Biomarkers and Treatment Strategies in Type2-low Asthma

Chin Kook Rhee, MD, PhD

Professor
Division of Pulmonary, Allergy and Critical Care Medicine
Department of Internal Medicine
Seoul St. Mary's Hospital
The Catholic University of Korea

Contents

- DDx
- Tezepelumab
- Tiotropium
- Macrolide
- TKI
- Roflumilast
- Obesity

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Box 1. Differential diagnoses in severe asthma*.

- **COPD**
- **Bronchiectasis**
- **Sarcoidosis**
- **Bronchiolitis obliterans**
- **Cystic Fibrosis**
- **Hypersensitivity pneumonitis**
- **Hypereosinophilic lung diseases**
- **Tracheobronchomalacia**
- **Pulmonary embolism**
- **Coronary Heart Failure**
- **Endobronchial tumor/foreign body**

*Differential diagnostic conditions which commonly co-exist with asthma are listed under co-morbidities in Table 2.

Porsbjerg C. Eur Clin Respir J 2018; 5: 1440868.

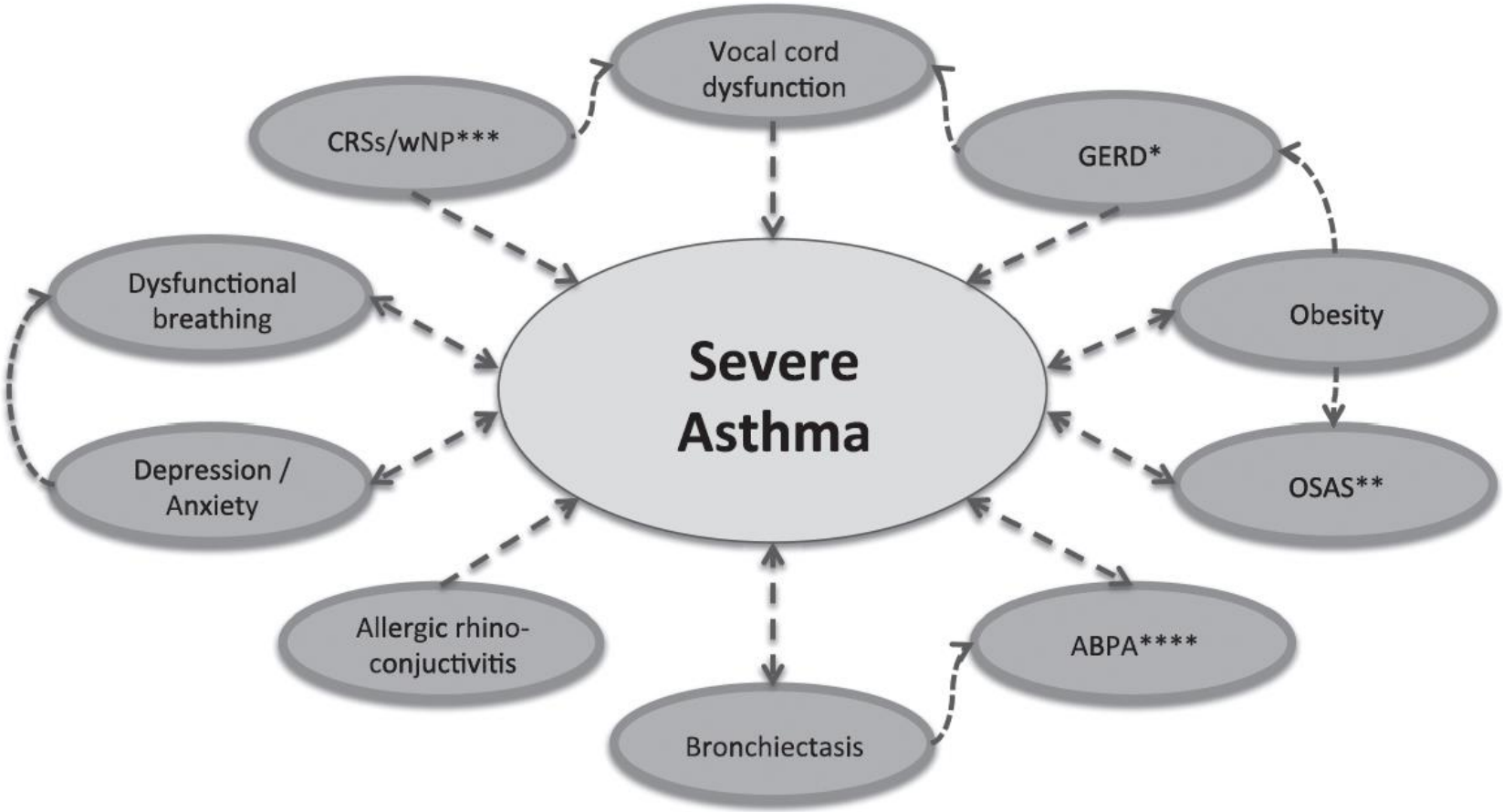

Figure 1 Co-morbidities in severe asthma: possible cause-and-effect relationships. ABPA, allergic bronchopulmonary aspergillosis; CRSsNP, chronic rhinosinusitis (CRS) without nasal polyps; CRSwNP, CRS with nasal polyps; GERD, gastroesophageal reflux disease; OSAS, obstructive sleep apnoea syndrome.

Respirology. 2017;22(4):651-661.

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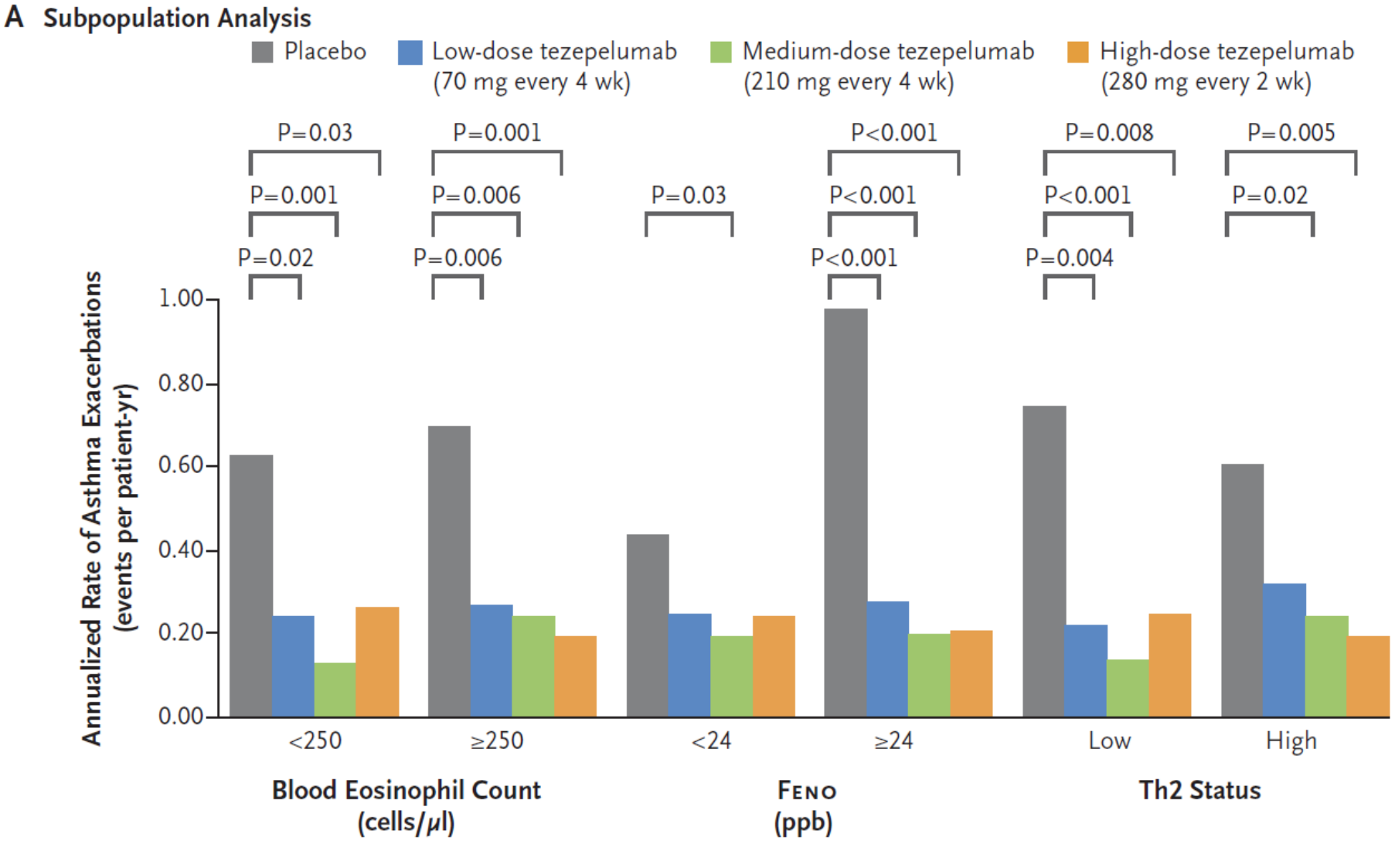
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

Corren J. N Engl J Med 2017; 377: 936-946.



Corren J. N Engl J Med 2017; 377: 936-946.

Clinical characteristics		Placebo (N = 148)	Low-dose tezepelumab (N = 145)	Medium-dose tezepelumab (N = 145)	High-dose tezepelumab (N = 146)	Tezepelumab Total (N = 436)
Inhaled glucocorticoid dose level	Medium(%)/High(%)	73 (49.3)/75 (50.7)	71 (49.0)/74 (51.0)	70 (48.3)/75 (51.7)	72 (49.3)/74 (50.7)	213 (48.9)/223 (51.1)
FEIA IgE	Positive(%)/Negative (%)	83 (61.5)/52 (38.5)	71 (53.0)/63 (47.0)	80 (60.2)/53 (39.8)	74 (55.2)/60 (44.8)	225 (56.1)/176 (43.9)
Eosinophil count (cells/µl)	Mean(SD) Median(min, max) ≥250, no. (%) <250, no. (%)	366 (323) 270.0 (0, 1870) 86 (58.1) 62 (41.9)	345 (284) 270.0 (10, 1600) 85 (58.6) 60 (41.4)	359 (347) 275.0 (0, 3180) 83 (57.2) 62 (42.8)	378 (423) 255.0 (0, 3990) 85 (58.2) 61 (41.8)	361 (356) 270.0 (0, 3990) 253 (58.0) 183 (42.0)
Total serum IgE (IU/ml)	Mean(SD) Median(min, max)	447 (1232) 135.0 (4, 11860)	314 (870) 109.3 (2, 7423)	464 (1366) 135.4 (2, 11430)	344 (579) 138.1 (2, 3814)	374 (992) 126.8 (2, 11430)
Th2 status^	Low, no. (%) High, no. (%)	71 (48.3) 76 (51.7)	81 (56.3) 63 (43.8)	76 (53.1) 67 (46.9)	78 (53.8) 67 (46.2)	235 (54.4) 197 (45.6)
F_{ENO} (ppb)	(n) Mean (SD)	(146) 36.3 (38.9)	(144) 34.5 (46.9)	(143) 30.4 (29.4)	(141) 32.6 (33.9)	(428) 32.5 (37.5)
	Median(min, max)	21.5 (3.5, 276.3)	22.0 (2.5, 349.0)	20.5 (4.0, 152.5)	19.7 (2.0, 217.5)	21.0 (2.0, 349.0)
	<24 ppb, no. (%)	80 (54.8)	77 (53.5)	83 (58.0)	79 (56.0)	239 (55.8)
	≥24 ppb, no. (%)	66 (45.2)	67 (46.5)	60 (42.0)	62 (44.0)	189 (44.2)

Corren J. N Engl J Med 2017; 377: 936-946.

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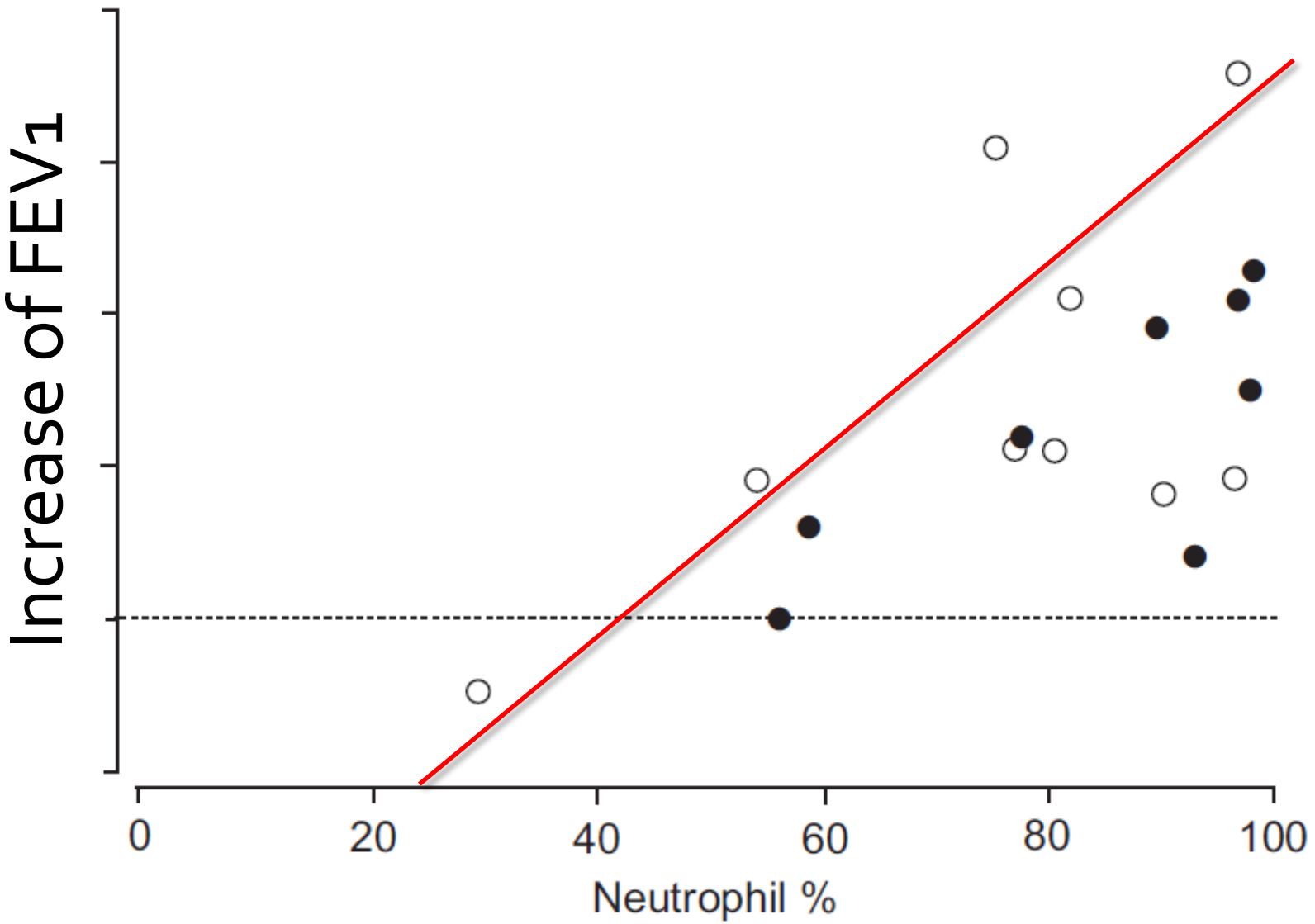
CORRE

Tiotr

none



Eur Respir J. 2008;31(6):1379-80.

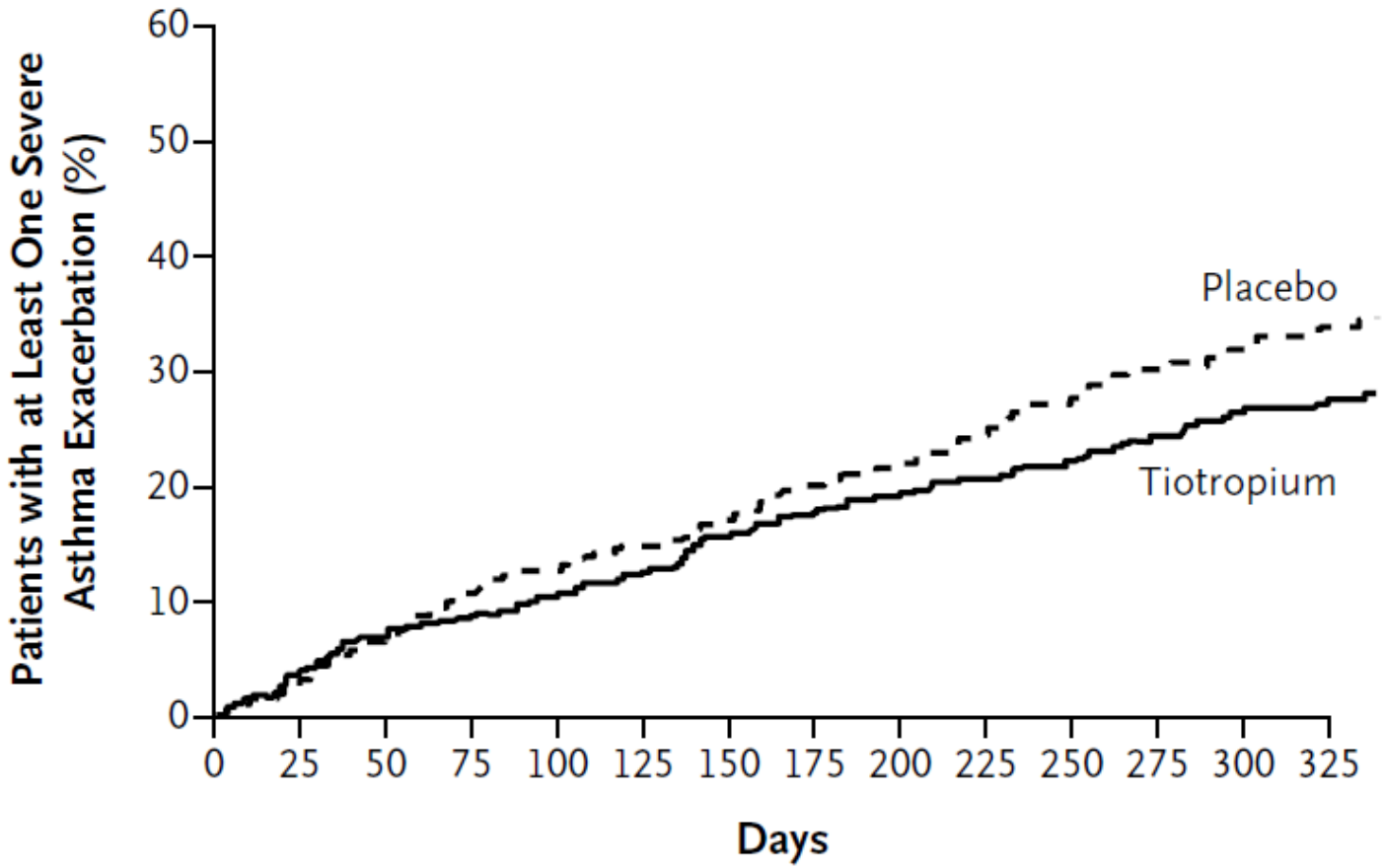
ORIGINAL ARTICLE

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

- Severe asthma
  - At least one exacerbation that was treated with systemic glucocorticoids in the previous year
- ICS+LABA
- Tio add on

N Engl J Med. 2012;367(13):1198-207.

C Severe Exacerbation



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

N Engl J Med. 2012;367(13):1198-207.

- Inclusion criteria
  - Age
    - 18 ~ 75
  - History
    - 5-year or longer history of asthma that was diagnosed before the age of 40
  - Persistent airflow limitation
    - postBD FEV_1 ≤ 80%
    - postBD FVC ≤ 70%
  - Smoking
    - Lifelong nonsmoker
    - Smoking ≤ 10 pyrs, ex smoker

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‡					
Race — no. (%)§					
White					
Median duration of asthm					
3–5					
Use of omalizumab — %					
Mean daily no. of puffs of					
Use of theophyllines — %					
Use of leukotriene modifi					
AQLQ score**§§					
Percent of predicted value before br		±12.4	54.6±12	.1±12.8	55.0
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

FEV1 (L) 1.603±0.540 1.596±0.546 1.558±0.537

preBD FEV1 (%) 54.8±12.4 54.6±12.2 54.6±12.2

postBD FEV1 (%) 62.2±12.7 61.5±12.5 62.7±12.6

Mean daily no. of puffs of 217±217 201±211 230±223

FVC (L) 2.744±0.900 2.715±0.923 2.704±0.912

FEV1/FVC (%) 58.4% 58.8% 57.6%

Figure 1. Screening, Randomization, and Study Completion.

A total of five patients in trial 2 were excluded because of compliance issues after randomization: two patients in the placebo group and three patients in the tiotropium group. See the Supplementary Appendix for additional information.

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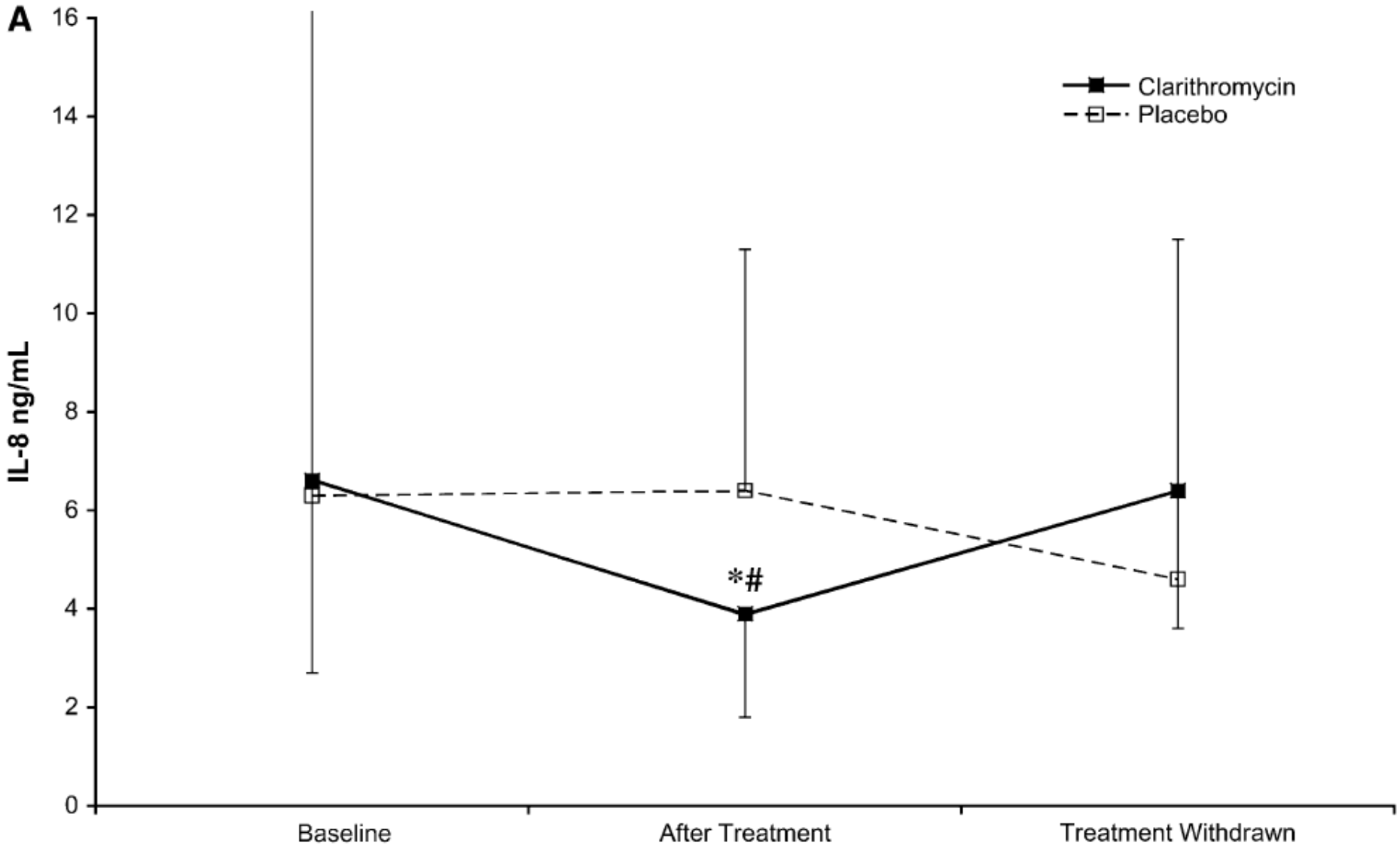
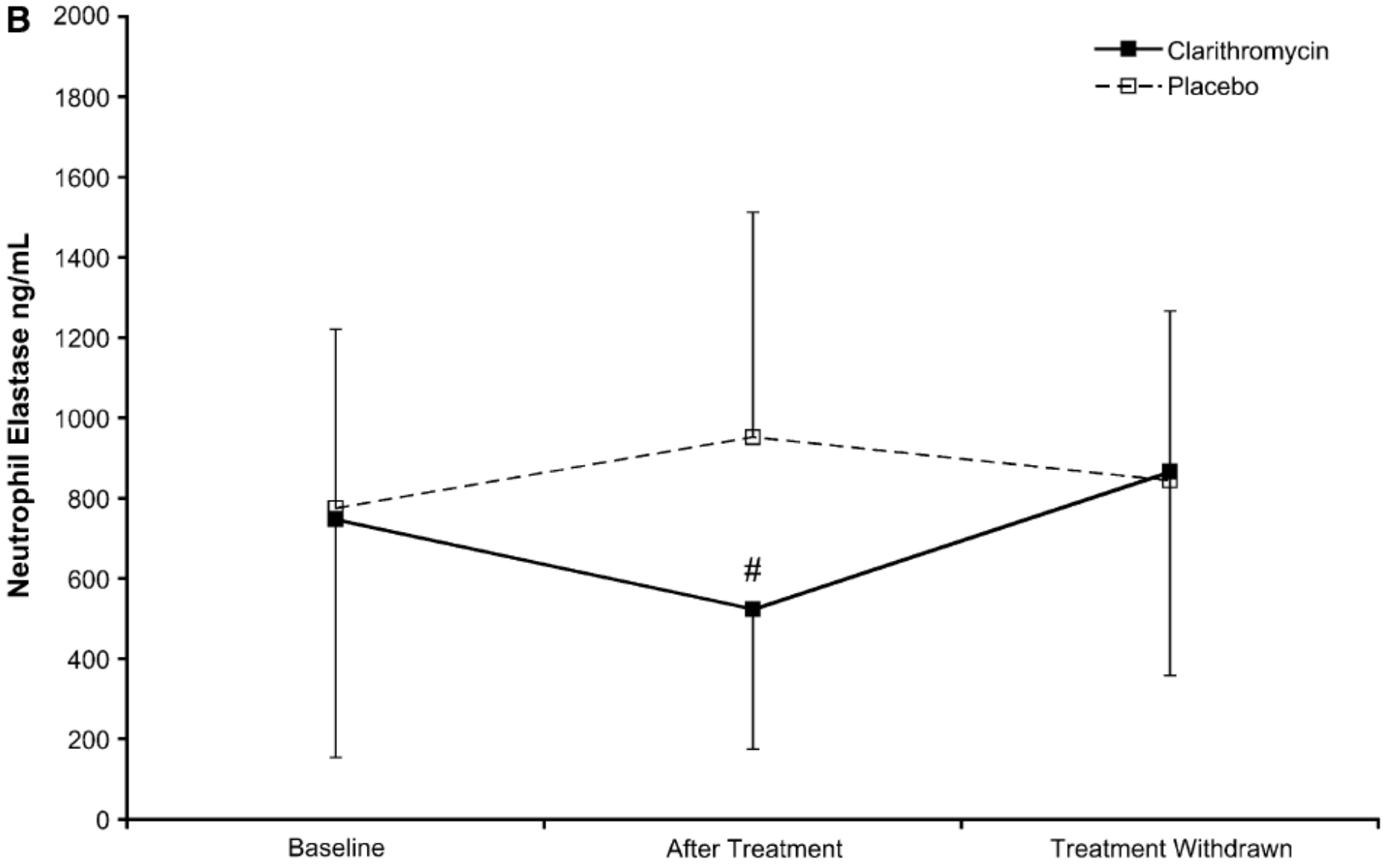
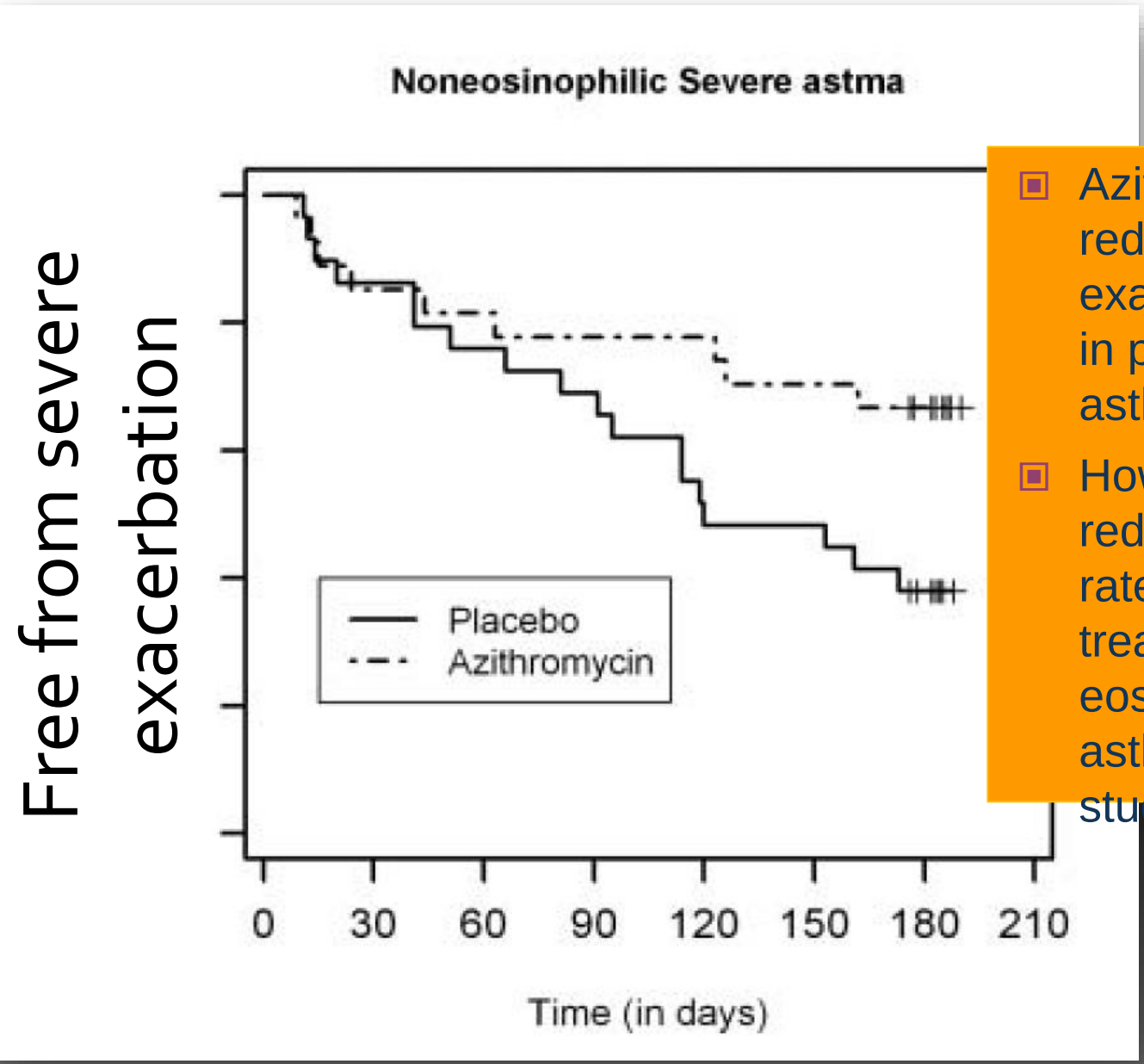
Macrolides

Curr Opin Pulm Med. 2014;20(1):95-102.



Simpson JL. Am J Respir Crit Care Med 2008; 177: 148-155.


B
Clarithromycin
Placebo
Neutrophil Elastase ng/mL
2000
1800
1600
1400
1200
1000
800
600
400
200
0
#
Baseline
After Treatment
Treatment Withdrawn



- Azithromycin did not reduce the rate of severe exacerbations and LRTI in patients with severe asthma.
- However, the significant reduction in exacerbation rate in azithromycin-treated patients with non-eosinophilic severe asthma warrants further study.

Brusselle GG. Thorax 2013; 68: 322-329.

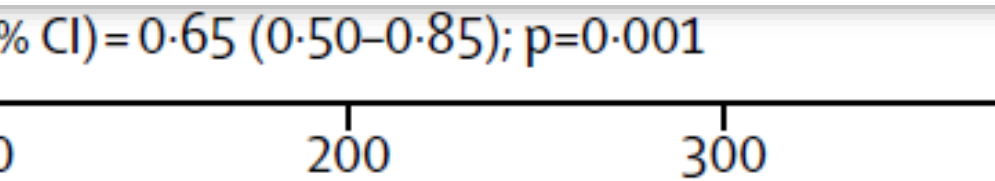
- Inclusion criteria
  - Never-smokers or ex-smokers with a smoking history of ≤10 pack-years

- Noneosinophilic group
  - FeNO ≤ upper limit normal
  - Blood eosinophil ≤ 200

Brusselle GG. Thorax 2013; 68: 322-329.

	Number	Exacerbations per person-year		Incidence rate ratio (95% CI)
		Placebo	Azithromycin	
Non-eosinophilic asthma	224	1·74	1·15	0·66 (0·47–0·93)
Eosinophilic asthma	196	1·98	0·96	0·52 (0·29–0·94)
Inhaled corticosteroid dose adjustment	420	1·86	1·07	0·58 (0·46–0·74)
Frequ				3)
Cough and sputum VAS	48	1·72	0·79	0·49 (0·26–0·95)
Bacteria–negative	188	1·85	1·18	0·61 (0·52–0·72)*
Bacteria–positive	48	2·64	1·11	0·39 (0·22–0·69)*

*Significant interaction between subgroup and treatment.



The Lancet. 2017;390(10095):659-668.

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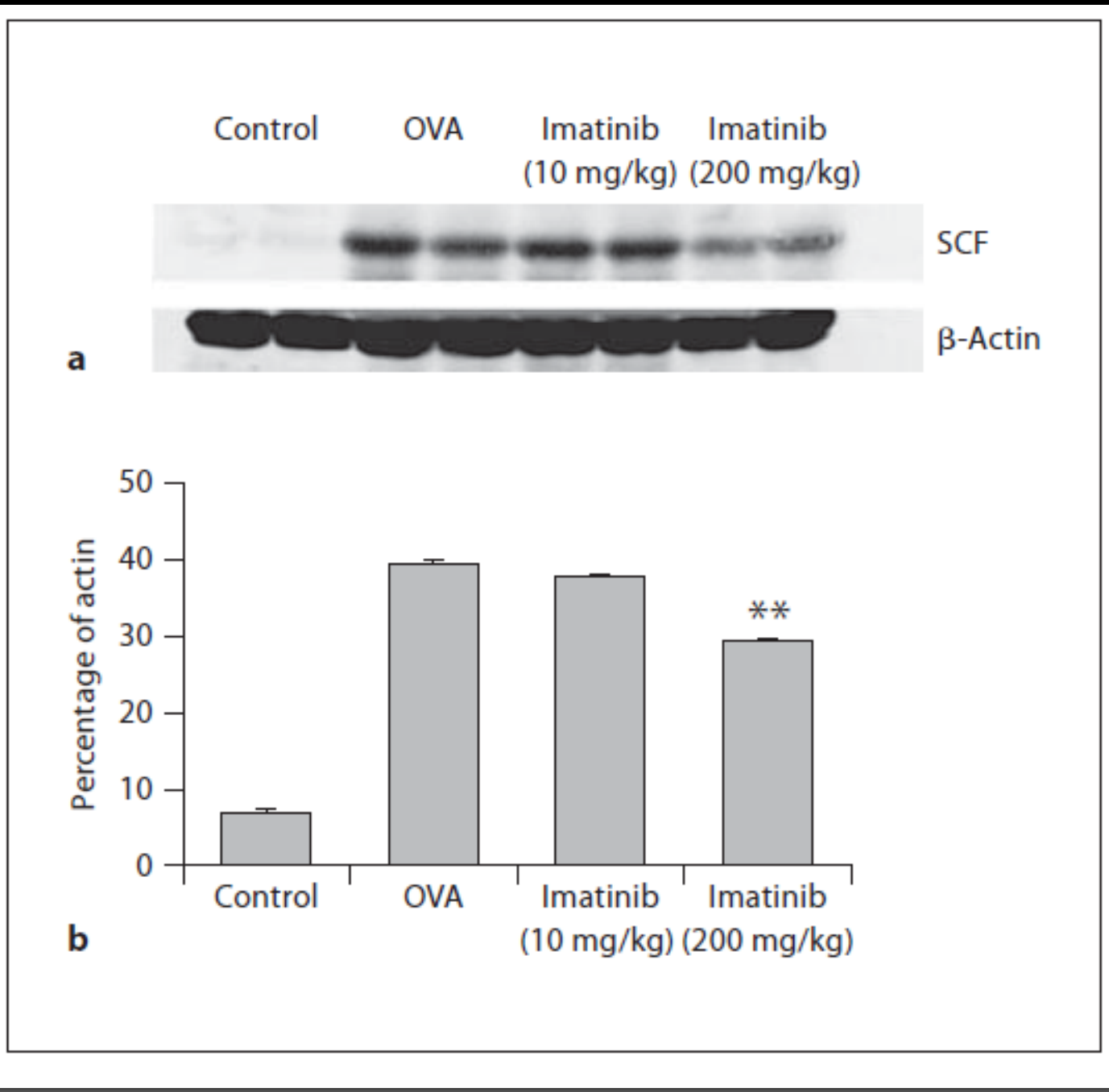
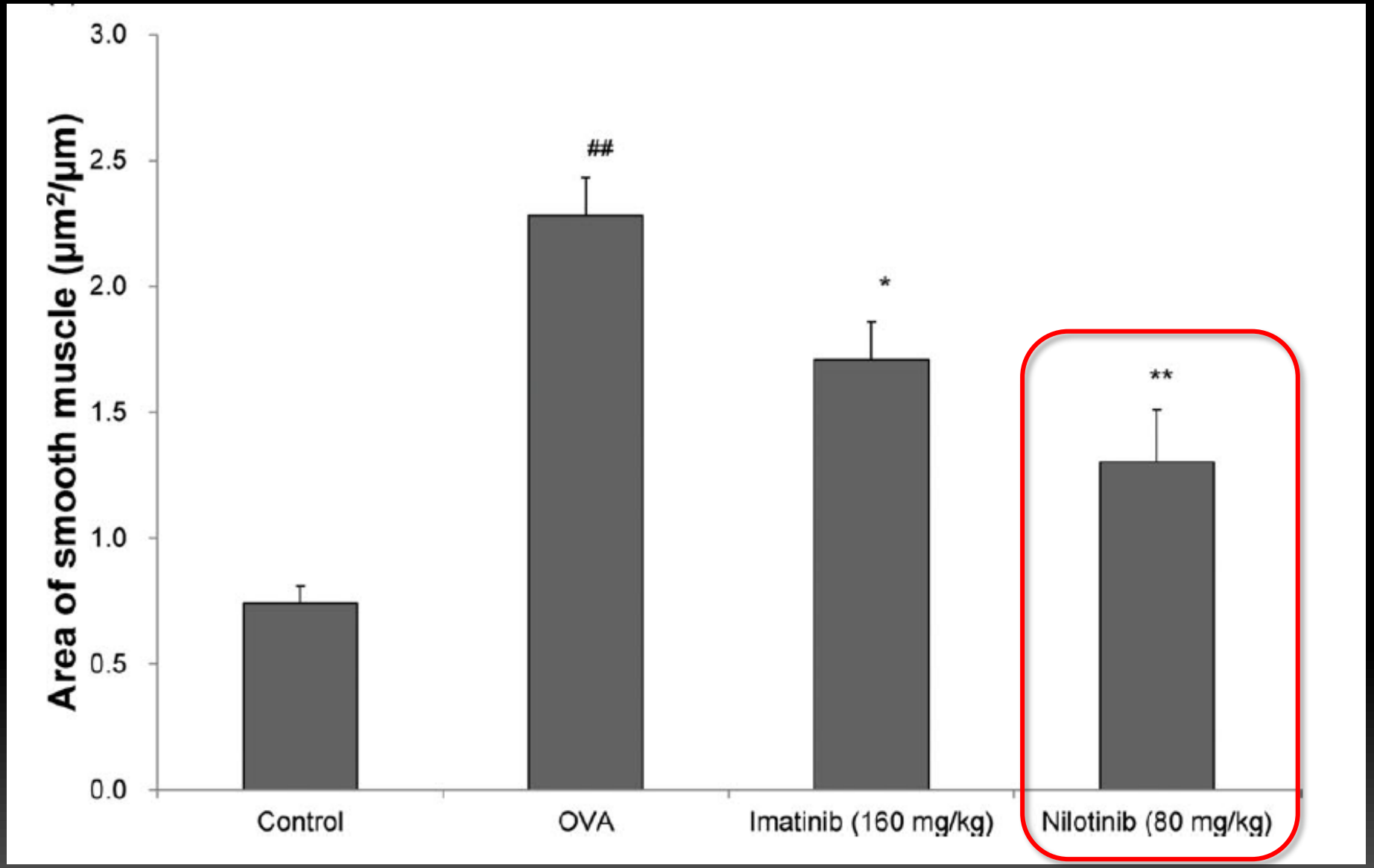
C-Kit, PDGFR tyrosine kinase

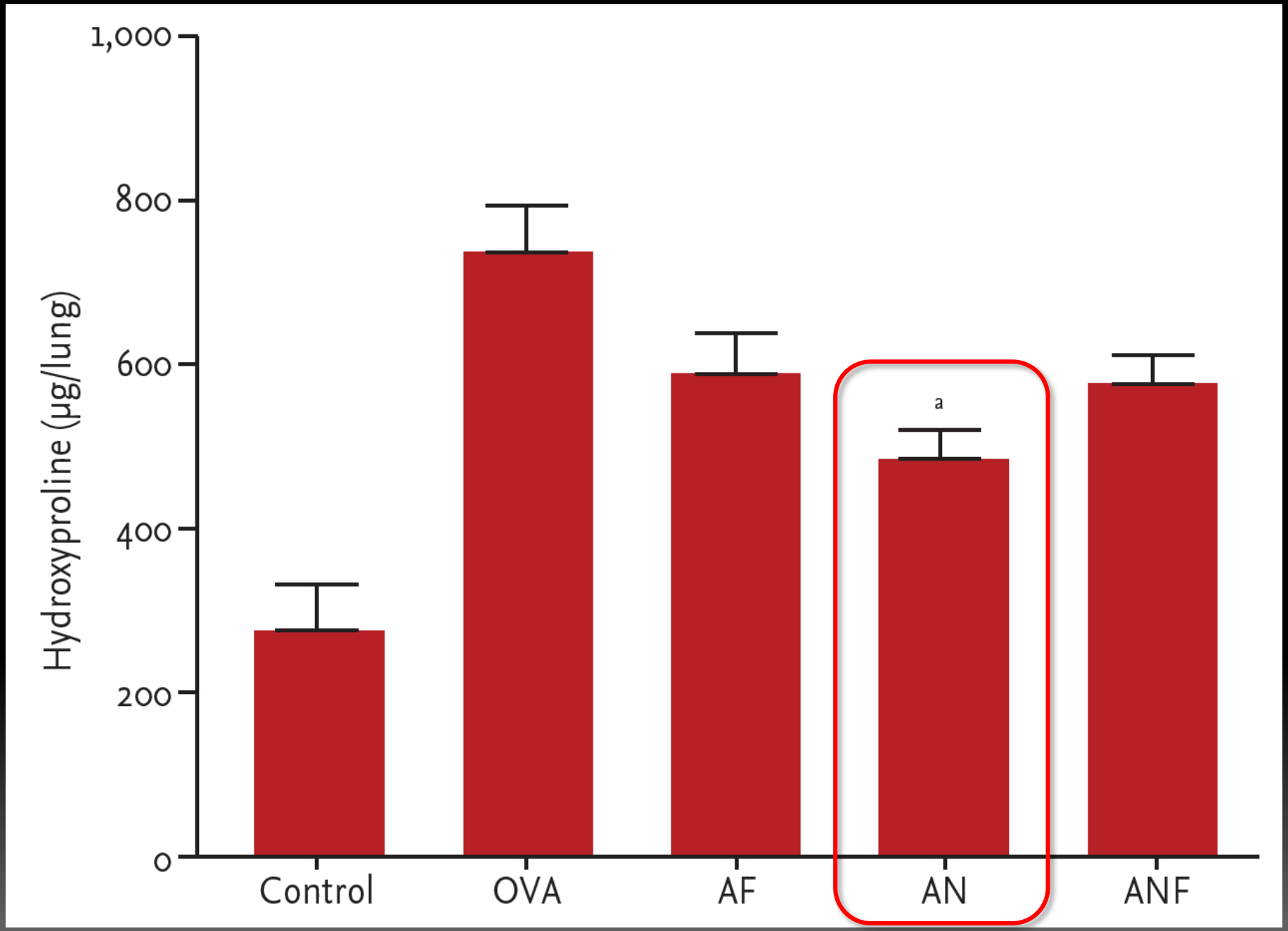
- Involved in airway inflammation & mast cell activation
- Associated with airway remodeling



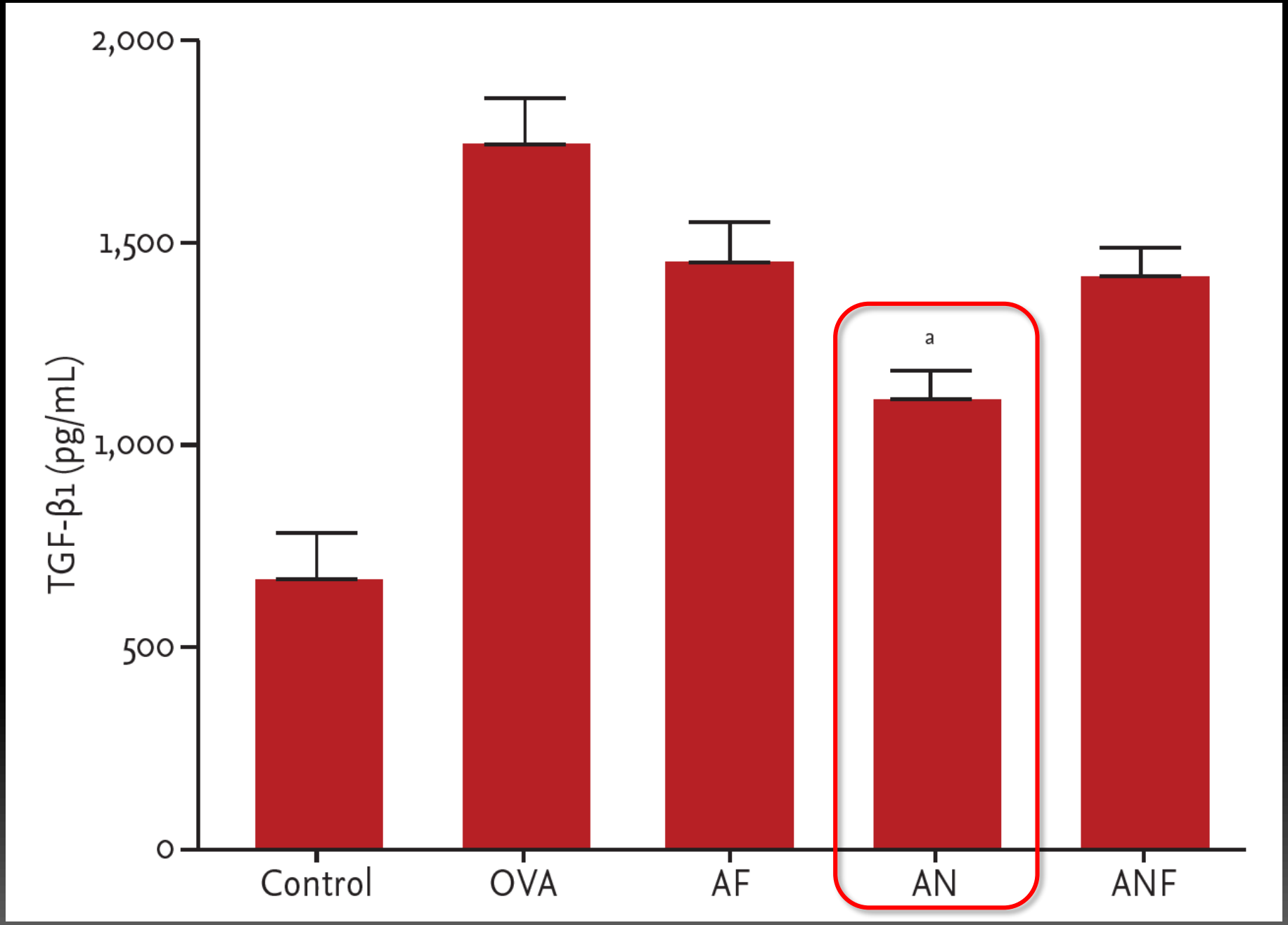
Rhee CK. Int Arch Allergy Immunol 2011;155:243–251



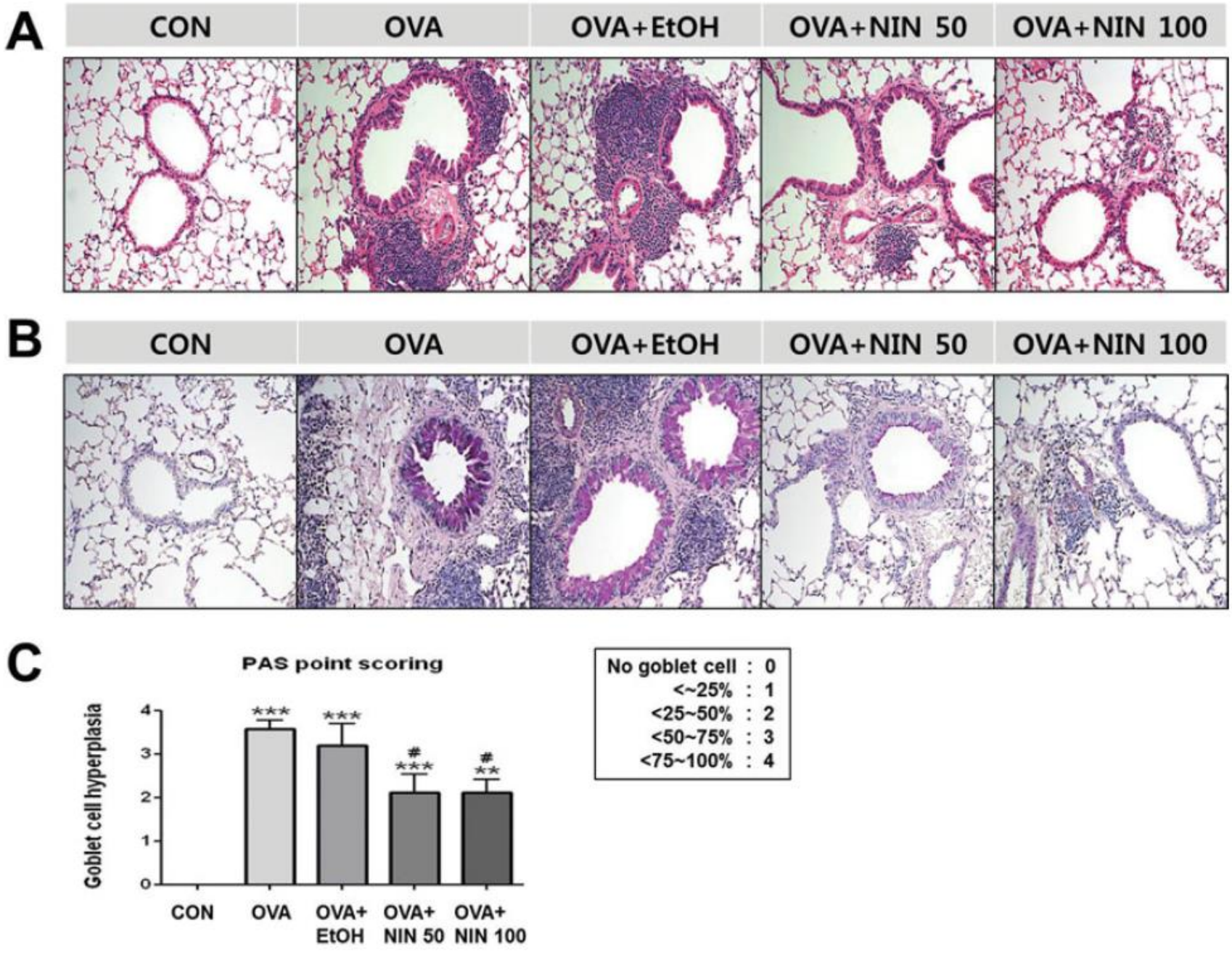
Rhee CK. Exp Lung Res 2014; 40: 199-210.



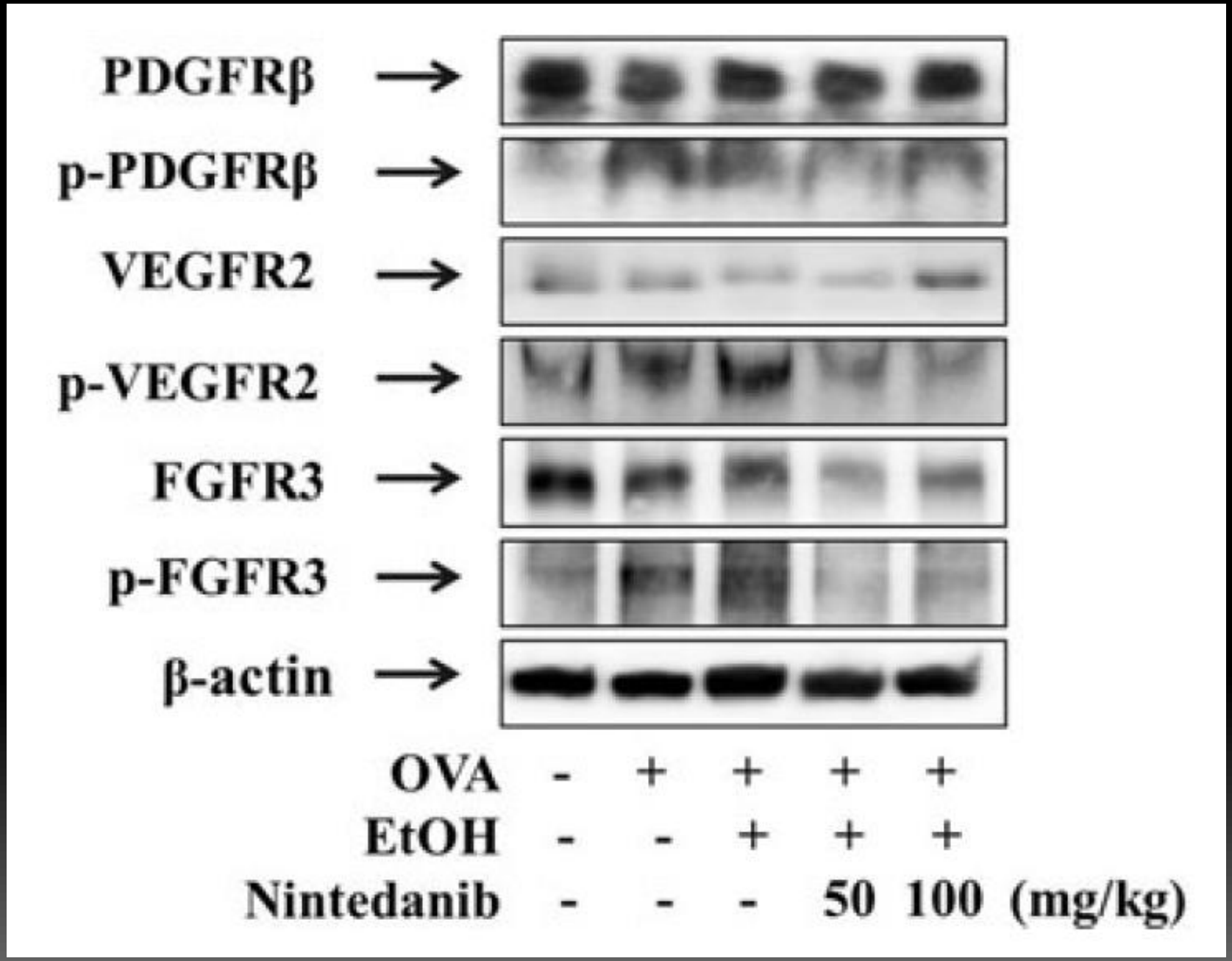
Kang HS. Korean J Intern Med 2016; 31: 1150-1158.



Kang HS. Korean J Intern Med 2016; 31: 1150-1158.



Lee HY. Exp Lung Res 2017; 43: 187-196.



Lee HY. Exp Lung Res 2017; 43: 187-196.

Allergy 2009: 64: 1194–1201

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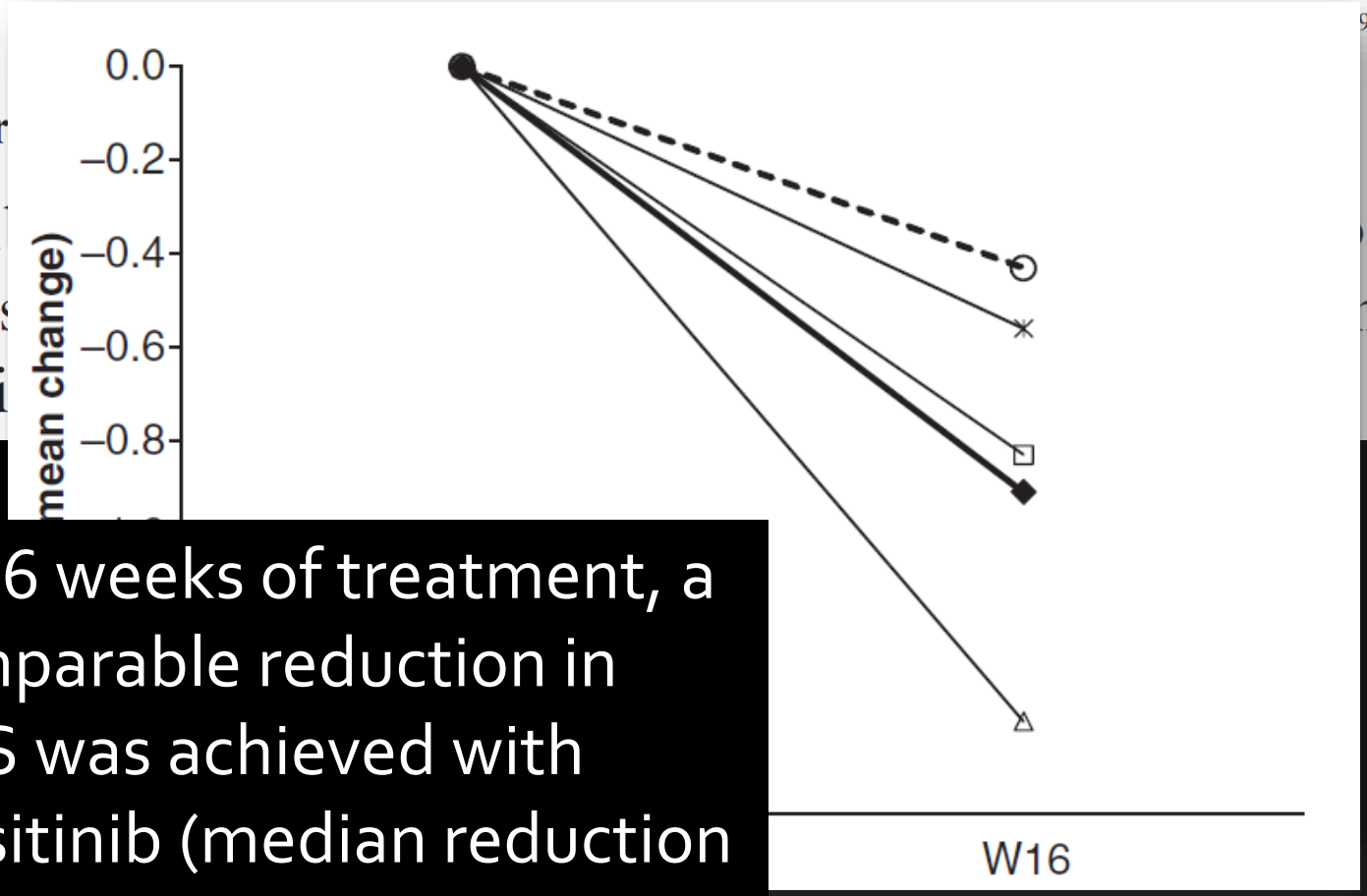


- At 16 weeks of treatment, a comparable reduction in OCS was achieved with masitinib (median reduction of) 78%
- ACQ score was significantly better in the masitinib arm

Humbert M. Allergy 2009; 64: 1194-1201.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 18, 2017 VOL. 376 NO. 20

KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma

Katherine N. Cahill, M.D., Howard R. Katz, Ph.D., Jing Cui, M.D., Ph.D., Juying Lai, M.D., Shamsah Kazani, M.D., Allison Crosby-Thompson, M.S., Denise Garofalo, B.A., Mario Castro, M.D., Nizar Jarjour, M.D., Emily DiMango, M.D., Serpil Erzurum, M.D., Jennifer L. Trevor, M.D., Kartik Shenoy, M.D., Vernon M. Chinchilli, Ph.D., Michael E. Wechsler, M.D., Tanya M. Laidlaw, M.D., Joshua A. Boyce, M.D., and Elliot Israel, M.D.

Cahill KN. N Engl J Med 2017; 376: 1911-1920.

Inclusion criteria

1. Patients 18-55 years of age, diagnosed with asthma for at least 1 year;
2. Refractory asthma, defined as reporting that their asthma has not been completely controlled in the past 3 months despite continuous treatment with high-dose inhaled corticosteroids (ICS) (fluticasone ≥ 1000 mg or equivalent) **and** LABA, with or without continuous oral corticosteroids (OCS);
3. ACQ ≥ 1.5 during the run-in period
4. FEV1 > 55% PREDICTED
5. Methacholine PC20 < 4 mg/ml
6. > 80% compliance with PEF recording and diary recording during the screening period

A

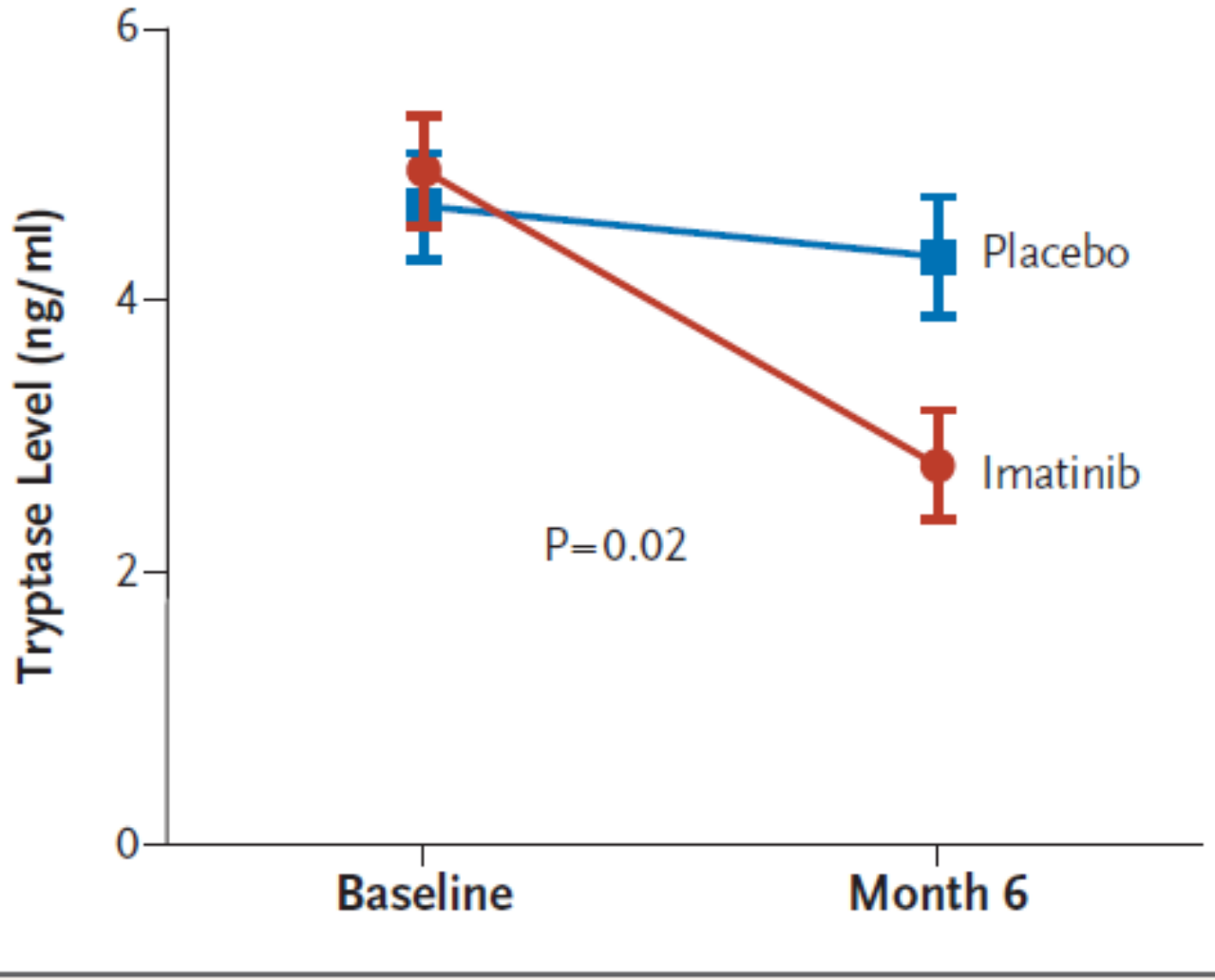
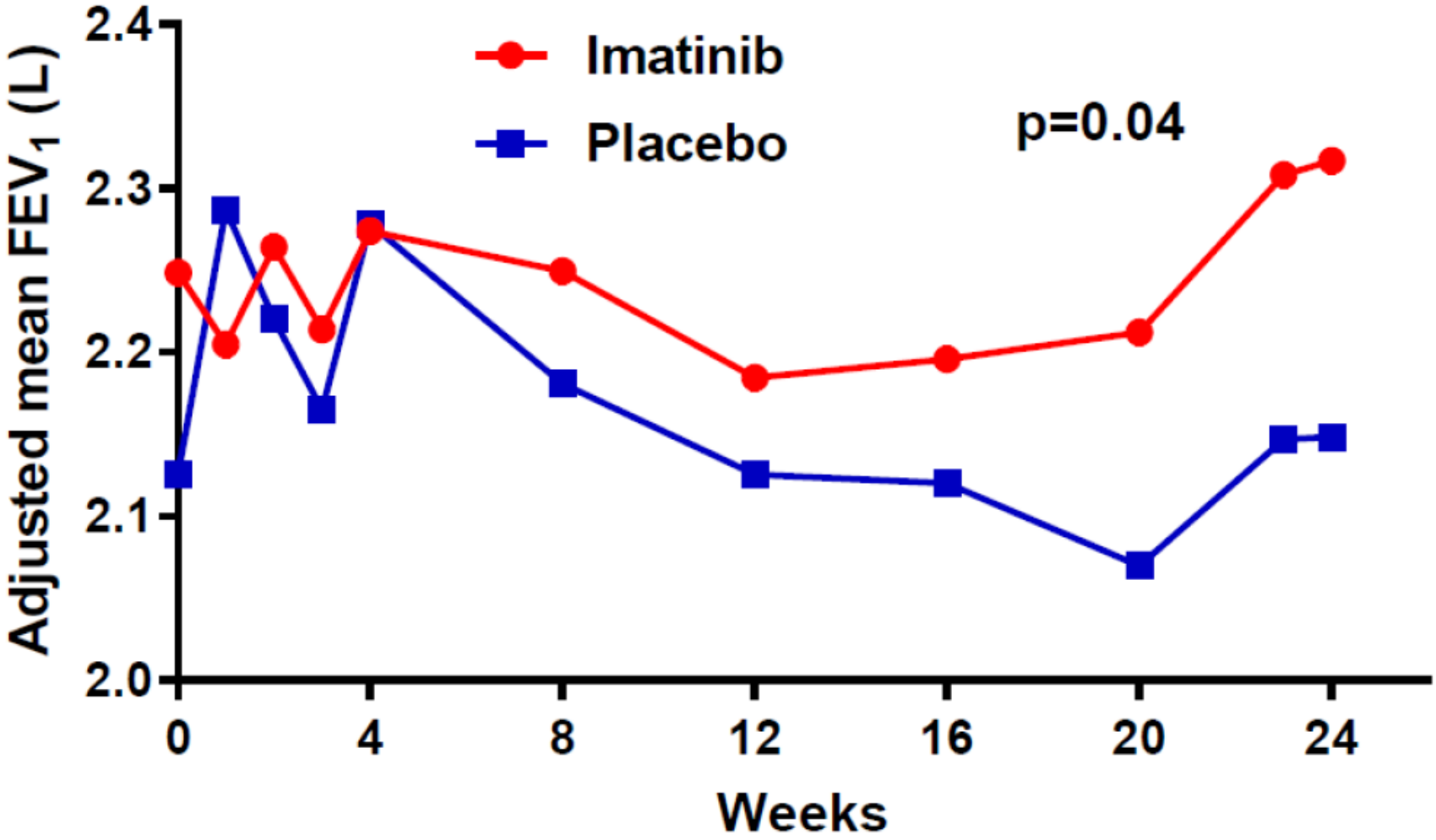
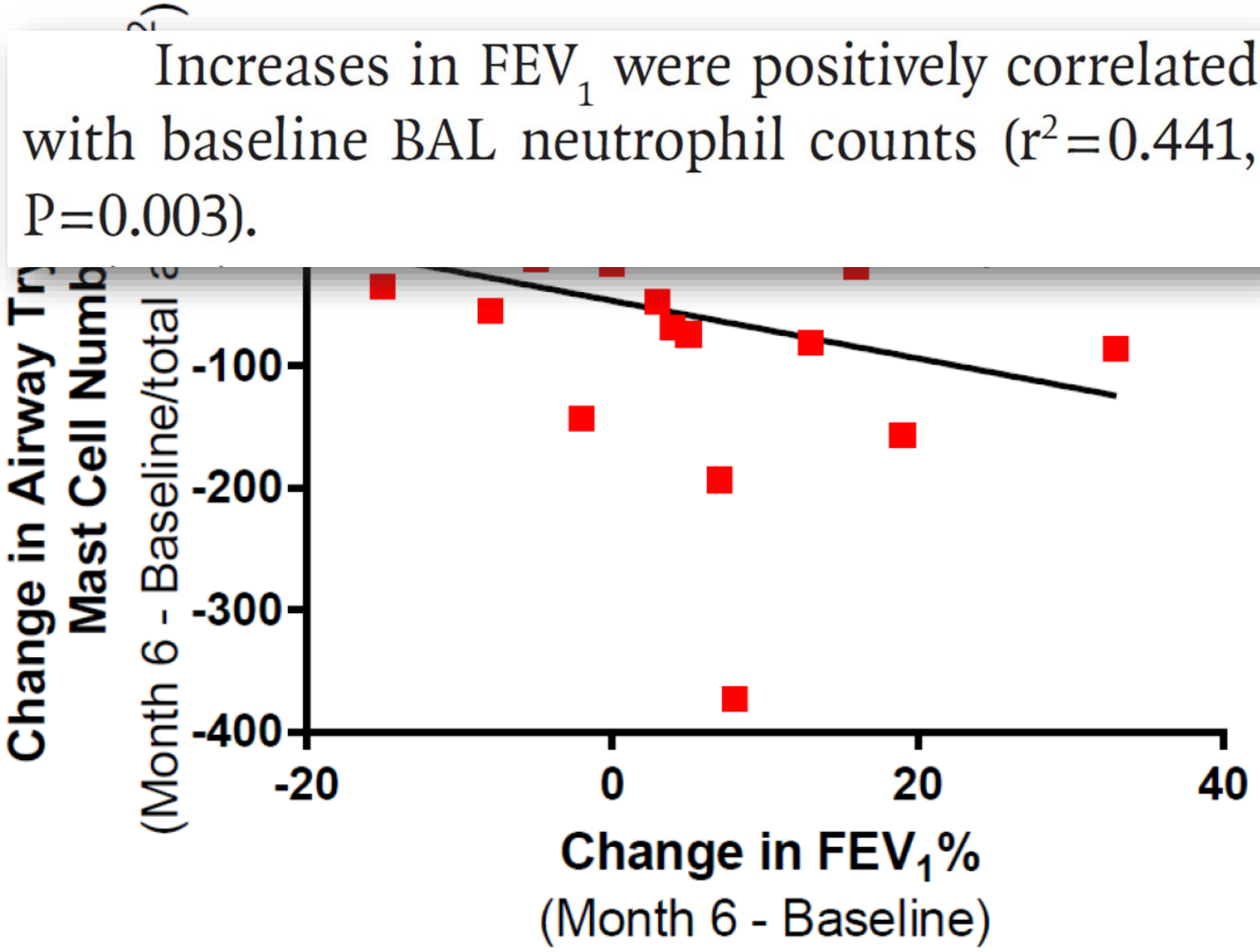


Figure 3. Total Tryptase Levels in Serum.

Cahill KN. N Engl J Med 2017; 376: 1911-1920.


Imatinib
Placebo
p=0.04
Adjusted mean FEV1 (L)
2.4
2.3
2.2
2.1
2.0
0
4
8
12
16
20
24
Weeks

Increases in FEV_1 were positively correlated with baseline BAL neutrophil counts ($r^2=0.441$, $P=0.003$).



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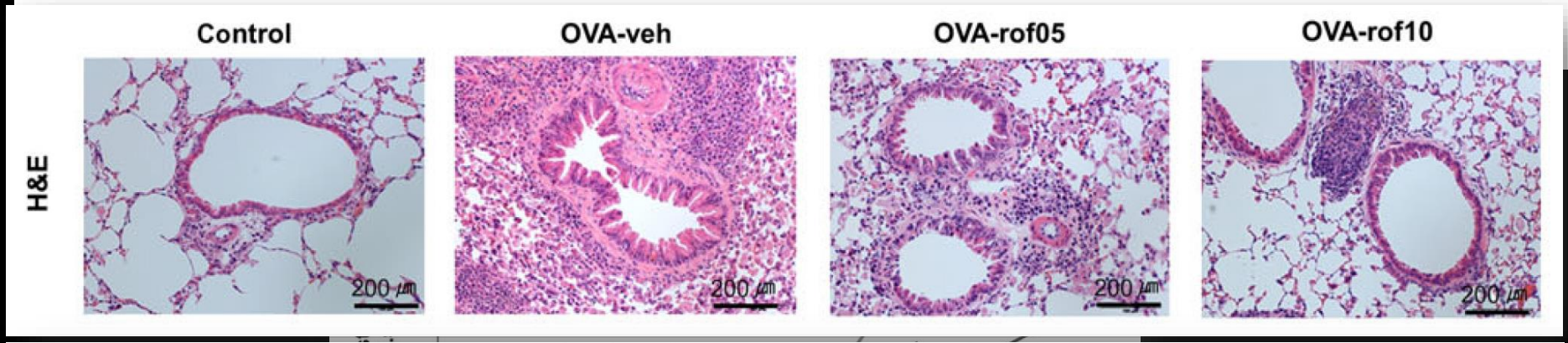
doi: 10.1111/cea.12670

Clinical & Experimental Allergy, **46**, 754–763

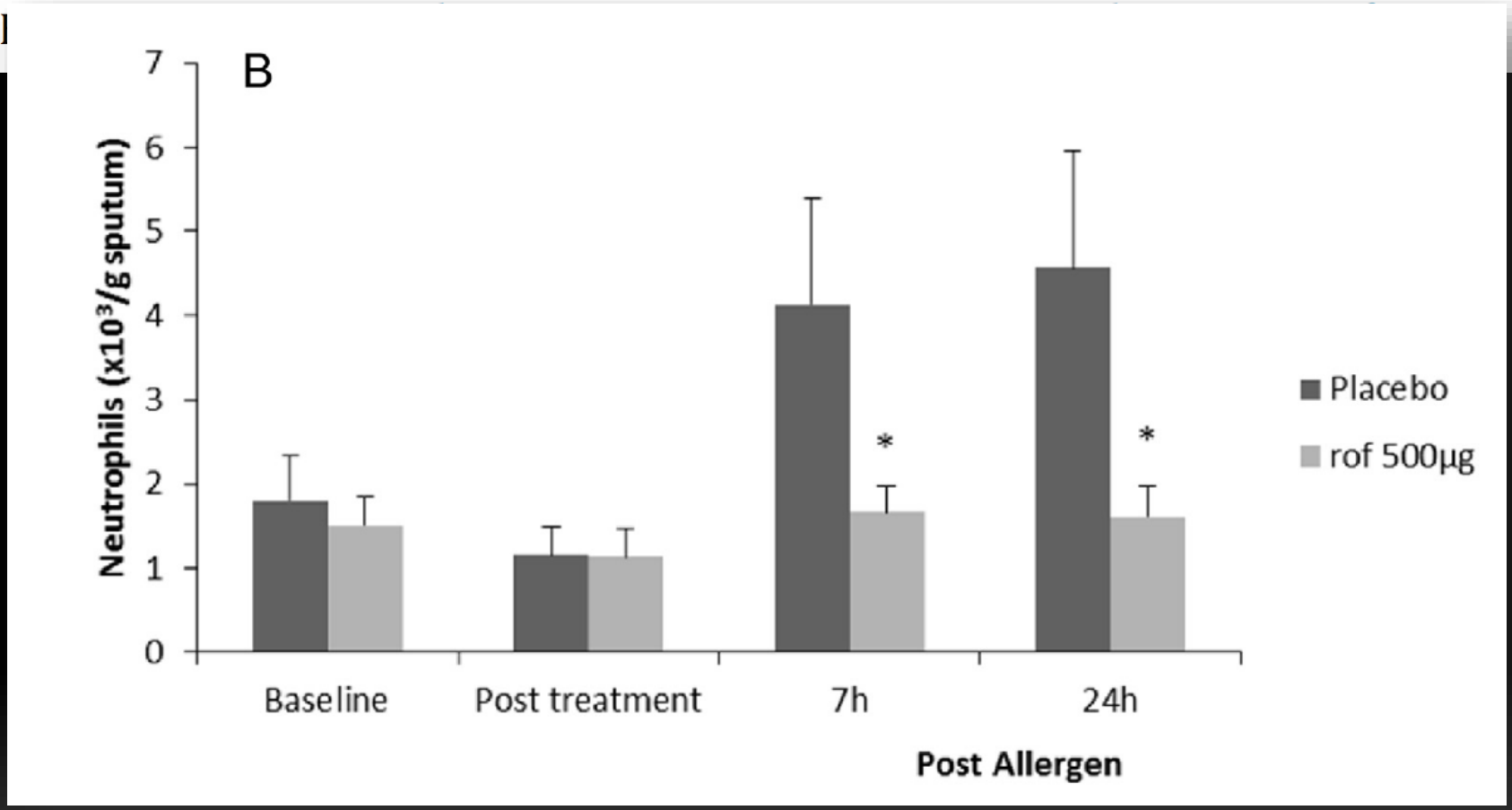
ORIGINAL ARTICLE Experimental Models of Allergic Disease

Effect of roflumilast on airway remodelling in a murine model of chronic



Clin Exp Allergy. 2016;46(5):754-763.

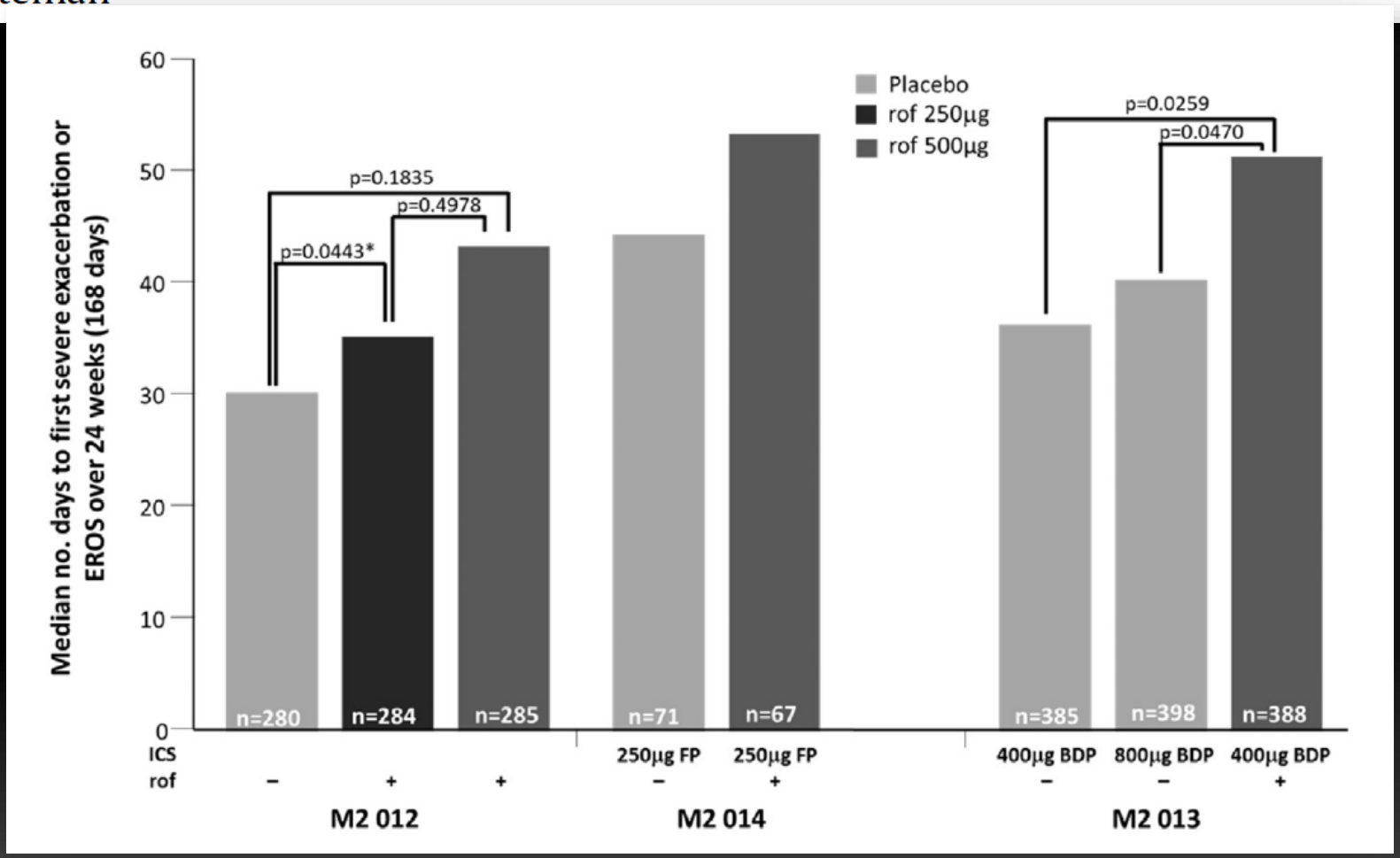
Roflumilast for asthma: Efficacy findings in mechanism of action studies



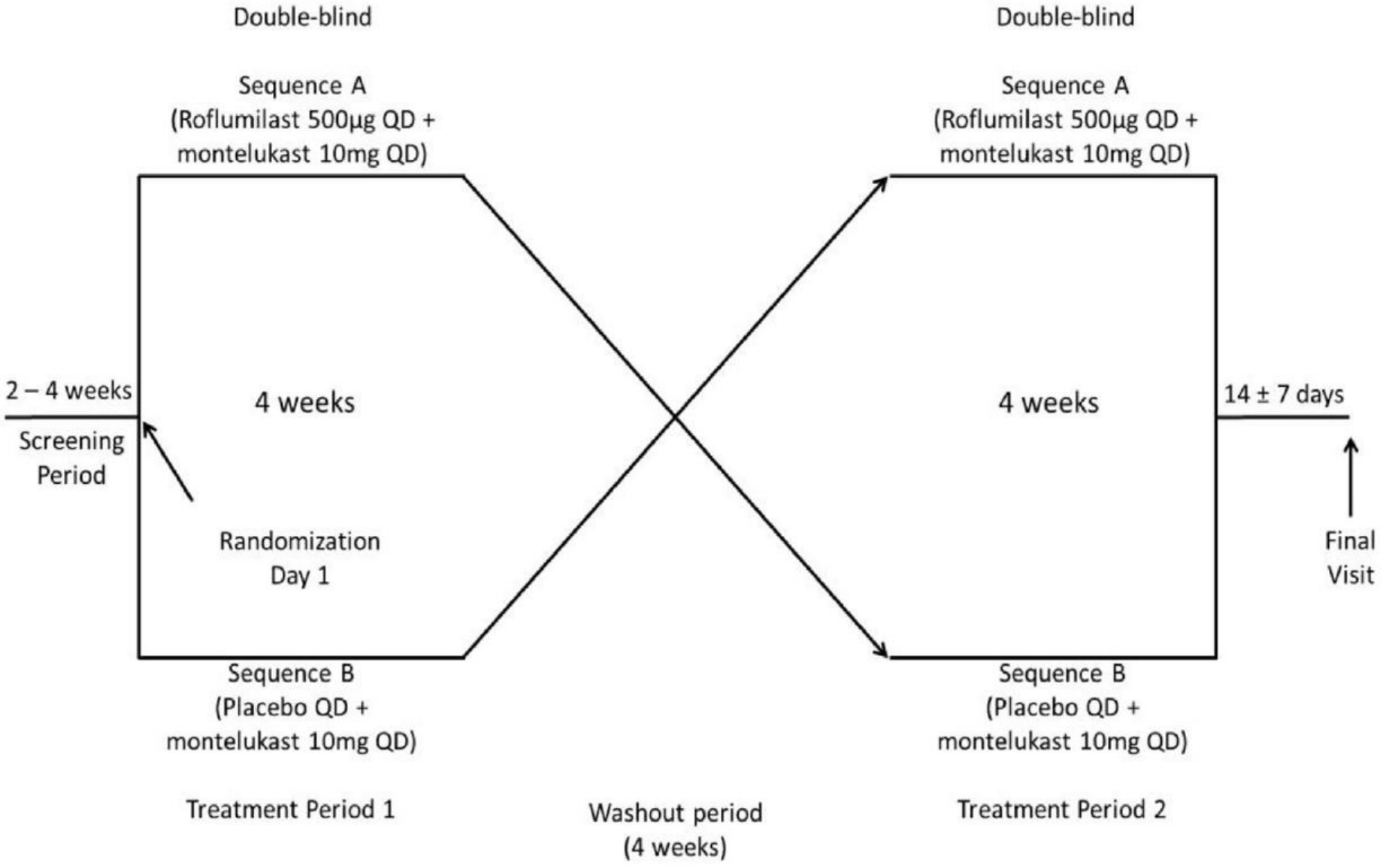
Pulm Pharmacol Ther. 2015;35 Suppl:S4-10.

Roflumilast for asthma: Efficacy findings in placebo-controlled studies

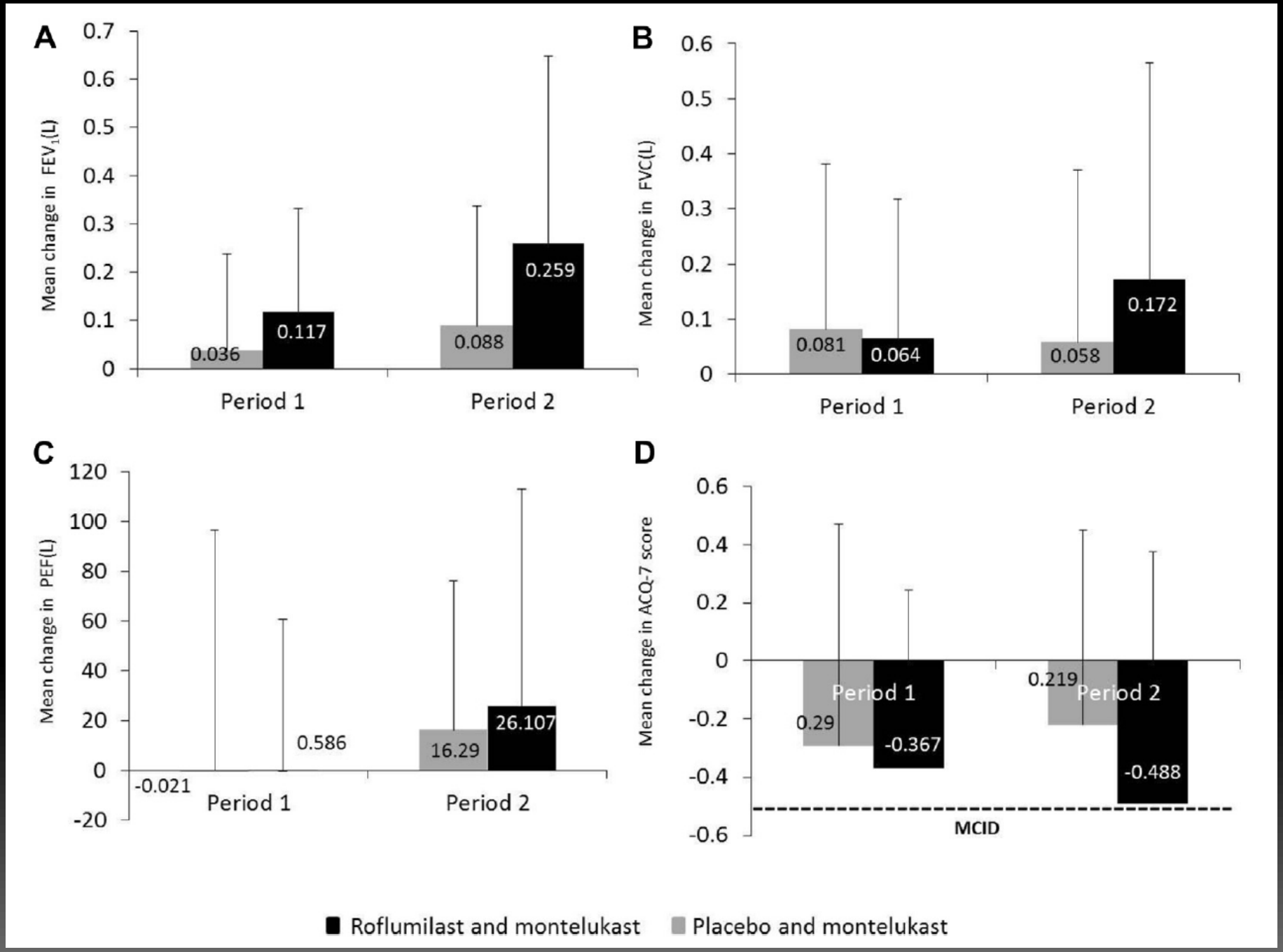
E.O. Meltzer [a, *], P. Chervinsky [b], W. Busse [c], K. Ohta [d], P. Bardin [e], D. Bredenbröker [f], E.D. Bateman [g]



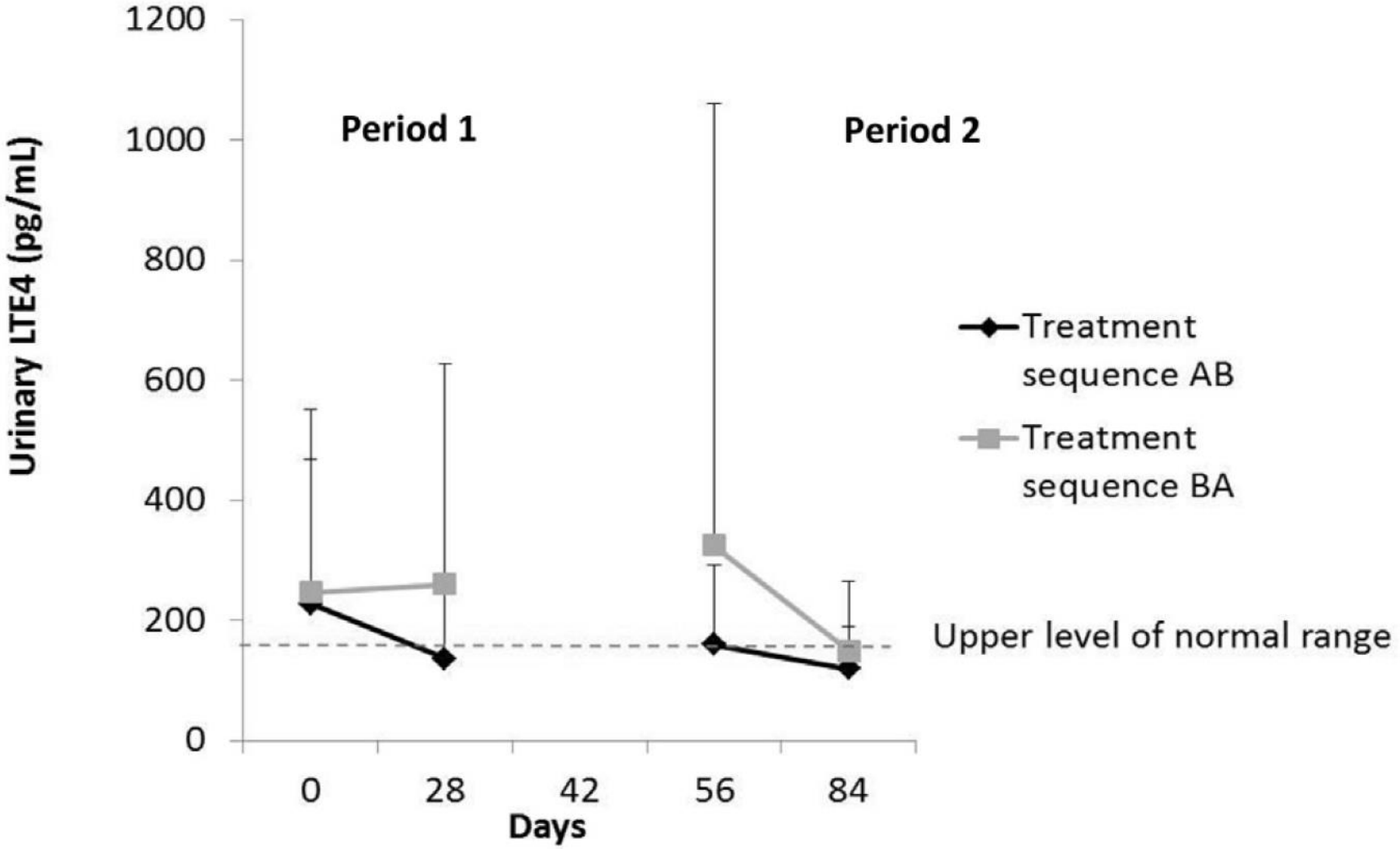
Pulm Pharmacol Ther. 2015;35 Suppl:S20-27.



Bateman ED. J Allergy Clin Immunol 2016; 138: 142-149.e148.



Bateman ED. J Allergy Clin Immunol 2016; 138: 142-149.e148.



Bateman ED. J Allergy Clin Immunol 2016; 138: 142-149.e148.

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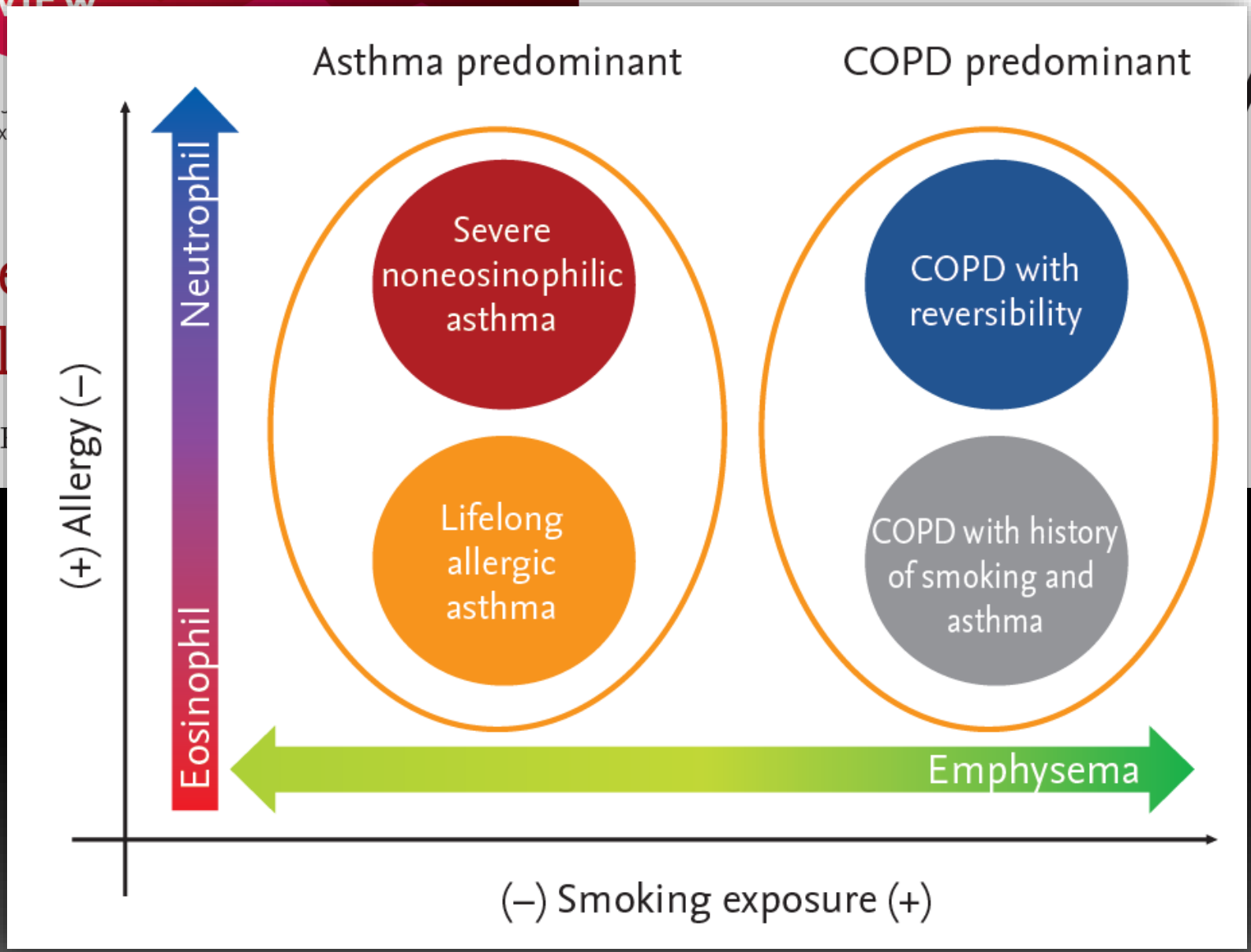
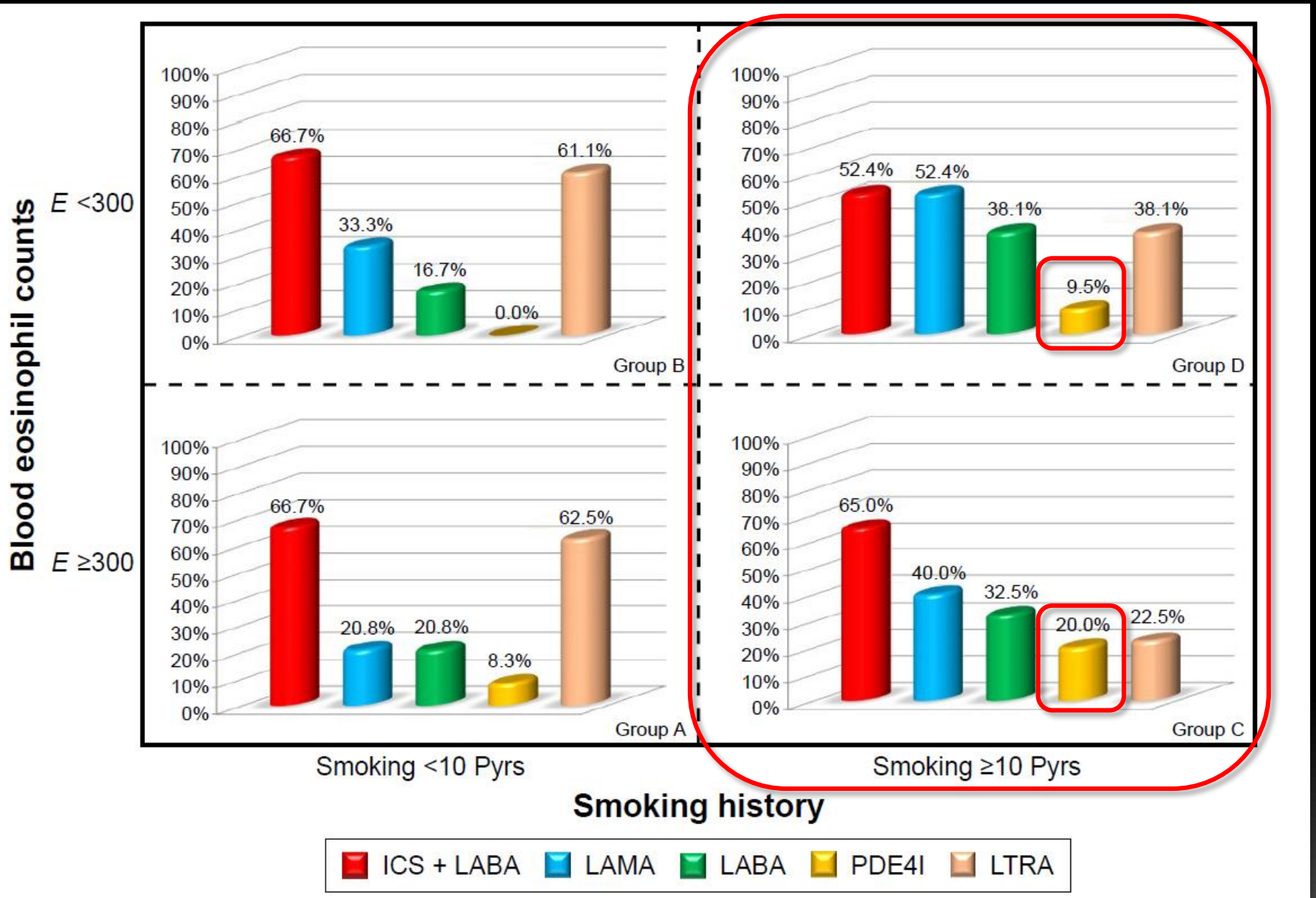
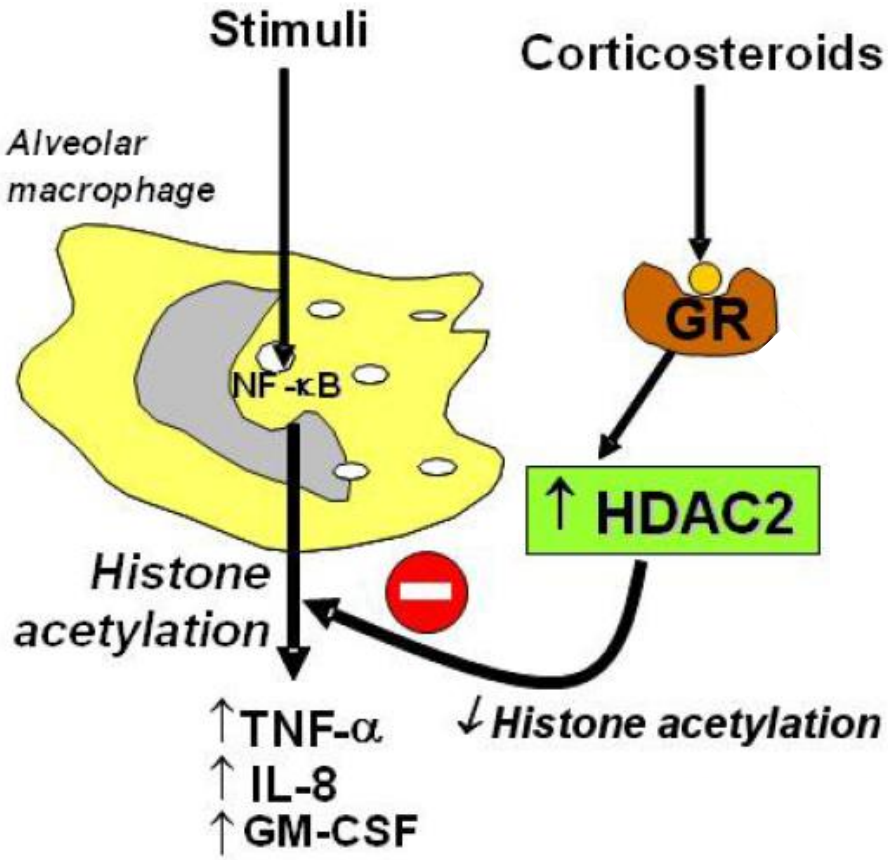


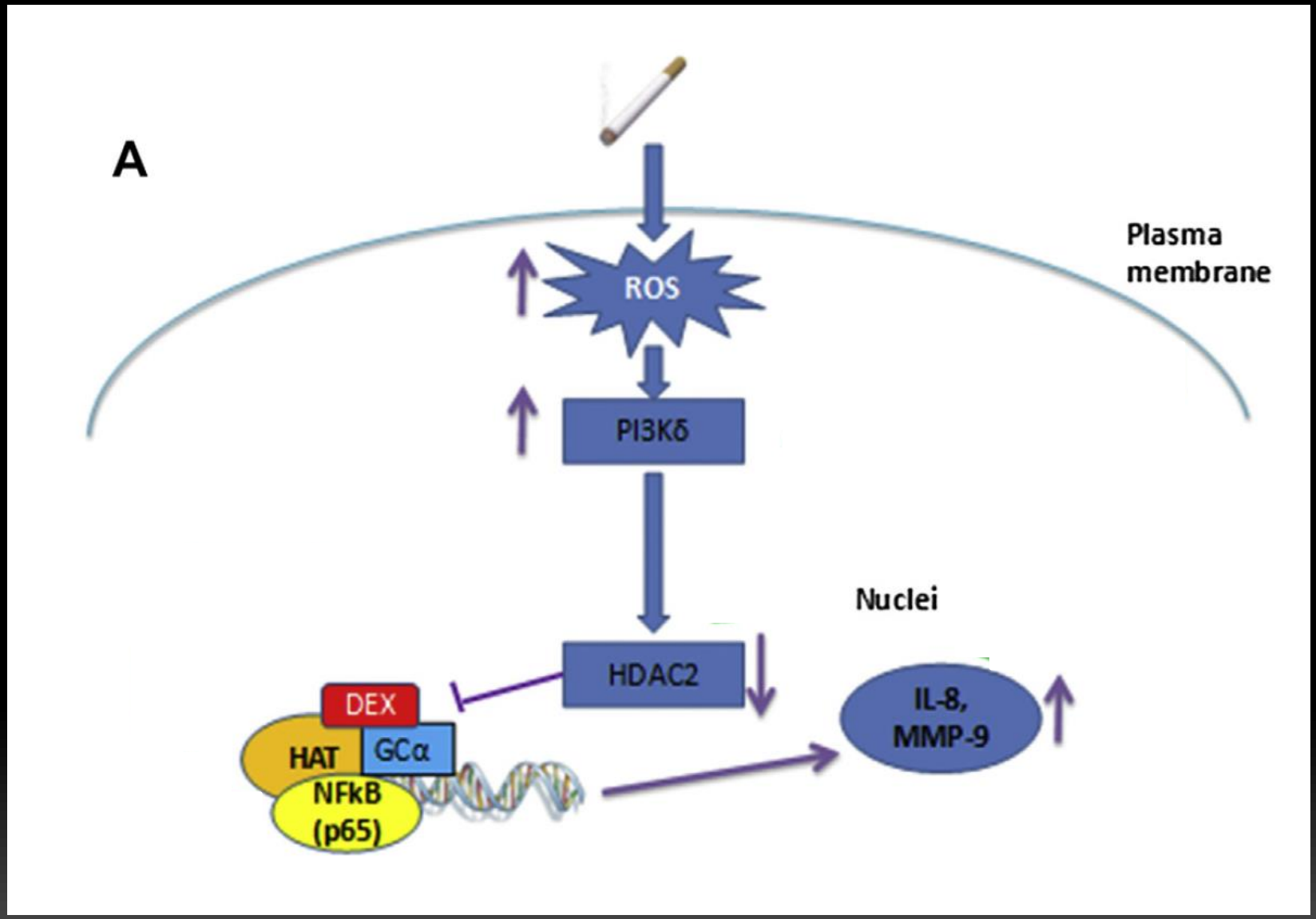
Rhee CK. Korean J Intern Med. 2015;30(4):443-449.



Joo H. Int J Chron Obstruct Pulmon Dis. 2017;12:697-703.

Mild asthma


Stimuli
Corticosteroids
Alveolar macrophage
NF-κB
GR
↑ HDAC2
Histone acetylation
↑TNF-α
↑ IL-8
↑GM-CSF
↓Histone acetylation



J Allergy Clin Immunol. 2014 Aug;134(2):314-22.

Effect of roflumilast on neutrophilic asthma model

Chin Kook Rhee,1 Hyoung Kyu Yoon2

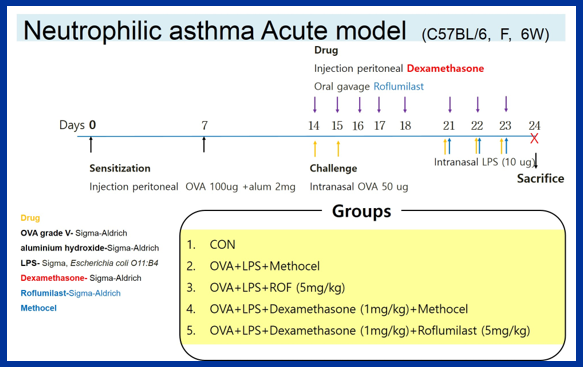
[1]Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, [2]Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea

Introduction

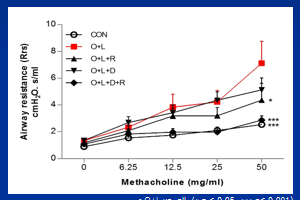
- Roflumilast is a selective phosphodiesterase-4 inhibitor that has an anti-inflammatory effect. Previously, we published that roflumilast was effective on chronic asthma model. However, little has been known for the effect of roflumilast on neutrophilic asthma model.
- We aimed to examine effect of roflumilast on neutrophilic asthma model.

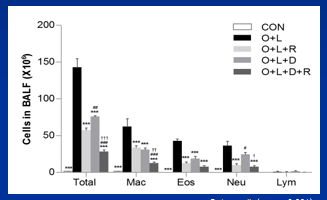
Methods

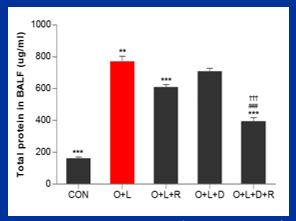
- Acute neutrophilic asthma model was developed. C57BL/6 mice sensitized to ovalbumin (OVA) were repeatedly exposed to intranasal OVA combined with intranasal lipopolysaccharide (LPS). Mice were grouped into 1) control, 2) OVA + LPS (O+L), 3) OVA + LPS + roflumilast (O+L+R), 4) OVA + LPS + dexamethasone (O+L+D), and 5) OVA + LPS + dexamethasone + roflumilast (O+L+D+R).

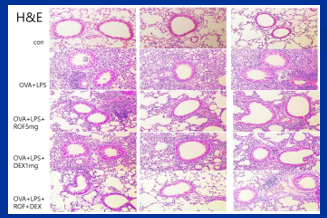


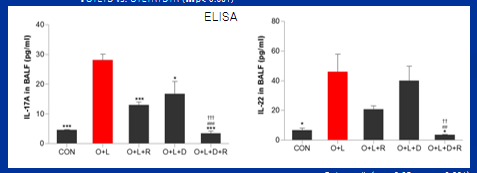
Results

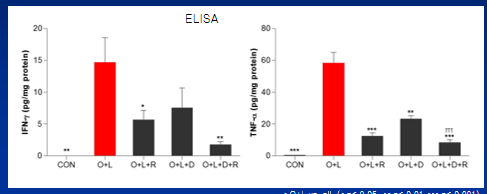


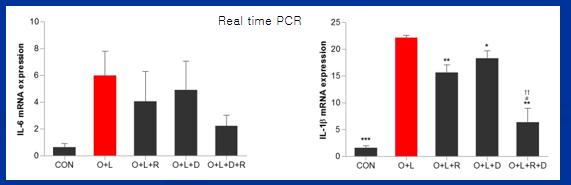


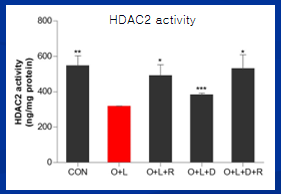


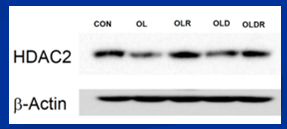










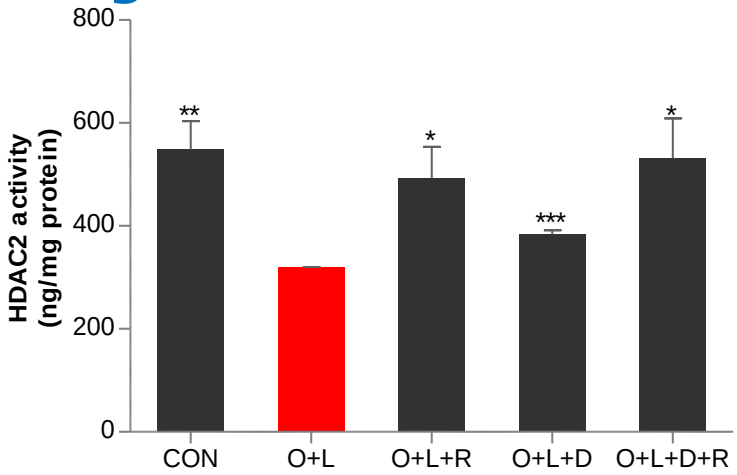


Conclusion

- These results suggest that the administration of roflumilast attenuates airway inflammation and AHR in neutrophilic asthma model. Adding roflumilast to dexamethasone resulted further beneficial effect. The beneficial effect of roflumilast may be related to HDAC pathways.

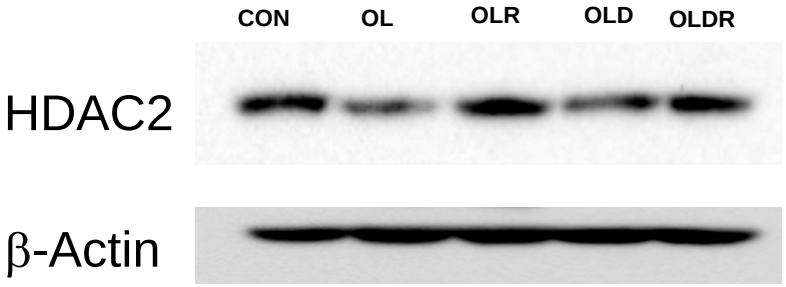
Rhee CK, 2017 ERS

HDAC2 activity



* O+L vs. all (* p< 0.05, ** p< 0.01, *** p< 0.001)
t-test

HDAC2 western



Contents

- DDx
- Tezepelumab
- Tiotropium
- Macrolide
- TKI
- Roflumilast
- Obesity

Contents

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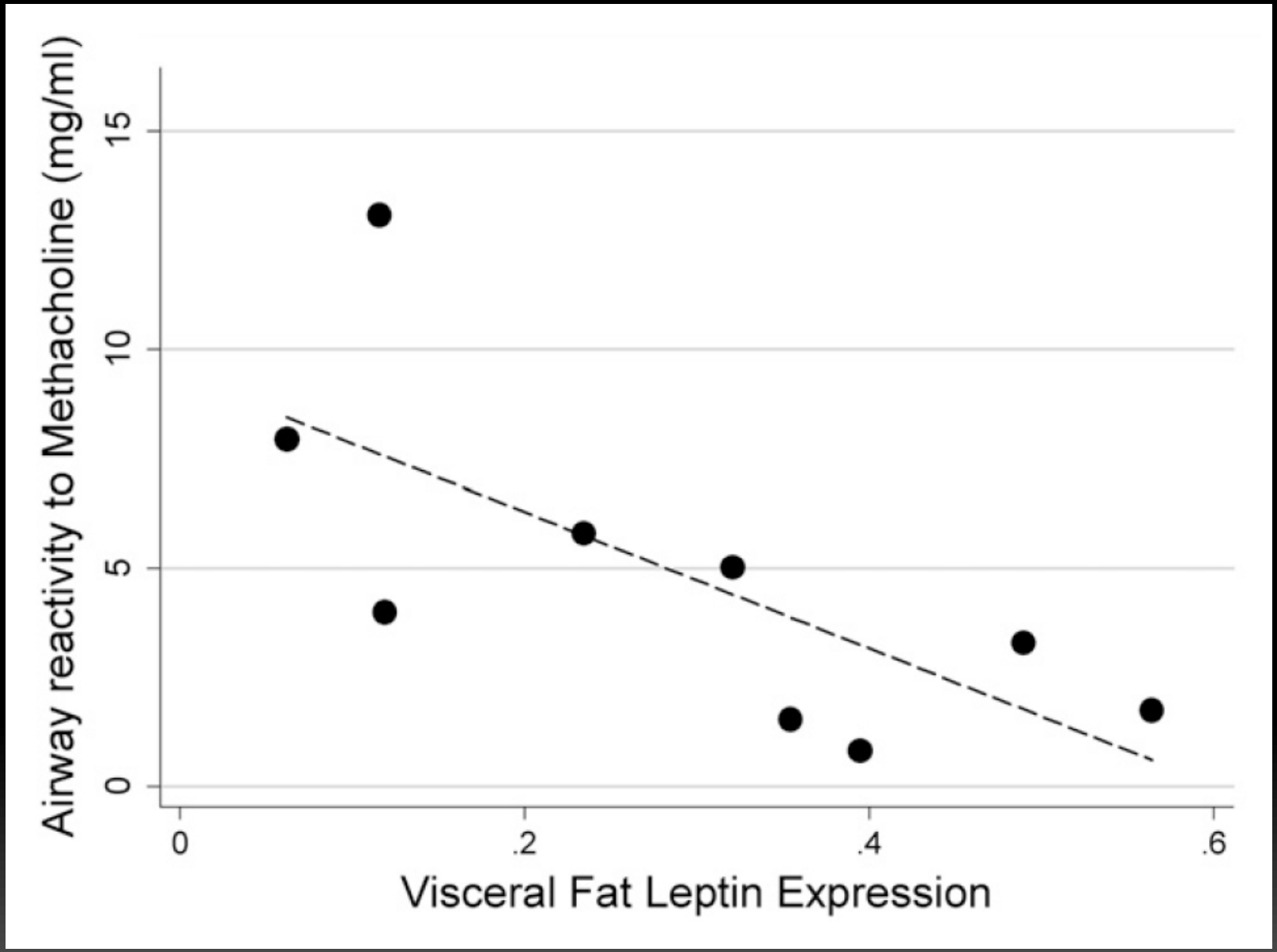
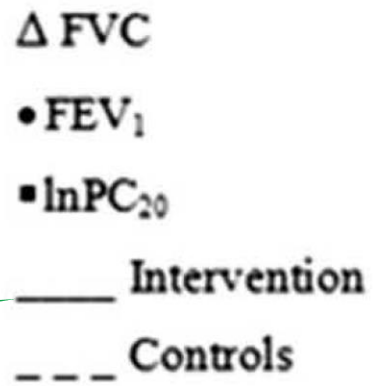
TABLE 3. ADIPOKINE GENE EXPRESSION AND CELL SIZE OF VISCERAL ADIPOSE TISSUE AT BASELINE

Adipokine	Obese Control 0	Asthma 0	P^*	Adjusted $P^\dagger$
Leptin	0.125 ± 0.016	0.305 + 0.047	0.002	0.026
Adiponectin	0.866 ± 0.134	0.347 + 0.037	<0.001	<0.001
CD-68	0.629 ± 0.048	0.979 + 0.109	0.015	0.012
MCP-1	0.848 ± 0.159	1.867 + 0.433	0.08	0.49
IL-6	2.847 ± 0.910	5.883 + 1.103	0.16	0.71
IL-8	0.924 ± 0.355	2.173 + 1.076	0.13	0.86
PAI-1	0.532 ± 0.132	0.948 + 0.243	0.15	0.63
TNF-α	1.275 ± 0.182	1.908 + 0.681	0.66	0.44
IFN-γ	3.232 ± 0.640	3.385 + 0.767	0.57	0.78
Cell size, μm	60.9 ± 9.48	59.8 ± 6.47	0.82	0.80

Sideleva O. Am J Respir Crit Care Med. 2012; 186: 598-605.

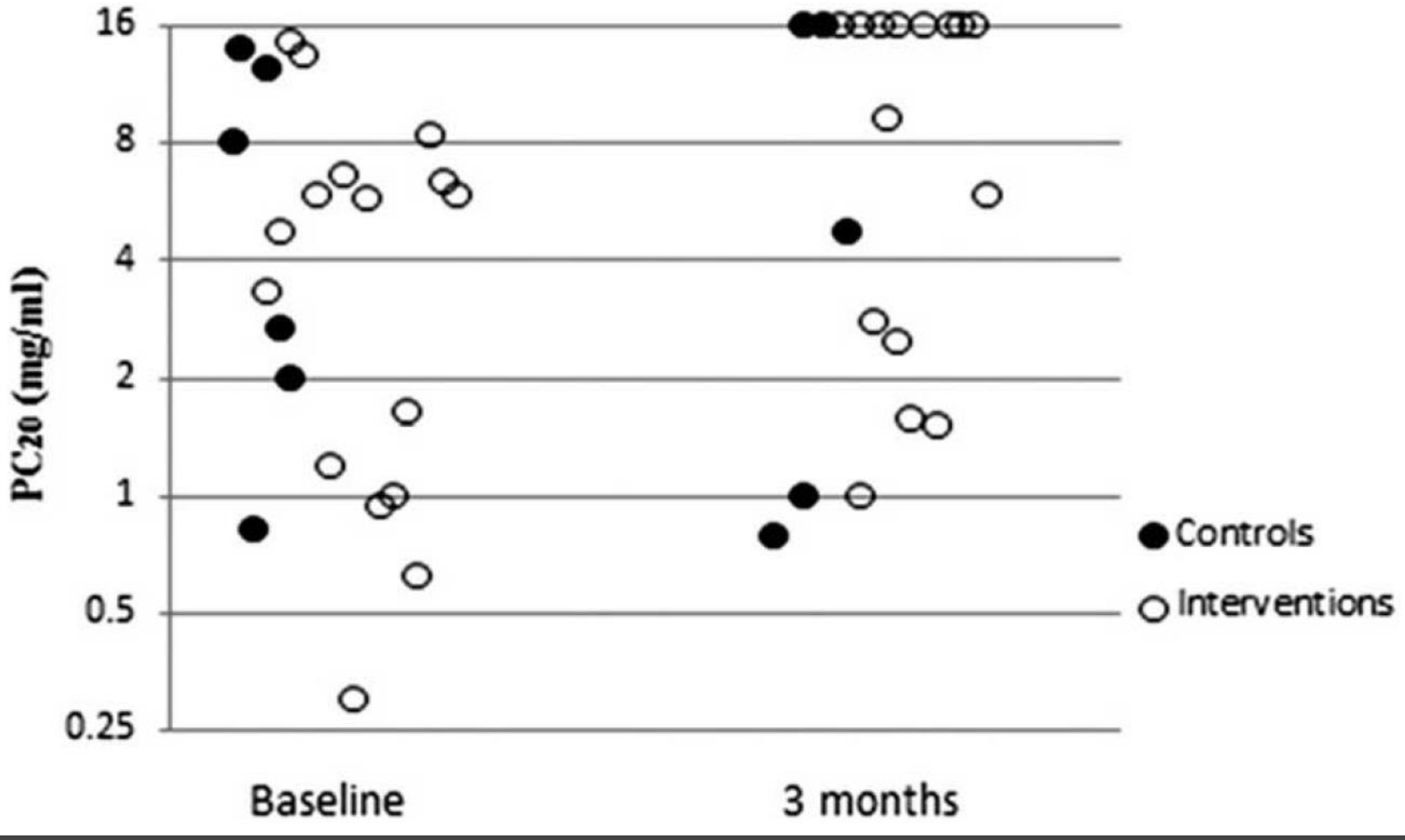


Sideleva O. Am J Respir Crit Care Med. 2012; 186: 598-605.

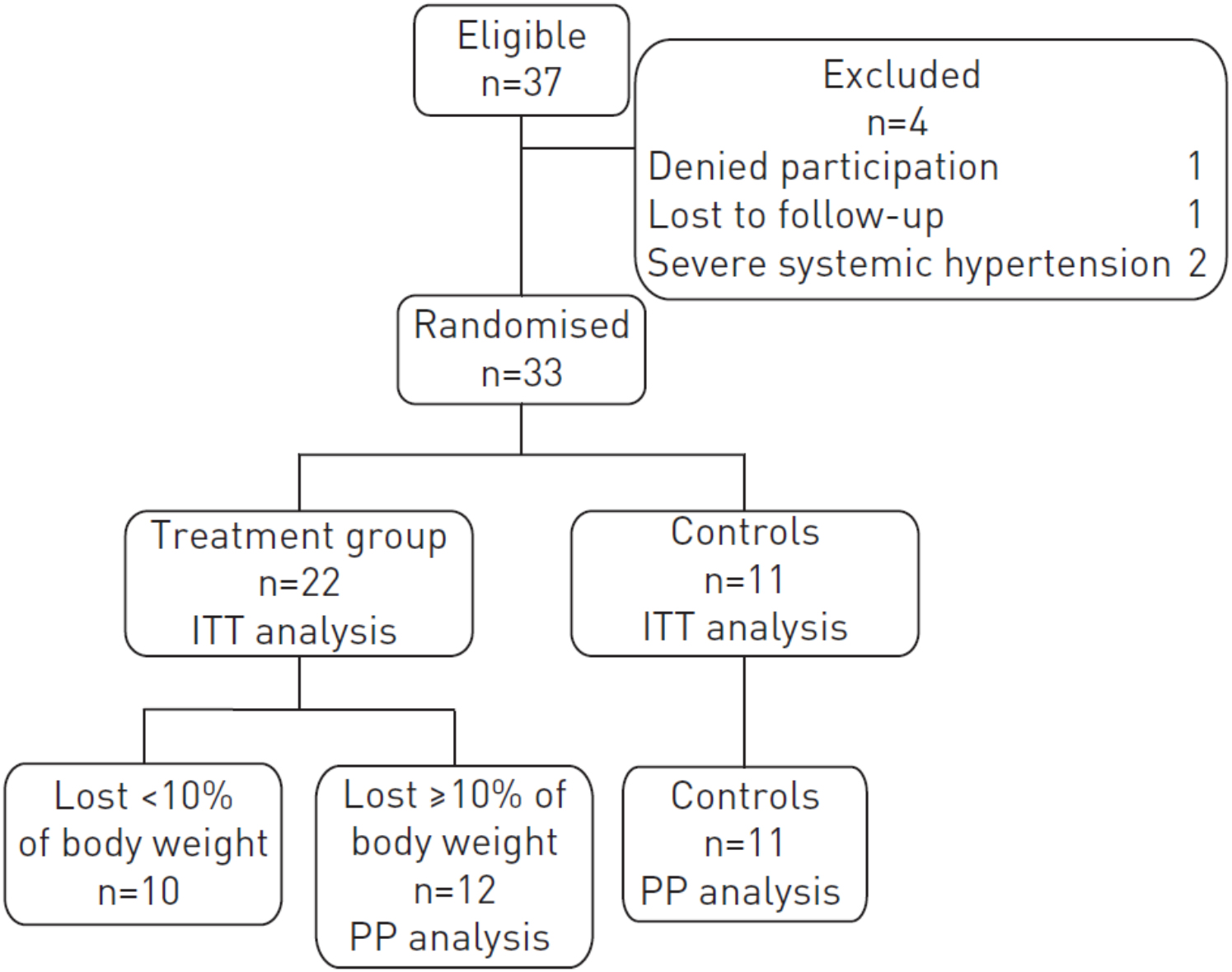


Behavioral weight reduction program for 3 months

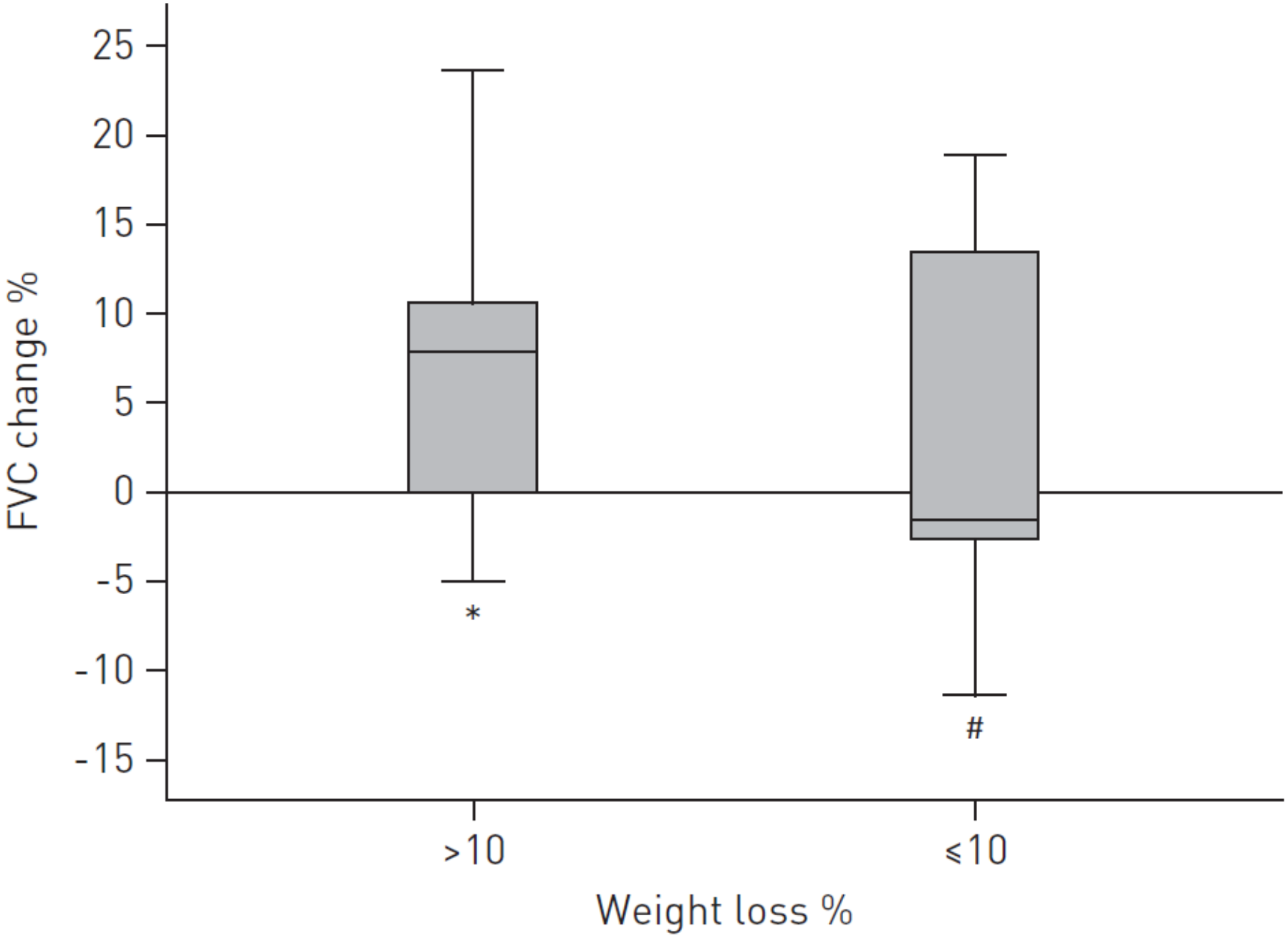
Pakhale S. Chest 2015; 147: 1582-1590.



Pakhale S. Chest 2015; 147: 1582-1590.



Dias-Junior SA. Eur Respir J 2014; 43: 1368-1377.



Dias-Junior SA. Eur Respir J 2014; 43: 1368-1377.

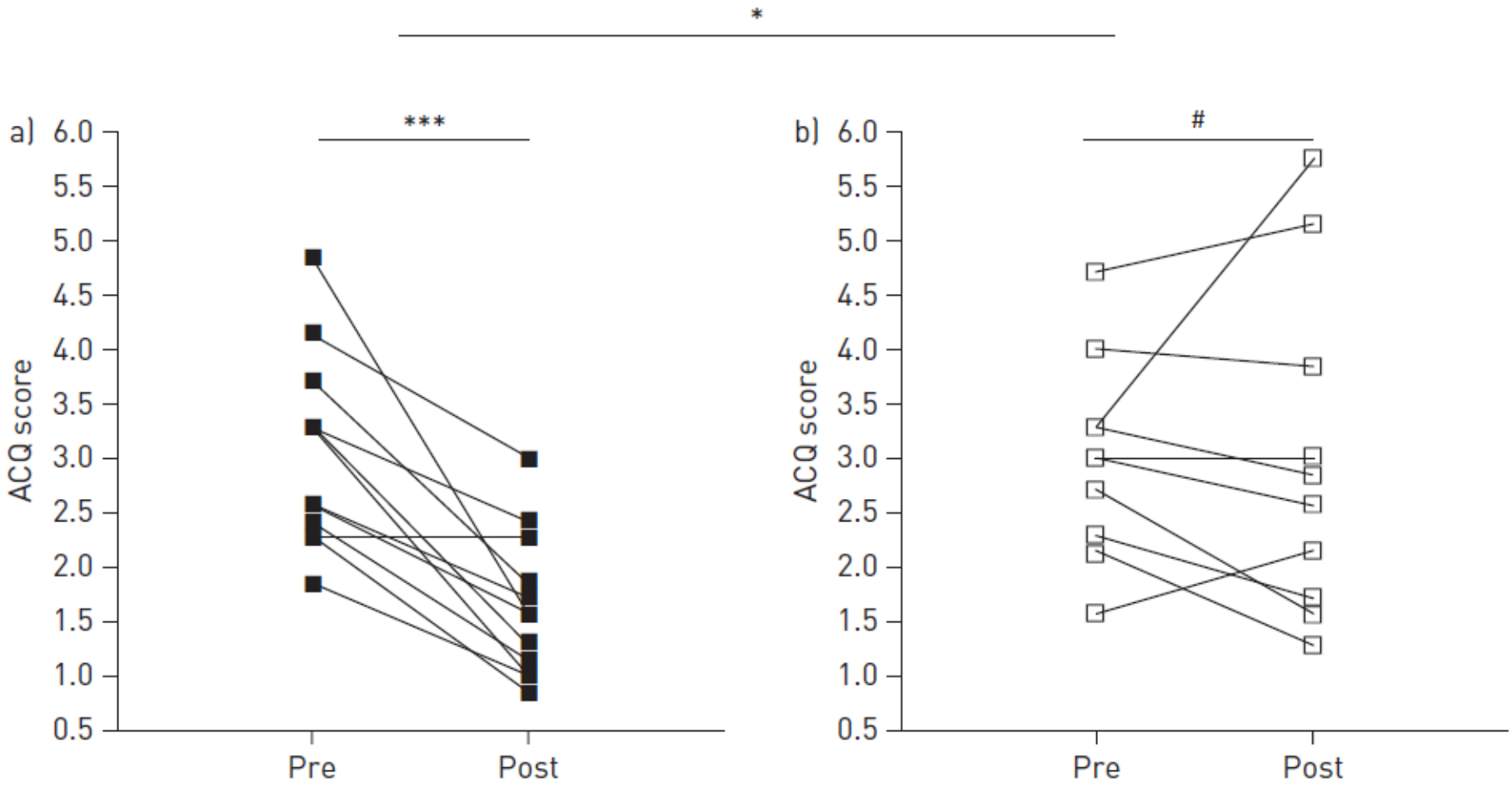
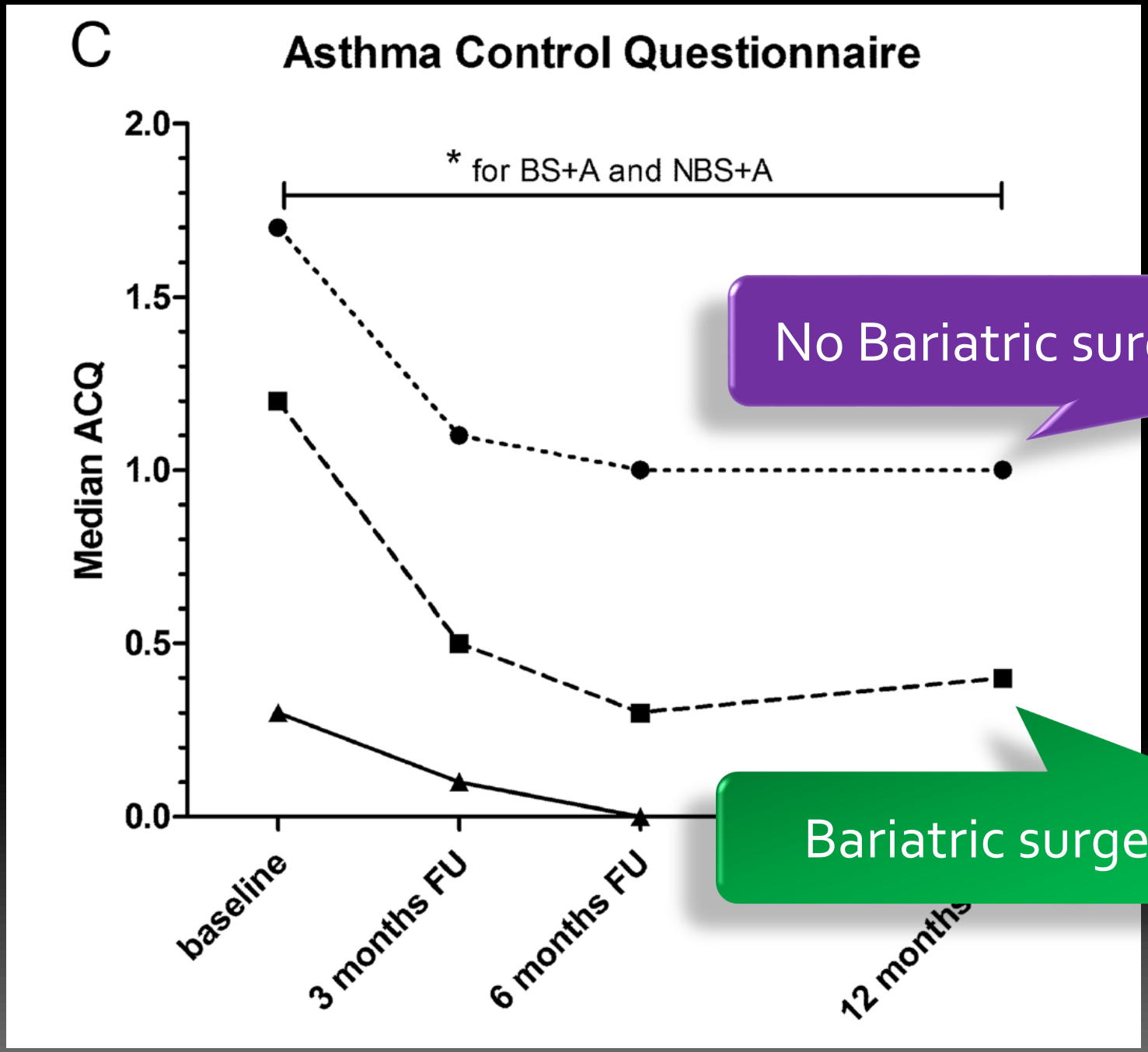
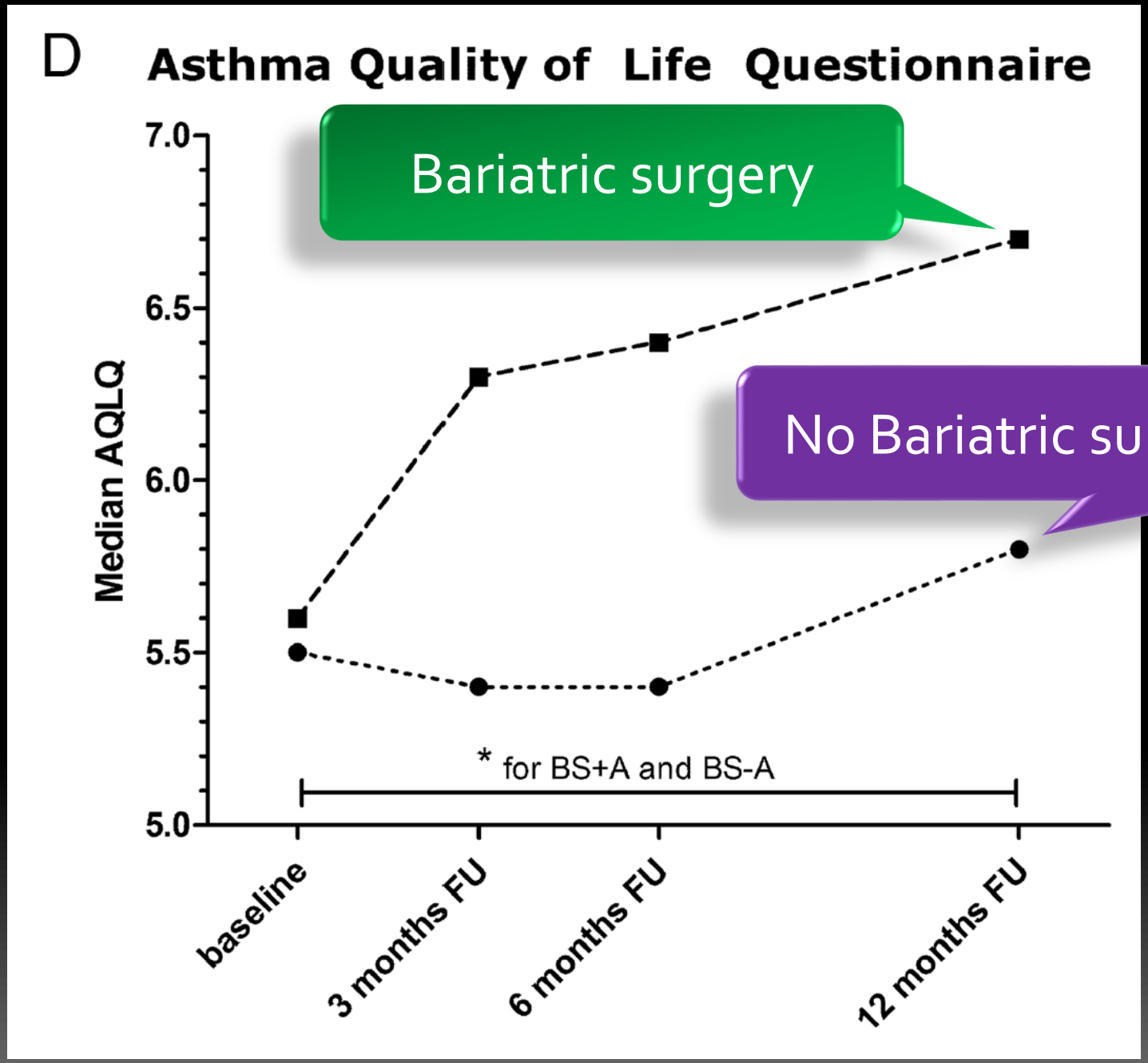


FIGURE 2 Impact of degree of weight loss on Asthma Control Questionnaire (ACQ) score. a) >10% weight loss; b) ⩽10% weight loss. *: $p<0.05$; ***: $p<0.001$; #: $p=0.974$.

Dias-Junior SA. Eur Respir J 2014; 43: 1368-1377.



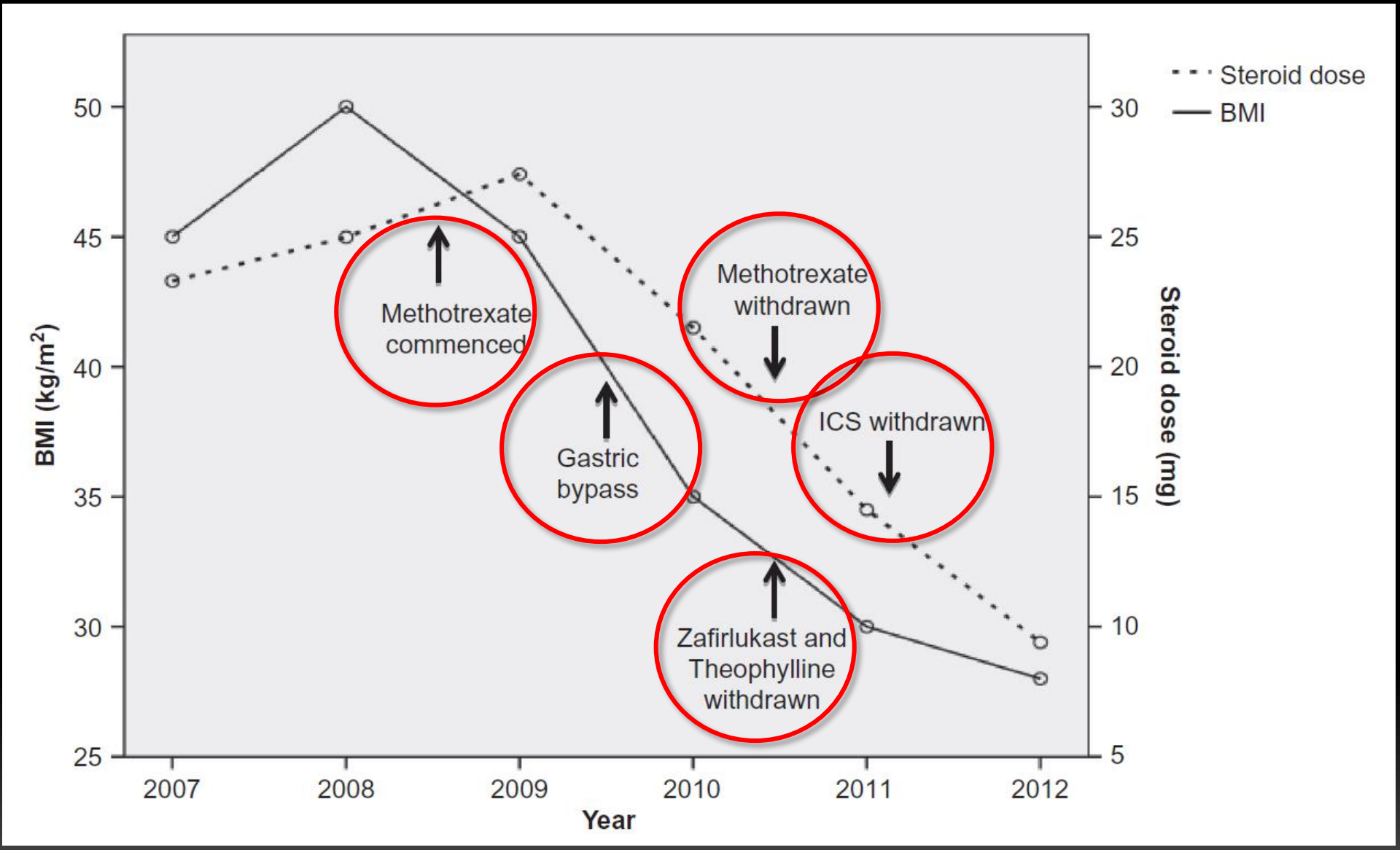
van Huisstede A. Thorax 2015; 70: 659-667.



van Huisstede A. Thorax 2015; 70: 659-667.

	BS+A			
	Baseline	6-month FU	12-month FU	p Value*
hs-CRP (ng/mL)	36.0 (4.3–142.0)	10.1 (1.8–75.6)	7.1 (0.8–139.5)	<0.001
IL-6 (pg/mL)	0.7 (0.7–2.1)	0.7 (0.7–6.9)	0.7 (0.7–5.1)	0.211
IL-8 (pg/mL)	3.9 (2.7–13.5)	4.3 (2.4–10.0)	4.8 (1.2–13.3)	0.124
TNFα (pg/mL)	0.8 (0.8–1.3)	0.8 (0.8–3.0)	0.8 (0.8–2.4)	0.715
GM-CSF (pg/mL)	0.6 (0.6–3.9)	0.6 (0.6–11.5)	0.6 (0.6–3.5)	0.401
Adiponectin (ng/mL)	12.0 (4.5–22.0)	17.0 (8.8–1000.0)	22.5 (9.7–1000.0)	<0.001
Leptin (ng/mL)	69 (18–100)	18 (2–98)	11 (0.2–69)	<0.001

van Huisstede A. Thorax 2015; 70: 659-667.



Evans S. J Asthma 2013; 50: 52-55.

OBES SURG (2014) 24:334–336
DOI 10.1007/s11695-013-1138-1

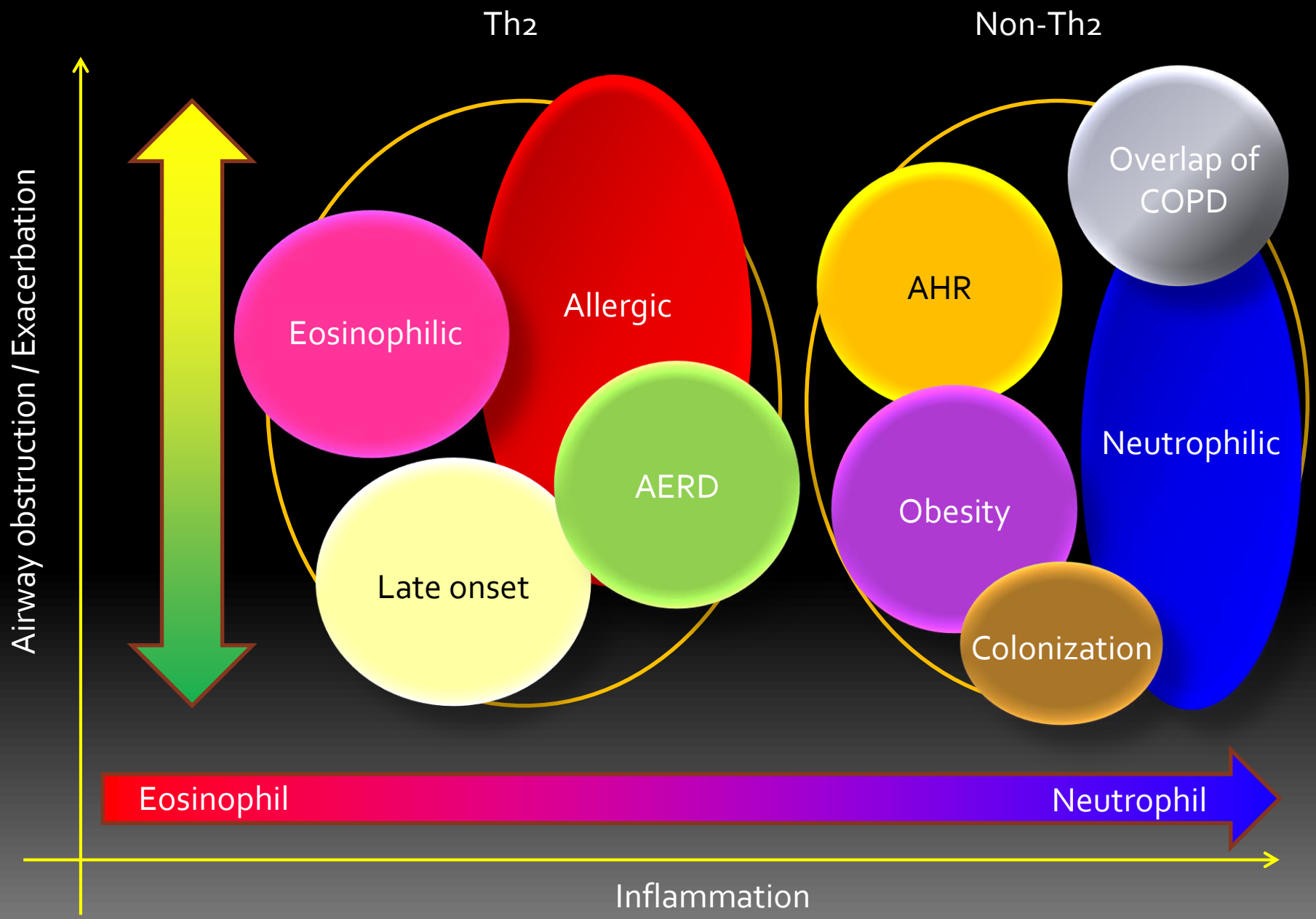
BRIEF COMMUNICATION

Can Bariatric Surgery be Performed Safely in Patients with Severe Treatment-Resistant Asthma?

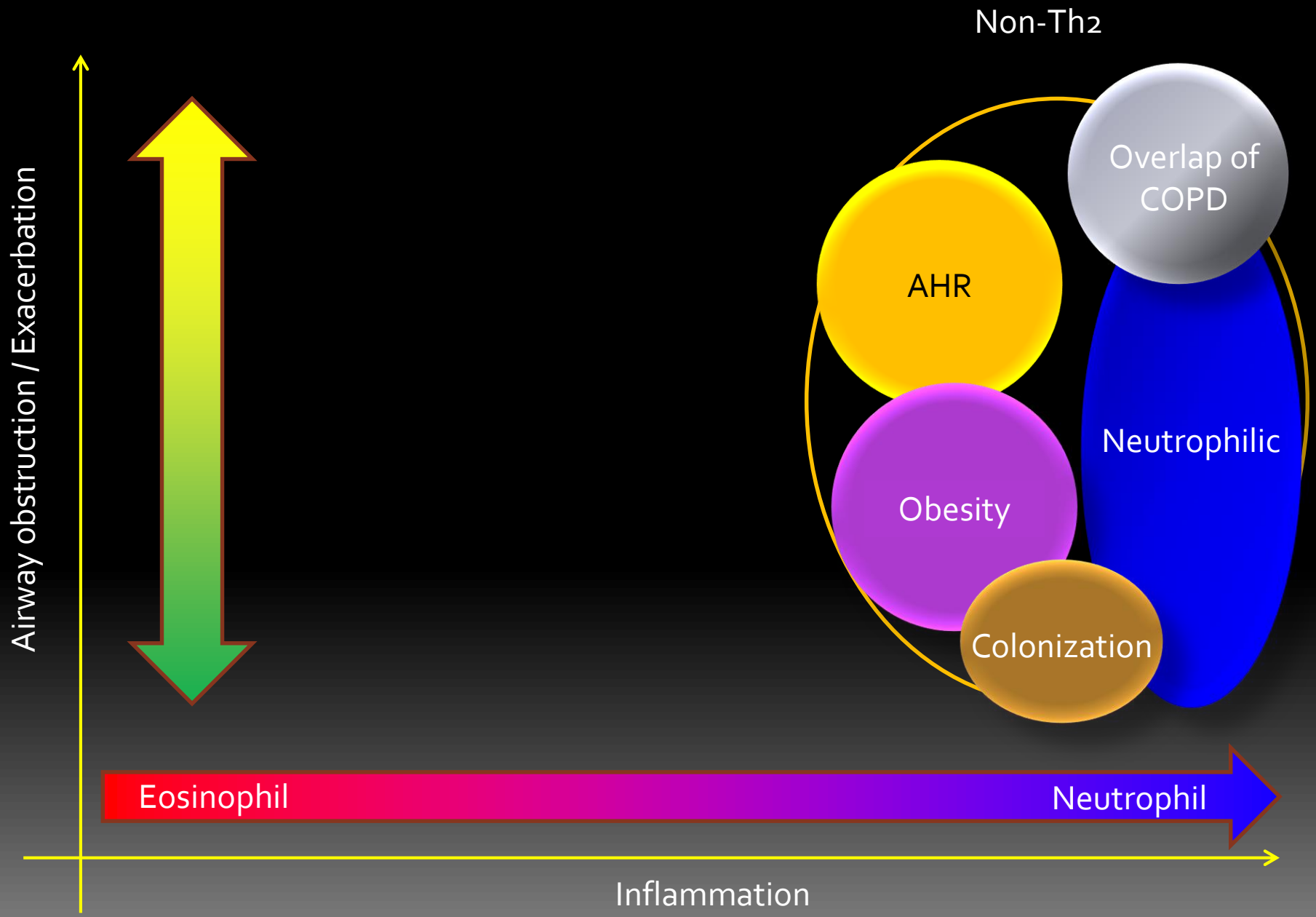
Joseph Jia Hong Toh · Shanker Pasupathy · Ruban A. L. Poopalalingam · Mariko Siyue Koh

Toh JJ. Obes Surg 2014; 24: 334-336.

Heterogeneity of severe asthma



Biomarkers & Tx Strategies in T2-low Asthma



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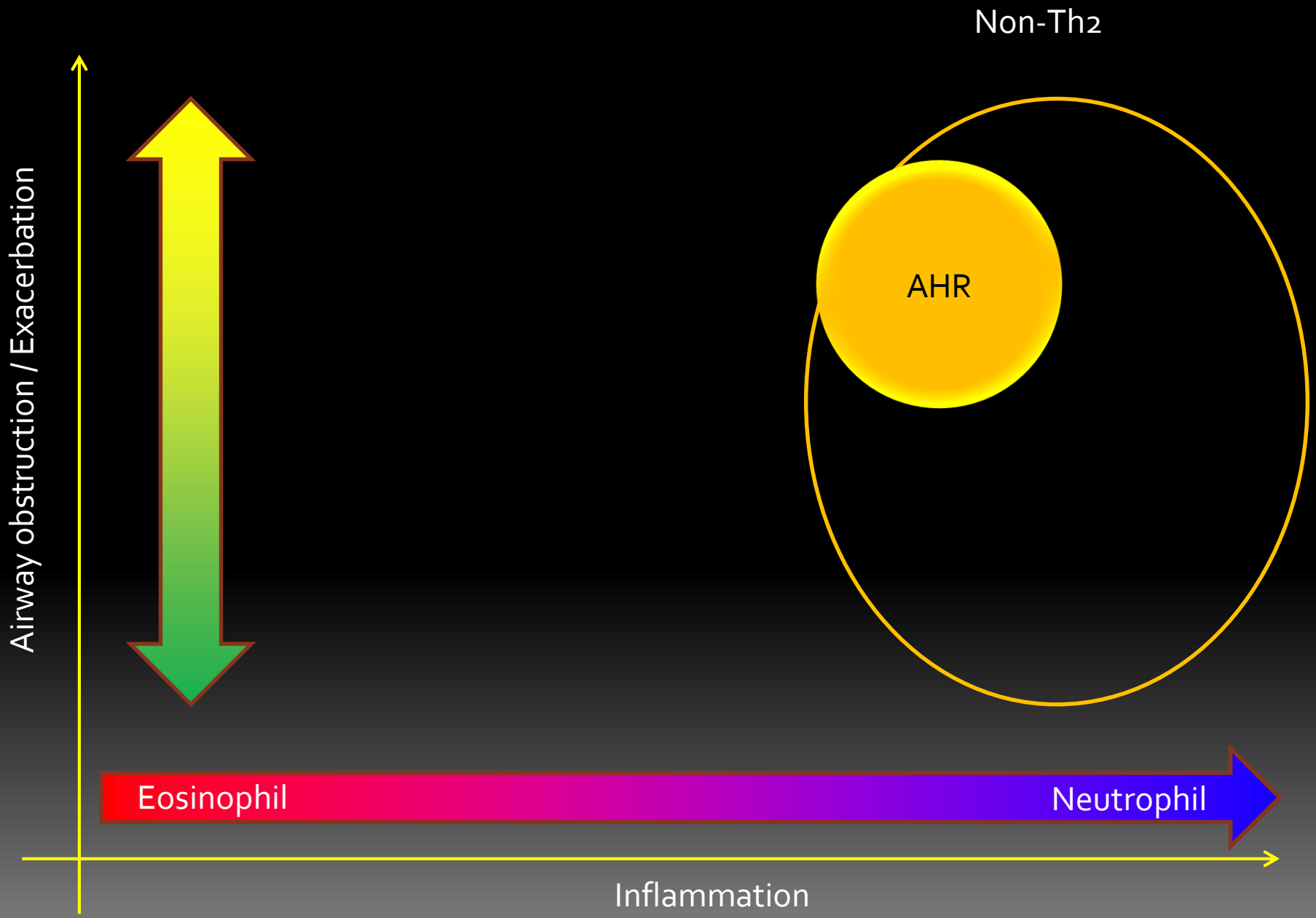

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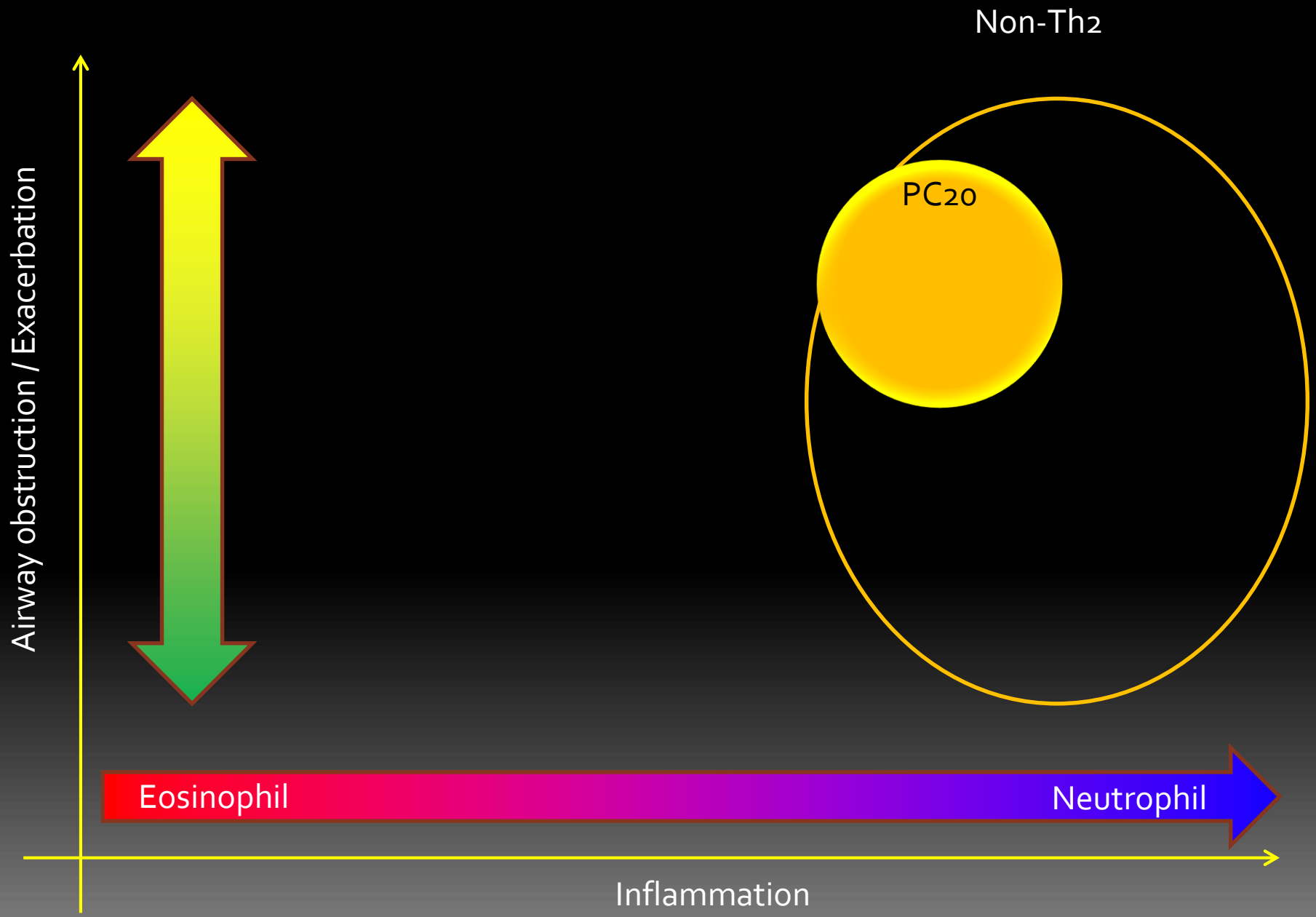

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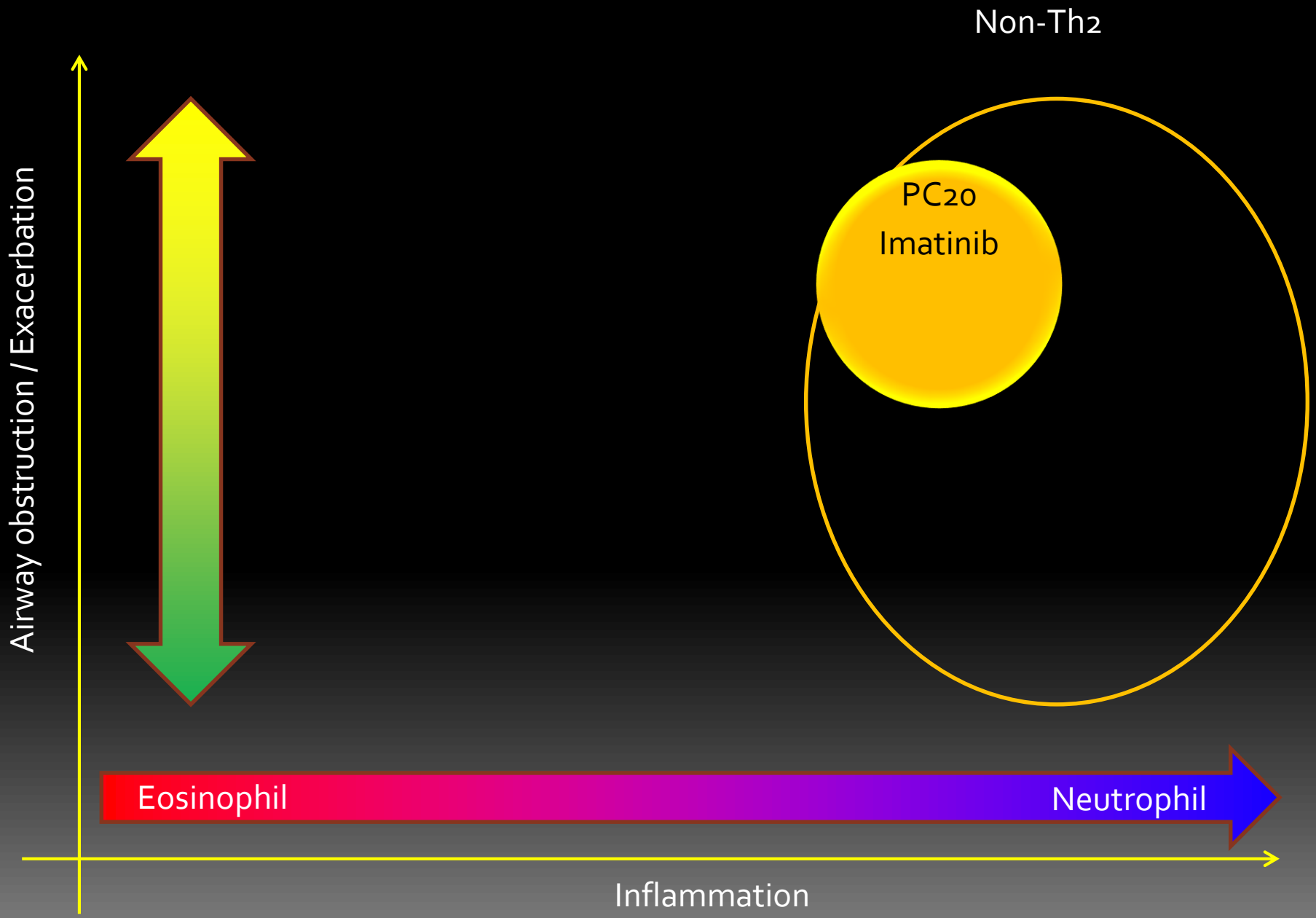

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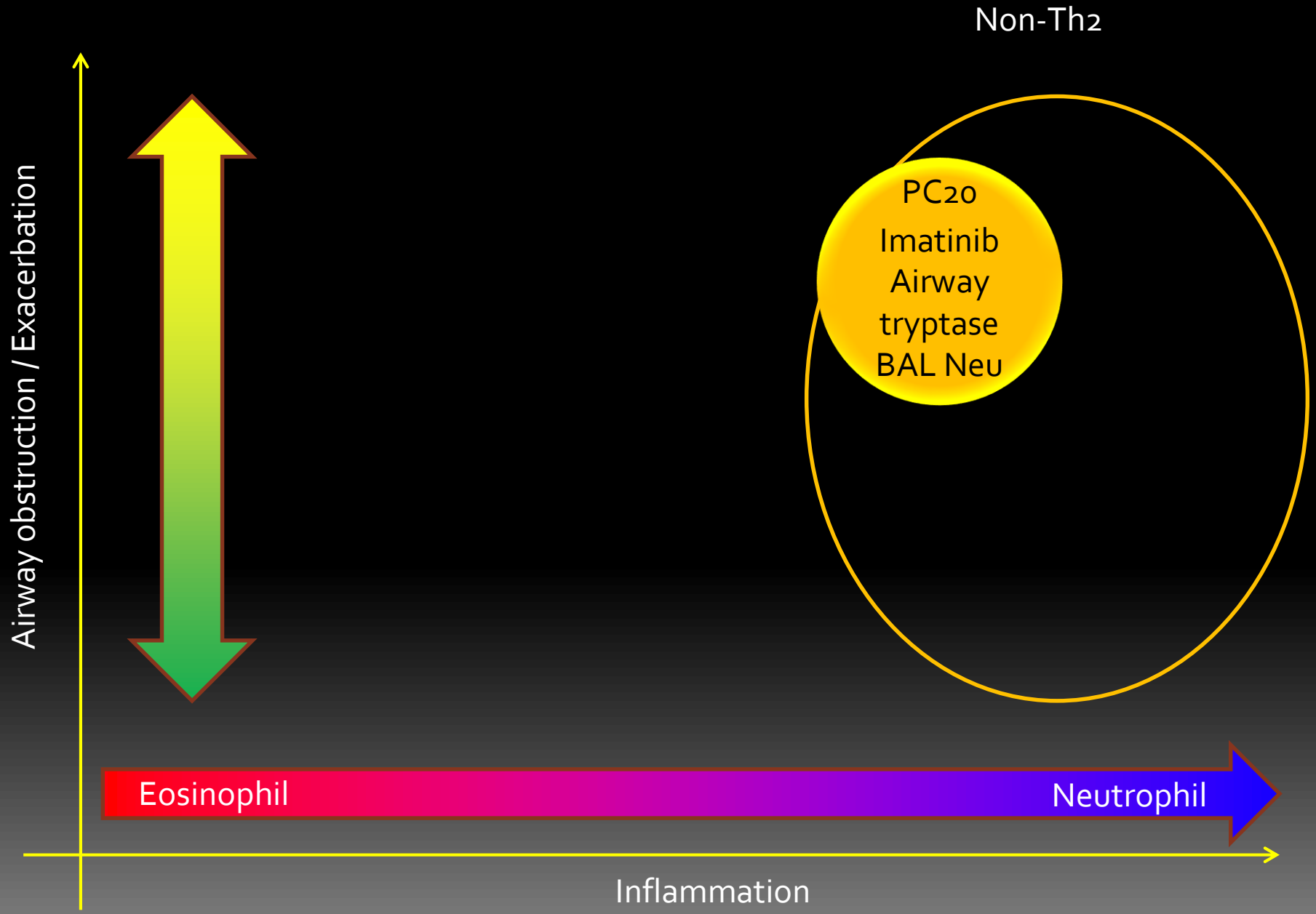

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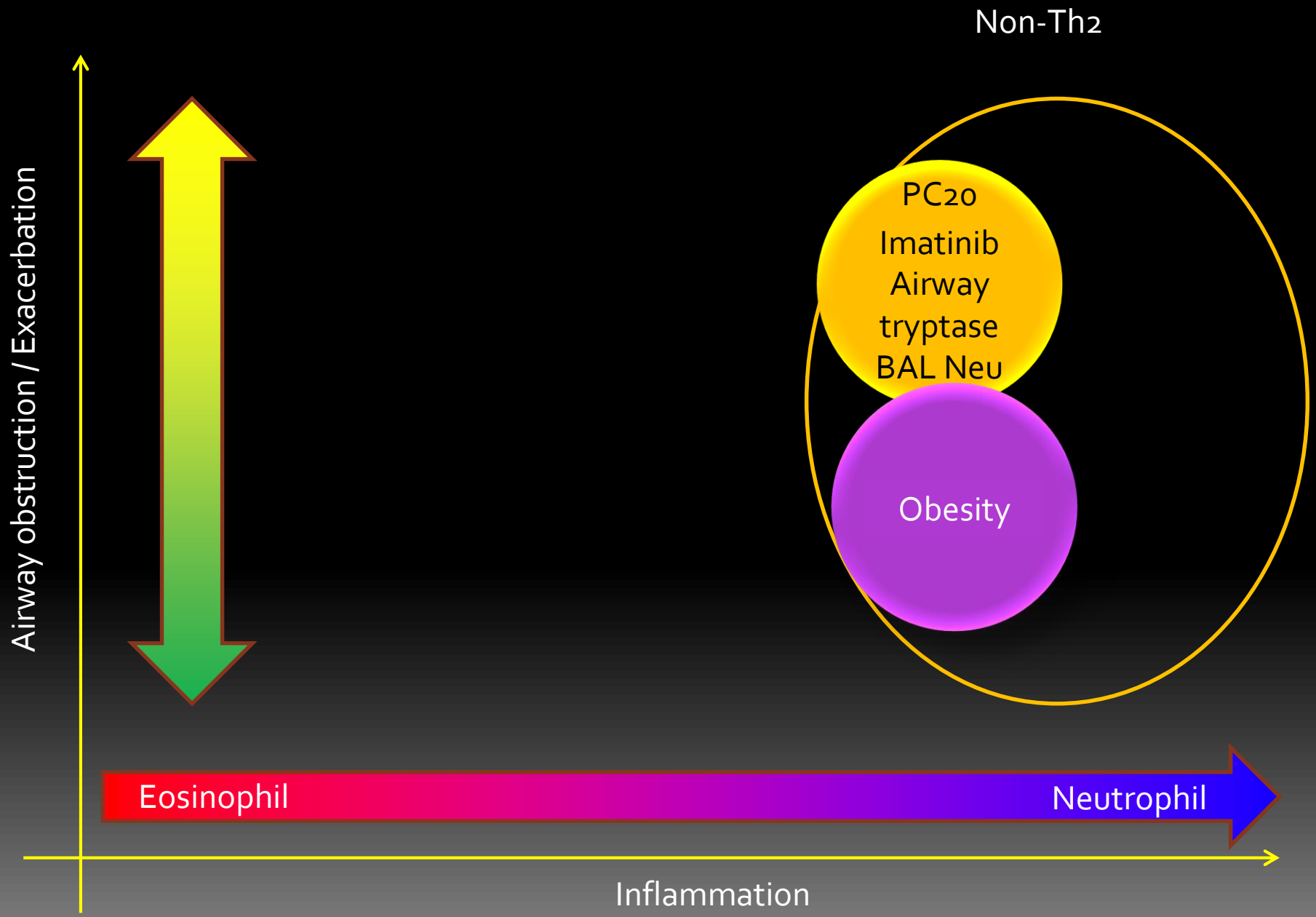

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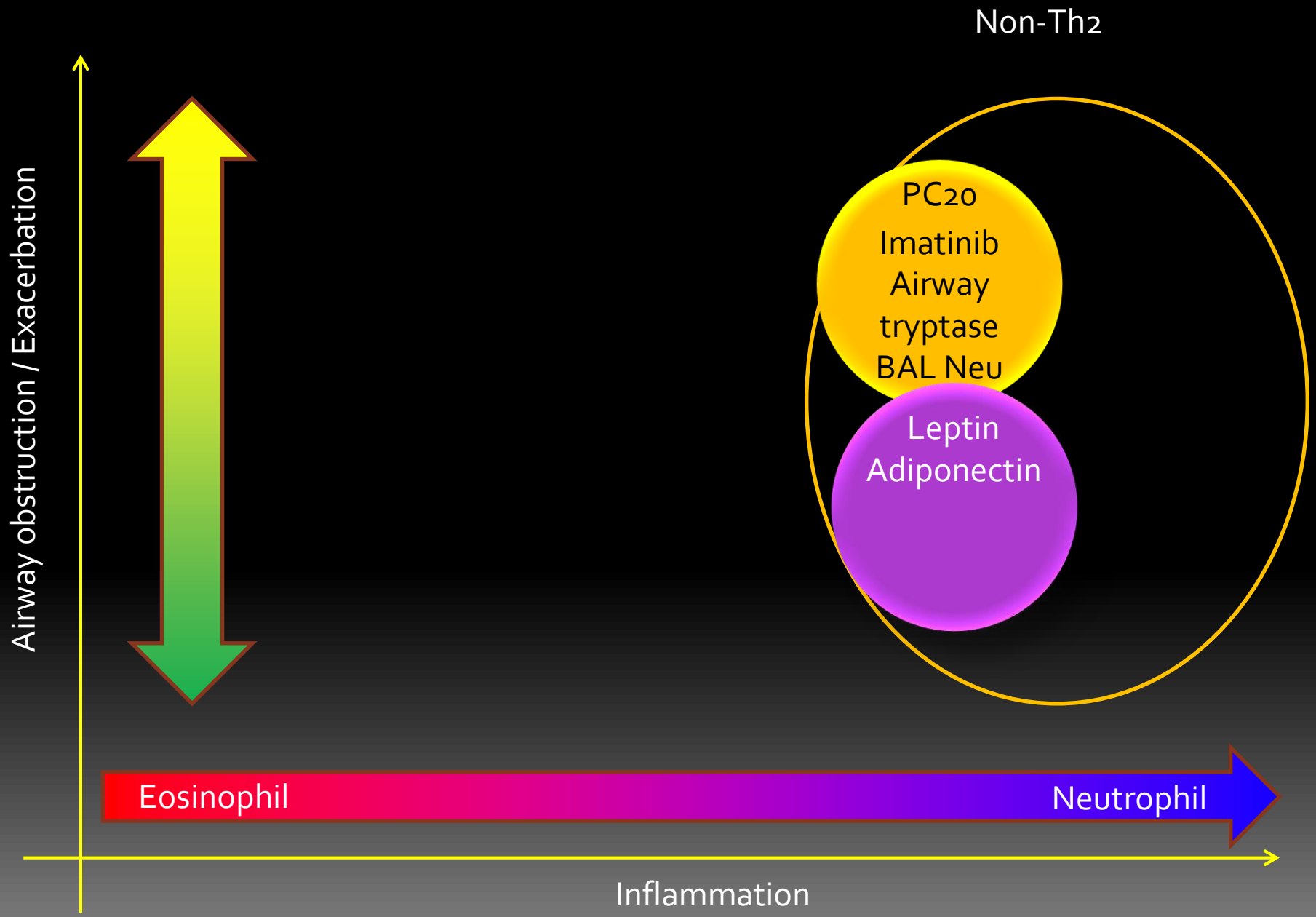

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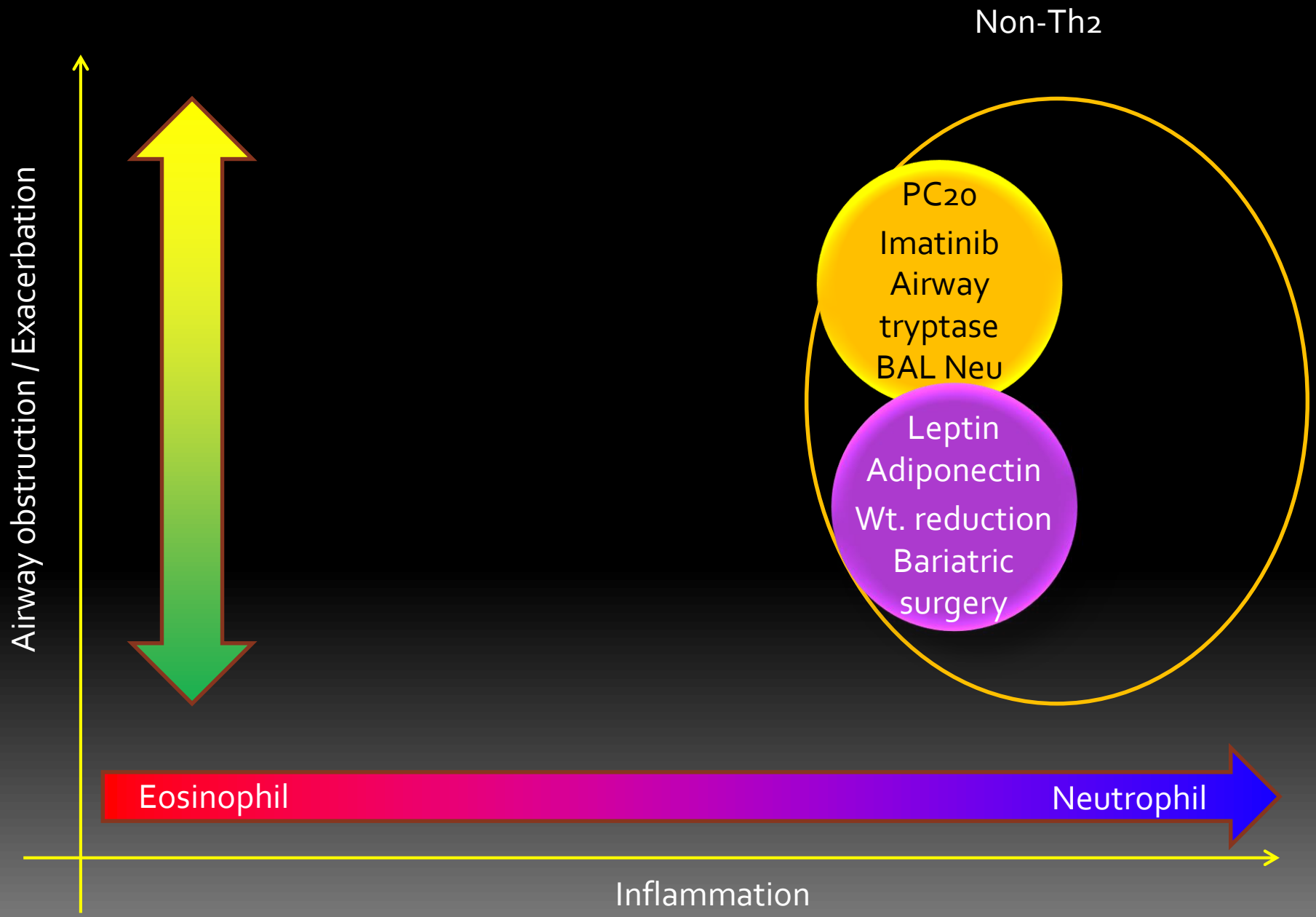

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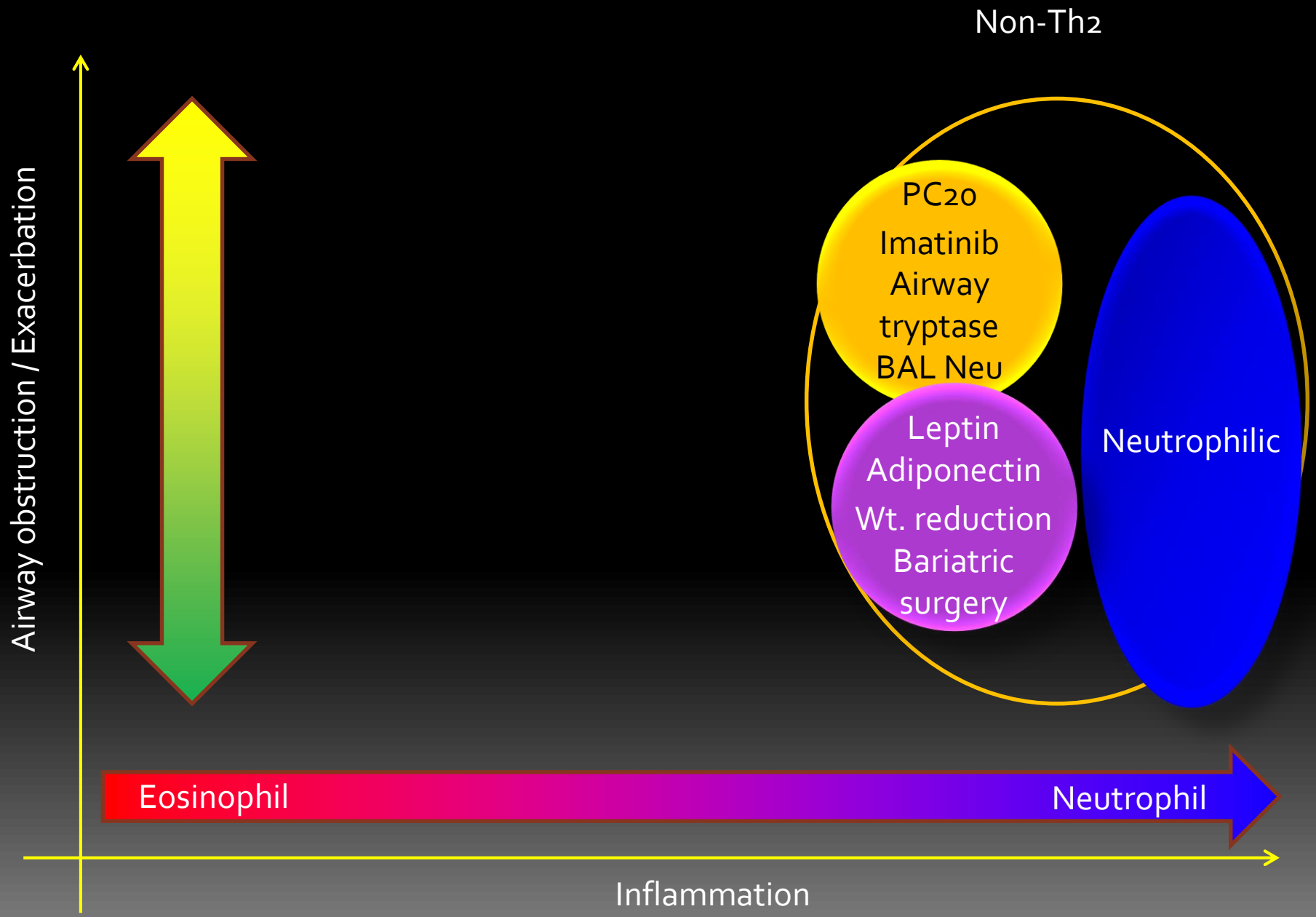

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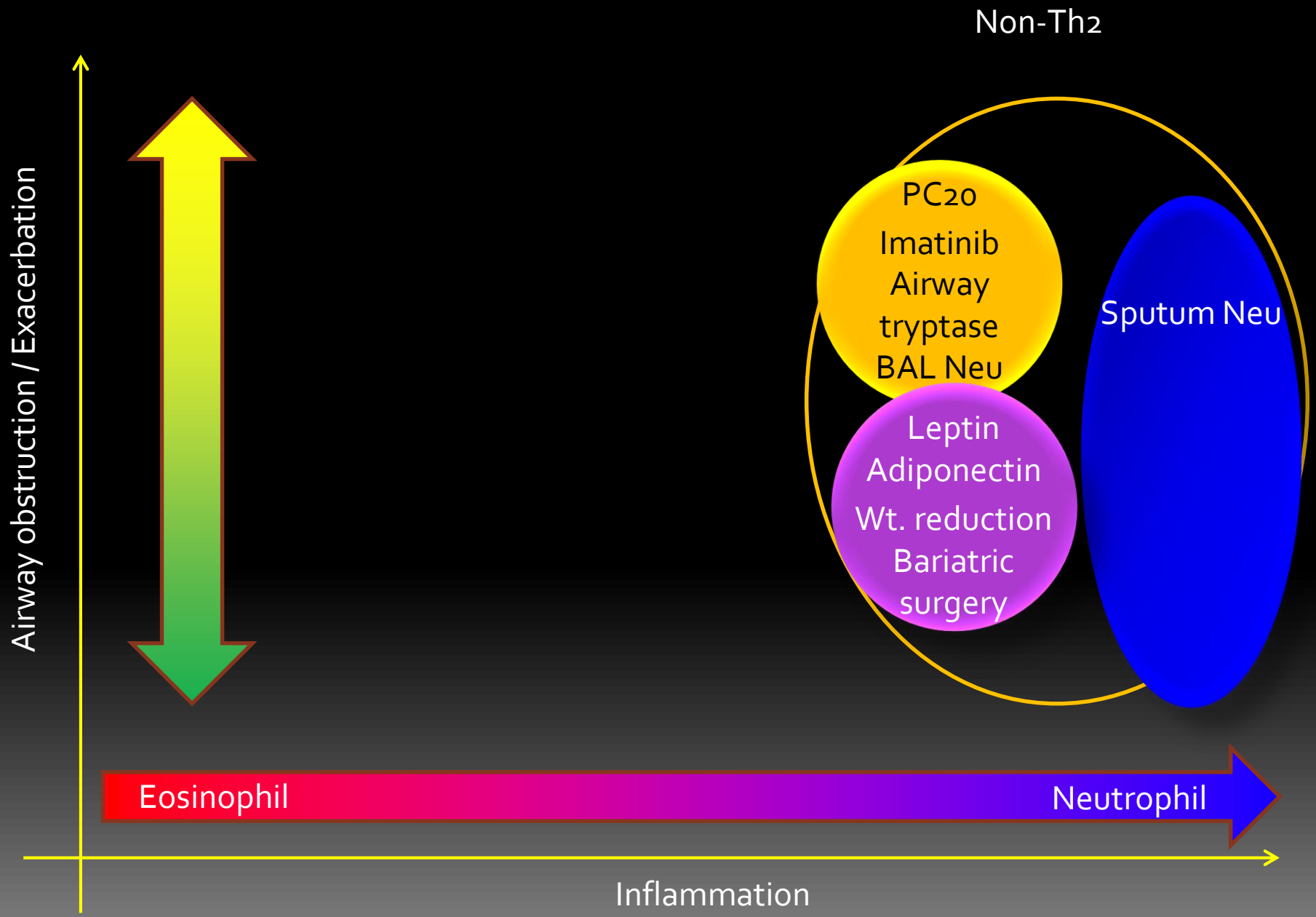

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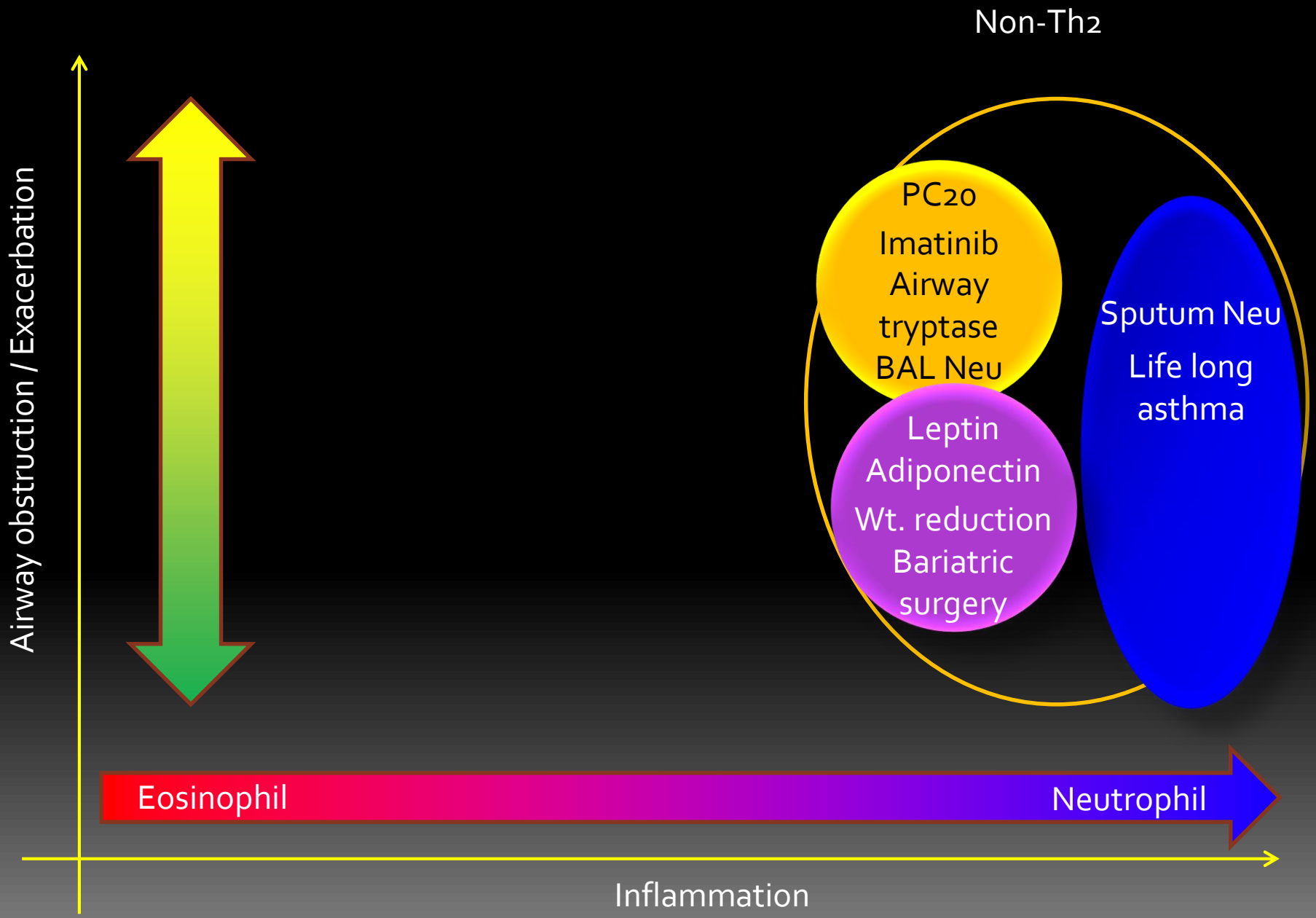

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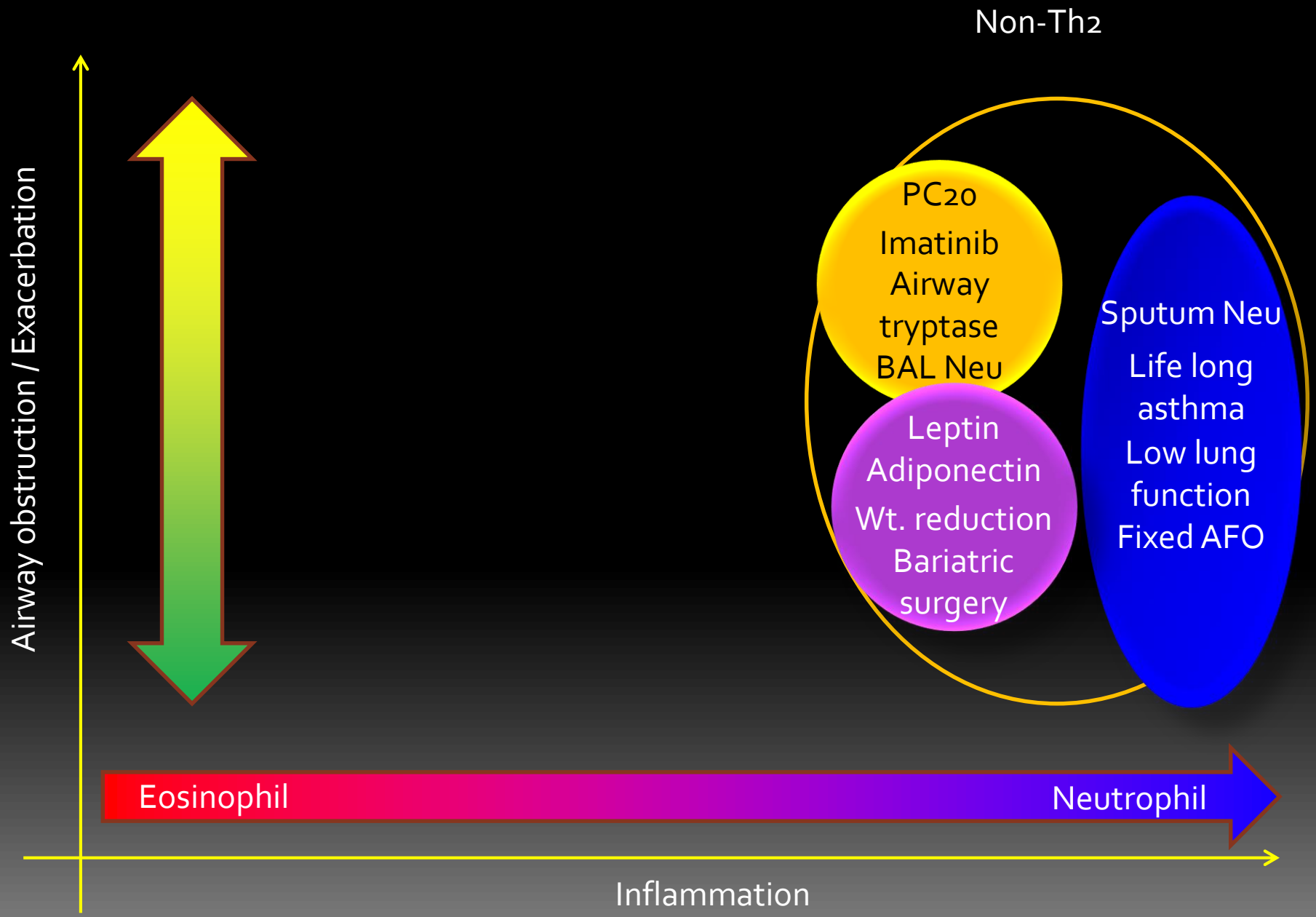

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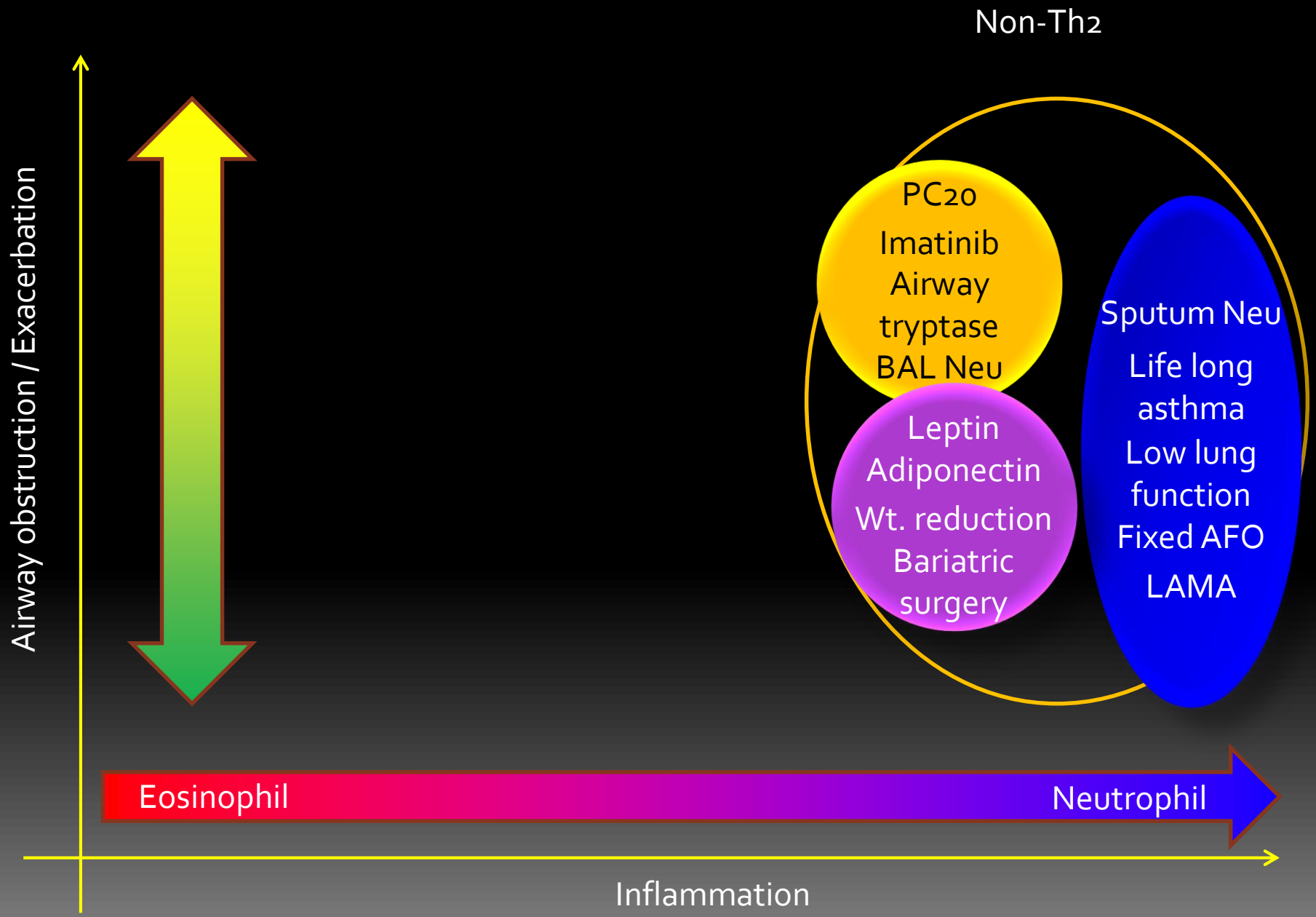

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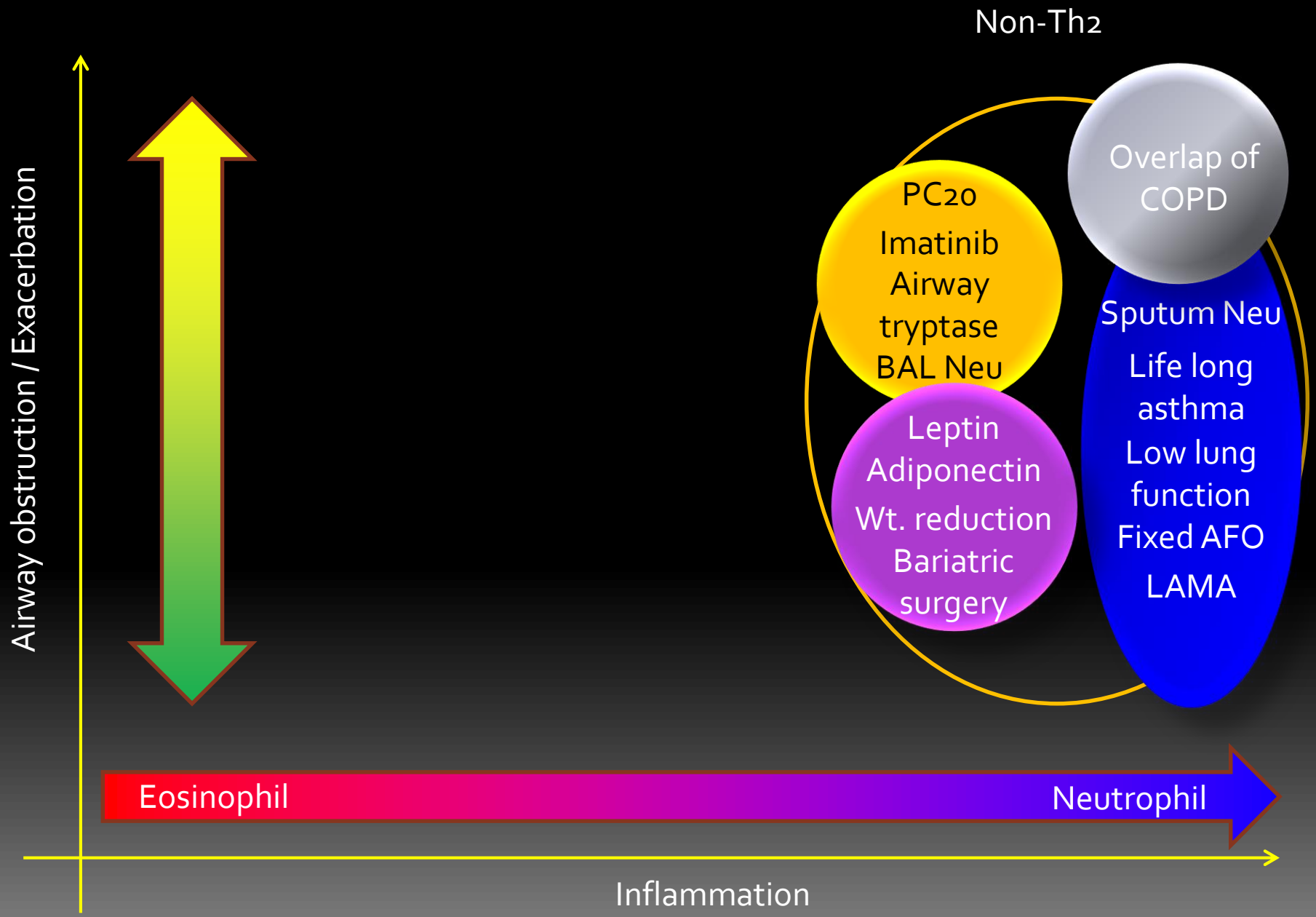

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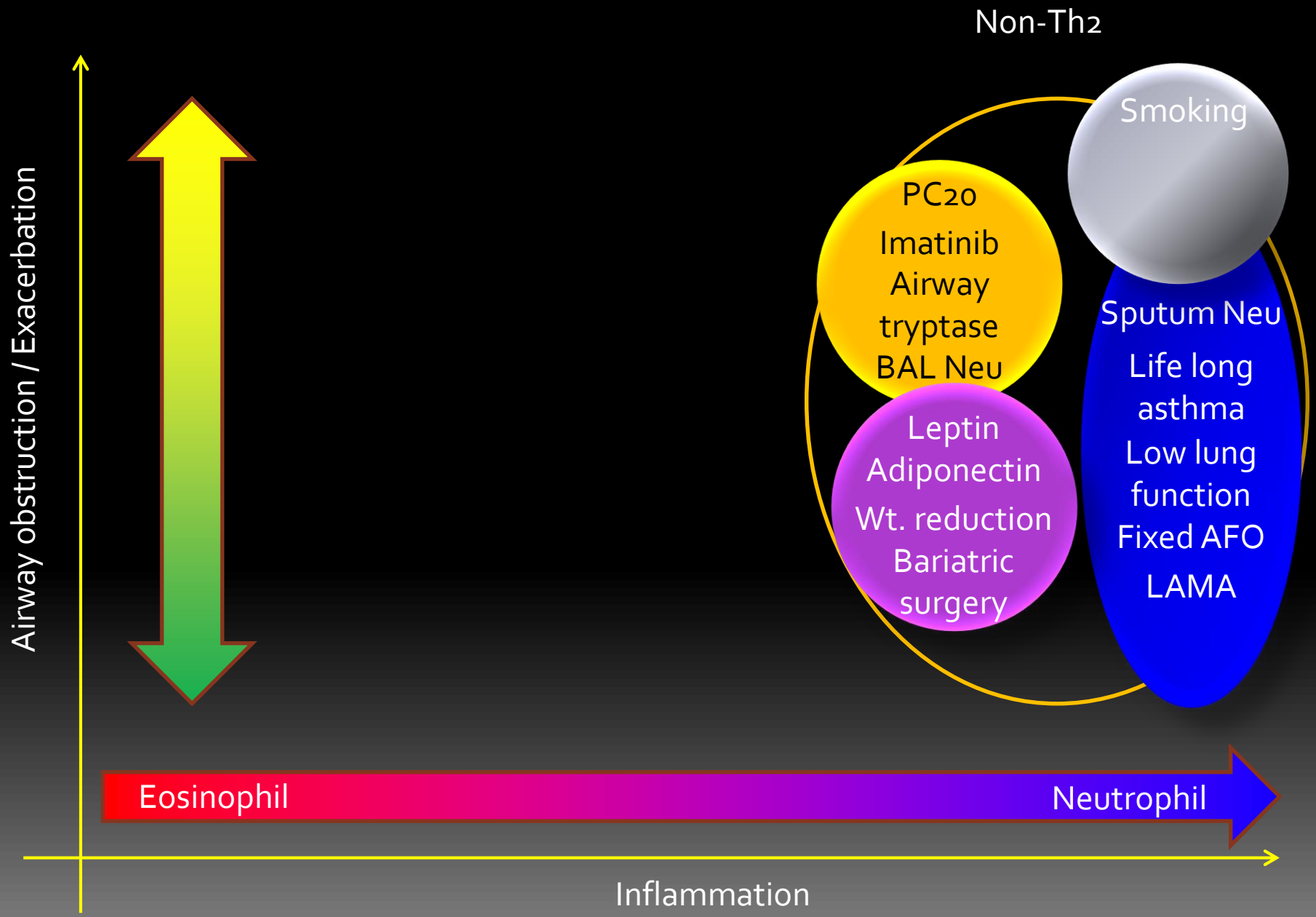

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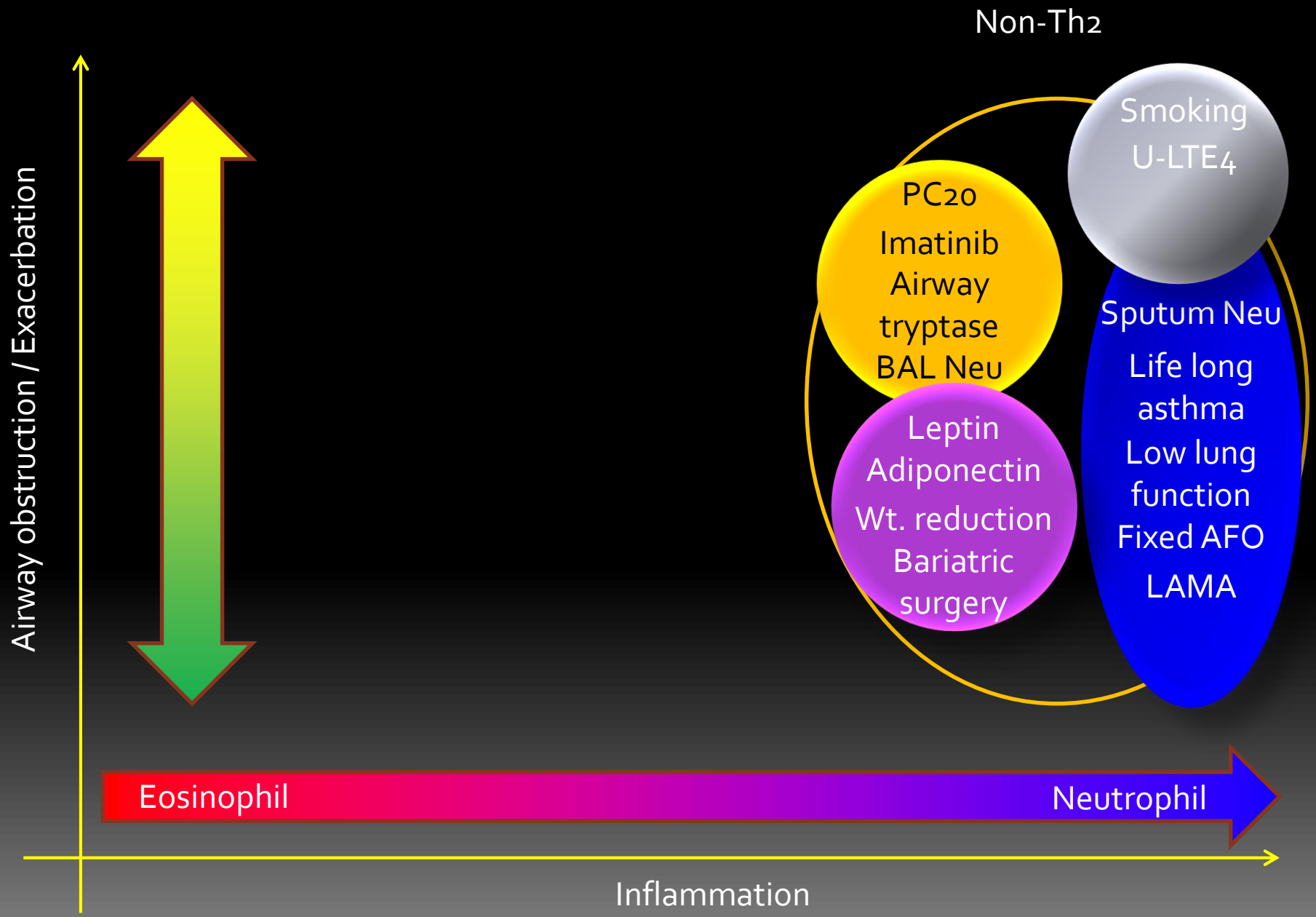

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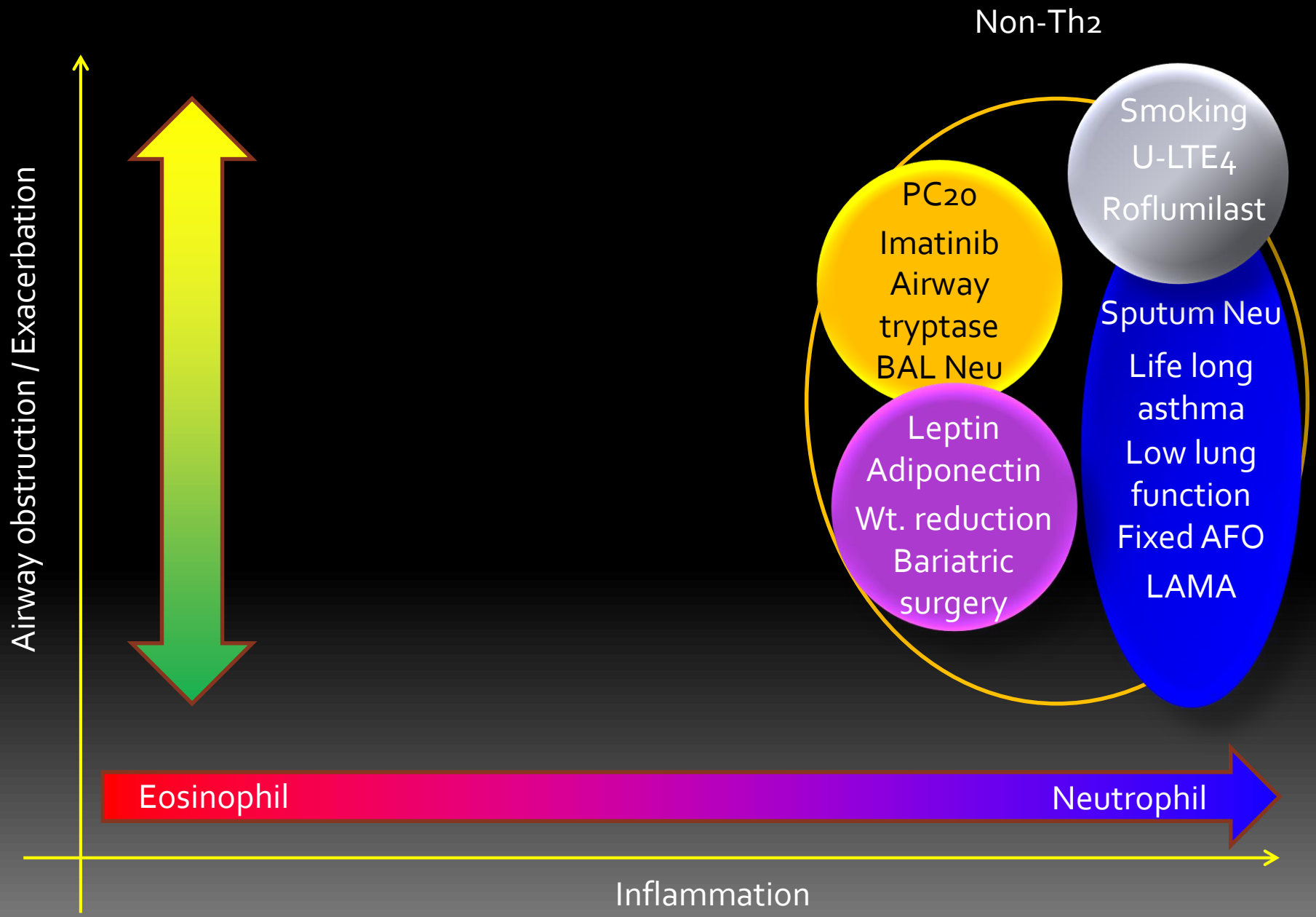

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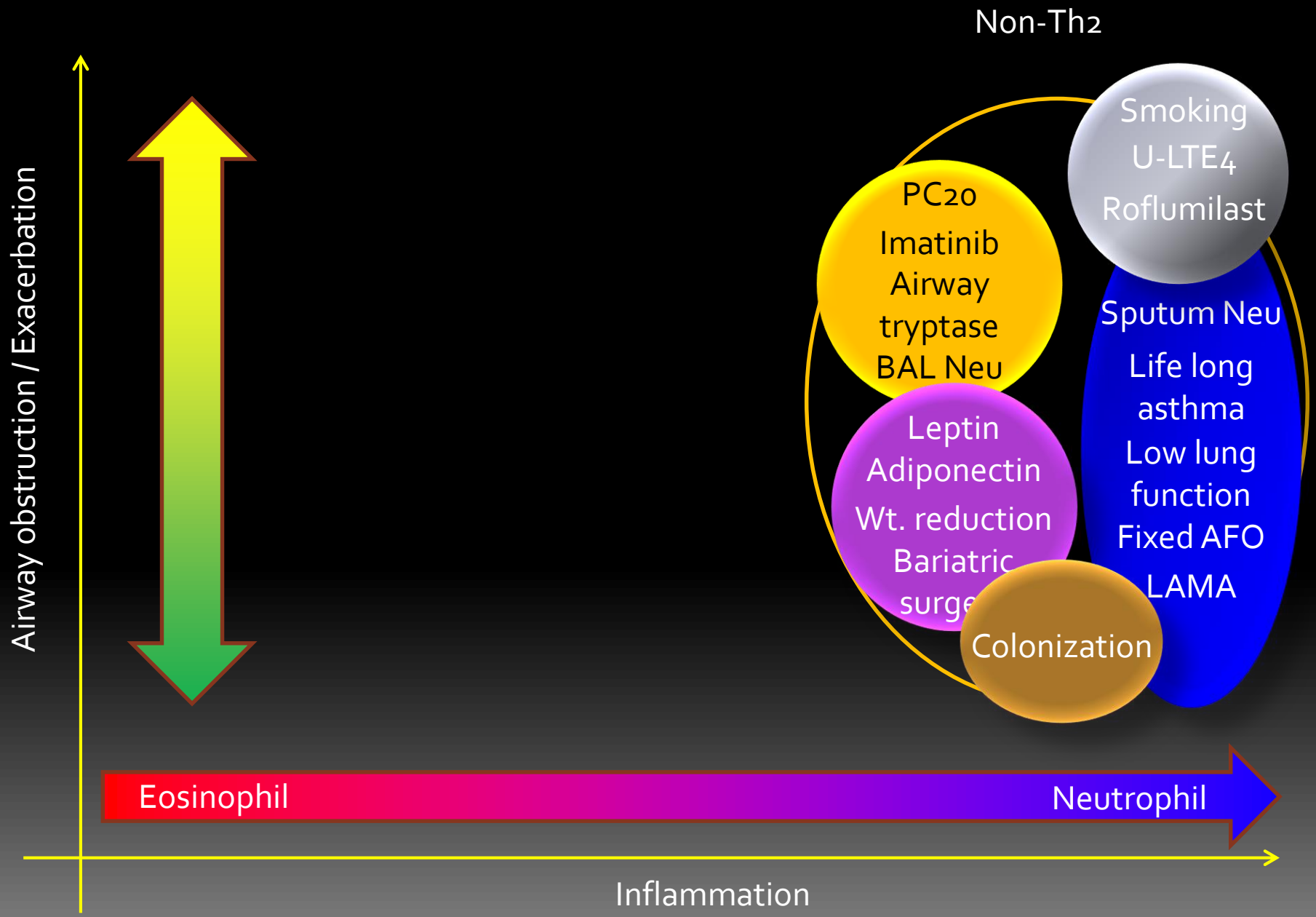

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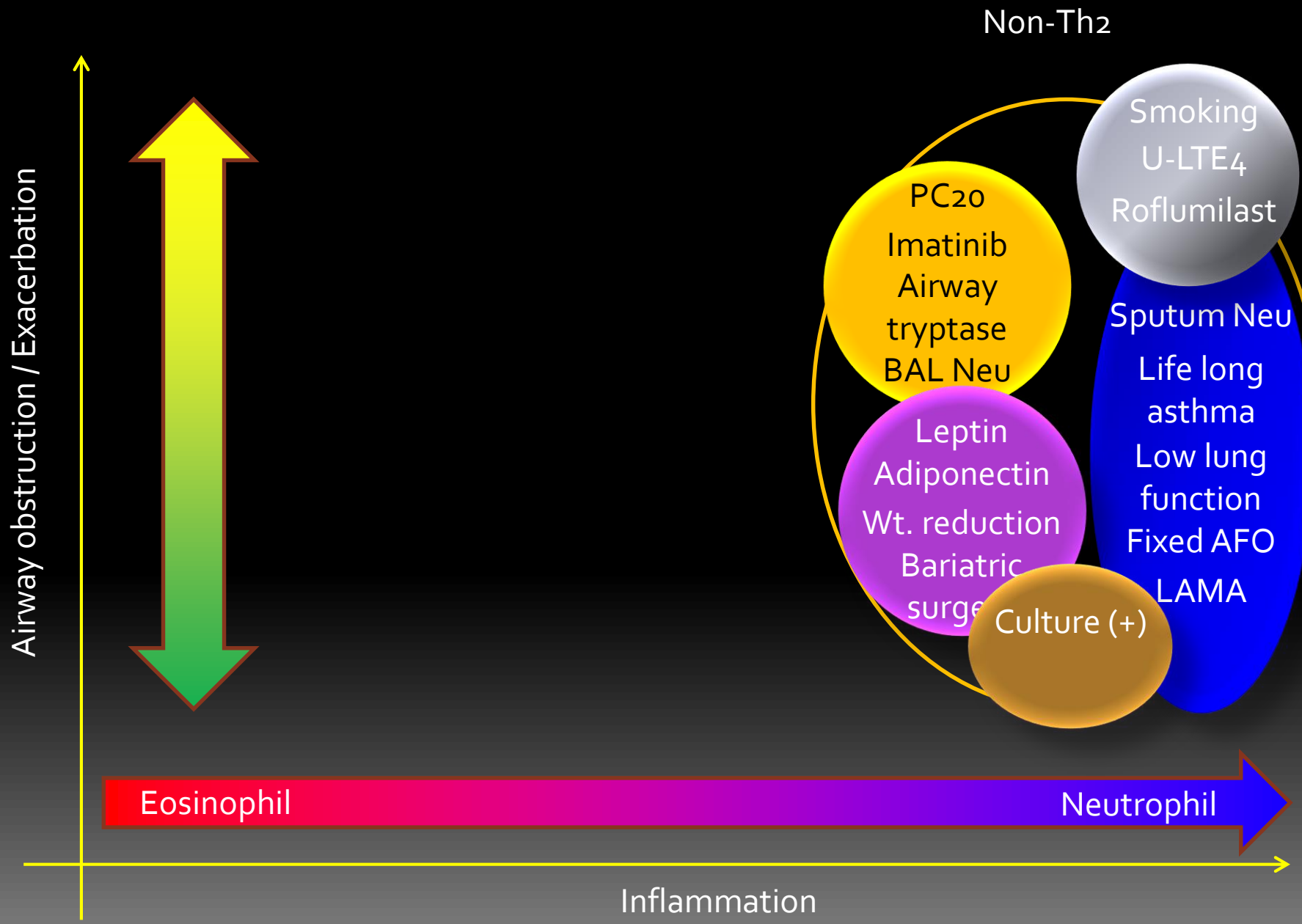

Biomarkers & Tx Strategies in T2-low Asthma

Tezepilumab

Airway obstruction / Exacerbation

Box 1. Differential diagnoses in severe asthma*.

- **COPD**
- **Bronchiectasis**
- **Sarcoidosis**
- **Bronchiolitis obliterans**
- **Cystic Fibrosis**
- **Hypersensitivity pneumonitis**
- **Hypereosinophilic lung diseases**
- **Tracheobronchomalacia**
- **Pulmonary embolism**
- **Coronary Heart Failure**
- **Endobronchial tumor/foreign body**

*Differential diagnostic conditions which commonly co-exist with asthma are listed under co-morbidities in Table 2.

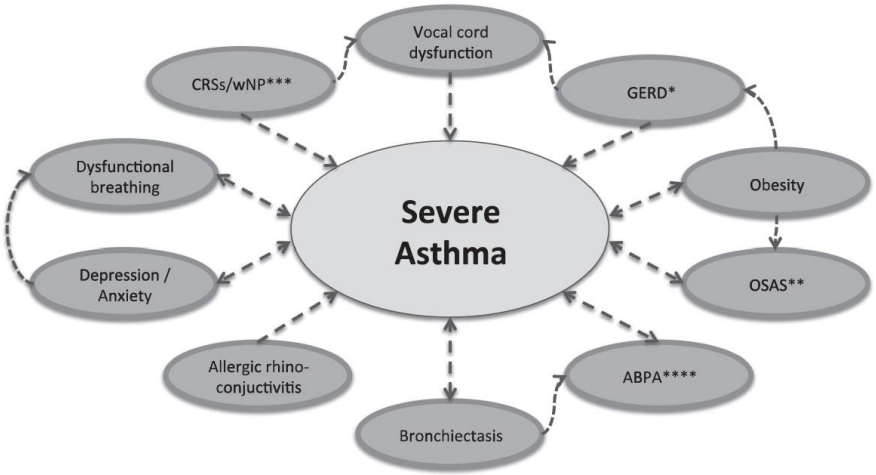

Figure 1 Co-morbidities in severe asthma: possible cause-and-effect relationships. ABPA, allergic bronchopulmonary aspergillosis; CRSsNP, chronic rhinosinusitis (CRS) without nasal polyps; CRSwNP, CRS with nasal polyps; GERD, gastroesophageal reflux disease; OSAS, obstructive sleep apnoea syndrome.

PC20
Imatinib
Airway tryptase
BAL Neu

Smoking
U-LTE4
Roflumilast

Sputum Neu
Life long asthma
Low lung function
Fixed AFO
LAMA

Leptin
Adiponectin
Vt. reduction
Bariatric surge

Culture (+)
Macrolide

Eos

Neutrophil

Inflammation