STORIA DELLA MEDICINA ED ANTROPOLOGIA MEDICA
Policlinico di Modena 28 Ottobre 2015 1600-1700
Aula T01 Centro Didattico di Ateneo, Facoltà di Medicina e Chirurgia

BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO): da malattia broncopolmonare a componente broncopolmonare della multimorbidità cronica

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ENVISIONING THE FUTURE IN COPD
Vicenza 6 June 2015

CONFLICTS OF INTEREST

Il sottoscritto Leonardo FABBRI

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi 2 anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Chiesi, GSK, Zambon, AZ, Almirall, BI, Pearl, Menarini, Malesci/Guidotti, Novartis, Takeda, Dompè, Mundipharma

HISTORY

Male, 61, BMI 24 Kg/m^2 , ex-smoker since 3 years (35 pk/yr), retired, no occupational exposure, formerly officer of the Airforce

Intense physical activity until 3 years ago

His father died of acute myocardial infaction

Hypothyrodiism, treated with levotiroxine

Arterial hypertension, treated with ARB

Chronic Heart Failure

HISTORY

Daily cough and sputum (small) + dyspnea mMRC 2 since 3 years, diagnosed as chronic bronchitis

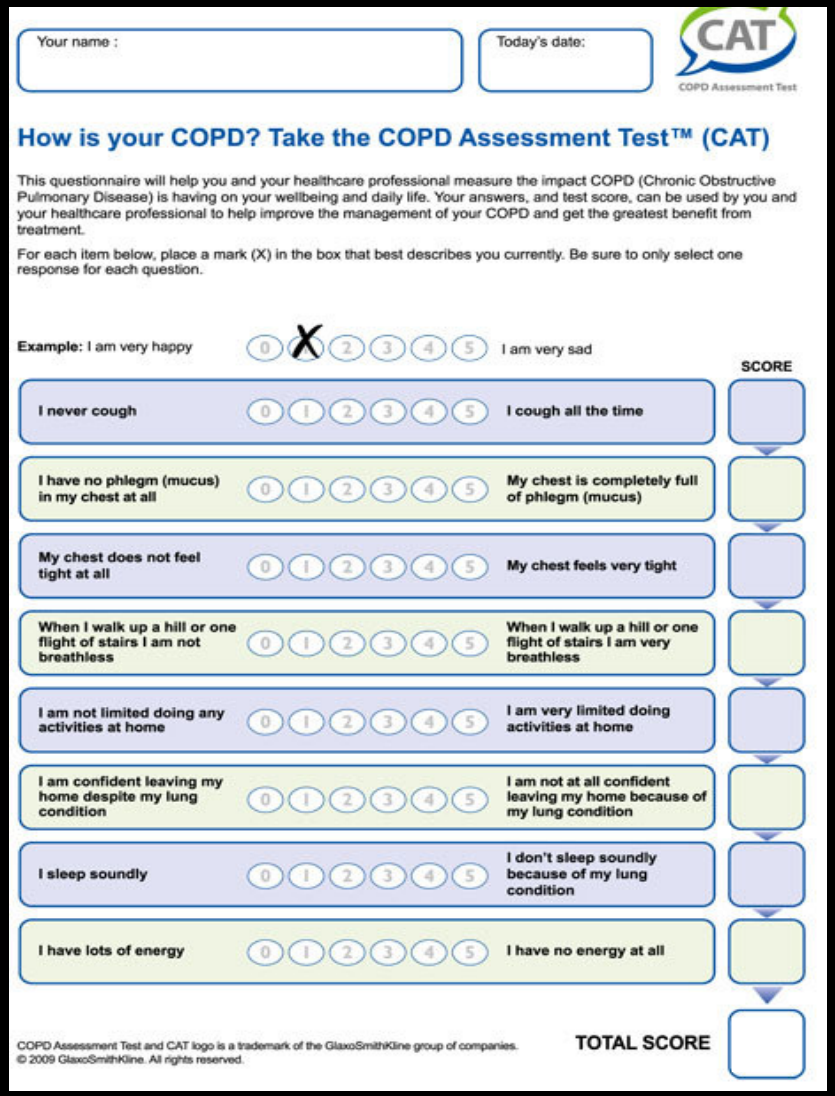
Treated with prn albuterol, acetylcysteine, mucolitic, low dose aspirin, ARB, levotiroxine

Admitted to hospital because of rapid worsening of respiratory symptoms, particuarly dyspnea. No purulence

Lost 3 Kg in the last few months

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy



Your name :

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

		SCORE
I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all
		TOTAL SCORE

The Modified Medical Research Council (MMRC) Dyspnoea Scale

Grade of dyspnoea	Description
0	Not troubled by breathlessness except on strenuous exercise
1	Shortness of breath when hurrying on the level *or* walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness *or* has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 m *or* after a few minutes on the level
4	Too breathless to leave the house *or* breathless when dressing or undressing

CAT : 11 ptt

mMRC: 2 ptt

Exacerbationsi: 3/yr

Hospitalization: 1

CLINICAL DATA

Timpanic percussion, no ronchi no crackles

BP: 120/80 mmHg

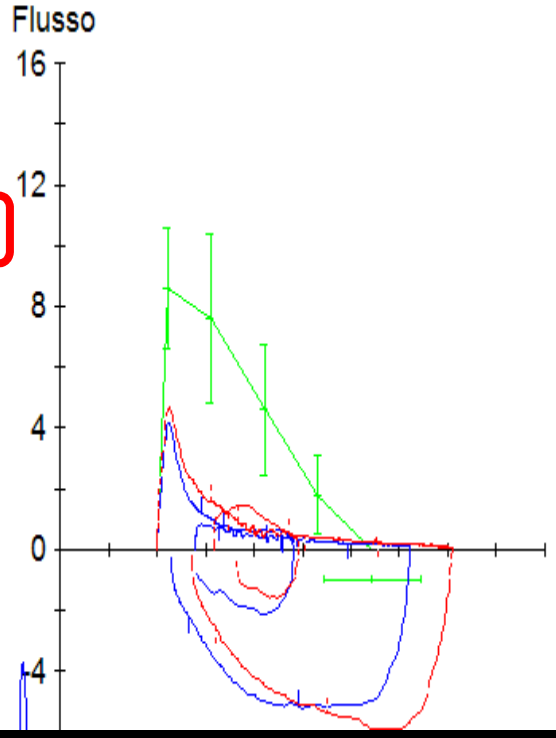
HR: 76 beats/min

RR: 17/min

SaO_2: 96% air

SPIROMETRY AT ADMISSION

Spirometria		Ref	CI	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
VC	Litri	4.62	0.92	** 5.80	** 125			
FVC	Litri	4.44	1.00	5.24	118	** 6.11	** 138	17
FEV1	Litri	3.48	0.84	** 1.39	** 40	** 1.69	** 49	22
FEV1/FVC	%	76	12	** 26	** 35	** 28	** 36	5
FEF25-75%	L/sec	3.57	1.71	** 0.29	** 8	** 0.36	** 10	24
IsoFEF25-75	L/sec			0.29		0.56		91
FEF25%	L/sec	7.59	2.81	** 0.71	** 9	** 1.04	** 14	46
FEF50%	L/sec	4.58	2.17	** 0.37	** 8	** 0.41	** 9	9
FEF75%	L/sec	1.77	1.28	** 0.18	** 10	** 0.20	** 12	16
PEF	L/sec	8.58	1.99	** 4.16	** 49	** 4.66	** 54	12
IC	Litri	3.20	0.74	3.07	96			
FIVC	Litri	4.44	1.00	4.96	112	5.40	9	122
FIV1	Litri			4.44		4.77	8	
PIF	L/sec			5.24		5.94	13	



- **GOLD 3**
- **Mild BD reversibility (FEV1 +22%/+300 mL)**

BODY PLETHYSMOGRAPH

Pletismografia

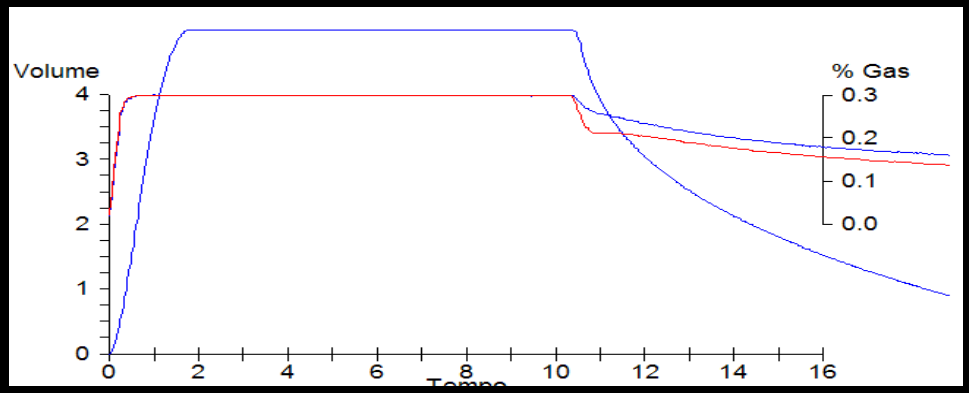
		Ref	CI	Pre Meas	Pre % Ref	
TLC	Litri	7.30	1.15	** 10.07	** 138	⇐
VC	Litri	4.62	0.92	** 5.80	** 125	
IC	Litri	3.20	0.74	3.07	96	
FRC PL	Litri	3.67	0.99	** 6.69	** 182	⇐
Vtg	Litri	4.08	1.21	** 6.55	** 161	
ERV	Litri	1.60	0.37	** 2.42	** 151	
RV	Litri	2.47	0.67	** 4.27	** 173	⇐
RV/TLC	%	38	9	42	112	

Raw	cmH2O/L/sec	1.07
sRaw	cmH2O/L/s/L	4.35
sGaw	L/s/cmH2O/L	0.230

MARKED HYPERINFLATION

CARBON MONOXIDE DIFFUSING CAPACITY (DLCO)

		Ref	CI	Pre Meas	Pre % Ref	Post Meas
DLCO	mL/mmHg/min	29.7	6.9	** 7.6	** 25	
DL Adj	mL/mmHg/min	29.7	6.9	** 7.6	** 25	
DLCO/VA	mL/mHg/min/L	4.07		1.24	31	
DL/VA Adj	mL/mHg/min/L	4.07		1.24	31	
VA	Litri	7.30	1.15	** 6.09	** 83	
Kroghs K	1/min			1.07		
BHT	Sec			11.30		
CO T.C.	Sec			55.9		
IVC	Litri			5.00		
VC	Litri	4.62	0.92	** 5.80	** 125	



ARTERIAL BLOOD GASES

pH: 7.44

PaO_2: 65 mmHg

$PaCO_2$: 36 mmHg

HCO_3-: 23,1 mmol

SaO_2: 95%

SIX MINUTE WALKING TEST (6MWT)

SaO2 pre: 95%

SaO2 post: 85%

PA pre 140/85 mm Hg

PA post 150/80 mm Hg

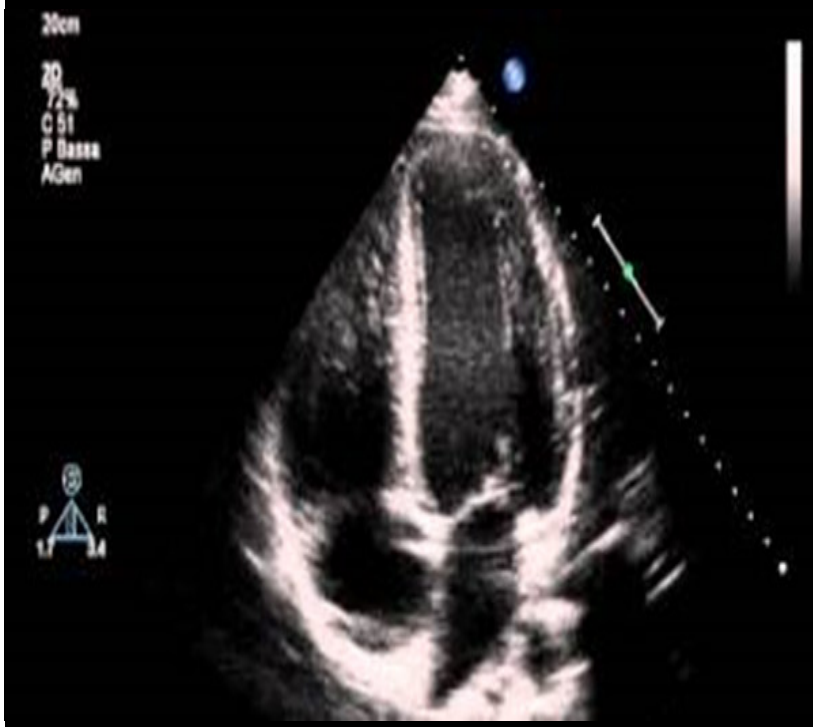
FC pre 70/min

FC post 88/min

Meters: 250

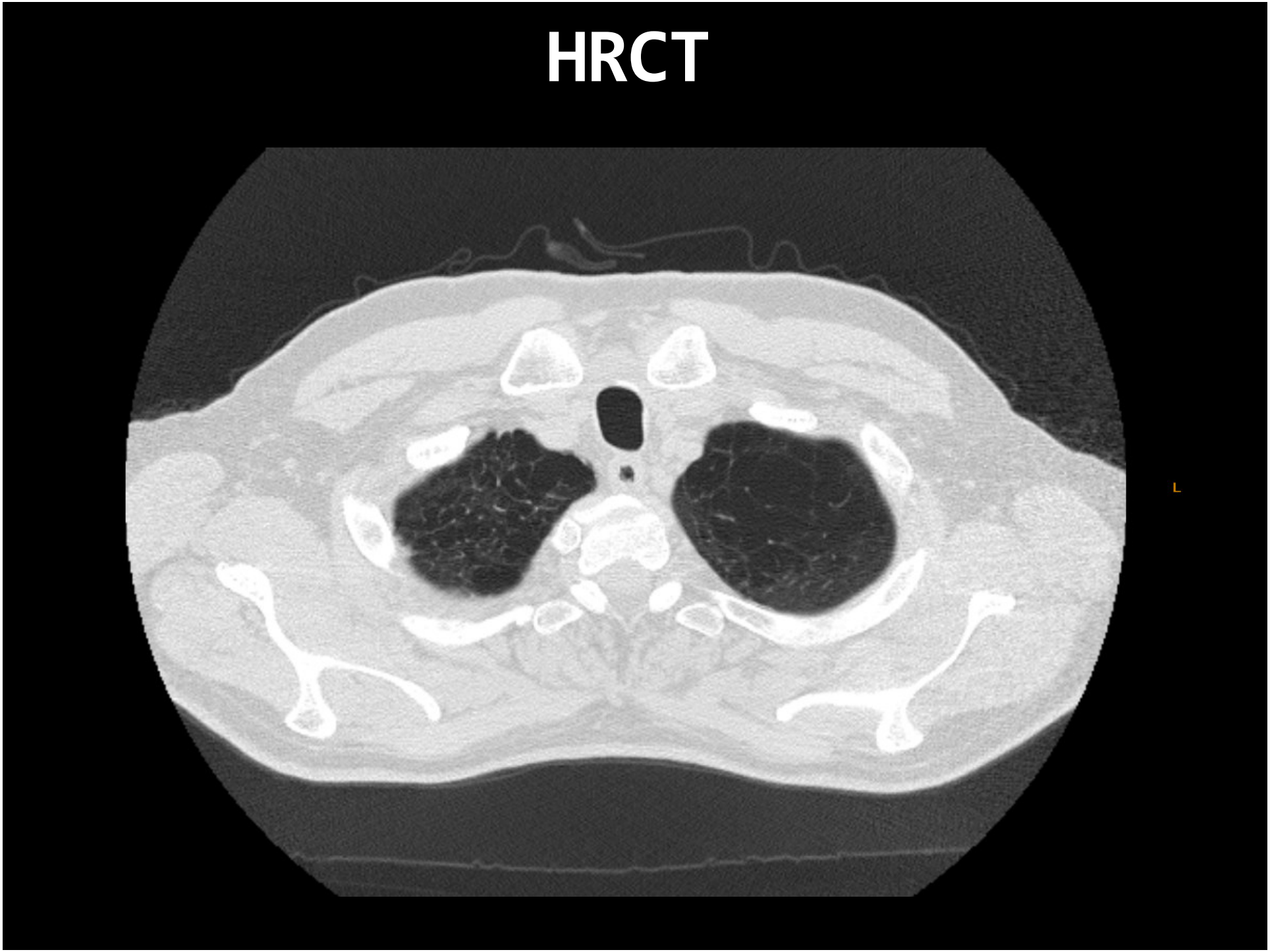
Meters:	≥350	Good
	250–349	Mild impairment
	150–249	Moderate
	≤149	Severe

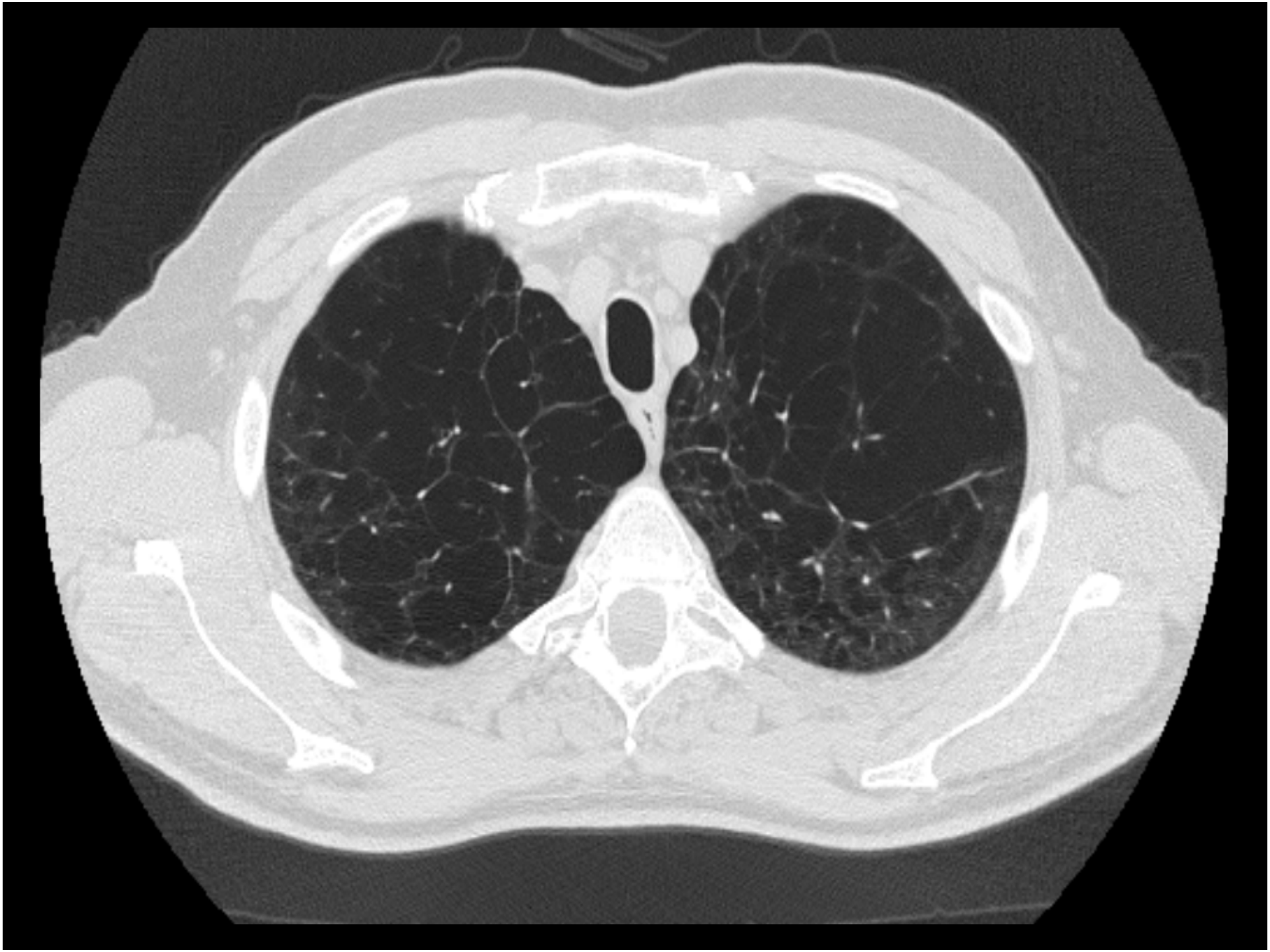
ECHOCARDIOGRAM

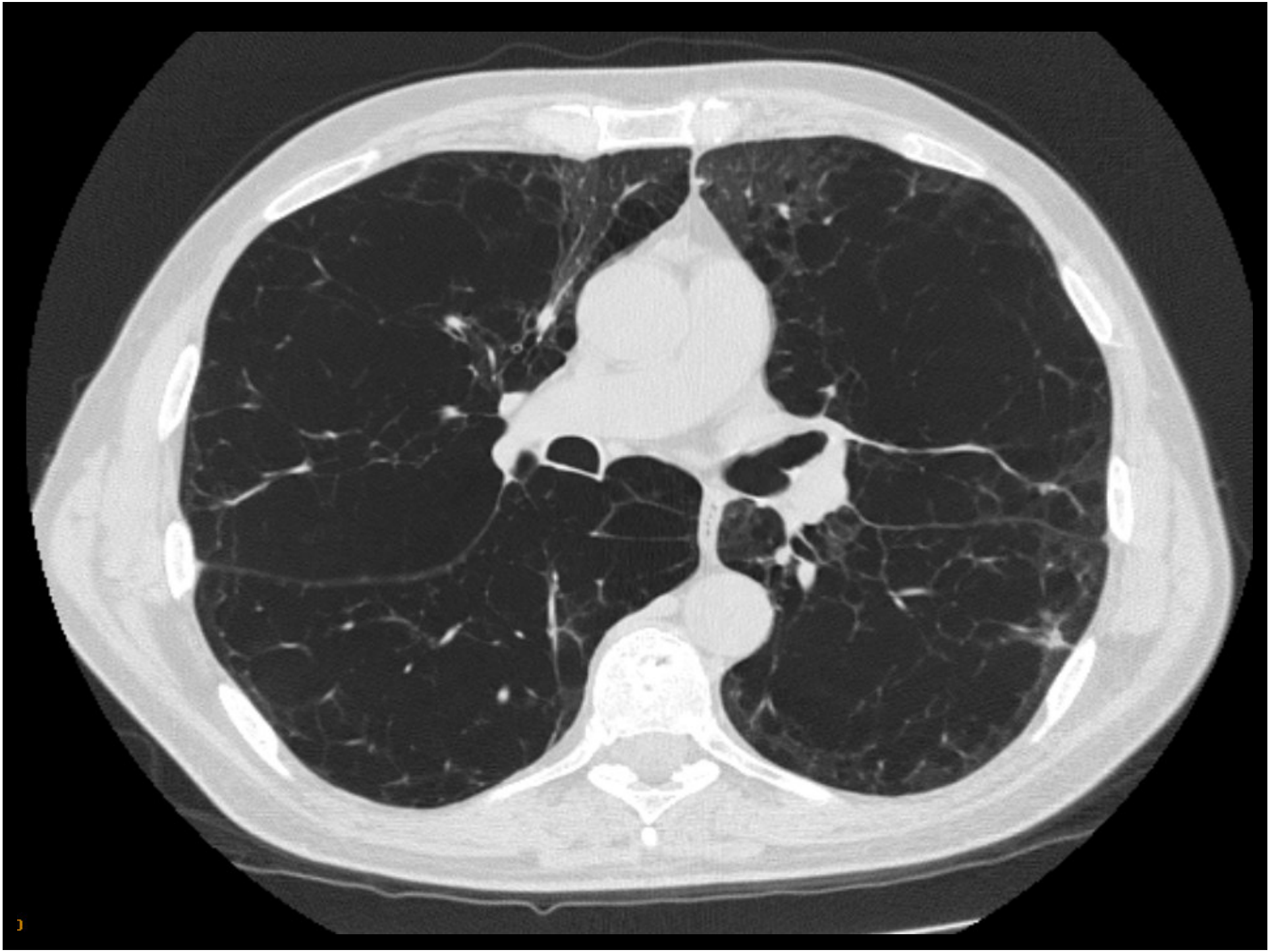


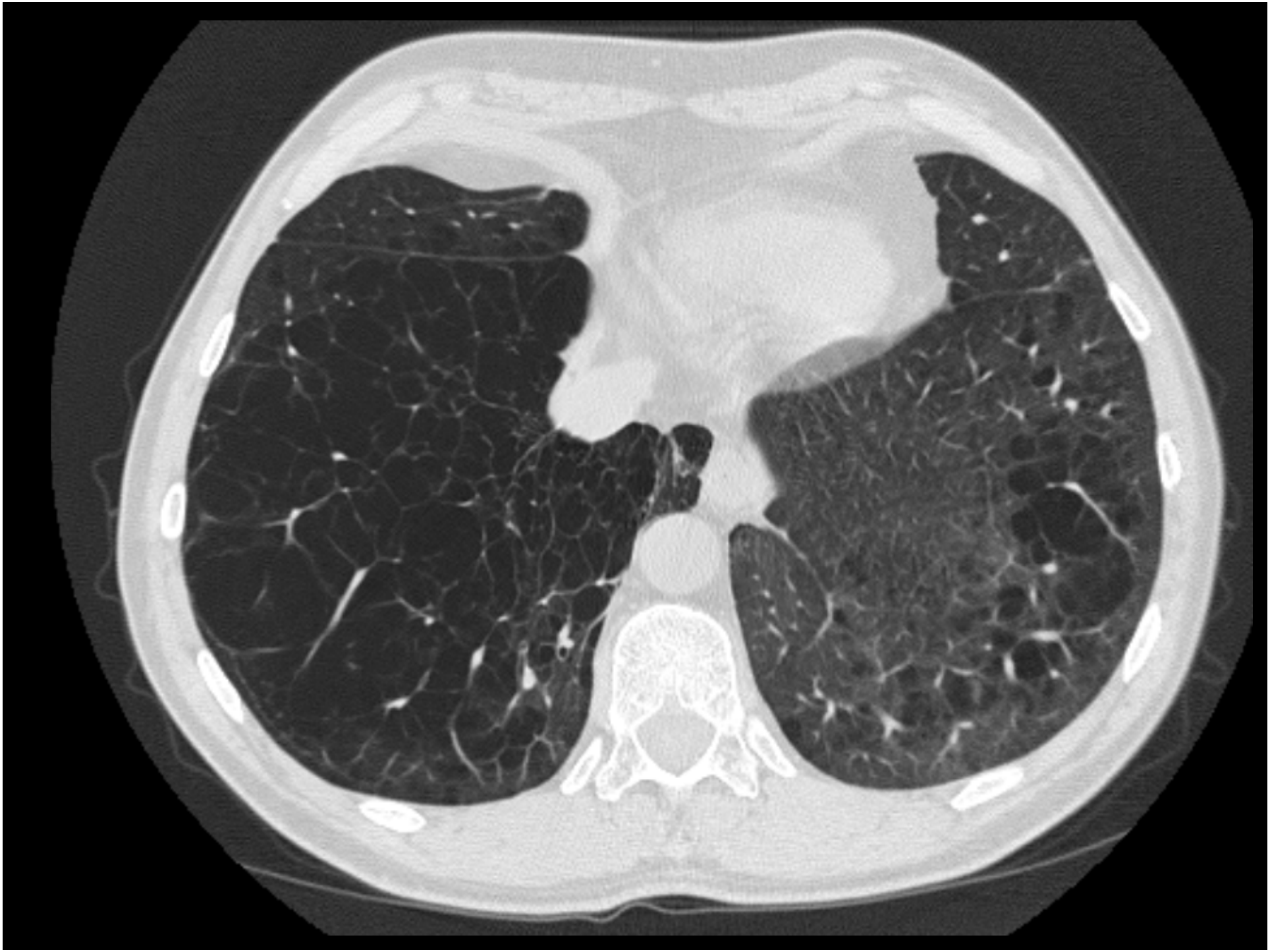
- LA: slight enlargement
- LV: normal cavitiy; slight concentric hypertrophy
- RH: OK
- Tricuspid valve: moderate insufficiency
- PaP: 40-45 mmHg
- EF: 60%

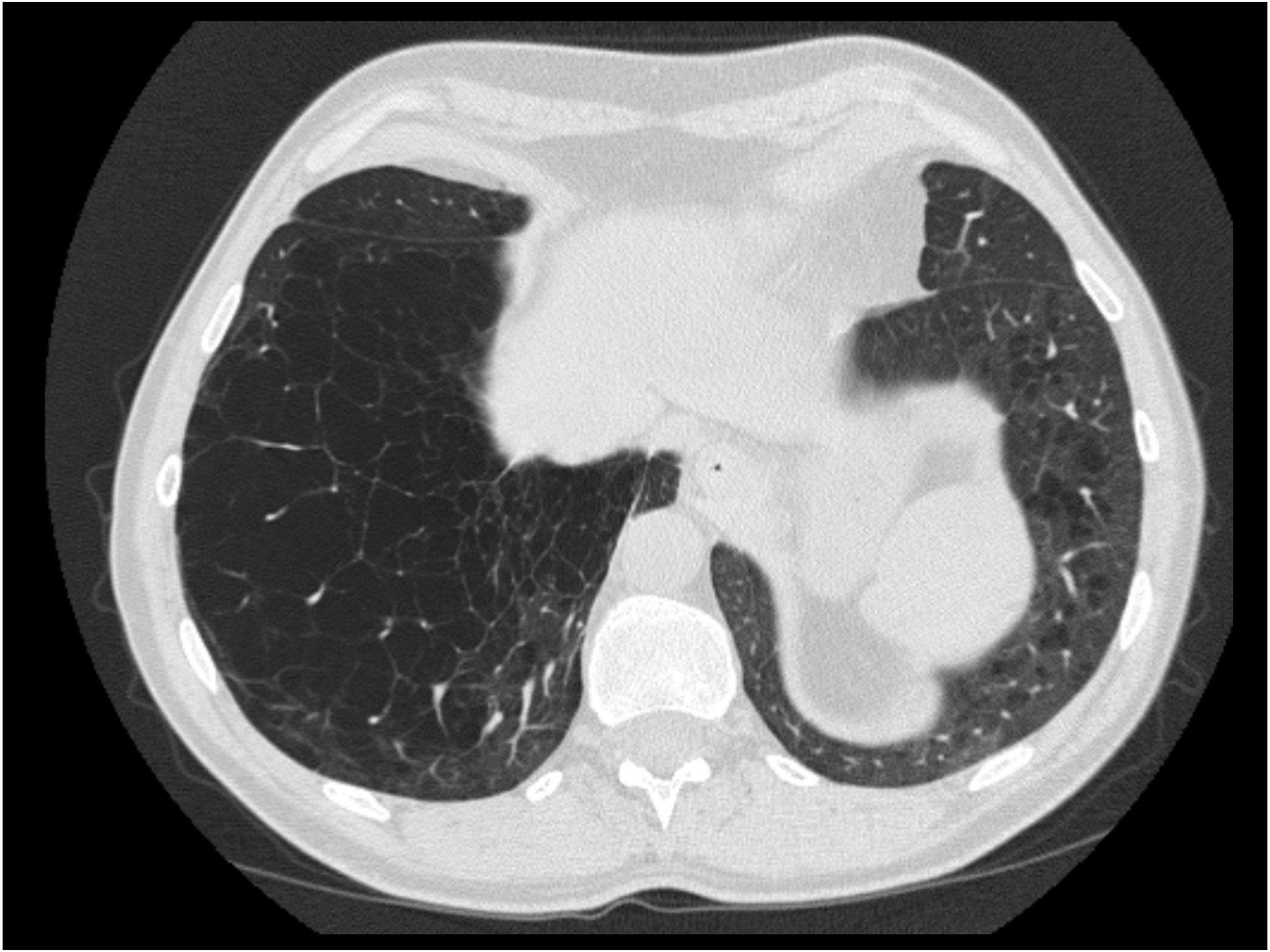
HRCT

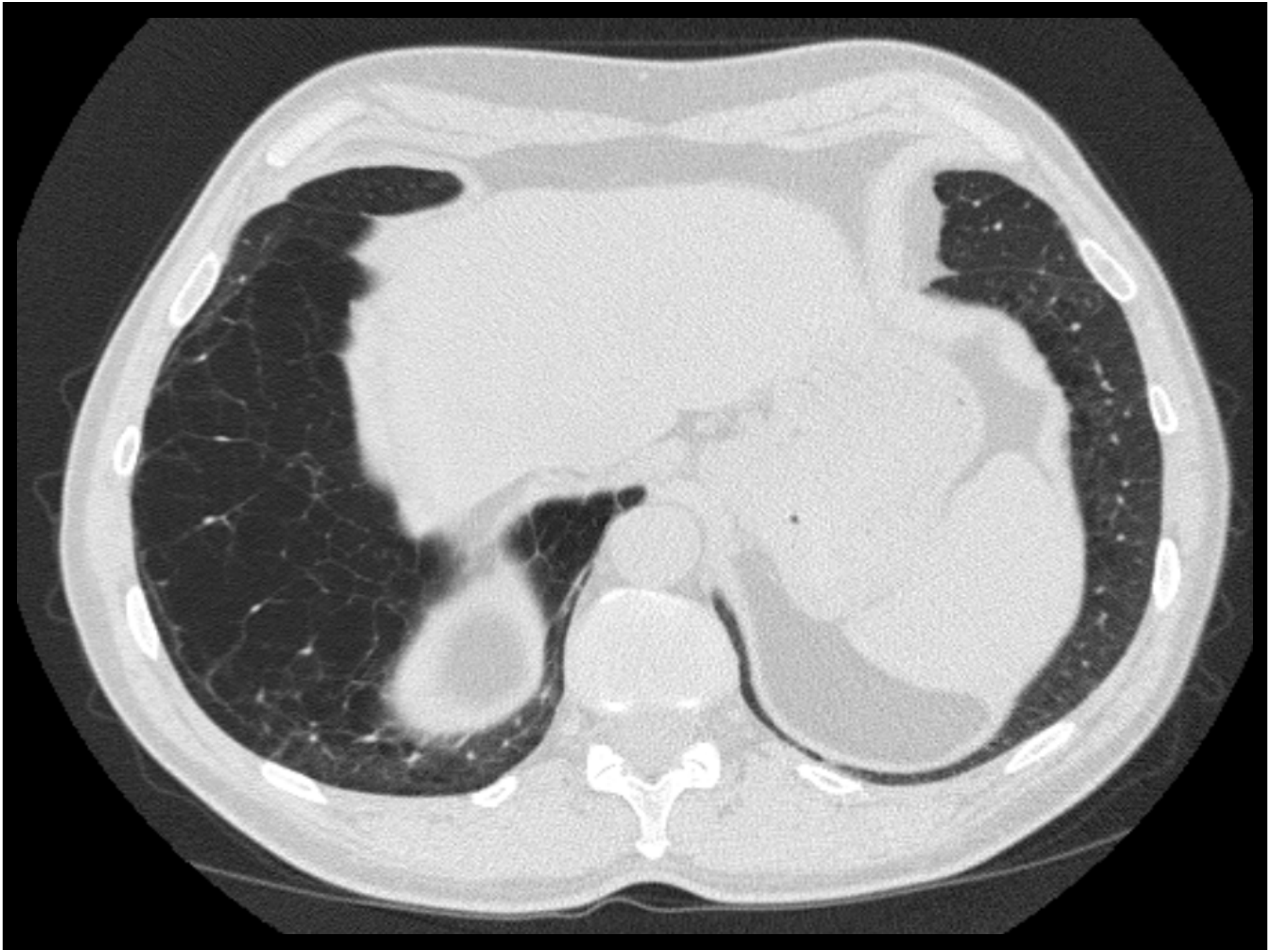












QUESTION

CHRONIC BRONCHITIS

COPD GOLD D?

COPD + ASTHMA ?

CHRONIC MULTIMORBIDITY ?

REALITY: patient was being treated with

Salmeterol/fluticasone propionate 50/500 1 bid +
Tiotropium 18 ug 1 OD

Aspirin 75 mg 1 tablet OD

Valsartan 160 mg 1 cp al mattino

O_2 1 L/min during exercise

No rehabilitation

HRCT

Panlobular emphysema, > right lung,

scar in the apical portion of the LLL

C.R. 20 October 2015

CLINICAL HISTORY-2

- Male, 88 year
- Moderate dyspnea on exercise
- No chronic bronchitis
- No occupational exposure
- Ex-smoker (20 p/y).
- Diagnosis of COPD 6 months ago in conjunction with an AECOP requiring hospitalization
- No regular inhalation treatment

C.R. 20 October 2015

Since 1 year:

- **Moderate progressive dyspnoea on exercise (mMRC2)**
- **Dyspnea in the early morning**
- **Occasional cough, no purulent sputum**
- **1 diagnosed and treated as AECOPD 6 months ago (oxygen, bronchodilators, steroids, antibiotics)**
- **Negative blood tests and CxR on that occasion**
- **Reduced vescicular murmur, in/espiratory ronchi, bilateral basal in/espiratory crackles**

C.R. 20 October 2015

SPIROMETRY

- **FEV_1: 1.37 L (50% predicted)**
- **Post-BD FEV1=1.40 L (+2%)**
- **FVC: 2.05 L 54% predicted)**
- **FEV_1/FVC: 68 %**
- **RV: 2.95 L (104 % predicted)**
- **RV/TLC: 59 %**
- **6MWT: 420 m, SaO2 97%-92%**

COMORBIDITIES

- Obesity (BMI=36)
- Diabetes
- Arterial hypertension
- Dyslipidemia
- Atrial fibrillation
- Heart failure with increased PaP (55mmHg)
- Benign Prostatic Hypertrophy

TREATMENT

- Metformin
- Olmesartan Medoximil
- Larcanedipin
- Carvedilol
- Finasteride
- Silodosin
- Warfain

CONCLUSIONS AND RECOMMENDATIONS AT FIRST VISIT

- Tiotropium 2.5 ug 2 inhalation in the evening
- Rehabilitation, including weight reduction
- Confirmed ongoing treatment of comorbidities
- Weekly telephone contact
- Haematochemical exams + chest X ray
- Clinical control at 1 month

QUESTIONS

- Is dyspnea due to COPD, heart failure, obesity, combination?
- Should a respiratory treatment be considered?
- Should tiotropium be used as first choice?
- Because of recent hospitalization, should we consider FF/VI as first choice?
- Should we consider FF/VI as add-on at follow up only once we have verified that LAMA is not sufficient?
- Should we consider LABA/LAMA instead?

BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO): da malattia broncopolmonare a componente broncopolmonare della multimorbidità cronica

Leonardo M. Fabbri

- **COPD as pulmonary component of chronic multimorbidity in the elderly**
- **COPD and chronic heart diseases**
- **Complexity of acute exacerbations**
- **Management of COPD and chronic multimorbidity**
- **Future therapies for COPD and multimorbidity**

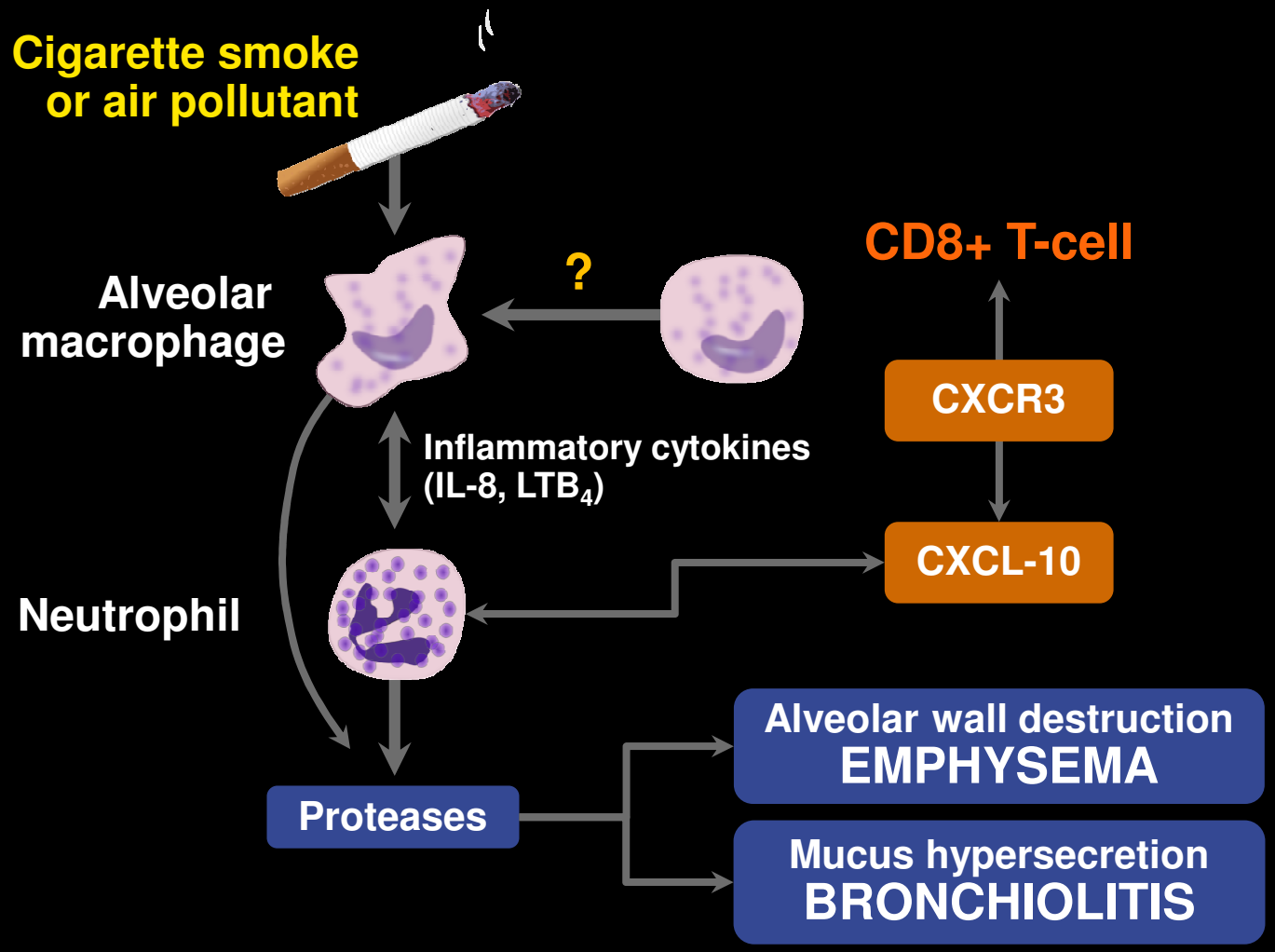
GLOBAL STRATEGY FOR DIAGNOSIS, MANAGEMENT AND PREVENTION OF COPD

DEFINITION OF COPD 2011

COPD, a common preventable and treatable disease, is characterized by **persistent airflow limitation** that is usually **progressive** and associated with an enhanced **chronic inflammatory response** in the airways and the lung to **cigarette smoking**

Exacerbations and comorbidities contribute to the overall severity in individual patients.

PATHOGENESIS OF COPD



Adapted from PJ Barnes, 2000; Fabbri, Sinigaglia, Papi, Saetta 2002; Cosio, Saetta and Cosio 2012

LEADING CAUSES OF DEATH IN U.S.

1. Myocardial Infarction
2. Cancer
3. Cerebrovascular Diseases
4. COPD

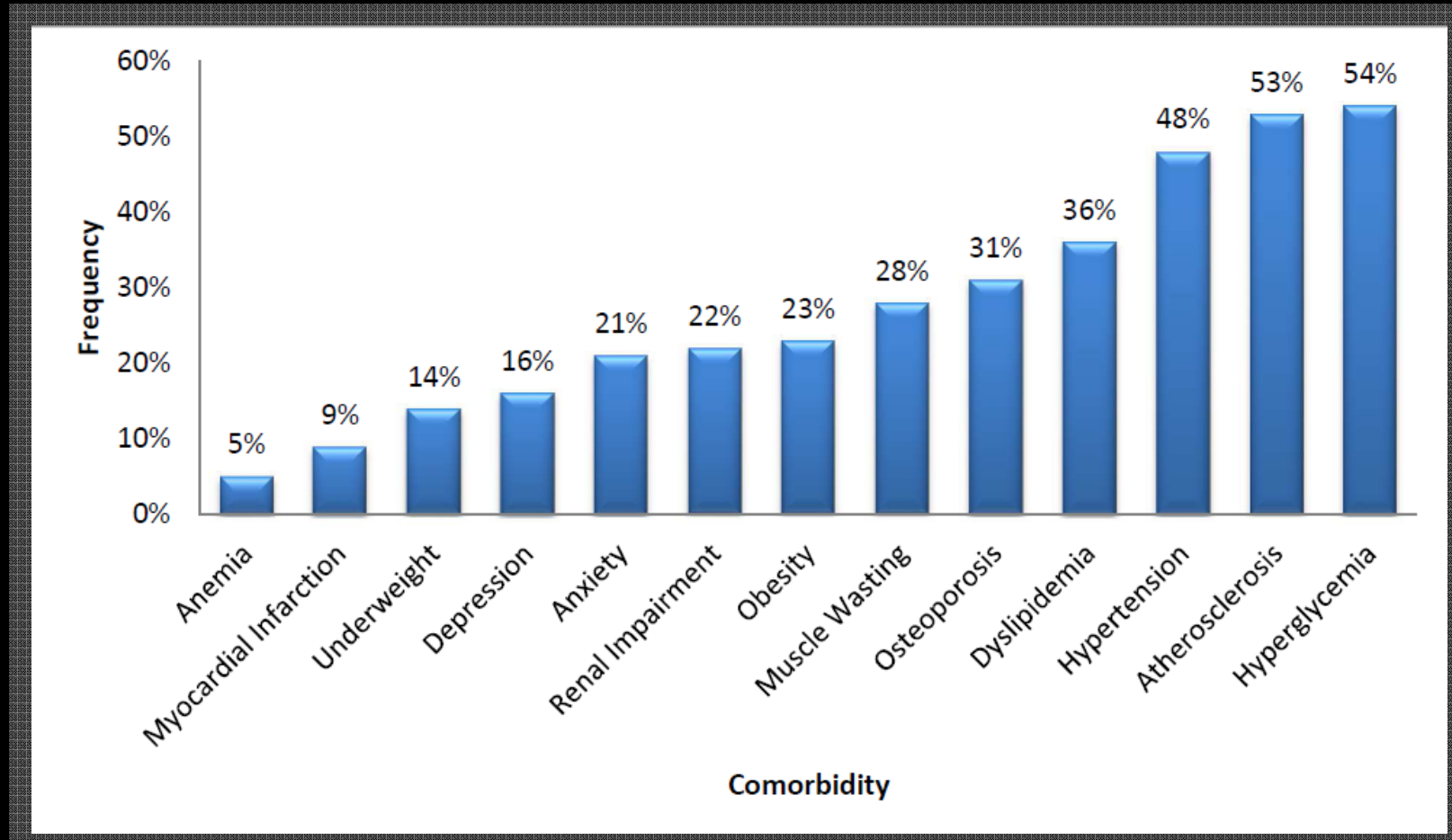
Cigarette Related Diseases
Leading Causes of Death Worldwide 2010

DEFINITION OF COPD 2011

COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases

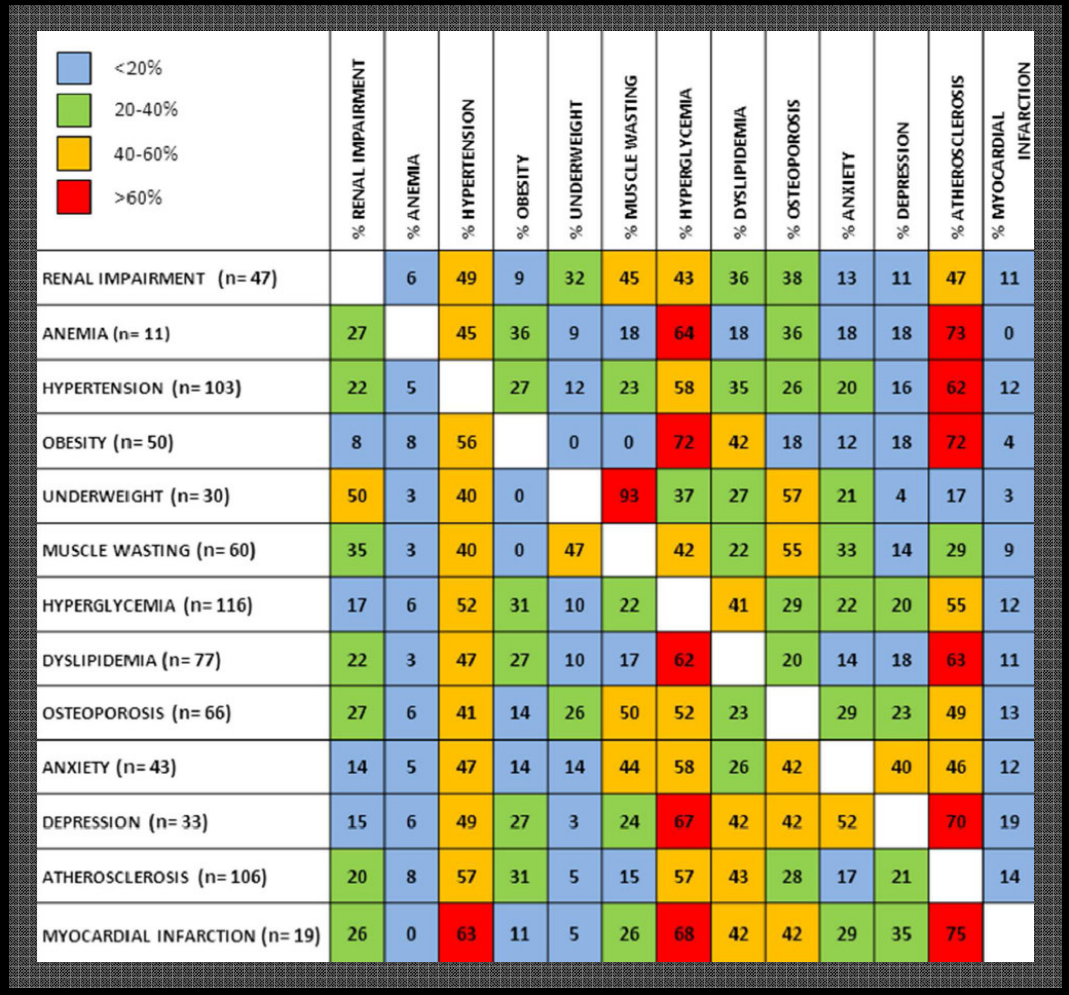
Exacerbations and **comorbidities contribute to the overall severity in individual patients**

FREQUENCIES OF OBJECTIFIED COMORBIDITIES



Vanfleteren L.E.G.W., et al. AJRCCM 2013 Apr;187(7):728-35.

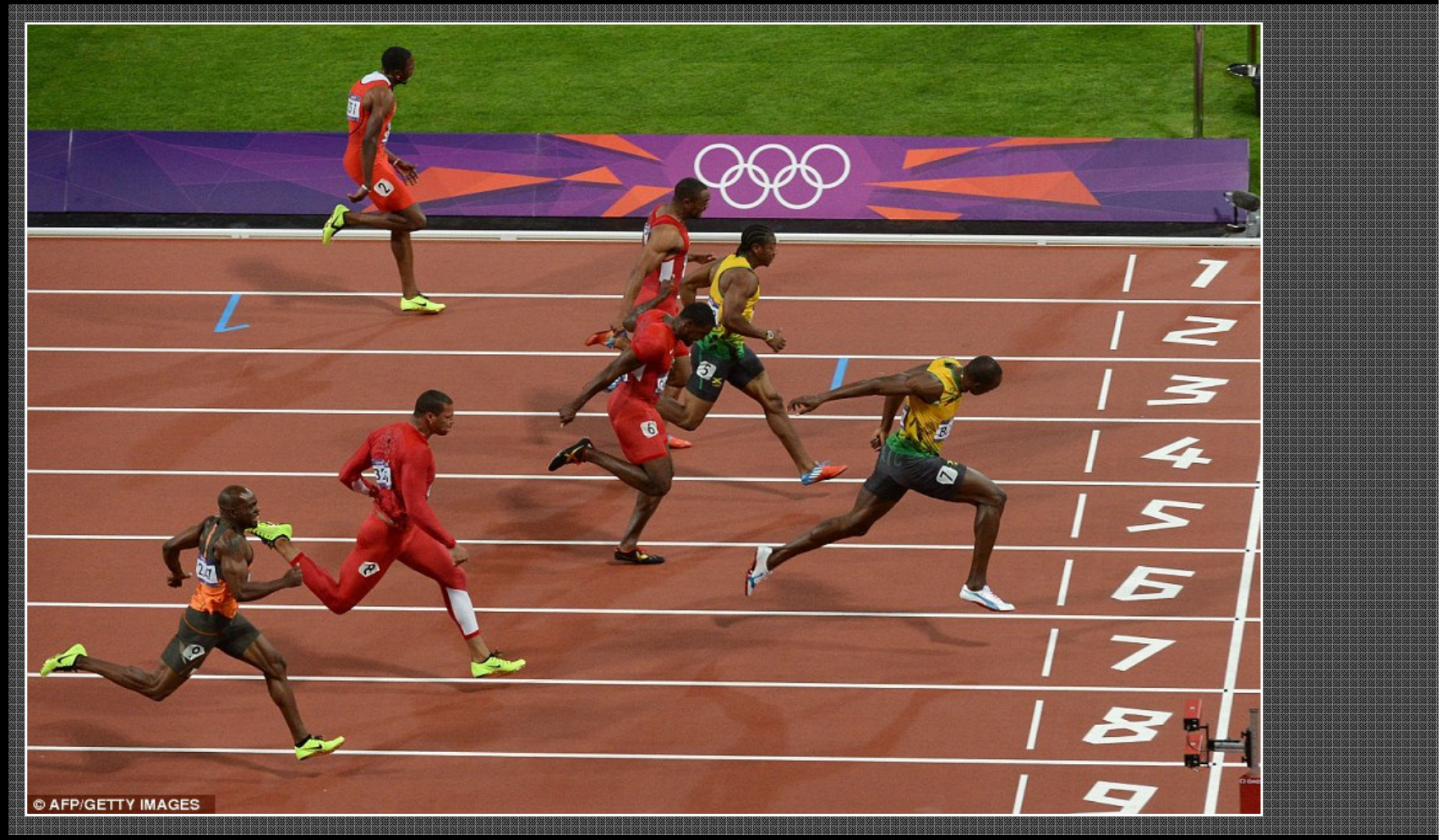
FROM COMORBIDITIES TO MULTIMORBIDITY



<20% 20-40% 40-60% >60%	% RENAL IMPAIRMENT	% ANEMIA	% HYPERTENSION	% OBESITY	% UNDERWEIGHT	% MUSCLE WASTING	% HYPERGLYCEMIA	% DYSLIPIDEMIA	% OSTEOPOROSIS	% ANXIETY	% DEPRESSION	% ATHEROSCLEROSIS	% MYOCARDIAL INFARCTION
RENAL IMPAIRMENT (n= 47)		6	49	9	32	45	43	36	38	13	11	47	11
ANEMIA (n= 11)	27		45	36	9	18	64	18	36	18	18	73	0
HYPERTENSION (n= 103)	22	5		27	12	23	58	35	26	20	16	62	12
OBESITY (n= 50)	8	8	56		0	0	72	42	18	12	18	72	4
UNDERWEIGHT (n= 30)	50	3	40	0		93	37	27	57	21	4	17	3
MUSCLE WASTING (n= 60)	35	3	40	0	47		42	22	55	33	14	29	9
HYPERGLYCEMIA (n= 116)	17	6	52	31	10	22		41	29	22	20	55	12
DYSLIPIDEMIA (n= 77)	22	3	47	27	10	17	62		20	14	18	63	11
OSTEOPOROSIS (n= 66)	27	6	41	14	26	50	52	23		29	23	49	13
ANXIETY (n= 43)	14	5	47	14	14	44	58	26	42		40	46	12
DEPRESSION (n= 33)	15	6	49	27	3	24	67	42	42	52		70	19
ATHEROSCLEROSIS (n= 106)	20	8	57	31	5	15	57	43	28	17	21		14
MYOCARDIAL INFARCTION (n= 19)	26	0	63	11	5	26	68	42	42	29	35	75	

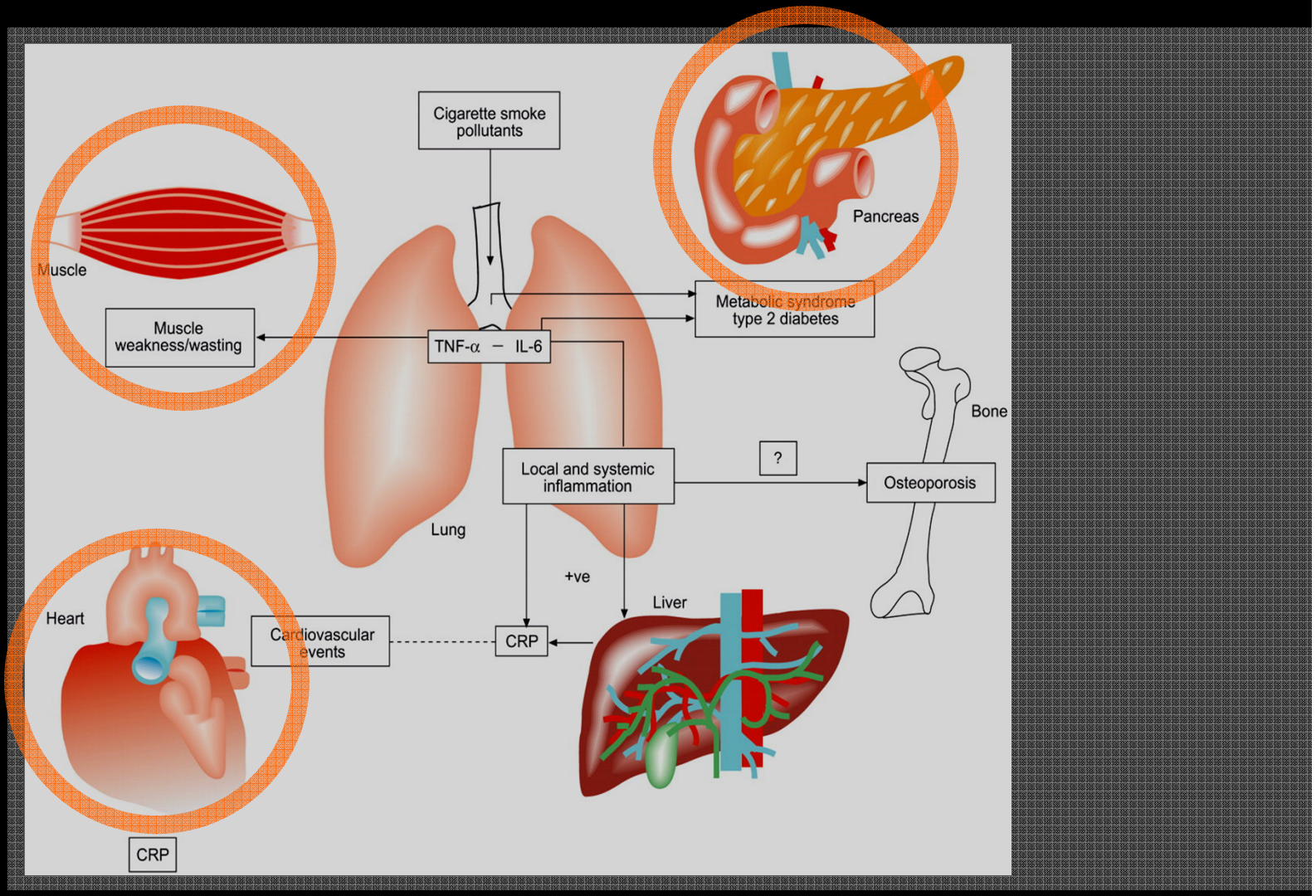
Vanfleteren LEGW et al. AJRCCM 2013 Apr;187(7):728-35

SIMULTANEOUS DEVELOPMENT OF CHRONIC DISEASES



Courtesy of K.F. Rabe, 2014

COPD AS THE PULMONARY COMPONENT OF MULTIMORBIDITY

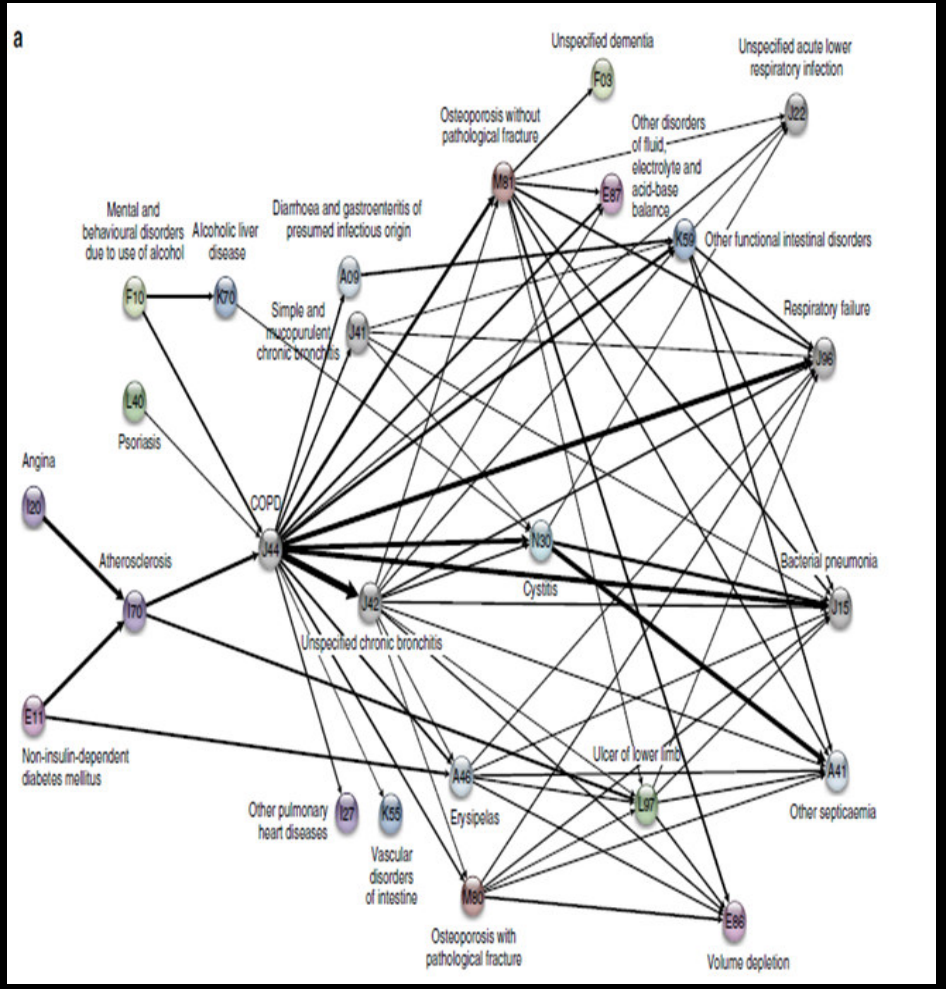


Fabbri LM, Luppi F, Beghe B, and Rabe KF - Eur Respir J 2008;31:204-212

TEMPORAL DISEASE TRAJECTORIES CONDENSED FROM POPULATION-WIDE REGISTRY DATA COVERING 6.2 (ALL) DANISH

Chronic obstructive pulmonary disease (COPD) is central to disease progression and hence important to diagnose early to < future risk

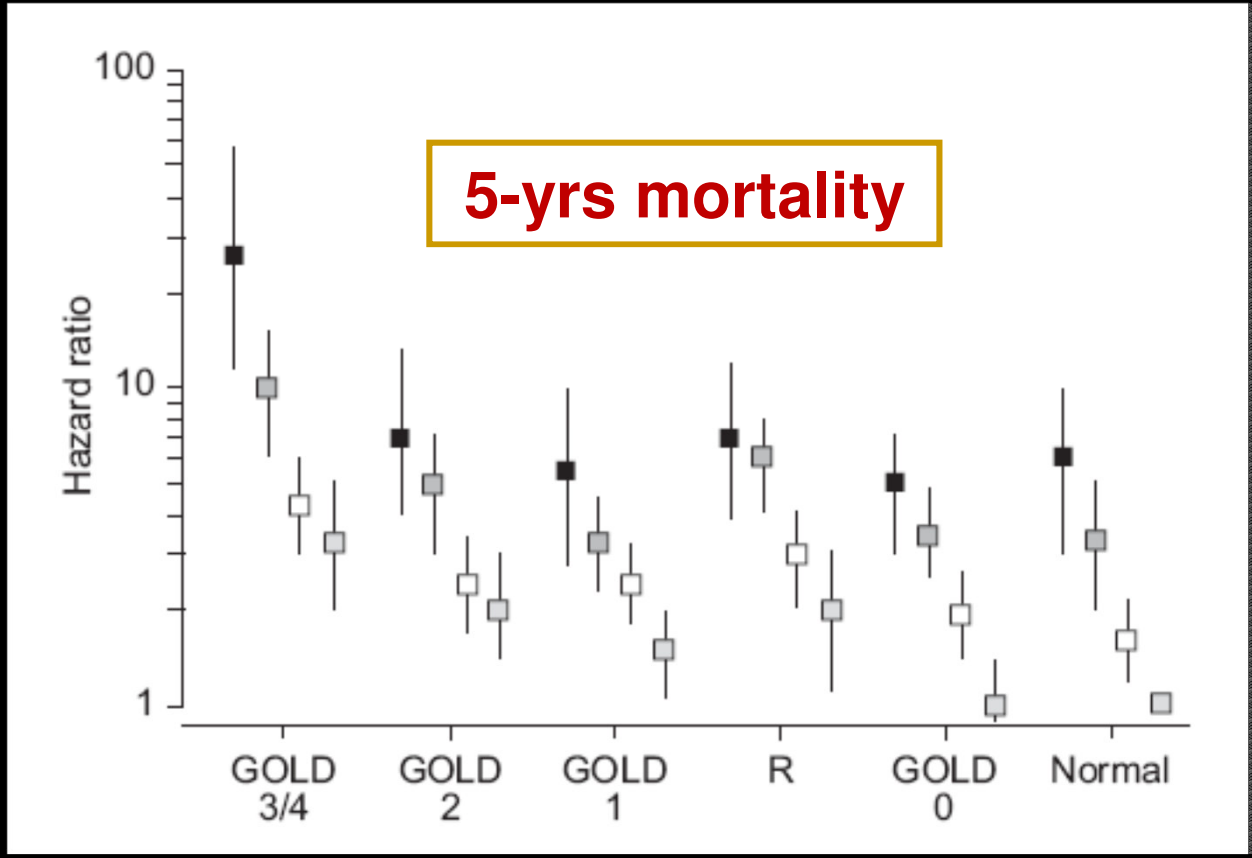
Trajectory analyses may be useful for predicting and preventing future diseases of individual patients



Jensen AB et al, Nature Communications, Published 24 Jun 2014

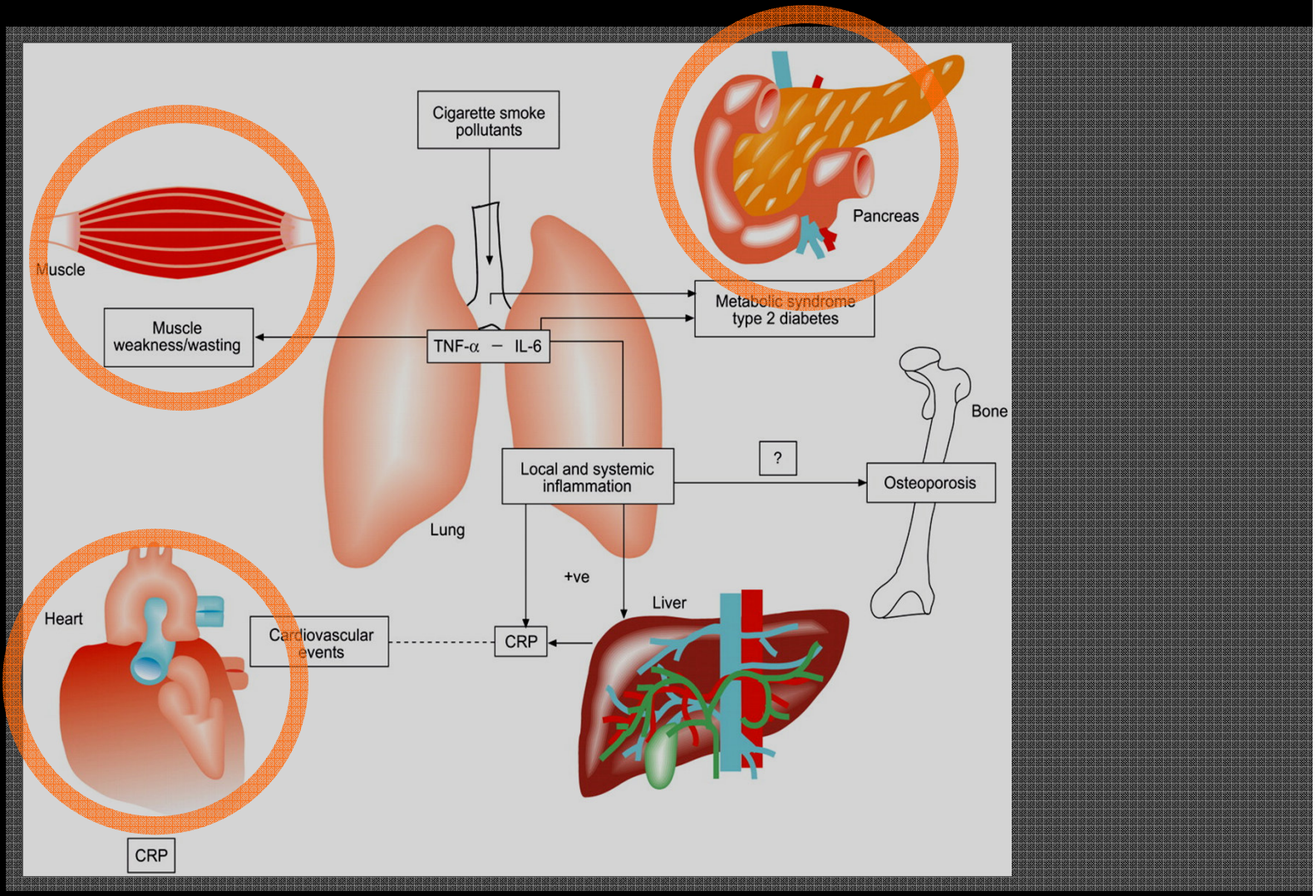
PREVALENCE AND OUTCOMES OF DIABETES HYPERTENSION AND CARDIOVASCULAR DISEASES IN COPD

The present study analysed data from 20,296 subjects aged >45 yrs at baseline in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study



Mannino et al, Eur Respir j 2008; 32: 962-969

COPD AS THE PULMONARY COMPONENT OF MULTIMORBIDITY



Fabbri LM, Luppi F, Beghe B, and Rabe KF - Eur Respir J 2008;31:204-212

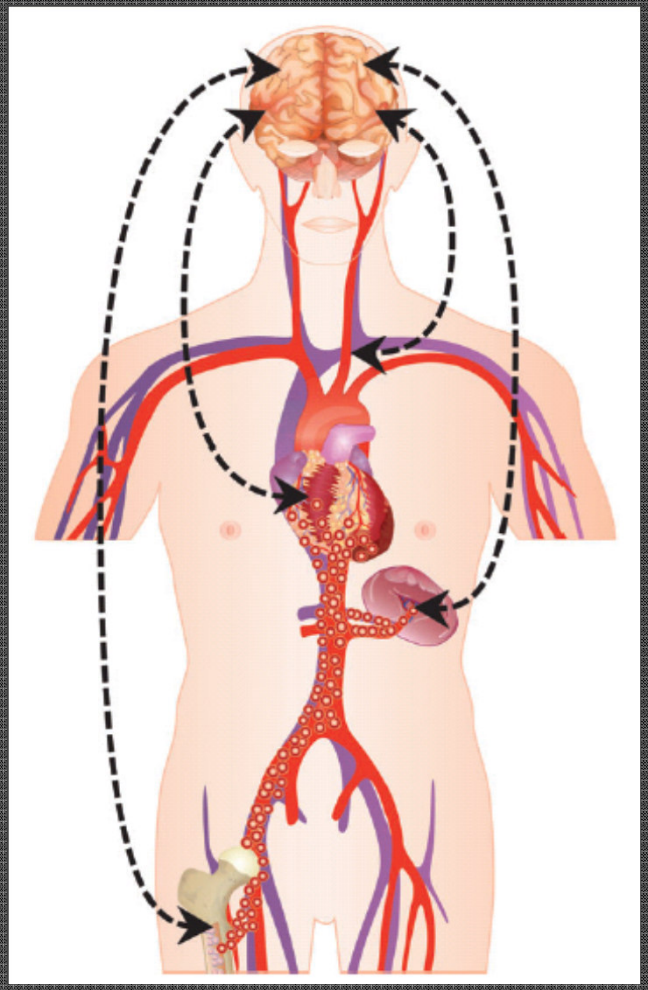
- COPD as pulmonary component of chronic multimorbidity in the elderly
- **COPD and chronic heart diseases**
- Complexity of acute exacerbations
- Management of COPD and chronic multimorbidity
- Future therapies for COPD and multimorbidity

CARDIOVASCULAR MORTALITY IN COPD

For every 10% decrease in FEV_1, cardiovascular mortality increases by approximately 28% and non-fatal coronary event increases by approximately 20% in mild to moderate COPD

Sin DD et al. Proc Am Thorac Soc 2005;2:8-11

HEART FAILURE AS A SYSTEMIC DISEASE

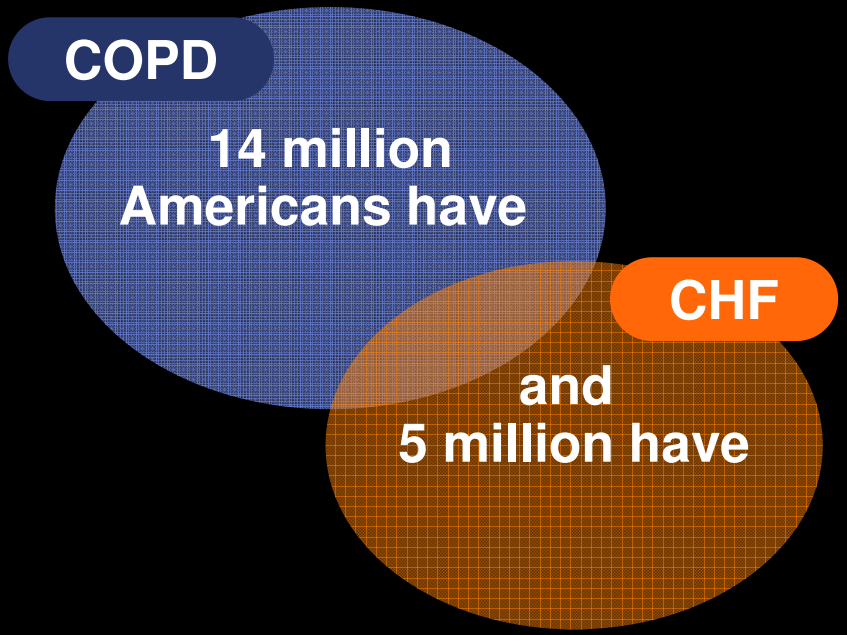


- Myocardial infarction causes the release of inflammatory cells from the spleen and bone marrow and their myocardial infiltration
- This leads to an accumulation of monocytes in the heart, predominantly located in the infarct border zone, and a decrease of monocytes in the spleen and bone marrow
- This may be mediated by activation of the sympathetic nervous system, angiotensin II, and/ or cytokine release.

Hofmasnn and Frantz. Eur Heart J 2014; 35: 314-5.

COPD vs CHRONIC HEART FAILURE

- Up to 1\5 of elderly pts. with COPD have CHF
- Up to 1\3 of elderly pts. with CHF have COPD



The risk ratio of developing HF in COPD pts is 4.5

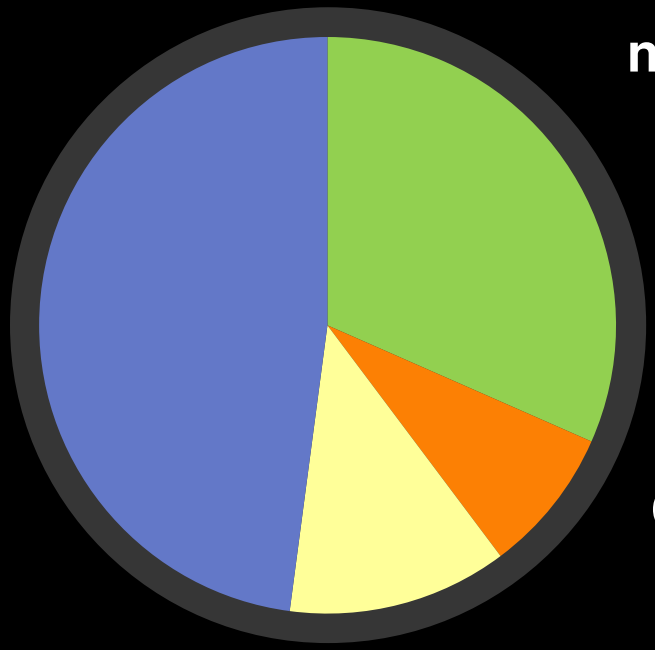
The rate-adjusted hospital prevalence of CHF is 3 times greater among pts. discharged with a diagnosis of COPD compared with patients discharged without mention of COPD

Padeletti-LeJemtel et al. Int. J Cardiology, 2008

UNRECOGNIZED CHRONIC HEART FAILURE IN ELDERLY PATIENTS WITH STABLE COPD

405 elderly with a diagnosis of COPD, but no CHF by GPs

Echo + spiro reassessment



no CHF, no COPD: 128 (32)%

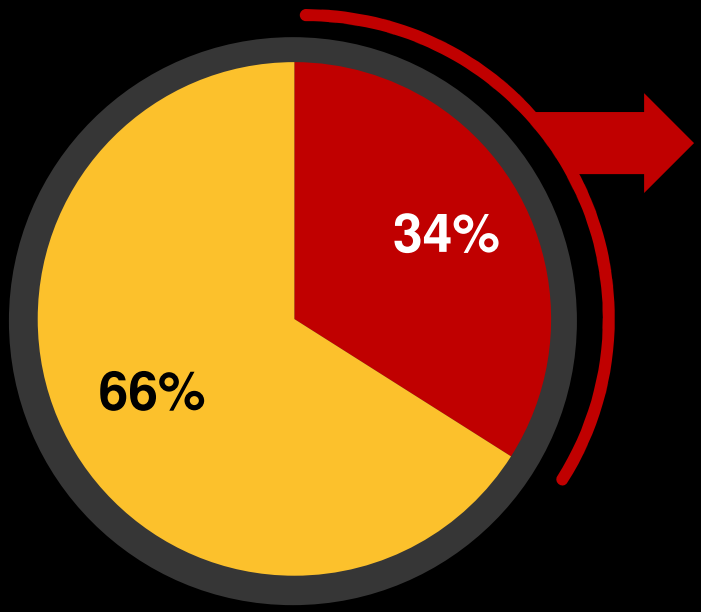
COPD only: 194 (48%)

COPD + CHF: 50 (12%)

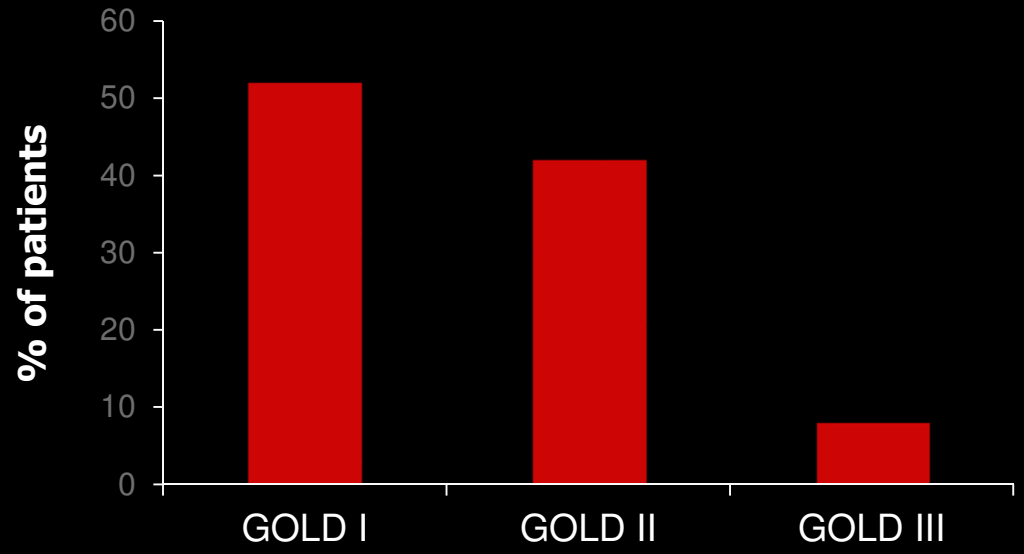
CHF only: 33 (8%)

Rutten FH et al, Eur Heart J 2005

ECHOCARDIOGRAPHY, SPIROMETRY, AND SYSTEMIC ACUTE-PHASE INFLAMMATORY PROTEINS IN SMOKERS WITH COPD OR CHF: AN OBSERVATIONAL STUDY



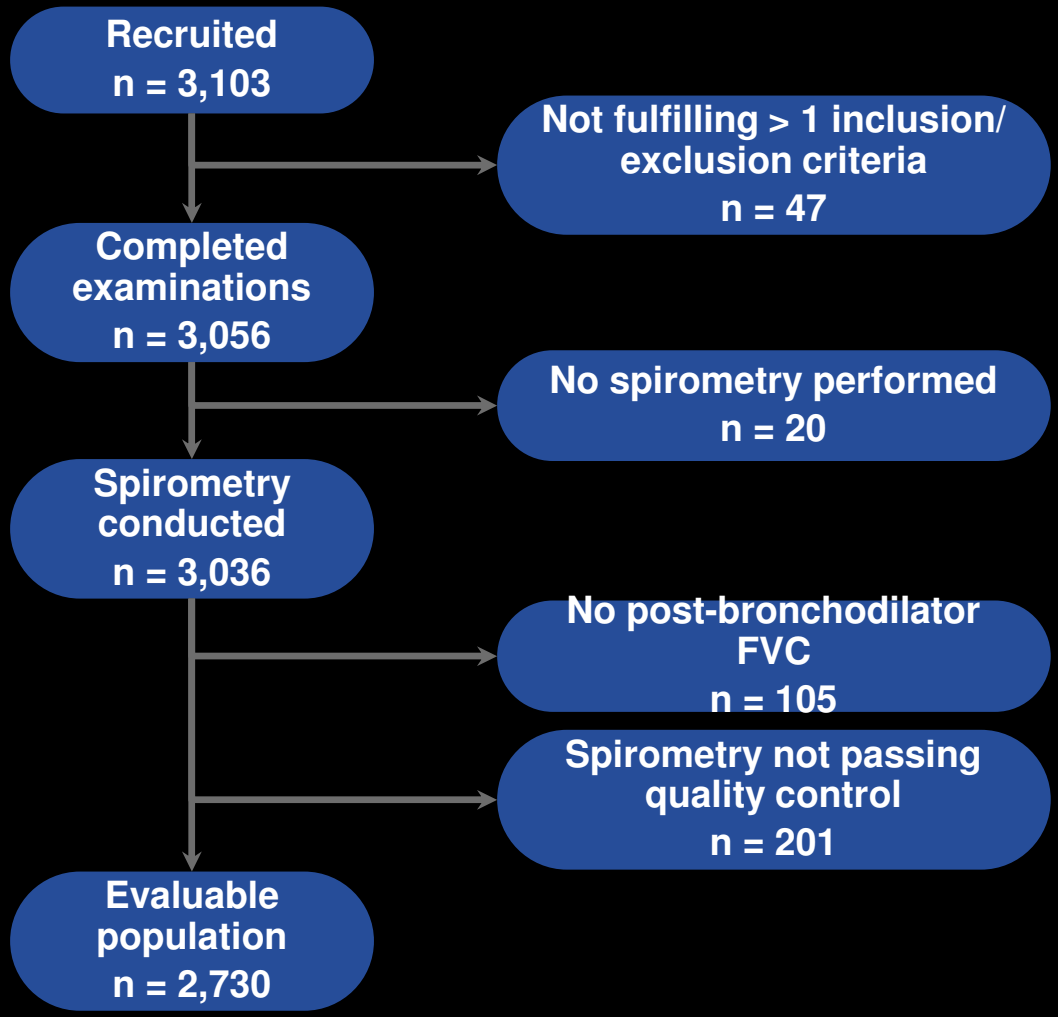
CHF patients



Only 10 of 42 (<25%) pts. with both CHF and COPD were aware of airflow limitation and properly treated

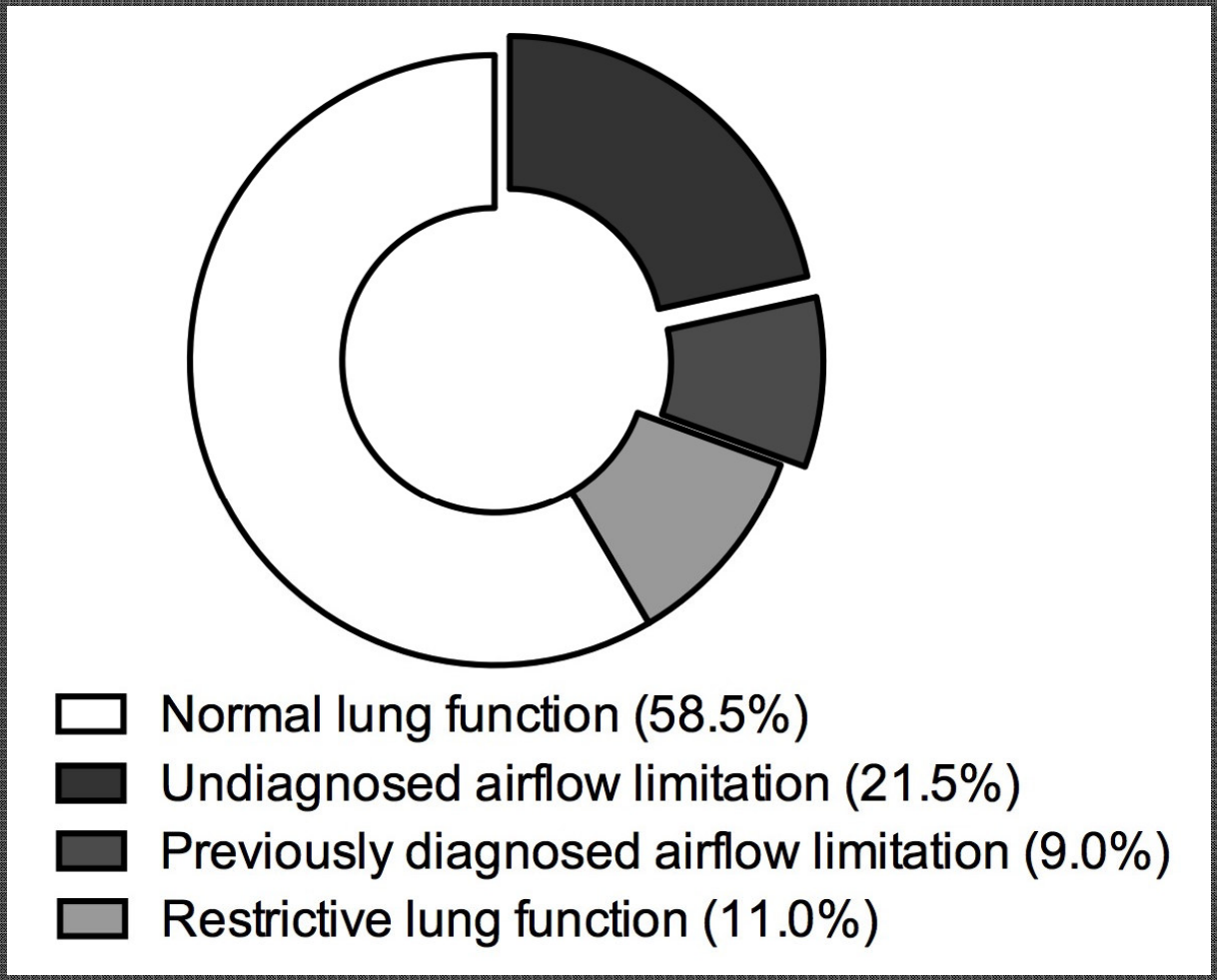
Beghé B et al. PlosOne 2013 Nov 11;8

LUNG FUNCTION ABNORMALITIES IN PATIENTS WITH ISCHEMIC HEART DISEASES



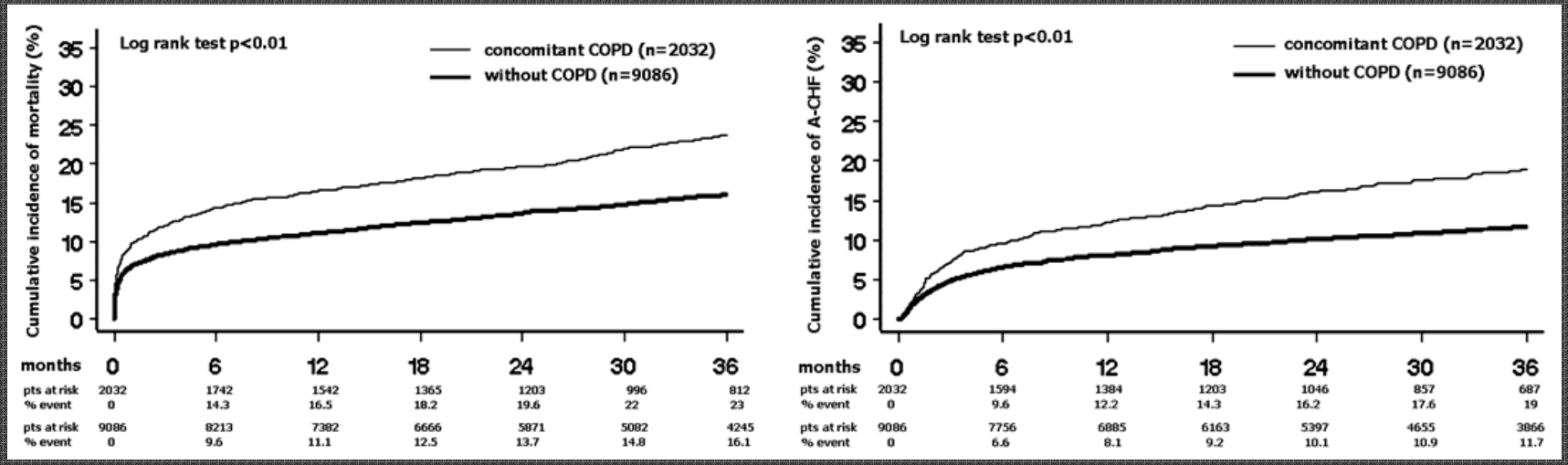
Franssen et al, Eur Heart J 2015, in preparation

LUNG FUNCTION ABNORMALITIES IN PATIENTS WITH ISCHEMIC HEART DISEASES



Franssen et al, Eur Heart J 2015, submitted

IMPACT OF COPD ON LONG-TERM OUTCOME AFTER STEMI RECEIVING PRIMARY PCI



As compared to patients without COPD, patients with STEMI and concomitant COPD are at greater risk for

- **death (25% vs 16.5%)**
- **hospital readmissions due to cardiovascular causes (recurrent MI, HF and bleedings)**

Campo G. et al. Chest 2013;144:750-7

RISK OF MYOCARDIAL INFARCTION (MI) AND DEATH FOLLOWING MI IN PEOPLE WITH COPD:
a systematic review and meta-analysis

COPD is associated with increased risk of MI

> risk of MI is during AECOPD

No > hospital mortality in COPD patients with MI

> longer term mortality in COPD patients with MI

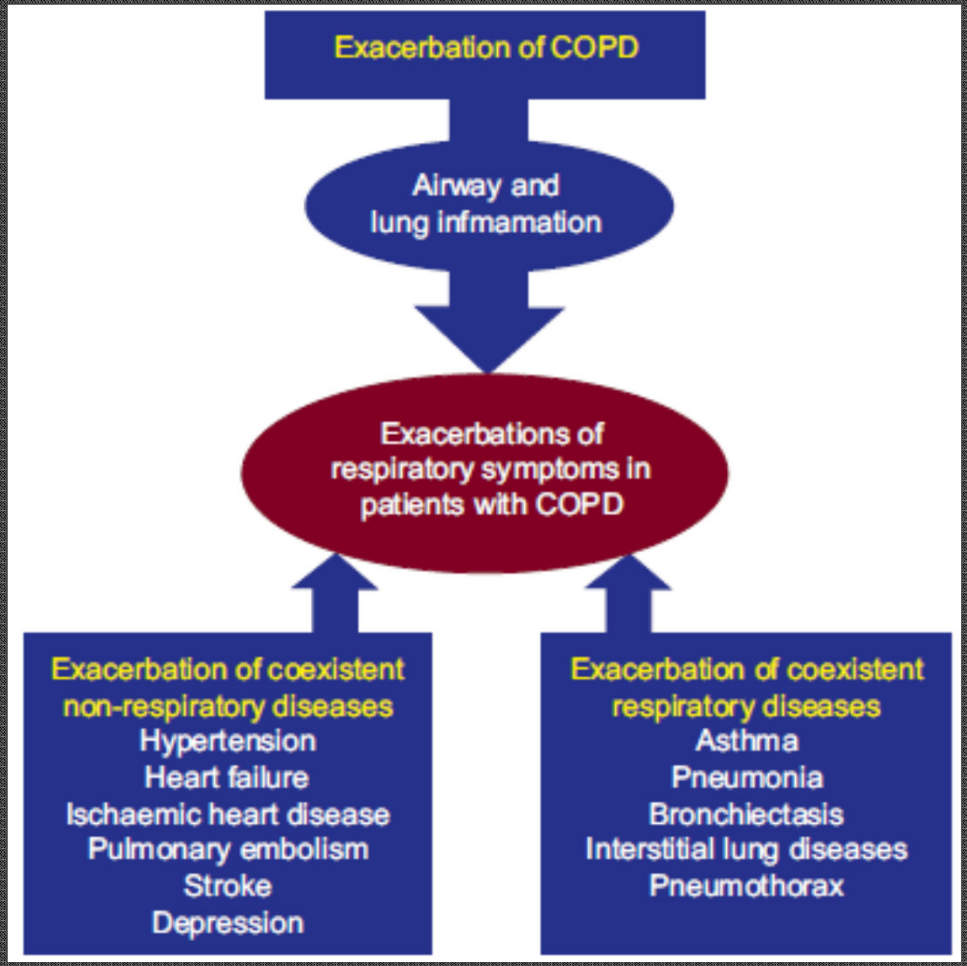
Rothnie KJ, et al. BMJ Open 2015;5:e007824

BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO): da malattia broncopolmonare a componente broncopolmonare della multimorbidità cronica

Leonardo M. Fabbri

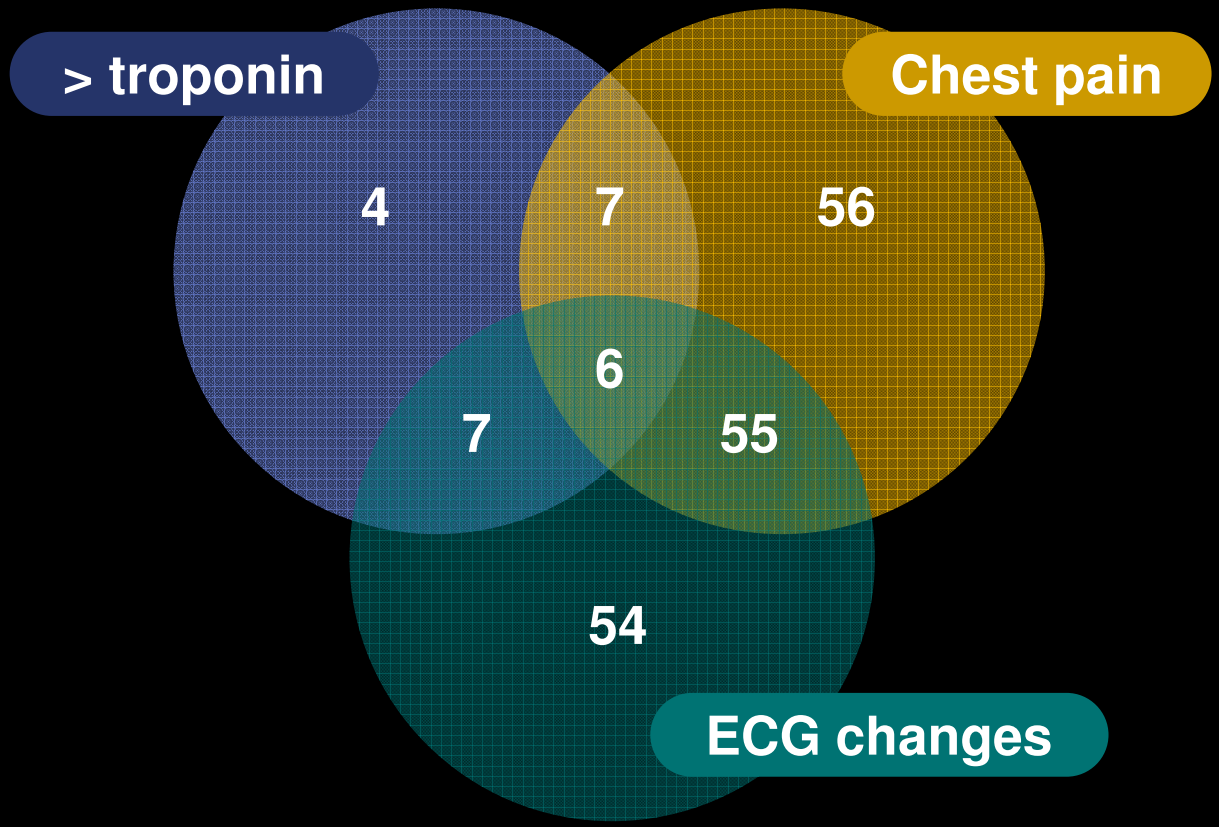
- **COPD as pulmonary component of chronic multimorbidity in the elderly**
- **COPD and chronic heart diseases**
- **Complexity of acute exacerbations**
- **Management of COPD and chronic multimorbidity**
- **Future therapies for COPD and multimorbidity**

EXACERBATIONS OF RESPIRATORY SYMPTOMS IN PATIENTS WITH COPD MAY NOT BE EXACERBATIONS OF COPD



Beghé B, Verduri A, Roca M and Fabbri LM. Eur Respir J 2013; 41: 993-5
Roca M, Verduri A, Clini EM, Fabbri LM and Beghé B. Eur J Clin Invest, 2013;43:510

BIOCHEMICAL MARKERS OF CARDIAC DYSFUNCTION PREDICT MORTALITY IN ACUTE EXACERBATIONS OF COPD



McAllister et al. Eur Respir J 2012; 3:1097-103

BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO): da malattia broncopolmonare a componente broncopolmonare della multimorbidità cronica

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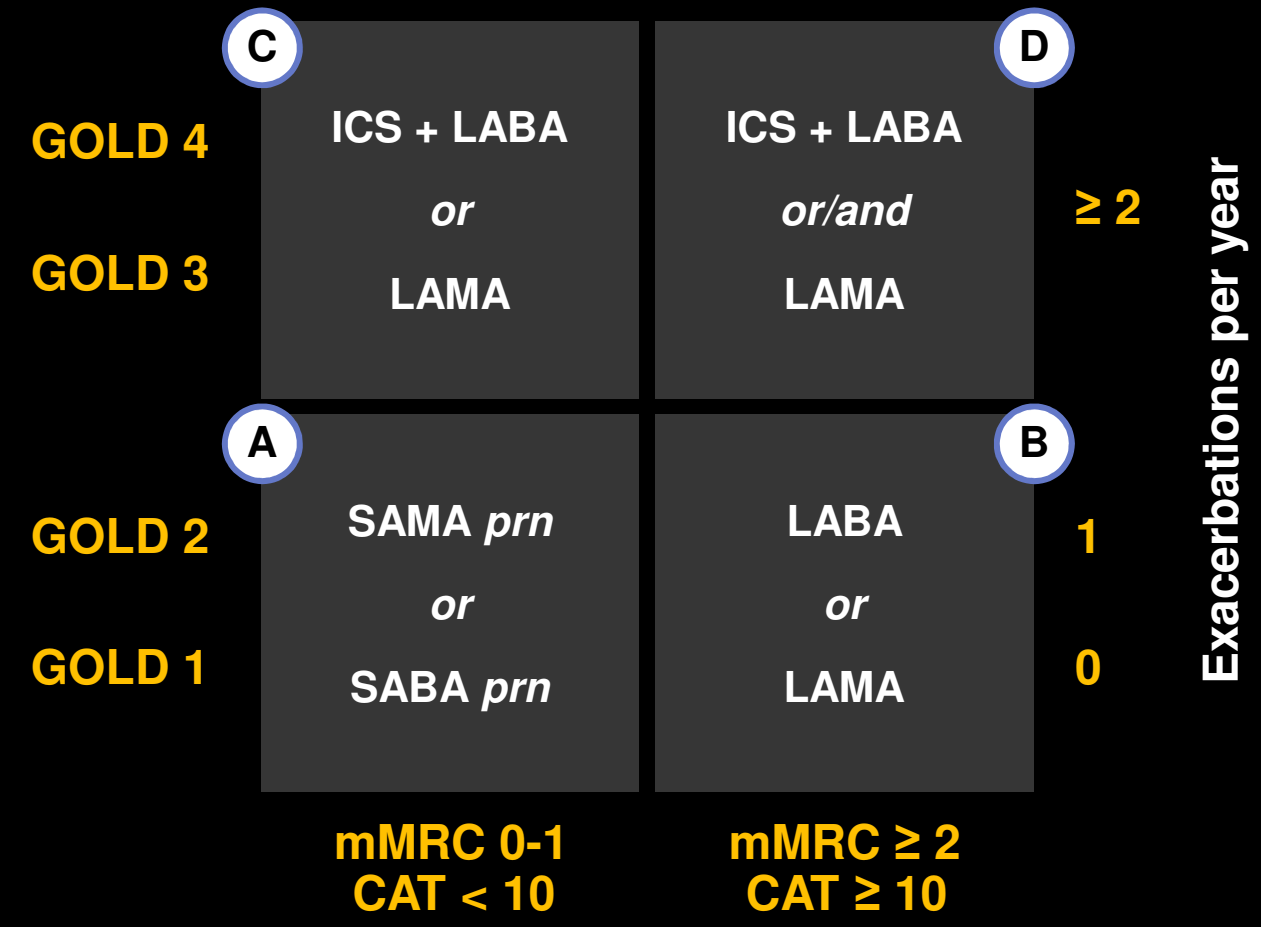
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

FIRST CHOICE

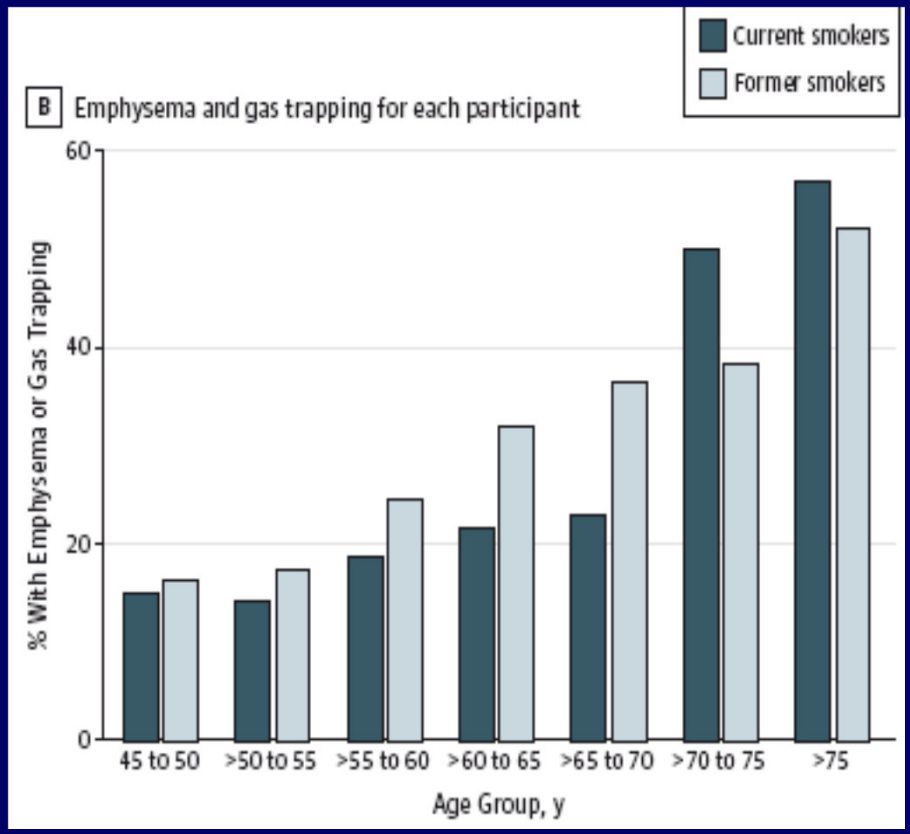


CLINICAL AND RADIOLOGIC DISEASE IN SMOKERS WITH NORMAL SPIROMETRY

Lung disease and impairments were common in smokers without spirometric COPD

Based on these results, we project that there are 35 million smokers > 55 years in the USA who may have unrecognized disease

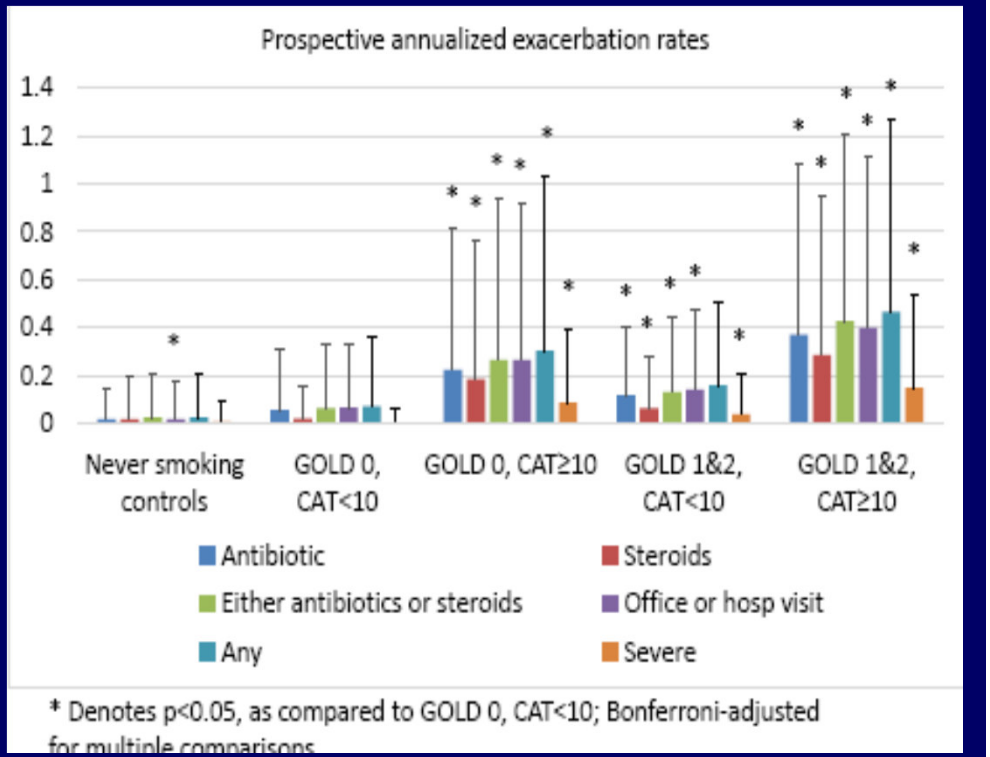
The effect of chronic smoking on the lungs and the individual is substantially underestimated when using spirometry alone.



Regan EA, et al. JAMA Intern Med. 2015 Sep 1;175(9):1539-49

CLINICAL SIGNIFICANCE OF SYMPTOMS IN SMOKERS WITH PRESERVED SPIROMETRY

Smokers with symptoms despite preserved FEV1/FVC have more frequent respiratory exacerbations, activity limitations and evidence of airway disease and are currently using a range of respiratory medications without any evidence base



Woodruff et al. N Engl J Med 2015, Sep, in press

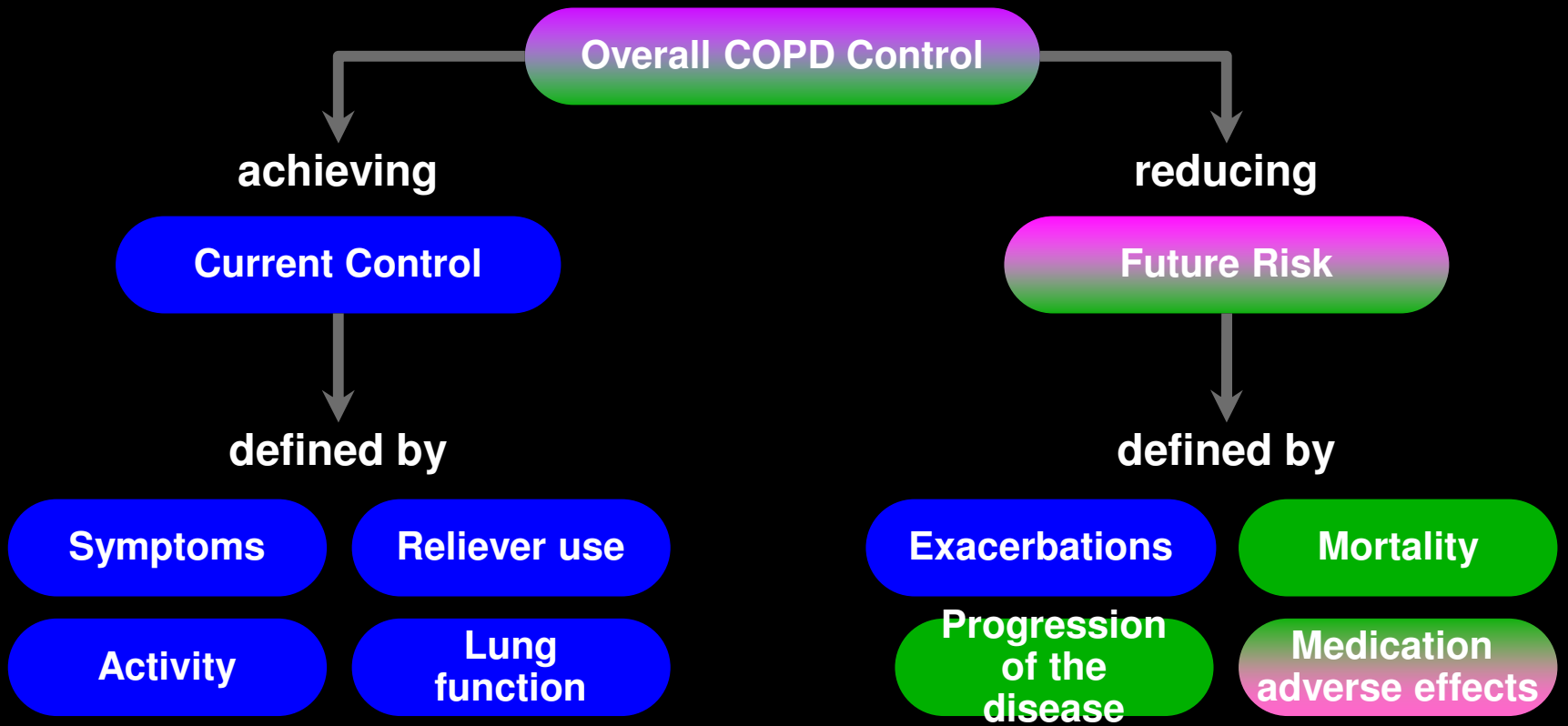
IS TIME TO MOVE BEYOND THE "O" IN COPD?

Central to COPD guidelines is the use of spirometry, a measurement of ventilatory function, without considering other factors that lead to the development and progression of COPD

We believe that a growing body of evidence suggests that airflow limitation alone is insufficient to convey the full burden of pathophysiology in early lung disease

Mannino DM and Make BJ. Eur Respir Med 2015, in press

GOALS OF COPD MANAGEMENT



www. goldcopd.org 2015

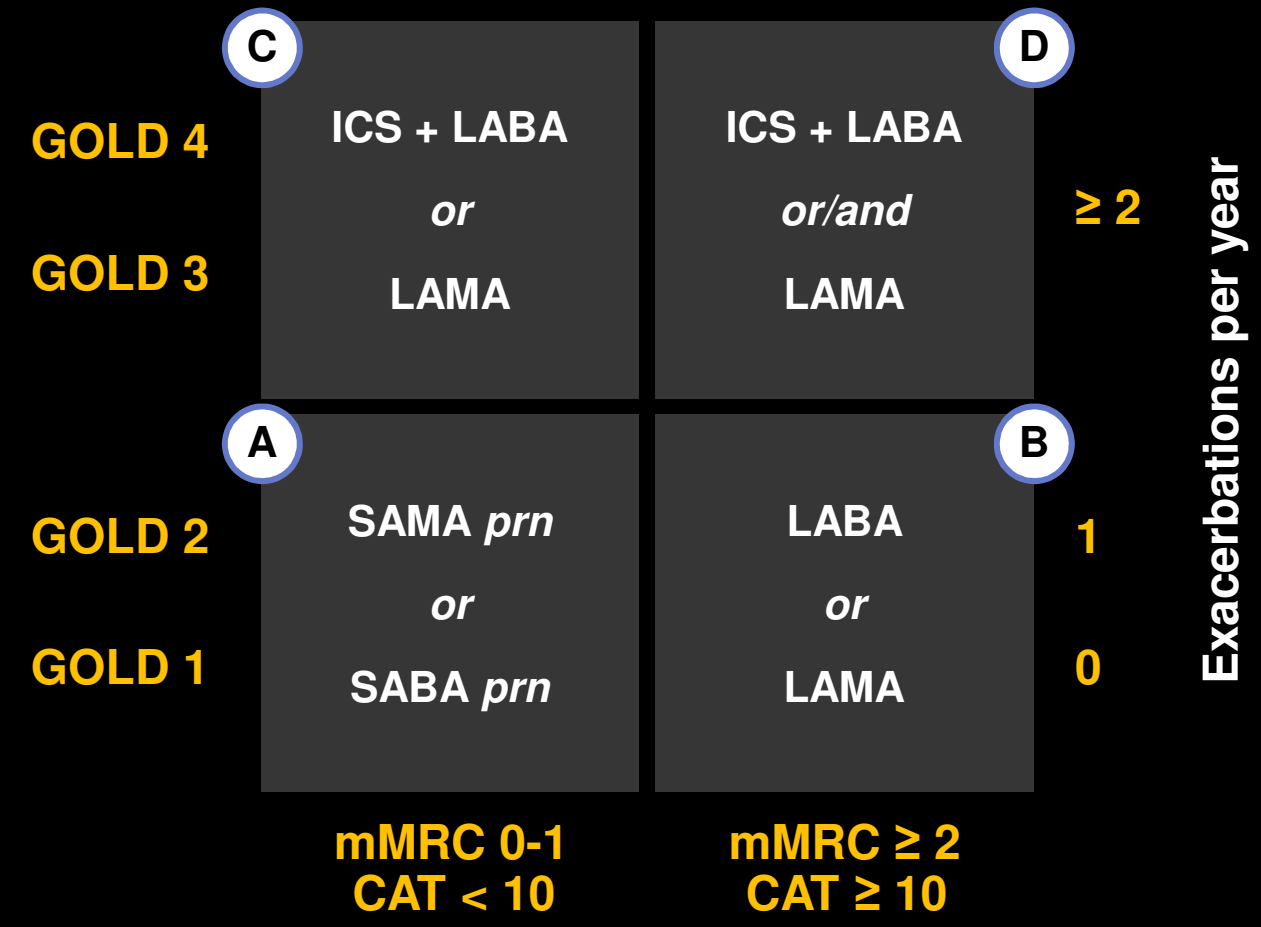
COPD EXACERBATIONS: PREVENTION

- Smoking cessation
- Consider Pulmonary rehabilitation
- Vaccination (influenza, pneumococcal)
- Consider Long-term oxygen therapy
- Pharmacotherapy

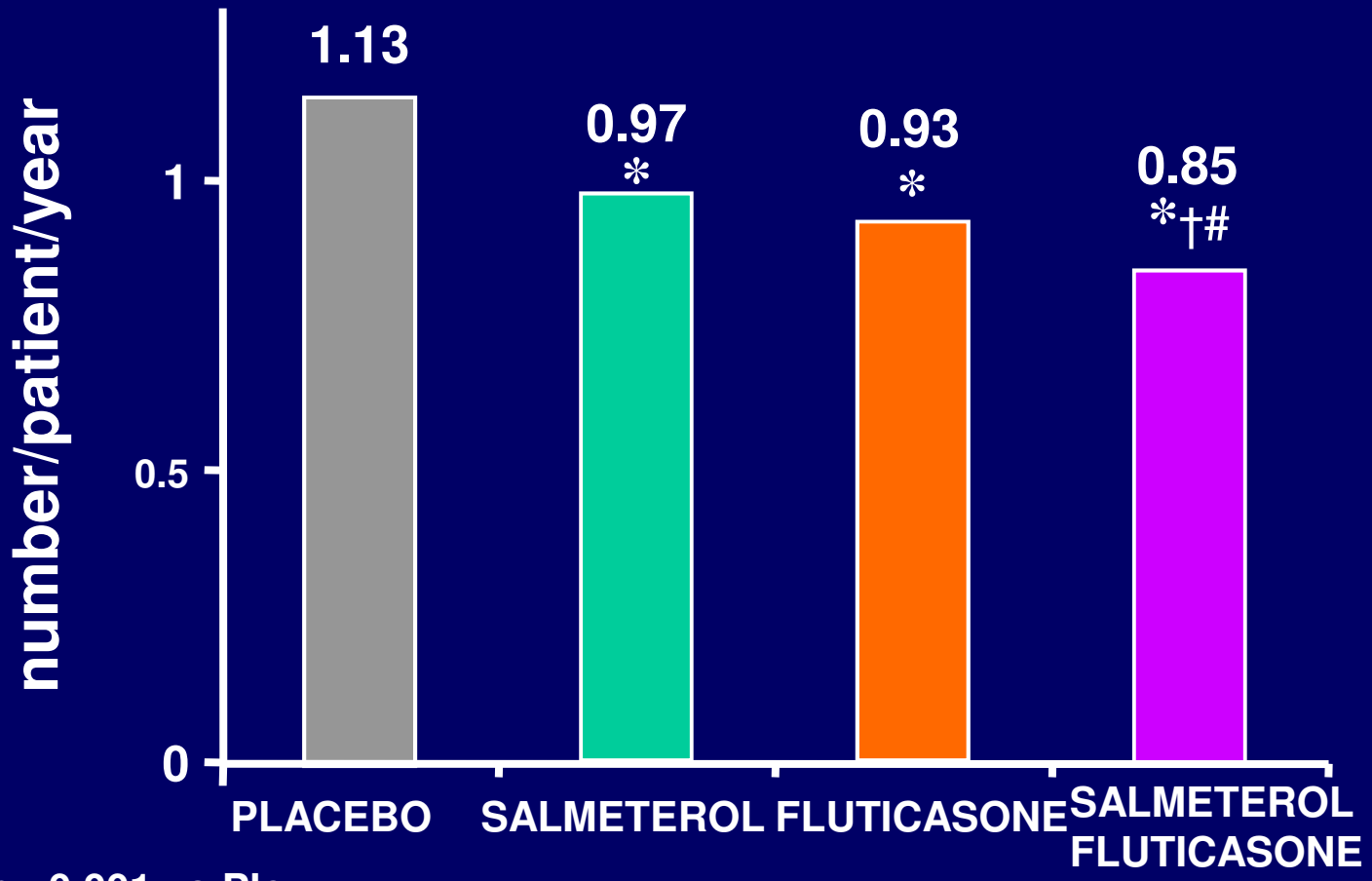
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

FIRST CHOICE



Rate of Exacerbations



* p< 0.001 vs Plc,
† p=0.002 vs SAL,
# p=0.024 vs FP

Calverley PMA et al, N Engl J Med. 356(8): 775-89.

ONCE-DAILY INHALED FLUTICASONE FUROATE AND VILANTEROL VERSUS VILANTEROL ONLY FOR PREVENTION OF EXACERBATIONS OF COPD: TWO REPLICATE DOUBLE-BLIND, PARALLEL-GROUP, RANDOMISED CONTROLLED TRIALS

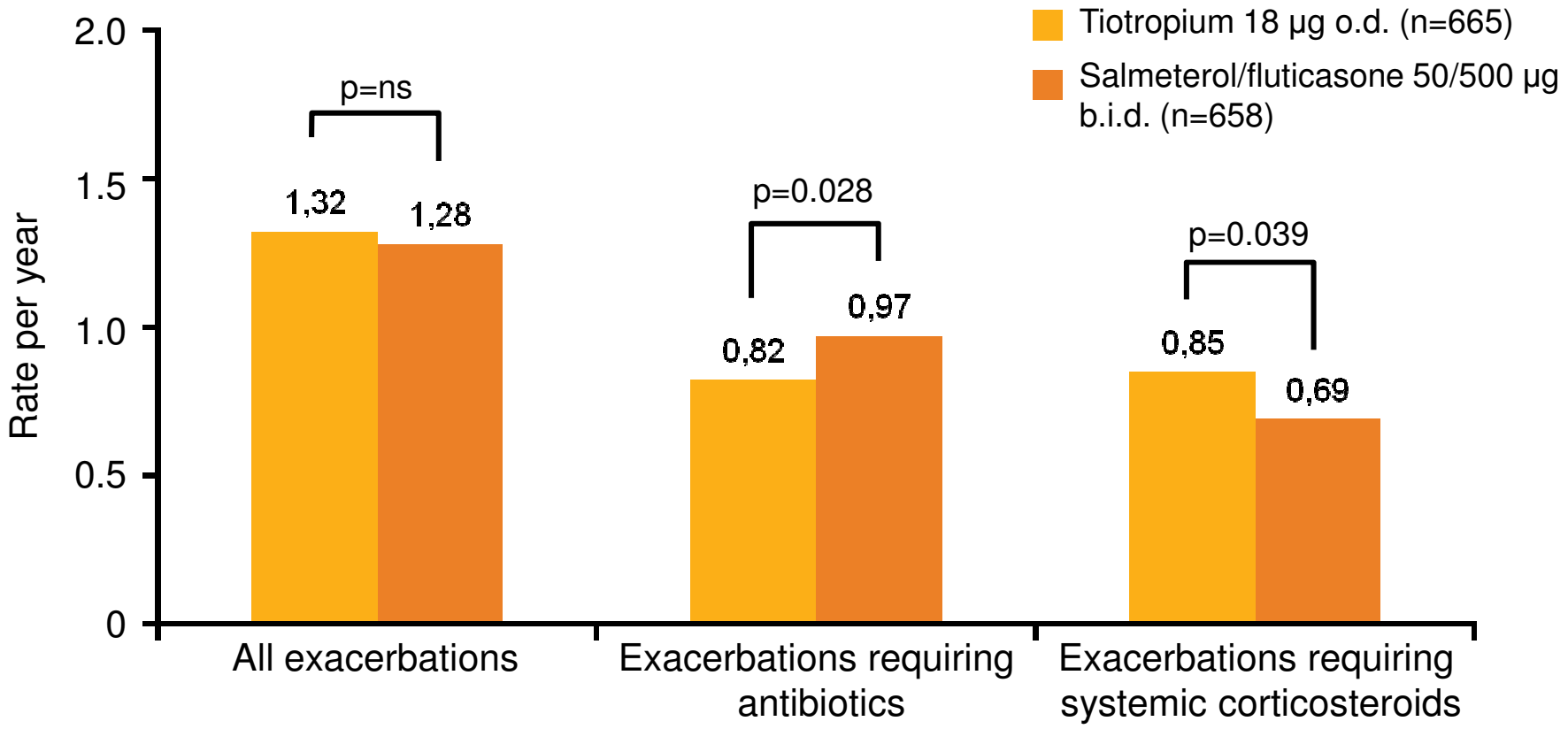
In COPD patients with a history of exacerbation, fluticasone furoate/vilanterol combination:

1. **decreased rate of moderate and severe exacerbations**
2. **a increased the risk of pneumonia**

Drasfield MT, et al. The Lancet Respiratory Medicine, 2013;1(3):210-223

Limited evidence for reduction in exacerbation rate with salmeterol/fluticasone vs tiotropium

- In the INSPIRE study, rates of 'All exacerbations' at 2 years were similar between tiotropium and salmeterol/fluticasone treatment groups



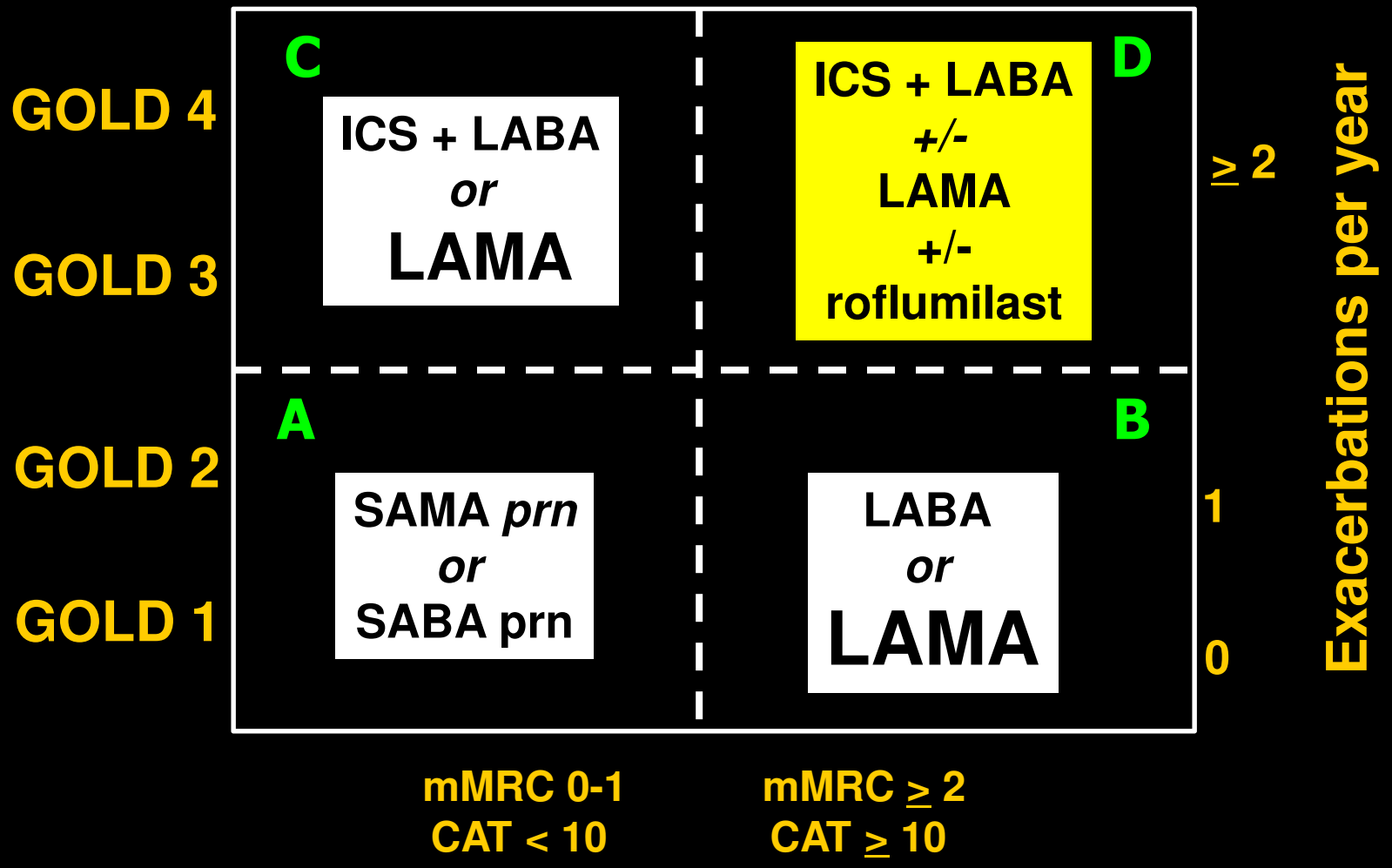
b.i.d., twice daily; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; o.d., once daily.

Reference. Wedzicha JA. Am J Crit Care Med 2008.

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage stable COPD: Pharmacologic therapy

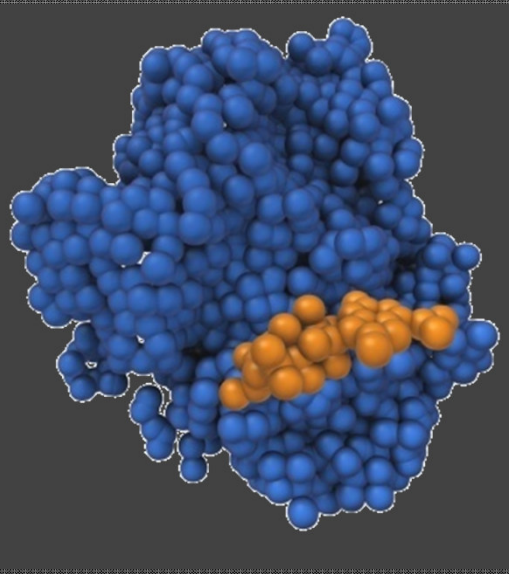
FIRST CHOICE (?)



ROFLUMILAST IN CLINICAL PRACTICE

Clinical benefits

- Roflumilast is an anti-inflammatory drug and not a bronchodilator
- In patients with severe COPD with chronic bronchitis and increased risk of exacerbations it
  - reduces exacerbations
  - improves lung function
- Add-on to bronchodilatory maintenance treatment with additive effects



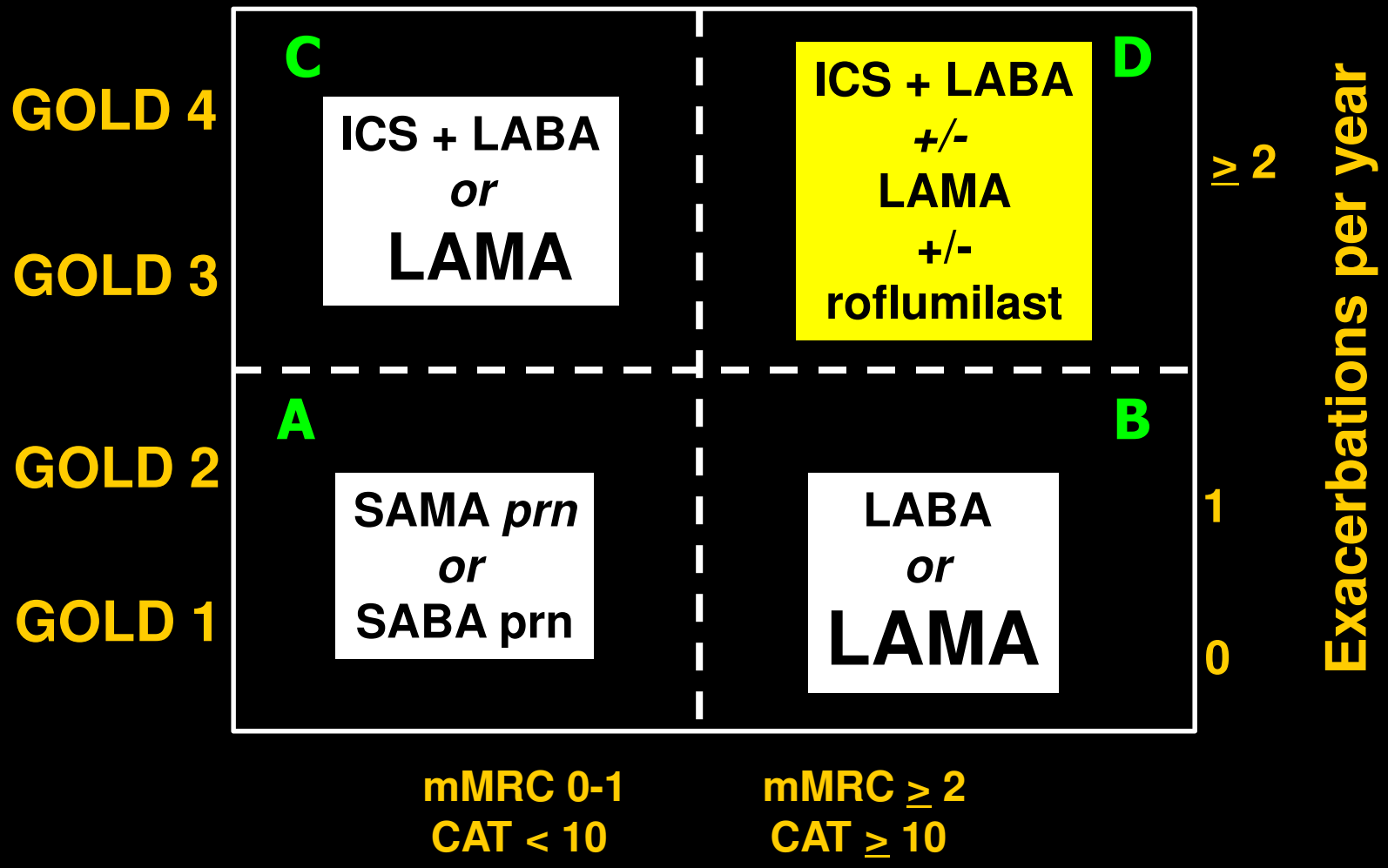
PDE4 inhibition

Calverley, et al. Lancet 2009; 374:685–9
Fabbri, et al. Lancet 2009; 374:695–703
Martinez FJ et al. Lancet 2015; 385: 857-66

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage stable COPD: Pharmacologic therapy

FIRST CHOICE (?)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

ABSTRACT

BACKGROUND

Long-acting beta-agonists and inhaled corticosteroids are used to treat chronic obstructive pulmonary disease (COPD), but their effect on survival is unknown.

METHODS

We conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed.

RESULTS

Of 6112 patients in the efficacy population, 875 died within 3 years after the start

From University Hospital Aintree, Liverpool, United Kingdom (P.M.A.C.); GlaxoSmithKline Research and Development, Greenford, United Kingdom (J.A.A.); Caritas St. Elizabeth's Medical Center, Boston (B.C.); Pulmonary Research Institute of Southeast Michigan, Livonia (G.T.F.); Woolcock Institute of Medical Research, Sydney (C.J.); St. George's University of London, London (P.W.J.); GlaxoSmithKline Research and Development, Research Triangle Park, NC (J.C.Y.); and Wythenshawe Hospital, Manchester, United Kingdom, and Hvidovre Hospital, Hvidovre, Denmark (J.V.). Address reprint requests to Dr. Calverley at the Department of Medicine, Clinical Science Centre, University Hos-

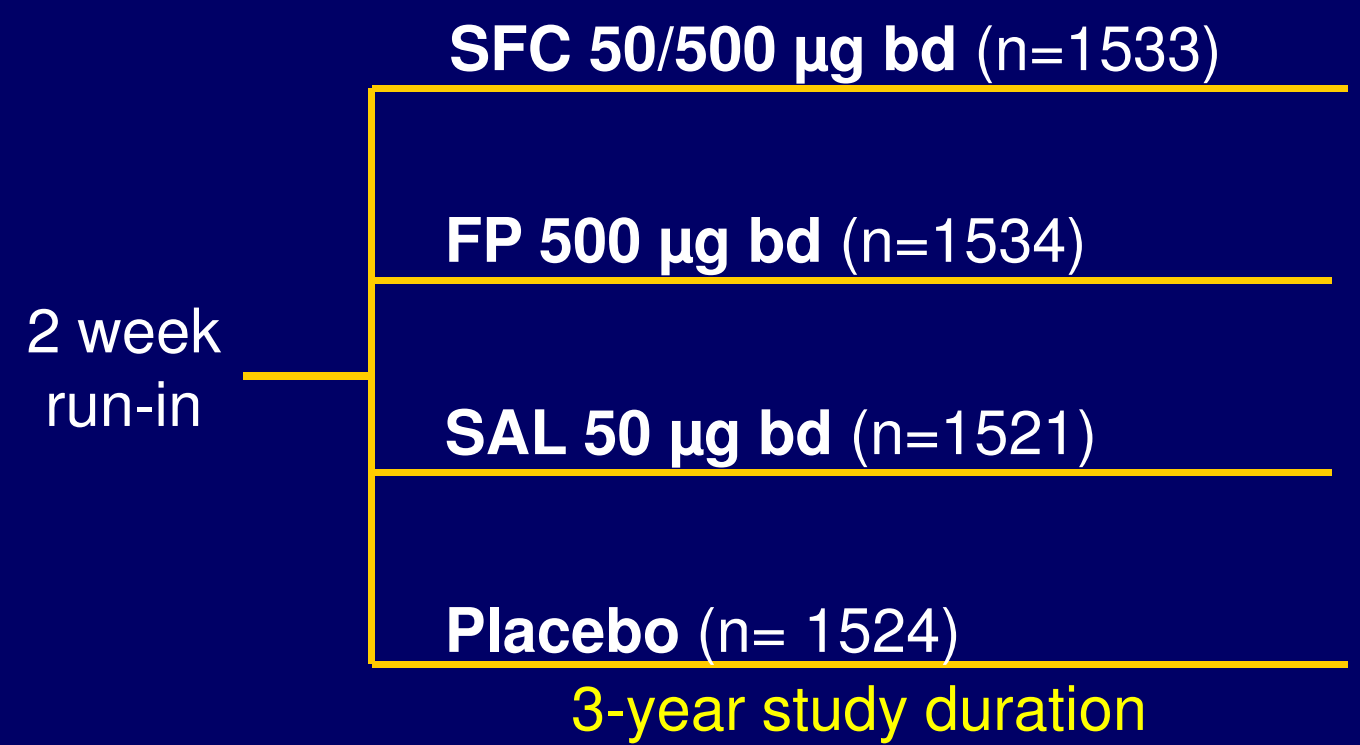
Calverley PMA et al, NEJM 2007; 356:775-78

TORCH: main objectives

- Primary objective
  - The effect of SFC 50/500 μg vs placebo on all-cause mortality over 3 years in patients with moderate-to-severe COPD
- Secondary objectives
  - The effect of SFC 50/500 μg on the rate of moderate and severe exacerbations
  - The effect of SFC 50/500 μg on health status (SGRQ)
  - The effect of SFC 50/500 μg on lung function decline

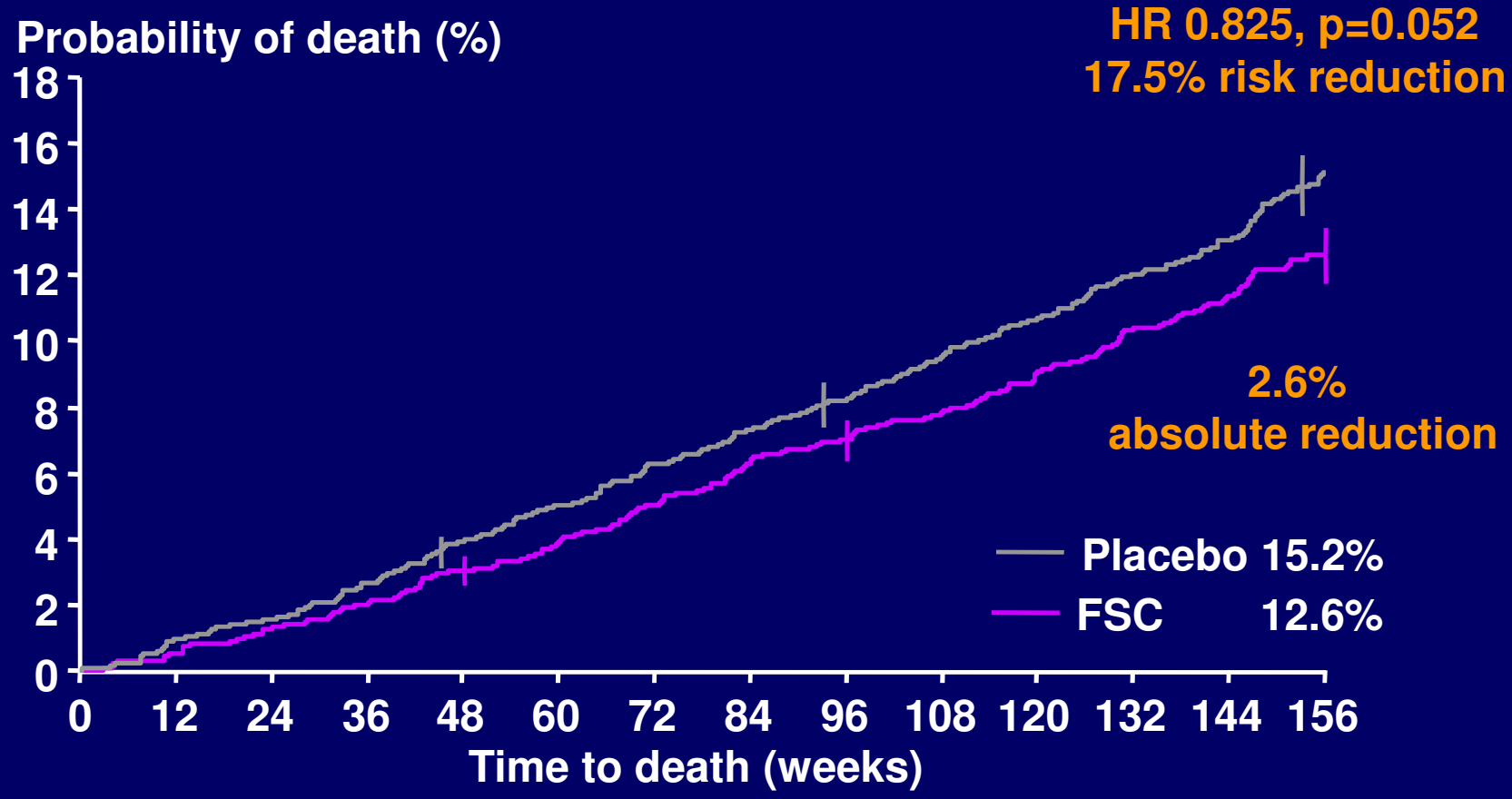
Calverley PMA et al, N Engl J Med. 356(8): 775-89.

TORCH: study design (6,000 COPD patients)



Calverley PMA et al, N Engl J Med. 356(8): 775-89.

Primary analysis: all-cause mortality at 3 years



Number alive	1524	1464	1399	1293 Plc
	1533	1487	1426	1339 SFC

Vertical bars are standard errors

Calverley PMA et al, N Engl J Med. 356(8): 775-89.

Primary analysis: All-cause mortality at 3 years

	Placebo (n = 1,524)	SALM/FP (n = 1,533)
Probability of death by 3 years (%)*	15.2	12.6

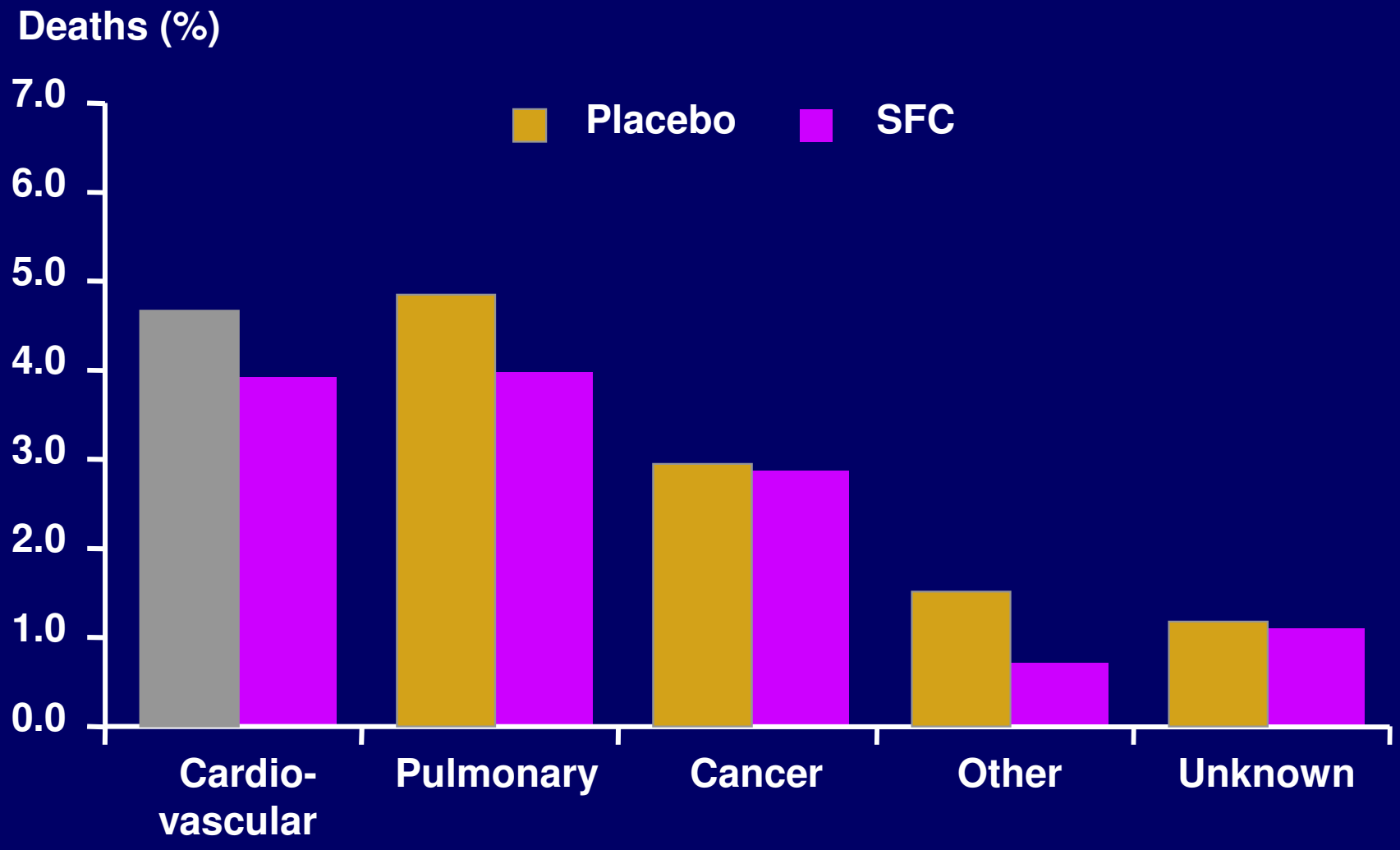
	HR	95% CI	p	Compare to sig level
Unadjusted	0.820	(0.677, 0.993)	0.041	0.040**
Adjusted†	0.825	(0.681, 1.002)	0.052	0.050

SPARCL stats?

*Kaplan-Meier estimate, stratified by smoking status
**Taking the interim analyses into account;
†Adjusted to a significance level of 0.05

Calverley PMA et al, N Engl J Med. 356(8): 775-89.

Cause of death on treatment (adjudicated by CEC)



Calverley PMA et al, N Engl J Med. 356(8): 775-89.

COMBINATION LABA AND ICS COMPARED WITH LABA ALONE IN OLDER ADULTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

As compared to LABA alone, LABA/ICS combination therapy was associated with a significantly lower risk of the composite outcome of death or COPD hospitalization

Gershon A et al, JAMA 2014; 312: 1114-21

COMBINATION LABA AND ICS COMPARED WITH LABA ALONE IN OLDER ADULTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Table 1. Selected Baseline Characteristics by Initially Prescribed Medication, Before and After Propensity Score Matching[a]

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Initially Prescribed Therapy			Initially Prescribed Therapy		
	LABAs and ICSs (n=34 289)	LABAs Alone (n=3258)	Standardized Difference	LABAs and ICSs (n=8712)	LABAs Alone (n=3160)	Standardized Difference
Demographics						
Age, mean (SD), y	76.26 (7.26)	77.12 (6.90)	0.12	76.78 (6.71)	76.98 (6.78)	0.03
Women	16 122 (47.0)	1537 (47.2)	0	4076 (46.8)	1485 (47.0)	0
Most recent hospitalization for COPD			0.24			0.05
<6 mo	8342 (24.3)	1044 (32.0)		2565 (29.4)	992 (31.4)	
6 mo to 5 y	4782 (13.9)	583 (17.9)		1491 (17.1)	554 (17.5)	
>5 y or never	21 165 (61.7)	1631 (50.1)		4656 (53.4)	1614 (51.1)	
Most recent hospitalization for COPD-related condition[b]			0.15			0.04
<6 mo	3811 (11.1)	492 (15.1)		1186 (13.6)	458 (14.5)	
6 mo to 5 y	3361 (9.8)	391 (12.0)		966 (11.1)	372 (11.8)	
>5 y or never	27 117 (79.1)	2375 (72.9)		6560 (75.3)	2330 (73.7)	
Most recent ED visit for COPD			0.05			0.02
<6 mo	1875 (5.5)	197 (6.0)		485 (5.6)	191 (6.0)	
6 mo to 5 y	2538 (7.4)	282 (8.7)		710 (8.1)	267 (8.4)	
>5 y or never	29 876 (87.1)	2779 (85.3)		7517 (86.3)	2702 (85.5)	
Most recent ED visit for COPD-related condition[b]			0.02			0.01
<6 mo	1301 (3.8)	112 (3.4)		316 (3.6)	110 (3.5)	
6 mo to 5 y	3225 (9.4)	305 (9.4)		811 (9.3)	296 (9.4)	
>5 y or never	29 763 (86.8)	2841 (87.2)		7585 (87.1)	2754 (87.2)	

Gershon A et al, JAMA 2014; 312: 1114-21

COMBINATION LABA AND ICS COMPARED WITH LABA ALONE IN OLDER ADULTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Table 2. Associations of Study Outcomes in New Users of LABA-ICS Combination Therapy Compared With New Users of LABAs Alone After Propensity Score Matching

Outcomes	New LABA and ICS Users, No. (%) (n = 8712)		New LABA Alone Users, No. (%) (n = 3160)		Difference in Outcomes at 5 y, % (95% CI)	Propensity Score-Matched Regression	
	Had Outcome	Had Outcome at 5 y	Had Outcome	Had Outcome at 5 y		Hazard Ratio (95% CI)[a]	*P* Value
Death or hospitalization for COPD	5594 (64.2)[b]	5010 (57.5)	2129 (67.4)[c]	1933 (61.2)	−3.7 (−5.7 to −1.7)	0.92 (0.88-0.96)	<.001
Death	4815 (55.3)	4142 (47.5)	1853 (58.6)	1613 (51.0)	−3.5 (−5.5 to −1.5)	0.92 (0.87-0.97)	<.001
Hospitalization for COPD[d]	2420 (27.8)	2199 (25.2)	950 (30.1)	881 (27.9)	−2.7 (−4.5 to −0.9)	0.91 (0.85-0.98)	.01
Hospitalization for pneumonia[d]	2486 (28.5)	2220 (25.5)	894 (28.3)	811 (25.7)	−0.2 (−2.0 to 1.8)	1.01 (0.93-1.08)	.88
Hospitalization for fracture of hip, wrist, or vertebrae[d]	495 (5.7)	423 (4.9)	159 (5.0)	145 (4.6)	0.3 (−0.6 to 1.2)	1.13 (0.95-1.35)	.17

Gershon A et al, JAMA 2014; 312: 1114-21

COMBINATION LABA AND ICS COMPARED WITH LABA ALONE IN OLDER ADULTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Among older adults with COPD, particularly those with asthma and those not receiving a LAMA, **LABA/ICS** combination therapy was associated with **a significantly lower risk of the composite outcome of death or COPD hospitalization**

Gershon A et al, JAMA 2014; 312: 1114-21

THE STUDY TO UNDERSTAND MORTALITY AND MORBIDITY IN COPD (SUMMIT) STUDY PROTOCOL

- 16,000 patients with moderate COPD, OD
- FF/VI (100/25 mcg)
- FF (100 mcg)
- VI (25 mcg)
- Placebo

Power: FF/VI vs placebo

Primary outcome : mortality

Secondary outcomes:
- decline FEV1
- composite cardiovascular endpoint

Vestbo J et al. Eur Respir J. 2012 Sep 27

THE STUDY TO UNDERSTAND MORTALITY AND MORBIDITY IN COPD (SUMMIT) STUDY

SUMMIT is a landmark study investigating the effect of inhaled medications on mortality in patients with COPD and CVD or CV risk

SUMMIT is one of the largest studies ever conducted in COPD and it is the first time that survival has been studied in this under-researched co-morbid patient population

Estimates of CVD prevalence in the population with COPD vary widely from 28-70% due to different definitions of CVD & differences in study design/setting

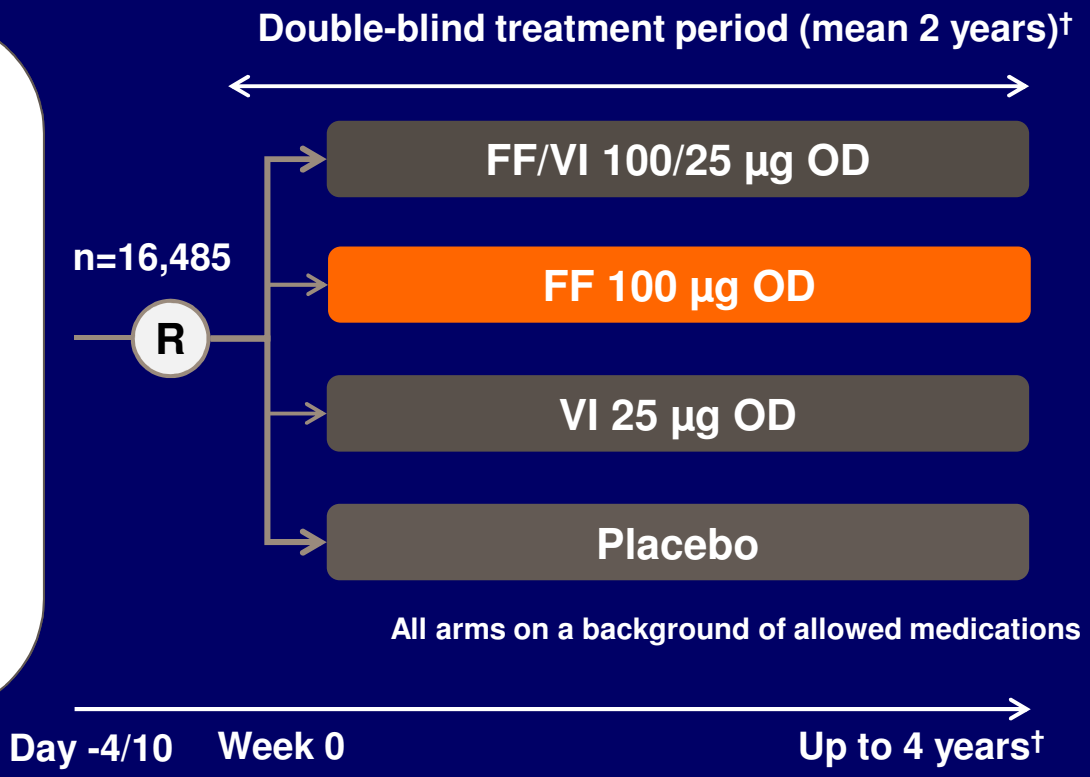
48% of COPD patients had CVD/CV risk as defined by the SUMMIT inclusion criteria in a prospective European study

In patients with COPD and CVD medical and total healthcare costs are 2.5 times higher when compared with the patients with COPD alone

THE STUDY TO UNDERSTAND MORTALITY AND MORBIDITY IN COPD (SUMMIT) STUDY

Participants

- 40–80 years
- COPD with moderate airflow limitation: FEV_1 ≥50–≤70% predicted normal
- FEV_1/FVC ≤0.70
- ≥10 pack-years smoking history
- History of CVD or at increased risk of CVD
- mMRC dyspnoea score ≥2



Vestbo J et al. Eur Respir J. 2012 Sep 27

Vestbo J et al, Press Conference 8 September 2015

THE STUDY TO UNDERSTAND MORTALITY AND MORBIDITY IN COPD (SUMMIT) STUDY PROTOCOL

MORTALITY AND SECONDARY ENDPOINTS

For the primary endpoint of the study, the risk of dying on FF/VI 100/25mcg was 12.2% lower than on placebo* over the study period, which was NOT statistically significant (p=0.137)

For the first of two secondary endpoints, FF/VI 100/25mcg reduced the rate of lung function decline (as measured by forced expiratory volume in one second, 'FEV*1*') by 8mL per year compared with placebo (p=0.019). As the primary endpoint was not met, statistical significance cannot be inferred from this result

For the other secondary endpoint, the risk of experiencing an on-treatment cardiovascular (CV) event (CV death, myocardial infarction, stroke, unstable angina and transient ischemic attack [TIA]) at any time was 7.4% lower in patients taking FF/VI 100/25mcg which was NOT statistically significant (p=0.475)

Vestbo J et al, Press Release 2015 Sep 8

CONCLUSIONS/OPEN QUESTIONS

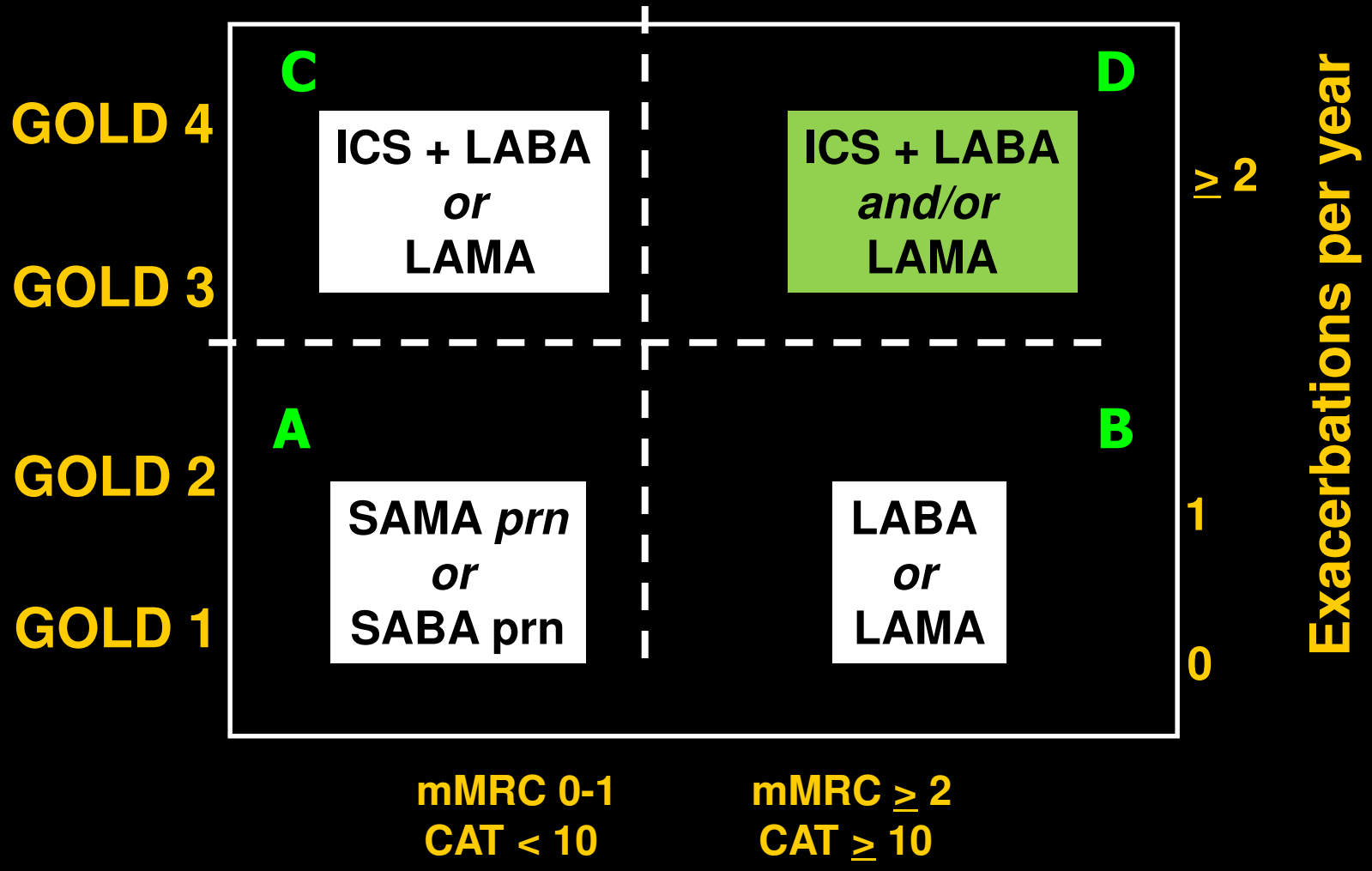
- Increased CV risk in COPD
- No effect of current treatment of COPD on mortality
- Importance of statistics on the primary outcomes
- Strength of evidence for primary (mortality) *vs* secondary outcomes (exacerbations, QoL, FEV)
- Relevance of adverse effects (pneumonia)
- Weight of evidence for guidelines

Calverley PMA et al, N Engl J Med. 356(8): 775-89
Vestbo J et al, Press Conference 8 September 2015

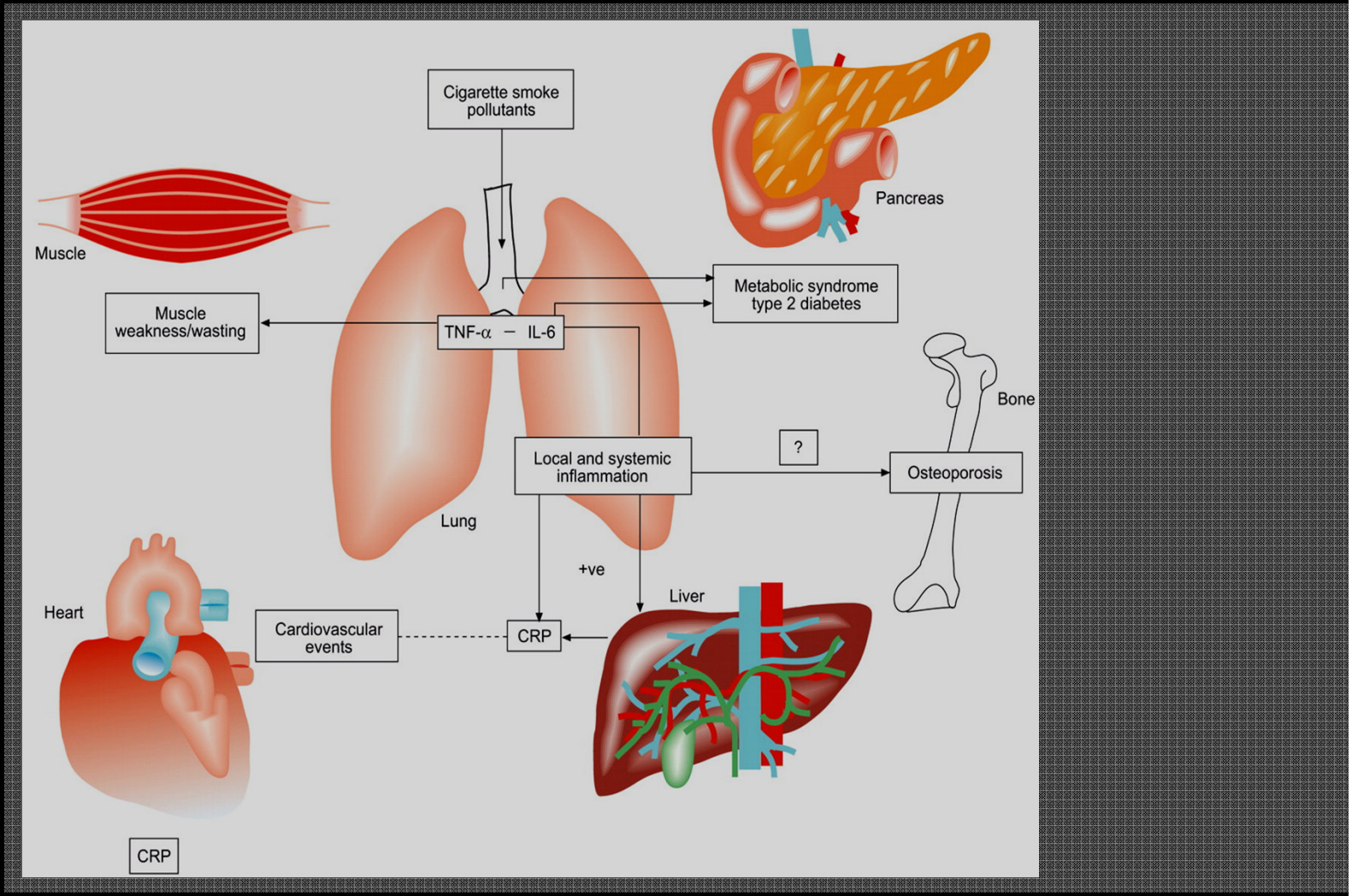
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

FIRST CHOICE

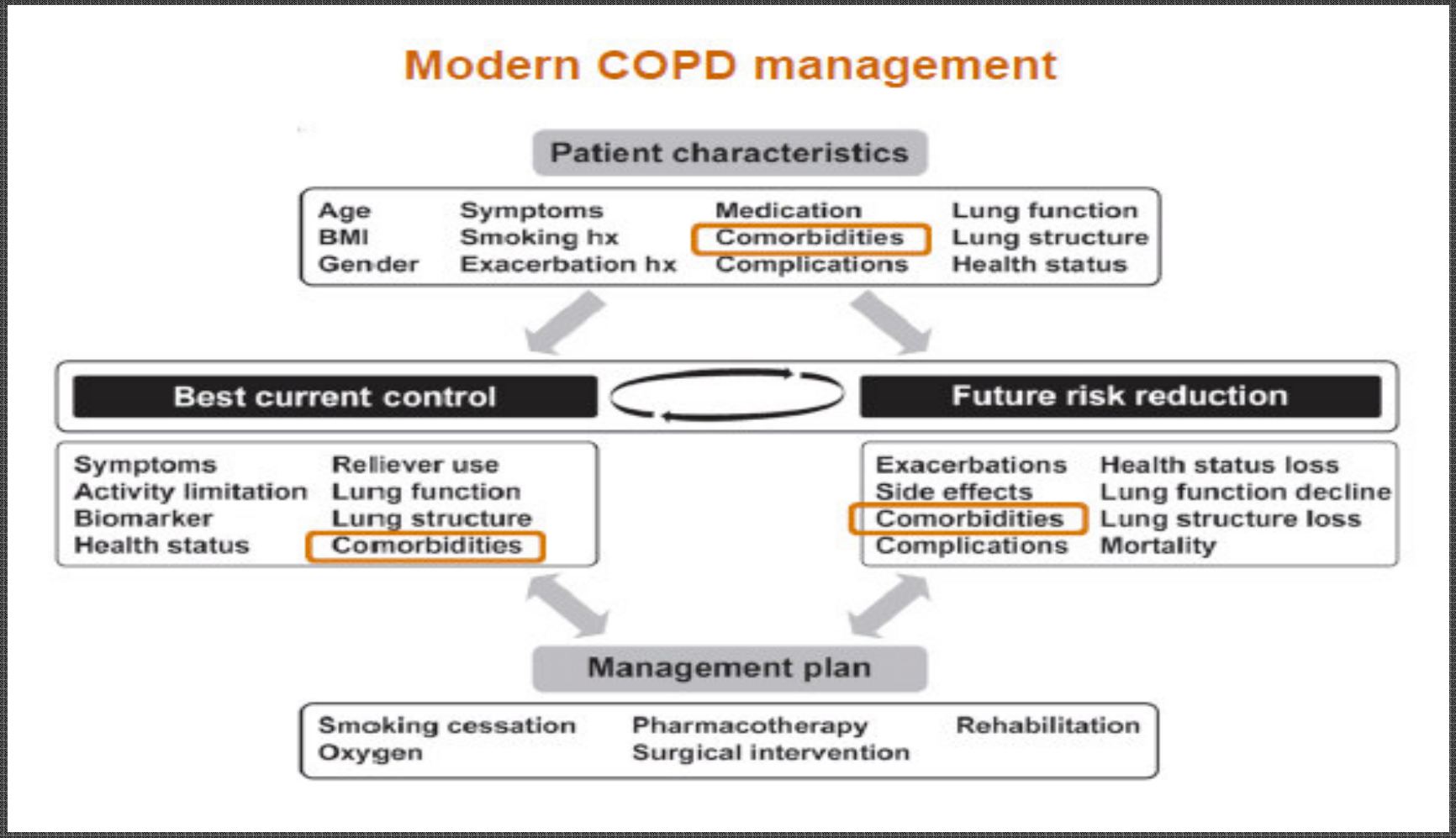


COMPLEX CHRONIC CO-MORBIDITIES OF COPD



Fabbri, Beghe, Luppi and Rabe, Eur Respir J 2008;31:204-212

GOAL OF COPD MANAGEMENT



Postma et al. Prim Care Respir J 2011

REDUCTION OF MORBIDITY AND MORTALITY BY STATINS, ACE INHIBITORS, AND ARBS IN PATIENTS WITH COPD

These agents may have dual cardiopulmonary protective properties, thereby substantially altering prognosis of patients with COPD

These findings need confirmation in randomized clinical trials

Mancini JB et al. J Am Coll Cardiol 2006;47(12):2554-60

STORIA DELLA MEDICINA ED ANTROPOLOGIA MEDICA
Policlinico di Modena 28 Ottobre 2015 1600-1700
Aula T01 Centro Didattico di Ateneo, Facoltà di Medicina e Chirurgia

BRONCOPNEUMOPATIA CRONICA OSTRUTTIVA (BPCO): da malattia broncopolmonare a componente broncopolmonare della multimorbidità cronica

Leonardo M. Fabbri, MD, FERS

Clinica di Malattie dell'Apparato Respiratorio
Università degli Studi di Modena e Reggio Emilia

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- **COPD and chronic heart diseases**
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- **Management of COPD and chronic multimorbidity**
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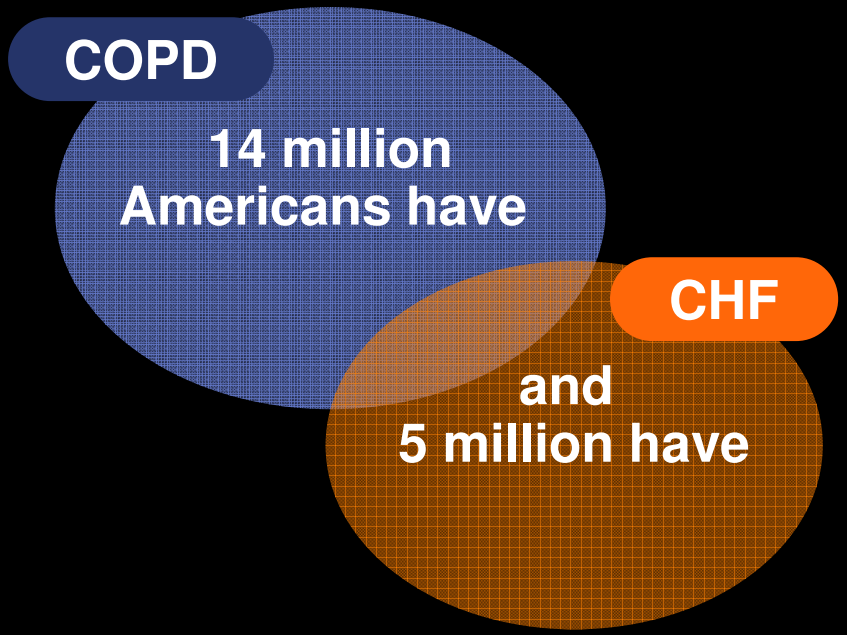
COPD PHENOTYPES AND PERSONALIZED TREATMENT

- COPD and Heart Failure
- Eosinophilic COPD/ACOS
- COPD-bronchectasis

COPD vs CHF

- Up to 1\5 of elderly pts. with COPD have CHF
- Up to 1\3 of elderly pts. with CHF have COPD



The risk ratio of developing HF in COPD pts is 4.5

The rate-adjusted hospital prevalence of CHF is 3 times greater among pts. discharged with a diagnosis of COPD compared with patients discharged without mention of COPD

Padeletti-LeJemtel et al. Int. J Cardiology, 2008

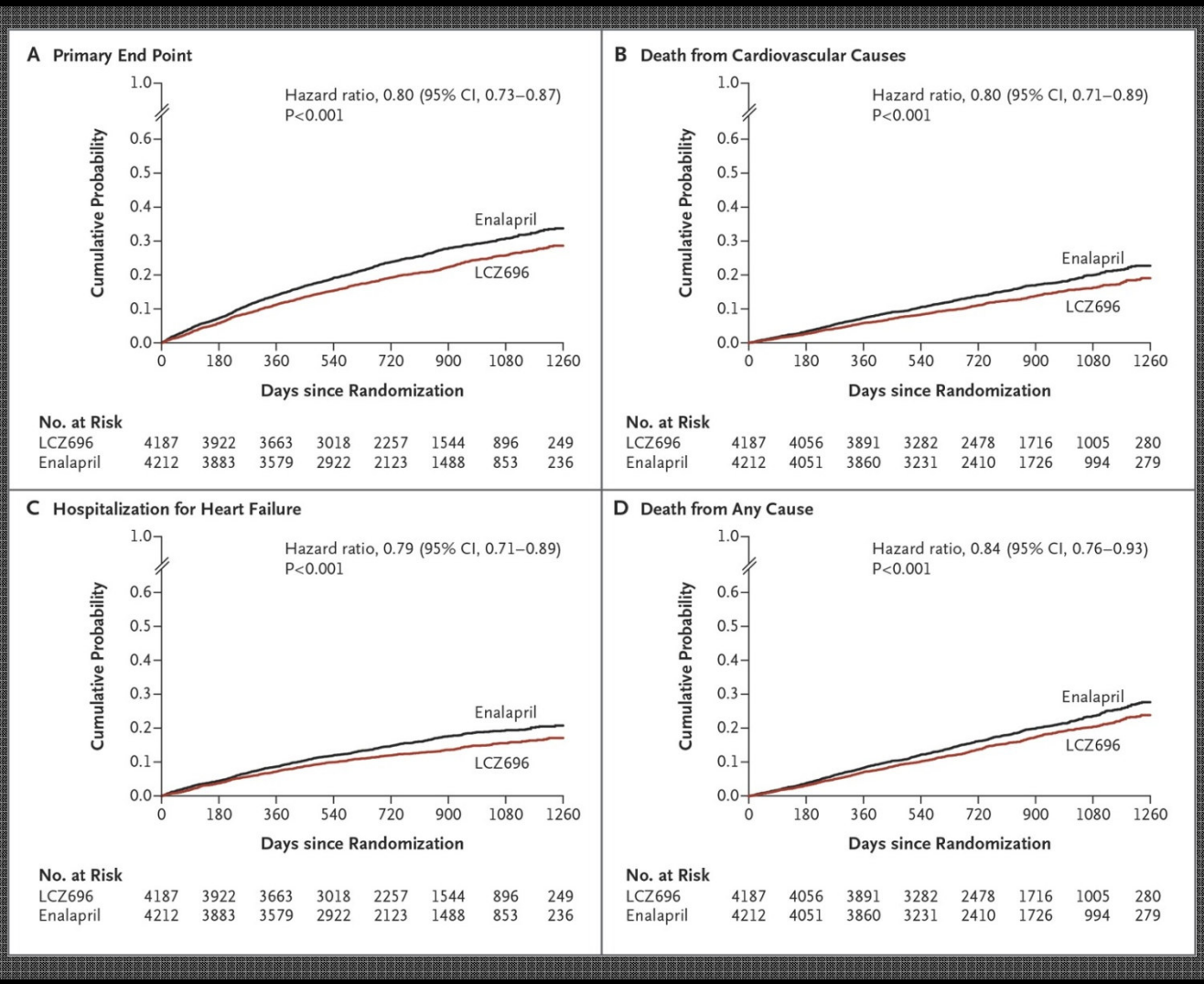
ANGIOTENSIN–NEPRILYSIN INHIBITION VERSUS ENALAPRIL IN HEART FAILURE

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction.

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure

McMurray JJV et al N Engl J Med 2014; 371(11):993-1004

ANGIOTENSIN–NEPRILYSIN INHIBITION VERSUS ENALAPRIL IN HEART FAILURE



McAllister et al. Eur Respir J 2012; 3:1097-103

HEART FAILURE: THE SEARCH FOR NEW TARGETS

NATRIURETIC PEPTIDES

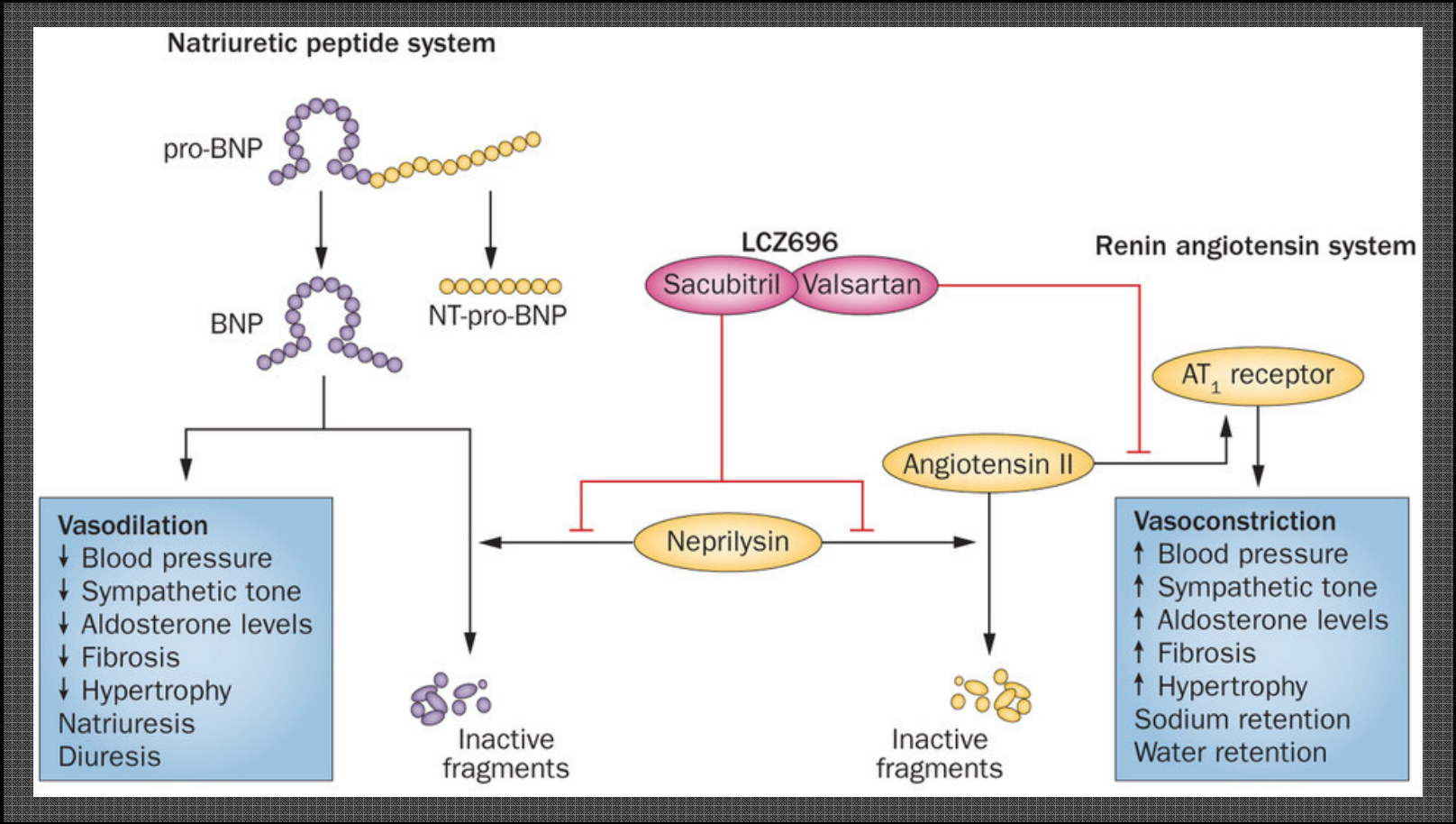
- promote vasodilatation and natriuresis
- inhibit abnormal growth, RAAS, vasopressin and the sympathetic nervous system
- degraded by neutral endopeptidase (NEP), eg neprilysin

BLOCKADE OF NATRIURETIC PEPTIDE BREAKDOWN

Novel therapeutic approach to increase natriuretic peptides

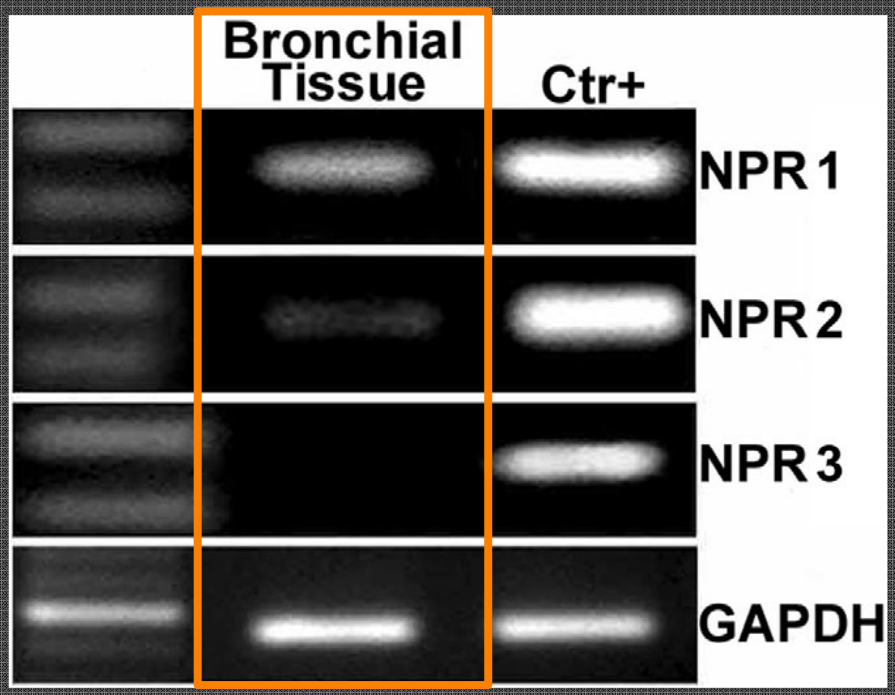
European Journal of Heart Failure (2013)15 , 1062–1073

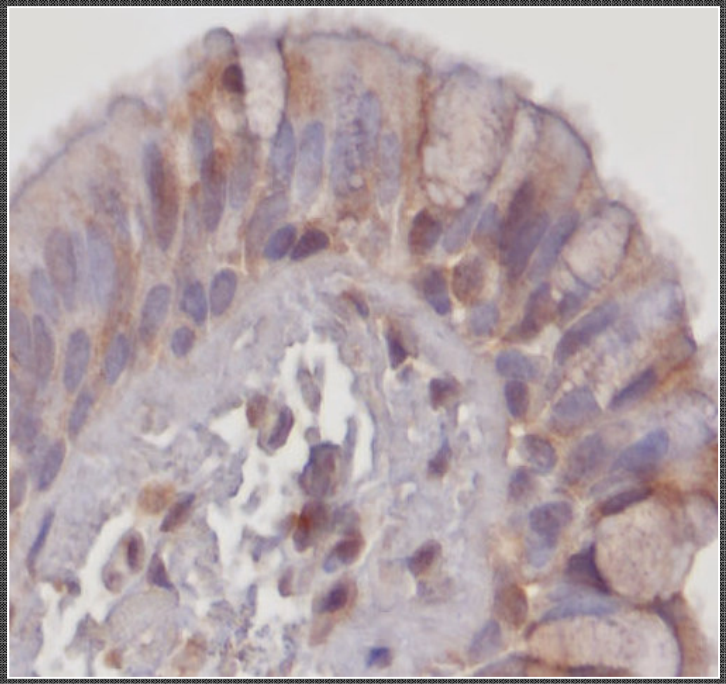
HEART FAILURE: THE BREAKING NEWS



Nature Reviews Cardiology 12, 73–75 (2015)

EXPRESSION OF BRAIN NETRIURETIC PEPTIDE RECEPTORS (NPRS) IN HUMAN AIRWAYS



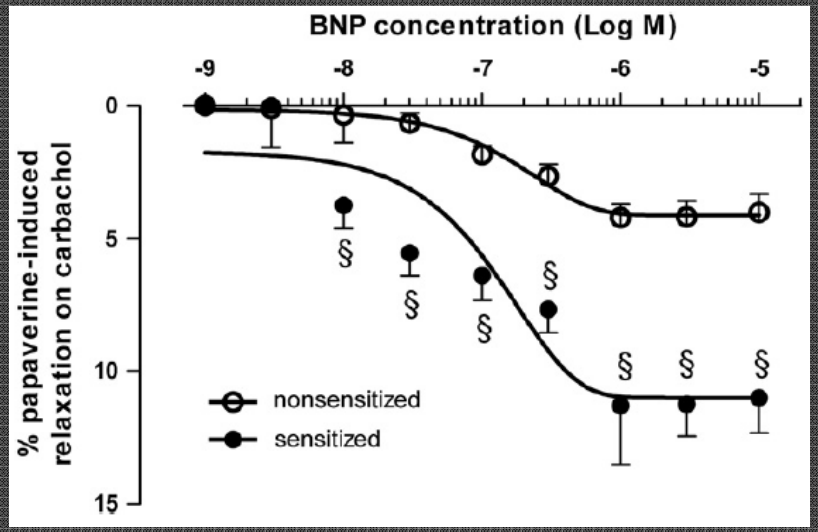


NPR-A is localized in the airway epitelium, not in the airway smooth muscle cells

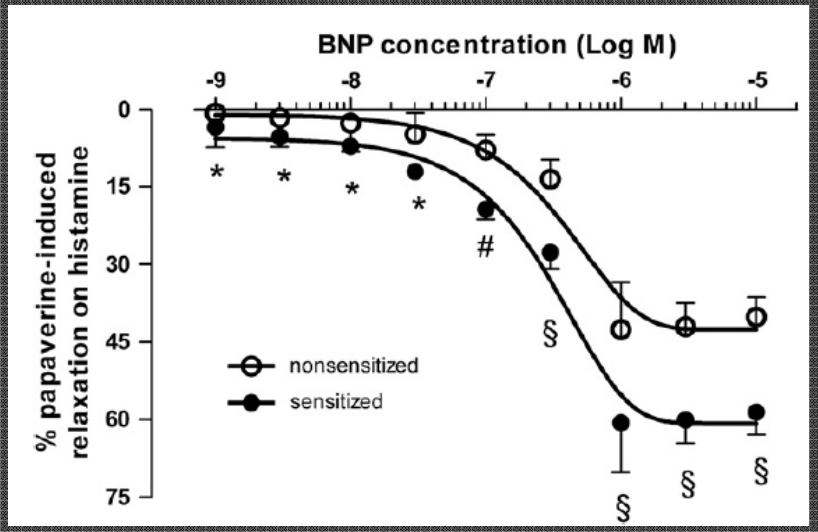
Matera et al, Br J Pharmacol 2011

HUMAN AIRWAY SMOOTH MUSCLE RELAXING EFFECT OF BRAIN NATRIURETIC PEPTIDE

Carbachol-induced contraction



Histamine-induced contraction



Matera et al, Pulm Pharmacol Ther 2009

Editorial

B-type Natriuretic Peptide – Not Only a Biomarker

Mario Cazzola[1,2] and Maria Gabriella Matera[3]

1. Chief, Unit of Respiratory Clinical Pharmacology, Department of Internal Medicine, University of Rome Tor Vergata; 2. Consultant, Department of Pulmonary Rehabilitation, San Raffaele Pisana Hospital, IRCCS; 3. Unit of Pharmacology, Department of Experimental Medicine, Second University of Naples

Increased levels of BNP may have beneficial effects not only in patients with chronic heart failure but also in patients with COPD

COPD PHENOTYPES AND PERSONALIZED TREATMENT

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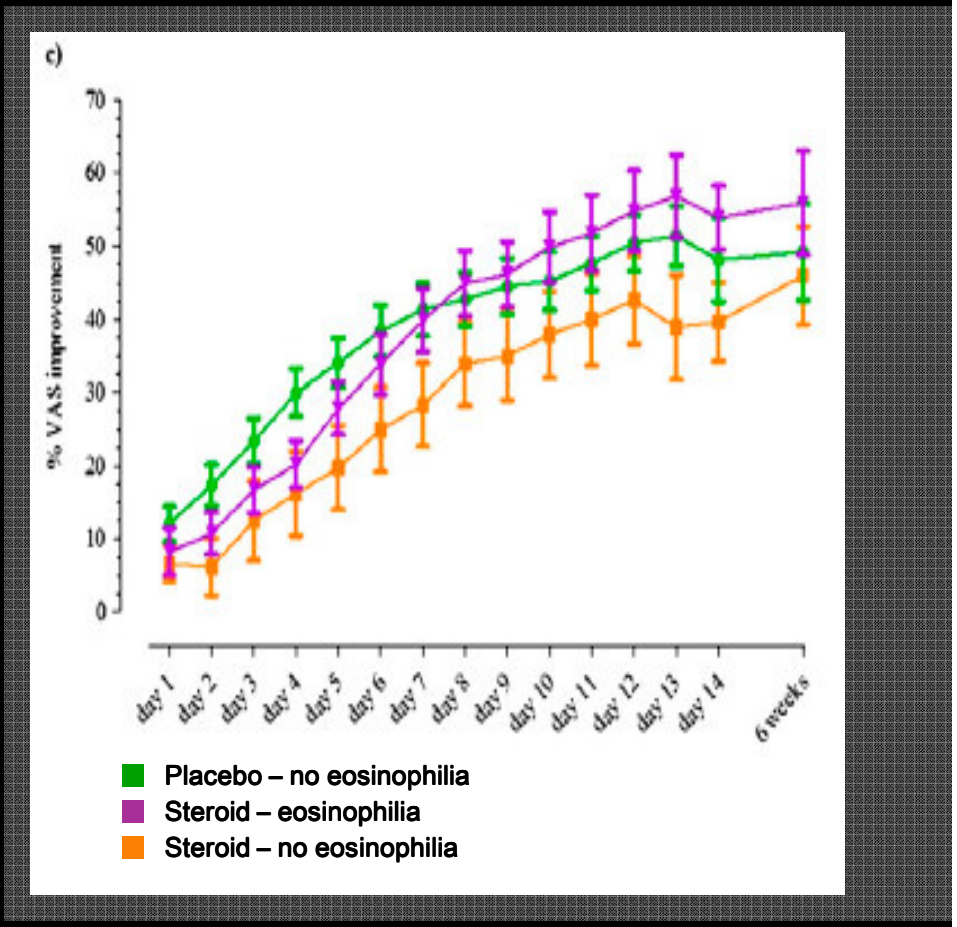
EOSINOPHILS TO DIRECT CORTICOSTEROID TREATMENT OF EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Corticosteroid therapy

> effective in COPD exacerbations associated with eosinophilia

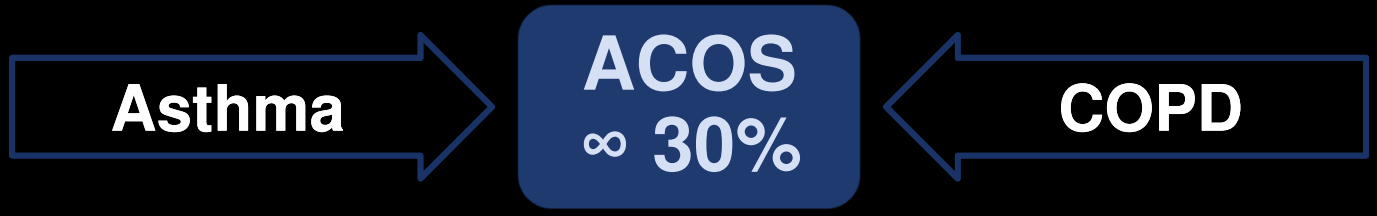
< effective in COPD exacerbations without eosinophilia



Brightling et al, Am J Respir Crit Care Med. 2012 ;86:48

ASTHMA-COPD OVERLAP SYNDROME (ACOS)

ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD

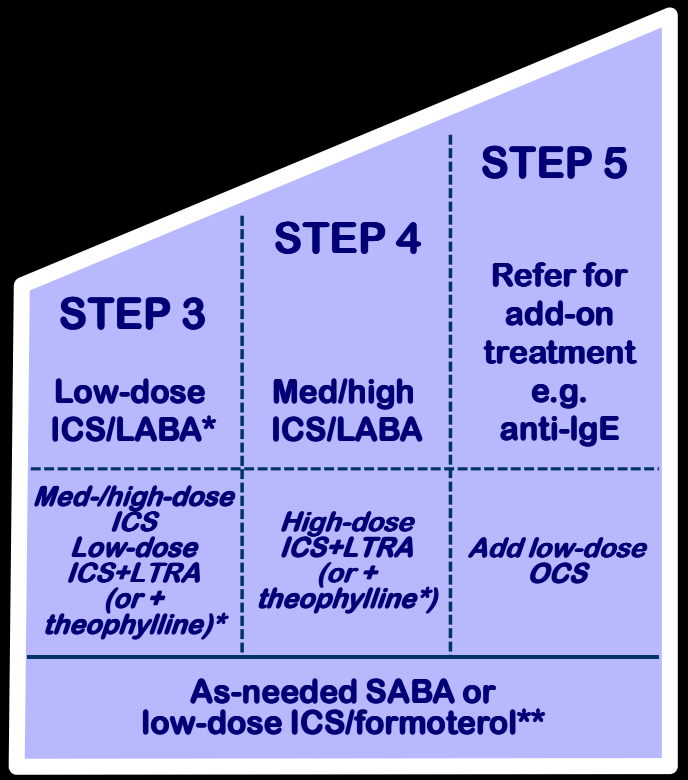


GINA STEP-WISE APPROACH TO PHARMACOLOGICAL TREATMENT (2015)

ACOS: Fulfills ATS/ERS Task Force definition for partially corticosteroid refractory asthma

Treat as for SEVERE ASTHMA

- **LAMA**
- **Roflumilast?**
- **Omalizumab (anti-IgE)**
- **Thermoplasty**
- **Mepolizumab/other new biologicals**



Available at http://www.ginasthma.org/local/uploads/files/GINA_Report_2014.pdf

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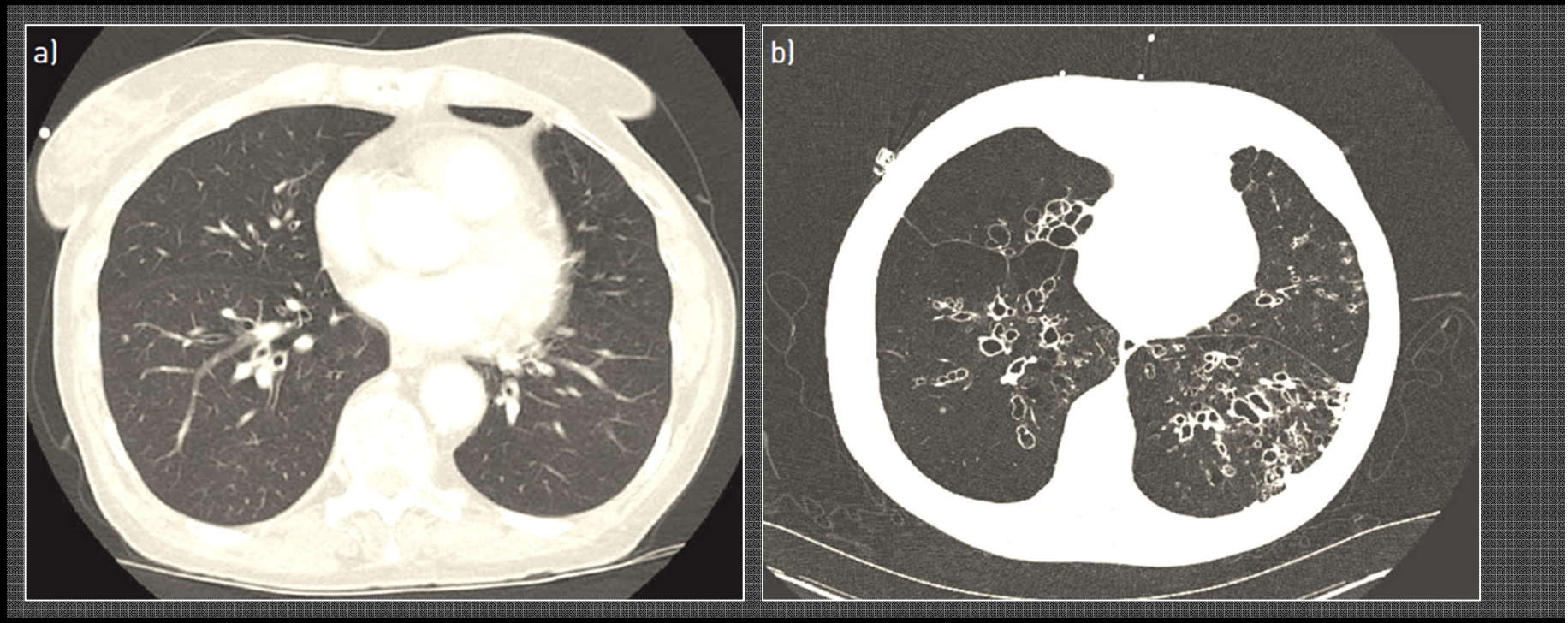
COPD–BRONCHIECTASIS OVERLAP SYNDROME



Hurst JR et al, Eur Respir J. 2015;45:310-3

LUNG FUNCTION, SYMPTOMS AND INFLAMMATION DURING EXACERBATIONS OF NON-CYSTIC FIBROSIS BRONCHIECTASIS

Exacerbations of non-CF bronchiectasis are inflammatory events, with worsened symptoms, lung function and health status, and a prolonged recovery period

Symptom diary cards, PEFR and CAT scores are responsive to changes at exacerbation and may be useful tools for their detection and monitoring

Brill SE et al, Respir Res. 2015 Feb 7;16(1):16

COPD–BRONCHIECTASIS OVERLAP SYNDROME
POSITION STATEMENT FROM THE BRONCH-UK CONSORTIUM

The overlap between chronic obstructive pulmonary disease (COPD) and bronchiectasis is a neglected area of research, and it is not covered by clinical guidelines

Recommendations based on expert consensus

Through discussion of COPD–bronchiectasis overlap, we also aim to promote research in the area, driving improvements in patient care

Hurst JR et al, Eur Respir J. 2015;45:310-3

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