

Obstructive Lung Diseases: Asthma and COPD

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Disclosure of Conflicts of Interest

None.

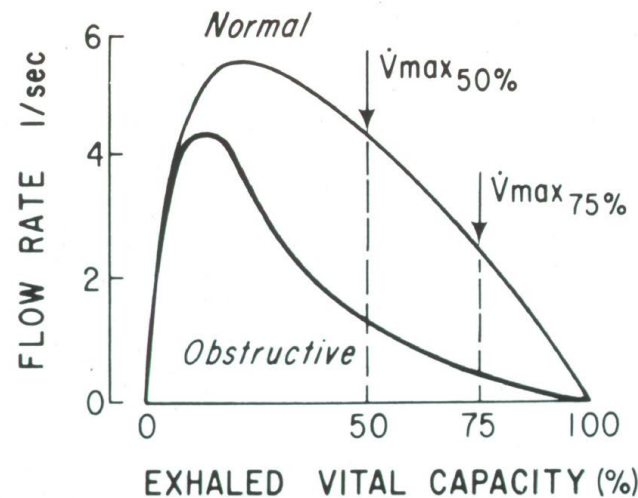
Obstructive Lung Diseases

- Asthma
 - COPD (Chronic Bronchitis and Emphysema)
-
- Bronchiectasis (including cystic fibrosis)
 - Bronchiolitis
 - Upper airway obstruction

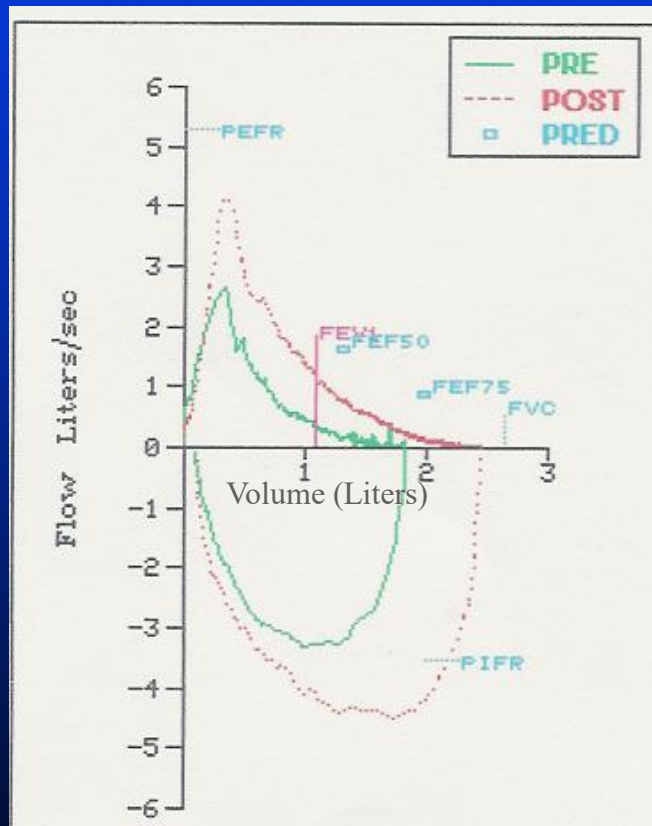
Defining (and Quantifying) an Obstructive Abnormality: Role of Spirometry

- Decreased FEV_1/FVC → Obstructive Defect
- Normal or Increased FEV_1/FVC → No Obstruction

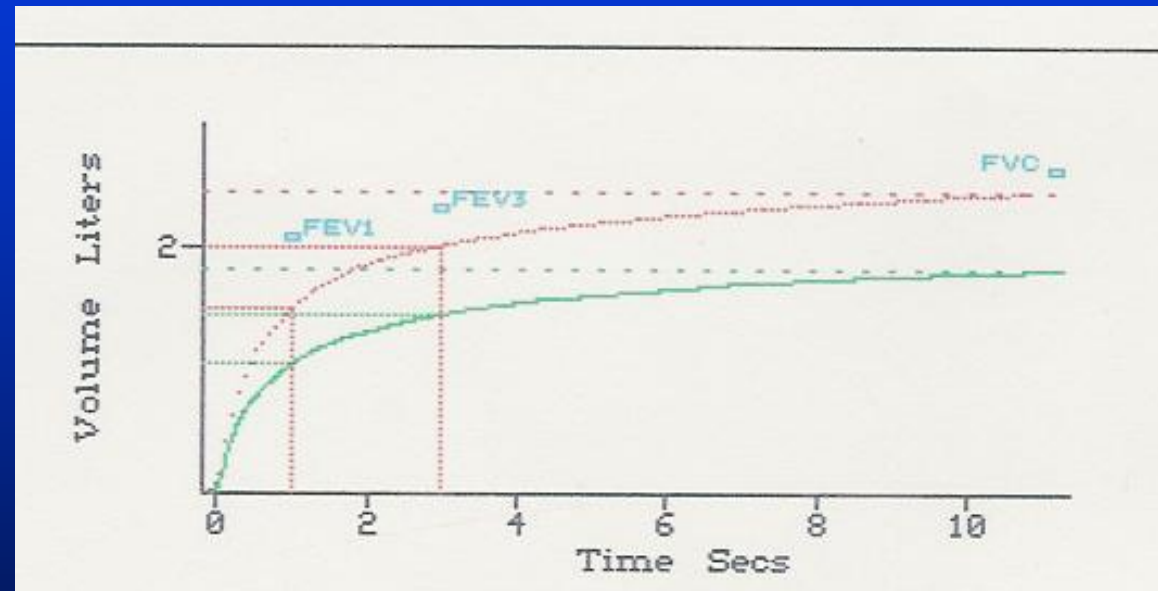
Obstructive Abnormality: Flow-Volume Curve



Pulmonary Function Testing



Flow-Volume Curve



Spirometry (Volume-Time Curve)

Bronchodilator Response

Significant bronchodilator response:

- Increase in FEV_1 of 12% and
- Absolute increase of 200 ml

“Asthmatic response”:

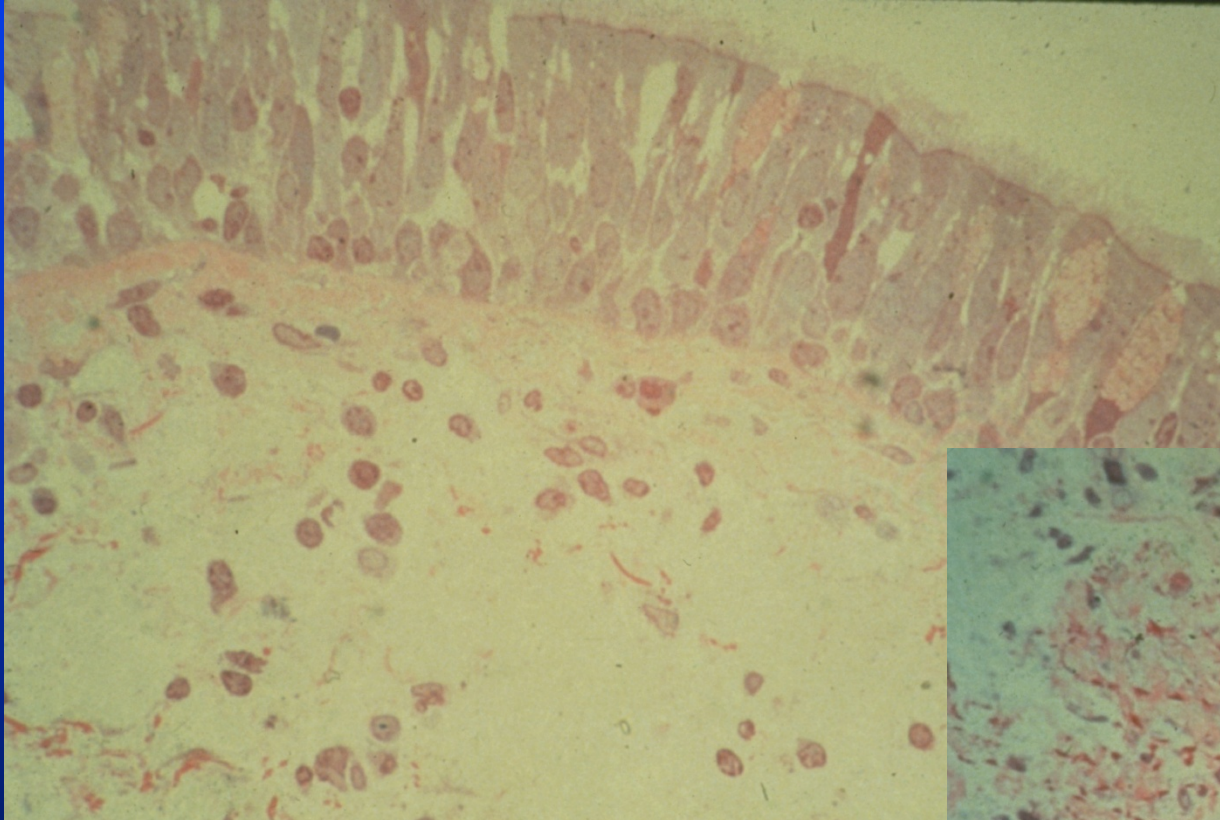
- Variably defined as 15% or 20% increase in FEV_1 following BD

Defining Features of Asthma

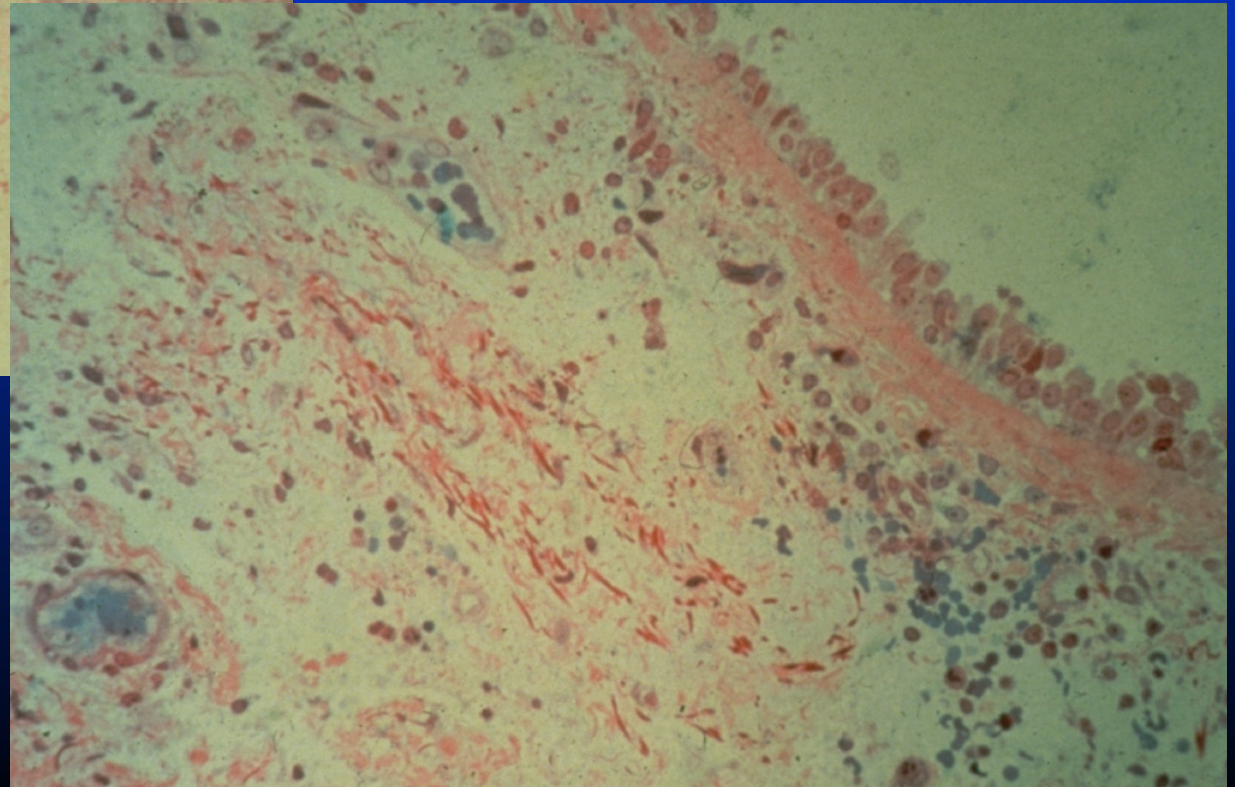
- Reversible airways obstruction;
- Non-specific bronchial hyperresponsiveness; and
- Airway inflammation

Normal

Bronchial Biopsies



Asthmatic



Potential Bio-Markers of Airway Inflammation in Asthma

- Exhaled nitric oxide
- Sputum eosinophilia
- Exhaled breath condensate

Nitrogen
oxide
analyzer



Treatment Approaches

- Allergen avoidance
- Pharmacotherapy
- (Allergen immunotherapy)

Allergic Sensitivity

+

Intense Allergen Exposure



More Severe Asthma

Common Aeroallergens in Asthma

- Animal danders
- Dust mite
- Mold
- Cockroach
- Pollens

Common Aeroallergens

- Animal danders
- Dust mites
- Mold
- Cockroaches
- Pollens

Diagnostic Testing:

Allergy skin tests

Blood tests (RAST)

Modern Therapeutic Paradigm

Controllers:

- Inhaled steroids
- Long-acting inhaled bronchodilators
- Leukotriene blockers
- Biologics: anti-IgE, anti-interleukin 5, anti-interleukin 4R

Quick-Relievers:

- Quick-acting beta-agonist bronchodilators

Staging Asthma Severity

Stage	Daytime Symptoms	Nighttime Symptoms	Lung Function (FEV ₁ or PEFR)
<i>Intermittent</i>	≤2 days/wk	≤2 nights/mo.	≥80
<i>Mild persistent</i>	3-6 days/wk	3-4 nights/mo.	≥80
<i>Moderate persistent</i>	Daily	≥5 nights/mo.	>60 - <80%
<i>Severe persistent</i>	Continual	Frequent	≤60%

Defining Good Asthma Control

Stage	Daytime Symptoms	Nighttime Symptoms	Lung Function (FEV ₁ or PEFR)
<i>Intermittent</i>	≤2 days/wk	≤2 nights/mo.	≥80
<i>Mild persistent</i>	3-6 days/wk	3-4 nights/mo.	≥80
<i>Moderate persistent</i>	Daily	≥5 nights/mo.	>60 - <80%
<i>Severe persistent</i>	Continual	Frequent	≤60%

Assessing Asthma Control

Two “Domains” :

- **Current impairment**
 - Symptoms (daytime, nighttime, and frequency of use of rescue bronchodilator)
 - Exercise limitation
 - Lung function
- **Future risk**
 - More than 1 oral steroid course in last year

Step 1 (Intermittent Asthma)

- Short-acting bronchodilator as needed
- Short-acting bronchodilator prior to exercise

Short-Acting Beta-Agonists

- Albuterol MDI [ProAir, Proventil, Ventolin]
- Albuterol Dry-Powder inhaler [ProAir Respiclick]
- Levalbuterol [Xopenex]
 - (single-isomer of albuterol)

Step 2 (Mild Persistent Asthma)

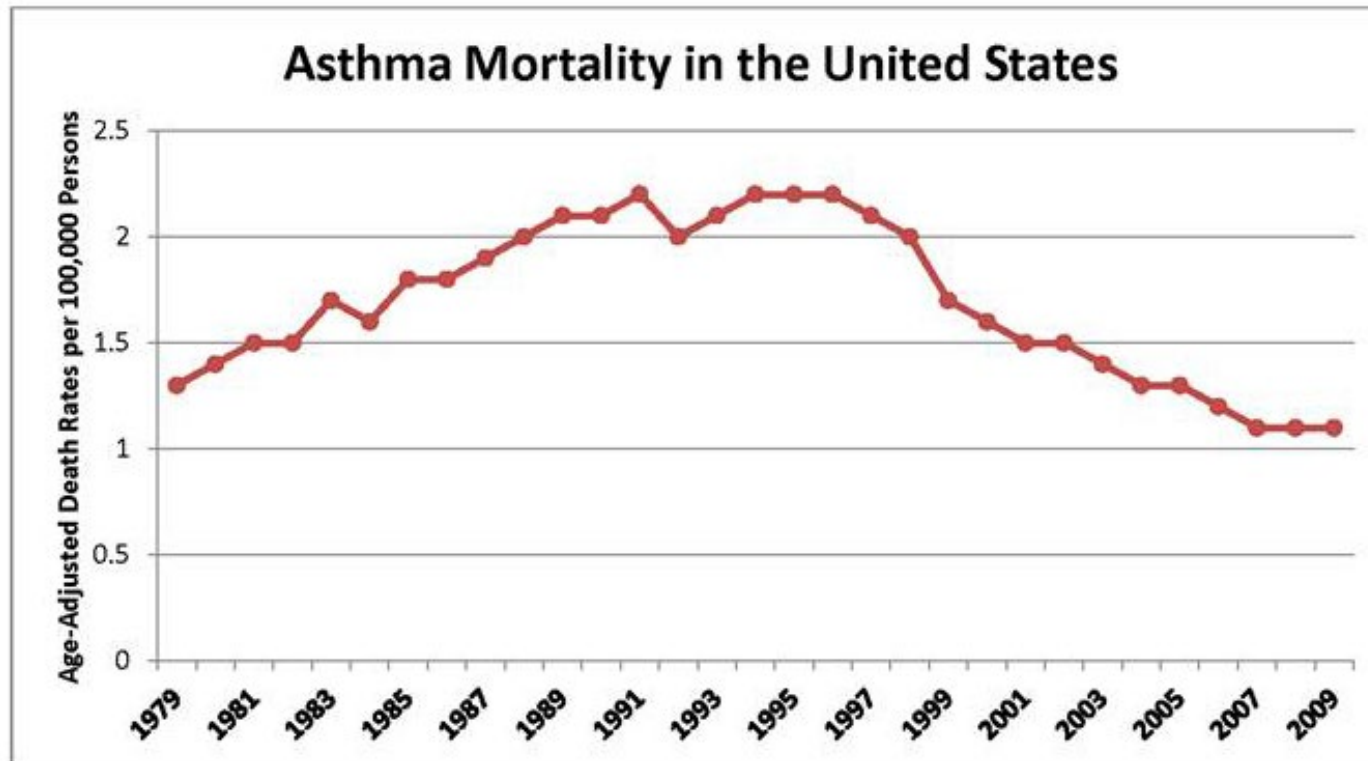
- Preferred: Low-dose inhaled corticosteroid
- Alternatives:
 - Leukotriene receptor antagonists
 - Mast cell stabilizer (cromolyn or nedocromil)
 - Theophylline

Inhaled Steroid Preparations

	<u>mcg/puff</u>
• Budesonide DPI* <i>Pulmicort</i>	90, 180
• Mometasone MDI-HFA* <i>Asmanex</i>	100, 200
• Mometasone DPI* <i>Asmanex Twisthaler</i>	110, 220
• Beclomethasone MDI-HFA* <i>Qvar</i>	40, 80
• Fluticasone MDI-HFA <i>Flovent</i>	44, 110, 220
• Fluticasone DPI <i>Flovent Diskus</i>	50, 100,
250 <i>Armonair Respiclick</i>	
55, 113, 232	
• Fluticasone furoate DPI* <i>Arnuity</i>	100, 200
• Ciclesonide MDI-HFA* <i>Alvesco</i>	80, 160
• Flunisolide MDI-HFA <i>Aerospan</i>	

* category B in pregnancy * approved for once-daily dosing

Trends in Asthma Deaths in U.S.



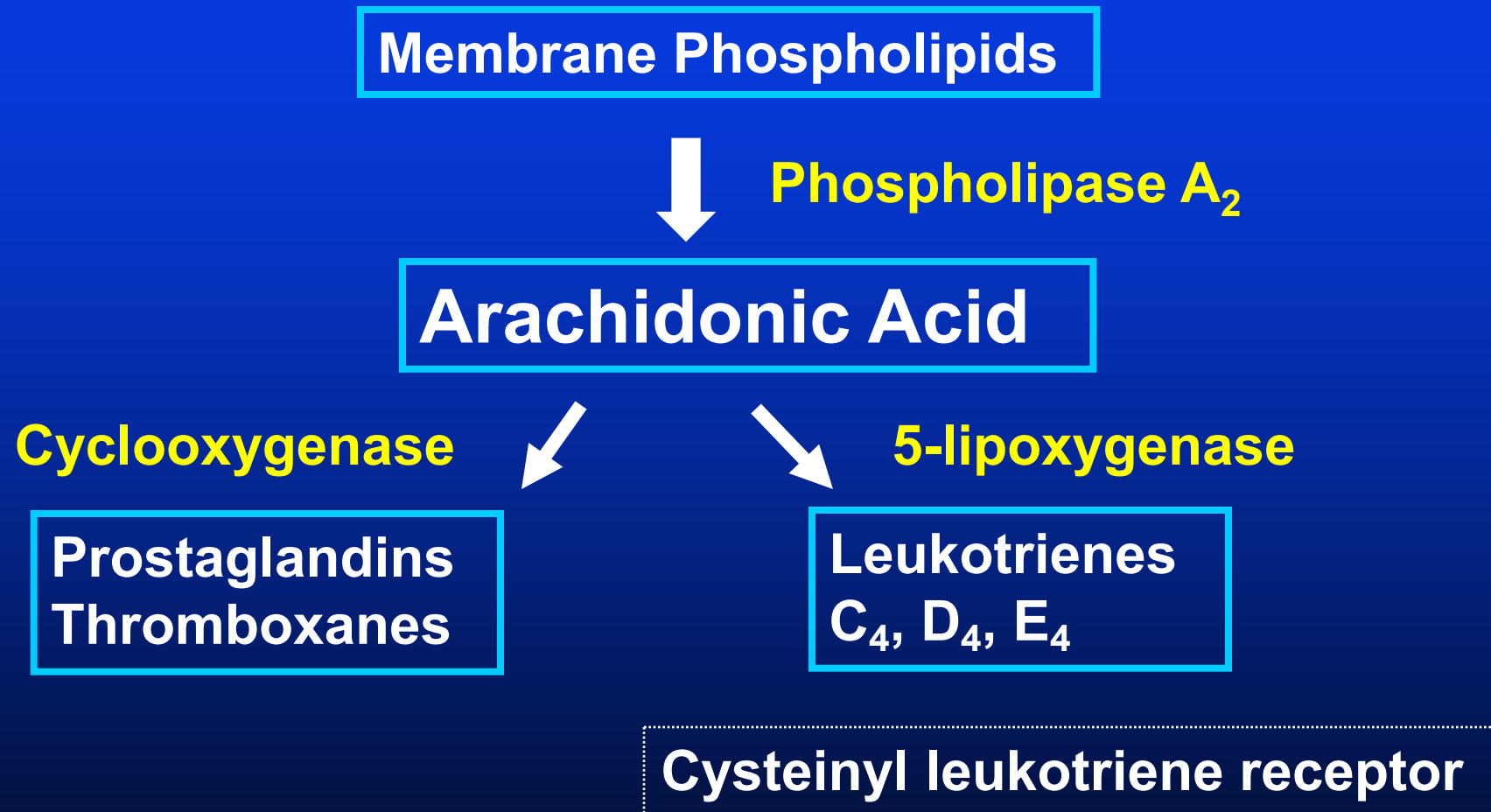
**Trends in
Asthma
Statistics,
Feb. 2010.
American
Lung
Association**



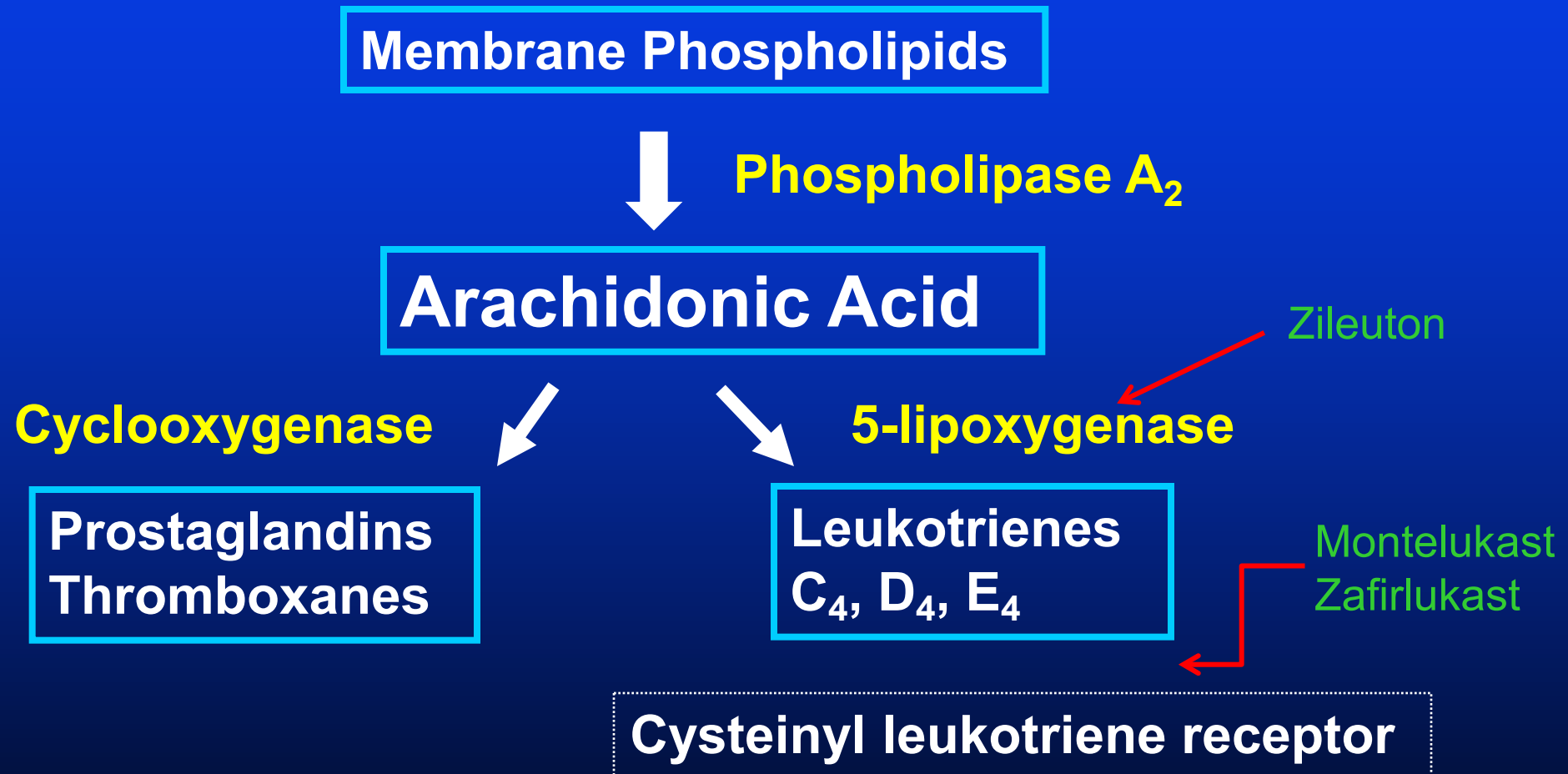
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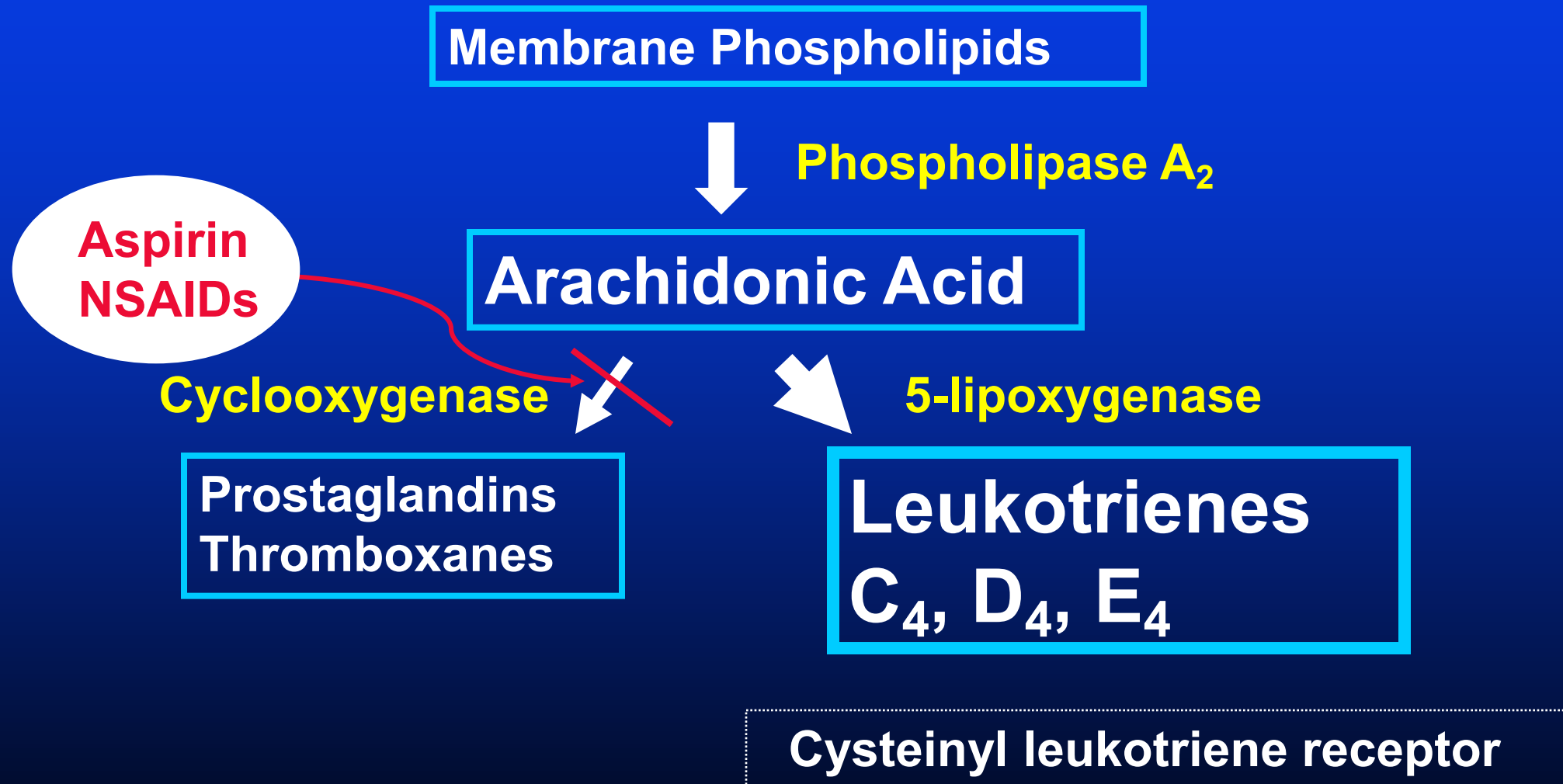
Arachidonic Acid Pathway



Arachidonic Acid Pathway



Arachidonic Acid Pathway



Step 3 (Moderate Persistent Asthma)

Equal weight given to two therapeutic options:

- Add LABA to low dose of ICS
- or -
- Increase the dose to ICS to medium-dose range

FDA-Mandated Trials on the Safety of Inhaled LABAs

- 4 placebo-controlled RCTs of ICS + LABA vs. ICS alone in adults (N = 11,700 each) and 1 in children 4-11 years (N = 6,200)
- Primary end point: composite of hospitalization, intubation, and asthma-related deaths
- 90% power to detect doubling of relative risk
- To begin in 2011, results in 2017



Fluticasone + Salmeterol vs. Fluticasone alone

- Among 11,679 patients randomized to fluticasone (in 3 doses) vs. fluticasone (3 doses) plus salmeterol
- No deaths; only 2 intubations (both in fluticasone alone group); overall no difference in “serious adverse events”
- Fewer severe asthma exacerbations in group treated with fluticasone + salmeterol.

Stempel DA, et al, *NEJM* 2016; 374:1822.

Combination ICS and LABA

Combination	Brand name	Dose per inhalation
Fluticasone + salmeterol	<i>Advair DPI</i> <i>Wixela DPA</i> <i>Advair HFA</i> <i>AirDuo DPI</i>	100/50, 250/50, 500/50 100/50, 250/50, 500/50 44/21, 115/21, 230/21 55/14, 113/14, 232/14
Budesonide + formoterol	<i>Symbicort HFA</i>	80/4.5, 160/4.5
Mometasone + formoterol	<i>Dulera HFA</i>	100/5, 200/5
Fluticasone furoate + Vilanterol	<i>Breo DPI</i>	100/25, 200/25



GINA Guidelines 2019: A Novel Approach to Intermittent and Mild Persistent Asthma

- A “symptom-guided” approach using formoterol + budesonide (*Symbicort*) taken as needed

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D.,
Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D.,
Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B.,
Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci.,
and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

Beasley R, et al. *N Engl J Med*
2019;380:2020-30.



“Novel START” study: Protocol

- 675 patients with intermittent and mild persistent asthma randomized to 52 weeks of therapy with:
 - Albuterol as needed
 - Formoterol/budesonide as needed
 - Twice-daily budesonide with albuterol as needed

Beasley R, et al. *N Engl J Med* 2019;
380:2020-30.



“Novel START” study:

Outcomes

- Significantly fewer exacerbations with formoterol/budesonide (Symbicort) combination used as needed.
 - Lower annualized steroid dose
 - No significant adverse effects
- Better symptom control (ACQ-5 score) with regular budesonide use.

Beasley R, et al. *N Engl J Med* 2019;
380:2020-30.



LABA/ICS As-Needed in Mild Asthma: Potential ~~Disadvantages~~

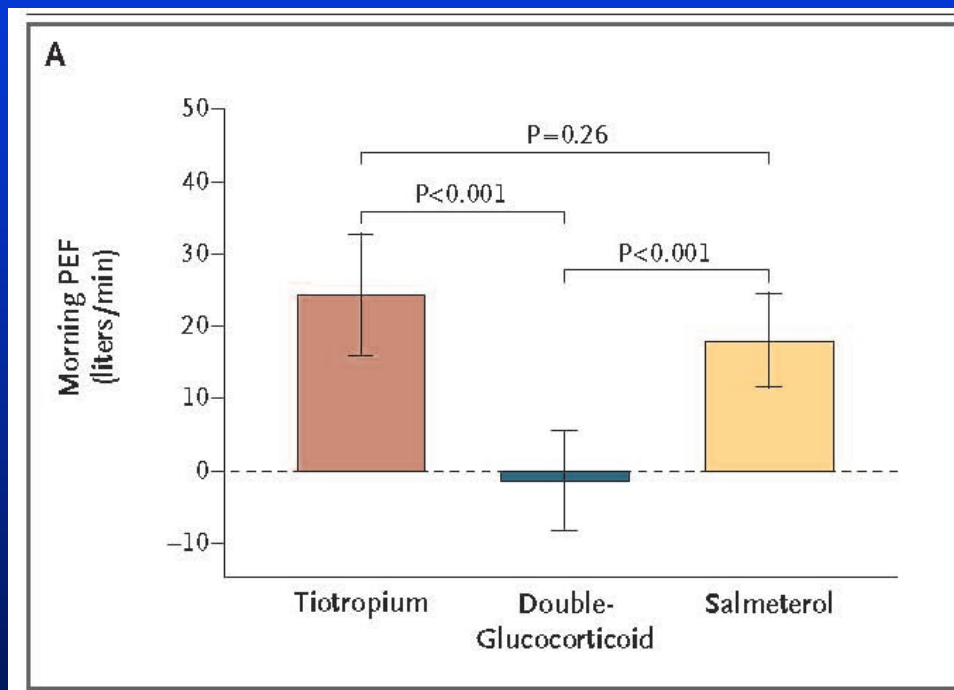
- Cost (compared with albuterol)
- Published data with single branded medication
- Off-label use (not FDA-approved)

Alternative Long-Acting BD: Anti-Cholinergic (Tiotropium)

- 210 subjects with asthma poorly controlled on beclomethasone 160 mcg/day
- Randomly assigned to:
 - Beclomethasone 320 mcg/day
 - Beclo 160 mcg/day + Salmeterol BID
 - Beclo 160 mcg/day + Tiotropium qD

Peters SP, et al (ACRN). *NEJM* 2010; 363:1715-26.

ICS + Tiotropium in Asthma (TALC)



Adding tiotropium to ICS was **non-inferior** to adding salmeterol in all outcomes measured.

Peters SP, et al (ACRN). *NEJM* 2010; 363:1715-26.

Step 4 (Moderate-to-Severe Persistent Asthma)

Recommended: Medium-dose ICS plus LABA

- Alternatives:
Medium-dose ICS plus leukotriene modifier or theophylline

Steps 5 and 6 (Severe Persistent Asthma)

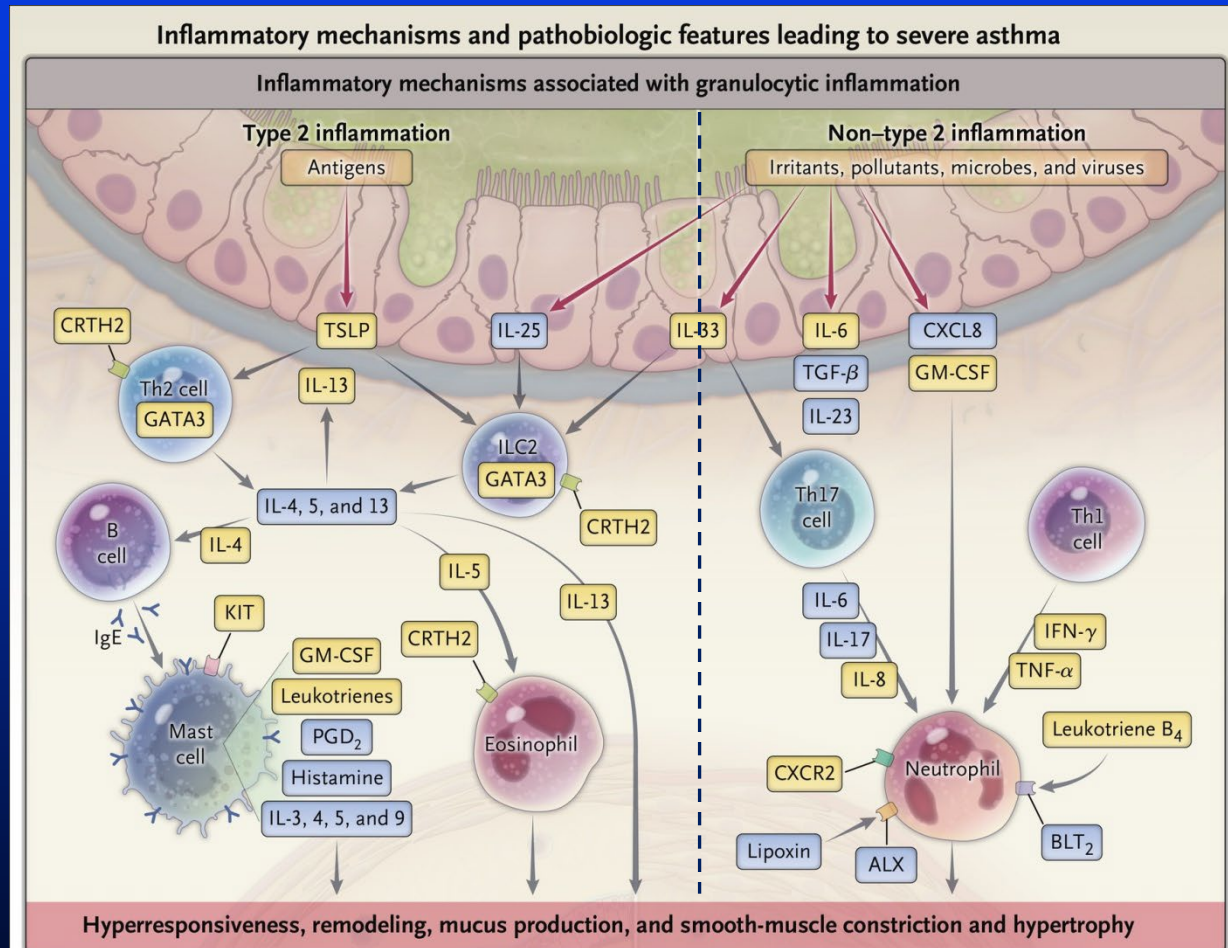
Recommended: High-dose ICS plus LABA

And

Consider omalizumab

(Systemic corticosteroids in Step 6)

Biochemical Pathways in Severe Asthma

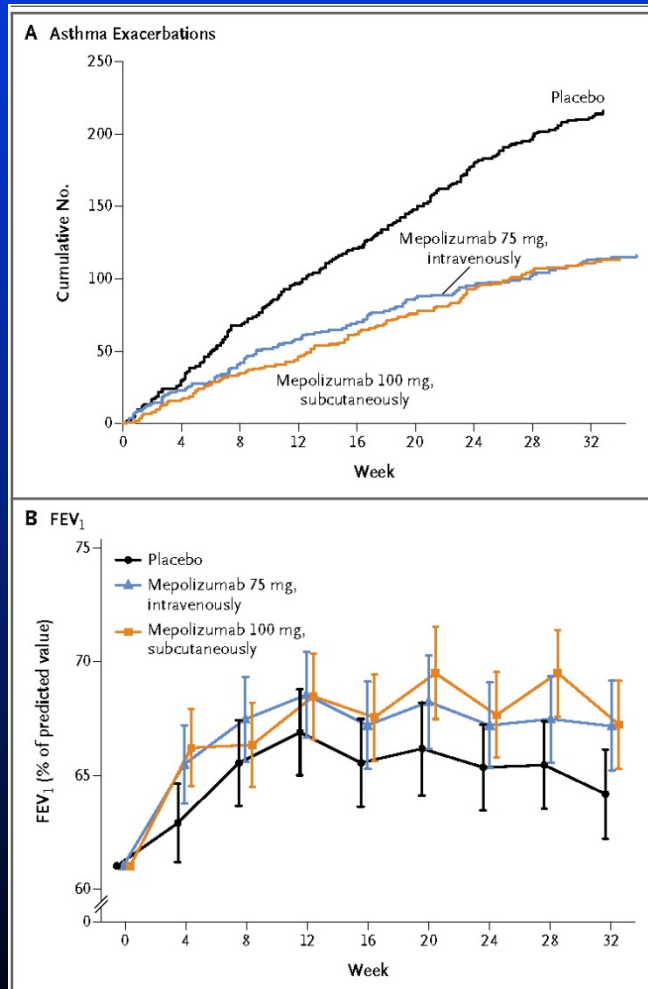


Israel E, et al. *NEJM* 2017; 377:965-76.

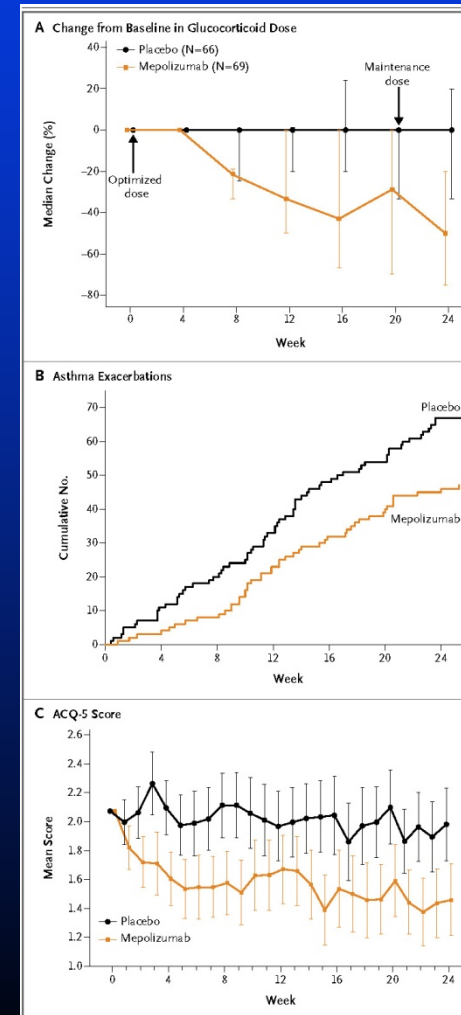
Novel Asthma Therapies

- Anti-IgE monoclonal antibody, omalizumab *Xolair*
- Anti-IL-5 monoclonal antibodies:
 - Mepolizumab *Nucala*
 - Benralizumab *Fasenra*
 - Reslizumab *Cinqair* - intravenous
- Anti-IL4R antibody, dupilumab *Dupixent*
- Bronchial thermoplasty

Mepolizumab in Eosinophilic Asthma



Ortega HG et al,
NEJM
2014; 371:1198.
(**MENSA**)



Bel EH, et al,
NEJM
2014; 371:1189.
(**SIRIUS**)

Dupilumab in Steroid-Dependent Asthma

210 pts;

Dupilumab 300 mg s.c. q. 2 weeks for 24 weeks:

- 70% reduction in oral steroid dose (vs. 42 % in placebo group)
- 59% fewer severe exacerbations vs placebo
- 22% increase in FEV₁ vs. placebo
- Other: approved for treatment of nasal polyposis and for severe atopic dermatitis

Rabe KF, et al, *NEJM* 2018; 378:2475.

Practicalities of Biologic Administration

- Subcutaneous administration every 2, 4, or 8 weeks depending on agent. (Reslizumab, *Cinqair* is given i.v.)
- Home administration possible (except omalizumab, *Xolair*).
- Side effects generally few (small risk of delayed anaphylaxis with omalizumab, *Xolair* → prefilled epinephrine autoinjector)

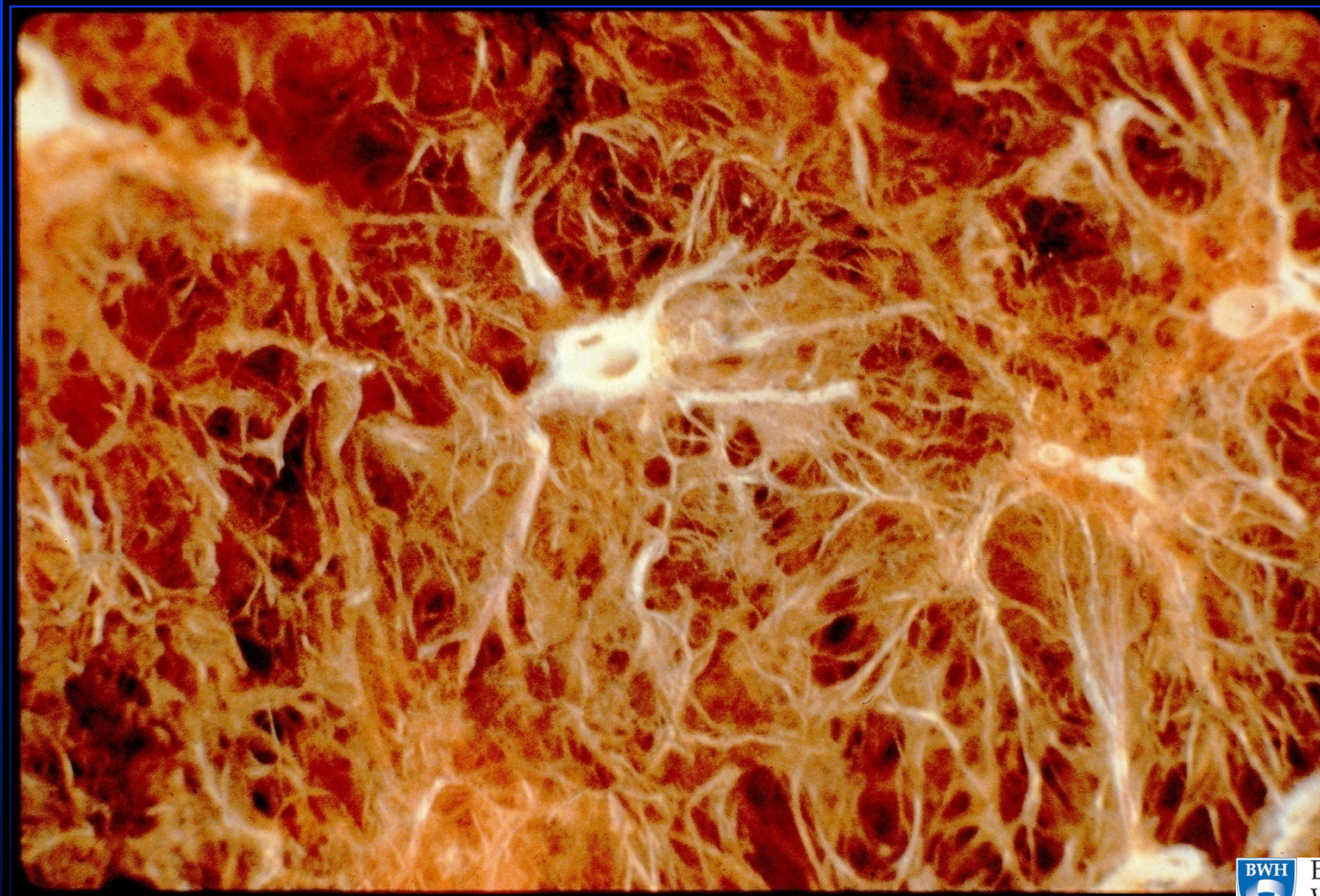
Negatives of Biologics

- COST!
- Indeterminate duration of therapy

COPD: Defining Terms

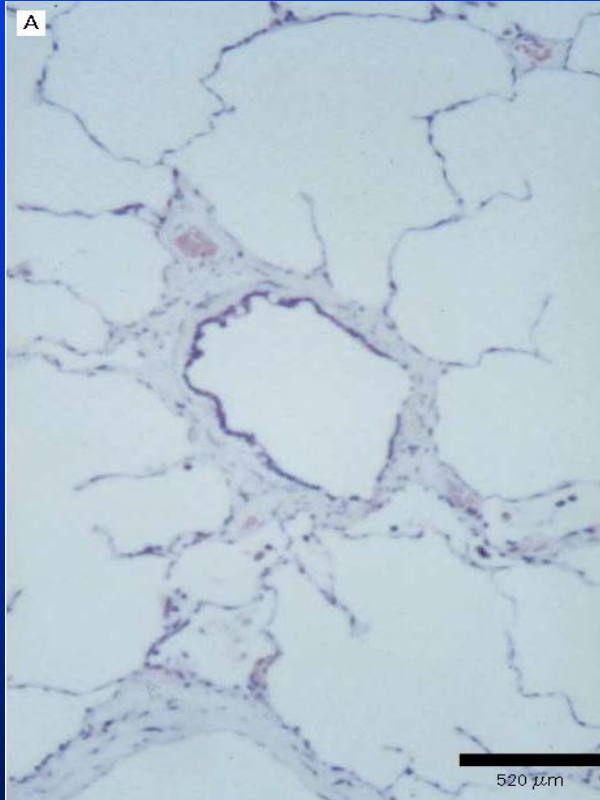
- **Chronic bronchitis:** daily cough and sputum production for at least 3 months out of the year for at least 2 consecutive years.
- **Emphysema:** abnormal dilation of airspaces due to destruction of alveolar walls.
- **COPD:** some combination of chronic bronchitis and emphysema, causing airflow obstruction that is not fully reversible.

Pathology of Emphysema



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Schematic of Emphysema Pathology

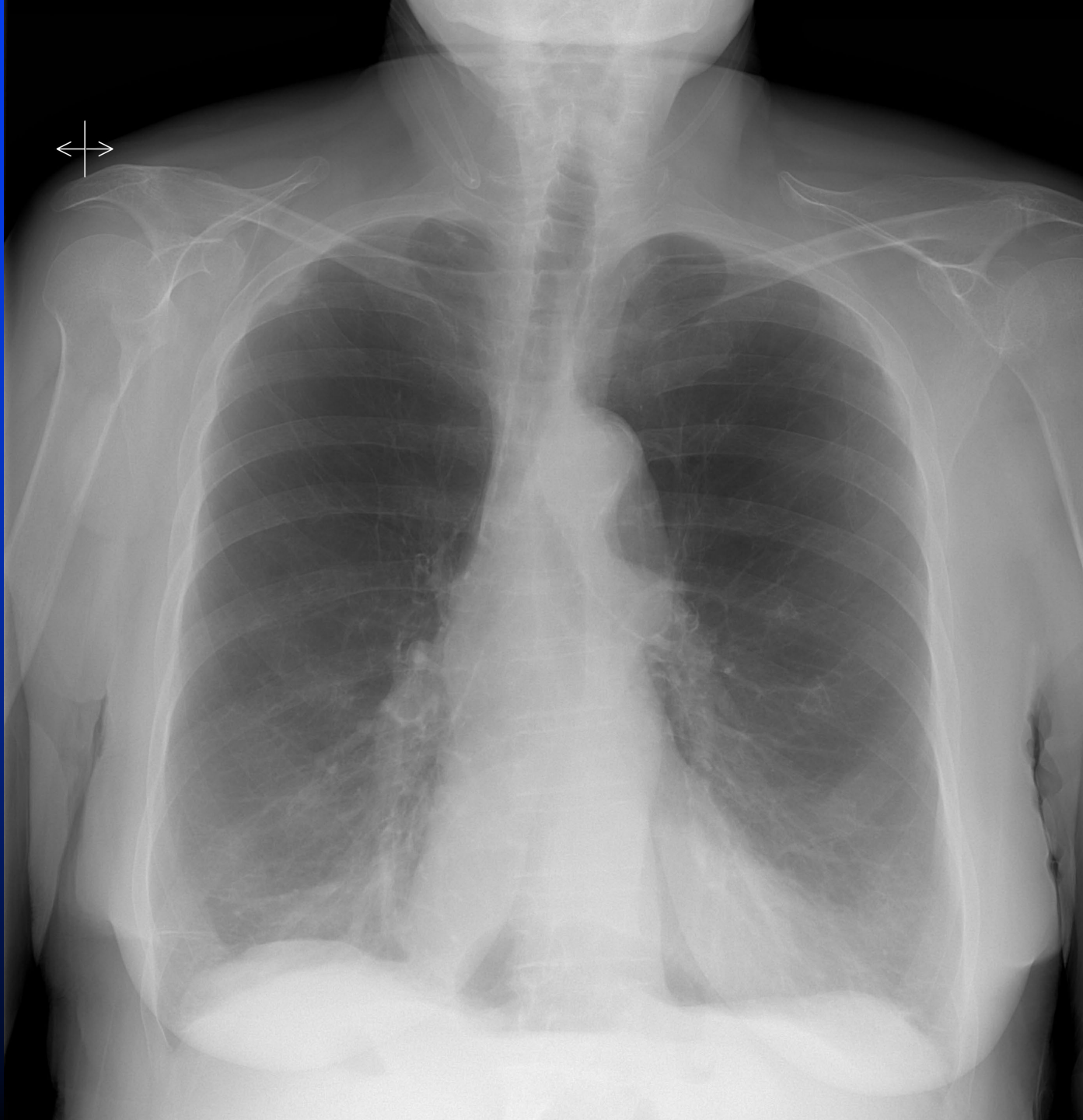


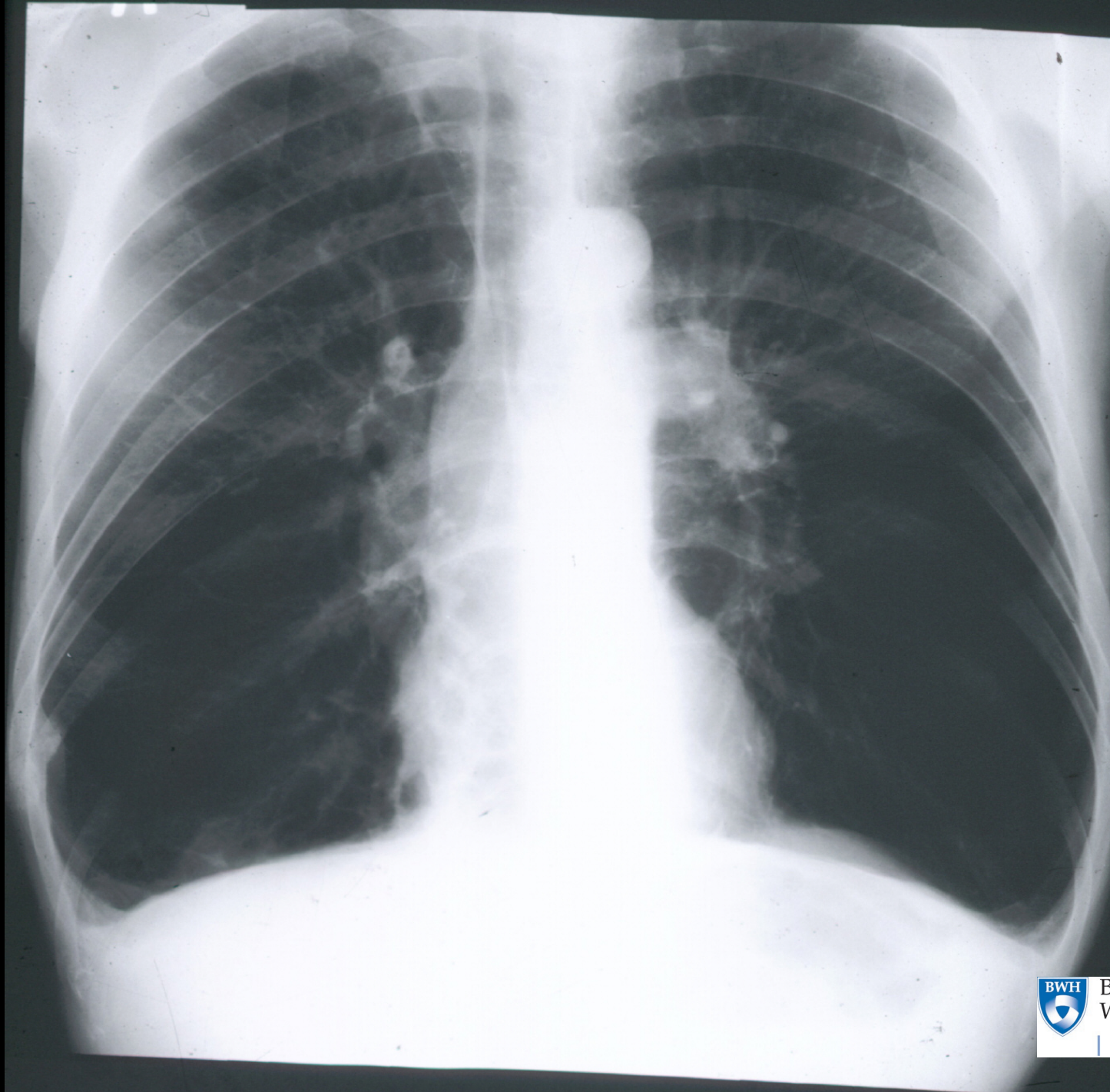
Normal



Emphysema

Barnes PJ, *NEJM* 2000;343:269-80.

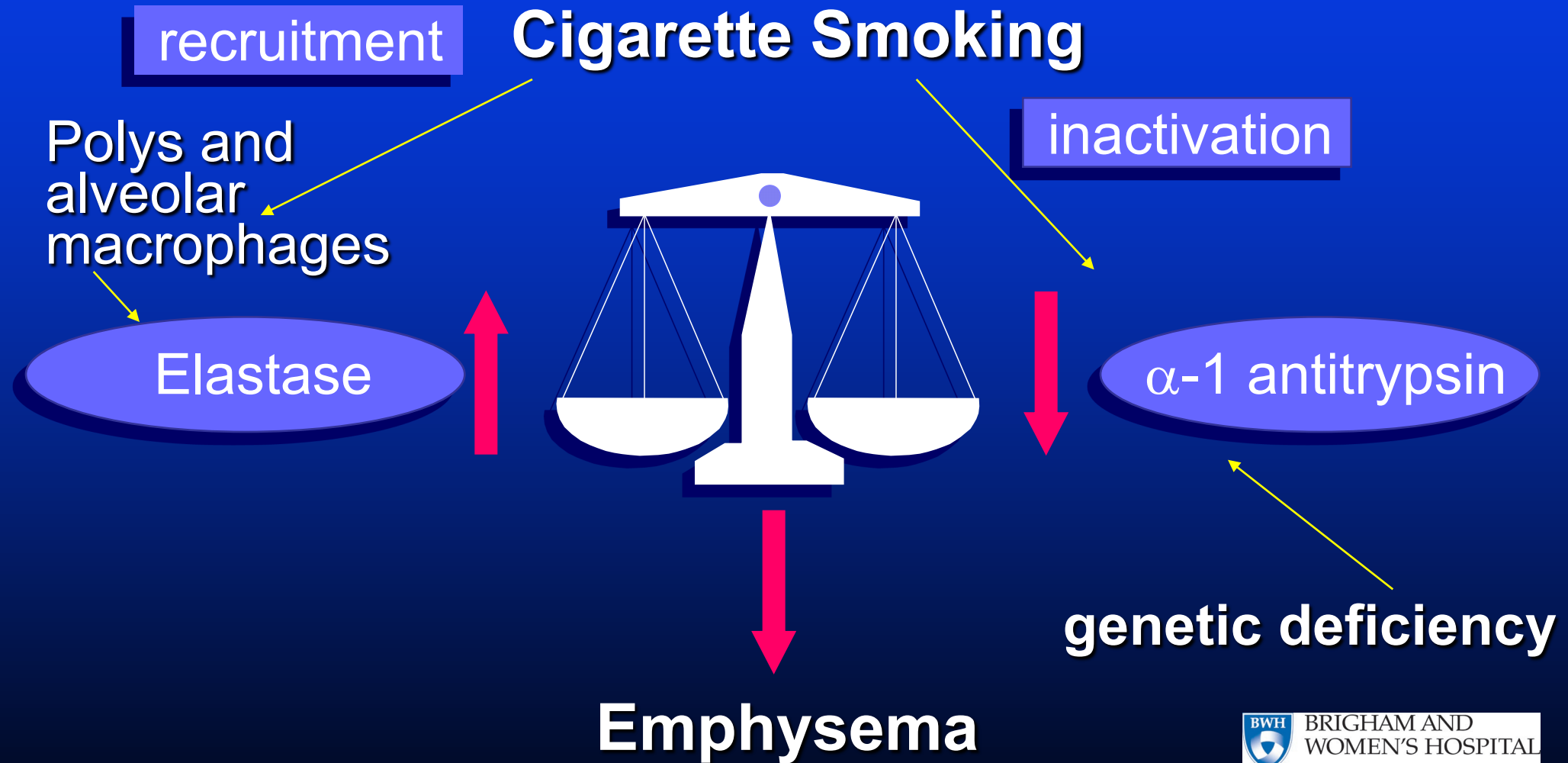




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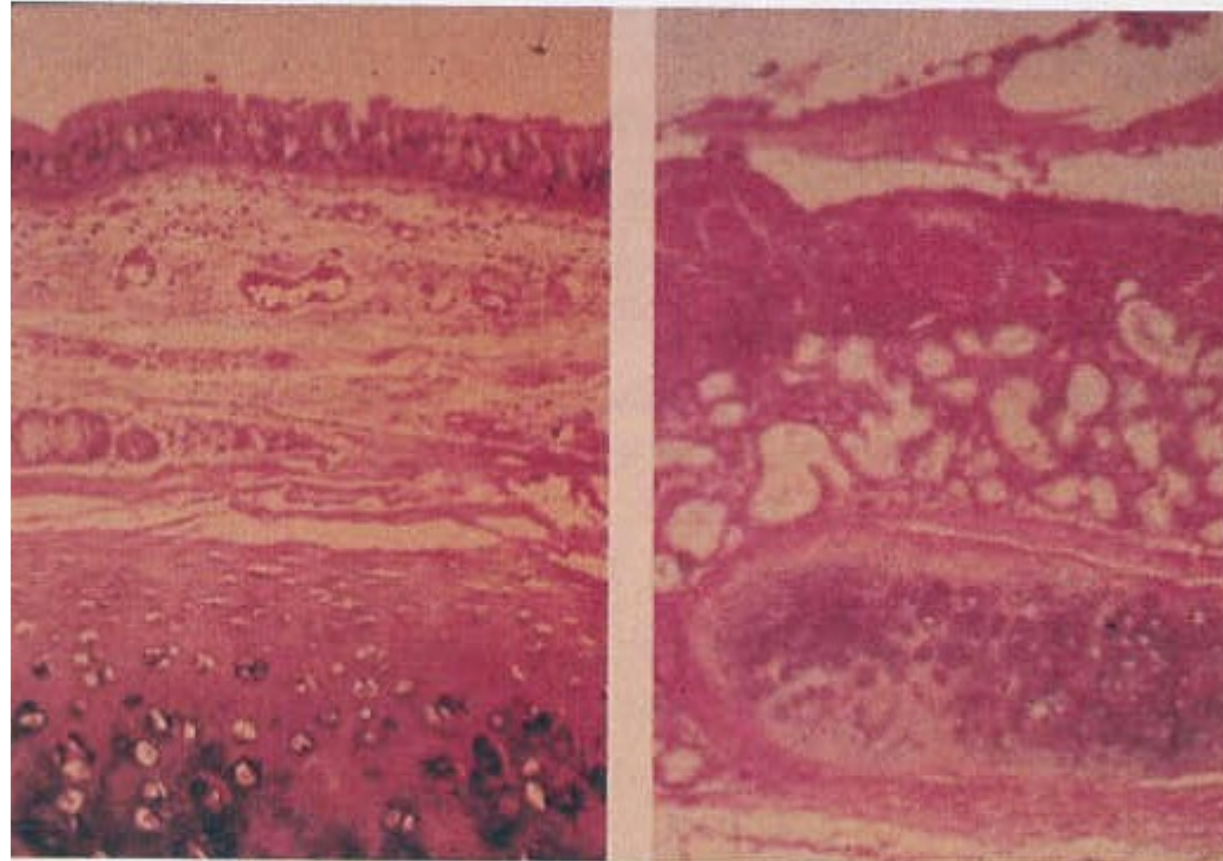
Pathogenesis of Emphysema





Pathology of Chronic Bronchitis - Large Airways

Normal



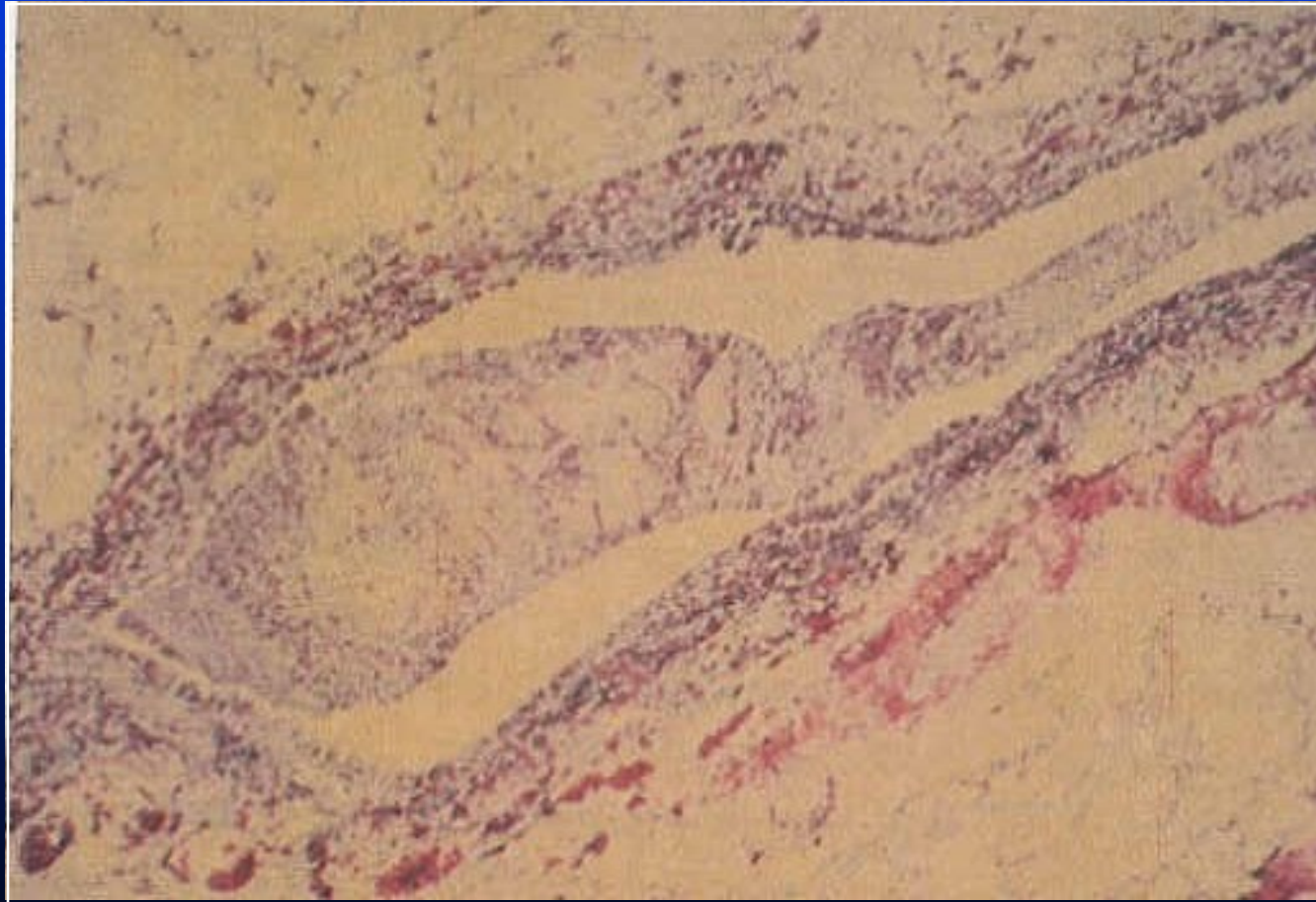
Chronic
Bronchitis



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Pathology of Chronic Bronchitis - Small Airways



1 14 82



Treatment of COPD

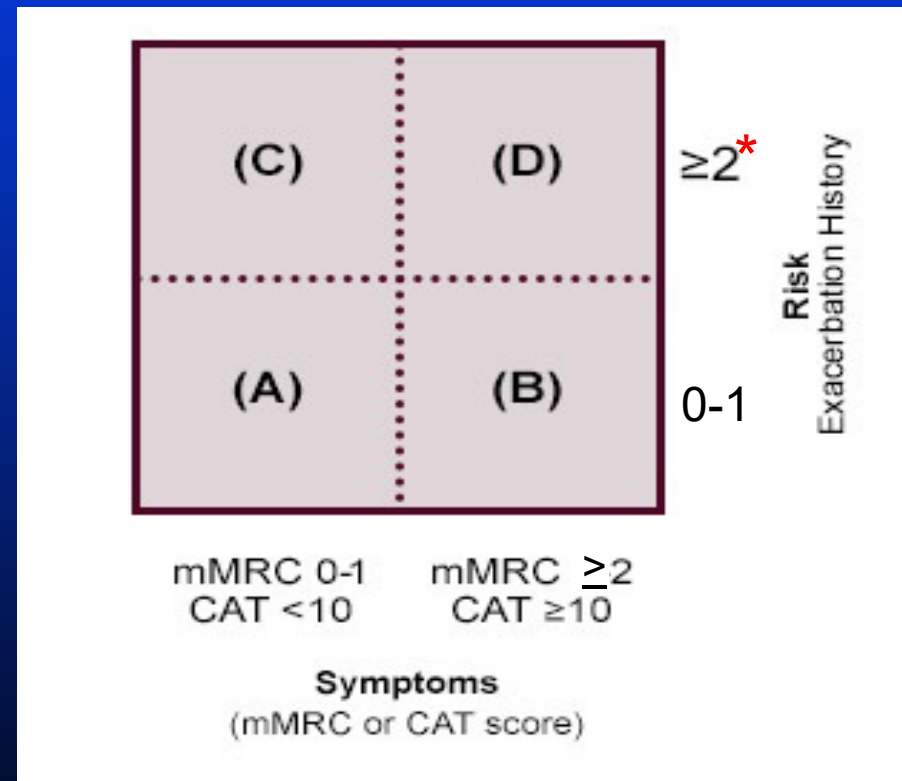
- Bronchodilators
- Corticosteroids
- Antibiotics
- Home Oxygen
- Smoking cessation
- Pulmonary rehab
- Lung volume reduction surgery

Staging Severity (GOLD 2017): Airflow Obstruction

- Grade 1: $FEV_1 \geq 80\%$ of predicted
- Grade 2: $FEV_1 \geq 50-80\%$
- Grade 3: $FEV_1 \geq 30-50\%$
- Grade 4: $FEV_1 < 30\%$

Other systems: **BODE** index (Body mass index, Obstruction on spirometry, Dyspnea score, and Exercise capacity)

Staging Severity (GOLD 2017): Symptoms / Risk of Exacerbations



* or ≥1 leading to hosp admission

www.goldcopd.org

mMRC 2: “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level.”

Goals of Rx in COPD

- Improve lung function
- Reduce frequency of exacerbations
- Improve patient-reported quality of life

Goals of Rx in COPD

- Improve lung function
- Reduce frequency of exacerbations
- Improve patient-reported quality of life

Pharmacologic therapy does ***not***:

- Slow the decline of lung function over time
- Prolong survival

Modern Bronchodilator Strategy in COPD: For Mild Disease

Quick-Acting Bronchodilators

- **Beta-Agonists:**
 - Albuterol; levalbuterol
- **Anticholinergics:**
 - Ipratropium (Atrovent)
- **Combination**
 - Albuterol + ipratropium (Combivent, Duonebs)

Treatment Options

- Long-acting beta agonist (LABA)
- Long-acting muscarinic antagonist (LAMA)
- LABA combined with inhaled steroid (LABA/ICS)
- LABA combined with LAMA
- LABA/LAMA/ICS combination

Combination LABA and LAMA

Combination	Brand name	Delivery System
Olodaterol + tiotropium*	<i>Stiolto</i>	Soft-mist inhaler (Respimat)
Vilanterol + umeclidinium*	<i>Anoro</i>	Multi-dose dry-powder inhaler (Ellipta)
Formoterol + glycopyrrolate	<i>Bevespi</i>	Metered-dose inhaler (Aerosphere)
Indacaterol + glycopyrrolate	<i>Utibron</i>	Single-dose dry-powder inhaler (Neohaler)
Formoterol + Aclidinium	<i>Duaklir</i>	Multi-dose dry-powder inhaler (Pressair)

*Once-daily dosing

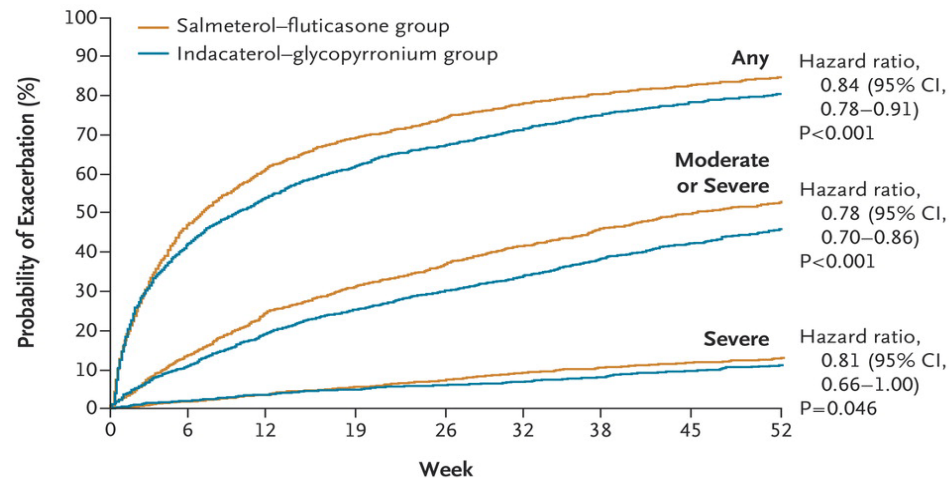
LABA/LAMA vs. LABA/ICS (FLAME)

- 3,300 patients with COPD.
- Randomly assigned to salmeterol-fluticasone (LABA/ICS) twice-daily vs. indacaterol-glycopyrronium (LABA/LAMA) once daily.
- 52-week, double-blind, double-dummy trial.

Wedzicha JA, et al., *NEJM* 2016; 374:2222-34.

LABA/LAMA vs. LABA/ICS (FLAME)

B Time to First Exacerbation



Patients at Risk

Any exacerbation					
Indacaterol-glycopyrronium group	1675	763	535	409	281
Salmeterol-fluticasone group	1679	642	415	313	217
Moderate or severe exacerbation					
Indacaterol-glycopyrronium group	1675	1299	1091	948	711
Salmeterol-fluticasone group	1679	1210	975	820	608
Severe exacerbation					
Indacaterol-glycopyrronium group	1675	1530	1434	1368	1138
Salmeterol-fluticasone group	1679	1507	1389	1303	1071

- LABA/LAMA caused significantly greater bronchodilation.
- Fewer pneumonias in LABA/LAMA group

Wedzicha JA, et al., *NEJM* 2016; 374:2222-34.

Combination LABA, LAMA, and ICS

Combination	Brand name	Dose / Delivery System
Vilanterol + umeclidinium + fluticasone furoate*	<i>Trelegy</i>	25/62.5/100 Multi-dose dry-powder inhaler (Ellipta)

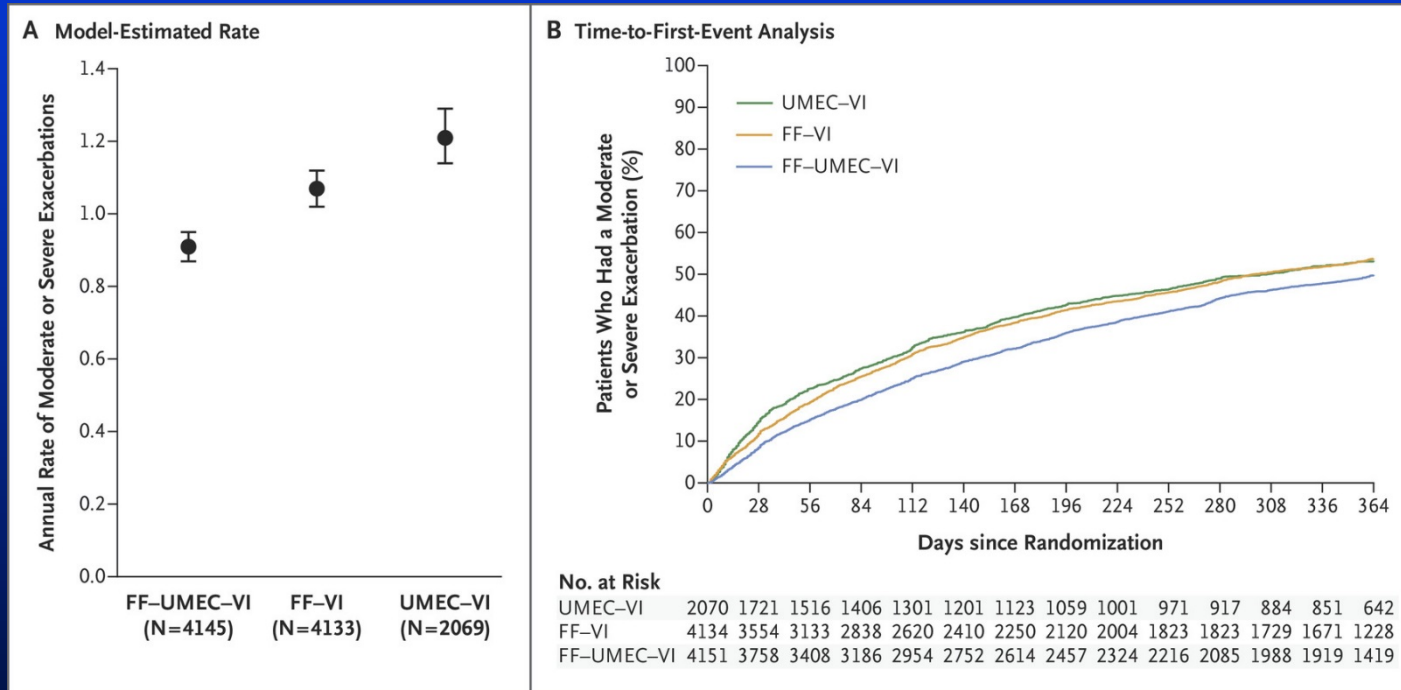
*Once-daily dosing

LABA/LAMA/ICS vs. LABA/ICS and LABA/LAMA (IMPACT)

- 10,355 patients with COPD.
- Randomly assigned to vilanterol/umeclidinium/fluticasone vs vilanterol/fluticasone or vilanterol/umeclidinium – all once-daily in identical DPI.
- 52-week, double-blind, parallel group trial.

Lipson DA, et al., *NEJM* 2018; 378:1671-80.

LABA/LAMA/ICS vs. LABA/ICS and LABA/LAMA (IMPACT)



- Triple therapy achieved fewer moderate-severe exacerbations.
- Also, improved lung function and quality of life scores.
- Increased risk of pneumonias in ICS groups.

Lipson DA, et al., *NEJM* 2018; 378:1671-80.

(My) Current Thinking

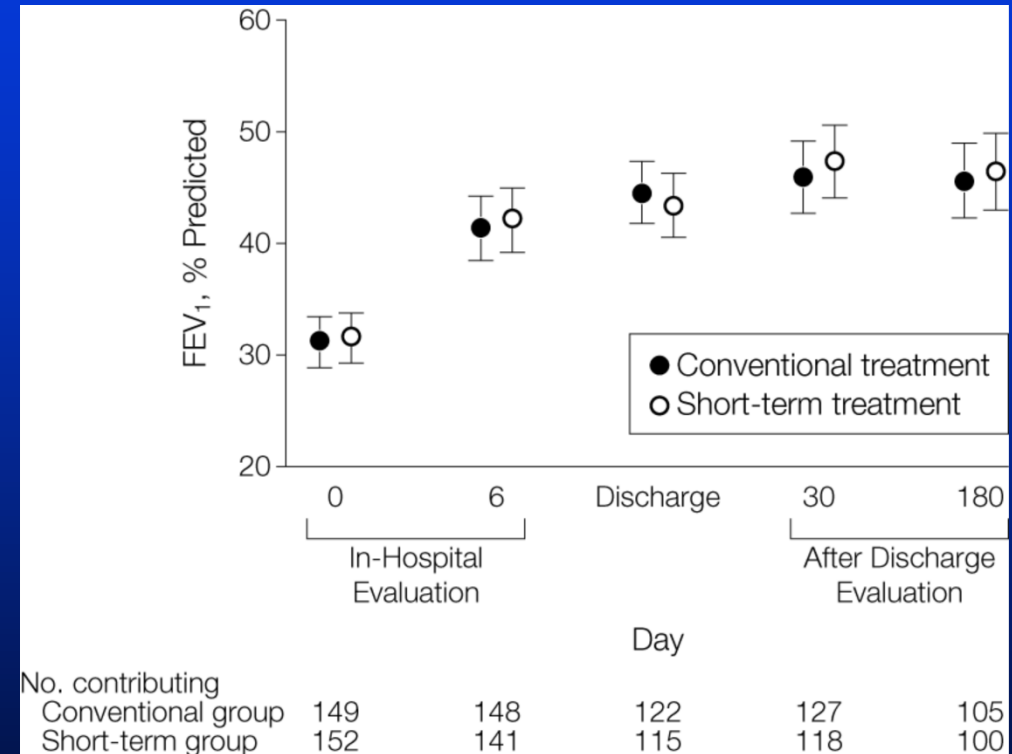
- Do not use ICS alone (increased risk of pneumonia).
- LAMA or LABA/ICS similar as first choice.
- LABA/LAMA provides greater improvement in lung function than LABA/ICS or LAMA alone.
- Triple therapy (LABA/LAMA/ICS) – particularly in eosinophilic phenotype and asthma-COPD overlap syndrome.

Initiating Therapy in Moderate-Severe COPD (cont.)

- Other considerations:
 - Delivery system (MDI, DPI, soft-mist inhaler)
 - Once- or twice-daily dosing
 - Cost / insurance coverage

Treatment of Exacerbations: Steroids

A 5-day course of prednisone 40 mg/day is equally effective as a 14-day course at the same dose (the REDUCE trial).



Leuppi JD, et al. *JAMA* 2013; 309:2223-31.

Antibiotic Therapy in Exacerbations of COPD

	Placebo	Antibiotics
	% (n)	% (n)
Success	55.0 (99)	68.1 (124)*
No Resolution (34)	23.3 (42)	18.7
Deterioration	18.9 (34)	9.9 (18)*
Other	2.9 (5)	3.2 (6)

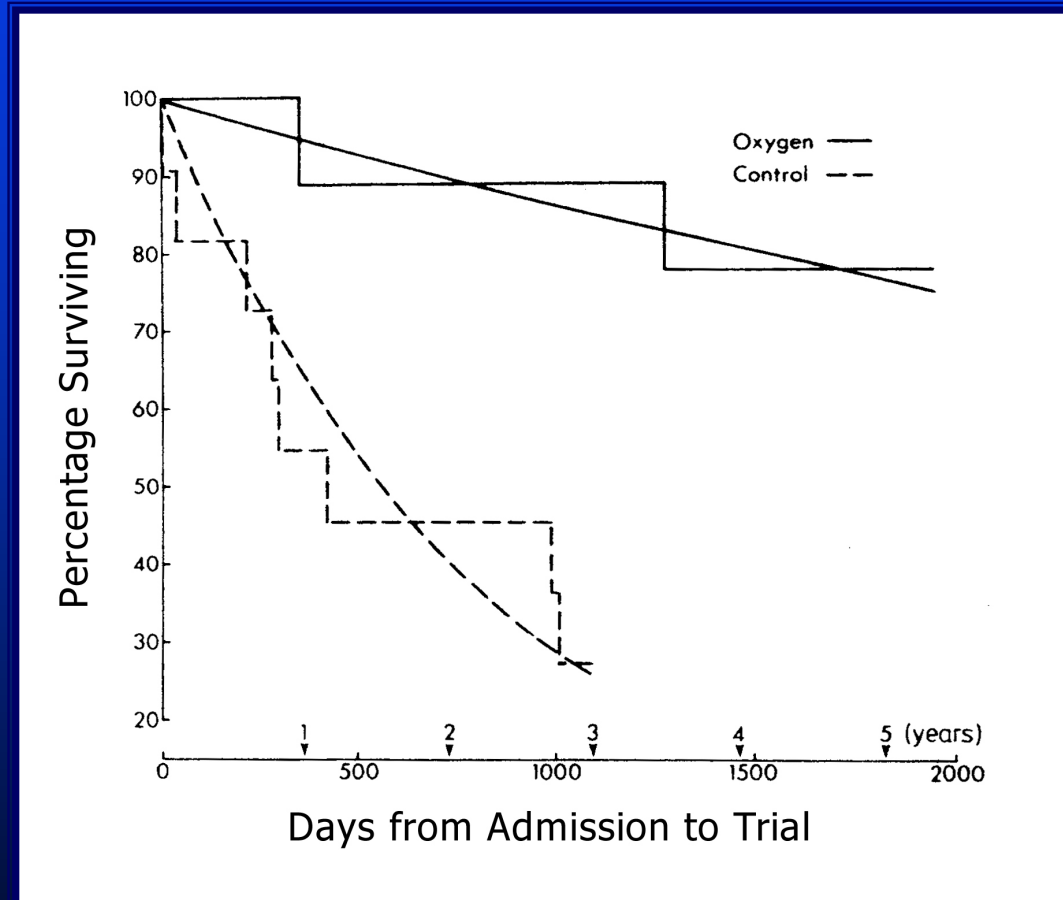
*p < 0.05

Anthony-Tiller NR, et al. *Ann Intern Med* 1987; 106:196.

Prevention of Frequent Exacerbations of COPD

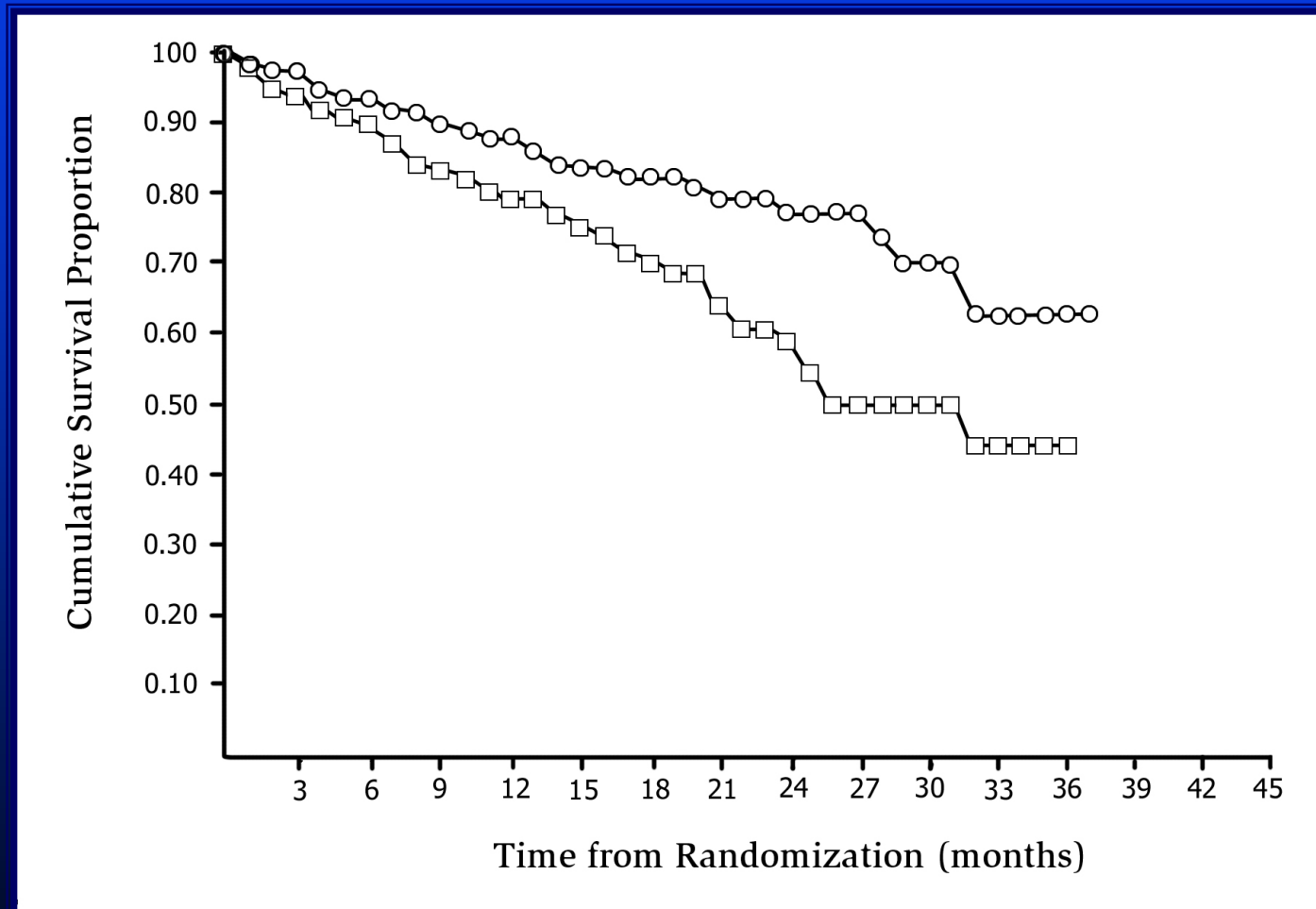
- Roflumilast (*Daliresp*)
 - Phosphodiesterase-4 inhibitor; once-daily tablet.
 - Weak bronchodilator properties.
- Azithromycin
 - Daily administration of 250 mg
 - Prolongs QT interval; increased risk of hearing loss

Home Oxygen Therapy: Effect on Survival



Lancet 1981; i:681

Nocturnal Oxygen Treatment Trial: Nocturnal vs. Continuous Oxygen Therapy



○ Continuous O₂
■ Nocturnal O₂

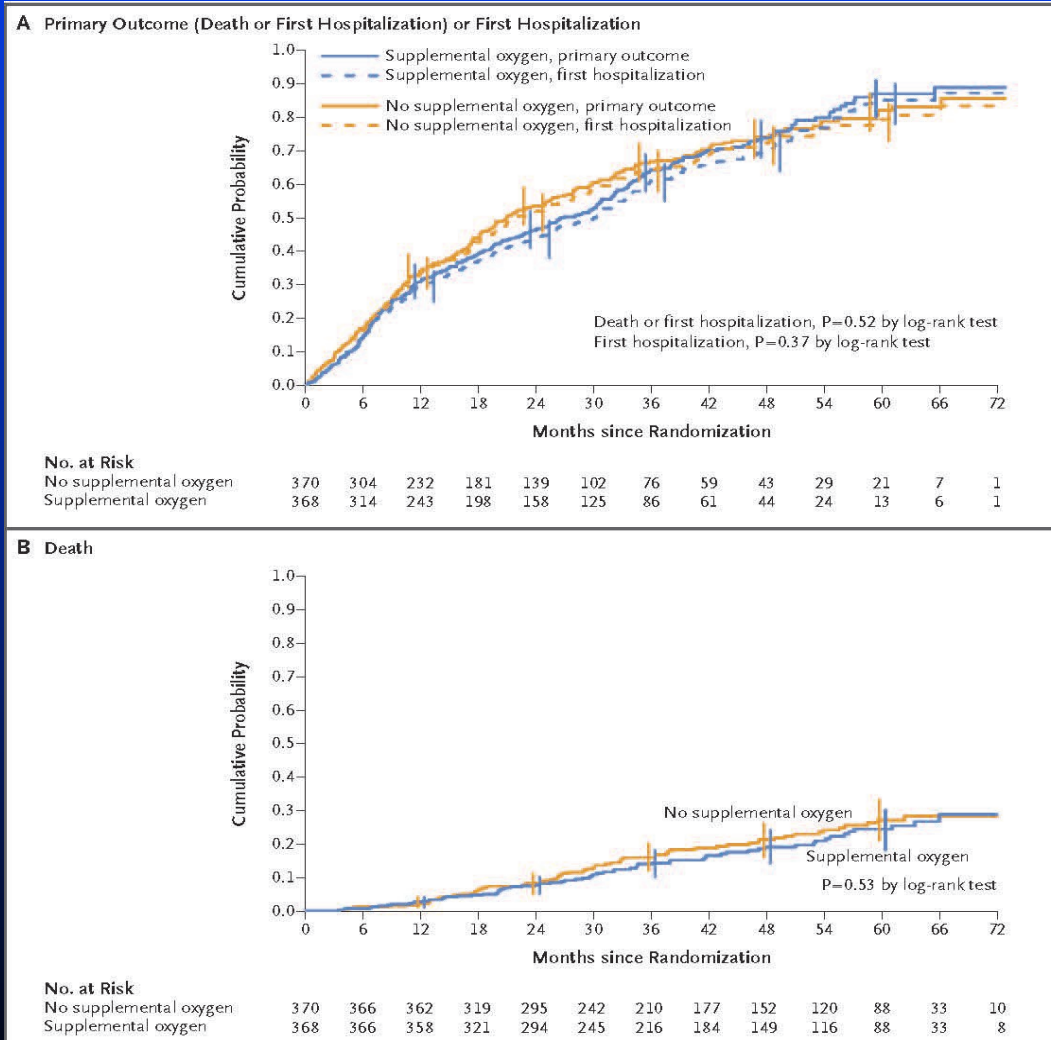
Ann Intern Med 1980; 93:391

Criteria for Home Oxygen

Following maximal medical therapy:

- $\text{PaO}_2 \leq 55$ mm Hg ($\text{SaO}_2 \leq 88\%$); or
- $\text{PaO}_2 \leq 59$ mm Hg ($\text{SaO}_2 \leq 90\%$) with
 - P pulmonale on ECG
 - Peripheral edema
 - Secondary erythrocytosis.

Mild Resting and Exercise-induced Hypoxemia (LOTT)



COPD with SaO_2 89-93% at rest and/or <90% with exertion

N Engl J Med 2016; 375:1617-27.

Smoking Cessation Aids

- Nicotine replacement therapy
 - gum, patch, nasal spray, inhaler, lozenge
- Bupropion (Wellbutrin, Zyban)
- Varenicline (Chantix) – partial agonist for nicotinic acetylcholine receptor subtype

Outpatient Pulmonary Rehabilitation

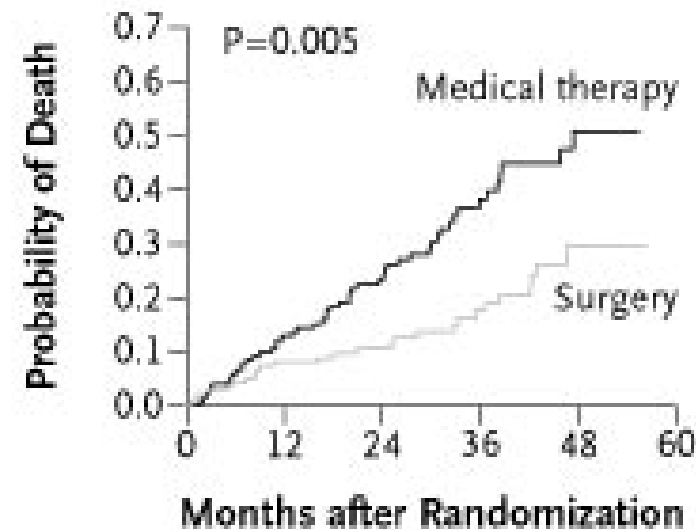
- Two Sessions per week for 8 weeks:
 - Supervised exercise with O_2 monitoring;
 - patient education about COPD;
 - social interaction with other persons with COPD.
- Outcomes:
 - Increased exercise capacity, and
 - improved sense of well-being.

Lung Volume Reduction Surgery

- **Operation:** resection of 25-30% of the most severely involved emphysematous lung tissue.
- **Purpose:** improved elastic recoil of remaining lung tissue and improved diaphragmatic function.
- **Risks:** prolonged bronchopleural fistula; ventilator dependence; death

NETT: Favorable Outcome in Subgroup Analysis

Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)



No. at Risk

Surgery	139	121	93	61	17
Medical therapy	151	120	85	43	13

National Emphysema Treatment Trial Research Group,
N Engl J Med 2003; 348:2059-2073



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| The Lung Center |

Bronchoscopic Approach to Lung Volume Reduction

- Novel, non-surgical approaches to lung volume reduction are being developed, including:
 - One-way endobronchial valves (Zephyr)
 - Shape-memory coils

Asthma vs. COPD

	Asthma	COPD
Age of onset	Childhood	Middle age
Risk factor	Allergy	Cigarette smoking
Pathology	Mast cells and eosinophils	Neutrophils and elastic tissue destruction
Reversible airflow obstr'n	Yes	Some

Asthma vs. COPD: Treatment

	Asthma	COPD
Bronchodilators & corticosteroids	Yes	Yes
Safe to use LABAs as monotherapy?	No	Yes
Leukotriene blockers, anti-IgE, bronchial thermoplasty	Yes	No
Supplemental O ₂ , pulmonary rehabilitation, lung volume reduction	No	Yes