Recent advances in Asthma and COPD management

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Asthma

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GINA 2007

- The patients current level of asthma control and current treatment determine the selection of pharmacologic treatment.
- For example, if asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved.
- If control has been maintained for at least three months, treatment can be stepped down with the aim of establishing the lowest step and dose of treatment that maintains control

3

Primary Factors which determine Asthma control

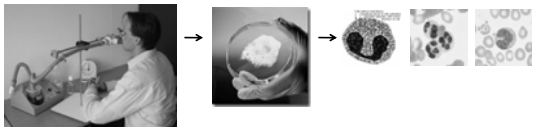
- Non compliance
- Non adherence
- Treatment is expensive?
- Doctors do not have much time to spend with the patient.

4

INVESTIGATIONS / DIAGNOSIS

- **Exhaled Nitric Oxide as a marker of airway inflammation.**

  Therapy based on routine monitoring of eNO
- **Sputum Cytology to decide appropriate pharmacotherapy**



Asthma Control Test

Asthma control is the backbone of asthma management guidelines

GINA: 2007

Asthma is a multi-dimensional disease

apacity
eter.

Symptoms

ality of life

Changes in lung functions

Most of the time they poorly correlate

ACT QUESTIONNAIRE (American Lung association)

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

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medication (such as albuterol)?

3 or more times a day	1 to 2 times a day	2-3 times/week	Once a week or less	Not at al
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

1. **If your patient scores 19 or less, it may be an indication that his asthma is not under control. Change your treatment**
2. **If your patient scores 20 or more, his/her asthma is well controlled.**

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- **Reliability of 85%**
- Significant correlation with **specialist rating asthma score and FEV1 (p<0.001)**
- Can affectively **discriminate poor and good asthma control (p<0.001)**

(Schartz et al; J Allergy Clin Immunol 2006)

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Can there be one maintenance and reliever inhaler?

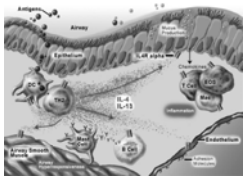
Formoterol + Budesonide inhaler

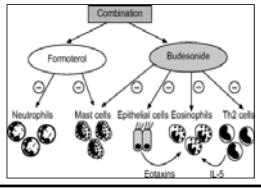
Single inhaler therapy

1. Formoterol structure similar to Salbutamol
2. Immediate onset of Action within 5 minutes.

SCIENCE OF Single inhaler Therapy

(exacerbation)

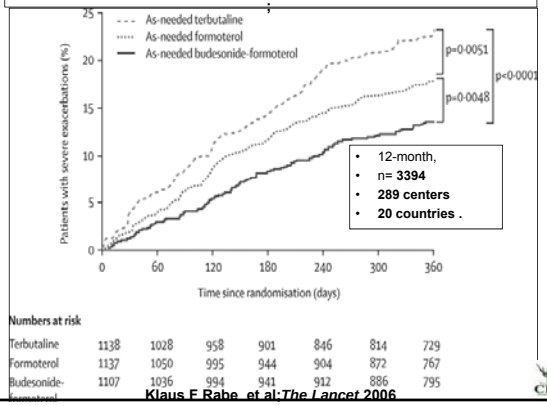




1. Immediate onset of Action of formoterol. Therefore can play the role of a SABA
2. **I step up the dose steroid when it is actually required (exacerbation) by the patient.**

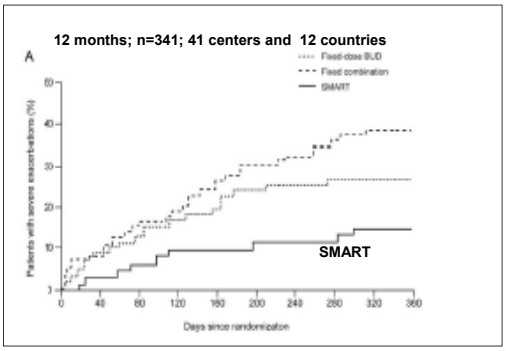
P. J. Barnes: Eur Respir J 2007; 29:587-595

Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study



Klaus F Rabe et al;*The Lancet* 2006

Budesonide/Formoterol Maintenance Plus Reliever Therapy* .A New Strategy in Pediatric Asthma



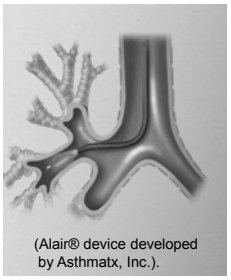
Hans Bisgaard ; *Chest 2006; 130; 1733-1743*

Outcomes of single inhaler therapy

- **Relieve patients symptoms immediately.**
- **Save patient from using excessive SABA.**
- **Reduce the cost of treatment**
- **Improve treatment compliance and have better Control on asthma**

Newer and Future treatments in Asthma

Bronchial thermoplasty



(Alair® device developed by Asthmatx, Inc.).

- Airways to be treated are approached through a bronchoscope, and treated with radiofrequency thermal waves, which a burn the smooth muscle.
- Airway smooth muscle, almost have no capacity for regeneration.
- The airway smooth muscle at is replaced by loose connective tissue.

Eur Respir J 2004; 24:659-663

ASTHMA PHARMACOGENOMICS

Mrs A

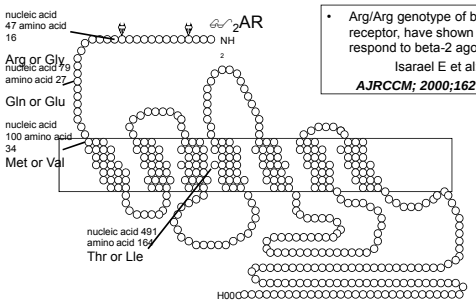
- 34 year old female
- Asthma for past 5 years
- Has taken treatment over 5 years, but insufficient
- Started on Salbutamol sos and inhaled budesonide
- Follow up after 4 weeks – needed a lot of salbutamol sos and symptoms same

Mrs B

- 36 year old female
- Asthma for past 4 years, but did not take any treatment
- Also started on Salbutamol and inhaled budesonide
- Follow up 4 weeks later - Very happy with her treatment

- It is estimated that 70-80% of variability in individual responses to therapy may have a genetic basis **Drazen,** *Br Med Bull* 2000; 56: 1054-1070

Beta Adrenergic receptor



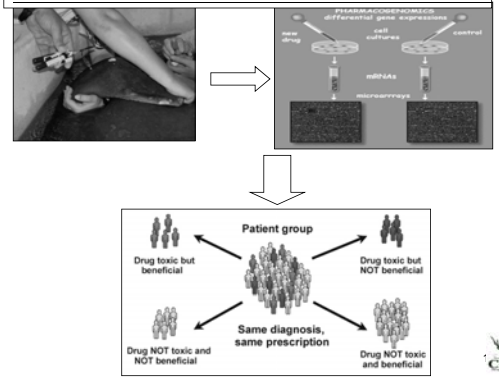
- Arg/Arg genotype of beta-2 receptor, have shown to not respond to beta-2 agonist.

Israael E et al:

AJRCCM; 2000;162; 75-80

Amino Acid sequence of the human 2AR. Shown are the location of polymorphisms in the DNA sequence that result in variation in amino acids at the indicated positions.? The red circles indicate codons where the DNA sequence is variable but does not result in variation in the encoded amino acid.

PHARMACOGENOMICS FUTURE IN ASTHMA MANAGMENT



NEW TREATMENTS

- **Ciclesonide :**Once a day Steroid; Ciclesonide-Formoterol could become potential Single inhaler therapy
- **R –enantiomer:** reduce the dose of asthma medications and may reduce the side effects profile.
- **Indacaterol:** Very long acting beta-2 Agonist 24 hours action
  (Clinical trials in progress).

ERS Munich 2006 -2007

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COPD

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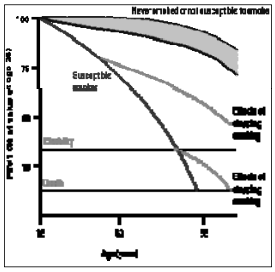
COPD

COPD is a progressive disease, characterized by progressive decline in the lung function and hence increase in the mortality rate and reduces quality of life.



- **till now except for stopping smoking there is no proven intervention which can alter rate of decline in FEV1.**

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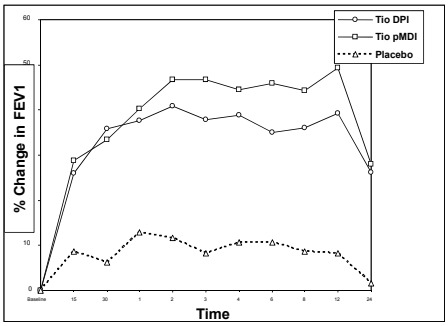
Tiotropium in COPD



Brashier et al; Respir Med. 2007 Dec;101(12):2464-71.

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Can tiotropium arrest rate of decline in FEV1 and reduce the Mortality rate?

Understanding Potential Long term Impacts on the Functions with Tiotropium (UPLIFT study)

- N= 6000
- Multi -center
- Primary End-point: Rate of FEV1 decline.
- Results expected in 2008

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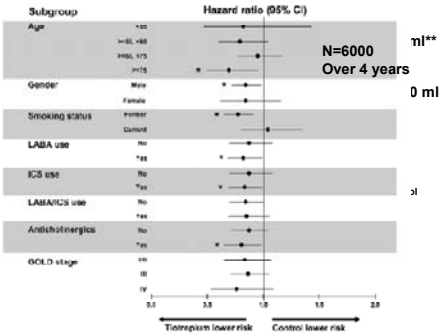
TIOTROPIUM

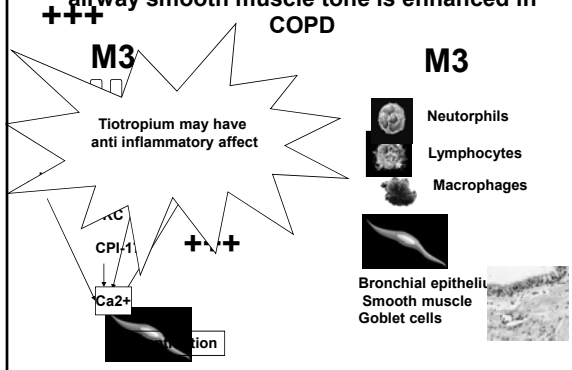
Understanding Potential Long term Impacts on the Functions with (UPLIFT)Trial



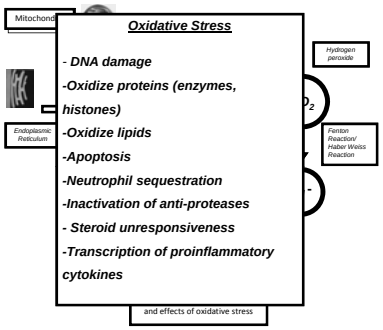
N=6000
Over 4 years

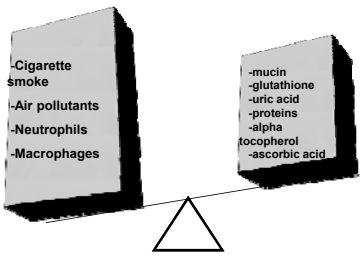
Celli et al. *AJRCCM.* Vol 180, 2009; 948-955

Muscranic (cholinergic) Receptor regulation of airway smooth muscle tone is enhanced in COPD

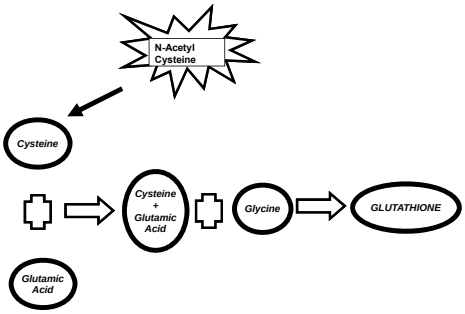


Gosen R et al. Respiratory Research 2006, 7: 73



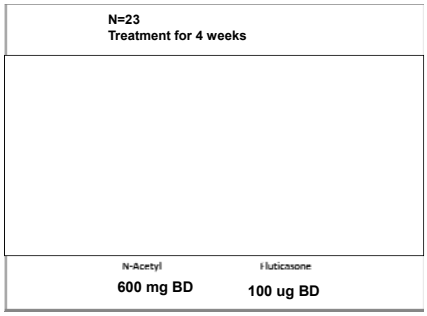


Oxidant-Antioxidant Imbalance



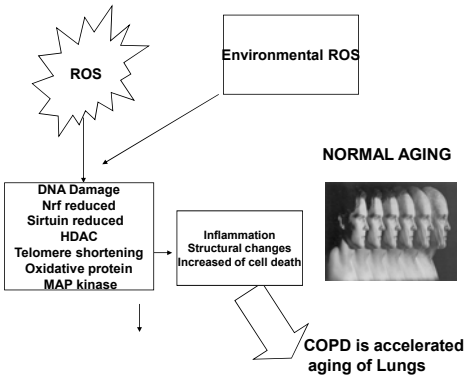
Glutathione synthesis

N Acetyl Cysteine (NAC)



Brashier et al; European Respiratory society; Sep 2009

Oxidative stress +aging in COPD



Ito etal: Chest 2009; 135:173-180

Antiaging- antioxidants

Resveratrol Sirtuin activato

Curcumin Macrophage inhibiting factor Decrease MMP-9 gelatinase

Sulforaphane Activates Nrf2

Rapamycin

ACE Inhibitors (enalapril)

Revisiting Theophylline > 70 years old drug

COPD Inflammation

Steroids

Histone acetylase +

Histone deacetyl (HDAC) -

IL8, (LTB4), GRO-alfa, MCP-1, MCP-2,, MIG

COPD: HDAC activity is reduced Due to Oxidative stress and other infllatory mediators

theophylline low dose increase activity Of HDAC

Barnes: *Chest*, 2006;129; 151-155

Statins in COPD

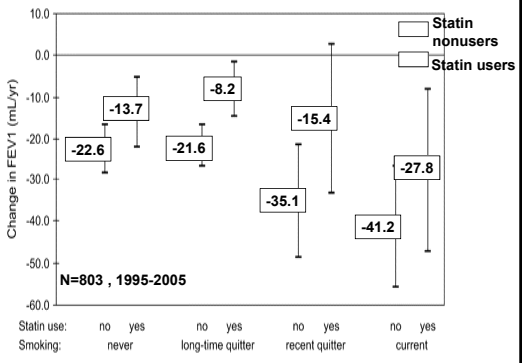
Lipid lowering

Simvastatin, Atrovastatin

Anti-inflammatory
Anti-apoptosis
Anti-Oxidant

Can Statins reduce the systemic inflammation in COPD?

Statin Use Reduces decline in Lung function
VA Normative aging study



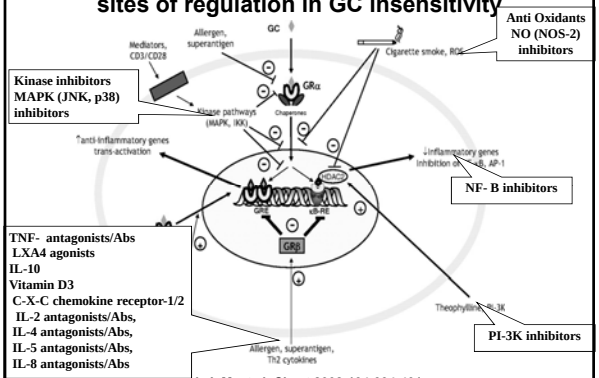
Stacey et al; *AJRCCM* Vol 176; 2007; 742-747

Statins in COPD

- Treatment with Statins was associated with improved survival in COPD patients. (HR 0.57 for statin versus non-statin user).
  V Soyseth et al ; *ERJ;* 2007 279-283
- Statins have shown to reduce IL-6 concentration in patients with COPD with co-morbid Cadiovascular diseases.
  Hurst et al; Chest 2007; 1409-1410

Can statins do the trick?

Mechanism of GC action by the GR and sites of regulation in GC insensitivity



Adcock, I. M. et al. Chest 2008;134:394-401

- **Very long acting β-2 agonists:**

- Carmoterol
- Indacaterol
- Milveterol
- GSK-642444
- BI-1744-CL
- Saligenin or indole containing β-2 agonists
- UK-503590
- Compound X

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- **Very long acting anti-muscarinic agents:**

- Aclidinium bromide
- Glycopyrronium bromide
- TD-4208
- QAT-370
- CHF 5407
- Darotropium bromide
- dexpirronium

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- **MABA (Muscarinic-antagonist- β-2-agonist):**

- GSK-91081
- Bicyclohept-7-ylamine derivatives

- **LABA and ICS:**
- Carmoterol and budesonide
- Formoterol and mometasone (MFF258)
- Formoterol and ciclesonide
- Indacaterol and mometasone (QMF-149)
- Indacaterol and QAE-397 (a novel corticosteroid)
- Fluticasone furoate and GSK-642444

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- **LABA, LAMA and anti-inflammatory compounds:**
- Tiotropium, salmeterol and fluticasone/ciclesonide
- Indacaterol, glycopyrronium and mometasone
- Milveterol, darotropium and fluticasone furoate
- GSK-642444, dartropium and fluticasone furoate

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Conclusions

- Tiotropium is a bronchodilators of choice
- NAC a promising antioxidant and should be added in the routine management of COPD.
- Add low dose theophylline along with steroids in treatment of severe COPDs.
- Statin in phase of trial could be possible anti-inflammatory treatment in COPD

Thank You

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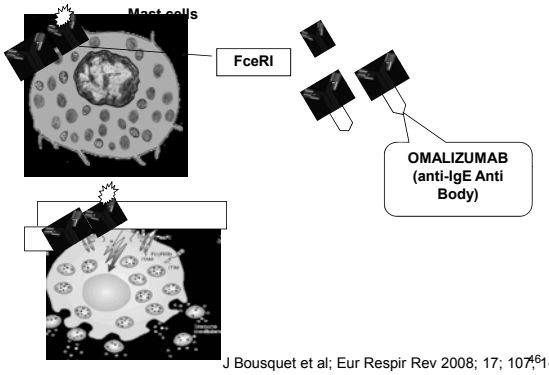
Anti- IgE Antibodies (Omalizumab)



J Bousquet et al; Eur Respir Rev 2008; 17; 107, 1-9

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Omalizumab

- GINA guidelines recommend this treatment in patients with poorly controlled asthma even with high doses of ICS and LABA.
- It cannot be used alone always has to be used as an add on therapy along with ICS and LABA.
- Good affect only in allergen induced asthma.
- Requires baseline IgE betwee 30-700IU/ml
- Administered by Subcutaneous Injection Every 4 Weeks
- Expensive treatment

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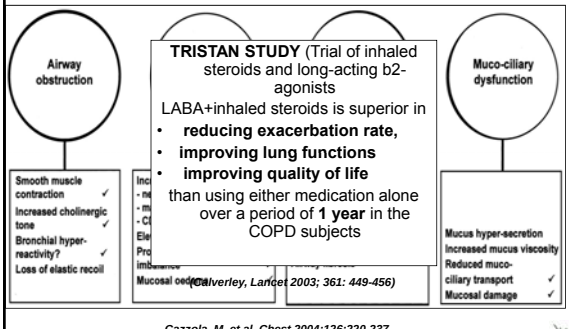
J Bousquet et al; Eur Respir Rev 2008; 17; 107, 1-9

Effects of LABA/ICS combination therapy on pathophysiology of COPD



Cazzola, M. et al. Chest 2004;126:220-237

- **Can ICS + LABA reduce rate of decline in FEV1?**
- **Can ICS + LABA reduce the Mortality in the COPD Subjects**

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Salmetrol and Fluticasone Propionate and Survival in COPD
Towards a Revolution in COPD Health
TORCH

- 444 centers; 42 countries
- **n=6184**
- **3 years**
- Treatment:

A. Placebo
B. Salmetrol
C. Fluticasone
D. Salmetrol + Fluticasone

RESULTS

LABA+inhaled steroids is superior in
- **reducing exacerbation rate**
- **improving lung functions**
- **improving quality of life**

Than those receiving either of the treatments **after 3 years**

LABA+inhaled steroids **did not**
- **Effect the Mortality rate**
- **Rate of decline in FEV1**

Than those receiving either of the treatments **after 3 years**

Calverly et al: *NEJM*; February 2007; vol 356 No. 8; 775-789

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Recent advances in COPD Management

1. **Treatment that will reduce rate of decline of lung functions patients**
2. **Treatment that increases survival of COPD patients**
3. **Treatment that reduces Number of exacerbations**
4. **Treatment that improves quality of life of COPD patients**

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LABA + ICS combination will improve Exacerbation Rate and Improve quality of life in patients with COPD, Hence should be routinely used in management of COPD, than either therapy alone .

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