PNEUMOMEDICINA 2022
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COMORBIDITA' CARDIOVASCOLARI E METABOLICHE NEL PAZIENTE BPCO

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Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report

GOLD Executive Summary

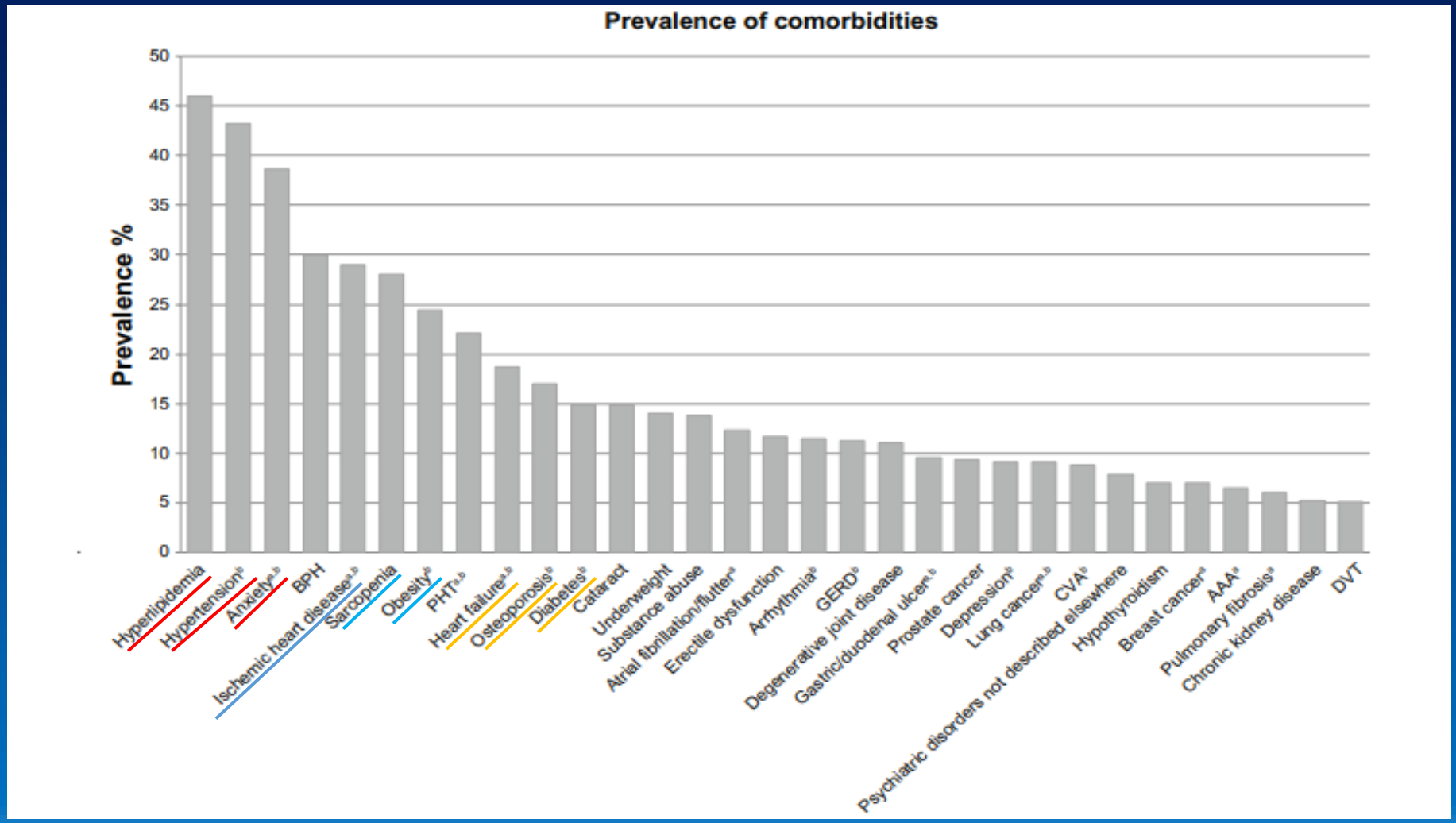
Key Points:

- COPD often coexists with other diseases (comorbidities) that may significantly impact patient outcomes.
- The presence of comorbidities should not alter COPD treatment, and comorbidities should be treated per usual standards regardless of the presence of COPD.
- When COPD is part of a multimorbidity care plan, attention should be directed to ensure simplicity of treatment and minimize polypharmacy.

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis (63, 296–302). Some of these arise independently of COPD, whereas others may be causally related, either with shared risk factors or by one disease increasing the risk or compounding the severity of the other (303). Management of the patient with COPD must include identification and treatment of its comorbidities; the most common in COPD are outlined below.

Vogelmeier CF et al. Am J Res Crit Care Med 2017; 195: 557-582

PREVALENZA DELLE COMORBIDITA' NEI PAZIENTI BPCO



Smith MC, Wrobel JP. Int J COPD 2014:9 871–888

PREVALENZA DELLE COMORBIDITA'
NEI PAZIENTI DELLO STUDIO ECLIPSE

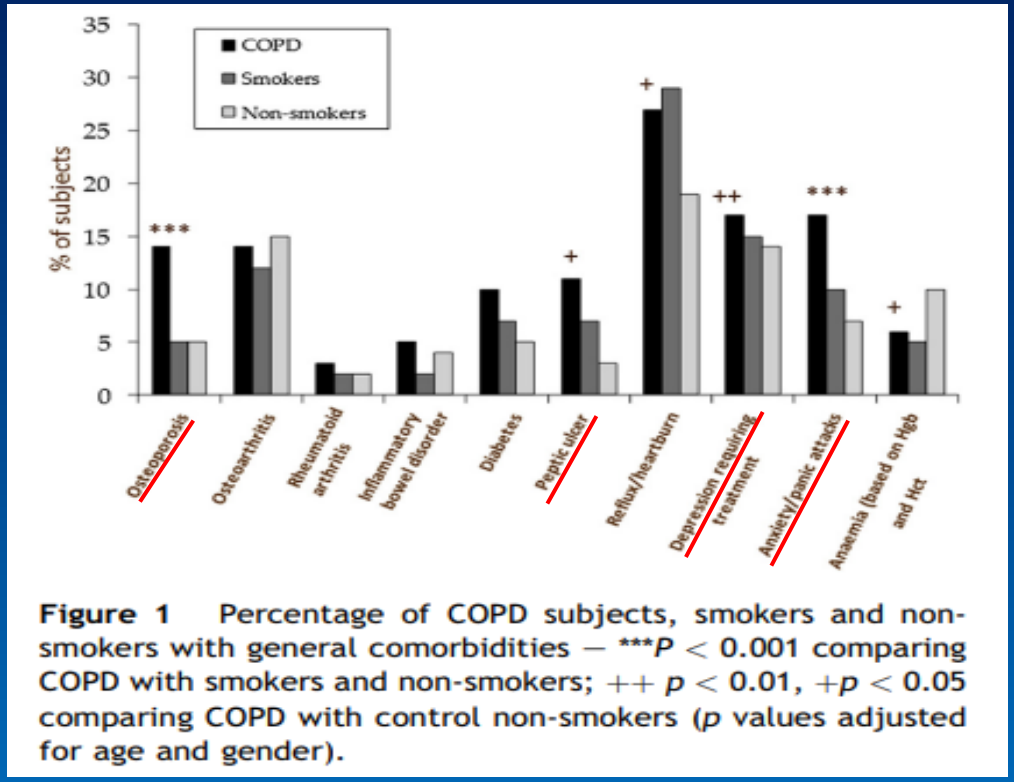


Figure 1 Percentage of COPD subjects, smokers and non-smokers with general comorbidities — ***$P < 0.001$ comparing COPD with smokers and non-smokers; ++ $p < 0.01$, +$p < 0.05$ comparing COPD with control non-smokers (p values adjusted for age and gender).

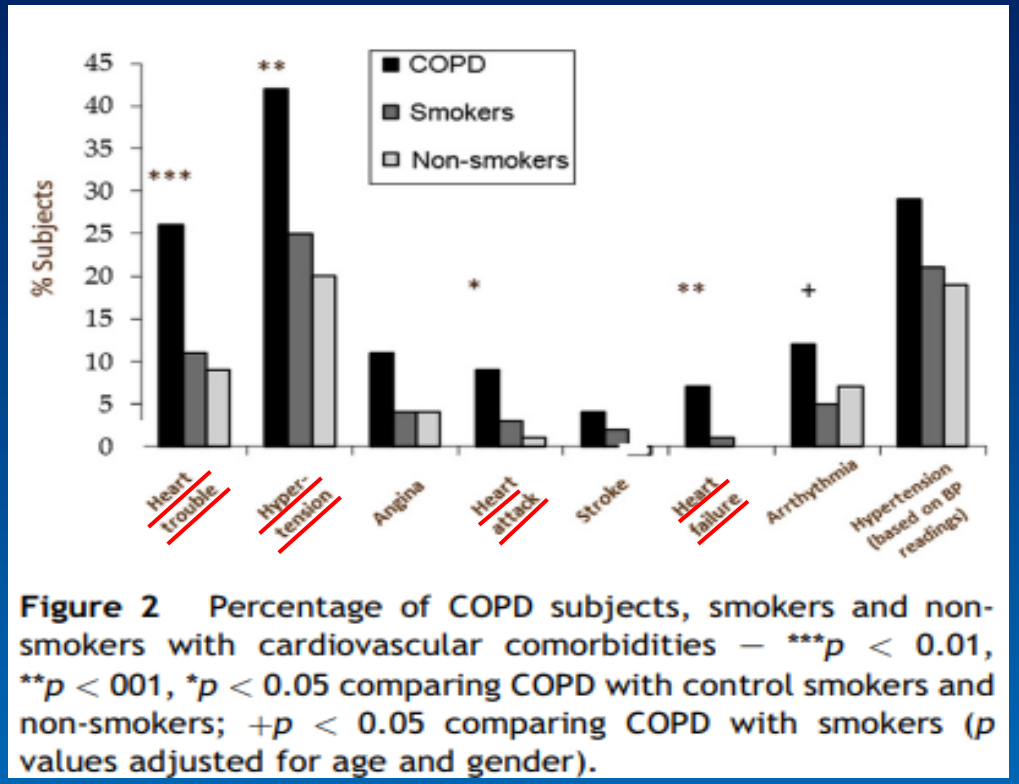


Figure 2 Percentage of COPD subjects, smokers and non-smokers with cardiovascular comorbidities — ***$p < 0.01$, **$p < 001$, *$p < 0.05$ comparing COPD with control smokers and non-smokers; +$p < 0.05$ comparing COPD with smokers (p values adjusted for age and gender).

2164 BPCO, 337 fumatori e 245 non fumatori

Miller J et al. Respir Med 2013; 107: 1376-1384

MANIFESTAZIONI SISTEMICHE E COMORBIDITA' DELLA BPCO

- ✓Sarcopenia e cachessia
- ✓Depressione e ansia
- ✓Sindrome delle apnee ostruttive del sonno
- ✓Ipertensione arteriosa polmonare
- ✓Cancro del polmone
- ✓Ipertensione arteriosa
- ✓Cardiopatia ischemica
- ✓Scompenso circolatorio
- ✓Aritmie
- ✓Arteriopatia periferica
- ✓Ictus
- ✓Dislipidemia
- ✓Diabete mellito tipo 2
- ✓Sindrome metabolica
- ✓Epatopatia steatosica non alcolica
- ✓Osteoporosi
- ✓Anemia normocitica
- ✓Reflusso gastroesofageo
- ✓Insufficienza renale cronica

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PREVALENZA DI SCOMPENSO CARDIACO, CARDIOPATIA ISCHEMICA E ARITMIE NEI PAZIENTI BPCO

Table 1. Prevalence of Selected Cardiac Comorbidities in Various Subsets of Patients with Chronic Obstructive Pulmonary Disease

Reference, Publication Year	Country, Years	Setting	Subjects with COPD (*N*)	HF Prevalence (%)	IHD Prevalence (%)	Arrhythmia Prevalence (%)
Almagro *et al.* (16), 2010	Spain, 2007–2008	Hospital	503	27	26	27
Antonelli-Incalzi *et al.* (17), 2003	Italy, 1996–1999	Community	381	10	16	—
Barr *et al.* (18), 2009	United States, 2005–2006	Community	1,003	<1	4	—
Baty *et al.* (19), 2013	Switzerland, 2002–2010	Hospital	340,948	11	25	13
Blanchette *et al.* (20), 2011	United States, 2003–2007	Community	11,674	9	37	11
Cazzola *et al.* (21), 2012	Italy, 2006	Community	15,018	8	16	14
Curkendall *et al.* (22), 2006	Canada, 1997–2000	Community	11,493	19	7	11
Chen *et al.* (23), 2009	Canada, 1999–2000	Hospital	108,726	17	26	15
Finkelstein *et al.* (24), 2009	United States, 2002	Community	958	11	16	29
García Rodríguez *et al.* (25), 2009	UK, 1996	Community	1,927	7	—	—
Holguin *et al.* (26), 2005	United States, 1979–2001	Hospital	9,864,278	10	15	—
Huiart *et al.* (27), 2005	Canada, 1990–1997	Community	5,648	14	13	4
Kollert *et al.* (28), 2011	Germany, 1992–2007	Hospital	326	17	16	15
Konecny *et al.* (29), 2014	United States, 2000–2009	Mixed	3,121	41	64	—
Lange *et al.* (30), 2010	Denmark, 2001–2003	Hospital	1,036	—	14	—
Lin *et al.* (31), 2010	United States, 2001–2003	Mixed	1,388	18	4	—
Mapel *et al.* (32), 2005	United States, 1998	Mixed	70,679*	25	34	19
Miller *et al.* (33), 2013	Multicentre, 2006–2010	Mixed	2,164	7	9	13
Miniati *et al.* (34), 2014	Italy, 2001–2003	Mixed	200	14	30	5
Schneider *et al.* (35), 2010	UK, 1995–2005	Community	18,361	16	36	14
Sidney *et al.* (36), 2005	United States, 1996–1999	Mixed	45,966	8	3	8
Sin and Man (37), 2003	United States, 1988–1994	Community	2,070	5	—	—
Sode *et al.* (38), 2011	Denmark, 1980–2006	Community	313,958	—	18	—

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; HF = heart failure; IHD = ischemic heart disease.

Roversi S et al. Am J Respir Crit Care Med 2016; 194: 1319–1336

COMORBIDITA' CARDIOVASCOLARI IN 341.329 PAZIENTI CON E SENZA BPCO inseriti nell'Health Search Database dei medici di famiglia italiani

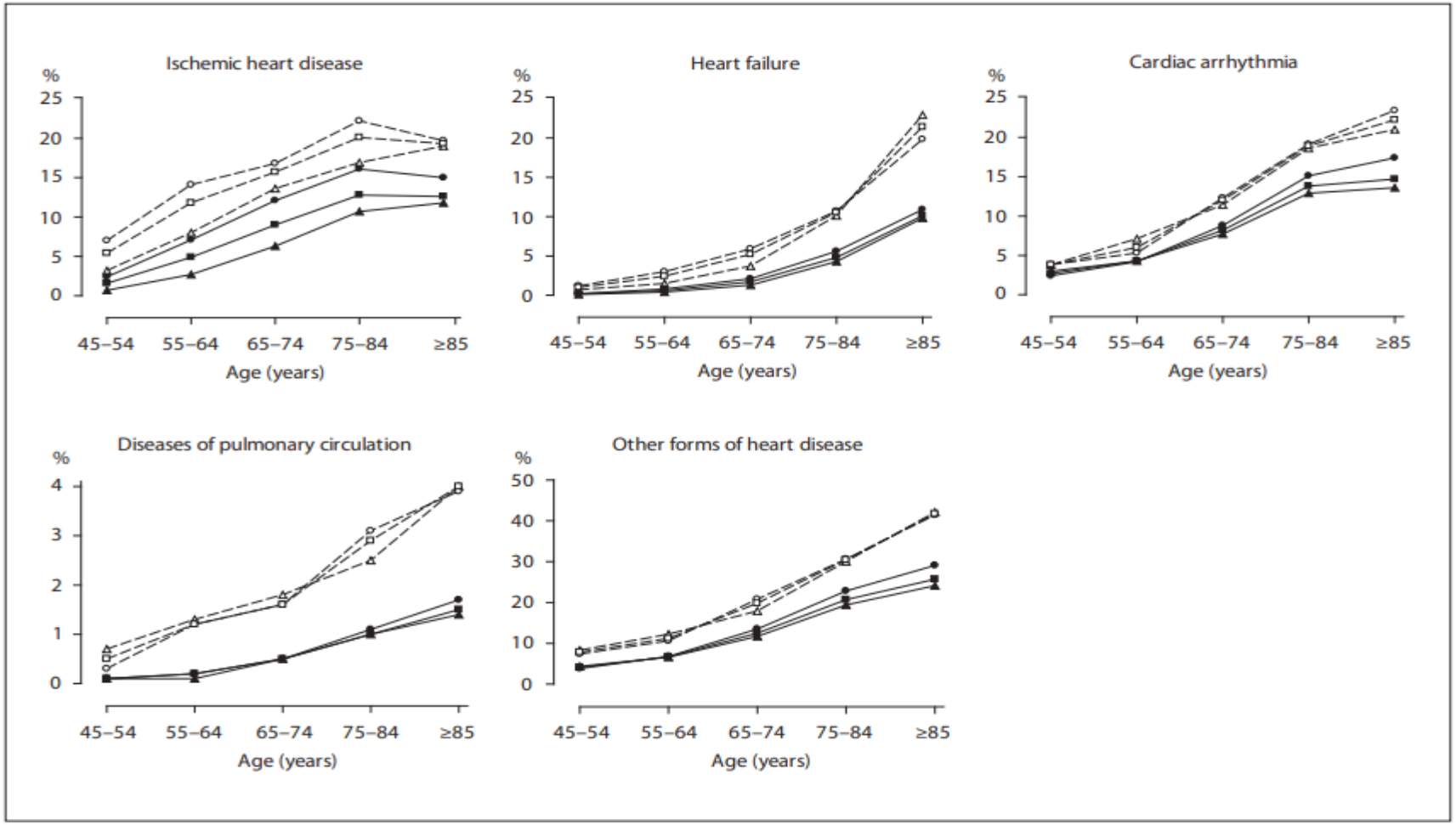

Fig. 1. People with (□ ○ △) and without COPD (■ ● ▲) who reported cardiovascular comorbidities by age group and gender (% of the examined population). ■ □ = Total; ● ○ = men; ▲ △ = women.

Cazzola M et al. Respiration 2010; 80: 112-119

RISCHIO RELATIVO PER PATOLOGIA CARDIOVASCOLARE NEI PAZIENTI BPCO CONFRONTATI CON I PAZIENTI SENZA BPCO
metanalisi di 27 studi

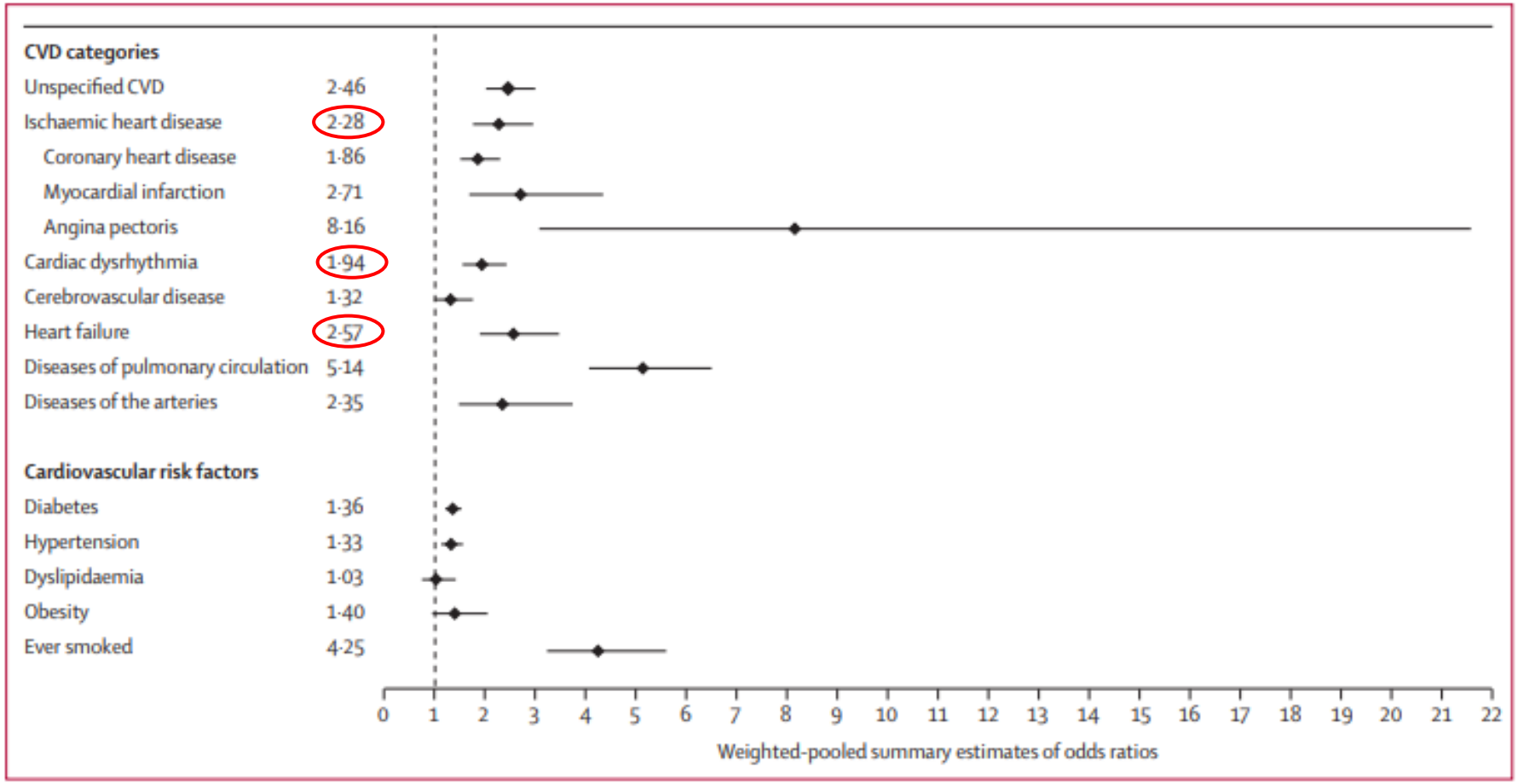

Figure 2: **Summary forest plot showing the weighted-pooled summary estimates of odds ratio (meta-OR) and the 95% CI for cardiovascular disease in COPD compared with non-COPD population**

The meta-odds ratio is indicated with a black diamond and the error bars span the 95% CI. The bold dash vertical line marks the border for significance. CVD=cardiovascular disease. COPD=chronic obstructive pulmonary disease.

Chen W et al. Lancet Respir Med 2015; 3: 632-639

DEFINIZIONE DI SINDROME METABOLICA

Criterio	WHO (iperglicemia e altri 2 criteri)	ATP III (≥3 criteri)	IDF (obesità e altri 2 criteri)
Alterato metabolismo glucidico	>110 mg/dL, o alterata tolleranza glucidica o diabete in trattamento	>110 mg/dL	>100 mg/dL o diabete in trattamento
Dislipidemia	TG>150 mg/dL o HDL <35 mg/dL per gli uomini e <39 mg/dL per le donne o trattamento ipolipemizzante in atto	TG>150 mg/dL o HDL <40 mg/dL per gli uomini e <50 mg/dL per le donne	TG>150 mg/dL o HDL <40 mg/dL per gli uomini e <50 mg/dL per le donne o trattamento ipolipemizzante in atto
Obesità centrale	Circonferenza vita/circonferenza fianchi >0.9 per gli uomini o >0.85 per le donne e/o BMI >30 kg/m2	Circonferenza vita ≥102 cm per gli uomini o ≥88 cm per le donne	Circonferenza vita ≥94 cm per gli uomini o ≥80 cm per le donne (caucasici)
Ipertensione arteriosa	PAS ≥140 mmHg o PAD ≥90 mmHg o terapia antipertensiva	PAS ≥130 mmHg o PAD ≥85 mmHg	PAS ≥130 mmHg o PAD ≥85 mmHg o terapia antipertensiva
Albuminuria	≥20 ug/min o ≥ 30 mg/g creatinina		

PREVALENZA DELLA SINDROME METABOLICA NEI PAZIENTI CON E SENZA BPCO
metanalisi di 19 studi

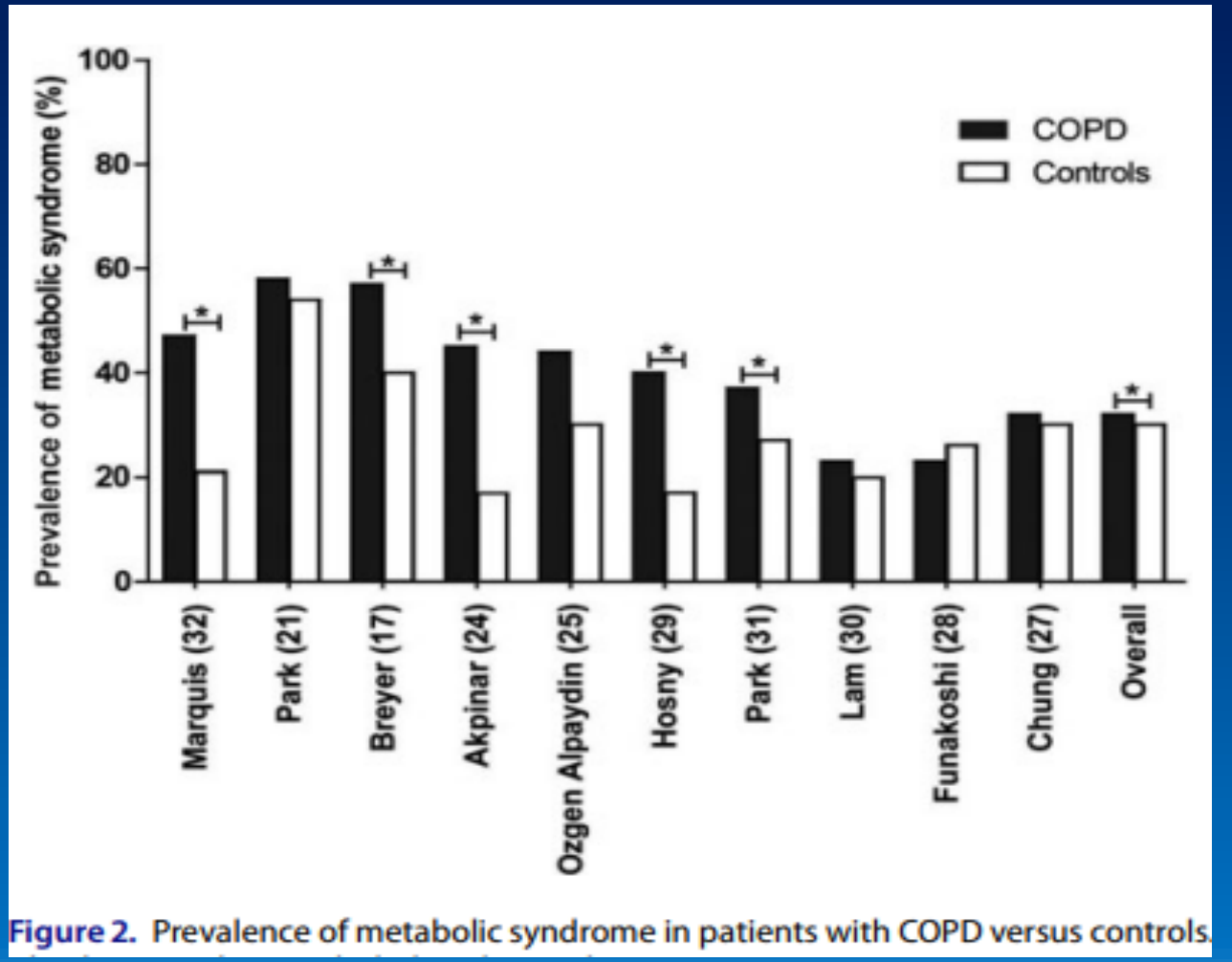

Figure 2. Prevalence of metabolic syndrome in patients with COPD versus controls.

Prevalenza SM
32% BPCO vs 30% controlli
(p=0.001)

N. Cebron Lipovec et al. COPD 2016; 13: 399-406

INCIDENZA DI IMA E STROKE IN 1.204.110 PAZIENTI CON E SENZA BPCO inseriti in un database britannico di medicina generale

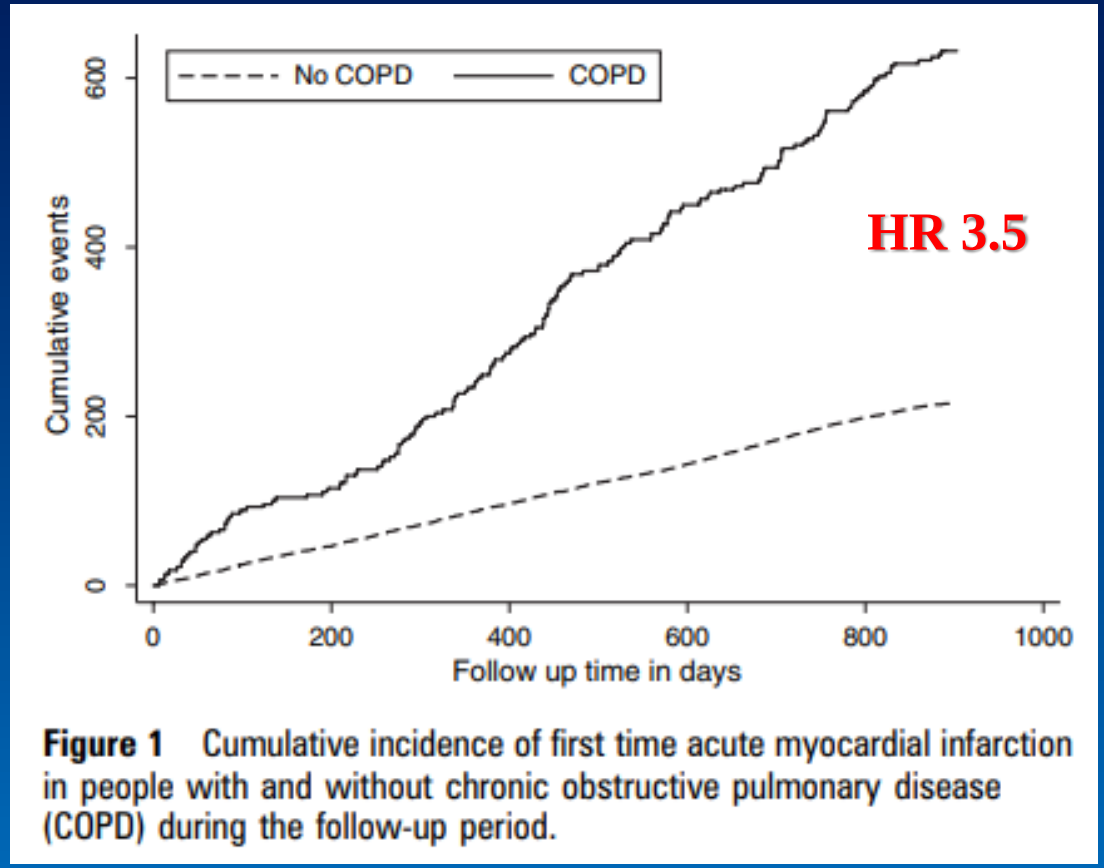

Figure 1 Cumulative incidence of first time acute myocardial infarction in people with and without chronic obstructive pulmonary disease (COPD) during the follow-up period.

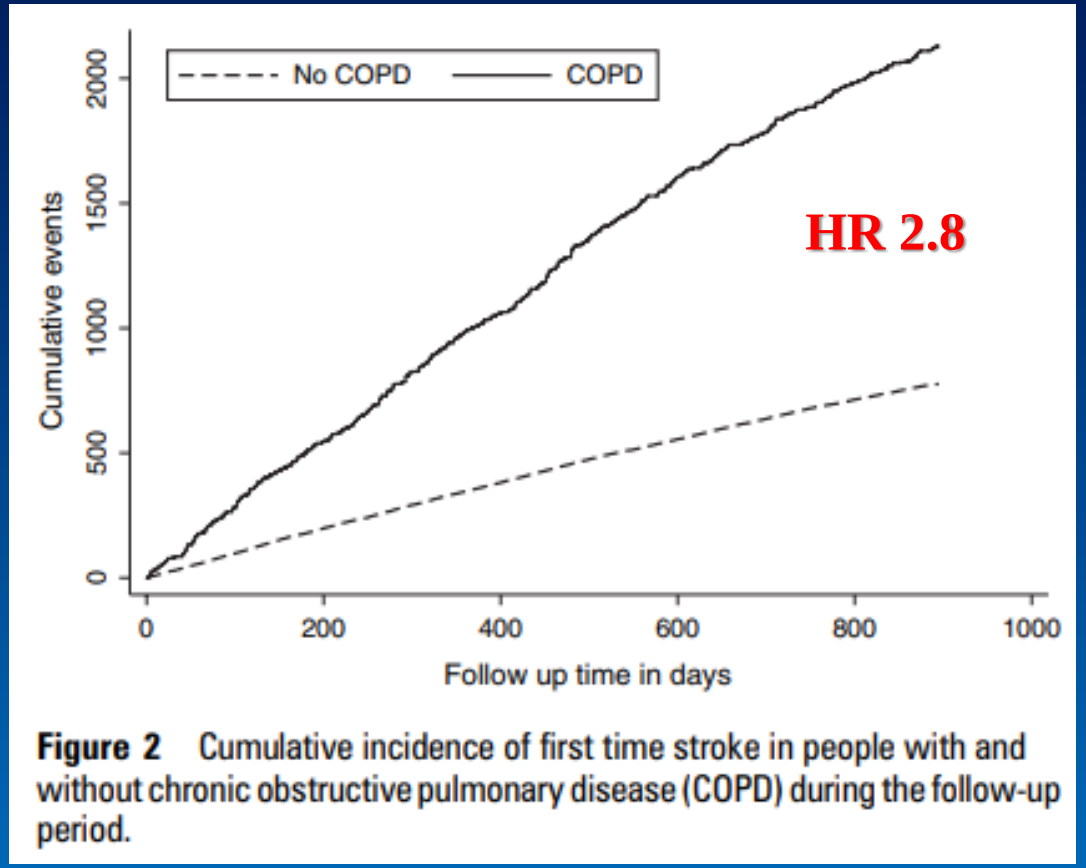

Figure 2 Cumulative incidence of first time stroke in people with and without chronic obstructive pulmonary disease (COPD) during the follow-up period.

Prevalenza BPCO al basale 2.5%
Follow up medio 895 giorni

Feary JR et al. Thorax 2010;65:956e962.

PRINCIPALI CAUSE DI MORTE NEI GRANDI TRIAL SULLA BPCO

Table 1. Causes of death in COPD; data from major clinical trials.

Mean FEV_1 (L)	Cause of death (% of trial participants)				Trial Reference	Study size (n)	Deaths	Study follow-up
	Cardio-vascular	Cancer	Respiratory (non-malignant)	Other				
2.75[a]	22%	54%	8%	16%	LHS III (13)	5887	731	up to 14.5 years
2.54[b]	39%	39%	11%	11%	EUROSCOP (14)	1277	18	3 years
1.41[a]	32%[c]	32%[c]	22%	13%[c]	ISOLDE (15)	751	68	3 years
1.22[a]	26%	21%	35%	18%	TORCH (16, 17)	6184	911	3+ years
1.32[a]	16%	22%	39%	23%	UPLIFT (18, 19)	5993	941	4 years + 30 days

Data from large COPD trials suggest that the predominant causes of death in patients with COPD changes with increasing COPD severity, shifting from mostly cancer and cardiovascular deaths in patients with mild to moderate COPD to non-malignant respiratory deaths in patients with severe COPD. Where FEV_1 is the forced expiratory volume in 1 second, [a] = post-bronchodilator value and [b] = pre-bronchodilator value. [c] Percent of deaths attributed to cardiovascular disease (32.4), cancer (32.4), and other causes (13.2%) were rounded down numerically in the table.

Berry CE, Wise RA. COPD 2010; 7:375–382

EFFETTO MOLTIPLICATIVO DELLA COMORBIDITA' SUL RISCHIO DI MORTE NELLO STUDIO ECLIPSE

Table 3 Cumulative effect of comorbidity mortality in COPD using a logistic regression model adjusting for age, gender and smoking.

Number of comorbidities	Number (%) of subjects with different number of comorbidities	Number of comorbidities	Odds ratio (95% confidence interval)	*p* Value
1	1023 (37%)	1 vs 0	1.74 (1.182–2.56)	0.005
2	902 (32%)	2 vs 0	1.73 (1.131 2.64)	0.011
3	551 (20%)	3 vs 0	2.00 (1.117)	0.011
4+	211 (8%)	4+ vs 0	4.57 (2.30)	<0.001

2164 BPCO, 337 fumatori e 245 non fumatori
Follow up 1060 giorni

Miller J et al. Respir Med 2013; 107: 1376-1384

COMORBIDITA' CARDIOVASCOLARI E METABOLICHE DELLA BPCO
Meccanismi etiopatogenetici

- **Conseguenze dirette della patologia polmonare primitiva**
  - ✓ ipertensione polmonare → disfunzione del ventricolo destro
  - ✓ incremento dei carichi meccanici intra-toracici → anomala funzione del ventricolo sinistro

- **Fattori di rischio condivisi**
  - ✓ fumo di sigaretta → coronaropatia

- **Meccanismi fisiopatologici comuni**
  - ✓infiammazione → aterosclerosi, diabete
  - ✓incremento della rigidità arteriosa → ipertensione arteriosa

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PATOLOGIA CARDIOVASCOLARE E BPCO
Ruolo centrale dell'infiammazione e della risposta immunologica

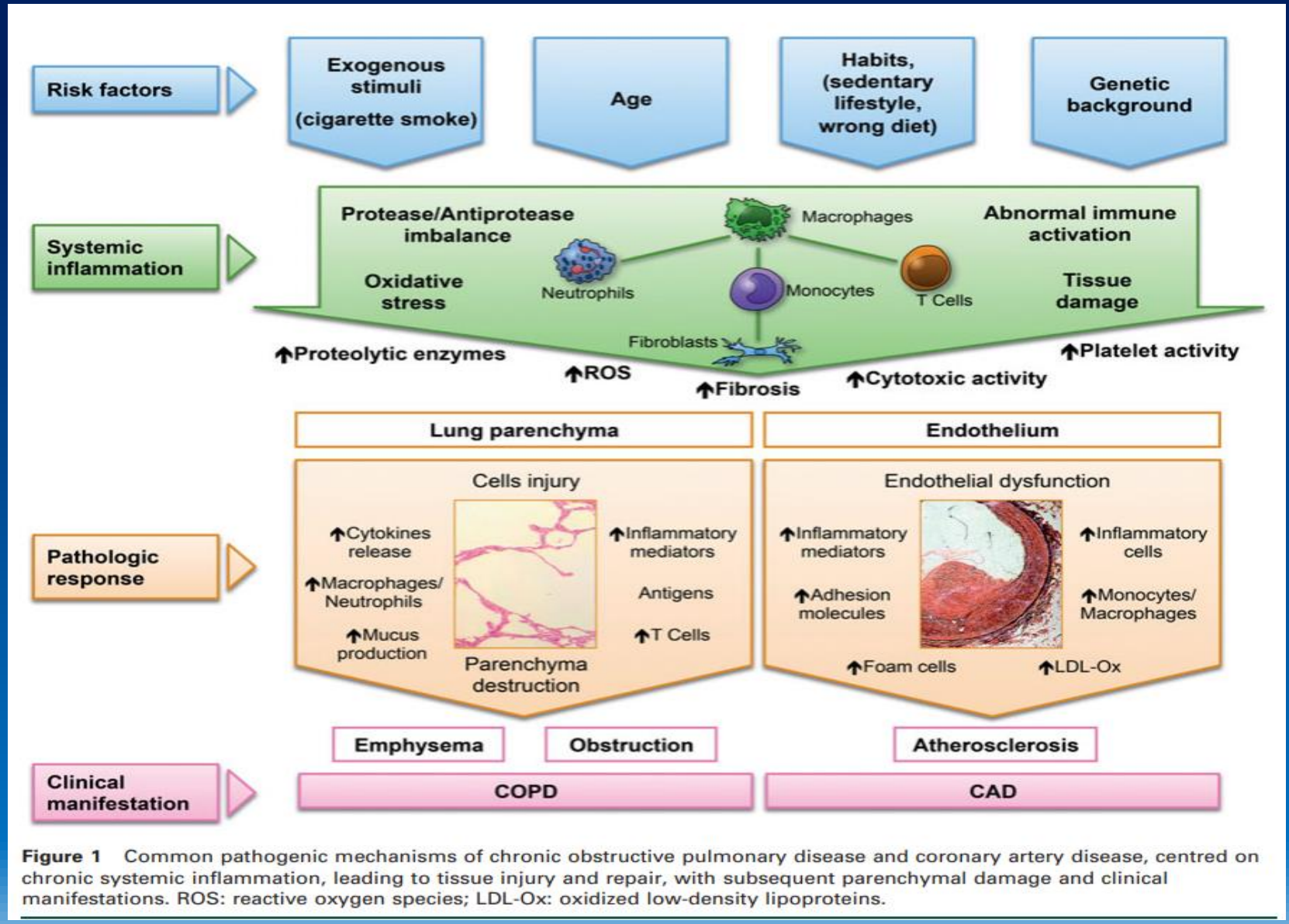


Figure 1 Common pathogenic mechanisms of chronic obstructive pulmonary disease and coronary artery disease, centred on chronic systemic inflammation, leading to tissue injury and repair, with subsequent parenchymal damage and clinical manifestations. ROS: reactive oxygen species; LDL-Ox: oxidized low-density lipoproteins.

Roversi S et al. Eur J Clin Invest 2014; 44: 93–102

INFIAMMAZIONE E BPCO
Correlazione tra BPCO e proteina C reattiva

Author	Group	N	Age (yr)	FEV_1 (% pred)	Current smoker (%)	Men (%)	CRP (mg/l)
Dentener[18]	COPD	55	69 (4)	36 (14)	NR	100	20.4 (21.1)
	Control	23	64 (3)	110 (17)	NR	70	9.0 (16.0)
Eid[19]	COPD	68	68 (7)	31 (8)	100	57	3.5 (3.4)
	Control	45	NR	NR	33	NR	3.1 (1.9)
Mannino[20]	COPD	2366	64 (16)	78 (20)	32	60	3.3 (2.0)
	Control	8446	40 (17)	103 (13)	21	48	2.7 (1.0)
Mendall[21]	COPD	349*	45–59	NR	NR	100	0.8 (2.8)*
	Control	349*	45–59	NR	NR	100	0 (0)
Yasuda[22]	COPD	39	66 (3)	35 (1)	41	69	18.7 (17.8)
	Control	22	66 (1)	82 (0)	32	68	0.9 (2.8)

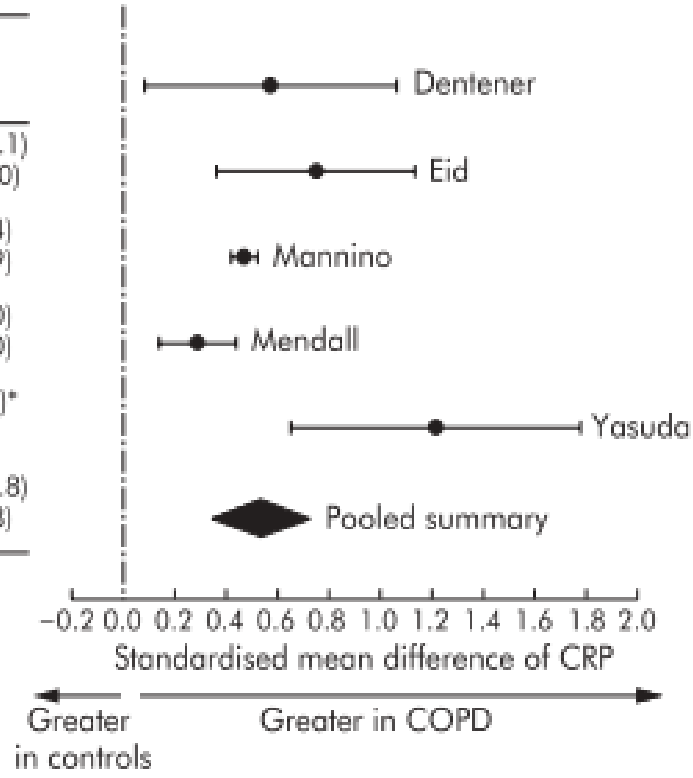


Figure 2 Relationship between C-reactive protein (CRP) and COPD. Continuous variables are expressed as mean (SD) unless otherwise specified. *Imputed from the regression coefficient between mean FEV_1 (25–75th percentile) and CRP.

Gan WQ et al. Thorax 2004; 59: 574-580

INFIAMMAZIONE E BPCO
Correlazione tra BPCO e fibrinogeno

Author	Group	N	Age (yr)	FEV_1 (% pred)	Current smoker (%)	Men (%)	Fibrinogen (g/l)
Alessandri[24]	COPD	37	68 (8)	1.1 (0.5)*	19	73	3.0 (0.9)
	Control	30	58 (10)	NR	20	70	2.3 (0.5)
Dahl[25] Smokers	COPD	1427	62 (12)	66 (15)	100	51	3.5 (1.0)
	Control	785	55 (15)	117 (9)	100	43	3.0 (0.8)
Engstrom[126] Smokers	COPD	720	47 (4)‡	<85	100	NR	3.8 (0.9)
	Control	449	47 (4)‡	>105	100	NR	3.6 (0.8)
Mannino[20]	COPD	2065	67 (12)	77 (21)	31	60	3.1 (0.6)
	Control	3488	57 (13)	104 (14)	17	47	2.8 (0.5)

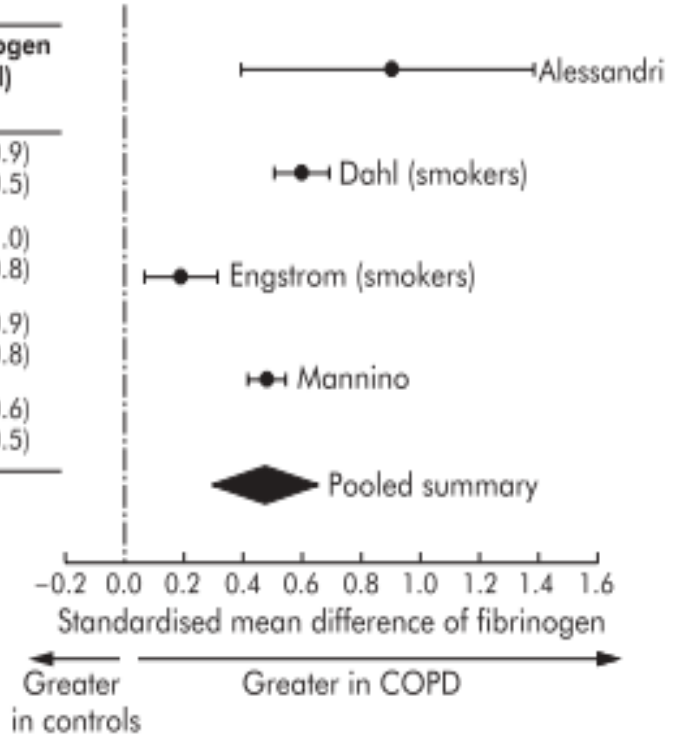


Figure 3 Relationship between fibrinogen and COPD. Continuous variables are expressed as mean (SD) unless otherwise specified. *FEV_1 in litres. †Based on forced vital capacity. ‡Estimated.

Gan WQ et al. Thorax 2004; 59: 574-580

INFIAMMAZIONE E BPCO

Indici infiammatori in 1755 pazienti BPCO, 297 fumatori con normale funzione polmonare e 202 non fumatori dello studio ECLIPSE

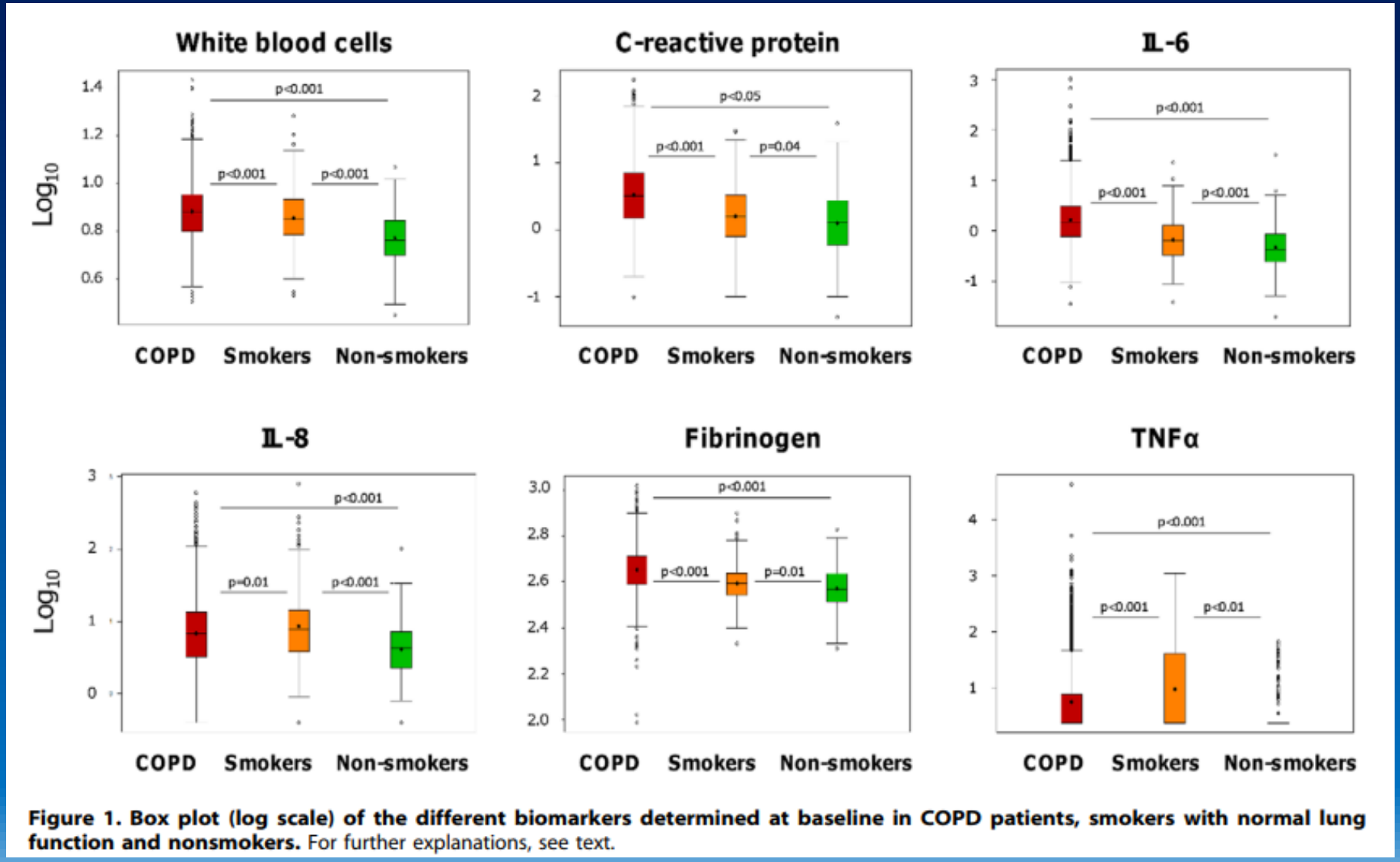


Figure 1. Box plot (log scale) of the different biomarkers determined at baseline in COPD patients, smokers with normal lung function and nonsmokers. For further explanations, see text.

Agusti A et al. PLoS ONE 2012; 7: e37483

INFIAMMAZIONE E BPCO
Indici infiammatori e sopravvivenza a 3 anni in 1843 pazienti BPCO dello studio ECLIPSE

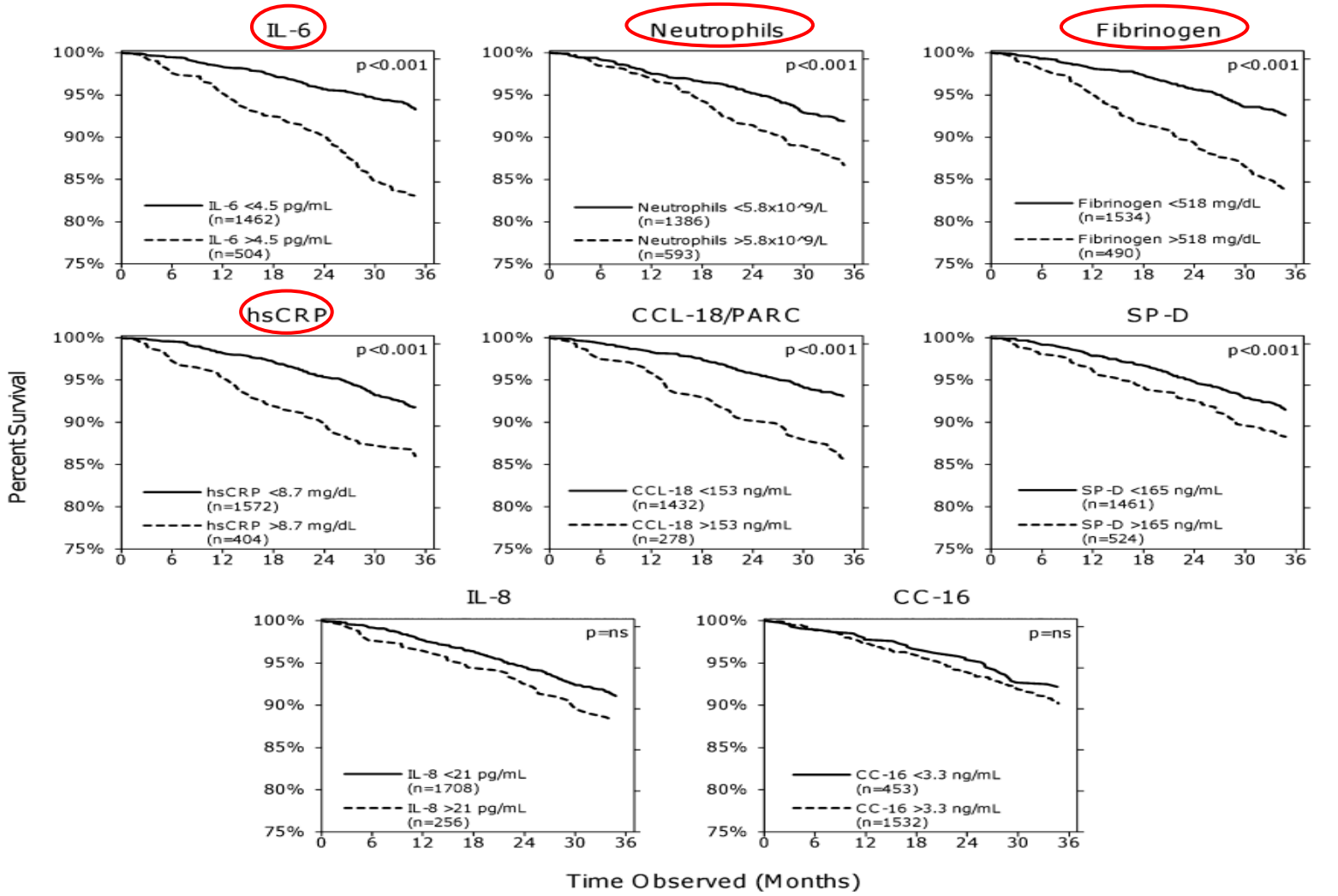
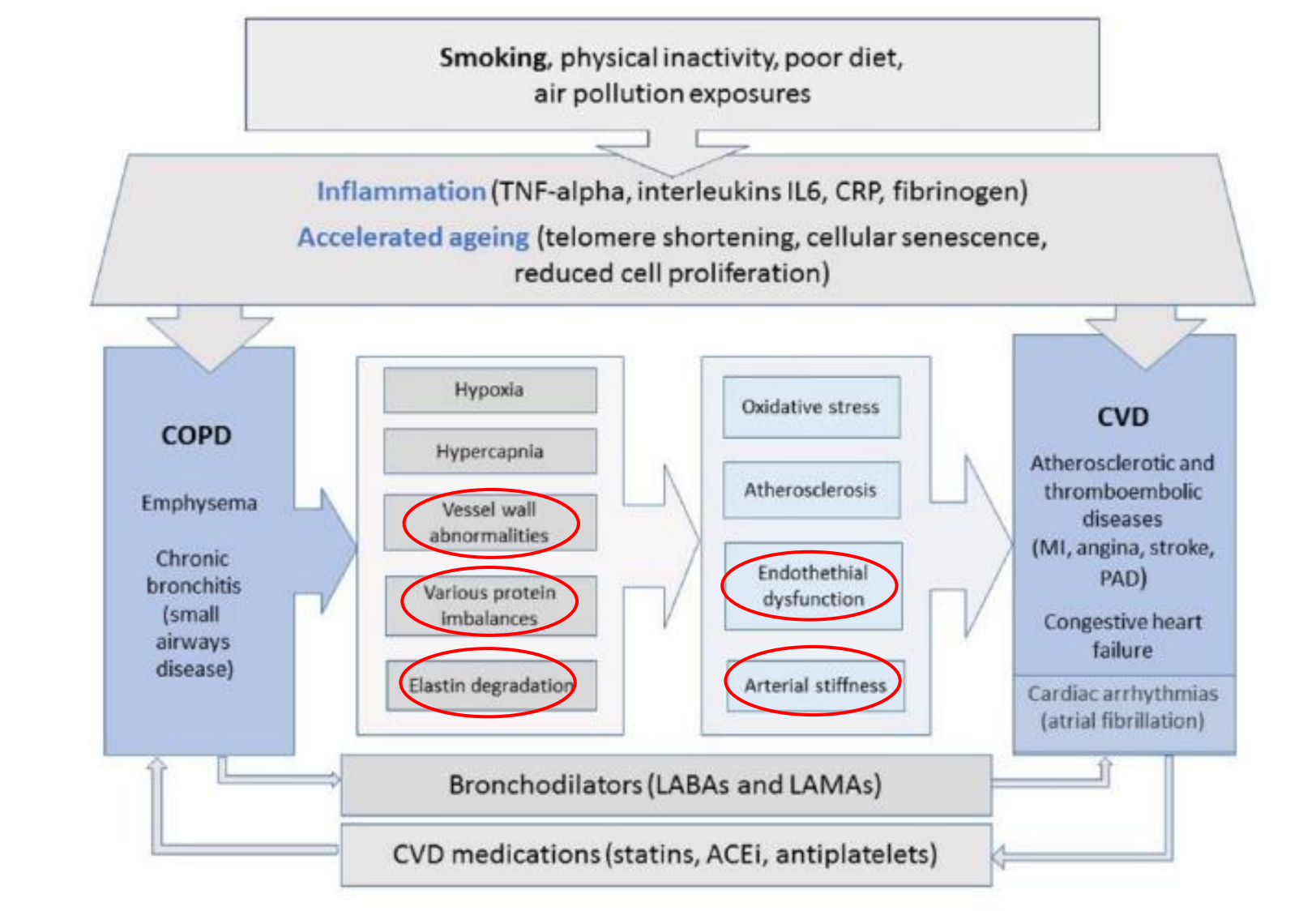


Figure 3. Kaplan-Meier survival curves for the panel of biomarkers analyzed (white blood cell curves are not included in the graph but were very similar to that of neutrophils). Cut-off values correspond to the 95% percentile determined in the nonsmoking control subjects included in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study. CC-16 = Clara cell secretory protein-16; CCL-18/PARC = chemokine ligand 18/pulmonary and activation-regulated chemokine; hsCRP = high-sensitivity C-reactive protein; SP-D = surfactant protein D.

Celli BR et al. Am J Respir Crit Care Med 2012; 185:1065–1072

COMORBIDITA' CARDIOVASCOLARI DELLA BPCO
Meccanismi fisiopatogenetici



Morgan AD et al. Ther Adv Res Dis 2018; 12: 1-16

ALTERAZIONI DELLA STIFFNESS VASCOLARE E BPCO
Correlazione tra la gravità dell'enfisema polmonare e rigidità arteriosa in 75 pazienti BPCO

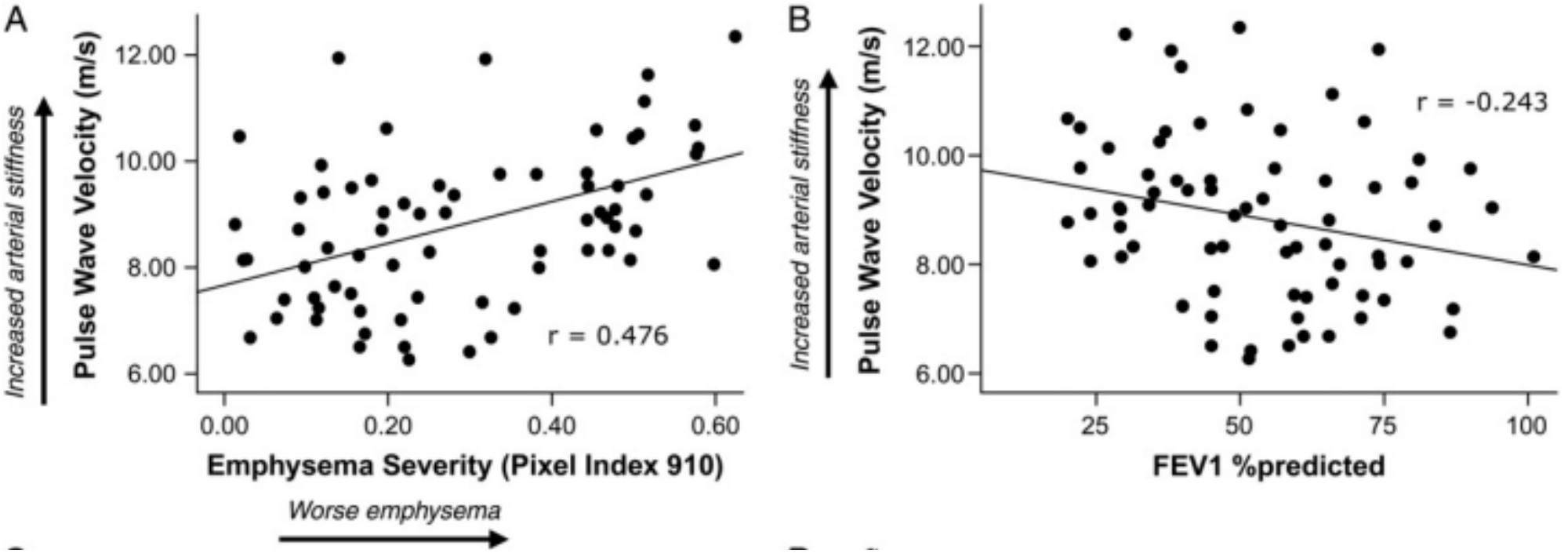


Figure 1. Associations between emphysema severity, FEV_1% predicted and arterial stiffness in the high-resolution computed tomography subgroup. Scatter plots of pulse wave velocity on emphysema severity (*A*), and airflow limitation (*B*). Scatter plot of emphysema severity on airflow

Nessuna correlazione tra PWV e hs-PCR, leucociti, p/ys

McAllister DA et al. Am J Respir Crit Care Med 2007; 176: 1208-1214

ALTERAZIONI DELLA STIFFNESS VASCOLARE E BPCO

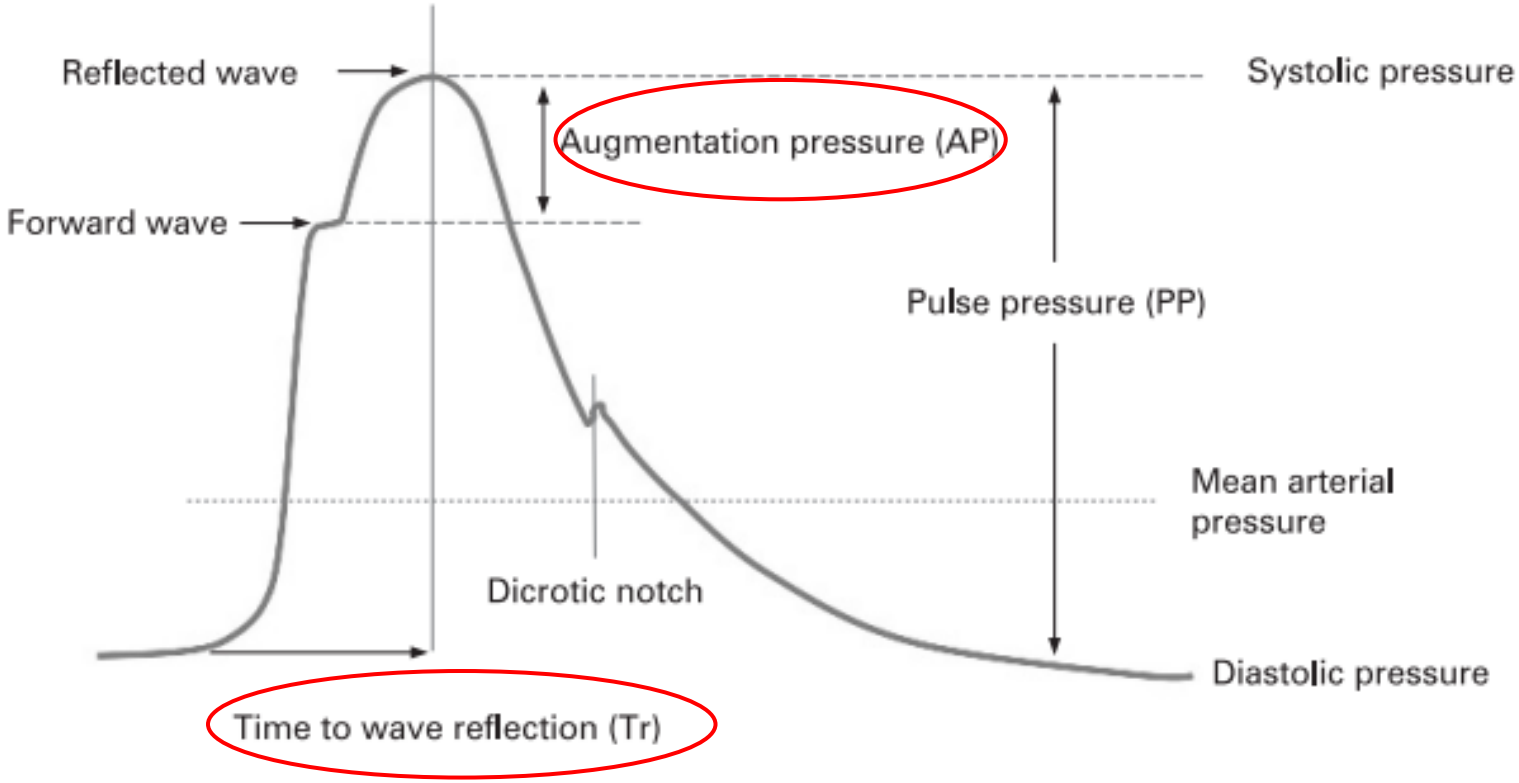


Figure 1 An aortic pulse waveform as produced by the SphygmoCor system from applanation tonometry of the radial artery. Augmentation pressure is the difference between the systolic peak (forward wave) and first systolic inflection (reflected wave) pressures. This difference divided by the pulse pressure generates the augmentation index. Adapted from Smith *et al* 2000.[35]

Mills NL et al. Thorax 2008; 63: 306-311

ALTERAZIONI DELLA STIFFNESS VASCOLARE E BPCO

Augmentation pressure media e tempo medio di riflessione dell'onda sfigmica in uno studio prospettico di 103 soggetti sani e 102 pazienti BPCO

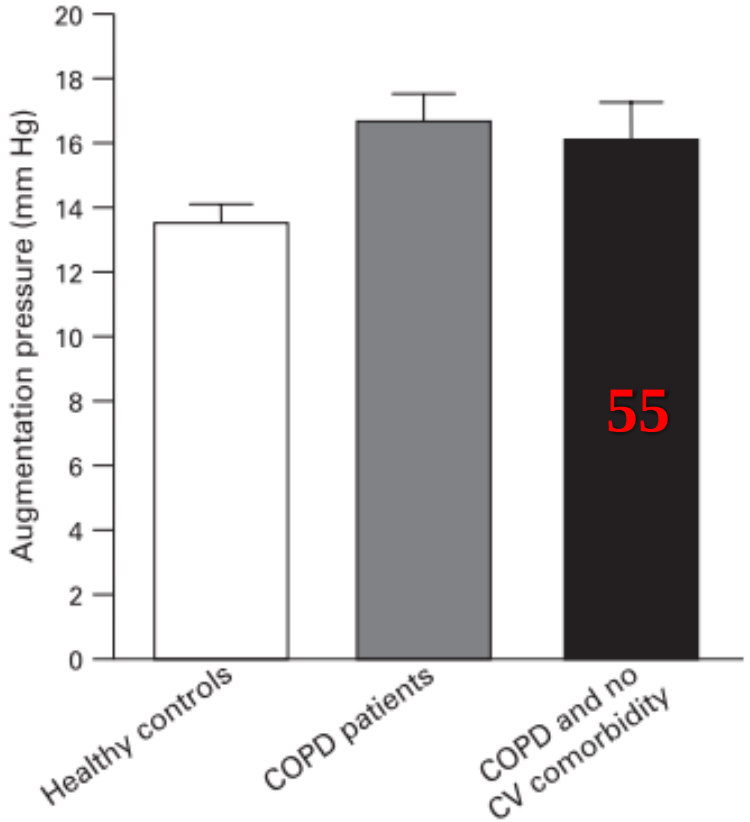


Figure 2 Mean augmentation pressure, a measure of arterial stiffness, was greater in patients with chronic obstructive pulmonary disease (COPD) ($p = 0.005$) and the subgroup of patients with COPD and no cardiovascular (CV) comorbidity ($p = 0.04$) compared with healthy controls matched for age and current smoking status.

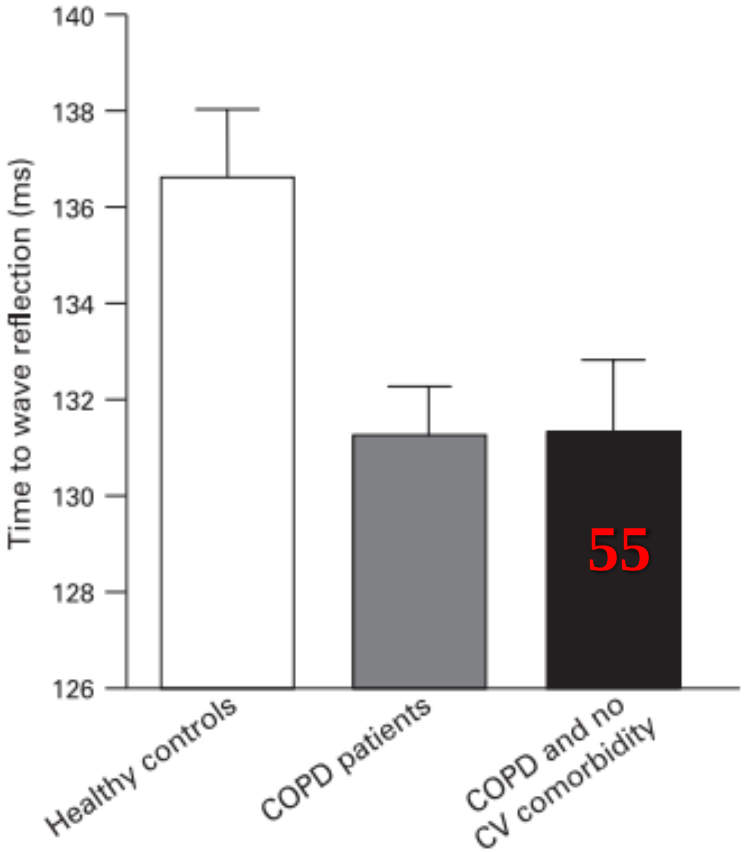
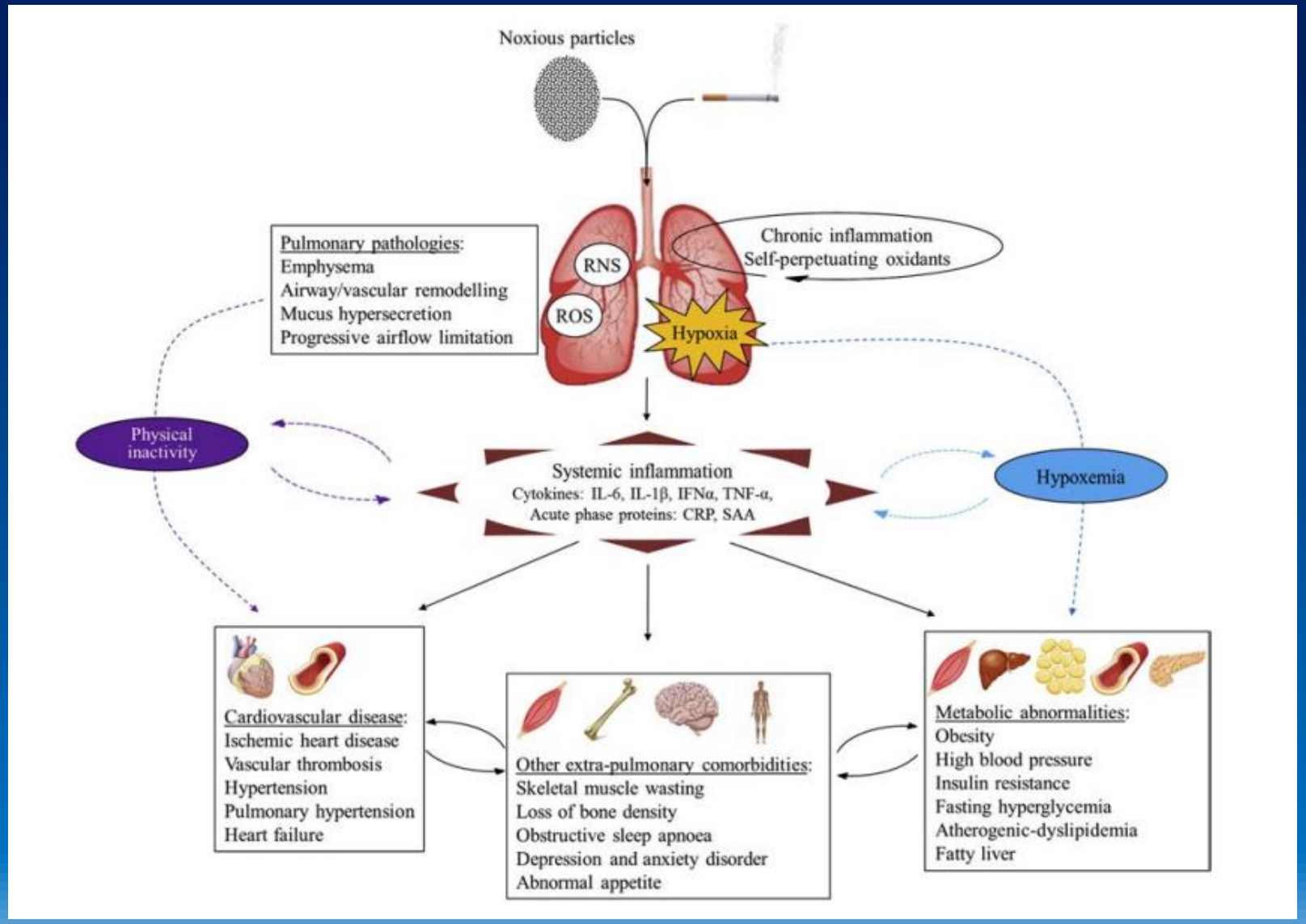


Figure 3 Mean time to wave reflection was reduced in patients with chronic obstructive pulmonary disease (COPD) ($p = 0.004$) and the subgroup of patients with COPD and no cardiovascular (CV) comorbidity ($p = 0.03$) compared with healthy controls matched for age and current smoking status.

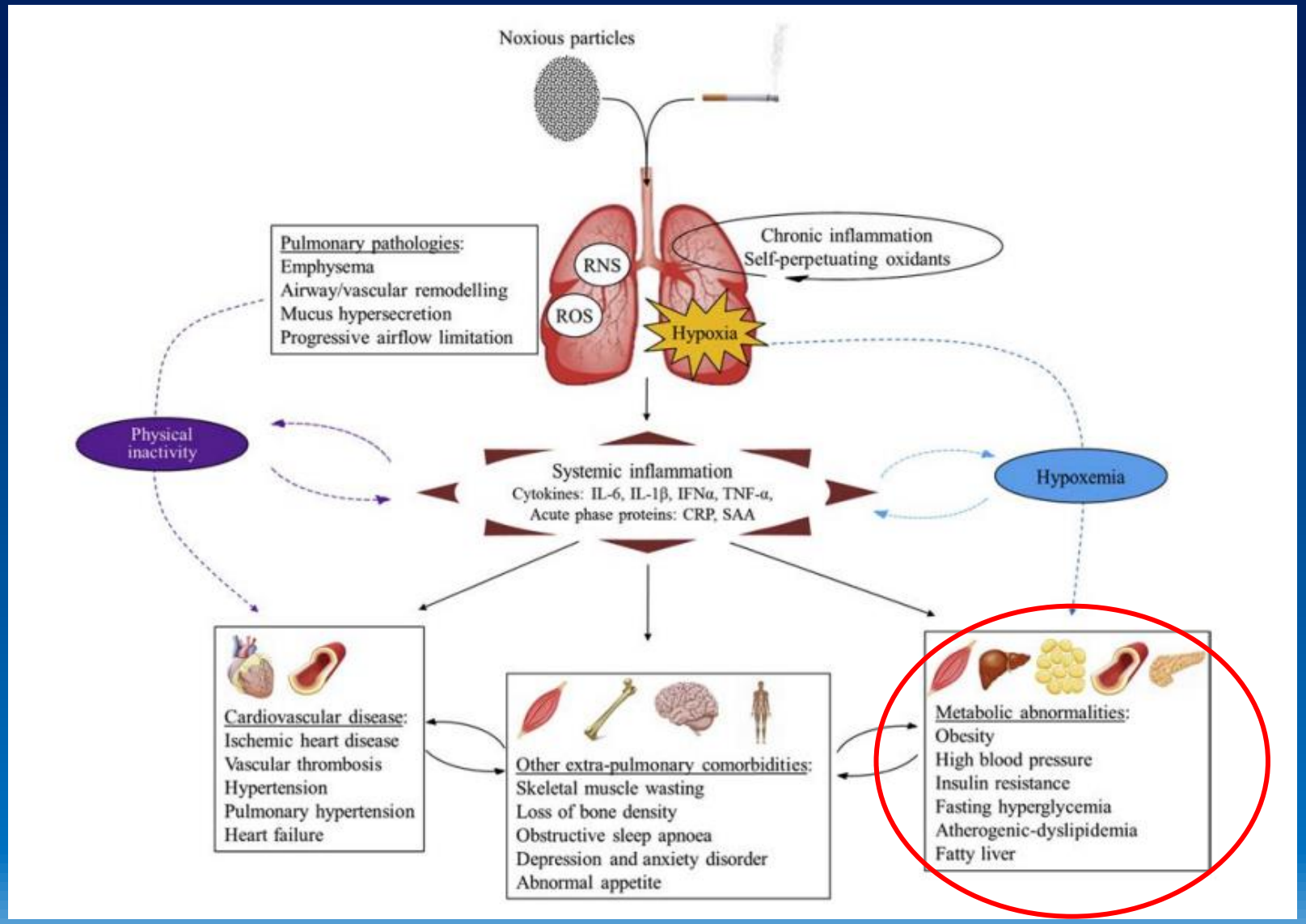
Mills NL et al. Thorax 2008; 63: 306-311

COMORBIDITA' METABOLICHE DELLA BPCO
Meccanismi fisiopatogenetici



SMH Chan et al. Pharmacol & Ther 2019; 198: 160–188

COMORBIDITA' METABOLICHE DELLA BPCO
Meccanismi fisiopatogenetici



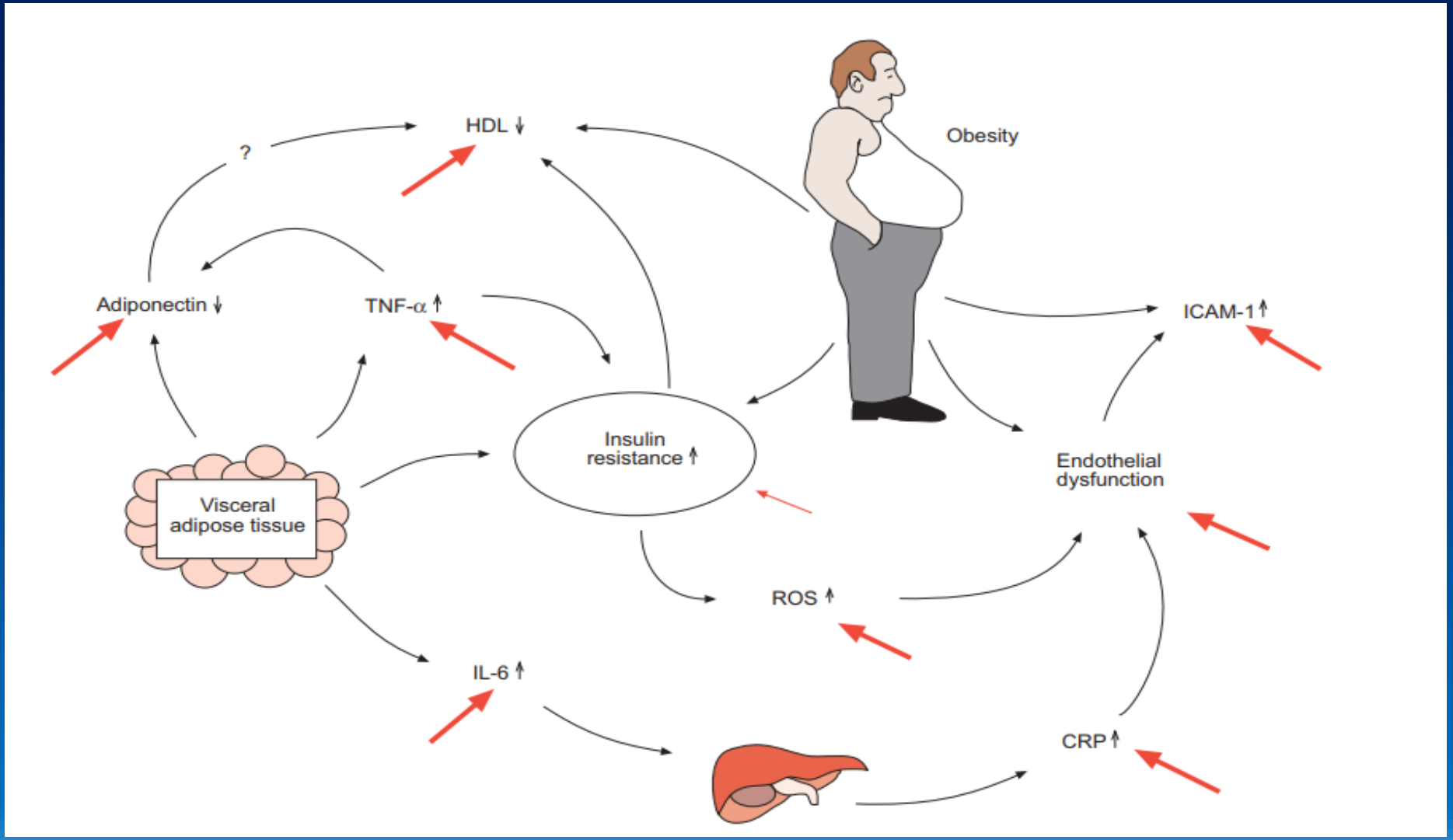
SMH Chan et al. Pharmacol & Ther 2019; 198: 160–188

COMORBIDITA' METABOLICHE DELLA BPCO
Sindrome Metabolica, Diabete Mellito tipo 2 e BPCO

- **Fumo di sigaretta:** il tabacco riduce direttamente l'attività insulinica e la captazione periferica di glucosio
- **Aumentata prevalenza di obesità:** l'aumento del BMI e del tessuto adiposo è associato all'infiammazione e ad una ridotta sensibilità insulinica
- **Ridotta attività fisica**
- **Infiammazione** legata alla patologia: le citochine proinfiammatorie provocano resistenza insulinica interferendo con il signaling del recettore insulinico
- **Stress ossidativo:** incrementa la resistenza insulinica e altera la produzione di energia
- **Esposizione ai corticosteroidi**

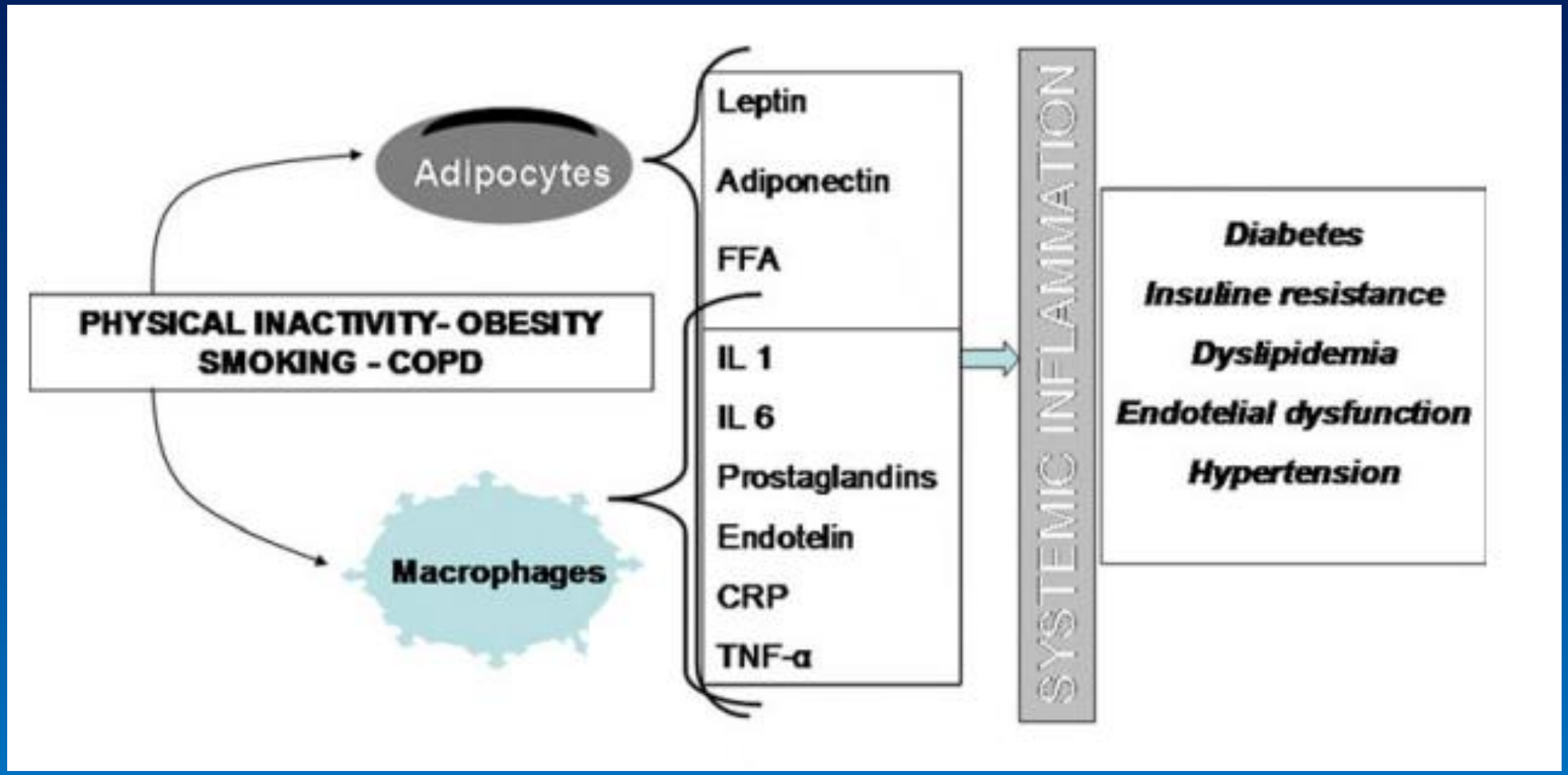
Cazzola M et al. Trends Pharmacol Sci 2017; 38: 940–951

FUMO, OBESITA' E COMORBIDITA' METABOLICHE DELLA BPCO
Meccanismi fisiopatogenetici



Fabbri LM et al. Eur Respir J 2008; 31: 204–212

COMORBIDITA' METABOLICHE DELLA BPCO
Meccanismi fisiopatogenetici e ruolo del tessuto adiposo

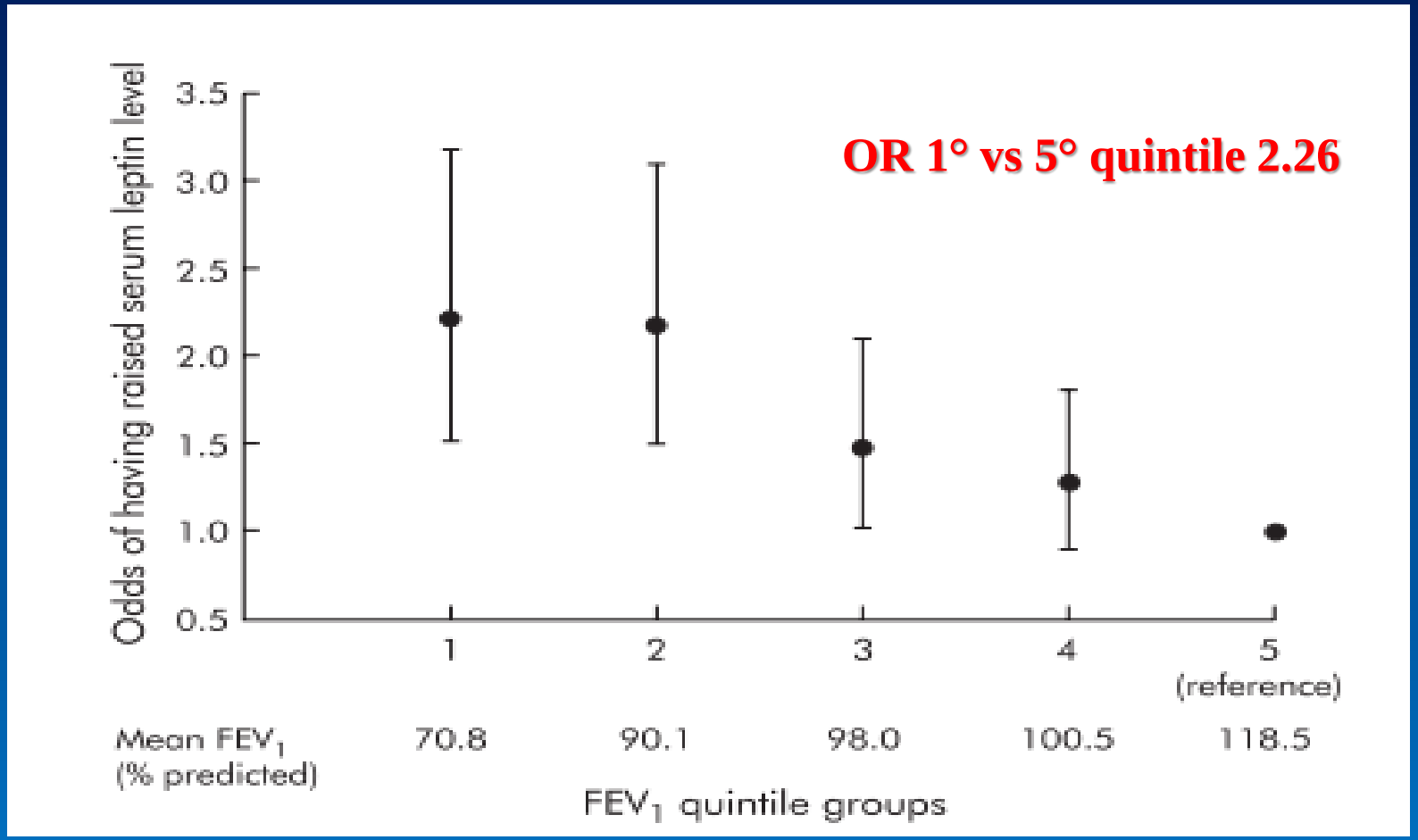


Clini C et al. Intern Emerg Med 2013; 8:283–289

COMORBIDITA' METABOLICHE DELLA BPCO

FEV-1 e livelli di leptina
in 2808 soggetti normopeso arruolati nel NHANES-3

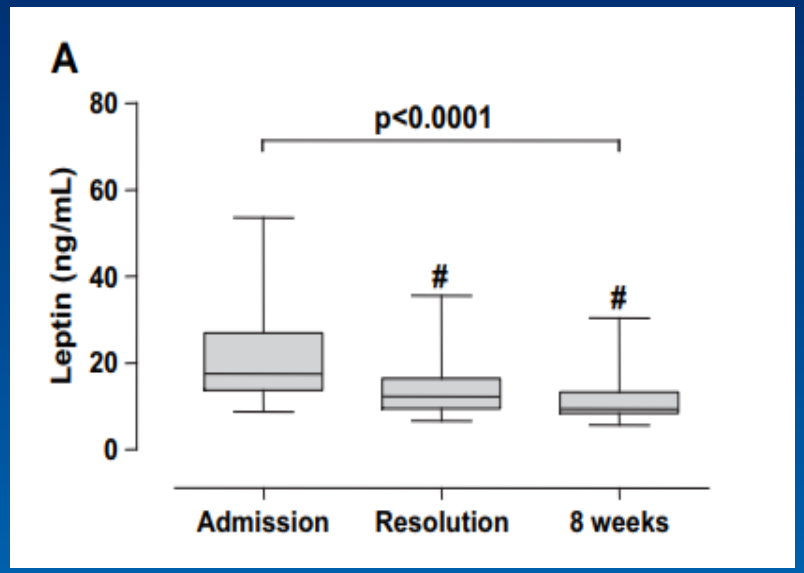
47.5% maschi
29.6% fumatori

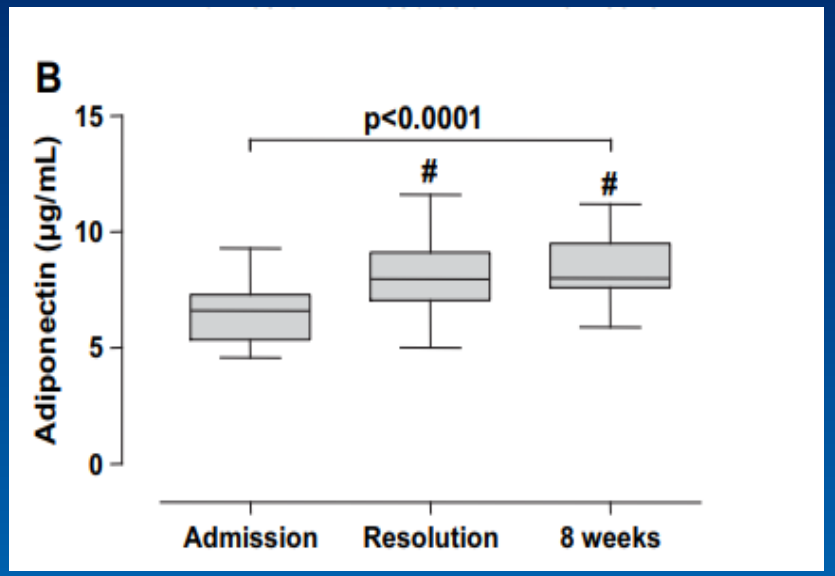


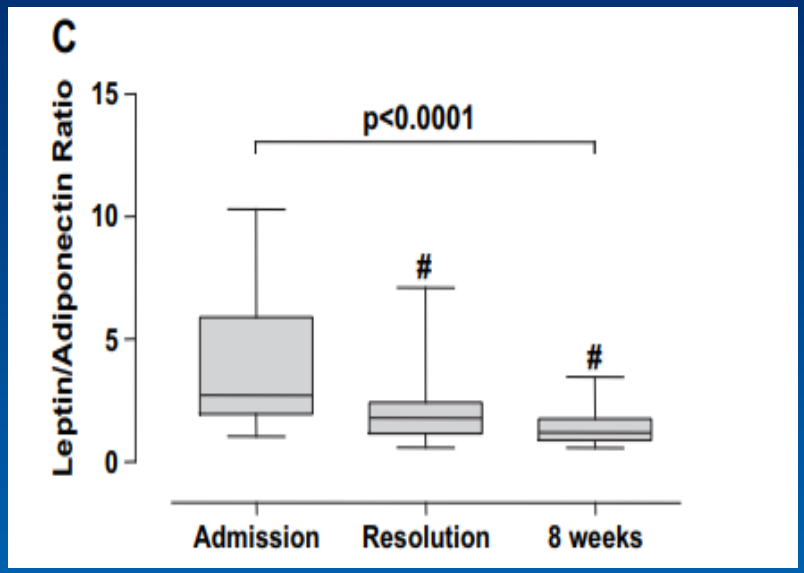
Sin DD et al. Thorax 2003;58:695–698

COMORBIDITA' METABOLICHE DELLA BPCO

Livelli di leptina e adiponectina in 63 pazienti senza comorbidità, ricoverati per riacutizzazione di BPCO al basale, dopo risoluzione dell'acuzie e dopo 8 settimane







# p <0.05 rispetto al basale

Krommidas G et al. Respiratory Medicine 2010; 104, 40-46

COMORBIDITA' METABOLICHE DELLA BPCO

Associazione tra leptina, adiponectina e citochine infiammatorie in 63 pazienti ricoverati per riacutizzazione di BPCO

Table 3 Associations between leptin, adiponectin and their ratio and the levels of inflammatory cytokines on admission.

	log Leptin			log Adiponectin			log Leptin/Adiponectin Ratio		
	B	95% CI for B	*p*-value	B	95% CI for B	*p*-value	B	95% CI for B	*p*-value
CRP	0.030	0.004–0.055	**0.025**	−0.015	−0.025–−0.005	**0.006**	0.041	0.005–0.076	**0.025**
IL-6	0.051	0021–0.082	**0.001**	−0.018	−0.031–−0.005	**0.008**	0.069	0.027–0.111	**0.002**
TNF-α	0.137	0.041–0.233	**0.006**	−0.036	−0.087–−0.006	**0.025**	0.166	0.032–0.300	**0.016**

Associations are presented after adjustment for age, gender, BMI, smoking habit, treatment regimens before admission, PaO_2/FiO_2 ratio and $PaCO_2$. B represents the unstandardized coefficient. Bold figures represent statistically significant linear relations. CI: confidence intervals, CRP: C-reactive protein, IL-6: interleukin-6, TNF-α: Tumor necrosis factor alpha.

Krommidas G et al. Respiratory Medicine 2010; 104, 40-46

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report

GOLD Executive Summary

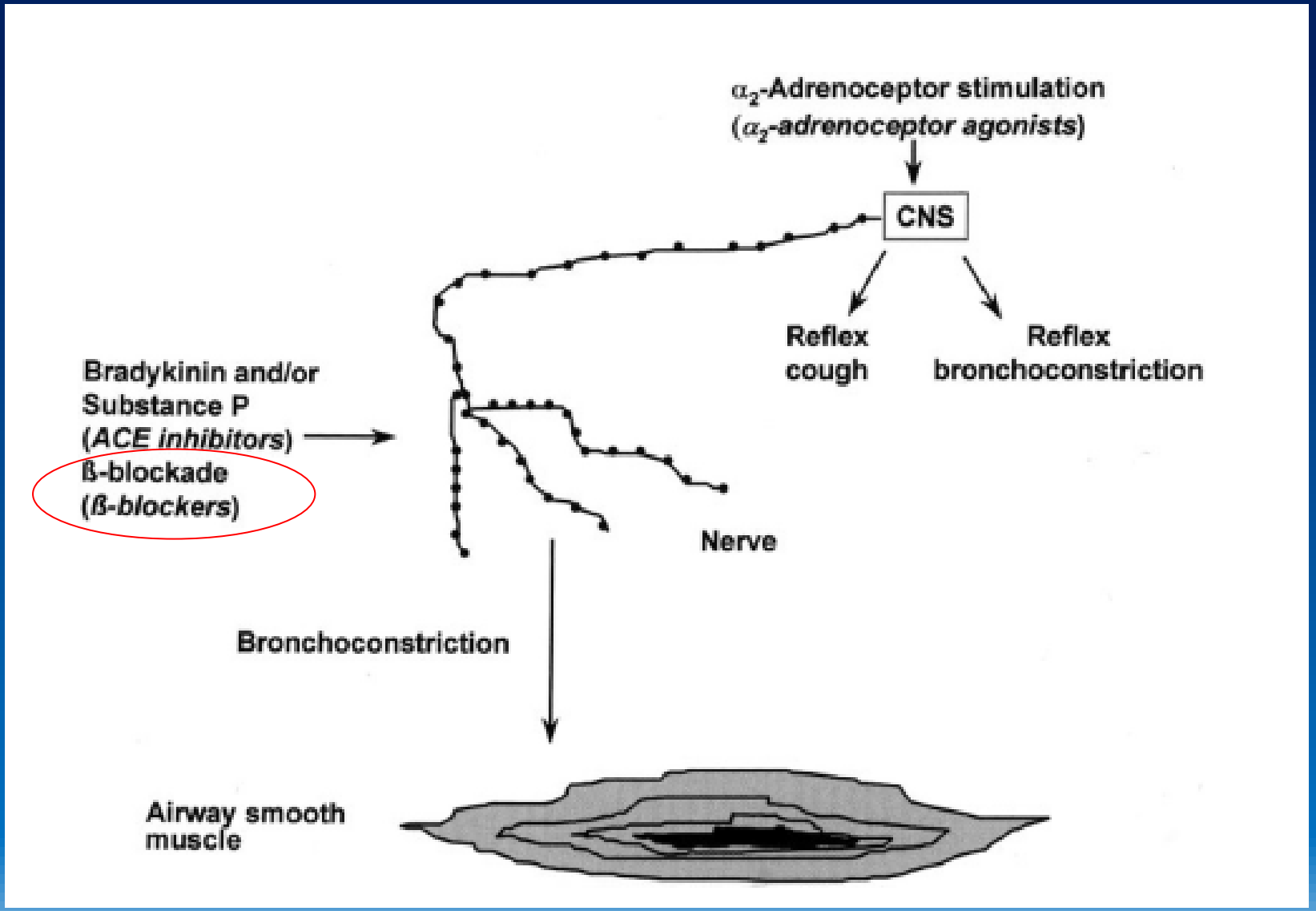
Key Points:

- COPD often coexists with other diseases (comorbidities) that may significantly impact patient outcomes.
- The presence of comorbidities should not alter COPD treatment, and comorbidities should be treated per usual standards regardless of the presence of COPD.
- When COPD is part of a multimorbidity care plan, attention should be directed to ensure simplicity of treatment and minimize polypharmacy.

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis (63, 296–302). Some of these arise independently of COPD, whereas others may be causally related, either with shared risk factors or by one disease increasing the risk or compounding the severity of the other (303). Management of the patient with COPD must include identification and treatment of its comorbidities; the most common in COPD are outlined below.

Vogelmeier CF et al. Am J Res Crit Care Med 2017; 195: 557-582

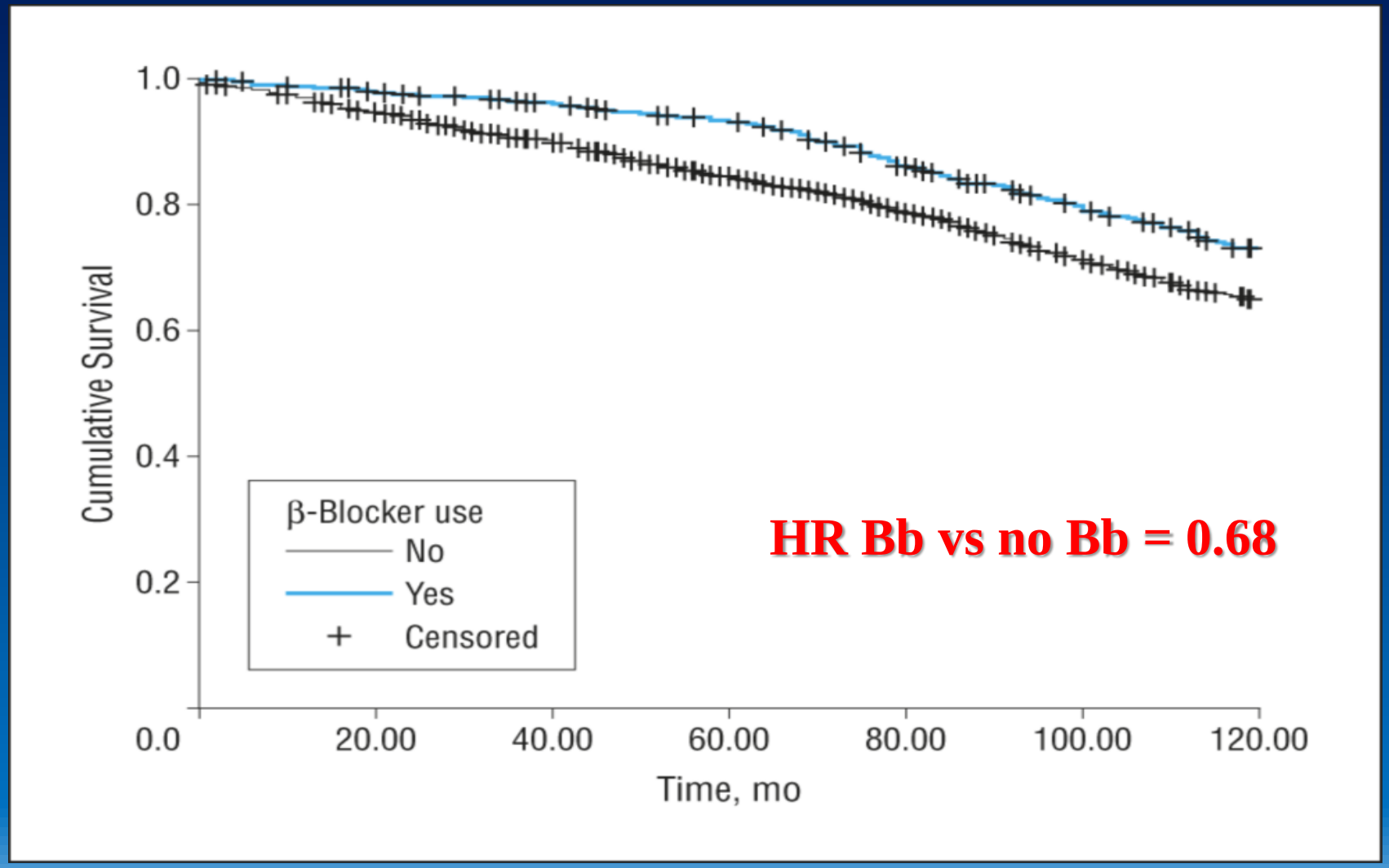
BETA BLOCCANTI E BPCO



Cazzola M et al. Chest 2002; 121:230–241

BETA BLOCCANTI E BPCO

Sopravvivenza cumulativa di 2230 pazienti BPCO di un database di medicina generale olandese sulla base dell'utilizzo di beta bloccanti



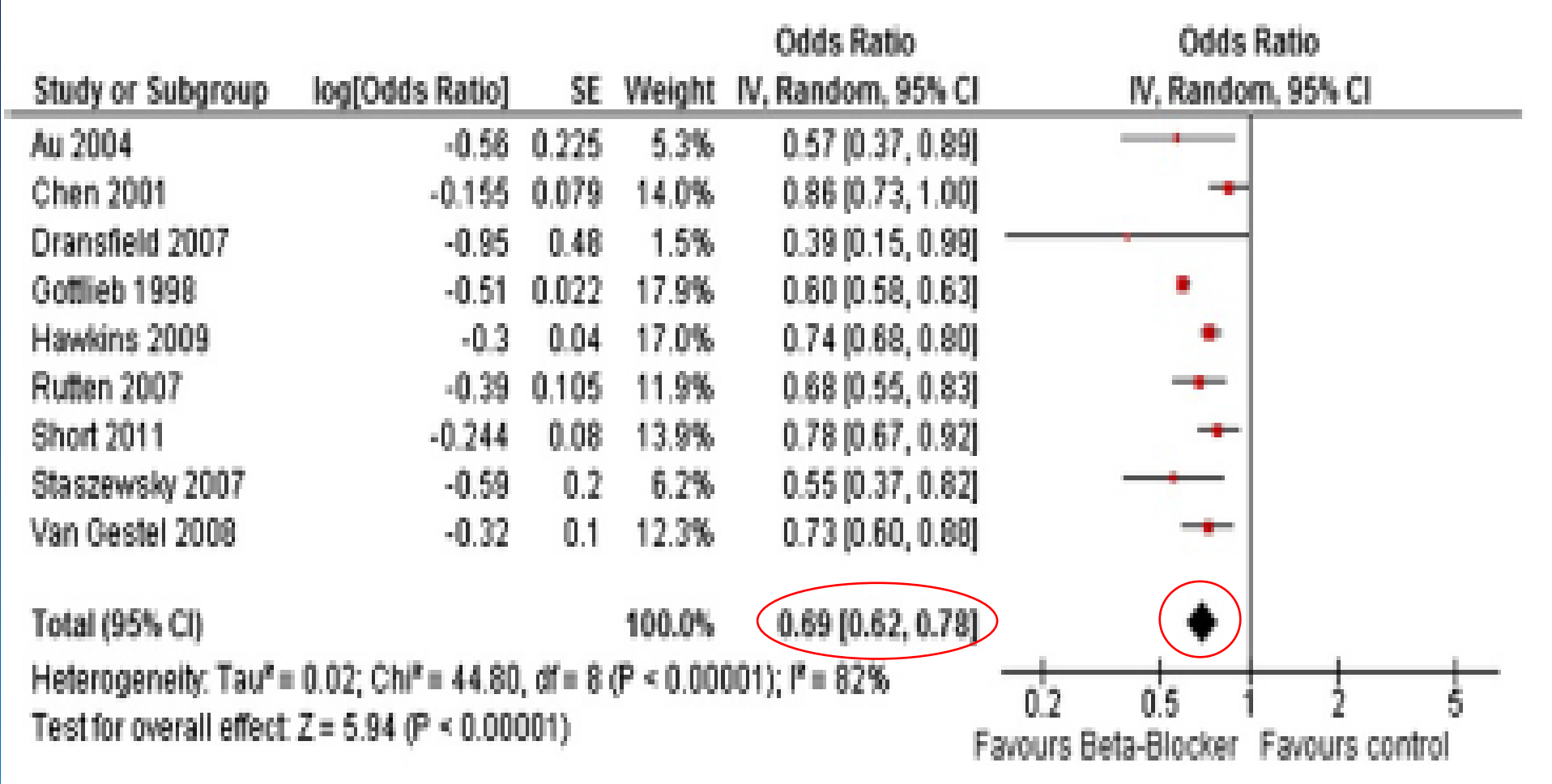
FU medio 7 anni
Mortalità 30.8%

Rutten FH et al. Arch Intern Med 2010;170: 880-887

BETA BLOCCANTI E BPCO

Rischio relativo di mortalità in pazienti BPCO sulla base dell'utilizzo di beta bloccanti

Metanalisi di 9 studi retrospettivi



Etminan M et al. BMC Pulm Med 2012;12: 48

BETA BLOCCANTI E BPCO

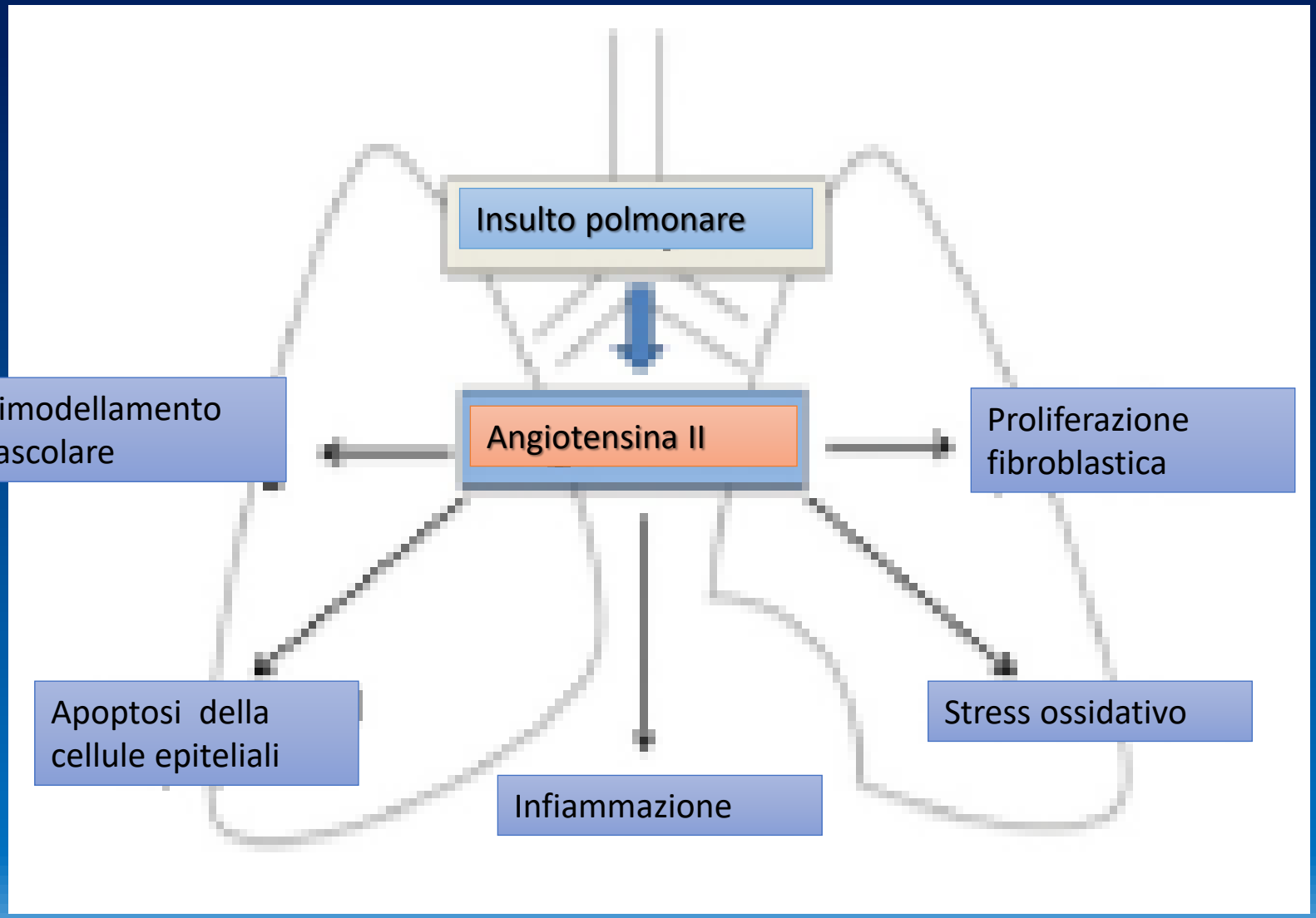
Table 2 Main studies evaluating the role of β-blockers in COPD patients

References	Patients (*n*)	COPD diagnosis	Study population characteristics	Design	Main findings
Rutten *et al.*[32]	2230	Age ≥ 45 years and incident or prevalent diagnosis of COPD (ICD 9 and 10)	Hospitalization for AECOPD	Observational cohort study	Reduction of mortality (HR 0.68; 95% CI 0.5–0.8) Reduction of AECOPD (0.71; 95% CI 0.6–0.8) Reduction of mortality in BB and LABA users (HR 0.6; 95% CI 0.5–0.8)
Short *et al.*[12]	5977	GOLD criteria	Hospitalization for COPD (ICD 9 and 10)	Retrospective cohort study	Reduction in mortality (HR 0.2; 95% CI 0.2–0.4)
Zeng *et al.*[22]	220	Spirometric data	Hospital admission in Geriatrics department	Retrospective cohort study	No relation with mortality
Quint *et al.*[27]	1063	Previous diagnosis of COPD	COPD patients experiencing first MI	Population-based cohort study	Reduction of mortality for BB chronically users (HR 0.59, 95% CI 0.4–0.7) Reduction of mortality for new prescribed BB (HR 0.5, 95% CI 0.3–0.7)
Angeloni *et al.*[33]	388	GOLD criteria	COPD patients undergoing CABG	Propensity-matched cohorts with prospective follow-up	Increased survival rate in BB users (91 ± 3% vs. 80 ± 4%) No variation in AECOPD
Lee *et al.*[34]	1062	Previous diagnosis of COPD (ICD 9 and 10)	Outpatient or hospital diagnosis within 12 months	Population-based cohort study	No difference in all-cause mortality

COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; ICD, international classification of disease; HR, hazard risk; CI, confidence interval; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BB, β-blockers; LABA, long-acting β2 agonists; CABG, coronary artery bypass graft.

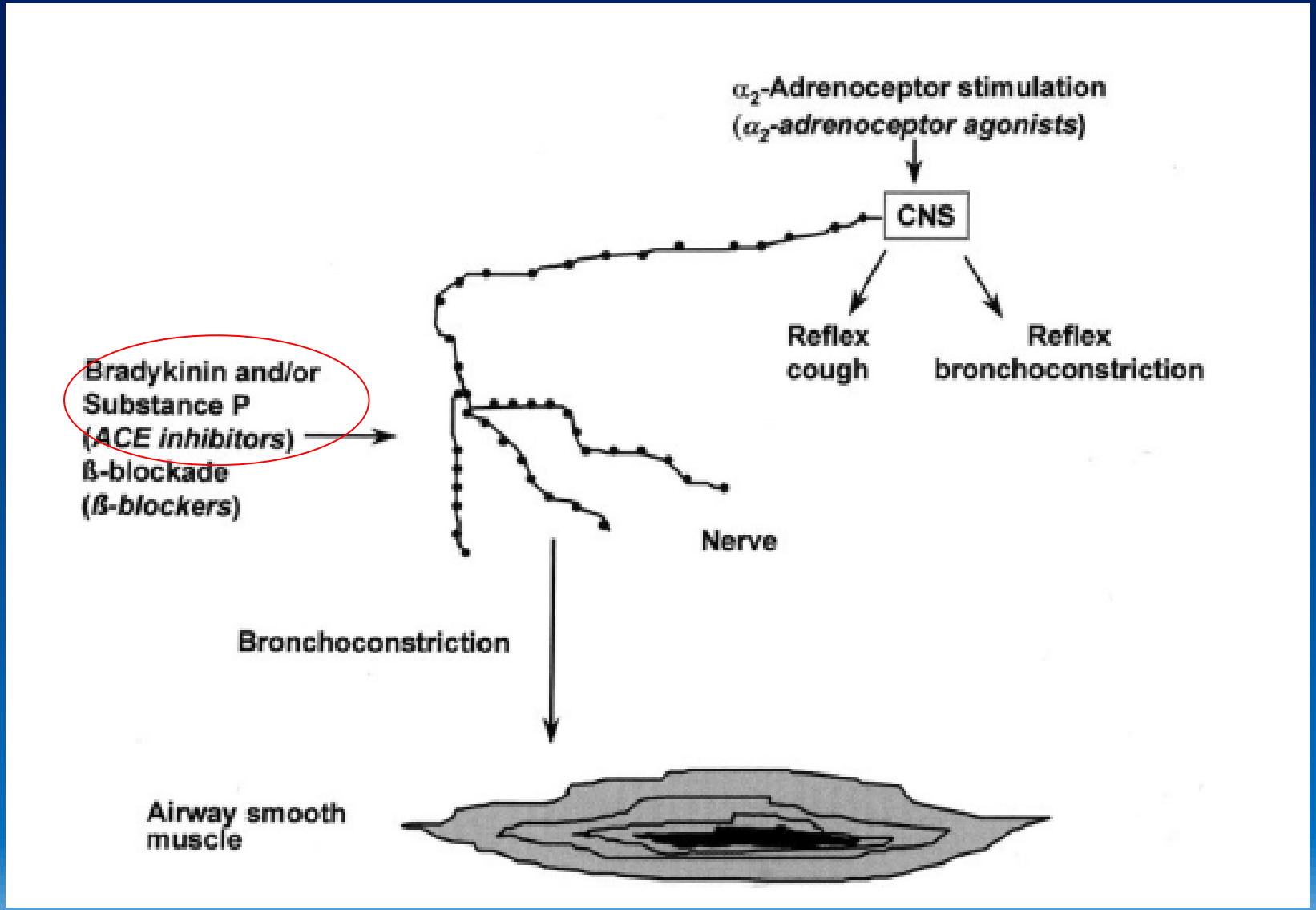
Campo G et al Eur Heart J Cardiovasc Pharmacother 2015; 1: 205–211

BLOCCANTI DEL SISTEMA RENINA-ANGIOTENSINA E BPCO



Shrikrishna S et al, Clinical Science 2012; 123: 487-498

BLOCCANTI DEL SISTEMA RENINA-ANGIOTENSINA E BPCO

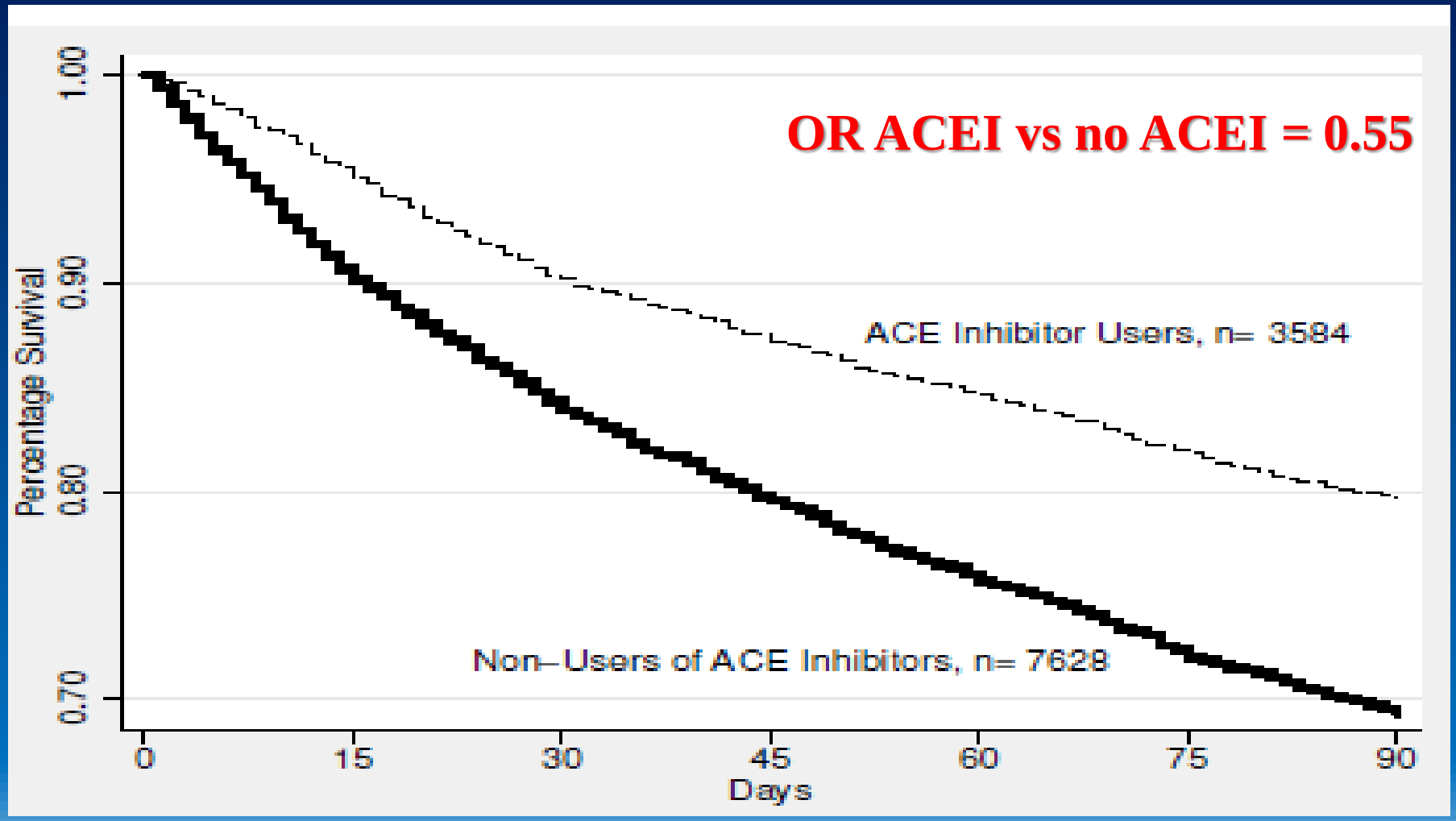


Cazzola M et al. Chest 2002; 121:230–241

BLOCCANTI DEL SISTEMA RENINA-ANGIOTENSINA E BPCO

Sopravvivenza cumulativa di 11212 pazienti ospedalizzati per riacutizzazione di BPCO sulla base dell'utilizzo di ACE Inibitori

Mortalità 12.4%



Mortensen EM et al. Resp Res 2009; 10: 45

BLOCCANTI DEL SISTEMA RENINA-ANGIOTENSINA E BPCO

Table I Main studies evaluating the role of angiotensin converting enzyme inhibitors or angiotensin receptor blockers in chronic obstructive pulmonary disease patients

References	Patients (*n*)	COPD diagnosis	Study population characteristics	Design	Main findings
Studies on all-cause mortality					
Mortensen *et al.*[20]	11 212	Previous diagnosis of COPD (ICD 9)	Hospitalization for AECOPD and treated with LABA, ICS, ACh	Retrospective	Reduction 90 days mortality (OR 0.55, 95% CI 0.46–0.66)
Mancini *et al.*[21]	5853 cases 116 871 controls	Previous prescription of LABA, ICS, ACh.	Cohort high CV risk (previous MI and/or CR); cohort low CV risk (absence of previous factors)	Retrospective	ARBs reduce mortality: – low CV risk and receiving ICS (HR 0.63, 95% CI 0.44–0.89) – low CV risk and not receiving ICS (HR 0.62; 95% CI 0.44–0.87) – high CV risk and receiving ICS (HR 0.61; 95% CI 0.51–0.73) – high CV risk and not receiving ICS (HR 0.53; 95% CI 0.44–0.64) ACE is do not reduce mortality in high CV risk patients ACE is reduce mortality in low CV risk patients: – receiving ICS (HR 0.74; 95% CI 0.65–0.85) – not receiving ICS (HR 0.68; 95% CI 0.60–0.77)
Ekström *et al.*[11]	2249	Physician diagnosed COPD	Patients starting long-term oxygen therapy for COPD	Prospective observational multicentre study	No reduction in mortality.
Zeng *et al.*[22]	220	Spirometry	Hospitalization in geriatric department	Retrospective	ACE is reduce mortality (HR 0.15; 95% CI 0.03–0.68) ARBs reduce mortality (HR 0.38; 95% CI 0.18–0.82)

COPD, chronic obstructive pulmonary disease; ACE I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; AECOPD, acute exacerbation of COPD; LABA, long-acting β2 agonists; ICS, inhaled corticosteroids; Ach, inhaled anti-cholinergics; Y, yes; OR, odds ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; CR, coronary revascularization; HR, hazard risk; N, no; NS, not specified; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; RCT, randomized clinical trial.

Modificato da Campo G et al Eur Heart J Cardiovasc Pharmacother 2015; 1: 205–211

BLOCCANTI DEL SISTEMA RENINA-ANGIOTENSINA E BPCO

Progressione radiologica dell'enfisema in 4472 soggetti trattati e non con ACEI e ARB

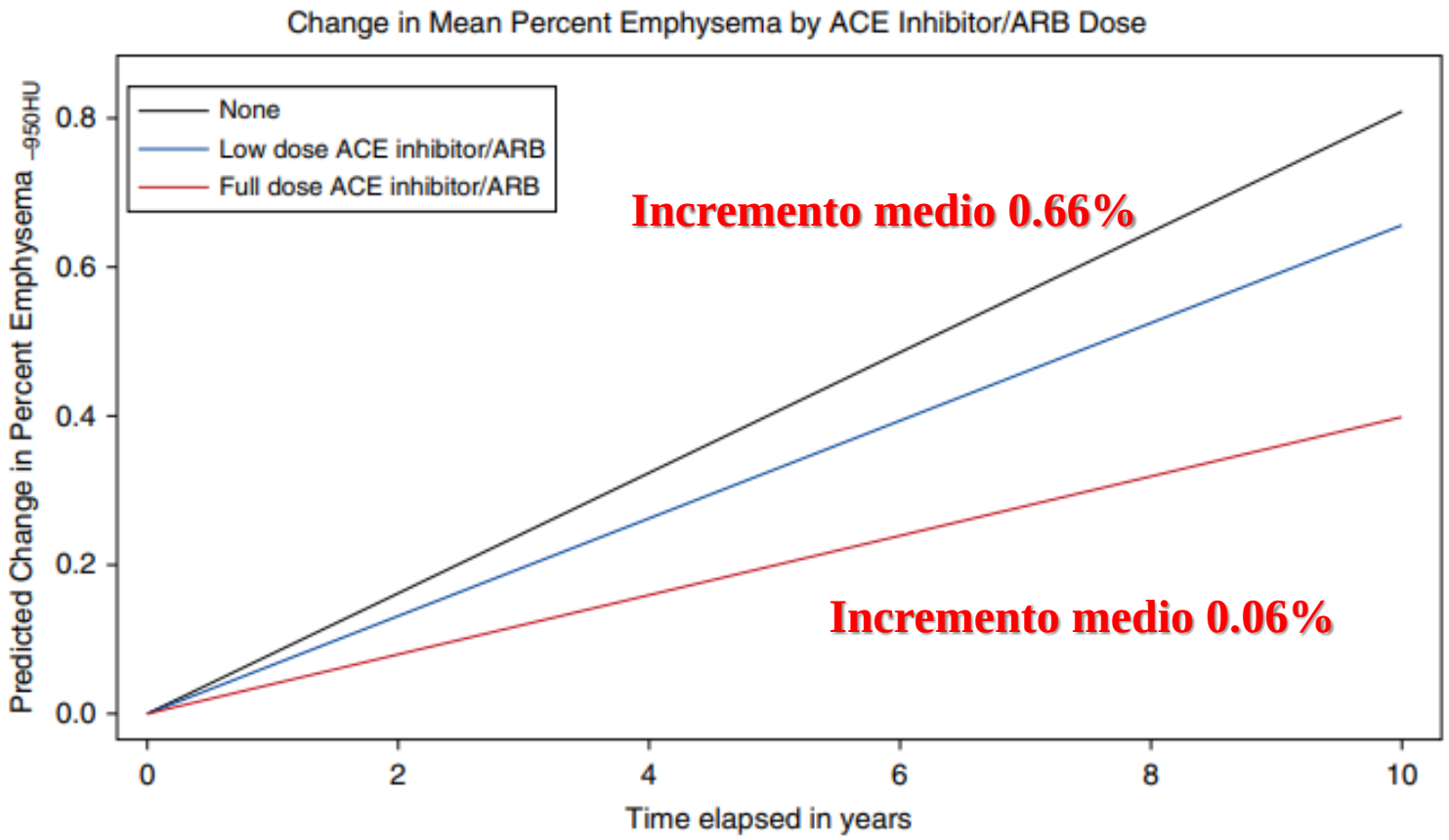


Figure 2. Predicted change in percent emphysema over time, by angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) dose. Low dose is defined as daily intake less than 50% of the maximum recommended dose. Full dose is defined as daily intake of at least 50% of the maximum recommended dose. HU = Hounsfield units.

FU mediano 9.3 anni

Parikh MA et al. Ann Am Thorac Soc 2017; 14:649–658

STATINE E BPCO

Table 3 Main studies evaluating the role of statins in chronic obstructive pulmonary disease patients

References	Patients (*n*)	COPD diagnosis	Study population characteristics	Design	Main findings
Mancini *et al.*[21]	5853 cases 116 871 controls	Previous prescription of LABA, ICS, ACh	Cohort high CV risk (previous MI and/or CR); cohort low CV risk (absence of previous factors)	Retrospective	Significant reduction in mortality: – high CV risk receiving ICS (HR 0.5; 95% CI 0.4–0.62) – high CV risk not receiving ICS (HR 0.53; 95% CI 0.45–0.65) – low CV risk receiving ICS (HR 0.53; 95% CI 0.44–0.64) – low CV risk not receiving ICS (HR 0.49; 95% CI 0.41–0.58)
Soyseth *et al.*[13]	854	Previous diagnosis of COPD (ICD 9 and 10)	Hospitalization for AECOPD	Retrospective cohort study	Reduction in mortality (HR 0.57; 95% CI 0.38–0.87)
Mortensen *et al.*[20]	11212	Previous diagnosis of COPD (ICD 9)	Hospitalization for AECOPD	Retrospective	Reduction in 90 days mortality (OR 0.51, 95% CI 0.4–0.64)
Sheng *et al.*[14]	1717	Previous diagnosis of COPD (ICD 9 and 10)	Outpatients	Retrospective cohort study	Primary prevention: – all-cause mortality reduction (HR 0.6; 95% CI 0.43–0.85) Secondary prevention: – all-cause mortality reduction (HR 0.58; 95% CI 0.35–0.97) – CV mortality reduction (HR 0.32, 95% I 0.13–0.7)
Lawes *et al.*[39]	1687	Diagnosis of COPD (ICD 10)	Outpatients	Cohort study	All-cause mortality reduction (HR 0.69; 95% CI 0.58–0.84)
Ekström *et al.*[11]	2249	Physician diagnosed COPD	Patients starting long-term oxygen therapy for COPD	Prospective multicentre study	No significant reduction in mortality
Lahousse *et al.*[40]	363 cases vs. 2345 controls	Spirometric data	Outpatients	Nested case–control analysis from a population-based cohort study	Reduction in mortality (RR 39; 95% CI 0.38–0.99) Patients with CRP > 3 mg/L: RR 78% (95% CI 0.06–0.74)

COPD, chronic obstructive pulmonary disease; LABA, long-acting β2 agonists; ICS, inhaled corticosteroids; ACh, inhaled anti-cholinergic; AECOPD, acute exacerbation of COPD; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; GOLD, global initiative for chronic obstructive lung disease; ICD, international classification of disease; CRP, C-reactive protein; RR, relative risk.

Campo G et al Eur Heart J Cardiovasc Pharmacother 2015; 1: 205–211

STATINE E BPCO
Effetti delle statine sulla capacità funzionale di pazienti BPCO
Metanalisi di 5 studi randomizzati controllati

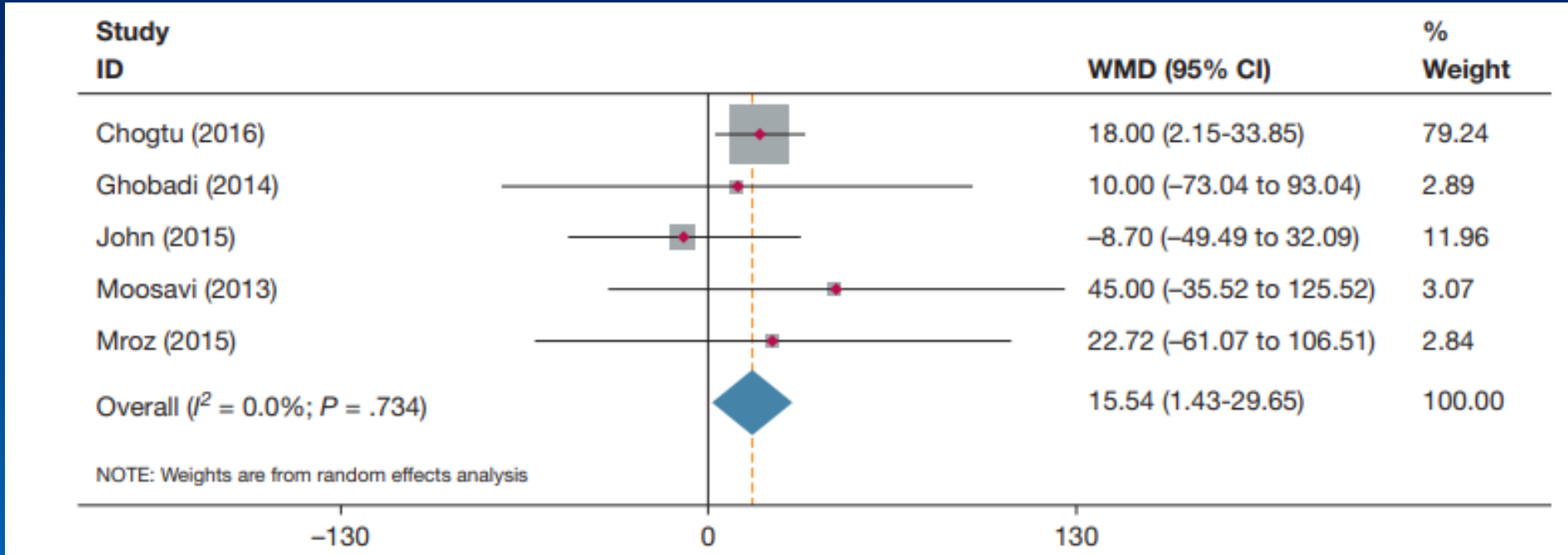


Figure 2 – *Summary effects of statin drugs vs placebo on changes in 6-min walk distance.*

Zhang W et al. Chest 2017; 152:1159-1168

STATINE E BPCO
Effetti delle statine sulla funzione polmonare di pazienti BPCO
Metanalisi di 5 studi randomizzati controllati

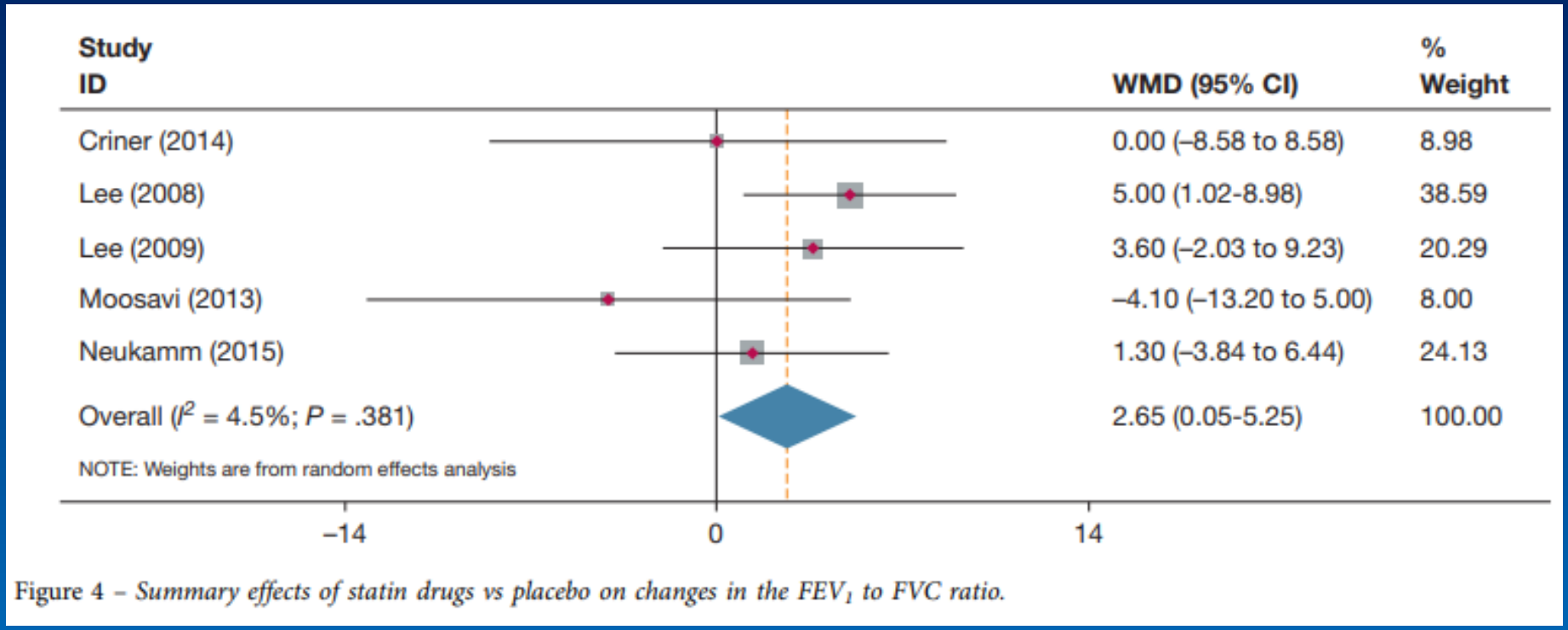
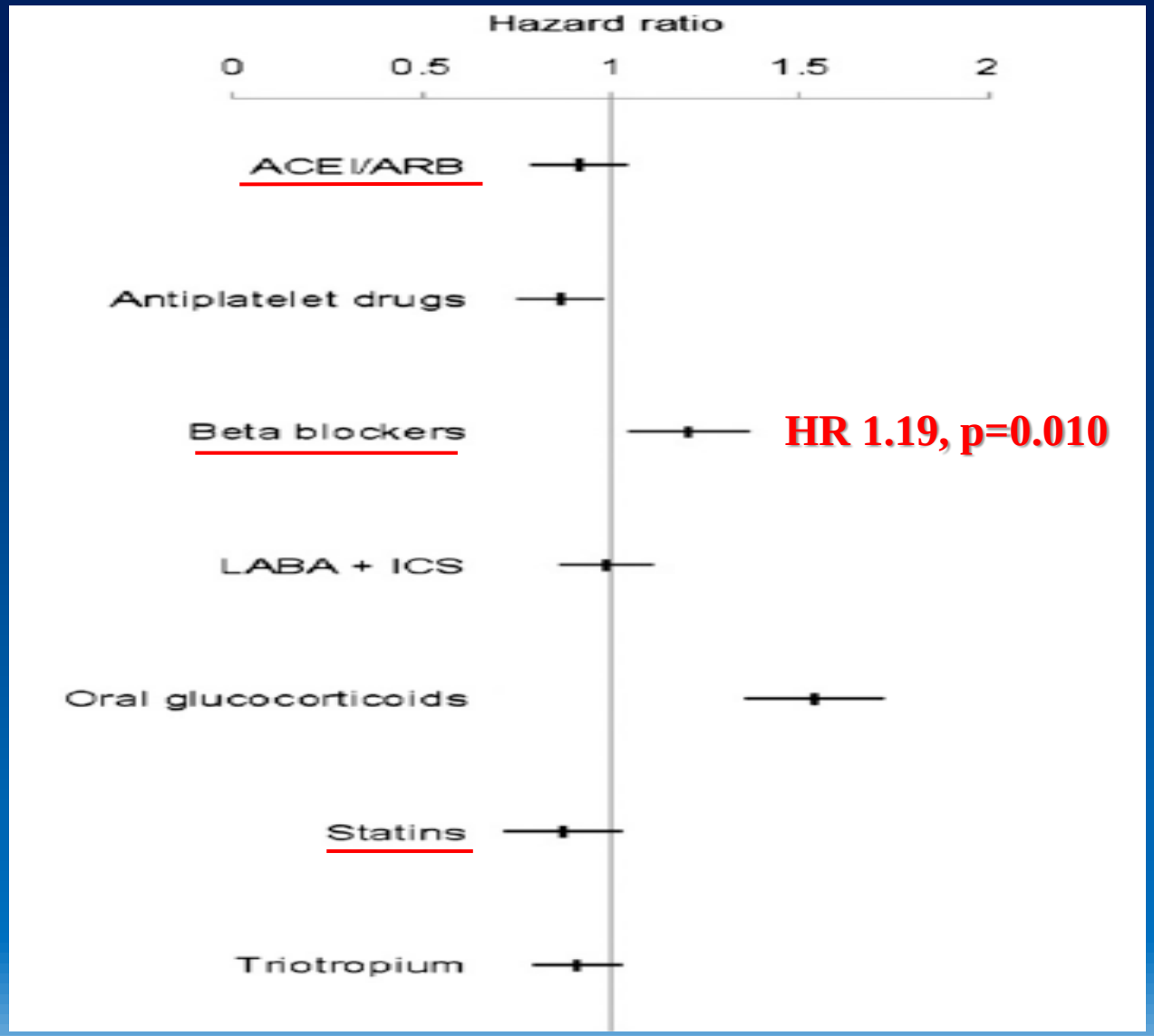


Figure 4 – *Summary effects of statin drugs vs placebo on changes in the FEV_1 to FVC ratio.*

Zhang W et al. Chest 2017; 152:1159-1168

FARMACI CARDIOVASCOLARI E BPCO

Rischio relativo di mortalità in 2249 pazienti BPCO in OTLT trattati vs non trattati con differenti farmaci cardiovascolari



FU 1 anno
Mortalità 50%

Ekstrom MP et al. Am J Respir Crit Care Med 2013;187: 715-720

COMORBIDITA' CARDIOVASCOLARI E METABOLICHE DELLA BPCO
CONCLUSIONI

- **Nella BPCO le comorbidità cardiovascolari e metaboliche sono frequenti, con prevalenze ed incidenze significativamente superiori rispetto alla popolazione generale**

- **L'associazione tra BPCO e comorbidità cardiovascolari e metaboliche si fonda su fattori di rischio condivisi e comuni meccanismi fisiopatologici**

- **Nei pazienti affetti da BPCO le comorbidità cardiovascolari e metaboliche devono essere attivamente ricercate e trattate allo stesso modo dei soggetti non portatori di pneumopatia, al fine di migliorare la prognosi**