長庚紀念醫院
Chang Gung Memorial Hospital

COPD Management

--Focus on bronchodilator and ICS

2019-01-21

Meng-Heng Hsieh M.D. Asst. Prof.
Department of Thoracic Medicine
Chang Gung Memorial Hospital

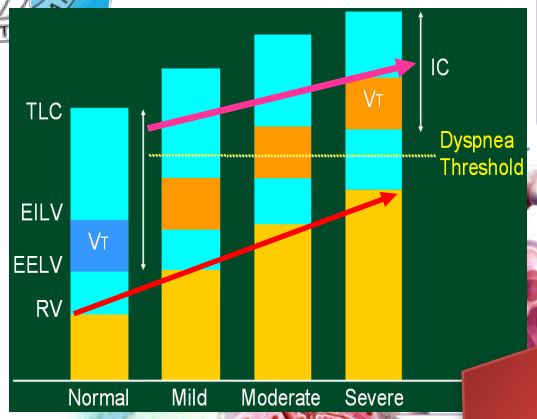



Outlines

- COPD : introduction
- The role of bronchodilators in COPD
- The role of eosinophil and ICS in COPD
- Pulmonary rehabilitation
- Summary

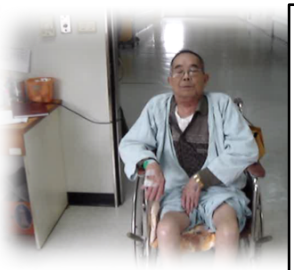
COPD

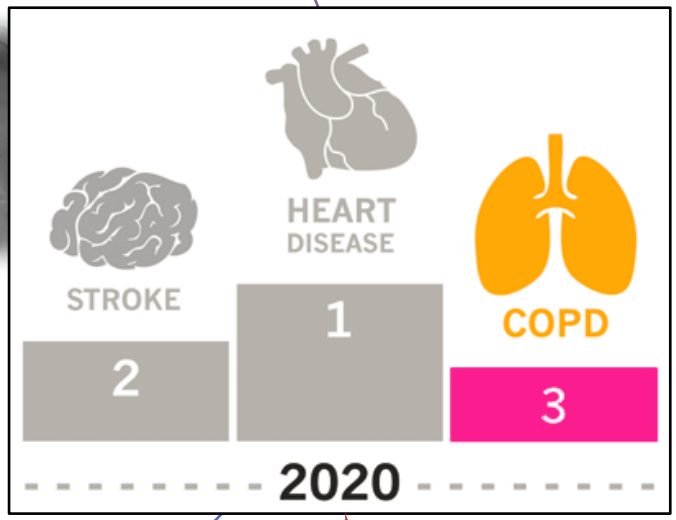
Lung hyperinflation



Panlobular (*orpanacinar*) emphysema

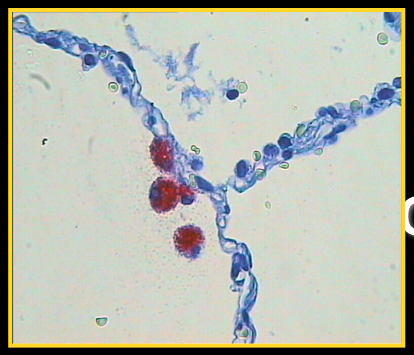
Centrilobular emphysema





vay nsiveness

Exacerbations → Comorbidities → Mortality



ALVEOLAR MACROPHAGES IN COPD

Cigarette smoke
Wood smoke

↑ Numbers (25X)
↑Secretion
Steroid resistance

ROS
NO

↓ HDAC
↓ Steroid response

↓ Phagocytosis

LTB_4
CXCL1
CXCL8

CCL2
CXCL1

CXCL9
CXCL10
CXCL11

Elastolysis
MMP-9, MMP-12
Cathepsins B,L,K

CXCR2

CCR2
CXCR2

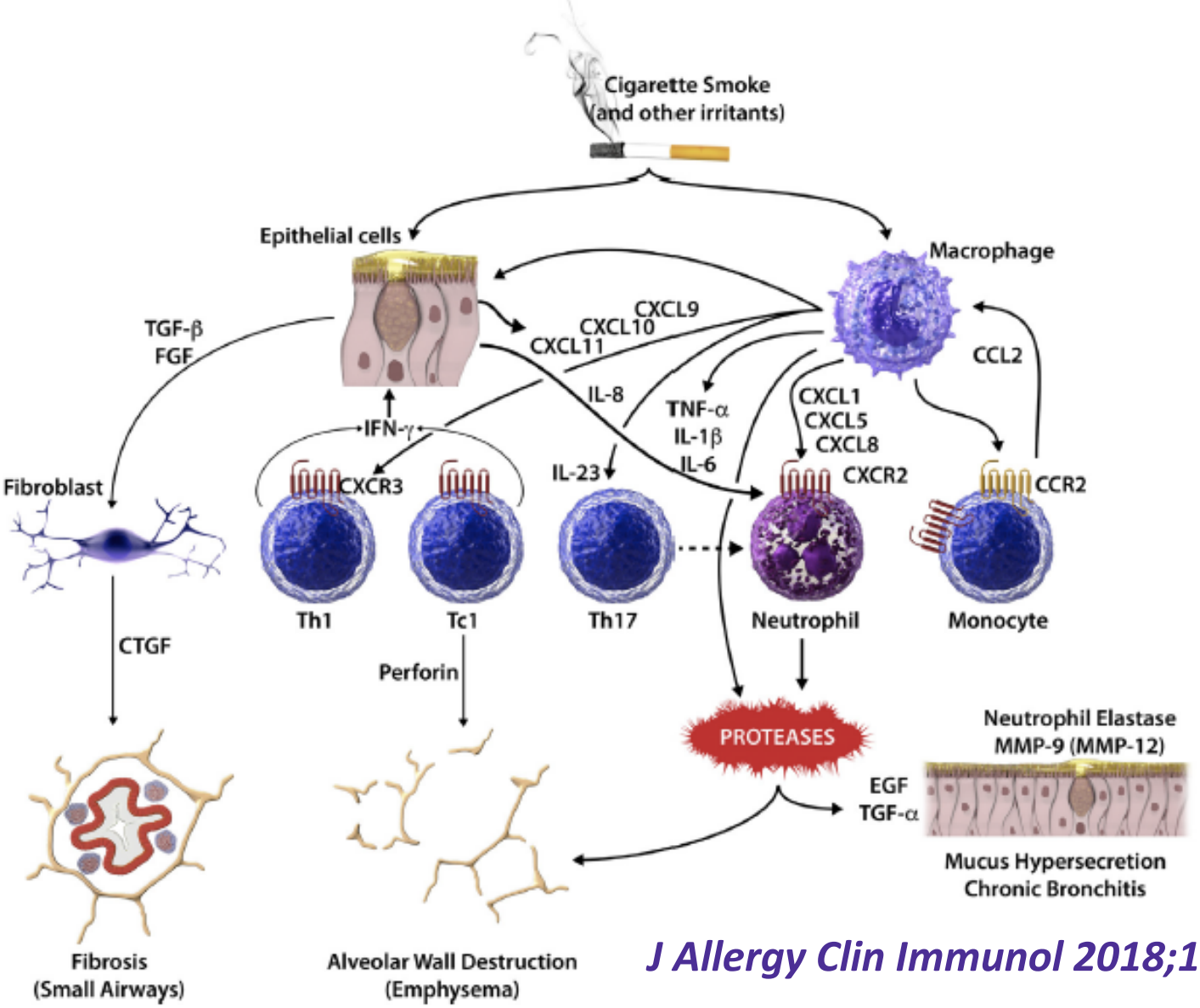
CXCR3

Neutrophils

Monocytes

$CD8^+$ cells

Emphysema



J Allergy Clin Immunol 2018;141:1983-91.

FIG 4. Neutrophilic airway inflammation in patients with COPD.[4] Inhaled irritants, such as cigarette smoke, activate epithelial cells and macrophages to release chemotactic factors that attract inflammatory cells to the lungs and cytokines (ie, IL-17), which promotes neutrophilic inflammation. These inflammatory cells, together with macrophages and epithelial cells, release proteases, such as matrix metalloprotease *(MMP)* 9, which cause elastin degradation, emphysema, mucus hypersecretion, and fibrosis around the small airways. *CTGF*, Connective tissue growth factor; *EGF*, epidermal growth factor; *FGF*, fibroblast growth factor.

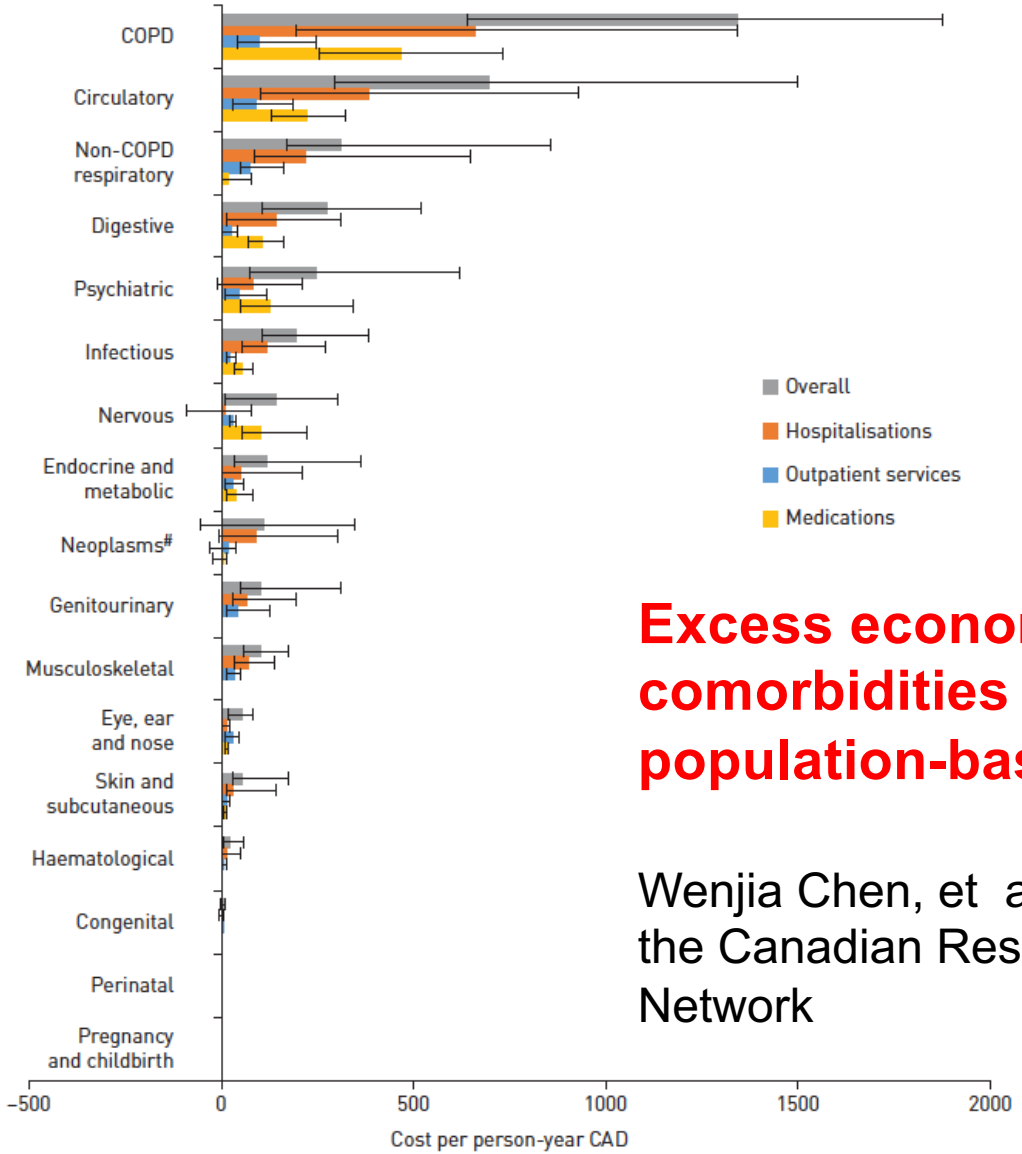


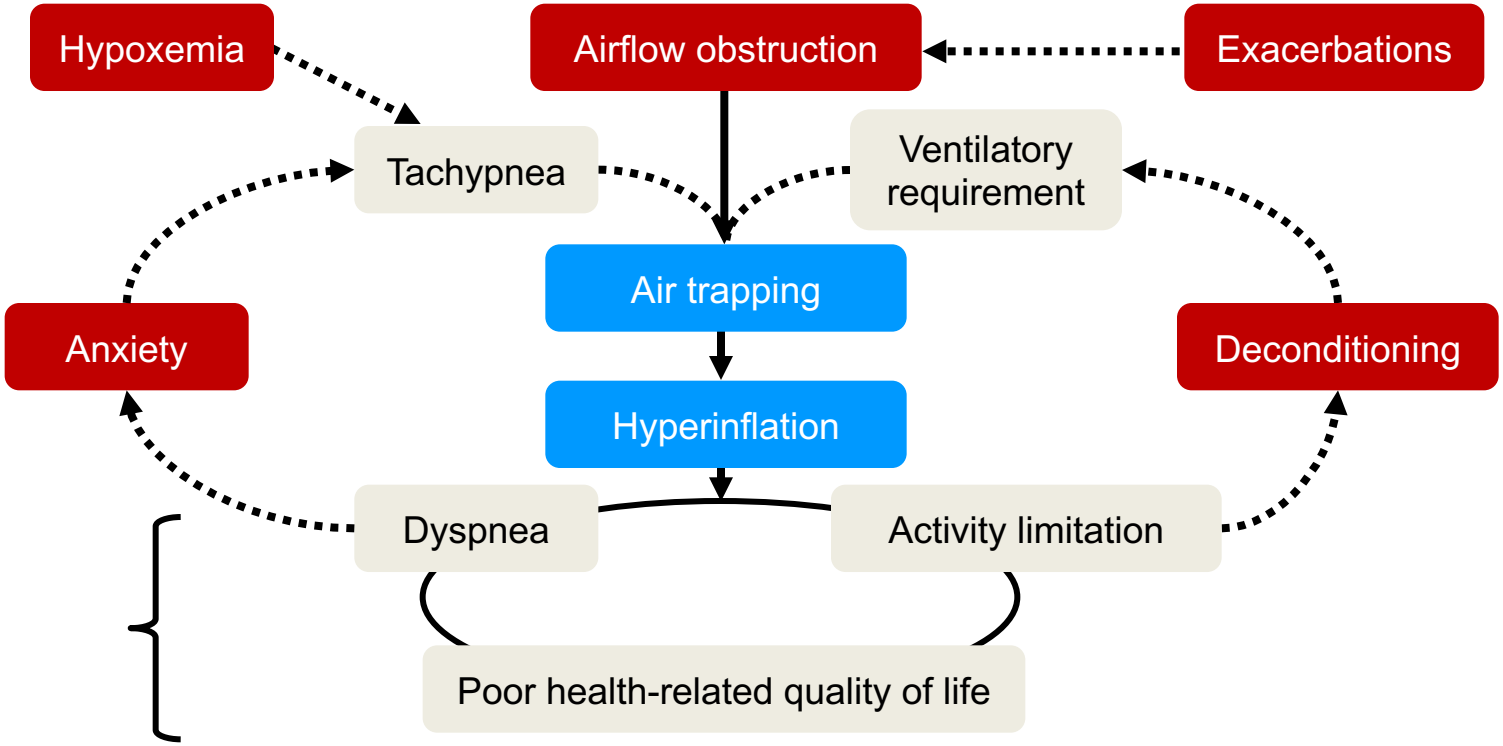
FIGURE 2 Estimated excess costs in patients with chronic obstructive pulmonary disease (COPD) during the 10-year follow-up period, by comorbid areas (CAD1.000=EUR0.706). #: costs of chemotherapy were not included in the PharmaNet medication costs [17].

Excess economic burden of comorbidities in COPD : a 15-year population-based study

Wenjia Chen, et al.
the Canadian Respiratory Research Network

Eur Respir J 2017; 50

COPD disease processes perpetuate symptoms of dyspnoea, aggravate activity limitation and lead to reduced quality of life



Cooper. Respir Med 2009

Global Initiative for Chronic
Obstructive
Lung
Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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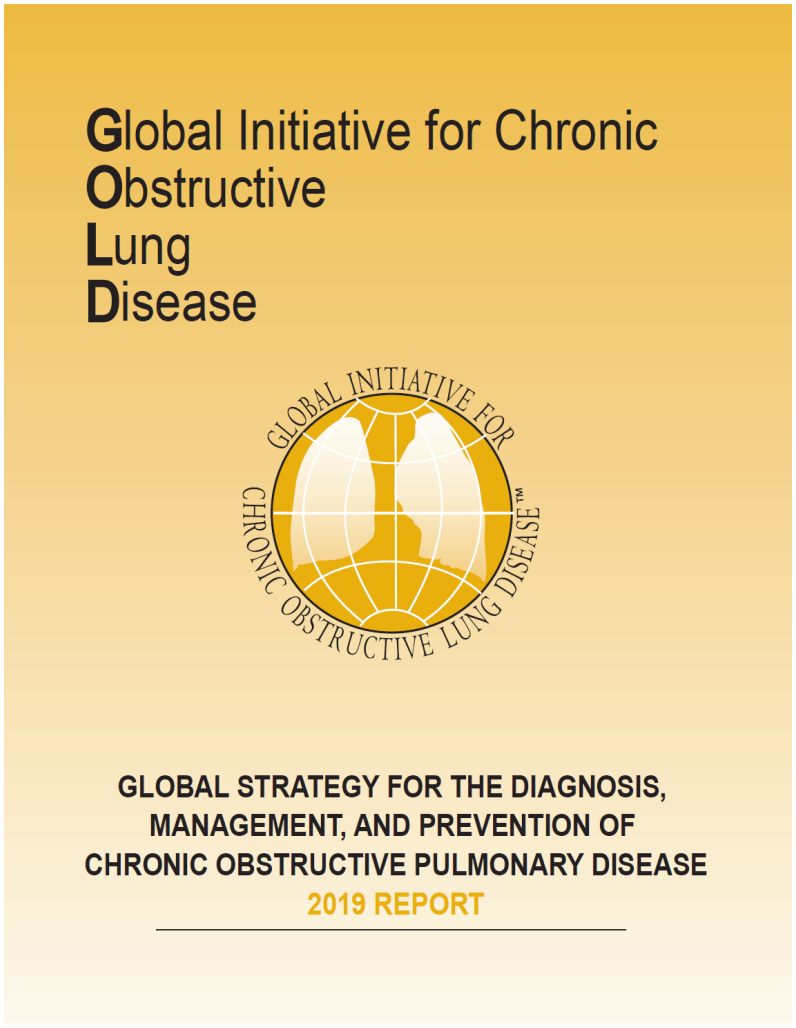
GOLD 2019 Report: Chapters



1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations
6. COPD and Comorbidities

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Chronic Obstructive Pulmonary Disease (COPD)

- COPD is currently the fourth leading cause of death in the world.[1]
- COPD is projected to be the 3rd leading cause of death by 2020.[2]
- More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; 3(11): e442.

© 2015 Global Initiative for Chronic Obstructive Lung Disease

Definition and Overview

OVERALL KEY POINTS (1 of 2):

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by **persistent respiratory symptoms** and **airflow limitation** that is due to **airway and/or alveolar abnormalities** usually caused by significant exposure to noxious particles or gases.

- The most common respiratory symptoms include **dyspnea, cough and/or sputum** production. These symptoms may be under-reported by patients.

- The main risk factor for COPD is tobacco **smoking** but other environmental exposures such as biomass fuel exposure and air pollution may contribute.

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Definition and Overview

OVERALL KEY POINTS (2 of 2):

- Besides exposures, **host factors** predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging.
- COPD may be punctuated by periods of acute worsening of respiratory symptoms, called **exacerbations.**
- In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and **mortality**.

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FEV_1 progression over time

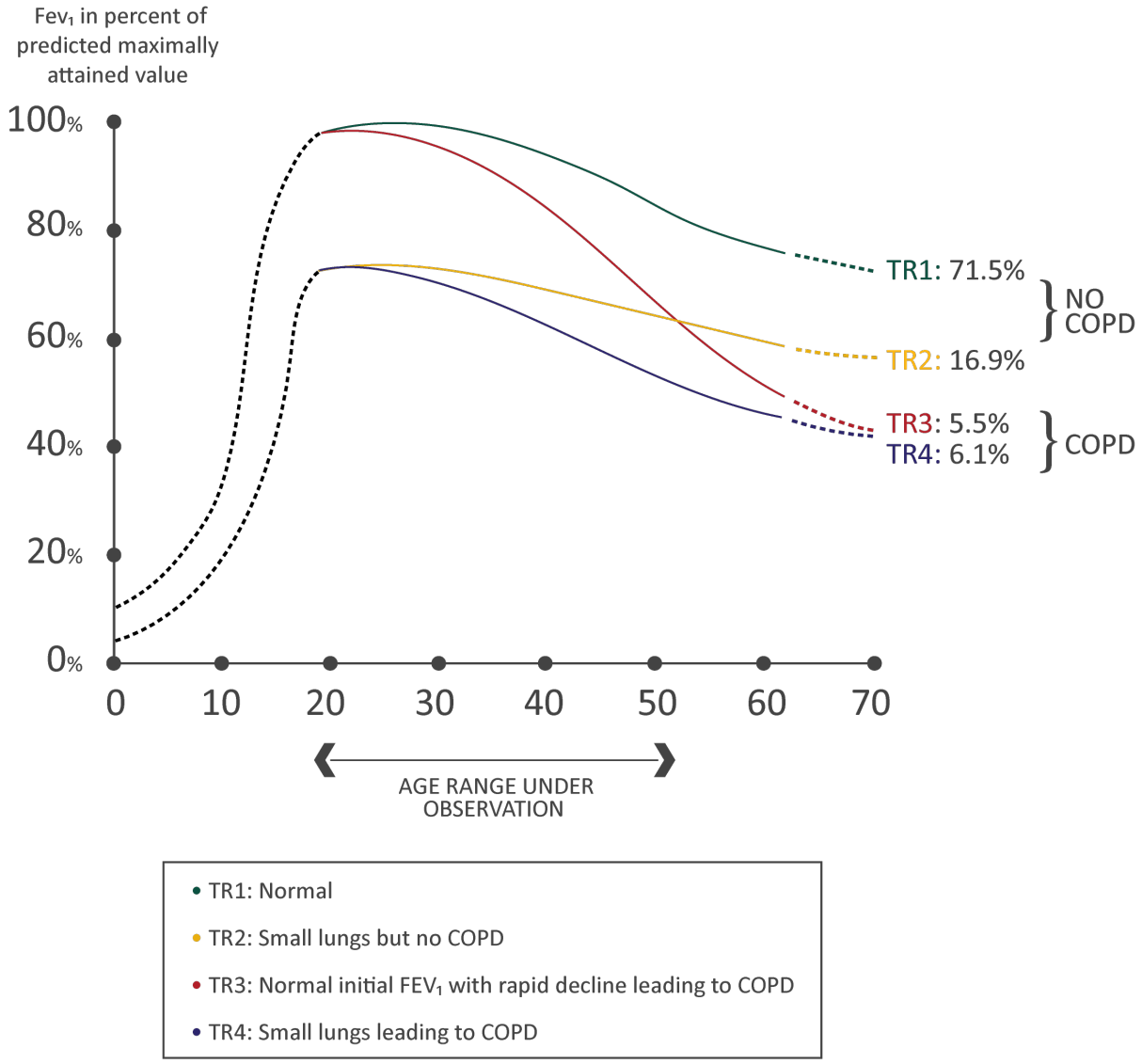

FIGURE 1.2

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COPD patients...

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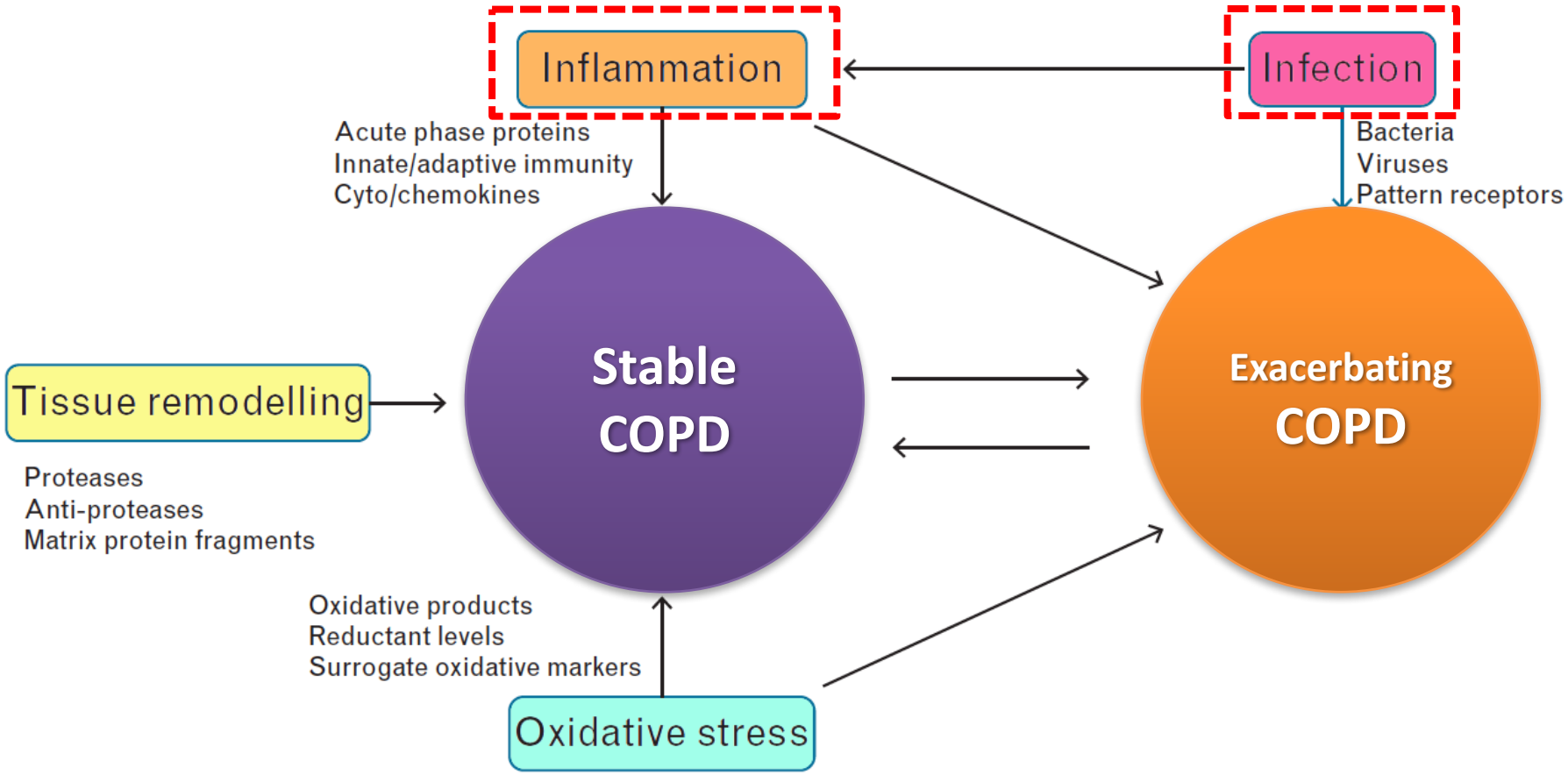
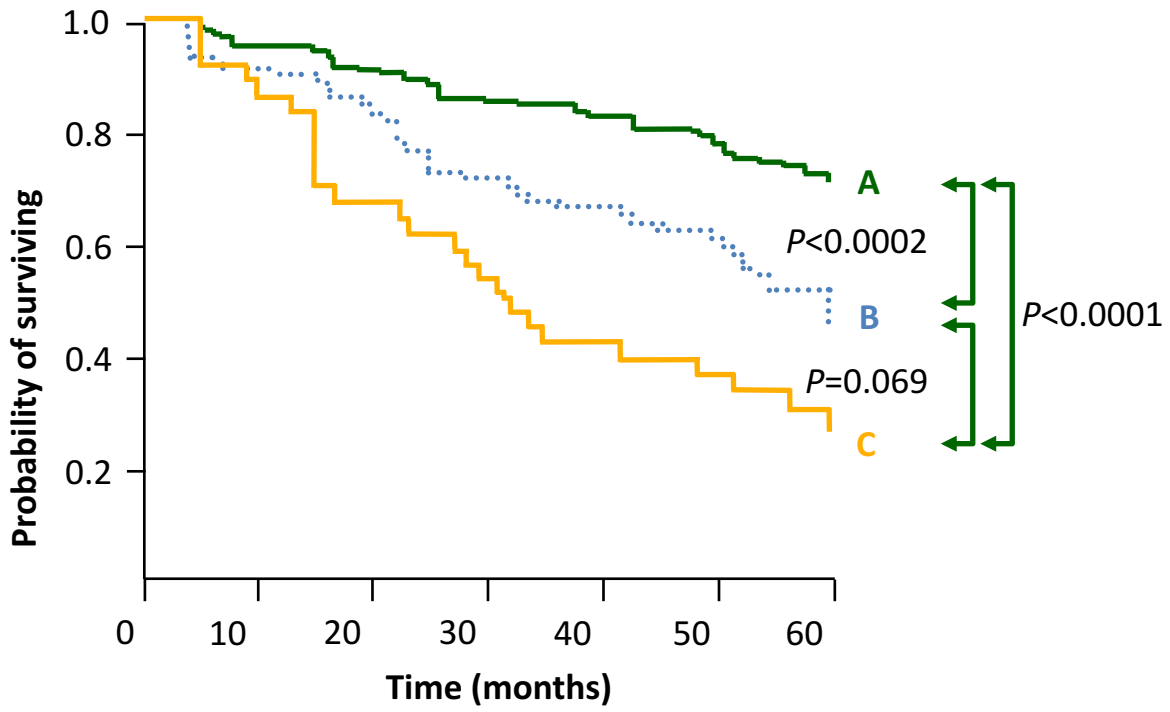
Exacerbations – the Big Risk

COPD Inflammatory Biomarkers



Curr Opin Pulm Med 2013, 19:103–108

Acute COPD Exacerbations and Mortality



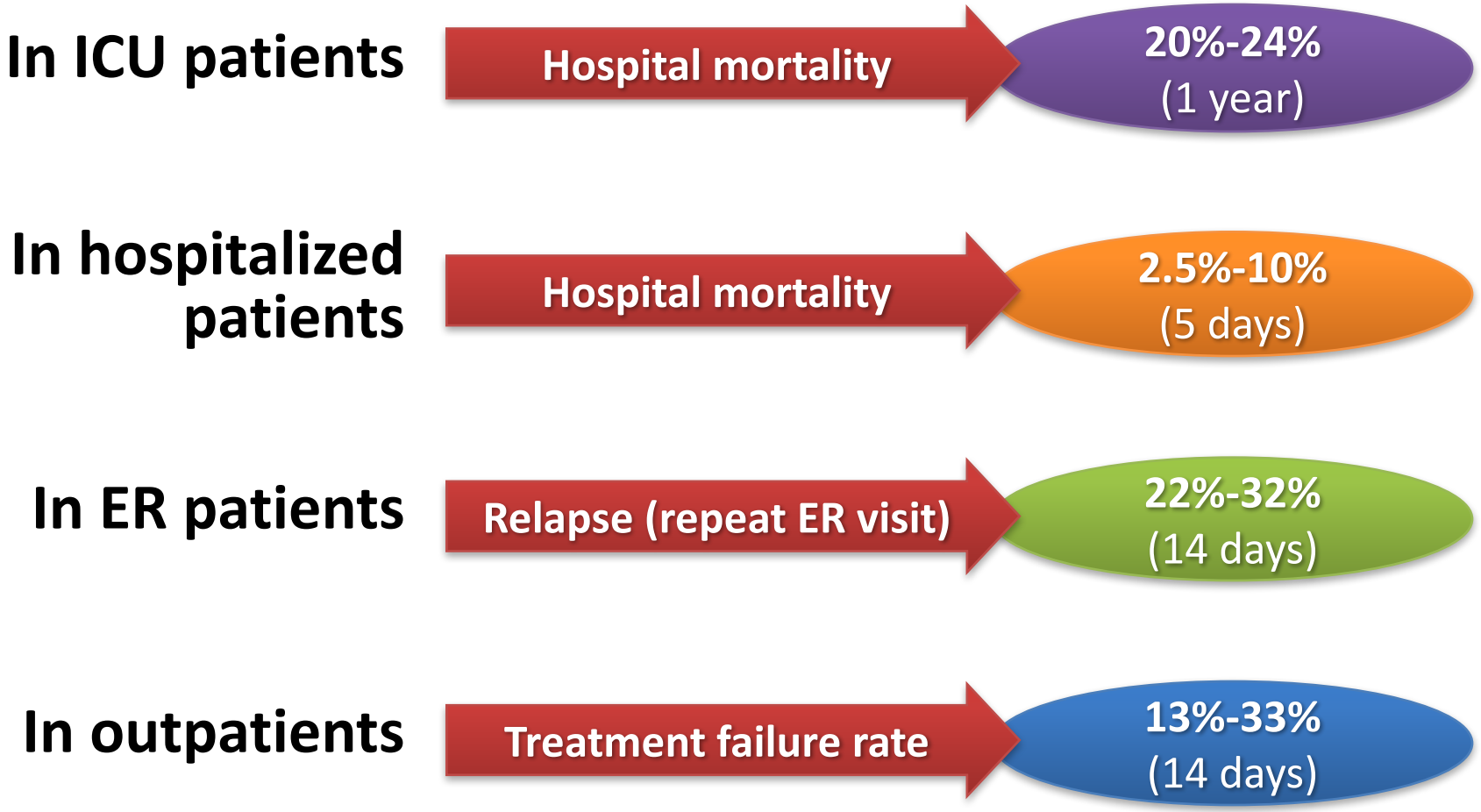
Group A
Patients with no acute exacerbations of COPD

Group B
Patients with 1-2 acute exacerbations of COPD requiring hospital management

Group C
Patients with ≥3 acute exacerbations of COPD requiring hospital management

Soler-Cataluña JJ, et al. Thorax 2005;60:925-931.

Outcome of COPD Exacerbations



Seneff et al. *JAMA. 1995*; 274:1852-1857; Murata et al. *Ann Emerg Med*. 1991;20:125-129; Adams et al. *Chest. 2000*; 117:1345-1352; Patil et al. *Arch Int Med*. 2003; 163:1180-1186.

Acute Event Mortality

COPD Exacerbation

22-43% of patients hsopitalized with AECOPD die within 1 year [1,2,3,4]

The in-hospital mortality rate for AECOPD is 8.0~11% [1,2]

Acute coronary syndrome

25% of men and 38% of women die within 1 year of a first recognized MI [5,6]

The in-hospital acute MI mortality rate is 8.0~9.4% [5,6]

1. Erikson N. et al. Ugeskr Laeger 2003;165:3499-3502
2. Groenewegen KH. Chest 2003;124: 459-467
3. Almagro P, et al. Chest 2002;121: 1441-1448
4. Connors AF, et al. ARJCCM 1996; 154: 959-967
5. Thom T. Circulation 2006; 113(6): e85-151
6. Heart and Stroke Foundation of Canada

PULMONARY PERSPECTIVE

Should We View Chronic Obstructive Pulmonary Disease Differently after ECLIPSE?

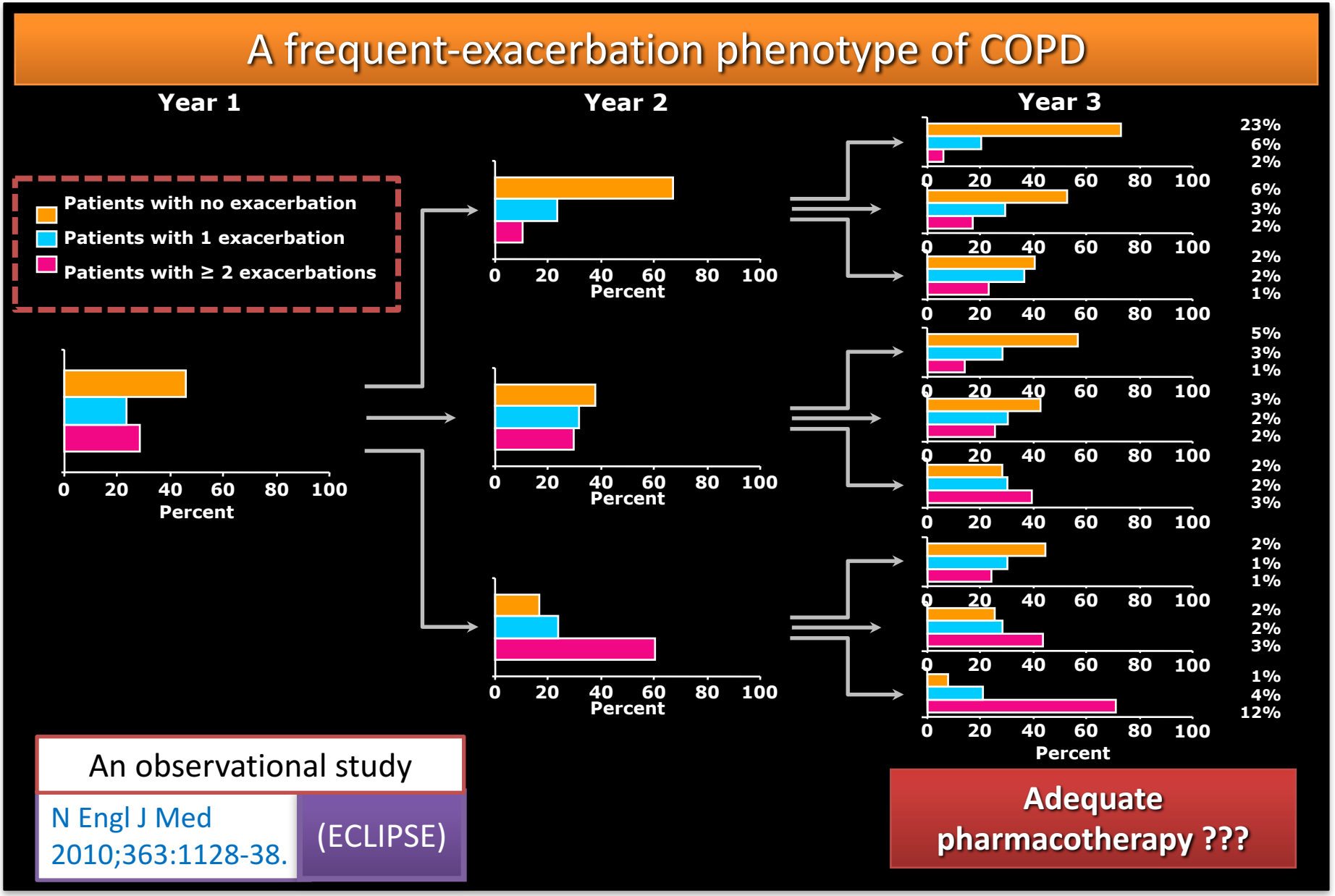
A Clinical Perspective from the Study Team

Jørgen Vestbo[1,2], Alvar Agusti[3], Emiel F. M. Wouters[4], Per Bakke[5,6], Peter M. A. Calverley[7], Bartolome Celli[8], Harvey Coxson[9], Courtney Crim[10], Lisa D. Edwards[10], Nicholas Locantore[10], David A. Lomas[11], William MacNee[12], Bruce Miller[13], Stephen I. Rennard[14], Edwin K. Silverman[8], Julie C. Yates[10], and Ruth Tal-Singer[13]; on behalf of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study Investigators*

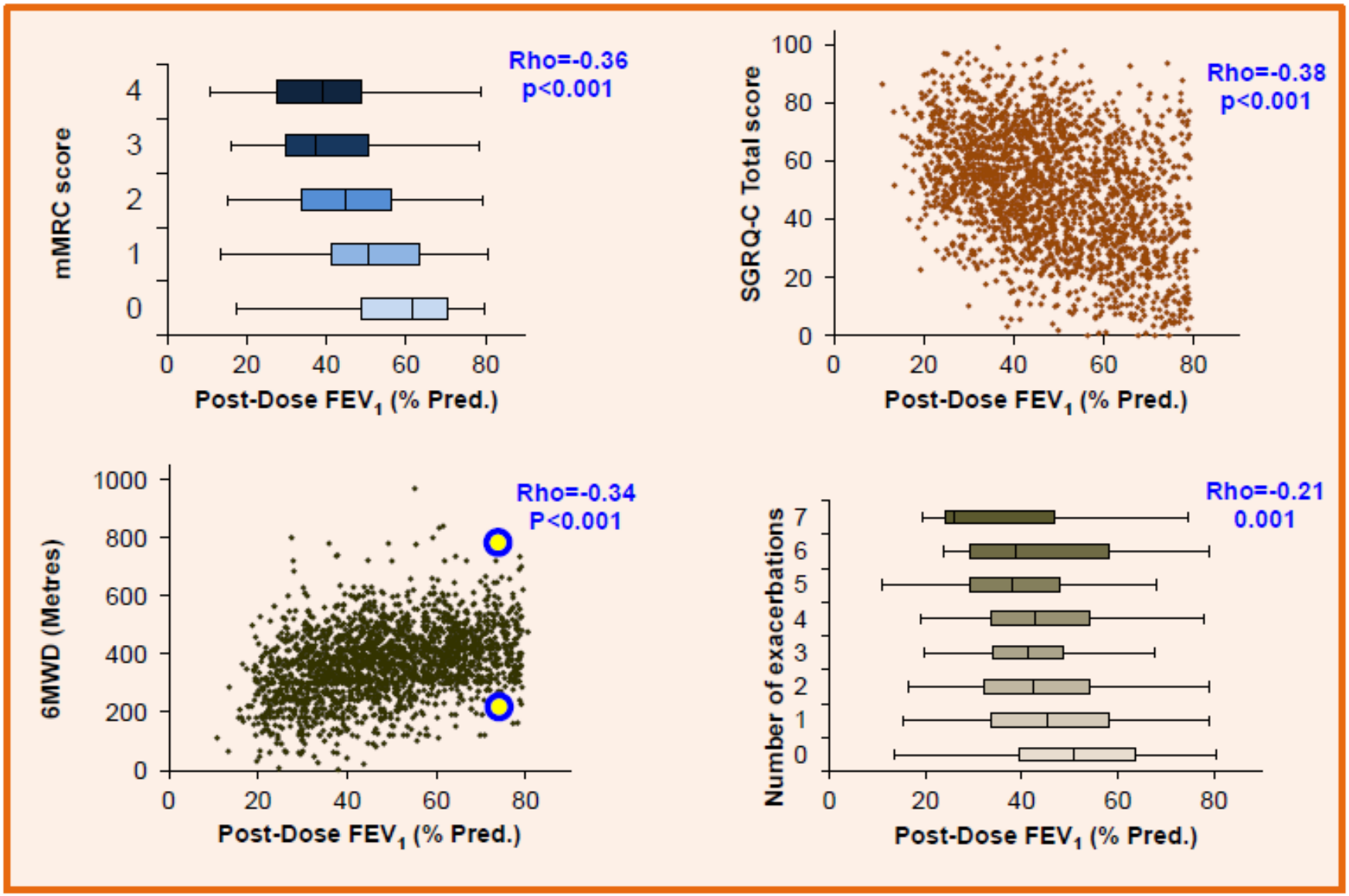
AJRCCM Vol 189, Iss 9, pp 1022–1030, May 1, 2014

Conclusions: By following a large, well characterized cohort of patients with COPD over 3 years, we have a clearer picture of a heterogeneous disease with **clinically important subtypes ("phenotypes")** and a variable and not inherently progressive course.

Frequent Exacerbations of COPD — A Distinct Phenotype



Weak correlation between disease outcome parameters and FEV_1



Agusti A, *et al. Respir Res* 2010; **11**: 122.

Spirometrically confirmed diagnosis → Assessment of airflow limitation → Exacerbation history → Assessment of symptoms/risk of exacerbations

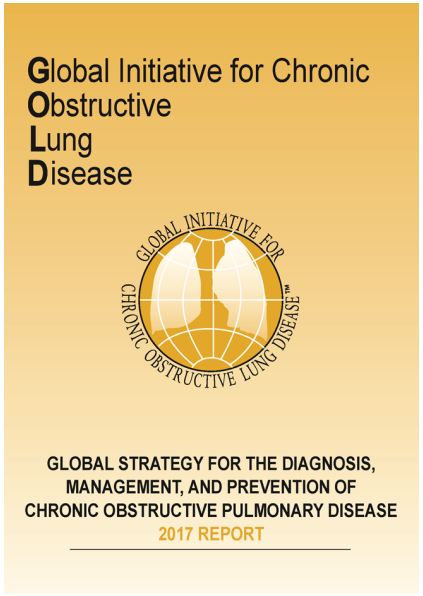
Post-bronchodilator $FEV_1/FVC < 0.7$

	FEV_1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50–79
GOLD 3	30–49
GOLD 4	< 30

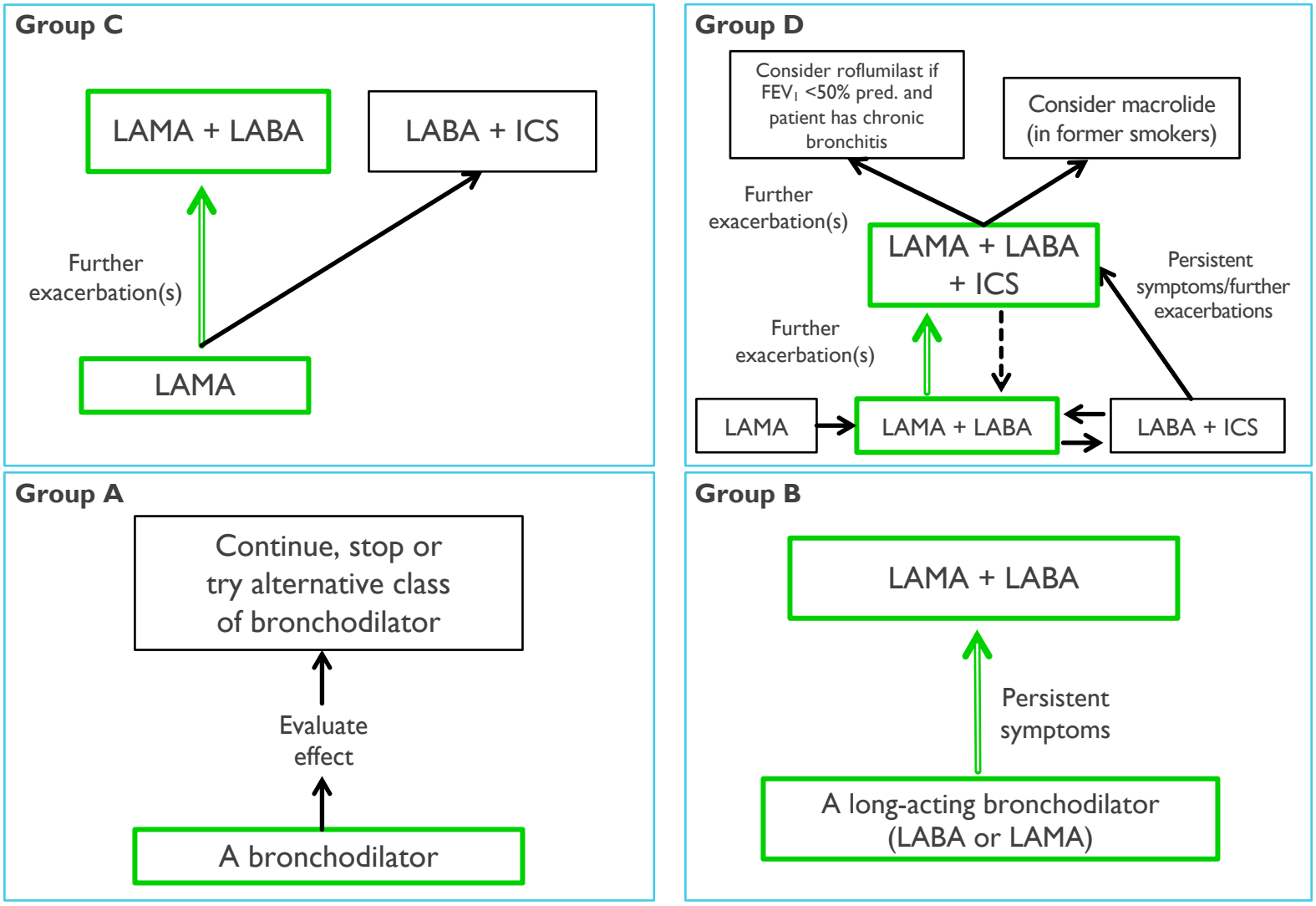
Exacerbation history:
- ≥ 2 or ≥ 1 leading to hospital admission
- 0 or 1 (not leading to hospital admission)

C	D
A	B
mMRC 0–1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

Symptoms



GOLD 2017: Treatment Recommendations



Preferred Treatment

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Outlines

- COPD : introduction
- The role of bronchodilators in COPD
- The role of eosinophil and ICS in COPD
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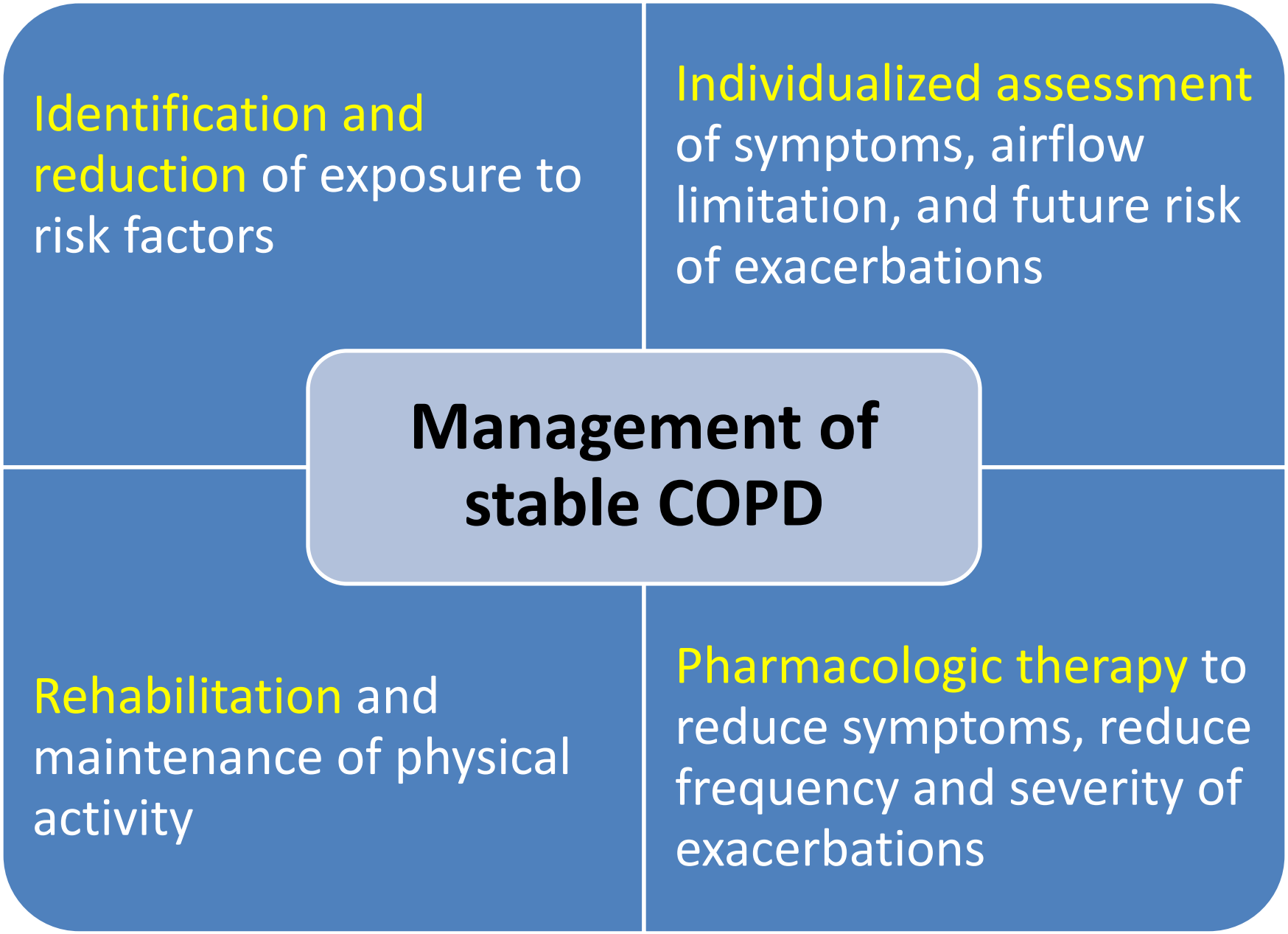

Identification and reduction of exposure to risk factors
Individualized assessment of symptoms, airflow limitation, and future risk of exacerbations
Management of stable COPD
Rehabilitation and maintenance of physical activity
Pharmacologic therapy to reduce symptoms, reduce frequency and severity of exacerbations

Fixed dose dual bronchodilators

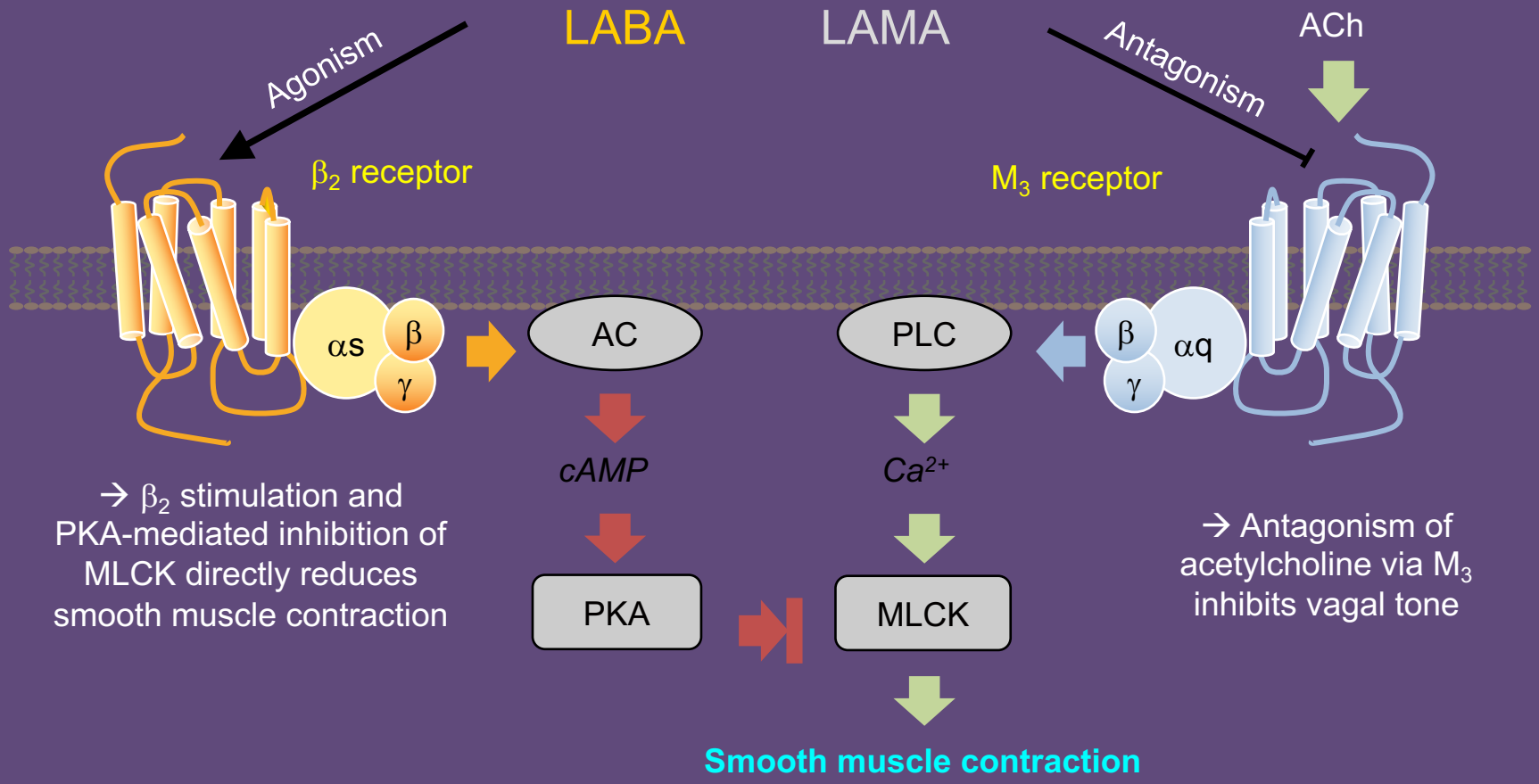
Glycopyrronium / Indacaterol (Ultibro)

Tiotropium / Olodaterol (Spiolto)

Umeclidinium / Vilanterol (Anoro)

Optimizing bronchodilation in COPD

Complimentary actions of β_2-agonists and antimuscarinics



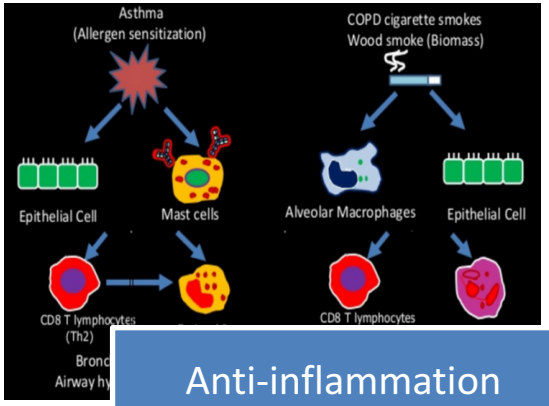
→ β_2 stimulation and PKA-mediated inhibition of MLCK directly reduces smooth muscle contraction

→ Antagonism of acetylcholine via M_3 inhibits vagal tone

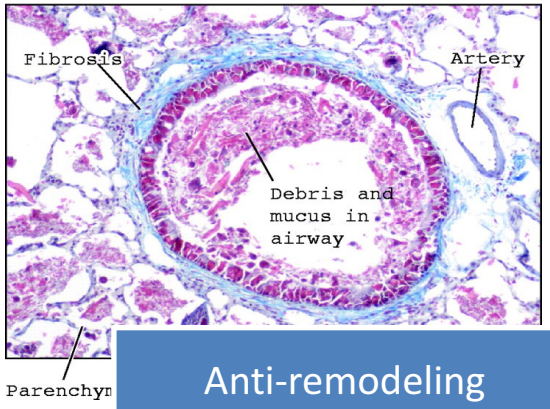
AC = adenylylcyclase Ach = acetylcholine
cAMP = cyclic adenosine 3',5' monophosphate MLCK = myosin light chain kinase PKA = protein kinase A
PLC = Phospholipase C

Cazzola & Molimard. Pulm Pharmacol Ther 2010

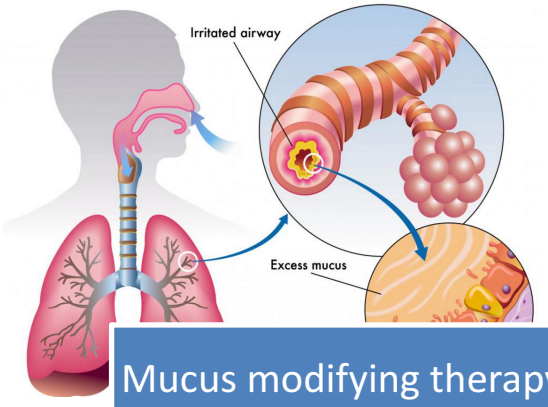
Alternative mechanisms of muscarinic receptor antagonists (beyond bronchodilation)



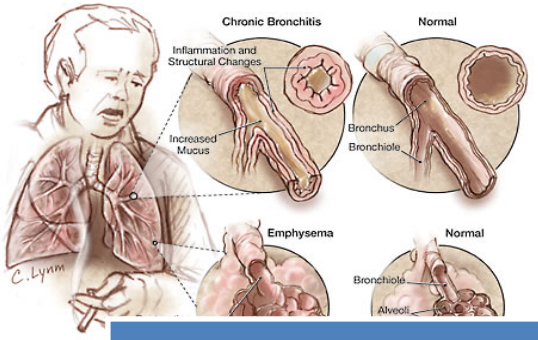
Anti-inflammation



Anti-remodeling



Mucus modifying therapy

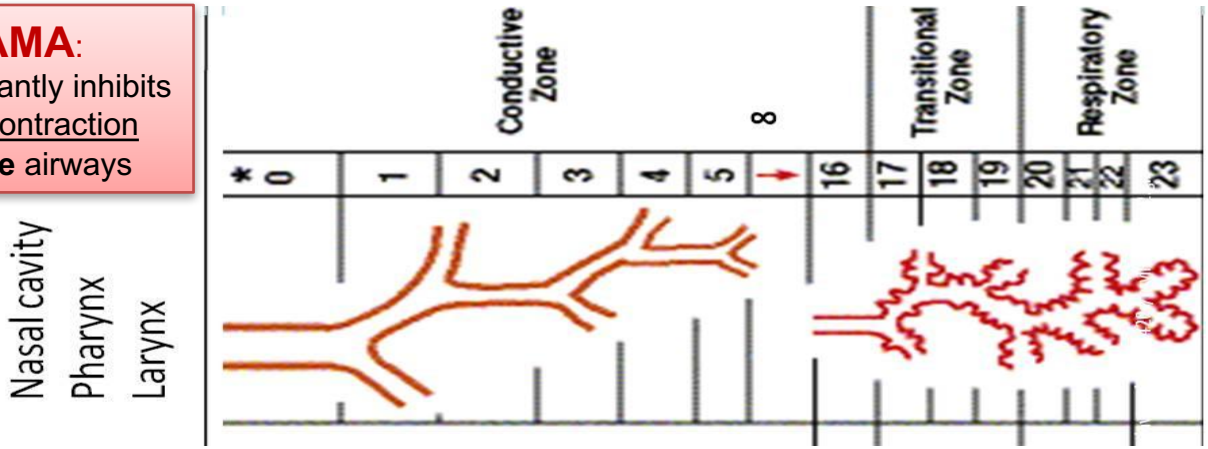


Anti-cough therapy

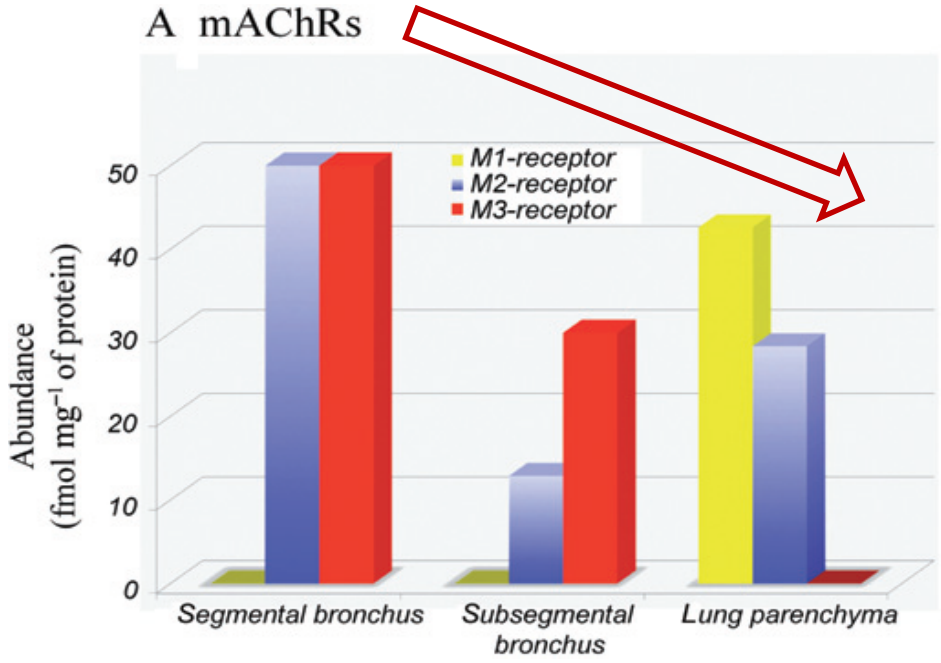
Matera MG *et al Handb Exp Pharmacol*. 2017;237:41-62

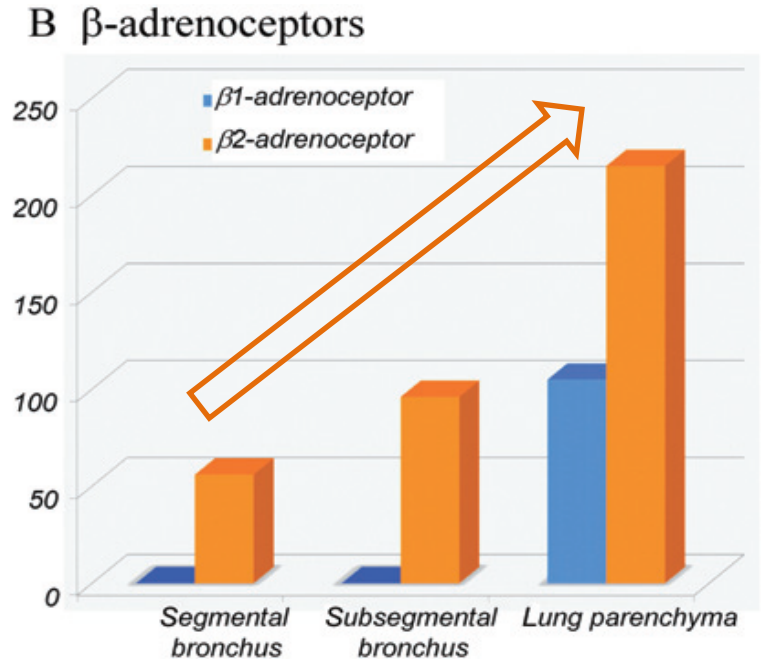
Distribution of M3 and β2 receptor in the airways is uneven

LAMA:
predominantly inhibits
tonic contraction
of **large** airways



LABA:
predominantly inhibits
phasic contraction
of **small** airways

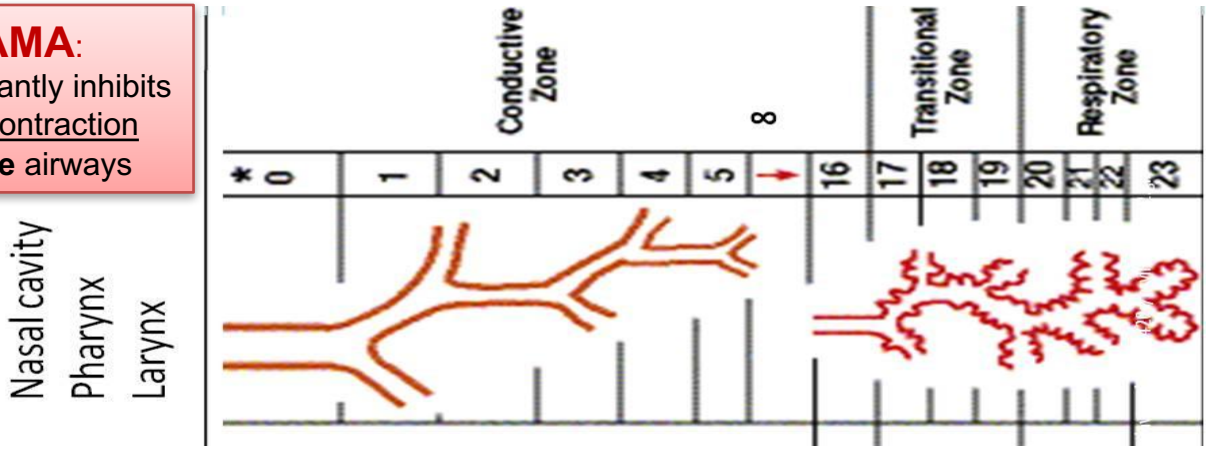




Ikeda T *et al. Br J Pharmacol*. 2012 Jul;166(6):1804-14

Differential advantages between LAMA and LABA

LAMA:
predominantly inhibits
tonic contraction
of **large** airways



LABA:
predominantly inhibits
phasic contraction
of **small** airways

Chest tightness

Breathlessness at rest

Cough

Sputum

Wheezes

Dynamic hyperinflation
- Exertional dyspnea
- Exercise capability

Vulnerability to
weather/environment change

ILLUMINATE

Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol/fluticasone in patients with COPD (ILLUMINATE): a randomised, double-blind, parallel group study

Claus F Vogelmeier, Eric D Bateman, John Pallante, Vijay KT Alagappan, Peter D'Andrea, Hungta Chen, Donald Banerji

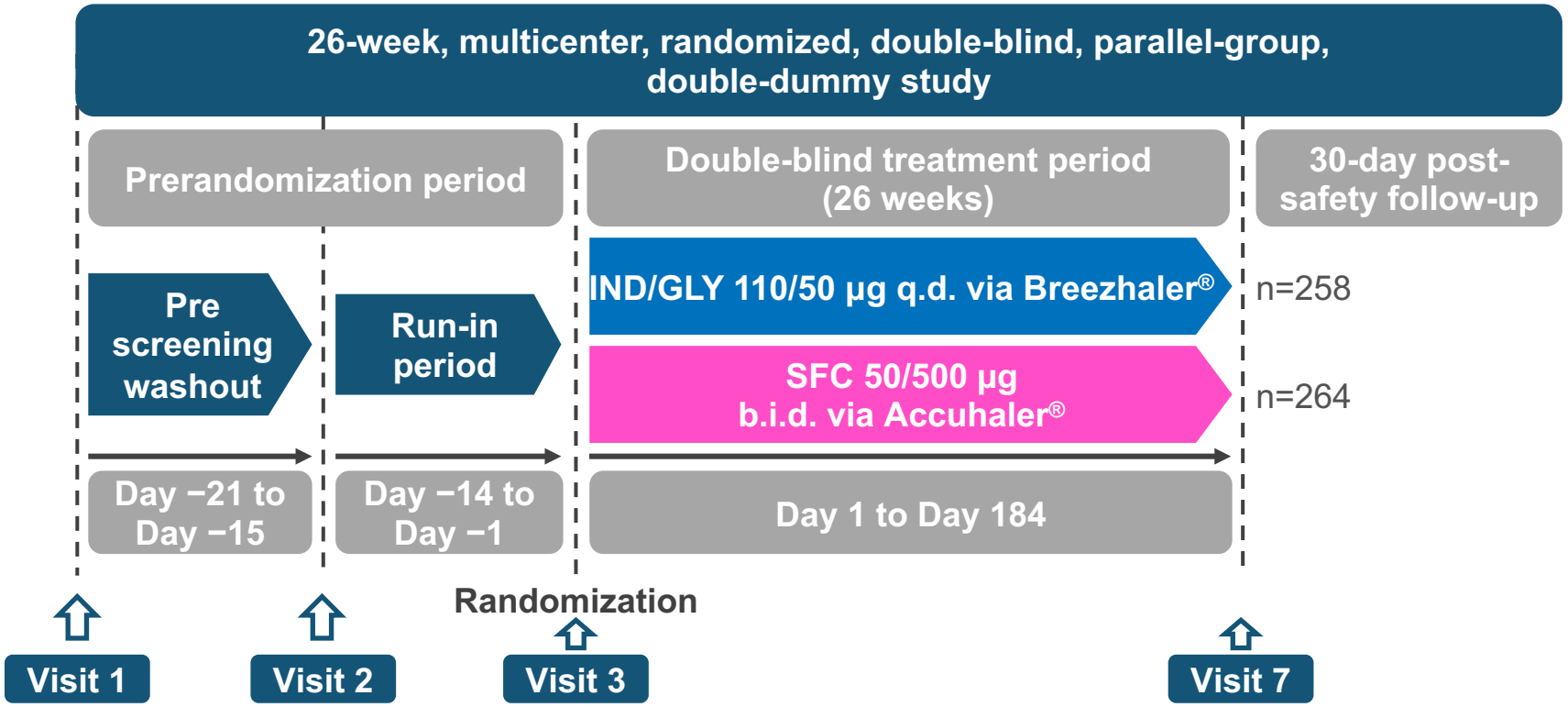
Lancet Respiratory Medicine 2013 (doi:10.1016/S0140-6736(08)61345-8)

NOVARTIS

2313 ILLUMINATE

ILLUMINATEE study design

- Safety and efficacy study (Europe, Asia)
- 523 patients randomized; 522 included in full analysis set
- Symptomatic patients with no history of moderate-severe exacerbations in the previous year



b.i.d. = twice daily; q.d. = once daily; SFC = salmeterol/fluticasone propionate

ILLUMINATE 2313

Vogelmeier et al. Lancet Respir Med 2013

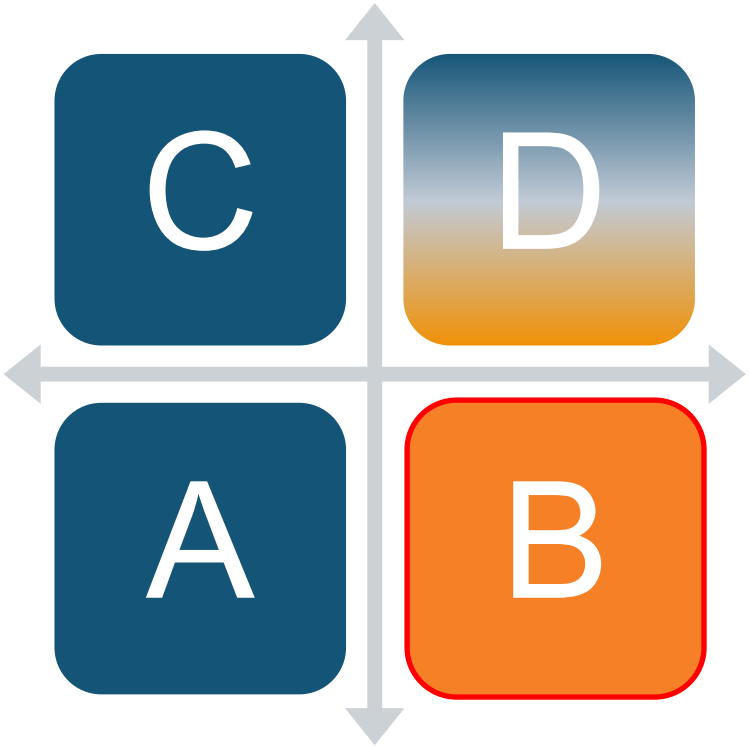
Patient population as classified by GOLD 2014 combined assessment of COPD

Inclusion criteria

- Post-bronchodilator FEV_1 40%–80% of predicted normal
- Symptomatic patients, defined as a total symptom score (on daily eDiary) of ≥1 on at least 4 of the last 7 days prior to randomization

Exclusion criteria

- COPD exacerbation requiring treatment with antibiotics, systemic corticosteroids or hospitalization within 1 year of randomization; history of asthma



Population characteristics

- Mean FEV_1 % predicted: 60.2%
- Exacerbations in previous year: No
- Symptomatic: Yes
- ICS users at baseline
  IND/GLY: 85/258 (32.9%)
  SFC: 98/264 (37.1%)

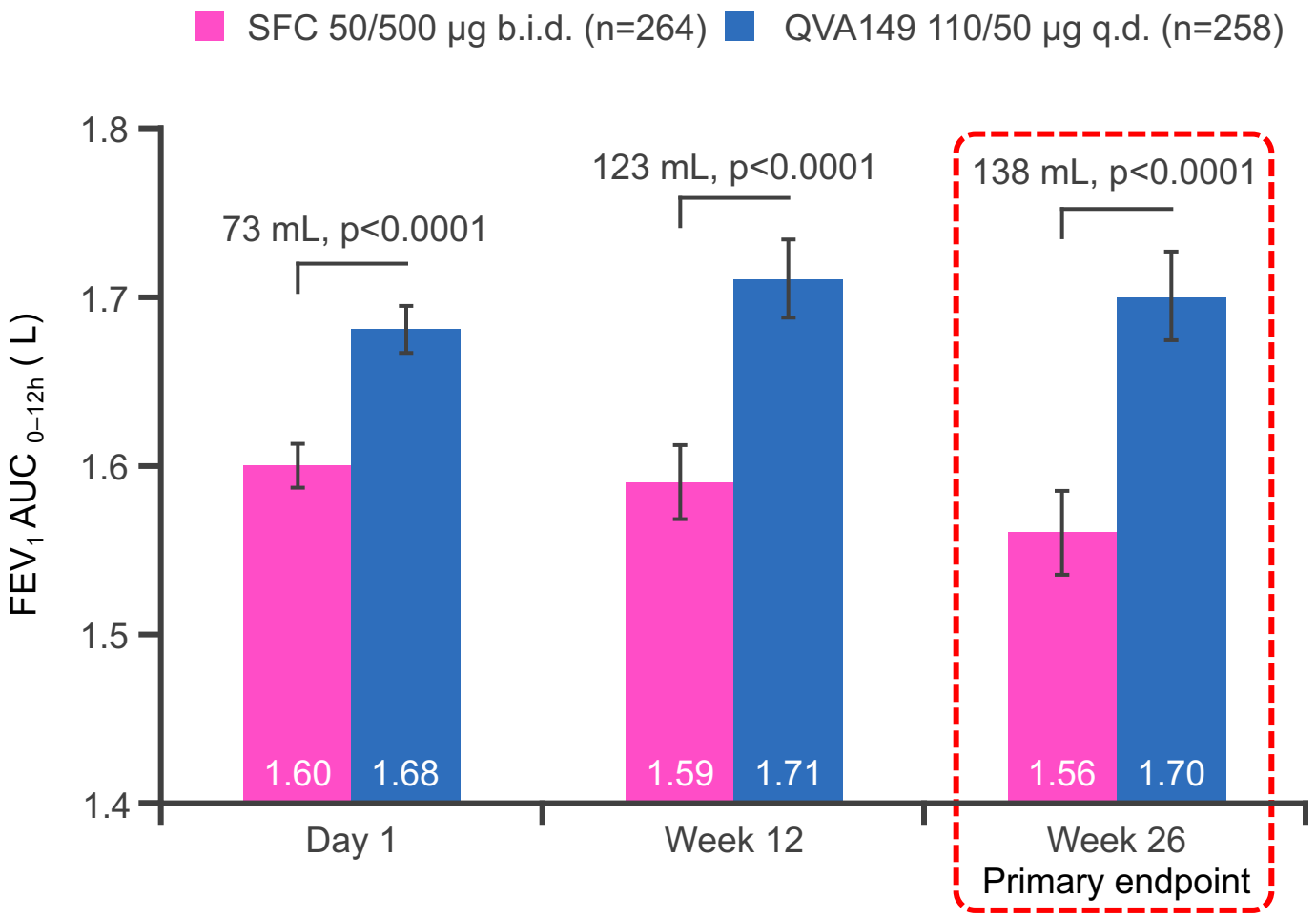
Patients targeted by inclusion criteria

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SFC = salmeterol/fluticasone propionate

ILLUMINATE 2313

Vogelmeier et al. Lancet Respir Med 2013
GOLD 2015

IND/GLY significantly improved FEV_1 $AUC_{0–12h}$ at Week 26 (primary endpoint) vs SFC



Data are least-squares mean ± standard error
AUC = area under the curve; b.i.d. = twice daily
FEV_1 = forced expiratory volume in 1 second; q.d. = once daily
SFC = salmeterol/fluticasone propionate

ILLUMINATE 2313

Vogelmeier et al. Lancet Respir Med 2013

Primary and secondary efficacy outcomes were improved with QVA149 compared to SFC

	Day 1		Week 12		Week 26	
	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison
TDI focal score†	–	–	0.58 (0.07, 1.08)	p=0.025	0.76 (0.26, 1.26)	p=0.0031
SGRQ-C total score			0.71 (–0.99, 2.41)	p=0.41	–1.24 (–3.33, 0.85)	p=0.25
Change from baseline in rescue medication use, puffs/day	–	–	–0.28 (–0.59, 0.04)	p=0.089	–0.39 (–0.71, –0.06)	p=0.019
Change from baseline in daytime rescue medication use, puffs/day	–	–	–0.26 (–0.45, –0.07)	p=0.0084	–0.32 (–0.52, –0.13)	p=0.0013

†Minimum clinically important difference is 100 mL (FEV_1) and 1-point (TDI score). SFC=salmeterol/fluticasone; LSM=least squares means; CI=confidence interval; TDI=Transition Dyspnoea Index; SGRQ-C=St George's Respiratory Questionnaire for COPD patients (a reduction indicates improvement).

ILLUMINATE 2313

Vogelmeier CF, et al. Lancet Resp Med. 2013

LANTERN

LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD

Zhong N, Wang C, Zhou X, Zhang N, Humphries M, Wang L, Thach C, Patalano F, Banerji D; LANTERN Investigators

Zhong et al. Int J COPD, 2015

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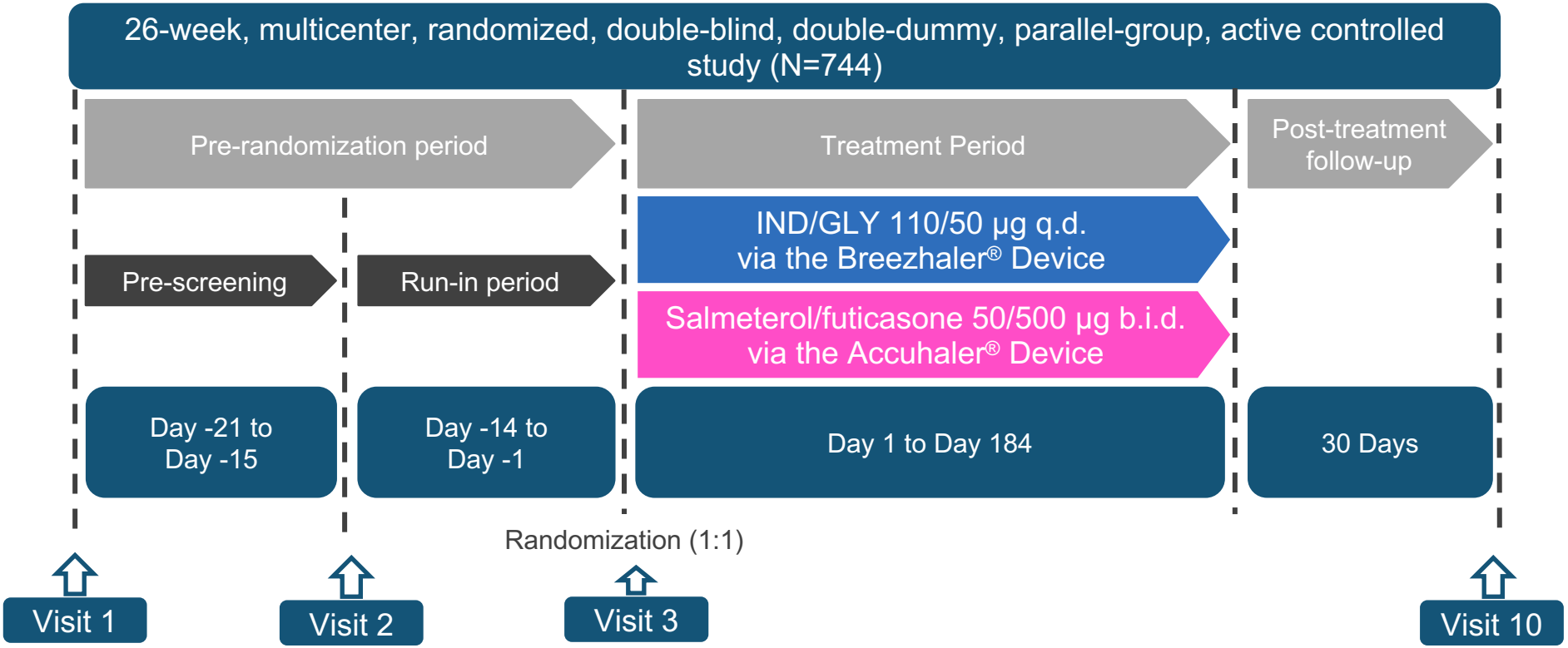
A2331 LANTERN

LANTERN Study design



Before the run-in period, patients discontinued LAMAs and the LABA indacaterol for at least 7 days and all other LABAs and LABA/inhaled corticosteroid combinations for 48 hours. o.d., once-daily

LABA=long-acting β_2 agonist; LAMA=long-acting muscarinic antagonist; o.d.=once daily; b.i.d.=twice daily

A2331 LANTERN

Zhong et al. Int J COPD, 2015

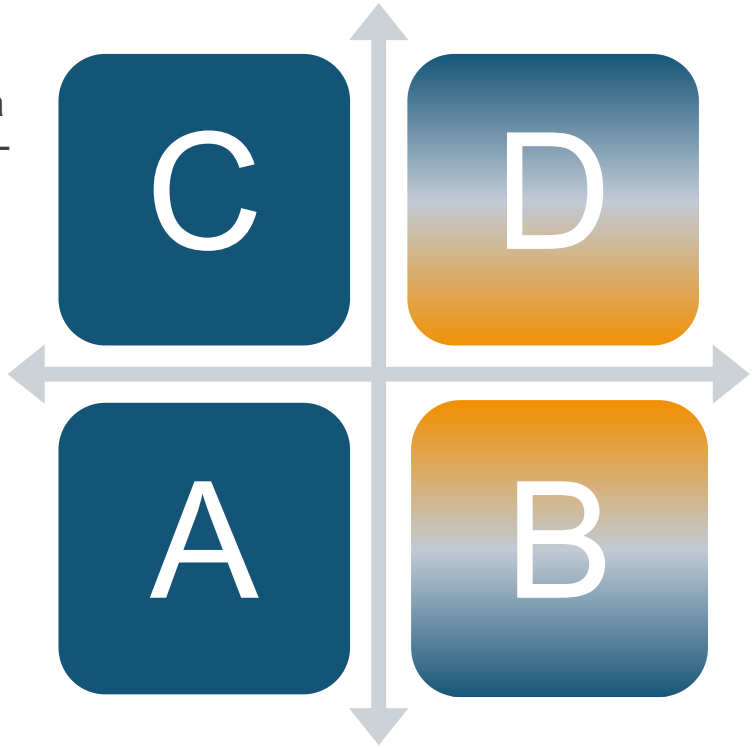
Patient population as classified by GOLD 2015 combined assessment of COPD

Inclusion criteria

- Post-bronchodilator FEV_1 30%–80% of predicted normal
- Current or ex-smokers with a smoking history of ≥ 10 pack-years

Exclusion criteria

- Patients with a history of ≥2 COPD exacerbations that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the past year before screening or patients who had a COPD exacerbation during 6 weeks before screening



Population characteristics

- Mean FEV_1% predicted: 51.8%
- Exacerbations in previous year:
  - 0 (79.2%)
  - 1 (20.65%)
- Symptomatic: Yes
- ICS users at baseline IND/GLY: 206/372 (55.4%)
  SFC: 200/369 (54.2%)

Patients targeted by inclusion criteria

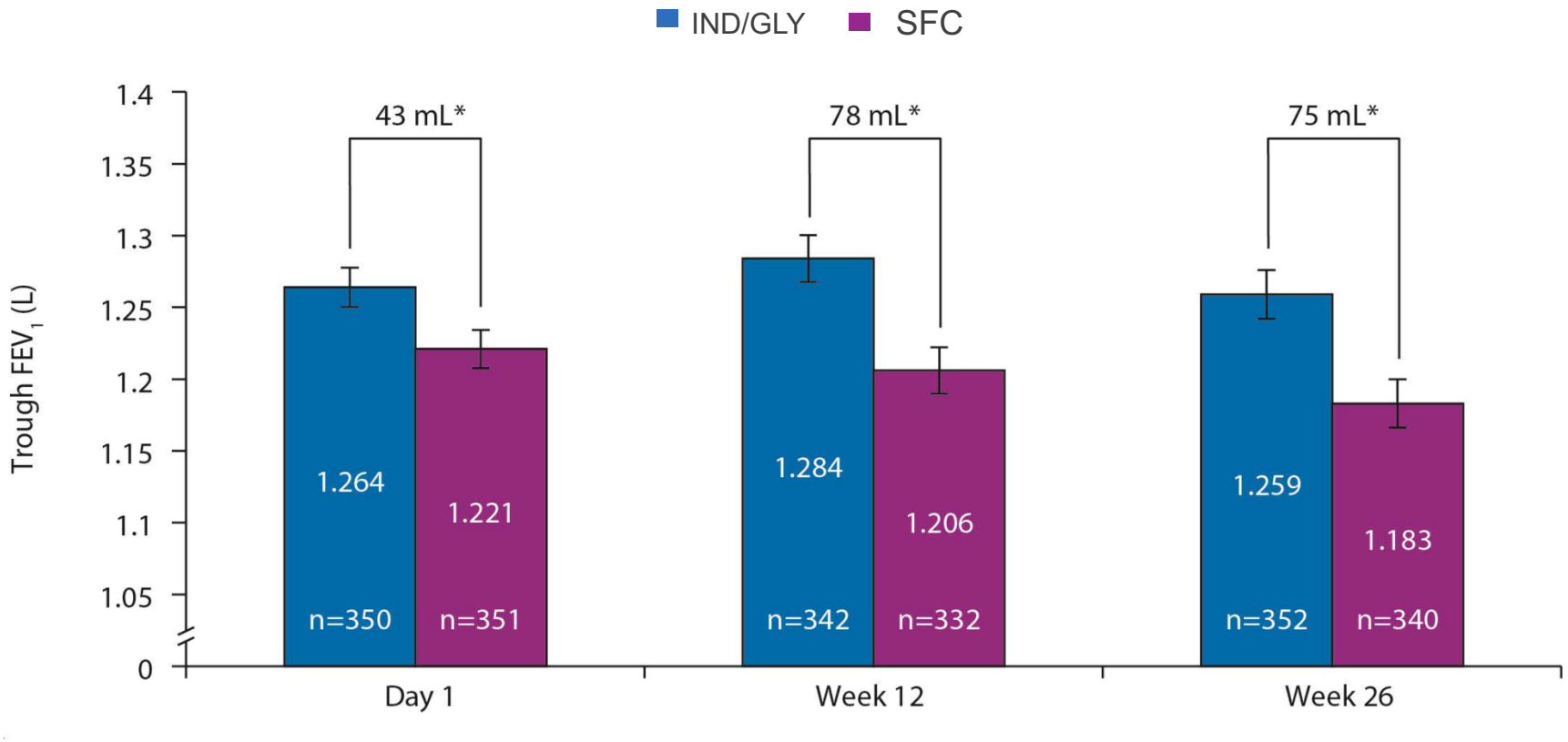
COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SFC = salmeterol/fluticasone propionate

A2331 LANTERN

1. Zhong et al. Int J COPD, 2015
2. GOLD 2015

Primary endpoint was met (non-inferiority) and IND/GLY demonstrated statistically significant superiority to SFC for trough FEV_1 at week 26

- Improvement in trough FEV_1 was consistent throughout the study period



*p<0.001; Date are least square means (standard error)

A2331 LANTERN

Zhong et al. Int J COPD 2015

Improvement in patient reported outcomes were comparable between two groups

	Day 1		Week 12		Week 26	
	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison
TDI focal score†	–	–	0.25 (-0.09, 0.59)	p=0.15	0.13 (-0.20, 0.47)	p=0.44
SGRQ-C total score			-0.74 (–2.35, 0.86)	n.s.	–0.69 (–2.38, 1.00)	n.s.
Change from baseline in mean daily number of puffs	–	–	–	–	–0.03 (–0.26, 0.21)	n.s.
CAT total score	–	–	0.3 (–0.4, 0.9)	n.s.	–0.2 (–0.9, 0.6)	n.s.

†Minimum clinically important difference is 100 mL (FEV_1) and 1-point (TDI score). SFC=salmeterol/fluticasone; LSM=least squares means; CI=confidence interval; n.s.=No significant; TDI=Transition Dyspnoea Index; SGRQ-C=St George's Respiratory Questionnaire for COPD patients (a reduction indicates improvement).

A2331 LANTERN

Zhong et al. Int J COPD 2015

FLAME

Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD

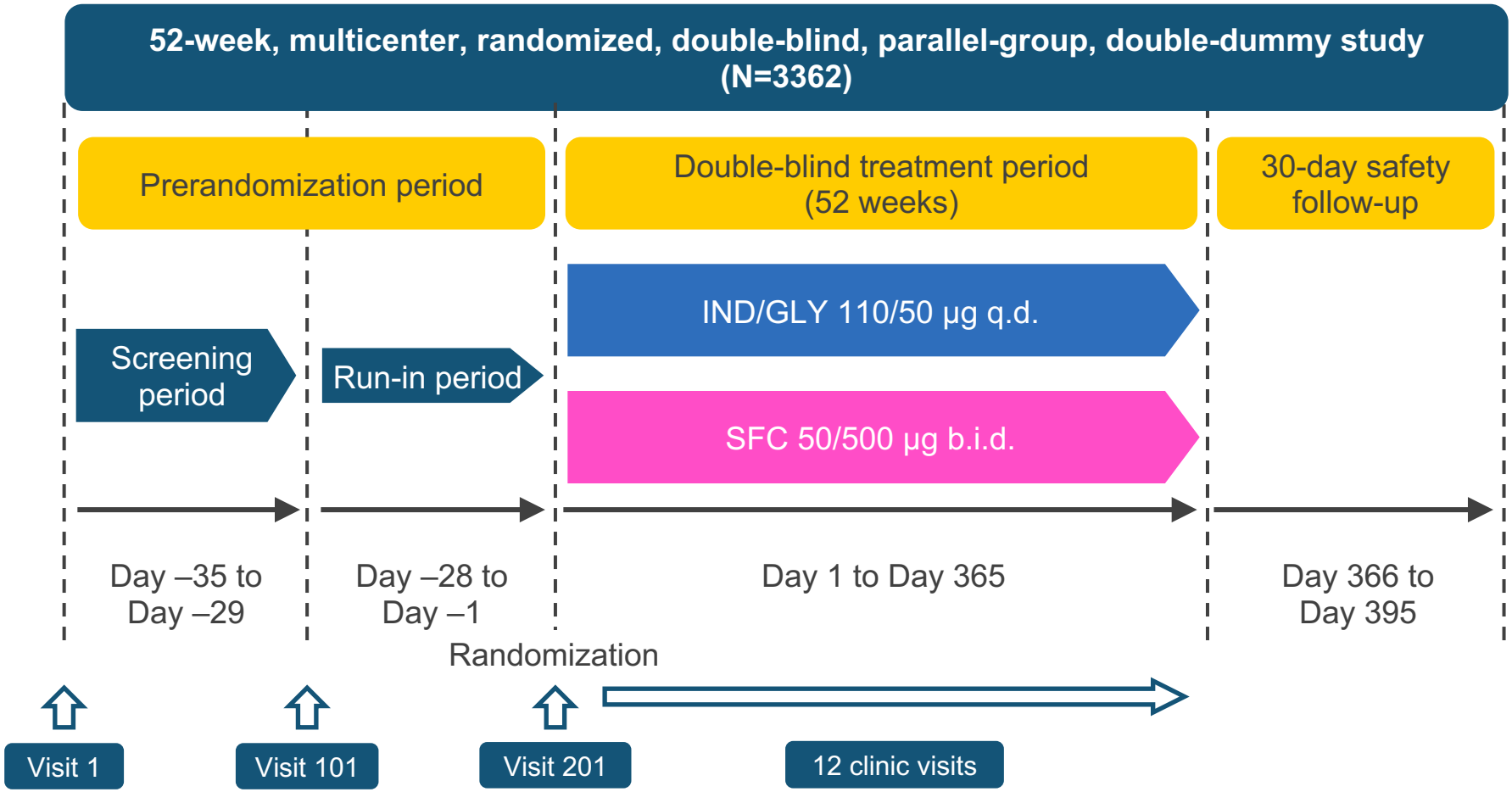
Jadwiga A. Wedzicha, Donald Banerji, Kenneth R. Chapman, Jørgen Vestbo, Nicolas Roche, R. Timothy Ayers, Chau Thach, Robert Fogel, Francesco Patalano, and Claus F. Vogelmeier, for the FLAME-COPD Investigators

New England Journal of Medicine 2016, Online May 15, 2016. DOI: 10.1056/NEJMoa1516385

NOVARTIS

2318 FLAME

FLAME study design



2318 FLAME

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34

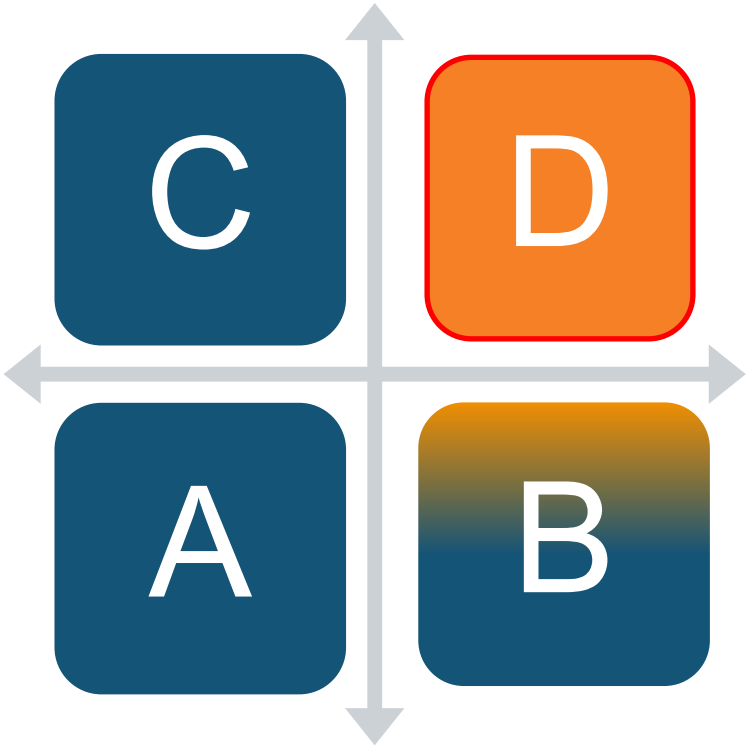
Patient population as classified by GOLD 2016 combined assessment of COPD

Inclusion criteria

- Post-bronchodilator FEV_1 ≥25% and 60% predicted
- ≥1 documented COPD exacerbation requiring treatment with antibiotics, systemic corticosteroids or hospitalization in previous year.

Exclusion criteria

- COPD exacerbation requiring treatment with antibiotics, systemic corticosteroids or hospitalization in 6 weeks prior visit 1



Population characteristics

- Mean FEV_1 % predicted: 44.1%
- Exacerbations in previous year: 1 (80.6%), ≥ 2 (19.3%)
- Symptomatic: Yes
- ICS users at baseline 56.3%

Patients targeted by inclusion criteria

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SFC = salmeterol/fluticasone propionate

FLAME 2318

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34

GOLD 2016

Primary endpoint: Non-inferiority and superiority for IND/GLY versus SFC was demonstrated for the rate all COPD exacerbations over 52 weeks

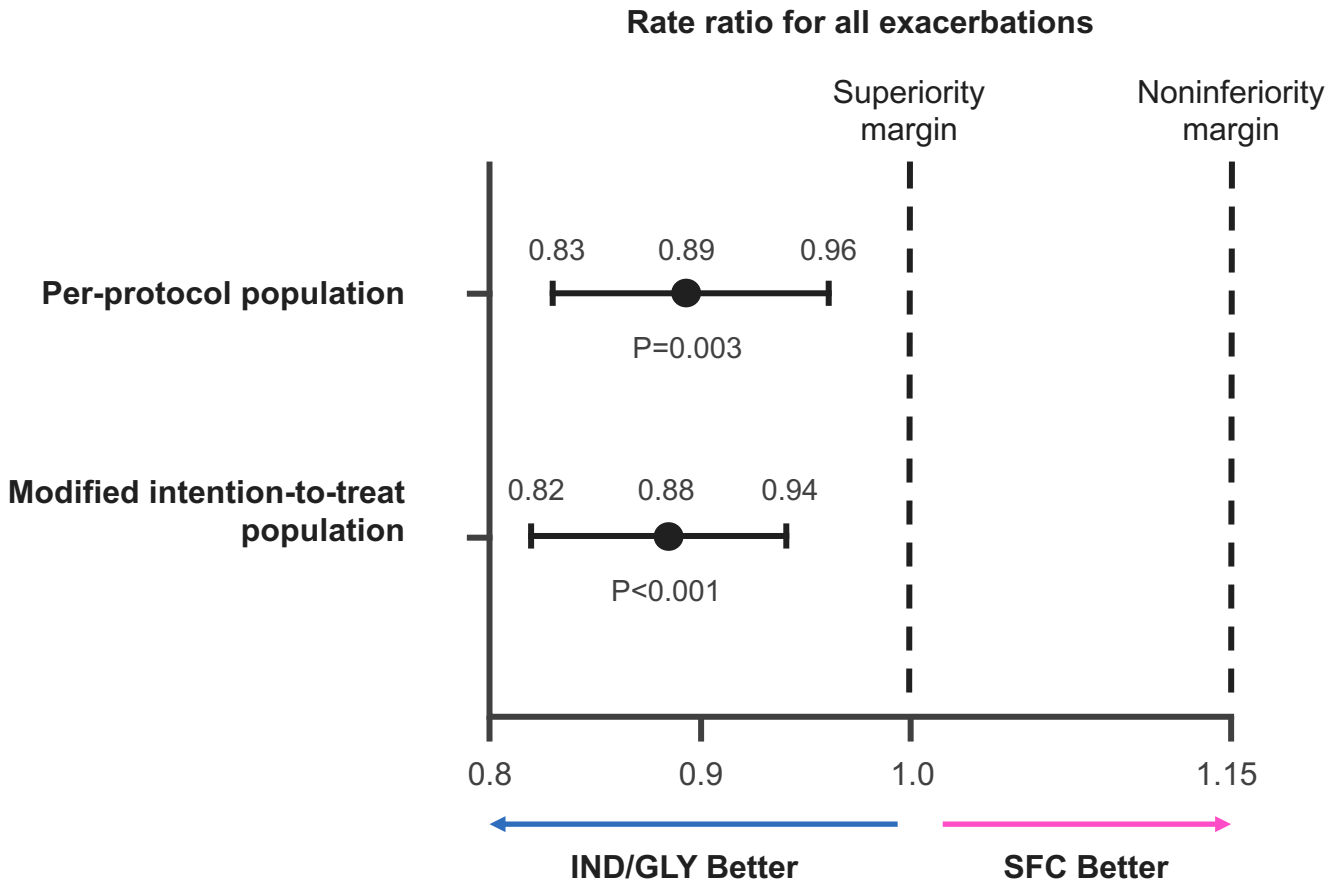
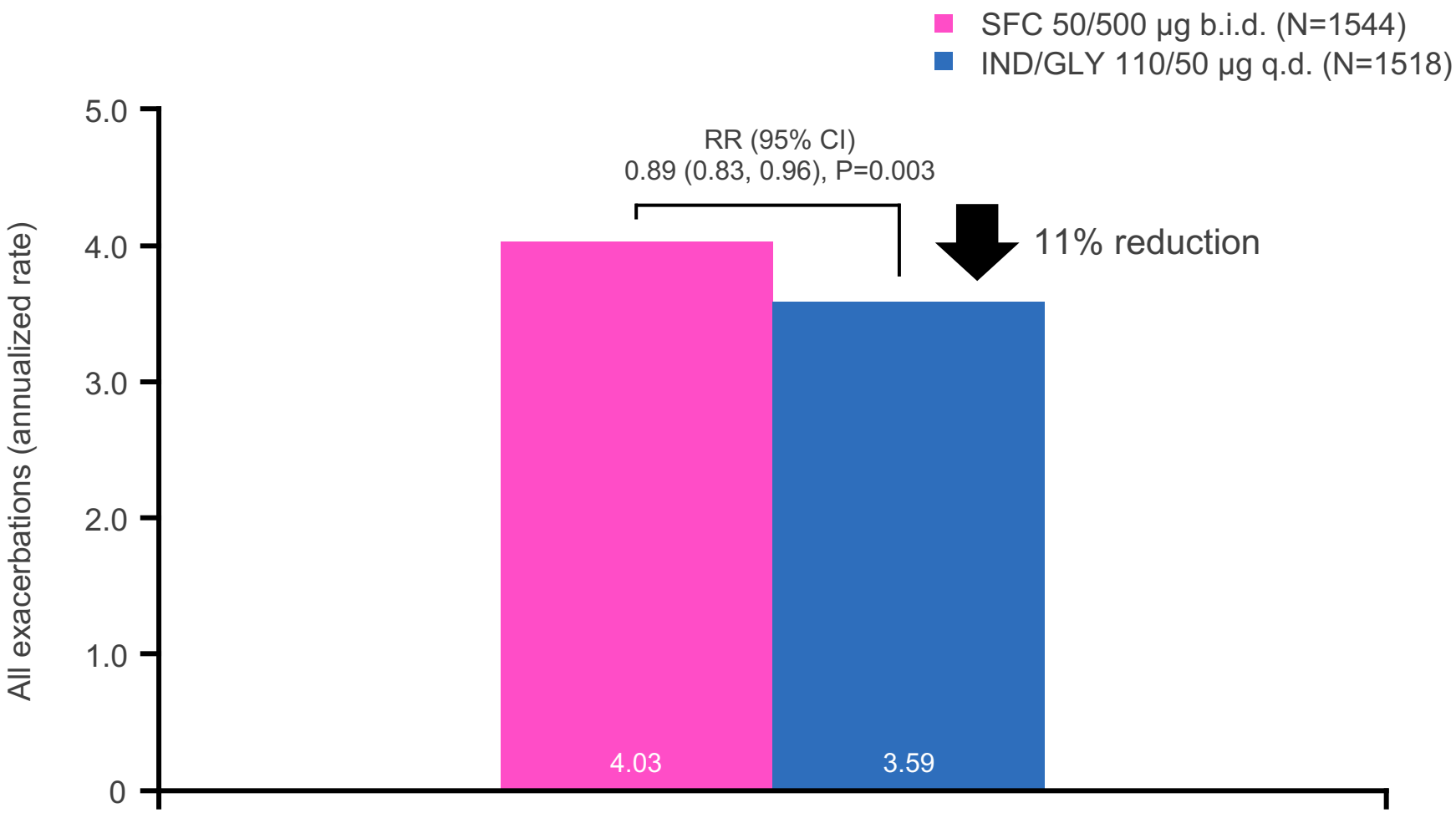


Figure shows the rate ratio for all exacerbations (mild, moderate, and severe) in the IND/GLY group versus the SFC group. The bars indicate 95% confidence intervals. The modified intention-to-treat population included all patients who underwent randomization, received at least one dose of a trial drug during the treatment period, and did not have major violations of compliance with Good Clinical Practice guidelines before unblinding occurred. The per-protocol population included all patients in the modified intention-to-treat population who did not have any major protocol deviations (definitions of major protocol deviations were specified before unblinding occurred).

FLAME 2318

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34

IND/GLY showed superiority in reducing the annual rate of all exacerbations (mild, moderate and severe) versus SFC

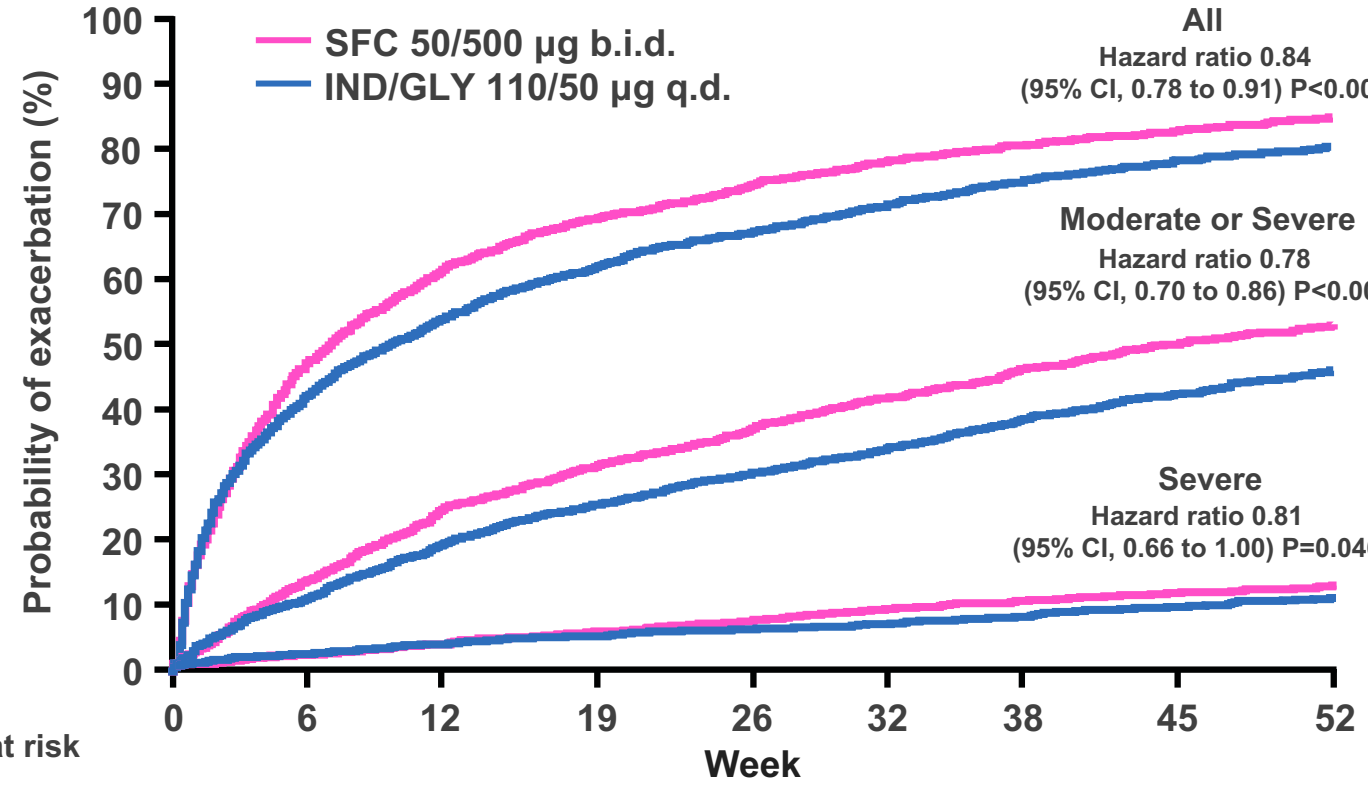


Analysis of the per protocol set (PPS)

2318 FLAME

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34

IND/GLY significantly delayed the time to first exacerbation compared with SFC



Patients at risk

All					
IND/GLY group	1675	763	535	409	281
SFC group	1679	642	415	313	217
Moderate or Severe					
IND/GLY group	1675	1299	1091	948	711
SFC group	1679	1210	975	820	608
Severe					
IND/GLY group	1675	1530	1434	1368	1138
SFC group	1679	1507	1389	1303	1071

Analysis of the modified intention-to-treat population (mITT)

b.i.d., twice daily; CI, confidence interval; GLY, glycopyrronium; IND, indacaterol; q.d., once daily; SFC, salmeterol/fluticasone propionate combination

A2318 FLAME

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34

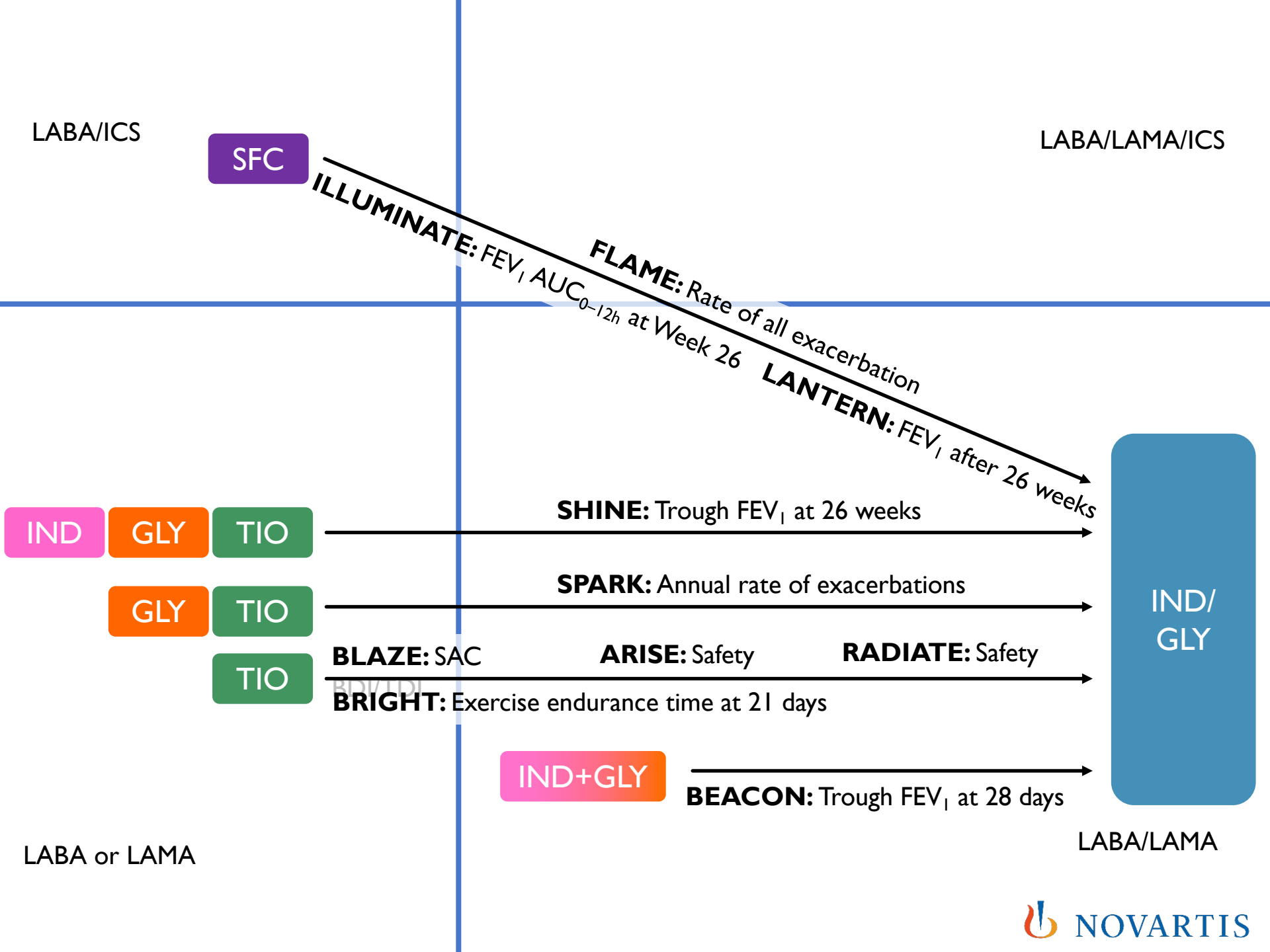
Secondary efficacy outcomes were significant improved with QVA149 compared to SFC

	Week 12		Week 26		Week 52	
	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison	Treatment difference QVA149 versus SFC (LSM, 95% CI)	p-value for treatment comparison
Change from baseline in trough FEV1 (mL)†	–	–	–	–	62	P<0.001
Change from baseline in FEV1 $AUC_{0\text{-}12h}$ (mL)					110	P<0.001
SGRQ-C total score	-1.3 (–2.0, –0.6)	p≤0.001	-1.2 (–2.0, –0.5)	p≤0.001	-1.3 (–2.1, –0.4)	p=0.003
Change from baseline in mean daily number of puffs	–	–	–	–	–0.25	P<0.001

†Minimum clinically important difference is 100 mL (FEV_1) and 1-point (TDI score). SFC=salmeterol/fluticasone; LSM=least squares means; CI=confidence interval; n.s.=No significant; TDI=Transition Dyspnoea Index; SGRQ-C=St George's Respiratory Questionnaire for COPD patients (a reduction indicates improvement).

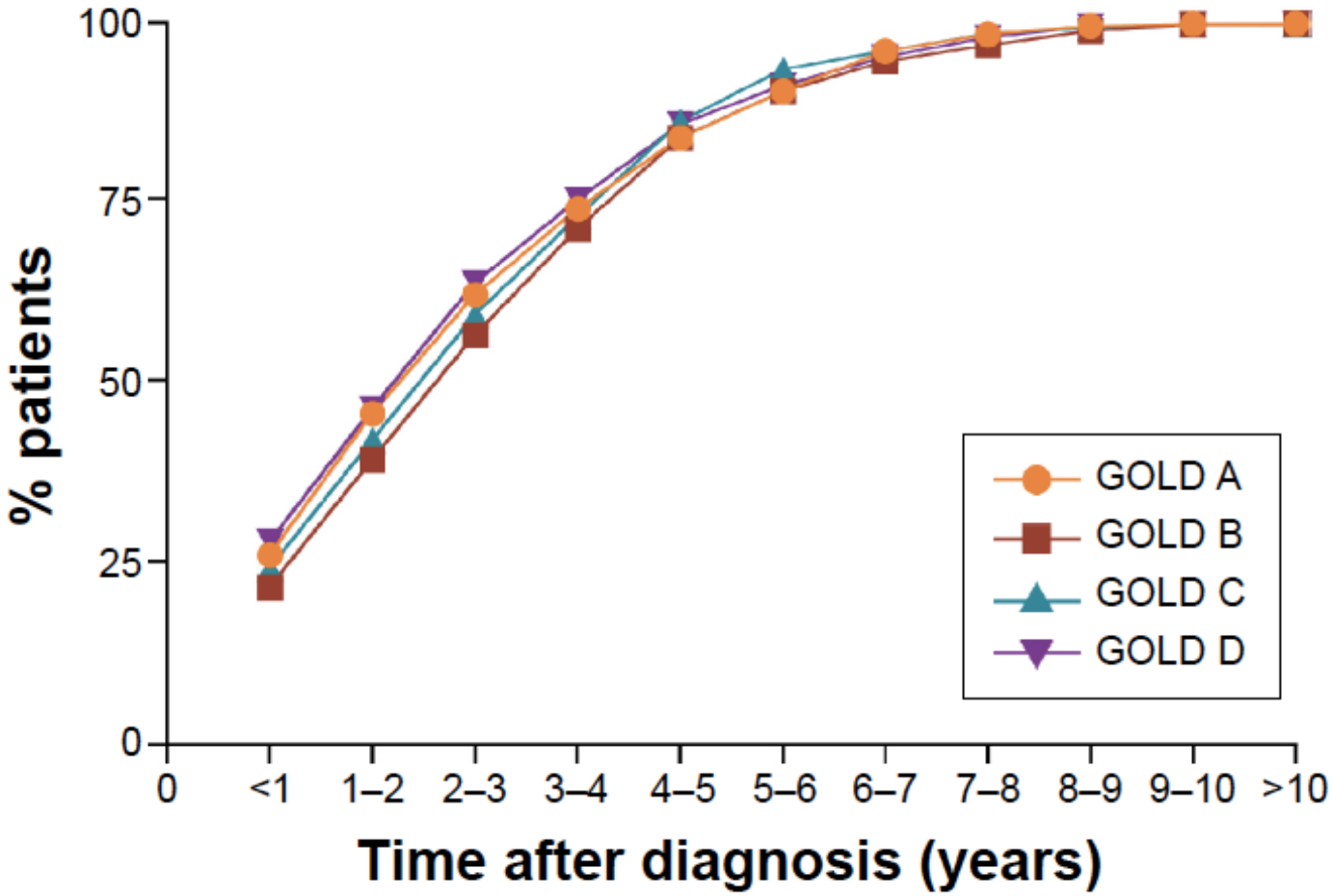
A2318 FLAME

Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34


LABA/ICS
LABA/LAMA/ICS
SFC
ILLUMINATE: FEV1 AUC0–12h at Week 26
FLAME: Rate of all exacerbation
LANTERN: FEV1 after 26 weeks
IND
GLY
TIO
SHINE: Trough FEV1 at 26 weeks
GLY
TIO
SPARK: Annual rate of exacerbations
TIO
BLAZE: SAC
ARISE: Safety
RADIATE: Safety
BRIGHT: Exercise endurance time at 21 days
IND+GLY
BEACON: Trough FEV1 at 28 days
IND/
GLY
LABA or LAMA
LABA/LAMA

NOVARTIS

The inevitable drift to triple therapy in COPD : an analysis of prescribing pathways in the UK



International Journal of COPD 2015:10 2207–2217

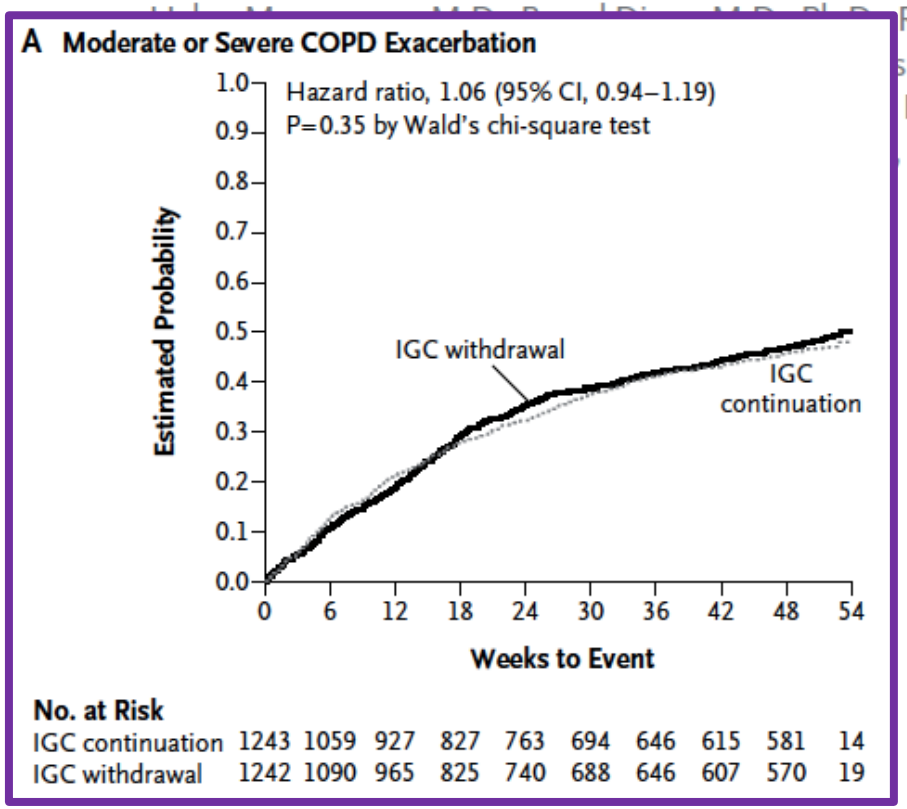
NOVARTIS

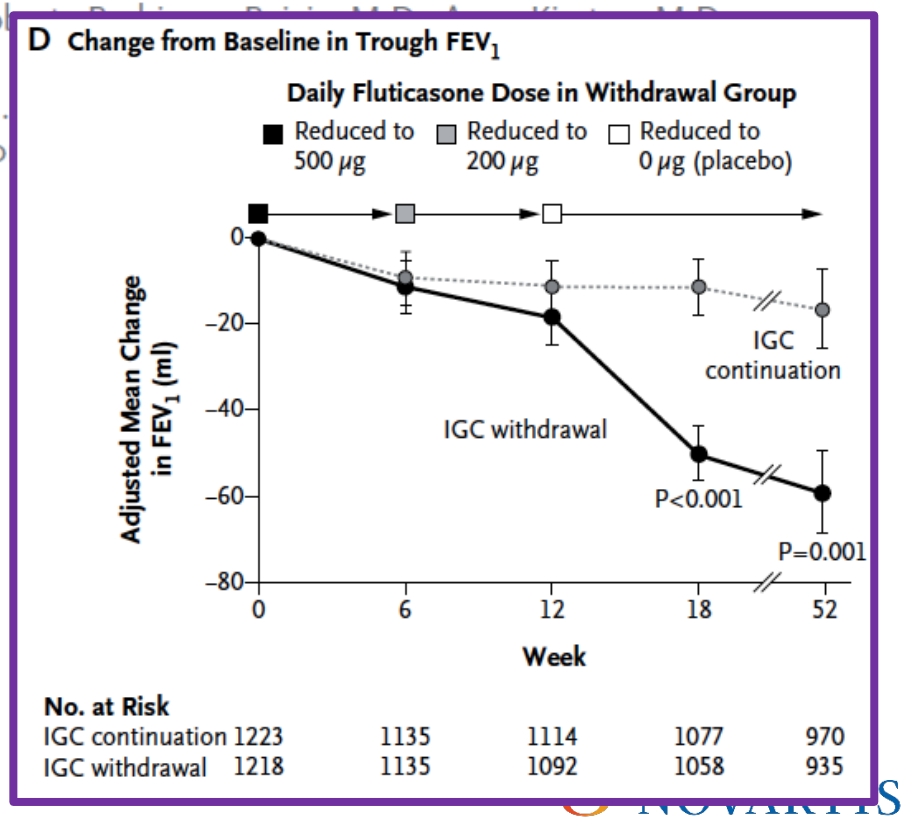
The NEW ENGLAND JOURNAL of MEDICINE

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

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

[illegible]

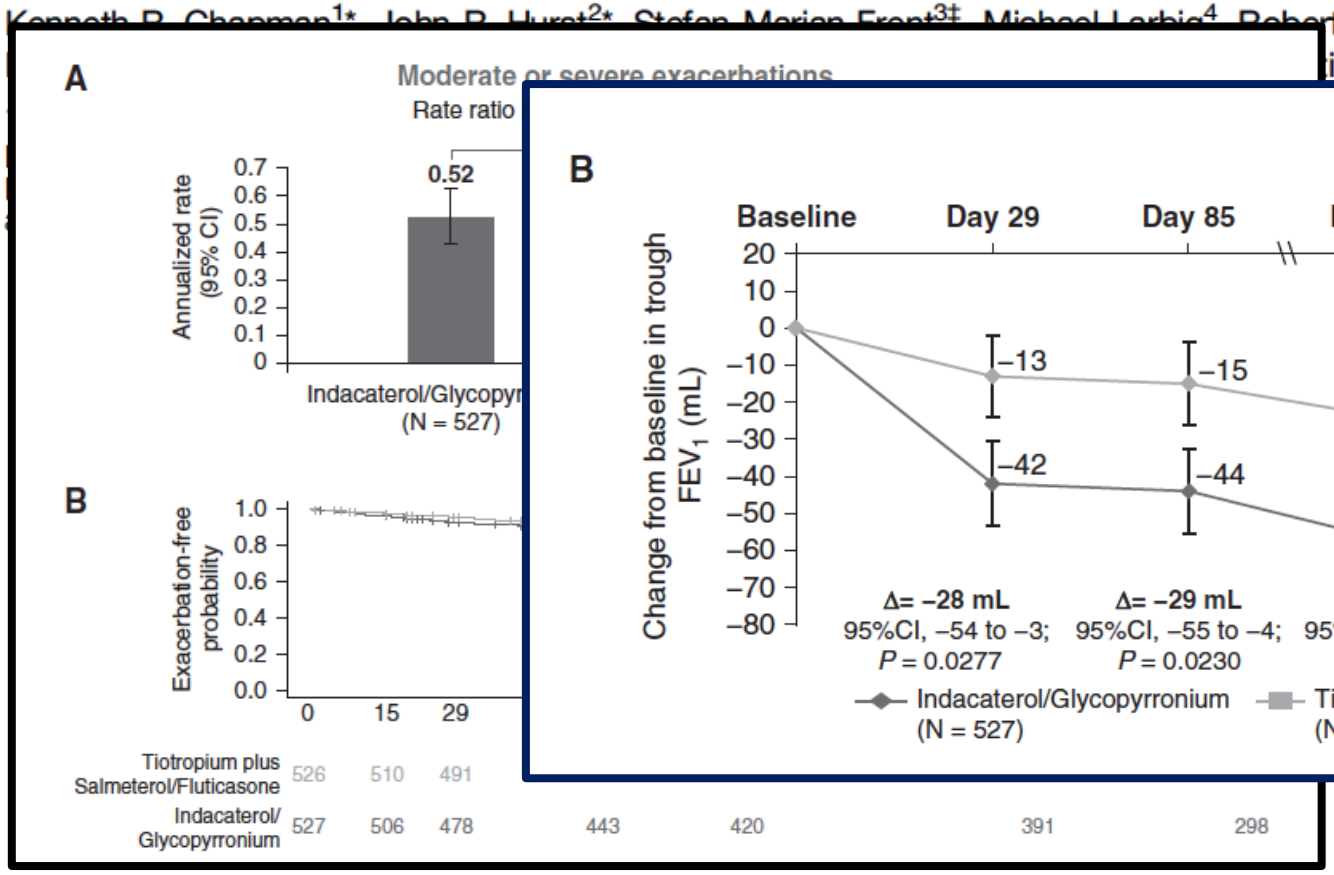




ORIGINAL ARTICLE

Long-Term Triple Therapy De-escalation to Indacaterol/ Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial

Kenneth R. Chapman[1*], John R. Hurst[2*], Stefan Marian Frent[3‡], Michael Larbig[4], Robert Fogel[5], Tadhg Guerin[6], ikas[4], and Jadwiga A. Wedzicha[7]



NOVARTIS

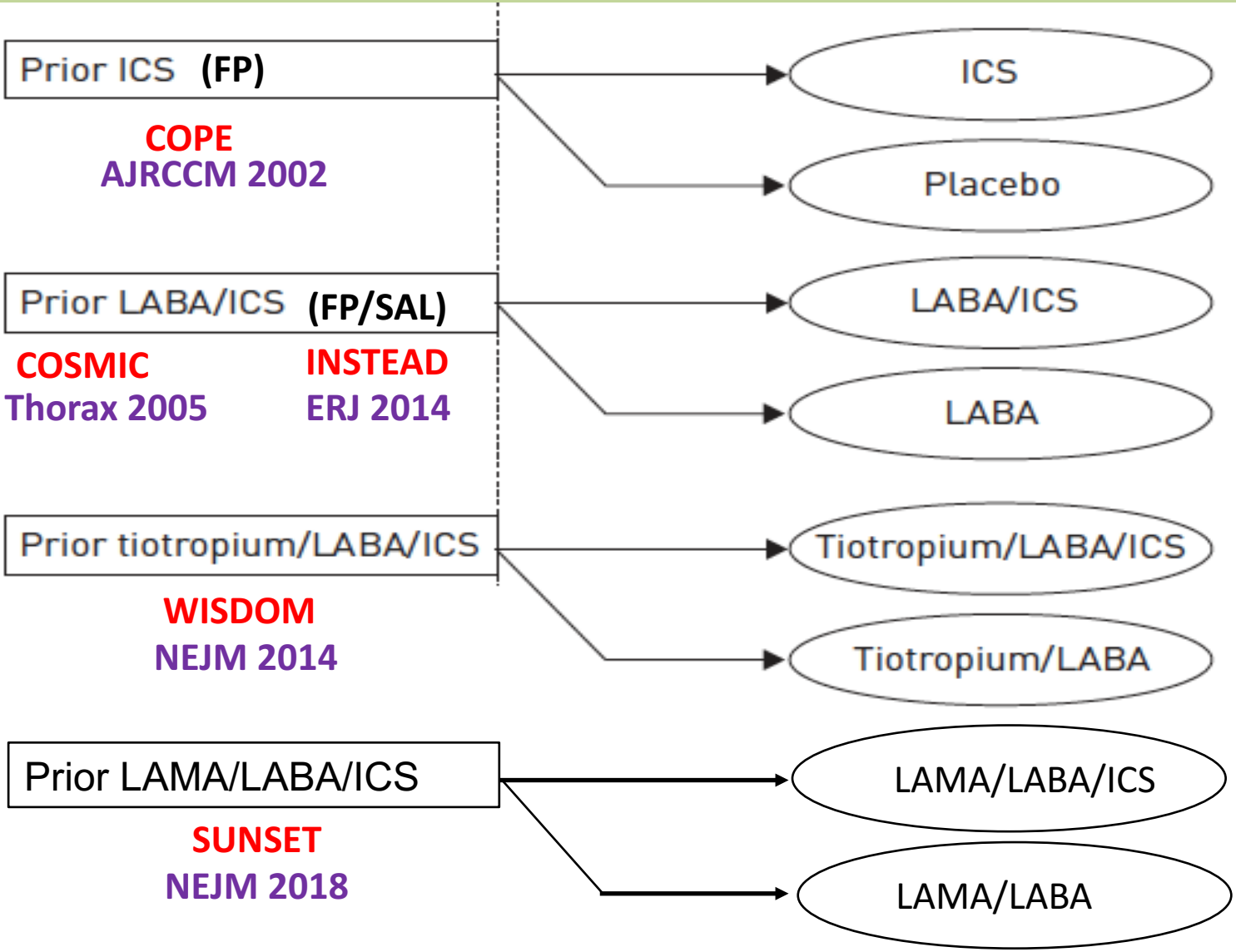
SUNSET AND WISDOM : CONTRASTING STUDY DESIGNS

- Gradual withdrawal of ICS following a 6 week run-in on triple therapy
- **39% of patients** receiving triple therapy at baseline
- Patients with severe-to-very severe COPD (FEV1<50% predicted) and a history of ≥ 1 exacerbation in the previous year

- Direct de-escalation from tiotropium + SFC to IND/GLY following 4 week run-in on triple therapy
- **All patients** receiving triple therapy for >=6 months prior to enrollment
- Patients with moderate-to-severe COPD (FEV1 40~80% predicted) and a history of ≤1 COPD exacerbation in the previous year

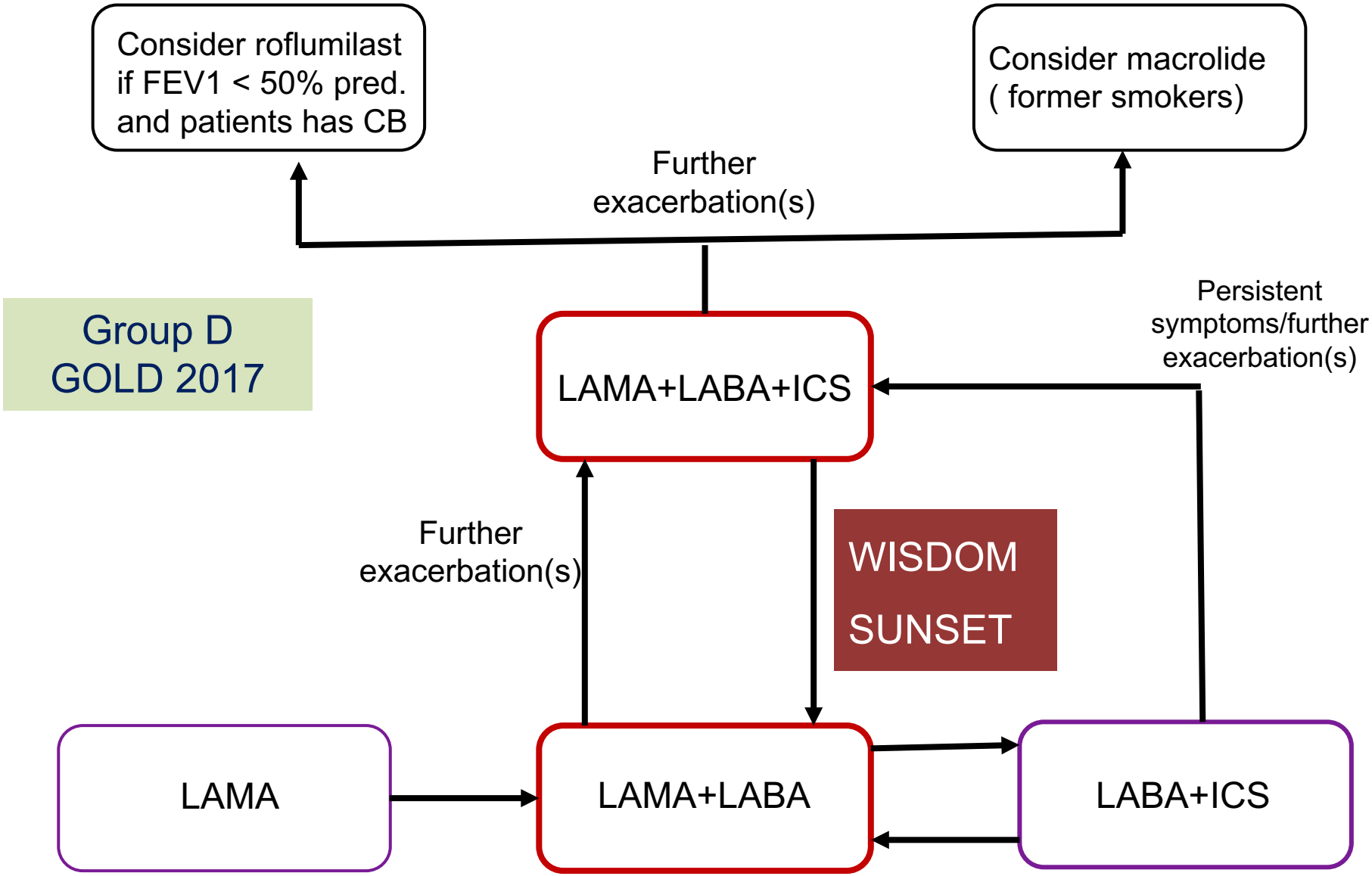
NOVARTIS

Summary of RCT of ICS withdrawal in COPD



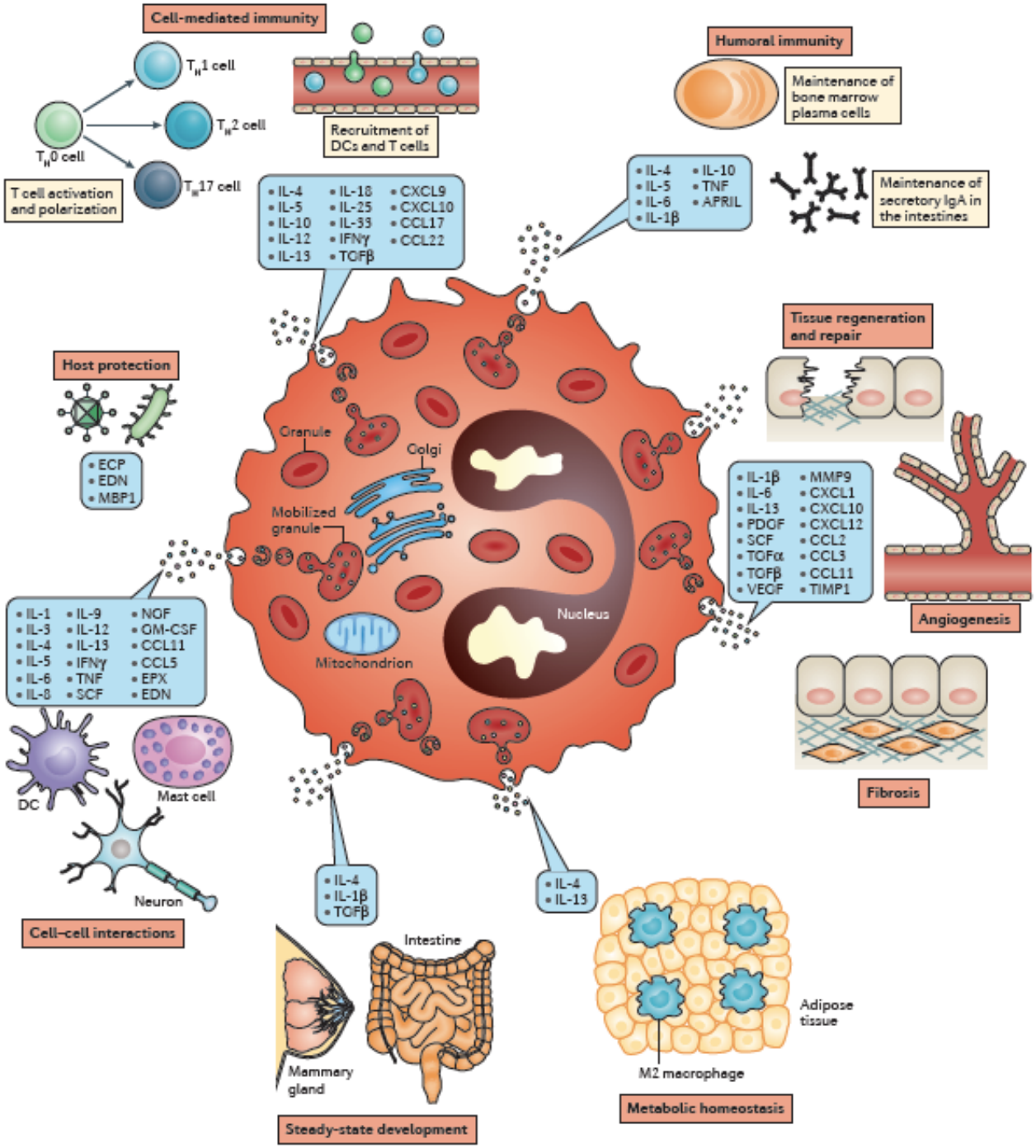
Format idea from Surssa ERJ 2015 Nov 46(5) 1232-1235

Summary


Consider roflumilast if FEV1 < 50% pred. and patients has CB
Consider macrolide (former smokers)
Further exacerbation(s)
Group D GOLD 2017
LAMA+LABA+ICS
Persistent symptoms/further exacerbation(s)
Further exacerbation(s)
WISDOM
SUNSET
LAMA
LAMA+LABA
LABA+ICS

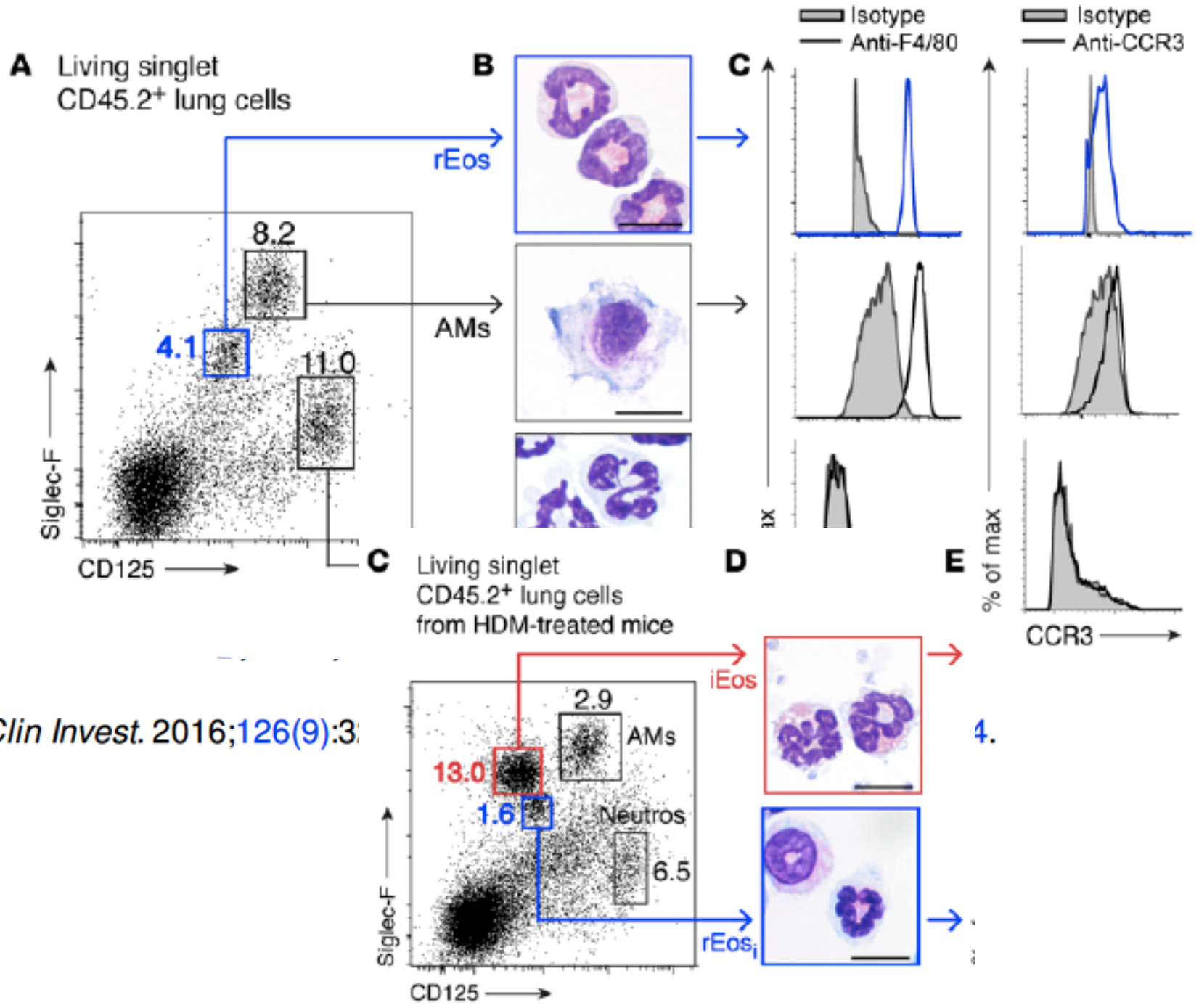
Outlines

- COPD : introduction
- The role of bronchodilators in COPD
- The role of eosinophil and ICS in COPD
- Pulmonary rehabilitation
- Summary

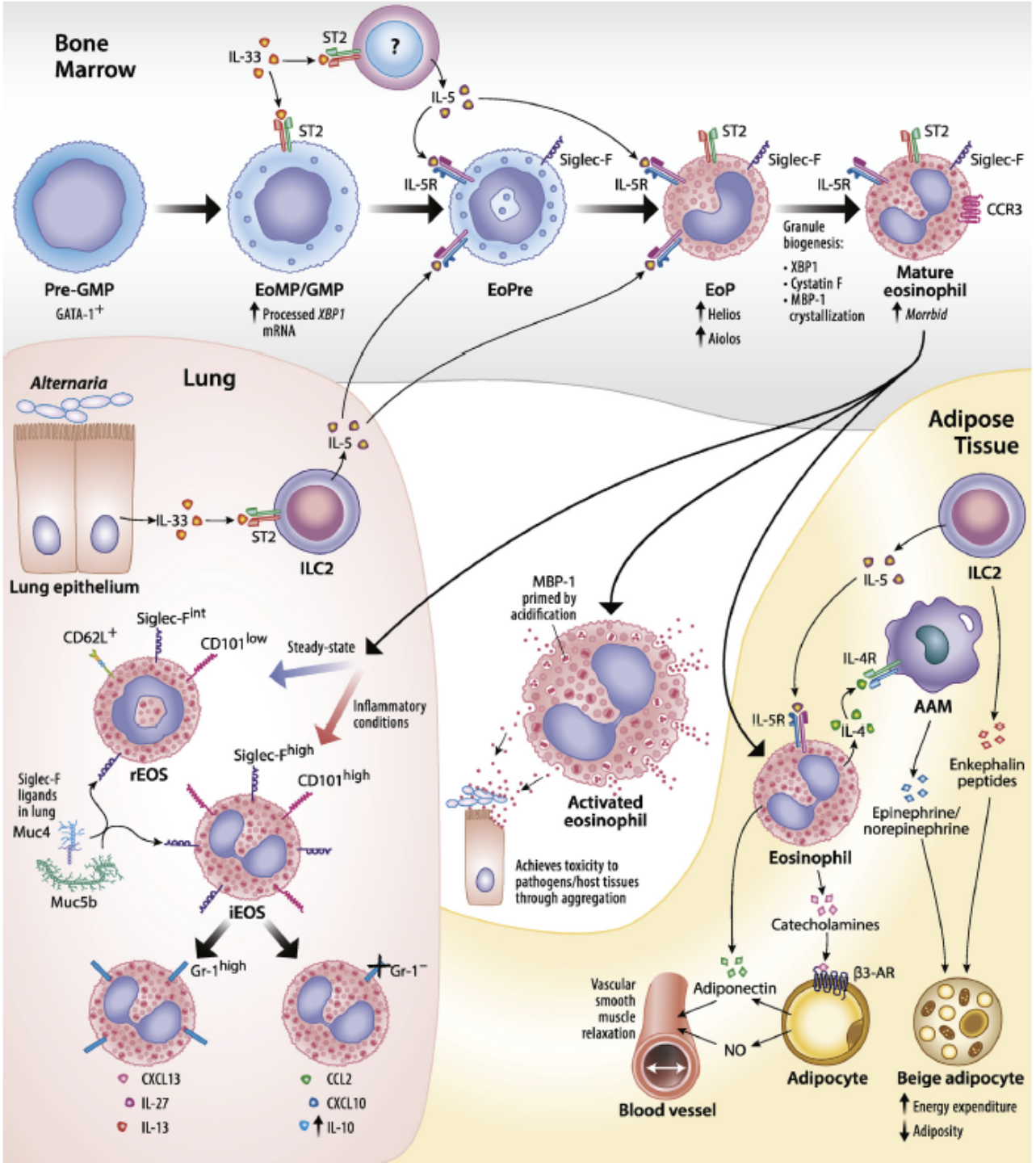


Nature review

PP 746 , Dec 2017 , Vol 17



J Clin Invest. 2016;126(9):3 4.



Eosinophils and eosinophil-associated diseases: An update

Jeremy A. O'Sullivan

J Allergy Clin Immunol 2017

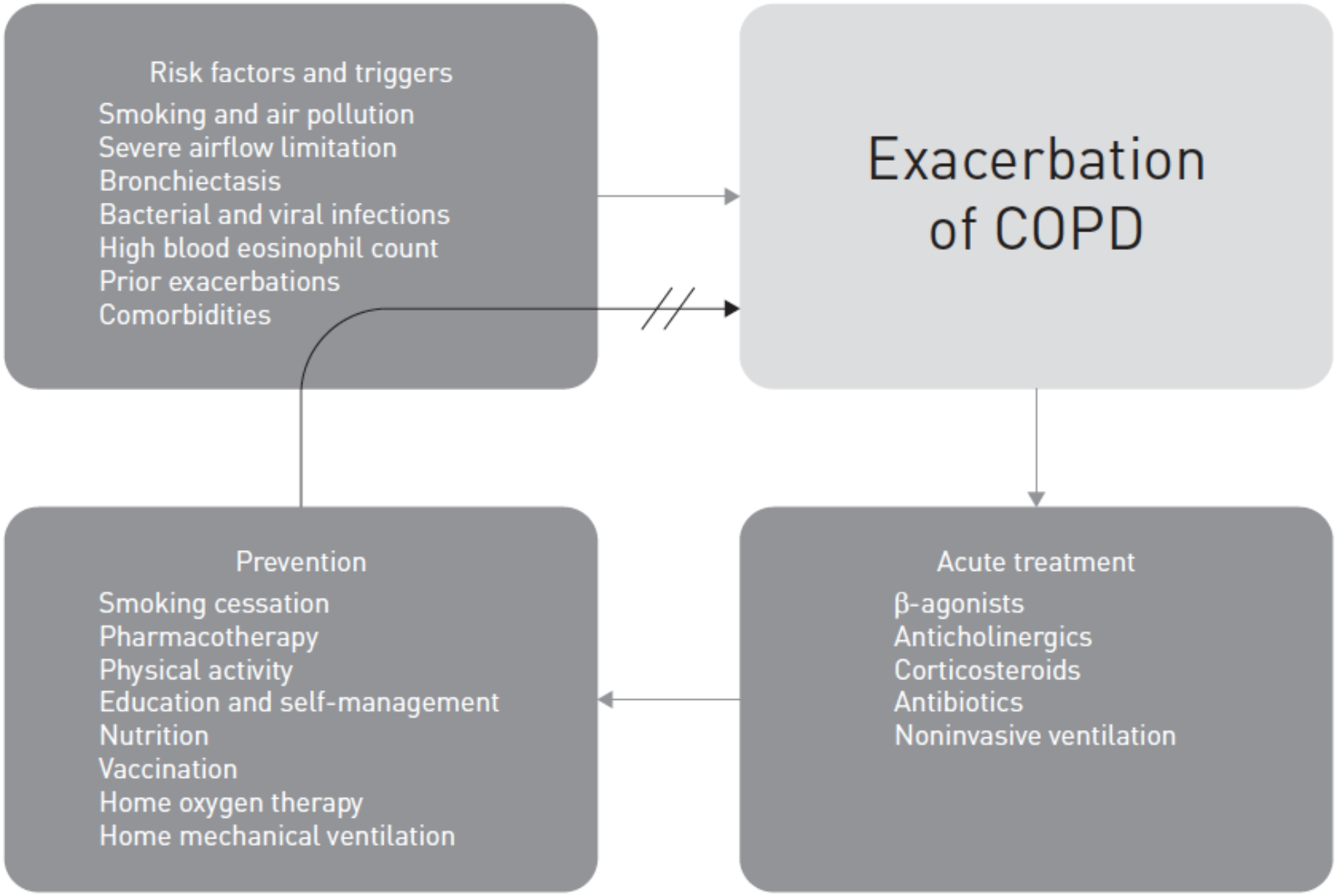
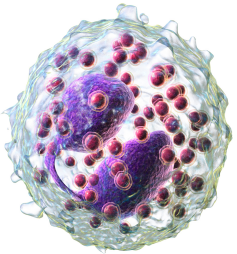


FIGURE 1 Several risk factors and triggers are involved in exacerbations of chronic obstructive pulmonary disease (COPD). In the acute setting, adequate treatment is necessary; then, appropriate measures for prevention of a subsequent exacerbation should be initiated.

Eur Respir Rev 2018; 27: 170103

Persist and reproducible ?



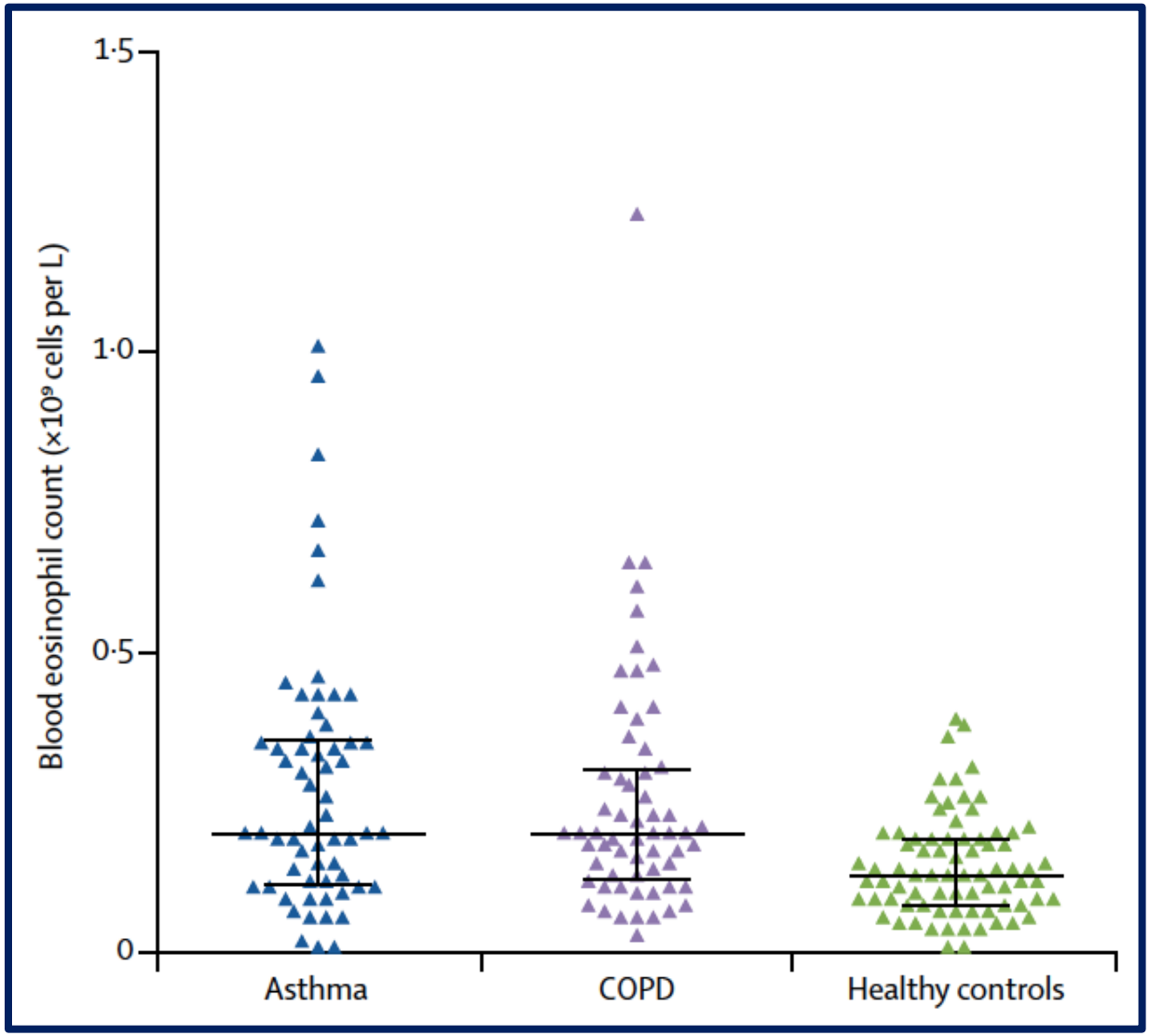
Predict exacerbation ?

Eosinophil

Mortality ?

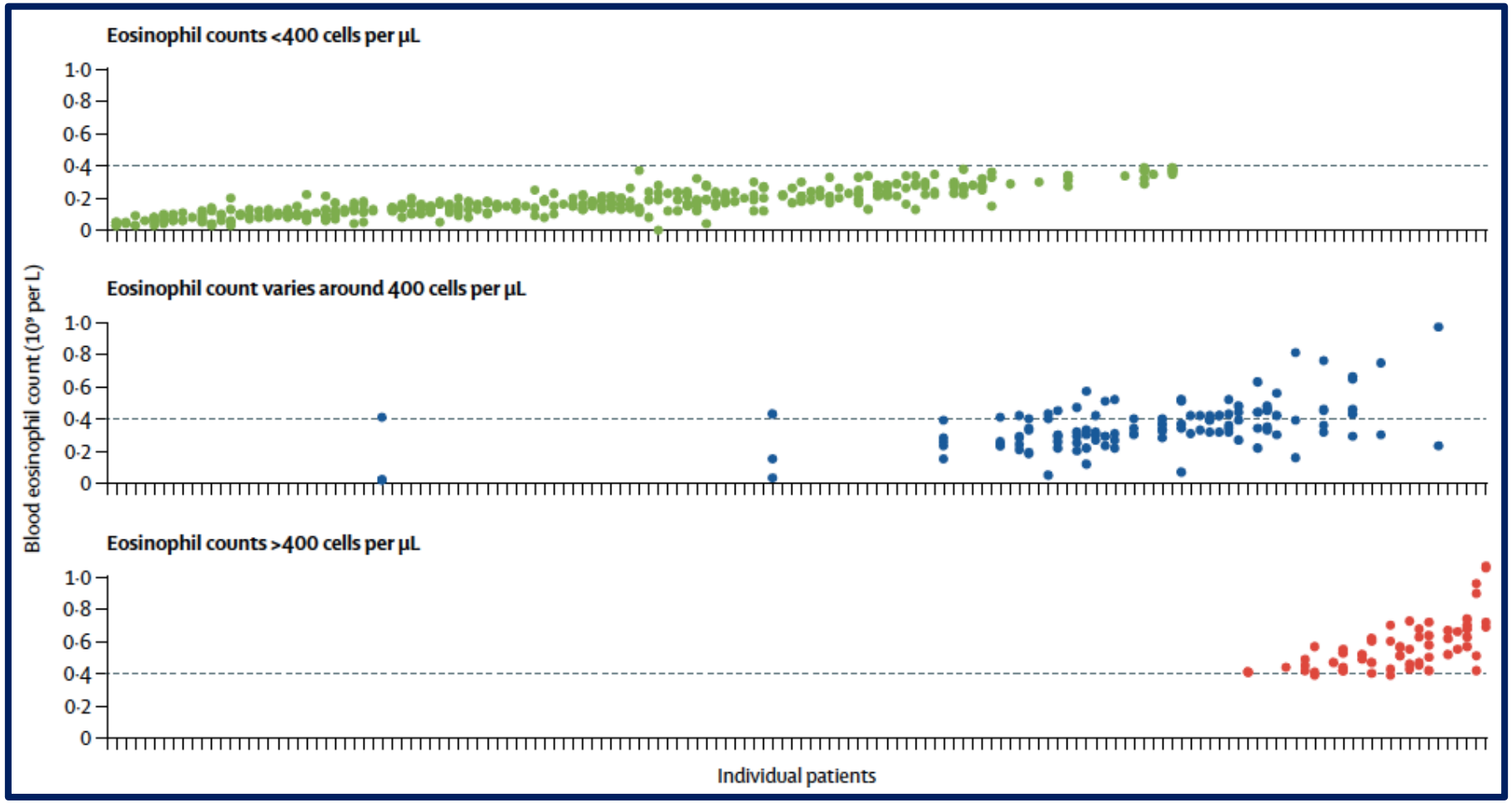
Response to ICS ?

Peripheral blood eosinophil counts in asthma, COPD, and healthy controls

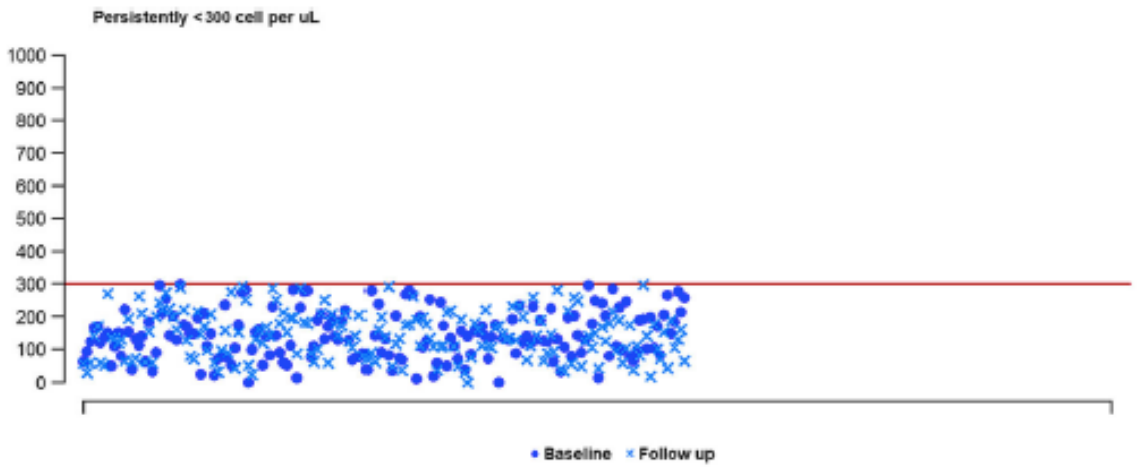


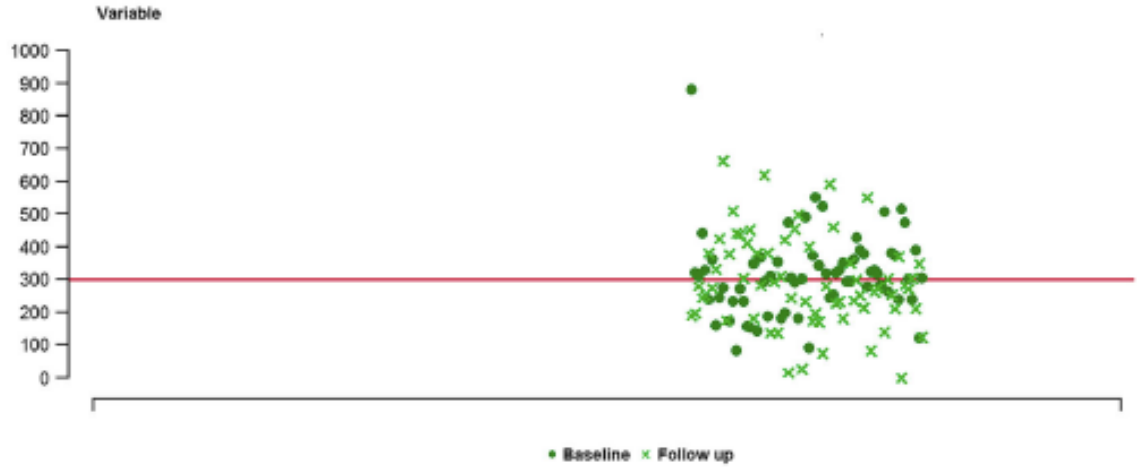
Bafadhel M, et al. Respiration 2012; 83: 36–44
Anand A, et al. Thorax 2015; 70: A111

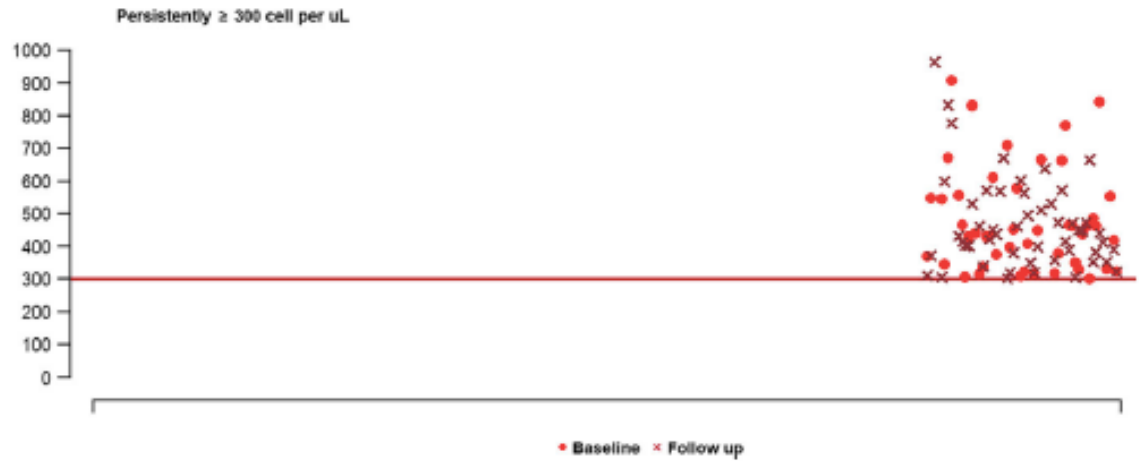
Repeated peripheral blood eosinophil counts during stable disease over 12 months in patients with COPD



Bafadhel M, et al. Am J Respir Crit Care Med 2011; 184: 662–71
Bafadhel M, et al. Am J Respir Crit Care Med 2012; 186: 48–55







Shin *et al. Resp*
https://doi.org

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RESEA

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Sun Hye Sh
Yeon-Mok (

ung Lee[7],

The reproducibility of COPD blood eosinophil counts

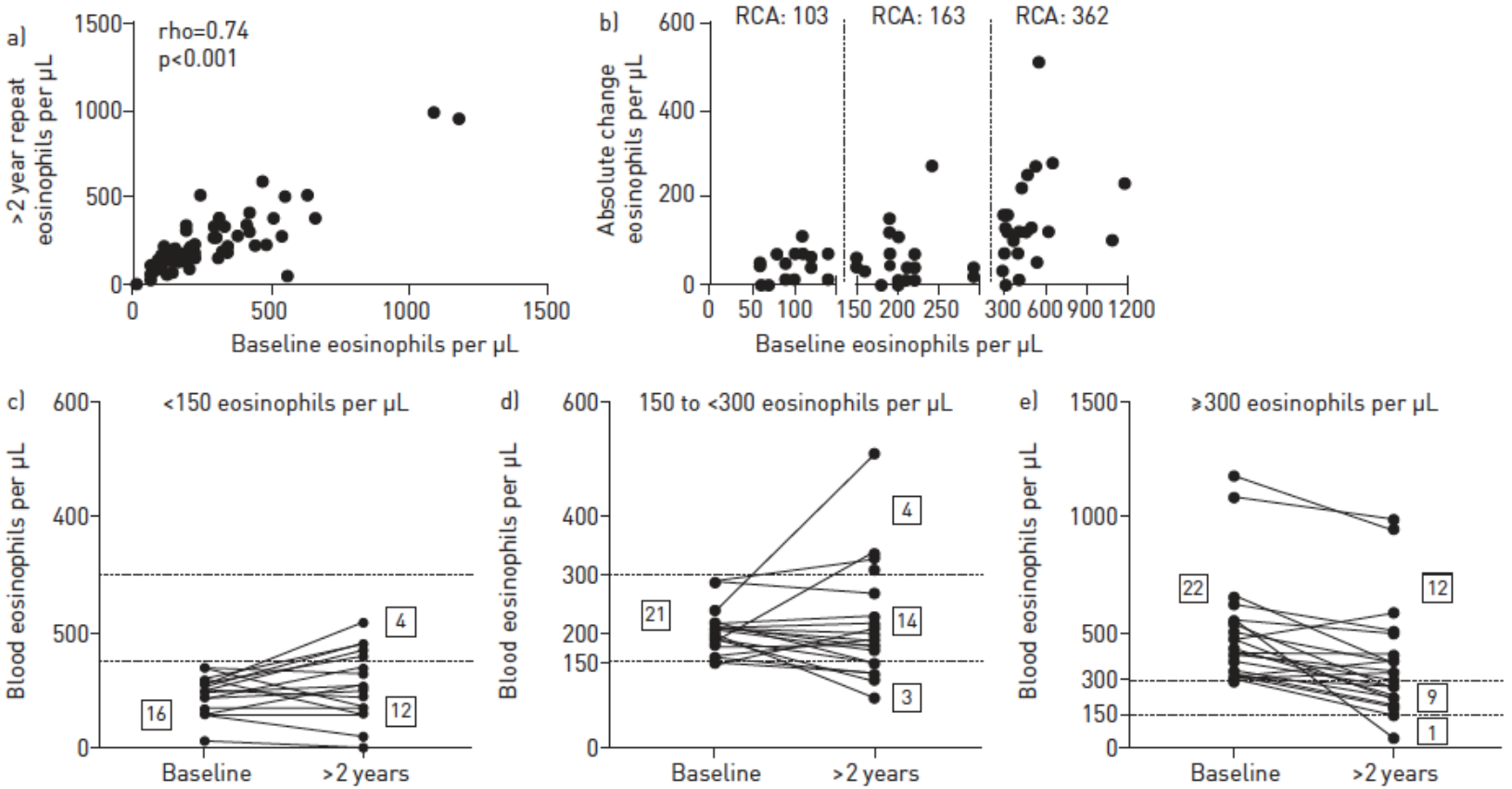
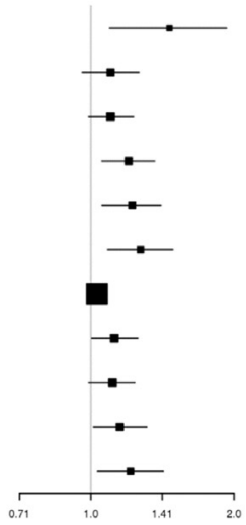


FIGURE 1 Variation of repeated measurements of chronic obstructive pulmonary disease blood eosinophils. a) Blood samples were collected at baseline and >2 years later. b) Baseline eosinophil samples were characterised as being either <150, 150–<300 or ⩾300 eosinophils per µL for repeatability coefficient analysis (RCA), which predicts where 95% of the repeat values will fall. c–e) Changes in these categories from baseline during repeat measurements (c) <150, d) 150 to <300 and e) ⩾300 eosinophils per µL). Boxed numbers describe the number of samples in each category. The dotted lines show the 150 and 300 eosinophils per µL cut-offs.

Eur Respir J 2018; 52: 1800427

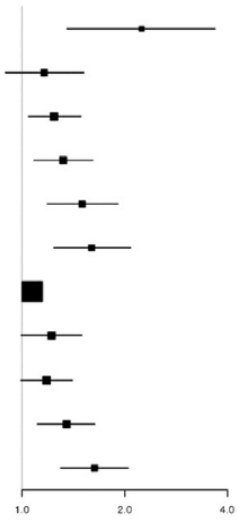
Blood eosinophil count thresholds and exacerbations in COPD

Eosinophil Cutoff	< n	≥ n	IRR	95% CI
continuous cells/uL	NA	1895	1.46	1.09-1.93
100 cells/uL	368	1527	1.1	0.96-1.26
200 cells/uL	1032	863	1.1	0.99-1.23
300 cells/uL	1477	418	1.2	1.05-1.36
340 cells/uL	1584	311	1.22	1.06-1.40
400 cells/uL	1668	227	1.27	1.08-1.48
continuous %	NA	1895	1.03	1.01-1.06
2 %	720	1175	1.12	1.00-1.25
3 %	1178	717	1.11	0.99-1.24
4 %	1476	419	1.15	1.01-1.31
5 %	1660	235	1.21	1.03-1.42



ECLIPSE cohort

Eosinophil Cutoff	< n	≥ n	IRR	95% CI
cell/uL continuous	NA	1540	2.24	1.35-3.68
100 cells/uL	223	1330	1.16	0.90-1.52
200 cells/uL	814	739	1.24	1.04-1.48
300 cells/uL	1187	366	1.32	1.08-1.61
340 cells/uL	1350	203	1.5	1.18-1.91
400 cells/uL	1398	155	1.6	1.24-2.08
% continuous	NA	1540	1.07	1.02-1.11
2 %	408	1145	1.22	0.99-1.50
3 %	859	694	1.18	0.99-1.40
4 %	1166	387	1.35	1.11-1.63
5 %	1334	219	1.63	1.30-2.05



COPDGene study

J Allergy Clin Immunol 2018;141:2037-47

How about the effect of smoking ?

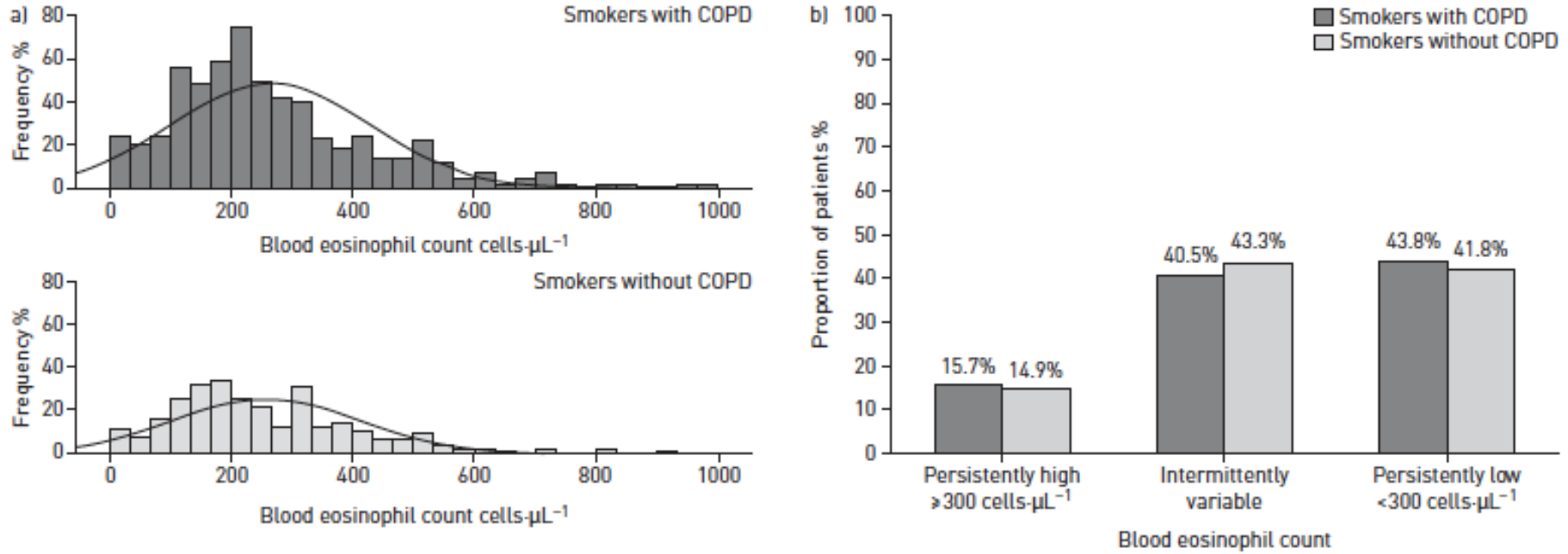
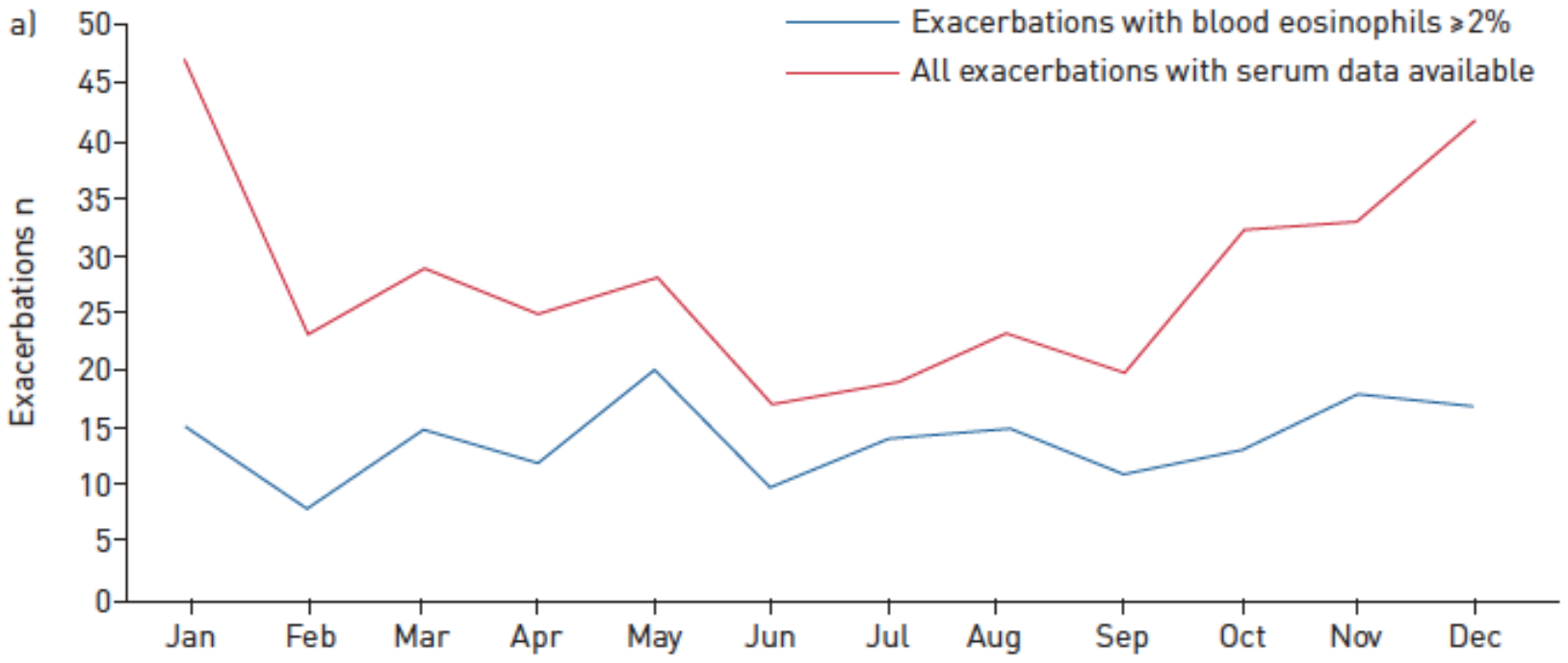


FIGURE 2 a) Distribution of blood eosinophil levels in smoker subjects with and without chronic obstructive pulmonary disease (COPD) in the CHAIN cohort at baseline. b) Longitudinal distribution of blood eosinophil levels in smoker subjects with and without COPD in the CHAIN cohort.

Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD

Eur Respir J 2017; 50: 1701162

How about the effect of seasons ?



Impact and associations of eosinophilic inflammation in COPD: analysis of the AERIS cohort

Eur Respir J 2017; 50: 1700853

Outlines

- COPD : introduction
- The role of bronchodilators in COPD
- The role of eosinophil and ICS in COPD
- Pulmonary rehabilitation
- Summary

Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

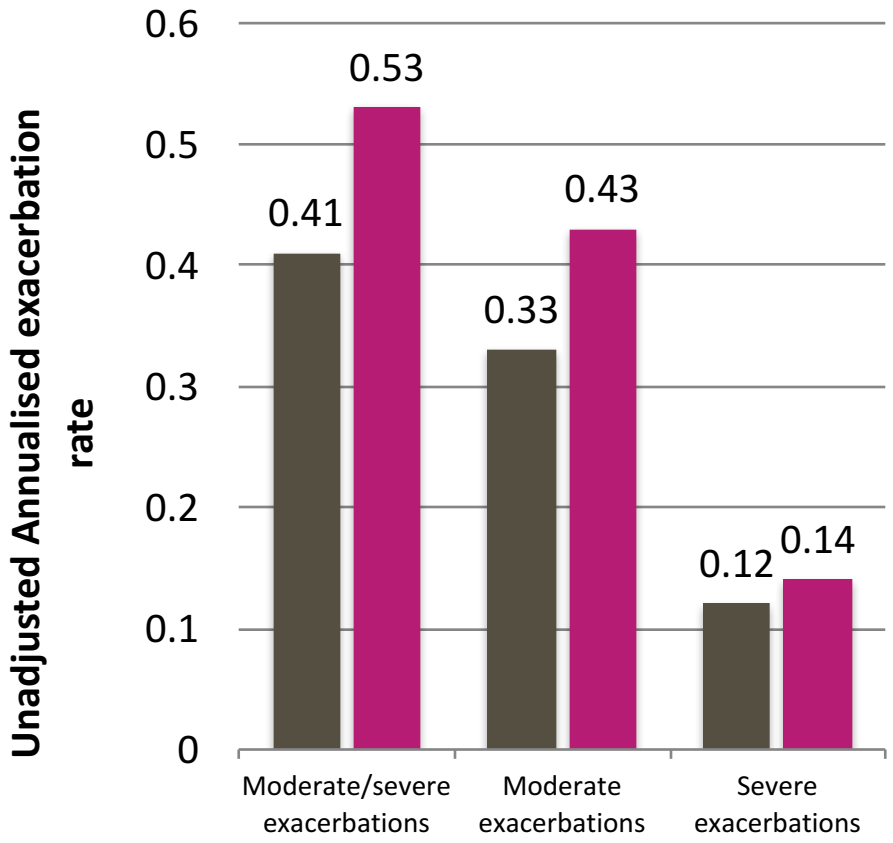
Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

Findings Between March 21, 2014, and Jan 14, 2016, 1368 patients received either BDP/FF/GB (n=687) or BDP/FF (n=681). At week 26, BDP/FF/GB improved pre-dose FEV_1 by 0·081 L (95% CI 0·052–0·109; p<0·001) and 2-h post-dose FEV_1 by 0·117 L (0·086–0·147; p<0·001) compared with BDP/FF. Mean TDI focal scores at week 26 were 1·71 for BDP/FF/GB and 1·50 for BDP/FF, with a difference of 0·21 (95% CI –0·08 to 0·51; p=0·160). Adjusted annual moderate-to-severe exacerbation frequencies were 0·41 for BDP/FF/GB and 0·53 for BDP/FF (rate ratio 0·77 [95% CI 0·65–0·92]; p=0·005), corresponding to a 23% reduction in exacerbations with BDP/FF/GB compared with BDP/FF. Adverse events were reported by 368 (54%) patients with BDP/FF/GB and 379 (56%) with BDP/FF. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group.

Interpretation We provide evidence for the clinical benefits of stepping up patients with COPD from an inhaled corticosteroid/long-acting β_2-agonist combination treatment to triple therapy using a single inhaler.

TRILOGY Study: Moderate-to-severe exacerbations

BDP/FF/GB showed a significant 23% reduction rate on moderate-to-severe exacerbations compare with BDP/FF group.



BDP/FF/G vs BDP/FF

23 % AE reduction

RR 0·77 (0·65–0·92) p=0·005

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

Lancet 2018; 391: 1076–84

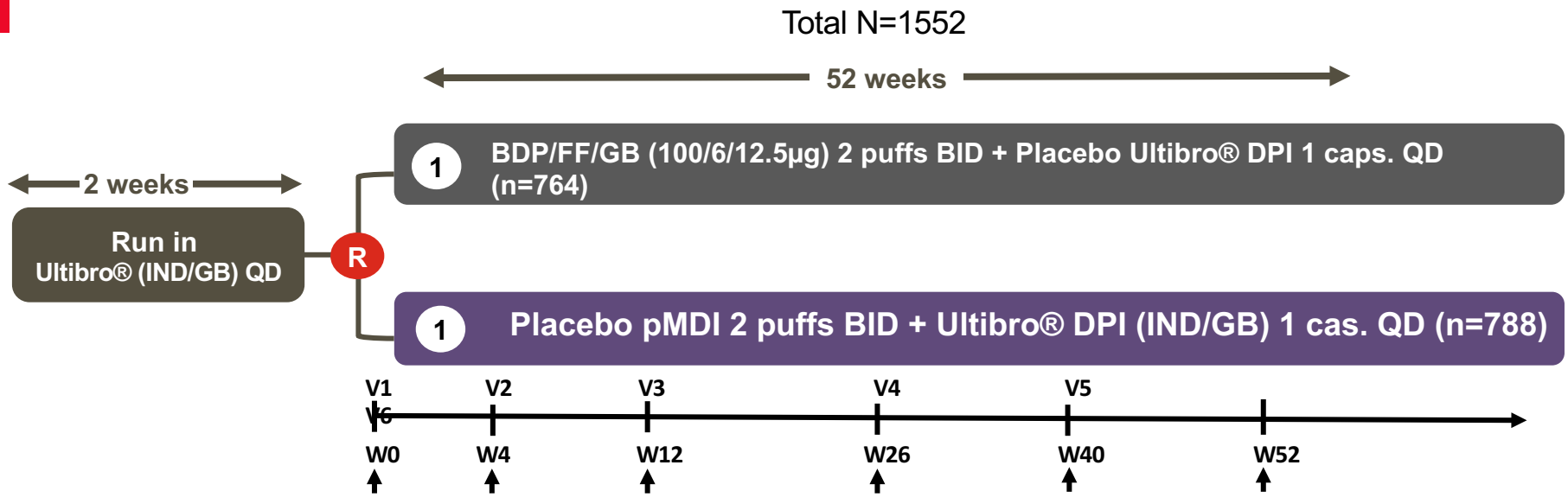
Published Online
February 8, 2018
http://dx.doi.org/10.1016/S0140-6736(18)30206-X

This online publication has been corrected. The corrected version

Summary

Background Evidence is scarce on the relative risk-benefit of inhaled triple therapy, consisting of inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting β_2-agonist, versus dual bronchodilation for chronic obstructive pulmonary disease (COPD). We aimed to compare a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) versus a single-inhaler dual bronchodilator combination of indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

TRIBUTE STUDY DESIGN



Primary Endpoint

- Moderate and severe COPD exacerbation rate at Week 52

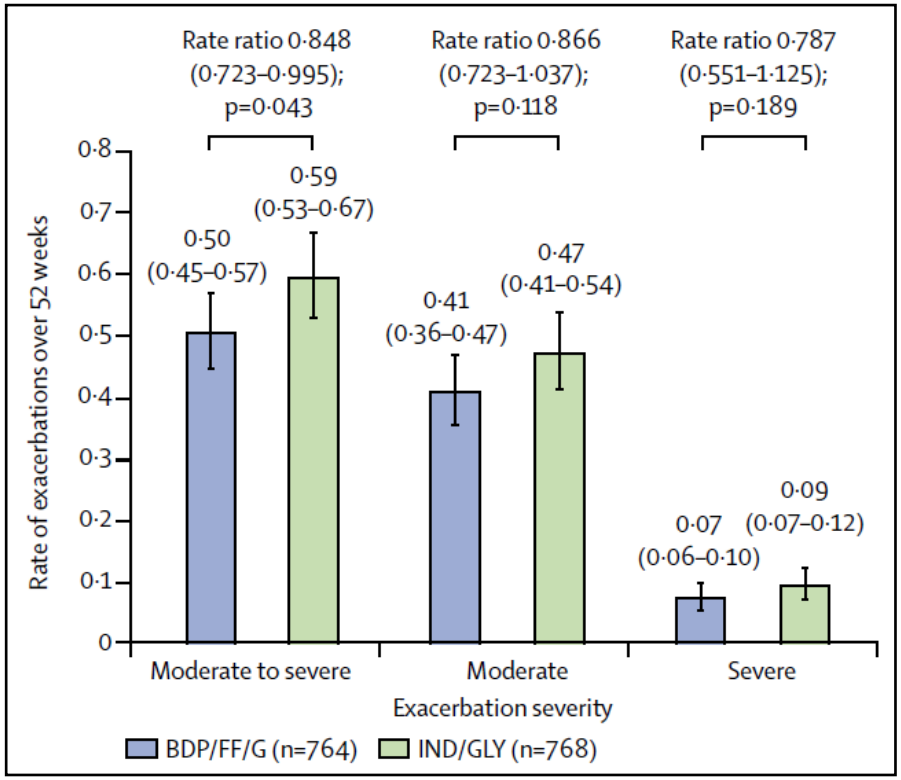
Secondary Objective

- Lung function parameters
- Safety and the tolerability

1. Papi, A et al. Lancet 2018; 391: 1076–84

TRIBUTE Study: Moderate-to-severe exacerbations

BDP/FF/G showed a significant 15% reduction rate on moderate to severe exacerbations compared with IND/GLY



BDP/FF/G vs IND/GLY

15 % AE Reduction

RR 0·85 (0·72–0·99) ,p=0·043

Note. Analysis was in the intention-to-treat population. Error bars and values in brackets with the exacerbation rates and rate ratios are 95% CIs. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium.

1. Papi, A et al. Lancet 2018; 391: 1076–84

Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

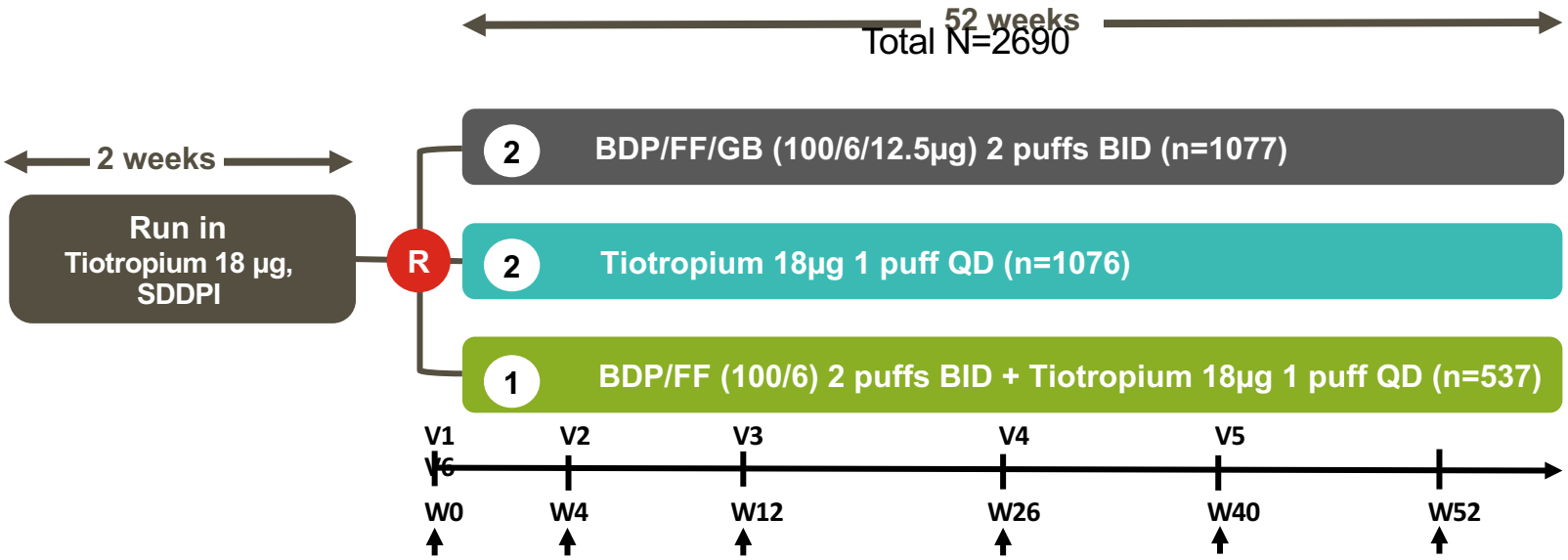
Jørgen Vestbo, Alberto Papi, Massimo Corradi, Viktor Blazhko, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Dave Singh

Summary

Background Limited data are available for the efficacy of triple therapy with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). We compared treatment with extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; fixed triple) with tiotropium, and BDP/FF plus tiotropium (open triple).

Lancet 2017; 389: 1919–29
Published Online
April 3, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30188-5

TRINITY STUDY DESIGN



Primary Endpoint

- Superiority of triple pMDI over tiotropium on moderate and severe COPD exacerbation at Week 52

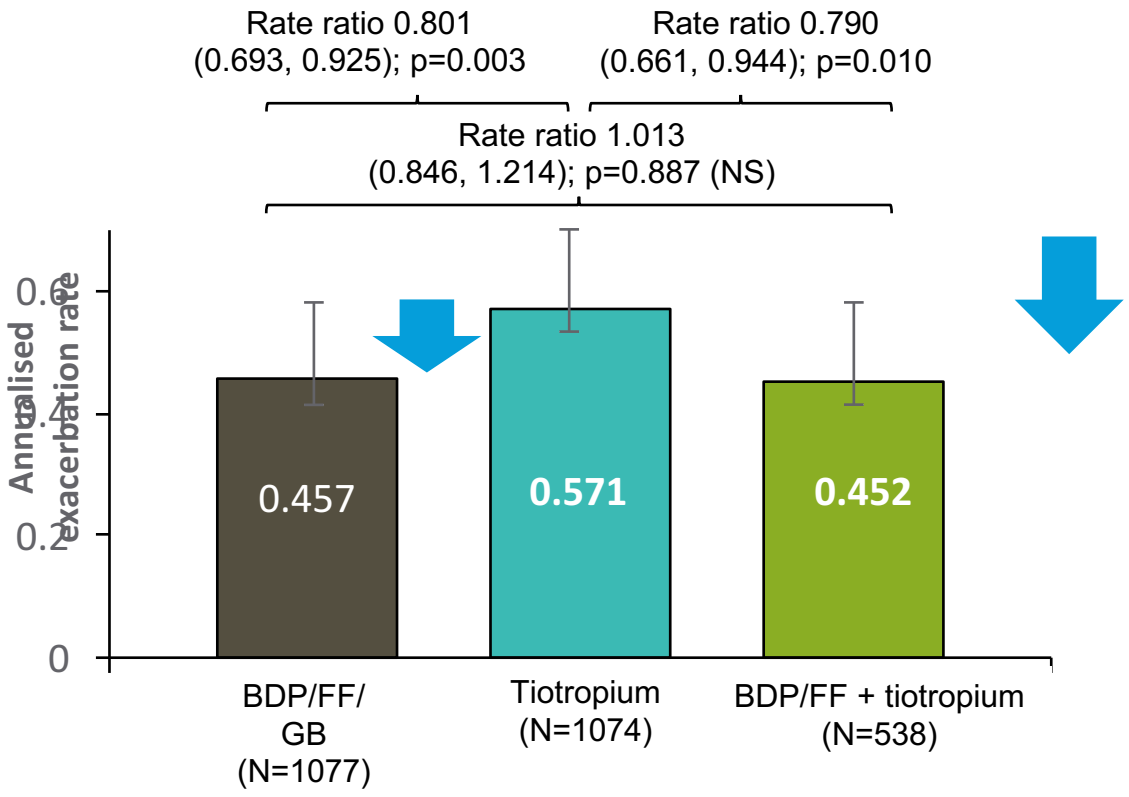
Secondary Objective

- Superiority of Triple pMDI over tiotropium on pre-dose morning FEV_1 at Week 52
- Non-inferiority of Triple pMDI relative to Foster pMDI + tiotropium on pre-dose morning FEV_1 at Week 52

Vestbo J et al. Lancet. 2017 May 13;389(10082):1919-1929

TRINITY Study: Moderate to severe exacerbations

Extra-fine fixed triple shows similar AE reduction efficacy with open triple, both superior to tiotropium.



Fixed Triple vs Tiotropium

20 % AE Reduction

RR 0·80 (95% CI 0·69–0·92)

p=0·0025

Vestbo J et al. Lancet. 2017 May 13;389(10082):1919-1929

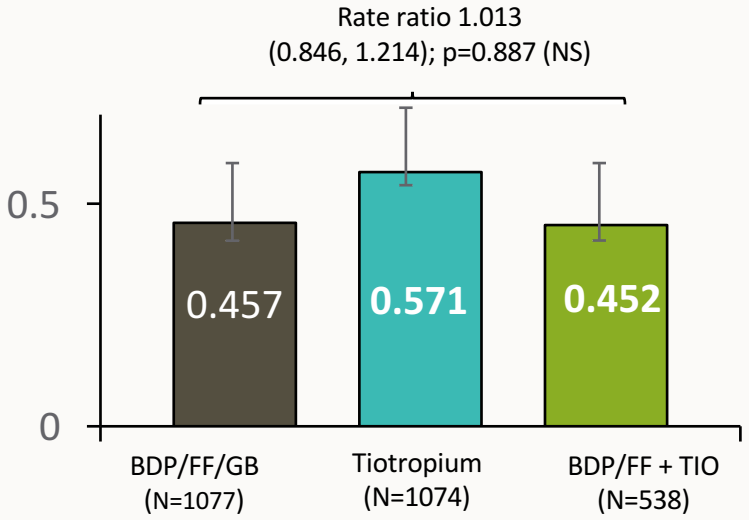
AE reduction rate from TRINITY in " Frequent Exacerbators "

Overall population

BDP/FF/G vs Foster + TIO

Similar efficacy

RR 0·80 (95% CI 0·69–0·92) p=0·0025

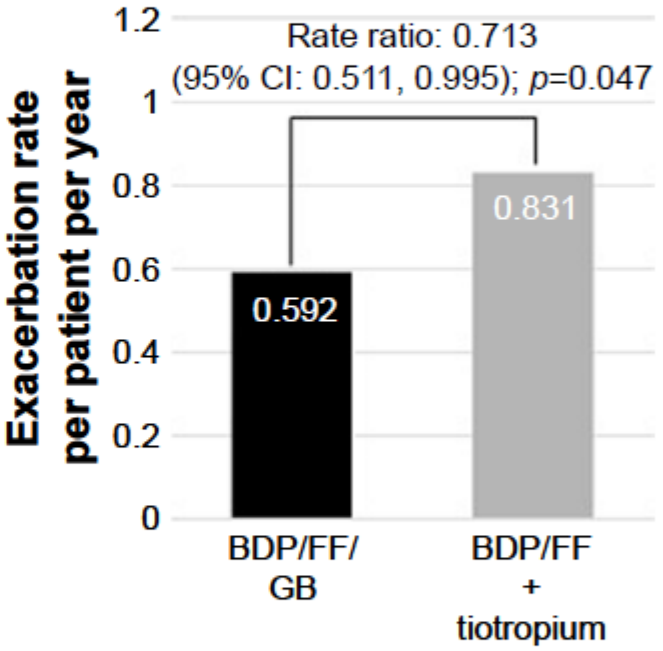


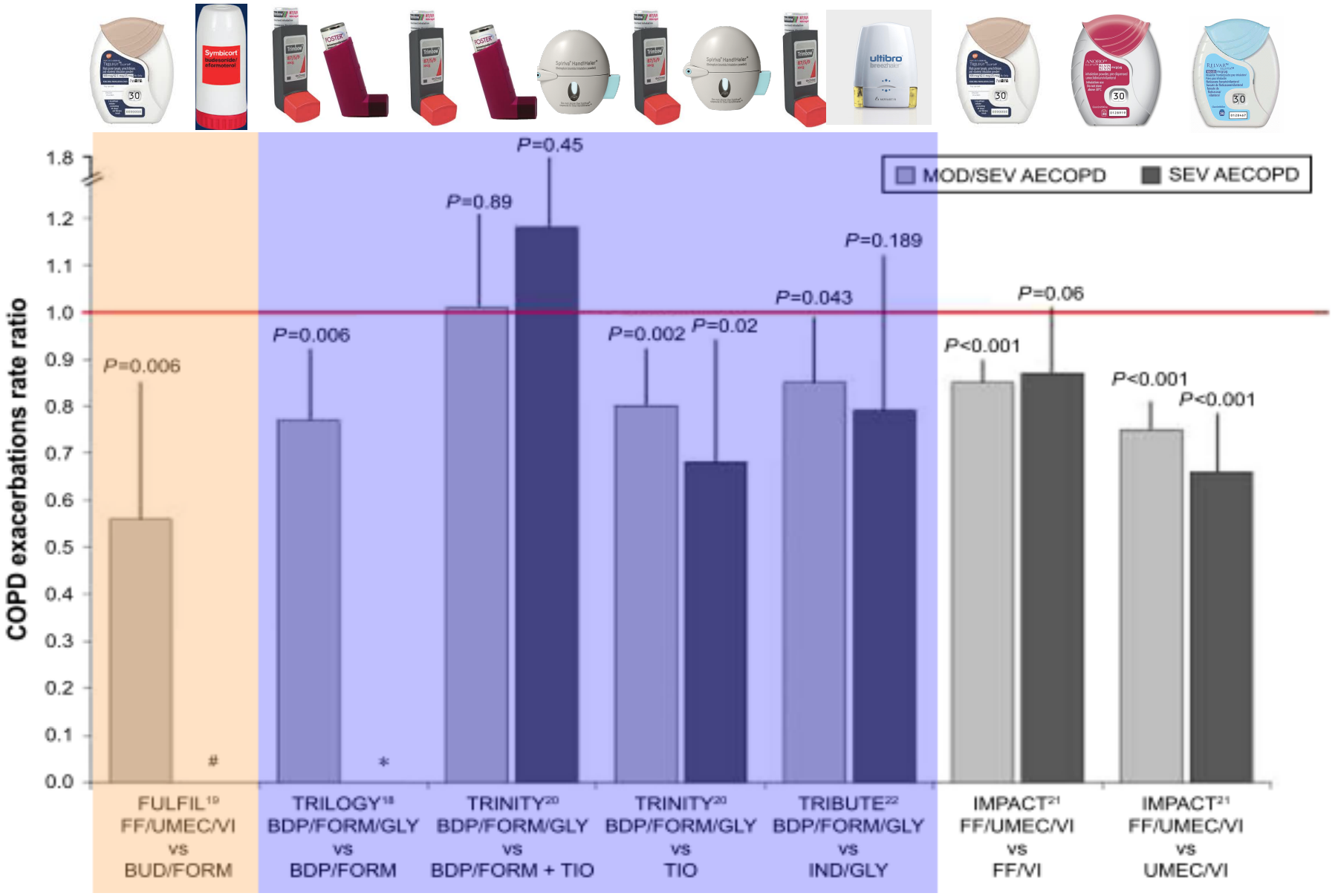
Hx AE≥2 population

BDP/FF/G vs Foster + TIO

29 % AE Reduction

RR 0·72 (0·55–0·95) p=0·02,





Management of severe COPD AE :

International Journal of COPD 2018:13 2319–2333

ERJ Express. Published on September 12, 2018 as doi: 10.1183/13993003.01230-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Mortality?

Research letter

Inhaled corticosteroid containing combinations and mortality in COPD

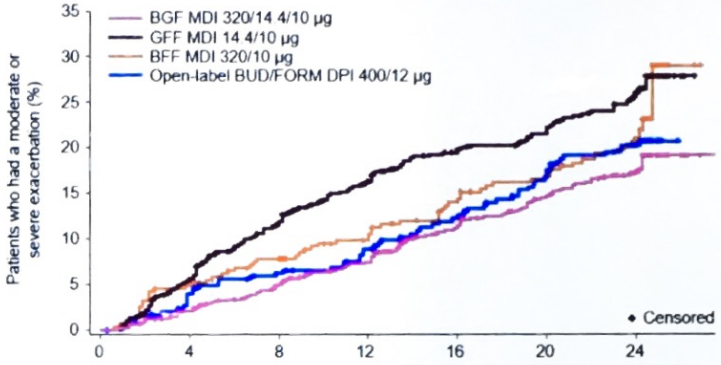
Jørgen Vestbo, Leonardo Fabbri, Alberto Papi, Stefano Petruzzelli, Mario Scuri, Alessandro Guasconi, Stefano Vezzoli, Dave Singh

ERS
INTERNATIONAL CONGRESS 2018
PARIS France,15-19 September

Time to First Moderate/Severe COPD Exacerbation

Risk of exacerbation

- **BGF vs GFF**
  - HR 0.593
  - p<0.0001 (Cox regression)
  - p=0.0001 (log rank)
- **BGF vs BFF**
  - HR 0.747
  - p=0.0635 (Cox regression)
  - p=0.0281 (log rank)



Number of patients at risk

BGF MDI 320/14 4/10 µg	639	620	590	561	526	498	428
GFF MDI 14 4/10 µg	625	585	532	492	463	446	371
BFF MDI 320/10 µg	314	295	277	260	242	233	196
Open-label BUD/FORM DPI 400/12 µg	318	297	282	271	257	241	203

BFF, budesonide/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; BUD/FORM, budesonide/formoterol fumarate dihydrate; GFF, glycopyrronium/formoterol fumarate dihydrate.

Gary T. Ferguson

KRONOS: 24-week study of triple fixed-dose combination budesonide/glycopyrronium/ formoterol (BGF) MDI via co-...

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Table 1. Patients (%) with fatal events and hazard ratios for the treatment group comparisons in TRILOGY, TRINITY and TRIBUTE

	Test (no. of patients)	Comparator (no. of patients)	No. of patients with fatal events (%) Test	No. of patients with fatal events (%) Comparator	Hazard ratio (95% CI), p-value
SINGLE STUDIES					
TRILOGY	BDP/FF/G (N=687)	BDP/FF (N=680)	15 (2.2%)	16 (2.4%)	-
TRILOGY, TRINITY, TRIBUTE	**BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)**	**TIO, IND/GB (N=1844)**	**56 (1.5%)**	**41 (2.2%)**	**0.65 (0.43-0.97) P=0.037**
POOLED ANALYSIS (ALL EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	75 (2.0%)	50 (2.7%)	0.71 (0.50-1.02) p=0.066
	BDP/FF/G (N=2528)	TIO, IND/GB (N=1844)	51 (2.0%)	50 (2.7%)	0.72 (0.49-1.06) p=0.096
POOLED ANALYSIS (NON-RESPIRATORY EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	56 (1.5%)	41 (2.2%)	0.65 (0.43-0.97) p=0.037
POOLED ANALYSIS (RESPIRATORY EVENTS)					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GB (N=1844)	19 (0.5%)	9 (0.5%)	1.01 (0.45-2.22) p=0.989

Conclusions

- Nevertheless, given the unidirectional effects seen in this analysis and the 4 previous studies, there may be cause for more optimism regarding the effect of more intense ICS-containing treatments on survivals in **symptomatic patients with severe and very severe COPD**. Particularly invariably required in these patients either to improve symptoms, quality of life, and/or to reduce exacerbations and hospitalizations.

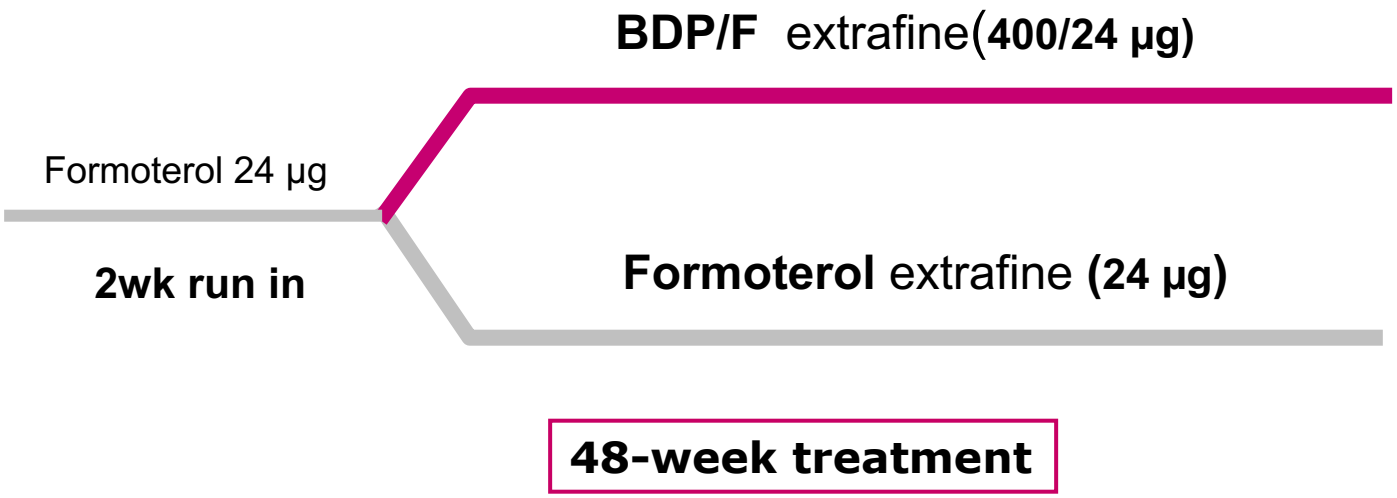
- Of course, a properly designed and powered new study mortality as primary outcome in these patients is required for this optimism to be confirmed.

Calverly PM et al TORCH study NEJM 2007 ; 356: 775-89
Vestbo J et al SUMMIT study Lancet 2016 ; 387: 1817-26
Wedzicha JA et al INSPIRE study AJRCCM 2008 ; 177: 19-26
Lipson D et al IMPACT study NEJM 2018 ; 378(18): 1671-80

The FORWARD study

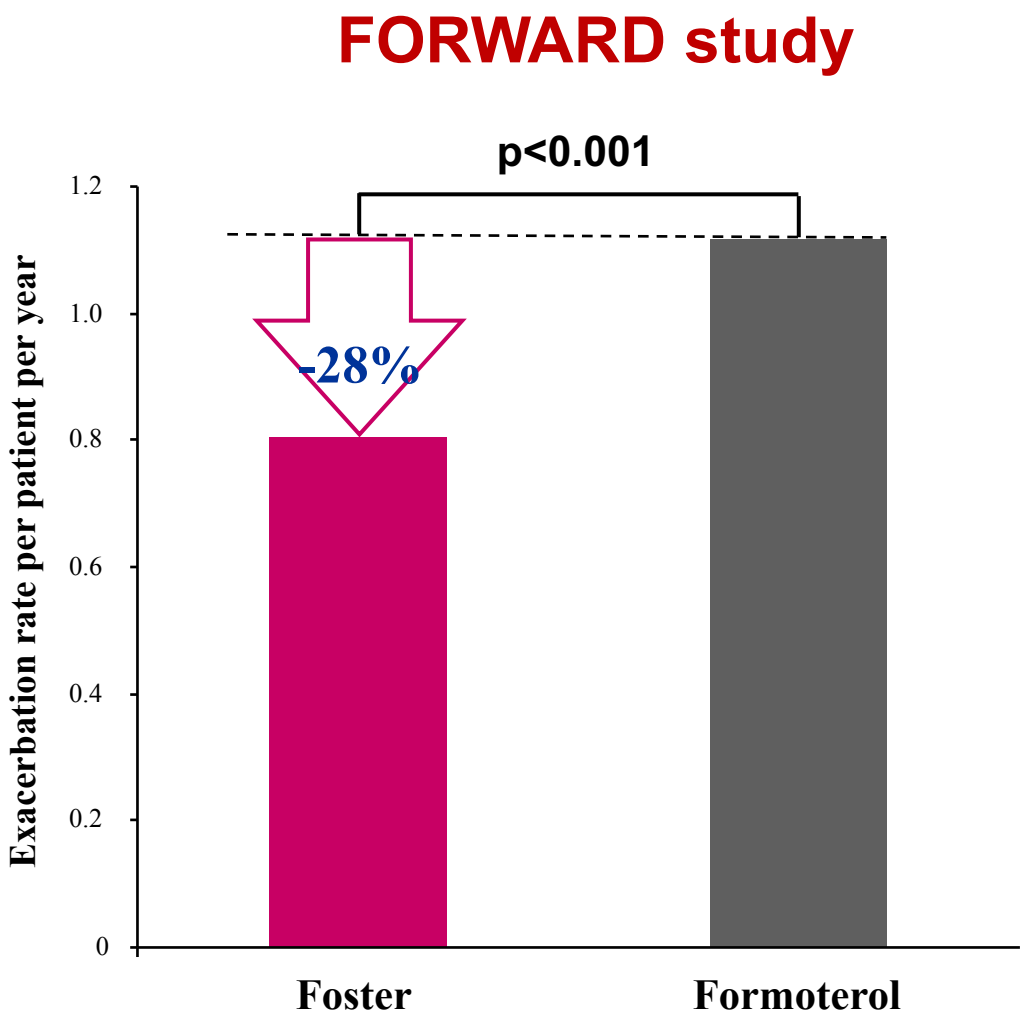
1199 COPD patients with a history of frequent exacerbations

Compares Foster and Formoterol among frequent exacerbation COPD patients



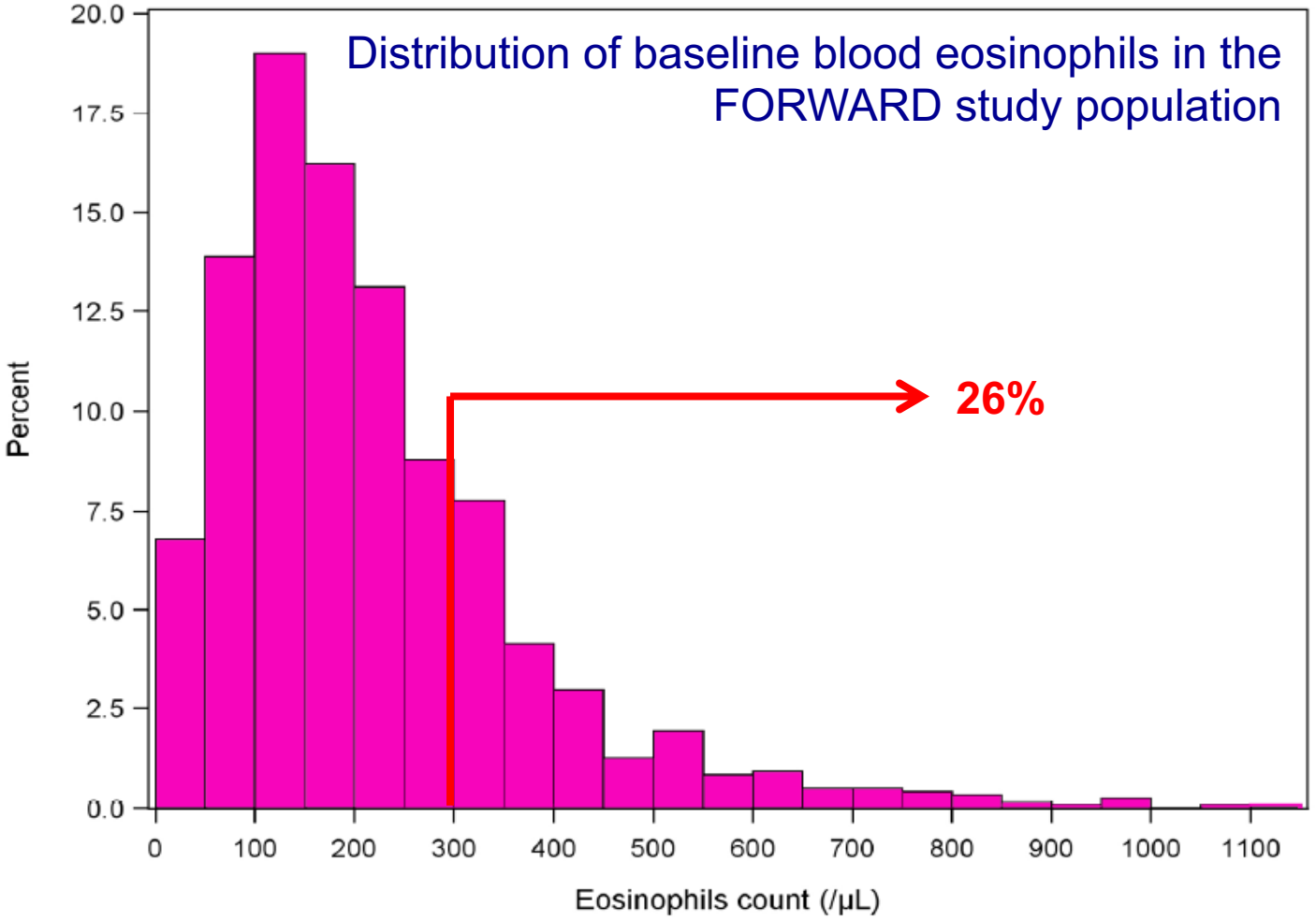
Wedzicha JA et al, RespMed 2014

Extrafine BDP/FF provides significant reduction of COPD exacerbation rate



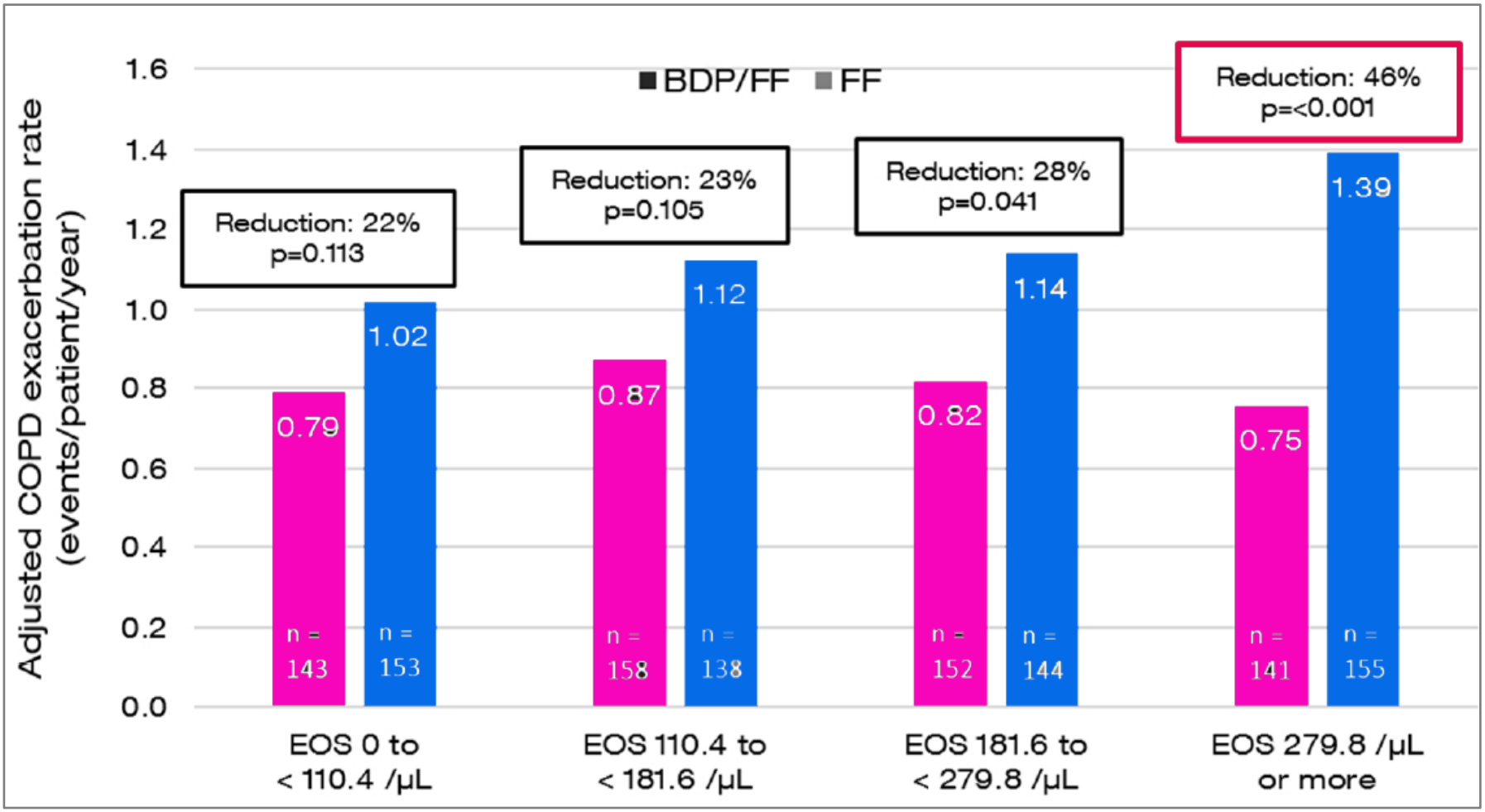
Wedzicha JA et al, RespMed 2014

FORWARD post-hoc Study showed that patients with ≥300 eosinophils count is around 26% of study population

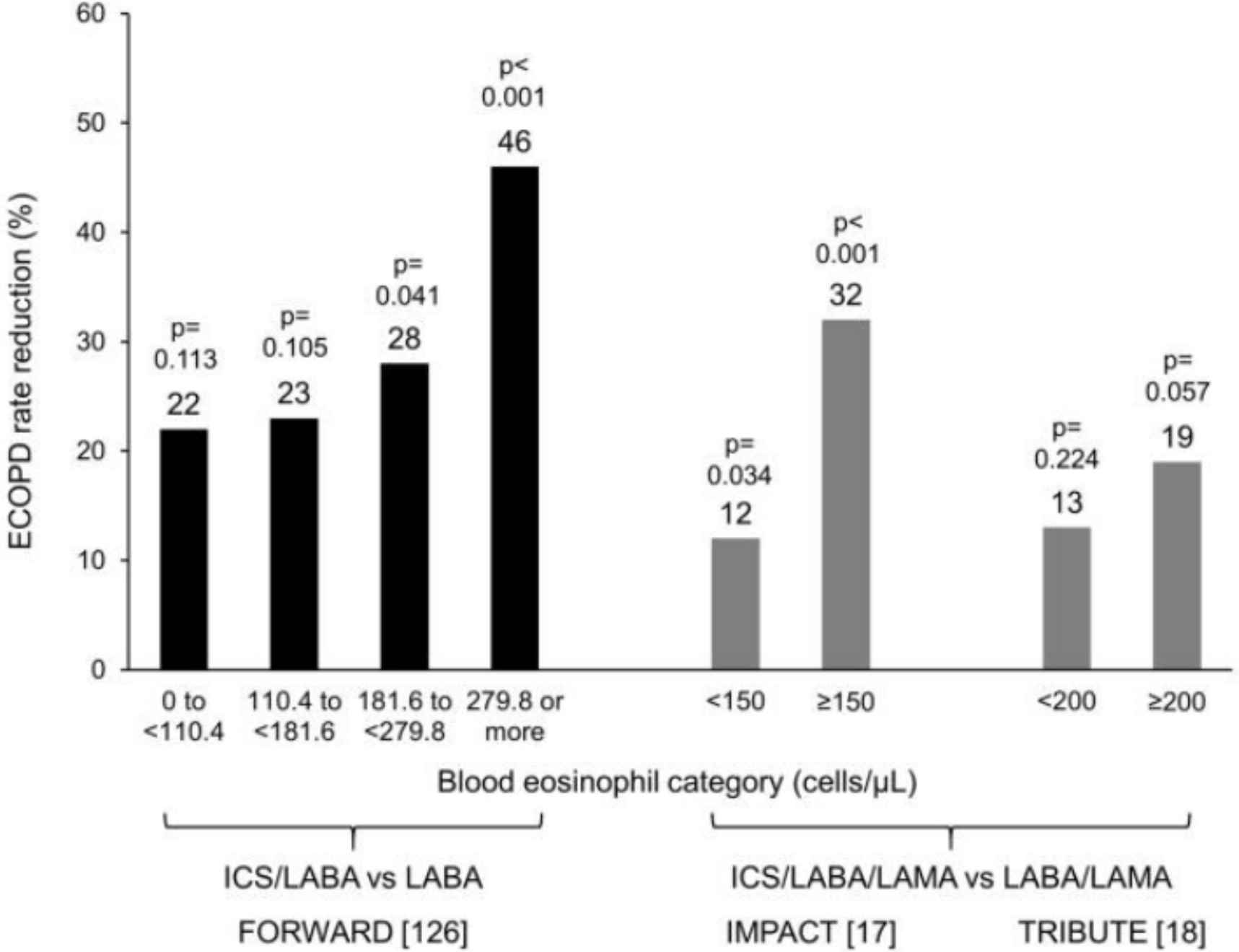


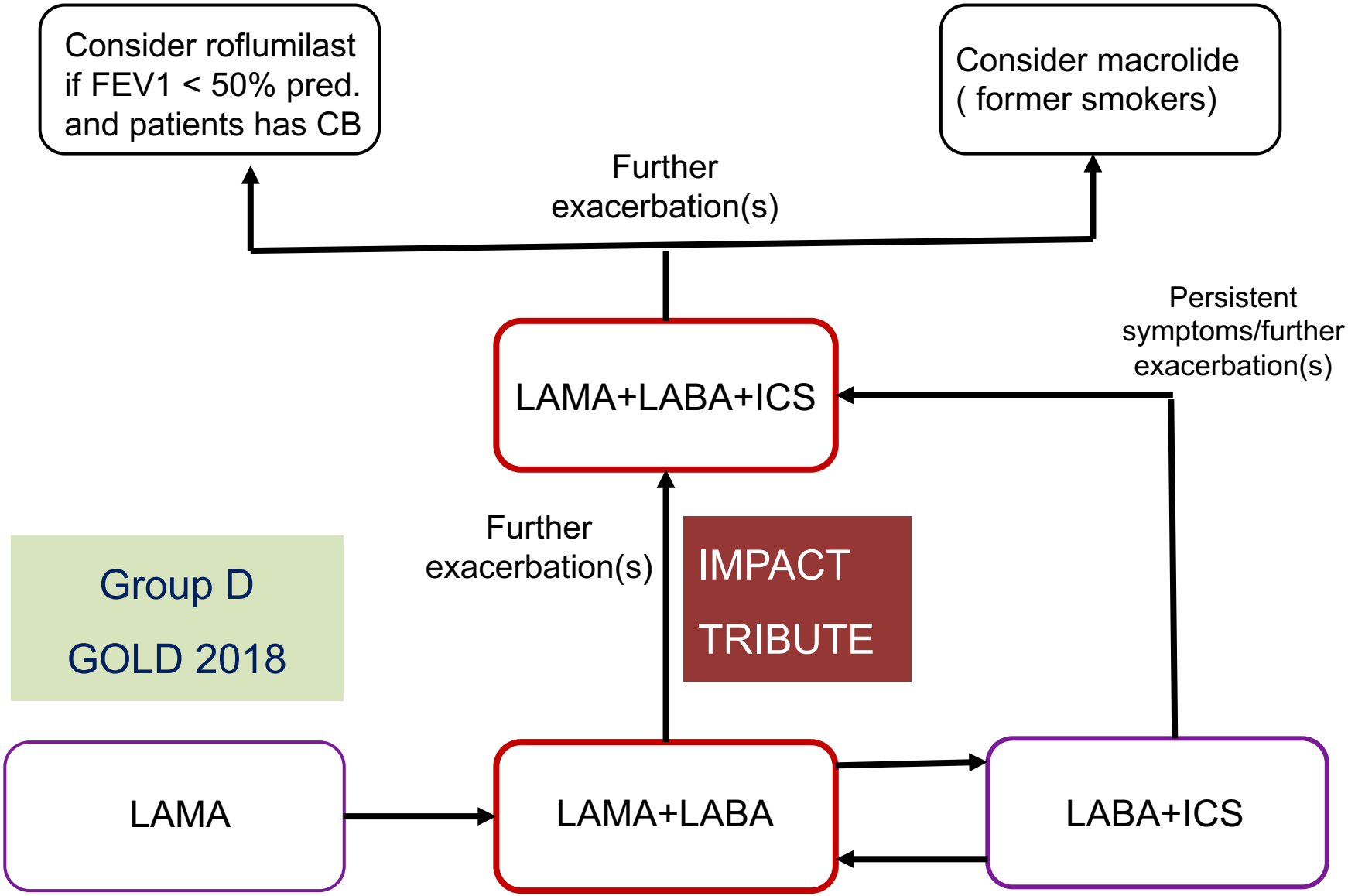
Am J Respir Crit Care Med. First published online 06 Jun 2015

Extrafine BDP/F provides significant reduction of COPD exacerbation rate in high eosinophils populations



Am J Respir Crit Care Med. First published online 06 Jun 2015


ECOPD rate reduction (%)
60
50
40
30
20
10
0
p= 0.113
22
p= 0.105
23
p= 0.041
28
p< 0.001
46
p= 0.034
12
p< 0.001
32
p= 0.224
13
p= 0.057
19
0 to <110.4
110.4 to <181.6
181.6 to <279.8
279.8 or more
<150
≥150
<200
≥200
Blood eosinophil category (cells/µL)
ICS/LABA vs LABA
FORWARD [126]
ICS/LABA/LAMA vs LABA/LAMA
IMPACT [17]
TRIBUTE [18]


Consider roflumilast if FEV1 < 50% pred. and patients has CB
Consider macrolide (former smokers)
Further exacerbation(s)
Persistent symptoms/further exacerbation(s)
LAMA+LABA+ICS
Further exacerbation(s)
IMPACT TRIBUTE
Group D
GOLD 2018
LAMA
LAMA+LABA
LABA+ICS

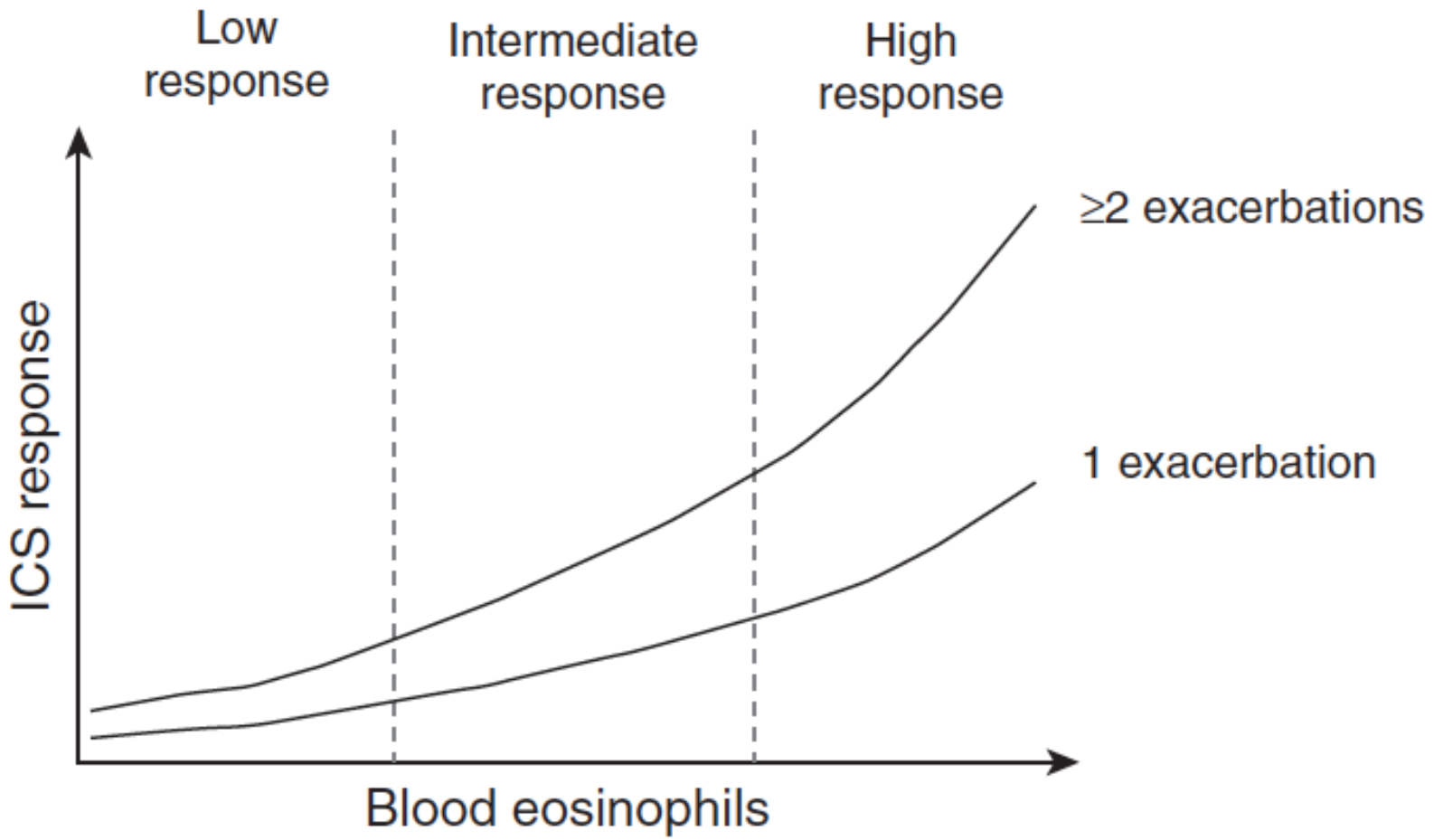


Figure 1. The relationship between blood eosinophil counts and inhaled corticosteroid (ICS) response (exacerbation prevention). Different

AJRCCM Volume 196 Number 9 | November 1 2017 pp 1098

Treatment of stable COPD

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

FIGURE 4.1

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

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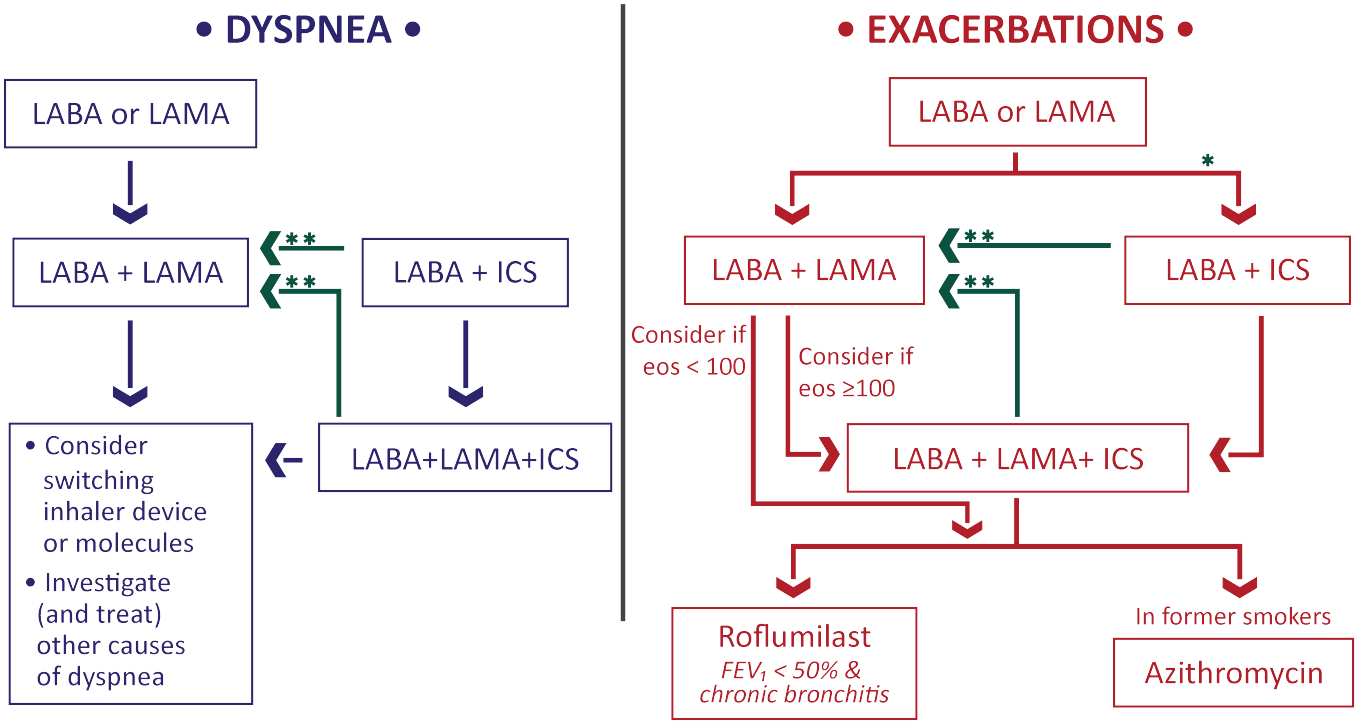
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

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Outlines

- COPD : introduction
- The role of bronchodilators in COPD
- The role of eosinophil and ICS in COPD
- Pulmonary rehabilitation
- Summary

Benefits of pulmonary rehabilitation in COPD

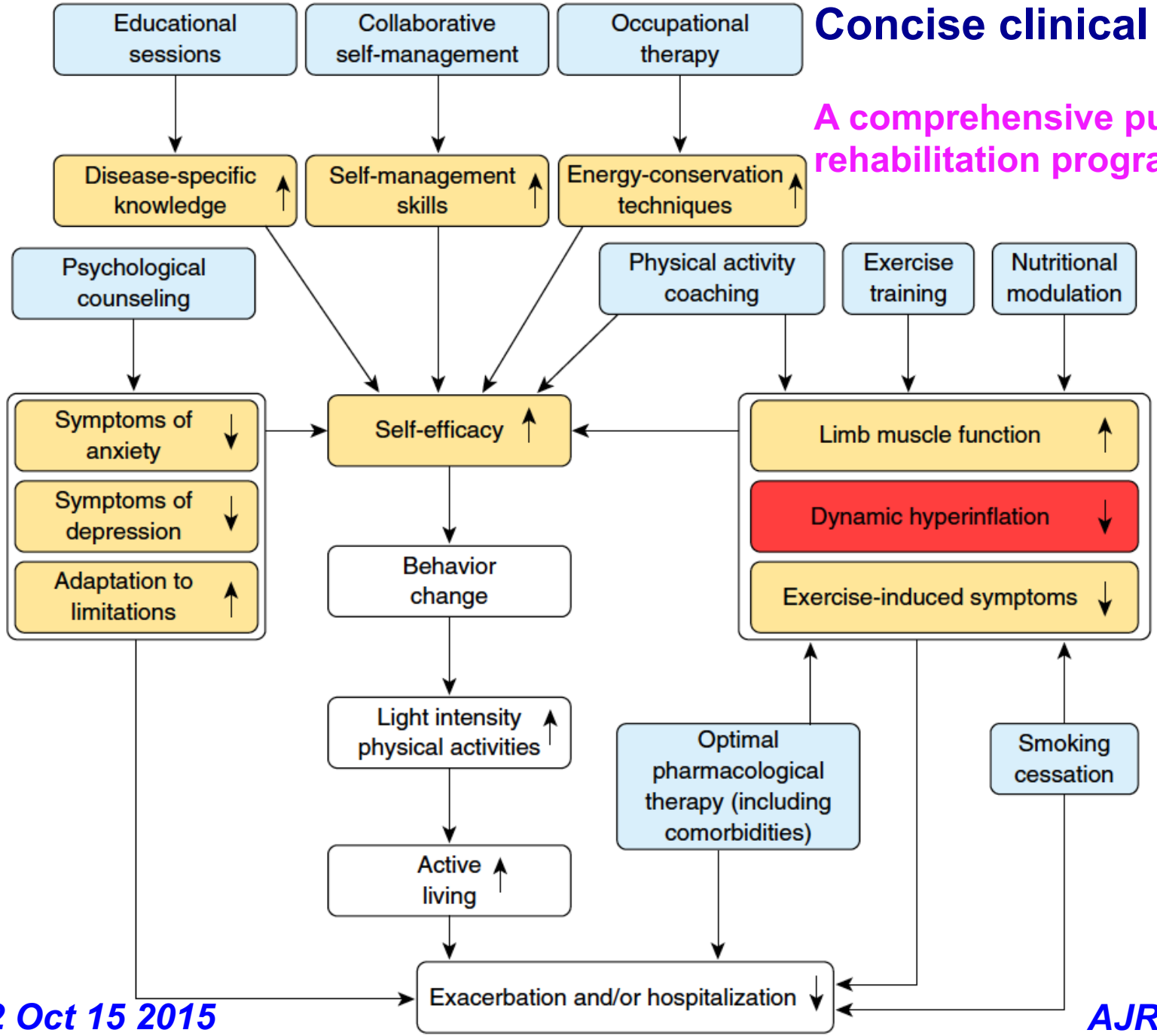
- Improves exercise capacity (**Evidence A**).
- Reduces the perceived intensity of breathlessness (**Evidence A**).
- Improves health-related quality of life **(Evidence A**).
- Reduces the number of hospitalizations and days in the hospital (**Evidence A**).
- Reduces anxiety and depression associated with COPD (**Evidence A**).
- Strength and endurance training of the upper limbs improves arm function (**Evidence B**).
- Benefits extend well beyond the immediate period of training (**Evidence B**).
- Improves survival (**Evidence B**).
- Respiratory muscle training can be beneficial, especially when combined with general exercise training (**Evidence C**).
- Improves recovery after hospitalization for an exacerbation [524] (**Evidence A**).
- Enhances the effect of long-acting bronchodilators (**Evidence B**).

Pulmonary rehabilitation

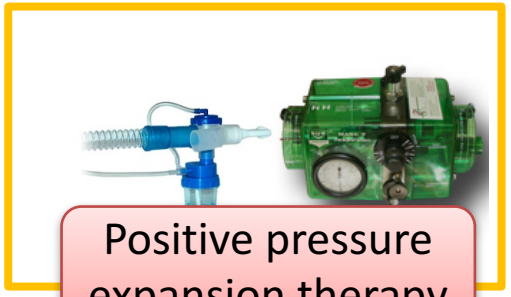
- Exercise therapy,
- Disease education,
- Behaviour change,
- Psychological support

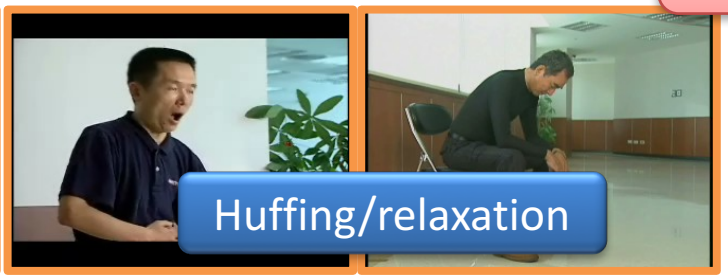
Concise clinical review

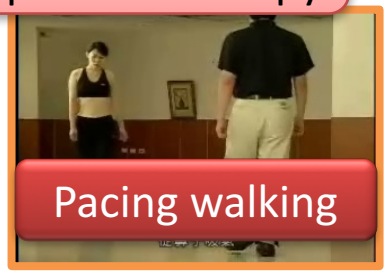
A comprehensive pulmonary rehabilitation program



Pulmonary rehabilitation







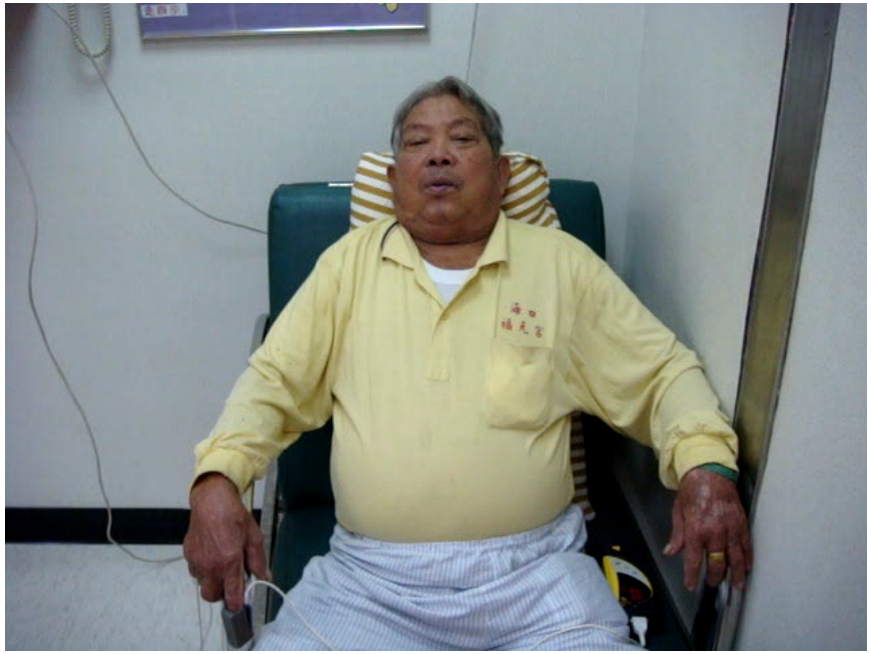
Breath training

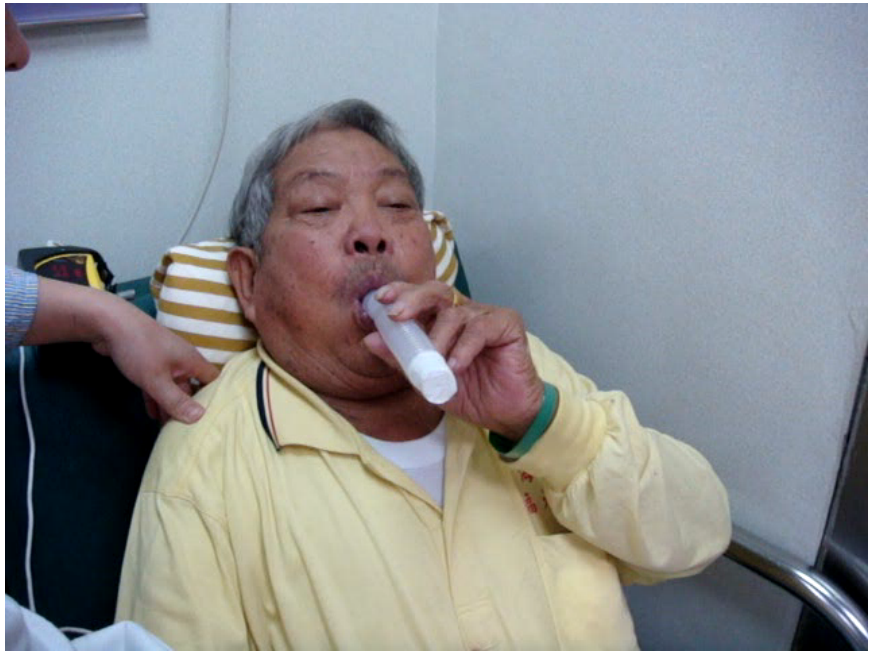
- Breathing strategies
  - pursed lip breathing
  - Yoga breathing
  - Positive expiratory pressure
  - Ventilation-feedback
  - Lean forward position
- Respiratory muscle resting
  - negative pressure ventilation
  - Non-Invasive Positive Pressure Ventilation, NIPPV
- Flexibility Training
- Energy conservation techniques in physical activities of daily life

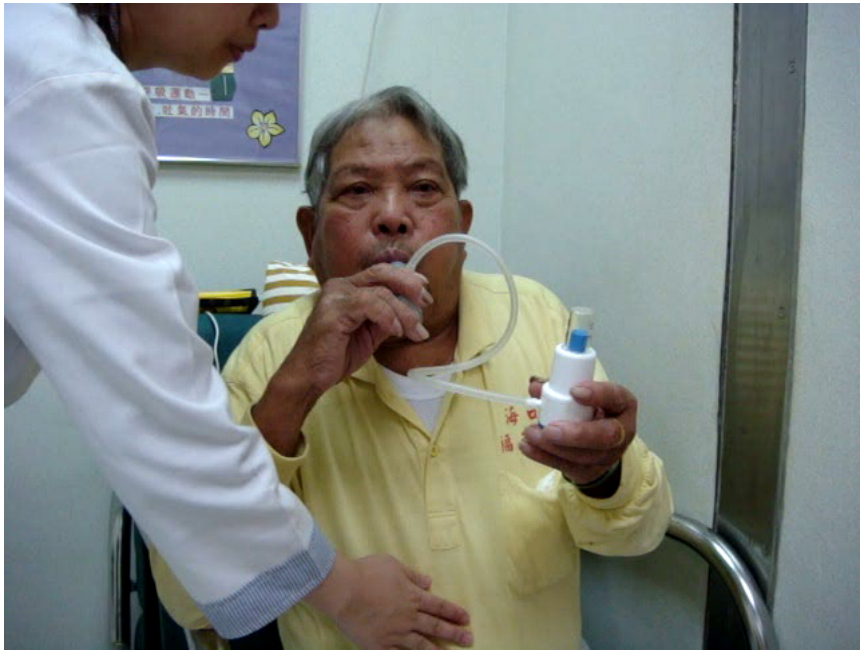
Exercise training

- Endurance Training
- Resistance/Strength Training
- Upper Limb Training
- Respiratory/Inspiratory Muscle
- Whole body vibration, WBV


NO SMOKING
禁煙



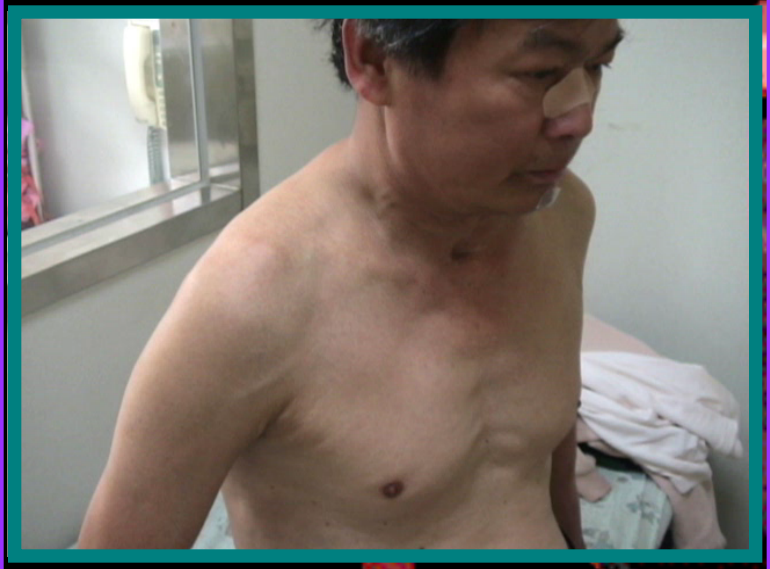




Pulmonary Rehabilitation on Hyperinflation

Breathing Control

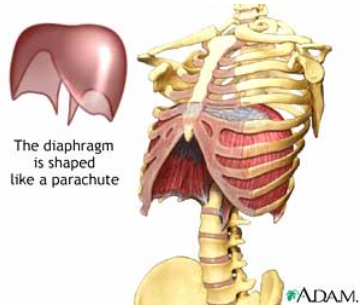
PURSED-LIP BREATHING
(like breathing out slowly into a straw)



Exhalation flow rate<100ml/min
Maintain I: E 1:2- 1:5 RR10-20

Pulmonary Rehabilitation for Respiratory Muscle Impairment

- Diaphragm training



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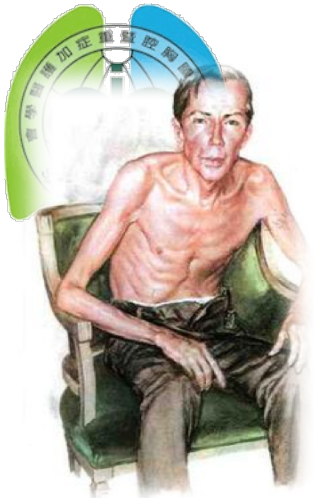


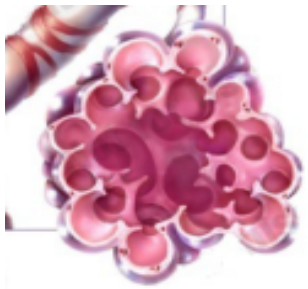
Initiative Inflammation

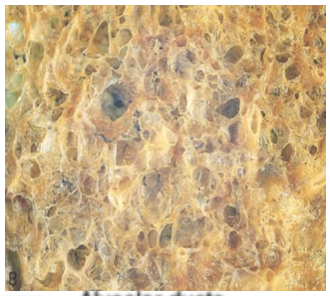
Protease/Anti-protease

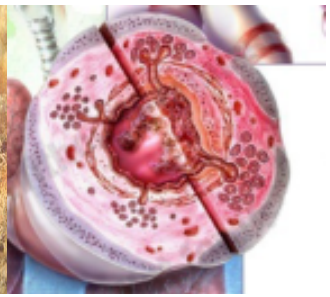
Oxidative Stress

Alveolar Inflammation

Airway Inflammation







Ongoing Inflammation

Hyperinflation (Air-Trapping)

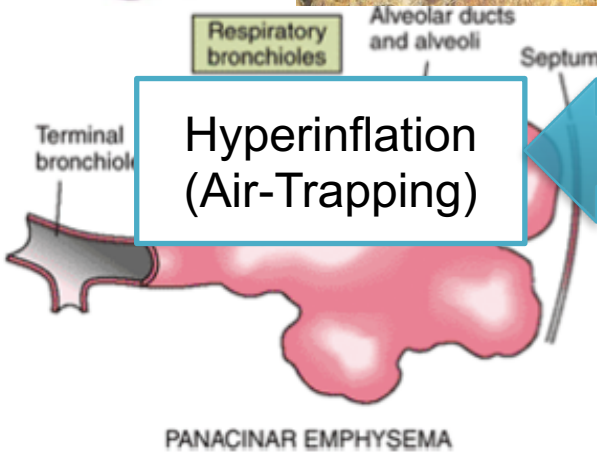
LAMA

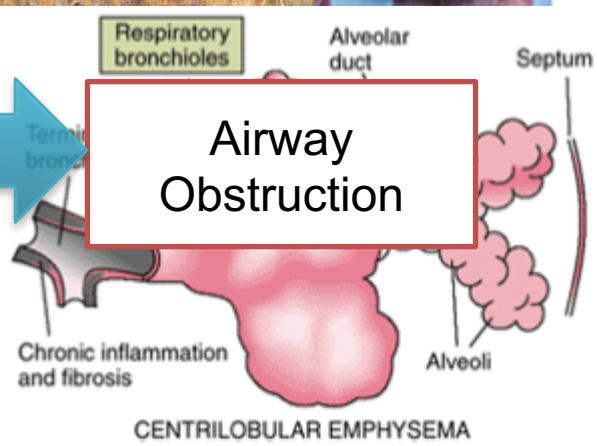
ICS

LABA

Airway Obstruction

Systemic Inflammation





Optimal COPD Control

(D$_{II}$)

Pulmonary Rehabilitation

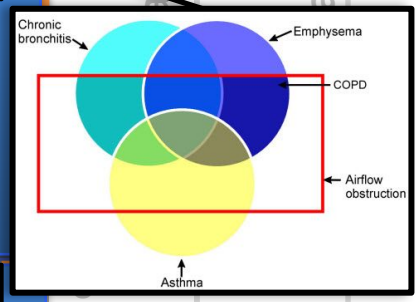
(D$_{I}$)

High Risk,
More Symptoms

ACO

(B$_{I}$)

Low Risk,
More Symptoms



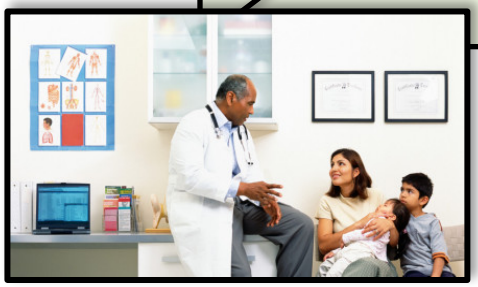
COPD Comorbidity

(B$_{II}$)

(A)

Early Intervention and Treatment of COPD

Low Risk,
Less Symptoms



Risk

(GOLD Classification of Airflow

3

2

1

≥2

≥1

tion History

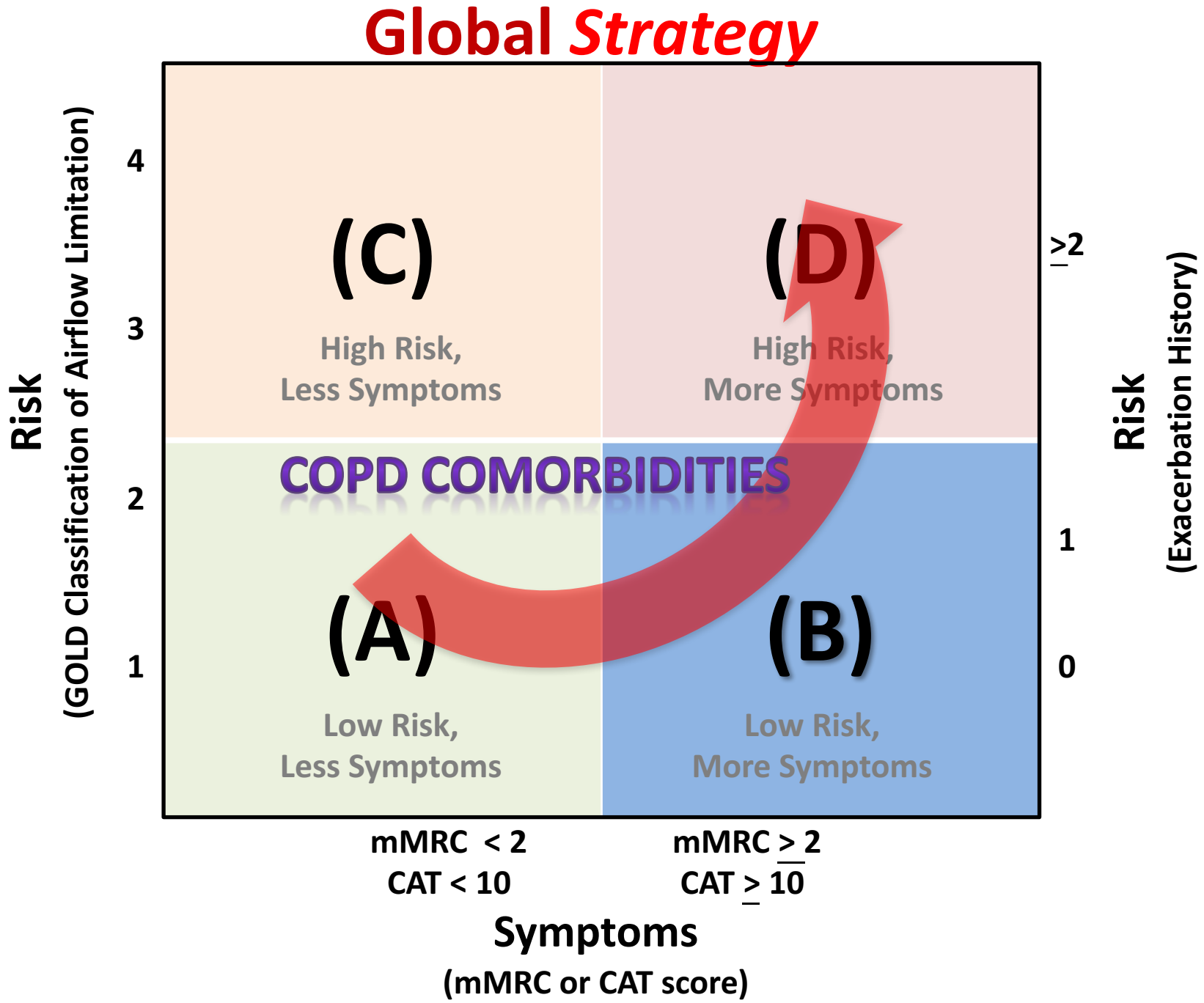
tion History

mMRC < 2
CAT < 10
CCQ <1

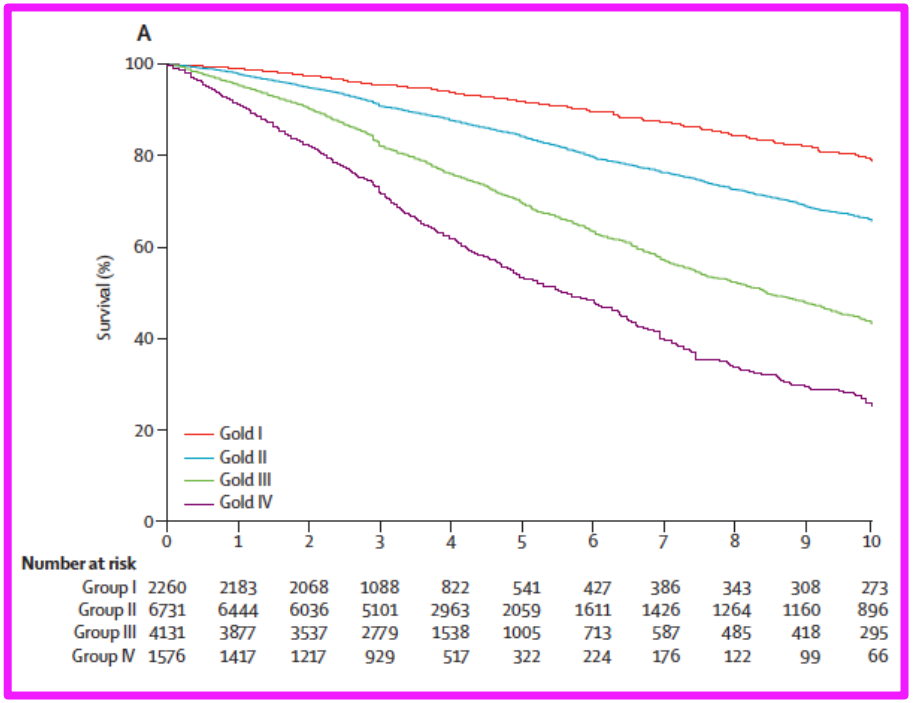
Symptom

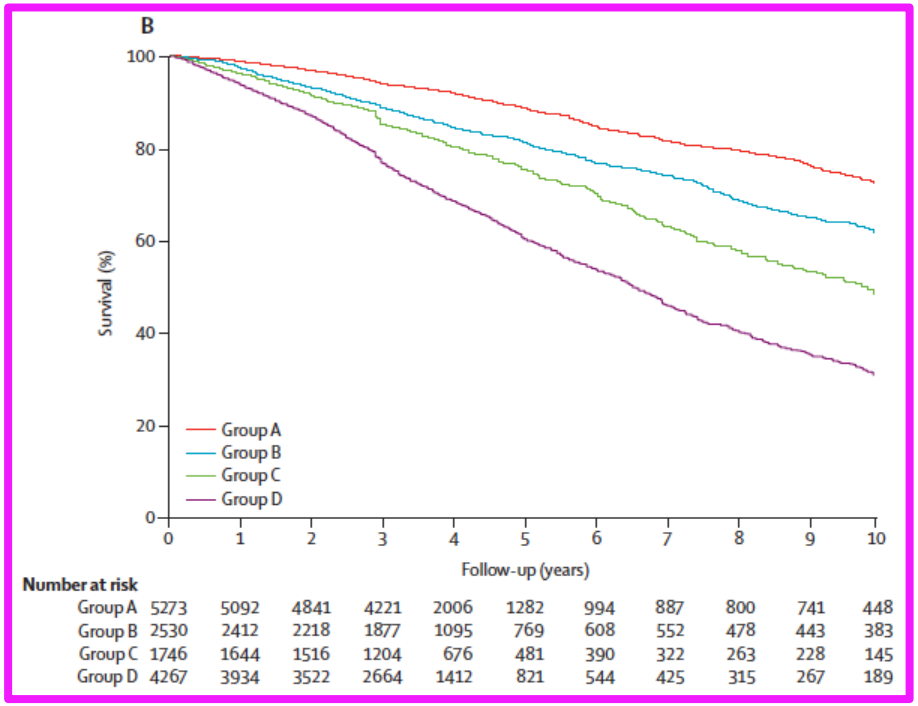

Thanks for Your Attentions!
隨裕而安
http://yuann.myphotos.cc/

Comorbidities
– the impact on Mortality


Global Strategy
Risk
(GOLD Classification of Airflow Limitation)
4
3
2
1
(C)
High Risk,
Less Symptoms
(D)
High Risk,
More Symptoms
COPD COMORBIDITIES
(A)
Low Risk,
Less Symptoms
(B)
Low Risk,
More Symptoms
≥2
1
0
Risk
(Exacerbation History)
mMRC < 2
CAT < 10
mMRC ≥ 2
CAT ≥ 10
Symptoms
(mMRC or CAT score)

Mortality prediction in COPD comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data



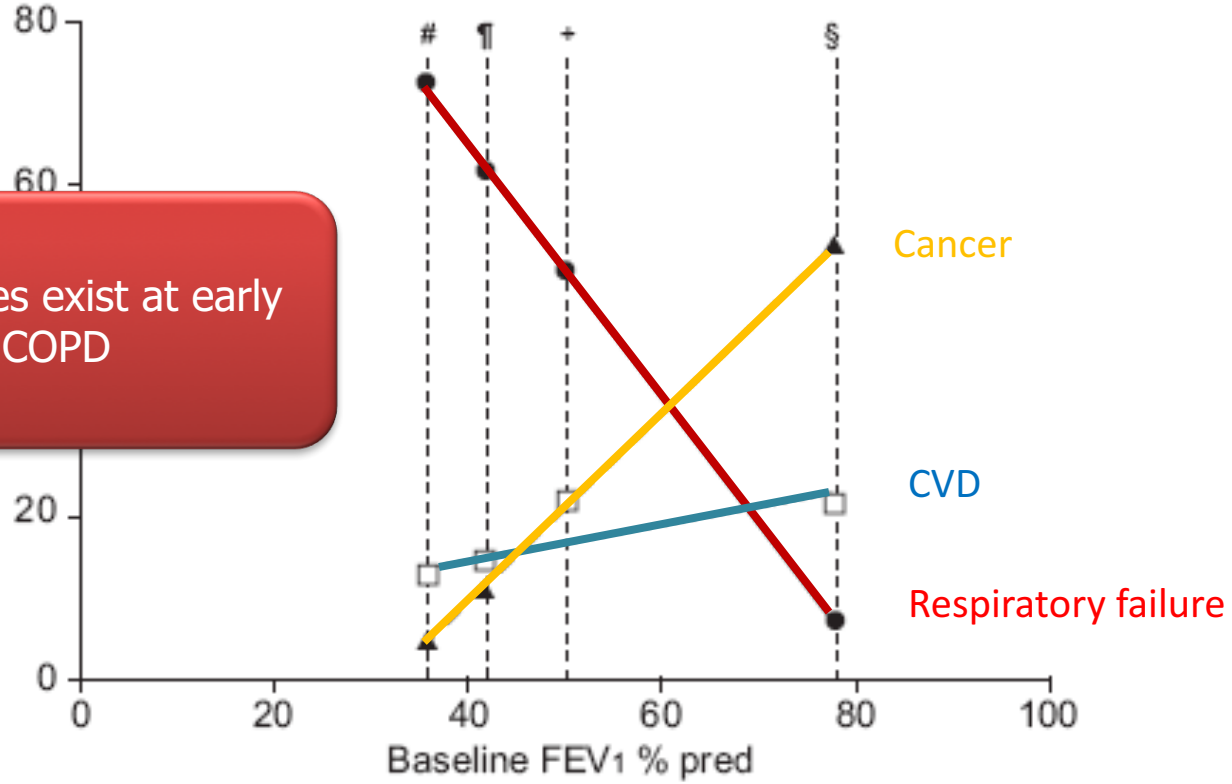


Lancet Respir Med 2015; 3: 443–50 Published Online May 18, 2015

Mortality in COPD: role of comorbidities

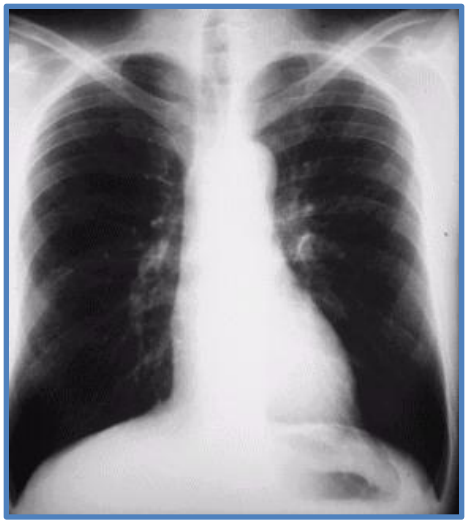
D.D. Sin*,#, N.R. Anthonisen¶, J.B. Soriano+,§,ƒ and A.G. Agusti+,**

Co-Morbid diseases exist at early stage of COPD



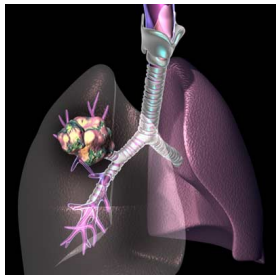
Eur Respir J 2006; 28: 1245–1257

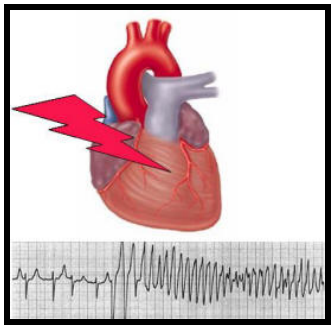
Big 3



COPD

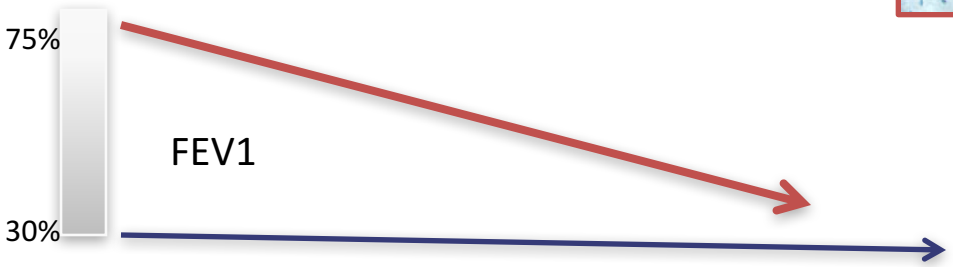
Lung cancer



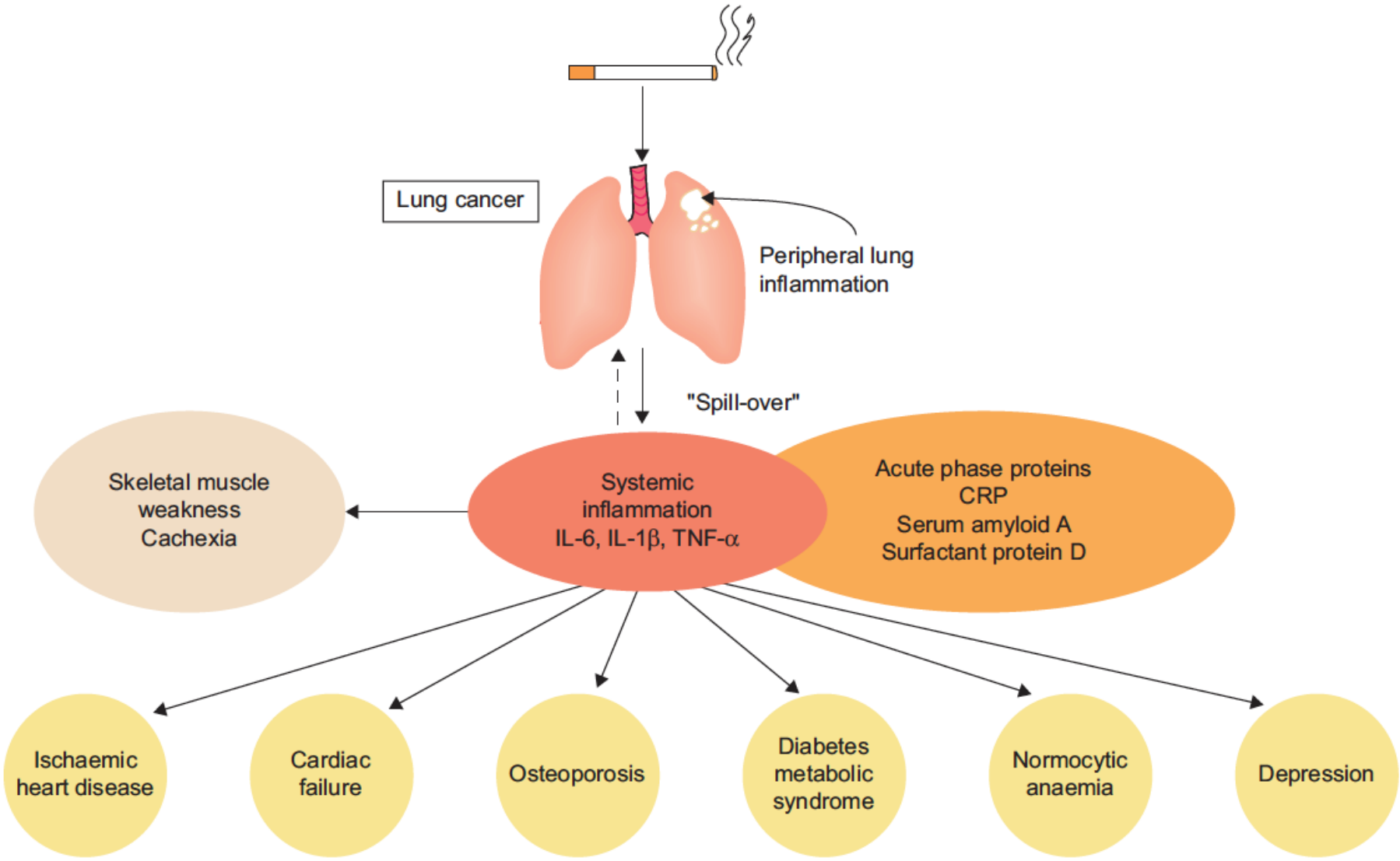


Cardiovascular disease

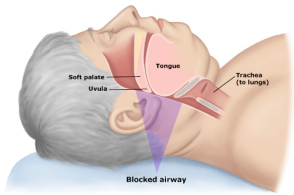
Respiratory failure



Systemic manifestations and comorbidities of COPD



Eur Respir J 2009; 33: 1165–1185



Exacerbation

COPD Comorbidities

43%

Cardiovascular disease

IHD, HF, Arrhythmia, PVD, HTN

Bronchiectasis

Longer exacerbation and increased mortality

Metabolic syndrome and Diabetes

70%

Osteoporosis

60%

Anxiety and Depression

Lung cancer

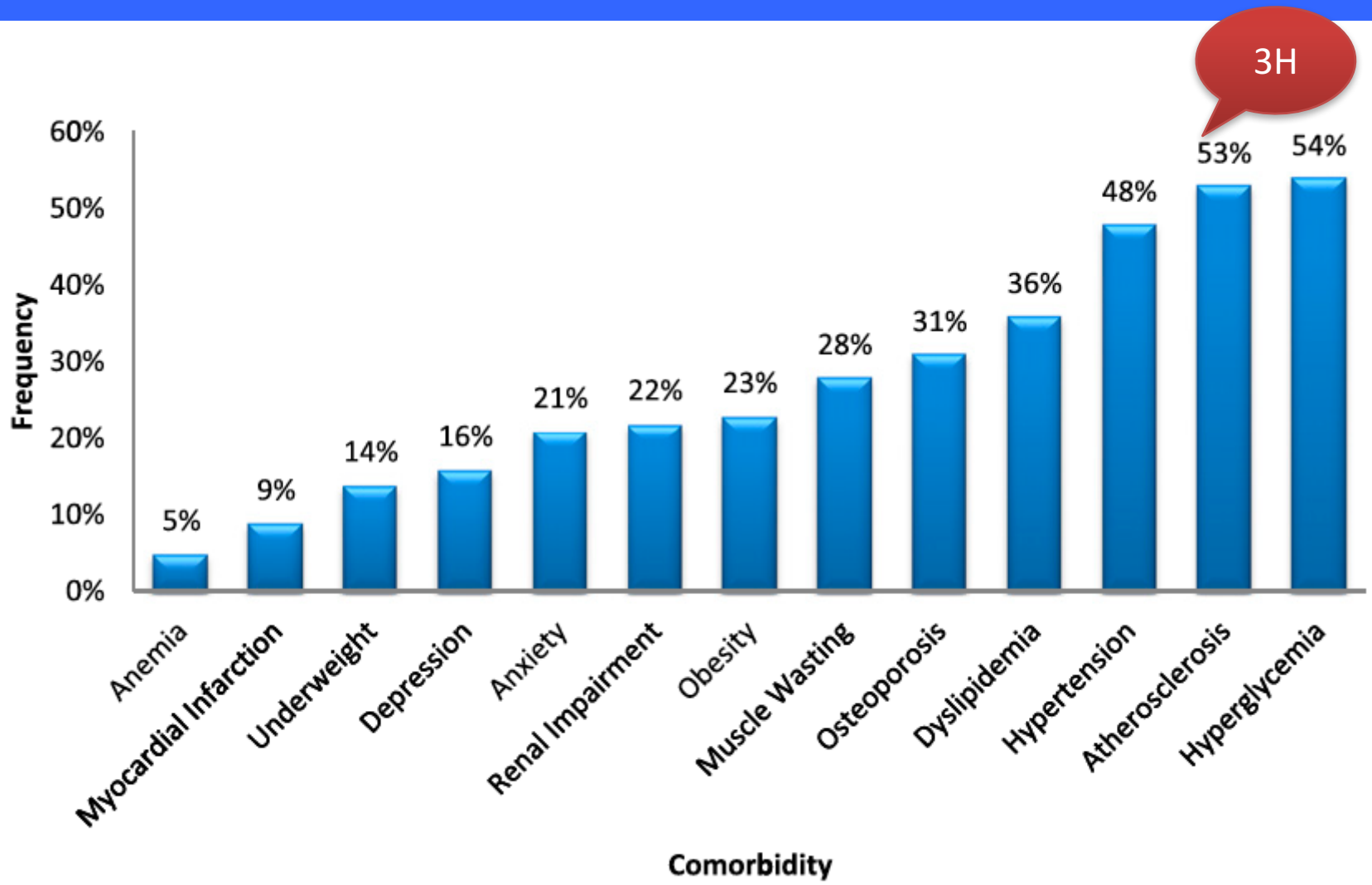
GERD

Obstructive sleep apnea

Dyspnea
Functional impairment

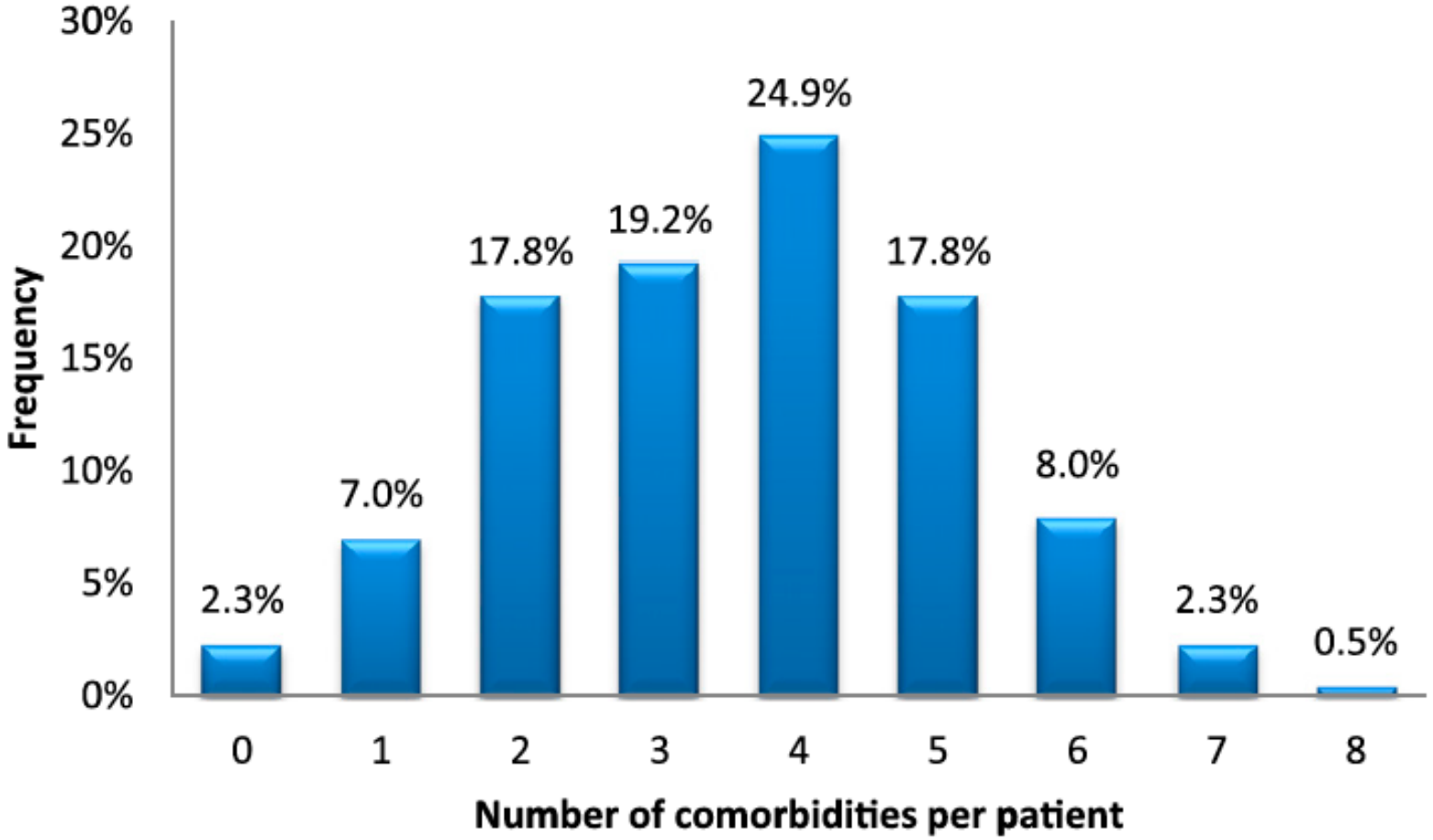
GOLD 2017 – Comorbidities may have a significant impact on prognosis

Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with COPD



AJRCCM Vol 187, pp 728–735, Apr 1, 2013

Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with COPD



AJRCCM Vol 187, pp 728–735, Apr 1, 2013

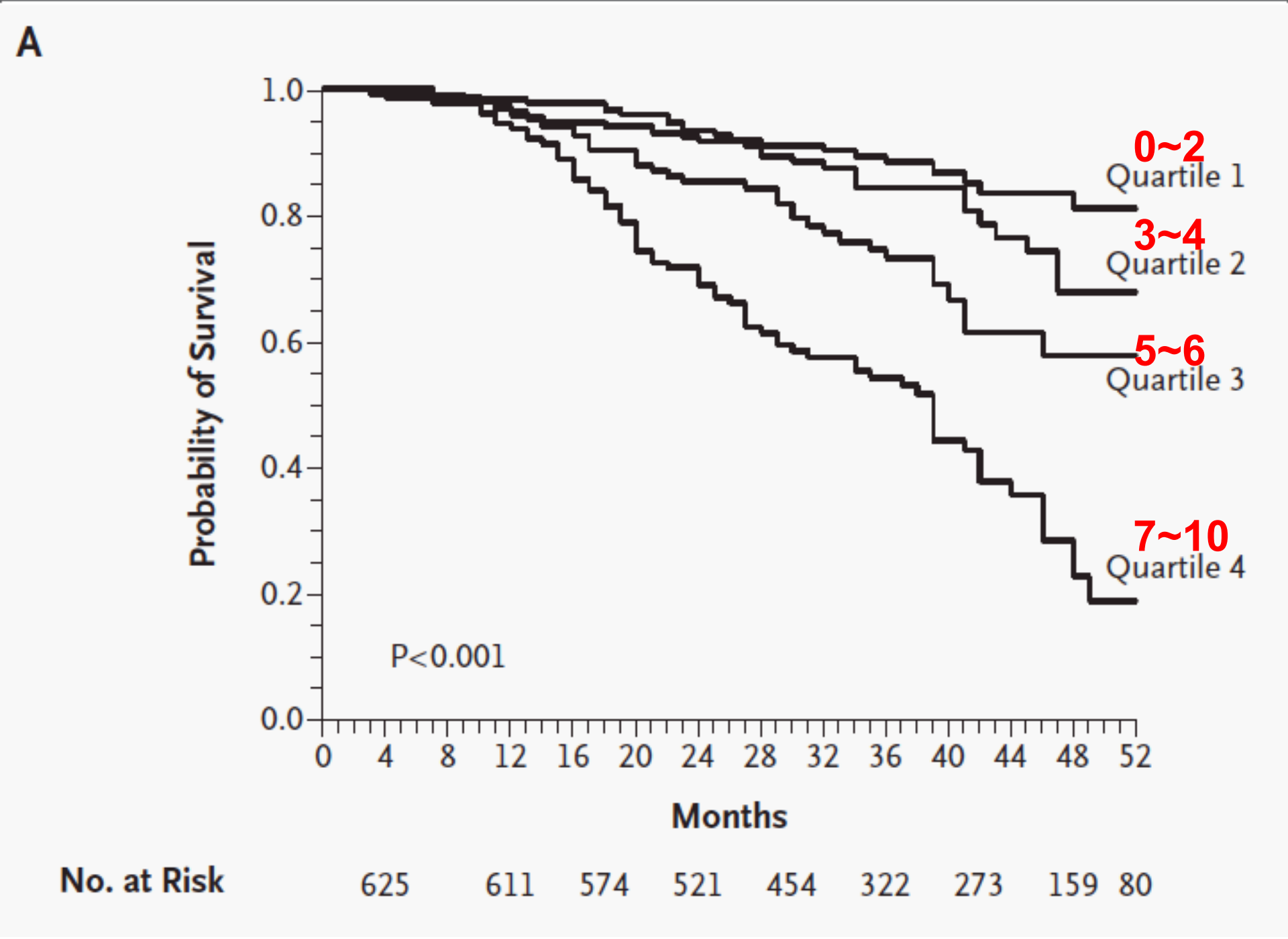
focus on Mortality

The Body-Mass Index, Airflow Obstruction,Dyspnea, and Exercise Capacity Index in COPD

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

N Engl J Med 2004;350:1005-12.


A
1.0
0.8
0.6
0.4
0.2
0.0
Probability of Survival
0~2
Quartile 1
3~4
Quartile 2
5~6
Quartile 3
7~10
Quartile 4
P<0.001
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Months
No. at Risk
625 611 574 521 454 322 273 159 80

Six-Minute-Walk Test in COPD

Minimal Clinically Important Difference for Death or Hospitalization

	No		Yes		Difference
	n	mean (m)	n	mean (m)	mean (m)
Death	1753	**-9.9**	94	**-39.6**	**29.7**
Hospitalization	1279	**-5.2**	323	**0.3**	**-5.5**
Death and/or Hospitalization	1228	**-4.2**	374	**-3.6**	**-0.7**

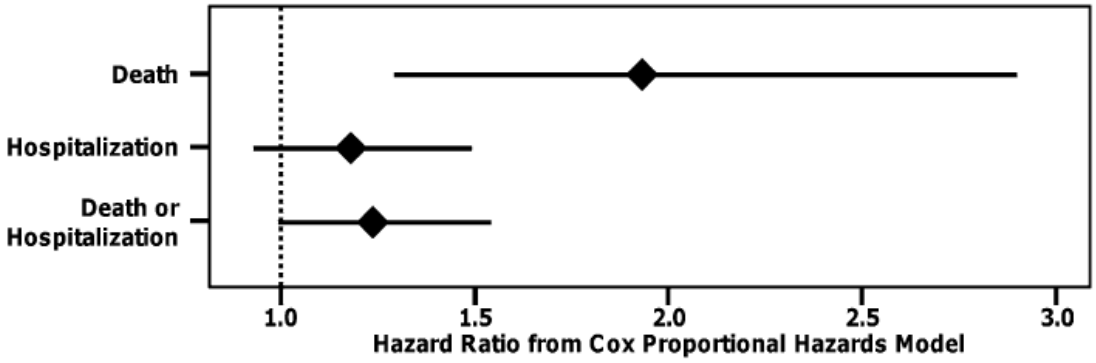


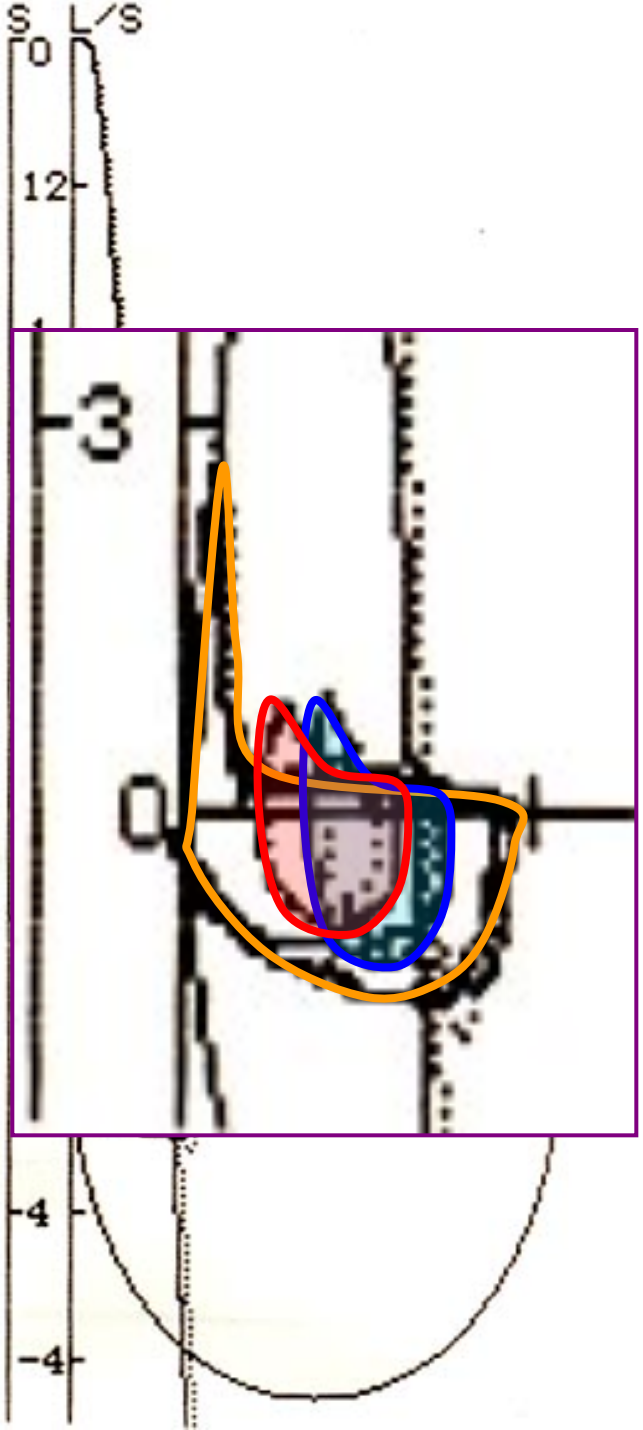
Figure 1. Cox proportional hazard model for hospitalization and death considered together and alone for a reduction in 6-minute-walk distance of more than 30 m.

AJRCCM Vol 187, Iss. 4, pp 382–386, Feb 15, 2013

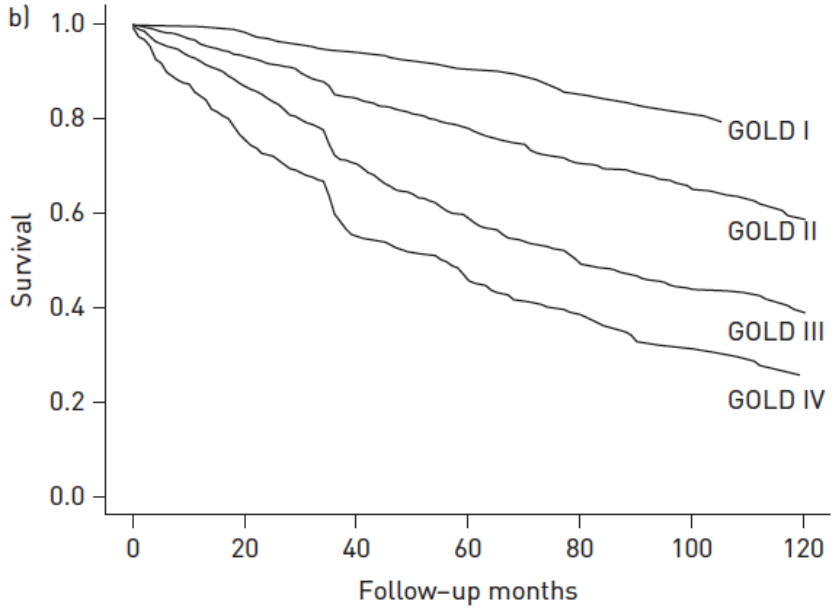
Six-min walking test

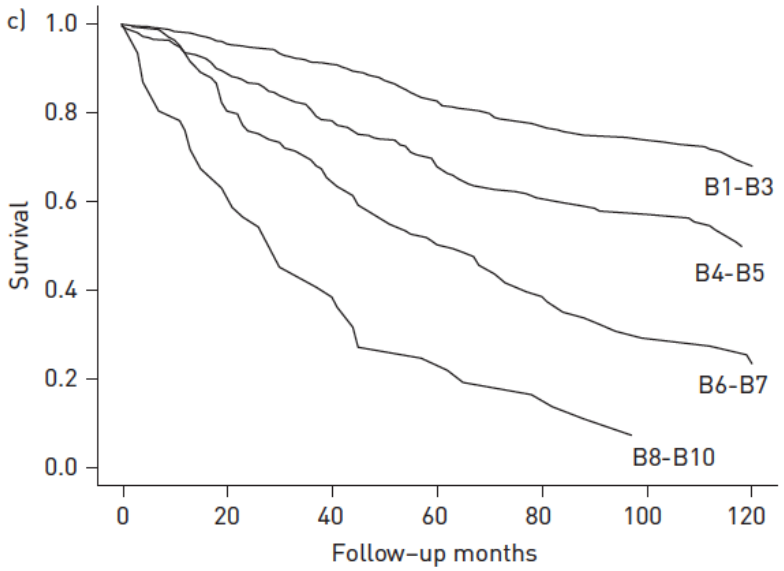
	Pre-Exercise			Post-Exercise	
FUNCTION	PRED	MEAS	%PR	MEAS	%CH
FVC	3.26	0.95	29	0.90	-3
FEV.5		0.21		0.23	10
FEV1	2.39	0.30	13	0.33	10
FEV3		0.59		0.63	7
FEV1%T					
FEV1%G	69.8	31.6	45	36.7	16
FEV3%T					
FEV3%G		62.1		70.0	13
MEFR		0.04		0.04	0
MMEF	3.35	0.13	4	0.15	15
EX TIME		6.95		5.48	-20
V EXT		0.02		0.03	50
FIVC		1.05		0.90	-11
FIV.5		0.46		0.51	9
FIV1		0.83		0.82	0
FIV1/FVC		87.4		91.1	4
FIV1/FIVC		79.0		91.1	15
FEV.5/FIV.5		0.46		0.45	0

O2 sat (%)	**93%**	**85%**
Heart rate (/min)	**120**	**112**
6 MWD (m)	**120**	



Multicomponent indices to predict survival in COPD: the COCOMICS study





Eur Respir J 2013; 42: 323–332 | DOI10.1183/09031936.00121012

Prognostic evaluation of COPD patients

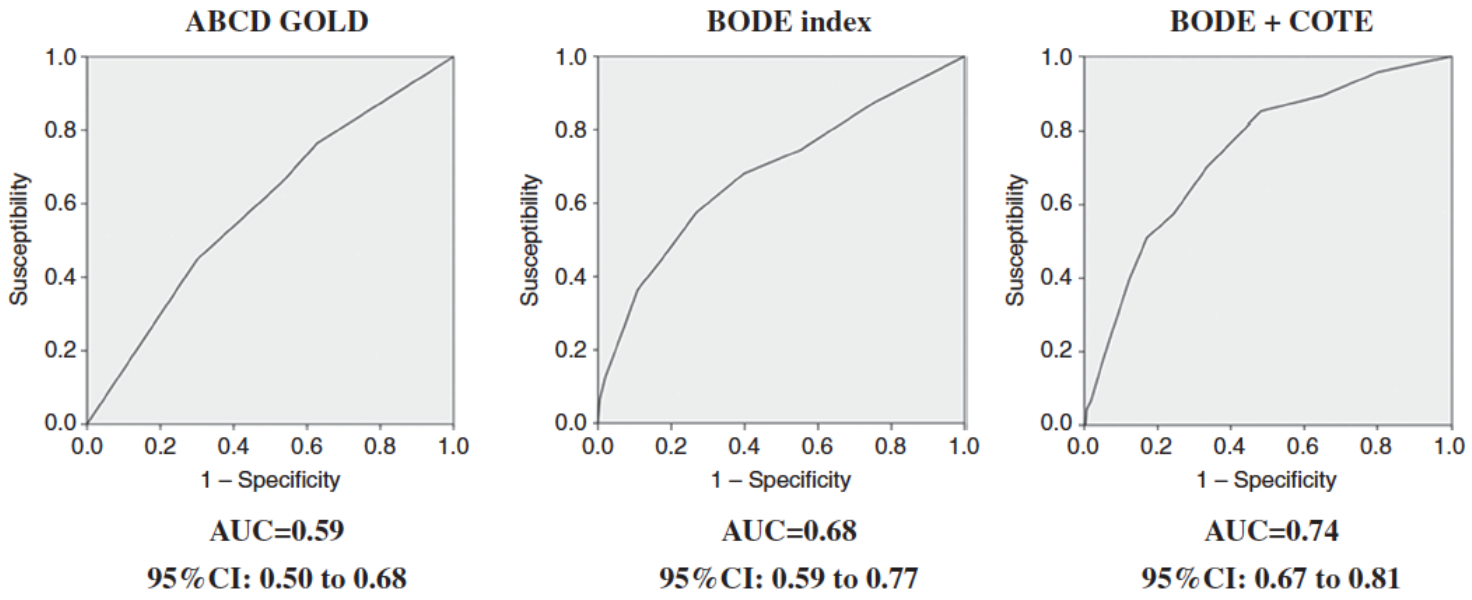


Figure 3 Mortality receiver operating curves (ROC) curves in the BMI, Obstruction, Dyspnea, Exercise (BODE) cohort for ABCD Global Obstructive Lung Disease (GOLD), BODE Index and BODE+Copd cO-morbidity TEst (COTE) and their respective area under the curve (AUC) at 24 months of follow-up.

Thorax 2014;69: 799–804.

TABLE 3. COMORBIDITIES AND POINT VALUES USED FOR THE COMPUTATION OF COTE INDEX

Comorbidity	Hazard Ratio	Point Assignment
Lung, esophageal, pancreatic, and breast* cancer	>2.00	6
Anxiety*	13.76	6
All other cancers		2
Liver cirrhosis	1.68	2
Atrial fibrillation/flutter	1.56	2
Diabetes with neuropathy	1.54	2
Pulmonary fibrosis	1.51	2
Congestive heart failure	1.33	1
Gastric/duodenal ulcers	1.32	1
Coronary artery disease	1.28	1

Hazard ratio $<1.5 = 1$, $\geqslant 1.5 = 2$, and 6 for lung, pancreatic, esophageal, and breast cancer, similar to the value assigned in the Charlson Comorbidity.

*Valid on the female population only.

Comorbidome

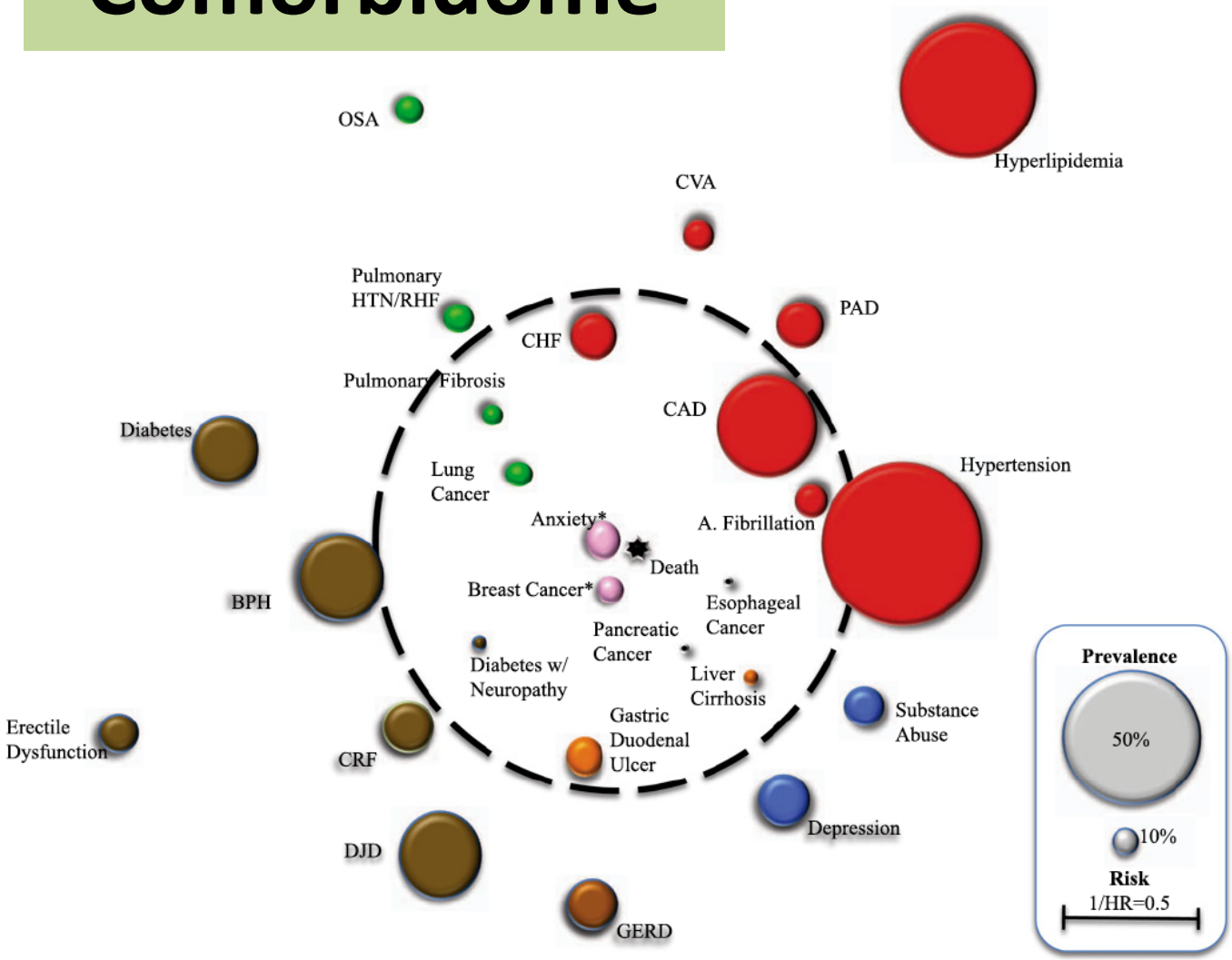
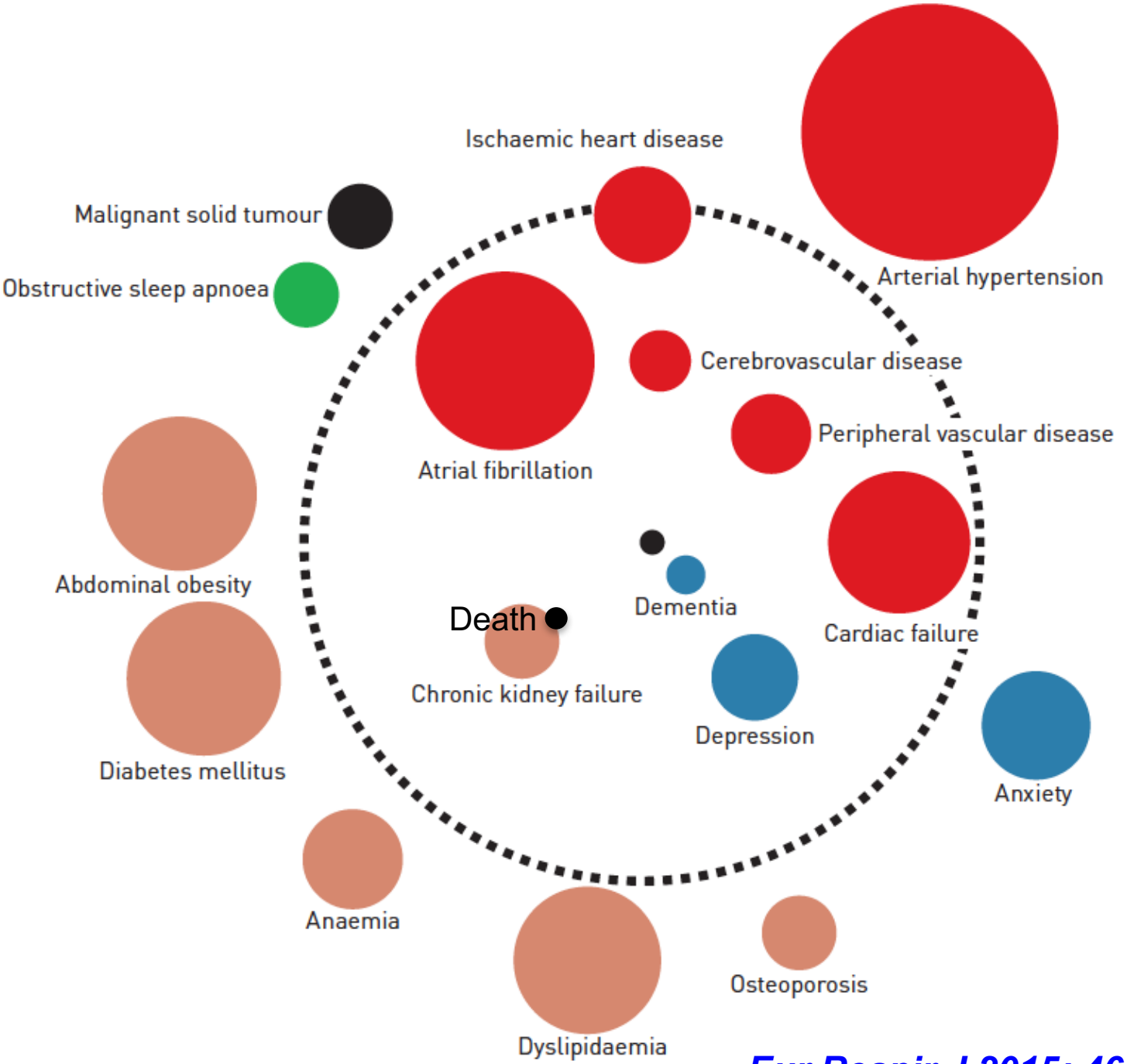


Figure 2. The "comorbidome" is a graphic expression of comorbidities with more than 10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio [HR], >1; 95% confidence interval, >1; $P \leq 0.05$). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the *dotted orbit* (1/HR <1). Bubble colors represent organ systems or disease clusters (cardiovascular = *red*, female-specific comorbidities = *pink*, pulmonary = *green*, psychiatric = *blue*, others = *brown* and *orange*). A. fibrillation = atrial fibrillation/flutter; BPH = benign prostatic hypertrophy; CAD = coronary artery disease; CHF = congestive heart failure; CRF = chronic renal failure; CVA = cerebrovascular accident; DJD = degenerative joint disease; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; PAD = peripheral artery disease; pulmonary HTN+RHF = pulmonary hypertension and right heart failure.

Comorbidome and short-term prognosis in hospitalised COPD patients: the ESMI study

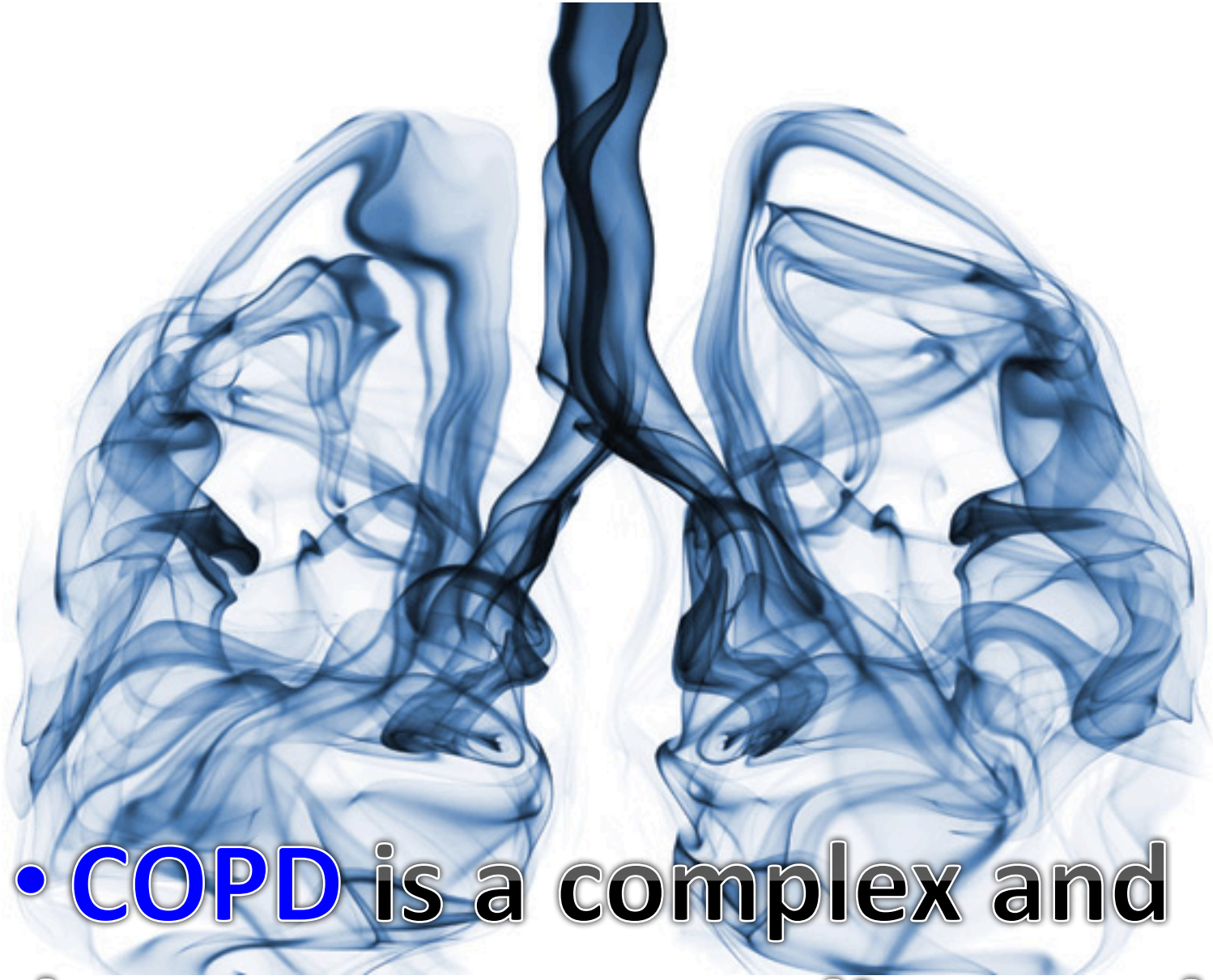
TABLE 1 Comorbidities and mortality: Cox regression analysis

Comorbidity	Prevalence %	Hazard ratio	95% CI	p-value
Systemic hypertension	63.4	0.9	0.44–2.28	NS
Diabetes mellitus	35.8	1.9	0.87–4.17	NS
Dyslipidaemia	33.8	1.16	0.48–2.78	NS
Heart failure	32.8	2.31	1.05–5.1	<0.01
Abdominal obesity	29.4	1.1	0.44–2.35	NS
Arrhythmias	24.9	2.8	1.28–6.15	<0.001
Ischaemic heart disease	20.8	1.29	1.04–1.61	<0.01
Anaemia	19.3	0.59	0.20–1.76	NS
Anxiety	18.3	0.55	0.29–1.30	NS
Peripheral vascular disease	16.8	3.83	1.71–8.57	<0.002
Kidney disease	16	3.91	1.75–8.73	<0.005
Osteoporosis	15.8	2.1	0.91–4.63	NS
Depression	15	3.24	1.02–10.1	<0.01
Obstructive sleep apnoea	12.2	3.49	0.47–25.87	NS
Cerebrovascular disease	11.7	3.44	1.49–7.99	<0.006
Malignant solid tumour	13.2	0.58	0.21–1.50	NS
Ulcer disease	10.4	1.85	0.25–13.73	NS
Dementia	3.6	5.17	1.76–15.28	p<0.001



Eur Respir J 2015; 46: 850–853

Summary



- **COPD** is a complex and heterogeneous disease !