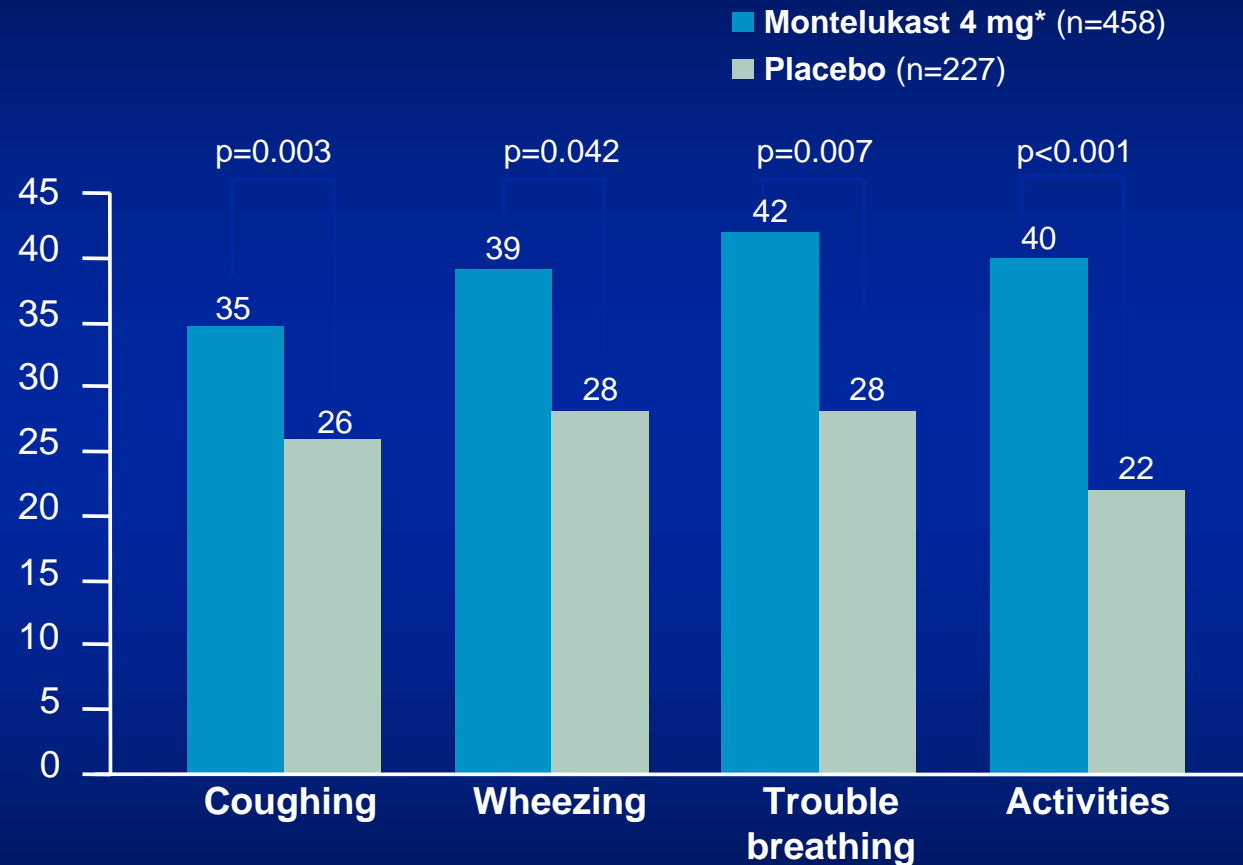
Short-acting β_2 agonists were used as needed in both groups.

Daytime symptom score included cough, wheeze, trouble breathing, and activity limitation.

*One chewable tablet once daily at bedtime

**Scale of 0 to 5 (no symptoms to very severe)

Montelukast Significantly Improved Individual Daytime Symptom Scores

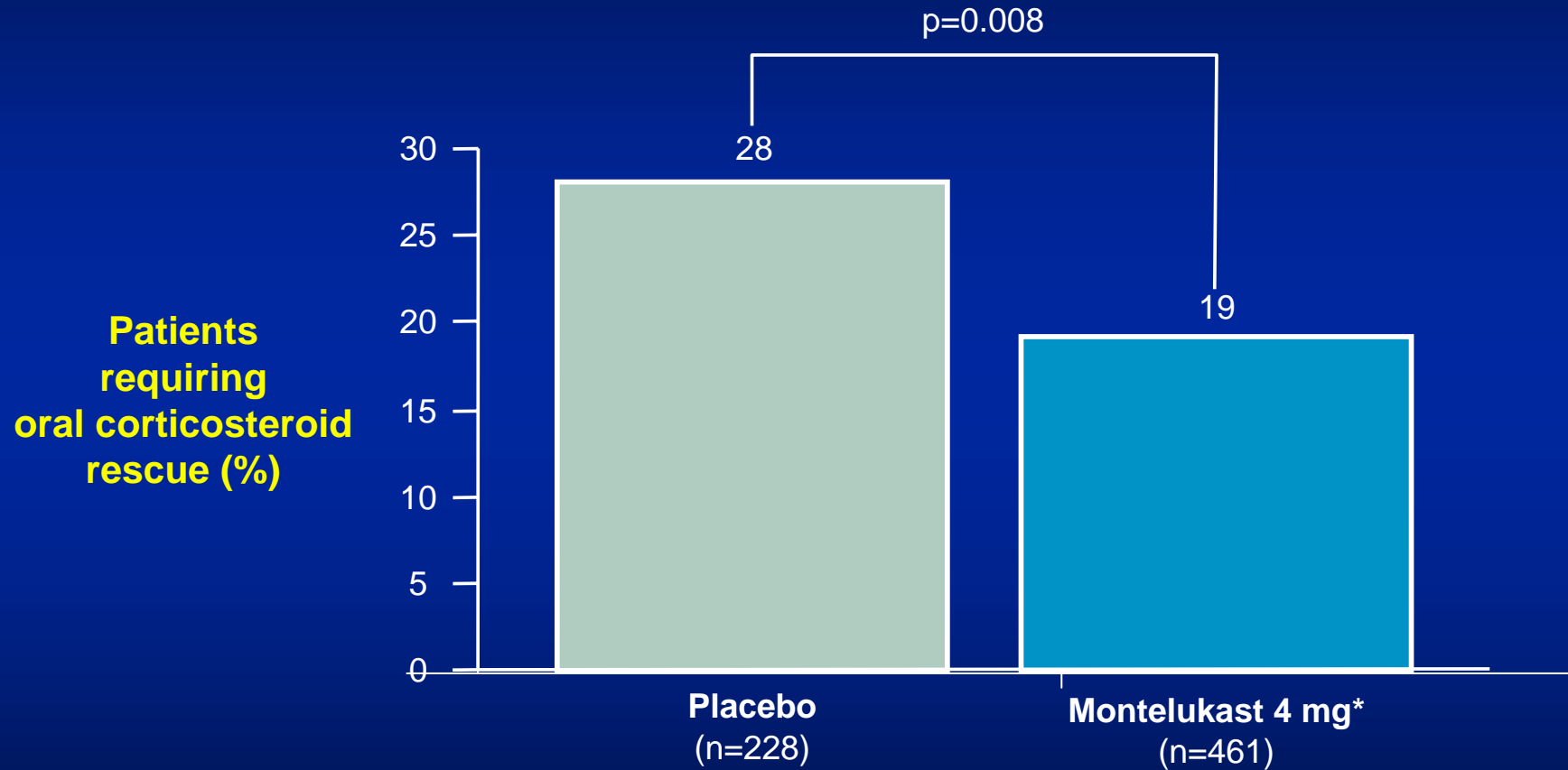


Post hoc analysis based on 0- to 5-point diary scale (no symptoms to very severe)

Short-acting beta₂ agonists were used as needed in both groups.

*One chewable tablet once daily at bedtime

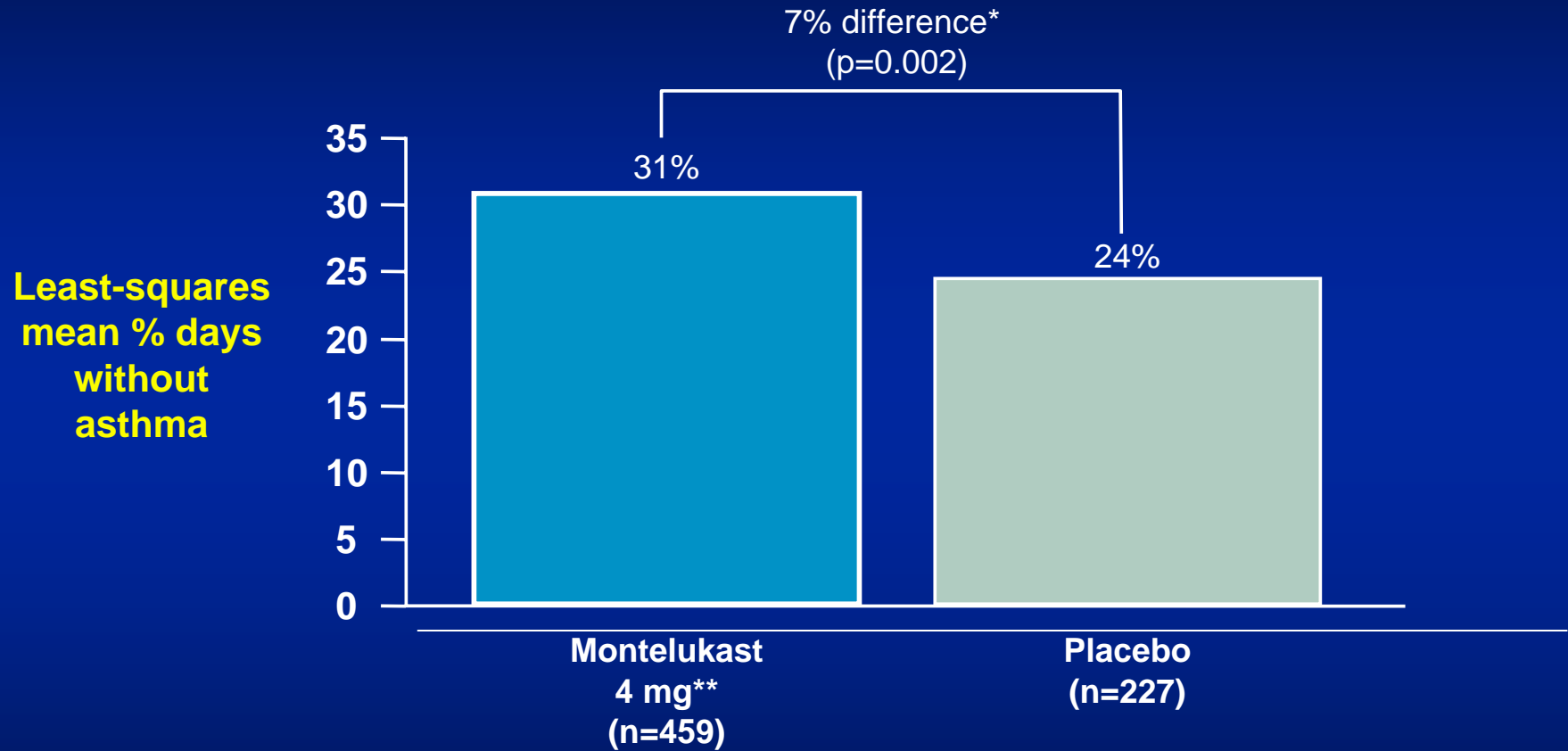
Montelukast Reduced the Need for Oral Corticosteroid Rescue



Short-acting beta₂ agonists were used as needed in both groups.

*One chewable tablet once daily at bedtime

Montelukast Increased Days without Asthma

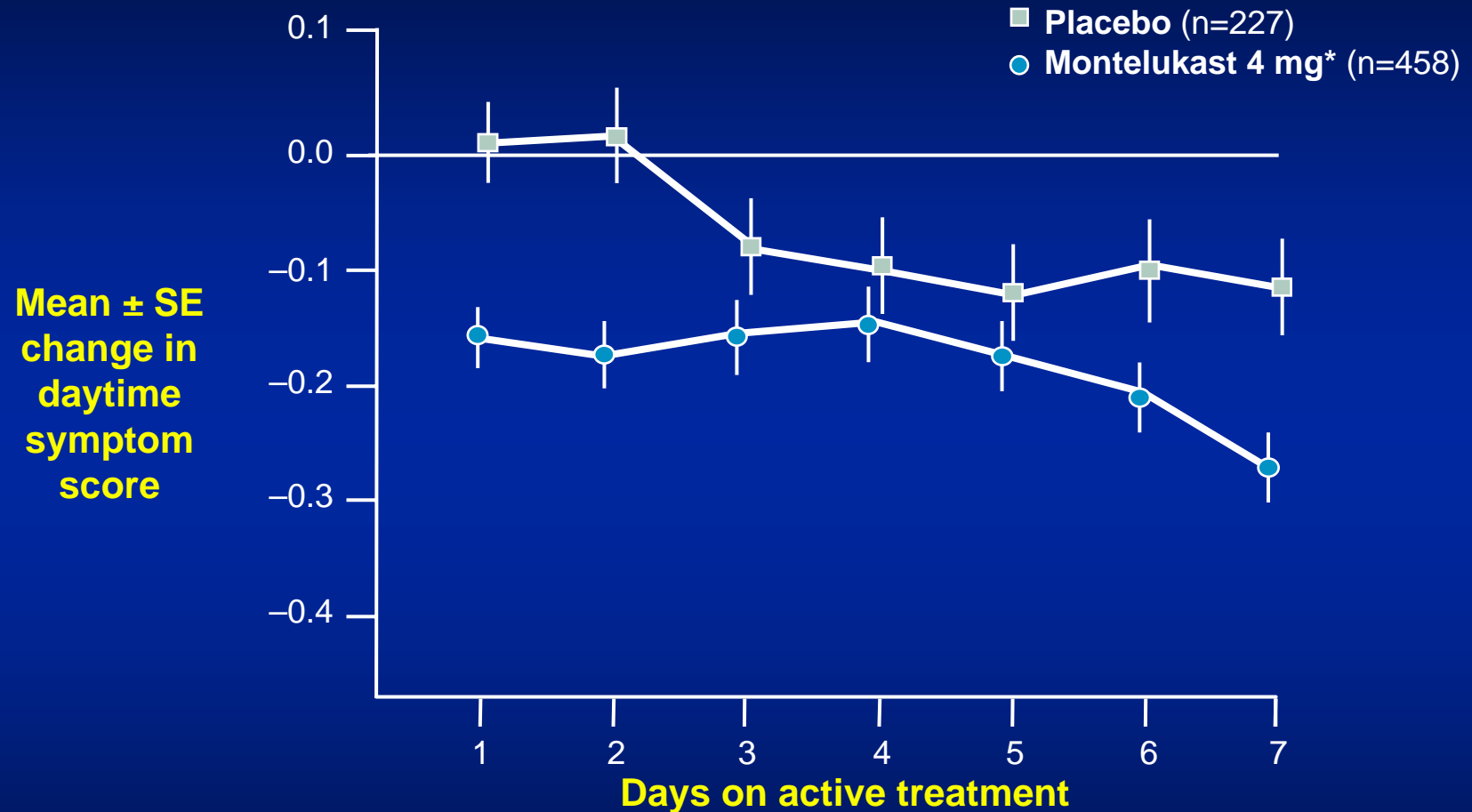


*Montelukast–placebo; **One chewable tablet once daily at bedtime

An asthma-free day was defined as a day with no daytime or nighttime symptoms, no beta₂-agonist use, and no asthma attacks.

Montelukast in Children 2–5 Years of Age

Onset of Action: Daytime Symptoms Improved from Day 1

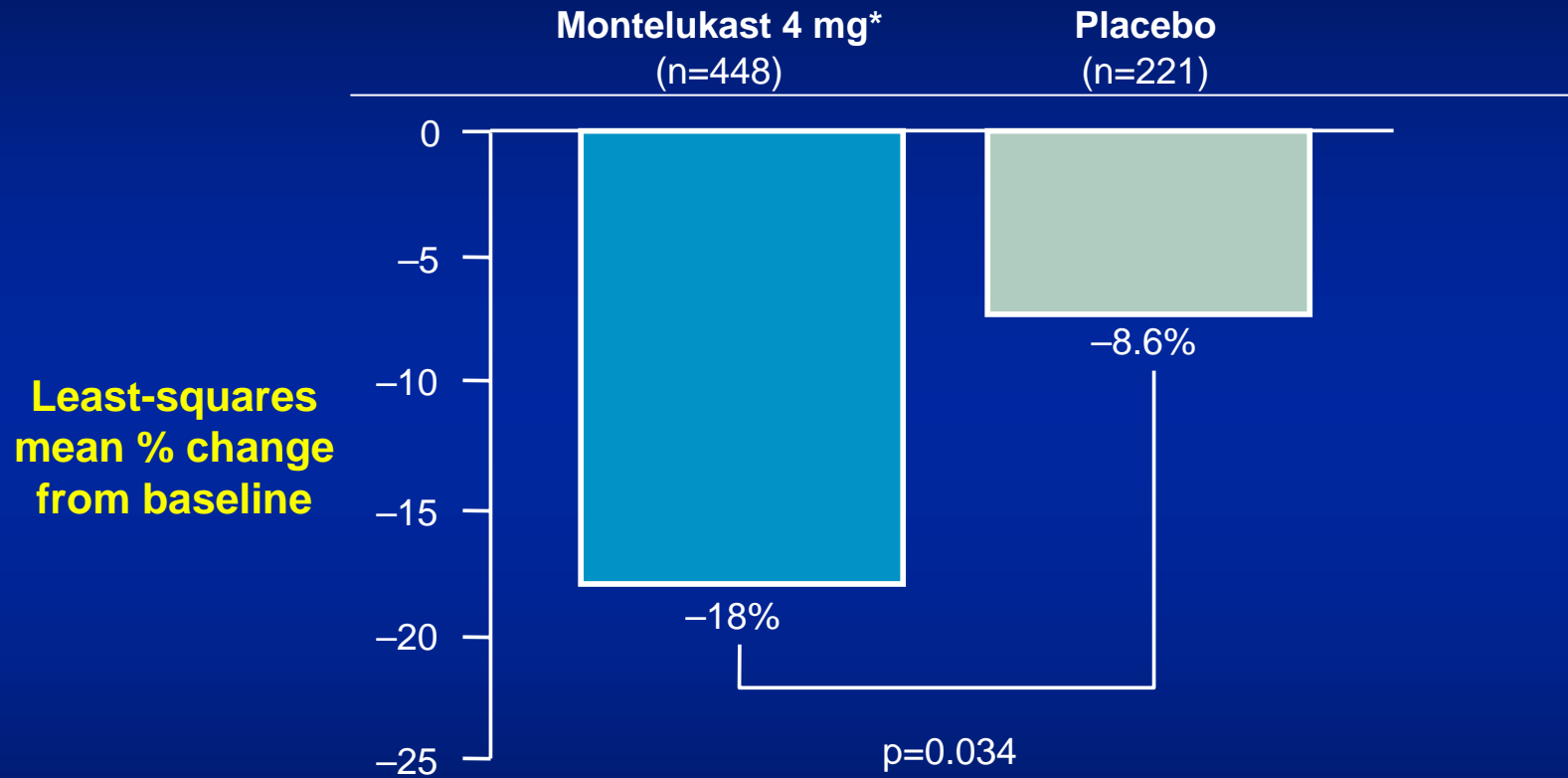


Post hoc analysis of the first 21 days of treatment; first 7 days shown on slide.

Short-acting beta₂ agonists were used as needed in both groups.

*One chewable tablet once daily at bedtime

Reduction in Peripheral Blood Eosinophils



ANCOVA analysis of least-squares mean
*One chewable tablet once daily at bedtime

Montelukast in Children 2–5 Years of Age

Tolerability Profile Comparable to Placebo Over 12 Weeks of Therapy

**Adverse Events in >10% of Patients Regardless of
Drug Relationship**

Adverse events	Montelukast 4 mg* (n=461)	Placebo (n=228)
Worsening asthma	29.7**	37.7
Fever	27.1	26.8
Upper respiratory infections	26.7	27.6
Vomiting	16.3	19.7
Cough	12.6	11.4
Pharyngitis	11.7	15.4
Abdominal pain	11.1	9.2

*One chewable tablet once daily at bedtime

**Notable difference between treatment groups of 8% (95% CI 0.18 to 16.36)

Antileucotrieni

Gli A. sono la prima terapia mediatore-specifica per l'asma.

Gli A. **sono attualmente indicati** per il trattamento dell'asma in quei pazienti con asma persistente che non sono adeguatamente controllati con i corticosteroidi per via inalatoria e nella profilassi dell'asma laddove la componente predominante è la broncocostrizione indotta dall'esercizio.

Gli A. **potrebbero essere indicati** in età prescolare nel trattamento di quelle forme di wheezing ricorrente indotto da virus.