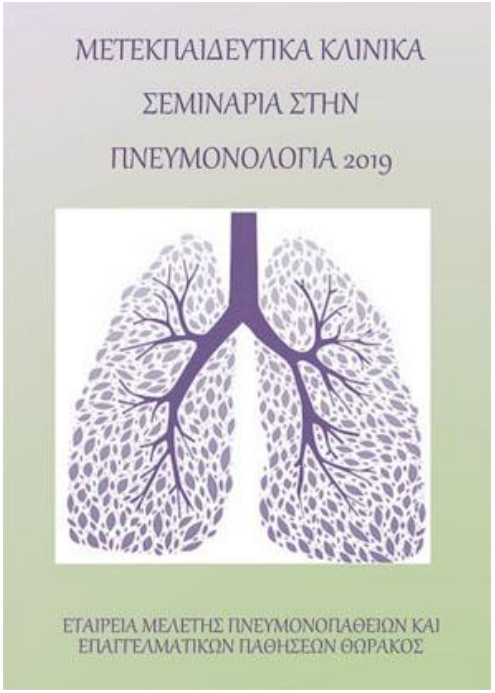


Ήπιο άσθμα: Τι θεραπεύουμε;

Θεσσαλονίκη 23/02/2019, Mediterranean Palace Hotel

Παπαϊωάννου Αντώνιος
Πνευμονολόγος-Επιστημονικός συνεργάτης Πνευμονολογικής κλινικής Α.Π.Θ.

Conflict of interest

Participated in advisory boards and received honoraria and travel grants of the following companies:

- AstraZeneca
- Boehringer-Ingelheim
- Chiesi
- Elpen
- GSK
- Innovis
- Menarini
- Novartis

Ορισμός άσθματος

Το άσθμα είναι μια ετερογενής νόσος, που συνήθως χαρακτηρίζεται από χρόνια φλεγμονή των αεραγωγών.

Χαρακτηρίζεται από ιστορικό αναπνευστικών συμπτωμάτων όπως συριγμός, αίσθημα βάρους στο στήθος και βήχα, συμπτώματα που αυξομειώνονται στην πάροδο του χρόνου, καθώς επίσης και από μεταβλητή απόφραξη των αεραγωγών.

ΠΑΘΟΓΕΝΕΙΑ ΑΣΘΜΑΤΟΣ

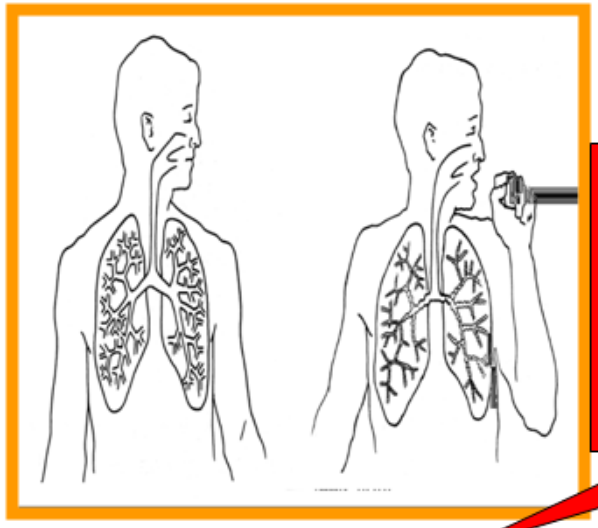
Asthma Triggers

Παθοφυσιολογία του άσθματος

- Σύσπαση των λείων μυικών ινών
- Πάχυνση του βλεννογόνου

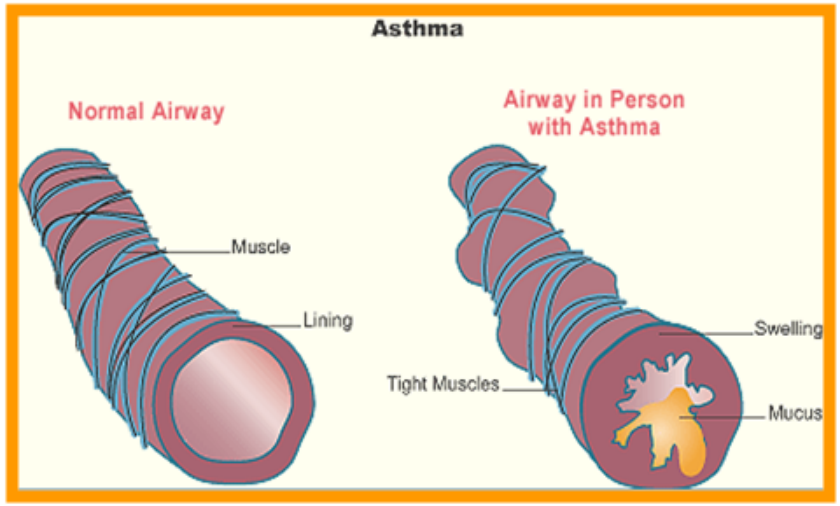
(από αγγειοδιαστολή, οίδημα, κυτταρική διήθηση)

- Συσσώρευση βλέννης και κυτταρικών υλικών στον αυλό των αεραγωγών



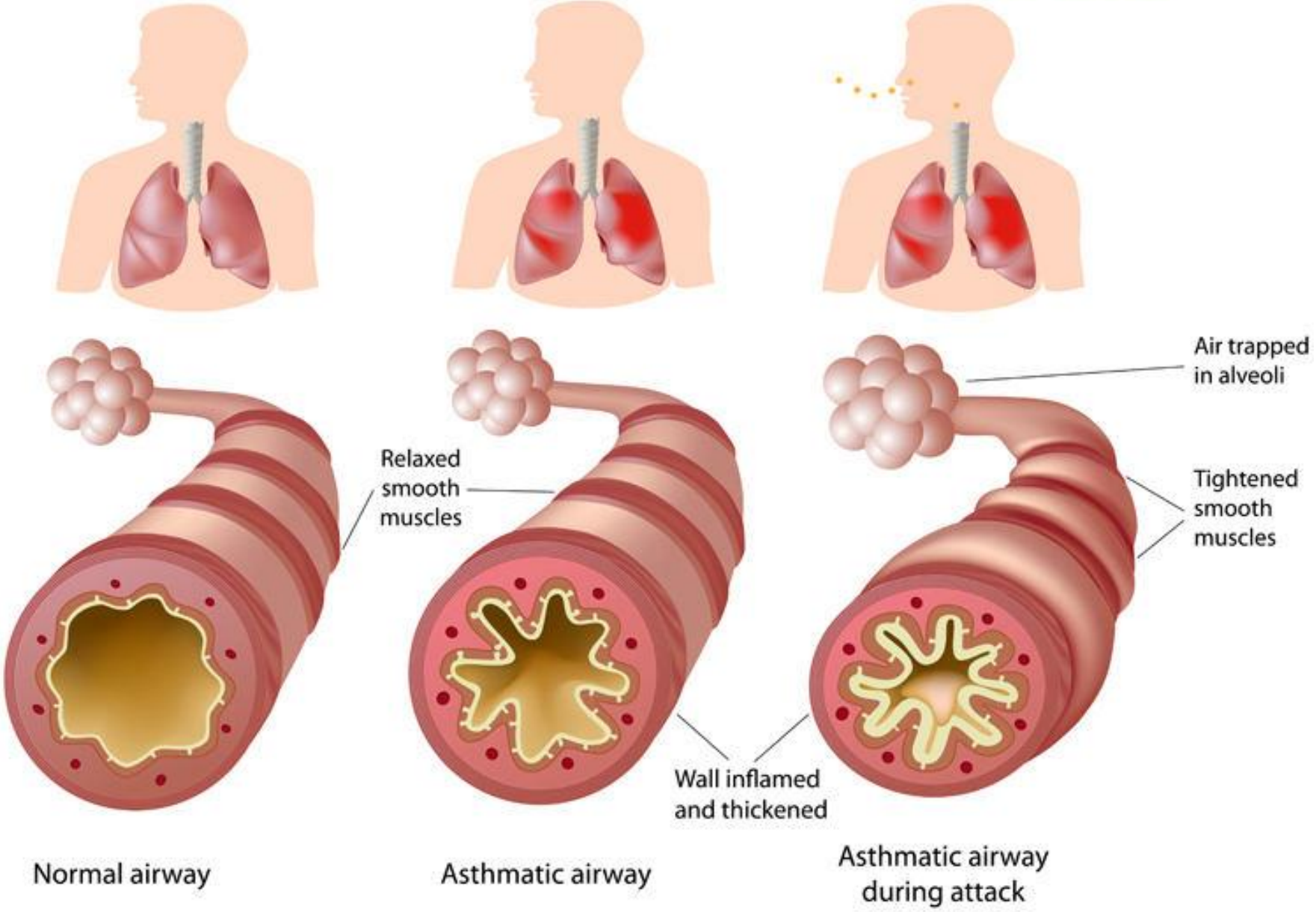
Στο άσθμα υπάρχει φλεγμονή των αεραγωγών

Φυσιολογικός Ασθματικός



Source: "What You and Your Family Can Do About Asthma" by the Global Initiative For Asthma
Created and funded by NIH/NHLBI, 1995

Pathology of Asthma



Μακροπρόθεσμες συνέπειες της φλεγμονής – παρούσες ακόμα και στο ήπιο άσθμα

Φυσιολογικός πνεύμονας

Πνεύμονας ήπιου ασθματικού ασθενούς

Evaluation of conditions that mimic asthma

Diagnosis	Clinical features	Testing
Alpha-1 antitrypsin deficiency	Dyspnea Family history emphysema	Alpha-1 antitrypsin: below 50 to 80 mg/dL (11 micromol/L) Genetic confirmation by isoelectric focusing or DNA PCR
Bronchiectasis	Daily sputum production Cough refractory to bronchodilators Sometimes end-inspiratory squeak May have rhinosinusitis	HRCT thorax: bronchiectasis
Bronchiolitis	History of respiratory infection, inhalational injury, CTD, or lung transplant Crackles and inspiratory squeaks on exam	PFTs: DLCO and oxygen saturation are reduced HRCT thorax: interstitial opacities in a mosaic pattern, inspiratory and expiratory views may show focal air trapping
Cardiac disease*	Crackles or wheezes	B type natriuretic peptide: elevated Chest xray: increased interstitial opacities, ±cardiomegaly Echocardiogram: reduced ejection fraction
Central airway obstruction	Dyspnea on exertion Sometimes monophonic wheeze or stridor	PFTs: flattening of flow volume loop HRCT with 3-D reconstruction: narrowed airway Direct visualization: airway obstruction
Chronic eosinophilic pneumonitis	Asthma predates or develops in over 50 percent of patients Fever, weight loss and night sweats are common	Peripheral blood: ±eosinophilia Chest xray: bilateral peripheral opacities BAL: eosinophilia >40 percent
COPD*	Smoking history	PFTs: irreversible airflow obstruction and sometimes low DLCO
Hypersensitivity pneumonitis	Exposure to an inciting agent Abrupt onset fever, chills Dyspnea without wheezing	PFTs: restrictive or mixed obstructive/restrictive pattern Chest xray: fleeting pulmonary infiltrates HRCT thorax: ground glass opacities and parenchymal micronodules BAL: lymphocytosis Lung biopsy: poorly formed granulomata
Obstructive sleep apnea*	Daytime hypersomnolence Nocturnal choking Snoring	Polysomnogram: elevated respiratory disturbance index
Sarcoidosis* (endobronchial)	Nonproductive cough Dyspnea Cutaneous stigmata of sarcoidosis May have nasal or sinus sarcoid	Chest xray: Hilar adenopathy with or without interstitial opacities PFTs: restriction and reduced DLCO Endobronchial biopsy: noncaseating granulomata
Strongyloidiasis, filariasis	Travel to endemic country	Peripheral blood: eosinophilia IgG antibodies to strongyloides or filaria: positive
Vocal cord dysfunction*	Hoarseness/stridor (can be inspiratory and/or expiratory) Symptoms provoked by exercise	Flow volume loop: slowing on inspiration Direct laryngoscopy (possibly during exercise or methacholine challenge): abnormal cord motion

ANCA: antineutrophil cytoplasmic antibodies; BAL: bronchoalveolar lavage; CTD: connective tissue disease; DLCO: diffusing capacity; GERD: gastroesophageal reflux disease; HRCT: high resolution computed tomography; PFTs: pulmonary function testing; PPI: proton pump inhibitor.
* These conditions can also co-occur with asthma

Βρογχικό άσθμα και συννοσηρότητες

REVIEW

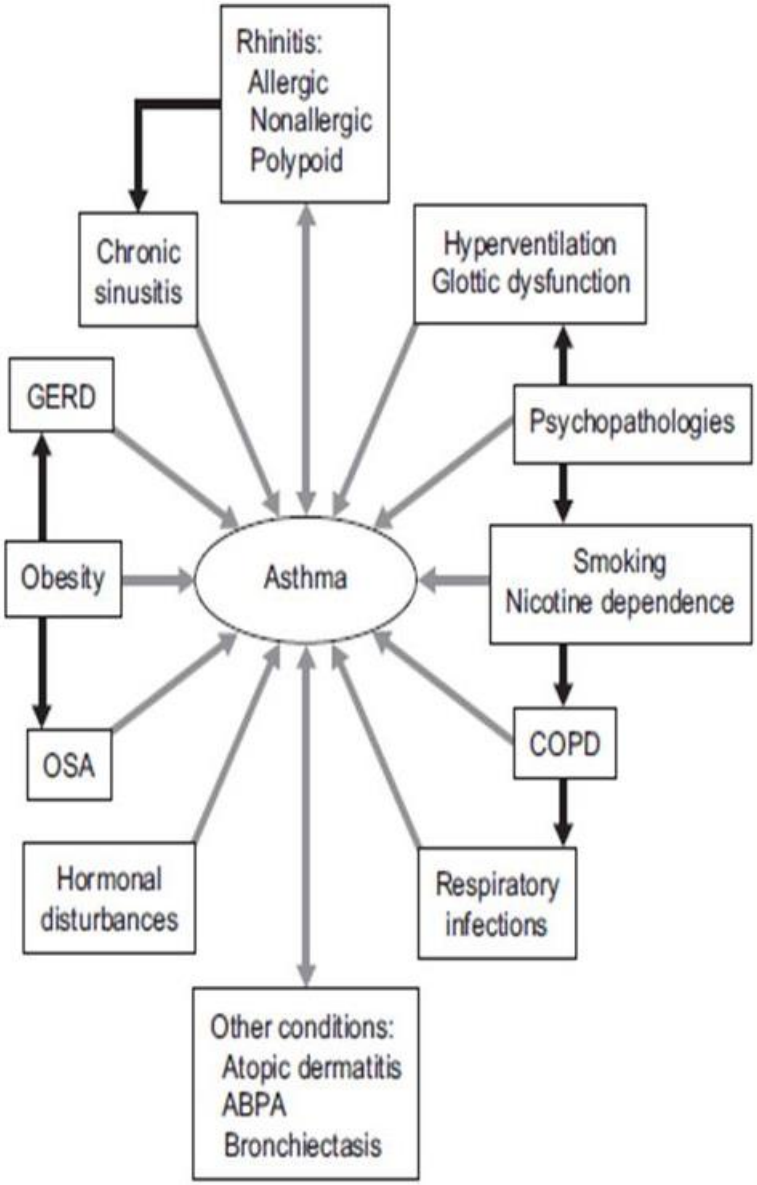
Influence of comorbid conditions on asthma

Eur Respir J 2009; 33: 897–906

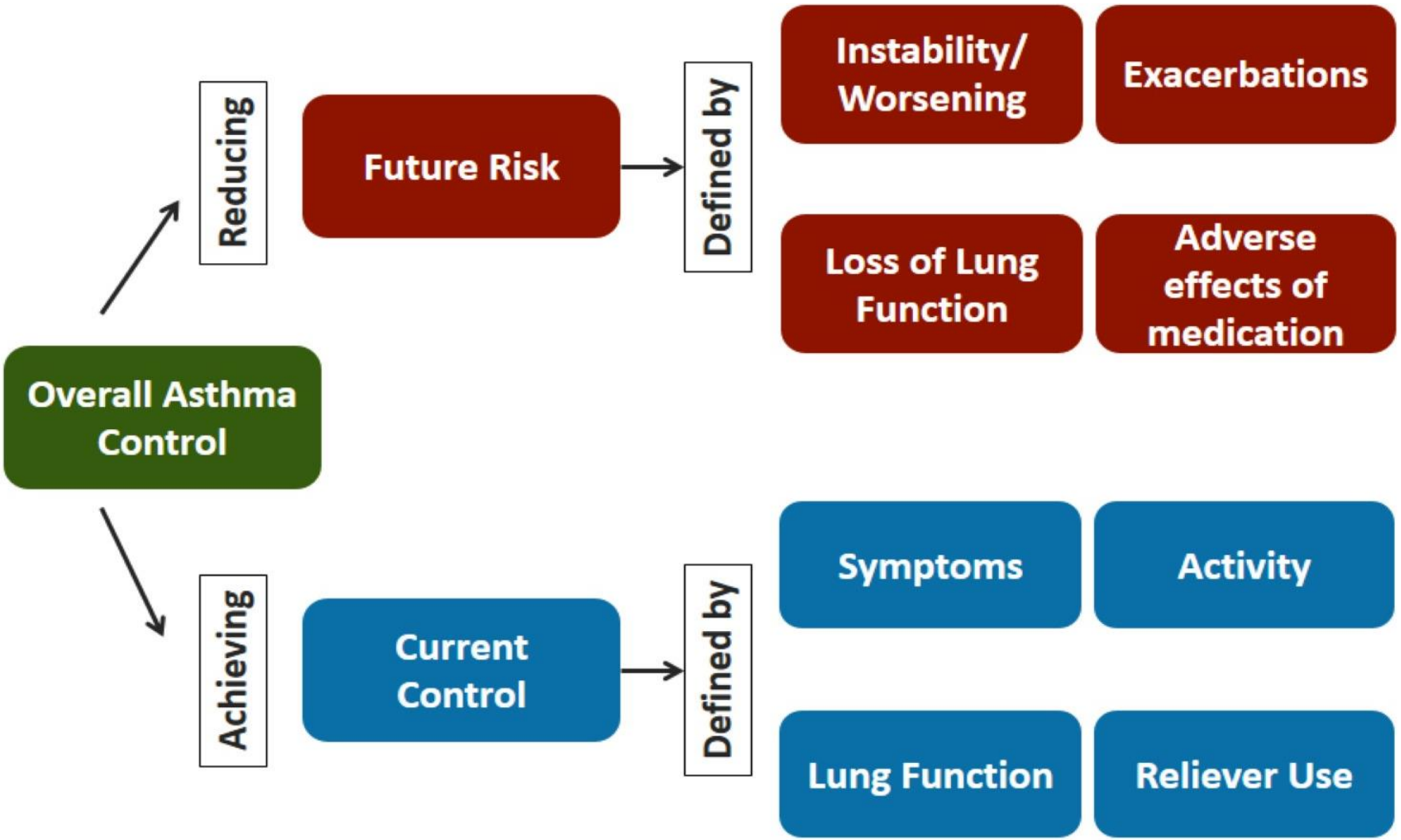
L-P. Boulet

Τα συχνότερα αναφερόμενα συνοδά νοσήματα είναι:

- Ρινίτιδα- Παρραρινοκολπίτιδα
- Κάπνισμα
- ΧΑΠ
- Γαστρο-οισοφαγική παλινδρομική νόσος (ΓΟΠΝ)
- Παχυσαρκία
- Σύνδρομο απνοιών στον ύπνο (ΣΑΥ)
- Ψυχικές διαταραχές
- Χρόνιες λοιμώξεις

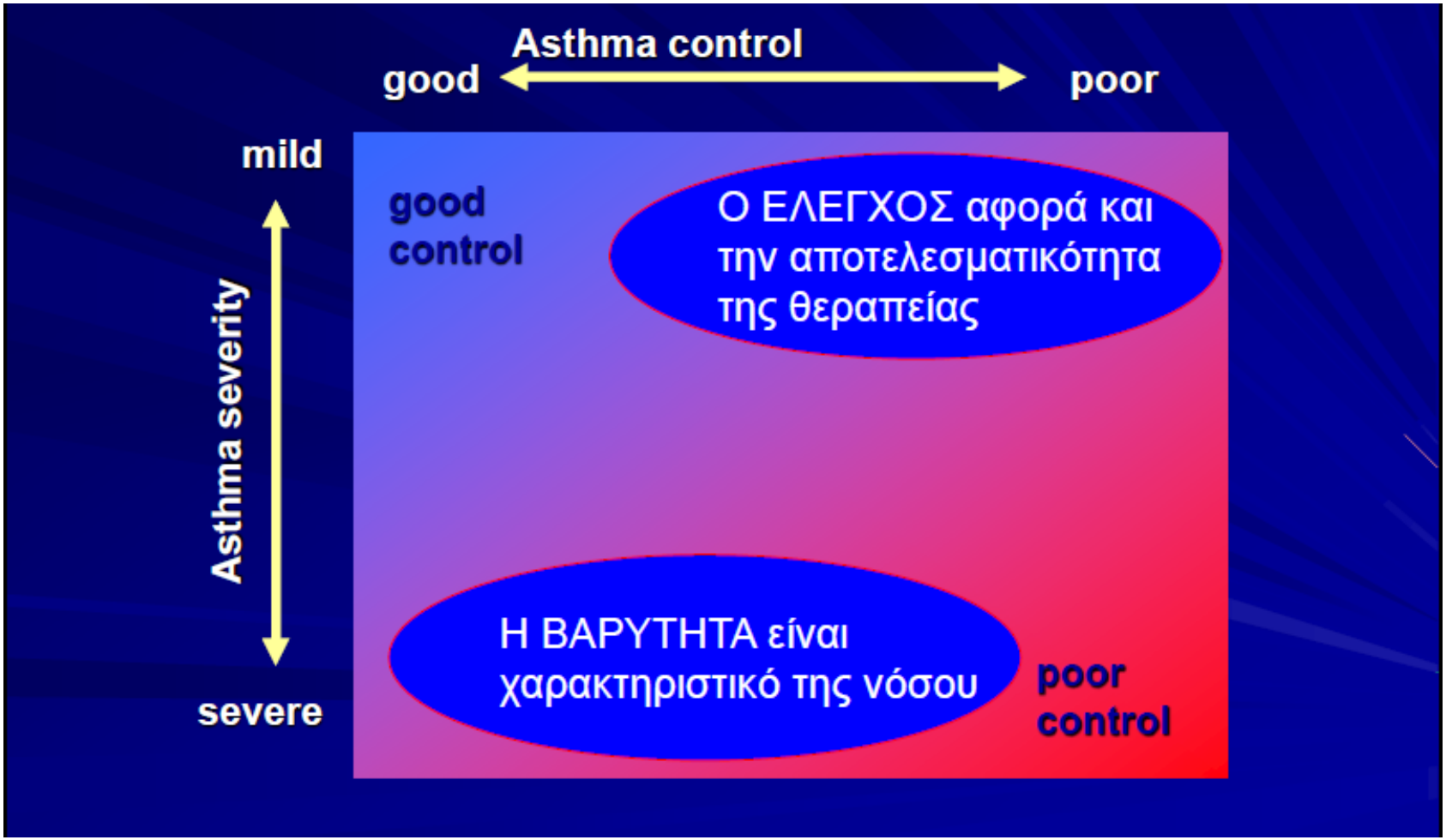


Τι έχει σημασία…



NAEPP website.
Taylor DR, et al. *Eur Respir J.* 2008;32:545-554.

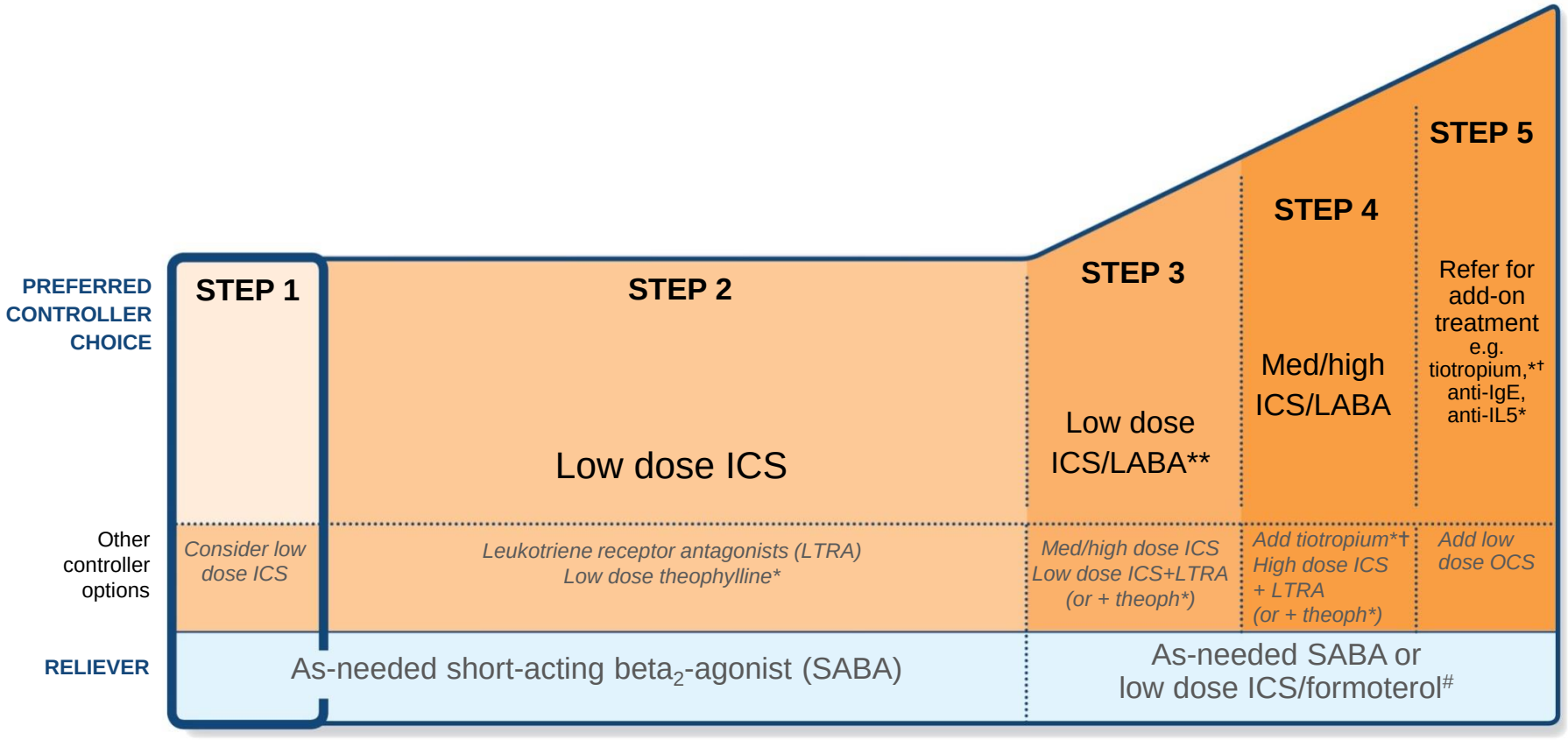
Άλλο βαρύτητα, άλλο έλεγχος άσθματος



Assessing asthma severity

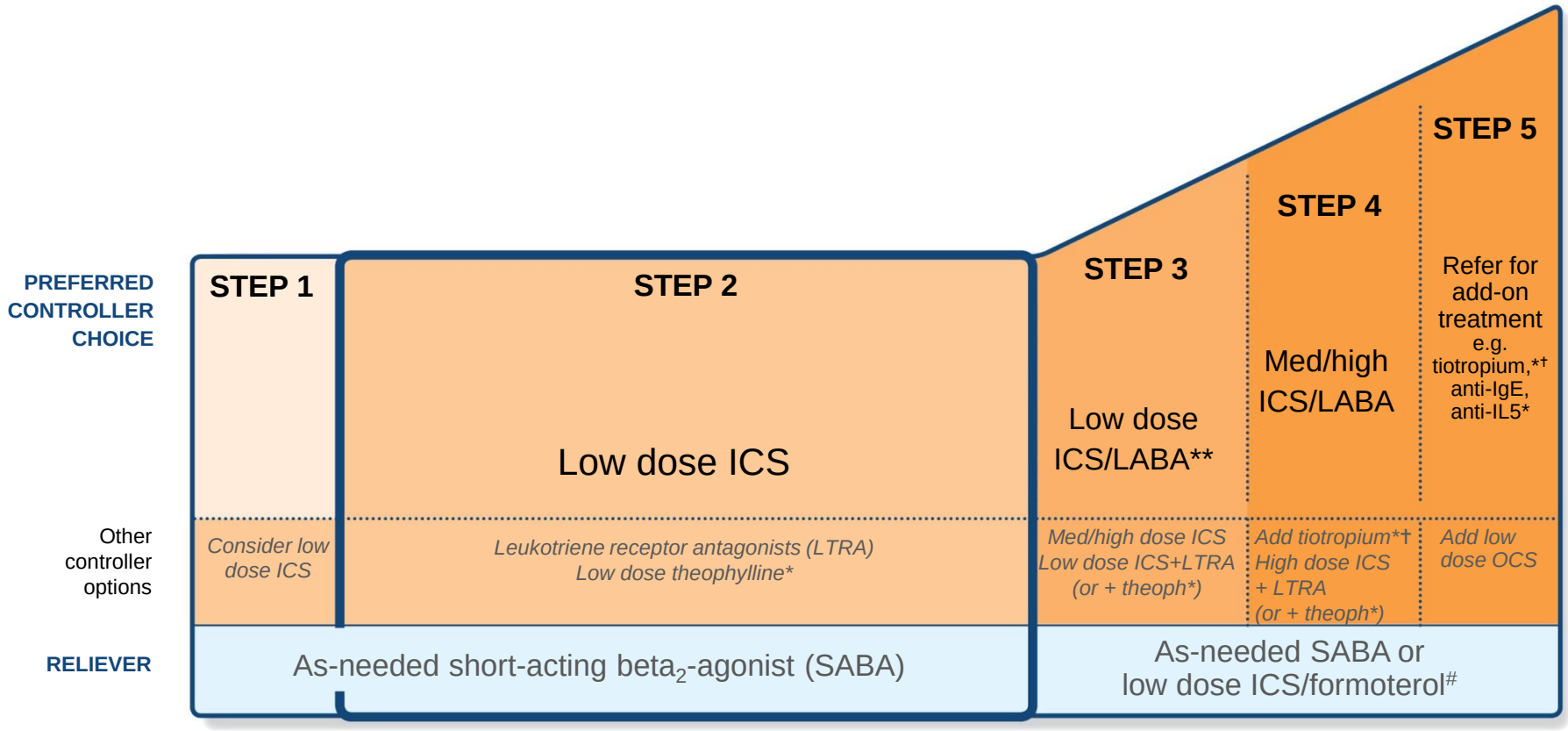
- How?
  - Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations
- When?
  - Assess asthma severity after patient has been on controller treatment for several months
  - Severity is not static – it may change over months or years, or as different treatments become available
- Categories of asthma severity
  - *Mild asthma:* well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
  - *Moderate asthma:* well-controlled with Step 3 (low-dose ICS/LABA)
  - *Severe asthma:* requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

Βήμα 1 - Όταν απαιτείται εισπνοή ανακούφισης με β2 διεγέρτη



*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Βήμα 2 – Χαμηλή δόση σταθεροποιητικού + εισπνοές SABA όταν απαιτείται



*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Το ήξερες ότι…;

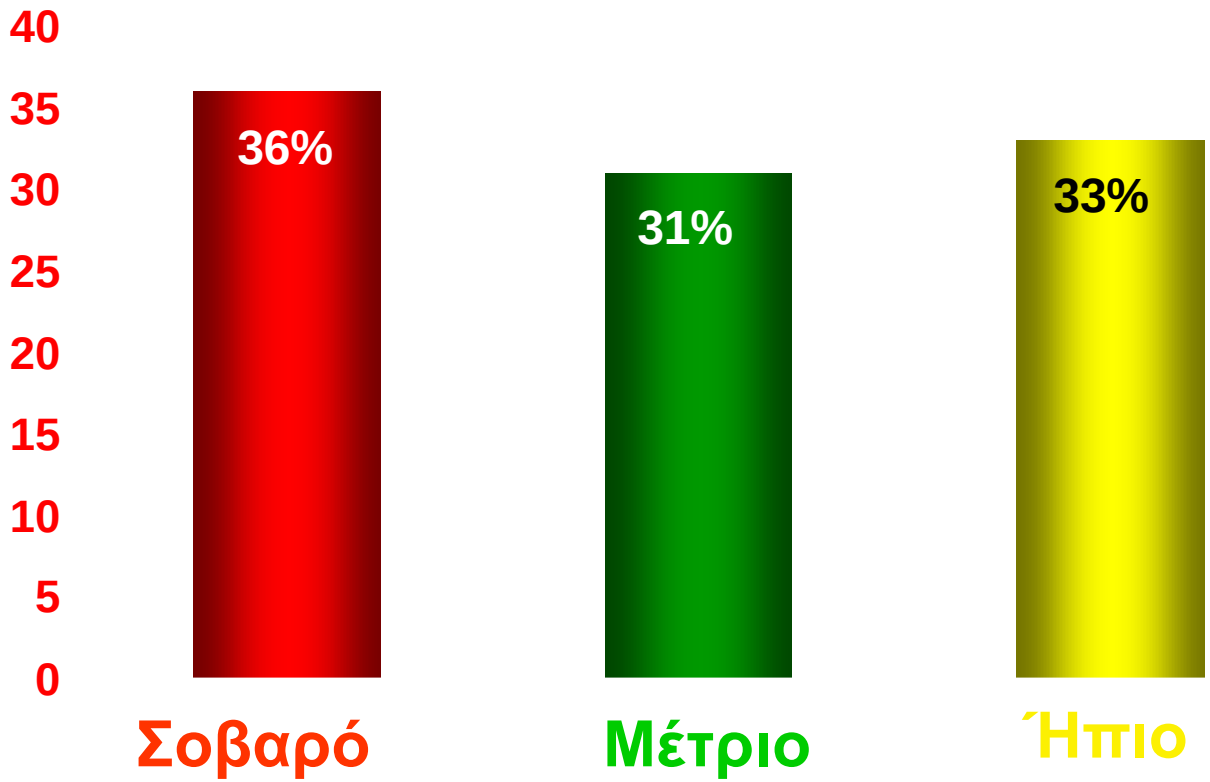
Το άσθμα σκοτώνει ανεξάρτητα με τη βαρύτητα του

1/3 των θανάτων από άσθμα έχουν ήπιο άσθμα

1/3 των θανάτων από άσθμα έχουν μέτριο άσθμα

1/3 των θανάτων από άσθμα έχουν σοβαρό άσθμα

Θάνατοι παιδιών με άσθμα:
τα παιδιά με ήπιο άσθμα βρίσκονται σε κίνδυνο

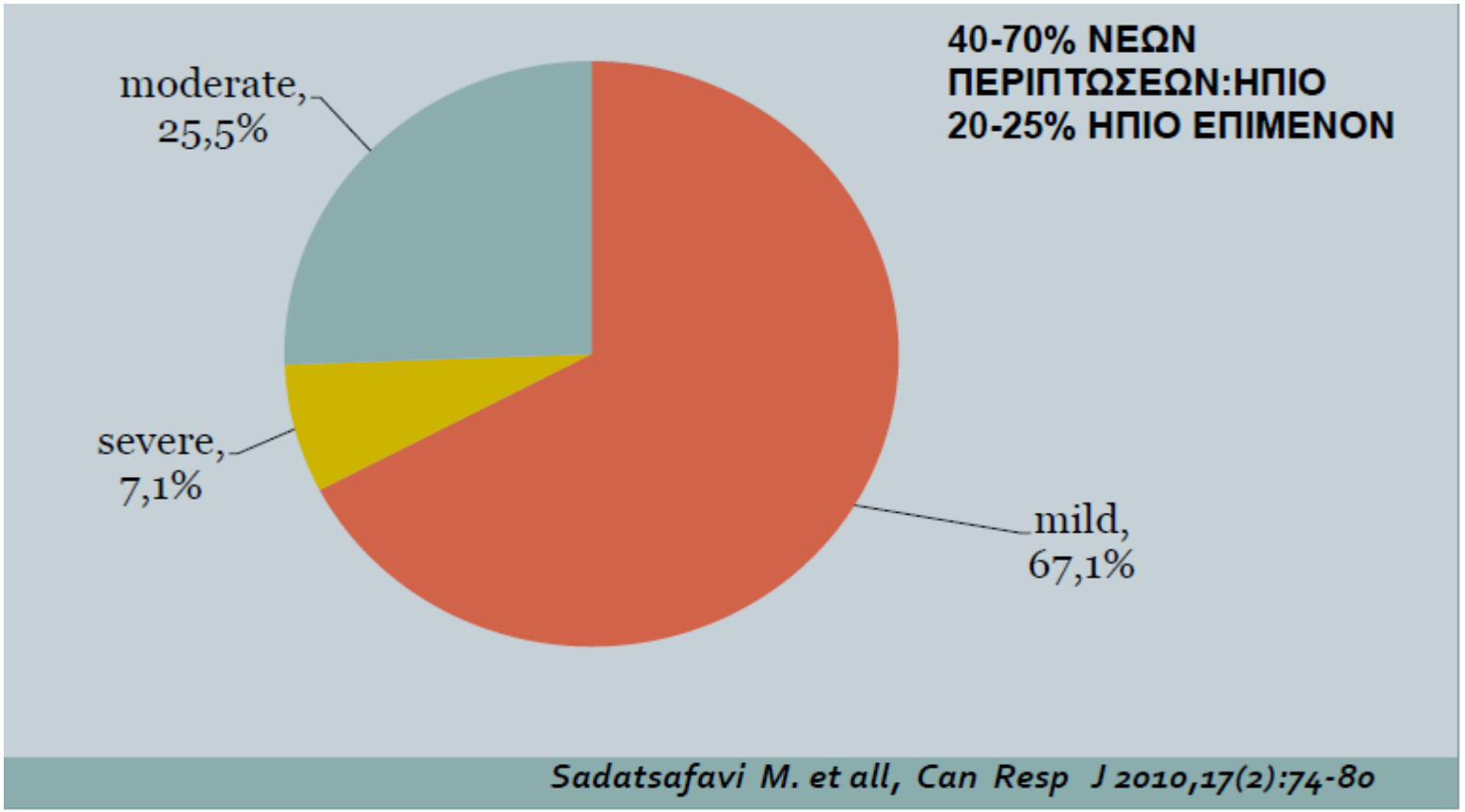


Findings from a cohort study reviewing all pediatric asthma-related deaths (n=51) in the Australian state of Victoria from 1986 to 1989.

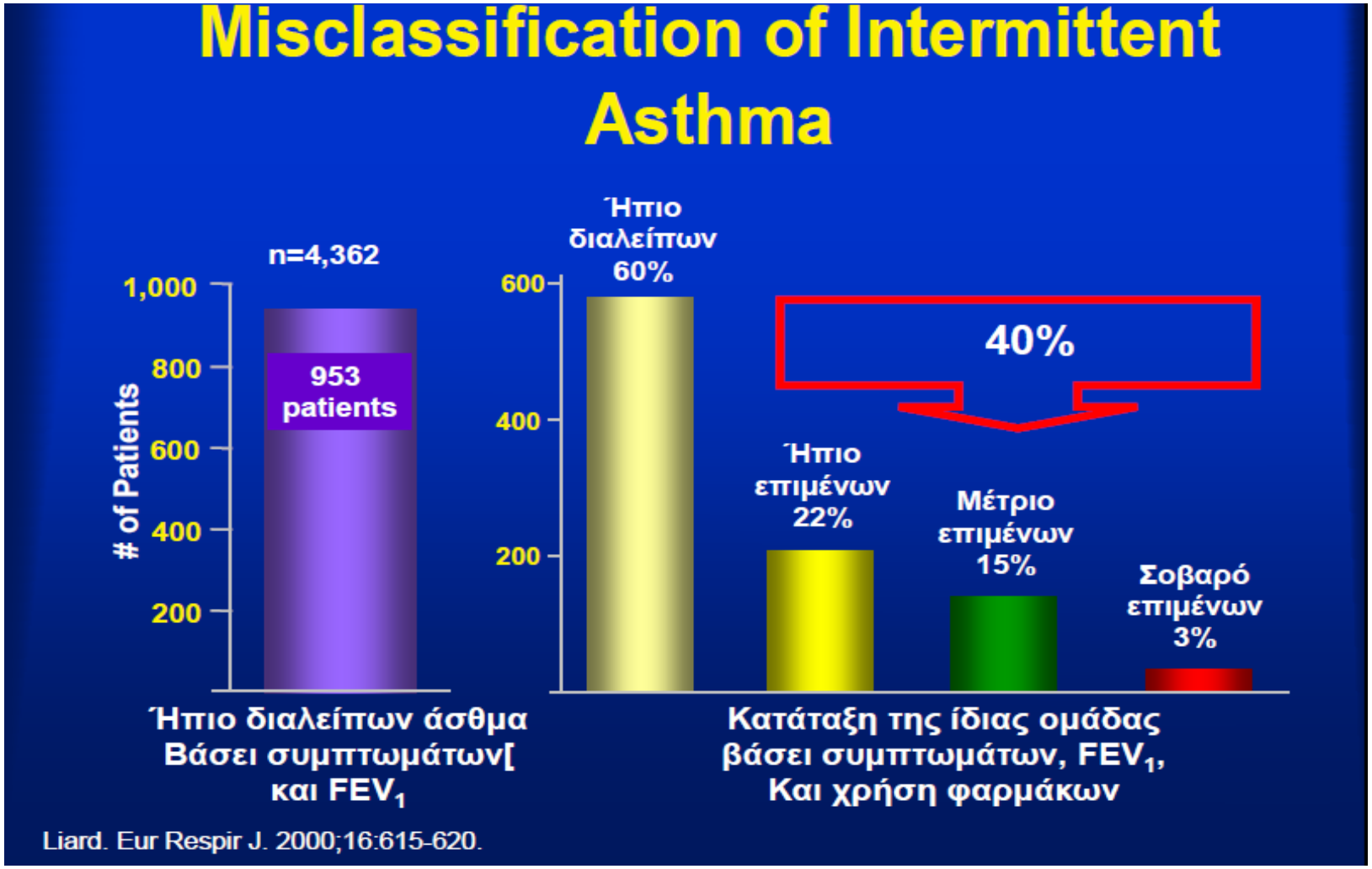
Robertson et al. Pediatr Pulmonol. 1992;13:95-100.

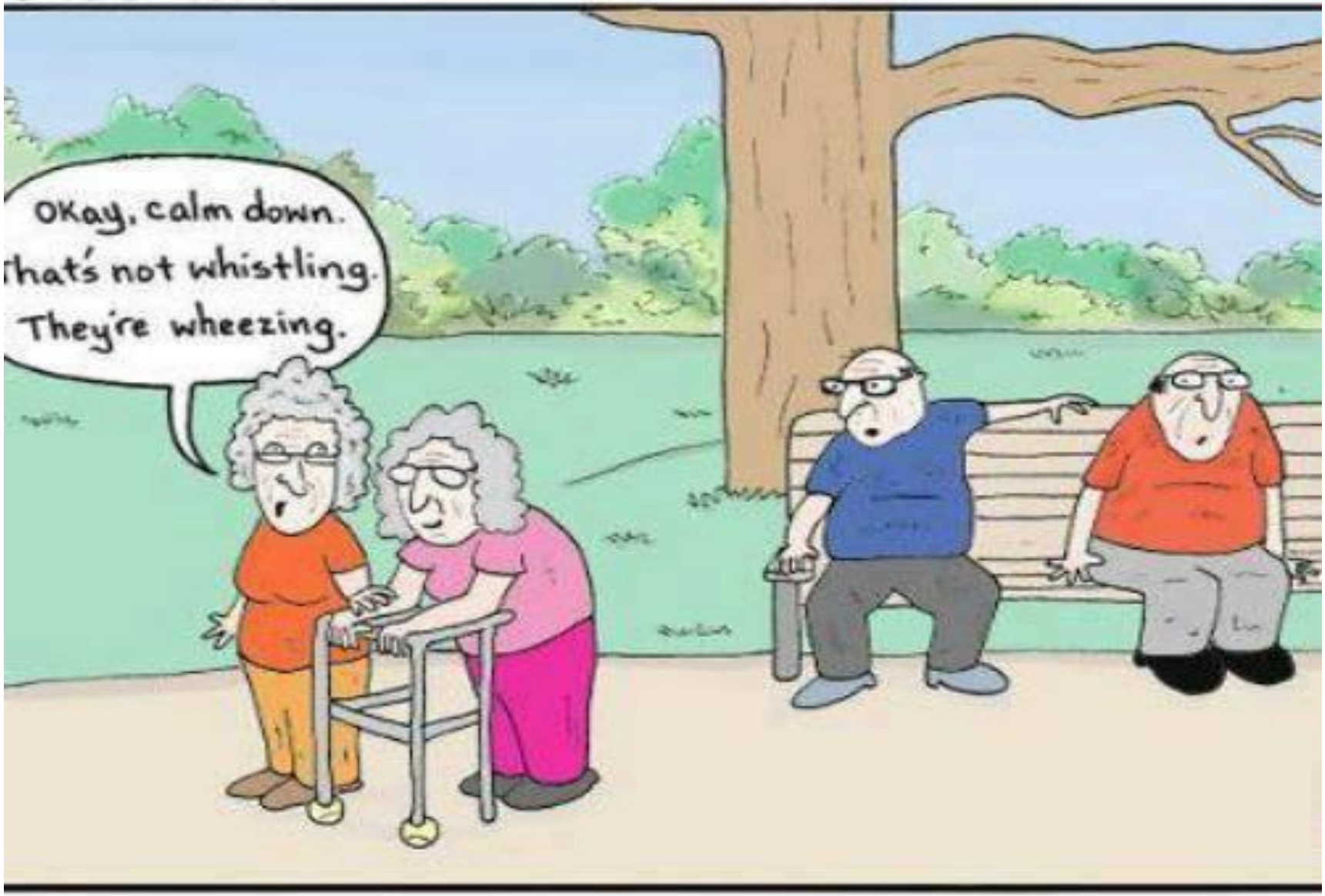
Ήπιο άσθμα

Οι ήπιοι ασθματικοί ασθενείς αποτελούν σημαντικό ποσοστό ασθενών (μέχρι 70% όλων των ασθματικών)



Ήπιο άσθμα


Misclassification of Intermittent Asthma
n=4,362
953 patients
# of Patients
1,000
800
600
400
200
Ήπιο διαλείπων άσθμα Βάσει συμπτωμάτων[και FEV1
Ήπιο διαλείπων 60%
600
400
200
40%
Ήπιο επιμένων 22%
Μέτριο επιμένων 15%
Σοβαρό επιμένων 3%
Κατάταξη της ίδιας ομάδας βάσει συμπτωμάτων, FEV1, Και χρήση φαρμάκων
Liard. Eur Respir J. 2000;16:615-620.



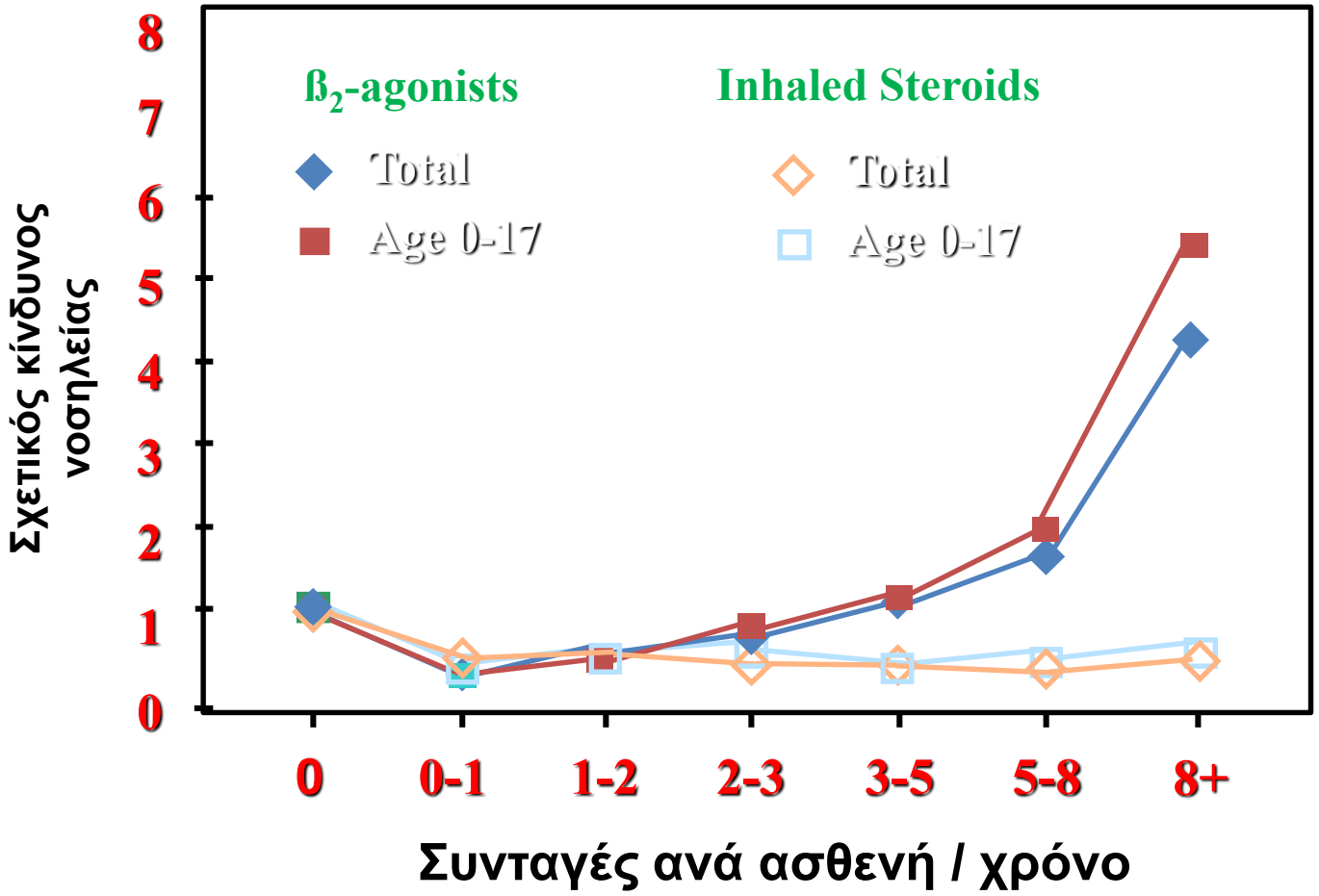
Δίλημμα 1

Καθημερινά ICS vs κατ΄ επίκληση β2 διεγέρτη

Inhaled steroids and the risk of hospitalization for asthma.

Retrospective cohort study

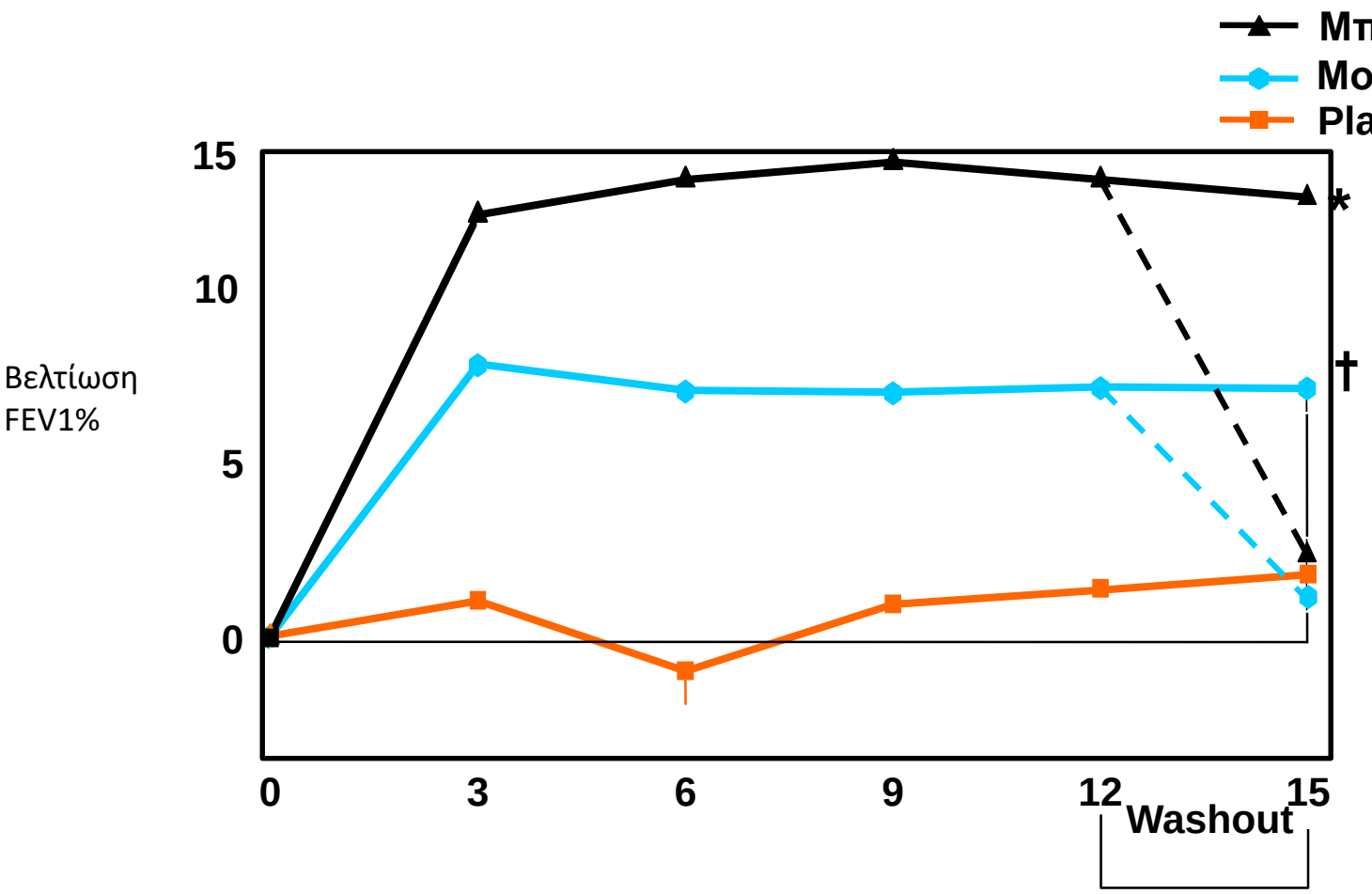
16941 eligible persons, 742 (4.4%) were hospitalized for asthma



Inhaled steroids confer significant protection against exacerbations of asthma leading to hospitalization

Donahue et al. *JAMA*. 1997;277:887-891.

Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group.



Randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 12-week study

895 patients 15 to 85 years of age with chronic asthma and an FEV1 50% to 85% of predicted

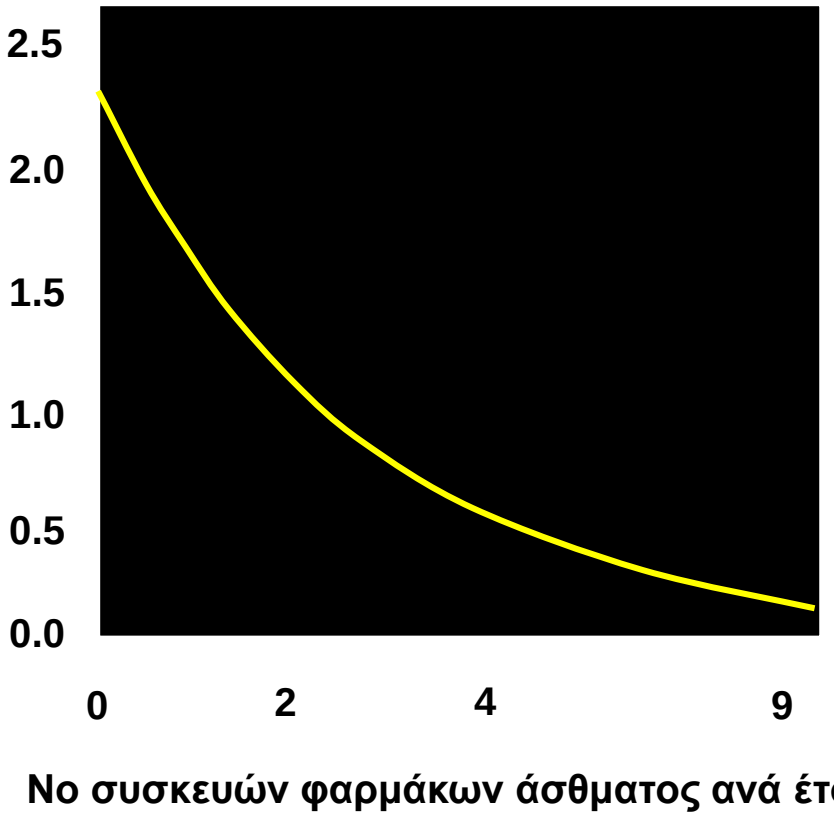
***P* < 0.01 Μπεκλομεθαζόνη vs Μοντελουκάστη και placebo.**
†*P* < 0.001 vs placebo.

Malmstrom K, et al. *Ann Intern Med.* 1999;130:487-495.

The New England Journal of Medicine

LOW-DOSE INHALED CORTICOSTEROIDS AND THE PREVENTION OF DEATH FROM ASTHMA

Rate Ratio
θανάτων από άσθμα



the rate of death from asthma decreased by 21 percent with each additional canister of inhaled corticosteroids used in the previous year

The cohort consisted of 30,569 subjects using antiasthma drugs during the period from 1975 through 1991

Of the 562 deaths, 77 were classified as due to asthma

Suissa et al. *N Engl J Med.* 2000;343:332-336.

Primary Care Respiratory Journal (2008): 17(1): 39-45

Primary Care RESPIRATORY JOURNAL www.thepcrj.org

ORIGINAL RESEARCH

Does continuous use of inhaled corticosteroids improve outcomes in mild asthma? A double-blind randomised controlled trial

44 subjects were randomised (23-fluticasone 250mcg/day, 21-placebo), double blind for 11 months

Table 2. Effect of treatment on primary and secondary outcome variables.

		On treatment values[1]			
		Active	Placebo	Difference (95% CI)	p value
Primary outcomes	Morning PEF L/min	459.7	443.8	15.93 (12.44-19.42)[2,3]	0.0001
	Morning FEV_1 L	2.87	2.72	0.15 (0.114-0.184)[2,3]	0.0001
Secondary outcomes	Morning PEF % predicted	101.60	98.06	3.54 (2.70-4.34)[2]	0.0001
	Morning FEV_1 % predicted	91.59	86.22	5.37 (4.30-6.44)[2]	0.0001
	Clinic FEV_1 % predicted	100.34	96.34	4.30 (1.25-7.36)[2]	0.007
	FeNO, ppb	12.30[4]	19.88[4]	0.63 (0.52-0.75)[5]	0.0001
	Symptom-free days, %	92.0[6]	90.2[6]	1.09 (0.99-1.18)[7]	0.07
	Reliever-free days, %	93.8[6]	91.3[6]	1.05 (0.96-1.14)[7]	0.31

Helen K Reddel, Primary care respiratory journal, 2008

Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial

7241 patients in 32 countries, aged 5-66

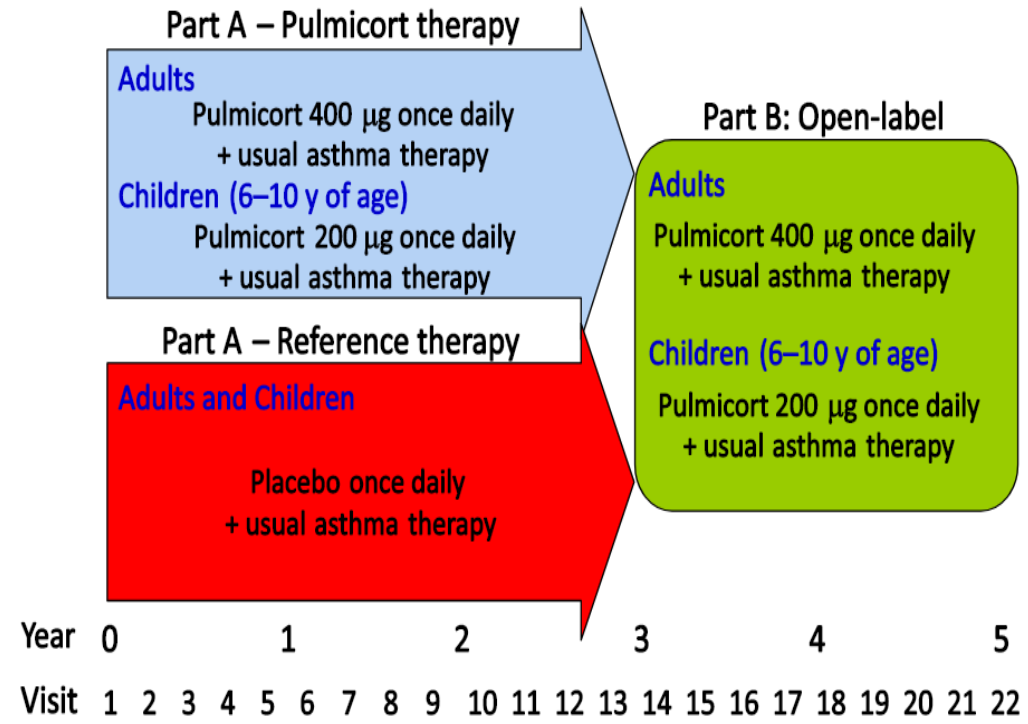
mild persistent asthma for less than 2 years

START trial

Primary Study Objective and Primary Variables

- Examines effect of early intervention with ICS on evolution of newly diagnosed asthma
- Primary outcome:
  - Time to first severe asthma-related event (SARE) during first 3 years of study
  - A severe event requiring hospitalization or emergency treatment due to worsening of asthma or death due to asthma
- Secondary outcome:
  - Change in postbronchodilator FEV_1
- Intent to treat analysis

Double-blind (Part A) and Open-label (Part B) Design



Pauwels RA, Busse WW, O'Byrne PM, et al. The inhaled Steroid Treatment as Regular Therapy in early asthma (START) study: rationale and design. *Control Clin Trials.* 2001;22(4):405–419

Pauwels et al. Lancet 2003

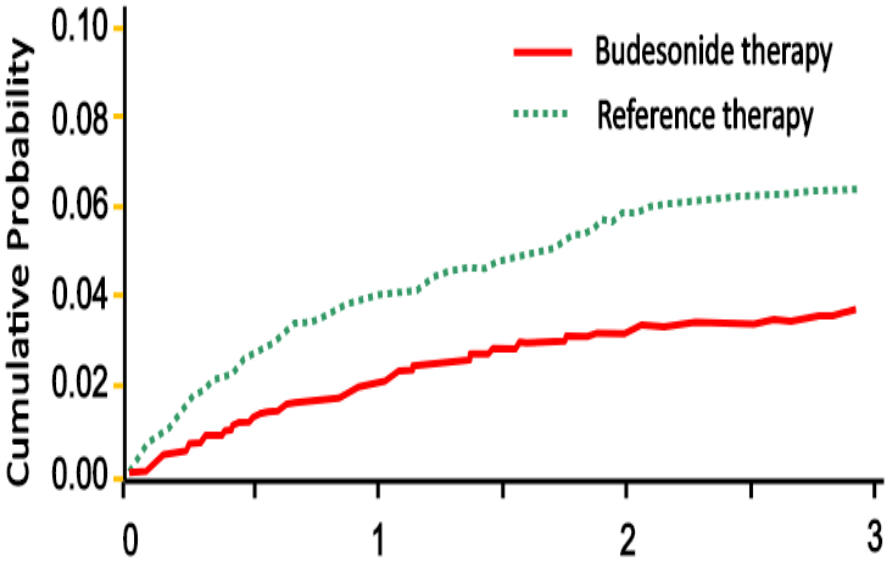
Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial

START trial

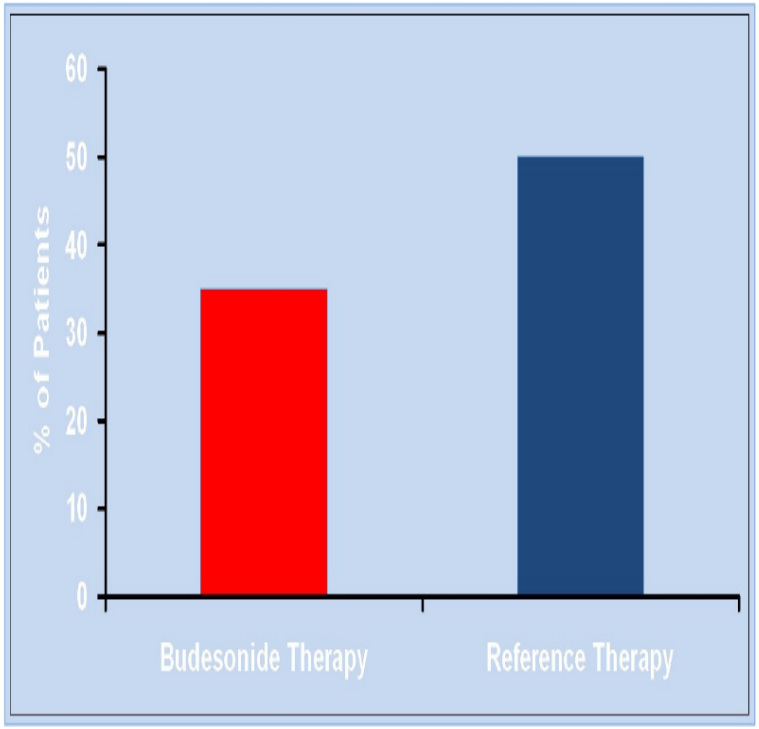
Long-term, once-daily treatment with low-dose budesonide decreases the risk of severe exacerbations and improves asthma control in patients with mild persistent asthma of recent onset

Time to First SARE

44% (95% CI, 29–55%) reduced risk of first SARE*



Patients Requiring Additional Corticosteroids*



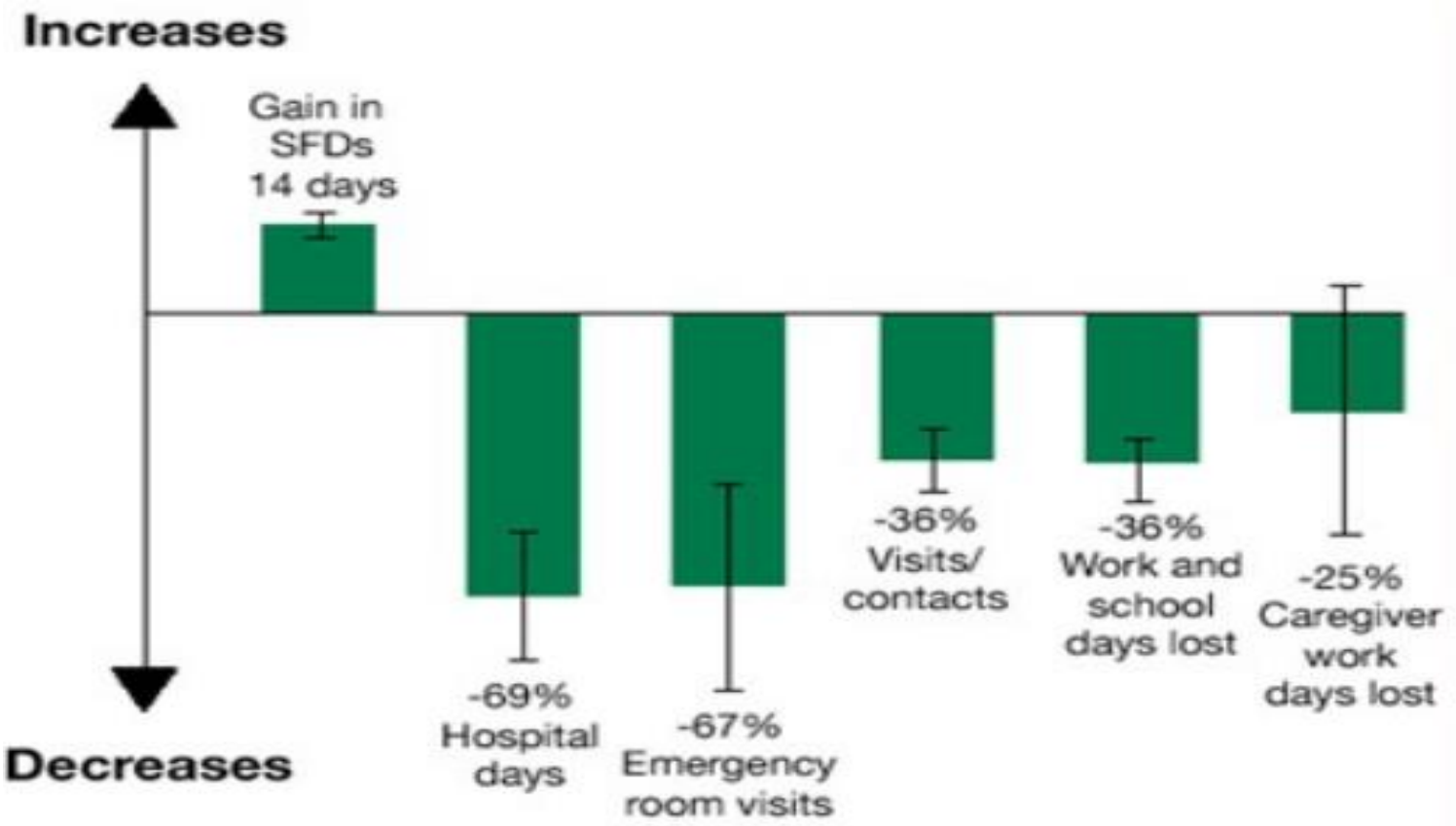
*Inhaled, oral, or systemic

Pauwels et al. Lancet 2003

Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial

START trial

Long-term, once-daily treatment with low-dose budesonide decreases the risk of severe exacerbations and improves asthma control in patients with mild persistent asthma of recent onset



Pauwels et al. Lancet 2003

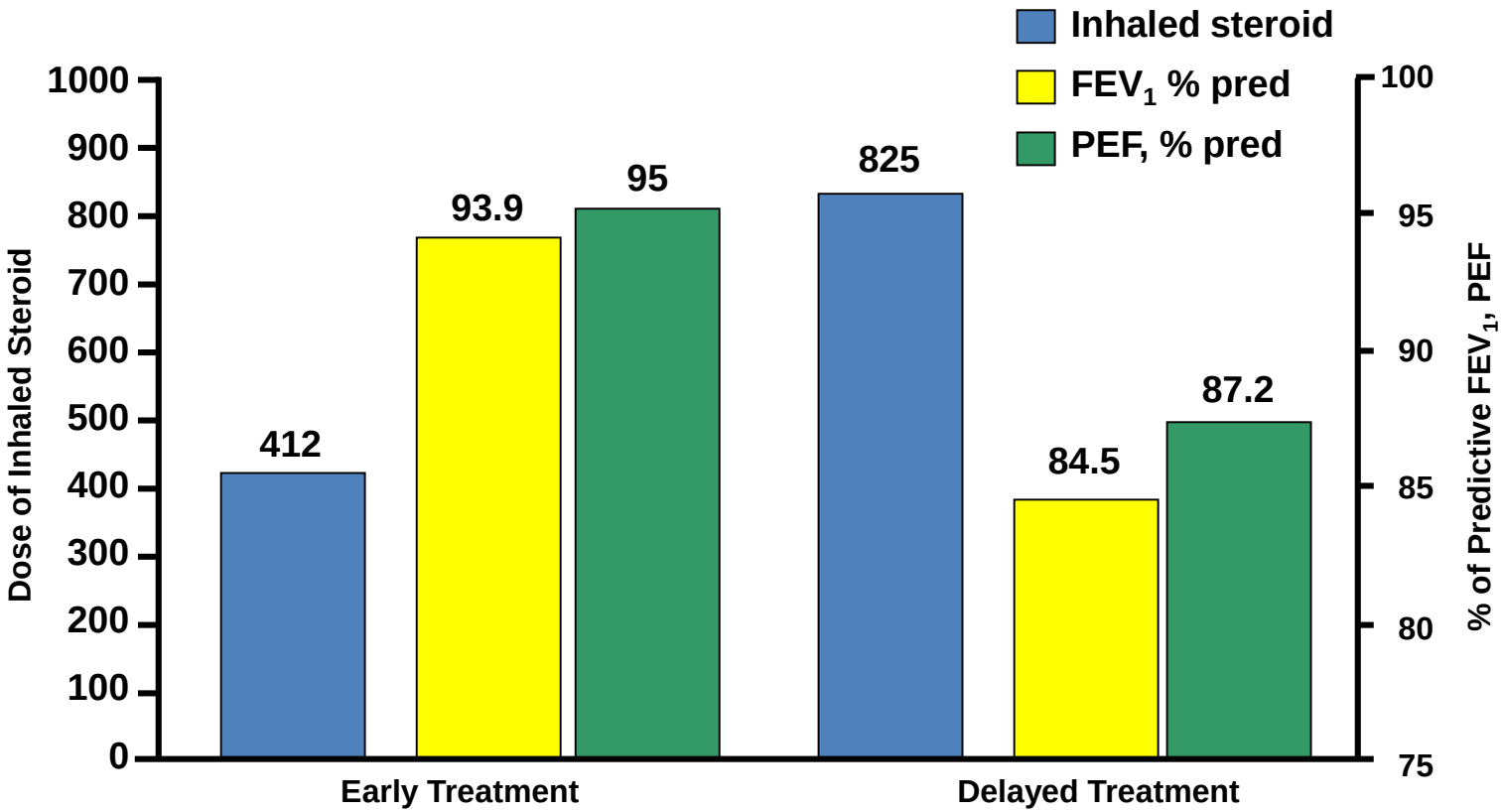
Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study

O. Selroos*, A.-B. Löfroos, A. Pietinalho, H. Riska

462 patients with persistent asthma

early treatment group with symptoms for <2 years was compared with a delayed treatment group (median duration 5 years and 3 months)

budesonide 400 microg twice daily as initial dose, 5-year follow-up



Selroos et al. Respir Med. 2004;98:254-262.

Δίλημμα 2

Καθημερινά ICS vs καθημερινά ICS+LABA

Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma

The OPTIMA Randomized Trial

698 patients, 1 year study

main outcomes were time to the first severe asthma exacerbation and poorly controlled asthma days

Bud/placebo & Bud+F/placebo = statistical difference

TABLE 2. RESULTS GROUP A: END VALUES (ADJUSTED MEANS)

				p Values Comparing:		
Variable	Placebo	BUD200	BUD200+F	BUD200 vs Placebo	BUD200+F vs BUD200	BUD200+F vs Placebo
Change in FEV_1, % pred	1.79	4.04	5.87	0.0045	0.023	0.0001
Change in PEF Morning, L/min	8.66	15.12	31.81	0.12	0.0001	0.0001
Days with symptoms, %	29.4	23.1	21.5	0.0074	0.48	0.0007
Number of rescue inhalations per day	0.75	0.51	0.51	0.0008	0.97	0.0008
Nights with awakenings, %	7.0	2.5	3.1	0.0001	0.52	0.0001
Rate per year of severe exacerbations	0.77	0.29	0.34	0.0001	0.50	0.0001

P.M. O' Byrne. Am J Respir Crit Care Med 2001

Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma

The OPTIMA Randomized Trial

budesonide alone reduced the risk for severe exacerbations by 60% and poorly controlled days by 48%;
adding formoterol increased lung function with no change in other end points

Bud + F / Bud = no statistical difference

TABLE 2. RESULTS GROUP A: END VALUES (ADJUSTED MEANS)

				p Values Comparing:		
Variable	Placebo	BUD200	BUD200+F	BUD200 vs Placebo	BUD200+F vs BUD200	BUD200+F vs Placebo
Change in FEV_1, % pred	1.79	4.04	5.87	0.0045	0.023	0.0001
Change in PEF Morning, L/min	8.66	15.12	31.81	0.12	0.0001	0.0001
Days with symptoms, %	29.4	23.1	21.5	0.0074	0.48	0.0007
Number of rescue inhalations per day	0.75	0.51	0.51	0.0008	0.97	0.0008
Nights with awakenings, %	7.0	2.5	3.1	0.0001	0.52	0.0001
Rate per year of severe exacerbations	0.77	0.29	0.34	0.0001	0.50	0.0001

P.M. O' Byrne. Am J Respir Crit Care Med 2001

Δίλημμα 3

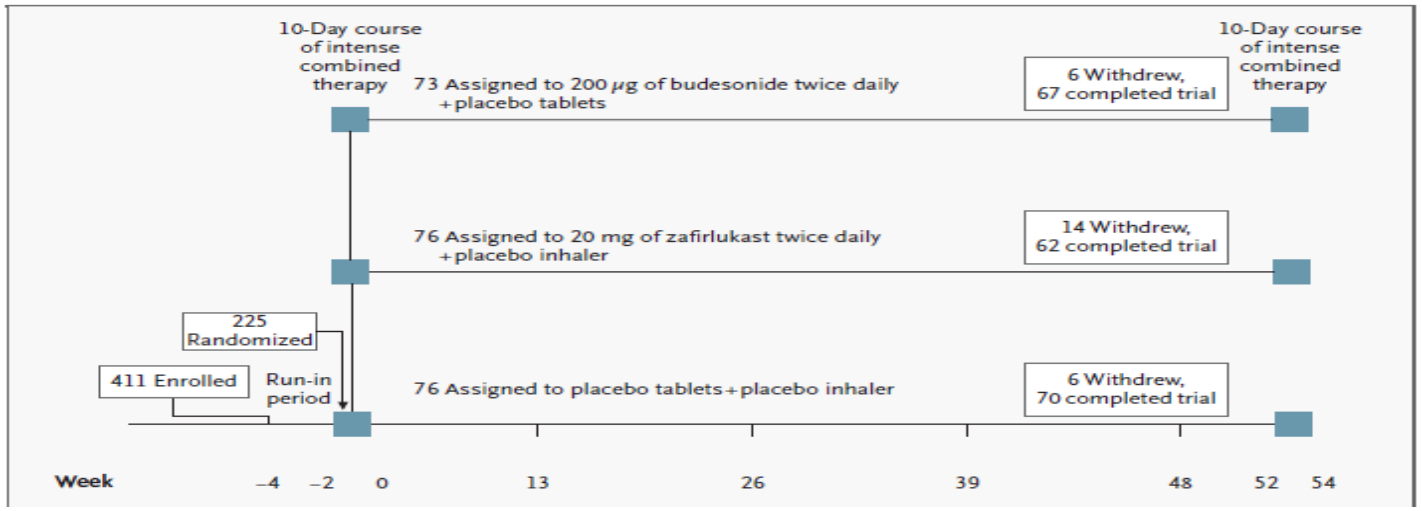
Καθημερινά ICS vs κατ΄ επίκληση ICS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 14, 2005 VOL. 352 NO. 15

IMPACT study

Homer A. Boushey. N Engl J Med 2005. IMPACT study

Daily versus As-Needed Corticosteroids for Mild Persistent Asthma



double-blind trial, 225 adults

primary outcome was morning peak expiratory flow (PEF)

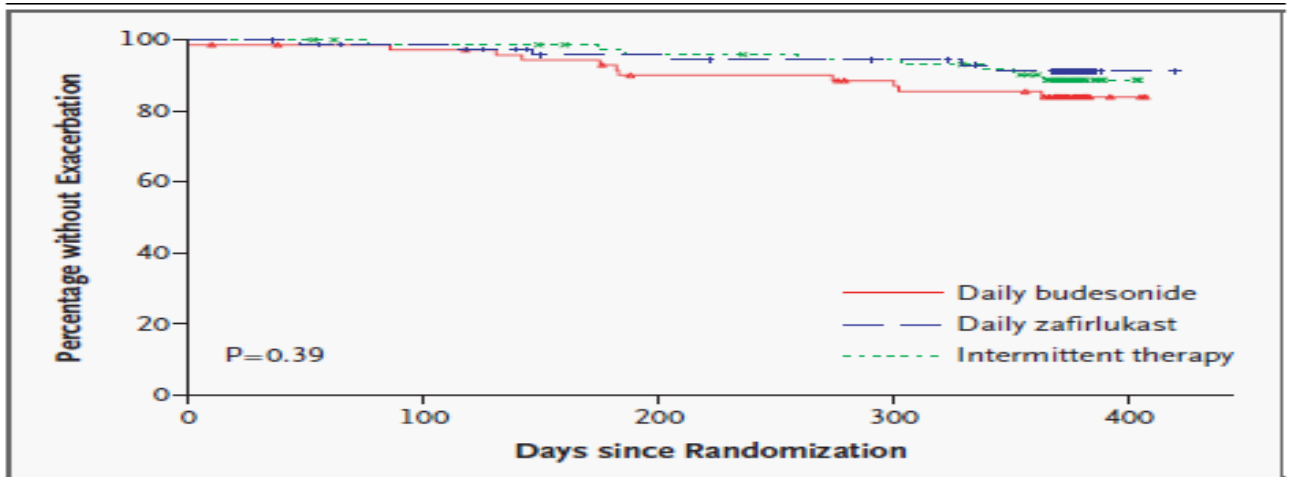


Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma.
There was no significant difference among the groups (P=0.39).

the intermittent-treatment group took budesonide, on average, for only 0.5 week of the year!!!

Table 2. Average Changes in Primary and Secondary Outcome Measures over a One-Year Period.*

Outcome	Daily Budesonide			Daily Zafirlukast			Intermittent Treatment			Overall P Value†
	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	No. of Patients	Value	Within-Group P Value	
Morning PEF (%)	66	8.3±1.9	<0.001	62	7.9±2.1	<0.001	70	7.1±2.0	<0.001	0.90
Morning PEF post-PICT (%)	66	5.7±1.7	0.002	62	5.6±1.8	0.002	69	3.5±1.7	0.05	0.61
FEV_1 (%)										
Pre-bronchodilator	67	4.0±1.2	0.001	62	−1.1±1.0	0.30	70	0.7±1.1	0.55	0.005
Post-bronchodilator	67	−1.7±0.5	0.002	61	−0.5±0.7	0.45	69	−1.0±0.5	0.04	0.29
Post-PICT	67	−1.5±0.7	0.03	62	−2.1±0.7	0.003	68	−0.6±0.6	0.34	0.27
Exhaled nitric oxide (%)	63		0.75	60		0.02	66		<0.001	0.006
Median		−14.4			12.4			26.6		
Interquartile range		−44.4 to 46.8		62	−24.6 to 82.8			−9.6 to 99.3	<0.001	
Sputum eosinophils (%)	34		0.03	26		0.71	35		0.03	0.007
Median		−0.3			0.0			0.2		
Interquartile range		−1.6 to 0.2			−0.9 to 0.3			−0.1 to 1.5		
PC_{20} (log_2)	63	1.8±0.2	<0.001	58	0.3±0.2	0.11	67	0.1±0.2	0.48	<0.001
Asthma Quality of Life score‡§	67	0.5±0.1	<0.001	64	0.3±0.1	<0.001	70	0.3±0.1	<0.001	0.18
Asthma control score‡¶	70	−0.4±0.1	<0.001	70	−0.2±0.04	<0.001	73	−0.3±0.05	<0.001	<0.001
No. of symptom-free days‡	70	4.0±0.4	<0.001	70	3.1±0.4	0.001	73	2.9±0.4	<0.001	0.03
Asthma Symptom Utility Index‡‖	70	0.06±0.01	<0.001	70	0.04±0.01	0.002	73	0.04±0.01	<0.001	0.06

Homer A. Boushey. N Engl J Med 2005. IMPACT study

similar increases in morning PEF and exacerbations

Daily *vs.* intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: A systematic review with meta-analysis

Gustavo J. Rodrigo [a,*], José A. Castro-Rodríguez [b,c]

Respiratory Medicine (2013) 107, 1133–1140

7 randomized, placebo-controlled trials, 1367 patients

Primary outcome was asthma exacerbations

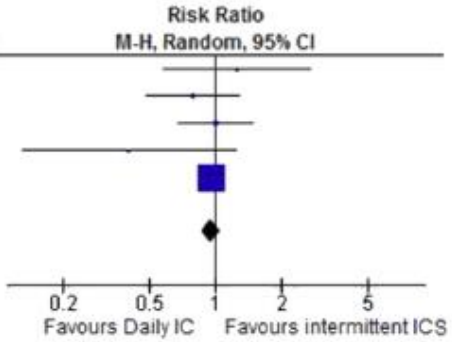
No significant differences
between daily and intermittent ICS in reducing
the incidence of asthma exacerbations was found

Παροξύνσεις

A

Study or Subgroup	Daily ICS Events	Total	Intermittent ICS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boushey (8)	12	73	10	76	1.8%	1.25 [0.58, 2.71]
Martinez (16)	20	72	25	71	4.6%	0.79 [0.48, 1.29]
Papi (23)	33	106	38	122	7.3%	1.00 [0.68, 1.47]
Papi (24)	4	110	10	110	0.9%	0.40 [0.13, 1.24]
Zeiger (25)	111	139	115	139	85.5%	0.97 [0.86, 1.08]
Total (95% CI)		**500**		**518**	**100.0%**	**0.96 [0.86, 1.06]**
Total events	180		198			

Heterogeneity: Tau² = 0.00; Chi² = 3.61, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)



Κορτικοειδή per os

B

Study or Subgroup	Daily ICS Events	Total	As-needed ICS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boushey (8)	10	73	8	76	27.6%	1.30 [0.54, 3.11]
Martinez (16)	22	71	22	71	52.7%	1.00 [0.61, 1.63]
Papi (23)	3	106	0	122	3.3%	8.05 [0.42, 154.02]
Papi (24)	2	110	6	110	10.7%	0.33 [0.07, 1.62]
Turpeinen (9)	1	57	3	58	5.7%	0.34 [0.04, 3.17]
Total (95% CI)		**417**		**437**	**100.0%**	**0.96 [0.56, 1.67]**
Total events	38		39			

Heterogeneity: Tau² = 0.09; Chi² = 5.03, df = 4 (P = 0.28); I² = 20%
Test for overall effect: Z = 0.13 (P = 0.90)

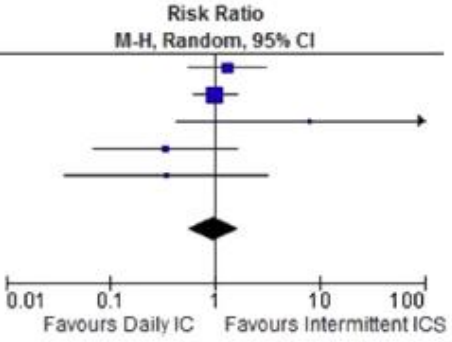


Figure 2 Pooled relative risk for asma exacerbations with 95% confidence intervals of eligible studies comparing daily vs. intermittent ICS use. Rate of exacerbations (Panel A) and number of patients with one or more exacerbations requiring oral corticosteroids (Panel B).

Daily *vs.* intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: A systematic review with meta-analysis

Gustavo J. Rodrigo [a,*], José A. Castro-Rodríguez [b,c]

Respiratory Medicine (2013) 107, 1133–1140

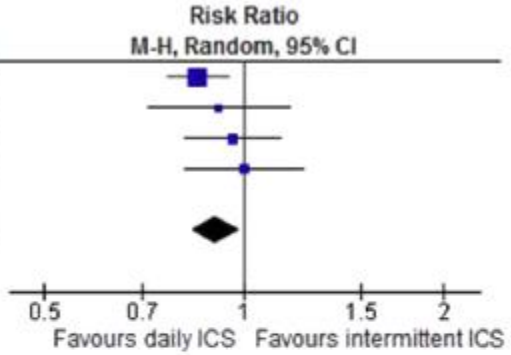
daily ICS strategy was superior in many secondary outcomes

Ημέρες ελεύθερης νόσου

A

Study or Subgroup	Intermittent ICS Events	Total	Daily ICS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boushey (8)	63	76	71	73	48.9%	0.85 [0.76, 0.95]
Papi (23)	62	124	60	110	11.7%	0.92 [0.72, 1.17]
Papi (24)	77	110	80	110	23.6%	0.96 [0.81, 1.14]
Zeiger (25)	78	139	78	139	15.9%	1.00 [0.81, 1.23]
Total (95% CI)		**449**		**432**	**100.0%**	**0.91 [0.83, 0.99]**
Total events	280		289			

Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 3 (P = 0.34); I² = 10%
Test for overall effect: Z = 2.22 (P = 0.03)



Β2 κατ΄επίκληση

B

Study or Subgroup	Daily ICS Mean	SD	Total	As-needed ICS Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Calhoun (26)	0.01	1.1	114	-0.02	1.1	113	7.5%	0.03 [-0.26, 0.32]
Martinez (16)	-0.3	0.26	72	-0.1	0.57	71	22.3%	-0.20 [-0.35, -0.05]
Papi (23)	-0.01	0.72	110	-0.07	0.66	124	16.7%	0.06 [-0.12, 0.24]
Papi (24)	-0.24	0.44	110	-0.17	0.38	110	32.1%	-0.07 [-0.18, 0.04]
Turpeinen (9)	-0.29	0.44	58	-0.22	0.38	58	21.5%	-0.07 [-0.22, 0.08]
Total (95% CI)			**464**			**476**	**100.0%**	**-0.07 [-0.15, 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 5.58, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 1.65 (P = 0.10)

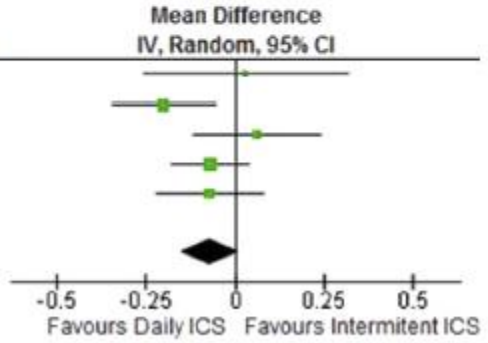
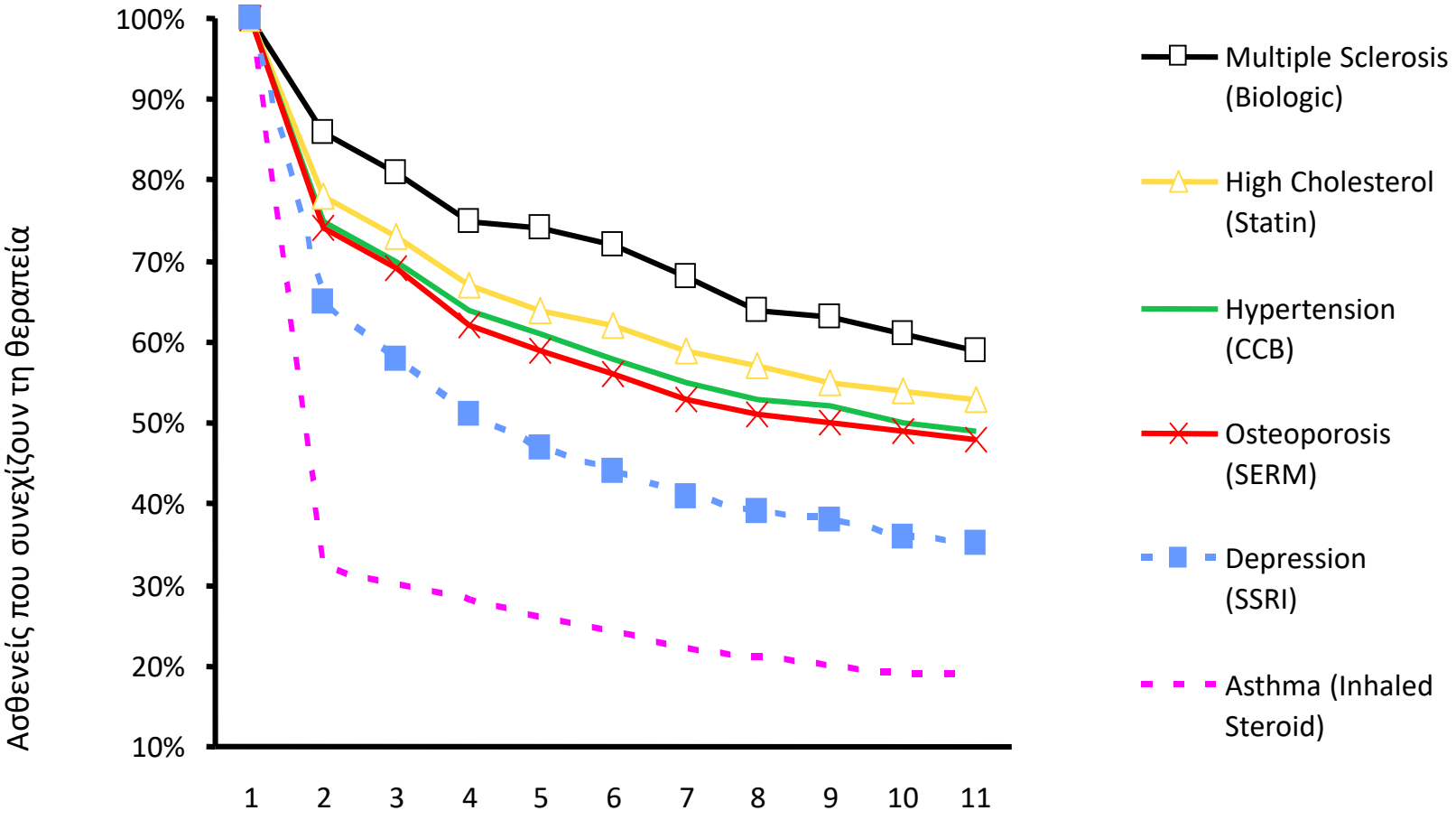


Figure 3 Pooled relative risk for percent asthma free days (Panel A) or mean difference for mean change in rescue medication (Panel B) with 95% confidence intervals of eligible studies comparing daily vs. Intermittent ICS use.

Δίλημμα 4

Καθημερινά ICS vs κατ΄ επίκληση β2 vs κατ΄ επίκληση ICS+LABA

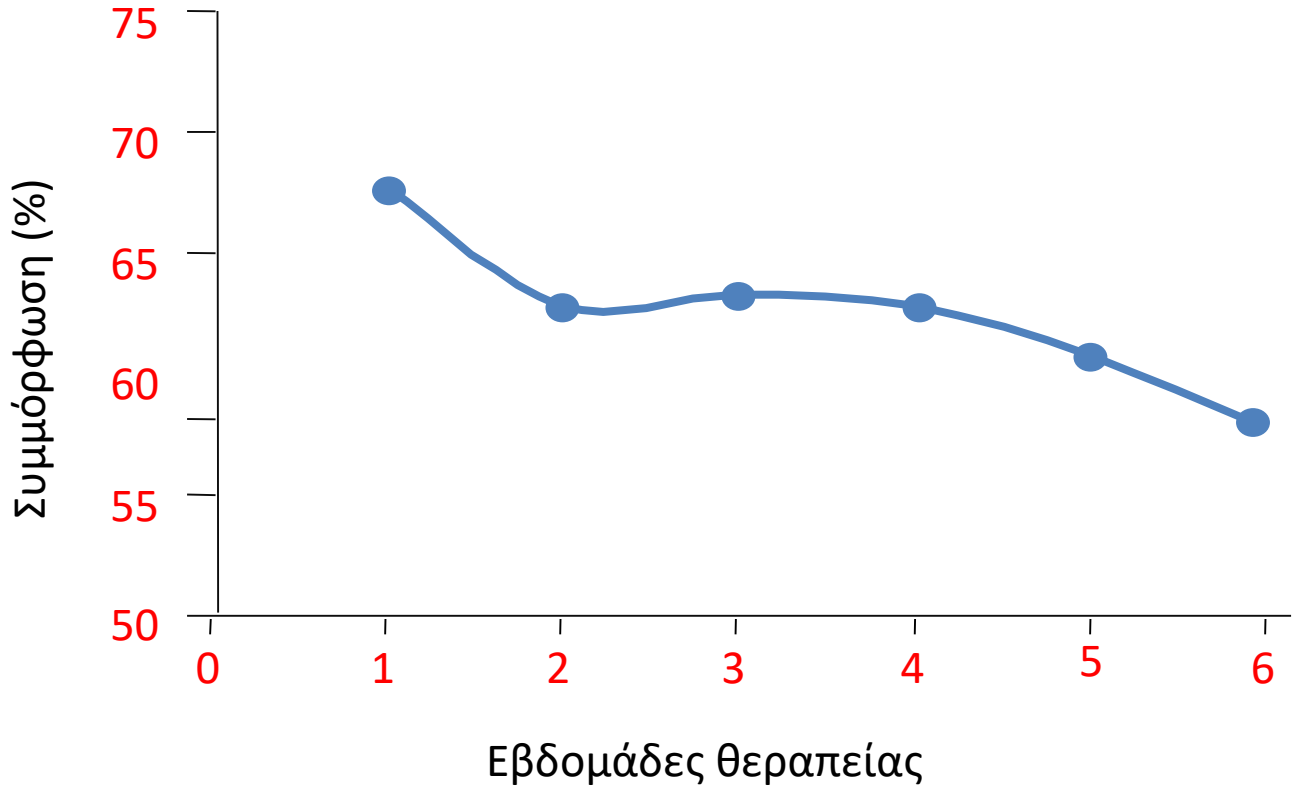
Συμμόρφωση στις θεραπείες



Vanelli *The Business and Medicine Report.* 2002

Συμμόρφωση στην θεραπεία άσθματος

- Ενήλικες με μέτριο επιμένον άσθμα (N=50)
- Θεραπεία με ICS 2 φορές την ημέρα



Κορεάτικες θέσεις ομοφωνίας για το άσθμα το 2014

Step	Current guideline*		Strategy 1		Strategy 2	
	Preferred controller	Reliever	Preferred controller	Reliever	Preferred controller	Reliever
Step 1	None	SABA as needed	Low-dose ICS†	SABA as needed	Patient-adjusted, symptom-driven, intermittent-to-regular treatment with low-dose ICSs/rapid-onset LABAs‡	
Step 2	Low-dose ICSs					
Step 3	Low-dose ICSs/LABAs					
Step 4	Medium/high ICS/LABA	SABA as needed or low-dose ICSs/rapid-onset LABAs§	Same as the current guideline (see the column of Current guideline)			
Step 5	Refer to add-on treatment					

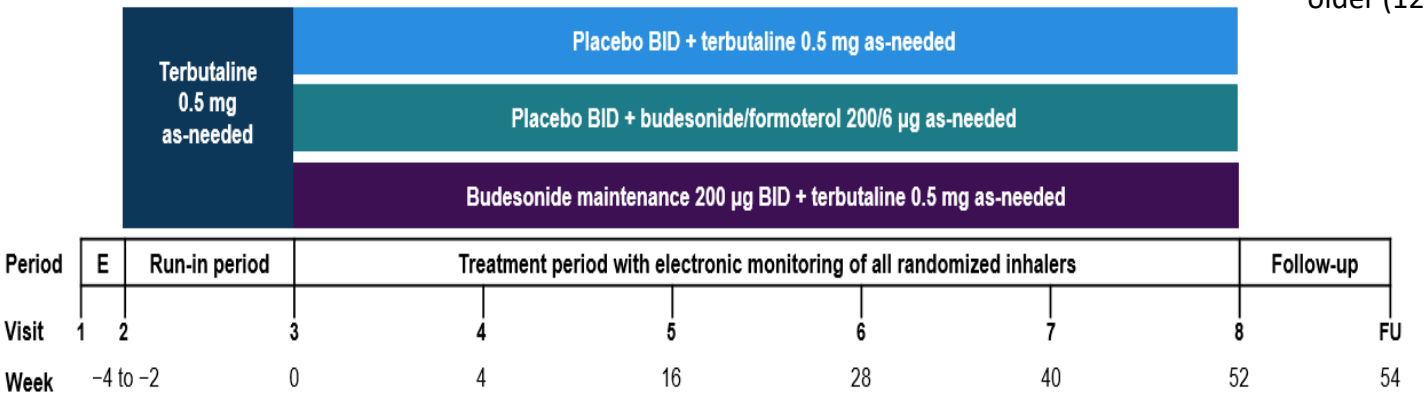
*Adopted and modified from the Korean Asthma Guideline 2014, according to the Creative Commons license Korean Academy of Tuberculosis and Respiratory Diseases[6]. †For persistent controller users. ‡The strategy might be applied from the step 1 to some cases of the step 2 in the Asthma Guideline. §Formoterol is an example.

SYGMA 1

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

3836 patients, 12 years or older (1277/1277/1282)



SYGMA 1[1,2]	
Primary Objective	**Show superiority:** budesonide/formoterol as-needed vs. terbutaline as-needed **Primary endpoint: WCAW**
Secondary Objectives	1) **Efficacy of budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed** 2) **Efficacy of budesonide/formoterol as-needed vs. terbutaline as-needed and budesonide maintenance BID + terbutaline as-needed** • **WCAW:** budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed (non-inferiority) • Annualised severe asthma exacerbation rate • Pre- and post-bronchodilator FEV_1 • ACQ-5 and AQLQ score • ICS use (or exposure) and rescue medication use

1. O'Byrne PM et al. *Trials.* 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed February 22, 2018;

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SYGMA 1[1]	Terbutaline 0.5mg As-needed (n=1272)	Budesonide/ Formoterol 200/6 µg As-needed (n=1269)
Mean % of WCAW per patient	31.1	34.4
Budesonide/formoterol as-needed vs. terbutaline as-needed		
Odds ratio **(2-sided 95% CI)**		**1.14 (1.00, 1.30)**
P-value		**0.046**

Budesonide/formoterol as-needed was *superior* to terbutaline as-needed on WCAW and increased the odds of a week being a WCAW by 14%[1]

[a]Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids[3]; [b]Upper CI of the 1-sided 95% CI is ≤1.2, indicating that budesonide/formoterol as-needed is non-inferior to maintenance budesonide BID.[2]

BID = twice daily; CI = confidence interval; LS = least-squares; NA = not applicable; SYGMA = SYmbicort Given as needed in Mild Asthma; WCAW = well-controlled asthma weeks.

1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 3. O'Byrne PM et al. *Trials*. 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed February 22, 2018.

SYGMA 1

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Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση ήταν κατώτερος της βουδεσονίδης στις WCAW

SYGMA 1 Secondary Endpoint (Non-inferiority)	Budesonide/Formoterol 200/6 µg As-needed (n=1277)	Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=1282)
Mean percentage of WCAW per patient	34.4	44.4
Budesonide/formoterol as-needed vs. comparator		
Odds ratio (2-sided 95% CI)[a]		0.64 (0.57, 0.73)
p-value		N/A

- Adherence to maintenance therapy was HIGH (79%)
- Comparing a symptom-driven treatment strategy with a maintenance treatment strategy
  - **83%** lower dose of anti-inflammatory in the budesonide/formoterol as-needed group versus the budesonide maintenance BID group
- As-needed medication use contributes to WCAW disqualification (“no more than 2 days”)

[a]Predefined non-inferiority limit of 0.8 (ie, if the lower 95% CI of the OR for as-needed budesonide/formoterol vs. maintenance budesonide BID was ≥0.8.)

BID = twice daily; CI = confidence interval; N/A = not applicable; WCAW = well-controlled asthma weeks.

O’Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876.

SYGMA 1

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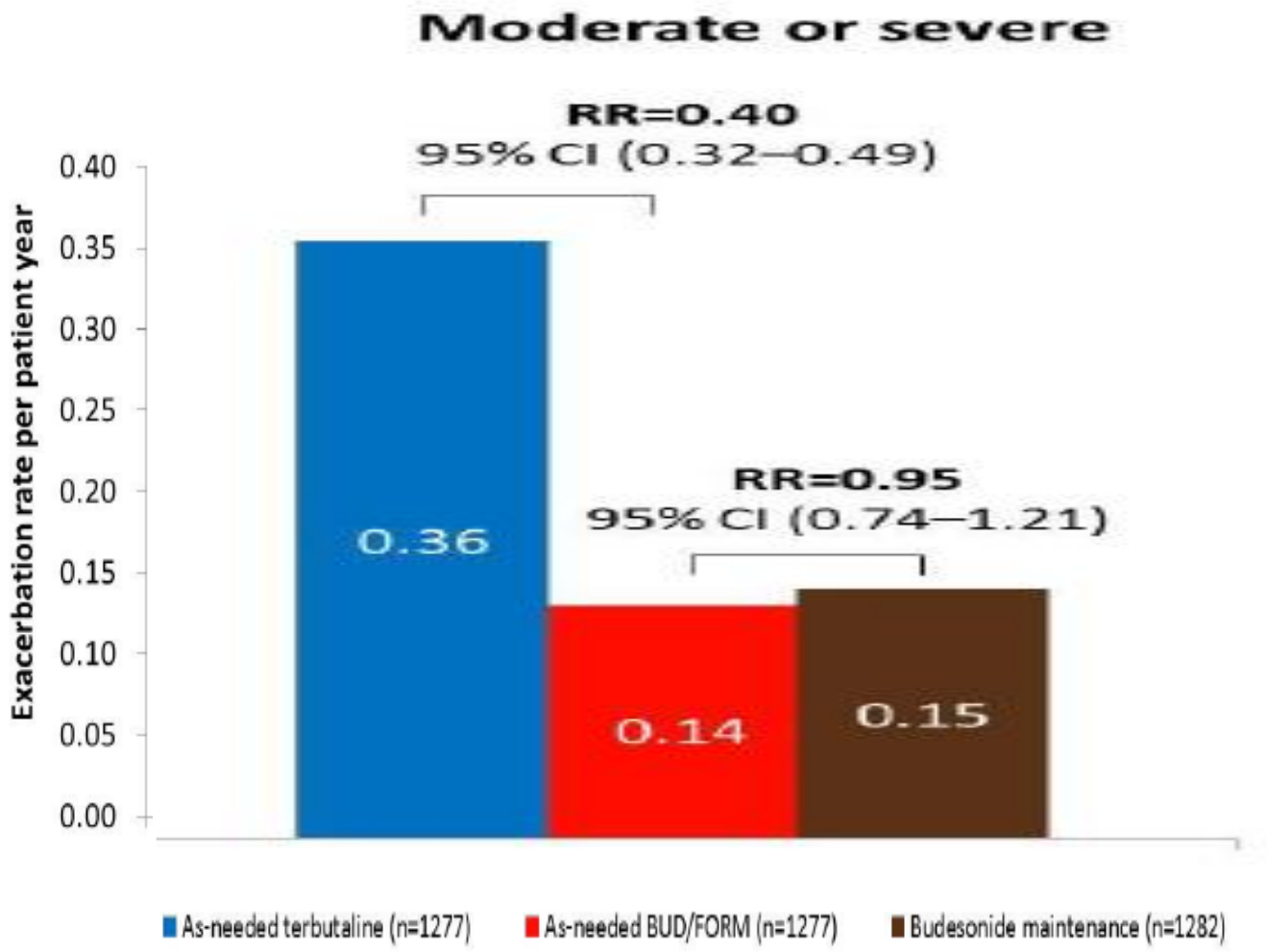

SYGMA 1

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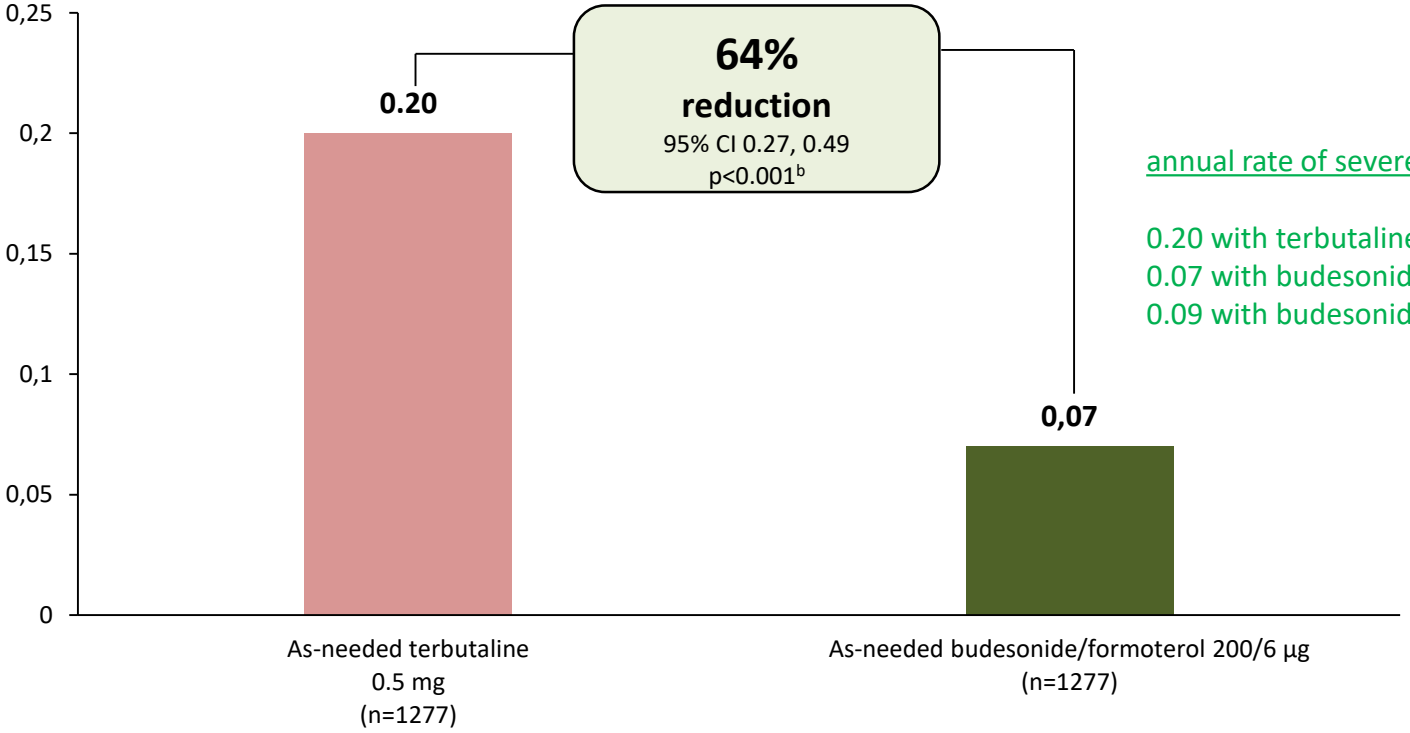
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση έδειξε 64% λιγότερες σοβαρές παροξύνσεις σε σχέση με τη τερβουταλίνη κατ' επίκληση



annual rate of severe exacerbations

0.20 with terbutaline
0.07 with budesonide–formoterol
0.09 with budesonide maintenance

[a]Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids; [b]P-values not controlled for multiplicity.

Note: Severe asthma exacerbation rates were analysed by a negative binomial regression model with randomized treatment, pre-study treatment, region, and number of severe exacerbations in the 12 months prior to screening (0 or ≥1) as factors.

BID = twice daily; CI = confidence interval; RR = rate ratio; SYGMA = SYmbicort Given as needed in Mild Asthma.

O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876.

SYGMA 1

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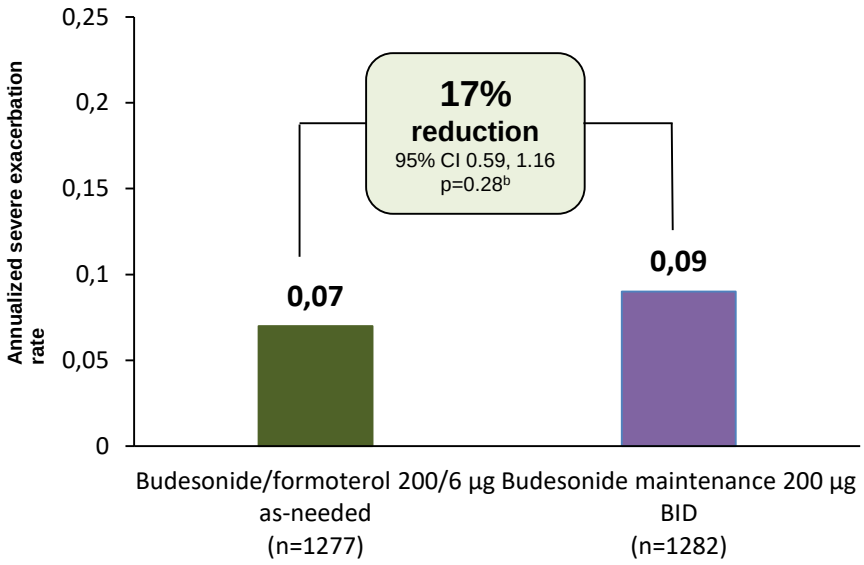
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση απέδειξε ανάλογο αποτέλεσμα στις σοβαρές παροξύνσεις με τη βουδεσονίδη



annual rate of severe exacerbations

0.20 with terbutaline
0.07 with budesonide–formoterol
0.09 with budesonide maintenance

Budesonide/formoterol as-needed was **equivalent** to budesonide maintenance BID in SYGMA 1 at preventing **severe exacerbations**[1]

[a]Severe exacerbations defined as worsening of asthma that is associated with a medical intervention, requiring either the use of systemic glucocorticoids for ≥3 days (or an injection of depot corticosteroids), or inpatient hospitalization or an emergency department visit (or other urgent, unscheduled health care visit) due to asthma that required systemic glucocorticoids[1,2]; [b]P-values not controlled for multiplicity[1]; [c]1-sided 95% CI for non-inferiority test; if the upper CI of the 1-sided 95% CI ≤1.2, then budesonide/formoterol as-needed is non-inferior to budesonide BID.[2]
BID = twice daily; CI = confidence interval; NA = not applicable; RR = rate ratio; SYGMA = SYmbicort Given as needed in Mild Asthma.
1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876;

SYGMA 1

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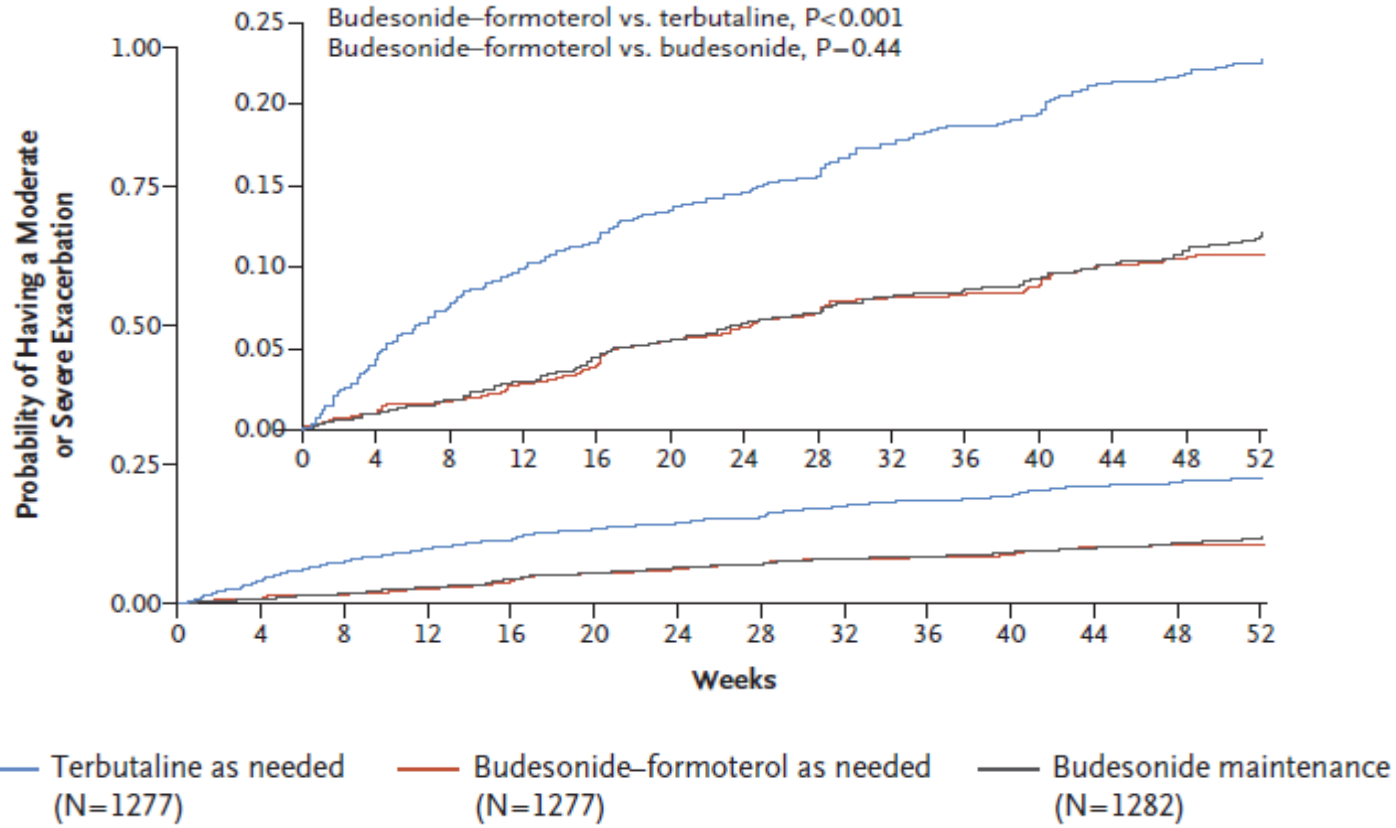
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Χρόνος μέχρι τη μέτρια ή σοβαρή παρόξυνση



Budesonide/formoterol as-needed was **non-inferior** to budesonide maintenance BID and **superior** to terbutaline as-needed in prolonging the **time to first severe exacerbation**[1,2]

1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876 2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1

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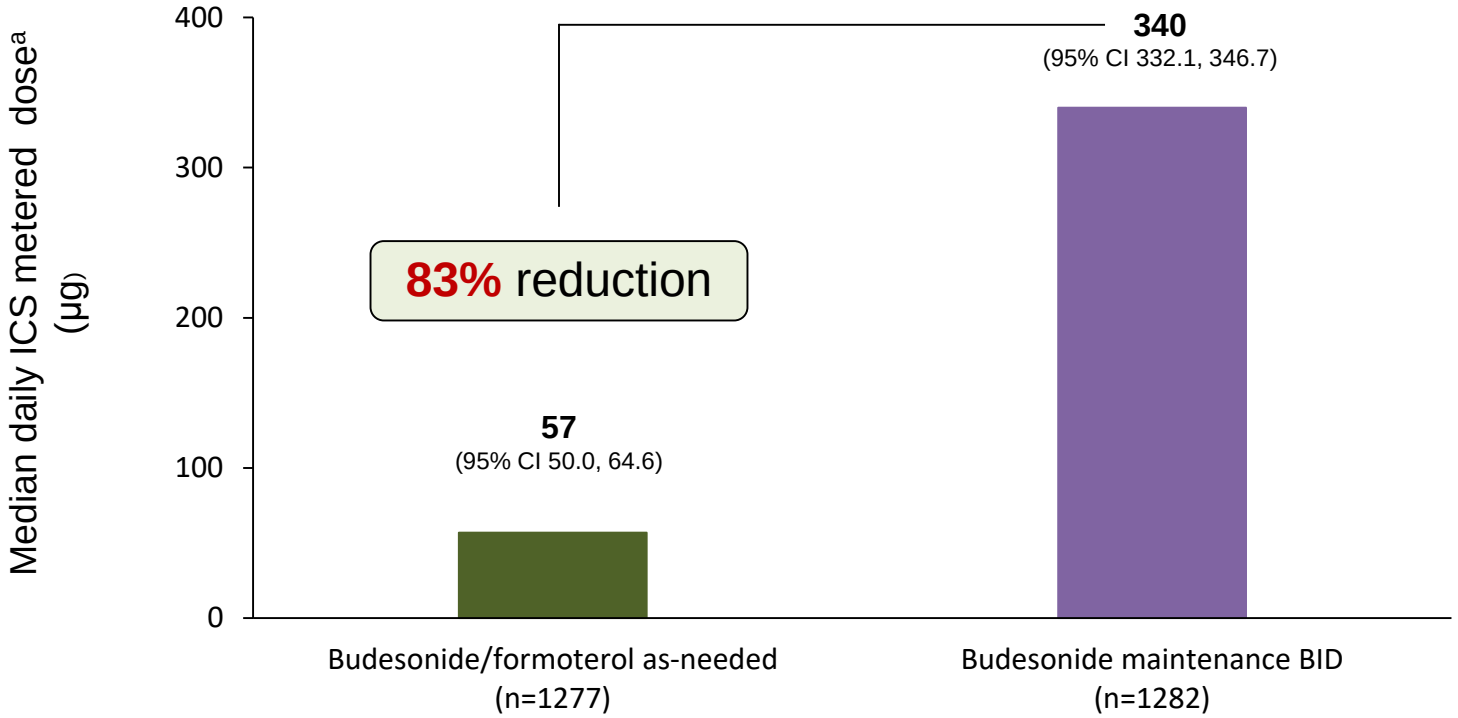
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση απέδειξε ανάλογο αποτέλεσμα στις σοβαρές παροξύνσεις με 83% λιγότερη δόση στεροειδών



O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876;

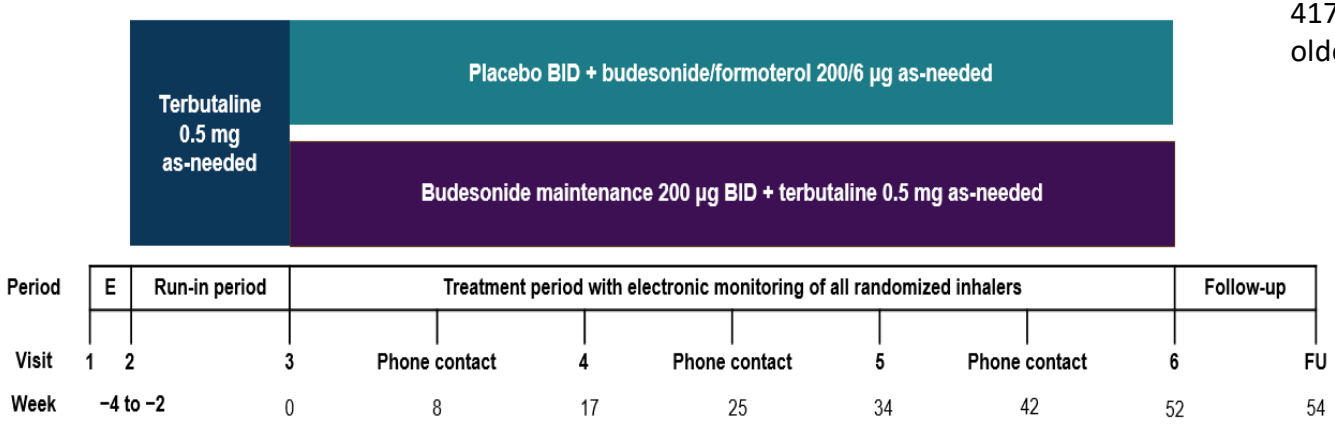
SYGMA 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

4176 patients, 12 years or older (2089/2087)



	SYGMA 2[1,3]
Primary Objective	**Show non-inferiority:** budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed **Primary endpoint: Annualised severe asthma exacerbation rate**
Secondary Objectives	1) **Efficacy of budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed** • Pre- and post-bronchodilator FEV_1 • ACQ-5 and AQLQ score • ICS use (or exposure) and rescue medication use

1. O'Byrne PM et al. *Trials.* 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed February 22, 2018; 3. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

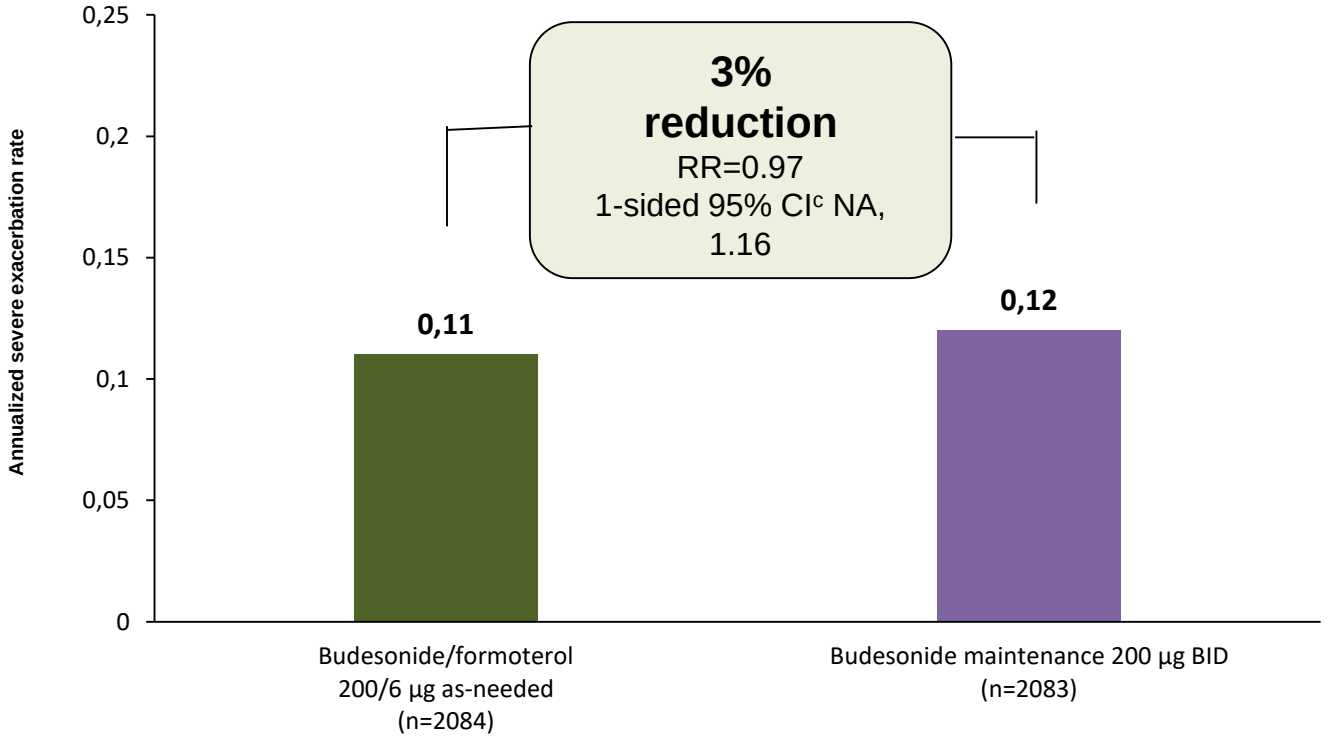
SYGMA 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση ήταν ισοδύναμος με τη Βουδεσονίδη στην πρόληψη των σοβαρών παροξύνσεων



2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887.

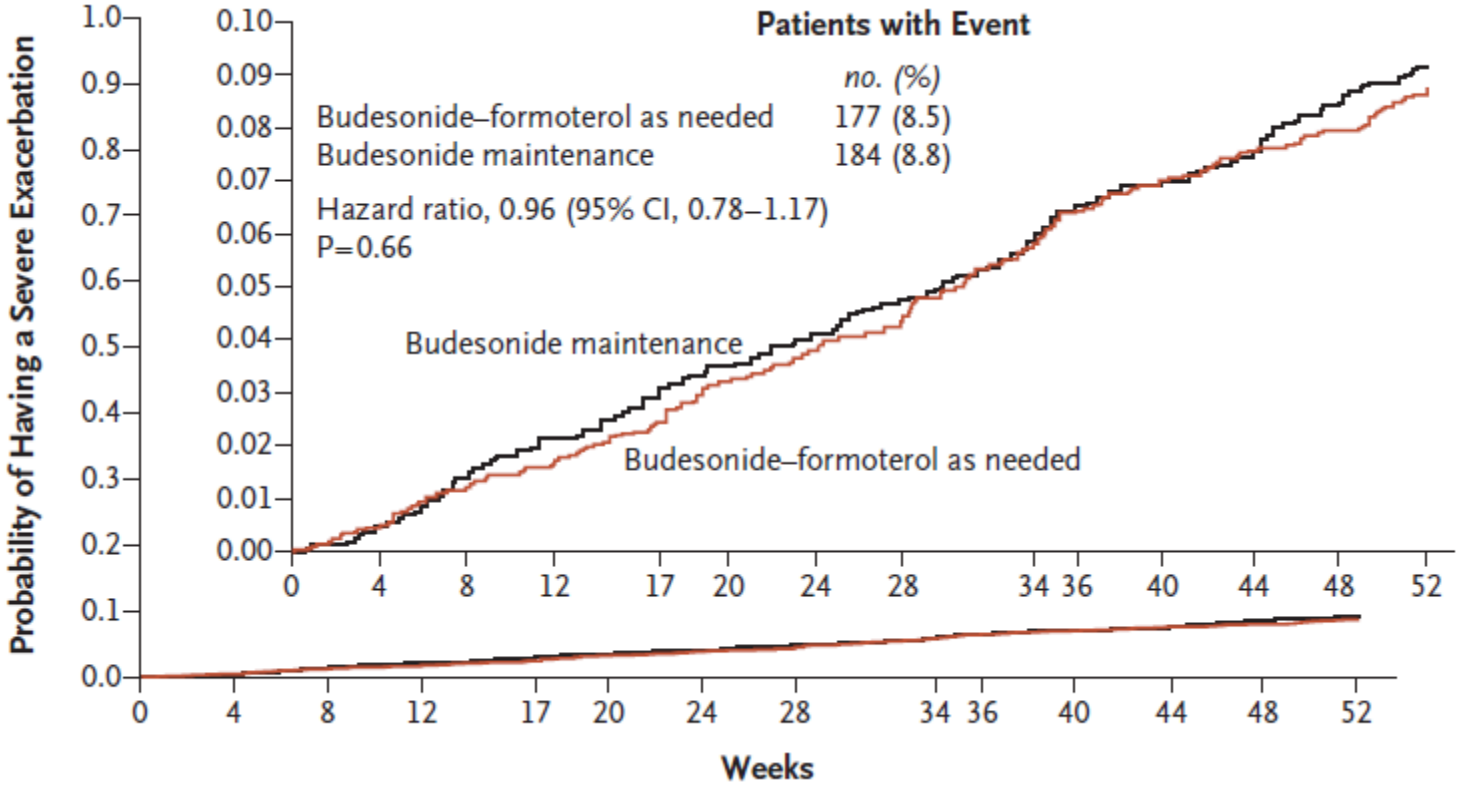
SYGMA 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Χρόνος μέχρι τη σοβαρή παρόξυνση (ίδιος)



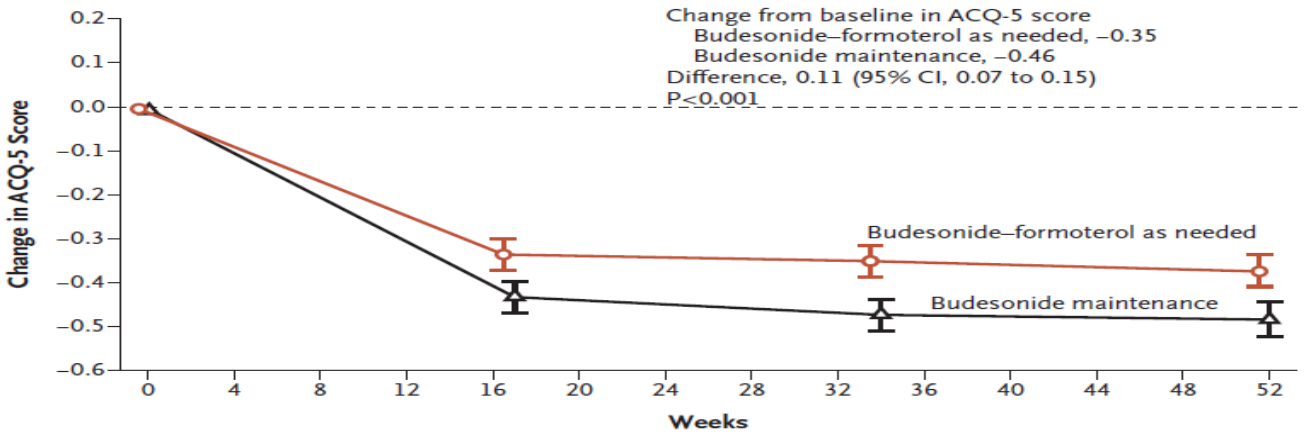
1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma



Αλλαγή του ACQ-5

Αλλαγή του Pre-BD FEV_1

	SYGMA 2[1]	
	Budesonide/Formoterol 200/6 µg As-needed (n=2079)	Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=2075)
Mean baseline, mL	2590	2610
LS mean change, mL	104.0	136.6
Treatment difference (95% CI)	-32.6 (-53,7, -11.4)	
Nominal p-value[a]	p=0.003	

SYGMA 2

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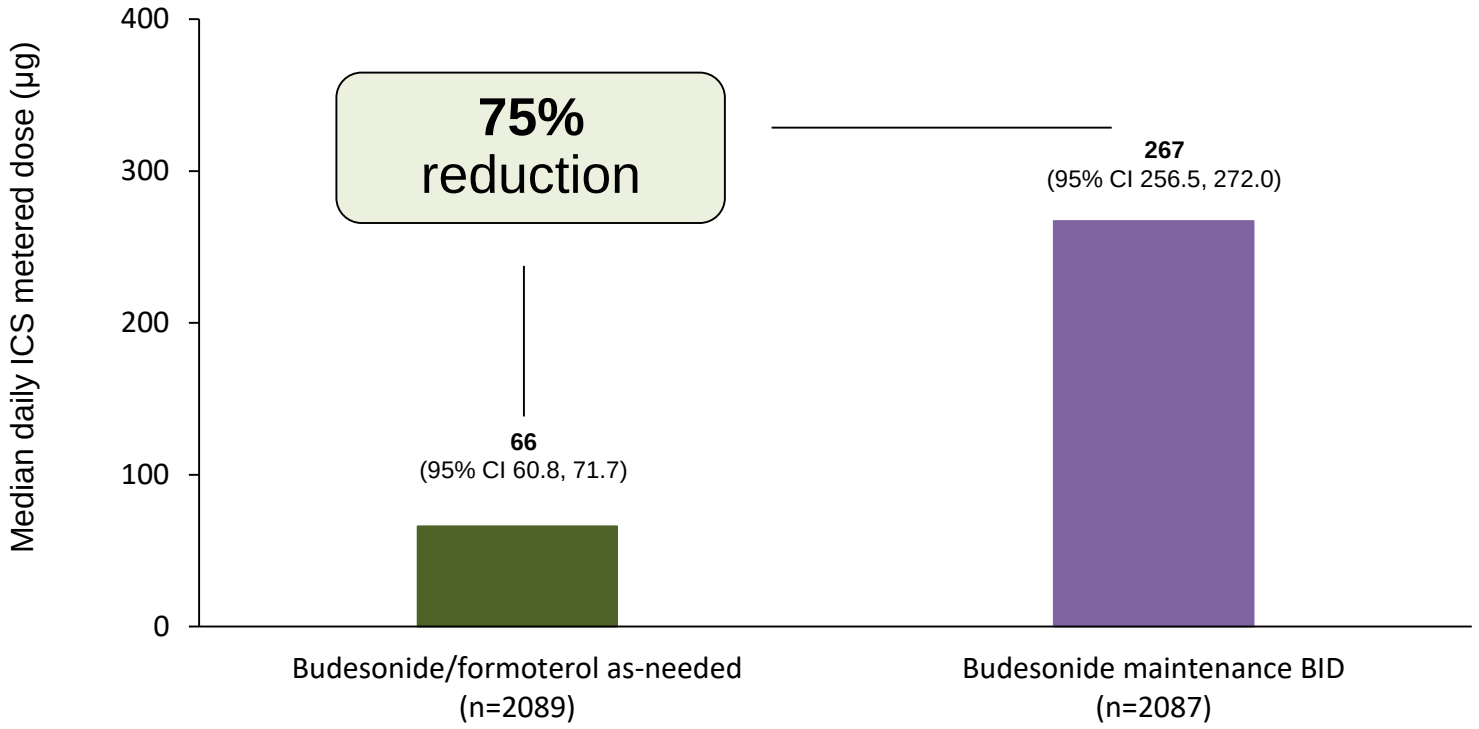
Ο συνδυασμός Βουδεσονίδης/Φορμοτερόλης κατ' επίκληση απέδειξε ανάλογο αποτέλεσμα στις σοβαρές παροξύνσεις με 75% λιγότερη δόση στεροειδών



Budesonide/formoterol as-needed achieved comparable risk of severe exacerbations to budesonide BID with a >75% lower inhaled steroid load over 1-year study period[1,2]

[a]1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

Συμπερασματικά-ήπιο άσθμα

- SABA, LTRA, ICS, ICS κατ΄ επίκληση, LABA/ICS κατ΄ επίκληση
- Συμμόρφωση, τεχνική λήψης, παρενέργειες, κόστος…όλα να συνεκτιμώνται

Συμπερασματικά-ήπιο άσθμα

- Βήμα 1+2 να γίνει ενιαίο;

  budesonide/formoterol κατ΄ επίκληση ή εναλλακτικά καθημερινά ICS

Ευχαριστώ πολύ!