Asthma – Getting it Right.

Diagnosis, phenotypes, guidelines Treating the right patient with the right treatment

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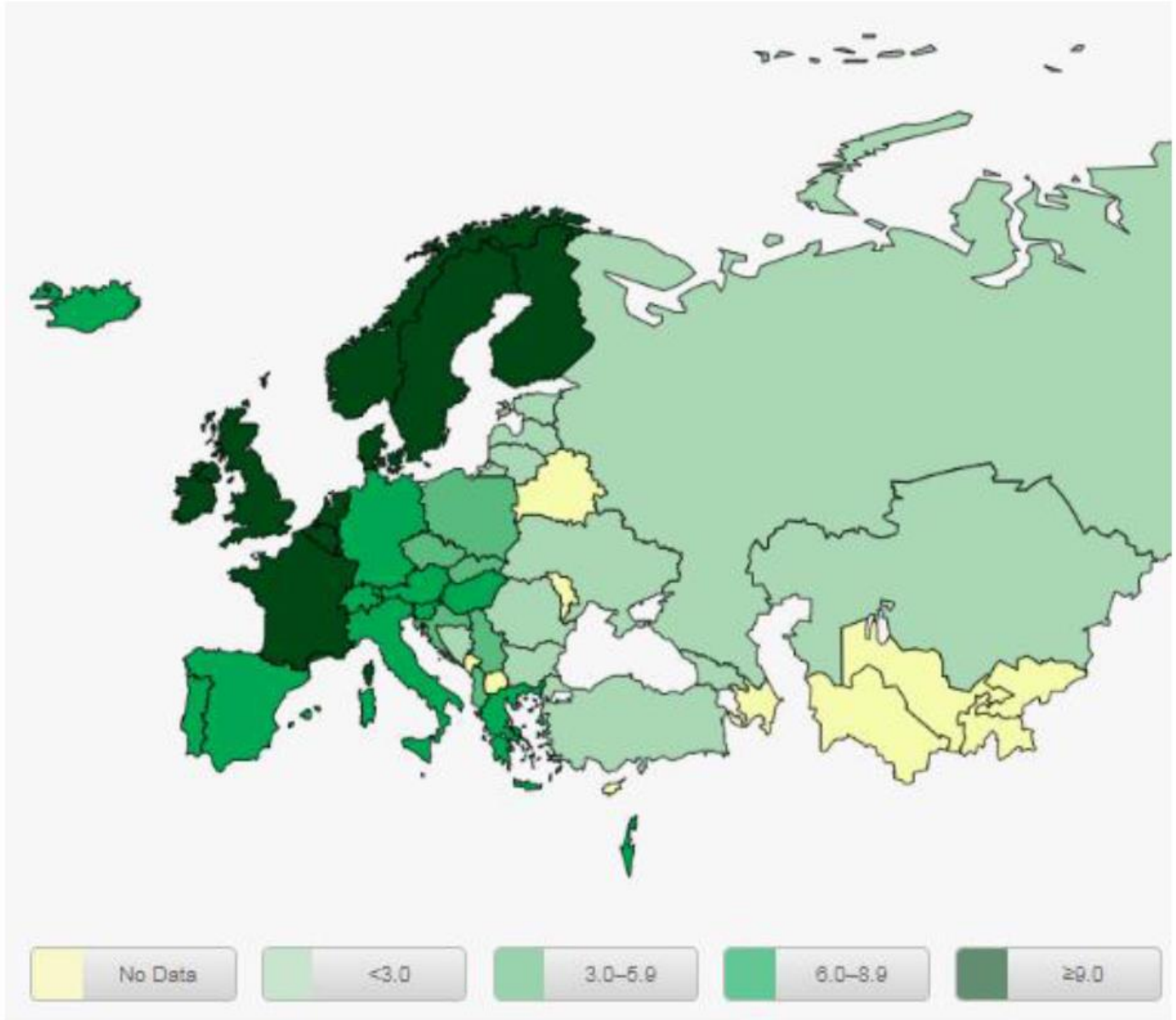
Learning objectives

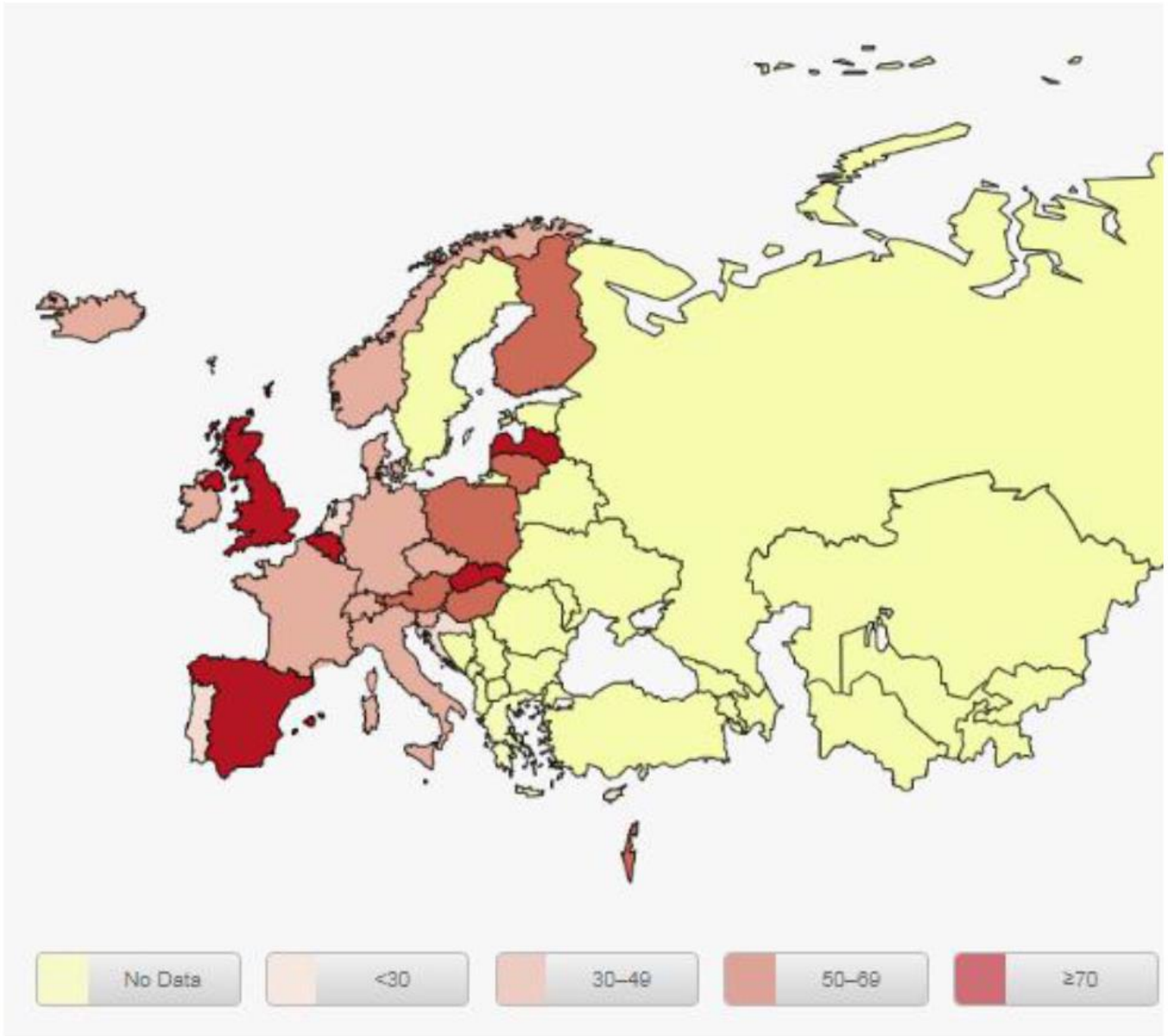
- Size of the problem
- What is asthma?. Common misdiagnosis, algorithms for assessment and treatment
- Phenotypes with focus on Obesity
- Guidelines
- Treatments
  - Basic
  - Phenotype based
  - Co-morbidities
  - Biologic treatments for severe asthma
  - Cases

European asthma prevalence

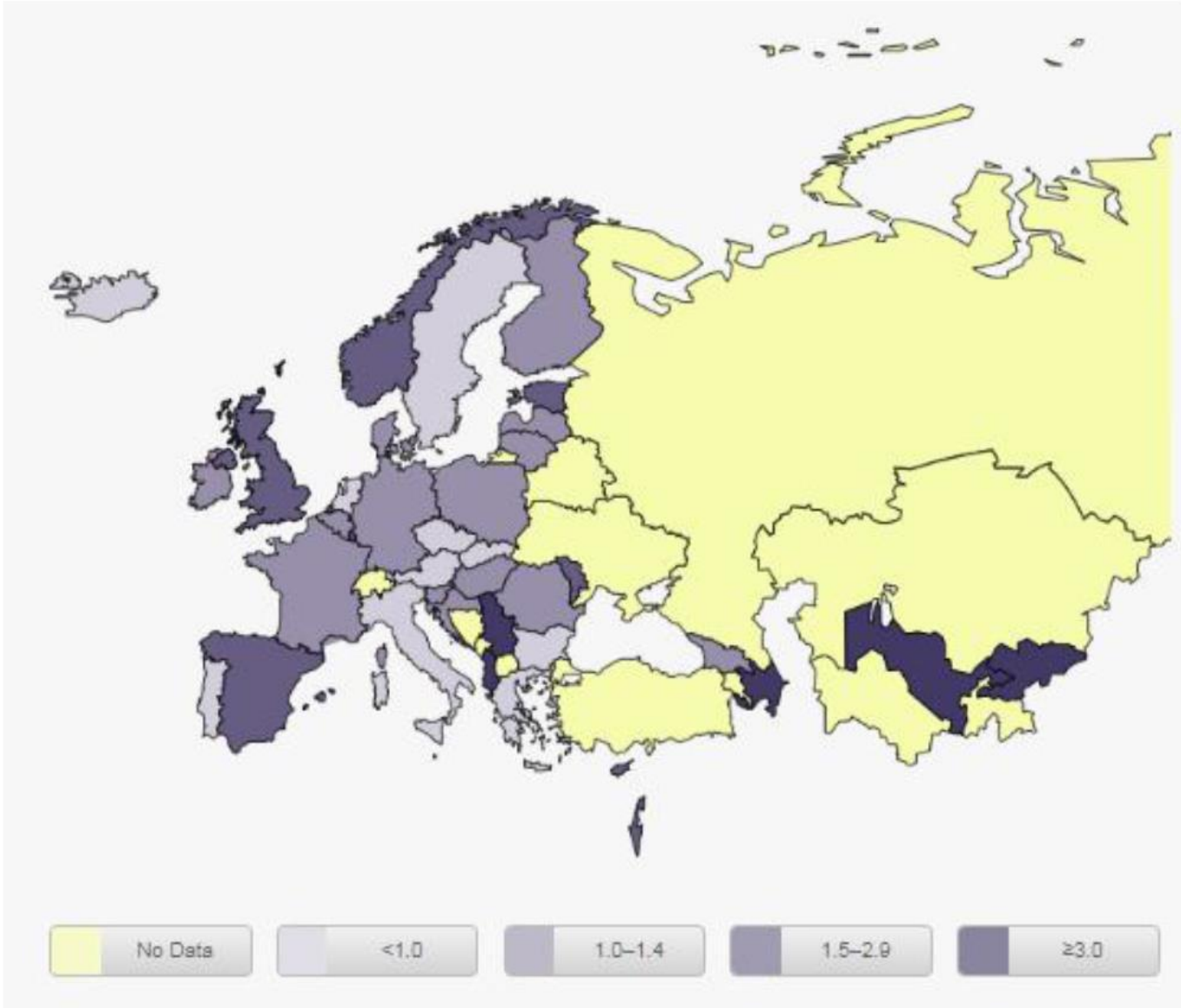


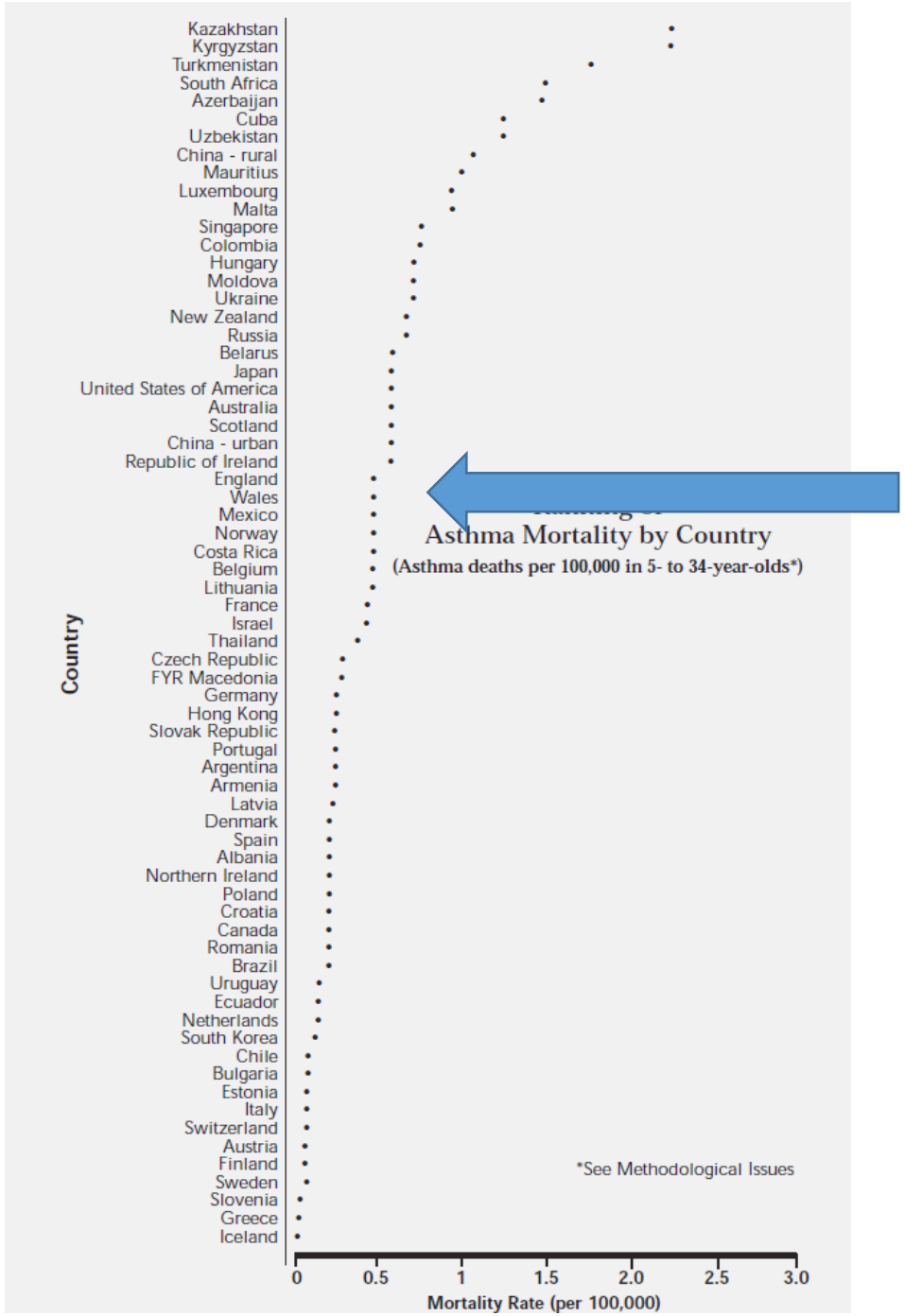
European hospital admission rates for asthma

NHS England



European asthma mortality

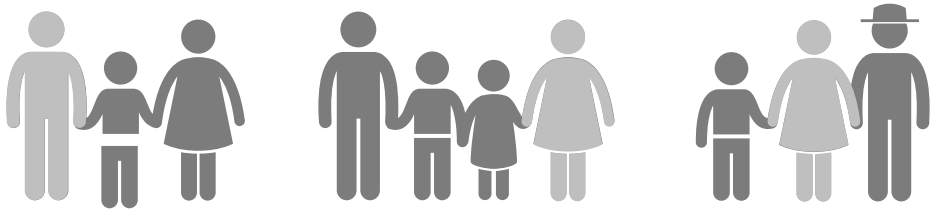



Asthma Mortality by Country
(Asthma deaths per 100,000 in 5- to 34-year-olds*)
Country
Kazakhstan
Kyrgyzstan
Turkmenistan
South Africa
Azerbaijan
Cuba
Uzbekistan
China - rural
Mauritius
Luxembourg
Malta
Singapore
Colombia
Hungary
Moldova
Ukraine
New Zealand
Russia
Belarus
Japan
United States of America
Australia
Scotland
China - urban
Republic of Ireland
England
Wales
Mexico
Norway
Costa Rica
Belgium
Lithuania
France
Israel
Thailand
Czech Republic
FYR Macedonia
Germany
Hong Kong
Slovak Republic
Portugal
Argentina
Armenia
Latvia
Denmark
Spain
Albania
Northern Ireland
Poland
Croatia
Canada
Romania
Brazil
Uruguay
Ecuador
Netherlands
South Korea
Chile
Bulgaria
Estonia
Italy
Switzerland
Austria
Finland
Sweden
Slovenia
Greece
Iceland
*See Methodological Issues
0
0.5
1
1.5
2.0
2.5
3.0
Mortality Rate (per 100,000)

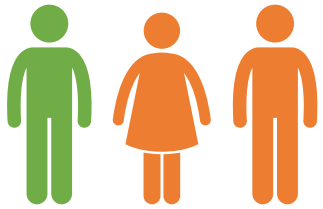
Asthma: The scale of the problem

5.4 million
People living with asthma in the UK

Every 10 seconds
someone is having a potentially life-threatening asthma attack in the UK



Every day, the lives of **three families** are devastated by the death of a loved one to an asthma attack…

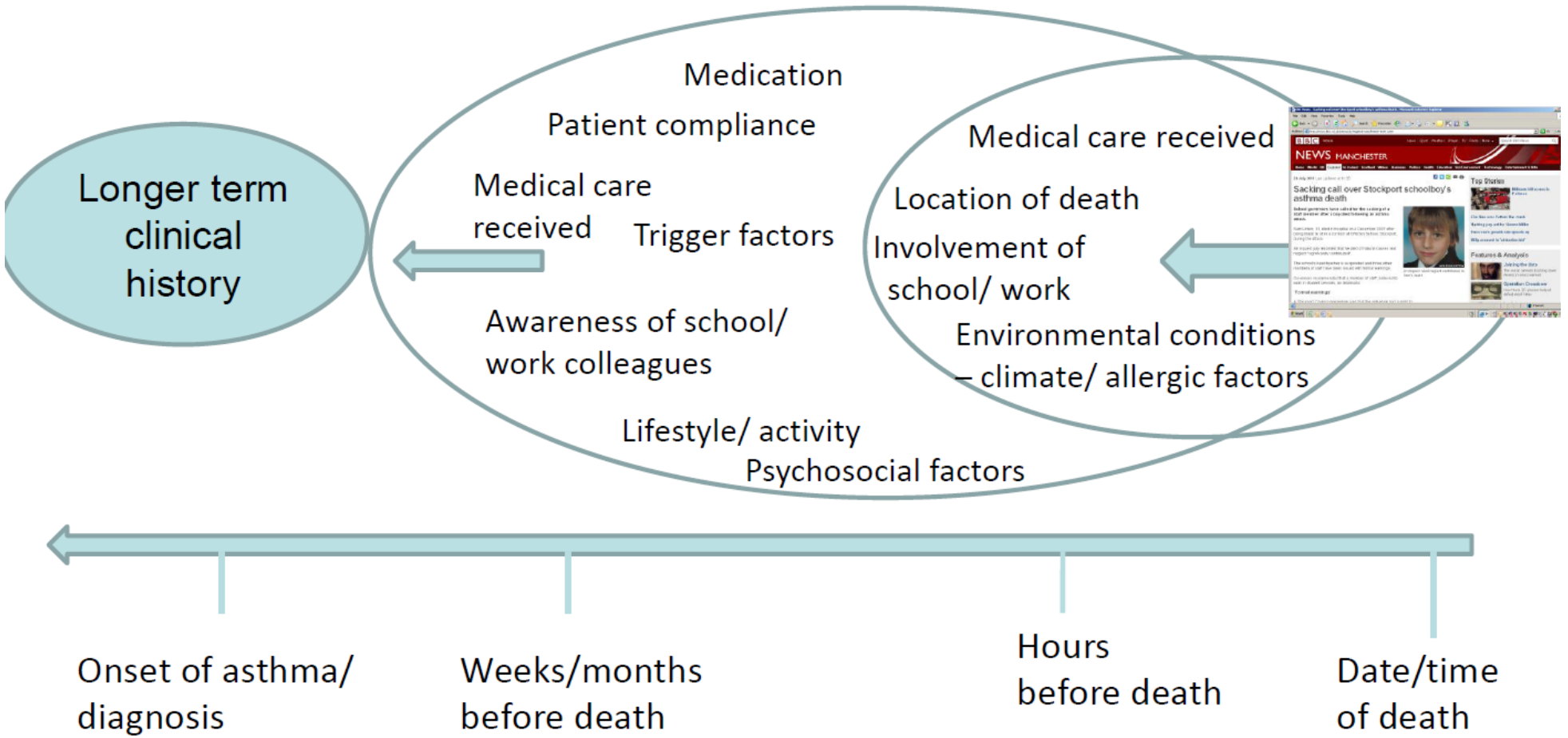


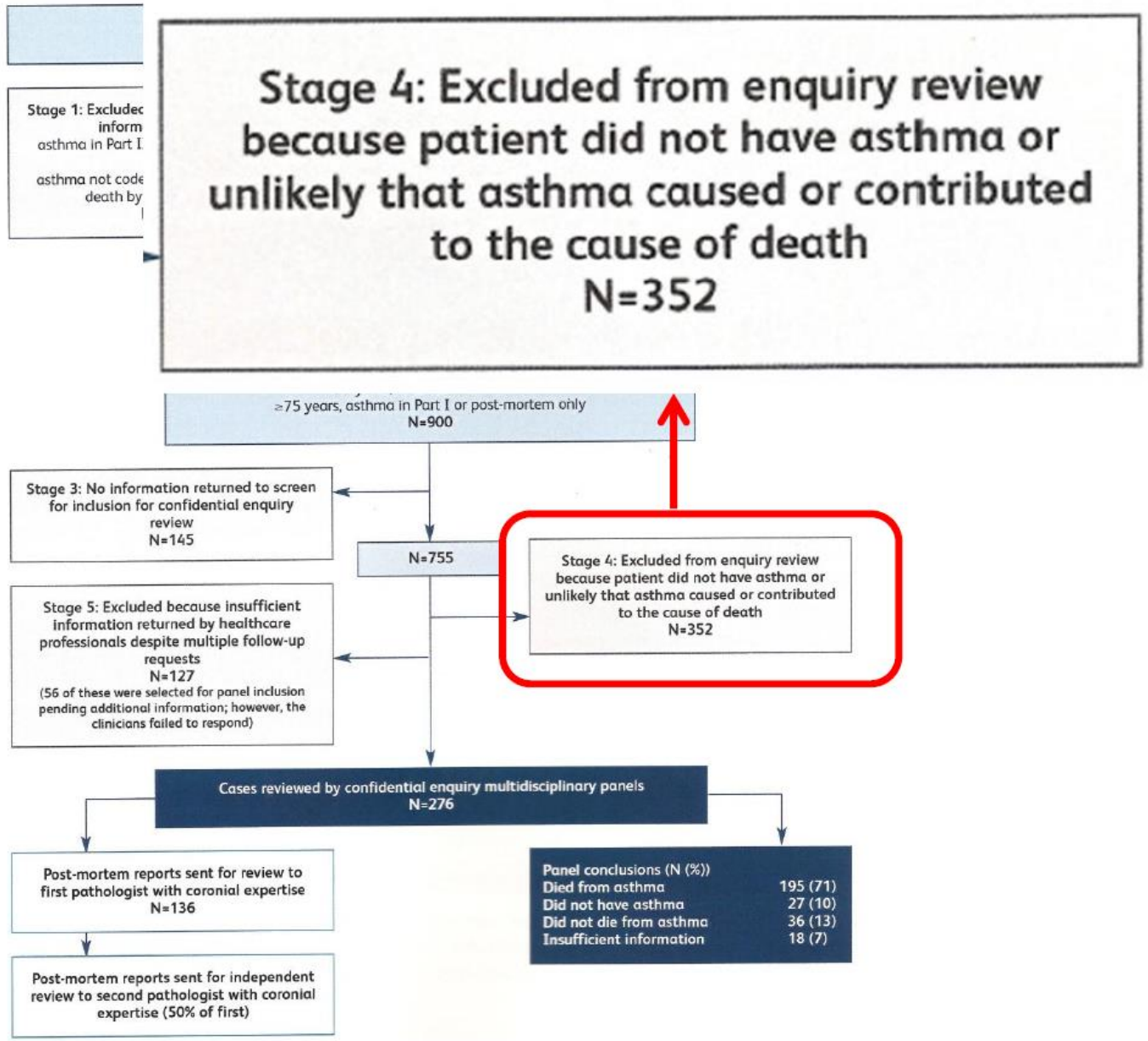
…yet **two-thirds** of these deaths are preventable

In 2015 **1,468** people died from asthma in the UK – the highest level for over 10 years

Adapted from Asthma UK. *Asthma facts and statistics* [online] 2016. Available from: https://www.asthma.org.uk/about/media/facts-and-statistics/ [Accessed: October 2017].

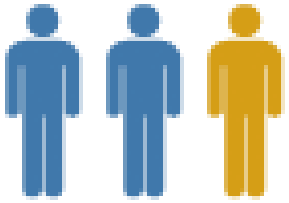
National Review of Asthma Deaths (NRAD)




Stage 4: Excluded from enquiry review because patient did not have asthma or unlikely that asthma caused or contributed to the cause of death
N=352
≥75 years, asthma in Part I or post-mortem only
N=900
Stage 3: No information returned to screen for inclusion for confidential enquiry review
N=145
N=755
Stage 4: Excluded from enquiry review because patient did not have asthma or unlikely that asthma caused or contributed to the cause of death
N=352
Stage 5: Excluded because insufficient information returned by healthcare professionals despite multiple follow-up requests
N=127
(56 of these were selected for panel inclusion pending additional information; however, the clinicians failed to respond)
Cases reviewed by confidential enquiry multidisciplinary panels
N=276
Post-mortem reports sent for review to first pathologist with coronial expertise
N=136
Post-mortem reports sent for independent review to second pathologist with coronial expertise (50% of first)
Panel conclusions (N (%))
Died from asthma 195 (71)
Did not have asthma 27 (10)
Did not die from asthma 36 (13)
Insufficient information 18 (7)

Asthma is both over- and under-diagnosed

- Asthma is a clinical diagnosis
- Symptoms can be misleading
- Objective information is rarely used in initial assessment of asthma

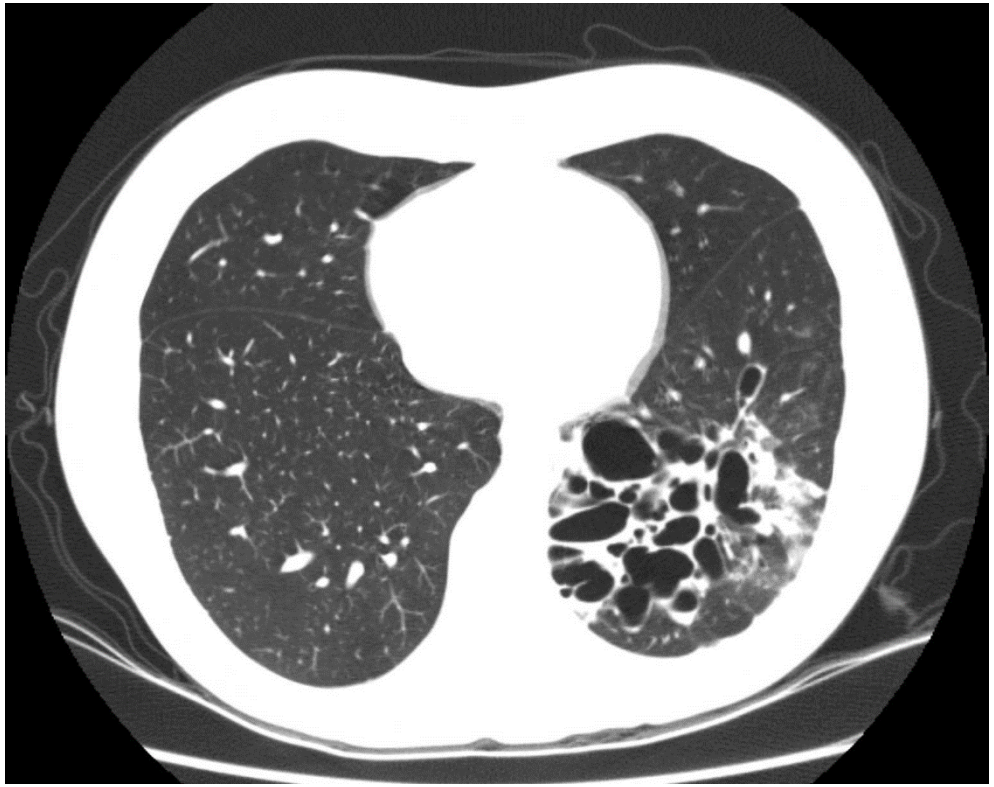


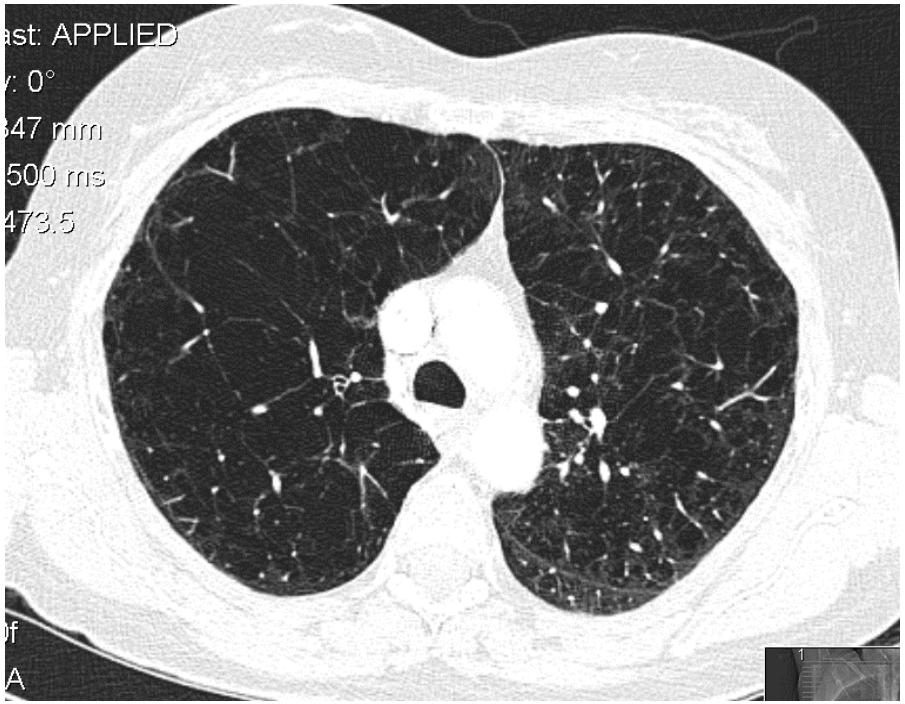
Approximately one-third of patients with asthma do not have asthma when objectively assessed[1]

71%

of misdiagnosed patients are on therapy[1]

1. Pakhale S et al. BMC Pulmon Med 2011;11:27




ast: APPLIED
y: 0°
347 mm
500 ms
473.5
of
A

Incorrect diagnosis of Asthma in severe asthma referrals to the Brompton

- 12% COPD
- Alpha 1 deficient emphysema
- Bronchiectasis
- Cardiomyopathy
- Obliterative bronchiolitis
- Respiratory Muscle inco-ordination
- Vocal cord dysfunction/Anxiety
- Adverse drug reactions
- Chronic cough syndrome
- OSA

Gibeon, D; Chung KF, Exp and Clinical Allergy 2012

The National review of Asthma Deaths (NRAD) report was the first national investigation of asthma deaths in the UK in May 2014

- NRAD aimed to understand the circumstances surrounding asthma deaths to identify avoidable factors and make recommendations to improve care and reduce the number of deaths

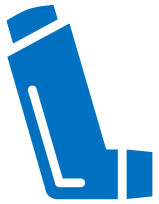
- Of 195 asthma deaths occurring between February 2012 and January 2013:
  - For 84 (43%) of those who died, there was no evidence of an asthma review in general practice in the previous year
  - 46% of asthma deaths were identified as being avoidable
  - The majority of people (58%) who died were thought to have mild or moderate asthma
  - PAAPs were provided in only 44 (23%) individuals who died from asthma
  - Exacerbating factors, or triggers (eg drugs, allergic reactions and viral infections), were documented in only half of those who died

NRAD=National Review of Asthma Deaths; PAAP=personalised asthma action plans.

Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Accessed: July 2017].

NRAD report: Excessive prescribing of SABAs and under-prescribing of preventer medication

Evidence of excessive prescribing of reliever medication



39% of patients on short-acting relievers* at the time of death had been prescribed more than **12** short-acting reliever inhalers in the year before they died

While **4%** had been prescribed more than **50** reliever inhalers

Evidence of under-prescribing of preventer medication

To comply with recommendations, most patients would usually need at least

12 preventer prescriptions per year

NRAD revealed;

38% of patients on preventer inhalers* received fewer than **4** inhalers in the year leading up to their death

and **80%** received fewer than **12** preventer inhalers

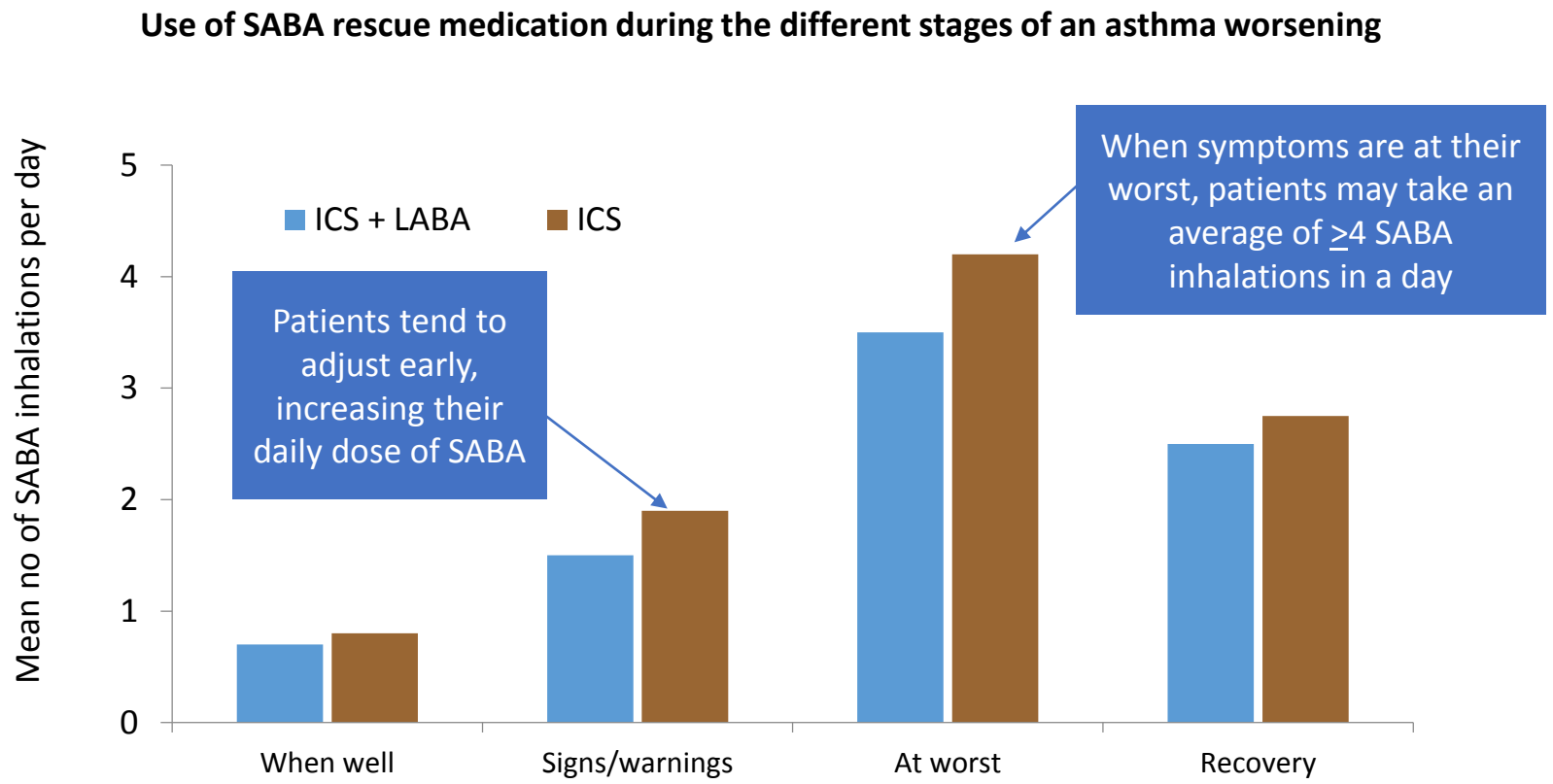
Adapted from NRAD (2014)

*Of those patients for which the number of prescriptions was known. Among 189 patients who were on short-acting relievers at the time of death, the number of prescriptions was known for 165. Among 168 patients on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128.

NRAD=National Review of Asthma Deaths; SABA=short-acting ß-agonist.

Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Accessed: July 2017].

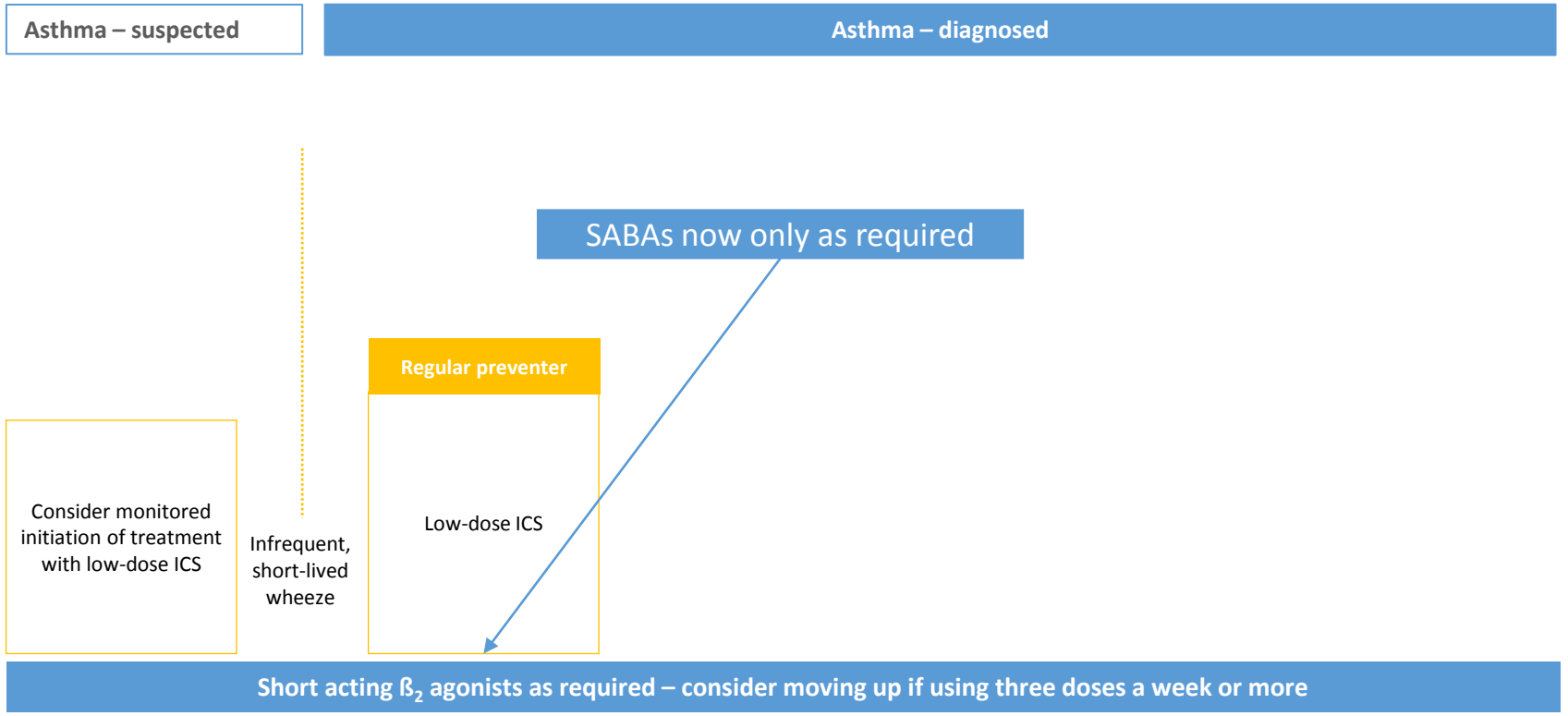
Regardless of the type of maintenance therapy prescribed, patients increase their use of SABA at the onset of symptoms



These results are from quantitative research using a structured questionnaire via telephone with 3,415 (16yrs and above) patients on regular ICS or ICS/LABA therapy who were recruited by their physicians. The Asthma Control Questionnaire (ACQ; 6-item version with forced expiratory volume in 1 s question omitted) was used to assess asthma control. 0 represents no impairment and 6 represents maximum impairment.

ICS=inhaled corticosteroid; LABA=long-acting ß-agonist; SABA=short-acting $ß_2$-agonist.
Adapted from Partridge M, et al. *BMC Pulm Med* 2006;6:13.

BTS 2016 guidelines removed step 1 and recommended low-dose ICS as the lowest controlling therapy

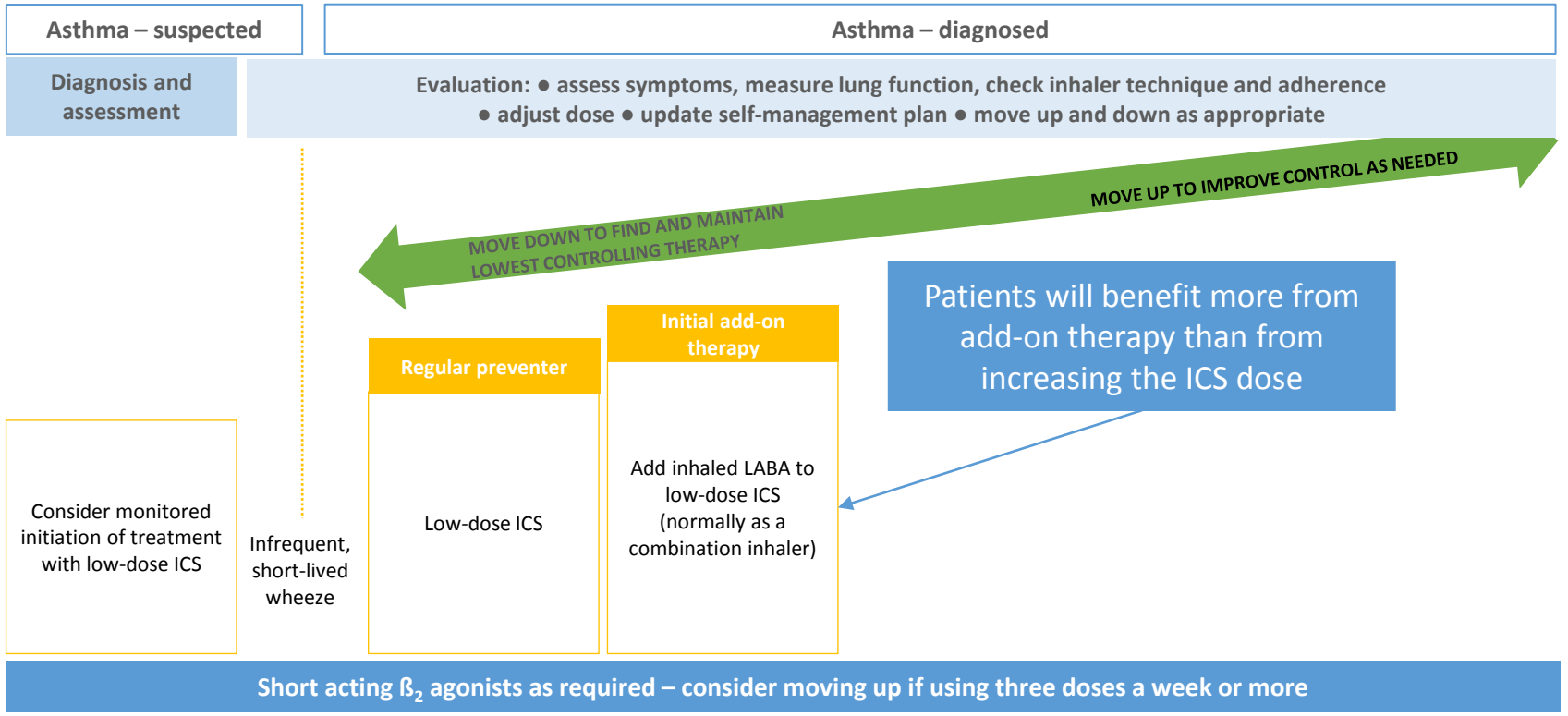


Summary of management in adults

Adapted from BTS 2016

BTS=British Thoracic society; ICS=inhaled corticosteroid; SABA=short-acting ß-agonist;
SIGN=Scottish Intercollegiate Guidelines Network.
British Thoracic Society. *BTS/SIGN British guideline on the management of asthma* [online] 2016. Available from: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/ [Accessed: July 2017].

Recommendations for patients with inadequate control on regular preventers have changed



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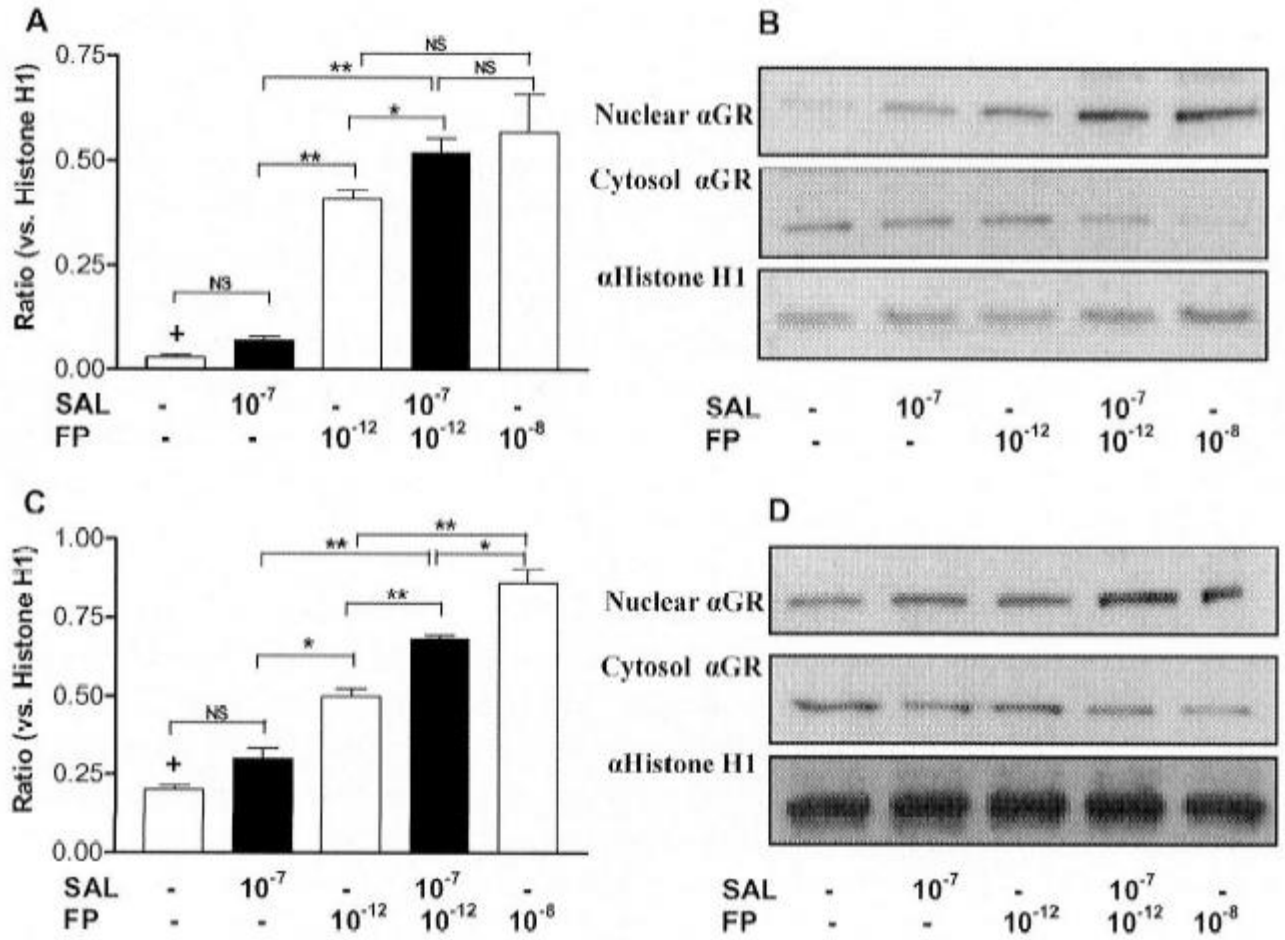
Glucocorticoid Receptor Nuclear Translocation in Airway Cells after Inhaled Combination Therapy

Omar S. Usmani, Kazuhiro Ito, Kittipong Maneechotesuwan, Misako Ito, Malcolm Johnson, Peter J. Barnes, and Ian M. Adcock

Airways Disease Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom

AJRCCM Sep 2005, 172: 704


A
Ratio (vs. Histone H1)
0.75
0.50
0.25
0.00
NS
**
NS
*
**
NS
+
SAL - 10-7 - 10-7 -
FP - - 10-12 10-12 10-8
B
Nuclear αGR
Cytosol αGR
αHistone H1
SAL - 10-7 - 10-7 -
FP - - 10-12 10-12 10-8
C
Ratio (vs. Histone H1)
1.00
0.75
0.50
0.25
0.00
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NS
+
SAL - 10-7 - 10-7 -
FP - - 10-12 10-12 10-8
D
Nuclear αGR
Cytosol αGR
αHistone H1
SAL - 10-7 - 10-7 -
FP - - 10-12 10-12 10-8

Evaluation: get the basics right then identify the phenotype

- Diagnosis wrong.
  - Pseudoasthma
  - Asthma plus
- Issues with adherence, inhaler technique, self management strategies
- Genuine severe disease
  - Clinically important inflammatory subtypes of severe airway disease
  - Phenotype specific treatment options

Suggested investigations for primary care

- FBC, BNP, IgE,
- Spirometry
- Peak flow chart
- FENO
- Chest Xray

- In secondary/tertiary care
- Lung function, HRCT, Echo, ENT, bronchoscopy, psychology, FENO

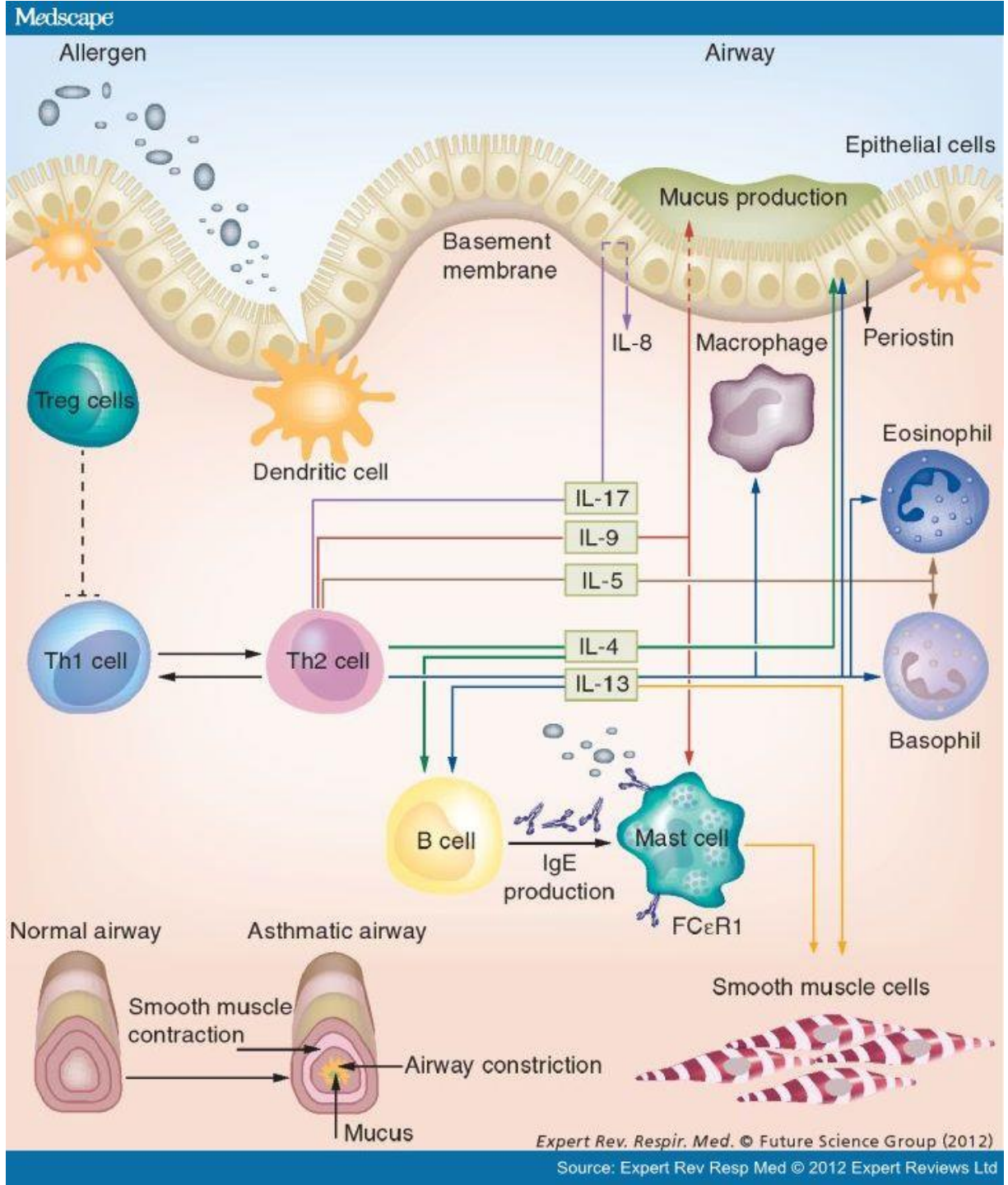

Medscape
Allergen
Airway
Epithelial cells
Mucus production
Basement membrane
IL-8
Macrophage
Periostin
Treg cells
Dendritic cell
Eosinophil
IL-17
IL-9
IL-5
Th1 cell
Th2 cell
IL-4
IL-13
Basophil
B cell
IgE production
Mast cell
FCεR1
Normal airway
Asthmatic airway
Smooth muscle cells
Smooth muscle contraction
Airway constriction
Mucus
Expert Rev. Respir. Med. © Future Science Group (2012)
Source: Expert Rev Resp Med © 2012 Expert Reviews Ltd

TABLE 2. CLUSTERS IN PRIMARY CARE

Variable	Primary Care (*n* = 184)	Cluster 1 Early-Onset Atopic Asthma (*n* = 61)	Cluster 2 Obese Noneosinophilic (*n* = 27)	Cluster 3 Benign Asthma (*n* = 96)	Significance (*P* Value)*
Sex†, % female	54.4	45.9	81.5	52.1	0.006
Age, yr (SD)	49.2 (13.9)	44.5 (14.3)	53.9 (14)	50.8 (13)	0.003
Age of onset†, yr (SD)	24.7 (19)	14.6 (15.4)	35.3 (19.6)	28.2 (18.3)	<0.001
Atopic status†, % positive	72.8	95.1	51.9	64.6	<0.001
Body mass index†, kg/m² (SD)	27.5 (5.4)	26.1 (3.8)	36.2 (5.5)	26 (3.6)	<0.001
PC_{20} methacholine†‡, mg/ml	1.04 (1.13)	0.12 (0.86)	1.60 (0.93)	6.39 (0.75)	<0.001
PC_{20} >8 mg/ml, n (%)	64 (34.7)	2 (3.3)	6 (22.2)	56 (58.3)	<0.001
Peak flow variability†‡, amp % mean	17 (0.38)	20 (0.47)	21.9 (0.32)	14.8 (0.32)	0.039
FEV₁ change with bronchodilator‡, %	1.63 (1.16)	4.5 (0.91)	1.82 (1.16)	0.83 (1.22)	<0.001
Post-bronchodilator FEV_1, % predicted	91.4 (21)	86.9 (20.7)	91.5 (21.4)	94.2 (20.7)	0.107
Sputum eosinophil count‡, %	1.32 (0.82)	3.75 (0.64)	1.53 (0.51)	0.83 (0.44)	<0.001
Fe_{NO}‡§, ppb	31.6 (0.33)	57.5 (0.27)	25.8 (0.29)	22.8 (0.27)	<0.001
Sputum neutrophil count‡, %	55.09 (0.31)	45.87 (0.24)	72.71 (0.13)	57.56 (0.36)	0.038
Modified JACS† (SD)	1.36 (0.74)	1.54 (0.58)	2.06 (0.73)	1.04 (0.66)	<0.001
Dose of inhaled corticosteroid, BDP equivalent/μg (SD)	632 (579)	548 (559)	746 (611)	653 (581)	0.202
Long-acting bronchodilator use, %	40.2	34.4	48.2	41.7	0.442
Previous hospital admission or emergency attendance, no. per patient	0.60 (1.57)	1.04	0.26	0.20	0.037
Previous outpatient attendance, % attended	15%	22%	19%	6%	0.121
Severe asthma exacerbations (requiring oral corticosteroids) in past 12 mo, no. per patient	1.25 (1.94)	1.86 (0.32)	1.07 (0.32)	0.39 (0.18)	0.002

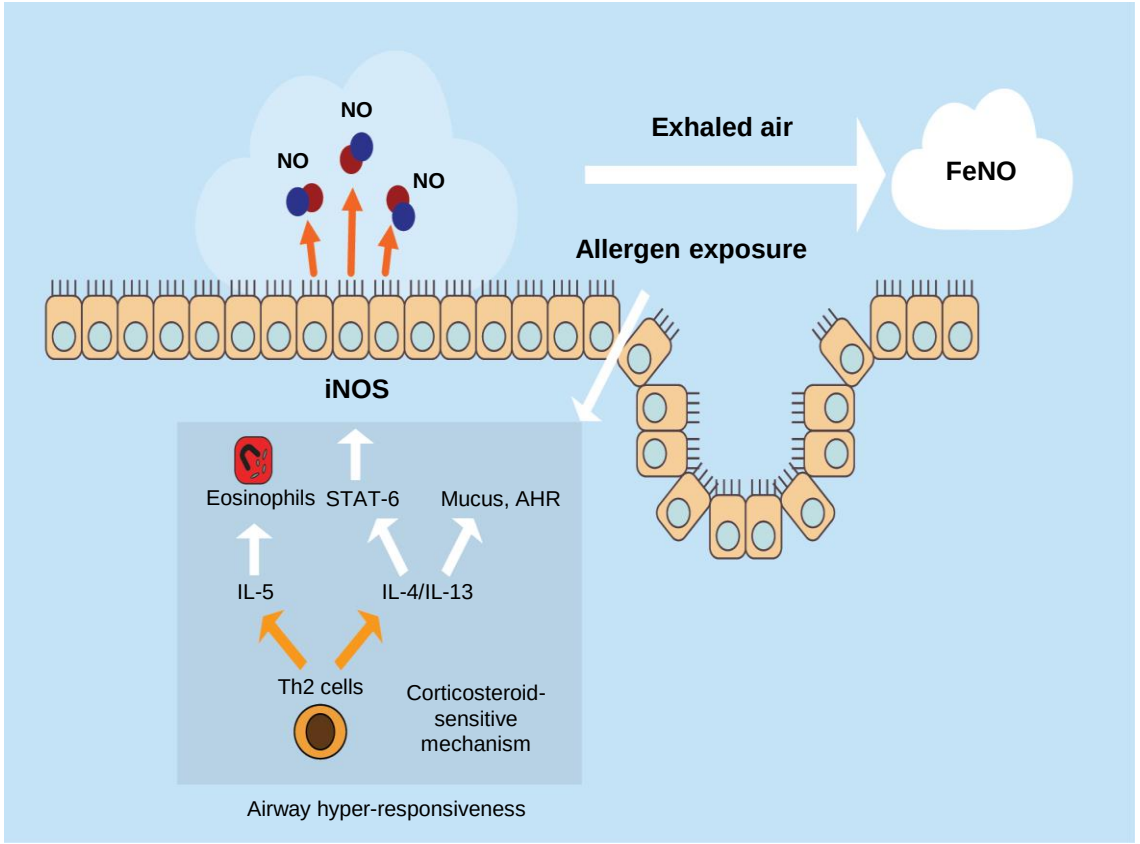
TABLE 3. CLUSTERS IN SECONDARY CARE

Variable	Secondary Care (*n* = 187)	Cluster 1 Early Onset, Atopic (*n* = 74)	Cluster 2 Obese, Noneosinophilic (*n* = 23)	Cluster 3 Early Symptom Predominant (*n* = 22)	Cluster 4 Inflammation Predominant (*n* = 68)	Significance (*P* Value)*
Sex†, % female	65.8	75.7	87	68.2	47.1	<0.001
Age, yr (SD)	43.4 (15.9)	39.4 (15.7)	42.7 (11.1)	35.5 (15.5)	50.6 (15.1)	<0.001
Age of onset†, yr (SD)	20.3 (18.4)	12.7 (12.9)	15.4 (15.2)	12.6 (15)	32.6 (19.1)	<0.001
Atopic status†, % positive	73.8	83.8	65.2	81.8	63.2	0.024
Body mass index†, kg/m² (SD)	28.5 (6.5)	27.6 (4.5)	40.9 (6.5)	23.6 (3.1)	27 (3.9)	<0.001
Peak flow variability‡, amp % mean	32.2 (0.48)	46.1 (0.35)	21.2 (0.76)	24.2 (0.65)	27.6 (0.36)	0.002
FEV_1 change with [illegible]	12.8 (0.41)	24.5 (0.31)	9.3 (0.35)	4.5 (0.33)	9.8 (0.34)	<0.001
Post-bronchodilator FEV_1, % predicted (SD)	82.1 (21.1)	79.0 (21.9)	79.0 (18.5)	79.5 (26.1)	87.2 (18.5)	0.093
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Fe_{NO}‖, ppb	43 (0.32)	51.2 (0.36)	24.2 (0.27)	22.6 (0.30)	53.1 (0.32)	<0.001
Sputum neutrophil count, %¶	46.7 (0.32)	45.4 (0.39)	49.3 (0.22)	51.3 (0.23)	45.9 (0.29)	0.892
Modified JACS† (SD)	2.02 (1.16)	2.63 (0.93)	2.37 (1.09)	2.11 (1.11)	1.21 (0.95)	<0.001
Dose of inhaled corticosteroid, BDP equivalent/μg (SD)	1,018 (539)	1,168 (578)	1,045 (590)	809 (396)	914 (479)	0.008
Long-acting bronchodilator use, %	93.0	91.9	95.4	90.9	94.1	0.999
Maintenance oral corticosteroid use, %	31.7	32.4	22.7	22.7	36.8	0.604
Median Nijmegen score (IQR) (% with score >23)#	16 (7–26.5)	20.5 (12–30.25) (44.6)	23 (12–33) (52.2)	16.5 (4.5–27.5) (31.8)	9 (1–17) (19.1)	0.004
Median anxiety score (IQR) (% with score ≥11)#	7 (4–10)	7.5 (4.75–10.25) (24.3)	8 (3–14) (34.8)	6 (3.75–8.25) (13.6)	6 (3–9) (19.1)	0.34
Median depression score (IQR) (% with score ≥11) #	4 (2–7)	4.5 (2–8) (13.5)	5 (2–7) (4.3)	4 (2–7) (4.5)	3 (1–6) (7.4)	0.104
Courses of oral corticosteroids for asthma exacerbations, n/case/yr	4.05 (2.33)	4.62 (0.27)	3.90 (0.38)	3.57 (0.49)	3.43 (0.27)	0.02
Hospital admissions for asthma, n/case/yr	1.54	1.64	1.61	1.54	1.23	0.703
Failed clinic appointments, % total appointments to DAC/yr	20.0	26.2	15.7	19.0	14.8	0.027

FeNO is a biomarker of allergic airway inflammation

Exhaled NO concentrations increase during Th2 (allergic) inflammation

- NO produced is generally higher in individuals with asthma than in those without asthma[2]
- Often correlates with eosinophilic inflammation[2]



Adapted from[1]

AHR, airway hyper-responsiveness; FeNO, fractional exhaled nitric oxide; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; STAT, signal transducer and activator of transcription; Th2, T helper type 2 cells

1. Ludviksdottir D et al. Clin Respir J 2012;6:193–207; 2. Alving K et al. Eur Respir Mon 2010;49:1–31

Interpretation and clinical utility of FeNO values

FeNO CATEGORY	NORMAL	ELEVATED	HIGH
FeNO value (ppb) Adults Children	<20–25 <15–20	20/25–50 15/20–35	>50 >35
Th2-driven inflammation	Unlikely	Likely	Significant
Diagnosis and interpretation in patients with suspected asthma	• Consider diagnosis other than asthma • Response to ICS unlikely	• Supports a diagnosis of asthma • Response to ICS likely	• Supports a diagnosis of asthma • Response to ICS likely
Management of, and interpretation in, existing patients with asthma	• Th2-driven inflammation under control • Step-down ICS if asthma controlled for 3–6 months	• Check treatment adherence, inhalation technique, allergen exposure • Step-up anti-inflammatory treatment if history of exacerbations*	• Check treatment adherence, inhalation technique, allergen exposure • Risk of exacerbations/ worsening of disease • Step-up anti-inflammatory therapy, especially if high blood eosinophil count* • Consider different ICS/ add-on systemic anti-inflammatory

*Regardless of symptoms

Adapted from[1]

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; ppb, parts per billion; Th2, T helper type 2 cells

1. Bjermer L et al. Respir Med 2014;108:830–41

FeNO helps improve asthma diagnosis and ongoing management

NICE recommends FeNO measurement for diagnosis and management of allergic asthma[1]

For diagnosis

- Assessment of inflammation:
  - Allows diagnosis of allergic airway inflammation or not
  - Provides objective evidence to support the diagnosis of asthma
  - Determines the likelihood of clinical response to ICS[2]
    - Aids differential diagnosis of respiratory symptoms not due to asthma

For management

- Option to support asthma management in people who are symptomatic despite using ICS[1]
- FeNO concentrations can:
  - Assist dose titration of anti-inflammatory treatments[2]
  - Monitor treatment response (disease control)
  - Detect non-adherence to ICS

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; NICE, National Institute for Health and Care Excellence

1. NICE diagnostics guidance [DG12] 2014: http://www.nice.org.uk/guidance/dg12;
2. Dweik RA et al. Am J Respir Crit Care Med 2011;184:602–15

ATS clinical practice guideline, 2011, recommends FeNO measurements

- The ATS recommends the use of FeNO measurement in:[1]
  - **Diagnosis of eosinophilic airway inflammation**
  - **Determining likelihood of steroid responsiveness** in individuals with chronic respiratory symptoms possibly due to airway inflammation
  - **Monitoring airway inflammation** in patients with asthma

ATS, American Thoracic Society; FeNO, fractional exhaled nitric oxide

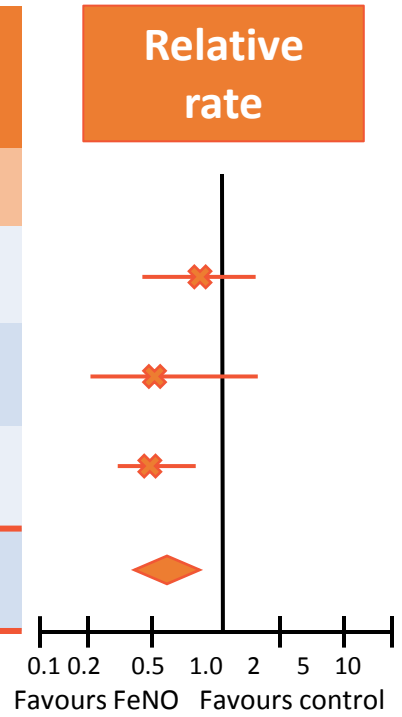
1. Dweik RA et al. Am J Respir Crit Care Med 2011;184:602–15

FeNO-guided therapy reduces exacerbation rate in adults

Study	FeNO strategy		Control strategy		Weight (%)	Relative rate (95% CI)
	Rate*	N†	Rate*	N†		
Shaw 2007	0.330	52	0.420	51	29.4	0.79 (0.43, 1.44)
Smith 2005	0.490	46	0.900	48	10.9	0.54 (0.20, 1.46)
Powell 2011	0.288	111	0.615	109	59.7	0.50 (0.33, 0.76)
Combined	**0.320**	**209**	**0.590**	**208**	**100.0**	**0.57 (0.41, 0.80)**

*Rate = exacerbation rate (number of exacerbations/patients over study period);
†total number of patients

Table and figure reproduced from[1]



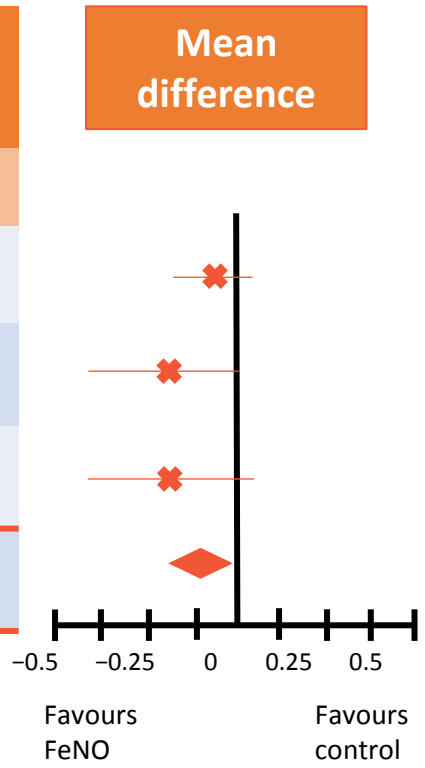
43%
reduction in relative exacerbation rate

CI, confidence interval; FeNO, fractional exhaled nitric oxide

1. Donohue J, Jain N. Respir Med 2013;107:943–52

FeNO-guided therapy is superior to a clinical management strategy in children

Study	FeNO strategy		Control strategy		Weight (%)	Mean difference
	Rate*	N†	Rate*	N†		
de Jongste 2009	0.18	75	0.25	72	64.2	−0.07 (−0.19, 0.04)
Pijnenburg 2005	0.19	42	0.38	47	20.5	−0.19 (−0.40, 0.01)
Szefler 2008	0.66	276	0.84	270	15.3	−0.18 (−0.40, 0.06)
Combined	**0.26**	**393**	**0.37**	**389**	**100.0**	**−0.11 (−0.21, −0.02)**



*Exacerbation rate; †total number of patients

30% reduction in exacerbation rate

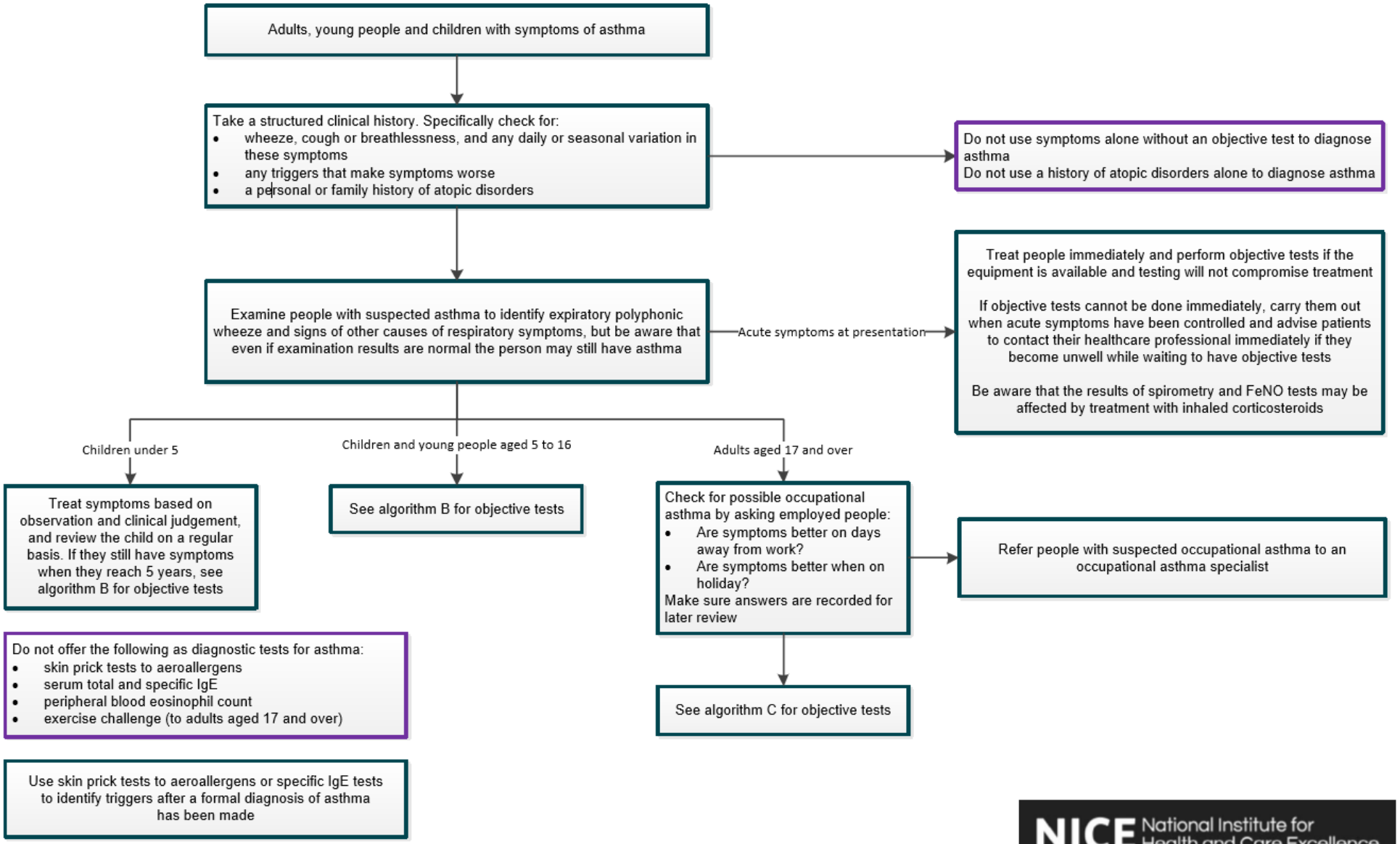
NOTE: percentage reduction is calculated from rate of exacerbation; study data did not include relative exacerbation rates

Table and figure reproduced from[1]

FeNO, fractional exhaled nitric oxide

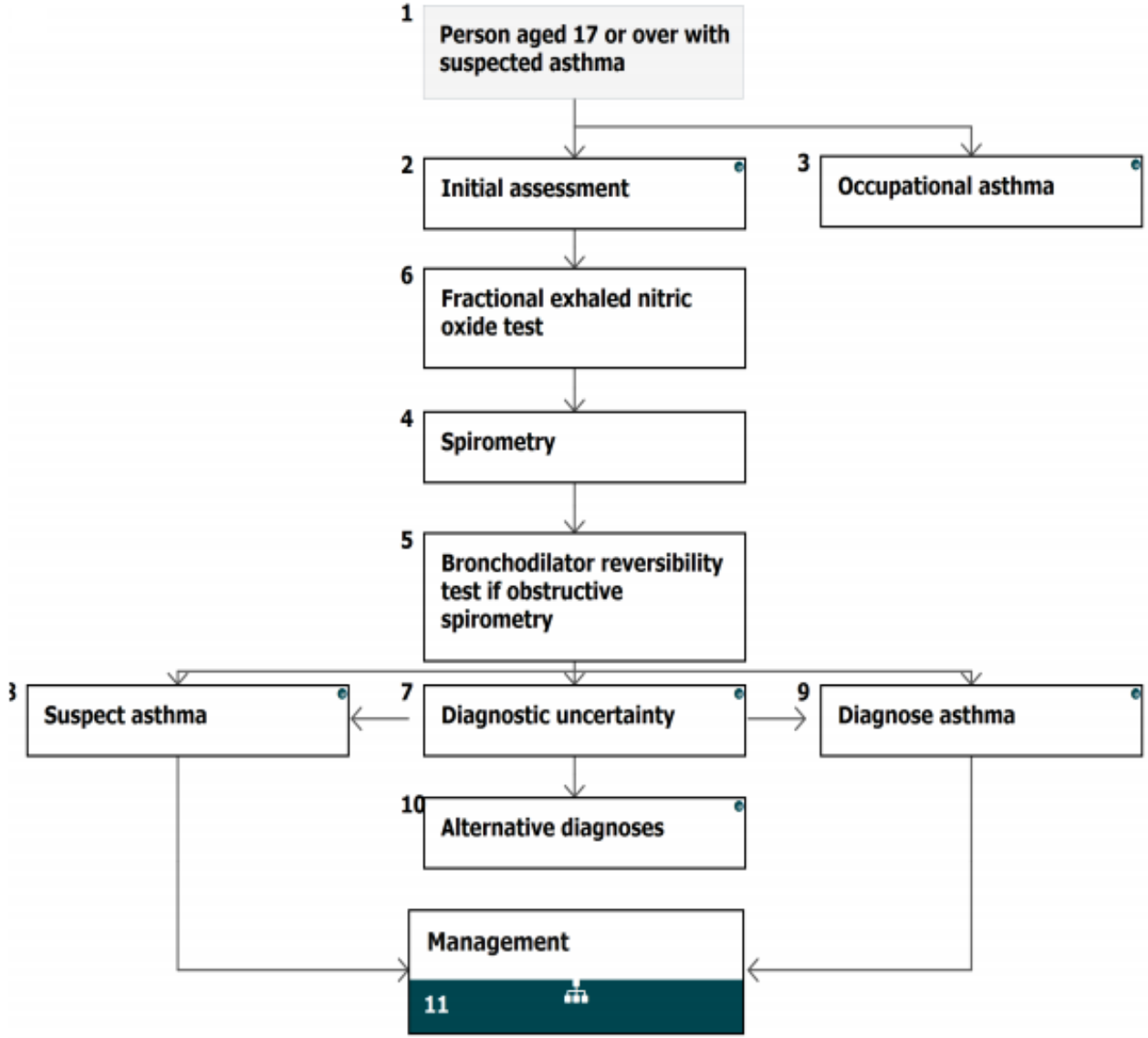
1. Mahr TA et al; Allergy Asthma Proc 2013;34:210–19

Algorithm A Initial clinical assessment for adults, young people and children with suspected asthma



This algorithm is based on recommendations from NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management (2017)

NICE National Institute for Health and Care Excellence


1
Person aged 17 or over with suspected asthma
2
Initial assessment
3
Occupational asthma
6
Fractional exhaled nitric oxide test
4
Spirometry
5
Bronchodilator reversibility test if obstructive spirometry
8
Suspect asthma
7
Diagnostic uncertainty
9
Diagnose asthma
10
Alternative diagnoses
Management
11

Algorithm C Objective tests for asthma in adults aged 17 and over

Order of tests

- Measure FeNO first followed by spirometry in adults with symptoms of asthma
- Carry out BDR test if spirometry shows an obstruction

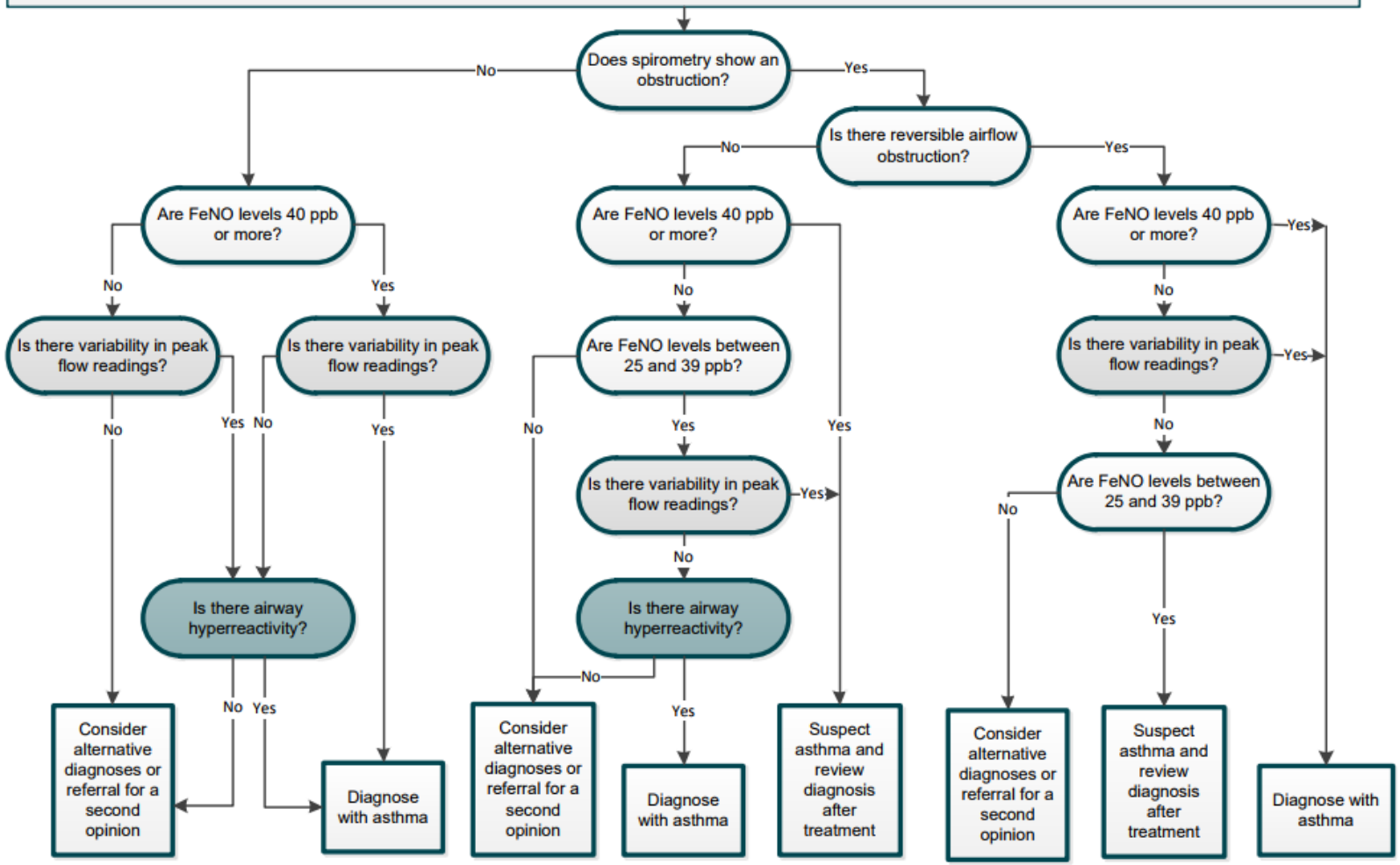
If diagnostic uncertainty remains after FeNO, spirometry and BDR, monitor peak flow variability for 2 to 4 weeks

If diagnostic uncertainty remains after measuring peak flow variability, refer for a histamine or methacholine direct bronchial challenge test

If histamine or methacholine direct bronchial challenge test is unavailable:

- suspect asthma and review diagnosis after treatment **or**
- refer to a centre with access to histamine or methacholine challenge testing

Interpretation of test results for adults aged 17 and over with symptoms suggestive of asthma



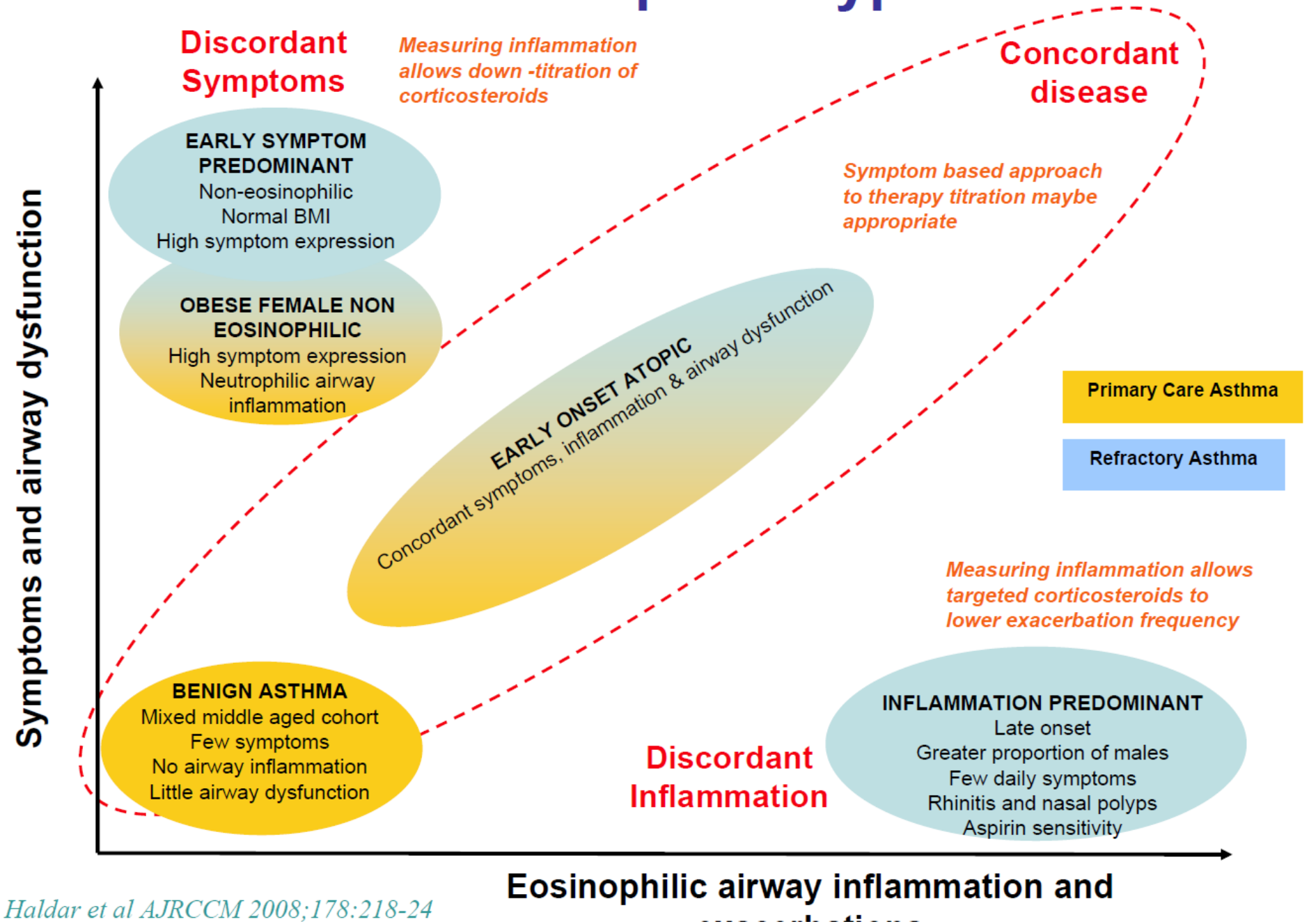
Abbreviations:
FeNO, fractional exhaled nitric oxide
BDR, bronchodilator reversibility

This algorithm is based on recommendations from NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management (2017)

Positive test thresholds
Obstructive spirometry: FEV1/FVC ratio less than 70% (or below the lower limit of normal if available)
FeNO: 40 ppb or more
BDR: improvement in FEV1 of 12% or more and increase in volume of 200 ml or more
Peak flow variability: variability over 20%
Direct bronchial challenge test with histamine or methacholine: PC20 of 8 mg/ml or less

NICE National Institute for Health and Care Excellence

Asthma phenotypes



Haldar et al AJRCCM 2008;178:218-24

Asthma Control Test™ (ACT)

Score

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

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

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

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

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

4 or more nights a week	2 or 3 nights a week	Once a week	Once or twice	Not at all
1	2	3	4	5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

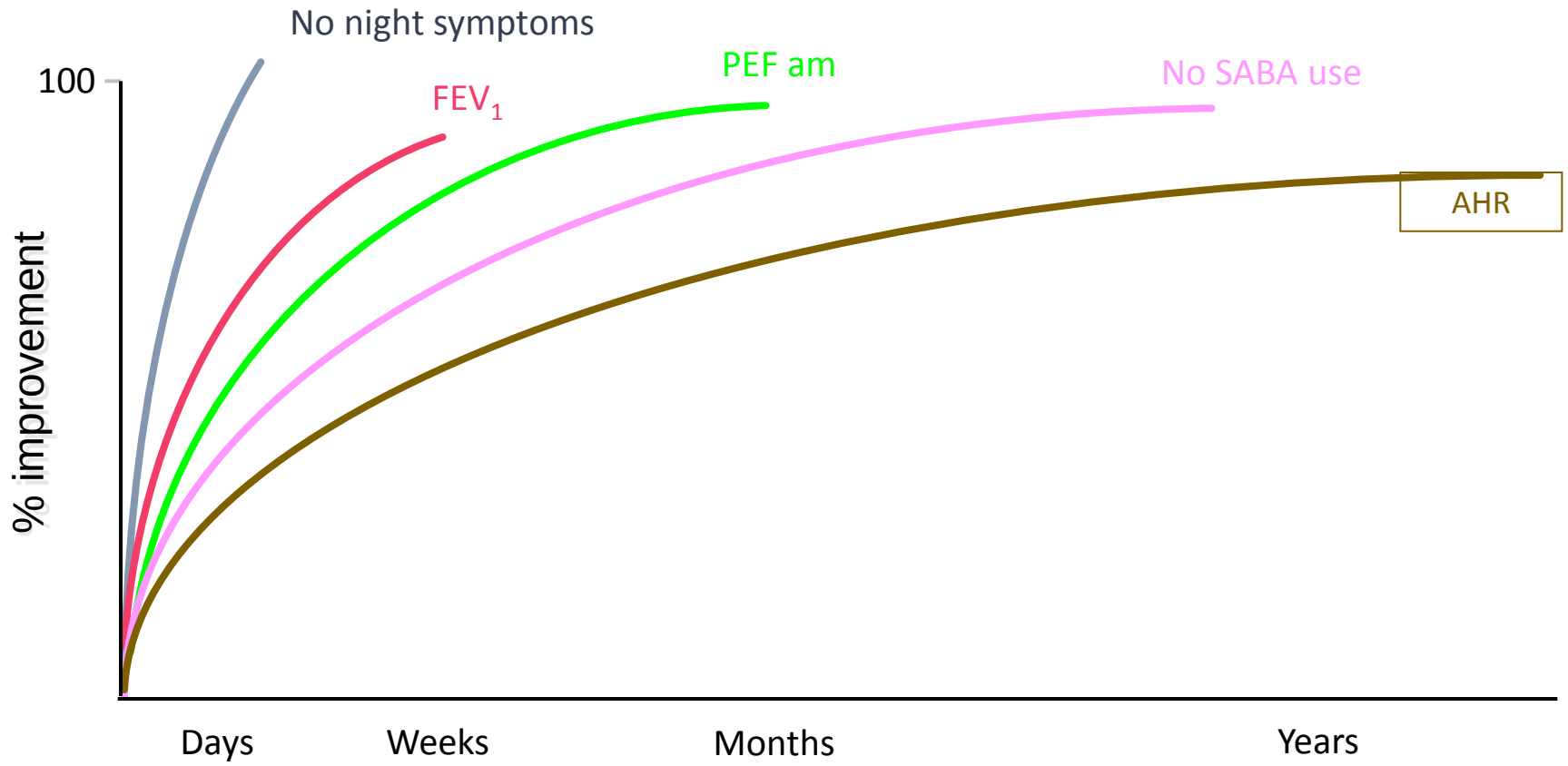
3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
1	2	3	4	5

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

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

Patient Total Score

TIME COURSE FOR THE IMPROVEMENT OF VARIOUS PARAMETERS



Woolcock, ERS 2000

BMJ

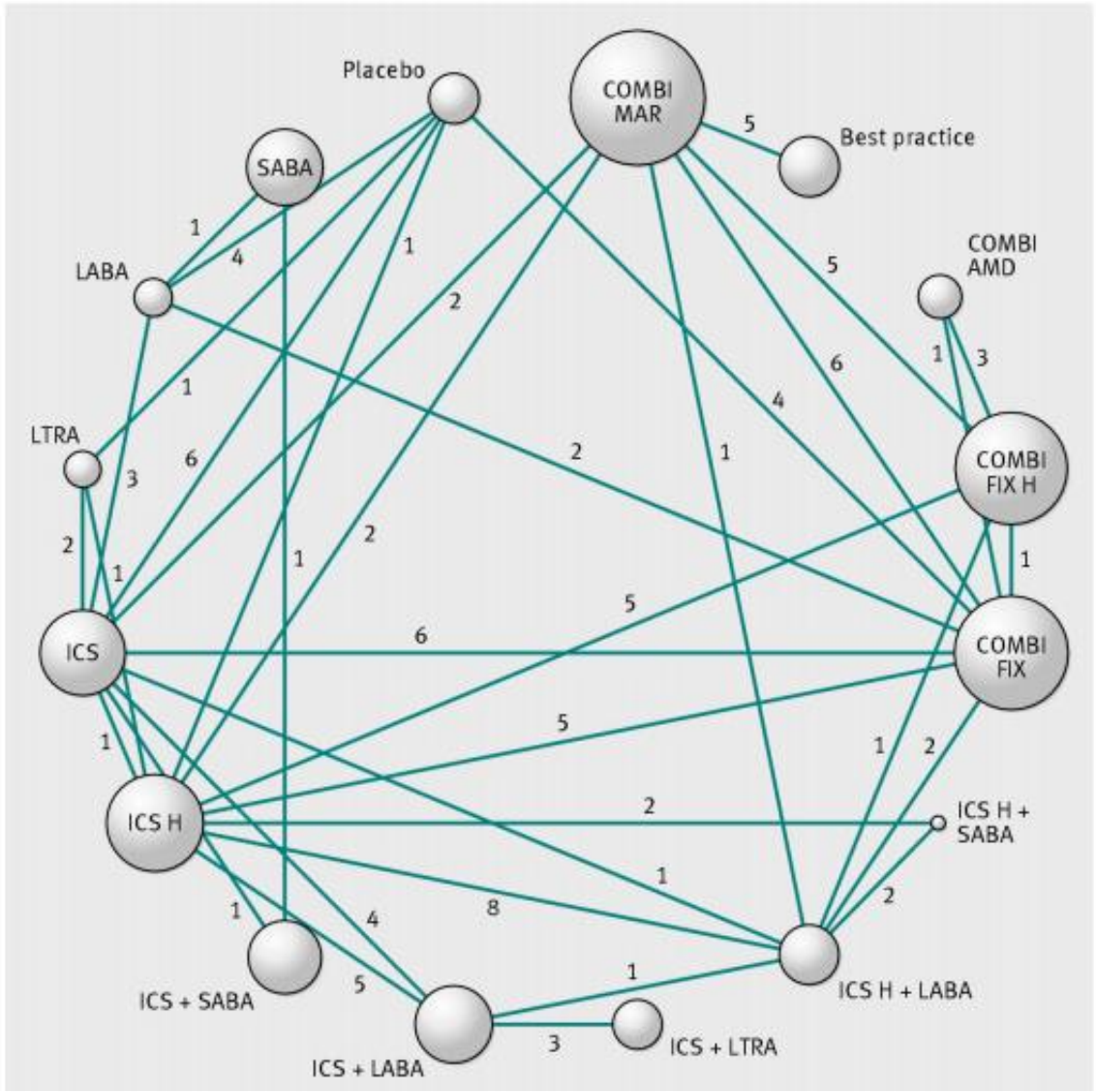
BMJ 2014;348:g3009 doi: 10.1136/bmj.g3009 (Published 13 May 2014)

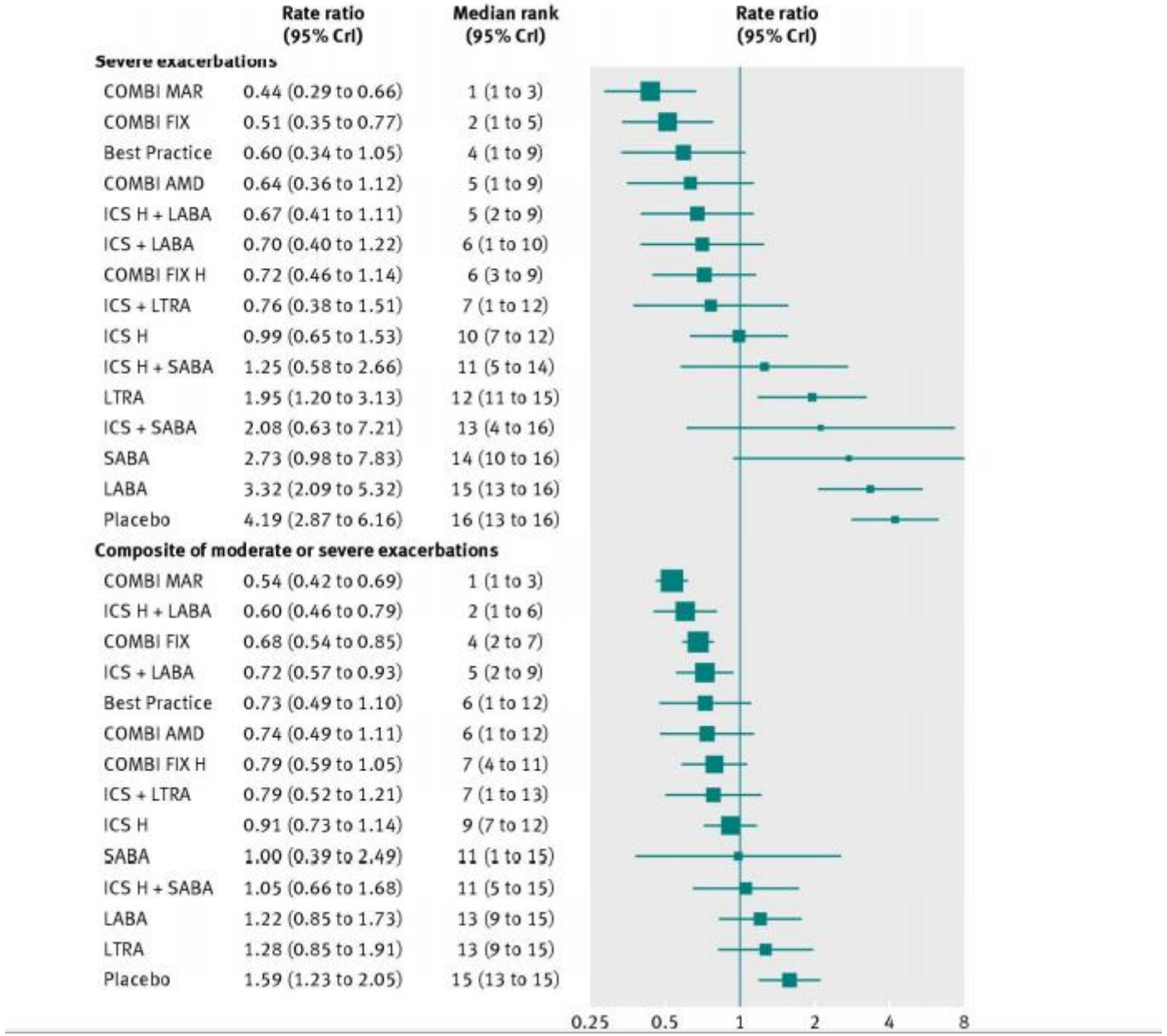
RESEARCH

Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis

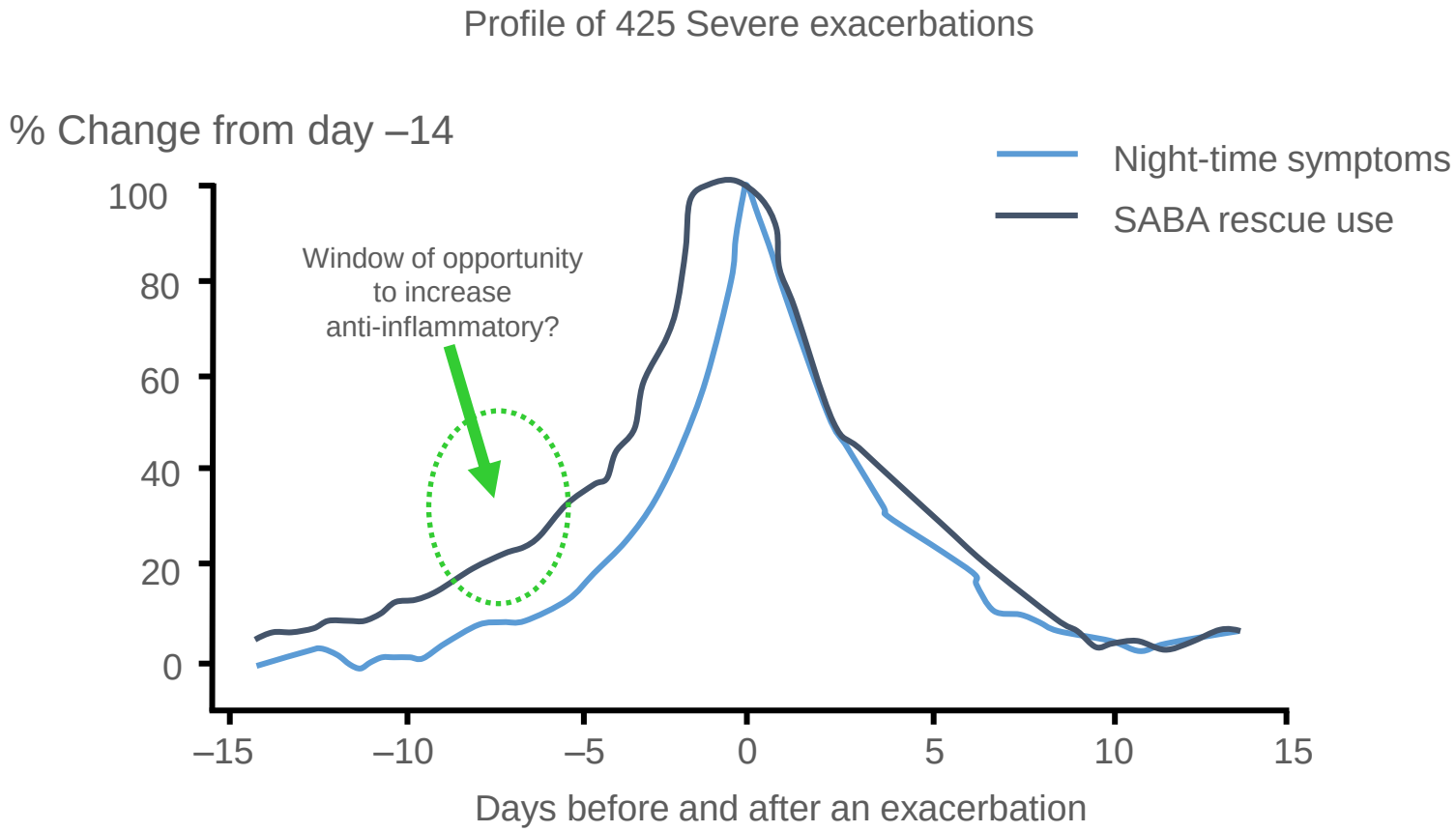
Rik J B Loymans *general practitioner*[1], Armin Gemperli *assistant professor*[2 3 4], Judith Cohen *general practitioner*[1], Sidney M Rubinstein *senior researcher*[5], Peter J Sterk *professor*[6], Helen K Reddel *research leader*[7], Peter Jüni *professor*[2], Gerben ter Riet *associate professor*[1]

[1]Department of General Practice, Academic Medical Center, University of Amsterdam, PO box 22700, 1105 DE, Amsterdam, Netherlands; [2]Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine, University of Bern, Berne, Switzerland; [3]Department of Health Sciences and Health Policy, University of Lucerne, Lucerne, Switzerland; [4]Swiss Paraplegic Research, Nottwil, Switzerland; [5]Department of Health Sciences, Section Health Economics and Health Technology Assessment, VU University Amsterdam, Amsterdam, Netherlands; [6]Department of


Placebo
COMBI MAR
Best practice
SABA
LABA
COMBI AMD
LTRA
COMBI FIX H
ICS
COMBI FIX
ICS H
ICS H + SABA
ICS + SABA
ICS H + LABA
ICS + LABA
ICS + LTRA


Rate ratio (95% CrI)
Median rank (95% CrI)
Rate ratio (95% CrI)
Severe exacerbations
COMBI MAR 0.44 (0.29 to 0.66) 1 (1 to 3)
COMBI FIX 0.51 (0.35 to 0.77) 2 (1 to 5)
Best Practice 0.60 (0.34 to 1.05) 4 (1 to 9)
COMBI AMD 0.64 (0.36 to 1.12) 5 (1 to 9)
ICS H + LABA 0.67 (0.41 to 1.11) 5 (2 to 9)
ICS + LABA 0.70 (0.40 to 1.22) 6 (1 to 10)
COMBI FIX H 0.72 (0.46 to 1.14) 6 (3 to 9)
ICS + LTRA 0.76 (0.38 to 1.51) 7 (1 to 12)
ICS H 0.99 (0.65 to 1.53) 10 (7 to 12)
ICS H + SABA 1.25 (0.58 to 2.66) 11 (5 to 14)
LTRA 1.95 (1.20 to 3.13) 12 (11 to 15)
ICS + SABA 2.08 (0.63 to 7.21) 13 (4 to 16)
SABA 2.73 (0.98 to 7.83) 14 (10 to 16)
LABA 3.32 (2.09 to 5.32) 15 (13 to 16)
Placebo 4.19 (2.87 to 6.16) 16 (13 to 16)
Composite of moderate or severe exacerbations
COMBI MAR 0.54 (0.42 to 0.69) 1 (1 to 3)
ICS H + LABA 0.60 (0.46 to 0.79) 2 (1 to 6)
COMBI FIX 0.68 (0.54 to 0.85) 4 (2 to 7)
ICS + LABA 0.72 (0.57 to 0.93) 5 (2 to 9)
Best Practice 0.73 (0.49 to 1.10) 6 (1 to 12)
COMBI AMD 0.74 (0.49 to 1.11) 6 (1 to 12)
COMBI FIX H 0.79 (0.59 to 1.05) 7 (4 to 11)
ICS + LTRA 0.79 (0.52 to 1.21) 7 (1 to 13)
ICS H 0.91 (0.73 to 1.14) 9 (7 to 12)
SABA 1.00 (0.39 to 2.49) 11 (1 to 15)
ICS H + SABA 1.05 (0.66 to 1.68) 11 (5 to 15)
LABA 1.22 (0.85 to 1.73) 13 (9 to 15)
LTRA 1.28 (0.85 to 1.91) 13 (9 to 15)
Placebo 1.59 (1.23 to 2.05) 15 (13 to 15)
0.25
0.5
1
2
4
8

Window of opportunity for Symbicort® SMART to prevent exacerbations?



Tattersfield investigated 425 severe exacerbations observed in the FACET study (double–blind, randomised, parallel-group, multi Centre study), which compared the effect of low- and high-dose budesonide with and without twice-daily treatment with formoterol. The primary end point was the number of severe and mild asthma exacerbations over the year of the stud
Severe exacerbations were defined by a fall in PEF of >30% from baseline values during the run-in period on 2 consecutive days or the need for a course of oral corticosteroids as judged by the patient or doctor.

Adapted from Tattersfield A, et al. *Am J Respir Crit Care Med* 1999;160:594–599.

COMPASS: Study objectives and endpoints

Objective

- To compare the efficacy and safety of the Symbicort maintenance and reliever therapy regimen with two-fold higher maintenance dose of Symbicort plus a SABA (terbutaline) or Seretide plus a SABA (terbutaline), as needed

Study design and population

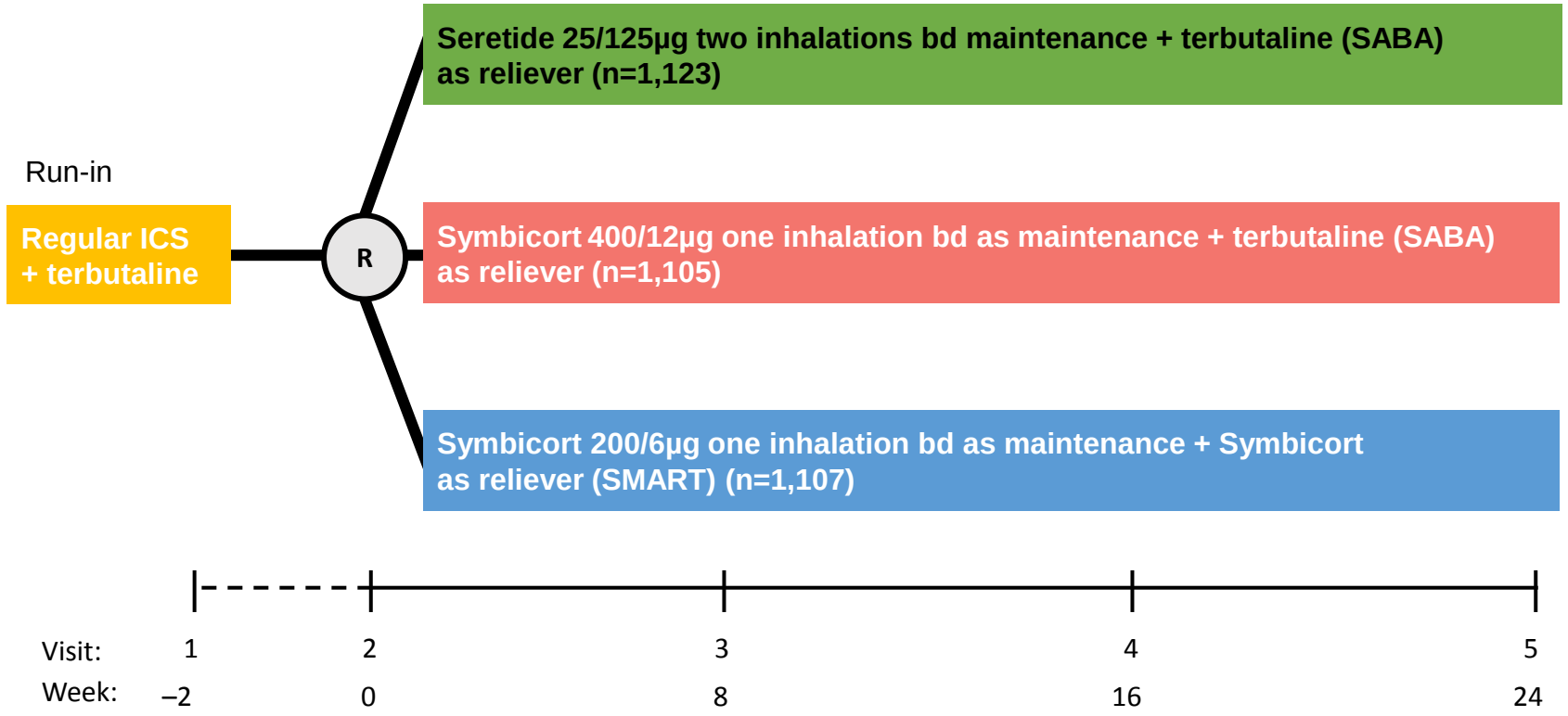
- A 6-month, randomised, double-blind parallel group study
- Carried out in 235 centres in 16 countries
- 3,335 patients aged 12 years or older

Primary outcome

- Time to first severe exacerbation*

SABA=short-acting ß-agonist.
*Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment, or the need for oral steroids for ≥3 days (as judged by the investigator).
Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

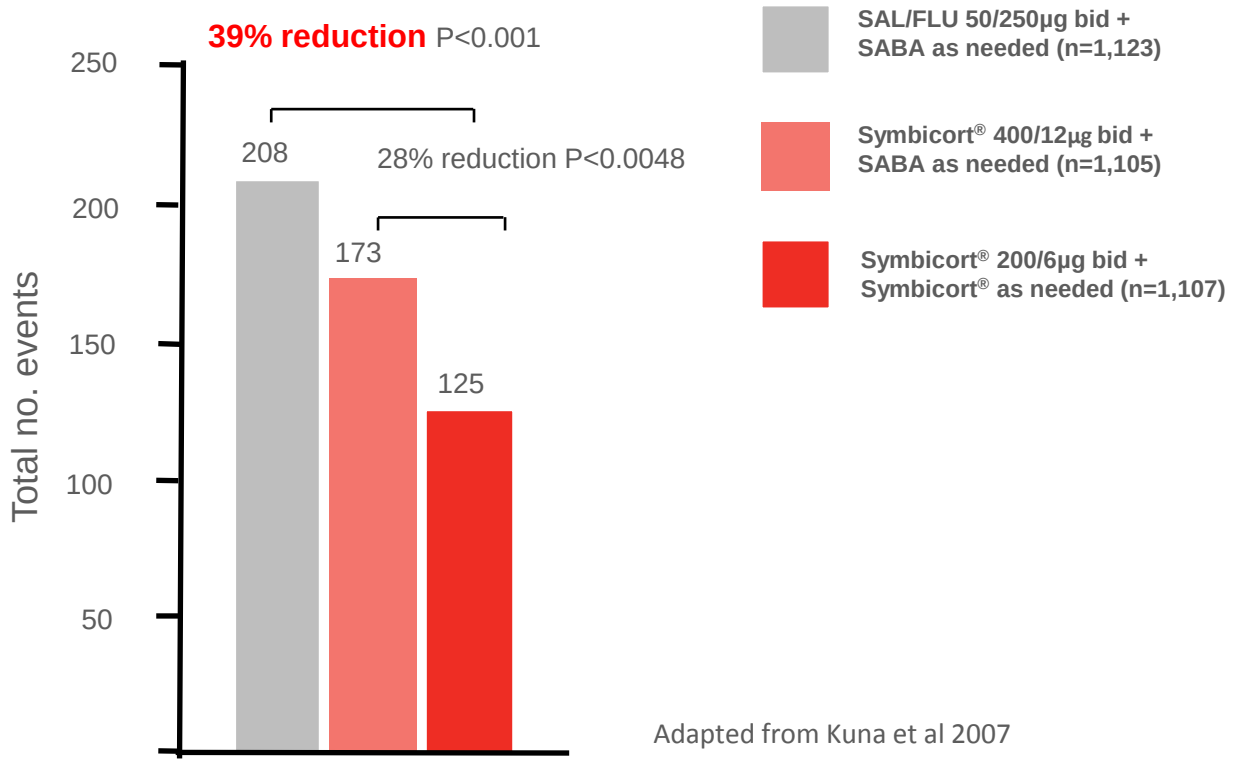
COMPASS: Study design



Bd=twice a day; ICS=inhaled corticosteroid; LABA=long-acting ß-agonist; SABA=short-acting $ß_2$-agonist.
Adapted from Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

Symbicort® SMART reduces severe exacerbations by 39% vs salmeterol/fluticasone over 6 months

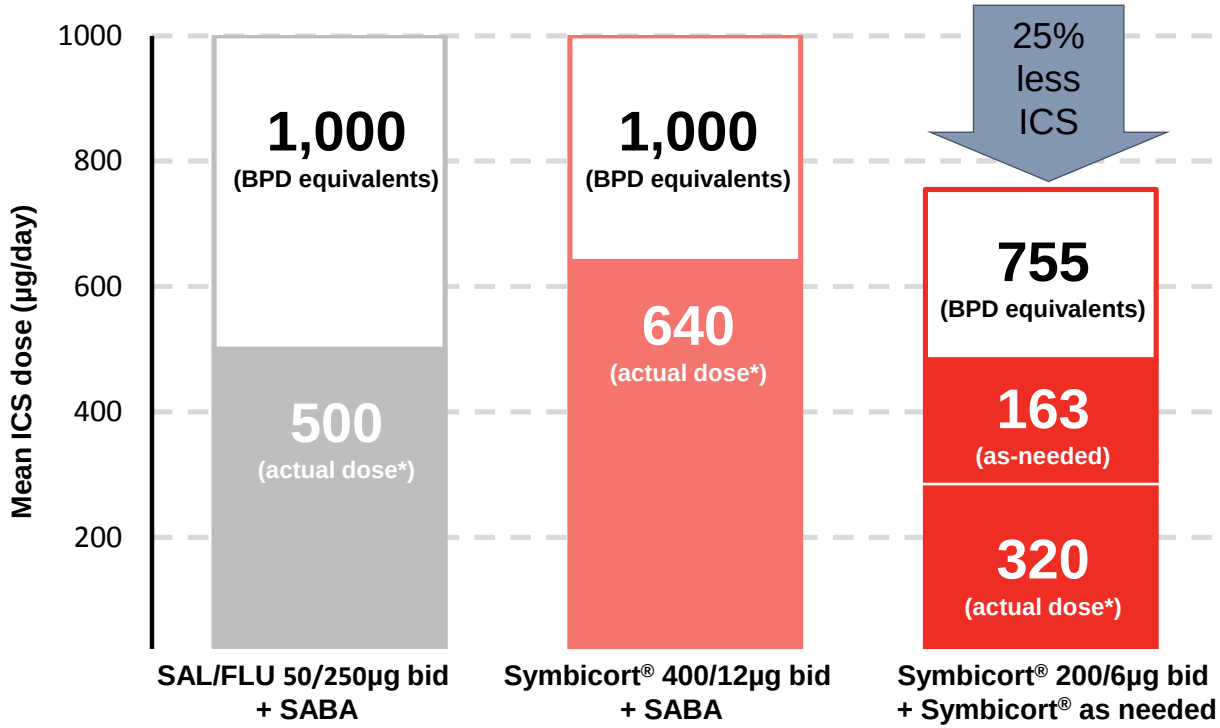
- As well as meeting its primary endpoint (time to first severe exacerbation), in this study, Symbicort® SMART reduced the total number of severe exacerbations over 6 months



Severe exacerbations were defined as exacerbations requiring either **A.** hospitalisation, **B.** emergency room treatment or **C.** treatment with oral steroids for 3 days or more.

Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

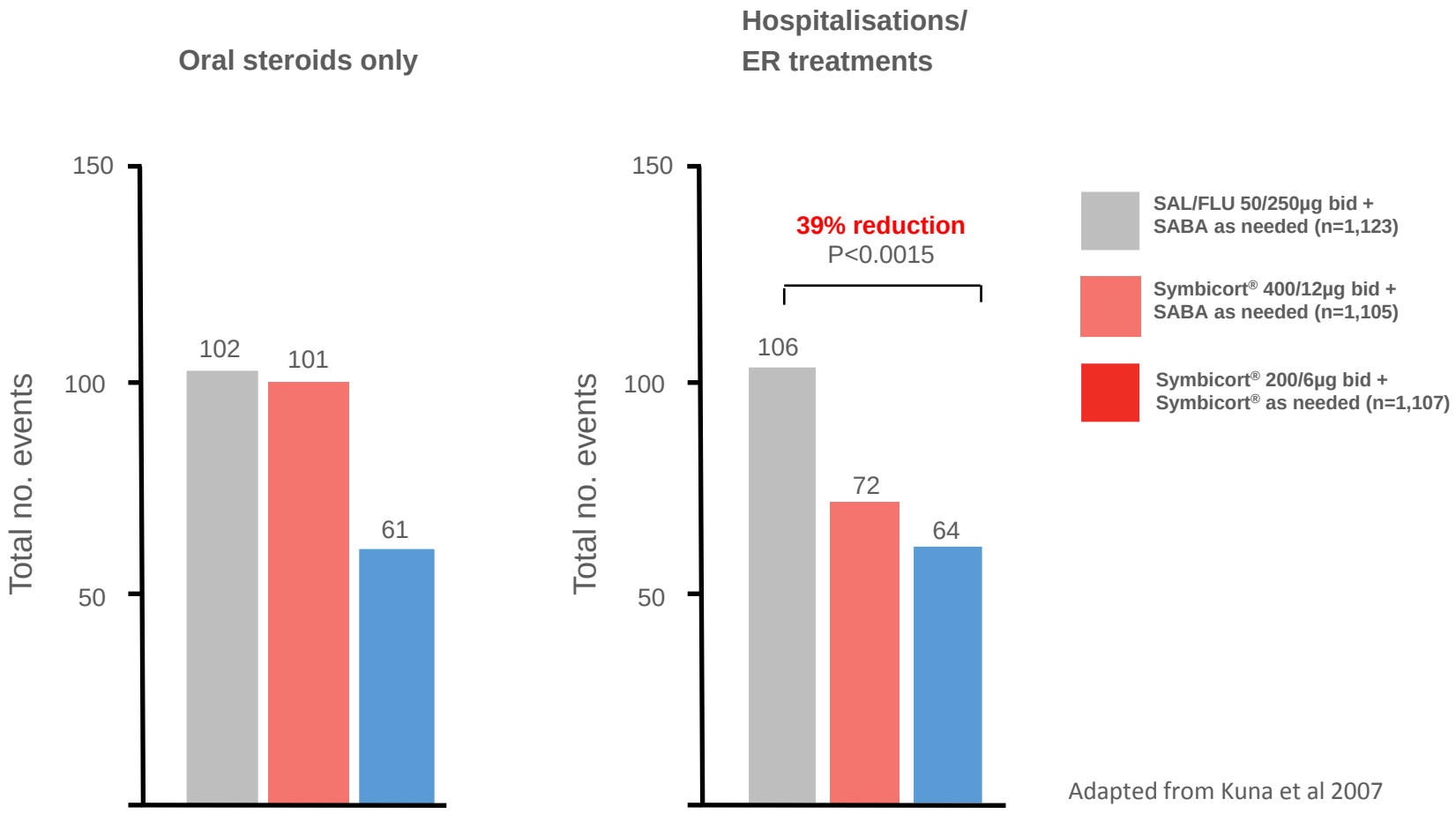
Symbicort® SMART provides similar symptom control to salmeterol/fluticasone at a lower BDP equivalent ICS dose



Adapted from Kuna et al 2007

*Actual dose = dose prescribed at randomisation.
Bid=twice daily; BDP=beclomethasone dipropionate; BUD/FORM=budesonide/formoterol; ICS=inhaled corticosteroid; SABA=short-acting β_2-agonist; SAL/FLU=salmeterol/fluticasone; SMART=budesonide/formoterol maintenance and reliever therapy.
Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

Symbicort® SMART reduces severe exacerbations requiring oral steroid/ER treatment vs salmeterol/fluticasone over 6 months



Severe exacerbations were defined as exacerbations requiring either **A.** hospitalisation, **B.** emergency room treatment or **C.** treatment with oral steroids for 3 days or more.

Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

SABA RELIEVERS

Bricanyl Turbuhaler † ^
terbutaline 500mcg

Ventolin Inhaler † ^
salbutamol 100mcg

Airomir Autohaler ‡ ^
salbutamol 100mcg

Asmol Inhaler † ^
salbutamol 100mcg

NON STEROIDAL PREVENTERS

Singulair Tablet [a]
montelukast
4mg • 5mg • 10mg

Montelukast Tablet [a]
montelukast
4mg • 5mg
Generic medicine suppliers

Intal Inhaler †
sodium cromoglycate
1mg • 5mg*
**Intal Forte*

Tilade Inhaler †
nedocromil sodium
2mg

ICS PREVENTERS

Flixotide Inhaler †
fluticasone propionate
50mcg* • 125mcg • 250mcg
**Flixotide Junior*

Flixotide Accuhaler †
fluticasone propionate
100mcg* • 250mcg • 500mcg

Pulmicort Turbuhaler †
budesonide
100mcg • 200mcg • 400mcg

Alvesco Inhaler †
ciclesonide
80mcg • 160mcg

QVAR Inhaler †
beclometasone
50mcg • 100mcg

QVAR Autohaler ‡
beclometasone
50mcg • 100mcg

RESOURCES

TREATMENT GUIDELINES

Australian Asthma Handbook: **asthmahandbook.org.au**
COPD-X Plan: **copdx.org.au**

INHALER TECHNIQUE

How-to videos, patient and practitioner information
nationalasthma.org.au

Inhalers/MDIs should be used with a compatible spacer

This chart was developed independently by the National Asthma Council Australia with support from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Mundipharma and Novartis

National Asthma Council Australia
leading the attack against asthma

ICS/LABA COMBINATIONS

Symbicort Turbuhaler ‡
budesonide/formoterol
100/6 • 200/6 • 400/12*

Symbicort Rapihaler ‡
budesonide/formoterol
50/3 • 100/3 • 200/6*

Seretide MDI ‡
fluticasone propionate/salmeterol
50/25 • 125/25 • 250/25*

Seretide Accuhaler ‡
fluticasone propionate/salmeterol
100/50 • 250/50 • 500/50*

Flutiform Inhaler ‡
fluticasone propionate/formoterol
50/5 • 125/5 • 250/10

Breo Ellipta ‡
fluticasone furoate/vilanterol
100/25* • 200/25

LABA MEDICATIONS

Oxis Turbuhaler ‡
formoterol
6mcg • 12mcg

Serevent Accuhaler ‡
salmeterol
50mcg

PBS PRESCRIBERS

† Asthma unrestricted benefit
‡ Asthma restricted benefit
[a] Asthma authority required benefit

^ COPD unrestricted benefit
# COPD restricted benefit
[c] COPD authority required benefit

Check TGA and PBS for current age and condition criteria

Onbrez Breezhaler ^
indacaterol
150mcg • 300mcg

LAMA MEDICATIONS

Spiriva Respimat ^
tiotropium 2.5mcg

Spiriva Handihaler ^
tiotropium 18mcg

Bretaris Genuair ^
aclidinium 322mcg

Seebri Breezhaler ^
glycopyrronium 50mcg

Incruse Ellipta ^
umeclidinium 62.5mcg

SAMA MEDICATION

Atrovent Metered Aerosol † ^
ipratropium 21mcg

LAMA/LABA COMBINATIONS

Spiolto Respimat [c]
tiotropium/olodaterol
2.5/2.5

Brimica Genuair [c]
aclidinium/formoterol
340/12

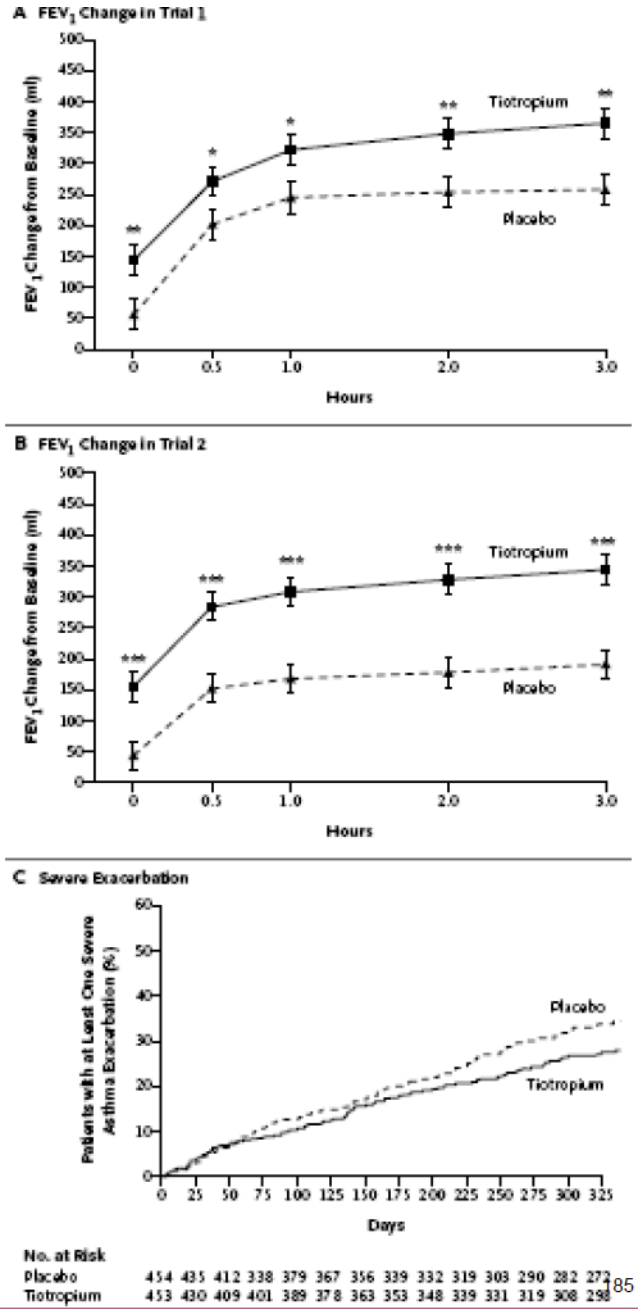
Ultibro Breezhaler [c]
indacaterol/glycopyrronium
110/50

Anoro Ellipta [c]
umeclidinium/vilanterol
62.5/25

ICS, inhaled corticosteroid | LABA, long-acting beta$_2$ agonist | LAMA, long-acting muscarinic antagonist | SABA, short-acting beta$_2$ agonist | SAMA, short-acting muscarinic antagonist

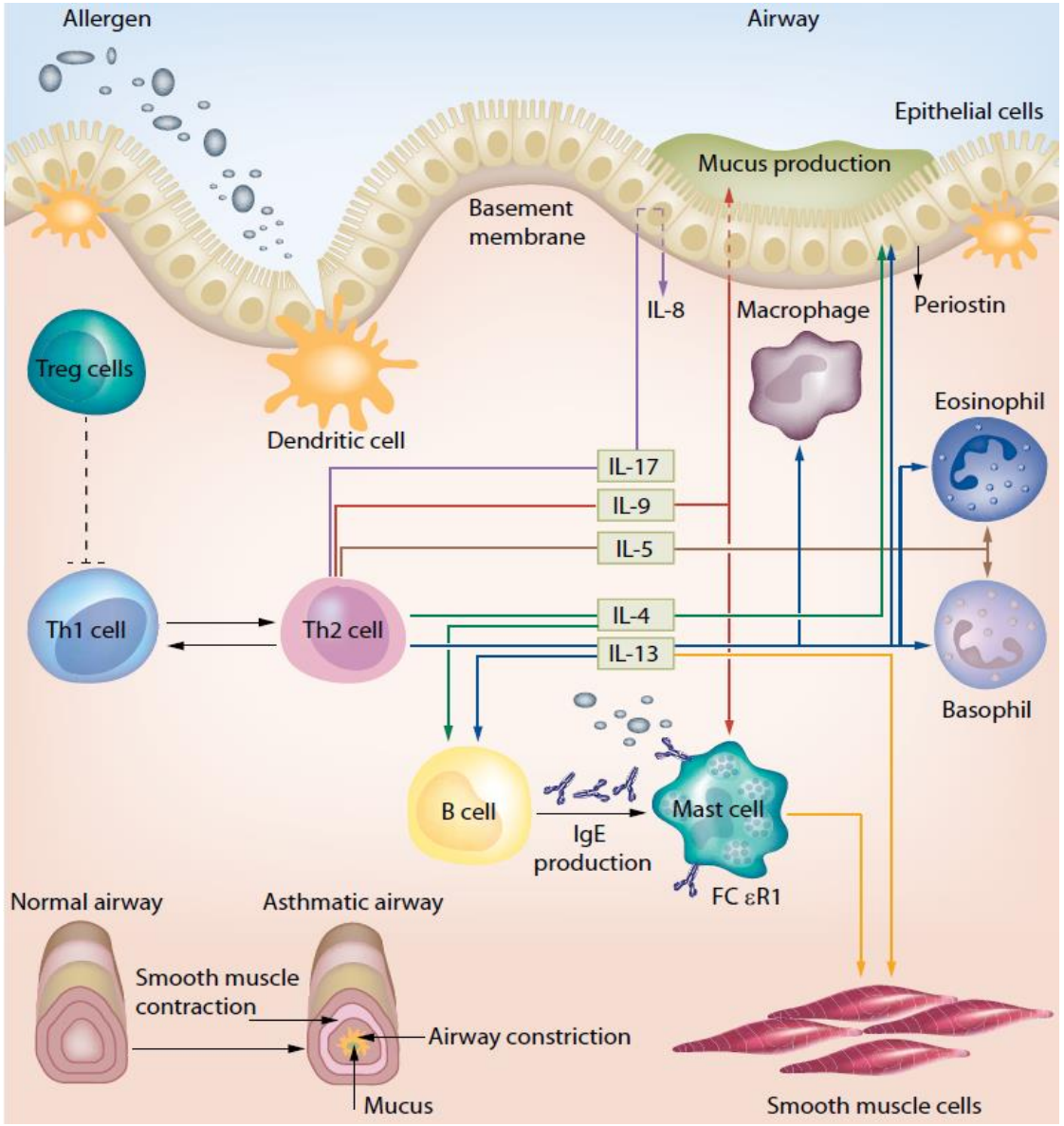
Tiotropium and severe asthma

- No specific recommendation
- Small positive effect on symptoms and AQLQ
- Biggest effect in men, former smokers and in those with impaired but reversible airflow obstruction
- Exacerbation numbers were low



Kerstijens et al. NEJM 2012;367:1198-207

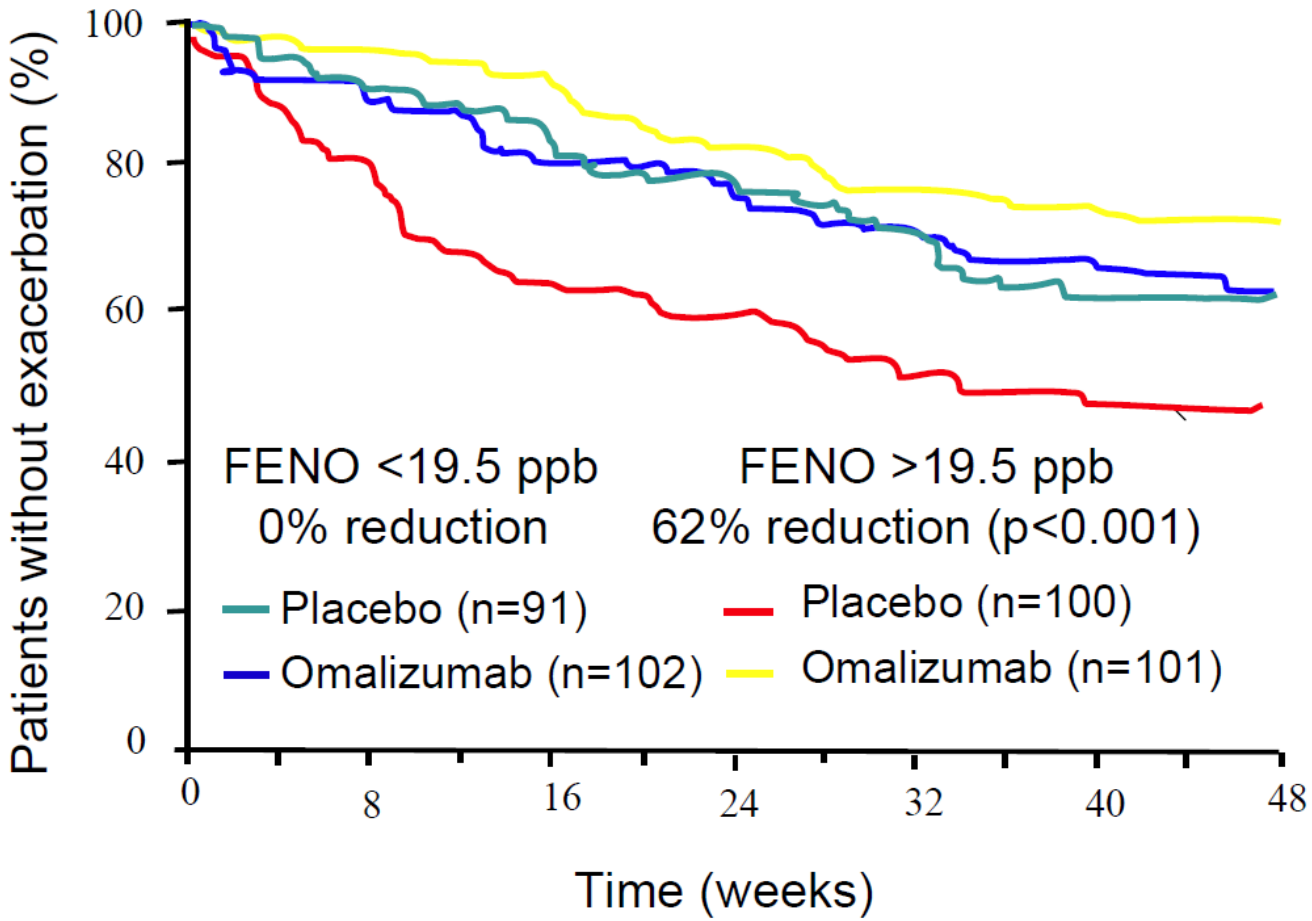
Future/current options



IL-5	Mepolizumab Reslizumab Benralizumab
IL-4/IL-13	Pitrakinra
IL-9	MEDI-528
IL-13	Lebrikizumab
IL-17	Secukinumab

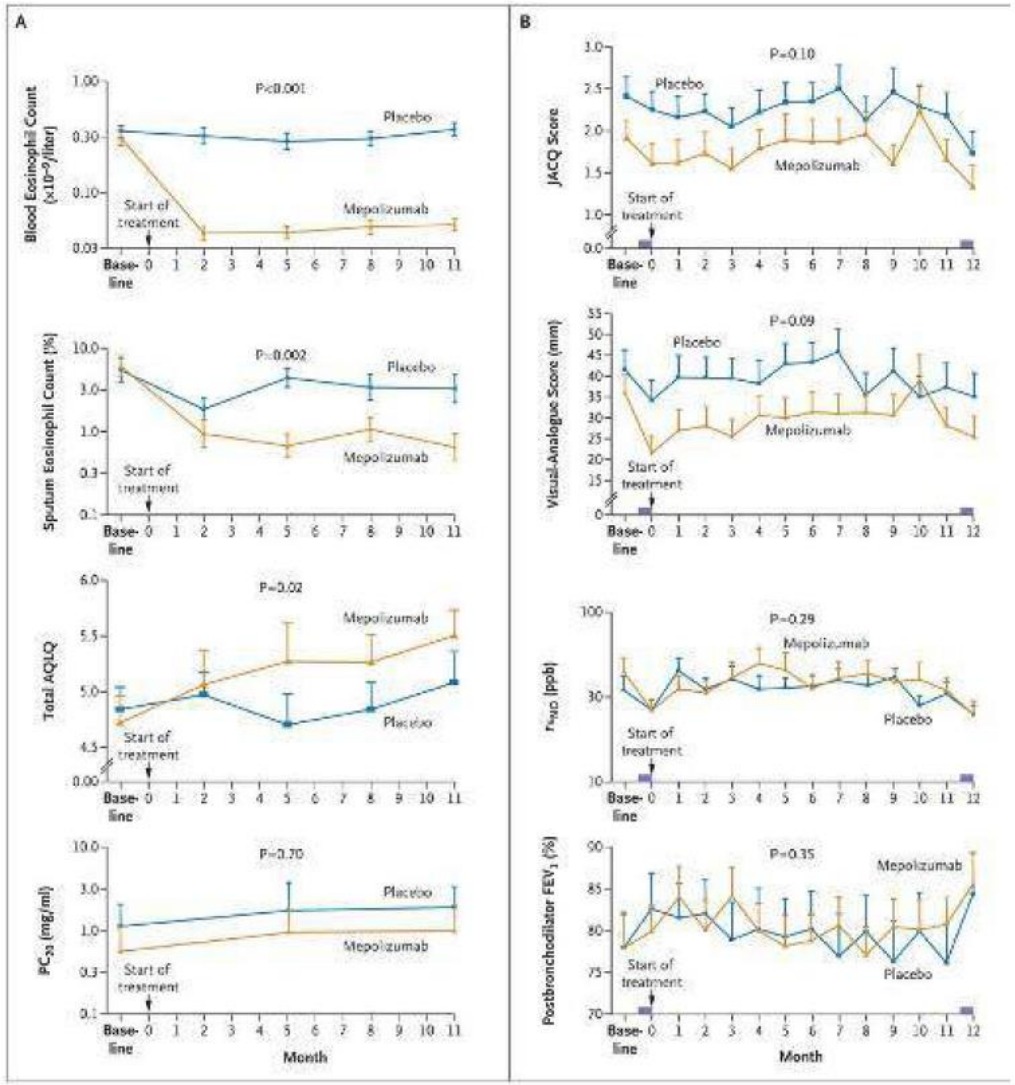
Gibeon D. Exp Rev Respir Med 2012

FeNO and the response to Omalizumab (anti-IgE)

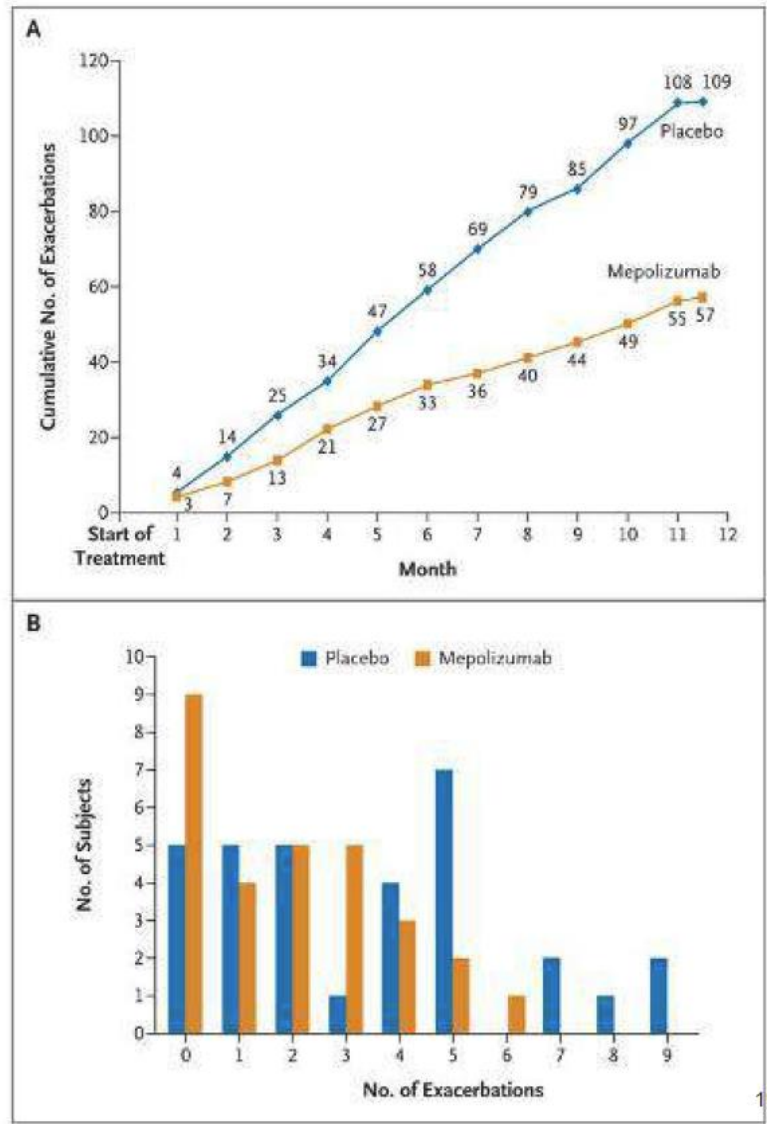


Hanania et al. AJRCCM 2013;187:804-811

Future therapies: Mepolizumab (anti-IL-5)

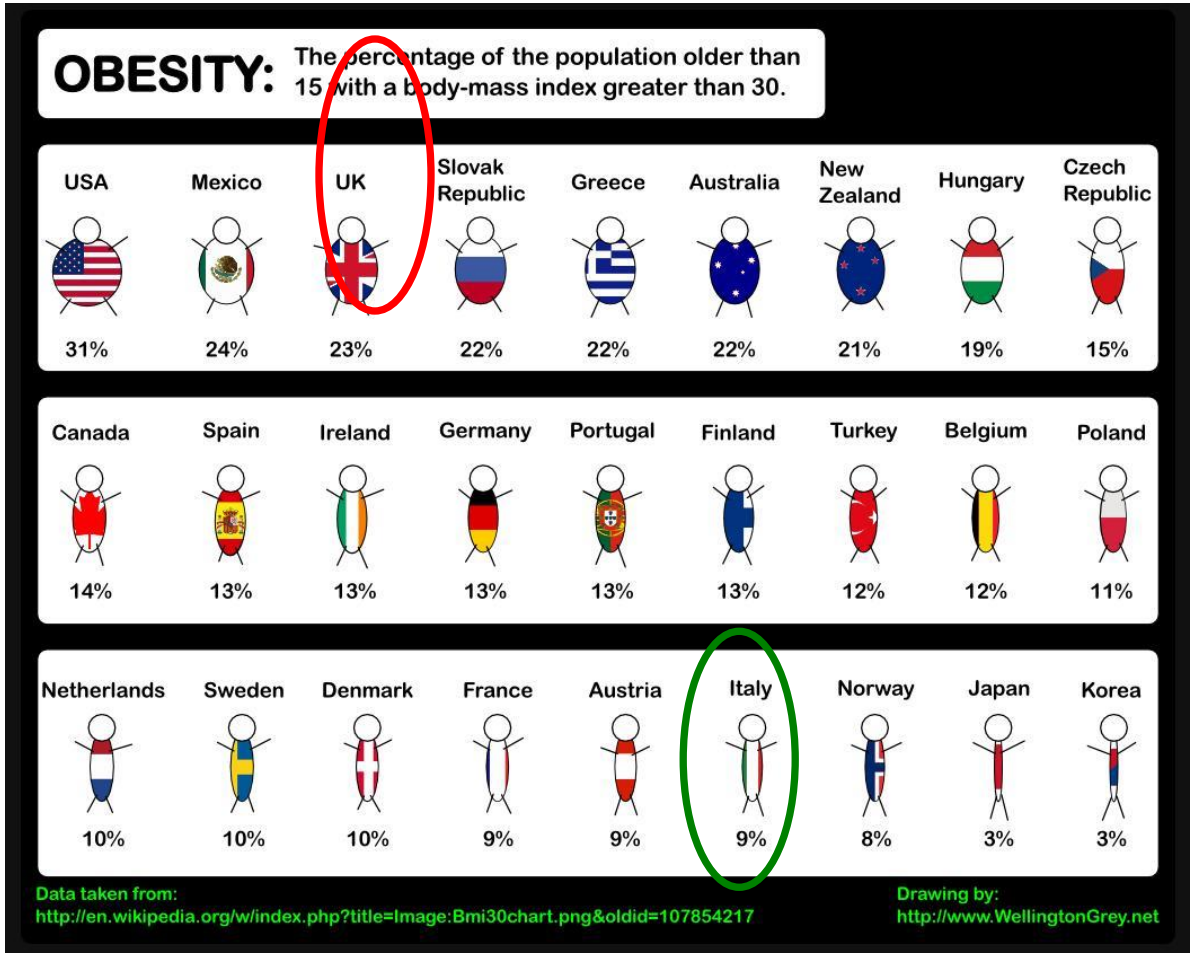


Haldar et al. NEJM 2009;360:973-84

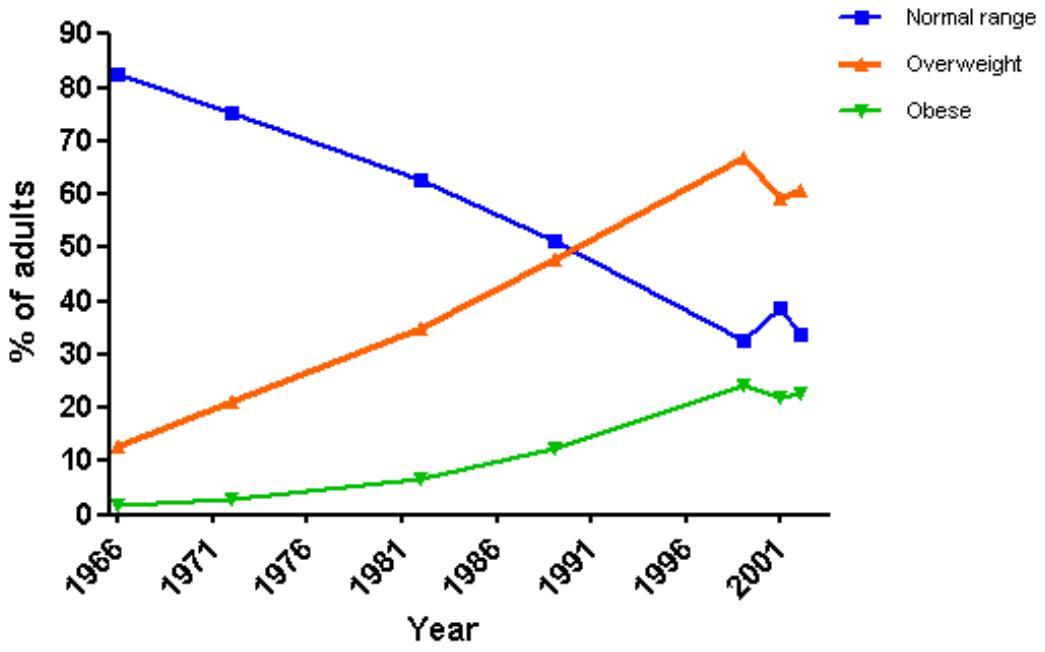


OBESITY

INCREASING PREVALENCE IN WESTERN COUNTRIES:



Obesity in the UK



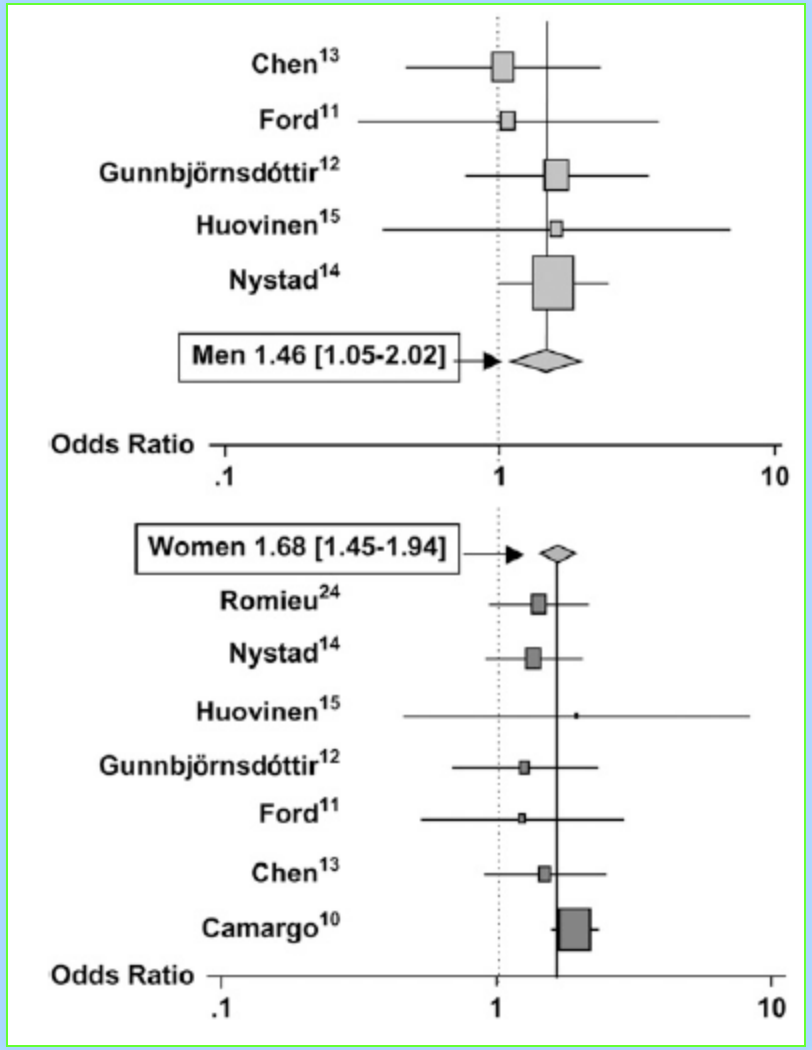
1993: 15% of adults are obese

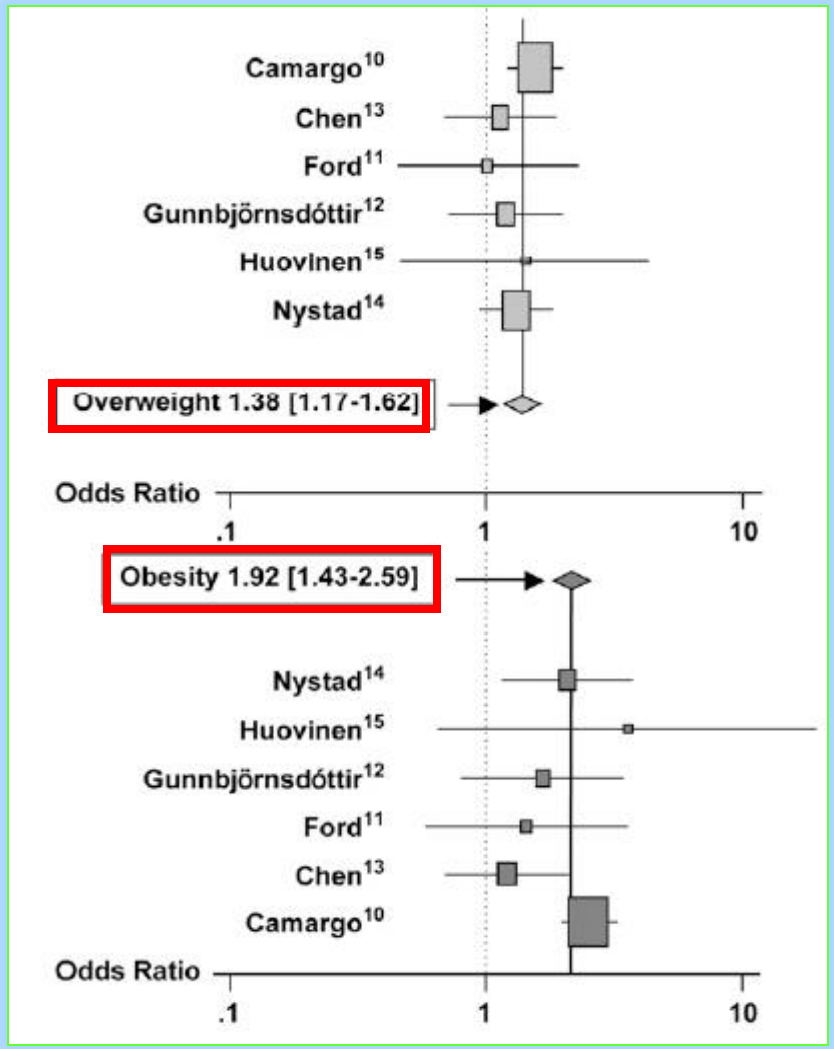
2006: 24% of adults are obese

World Health Organization Global Database on Body Mass Index

- 2009: 61.3% of adults were overweight or obese
- By 2050 approximately 60% of men and 50% of women will be obese
- Obesity contributes to about 1000 deaths per week in the NHS
- Adult obesity has almost doubled since the mid 1980's

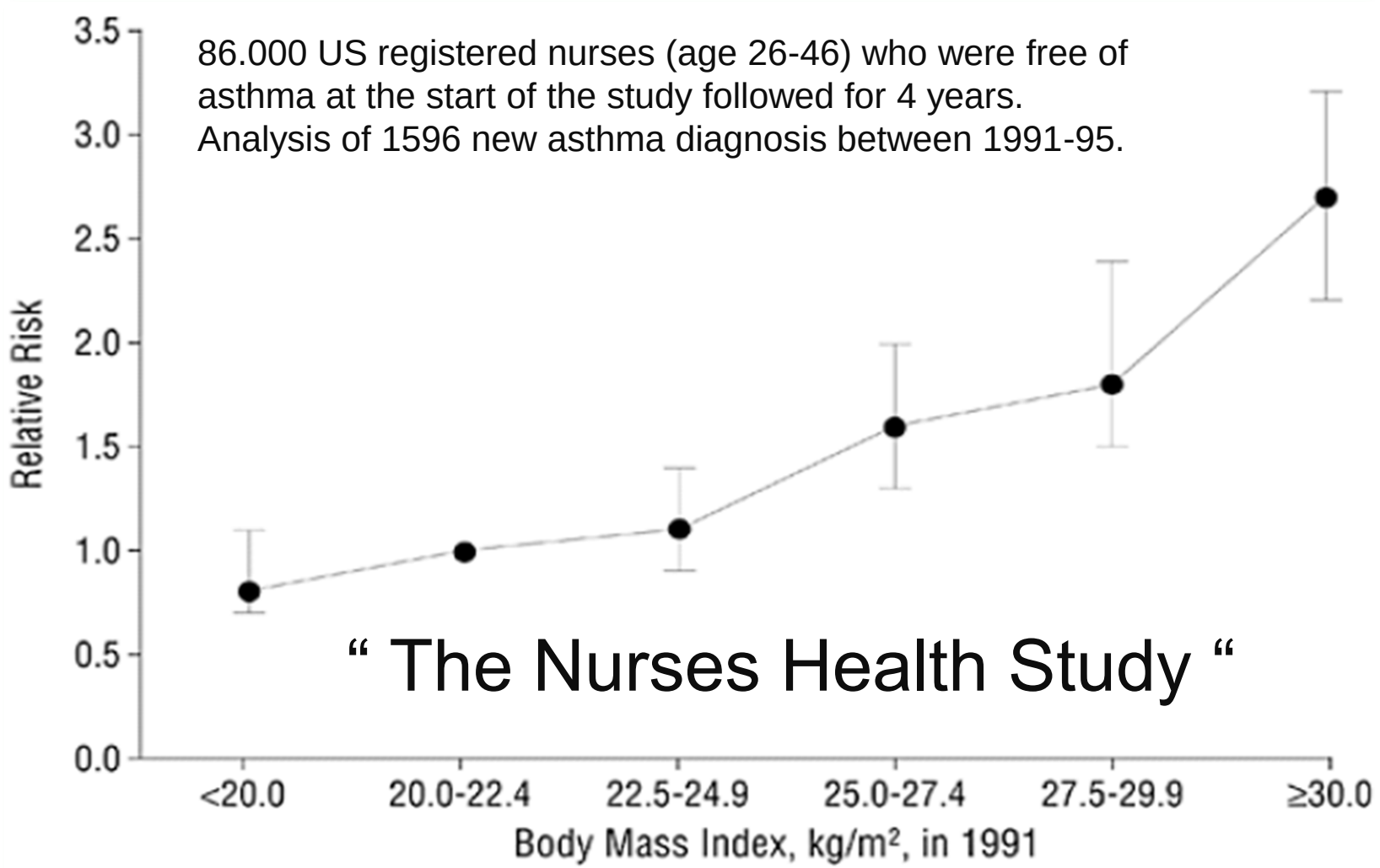
OBESITY & ASTHMA





Beuther DA & Sutherland ER – Overweight, obesity, and incident asthma. A meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175:661.666

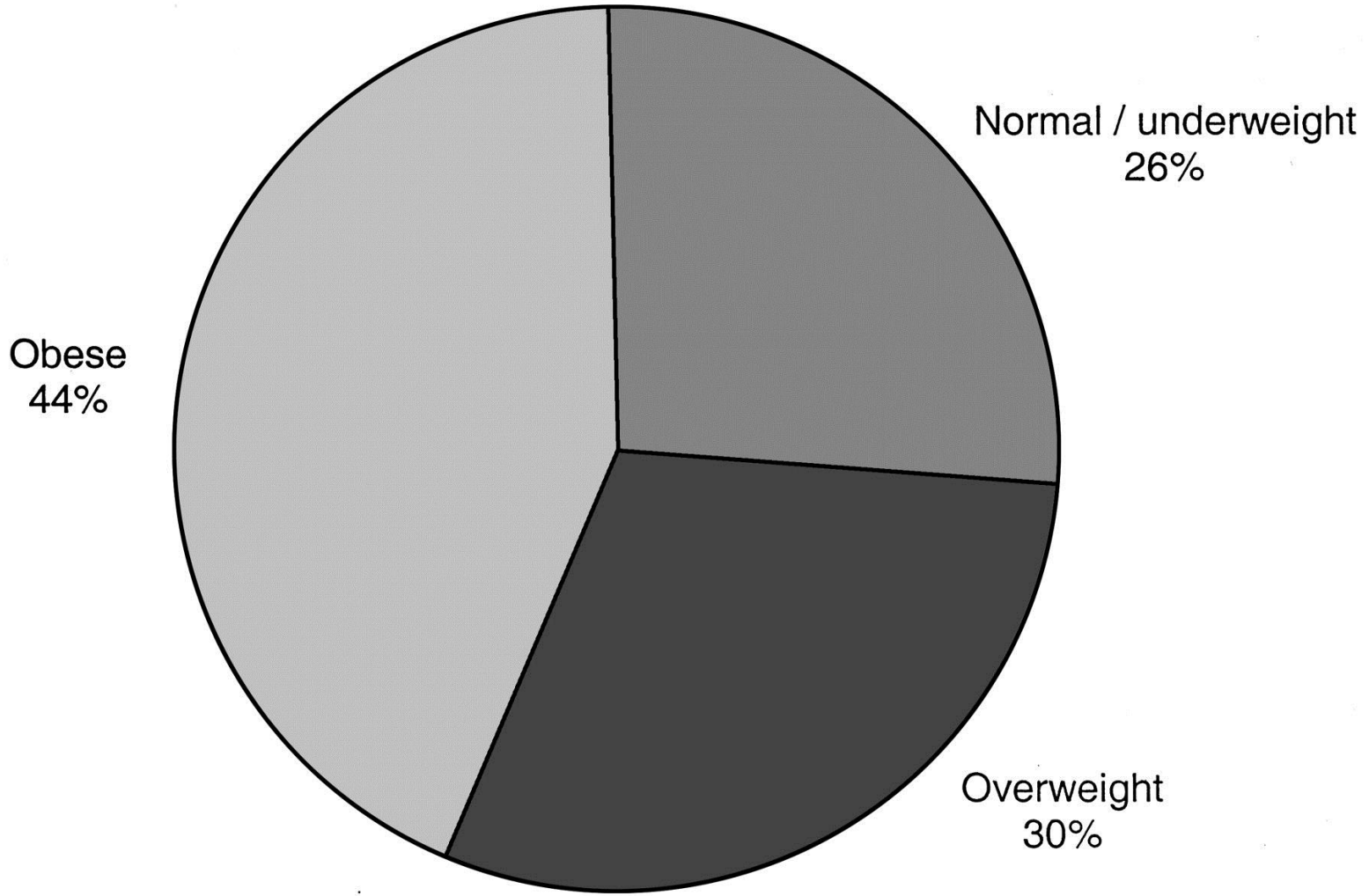
OBESITY & ASTHMA



Camargo CA et al – Prospective study of Body Mass Index, weight change and risk of adult-onset of asthma in women. *Arch Internal Med* 1999;159:2582-2588

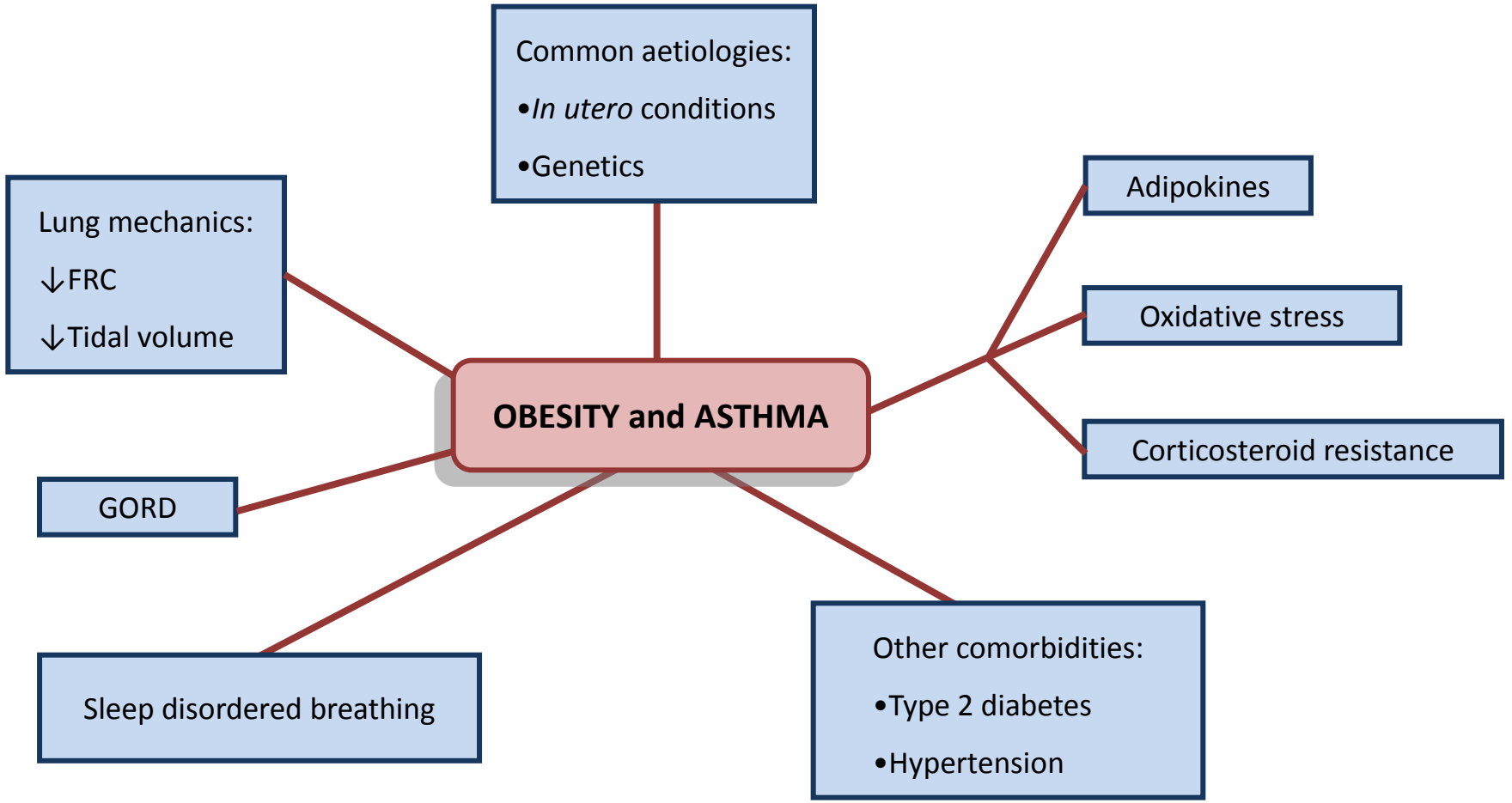
OBESITY & ASTHMA

Distribution of BMI among adults presenting to the ED with acute asthma.

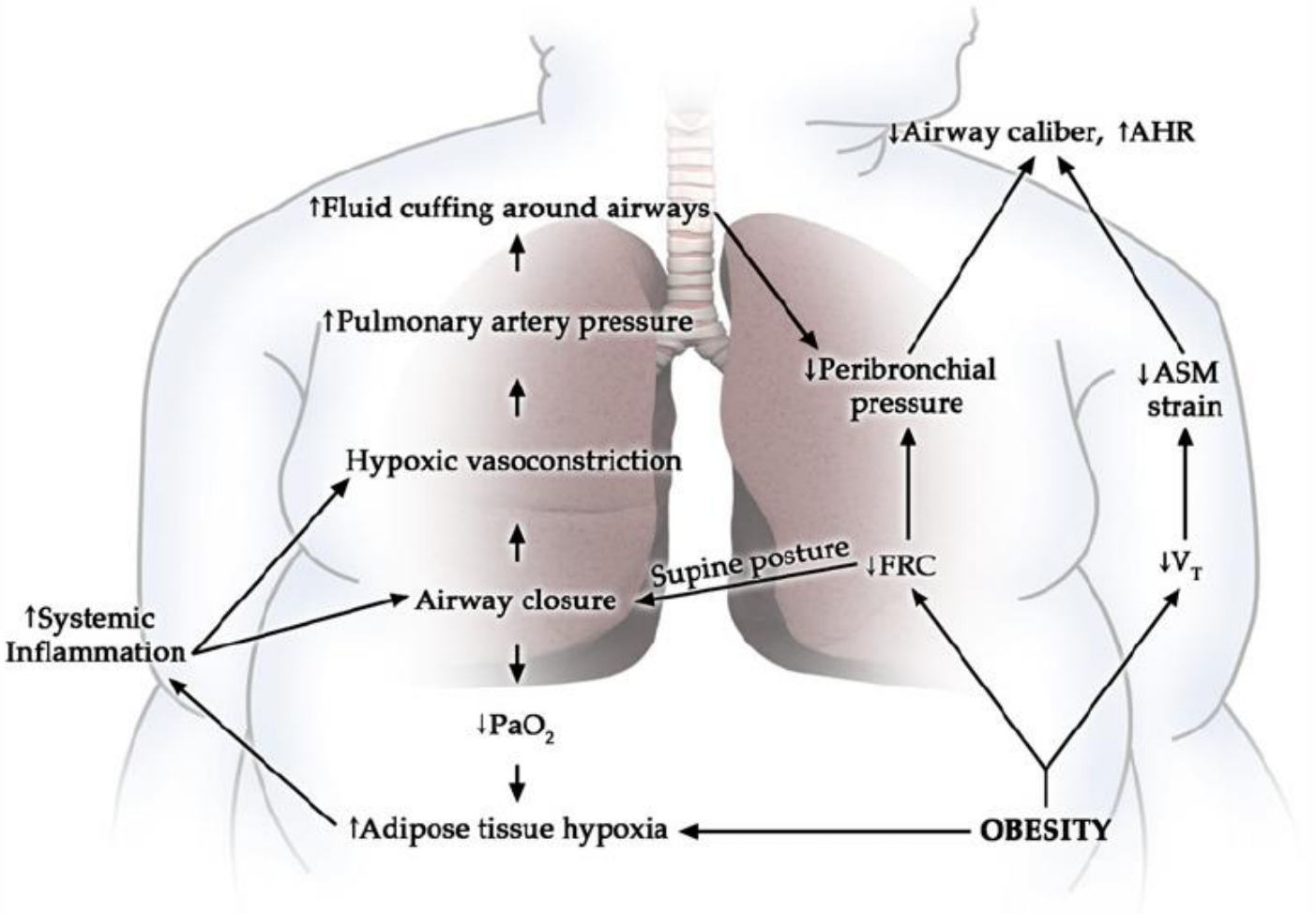


Thomson CC et al. Chest 2003;124:795-802

Mechanisms involved in the relationship between asthma and obesity

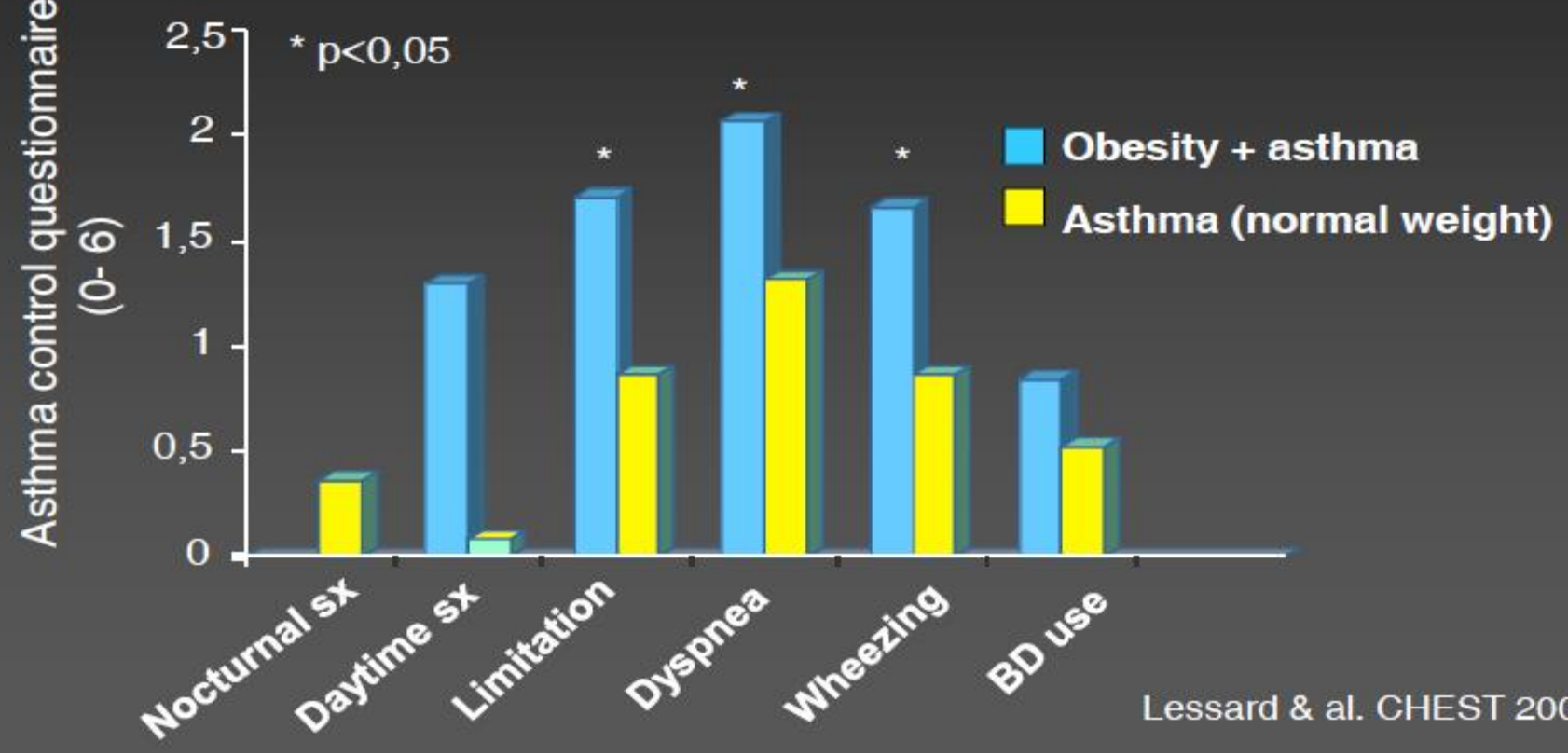


Lung mechanics, obesity and asthma



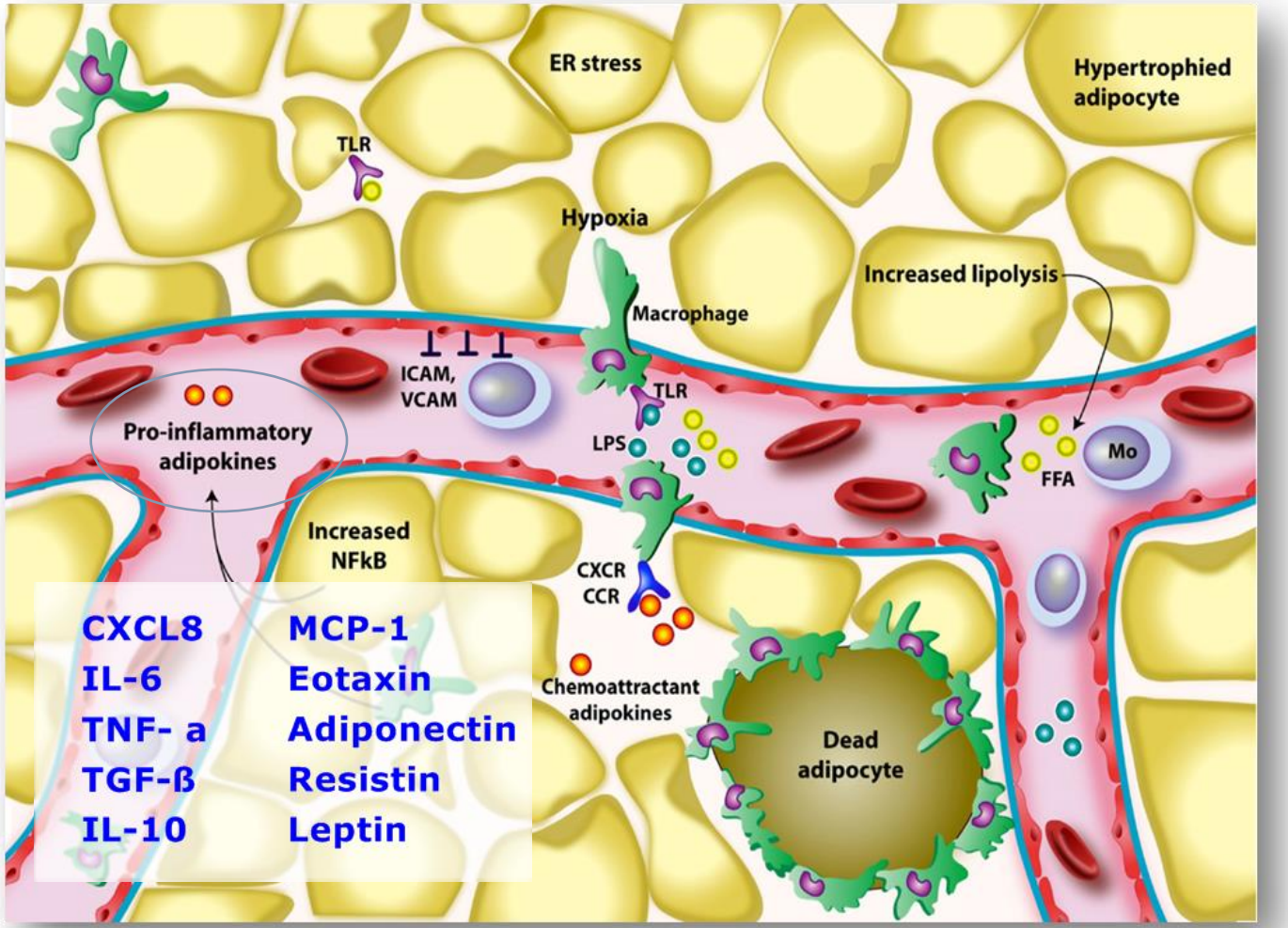
Shore S. JACI 2008

Asthma control



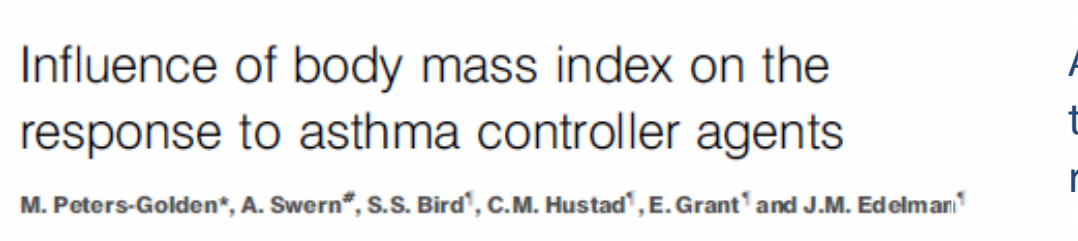
Lessard & al. CHEST 2008

Inflammation in obesity



Maury E, Brichard SM. Molecular and cellular endocrinology, 2010.

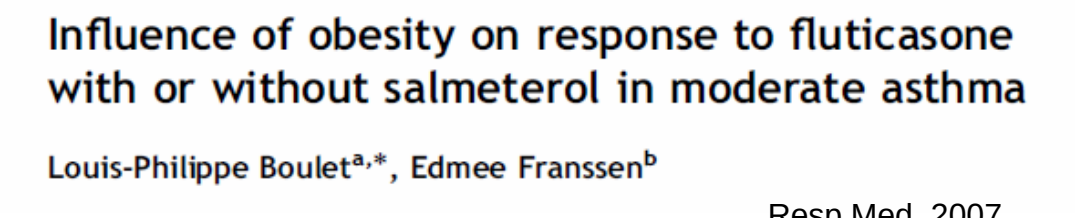
Corticosteroid insensitivity in obesity


Influence of body mass index on the response to asthma controller agents

M. Peters-Golden*, A. Swern#, S.S. Bird¶, C.M. Hustad¶, E. Grant¶ and J.M. Edelman¶

ERJ, 2006

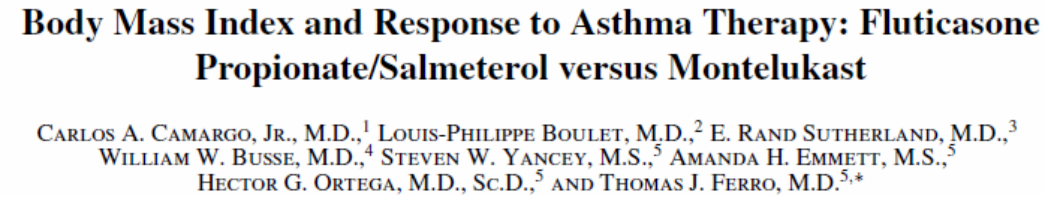
Asthma severity significantly greater in the overweight and obese and reduced response to ICS


Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma

Louis-Philippe Boulet[a,*], Edmee Franssen[b]

Resp Med, 2007

Obese asthmatics less likely to achieve symptomatic control and reduced response to ICS


Body Mass Index and Response to Asthma Therapy: Fluticasone Propionate/Salmeterol versus Montelukast

Carlos A. Camargo, Jr., M.D.,[1] Louis-Philippe Boulet, M.D.,[2] E. Rand Sutherland, M.D.,[3] William W. Busse, M.D.,[4] Steven W. Yancey, M.S.,[5] Amanda H. Emmett, M.S.,[5] Hector G. Ortega, M.D., Sc.D.,[5] and Thomas J. Ferro, M.D.[5,*]

J Asthma, 2010

Altered response to ICS with higher BMI

Weight loss and bariatric surgery

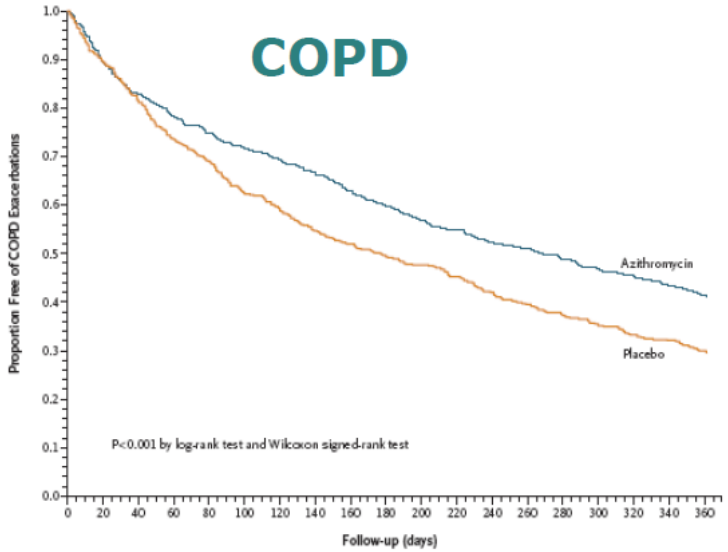
- Al-Alwan et al, ATS 2012
  - 11 obese non-atopic asthmatics and 15 controls
  - 1 year post surgery: improvements in lung function in control group, improvements in impedance in asthmatics

- Dixon et al, JACI 2011
  - 23 asthmatic and 21 non asthmatic patients
  - Significant improvements in asthma control and AHR post surgery
  - Increased BAL cytokines at 1 year in asthmatic group

- Reddy et al, 2011
  - 13,057 bariatric surgery patients
  - 2,562 (18.6%) were on asthma medications
  - 257 followed up for one year post surgery
    - 13 of 28 had stopped oral steroids
    - ICS use decreased from 50% to 30%

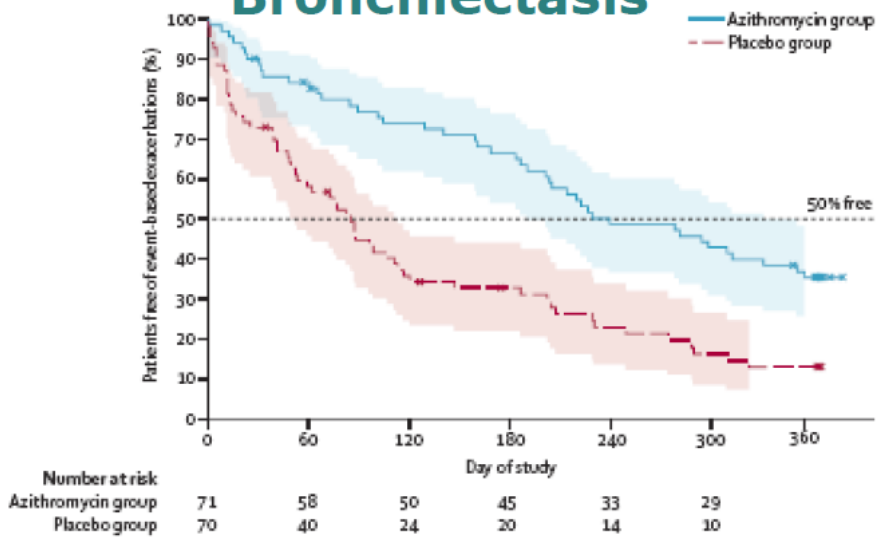
Macrolides and severe airway disease

COPD



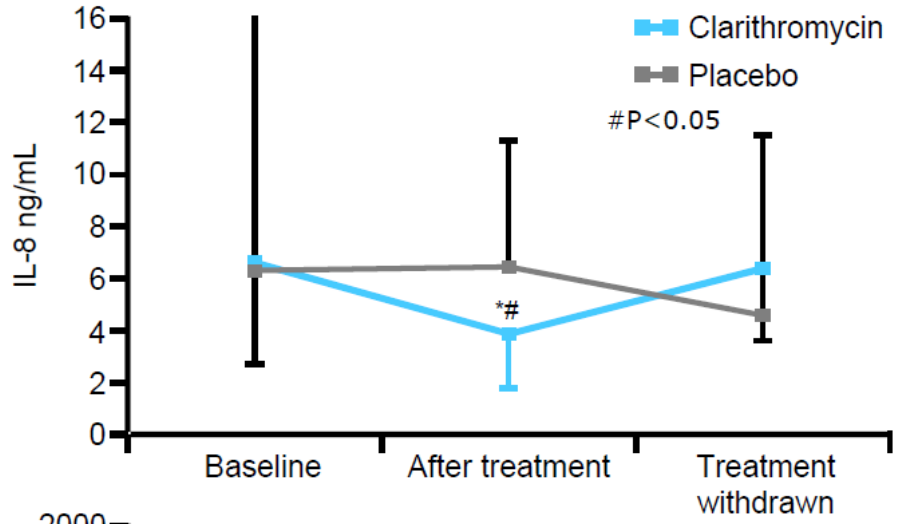
Albert et al. NEJM 2011;365:689-98

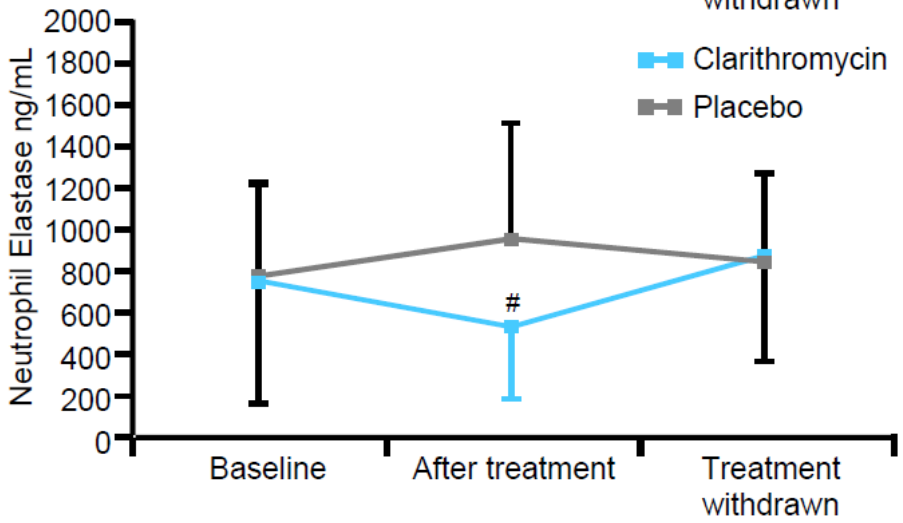
Bronchiectasis



Wong et al. Lancet 2012;380:660-7

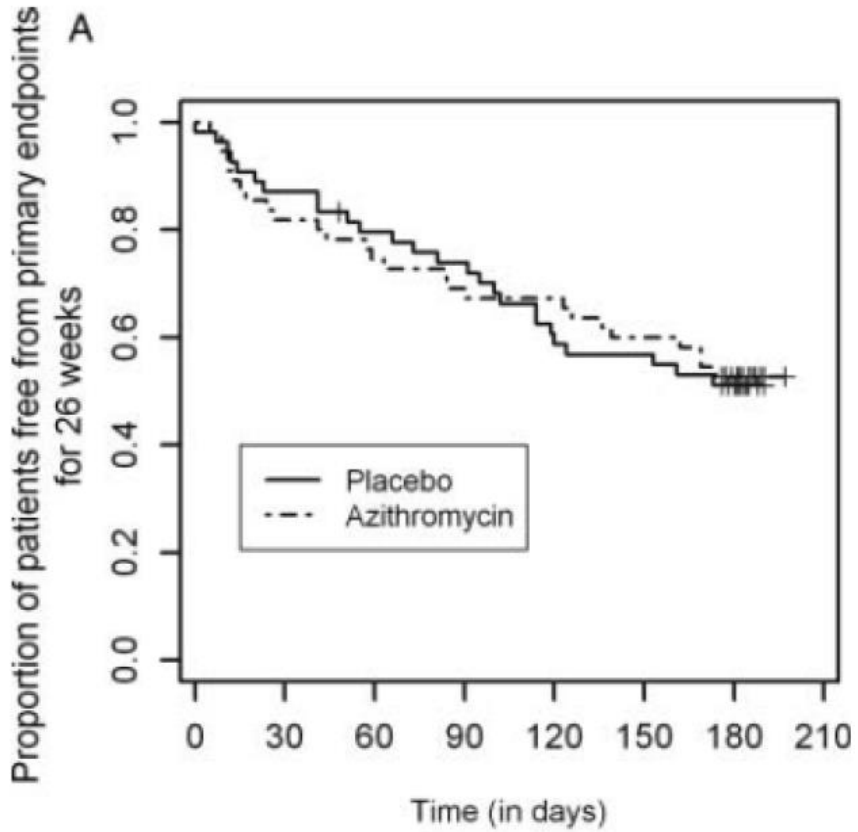
Asthma

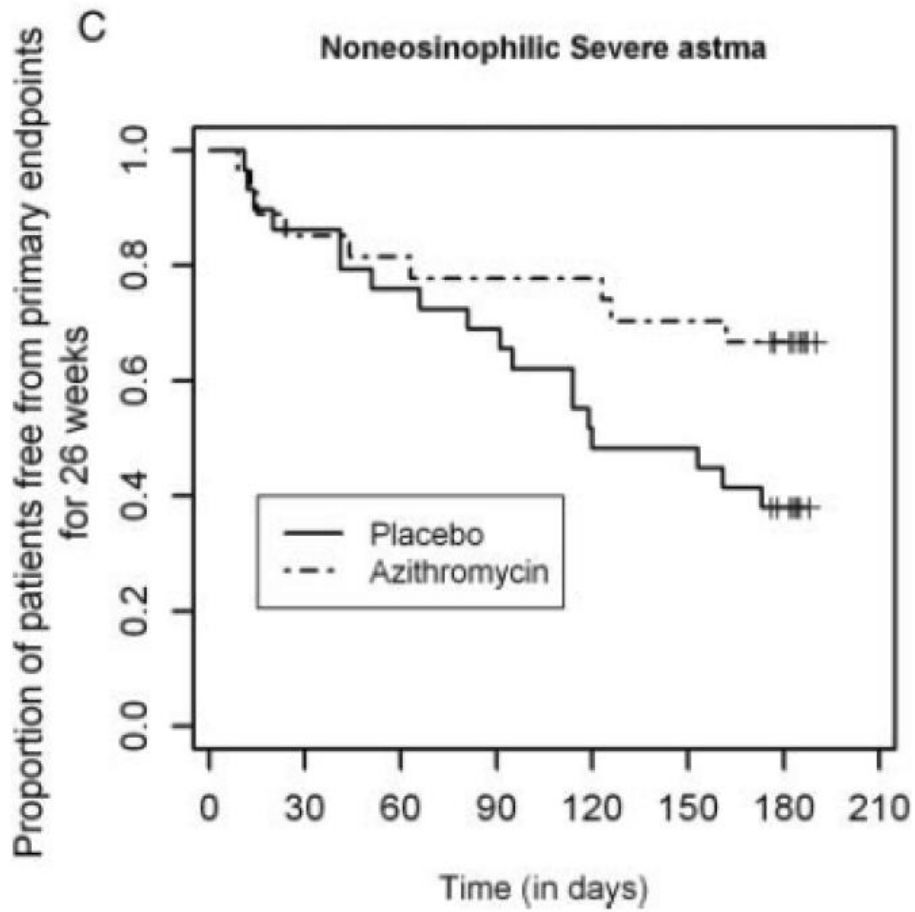




Simpson et al. AJRCCM 2008;177:148–155

Macrolides and non-eosinophilic asthma: the AZISAST study





Brusselle et al. Thorax 2013;68:322-9

Summary

- In 2015, 1,468 people died from asthma in the UK – the highest level for over 10 years[1]
- The NRAD, Asthma UK, ERS White book all suggest 30% incorrect diagnosis of Asthma
- The 2014 NRAD report highlighted excessive prescribing of SABAs and under-prescribing of preventer medication[2]
- BTS 2016 dropped Step 1 (SABA alone)
- Symbicort SMART (budesonide/formoterol) allows use of a single inhaler for both maintenance and reliever therapy in asthma[3,4]
- Use of a Symbicort SMART regimen reduces:[5,6] the risk of severe exacerbations by 39% vs salmeterol/fluticasone + SABA[6]
  - the steroid load by 25% in terms of BDP equivalents vs salmeterol/fluticasone + SABA[6]
  - the need for reliever therapy[6]

From 1st January 2018 The price of Symbicort Turbohaler will be aligned across all strengths at £28

- NICE recommends Spirometry, FENO for diagnosis
- All that wheezes – not ICS requiring asthma
- Tiotropium, Biologics, Macrolides all present

NRAD=National Review of Asthma Deaths; SABA=short-acting ß$_2$-agonist. SMART= Symbicort Maintenance and Reliever Therapy.

1. British Thoracic Society. *Updated national guidance launched to help reduce asthma attacks and save lives* [online] 2016. Available from: https://www.brit-thoracic.org.uk/pressmedia/2016/updated-national-guidance-launched-to-help-reduce-asthma-attacks-and-save-lives/ [Accessed: July 2017]; 2. Royal College of Physicians. *Why Asthma Still Kills? The National Review of Asthma Deaths (NRAD)* [online] 2014. Available from: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [Accessed: July 2017]; 3. AstraZeneca UK. Symbicort Turbohaler 100/6: Summary of Product Characteristics. 2017; 4. AstraZeneca UK. Symbicort Turbohaler 200/6: Summary of Product Characteristics. 2017; 5. Rabe KF, et al. *Lancet* 2006;368:744–753; 6. Kuna P, et al. *Int J Clin Pract* 2007;61:725– 736.