GlaxoSmithKline

Breakfast Session

Prof Neil Barnes

Professor of Respiratory Medicine
London Chest Hospital &
The Royal London Hospital
United Kingdom

Beyond Symptoms: Addressing Future Risk in Asthma - GlaxoSmithKline Breakfast Session

Sunday, 18 August 2013 Start 7:30am Duration: 45mins Plenary

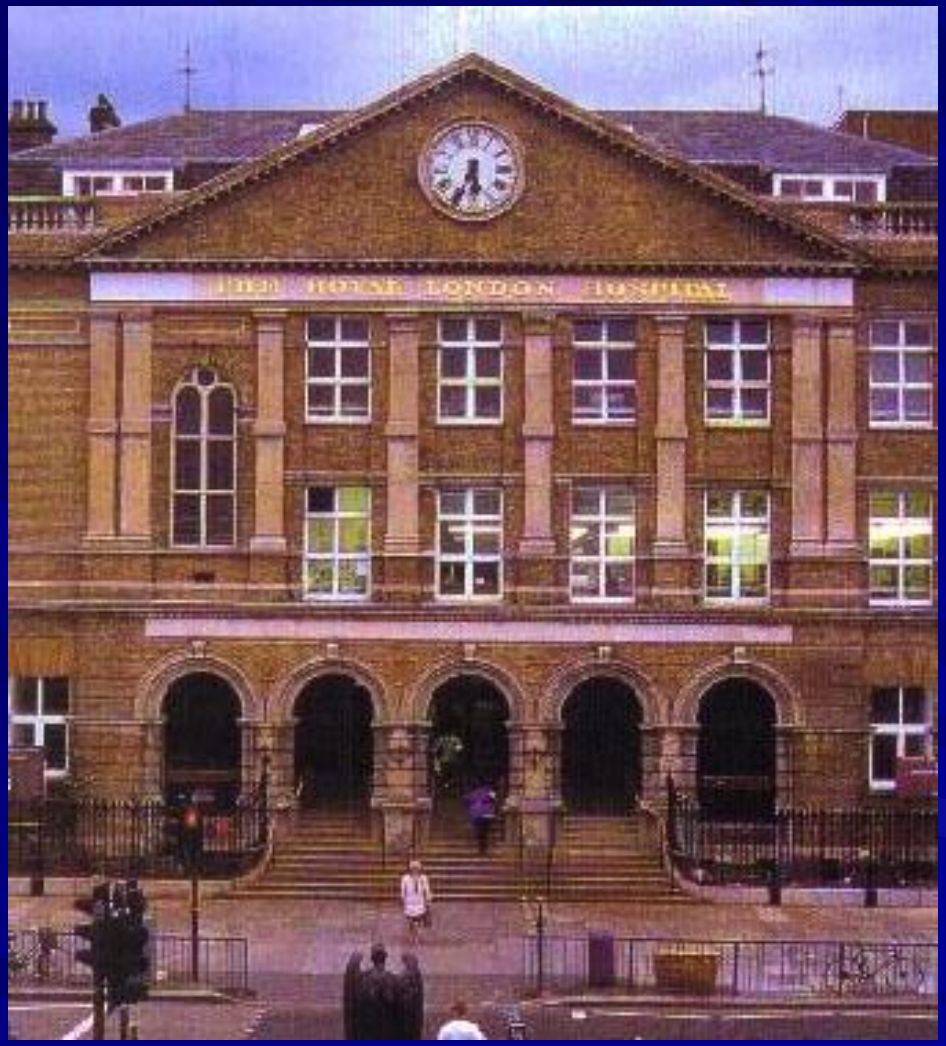
BEYOND SYMPTOMS ADDRESSING FUTURE RISK IN ASTHMA

South GP CME 2013, Dunedin Sunday 18th August 2013

Professor Neil Barnes
Consultant Respiratory Physician
London Chest Hospital, Bart`s Health NHS Trust
Bart`s and the London School of Medicine and Dentistry

neil.barnes@bartshealth.nhs.uk


© XPOSURE


LONDON

DISCLAIMER

Professor Neil Barnes, has been appointed GSK Global Respiratory Medical Head effective 1st October 2013.

WHAT IS GOOD ASTHMA CONTROL?

- no (or minimal) daytime symptoms
- no nocturnal symptoms or awakenings
- no (or minimal) need for “rescue” treatment
- no limitations on activities
- (near) normal lung function
- no exacerbations

UK ASTHMA GUIDELINES – BTS/SIGN 2011

- No daytime symptoms
- No night-time awakening due to asthma
- No need for rescue medication
- No exacerbations
- No limitation on activity including exercise
- Normal lung function (FEV_1 and/or PEF >80% predicted or best) with minimal side effects

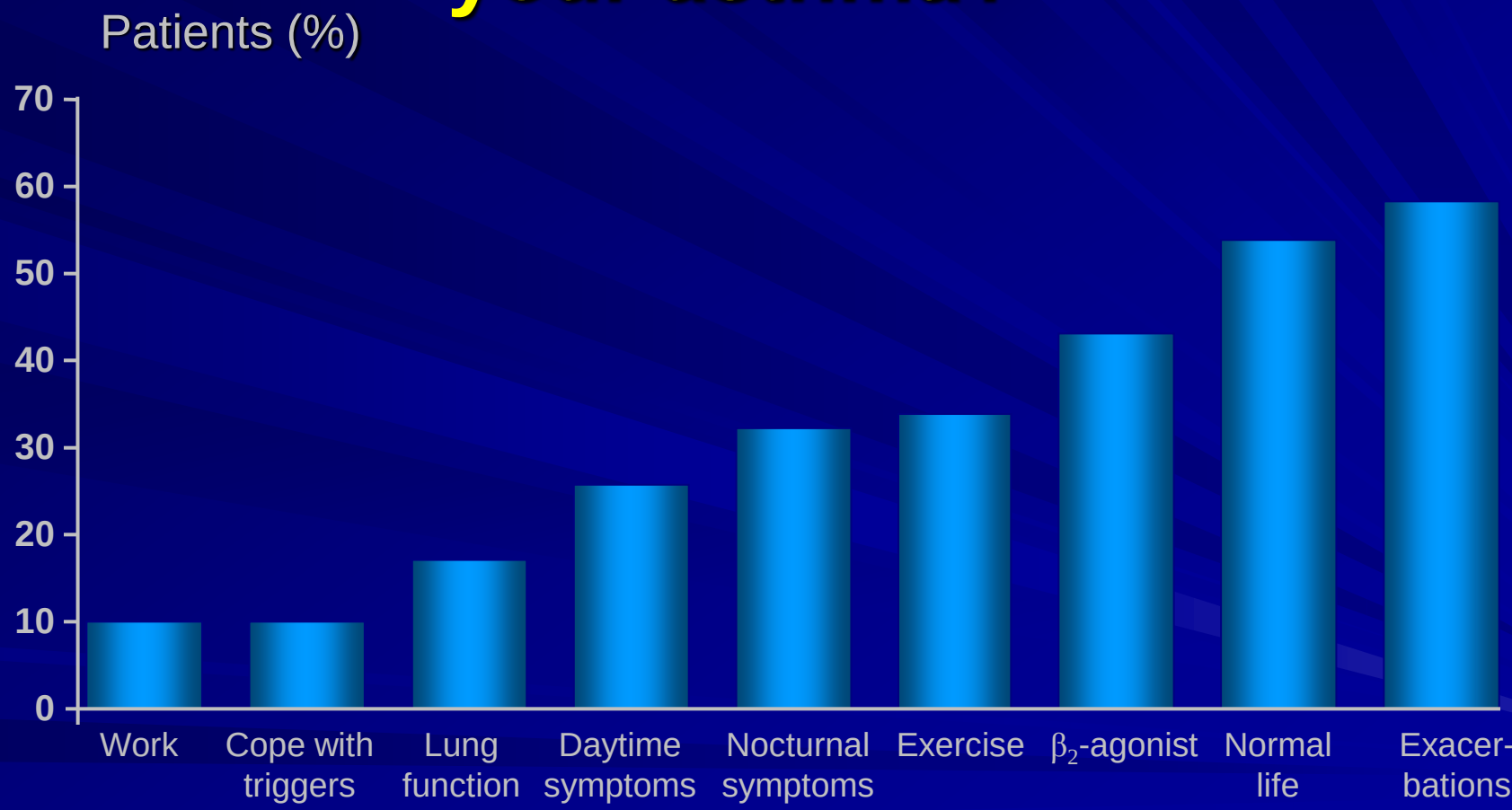
- May need to vary for individual patients

WHY AIM FOR CONTROL?

- Patient`s perspective
- Clinician`s perspective
- Payer`s perspective

PATIENT PERSPECTIVE

What do you want to be better about your asthma?



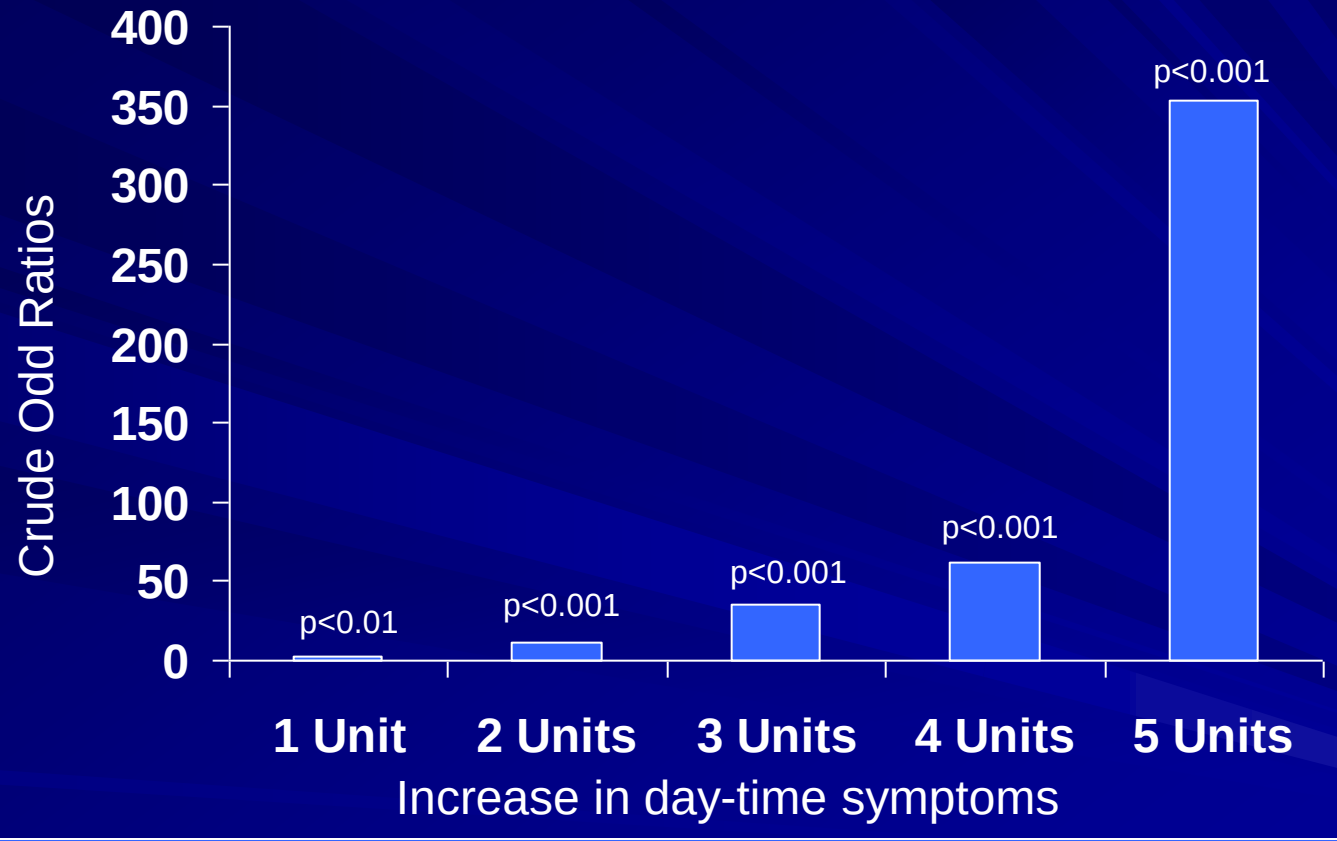
Price & Pearson. ATS 1998

WHAT PREDICTS AN EXACERBATION?

- Database of over 1000 patients followed for one year in the TRUST study
- Comparison of regular and as required β2 agonists
- Primary outcome measure severe exacerbations
- Daily diary cards and PEF measurements

Dennis et al Clin & Exp Allergy 2005

EFFECT OF DAILY SYMPTOMS ON THE ORS OF STARTING A COURSE OF ORAL CORTICOSTEROIDS



Best predictor of an exacerbation is an increase in day-time symptoms.

Similar findings from the FACET database

Dennis SM, et al. Clin & Exp Allergy 2005

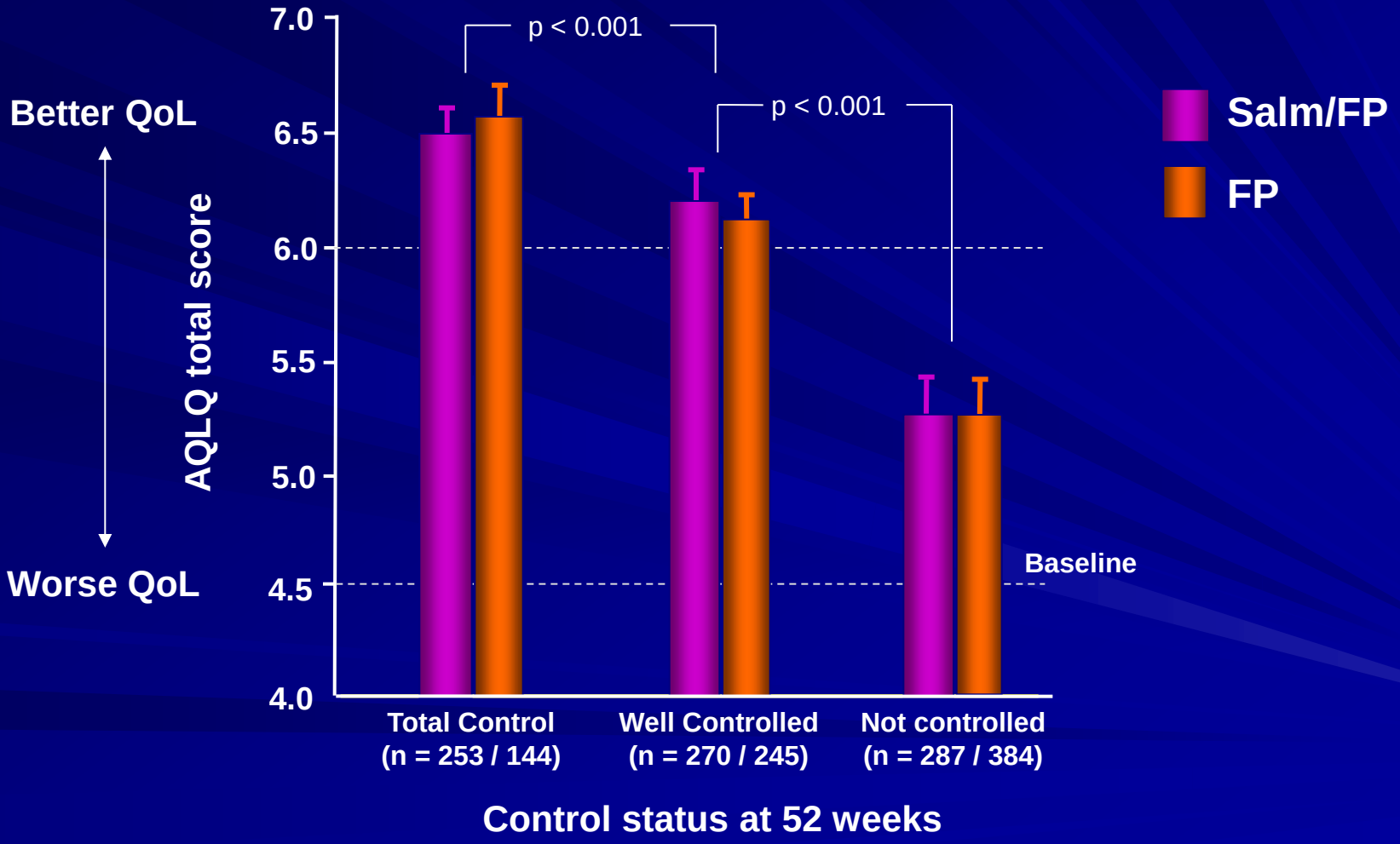
Final 5 items selected for ACT™

Item description	Chi-squared	P value
Shortness of breath	54.4273	0.00001
Patient rating of control	14.1044	0.0002
Use of rescue medication	7.1375	0.0075
Asthma keeps you from getting much done at work / school / home	5.8535	0.0155
Asthma symptoms wake you up	4.1618	0.0413

Based on logistic regression

Nathan et al. J Allergy Clin Immunol 2004

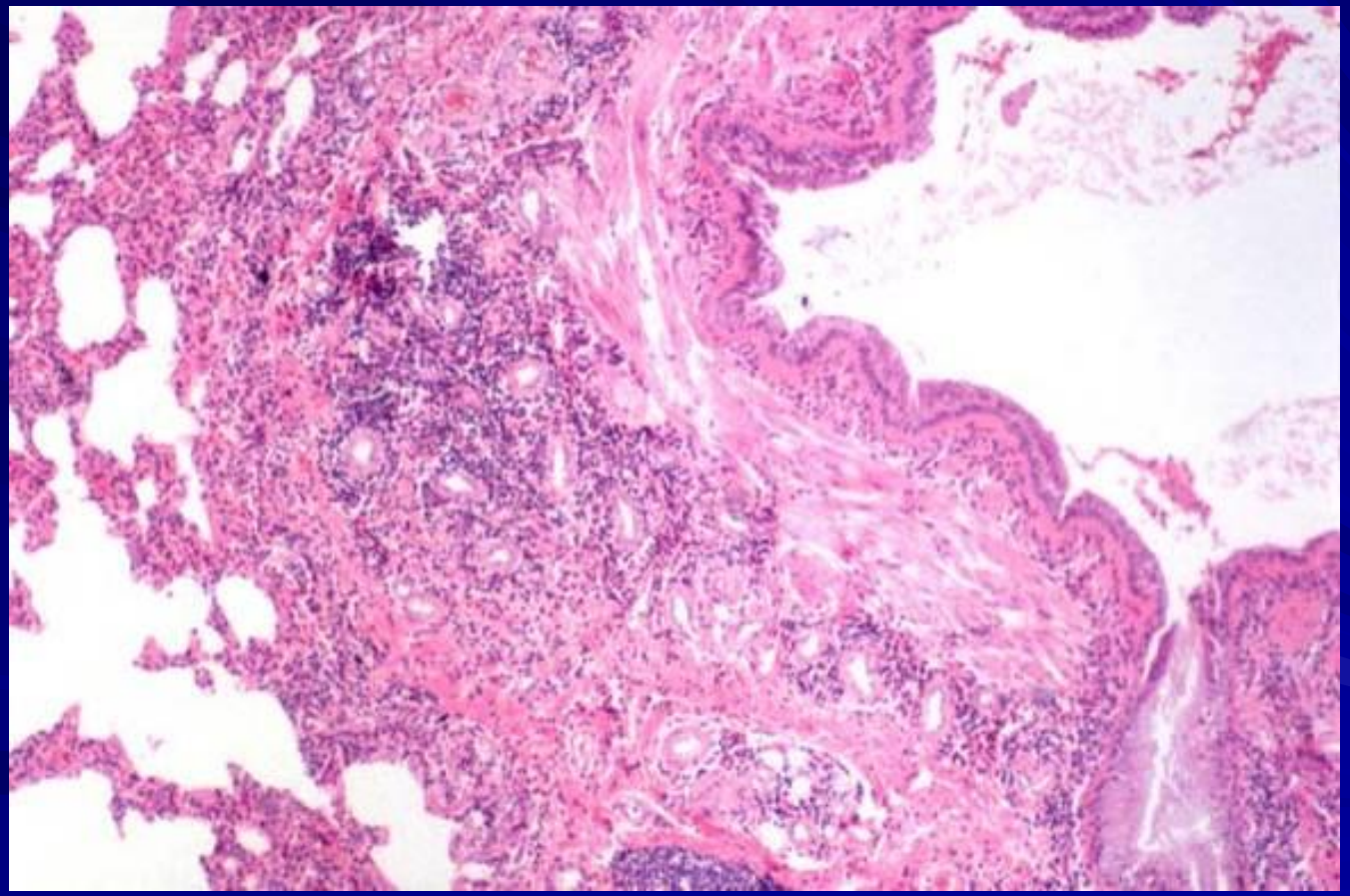
GOAL STUDY: QUALITY OF LIFE AFTER ONE YEAR BY CONTROL STATUS



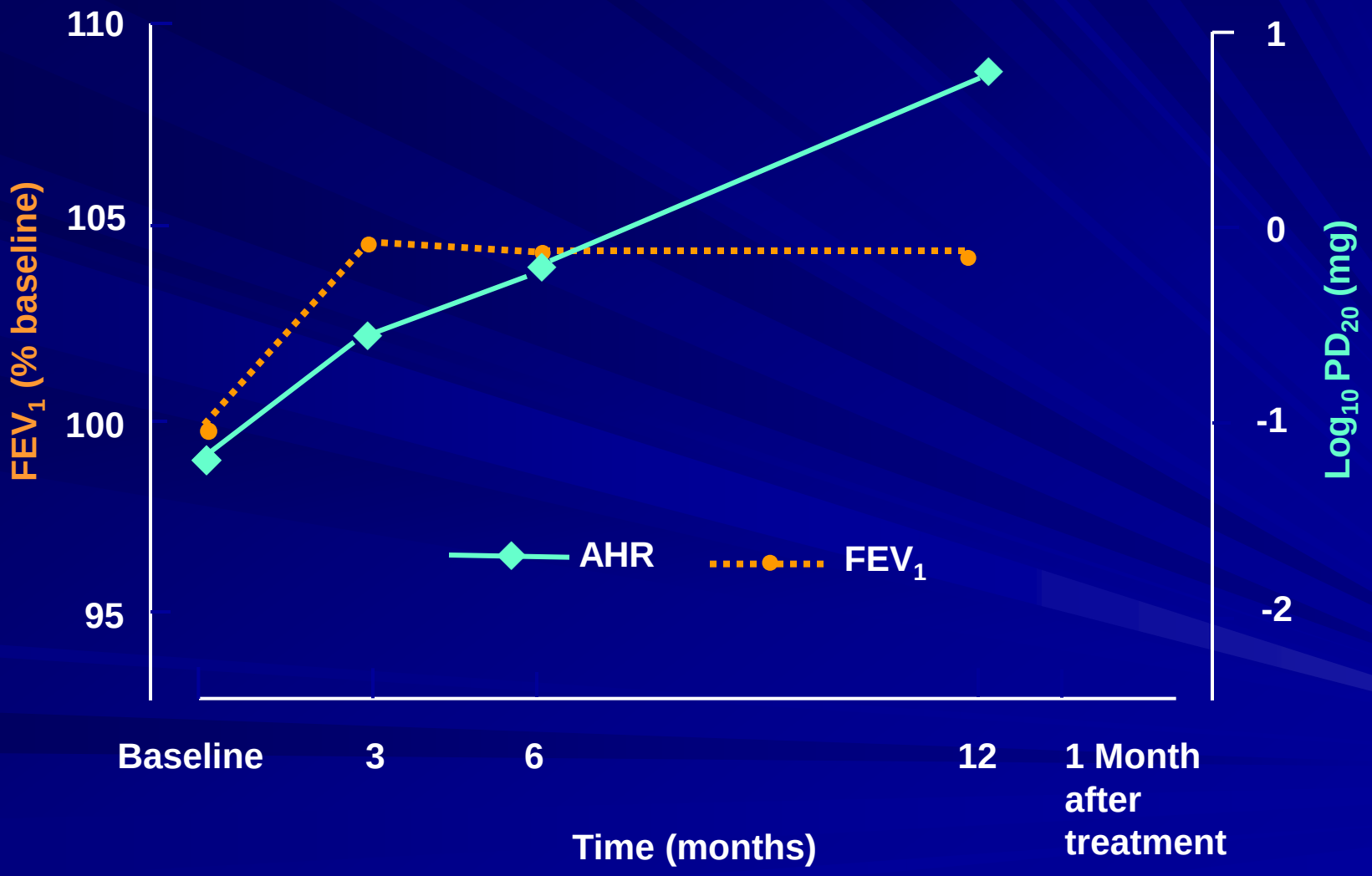
Bateman *et al*. ERJ 2007

CLINICIAN`S PERSPECTIVE

ASTHMA IS AN INFLAMMATORY DISEASE



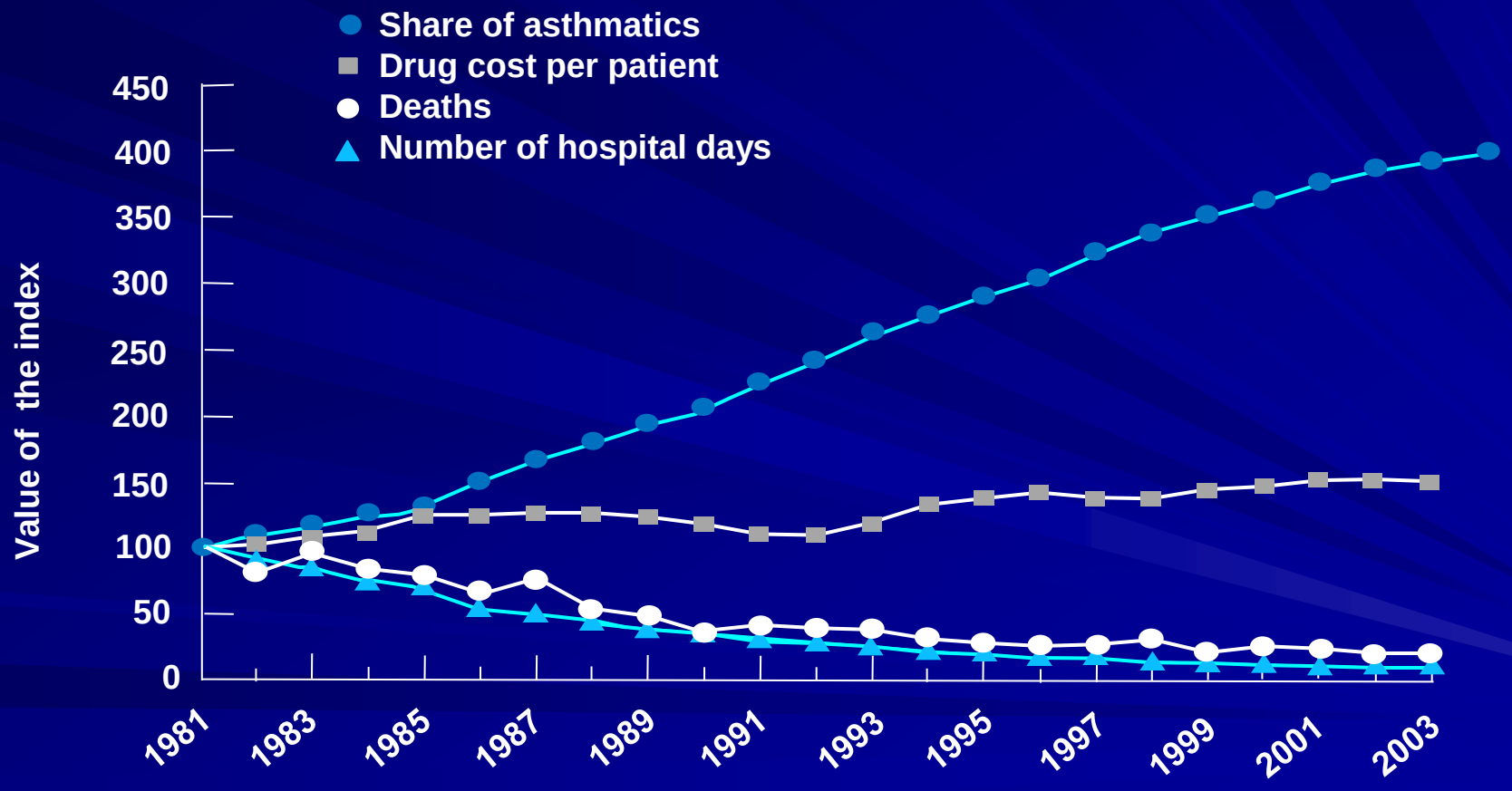
AHR CONTINUES TO IMPROVE EVEN AFTER LUNG FUNCTION HAS PLATEAUED



Ward *et al*. Thorax 2002

PAYER`S PERSPECTIVE

ASTHMA IN FINLAND 1981 - 2003

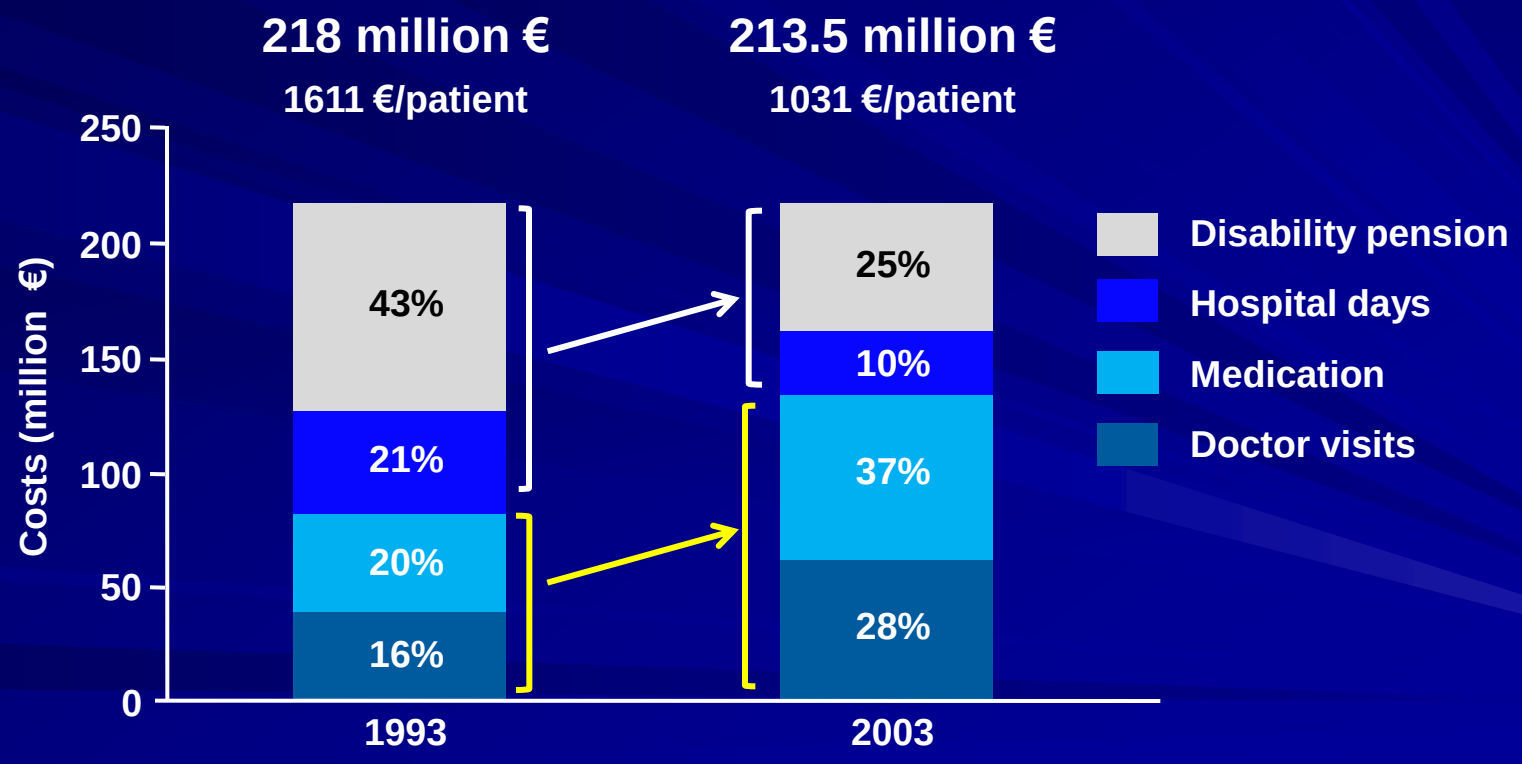


Finnish Asthma Programme 2005

Haahtela et al. Thorax 2006

ASTHMA IN FINLAND 1981 - 2003

Patients are being treated effectively outside the hospital



Haahtela et al. Thorax 2006

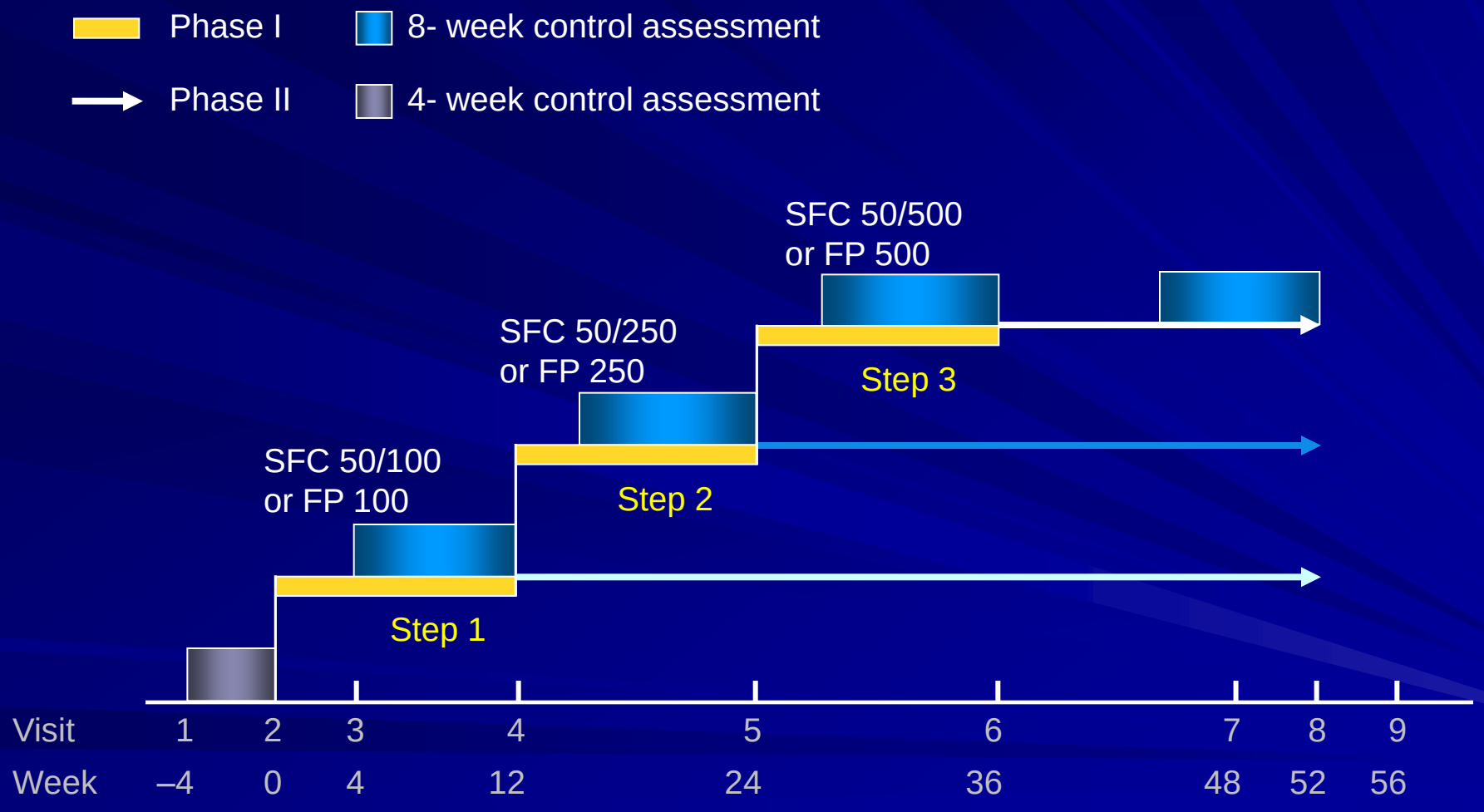
MANAGEMENT APPROACH BASED ON CONTROL

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education **Environmental control**				
As needed rapid-acting ß$_2$-agonist	**As needed rapid-acting ß$_2$-agonist**			
Controller options	**Select one**	**Select one**	**Add one or more**	**Add one or more**
	Low-dose inhaled ICS	**Low-dose ICS plus long-acting ß$_2$-agonist**	**Medium- or High-dose ICS plus long-acting ß$_2$-agonist**	**Oral glucocorticosteroid (lowest dose)**
	Leukotriene modifier	**Medium- or High-dose ICS**	**Leukotriene modifier**	**Anti-IgE treatment**
		Low-dose ICS plus leukotriene modifier	**Sustained release theophyline**	
		Low-dose ICS plus sustained release theophyline		

In most cases, preferred controller option is an ICS/LABA combination

GINA Report 2007

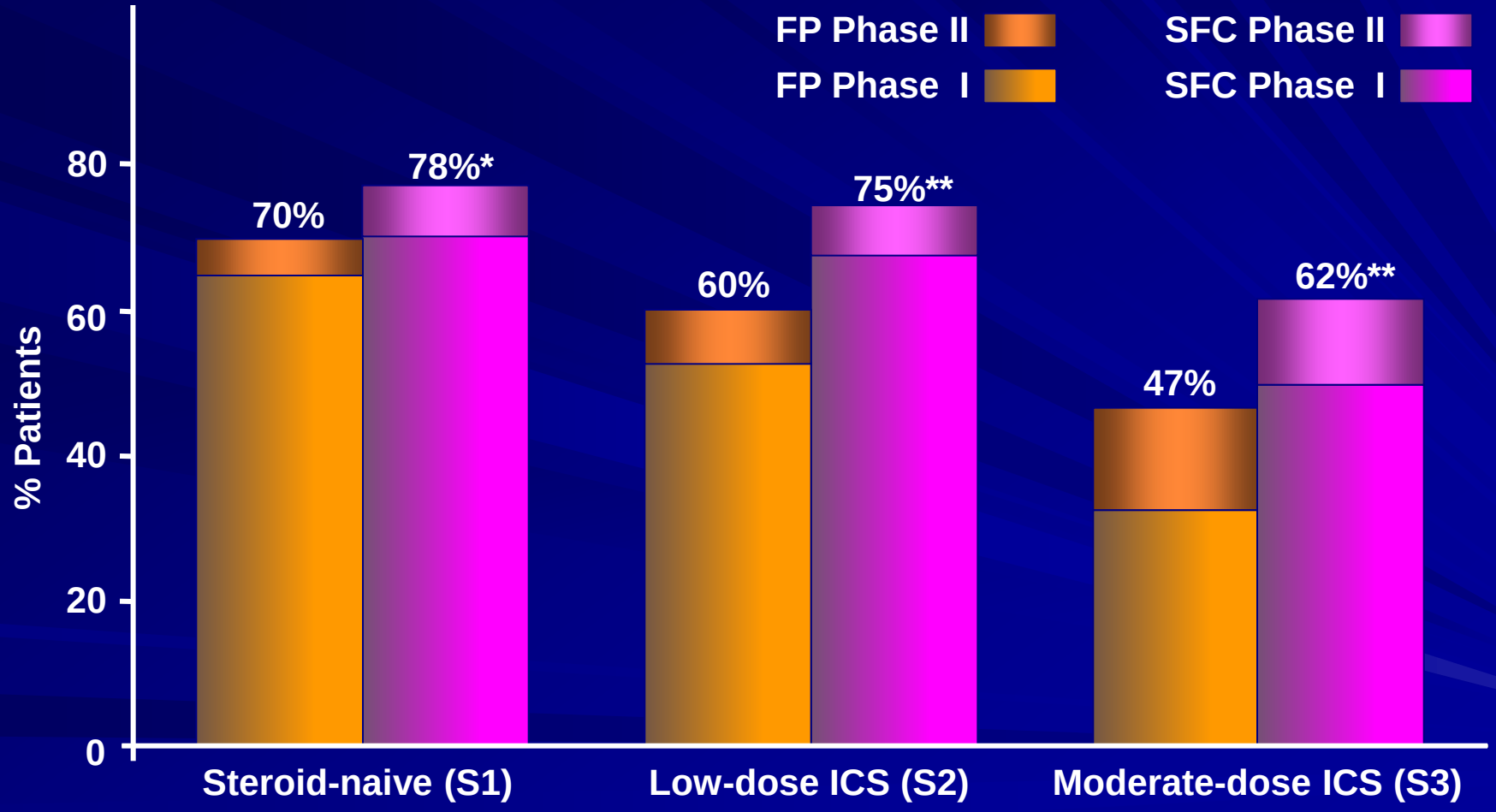
GOAL: STUDY DESIGN



SFC = Salmeterol/fluticasone propionate

GOAL Study, Bateman E, et al. ARJCCM

COMPOSITE MEASURE OF ASTHMA CONTROL: WELL-CONTROLLED ASTHMA OVER 8 WEEK PERIODS (GOAL)



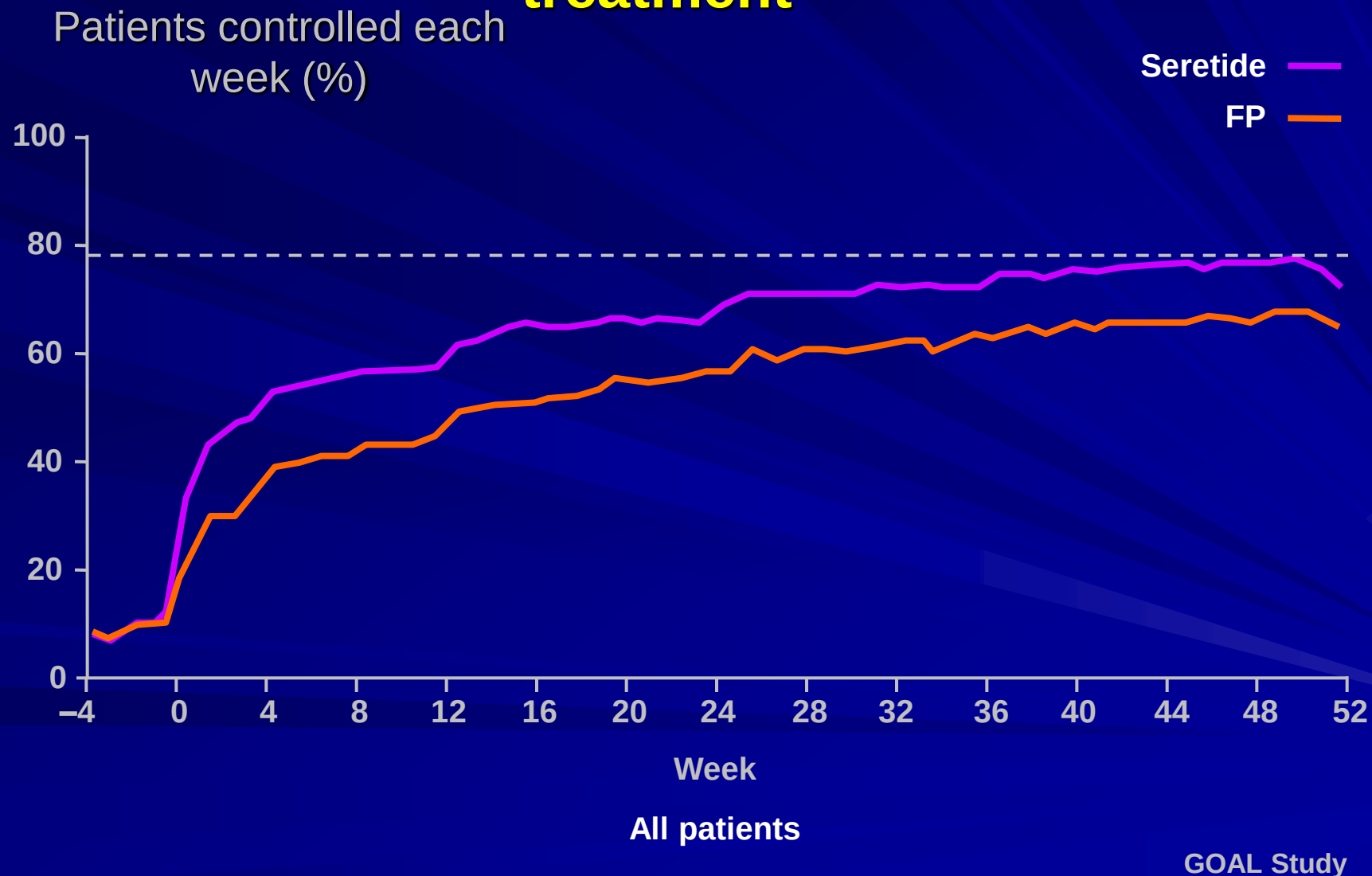
* *P* = 0.003
** *P* < 0.001

SFC = Salmeterol/fluticasone propionate

GOAL Study, Bateman E, et al. ARJCCM

WELL CONTROLLED ASTHMA

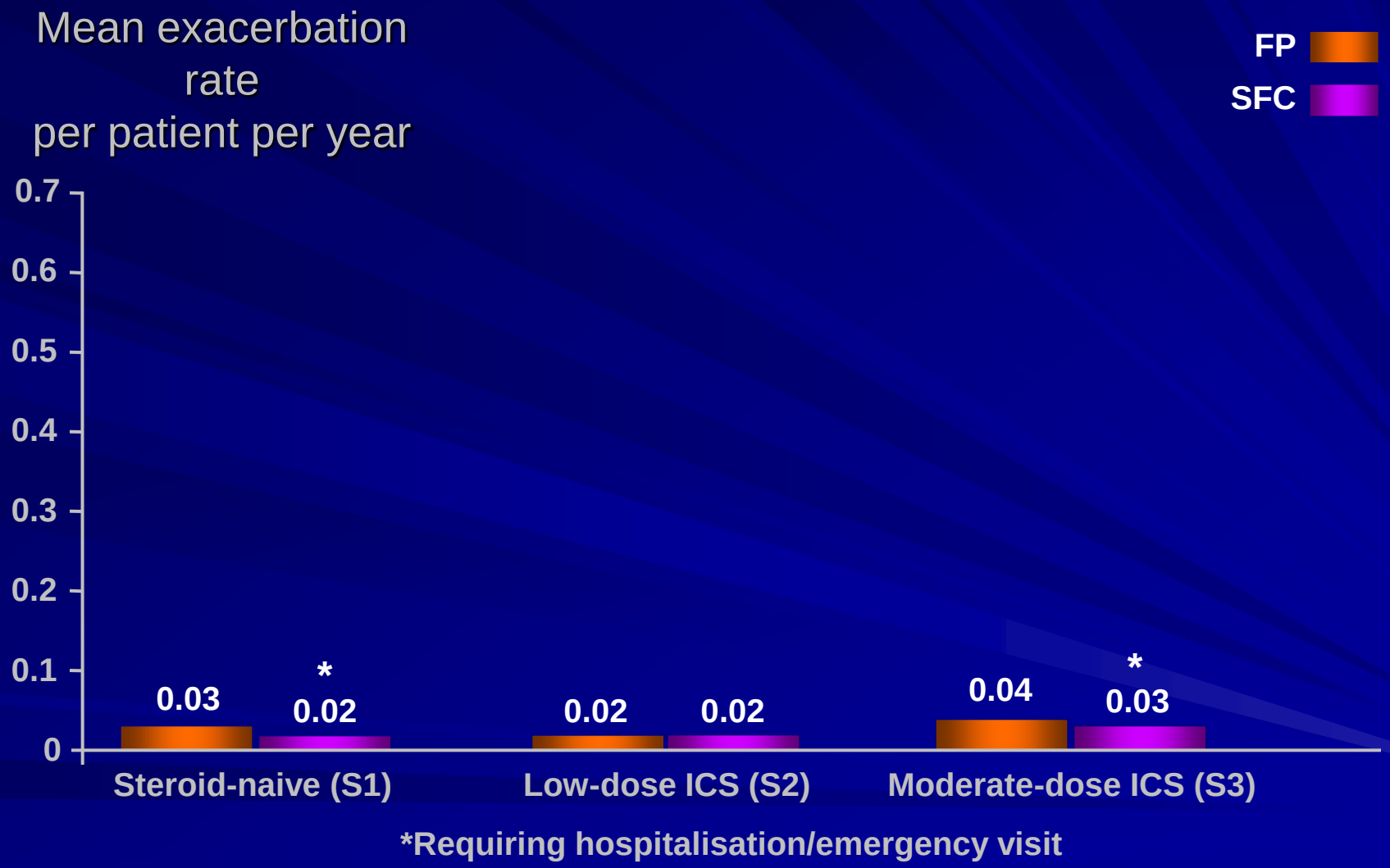
Continued improvements with sustained treatment



All patients

GOAL Study

SEVERE EXACERBATIONS GOAL



*$P \leq 0.014$

GOAL Study

SAFETY PROFILE FROM GOAL

	SFC	FP
Pneumonia	<1%	<1%
Nasopharyngitis	13%	14%
URTI	14%	14%
Sinusitis	5%	4%
Oral candidiasis	3%	3%
Mean cortisol/creatinine (nmol/mmol)		
Baseline	3.74	3.92
Week 52	3.04	2.85
Week 52 (high dose 2000BDP)	2.90	2.73

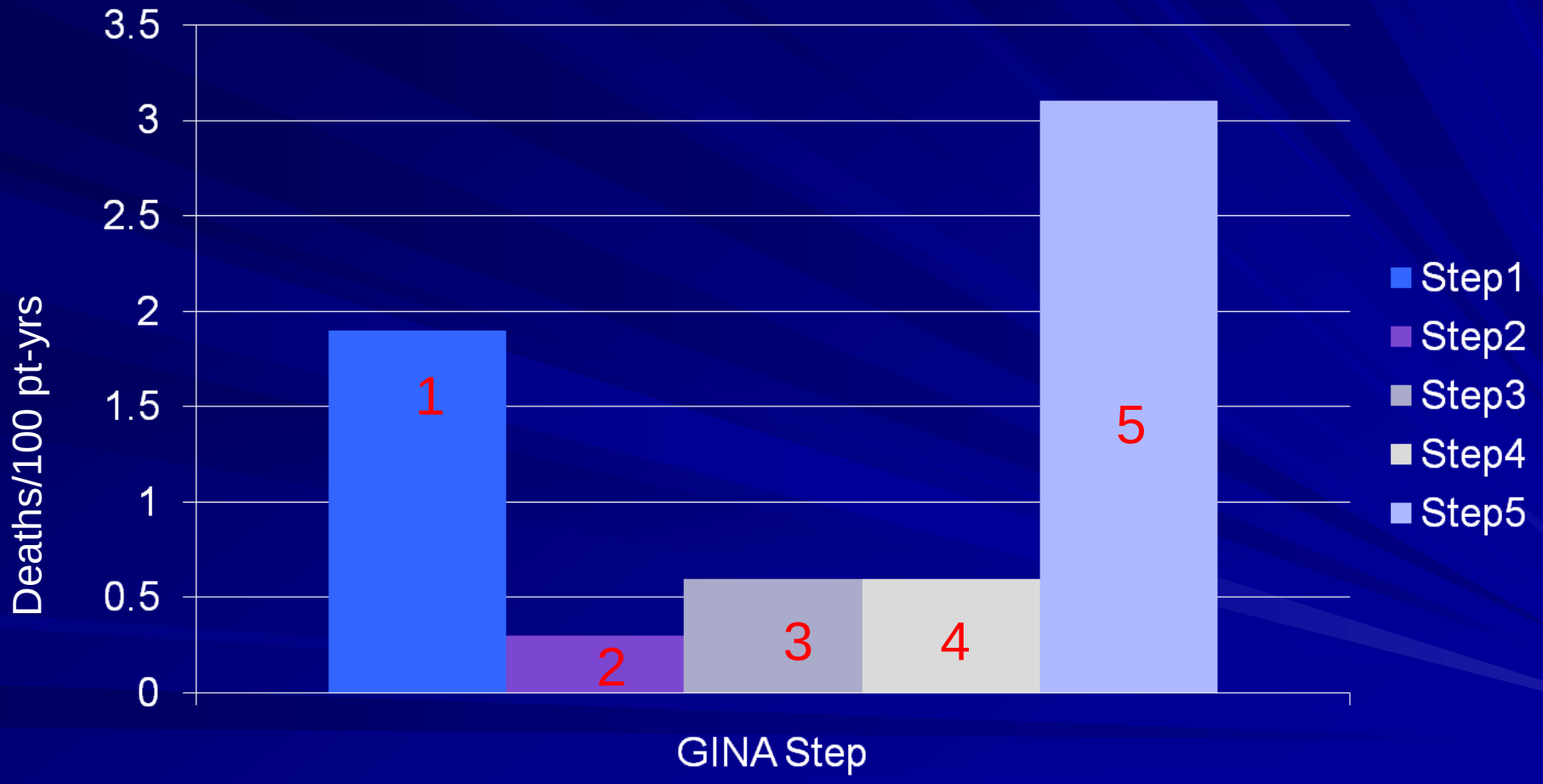
Bateman *et al.* Am. J. Respir. Crit. Care Med 2004 170: 836-844

GPRD STUDY

- UK General Practice Research Database
- Funded by MHRA
- 507,966 patients
- 5,500,000 SABA
- 4,000,000 ICS
- 1,300,000 LABA

de Vries et al ERJ 2010

RELATIVE RATE OF MORTALITY



de Vries et al ERJ 2010

MHRA HOT TOPIC

- Long acting β2 agonists safe if used with inhaled steroids
- Best used as a combination inhaler

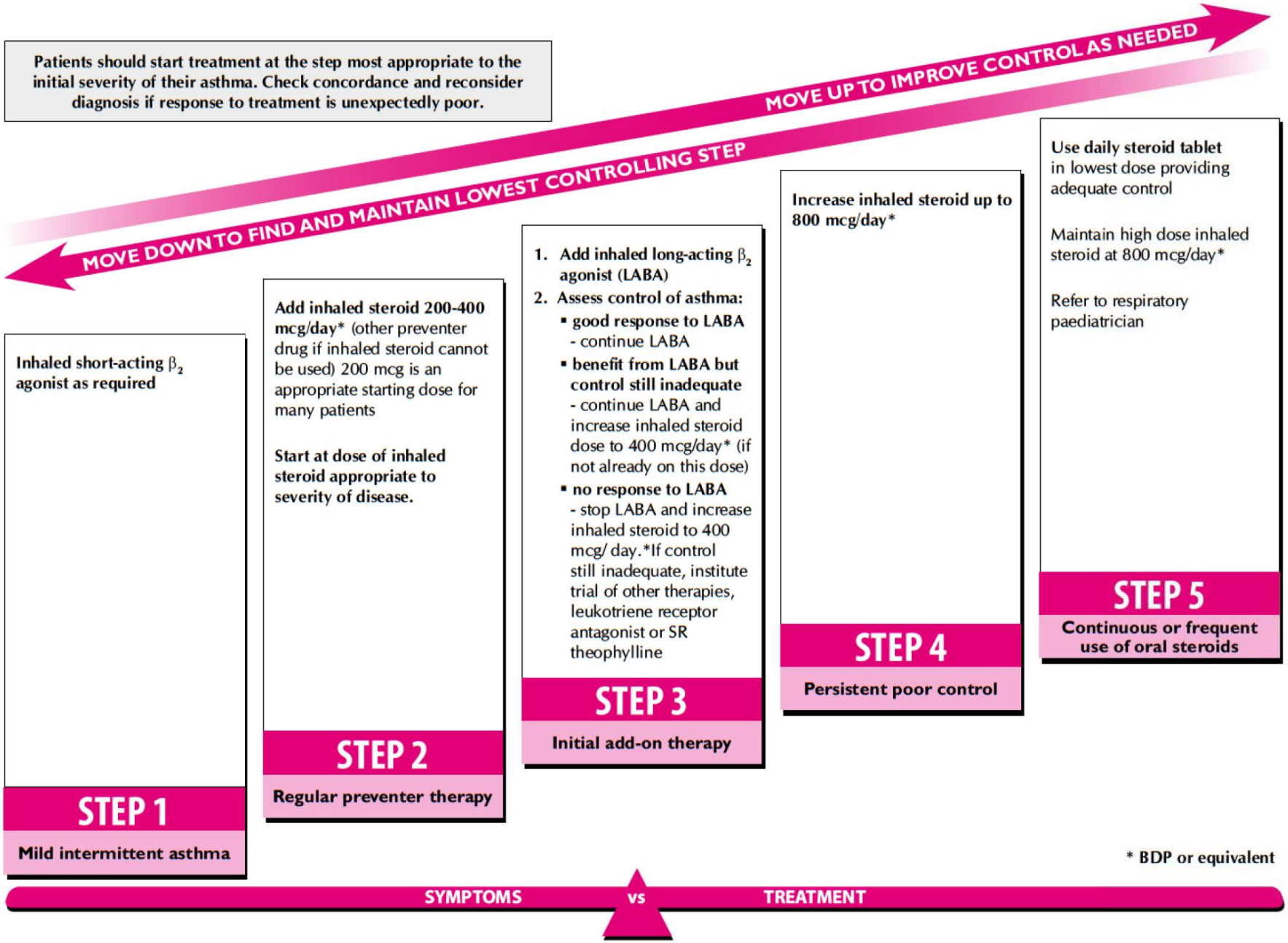
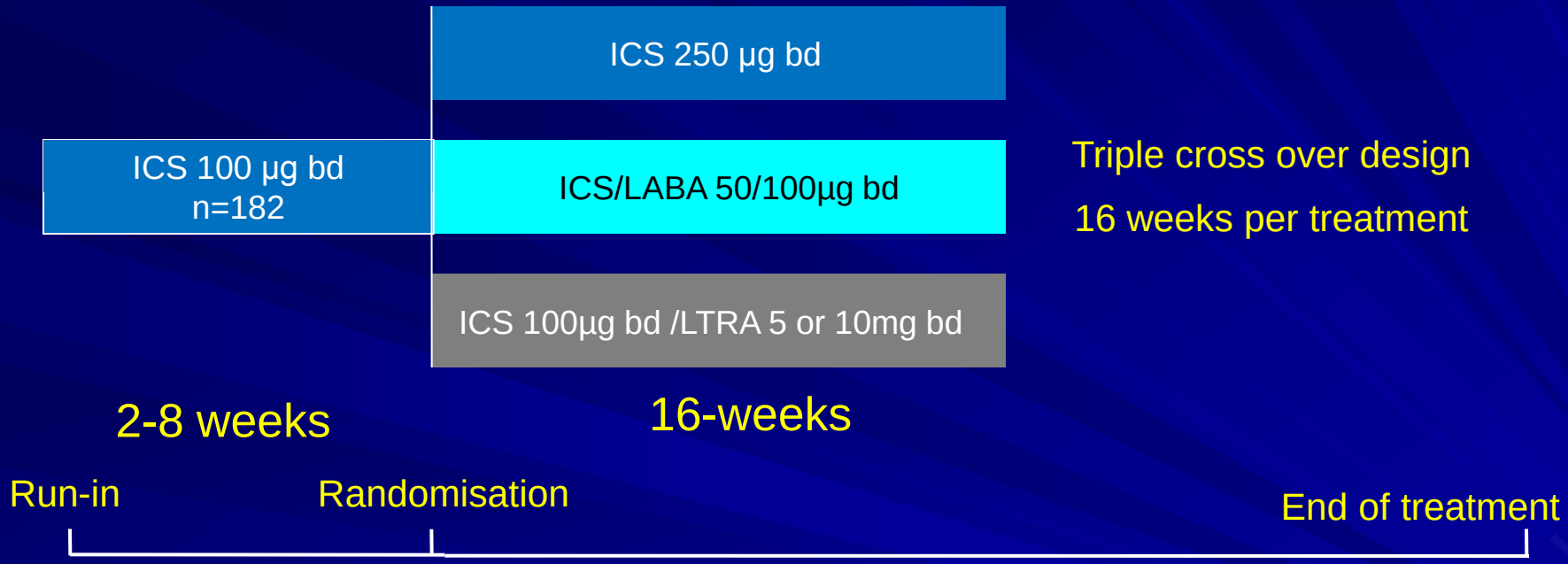


Figure 5: Summary of stepwise management in children aged 5-12 years

Badger – Study design

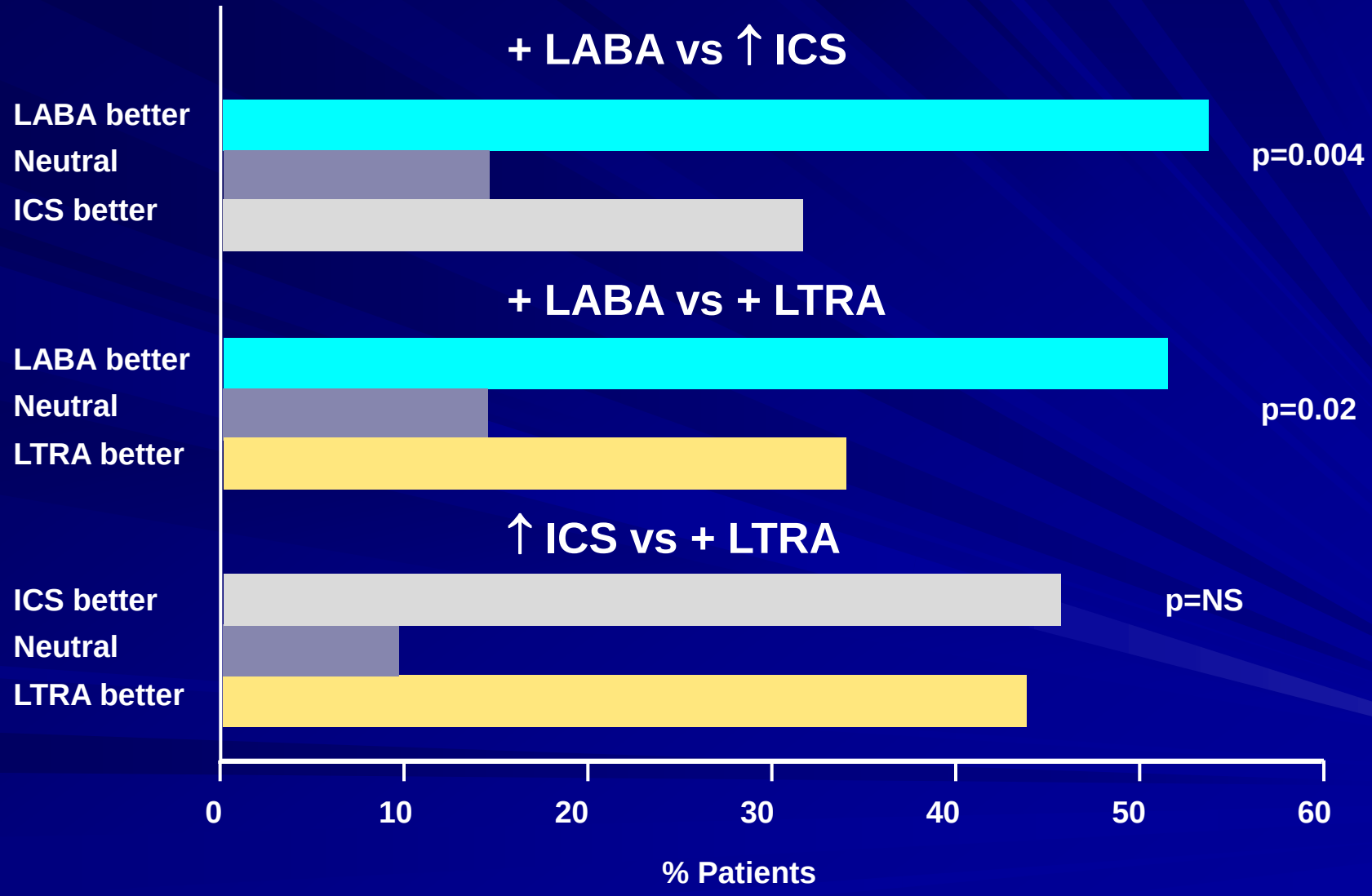


Primary endpoint: composite of exacerbations, asthma-control days and FEV_1 to assess whether differential response to step-up regimens >25%

n=182 children (6–17 years of age)

Lemanske et al. N Engl J Med 2010

Results



Lemanske et al. N Engl J Med 2010

ADHERENCE/COMPLIANCE

TYPES OF NON-COMPLIANCE

- Unintentional (forgetfulness)
- Intentional
- Rational

ELICITING THE RATE OF COMPLIANCE

- This is a very important treatment, are you taking it?
- The new inhaler I started you on last time, are you taking it?

ELICITING THE RATE OF COMPLIANCE

- You are on a lot of treatment do you ever forget to take them?
- If you are feeling good do you miss our treatment out?

PRESCRIPTION FILLING AND HEALTH CARE UTILISATION

Prescription filling

	<50% ICT n=63	>50% ICT n=119	p value
Sex M/F	16/47	53/66	0.02
Admissions in last 12 months	25%=3	10%=3	0.02
	5%=2	9%=2	
	18%=1	16%=1	
	52%=0	65%=0	
Nebuliser	31(49%)	35(29%)	0.01
Total SABA nebules	99	42	0.03

Gamble et al AJRCCM 2009

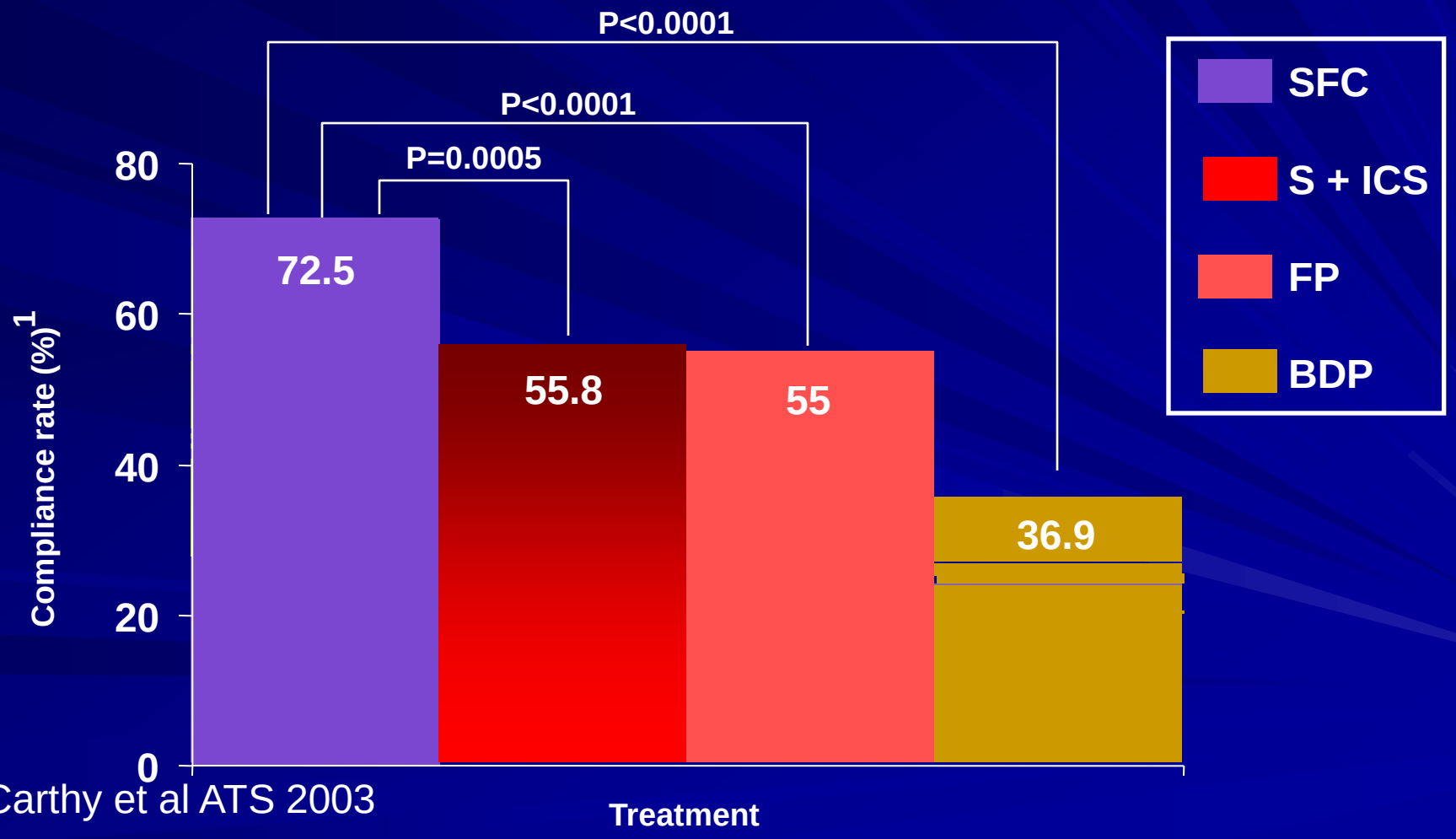
BELIEFS

- That inhaler is only for people with bad asthma
- If I take the inhaler now it will not help me when I am bad
- The effect of the treatment will wear off if I take it regularly
- I might get addicted

COMPLIANCE PHYSICIAN/PATIENT INTERACTION FACTORS

- Compliance is better if the treatment is perceived to address the patients concerns
- Compliance is improved if the patient feels the doctor has listened to their concerns
- Improved by written information
- Improved by repetition

COMPLIANCE RATES OF CHILDREN WITH DIFFERING TREATMENTS



McCarthy et al ATS 2003

PRACTICAL TIPS TO IMPROVE COMPLIANCE

- Open ended questions eg “If we could make one thing bettter about your asthma what would it be?”
- Make it clear you are listening to and responding to the patients concerns and goals
- Reinforce practical information and treatment plans with written information
- Reminder strategies
- Recall patients who miss appointments

UK Asthma Guidelines 2003


But if you had asked me about last week.....
How are you?
Fine
Great!Next Patient Please!

ASTHMA CONTROL TEST

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

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

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

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

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

Patient Total Score

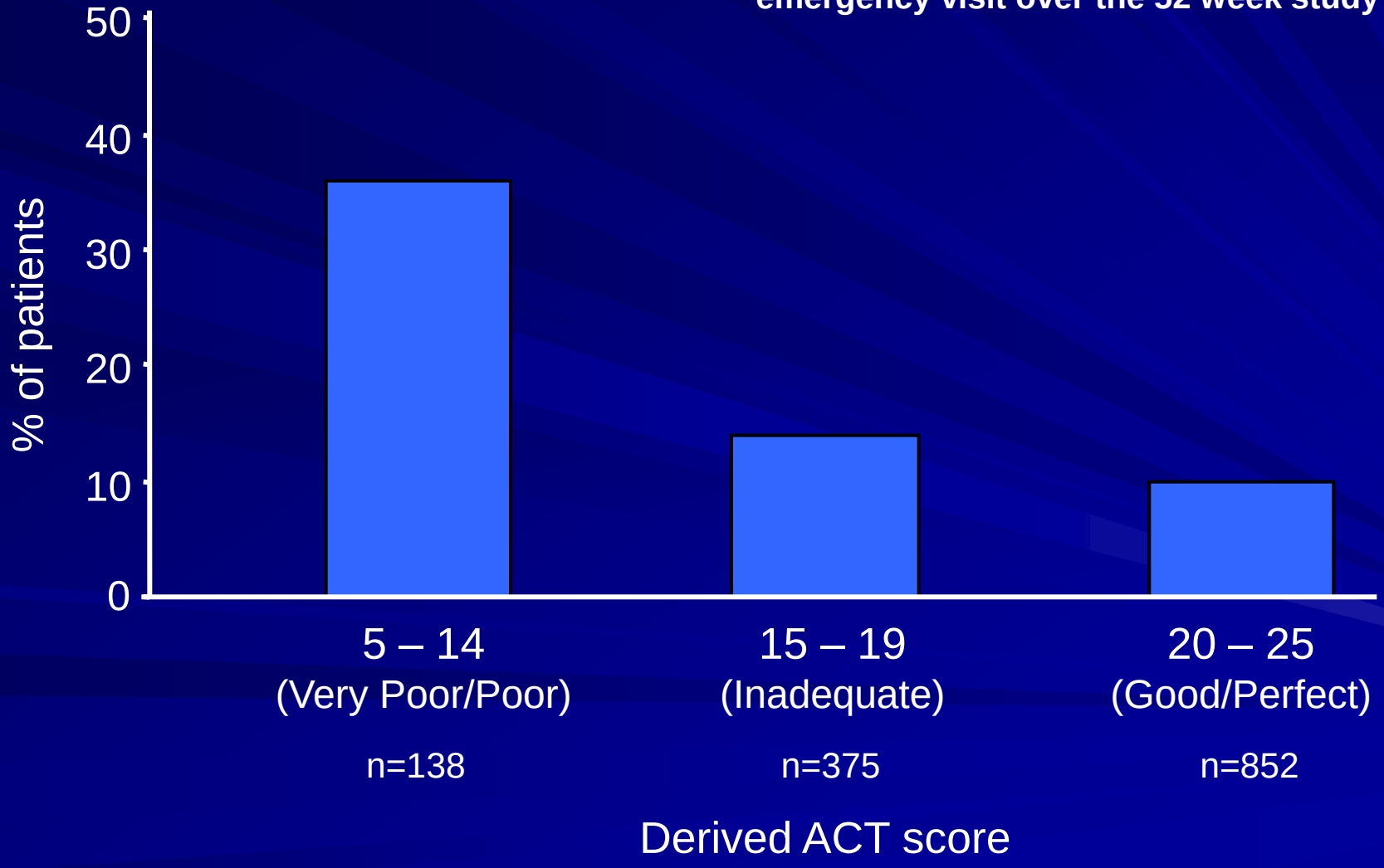
USING THE ACT SCORE

ACT score	Level of control	Level of control
20 - 25	Good	Well controlled
15 - 19	Inadequate	Not well controlled
10 - 14	Poor	
5 - 9	Very Poor	

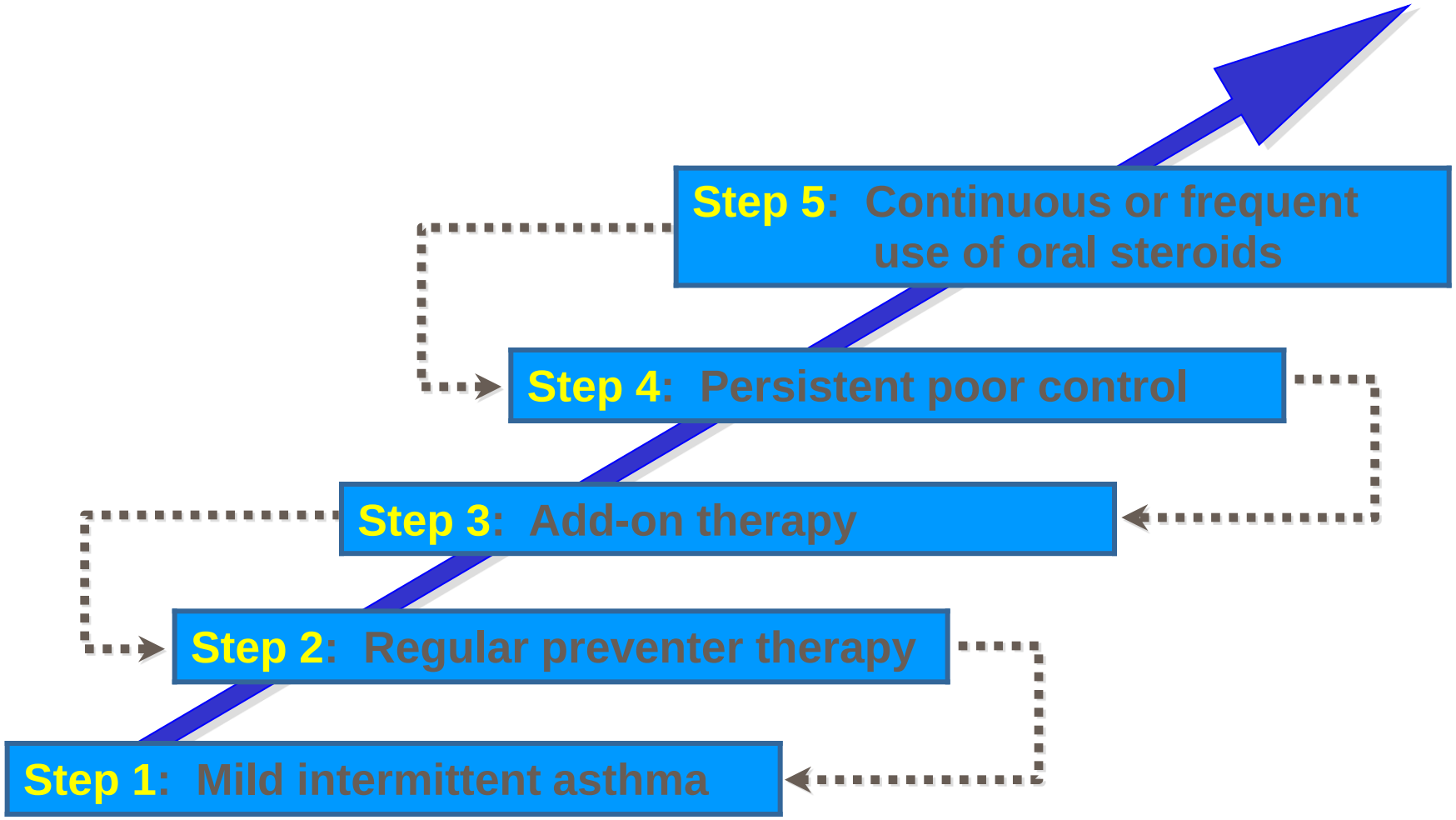
Schatz M, et al. J Allergy Clin Immunol 2006; Nathan RA, et al. *JACI* 2004

A LOWER ACT SCORE IS ASSOCIATED WITH HIGHER RISK OF EXACERBATIONS*

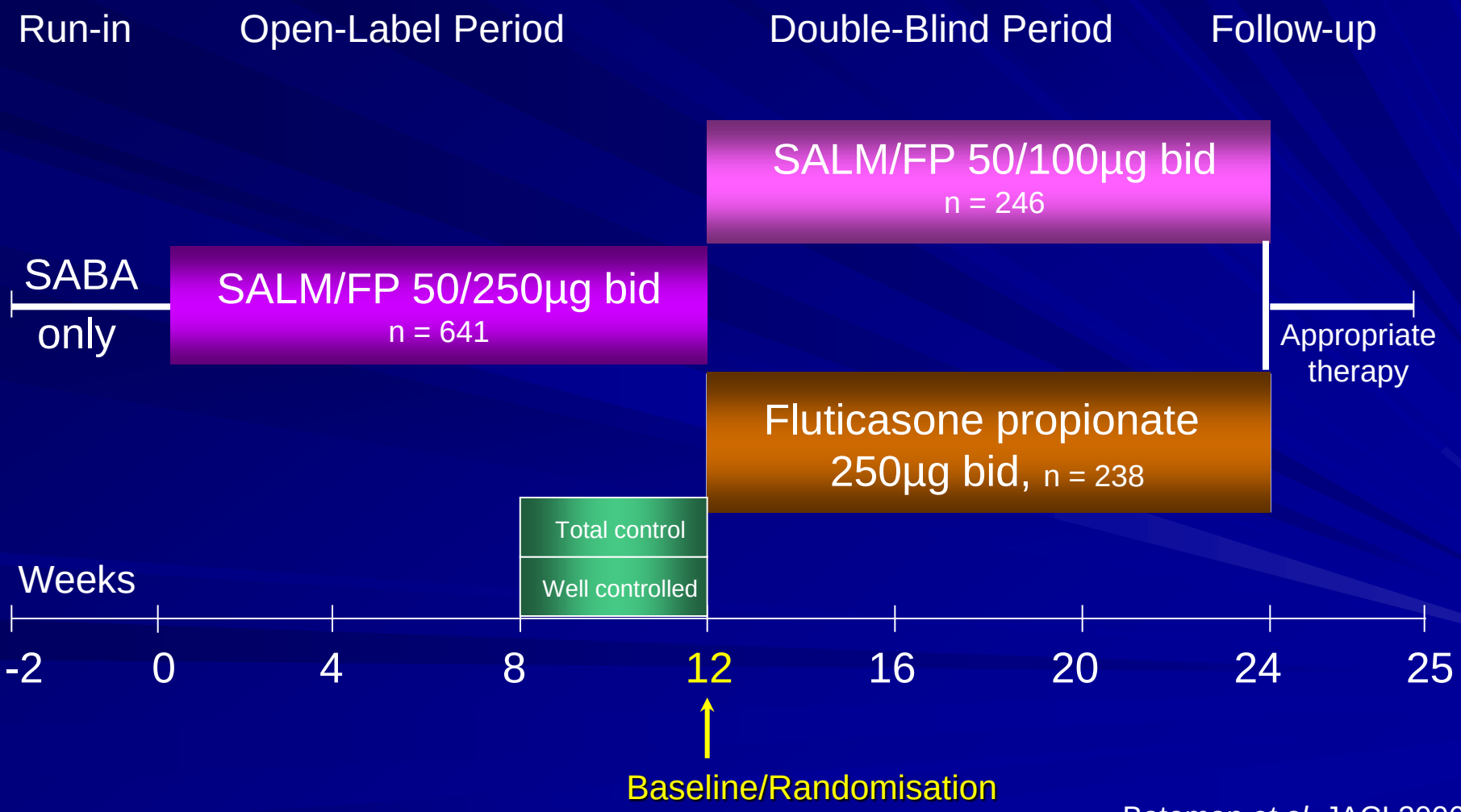
***Requiring oral steroids, hospitalisations emergency visit over the 52 week study period**



Stepwise management of asthma in adults

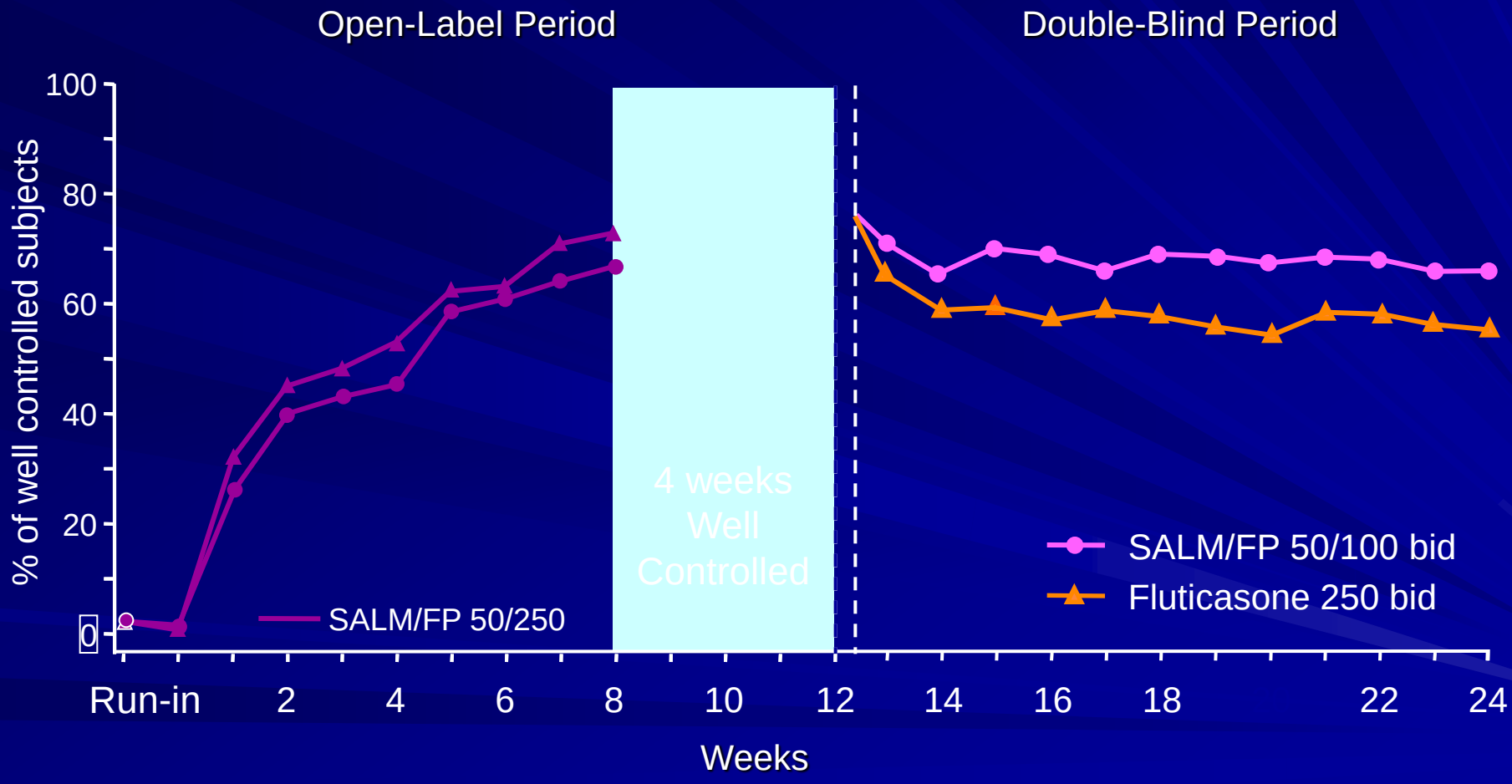


STEP DOWN COMBINATION THERAPY OR CHANGE TO ICS ALONE

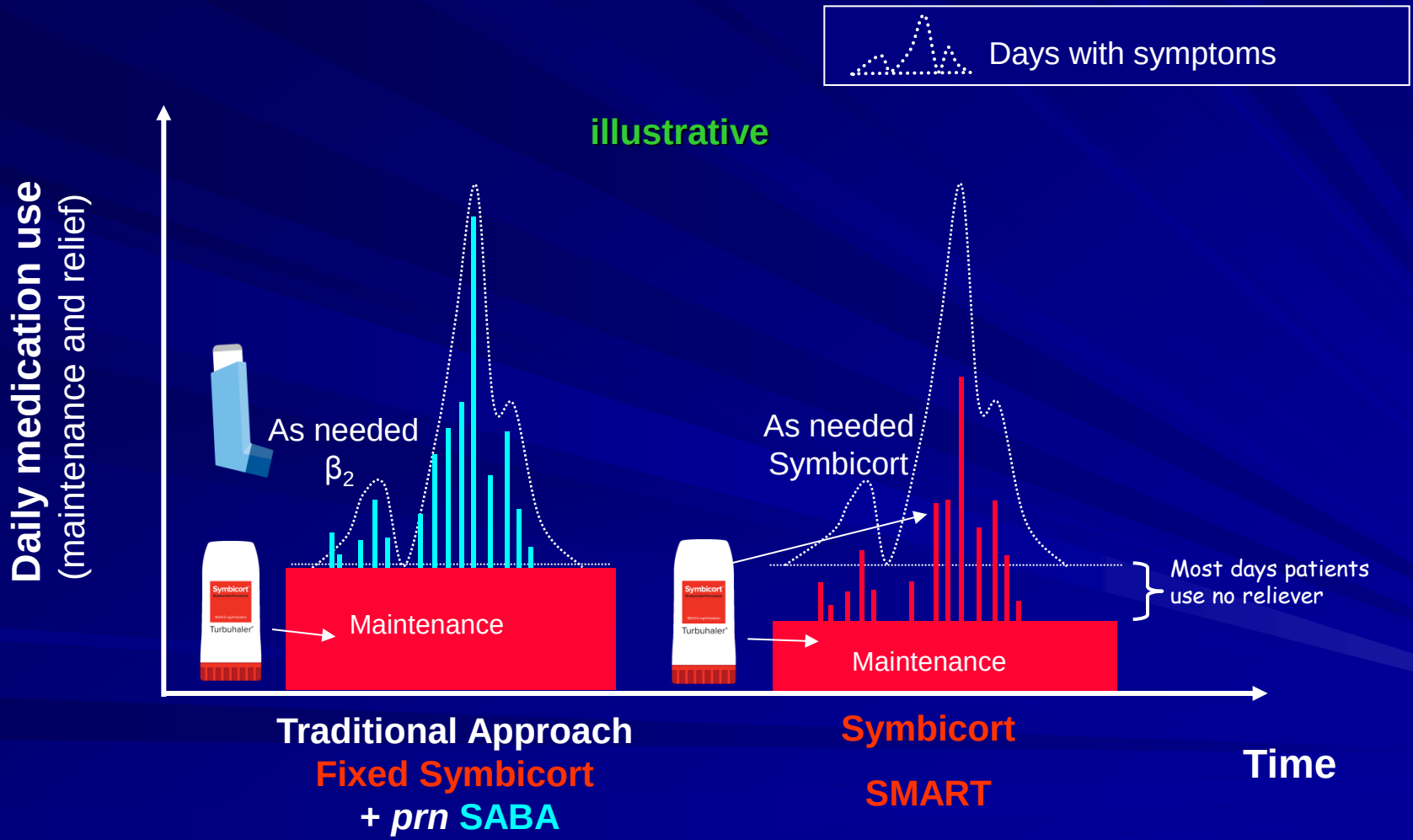


Bateman *et al*, JACI 2006

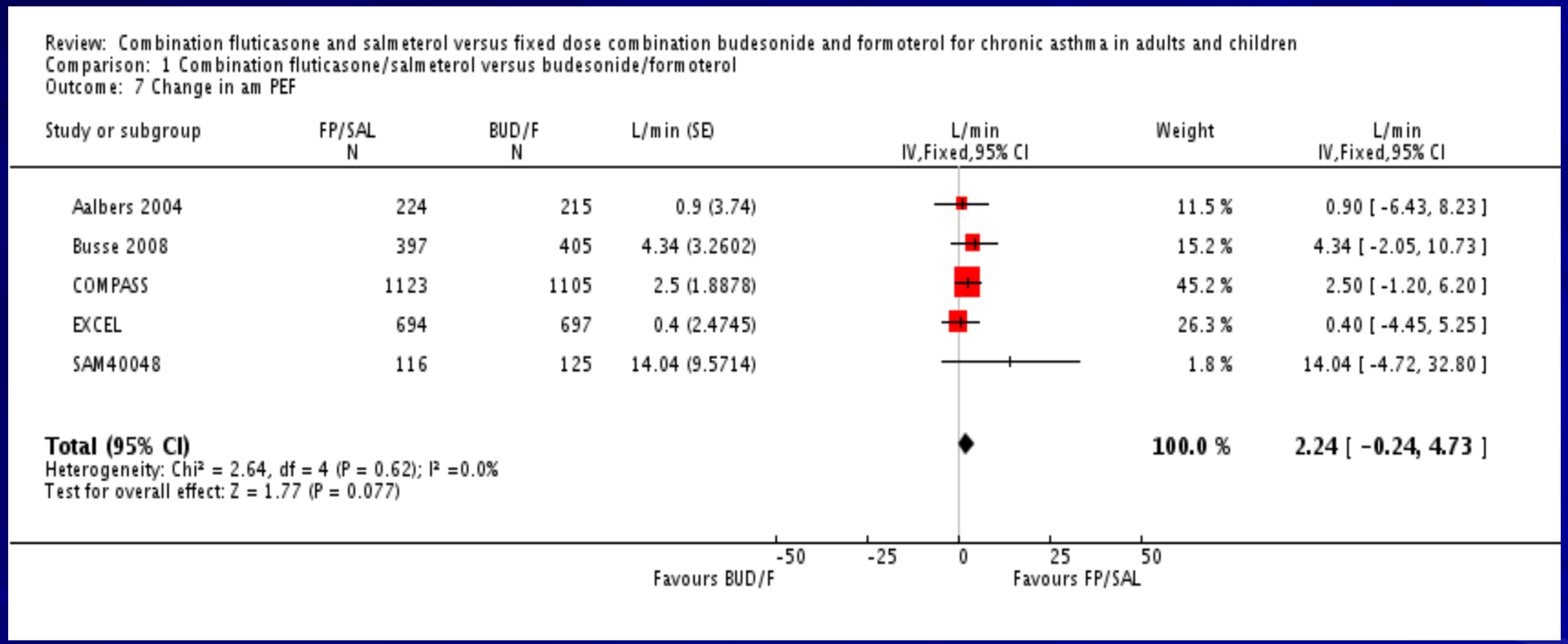
MAINTENANCE OF ASTHMA CONTROL DURING STEP DOWN



TRADITIONAL APPROACH AND SYMBICORT MAINTENANCE AND RELIEVER THERAPY (SMART)



FP/SALM VS BUD/FORM am PEF



Cochrane Review

SMART CONTROL OUTCOMES: COMPARED TO GINA GUIDELINE TARGETS

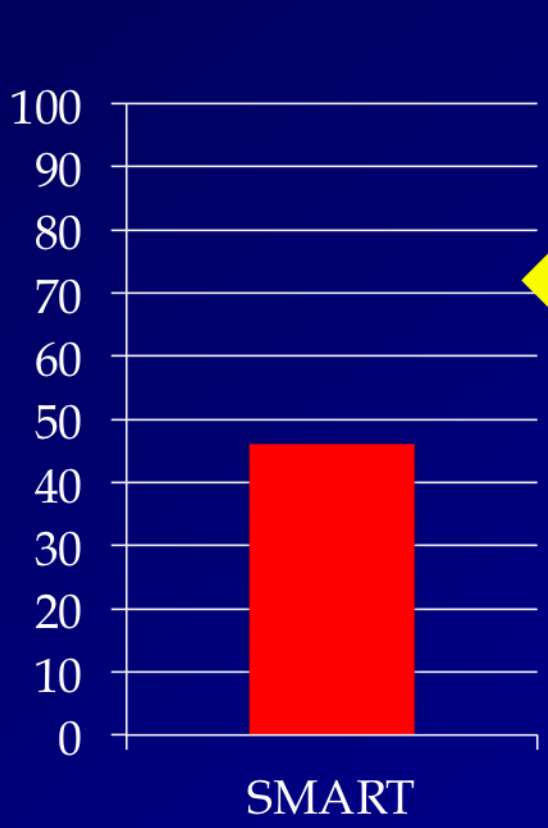


Figure 2-4. Levels of Asthma Control

Characteristic	Controlled (All of the following)
Daytime symptoms	Twice or less/week
Limitations of activities	None
Nocturnal symptoms/awakening	None
Need for reliever/ rescue treatment	Twice or less/week
Lung function (PEF or FEV_1)[†]	Normal

Adapted from Chapman et al 2010

SMART CONTROL OUTCOMES: COMPARED TO GINA GUIDELINE TARGETS

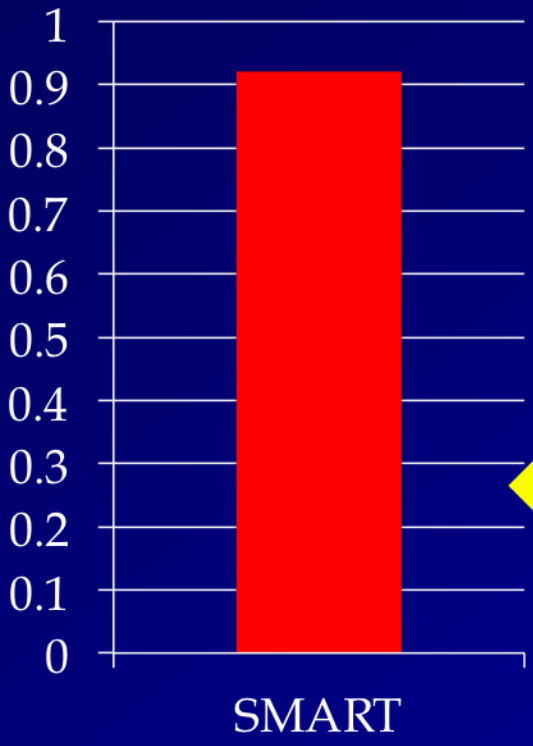


Figure 2-4. Levels of Asthma Control

Characteristic	Controlled (All of the following)
Daytime symptoms	Twice or less/week
Limitations of activities	None
Nocturnal symptoms/awakening	None
Need for reliever/ rescue treatment	Twice or less/week
Lung function (PEF or FEV_1)[t]	Normal

Adapted from Chapman et al 2010

CONTROL OUTCOMES IN SMART-TREATED PATIENTS

Studies analyzed:

Rabe et al. *Lancet* 2006.

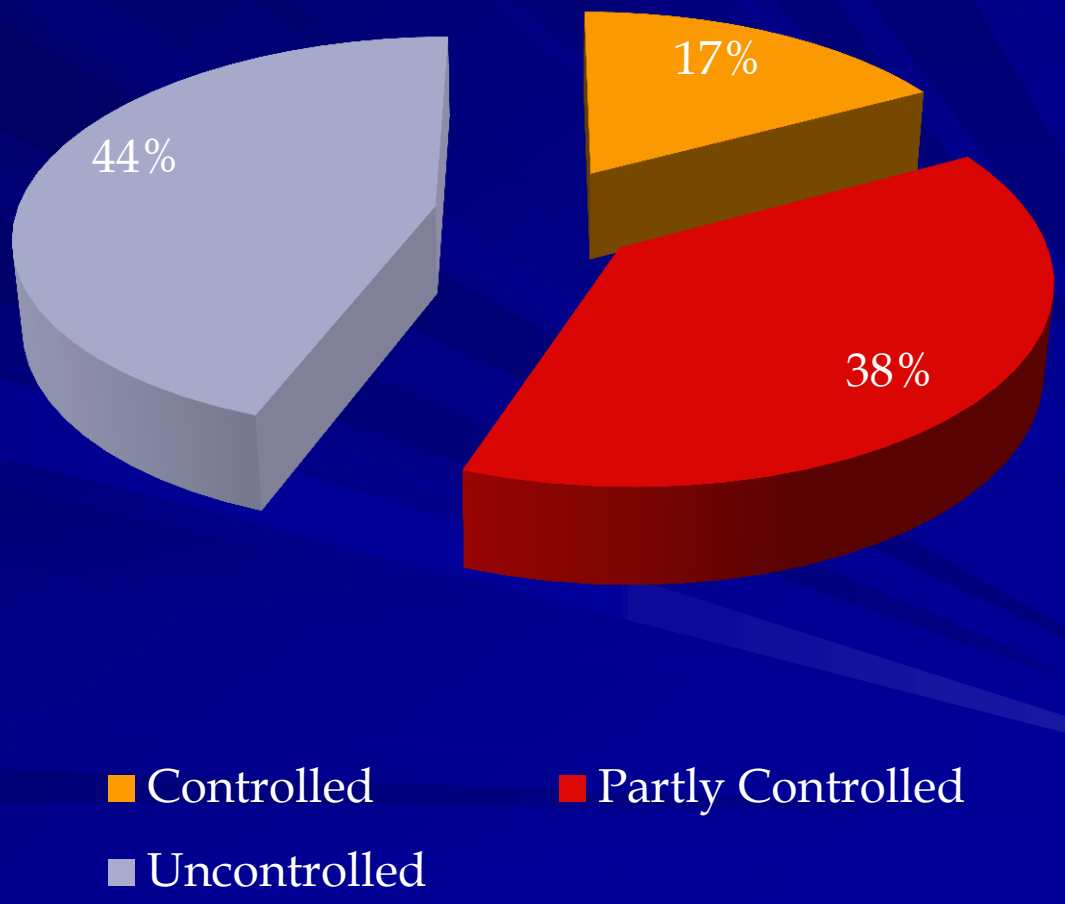
O'Byrne et al. *AJRCCM* 2005.

Scicchitano *Curr Med Res Opin* 2004.

Kuna *Int J Clin Pract* 2007

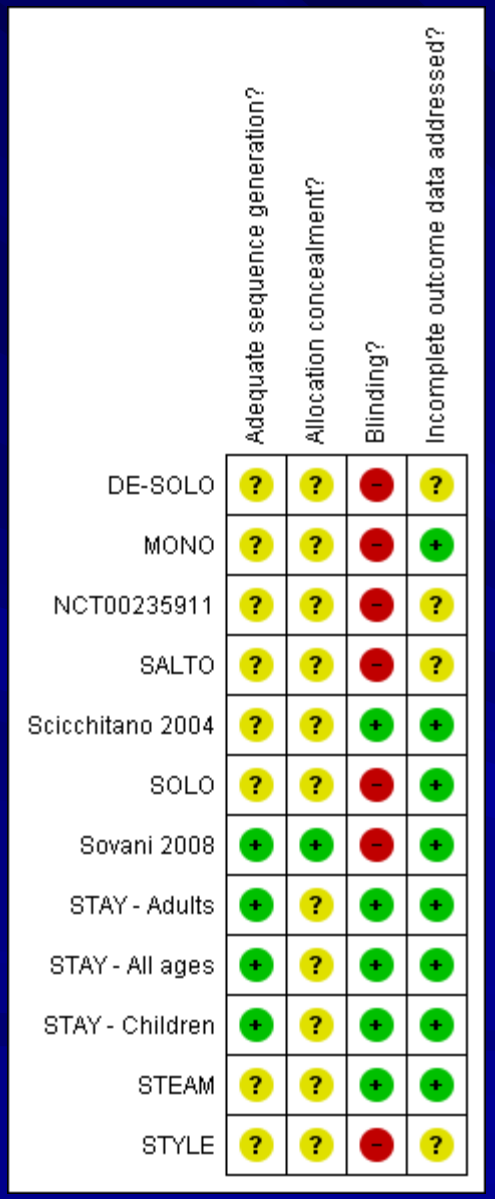
Bousquet *Respir Med* 2007.

n = 5,246



Bateman et al. JACI 2010

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



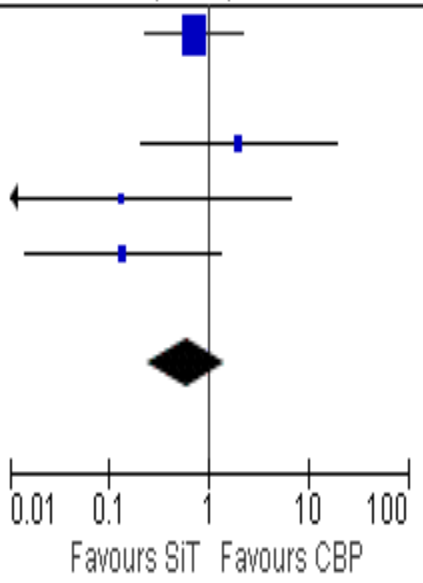
Cates & Lasserson 2009

SMART vs BEST CLINICAL PRACTICE Rate of exacerbation

	Single inhaler therapy		Current best practice			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
MONO	5	921	7	914	63.1%	0.71 [0.23, 2.21]	
NCT00235911	0	54	0	48		Not estimable	
SALTO	2	450	1	458	15.8%	1.99 [0.21, 19.14]	
SOLO	0	772	1	766	5.3%	0.13 [0.00, 6.77]	
STYLE	0	497	3	498	15.8%	0.14 [0.01, 1.30]	
Total (95% CI)		**2694**		**2684**	**100.0%**	**0.59 [0.24, 1.45]**	
Total events	7		12				

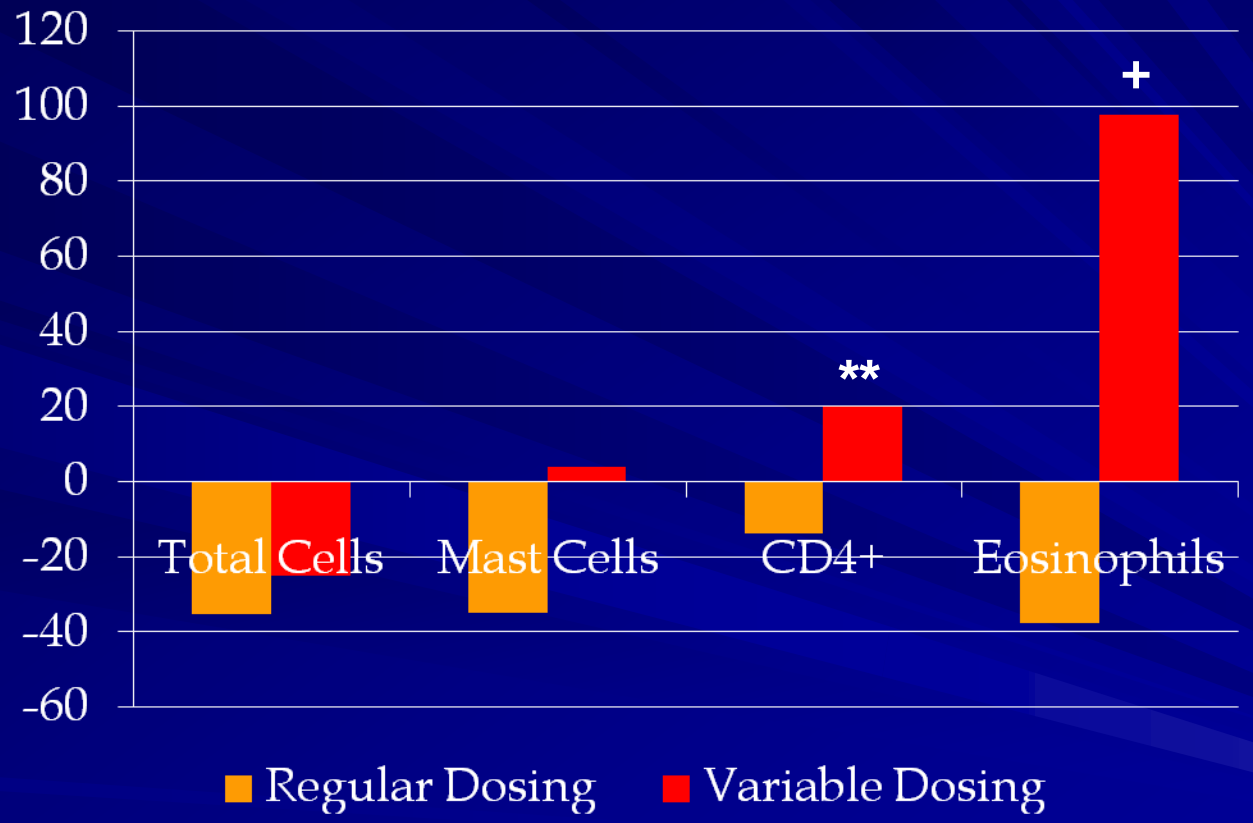
Heterogeneity: Chi² = 3.38, df = 3 (P = 0.34); I² = 11%

Test for overall effect: Z = 1.15 (P = 0.25)



Cates & Lasserson 2009

REGULAR DOSING VS. VARIABLE DOSING: BIOPSY INFLAMMATORY CELLS



+ p < 0.001

** p = 0.0012

n = 127

Pavord et al JACI 2009

SUMMARY

- Asthma control is what patient`s, clinician`s and payer`s want
- With the use of ICS or ICS/LABA control can be achieved in the majority of patient`s
- Poor adherence is the main barrier to good control
- Variable, symptom-driven dosing (SMART) is associated with poor control and increasing airways inflammation.

Adults

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

MOVE UP TO IMPROVE CONTROL AS NEEDED

MOVE DOWN TO FIND AND MAINTAIN LOWEST CONTROLLING STEP

STEP 1

Mild intermittent asthma

Inhaled short-acting β_2 agonist as required

STEP 2

Regular preventer therapy

Add inhaled steroid 200-800 mcg/day*

400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 3

Initial add-on therapy

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
   - good response to LABA - continue LABA
   - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
   - no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/ day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 4

Persistent poor control

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 5

Continuous or frequent use of oral steroids

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

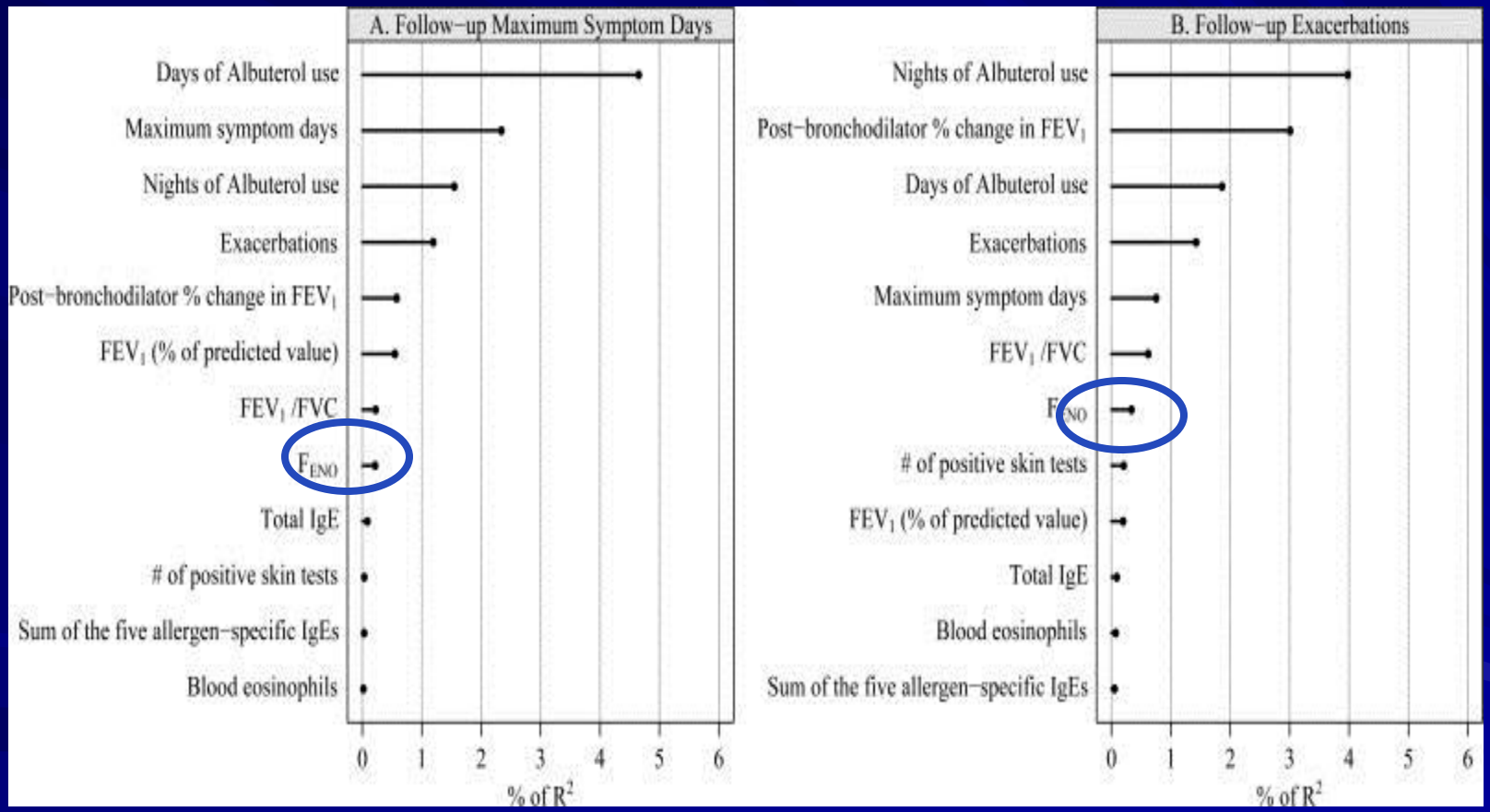
Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

* BDP or equivalent

SYMPTOMS vs TREATMENT

VALUE OF MEASURES IN ASSESSING EXACERBATION RISK



Gruschella et al JACI 2009