

Asthma Therapeutics: What's In The Pipeline?

Paul A. Greenberger, M.D.

10/18/2010

Disclosure of Conflict of Interest Information

I have the following relationships that exist related to this presentation:

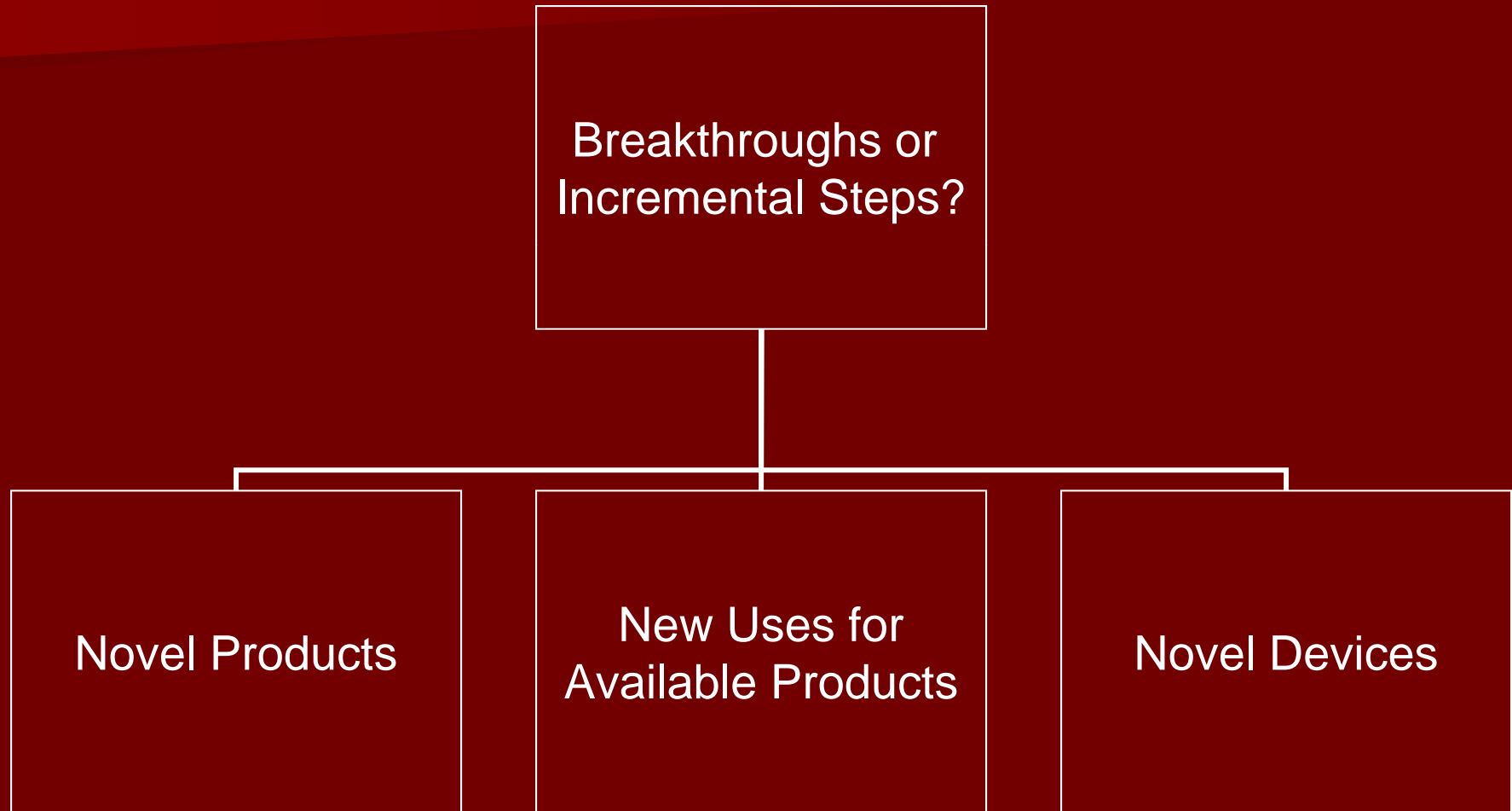
- AAAAI past president
- Consultant (Mylan)
- Miscellaneous Legal (Drug allergy, immunology, asthma)

Additionally, I will be discussing information about a product/procedure/technique that is not yet approved.

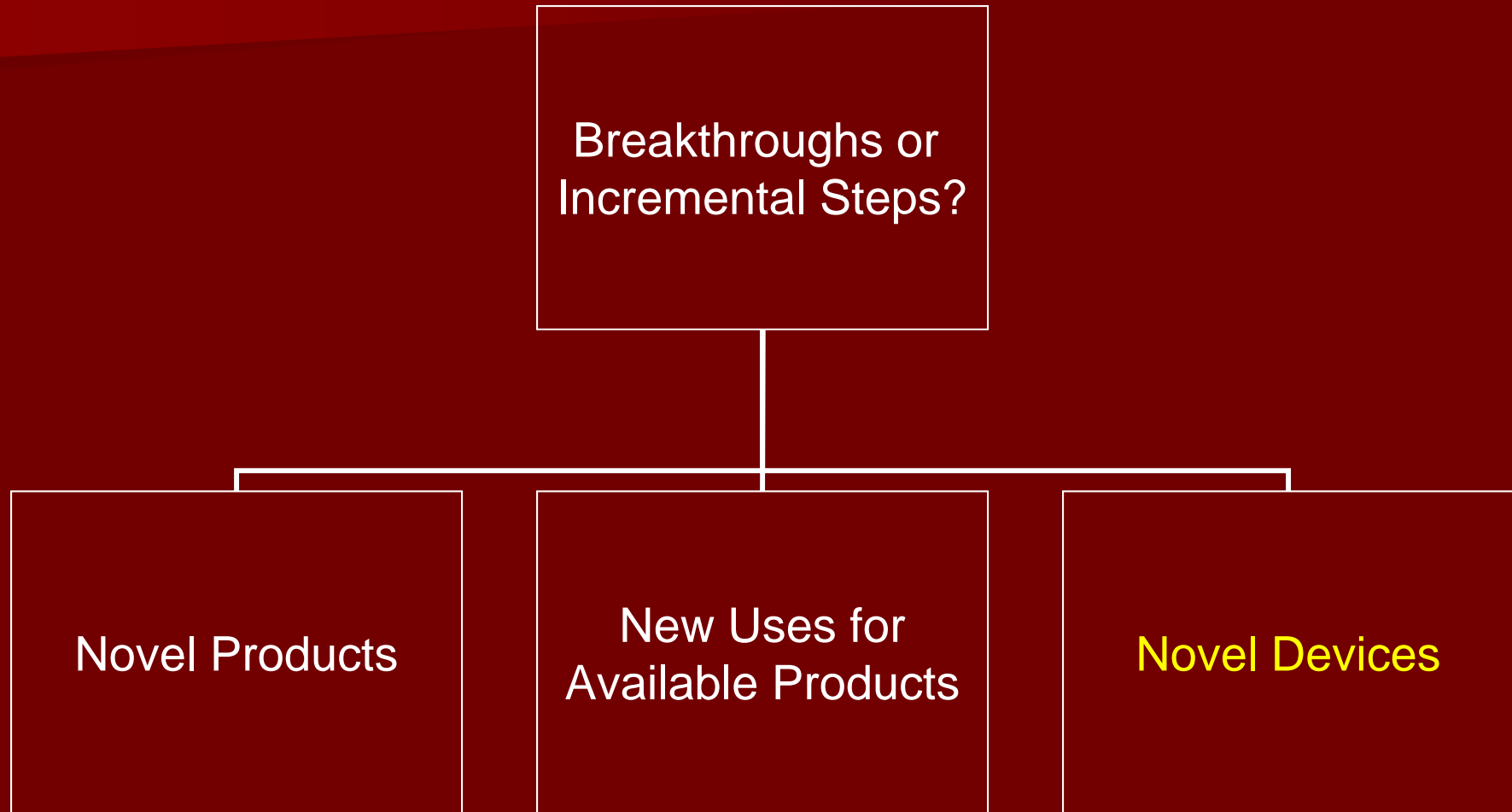
Objectives

- Review novel products for management of persistent asthma
- Explore aspects of novel uses of approved products for persistent asthma
- Learn about a newly approved device for persistent severe asthma

The Pipeline—To Improvements For Patients



The Pipeline—To Improvements For Patients

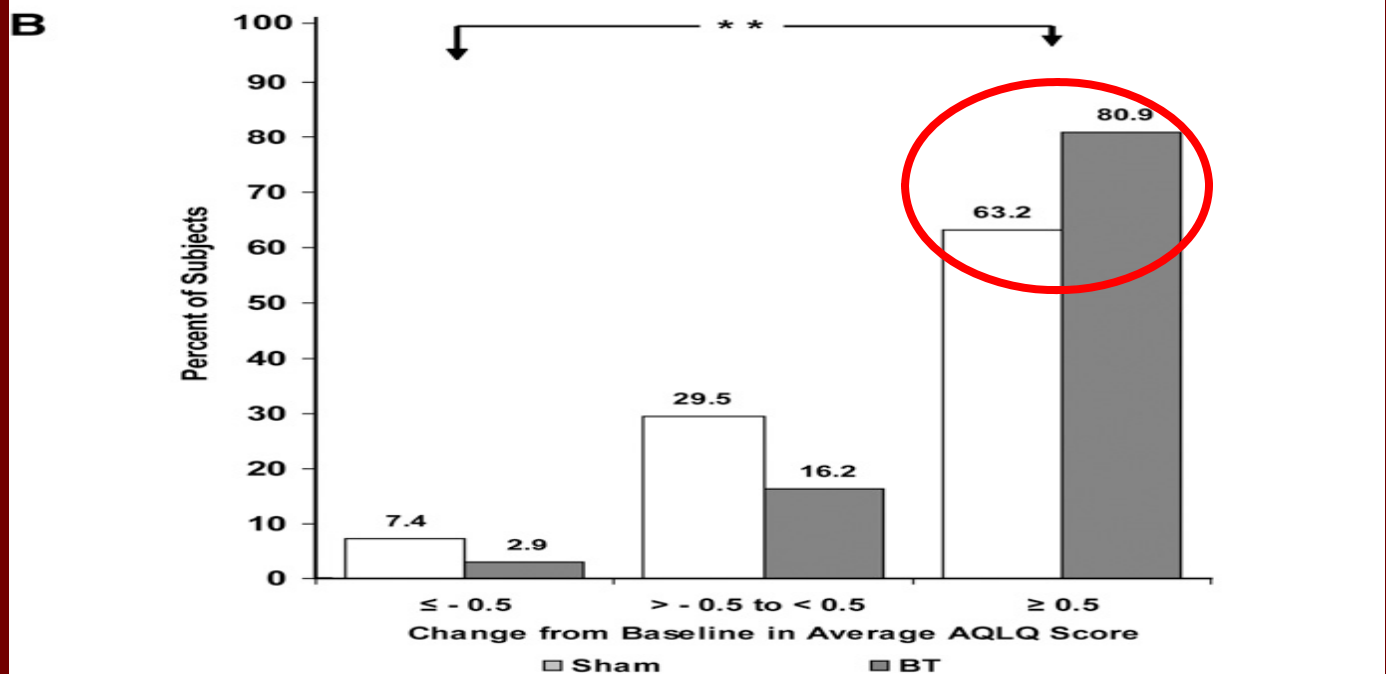
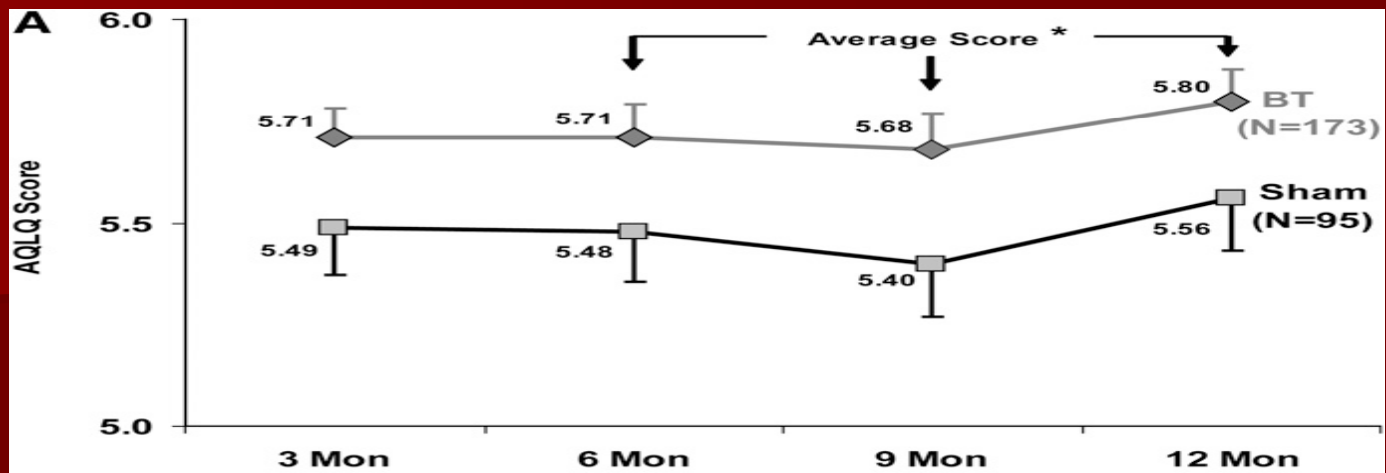


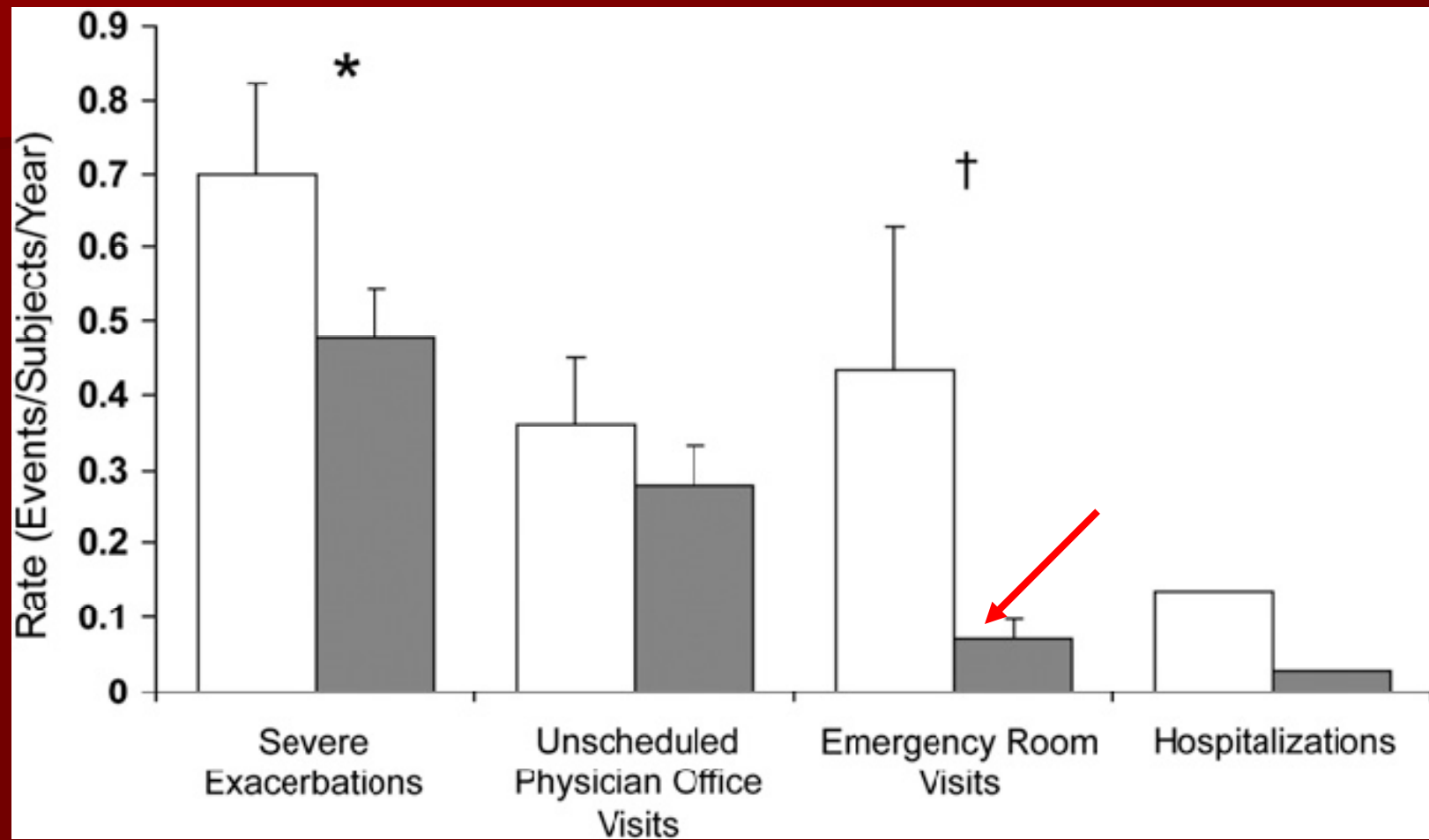
Novel Device

- A Novel Bronchial Thermoplasty; approved 4/2010
- Indication-persistent severe asthma
- Premise-*reduce increased amount of airway smooth muscle*
- Insert catheter to distal targeted airway
- Heat 5mm area to 65°C...3 separate but contiguous locations of the airway.....total of 3 procedures

Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma

- AJRCCM 2010;181:116-24
- Primary outcome: AQLQ score
- Inclusion criteria: combination therapy
- At entry Beclomethasone dipropionate 1900 ug in each group + LABA
- AQLQ: 4.3 in each group





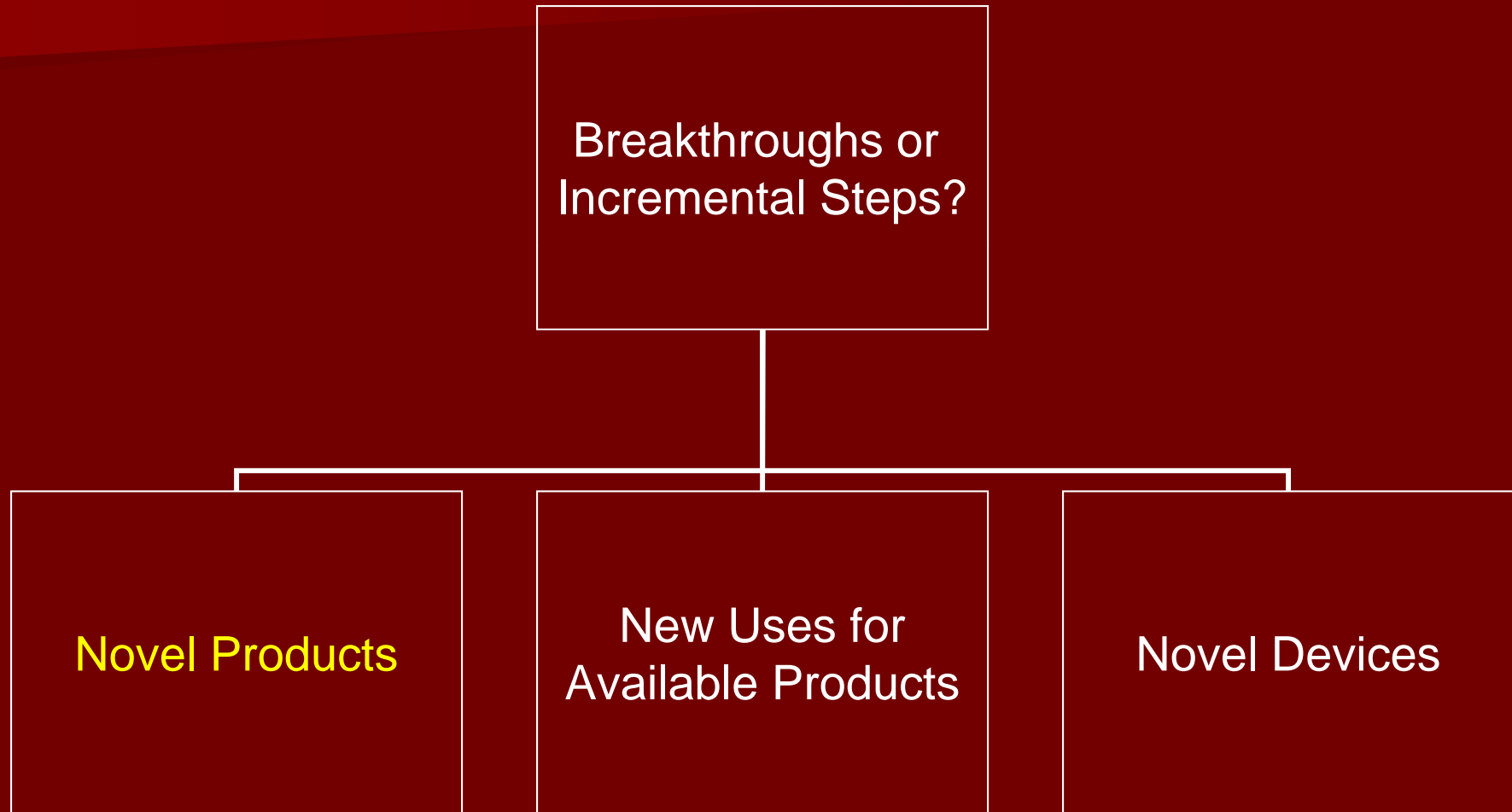
Comments/Questions

- In the sham group, what happens to self-care by study participants?
-

- What does this effect do to the potential benefit of the active treatment?
-

- “There was an 84% reduction in risk of ED visits (0.07 vs 0.43 visits/subject/year)

The Pipeline—To Improvements For Patients



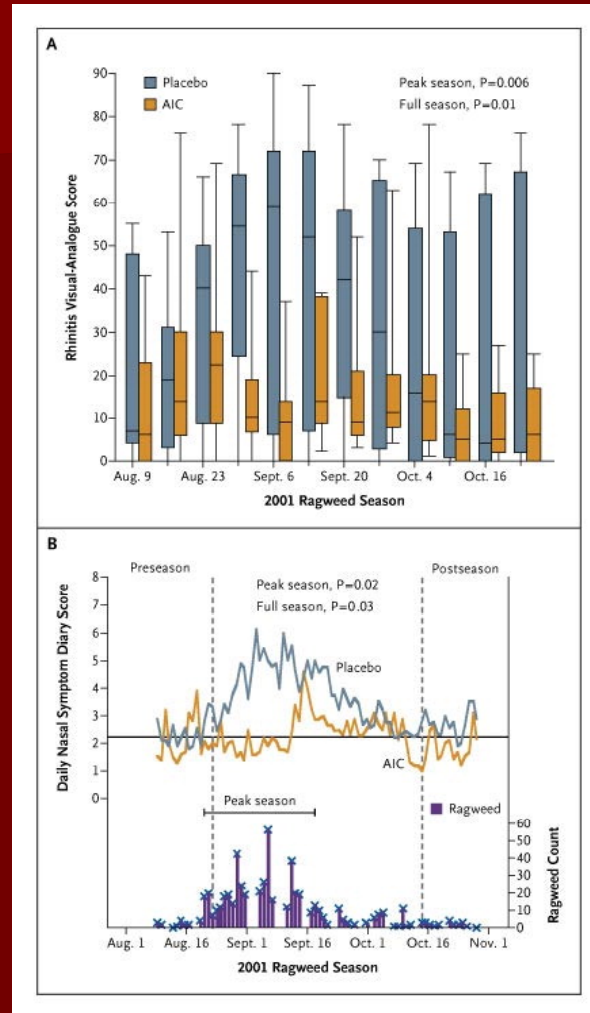
Novel Products (1)

- Immunotherapy-Immunostimulatory oligodeoxynucleotide Amb a 1
- Some success (?) in Ragweed Allergic Rhinitis—primary outcome measure (vascular permeability) not met
- Reduction in VAS in symptoms in year 1
- Trend to decreased NASAL symptoms year 2—was decreased at peak season
- Trial for asthma

Rationale ISS

- Immunostimulatory DNA Sequences (ISS)
- ISS binding to TLR-9 on plasmacytoid dendritic cells
- Promotes Th1 cytokines
- Decrease Th2 cytokines including less eosinophils
- Unmethylated CpG dinucleotides serve as potent **agonists to boost** vaccine efficacy---combine with Ragweed for benefit
- Methylated CpG dinucleotides suppress responses

Results for the First Ragweed Season (2001).

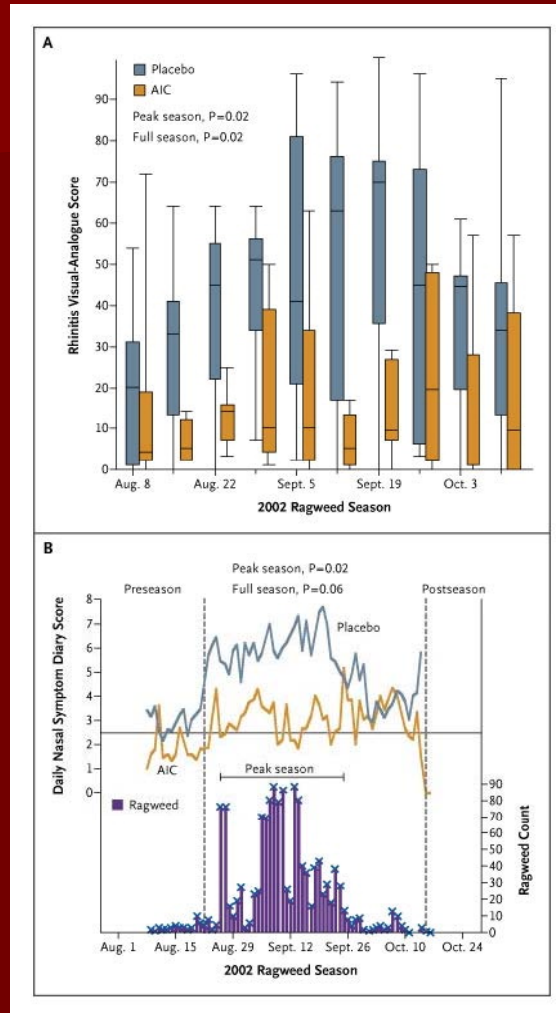


Creticos PS et al. N Engl J Med 2006;355:1445-1455.



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Results for the Second Ragweed Season (2002).



Creticos PS et al. N Engl J Med 2006;355:1445-1455.



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ISS for Ragweed Asthma

- Stay tuned

Novel Products (2)

- **Sub-lingual immunotherapy (SLIT)**
- Contact with mucosa (tablets, liquids, modified allergens, unmodified allergens)
- Home use; widespread use in Europe especially for grasses
- Reduction in symptoms for allergic rhinitis and asthma-especially mono-sensitized patients
- Reduced new sensitivities
- Not approved for use in US.....1 positive study; 3 negative studies

Novel Immunotherapy (3)

- Immunoglobulin-allergen FUSION protein ($Fc\gamma$ - $Fc\epsilon$) suppresses activation of mast cells and basophils by use of **inhibiting $Fc\gamma$ RIIb receptor**

Novel Products (4)

- Leukotriene Pathway....FLAP inhibitor??
- Leukotriene Pathway...superior inhibitors/antagonists compared to zileuton/montelukast and zafirlukast
- IV monteukast 7mg for acute asthma- disappointing clinically but some pharmacologic effect on increase in FEV₁

A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma

- JACI 2010;125:374-80
- Treatment failure and total Beta agonist use not different

Novel Products (5)

- Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma
(NEJM 2009;360:973-84)

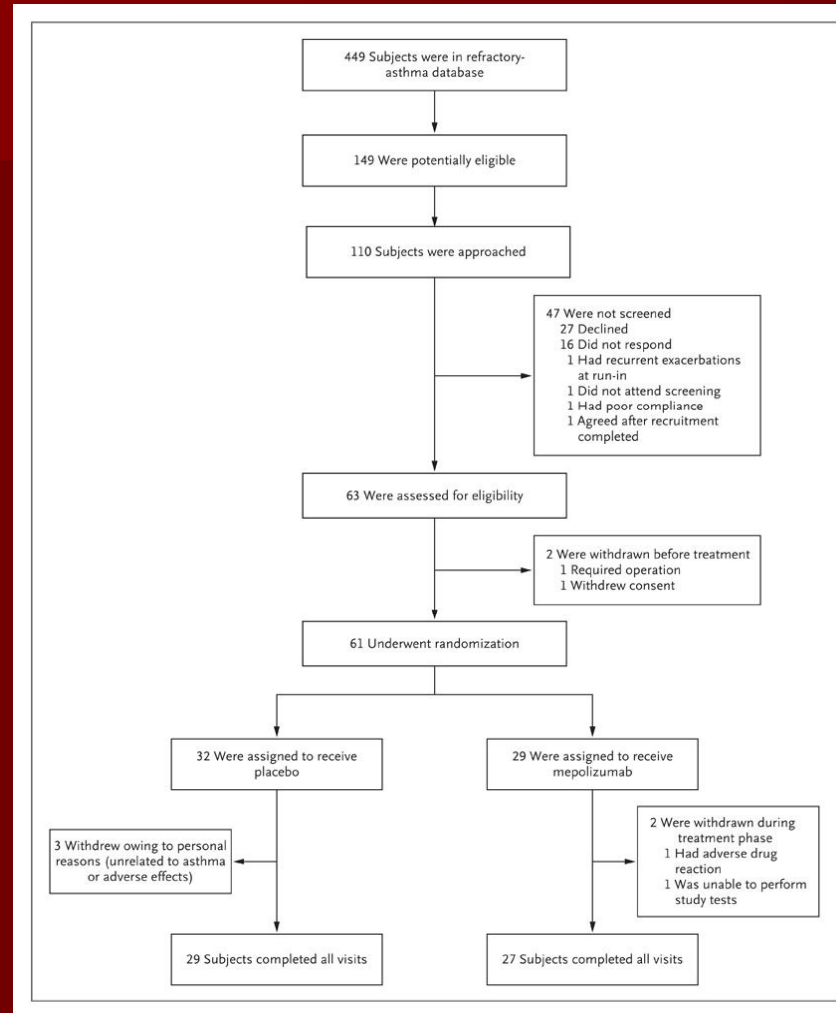
Decreased number of severe exacerbations: 2.0 vs 3.4/subject

Increased AQLQ (+ 0.55 vs + 0.19)

Decreased blood and sputum eosinophils

No change in FEV₁ and bronchial hyperresponsiveness

Numbers of Patients Who Were Screened, Enrolled, and Assigned to a Study Group and Who Completed the Study.

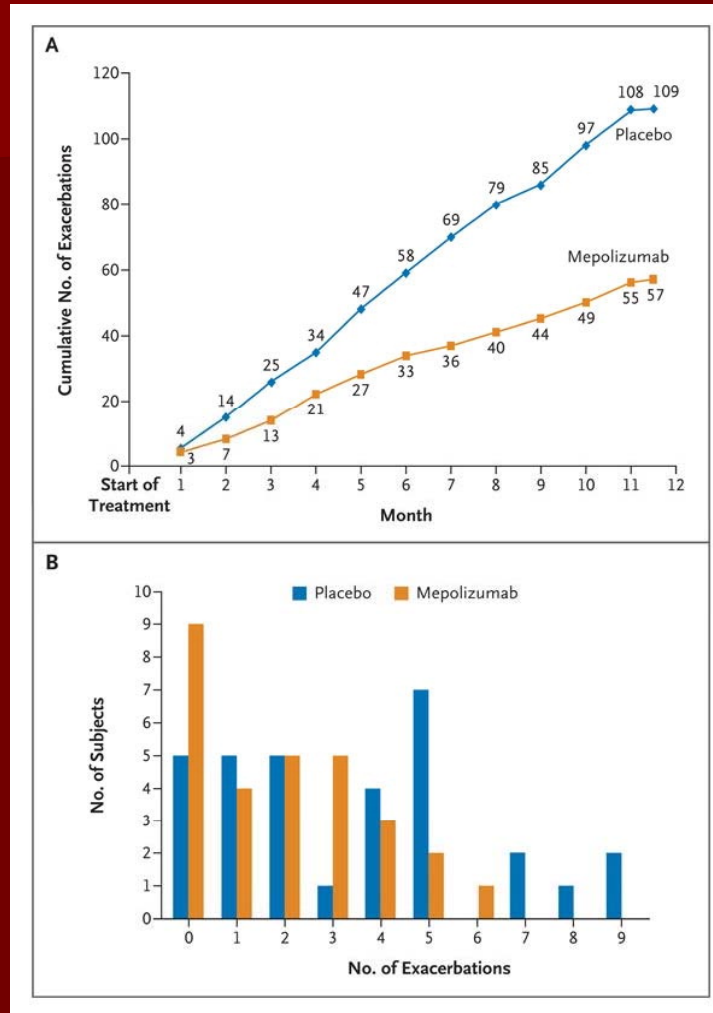


Haldar P et al. N Engl J Med 2009;360:973-984.



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Severe Exacerbations during the Course of the Study.



Haldar P et al. N Engl J Med 2009;360:973-984.

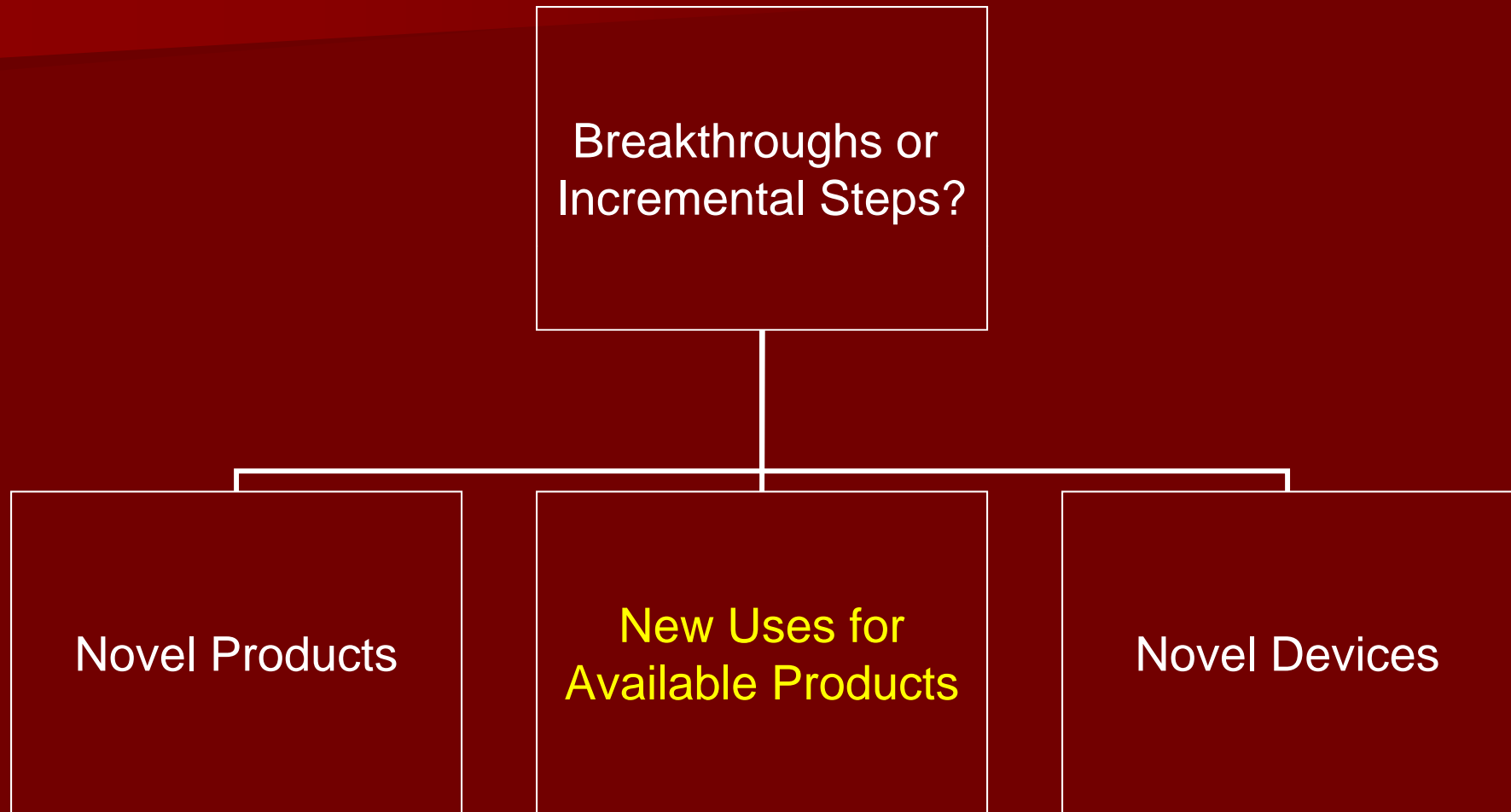


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Novel Products (6)

- AB 1010 for persistent severe asthma
- Masitinib—oral selective tyrosine kinase inhibitor targeting KIT (the receptor-designated CD 117- for stem cell factor)
- Stem cell factor is up-regulated in multiple inflammatory conditions---there is GAIN of FUNCTION mutation in mastocytosis causing activation of tyrosine kinase...also true in leukemias and other tumors

The Pipeline—To Improvements For Patients



**USING
APPROVED
PRODUCTS**

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graph TD; A[USING APPROVED PRODUCTS] --> B[ITRACONAZOLE (ANTI-FUNGAL)]; A --> C[MACROLIDES]; A --> D[VITAMIN D]; A --> E[SLIT (SUBLINGUAL IMMUNOTHERAPY)];
```

**ITRACONAZOLE
(ANTI-FUNGAL)**

MACROLIDES

VITAMIN D

**SLIT
(SUBLINGUAL
IMMUNOTHERAPY)**

**USING APPROVED
PRODUCTS
MORE
EFFECTIVELY**

**PERSONALIZED
MEDICINE**

SMART (2)

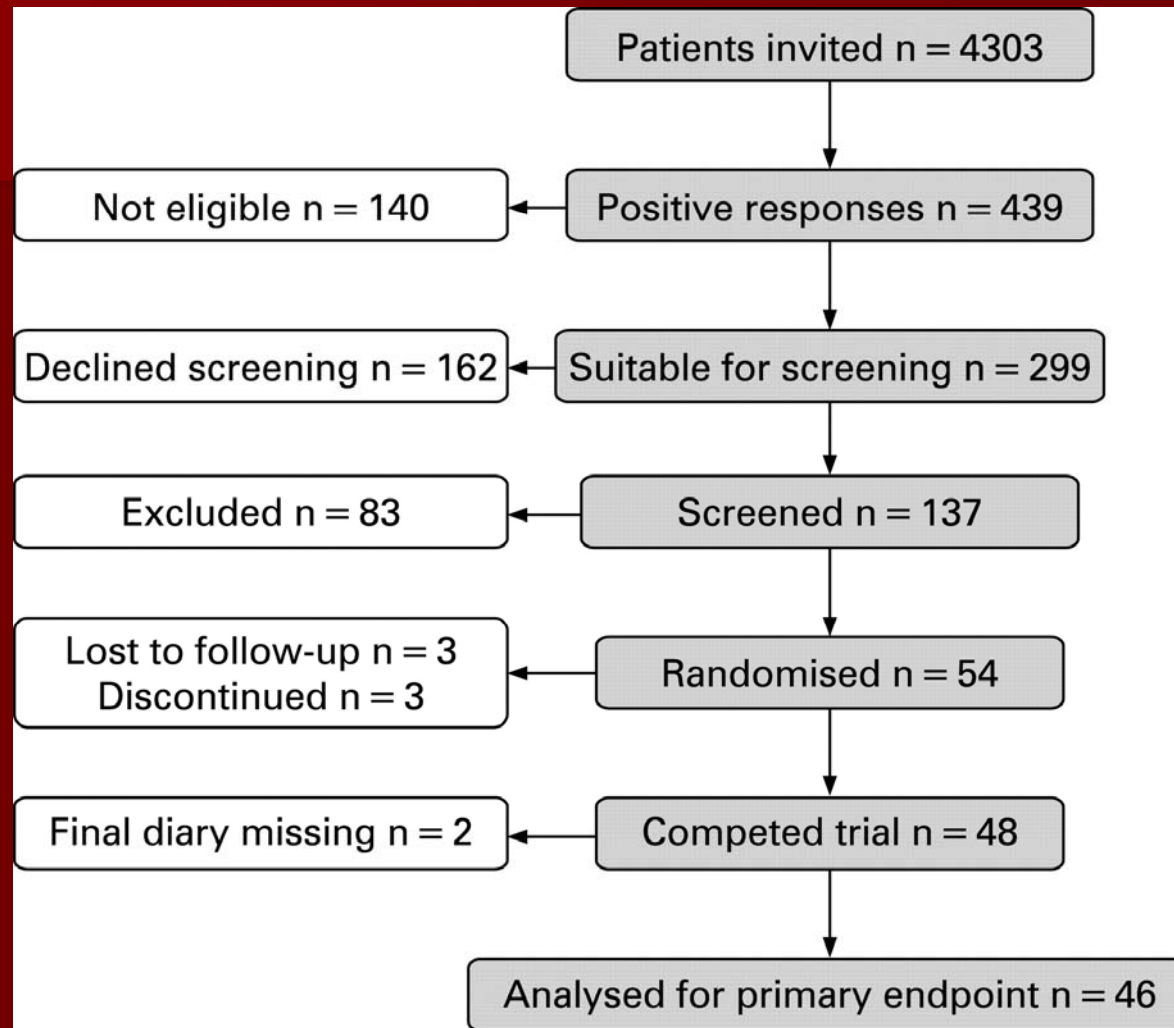
**PRN ICS FOR
PERSISTENT
MILD ASTHMA-
*IMPACT***

**ICS AT
FOURFOLD
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DOSAGE
FOR
EXACERBATIONS**

Effects of atorvastatin added to inhaled corticosteroids on lung function and sputum cell counts in atopic asthma

- Thorax 2008;63:1070-75
- 3-HMG Co A reductase inhibitor-the rate limiting step in cholesterol synthesis
- Anti-inflammatory
- In RA, decreased CRP, ESR, IL-6
- Anti-inflammatory effect in murine asthma

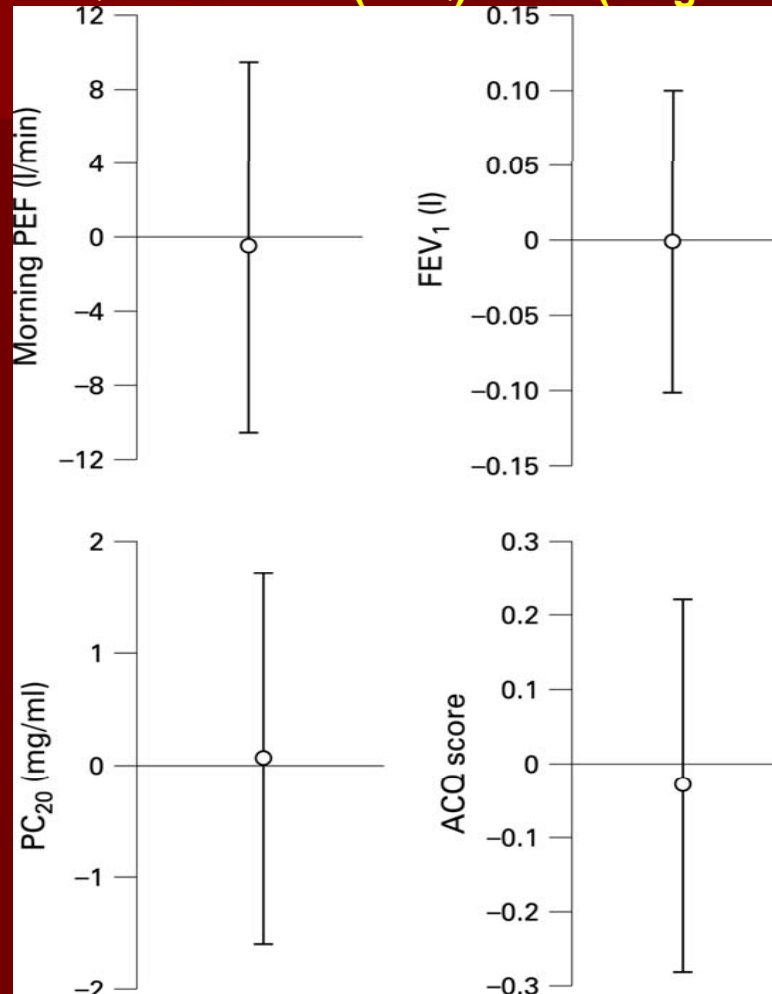
Flow of subjects through the study.



Hothersall E J et al. *Thorax* 2008;63:1070-1075



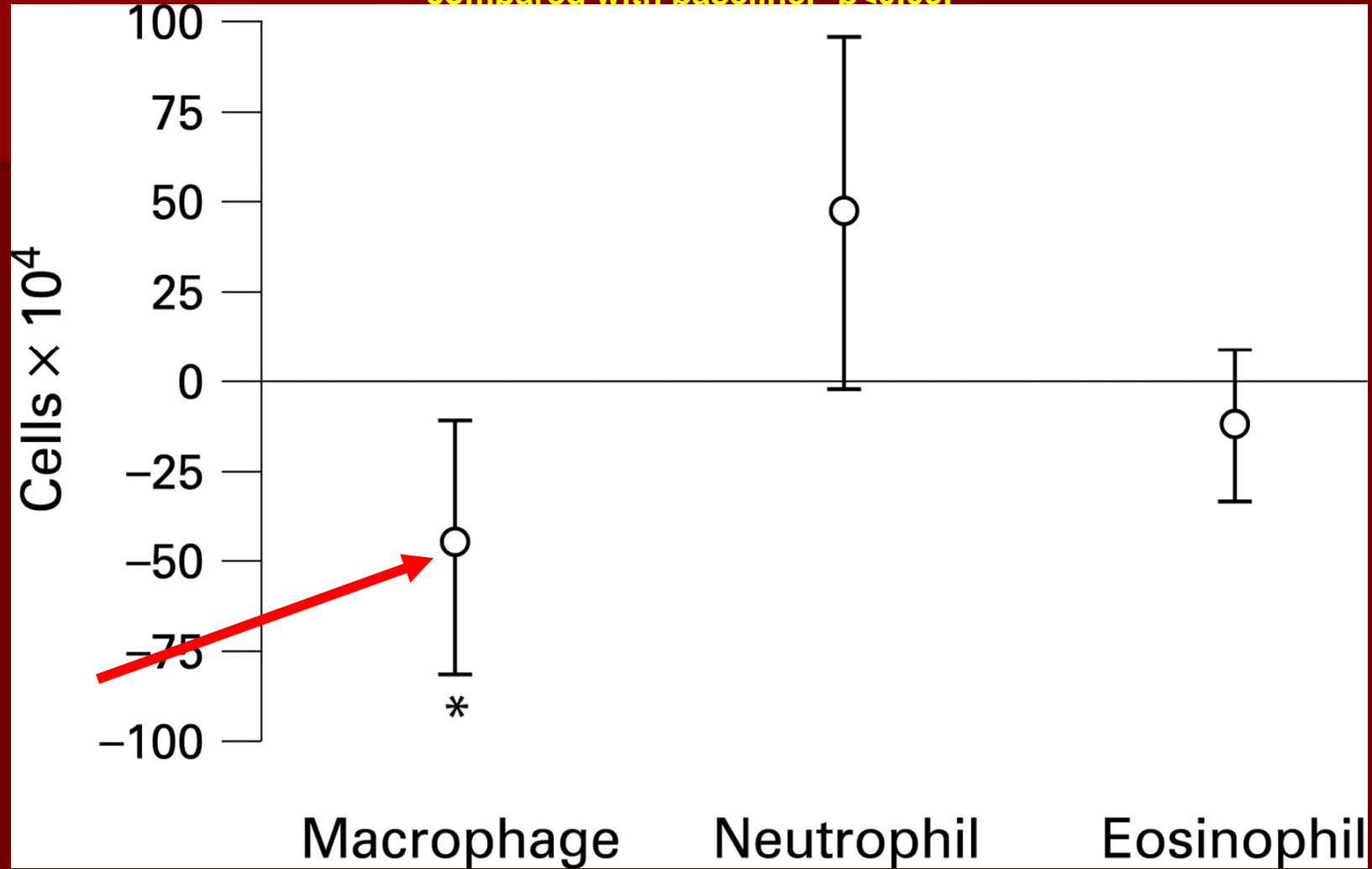
Mean (95% confidence interval) difference between atorvastatin and placebo treatment periods in morning peak expiratory flow (PEF), forced expiratory volume in 1 s (FEV₁), concentration of methacholine that reduces the FEV₁ by 20% (PC₂₀) and Asthma Control Questionnaire (ACQ) score (range 0–6).



Hothersall E J et al. *Thorax* 2008;63:1070-1075



Mean (95% confidence interval) difference between atorvastatin and placebo treatment periods in change in absolute macrophage, neutrophil and eosinophil counts ($\times 10^4$ cells) compared with baseline. * $p < 0.05$.



Hothersall E J et al. Thorax 2008;63:1070-1075



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Difficult Phenotypes

- *Severe Asthma with Fungal Sensitization (SAFS)* vs Allergic Bronchopulmonary Aspergillosis vs Allergic Bronchopulmonary Mycosis

Effect of environmental molds on risk of death from asthma during the pollen season

Paul V. Targonski, MPH, Victoria W. Persky, MD, and
Viswanathan Ramekrishnan, PhD *Chicago, Ill.*

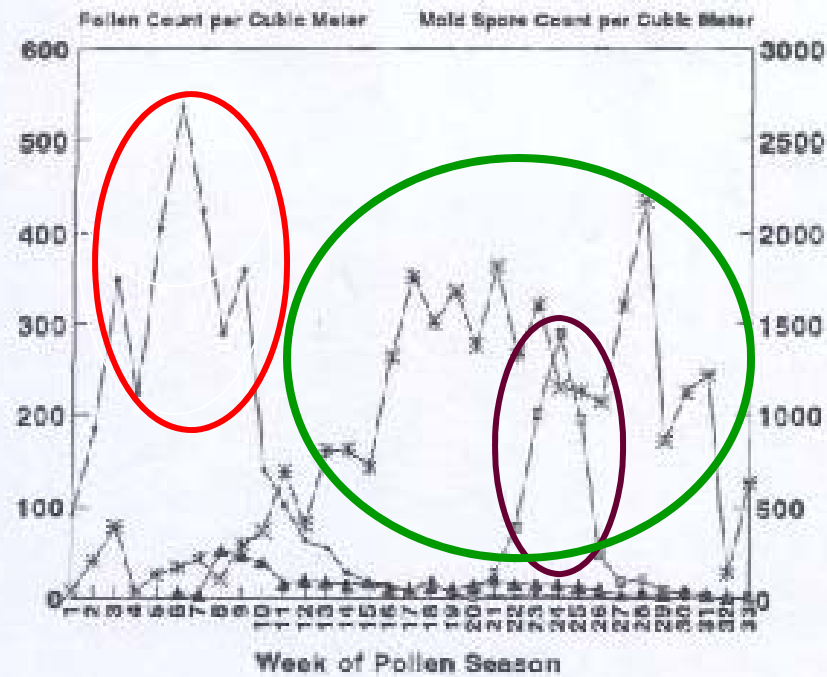


FIG. 2. Mean weekly pollen and mold spore levels from March 21 to October 31, 1983. Tree (—■—); grass (---△---); mold (·····○·····); ragweed (-·-◇-·-).

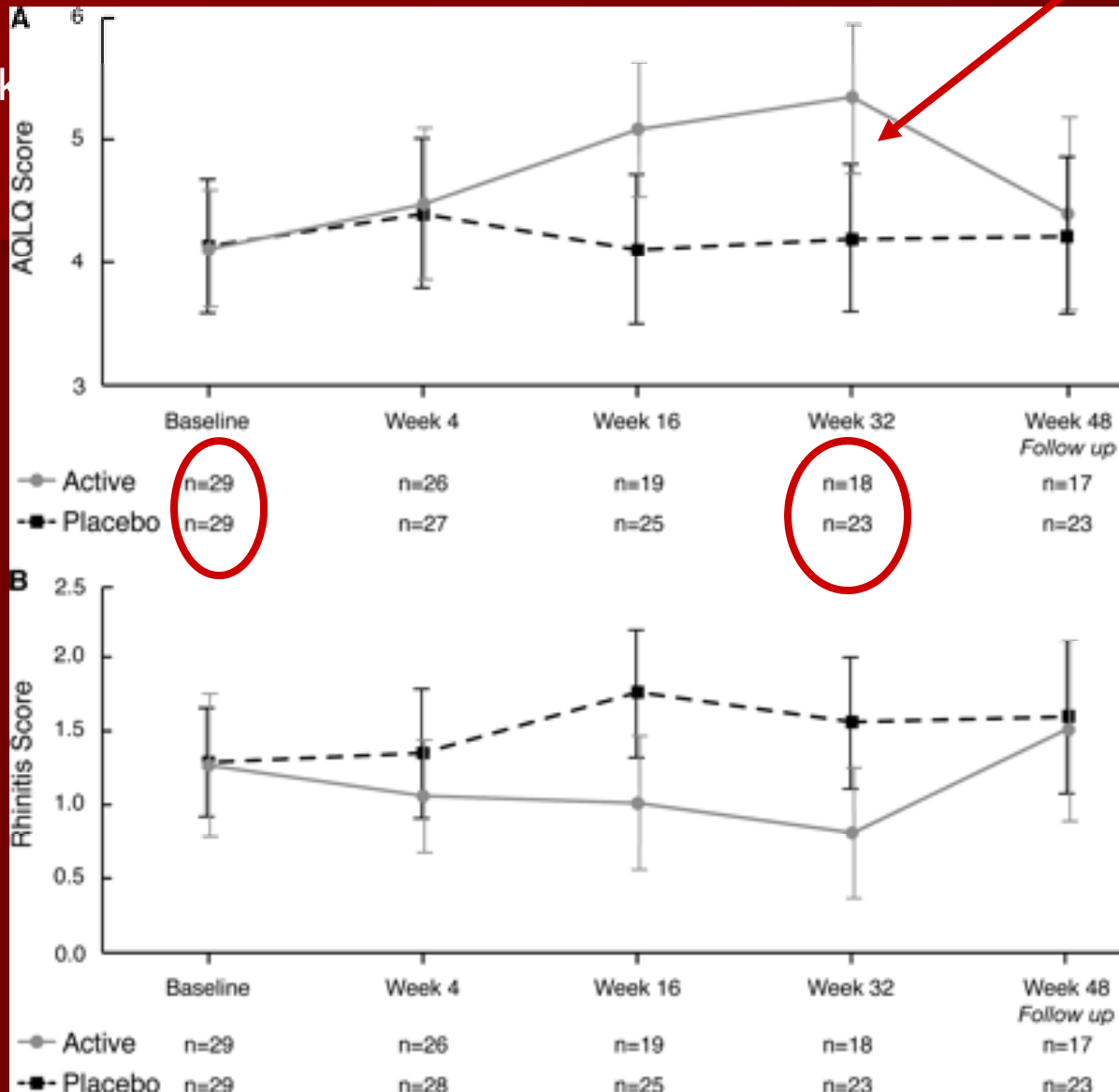
Randomized Controlled Trial of Oral Antifungal
Treatment for Severe Asthma with Fungal Sensitization
The Fungal Asthma Sensitization Trial (FAST) Study

- AJRCCM 2009;179:11-18
- **Severe Asthma with Fungal Sensitization (SAFS)**
- BDP \geq 1000 ug; FP 500 \geq 500 ug
- Continuous prednisolone \geq 5mg for at least 6 months or 4-6 courses of oral/IV steroids in past 12-24 months
- + prick test
- Total IgE < 1000 kU/L (IU/mL); A fum precip -

Methods

- Itraconazole 200mg bid or placebo
- 32 weeks of treatment
- Plasma concentrations of itraconazole at weeks 2, 4, 12, and 20
- Treating MDs not informed of test results
- Worsening of asthma: increase pred at least by 10 mg
- Primary end point = **change in AQLQ at 32 weeks**

Click



Itracon + 0.85

Placebo -0.01

Placebo + 0.17

Itracon -0.43

Other Results

- FEV₁ unchanged
- PEF in AM: 20.8 L vs -5.5 L (p = 0.028)
- PEF in PM: 16.8 L vs 8.9 L (p = 0.74)
- Change in Total IgE -27% vs + 12% (p < 0.01)
- Plasma cortisol < 50 nmole/L in 6/13 itraconazole treated vs none in placebo
- Change in AQLQ similar in those with or without an interaction on cortisol

Comments

- Good responders to itraconazole vs non-responders were identified
- 62% of patients continued itraconazole for the full 32 weeks
- No relationship of itraconazole concentrations at 32 weeks and response (AQLQ score)
- Mechanism of itraconazole on immunologic processes? Decreased Th2 cytokine production; upregulates Th1? (voriconazole does); increases concentrations of corticosteroids? (Budesonide and Fluticasone)

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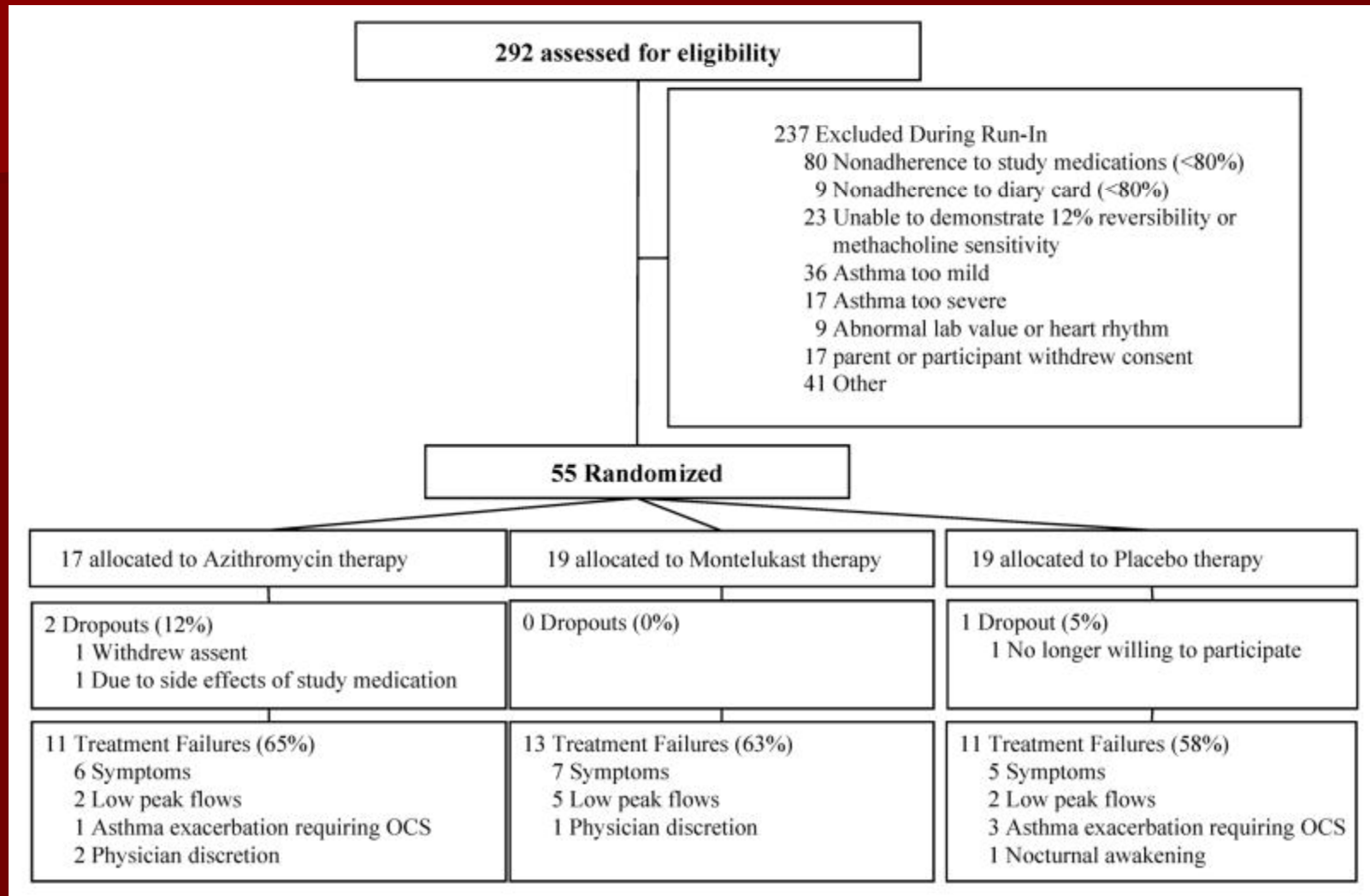
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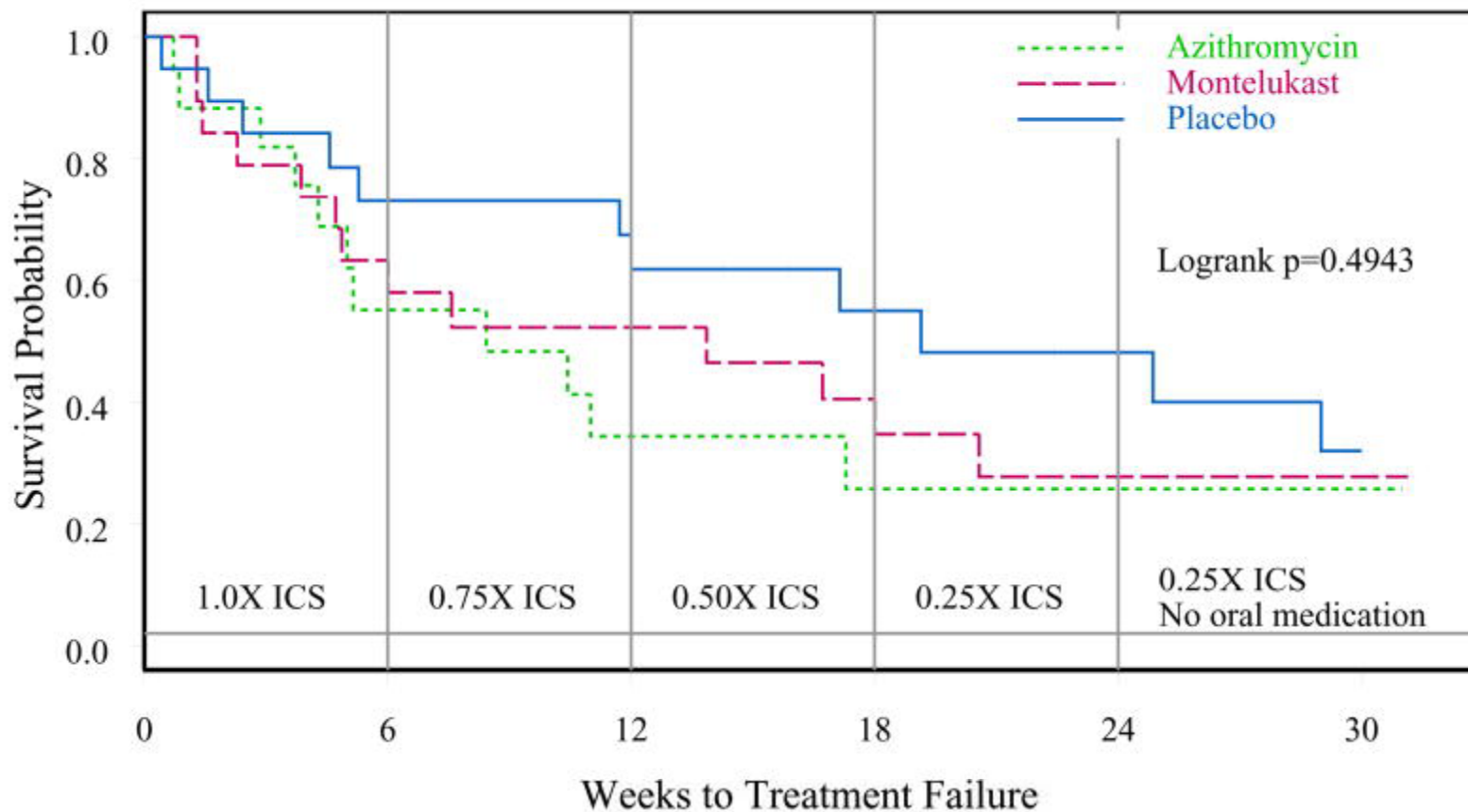
**SLIT
(SUBLINGUAL
IMMUNOTHERAPY)**

Azithromycin or Montelukast as Inhaled Corticosteroid-Sparing Agents in Moderate to Severe Childhood Asthma Study (MARS)

- Azithromycin vs montelukast for severe asthma added to budesonide 400 ug bid and salmeterol bid
- JACI 2008;122:1138-44
- Results: Neither effective
- Nasal washes collected at baseline and 18 weeks
- “None of the 140 samples assayed had evidence of DNA from Mycoplasma pneumoniae and Chlamydia pneumoniae”



Product-Limit Survival Function Estimates



	No. of Subjects	Event	Censored	Median Survival (95% CI)
Azithromycin	17	65% (11)	35% (6)	8.43 (4.29, 17.29)
Montelukast	19	68% (13)	32% (6)	13.86 (4.71, 20.57)
Placebo	19	58% (11)	42% (8)	19.14 (11.71, NA)

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Vitamin D

- Deficiency leads to less IL-10 suppression by CD4⁺CD25⁺Foxp3⁺ cells, smooth muscle dysfunction, steroid insensitivity. IL-10 is a potent anti-inflammatory cytokine and inhibits Th1 and Th2 responses
- What is vitamin D deficiency, sufficiency, insufficiency?
- Vitamin D varies by 5-10 ng/mL between winter and summer
- There is an association between vitamin D deficiency and presence of asthma

UVB

Pre-vitamin D3

7-dehydrocholesterol
Found in the Skin

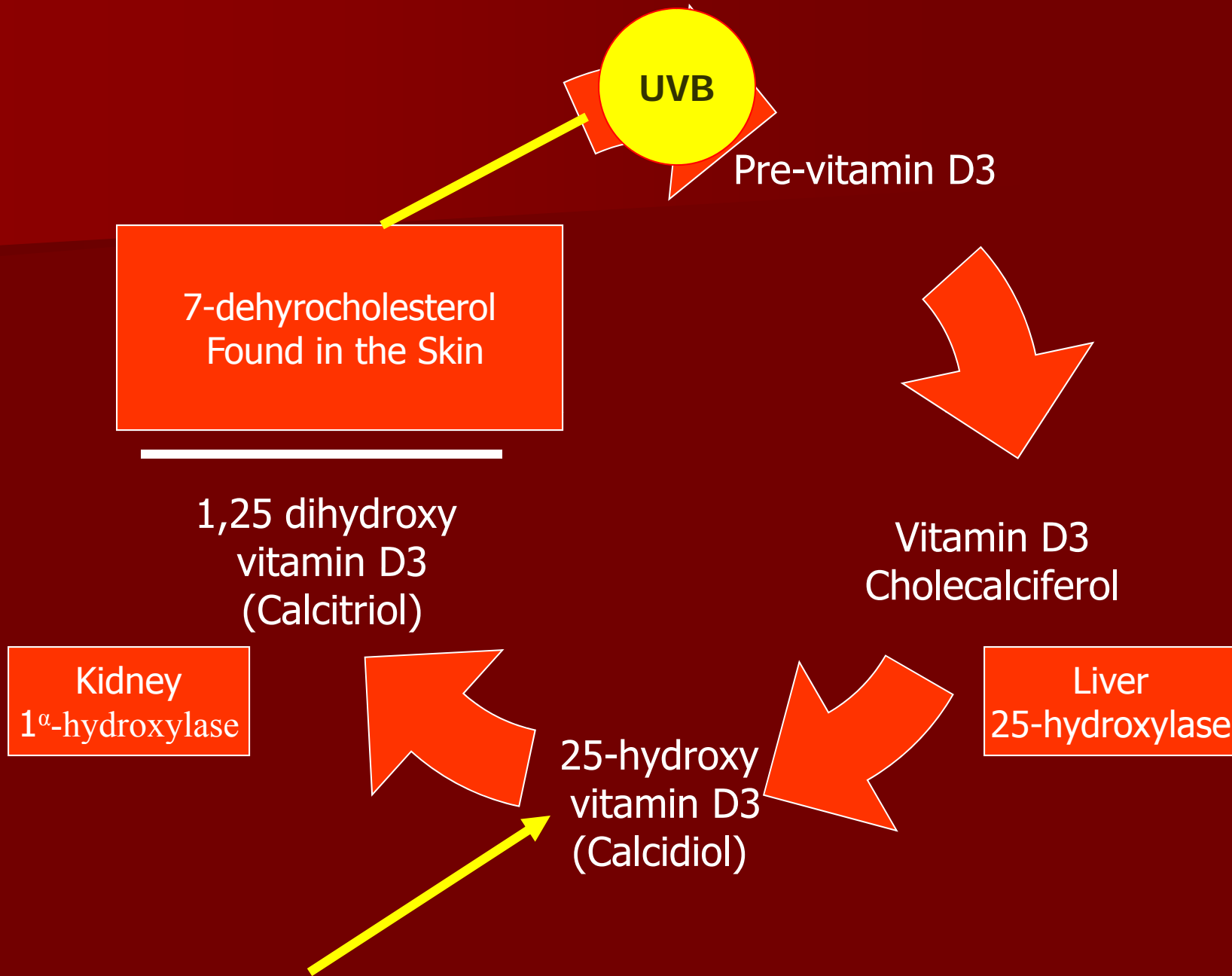
1,25 dihydroxy
vitamin D3
(Calcitriol)

Vitamin D3
Cholecalciferol

Kidney
 1^{α} -hydroxylase

25-hydroxy
vitamin D3
(Calcidiol)

Liver
25-hydroxylase



Vitamin D concentrations

- 25-hydroxy vitamin D3 (calcidiol)
 - sufficiency > 30 ng/mL
 - insufficiency < 20 ng/mL
 - deficiency < 12 ng/mL
-
- Low Vitamin D3 < 30 ng/mL....and occurs despite abundant sun exposure

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SMART (2)

**PRN ICS FOR
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PERSONALIZED MEDICINE

- UTILIZE INDIVIDUAL GENE-BIOLOGIC INFORMATION TO UNDERSTAND THE UNIQUE REQUIREMENTS FOR OPTIMAL TREATMENT, HEALTH MAINTENANCE, AND DISEASE PREVENTION
- EMPLOY BIOMARKERS
- Anticipate the process leading to PERSONALIZED HEALTHCARE INSTEAD OF PERSONALIZED MEDICINE

VARIATION OF RESPONSES-SOME CHARACTERISTICS

- SHORT ACTING BETA AGONISTS
(**White > African-Americans;**
Mexicans > Puerto Ricans)
- LONG ACTING BETA AGONISTS
- INHALED CORTICOSTEROIDS (**albuterol +, allergic inflammation +, decreased lung function**)
- ORAL CORTICOSTEROIDS (**Steroid Sensitive, Adherent, Non-Smoking, not VCD without asthma**)

VARIATION OF RESPONSES (Cont.)

- LEUKOTRIENE BIOSYNTHESIS INHIBITORS
- LEUKOTRIENE RECEPTOR ANTAGONISTS
(**uLTE4+, age, decreased lung function, AERD?**)
- OMALIZUMAB (**FEV₁ ≤65%, Unscheduled Care, high dosage ICS**)

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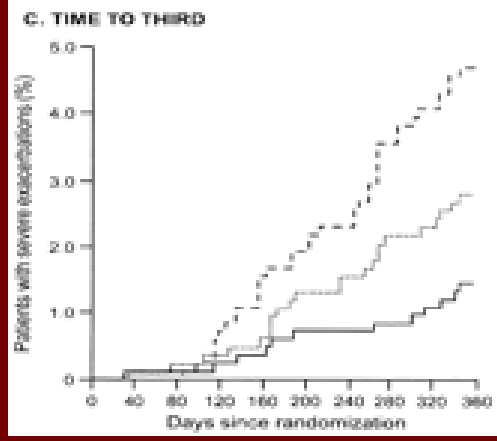
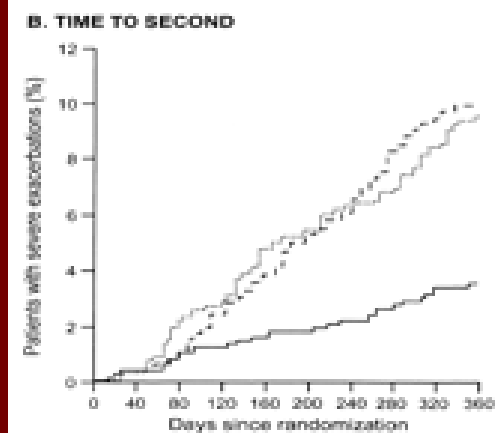
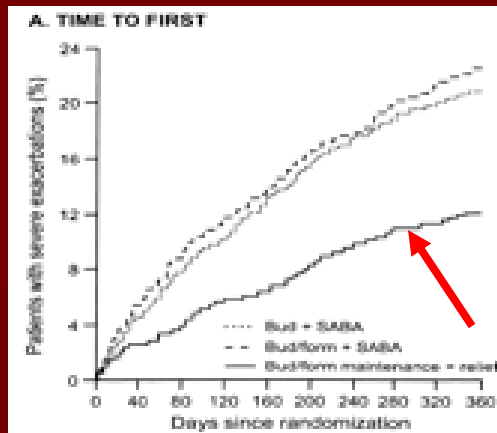
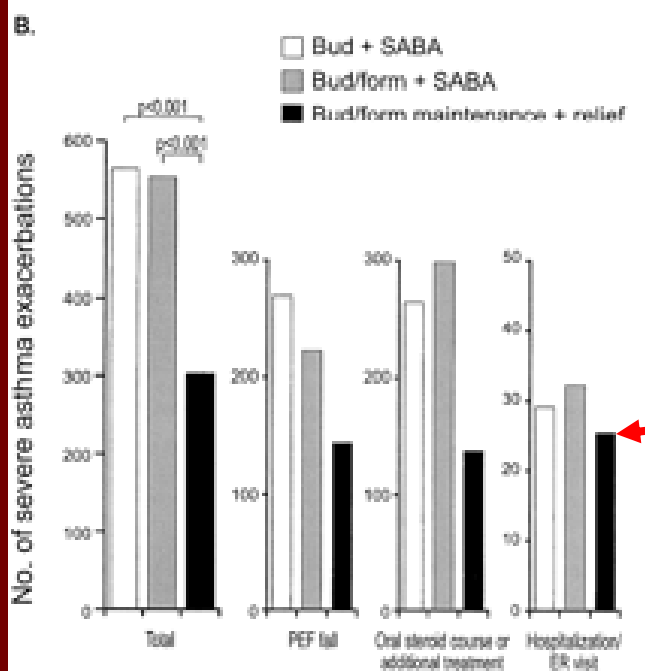
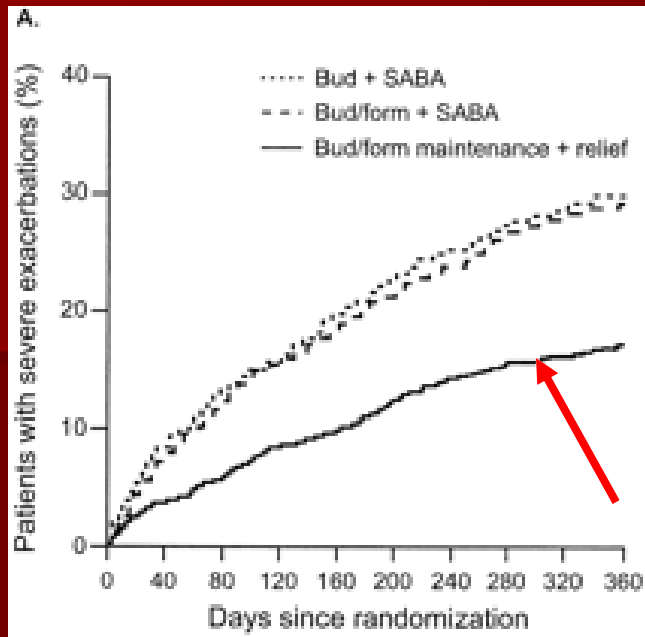
SMART (2)

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SMART (2)

- S_____ as Maintenance and Reliever Treatment
- AJRCCM 2005;171:129-36
- S_____ (budesonide/formoterol) used up to 10x daily.
- No increase in cardiovascular adverse events with as needed S_____



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Quadrupling the Dose of Inhaled Corticosteroid to Prevent Asthma Exacerbations

- AJRCCM 2009;180:598-602
- Study results **did not confirm** their primary hypothesis to reduce need for oral steroids
- Action: if PEF fell by 15% for 2 consecutive days; or 30% on 1 day; or if they felt asthma was deteriorating; URI associated flare

TABLE 2. PRIMARY AND SECONDARY OUTCOMES

	Active	Placebo	Risk Ratio (95% CI)	<i>P</i> Value
Number randomized	197	206		
Number requiring oral corticosteroids	18	29	0.64 (0.37 to 1.11)	0.11
Number who started the study inhaler	56	38		
Number requiring oral corticosteroids	12	19	0.43 (0.24 to 0.78)	0.004

Conclusions

- Asthma is complex
- Clinical reasoning is an important skill
- If a patient isn't responding, step back, consider co-morbidities, personalized approach.
- For Ice Hockey Fans.....

Wayne Gretsky (Hockey Great)

- "I don't skate to where the puck is.....I skate to where it is going to be"