

# Safety of Long-acting beta-agonists in Patients with Respiratory Disease

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# Overview

- LABA safety in asthma
  - Evidence on risk
  - FDA meta-analysis
  - Why is it important?
  - FDA recommendations, goals and next steps
- LABA safety in COPD

# Initial “Black Box” Safety Warning

## **WARNING**

Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT<sup>®</sup> Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

# LABA Safety Concerns

- SMART – Salmeterol Multicenter Asthma Research Trial
  - Nelson et al. *Chest* 2006
- 28 week, RCT of 26,355 subjects comparing salmeterol treatment to placebo
- Stopped early due to increase risk of mortality and difficulty enrolling patients

# SMART Results

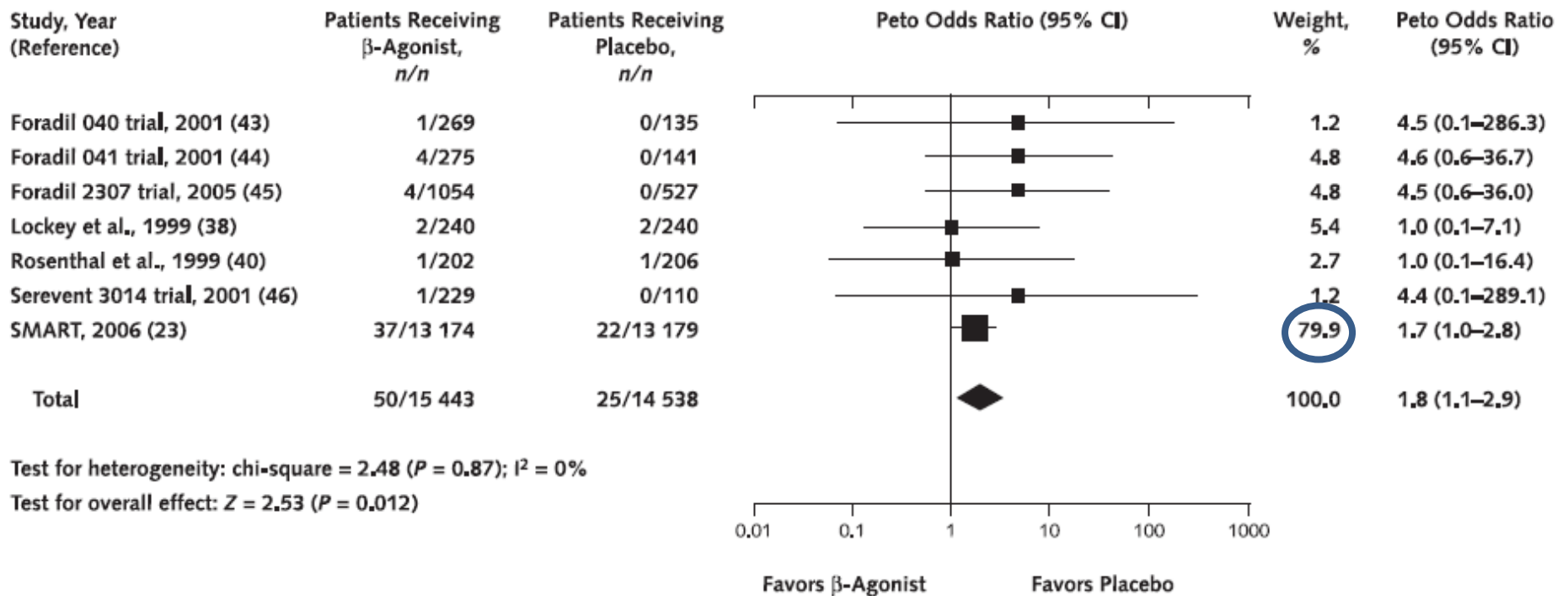
Outcomes	Total Population			African Americans		
	Salmeterol (n = 13,176)	Placebo (n = 13,179)	RR (95% CI)	Salmeterol (n = 2,366)	Placebo (n = 2,319)	RR (95% CI)
Primary end point						
Combined respiratory-related deaths or life-threatening experiences	50 (< 1)	36 (< 1)	1.3952 (0.9097 to 2.1398)	20 (< 1)	5 (< 1)	4.0997 (1.5414 to 10.9042)
Secondary end points						
Combined asthma-related death or life-threatening experiences	37 (< 1)	22 (< 1)	1.7068 (1.0075 to 2.8912)	19 (< 1)	4 (< 1)	4.9244 (1.6779 to 14.4519)
All-cause death	42 (< 1)	32 (< 1)	1.3037 (0.8236 to 2.0635)	12 (< 1)	7 (< 1)	1.6885 (0.6660 to 4.2807)
All-cause hospitalization	469 (4)	420 (3)	1.1096 (0.9750 to 1.2627)	102 (4)	77 (3)	1.2897 (0.9652 to 1.7233)
Combined all-cause death or life-threatening experience	70 (< 1)	59 (< 1)	1.1887 (0.8415 to 1.6793)	24 (1)	11 (< 1)	2.1668 (1.0640 to 4.4125)
Respiratory-related death	24 (< 1)	11 (< 1)	2.1627 (1.0599 to 4.4130)	8 (< 1)	2 (< 1)	3.8819 (0.8253 to 18.2593)
Asthma-related death	13 (< 1)	3 (< 1)	4.3715 (1.2460 to 15.3367)	7 (< 1)	1 (< 1)	7.2580 (0.8937 to 58.9439)

From Nelson et al. *Chest* 2006

- Treatment with ICS modified effect of LABA
  - No ICS = ↑ Risk; LABA + ICS = **No** ↑ Risk

# LABA Meta-Analysis in Asthma

Figure 3. Effect of long-acting  $\beta$ -agonists compared with placebo on odds ratio of life-threatening asthma exacerbations.



From Salpeter et al. *Ann Intern Med* 2006

- Mortality analysis showed pooled risk difference of 0.07% over 6 months
  - Equates to a NNH of ~1400

# FDA Meta-Analysis

- FDA conducted meta-analysis using patient level data to inform meeting of the Pediatric and Allergy Drugs and Risk Management and Drug Safety committees
- Included data from RCTs of LABAs
- Focused on trials containing one of the following:
  - Formoterol; formoterol + budesonide; salmeterol; salmeterol + fluticasone
- Only included asthma trials
- Available at:  
<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>

# FDA Meta-Analysis: Study Characteristics

- Data from 110 RCTs included in the analysis
- A total of 60,954 subjects
  - Salmeterol = 43,824
  - Salmeterol + fluticasone = 13,212
  - Formoterol = 3,765
  - Formoterol + budesonide = 1,270
- Majority of subjects included in the analysis were white (72%), female (57%), 18-64 yrs (77%) and in US studies (69%)

# FDA Meta-Analysis Findings

**Table 1—Risk Differences for LABA vs Non-LABA for Asthma Related-Deaths, Deaths and Intubations, Hospitalizations, and the Composite Outcome, Reported in the FDA Metaanalysis**

All Trials	LABA	Non-LABA	RD (95% CI)
Risk differences for specific and composite outcomes			
Asthma death	16/30,148	4/30,806	0.40 (0.11–0.69)
Death or intubation	44/30,148	27/30,806	0.57 (0.01–1.12)
Hospitalization	369/30,148	299/30,806	2.57 (0.90–4.23)
Composite outcome (death, intubation, or hospitalization)	381/30,148	304/30,806	2.80 (1.11–4.49)
Composite outcome stratified by use or nonuse of randomized (mandatory) ICS therapy			
Trials of LABA without randomized ICS vs no LABA	350/22,286	279/24,474	3.63 (1.51–5.75)
Trials of LABA with randomized ICS vs randomized ICS therapy	31/7,862	26/7,330	0.25 (–1.69–2.18)

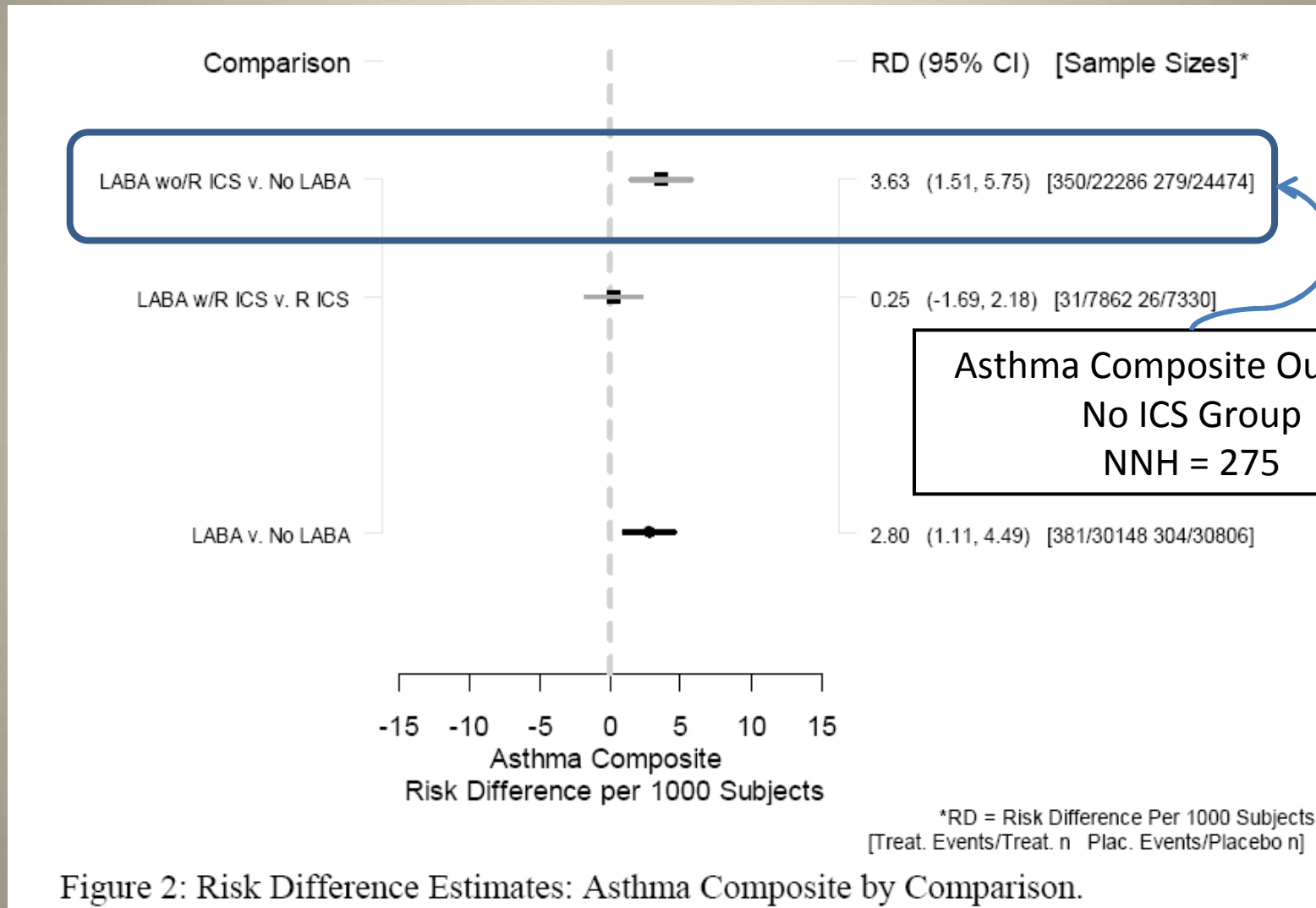
Values are given as No. of events/No. of patients at risk unless otherwise indicated. RD = additional risk of outcome per 1000 subjects treated with LABA compared with no LABA; 0.0 indicates no increased risk. The data are from Table 5 and Figure 1 of Levenson.<sup>3</sup>

From Sears *CHEST* 2009

Asthma Death  
NNH = 2500

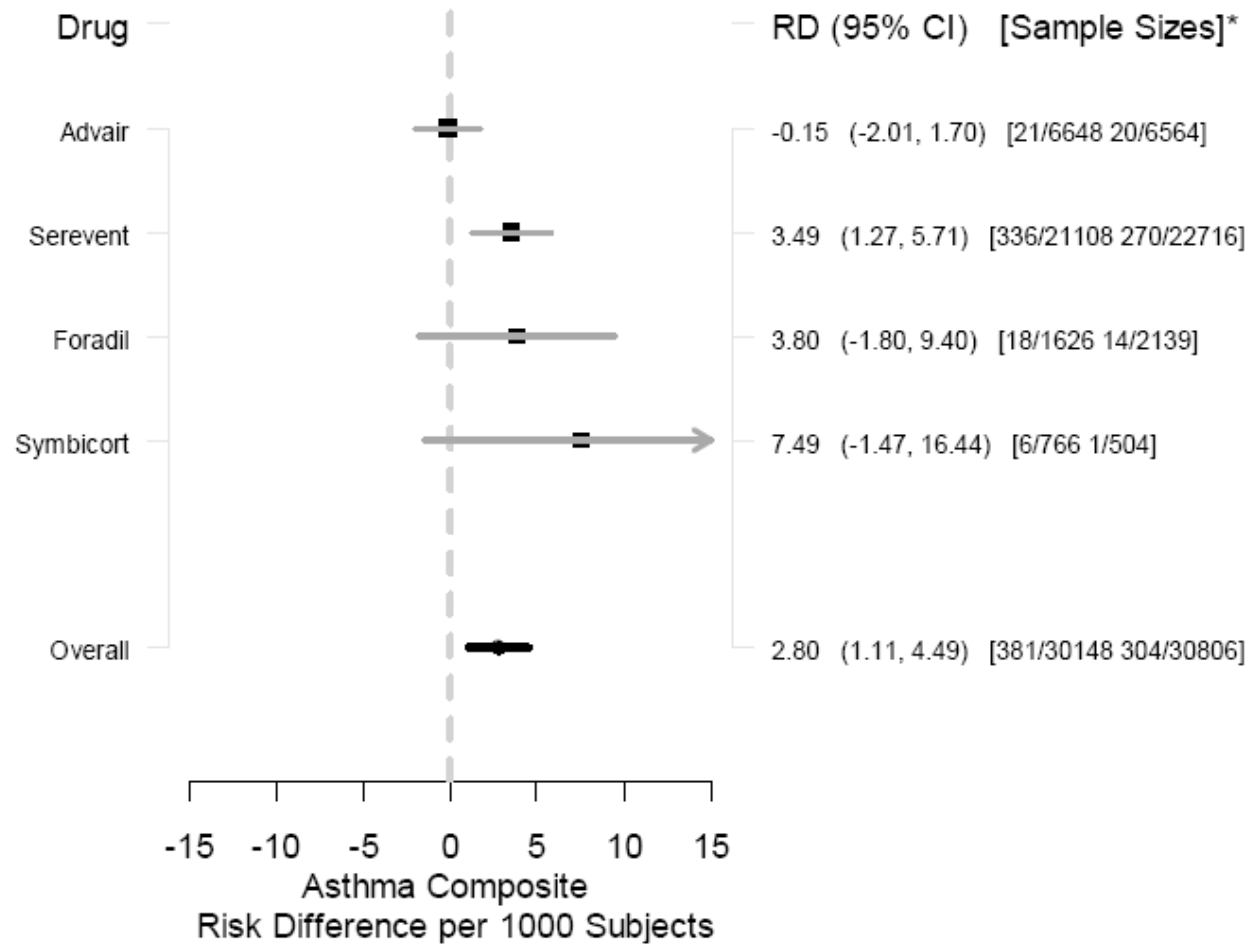
Asthma Composite Outcome  
NNH = 357

# FDA Meta-Analysis: ICS vs. No ICS



From <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>

# FDA Meta-Analysis: Results by Drug



\*RD = Risk Difference Per 1000 Subjects  
[Treat. Events/Treat. n Plac. Events/Placebo n]

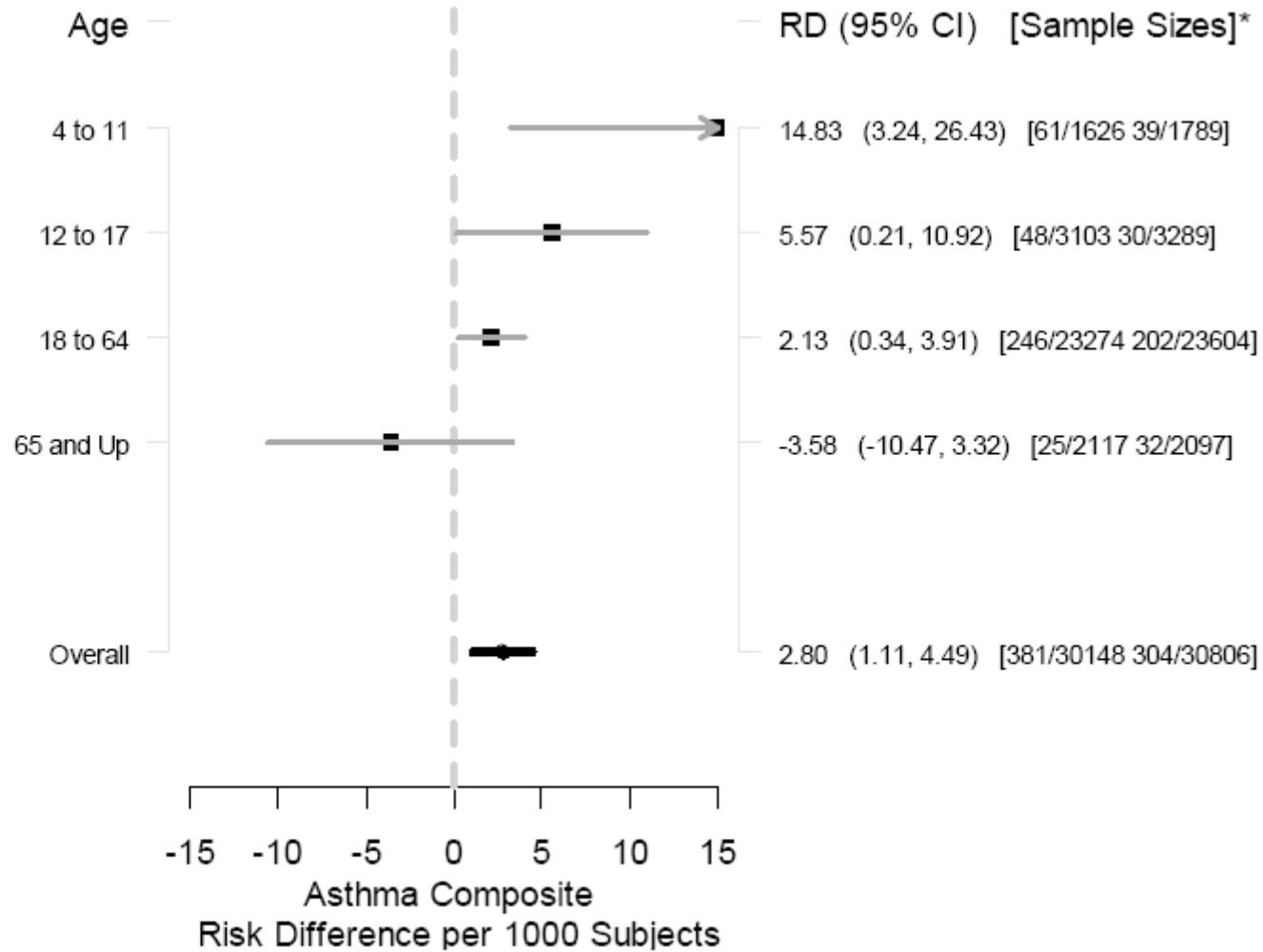
Figure 3: Risk Difference Estimates: Asthma Composite by Drug.

From <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>

# FDA Meta-Analysis: Other Sub-Groups

- Larger risk differences associated with younger age
- Largest risk difference in African-Americans
- Larger risk difference among females

# Age

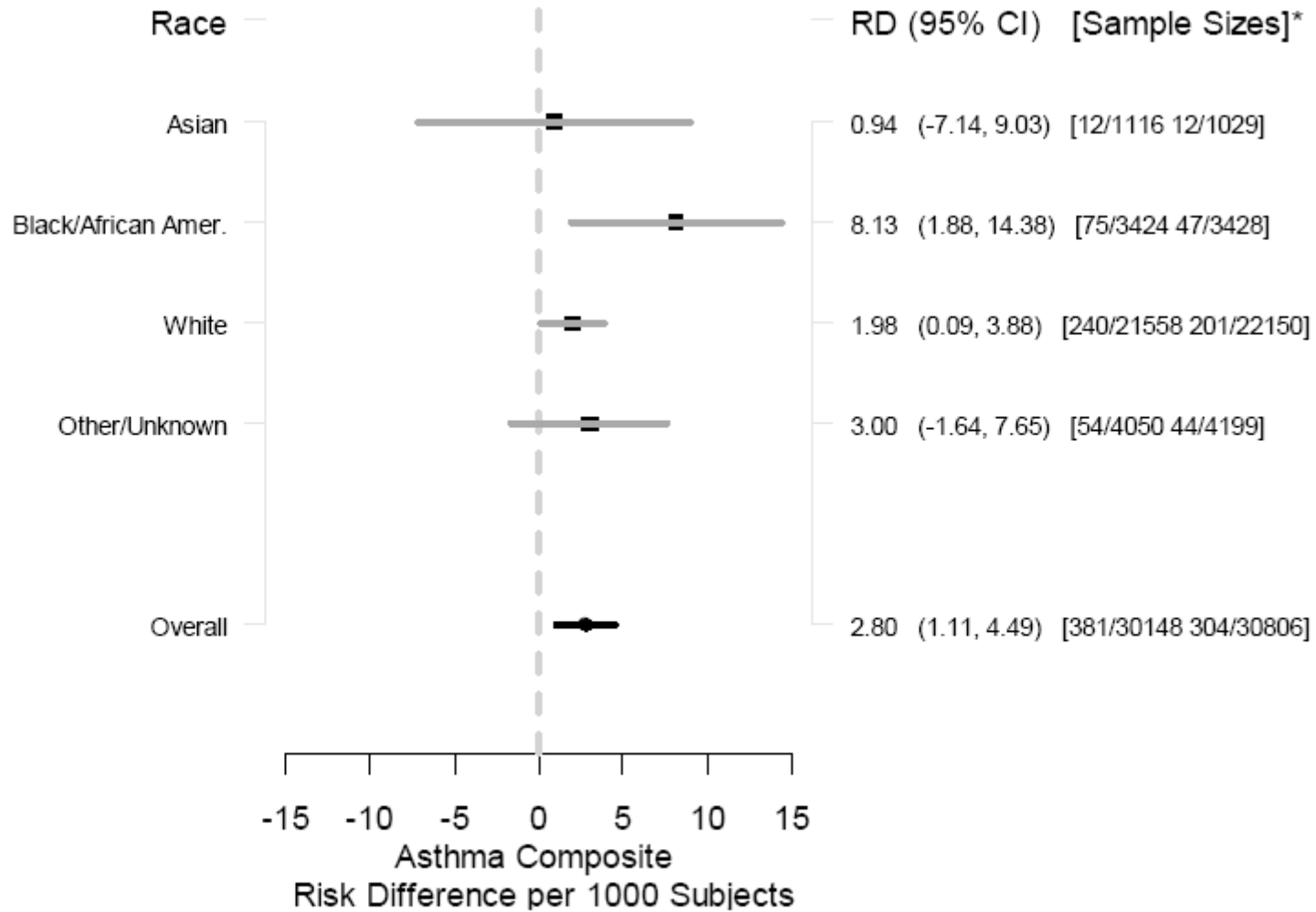


\*RD = Risk Difference Per 1000 Subjects  
[Treat. Events/Treat. n Plac. Events/Placebo n]

Figure 4: Risk Difference Estimates: Asthma Composite by Age Subgroups.

From <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>

# Race



\*RD = Risk Difference Per 1000 Subjects  
[Treat. Events/Treat. n Plac. Events/Placebo n]

Figure 5: Risk Difference Estimates: Asthma Composite by Race Subgroups.

From <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>

# Gender

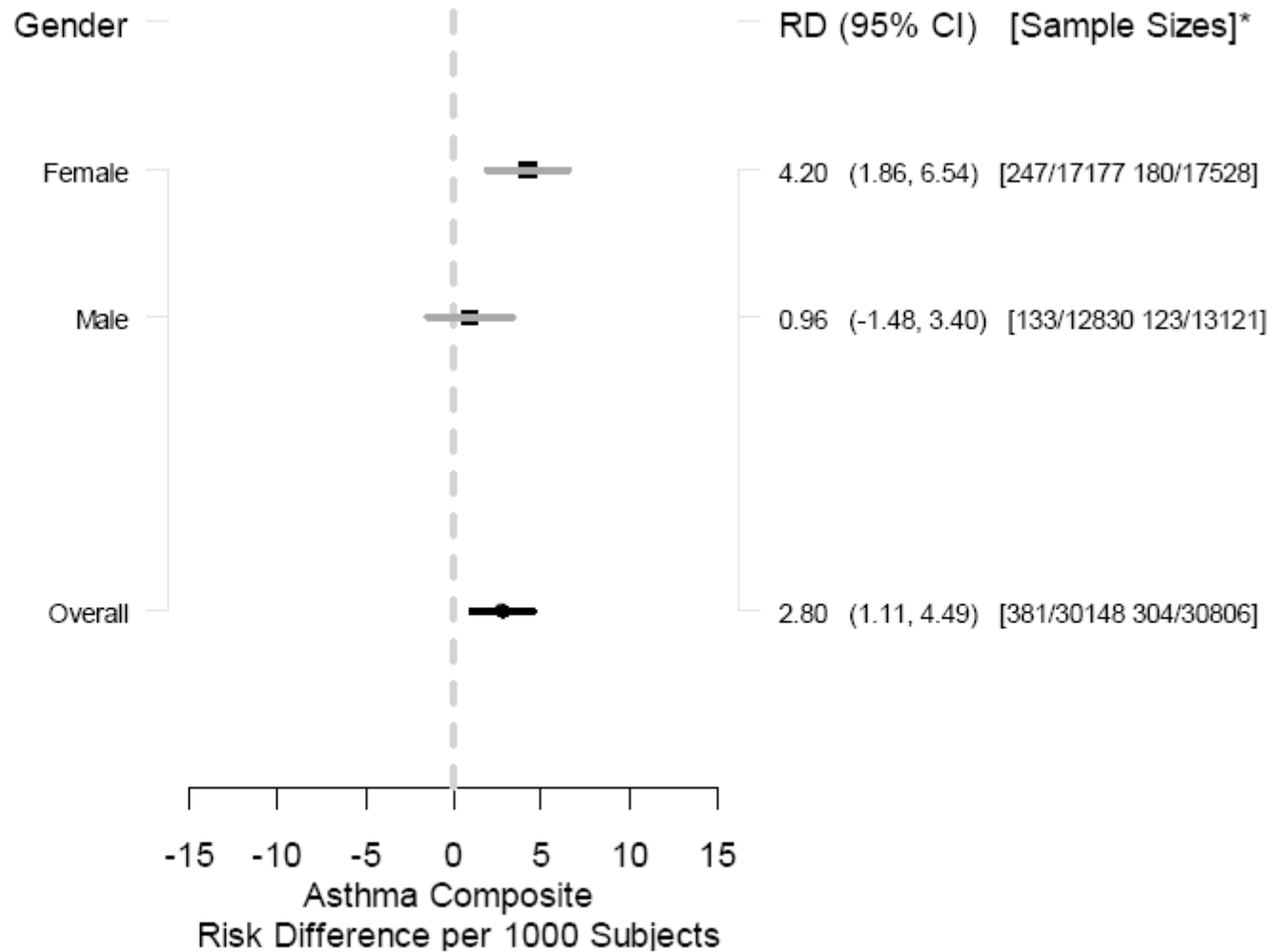


Figure 6: Risk Difference Estimates: Asthma Composite by Gender Subgroups.

# FDA Meta-Analysis: Sensitivity Analyses

- SMART Exclusion
  - Similar to previous meta-analyses, SMART contributed majority of patients
  - SMART provided 26,000+ patients to base case analysis
  - After excluding, results were similar
  - Risk difference in the composite endpoint for those in the LABA arm was 3.15 (1.04, 5.26)
- Serevent Nationwide Surveillance (SNS) Inclusion
  - Included only asthma deaths and hospitalizations
  - Asthma deaths risk difference = 0.42 (0.17, 0.68)
  - Asthma hospitalizations risk difference = 1.74 (0.30, 3.18)

# Summary of LABA Safety in Asthma

- Data indicates an increased risk for asthma-related deaths, asthma-hospitalizations and near fatal events
- Effect may be modified by the use of concomitant ICS

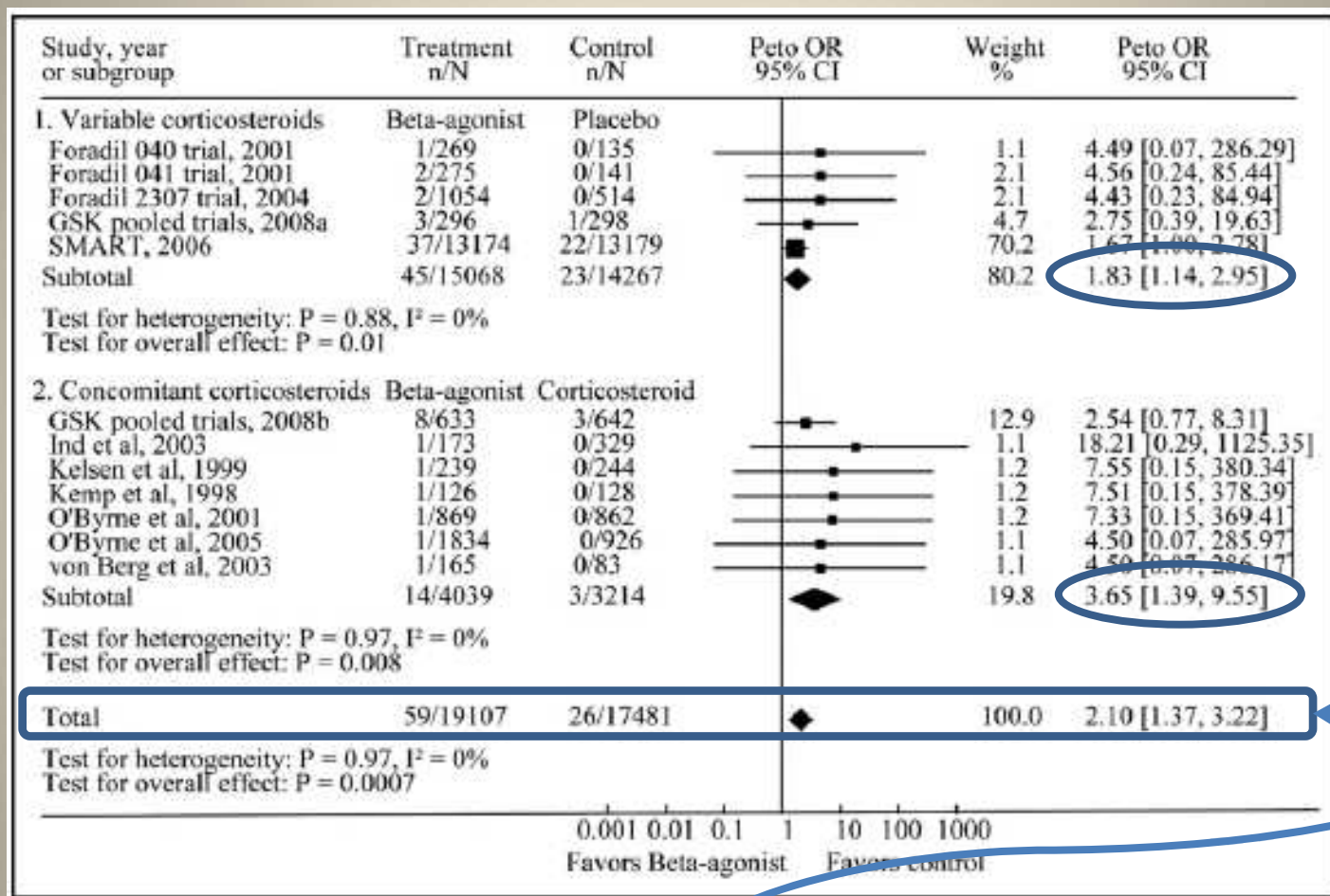
# Possible Mechanisms of Harm

- Tolerance
  - Bronchodilator effect of LABAs decreases over time as tolerance develops
  - Requires more medication to achieve desired effect
- Inappropriate use
  - LABAs used as a rescue medication to treat acute symptoms on an exacerbation
- Symptom masking
  - Bronchodilation provides symptom relief such that it may mask symptoms of an acute exacerbation
- Cardiovascular risk?
  - Non-selective beta-agonists

## But wait ...

- Not all results showed harm completely eliminated by combination use of LABA + ICS

# LABA Meta-Analysis by ICS Treatment



From Salpeter et al. *Am J Med* 2010

Risk Difference = 1.6 per 1,000  
 NNH = 625

# LABA Meta-Analysis by ICS Treatment

**Table 4** Odds ratio for risk of death and other outcomes associated with salmeterol treatment: salmeterol/ICS (randomised or background) versus ICS (randomised or background) (127 studies)

Primary analyses: Peto method

Outcome	No of studies with data	Odds ratio (95% CI)	
		Fixed effect	Random effects
Asthma deaths	2	2.1 (0.6 to 7.9)	2.2 (0.5 to 9.3)
All deaths	8	1.5 (0.8 to 2.7)	1.5 (0.8 to 2.7)
Hospitalisations	55	1.3 (1.1 to 1.5)	1.4 (1.1 to 1.8)
Intubations	6	1.7 (0.9 to 3.4)	1.7 (0.9 to 3.4)

From Weatherall et al. *Thorax* 2010

# FDA Meta-Analysis: ICS vs. No ICS During Trial

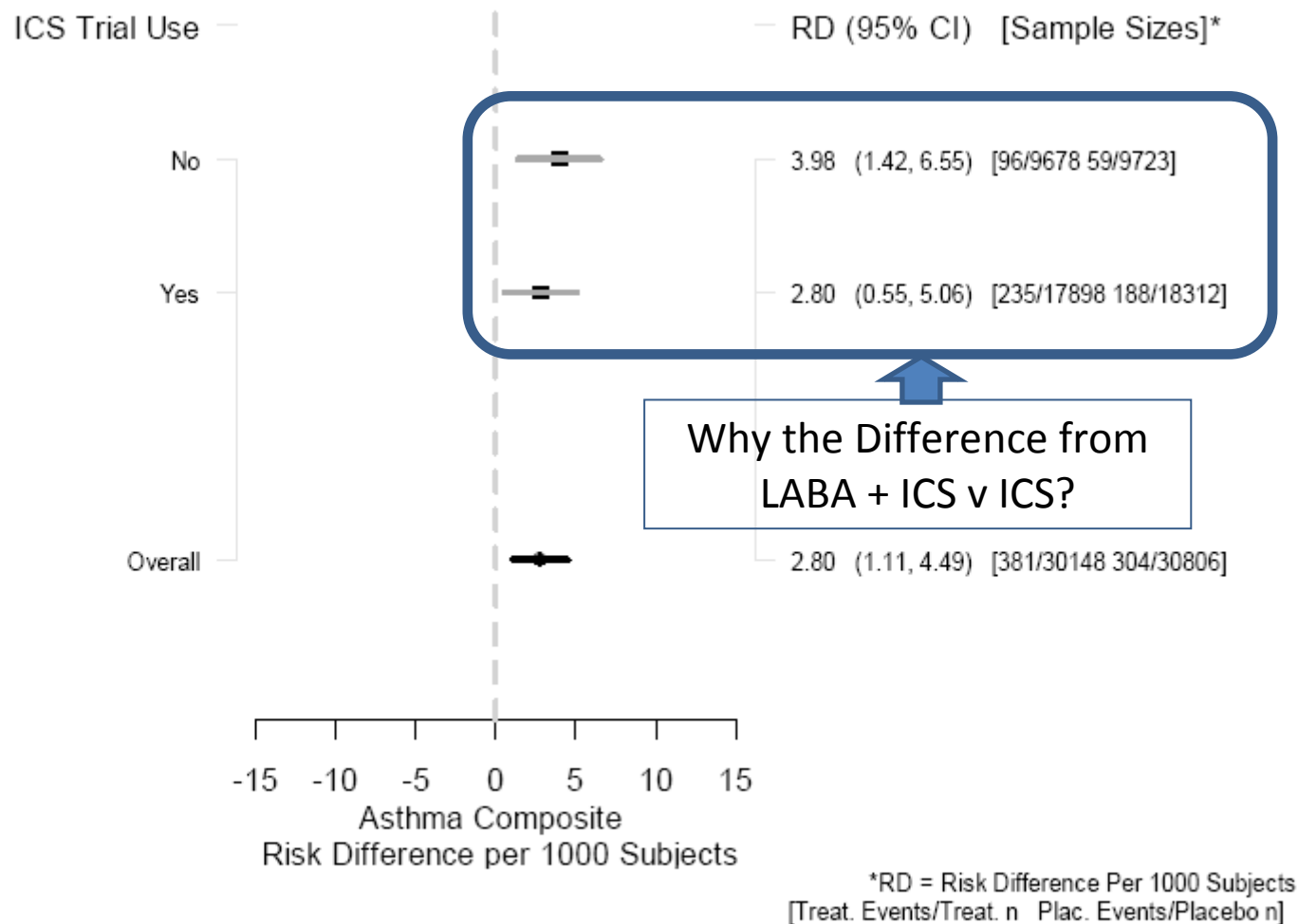


Figure 10: Risk Difference Estimates: Asthma Composite by ICS Trial Use Subgroups.

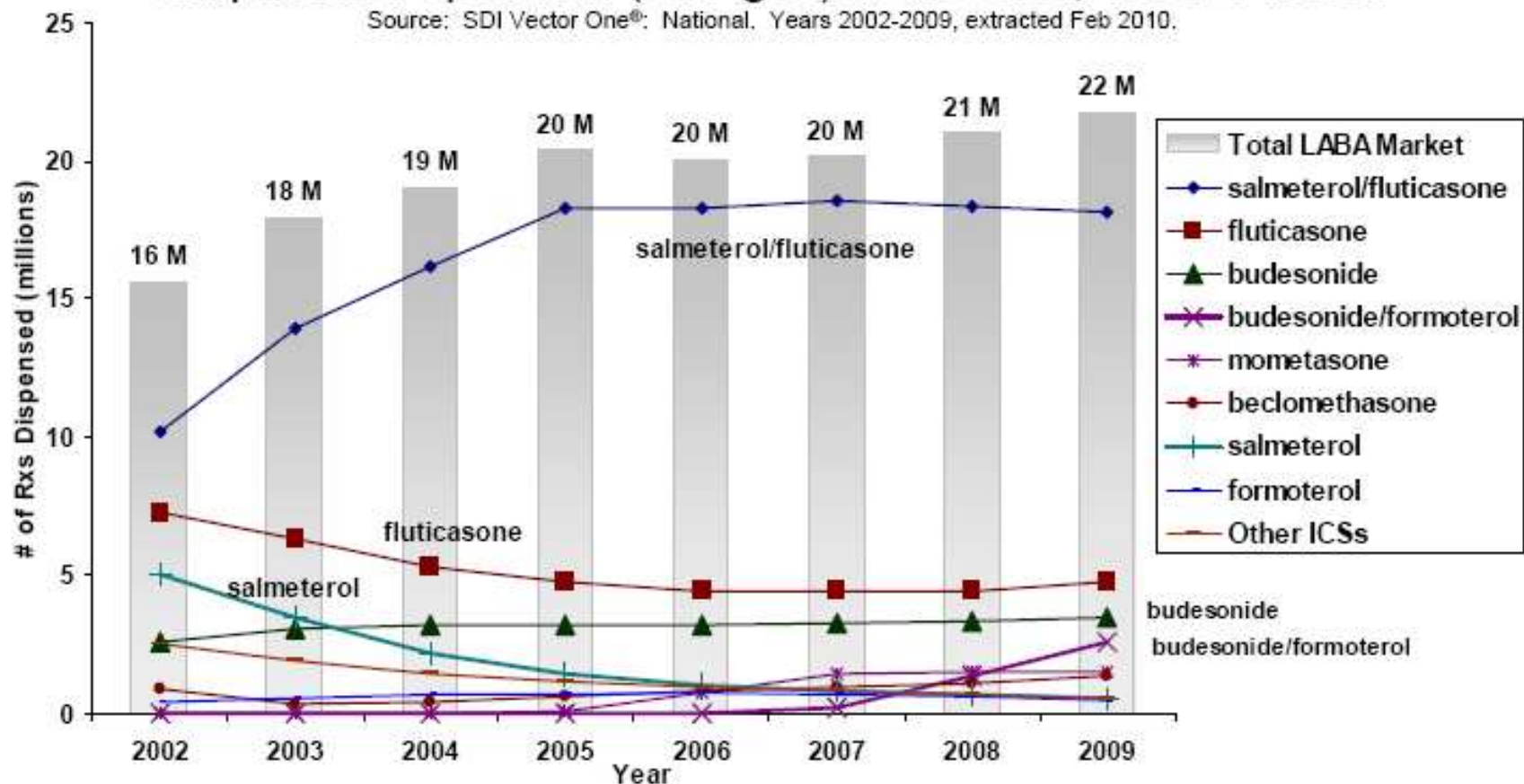
# Now what?

- Majority of evidence from meta-analyses indicate risk with LABAs is lessened when used with ICS
- More recent meta-analyses show risk may not be completely removed
- What is the message for patients and providers?

# How Big is the Issue?

## Dispensed Prescriptions for LABA and Inhaled Corticosteroids (ICS) in Outpatient Population (All Ages) in the U.S., Y2002-Y2009

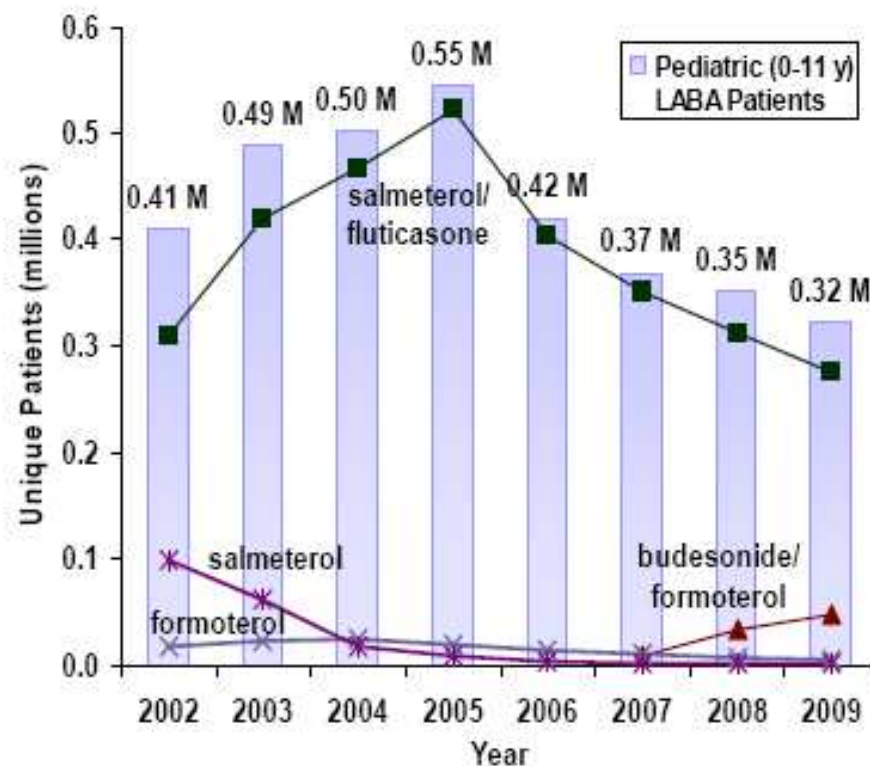
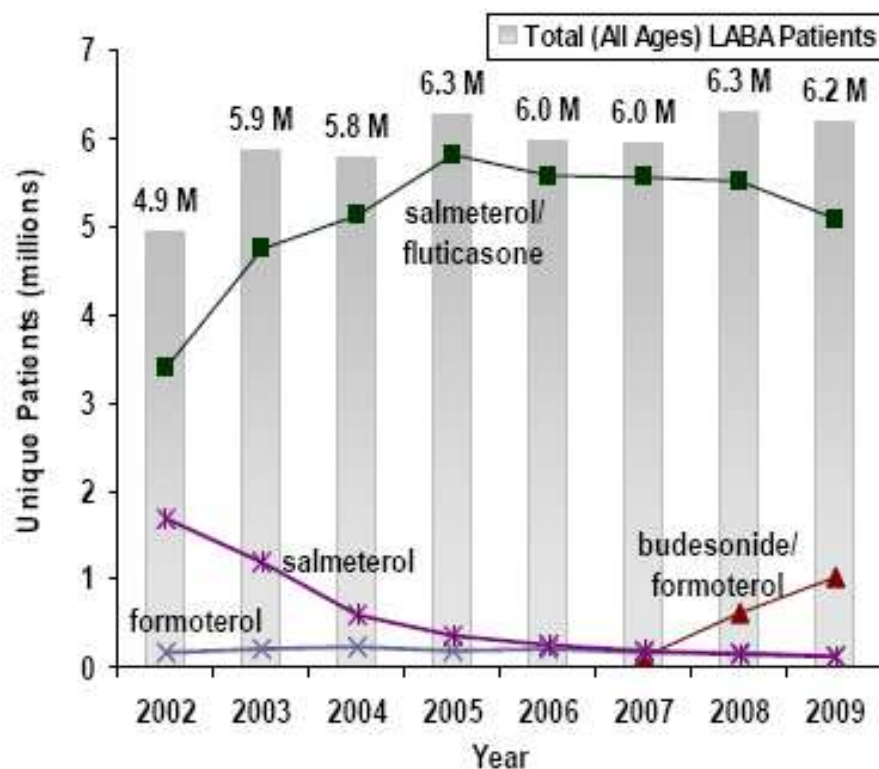
Source: SDI Vector One®: National. Years 2002-2009, extracted Feb 2010.



- Combination LABA products accounted for 62% of all LABAs and ICS in Y2009
- Single-agent LABA salmeterol decreased from 5M to 532K Rx in Y2002 to Y2009

## Number of Unique Patients by Age Receiving LABA Prescriptions from U.S. Outpatient Retail Pharmacies, Y2002-Y2009

Source: SDI Vector One®: Total Patient Tracker. Years 2002-2009, extracted Feb 2010.



- Total number of patients of all ages in Y2009: 6.2 million LABA patients
- 5.2% of the total patients were pediatric patients (0-11 years) in Y2009: 322,000 pediatric LABA patients

# FDA Recommendations and Goals

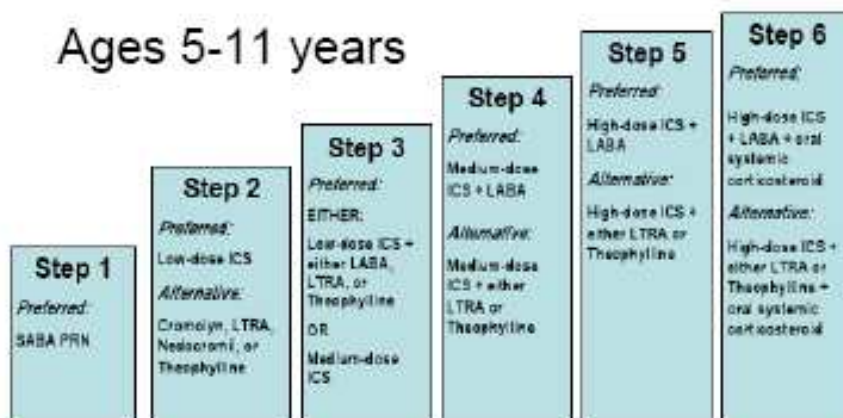


# Guideline Recommendation on LABAs in the Management of Persistent Asthma

Ages ≥12 years



Ages 5-11 years



- Long-term control medications
- Not for use as monotherapy
- To be used in combination with ICSs for long-term control (step 3 or higher in patients 5 years of age and older)
- For patients not adequately controlled on low-dose ICS, increase of ICS given equal weight to addition of LABA
- Step down of ICS preferred in stepwise approach for managing asthma

NAEPP ERP 3, 2007: pages 213, 336, 343<sup>28</sup>

# FDA Advisory Committee Meeting

- FDA held joint advisory committee meeting
  - Pulmonary-Allergy Drugs Advisory Committee
  - Drug Safety and Risk Management Advisory Committee
- Focus on safety of LABAs
- Meeting held December 2008
- Key question: Do benefits of LABAs outweigh risks?



# US FDA December 10-11, 2008, Advisory Committee Meeting

Vote on Questions: Do Benefit outweigh the risk for ... ..?

	<b>Serevent</b>			<b>Foradil</b>		
	Yes	No	Abstain	Yes	No	Abstain
> 18 yrs	10	17	0	9	18	0
12-17 yrs	6	21	0	6	21	0
4/5-11 yrs	0	27	0	0	27	0

	<b>Advair</b>			<b>Symbicort</b>		
	Yes	No	Abstain	Yes	No	Abstain
> 18 yrs	27	0	0	26	0	1
12-17 yrs	23	3	1	20	5	2
4/5-11 yrs	13	11	3	NA	NA	NA

# FDA Recommendations and Labeling Changes

- February 18, 2010 Advisory Committee Meeting
  - All LABA products will remain on market with labeled indication for asthma
  - Change drug labels
  - Safe use initiatives
  - Require manufacturers to conduct large clinical trials to evaluate risk of addition of LABAs to ICS

## Risk-Benefit Assessment of LABAs

- Risk
  - Serious asthma exacerbation resulting in asthma-related deaths, intubations, and hospitalizations
- Benefit
  - Symptomatic benefit in the form of improved lung function (FEV<sub>1</sub>, PEF<sub>R</sub>), reduced nocturnal awakening from asthma symptoms, and decreased use of rescue SABA for asthma exacerbations

*SABAs may have similar risk and benefit*

# Labeling Changes

## Specific Label Changes for Long-Acting Beta-Agonists (LABAs).

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.
2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.
3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.
4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.

From Chowdhury and Dal Pan NEJM 2010

**FOR ORAL INHALATION**

Initial US Approval: 2006

**WARNING: ASTHMA-RELATED DEATH** *(See full prescribing information for complete boxed warning.)*

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)
- When treating patients with asthma, prescribe SYMBICORT only for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (1.1, 5.1)

----- **RECENT MAJOR CHANGES** -----

Boxed Warning	May 2010
Indications and Usage, Treatment of Asthma (1.1)	May 2010
Dosage and Administration, Asthma (2.1)	May 2010
Warnings and Precautions, Asthma-Related Death (5.1)	May 2010

----- **INDICATIONS AND USAGE** -----



## Professional Drug Label Changes

### **Goal – Assure LABAs are used with a long-term control medication, such as ICS**

- Contraindicate use of LABAs in asthma for all ages without concomitant use of a long-term control medication, such as ICS
  - Contraindication is a strong clear message
  - Use of LABA with ICS is already common practice
- Recommend fixed-dose combination product containing LABA and ICS in pediatric and adolescent patients who require addition of a LABA to an ICS
  - New recommendation to single out younger patients
  - To ensure compliance



## Professional Drug Label Changes

### Goal – Reduce overall use of LABAs

- Stop LABA, if possible, once asthma control is achieved and maintain the use of a long-term control medication, such as ICS
  - New labeling concept
  - Step down LABA in preference over ICS
- Recommend against LABA use in patients whose asthma is adequately controlled on low- or medium-dose ICS
  - New labeling concept
  - Optimize ICS prior to adding LABA

# FDA Actions

- Safe use initiatives
  - Work with partners to monitor prescribing patterns and medication use
- Risk Evaluation and Mitigation Strategy (REMS)
  - Revised medication guide written for patients
  - Plan to educate healthcare providers

# Safety Clinical Trials

- FDA requiring manufacturers to conduct 5 randomized, double-blind controlled trials focused on safety of LABAs
- Trials will compare ICS + LABA vs. ICS alone

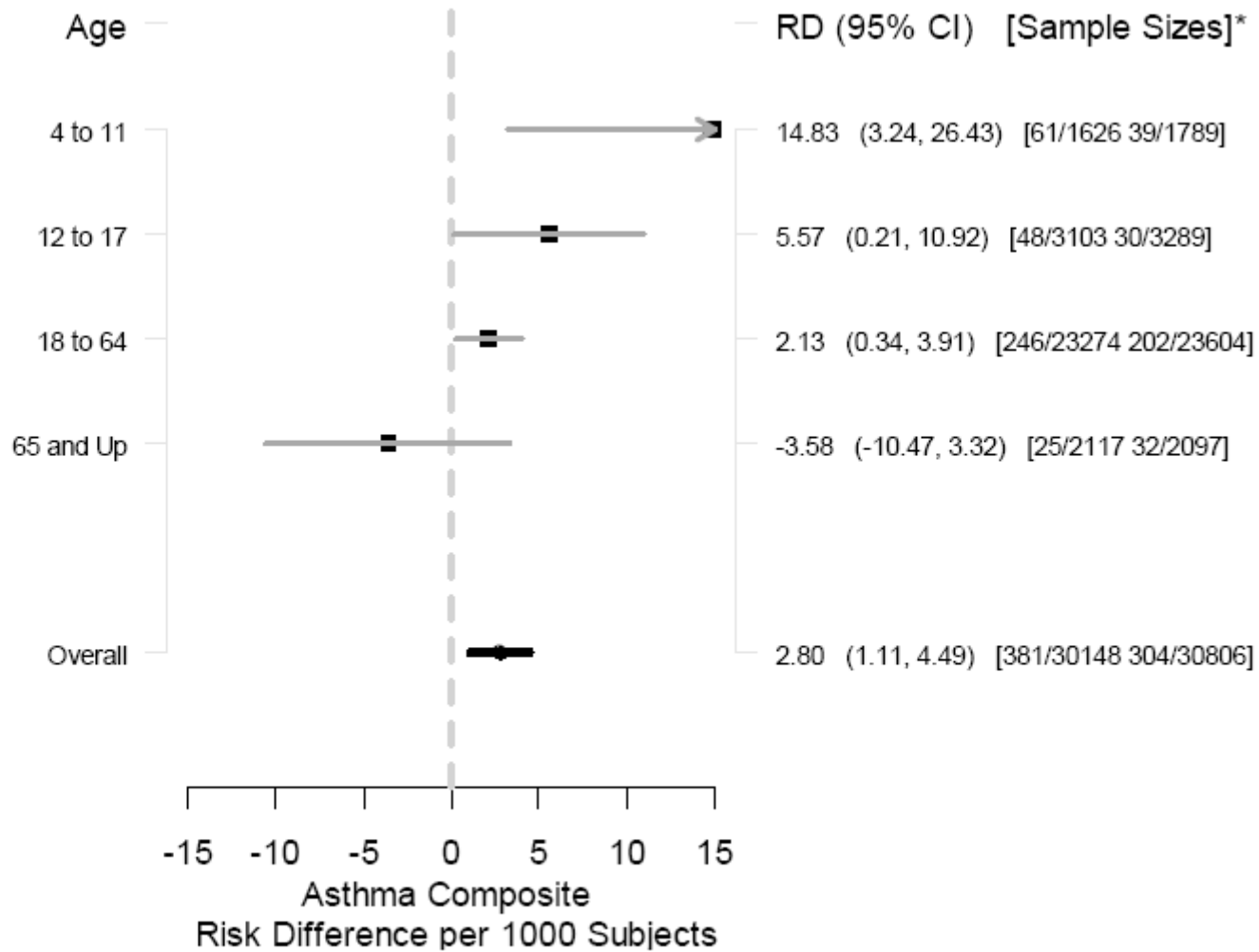
# Safety Clinical Trials

- Four clinical trials will be conducted in adult and adolescent patients 12 years of age and older.
- Adult and adolescent trials will include 11,700 patients in *each* trial for a total of 46,800 patients.
- Each trial will evaluate one of the following LABA-containing drugs: 1) Symbicort (budesonide and formoterol); 2) Advair Diskus (fluticasone and salmeterol); 3) Dulera (mometasone and formoterol); and 4) Foradil (formoterol). The Foradil trial will also include treatment with fluticasone, which will be provided in a separate inhaler.
- One clinical trial will be conducted in pediatric patients aged 4 to 11 years with Advair Diskus.
- The pediatric trial will include 6,200 patients.

# Safety Clinical Trials

- Patients in all trials will be treated for *six* months
- Primary endpoint will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalization.
- Pediatric trial will also assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness.
- The clinical trials will begin in 2011 and FDA expects to receive results in 2017.

# Safety Clinical Trial Concerns



\*RD = Risk Difference Per 1000 Subjects  
[Treat. Events/Treat. n Plac. Events/Placebo n]

Figure 4: Risk Difference Estimates: Asthma Composite by Age Subgroups.

# Implications in Asthma

- Increased risk associated with LABAs in patients with asthma
- Controversy regarding impact of ICS on risk
- Minimize use/dose of LABAs in asthma patients
- If used, do so in combination with ICS
- Communicate risks to patients
  - Require more/better tools
- Other respiratory medications not without risks
  - ICS
  - Anticholinergics

# LABA in COPD



The Blue Bloater



# GOLD Treatment Recommendations

I: Mild

II: Moderate

III: Severe

IV: Very Severe

- $FEV_1/FVC < 70\%$
- $FEV_1 \geq 80\%$  predicted

- $FEV_1/FVC < 70\%$
- $50\% \leq FEV_1 < 80\%$  predicted

- $FEV_1/FVC < 70\%$
- $30\% \leq FEV_1 < 50\%$  predicted

- $FEV_1/FVC < 70\%$
- $FEV_1 < 30\%$  predicted  
or  $FEV_1 < 50\%$  predicted plus chronic respiratory failure

Active reduction of risk factor(s); influenza vaccination

**Add** short-acting bronchodilator (when needed)

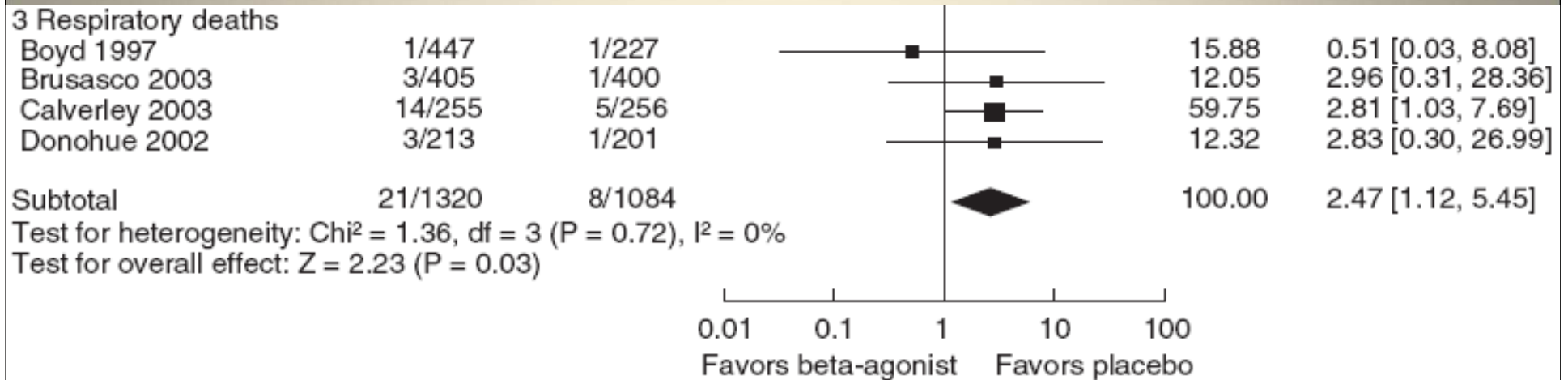
**Add** regular treatment with one or more long-acting bronchodilators (when needed); **Add** rehabilitation

**Add** inhaled glucocorticosteroids if repeated exacerbations

**Add** long term oxygen if chronic respiratory failure.  
**Consider** surgical treatments



# LABA Meta-Analysis in COPD



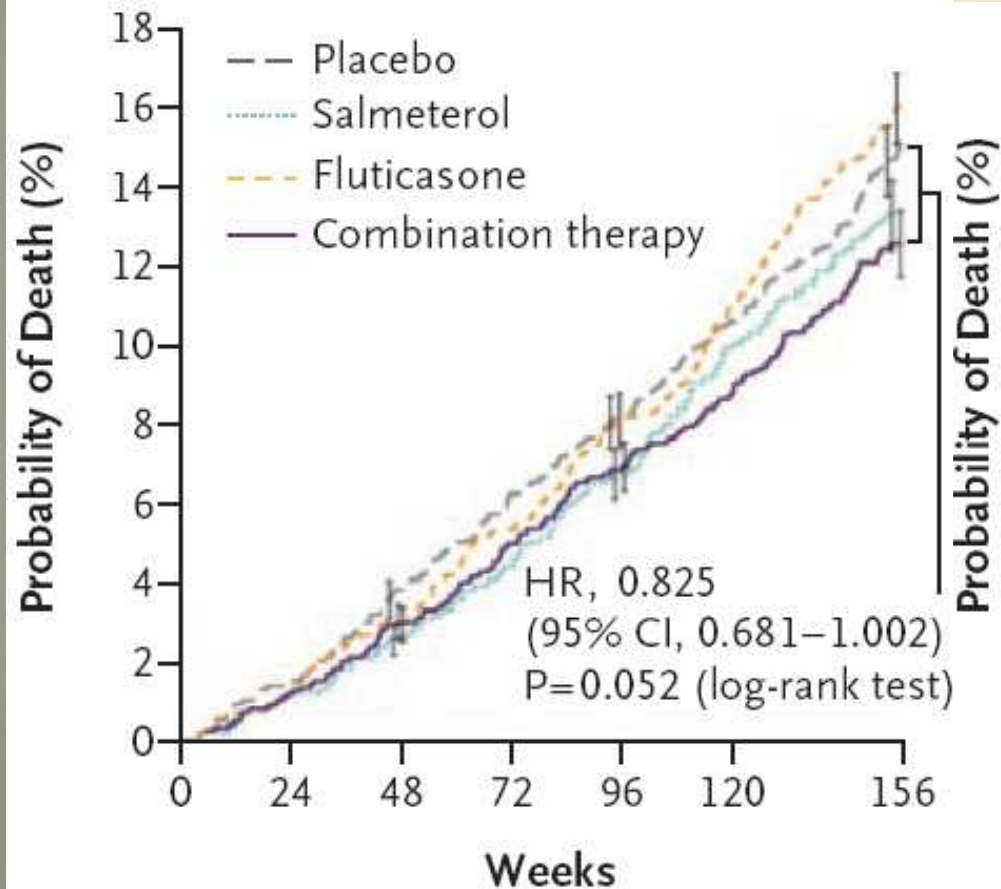
From Salpeter et al. *J Gen Intern Med* 2006

# TORCH

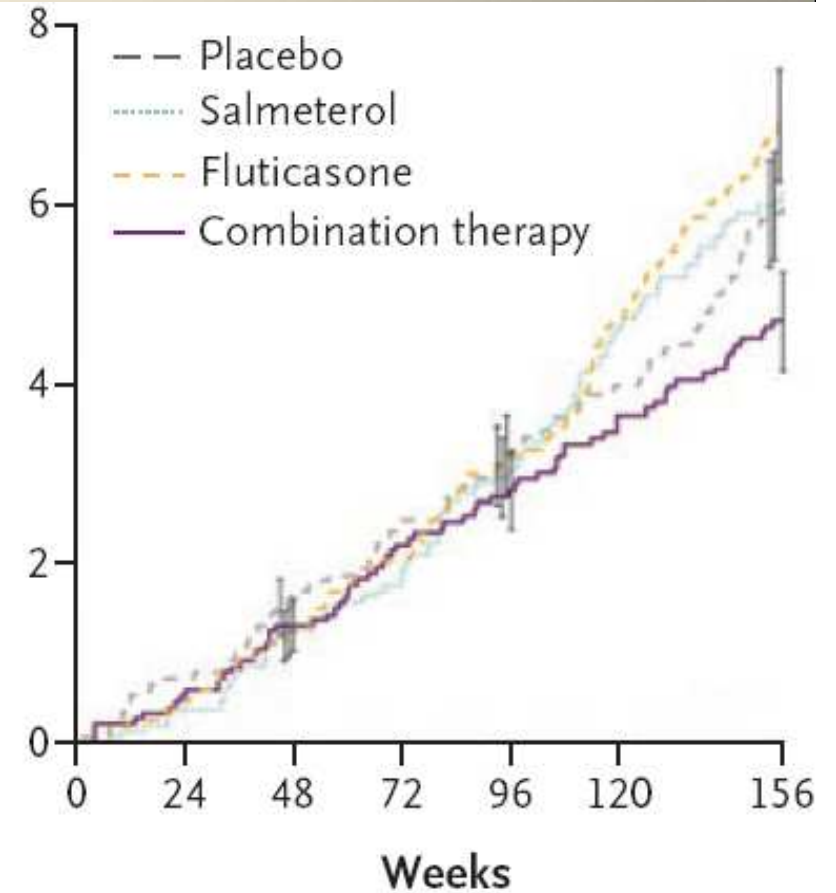
- Towards a Revolution in COPD Health (TORCH) trial
  - 4 arm, 3 year RCT of COPD treatment
    - Placebo, ICS, LABA, ICS + LABA
    - 444 centers in 43 countries
    - Patients with moderate to severe COPD
    - 6184 patients randomized

# TORCH Results

Death from Any Cause



COPD-Related Death



From Calverly et al. *N Engl J Med* 2007

# CHEST Meta-Analysis

## All Cause Mortality

Group/Subgroup Comparisons	RR (95% CI)
LABA vs placebo	
Salmeterol vs placebo	0.89 (0.75 to 1.05)
Formoterol vs placebo	1.14 (0.49 to 2.66)
LABA vs placebo (both study arms exposed to ICS)	1.23 (0.56 to 2.57)
LABA vs placebo (both study arms not exposed to ICS)	0.95 (0.80 to 1.14)

Comparison/Outcome	Studies, No.	Patients, No.
LABA vs placebo		
Severe COPD exacerbations	14	6,453
All-cause mortality	13	8,400
Respiratory deaths	12	8,049

Only 6 studies of 12 mos duration or longer (only TORCH longer)

From Rodrigo et al. CHEST 2008

# CHEST Meta-Analysis

## Respiratory Mortality

Group/Subgroup Comparisons	RR (95% CI)
LABA vs placebo	
Salmeterol vs placebo	1.09 (0.71 to 1.66)
Formoterol vs placebo	0.74 (0.04 to 14.0)
LABA vs placebo (both study arms exposed to ICS)	0.89 (0.06 to 14.2)
LABA vs placebo (both arms not exposed to ICS)	1.10 (0.35 to 3.39)
LABA plus ICS vs LABA	0.35 (0.14 to 0.93);

Comparison/Outcome	Studies, No.	Patients, No.
LABA vs placebo		
Severe COPD exacerbations	14	6,453
All-cause mortality	13	8,400
Respiratory deaths	12	8,049

From Rodrigo et al. CHEST 2008

# LABA + ICS v LABA alone in COPD

Outcomes	References	LABAs + ICS, No./Total No. (%)	LABAs, No/ Total No. (%)	Measure (95% CI)
COPD exacerbations (requiring hospitalization or withdrawal)	15–17,19–30	757/6,685 (11.3)	704/5,612 (12.5)	RR = 0.91 (0.82–1.01)
COPD exacerbations requiring systemic corticosteroids	15–26,29	794/4,532 (17.5)	1,015/5,058 (20.1)	RR = 0.84 (0.74–0.96); p = 0.008/NNTB = 31 (20–93)
All-cause mortality	11, 18–30	240/5,292 (4.5)	261/4,721 (5.5)	RR = 0.90 (0.76–1.06)
Respiratory deaths	16,17,20,21, 23–26,28–30	94/5,292 (1.8)	114/4,721 (2.4)	RR = 0.80 (0.61–1.05)
Cardiovascular mortality	16,21,23–26, 28–30	72/5,856 (1.6)	63/5,299 (1.4)	RR = 1.22 (0.88–1.71)

From Rodrigo et al. CHEST 2009

# Evidence from Non-Randomized Studies

- COPD patients in RCTs often very different from 'typical' COPD population
- Evidence from observational studies may offer insight to risks in non-RCT population
- No increased risk for LABAs in patients with COPD

# LABAs in COPD in the VA

Regimen	Adjusted Odds Ratio (95% CI)			
	All-Cause Mortality*	Respiratory Death†	Cardiovascular Death‡	Respiratory or Cardiovascular Death§
<b>Medication</b>				
None or short-acting $\beta$ -agonists only	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Inhaled corticosteroids	0.80 (0.78–0.83)	0.88 (0.79–1.00)	0.80 (0.72–0.88)	0.86 (0.80–0.93)
Ipratropium	1.11 (1.08–1.15)	1.07 (0.96–1.20)	1.34 (1.22–1.47)	1.27 (1.19–1.36)
Long-acting $\beta$ -agonists	0.92 (0.88–0.96)	1.12 (0.97–1.30)	0.97 (0.84–1.11)	0.98 (0.89–1.09)
Theophylline	1.05 (0.99–1.10)	1.71 (1.46–2.00)	1.16 (0.99–1.37)	1.40 (1.25–1.57)

# Implications in COPD

- No increased risk associated with LABAs in COPD
- Not necessarily the case for all COPD treatments
  - Anticholinergic risks
- Evidence of benefit in reducing rate of exacerbations in combination with ICS
- Risks and response by FDA have solely focused on asthma

