



Prof Neil Barnes

Respiratory and General Medicine

London Chest Hospital and The Royal
London Hospital

Asthma: When everything fails, what do you do? - Concurrent Workshop Repeated

Saturday, 17 August 2013

Start 11:00am

Duration: 55mins

Pyramids

Start 12:05pm

Duration: 55mins

Pyramids



South GP CME 2013

General Practice Conference & Medical Exhibition

15-18 August | Edgar Centre | Dunedin

ASTHMA: WHEN EVERYTHING FAILS WHAT DO YOU DO?

South GP CME 2013, Dunedin
Saturday 17th August 2013

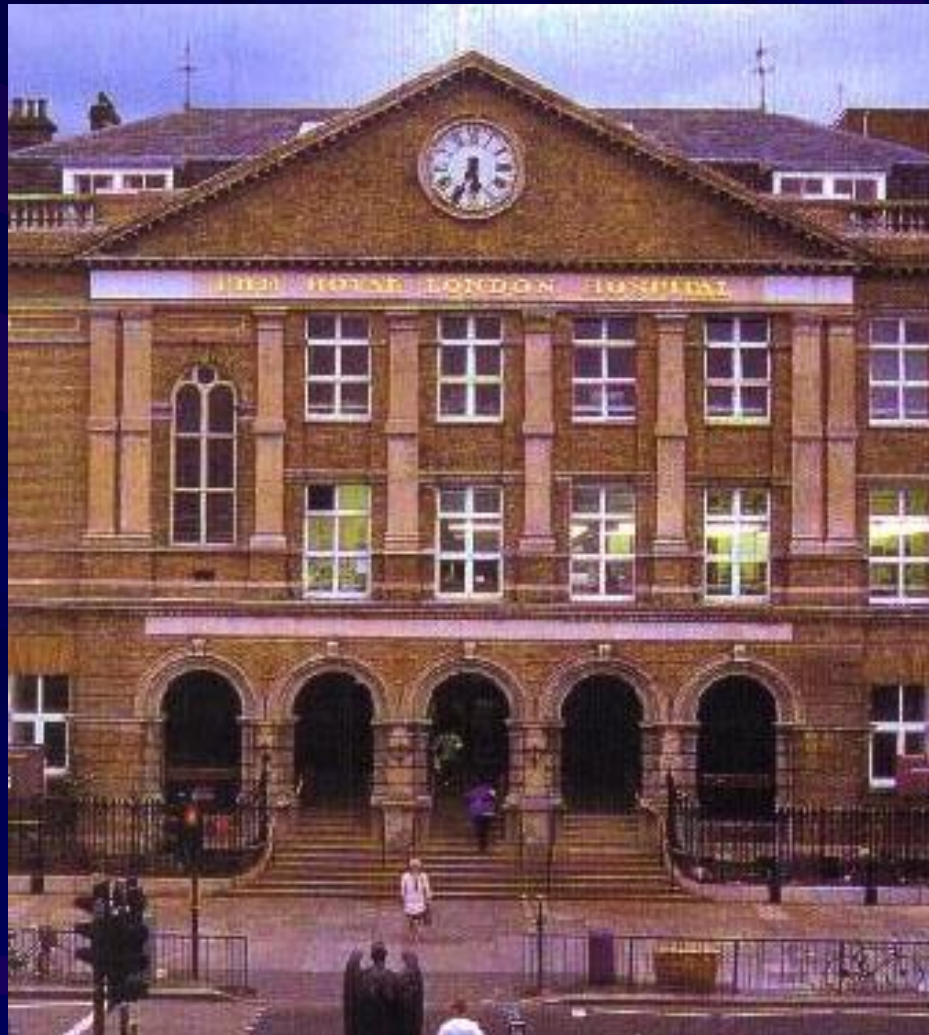
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Disclaimer

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

DEFINITION OF DIFFICULT OR POORLY CONTROLLED ASTHMA

- Uncontrolled at Step 4 or 5

- Ventilation or near miss ventilation

DIFFICULT OR SEVERE?

- Difficult asthma symptomatic and/or exacerbations despite treatment at step 4 of the asthma guidelines

DIFFICULT OR SEVERE?

- Difficult asthma symptomatic and/or exacerbations despite treatment at step 4 of the asthma guidelines
- May be difficult due to co-morbidities
 - wrong diagnosis
 - adherence/compliance issues

SEVERE ASTHMA

- Uncontrolled at step 4 once
- Co-morbidities
- Wrong diagnosis
- Adherence/compliance issues dealt with

A 40 YEAR OLD WOMEN WITH FREQUENT ADMISSIONS

- 10 admissions in last year
- On prednisolone plus multiple other treatments

A 40 YEAR OLD WOMEN WITH FREQUENT ADMISSIONS

- Not Cushingoid
- Overbreathing
- Many admissions PEF > 400l/min

A 40 YEAR OLD WOMEN WITH FREQUENT ADMISSIONS

- Cortisol normal
- No detectable prednisolone

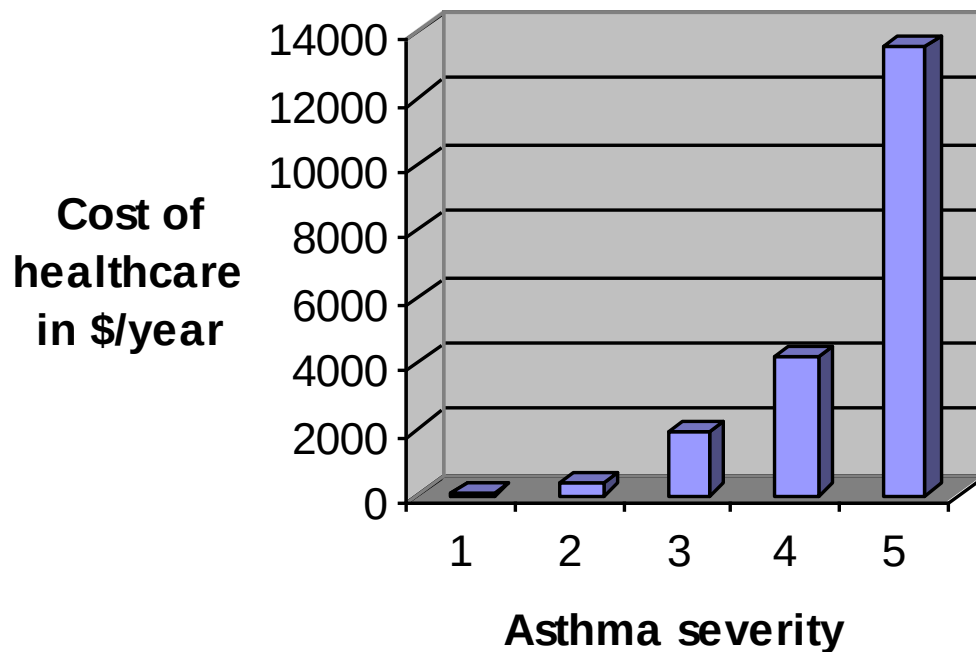
A 40 YEAR OLD WOMEN WITH FREQUENT ADMISSIONS

- 3 week in patient stay physiotherapy input
- Genuine worsening with wheeze and low PEF responding to prednisolone
- Cough due to proven reflux
- Only one admission in last 18months

MOST IMPORTANT MESSAGE

- Asthma responds to treatment
- If a patient does not improve the most likely causes are
 - wrong diagnosis
 - non-compliance
- After excluding these think about other treatments

COST OF ASTHMA CARE BY SEVERITY IN USA 1990



1. Very mild

2. Mild

3. Moderate

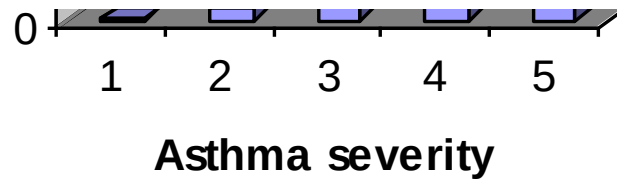
4. Severe

5. Very severe

Cost
in \$



**THE WORST 10% OF
ASTHMA COSTS >50% OF
THE TOTAL**



5. Very severe

FACTORS IN POORLY CONTROLLED ASTHMA

- Difficult asthma
- Other diseases in association with asthma
- Psychological issues
- Adherence/compliance issues

IS IT ASTHMA?

- NOT ASTHMA

- COPD

- Bronchiectasis

- Upper airways disease

- Gastroesophageal reflux

- Central tumours

- Foreign bodies

- Hyperventilation

- ASTHMA PLUS

- Bronchiectasis

- Upper airways disease

- Gastroesophageal reflux

- ABPA

- Occupational asthma

- NSAIDs and asthma

- Churg-Strauss syndrome

- Hyperventilation

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

- Central bronchiectasis
- Positive skin tests to aspergillus
- Evidence that itraconazole is of benefit

UPPER AIRWAYS DISEASE

- Asthma and rhinitis and/or sinusitis frequently co-exist
- Symptoms may be confused with asthma
- Treating rhinitis and sinusitis does not seem to improve asthma

REFLUX

- The commonest cause of cough no obvious cause
- Occurs with asthma and is suggested when cough is excessive
- Not always accompanied by dyspepsia
- Treatment improves cough but not asthma

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 nebulers	99	42	0.03

ORAL STEROID COMPLIANCE

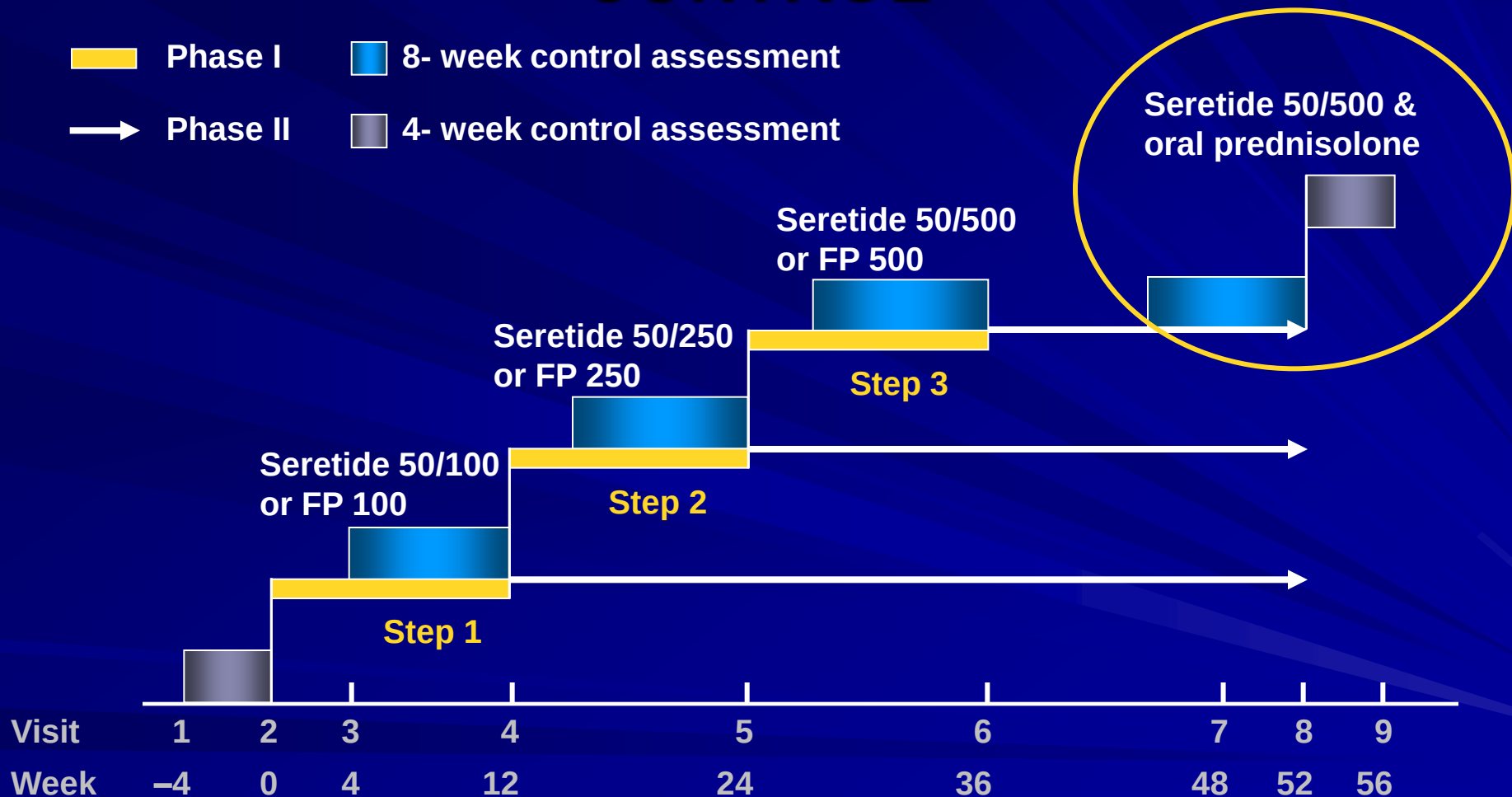
	Nonadherent n=23	Adherent n=26
Blood plasma prednisolone $\mu\text{g/L}$	ND	194+/-160
Blood plasma cortisol nmol/L	212+/-116	ND

FACTORS IN POORLY CONTROLLED ASTHMA

- **Difficult asthma**
- Other diseases in association with asthma
- Psychological issues
- Adherence/compliance issues

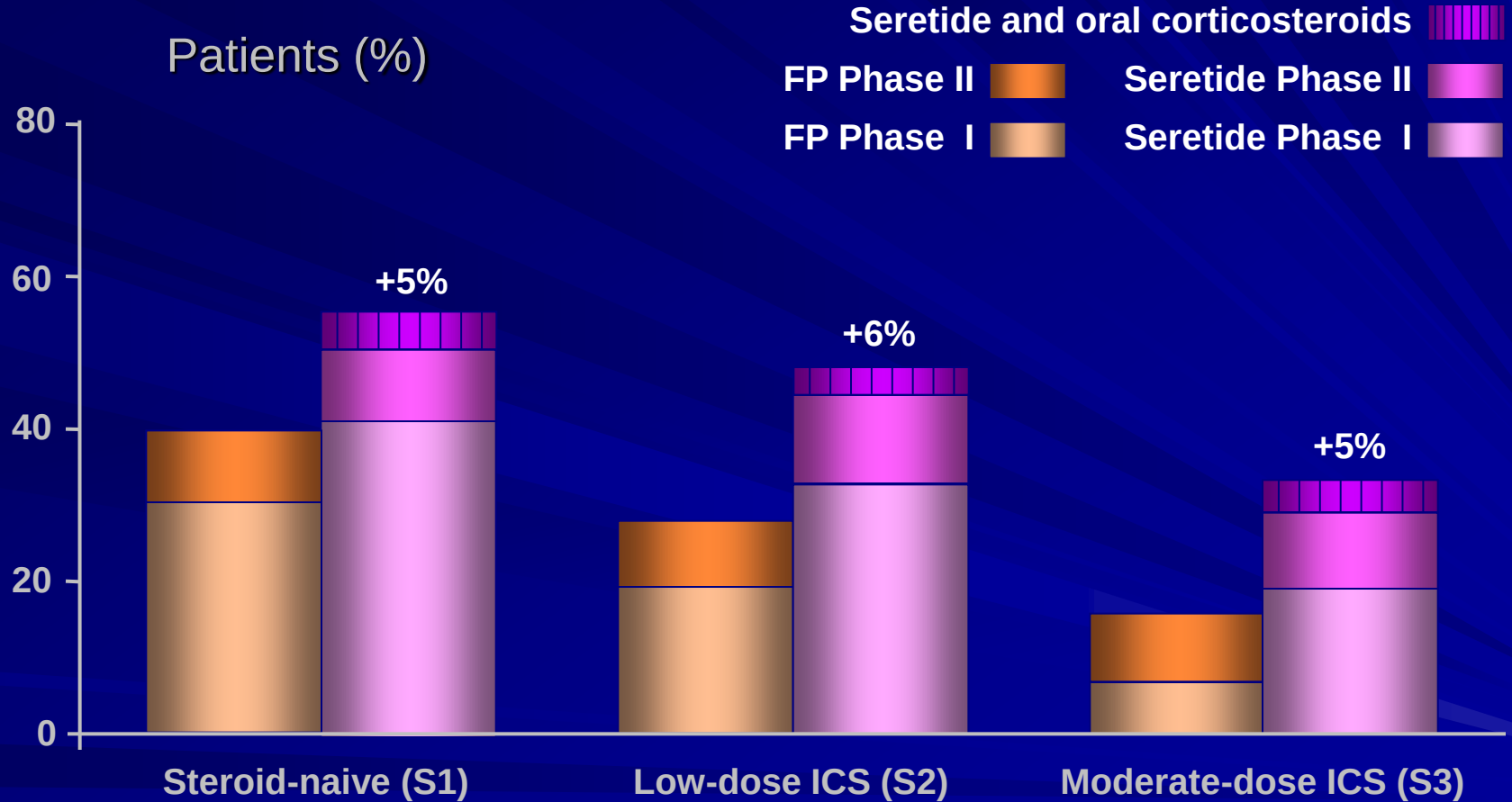
Open-label phase

For patients not achieving TOTAL CONTROL



TOTAL CONTROL

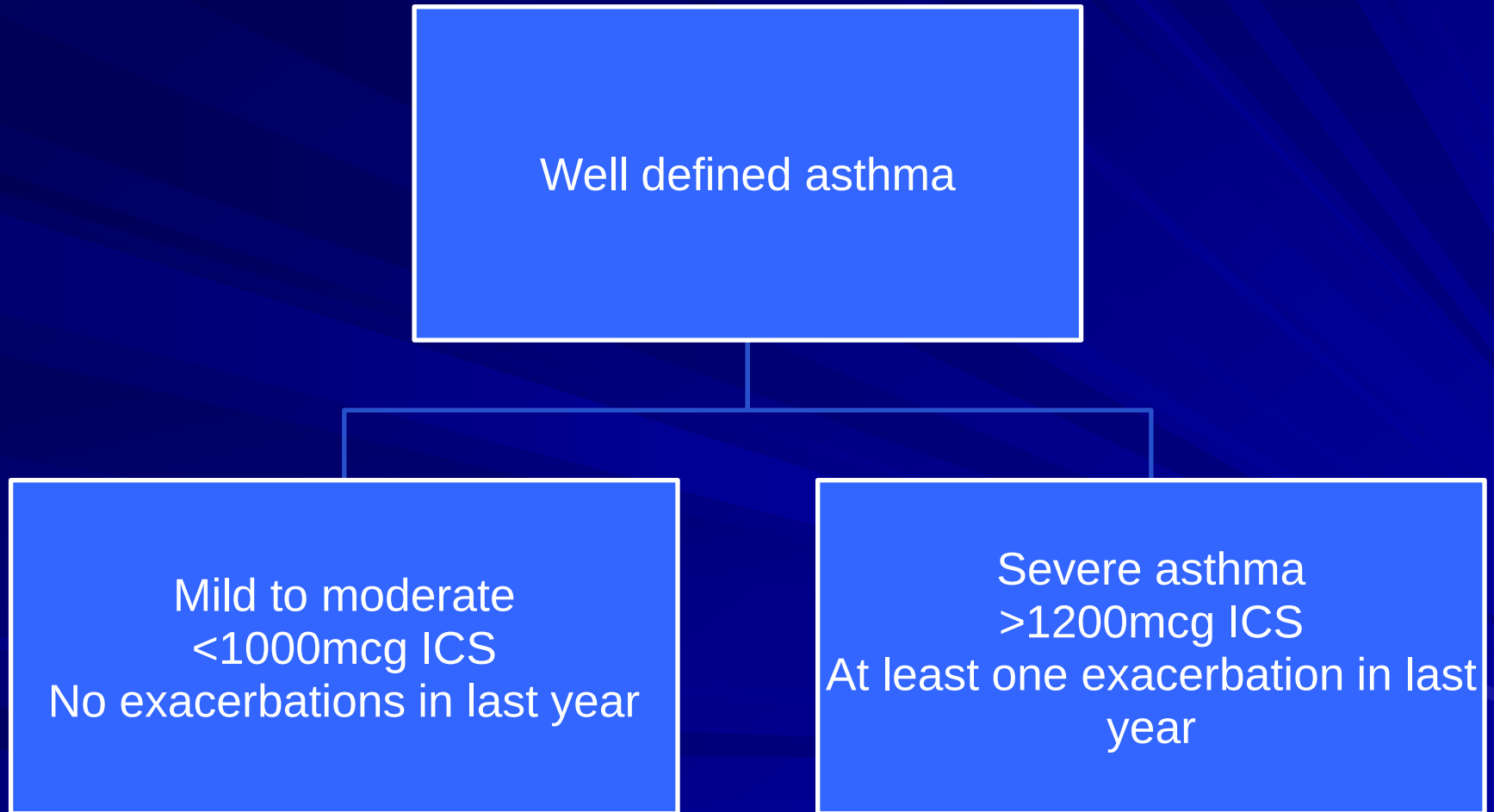
EFFECT OF ADDING ORAL CORTICOSTEROIDS



ENFUMOSA STUDY

- 12 European centres
- Age 17-65 years
- Diagnosed <45 years
- Well documented asthma
- <5 pack years smoking
- No other chronic lung disease

ENFUMOSA STUDY DESIGN



ENFUMOSA STUDY TREATMENT

	Controlled	Severe
Median dose ICS mcg	666	1773
% on long acting inhaled bronchodilator	24.7	95.5
% on theophyllines	2.5	45.5
Oral steroids	0/158	53/163

ENFUMOSA STUDY

DEMOGRAPHICS

	Controlled	Severe	Controlled vs severe
Subjects	158	163	
Age years	40.9	42.4	ns
Duration of asthma	20.2	20.8	ns
Female :male	1.6:1	4.4:1	p<0.001
Atopy IgE	148	108	p<0.05

SEVERE ASTHMA CROSS-SECTIONAL STUDY

	Persistent airflow obstruction n=66	No persistent airflow obstruction n=66	p value
Male %	37.9	22.9	0.056
Age years	49.3	41.7	0.002
Asthma duration years	26.5	15.0	0.002
Ex-smoker %	43.9	34.3	0.25
Baseline FEV1 % predicted	46.5	84.9	<0.001
Postbronchodilator % predicted	57.7	96.4	<0.001

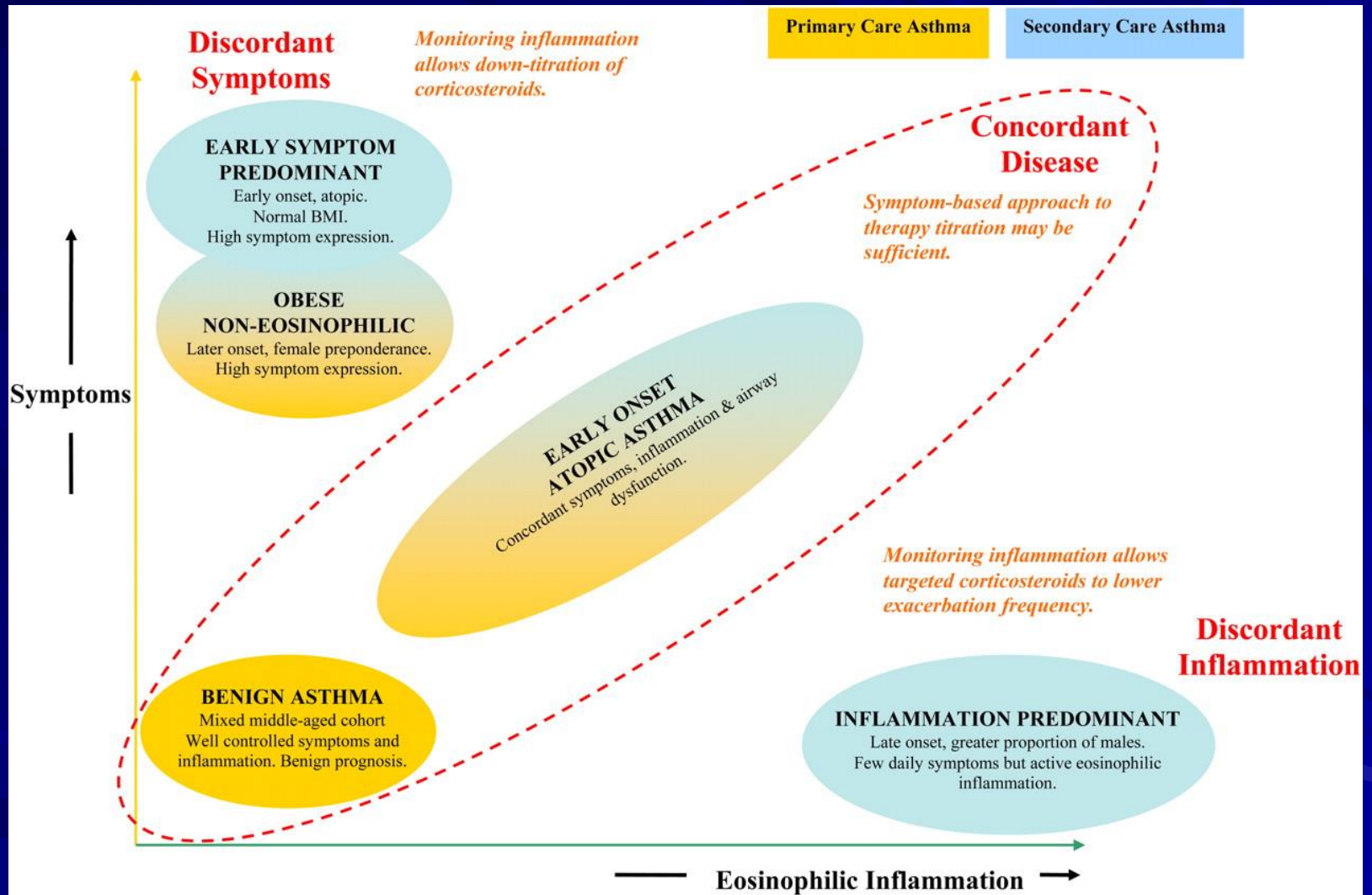
RISK FACTORS ASSOCIATED WITH PERSISTENT AIRFLOW OBSTRUCTION

	Adjusted OR	95% CI
Adult onset of asthma	3.3	1.2-9.0
Reversability of FEV1 >9%	1.7	0.8-3.6
Ex-smoker	1.3	0.6-2.9
Atopic	0.8	0.4-1.9

TYPICAL SEVERE ASTHMA PATIENT

- Female
- Age >40 years
- Adult onset
- Atopy not an important feature of the disease

CLUSTER ANALYSIS



OTHER FACTORS

- Smoking
- Obesity

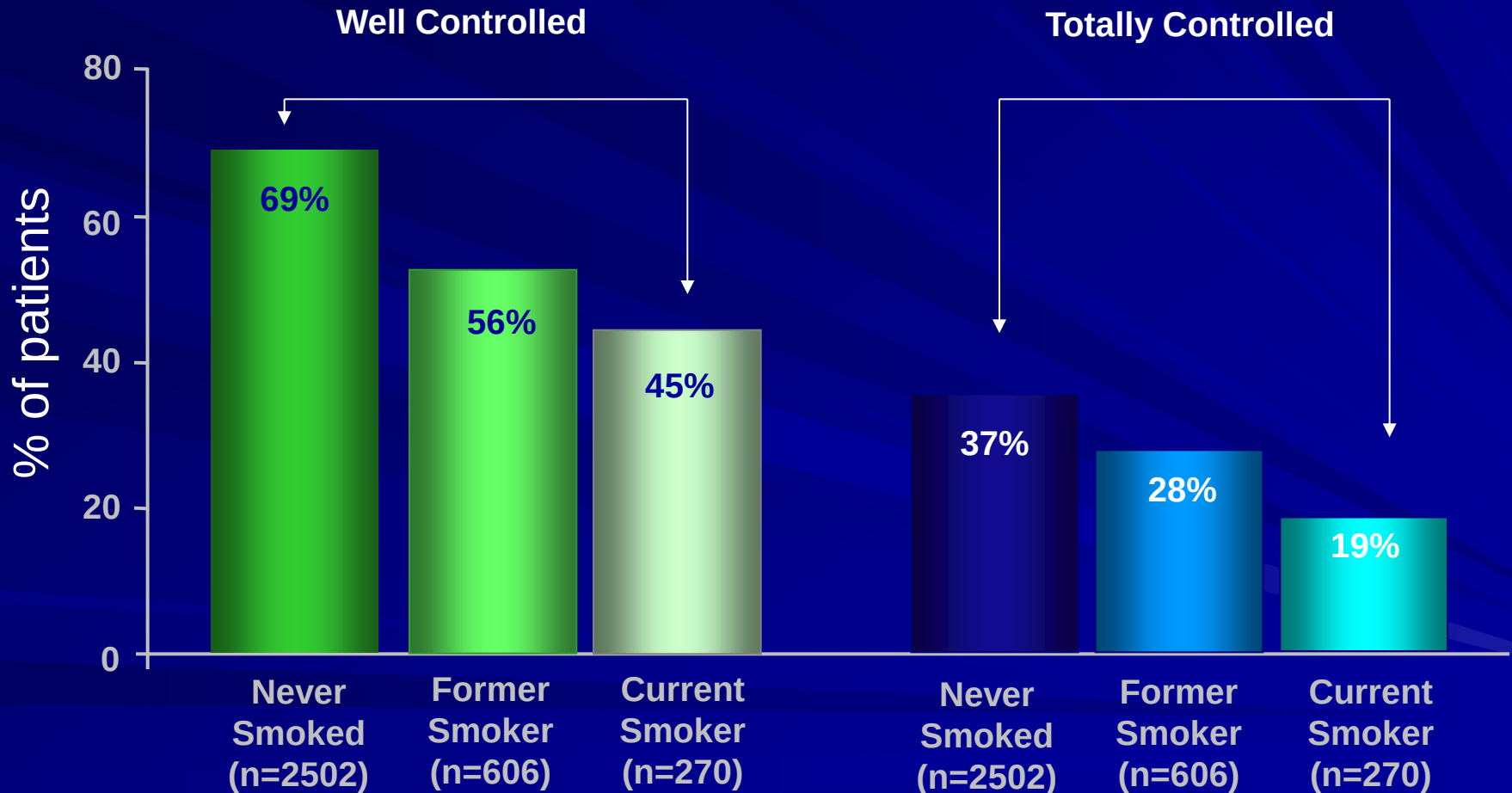
GOAL by Smoking Status

GOAL: SMOKERS* AS A SUBSET

	Stratum 1		Stratum 2		Stratum 3	
	FP (550)	SM/FP (548)	FP (578)	SM/FP (585)	FP (579)	SM/FP (576)
Non Smoker	76%	77%	75%	74%	70%	71%
Former Smoker	10%	9%	7%	6%	8%	7%
Current Smoker	14%	13%	18%	20%	22%	22%

* Protocol required ≤ 10 pack years for entry into study

ASTHMA CONTROL STATUS AND SMOKING HISTORY



OBESITY AND ASTHMA

- Obesity increases risk of asthma
- Obesity increases asthma severity
- Weight loss improves asthma control
- OSA common but treatment does not help asthma

INVESTIGATION

LUNG FUNCTION

- Peak flow may be unreliable
- FEV1 may be unreliable
- Flow volume loop
- Consider measuring resistance or conductance with body box

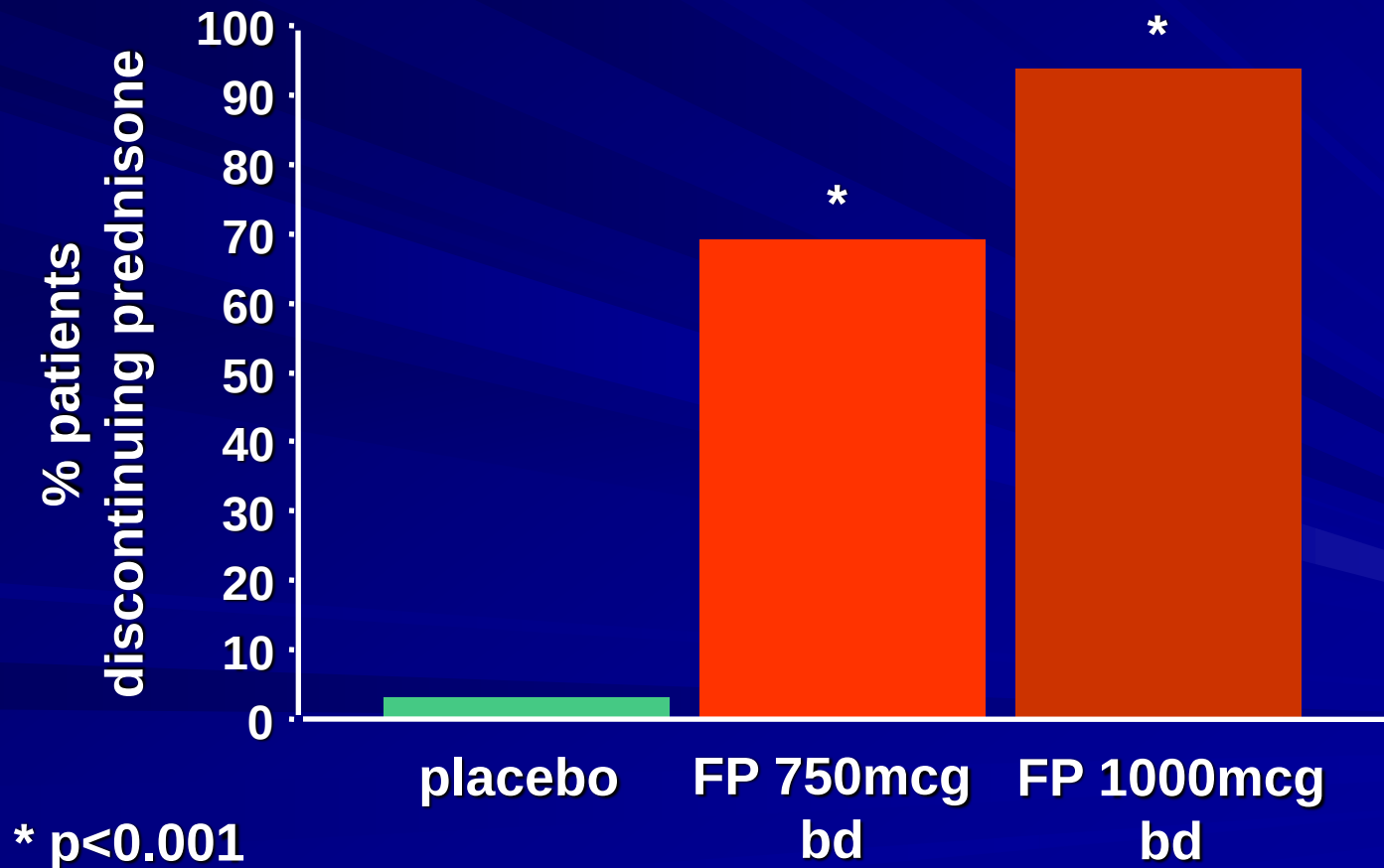
OTHER TESTS

- FBC and differential
- ANCA
- IgE
- Immunoglobulins
- Aspergillus skin tests
- HRCT
- Exhaled NO
- Sputum eosinophilia
- Admission for observation
- Bronchoscopy

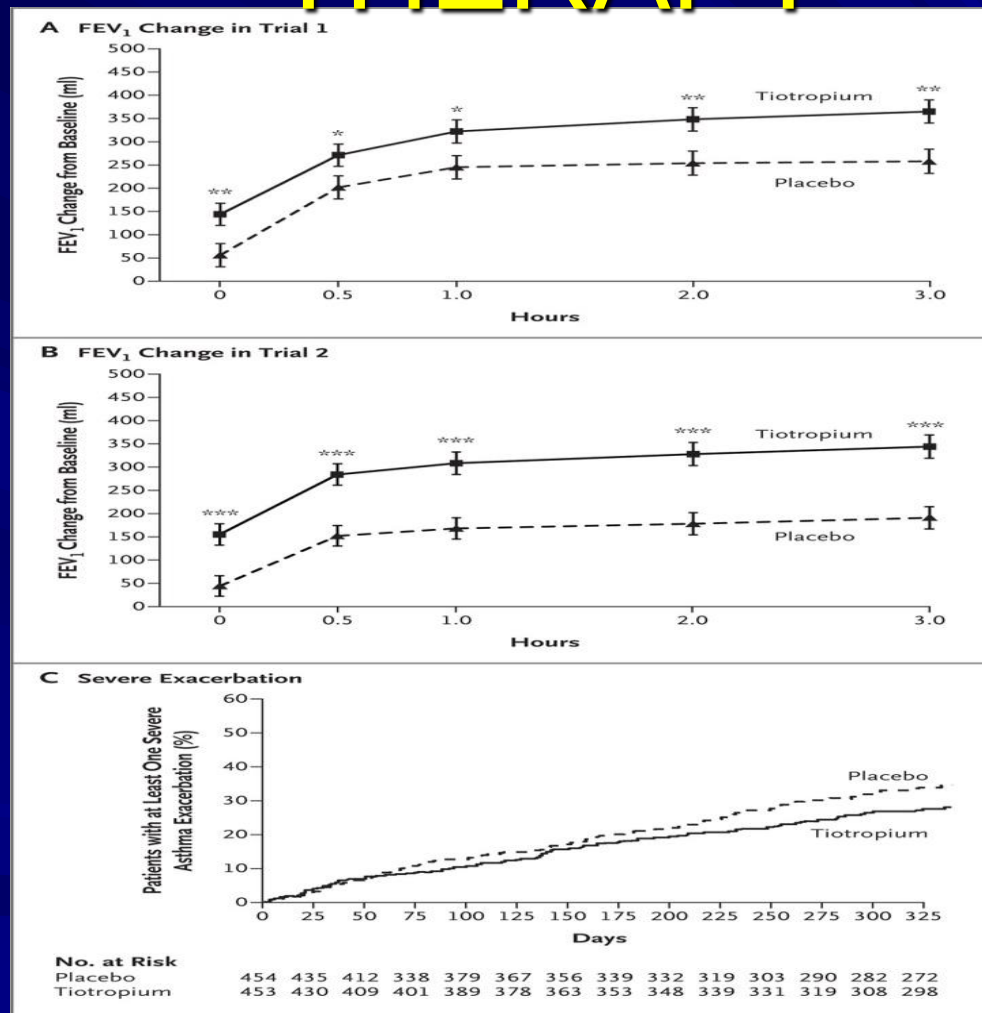
TREATMENT

- Address adherence
- Remove any triggers
- Maximise inhaled steroids and other treatments
- Consider omalizumab
- Consider an immunosuppressant

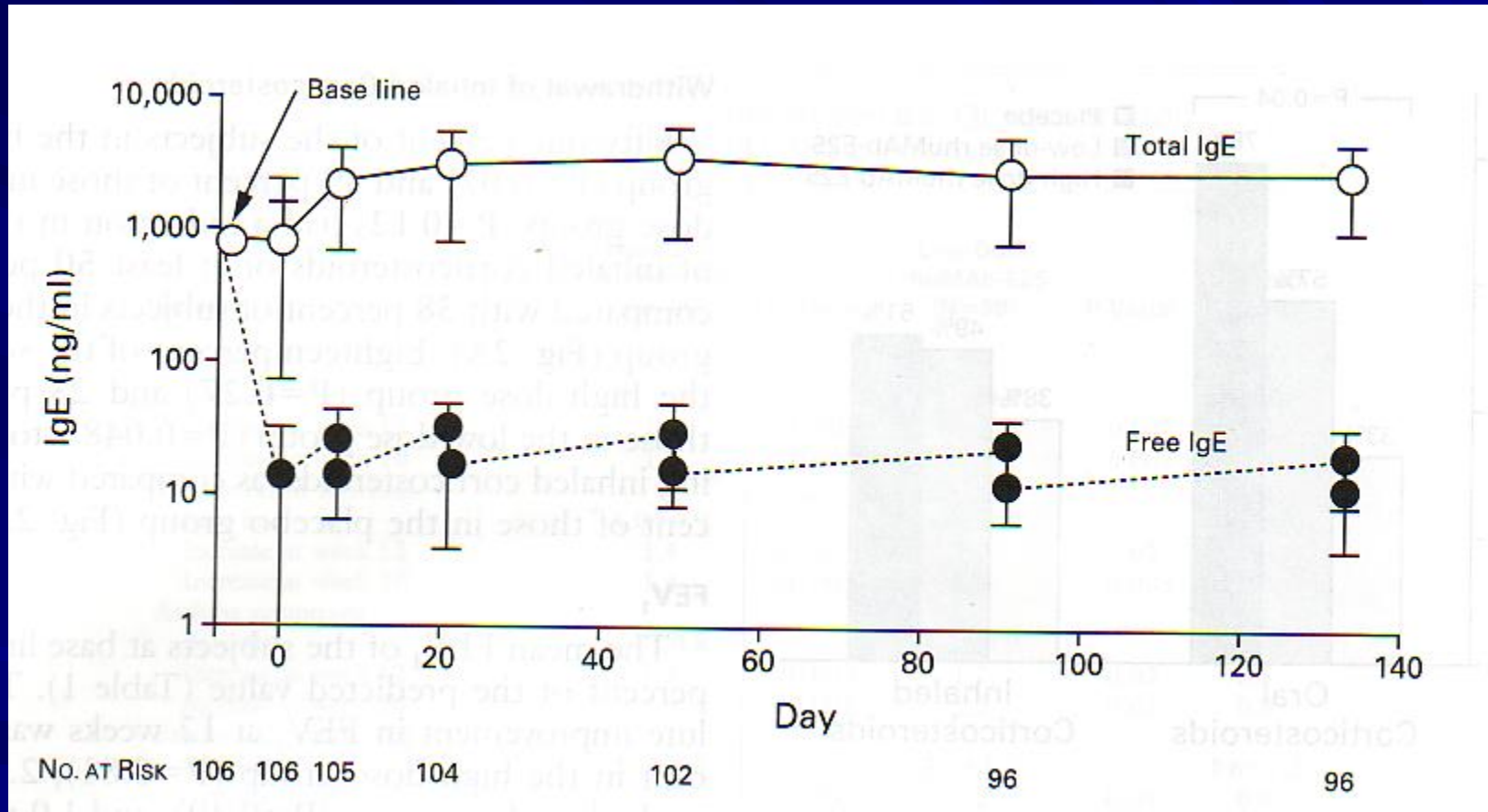
Reduction in oral prednisone requirements in patients with severe asthma



TIOTROPIUM AS ADD ON THERAPY



EFFECT OF ANTI-IgE ON SERUM IgE



OMALIZUMAB

- Step 4 of asthma guidelines
- Impaired lung function
- Symptomatic
- Frequent exacerbations
- Allergy an important cause of asthma

OMALIZUMAB

- IgE <700 iu/litre
- Less than 70 iu/litre less effective

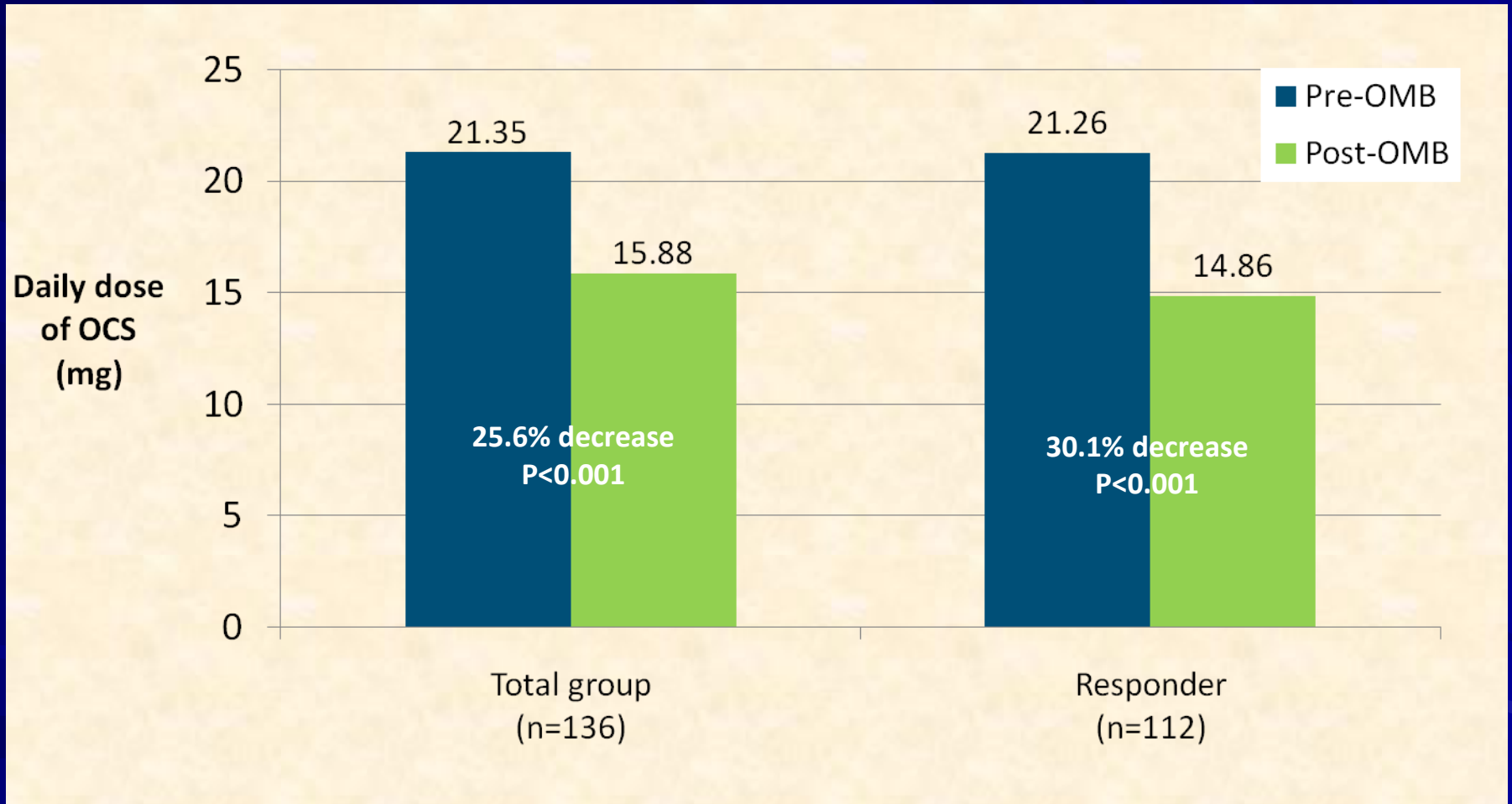
INNOVATE STUDY

- 419 patients
- FEV1 61% predicted
- 28 weeks treatment
- 19% reduction in exacerbations NS
- 26% reduction when corrected for imbalance of exacerbation history

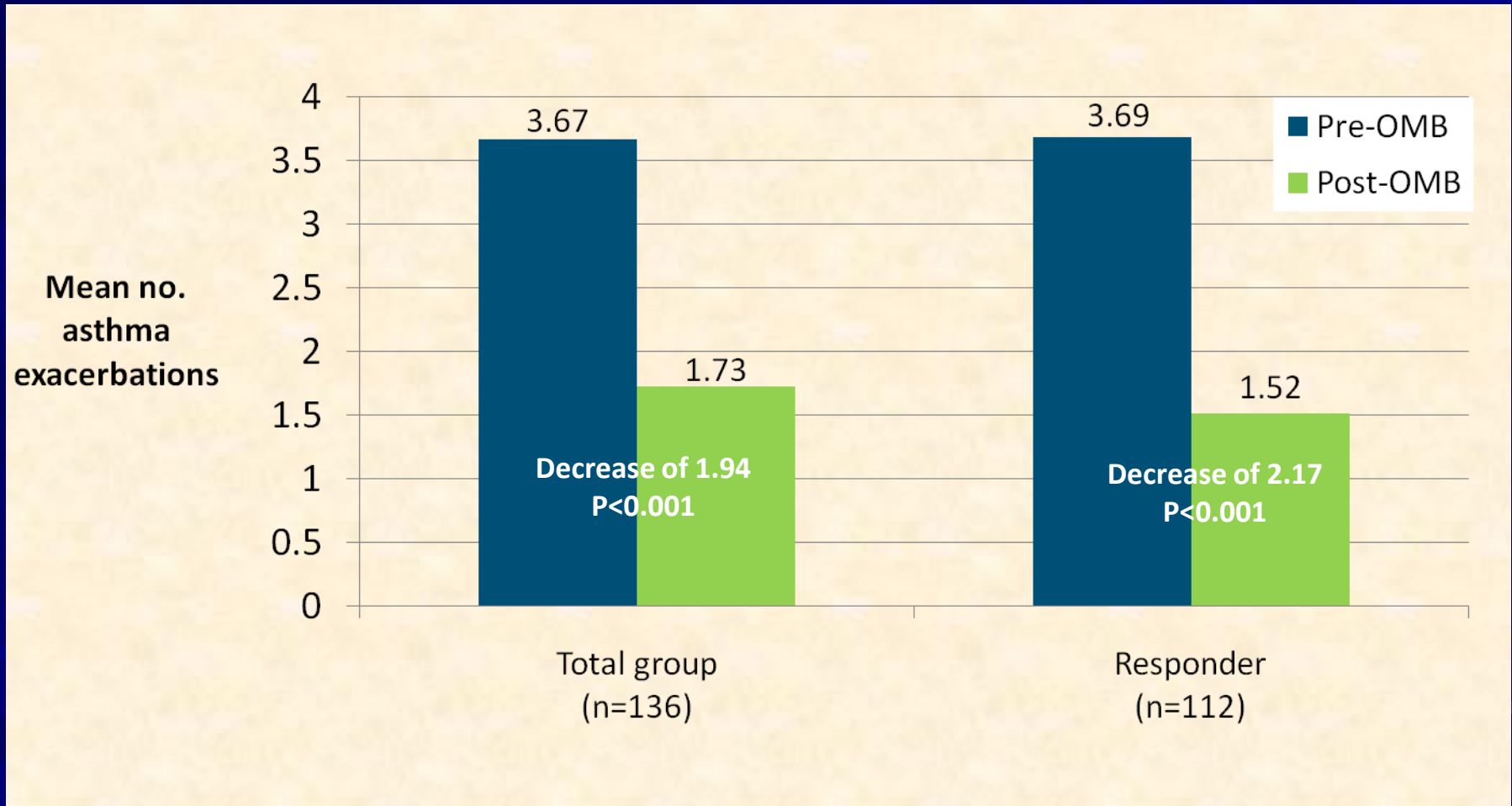
INNOVATE STUDY

- FEV1 2.8% predicted better
- 0.5 puffs/day less NS
- 60.8% vs 47.8% significant 0.5 change in AQLQ

ORAL STEROID DAILY DOSE



ASTHMA EXACERBATIONS PRE AND POST OMB



IMMUNOSUPPRESSIVE AGENTS

Good evidence

- Gold
- Methotrexate
- Ciclosporin A

IMMUNOSUPPRESSIVE AGENTS

Inadequate evidence

- Azathioprine
- Mycophenolate
- Rapamycin
- Cyclophosphamide

IMMUNOSUPPRESSIVE AGENTS

Evidence of lack of efficacy

- Troleandomycin
- Colchicine
- Hydroxychloroquine
- Gamma globulin
- Anti TNF α therapies

A CONTROLLED TRIAL OF METHOTREXATE IN SEVERE STEROID-DEPENDENT ASTHMA

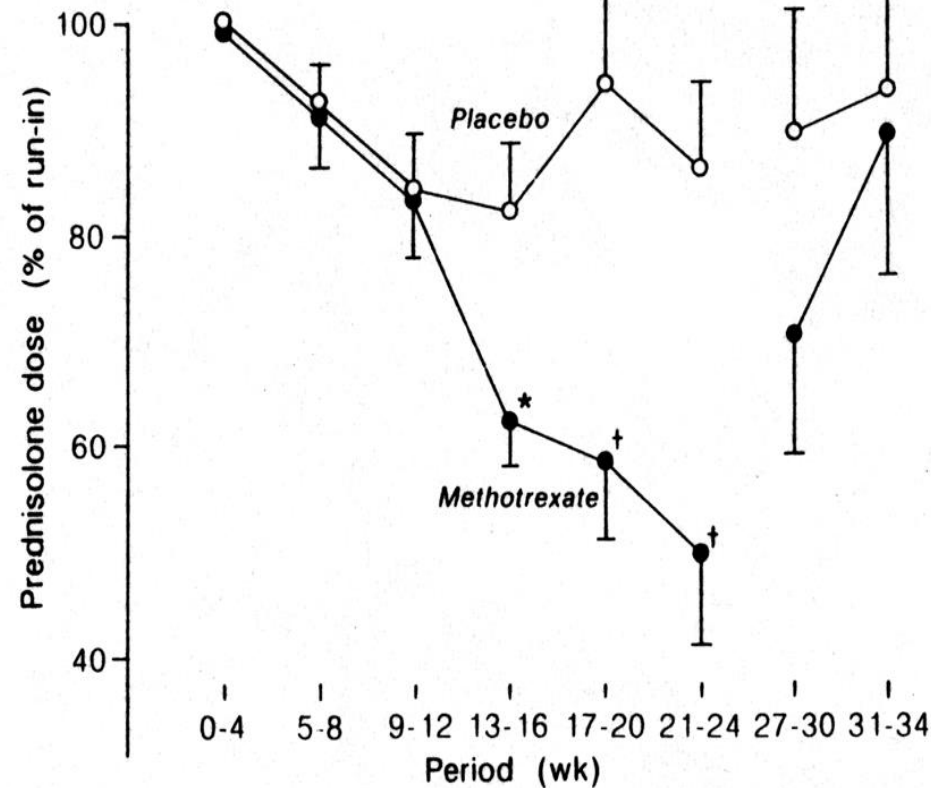
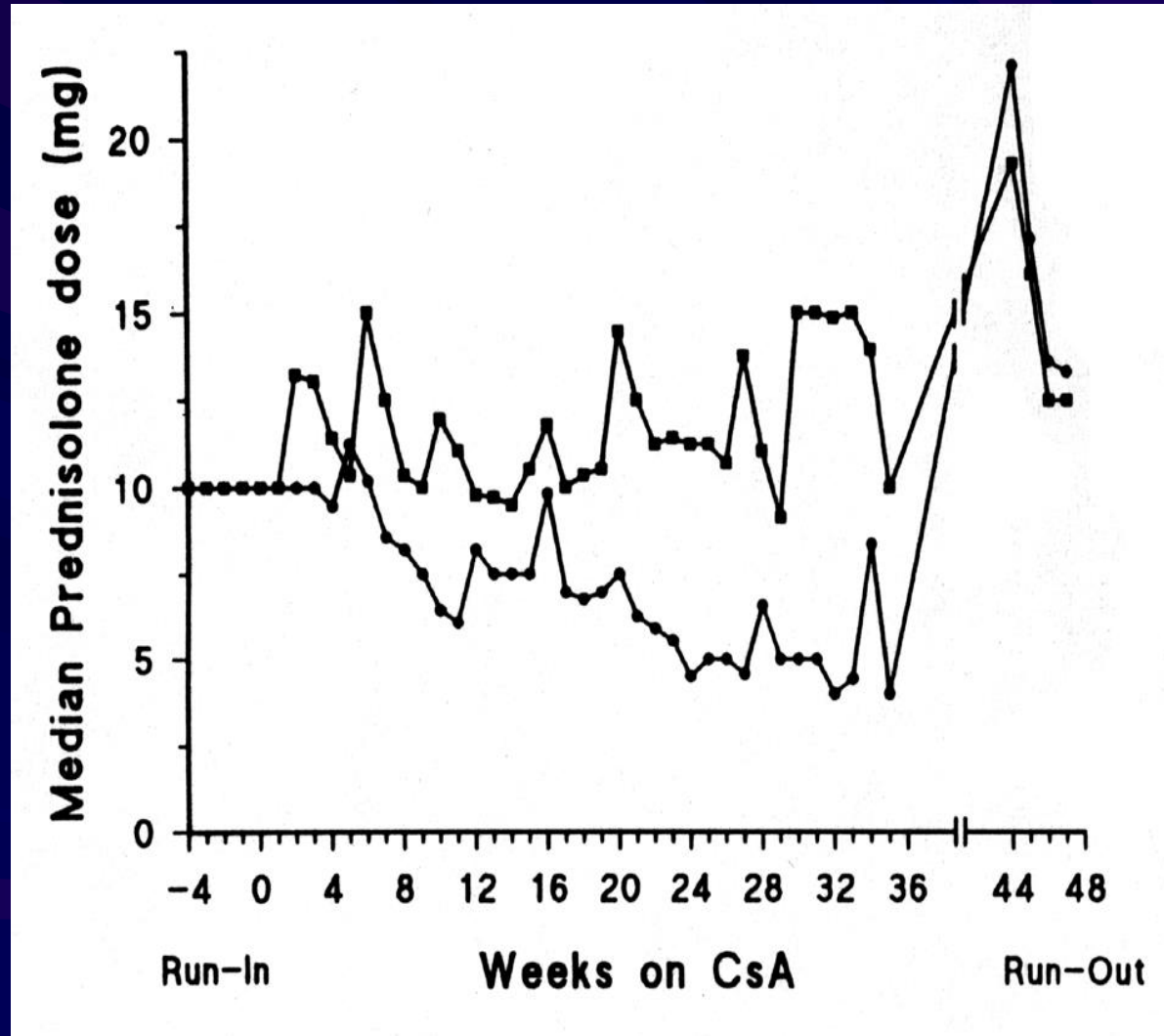


Fig 1—Effect of methotrexate of placebo on mean (SEM) daily dose of prednisolone.

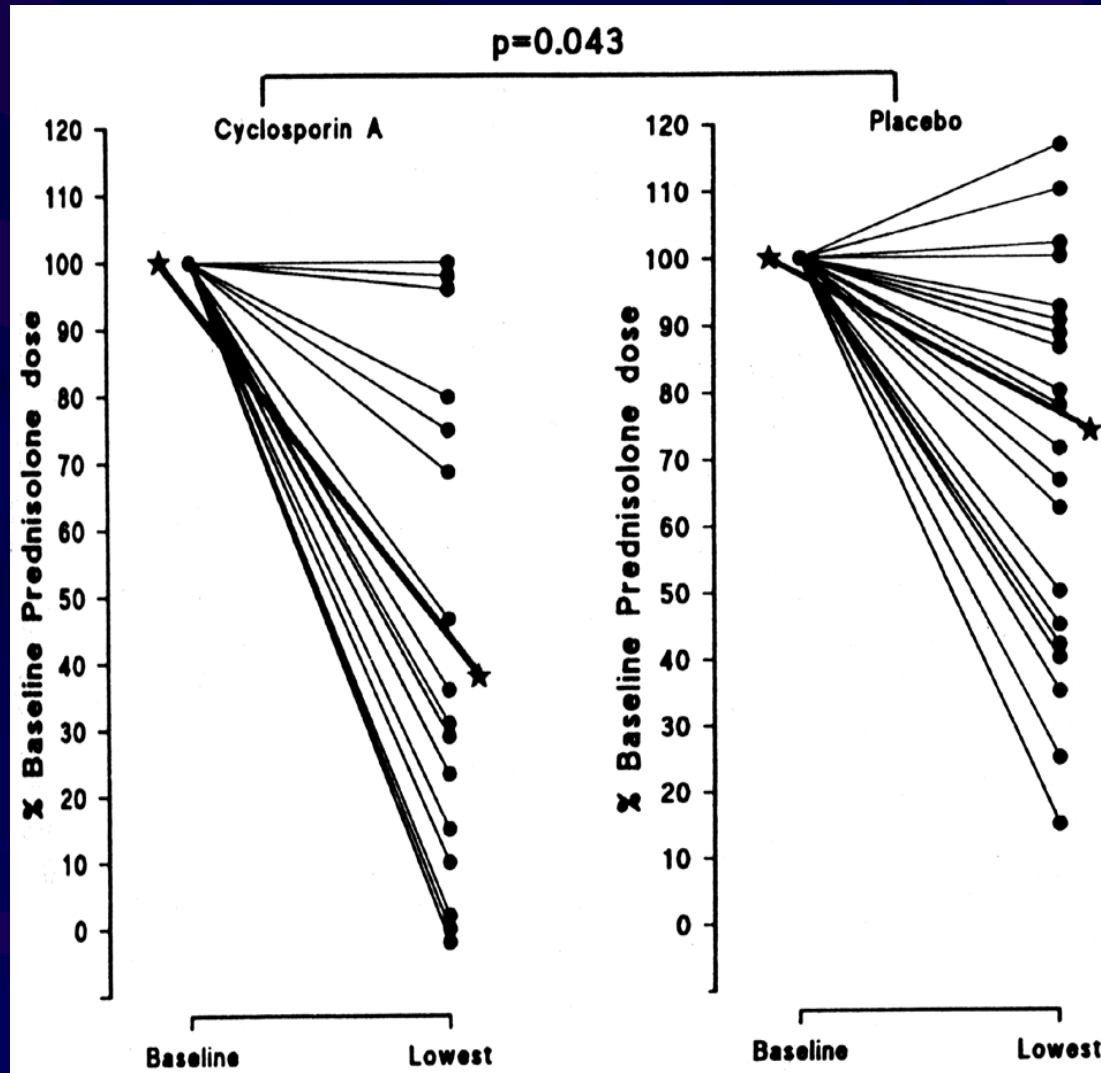
* $p < 0.05$; † $p < 0.005$.

CICLOSPORIN A IN STEROID-DEPENDENT ASTHMA



Lock et al AJRCCM 1996

LOWEST MAINTAINED STEROID DOSE ON CICLOSPORIN A IN STEROID-DEPENDENT ASTHMA



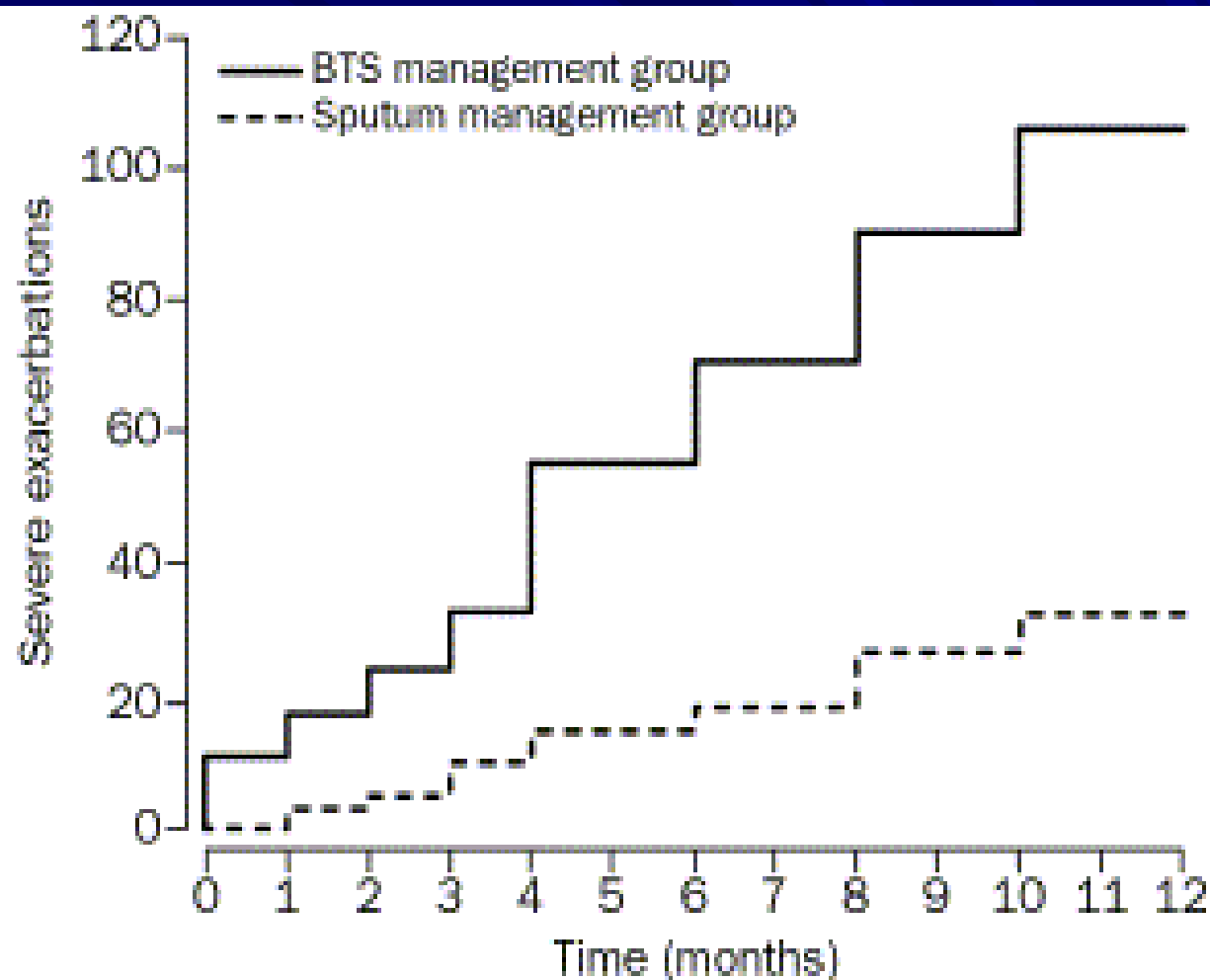
Lock et al AJRCCM 1996

MONITORING

PREDICTIVE VALUE

- ...the absence of eosinophilia does not imply the absence of treatment response

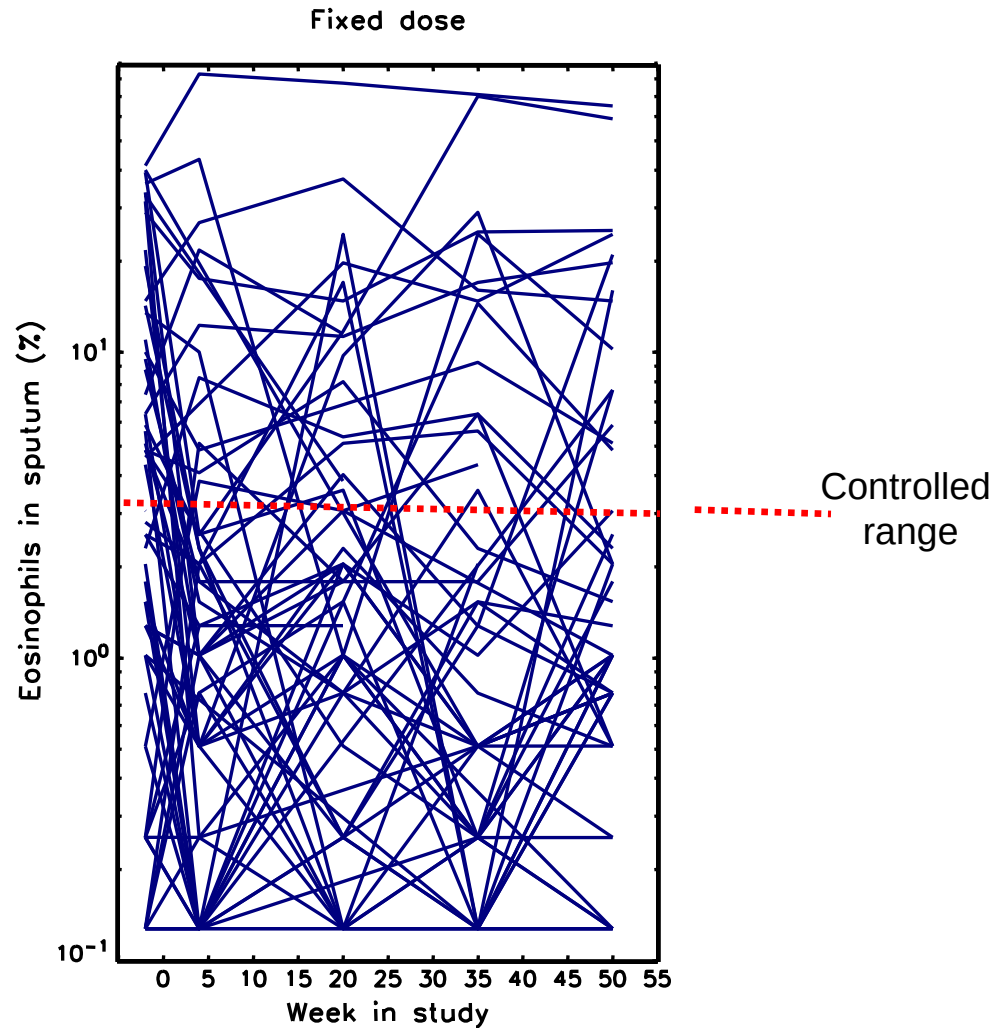
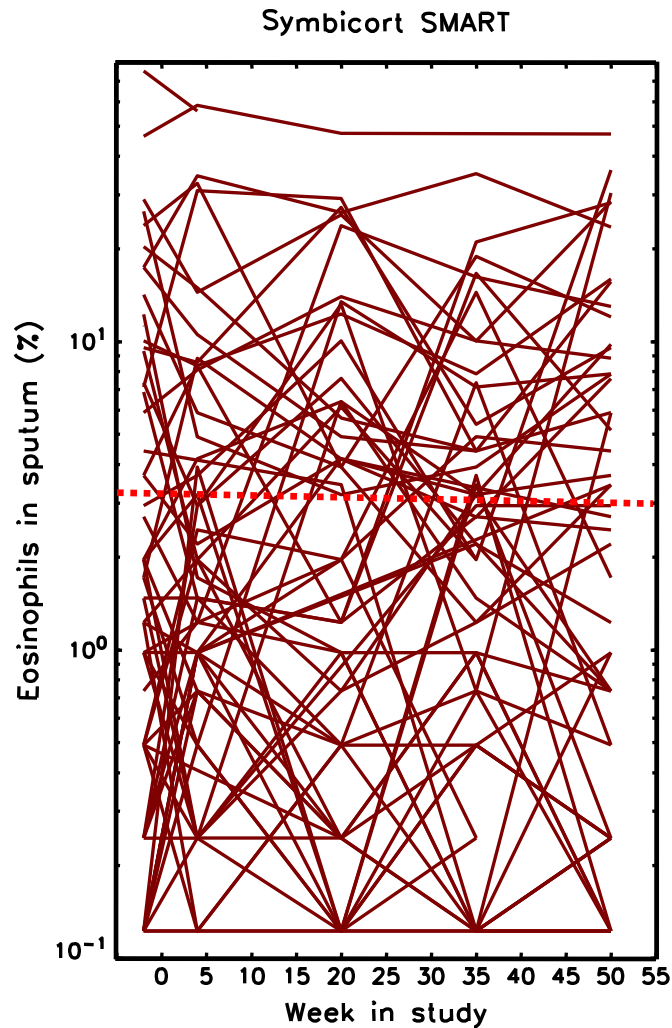
ALTERING INH STEROID DOSE ACCORDING TO SPUTUM EOSINOPHILIA IMPROVES CONTROL



Number of exacerbations

BTS group	0	12	19	26	35	55	71	90	105	109
Sputum group	0	1	4	7	12	17	21	27	30	35

Eosinophils in sputum (%) (individual curves)



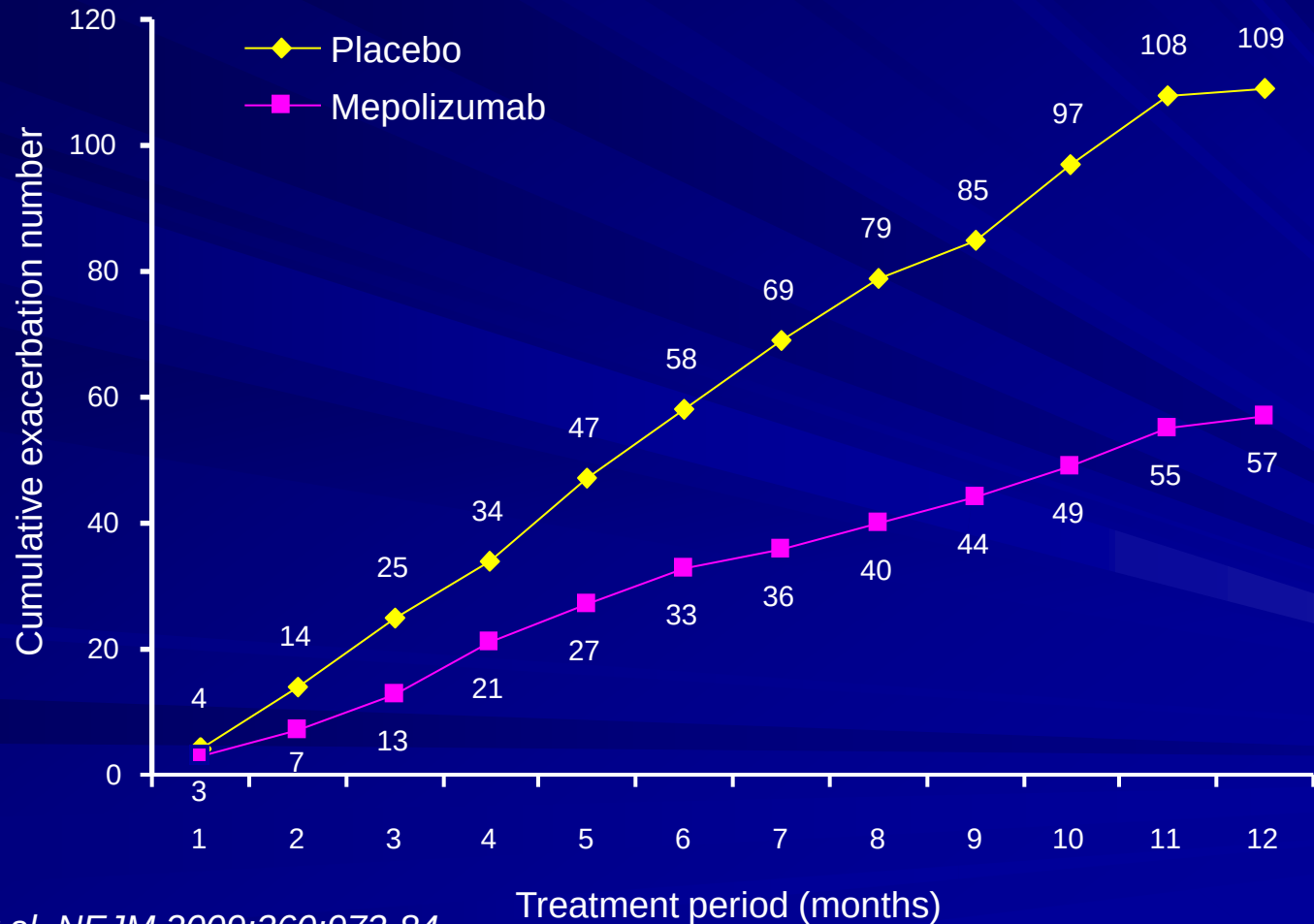
NOVEL THERAPIES

- Anti-IL5 Mepoluzimab
- Anti-IL2 Daciluzimab
- Anti-IL13 Lebrikizumab
- Anti-TNF α Golimumab

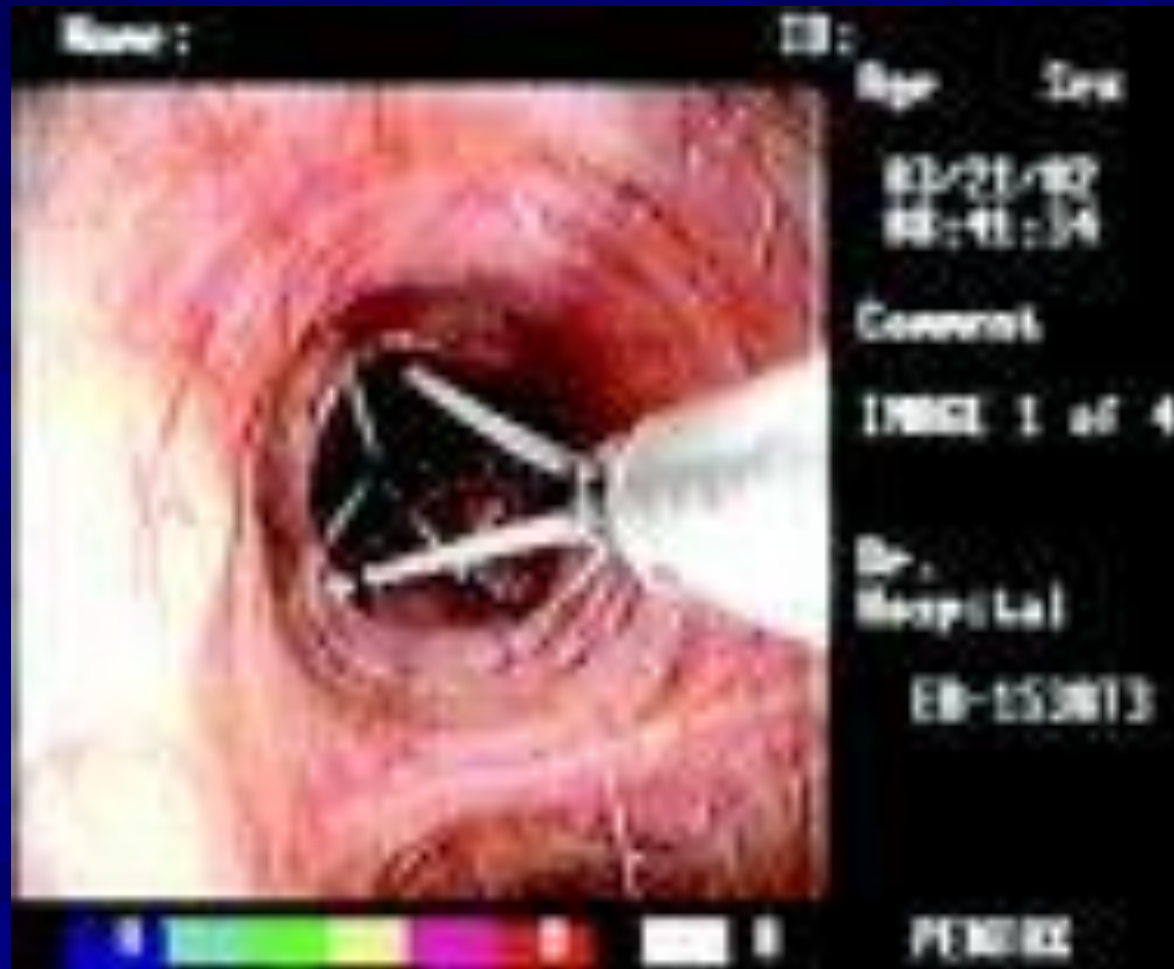
MEPOLIZUMAB IN REFRACTORY EOSINOPHILIC ASTHMA

- Parallel group, double blind, placebo controlled trial
- 61 patients with refractory severe eosinophilic asthma randomised to IV mepolizumab 750 mg monthly or placebo for 12 months
- Primary outcome: severe exacerbations

EFFECT ON SEVERE EXACERBATIONS



BRONCHIAL THERMOPLASTY



CONCLUSIONS

- Review is it asthma
- Is it asthma plus another disease
- Assess compliance
- Optimise conventional management
- Consider omalizumab
- Consider immunosuppressant

THANK YOU