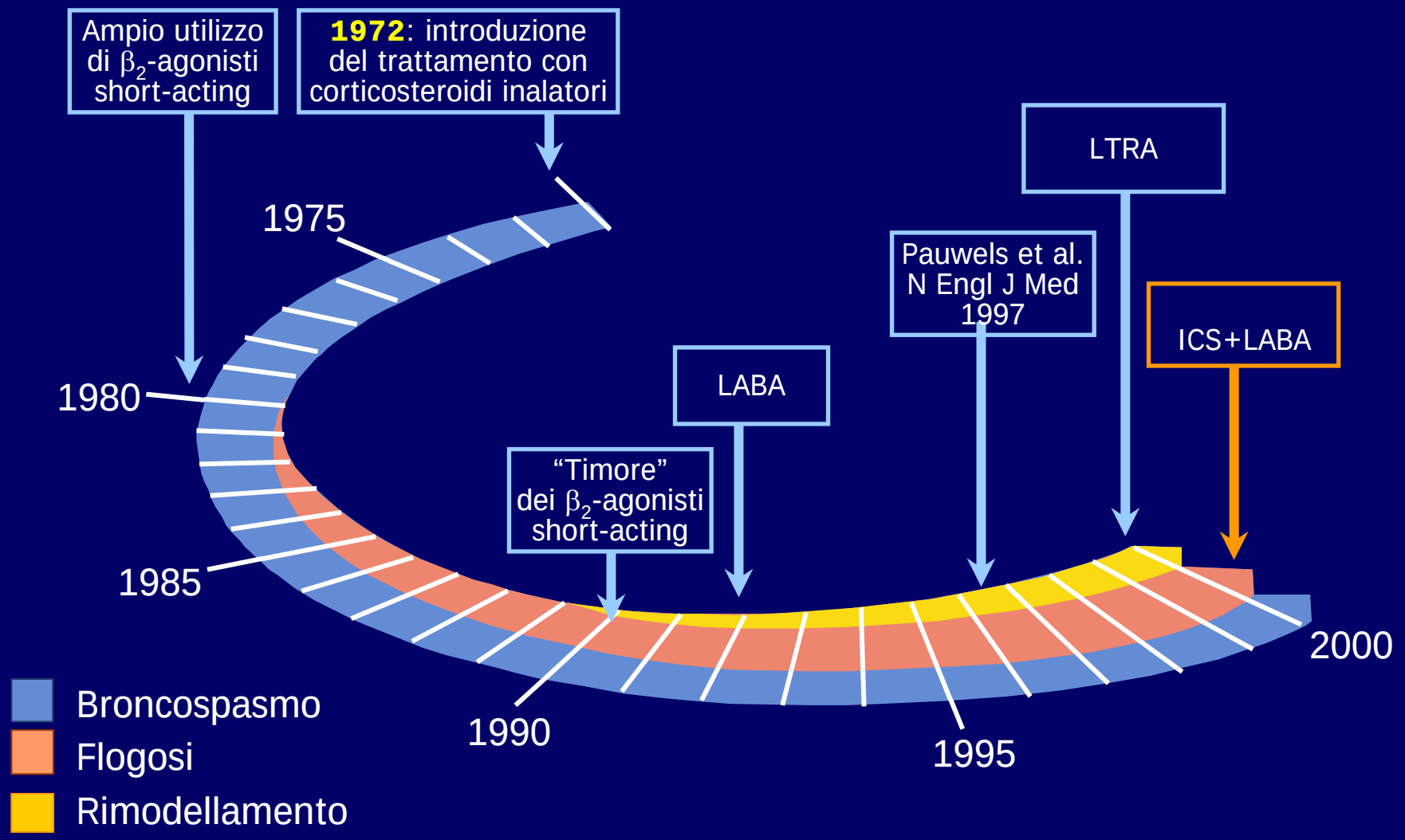
La terapia di associazione nell'asma: i β_2 long-acting

Eugenio Baraldi
Ospedale del Bambino
Padova

1594

Società Italiana di Pediatria Preventiva e Sociale

Evoluzione della terapia dell'asma



Global

INitiative for

Asthma

Linee-Guida Italiane – Aggiornamento 2004

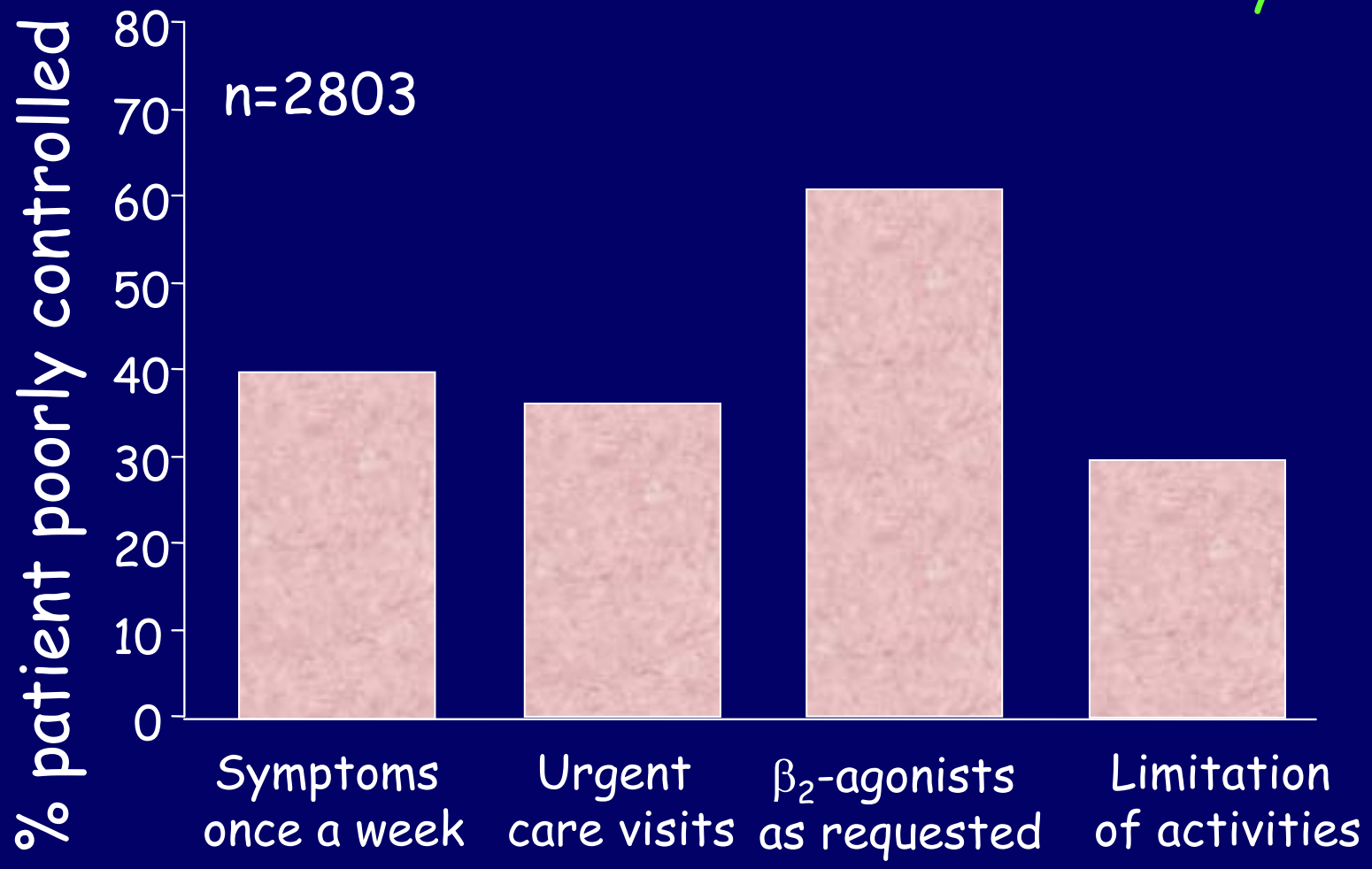
www.ginasma.it

Obiettivi della gestione a lungo termine

- Raggiungere e mantenere il controllo dei sintomi
- **Prevenire le riacutizzazioni dell' asma**
- Mantenere la funzione respiratoria il più vicina possibile ai livelli normali
- Mantenere i normali livelli di attività, incluso l'attività fisica
- ……

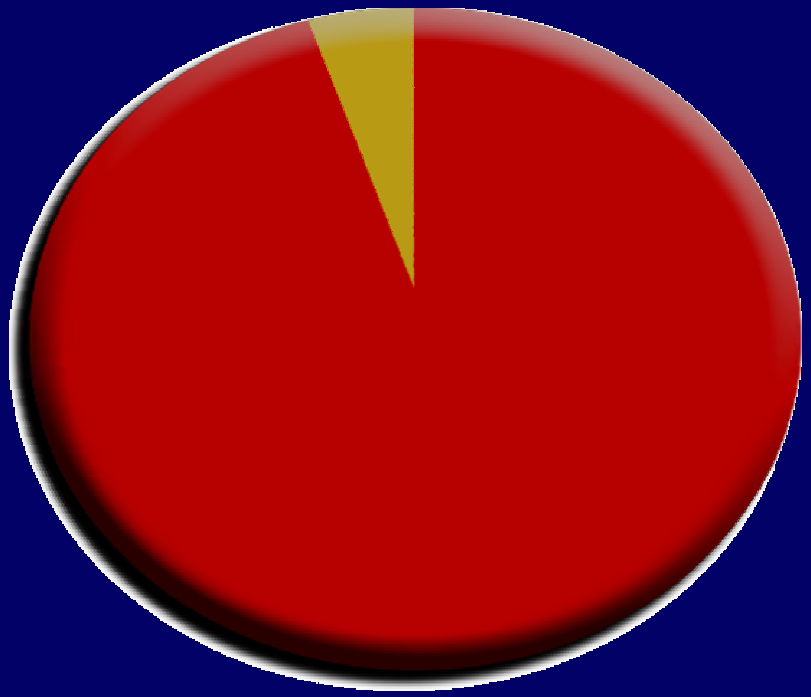
Current level of asthma control in Europe

AIRE study ERJ 2000



AIRE study

Rabe et al ERJ 2000



n=2803 asthmatics
(753 children)

Only 5.8% of children met all the GINA criteria for asthma control

Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations with considerable disruption to their daily life

P.J. Barnes AJRCCM 2005

Farmaci anti-asma raccomandati Livello 1: Bambini Intermittente

Gravità	Farmaci di fondo giornalieri	Altre opzioni
Livello 1: **Intermittente**	• Nessuno	• Nessuno

- Sintomi < 1 volta/settimana
- Sintomi notte non piu' di 2 volte/mese
- FEV1 > 80%

Farmaci sintomatici:

β_2-agonisti per via inalatoria ad azione rapida al bisogno

GINA Italia 2004

Asma intermittente

- Sintomi < 1 volta/settimana
- Sintomi di notte non piu' di 2 volte/mese
- FEV1 > 80%

Quindi un bambino con sintomi di asma 3 volte al mese va inquadrato come asma intermittente?

Solo β_2-agonisti al bisogno?

Farmaci anti-asma raccomandati Bambini Persistente Lieve

Gravità	Farmaci di fondo giornalieri	Altre opzioni (ordine di efficacia)
Livello 2: **Persistente Lieve**	• **Glucocorticoidi** per via inalatoria a **basso dosaggio**	•Antileucotrienici, *oppure* •Cromoni

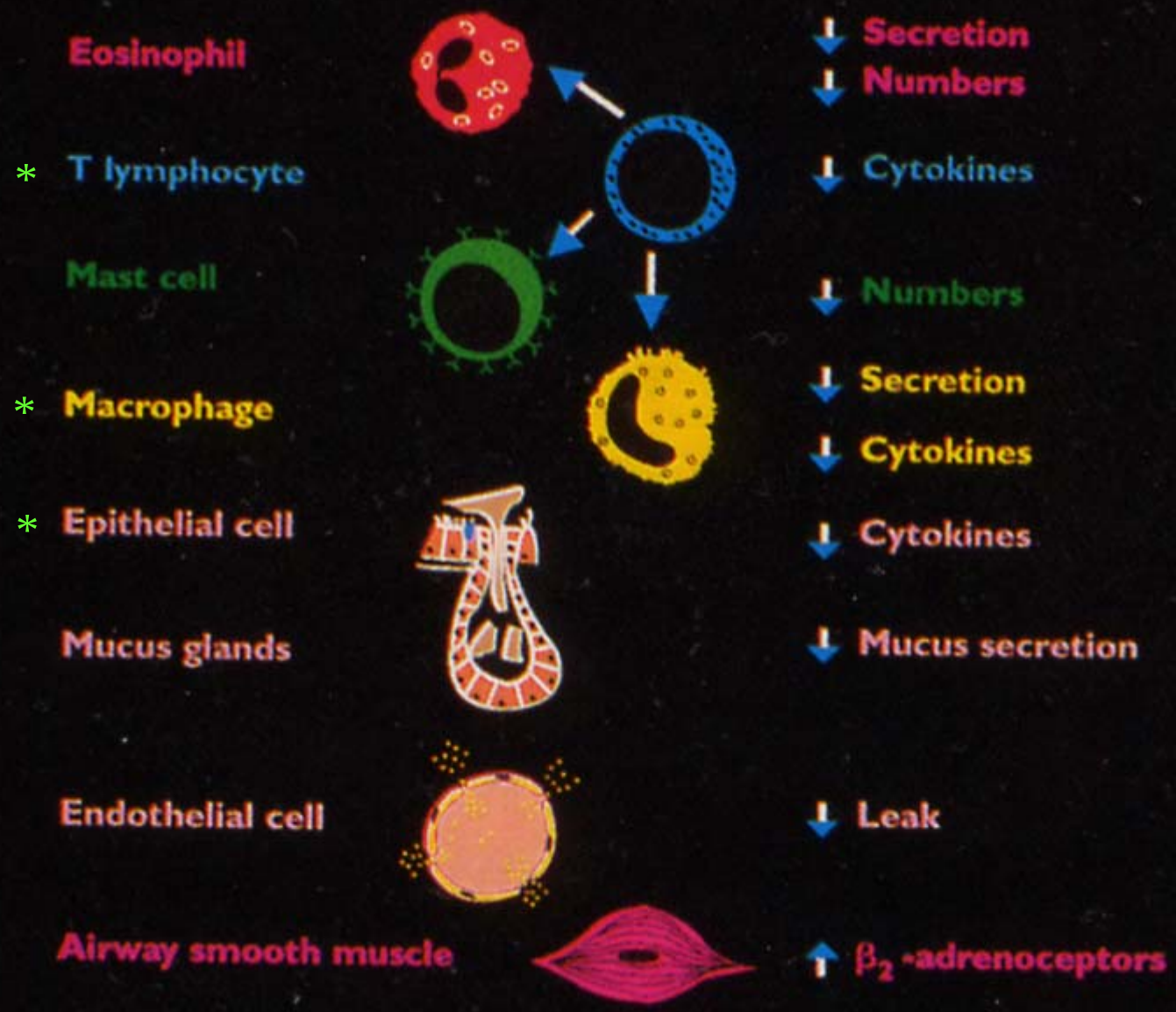
- Sintomi > 1 volta settimana
- Riacutizzaz. che disturbano il sonno e la normale attività
- Sintomi notte > 2 v/mese
- FEV_1 > 80%

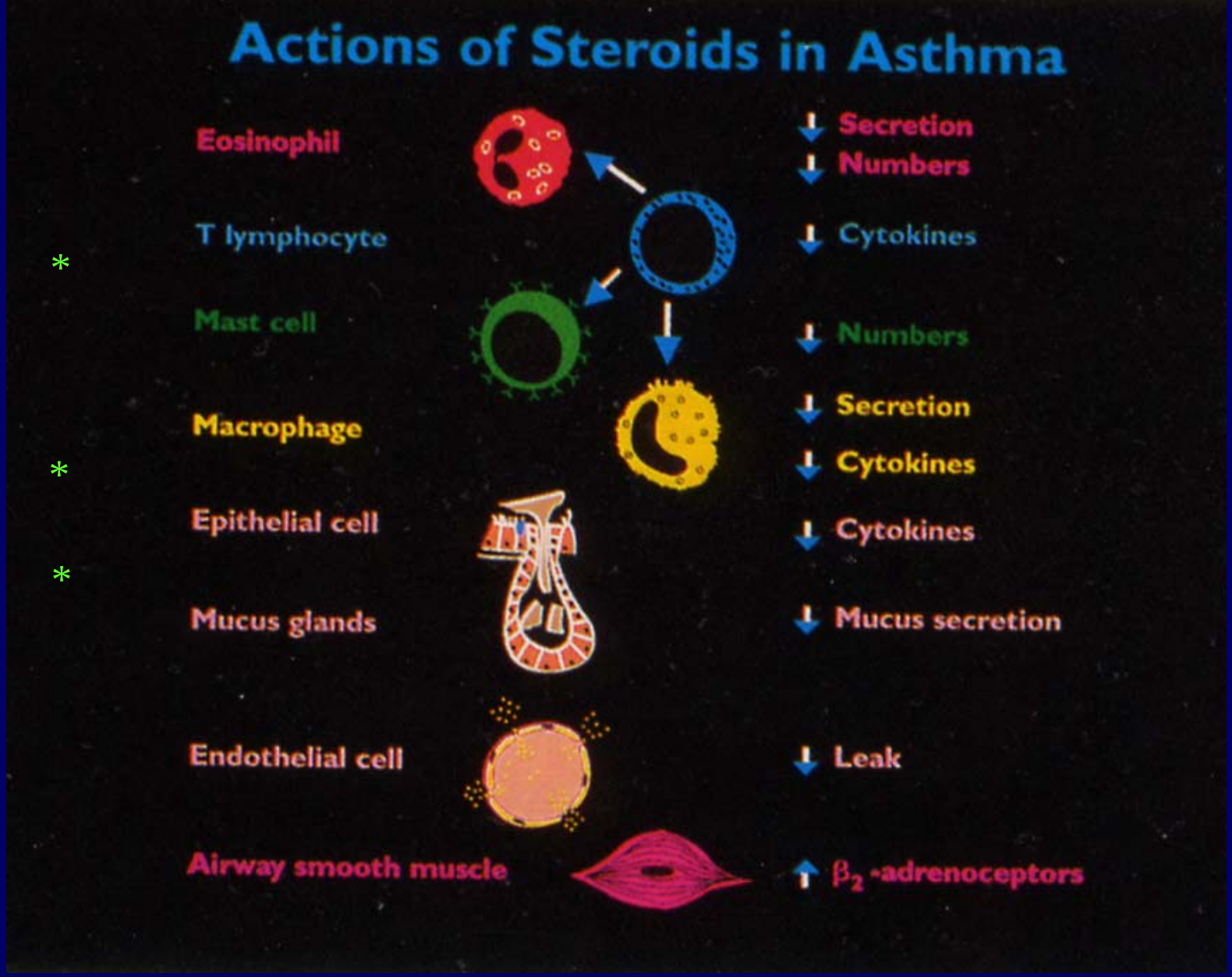
GINA Italia 2004

Stabilire piani per il trattamento a lungo termine dell'asma

- Ad oggi, i glucocorticosteroidi inalatori sono i più efficaci farmaci per il controllo dell'asma e sono raccomandati per l'asma persistente ad ogni livello di gravità

Actions of Steroids in Asthma





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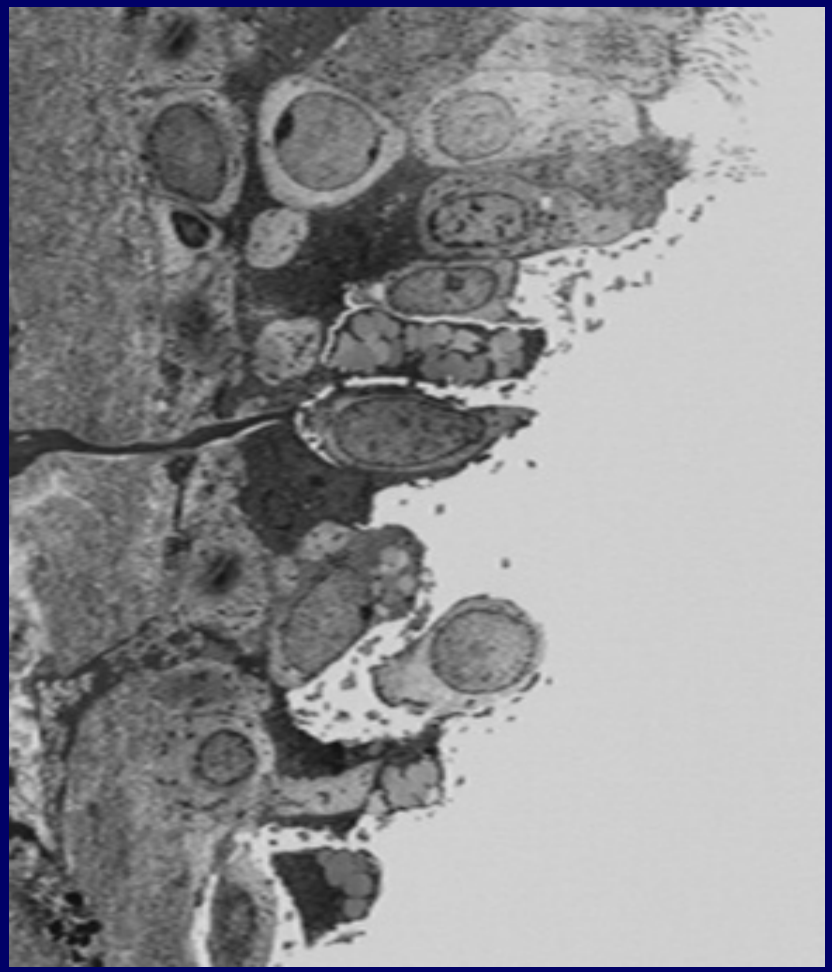
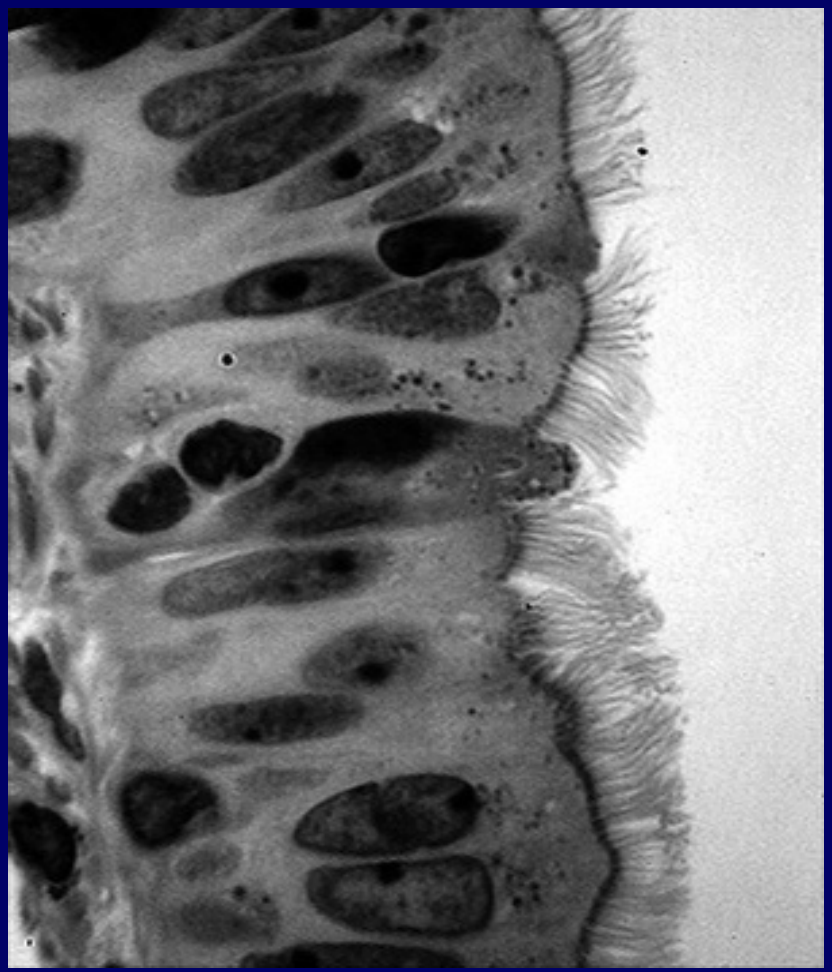
Su quali cellule non sono attivi?

Epithelial repair following steroid treatment



Before



After

P Howarth, 199

AIRE study

Rabe et al ERJ 2000

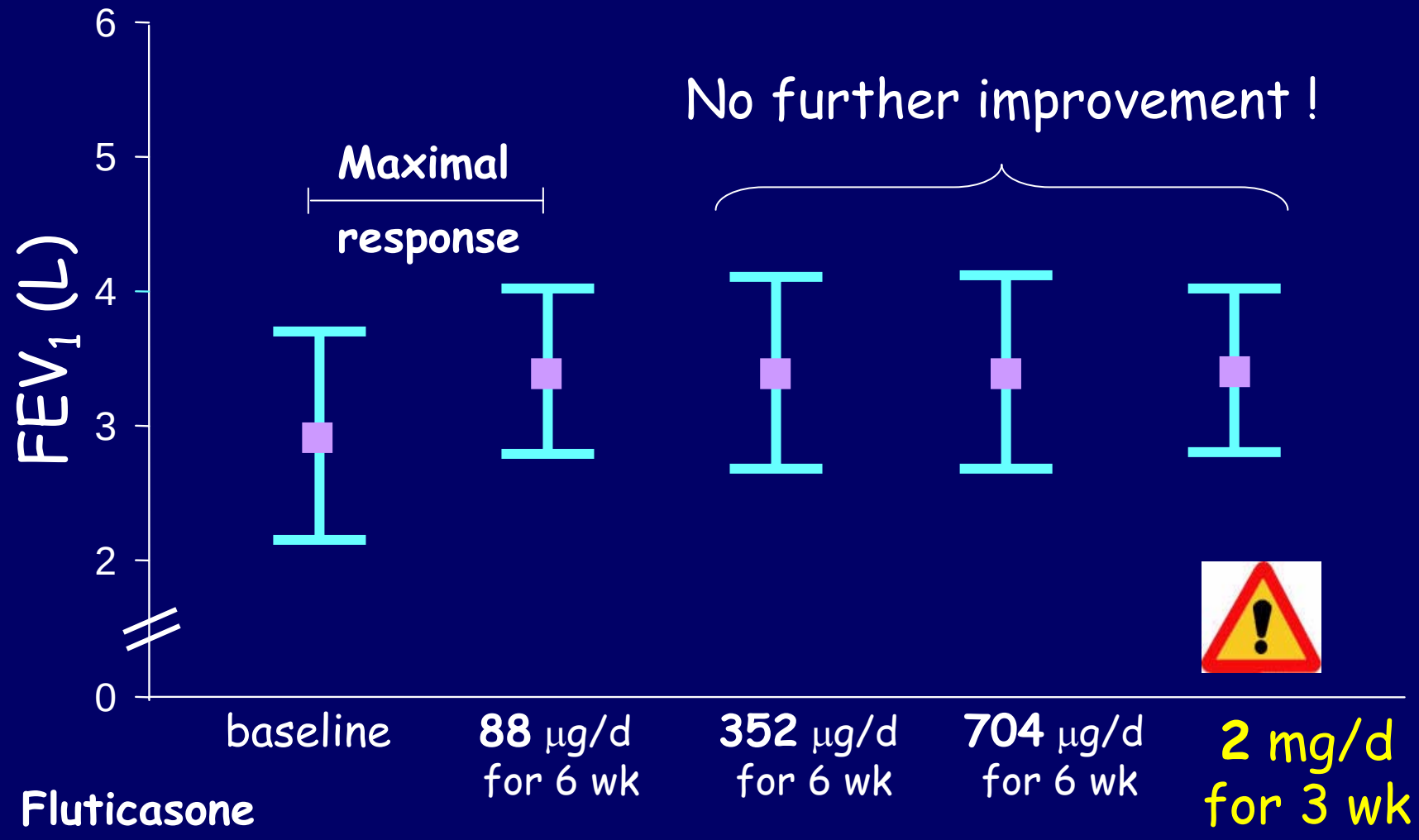
Only 5.8% of children met all the GINA criteria for asthma control

n=2803 asthmatics (753 children)

Only **30%** of children with persistent asthma used ICS

INCREASING DOSE OF FLUTICASONE DOES NOT IMPROVE FEV_1

Szefler JACI 2002;109:410



Dosaggio giornaliero comparativo stimato degli steroidi inalatori - bambini

2004

Farmaco	Dose bassa	Dose media	Dose elevata
Beclometasone	**CFC 100-250 μg** **HFA 50-200 μg**	250-500 μg 200-400 μg	>500 μg >400 μg
Budesonide	**DPI 100-200 μg**	200-600 μg	>600 μg
Fluticasone propionato	**100-200 μg**	200-400 μg	>400 μg
Flunisolide	**500-750 μg**	1000-1250 μg	>1250 μg

HFA=hydrofluoroalkane CFC=chlorofluorocarbon

Dosaggio giornaliero comparativo stimato degli steroidi inalatori - bambini

2002

Farmaco	Dose bassa	Dose media	Dose elevata
Beclometasone dipropionato	**100-400 μg**	400-800 μg	>800 μg
Budesonide	**100-400 μg**	400-800 μg	>800 μg
Fluticasone propionato	**50-200 μg**	200-400 μg	>400 μg
Flunisolide	**500-750 μg**	1000-1250 μg	>1250 μg

Scelta del dispositivo per inalazione nel bambino

Età	Dispositivo da preferire	Dispositivo alternativo
Sotto i 4 anni	MDI* con camera di espansione e maschera facciale	Nebulizzatore con maschera
4 - 6 anni	MDI* con camera di espansione con boccaglio o maschera facciale	Nebulizzatore con maschera o boccaglio

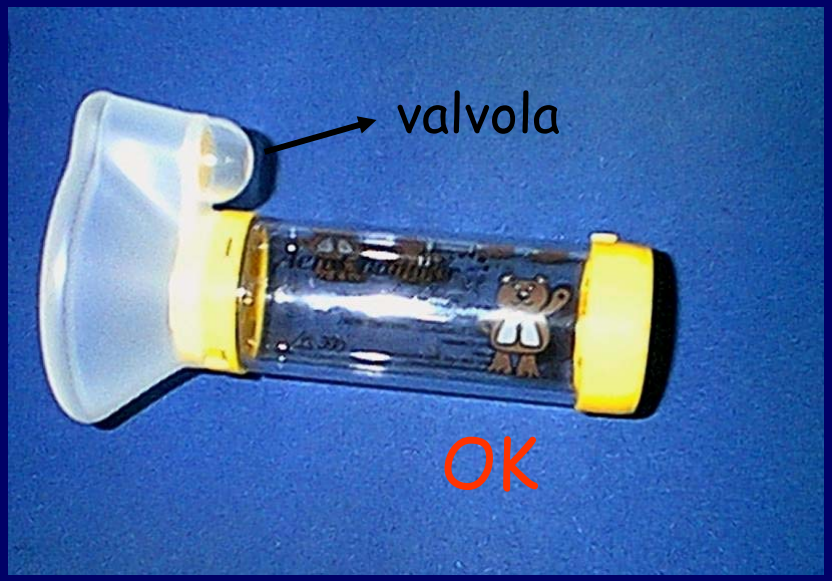
***MDI:** aerosol in bombolette pressurizzate

Prescrivere I dispositivi solo dopo aver adeguatamente educato bambini e genitori e verificare la tecnica di inalazione con regolarità

BAMBINI sotto ai 4-5 ANNI

Babyhaler (PubM=27)

Aerochamber (PubM=38)



Fluspacer (PubM=0)

OK dopo i 6 anni

Erogatore spray

Erogatori a polvere secca

Erogatori a polvere secca

Dopo i 6-7 anni !

Le domande per valutare se l'asma è in buon controllo

SONO STATI RAGGIUNTI GLI OBBIETTIVI DI UN BUON CONTROLLO?

1) Il bambino si è svegliato per asma durante la notte?

2) Quante volte ha usato salbutamolo nelle ultime 3 settimane?

3) Ha presentato "fischio" o mancanza di respiro?

4) Ha partecipato senza problemi alle normali attività fisiche o sportive?

GINA 2004

Farmaci anti-asma raccomandati Bambini Persistente moderato

Gravità	Farmaci di fondo giornalieri	Altre opzioni
Livello 3: **Persistent Moderata**	**Glucocorticoidi** per via inalatoria a **dose media**	• **Glucocorticoidi** per via inalatoria a basso (medio) dosaggio *più* **β_2-agonisti long-acting** (> 4 anni), *oppure* • **Glucocorticoidi** per via inalatoria a basso (medio) dosaggio *più* **antileucotrienici** (> 6 mesi)

- sintomi giornalieri
- Riacutizzaz. che disturbano il sonno e la normale attività
- Sintomi notte > 1 v/settimana
- Uso giornaliero di beta-2
- FEV_1 60- 80% pred

Dinamicità

GINA Italia 2004

Combination therapy in children (moderate persistent asthma)

long-acting β_2 -agonists

+

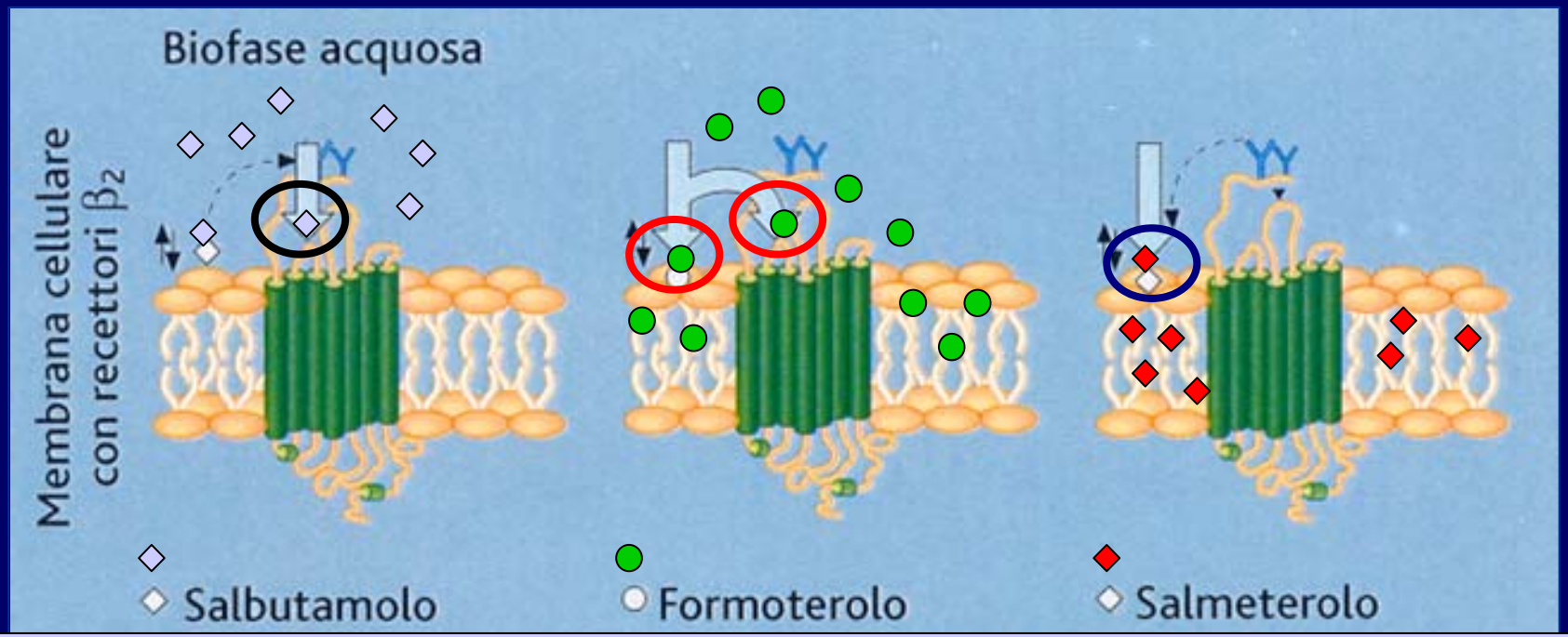
low (medium) doses of ICS

OR

Low (medium) doses of ICS

+

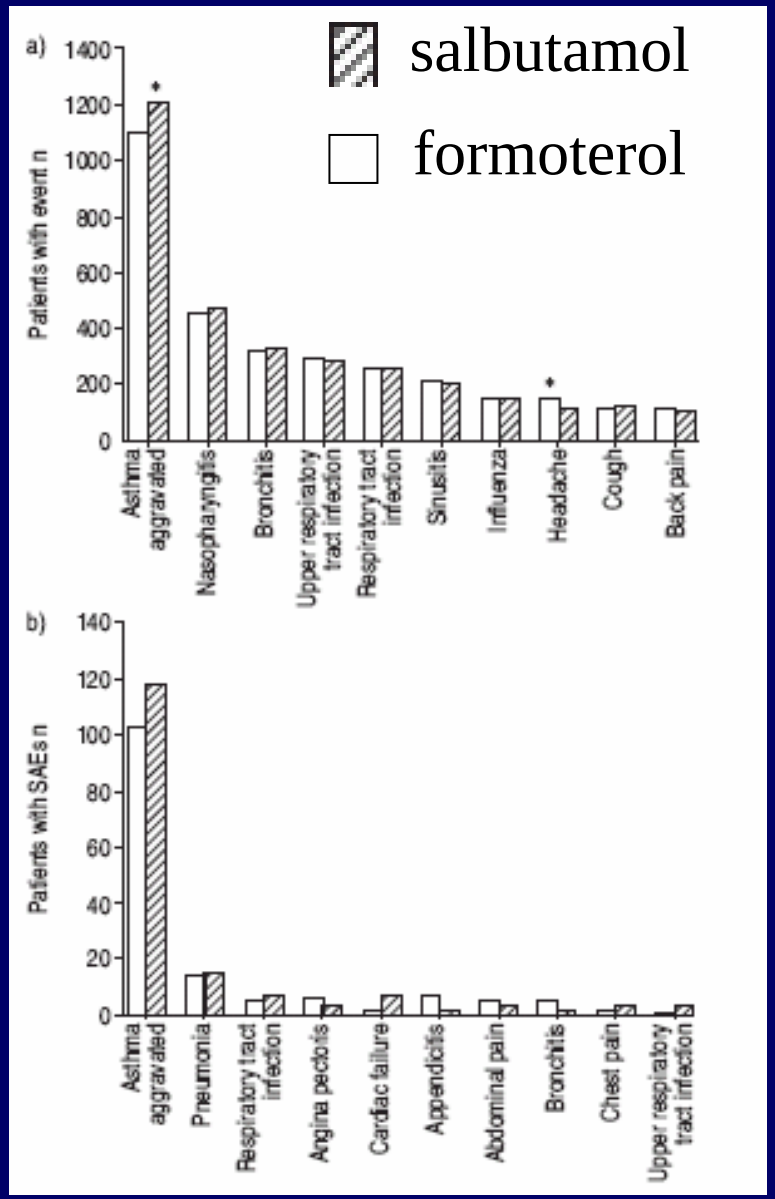
leukotriene modifier



Salbutamolo	Formoterolo	Salmeterolo
• hydrophilic	• lipophilic ++	• lipophilic ++++
• onset 3’	• onset action 3’	• onset action 15’
• max action 15’	• max 10-15’	• max 30’
• duration 4-5 h	• duration > 12h	• duration > 12 h
	• full agonist	• partial agonist
	• dose-dependent effect	• no dose-depend effect over 50 mcg

Sears Resp Med 2005

Formoterol as reliever medication in asthma



n= 18124 subjects
age 5-91 years
6 months study

Formoterol as needed has a similar safety profile to salbutamol with fewer asthma exacerbation

FDA approved as rescue medication

Pauwels ERJ 2003; 22: 787-794

The **ultra** long-acting β_2-agonist

Indacaterol

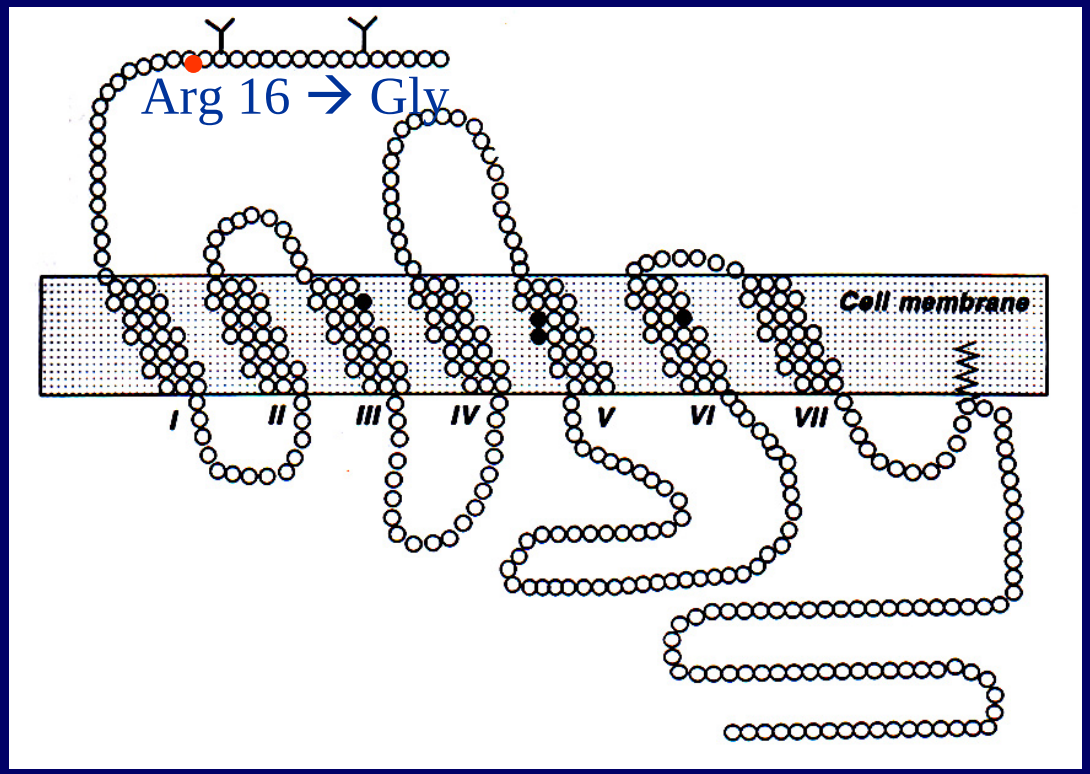
the first one-daily β_2-agonist with
24-hour bronchodilation

ERS Annual Congress 2005

β_2-adrenergic receptor polymorphism is asthma

Israel Lancet 2004

HUMAN β_2 ADRENOCEPTOR STRUCTURE



Arg 16 allele: poorer long-term response to salbutamol

Development of tolerance to β_2-agonists

Daily treatment with SABA and LABA may induce tolerance

1) possible reduction in the bronchodilation to short-acting β_2 +-

2) reduction in the protective effect against bronchial challenge i.e. methacholine, exercise ++

This is not associated with loss of asthma control (Boulet AJRCCM 2000)

May have clinical implication with EIA

Lotvall Curr Med Res 2005

Development of tolerance to β_2-agonists

Daily treatment with SABA and LABA may induce tolerance

1) possible reduction in the bronchodilation to short-acting β_2 +-

2) reduction in the protective effect against bronchial challenge i.e. methacholine, exercise* ++

* may have clinical implication with EIA

Lotvall Curr Med Res 2005

Monotherapy with long-acting β_2-agonists is <u>not</u> recommended

Patients tacking salmeterol without ICS had an increased risk of asthma-related death

FDA warning 2003

Anti-inflammatory effects of LABA in asthma

Salmeterol reduces neutrophils in bronchial biopsies
Jeffrey ERJ 2002

Salmeterol reduced IL-8 in BAL
Reid ERJ 2003

Formorerol reduces neutrophils in sputum
Maneechotesuwan Chest 2005

COMBINATION THERAPY
ICS + LABA

IN SEPARATE INHALERS (CONCURRENT)

IN A SINGLE INHALER (COMBINATION)

Combination therapy with ICS and LABA in separate inhalers (CONCURRENT)

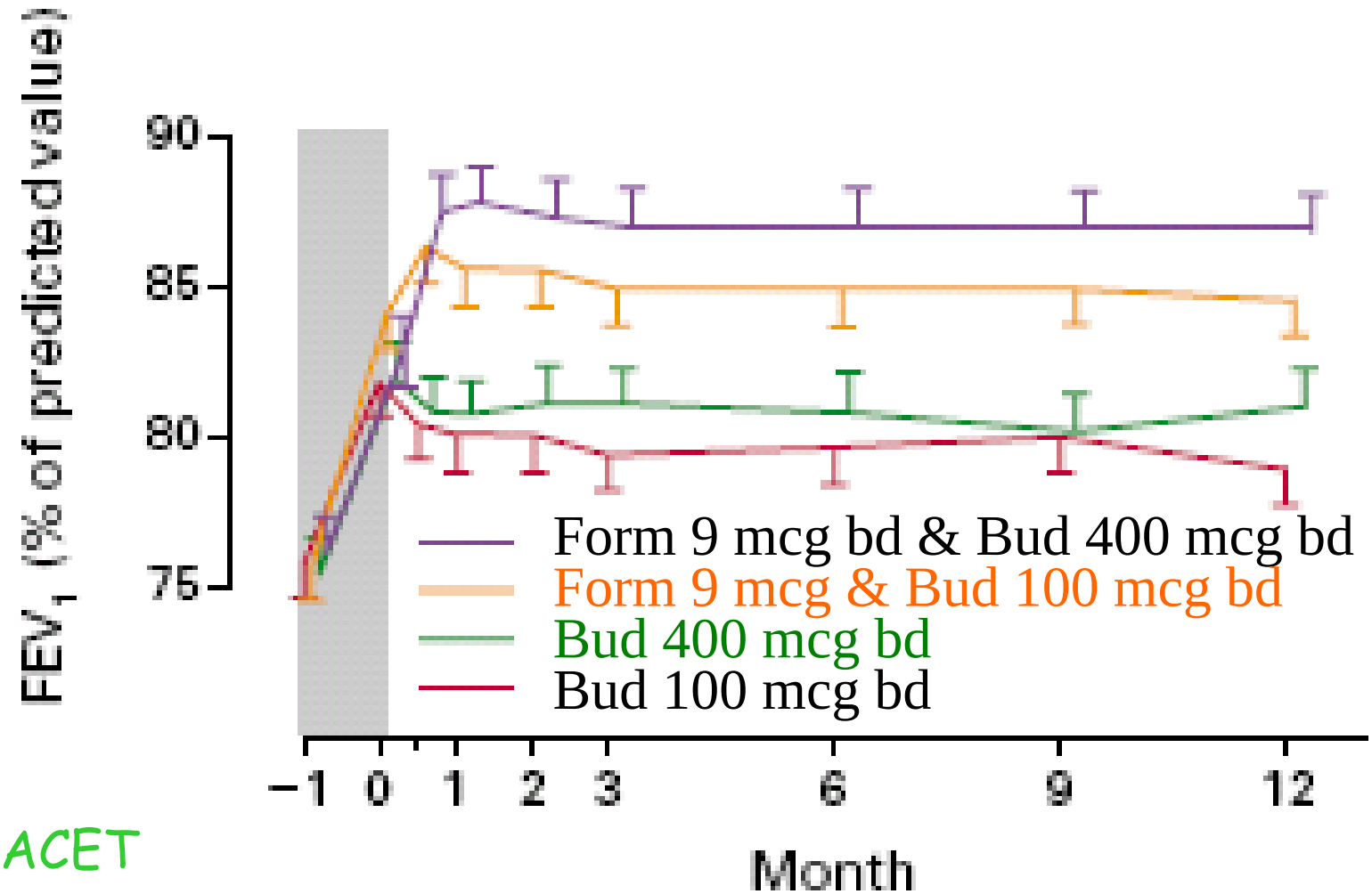
- Controls asthma at lower doses of ICS compared to ICS alone (X 2-4)
- Improves lung function to a greater degree than higher dose of ICS
- Reduces risk of severe exacerbation
- May mask underlying airway inflammation?

simultanea

Sears Resp Med 2005

The New England Journal of Medicine

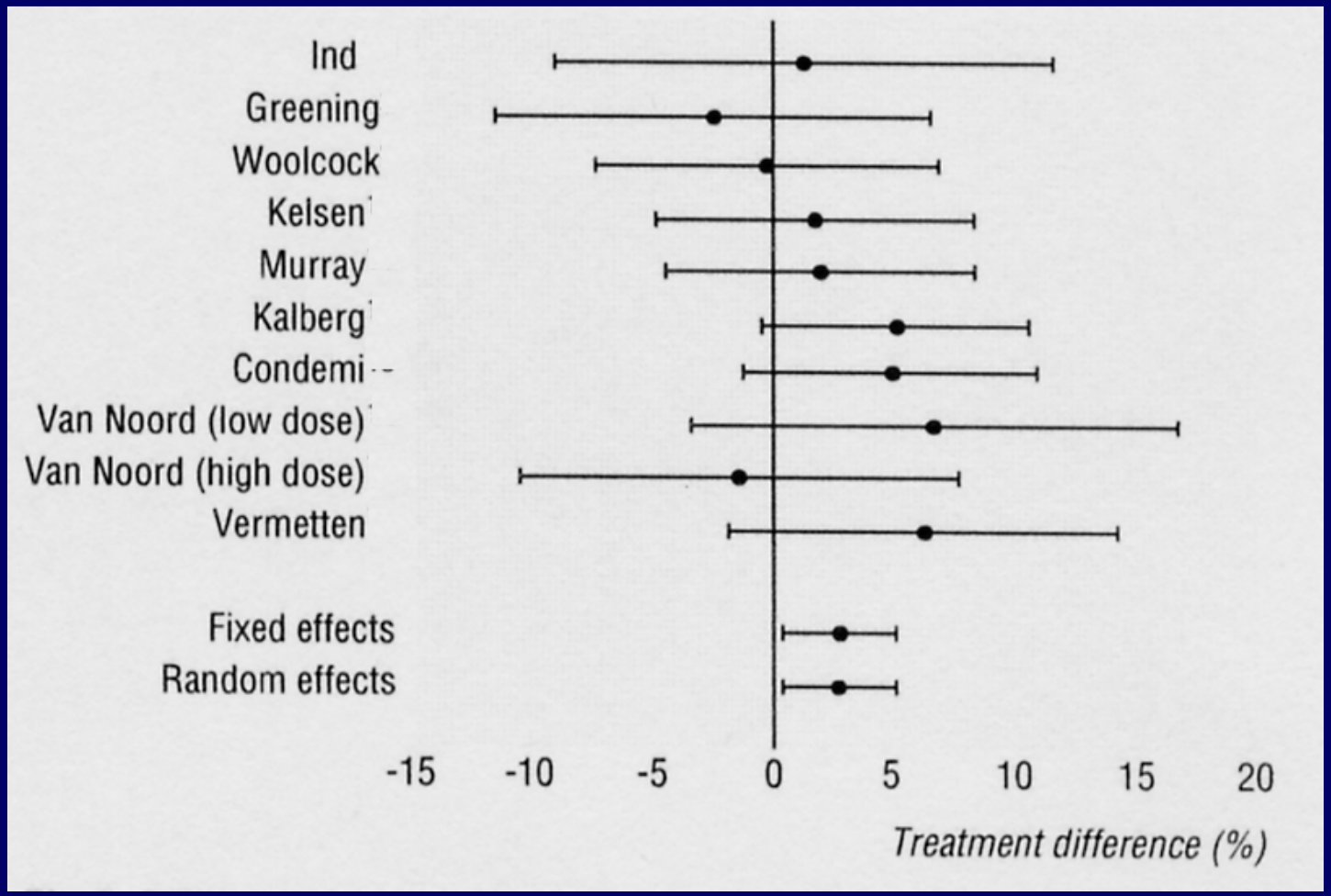
Pauwels et al NEJM 1997;337:1405-11



FACET

A meta-analysis of increasing inhaled steroids or adding salmeterol on symptomatic asthma (MIASMA)

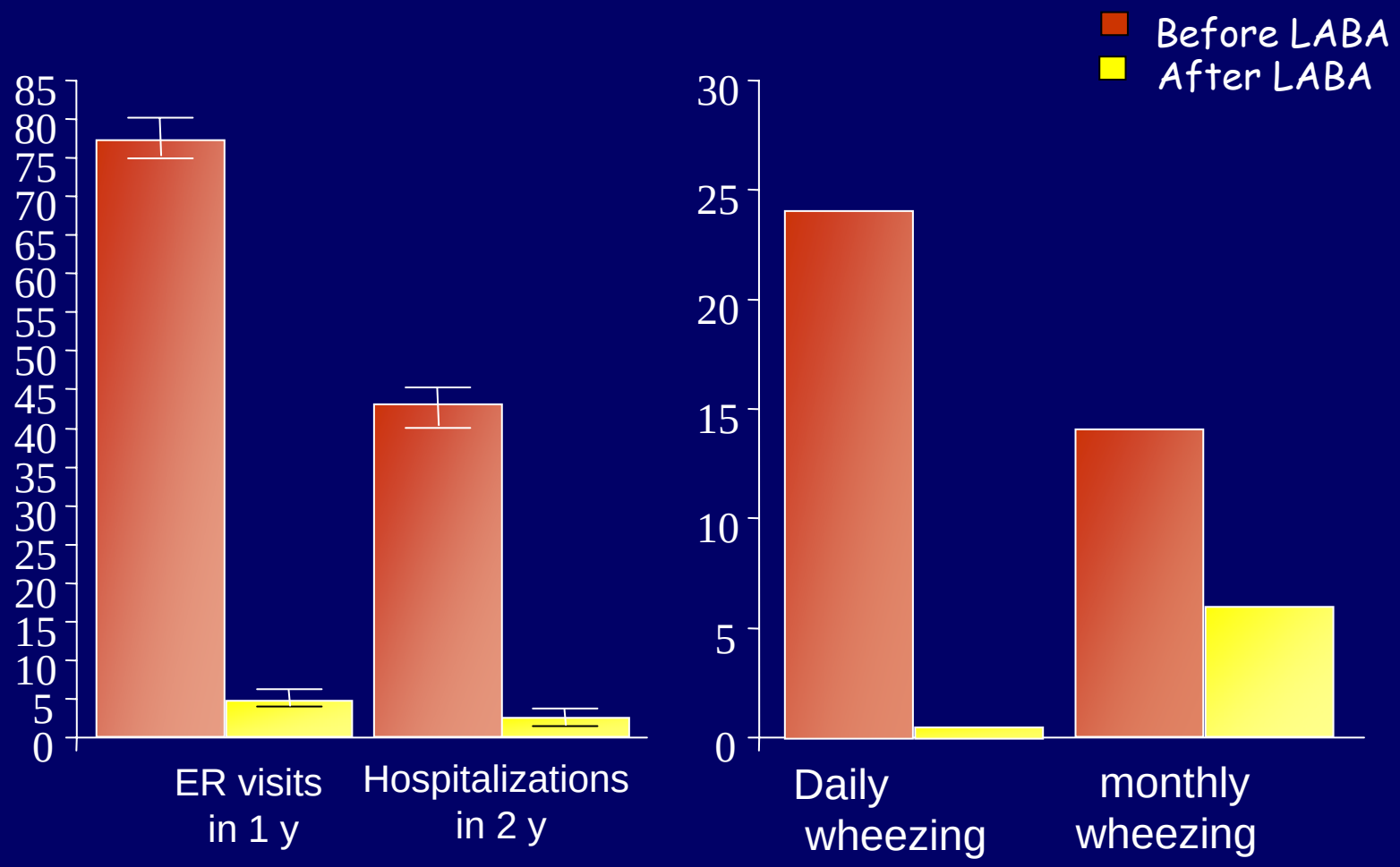
Shrewsbury BMJ 2000



Difference in % of patients with one or more exacerbation

Efficacy and safety of ICS in combination with LABA in asthmatic children under age 5

Sekhsaria J Asthma 2004; 41:575-82



COMBINATION THERAPY
ICS + LABA

IN SEPARATE INHALERS (CONCURRENT)

IN A SINGLE INHALER (COMBINATION)

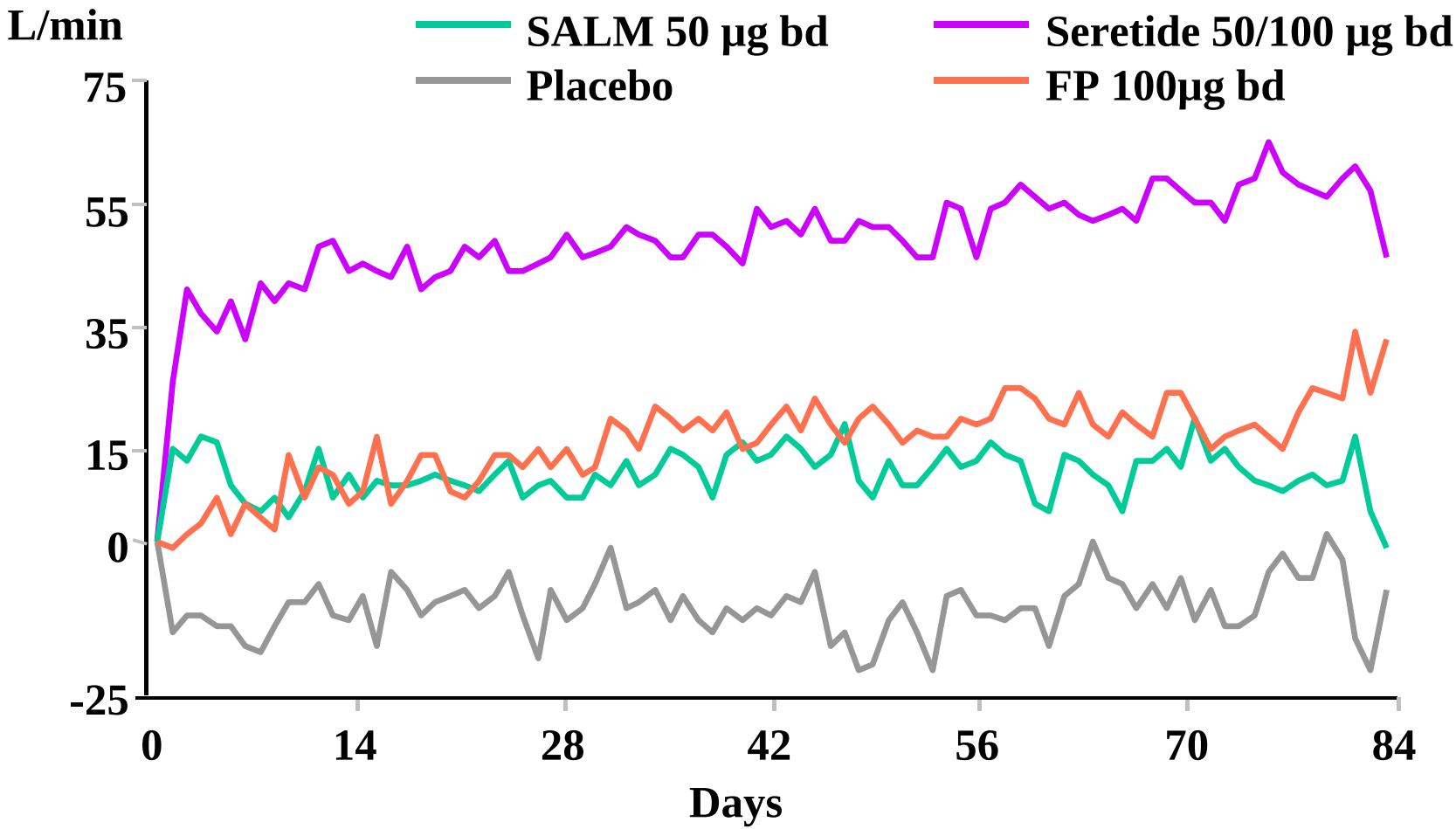
Combination therapy with ICS and LABA in a single inhaler (COMBINATION)

- Controls asthma at lower doses of ICS
- Improves lung function to a greater degree than higher dose of ICS
- Reduces risk of severe exacerbation

- Simplify treatment (single inhaler)
- Prevent over-relying of LABA or SABA at expense of ICS therapy avoiding the risks related to LABA monotherapy!
- Additional benefit on lung function (molecular interactions on receptors ?)

Problem: lack of flexibility when ICS dose needs to be adjusted stepping-down

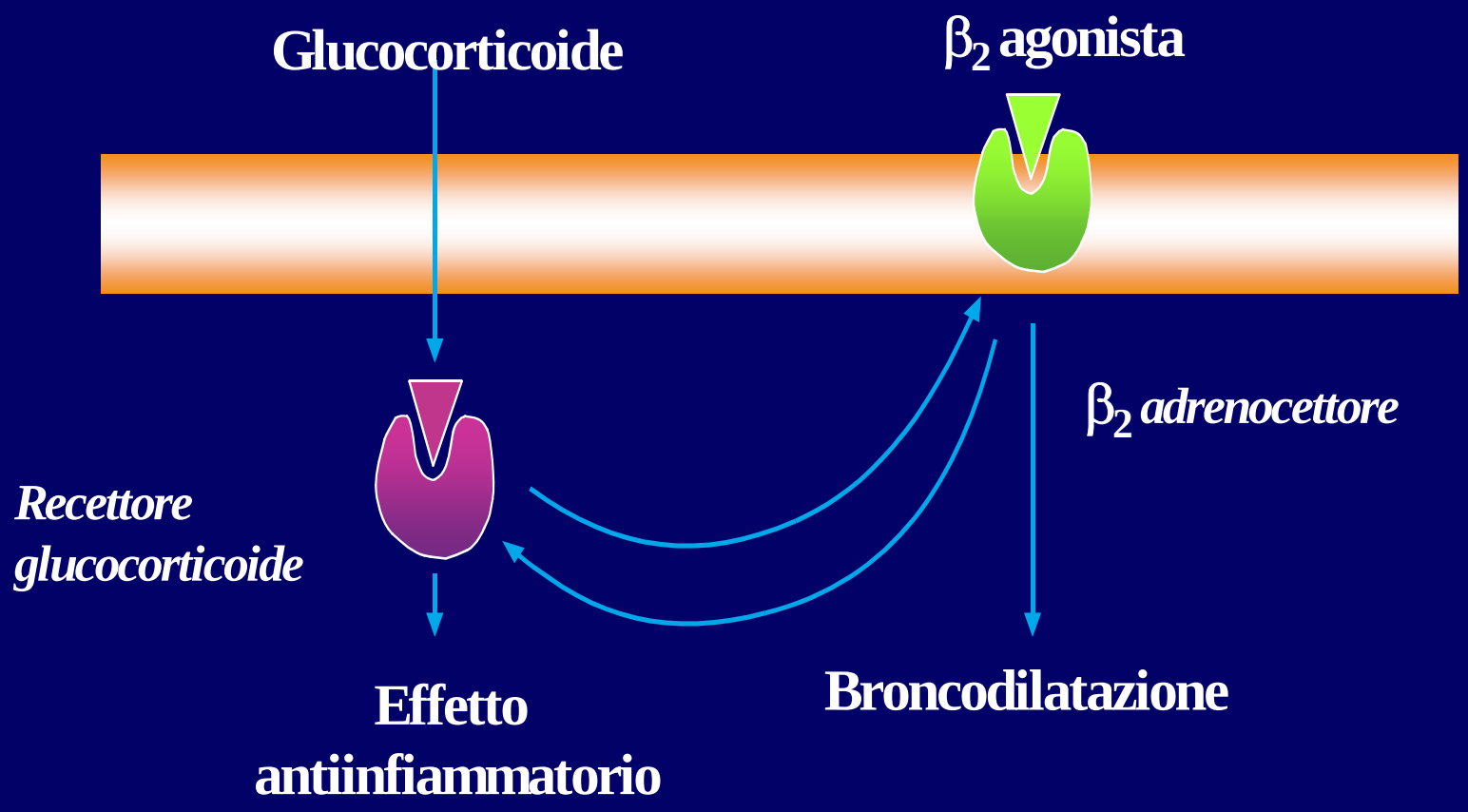
S&FP vs individual components: Change from baseline in mean PEF am



70% of patients previously treated with ICS

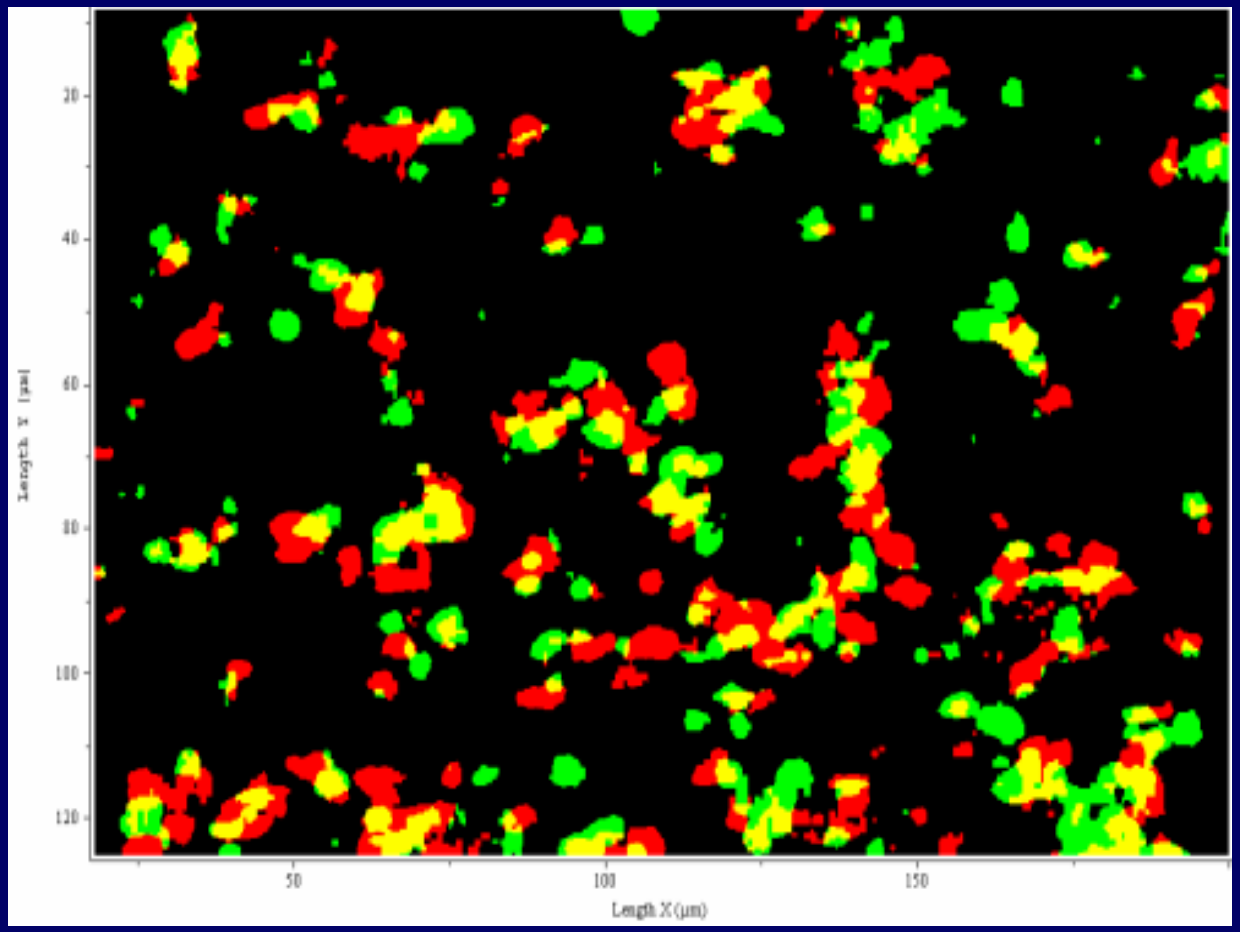
Kavuru, JACI, 2000

CORTICOSTEROIDI E β_2 AGONISTI
AZIONE SINERGICA



- **Effetto del glucocorticoide sul β_2 recettore** (riconversione e ↑ sintesi
- **Effetto del β_2 agonista sul recettore glucocorticoide**

Raman Laser Analysis of combination therapy salmeterol (red) + fluticasone (green) formulation



Nelson JACI 2003

Particle agglomeration of the 2 drugs (yellow)

Dosing regimens with combination therapy
(LABA + ICS)

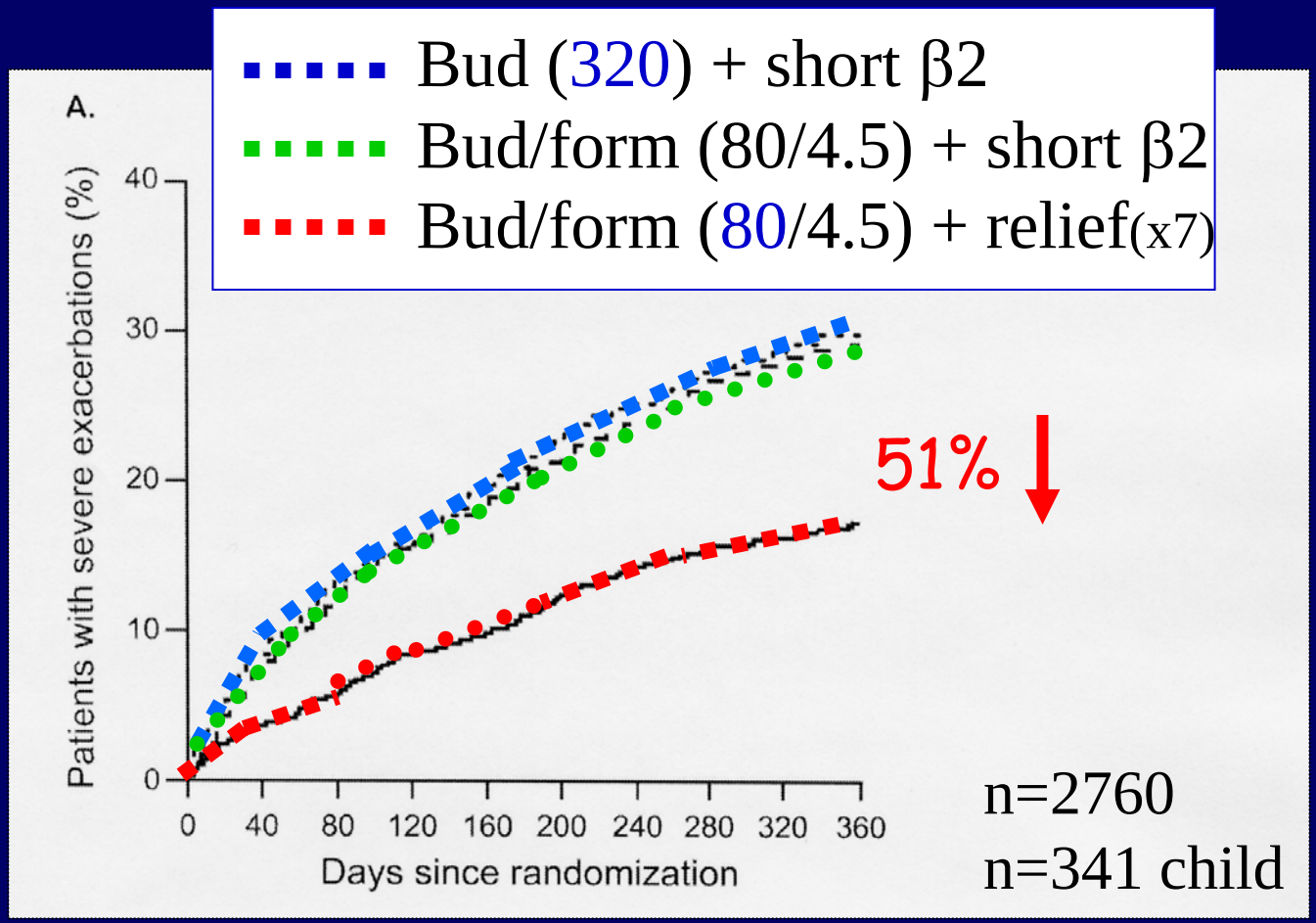
- Fixed maintenance dose
  salm/flutic
  bud/formot

- Adjustable (flexible) dosing regimen
  bud/formot

  Allows to titrate the dose of ICS

Sears Resp Med 2005

Budesonide/Formoterol combination therapy as both maintenance and reliever medication in asthma



O'Byrne
AJRCCM 2005
Bisgaard
ERJ 2005

Editorial

A single inhaler for both maintenance and rescue therapy?

Barnes AJRCCM 2005; 171: 95

WARNING FOR ASTHMA DRUGS
2005

LABA: boxed warning added on product label

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS and CLINICAL PHARMACOLOGY: Clinical Trials: *Asthma: Salmeterol Multi-center Asthma Research Trial*).

" Doctors must prescribe them properly
and only for those who need "

(Lancet 2005)

TAKE HOME MESSAGES

- una terapia con basse dosi di steroidi riduce le riacutizzazioni e migliora la funzionalità respiratoria in un'alta % di pazienti

- se un bambino non risponde alla terapia:
  1) verifica come usa i devices
  2) considera terapia associazione ICS + LABA
     ICS + montelukast

- l'esperienza con LABA + ICS nei bambini è limitatata !

Combination therapy
LABA + ICS

May mask underlying inflammation ?