Respiratory Reviews in Asthma 2013

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Contents

- New treatment options
- Effect of treatment adjustment
- Useful diagnostic markers in asthma
- Scoring systems for predicting exacerbation
- Results from GWAS

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- **New treatment options**
- Effect of treatment adjustment
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1. Mepolizumab

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

✓ Mepolizumab (monoclonal Ab against IL-5)

-Reduced risk of AE in eosinophilic airway inflammation.

-Reduced steroid doses Nair P et al. N Engl J Med 2009; 360: 985–93.

✓ DREAM : multi-center, double blind, placebo-controlled trial

(**D**ose **R**anging **E**fficacy **A**nd safety with **M**epolizumab in severe asthma)

- Nov. 2009~Dec.2011, 81 centers in 13 countries including Korea

- Mepolizumab reduces the frequency of AE?
- Effects on blood/sputum eosinophil, asthma control, QOL, FEV1

Patient characteristics

Mepolizumab

- >= 2 exacerbation requiring systemic CS in previous year
- sputum eosinophil count >=3 %
- FENO >=50 ppb
- asthma-related PB eosinophil >=0.3×10^9/L
- prompt deterioration of asthma control after <=25% reduction in regular maintenance ICS/OCS

	Pl (r			
Women				
Age (years)				
White ethnic origin				
Body-mass index (kg/m^2)				
Former smoker				
Duration of asthma (years)				
Use of longacting β-agonists	150 (97%)	143 (93%)	145 (95%)	151 (97%)
Maintenance use of oral corticosteroids	45 (29%)	46 (30%)	50 (33%)	47 (30%)
Daily dose (mg)*	10 (10–20)	10 (10–20)	10 (8–20)	13 (10–20)
Nasal polyps†	16 (10%)	11 (7%)	22 (14%)	13 (8%)
Atopy‡	81 (52%)	78 (51%)	76 (50%)	76 (49%)
Prebronchodilator FEV_1 (mL)	1900 (653)	1810 (637)	1850 (672)	1950 (670)
Postbronchodilator FEV_1 (mL)	2290 (773)	2150 (695)	2220 (732)	2260 (784)
Percentage of predicted prebronchodilator FEV_1	59% (15)	60% (16)	59% (17)	61% (16)
Postbronchodilator FEV_1/FVC	67% (12)	68% (12)	66% (13)	68% (20)
Score on asthma control questionnaire	2·5 (1·1)	2·2 (1·1)	2·4 (1·1)	2·3 (1·2)
Score on asthma quality of life questionnaire	4·1 (1·2)	4·2 (1·2)	4·2 (1·2)	4·2 (1·2)
Blood eosinophil count (×10^9/L)§¶	0·28 (1·01)	0·25 (0·95)	0·23 (1·20)	0·25 (0·93)
Sputum eosinophil count (%)§¶	6·8% (2·01); n=24	13·9% (1·47); n=18	8·1% (1·79); n=23	5·8% (2·15); n=21
FE_{NO} (ppb)§¶	33·7 (0·79)	29·2 (0·76)	31·4 (0·80)	31·6 (0·81)
Severe exacerbations in previous year	3·7 (3·8)	3·7 (3·1)	3·4 (2·4)	3·5 (2·8)
Exacerbations requiring admission in previous year	40 (26%)	35 (23%)	36 (24%)	39 (25%)

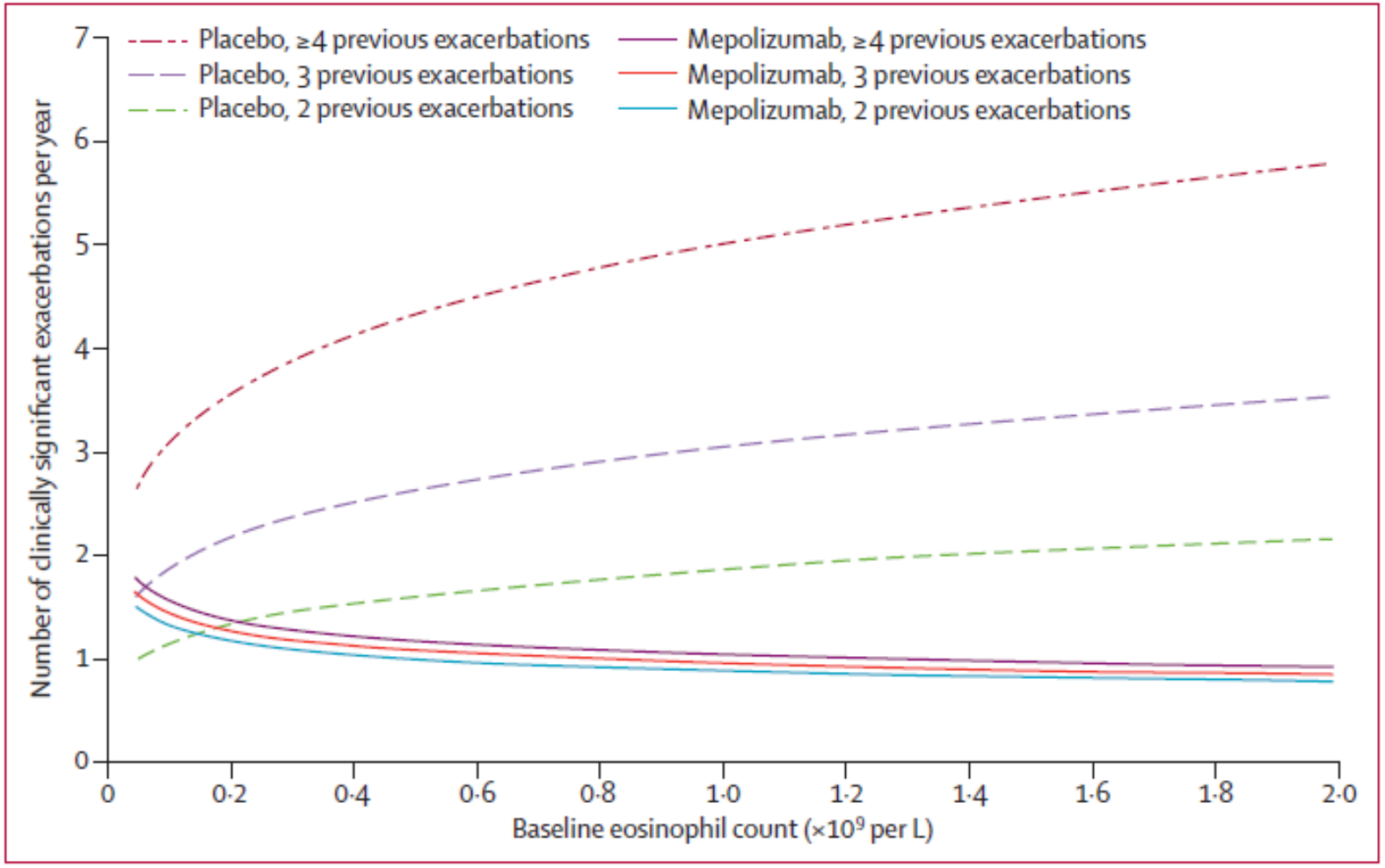
Data are n (%), mean (SD), or median (IQR), unless otherwise stated. *Prednisolone equivalent. †Self reported. ‡Positive atopic status was defined as a positive radioallergosorbent test for any of four specified aeroallergens. §Values below lower limit of quantification were replaced by half the lower limit of quantification. ¶Geometric mean on $\log_e$ scale.

Table 1: **Baseline characteristics of the intention-to-treat population**

Clinically significant exacerbations

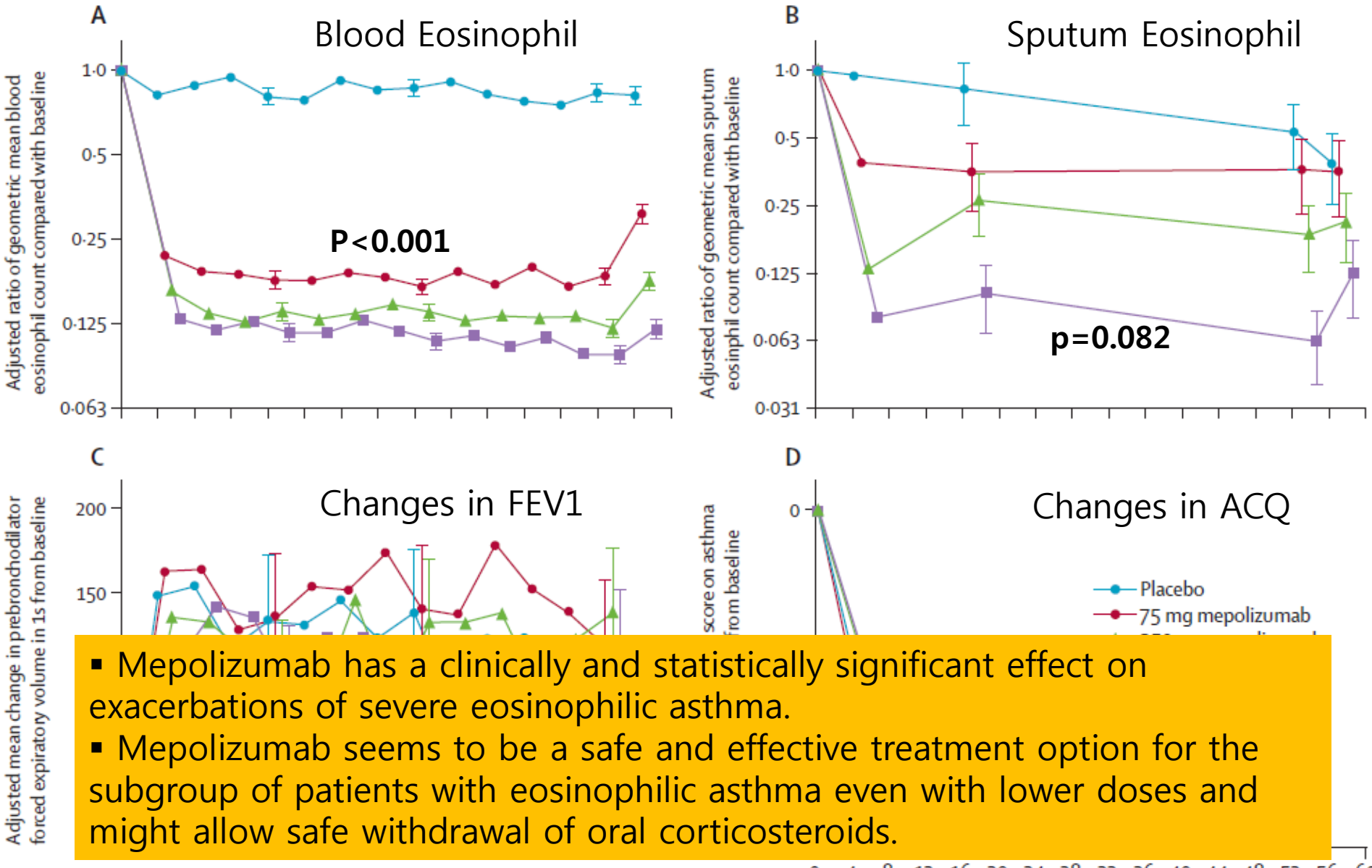
Mepolizumab

	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Rate of clinically significant exacerbations per patient per year*	2·40 (0·11)	1·24 (0·12)	1·46 (0·11)	1·15 (0·12)
Ratio to placebo	..	0·52 (0·39 to 0·69)	0·61 (0·46 to 0·81)	0·48 (0·36 to 0·64)



Secondary Outcomes

Mepolizumab



- Mepolizumab has a clinically and statistically significant effect on exacerbations of severe eosinophilic asthma.
- Mepolizumab seems to be a safe and effective treatment option for the subgroup of patients with eosinophilic asthma even with lower doses and might allow safe withdrawal of oral corticosteroids.

2. Azithromycin

Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial

Guy G Brusselle,[1] Christine VanderStichele,[1] Paul Jordens,[2] René Deman,[3]

- Non-eosinophilic asthma – Poor response to corticosteroids(CS)
- Severe asthma : older, longer duration, less atopy, frequent need for CS
- Maintenance macrolides proven to be effective in chronic neutrophilic airway inflammation including CF, BE, and DPB, prevent AE in COPD

- **AZI**thromycin in **S**evere **AST**hma:multi-center RCT in Belgium, for 26W
  - Azithromyci
  - Severe asth
  - pre/post-BD

- Persistent asthma with GINA step 4 or 5
- High dose ICS +LABA for >=6 months
- at least 2 severe asthma exacerbation and/or LRTI
- never smokers or ex-smoker < 10PY
- FENO below ULN

Thorax 2013;**68**:322–329.

Patients characteristics

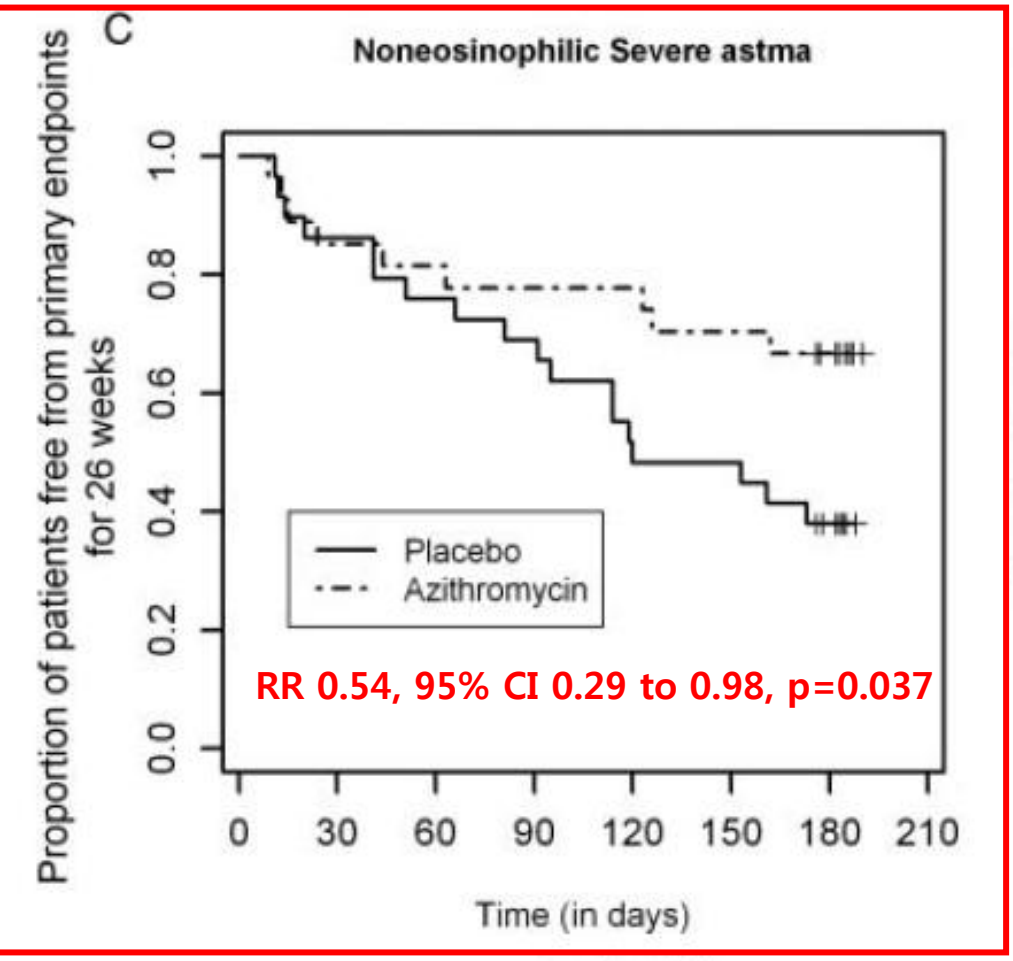
Azithromycin

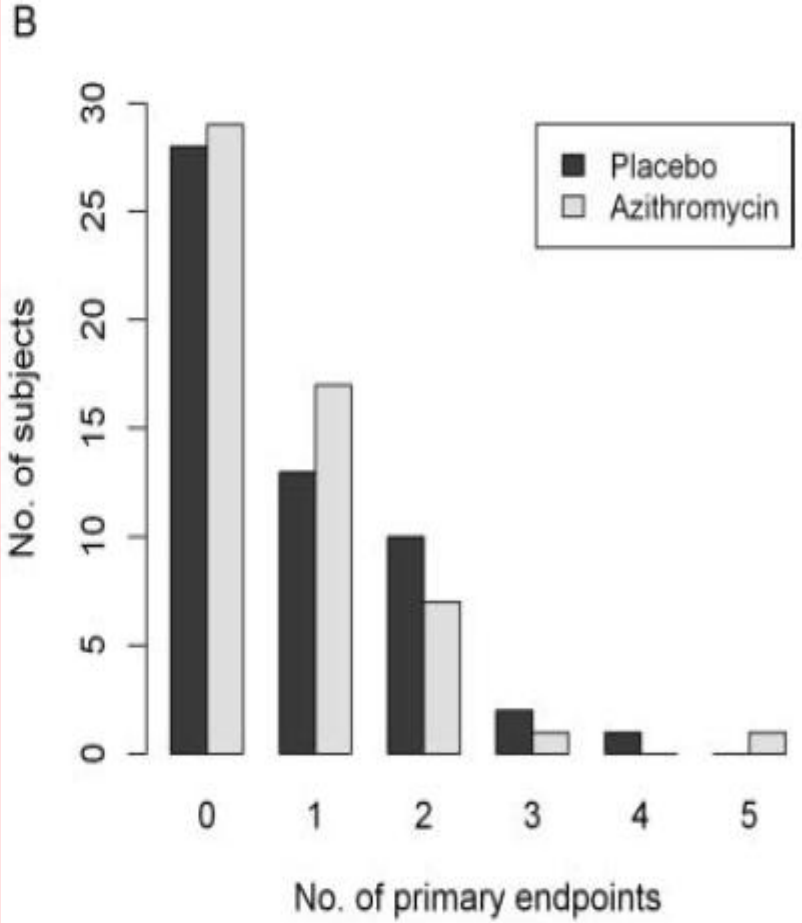
Table 1 Baseline characteristics of subjects in the intention-to-treat population

Characteristic	Placebo (N=54)	Azithromycin (N=55)	p Value
Sex, n			
Male	16 (30%)	26 (47%)	0.077
Female	38 (70%)	29 (53%)	
Age, years			
Median (range), IQR	53 (20–74), (36–60)	53 (19–76), (46–64)	0.097
Age at onset of symptoms, years			
Median (range), IQR	17 (1–72), (6–38)	20 (0–71), (3–40)	0.828
Asthma duration, years			
Median (range) IQR	23 (1–63), (12.8–41.3)	27 (2–70), (11–45)	0.263
Race, n (%) of subjects			
Caucasian	54 (100%)	55 (100%)	–
Body mass index*			
Mean (SD)	26.4 (5.4)	26.5 (4.9)	0.926
Positive atopic status, n (%) of subjects†	38 (70%)	35 (64%)	0.542
Total IgE (IU/ml)			
Median (range), IQR	87.3 (2–4500), (25.2–702.7)	111.3 (1–5000), (30.4–266.0)	0.685
History of nasal polyps, n (%) of subjects	6 (11%)	11 (20%)	0.291
Hospitalisations due to asthma in previous year, n (%) of subjects	13 (24%)	13 (24%)	1.000
Emergency room visits due to asthma in previous year, n (%) of subjects	8 (15%)	4 (7%)	0.237
Severe asthma exacerbations requiring OCS in previous year, n (%) of subjects	47 (87%)	49 (89%)	0.776
LRTI requiring antibiotics in previous year, n (%) of subjects	44 (82%)	46 (84%)	0.805
Severe asthma exacerbations and/or LRTI requiring antibiotics in previous year			
N (mean)	3.0 (1.28)	3.4 (2.08)	0.536

Primary endpoint : severe AE or LTRI

Azithromycin





Secondary outcomes : Lung function, ACQ, AQLQ

Azithromycin

Table 2 Secondary efficacy outcomes

Outcome	At 26 weeks after randomisation			
	Placebo (N=45–50)Mean (SD)	Azithromycin (N=47–53)Mean (SD)	DifferenceMean (95% CI)	p Value
Change in ACQ score, baseline to week 10 or 26	–0.12 (0.70)	–0.24 (0.93)	–0.12 (–0.44 to 0.21)	0.485
Change in AQLQ total score, baseline to week 10 or 26	0.20 (0.73)	0.32 (0.89)	0.12 (–0.20 to 0.44)	0.467
Absolute change in morning PEF, baseline to week 10 or 26 (l/min)	–5.77 (48.20)	–1.81 (45.27)	3.96 (–15.40 to 23.32)	0.686
Absolute change in evening PEF, baseline to week 10 or 26 (l/min)	–4.65 (78.68)	–0.81 (48.47)	3.84 (–23.10 to 30.78)	0.778
Change in pre-BD FEV_1, baseline to week 10 or 26 (%)	–0.90 (11.79)	–0.02 (10.06)	0.88 (–3.44 to 5.19)	0.688
Change in post-BD FEV_1, baseline to week 10 or 26 (%)	–0.66 (8.84)	1.29 (12.50)	1.95 (–2.42 to 6.33)	0.378
Change in use of rescue medication (number of puffs per day)	0.24 (2.11)	0.08 (1.14)	–0.16 (–0.88 to 0.55)	0.655
Change in FeNO (ppb), median (Q1; Q3)	2.1 (–4.2; 6.0)	0.5 (–6.7; 6.7)	–1.6	0.666

- First RCT examining the efficacy and safety of add-on low-dose azithromycin in adults with exacerbation-prone severe asthma.
- Although azithromycin was not superior to placebo in the total population, we demonstrated a significant reduction in primary endpoints in non-eosinophilic severe asthma, suggesting possibility of phenotypic treatment.

3. Tiotropium

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

- 2 replicate, randomized, placebo-controlled trials
- Efficacy and safety of adding tiotropium to ICS/LABA treatment
- Effects on lung function, exacerbation frequency, and other end points during 48 weeks period in poorly controlled asthma

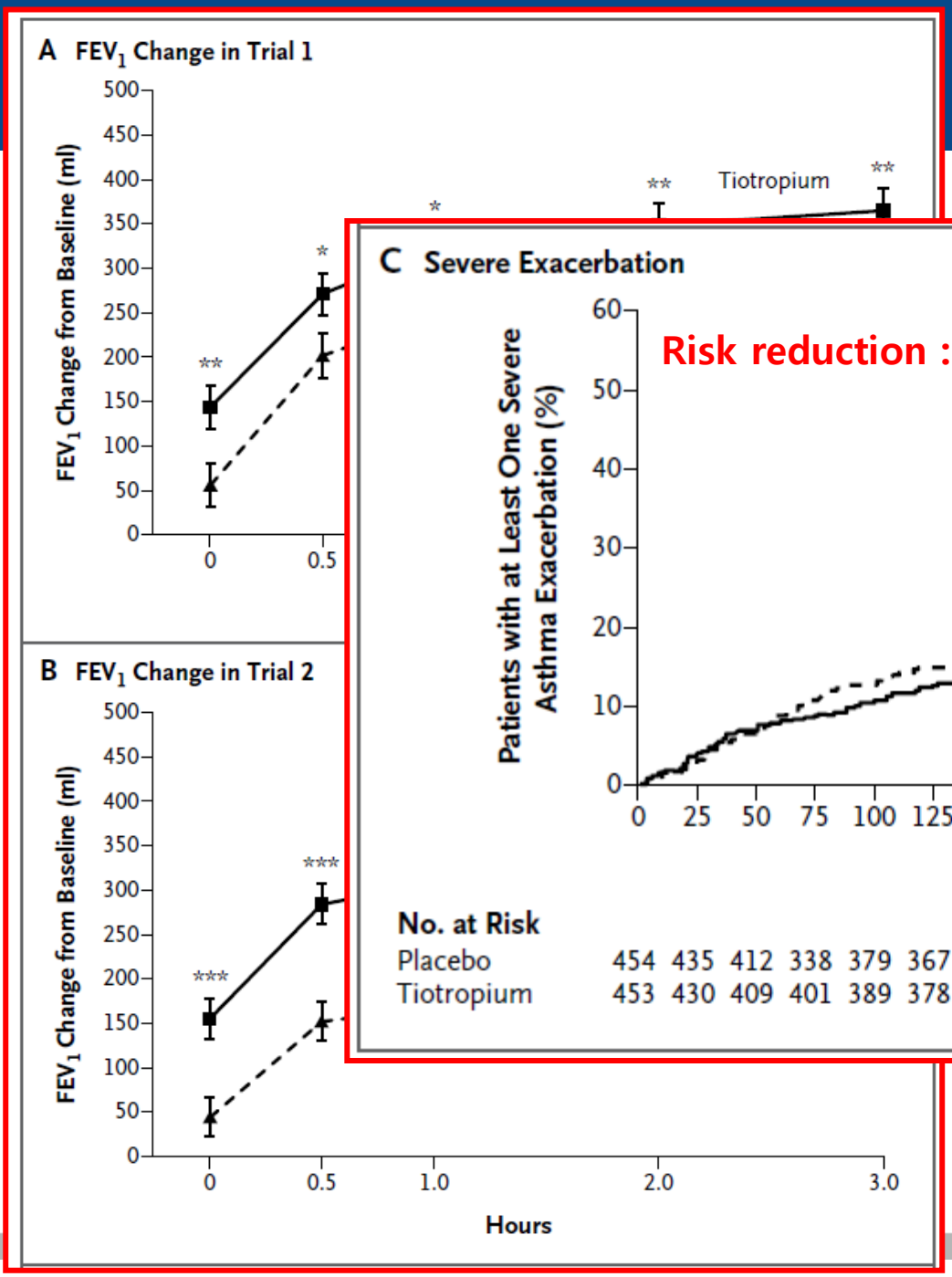
- ACQ=> 1.5 with ICS/LABA
- persistent airflow limitation : post-BD FEV1=< 80% predicted
  post-BD FVC =< 70%
- At least 1 exacerbation needs systemic GCS in the previous year

N Engl J Med 2012;367:1198-207.

Baseline characteristics

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=912)	Trial 1		Trial 2	
		Tiotropium (N=237)	Placebo (N=222)	Tiotropium (N=219)	Placebo (N=234)
Female sex — no. (%)	551 (60.4)	146 (61.6)	143 (64.4)	127 (58.0)	135 (57.7)
Age — yr	53.0±12.4	52.9±12.4	53.9±12.8	51.4±12.5†	53.6±11.7
Body-mass index‡	28.2±6.0	28.2±5.8	28.1±6.4	28.2±5.9	28.2±5.9
Use of maintenance oral glucocorticoids — %**	5.3	6.8	5.0	3.7	5.6
Use of omalizumab — %	3.9	2.5	4.5	2.7	6.0
Mean daily no. of puffs of short-acting beta-agonists††	3.2	2.8	3.3	3.4	3.3
Use of theophyllines — %	16.7	18.6	21.2	14.2	12.8
Use of leukotriene modifiers — %	22.3	25.3	27.5	16.4	19.7
Use of antihistamines — %	14.7	20.3	16.2	14.2†	8.1
ACQ-7 score**‡‡	2.6±0.7	2.7±0.7	2.7±0.7	2.6±0.7	2.6±0.7
AQLQ score**§§	4.6±1.1	4.6±1.1	4.6±1.1	4.6±1.0	4.7±1.1
Forced expiratory volume in 1 sec					
Value before bronchodilation — liters**	1.603±0.540	1.596±0.546	1.558±0.537	1.659±0.569	1.598±0.506
Percent of predicted value before bronchodilation	54.8±12.4	54.6±12.2	54.6±12.2	55.1±12.8	55.0±12.6
Percent of predicted value after bronchodilation	62.2±12.7	61.5±12.5	62.7±12.6	62.6±12.5	62.3±13.0
Reversibility — ml	217±217	201±211	230±223	228±206	209±229
Forced vital capacity — liters**	2.744±0.900	2.715±0.923	2.704±0.912	2.894±0.909	2.788±0.851


A FEV1 Change in Trial 1
FEV1 Change from Baseline (ml)
500
450
400
350
300
250
200
150
100
50
0
0
0.5
Tiotropium
**
*
**
**
B FEV1 Change in Trial 2
FEV1 Change from Baseline (ml)
***
***
0
0.5
1.0
2.0
3.0
Hours

C Severe Exacerbation
Patients with at Least One Severe Asthma Exacerbation (%)
60
50
40
30
20
10
0
Risk reduction : 21% (HR, 0.79; P = 0.03)
Placebo
Tiotropium
0 25 50 75 100 125 150 175 200 225 250 275 300 325
Days
No. at Risk
Placebo 454 435 412 338 379 367 356 339 332 319 303 290 282 272
Tiotropium 453 430 409 401 389 378 363 353 348 339 331 319 308 298

Difference in change from baseline

Tiotropium

Table 2. Mean Difference between Tiotropium and Placebo in the Change from Baseline to Week 24 and Week 48 in the Two Trials.*

Measure and Week	Trial 1		Trial 2	
	No. of Patients	Difference in Change *mean (95% CI)*	No. of Patients	Difference in Change *mean (95% CI)*
Forced expiratory volume in 1 sec				
Peak at 0–3 hr (ml)				
24 wk†	428	86 (20 to 152)‡	423	154 (91 to 217)§
48 wk	417	73 (5 to 140)‡	403	152 (87 to 217)§
Trough (ml)				
24 wk†	428	88 (27 to 149)¶	422	111 (53 to 169)§
48 wk	417	42 (–21 to 104)	402	92 (32 to 151)¶
Forced vital capacity				
Peak (ml)				
24 wk	428	89 (6 to 173)‡	423	94 (10 to 177)‡
48 wk	417	125 (40 to 210)¶	403	114 (29 to 200)¶
Trough (ml)				
24 wk	428	136 (58 to 214)§	422	106 (25 to 186)¶

- In patients with poorly controlled asthma despite treatment with ICS/LABA, adding tiotropium significantly reduced the risk of episodes of worsening of asthma and asthma exacerbations and provided sustained bronchodilation.
- These implicates the possibility of tiotropium as a good treatment option in severe asthma subgroup.

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Treatment strategies for ICS adjustment

Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma

The BASALT Randomized Controlled Trial

- randomized, parallel, 3-group, placebo-controlled, multiply-blinded trial of 342 adults with mild to moderate asthma controlled by low-dose ICS therapy

- For physician assessment–based adjustment(PABA) and biomarker-based (FENO) adjustment(BBA), the dose of ICS was adjusted every 6 weeks
- for symptom-based adjustment(SBA), ICS were taken with each albuterol rescue use.

- The primary outcome : time to treatment failure.

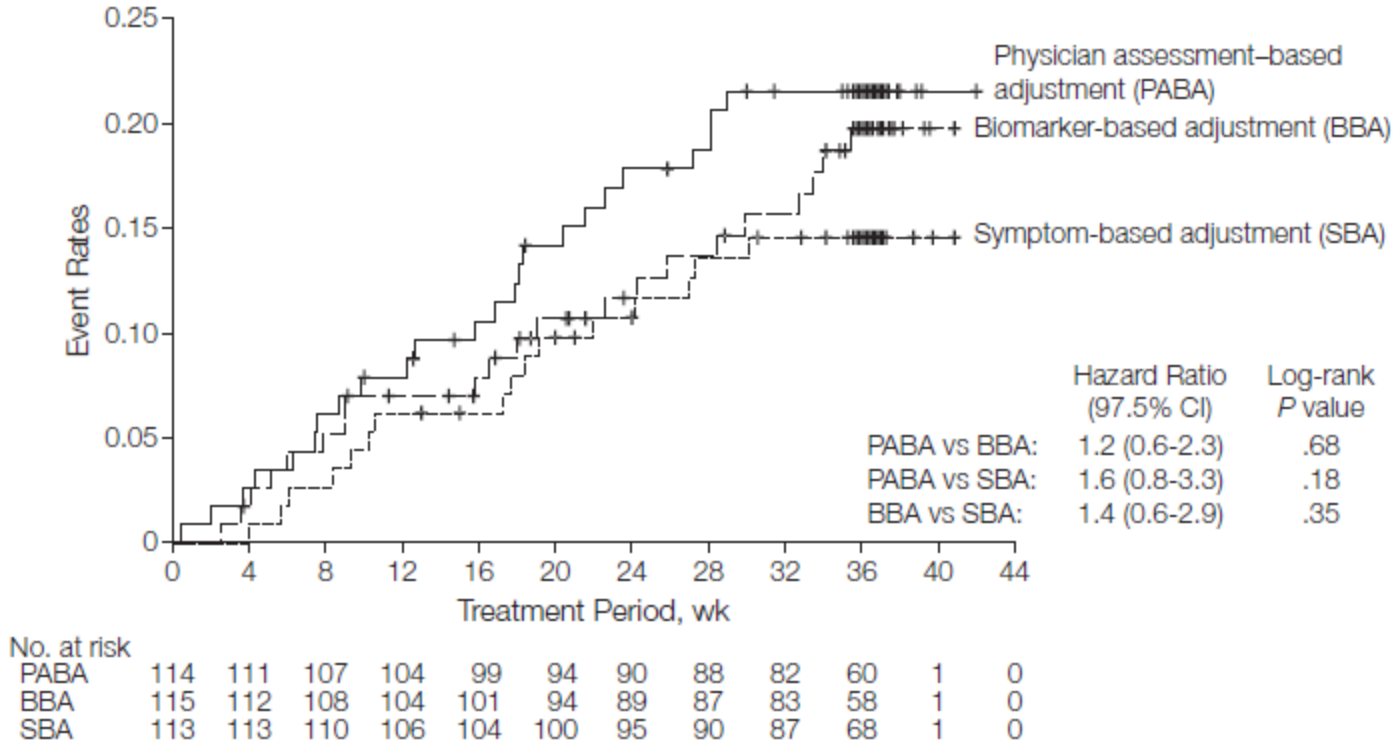
JAMA. 2012;308(10):987-997

Table 1. Demographics of Participants

	No. (%) by Adjustment Strategy			
	Physician (n = 114)	Biomarker (n = 115)	Symptom (n = 113)	*P* Value
Male sex	42 (36.8)	33 (28.7)	30 (26.5)	.21[a]
Race/ethnicity				
American Indian/Alaska Native	0	0	1 (0.9)	.03[a]
Asian/Pacific Islander	1 (0.9)	2 (1.7)	10 (8.8)	
Black	24 (21.1)	28 (24.3)	17 (15.0)	
White	76 (66.7)	71 (61.7)	69 (61.1)	
Hispanic	11 (9.6)	13 (11.3)	14 (12.4)	
Other[b]	2 (1.8)	1 (0.9)	2 (1.8)	
Skin test atopic status[c]	97 (85.1)	99 (86.1)	93 (82.3)	.70[a]
	Median (IQR)			
Two-week average prior to visit 4				
Daily symptoms[k]	0.05 (0-0.14)	(n = 114) 0.06 (0.01-0.21)	0.05 (0-0.20)	.26[l]
Albuterol rescue use (puffs)	0.04 (0-0.29)	(n = 114) 0.07 (0-0.43)	(n = 112) 0 (0-0.31)	.42[l]
Exhaled breath condensate pH at visit 4	8.52 (8.25-8.64)	(n = 110) 8.48 (8.29-8.60)	(n = 107) 8.47 (8.21-8.61)	.83[l]
Sputum eosinophils at visit 3	(n = 79) 0.40 (0-1.20)	(n = 67) 0.20 (0-0.80)	(n = 76) 0.40 (0-1.40)	.09[l]
Blood eosinophils at visit 2, /mm^3	(n = 111) 132.0 (100.0-222.0)	(n = 108) 178.5 (100.0-300.0)	(n = 108) 169.0 (100.0-224.0)	.17[l]
Postalbuterol (4 puffs), L	3.32 (0.75)	3.21 (0.81)	3.16 (0.71)	.31[a]
AM Peak flow 2-week average prior to visit 4, L/min	460.1 (111.3)	(n = 114) 442.8 (117.5)	436.9 (104.5)	.26[d]
PM Peak flow 2-week average prior to visit 4, L/min	466.5 (112.7)	(n = 114) 445.3 (118.2)	441.3 (104.0)	.19[d]
ACQ average score at visit 4[f]	0.72 (0.50)	0.79 (0.54)	0.73 (0.49)	.57[d]
AQLQ average score at visit 3[g]	(n = 112) 6.27 (0.76)	6.16 (0.77)	6.25 (0.72)	.48[d]
ASUI average score at visit 4[h]	0.90 (0.10)	0.88 (0.12)	0.90 (0.10)	.39[d]
Exhaled nitric oxide at visit 4, ppb[i]	(n = 108) 21.38 (0.62)	(n = 114) 18.88 (0.66)	(n = 110) 20.78 (0.54)	.28[j]
Imputed PC_{20} at visit 4, mg/mL[i]	(n = 99) 3.50 (1.43)	(n = 100) 2.37 (1.54)	(n = 98) 2.64 (1.27)	.14[j]
IgE at visit 2, IU/mL[i]	(n = 107) 130.0 (1.5)	(n = 105) 118.9 (1.4)	(n = 101) 133.8 (1.4)	.83[j]

Time to first treatment failure

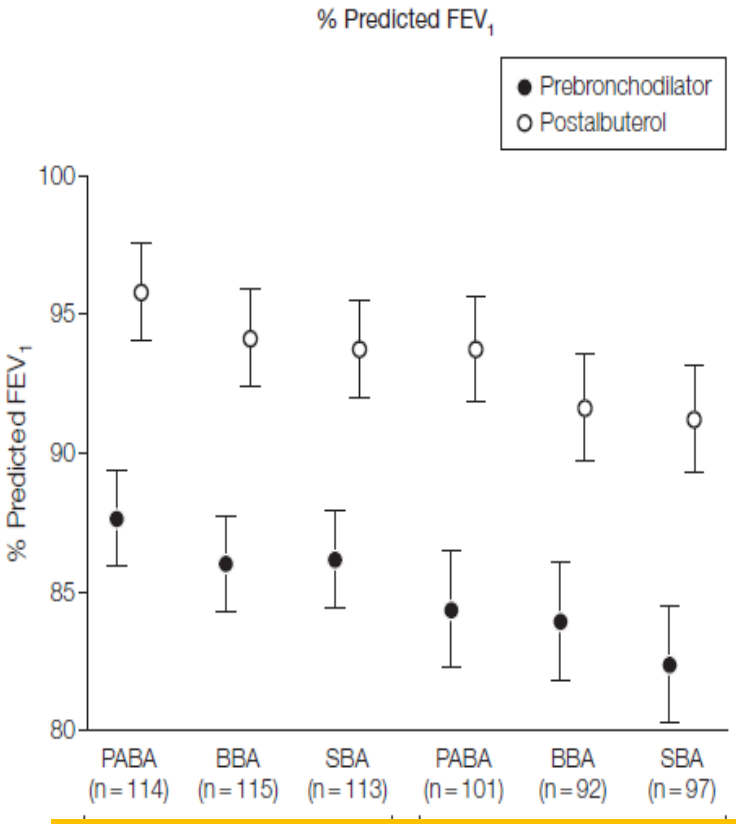
Figure 2. Time to First Treatment Failure

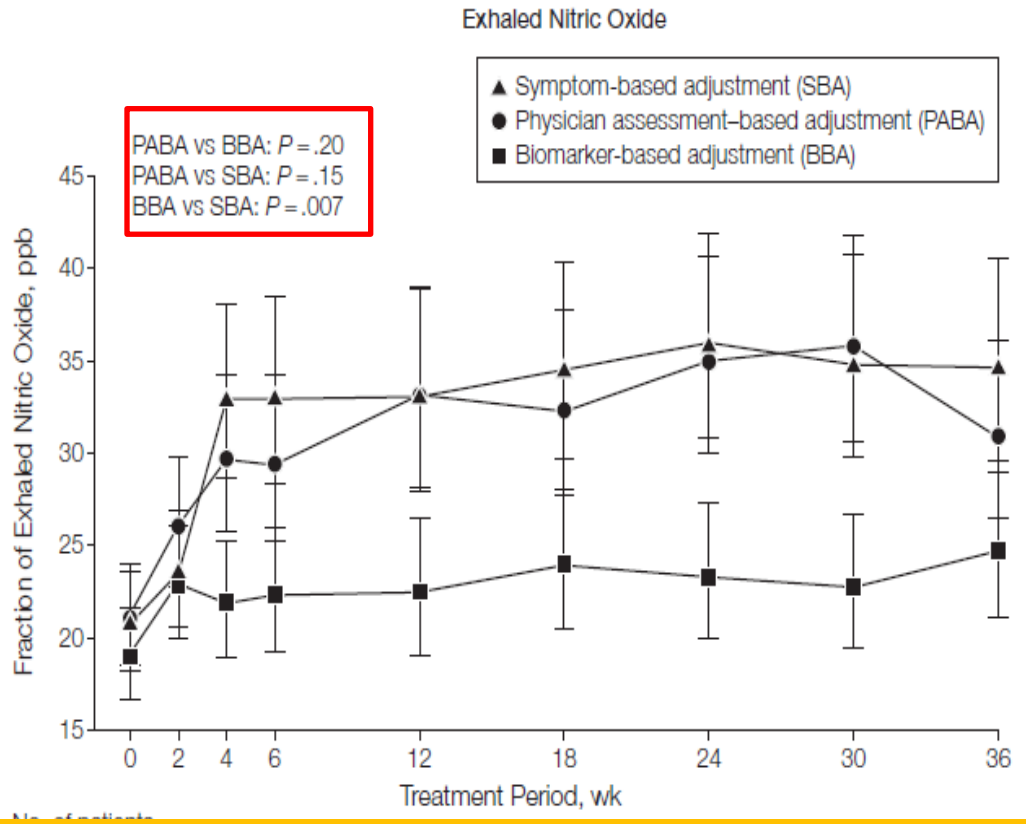


- Treatment failure : acute exacerbation, at-home measurements of PEF, albuterol use, in-clinic measurements of FEV1, safety or dissatisfaction

Lung function and FENO

Figure 4. Mixed-Model Treatment Means of Pulmonary Function and Exhaled Nitric Oxide





- Among adults with mild to moderate persistent asthma controlled with low-dose ICS, the use of either biomarker-based or symptom based adjustment of ICS was not superior to physician assessment–based adjustment of ICS in time to treatment failure.

Strategy for LABA adjustment

Step-off LABA

Long-Acting β_2-Agonist Step-off in Patients With Controlled Asthma

Systematic Review With Meta-analysis

Jan L. Brozek, MD, PhD; Monica Kraft, MD; Jerry A. Krishnan, MD, PhD; Michelle M. Cloutier, MD; Stephen C. Lazarus, MD; James T. Li, MD, PhD; Nancy Santesso, RD, MLIS; Robert C. Strunk, MD; Thomas B. Casale, MD

- Safety concerns for LABA use in asthma → withdrawal of the LABA once asthma is controlled by ICS/LABA is recommended
- Effect of LABA discontinuation ???

- Systematic Review with Meta-analysis from MEDLINE, EMBASE, Cochrane Centrals through Aug 2010

Arch Intern Med. 2012;172(18):1365-1375.

Table 2. LABA Step-off vs Continued Use of LABAs in Patients With Asthma That Is Well Controlled With a Combination of ICS and LABA

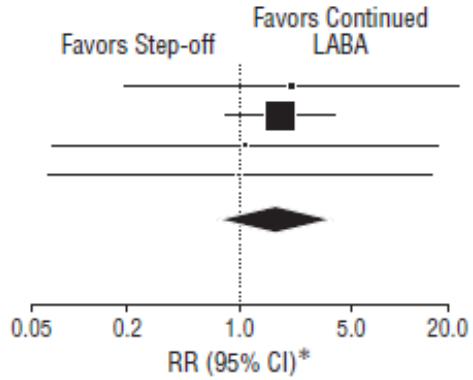
Outcome	No. of Studies	No./Total No. (%) of Patients: LABA Step-off	No./Total No. (%) of Patients: Continued Use of LABA	Effect (95% CI)
Death	5	0/660	0/692	. . .
ICU admission	5	0/660	0/692	. . .
Mechanical ventilation	5	0/660	0/692	. . .
Hospitalization	5	0/660	0/692	. . .
Emergency department visit or unscheduled consultation for asthma	3	11/464 (2.4)	5/485 (1.0)	RR, 2.24 (0.79 to 6.35)
Any use of systemic corticosteroids for treatment of asthma	4	20/618 (3.2)	12/639 (1.9)	RR, 1.68 (0.84 to 3.38)
Quality of life (AQLQ)	2	171	188	MD, 0.32 (0.14 to 0.51) point lower
Asthma control (ACQ)	3	315	330	MD, 0.24 (0.13 to 0.35) point higher
Loss of asthma control	3	140/339 (41.3)	118/347 (34.0)	RR, 1.24 (0.79 to 1.95)
Symptom score	4	437	478	SMD, 0.27 higher (0.11 lower to 0.65 higher)
Symptom-free days	4	608	622	MD, 9.15% fewer (1.62% to 16.69% fewer)
Withdrawal owing to lack of efficacy or loss of asthma control	4	87/618 (14.1)	27/639 (4.2)	RR, 3.27 (2.16 to 4.96)
Awakening-free nights	4	519	576	MD, 1.47% fewer (3.18% fewer to 0.23% more)
Rescue bronchodilator use	4	605	621	MD, 0.71 (0.29 to 1.14) more puffs/d
Rescue-free days	3	410	445	MD, 7.87% fewer (16.78% fewer to 1.03% more)
Any adverse event	5	316/660 (47.9)	354/682 (51.9)	RR, 0.93 (0.86 to 1.02)
Serious adverse event	5	7/660 (1.1)	9/682 (1.3)	RR, 0.79 (0.29 to 2.09)
Withdrawal owing to adverse event	5	17/660 (2.6)	19/682 (2.8)	RR, 0.92 (0.47 to 1.8)
Prebronchodilator FEV_1[a]	4	454	471	MD, 0.13 L (0.02 to 0.23) lower
Morning PEF[a]	4	574	596	MD, 19.72 L/min (14.96 to 24.49) lower

Any use of systemic corticosteroids

Study	LABA Step-off Events	LABA Step-off Total	LABA Continued Events	LABA Continued Total	Weight, %	RR (95% CI)*
Berger et al,[37] 2010†	2	144	1	152	8.5	2.11 (0.19 to 23.03)
Godard et al,[39] 2008	16	154	9	154	78.8	1.78 (0.81 to 3.90)
Koenig et al,[42] 2008†	1	159	1	172	6.4	1.08 (0.07 to 17.15)
SAS40037,[51] 2005†	1	161	1	161	6.4	1.00 (0.06 to 15.85)
Total (95% CI)	**20**	**618**	**12**	**639**	**100.0**	**1.68 (0.84 to 3.38)**

Heterogeneity: $\tau^2=0.00$; $\chi^2_3=0.29$ ($P=.96$); $I^2=0\%$

Test for overall effect: $z=1.47$ ($P=.14$)

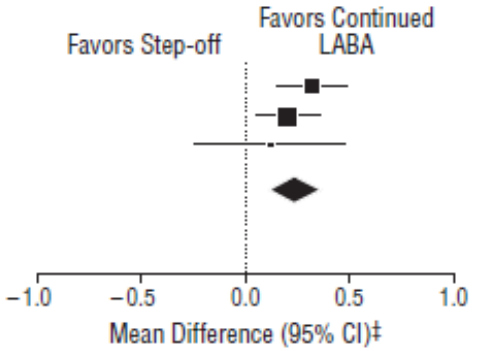


Asthma control (ACQ)

Study	LABA Step-off Mean	LABA Step-off SD	LABA Step-off Total	LABA Continued Mean	LABA Continued SD	LABA Continued Total	Weight, %	Mean Difference (95% CI)‡
Berger et al,[37] 2010†	0.38	0.811	139	0.06	0.632	151	40.9	0.32 (0.15 to 0.49)
Godard et al,[39] 2008†	0.8	0.6	141	0.6	0.7	142	50.2	0.20 (0.05 to 0.35)
Reddel et al,[47] 2010	1.13	0.86	35	1.01	0.69	37	8.9	0.12 (−0.24 to 0.48)
Total (95% CI)			**330**			**330**	**100.0**	**0.24 (0.13 to 0.35)**

Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.56$ ($P=.46$); $I^2=0\%$

Test for overall effect: $z=4.41$ ($P<.001$)

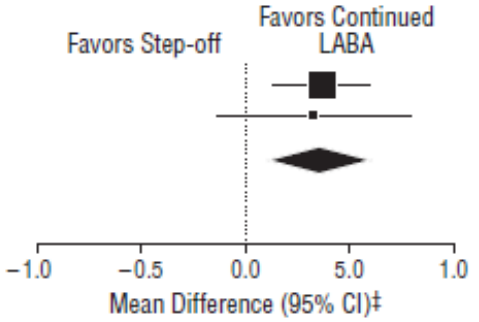


Quality of life

Study	LABA Step-off Mean	LABA Step-off SD	LABA Step-off Total	LABA Continued Mean	LABA Continued SD	LABA Continued Total	Weight, %	Mean Difference (95% CI)‡
Berger et al,[37] 2010§	0.27	0.89	136	−0.06	0.9	151	79.9	0.37 (0.13 to 0.60)
Reddel et al,[47] 2010‖	1.61	1.54	35	1.18	1.03	37	20.1	0.33 (−0.14 to 0.79)
Total (95% CI)			**171**			**188**	**100.0**	**0.36 (0.15 to 0.57)**

Heterogeneity: $\tau^2=0.00$; $\chi^2_1=0.02$ ($P=.88$); $I^2=0\%$

Test for overall effect: $z=3.37$ ($P<.001$)

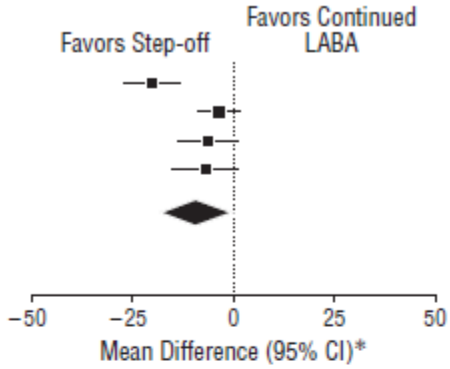


Deterioration of symptoms (proportion of symptom-free days, %)

Study	LABA Step-off Mean	SD	Total	LABA Continued Mean	SD	Total	Weight, %	Mean Difference (95% CI)*
Berger et al,[37] 2010†‡	−16.2	34.746	144	4.08	26.661	152	24.8	−20.28 (−27.36 to −13.20)
Godard et al,[39] 2008‡§	85.8	24	153	89.4	20.7	149	27.8	−3.60 (−8.65 to 1.45)
Koenig et al,[42] 2008†	−0.5	33.51	154	5.7	34.89	167	24.2	−6.20 (−13.68 to 1.28)
SAS40037,[51] 2005†	−1.9	36.34	157	5.1	35.99	154	23.3	−7.00 (−15.04 to 1.04)
Total (95% CI)			**608**			**622**	**100.0**	**−9.15 (−16.69 to −1.62)**

Heterogeneity: $\tau^2=46.57$; $\chi^2_3=14.72$ ($P=.002$); $I^2=80\%$

Test for overall effect: $z=2.38$ ($P=.02$)

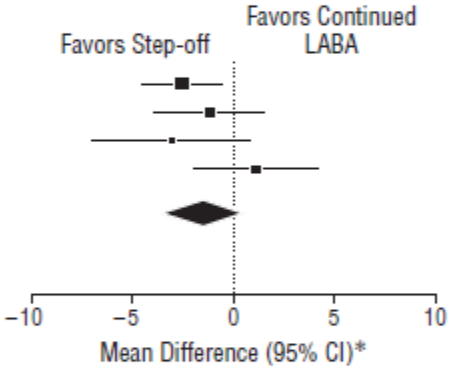


Night-waking due to asthma (proportion of awakening-free nights, %)

Study	LABA Step-off Mean	SD	Total	LABA Continued Mean	SD	Total	Weight, %	Mean Difference (95% CI)*
Berger et al,[37] 2010†‡	−4.8	10.257	144	−2.26	7.046	152	36.6	−2.54 (−4.56 to −0.52)
Godard et al,[39] 2008‡§	95.1	13.5	153	96.3	10.3	150	26.0	−1.20 (−3.90 to 1.50)
Koenig et al,[42] 2008†	0.1	15.66	109	3.2	15.65	145	15.3	−3.10 (−6.99 to 0.79)
SAS40037,[51] 2005†	3.1	11.69	113	2	12.49	129	22.1	−1.10 (−1.95 to 4.15)
Total (95% CI)			**519**			**576**	**100.0**	**−1.47 (−3.18 to 0.23)**

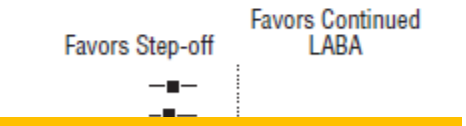
Heterogeneity: $\tau^2=1.01$; $\chi^2_3=4.50$ ($P=.21$); $I^2=33\%$

Test for overall effect: $z=1.69$ ($P=.09$)



Any serious adverse effect

Study	LABA Step-off Events	Total	LABA Continued Events	Total	Weight, %	OR (95% CI)
Berger et al,[37] 2010‖	1	145	3	154	25.3	0.39 (0.05 to 2.77)
Godard et al,[39] 2008¶	1	154	3	154	25.3	0.36 (0.05 to 2.61)



- Evidence suggests that discontinuing LABA therapy in adults and older children with asthma controlled with a combination of ICSs and LABAs results in increased asthma-associated impairment.
- Additional trials measuring all long-term patient-important outcomes are needed.

ICS/LABA vs. ICS for AE

The relationship between combination inhaled corticosteroid and long-acting β-agonist use and severe asthma exacerbations in a diverse population

Karen E. Wells, MPH,[a,b] Edward L. Peterson, PhD,[a] Brian K. Ahmedani, PhD,[c] Richard K. Severson, PhD,[b] Julie Gleason-Comstock, PhD, MCHES,[d] and L. Keoki Williams, MD, MPH[c,e] *Detroit, Mich*

- Benefits and risks of LABAs in asthma?
- **S**almeterol **M**ulticenter **A**sthma **R**esearch **T**rial (2003)

-a higher proportion of deaths and serious events, particularly in African Americans than placebo with Salmeterol.

- Mitigating effects of ICS for risks from Salmeterol?

- To estimate the effect of ICS therapy and fixed-dose ICS/LABA combination therapy on severe asthma exacerbations in a racially diverse population.

- Asthma severity classification based on SABA fills/OCS fills in baseline year

J Allergy Clin Immunol 2012;129:1274-9.

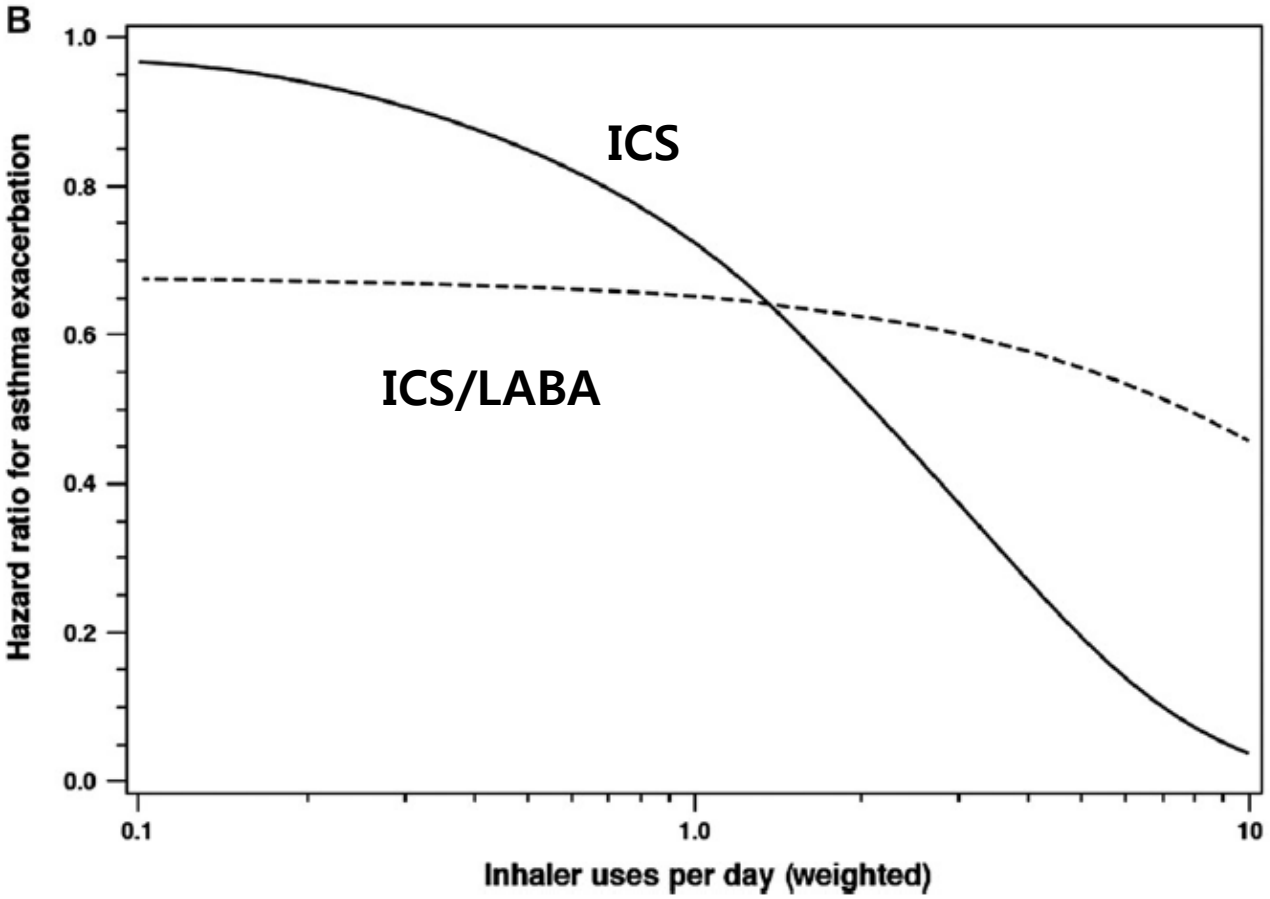
TABLE I. Characteristics of patients with asthma stratified by treatment group (N = 1828)

Characteristic	ICS (n = 846)	ICS/LABA (n = 982)
Age categories (y), n (%)*†		
<18	213 (25.2)	94 (9.6)
≥18	633 (74.8)	888 (90.4)
Female, n (%)	555 (65.6)	641 (65.3)
Race-ethnicity, n (%)		
African American	308 (36.4)	360 (36.6)
White	538 (63.6)	622 (63.3)
Asthma severity categories, n (%)‡		
Low	246 (29.1)	307 (31.3)
Low-to-moderate	374 (44.2)	413 (42.1)
Moderate-to-severe	171 (20.2)	189 (19.3)
Severe	55 (6.5)	73 (7.4)
Index ICS medication, n (%)		
Fluticasone	496 (58.6)	–
Triamcinolone acetonide	185 (21.9)	–
Budesonide	158 (18.7)	–
Flunisolide	4 (0.5)	–
Beclomethasone	3 (0.4)	–
Index ICS/LABA medication, n (%)		
Fluticasone/salmeterol	–	976 (99.4)
Budesonide/formoterol	–	6 (0.6)
Other asthma controller medication use, n (%)*	109 (12.9)	201 (20.5)
Antileukotrienes	96 (11.4)	190 (19.4)
Cromolyn sodium	2 (0.2)	5 (0.5)
Omalizumab	0 (0.0)	2 (0.2)
Theophylline derivatives	16 (1.9)	18 (1.8)

TABLE II. Relationship between ICS and ICS/LABA combination therapy use and severe asthma exacerbations*

Overall	aHR (95% CI)† ICS	aHR (95% CI)† ICS/LABA
Unweighted controller estimate	0.56 (0.42-0.76)	0.41 (0.29-0.60)
Weighted controller estimate	0.72 (0.53-0.98)	0.65 (0.47-0.90)
Age (y)		
<18	1.59 (0.70-3.65)	1.36 (0.61-3.04)
≥18	0.64 (0.46-0.88)	0.58 (0.41-0.83)
Sex		
Female	0.78 (0.54-1.12)	0.75 (0.51-1.10)
Male	0.60 (0.34-1.07)	0.46 (0.25-0.83)
Race-ethnicity		
African American	0.66 (0.39-1.13)	0.59 (0.36-0.98)
White	0.76 (0.52-1.12)	0.69 (0.45-1.05)
Asthma severity‡		
Low/low-to-moderate	0.70 (0.48-1.01)	0.72 (0.49-1.06)
Moderate-to-severe/severe	0.58 (0.35-0.95)	0.39 (0.23-0.68)

Risk of asthma exacerbation



Clinical implications: When used in fixed-dose combinations with inhaled corticosteroids, inhaled long-acting beta-agonist medication appears to additionally reduce severe asthma exacerbations. This beneficial effect appears consistent even among high-risk subgroups.

Contents

- New treatment options
- Effect of treatment adjustment
- **Useful diagnostic markers in asthma**
- Scoring systems for predicting exacerbation
- Results from GWAS

Diagnosis of asthma

MCT

Methacholine challenge test: Diagnostic characteristics in asthmatic patients receiving controller medications

Kaharu Sumino, MD, MPH,[a] Elizabeth A. Sugar, PhD,[b] Charles G. Irvin, PhD,[c] David A. Kaminsky, MD,[c] Dave Shade, JD,[b] Christine Y. Wei, MS,[b] Janet T. Holbrook, PhD, MPH,[b] Robert A. Wise, MD,[d] and Mario Castro, MD, MPH,[a] for the American Lung Association Asthma Clinical Research Centers* *St Louis, Mo, Baltimore, Md, and Burlington, Vt*

- Methacholine challenge test(MCT): assess airway hyperresponsiveness
- Diagnostic characteristics of MCT in asthmatic patients receiving controller after the use of high-potency ICS ?
- Cohort-control study in asthmatic participants (n=126) with regular controller and non-asthmatic control (n=93)
- to evaluate the sensitivity and specificity of the MCT.
- MCT positive : PC20 <=8 mg/mL

J Allergy Clin Immunol 2012;130:69-75.

Participants' characteristics

MCT

TABLE I. Participants' characteristics

Characteristics	Healthy control participants (n = 93)	Asthmatic patients (n = 126)	*P* value*
General characteristics			
Male sex	37 (40)	42 (33)	.401
Race/ethnicity			
White	63 (68)	77 (61)	.062
African American	14 (15)	34 (27)	
Latino/Hispanic	10 (11)	13 (10)	
Others	6 (6)	2 (2)	
Age at enrollment (y), mean	32.9 ± 12.8	38.3 ± 15	.006
Former smoker	3 (3)	13 (10)	.084
BMI	25.9 ± 4.9	29.2 ± 7.6	.002
Other conditions			
Eczema	1 (1)	17 (13)	.002
Sinusitis	1 (1)	23 (18)	<.001
Hay fever/rhinitis	7 (8)	78 (62)	<.001
GERD	4 (4)	34 (27)	<.001
Food allergy	1 (1)	24 (19)	<.001
Family history of asthma	26 (28)	79 (63)	<.001
Atopy			
Median no. of positive allergy skin test results	0 (0-8)	3.5 (0-14)	<.001
≥1 Positive allergy skin test results	43 (46)	102 (81)	<.001
Lung function			
Percent predicted FEV_1 (before BD)	95.1 ± 10.4	88.6 ± 11.9	<.001
Percent predicted FVC (before BD)	97.1 ± 10.7	96.7 ± 11.7	.720
Asthma characteristics			
Median age of onset (y)	NA	11.0 (1-53)	
Asthma treatment (%)			
ICS/LABA combination	NA	74 (59)	
ICS alone	NA	39 (31)	
No ICS	NA	13 (10)	
Antileukotriene alone or in combination	NA	30 (24)	
Asthma control			
Use of daily SABA	NA	27 (21)	
ACQ	NA	1.1 ± 0.7	
Urgent care visit (%) in 12 mo	NA	36 (29)	
Prednisone burst (%) in 12 mo	NA	29 (23)	

TABLE II. Overall sensitivity and specificity of the MCT to detect a physician's diagnosis of asthma by race, sex, and atopy

	No.	Sensitivity	Specificity	PPV	NPV
Overall	217*	77% (68% to 84%)	96% (89% to 99%)	96% (90% to 99%)	75% (66% to 83%)
Race					
White	139	69% (57% to 79%)	95% (86% to 99%)	95% (85% to 99%)	71% (60% to 81%)
African American	48	91% (76% to 99%)	93% (66% to 100%)	97% (83% to 100%)	81% (54% to 96%)
Sex					
Female	138	73% (62% to 83%)	98% (90% to 100%)	98% (91% to 100%)	71% (59% to 81%)
Male	79	83% (68% to 94%)	92% (78% to 99%)	92% (78% to 99%)	83% (67% to 93%)
Atopy†					
No	72	52% (30% to 74%)	94% (83% to 99%)	80% (51% to 96%)	81% (68% to 90%)
Yes	145	82% (73% to 90%)	98% (87% to 100%)	99% (93% to 100%)	70% (56% to 82%)

TABLE III. Comparison of the characteristics of asthmatic participants with positive and negative MCT results

	Positive MCT result (n = 96)	Negative MCT result (n = 29)	*P* value
Characteristics			
Male sex	35 (36)	7 (24)	.314
Race/ethnicity			
White	53 (55)	24 (83)	.056
Black	31 (32)	3 (10)	
Others	12 (12)	2 (7)	
Age at enrollment (y), mean	39.1 ± 15.0	35.3 ± 15.1	.225
Former smoker	11 (11)	2 (7)	.72
BMI	29.2 ± 7.3	29.4 ± 8.8	.822
Lung function			
Percent predicted FEV_1	87.1 ± 11.9	93.8 ± 10.8	.003
Percent predicted FVC	96.4 ± 12.2	98.2 ± 10.3	.486
Peak flow (L/min)	418.6 ± 79.7	394.1 ± 98.8	.234
Asthma characteristics			
Family history of asthma	61 (64)	18 (62)	>.999
Median age of onset (y)	11.5 (1-53)	10.0 (1-52)	.495

- The sensitivity and specificity of MCT varies with several factors.
- MCT should be not be used as the sole method for excluding the diagnosis of asthma, especially in white and non-atopic subjects

Diagnosis of eosinophilic inflammation

Periostin

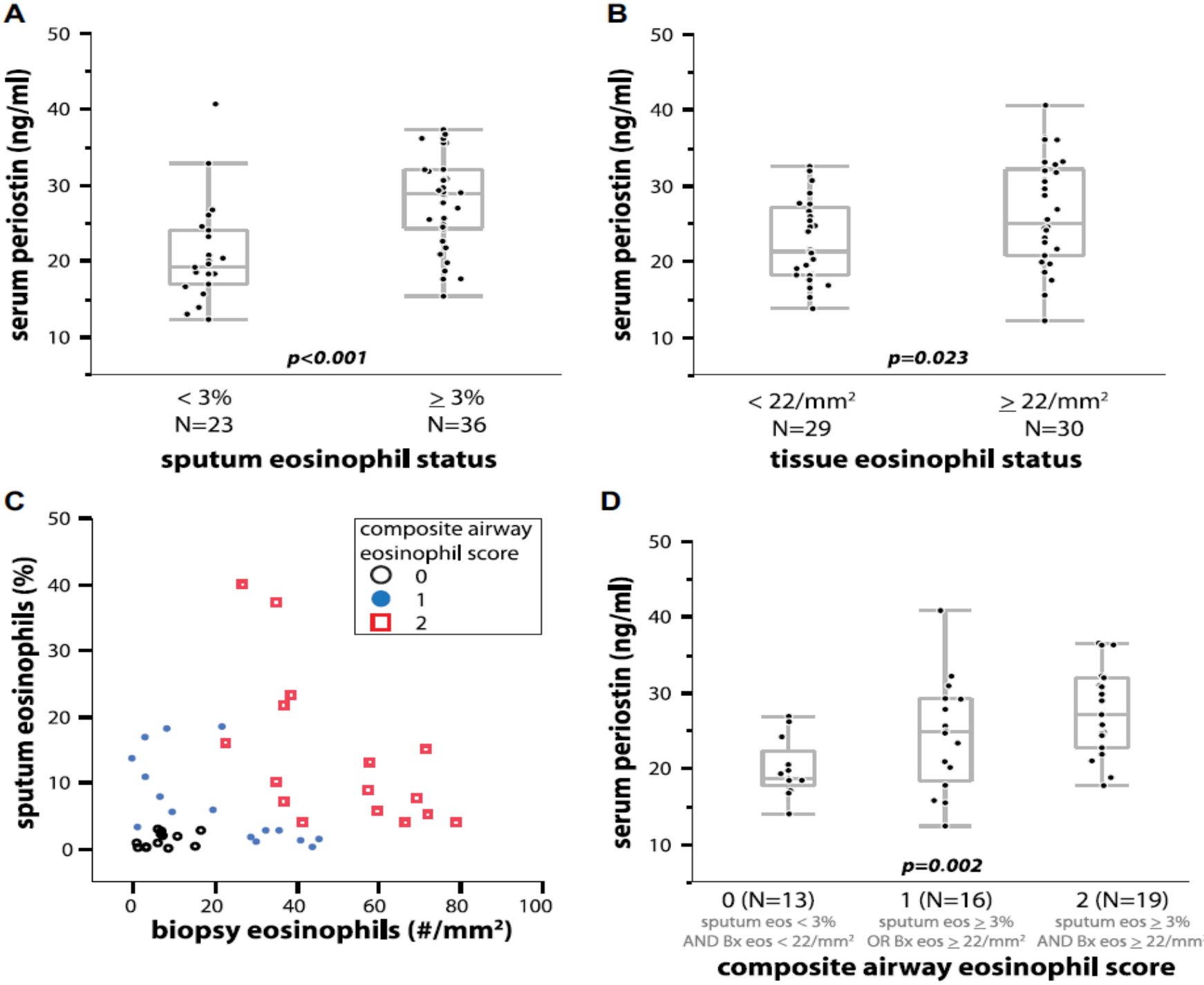
Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients

Guiquan Jia, MD,[a]* Richard W. Erickson, BS,[b]* David F. Choy, BS,[a] Sofia Mosesova, PhD,[c] Lawren C. Wu, PhD,[d] Owen D. Solberg, PhD,[f,g] Aarti Shikotra, BSc,[h] Richard Carter, MRCP,[h] Séverine Audusseau, MSc,[j] Jeffrey M. Harris, MD, PhD,[e] and Joseph R. Arron, MD, PhD,[a] on behalf of the Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) Study Group‡ *South San Francisco and San Francisco, Calif,*

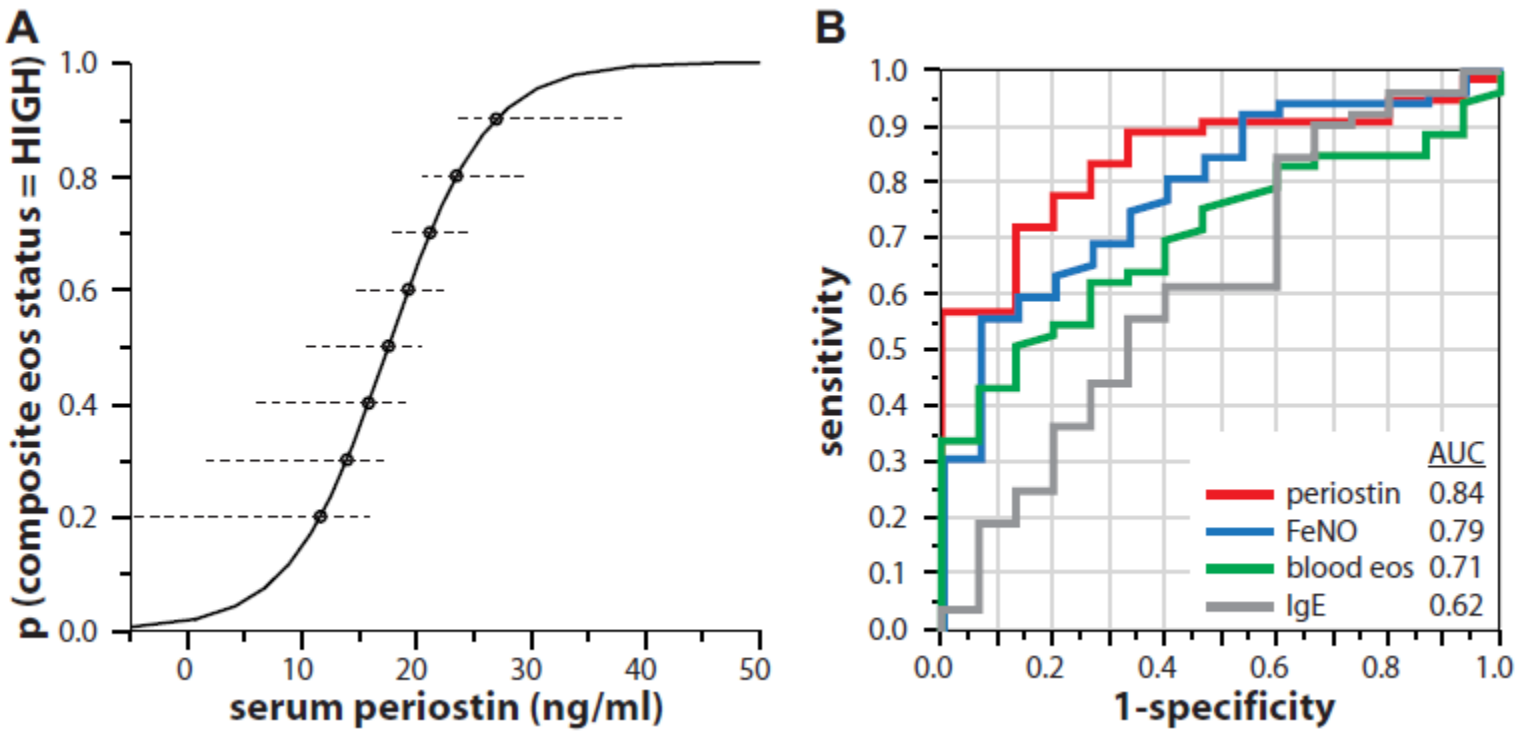
TABLE I. Demographic and clinical data: range of values for biomarker assessments in the BOBCAT study

No. of subjects	67
Age (y)	46 (12)
Sex (M/F)	32/35
FEV_1 (% predicted)	60 (11)
ACQ score	2.7 (0.8)
Daily ICS dose (μg FPI) equivalent	>1000*
BAL eosinophils (% nonsquamous cells)	0.7 (0.1-2.4), n = 59
Sputum eosinophils (% nonsquamous cells)	5.2 (1.8-16.4), n = 59
Biopsy eosinophils/mm^2	23.0 (7.0-44.0), n = 59
Blood eosinophils ($\times 10^9$/L)	0.24 (0.13-0.38)
Serum IgE (IU/mL)	160 (40-373)
FENO (ppb)	25 (17-46), n = 66
Periostin (ng/mL), serum or plasma	24.5 (19.6-30.6)
YKL-40 (ng/mL), serum or plasma	67 (42-111), n = 65

J Allergy Clin Immunol 2012;130:647-54.


A
serum periostin (ng/ml)
50
40
30
20
10
p<0.001
< 3%
N=23
≥ 3%
N=36
sputum eosinophil status
B
serum periostin (ng/ml)
50
40
30
20
10
p=0.023
< 22/mm²
N=29
≥ 22/mm²
N=30
tissue eosinophil status
C
sputum eosinophils (%)
50
40
30
20
10
0
composite airway
eosinophil score
0
1
2
0
20
40
60
80
100
biopsy eosinophils (#/mm²)
D
serum periostin (ng/ml)
50
40
30
20
10
p=0.002
0 (N=13)
sputum eos < 3%
AND Bx eos < 22/mm²
1 (N=16)
sputum eos ≥ 3%
OR Bx eos ≥ 22/mm²
2 (N=19)
sputum eos ≥ 3%
AND Bx eos ≥ 22/mm²
composite airway eosinophil score

Sensitivity of biomarkers for eosinophilic inflammation



Clinical implications: Periostin levels in peripheral blood identify asthmatic patients with increased airway eosinophil numbers and therefore might be a clinically useful biomarker to select patients for T_H2-targeted asthma therapies.

Contents

- New treatment options
- Effect of treatment adjustment
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- **Scoring systems for predicting exacerbation**
- Results from GWAS

Scoring system predicting outcome

ADAS

The Asthma Disease Activity Score: A discriminating, responsive measure predicts future asthma attacks

Steven Greenberg, MD,[a,b] Nancy Liu, PhD,[c] Amarjot Kaur, PhD,[c] Mani Lakshminarayanan, PhD,[c] Yijie Zhou, PhD,[c] Linda Nelsen, MHS,[d] Davis F. Gates, Jr, PhD,[c] Wen-Ling Kuo, PhD,[c] Steven S. Smugar, MD,[e] Theodore F. Reiss, MD,[a]* Neil Barnes,[f] Anne Fuhlbrigge, MD, MPH,[g] Henry Milgrom, MD,[h] Michael Schatz, MD, MS,[i] and Barbara Knorr, MD[a] *Whitehouse Station, NJ, New York, NY, London, United Kingdom, Boston, Mass, Denver, Colo, and San Diego, Calif*

- Classifying asthma severity or activity using weighted composite measures of asthma disease activity ?
- Discriminant and multiple regression analyses based on 2 clinical trials

- ADAS-6=4.6534 +0.1118(Rescue b-agonist puffs/day)-0.0236(FEV1 %)-0.2602(AQLQ-Symptom domain)+ 4.3633(Diurnal variability in PEF)+0.5765 (Diurnal variability in rescue b-agonist use)+0.1226(Nighttime awakenings)

- Definition of asthma activity : GINA/ ERP-3
  -high : any of the lower-limit criteria (FEV1 <60% or >4 puffs/d of rescue use)
  - low : all of the upper-limit criteria (FEV1 >80% & <1 puff/d of rescue use).

J Allergy Clin Immunol 2012;130:1071-7

TABLE I. ADAS-6 values and various outcome measures in subjects with different levels of overall disease activity at week 12

End point	Disease activity	Mean	SD	T values (mean difference/SE)* Moderate vs low	Moderate vs high	High vs low
ADAS-6	Low	1.6	0.5	10.2	−28.9	25.5
	Moderate	2.7	0.8			
	High	4.4	1.1			
ADAS-4	Low	1.5	0.4	8.5	−32.7	25.5
	Moderate	2.3	0.5			
	High	4.0	1.1			
FEV_1 (L)	Low	3.2	0.8	−5.2	12.0	−11.4
	Moderate	2.8	0.7			
	High	2.3	0.8			
Rescue β-agonist use (puffs/d)	Low	0.3	0.3	3.9	−26.9	17.8
	Moderate	1.5	1.1			
	High	5.6	3.5			
Nighttime awakenings (nights/wk)	Low	0.2	0.3	3.2	−26.0	16.6
	Moderate	1.0	1.2			
	High	4.2	2.7			
AQLQ	Low	5.3	0.6	−5.8	15.2	−13.8
	Moderate	4.6	0.9			
	High	3.8	1.1			
Daytime symptom score	Low	0.6	0.5	8.3	−17.8	17.6
	Moderate	1.4	0.9			
	High	2.3	0.9			

*The greater the absolute value of the T values, the more discriminating the end point.

TABLE II. Predictive validity: estimated odds ratio of an asthma attack between weeks 3 and 12 given 1 SD unit of change at week 3

Change in outcome variable (1 SD) at week 3	Estimated odds ratio	Lower bound of 95% CI	Upper boun of 95% CI
ADAS-6	2.05	1.67	2.52
ADAS-4	2.07	1.71	2.52
FEV_1 (L)	1.67	1.40	2.00
Rescue β-agonist use (puffs/d)	1.57	1.31	1.89
Nighttime awakenings (nights/wk)	1.41	1.18	1.69
AQLQ score	1.36	1.14	1.63
Daytime symptom score	1.66	1.39	1.99

Clinical implications: Use of this novel, weighted, and highly responsive measure of asthma disease activity might better differentiate levels of disease burden and help identify populations of responders to asthma therapy.

Scoring system for prediction of asthma outcome

Severity of Asthma Score Predicts Clinical Outcomes in Patients With Moderate to Severe Persistent Asthma

Mark D. Eisner, MD, MPH; Ashley Yegin, MD; and Benjamin Trzaskoma, MS

- Severity of Asthma Score : Validated disease-specific questionnaire with frequency of asthma symptoms, use of systemic CS, use of other asthma medications, and history of hospitalization or intubation for asthma.
- Ability of SOA to predict clinical outcomes?
- EXCELS (Epidemiological Study of Xolair [omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma)

- Baseline scores for SOA, ACT, work productivity and impairment index-asthma (WPAI-A), and FEV 1 %
- 5 important clinical outcome (hospitalization, ER visit, steroid burst, Exacerbation, unscheduled office visit)

CHEST 2012; 141(1):58–65

Severity of Asthma : scoring and correlation

Table 1—*Severity of Asthma: Items and Scoring*

Item No.	Description	Scoring
1	Symptoms during past 2 wk? (choose only one)	0-4
	None	0
	Minimal	1
	Occasional	2
	Most days or nights	3
	Every day or night	4
	Systemic corticosteroid use? (choose one or more)	
2	Ever used	0 or 2
3	Used in the past y	0 or 2
4	Used ≥3 mo within past 2 y	0 or 3
	Other asthma medication use during past 2 wk?	
5	Inhaled β-agonists (SABA/LABA) (none, <2, ≥2 puffs/d)	0, 1, or 2
6	ICS by MDI (none, <20, ≥20 puffs/d)	0, 1, or 2
7	Cromolyn/nedocromil	0 or 1
8	Anticholinergic therapy	0 or 1
9	Theophylline, oral β-agonist, or leukotriene modifier	0 or 1
10	Antihistamine, decongestant, or nasal spray	0 or 1
11	Home nebulizer use	0 or 1
12	Ever hospitalized for asthma? (no or yes)	0 or 3
13	Ever intubated for asthma? (no or yes)	0 or 5
	Total possible score	0-28

Table 3—*Correlation of SOA Score With Other Asthma Instruments at Baseline*

Comparison of Instruments (Ranked by |r|)	EXCELS Nonomalizumab Cohort		
	r^a	*P* Value	No.[b]
SOA vs ACT	−0.54	<.0001	2,852
SOA vs WPAI-A	0.40	<.0001	2,667
SOA vs FEV_1 % predicted	−0.15	<.0001	2,620
ACT vs WPAI-A	−0.67	<.0001	2,676
ACT vs FEV_1 % predicted	0.15	<.0001	2,626
WPAI-A vs FEV_1 % predicted	−0.11	<.0001	2,458

CART analysis and logistic regression

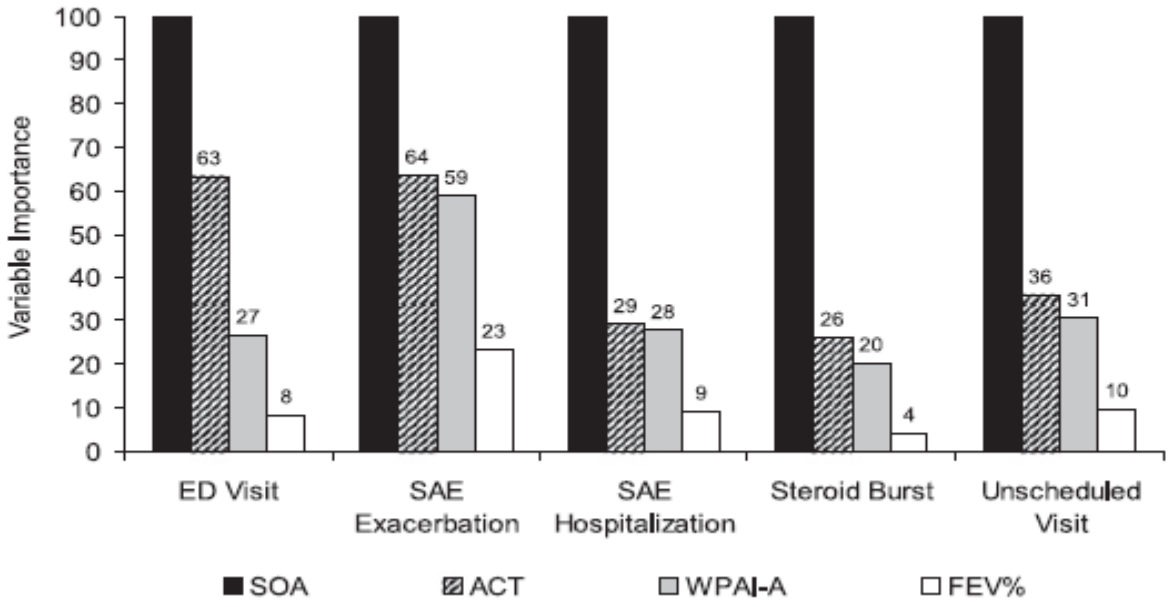


Table 4—*Logistic Regression Analysis: First-Stage Modeling*

Asthma Assessment Tool	Steriod Bursts	ED Visits	SAE Exacerbations	SAE Hospitalizations	Unscheduled Doctor Visits
ACT	.1203[a]	< .0001	.0165	ns (.4806)	.0006

- **SOA score was a powerful predictor of adverse clinical outcomes in moderate to severe asthma, as evaluated by either logistic regression analysis or CART analysis.**

Contents

- New treatment options
- Effect of treatment adjustment
- Useful diagnostic markers in asthma
- Scoring systems for predicting exacerbation
- **Results from GWAS**

GWAS for severe asthma

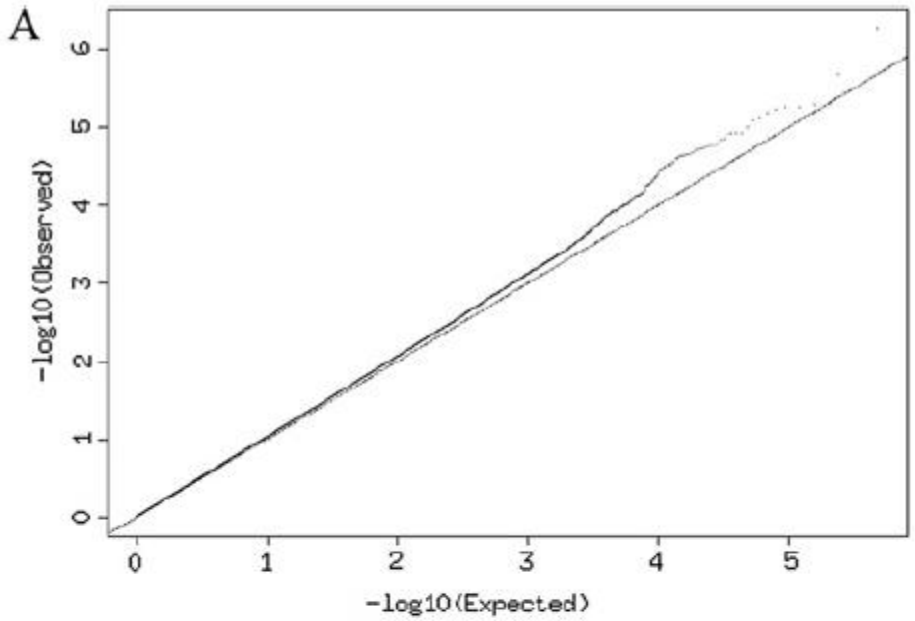
Genome-wide association study to identify genetic determinants of severe asthma

Y I Wan,[1,*] N R G Shrine,[2,*] M Soler Artigas,[2] L V Wain,[2] J D Blakey,[1]

- The genetic basis for developing asthma has been extensively studied, mostly focused on mild to moderate disease, resulting unclear genetic risk factors for severe asthma
  → To identify common genetic variants affecting susceptibility to severe asthma.

- A genome-wide association study in 933 European ancestry individuals with severe asthma and 3346 clean controls(AUGOSA study)
  - 480,889 genotyped SNPs tested
  - Largest GWAS of severe asthma to date
- Validation cohort with 231 severe asthma and 1345 controls (AAGC study)

Thorax 2012;**67**:762–768.


A
-log10(Observed)
-log10(Expected)
0
1
2
3
4
5
6

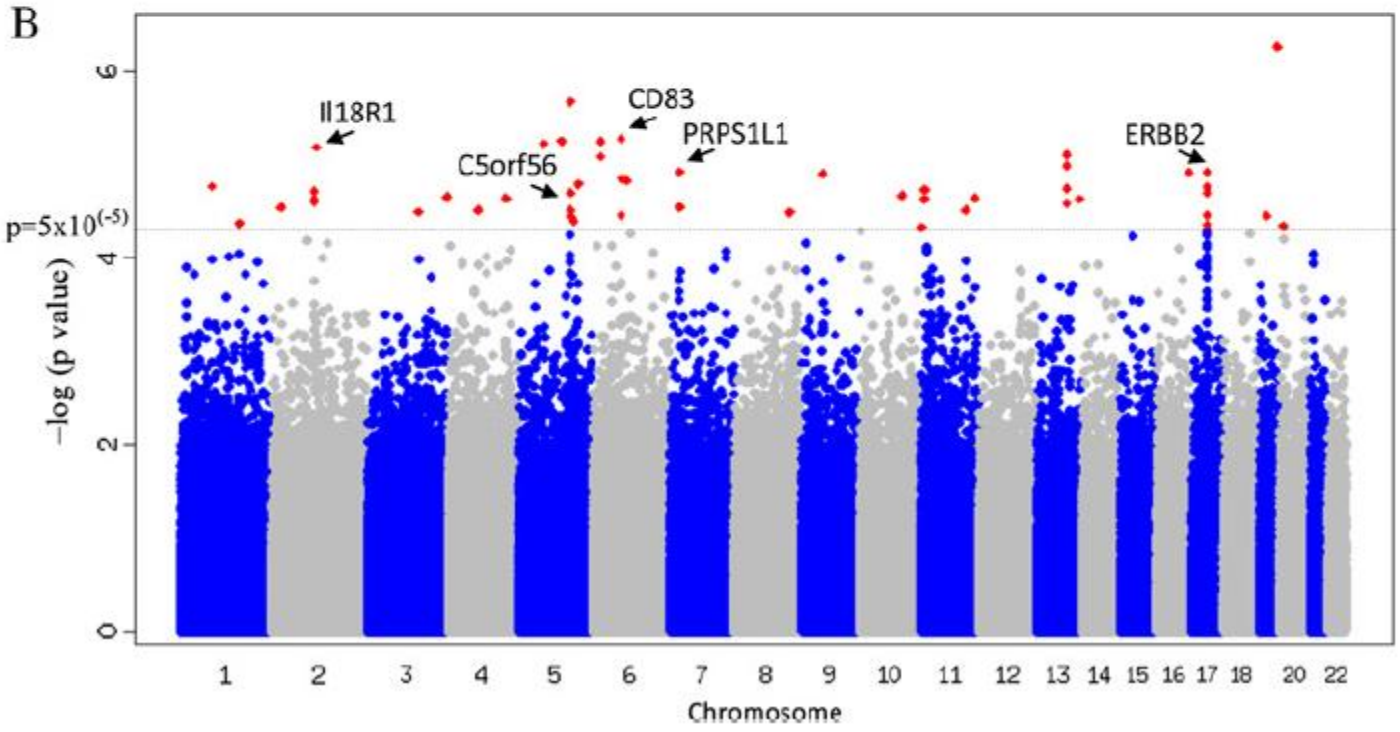

B
Il18R1
CD83
PRPS1L1
C5orf56
ERBB2
p=5x10(-5)
-log (p value)
Chromosome
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22

Table 1 Single nucleotide polymorphisms (SNPs) showing highest association signals for severe asthma

				AUGOSA (933 cases, 3346 controls)			AAGC (231 cases, 1345 controls)			Meta-analysis	
Chromosome	Locus	SNP	Position	r^2_{imp}	OR (95% CI)	p Value	r^2_{imp}	OR (95% CI)	p Value	OR (95% CI)	p Value
Six genotyped SNPs from regions identified in genotyped SNP analyses											
2	IL18R1	rs3771166	102352654	GENO	0.79 (0.71 to 0.88)	**$1.93\times10^{(-5)}$**	GENO	0.71 (0.57 to 0.87)	**0.001**	0.77 (0.70 to 0.85)	$1.24\times10^{(-7)}$
5	C5orf56	rs11745587	131824821	GENO	1.30 (1.17 to 1.45)	**$2.09\times10^{(-6)}$**	GENO	1.13 (0.92 to 1.39)	0.25	1.26 (1.15 to 1.39)	$2.13\times10^{(-6)}$
6	CD83	rs9382936	14173097	GENO	1.31 (1.17 to 1.48)	**$5.61\times10^{(-6)}$**	GENO	1.00 (0.79 to 1.25)	0.98	1.24 (1.12 to 1.38)	$5.68\times10^{(-5)}$
7	PRPS1L1	rs12699949	18010787	GENO	0.77 (0.69 to 0.87)	**$1.19\times10^{(-5)}$**	GENO	0.89 (0.72 to 1.10)	0.27	0.80 (0.72 to 0.88)	$1.19\times10^{(-5)}$
13	*Intergenic*	rs2496764	84477159	GENO	1.34 (1.18 to 1.52)	**$7.86\times10^{(-6)}$**	GENO	0.99 (0.78 to 1.27)	0.96	1.26 (1.12 to 1.41)	$8.03\times10^{(-5)}$
17	ERBB2	rs1810132	35119531	GENO	1.28 (1.14 to 1.43)	**$1.73\times10^{(-5)}$**	GENO	1.07 (0.86 to 1.32)	0.56	1.23 (1.11 to 1.36)	$4.54\times10^{(-5)}$
Four imputed SNPs in regions above with a lower p value than the original genotyped SNP in imputed SNP analyses											
2	IL18R1	rs9807989	102337632	0.91	0.76 (0.67 to 0.85)	**$5.20\times10^{(-6)}$**	0.91	0.72 (0.58 to 0.89)	**0.003**	0.75 (0.68 to 0.83)	$5.59\times10^{(-8)}$
7	PRPS1L1	rs12699948	18010735	0.92	0.75 (0.66 to 0.85)	**$4.84\times10^{(-6)}$**	0.93	0.92 (0.74 to 1.15)	0.46	0.79 (0.71 to 0.88)	$1.44\times10^{(-5)}$
13	*Intergenic*	rs9547037	84476839	0.90	1.38 (1.20 to 1.58)	**$6.60\times10^{(-6)}$**	0.90	1.00 (0.78 to 1.29)	0.97	1.28 (1.13 to 1.44)	$8.01\times10^{(-5)}$
17	STARD3	rs9972882	35061224	0.98	1.32 (1.17 to 1.49)	**$5.17\times10^{(-6)}$**	0.99	1.07 (0.85 to 1.34)	0.55	1.26 (1.13 to 1.40)	$1.64\times10^{(-5)}$
Two SNPs with $p>10^{(-5)}$ responsible for secondary peaks in regions with known asthma genes											
2	IL1R1	rs13035227	102130269	0.96	1.36 (1.16 to 1.58)	**$8.91\times10^{(-5)}$**	GENO	1.53 (1.17 to 1.99)	**0.002**	1.40 (1.22 to 1.59)	$6.69\times10^{(-7)}$
5	IL13	rs847	132024568	0.86	1.35 (1.17 to 1.55)	**$4.05\times10^{(-5)}$**	0.94	1.12 (0.88 to 1.43)	0.37	1.29 (1.14 to 1.45)	$6.43\times10^{(-5)}$
Twelve SNPs from new regions identified by imputation with $p<10^{(-5)}$ and $r^2_{imp}=0.7$ (includes two secondary peaks in previously identified 17q12-21 region)											
2	*Intergenic*	chr2:211694960	211694960	0.70	1.76 (1.40 to 2.21)	**$1.27\times10^{(-6)}$**	0.78	1.11 (0.73 to 1.70)	0.62	1.59 (1.30 to 1.94)	$6.80\times10^{(-6)}$
5	FLJ37543	rs7715669	60972053	GENO	0.74 (0.65 to 0.84)	**$5.92\times10^{(-6)}$**	GENO	0.93 (0.74 to 1.18)	0.56	0.78 (0.69 to 0.87)	$2.29\times10^{(-5)}$
5	NDFIP1	rs6867913	141426164	0.99	0.72 (0.63 to 0.82)	**$1.74\times10^{(-6)}$**	0.97	0.90 (0.69 to 1.15)	0.39	0.75 (0.67 to 0.85)	$3.82\times10^{(-6)}$
6	GCLC	rs9395865	53415653	GENO	0.76 (0.67 to 0.85)	**$5.27\times10^{(-6)}$**	GENO	1.15 (0.93 to 1.42)	0.19	0.84 (0.76 to 0.93)	$9.27\times10^{(-4)}$

- The first GWAS of severe asthma was undertaken which identified the contribution of some but not all genetic loci previously associated with mild to moderate disease. Suggestive evidence for a number of novel loci associated with severe disease is also reported.
- Novel loci, which may be specific to severe asthma, potentially provide further insight into disease mechanisms and warrant further study.

AAGC, Australian Asthma Genetics Consortium; AUGOSA, Asthma UK Genetics of Severe Asthma.

IL6R variation SNP and lung function/AE

The *IL6R* variation $Asp^{358}Ala$ is a potential modifier of lung function in subjects with asthma

Gregory A. Hawkins, PhD,[a,b] Mac B. Robinson, PhD,[a] Annette T. Hastie, PhD,[a,b] Xingnan Li, PhD,[a,b] Huashi Li, MS,[a,b] Wendy C. Moore, MD,[a,b] Timothy D. Howard, PhD,[a] William W. Busse, MD,[b] Serpil C. Erzurum, MD,[b] Sally E. Wenzel, MD,[b] Stephen P. Peters, MD, PhD,[a,b] Deborah A. Meyers, PhD,[a,b] and Eugene R. Bleecker, MD,[a,b] on behalf of the National Heart, Lung, and Blood Institute–sponsored Severe Asthma Research Program (SARP)* *Winston-Salem, NC*

- IL6R SNP rs4129267 : an asthma susceptibility locus
  - in linkage disequilibrium with the IL6R coding SNP rs2228145 (Asp358Ala)
  - IL6R coding change ∝ IL-6R shedding, IL-6 trans-signaling.
- IL6R SNP rs2228145 respect to asthma severity phenotypes?

- IL6R SNP rs2228145 in subjects of European ancestry with asthma from the Severe Asthma Research Program (SARP).
- Lung function associations were replicated in the Collaborative Study on the Genetics of Asthma (CSGA) cohort.
- Serum soluble IL-6R in SARP subjects
- IHC stain for qualitative evaluation of IL-6R protein expression in tissue/cells

(J Allergy Clin Immunol 2012;130:510-5.)

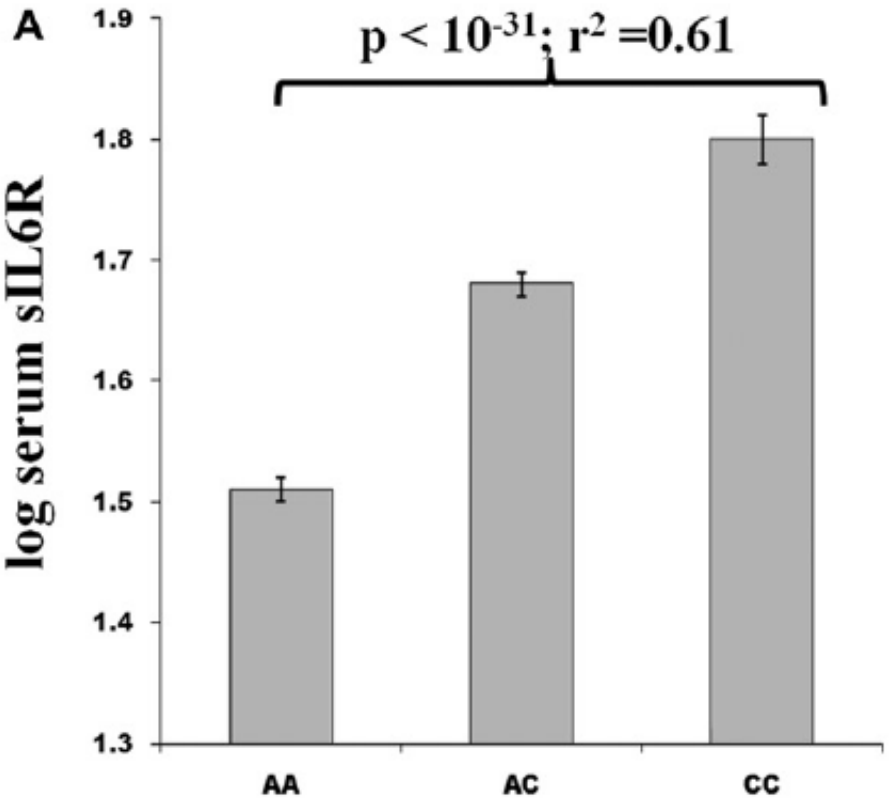
TABLE II. Association of the *IL6R* mutation Asp^{358}Ala with lung function in subjects with asthma in SARP, CSGA, and combined analyses

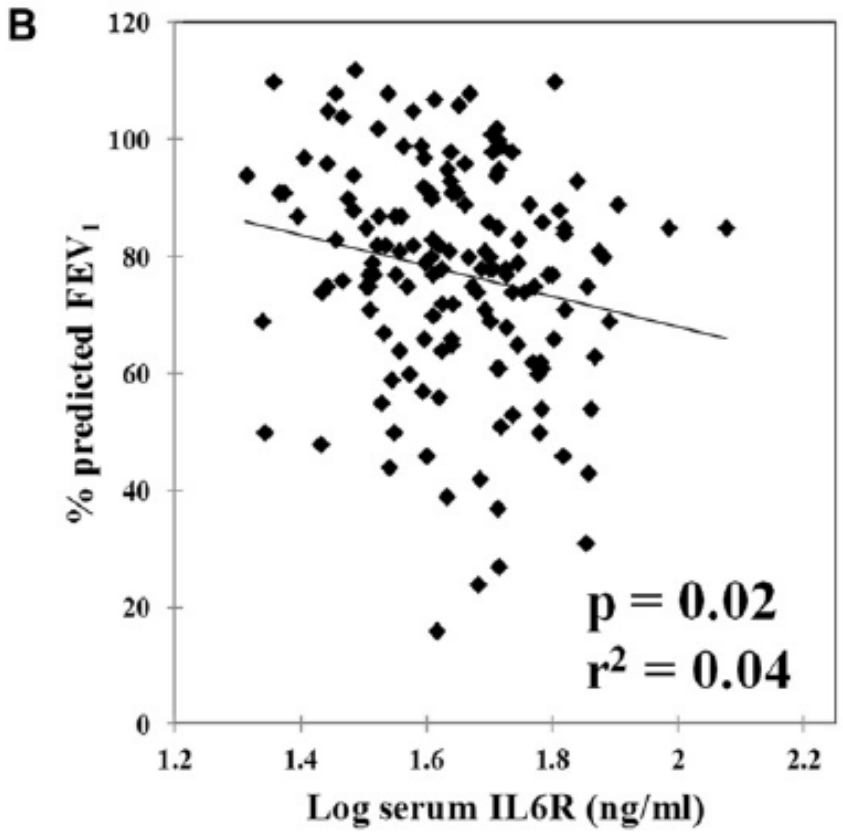
	% Predicted FEV_1			% Predicted FVC			FEV_1/FVC ratio			Log PC_{20}		
	N	Mean (SD)	*P* value	N	Mean (SD)	*P* value	N	Mean (SD)	*P* value	N	Mean (SD)	*P* value
SARP												
rs2228145												
AA	160	74.9 ± 23.4		154	85.5 ± 18.6		156	0.71 ± 0.13		102	0.14 ± 0.8	
AC	241	75.9 ± 22.6	.005	225	87.5 ± 18.5	.047	235	0.71 ± 0.13	.01	167	0.14 ± 0.7	.58
CC	98	67.7 ± 23.8		90	81.7 ± 19.1		95	0.67 ± 0.13		59	0.04 ± 0.6	
CSGA												
rs2228145												
AA	86	89.8 ± 17.14		85	94.5 ± 14.8		85	0.80 ± 0.01		87	0.26 ± 0.7	
AC	100	83.3 ± 15.43	.008	99	90.8 ± 13.1	.15	99	0.77 ± 0.12	.07	96	0.06 ± 0.7	.017
CC	39	82.4 ± 25.01		38	90.3 ± 19.9		38	0.76 ± 0.15		35	−0.13 ± 0.6	
Combined												
rs2228145												
AA	246	80.1 ± 22.5		239	88.7 ± 17.8		241	0.74 ± 0.13		189	0.20 ± 0.7	
AC	341	78.1 ± 21.0	.003	324	88.5 ± 17.1	.08	334	0.73 ± 0.13	.006	263	0.11 ± 0.7	.033
CC	137	71.9 ± 24.96		128	84.2 ± 19.7		133	0.69 ± 0.14		94	−0.02 ± 0.6	

TABLE III. Evaluation of *IL6R* rs2228145 (Asp^{358}Ala) and serum sIL-6R levels in SARP asthma phenotypic clusters

	Cluster 1: mild	Cluster 2: moderate	Clusters 4 + 5: severe	*P* value
rs2228145 (Asp^{358}Ala)	N	N	N	
AA	23	48	41	.003
AC	40	80	49	
CC	7	30	37	
Log serum sIL-6R	1.58 ± 0.11 (n = 21)	1.64 ± 0.14 (n = 62)	1.69 ± 0.13 (n = 40)	.016*
Mean $ppFEV_1$	99.1%	83.4%	54.3%	<.0001*

SNP, IL6 R and lung function





- The IL6R coding SNP rs2228145 (Asp358Ala) is a potential modifier of lung function in subjects with asthma and might identify subjects at risk for more severe asthma.
- IL-6 transsignaling might have a pathogenic role in the lung.

Summary

- Many studies for new treatment strategy based on phenotypic variation were in progress.
- Treatment strategy with risk- benefit evaluation for treatment adjustment is needed.

- Many diagnostic markers, which old or new, should be evaluated for their sensitivity, specificity and clinical implication, in various replicative populations.
- Scoring systems for disease activity and prediction of exacerbation could have another clinical value.

- With more extensive GWAS data for genetic susceptibility, differentiation of severe asthma candidates or pharmacogenetic response could be another treatment concern.

Thank you for your attention!!