Controversies in Asthma Care for Children

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Objectives

- Understand the heterogeneity of response to asthma treatments among children.
- Understand the utility of inhaled corticosteroids for the treatment of asthma exacerbations
- Understand the utility of combination inhalers for treating persistent asthma in children

Epidemic of Wheezing in Developed Countries

- 50% of children wheeze at least once before age 5 years.
- 30% of preschool children wheeze >2 times by age 3 years.
- 2 of 3 children who wheeze between 1 and 3 years of age do not do so by age 5-6 years.
- Asthma occurs in 8.5% of children in the US. It is the most common respiratory disease in childhood.

There are >50,000 articles on asthma and childhood cited on PubMed.

Clinically Important Types of Asthma and Outcome Measures

Bothersome Asthma	Symptoms
Atopic/Non-Atopic Asthma*	Skin test, IgE, FeNO
Persistent Asthma*	Initial Frequency of ss, Rx use
Active/Uncontrolled Asthma*	After initiation of Rx
Severe Asthma*	Treatment Failure
Irreversible Asthma	Lung Functions
Labile Asthma	Urgent Visits
Steroid-Resistant Asthma*	
Life-threatening Asthma*	ICU/Intubation

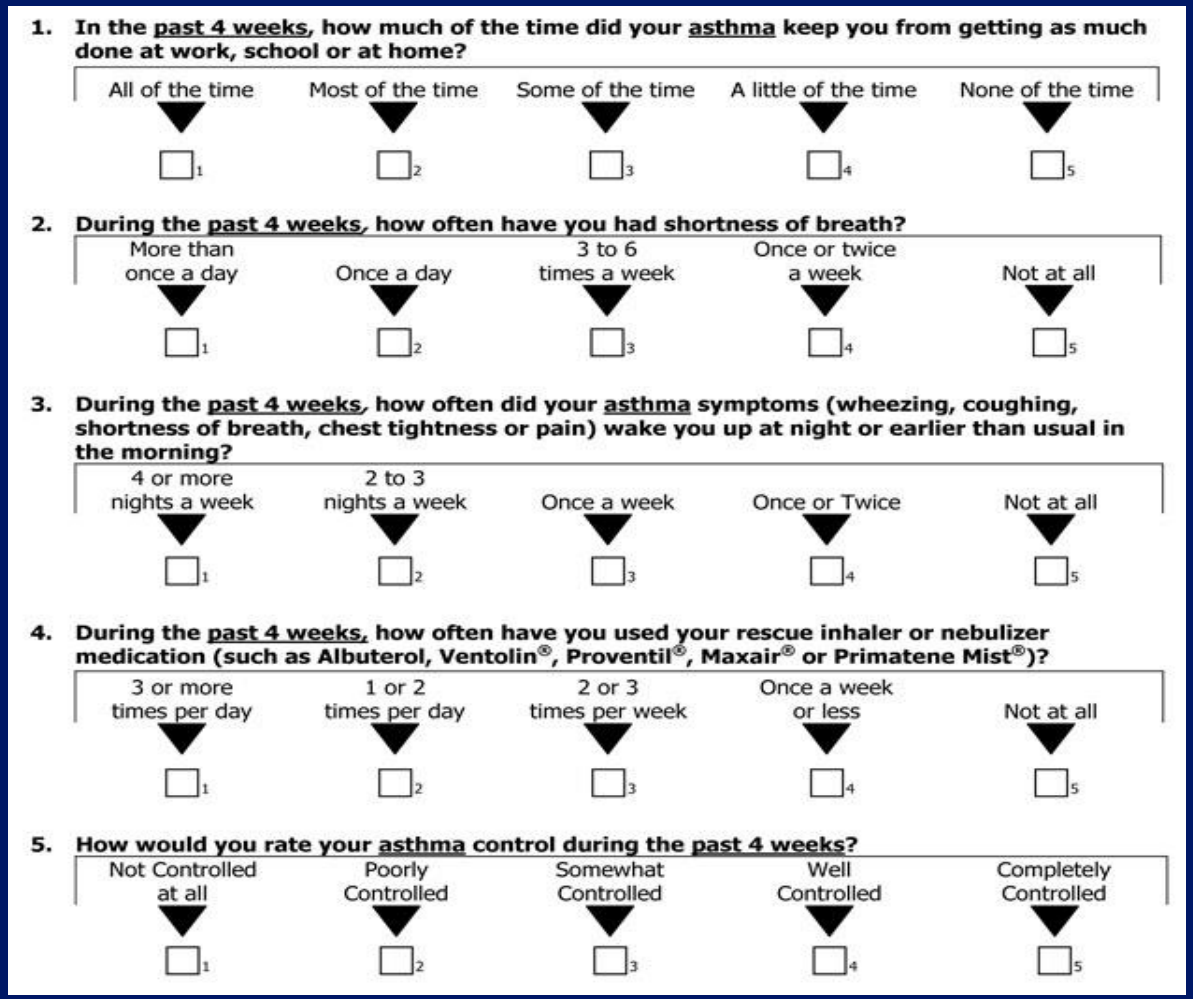
*defined by published criteria

NHLBI: Persistent Asthma and the Need for Asthma Controller Treatment: Rule of 2's

Asthma symptoms altering daily life	2x/week
Use of albuterol/salbutamol (include use before exercise)	2x/week
Awakening due to asthma	2x/month
ED/Hospital admission	2x/year
Need for prednisone (?)	3-4x/year

Problem: Asthma can wax and wane each year and over years. Persistent asthma can emerge or go away.

Asthma Control Tests for Use in the Office



1. **In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. **During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. **During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair® or Primatene Mist®)?**

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. **How would you rate your asthma control during the past 4 weeks?**

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

Level of Control

≥20 = Controlled

16 -19 = Not Controlled

≤15 = Poorly Controlled

GINA: Assessing Asthma Control

Symptoms over the last month +

- Risk factors for Poor Asthma Outcomes
  - >1 Asthma Flares over last 12 months
  - High risk Season for Asthma Flares (respiratory viral season, cold weather, allergens, etc.)
  - Indoor Irritants, e.g. tobacco or woodstove use
  - Poor adherence to daily treatments
  - Family stress/dysfunction
  - Oral corticosteroid use (>3 times/year)

Important RCTs in Childhood Asthma that shape current treatment strategies

- Age of subjects : school age vs pre-school
- Degree of asthma studied: mild vs moderate persistent
- Enrichment: Asthma Predictive Index, Family history of asthma or allergies
- Duration of trial: weeks to months
- Maintenance vs Rescue Therapy
- Primary Outcome variable

Pediatric Asthma Controller Trial (PACT) Study: 2006

- 285 6-14 year old children with persistent moderately severe asthma

- Treated for 48 weeks with one of three regimens:

  Fluticasone (100 mcg BID)

  VS

  Fluticasone 100 mcg once/day plus salmeterol twice/day

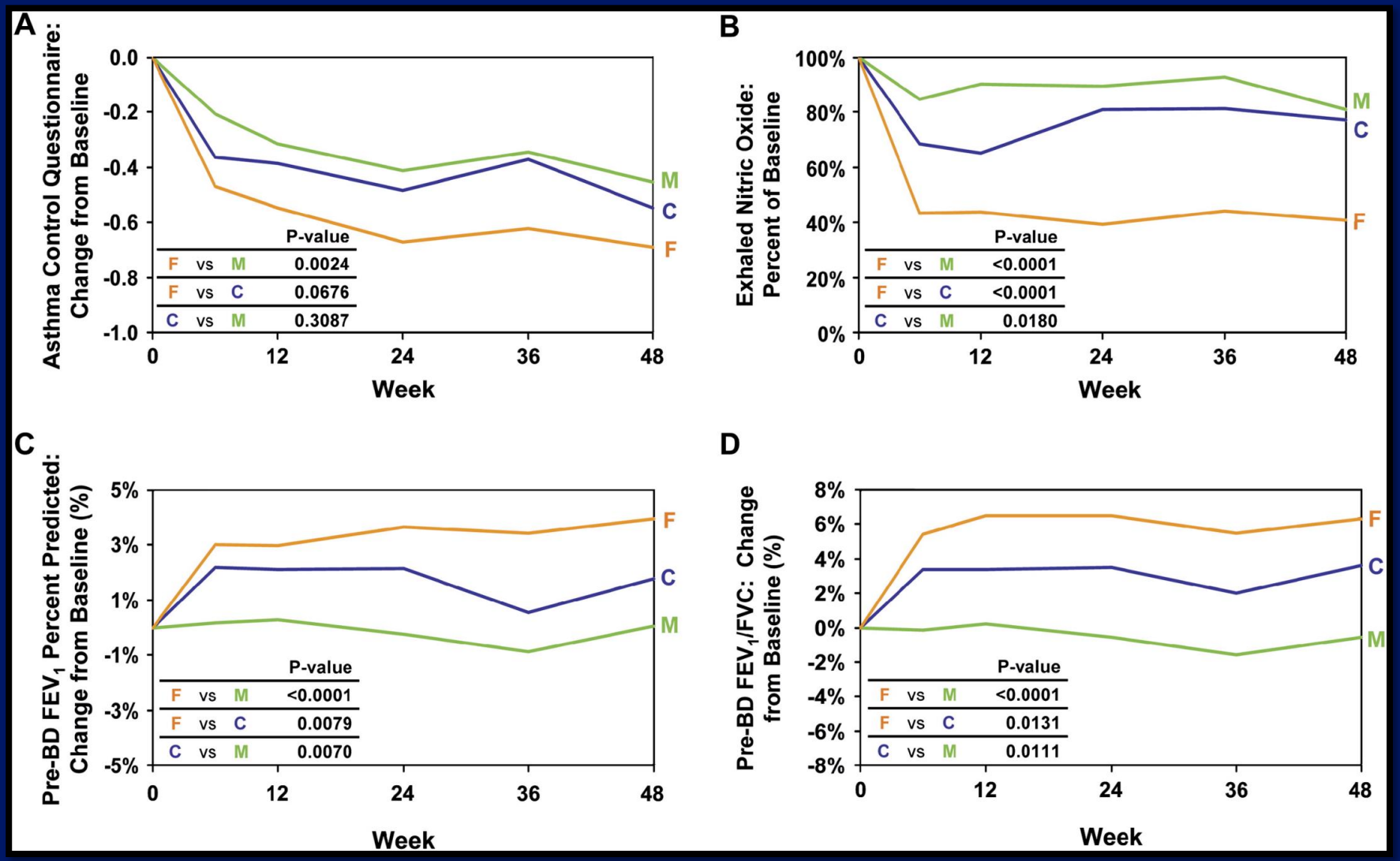
  VS

  Montelukast 5 or 10 mg OD

- Primary end point: Asthma control days and exacerbation frequency

Sorkness, et al. *JACI* 119(1):64-72, 2006.

Pediatric Asthma Control: ICS vs Montelukast



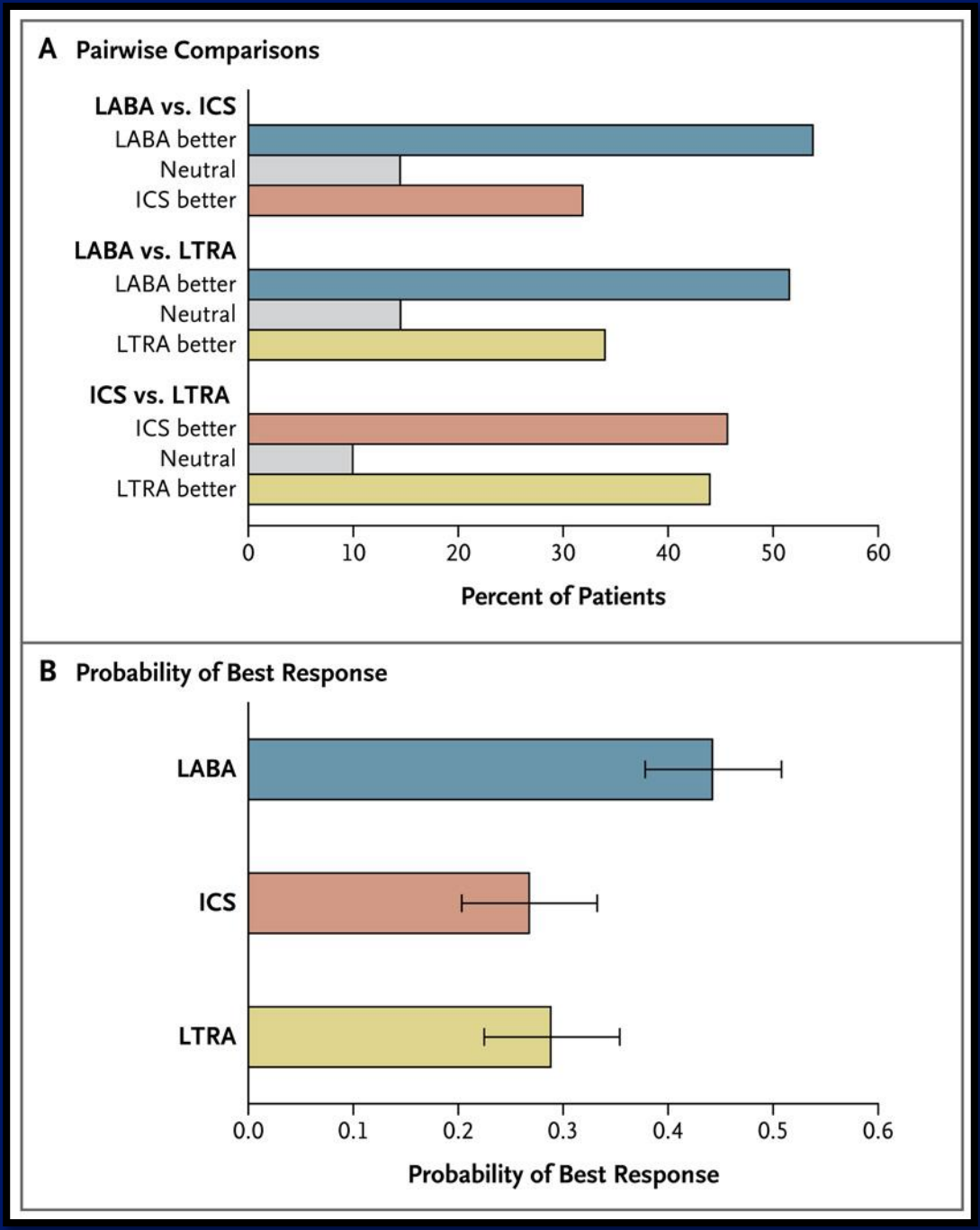
Sorkness CA, et al. *J Allergy Clin Immunol* 119(1):64-72, 2007.

Best Add-on Therapy Giving Effective Response (BADGER)

182 children 6-17 years old with mild to moderate persistent asthma on low dose ICS but uncontrolled asthma

- Double blind double dummy randomized triple crossover trial of 3 16 week treatments
  - High dose daily ICS (250 mcg fluticasone BID)
  - Low dose ICS (100 mcg fluticasone) + salmeterol in combination BID
  - Low dose ICS BID + Montelukast QD
- Outcomes: preferential improvement in one or more of 3 outcomes
  - Reduced need for prednisone
  - Increase in symptom free days by 31 days/year (annualized)
  - Improvement in FEV1 (by >5% of baseline)

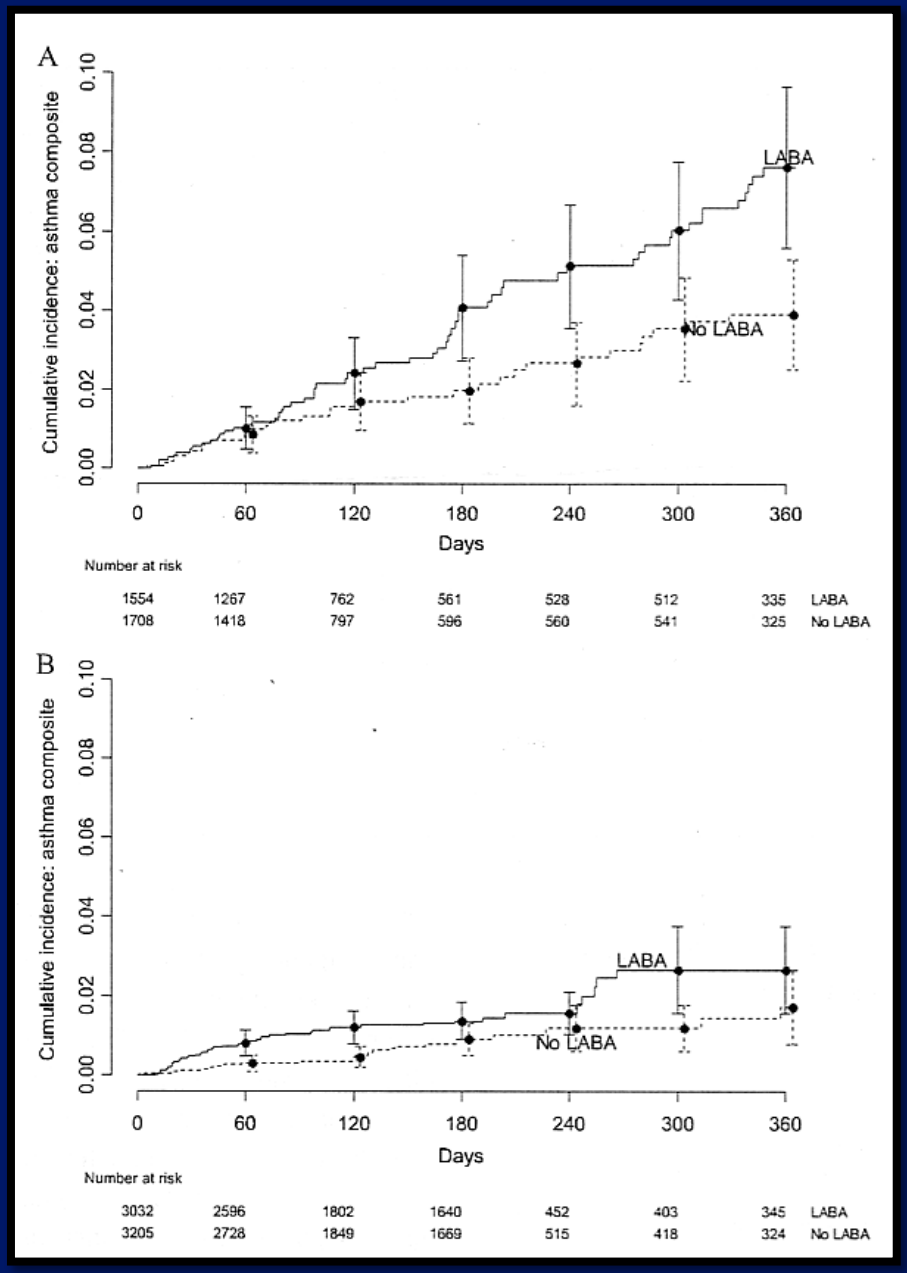
L:emanske et al, *NEJM* 2010 362:975-985.



Lemanske RF, et al. *New Engl J Med* 362(11):975-985, 2010.

Are Long-acting Beta Adrenergic drugs safe to use in children for long-term treatment of persistent asthma?

Cumulative Risk of Hospitalization for Asthma on LABA Therapy: Pediatric Data



McMahon AW, et al. *Pediatrics* 128(5):e1147-1154, 2011.

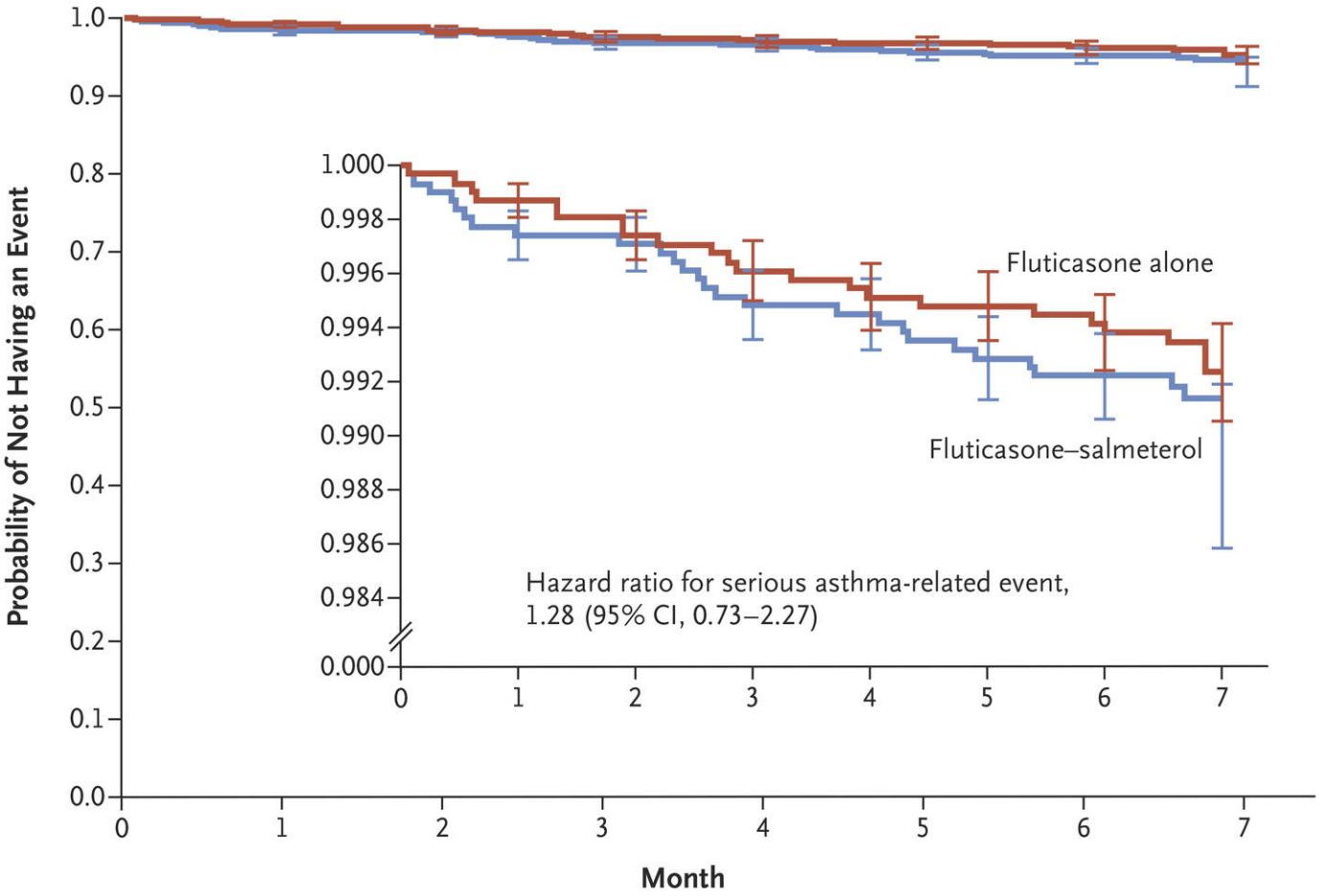
Safety of Adding Salmeterol to Fluticasone In Children with Asthma

- 6,208 4-11 year olds with diagnosed persistent asthma on ICS treatment from 32 countries
- + Hx of an asthma exacerbation in the last 12 months
- Are there more serious adverse events using a LABA with ICS than ICS alone, i.e. excess risk due to LABAs?
- Primary outcome: time to first asthma exacerbation (at least 3 days of oral corticosteroid use or more).

- 2 Doses of fluticasone (100 mcg vs 250 mcg twice daily) with and without salmeterol (50 mcg per inhalation) for 22 weeks were compared.
- Double blind randomized trial blinded to use of salmeterol.

Stempel D, et al. NEJM 375:840-9, 2016.

Time to First Acute Asthma Exacerbation



No. at Risk

Fluticasone–salmeterol	3107	3088	3079	3070	3053	3045	3028	273
Fluticasone alone	3101	3091	3077	3067	3054	3050	3030	318

Stempel DA, et al. *N Engl J Med* 375(9):840-9, 2016.

FDA Black Box Update on Long-Acting Beta Adrenergic Medications for Asthma December 20, 2017

- The black box warning on Long-Acting beta agonists (salmeterol and formoterol) was removed on products that contain both a LABA and an inhaled corticosteroid.
- The change was based on 4 clinical trials involving 41,000 patients. One study involved children 4-11 years old. The trials demonstrated that using ICS+LABA is more effective than using ICS alone for asthma.
- The black box warning remains on LABA single ingredient products.

Use of Beclomethasone as a Rescue Treatment for Children with Mild Persistent Asthma (TREXA study)

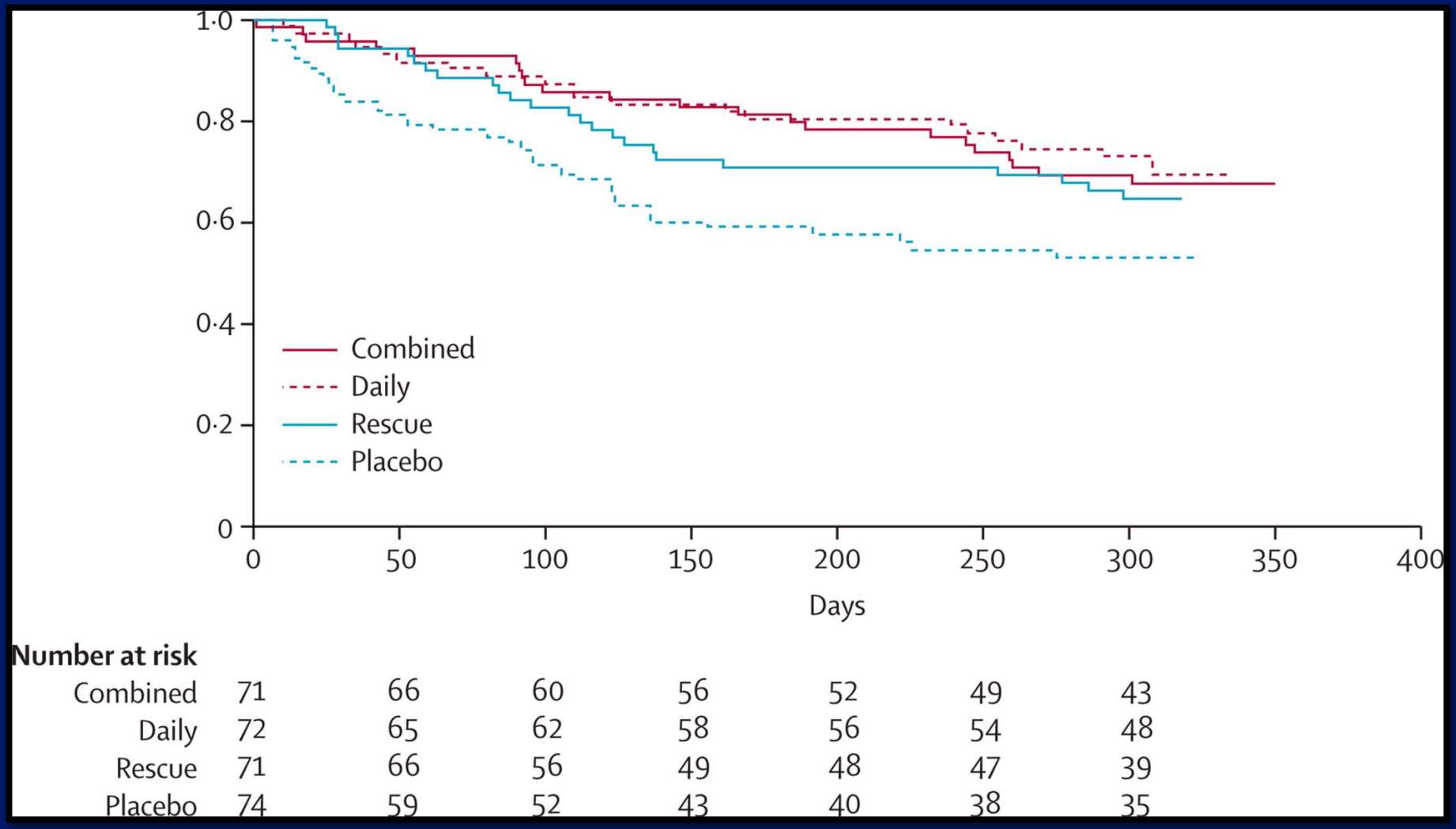
Does ICS as rescue therapy improve asthma control in mild persistent asthmatic children?

288 5-18 y/o with mild asthma on prn albuterol, 44 week randomized, double-blind, placebo controlled

Controller	Plus	Rescue
1. ICS (Beclomethasone 40 mg) BID		ICS (Beclo 160 mg) & albuterol Rescue
2. ICS (Beclomethasone 40 mg) BID		Albuterol
3. Placebo		ICS (Beclomethasone 160) & albuterol
4. Placebo		Albuterol

Martinez F, et al. *Lancet* 377:650-656, 2011.

Time to “Exacerbation” on Daily vs Rescue ICS Treatment



Number at risk

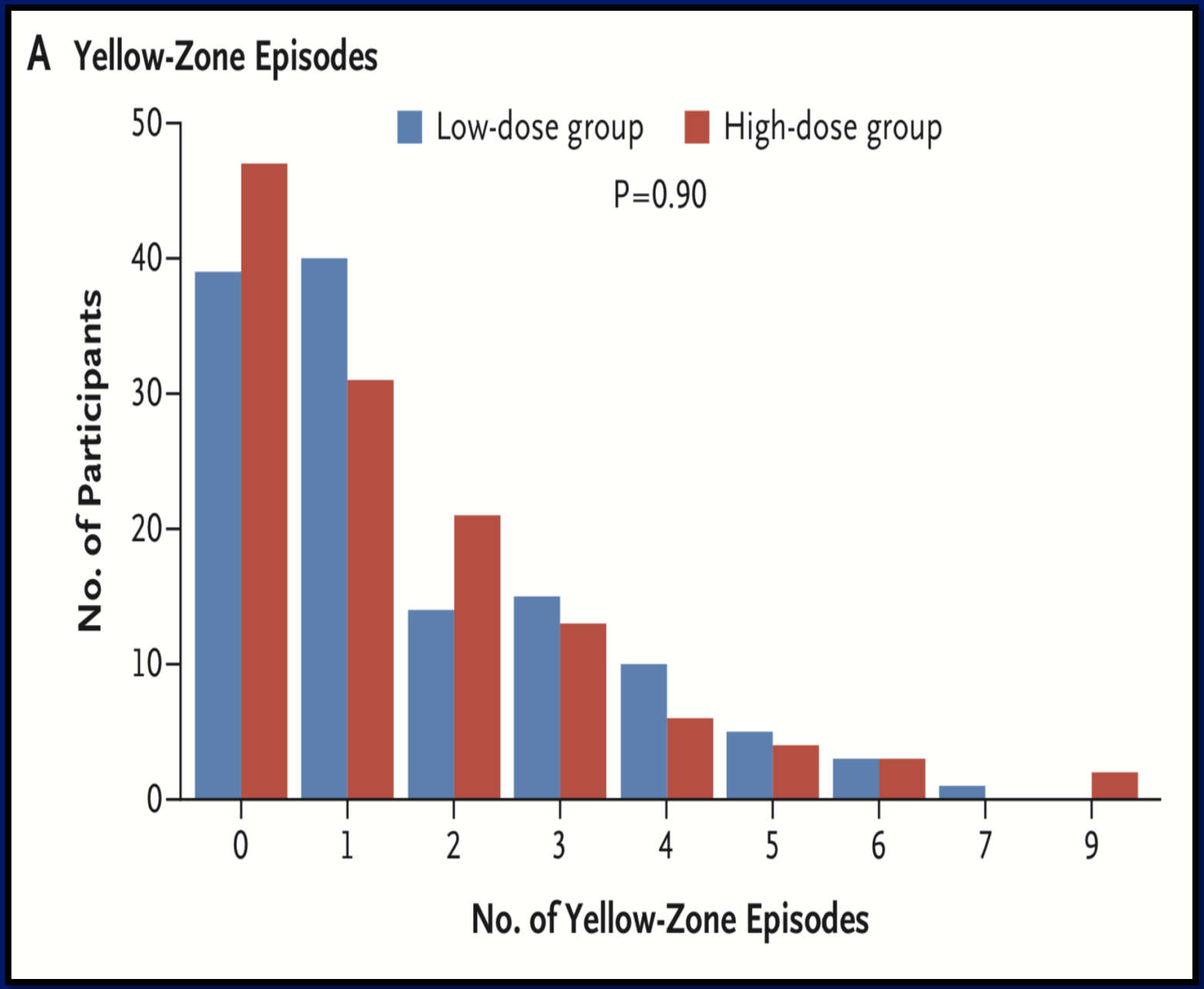
Combined	71	66	60	56	52	49	43
Daily	72	65	62	58	56	54	48
Rescue	71	66	56	49	48	47	39
Placebo	74	59	52	43	40	38	35

Martinez FD, et al. *Lancet* 377:650-657, 2011.

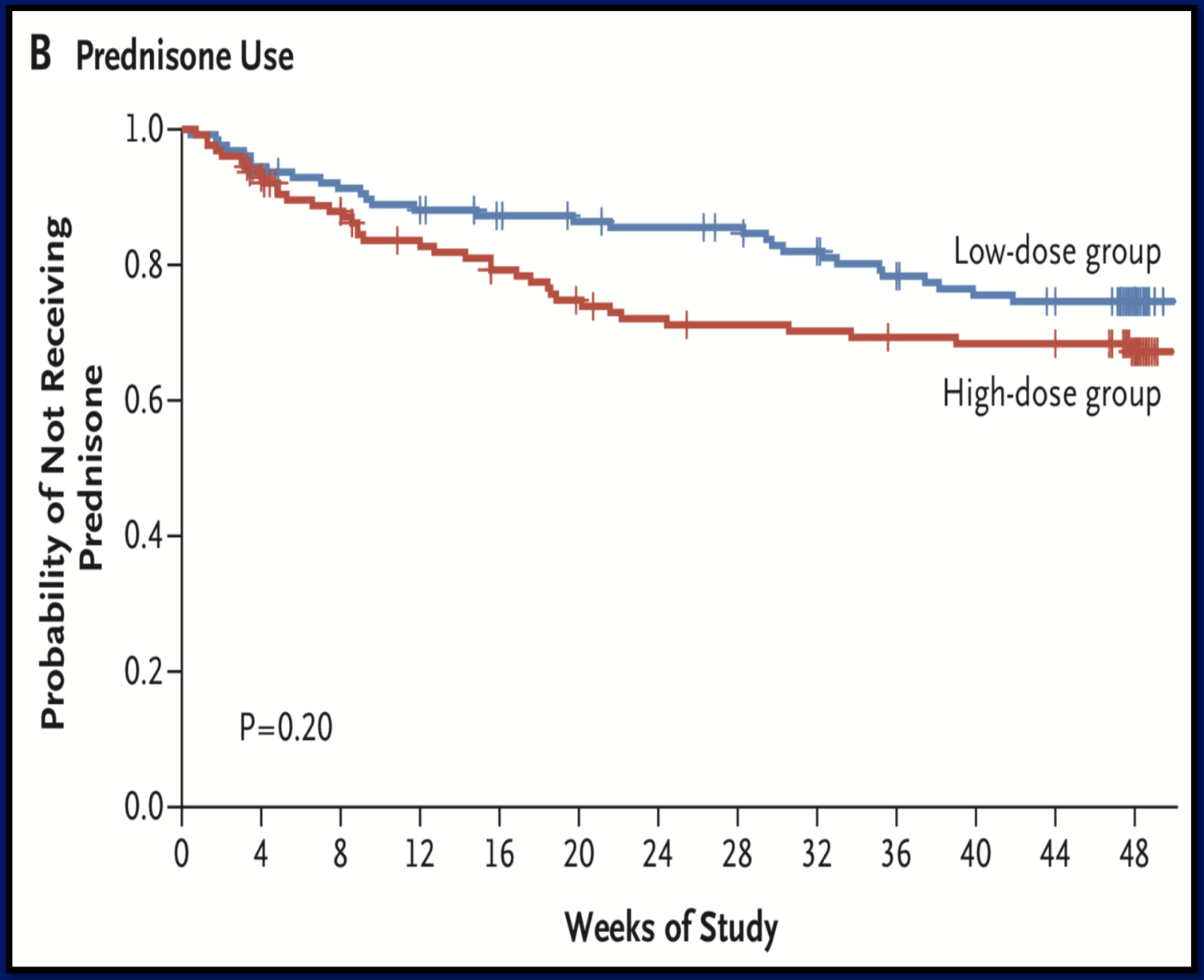
Quintupling ICS to Prevent Acute Asthma Exacerbations

- N=254 children ; 8+/- 2 years old with persistent mild to moderate asthma.
- Low dose fluticasone (88 mcg twice per day) vs intermittent high dose (440 mcg twice/day for 7 days with “yellow zone” asthma symptoms).
- 52 week study (4 week run in to assess adherence)
- 68 (38 vs 30 children/group) had severe exacerbations requiring oral corticosteroids.

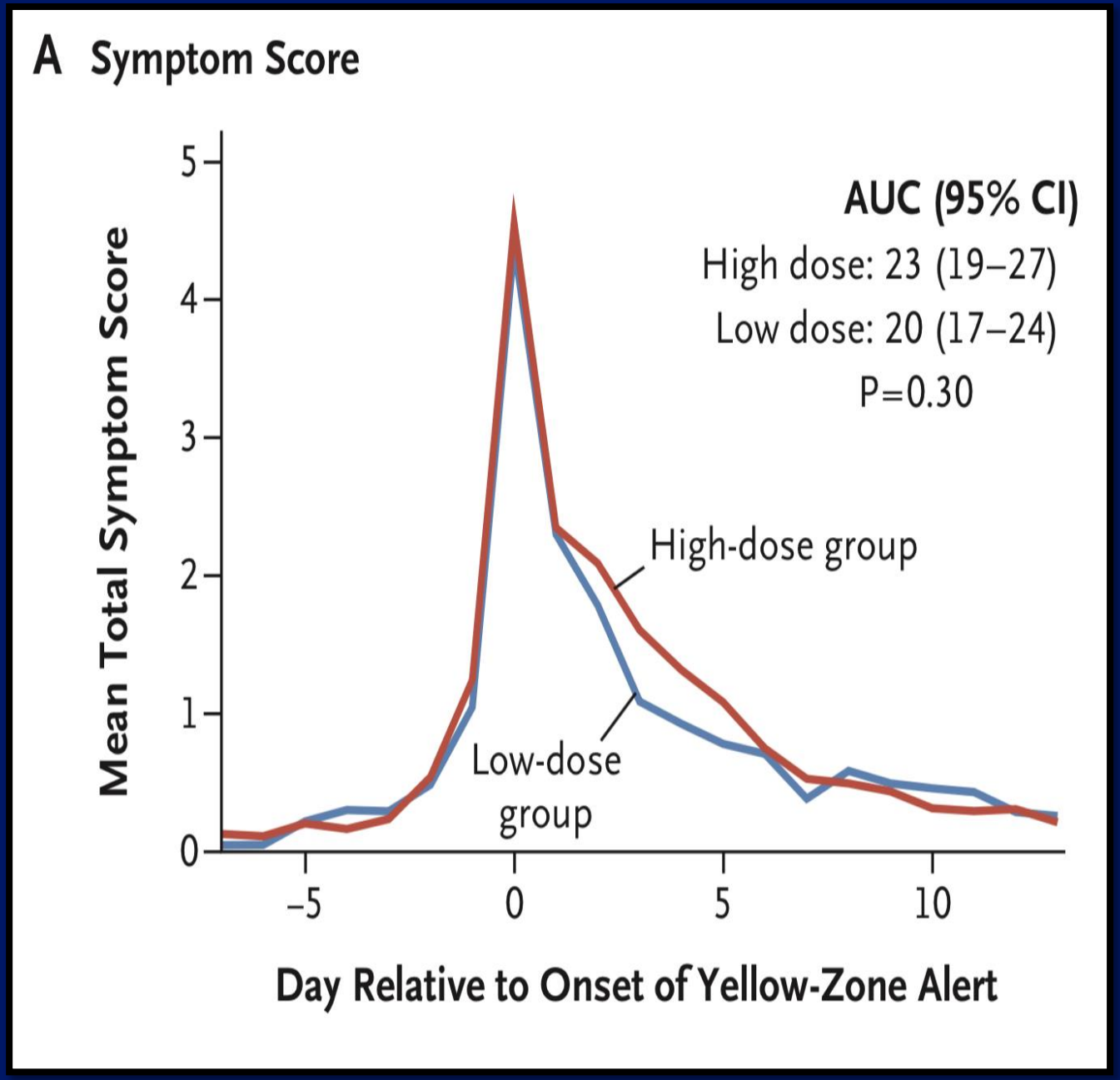
Jackson et al, *NEJM* 378(10): 891-901, 2018.



Jackson et al, *NEJM* 378(10): 891-901, 2018.



Jackson et al, *NEJM* 378(10): 891-901, 2018.



Jackson et al, *NEJM* 378(10): 891-901, 2018.

Intermittent ICS in Preschool Wheezers

- Bronchiolitis vs Recurrent Wheezing (2 vs 4 x/year) vs Infantile Asthma
- Respiratory viruses cause 65-85% of acute exacerbations among children with asthma
- Most children with life-long asthma began to have symptoms when < 3 years of age.
- Asthma Predictive Index (Enriched populations):
  - Maternal Asthma
  - Infant Eczema
  - Minor Criteria
    - Eosinophilia >4%
    - Wheezing apart from colds
    - MD diagnosed allergic rhinitis

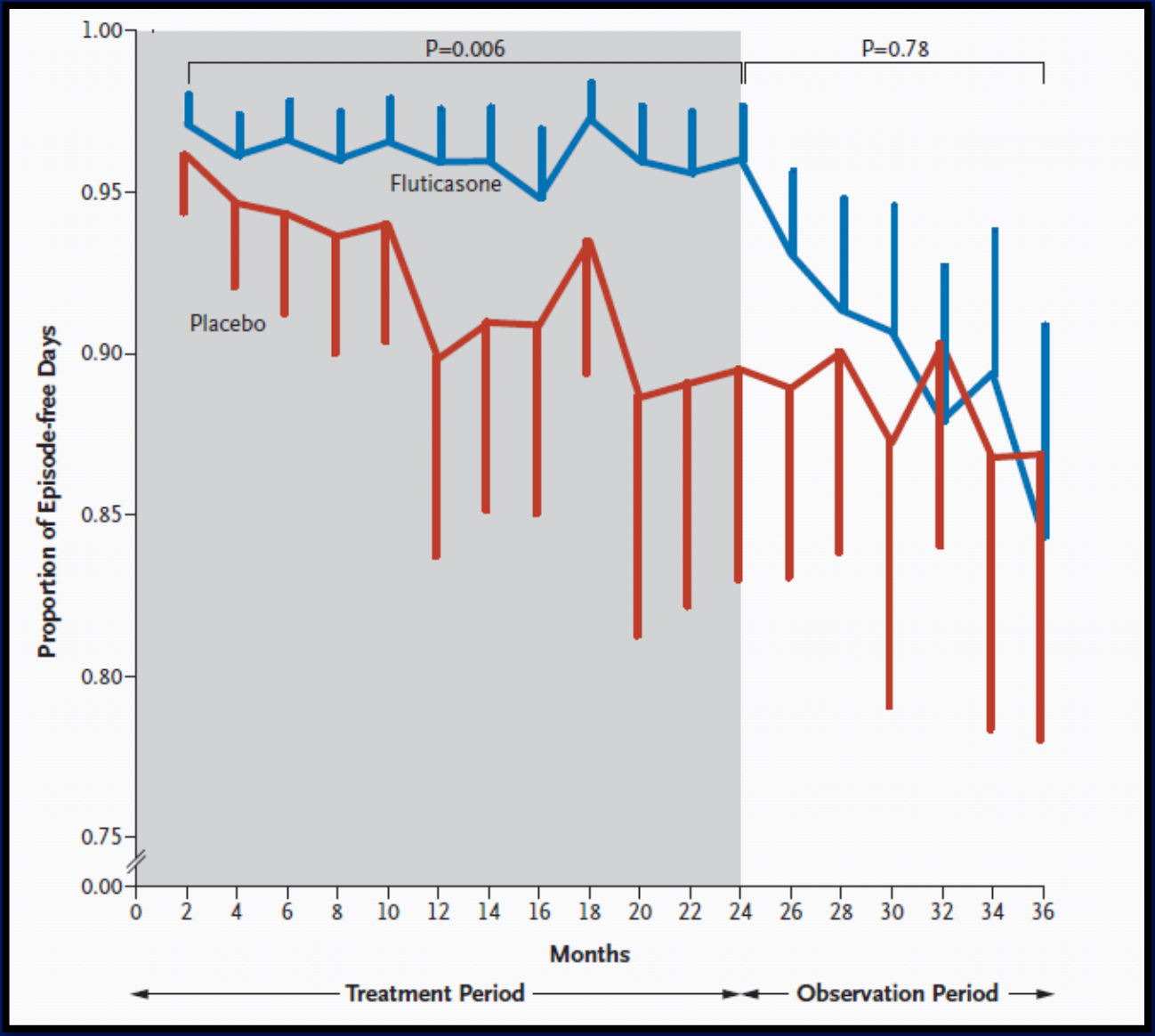
Prevention of Early Asthma in Kids (PEAK) Study: 2006

- 285 1-3 year olds with higher likelihood of asthma
- Fluticasone 88 mcg BID for 2 year vs placebo plus 1 year observational period off treatment
- Primary outcome: asthma episode-free days
- Secondary outcome: treatment courses with prednisone

- Does prolonged ICS treatment in young children alter the natural course of their disease?

Guilbert et al. *NEJM* 354:1985-1997, 2006.

High Risk 2 Year Old Wheezy Children: Treatment and Post-treatment Effects of ICS Treatment



Guilbert TW, et al. *NEJM* 354(19):1985-1997, 2006.

Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) Trial: 2011

- 213 1-4 years olds with higher risk of asthma, 4 episodes of wheezing, one course of prednisone

- 1 year study involving 2 treatment arms:

Budesonide 0.5 mg once/daily (n=113)

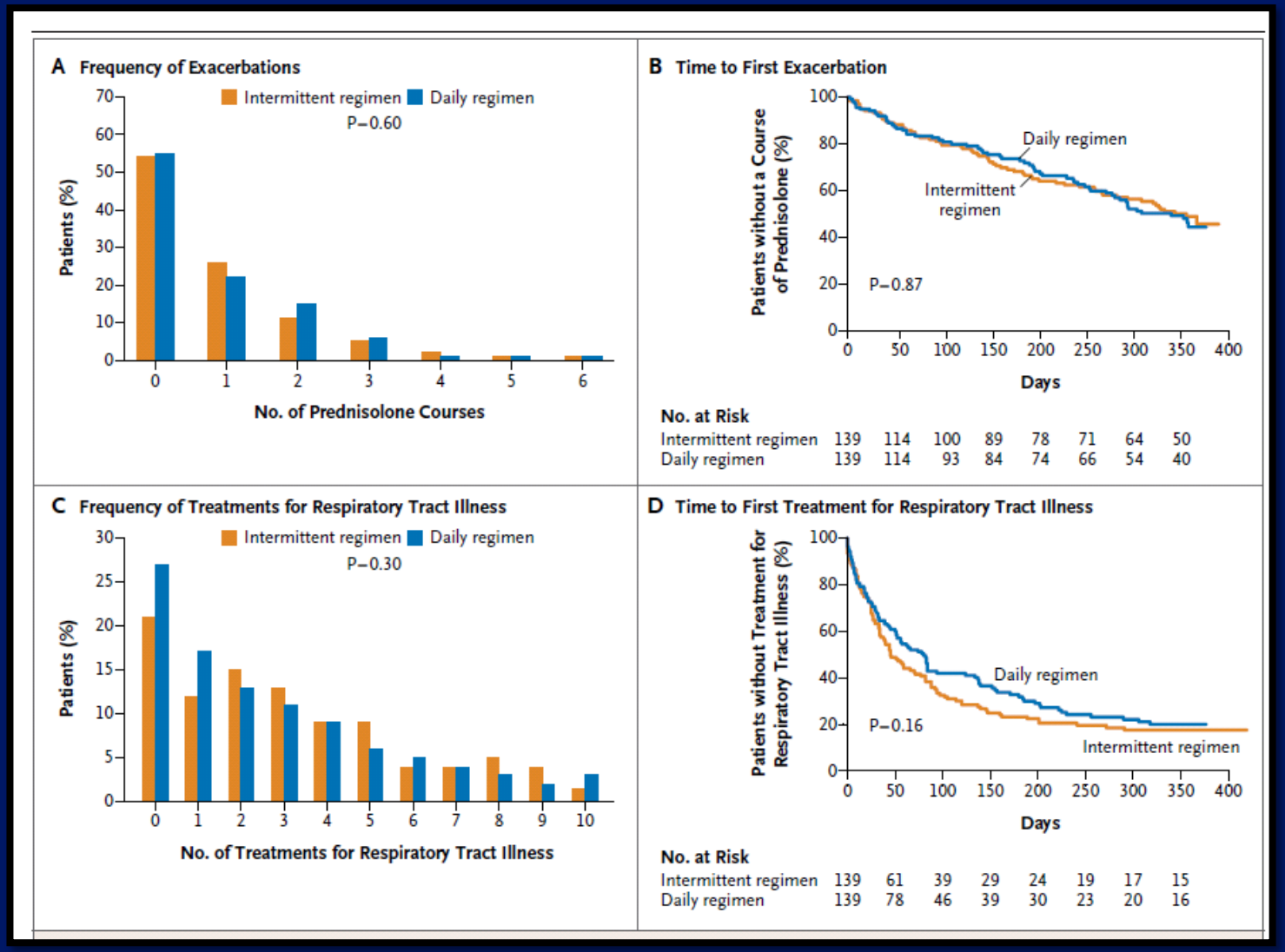
vs

Budesonide 2 mg (1 mg BID) for 7 days with the onset of wheeze or URI symptoms (n=100)

- Primary Outcome: frequency of exacerbations, rate of treatment failure, growth effects

Zeiger et al. *NEJM* 365:1990-2001, 2011.

Outcomes of Daily vs Intermittent ICS Treatment



Zeiger RS, et al. *N Engl J Med* 365:1990-2001, 2011.

Pre-emptive use of High Dose Fluticasone in Recurrent Pediatric Wheezers

- 129 children 1-6 years olds with 3 lifetime wheezing episodes
- Placebo vs Fluticasone 750 mcg BID at onset of URI signs + prn albuterol every 4 hours (62 RX vs 67 placebo)
- Used until 48 hours after symptoms resolved (usually < 10 days)
- Studied over 12 months
- Outcome: Need for oral corticosteroids

Ducharme FM, et al. *NEJM* 360(4):339-53, 2009.

Results

- Ages were 2.8+/-1 year in both groups
- 18% with family Hx of asthma in both groups
- + Eczema Hx in 34% in Rx'd group vs 51% in placebo group
- # URIs: 521 in Rx'd group and 526 in placebo (8/year
- Duration of acute illness: 6 days (4-9) in Rx'd vs 7 days (5-10)* in placebo group
- 8% fluticasone vs 18% in placebo group needed oral corticosteroid treatment
- Greater impact on height in fluticasone group over 1 year

Ducharme FM, et al. *NEJM* 360(4):339-53, 2009.

Summary

- Children with asthma are not all the same and will respond to different accepted treatments differently.
- Daily asthma “controller” treatment is the best way to manage persistent (Rule of 2s) asthma.
- Intermittent “high dose’ inhaled corticosteroids have a role in children with mild intermittent asthma on albuterol alone during acute exacerbations.
- Intermittent “high dose” inhaled corticosteroids have an unproven role in children with persistent asthma already on inhaled corticosteroids.
- ICS+LABA combinations are an important part of treatment

Choice of Drugs for Asthma Care

Inhaled Corticosteroid

Beclomethasone
Budesonide
Fluticasone (furoate & proprionate)
Mometasone
Ciclisonide

Strategies

Pick 1 or 2 to use

Consider drug delivery device

Understand “high” vs “low” doses

Starting moderate dose of ICS

End points to increase dose or add a drug

Know the lowest dose that does the most good

Alternative Therapies

Montelukast, Zafirlukast
Theophylline

Add-On Therapies

Long-Acting Berta Agonists
-Salmeterol
-Formoterol
-Vilanterol
Leukotriene Receptor Antagonists
-Montelukast

Biologics

Omalizumab (Anti-IgE) ≥6 y/o
Mepolizumab (Anti-IL5) >12 y/0
Benralizumab (Anti-IL-5 receptor)