Montelukast e cortisonici topici: insieme o da soli?

V GIORNATA DI
ALLERGOLOGIA ED IMMUNOLOGIA PEDIATRICA

1/2 APRILE 2011
Sala Conferenze
Ospedale Fatebenefratelli - Benevento

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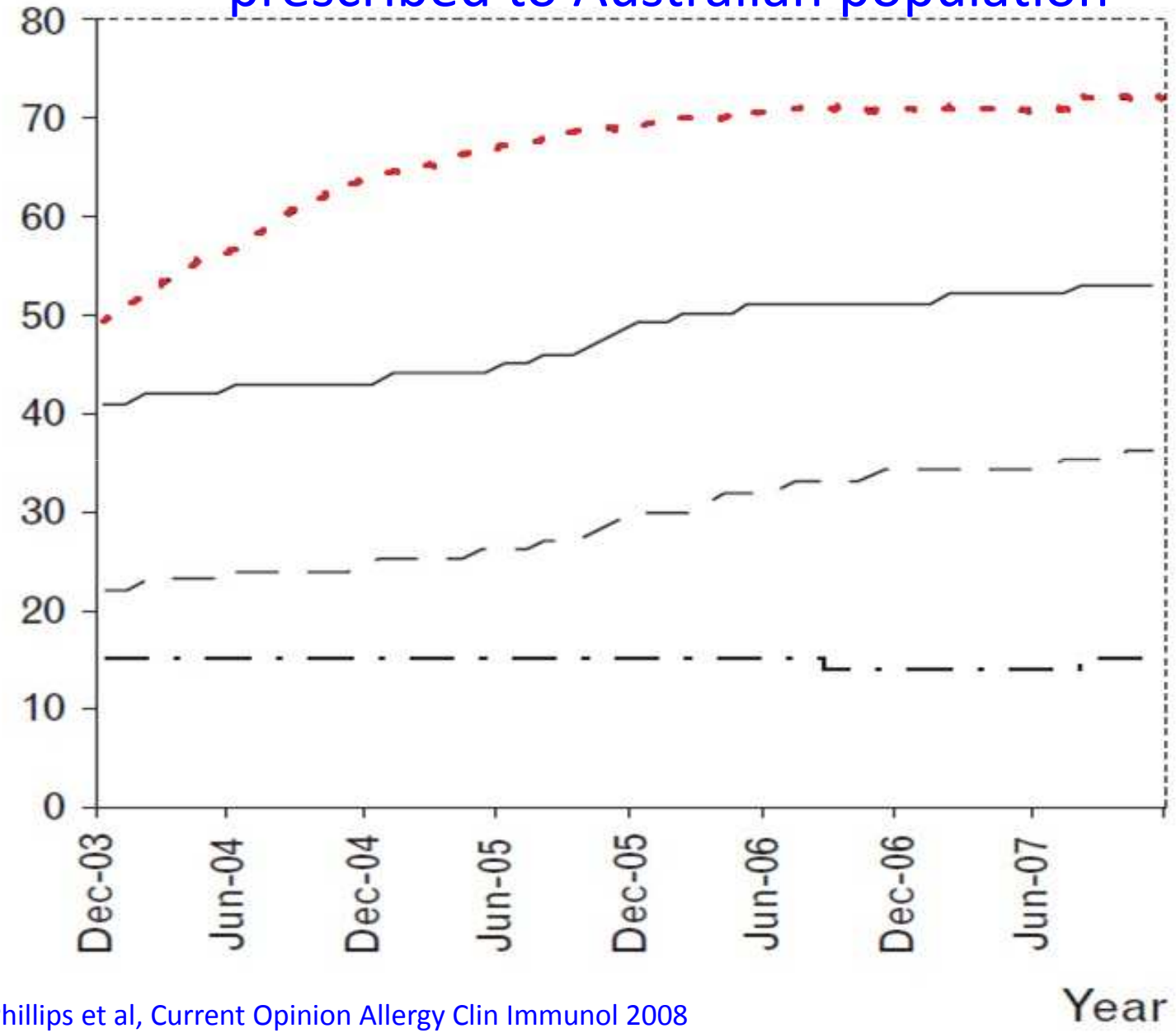
ICS
LTRA

Percentage of all asthma medications prescribed to Australian population



LRTA

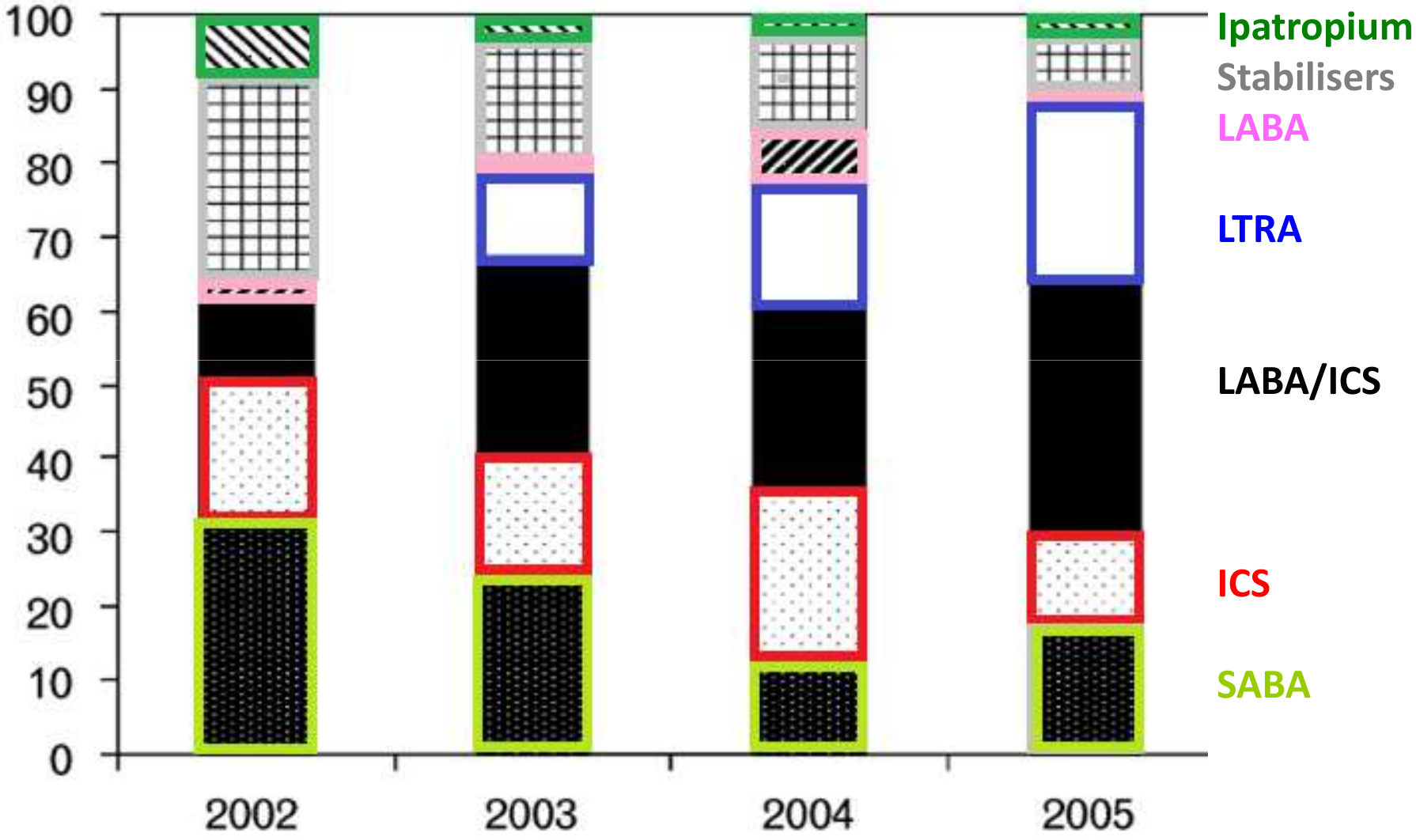
CS

FC

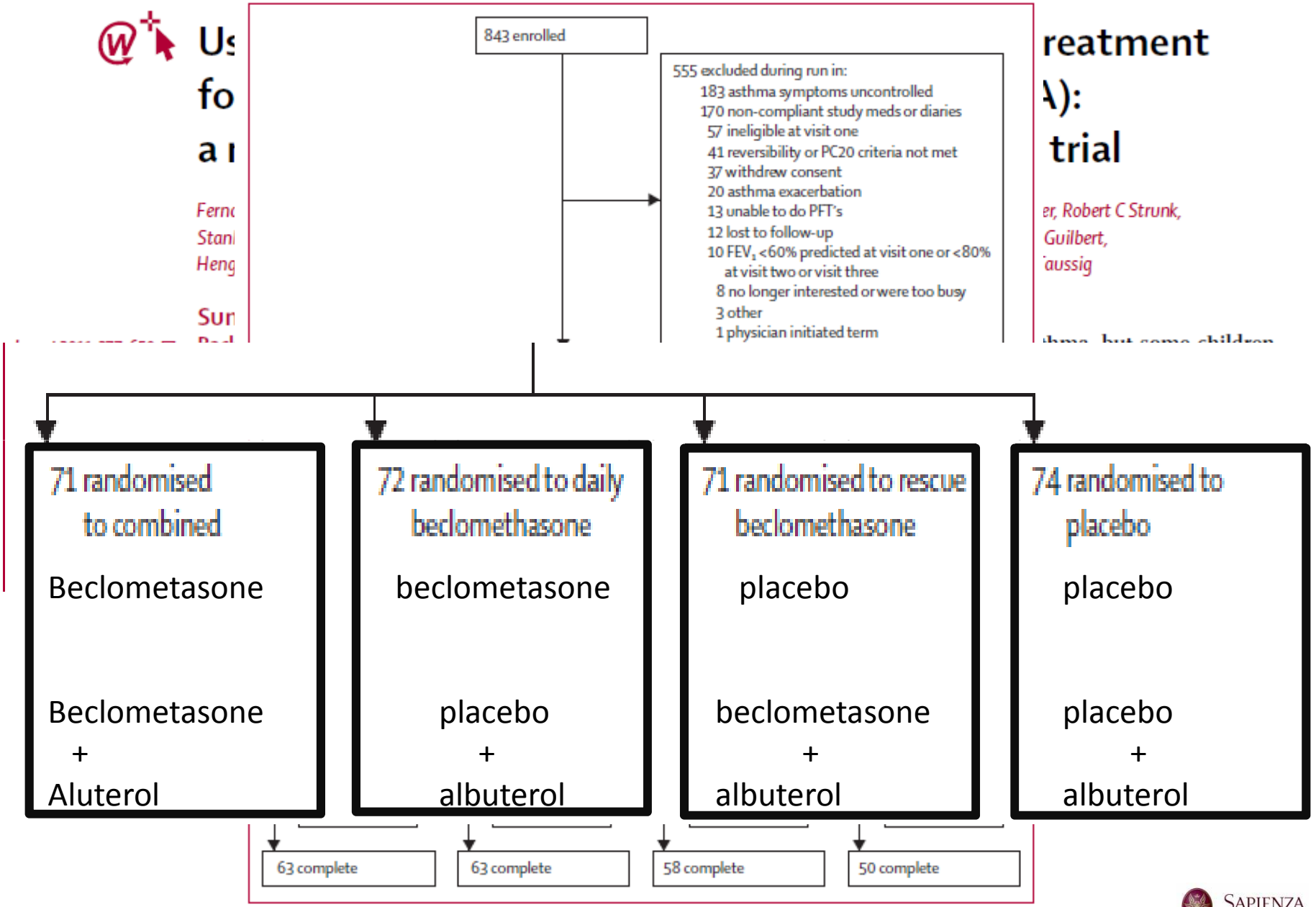
LABA

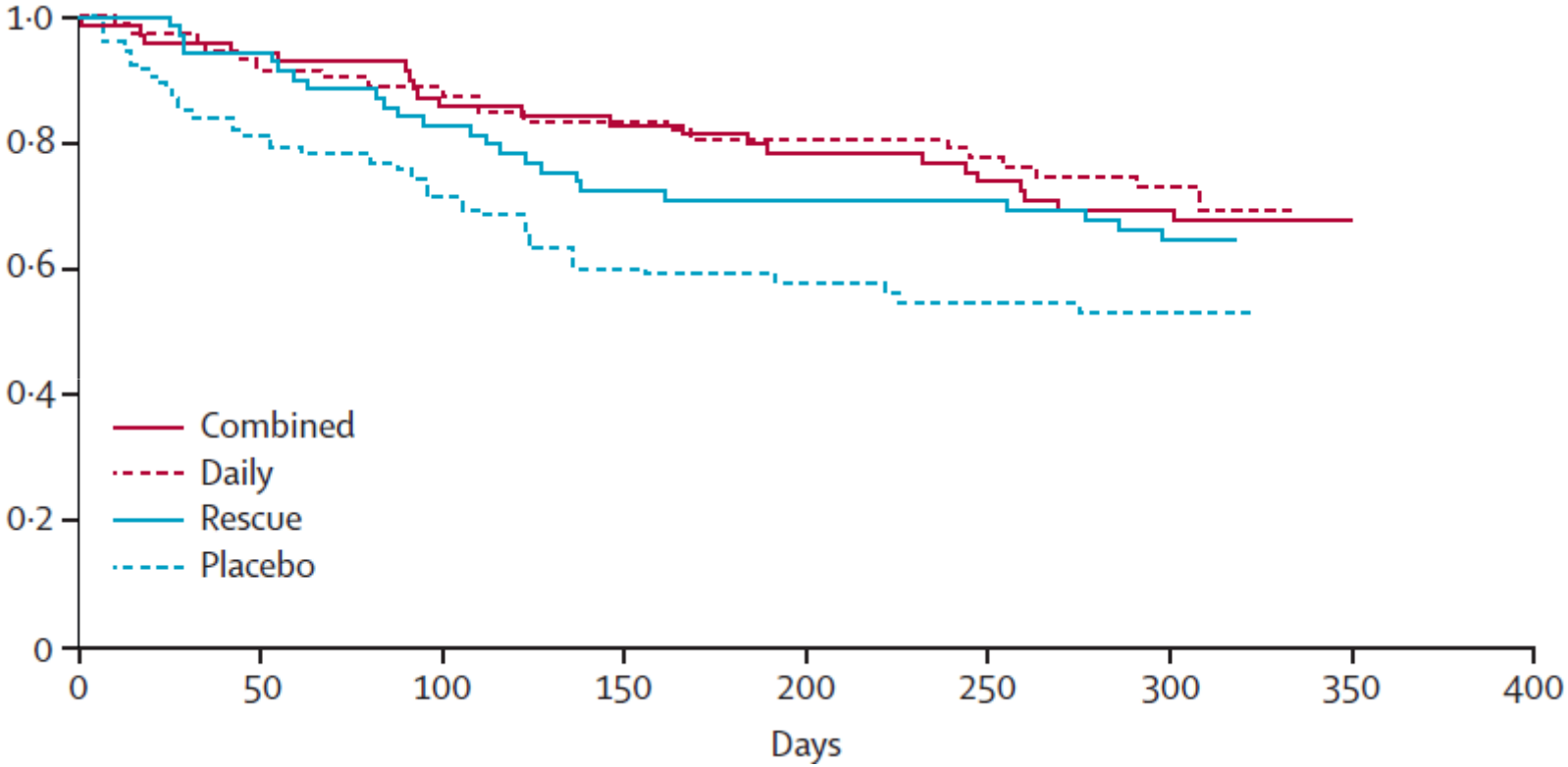
C. Phillips et al, Current Opinion Allergy Clin Immunol 2008

Changes in prescription claims for asthma medications for children in the Australian Capital Territory, aged 5 y



C. Phillips et al, Current Opinion Allergy Clin Immunol 2008

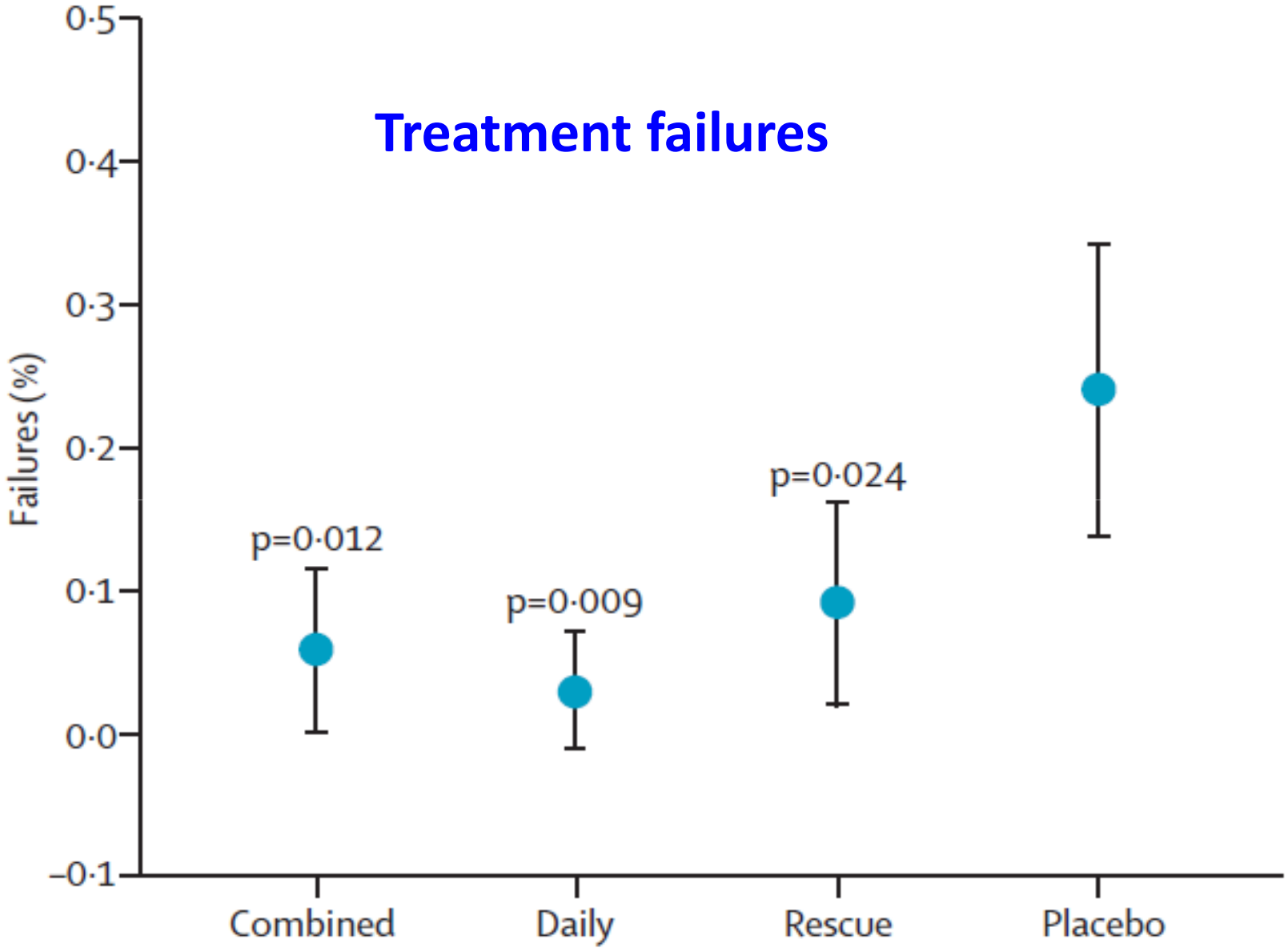

843 enrolled
555 excluded during run in:
183 asthma symptoms uncontrolled
170 non-compliant study meds or diaries
57 ineligible at visit one
41 reversibility or PC20 criteria not met
37 withdrew consent
20 asthma exacerbation
13 unable to do PFT's
12 lost to follow-up
10 FEV1 <60% predicted at visit one or <80% at visit two or visit three
8 no longer interested or were too busy
3 other
1 physician initiated term
71 randomised to combined
Beclometasone
+
Aluterol
72 randomised to daily beclomethasone
beclometasone
+
albuterol
71 randomised to rescue beclomethasone
placebo
+
beclometasone
74 randomised to placebo
placebo
+
albuterol
63 complete
63 complete
58 complete
50 complete



Kaplan-Meier curves showing the time to fi rst exacerbation

Martinez FD et al, LANCET 2011

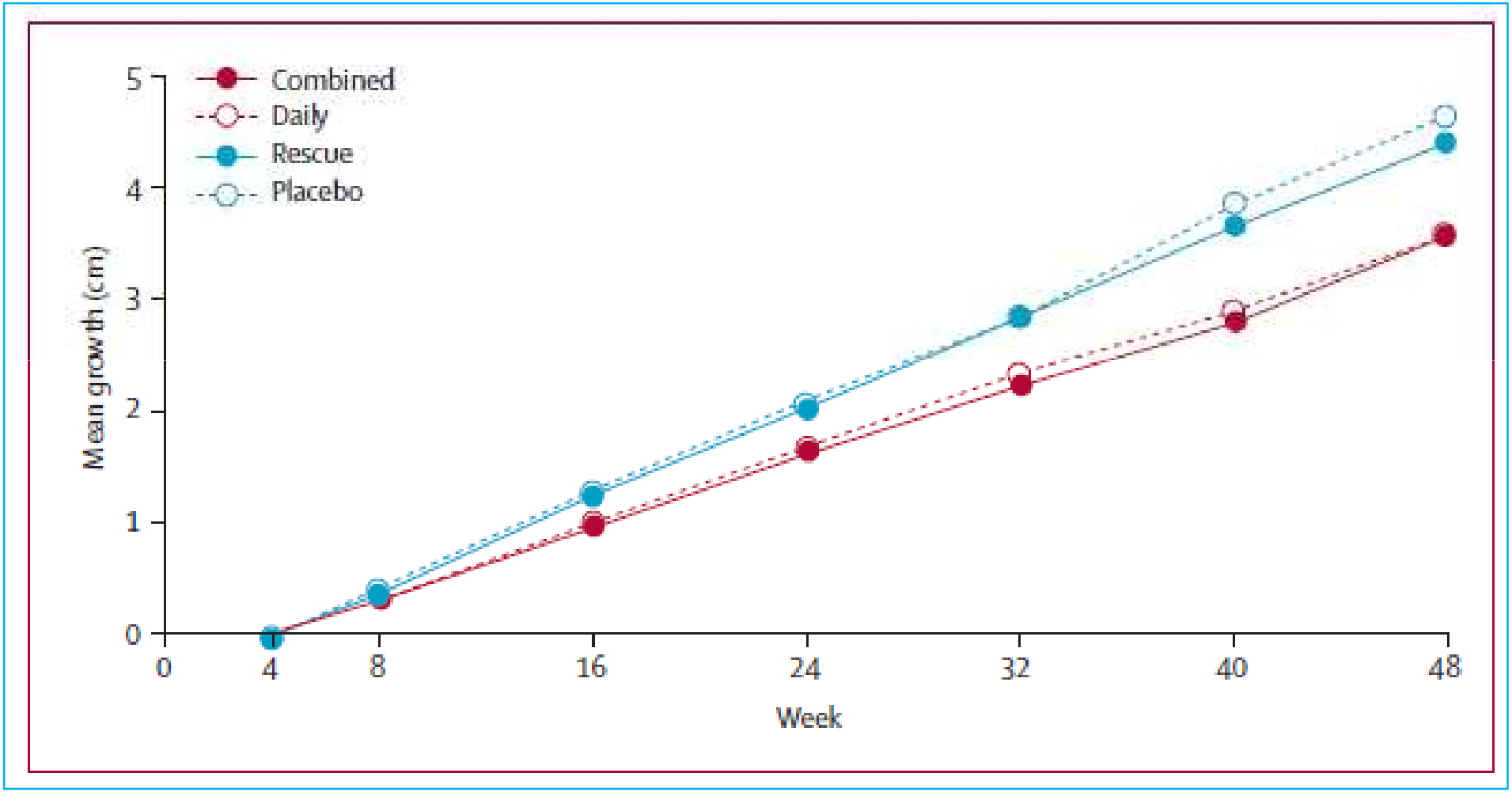
Treatment failures



each treatment group vs the placebo group

Martinez FD et al, LANCET 2011

Linear growth by treatment group



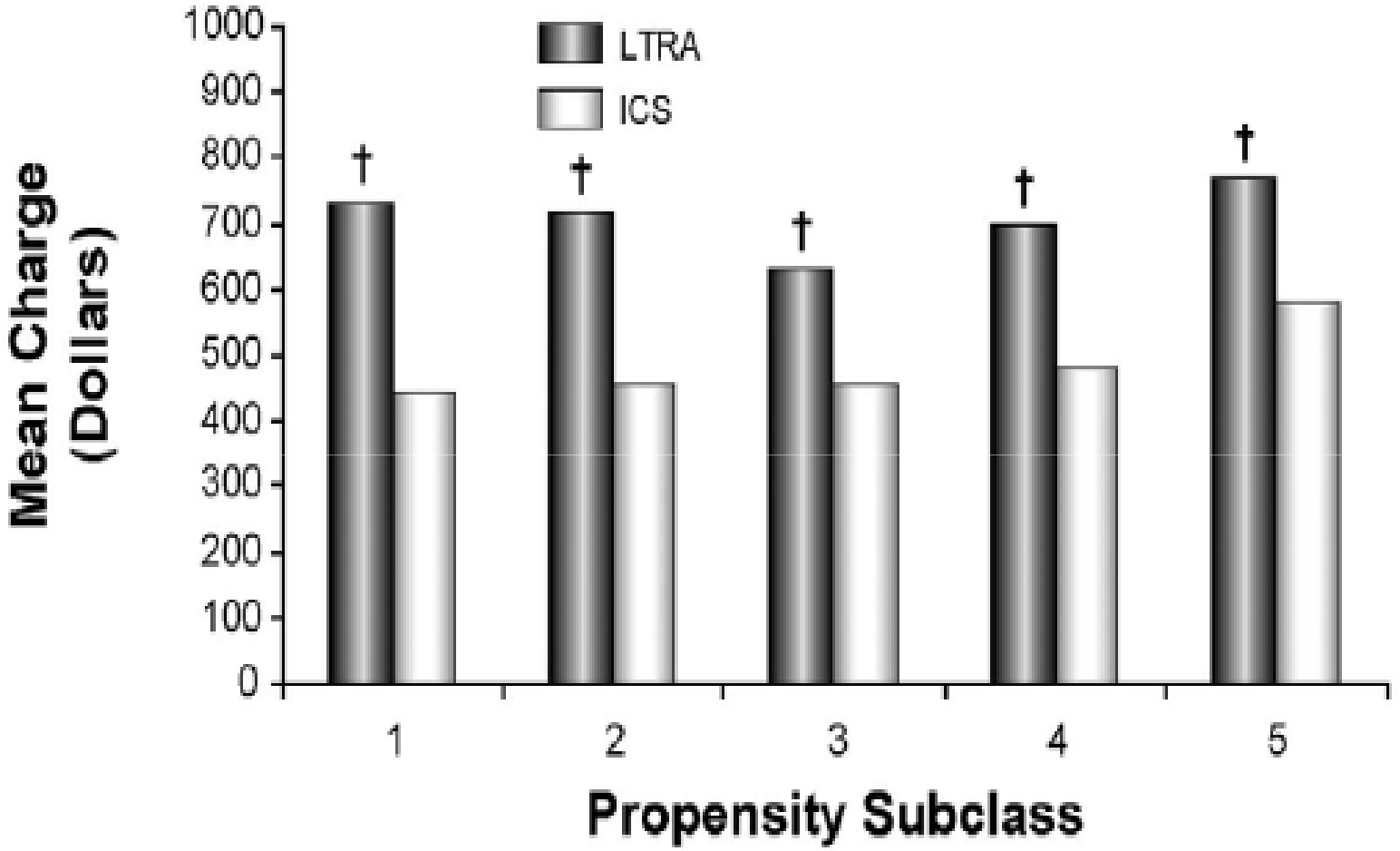
Martinez FD et al, LANCET 2011

Inhaled corticosteroids vs leukotriene receptor antagonists: health care costs across varying asthma severities

Richard D. O'Connor, MD*; Bhash Parasuraman, PhD†; Craig Roberts, PharmD, MPA‡; and Christopher Leibman, PharmD, MS§

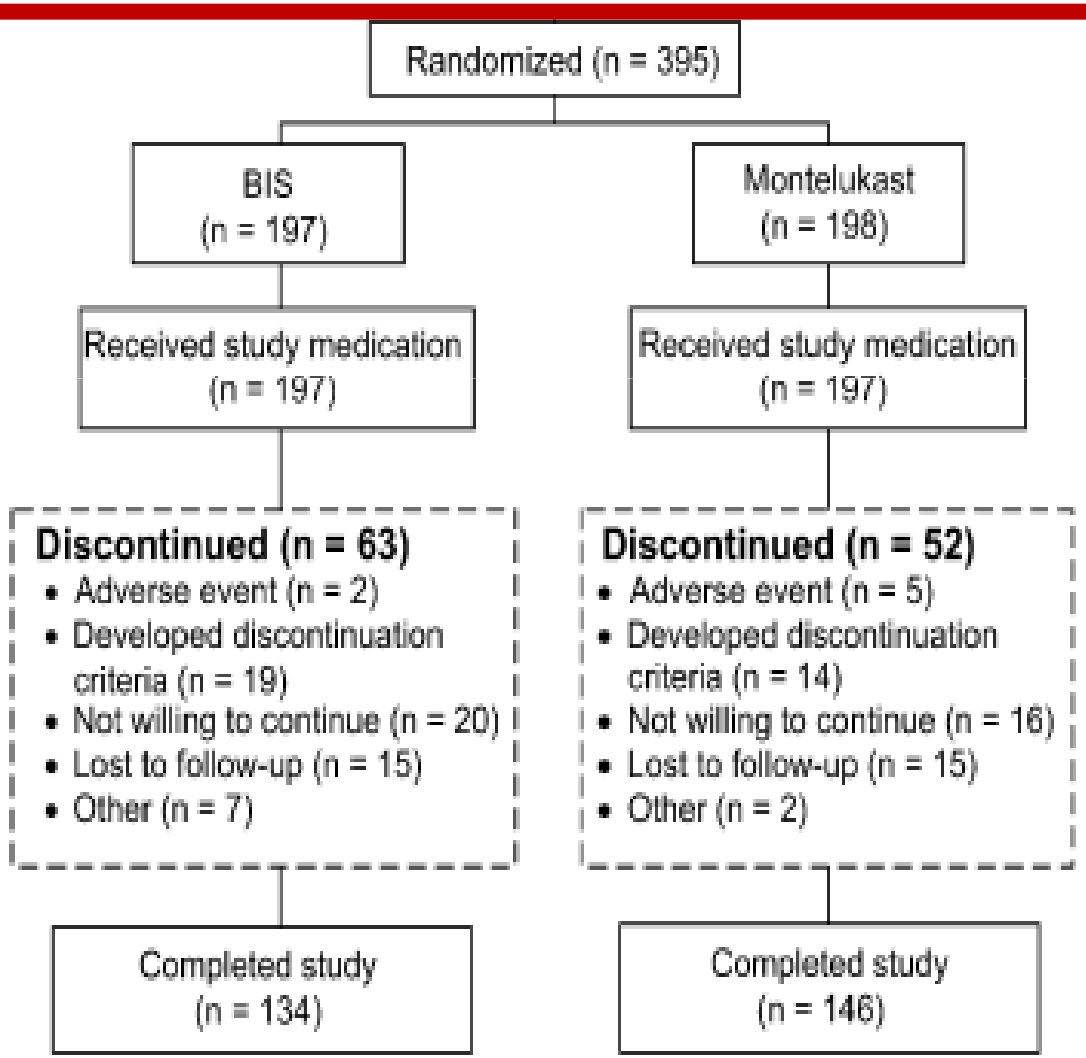
Demographic	No. (%) of patients	
	LTRAs (n = 7,385)	ICSs (n = 24,475)
Mean ± SD age, y	28.2 (19.1)	32.3 (18.7)
Patients by age group, y		
0–18	3,373 (45.7)	8,346 (34.1)
19–39	1,504 (20.4)	6,047 (24.7)
40–49	1,188 (16.1)	4,667 (19.1)
50–59	956 (12.9)	3,876 (15.8)
≥60	364 (4.9)	1,539 (6.3)

Ann Allergy Asthma immunol 2006



'O Connors et al, Ann Allergy Asthma immunol 2006

Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma

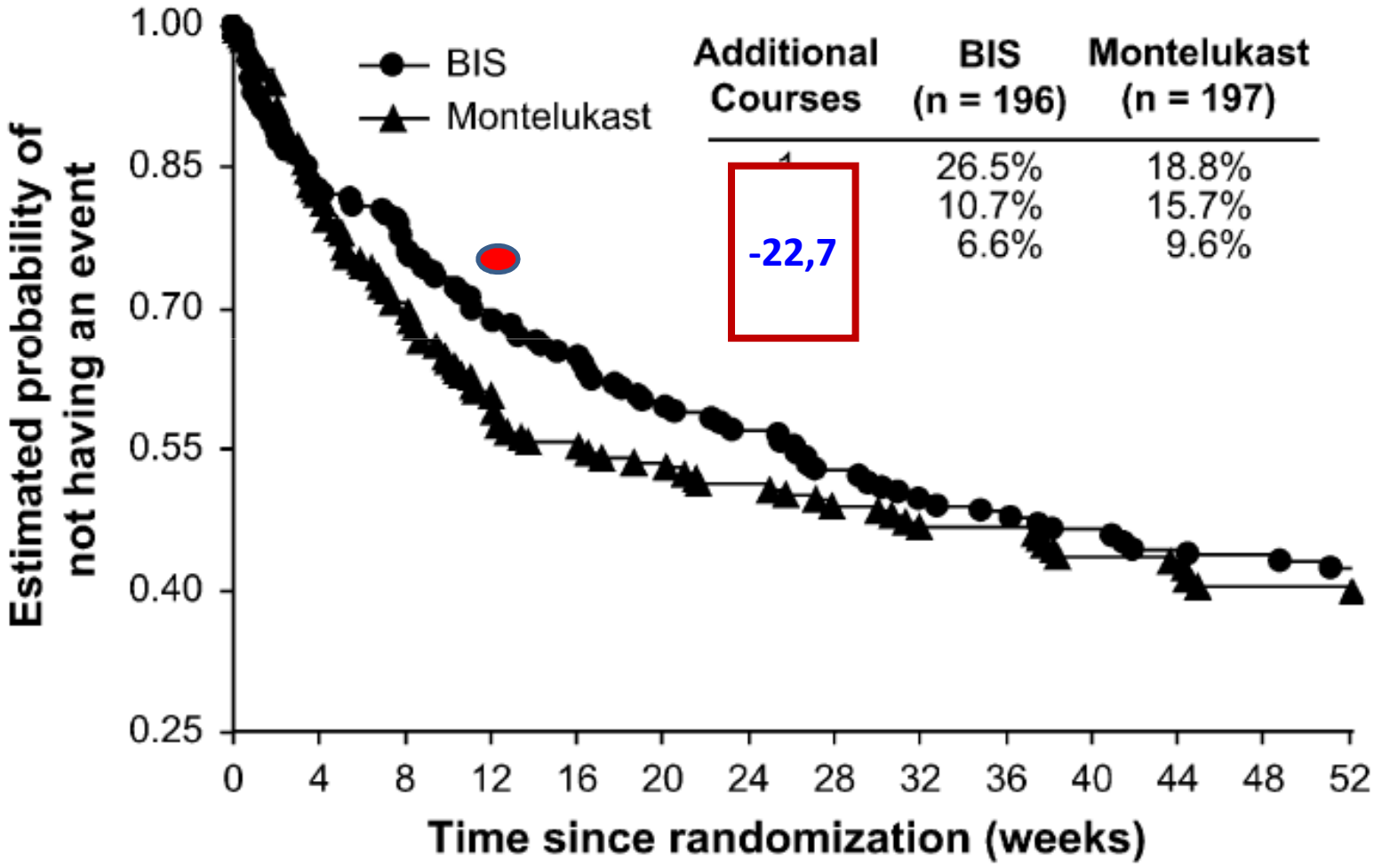


- **1 anno 2 /0**
- **≤ 5 anni 129/126**
- **Uso ICS: 25/24**
- **Uso LABA: 6/4**

- **FU 52 wks**

SJ. Szefler et al, JACI 2007

Kaplan-Meier probability curve for the time to first additional asthma medication (step-up BIS or oral corticosteroids) over the 52-week study period. *Unadjusted P = 0.05.



S J. Szefler et al, JACI 2007

Variable	Treatment	n*	Value	*P* value (BIS – montelukast)
Exacerbations				
Mild or severe asthma exacerbations, events/subject/y	BIS	196	1.23	.034
	Montelukast	197	1.63	
Diary-related variables, adjusted mean (SEM) change from baseline†				
AM asthma symptom score	BIS	195	−0.40 (0.04)	.36
	Montelukast	196	−0.35 (0.04)	
PM asthma symptom score	BIS	195	−0.43 (0.04)	.12
	Montelukast	196	−0.35 (0.04)	
24-h rescue medication use	BIS	195	−0.69 (0.11)	.84
	Montelukast	196	−0.72 (0.11)	
Rescue medication–free days, %	BIS	190	38.74 (2.14)	.59
	Montelukast	194	37.24 (2.13)	
Asthma-free days, %	BIS	190	19.91 (1.99)	.19
	Montelukast	194	16.48 (1.97)	
AM PEF	BIS	169	21.07 (2.30)	.007
	Montelukast	161	14.03 (2.28)	
PM PEF	BIS	171	16.83 (2.30)	.005
	Montelukast	163	9.42 (2.27)	
Pulmonary function variables, adjusted mean (SEM) change from baseline†				
FEV_1 (L)	BIS	77	0.09 (0.02)	.19
	Montelukast	82	0.05 (0.02)	
% Predicted FEV_1	BIS	77	7.52 (1.59)	.64
	Montelukast	80	6.55 (1.62)	

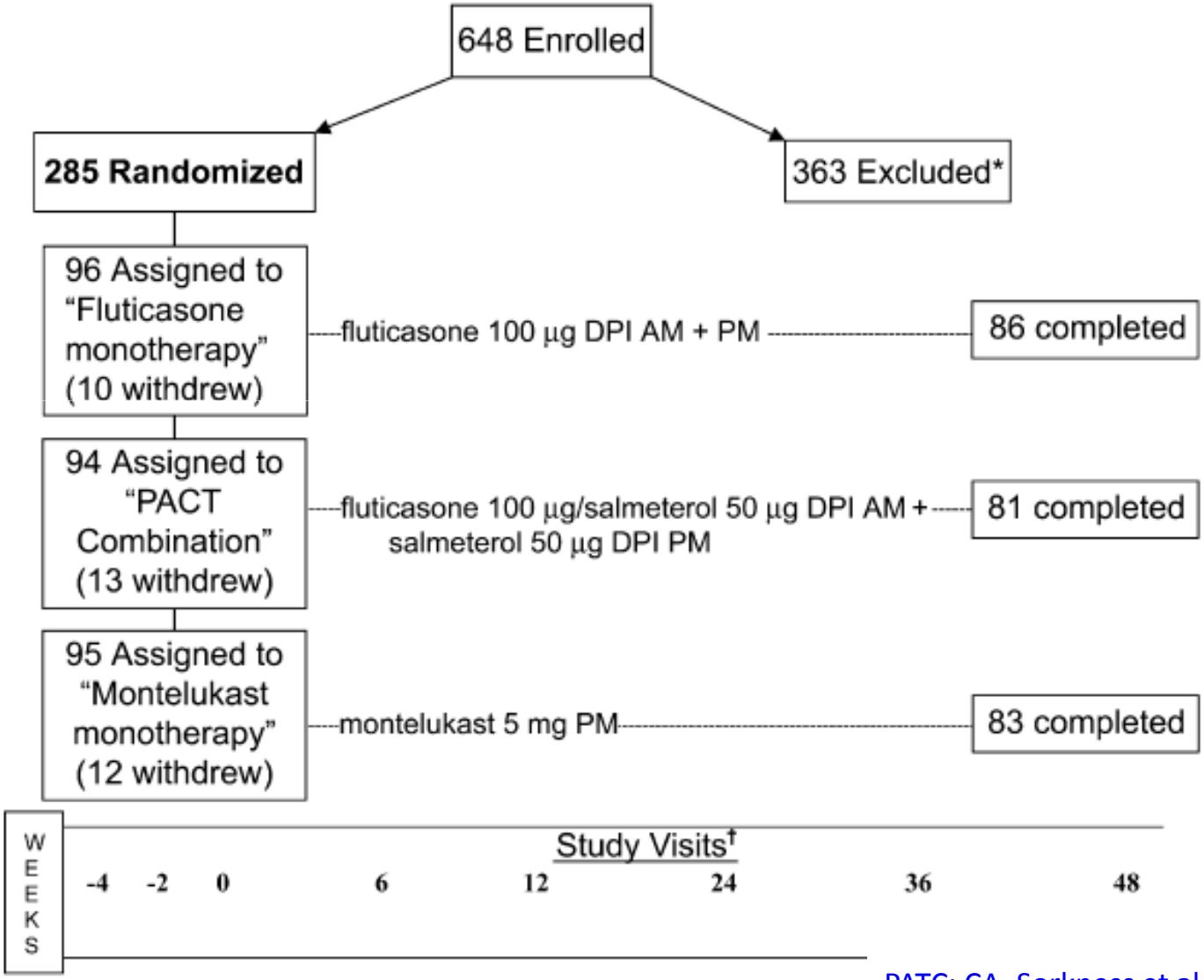
40%

*Subjects with baseline and postbaseline values at week 12.

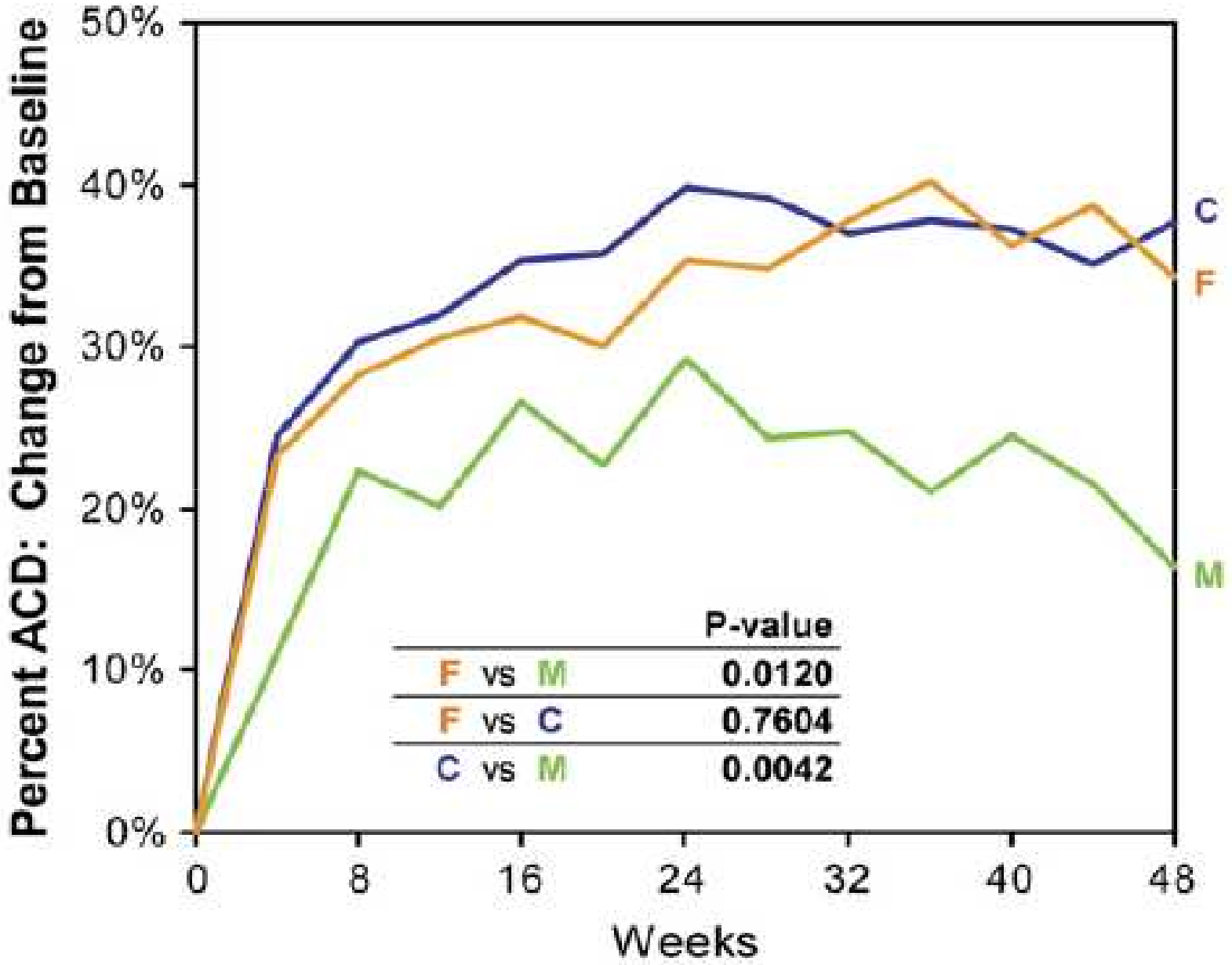
†Change from baseline to the average for weeks 1 through 12 using the last observation carried forward.

S J. Szefler et al, JACI 2007

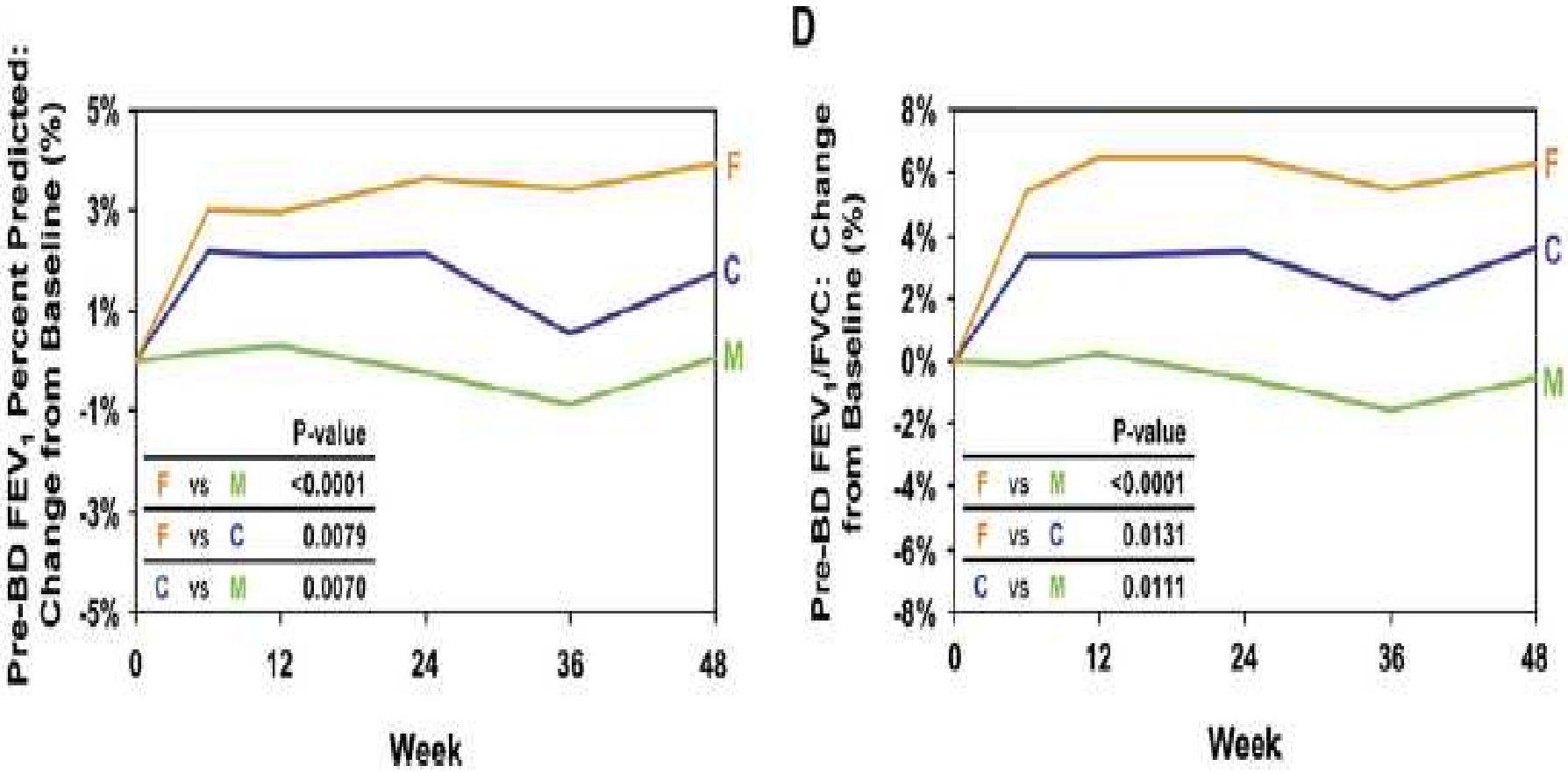
Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial



PATC; CA. Sorkness et al, JACI 2007

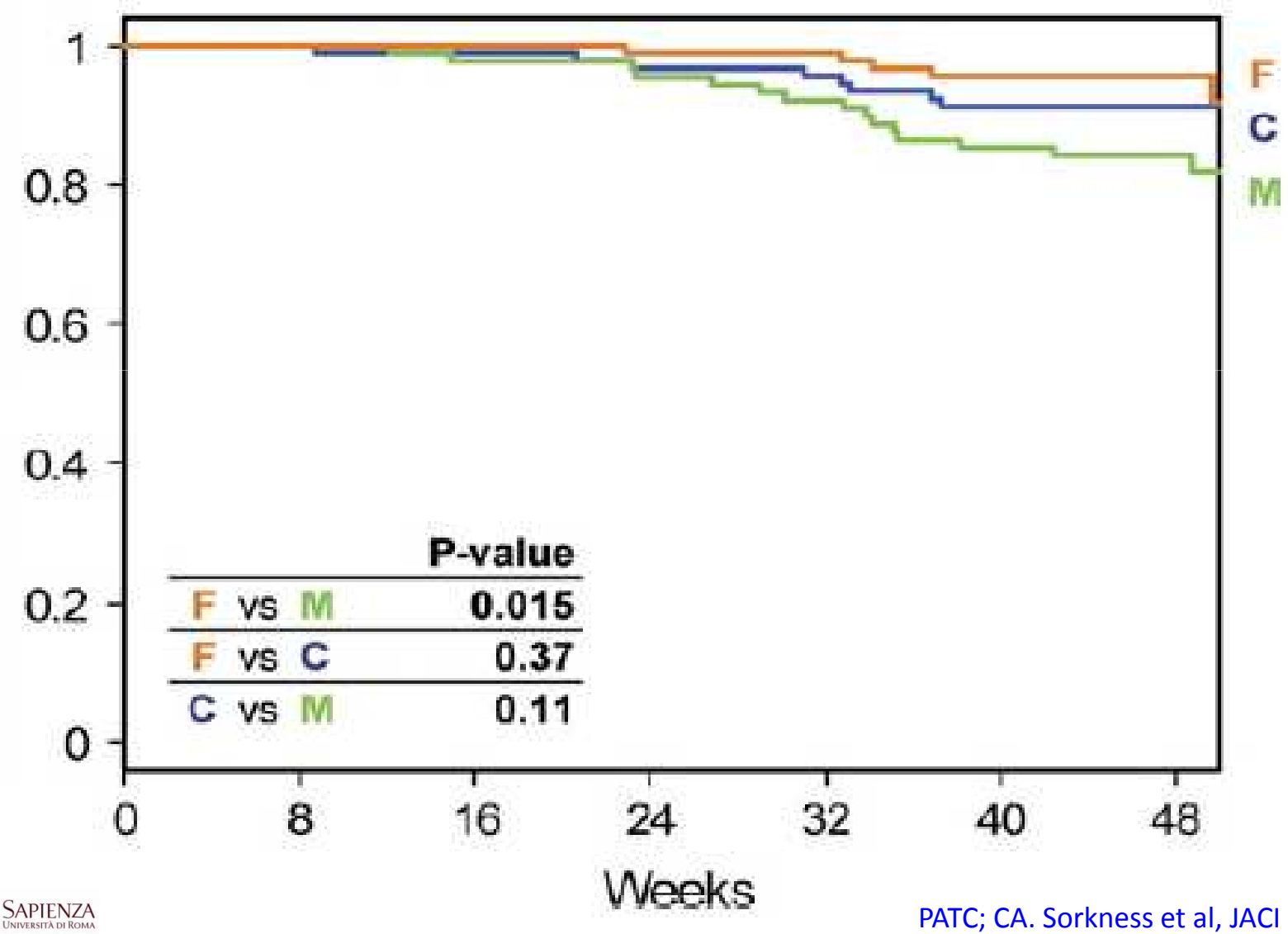


PATC; CA. Sorkness et al, JACI 2007



PATC; CA. Sorkness et al, JACI 2007

Proportion of participants not experiencing a treatment failure



PATC; CA. Sorkness et al, JACI 2007

Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the Pediatric Asthma Controller Trial

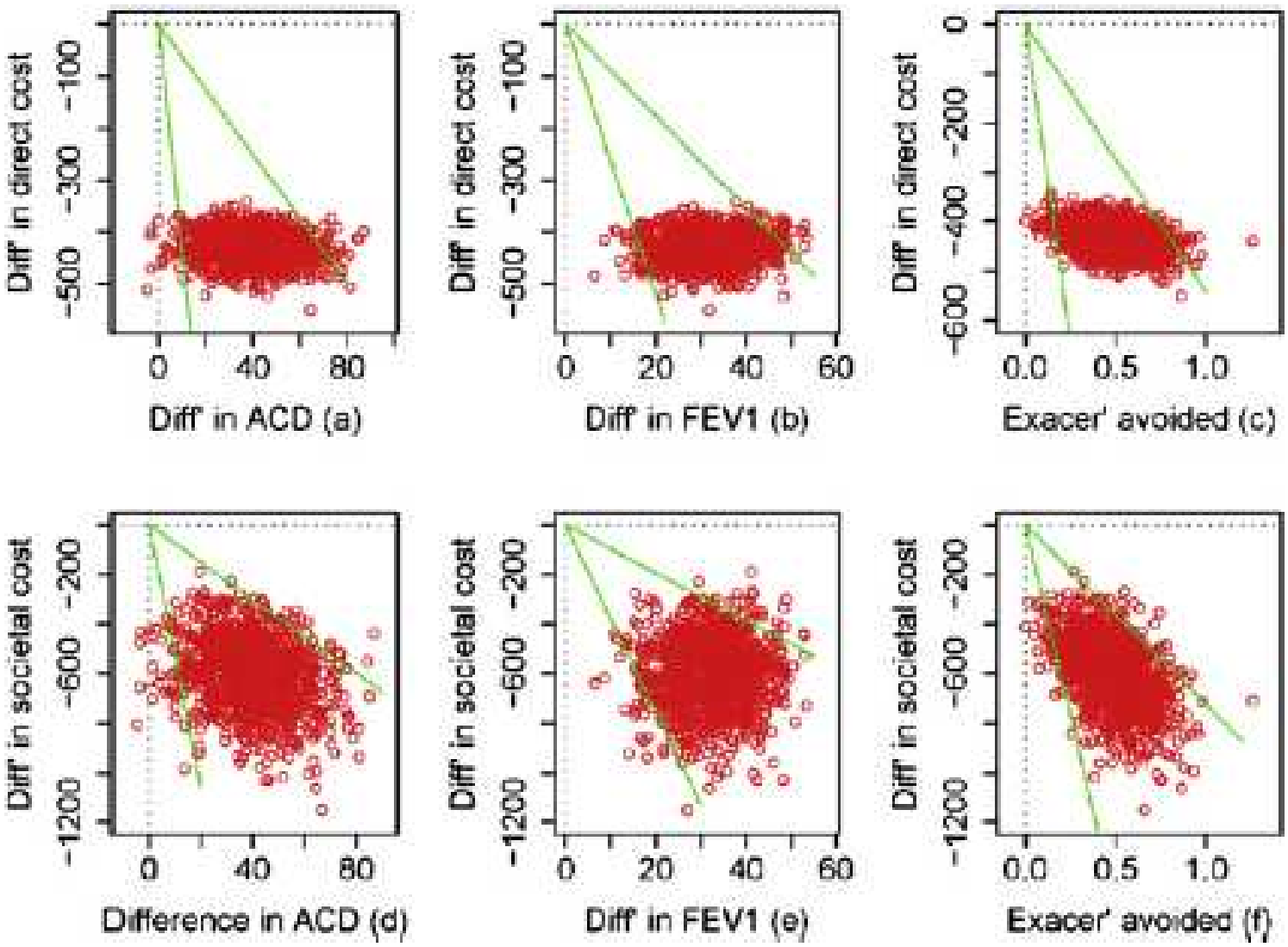
TABLE III. ICER for fluticasone versus montelukast during the study period

$\frac{\Delta DC}{\Delta ACD}$	$\frac{\Delta DC}{\Delta FEV}$	$\frac{\Delta DC}{\text{Avoided Exacer}}$	$\frac{\Delta SC}{\Delta ACD}$	$\frac{\Delta SC}{\Delta FEV}$	$\frac{\Delta SC}{\text{Avoided Exacer}}$
−11 (−6 to −42)	−13 (−26 to −9)	−916 (−2,095 to −531)	−15 (−55 to −8)	−19 (−10 to −38)	−1,272 (−2,616 to −745)

The ICER is defined as ΔCost/ΔEffect, where Δ stands for the difference between fluticasone and montelukast. The negative sign of ICER resulted from the fact that fluticasone had lower costs and higher effectiveness than montelukast. The negative sign of 95% CI indicated that the dominance of fluticasone held at least 95% of the time.
DC, Direct costs; *Exacer*, exacerbation; *SC*, societal costs.

Lo steroide è vantaggioso sia in termini personali che sociali

Li Wang et al, JACI 2011



Li Wang et al, JACI 2011

Univariable and multivariable analyses for predictors of response to fluticasone versus montelukast (PACT)

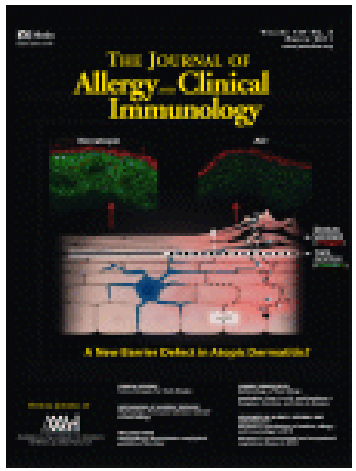
		Percentage ACDs		FEV_1 percent predicted		Morning PEF percent predicted		Time to first exacerbation	
Predictor	Subgroup	Average difference*	*P* value†	Average difference*	*P* value†	Average difference*	*P* value†	Hazard ratio*	*P* value†
ACQ	≤1.1	2.3 (− 9.8 to 14.3)	.08 (.3)						
	>1.1	17.4 (5.5 to 29.2)							
eNO	<25 ppb	−4.0 (−15.9 to 7.9)	.002 (.01)						
	≥25 ppb	23.0 (11.4 to 34.6)							
Eosinophils	<5%	−4.1 (−16.7 to 8.5)	.005 (.9)						
	≥5%	20.5 (9.2 to 31.8)							
IgE	≤150 kU/L	−2.3 (−15.1 to 10.5)	.03 (.6)						
	>150 kU/L	16.6 (5.1 to 28)							
Parental asthma	No	3.9 (−8.9 to 16.8)	.07 (.02)					0.7 (0.4 to 1.4)	.05 (.05)
	Yes	20.1 (8.4 to 31.7)						0.3 (0.1 to 0.5)	
PC_{20} (mg/mL)	≥2	−7.2 (−22.1 to 7.7)	.007 (.2)					1.1 (0.5 to 2.5)	.02 (.03)
	<2	17.8 (7.7 to 27.8)						0.4 (0.2 to 0.6)	
ULT	<100			9.1 (4.8 to 13.4)	.08 (.1)				
	≥100			3.5 (−0.9 to 7.9)					
Age at diagnosis	≤3 y			4.1 (−0.1 to 8.3)	.06 (.8)				
	>3 y			9.8 (5.6 to 13.9)					
Age at entry	6-10 y					6.6 (2.9 to 10.4)	.09		
	10-14 y					1.7 (−2.6 to 6.1)			
ICS use (past year)	No							1.0 (0.5 to 2.0)	.008 (.01)
	Yes							0.3 (0.2 to 0.6)	

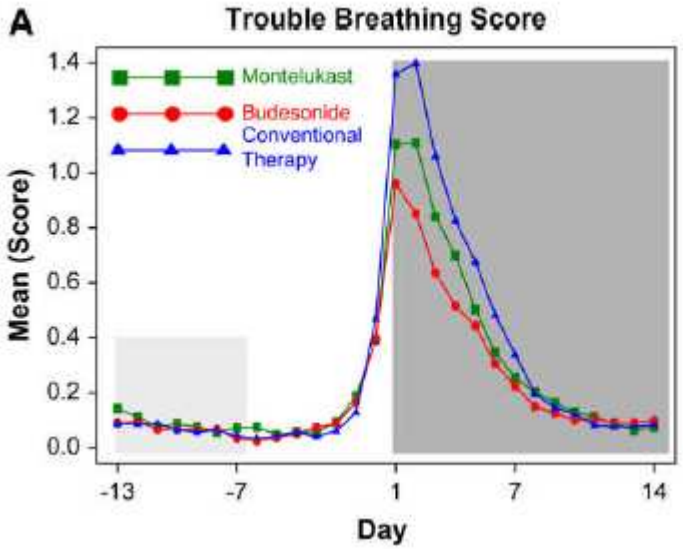
JE. Knuffman et al, JACI 2009

Original article

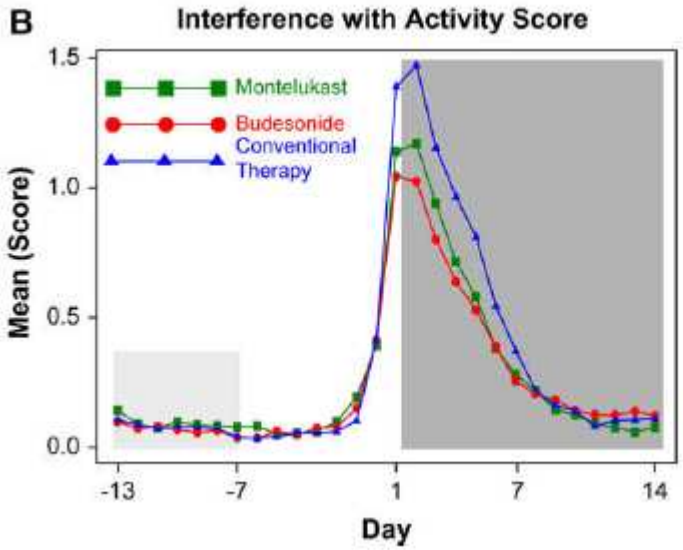
Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing

Leonard B. Bacharier, MD,[a] Brenda R. Phillips, MS,[b] Robert S. Zeiger, MD, PhD,[c,d] Stanley J. Szefler, MD,[e] Fernando D. Martinez, MD,[f] Robert F. Lemanske, Jr, MD,[g] Christine A. Sorkness, PharmD,[h] Gordon R. Bloomberg, MD,[a] Wayne J. Morgan, MD,[f] Ian M. Paul, MD,[b] Theresa Guilbert, MD,[i] Marzena Krawiec, MD,[e] Ronina Covar, MD,[e] Gary Larsen, MD,[e] Michael Mellon, MD,[c,d] Mark H. Moss, MD,[g] Vernon M. Chinchilli, PhD,[b] Lynn M. Taussig, MD,[e] and Robert C. Strunk, MD,[a] for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute* *St Louis, Mo, Hershey, Pa, San Diego, Calif, Denver, Colo, Tucson, Ariz, and Madison, Wis*





	Montelukast	Budesonide	Conventional Therapy
Trouble Breathing Score AUC	4.2 (3.1, 5.3)	4.2 (3.1, 5.2)	6.7 (5.2, 8.1)
P-value vs. Conventional Therapy	0.003	0.003	–



	Montelukast	Budesonide	Conventional Therapy
Interference with activity score AUC	4.3 (3.1, 5.4)	4.8 (3.7, 5.9)	7.0 (5.5, 8.6)
P-value vs. Conventional Therapy	0.001	0.01	–

Bacharier LB et al, JACI 2008

Original article

Azithromycin or montelukast as inhaled corticosteroid–sparing agents in moderate-to-severe childhood asthma study

Robert C. Strunk, MD,[a] Leonard B. Bacharier, MD,[a] Brenda R. Phillips, MS,[b] Stanley J. Szefler, MD,[e] Robert S. Zeiger, MD, PhD,[c,d] Vernon M. Chinchilli, PhD,[b] Fernando D. Martinez, MD,[f] Robert F. Lemanske, Jr, MD,[g] Lynn M. Taussig, MD,[e] David T. Mauger, PhD,[b] Wayne J. Morgan, MD,[f] Christine A. Sorkness, PharmD,[h] Ian M. Paul, MD,[b] Theresa Guilbert, MD,[i] Marzena Krawiec, MD,[e] Ronina Covar, MD,[e] Gary Larsen, MD,[e] for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute* *St Louis, Mo, Hershey, Pa, San Diego, Calif, Denver, Colo, Tucson, Ariz, and Madison, Wis*

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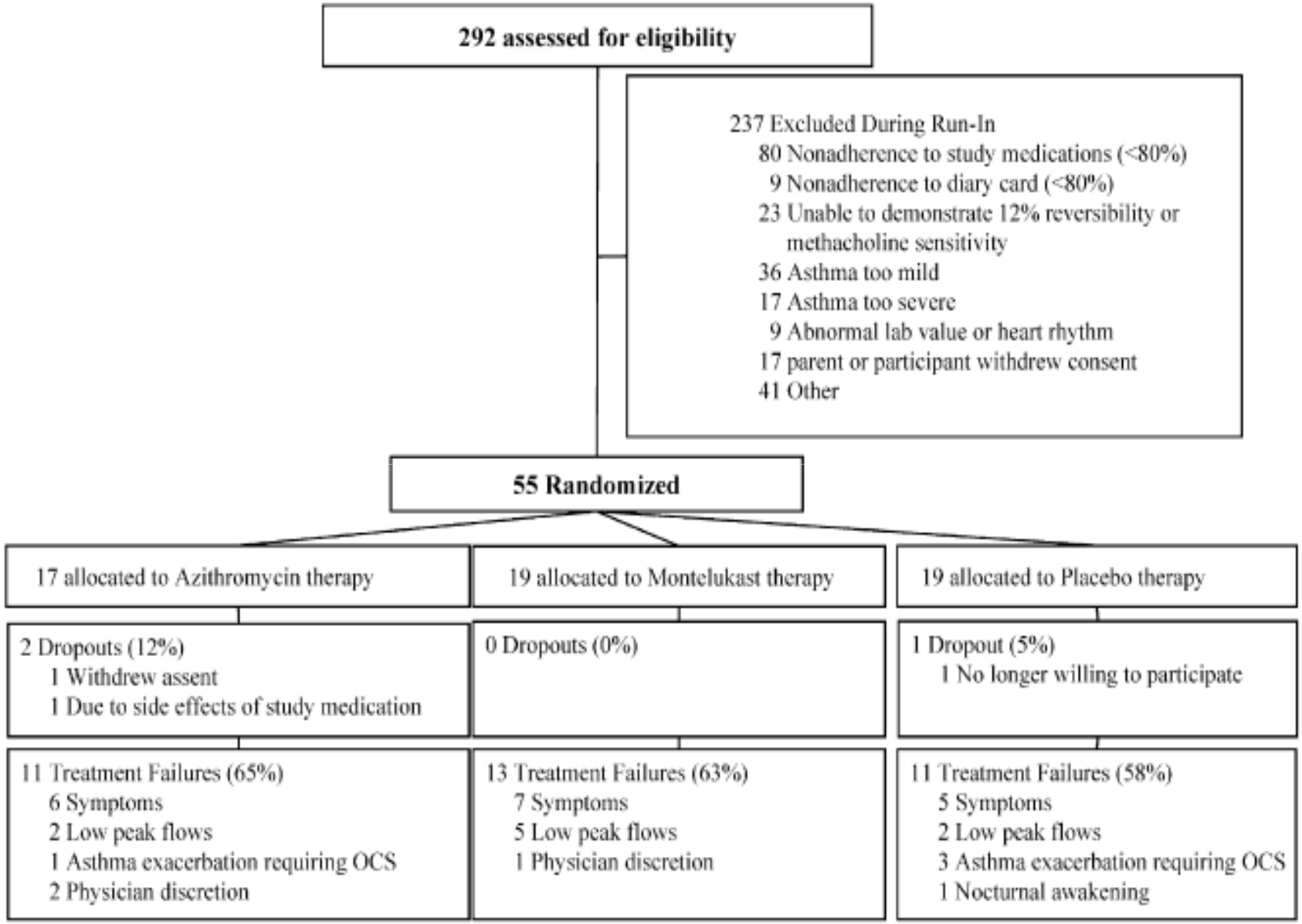
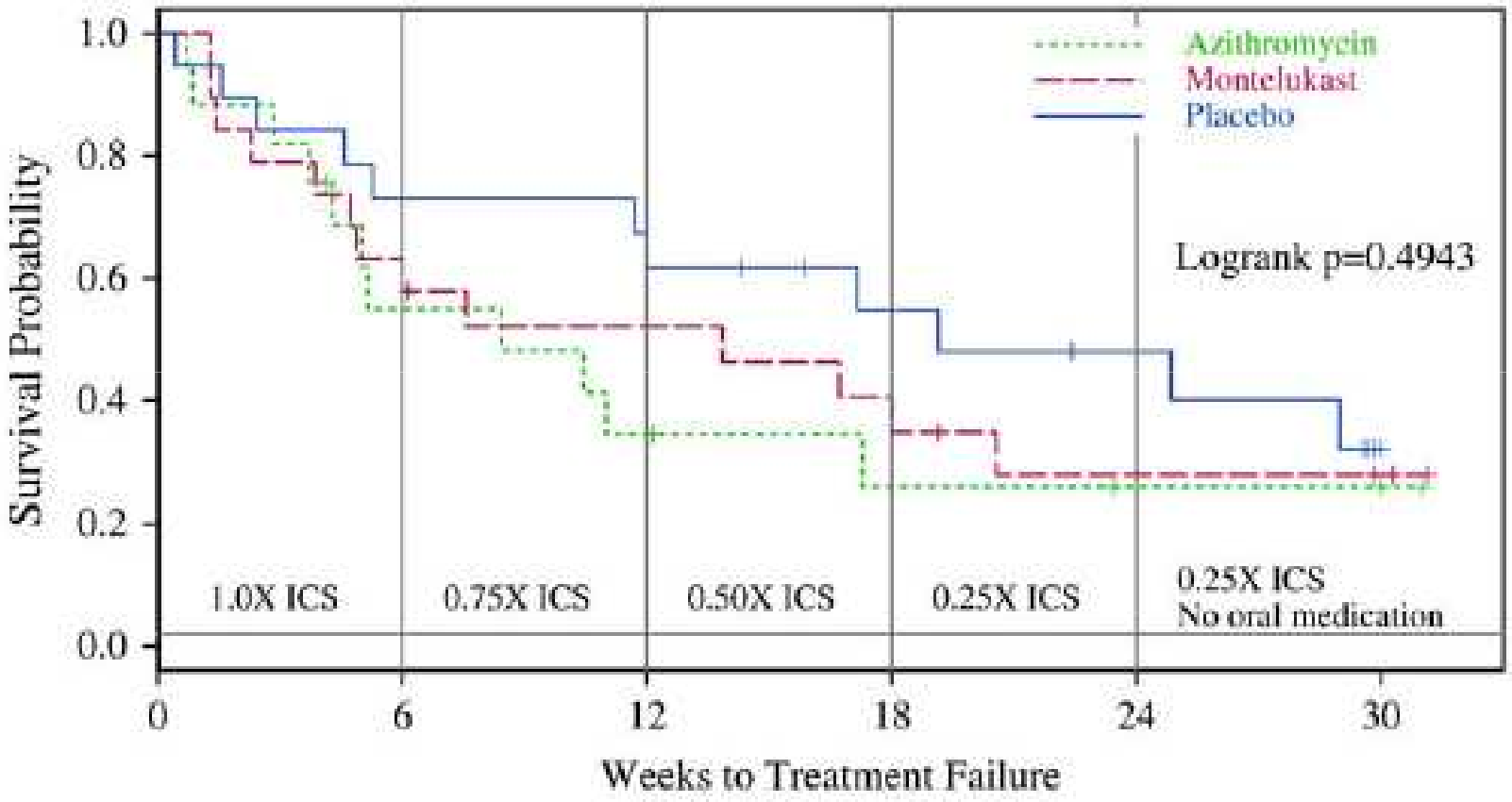

292 assessed for eligibility
237 Excluded During Run-In
80 Nonadherence to study medications (<80%)
9 Nonadherence to diary card (<80%)
23 Unable to demonstrate 12% reversibility or methacholine sensitivity
36 Asthma too mild
17 Asthma too severe
9 Abnormal lab value or heart rhythm
17 parent or participant withdrew consent
41 Other
55 Randomized
17 allocated to Azithromycin therapy
19 allocated to Montelukast therapy
19 allocated to Placebo therapy
2 Dropouts (12%)
1 Withdrew assent
1 Due to side effects of study medication
0 Dropouts (0%)
1 Dropout (5%)
1 No longer willing to participate
11 Treatment Failures (65%)
6 Symptoms
2 Low peak flows
1 Asthma exacerbation requiring OCS
2 Physician discretion
13 Treatment Failures (63%)
7 Symptoms
5 Low peak flows
1 Physician discretion
11 Treatment Failures (58%)
5 Symptoms
2 Low peak flows
3 Asthma exacerbation requiring OCS
1 Nocturnal awakening

JACI 2008



JACI 2008

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

Ducharme FM, Lasserson TJ, Cates CJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3 Updated 2006

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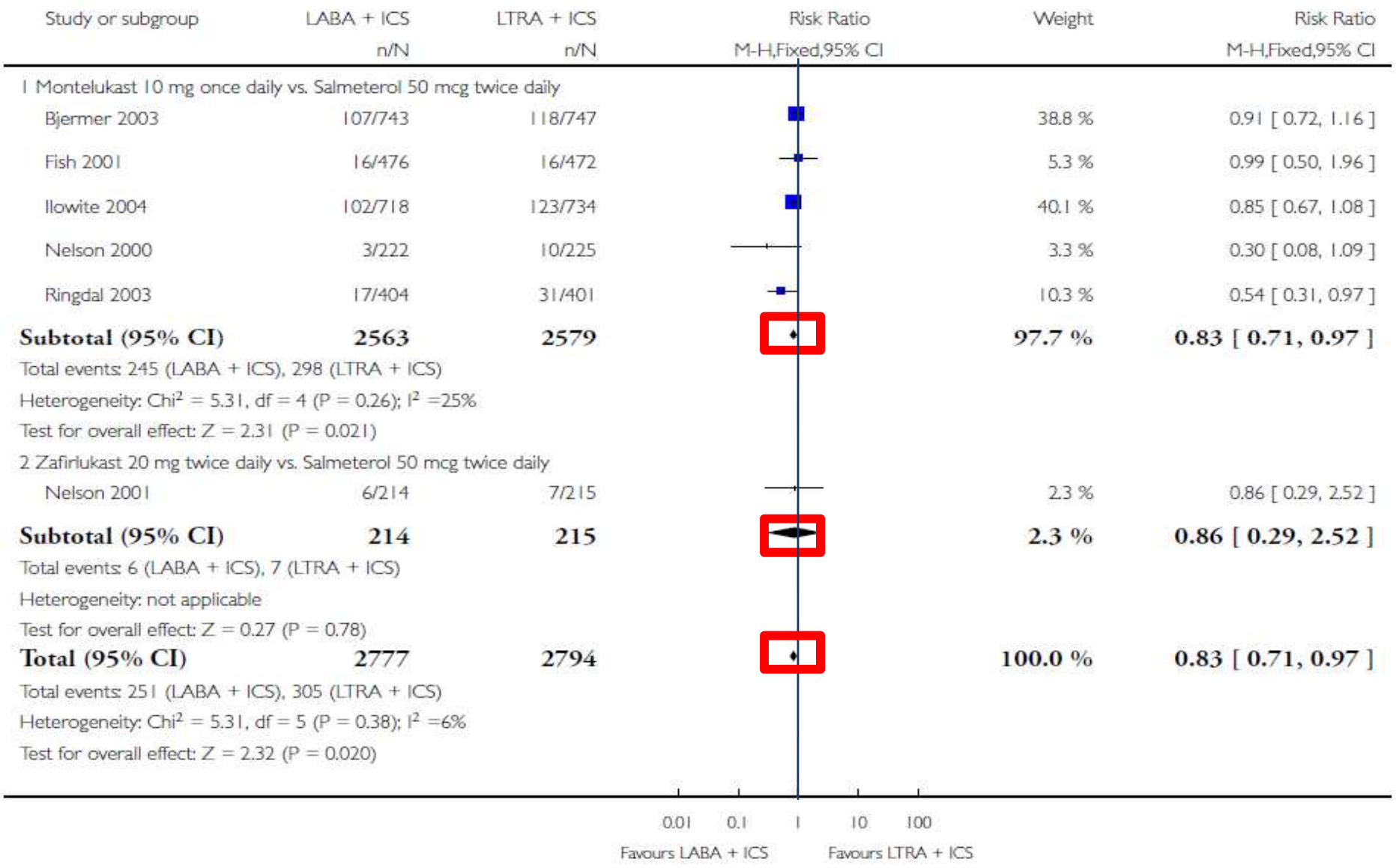
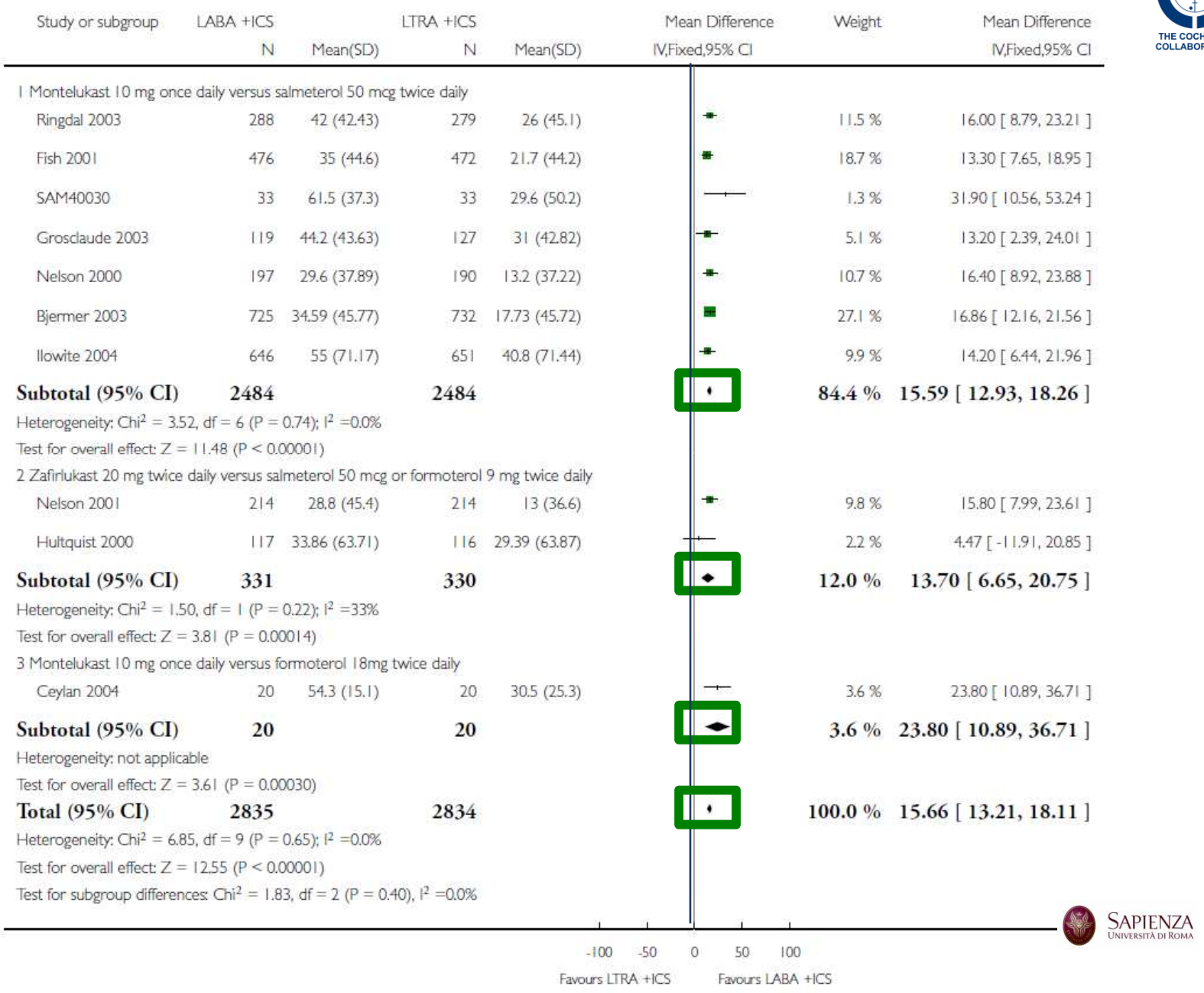
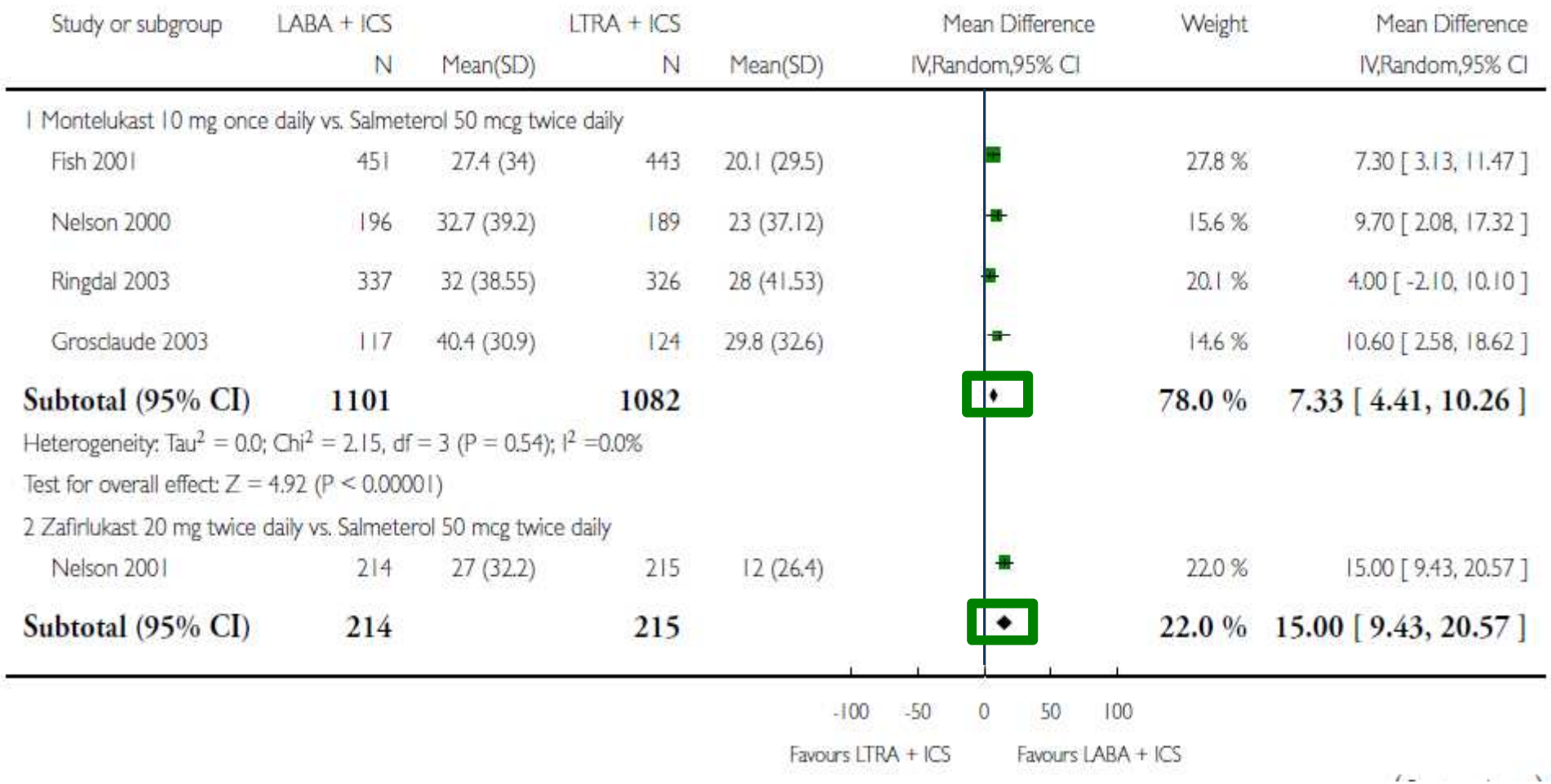
LRTA + ICS versus LABA+ ICS: Participants with one or more exacerbations requiring systemic corticosteroids



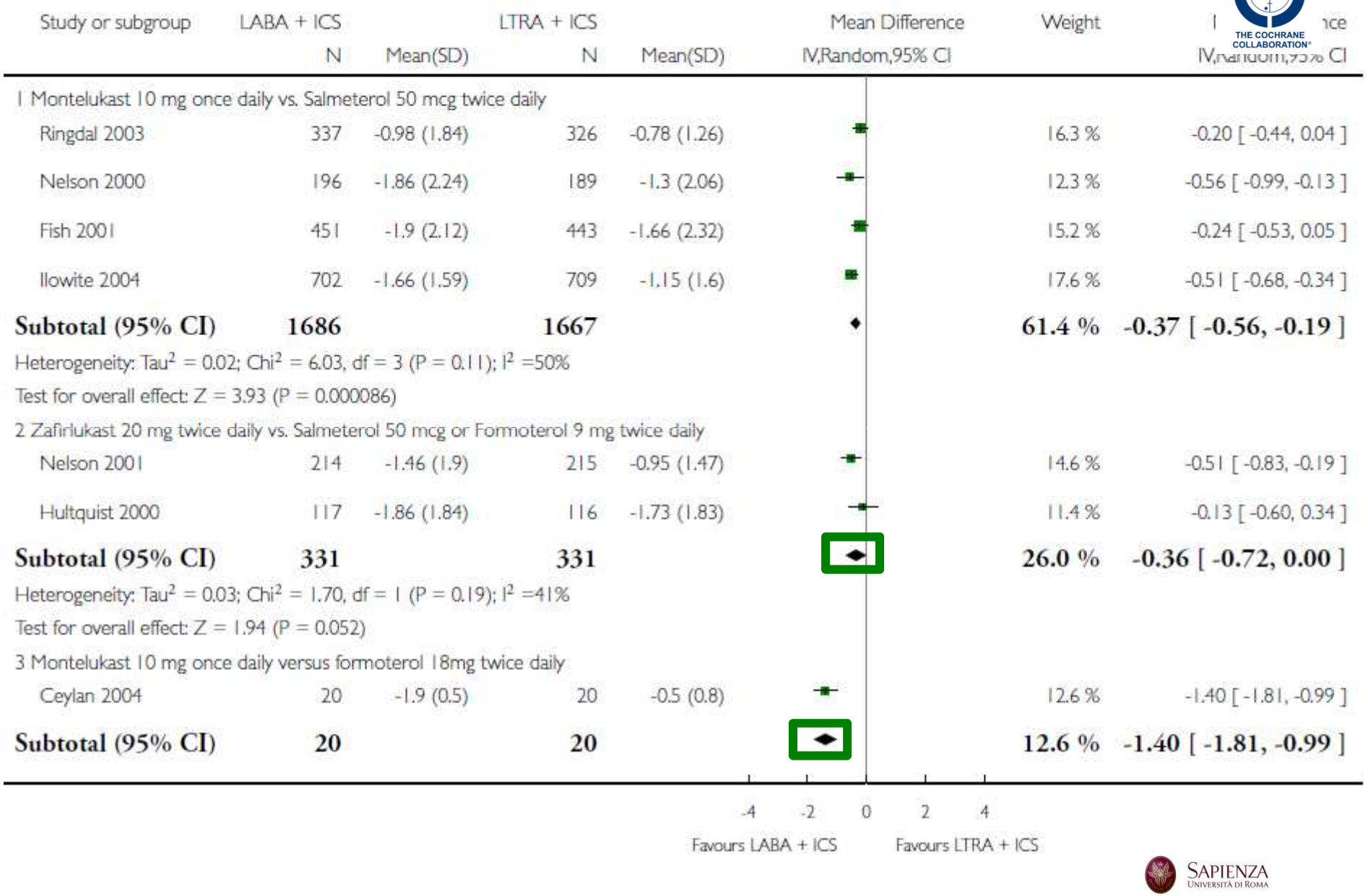
Morning PEF


Study or subgroup
LABA +ICS N Mean(SD)
LTRA +ICS N Mean(SD)
Mean Difference IV,Fixed,95% CI
Weight
Mean Difference IV,Fixed,95% CI
1 Montelukast 10 mg once daily versus salmeterol 50 mcg twice daily
Ringdal 2003 288 42 (42.43) 279 26 (45.1) 11.5 % 16.00 [8.79, 23.21]
Fish 2001 476 35 (44.6) 472 21.7 (44.2) 18.7 % 13.30 [7.65, 18.95]
SAM40030 33 61.5 (37.3) 33 29.6 (50.2) 1.3 % 31.90 [10.56, 53.24]
Grosclaude 2003 119 44.2 (43.63) 127 31 (42.82) 5.1 % 13.20 [2.39, 24.01]
Nelson 2000 197 29.6 (37.89) 190 13.2 (37.22) 10.7 % 16.40 [8.92, 23.88]
Bjermer 2003 725 34.59 (45.77) 732 17.73 (45.72) 27.1 % 16.86 [12.16, 21.56]
Ilowite 2004 646 55 (71.17) 651 40.8 (71.44) 9.9 % 14.20 [6.44, 21.96]
Subtotal (95% CI) 2484 2484 84.4 % 15.59 [12.93, 18.26]
Heterogeneity: Chi² = 3.52, df = 6 (P = 0.74); I² =0.0%
Test for overall effect: Z = 11.48 (P < 0.00001)
2 Zafirlukast 20 mg twice daily versus salmeterol 50 mcg or formoterol 9 mg twice daily
Nelson 2001 214 28.8 (45.4) 214 13 (36.6) 9.8 % 15.80 [7.99, 23.61]
Hultquist 2000 117 33.86 (63.71) 116 29.39 (63.87) 2.2 % 4.47 [-11.91, 20.85]
Subtotal (95% CI) 331 330 12.0 % 13.70 [6.65, 20.75]
Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² =33%
Test for overall effect: Z = 3.81 (P = 0.00014)
3 Montelukast 10 mg once daily versus formoterol 18mg twice daily
Ceylan 2004 20 54.3 (15.1) 20 30.5 (25.3) 3.6 % 23.80 [10.89, 36.71]
Subtotal (95% CI) 20 20 3.6 % 23.80 [10.89, 36.71]
Heterogeneity: not applicable
Test for overall effect: Z = 3.61 (P = 0.00030)
Total (95% CI) 2835 2834 100.0 % 15.66 [13.21, 18.11]
Heterogeneity: Chi² = 6.85, df = 9 (P = 0.65); I² =0.0%
Test for overall effect: Z = 12.55 (P < 0.00001)
Test for subgroup differences: Chi² = 1.83, df = 2 (P = 0.40), I² =0.0%
-100 -50 0 50 100
Favours LTRA +ICS
Favours LABA +ICS

Rescue free days (%)



Rescue medication use (puffs/day) - change from baseline



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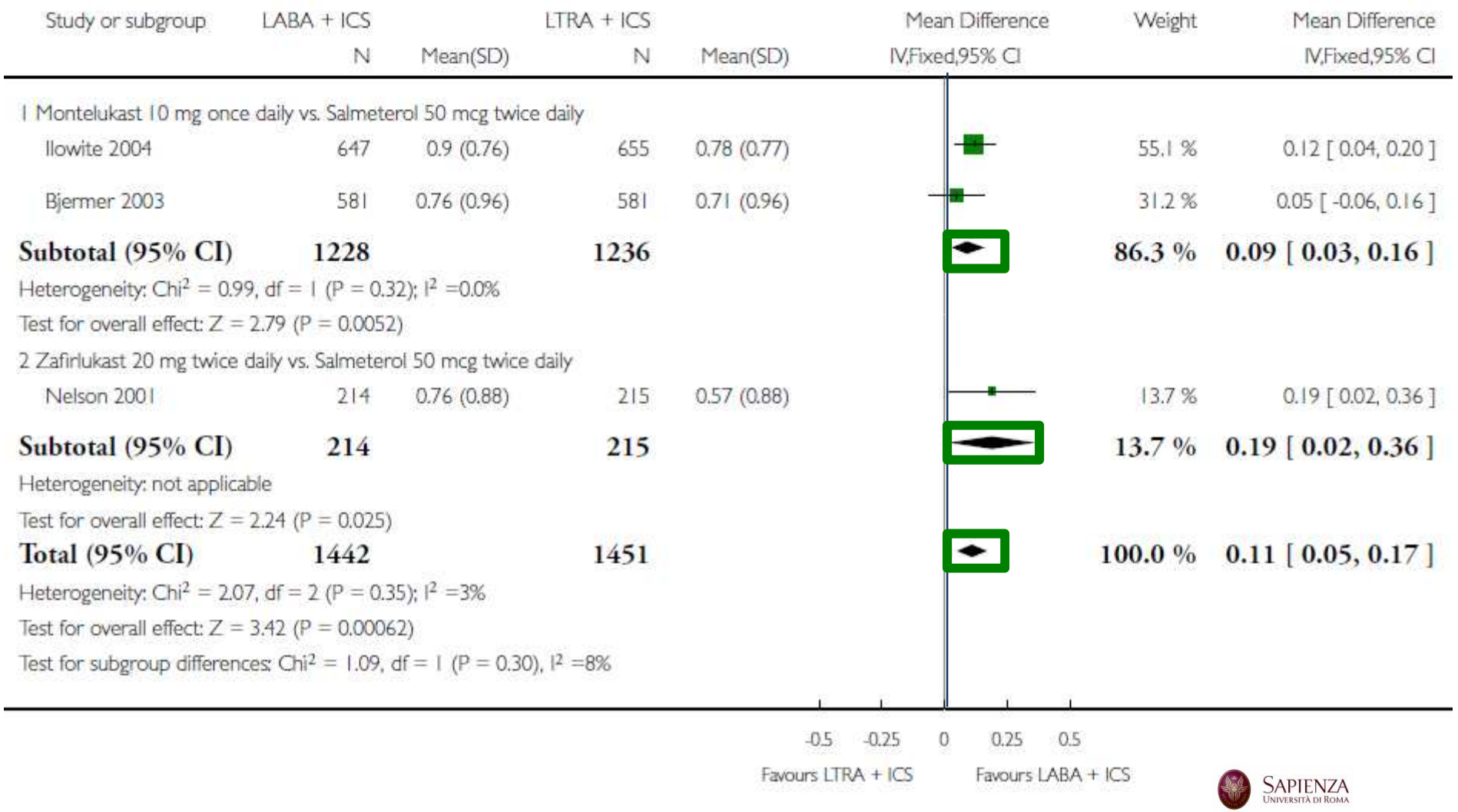
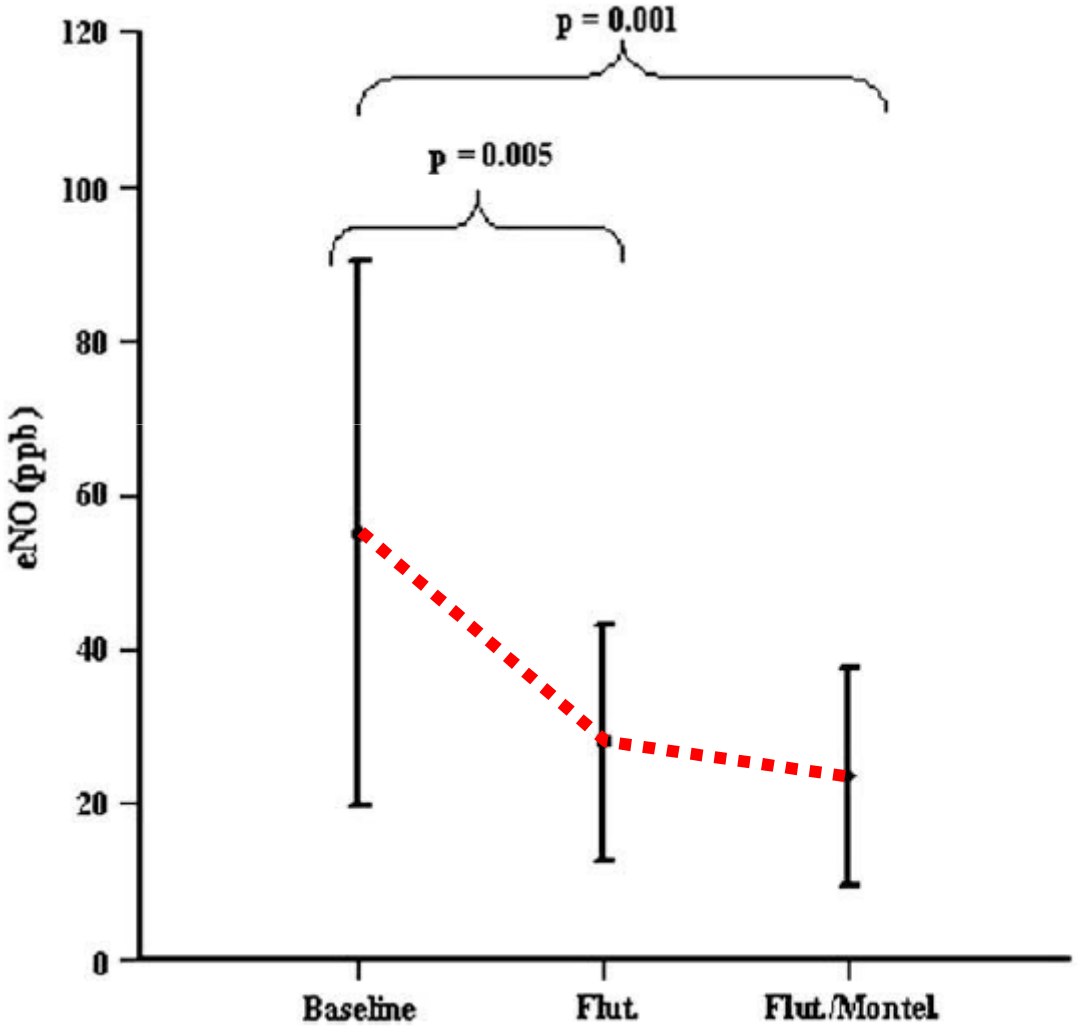
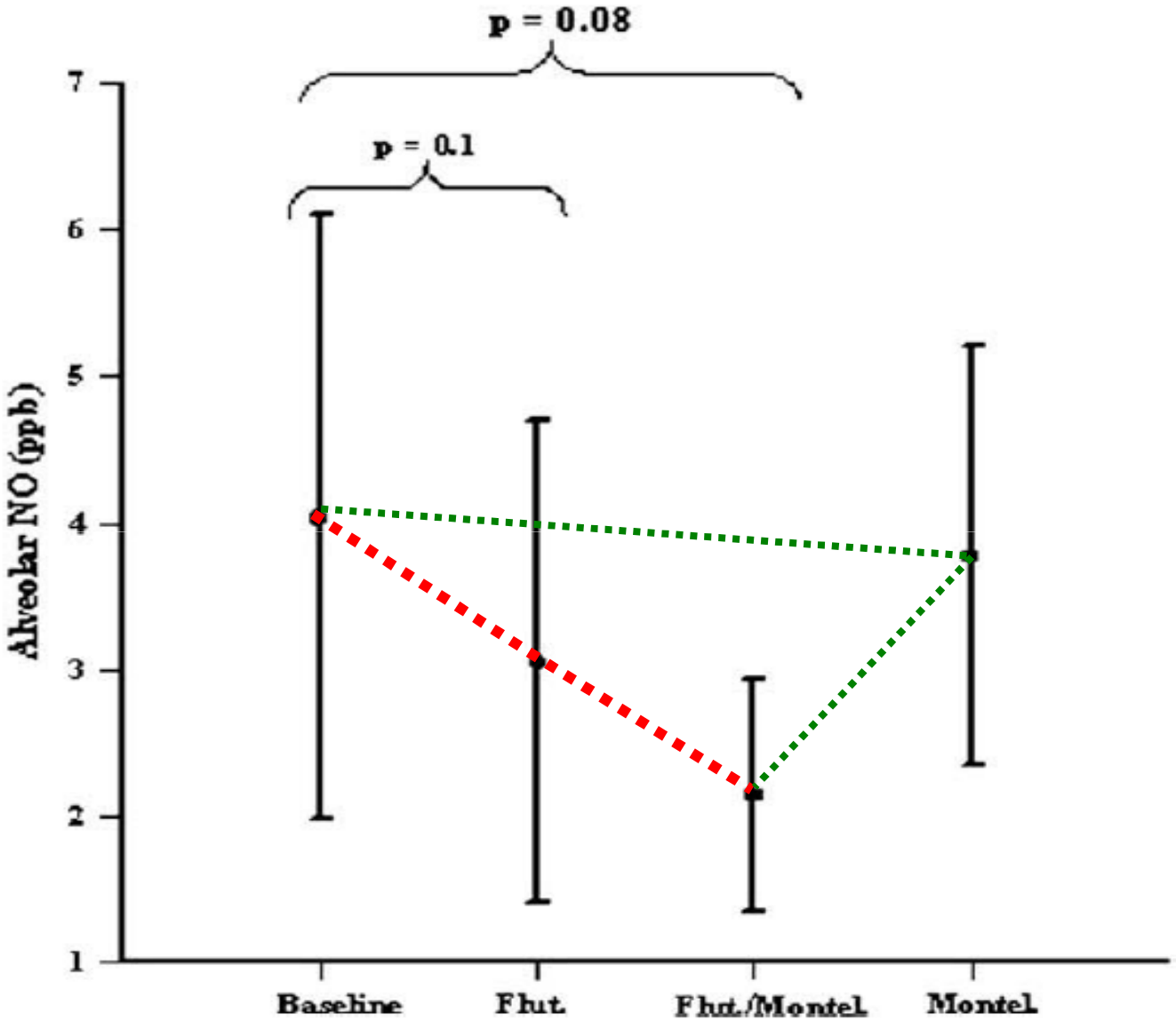
Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline



The effect of montelukast on exhaled nitric oxide of alveolar and bronchial origin in inhaled corticosteroid-treated asthma



LG. Fritscher et al, Respiratory Medicine 2008



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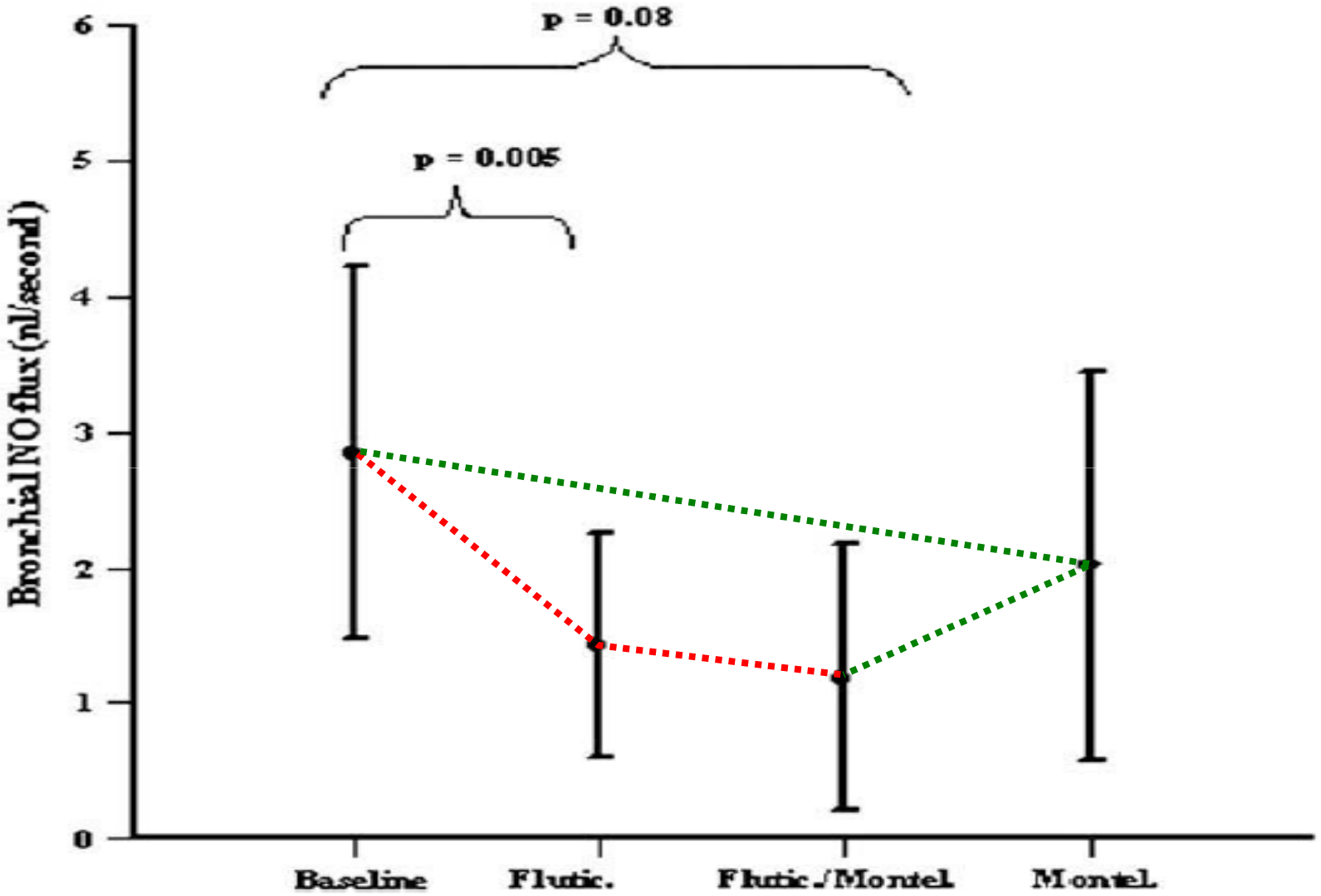

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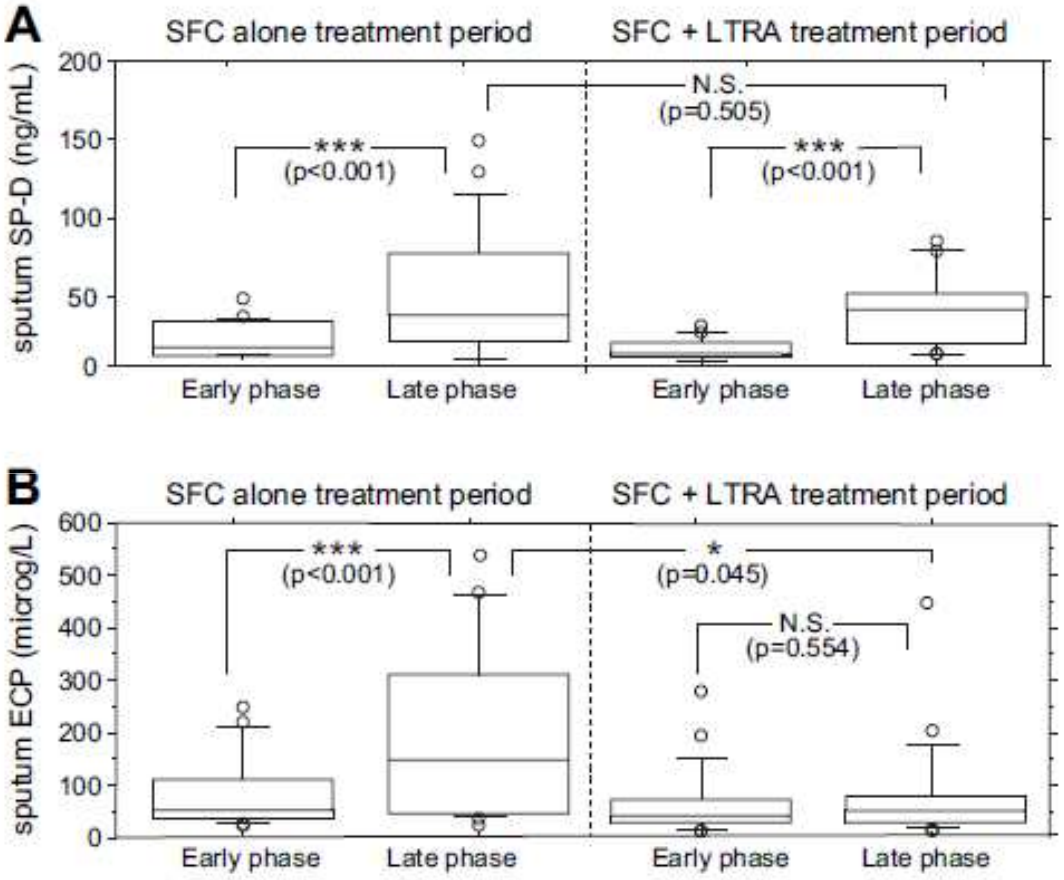

Hiroyuki Ohbayashi et al Pulmonary Pharmacology & Therapeutics 2009

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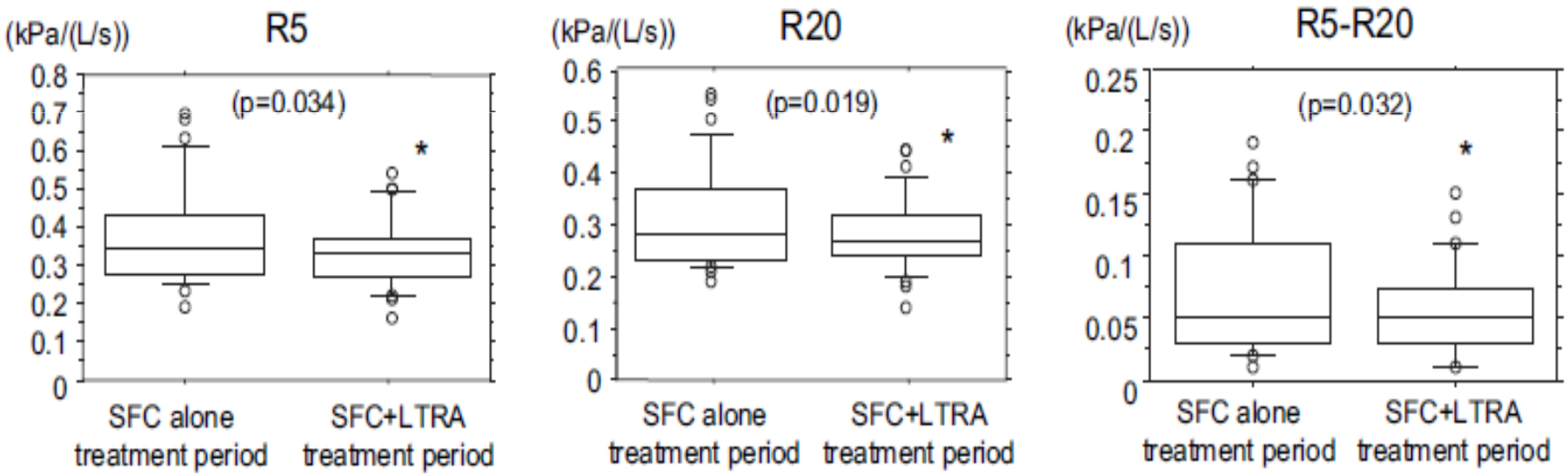
Additional effects of pranlukast in salmeterol/fluticasone combination therapy for the asthmatic distal airway : a randomized crossover study

resistance

distal airway **central airways**



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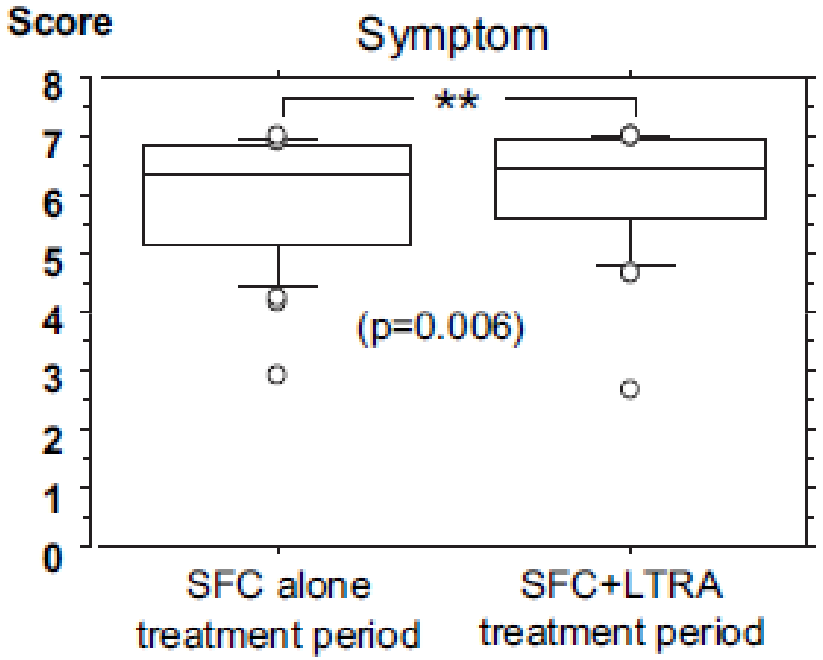
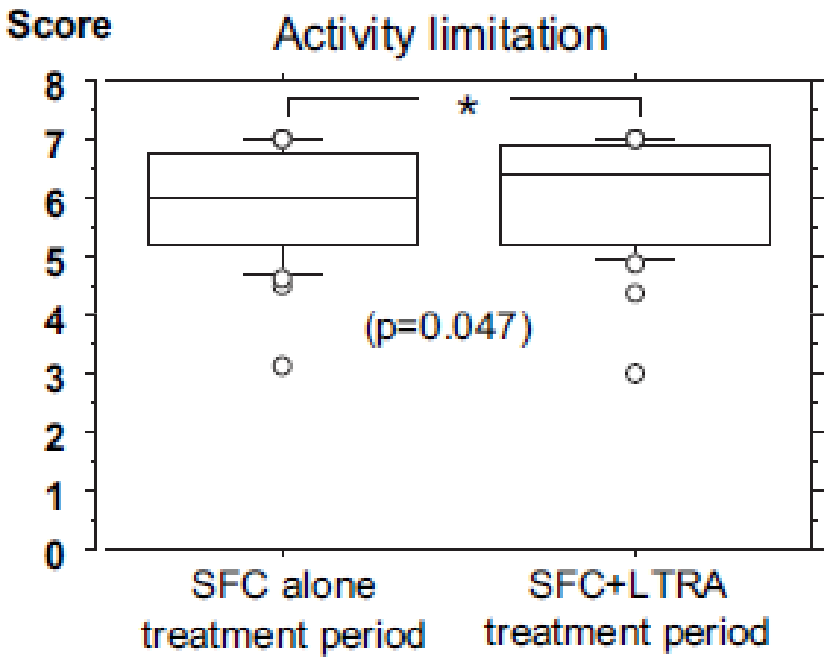
H. Ohbayashi et al, Pulmonary Pharmacology & Ther 2009

Additional effects of pranlukast in salmeterol/fluticasone combination therapy for the asthmatic distal airway : a randomized crossover study





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H. Ohbayashi et al, Pulmonary Pharmacology & Ther 2009

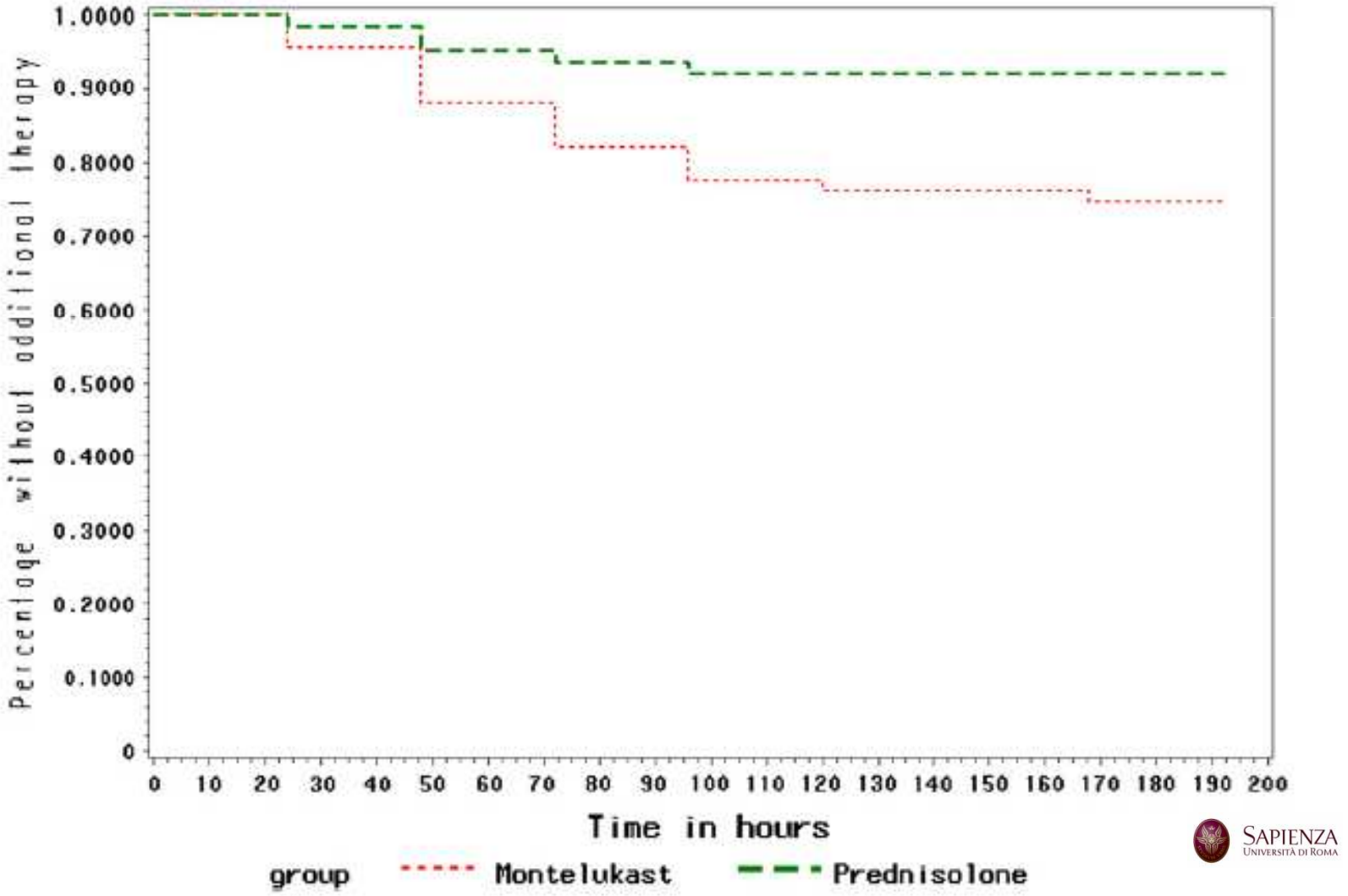
THE JOURNAL OF PEDIATRICS • www.jpeds.com 2009

ORIGINAL ARTICLES

Can Montelukast Shorten Prednisolone Therapy in Children with Mild to Moderate Acute Asthma? A Randomized Controlled Trial

Suzanne Schuh, MD, FRCPC, Andrew R. Willan, PhD, Derek Stephens, MSc, Paul T. Dick, MDCM, FRCPC, and Allan Coates, MD, FRCPC

Proportion of patients remaining without any additional therapy with time



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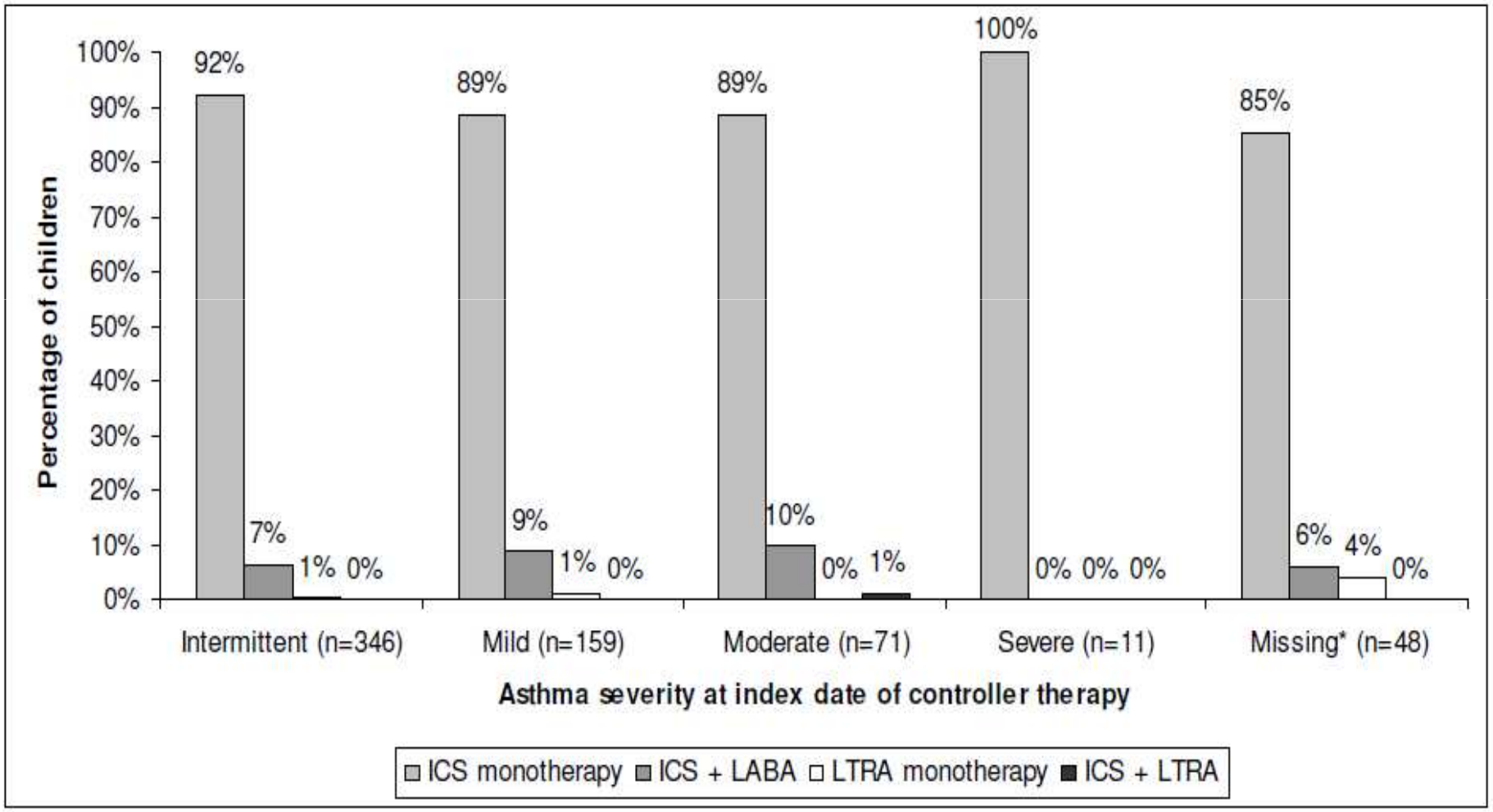
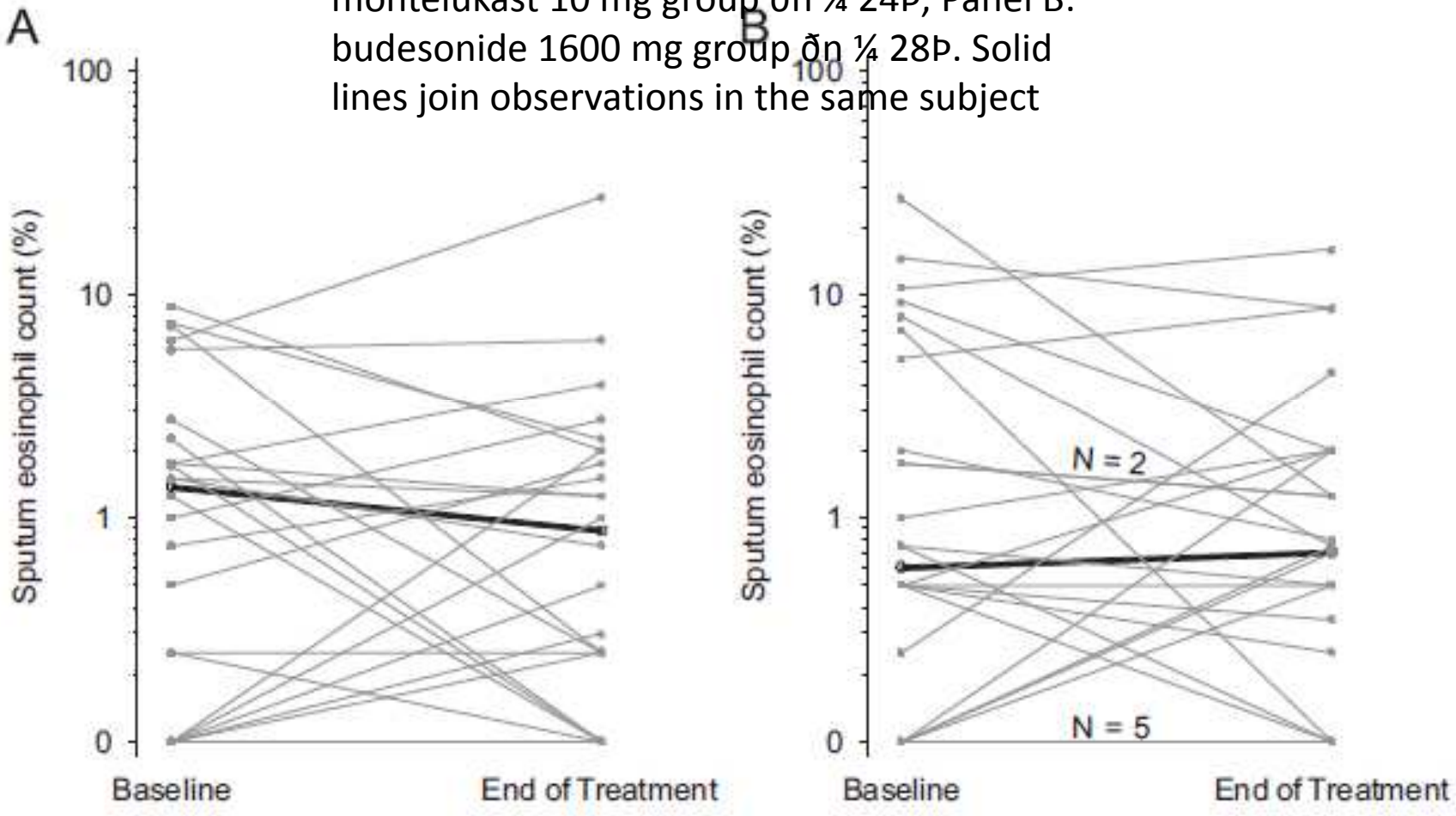
LTRA
Bronchiolite
wheezing
ICS
Asma on demand?

Asthma controller therapy prescription, by asthma severity, for 635 children ≤ 14 years old. Data were derived from the UK General Practice Research Database



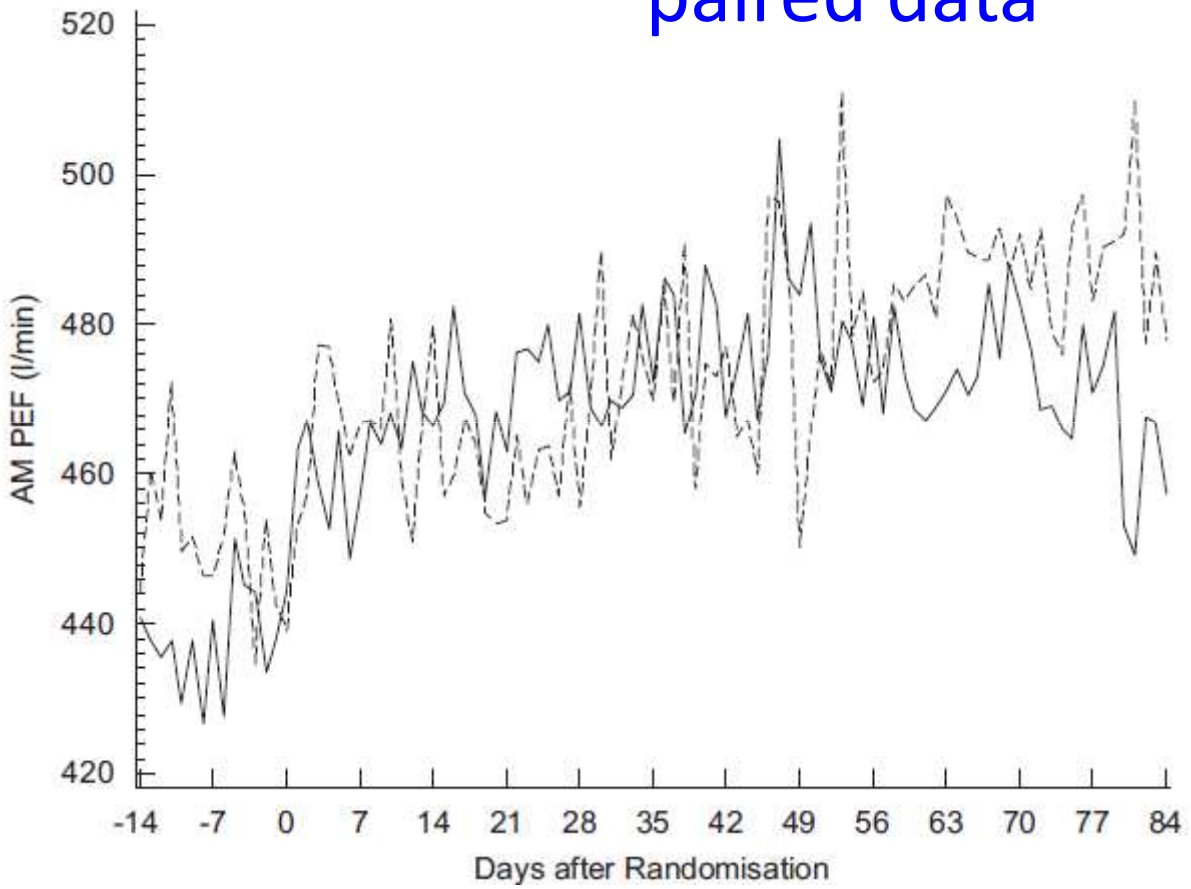
Thomas *et al. BMC Pulmonary Medicine 2010,* ***10:29***

individual sputum eosinophil counts (%) at baseline and end of treatment. Panel A: budesonide 800 mg þ
montelukast 10 mg group ðn ¼ 24Þ, Panel B: budesonide 1600 mg group ðn ¼ 28Þ. Solid lines join observations in the same subject



Neil Barnes, Respiratory medicine 2007

Morning PEF over the 12-week treatment period, paired data



Neil Barnes, Respiratory medicine 2007