Virginia Mason™

Pulmonary Update

Steven Kirtland, MD FCCP
Virginia Mason Medical Center

No relevant financial relationships with commercial interests to disclose

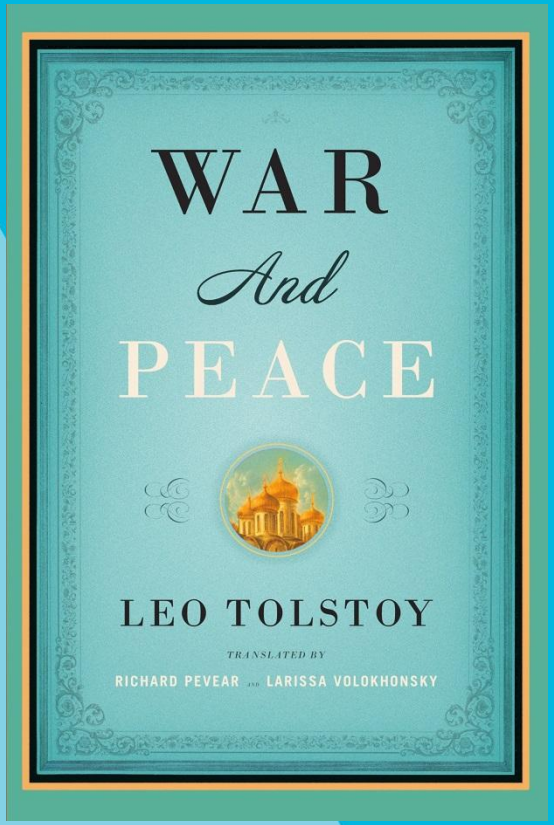
Ask

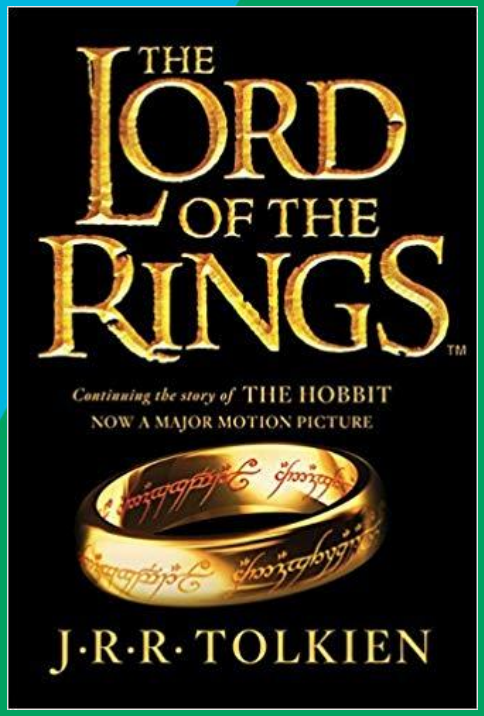
--Know and understand the diagnosis and treatment of common pulmonary diseases including COPD, Bronchitis, Bronchiectasis and Pulmonary Embolism.

-- To discuss the role that primary care providers have in the management of pulmonary disease.

--To discuss and review new treatments and the medical management of the above diseases

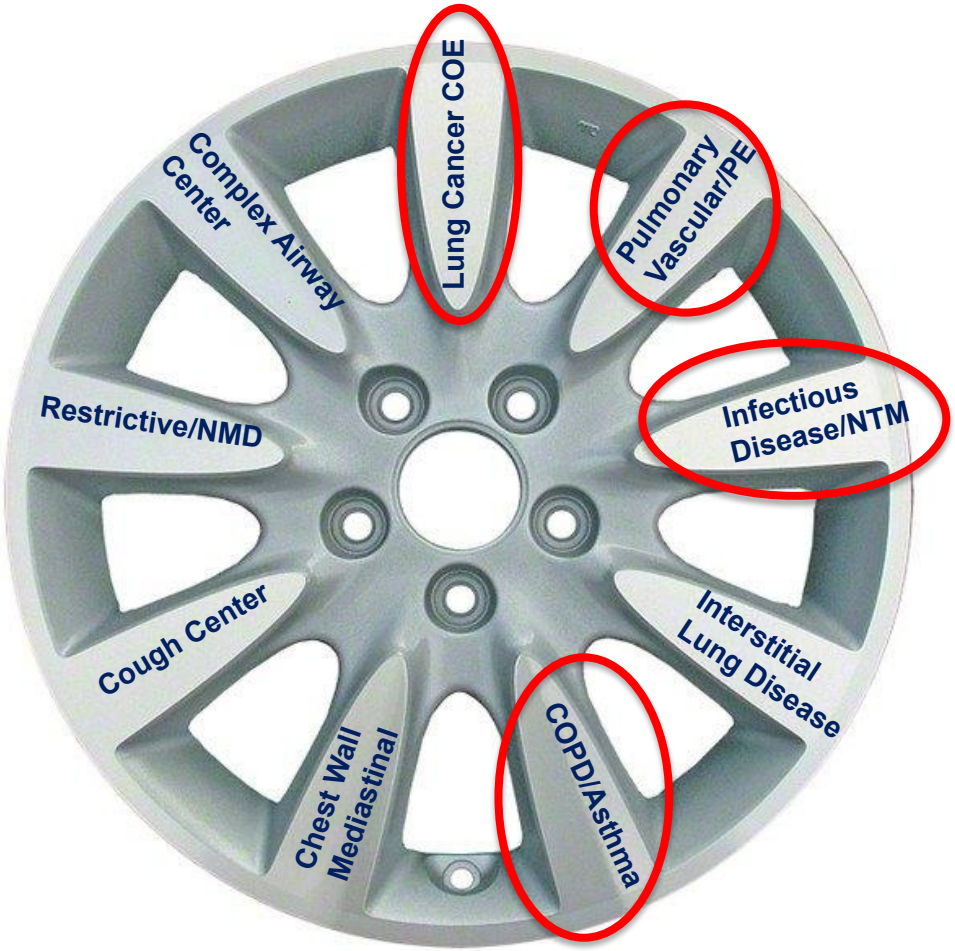

HOLY
BIBLE


WAR
And
PEACE
LEO TOLSTOY
TRANSLATED BY
RICHARD PEVEAR AND LARISSA VOLOKHONSKY

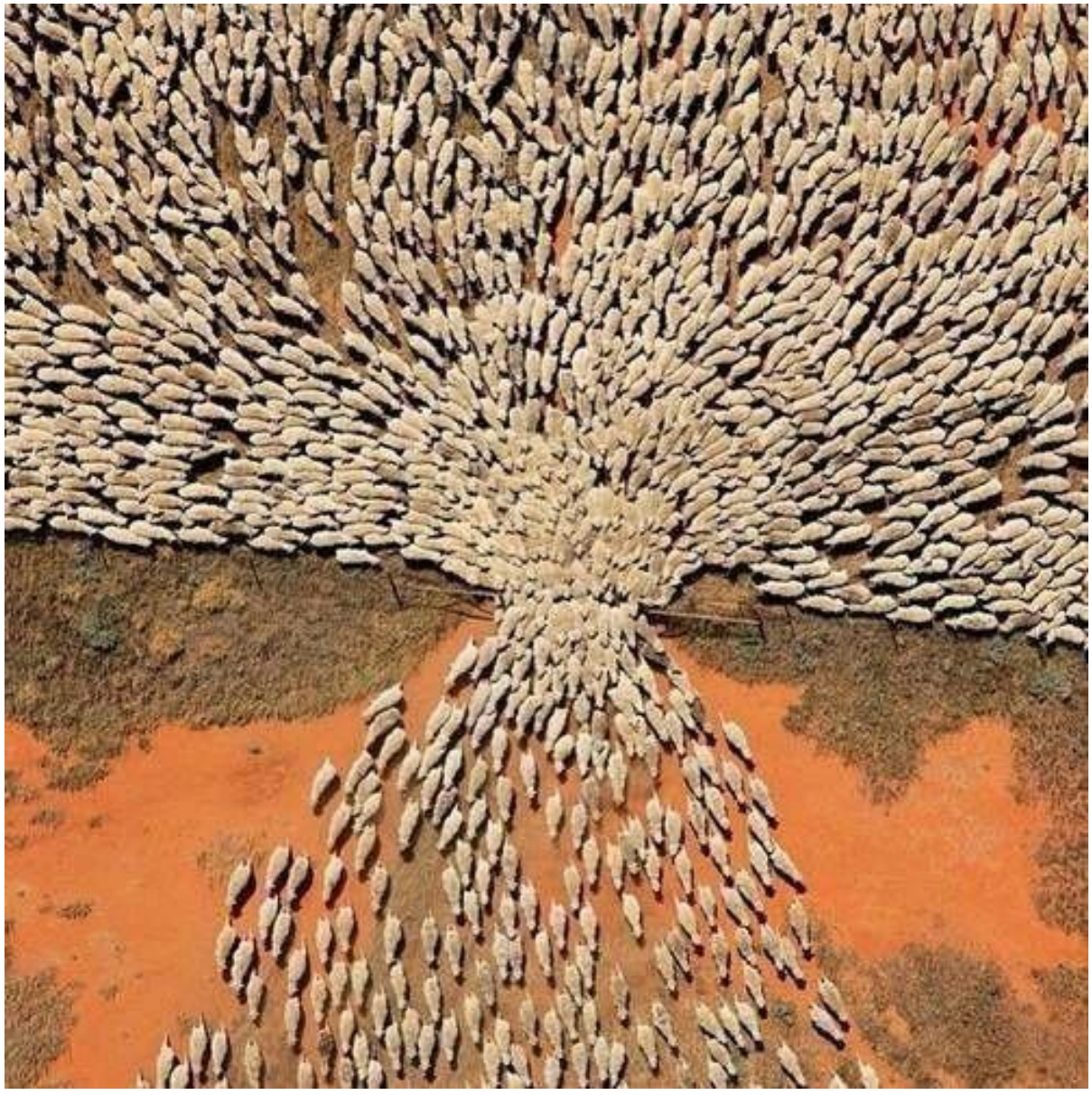

THE
LORD
OF THE
RINGS
Continuing the story of THE HOBBIT
NOW A MAJOR MOTION PICTURE
J·R·R· TOLKIEN


MARGARET MITCHELL'S
GONE
WITH THE
WIND
THE EPIC NOVEL OF OUR TIME

Virginia Mason Thoracic Center



Primary Care Role



Vaping

In a car

2018 LUNG CANCER FACTS

EVERY DAY

422

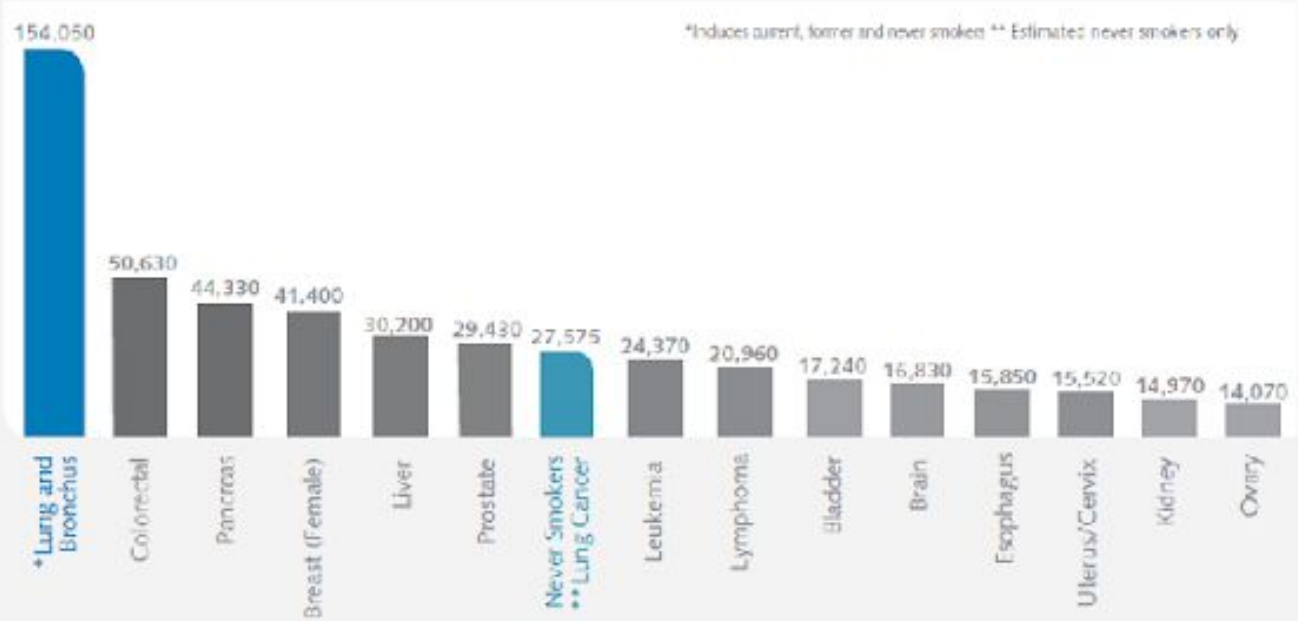
AMERICANS DIE OF LUNG CANCER.

Lung cancer is the leading cancer killer of men & women in **EVERY ETHNIC GROUP.**

Of the men and women with lung cancer, 17.9% are **NEVER SMOKERS.**[2]

Lung cancer makes up 25% of all **CANCER DEATHS.**

LUNG CANCER IS THE LEADING CAUSE OF CANCER DEATH[1]



PROFILE OF NEW LUNG CANCER CASES[3]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD

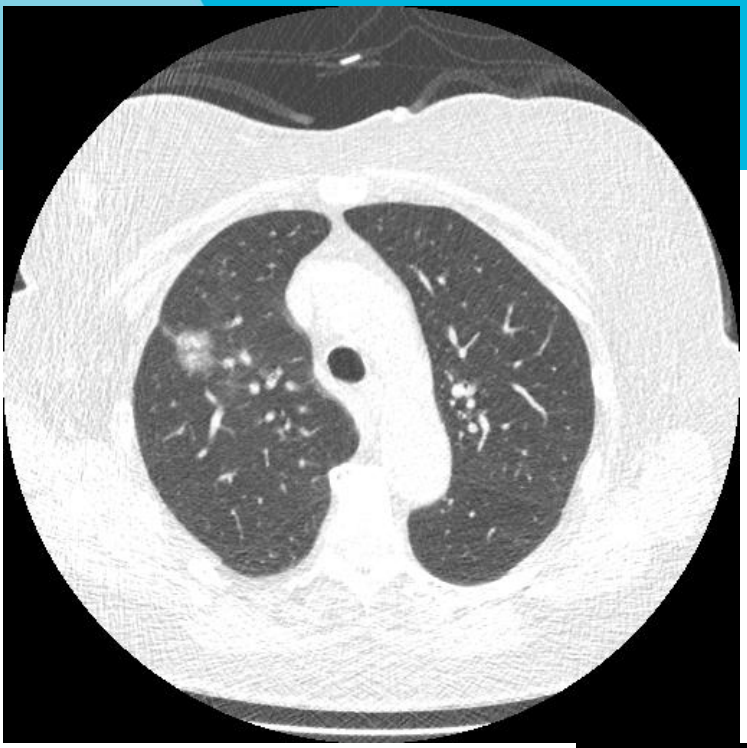
Table 2. Results of Three Rounds of Screening.*

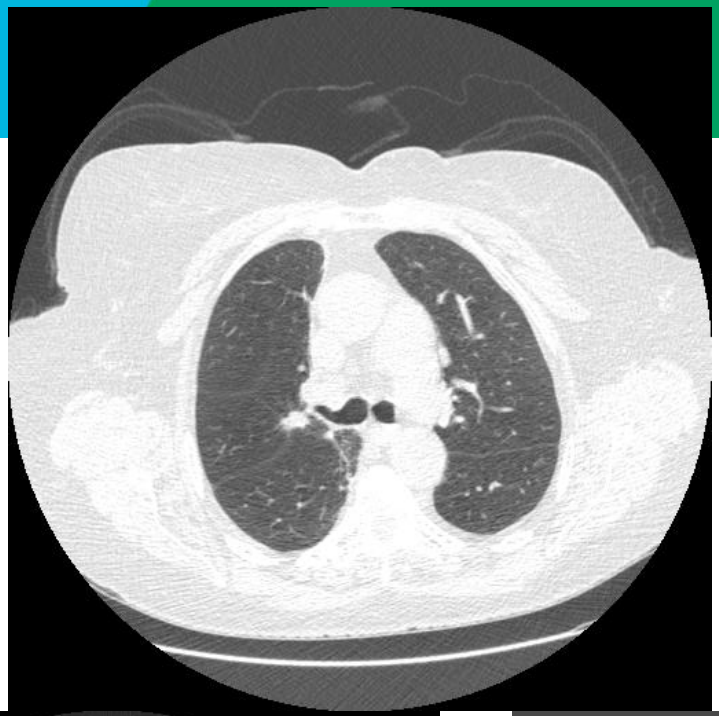
Screening Round	Low-Dose CT				Chest Radiography			
	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality
			no. (% of screened)				*no. (% of screened)*	
T0	26,309	7191 (27.3)	2695 (10.2)	16,423 (62.4)	26,035	2387 (9.2)	785 (3.0)	22,863 (87.8)
T1	24,715	6901 (27.9)	1519 (6.1)	16,295 (65.9)	24,089	1482 (6.2)	429 (1.8)	22,178 (92.1)
T2	24,102	4054 (16.8)	1408 (5.8)	18,640 (77.3)	23,346	1174 (5.0)	361 (1.5)	21,811 (93.4)

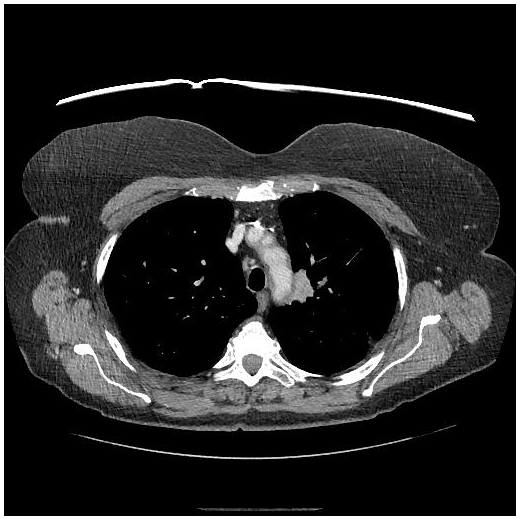
needed to screen to prevent one death: 320

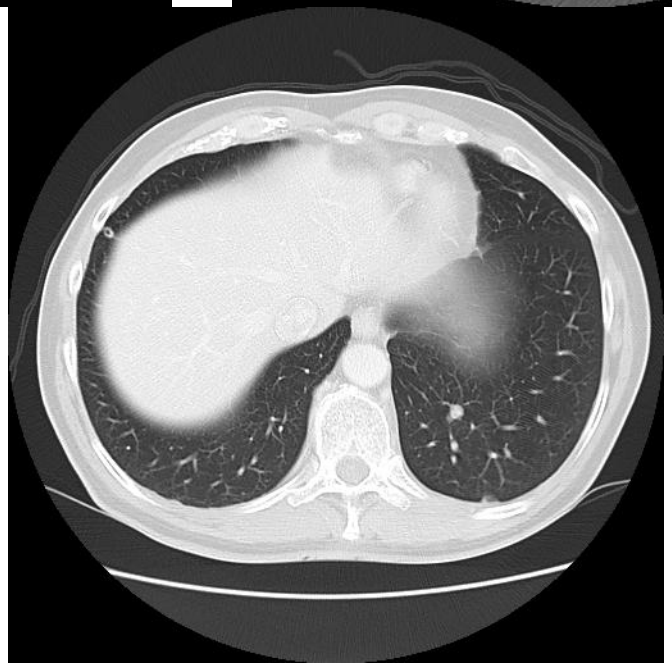
	LDCT	CXR
Cancers Diagnosed	645/100,000	572/100,000
Lung CA Deaths	247/100,000	309/100,000

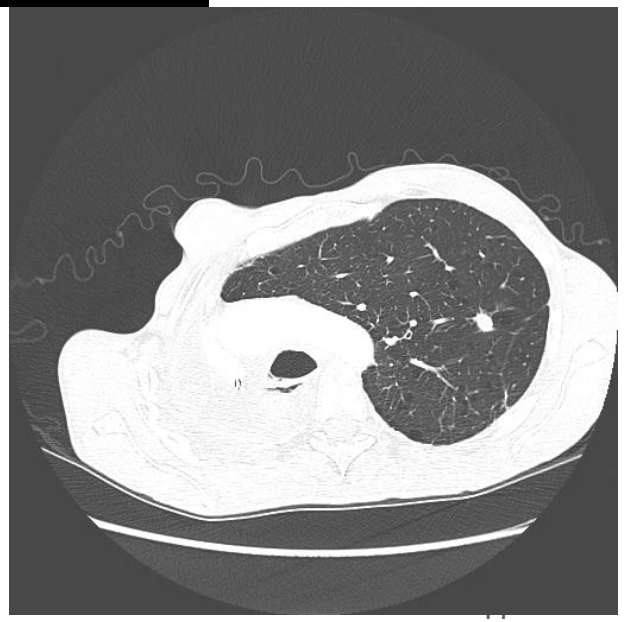
Reduction in lung CA mortality: 20% (p=0.004)
Reduction in overall mortality: 6.7% (p=0.02)











Pulmonary Nodule Board

The Pulmonary Nodule Board at Virginia Mason Medical Center routinely reviews large or unusual nodules to help determine their seriousness and make treatment recommendations where appropriate.

We strive to:

- Catch cancer at an early stage when treatment is most effective
- Treat each patient as unique and provide recommendations based on that patient's particular history and circumstances
- Blend our specific skills and experience with the primary physician's knowledge and ongoing expert care of the patient

Nodule criteria:

- We will assess any nodule that causes concern or raises questions.
- We regularly review nodules that are:
  - Larger than 6 mm in high-risk patients (see risk criteria below)
  - Larger than 8 mm in low-risk patients
  - Sub-solid nodules with solid component >5 mm
  - Ground-glass nodules >5 mm
  - Showing interval growth
  - LungRADS 3 or 4A as noted on Lung Cancer Screening CTs

Our specialty is high-risk patients who have:

- A history of smoking (> occasional use), personal diagnosis of cancer or emphysema, family history of lung cancer, or an environmental exposure to asbestos, radon, or another known hazard.

How we make decisions and recommendations:

- The Pulmonary Nodule Board is comprised of a pulmonologist, a thoracic surgeon, a radiologist and the pulmonary nodule coordinator RN who use published national guidelines (the Fleichner criteria) in conjunction with the individual characteristics of both patient and nodule, such as amenability to both non-invasive and invasive diagnostics.

How the Board delivers its recommendations:

- Based on the method requested on the referral form, physicians may get a phone call or fax followed by a letter. Physicians also have the option of calling in to listen to the Pulmonary Nodule Board's discussion of a patient's nodule. This is an excellent opportunity to understand how the recommendations are reached and learn what options were considered.
- The Board's Recommendation Form will also include the name and phone number of a pulmonologist available to answer any questions that may arise.

TO RECEIVE A PATIENT ASSESSMENT:

- Fax a Pulmonary Nodule Referral form to **(206) 341-1746** *or*
- Call Kristin Bohreer at **(Kristin's direct line)**

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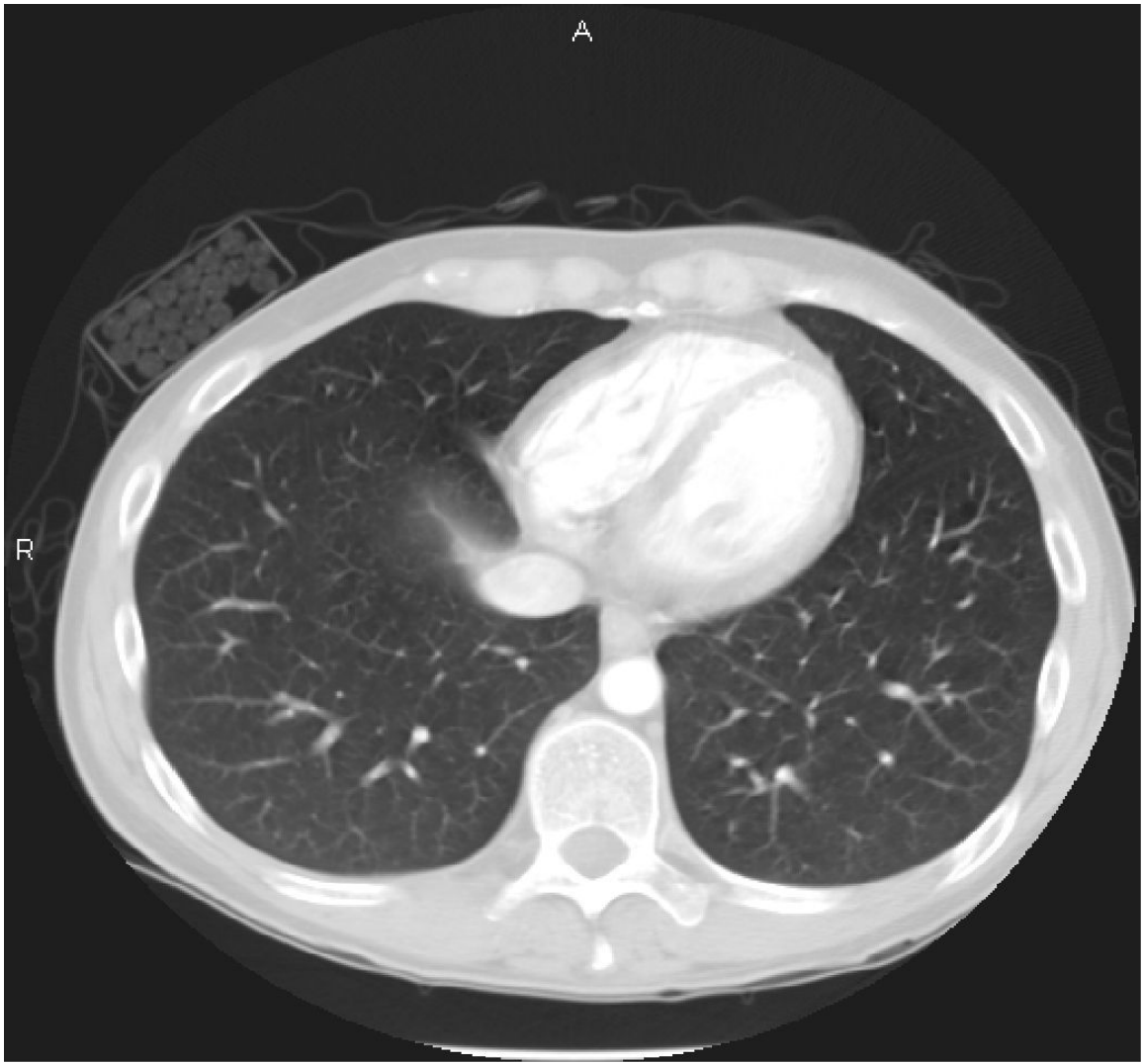
VirginiaMason.org

Pulmonary Nodule Board

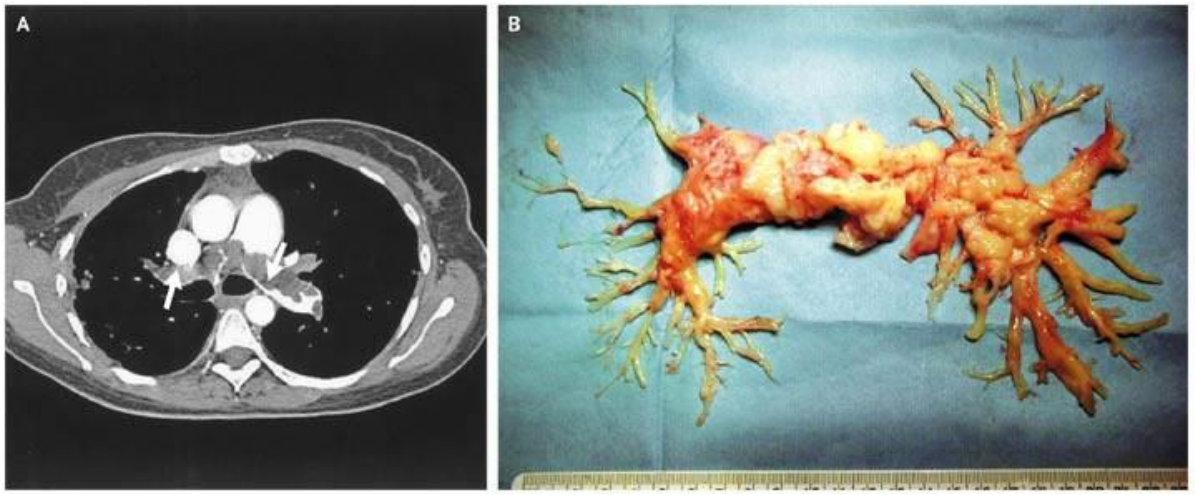
Disclosures

- Kirtland: Medtronics-Consultant



Why Venous Thromboembolism

- 900,000 events per year, 1/3 recur in 10 years
- ~100,000 deaths per year, 10-30% in first month
- Most common preventable cause of hospital death
- DVT is associated with long-term complications, such as post-thrombotic syndrome in up to 50%
- About two-thirds of all VTE events are related to hospitalization



Top 10

- What anticoagulant should I use?
- How long should I treat?
- What about cancer?
- Provoked vs unprovoked?
- What do I do with the “incidental” PE?
- UEDVT and PICCS….Treat?
- Should I use thrombolytics, CDT/EKOS?
- Should I put in an IVC filter?
- Should I do a hypercoagulopathy workup?
- When can I operate?

Case 1

- 53 yo female on HRT with recent THR 3 weeks ago in Orlando now visiting her grandchildren.
- PMH: HTN, CAD, hx of PUD with prior gi bleed in distant past
- Meds: metoprolol, HCTZ, ASA
- CC: Acute dyspnea, pleuritic chest pain
- PE: + Pratts sign
- CXR: clear

What do you order?

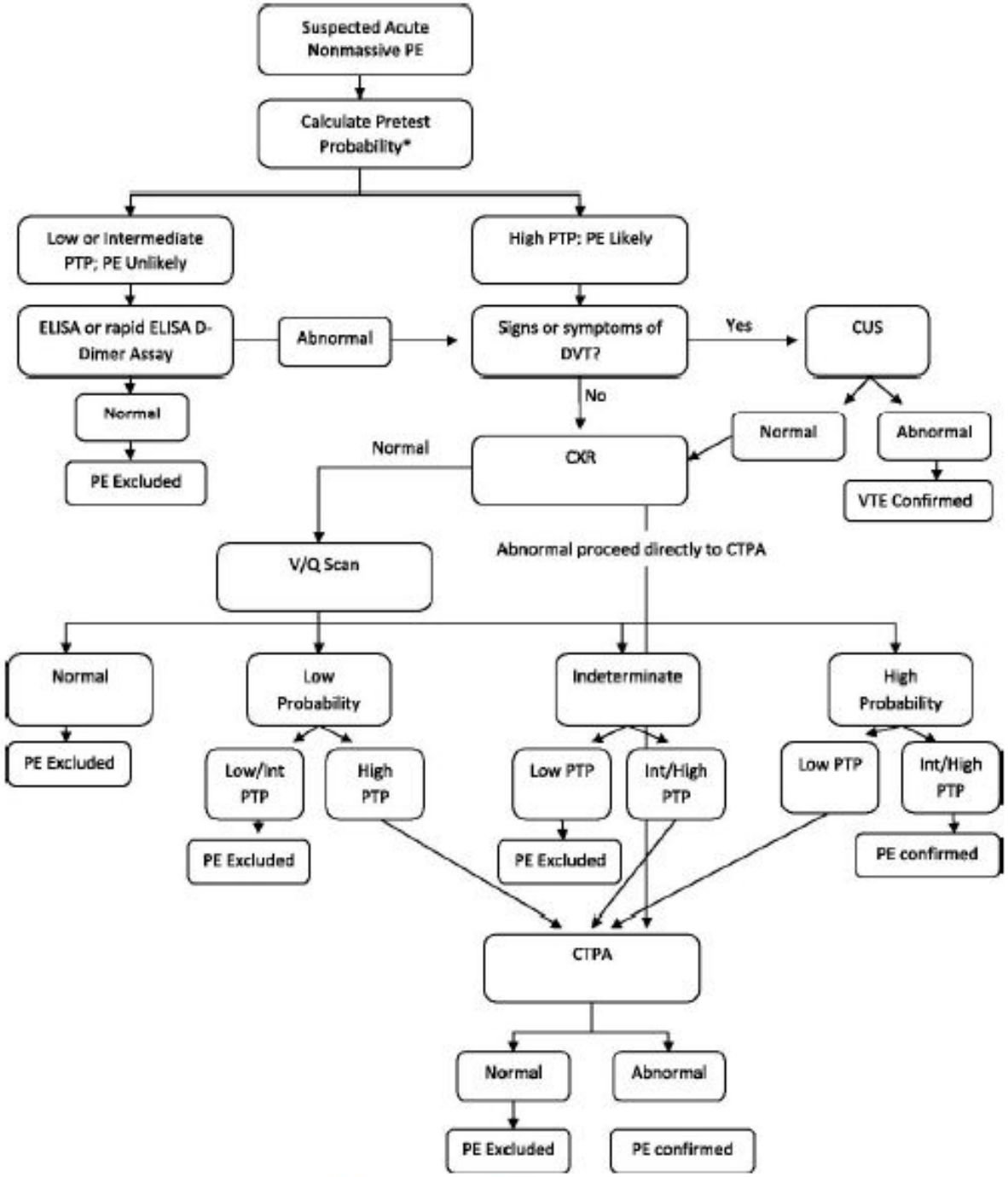
a. Echocardiogram
b. Chest CTPA
c. V/Q scan
d. D-dimer
e. Troponin

Modified Wells criteria

Modified Wells criteria: clinical assessment for pulmonary embolism

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment*	
PE likely	>4.0
PE unlikely	≤4.0

Data from van Belle, A, et al. JAMA 2006; 295:172.


Suspected Acute Nonmassive PE
Calculate Pretest Probability*
Low or Intermediate PTP; PE Unlikely
High PTP: PE Likely
ELISA or rapid ELISA D-Dimer Assay
Abnormal
Signs or symptoms of DVT?
Yes
CUS
Normal
PE Excluded
No
Normal
CXR
Normal
Abnormal
VTE Confirmed
Abnormal proceed directly to CTPA
V/Q Scan
Normal
PE Excluded
Low Probability
Low/Int PTP
High PTP
PE Excluded
Indeterminate
Low PTP
Int/High PTP
PE Excluded
High Probability
Low PTP
Int/High PTP
PE confirmed
CTPA
Normal
PE Excluded
Abnormal
PE confirmed

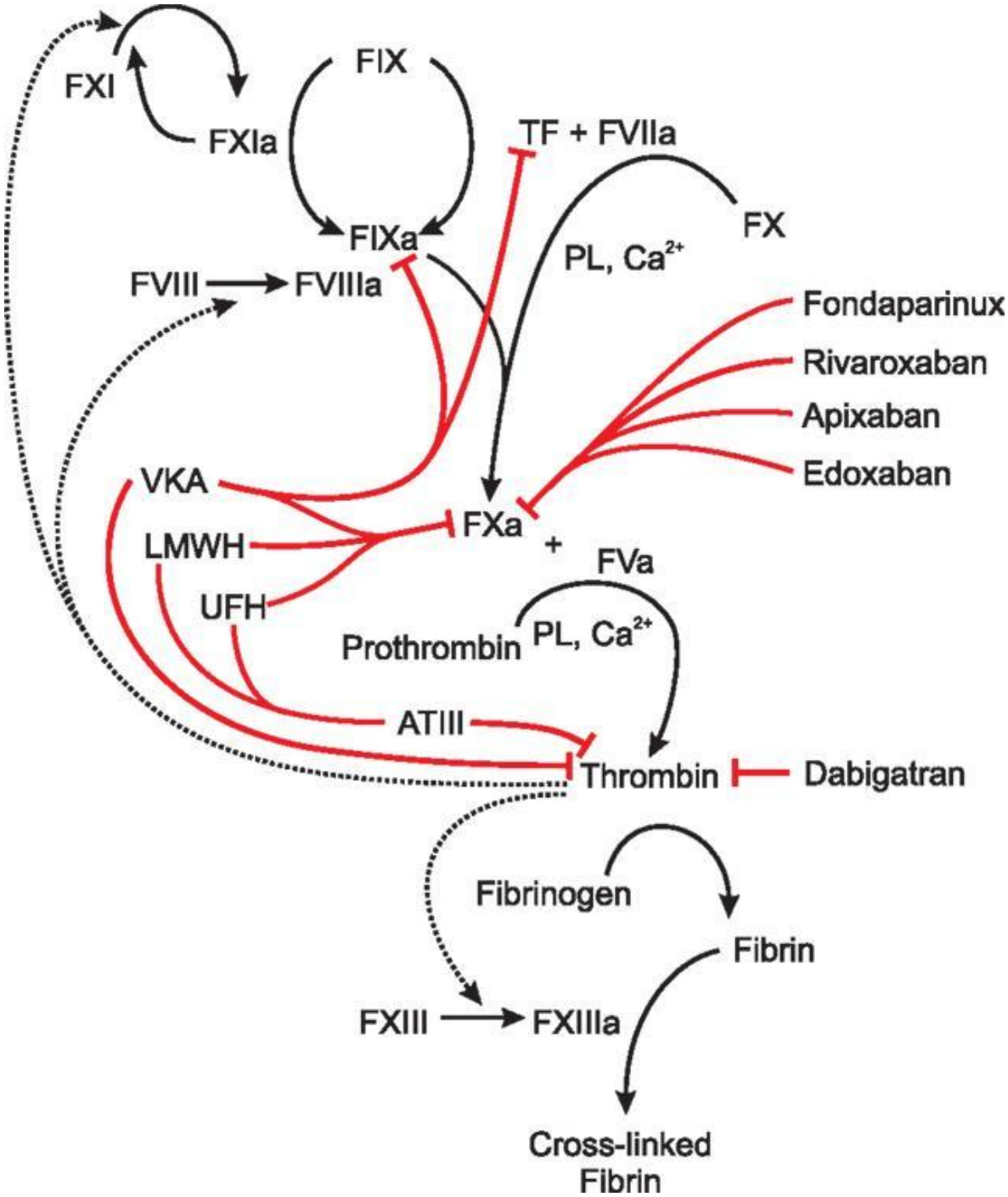
What would you treat her with?

- a. LMWH
- b. LMWH followed by Vka
- c. DOAC
- d. aspirin
- e. Would not treat
  f. I am not sure

Acronym Evolution

- TSOAC = Targeted Specific Oral Anticoagulant
- NOAC = Novel Oral Anticoagulant
- DOAC = Directed Oral Anticoagulant

OOAC = Old Oral Anticoagulant
ROOAC = Really Old Oral Anticoagulant


FXI
FXIa
FIX
FIXa
TF + FVIIa
FX
PL, Ca2+
FVIII
FVIIIa
Fondaparinux
Rivaroxaban
Apixaban
Edoxaban
VKA
LMWH
UFH
FXa
+
FVa
Prothrombin
PL, Ca2+
ATIII
Thrombin
Dabigatran
Fibrinogen
Fibrin
FXIII
FXIIIa
Cross-linked
Fibrin

1. How Long to Treat

a. Don’t treat
b. 6 weeks
c. 3 months
d. One year
e. Indefinitely

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

PODCAST

BACKGROUND: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

METHODS: We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence.

RESULTS: For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over low-molecular-weight heparin (LMWH; Grade 2C). For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C). We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy. For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B). For DVT, we suggest not using compression stockings routinely to prevent PTS (Grade 2B). For subsegmental pulmonary embolism and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We suggest thrombolytic therapy for pulmonary embolism with hypotension (Grade 2B), and systemic therapy over catheter-directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C); for recurrent VTE on LMWH, we suggest increasing the LMWH dose (Grade 2C).

CONCLUSIONS: Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.

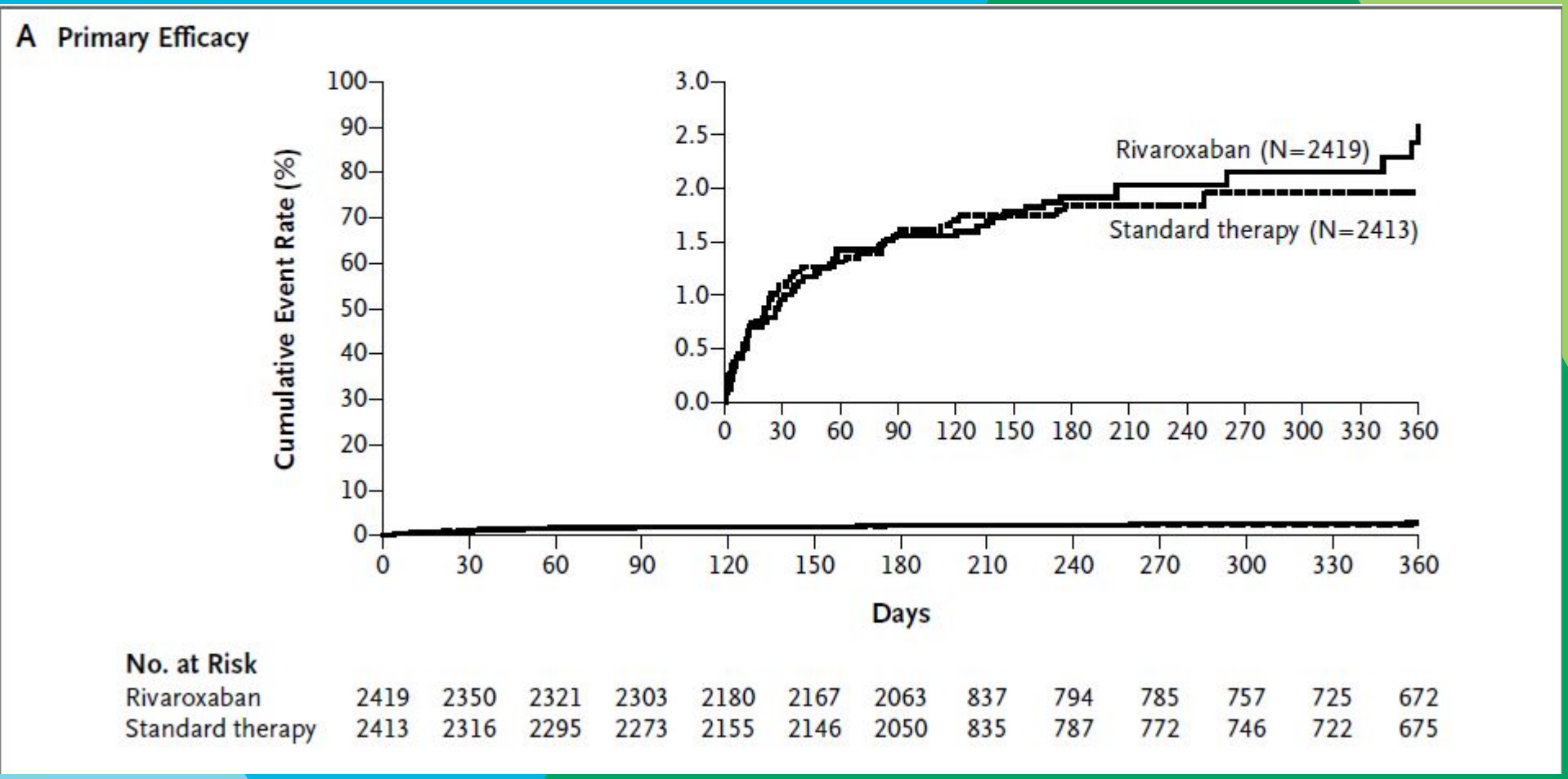
CHEST 2016; 149 (2):315-52

Study	Einstein DVT + PE	AMPLIFY	RE-COVER I + II	Hokusai-VTE
Drug	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Total number of patients	8246	5365	5107	8240
Target	Factor Xa-inhibition	Factor Xa-inhibition	Thrombin-inhibition	Factor Xa-inhibition
Primary efficacy outcome	Recurrent venous thromboembolism			
Principal safety outcome	Major- or clinically relevant non-major bleeding			
Study design	Open-label, randomized non-inferiority trial	Randomized, double-blind trial	Randomized, double-blind, non-inferiority trial	Randomized, double-blind, non-inferiority trial
Time INR in therapeutic range[a]	57.7%	61%	60%	63.5%
Regimen/dose (mg)	15 mg twice daily for the first 3 weeks followed by 20 mg once daily	10 mg twice daily for the first 7 days, followed by 5 mg twice daily	Initial treatment (at least 5 days) with parenteral anticoagulant, followed by 150 mg twice daily	Initial treatment (at least 5 days) with parenteral anticoagulant, followed by 60 mg once daily
Treatment duration	3-, 6-, and 12 months	6 months	6 months	3–12 months duration determined by the treating physician based on patient's clinical features and preference
Dose adjustment	No	No	No	Yes[b]
Dose reduction criteria	Not assessed	Not assessed	Not assessed	30 mg once daily in patients with a CrCl 30–50 mL/min, body weight ≤60 kg or concomitant treatment with potent P-glycoprotein inhibitor
Most important exclusion criteria as listed in the publications (full list of exclusion criteria provided in the study protocols)	Another indication for VKA, CrCl <30 mL/min, liver disease, bacterial endocarditis, contraindications for anticoagulant treatment, systolic blood pressure >180 mmHg or diastolic blood pressure >110, childbearing potential without proper contraceptive measures, pregnancy or breast feeding, concomitant use of strong cytochrome P450 3A4 inhibitors, bacterial endocarditis	Contraindications to heparin or warfarin, CrCl <25 mL/min or creatinine level >2.5 mg/dL, liver disease, cancer with long-term treatment with LMWH, provoked DVT or PE in the absence of a persistent risk factor for recurrence, another indication for long-term anticoagulation therapy, dual antiplatelet therapy, aspirin at a dose of more than 165 mg daily, hemoglobin <9 mg/dL, platelet count <100.000/mm^3	Another indication for a VKA or heparin, CrCl <30 mL/min, liver disease, PE with hemodynamic instability or requiring thrombolytic therapy, recent unstable cardiovascular disease, high risk of bleeding, liver disease, contraindication to heparin, pregnancy, risk for becoming pregnant long-term antiplatelet therapy (aspirin ≤100 mg accepted), life expectancy less than 6 months	Another indication for VKA, CrCl <30 mL/min, contraindications to heparin or warfarin, cancer with long-term treatment with LMWH, treatment with aspirin at a dose of more than 100 mg daily or dual antiplatelet therapy

Liver Disease, Renal Disease, Pregnancy, SBE, Cancer

[a] *Target INR (vitamin K antagonist) in all studies: 2.0–3.0.*
CrCL, creatinine clearance; VKA, vitamin K antagonist; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism.
[b] *In the Hokusai-VTE study, 17.8% of patients received the adjusted dose of edoxaban (30 mg once daily) at randomization.*

Rivaroxaban compared with Enox/VitkA



Rate of DVT/PE at One Year

more

- Oral agents easier
- No injections
- Less expensive?
- No head to head trials with DOACs
- No DOAC vs LMWH trials

So which Agent do I choose?

Factors affecting choice

TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

INR = International Normalized Ratio; NOAC = non-vitamin K oral coagulant. See Table 1 legend for expansion of other abbreviations.

DOAC Drug Interactions

DRUG INTERACTIONS WITH TARGET SPECIFIC ORAL ANTICOAGULANTS (TSOAC)

Rivaroxaban Drug Interactions

Pharmacodynamic Interactions
The concurrent use of rivaroxaban with other anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents is expected to increase the risk of bleeding in comparison to use of rivaroxaban alone.

Pharmacokinetic Interactions
1. The absorption of rivaroxaban is mediated by P-glycoprotein (P-gp). P-gp inhibitors can increase the absorption of rivaroxaban, increasing both AUC and Cmax. Conversely, P-gp inducers can reduce the absorption of rivaroxaban, decreasing AUC and Cmax.
2. The metabolism of rivaroxaban is mediated by CYP3A4. CYP3A4 inhibitors can decrease the metabolism of rivaroxaban, increasing both AUC and Cmax. Conversely, CYP3A4 inducers can increase the metablism of rivaroxaban, decreasing AUC and Cmax.
3. Agents that interfere with both P-gp and CYP3A4 are likely to cause more significant interactions with rivaroxaban than agents that interfere with P-gp or CYP3A4 alone.

Drug Class	Examples	Known or Probable Effect	US PI Recommendation	Virginia Mason Medical Center Best Practice Guidelines
Combined P-gp inhibitor and *strong* CYP3A4 inhibitor	boceprevir, cobicistat, conivaptan, delavirdine, diltiazem, dronedarone, all HIV protease inhibitors (eg. ritonavir), imatinib,indinavir, itraconazole,ketoconazole, nefazodone, posaconazole, telaprevir, telithromycin, voriconazole	Significant increase in rivaroxaban concentration	Avoid use of combined P-gp and strong CYP3A4 inhibitors (eg: ketoconazole, intraconazole, lopinavir-ritonavir, indinavir-ritonavir, ritonavir, conivaptan)...	AVOID USE Risk higher in pts with renal impairment
Combined P-gp inhibitor and/or	amoidarone, azithromycin, chloramphenicol, cimetidine, erythromycin, clarithromycin, cyclosporin, diltiazem,	Moderate increase in rivaroxaban	No precaution is	USE WITH CAUTION in patients with

DRUG INTERACTIONS WITH TARGET SPECIFIC ORAL ANTICOAGULANTS (TSOAC)

moderate 3A4 inhibitor	dronedarone, felodipine, fluconazole, grapefruit, lapatinib, mifepristone, nicardipine, quinidine, ranolazine, tamoxifen, telithromycin, ticagrelor, verapamil	concentration in patients with normal renal function. Significant increase in rivaraxaban concentrations in patients with renal impairment	necessary	normal renal function. AVOID USE in patients with renal impairment (CrCl < 30ml/min)
Combined P-gp inducer and *strong* CYP3A4 inducer	carbamazepine, dexamethsone, phenytoin, rifampin, St John's wort	Significant reduction in rivaroxaban concentration Effect may persist for several weeks following discontinuation of strong inducers of P-gp and/or CYP3A4	Avoid use with strong inducers of P-gp and CYP3A4 (eg: carbamazepine, phenytoin, rifampin, St Johns wort)	AVOID USE
Inducers of P-gp	doxorubicin, prazosin, tipranavir, trazodone, vinblastine		Not specifically addressed	AVOID USE
Strong inducers of CYP3A4	barbiturates, bosentan, efavirenz, etravirine, fosphenytoin, nafcillin, nevirapine, oxarbazepine, phenytoin, primidone, rifabutin, rifapentine		Not specifically addressed	AVOID USE

Can I treat her at home?

- (1) clinically stable with good cardiopulmonary reserve (no inc troponin)
- (2) no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia(ie, <70,000/mm3)
- (3) expected to be compliant with treatment
- (4) the patient feels well enough to be treated at home.
- (5) PESI score <85 not necessary

- In patients with low-risk PE and whose home
- circumstances are adequate, we suggest treatment at
- home or early discharge over standard discharge
- (eg, after the first 5 days of treatment) (Grade 2B).

Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism

van der Pol Liselotte M; Tromeur Cecile; Bistervels, Ingrid M; Ni Ainle Fionnuala; Thomas, van Bemmel; et al.

The New England Journal of Medicine; Boston Vol. 380, Iss. 12, (Mar 21, 2019): 1139-1149. DOI:10.1056/NEJMoa1813865

Full text | Full text - PDF | Abstract/Details

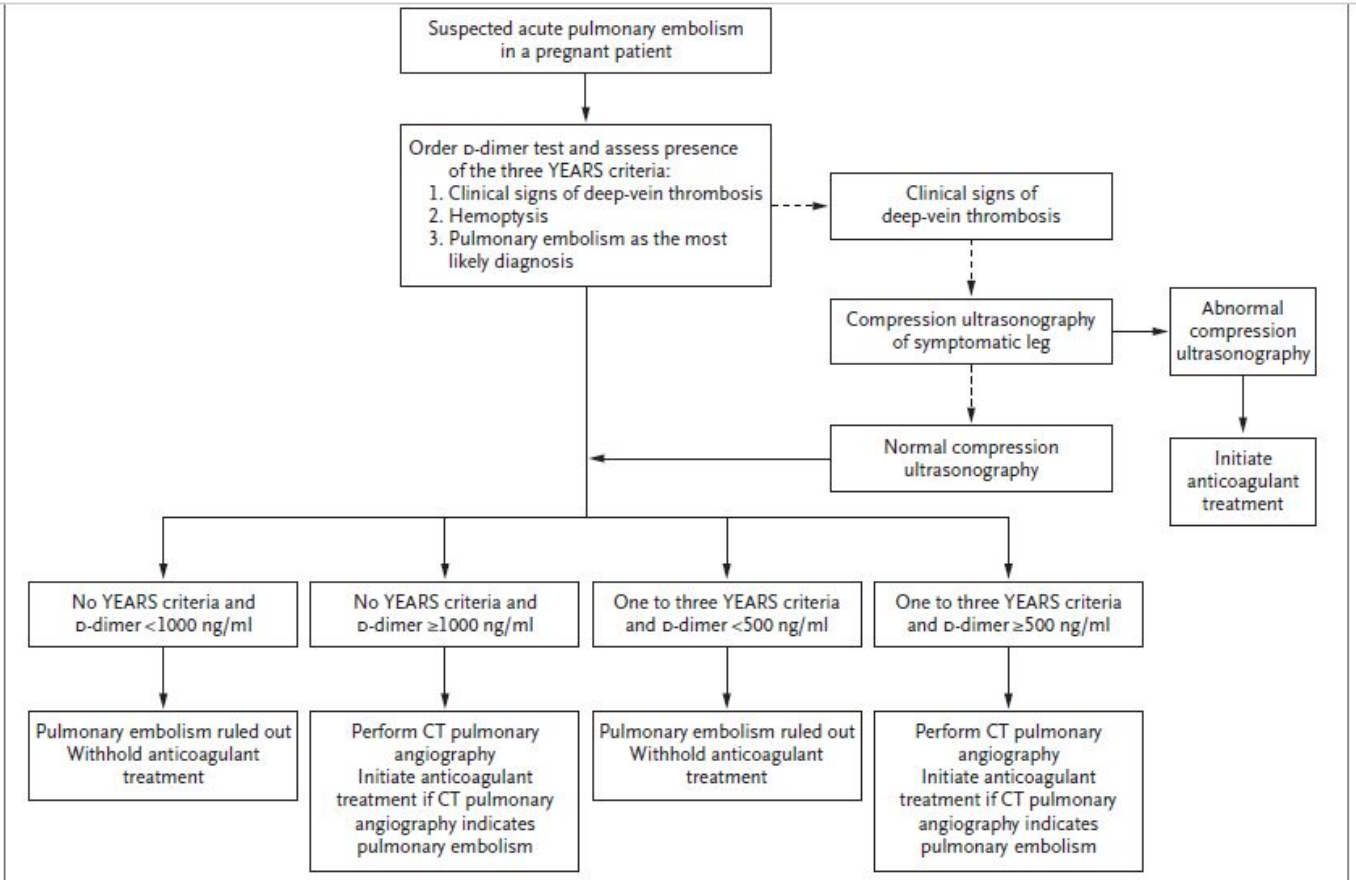
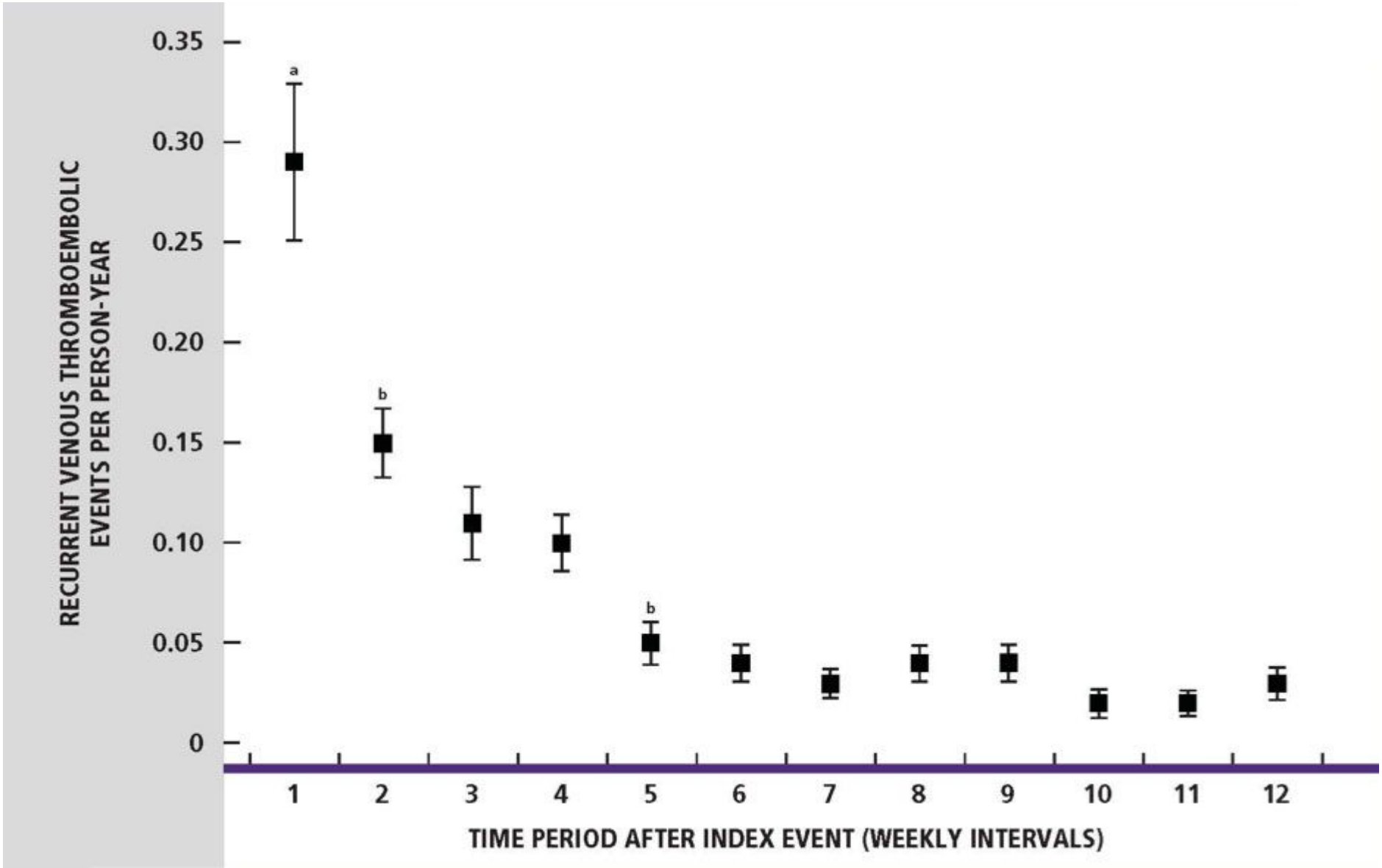


Figure 1. Pregnancy-Adapted YEARS Algorithm for the Management of Suspected Acute Pulmonary Embolism in Pregnant Patients.
CT denotes computed tomography.

Questions

- Why not 6 weeks?
- What is Provoked?
- What about Cancer?
- What if she cannot stop her HRT?
- When can I operate?

Risk of recurrence on therapy



What is Provoked?

- Surgery
- Medication
- Inactivity (flight >8 hours)
- Cancer

Proximal DVT/PE in active cancer

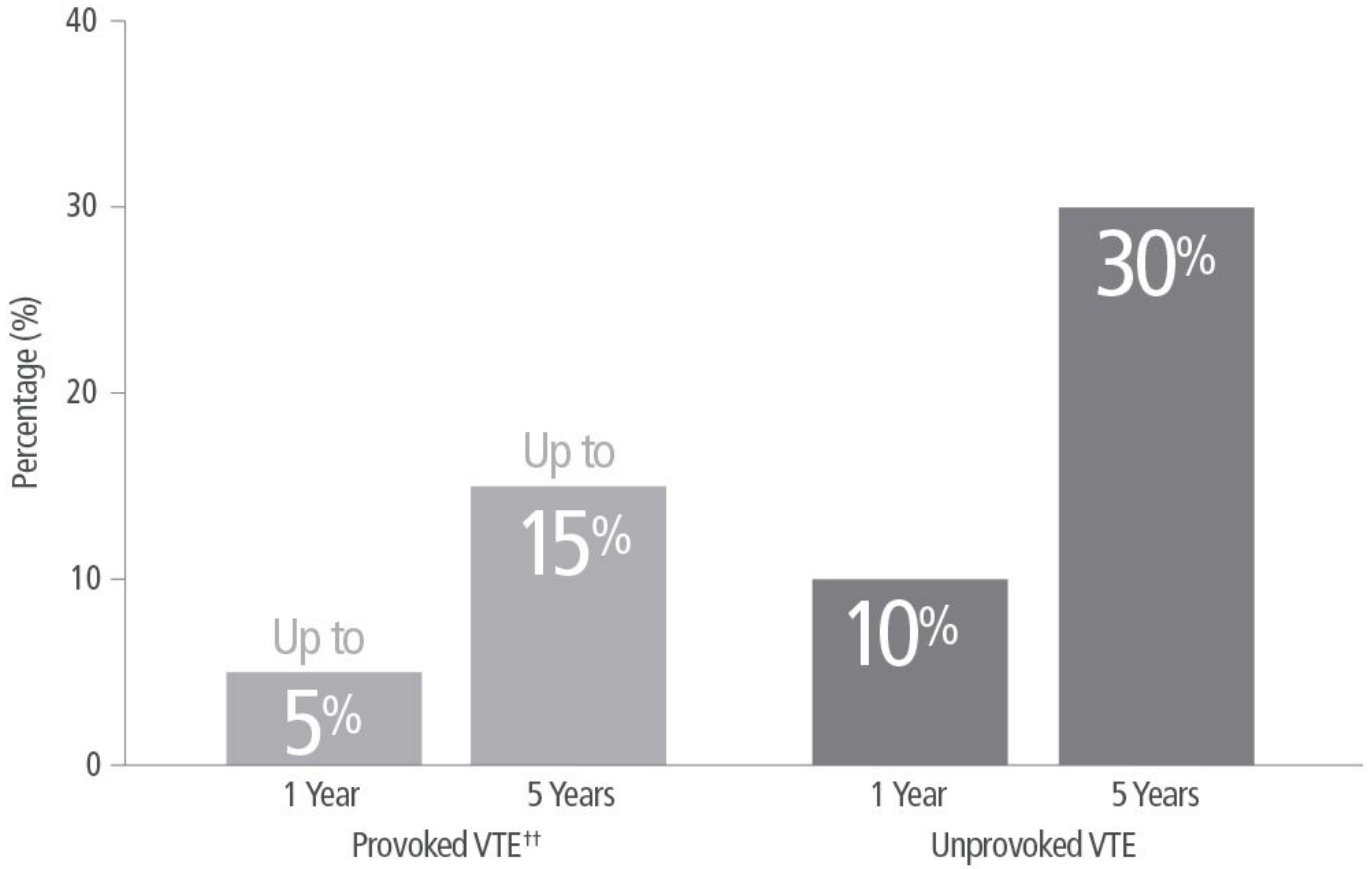
- Extended therapy
- LMWH > VitKa = DOAC
- Recommended with low and medium bleeding risk
- Suggested with high risk

- Non-oral, short ½ life

Treatment during Pregnancy

- LMWH
- UFH
- VitKa potentially teratogenic
- ? DOAC (excluded)

Rate of Recurrent DVT and PE in Provoked and Unprovoked Patients at 1 and 5 Years After Initial Treatment Completion[8]



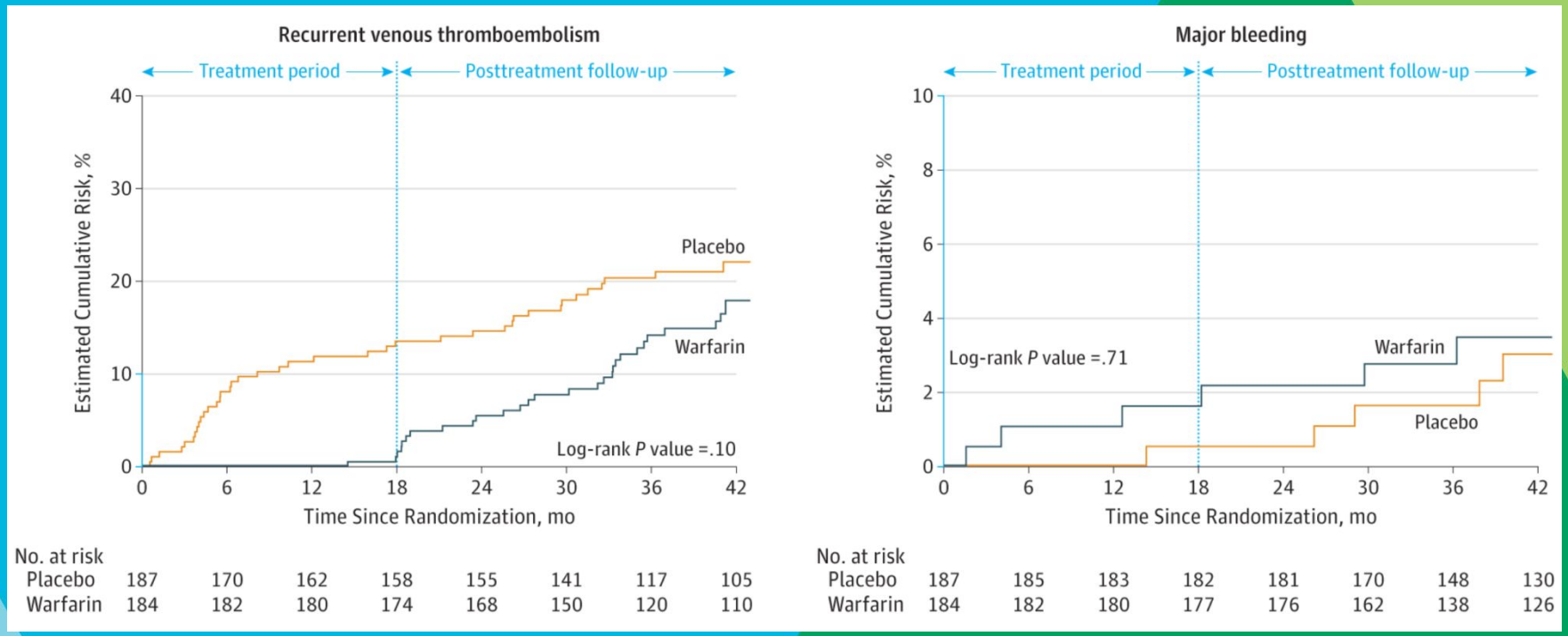
Duration: Provoked

- Surgical: 3 mo (1B)
- Nonsurgical: 3 mo (1B-HR, 2B-LR)
- Distal DVT: 3 mo (1B) or none

Duration: Unprovoked

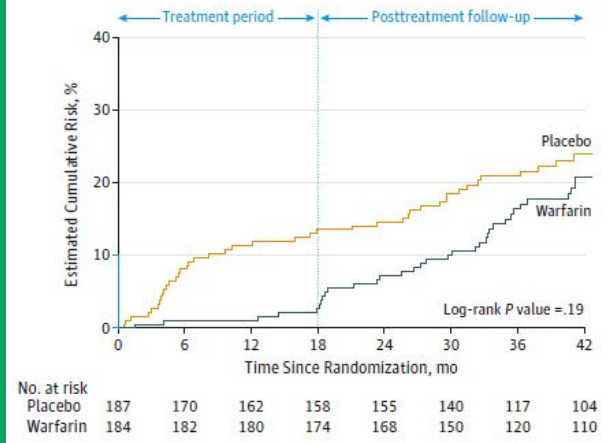
- Initial: high BR: 3 mo (1B) (R)
- Low-mod BR: Extended*^ (2B) (S)
- Recurrent: HR: 3 mo (2B) (S)
- ModR: Extended (2B) (S)
- LR: Extended (1B) (R)

- *Consider sex, d-dimer
- ^Reevaluate annually



PADiS-PE Trial JAMA July 2015

Figure 2. Probability of the Composite Outcome of Recurrent Venous Thromboembolism and Major Bleeding Throughout the Study Period



The unadjusted hazard ratios for warfarin-placebo were 0.23 (95% CI, 0.09-0.55) during the treatment period and 0.74 (95% CI, 0.47-1.17) for the entire study period. The y axis that is shown in blue indicates the range of estimated cumulative risk from 0% to 10%.

Effect of Sex on recurrence rate

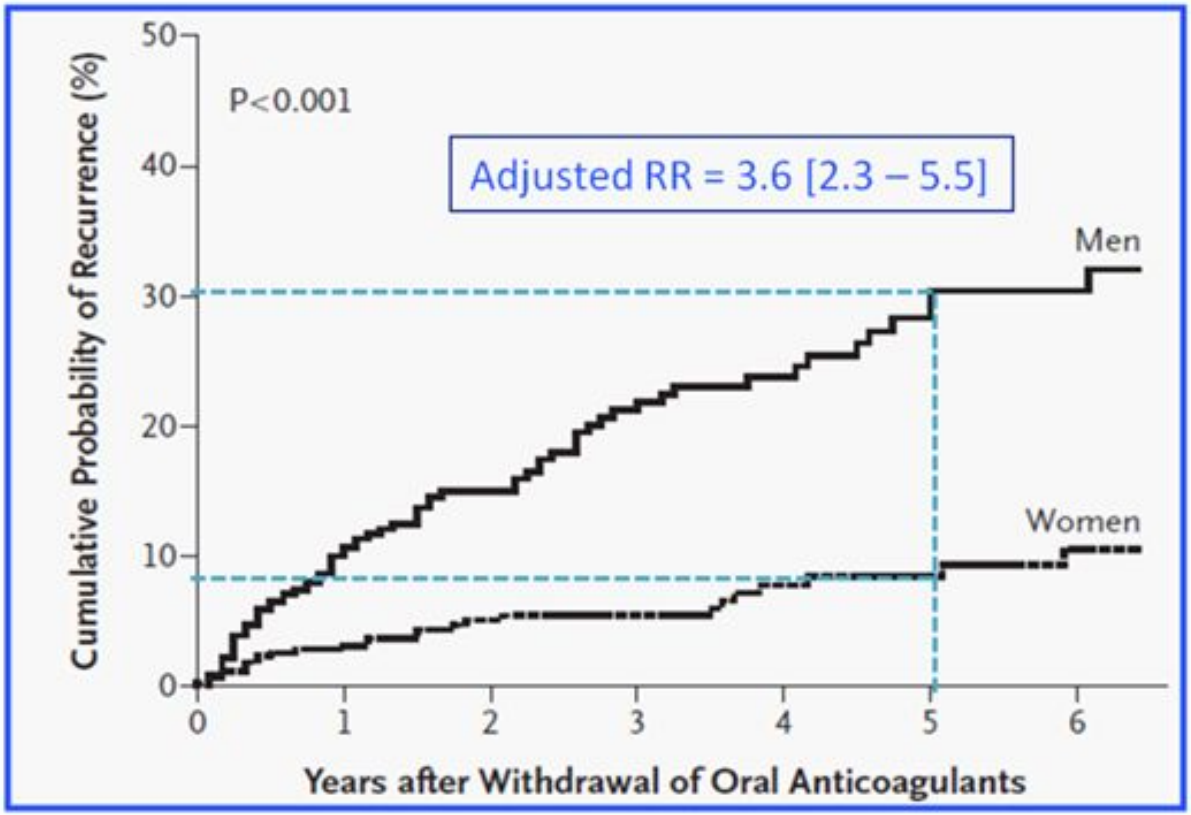


Figure 4

D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked VTE

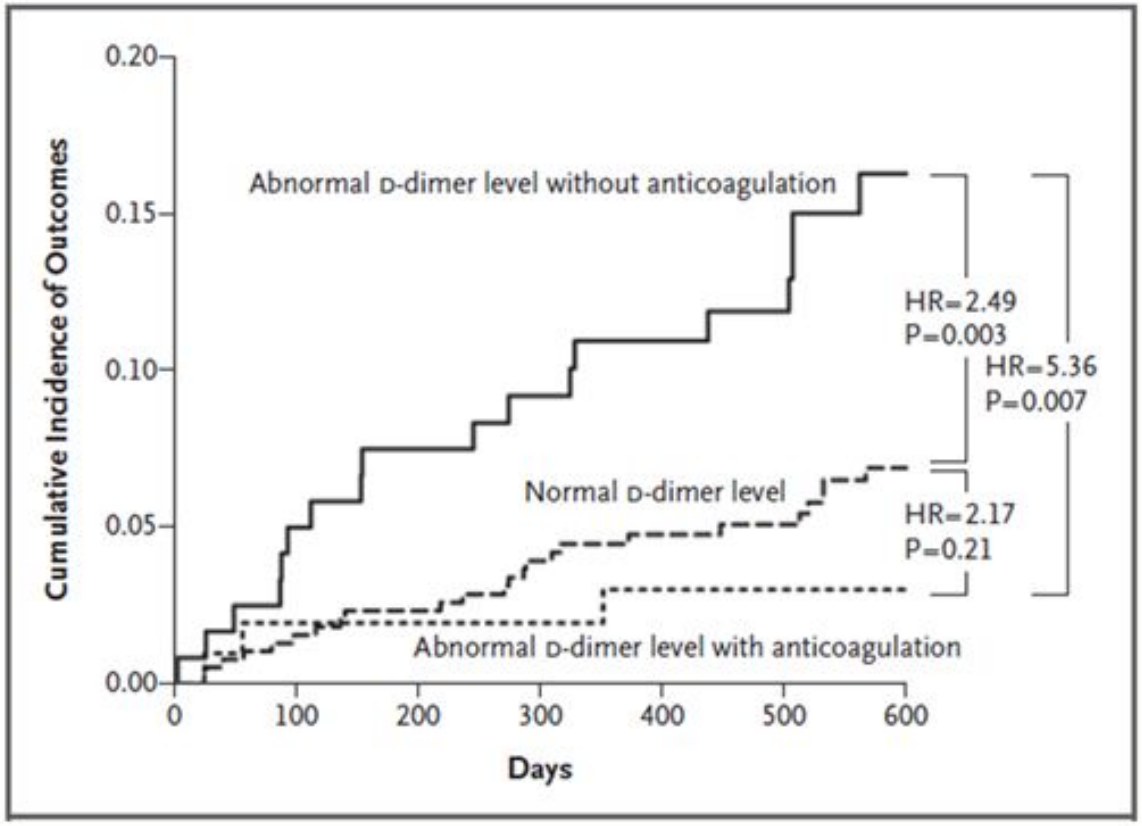
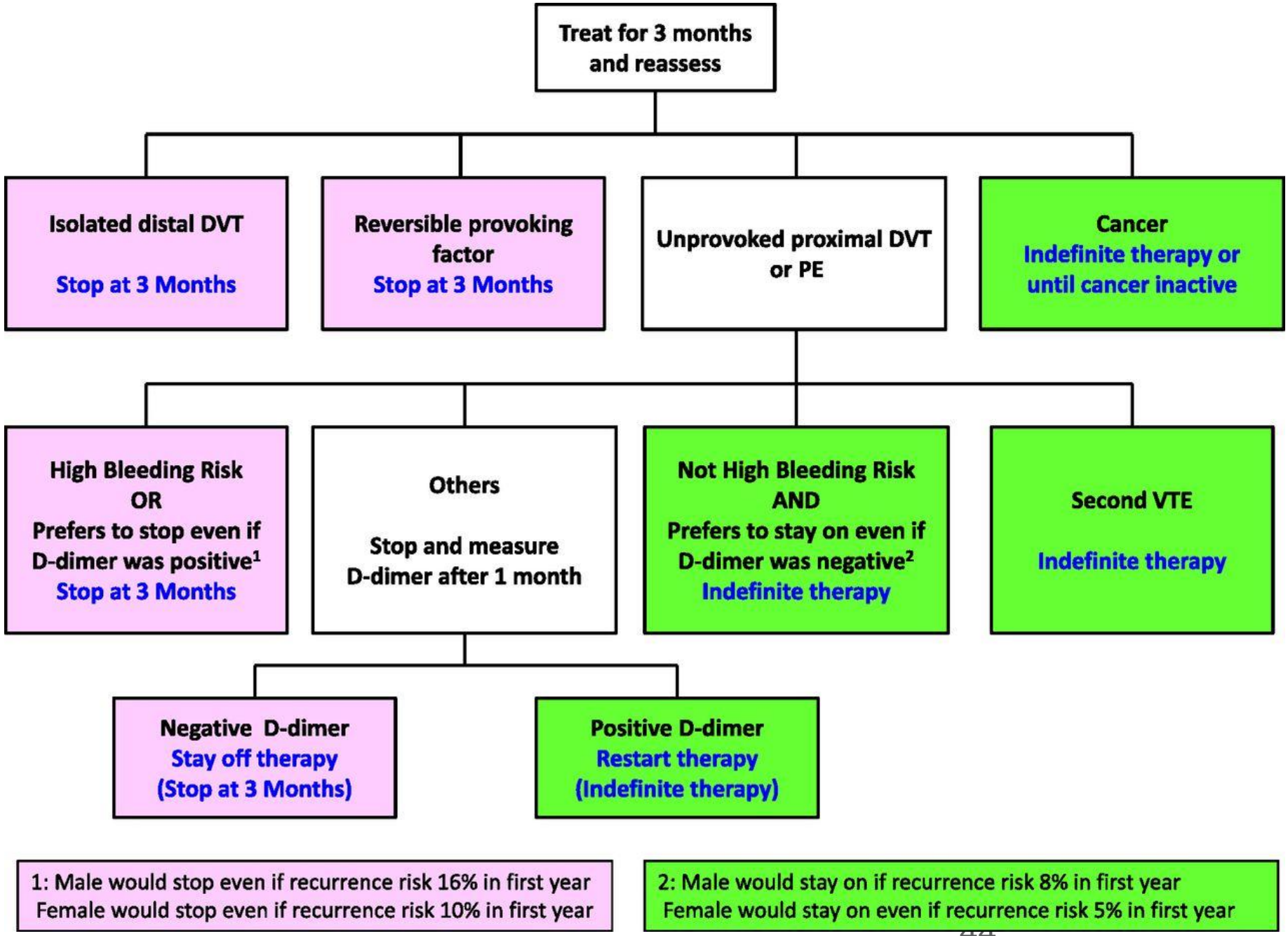


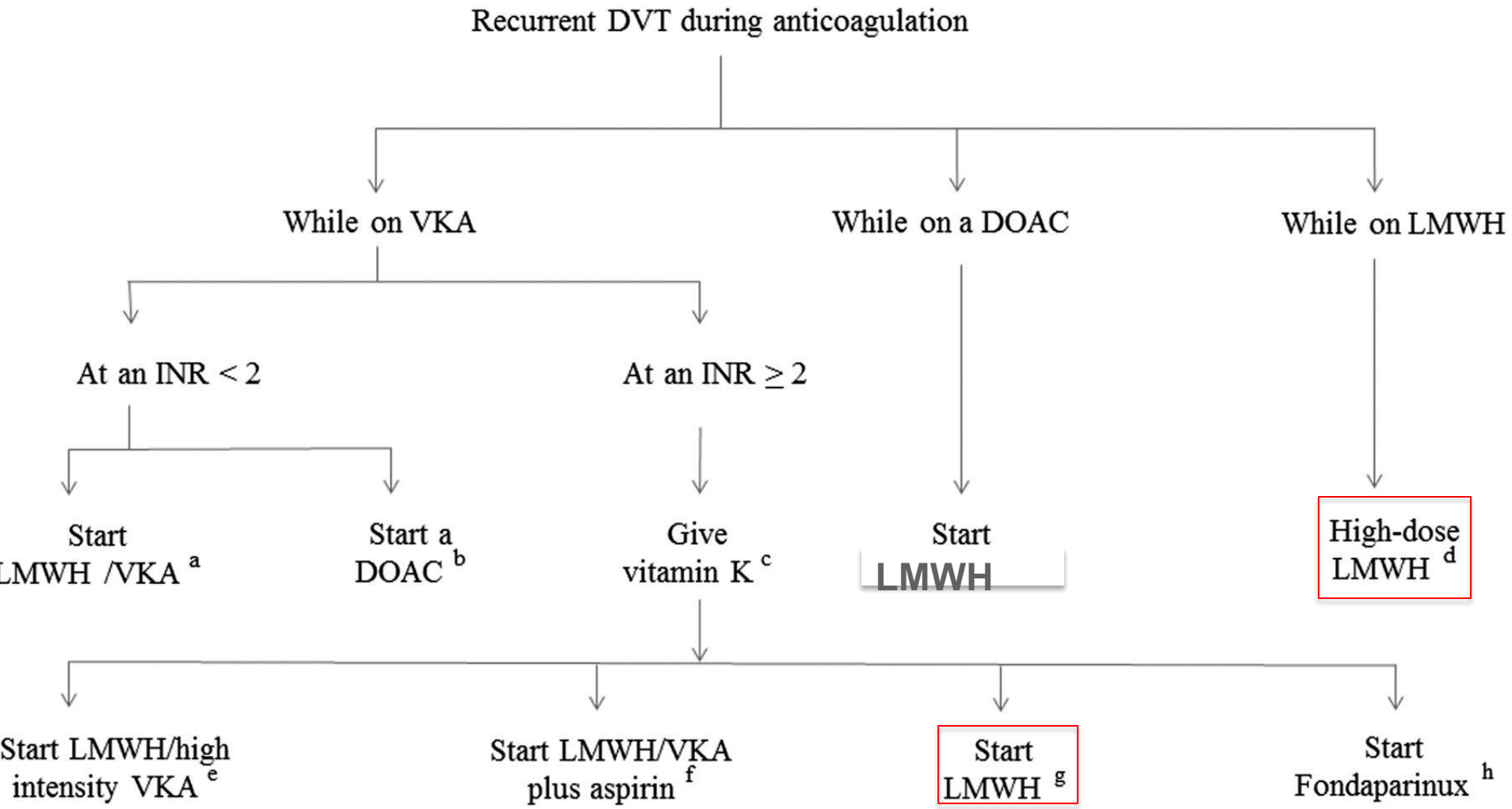
Figure 3



1: Male would stop even if recurrence risk 16% in first year
Female would stop even if recurrence risk 10% in first year

2: Male would stay on if recurrence risk 8% in first year
Female would stay on even if recurrence risk 5% in first year

Treatment of Recurrent VTE



What about Aspirin?

- 2 trials
- Initial unprovoked VTE treated with 3-18 mo of AC (Vka), no inc BR
- Reduced risk of recurrence by 33% (compared with 80%)
- Increased bleeding but not significant

Aspirin?

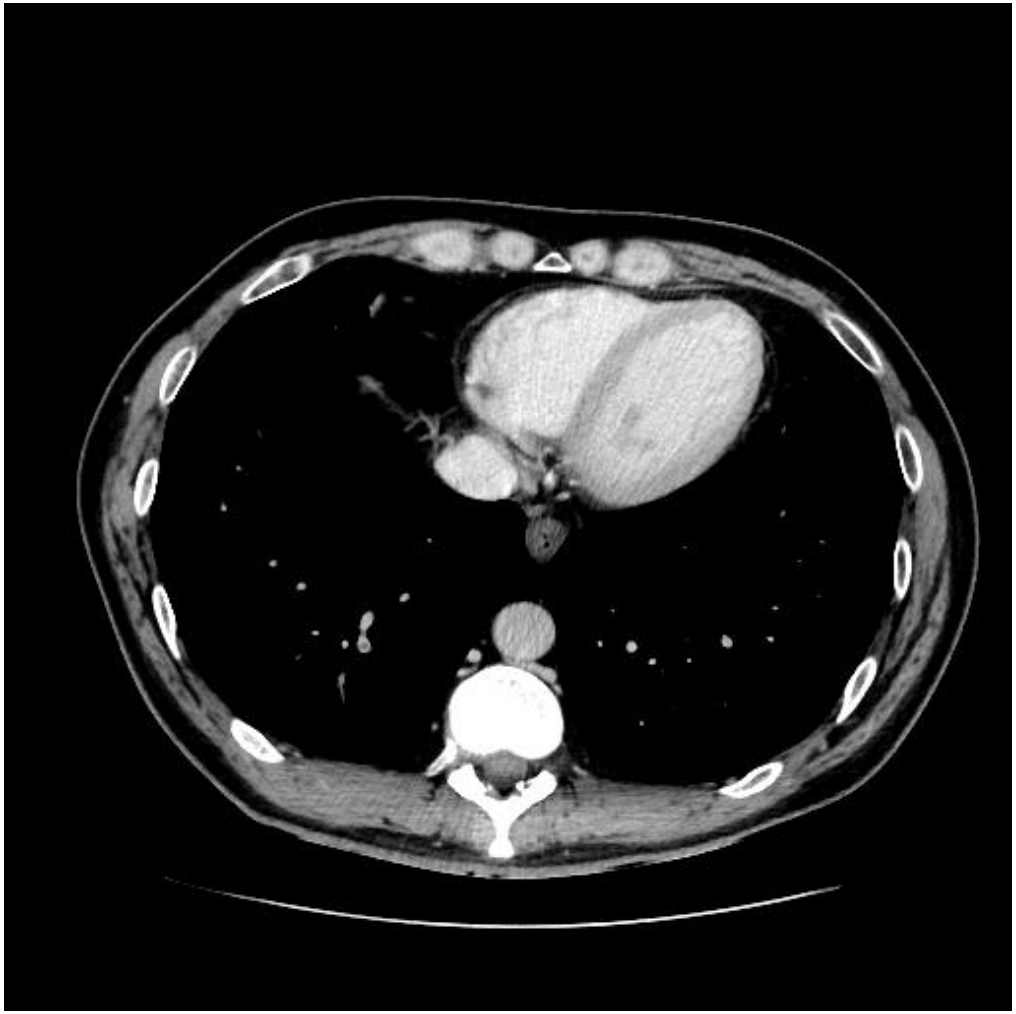
- In patients with an unprovoked proximal DVT
- or PE who are stopping anticoagulant therapy and
- do not have a contraindication to aspirin, we suggest
- aspirin over no aspirin to prevent recurrent VTE
- (Grade 2B).

True or False

- Incidental PE's should be anticoagulated.

MAYBE

Incidental PE

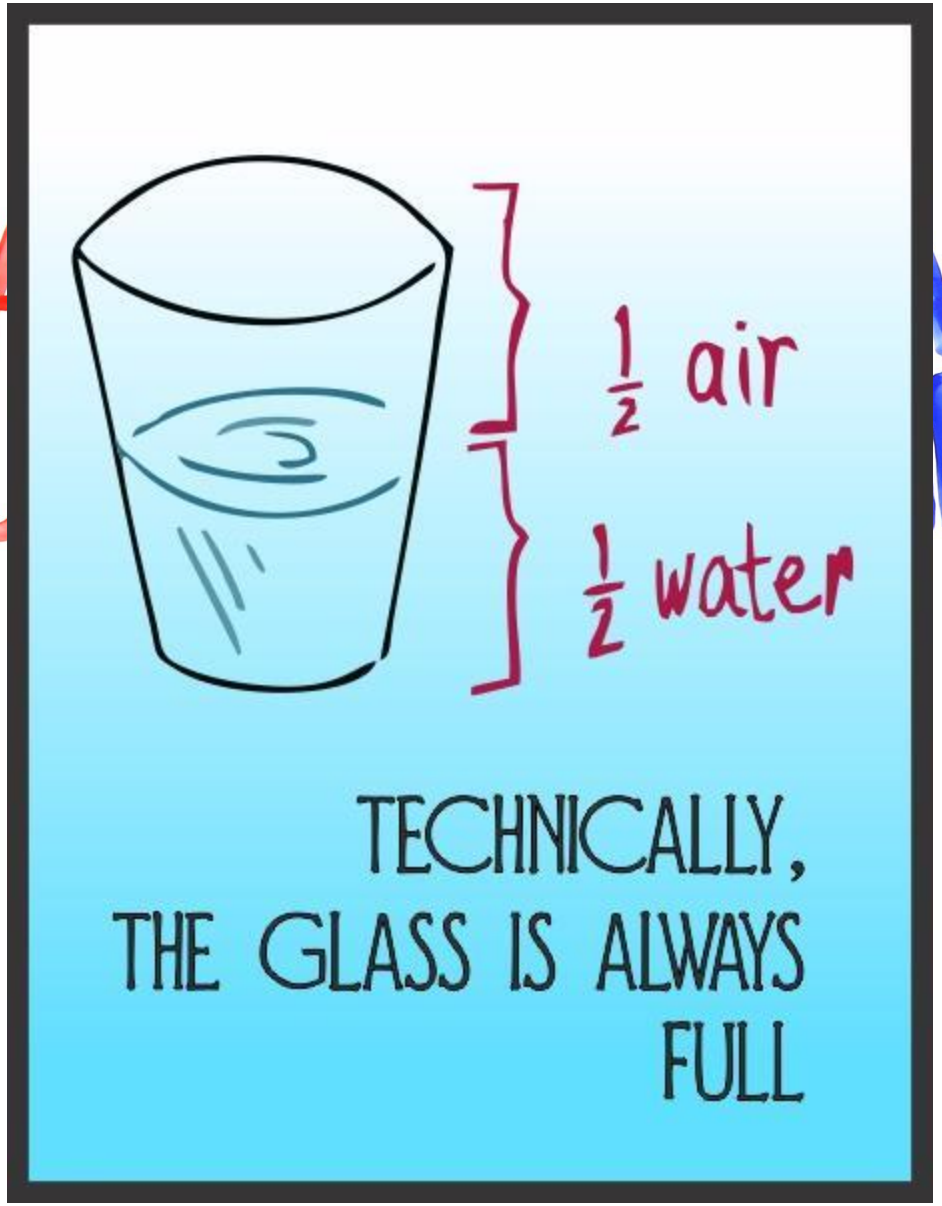


Incidental PE

- 2.5% prevalence
- Occurring more commonly
- ~30% segmental/subsegmental
- 45-91% treated in multiple studies
- Significant recurrence if not treated in some
- No RCT's
- Need to treat dependent upon size and absence of proximal DVT and risk of recurrence

Caveats

- May want to do serial US
- Recurrence: immobility, cancer, idiopathic
- More apt to follow if good cardiopulmonary reserve and high risk of bleeding
- Grade: 2c


½ air
½ water
TECHNICALLY,
THE GLASS IS ALWAYS
FULL

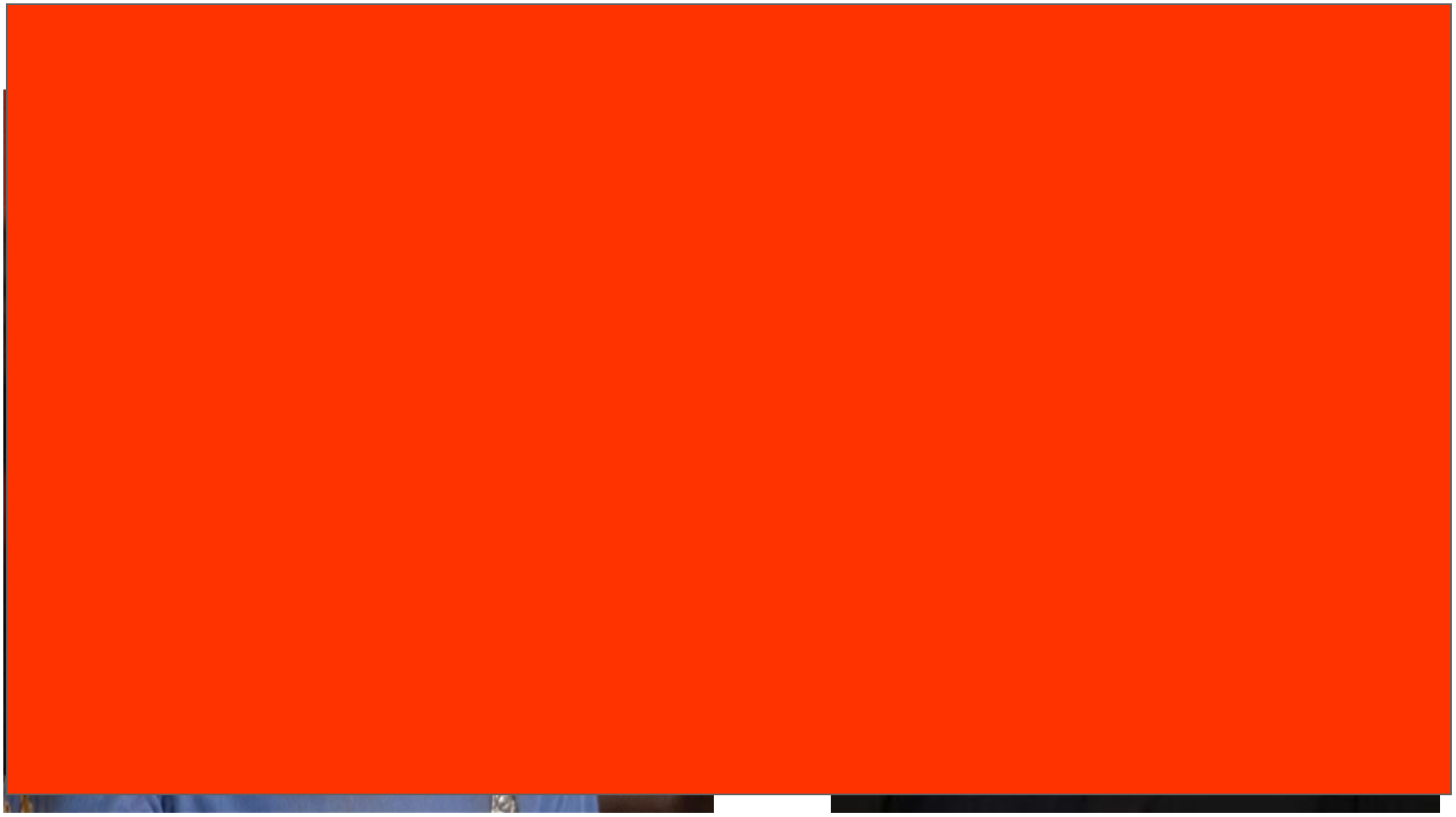
The Opportunist's Viewpoint

COPD matters

Top 5 Killers in US	Rank 1990	Mortality 1990	Rank 2010	Mortality 2010	% median change
Ischemic Heart Disease	1	648K	1	563K	Down 14%
Stroke	2	177K	2	172K	Down 3%
Lung Cancer	3	143K	3	163K	Up 14%
COPD	4	97K	4	154K	Up 58%
Lower Respiratory Tract Infections	5	90K	7	85K	Down 8%

Murray CJL , et al. JAMA. 2013; 310 (6): 591-608

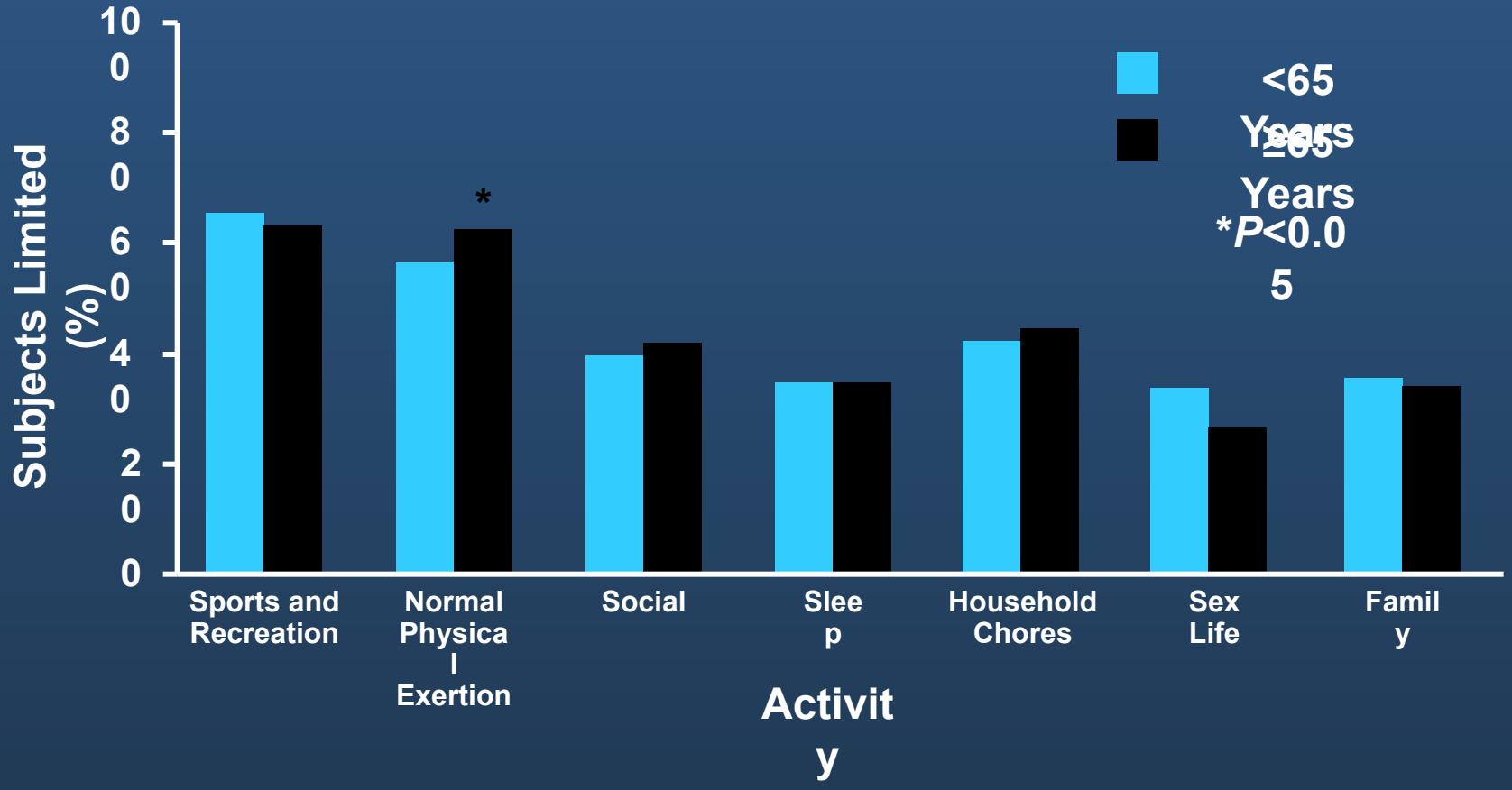
May the force……



Woman's World

- ~72, 000 women died (2009)….53%
- More hospitalizations (57% of 715,000)
- More severe and younger
  - 71% LVRS/transplant group (<53yo, FEV1<40%) 2000
  - 66% of very severe (FEV1<50%, <55yo) 2011
  - ~80% of nonsmoking COPD (15%) and majority of nonsmoking NSCCA in women

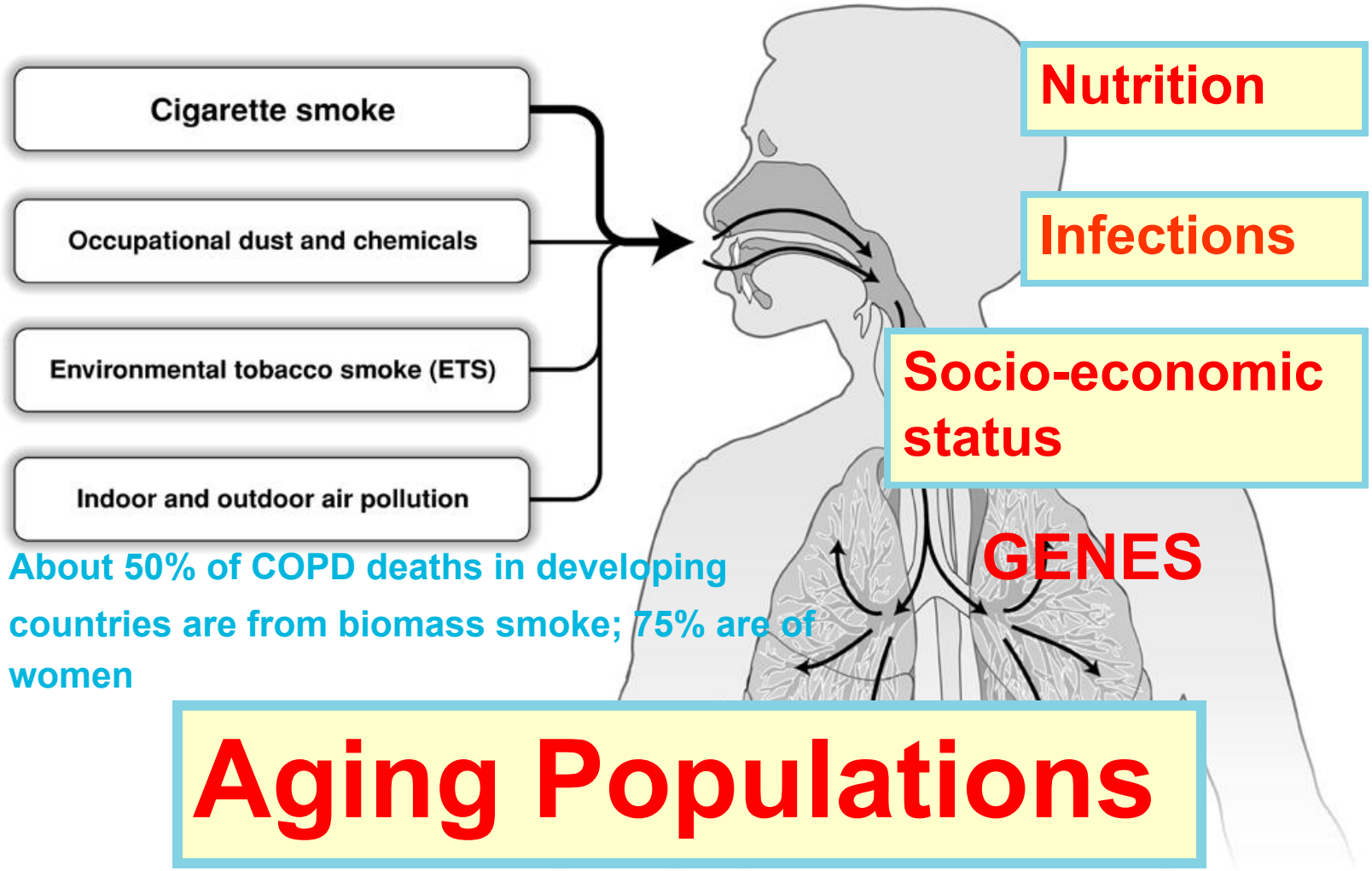
COPD Limits Daily Activities for Patients Regardless of Age



P17. How much do you feel your respiratory condition limits what you can do in each of the following areas? n=3,265

Bernard S, et al. *Eur Respir J.* 2002;20:799-805.

Risk Factors for COPD



- About 50% of COPD deaths in developing
- countries are from biomass smoke; 75% are of
- women

Aging Populations

Definition of COPD

- **C**hronic **O**bstructive **P**ulmonary **D**isease is a **preventable and treatable** disease with some significant extrapulmonary effects.
- The pulmonary component is characterized by airflow limitation that is not fully reversible. **FEV/FVC<0.70**
- The airflow limitation is usually **progressive** and associated with an abnormal inflammatory response of the lung to noxious particles or gases.
- Severe **COPD** leads to respiratory failure, hospitalization and death

Global Initiative for Chronic Obstructive Lung Disease. Goldcopd.org. NIHLBI & WHO

COPD: WHAT IT IS!

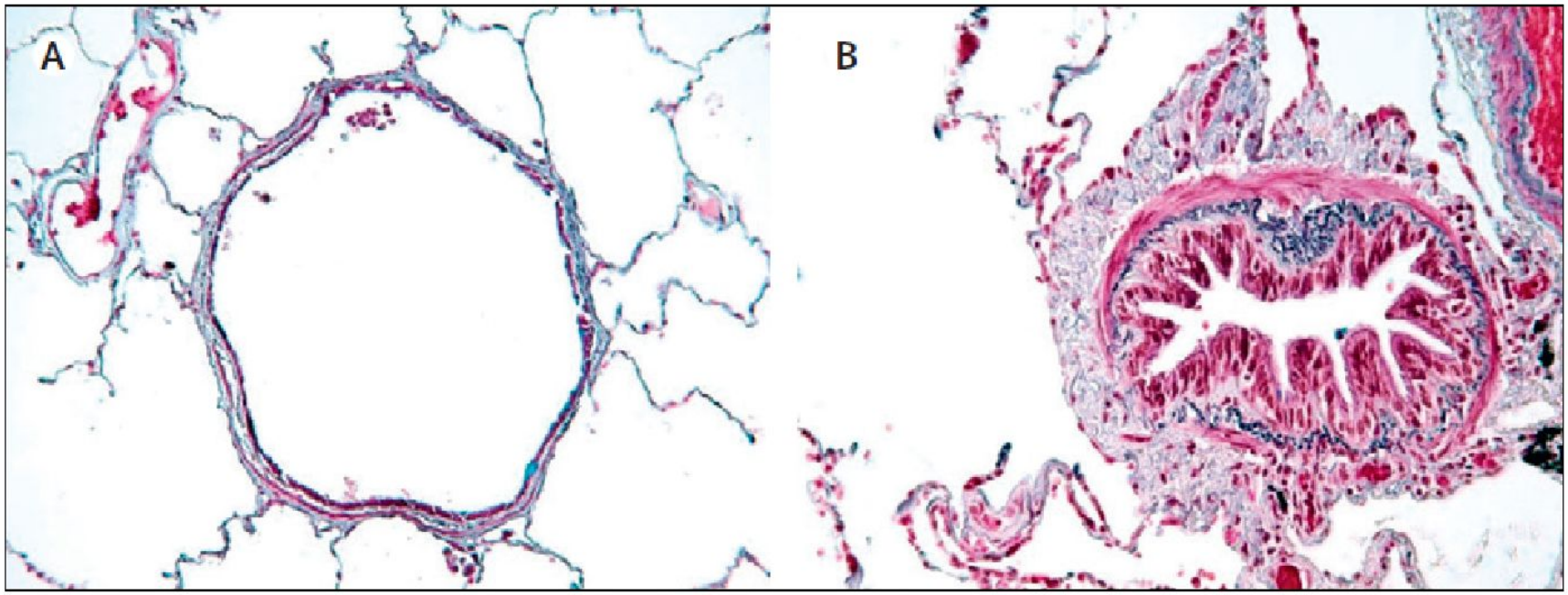
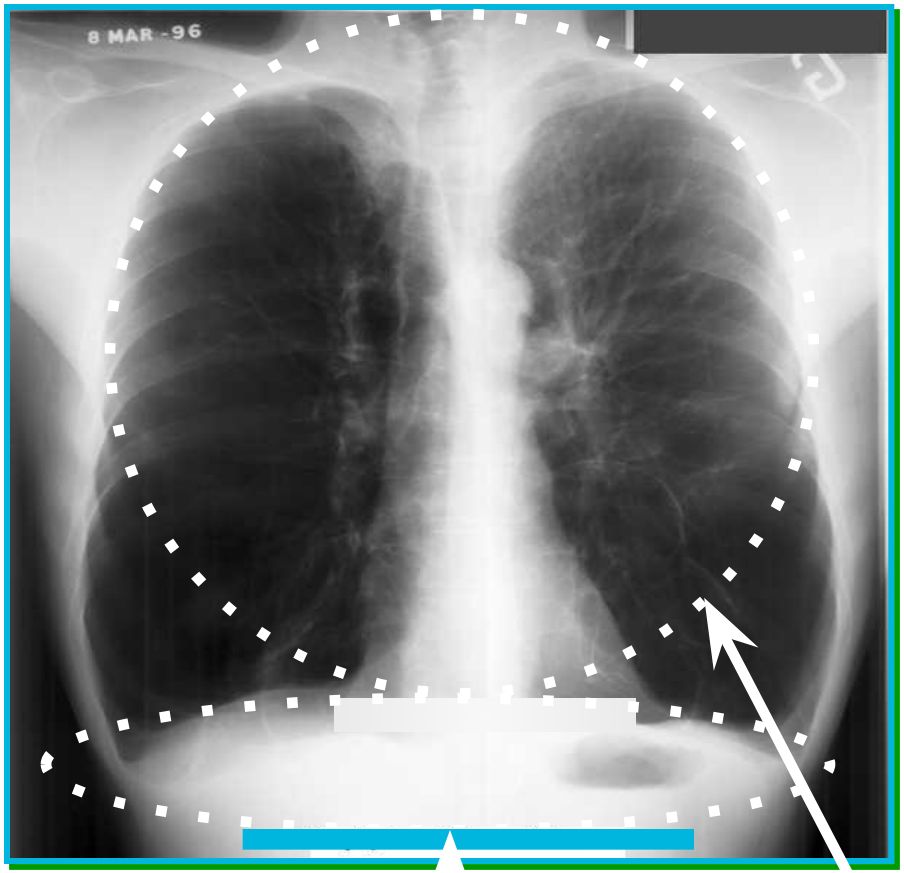


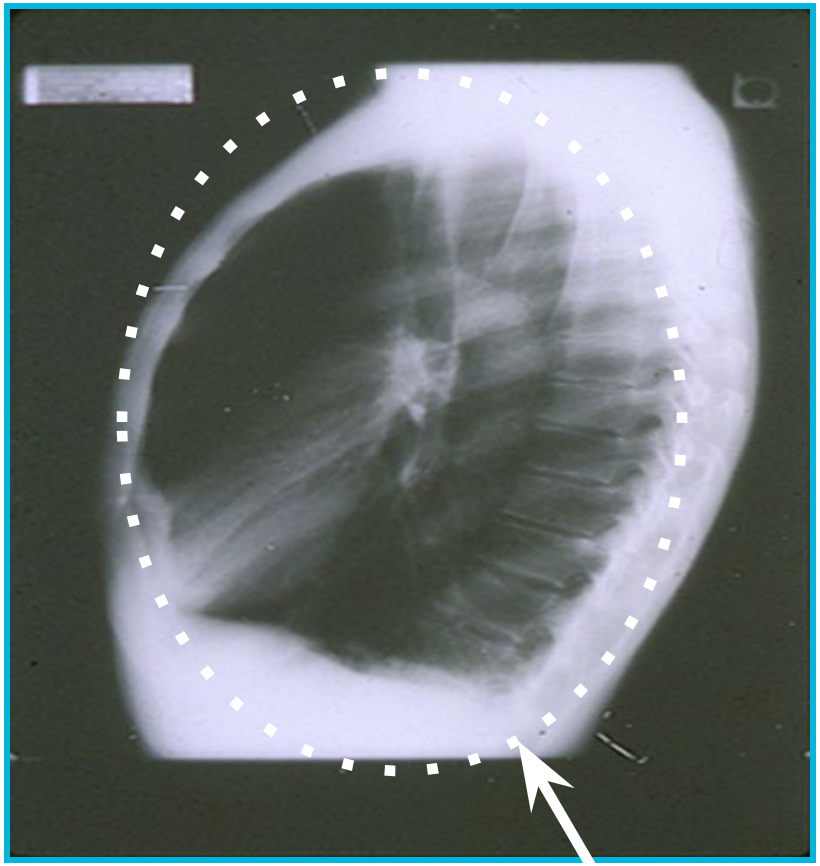
Figure 1: Comparison of airway features in a healthy individual and in a patient with chronic obstructive pulmonary disease

(A) Normal airway. (B) In chronic obstructive pulmonary disease airways are narrowed by infiltration of inflammatory cells, mucosal hyperplasia, and deposition of connective tissue in the peribronchiolar space.[23]

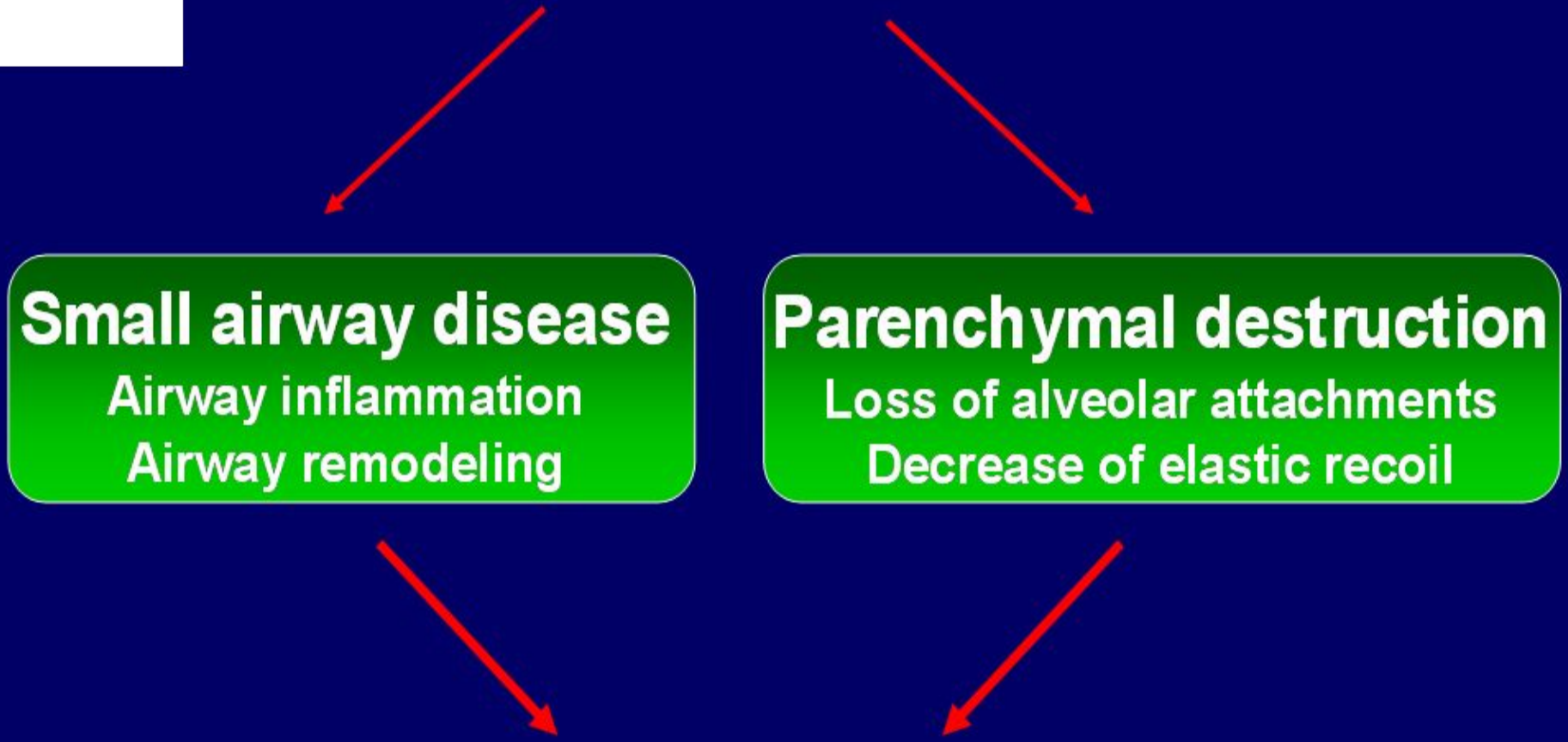
Decramer M, et al. Lancet. 2012; 379: 1341-51

Radiographic Changes in COPD





INFLAMMATION IN COPD



Must have spirometry

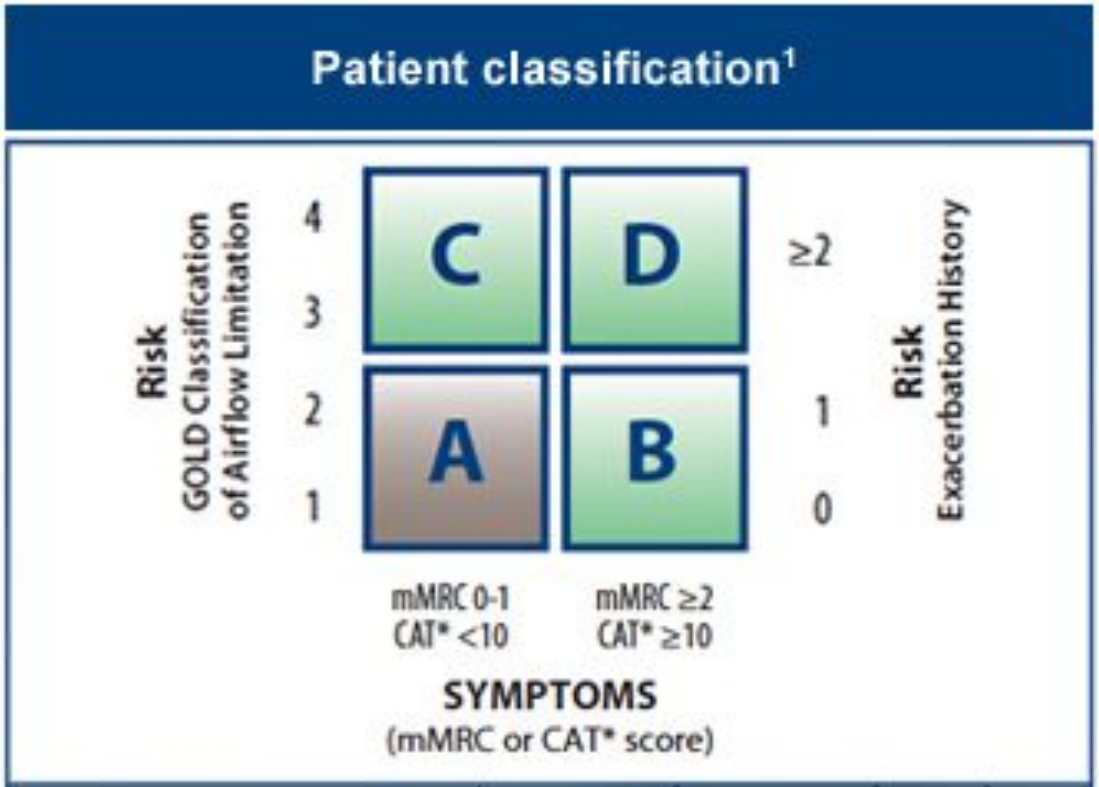
- COPD is not a *clinical diagnosis*
- Requires documentation of airflow obstruction that is not completely reversible
- Spirometry should be measured in stable, symptomatic patients

Must have spirometry

- COPD is not a *clinical diagnosis*
- Requires documentation of airflow obstruction that is not completely reversible
- Spirometry should be measured in stable, symptomatic patients
- Review of VA patients with diagnosis of COPD, 48% of VA patients did not have airflow obstruction

David Au, University of Washington Grand Rounds, 2013

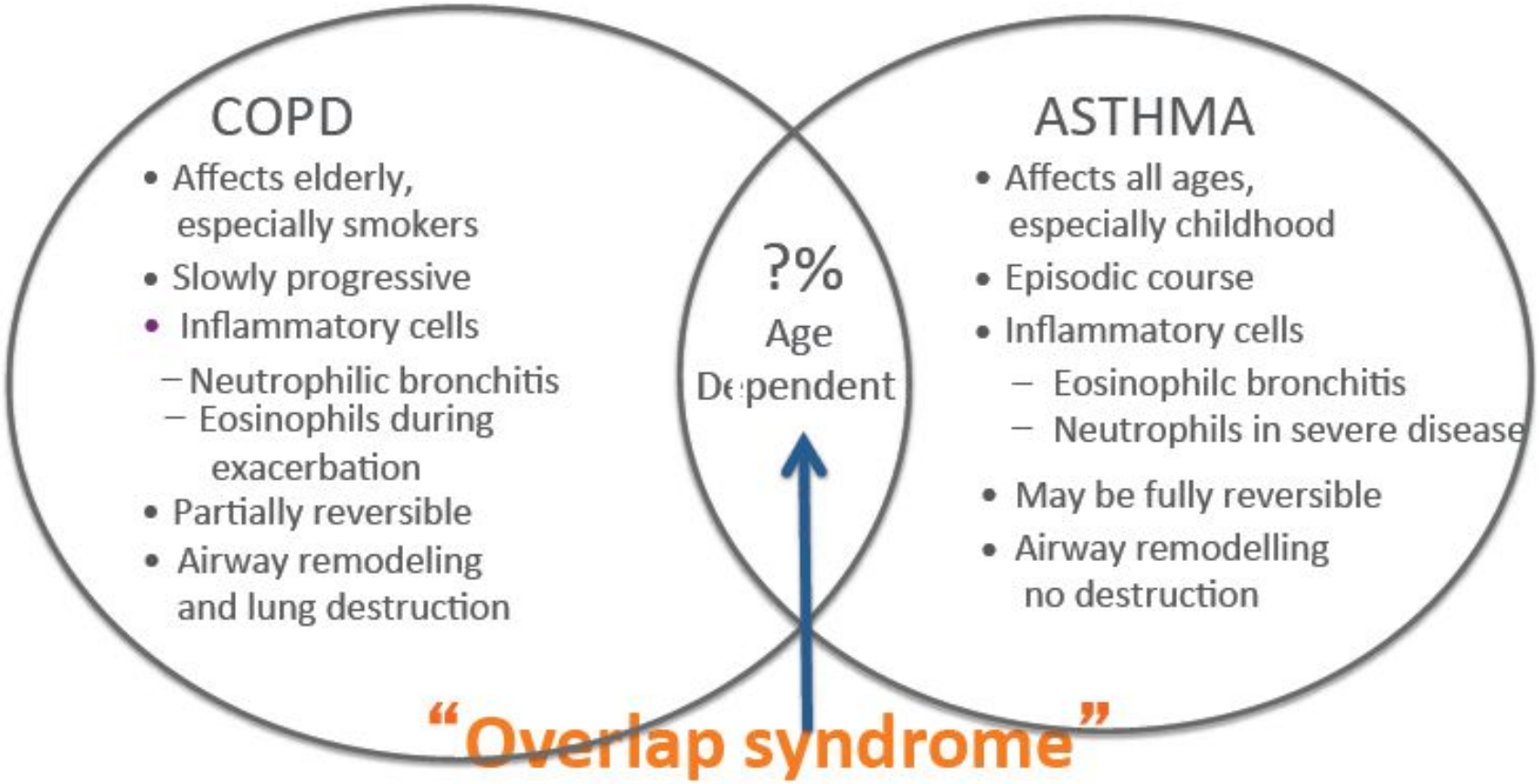
GOLD combined assessment



	Spirometric classification	Exacerbations per year	mMRC	CAT*
GROUP A: low risk, less symptoms	GOLD 1-2	≤1	0-1	<10
GROUP B: low risk, more symptoms	GOLD 1-2	≤1	≥2	≥10
GROUP C: high risk, less symptoms	GOLD 3-4	≥2	0-1	<10
GROUP D: high risk, more symptoms	GOLD 3-4	≥2	≥2	≥10

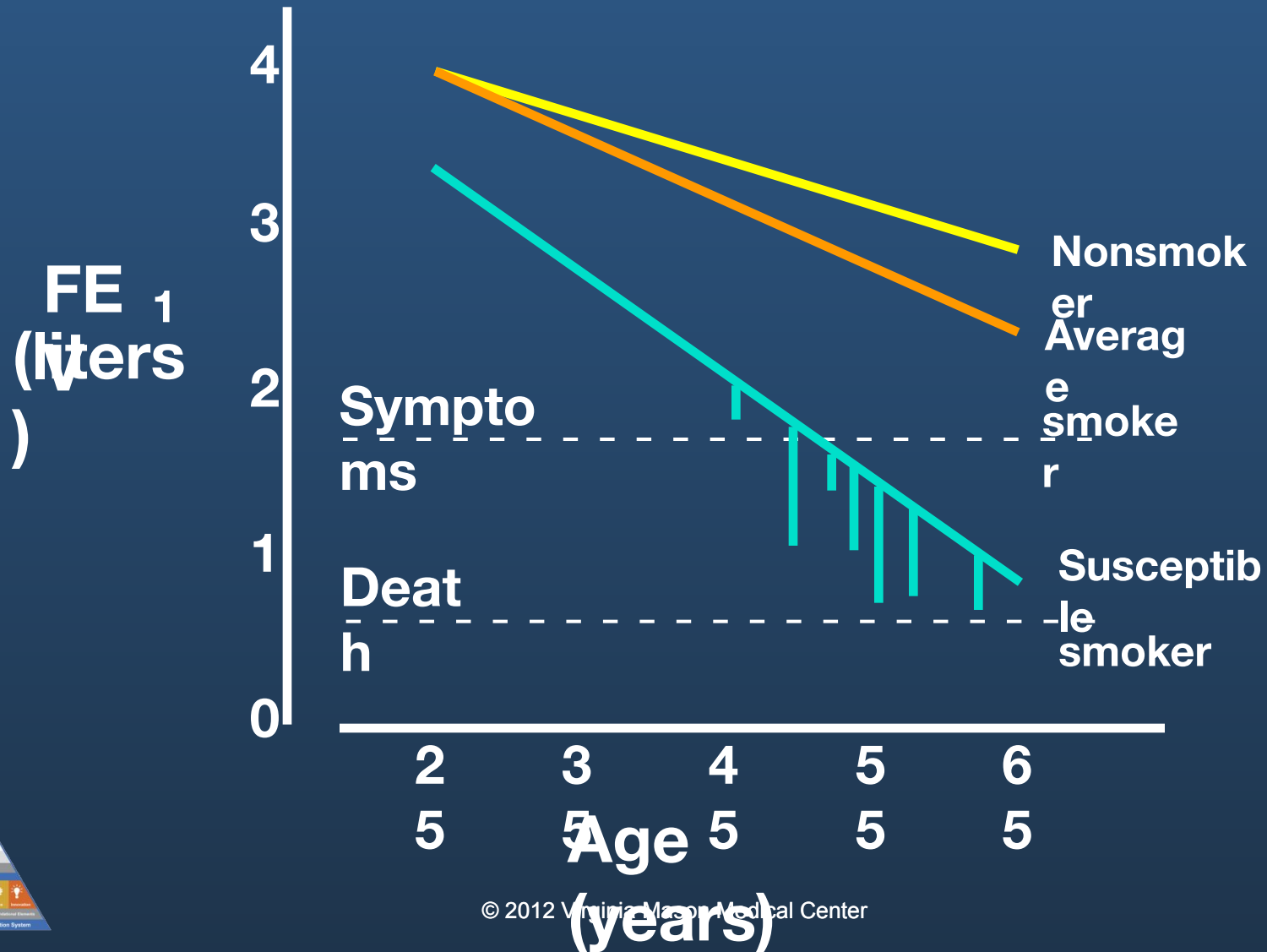
GOLD 2013

Overlap Syndrome



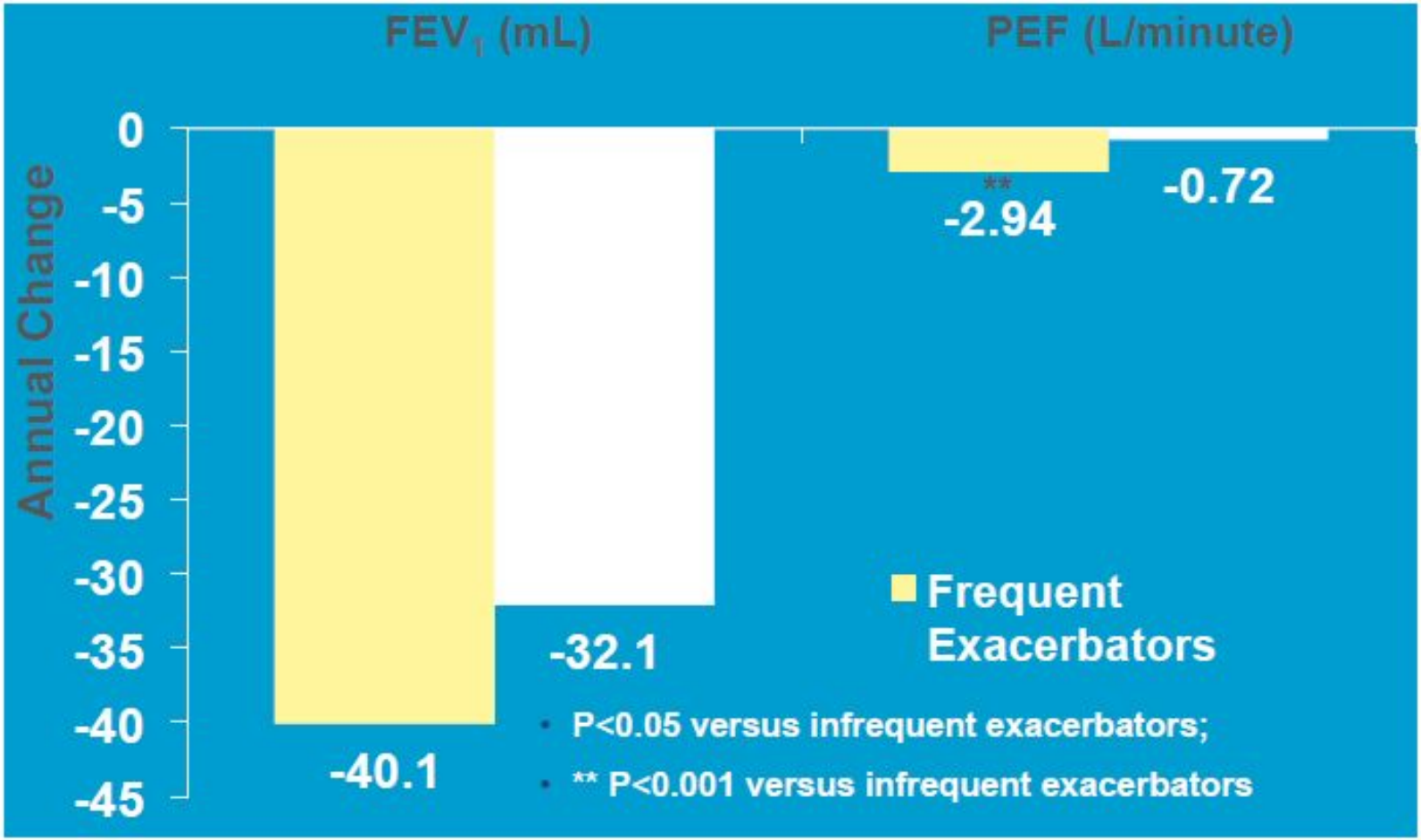
Some patients with asthma cannot be distinguished from COPD with the current diagnostic tests. The management of these patients should be similar to that of asthma. ATS Guidelines 2004

Natural History of COPD



Effect of Frequent Exacerbations

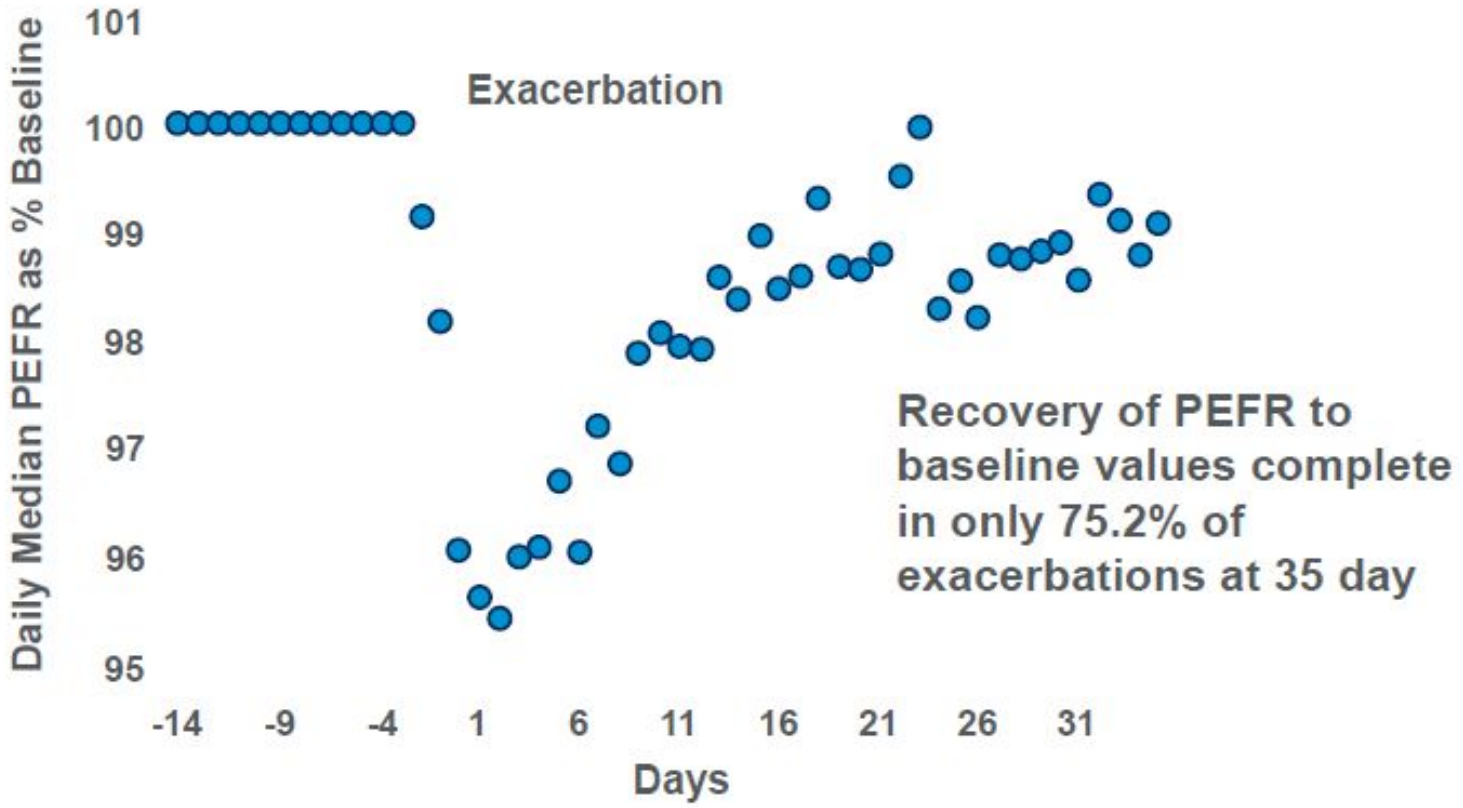
Associated With More Rapid Decline in Pulmonary Function



Donaldson GC, et al. *Thorax*. 2002;57:847-852.

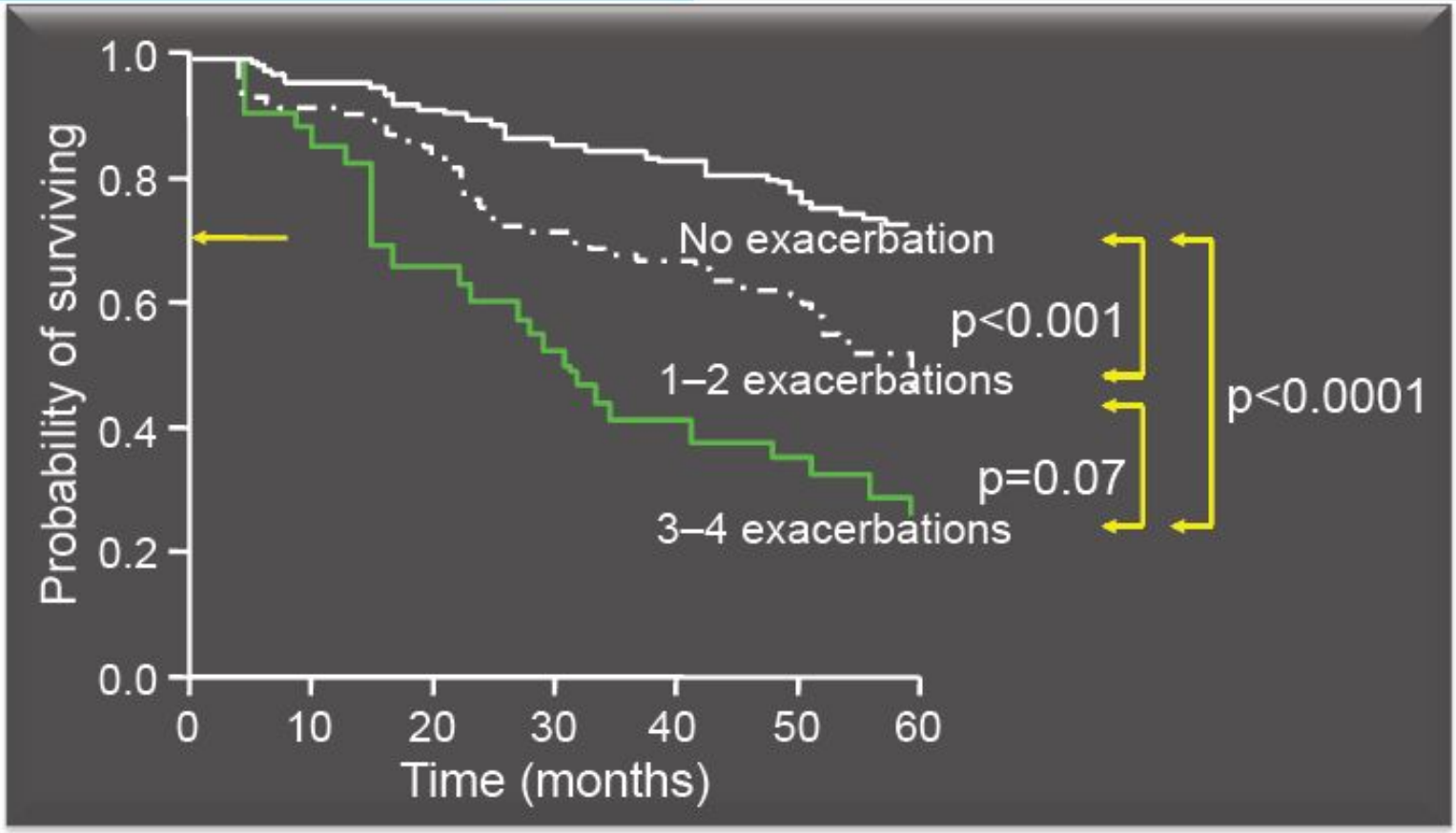
Recovery After Exacerbation

Pulmonary Function Recovers Slowly After an Exacerbation



Seemungal TA, et al. *Am J Respir Crit Care Med.* 2000;161:1608–1613.

Exacerbations Impact Survival



Soler-Cataluña JJ et al. *Thorax*. 2005;64:925-31

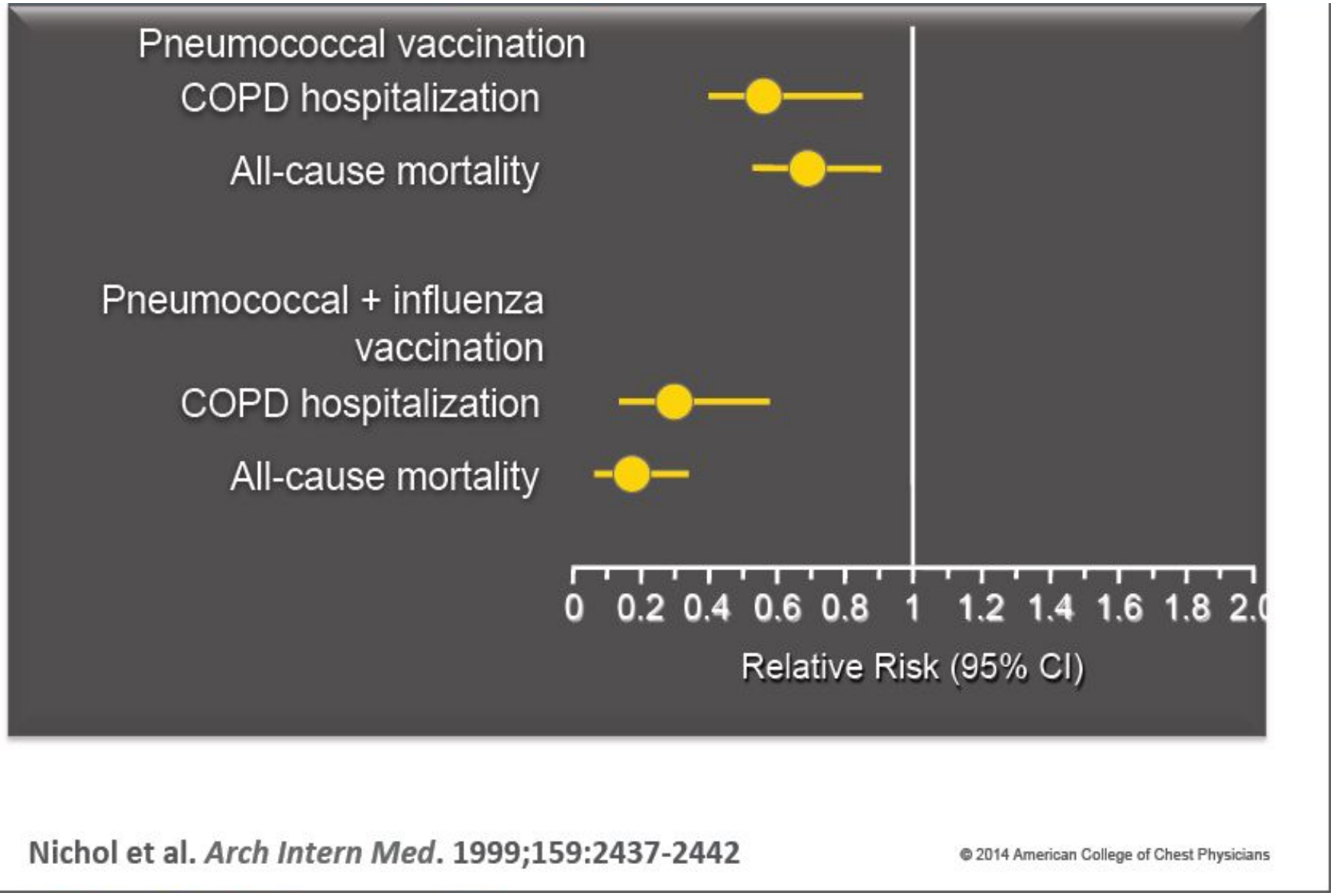
Management

Treatment for all with COPD

1. Smoking Cessation
   - Commit to quit
   - Nicotine replacement
   - Wellbutrin
   - Varenicline
   - QUIT LINE: 1-800-QUIT-NOW
2. Intermittent bronchodilator therapy
   - Albuterol, ipratropium, or combination
3. Influenza and pneumococcal vaccine
   - Influenza vaccine decreases serious illness and death by 50% (NIHLBI/WHO)
4. Education, exercise, diet

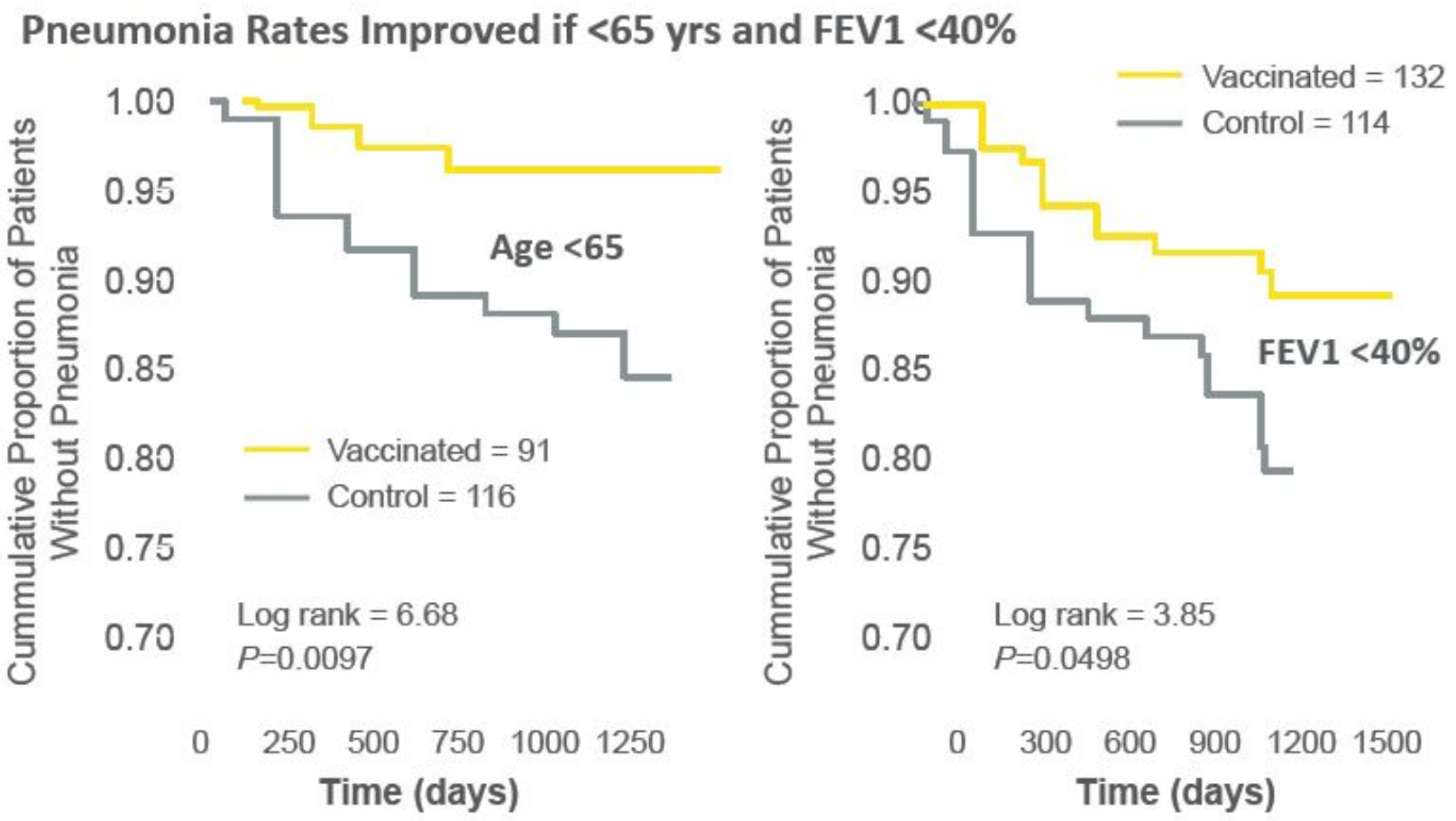
Global Initiative for Chronic Obstructive Lung Disease. Goldcopd.org. NIHLBI & WHO

Vaccines Reduce Exacerbations



Nichol et al. *Arch Intern Med*. 1999;159:2437-2442

Pneumococcal Vaccine



Alfageme I, et al. *Thorax*. 2006;61:189-195.

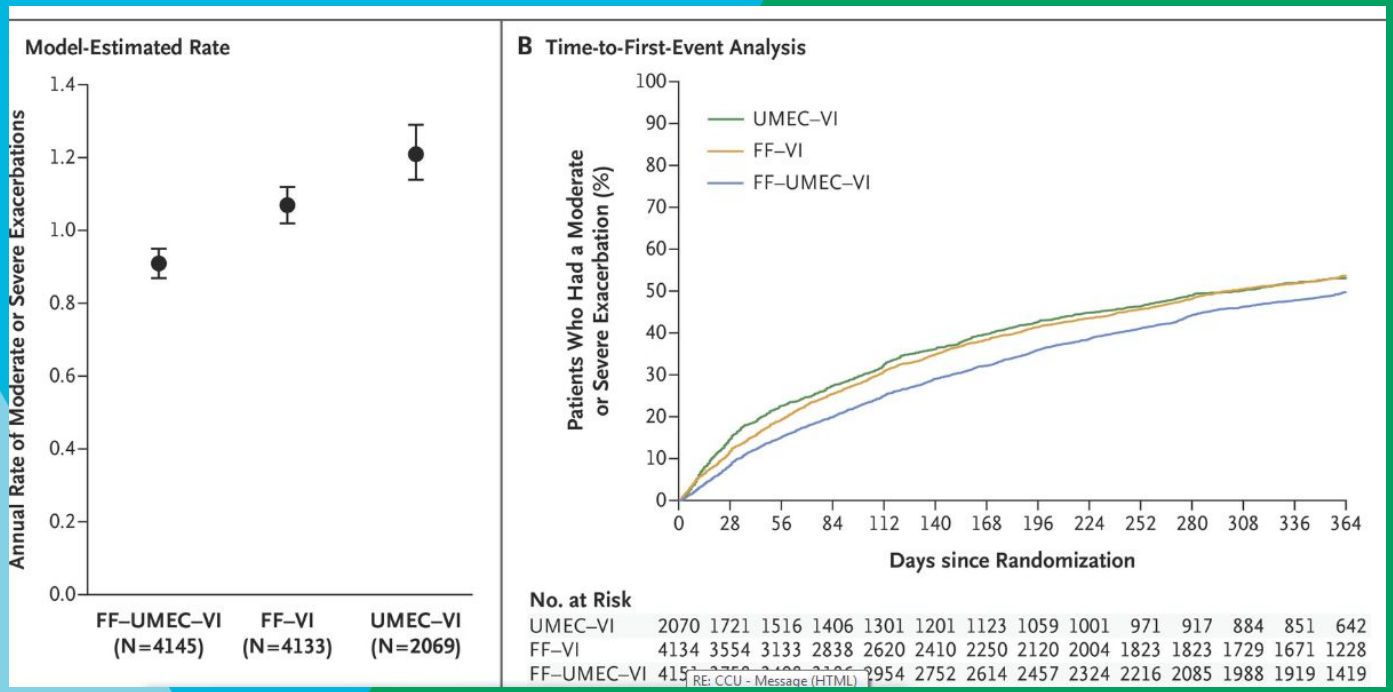
Inhaled controller therapies for COPD

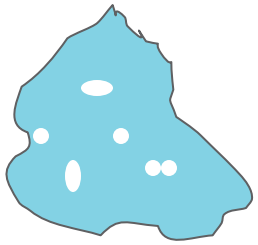
- **Anti-inflammatory**
  - **ICS**: inhaled corticosteroids
    - Ex: fluticasone, budesonide, mometasone
- **Long acting bronchodilators**
  - **LABA**: inhaled long acting B2 agonists
    - Ex: salmeterol, formoterol , afomoterol, indacaterol, vilanterol, olodaterol
  - **LAMA**: long acting muscarinic antagonist
    - Ex: tiotropium, aclidinium (Tudorza), umeclidinium
    - glycopyrronium bromide NVA237 (Seebri)
- **Combinations**: budesonide/formoterol, fluticasone/salmeterol, mometasone/formoterol, fluticasone/vilanterol (Breo), Umec/vilant (Ellipta), glyco/indacaterol

ORIGINAL ARTICLE

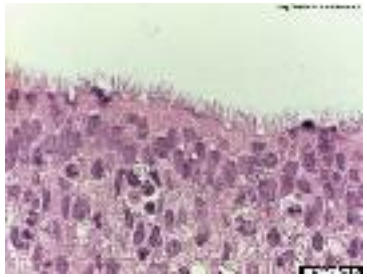
Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

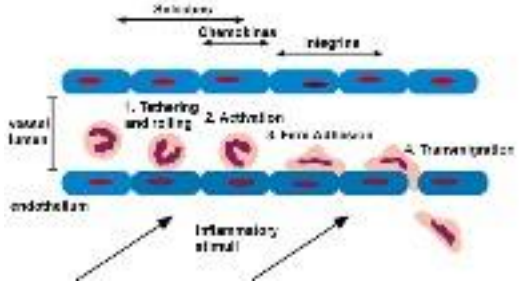
David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., et al., for the IMPACT Investigators





Decrease bronchial hyper-responsiveness





Protection from reactive O2 species
Increase β defensins

Mucous secretion

- Decrease volume
- Improves mucociliary clearance, elasticity, and ciliary motility
- Inhibition of genes for mucoid proteins

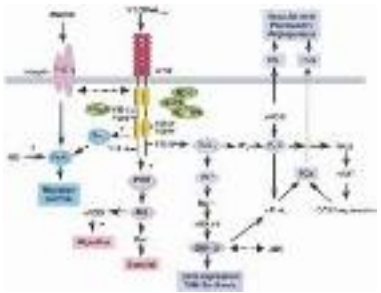
MACROLIDES

- Reduction in adhesion molecules (ICAM-1, sICAM-1, e-selectin, β-2 integrins, VCAM-1, LFA-3, Mac-1)
- Reduction in bacteria adhesion

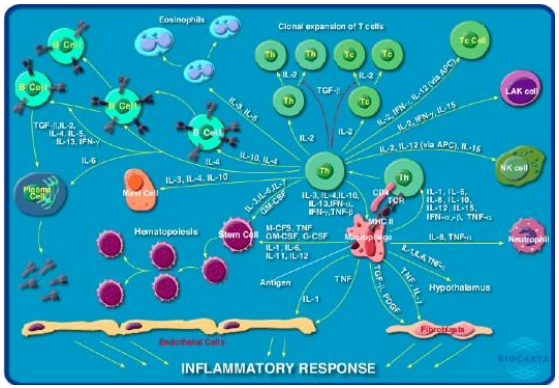
PMNs: reduced elastase, stabilization of degranulation

Inhibits P. aeruginosa

- Adhesion
- Alters virulence factors
- Decreased biofilm production
- Altered quorum sensing
- Altered gene expression



Alters signaling pathways like VEGF and NFκB



Friedlander AL. et al. Chest. 2010

Zarogoulidis, et al. Eur J Clin Pharmacol. 2011

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

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., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

- N=1577, >40 years of age, U.S.
- Clinical dx of COPD:
  - Pack year >10
  - FEV1/FVC <70, without complete reversibility
  - Supplement O2 or steroids/or ER visit for AECOPD
  - No AECOPD for 4 weeks prior to enrollment
  - No asthma, HR>100, QTc>450, documented hearing loss

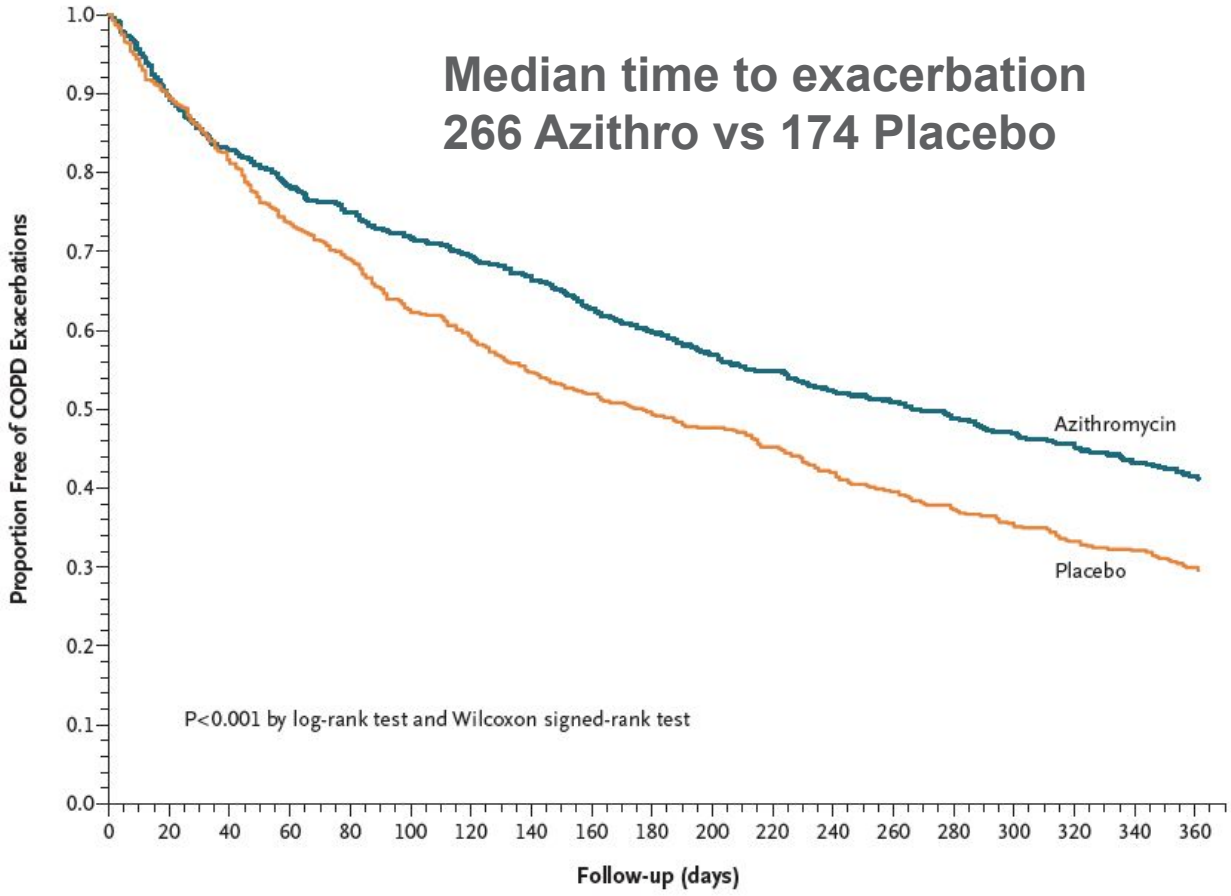


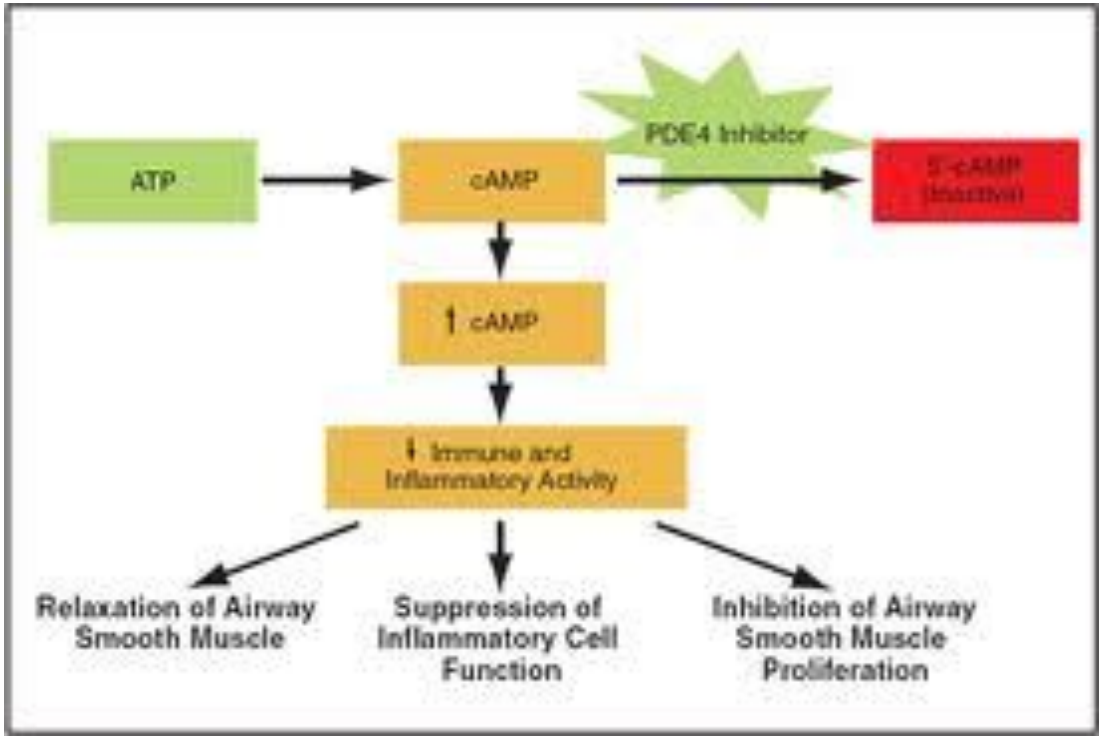
Figure 2. Proportion of Participants Free from Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) for 1 Year, According to Study Group.

The analyses were based on the participants who were randomly assigned to the group minus those who did not return for any follow-up assessment — 558 participants in the azithromycin group, of whom 317 (57%) had an acute exacerbation, and 559 in the placebo group, of whom 380 (68%) had an acute exacerbation.

Albert RK, et al. NEJM 2011; 365 (8): 689-98

Phosphodiesterase inhibition

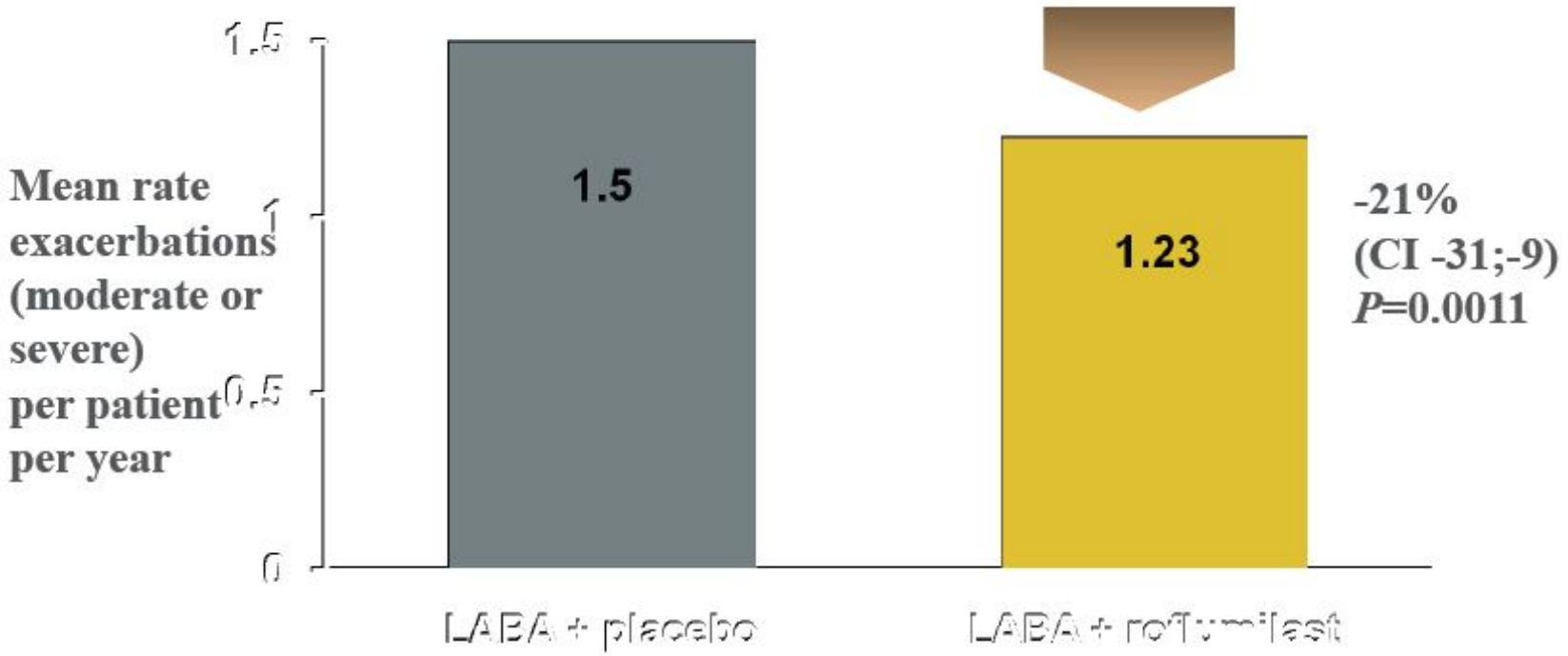
- Hydrolase of cAMP in inflammatory cells



Journal of COPD Management 2006

Roflumilast and exacerbations

Significant Reduction in Exacerbations When Added to LABA

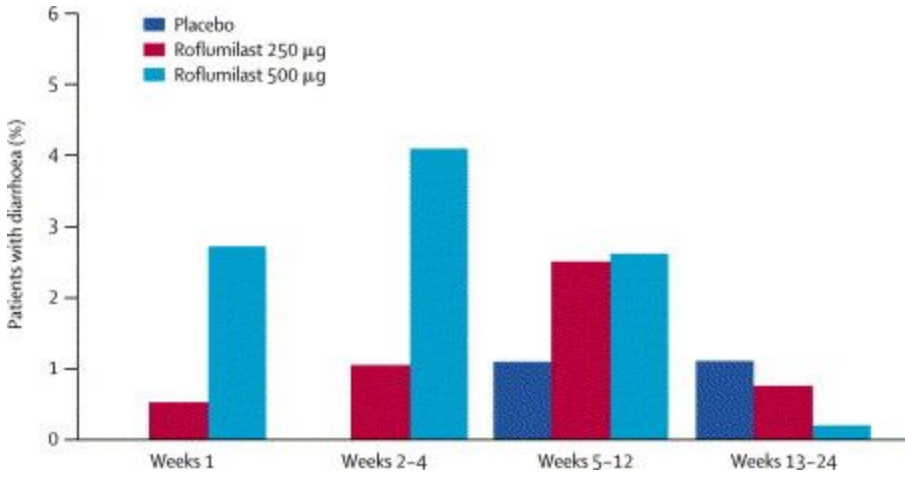


Hanania et al. *Am J Respir Crit Care Med* 2010;181:A4435
Fabbri et al *Lancet* 2009;374:695-703.

Side effects-roflumilast

- Nasopharyngitis
- Nausea
- Headache
- 17% of patients on 500mcg dose had a side effect
  - 15% discontinued
- Weight loss, avg 2kg

- Diarrhea



Therapy at Each Stage of COPD

I: Mild	II: Moderate	III: Severe	IV: Very Severe
▪ $FEV_1/FVC < 70\%$ ▪ $FEV_1 \geq 80\%$ predicted	▪ $FEV_1/FVC < 70\%$ ▪ $50\% \leq FEV_1 < 80\%$ predicted	▪ $FEV_1/FVC < 70\%$ ▪ $30\% \leq FEV_1 < 50\%$ predicted	▪ $FEV_1/FVC < 70\%$ ▪ $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus chronic respiratory failure

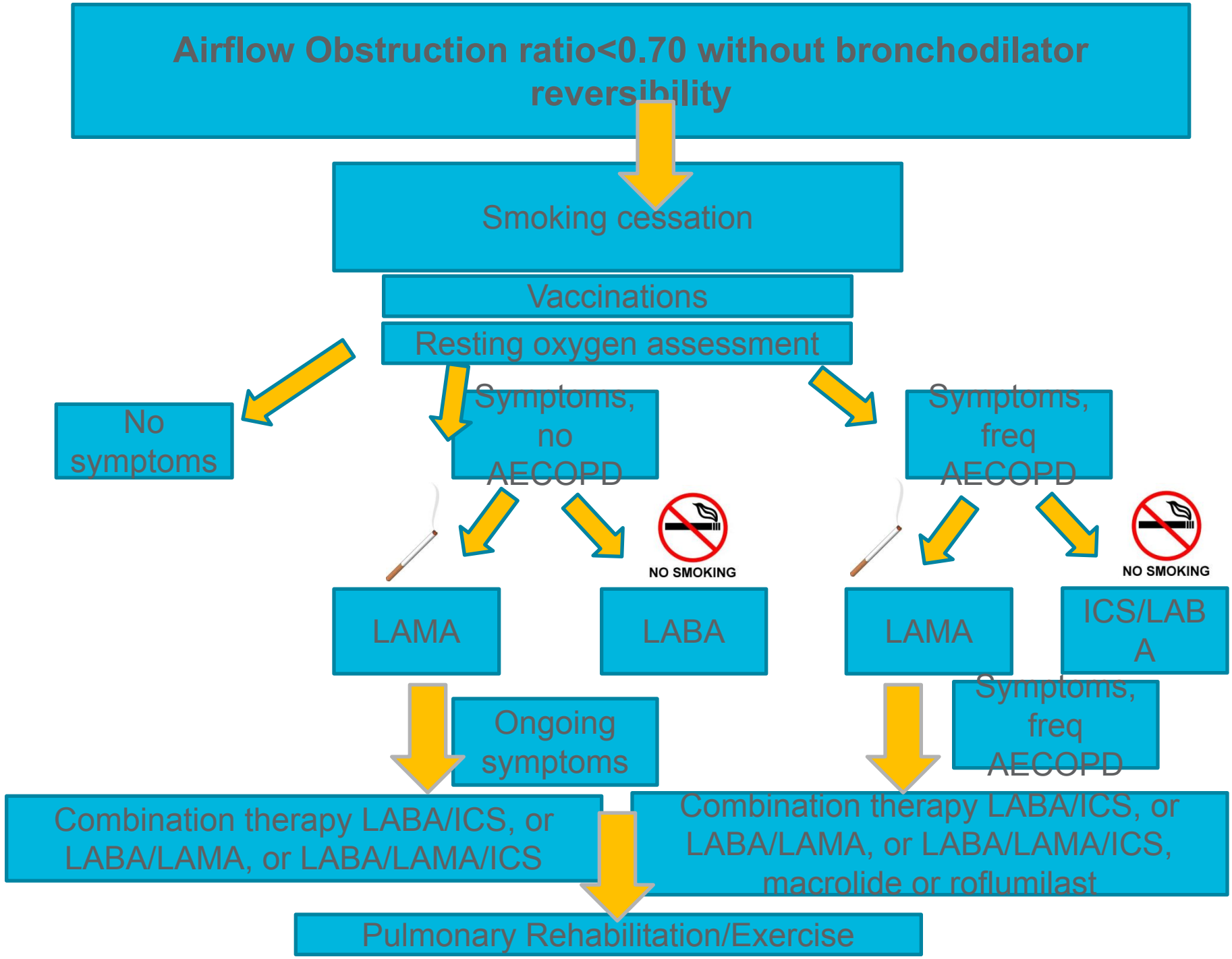
Active reduction of risk factor(s); influenza vaccination

Add short-acting bronchodilator (when needed)

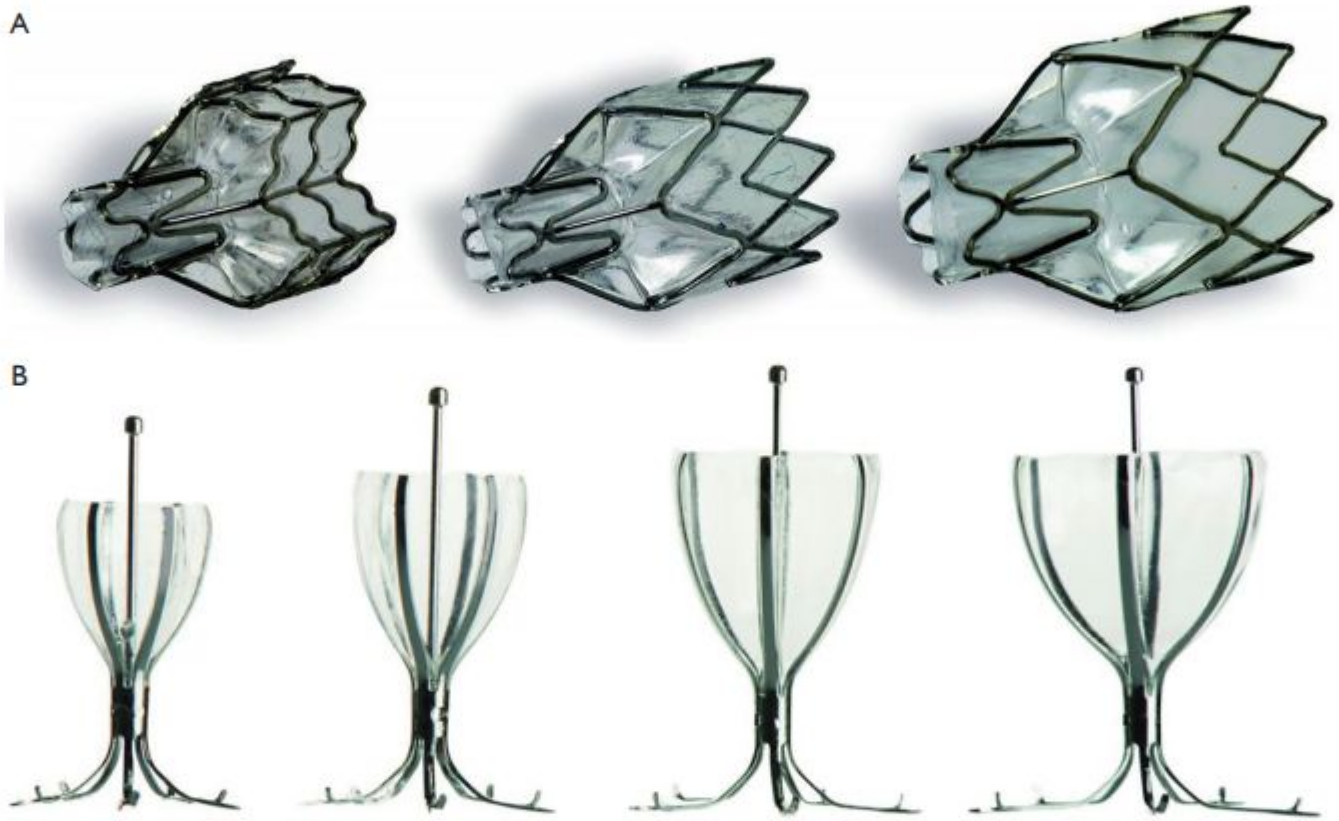
Add regular treatment with one or more long-acting bronchodilators (when needed); ***Add*** rehabilitation

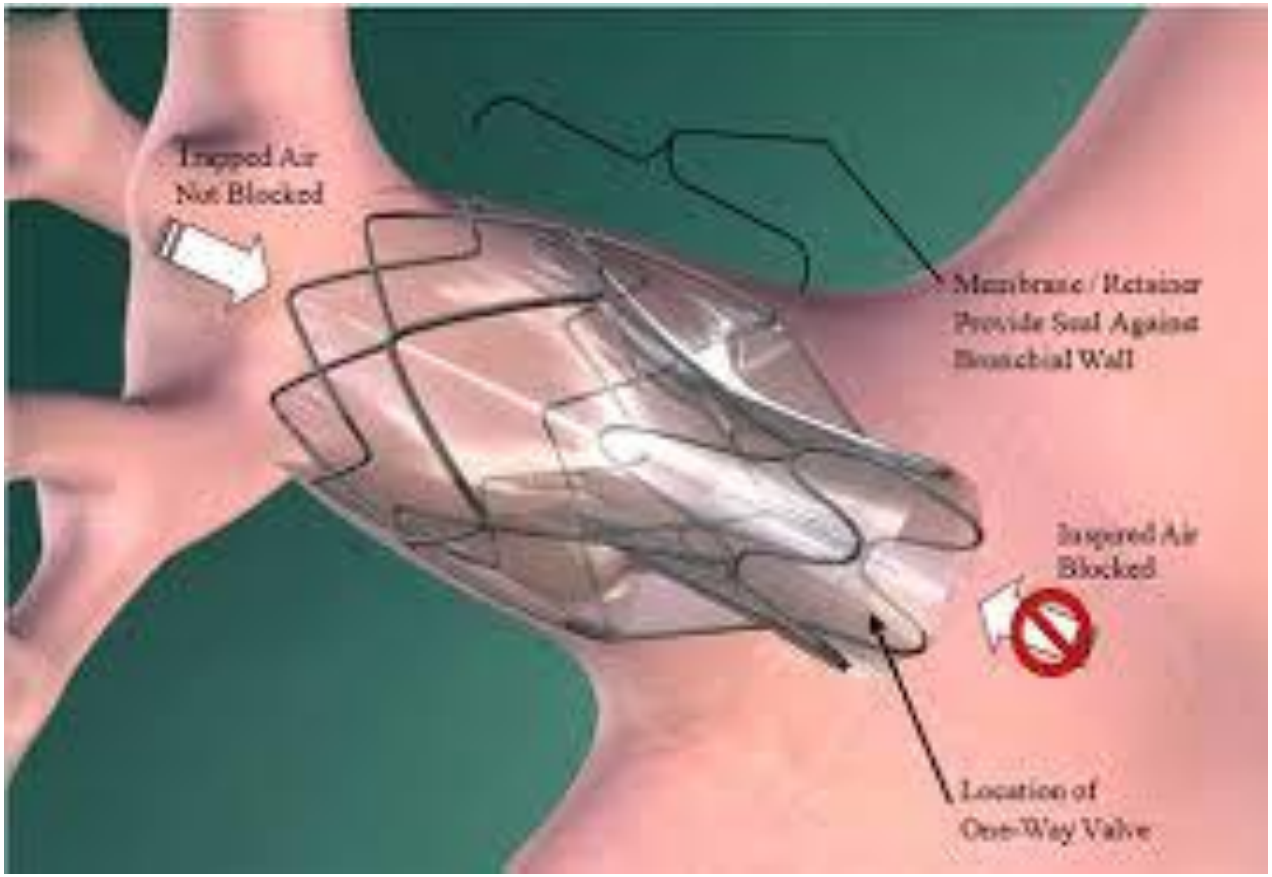
Add inhaled glucocorticosteroids if repeated exacerbations

Add long term oxygen if chronic respiratory failure. ***Consider*** surgical treatments

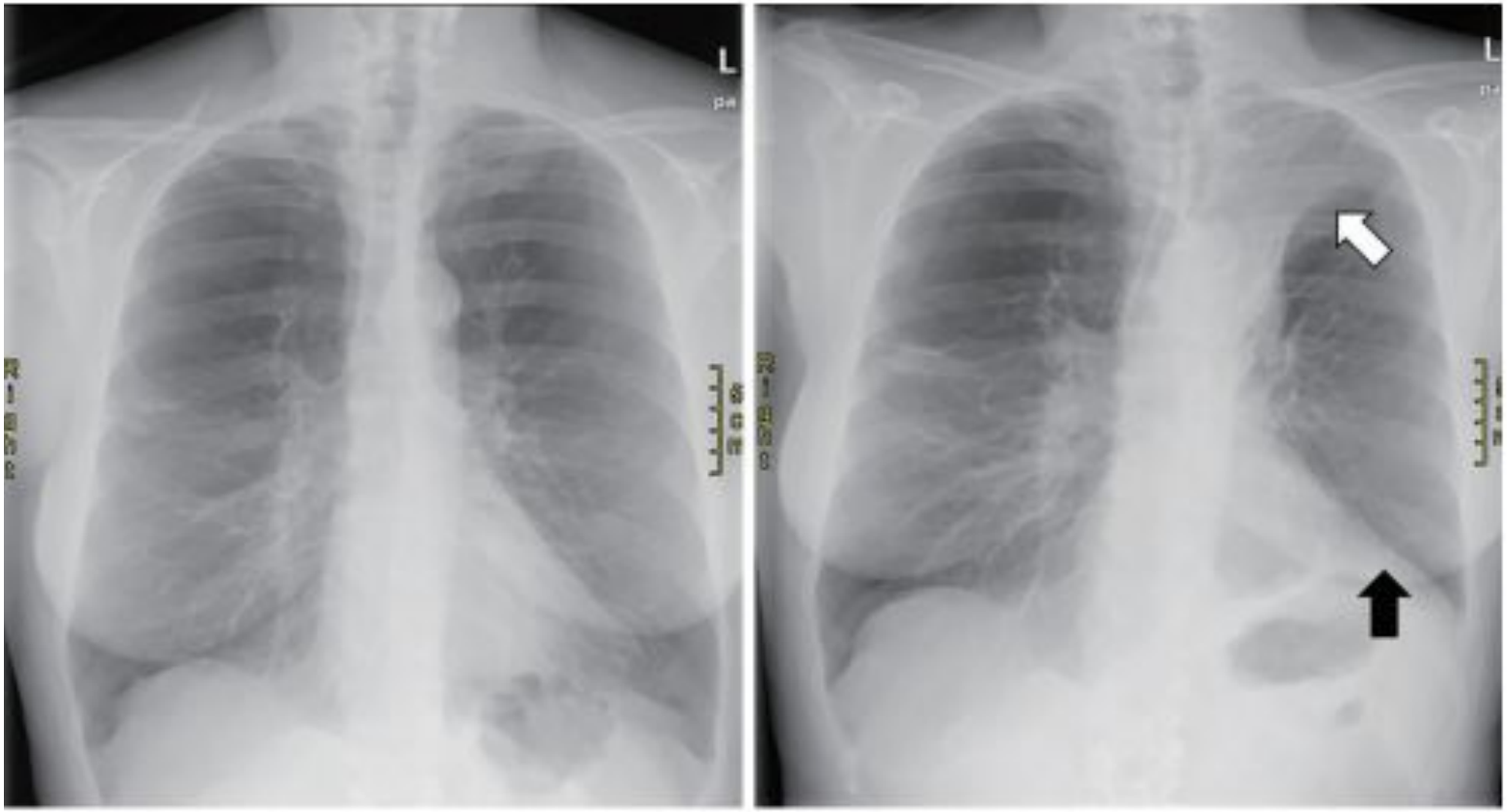

Airflow Obstruction ratio<0.70 without bronchodilator reversibility
Smoking cessation
Vaccinations
Resting oxygen assessment
No symptoms
Symptoms, no AECOPD
Symptoms, freq AECOPD
NO SMOKING
NO SMOKING
LAMA
LABA
LAMA
ICS/LABA
Ongoing symptoms
Symptoms, freq AECOPD
Combination therapy LABA/ICS, or LABA/LAMA, or LABA/LAMA/ICS
Combination therapy LABA/ICS, or LABA/LAMA, or LABA/LAMA/ICS, macrolide or roflumilast
Pulmonary Rehabilitation/Exercise

Endobronchial Valve LVR





EBV effect



Pre valve treatment

Post valve treatment

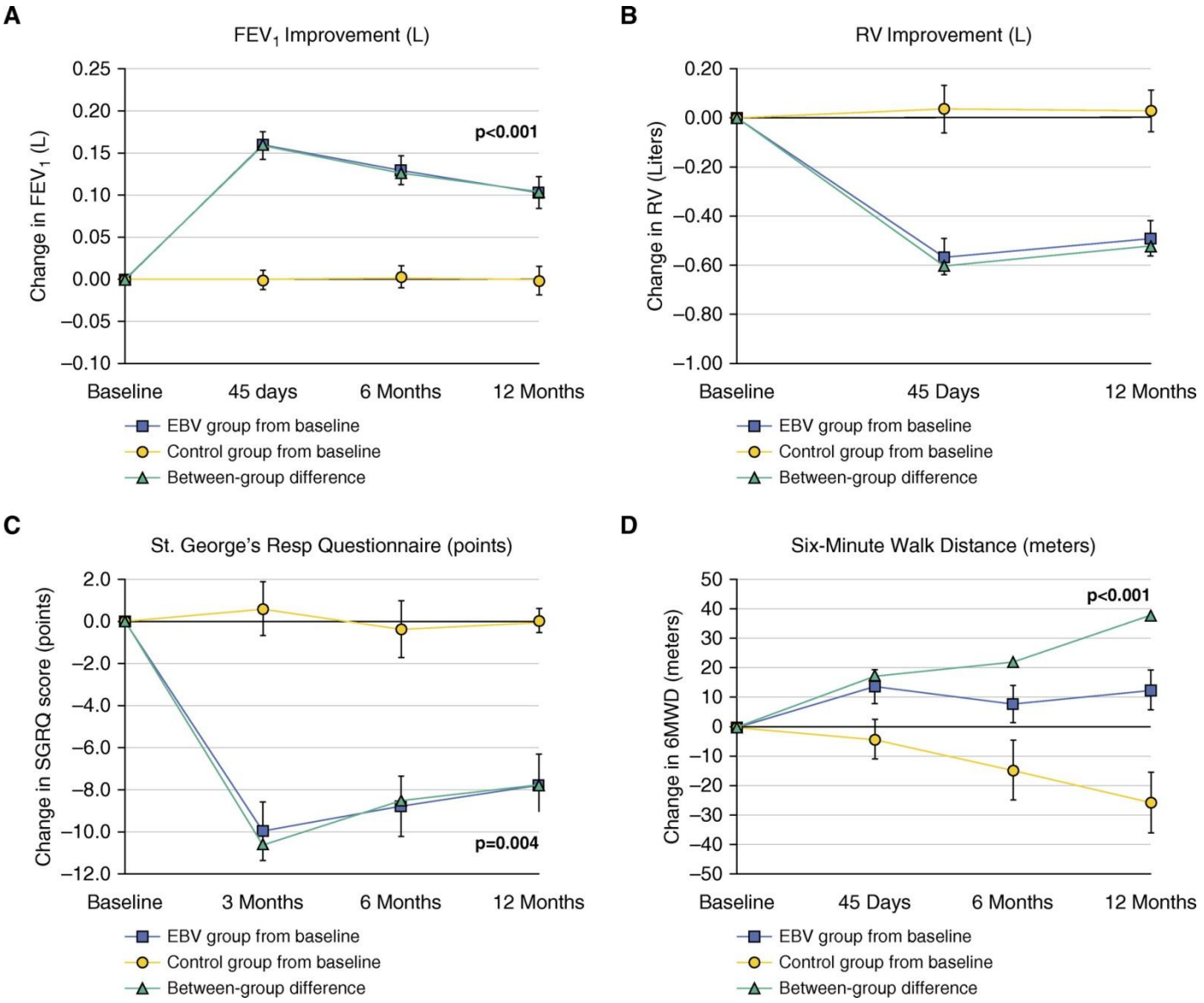
EBV LVR

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

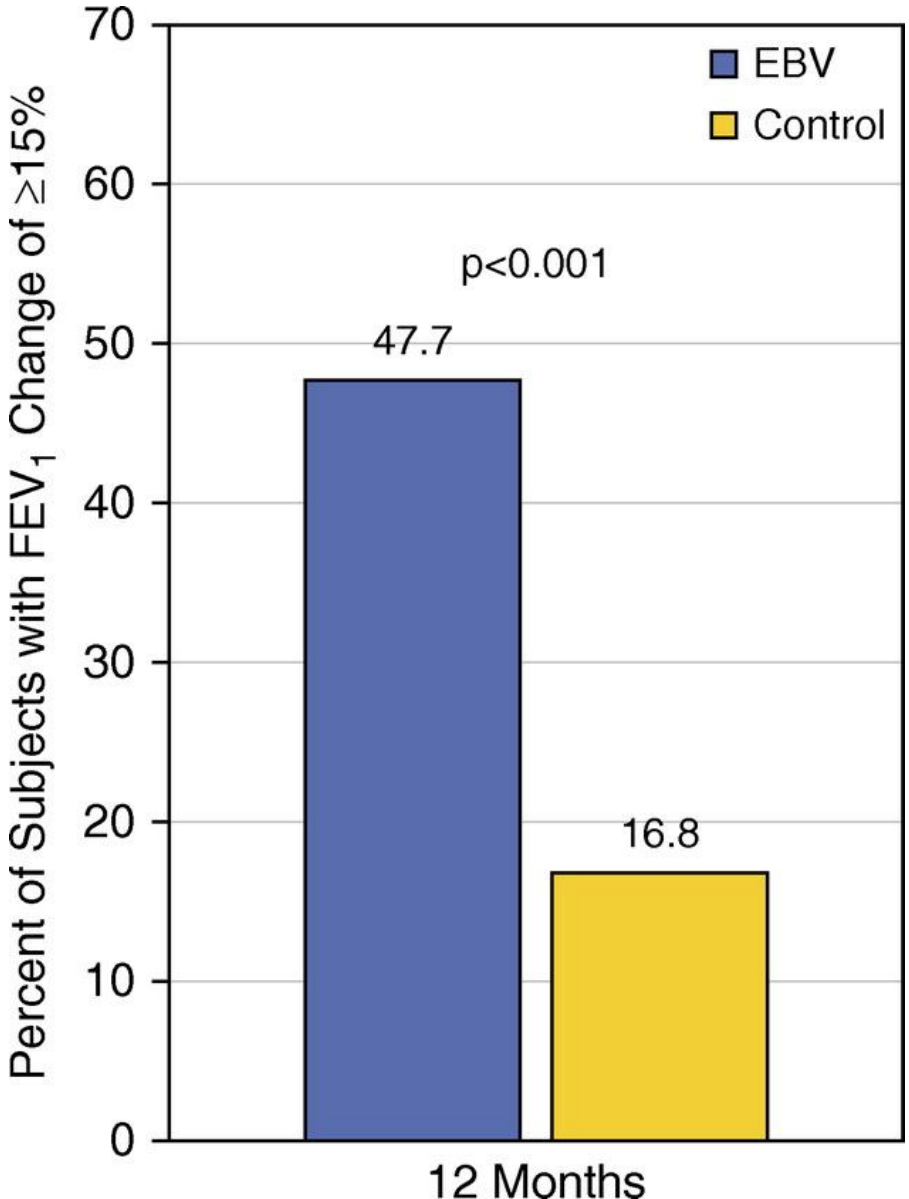
Gerard J. Criner[1], Richard Sue[2], Shawn Wright[2], Mark Dransfield[3], Hiram Rivas-Perez[4], Tanya Wiese[4], Frank C. Sciurba[5], Pallav L. Shah[6], Momen M. Wahidi[7], Hugo Goulart de Oliveira[8], Brian Morrissey[9], Paulo F. G. Cardoso[10], Steven Hays[11], Adnan Majid[12], Nicholas Pastis, Jr.[13], Lisa Kopas[14], Mark Vollenweider[15], P. Michael McFadden[16], Michael Machuzak[17], David W. Hsia[18], Arthur Sung[19], Nabil Jarad[20], Malgorzata Kornaszewska[21], Stephen Hazelrigg[22], Ganesh Krishna[23], Brian Armstrong[24], Narinder S. Shargill[25], and Dirk-Jan Slebos[26]; for the LIBERATE Study Group

[1]Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; [2]St. Joseph's Hospital and Medical Center, Phoenix, Arizona; [3]University of Alabama at Birmingham UAB Lung Health Center, Birmingham, Alabama; [4]Department of Medicine, University of Louisville, Louisville, Kentucky; [5]Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; [6]Royal Brompton Hospital and Imperial College, London, United Kingdom; [7]Duke University Medical Center, Duke University, Durham, North Carolina; [8]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [9]Division of Pulmonary, Critical Care and Sleep Medicine, University of California, Davis, Sacramento, California; [10]Instituto do Coracao, Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil; [11]University of California, San Francisco, San Francisco, California; [12]Interventional Pulmonology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [13]Medical University of South Carolina, Charleston, South Carolina; [14]Pulmonary Critical Care and Sleep Medicine Consultants, Houston Methodist, Houston, Texas; [15]Orlando Health Pulmonary and Sleep Medicine Group, Orlando Regional Medical Center, Orlando, Florida; [16]Keck School of Medicine, University of Southern California, Los Angeles, California; [17]Center for Major Airway Diseases, Cleveland Clinic, Cleveland Clinic Foundation, Respiratory Institute, Cleveland, Ohio; [18]Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles, Torrance, California; [19]Stanford Hospital and Clinics, Stanford, California; [20]University Hospital Bristol NHS Foundation Trust, Bristol, United Kingdom; [21]Department of Cardiothoracic Surgery, University Hospital of Wales, Cardiff, United Kingdom; [22]Division of Cardiothoracic Surgery, Department of Surgery, Southern Illinois University School of Medicine, Springfield, Illinois; [23]Palo Alto Medical Foundation, El Camino Hospital, Mountain View, California; [24]QST Consultations Ltd., Allendale, Michigan; [25]Pulmonx Corporation, Redwood City, California; and [26]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

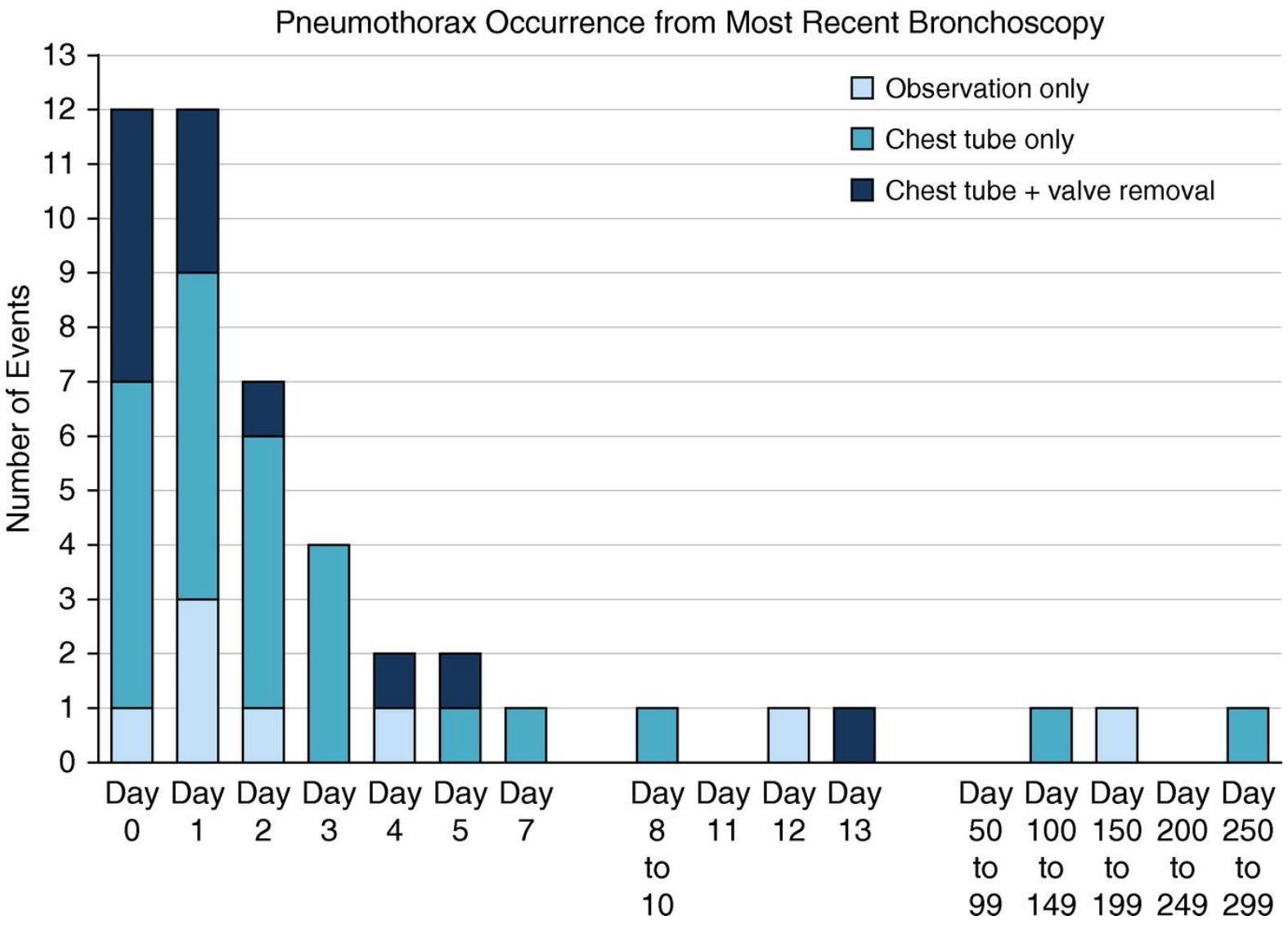
12 month outcomes



FEV1



Pneumothorax rate



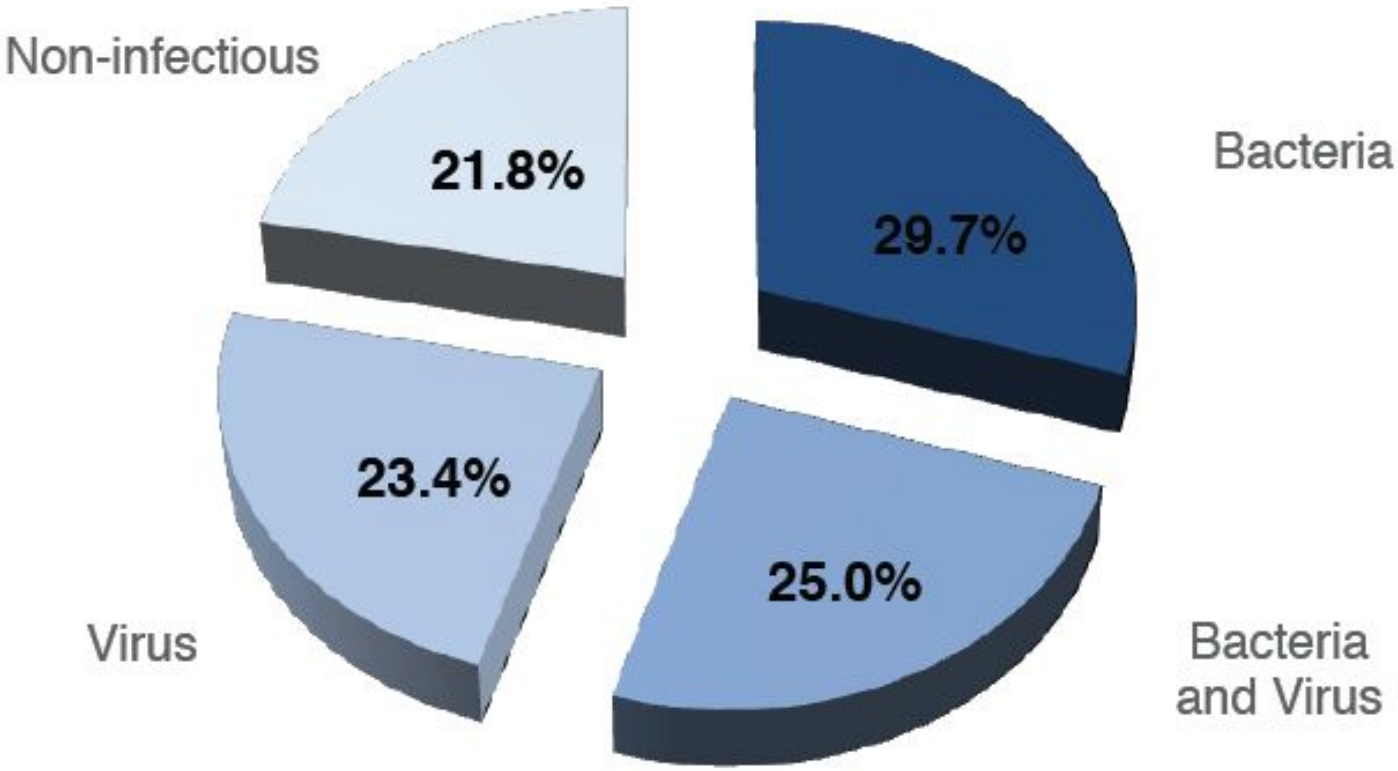
COPD EXACERBATIONS

- COPD exacerbations defined:

  "An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."

Causes

Causes of exacerbations requiring hospitalization in patients (N=64)



Pulmonary Embolism in "Unexplained" AECOPD

- Spiral CT and US
  - 211 pts with AECOPD
    - Not requiring mechanical ventilation
    - No acute bronchitis
    - Disparity between CXR and ABG's
  - 49/197 (25%) positive for PE
    - 43 by CT (19 pos US)
    - 6 by US
  - Associations:
    - Prior PE, malignancy, drop of 5 mmHg CO_2

Tillie-Leblond, Ann Int Med 2006

AECOPD--Steroids

- Beneficial
- Decrease length of stay
- Accelerate return of FEV1
- SCOPE (2 vs 8 week) similar
- Cochrane review: no difference between <7 days and > 7 days

Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbationsof Chronic Obstructive Pulmonary Disease

The REDUCE Randomized Clinical Trial

- 314 pts presented to 1/5 Swiss ER's
- RDBCT of 40 mg prednisolone for 5 vs 14 days
- Noninferiority trial
- PO: time to exacerbation <180 days

REDUCE Trial--Results

- Exacerbation rates were similar (36% vs 37%
- Time to exacerbation 43 days vs 29 days
- No difference in # of patients requiring mechanical ventilation, or time to death
- Lung function at 4 different time points after discharge no different (improvement in 1/3)
- No difference in steroid-related adverse events

The NEW ENGLAND JOURNAL of MEDICINE

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C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., Kerenza Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

ABSTRACT

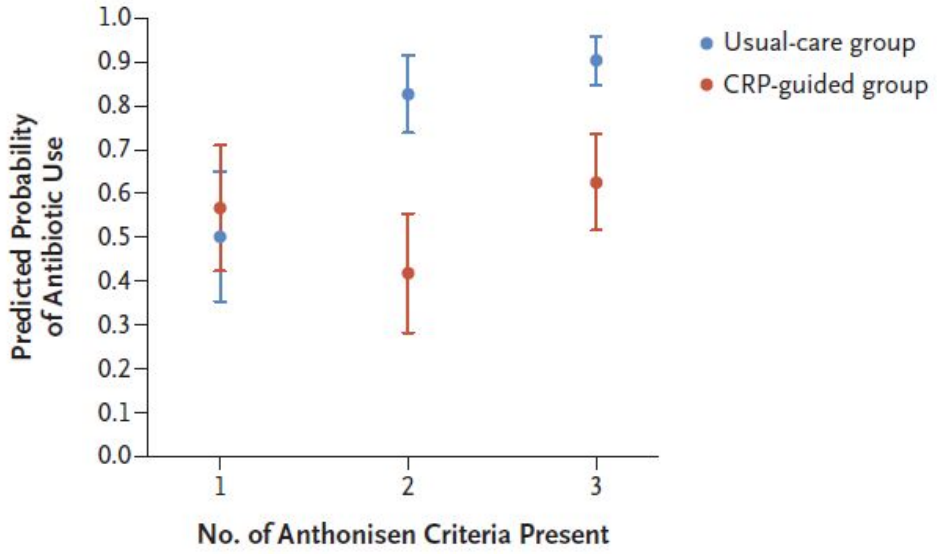
BACKGROUND

Point-of-care testing of C-reactive protein (CRP) may be a way to reduce unnecessary use of antibiotics without harming patients who have acute exacerbations of chronic obstructive pulmonary disease (COPD).

METHODS

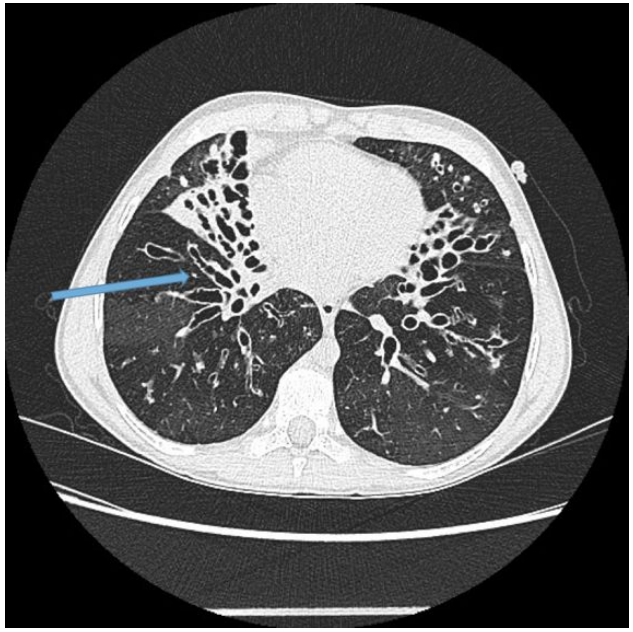
We performed a multicenter, open-label, randomized, controlled trial involving patients with a diagnosis of COPD in their primary care clinical record who consulted a clinician at 1 of 86 general medical practices in England and Wales for an acute exacerbation of COPD. The patients were assigned to receive usual care guided by

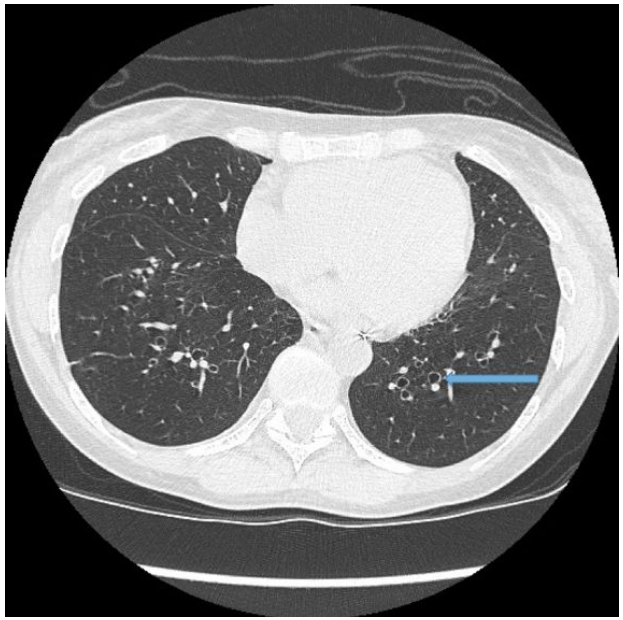
From the Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford (C.C.B., E.R.), the Centre for Trials Research (D.G., J.B., R.L., E.T.-J., K.H., N.K.), the Division of Population Medicine (R.P., G.N., N.A.F.), and Wales Centre for Primary and Emergency Research, School of Medicine (M.G.), Cardiff University, the Specialist Antimicrobial Chemotherapy Unit, Public Health Wales, University Hos-



Bronchiectasis

- 500k in US
- Age (10x > in > 60 yo)
- Women
- Chronic cough in nonsmokers



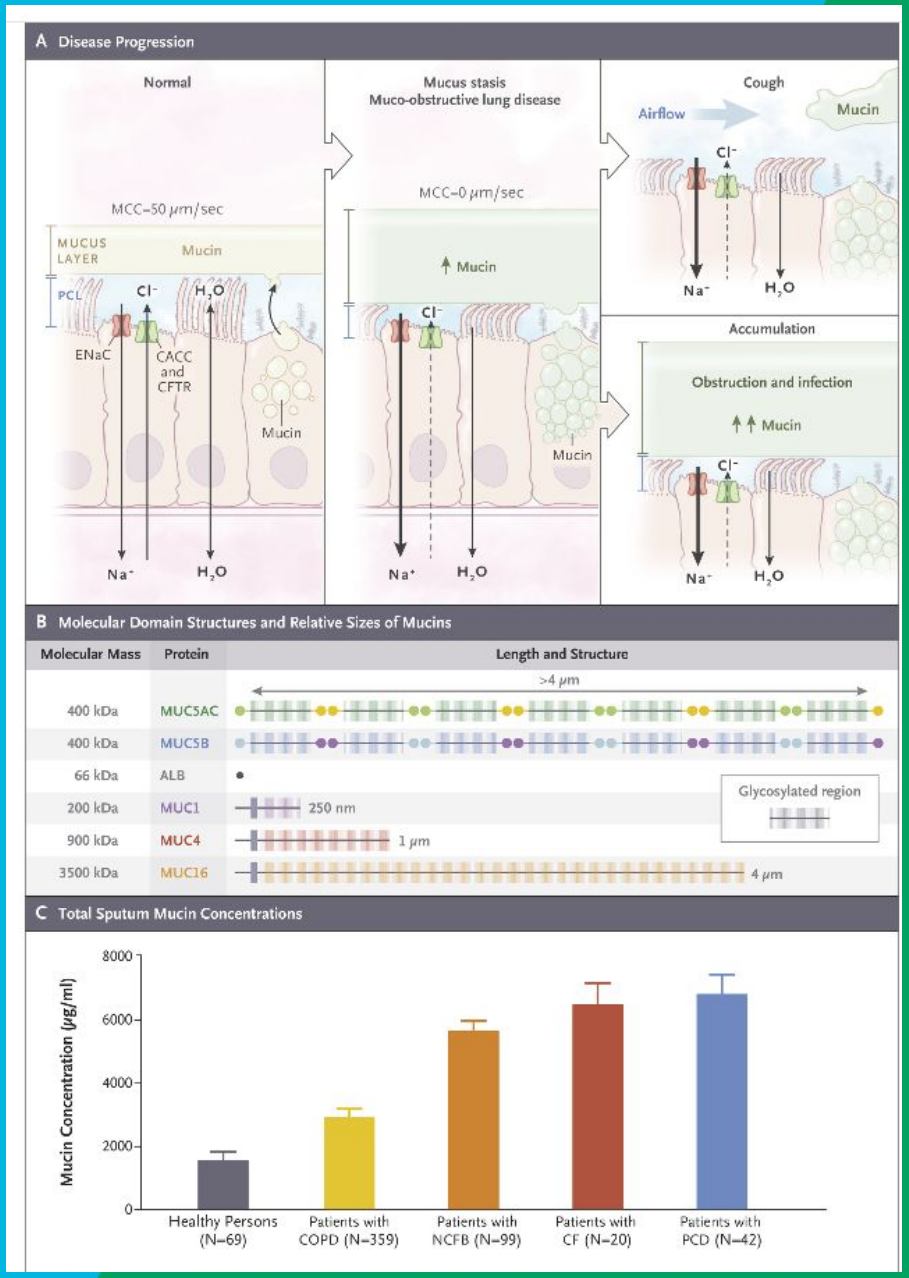


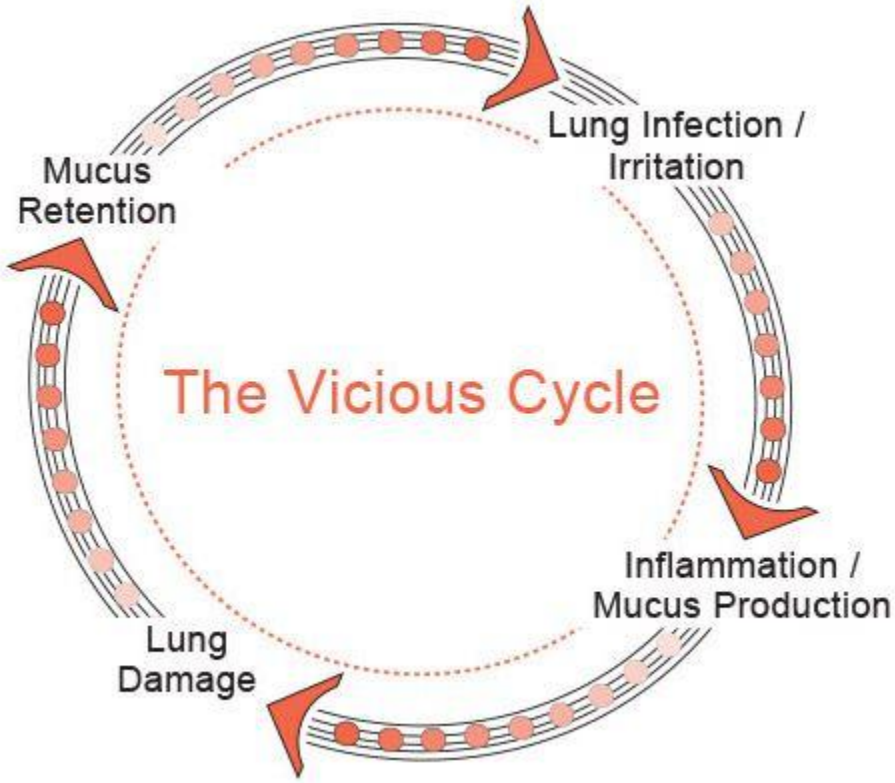
Pathophysiology

- Infection
- Impaired airway clearance
- PMN factor
- Sputum properties
- Atopy
- Vit D deficiency
- CFTR heterozygotes

Etiologies

- Airway obstruction
- Tracheobronchomegaly
- Young syndrome
- PCD
- Systemic disease
- Alpha-1 antitrypsin deficiency
- Pulmonary infections
- Mycobacterial
- ABPA


A Disease Progression
Normal
MCC–50 μm/sec
MUCUS LAYER
Mucin
PCL
Cl⁻
H₂O
ENaC
CACC and CFTR
Mucin
Na⁺
H₂O
Mucus stasis
Muco-obstructive lung disease
MCC–0 μm/sec
Mucin
Cl⁻
Mucin
Na⁺
H₂O
Cough
Airflow
Mucin
Cl⁻
Na⁺
H₂O
Accumulation
Obstruction and infection
Mucin
Cl⁻
Na⁺
H₂O
B Molecular Domain Structures and Relative Sizes of Mucins
Molecular Mass
Protein
Length and Structure
>4 μm
400 kDa
MUC5AC
400 kDa
MUC5B
66 kDa
ALB
200 kDa
MUC1
250 nm
900 kDa
MUC4
1 μm
3500 kDa
MUC16
4 μm
Glycosylated region
C Total Sputum Mucin Concentrations
Mucin Concentration (μg/ml)
8000
6000
4000
2000
0
Healthy Persons (N–69)
Patients with COPD (N–359)
Patients with NCFB (N–99)
Patients with CF (N–20)
Patients with PCD (N–42)

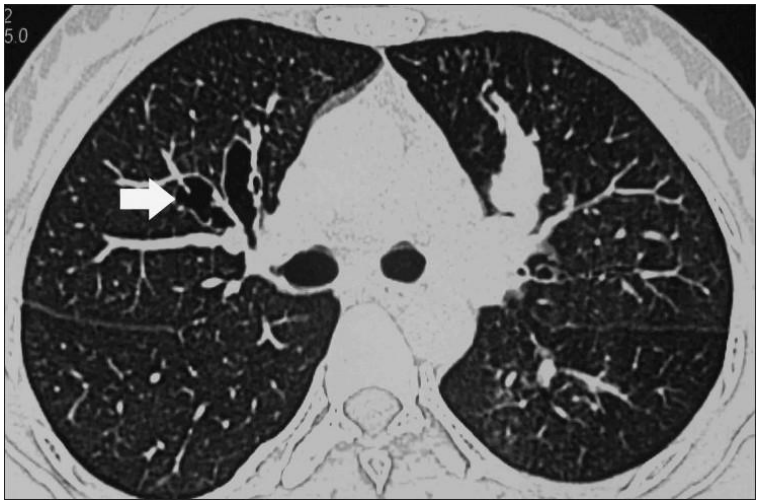


Diagnosis

- Cough, daily sputum, dyspnea, fatigue,
- PE: wheeze
- Lab: cbc , Ig, alpha -1, RF, SSA
- CXR, CT
- FVC, 6 minute walk

CT findings

- Airway dilation (1.5x > blood vessel)
- Signet ring, tram track, saccular, cylindrical
- Tree-in-bud
- Distribution
- Traction bronchiectasis



Treatment-When

Based on symptoms

Sputum elastase?

Frequent organisms

Sputum dictates treatment choice

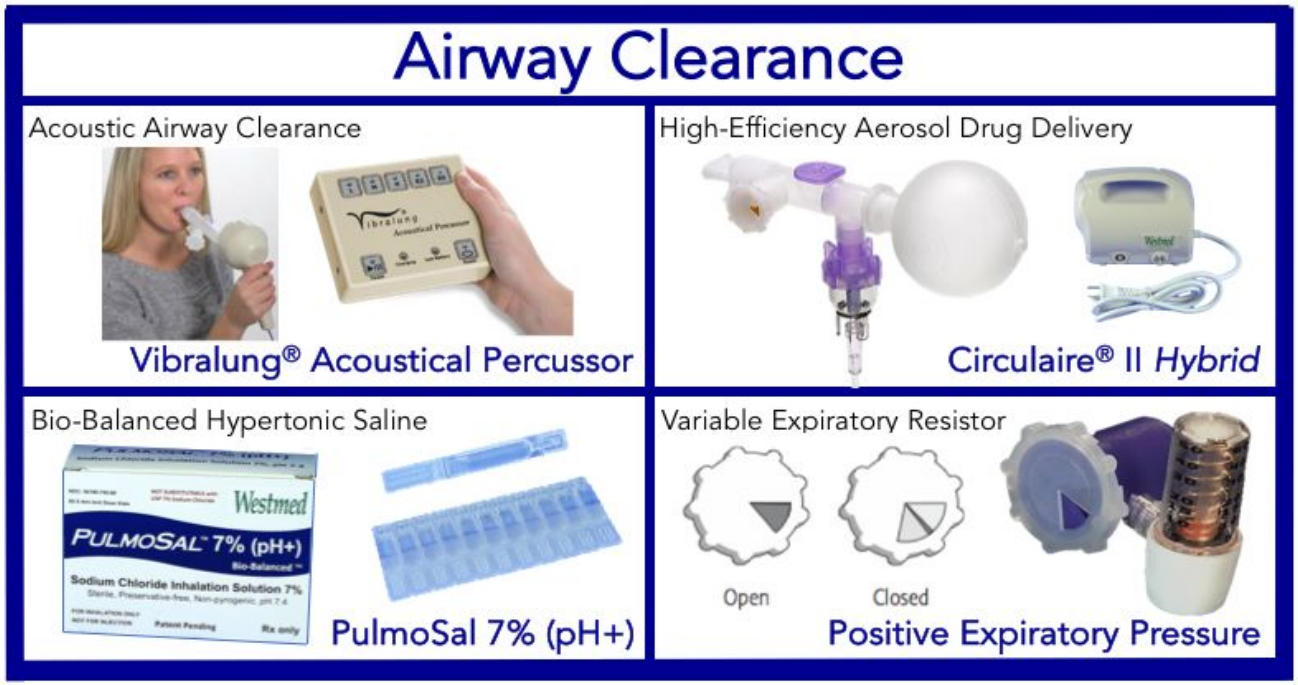
Inhaled therapy?

14 day duration

Prevention

- Macrolides
- Inhaled
- Oral (macrolide intolerant)
- Hypertonic saline, nebulized mannitol
- Mucolytic agents
- Hydration

Airway clearance



Other Therapies

- Steroids
- Nsaids
- Statins
- Immunizations
- Pulmonary Rehabilitation
- Surgery

Bronchitis

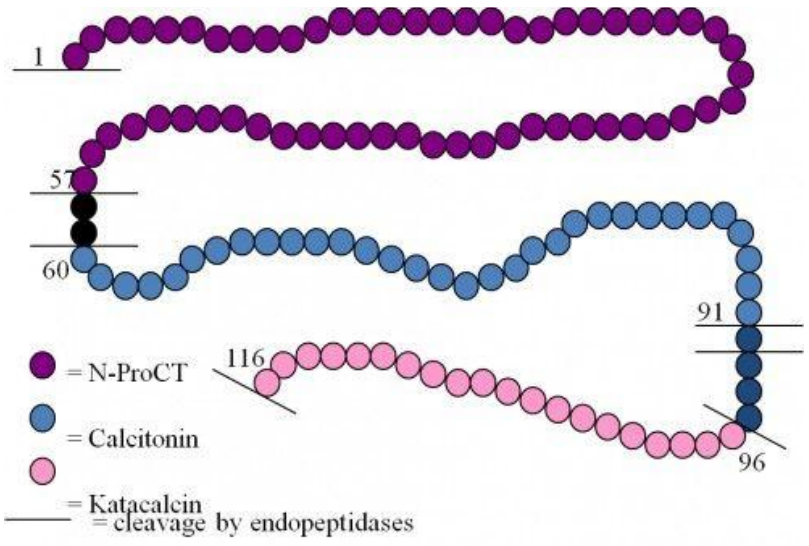
Bronchitis

- 10% of ambulatory care visits
- Viral 60%
- Bacterial 6%
- Cough 1-3 weeks, purulent, BHR, wheeze
- Whoop, cough-vomit, fever
- Focal sx, egophony, rub
- CXR: Fever, tachy, MS changes, focal sx, hemoptysis, immunocompromised
- Lab: flu, pertussis PCR/serology

Procalcitonin

Specific levels of serum Procalcitonin, an inflammatory biomarker, can be used to identify non-bacterial respiratory tract Infections and reduce antibiotic use….

- True
- False
- Uncertain



Procalcitonin

Specific levels of serum Procalcitonin, an inflammatory biomarker, can be used to identify non-bacterial respiratory tract Infections and reduce antibiotic use….

- True
- False
- Uncertain

13 kD protein, normally not detectable in serum

Bacterial infection: Procalcitonin released into serum w/in 3-6 hours vs CRP & ESR, delayed ~24 hours

--Potent stimuli: Endotoxin (gram negatives), IL-1, TNF

--Gram positive bacteria less potent but markedly greater than viruses/mycoplasma

Virus infection: Interferon-g release suppresses procalcitonin

Cochrane Meta Analysis 2011, updated 2017 supports Procalcitonin Guided Treatment (international)

- High quality data from 26 RCT both severe & not RTI
- Withhold antibiotics & shorten antibiotic duration
- Lower risk for mortality
- Fewer antibiotic related AE's (ie, C diff)

Why isn't procalcitonin algorithm widely used US?

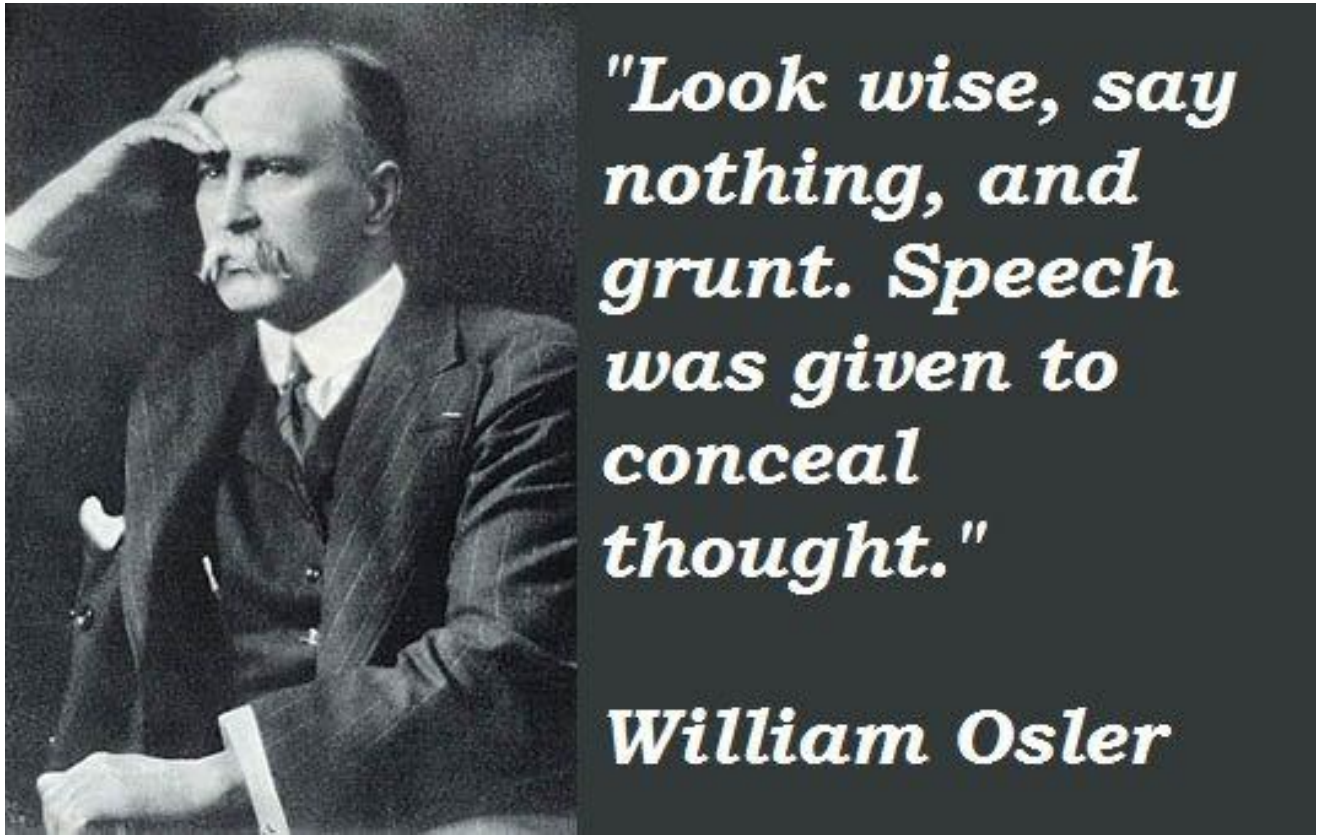
- Sporadic skepticism remains in the US
- Recent: Failed to reduce antibiotic use in 14 US ED's

Huang DM, et al. NEJM 2018;379(3):236-49

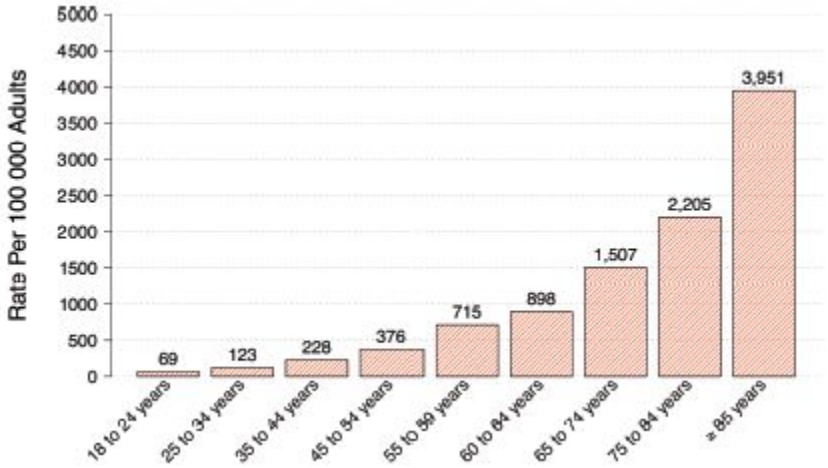
Treatment

- Education
- Guaifenisin
- Albuterol if wheezing
- Ipratropium nasal spray
- No antibiotics
- No prednisone
- No herbal medications

Thank You for your Attention



Pneumonia with age



Ramirez JA et al. *CID* 2017;65(11):1806-12