Asthma-COPD Overlap

Craig P. Hersh, MD, MPH
Brigham and Women's Hospital
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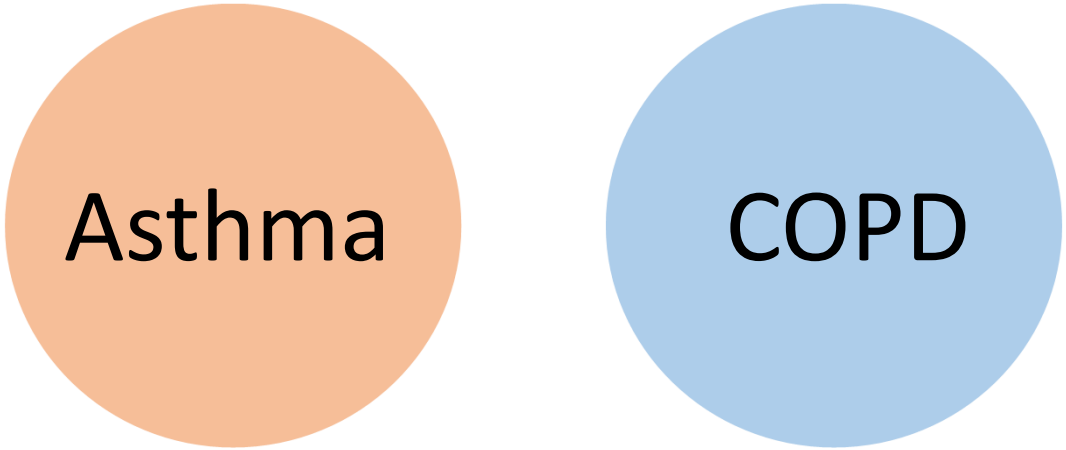
Disclosures

- Personal Fees
  - Takeda
  - AstraZeneca
  - Sanofi
- Grant support
  - Bayer
  - Boehringer-Ingelheim
  - Vertex

Asthma-COPD overlap: outline

- Asthma vs COPD: one disease or two?
  - Dutch Hypothesis
- Epidemiology and significance
- Definition(s)
- COPDGene study
- Treatment
- Treatable traits in airway disease
  - Eosinophilic COPD
- Precision medicine

Asthma vs. COPD: Two diseases?

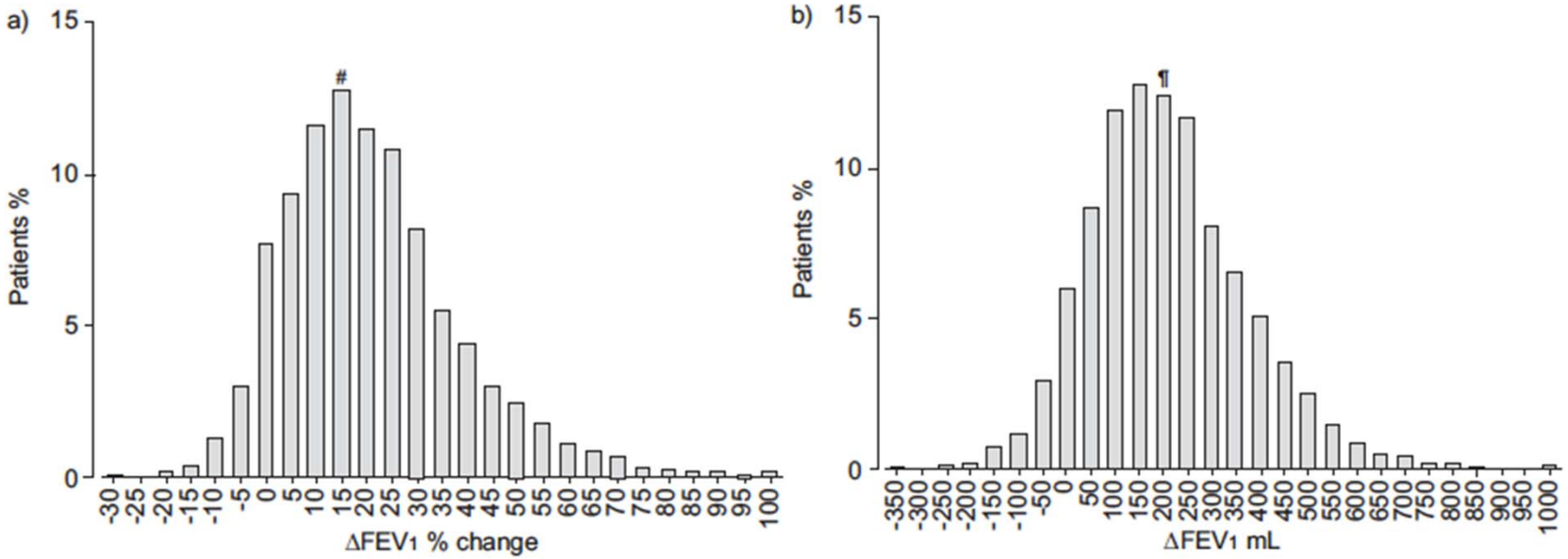


Asthma vs. COPD: differences

	Asthma	COPD
Age of onset	Childhood	Mid-life
Risk factor	Allergy Family history	Tobacco smoke Other exposures
Inflammation	Eosinophils Mast cells CD4+ lymphocytes	Neutrophils Macrophages CD8+ lymphocytes
Symptoms	Vary day to day Worse at night/early am	Slowly progressive
Reversible airflow obstruction	Yes	No

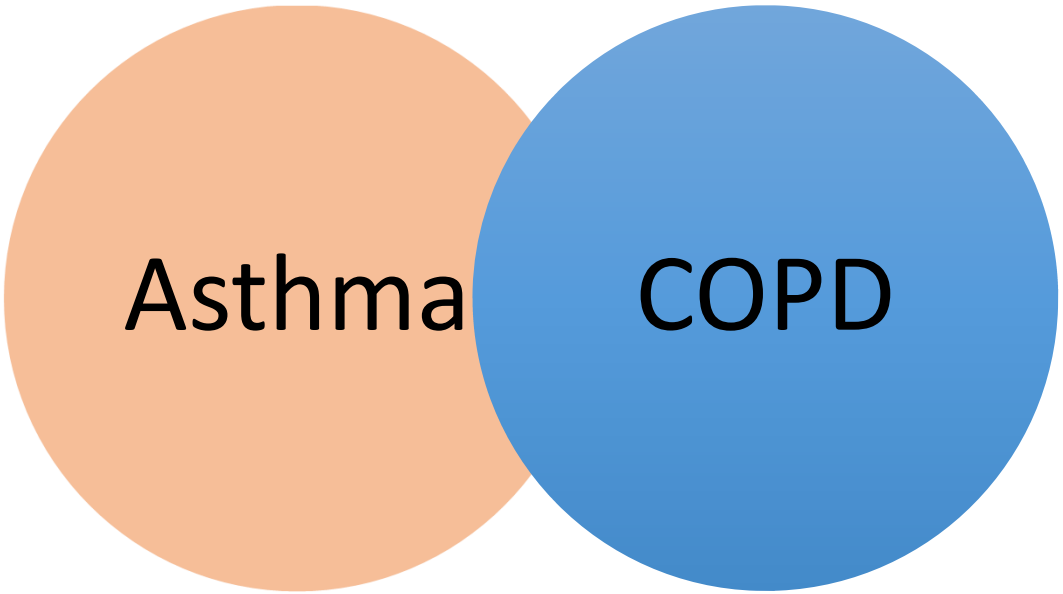
Adapted from GOLD report 2011

"Asthmatic" feature of COPD: Bronchodilator response in the UPLIFT Study



Tashkin, ERJ 2008;31:752

Asthma-COPD Overlap



Dutch hypothesis

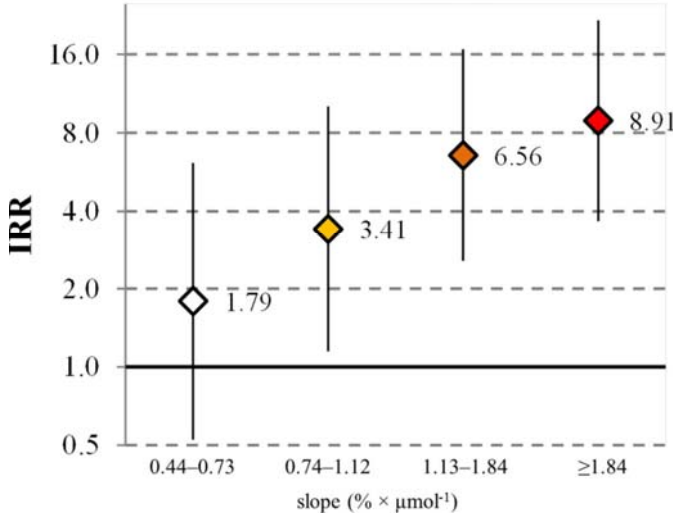
- Orie 1961
- Common host factors for asthma and COPD
  - Airway hyperreponsiveness
  - Atopy
- “Chronic non-specific lung disease”

- British hypothesis: Fletcher 1959
  - Recurrent bronchial infections

Dutch Hypothesis: the evidence

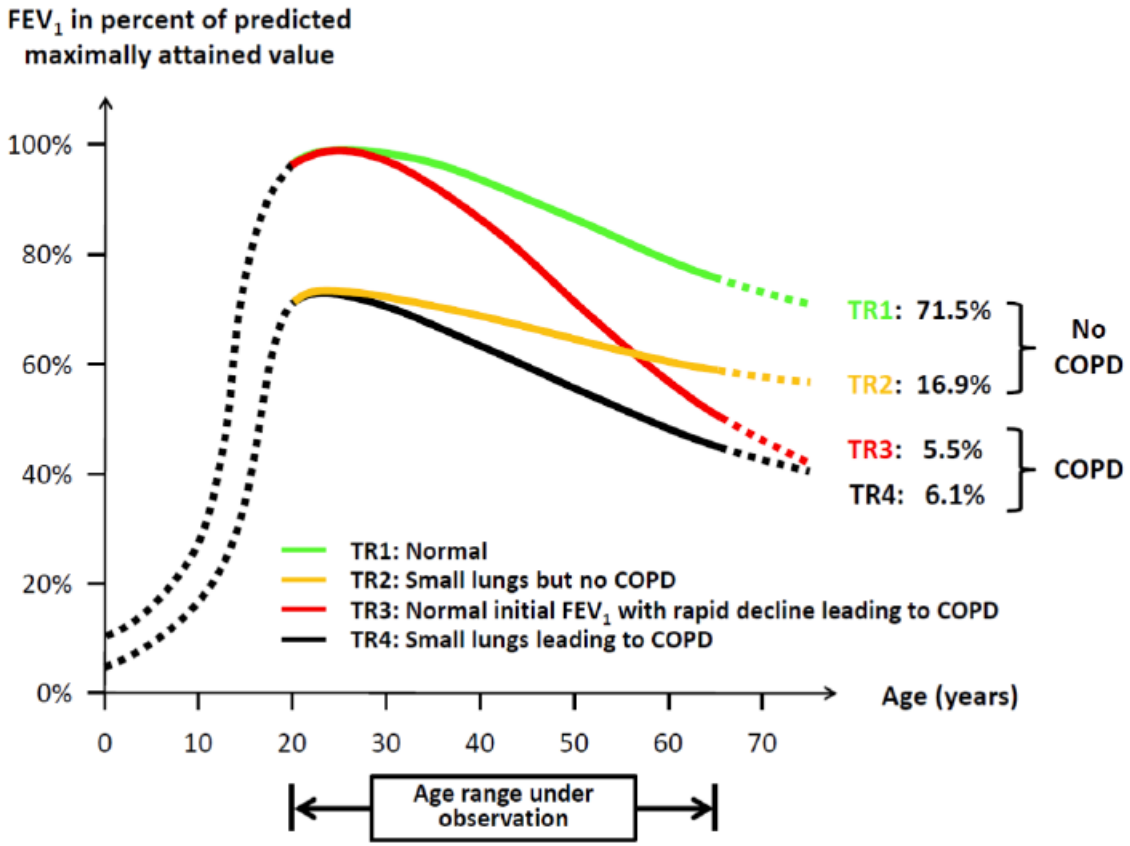
- AHR and accelerated lung function decline
  - Parker, ARRD 1990;141:589
  - Rijcken, AJRCCM 1995;151: 1377
  - Tashkin, AJRCCM 1996;153:1802
- AHR and COPD mortality
  - Hospers, Lancet 2000;356:1313
- Atopy and lung function decline
  - Weak evidence
  - See Weiss, AJRCCM 2000;162:S134

Incidence of COPD (median 9 yr)



Marcon A, Thorax 2018; 73:825

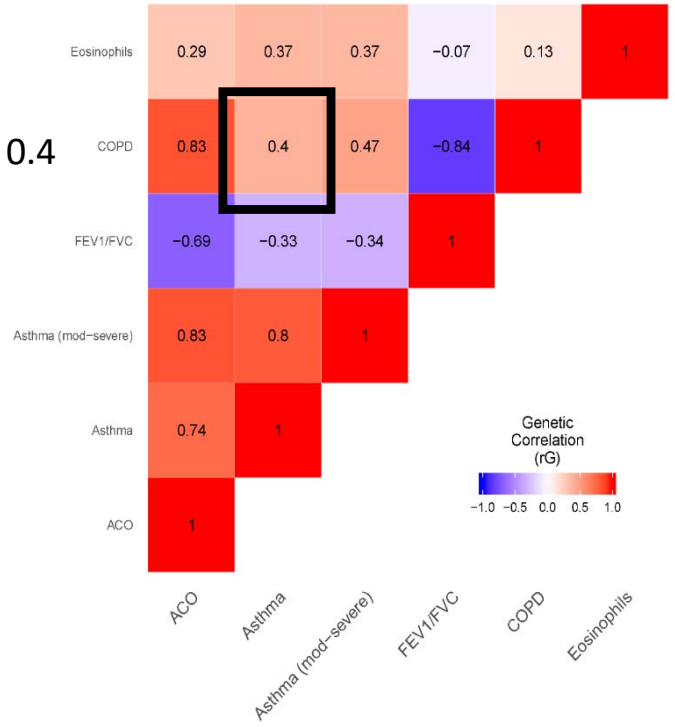
COPD is not just rapid FEV_1 decline



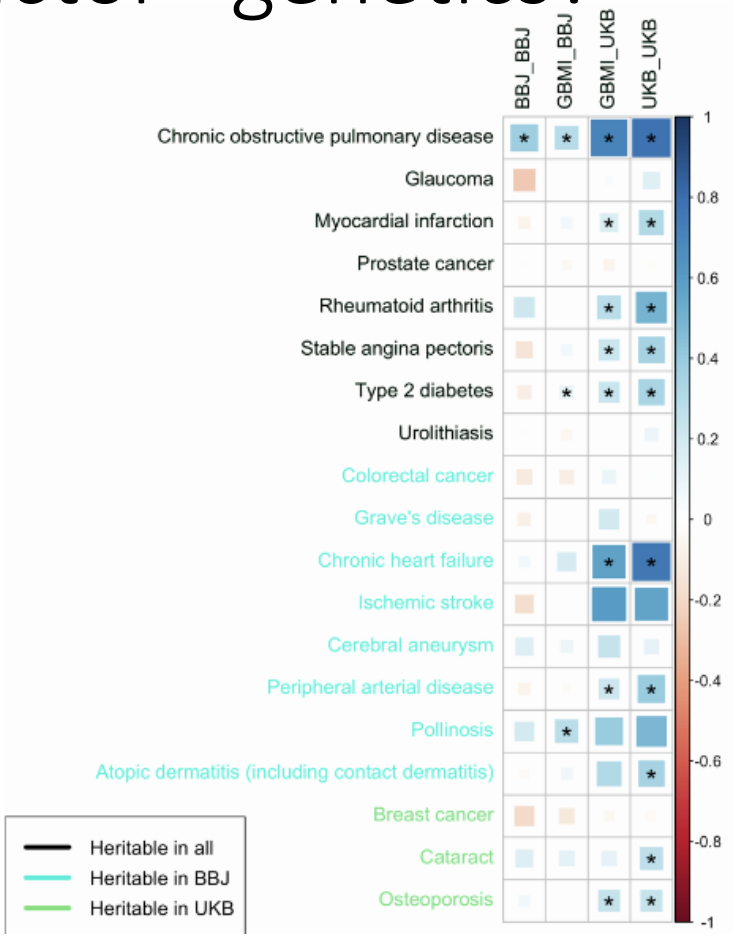
Lange P, NEJM 2015;373:111

Dutch Hypothesis:
Is the “common host factor” genetics?

r = 0.4



John C, Guyatt AL, et al, Chest 2022



r = 0.67

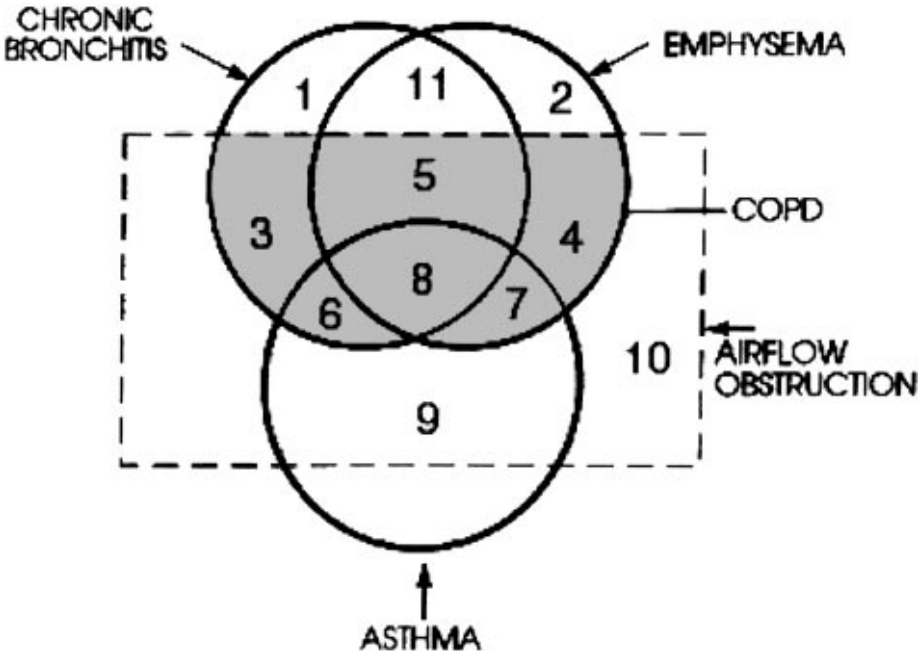
Tsuo K, et al,
Cell Genom 2022

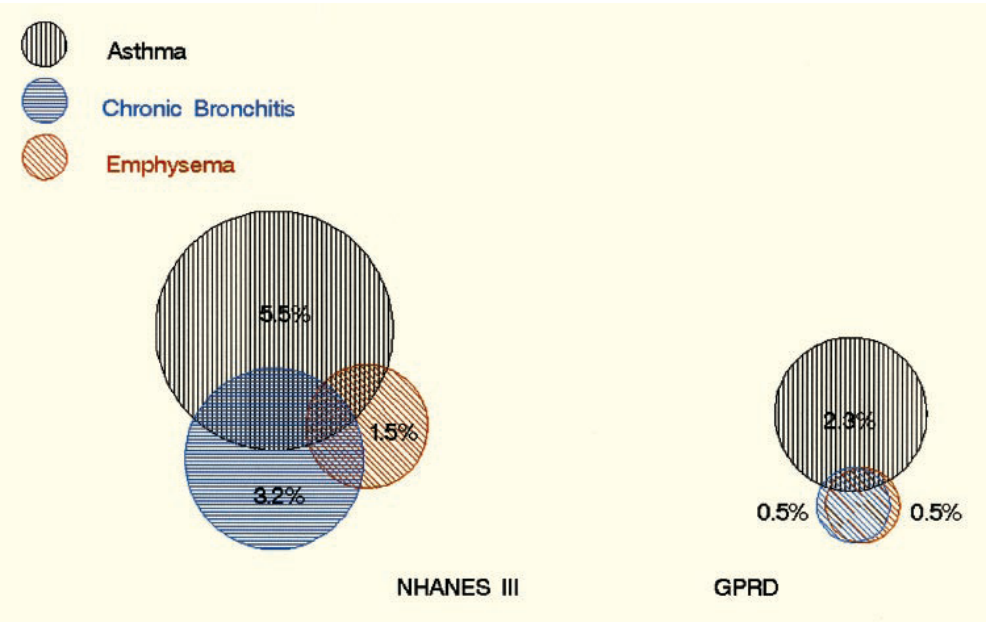
Asthma-COPD overlap is common

Country/region	Criteria	% of COPD
Spain	Self-report of MD diagnosis	17%
Italy	Self-report of MD diagnosis	25-33%
Latin America	Self-report of MD diagnosis Wheeze + BDR	23% 15%
Finland	Hospital discharges	16%
Korea	Health insurance database	55%
Maryland, USA	Medicaid database	43%
Worldwide (NOVELTY study*)	MD diagnosis	26%

Miravitlles, Resp Med 2013;107:1053, deMarco, PLOS ONE 2013;8:e62985,
Talamo, Chest 2007;131:60, Menezes, Chest 2014;145:297, Andersen, Clin Respir J 2013;7:342,
Rhee, COPD 2014;11:163, Shaya, Chest 2008;134:14, *Reddel, ERJ 2021;58:2003927

Venn diagrams of obstructive lung disease in US and UK





Soriano, Chest 2003;124:474-481

Clinical significance of ACO

- More symptoms
- Lower health-related quality of life
- More medications
- More exacerbations
- More ED visits/hospitalizations
- Greater healthcare costs

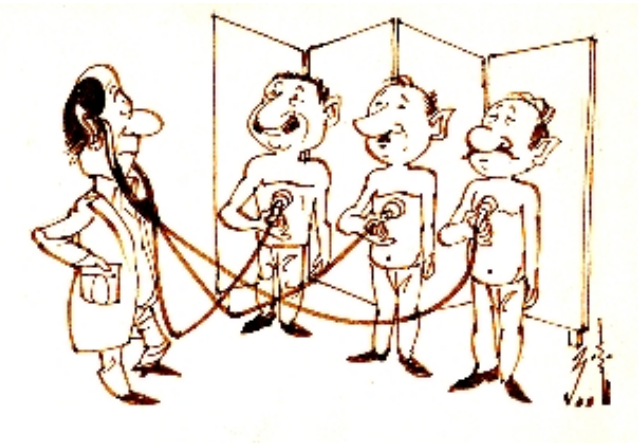
Miravitlles, Resp Med 2013; deMarco, PLOS ONE 2013; Menezes, Chest 2014; Andersen, Clin Respir J 2013; Rhee, COPD 2014; Shaya, Chest 2008; Kauppi, J Asthma 2011; Alshabanat, PLOS ONE 2015; Hardin M, Resp Res 2011

Why are the data so limited?

- Mostly database studies
- Excluded from clinical trials
  - Halpin D, Respir Res 2016;17:120
    - 31 RCTs of long-acting bronchodilators in COPD 1999-2013
    - All excluded patients with asthma
  - Pahus L, BMC Pulm Med 2019;19:127
    - 16 RCTs to reduce COPD exacerbations 2000-2016
    - 87% excluded asthma
  - Herland K, Respir Med 2005;99:11
    - Asthma trials exclude smokers
- How do you define ACO…

Diagnosis of COPD-asthma?

- COPD: Spirometry, exposure (smoking)
- Asthma overlap?
- Doctor's diagnosis
  - Gender bias Chapman, Chest 2001;119:1691
- Bronchodilator response
- Blood or sputum eosinophilia
- Serum IgE



Early Definitions

Canadian Thoracic Society 2007 (O'Donnell, Can Respir J)

- Bronchodilator response: FEV_1 change >400ml
- Diurnal variability in peak flow
- Large improvement in spirometry following inhaled or oral steroids

Japanese Respiratory Society 2009 (Nagai, et al.)

Diagnostic indices for concurrent asthma

1. Paroxysmal dyspnea
2. Wheezing and cough, especially when they occur during the night and in the early morning
3. Presence of atopic predisposition (IgE antibodies to environmental allergens)
4. Increased eosinophil count in sputum and peripheral blood

Arch Bronconeumol. 2012;48(7):247–257

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Recommendations of SEPAR

Spanish COPD Guidelines (GesEPOC): Pharmacological Treatment of Stable COPD☆,☆☆,★

Marc Miravitlles,[a,b,*] Juan José Soler-Cataluña,[c] Myriam Calle,[d] Jesús Molina,[e] Pere Almagro,[f] José Antonio Quintano,[g] Juan Antonio Riesco,[h] Juan Antonio Trigueros,[i] Pascual Piñera,[j] Adolfo Simón,[k] José Luis López-Campos,[l,b] Joan B. Soriano,[m] Julio Ancochea[n]

Table 1
Major and Minor Criteria for Establishing the Diagnosis of Mixed COPD Asthma Phenotype in COPD.[20]

Major criteria
Very positive bronchodilator test (increase in FEV_1 >15% and >400 mL)
Eosinophilia in sputum
Personal history of asthma
Minor criteria
High levels of total IgE
Personal history of atopy
Positive bronchodilator test on at least two occasions (increase of FEV_1 >12% and >200 mL)

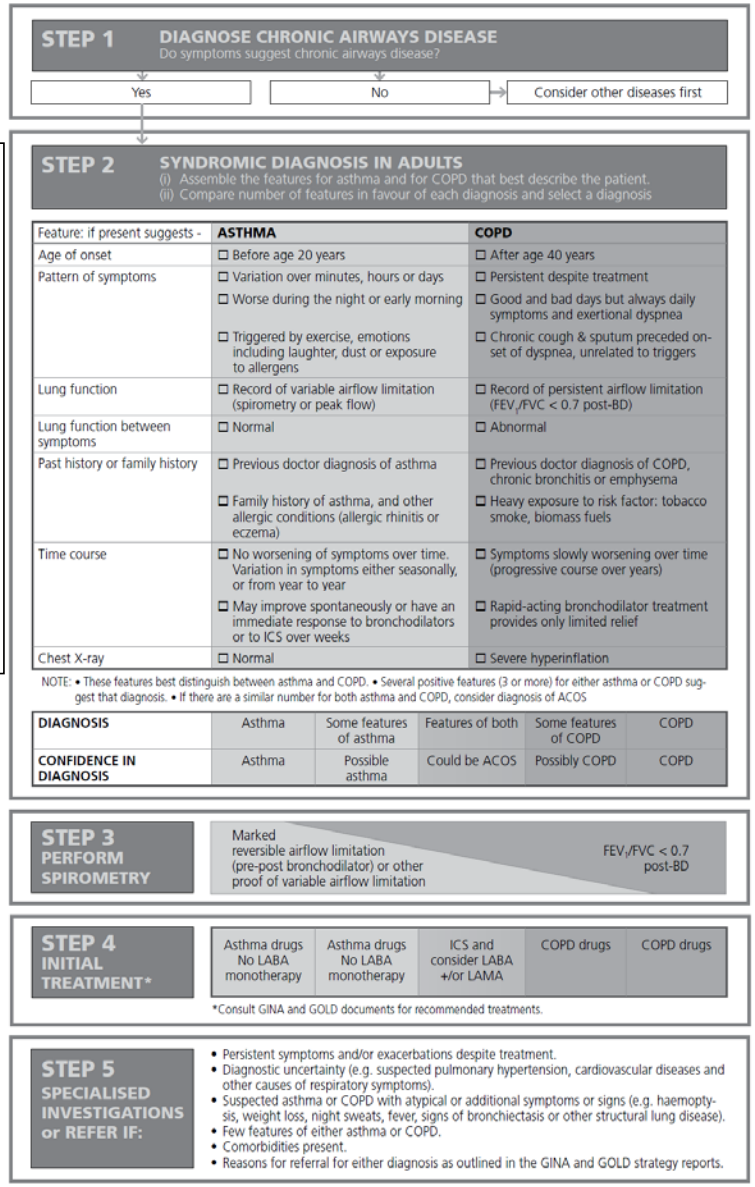
2 major criteria
OR
1 major and 2 minor

GLOBAL INITIATIVE FOR ASTHMA

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)

www.ginasthma.org
www.goldcopd.org
2014



STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

Yes → **STEP 2**

No → Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Feature: if present suggests -	ASTHMA	COPD
Age of onset	☐ Before age 20 years	☐ After age 40 years
Pattern of symptoms	☐ Variation over minutes, hours or days ☐ Worse during the night or early morning ☐ Triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Persistent despite treatment ☐ Good and bad days but always daily symptoms and exertional dyspnea ☐ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	☐ Record of variable airflow limitation (spirometry or peak flow)	☐ Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
Lung function between symptoms	☐ Normal	☐ Abnormal
Past history or family history	☐ Previous doctor diagnosis of asthma ☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ☐ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	☐ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ☐ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	☐ Symptoms slowly worsening over time (progressive course over years) ☐ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	☐ Normal	☐ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Possible asthma	Could be ACOS	Possibly COPD	COPD

STEP 3 PERFORM SPIROMETRY

Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation

$FEV_1/FVC < 0.7$ post-BD

STEP 4 INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS and consider LABA +/or LAMA	COPD drugs	COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5 SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

Expert consensus

Sin DD, et al. ERJ 2016;48:664

Major (all three should be present)	**Minor** (at least one)
1. Persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.70$ or LLN) in individuals 40 years of age or older; LLN is preferred	1. Documented history of atopy or allergic rhinitis
2. At least 10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure (*e.g.* biomass)	2. BDR of FEV_1 ≥200 mL and 12% from baseline values on 2 or more visits
3. Documented history of asthma before 40 years of age OR BDR of >400 mL in FEV_1	3. Peripheral blood eosinophil count of ≥300 cells·uL^{-1}

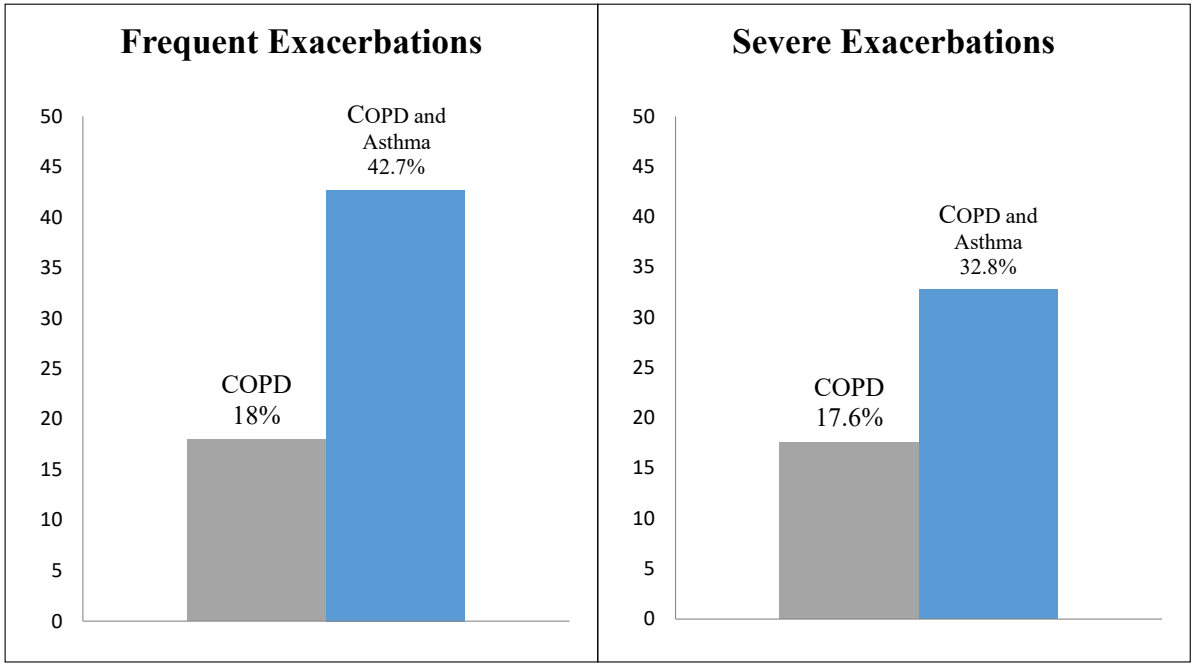
COPDGene Study

- Observational study, 21 clinical centers
- 10,300 smokers (≥ 10 pack-years) with and without COPD
- Spirometry, questionnaires, 6-minute walk, chest CT scan, blood draw
- 5-year follow-up complete, 10-year ongoing

www.copdgene.org

COPD-asthma overlap: COPDGene Study

- 1st 2500 subjects
- COPD
  - FEV_1<80%, FEV_1/FVC<0.7
  - GOLD 2-4
- Asthma
  - self-report of doctor's diagnosis
  - before age 40



- Adopted by consensus report as major criteria
  - Sin DD, Eur Respir J 2016;48:664

Hardin M, Resp Res 2011;12:127

COPDGene Study: full dataset

Hardin M, ERJ 2014;44:341

	COPD	Asthma-COPD (12%)	P-value*
Female	1335 (43%)	252 (56%)	<0.001
African American	627 (20%)	167 (37%)	<0.001
BDR (ATS)	1120 (36%)	177 (39%)	0.1
BDR (ml)	90 (±160)	110 (±160)	0.03
SGRQ	40 (±22)	47 (±23)	<0.001
Exacerbation rate	0.7 (±1.2)	1.2 (±1.6)	<0.001
Hay fever	442 (18%)	186 (50%)	<0.001
Maternal asthma	162 (7%)	57 (19%)	<0.001
Paternal asthma	123 (6%)	47 (18%)	<0.001
Log emphysema %	1.9 (± 1.4)	1.4 (± 1.6)	<0.001
Wall area %, segmental airways	62.8 (± 3.0)	63.6 (± 3.3)	<0.001
Wall area %, subsegmental airways	65.6 (± 2.3)	66.4 (± 2.7)	0.001

*regression models adjusted for age, race, gender, pack-years smoking. CT scan variables also adjusted for BMI and CT scanner model.

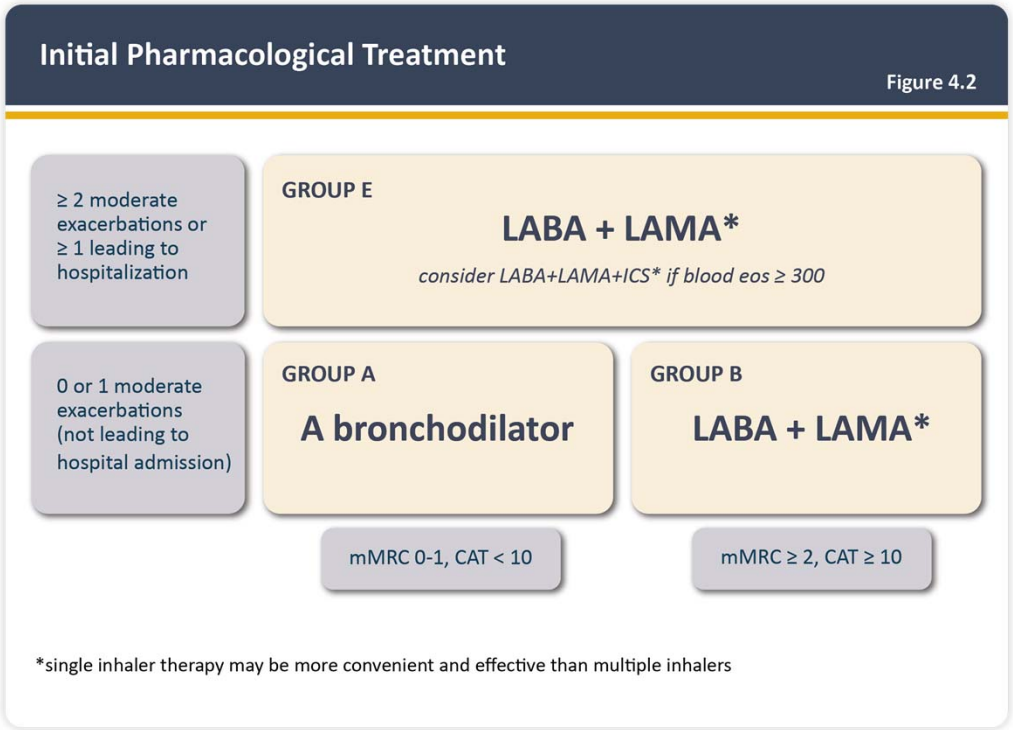
General principles of COPD treatment

<u>Non-pharmacologic</u>

- Smoking cessation
- Supplemental O_2
- Vaccines
- Pulmonary rehabilitation

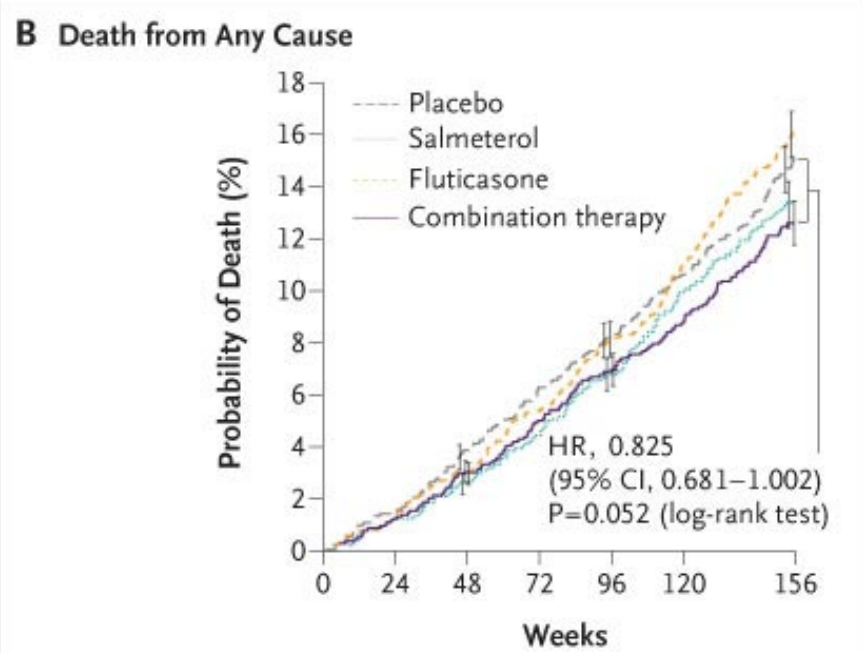
<u>Medications</u>

- GOLD: Symptoms and exacerbation risk
- Bronchodilator first
  - LAMA, LABA or LAMA/LABA combination
- ICS as add-on
  - Increase risk of pneumonia



www.goldcopd.org

Asthma medication for COPD: ICS/LABA TORCH study (Calverley, NEJM 2007;356:775)



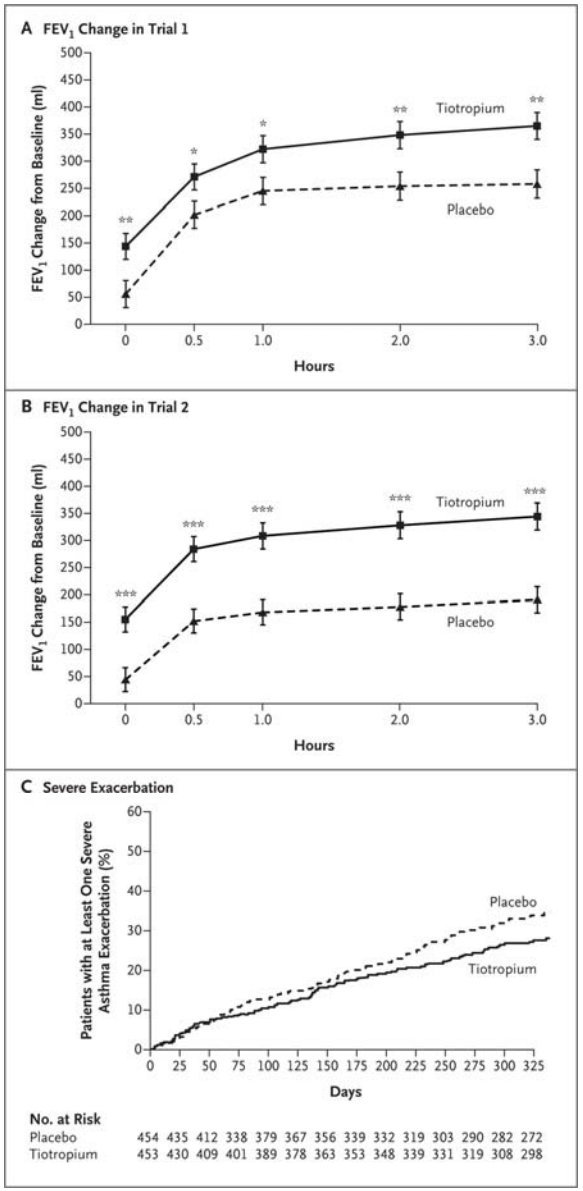
- N=6112
- 4 arms
  - Salmeterol/Fluticasone
  - Salmeterol alone
  - Fluticasone alone
  - Placebo
- Mortality effect N.S. (p=0.052)
- Reduced exacerbations
- Improved health status
- All 3 treatments reduced FEV_1 decline vs. placebo (Celli, AJRCCM 2008)

COPD medication for asthma: Tiotropium

- Asthma poorly controlled on ICS/LABA
  - Added tiotropium vs. placebo added

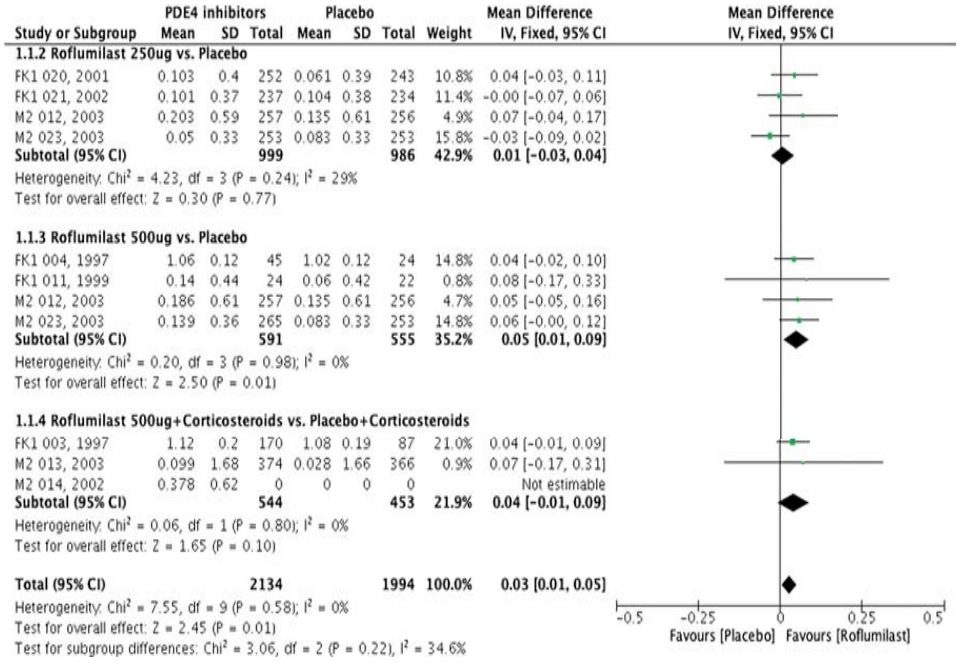
Kerstjens, NEJM 2012;367:1198

- Add on/triple therapy included in GINA steps



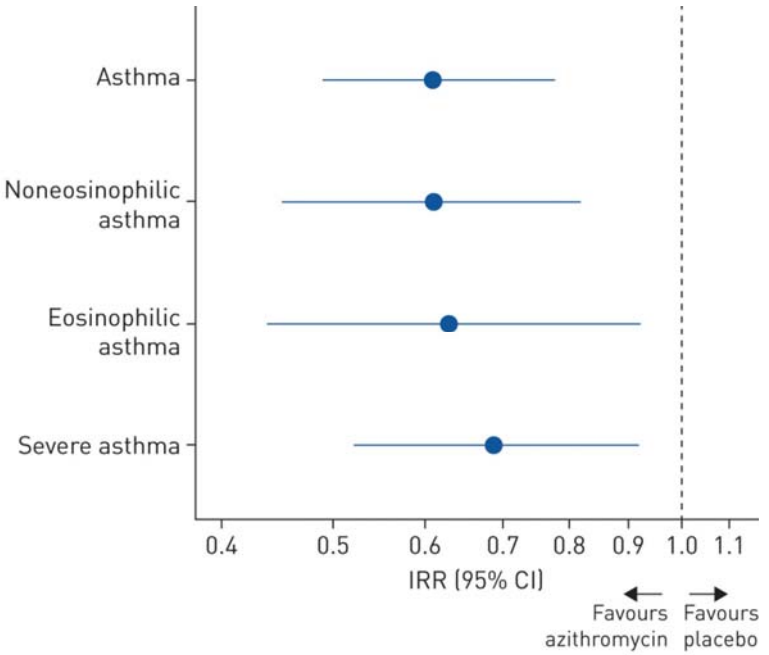
Other COPD medications in asthma

Roflumilast: ↑ FEV_1, ↓ exacerbations



Luo J, Respirology 2018;23:467

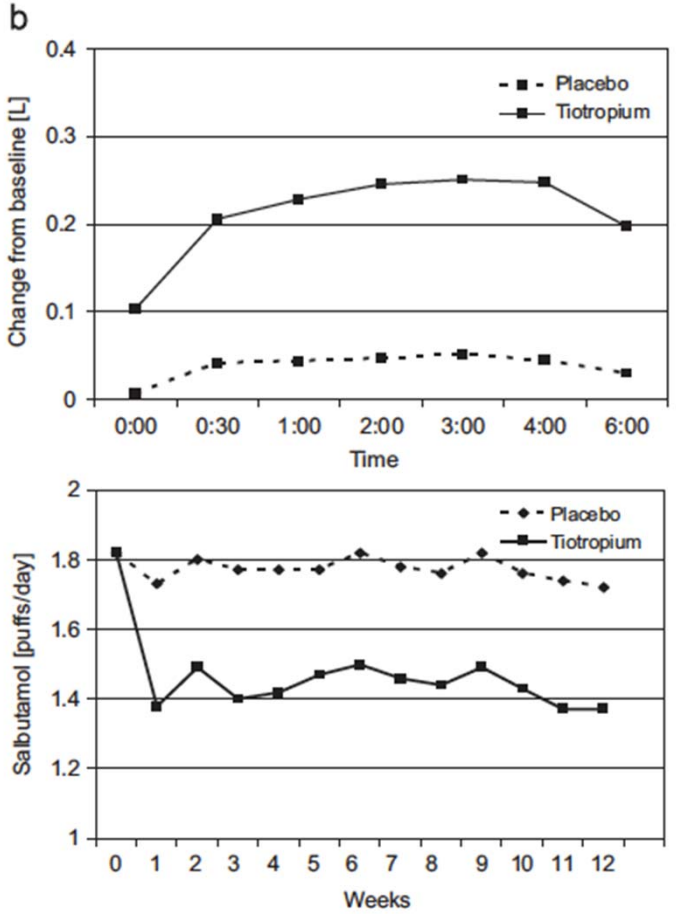
Azithromycin: ↓ exacerbations



Hiles SA, ERJ 2019;54:1901381

RCT in asthma-COPD: Tiotropium

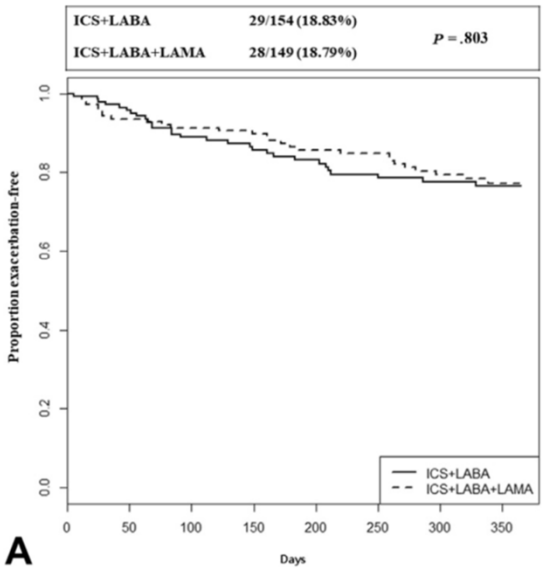
- N=472
- COPD: FEV_1<80%, FEV_1/FVC<0.7; ≥10 pack-years
- Physician diagnosis of Asthma
- BDR: FEV_1 increase ≥12% and ≥200ml
- All taking ICS, 70% LABA
- Add on Tiotropium vs. placebo

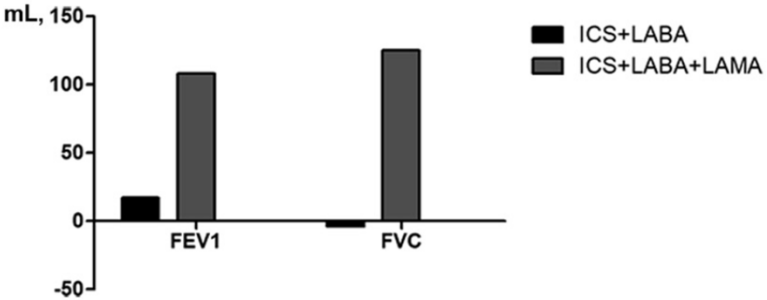


Magnussen, Resp Med 2008;102:50

RCT in asthma-COPD: Triple therapy

- ACO N=303
  - Pre-BD $FEV_1/FVC<0.7$ for 3 months
  - BDR 12% and 200ml
  - 50% ever smokers
- Already on ICS/LABA
  - Randomized to add-on Tiotropium
- 48 week trial





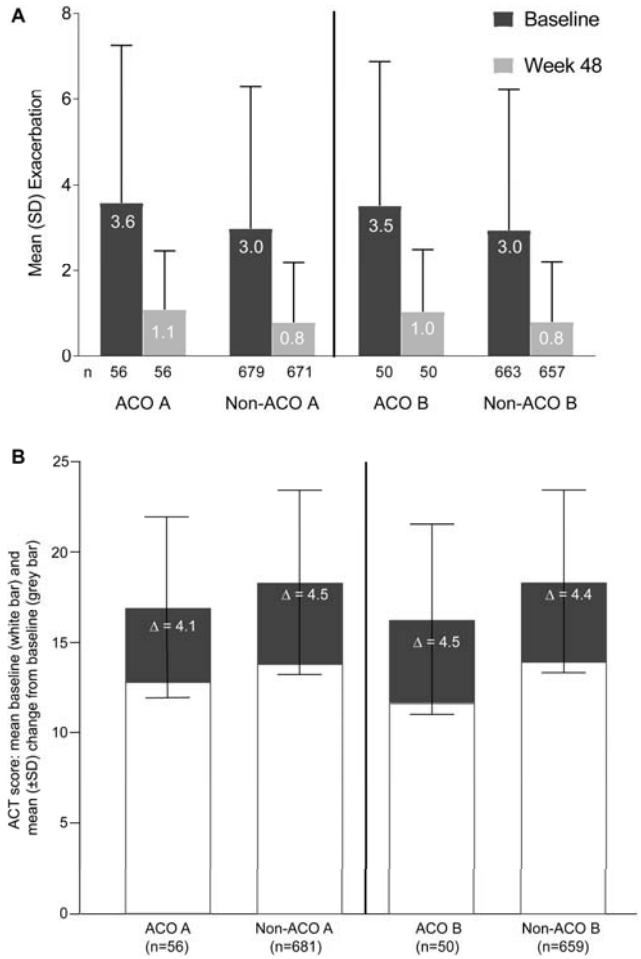
Park SY, JACI Pract 2021;9:1304

Treatment of asthma-COPD: Omalizumab

- PROSPERO asthma study: n=737
- 2 ACO definitions

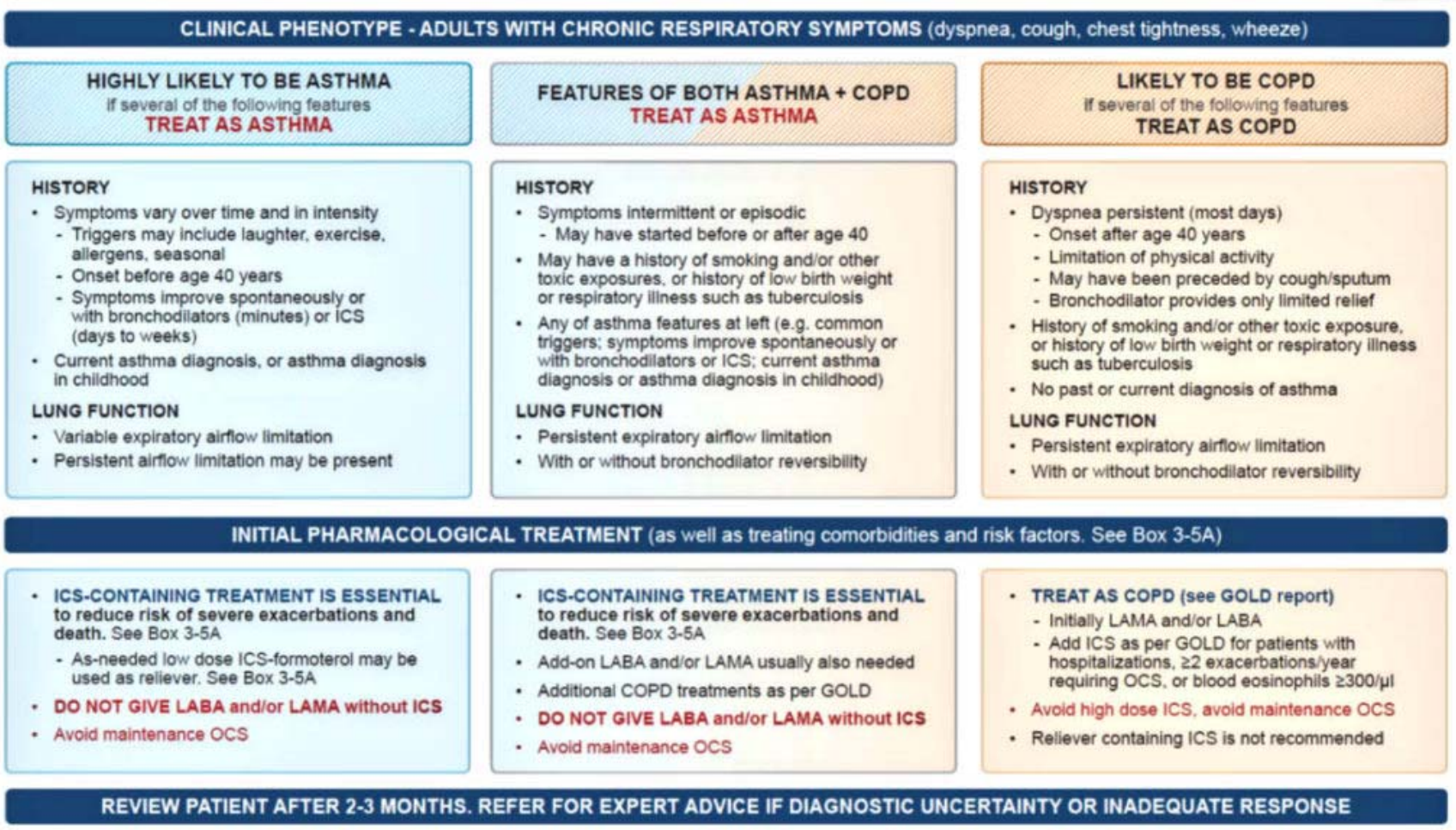
A (n=56): COPD diagnosis or self-report

B (n=50): post-BD FEV_1/FVC <0.7 AND ≥10 pack-years smoking



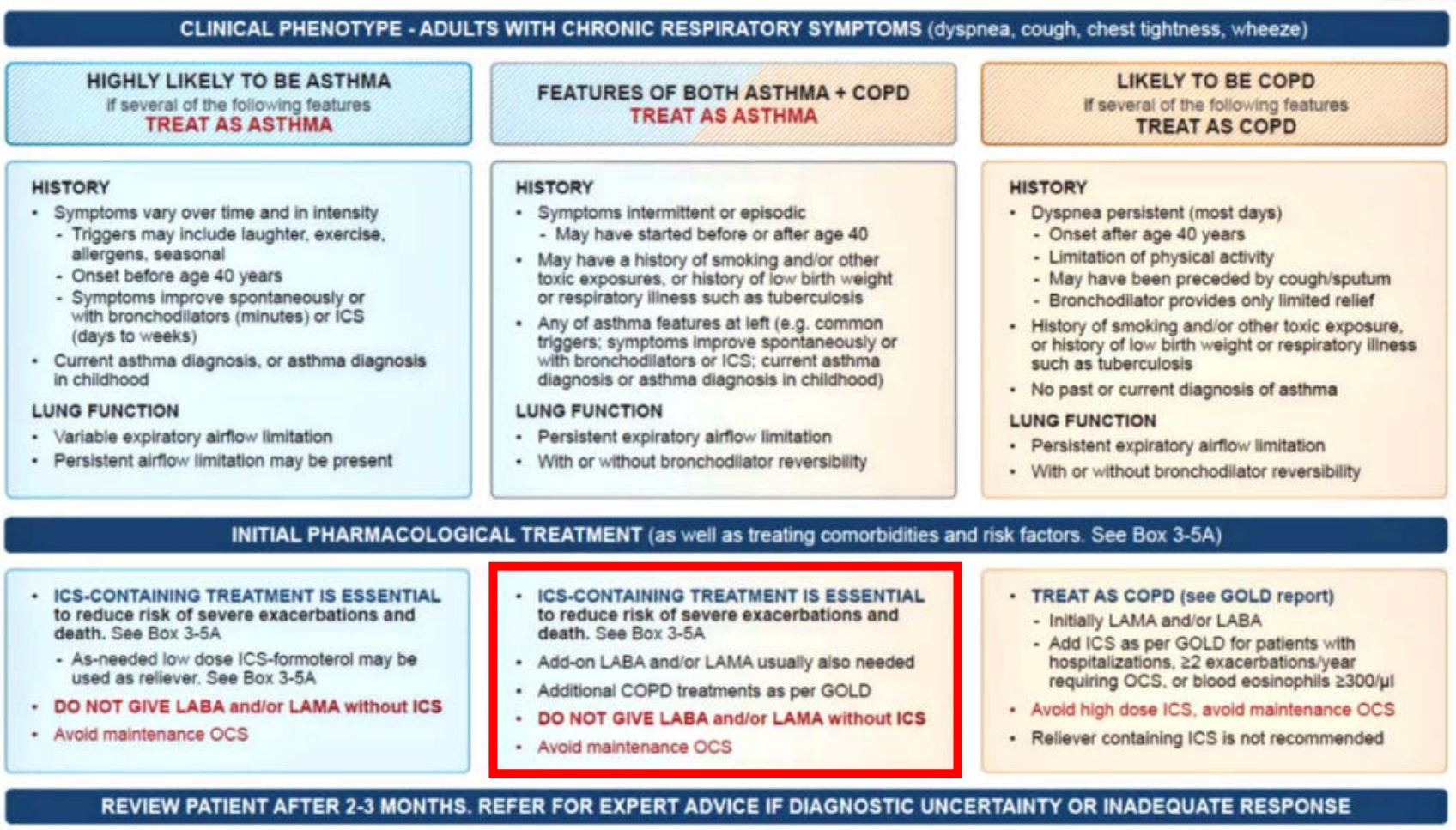
Hanania N, JACI 2019;143:1629

Asthma + COPD Treatment: GINA



www.ginasthma.org

Asthma + COPD Treatment: GINA



www.ginasthma.org

Treatable traits: toward precision medicine of chronic airway diseases

ERJ 2016;47:359

Alvar Agusti[1], Elisabeth Bel[2], Mike Thomas[3], Claus Vogelmeier[4], Guy Brusselle[5,6], Stephen Holgate[7], Marc Humbert[8], Paul Jones[9], Peter G. Gibson[10], Jørgen Vestbo[11], Richard Beasley[12] and Ian D. Pavord[13]

- Pulmonary:
  - airflow limitation, eosinophilic inflammation, chronic bronchitis, chronic respiratory failure
- Extrapulmonary:
  - deconditioning, obesity, cachexia, sleep apnea, cardiovascular disease
- Behavior/lifestyle
  - smoking/exposures, side effects, adherence

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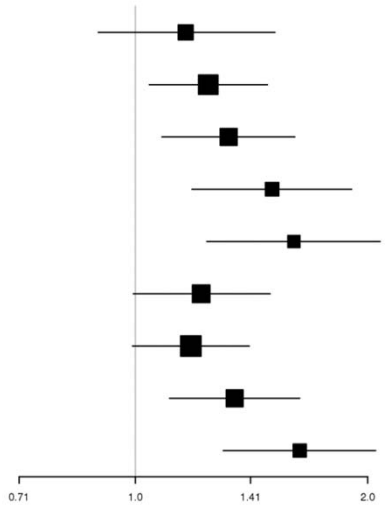
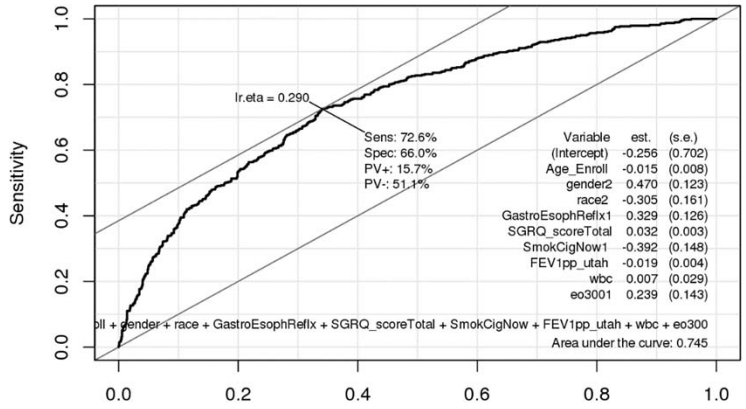
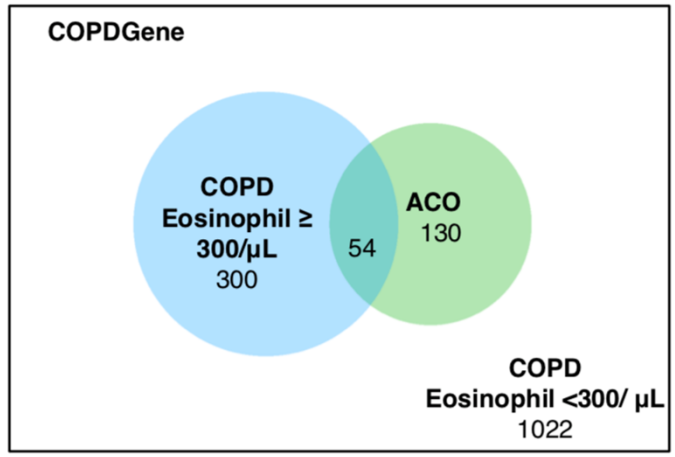
Increased eosinophil counts are associated with COPD exacerbations

Eosinophil Cutoff	< n	≥ n	IRR
100 cells/uL	223	1330	1.162
200 cells/uL	814	739	1.243
300 cells/uL	1187	366	1.321
340 cells/uL	1350	203	1.504
400 cells/uL	1398	155	1.605
2 %	408	1145	1.217
3 %	859	694	1.18
4 %	1166	387	1.345
5 %	1334	219	1.633







Yun JH, JACI 2018;141:2037

Eosinophilic COPD: GOLD

Initial Pharmacological Treatment

Figure 4.2

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

GROUP E

LABA + LAMA*

consider LABA+LAMA+ICS if blood eos ≥ 300*

0 or 1 moderate exacerbations (not leading to hospital admission)

GROUP A

A bronchodilator

mMRC 0-1, CAT < 10

GROUP B

LABA + LAMA*

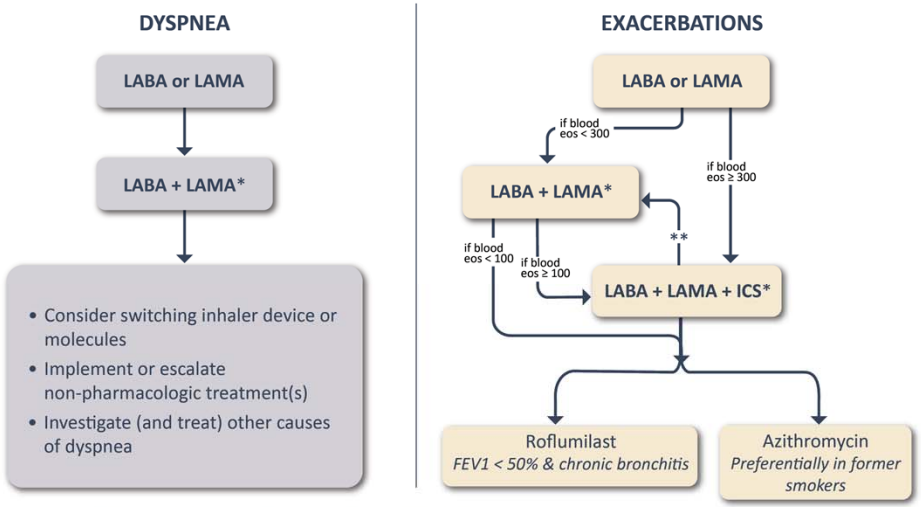
mMRC ≥ 2, CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers

Follow-up Pharmacological Treatment

Figure 4.4

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

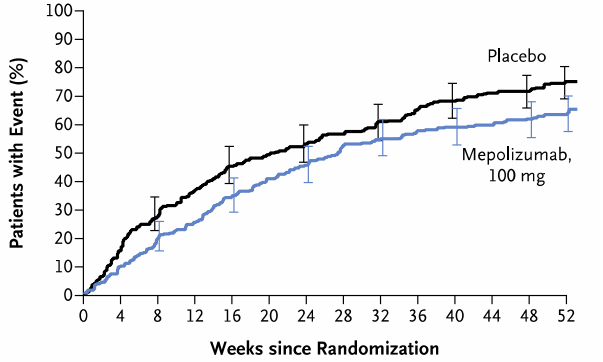
www.goldcopd.org

Eosinophilic COPD: clinical trials

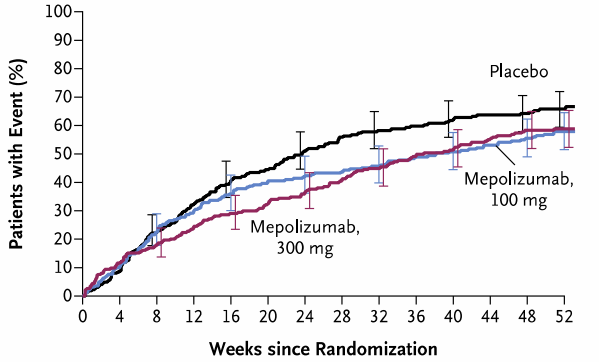
Mepolizumab: anti-IL5

Eos >150 screening or >300 in past year

A METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype



C METREO Modified Intention-to-Treat Population

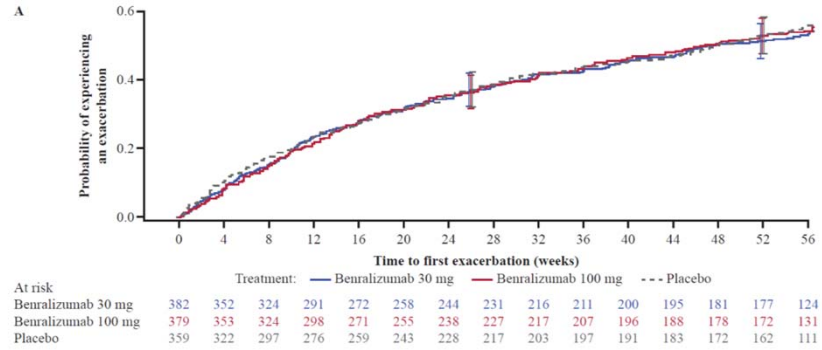


Pavord, NEJM 2017;377:1613

Benralizumab: anti-IL5Ra

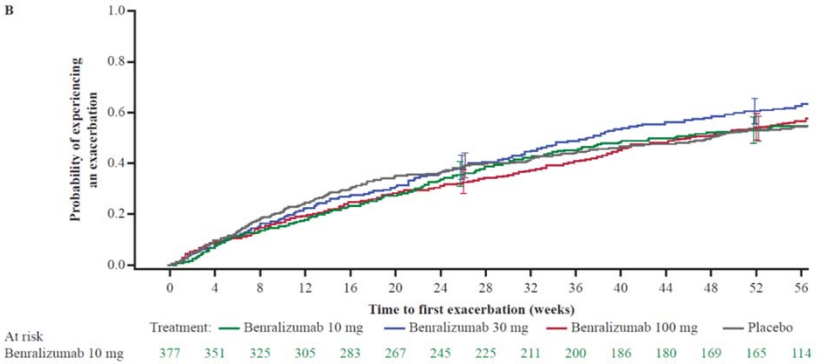
Eos >220

A



At risk															
Benralizumab 30 mg	382	352	324	291	272	258	244	231	216	211	200	195	181	177	124
Benralizumab 100 mg	379	353	324	298	271	255	238	227	217	207	196	188	178	172	131
Placebo	359	322	297	276	259	243	228	217	203	197	191	183	172	162	111

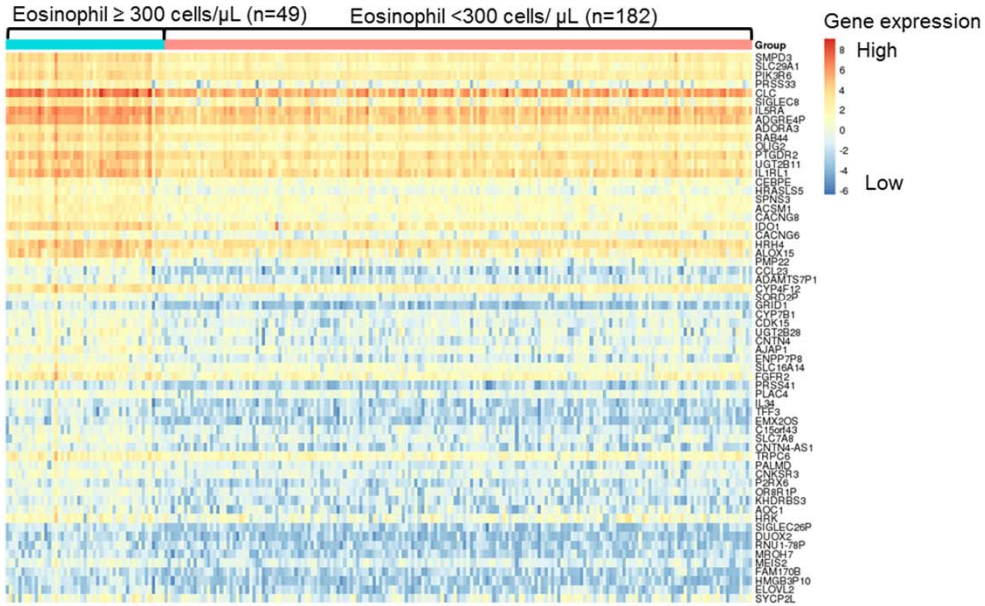
B



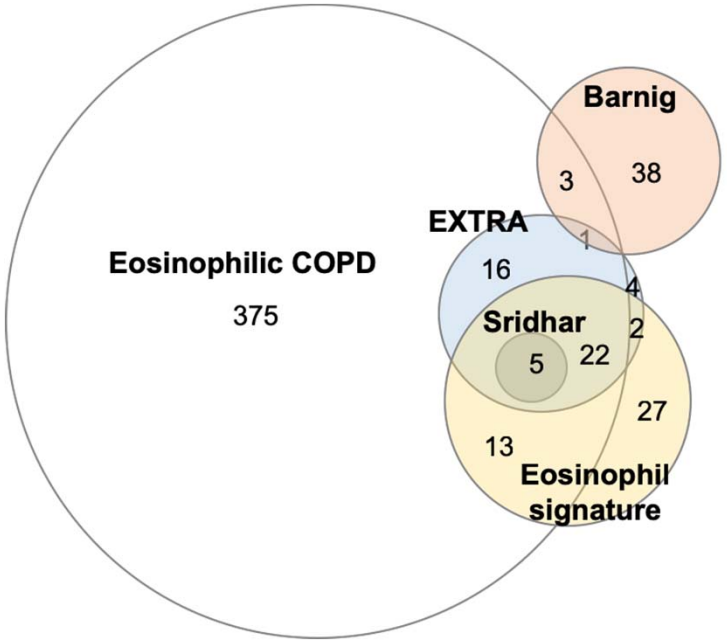
At risk															
Benralizumab 10 mg	377	351	325	305	283	267	245	225	211	200	186	180	169	165	114
Benralizumab 30 mg	394	367	335	304	281	266	244	224	207	186	168	156	147	137	94
Benralizumab 100 mg	386	348	326	304	284	269	260	246	233	219	202	191	181	169	107
Placebo	388	351	319	291	268	248	242	228	222	209	200	194	183	169	127

Criner, NEJM 2019;381:1023

Are the eosinophils doing the same thing as in asthma? Blood RNA-sequencing in Eosinophilic COPD



505 differentially expressed genes:
SMPD3, CLC, IL5RA

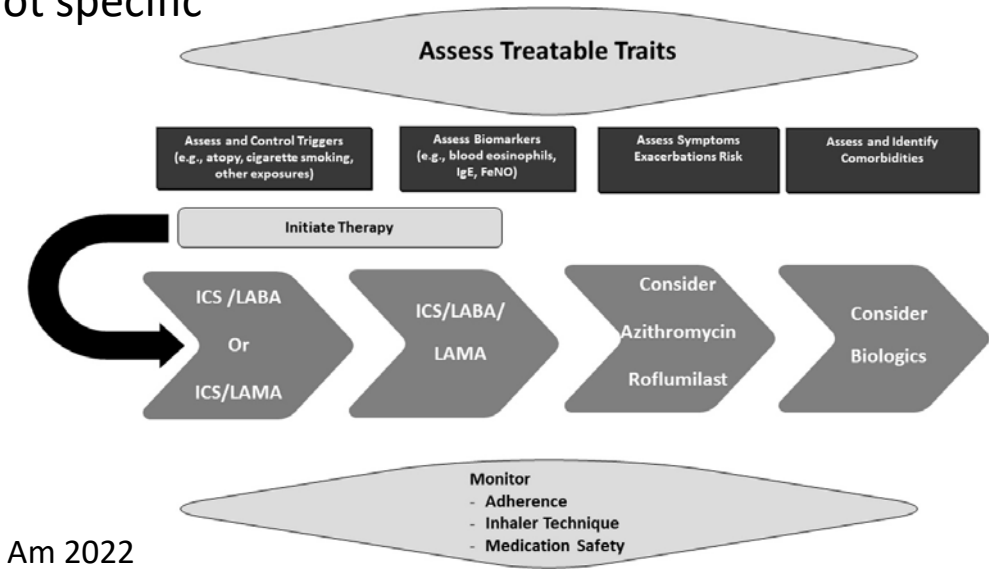


Overlap with eosinophil signature, asthma, benralizumab response gene sets

J. Yun, AJRCMB 2019;61:398-401

Asthma-COPD overlap: summary

- ACO is common
  - Clinical significance
  - Recognizable by physicians
- ACO is challenging for clinical and epidemiology studies
  - No objective definitions: start with COPD
  - Heterogeneous: Biologic mechanisms are not specific
- ACO treatment
  - ICS plus LABA and/or LAMA
- Eosinophilic COPD
  - Not the same as ACO
  - Potential for biologics



Hanania & Miravitlles, Immunol Allergy Clin North Am 2022