Biologics: Not Just for Asthma Anymore?

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Disclosures

- None

Objectives

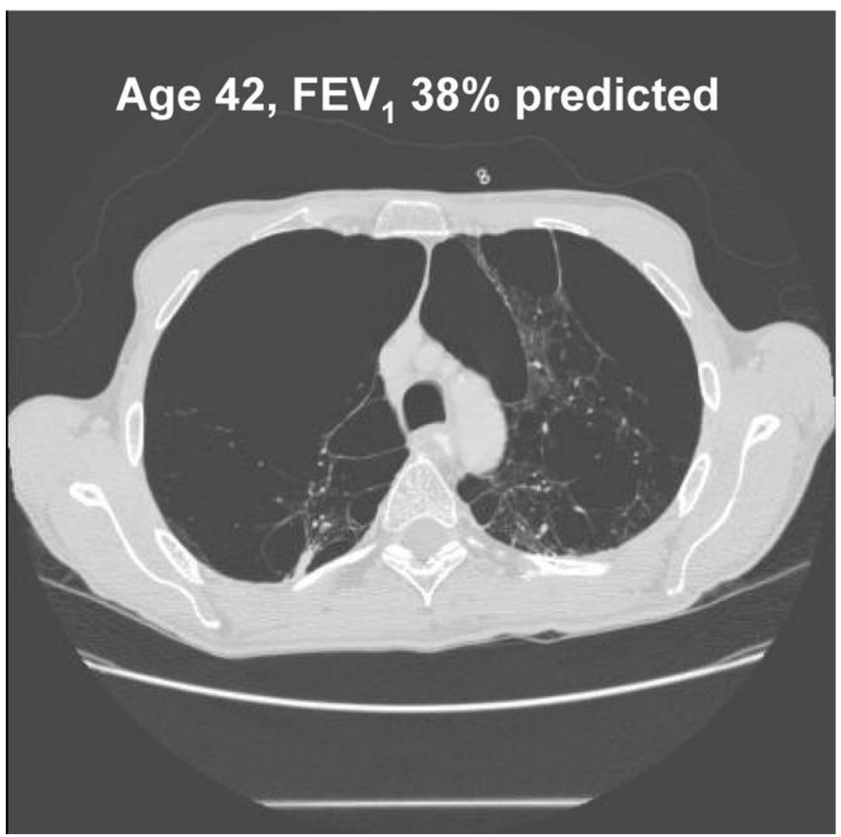
- Discuss the heterogeneity of COPD, and how exacerbations affect future outcomes
- Discuss the role of eosinophils as a biomarker in predicting severe COPD and future exacerbations
- Discuss the recent approval of dupilumab for COPD, and future areas of investigation

What is COPD?

- GOLD (2024): “A heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.”
- In practice multiple progressive lung diseases included such as chronic bronchitis, emphysema, asthma/COPD overlap, and some bronchiectasis
- Refractory symptoms including dyspnea on exertion, chronic cough, and increased sputum production

Not All COPD Is The Same

A



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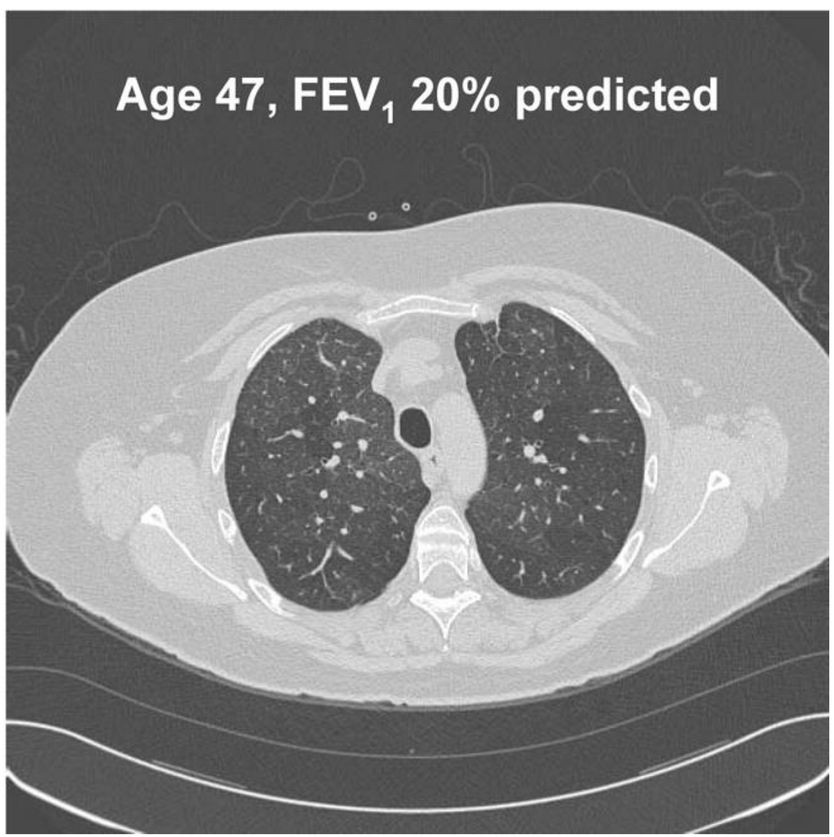
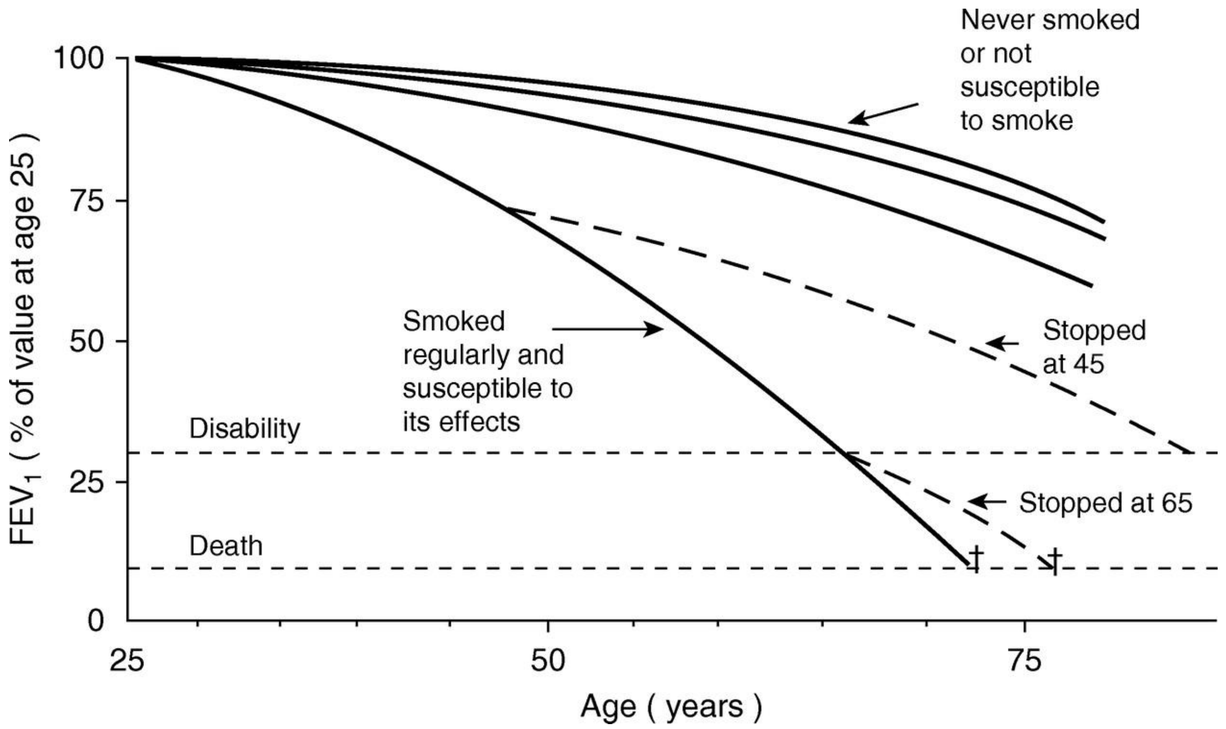


Hersh, C. P., Jacobson, F. L., Gill, R., & Silverman, E. K. (2007). Computed Tomography Phenotypes in Severe, Early-Onset Chronic Obstructive Pulmonary Disease. COPD: Journal of Chronic Obstructive Pulmonary Disease, 4(4), 331–337. https://doi.org/10.1080/15

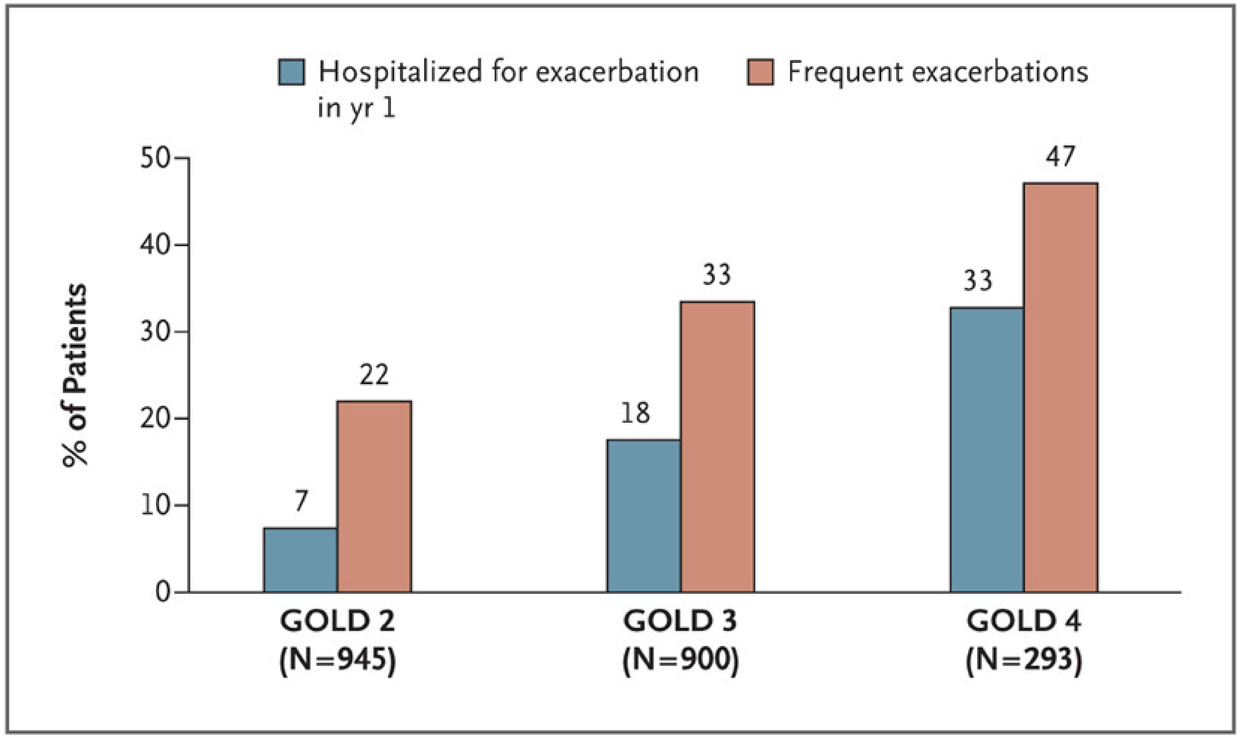

Never smoked
or not
susceptible
to smoke
Smoked
regularly and
susceptible to
its effects
Stopped
at 45
Stopped at 65
Disability
Death
100
75
50
25
0
25
50
75
FEV1 (% of value at age 25)
Age (years)

Variability of COPD and Exacerbations

- COPD has heterogeneity in presentation and progression
- Exacerbations drive cost in COPD care
- Identifying patients at risk of exacerbation and mediating that risk is key in COPD care

Progression of COPD

- As COPD progresses, exacerbations increase
- However, there is a “high exacerbation” phenotype in people even with mild COPD



Hurst et al., NEJM 2010; 363: 1128-1138.

relax tight muscles in airways and

ProAir® Digihaler™
117 mcg
albuterol sulfate
123 A

ProAir® HFA
100 mcg
albuterol sulfate
123
A G

ProAir RespiClick®
117 mcg
albuterol sulfate inhalation powder
123 A

Proventil® HFA
120 mcg
albuterol sulfate
123
A

Ventolin® HFA
90 mcg
albuterol sulfate
123
A G

Xopenex HFA®
59 mcg
levalbuterol tartrate
A G

Arcapta™ Neohaler™
75 mcg
indacaterol inhalation powder
C

Serevent® Diskus®
50 mcg
salmeterol xinafoate inhalation powder
123 A C

Striverdi® Respimat®
2.5 mcg
olodaterol hydrochloride
123 C

INHALED CORTICOSTEROIDS
reduce and prevent swelling of airway tissue; they do not relieve sudden symptoms of coughing, wheezing or shortness of breath

Alvesco® HFA
80, 160 mcg
ciclesonide
123 A

ArmonAir® Digihaler™
55, 113, 232 mcg
fluticasone propionate inhalation powder
123 A

ArmonAir® RespiClick®
55, 113, 232 mcg
fluticasone propionate inhalation powder
123 A

Arnuity® Ellipta®
50, 100, 200 mcg
fluticasone furoate inhalation powder
123
A

Asmanex® HFA
100, 200 mcg
mometasone furoate
123 A

Asmanex® Twisthaler®
110, 220 mcg
mometasone furoate inhalation powder
123 A

Flovent® Diskus®
50, 100, 250 mcg
fluticasone propionate inhalation powder
123 A

Flovent® HFA
44, 110, 220 mcg
fluticasone propionate
123 A

Pulmicort Flexhaler®
90, 180 mcg
budesonide inhalation powder
123 A

QVAR® Redihaler™
40, 80 mcg
beclomethasone dipropionate
123 A

COMBINATION MEDICATIONS
contain both inhaled corticosteroid and long-acting beta$_2$-agonist (LABA)

Advair Diskus®
100/50, 250/50, 500/50 mcg
fluticasone propionate and salmeterol inhalation powder
123 A C G

Advair® HFA
45/21, 115/21, 230/21 mcg
fluticasone propionate and salmeterol xinafoate
123
A G

AirDuo® Digihaler™
55/14, 113/14, 232/14 mcg
fluticasone propionate and salmeterol inhalation powder
123
A

AirDuo® RespiClick®
55/14, 113/14, 232/14 mcg
fluticasone propionate and salmeterol inhalation powder
123
A G

Breo® Ellipta®
100/25, 200/25 mcg
fluticasone furoate and vilanterol inhalation powder
123
A C

Dulera®
100/5, 200/5 mcg
mometasone furoate and formoterol fumarate dihydrate
123 A

Symbicort®
80/4.5, 160/4.5 mcg
budesonide and formoterol fumarate dihydrate
123 A C

Wixela™ Inhub™
100/50, 250/50, 500/50 mcg
fluticasone propionate and salmeterol xinafoate (approved generic of Advair Diskus)
123 A C

contain both long-acting beta$_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA)

Anoro® Ellipta®
62.5/25 mcg
umeclidinium and vilanterol inhalation powder
123 C

Bevespi Aerosphere®
9/4.8 mcg
glycopyrrolate and formoterol fumarate
123 C

Stiolto™ Respimat®
2.5/2.5 mcg
tiotropium bromide and olodaterol
123 C

Utibron™ Neohaler®
27.5/15.6 mcg
indacaterol and glycopyrrolate inhalation powder
C

contains inhaled corticosteroid, long-acting beta$_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA)

Trelegy® Ellipta®
100/62.5/25 mcg
fluticasone furoate, umeclidinium and vilanterol inhalation powder
123 C

MUSCARINIC ANTAGONIST (ANTICHOLINERGIC)
relieve cough, sputum production, wheeze and chest tightness associated with chronic lung diseases

Short-acting

Atrovent® HFA
17 mcg
ipratropium bromide
123 C

Long-acting

Incruse® Ellipta®
62.5 mcg
umeclidinium inhalation powder
123 C

Seebri™ Neohaler®
15.6 mcg
glycopyrrolate inhalation powder
C

Spiriva® HandiHaler®
18 mcg
tiotropium bromide inhalation powder
C

Spiriva® Respimat®
1.25, 2.5 mcg
tiotropium bromide
123 A C

Tudorza™ Pressair™
400 mcg
aclidinium bromide inhalation powder
123 C

COMBINATION
contains muscarinic antagonist and beta$_2$-agonist

Short-acting

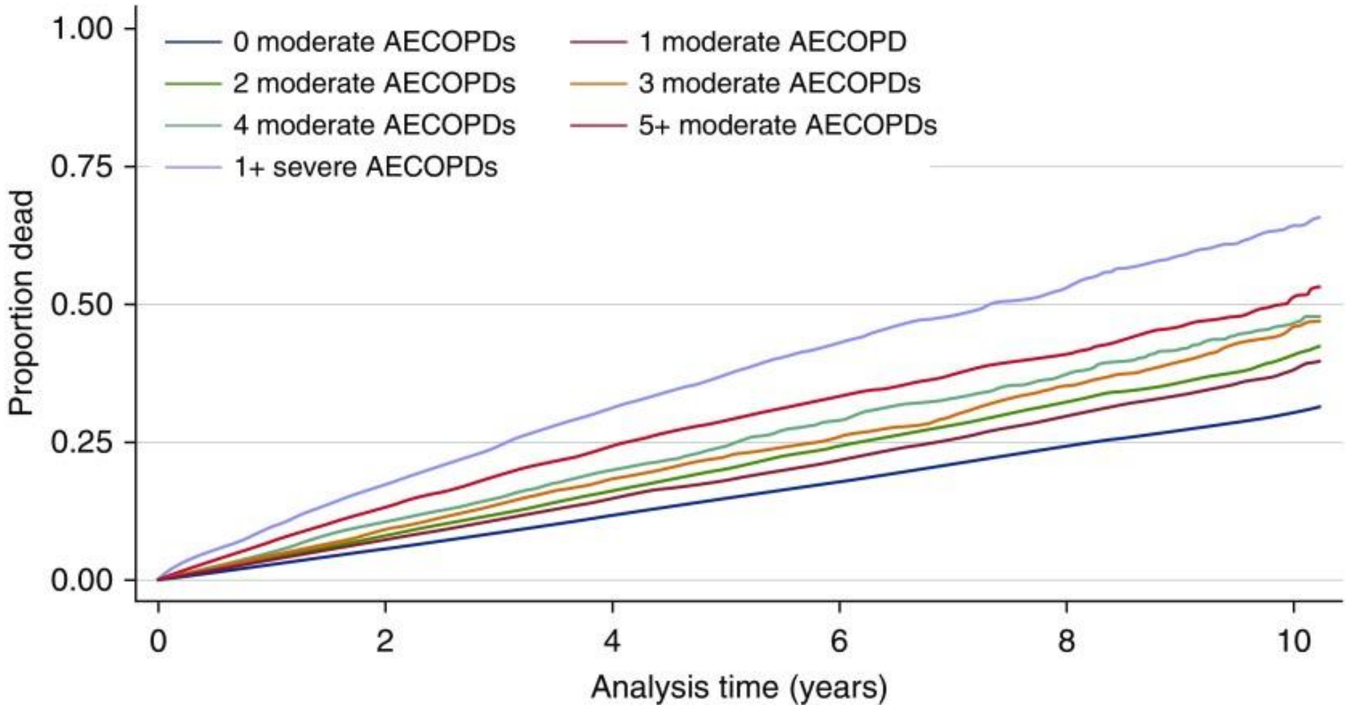
Combivent® Respimat®
20/100 mcg
ipratropium bromide and albuterol
123 C

Long-acting

Duaklir® Pressair®
400, 12 mcg
aclidinium bromide and formoterol fumarate dihydrate
123 C

Exacerbations Affect Future Outcomes

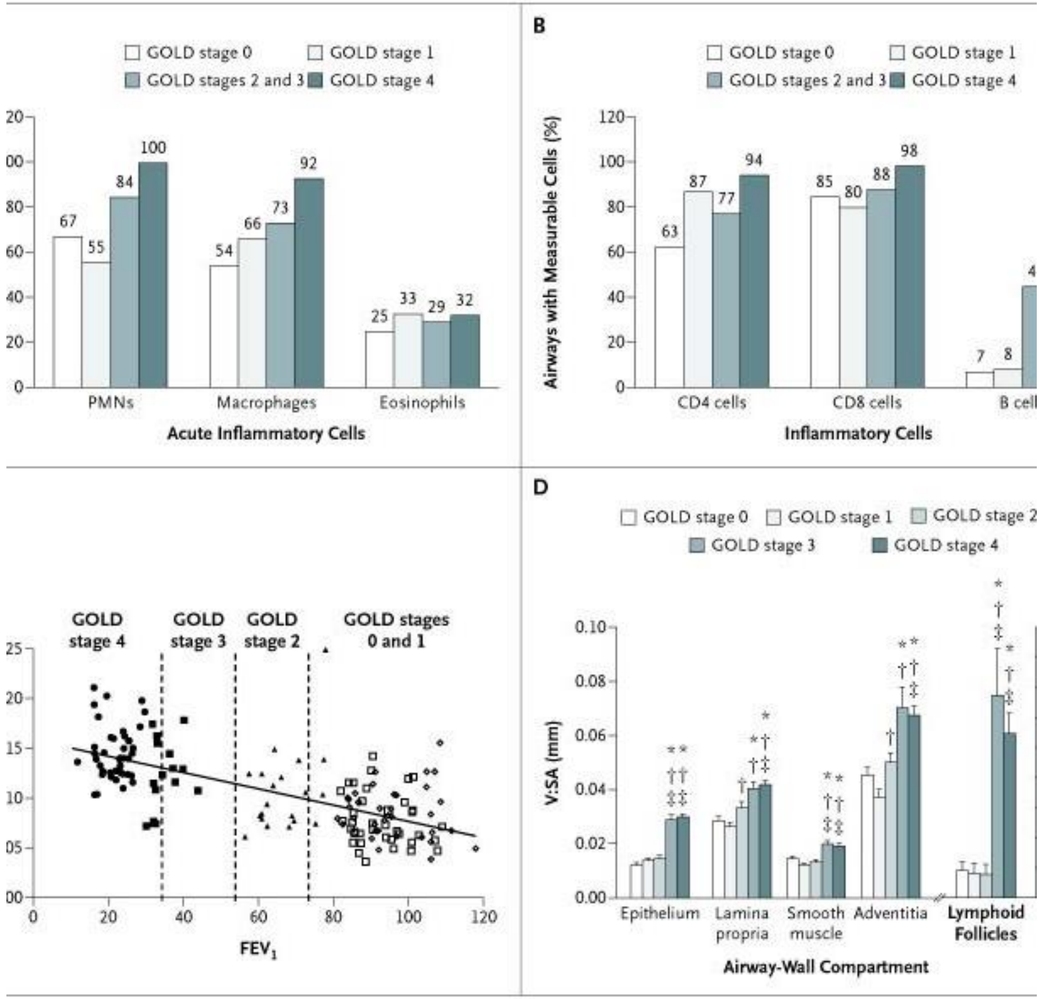
- COPD exacerbations predict probability of future exacerbations
- Clear effect seen on exacerbations and mortality
- Biomarkers that could identify susceptibility to exacerbation would be helpful



Rothnie KJ, et al.. Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice-based Population with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018 Aug 15;198(4):464-471.

Eosinophils Known to Have a Role

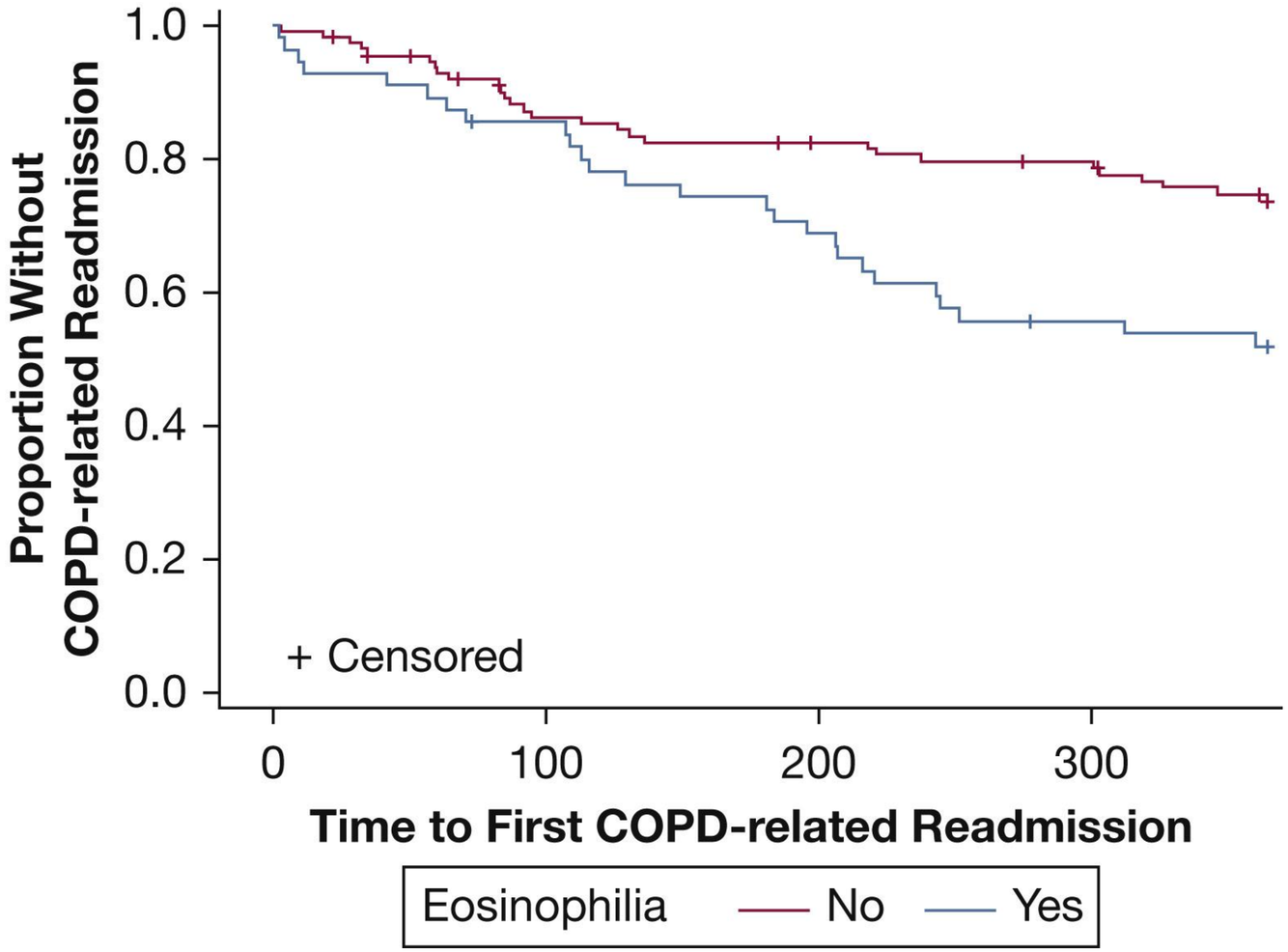
- Hogg et al. studied surgically resected lung tissue of COPD patients to better understand small airway obstruction
- Noted that eosinophils seen in the airway of COPD patients, across all GOLD stages



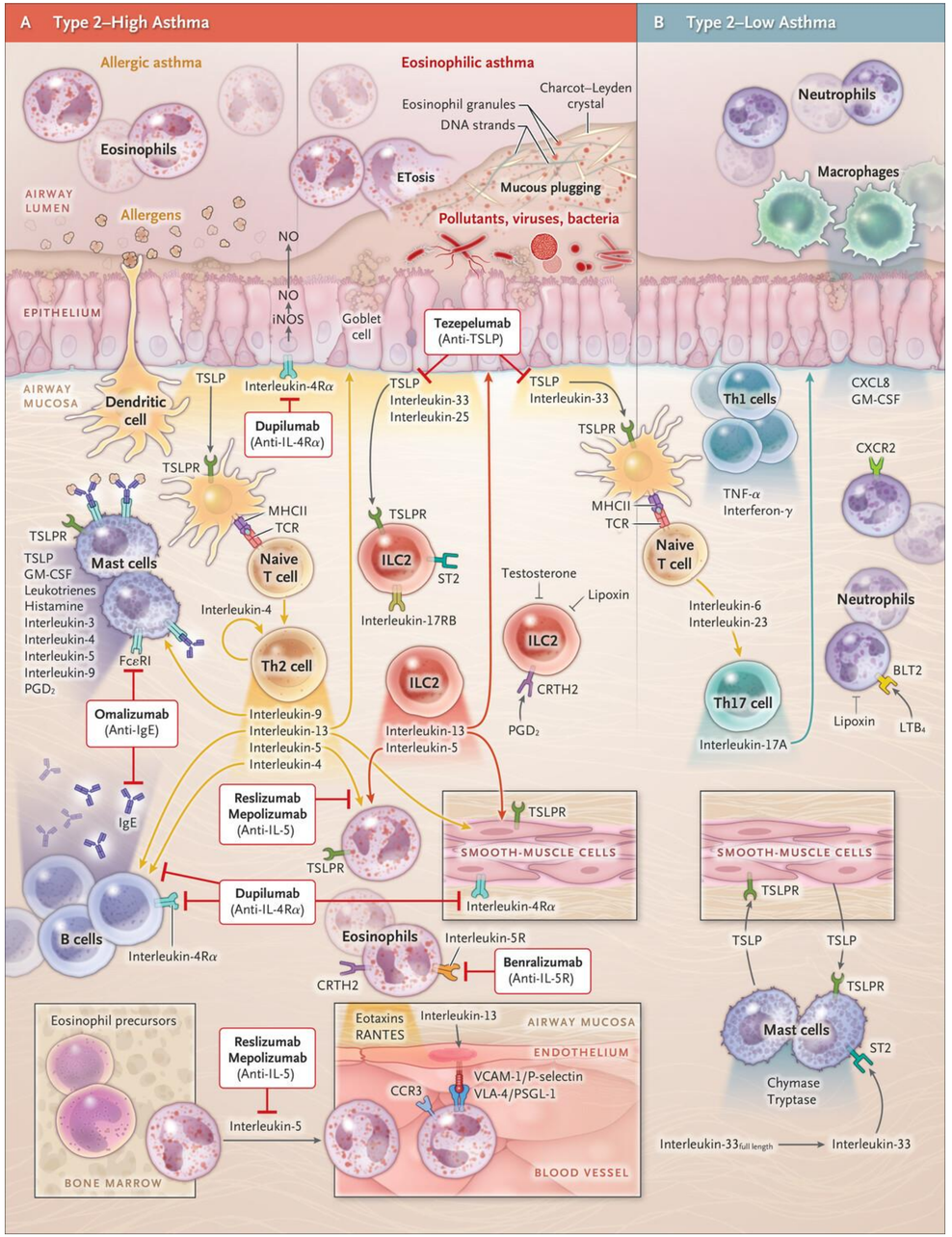
N Engl J Med 2004;350:2645-2653

Eosinophils Associated with Exacerbations

- Couillard et al. investigated outcomes of severe COPD exacerbations in patients with eosinophilia
- Eosinophils associated with increased risk of 12-month COPD associated readmission, all cause readmission, and shorter time to first COPD-related readmission
- Eosinophils reflect readmission rates



CHEST 2017; 151(2), 366 - 373

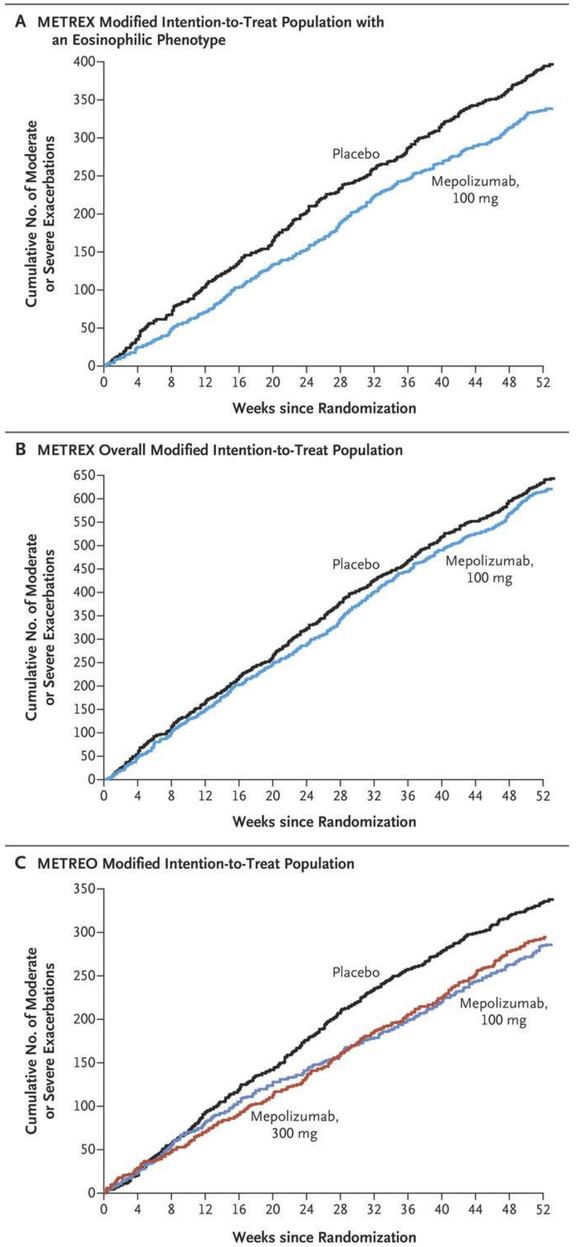


N Engl J Med 2022;386:157-171

Mepolizumab

- COPD with an eosinophilic phenotype
- Two separate trials- METREX and METREO
- METREX- 100 mg dose, patients not initially selected by eosinophil count though subgroup with eosinophilia was examined
- METREO- 100 mg and 300 mg dose, all patients had eosinophil level of 150 per cubic mm at screening or 300 over last year
- End point- rate of moderate or severe exacerbations

N Engl J Med 2022;386:157-171


A METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype
Cumulative No. of Moderate or Severe Exacerbations
Placebo
Mepolizumab, 100 mg
Weeks since Randomization
B METREX Overall Modified Intention-to-Treat Population
Cumulative No. of Moderate or Severe Exacerbations
Placebo
Mepolizumab, 100 mg
Weeks since Randomization
C METREO Modified Intention-to-Treat Population
Cumulative No. of Moderate or Severe Exacerbations
Placebo
Mepolizumab, 100 mg
Mepolizumab, 300 mg
Weeks since Randomization

FDA Advisory Committee

- Voted against approval of mepolizumab for treatment of COPD- 2018
- Questioned efficacy, variables about patient history (were they asthmatics), and lack of consensus definition of eosinophil COPD
- No safety concerns

Benralizumab

- GALATHEA and TERRANOVA trials
- Enrolled COPD patients with frequent exacerbations to receive benralizumab in GALATHEA (30 or 100 mg) or TERRANOVA (10, 30, or 100 mg)
- Assessed annualized COPD exacerbation rate ratio at week 56 vs. placebo
- No benefit seen as add on to standard therapy vs. placebo

Dupilumab

- BOREAS trial
- Patients who met eligibility criteria assigned 300 mg dupilumab or placebo once every 2 weeks for 52 weeks
- Primary endpoint: Annualized rate of moderate or severe exacerbations of COPD
- Secondary endpoints: Changes in prebronchodilator FEV1 and scores on St. George's Respiratory Questionnaire and Evaluating Respiratory Symptoms in COPD (E-RS-COPD)

N Engl J Med 2023;389:205-214

Table 1. Selected Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N = 471)	Dupilumab (N = 468)	Total (N = 939)
Age — yr	65.2±8.1	65.0±8.0	65.1±8.1
Male sex — no. (%)	322 (68.4)	298 (63.7)	620 (66.0)
Race or ethnic group — no. (%)†			
White	397 (84.3)	393 (84.0)	790 (84.1)
Black	2 (0.4)	3 (0.6)	5 (0.5)
Asian	67 (14.2)	67 (14.3)	134 (14.3)
American Indian or Alaska Native	4 (0.8)	3 (0.6)	7 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.1)
Multiple	0	2 (0.4)	2 (0.2)
Hispanic or Latino ethnic group — no. (%)†			
Hispanic or Latino	129 (27.4)	132 (28.2)	261 (27.8)
Non-Hispanic or non-Latino	342 (72.6)	335 (71.6)	677 (72.1)
Unknown	0	1 (0.2)	1 (0.1)
Smoking status — no. (%)			
Former smoker	323 (68.6)	334 (71.4)	657 (70.0)
Current smoker	148 (31.4)	134 (28.6)	282 (30.0)
Smoking history — pack-yr‡	41.4±24.4	39.6±22.3	40.5±23.4
Body-mass index§	27.6±5.7	27.5±5.4	27.6±5.6
Background medication — no. (%)¶			
Triple therapy‖	461 (97.9)	455 (97.2)	916 (97.6)
Inhaled high-dose glucocorticoid	126 (26.8)	131 (28.0)	257 (27.4)
Biomarkers of type 2 inflammation			
Blood eosinophil count at randomization			
Mean — per μl	408±331	394±261	401±298
Median (interquartile range) — per μl	330 (230–460)	340 (250–460)	340 (240–460)
Postbronchodilator $F_{E}NO$ — ppb**	23.51±22.00	25.18±22.79	24.33±22.40
Distribution — no./total no. (%)			
≥20 ppb	188/442 (42.5)	195/433 (45.0)	383/875 (43.8)
<20 ppb	254/442 (57.5)	238/433 (55.0)	492/875 (56.2)
No. of moderate or severe COPD exacerbations in previous yr	2.3±1.0	2.2±1.1	2.3±1.0
Lung function			
Prebronchodilator FEV_1 — liters	1.32±0.46	1.28±0.45	1.30±0.46
Postbronchodilator FEV_1			
Volume — liters	1.41±0.47	1.39±0.47	1.40±0.47
Percent of predicted value	50.6±13.0	50.6±13.3	50.6±13.1
Postbronchodilator ratio of FEV_1 to FVC	0.5±0.1	0.5±0.1	0.5±0.1
SGRQ total score††	48.4±17.8	48.4±17.0	48.4±17.4
E-RS–COPD total score‡‡	13.0±6.9	12.9±7.2	12.9±7.1

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, $F_{E}NO$ fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, and ppb parts per billion.

† Race and ethnic group were reported by the patient.

‡ This analysis included 377 patients in the placebo group, 389 patients in the dupilumab group, and 766 patients overall.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ Patients could have been included in both medication categories.

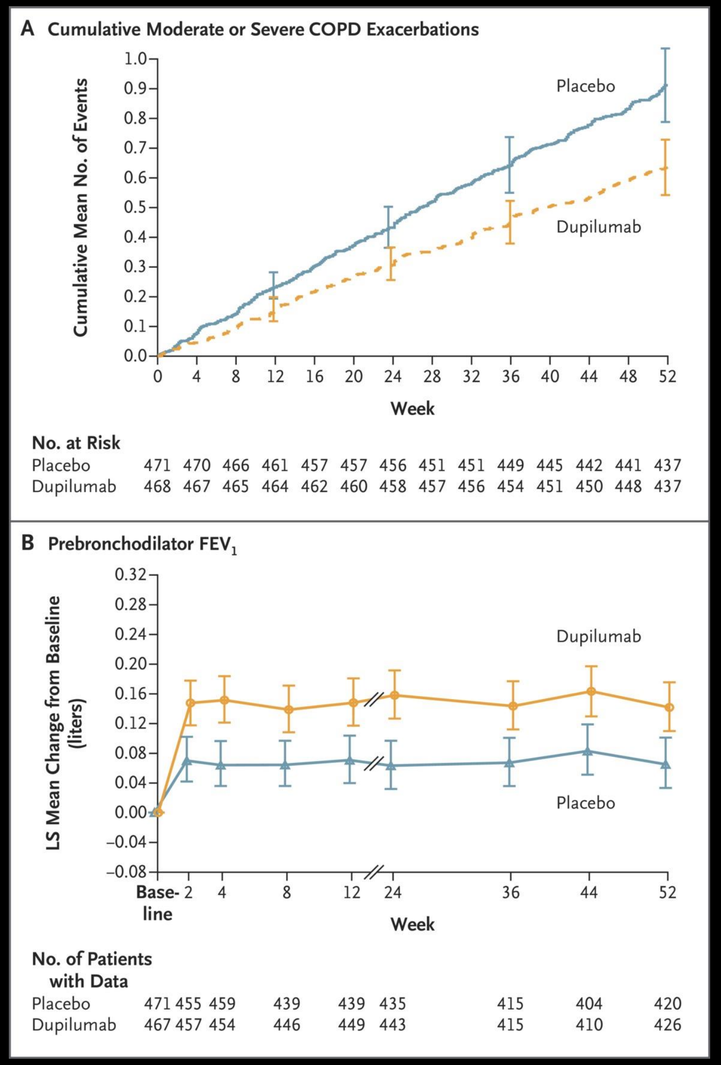
‖ Patients were receiving triple therapy consisting of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA) unless inhaled glucocorticoid was contraindicated, in which case therapy included only LAMA and LABA.

** This analysis included 442 patients in the placebo group, 433 patients in the dupilumab group, and 875 patients overall.

†† The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. Total scores range from 0 to 100, with lower scores indicating a better quality of life; the minimum clinically important difference is 4 points.[17]

‡‡ The Evaluating Respiratory Symptoms in COPD (E-RS–COPD) instrument is an 11-item derivative tool used to measure the effect of a treatment on the severity of respiratory symptoms in patients with stable COPD. Total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms.

Moderate or Severe COPD Exacerbations and Change in Prebronchodilator FEV1 over Time.



Bhatt SP et al. N Engl J Med2023;389:205-214

The NEW ENGLAND JOURNAL of MEDICINE

End Points Corrected for Multiplicity (Intention-to-Treat Population).

Table 2. End Points Corrected for Multiplicity (Intention-to-Treat Population).*

End Point	Placebo (N=471)	Dupilumab (N=468)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.10 (0.93 to 1.30)	0.78 (0.64 to 0.93)	
Rate ratio vs. placebo (95% CI)	—	0.70 (0.58 to 0.86)	<0.001
Secondary and other end points			
Change in prebronchodilator FEV_1 from baseline to wk 12			
Least-squares mean change (95% CI) — liters	0.077 (0.042 to 0.112)	0.160 (0.126 to 0.195)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.083 (0.042 to 0.125)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 52			
Least-squares mean change (95% CI) — liters	0.070 (0.033 to 0.107)	0.153 (0.116 to 0.189)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.083 (0.038 to 0.128)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 12 among patients with a baseline F_ENO ≥20 ppb			
Least-squares mean change (95% CI) — liters	0.108 (0.038 to 0.177)	0.232 (0.164 to 0.299)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.124 (0.045 to 0.203)	0.002
Change in prebronchodilator FEV_1 from baseline to wk 52 among patients with a baseline F_ENO ≥20 ppb			
Least-squares mean change (95% CI) — liters	0.120 (0.047 to 0.192)	0.247 (0.176 to 0.318)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.127 (0.042 to 0.212)	0.003
Change in SGRQ total score from baseline to wk 52			
Least-squares mean change (95% CI)	−6.4 (−8.0 to −4.8)	−9.7 (−11.3 to −8.1)	
Least-squares mean difference vs. placebo (95% CI)	—	−3.4 (−5.5 to −1.3)	0.002
SGRQ total score improvement ≥4 points at wk 52			
Percentage of patients (95% CI)	43.1 (38.6 to 47.7)	51.5 (46.9 to 56.1)	
Odds ratio vs. placebo (95% CI)	—	1.4 (1.1 to 1.9)	0.009
Change in E-RS–COPD total score from baseline to wk 52			
Least-squares mean (95% CI)	−1.6 (−2.1 to −1.1)	−2.7 (−3.2 to −2.2)	
Least-squares mean difference vs. placebo (95% CI)	—	−1.1 (−1.8 to −0.4)	0.001
Annualized rate of moderate or severe exacerbations of COPD among patients with a baseline F_ENO ≥20 ppb			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.12 (0.83 to 1.50)	0.70 (0.51 to 0.96)	
Rate ratio vs. placebo (95% CI)	—	0.62 (0.45 to 0.87)	0.005

* End points are listed in the order in which they were hierarchically tested.

Bhatt SP et al. N Engl J Med2023;389:205-214

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Conclusions

- Among patients with COPD who had type 2 inflammation as indicated by elevated blood eosinophil counts, those who received dupilumab had fewer exacerbations, better lung function and quality of life, and less severe respiratory symptoms than those who received placebo.

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Dupilumab- NOTUS Trial

- Confirmatory second phase 3 trial
- Dupilumab 300 mg or placebo every 2 weeks
- Primary end point: Rate of annualized exacerbations
- Secondary end points: changes from baseline prebronchodilatory FEV1 at 12 and 52 weeks, and in SGRQ in week 52

NEJM 390(24): 2274-2283

Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N = 465)	Dupilumab (N = 470)	Total (N = 935)
Age — yr	64.9±8.5	65.2±8.1	65.0±8.3
Male sex — no. (%)	312 (67.1)	320 (68.1)	632 (67.6)
Race or ethnic group — no. (%)†			
White	416 (89.5)	422 (89.8)	838 (89.6)
Black	8 (1.7)	4 (0.9)	12 (1.3)
Asian	3 (0.6)	7 (1.5)	10 (1.1)
American Indian or Alaska Native	26 (5.6)	22 (4.7)	48 (5.1)
Native Hawaiian or Pacific Islander	0	1 (0.2)	1 (0.1)
Multiple	8 (1.7)	12 (2.6)	20 (2.1)
Not reported	4 (0.9)	2 (0.4)	6 (0.6)
Hispanic or Latino ethnic group — no. (%)			
Hispanic or Latino	149 (32.0)	151 (32.1)	300 (32.1)
Non-Hispanic or non-Latino	308 (66.2)	315 (67.0)	623 (66.6)
Unknown	2 (0.4)	0	2 (0.2)
Not reported	6 (1.3)	4 (0.9)	10 (1.1)
Smoking status — no. (%)			
Former smoker	331 (71.2)	328 (69.8)	659 (70.5)
Current smoker	134 (28.8)	142 (30.2)	276 (29.5)
Smoking history — pack-yr	42.1±30.2	38.6±23.7	40.3±27.2
Emphysema — no. (%)‡	150 (32.3)	134 (28.5)	284 (30.4)
Body-mass index§	27.8±5.6	28.1±5.3	27.9±5.4
Background medication — no. (%)			
Inhaled triple therapy¶	458 (98.5)	466 (99.1)	924 (98.8)
Inhaled high-dose glucocorticoid	134 (28.8)	127 (27.0)	261 (27.9)
Biomarkers of type 2 inflammation			
Blood eosinophil count at randomization — per μl			
Mean	402±314	412±357	407±336
Median (interquartile range)	330 (220–470)	340 (230–460)	330 (220–460)
Category at randomization — no. (%)			
<300 cells/μl	188/465 (40.4)	184/469 (39.2)	372/934 (39.8)
≥300 cells/μl	277/469 (59.6)	285/469 (60.8)	562/934 (60.1)
Postbronchodilator FᴇNO — ppb			
Mean	24.4±23.4	24.8±28.3	24.6±26.0
Median (interquartile range)	16 (10–30)	16 (10–27)	16 (10–29)
FᴇNO — no./total no. (%)			
<20 ppb	240/423 (56.7)	257/429 (59.9)	497/852 (58.3)
≥20 ppb	183/423 (43.3)	172/429 (40.1)	355/852 (41.7)
No. of moderate or severe COPD exacerbations in previous yr	2.1±0.7	2.2±1.0	2.1±0.9
Lung function			
Prebronchodilator FEV_1 — liters	1.38±0.50	1.35±0.49	1.36±0.50
Postbronchodilator FEV_1			
Volume — liters	1.46±0.50	1.43±0.49	1.45±0.49
Percent of predicted value	50.7±12.6	49.5±12.6	50.1±12.6
Postbronchodilator FEV_1:FVC	0.5±0.1	0.5±0.1	0.5±0.1
SGRQ total score‖	51.1±16.5	52.0±17.5	51.5±17.0
E-RS–COPD total score**	13.3±7.2	13.4±6.7	13.3±7.0

* Plus–minus values are means ±SD. The intention-to-treat population included all patients who underwent randomization, with data analyzed according to group assignment. Percentages may not total 100 because of rounding. Additional data on baseline characteristics and characteristics of patients who reached the 52-week assessments (721 patients) are provided in the Supplementary Appendix. COPD denotes chronic obstructive pulmonary disease, FᴇNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, and ppb parts per billion.

† Race and ethnic group were reported by the patient.

‡ Emphysema was reported by the investigator.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ Patients were receiving triple therapy consisting of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β2-agonist (LABA) unless inhaled glucocorticoid was contraindicated, in which case therapy included only LAMA and LABA.

‖ The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. Total scores range from 0 to 100, with lower scores indicating a better quality of life; the minimum clinically important difference is 4 points.

** The Evaluating Respiratory Symptoms in COPD (E-RS–COPD) instrument is an 11-item derivative tool used to measure the effect of a treatment on the severity of respiratory symptoms in patients with stable COPD. Total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms.

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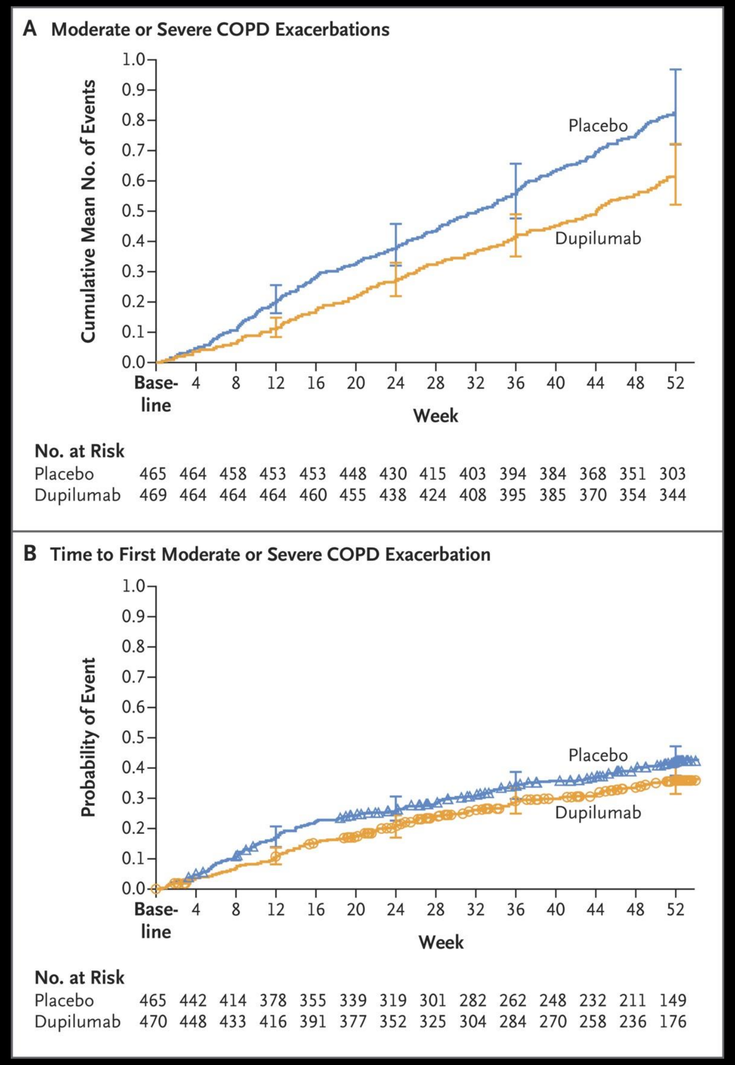
Cumulative Moderate or Severe COPD Exacerbations and Time to the First Moderate or Severe COPD Exacerbation Event during the 52-Week Trial Period.



Bhatt SP et al. N Engl J Med2024;390:2274-2283

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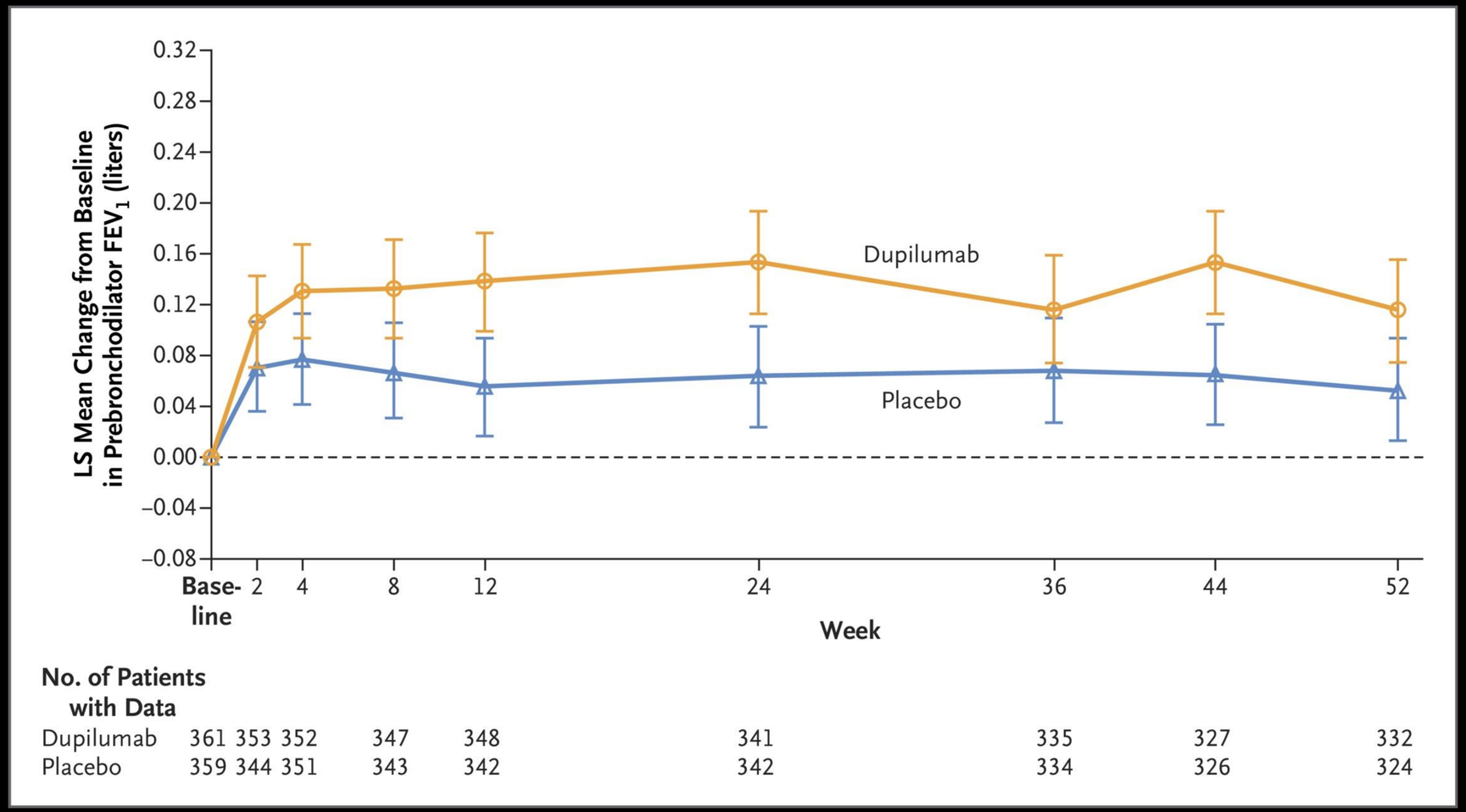
Change in Prebronchodilator FEV1 over Time.



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NOTUS Results

- In patients with COPD and type 2 inflammation (elevated eosinophils), dupilumab was associated with fewer exacerbations and better lung function than placebo
- Dupilumab approved by FDA on September 27, 2024 as add on therapy for COPD with eosinophilic phenotype

Next Directions

- Studies of other agents (IL-5, drugs with other mechanisms)
- Studies of patients with varying eosinophil counts
- More investigation of low inflammation phenotypes

Thank You!