Simposio SIGG – Torino

PATOLOGIE OSTRUTTIVE BRONCHIALI, MANAGEMENT E NUOVE OPZIONI TERAPEUTICHE

28 NOVEMBRE 2013

Comorbilità cardiovascolare ed impatto dei sintomi nel paziente anziano

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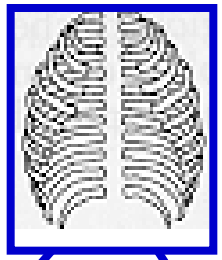
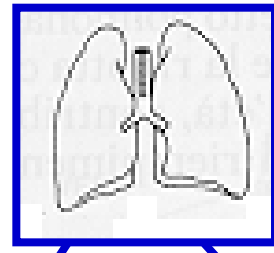
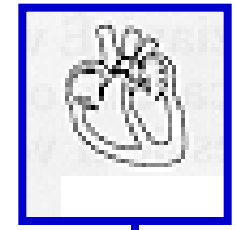
Istituto Scientifico di Telese Terme (BN) - Fondazione S. Maugeri. IRCCS

Il polmone senile







Riduzione della forza dei muscoli respiratori

Rigidità della gabbia toracica

V_E eccessiva rispetto allo sforzo

Riduzione del potere del ritorno elastico

Mal distribuzione di aria e sangue

Riduzione della portata cardiaca

Aumento del volume di chiusura

Diseguaglianza V_A - Q

Aumento del lavoro della reapirazione

Riduzzione dei flussi espiratori

Riduzione della disponibilità di O2

Ridotta tolleranza allo sforzo

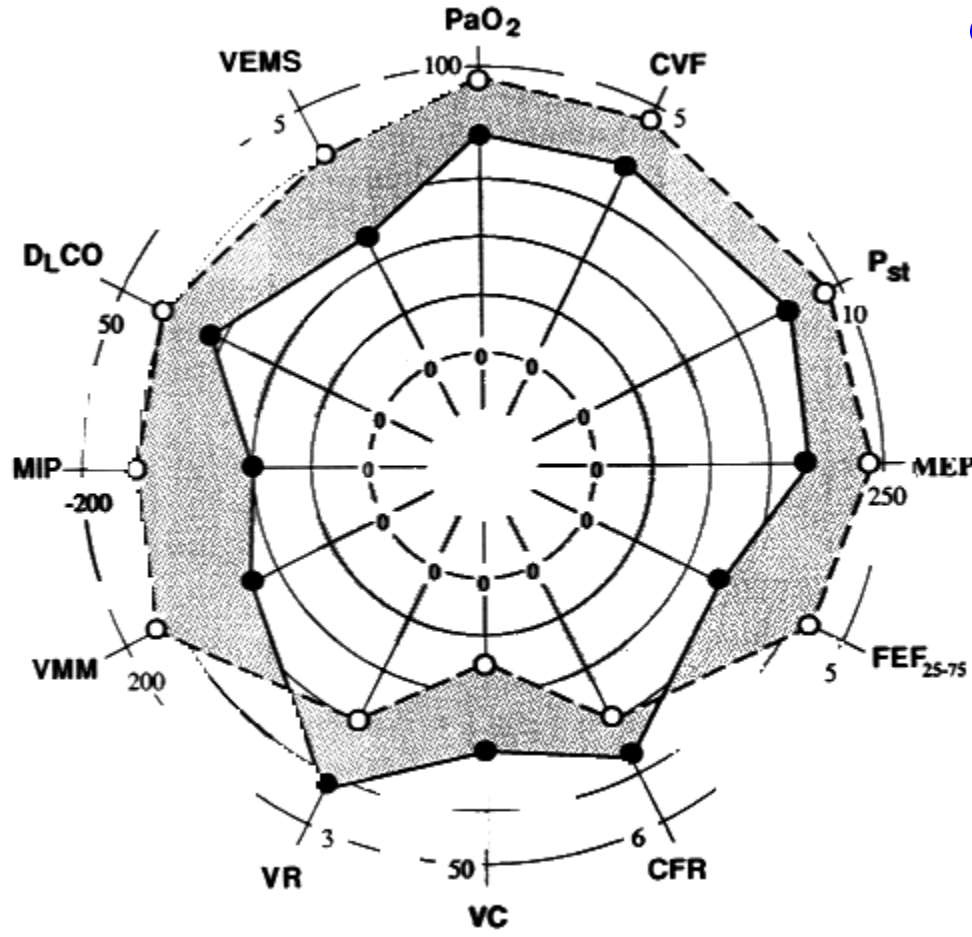
Vita sedentaria

Grassi V In: Aging lung: dalla fisiologia alla clinica. Scientific press 1997

Functional profile of aging lung

○ = adults (20-30 years)

● = elderly (70-80 years)



Grassi V In: Aging lung: dalla fisiologia alla clinica. Scientific press 1997

Cardiovascular *structural* modifications

Age-related changes	Plausible mechanisms	Implications to human desease
↑ Vascular intimal thickness	↑ Matrix production	Atherosclerosis
↑ Vascular stiffness	↑ Elastase activity ↑ Collagen production	Systolic hypertension Stroke, Atherosclerosis
↑ LV wall thickness	↑ myocyte volume ↓ Myocyte number (necrosis, apoptosis)	Ritarded early diastolic Cardiac filling Diastolic heart failure
↑ Left atrial size	↑ Left atrial pressure/volume	↑ Prevalence of lone atrial fibrillation

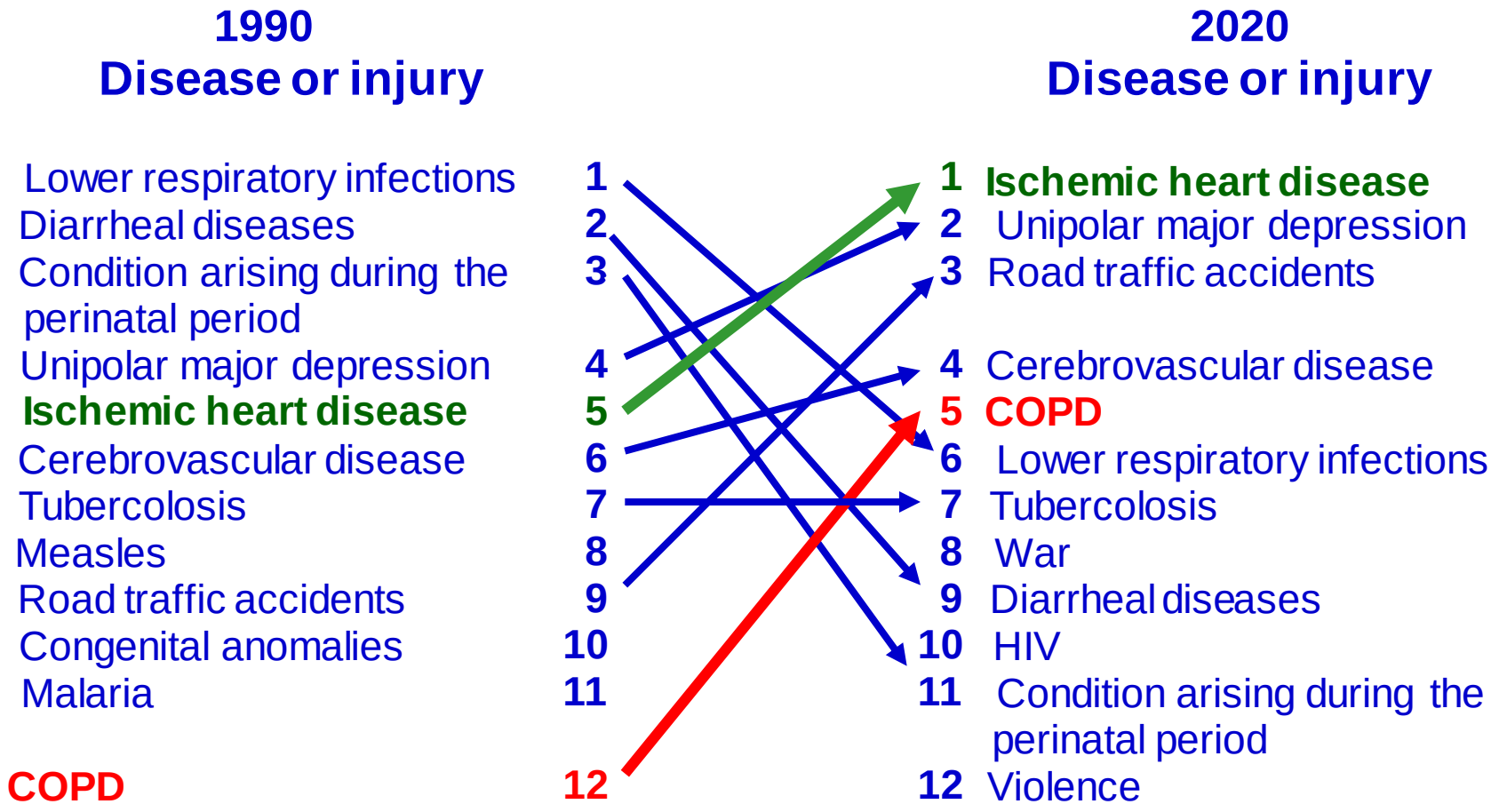
Ferrara N et al, Aging 1997

Cardiovascular *functional* modifications

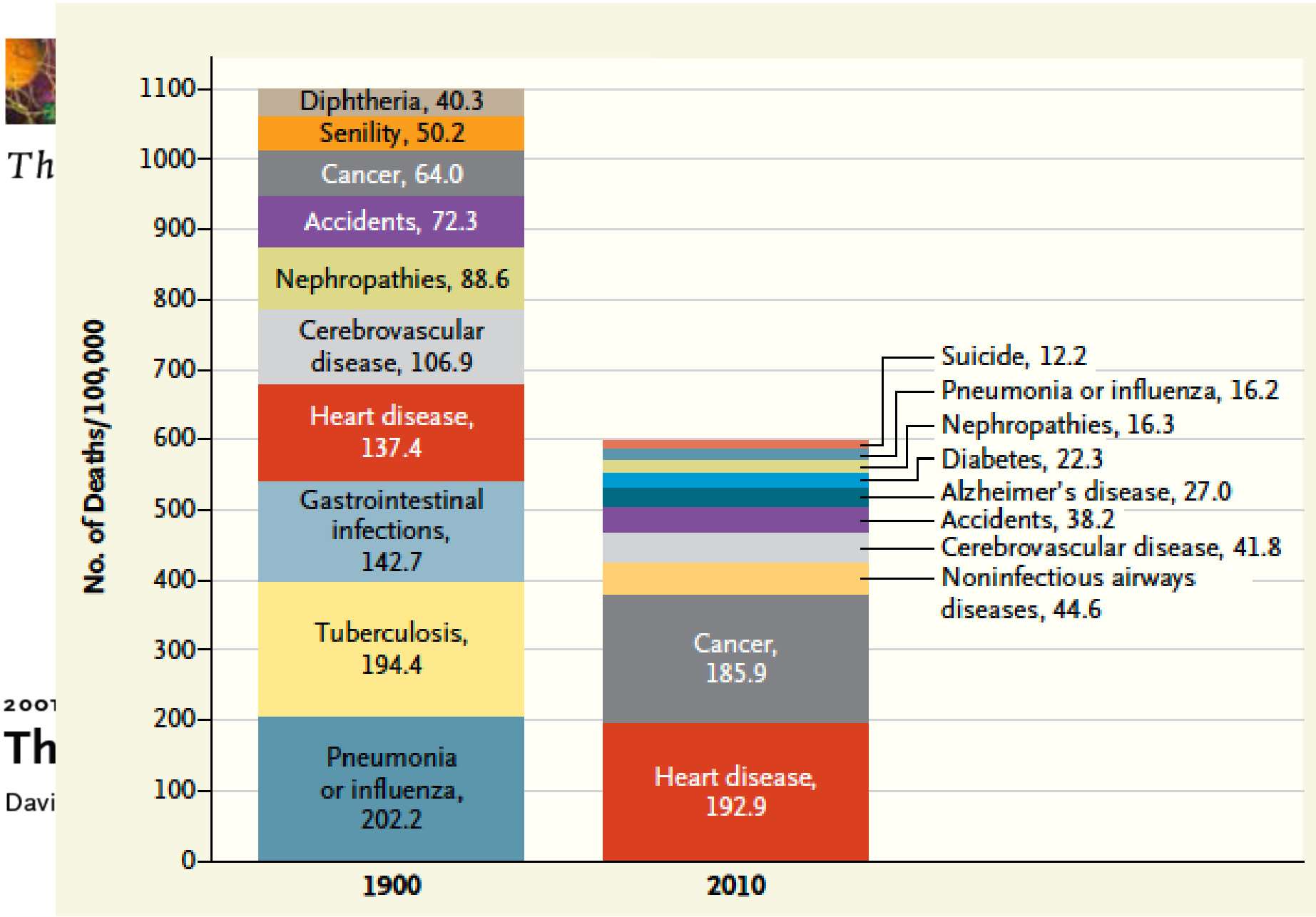
Age-related Changes	Plausible mechanisms	Implications to human desease
Altered regulation of vascular tone	NO production/effects	Vascular stiffness, hypertension Early atherosclerosis
↓ Threshold Ca^{2+}	Changes in gene expression of protein that regulate Ca^{2+} handling	Lowered threshold for atrial and for overload ventricular arrhytmias, reduced diastolic and systolic function
↓ Cardiovascular reserve	↑ Vascular load ↓ Myocardial contractility ↑ Plasma levels of catecholamines ↓ of β–adrenergic modulation	
↓ Physical activity	Learned lifestile	Negative impact on atherosclerotic vascular desease, hypertension and heart failure

Ferrara N et al, Aging 1997

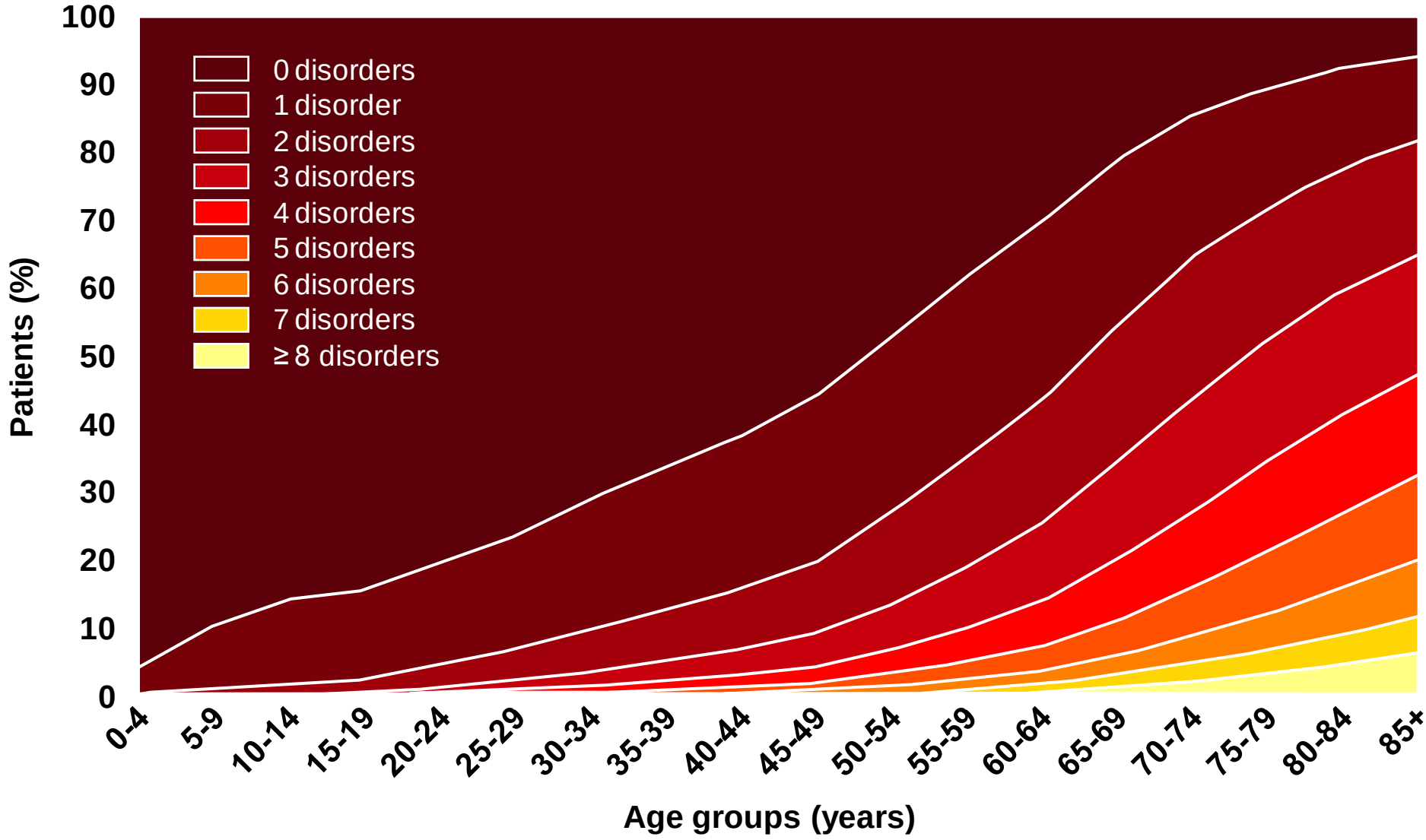
The global burden of disease



Lopez AD & Murray CJL Nature Medicine 1998

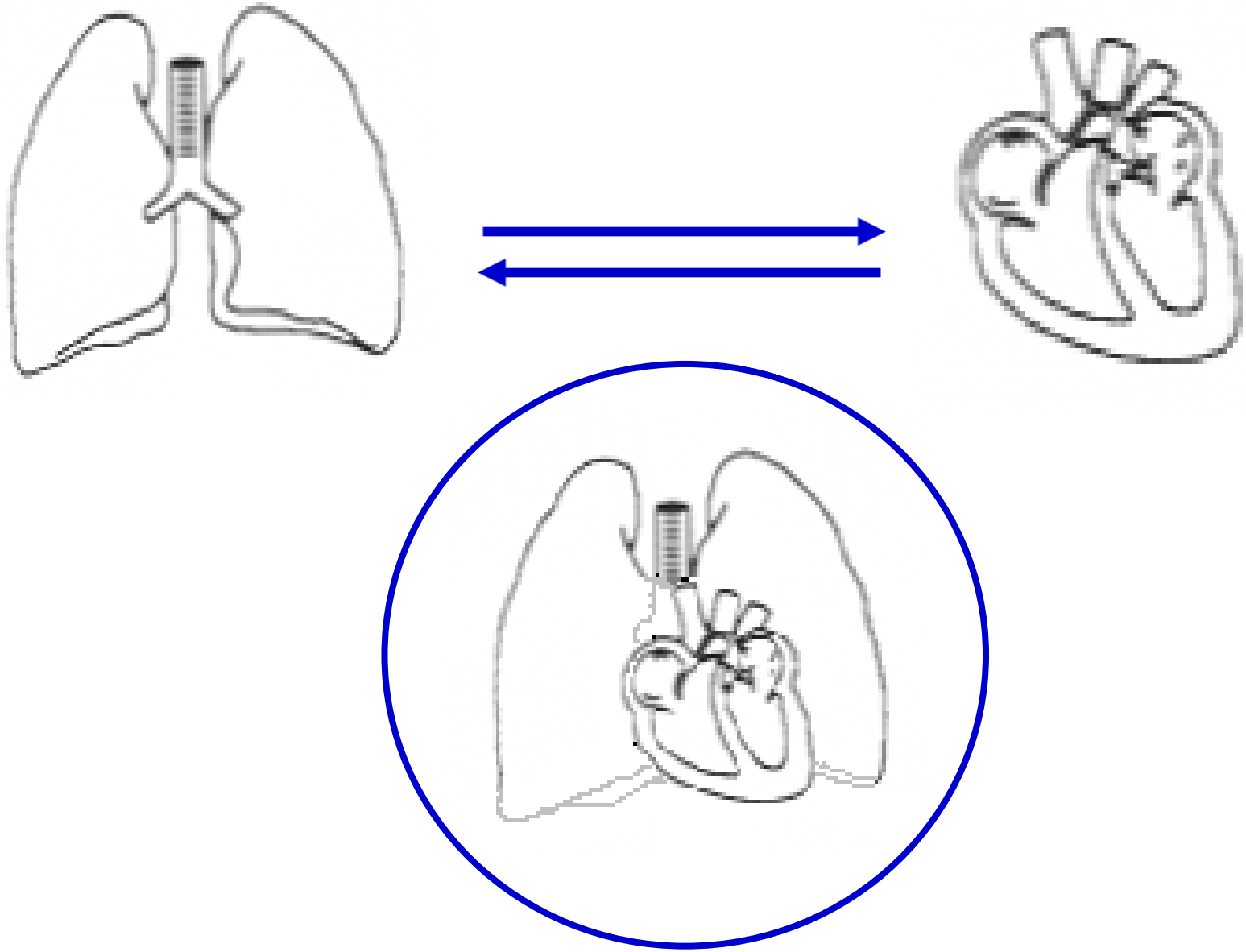

No. of Deaths/100,000
1100
1000
900
800
700
600
500
400
300
200
100
0
Diphtheria, 40.3
Senility, 50.2
Cancer, 64.0
Accidents, 72.3
Nephropathies, 88.6
Cerebrovascular disease, 106.9
Heart disease, 137.4
Gastrointestinal infections, 142.7
Tuberculosis, 194.4
Pneumonia or influenza, 202.2
Cancer, 185.9
Heart disease, 192.9
Suicide, 12.2
Pneumonia or influenza, 16.2
Nephropathies, 16.3
Diabetes, 22.3
Alzheimer's disease, 27.0
Accidents, 38.2
Cerebrovascular disease, 41.8
Noninfectious airways diseases, 44.6
1900
2010

No. di disturbi cronici per classi di età



Barnett K et al. Lancet 2012;380(9836):37-43

BPCO e patologie cardiovascolari



Aging Clinical and Experimental Research

Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease

Gianluigi Galizia[1,6], Francesco Cacciatore[2], Gianluca Testa[1,3], David Della-Morte[1,4], Francesca Mazzella[1,2], Assunta Langellotto[1], Carolina Raucci[1], Gaetano Gargiulo[1], Nicola Ferrara[2,5], Franco Rengo[1,2] and Pasquale Abete[1]

Cacciatore et al Aging Clin Exp Res 2011; 23: 118-1252

Baseline characteristics of 1288 subjects stratified for presence or absence of COPD

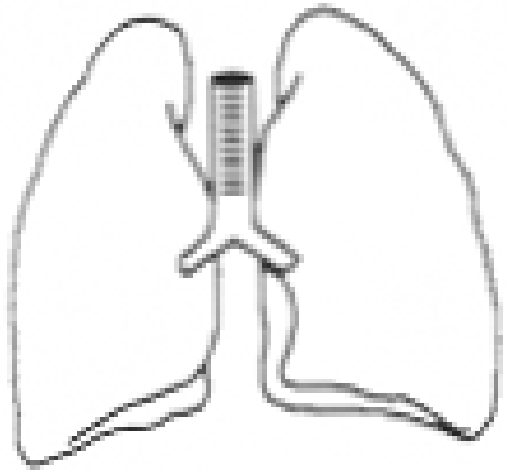
Variables	All (n=1288)	COPD		p
		No (n=799; 62%)	Yes (n=489; 38%)	
Age (yrs)	74.2±6.3	73.7±6.3	74.9±6.3	<0.001
Sex (female, %)	57.0	64.2	45.2	<0.001
BMI (Kg/m^2)	26.5±4.9	26.4±4.6	26.6±5.2	0.55
Current smoking (%)	16.9	13.6	22.3	<0.001
Former smoking (%)	19.8	16.0	26.0	<0.001
Heart rate (bpm)	75.3±10.2	74.8±10.2	76.2±10.1	<0.001
Systolic BP (mmHg)	145.65±19.3	145.9±19.3	145.1±19.2	0.49
Diastolic BP (mmHg)	82.3±9.4	82.1±9.3	82.6±9.5	0.33
Pulse BP (mmHg)	63.3±16.1	63.8±16.3	62.4±15.4	0.57
Effort dyspnea (%)	17.4	8.6	31.8	<0.001
Charlson comorbidity index	1.6±1.6	1.0±1.3	2.6±1.7	<0.001
Drug number	2.2±2.0	1.9±1.8	2.8±2.2	<0.01
Beta-agonist (%)	6.4	0.5	16.0	<0.001
Steroids (%)	2.7	1.6	4.5	<0.001
MMSE	25.3±4.8	25.4±4.73	25.3±4.9	0.67
GDS	11.4±6.6	10.7±6.6	12.5	<0.001
BADL (≥1%)	6.8	5.7	8.6	<0.001
Social support (score)	13.1±2.7	13.5±2.8	12.9±2.6	0.54
Frailty subjects (n, %)	533 (41.3)	294 (36.8)	239 (48.9)	0.062
Frailty impaired domains (n, means±SD)	2.0±1.2	1.91±1.2	2.1±1.3	0.049

BMI: body mass index; BP: blood pressure; MMSE: Mini Mental State Examination (range 0-30); GDS: Geriatric Depression Scale (range 0-15); BADL: Basic Activity of Daily Living. Social support (score 0-17, highest score indicating lowest social support).

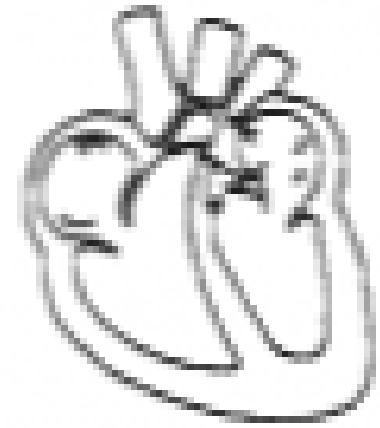
Thrive Kurtis

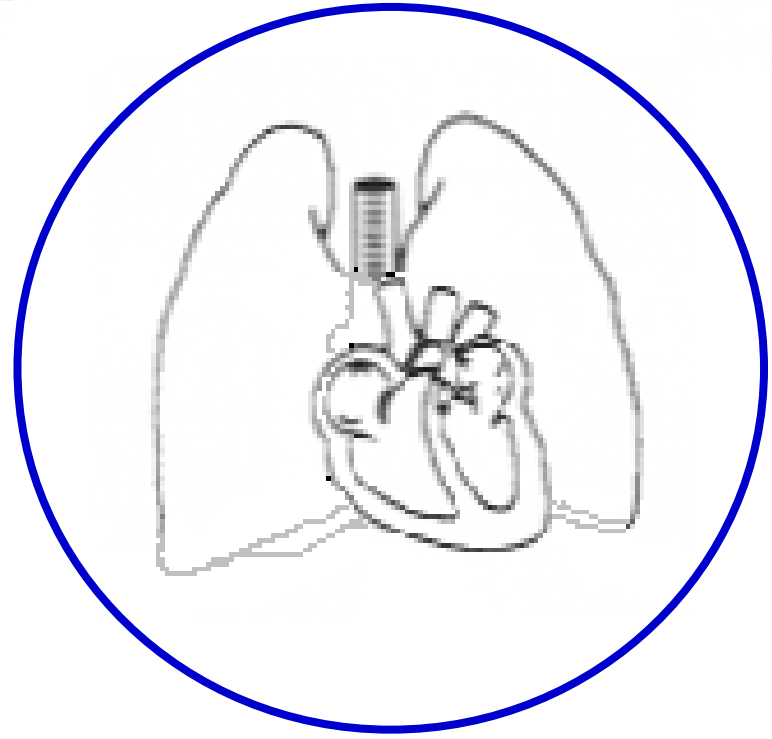
Cacciatore et al Aging Clin Exp Res 2011; 23: 118-125

BPCO e patologie cardiovascolari

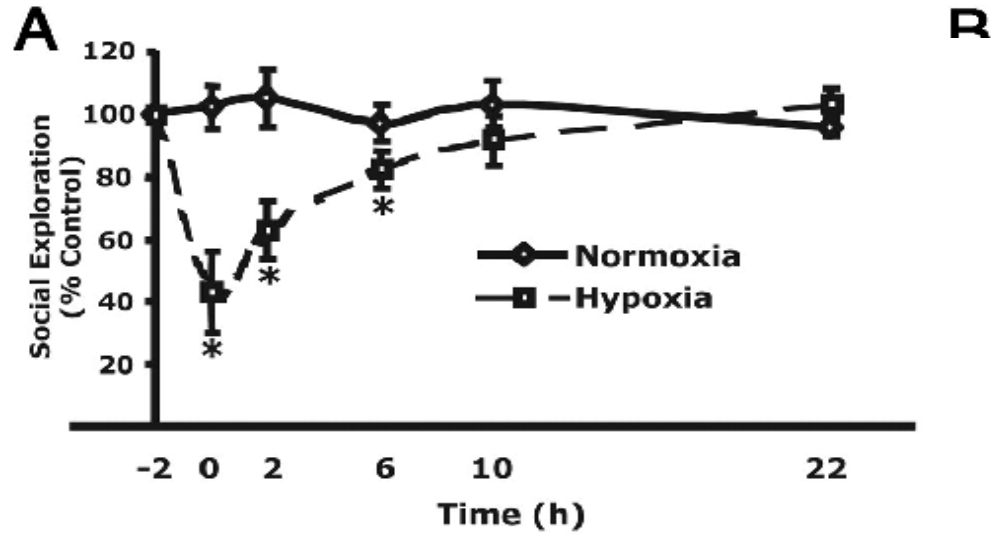


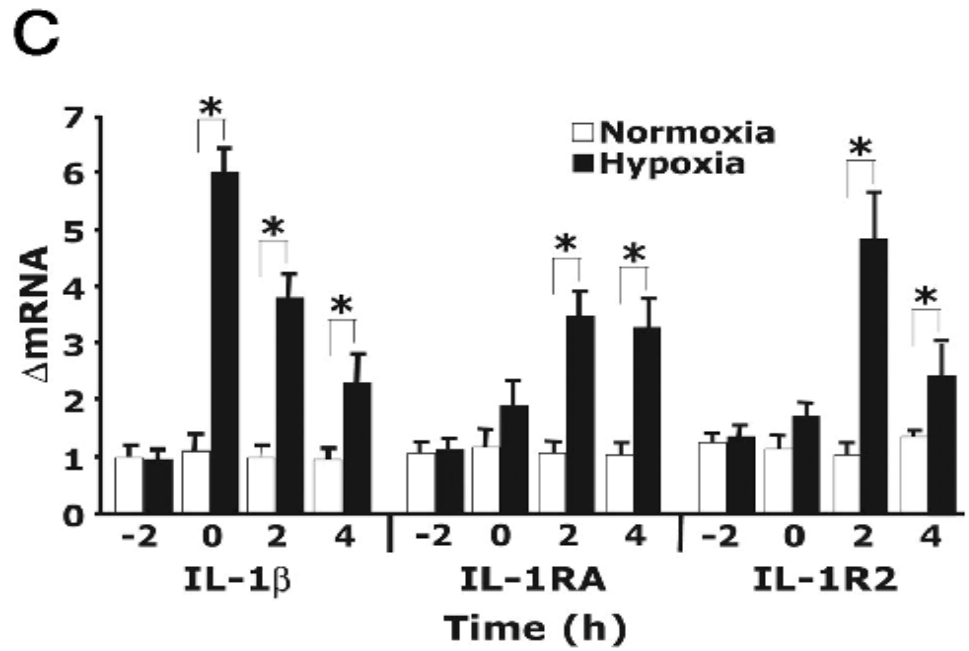
Infiammazione





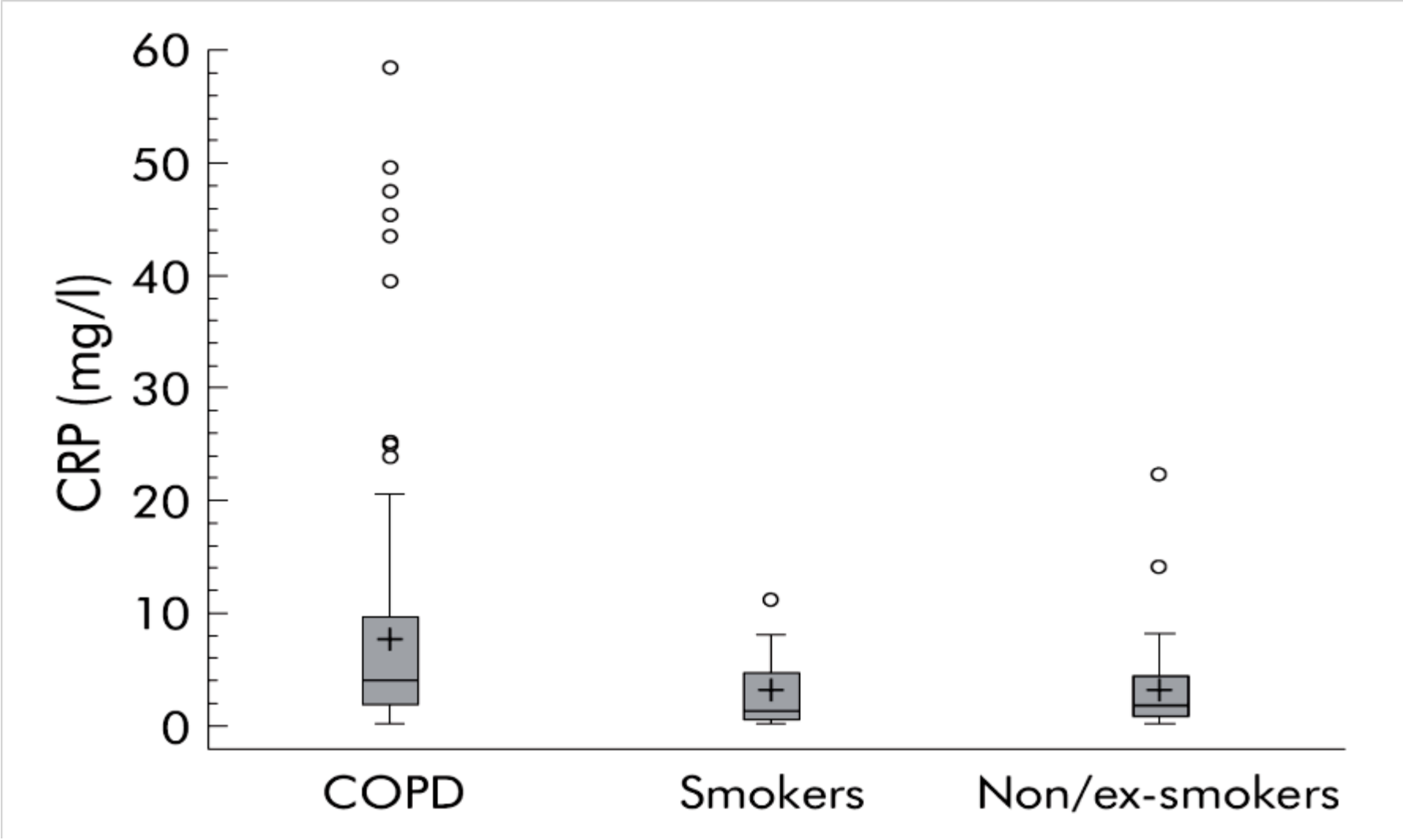
Hypoxemia: mouse model





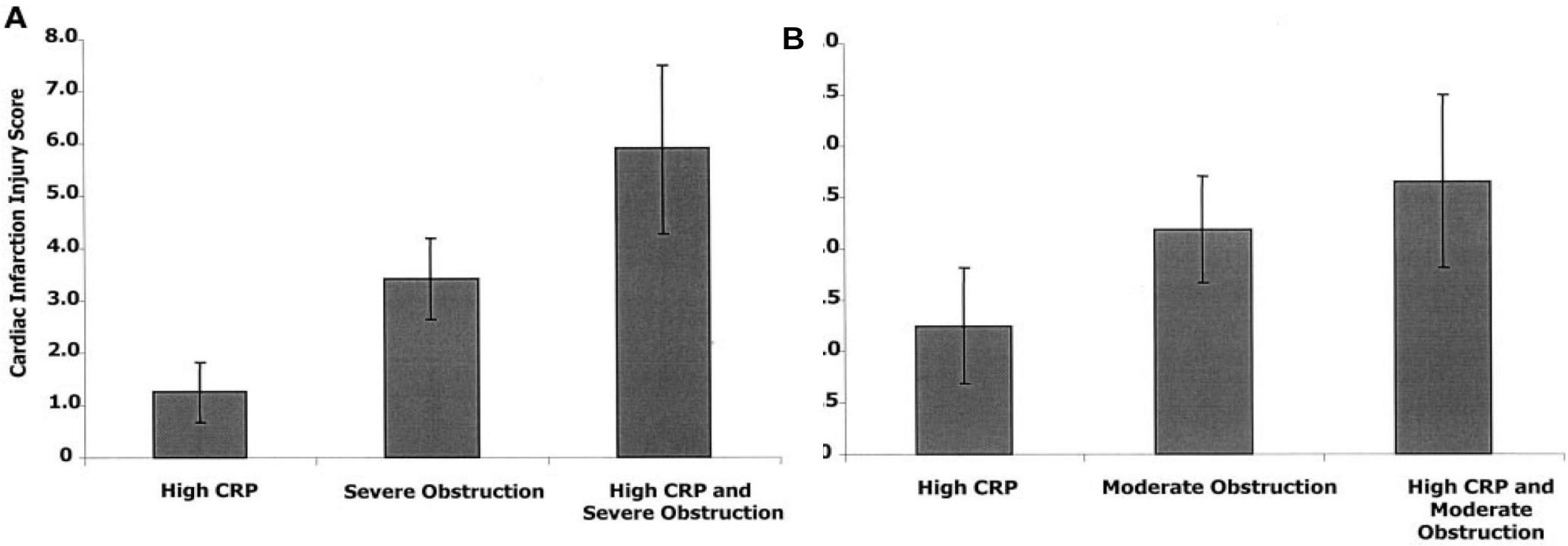
Johnson et al, Journal of Neuroscience 2007

C-reactive protein (CRP) value distribution in COPD patients, control smokers and control non-smokers.



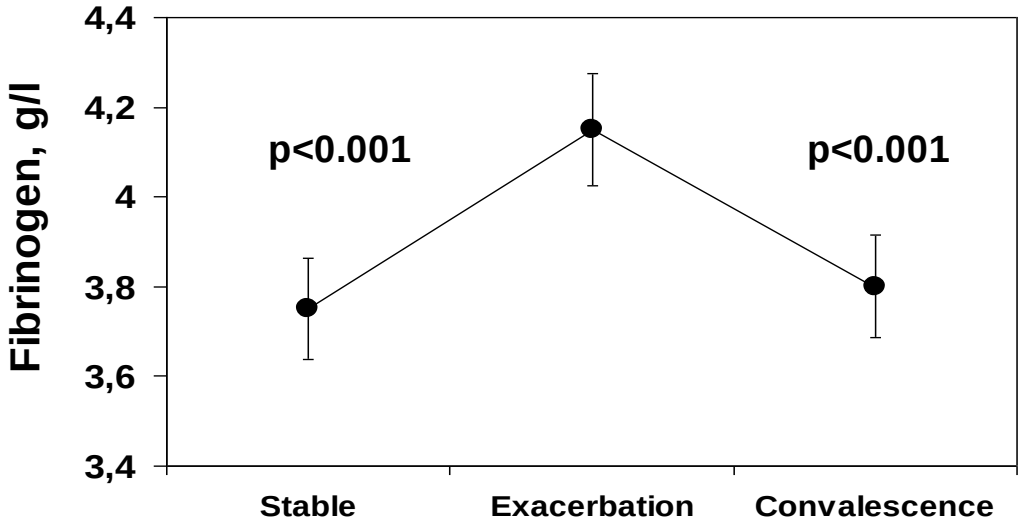
Pinto-Plata VM et al, Thorax 2006

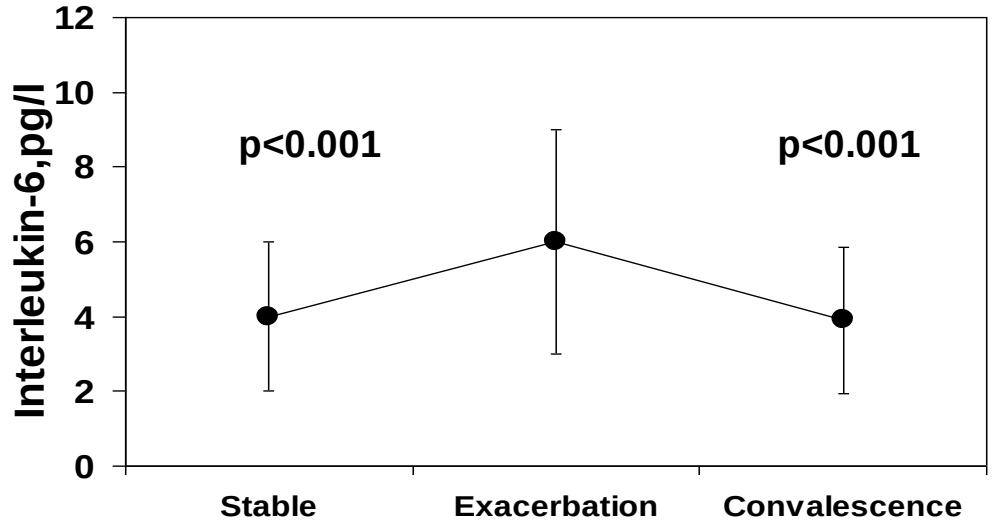
Relationship of CRP and severe (A) and moderate (B) airflow obstruction to cardiac infarction injury score



Sin DD et al, Circulation 2003

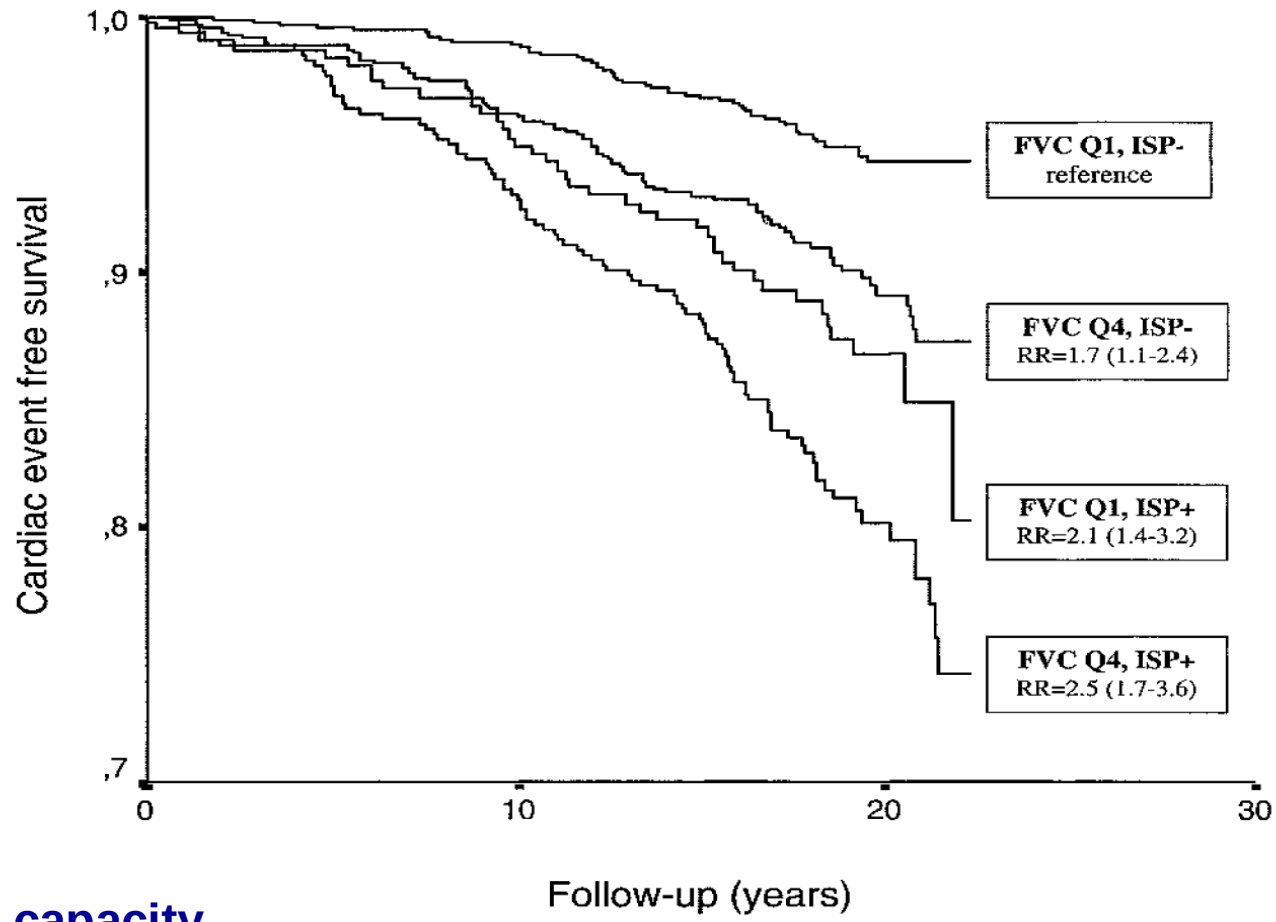
Plasma fibrinogen and interleukin-6 (IL-6) in patients with COPD





Wedzicha JA et al, Thromb Haemost 2000

Cardiac event rates among men stratified in quartiles of forced vital capacity and inflammation proteins



FVC = forced vital capacity

ISP = inflammation-sensitive plasma proteins

Engstrom G et al, Circulation 2002

Int. J. Mol. Sci. **2013**, *14*, 12696-12713; doi:10.3390/ijms140612696

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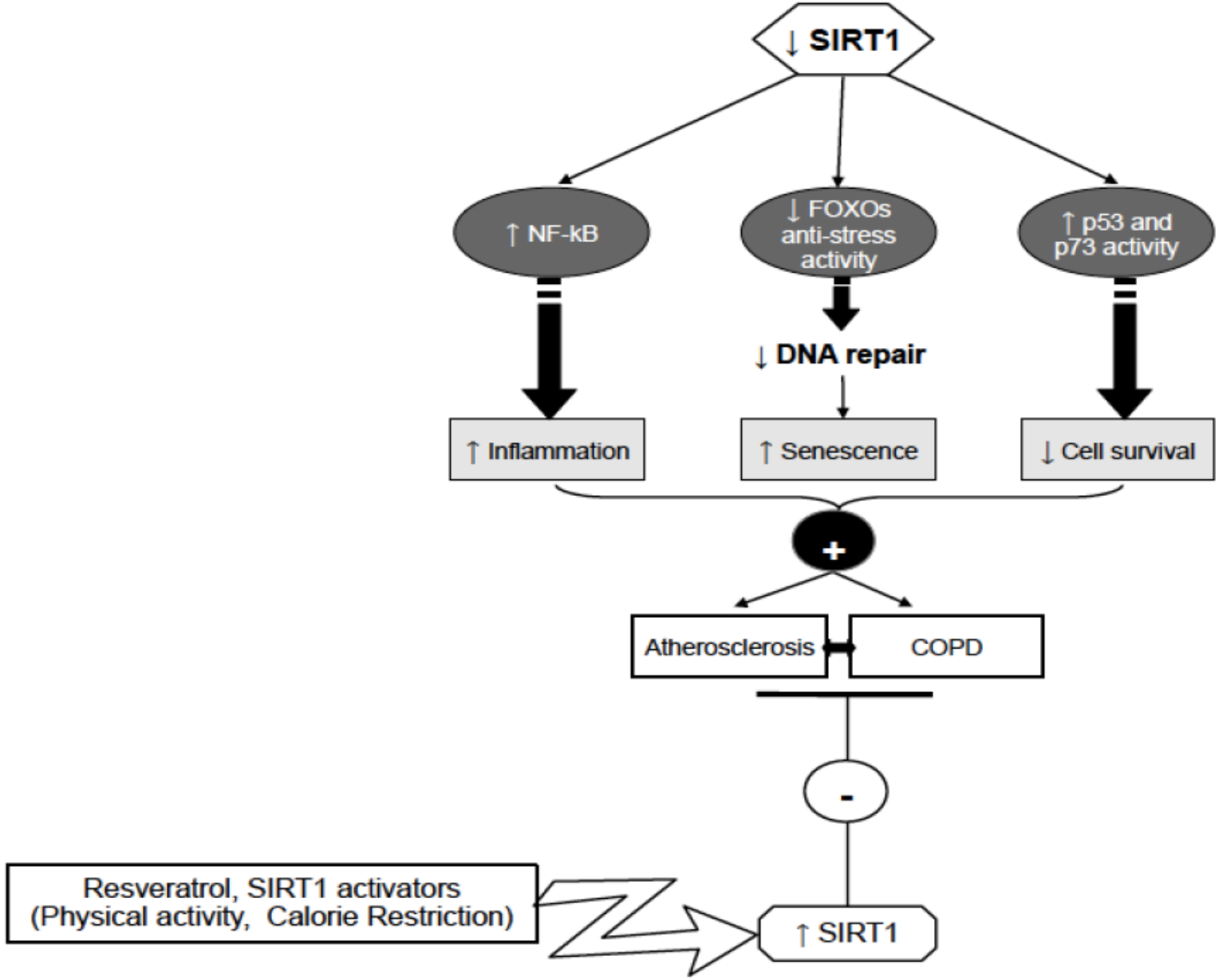
Review

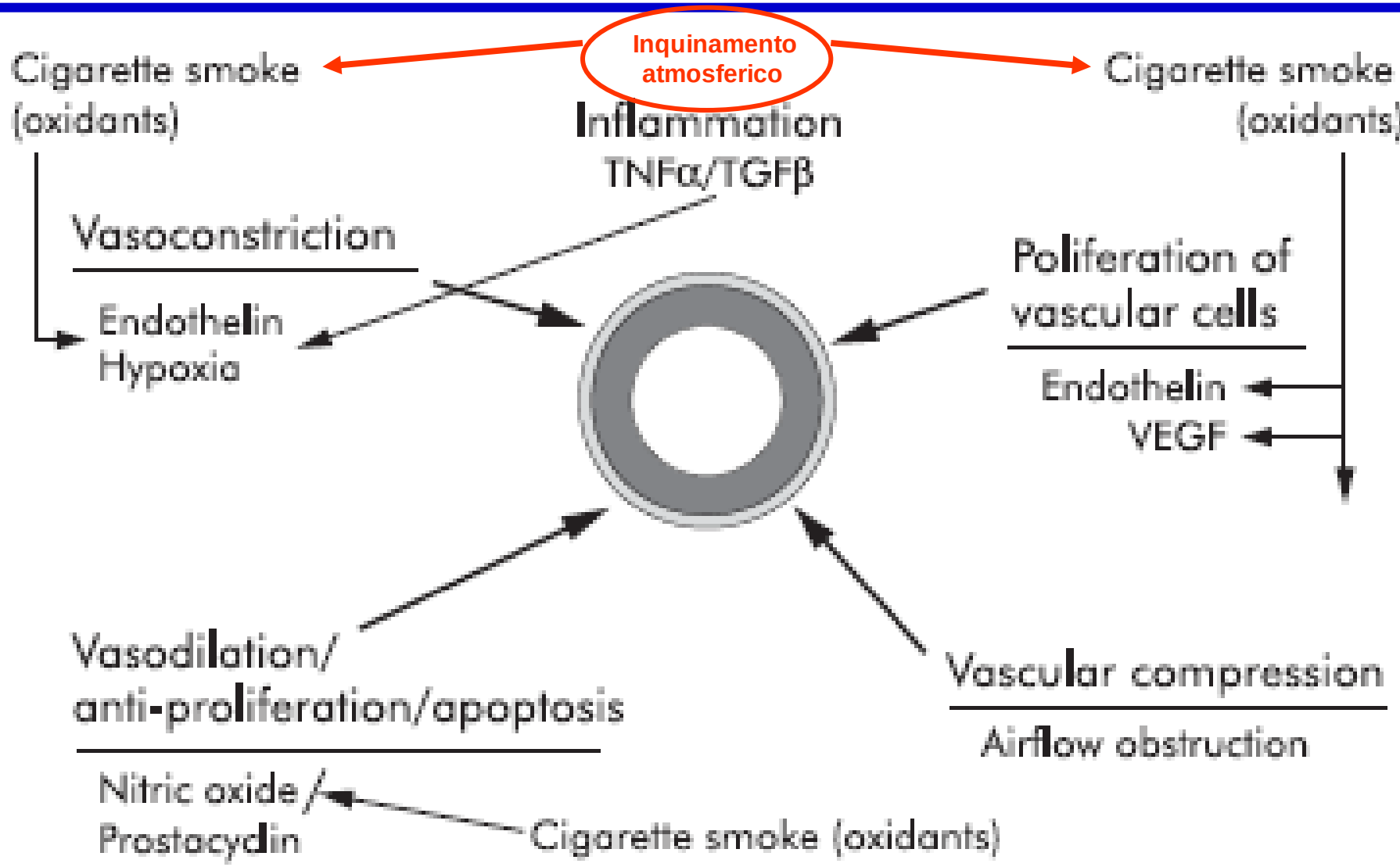
Potential Mechanisms Linking Atherosclerosis and Increased Cardiovascular Risk in COPD: Focus On Sirtuins

Graziamaria Corbi [1,†], Andrea Bianco [1,†], Viviana Turchiarelli [1,*], Michele Cellurale [1], Federica Fatica [1], Aurora Daniele [2,3], Gennaro Mazzarella [4] and Nicola Ferrara [5,6]



Corbi et al Int. J. Mol. Sci. 2013, 14, 12696-12713

Patogenesi della ipertensione arteriosa nella BPCO



Wright JL et al, Thorax 2005

BPCO e cuore polmonare cronico

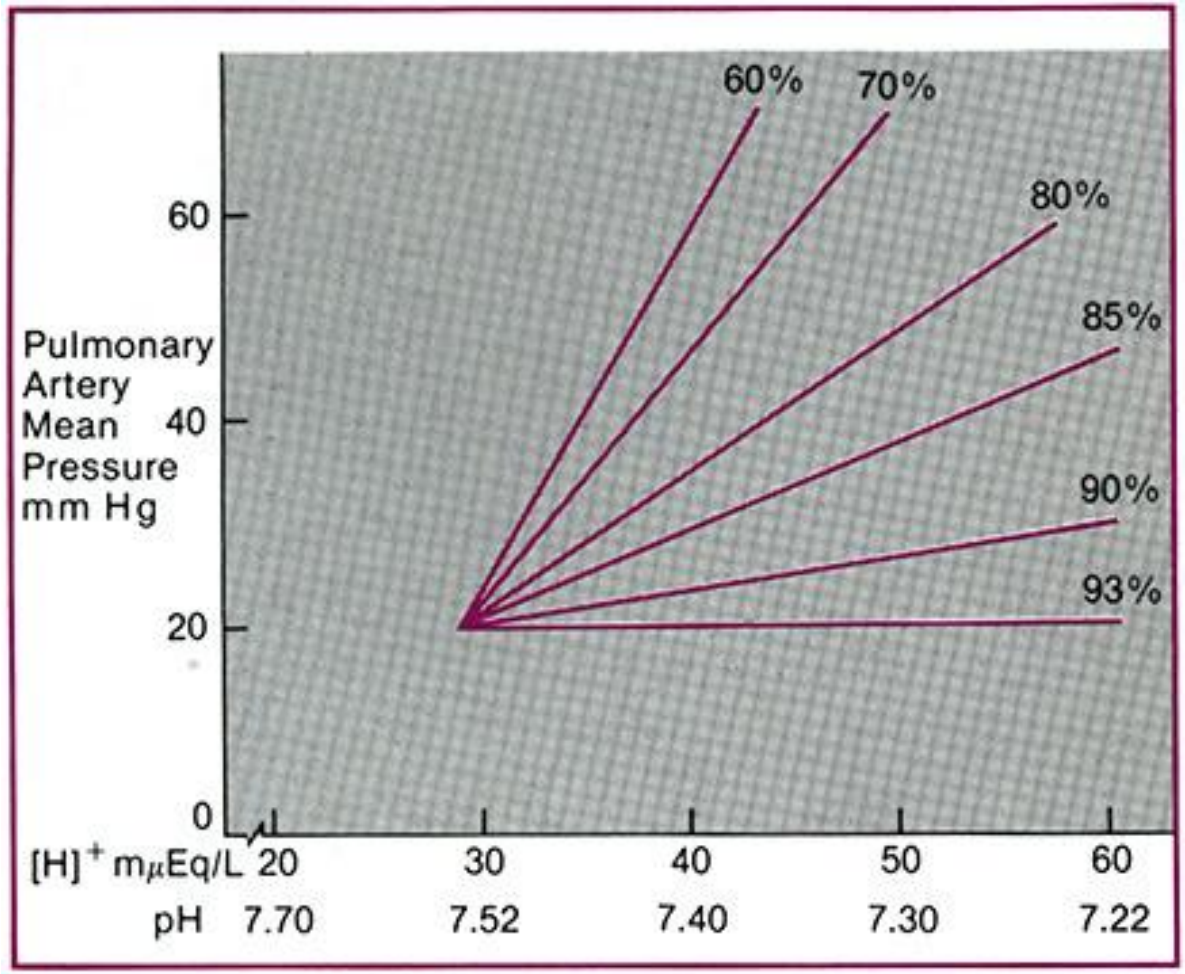
"Ipertrofia e/o dilatazione del ventricolo destro secondaria a malattie che compromettono la funzione e/o la struttura dello apparato respiratorio, escluse le cardiopatie congenite e le patologie del cuore sinistro"

OMS 1961

"Ipertensione arteriosa polmonare secondaria a malattie che compromettono la funzione e/o la struttura dello apparato respiratorio"

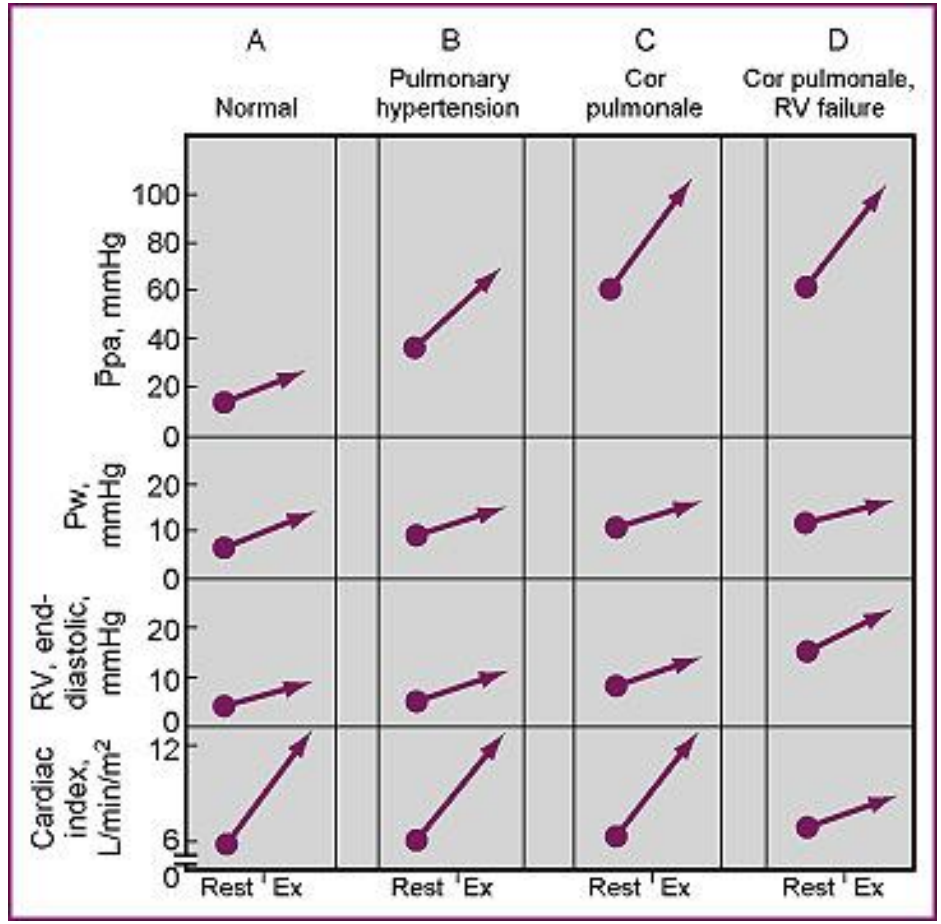
Fishman AP, Am Rev Respir Dis 1978

Relazione tra saturazione di ossigeno, pH e pressione arteriosa polmonare media



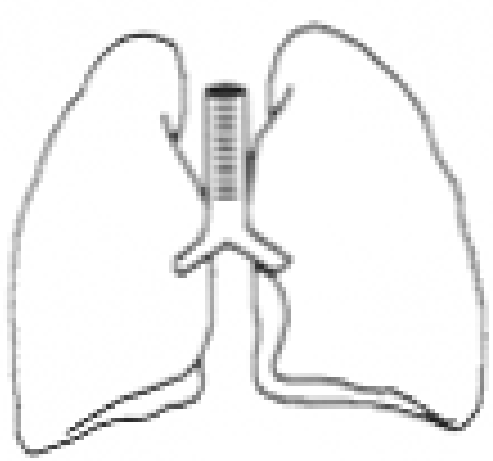
Wiedemann HP & Matthay RA: Cor pulmonale. In: Braunwald E, Heart diseases 1997

Evoluzione emodinamica del cuore polmonare cronico

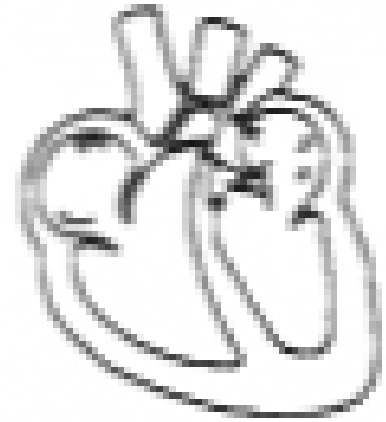


Wiedemann HP & Matthay RA: Cor pulmonale. In: Braunwald E, Heart diseases 1997

4. BPCO e COMORBILITA' CARDIOVASCOLARI



Comorbilità



COPD and comorbidity

Comorbidity …

1. ***Causali*** (con FdR a comune: età avanzata, fumo)
2. ***Complicanti*** (per effetti sistemici della COPD: stato pro-infiammatorio)
3. ***Concomitanti*** (malattie croniche senza relazione causale nota con la COPD)

Fabbri L & Ferrari R, Breathe 2006

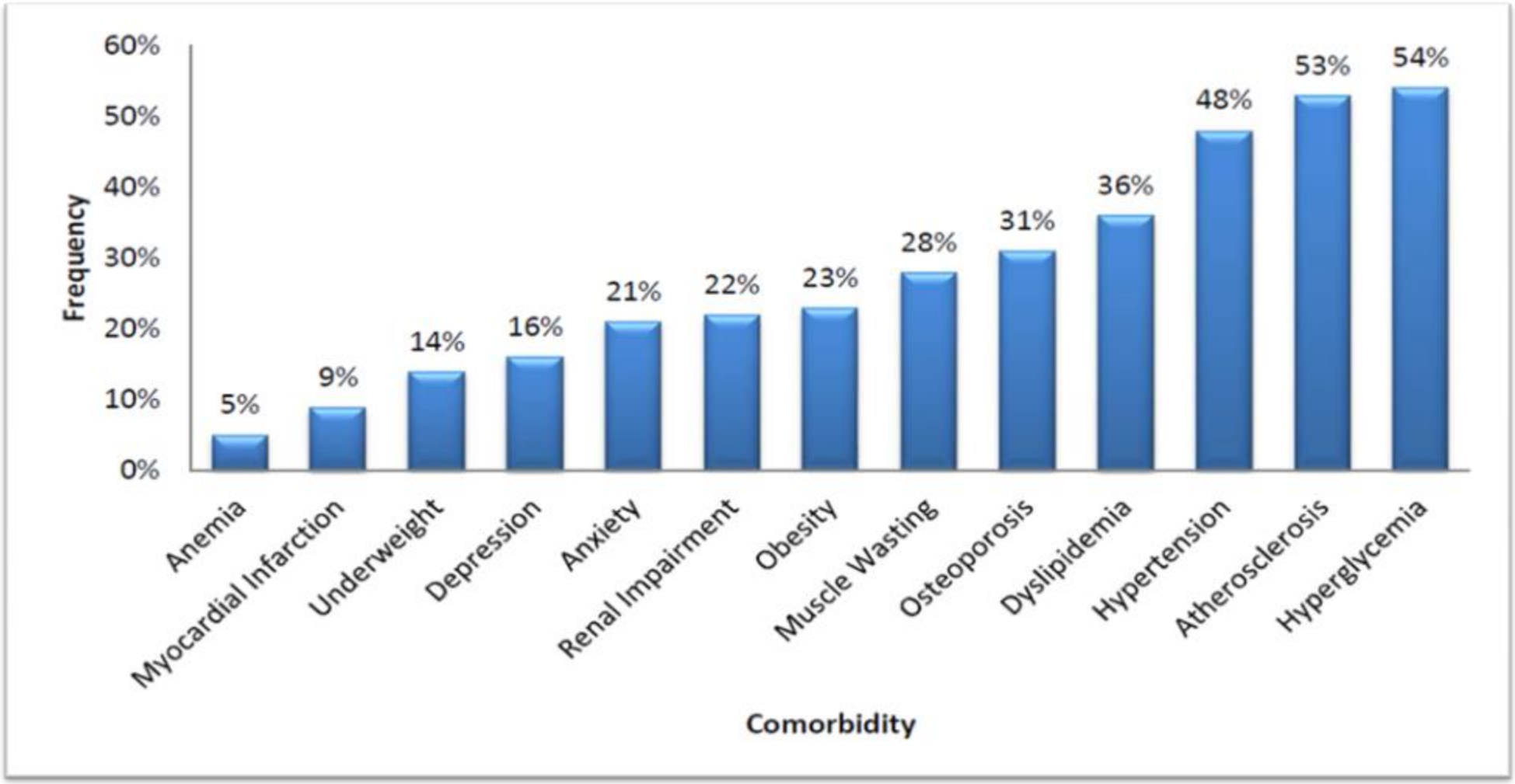
Classifications of the most common comorbidities of COPD based on the clinical or epidemiological link

Con-causal	Complicating COPD	Coexisting[a]
Atherosclerotic disease: coronary, cerebral, lower limbs	Depression	Glaucoma
Chronic kidney disease	Cognitive impairment	Obstructive sleep apnea
Lung cancer	Osteoporosis	Diabetes
CHF	Sarcopenia	
Aortic aneurysm	Arrhythmias	
	Pulmonary embolism	

CHF, congestive heart failure.
[a] On purely epidemiological bases.

Corsonello et al. Curr Opin Pulm Med. 2011 Dec;17 Suppl 1:S21-8.

Prevalenza delle Co-morbidità in BPCO

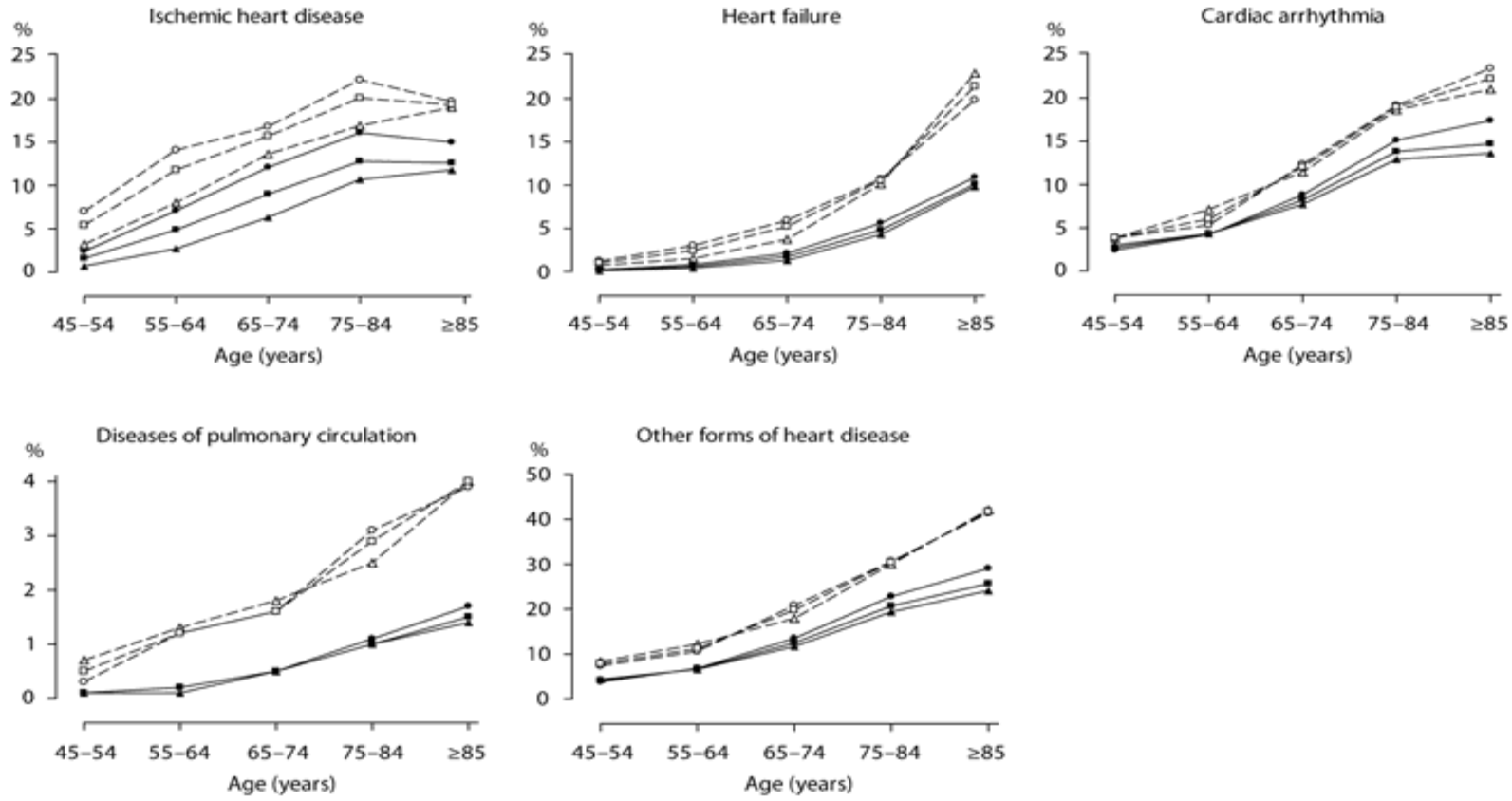


Vanfleteren L et al. AJRCCM 2013; 187(7):728-35

- Patients with and without COPD who reported other selected chronic conditions by age and gender (% of the population examined)

Comorbidity	COPD absent			COPD present		
	total	men	women	total	men	women
Ischemic heart disease	6.6	8.4	5.1	15.9	17.5	13.5
Diseases of the pulmonary circulation	0.4	0.4	0.5	2.1	2.1	2.2
Cardiac arrhythmia	6.9	6.8	7.0	13.6	13.5	13.6
Heart failure	2.0	2.0	2.0	7.9	7.8	7.9
Other forms of heart disease	10.7	10.6	10.8	23.1	22.9	23.4
Metabolic syndrome	0.4	0.4	0.3	0.6	0.7	0.6
Diabetes mellitus	10.5	11.8	9.4	18.7	19.4	17.6
Osteoporosis	10.8	1.7	18.4	14.8	4.6	30.5
Neurotic disorders, personality disorders and other non-psychotic mental disorders	25.8	20.4	30.4	34.2	30.1	40.6
Depressive disorders not elsewhere classified	5.3	3.4	5.3	7.4	5.5	10.3
Malignant neoplasms of the trachea, bronchus, and lung	0.4	0.7	0.2	1.9	2.7	0.6

Cazzola et al Respiration 2010;80:112–119



People with (□○▵) and without COPD (■●▲) who reported cardiovascular comorbidities by age group and gender (% of the examined population). ■ = Total;●○= men;▲▵ = women.

Cazzola et al Respiration 2010;80:112–119

Co-morbidity contributes to predict mortality of patients with COPD

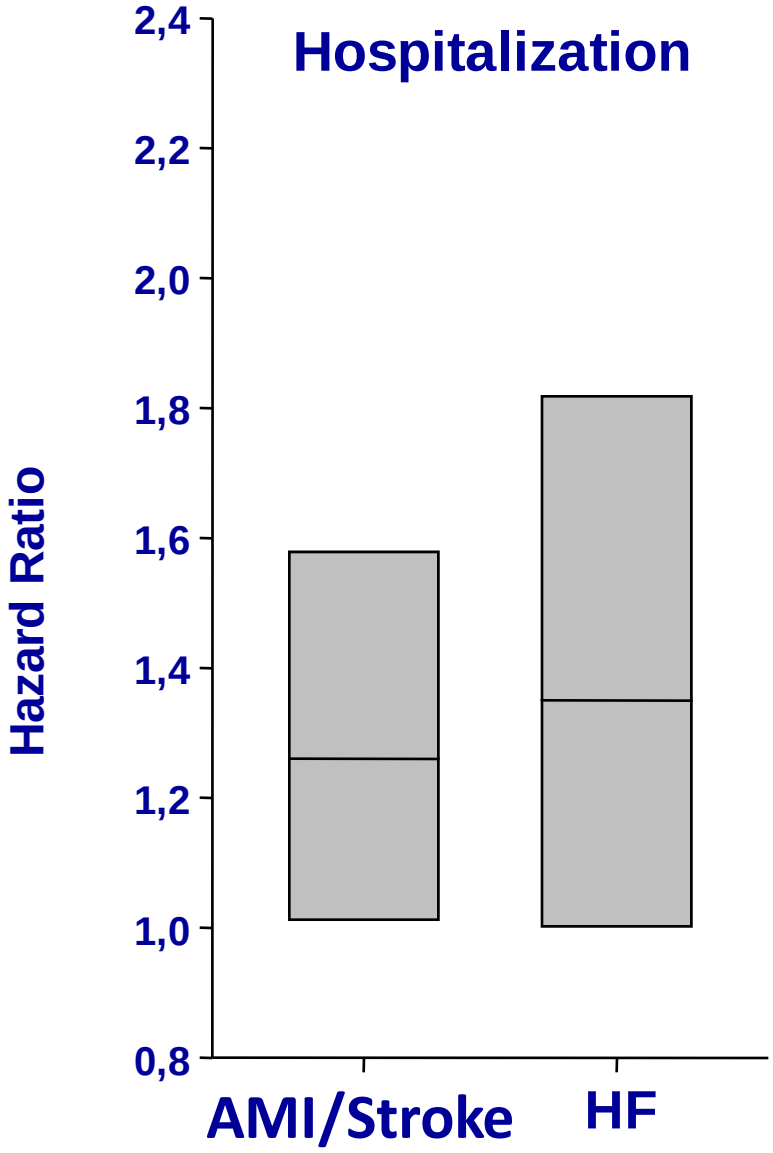
Prognostic score attributed to each variable significantly correlated with mortality at the multivariate analysis

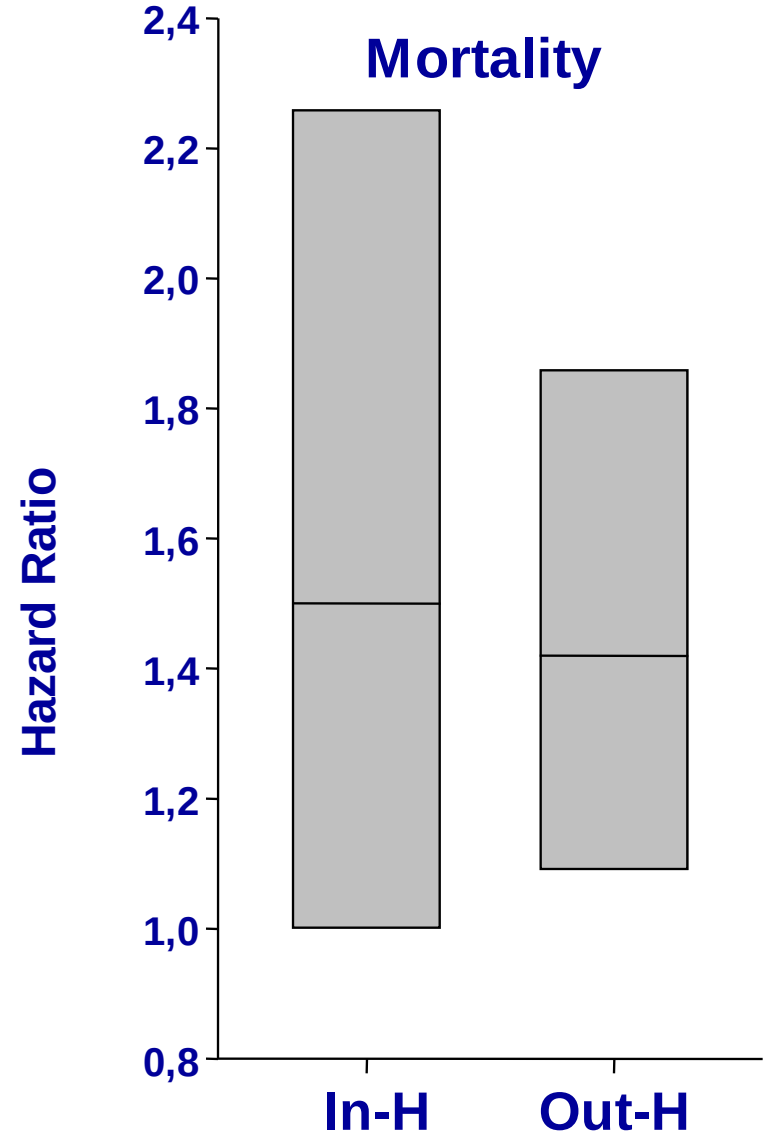
Variable	Score
Chronic renal failure	10
ECG signs of RVH or overload	9.7
FEV_1 <590 mL	6.7
ECG signs of ischaemic heart disease	5.7
Age+	0.62

ECG: electrocardiogram; RVH: right ventricular hypertrophy; FEV_1: forced expiratory volume in one second. Score: arithmetical sum of scores assigned to individual variable. +: age as a continuous and not a categorical variable, the corresponding value (0.62) was multiplied by the age of each patient (in years).

Antonelli Incalzi RA et al, Eur Respir J 1997

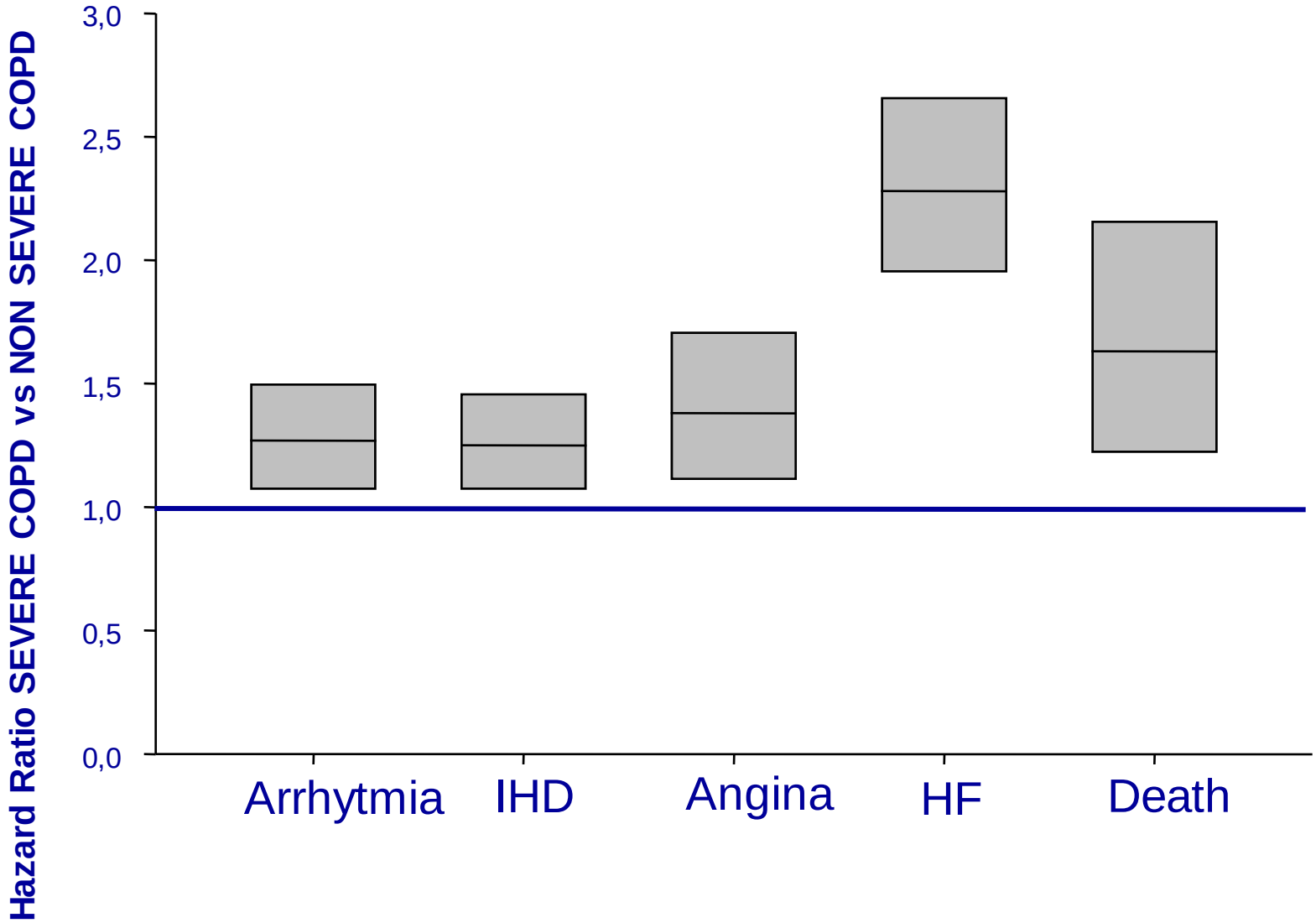
The prognostic influence of COPD in CHF patients





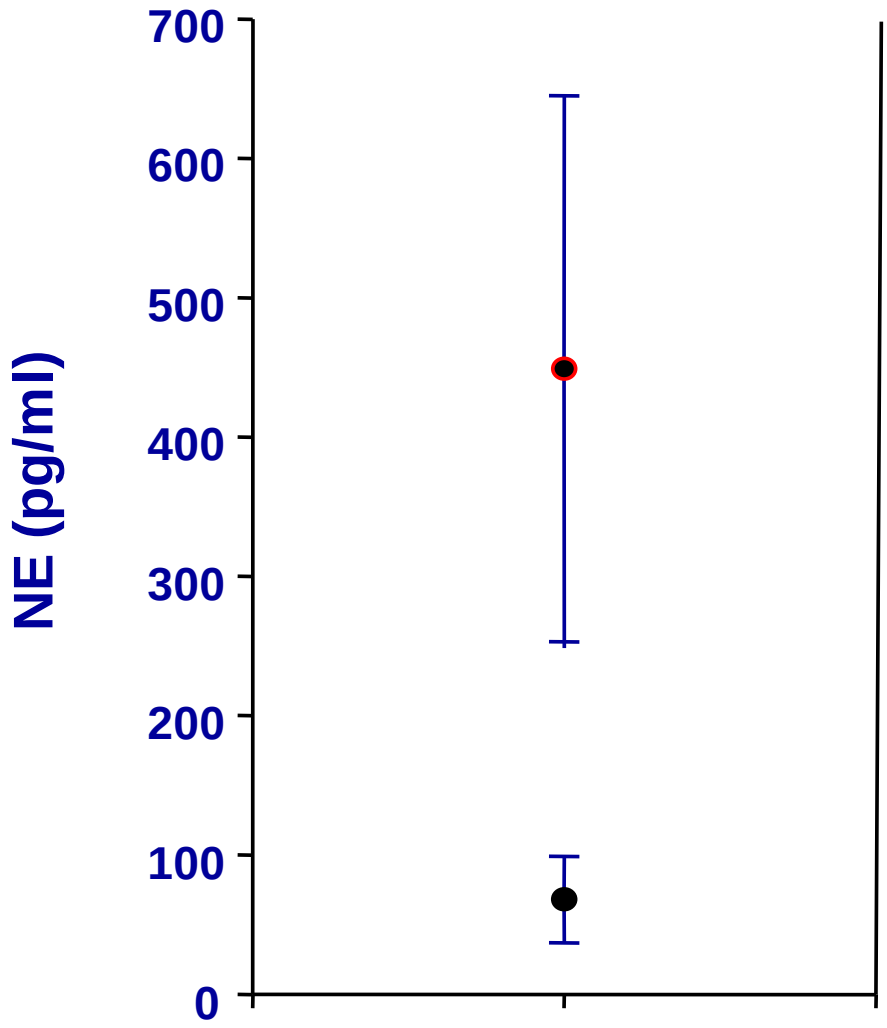
Macchia et al. Eur J Heart Fail 2007

COPD severity and cardiovascular outcomes



Curkendall et al, Ann Epidemiol 2006

Impact of hypoxaemia on catecholamine secretion in COPD



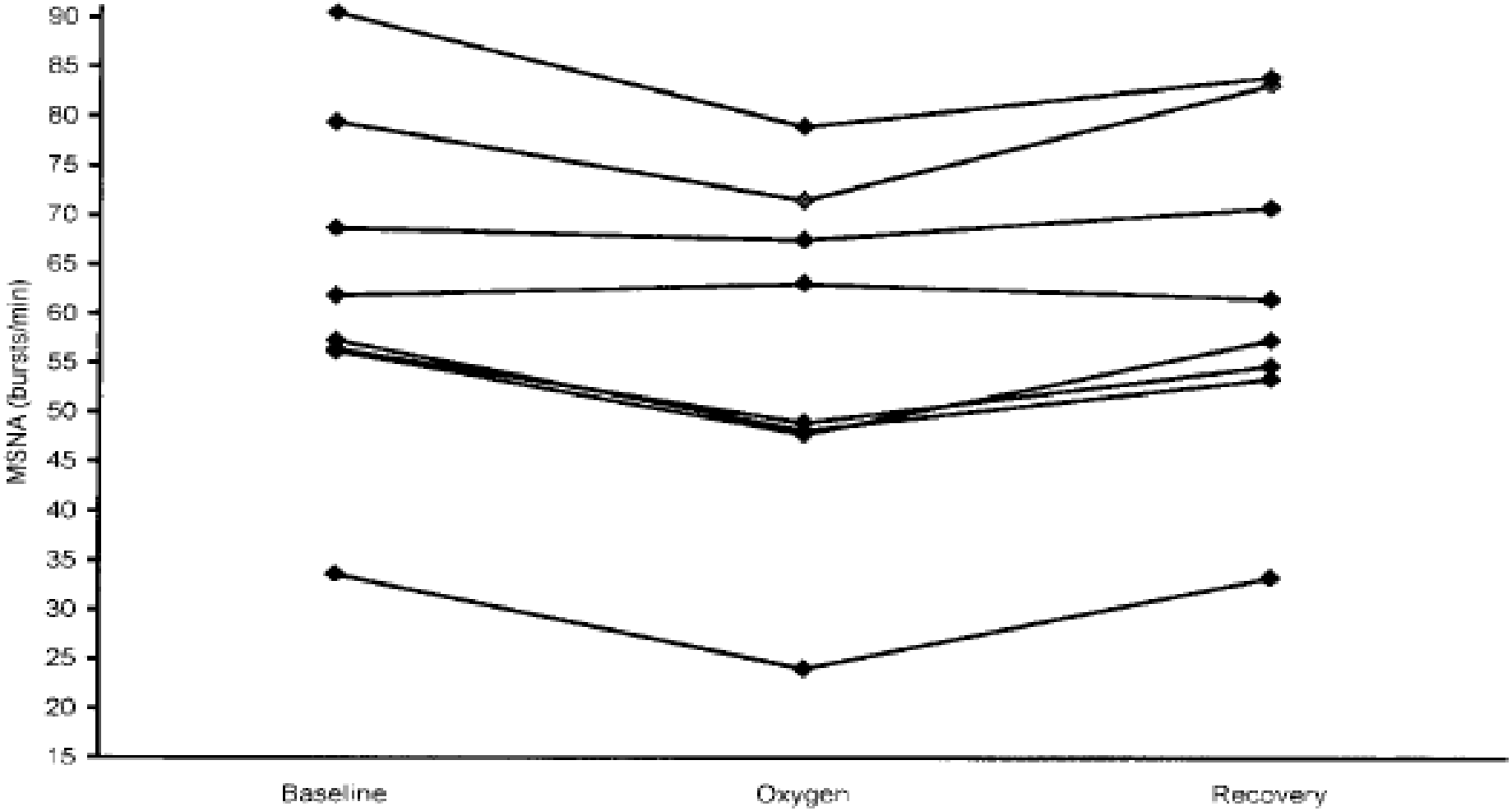
COPD

Control

Bratel et al, Respiratory Medicine 2000

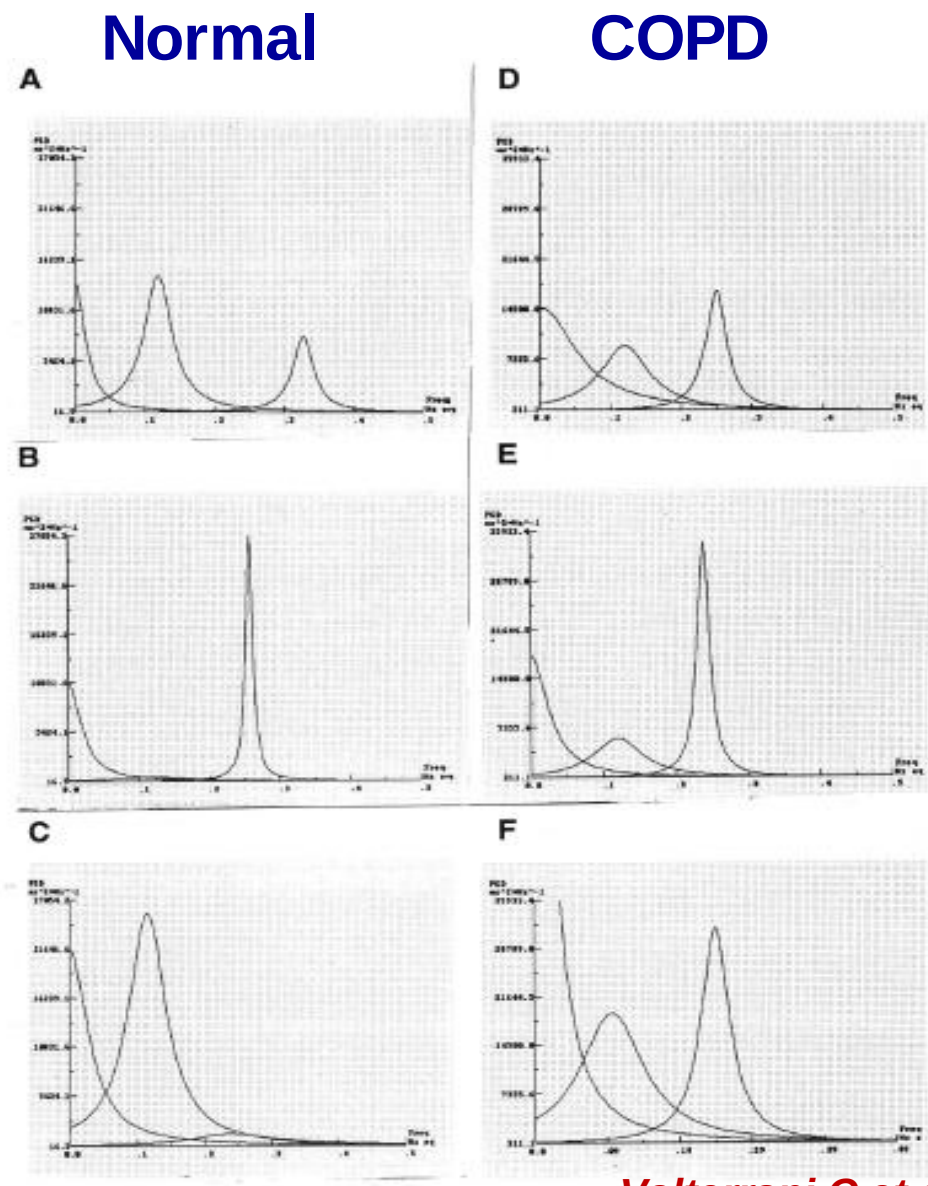
Peripheral Sympathetic Activation

muscle sympathetic nerve activity (MSNA) by
microneurography of the peroneal nerve



Heindl et al, AJRCCM 2001

Cardiac Sympathetic Activation



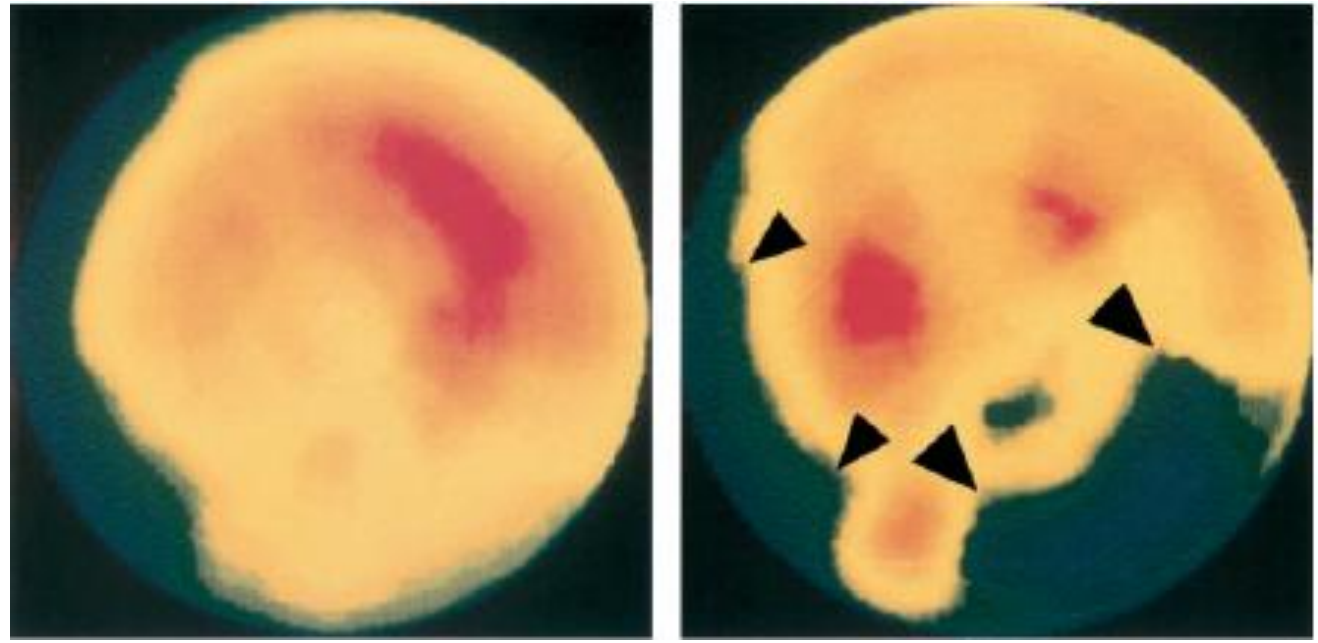
Volterrani C et al, Chest 1994

Cardiac Sympathetic Activation

LV sympathetic nervous function in patients with COPD using ^{123}I-Metaiodobenzylguanidine (MIBG)

Sakamaki et al, Chest 1999

Decreased 123I-MIBG uptake in the myocardium of patients with different COPD grade



GRADE 1 GRADE 3

Sakamaki et al, Chest 1999

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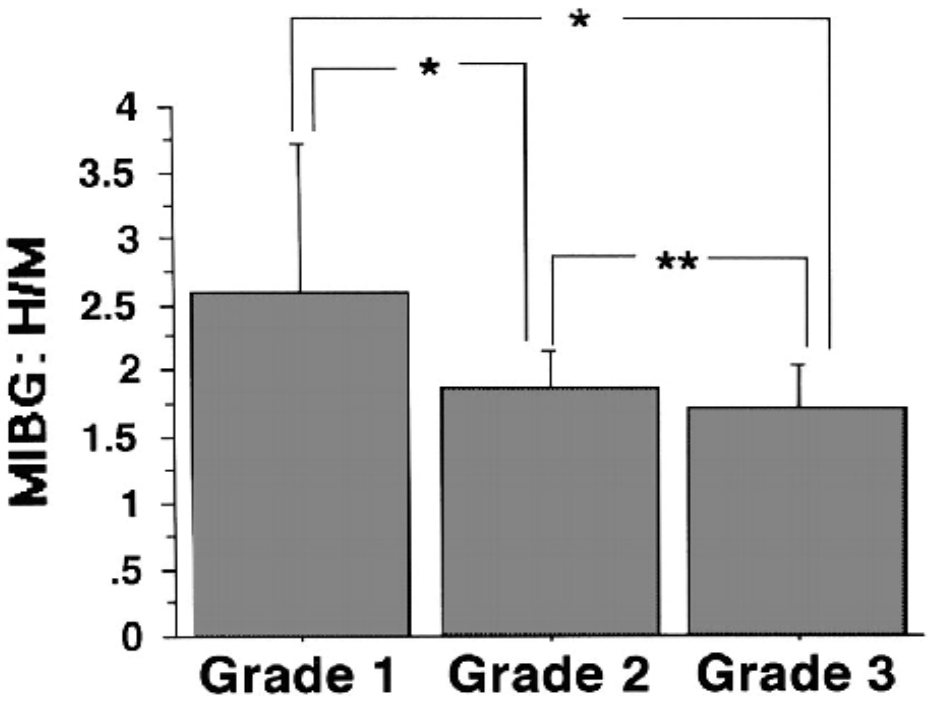

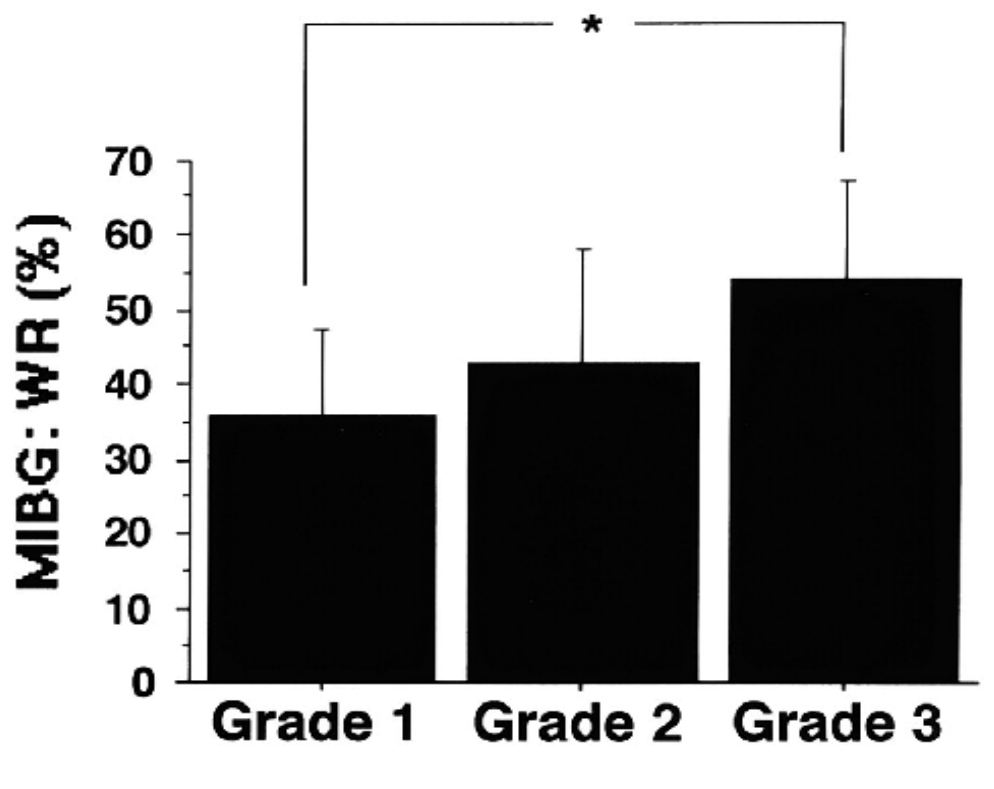

Sakamaki et al, Chest 1999

Condizioni di peggioramento della BPCO

- Riacutizzazioni infettive
- Aritmie
- Peggioramento dell'insufficienza cardiaca dx
- Insufficienza cardiaca sinistra
- Trombo-embolia polmonare
- Sindrome coronarica acuta
- Insufficienza renale
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COMMON SYMPTOMS IN COPD

- Chronic cough
- Breathlessness with physical exertion
- Regularly coughing up phlegm
- Weight loss
- Tiredness and fatigue
- Waking up at night as a result of breathlessness
- Swollen ankles

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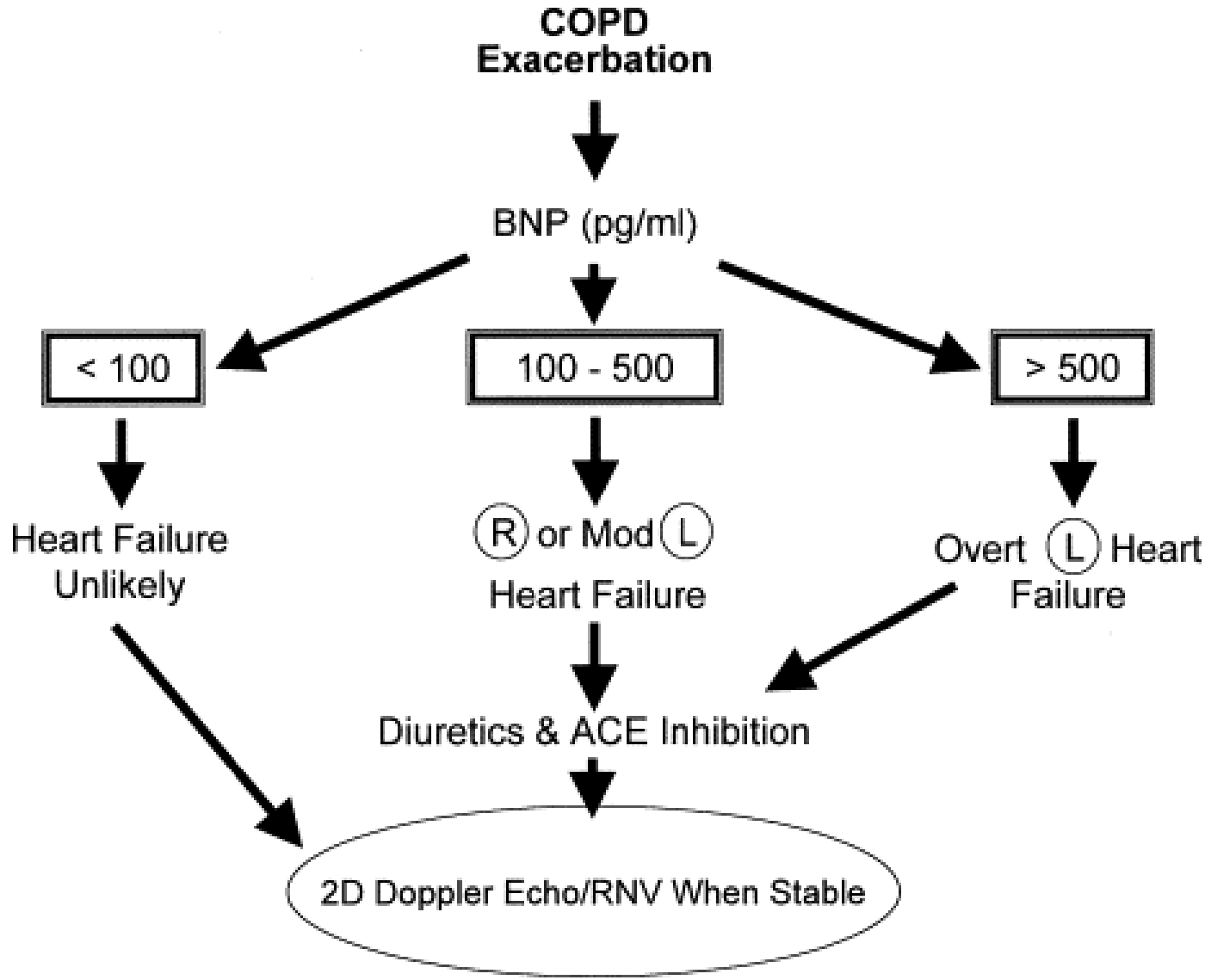
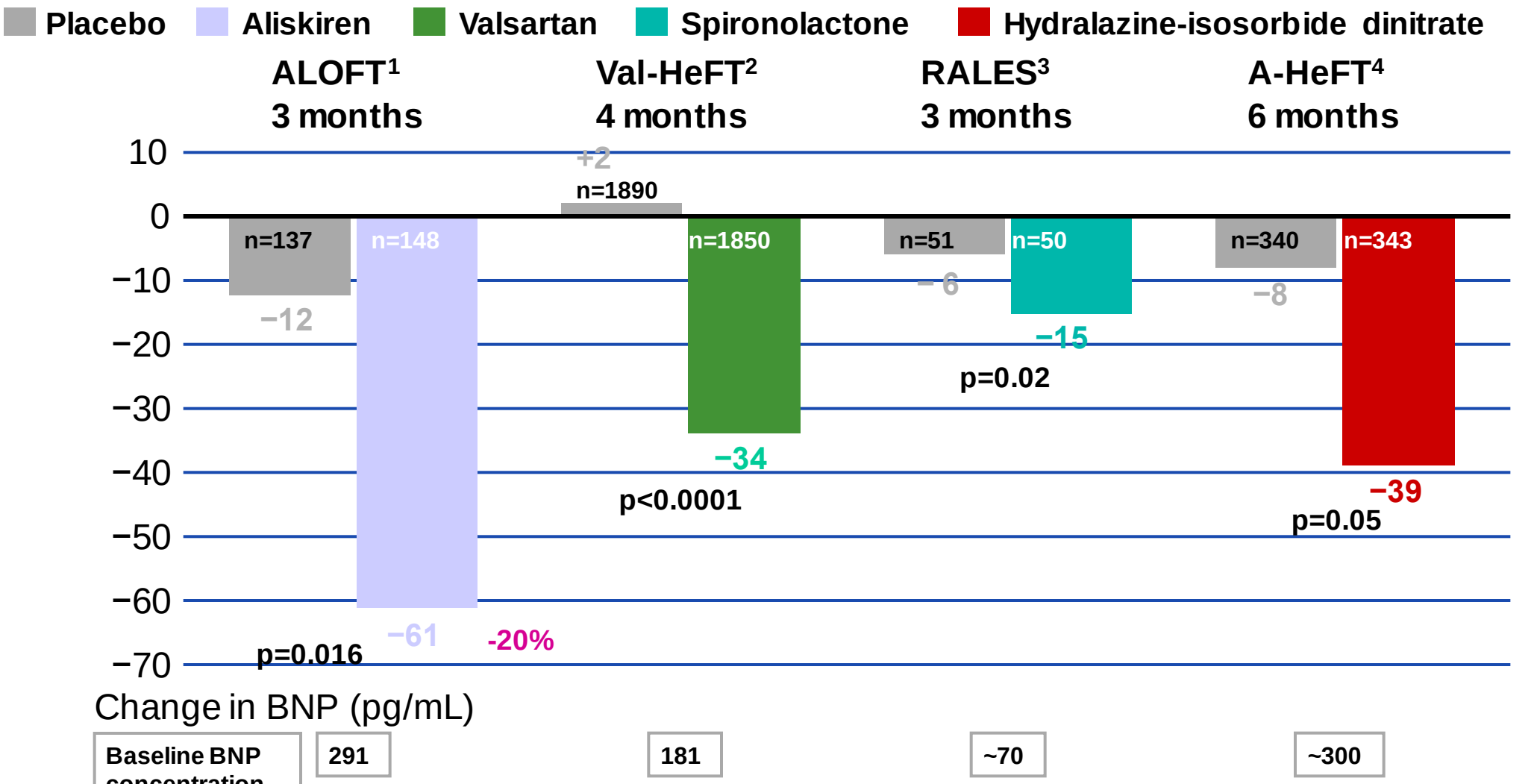
COMMON SYMPTOMS IN COPD AND CHF IN THE ELDERLY

Cardiac and Pulmonary etiologies account for about 85% of cases of shortness of breath.

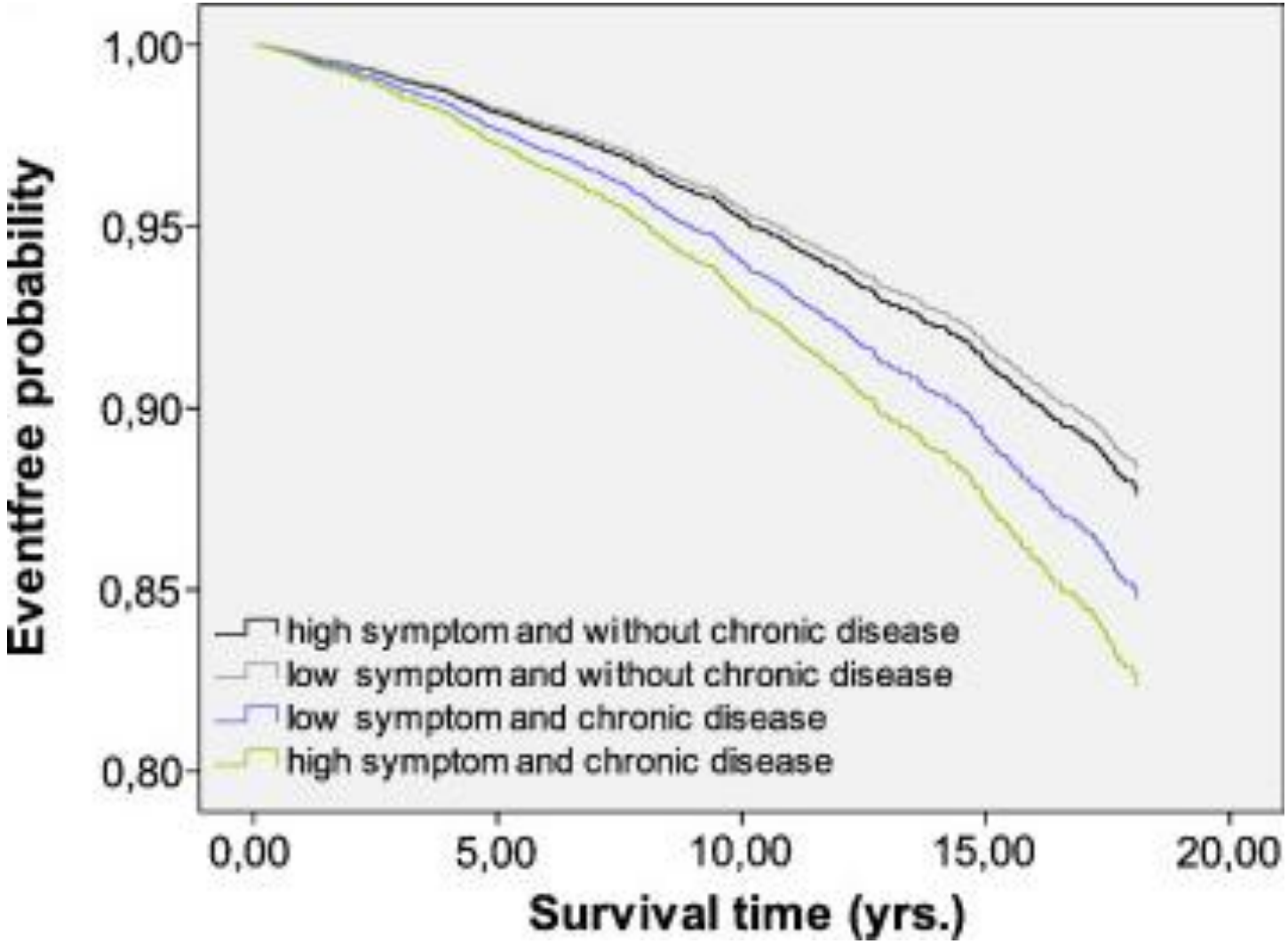

COPD
Exacerbation
BNP (pg/ml)
< 100
100 - 500
> 500
Heart Failure
Unlikely
R or Mod L
Heart Failure
Overt L Heart
Failure
Diuretics & ACE Inhibition
2D Doppler Echo/RNV When Stable

Effect of different drugs on BNP levels in clinical studies



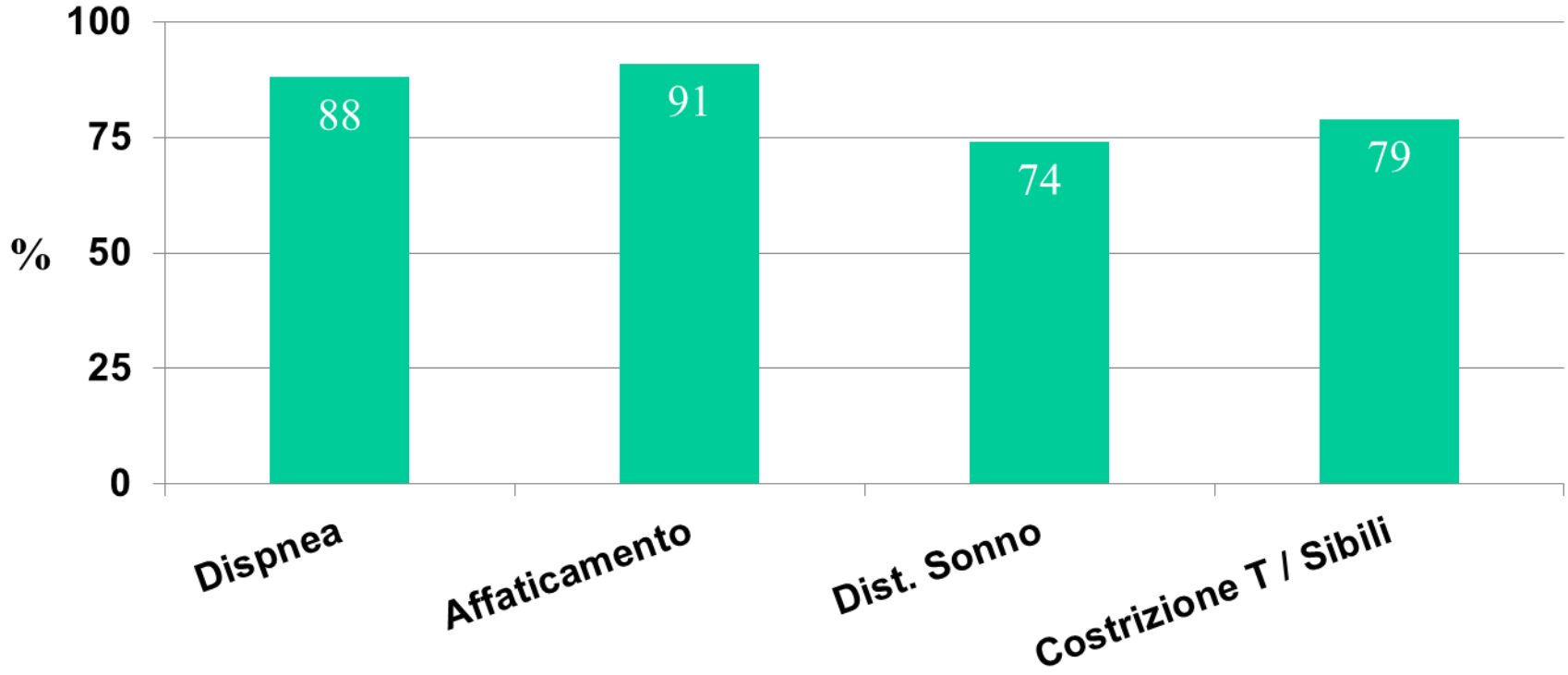
1. McMurray JJV. 2007; 2. Latini R, et al. 2002; 3. Rousseau MF, et al. 2002; 4. Cohn JN, et al. 2007

Survival curves for Male with high and low symptom reporting and presence/absence of chronic disease, adjusted for age, survey, psychological symptoms, and self-perceived health



J Psychosomatic Res 2010;68:427–437

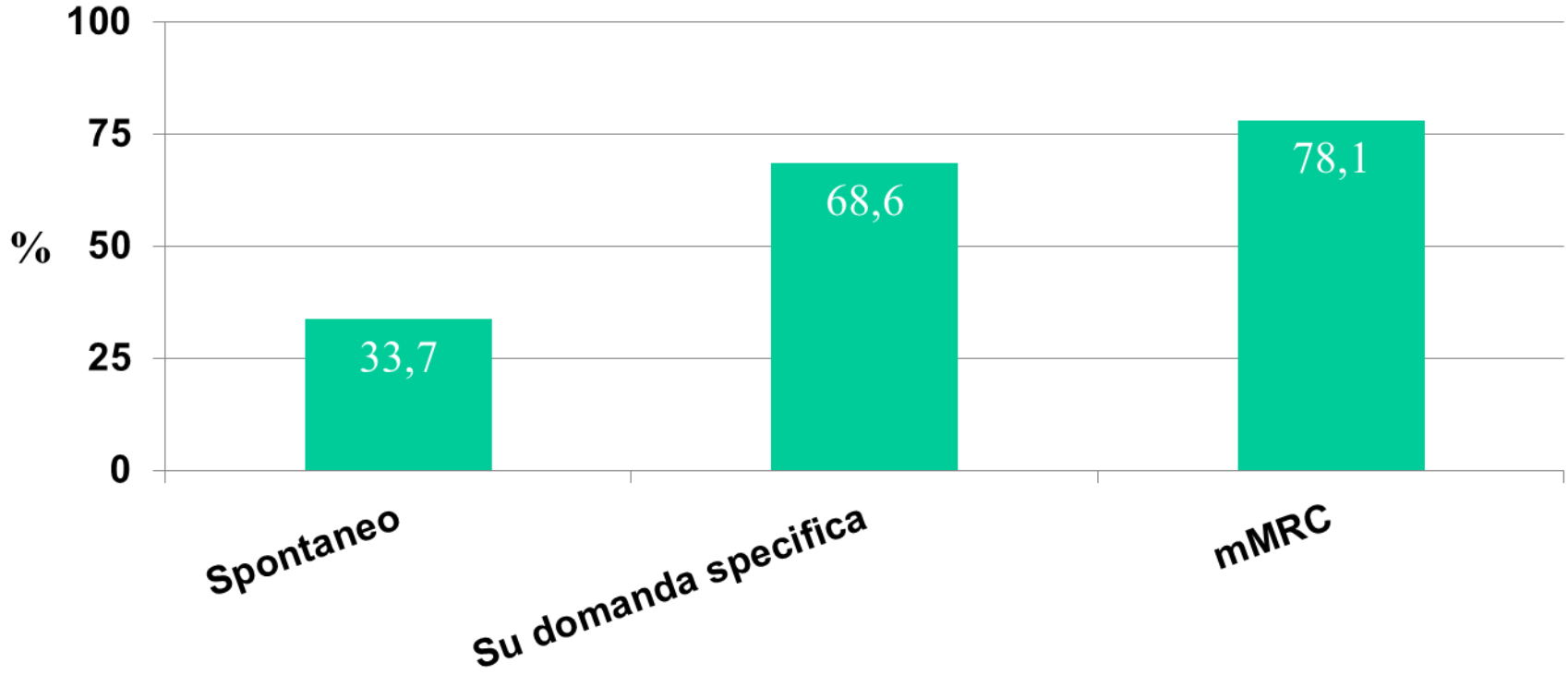
Sintomatologia percepita dal paziente BPCO



146 pazienti BPCO

Kinsman RA et al. J Behav Med 1983;6(4):339-357; Kinsman RA et al. Chest 1983;83(5):755-61

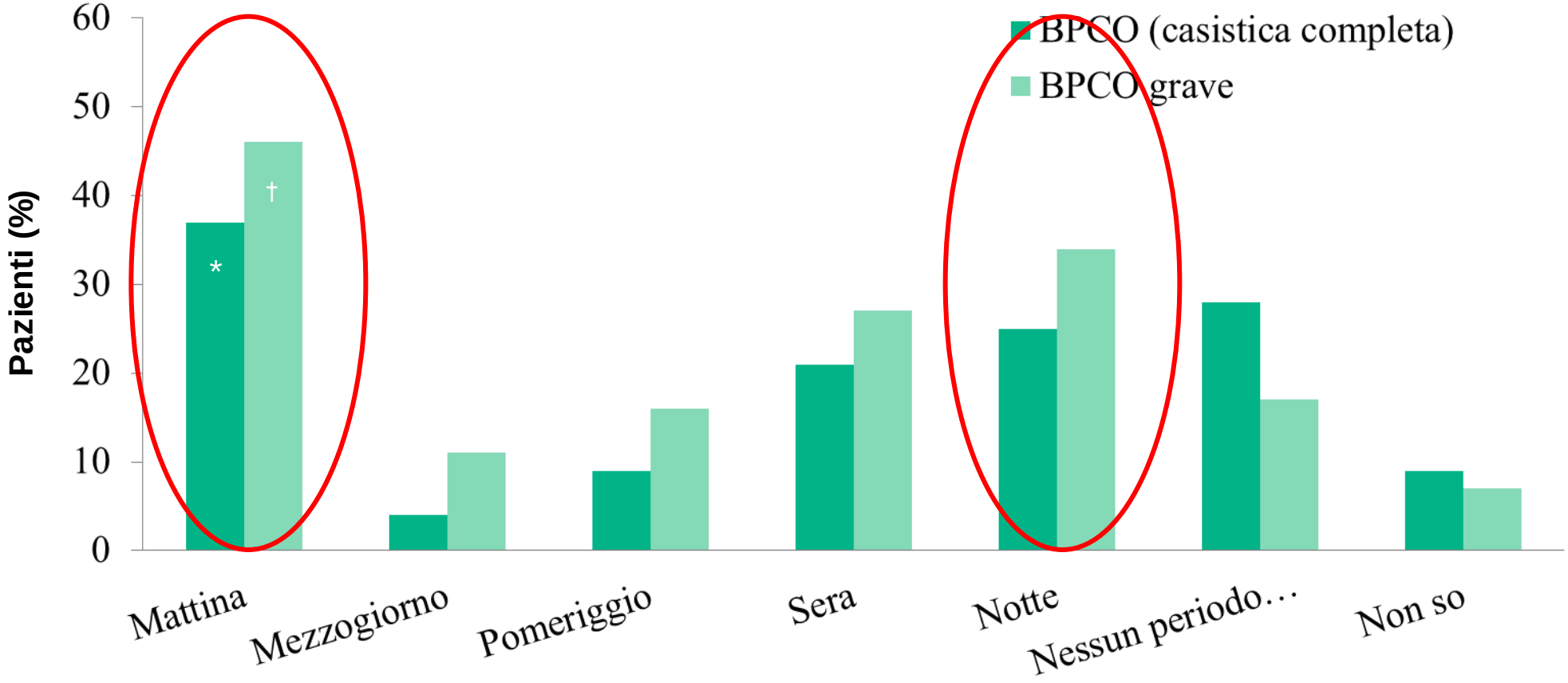
Dispnea, l'importanza di indagare



1991 soggetti affetti o a rischio di BPCO

Roche N et al. Presse Med, 2009; 38(7-8):1041-8

BPCO - Quando la sintomatologia è peggiore

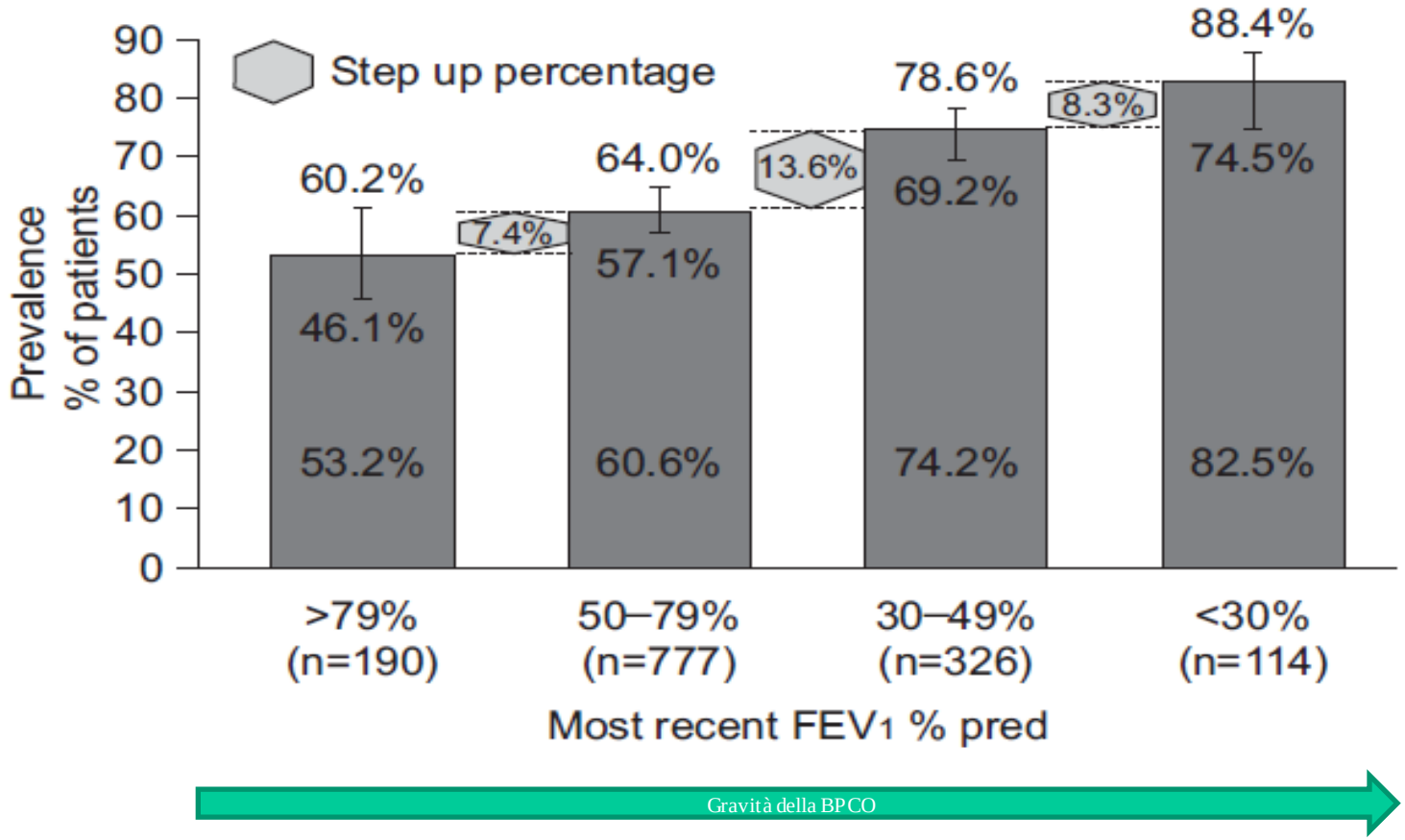


*p<0.001 vs tutti gli altri periodi; †p<0.001 vs mezzogiorno
BPCO grave (n= 289)

Survey effettuata via web.
Pazienti intervistati: 803 affetti da BPCO

Partridge MR et al. Curr Med Res Opin 2009;25(8):2043-2048

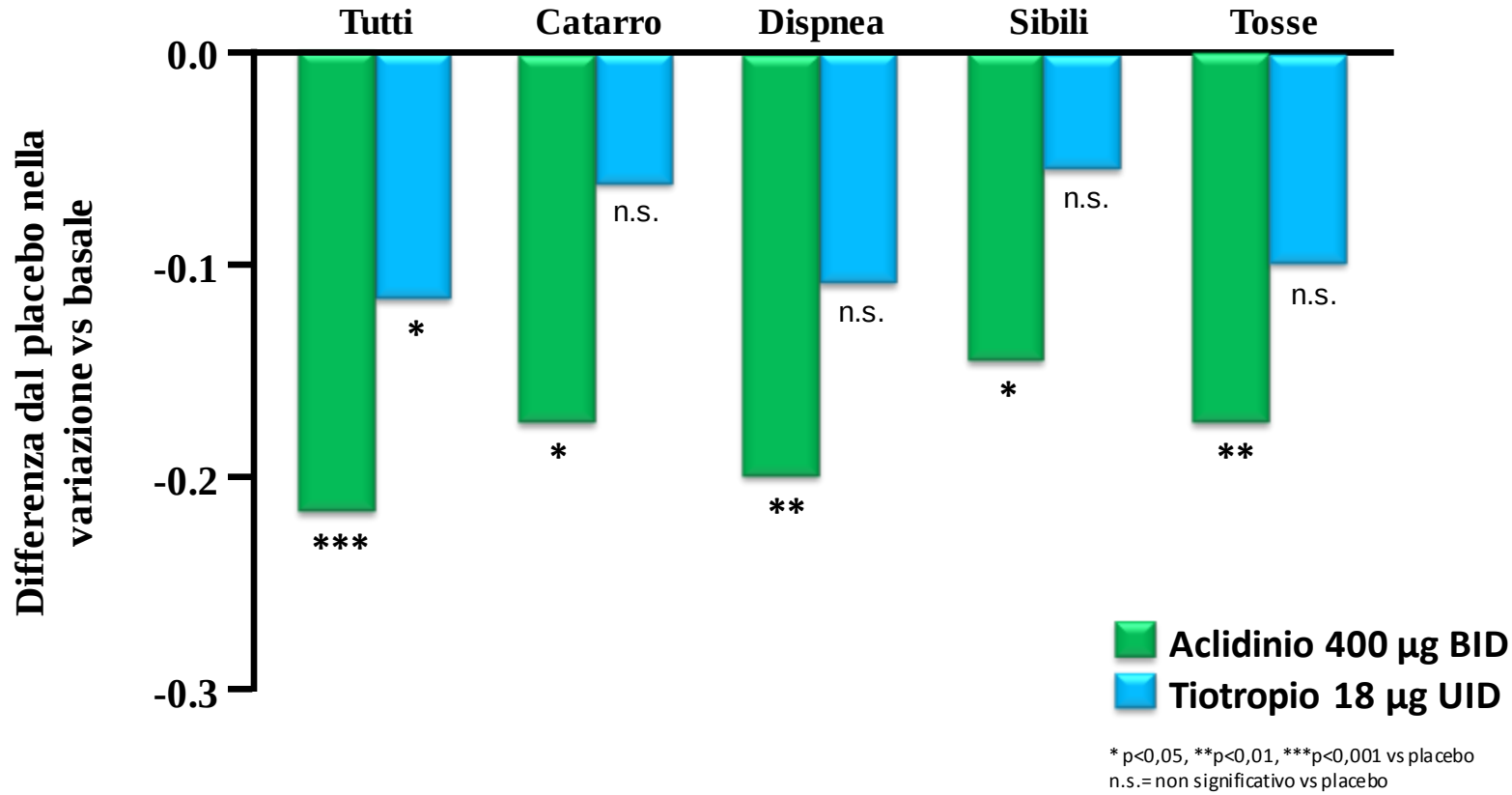
Prevalenza dei sintomi notturni in BPCO



Survey pan-europea condotta in pazienti BPCO

Agusti A. et al. Eur Respir Rev 2011;20(121):183-194

Miglioramento dei sintomi mattutini

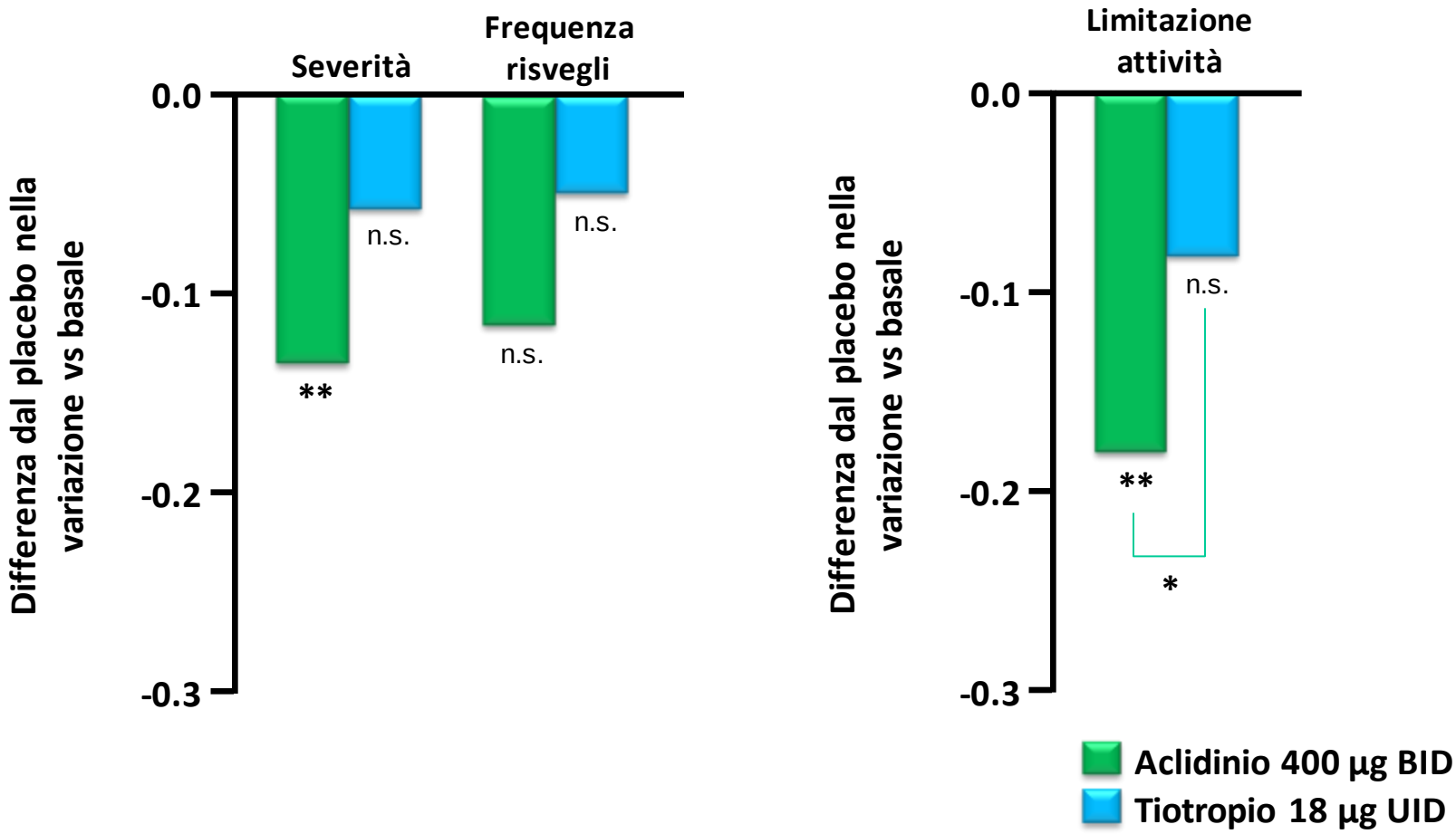


* p<0,05, **p<0,01, ***p<0,001 vs placebo
n.s.= non significativo vs placebo

Studio randomizzato a bracci paralleli, controllato vs placebo e tiotropio in condizioni di doppia cecità mediante la tecnica del double-dummy.
Pazienti randomizzati: 414 affetti da BPCO moderata-grave. Durata del trattamento: 6 settimane

Beier J et al. COPD 2013;10(4):511-522

Miglioramento dei sintomi notturni e della limitazione delle attività



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Beier J et al. COPD 2013;10(4):511-522

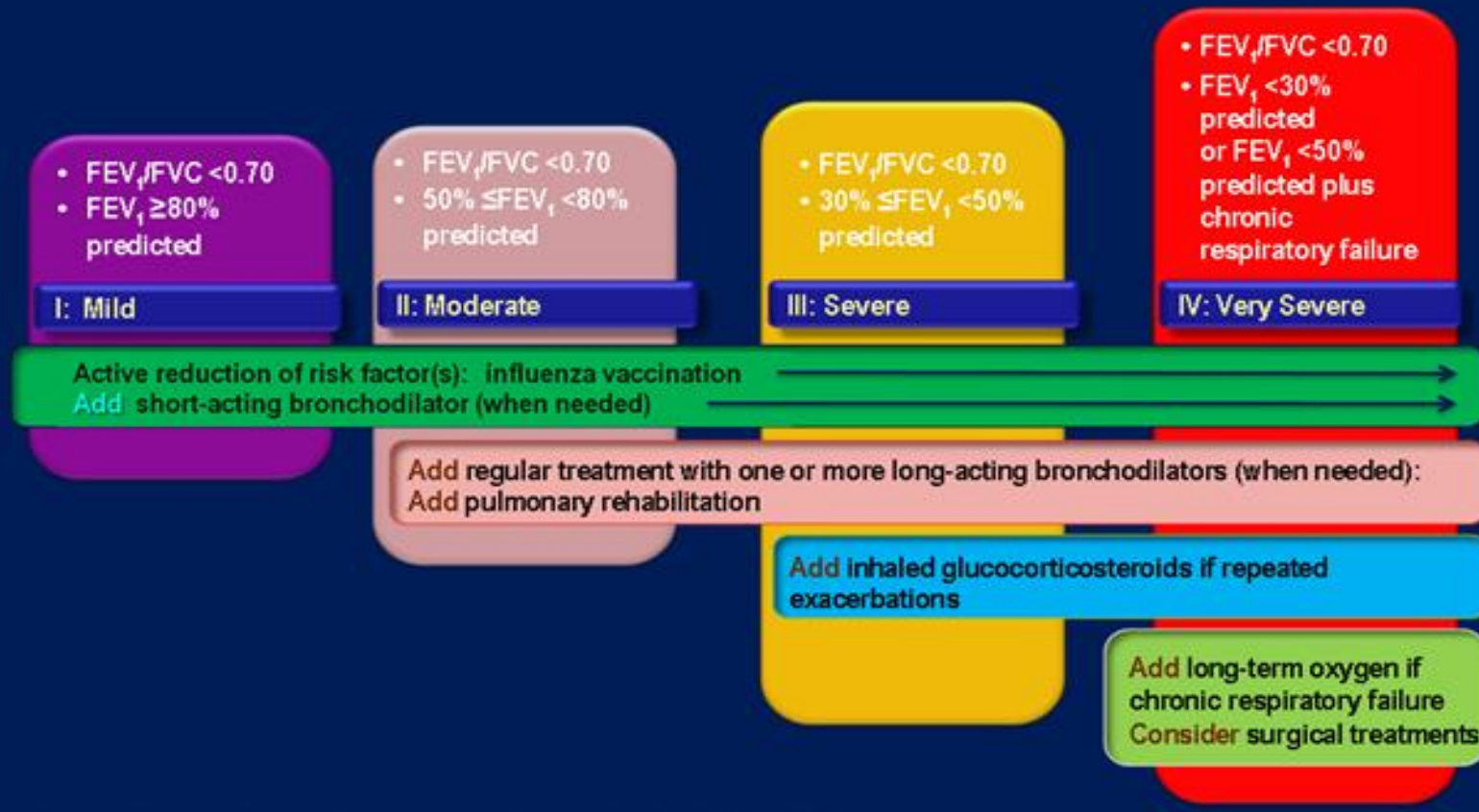
Consequences of nocturnal hypoxaemia and hypercapnia in chronic obstructive pulmonary disease (COPD)

Parameter/outcome	Acute consequences	Chronic consequences
Sleep structure	Altered in severe COPD, but inconsistent improvement of sleep with oxygen administration	Worse sleep among pink puffers (mild desaturators) than blue bloaters (severe desaturators)
Arrhythmias	Observed during severe sleep desaturations; prevented by oxygen administration	Risk not directly documented
Pulmonary artery pressure	Increased	Inconsistent finding with regard to differences between desaturators and nondesaturators
Diurnal blood gases		Similar wake blood gas evolution among desaturators and nondesaturators; possible worsening of blood gases in severe COPD suggested by beneficial effects of ventilatory treatment
Mortality	Some suggestion that death may preferentially occur at night among patients with exacerbations (not systematically evaluated)	Prognosis independent of nocturnal hypoxaemia measured in stable conditions
Cardiovascular and cerebrovascular risk	Increased ventricular ectopic events during periods of hypoxaemia	Increased, possibly as a result of increased sympathetic activity and altered peripheral vascular tone due to recurrent nocturnal hypoxia
Inflammatory mechanisms	Pronounced activation among desaturators	

Night-time symptoms

Night-time symptoms and the consequent sleep disturbance have the potential to impact a range of long-term outcomes in patients with COPD that includes lung function changes, exacerbation frequency, the emergency of cardiovascular disease , cognitive effects, depression, quality of life and mortality.

GOLD Therapy at Each Stage of COPD



Global Initiative for Chronic Obstructive Lung Disease (GOLD). NHLBI/WHO Workshop report. Available from: www.goldcopd.com.

What systemic aspects of COPD can be affected by therapy

- **Weakness**
- **Weight loss**
- **Cardiac risk**
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- **Depression**
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