Step-up and Step-down Strategies in the Treatment of Asthma

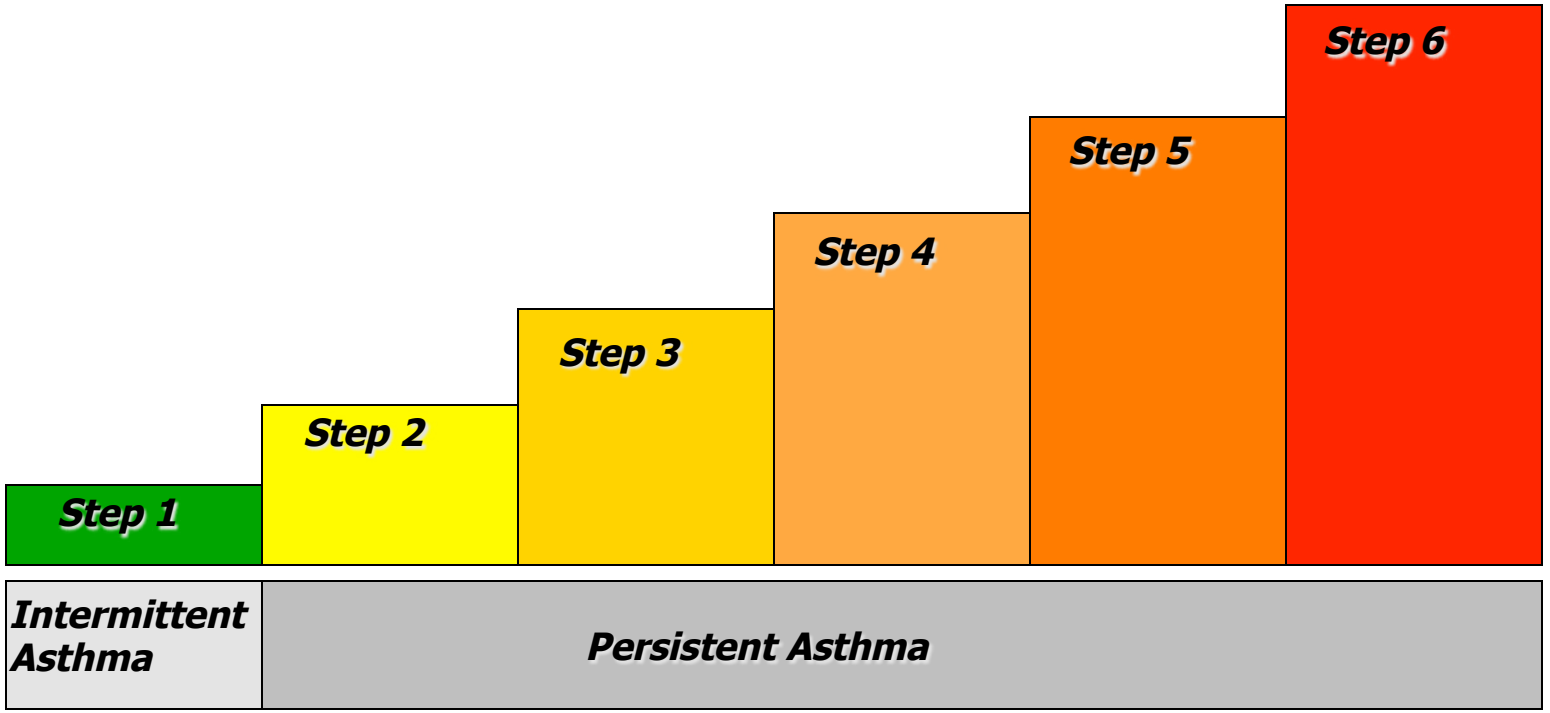
Robert F. Lemanske, Jr., M.D.

Professor of Pediatrics and Medicine

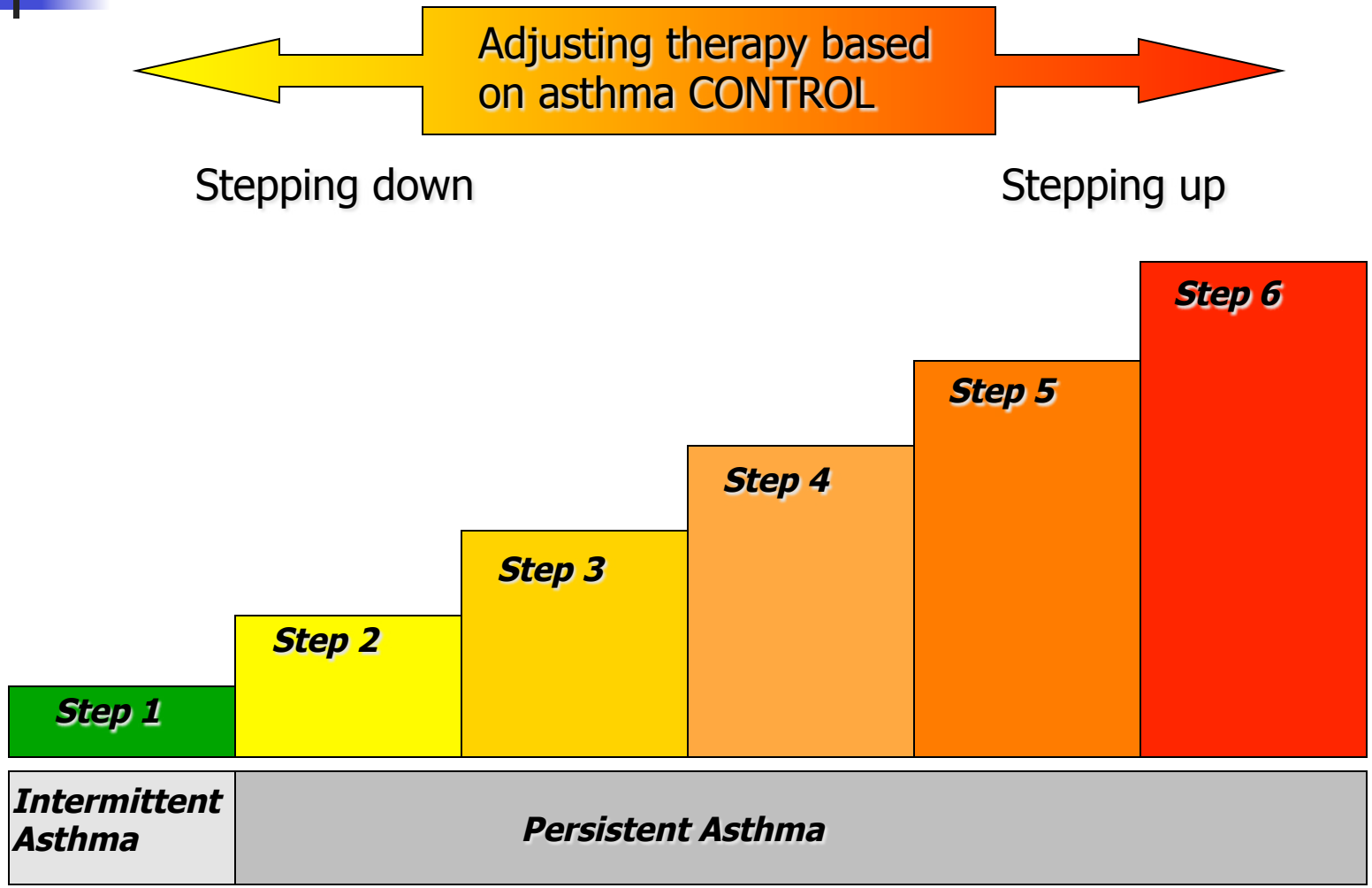
University of Wisconsin School of Medicine and Public Health

Step-wise Approach to Asthma Therapy

Choosing the initial step in therapy based upon Asthma SEVERITY



Step-wise Approach to Asthma Therapy

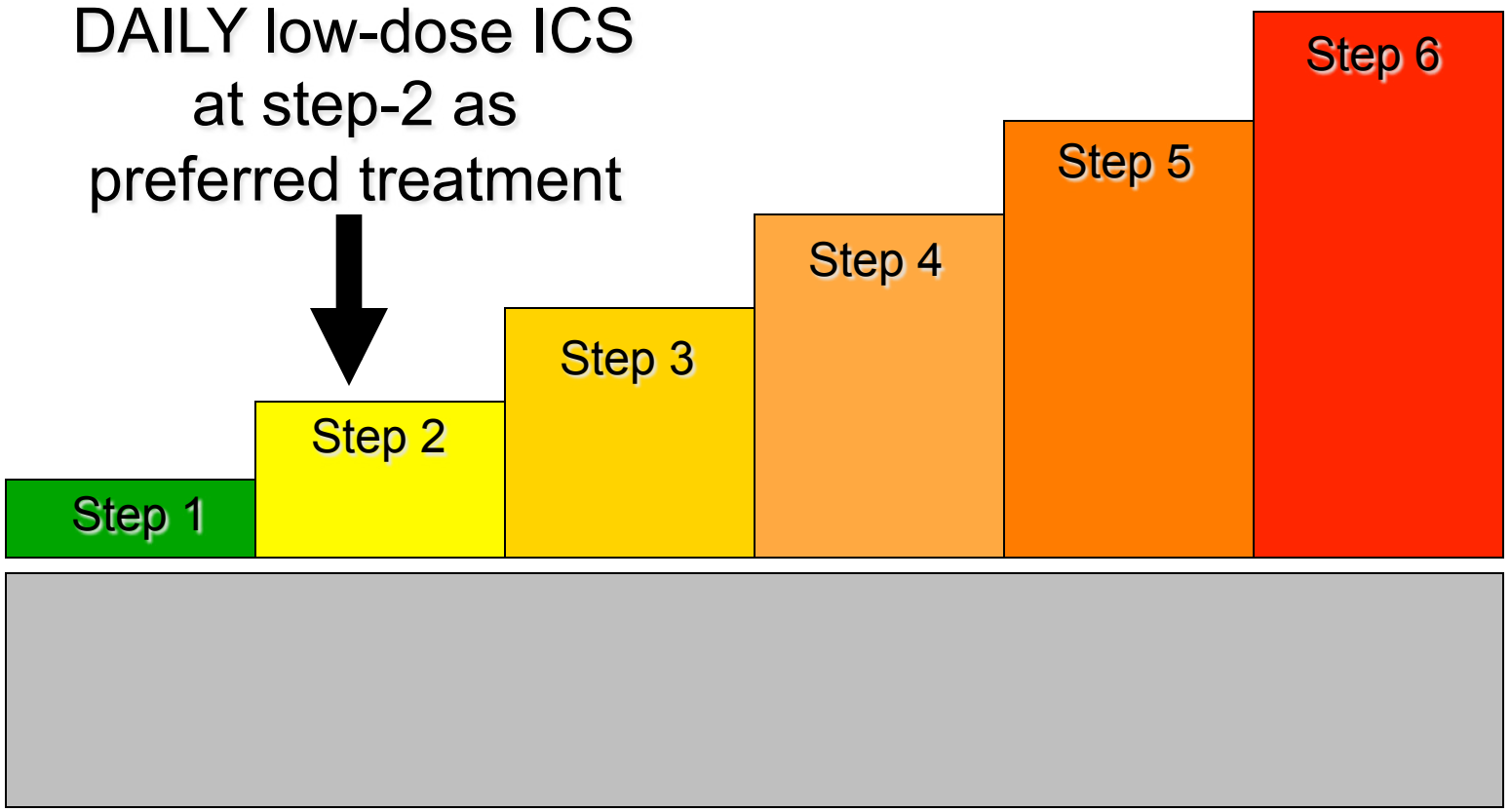


Step-up Approaches in Asthma

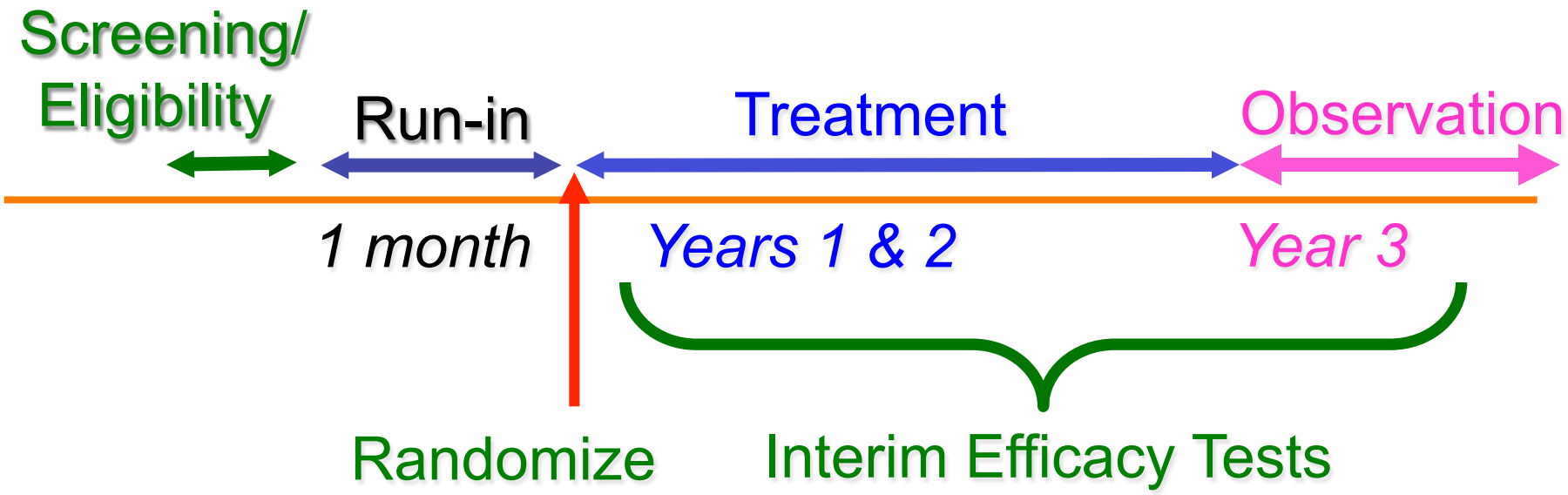
STEP-UP LONG-TERM **(SLT)**	STEP-UP SHORT-TERM **(SST)**	STEP-UP INTERMITTENT **(SUI)**
increase in therapy for uncontrolled asthma (weeks)	increase in therapy for brief loss of control (days)	increase in therapy for variable symptoms (day-to-day)
persistent loss of control	brief loss of control (upper respiratory tract infections, pet exposure)	mild symptoms
step-down therapy when control achieved after 3-6 months	step-down therapy when control achieved after 3-10 days	intermittent use

Thomas, Lemanske & Jackson, JACI 128:915, 2011

EPR-3 Recommendations For Frequent Preschool Wheeze & + API



Prevention of Early Asthma in Kids



- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 two & three y/o kids at high-risk for asthma (mAPI +)
- Fluticasone 44 μg/puff vs. placebo (2 puffs b.i.d.)

Guilbert, *NEJM* 2006

PEAK – Outcomes

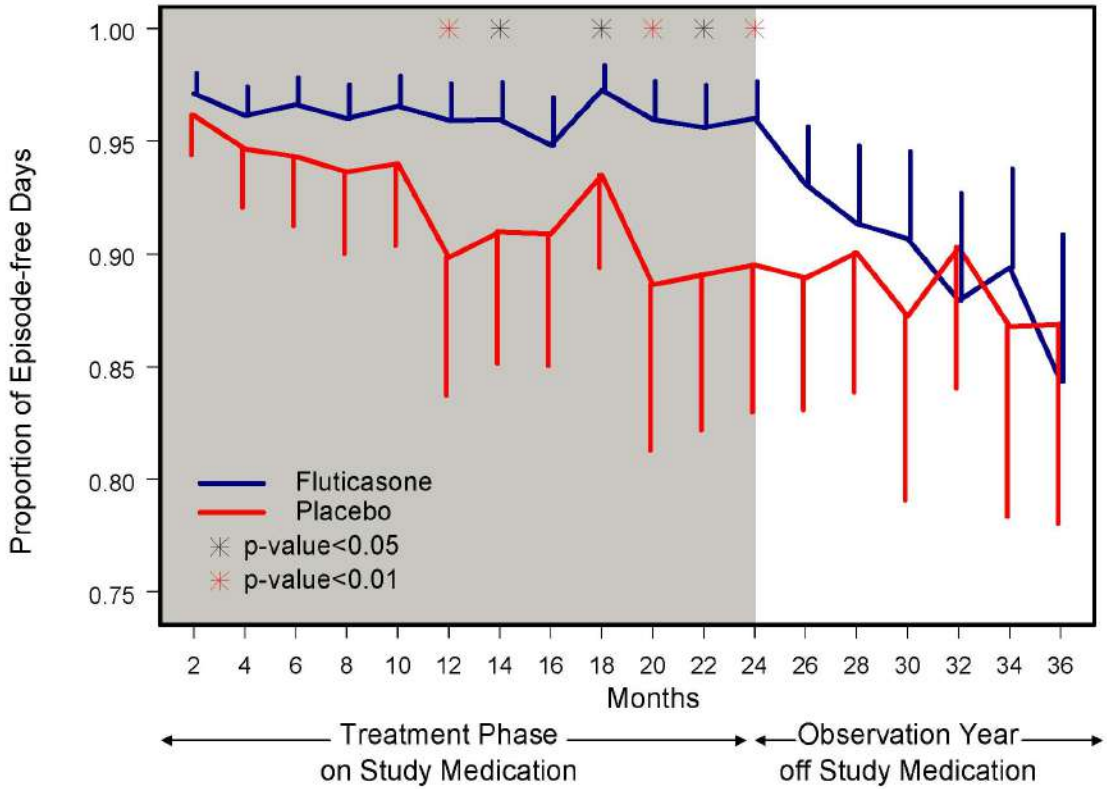
EFD: No cough or wheeze, unscheduled clinic, urgent care, ED or hospital visits; no use of asthma medications including bronchodilator pre-treatment before exercise

Treatment Phase:

↓ Exacerbations

↓ Supplemental medications (ICS and LTRA)

= bronchodilator use and unscheduled visits



Observation Phase:

= Exacerbations

= Supplemental medications (ICS and LTRA)

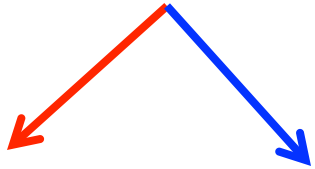
= Bronchodilator use and unscheduled visits

Guilbert, *NEJM* 2006

Conundrum with Daily ICS Use

- Most effective and guideline preferred controller for persistent pediatric and adult asthma as it improves day-to-day asthma control and prevents exacerbations
- However, exacerbations occur yearly in about 30% of children with mild and 40% of children with mild-moderate asthma prescribed daily ICS in trials
- Long-term adherence with daily ICS is consistently low: 30-50% in general pediatric practice
- Growth effects small but may be permanent

ICS Options for Preschool Children with Recurrent Wheeze and Past Year Exacerbations



Daily	Intermittent

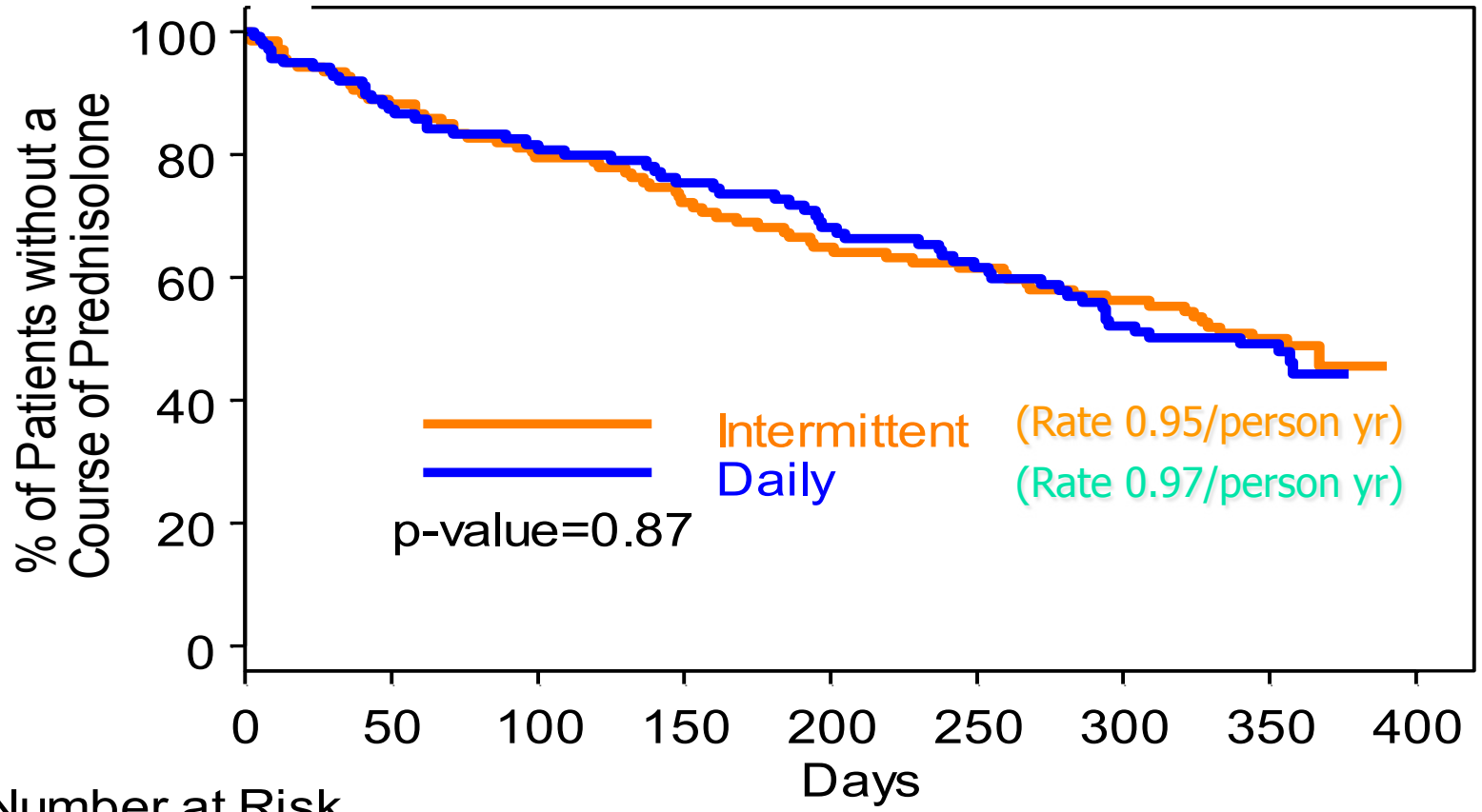
MIST Protocol: Overview

Cohort (N=278): Ages 12-53 mo, frequent wheeze, modified API, past year exacerbation, intermittent illnesses

Run-in: placebo respule nightly + albuterol prn

Treatment Phase: 52 Weeks		
Randomized Treatment Group	Nightly EXCEPT During Respiratory Tract Illnesses	During Respiratory Tract Illnesses ONLY for 7 days
Daily low-dose Budesonide	Budesonide 0.5 mg PM	Placebo AM Budesonide 0.5 mg PM
Intermittent high-dose Budesonide	Placebo PM	Budesonide 1.0 mg AM 1.0 mg PM

Time to 1st Exacerbation Similar with Daily vs Intermittent ICS



Number at Risk

Intermittent	139	114	100	89	78	71	64	50
Daily	139	114	93	84	74	66	54	40

Lessons from MIST

In API positive preschoolers with frequent wheeze & prior year exacerbations

- Illness burden is substantial despite ICS therapy
- Intermittent high-dose budesonide started early during predefined respiratory tract illnesses and continued for 7 days, may be an alternative option to daily low-dose budesonide given its

✓ similar outcomes

✓ less frequent use

✓ lower ICS exposure

Are there alternative approaches to daily ICS in school age asthma?

Is a Long Acting Beta Agonist Necessary for Control?

- Mild asthma subjects (n=455)
- Six months treatment
- Primary outcome: AM PEF

Treatment Group	Scheduled	As needed
A	Placebo	BDP 250 mcg + Albuterol 100 mcg
B	Placebo	Albuterol 100 mcg
C	BDP 250 mcg	Albuterol 100 mcg
D	BDP 250 mcg + Albuterol 100 mcg	Albuterol 100 mcg

Results:

- AM PEF and Exacerbations:

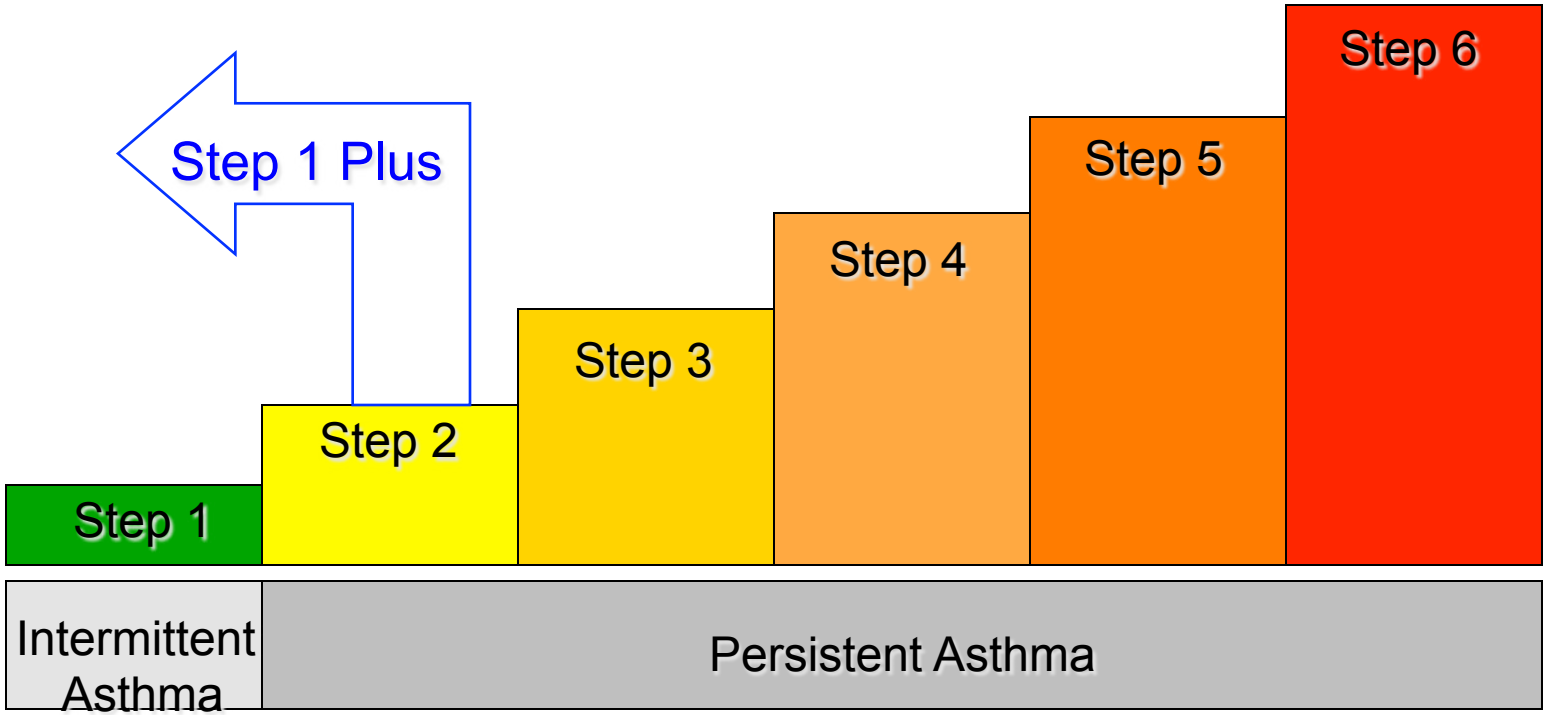
  Group A = C = D > B

- Cumulative dose of ICS lower in Group A compared to C and D

Papi A et al. NEJM 356:2040, 2007

Unanswered Questions in Children with Controlled Mild Persistent Asthma

Is rescue ICS (step-up intermittent) a better approach as step-down care to ICS discontinuation?



The TReating Of Children To Prevent EXacerbations Of Asthma (TREXA) Trial

Martinez FD for the CARE Network
Lancet 2011; 377:650-7

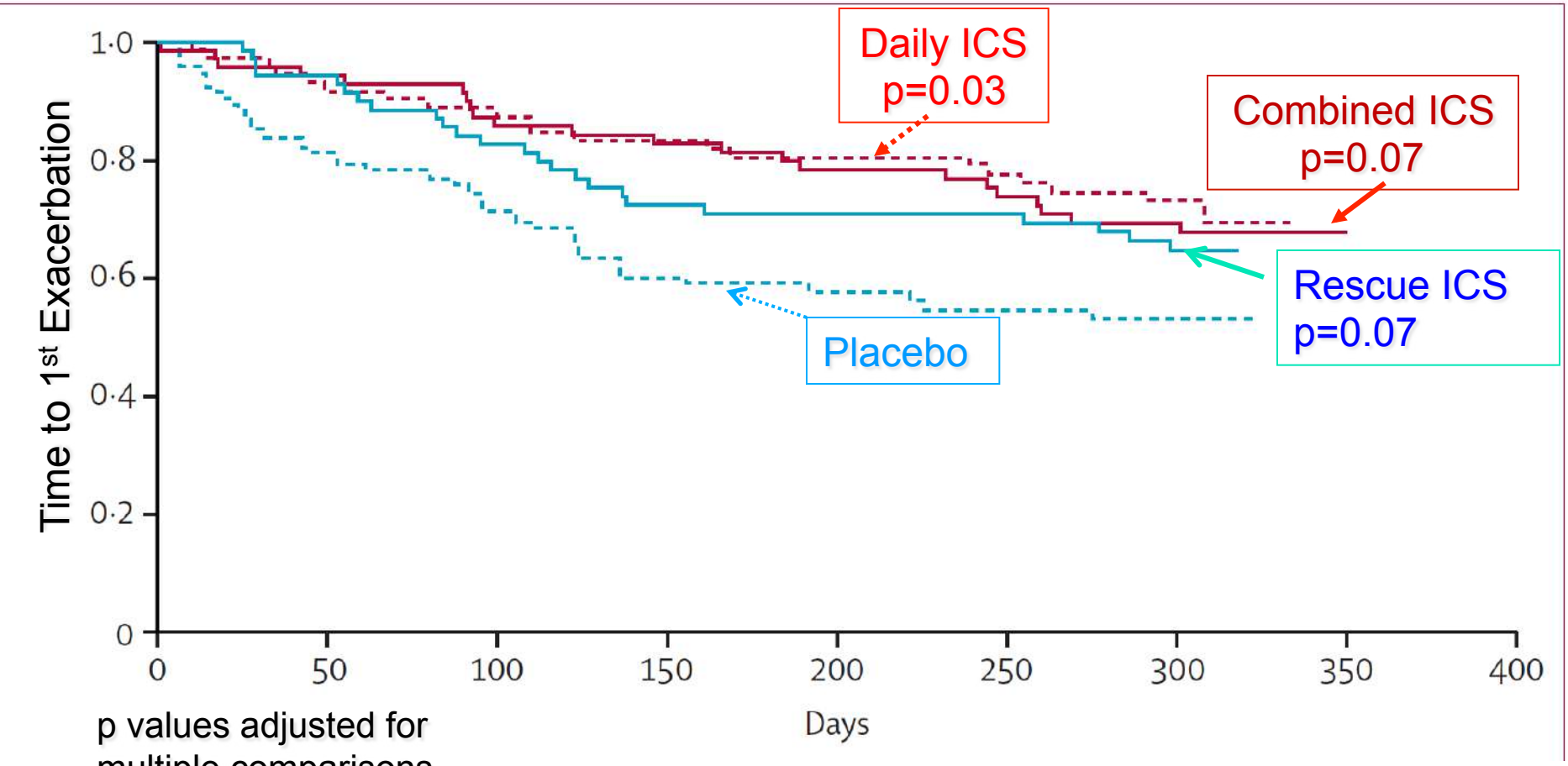
TREXA Trial Design

Cohort (N=288): ages 5 – 18 years

Controlled mild persistent asthma after 4-week run-in on beclomethasone 40 ug BID with placebo rescue + albuterol

Randomization groups	Rescue Therapy + albuterol	Daily Therapy (BID)
Combined ICS	Beclomethasone (80 ug)	Beclomethasone (40 ug)
Daily ICS	Placebo	Beclomethasone (40 ug)
Rescue ICS	Beclomethasone (80 ug)	Placebo
Placebo	Placebo	Placebo

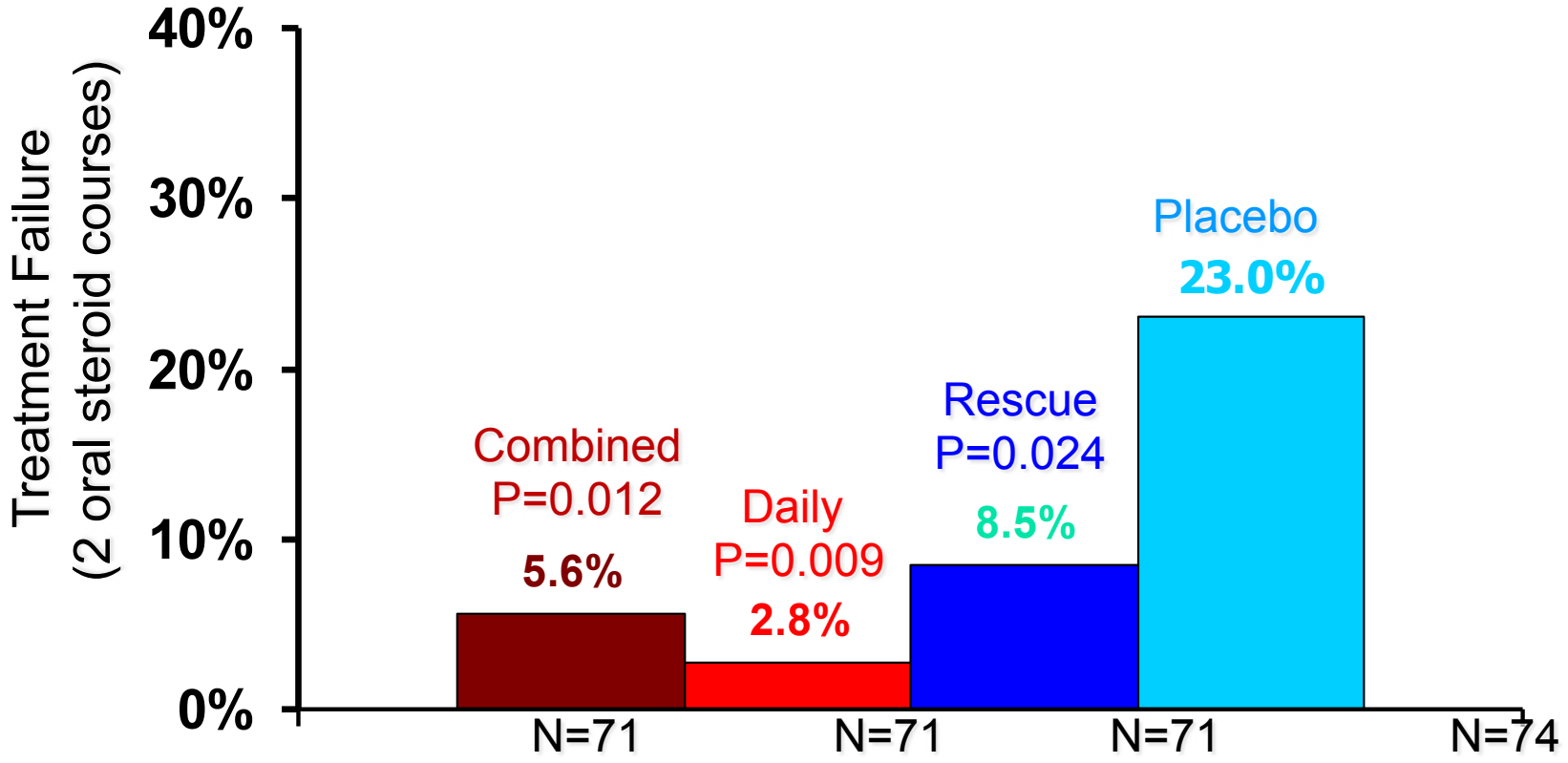
TREXA: Regimens on Exacerbations Requiring Oral Corticosteroids



p values adjusted for multiple comparisons (Hochberg-Bonferroni)

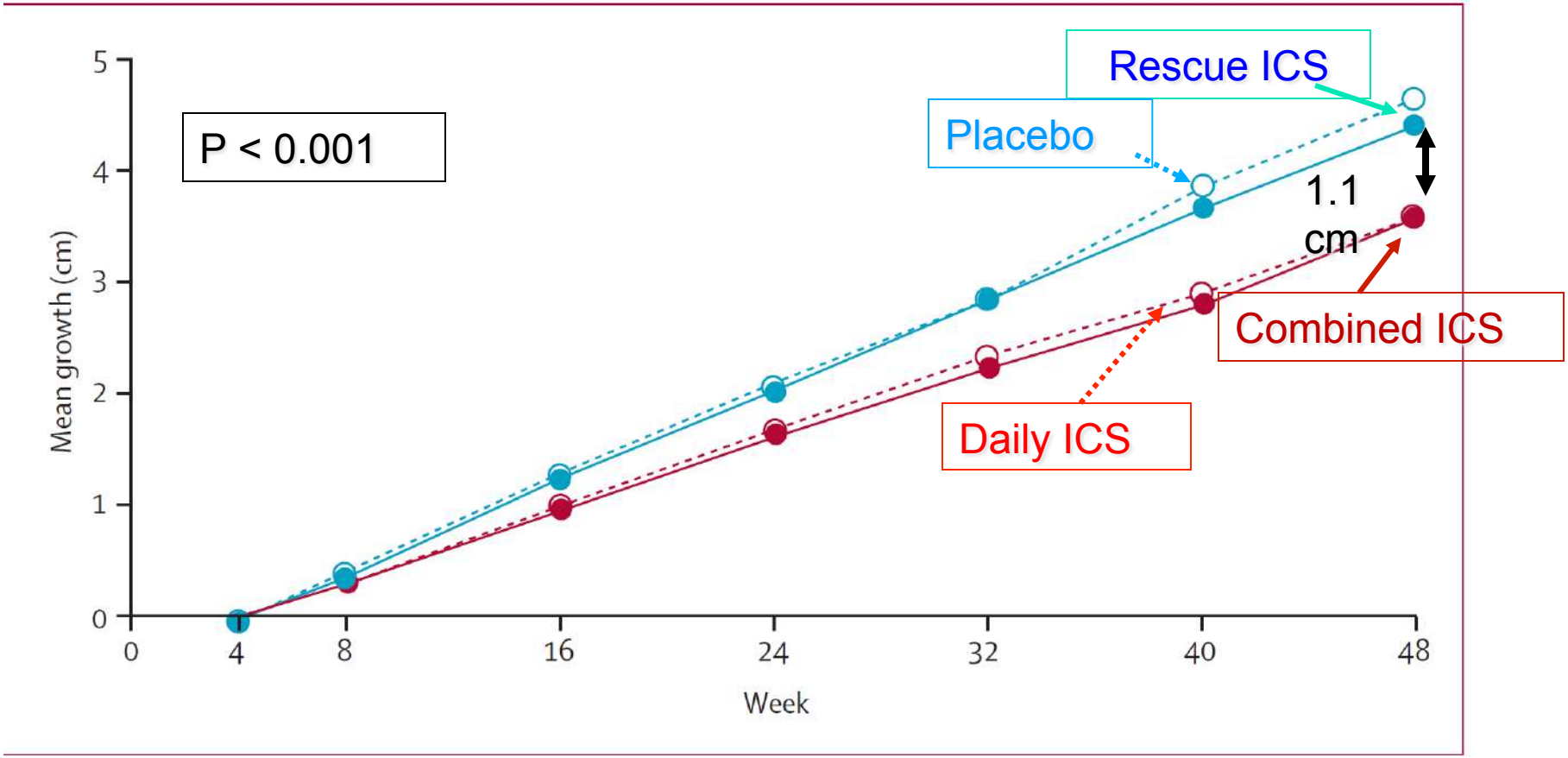
(Martinez F, Lancet 2011;377:650-7)

TREXA: Regimens on Treatment Failures



(Martinez F, Lancet 2011;377:650-7)

TREXA: Regimens on Linear Growth



(Martinez F, Lancet 2011;377:650-7)

TREXA - Conclusions

- Discontinuing ICS causes an unacceptable increase in exacerbations in children with well-controlled, mild persistent asthma
- Daily ICS is the most effective treatment for preventing exacerbations; adding rescue ICS to daily ICS does not add benefit
- Rescue ICS with albuterol (step-up intermittent therapy) demonstrates benefits over albuterol alone and avoids daily ICS administration and its growth effects

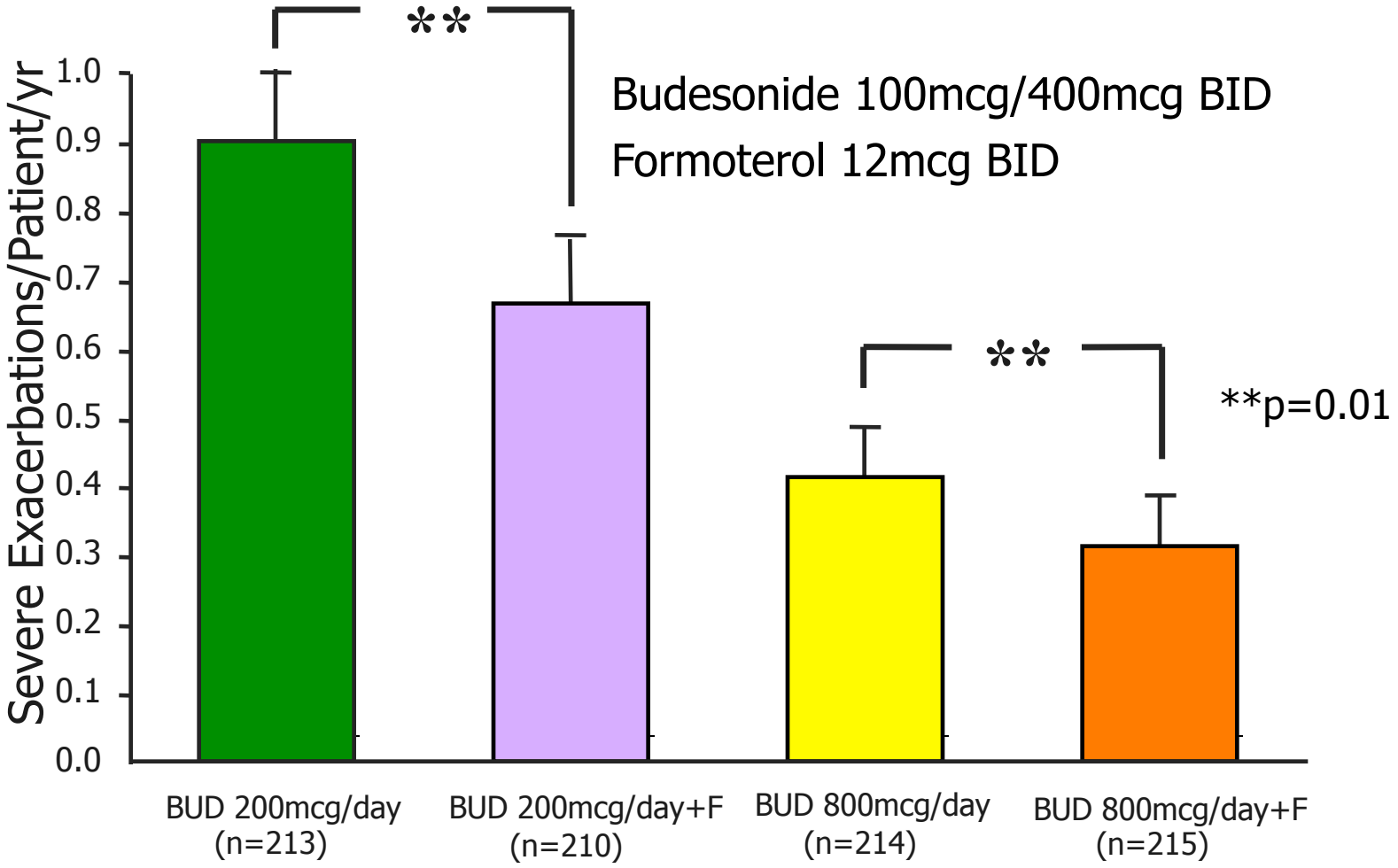
Combination Therapy

More ICS or add a LABA?

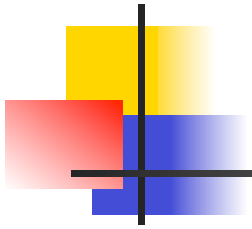
- Greening, A. et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 344 (8917):219-224, 1994.
  - Improved impairment; no difference in risk domain

- Woolcock, A et al. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *AJRCCM* 153 (5): 1481-1488, 1996.
  - Improved impairment; no difference in risk domain

FACET Study: Formoterol and Budesonide in Moderate Asthma

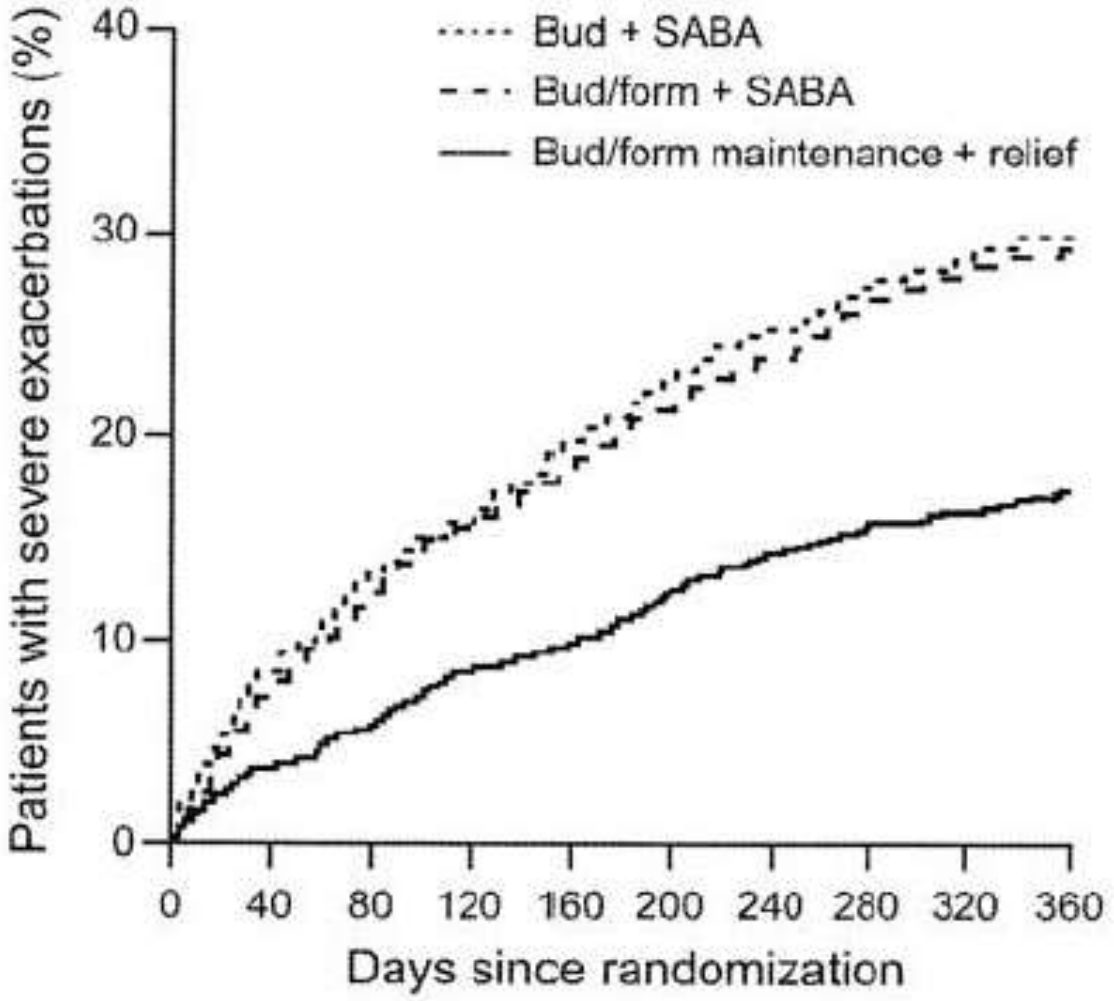


Pauwels, et al. N Engl J Med 1997; 337: 1405-1411



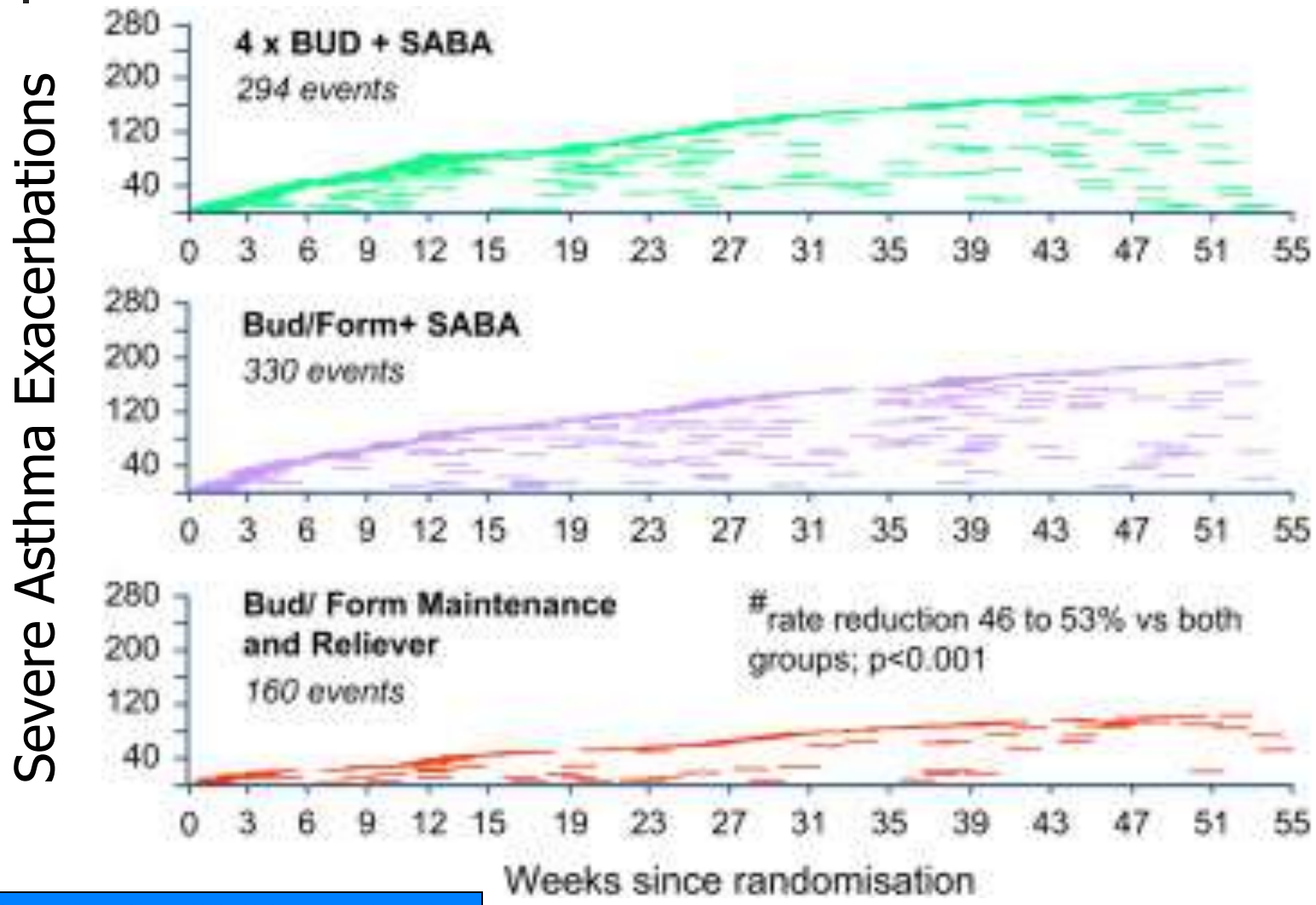
Beta Agonists + ICS: Maintenance and Reliever Therapy?

Combination Therapy as both Maintenance and Reliever Therapy



O'Byrne PM et al. AJRCCM 171: 129, 2005

Combination Therapy: STAY Study



O' Byrne PM et al. AJRCCM 171:129, 2005

Step-Up Long Term in Children

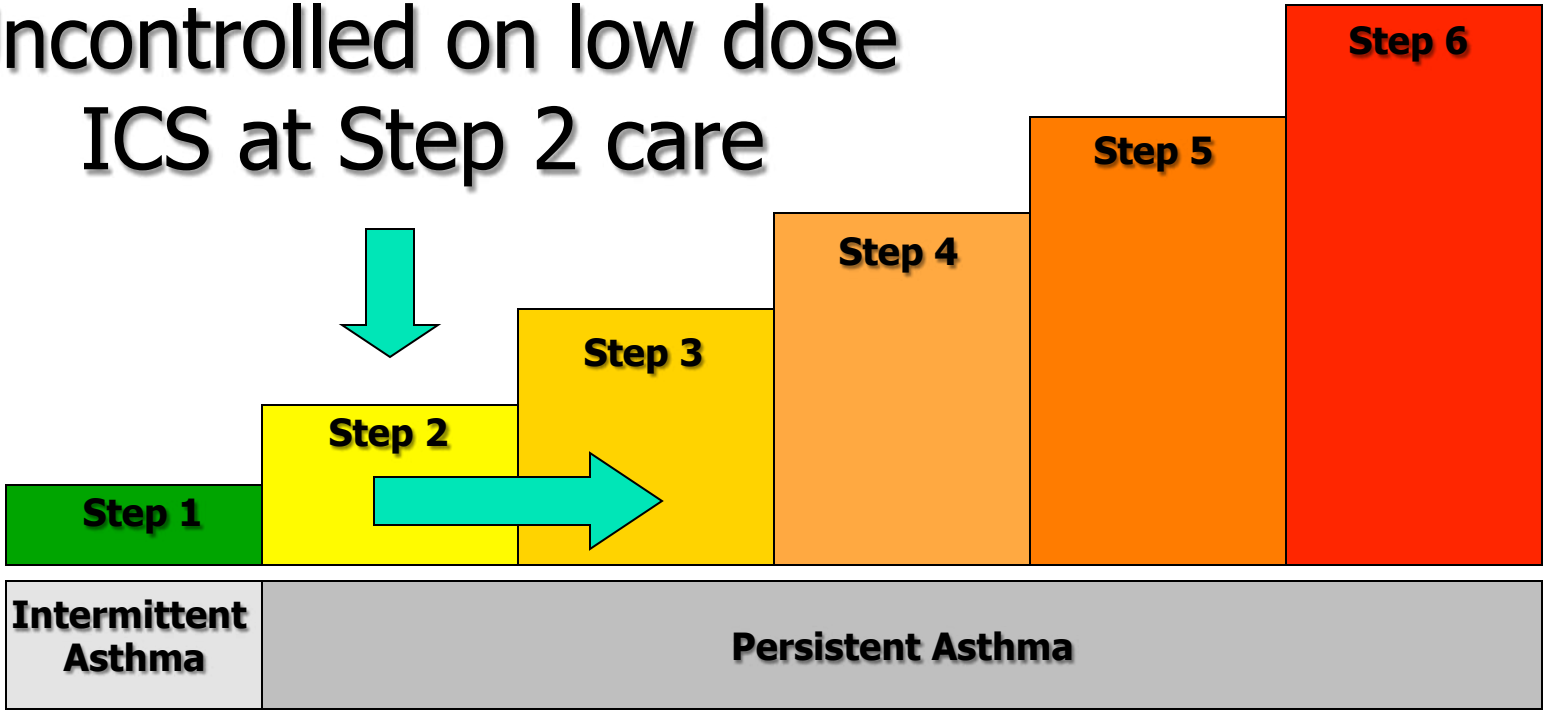
BADGER
Best Add-on Therapy Giving Effective Responses

- In patients receiving daily low dose ICS treatment who are not well controlled, what are the next best treatment options?

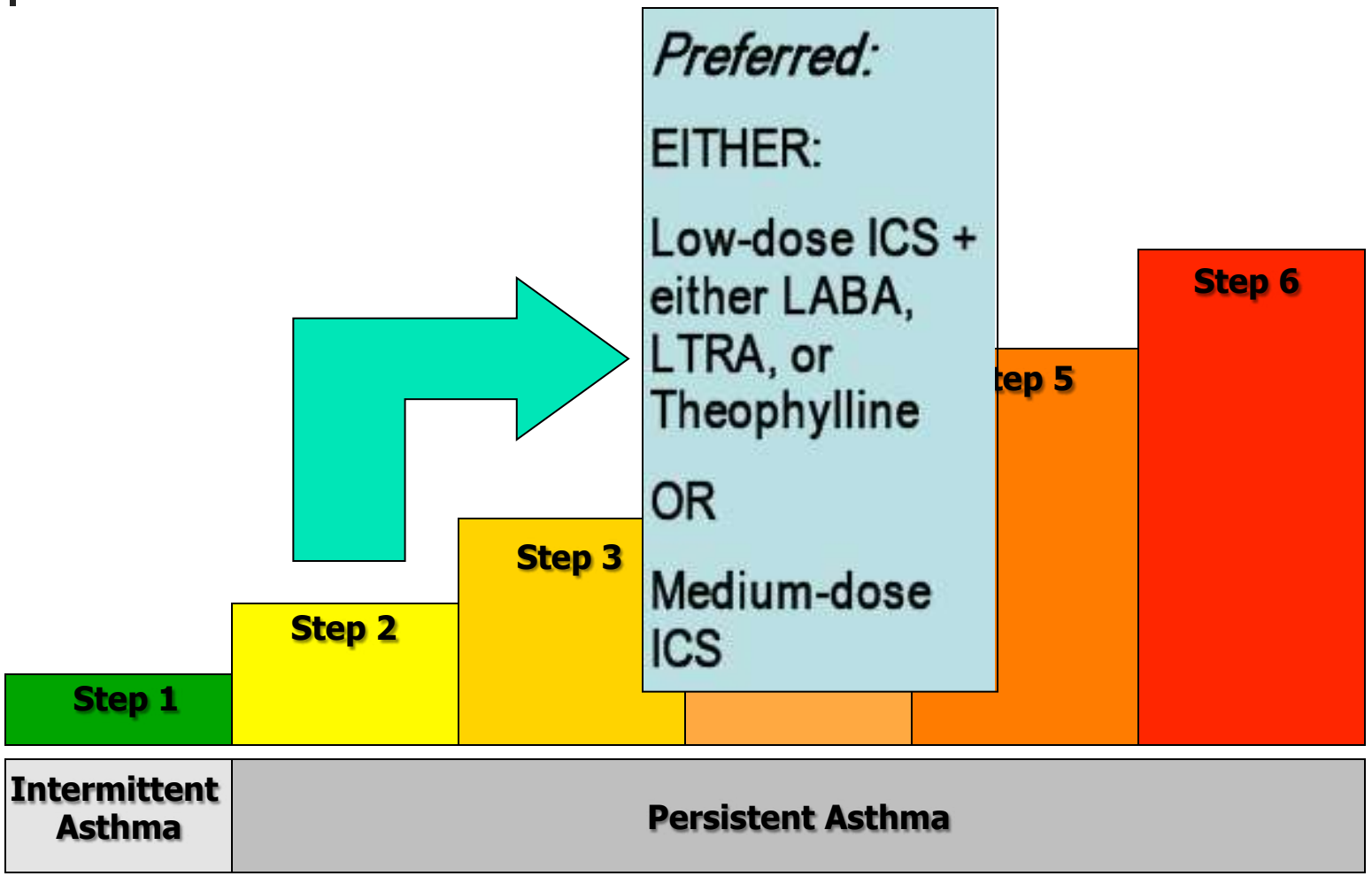
Lemanske RF et al. NEJM 362:975, 2010

Unanswered Questions in Childhood Asthma

Uncontrolled on low dose ICS at Step 2 care



EPR-3 Recommendations



BADGER: Research Question

- In children not satisfactorily controlled on low dose ICS (fluticasone 100 µg BID) therapy, what is the next best treatment approach?
  - Increased doses of ICS (fluticasone 250 µg BID)?
  - Add a LABA (salmeterol/fluticasone combination)?
  - Add a LTRA (montelukast)?

BADGER: Novel Trial Design

- Each participant would receive all 3 treatment options

- Determine the presence or absence of a differential response among those treatments using a composite outcome that evaluated 3 components in defining asthma control:
  - Impairment domain
    - Asthma control days
    - Pulmonary function (FEV_1)
  - Risk domain
    - Asthma exacerbations

CARE
Childhood Asthma Research & Education Network

Research Questions

- Could a differential response be demonstrable in at least 25% of participants?
- If so, what was the direction of the response (i.e., which therapy had the greatest probability of producing the best response?)
- Were there baseline characteristics that could predict the probability of a differential response?
  - Methacholine PC_{20}
  - FeNO
  - Asthma Control Test (ACT®) scores
  - B16 genotype (Arg/Arg)

Differential Response

- At the end of the study, each child was identified as either a differential or non-differential treatment responder.
- A differential responder was someone who exhibited significantly better outcomes on one treatment than on another.
- Effective treatment response was based on (in order of importance):
  1. Asthma exacerbations
  2. Asthma control days (ACD)
  3. Change in FEV_1.

Definitions for Differential Response: Asthma Exacerbations

- Differential response with respect to asthma exacerbations occurrred when the total amount of prednisone prescribed to control asthma symptoms was at least 180 milligrams* greater on one treatment than on either of the other two treatments.

*Based on “prednisone burst” of 2 mg/kg/day for 2 days, 1 mg/kg/day for 2 days to a maximum of 60-60-30-30 mg

Definitions for Differential Response: Asthma Control Days

- Differential response with respect to ACD occurred when the number of annualized ACD (AACD) achieved on one treatment was at least 31 days more than on either of the other two treatments.

Asthma Control Day (ACD)

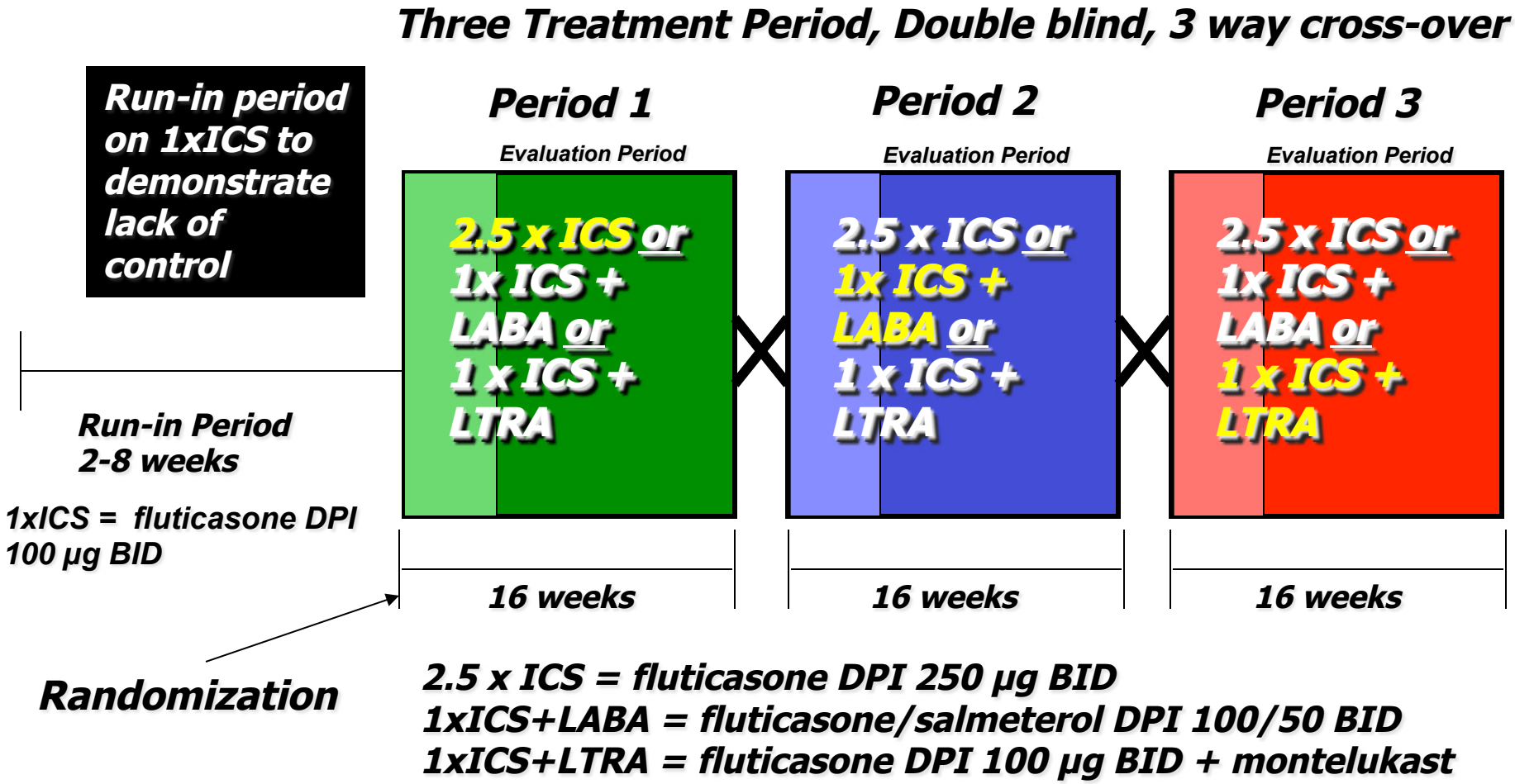
- An ACD was defined as a day without:
  - Albuterol rescue use (pre-exercise treatment permitted)
  - Use of non-study asthma medications
  - Nighttime awakenings
  - Daytime asthma symptom score more than mild
  - Unscheduled health care provider visits for asthma
  - Yellow-zone PEF or Red-zone PEF

Definitions for Differential Response: FEV1

- Differential response with respect to FEV_1 occured when the FEV_1 change on one treatment was at least 5% higher than on either of the other two treatments.
- The FEV_1 change for each treatment was defined as the percent difference between the FEV_1 from the end of the run-in to the end of the treatment period

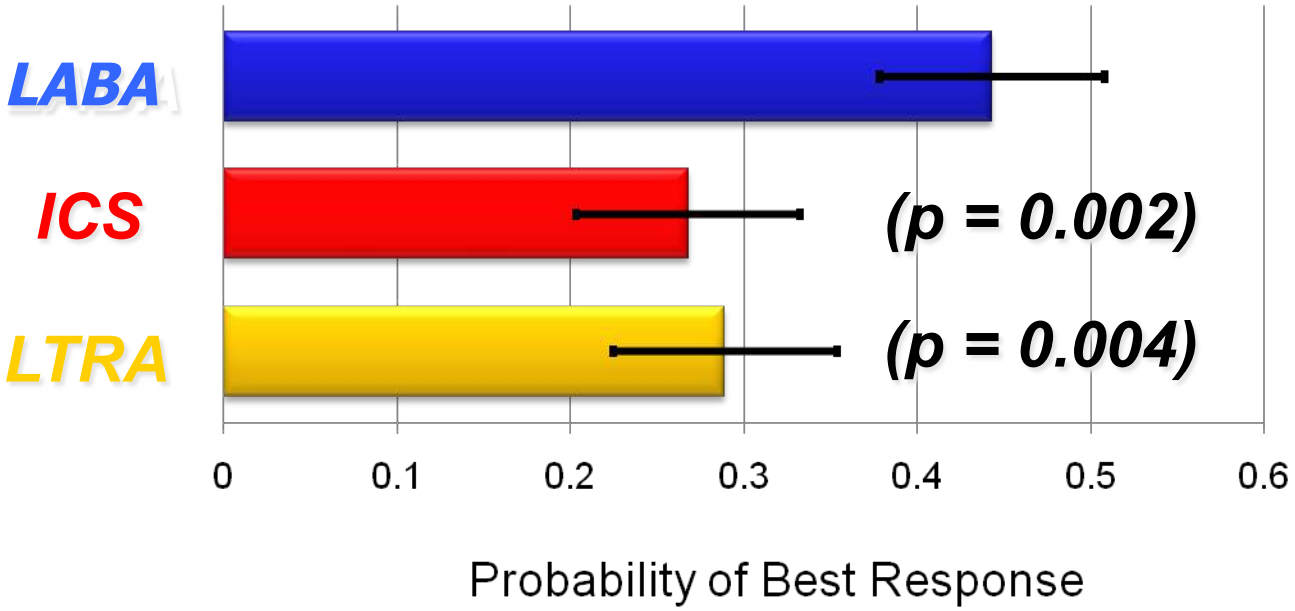
$$\frac{FEV_{treatment} - FEV_{run\text{-}in}}{FEV_{run\text{-}in}}$$

BADGER Protocol: Overview



Primary Outcome: Probability of BEST Response Based on Composite Outcome*

LABA step-up was more than 1.5 times as likely to produce the best response



**Covariate adjusted model*

Lemanske RF et al. NEJM 362:975, 2010

CARE
Childhood Asthma Research & Education Network

BADGER: Conclusions

A differential response to step-up therapy was demonstrated in nearly all subjects (≥ 95%) and more than 1.5 times as likely with LABA step-up. Many children demonstrated a best response to either ICS or LTRA step-up, highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy.