Asthma Update

Stephen Child
General Physician
Respiratory Interest
Director of Clinical Training
Auckland District Health Board

Declaration of Interests

Past recipient of Speaker engagement funds from AstraZeneca Pharmaceuticals and GlaxoSmithKline

Annual attendance at Boehringer Ingelheim sponsored Respiratory Update conference

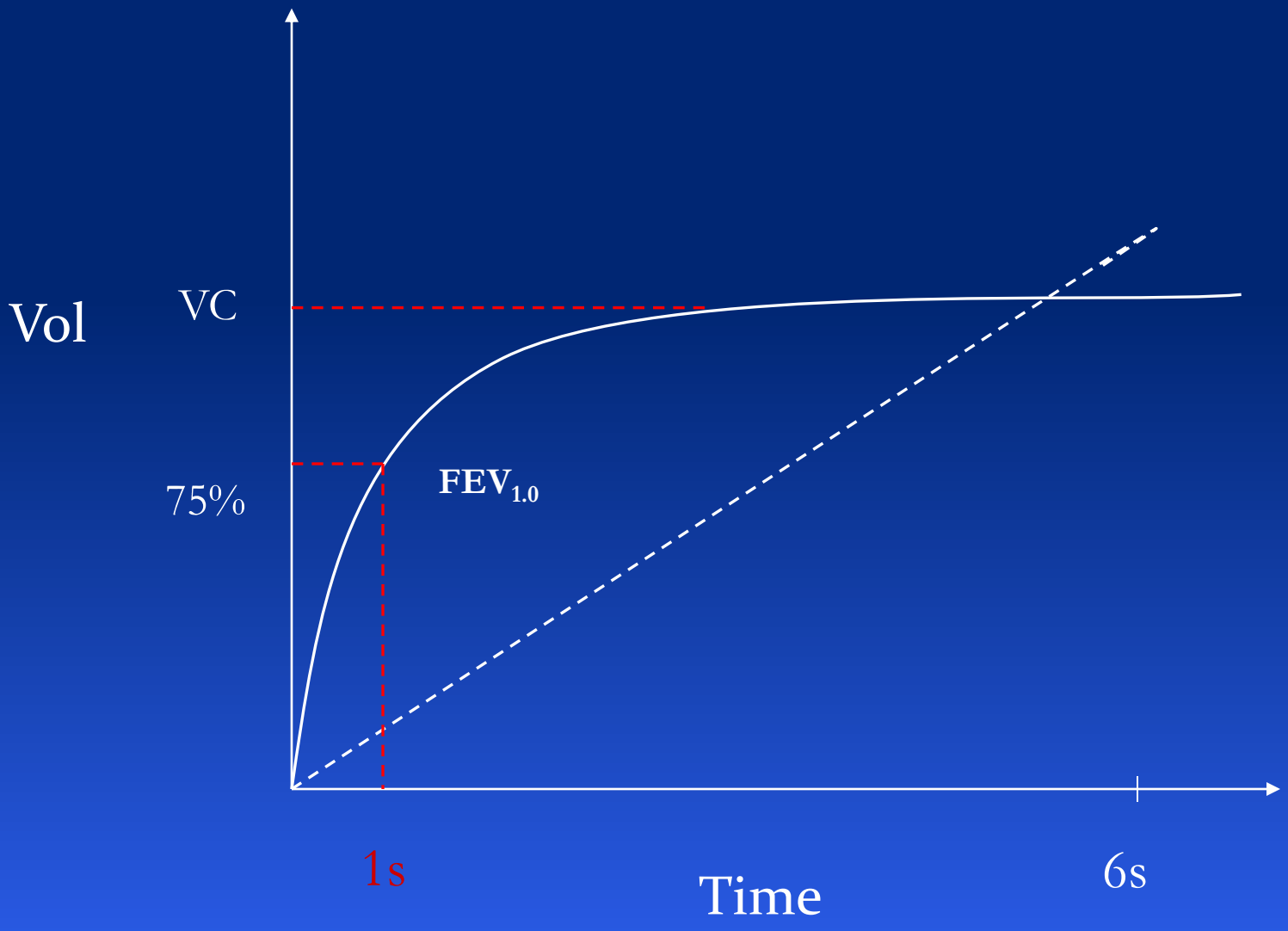
Outline

- Asthma Diagnosis
- Remodelling
- Single Inhaler Therapy (? SMART)
- Adherence
  - Role of Spirometry
  - FeNO
  - B Blockers

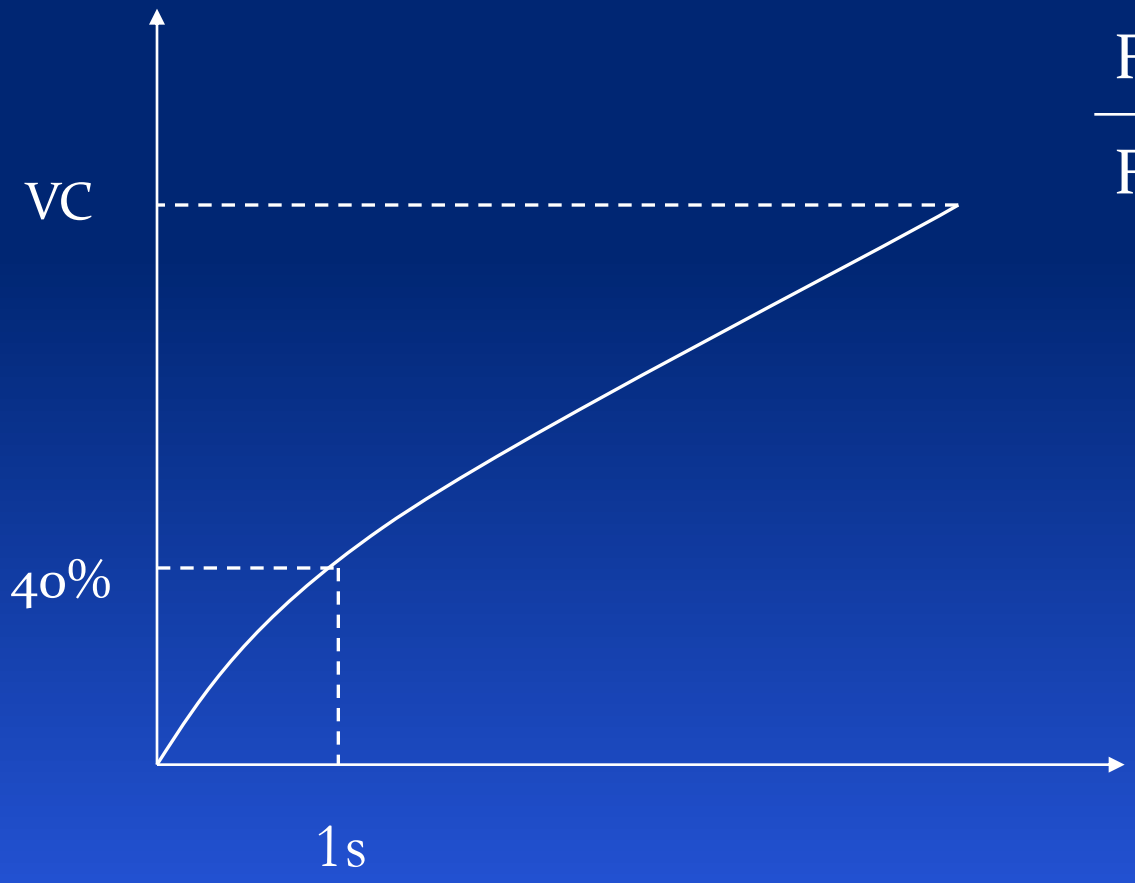
Mariana

- 44 yr old female, non-smoker, asthma > 25 years
- ICS / LABA / SABA
- Comorbidities:
  - Obesity
  - DM
  - Gout
  - High cholesterol

- Is the diagnosis correct?
- Other exacerbating factors?
- Control ?
- Adherence to treatment?
- Role of spirometry?


Vol
VC
75%
FEV1.0
1s
Time
6s

Obstruction



$$\frac{FEV_{1.0}}{FVC} < 0.70$$

Severity (1)

$FEV_{1.0}$

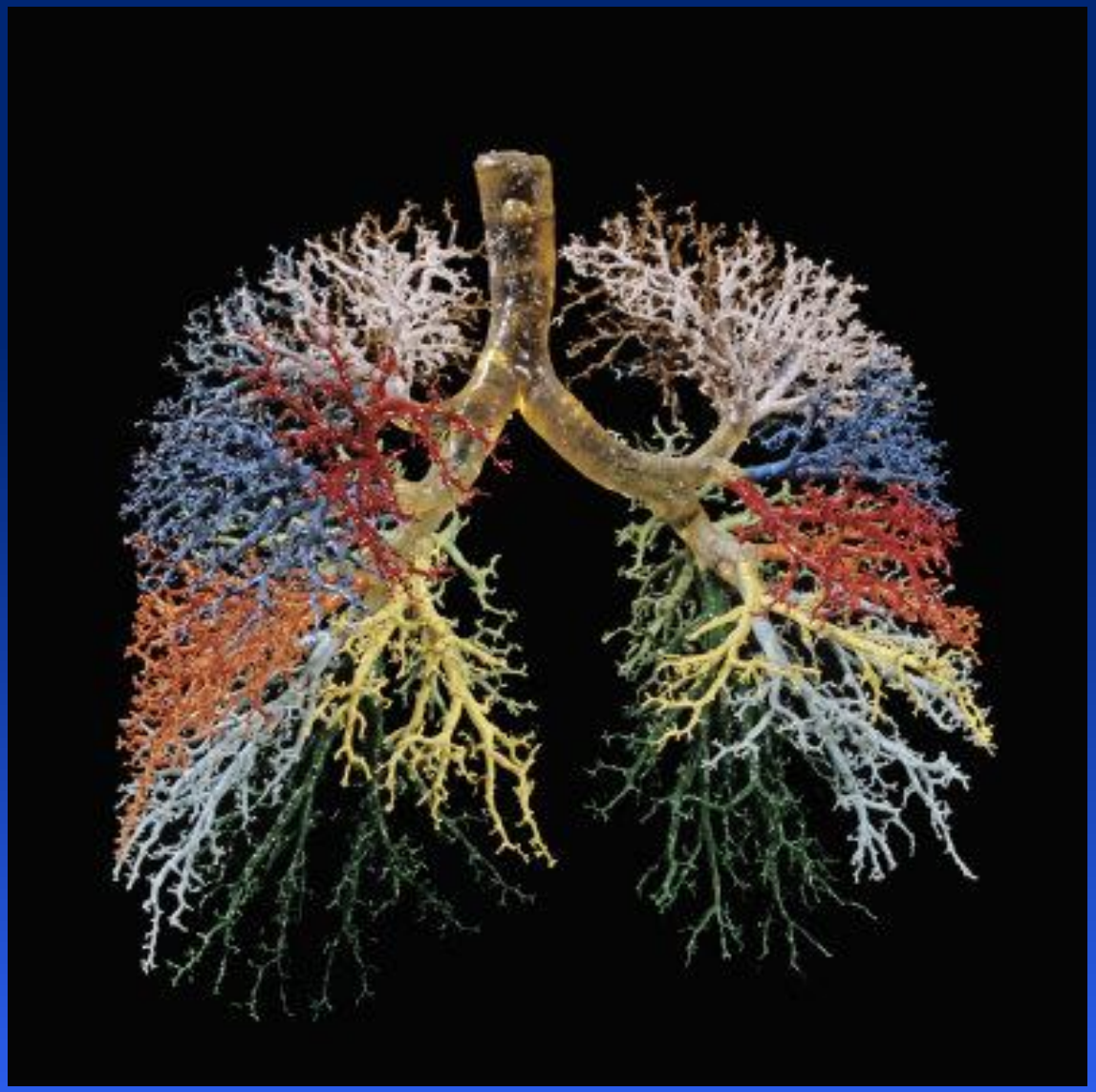
Obstruction **Normal> 80% predicted**

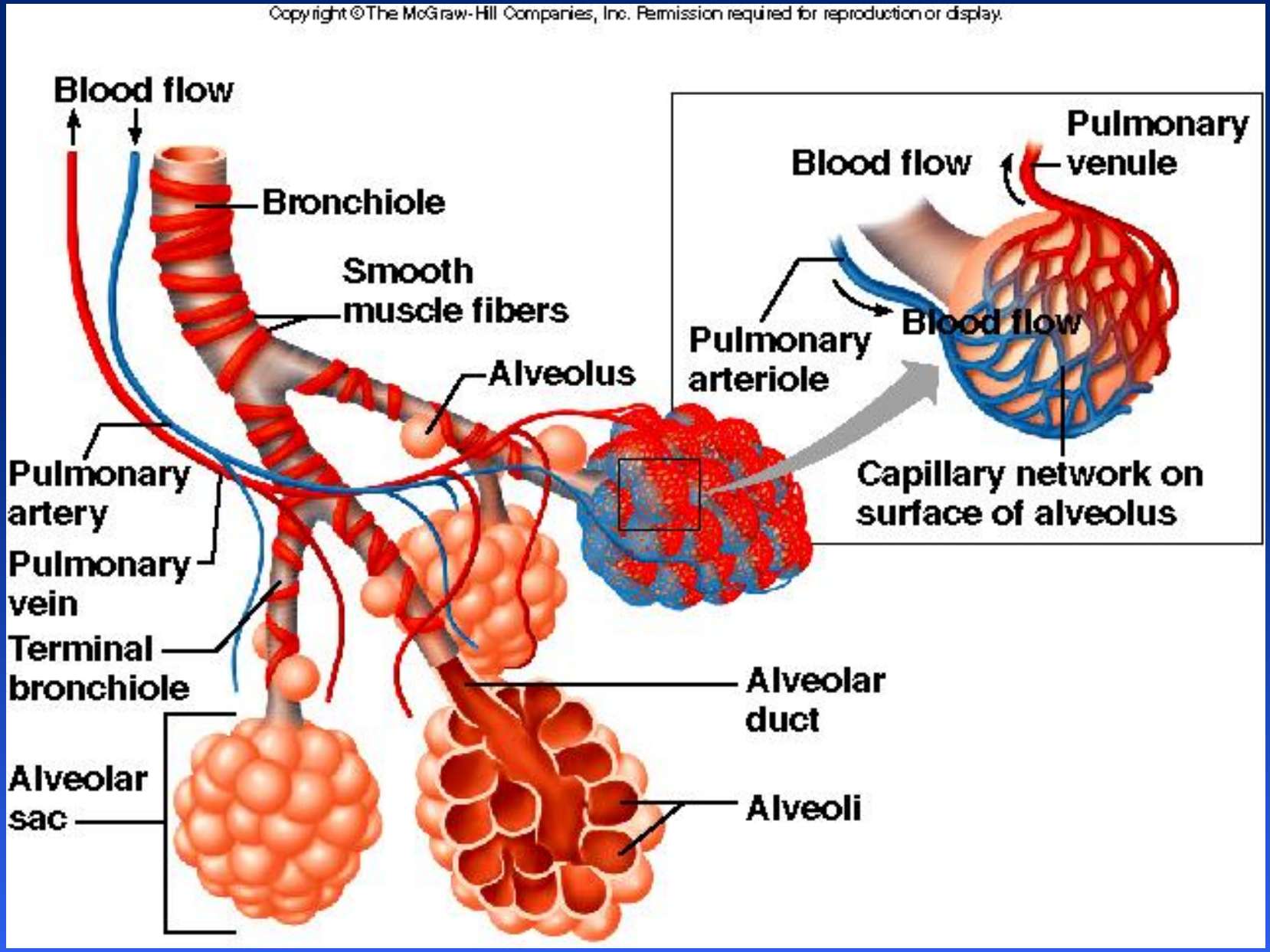
Mild 65-80% predicted

Moderate 50-65% predicted

Severe < 50% predicted

…LABA / ICS < 50% ; Tiotropium < 60% pred





Obstructive Airways Diseases

- Asthma/COPD
- Bronchiectasis
- Allergic Bronchopulmonary Aspergillosis
- Cystic Fibrosis
- Sarcoidosis
- CHF
- Broncholitis- obliterans (COP/other)
- Allergy/Anaphylaxis
- Obesity ??
- Other- Eg: aspiration,FB,etc

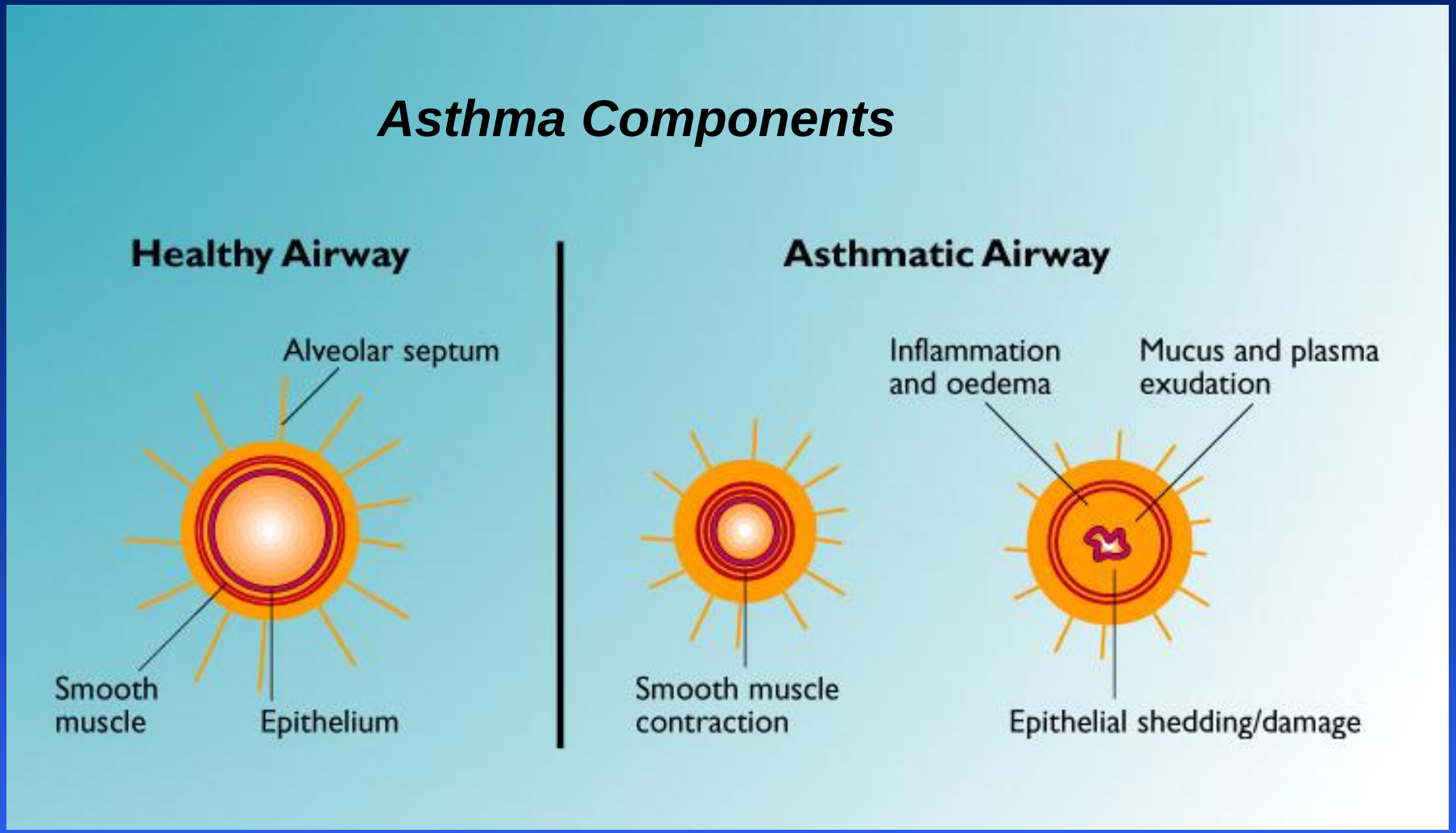
Take Home

Wheeze = Bronchiolitis ?

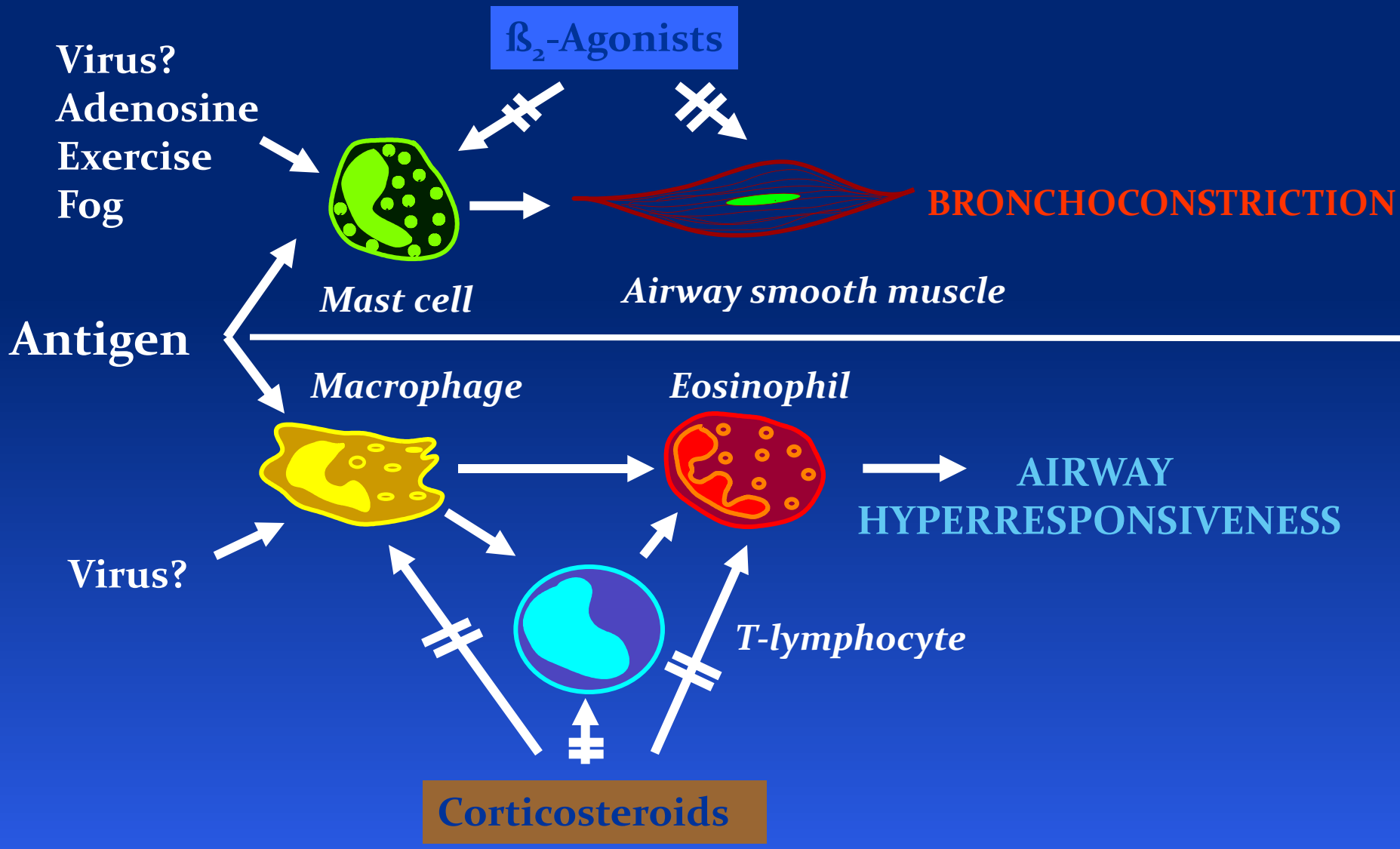
"All that wheezes is not asthma ! "

% predicted NOT ratio

Epidemiology/Pathology

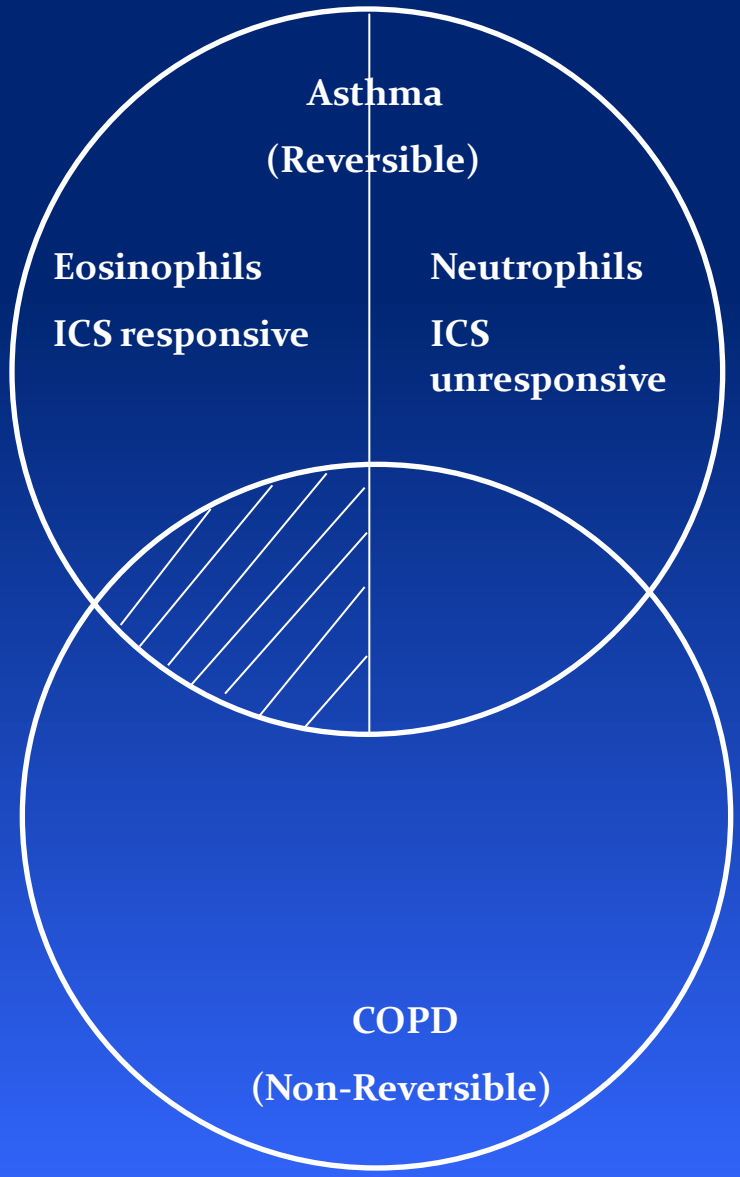


Barnes PJ


ß2-Agonists
Virus?
Adenosine
Exercise
Fog
BRONCHOCONSTRICTION
Mast cell
Airway smooth muscle
Antigen
Macrophage
Eosinophil
AIRWAY
HYPERRESPONSIVENESS
Virus?
T-lymphocyte
Corticosteroids

Barnes PJ

Airflow Obstruction



?Reversible vs Steroid Responsive

- "Twitchy" = History
  PEFR Diurnal change
  Challenge
  Sputum Eosinophils
  FeNO

FeNO = Fraction exhaled NO

- 1987 = EDRF
- NO = bronchodilation
  = vasodilation
  = cilia beating
  = NANC neurotransmitter
  = metabolite OONO – toxic

.....NO.....= Eosinophil ???

FeNO

- (n = 2319) reference range 7.8 – 41.1
- Increased = asthma
  sputum eosinophils
  Plicatic acid
  HV cold-dry air
  ?COPD, URTI, Sarcoidosis
- Correlate with BHR

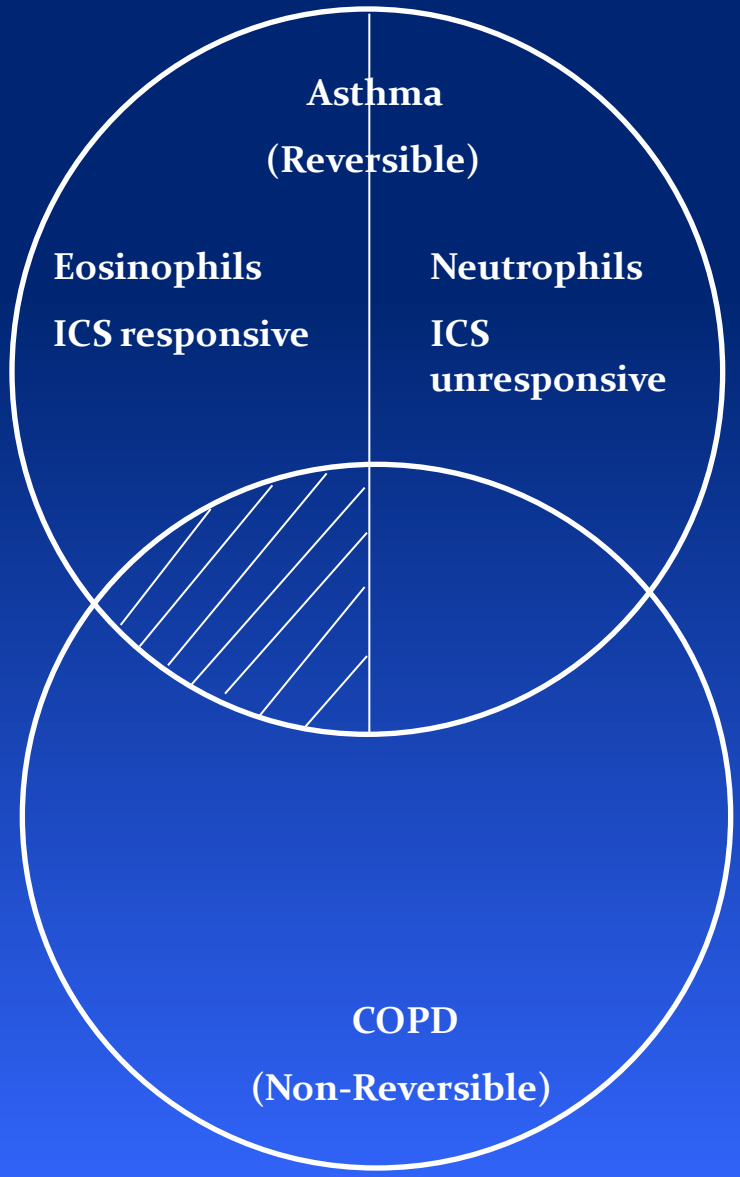
FeNO

Dunedin: Robin Taylor N=52 respiratory clinic

Fe NO > 47 ppb correlated with best BHR improvement to 4 weeks Flixotide

AMJ Respir Crit Care Med 2005; 172:453-59

Airflow Obstruction



Asthma

1. SABA prn
2. ICS + SABA
3. ICS + LABA
4. Other

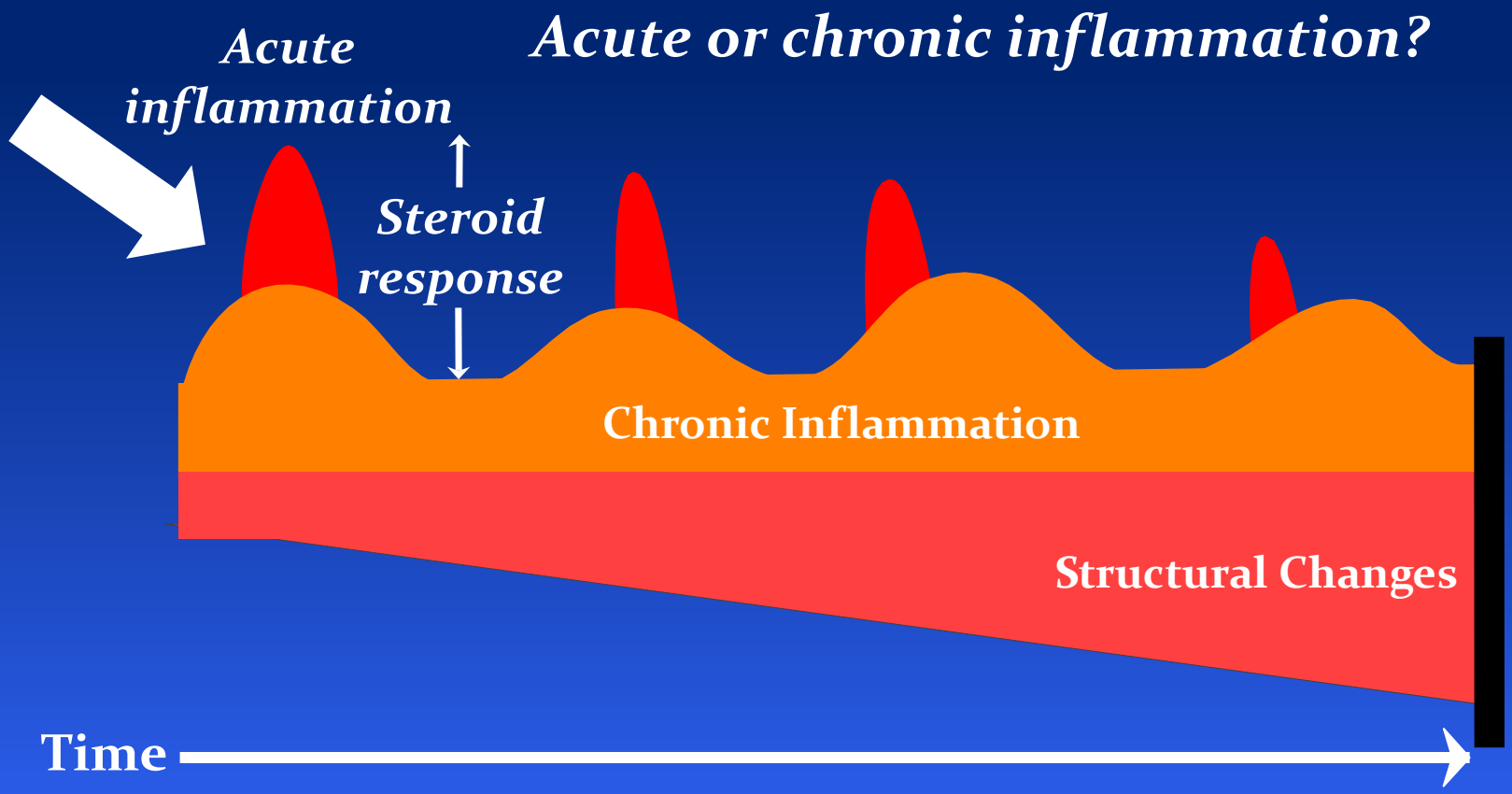
COPD

1. SA B.D prn
2. LA B.D (LABA or Tio (if < 60%)
3. ICS if < 50%
4. Other

Take Home- 1

- “More twitchy and eosinophils ……more likely steroid response”
- Not all obstruction needs steroids

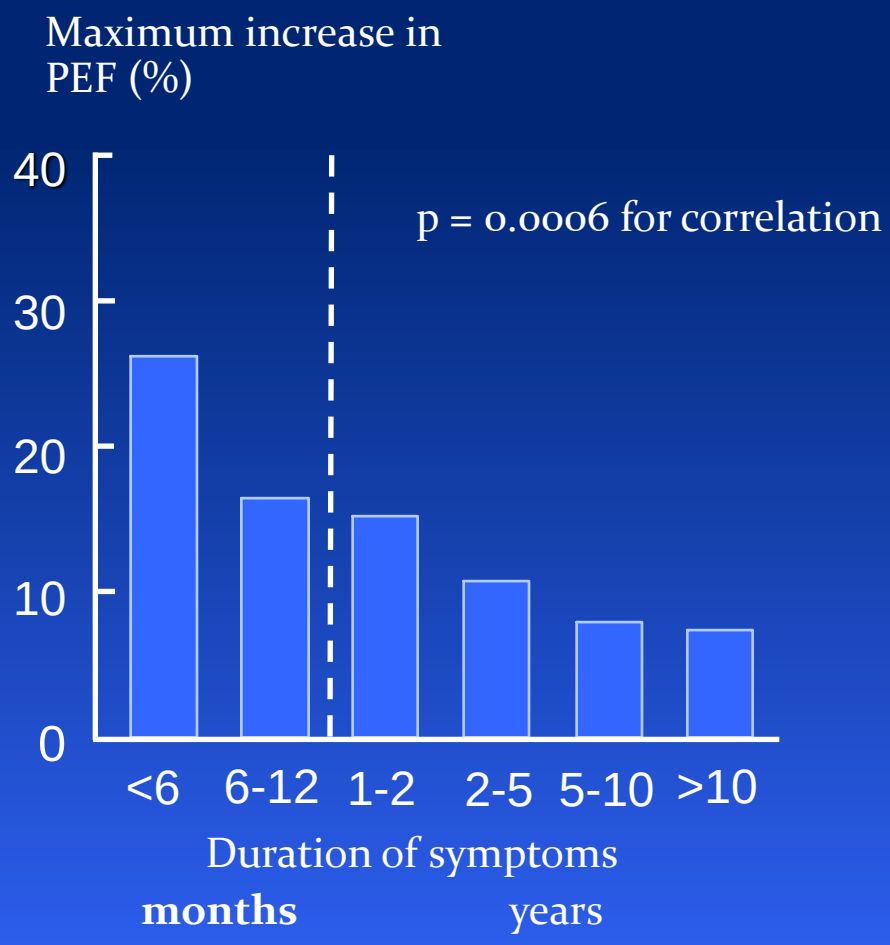
Inflammation in Asthma



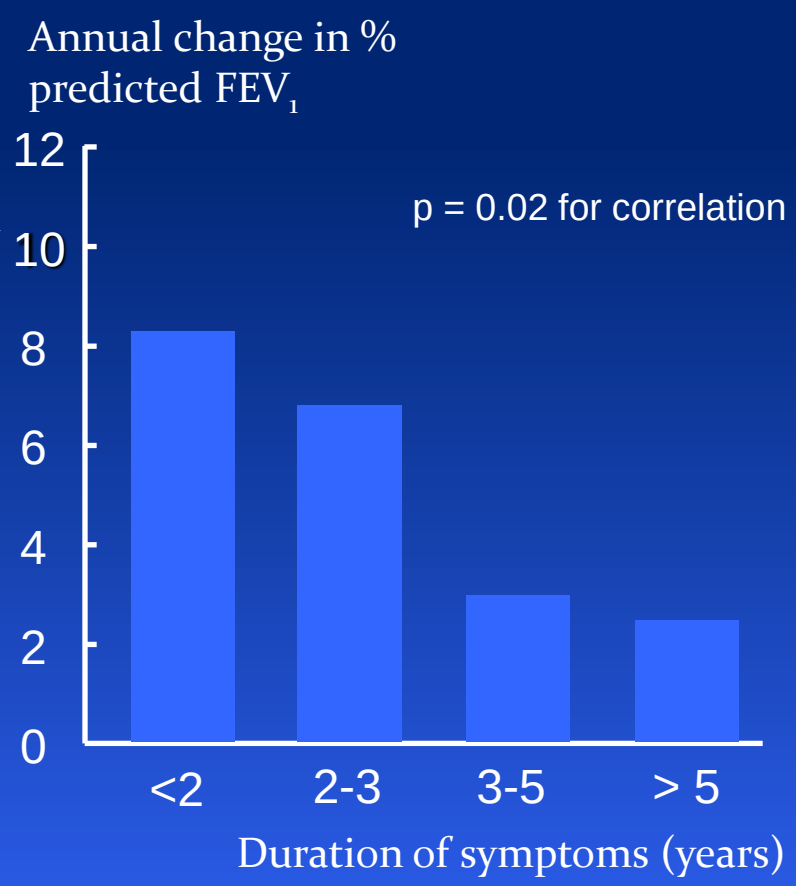
Barnes PJ

Early Intervention with Inhaled Steroid

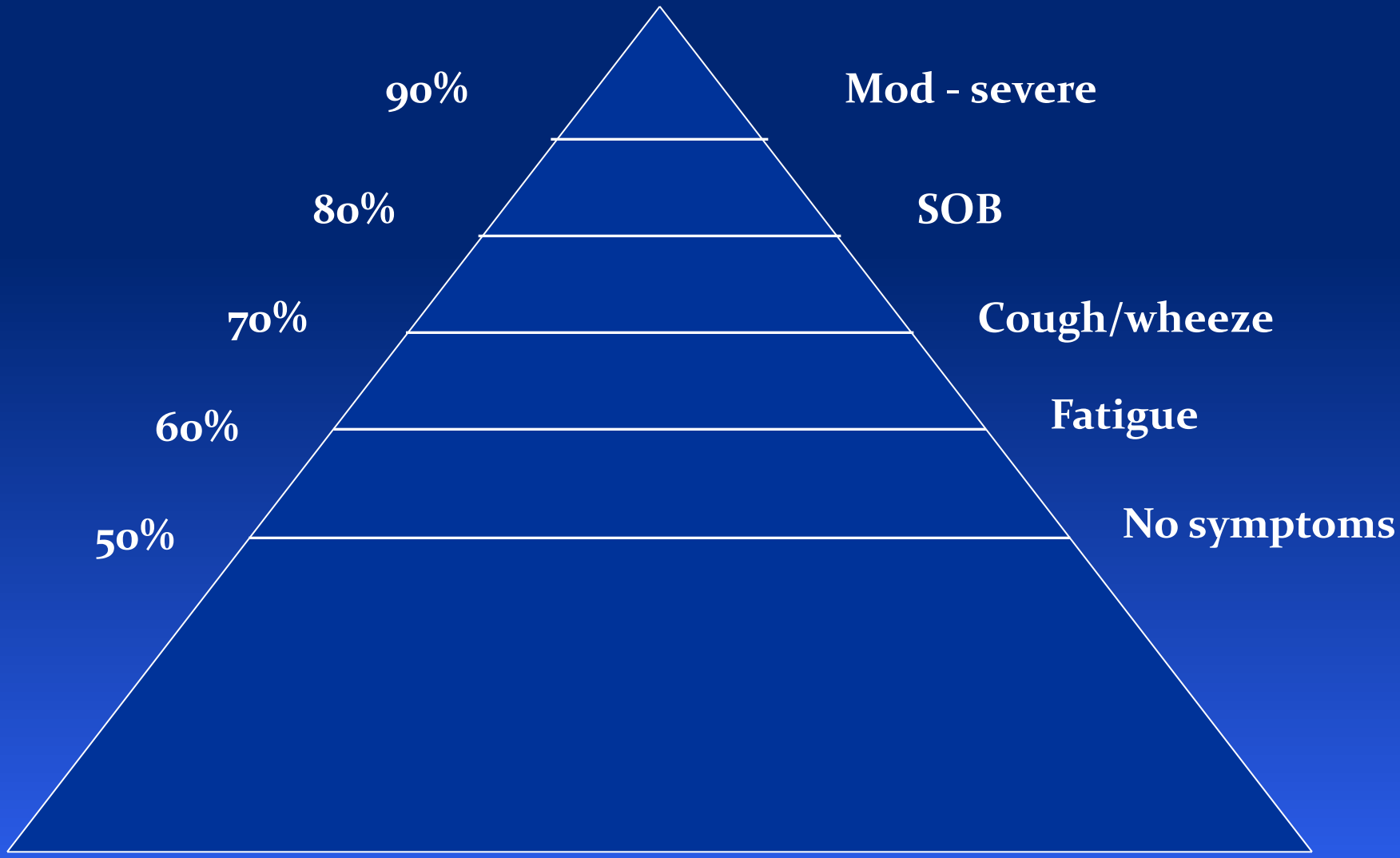
Adults[1]



Children[2]



1. Selroos et al, Chest 1995 2. Agertoft and Pedersen, Respir Med 1994


90%
Mod - severe
80%
SOB
70%
Cough/wheeze
60%
Fatigue
50%
No symptoms

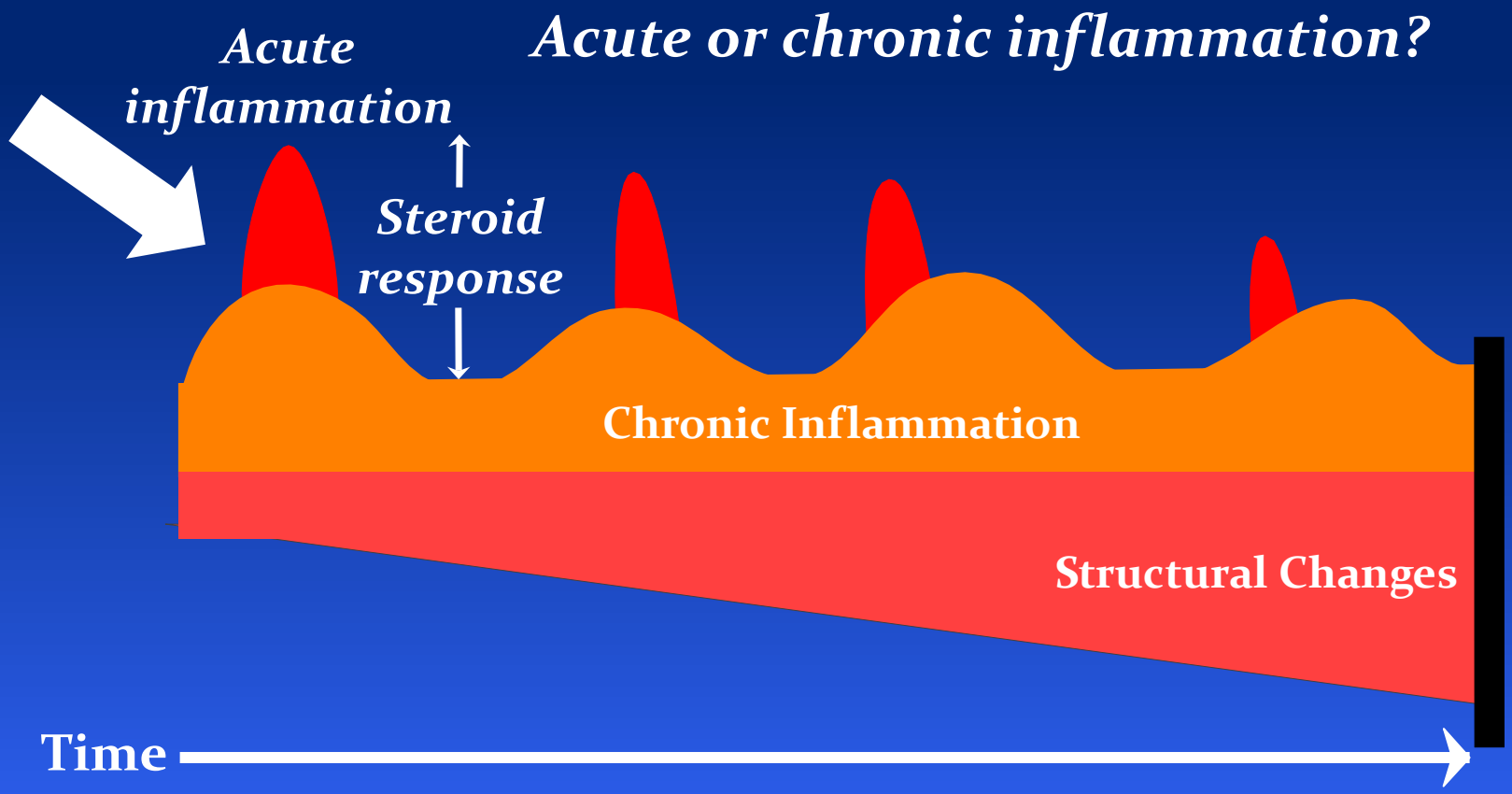
Airway Remodelling
(New England J Med 2011; 364(21):2006-15)

n = 48 asthmatics

4 Challenges x 3 q 48 hours	then	Bronchial Biopsy Day 21
1. Allergen	↑ Eos	↑ BM, ↑ mucous glands
2. Methacholine	_	Increased BM, glands_
3. Pre-Vent + Methacholine	_	_
4. Pre-vent + Saline	_	_

ie: ? Constriction causes inflammation / remodelling ?

Inflammation in Asthma



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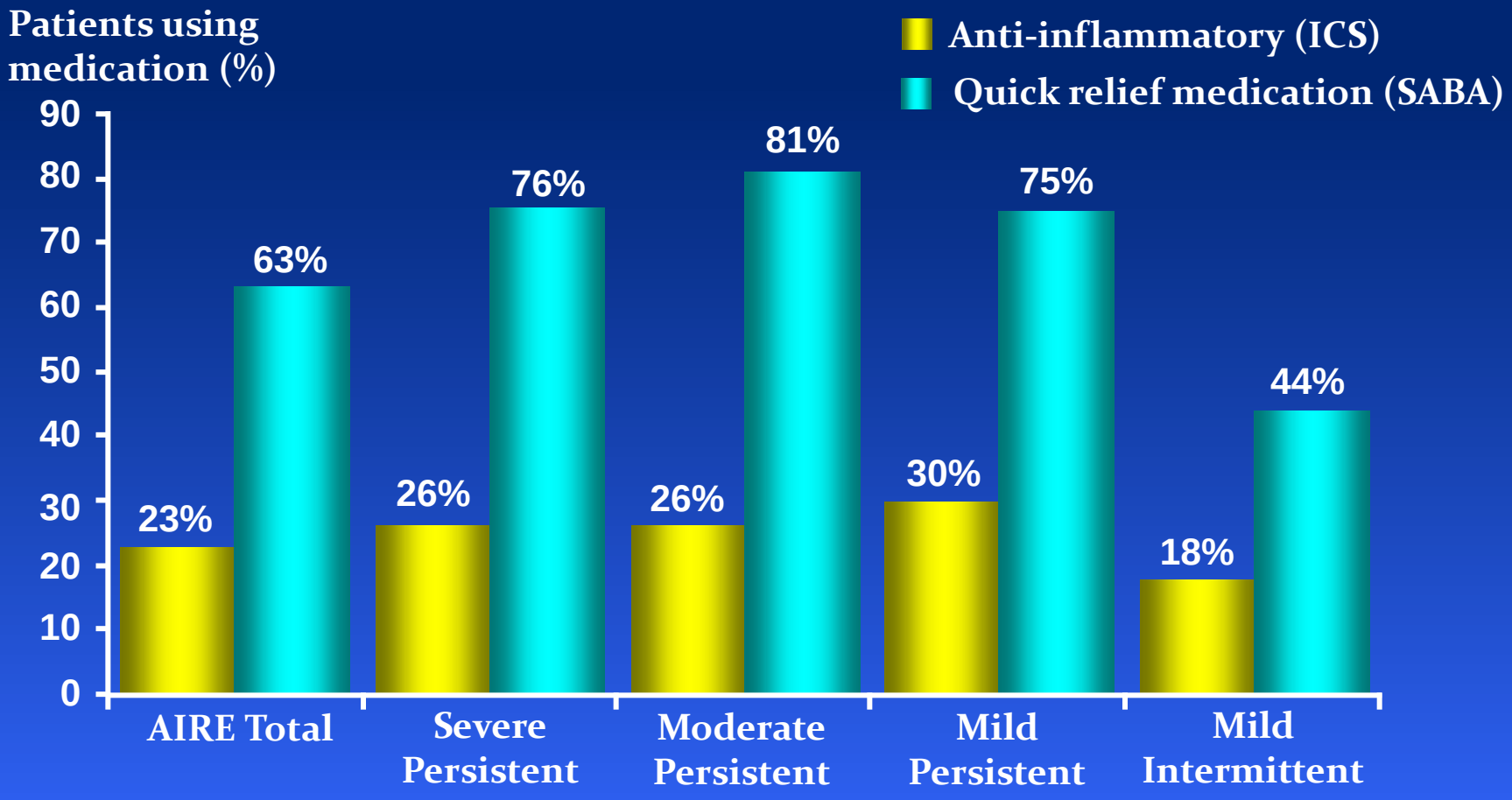
Patients over-rely on SABAs vs ICS irrespective of asthma severity

SABA and ICS use according to symptom severity



AIRE, Asthma Insights and Reality in Europe

Rabe KF, et al. Eur Respir J 2000;16:802–807.

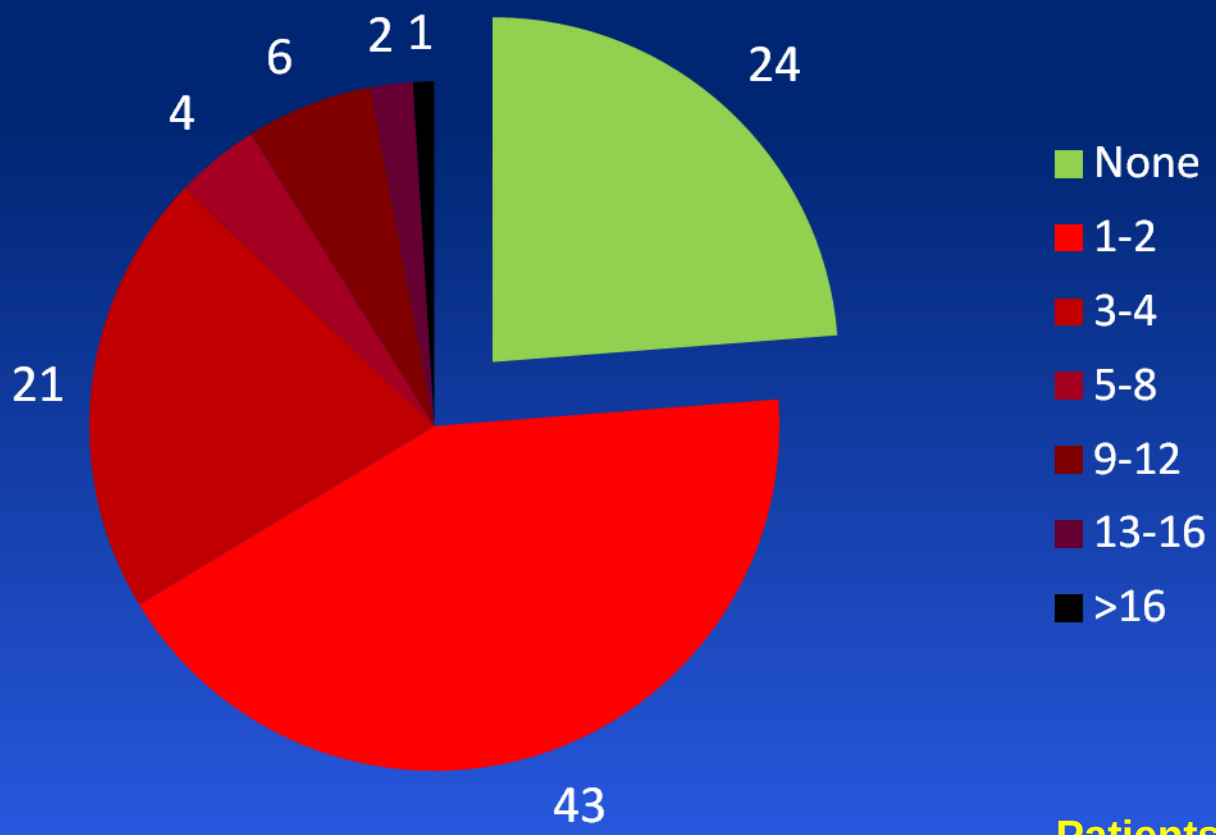
Adherence

- 23% “steroid dep” asthma…..not taking steroids
- >50% non ICS compliance

Neil Barnes, London Chest Clinic, March 2012

SABA use as an indicator of poor control

Inhalations per day in the last week

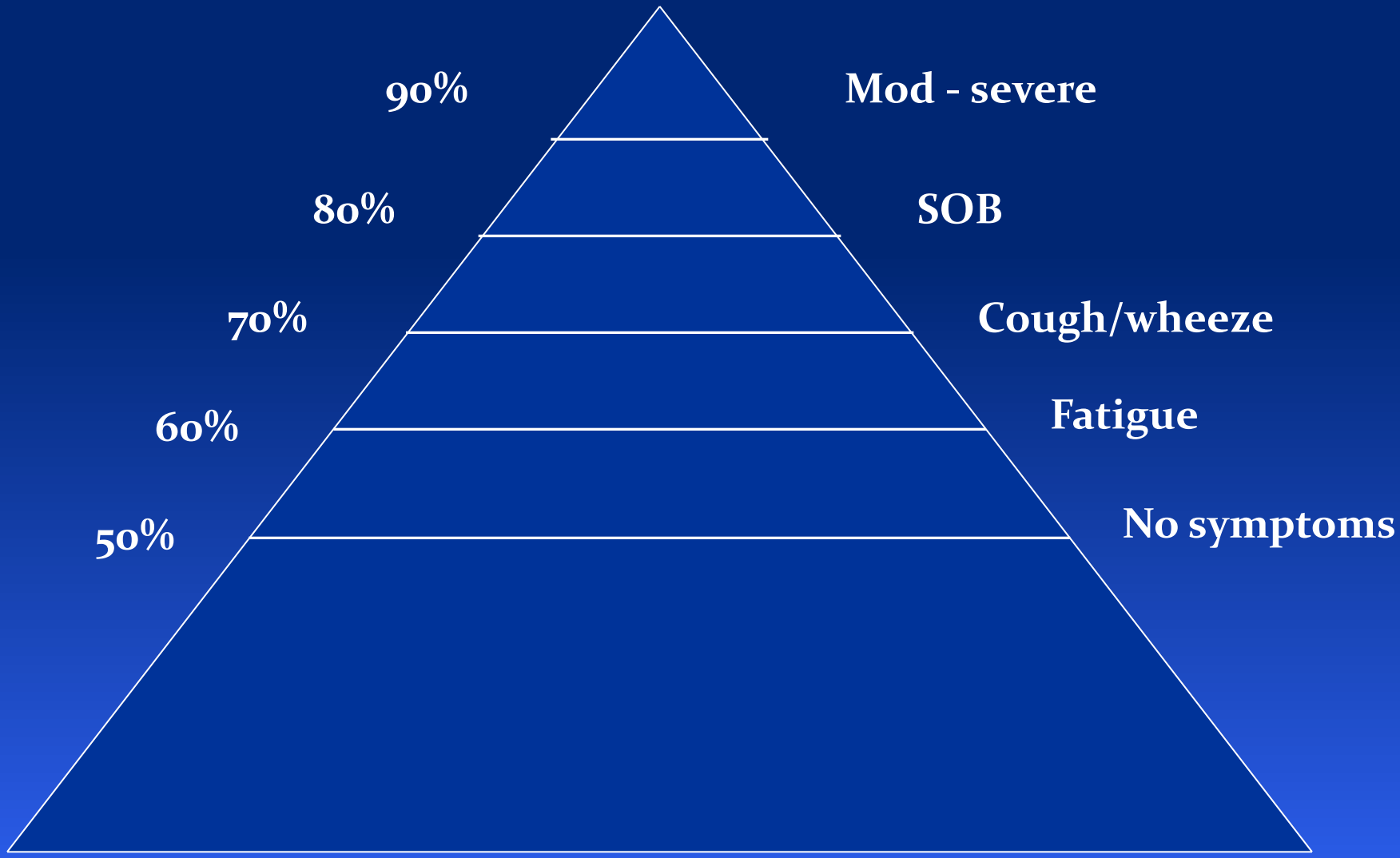


Patients (%) (n=106

Holt NZ Mini Inspire Study 2007

Measuring Asthma Control

ACQ – 5	- Asthma Control Questionnaire
GOAL	- Gaining Optimal Asthma Control
GINA	- Global Initiative for Asthma
ACT	- Asthma Control Test - NZ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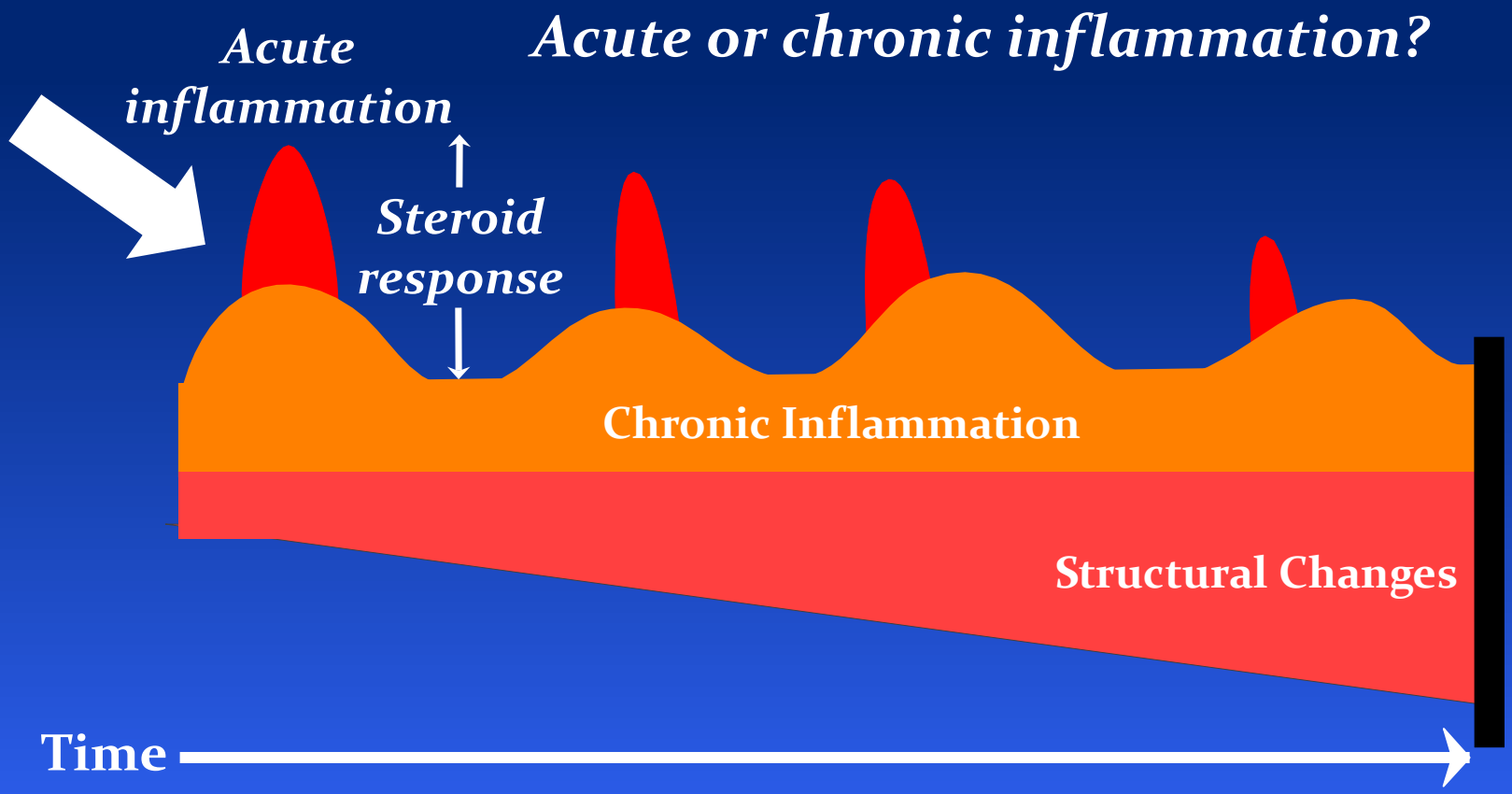
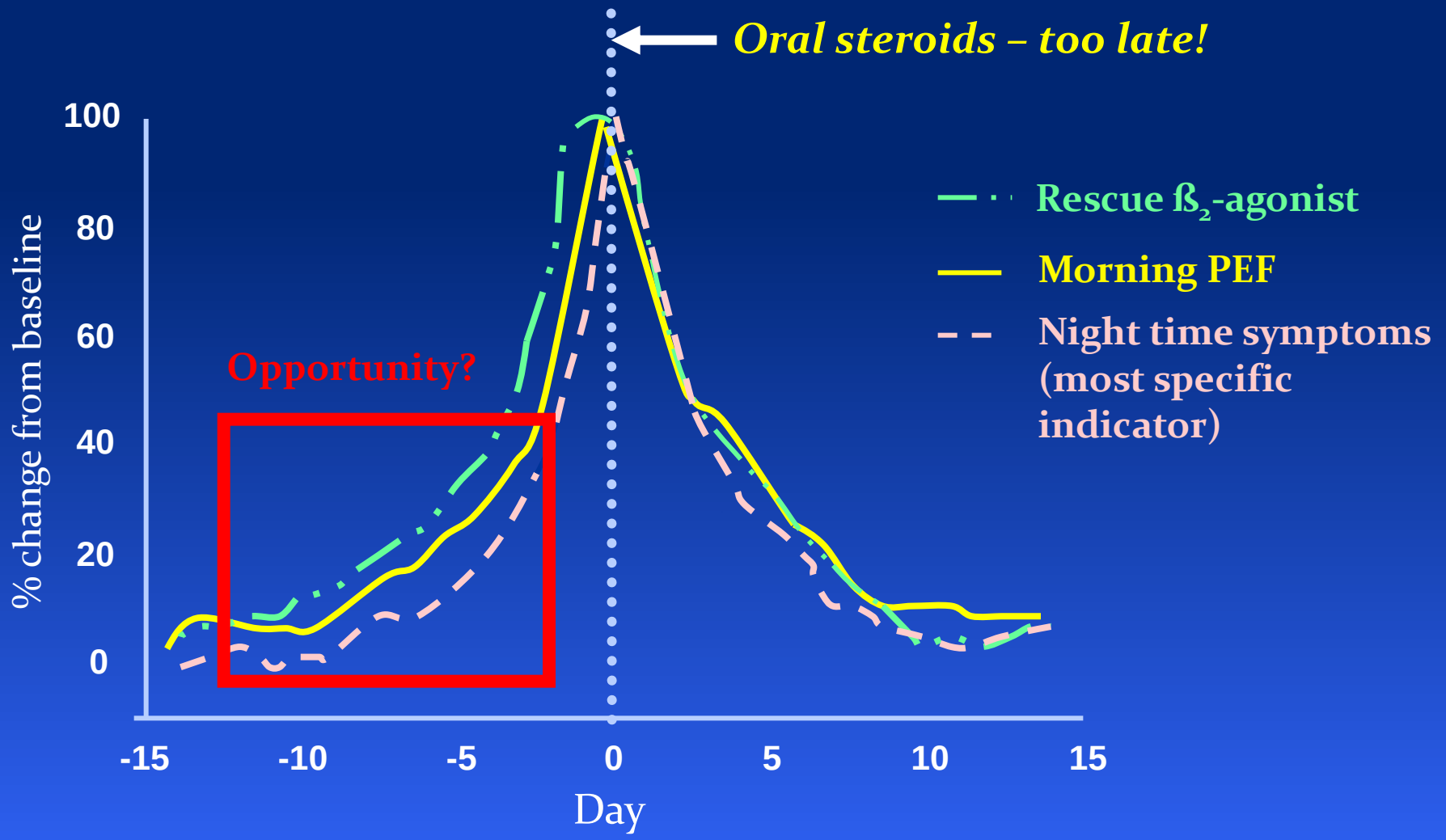
Inflammation in Asthma



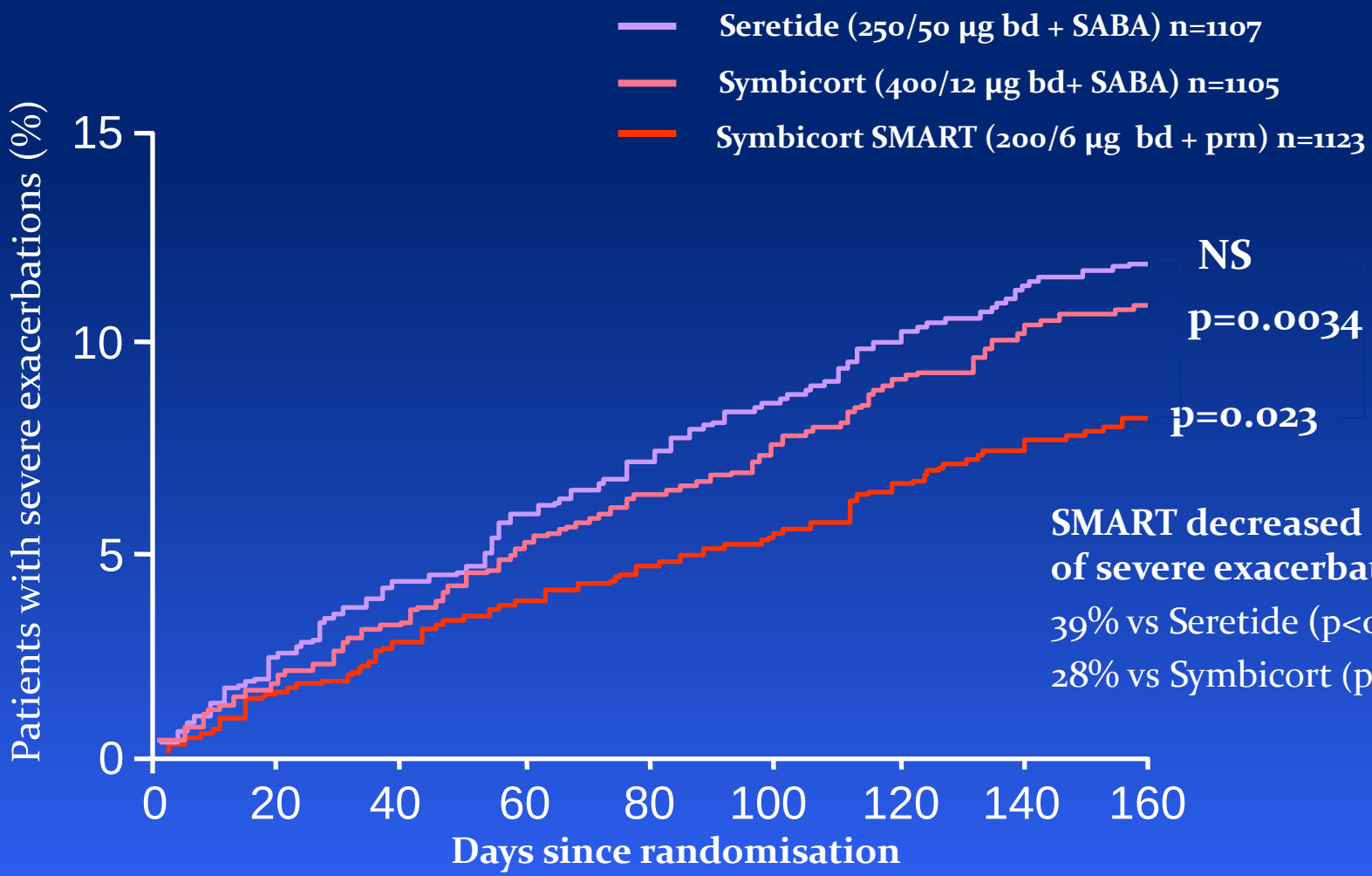
Barnes PJ

Opportunity for Early Intervention?



425 severe exacerbations in the FACET Study. Tattersfield A *et al. AJRCCM* 1999; 160: 594–9.

Time to First Severe Exacerbation



SMART decreased number of severe exacerbations by

39% vs Seretide (p<0.001)

28% vs Symbicort (p<0.01)

Kuna P *et al. Int J Clin Pract* 2007; 61(5): 725-736

SMART Criticism

K. Chapman, N. Barnes, A. Greening et al
Thorax June 2010, 65:747-752

1. SMART vs other combination
   - not blinded
   - poor dose adjustment strategy in fixed arm

2. Poor asthma control
   - selected “severe” patients
   - only 17% achieve control

SMART Criticism

K. Chapman, N. Barnes, A. Greening et al
Thorax June 2010, 65:747-752

4. Sputum and biopsy eosinophilia??

SMART Summary(Steve's)

- SMART "at least equal"??
- Beware Underlying "Control"
- Patient adherence paramount !

Future and Pearls?

- 24 hour LABA and steroid
- Adherence improvements- ACT
- Asthma vs COPD – ICS? Unopposed LABA?
- Selective B Blockers safe
- Intermittent ICS in kids = continuous?
- ASA, all COX and ? paracetomol

Take Home

- All that wheezes is not asthma
- Twitchy or eosinophils responds steroids
- Adherence paramount
- Combination cornerstone
- Consider single inhaler therapy- caveats
- Distinguish Asthma vs COPD re Tio and ICS
- Unopposed LABAs? (= NO in Asthma !)

Which long-acting in Step 2 COPD?

POET – COPD – Vogelmeier et al; NEJM Mar, 2011

n = 7376 – Salm vs Tio 1 year

- Time to first exacerbation

  - symptom increase > 3 days needing steriods/Abx

Which long-acting in COPD?

- > 40; $FEV_{1.0}$ < 70% pred; prev exacerbation
  (mean 50% pred)

- ICS with Tio = 18%
  ICS with LABA = 43%

Any ICS = 53.6%

Which long-acting?

Time to exac = Tio – 187 days
Salm – 145 days

exac = Tio 0.64/yr
Salm 0.72/yr

Intermittent ICS ?

N = 278 Age 1 – 4 ½ "Recurrent wheezer"
Inhaled Therapy

Bud 1 mg bid x 7/7	vs	0.5 mg nocte x 1 yr
- 0.95 exac/year		0.97 exac/year

Same time to first

Same A/E

(104 mg Bud less)

Zieger et al

N.Engl.J.Med 2011; 365(21):1990-2001

B-Blockers and Asthma (Thorax 2011: 66(6):502-7)

Observational 53,994 asthma/ 1527 B blocker/ 441 with "active" asthma
Scotland Database 1.76 million

F/U – 367 patients

→ Pre-B-Blockers - 3.4 pts / 2 weeks given rescue Pred

Post B-Blockers - 3.0 pts week 0-2/ wk 2-4

= ? No change??

Montelukast vs Fluticasone

Pediatrics 2005 Aug 116 (2): 360-9

MOSAIC Study n = 495 Age 6 -14 12 mo.

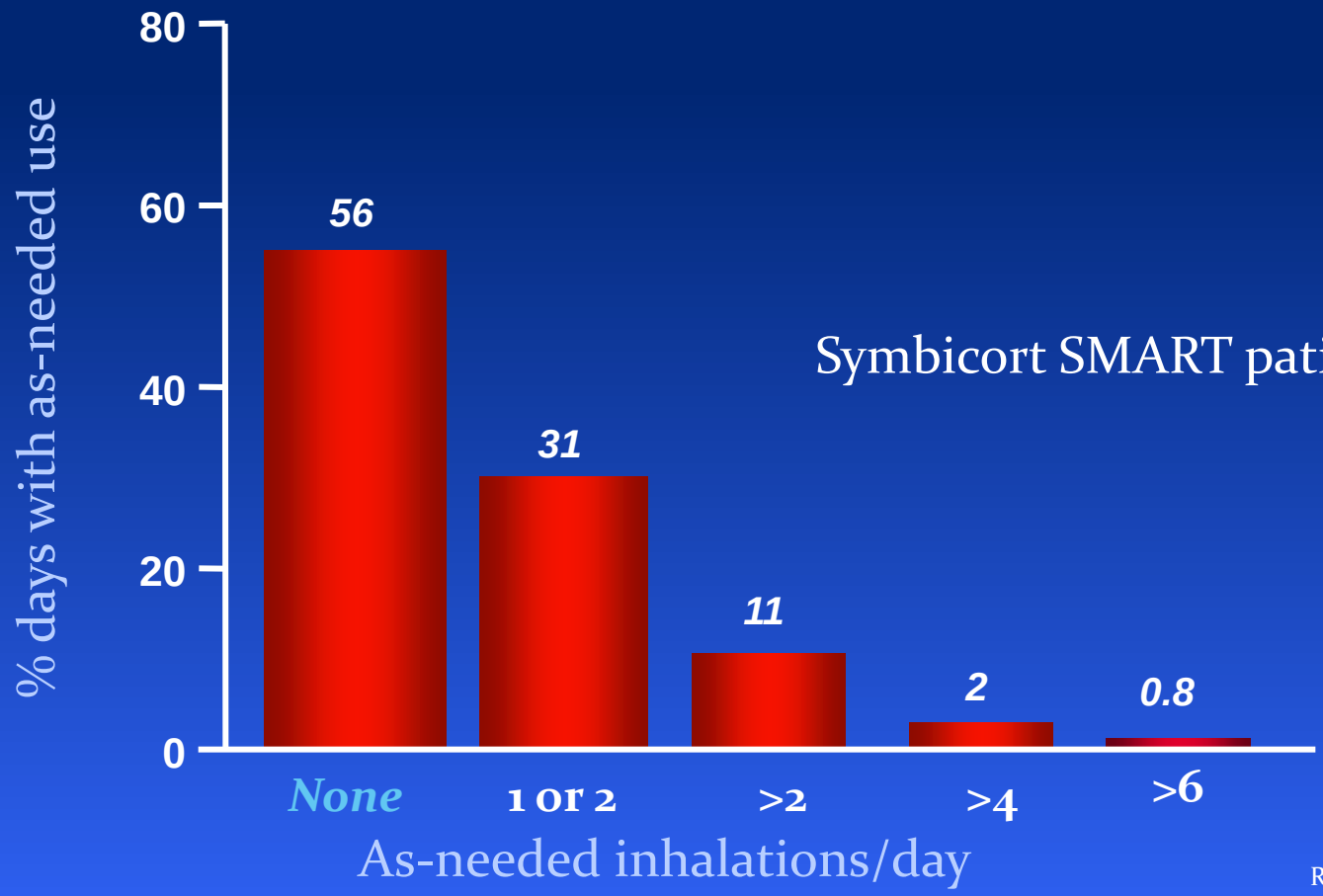
- Flutic 100 bid vs Montelukast 5 mg daily
- Rescue Free days
  84% Montelukast – no significant difference
  86.7% Flixotide
- QOL, $FEV_{1.0}$ better with Flixotide

Asthma and ASA/NSAID/ COX 2

- Asthma induced within 2-4 hours ingestion
- Up to 20% of asthmatics
- Nasal polyps and dipping = Samter's
- Due to COX 1 inhibition ie BOTH aspirin and NSAIDs
- Theoretically safe with COX 2….but
- Note Paracetamol reports

As-needed use of Symbicort SMART in Five Studies

Combined Data (STEAM, STAY, STEP, SMILE & COMPASS)

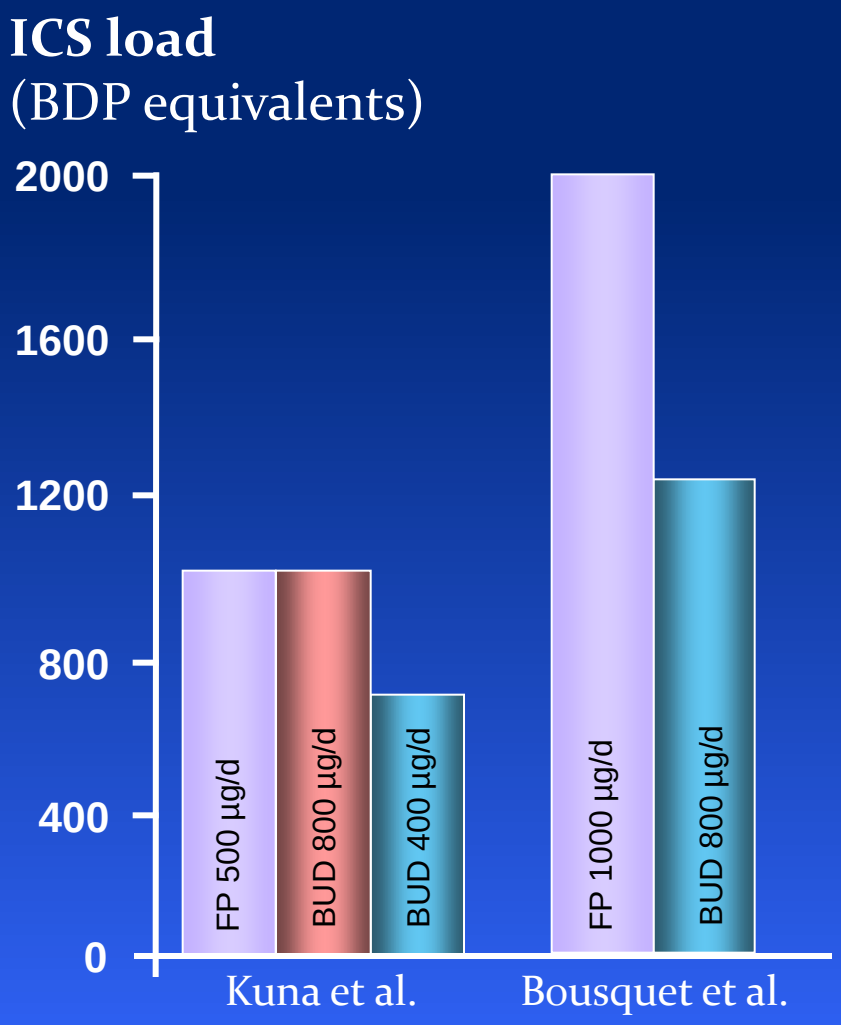


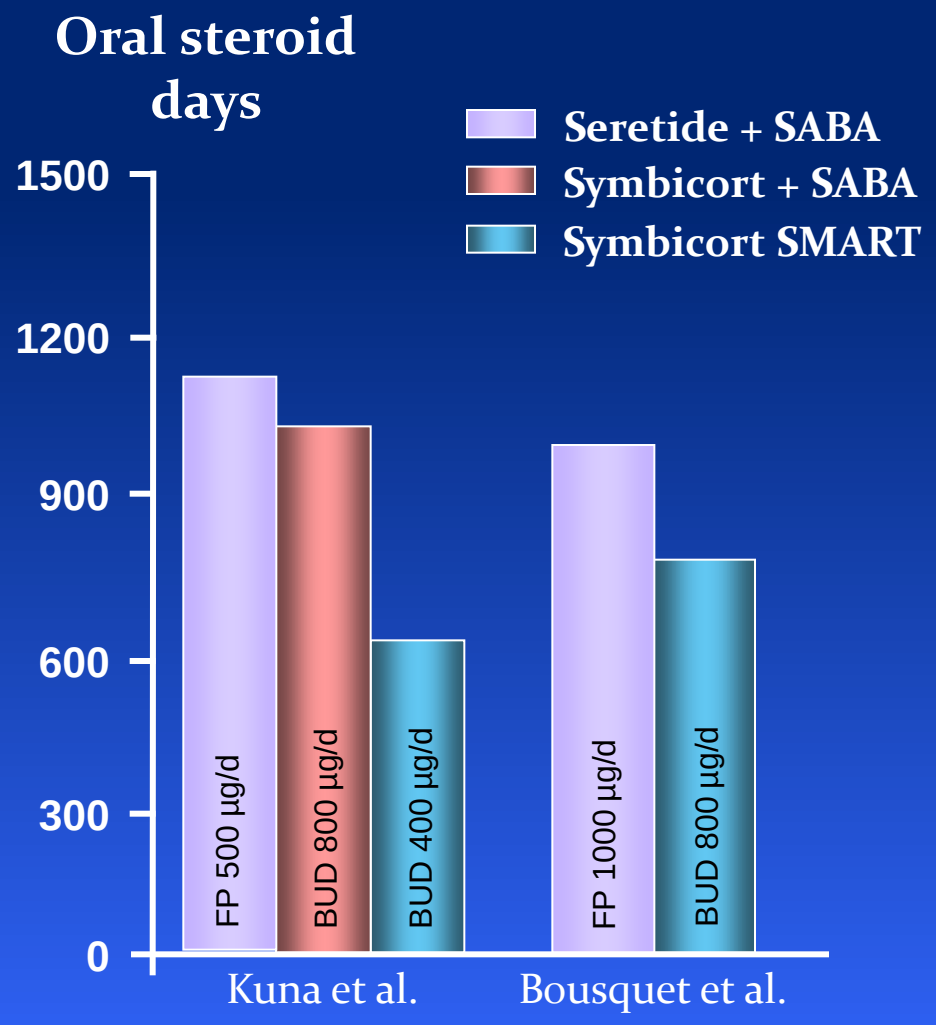
Symbicort SMART patients (n=4417)

Rabe KF, *et al. Chest* 2006;129:246–256;
O'Byrne PM, *et al. Am J Respir Crit Care Med* 2005;171:129–136;
Scicchitano R, *et al. Curr Med Res Opin* 2004;20:1403–1418;
Rabe KF, *et al. Lancet* 2006;368:744–753; Kuna P, *et al. Int J Clin Pract* 2007;61:725-736.

Lower steroid load for Symbicort SMART

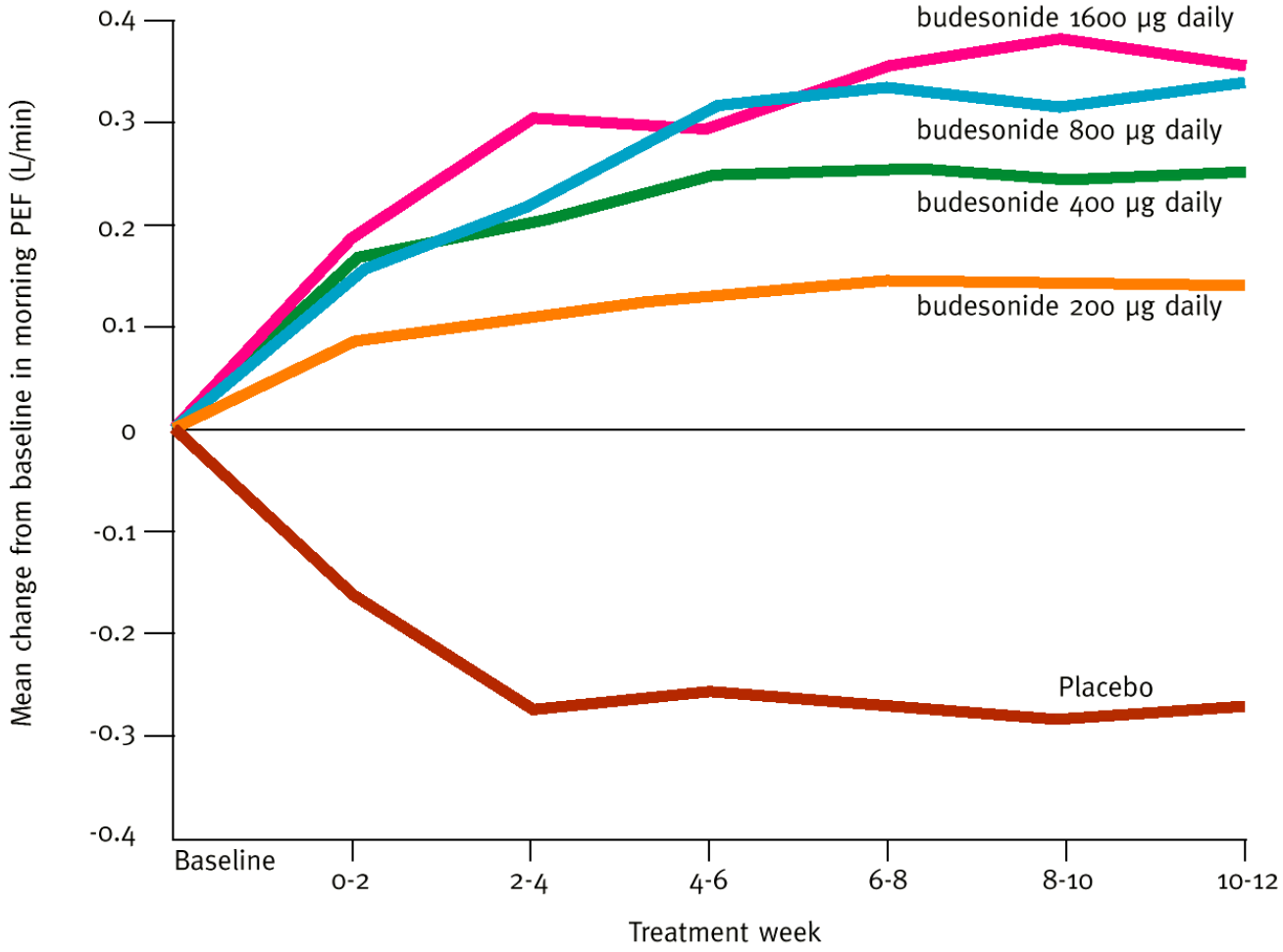
compared with ICS/LABA+SABA





Kuna P, et al. Int J Clin Pract 2007
Bousquet J, et al. Respir Med 2007

Dose Response of ICS



Adapted from Busse 1998[1]

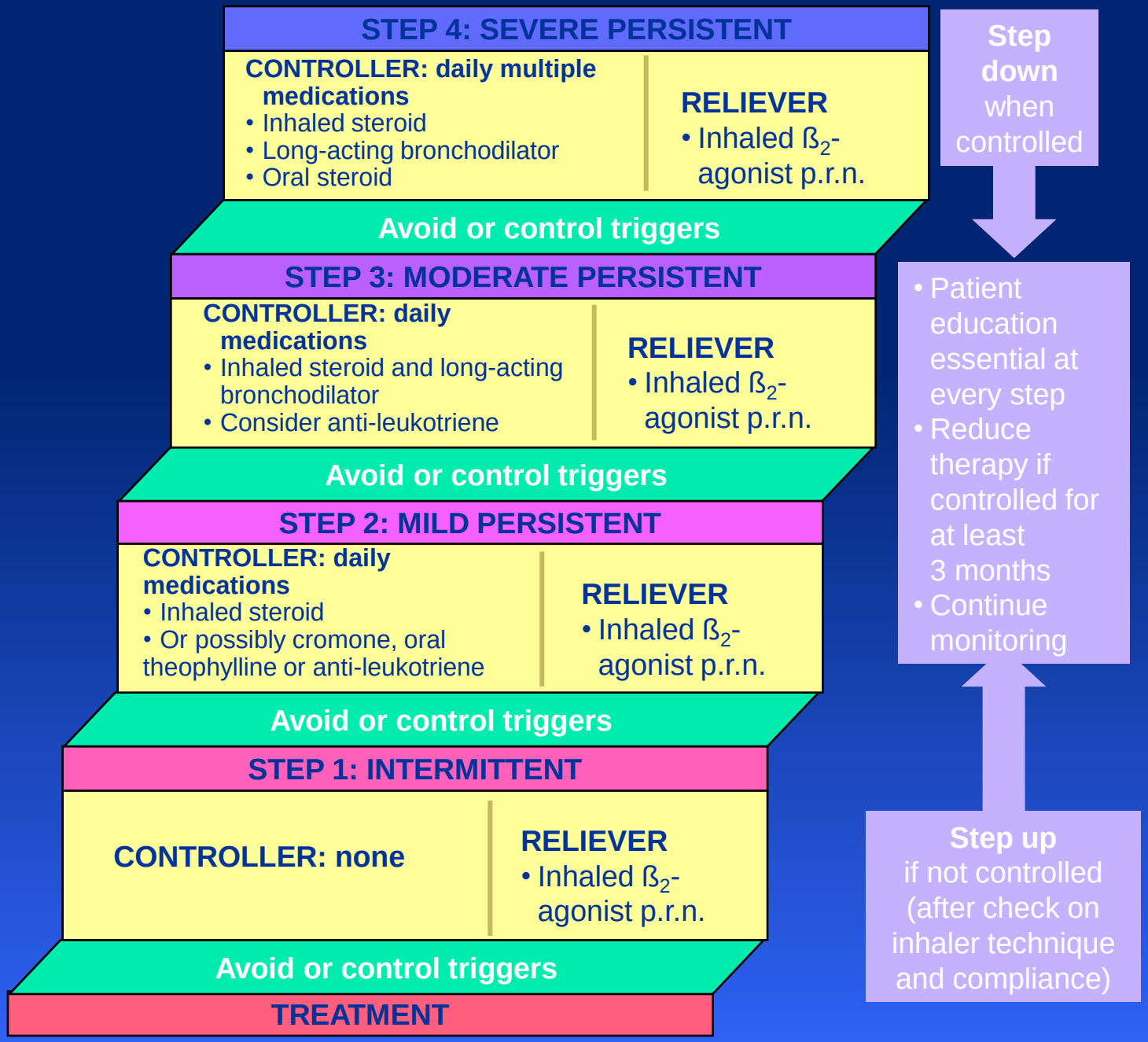
Summary

When will spirometry help me ?

1. Obstruction or restriction ?
   - Asthma, COPD, bronchiectasis, CHF, fibrosis, etc.

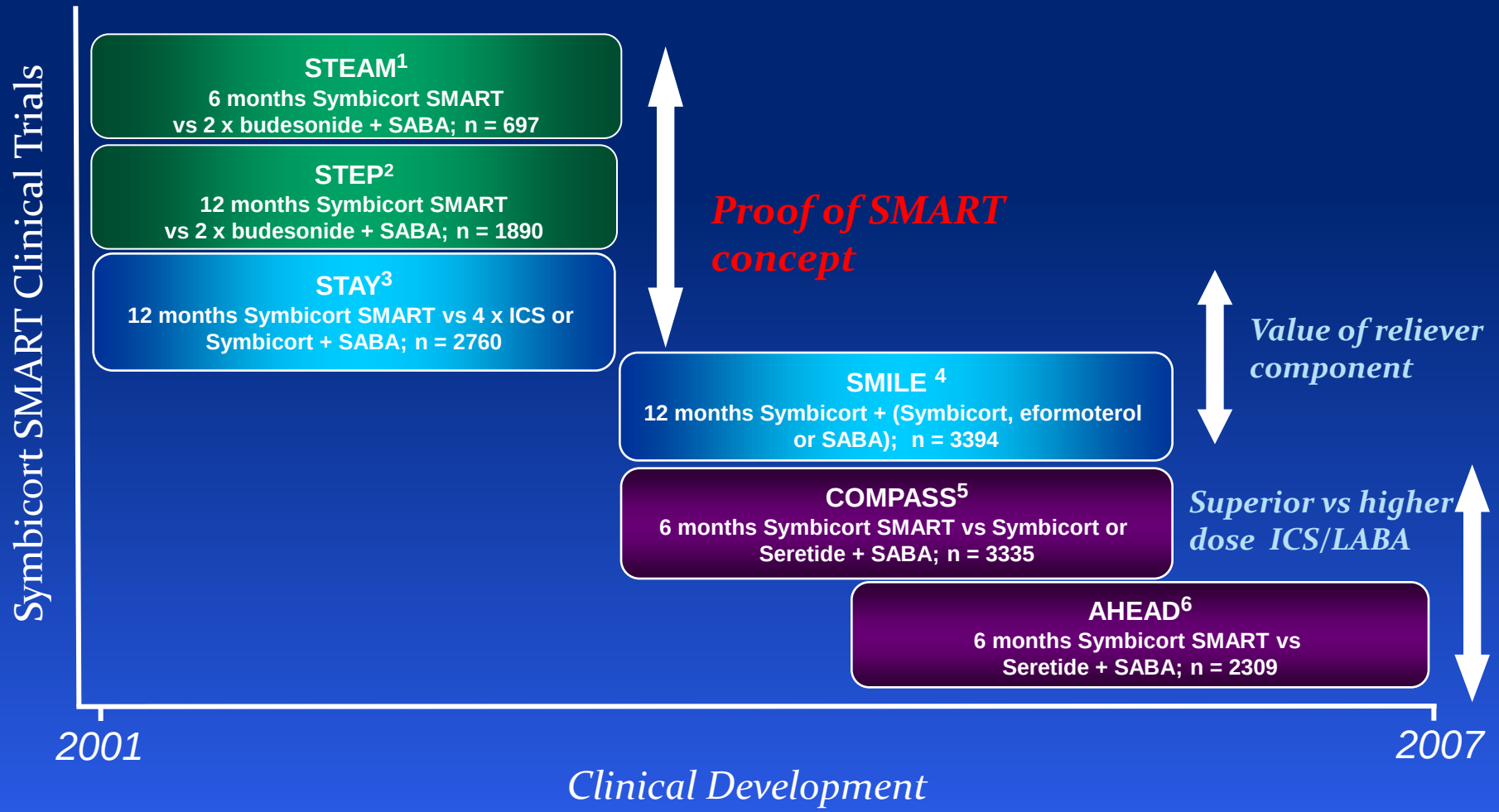
2. How severe ?
   - ABG, O_2, Tiotropium / LABA, pre-op

3. Reversibility ?



GINA Guidelines 1998

Symbicort SMART: Clinical Programme
(six double-blind studies in >14,000 patients)



[1]Rabe KF, et al. Chest 2006; [2]Scicchitano R, et al. Curr Med Res Opin 2004; [3]O'Byrne PM, et al. Am J Respir Crit Care Med 2005; [4]Rabe KF et al Lancet, [5]Kuna P, et al. Int J Clin Pract 2007; [6]Bousquet J, et al. Respir Med 2007

Demoly et al

- SMART vs Dr's choice ("best practice")

  - 29% greater likelihood "well controlled"

  - 15% fewer exacerbations

  - 27% less ICS

Demoly et al, Respiratory Medicine 2009

LABA & SMART
NZ Perspective – Julian Crane

LABA - No mortality change with introduction at bid
- SABAs risk is dose dependent !!

Beware SMART “overuse” and in “acute”

Stress and Asthma

(Eur Respiratory Journal 2011; 37(5):1068-75)

n = 1772 Germany General Population

PTSD ↑ Asthma related symptoms (OR – 3.2 – 8.8)

↑ Airflow obstruction ! (OR – 4.2 – 7.8)

“Asthma nervosa” - ? Pro inflammatory

Asthma Prevention

Primary	Secondary
Smoking – passive	Housing
– active	Dust mite
	Medications
	Wood burning
	Pollution
	etc

22 year old presents with aspirin induced wheezing; Is it safe for them to take NSAIDS?

- Yes
- No

What is the goal of asthma treatment?

a) Prevent exacerbations
b) Improve quality of life
c) Prevent long-term disability
d) Decrease mortality

Daily or intermittent budesonide in preschool children with recurrent wheezing

Authors: Zeiger RS et al

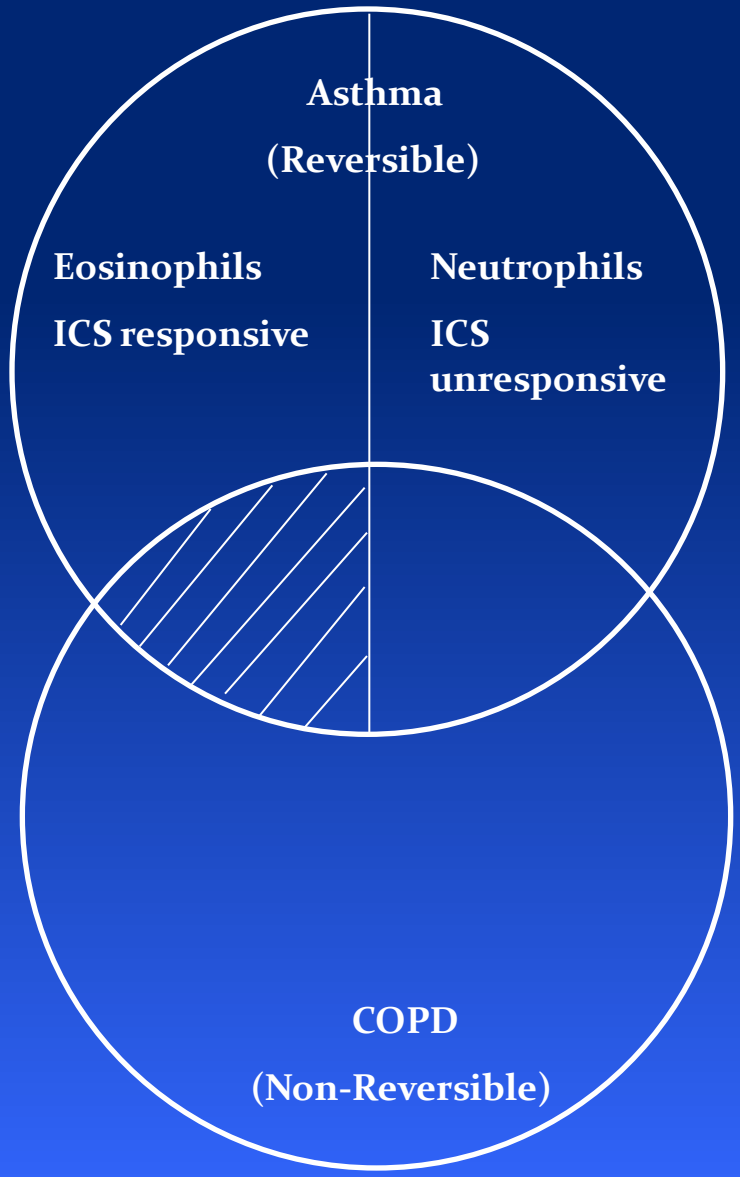
Summary: This study followed 278 children between the ages of 1 and 4.5 years at risk of developing asthma and who had wheezing episodes during respiratory illnesses but who had very few or no symptoms between episodes. They were randomly assigned to receive a budesonide inhalation suspension for 1 year as either an intermittent high-dose regimen (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness) or a daily low-dose regimen (0.5 mg nightly) with corresponding placebos. There was no between-group difference for the frequency of exacerbations, with a rate per patient-year for the daily regimen of 0.97 (95% CI, 0.76 to 1.22) versus a rate of 0.95 (95% CI, 0.75 to 1.20) for the intermittent regimen (relative rate in the intermittent-regimen group, 0.99; 95% CI, 0.71 to 1.35; p=0.60). There were also no significant between-group differences in other measures of asthma severity, including the time to the first exacerbation, or adverse events. The mean exposure to budesonide was 104 mg less with the intermittent regimen than with the daily regimen.

Comment: The hardest thing in the administration of any sort of prophylactic medication is to get patients to take it when they are asymptomatic. This paper represents what I suspect really happens in the "real world". Patients stop their inhaled steroid (how many times do they just want the blue inhaler, as they have plenty of the other one) and start again when they perceive that they are getting an exacerbation. Both groups received the budesonide in a different way to usual administration in New Zealand in so far that it was administered in essentially a nebulised form, in contrast to the Turbuhaler™ in common use here. Nonetheless, the dose given on a regular daily basis (0.5mg) was comparable to both regions. The group who were administered a high dose of budesonide (the equivalent of 5 inhalations of the 200 µg strength Turbuhaler™ twice daily) early on in what was perceived to be an impending asthma attack were no worse off in overall outcome, and also this group had a reduction in total budesonide administration. My only comment would be, as with the promoted SMART© regime for adults, to closely monitor total steroid dose and select patients carefully – there are horses for courses!

Reference: N Engl J Med. 2011;365(21):1990-2001.

http://www.nejm.org/doi/full/10.1056/NEJMoa1104647

Airflow Obstruction



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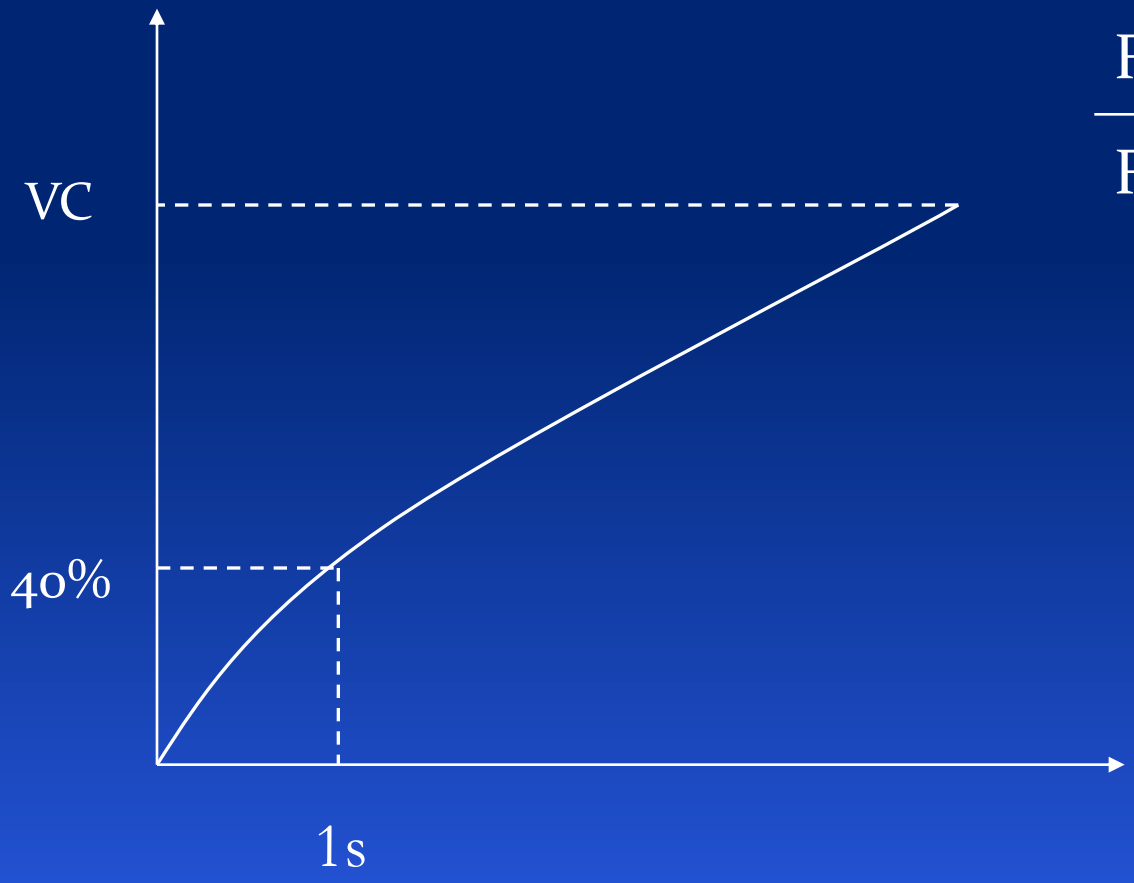

$$\frac{FEV_{1.0}}{FVC} < 0.70$$