Missouri ACP Meeting 2019 Updates in COPD

B.O.A.T.S (based on a true story)

Movie – The Princess Bride

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Disclosures

- Speakers Bureau for Sunovion, Boehringer Ingelheim
- Consultant and speaker for Biodesix (Genestrat/Verastrat), Cheetah
- https://www.medscape.com/viewarticle/915834_2
- Images are from images.google.com
- 10000 foot overview

Patient scenario

- 63 y/o male; has been a patient for 5 years; Smoker; Known COPD; Last FEV1 in Feb 2019 was 18%.
- Sig SOB; cough; No night time or exertional O2; Quit smoking after last PFTs done; multiple exacerbations
- On multiple inhalers through the years. Now on ICS/LABA and LAMA.
- Asking for more options for treatment…

Which of the following is the next best option for the treatment of this patient's COPD?

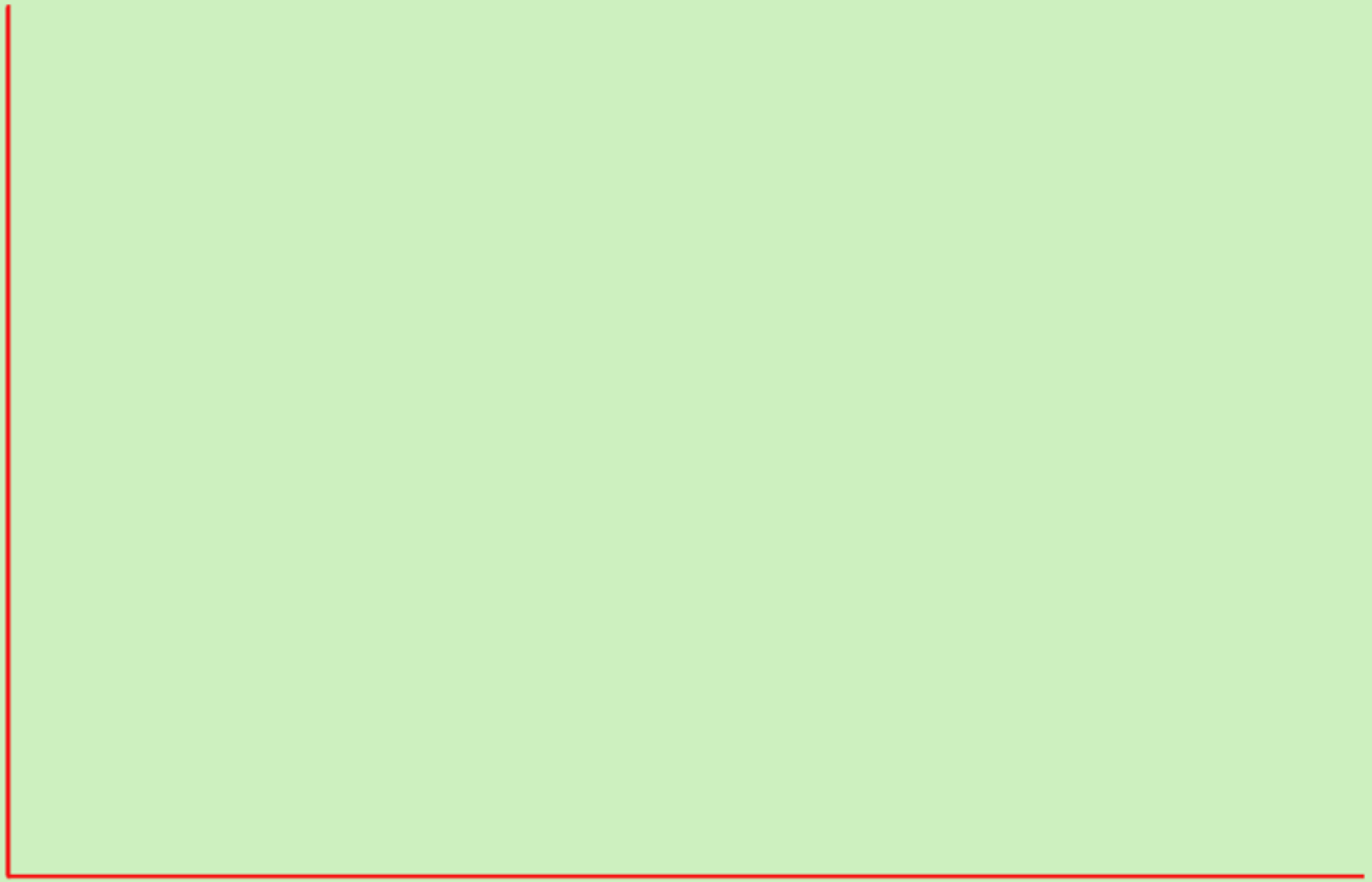
Using blood Eosinophil levels to guide treatment.

Using combination therapy (LABA/LAMA/ICS).

Adding Theophylline.

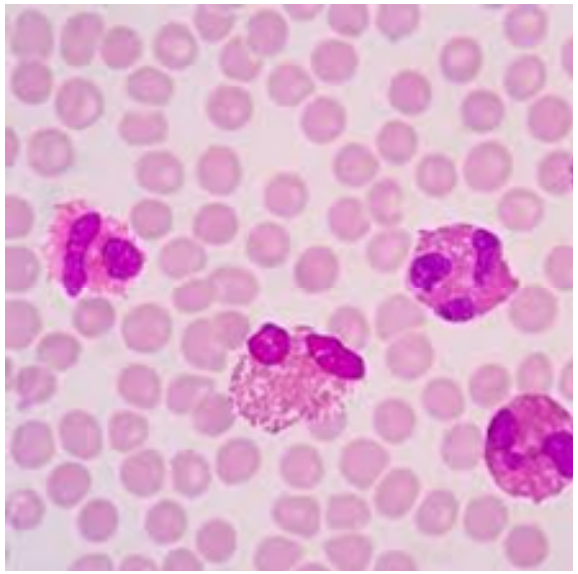
Focusing on Exacerbation reduction.

Bronchoscopic Lung Volume Resection/Reduction.



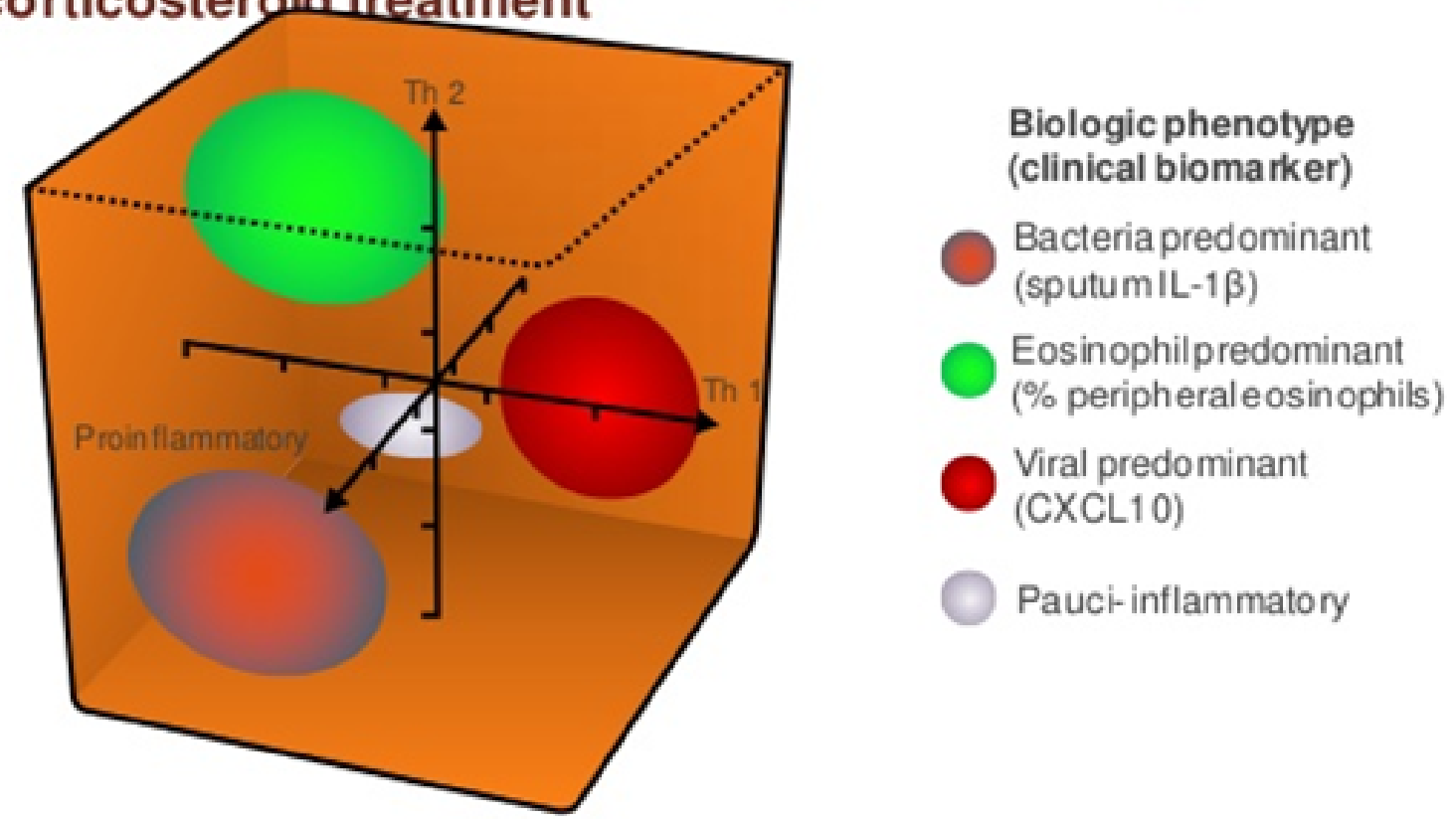
Agenda

- ***Eosinophils***
- Combination therapy
- Theophylline
- Exacerbation reduction
- Bronchoscopic Lung Volume Resection



COPD exacerbation phenotypes and responsiveness to steroids

- This observational, 1-year study of 182 exacerbations in 86 patients identified four distinct biologic COPD exacerbation phenotypes
  - **Eosinophil-predominant phenotype is most responsive to corticosteroid treatment**



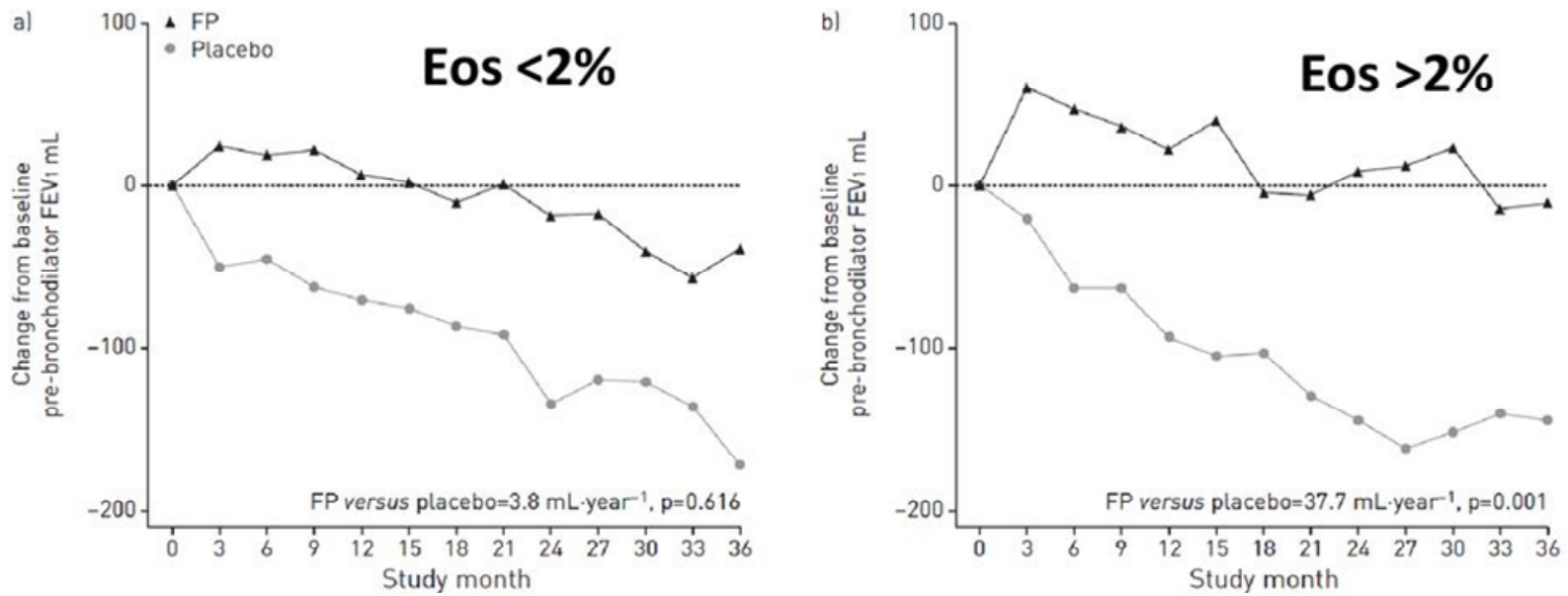
COPD = chronic obstructive pulmonary disease

Bafadhel et al. Am J Respir Crit Care 2011

Eosinophils are a marker of response to ICS in COPD

Effect on lung function

A baseline blood eosinophil count of ⩾2% identifies a group of COPD patients with slower rates of decline in FEV1 when treated with ICS



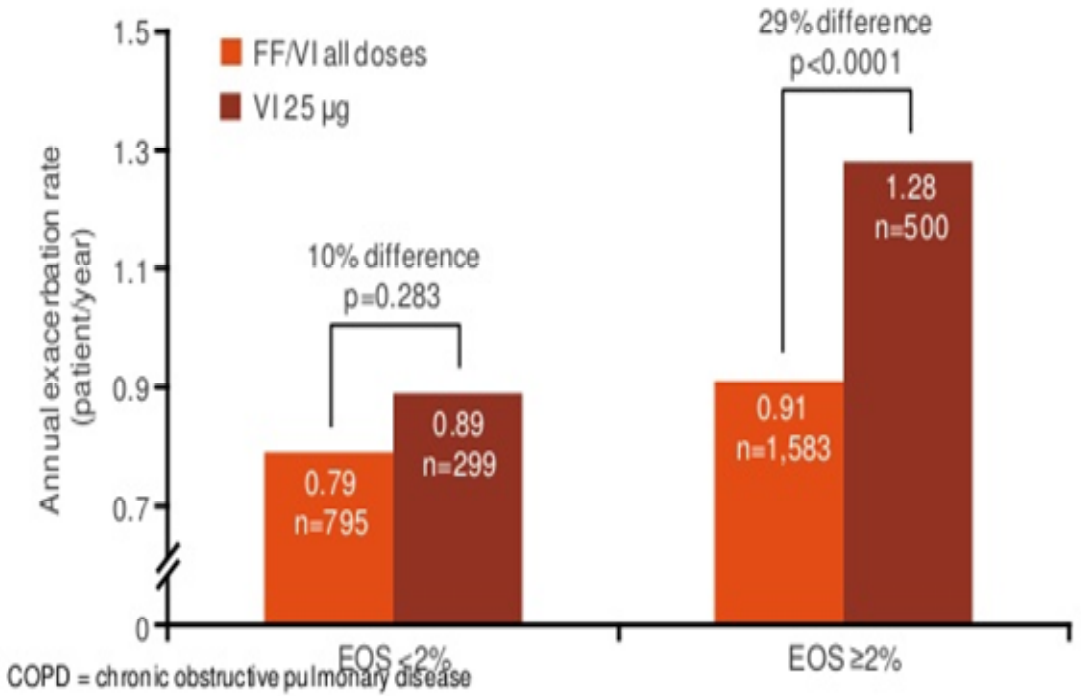
Barnes N et al. ERJ 2016

Relationship between blood Eos and ICS response tends to be linear

Threshold of 150-300 cells/mm^3 (or a differential count of 2%) has been used as decision point

Post-hoc analysis suggests that blood eosinophils are a potential biomarker of ICS effectiveness in reducing exacerbation rates

- Further research is required to help establish blood eosinophilia as a biomarker for treatment response

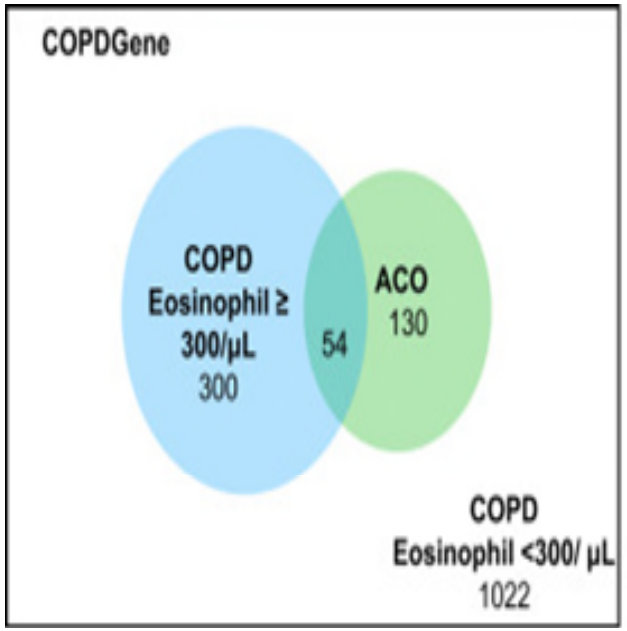


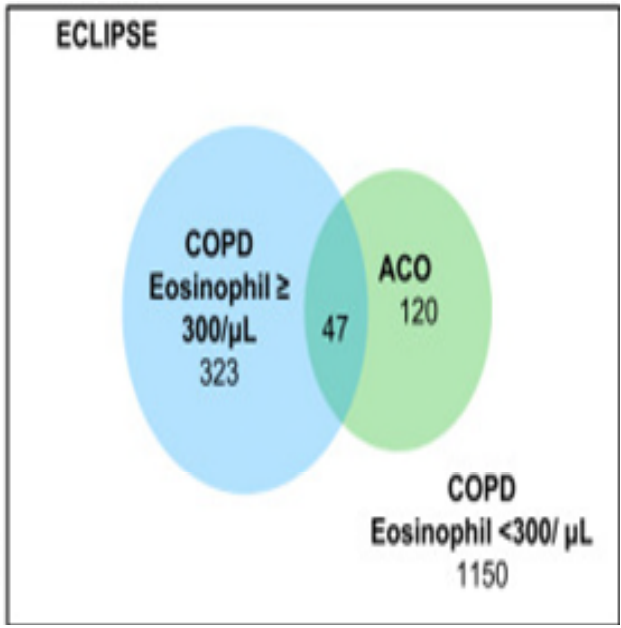
COPD = chronic obstructive pulmonary disease

EOS = eosinophil; FF/VI = fluticasone furoate/vilanterol

ICS = inhaled corticosteroid; VI = vilanterol

Pascoe et al. Lancet Respir Med 2015

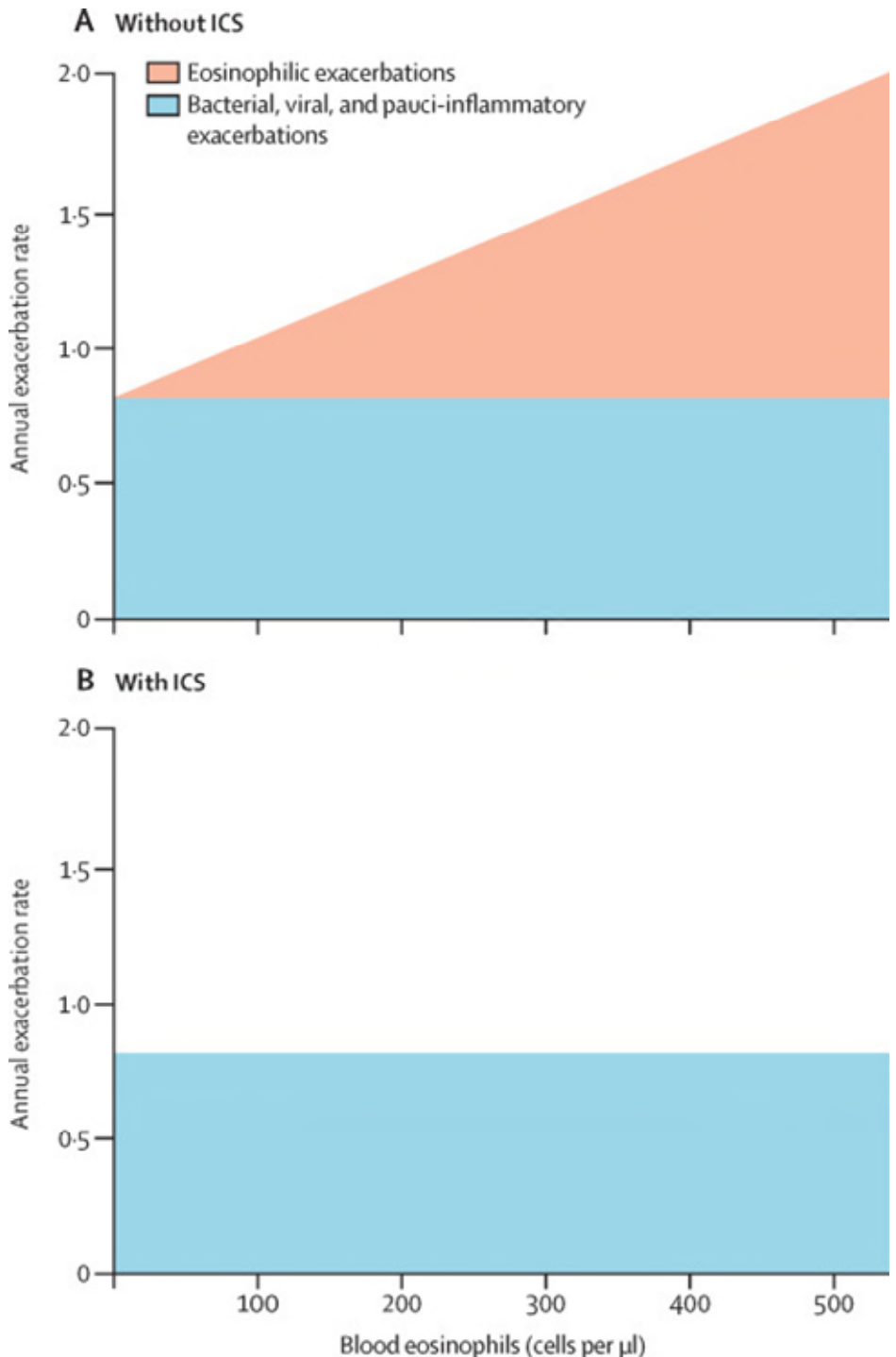




Yun JH and COPDGene and ECLIPSE Investigators. Blood eosinophil count thresholds and exacerbations in patients with COPD. J Allergy Clin Immunol. 2018 Jun;141(6):2037-2047.e10. doi: 10.1016/j.jaci.2018.04.010. Epub 2018 Apr 28.

- Mechanism of increased ICS effect in COPD patients with higher blood Eos is not completely known.

- Effect of ICS containing regimens is higher in patients with high exacerbation risk (≥ 2 exac and/or 1 hosp in the previous year)



https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30095-X/fulltext

Blood Eos and ICS Effect – Positives

- Blood Eos predict the magnitude of effect of ICS (added on top of regular maintenance BD Rx) in preventing future exacerbations.
- Higher effects at higher counts (Continuous relationship)
- Minimal effect of ICS at < 100 cells/µL. (? identify patients who wont respond)
- Highest effect at > 300 cells/µL. (? identify patients with greatest Rx benefit)
- Possible use as a biomarker in conjunction with clinical assessment

-Lipson DA et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378(18):1671-80.
-Bafadhel M et al. Predictors of exacerbation risk and response to budesonide in patients with COPD: a post-hoc analysis of three randomised trials. The Lancet Respiratory medicine 2018; 6(2): 117-26.
-Pascoe S et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with COPD: a secondary analysis of data from two parallel randomised controlled trials. The Lancet Respiratory medicine 2015;3(6): 435-42.

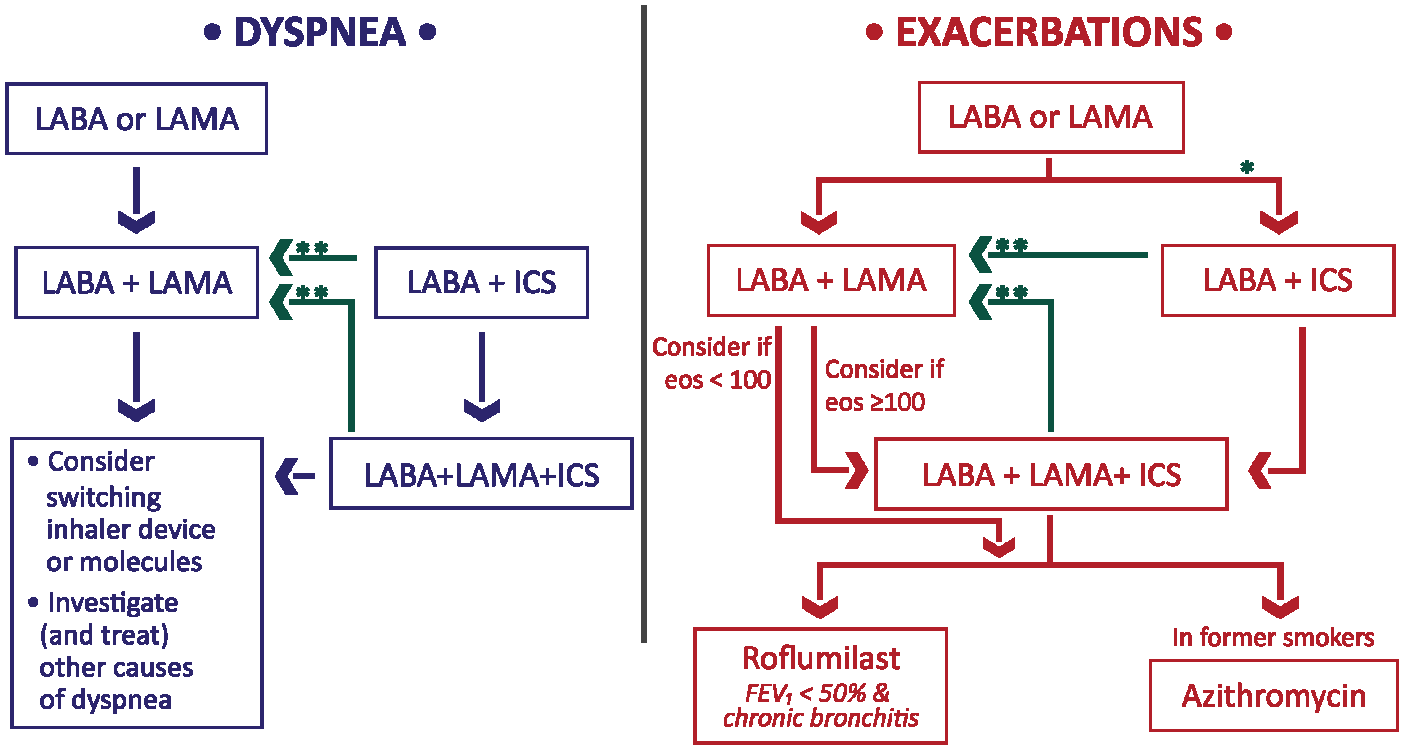
Blood Eos and ICS Effect – “Not so positive”

- Studies have differing results with regard to the ability of blood Eos to predict future exacerbation outcomes.
- Either no relationship or a positive relationship.
- There is insufficient evidence to recommend that blood Eos should be used to predict future exacerbation risk on an individual basis in COPD patients.

- Casanova C et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. EurRespir J 2017; 50(5).
- Vedel-Krogh S et al. Blood Eosinophils and Exacerbations in COPD. The Copenhagen General Population Study. Am J respir Crit Care Med 2016; 193(9): 965-74.
- Yun JH et al. Blood eosinophil count thresholds and exacerbations in patients with COPD. J Allergy Clin Immunol 2018; 141(6): 2037-47.e10.

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ 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 ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

Agenda

- Eosinophils
- ***Combination therapy***
- Theophylline
- Exacerbation reduction
- Bronchoscopic Lung Volume Resection

Types of Handheld Inhalers

- **MDIs** — Metered Dose Inhalers → Use propellant, not breath-actuated
- **DPIs** — Dry Powder Inhalers → Do not use propellant, breath-actuated
- **SMIs** — Slow Mist Inhalers → Do not use propellant, not breath-actuated

10 (and counting) handheld inhalers

MDIs -Aerosphere -HFA	DPIs -Diskus -Inhub -Handihaler -Pressair -Aerolizer -Ellipta -Neohaler	SMI -Respimat

LABA	LAMA	Inhaler	Company
Olodaterol	Tiotropium	Respimat Soft Mist	Boehringer Ingelheim
Indacaterol	Glycopyrronium	Breezhaler	Novartis
Vilanterol	Umeclidinium	Ellipta	GlaxoSmithKline
Formoterol	Aclidinium	Genuair	Almirall

Abbreviations: LABA, long-acting β_2-adrenoceptor agonists; LAMA, long-acting muscarinic receptor antagonists.

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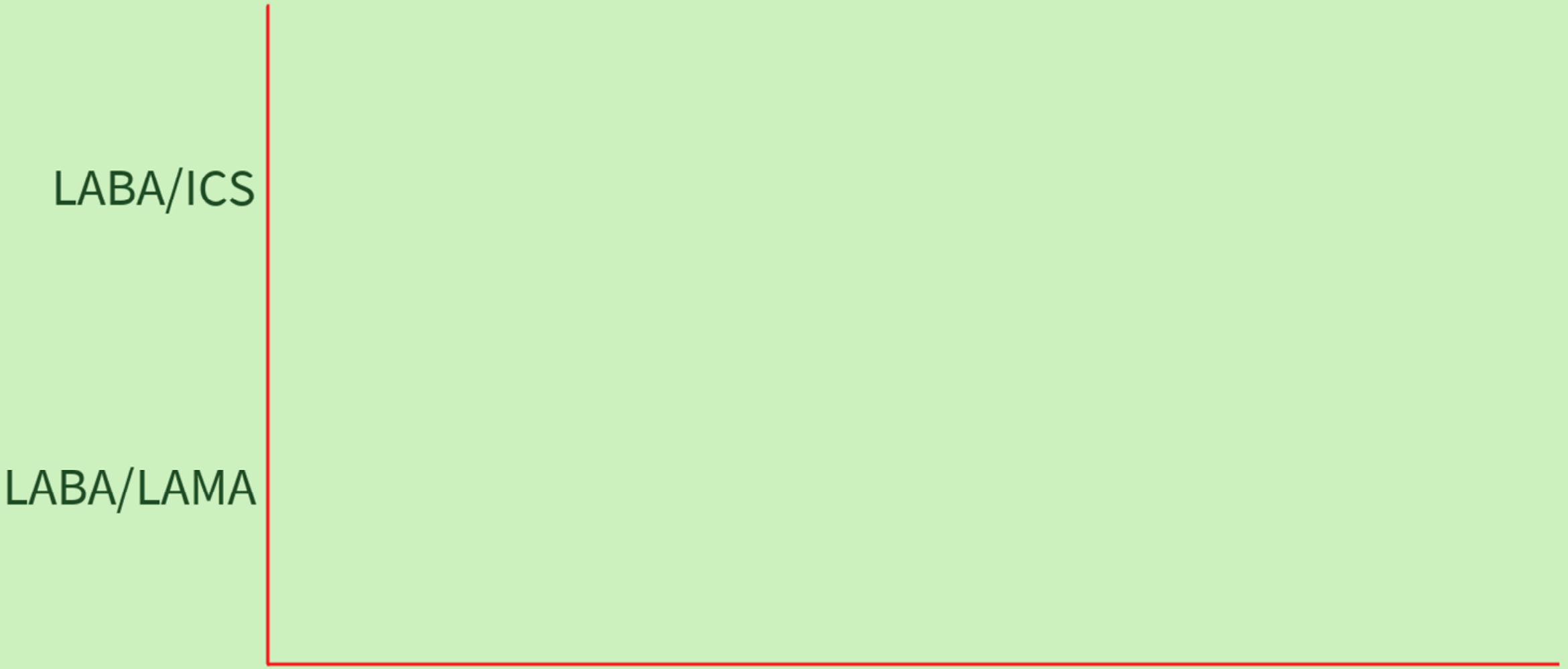
Which combination is better for patients with COPD?

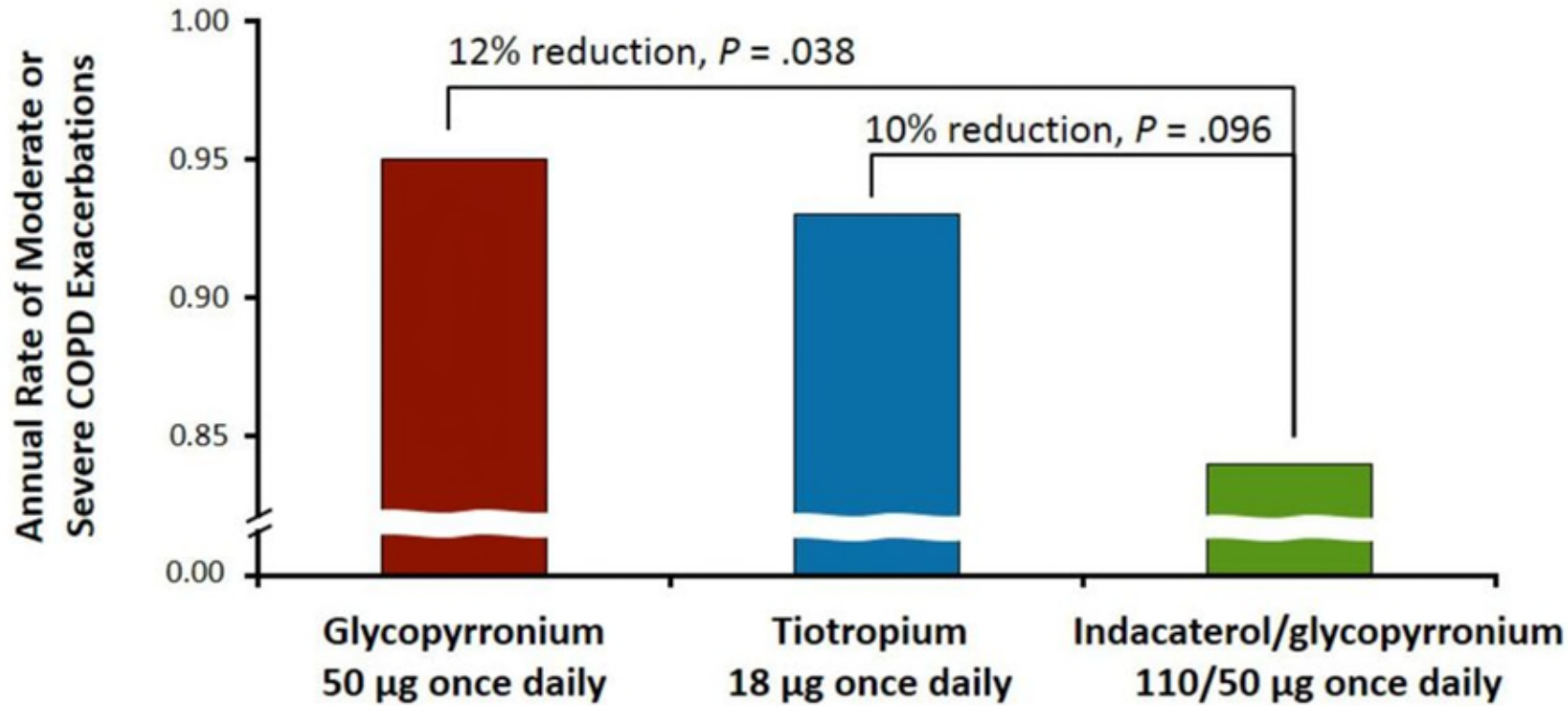


LABA/LAMA vs monotherapy

- Most studies with LABA/LAMA combinations have been performed in patients with a low rate of exacerbations.

- (SPARK) Wedzicha et al. 2013 → In patients with a history of exacerbations, a combination of LA BD is more effective than LA monotherapy for preventing exacerbations.
- (1+1=2)
- (DYNAGITO) Calverley et al. 2018 → combining LABA + LAMA did NOT reduce exacerbation rate as much as expected compared with a LAMA alone.
- (1+1≠2)

Annualized Rate of Moderate or Severe Exacerbations: SPARK

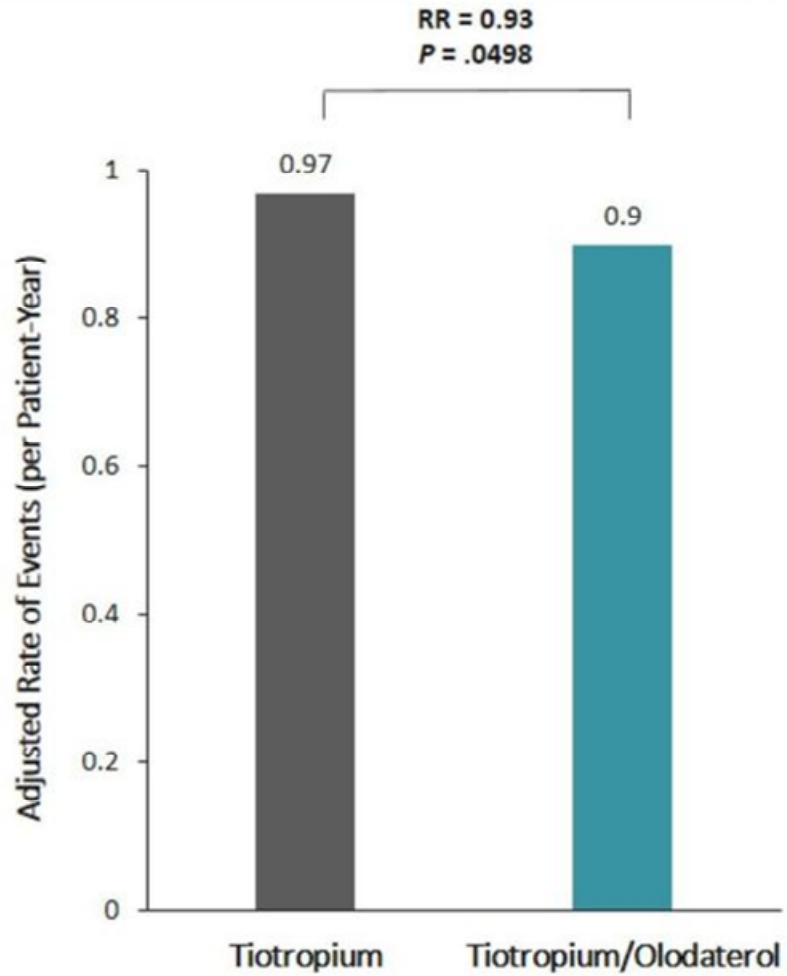


Wedzicha JA, et al. *Lancet Respir Med*. 2013;1:199-209.

DYNAGITO Study Design: Tiotropium and Olodaterol in the Prevention of COPD Exacerbations (cont)

Rate of Moderate-to-Severe Exacerbations

	Tiotropium 5 µg	Tiotropium/ Olodaterol 5/5 µg
Number of treated patients, n	3941	3939
Adjusted rate of events, per patient-year		
Mean	0.97	0.90
99% CI	0.90, 1.03	0.84, 0.96
Rate ratio of events vs tiotropium 5 µg		
Mean	**0.93**	
99% CI	**0.85, 1.02**	



Calverley PMA, et al. *Lancet Respir Med*. 2018;6:337-344.

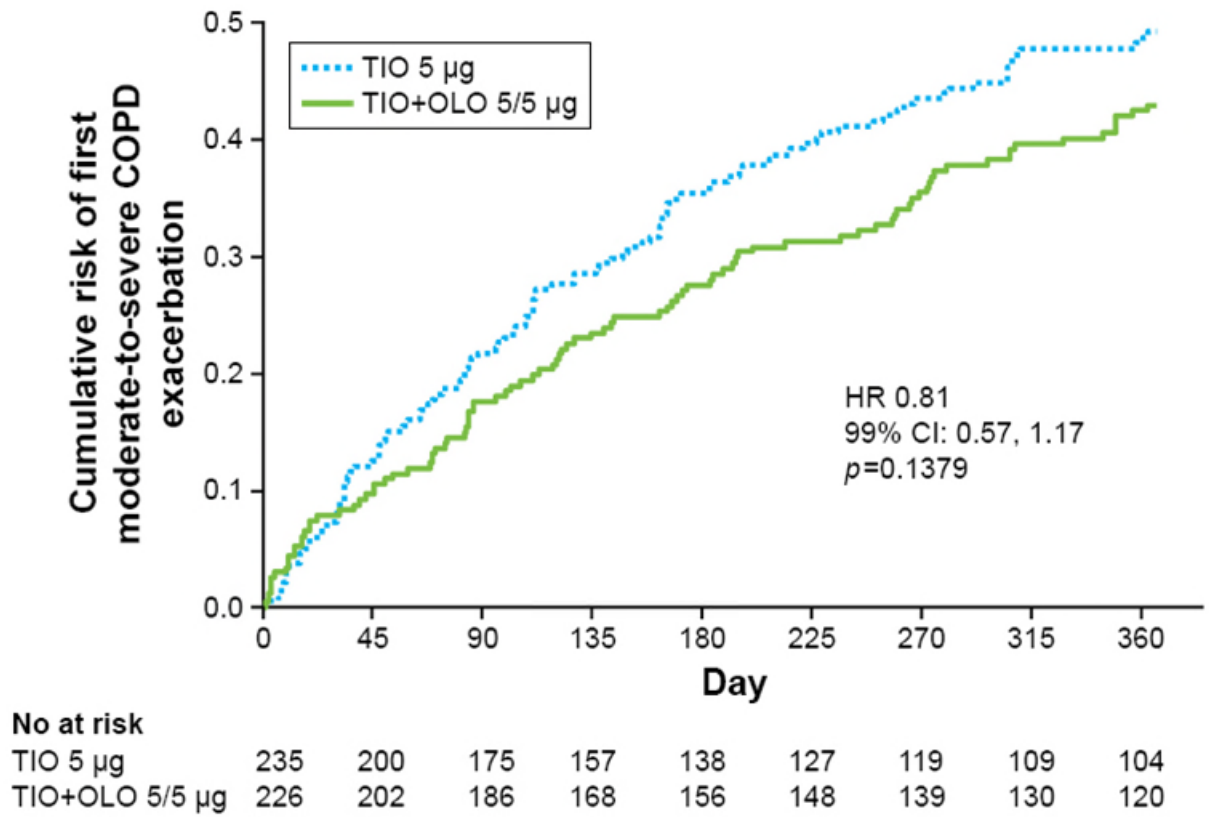


Figure 5 Cumulative risk of first moderate-to-severe COPD exacerbation by treatment group.
Abbreviations: OLO, olodaterol; TIO, tiotropium.

ICS/LABA vs LABA/LAMA

- (FLAME) Wedzicha et al. 2014 → In patients with a h/o exacerbations, combination LABA/LAMA decreased exacerbations to a greater extent than ICS/LABA combination. (LABA+LAMA > ICS/LABA)

- (IMPACT) Lipson et al. 2018 → High exacerbation risk population (≥ 2 exac and/or 1 hosp in the previous year); ICS/LABA decreased exacerbations to a greater extent than a LABA/LAMA combination (at higher blood eosinophil concentrations). (ICS/LABA > LABA/LAMA)

FLAME: Indacaterol-Glycopyrronium (LABA+LAMA) versus Salmeterol-Fluticasone (LABA+ICS) for COPD

Randomized, double-blind, double-dummy, noninferiority trial

Objective: To compare LABA + LAMA with LABA + ICS for reducing COPD exacerbations in patients with COPD and mMRC dyspnea grade ≥2 symptoms

3,362 patients (≥40 years) who are current or former smokers
Stable COPD per GOLD 2011 criteria on a stable medication

Indacaterol+glycopyrronium (LABA + LAMA) n=1680

vs

Salmeterol+fluticasone (LABA + ICS) n=1682

Primary Outcomes

Treatment continued for 52 weeks

3.59 vs **4.09**

Annual rate of COPD exacerbations

RR 0.88; 95% CI 0.82-0.94; P<0.001

Secondary Outcomes

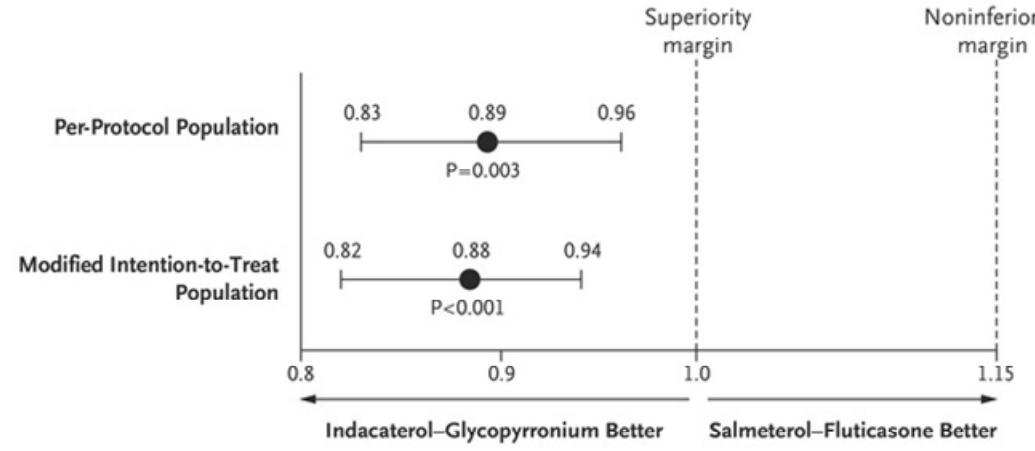
Annual rate of moderate or severe exacerbations

RR 0.83; 95% CI 0.75-0.91; P<0.001

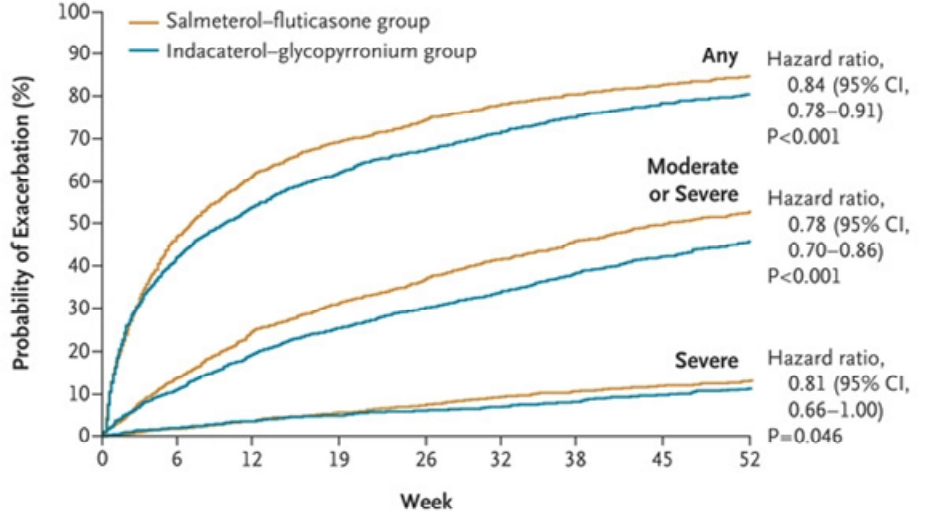
Conclusion: Indacaterol+glycopyrronium (LABA+LAMA) is associated with a 11% reduction in the rate of annual COPD exacerbations when compared to salmeterol+fluticasone (LABA+ICS)

Wedzicha JA, et al. NEJM. 2016. 374(23):2222-2234.

A Rate Ratio for All Exacerbations



B Time to First Exacerbation

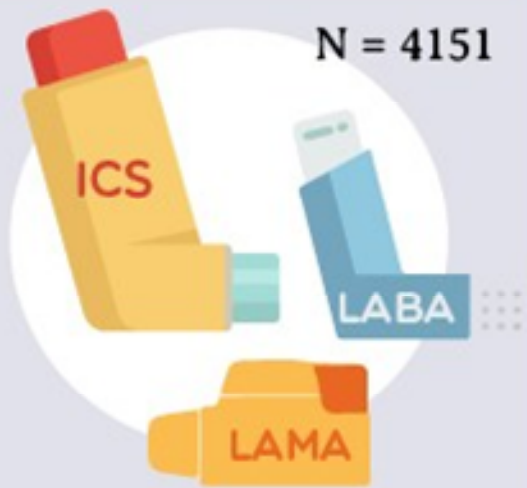


Patients at Risk

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

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD - The IMPACT Trial

RANDOMIZED TRIAL INVOLVING 10,355 PATIENTS WITH COPD



	N = 4151		N = 4134	N = 2070
Rate of COPD Exacerbations per year	0.91	P<0.001	1.07	1.21
Incidence of Pneumonia per year	7%	P<0.001	6%	4%

TRIPLE THERAPY > DUAL THERAPY IN TERMS OF COPD EXACERBATIONS BUT LEADS TO INCREASED RATES OF PNEUMONIA

N Engl J Med 2018 DOI: 10.1056/NEJMoa1713901

David A. Lipson et al. | visualmed.org

WISDOM trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 2, 2014 VOL. 371 NO. 14

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

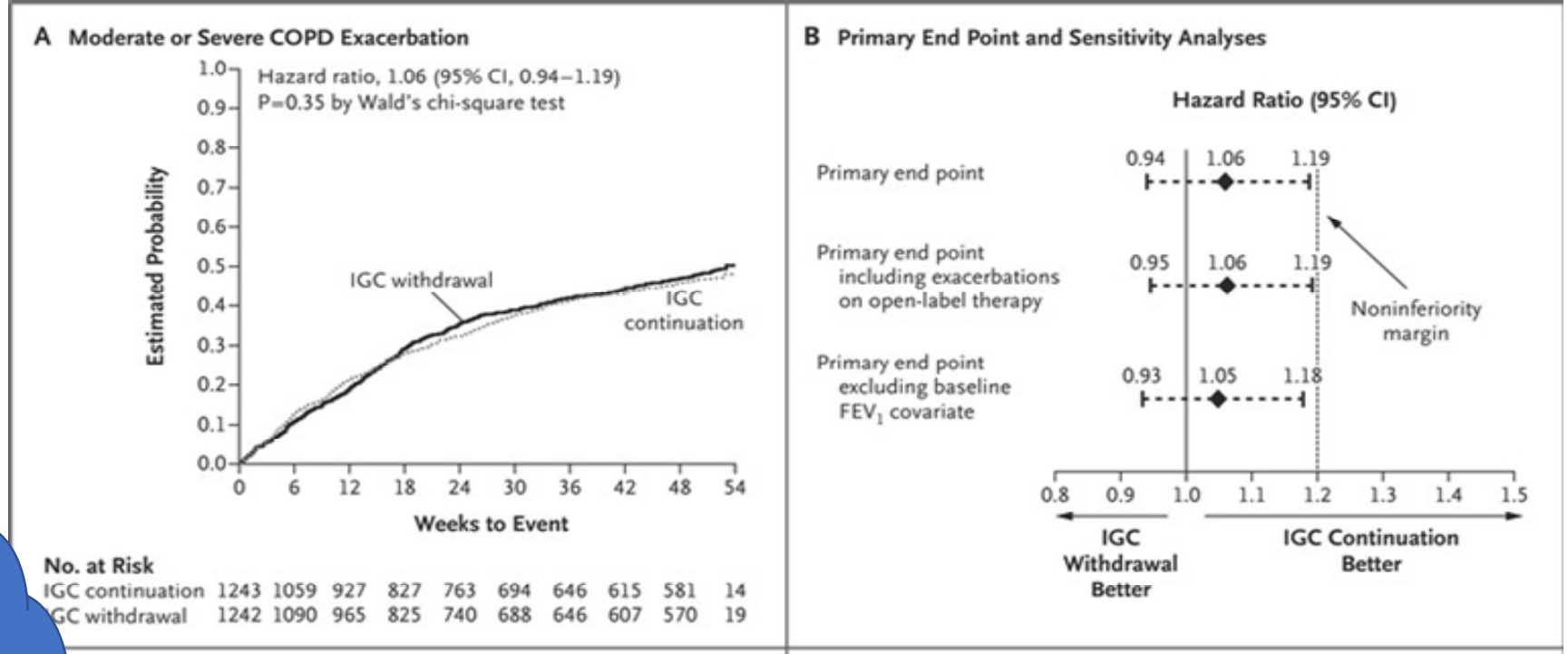
ABSTRACT

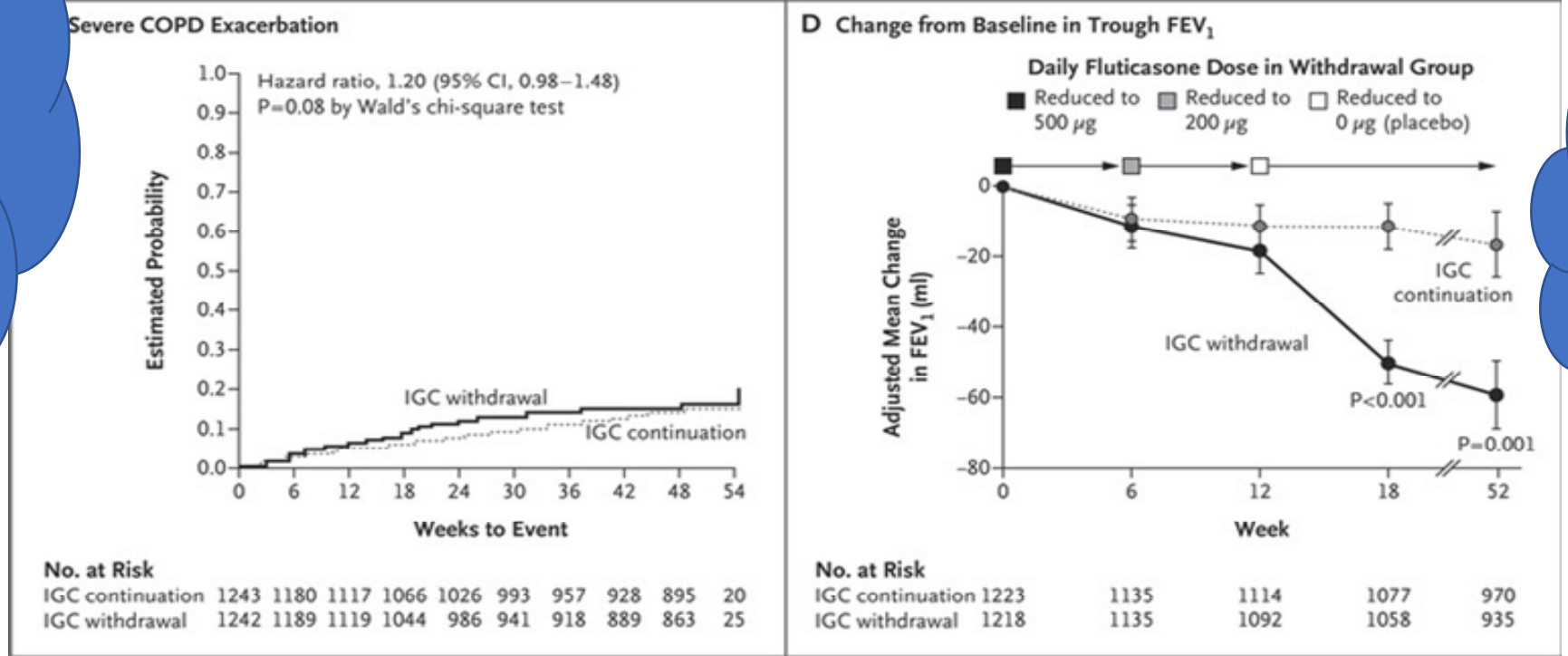
BACKGROUND

Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to two long-acting bronchodilators has not been fully explored.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Magnussen at the Pulmonary Research Institute at Lung Clinic Grosshansdorf, Woehrendamm 80, D-22927 Grosshansdorf, Germany, or at magnussen@

ICS withdrawal did not increase exacerbations in moderate to severe COPD or severe COPD





ICS withdrawal lead to a small significant decrease in FEV1

FOLLOW-UP PHARMACOLOGICAL TREATMENT

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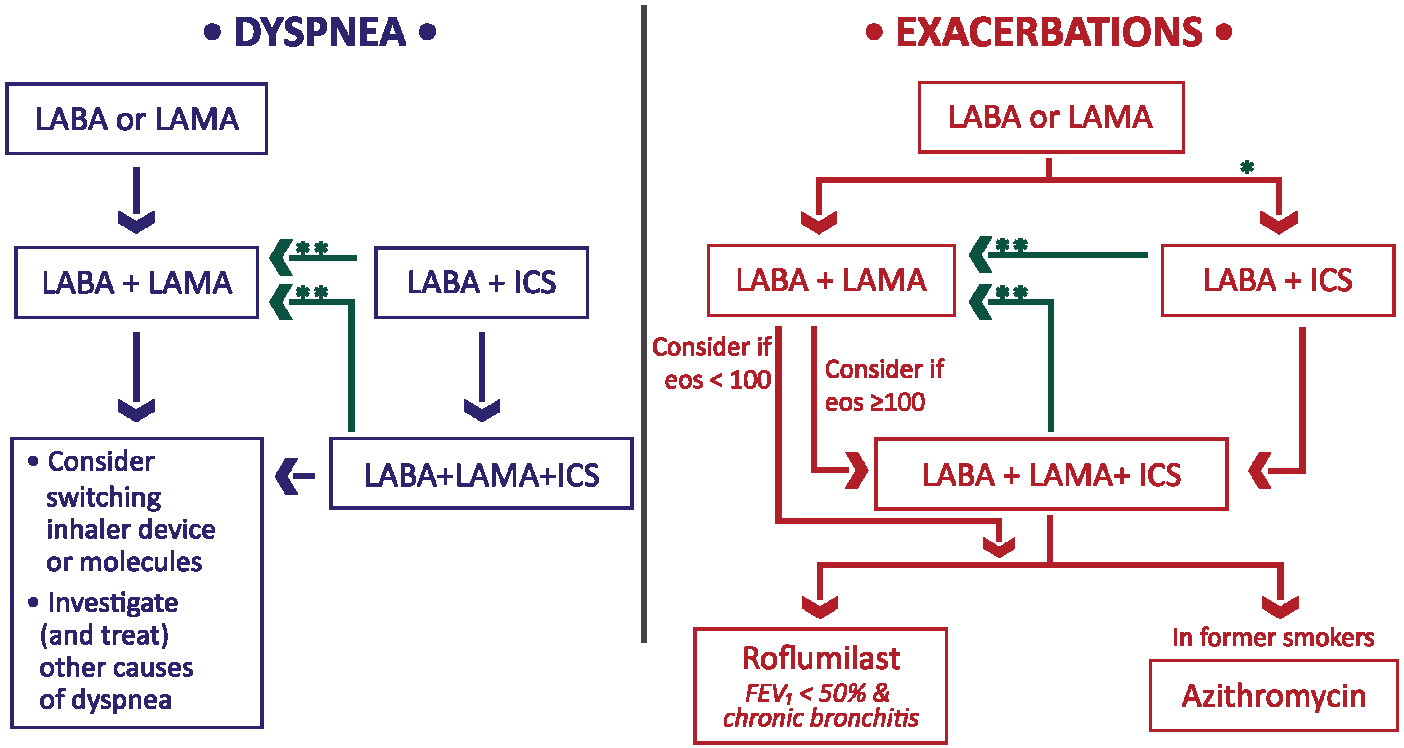

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FIGURE 4.3

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- Eosinophils
- Combination therapy
- ***Theophylline***
- Exacerbation reduction
- Bronchoscopic Lung Volume Resection

https://medimoon.com/2013/04/counseling-parameters-for-theophylline/

PubMed theophylline and copd

Create RSS Create alert Advanced

Format: Summary **Sort by**: Most Recent **Per page**: 20

Best matches for theophylline and copd:

Doxofylline is not just another **theophylline**!
Matera MG et al. Int J Chron Obstruct Pulmon Dis. (2017)

Association of pre-hospital **theophylline** use and mortality **disease** patients with sepsis.
Shih YN et al. Respir Med. (2017)

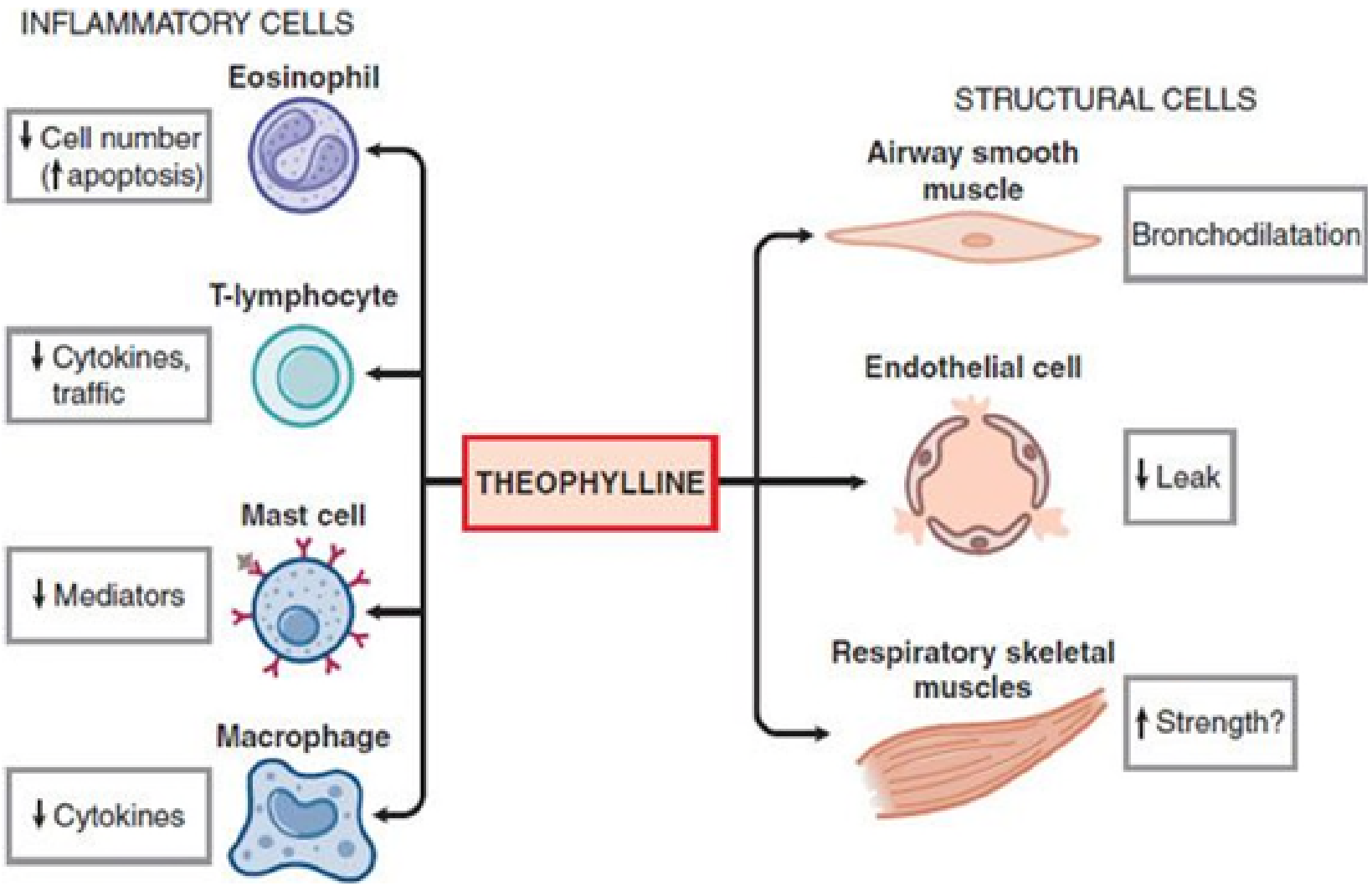
Therapeutic approaches of asthma and **COPD** overlap.
Kondo M et al. Allergol Int. (2018)

Switch to our new best match sort order

Search results

Items: 1 to 20 of 964

https://memegenerator.net/instance/67668635/exorcism11-i-did-cocaine-and-theophylline



http://learninglocker.nav.pitt.edu/assets/css/mechanism-action-theophylline-treating-copd.58.5840.17.php

Increased clearance
- P450 enzyme induction by drugs (rifampicin, phenobarbitone, carbamazepine, ethanol)
- Smoking (tobacco, marijuana)
- High-protein, low-carbohydrate diet
- Barbecued meat
- Childhood

Decreased clearance
- P450 enzyme inhibition by drugs (cimetidine,* erythromycin,† fluoroquinolone antibiotics, allopurinol, zileuton, fluvoxamine, phenytoin, fluconazole, ketoconazole, acyclovir, ritonavir, diltiazem, verapamil, interferon-α, estrogens, pentoxifylline)
- Congestive heart failure
- Liver disease
- Pneumonia
- Viral infection
- Vaccination (influenza immunization)
- High carbohydrate diet
- Old age

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* Not ranitidine.
† Also clarithromycin but not azithromycin.

https://www.researchgate.net/figure/FACTORS-AFFECTING-CLEARANCE-OF-THEOPHYLLINE_tbl1_236835798

TWICS (theophylline with ICS) Trial

- Double-blind, placebo-controlled, randomized
- ≥ 2 exacerbations (Rx with Abx, OCS, or both) last year & on ICS (~80% ICS/LABA/LAMA)

	Theo	Placebo
Total 1578 pts Low-dose theo (200 mg) For conc 1-5 mg/L] Based on IBW and smoking	791 pts	787 pts
3430 exacerbations	1727 (mean 2.24 exac/yr)	1703 (mean 2.23 exac/yr)

CONCLUSION - Addition of low-dose theo, did not reduce the number of COPD exac over a 1-year period

Devereux G, Cotton S, Fielding S, et al. Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD: a randomized clinical trial. JAMA. 2018;320:1548-1559.

- Outside of areas where cost and access to healthcare and drugs is problematic, ? use of low-dose theophylline

http://www.scaryforkids.com/coffin/

Agenda

- Eosinophils
- Combination therapy
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- ***Exacerbation reduction***
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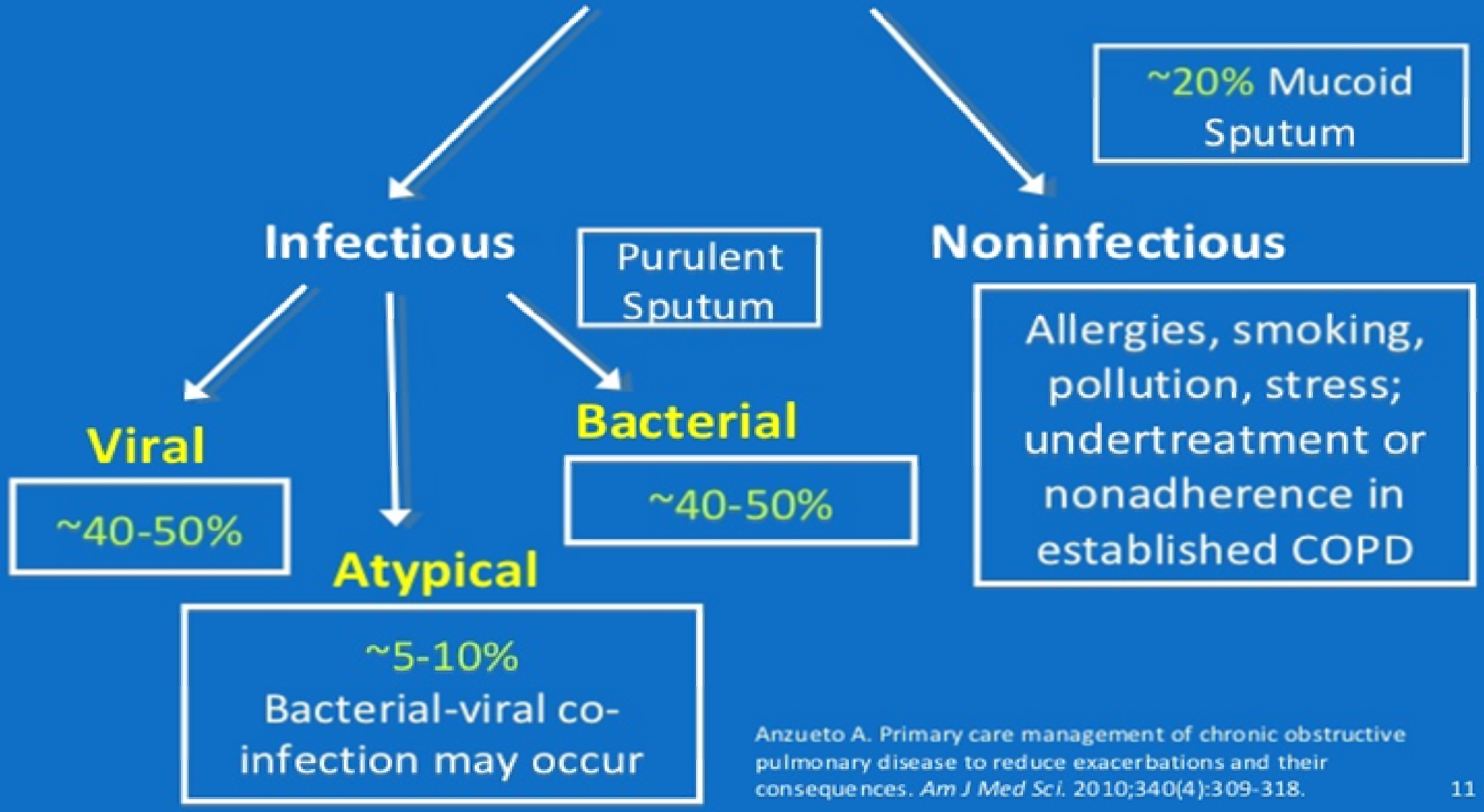
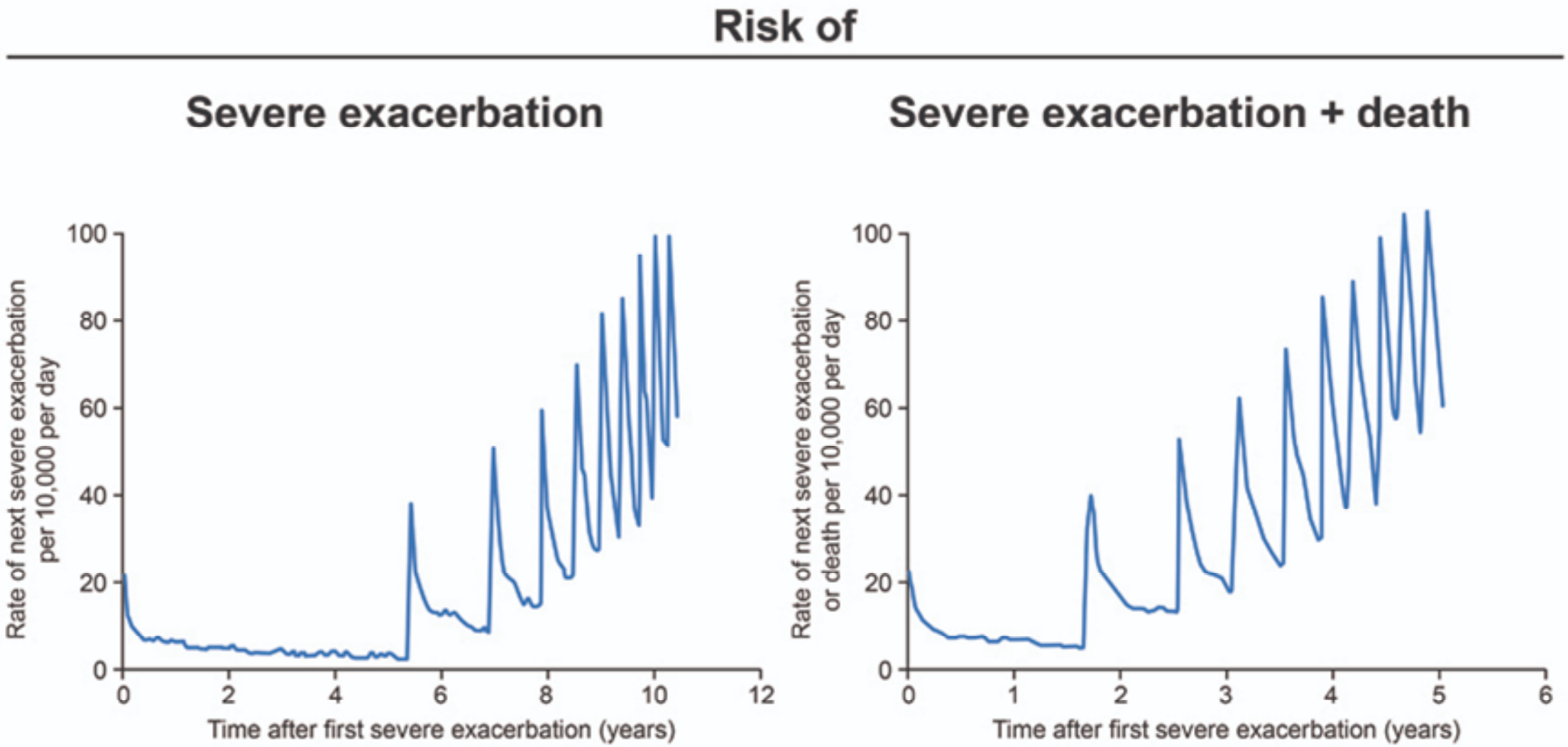
Etiology of COPD Exacerbations



Anzueto A. Primary care management of chronic obstructive pulmonary disease to reduce exacerbations and their consequences. *Am J Med Sci.* 2010;340(4):309-318.

Figure 4.



Hazard function of successive hospitalized COPD exacerbations (per 10,000 per day) from the time of their first ever hospitalization for a COPD exacerbation over the follow-up period. For further explanations, see text. Reproduced from *Thorax* with permission from BMJ Publishing Group, Ltd.[58]

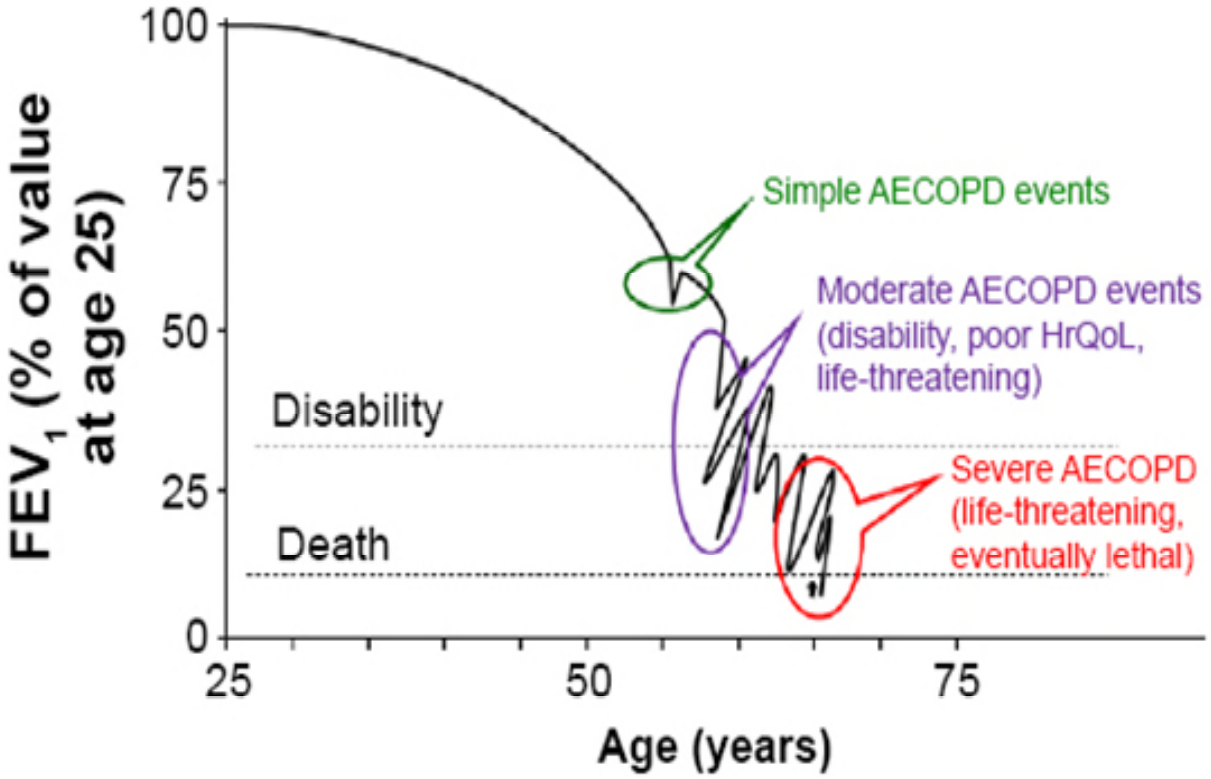


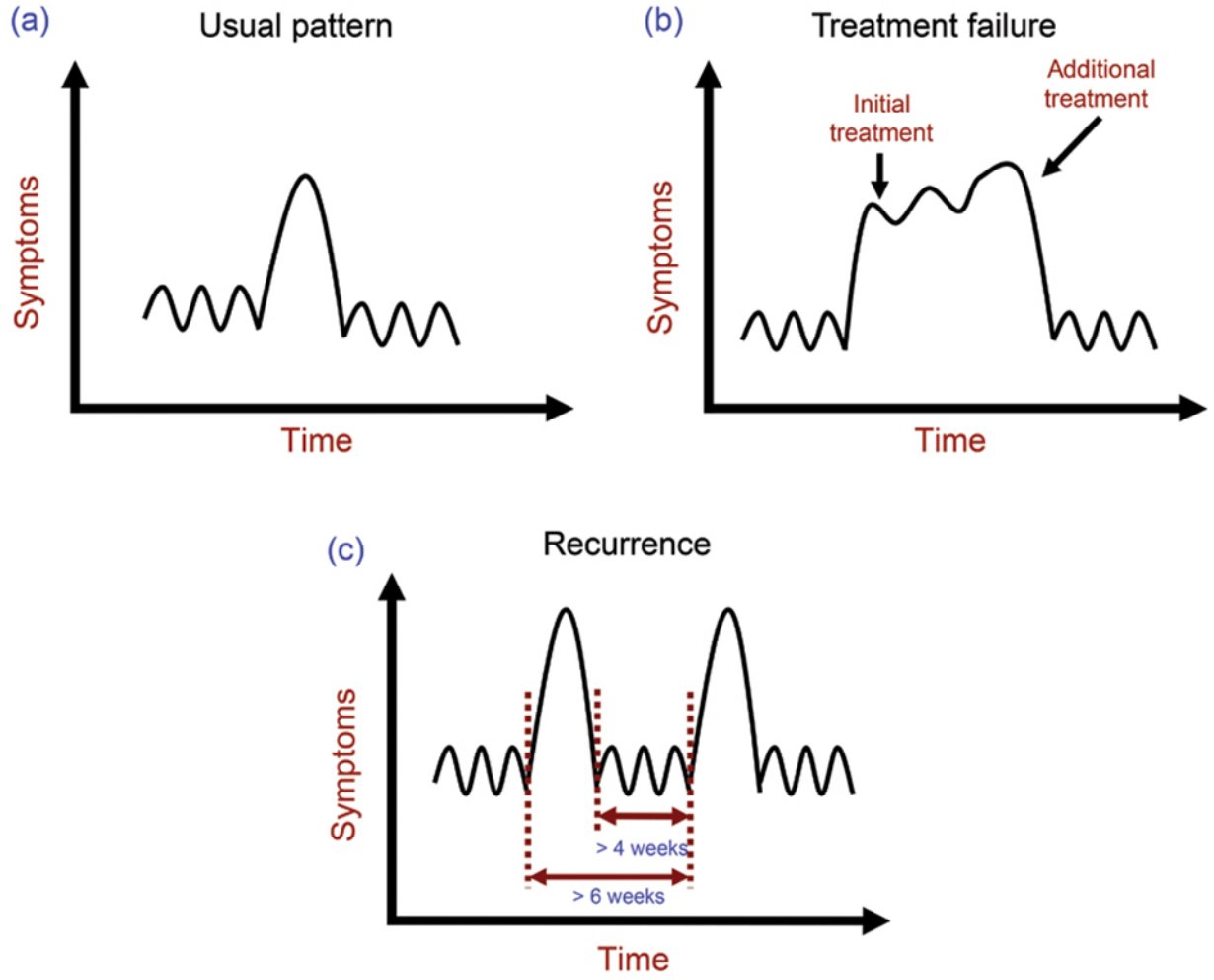
Figure 1 Fletcher–Peto diagram modified: lung function decline is not a constant, stable process.

Notes: It is the accumulated result of mild losses during steady state and sharp losses, due to acute exacerbations that accelerate as exacerbations become more frequent and more severe over time, during the natural course of the disease.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HrQoL, health-related quality of life.

Hillas G, Perlikos F, Tzanakis N. Acute exacerbation of COPD: is it the "stroke of the lungs"? 2016:11(1) Pages 1579—1586. https://doi.org/10.2147/COPD.S106160

Figure 1.



Proposed time-course patterns of COPD exacerbations: (a) *usual pattern*, (b) *treatment failure* (c) *recurrence*. For further explanations, see text. Reproduced with permission from Informa Healthcare, copyright ©2010, Informa Healthcare.[25]

Which of the following medications is the BEST for reducing exacerbations in COPD?

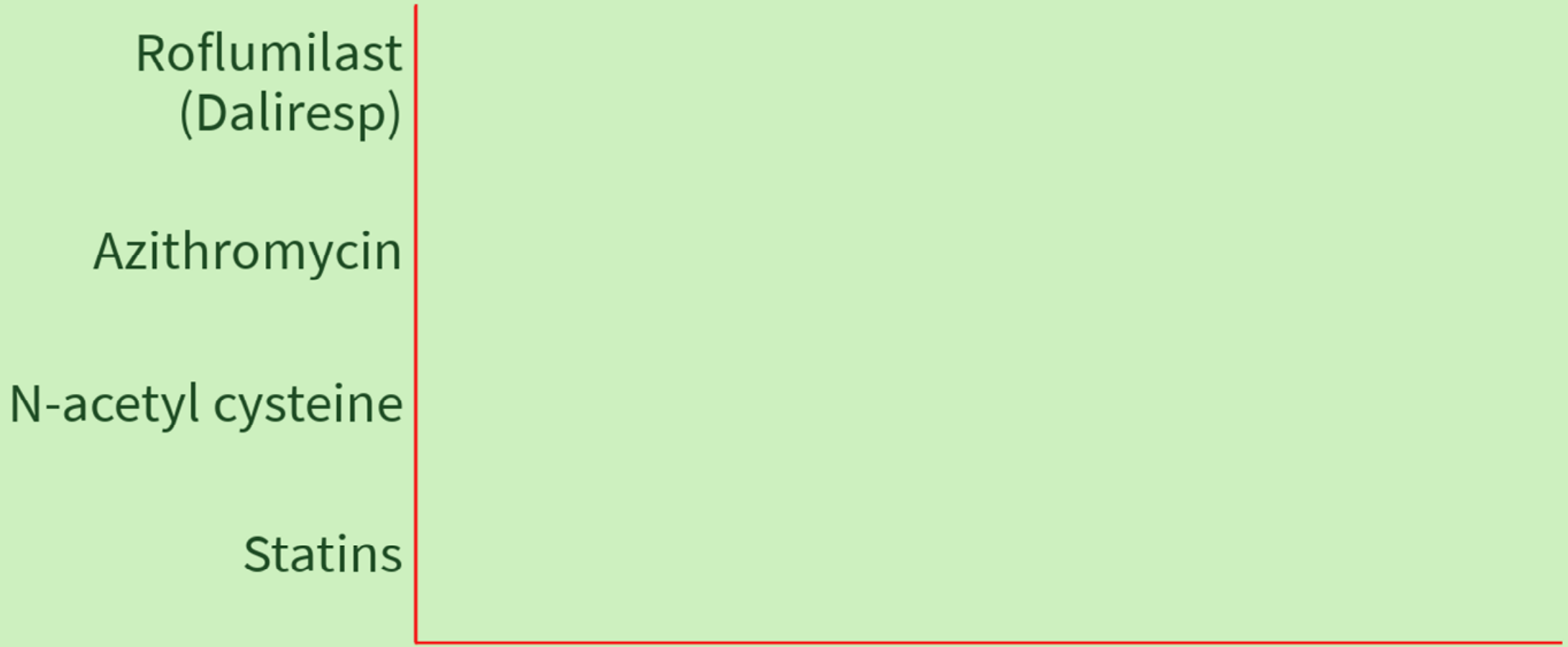


Table 2. Efficacy of Different Approaches to Decreasing Risk for Exacerbations

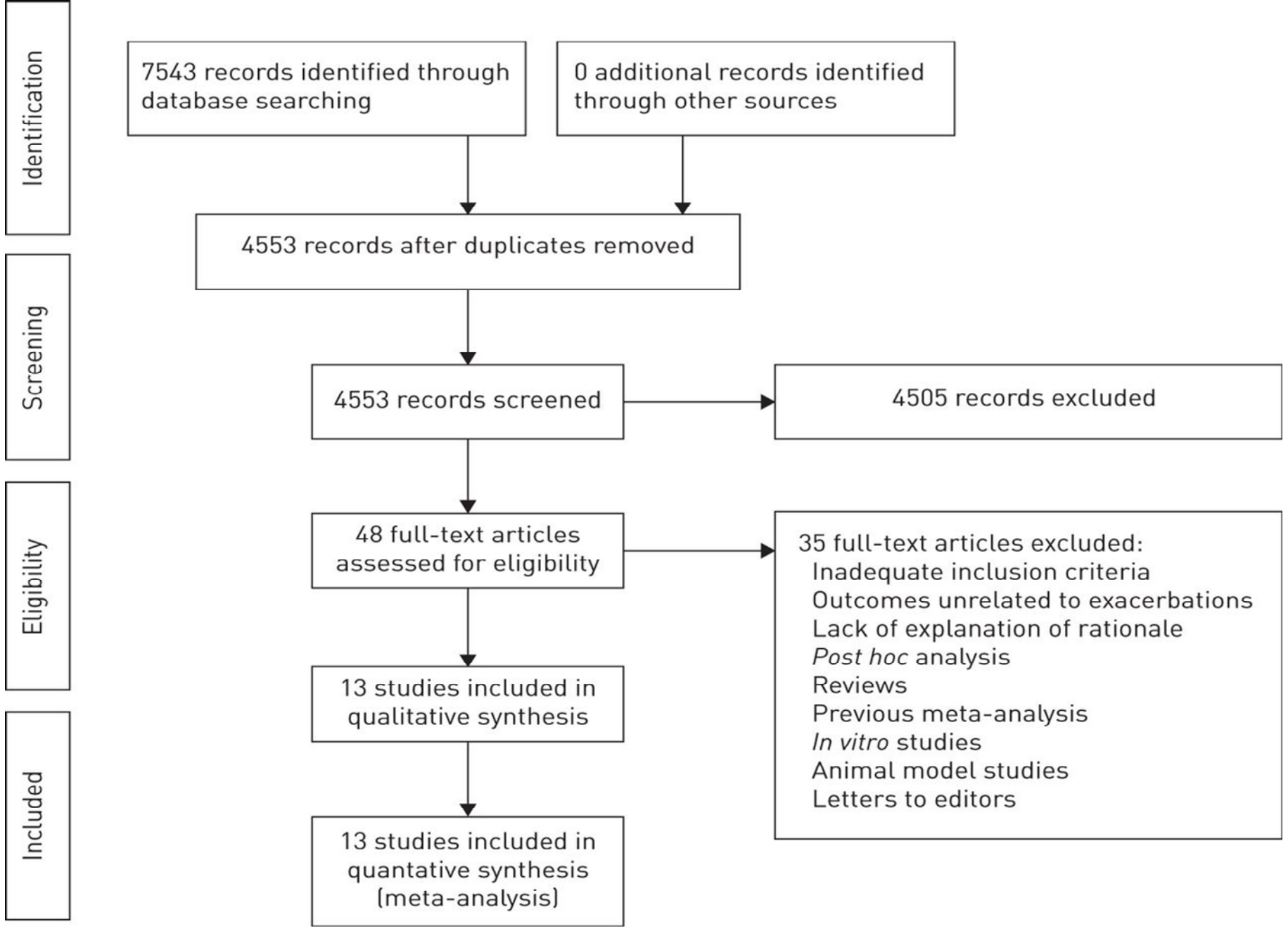
	Efficacy	Support	References
Non-pharmacologic Interventions			
Smoking Cessation	Supported	Large-scale observational study	66
Pulmonary Rehabilitation	Supported	Small-scale clinical studies	68, 69
Vaccination Against Pneumococcal and Influenza Virus Infection	Very strongly supported	Multiple clinical trials and meta-analyses	70-74
Pharmacotherapy			
LABA	Very strongly supported	Meta-analyses and multiple clinical trials	13, 76
LAMA	Very strongly supported	Meta-analyses and multiple clinical trials	57, 79, 80, 82, 83
LABA + LAMA vs. Monotherapy	Supported for LABA + LAMA vs LAMA monotherapy	Clinical trial	132
ICS Monotherapy	Supported	Meta-analysis, benefit limited to patients with FEV_1 <50%	91
ICS + LABA vs ICS or LABA monotherapy	Very strongly supported	Multiple clinical trials	56, 94
Triple Combination Therapy vs. Components	Variable results	Small-scale clinical trials provide conflicting results; meta-analysis indicates no significant benefit; large-scale observational study supports	102-105, 133
Systemic Treatments			
Roflumilast	Very strongly supported as add-on treatment to bronchodilators	Multiple large-scale clinical trials and meta-analysis	106-109
Macrolides/Quinolones	Strongly supported	Supported by large-scale clinical trials	116, 117
Statins	Supported	Supported by multiple observational studies, but no controlled trials to date	121, 122

ICS = inhaled corticosteroid, LABA = long-acting ß2-agonist LAMA = long-acting muscarinic antagonist

Agusti A, Calverley PM, Decramer M, Stockley RA, Wedzicha JA. Prevention of exacerbations in COPD: knowns and unknowns. *Chronic Obstr Pulm Dis*. 2014; 1(2): 166-184. doi: http://doi.org/10.15326/jcopdf.1.2.2014.0134

N-acetylcysteine (NAC)

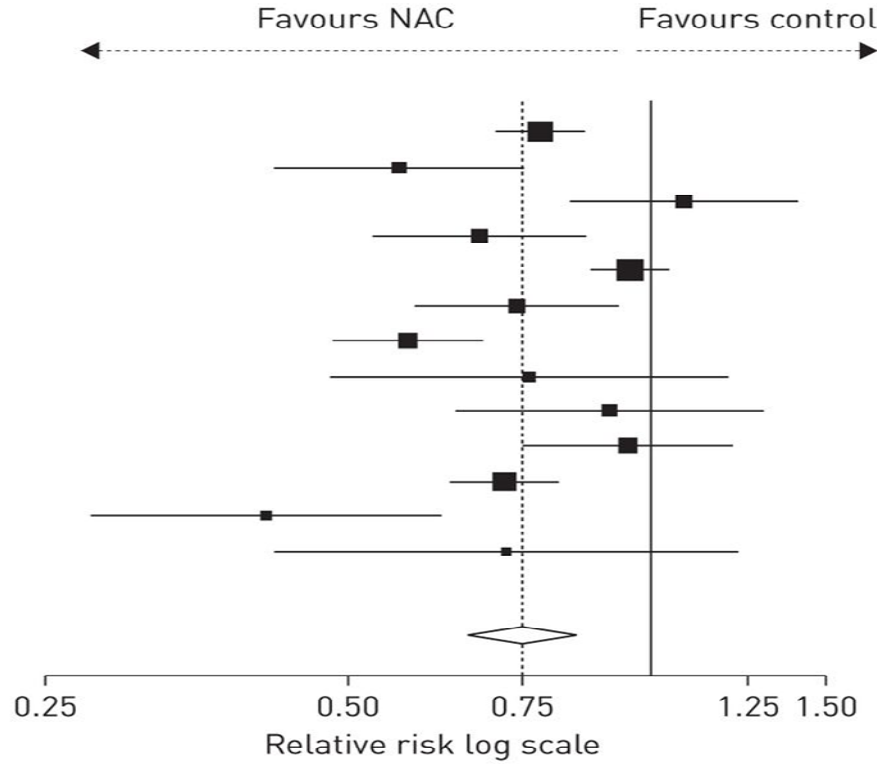
https://images.app.goo.gl/XzGHrW7mvtdUEovV6



Mario Cazzola, Luigino Calzetta, Clive Page, et al. Influence of *N*-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. European Respiratory Review Sep 2015, 24 (137) 451-461; **DOI:** 10.1183/16000617.00002215

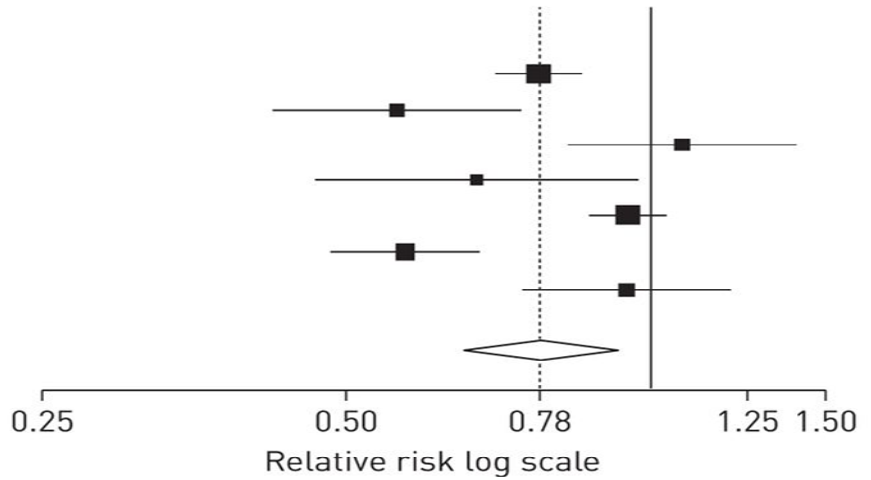
a)

Study [ref.], year	Estimate	(95% CI)
Zheng *et al.* [1], 2014	0.78	(0.70–0.86)
Tse *et al.* [20], 2013	0.56	(0.42–0.75)
Schermer *et al.* [26], 2009	1.08	(0.83–1.40)
Bachh *et al.* [27], 2007	0.67	(0.53–0.86)
Decramer *et al.* [3], 2005	0.95	(0.87–1.04)
Gerrits *et al.* [29], 2003	0.73	(0.58–0.93)
Pela *et al.* [24], 1999	0.57	(0.48–0.68)
Hansen *et al.* [19], 1994	0.76	(0.48–1.19)
Rasmussen and Glennow [25], 1988	0.91	(0.64–1.29)
McGavin *et al.* [22], 1985	0.95	(0.75–1.21)
Boman *et al.* [23], 1983	0.71	(0.63–0.81)
Babolini *et al.* [21], 1980	0.41	(0.28–0.62)
Grassi and Morandini [28], 1976	0.72	(0.42–1.22)
Overall (I^2=80%, p<0.01)	0.75	(0.66–0.84)



b)

Study [ref.], year	Estimate	(95% CI)
Zheng *et al.* [1], 2014	0.78	(0.70–0.86)
Tse *et al.* [20], 2013	0.56	(0.42–0.75)
Schermer *et al.* [26], 2009	1.08	(0.83–1.40)
Bachh *et al.* [27], 2007	0.67	(0.47–0.97)
Decramer *et al.* [3], 2005	0.95	(0.87–1.04)
Pela *et al.* [24], 1999	0.57	(0.48–0.68)
McGavin *et al.* [22], 1985	0.95	(0.75–1.21)
Overall (I^2=86%, p<0.01)	0.78	(0.65–0.93)



- In COPD patients not receiving ICS, regular treatment with mucolytics such as erdosteine, carbocysteine and N-acetylcysteine may reduce exacerbations and modestly improve health status.

- Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow one to identify precisely the potential target population for antioxidant agents in COPD.

https://images.app.goo.gl/KvvTvF4HUAEjvFwt6

EOS and HELIOS Trials

EOS - Salmeterol + Roflumilast → 466 pts vs 467 placebo

HELIOS - Tio + Roflumilast → 371 pts vs 372 placebo

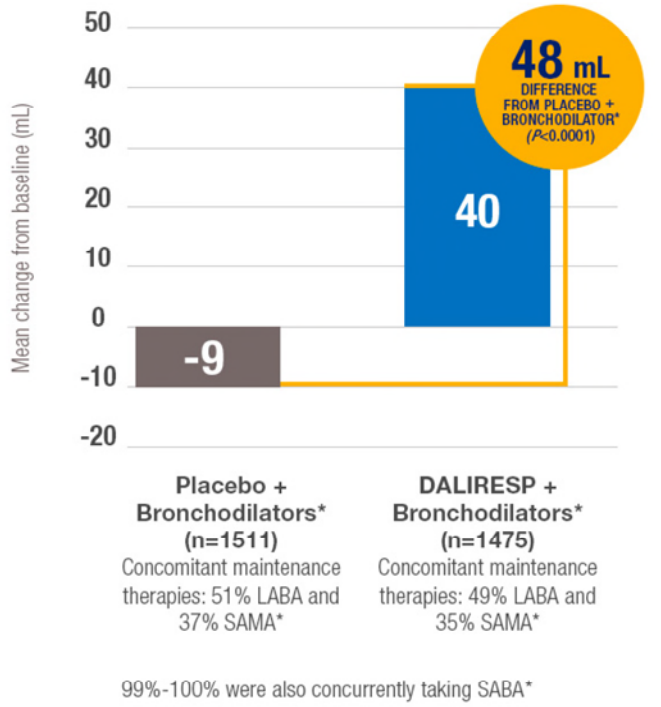
- Pts with severe COPD
- Allowed continuation of LABA and LAMA
- The preBD FEV_1 improved modestly when roflumilast was added to a long-acting bronchodilator
- EOS - mean preBD FEV1 ↑ by 49 mL (p<0·0001)
- HELIOS – mean preBD FEV1 ↑by 80 mL (p<0·0001)
  - Studies ran for only 24 weeks
  - Rate of acute exacerbations was not a primary end point
  - Trend toward reduction of exacerbations

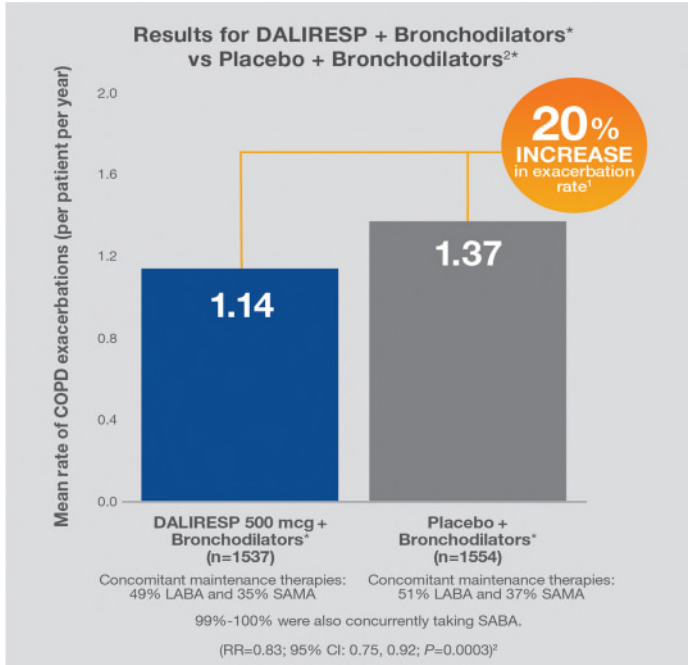
Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al; M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe COPD treated with long acting bronchodilators: two randomized clinical trials. Lancet 2009; 374:695–703.

Pooled analysis NNT 5

AURA and HERMES Trials

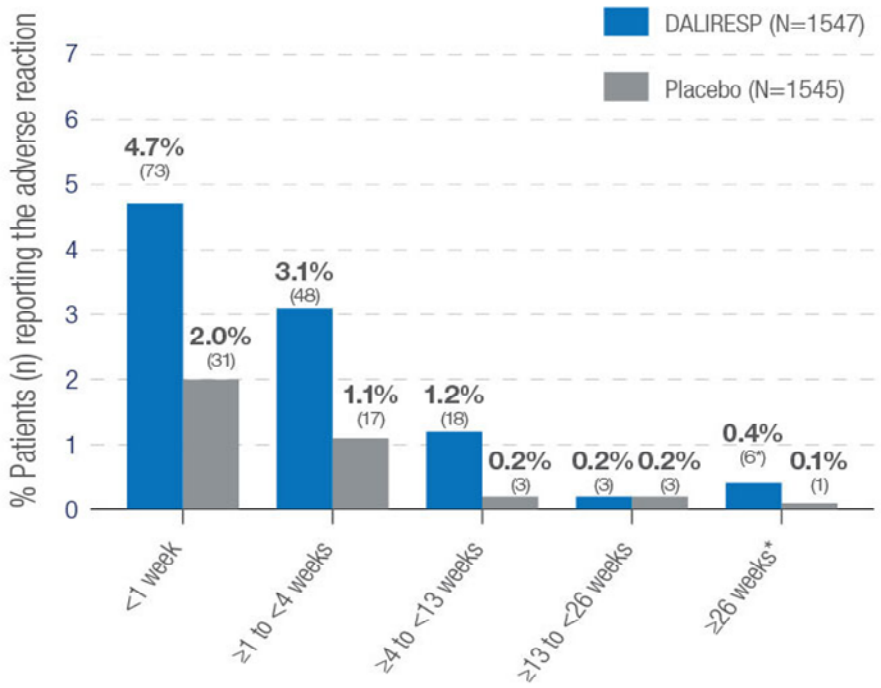
- 2009; Two 52-week placebo-controlled trials
- Patients with severe COPD with chronic bronchitis and a history of frequent exacerbations
- Maintenance therapy with LABA was continued
- ICS and LAMA were held
- Statistically significant improvements in preBD FEV_1 and reduction in the rate of exacerbations were observed (17% reduction, 95% CI 8–25, 1.14 v 1.37; $P < 0.0003$)





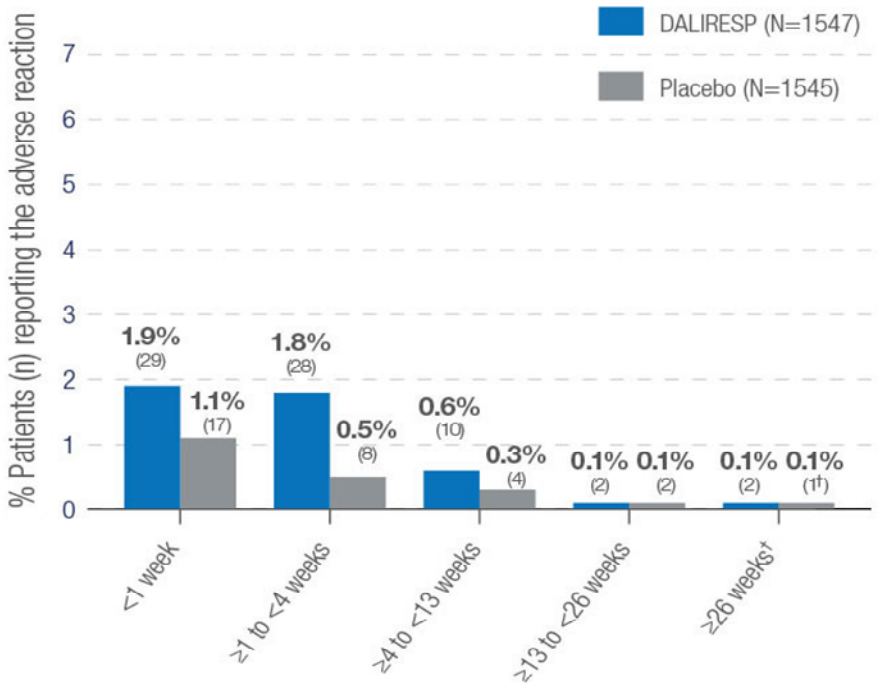
Calverley PM, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic COPD: two randomized clinical trials. Lancet 2009; 374:684–95.

DIARRHEA



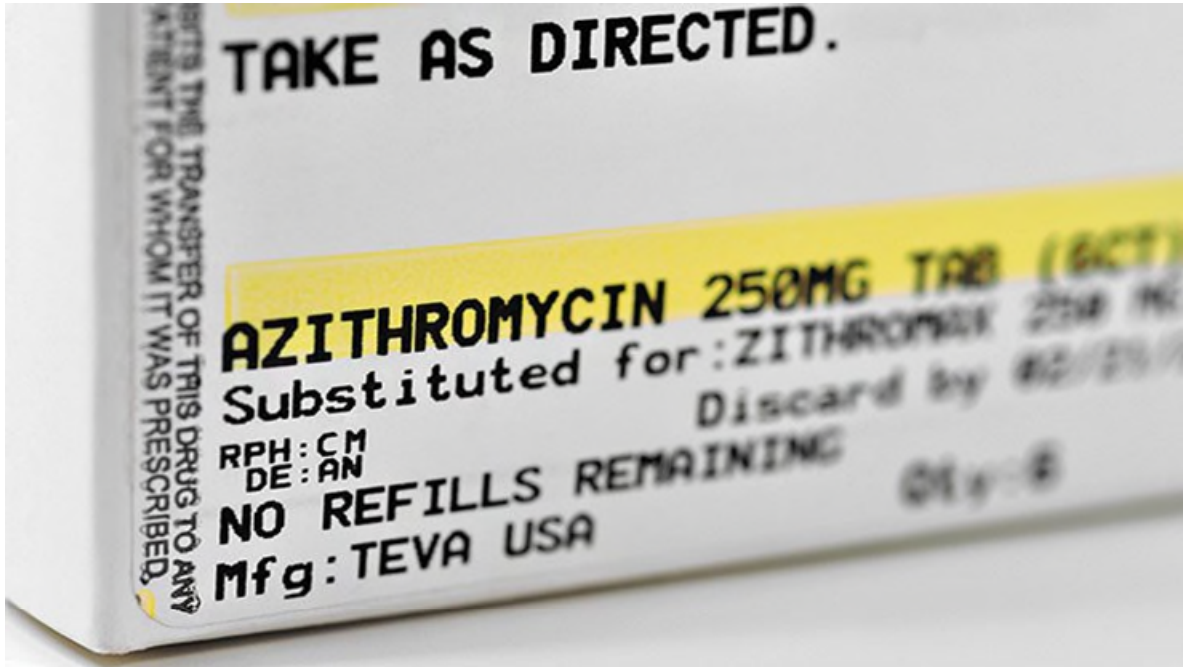
In these two studies, total incidence of diarrhea was 148 (9.6%) for DALIRESP and 55 (3.6%) for placebo.

NAUSEA



In these two studies, total incidence of nausea was 71 (4.6%) for DALIRESP and 32 (2.1%) for placebo.

Pooled AURA and HERMES data
14% vs 11%
NNH - 35



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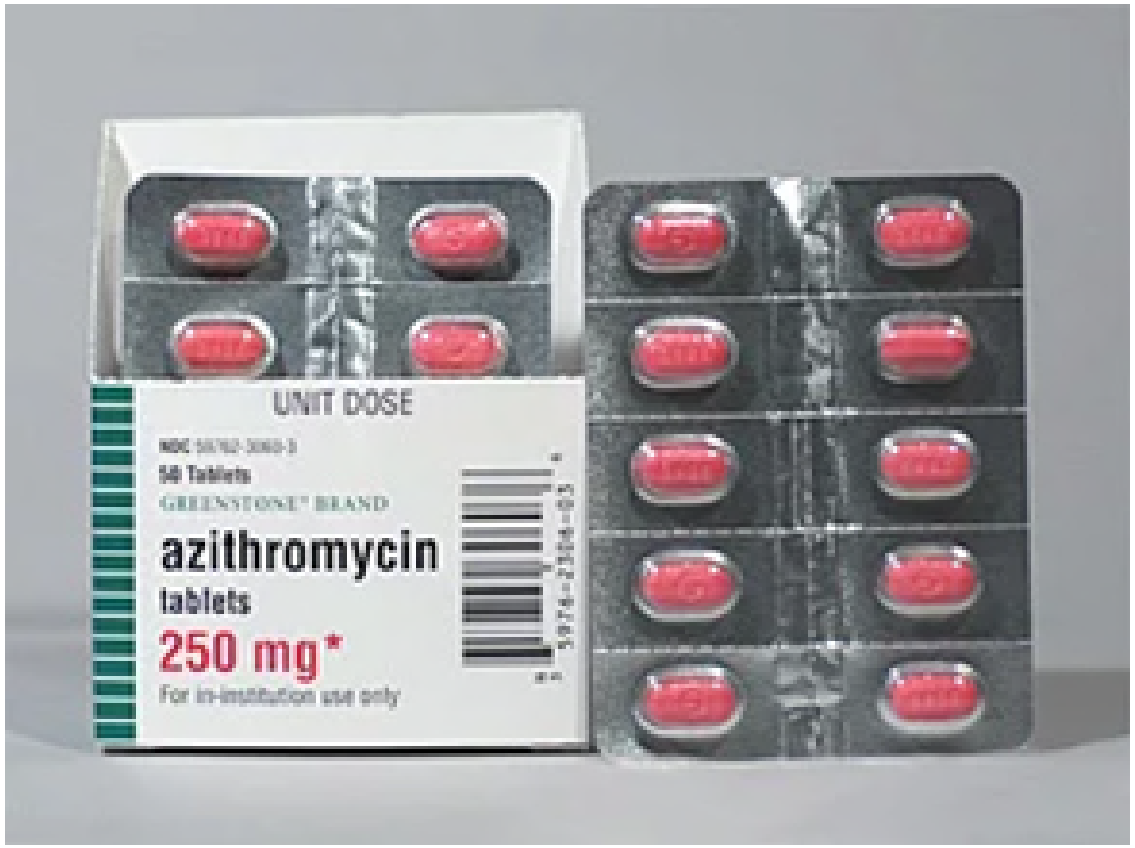

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ORIGINAL ARTICLE

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., et al., for the COPD Clinical Research Network

August 25, 2011
N Engl J Med 2011; 365:689-698
DOI: 10.1056/NEJMoa1104623

- 570 Azithro (250 mg daily) VS 572 placebo for 1 year + usual care.
- Time to first exacerbation → 266 days (95% CI, 227-313) for Azithro VS 174 days (95% CI, 143-215) for placebo (P<0.001).
- Frequency of exacerbations → 1.48 per pt-year for Azithro VS 1.83 per pt-year for placebo (P=0.01).

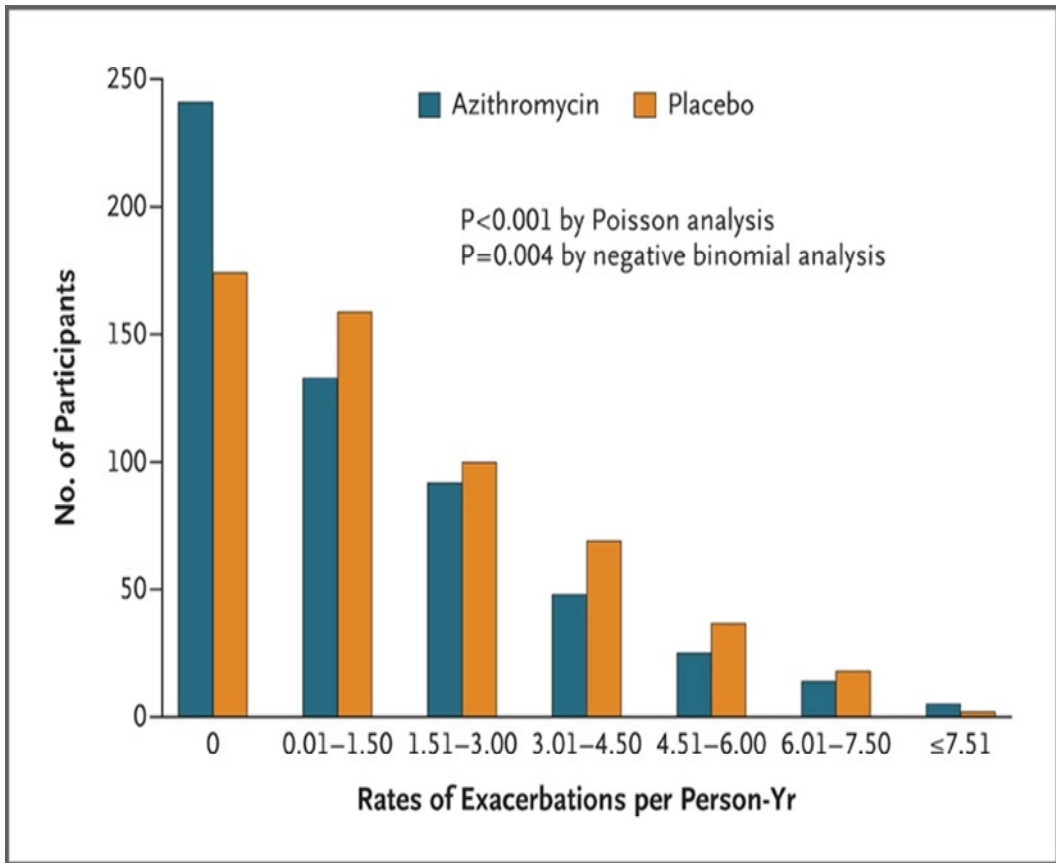

Figure 3. Rates of AECOPD per Person-Year, According to Study Group.

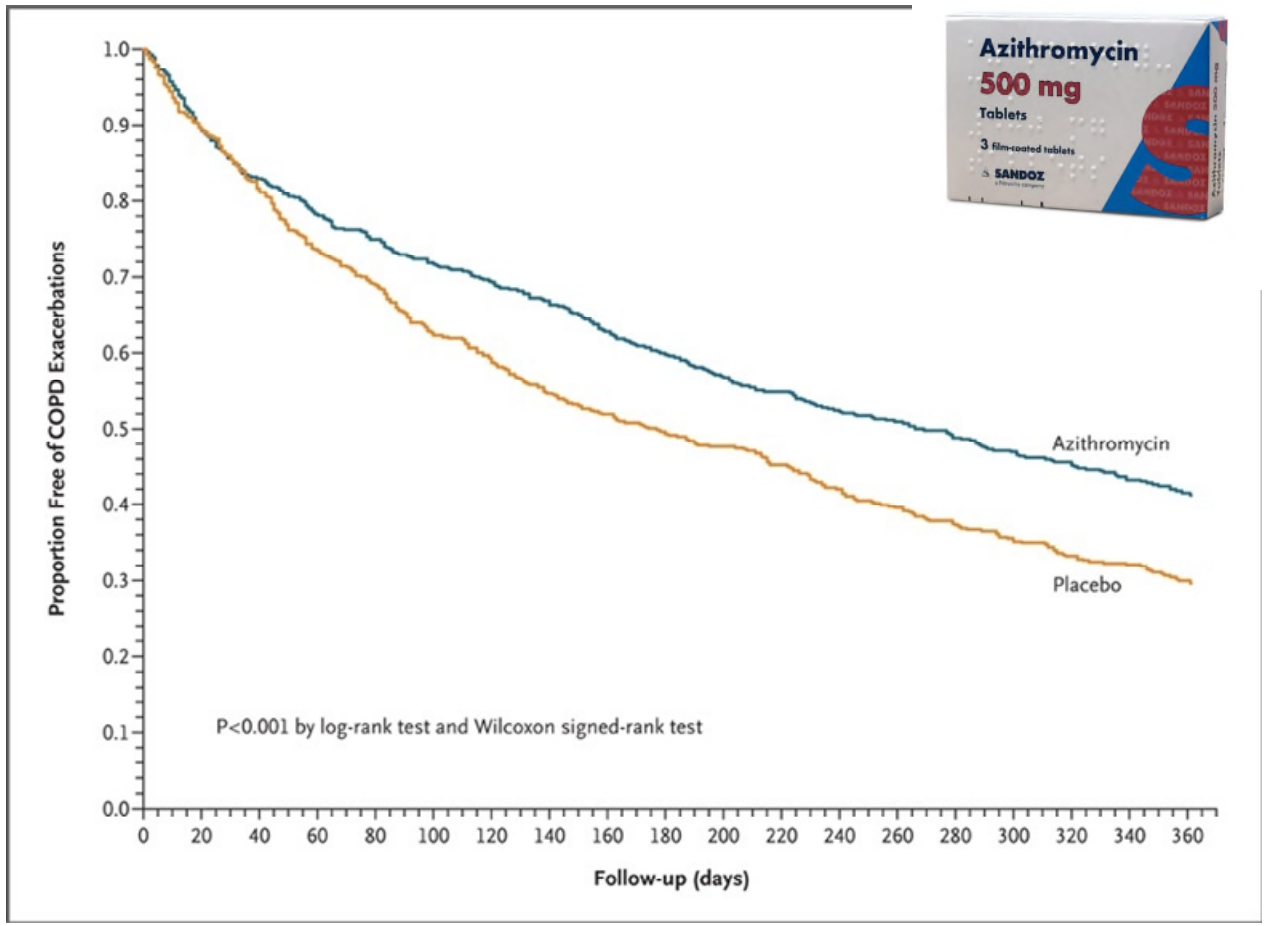

Figure 2. Proportion of Participants Free from AECOPD for 1 Year, According to Study Group.

- Hazard ratio for having an AECOPD per pt-year in the Azithro group was 0.73 (95% CI, 0.63 to 0.84; P<0.001).
- Hearing decrements – more in the Azithro group than in the placebo group (25% vs. 20%, P=0.04).
- NNT to prevent one AECOPD was 2.86.

Agenda

- Eosinophils
- Combination therapy
- Theophylline
- Exacerbation reduction
- ***Bronchoscopic Lung Volume Resection***

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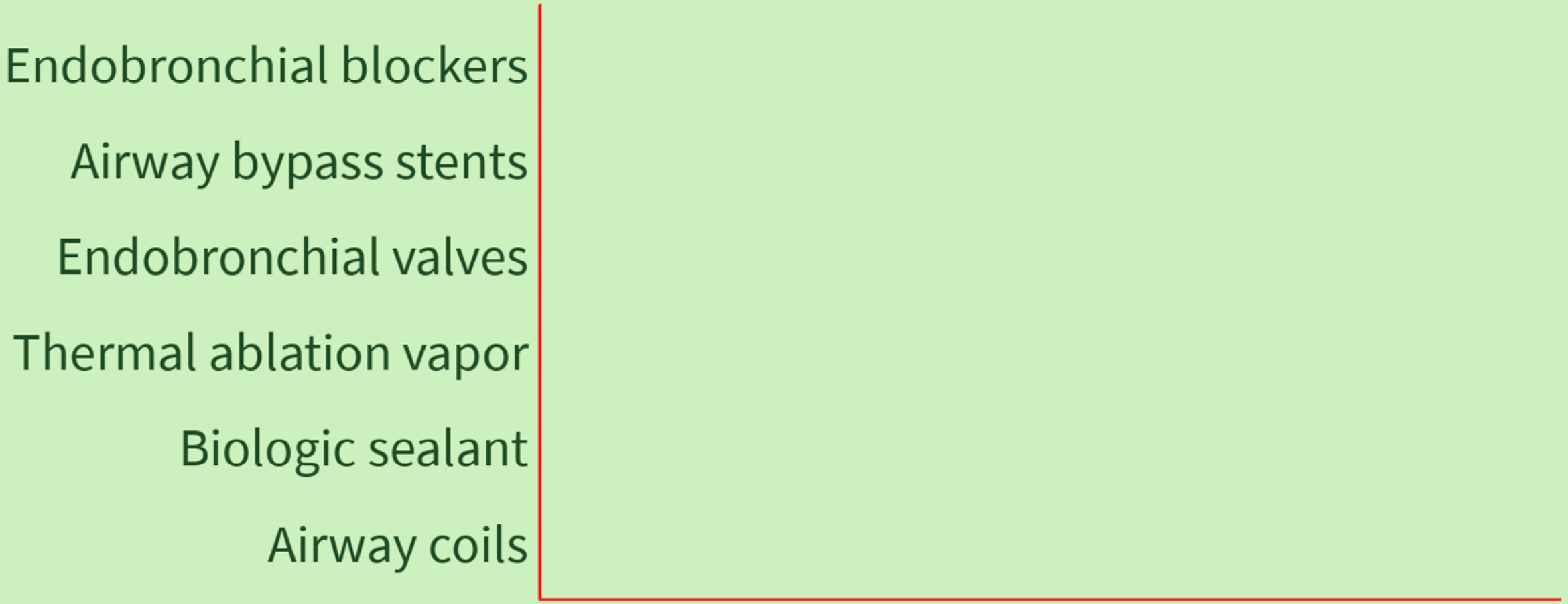
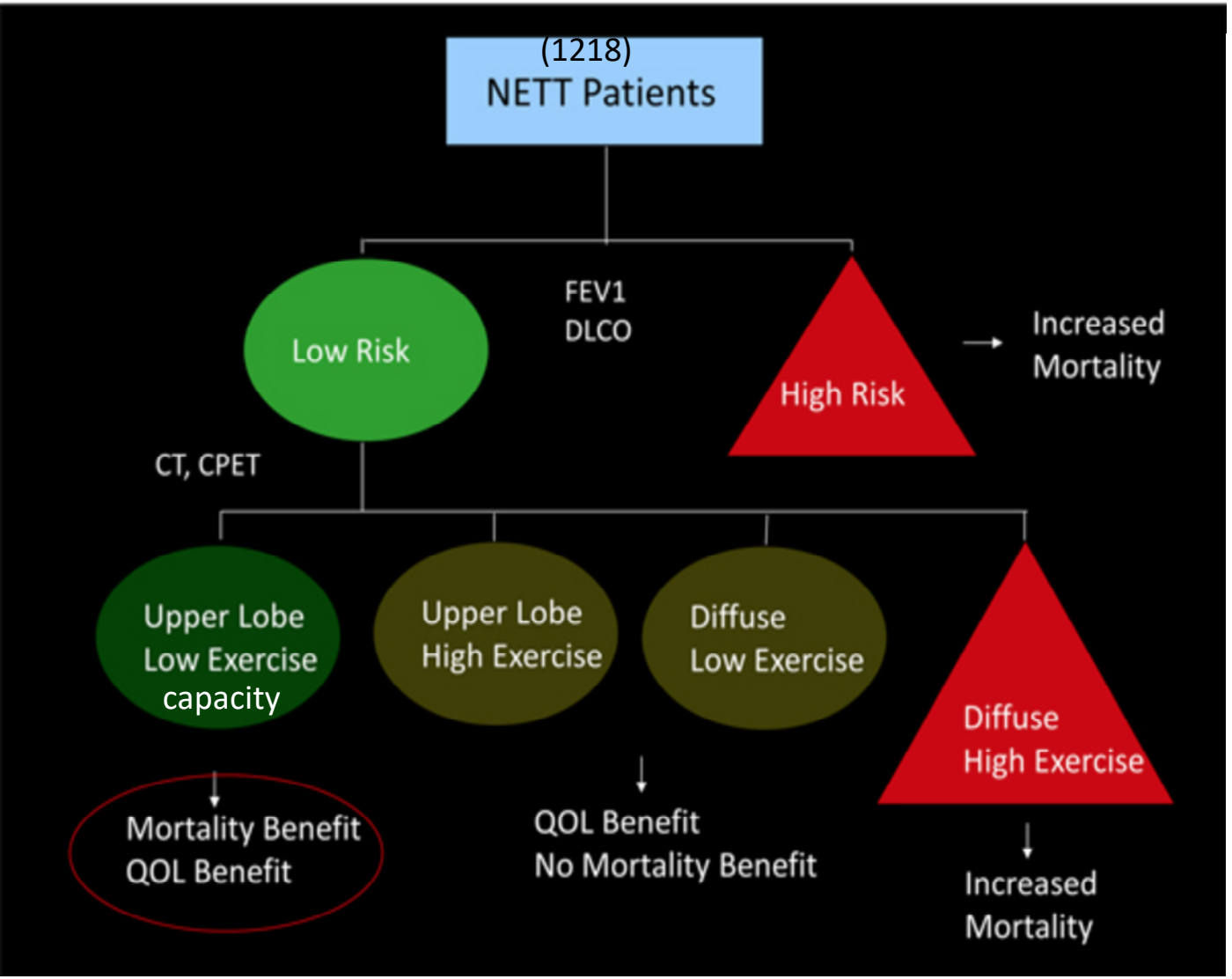
Which of the following bronchoscopic lung volume reduction modalities is approved for use in the US?





2003

NETT

stands for

National Emphysema Treatment Trial

Abbreviations.com

NETT trial – non high risk patients

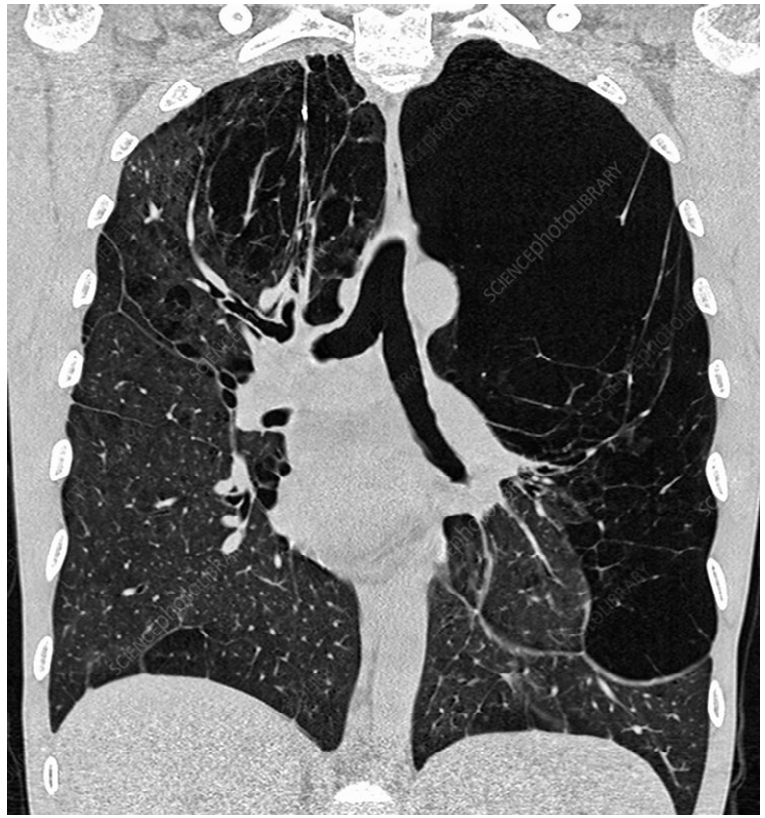
	Predominantly upper lobe emphysema	Predominantly non-upper lobe emphysema
Low exercise capacity	RR 0.47 p=0.005	RR 0.81 p=0.49
High exercise capacity	RR 0.98 p=0.70	RR 2.06 p=0.02

Quezada W, Make B. Interventional Options for COPD- LVRS, Bronchoscopic Therapies and the Future. Chronic Obstr Pulm Dis. 2016 Jan 15;3(1):446-453. doi: 10.15326/jcopdf.3.1.2015.0171.

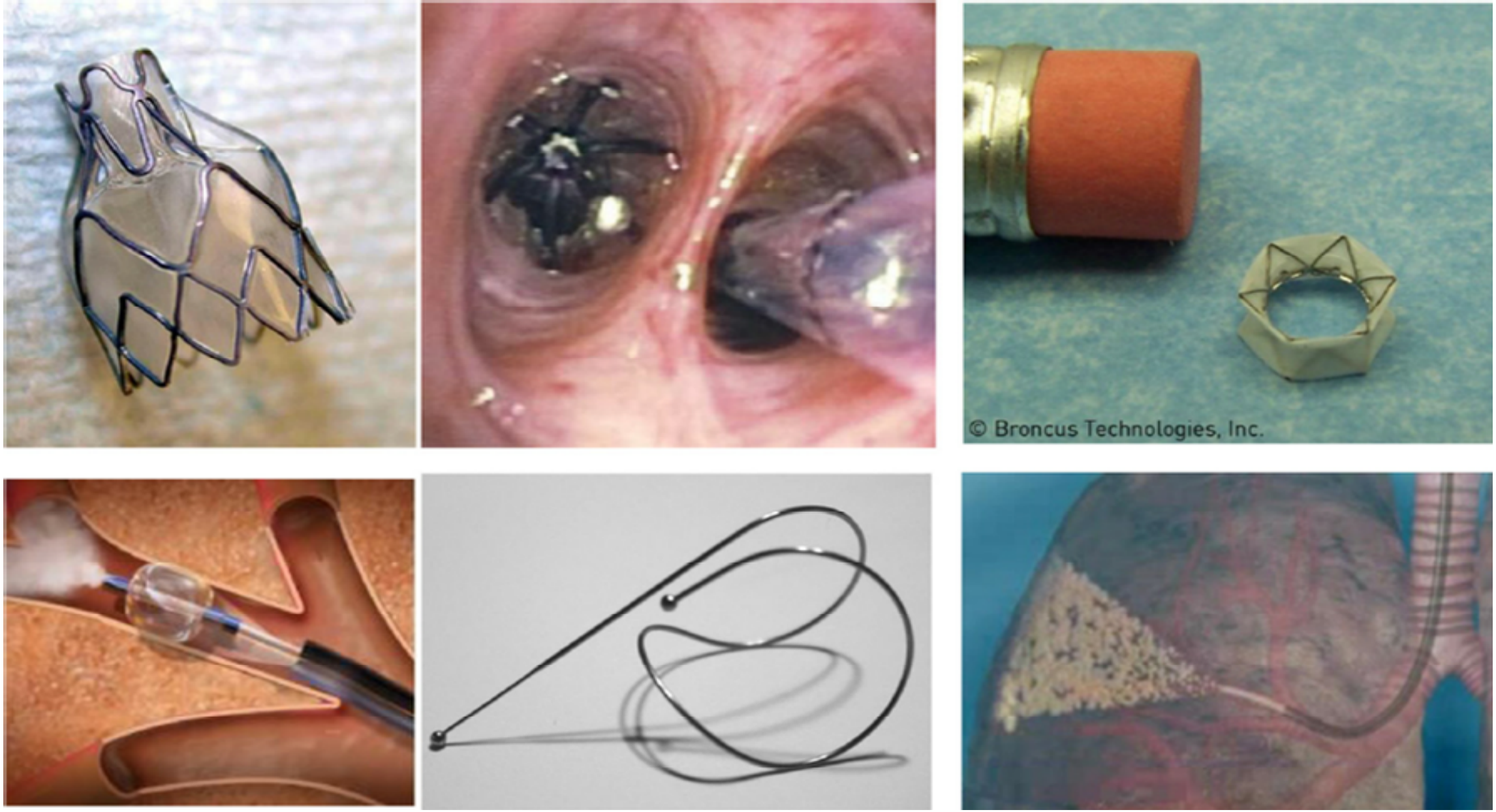
Bronchoscopic Lung Volume Resection

- Occlude airways proximal to nonfunctioning, hyperinflated areas of lungs.

- Blocking
  - Endobronchial and intrabronchial valves
- Nonblocking
  - Coils
  - Thermal ablation



Fernandez-Bussy S, Labarca G, Herth FJF. Bronchoscopic lung volume reduction in patients with severe emphysema. Semin Respir Crit Care Med. 2018;39:685-692.

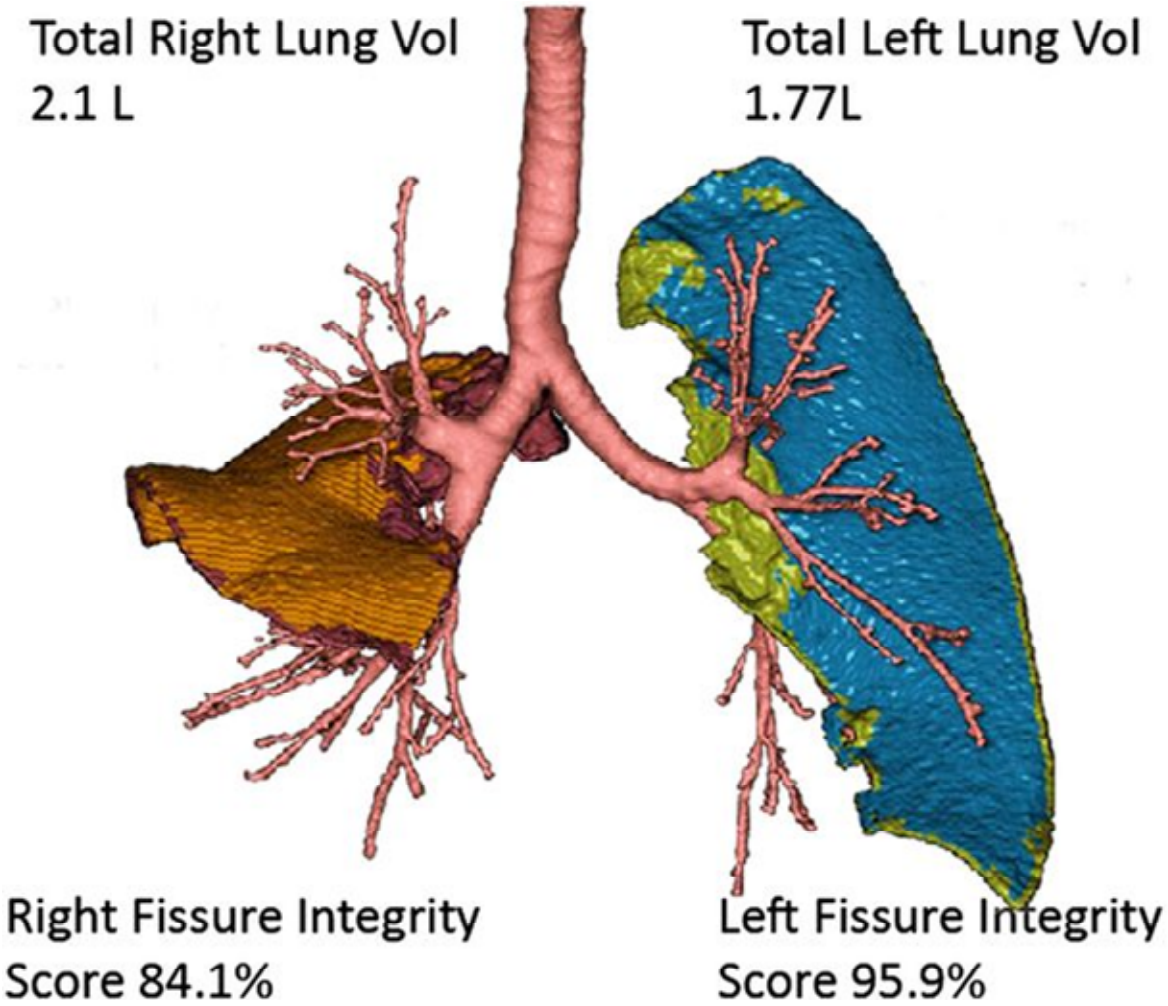


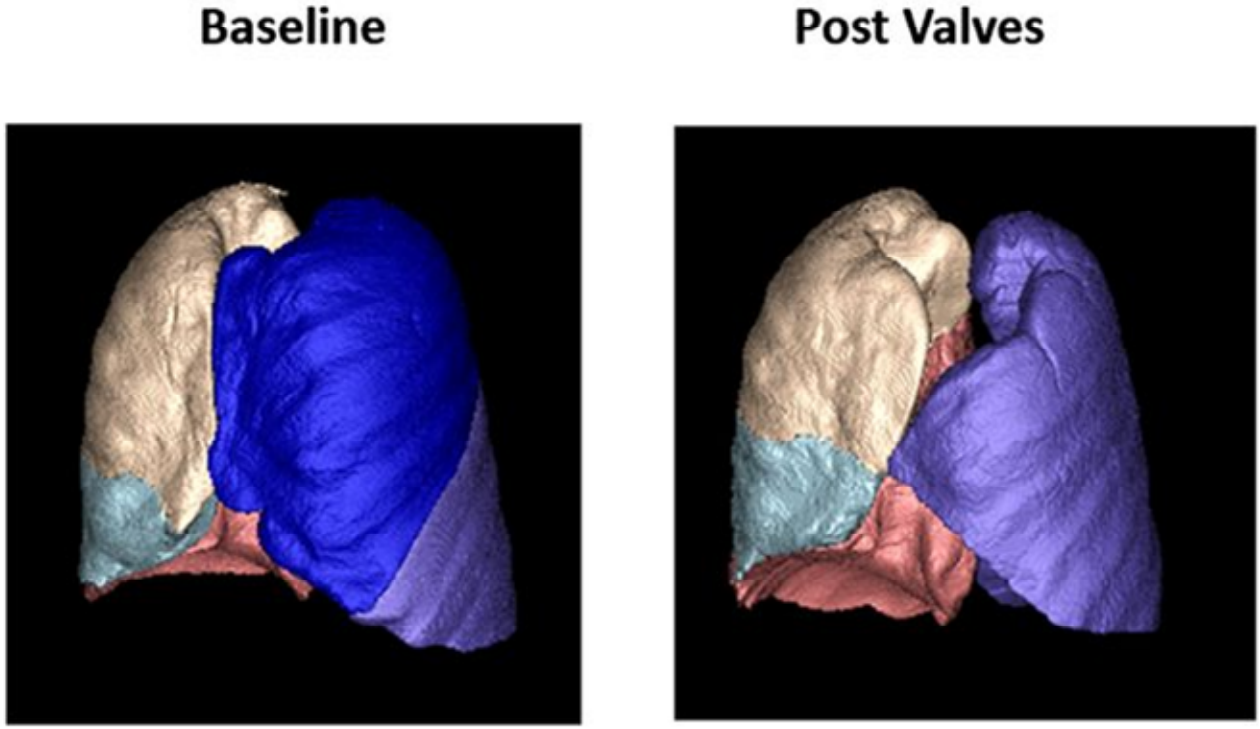
Lee HJ1, Shojaee S, Sterman DH. Endoscopic lung volume reduction. An American perspective. Ann Am Thorac Soc. 2013 Dec;10(6):667-79. doi: 10.1513/AnnalsATS.201306-145FR.

Types of Valves

- Zephyr Endobronchial Valve (Pulmonx Corporation; Redwood City, California)

- Spiration Valve System (Olympus Respiratory America; Redmond, Washington)

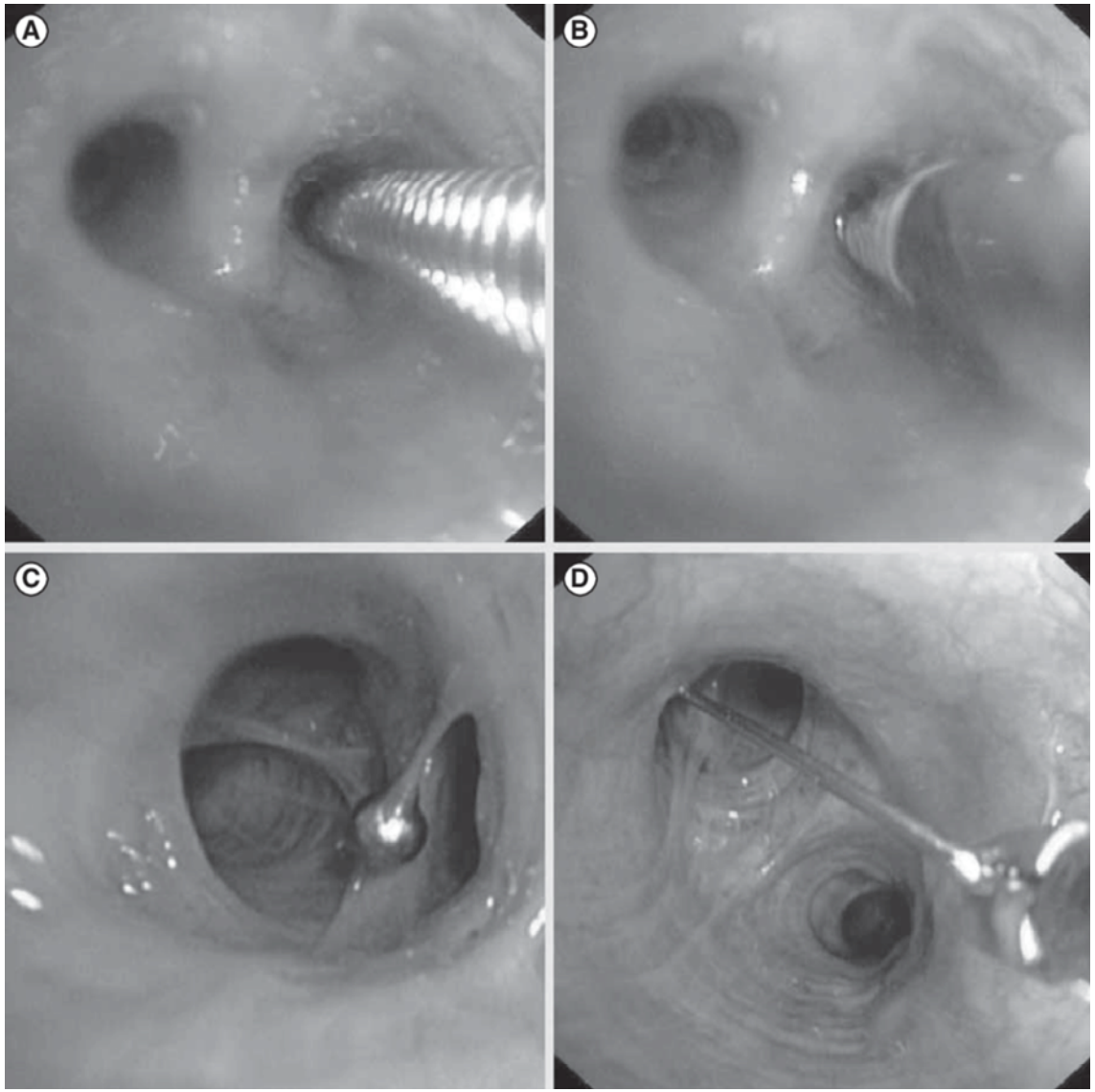


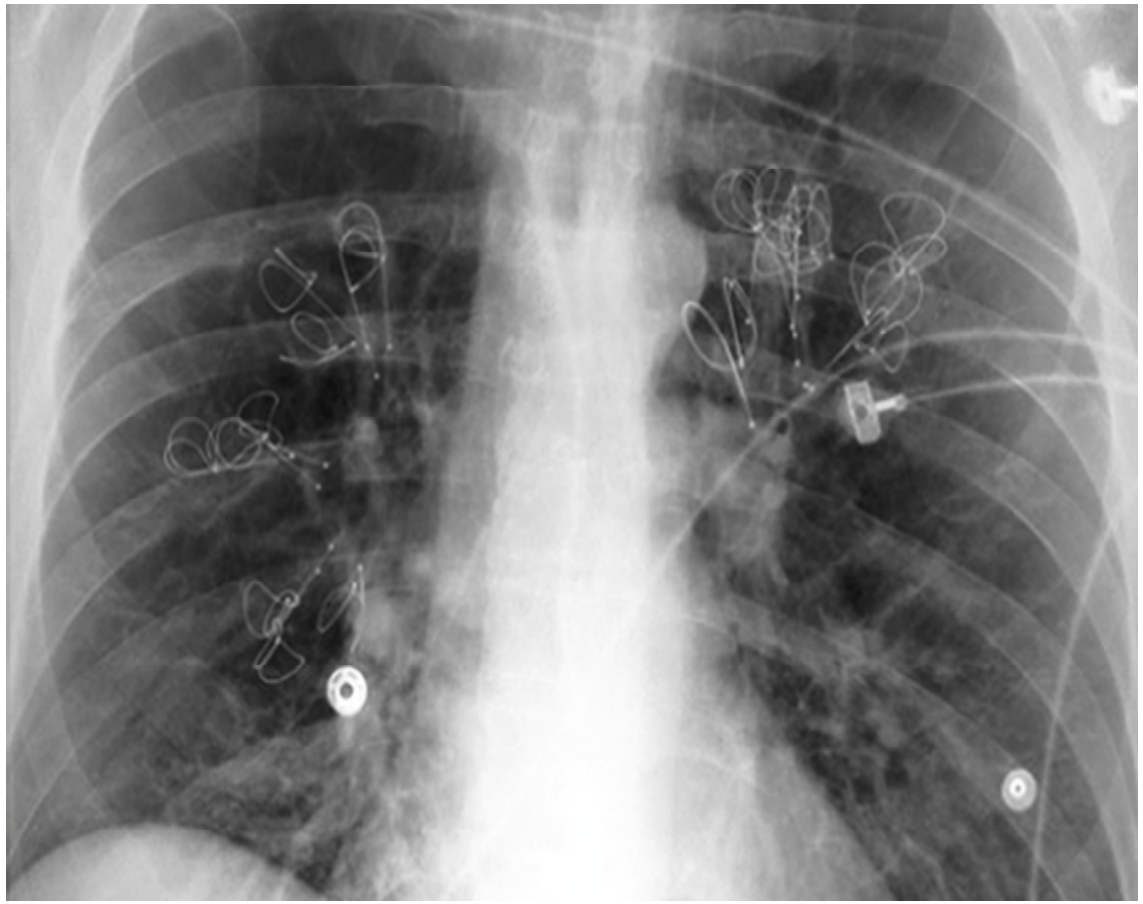


Typically, collateral ventilation is assessed using quantitative CT software or the Chartis System (Pulmonx Corporation)

Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax. 2014 Mar;69(3):280-6. doi: 10.1136/thoraxjnl-2013-203743. Epub 2013 Sep 5.

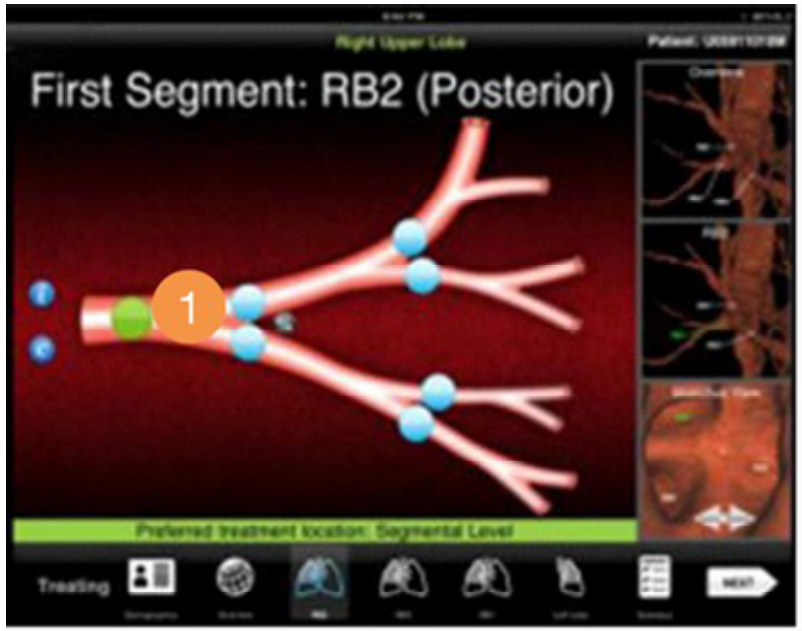
**Endobronchial coils are not approved for use in the United States*



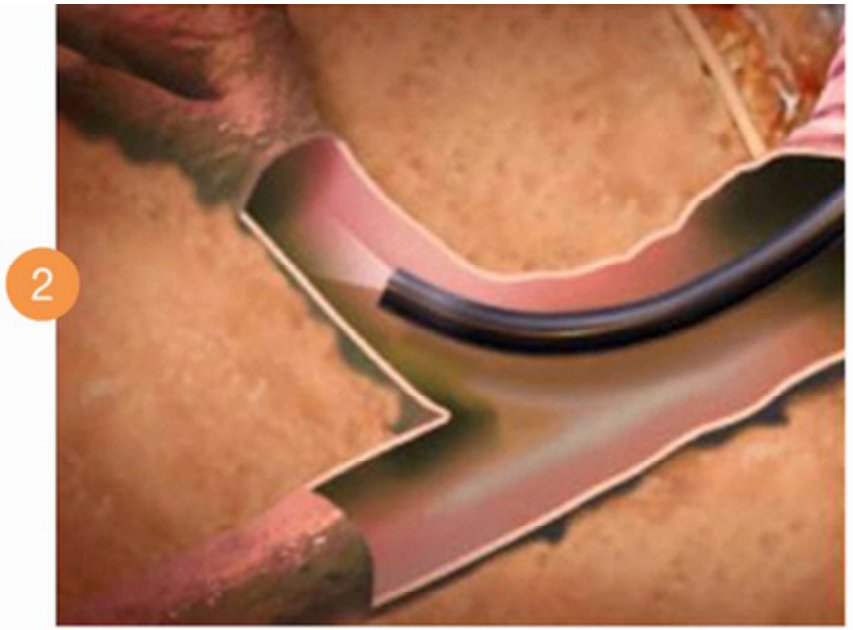


Klooster K, Ten Hacken NH, Slebos DJ. The lung volume reduction coil for the treatment of emphysema: a new therapy in development. Expert Rev Med Devices. 2014 Sep;11(5):481-9. doi: 10.1586/17434440.2014.929490. Epub 2014 Aug 4.

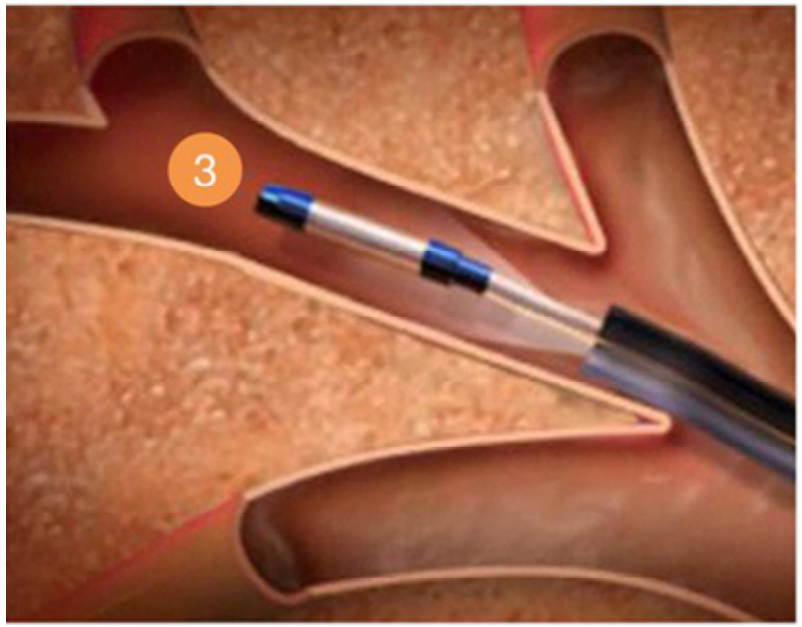
**Thermal vapor therapies are not approved for use in the United States*



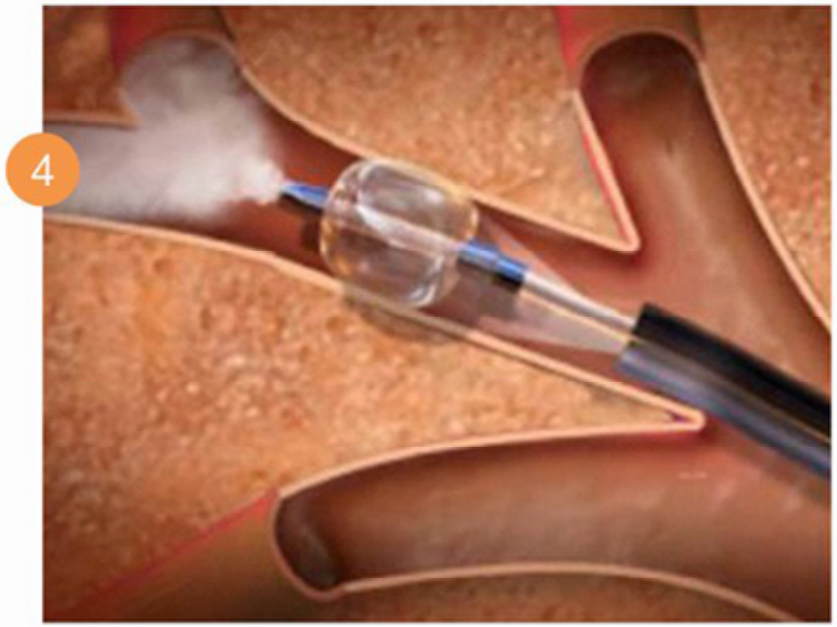
IP3 identifies diseased region for treatment



Bronchoscope is positioned into airway of diseased region



Vapor catheter placed via bronchoscope in airway



Vapor delivered for 3 to 10 seconds based on mass of region

- Head-to-head comparisons between therapies are not available
- Guidelines exist*
- Both valve types improve symptoms, QOL, and lung function

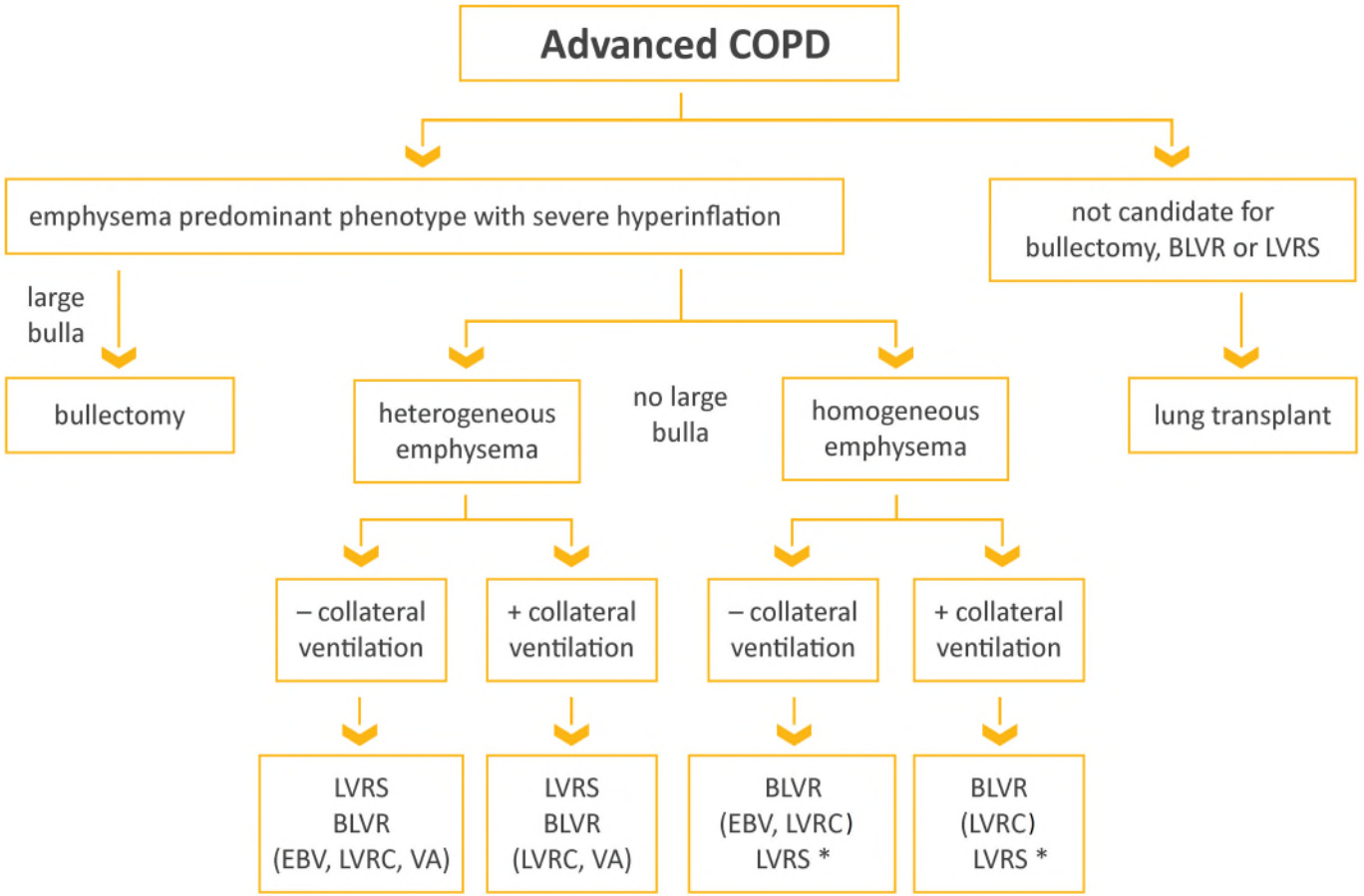
- Patient Selection -
- Evidence of air trapping on lung testing (RV > 175%)
- Absence of collateral ventilation (CV) distal to the target area

* Slebos D, Shah PL, Herth FJF, Valipour A. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from Expert Panel on Endoscopic Lung Volume Reduction. Respiration. 2017;93:138-150.

Bronchoscopic lung volume reduction modality	Indications	Common complications
Endobronchial blockers	Heterogeneous Emphysema	(1) Blocker migration (2) Postobstructive pneumonia
Airway bypass stents	Homogenous Emphysema	(1) COPD exacerbation (2) Pneumonia/bronchitis (3) Air leak/pneumomediastinum
Endobronchial valves	Heterogeneous Emphysema	(1) COPD exacerbation (2) Pneumothorax (3) Bleeding (4) Pneumonia
Thermal vapor ablation	Heterogeneous Emphysema	(1) COPD exacerbation (2) Pneumonitis
Biological sealants	Both homogenous and heterogeneous emphysema	(1) COPD exacerbation (2) Pneumonia/aspiration
Airway implants/coils	Both homogenous and heterogeneous emphysema	Data not yet available

INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.



Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

*at some but not all centers

FIGURE 4.5

Patient scenario

- 63 y/o male; has been a patient for 5 years; Smoker; Known COPD; Last FEV1 in Feb 2019 was 18%.
- Sig SOB; cough; No night time or exertional O2; Quit smoking after last PFTs done; multiple exacerbations
- On multiple inhalers through the years. Now on ICS/LABA and LAMA.
- Asking for more options for treatment…

Which of the following is the next best option for the treatment of this patient's COPD?

Using blood Eosinophil levels to guide treatment.	A
Using combination therapy (LABA/LAMA/ICS).	B
Adding Theophylline.	C
Focusing on Exacerbation reduction.	D
Bronchoscopic Lung Volume Resection/Reduction.	E

References

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- Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; and the **UPLIFT** Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543-1554. doi: http://dx.doi.org/10.1056/NEJMoa0805800
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https://images.app.goo.gl/4Wg7bZeHZRimJtEf7

https://images.app.goo.gl/FEodaPhd9iLSwZhd7