

# Clinical Features and Therapeutic Intervention in ACOS

Joo Hun Park, M.D.

Dept. of Pulmonary and Critical Care Medicine  
Ajou University School of Medicine



# Key Questions

- Does ACOS exist ?
- Clinical course of ACOS is different from COPD therapy ?
- Therapy for ACOS is different from COPD therapy ?

# Outline

---

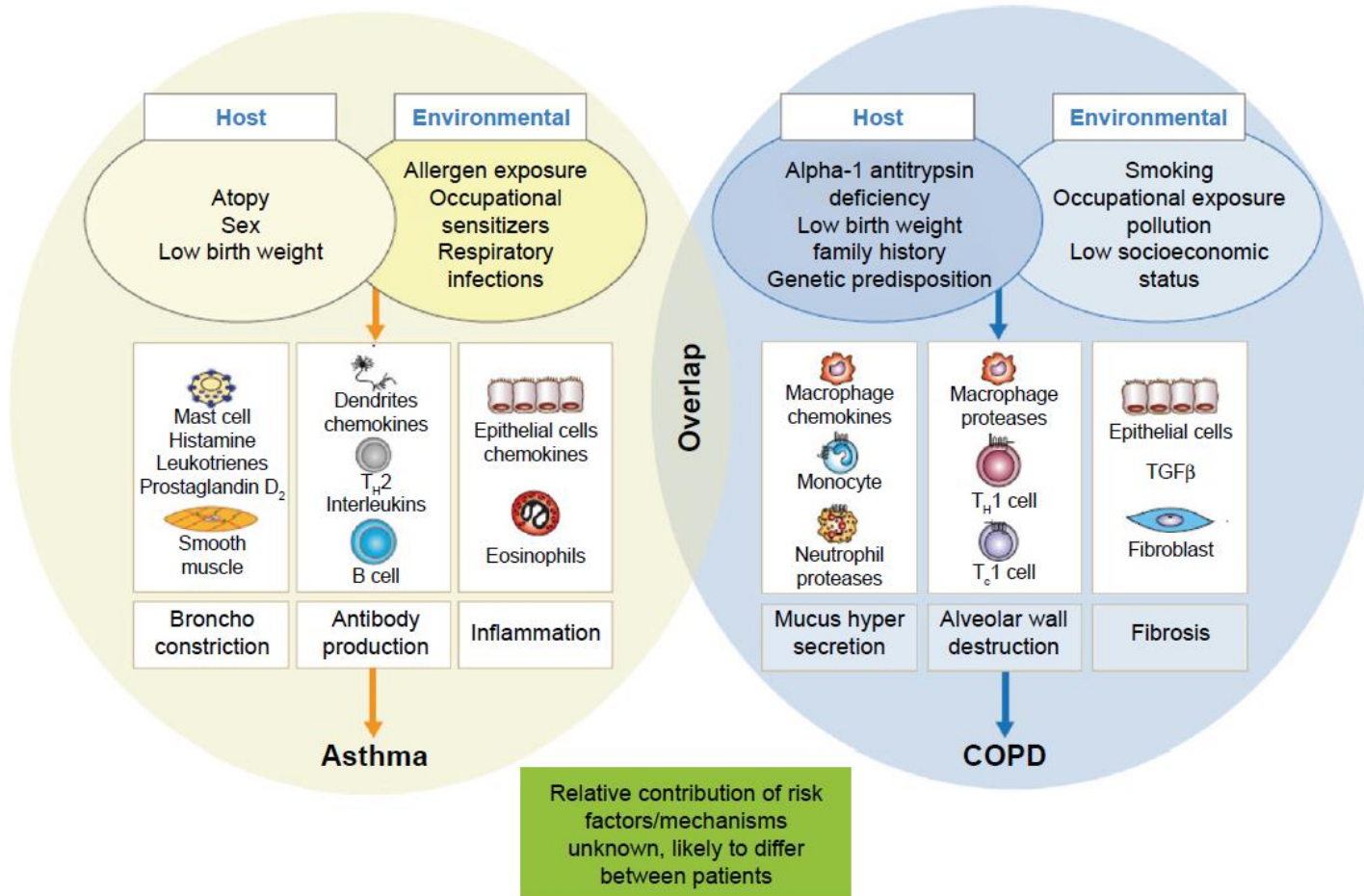
- Overview
- Early studies
  - Asthma as a risk factor for COPD
- Cohorts for ACOS
  - ACOS in general population
  - ACOS in COPD
- Treatment
- Conclusion

# Overview

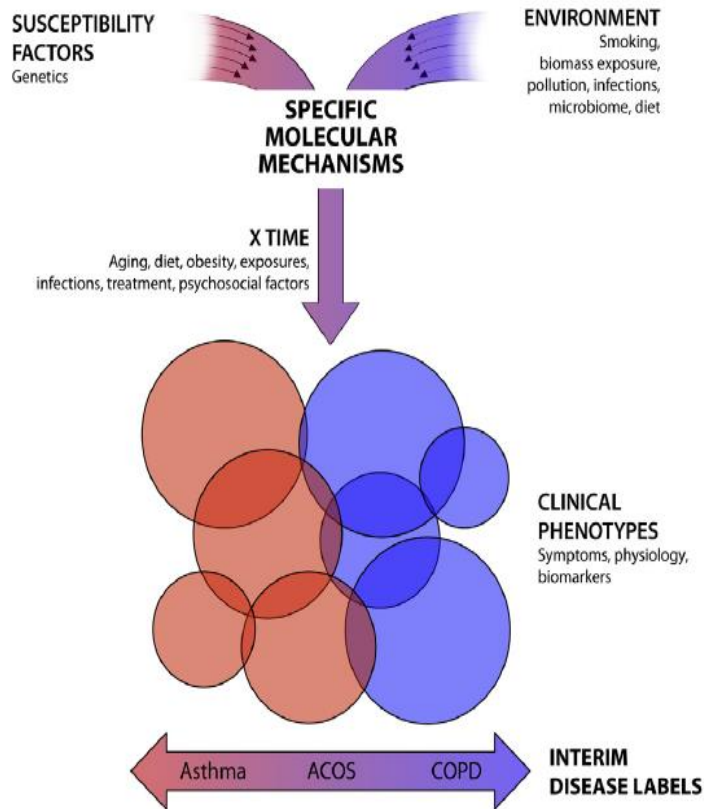
---



# Pathophysiology of ACOS, asthma, and overlap



# Dutch vs. British



VS.

No common genetic component in asthma and COPD

Smolonska J et al. Eur Respir J. 2014 Oct;44(4):860-72

Asthma COPD overlap (ACO) rather than ACOS

Barnes PJ Chest. 2016 Jan;149(1):7-8

Wurst et al. Resp Med 2010 ; 110: 1-11.

# Overview

## Why is ACOS important?

---

- Overlapping asthma and COPD have been excluded from clinical trials.
  - 30% of asthmatics : smokers
  - Smoking asthmatics : relative resistance to ICS
- Clinician are confused as to differentiating asthma from COPD
- Overlap syndrome may identify mechanistic pathways to the development of COPD.

# Definition of ACOS

---

- Major
  1. Post-BD **FEV<sub>1</sub>/FVC** <**70%** or LLL
  2. **Smoking** ≥ **10 PY**  
or air pollution exposure
  3. **History of asthma**  
or **BDR** of >400 in FEV<sub>1</sub>
- Minor
  1. History of atopy or allergic rhinitis
  2. BDR of FEV<sub>1</sub> ≥200 and 12% from baseline on 2 or more visits
  3. Peripheral **eosinophilia** ≥300 cells / μL

# Role of Asthma in Earlier Studies without the Concept of ACOS



# A 15-year follow-up study in adults with asthma.

---

- Copenhagen cohort
  - 17,506 subjects (8136 men and 9370 women),
  - 1095 asthmatics
  - Over a 15-year period

Lange P et al. N Engl J Med 1998 ;339(17):1194-200

# A 15-year follow-up study in adults with asthma.

---

- Decline in  $FEV_1$ 
  - Asthma : 38 ml per year,
  - Those without asthma : 22 ml per year
- Asthmatics : greater declines in  $FEV_1$  over time

Lange P et al. N Engl J Med 1998 ;339(17):1194-200

# Asthma as a Risk Factor for COPD in a Longitudinal Study

---

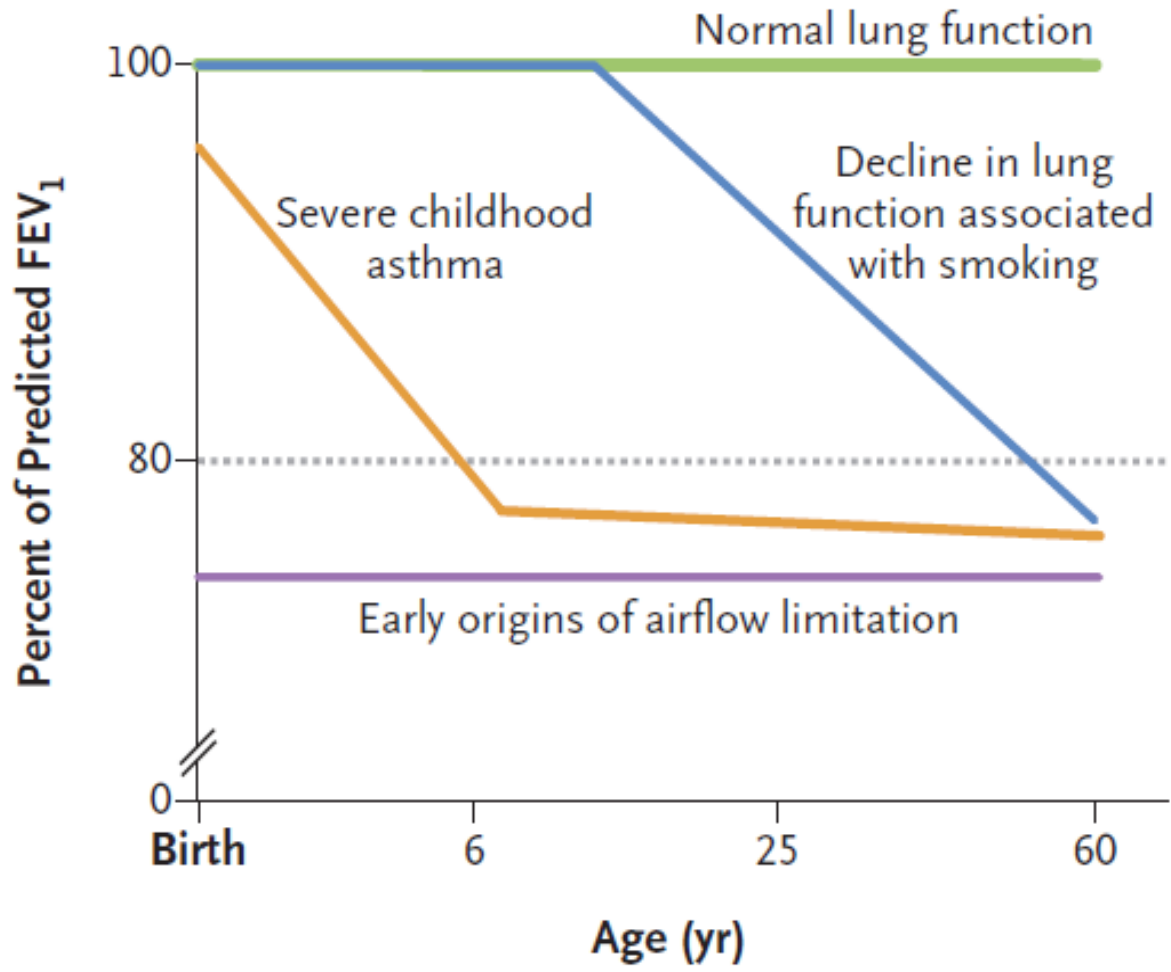
- A cohort of 3099 patients in Arizona
- Evaluation of COPD and physician-diagnosed asthma
- Prospective observational study over 20 years from 1970

Silva GE et al. Chest 2004; 126; 59-65

# Asthma as a Risk Factor for COPD in a Longitudinal Study

---

- Increased risk of each disease in asthmatics after adjusting for smoking and other factors
  - Chronic bronchitis : 10 times
  - Emphysema : 17 times
  - COPD : 12.5 times



Martinez F. N Engl J Med 2016;375:871-878

# Role of Airway Hyperresponsiveness (AHR)



# Risk Factors for COPD in a European Cohort of Young Adults

---

- European Community Respiratory Health Survey (ECRIS) in 10 European countries
  - First in 1991-1993
  - Second in 1999-2002
- In 4636 subjects without asthma (20-44 yr old)
- COPD definition
  - Post BD  $FEV_1/FVC < 70\%$ , LLN

de Marco R et al. AJRCCM 2011;183(7):891-7.

# Risk Factors for COPD in a European Cohort of Young Adults

	IRR (95% CI)		
	GOLD	LLN (Quanjer)	LLN (LuftiBus)
Age ( $\geq 35$ vs. $< 35$ yr)	2.24 (1.48, 3.39) <sup>†</sup>	1.25 (0.65, 2.39)	0.92 (0.53, 1.60)
BMI (vs. normal)			
Underweight	3.55 (1.59, 7.93)*	2.35 (0.72, 7.64)	1.14 (0.31, 4.22)
Overweight/obese	0.62 (0.42, 0.91)*	0.78 (0.30, 2.00)	1.03 (0.55, 1.94)
Smoking habits (vs. nonsmoker)			
Quitter/sustained quitter	2.08 (1.34, 3.21)*	1.69 (0.92, 3.10)	1.30 (0.81, 2.09)
Persistent smoker/new smoker/restarter	2.61 (1.62, 4.20) <sup>†</sup>	2.42 (1.35, 4.33)*	2.43 (1.25, 4.73)*
AHR	3.97 (2.07, 7.65) <sup>†</sup>	3.89 (1.78, 8.53) <sup>†</sup>	3.39 (1.72, 6.70) <sup>†</sup>
IgE sensitization	0.69 (0.44, 1.10)	0.86 (0.46, 1.60)	1.11 (0.68, 1.79)
Respiratory infections in childhood	1.88 (1.02, 3.46)*	1.97 (0.86, 4.54)	2.23 (1.64, 3.04) <sup>†</sup>
Family history of asthma	1.95 (1.25, 3.04)*	2.24 (1.12, 4.48)*	2.09 (1.26, 3.47)*

IRR = incidence rare ratio

LLN = lower limit of normal

de Marco R et al. AJRCCM 2011 Apr 1;183(7):891-7.

# Risk Factors for COPD in a European Cohort of Young Adults

---

- Cases of COPD
  - Smoking : 29-39 %
  - AHR : 15 -17 %,
  - Respiratory infection : 8%

de Marco R et al. AJRCCM 2011; 183(7): 891-7.

# Risk Factors for COPD in a European Cohort of Young Adults

---

- COPD may start early in life.
- Other important determinants of COPD
  - Airway hyperresponsiveness
  - Family history of asthma
  - Respiratory infections in childhood

# Lung Function Decline in COPD (ECLIPSE STUDY)

---

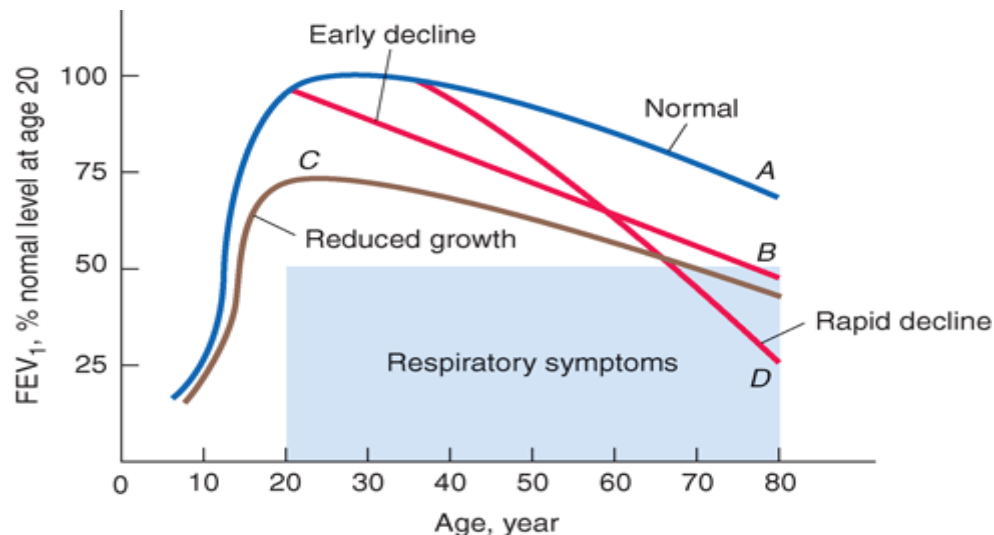
Increased rates of decline FEV1

- Current smokers
- Acute Exacerbation
- Bronchodilator reversibility
- Emphysema

# Lung-Function Trajectories Leading to COPD

- Low FEV<sub>1</sub> in early adulthood is important in the genesis of COPD
- Accelerated decline in FEV1 is not an obligate feature of COPD.

Lange P et al. N Engl J Med 2015;373:111-22.



# AHR in COPD

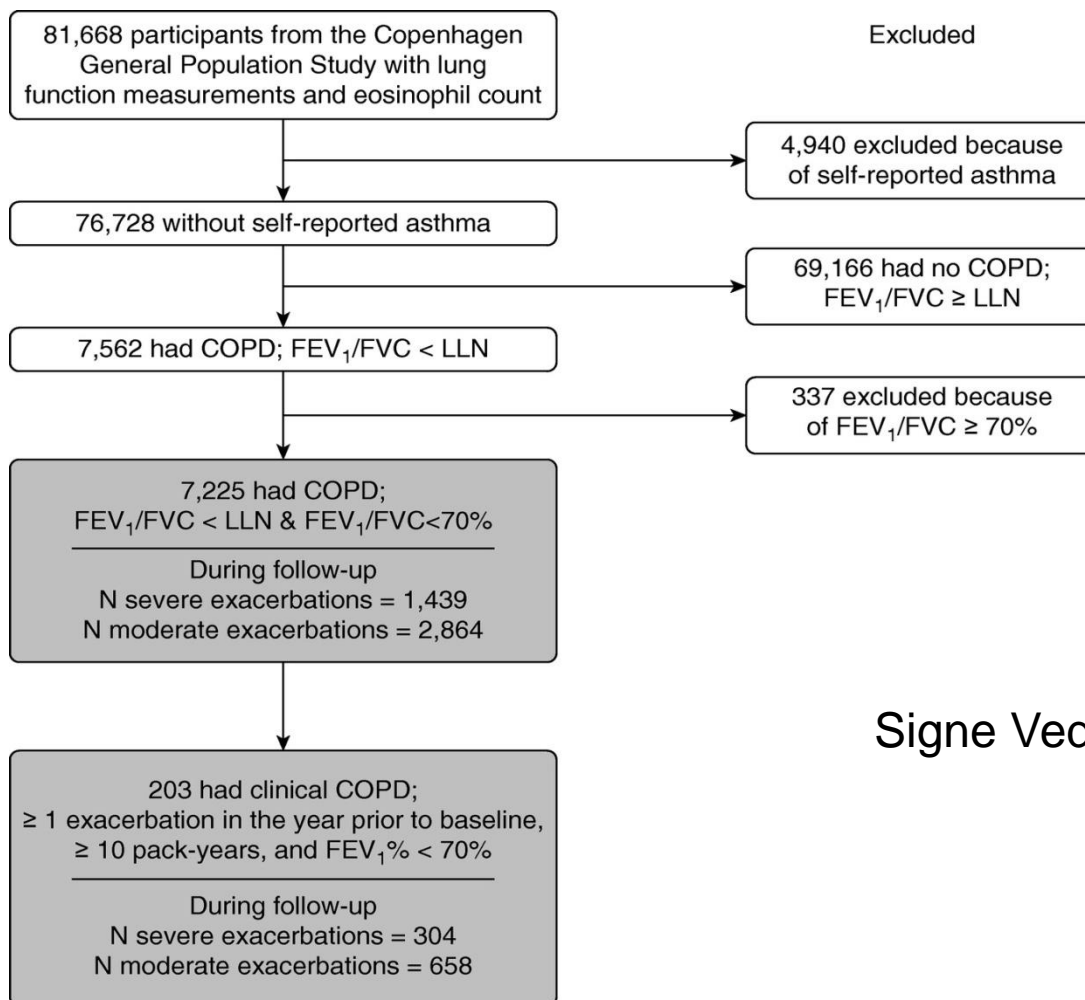
---

- Airway hyperresponsiveness
  - Independent phenotype
  - Greater declines in FEV<sub>1</sub>
  - COPD risk ↑

# Role of Serum Eosinophilia

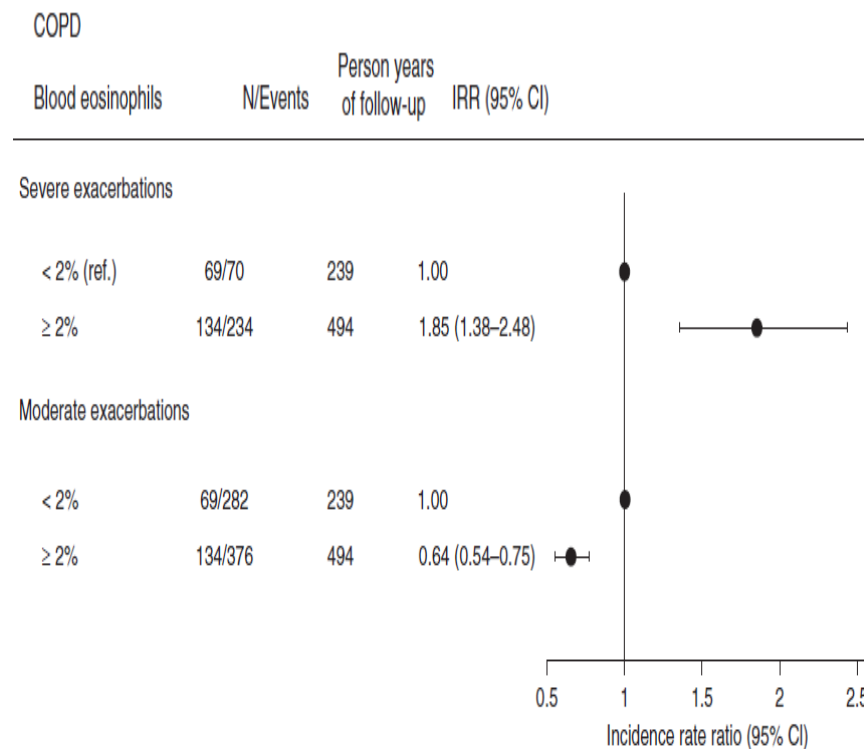
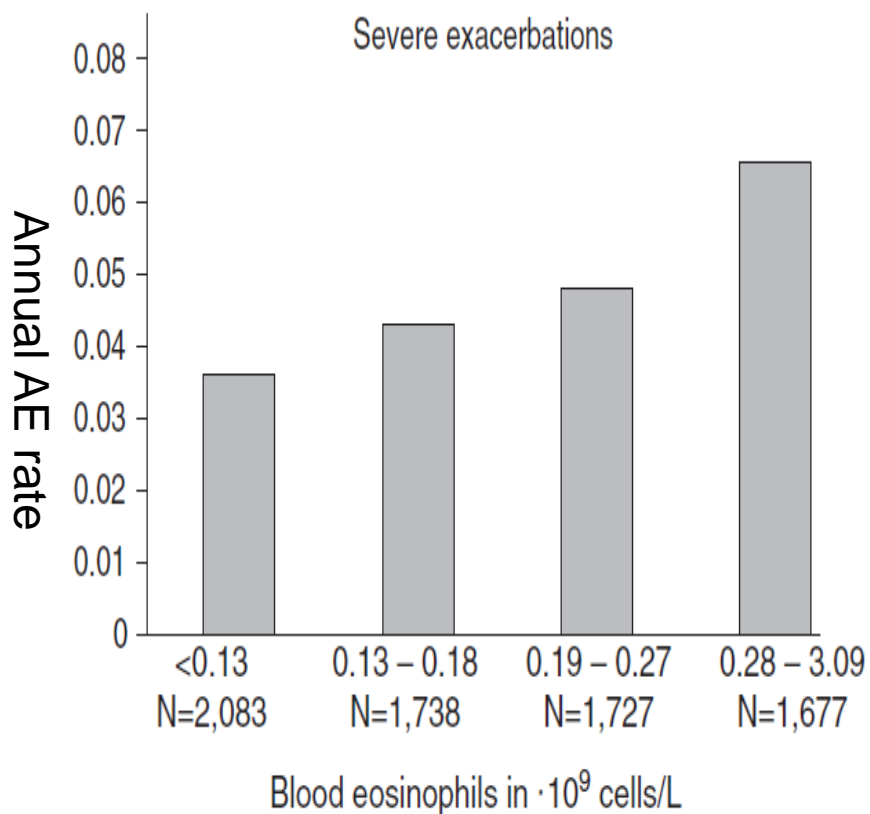


# Blood Eosinophils and Exacerbations in COPD Copenhagen General Population Study



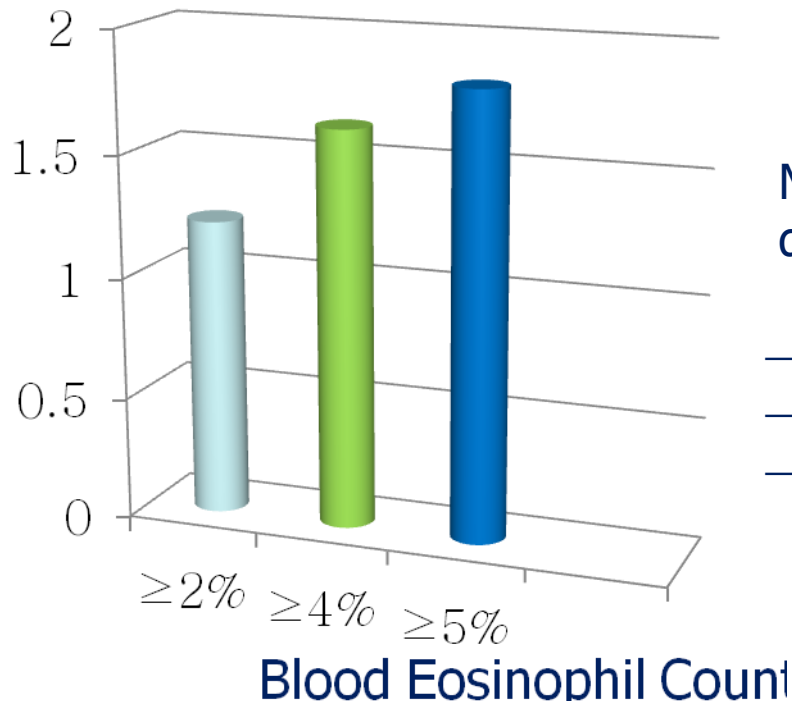
Signe Vedel-Krogh et al. *AJRCCM*  
2016 ;193(9):965-74

# Blood Eosinophils and Exacerbations in COPD Copenhagen General Population Study



# Blood Eosinophil and Exacerbations in Severe COPD after Withdrawal of ICS

A post-hoc analysis of the WISDOM trial. :  
In the 2296 patients receiving treatment after ICS withdrawal,



Moderate or severe exacerbation rate depending on eosinophil counts

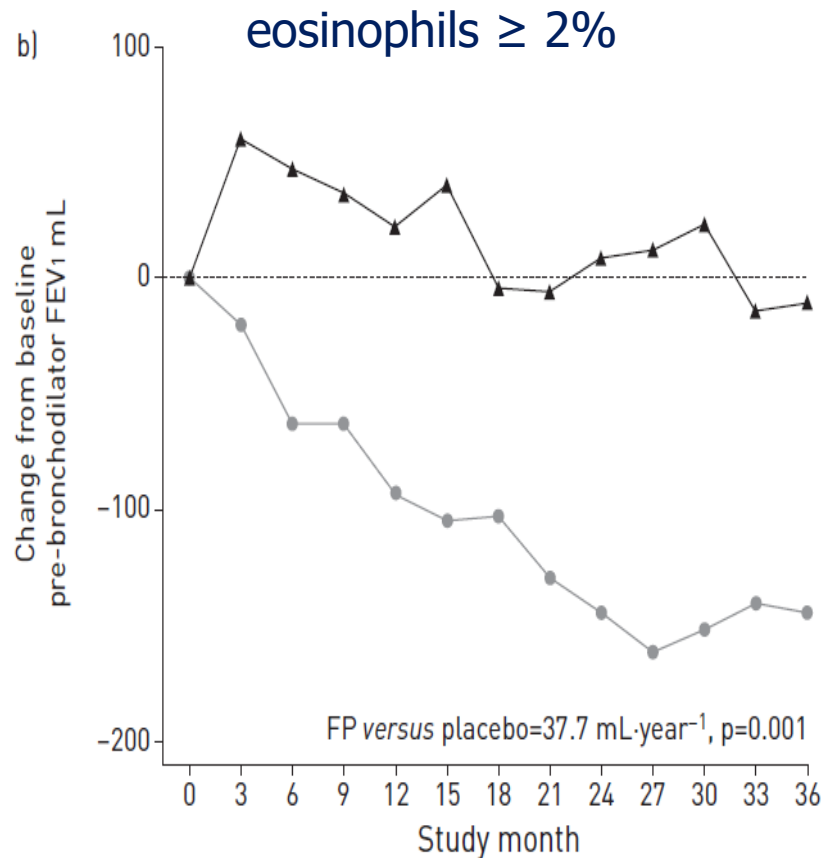
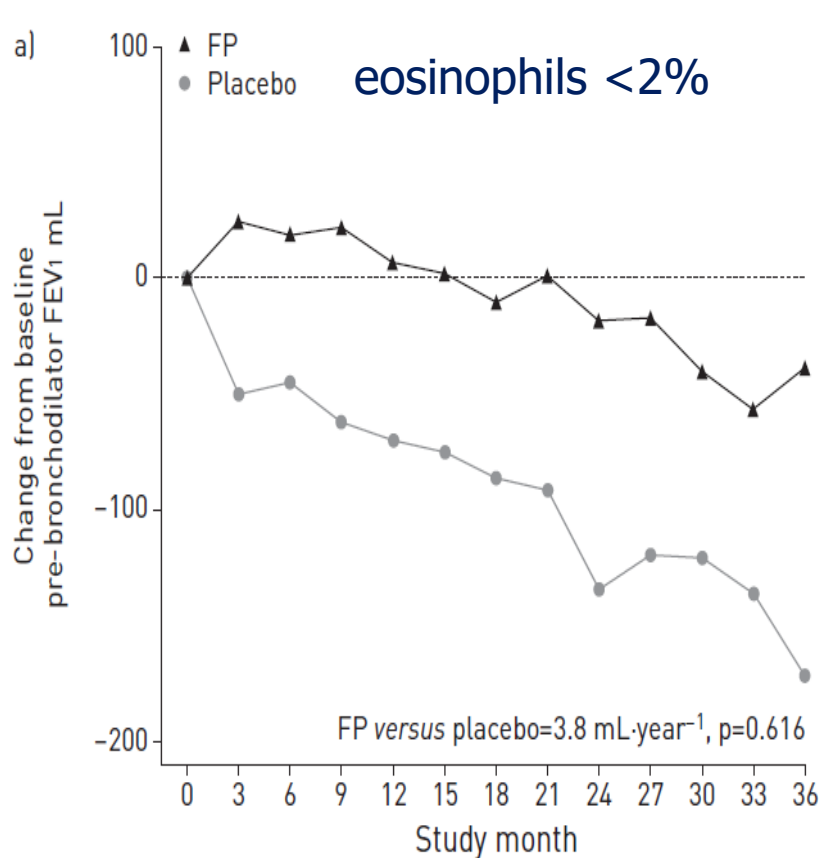
- 2% or greater = RR 1.22 [95% CI 1.02-1.48]
- 4% or greater = 1.63 [1.19-2.24]
- 5% or greater = 1.82 [1.20-2.76]

# Blood Eosinophil as a Marker of Response to ICS in COPD (ISOLDE study)

---

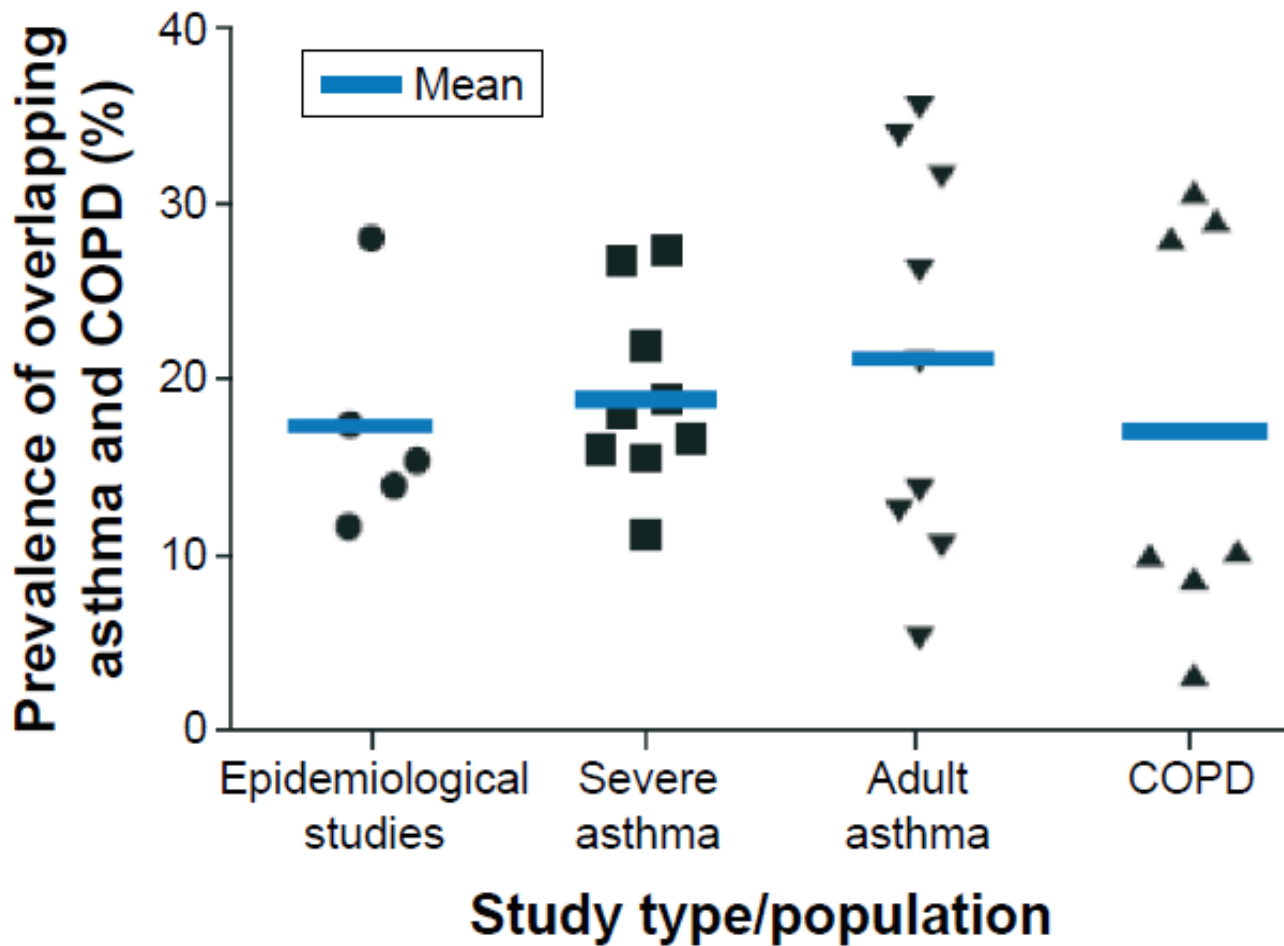
- Randomised 751 patients to fluticasone 500 µg twice daily or placebo for 3 years,
- No difference in FEV1 rate of decline ( $p = 0.16$ )
- A significant reduction in median exacerbation rate with fluticasone versus placebo ( $p = 0.026$ ).

# Blood Eosinophil as a Marker of Response to ICS in COPD (ISOLDE study)



# Clinical Features in Cohort Studies of ACOS





# Variability of ACOS Prevalence

---

- COPD and asthma diagnostic criteria
- Disease ascertainment methods
  - Spirometry-based
  - Clinical or symptom-based diagnoses
  - Claims data
- Population characteristics including age, gender and smoking

# Features of ACOS in General Population Cohorts



# PLATINO study

---

- PLATINO study
  - Multicenter population-based survey
  - Five Latin American cities
  
- Questionnaires
  - Hospitalizations
  - Exacerbations
  - General health status

# PLATINO study

---

- COPD :
  - Post-BD FEV1/FVC ratio  $< 0.70$
- Asthma :
  - Presence of wheezing in the last year
  - Post-BD increase in FEV1 or FVC  $\geq 12\%$  and 200 mL
- Overlap COPD-asthma :
  - Combination of the two.

# PLATINO study

---

- COPD-asthma overlap compared with COPD.
  - Exacerbations ↑ (PR, 2.11; 95%CI, 1.08-4.12)
  - Hospitalizations ↑ (PR, 4.11; 95%CI, 1.45-11.67)
  - Gen.health status ↓ (PR, 1.47; 95%CI, 1.18-1.85)

PR : prevalence ratio

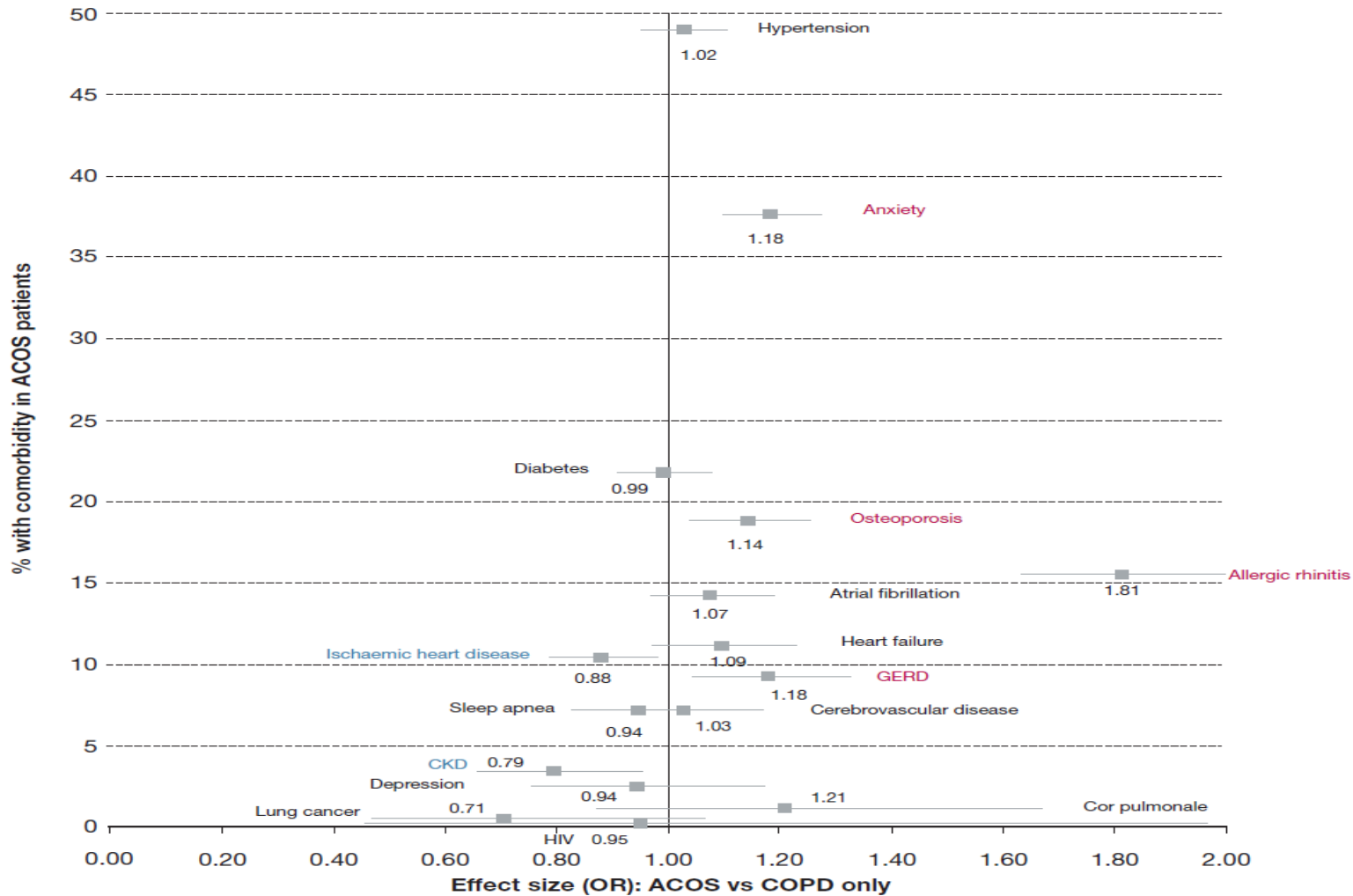
# Retrospective MAJORICA cohort (Majorca Real-Life Investigation in COPD and Asthma)

- Combined data from primary care, hospitalization, and pharmacy data in Spain ( $\pm$  1.1 million subjects),
- Physician-confirmed diagnosis of both asthma and COPD

**TABLE 1 ]** Demographic Characteristics of Patients With Asthma-COPD Overlap Syndrome vs Patients With COPD Only

Patient Characteristics	Main Analysis		
	ACOS (N = 5,093)	COPD Only (N = 22,778)	P Value
Male, No. (%)	2,373 (46.6)	15,766 (69.2)	< .001
Age, mean (SD), y	64.0 (15.1)	65.8 (13.3)	< .001
Never smoker, No. (%)	2,108 (41.4)	5,036 (22.1)	< .001
Former smoker, No. (%)	1,155 (22.7)	6,227 (27.3)	
Current smoker, No. (%)	1,305 (25.6)	8,236 (36.2)	
Unknown, No. (%)	525 (10.3)	3,279 (14.4)	

# Comorbidity, Pattern, and Impact of Asthma-COPD Overlap Syndrome in Real Life

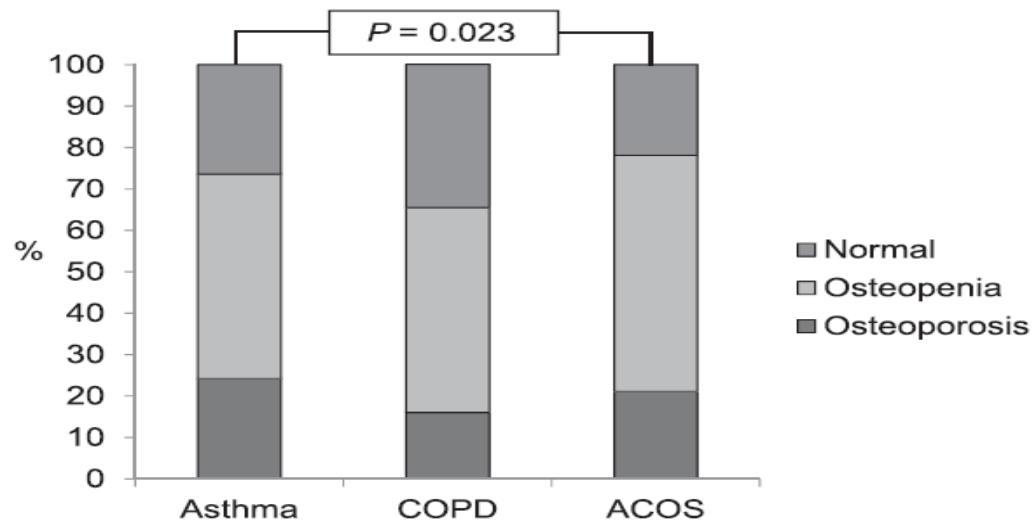


# Comorbidity, Pattern, and Impact of Asthma-COPD Overlap Syndrome in Real Life

---

- ACOS
  - Younger, non-smoker, female
- More frequent in ACOS
  - Allergic rhinitis, anxiety, GERD, osteoporosis
- Less frequent in ACOS
  - Chronic kidney disease, ischemic heart disease

# A Comparative Study of Bone Mineral Density among Patients with Obstructive Lung Diseases in Korea



- ACOS had a higher risk of developing osteopenia and low BMD than those with COPD.

# ACOS in COPD Cohort

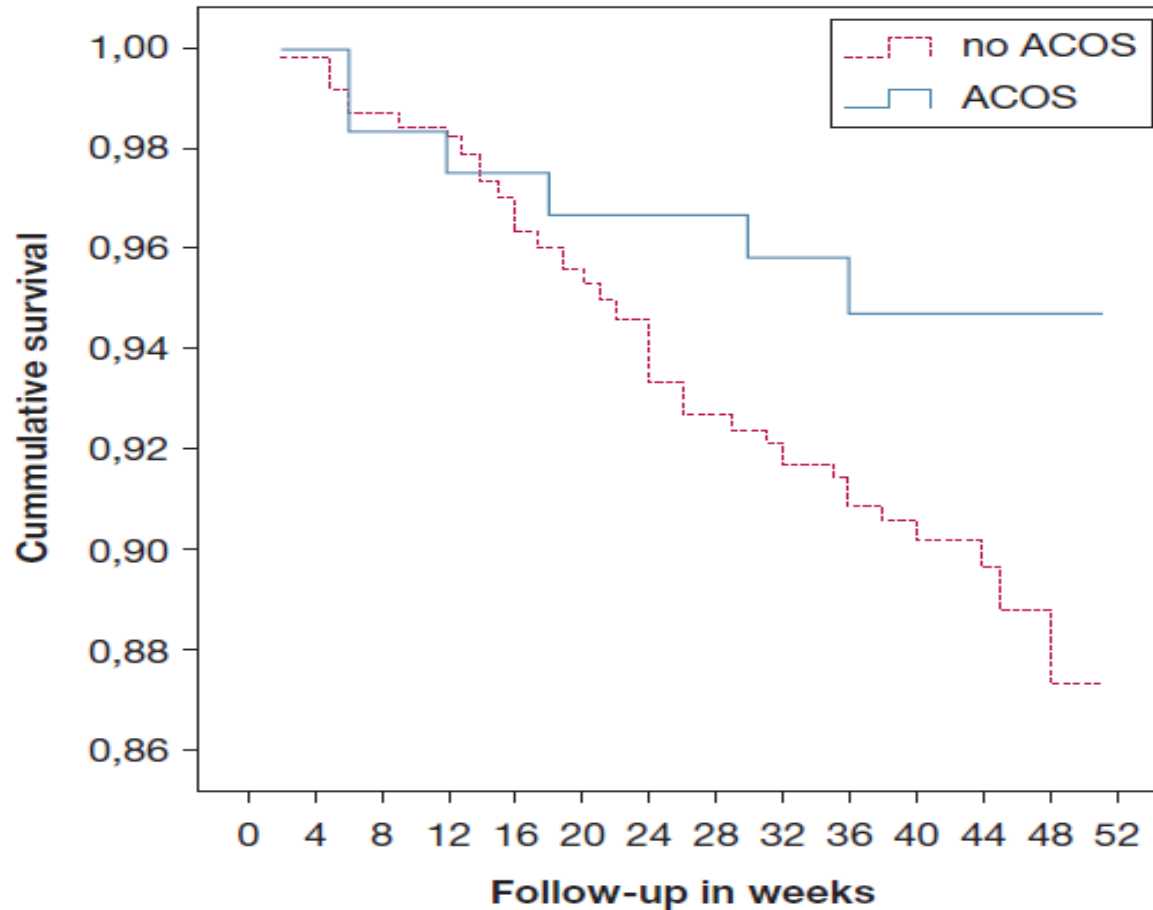


# Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort.

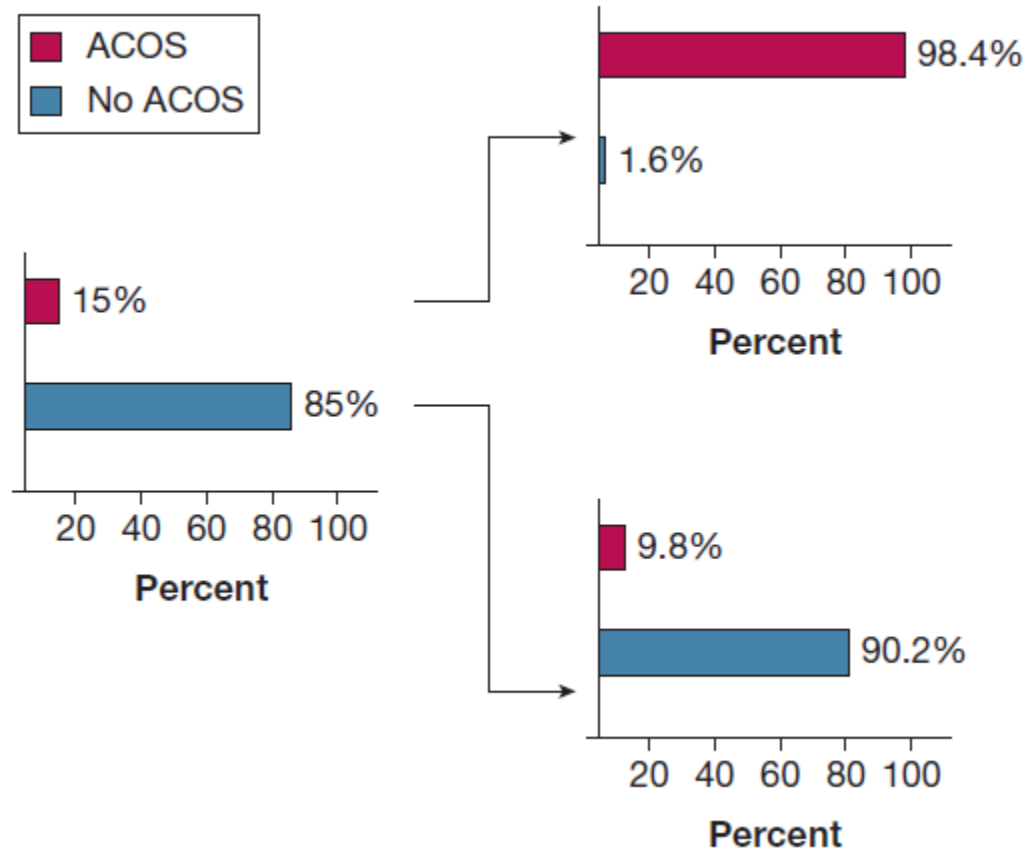
---

- COPD History Assessment in Spain (CHAIN) cohort
  - Multicenter study
  - 36 Spanish prospective cohorts
  - University hospitals

# Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort.



# One Year Follow up for ACOS



# Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort.

---

- ACOS
  - 15% of COPD cohort
  - Better 1-year prognosis than clinically similar COPD without ACOS

# Clinical Features of ACOS between COPD and Asthma

---

- ACOS vs COPD

- Age (61.3 vs 64.7 years,  $p < 0.01$ )

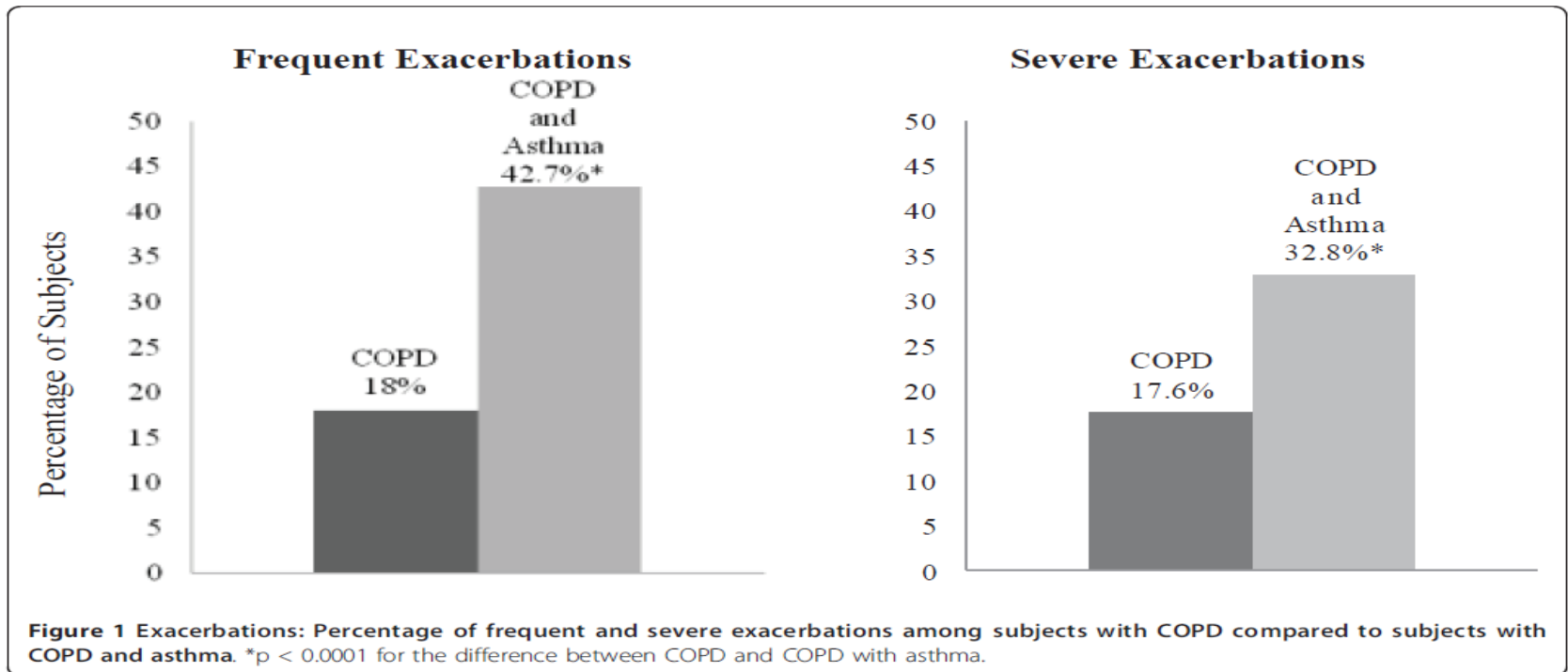
- Worse quality of life (SGRQ ; 44.0 vs. 38.6,  $p < 0.01$ )

- Hay fever (57.0 vs. 32.8 %,  $p < 0.01$ )

- Smoking pack years (43.7 vs. 55.1,  $p < 0.01$ )

# Clinical Features of Overlap between COPD and Asthma

- Data from the COPD Gene Study.
- 119 (13%) physician-diagnosed asthma out of 915 patients with COPD



# Treatment



# Treatment

---

- No RCT reported on ACOS
- ICS : Limited evidence
  - ICS monotherapy is not indicated in COPD
- LABA : Limited evidence
  - LABA monotherapy is not indicated in Asthma
- GINA/GOLD
  - Treatment by ICS/LABA for asthma if asthma or ACOS is suggested.

Louie s et al Expert Rev Clin Pharmacol 2013; 6: 197-219

Kostikas K et al Int J COPD 2016; 11: 1297 -1306

# Other Options in Treatment

---

- LTRA in mild Asthmatic smokers
  - Attenuated response to ICS
  - Improvement of some outcomes in smokers treated with montelukast

Lazarus et al AJRCCM. 2007 Apr 15;175(8):783-90

- Low-dose theophylline plus ICS
  - Improvements in lung function and symptoms in smokers with asthma.

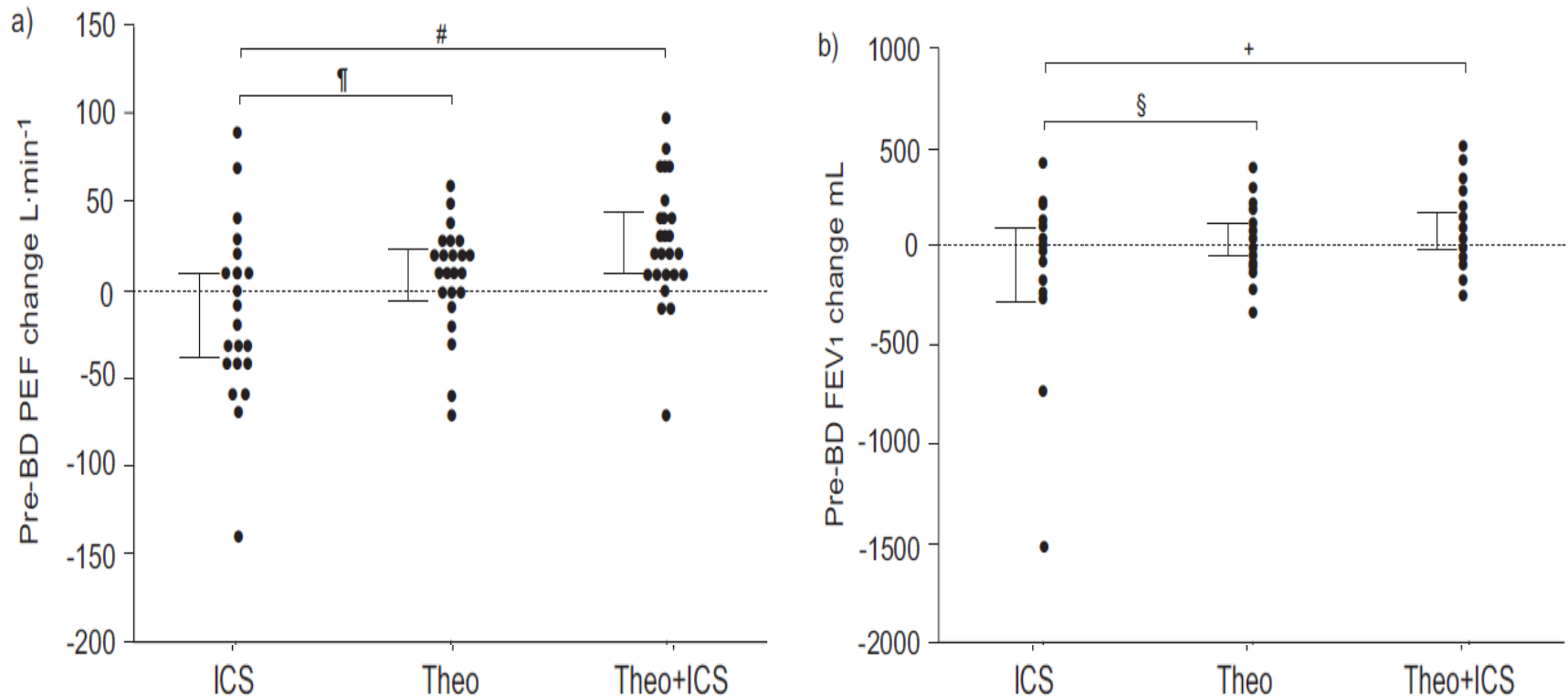
Spears M et al ERJ 2009 May;33(5):1010-7.

# Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma

---

- In a double-blind of 68 asthmatic smokers
- Randomised for 4 weeks
  - Inhaled beclometasone (200  $\mu$ g/day)
  - Theophylline (400 mg/day)
  - Both treatments combined

# Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma



# Smoking affects response to ICS or leukotriene receptor antagonists in asthma

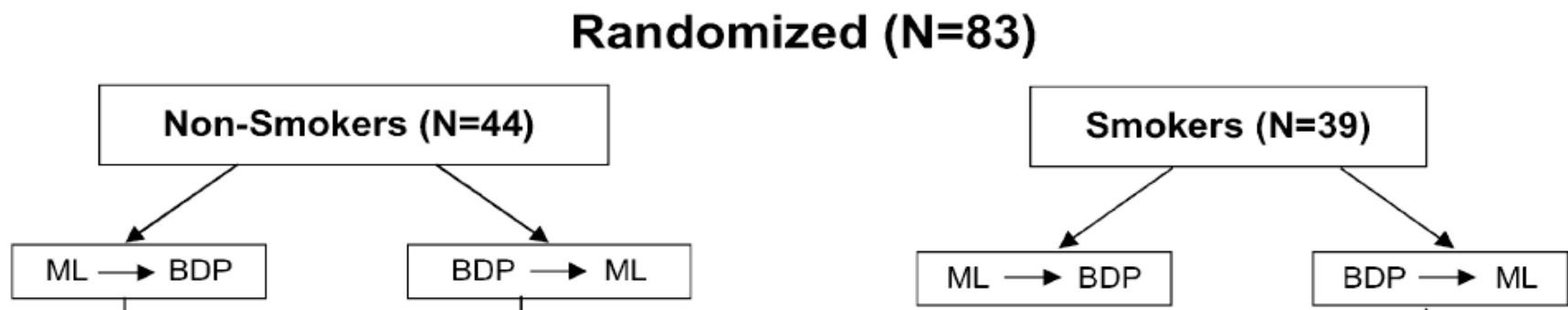
---

- Placebo-controlled, double-blind, crossover trial, 44 nonsmokers and 39 light smokers with mild asthma

# Smoking affects response to ICS or leukotriene receptor antagonists in asthma

---

- Placebo-controlled, double-blind, crossover trial with twice daily inhaled beclomethasone (BDP) and once daily oral montelukast (ML)
  - 44 nonsmokers with mild asthma
  - 39 light smokers with mild asthma



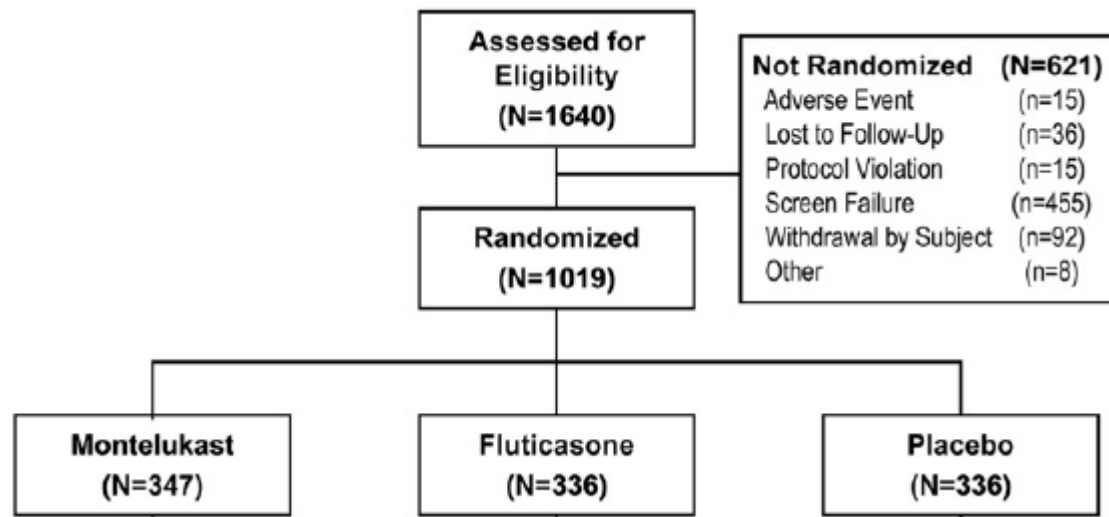
# Smoking affects response to ICS or leukotriene receptor antagonists in asthma

---

- Beclomethasone
  - Reduced sputum eosinophils in both smokers and nonsmokers
  - Increased FEV<sub>1</sub> (170 ml,  $p = 0.0003$ ) only in nonsmokers
- Montelukast
  - Increased morning peak expiratory flow in smokers (12.6 L/min,  $p = 0.002$ ), but not in nonsmokers

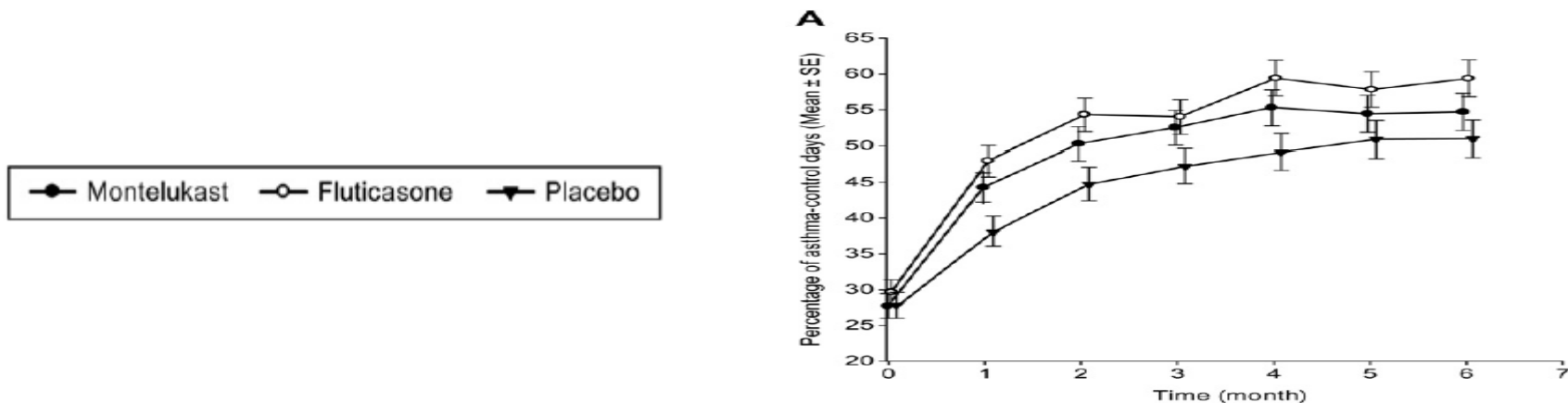
# Effect of montelukast for treatment of asthma in cigarette smokers.

- Patients with smoking asthma
  - Age 18-55 years, FEV<sub>1</sub> of 60% to 90%
  - 6-month, double-blind treatment

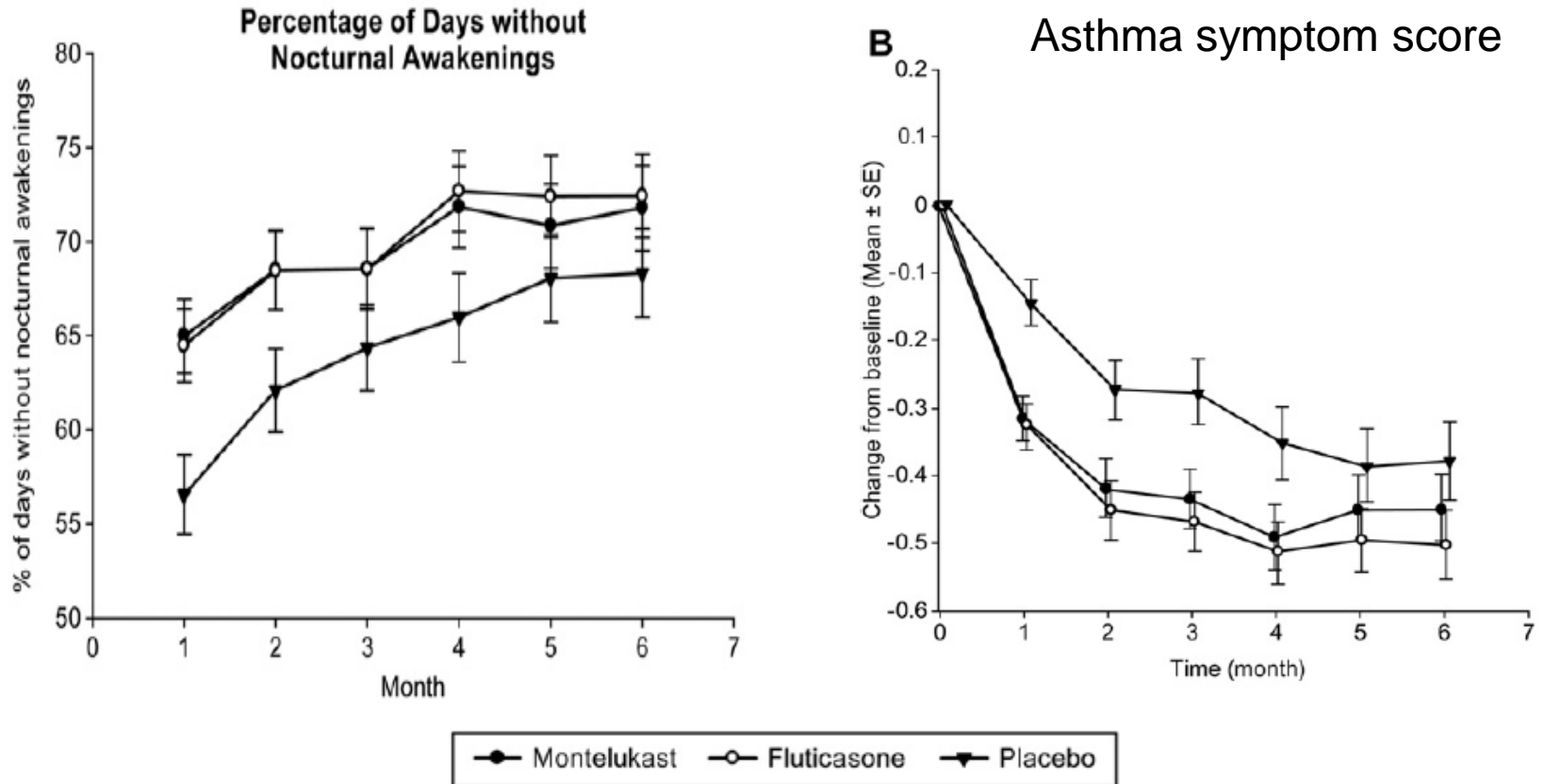


# Effect of montelukast for treatment of asthma in cigarette smokers.

- Asthma control days
  - No difference between LTRA and ICS ( $p = 0.14$ ).
  - 45% (montelukast,  $P < .05$  vs placebo)
  - 49% (fluticasone,  $P < .001$  vs placebo)
  - 39% (placebo);



# Effect of Montelukast for Asthma in Smokers.



# Effect of montelukast for treatment of asthma in cigarette smokers.

---

- Smoking  $\leq 11$  pack years  
→ More benefit with fluticasone.
- Smoking  $> 11$  pack years  
→ More benefit with montelukast.

# Conclusion



# Conclusion

---

- ACOS
  - More frequent AE
  - Worse quality of life
  - Worse lung function decline
  - Survival : controversial
- Clinical features of ACOS vary based on diagnostic criteria and population characteristics.

# Conclusion

---

- Co-morbidities of ACOS  
→ Allergic rhinitis, Anxiety, GERD, Osteoporosis
- Treatment by ICS/LABA for asthma if asthma or ACOS is suggested.
- Leukotriene antagonist is a good therapeutic option for smoking asthma.