Overlapping Respiratory Diseases: Asthma-COPD

Jung-Kyu Lee, MD, FAPSR

Seoul National University

SMG-SNU Boramae Medical Center

SNUH
서울대학교병원운영
서울특별시보라매병원

Definition of asthma and COPD

Asthma [GINA2025]

- Heterogeneous disease, usually characterized by chronic airway inflammation
- Defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation

Chronic Obstructive Pulmonary Disease (COPD) [GOLD2026]

- Heterogenous lung condition characterized by
  - ✓ Chronic respiratory symptom (dyspnea, cough, sputum production and/or exacerbations)
  - ✓ Due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction

Definition of asthma-COPD overlap

Asthma + COPD (asthma-COPD overlap) [GINA2025]

- Terms used to collectively describe patients who have persistent airflow limitation(PAL) together with clinical features that are consistent with both asthma and COPD.
- Not a definition of a single disease entity, but a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms

Case

62세, 남자

3개월 전에 감기를 심하게 앓은 후 기침과 가래가 지속됨. 하루 10번 이상.
증상이 약을 먹을 때 약간 낫지만, 반복되는 양상.
아침에 자다 일어날 때 숨이 답답한 증상 동반됨.

165cm, 69kg
HTN/dyslipidemia on medication
Current smoker, 1PPD*40 years

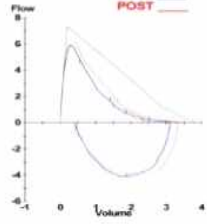
BEC 290 cells/μL, total IgE 340 IU/mL

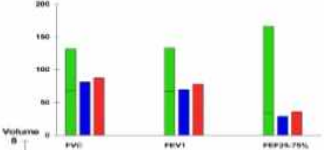
PFT (Spirometry, bronchodilator response)

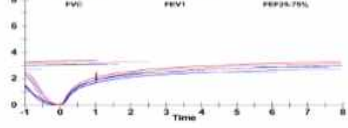
Spirometry (BTPS)

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	3.83	3.12	81	3.35	87	7
FEV1	Liters	2.74	1.91	70	2.13	78	12
FEV1/FVC	%	72	61		63		
FEF25-75%	L/sec	2.78	0.81	29	0.99	36	22
FEF25%	L/sec		3.96		4.62		17
FEF50%	L/sec	3.48	1.27	36	1.55	45	23
FEF75%	L/sec	1.21	0.27	22	0.33	27	23
PEF	L/sec	7.35	5.93	81	6.16	84	4
FVL ECode			000010		000010		
DLCO	mL/mmHg/min	19.3	18.4	96			
DLCO/VA	mL/mHg/min/L	3.84	3.73	97			
VA	Liters	6.10	4.95	81			
CO T.C.	Sec	17.5	18.7	106			
IVC	Liters		2.63				
PI max	cmH2O	109					
PI Volume	Liters						
PE max	cmH2O	204					
PE Volume	Liters						

PRED
PRE
POST







Comments:

BDR positive (+12%, +220mL)

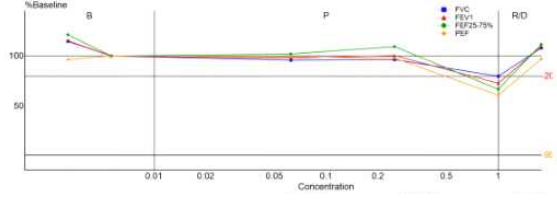
FeNO 20 ppb

Methacholine provocation test

Bronchial Challenge Test (Provocholine)

		Pred	Base	Base 2	Prov	Prov 2	Prov 3	Dilut.
Conc	%		0.0000	9.0000	0.0625	0.2500	1.0000	2.0000
FVC	L	3.82	2.76	2.41	2.30	2.32	1.92	2.60
FVC (%Pred)			72	63	60	61	50	68
FVC%···	%		14.5	0.0	-4.3	-3.7	-20.4	7.9
FEV1	L	2.73	1.85	1.60	1.57	1.61	1.17	1.75
FEV1 (%Pred)			68	59	57	59	43	64
FEV1%···	%		15.0	0.0	-2.1	0.3	-27.3	9.3
FEF25-75%L/s		2.78	1.16	0.96	0.98	1.05	0.64	1.07
FEF25-75%···			42	35	35	38	23	39
FEF25-75%··%			21.1	0.0	1.9	9.2	-33.4	11.4
PEF	L/s	7.34	4.58	4.75	4.71	4.65	2.89	4.61
PEF (%Pred)			62	65	64	63	39	63
PEF%···	%		-3.8	0.0	-0.9	-2.3	-39.3	-3.0

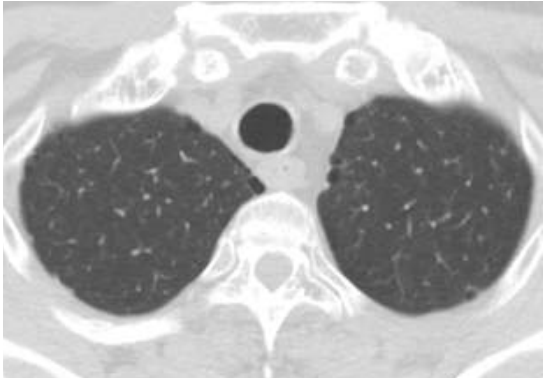
PC[-99] FVC not reached
PC[-20] FEV1 = 0.692 mg/ml Methacholin
PC[-99] FEF25-75% not reached
PC[-99] PEF not reached

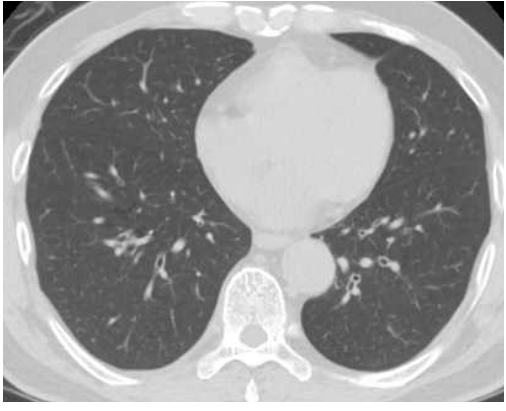


MBPT positive

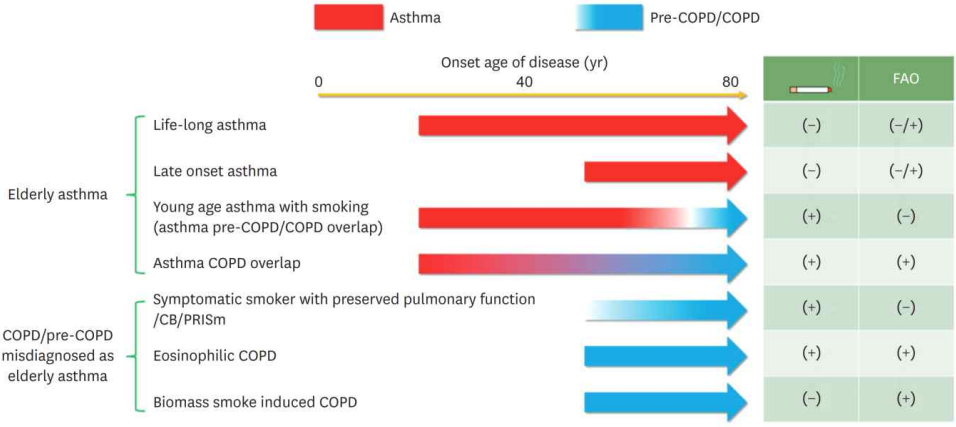
(PC20, 0.692mg/mL)

Chest CT findings



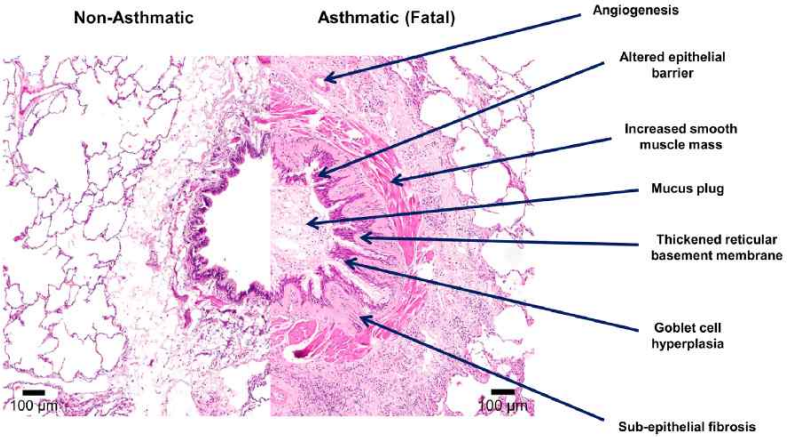


Various phenotypes in elderly patients



Rhee CK, et al. Allergy Asthma Immunol Res 2024;16(6):563-566.

Airway remodeling in asthma



Hsieh A, et al. Front Physiol 2023;14:1113100.

Development of PAL in non-adults

- Children and adolescents with clinically stable asthma, 6-8 years old
- Development of PAL: 9.5% during 4-year follow-up

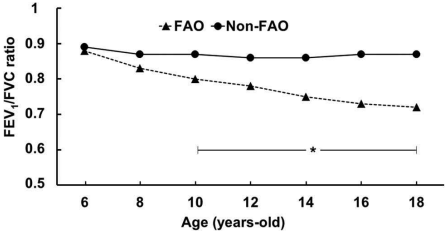
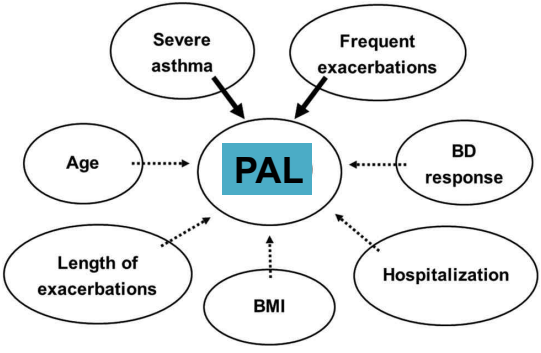


TABLE 3 Multiple logistic regression analysis for risk factors for FAO development in children and adolescents with asthma

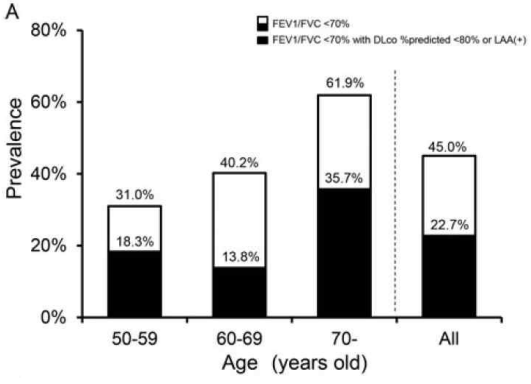
	Risk relative	95% CI	*P* value
Frequent exacerbations	4.0	1.3-11.7	.002
Asthma severity categorized as steps 4-5	3.5	1.6-7.6	<.001

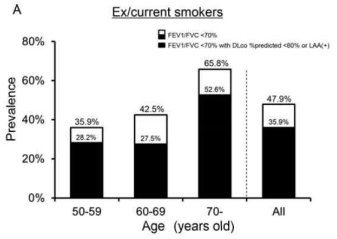


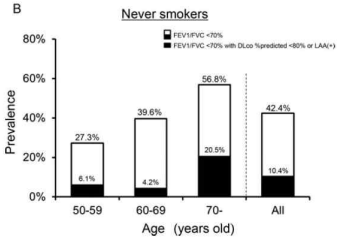
Sousa AW, et al. Pediatr Pulmonol 2020;55(3):591-598.

Prevalence of PAL in elderly asthma

- 45% of patients ≥ 50 years old from Japanese multi-center study







Tamada T, et al. J Asthma 2017;54(6):606-615.

Clinical phenotypes in patients with asthma and/or COPD

CLINICAL PHENOTYPE - ADULTS WITH CHRONIC RESPIRATORY SYMPTOMS (dyspnea, cough, chest tightness, wheeze)

HIGHLY LIKELY TO BE ASTHMA
if several of the following features
TREAT AS ASTHMA

HISTORY

- Symptoms vary over time and in intensity
  - Triggers may include laughter, exercise, allergens, seasonal
  - Onset before age 40 years
  - Symptoms improve spontaneously or with bronchodilators (minutes) or ICS (days to weeks)
- Current asthma diagnosis, or asthma diagnosis in childhood

LUNG FUNCTION

- Variable expiratory airflow limitation
- Persistent airflow limitation may be present

FEATURES OF BOTH ASTHMA + COPD
TREAT AS ASTHMA

HISTORY

- Symptoms intermittent or episodic
  - May have started before or after age 40
- May have a history of smoking and/or other toxic exposures, or history of low birth weight or respiratory illness such as tuberculosis
- Any of asthma features at left (e.g. common triggers; symptoms improve spontaneously or with bronchodilators or ICS; current asthma diagnosis or asthma diagnosis in childhood)

LUNG FUNCTION

- Persistent expiratory airflow limitation
- With or without bronchodilator reversibility

LIKELY TO BE COPD
if several of the following features
TREAT AS COPD

HISTORY

- Dyspnea persistent (most days)
  - Onset after age 40 years
  - Limitation of physical activity
  - May have been preceded by cough/sputum
  - Bronchodilator provides only limited relief
- History of smoking and/or other toxic exposure, or history of low birth weight or respiratory illness such as tuberculosis
- No past or current diagnosis of asthma

LUNG FUNCTION

- Persistent expiratory airflow limitation
- With or without bronchodilator reversibility

Characteristics of patients with asthma according to PAL

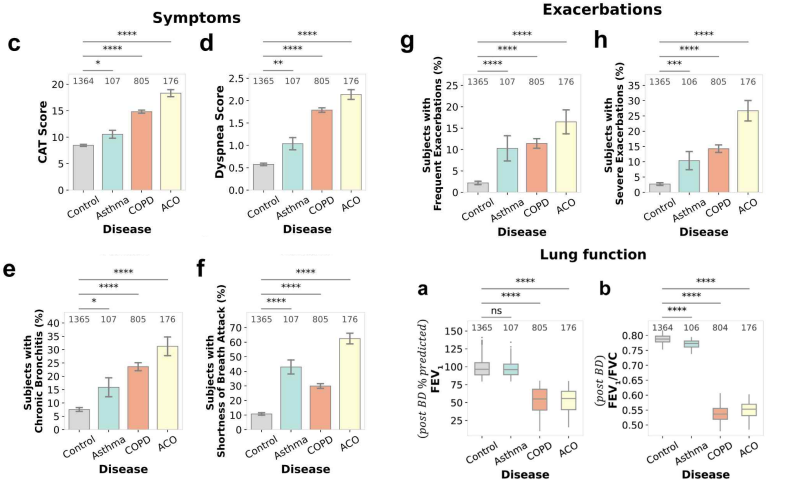
- 773 patients from post-hoc of ATLANTIS study
- Full range of asthma severity: PAL prevalence, 33%

	Asthma with PAL (n = 248)	Asthma without PAL (n = 512)	P-value
Age, years	46.15 ± 12.49	43.48 ± 13.12	0.008
Age at diagnosis, years	17.80 (5.62-38.77)	27.0 (12.0-31.54)	<0.001
Duration of asthma, years	24.03 (10.29-35.75)	12.13 (4.43-24.76)	<0.001
Male sex	126 (51%)	193 (38%)	<0.001
GINA step			<0.001
1	21 (8%)	112 (22%)	
2	24 (10%)	59 (12%)	
3	62 (25%)	143 (28%)	
4	111 (45%)	183 (36%)	
5	30 (12%)	15 (3%)	
Median ACQ6 score (IQR)	0.83 (0.33-1.66)	0.67 (0.17-1.50)	0.021
Blood eosinophil count, x10^9 cells/L	0.27 (0.17-0.40)	0.20 (0.12-0.34)	<0.001
FEV$_1$ % predicted (post-bronchodilator)	77.30 ± 16.02)	95.42 ± 13.49	<0.001
RV/TLC, % predicted	106.8 ± 27.4	97.35 ± 21.58	<0.001
FeNO, ppb, median	27.0 (17.0-40.0)	24.0 (15.0-35.75)	0.043
R5-20, kPa/L/s, median (IQR)	0.07 (0.03-0.14)	0.04(0.02-0.08)	<0.001

Kole TM, et al. Lancet Respir Med 2023;11:55-64.

Distinct characteristics of ACO in smokers

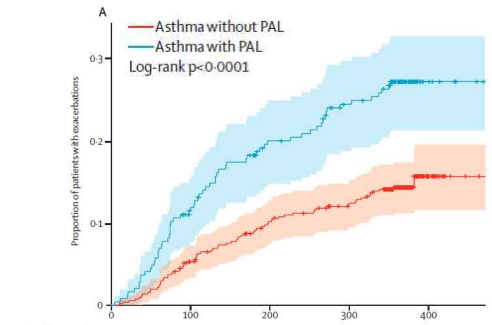
- COPDGene cohort (45-80 years, ≥10 pack-years)



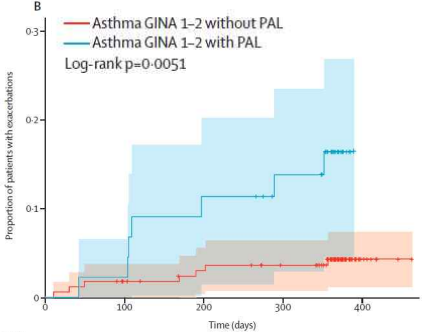
Fangal VD, et al. EBioMedicine 2024;110:105453.

Risk of asthma exacerbations according to PAL

All patients with asthma



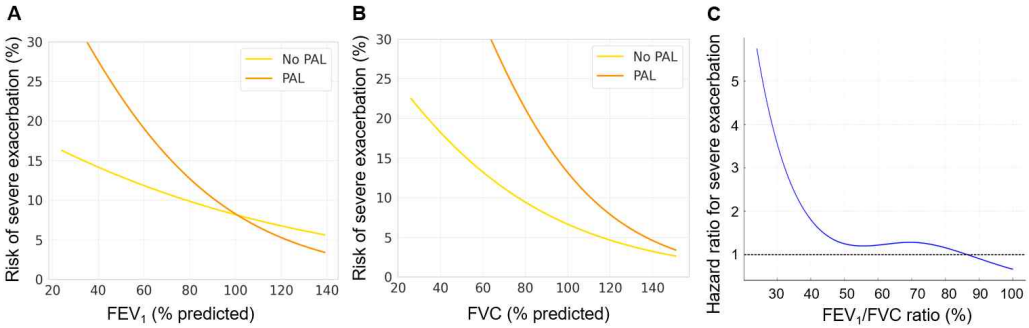
Patients with GINA step 1-2 asthma



Kole TM, et al. Lancet Respir Med 2023;11:55-64.

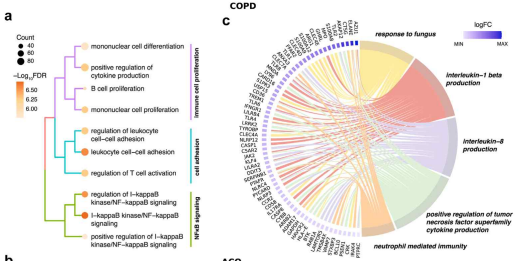
Risk of asthma exacerbations according to PAL

- Korean ISAR cohort + retrospective cohort from SNUH/Boramae medical center
- 849 patients with asthma, real-world data



(unpublished)

Differential expression of transcriptomics



COPD

- Tissue damage/destruction
  - ✓ NF-κB activation
  - ✓ NET(neutrophil extracellular trap)osis
  - ✓ Necroptosis

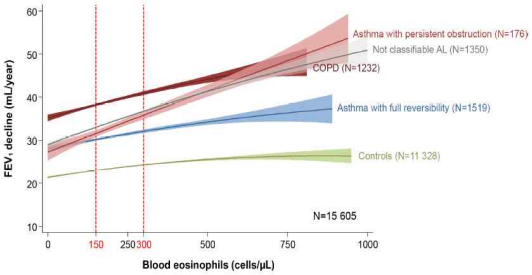
ACO

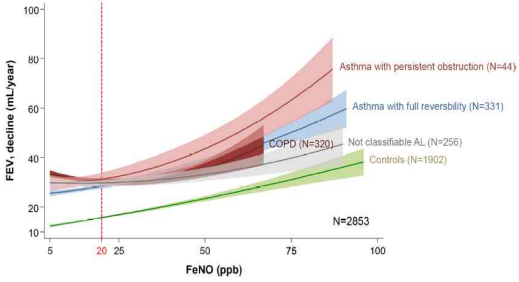
- Hypoxia adaptation and fibrosis/remodeling
  - ✓ HIF-1 signaling
  - ✓ Metabolic reprogramming
  - ✓ Adaptive/innate immune activation

Fangal VD, et al. EBioMedicine 2024;110:105453.

Lung function decline in chronic airway disease

- Adults from the Copenhagen General Population Study with measurements of blood eosinophils and FeNO
- Longitudinal lung function change according to type 2 biomarkers

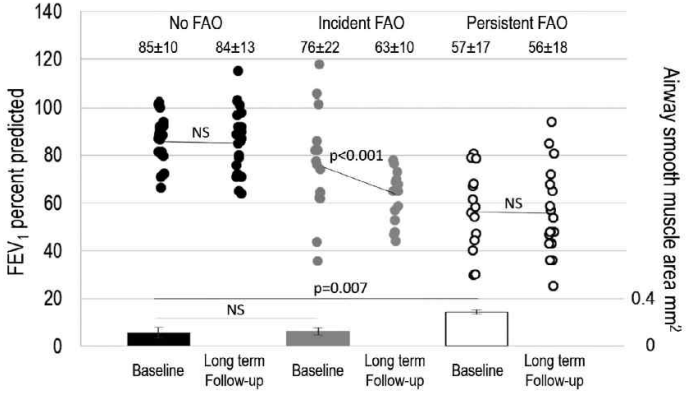




Colak Y, et al. Thorax 2024;79:349-358.

Long-term trajectories

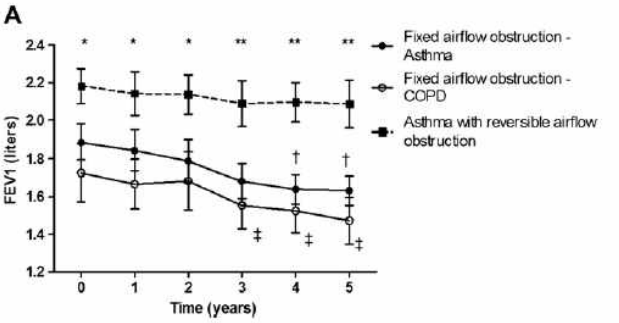
- 62 patients with moderate-to-severe asthma, median 7.9 years follow-up



Smith BM, et al. Clin Exp Allery 2021;51(1):39-48.

Longitudinal changes of lung function

- Patients with PAL due to asthma or COPD vs. control (asthma with fully reversible airflow obstruction), 5-year follow-up



Contoli M, et al. J Allergy Clin Immunol 2010;125(4):830-7.

Initial pharmacological treatment

HIGHLY LIKELY TO BE ASTHMA if several of the following features TREAT AS ASTHMA	FEATURES OF BOTH ASTHMA + COPD TREAT AS ASTHMA	LIKELY TO BE COPD if several of the following features TREAT AS COPD
INITIAL PHARMACOLOGICAL TREATMENT (as well as treating comorbidities and risk factors. See Box 3-12)		
• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** - GINA Track 1 with ICS-formoterol as reliever is the preferred regimen. See Box 4-6 and Box 4-8 • **DO NOT GIVE LABA and/or LAMA without ICS** • Maintenance OCS only as last resort	• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** • Add-on LABA and/or LAMA usually also needed • Additional COPD treatments as per GOLD • **DO NOT GIVE LABA and/or LAMA without ICS** • Maintenance OCS only as last resort	• **TREAT AS COPD (see GOLD report)** - Initially maintenance LABA-LAMA - Add ICS as per GOLD for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/µl • Avoid high dose ICS, avoid maintenance OCS • Reliever containing ICS is not recommended
REVIEW PATIENT AFTER 2-3 MONTHS. REFER FOR EXPERT ADVICE IF DIAGNOSTIC UNCERTAINTY OR INADEQUATE RESPONSE		

Effect to lung function of adding LAMA therapy

- Post-hoc analyses of TRIMARAN and TRIGGER

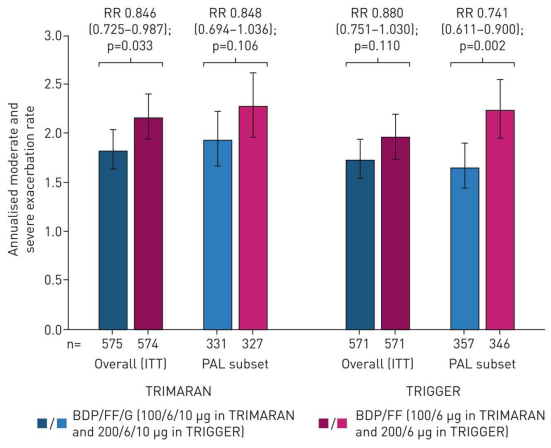
BDP/FF/G vs. BDP/FF differences
in change from baseline in lung functions at week 26

	TRIMARAN		TRIGGER	
	Overall (n=1149)	PAL subset (n=658)	Overall (n=1142)	PAL subset (n=703)
Pre-dose FEV1, mL	57 (15-99); P=0.008	89 (38-140); P<0.001	73 (26-120); P=0.003	130 (79-181); P<0.001
Peak FEV1, mL	84 (40-129); P<0.001	119 (64-175); P<0.001	105 (57-153); P<0.001	154 (100-208); P<0.001
PEF, L/min	8.5 (3.6-13.3); P<0.001	11.3 (5.3-17.2); P<0.001	7.8 (3.0-12.6); P=0.001	14.6 (8.8-20.5); P<0.001

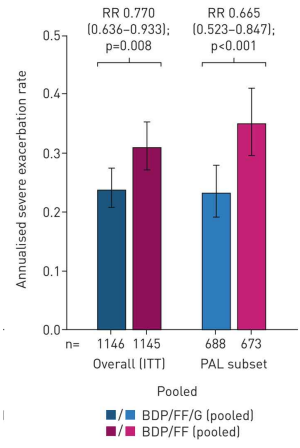
Singh D, et al. Eur Respir J 2020;56(3):2000476.

Effect to exacerbation of adding LAMA therapy

Moderate and severe exacerbations



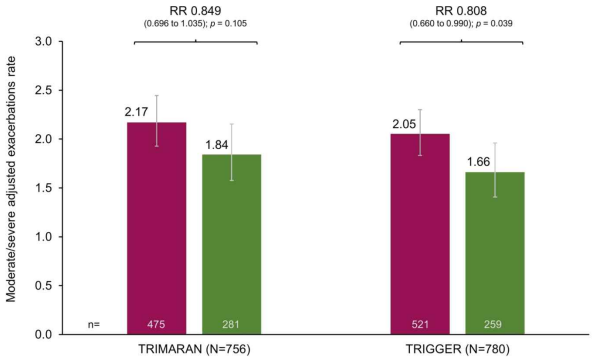
Severe exacerbations



Singh D, et al. Eur Respir J 2020;56(3):2000476.

Prognosis according to normalization of airflow limitation

- Post-hoc analyses of TRIMARAN and TRIGGER
- Subgrouped according to post-salbutamol PAL status at screening, and airflow limitation over the 52-week treatment period



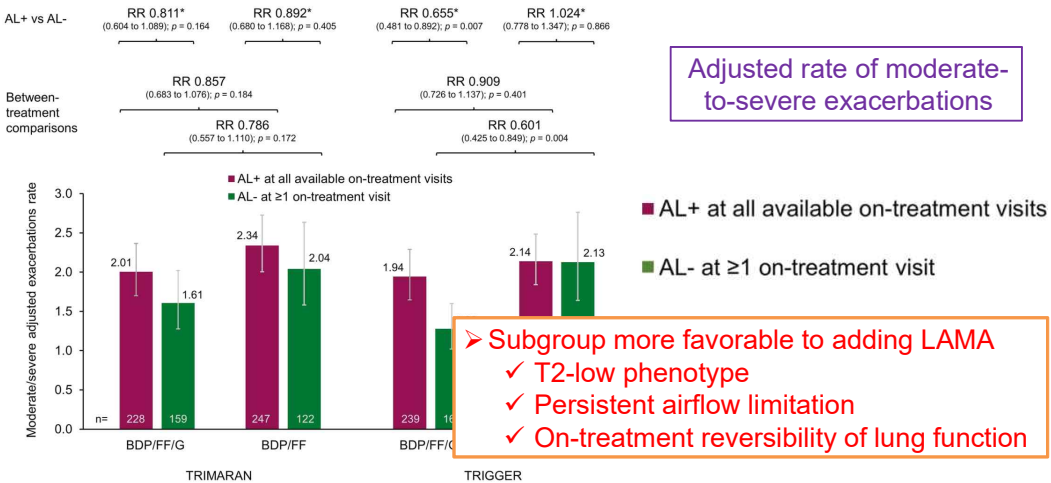
Adjusted rate of moderate-to-severe exacerbations

AL+ at all available on-treatment visits

AL- at ≥1 on-treatment visit

Papi A, et al. Clin Transl Allergy 2022;12(4):e12145.

Prognosis according to normalization of airflow limitation



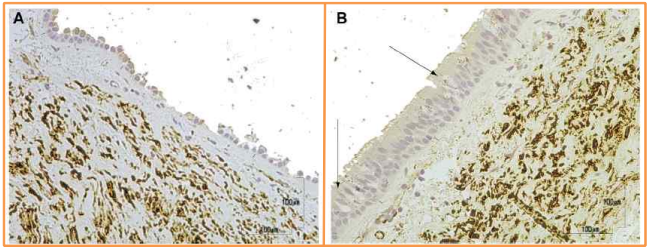
Adjusted rate of moderate-to-severe exacerbations

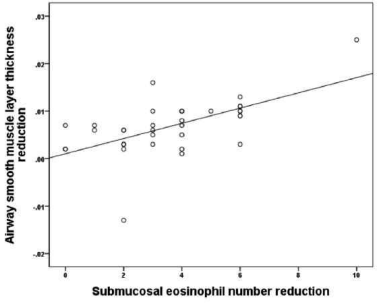
- Subgroup more favorable to adding LAMA
  - ✓ T2-low phenotype
  - ✓ Persistent airflow limitation
  - ✓ On-treatment reversibility of lung function

Papi A, et al. Clin Transl Allergy 2022;12(4):e12145.

Promising effect of biologics use in SEA with PAL

- 41 late-onset SEA patients with post-bronchodilator FEV_1/FVC <0.7, poor control with high-dose ICS containing triple inhaler, MESILICO
- Endobronchial biopsy: before and after 12-month treatment of mepolizumab





- Improvement of airway remodeling
  - ✓ Sub-basement membrane thickness: 17%↓
  - ✓ Airway smooth muscle area: 24.4%↓
  - ✓ Airway smooth muscle layer thickness: 26% ↓
  - ✓ Extent of epithelial damage: 38.8%↓
  - ✓ Tissue eosinophil: 47.9%↓

Domvri K, et al. J Allergy Clin Immunol 2025;155:425-35.

Summary

- ACO as a heterogeneous overlap of asthma and COPD features
- Underlying mechanism: chronic inflammation → airway remodeling → PAL
- COPD-like physiology in asthma with PAL: distinct remodeling/fibrosis biology
- Asthma with PAL = high-risk phenotype (lung function, exacerbations)
- Trait-based management: ICS mandatory; consider LAMA/triple therapy; biologics

Thank You for Your Attention