

Is it SAFE ??



A. Ariel

**Asthma pathophysiology and the Beta agonist Saga
Where are we now?**

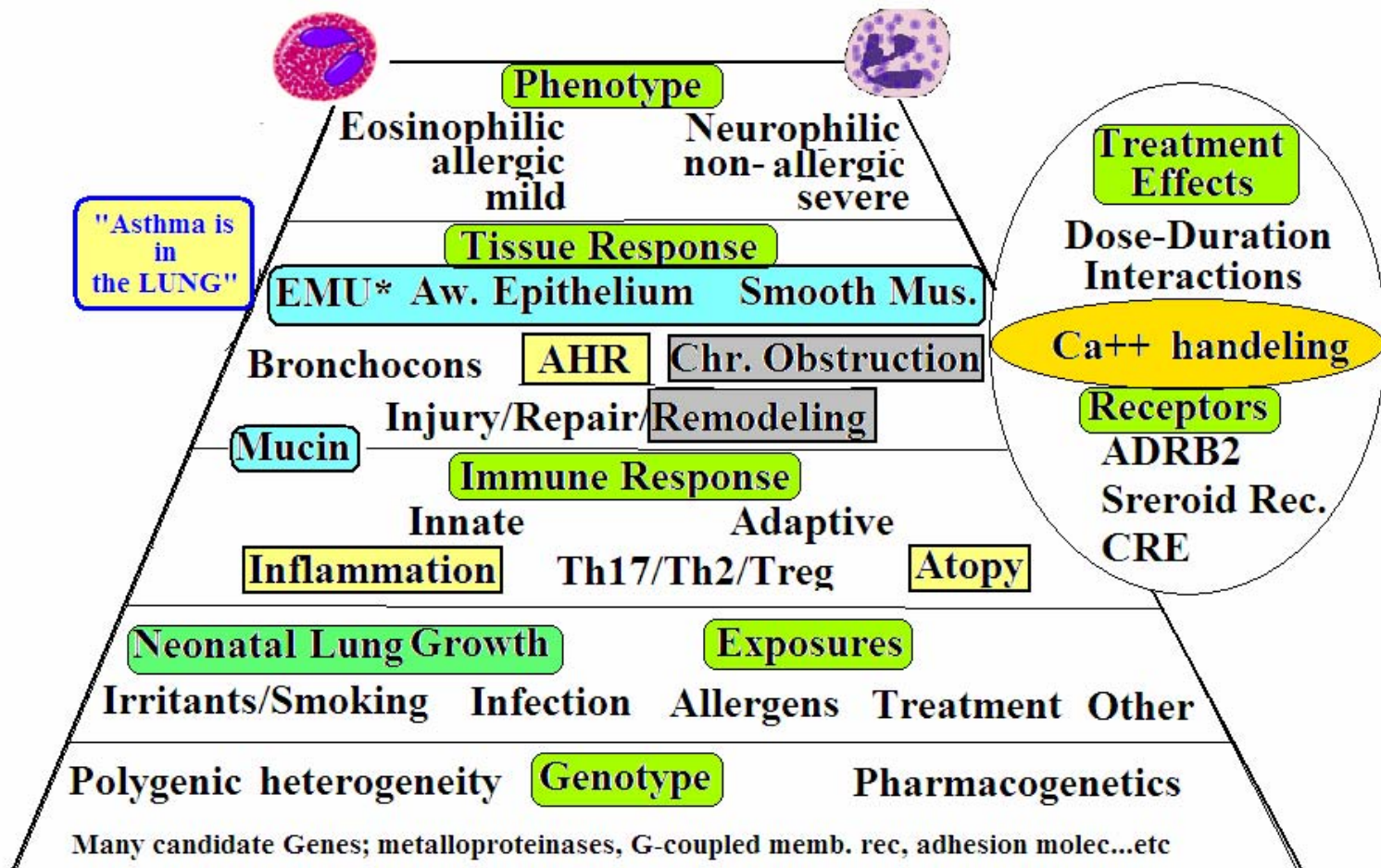
Asthma – complex syndrome

- **Pathophysiological Definition;** a **chronic, immunologically mediated** condition with a **disturbance of the normal airway repair** mechanism, which results in **inflammatory changes and airway remodeling**. The airway inflammation and remodeling together likely explain the clinical manifestations of asthma.
- **Clinical Definition;** Asthma manifests clinically with **repeated, variable, episodic attacks of breathlessness**, cough, and wheeze occurring secondary to **bronchoconstriction** in the setting of **airway hyperresponsiveness** and mucous hypersecretion.
- **No “GOLD STANDARD DIAGNOSTIC TEST”**

Asthma Pathophysiology

“Complex heterogeneity”

Heterogeneous & variable phenotype - interaction of **complex genetic background** with various **environmental triggers** <infection, allergy, irritant> inducing a **complex immune/resident cell response** variably **affected by therapeutic measures**.



Beta Agonist Risk/Harm

Questions and Possible Mechanisms

Questions

- ? Evidence
- ? Mechanism/s
- ? Protection by concomitant ICS

Susceptibility

- **Pharmacogenetics; ADRB2**
- **No concomitant ICS Rx**
- Asthma Phenotype/Severity
- Behavioral-Socioeconomic; delayed/non-monitoring, selective ICS discontinuation

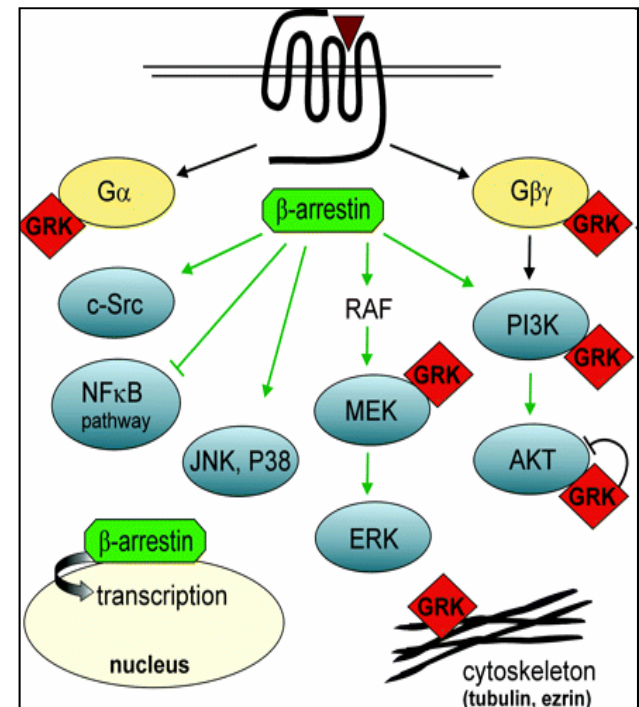
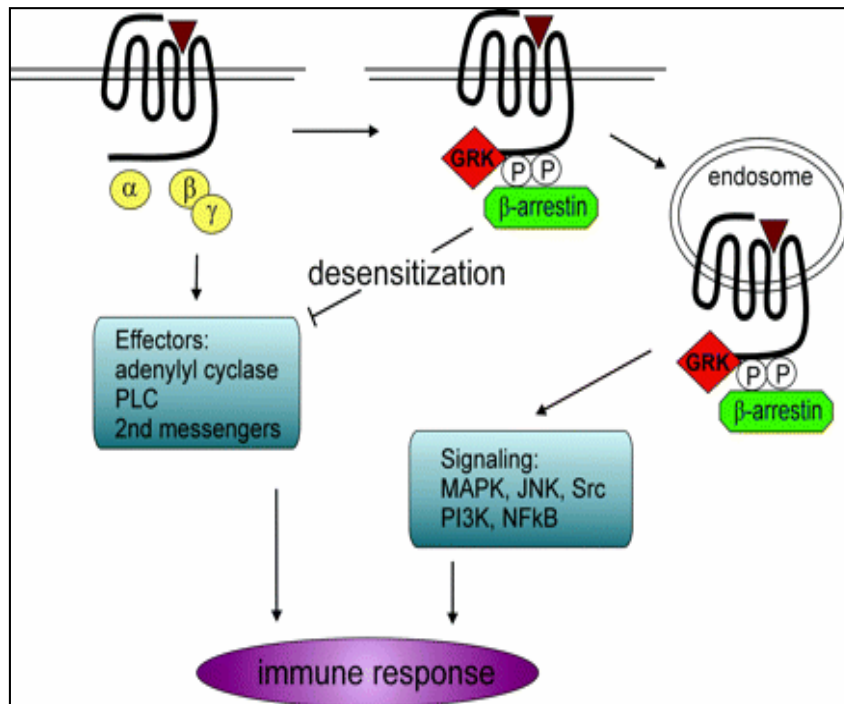
Potential Factors & Mechanism/s

- **Masking** of inflammation
- **Pharmacogenetic** – ADRB2 polymorphism, other
- **Steroid Resistance**
- **Drug Dose & Duration Related**
 - **Pro-inflammatory**
 - **Neurogenic** inflammation
 - Contractile dysfunction
 - **The CHF Paradigm; Beta blocker Rx in Asthma?**

β 2AR Activ/Deactivation - GRK-arrestin

Homologous desensitization & cellular signaling

- **β 2AR Activ.** \Rightarrow Gas&Gai \Rightarrow adenylate cyclase \Rightarrow cAMP \Rightarrow prot. kinase A (PKA) \Rightarrow Ca²⁺ \downarrow \Rightarrow **SM relaxation**
- **Homologous desensitization:** Agonist-activated GPCRs phosphorylated by GRKs \Rightarrow **recruitment of arrestins**. \Rightarrow prevents further coupling of the receptor to its G protein, \downarrow receptor signaling.
- **GRKs and arrestins can also act as signal transducers** in various **signaling/inflammatory pathways.** - in both immune & structural cells (eg. ASM)

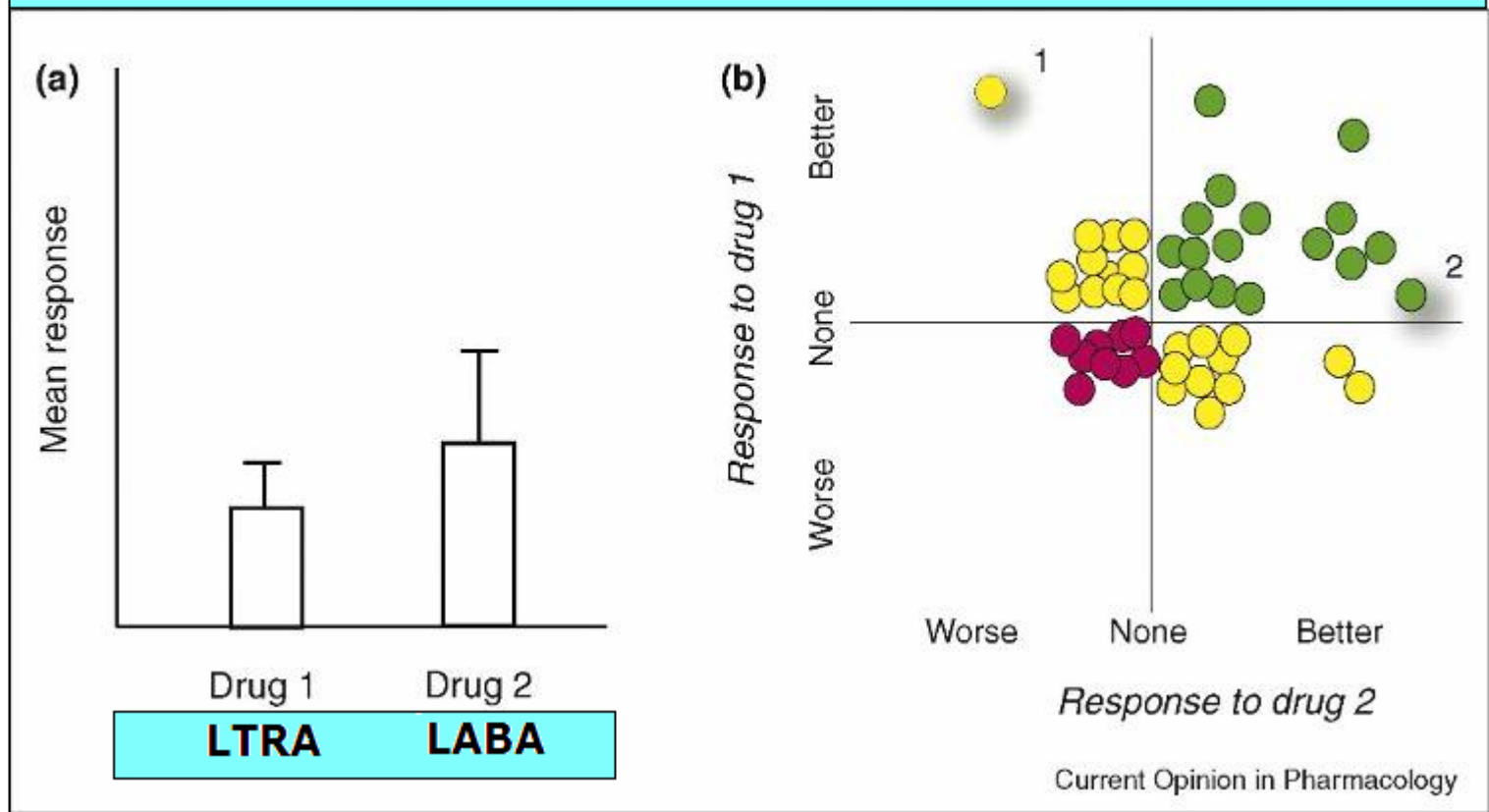


Pharmacogenetics

Average effect \neq Individual Effect

- For example; B2-Agonists vs Anti-Cholinergics; ICS vs LTRA
- (Panel a) “Overall” RX effect – Drug 1 better Than Drug 2
- (Panel b) Individual Rx effect;
 - **Subj. #1 (LTRA/better>>LABA/worse); ?SAE risk with LABA/ICS**

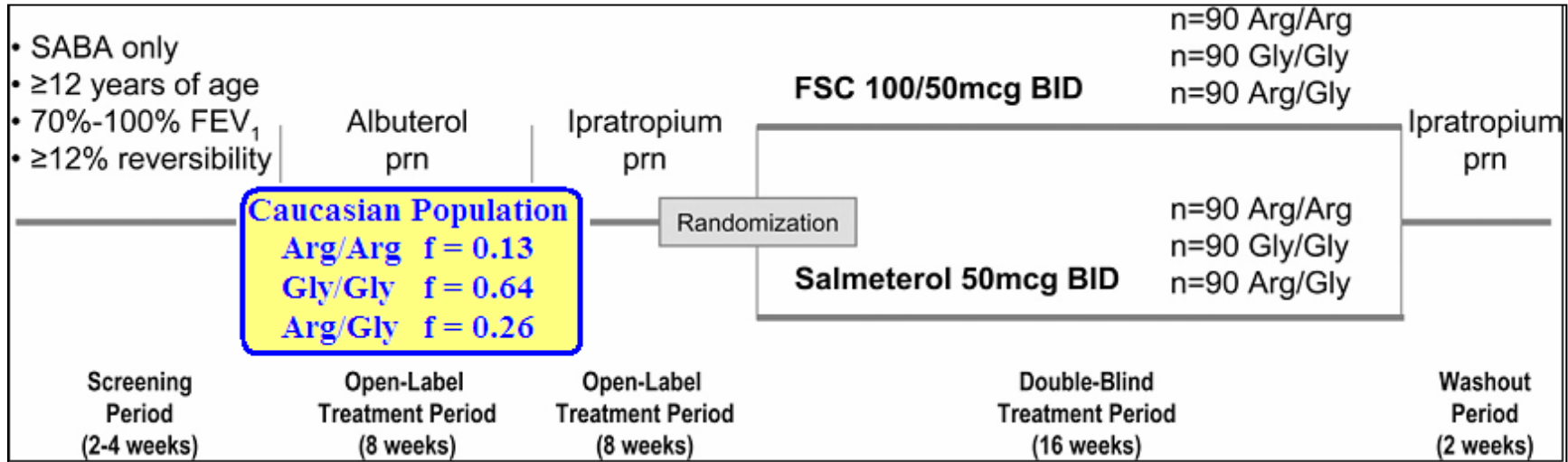
Hypothetical Case - Add on Controller to ICS in Asthma



Parmacogenetics - ADRB2 Polymorphism

Bleecker, et al.(N.Carolina): b-Agonist Receptor Polymorphisms and Salmeterol
Am J Respir Crit Care Med Vol 181. pp 676–687, 2010

“Complex” Pharmacogenetics



- This is the **first prospective pharmacogenetic trial** to evaluate **LABA therapy with and without ICS**.
- The results showed **no evidence of a pharmacogenetic effect** of ADRB2 variation **on therapeutic response to salmeterol** (FEV₁, PEF, Symptoms).
- These results **refute previous retrospective studies**, suggesting a negative response to LABAs based on **ADRB2-Arg16Gly genotypes** and support the benefits of LABA-ICS for the treatment of persistent asthma.

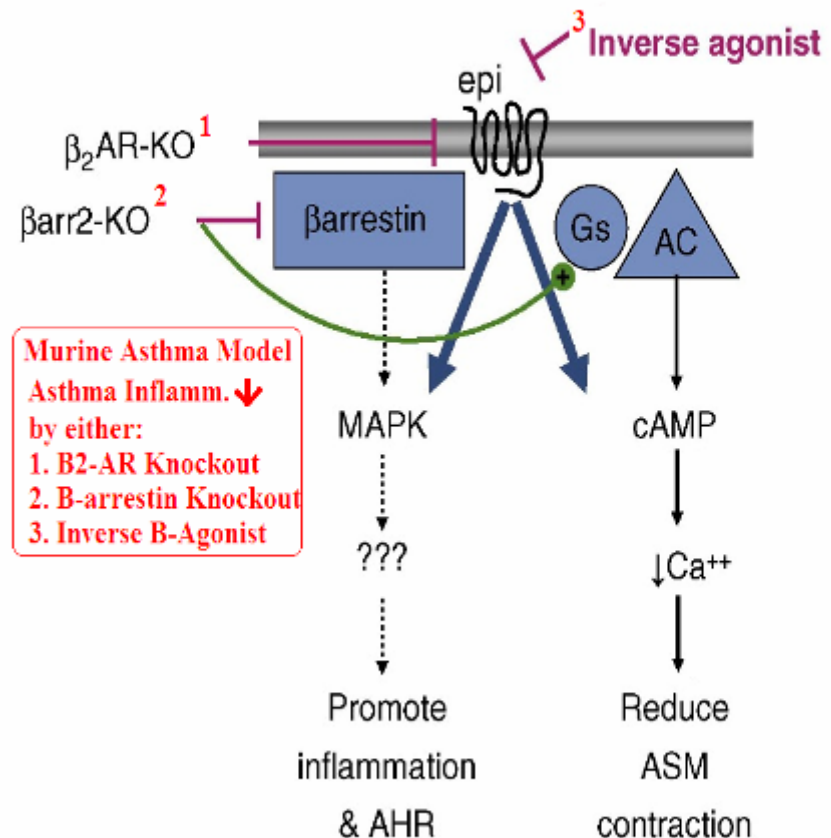
ADRB2 desensitization, B-Arrestin & Possible Proinflammatory effects

b2-AR signaling pathways;

- **Canonical Adenylate Cyclase pathway;** mediated bronchodilation/bronchoprotection (Airway Smooth Muscle)
- **Non-Cannonical, Constitutional Arrestin pathway;** essential for inflammation & AHR (? Th2 & Epithelial cell effect)
- **b-Arrestin gene knock out is more effective** in protection from asthma in murine model – possibly indicating non-b2AR mechanisms of arrestin activation.
- **b-AR inverse agonists may produce beneficial chronic effects by inhibiting constitutive or ligand (inflammation, b2-Agonist) induced activation of this pathway.**

Alternative Signaling by β_2 AR

β_2 -AR in asthma Dickey et al. Current Opinion in Pharmacology 2010, 10:1-6

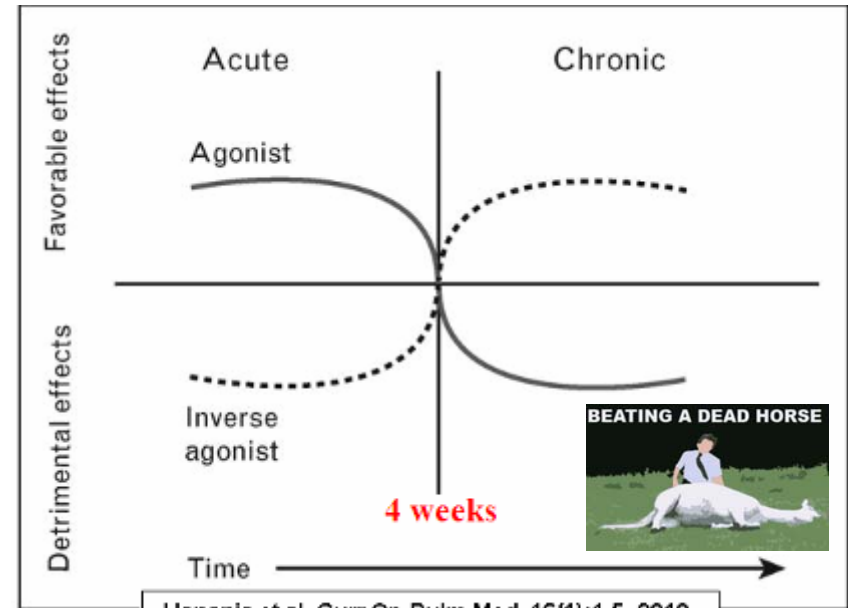
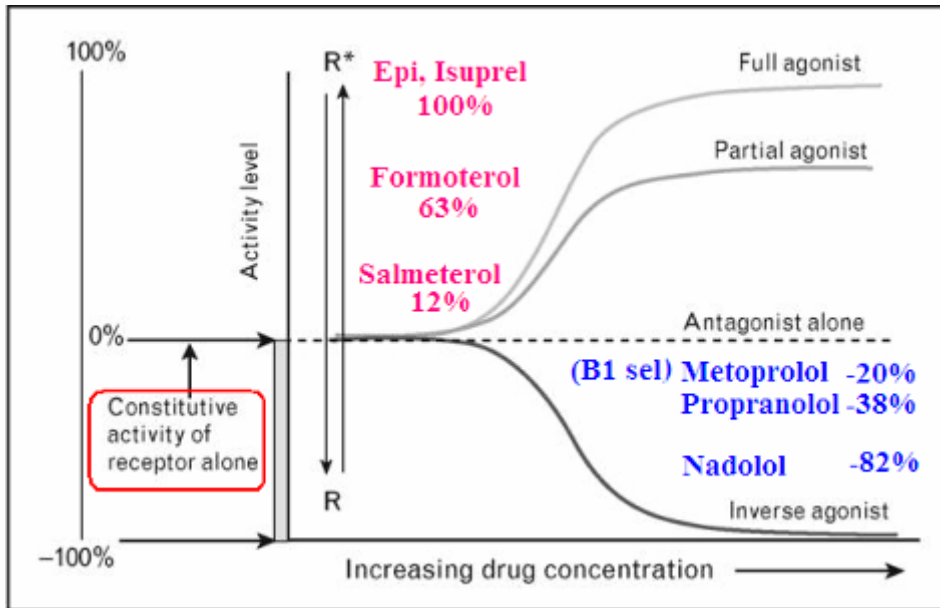


Intrinsic Activity & Drug Duration Effects

Acute-agonist & Chronic-Inverse Antagonists Rx.

Many G-protein-coupled receptors (GPCRs), including ADRB2, exhibit basal, agonist-independent activity.

- **b-Agonists** may be acutely beneficial but chronically can induce desensitization of the receptor.
- Whereas **inverse agonists** (b-blockers) may be acutely detrimental but chronically beneficial.



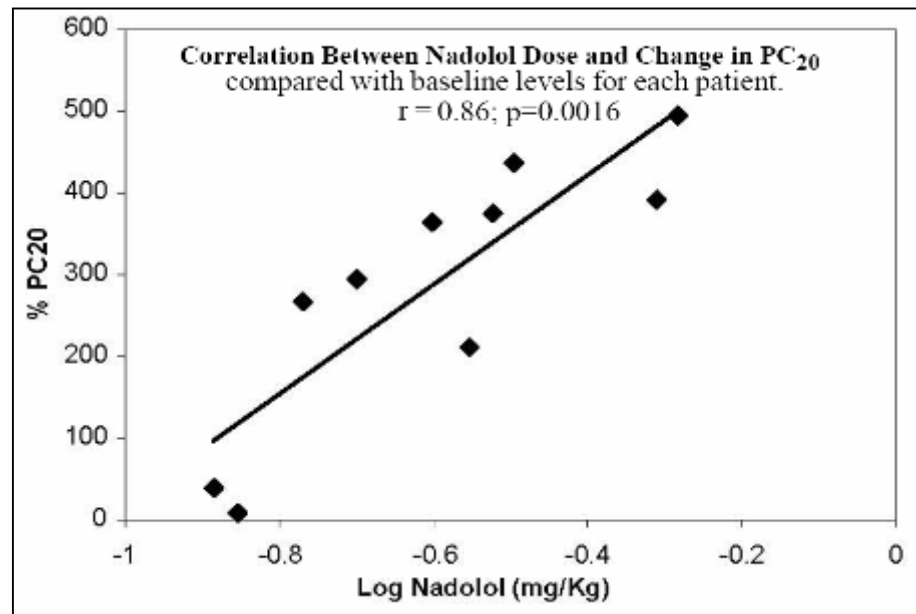
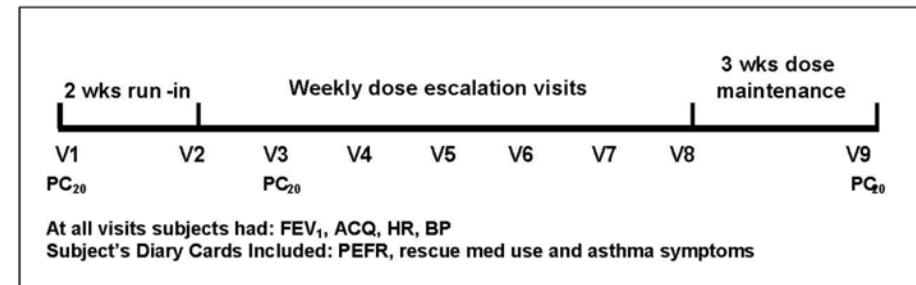
Hanania et al, Curr Op Pulm Med. 16(1):1-5, 2010.

CHF Paradigm – stop beating a dead horse

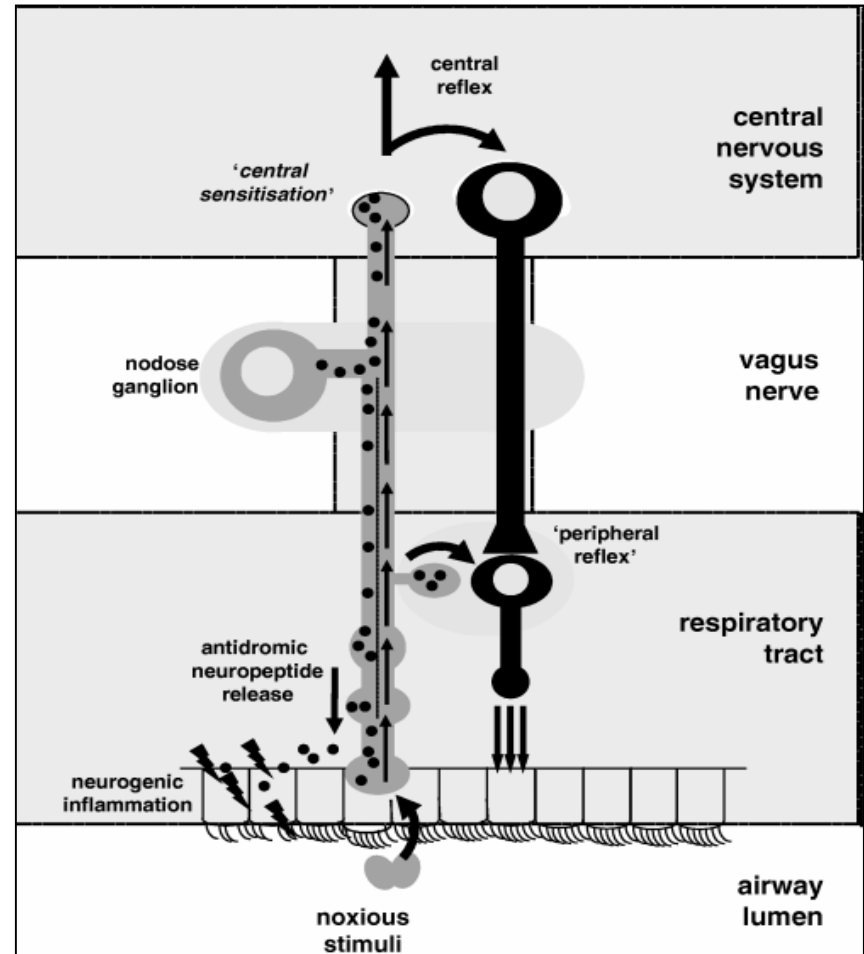
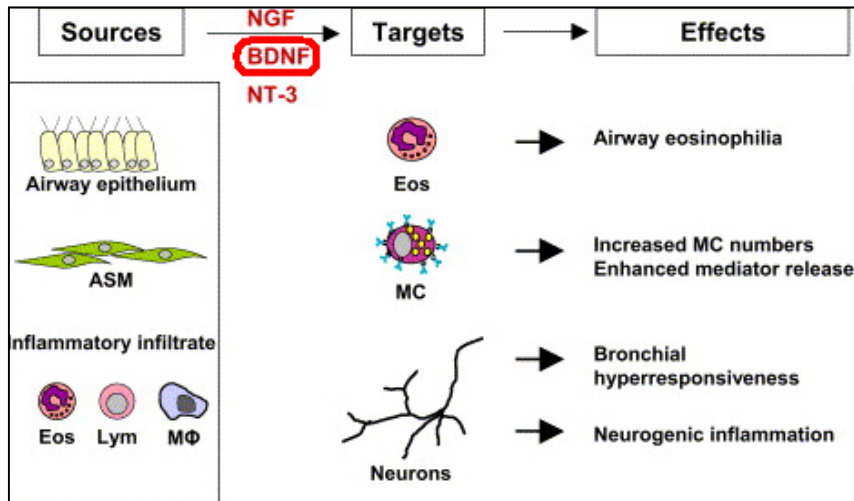
Beta Blocker Rx in Asthma?

Hanania et al. The Safety and Effects of the Beta-Blocker, Nadolol, in Mild Asthma; An Open-label Pilot Study. Pulm Pharmacol Ther. 2008 ; 21(1): 134–141

- In 8/10 subjects, 9 wks escalating nadolol produced a significant, dose-dependent increase in PC₂₀ - 2.1 doubling doses at 40 mg ($p < 0.0042$).
- However, there was also a dose-independent 5% reduction in mean FEV₁ over the study period ($p < 0.01$).
- Most patients with mild asthma, the dose-escalating administration of nadolol, is well tolerated and may have beneficial effects on airway hyperresponsiveness.



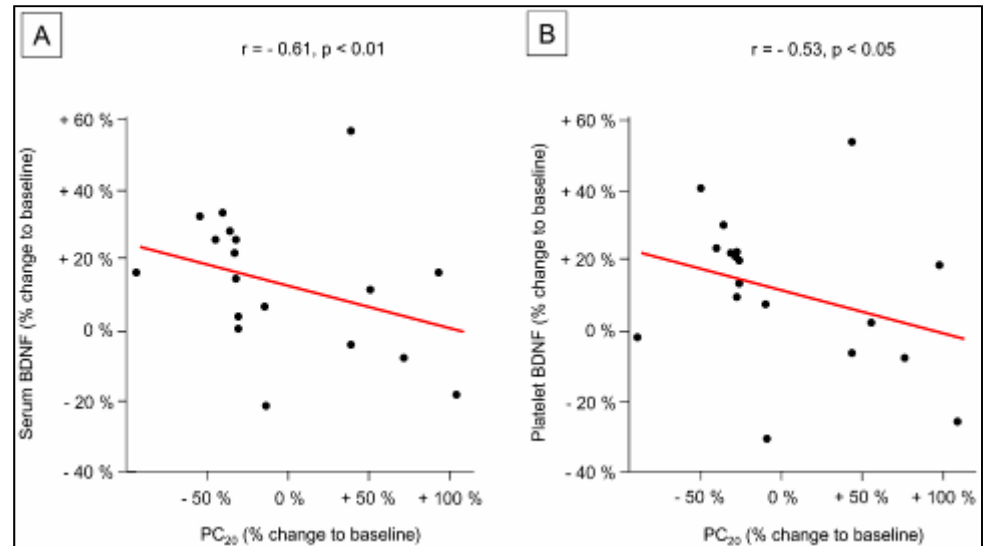
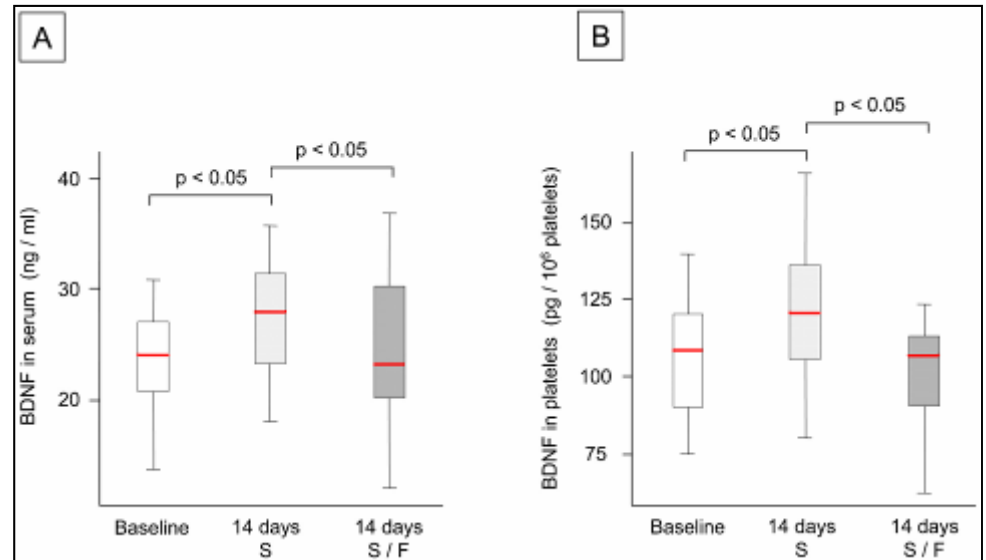
Neurogenic Inflammation



Neurogenic inflammation- BDNF

Adverse effects of salmeterol in asthma: a neuronal perspective. M Lommatzsch et al. Thorax 2009;64:763–769

- **18 mild nonsmoking asthmatics** (>18yo, FEV1>80%p, PC20>8mg/ml, SABA prn Rx)
- **2 wks SAL 100 mcg bid -> 2 wks SAL/FP 50/100 mcg bid**, Blood leves, PFT, PC20
- **In vivo: SAL Monotherapy significantly ↑ BDNF in serum and platelets.**
- **BDNF correlated with the deterioration of AHR following SAL monotherapy.**
- **This detrimental effect was abolished by the addition of fluticasone**
- **In vitro: SAL increased the release of BDNF by mononuclear cells**
- **This was inhibited by co-incubation with fluticasone.**
- **↑ BDNF may underly the adverse effects of SAL monotherapy on AHR in asthma.**



CS induced Neutrophilic “Switch”

CS induced neutrophilia

Effects of steroid therapy on inflammatory cell subtypes in asthma

Cowan et al (New Zealand), Thorax 2010;65:384

To compare ICS response in **Eosinophilic (>2%) versus Non-eosinophilic Asthma (PMN; >61% -Neutrophilic, ≤61% - Paucigranulocytic)**

Methods

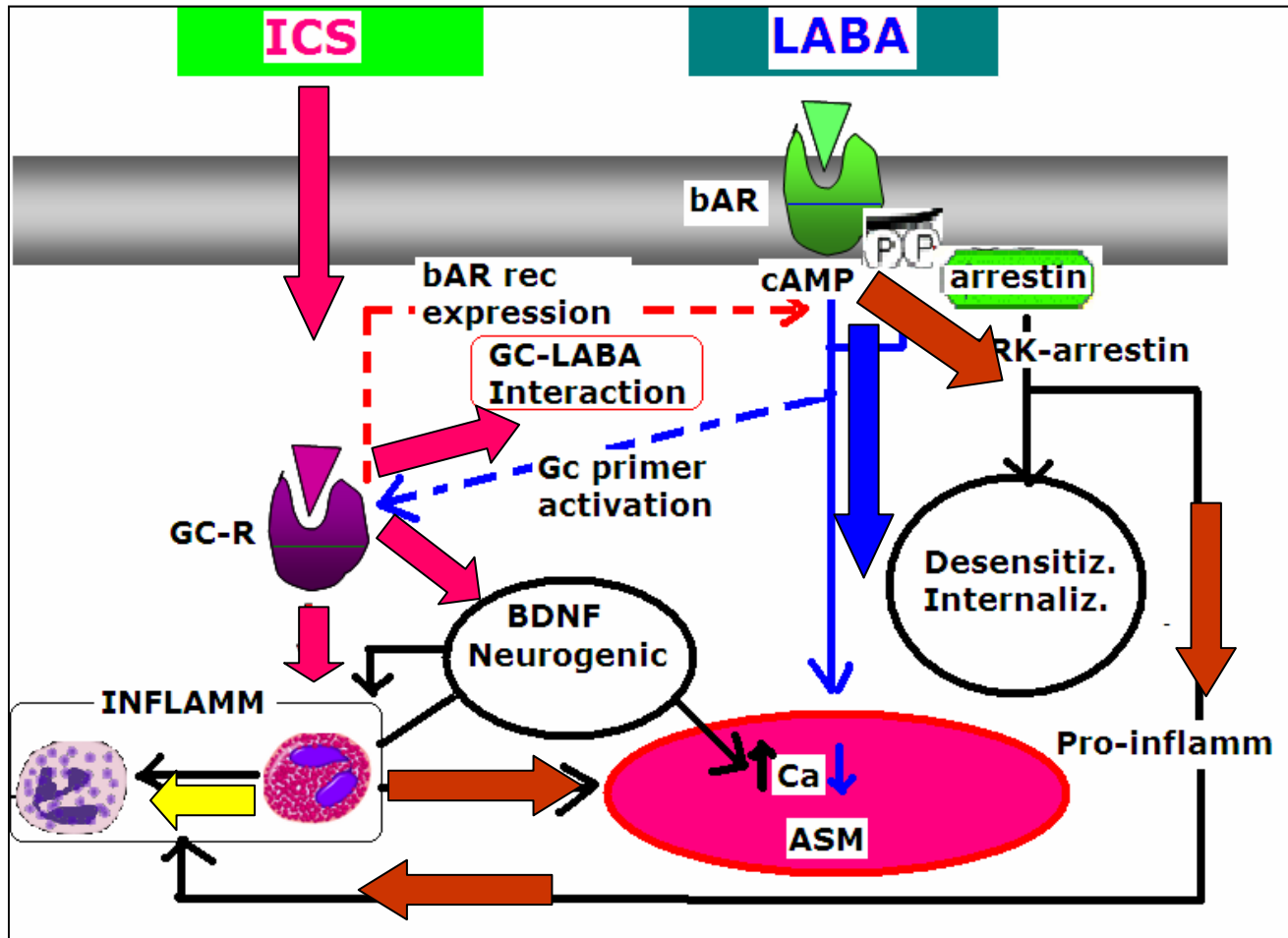
- **ICS withdrawal** until loss of control or 28 days.
- Those with AHR took inhaled fluticasone 1000mcg/d for 28+ days.

Results

- **After steroid withdrawal (“Monotherapy switch”;n=94)**, 67% of subjects were eosinophilic, 31% paucigranulocytic and 2% mixed; **there were no neutrophilic subjects.**
- **With ICS (n=88)**, 39% were eosinophilic, 46% paucigranulocytic, 3% mixed and 5% neutrophilic. **Sputum neutrophils increased from 19.3% to 27.7% (p=0.024).**
- **The treatment response was greater in EA** for symptoms, quality of life, AHR and FENO.
- **Lesser but significant changes occurred in NEA** (ie, paucigranulocytic asthma).
- **Conclusions:**
- **ICS use led to phenotype misclassification.**
- **Steroid responsiveness was greater in EA, but the absence of eosinophilia did not indicate the absence of a steroid response.** In NEA this was best predicted by baseline exhaled nitric oxide.

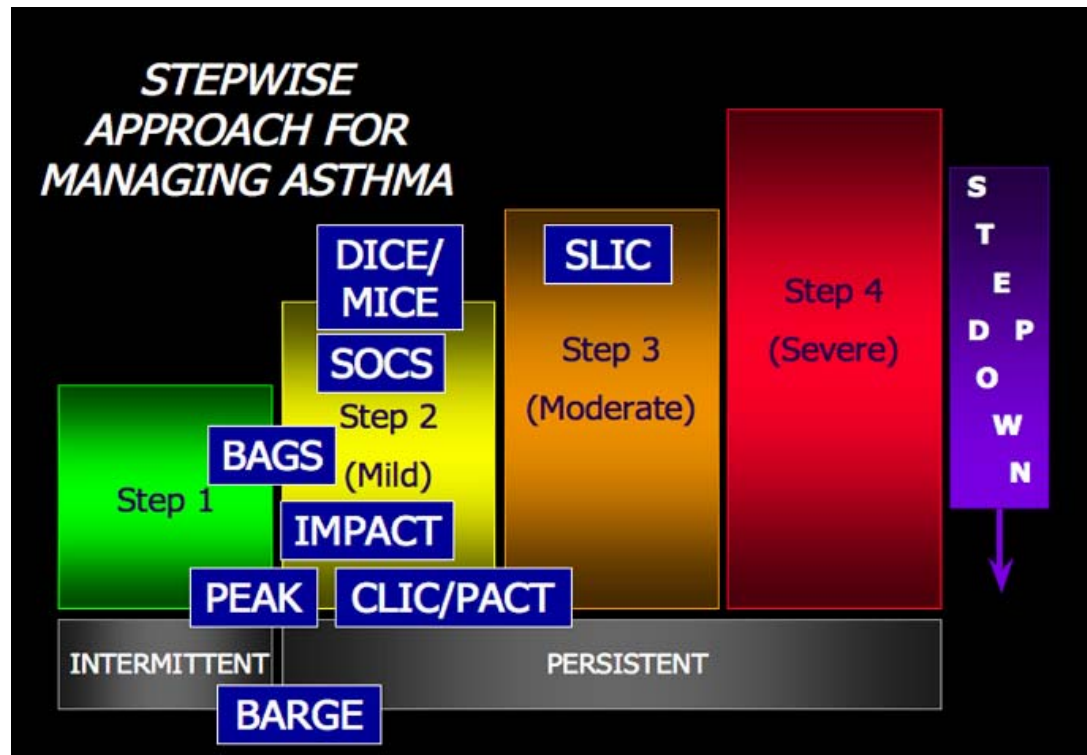
Acute BA effect - Chr BA effect

Short term ICS effect - Long term ICS effect??



ICS use – LABA/ICS

- **B-Agonist-CS “synergic” Interaction** – in vitro (fig) & in vivo (OPTIMA & many other RCTs)
- **LABA Monotherapy** - ↑ inflammation, ↓ B-adr. Efficacy
- **LABA/ICS – risk of asthma SAE confined to a small pt. group seemingly unrelated to dose or benefit, (?Pharmacogenetic)**
- **? Steroid dose-duration** – too much ? Too long → Neutrophilia? Tolerance?
- **? Steroid resistance ; ? B-ADR Dysfunction**



FDA: Long-Acting Beta-Agonists (LABAs): New Safe Use Requirements

UPDATED 06/03/2010

1. **Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.** <<NO LABA MONORx>>
2. **LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.** <<Limit to Step 3-4 Rx>>
3. **LABAs should be used for the shortest duration** of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication. <<Short use - ?evidence?>>
4. Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should **use a combination product** containing both an **inhaled corticosteroid and a LABA**, to ensure compliance with both medications. <<Combination inhalers>>
5. **FDA has determined that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when used appropriately** with an asthma controller medication in patients who need the addition of LABAs. FDA believes the safety measures recommended will improve the safe use of these drugs. <<Benefit>>Risk>>

Avoid LABA MonoRX in Asthma

GINA 2009

10. The roles in therapy of several medications have evolved since previous versions of the report:

- Recent data indicating a possible increased risk of asthma-related death associated with the use of long-acting β_2 -agonists in a small group of individuals has resulted in increased emphasis on the message that long-acting β_2 -agonists should not be used as monotherapy in asthma, and must only be used in combination with an appropriate dose of inhaled glucocorticosteroid.

Asthma step Rx – GINA 2009

Treatment Steps				
← Reduce				Increase →
Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education Environmental control				
As needed rapid-acting β_2 -agonist	As needed rapid-acting β_2 -agonist			
Controller options***	Select one	Select one	To Step 3 treatment, select one or more	To Step 4 treatment, add either
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2 -agonist	Medium- or high-dose ICS plus long-acting β_2 -agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium- or high-dose ICS Low-dose ICS plus leukotriene modifier	Leukotriene modifier Sustained release theophylline	Anti-IgE treatment
		Low-dose ICS plus sustained release theophylline		

* ICS = inhaled glucocorticosteroids
 ** = Receptor antagonist or synthesis inhibitors
 *** = Preferred controller options are shown in shaded boxes

Canadian Thoracic Society Asthma Committee commentary on long-acting beta-2 agonist use for asthma in Canada

Can Respir J Vol 17 No 2 March/April 2010

- FDA has deemed that the benefits of LABAs outweigh the potential risk, when used appropriately. Our committee concurs with this recommendation.
 - **However, our committee cautions that the FDA recommendation that “LABA be used for the shortest duration possible to achieve control of asthma symptoms and then discontinued” is not evidence based.** We identify the safety of this approach as a priority for future research.
 - Moreover, **efforts to maintain control using the least amount of medication require supervision by a health care provider.**
- **LABAs should never be used as monotherapy** for asthma in any age group
 - LABAs should **only be used as add-on therapy to an anti-inflammatory controller (such as ICS, ideally, in the same inhaler device)** in any age group
 - All patients and caregivers should receive **self-management education**, including the role and proper use of medications, and a written action plan
 - All patients with asthma should receive **regular medical review**
 - Asthma controller therapy should be adjusted to the least amount required to maintain control.

Keypoints

- **LABA monotherapy/switch** is associated with increased risk of loss of asthma control and is thus unanimously contraindicated.
- **Combination LABA/ICS use**, is effective and generally safe – thus remaining the recommended step 3-4 Rx in asthma uncontrolled by ISC+SABA.
- **Patient education and follow-up is essential** to detect the **unusual patient with an serious adverse reaction to long term LABA/ICS Rx**
- These patients require specialist care and are best investigated and managed individually. **Therapeutic options include; steroid dose adjustment, LTRA, LD-theophylline?, long term use of tiotropium, and limiting LABA use to “acute bursts” during asthma exacrbations.**
- **Inverse beta-antagonist** (blocker) use is a subject for future research.
- **Large scale Nested Case-Control Studies** may assist ininvestigating the **rare episodes of asthma death.**
- **Large long term (>12mo) RCT** can address the more common occurance of Asthma hospitalizations on patients treated by Non-LABA/ICS cs. LABA ICS.

Panel, Discussion & Summary
How should we use LABA?
Q&A, Summary & close

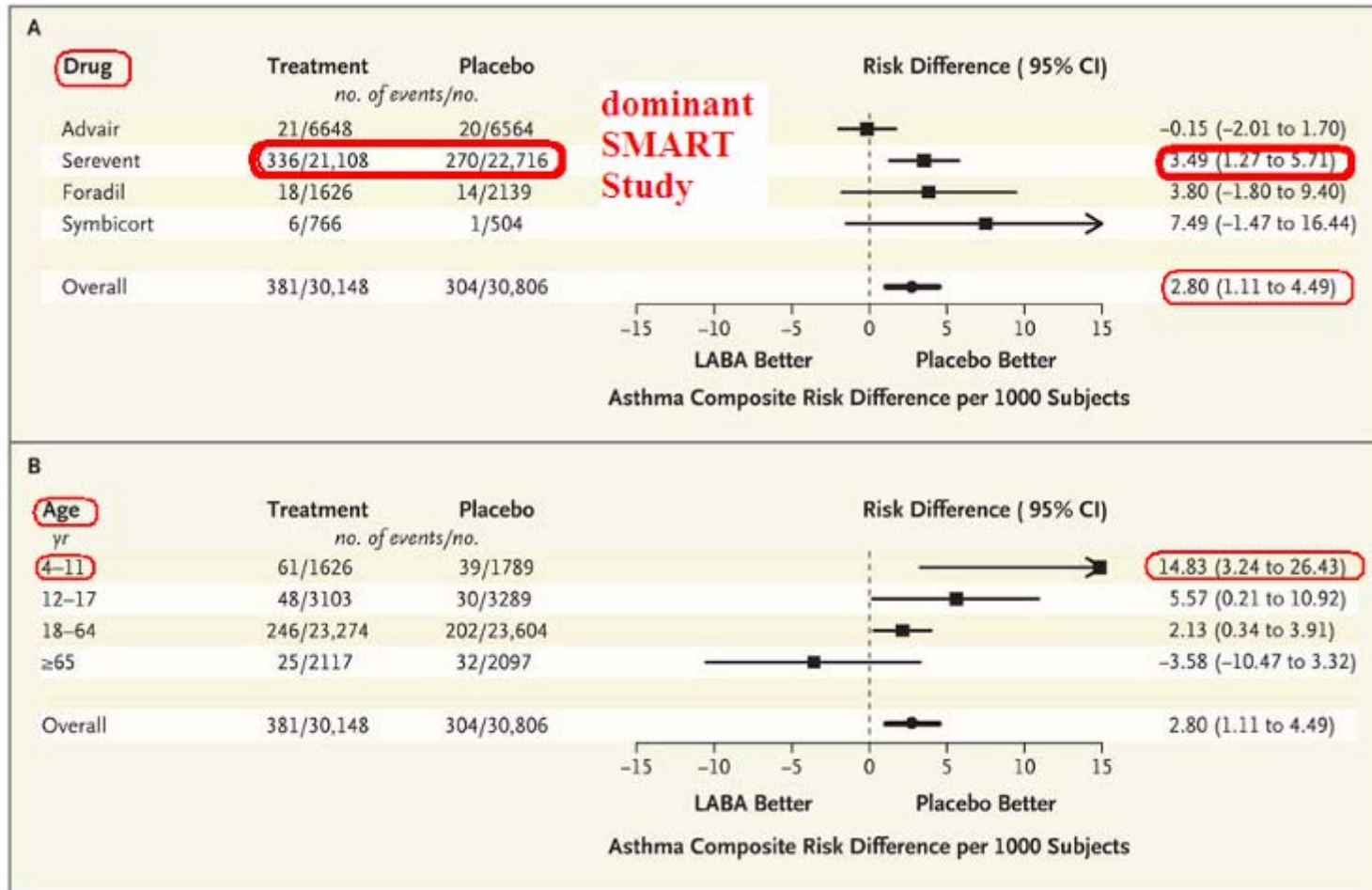


SMART: Key Findings

- Treatment with salmeterol compared with placebo resulted in statistically significant higher incidence of asthma-related deaths, combined asthma-related deaths or asthma-related life-threatening experiences, and respiratory-related deaths alone
- **The data from SMART are not adequate to determine, nor was the study designed to determine, whether concurrent use of inhaled corticosteroids, modifies this risk of asthma-related death**
- Given the similar mechanism of action of beta₂-agonists, it is possible that the findings of SMART may represent a class effect

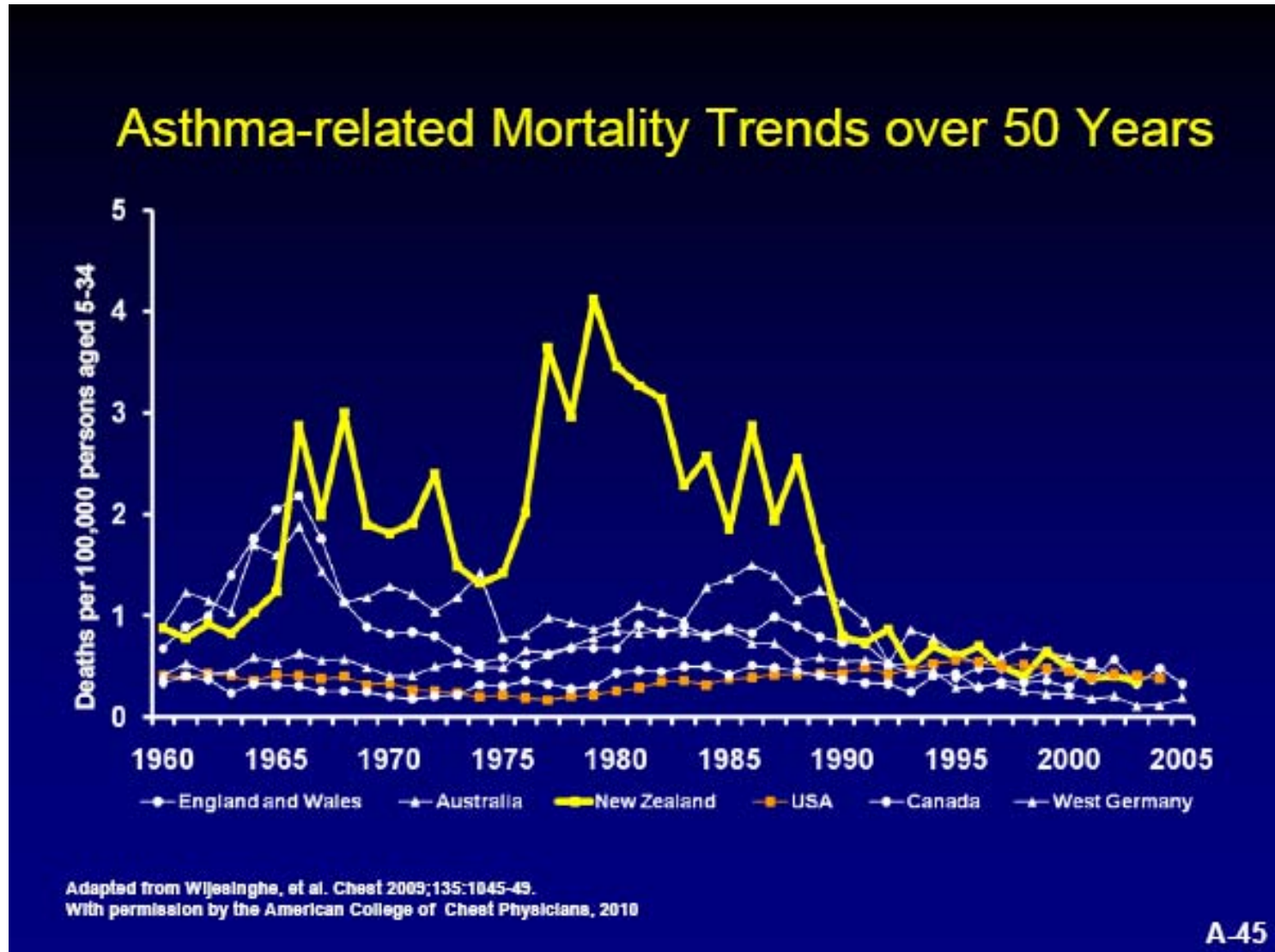
FDA Metaanalysis – LABA Safety (Levenson 2008)

Differences in the Risk of Asthma-Related Death, Intubation, or Hospitalization According to Medication Used (Panel A) and Age Group (Panel B)



Adding LABA to ICS increases Mortality?

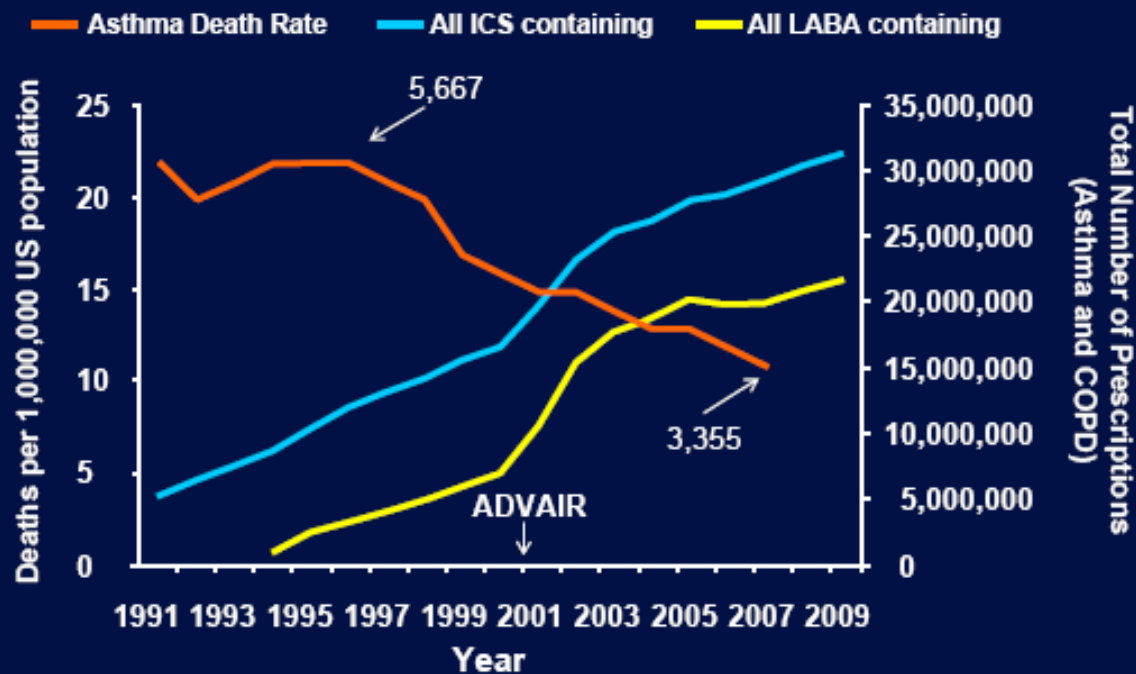
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LABA/ICS increases ICS Adherence and Decreases Asthma Mortality?

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Age-adjusted Asthma Mortality in the US *Relationship to ICS and LABA Use*



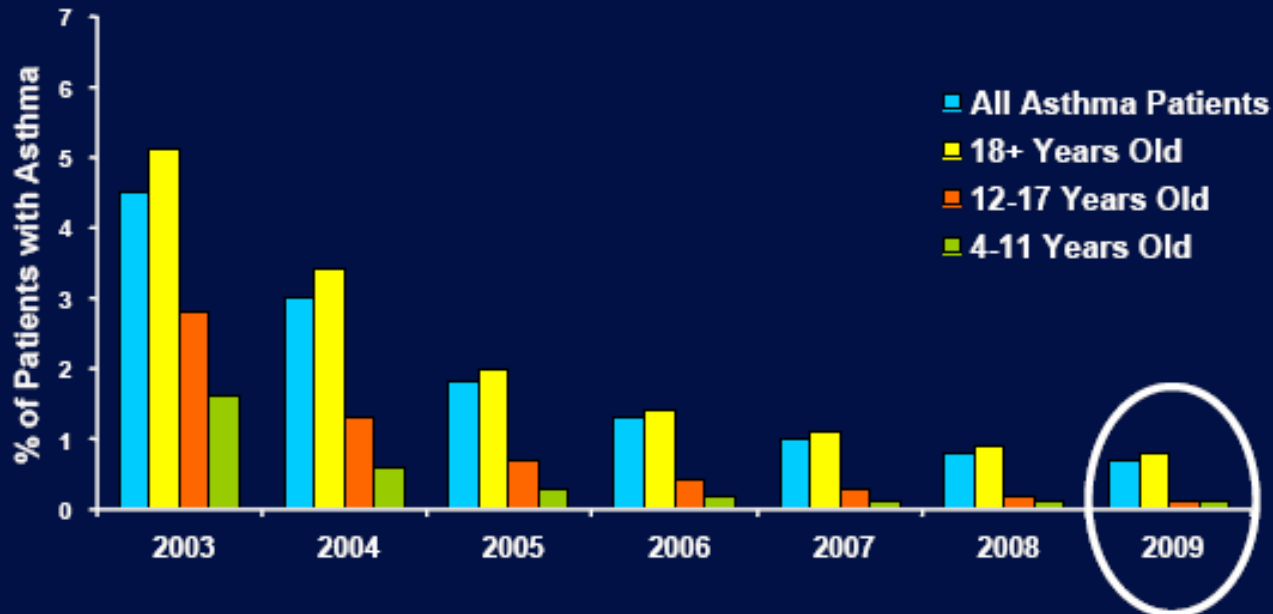
1. BDI Vector One National (VONA) [database]
2. American Lung Association Epidemiology & Statistics Unit Research Program Services. Trends in Asthma Morbidity and Mortality. February 2010. Available at: www.lungusa.org
3. Xu J et al. CDC National Vital Statistics Reports. Preliminary Death Data for 2007: 58(1): Aug, 2009; available at <http://www.cdc.gov/nchs>

LABA/ICS Decreases LABA Monotherapy

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Salmeterol Dispensings *Patients with Asthma*

- 1994 – 1996: ~33% SEREVENT alone



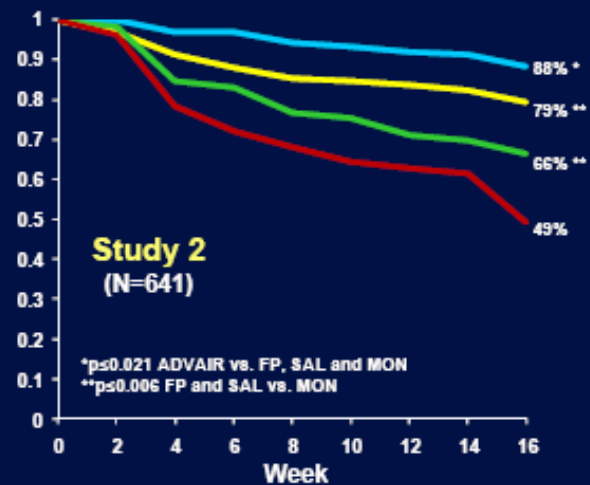
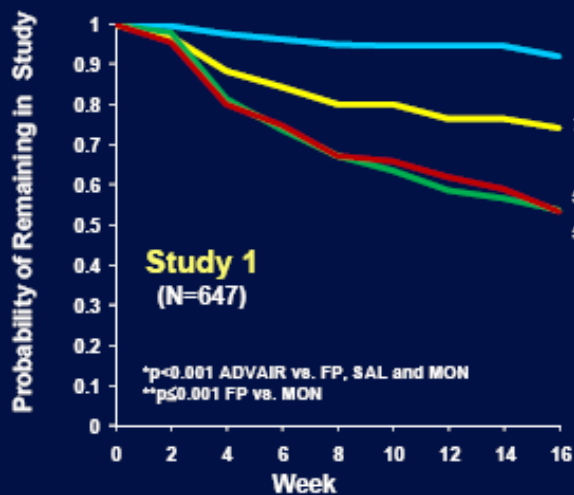
- 2009: <1% SEREVENT alone

Discontinuation of ADVAIR

Withdrawals Due to Worsening Asthma

Patients stable on ADVAIR 100/50 randomized to:

— ADVAIR 100/50 — FP 100 — SAL 50 — MON 10



Study 1: Koenig S. et al. J Asthma 2008;45:681-87.
Study 2: SAS40037; available at <http://www.gsk-clinicalstudyregister.com>

Asthma Mortality – Rare event

GSK Slide

Relevance of Composite Endpoint

Asthma-related Death or Intubation or Hospitalization

- Composite of asthma-related death or intubation or hospitalization has been proposed
- Asthma-related intubations are also very rare
- Asthma-related hospitalizations do not inform on asthma-related death

