COPD EXACERBATIONS

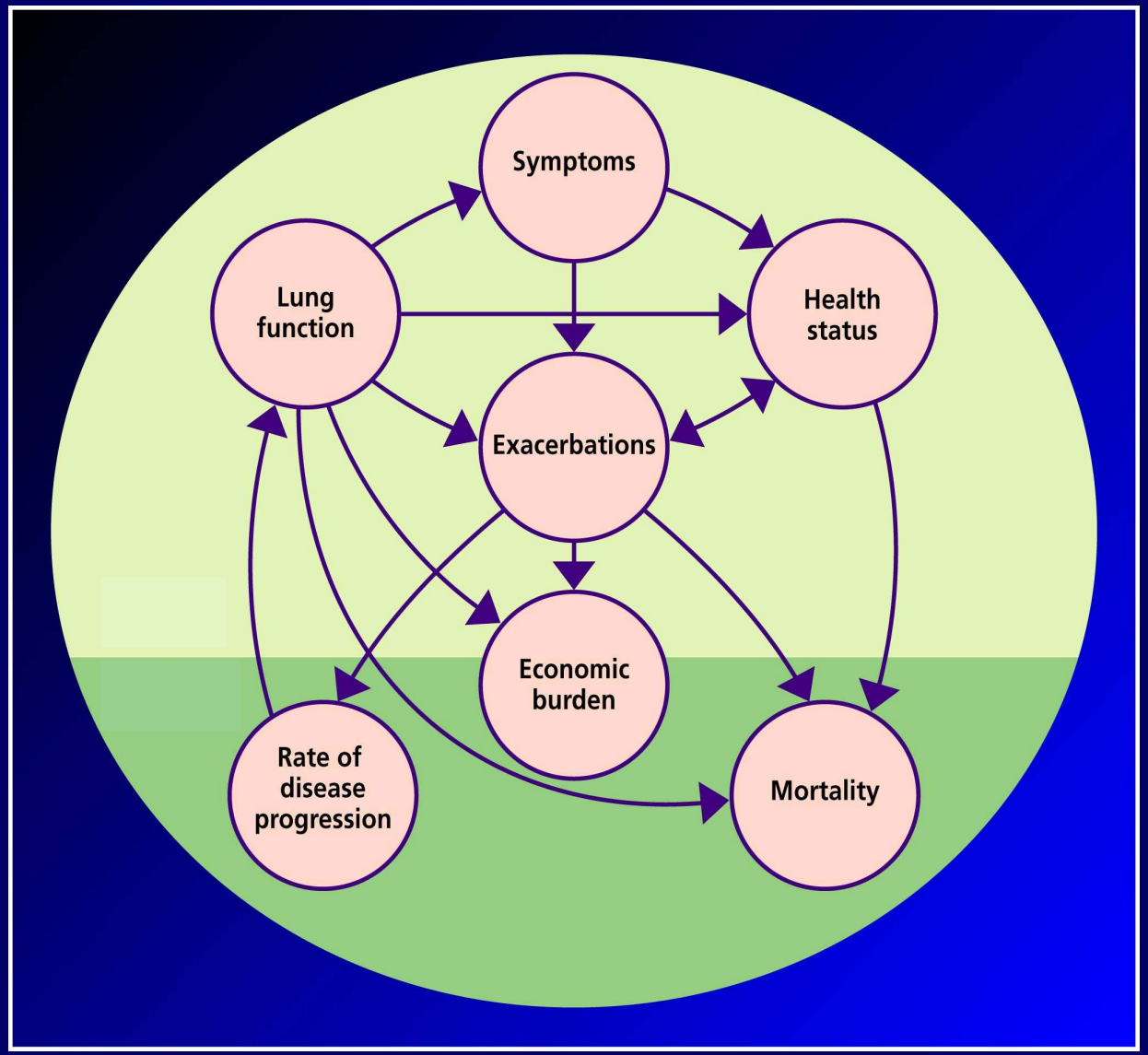
Francesco Blasi

Head Respiratory Medicine Section

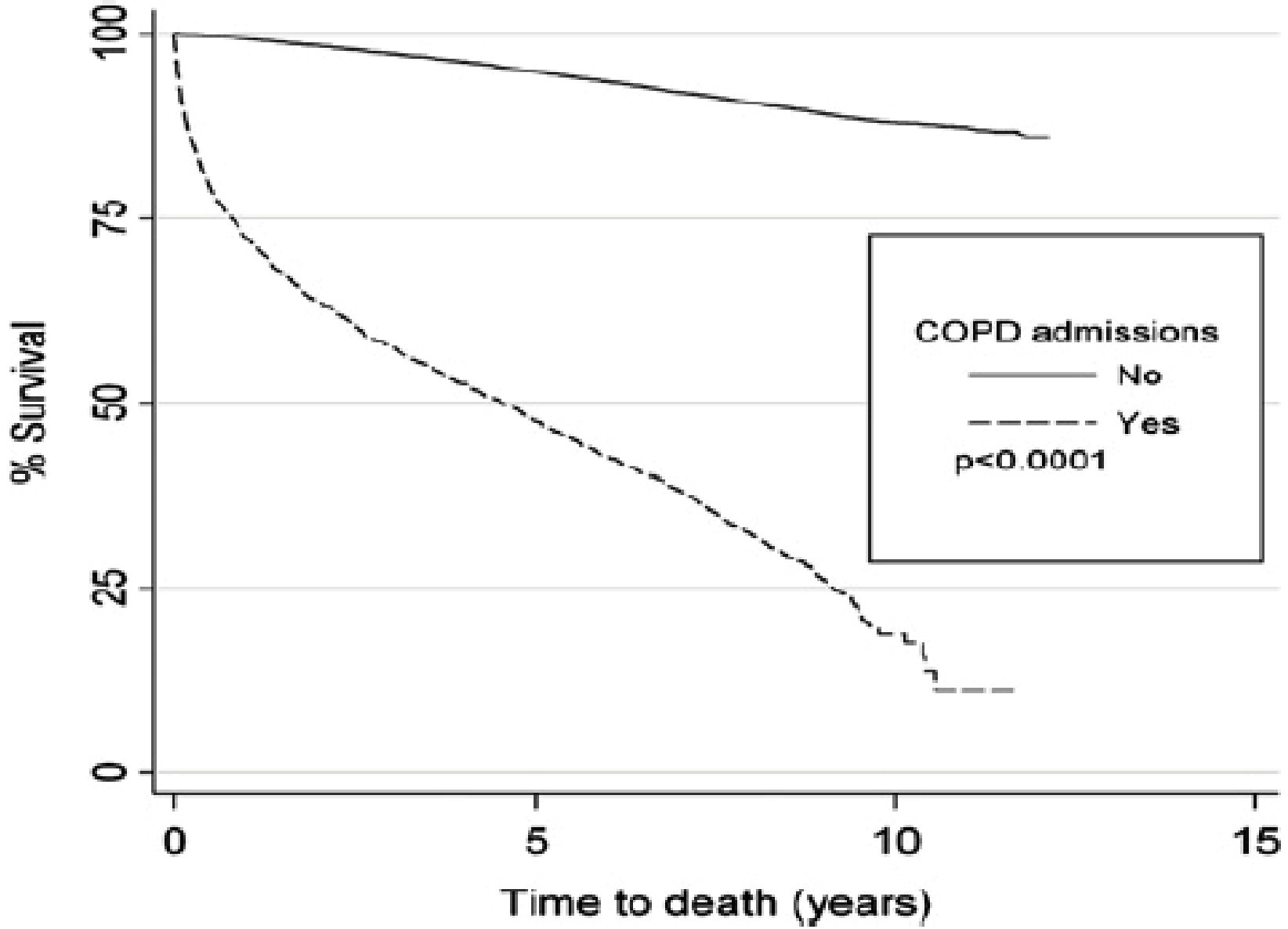
Cardio-Thoracic Department

University of Milan, Italy

COPD OUTCOMES



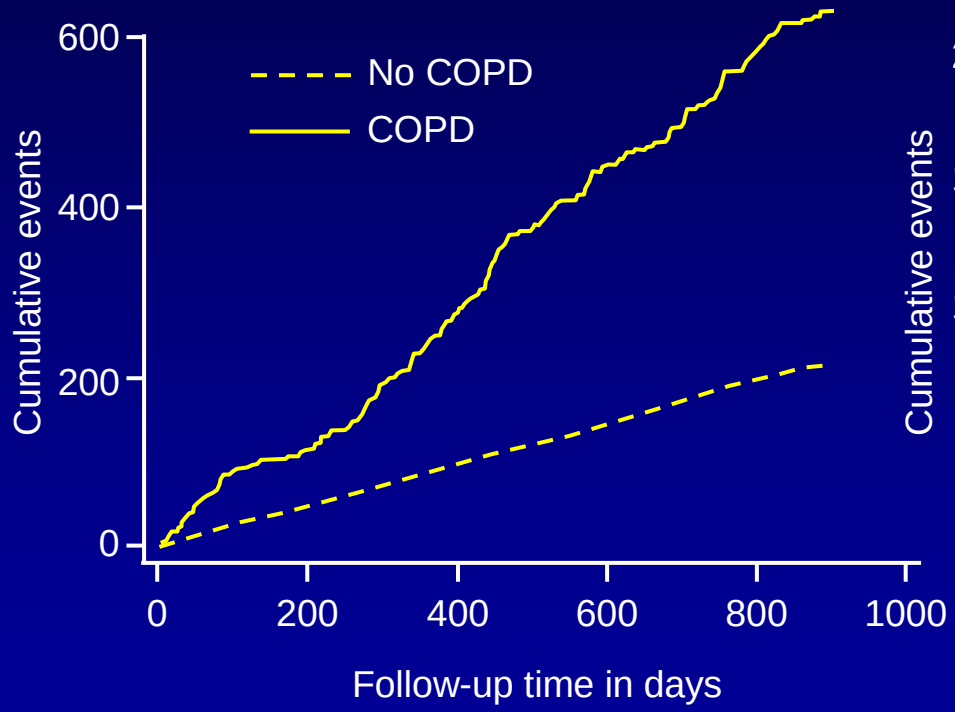
Cazzola M et al. ERJ 2008



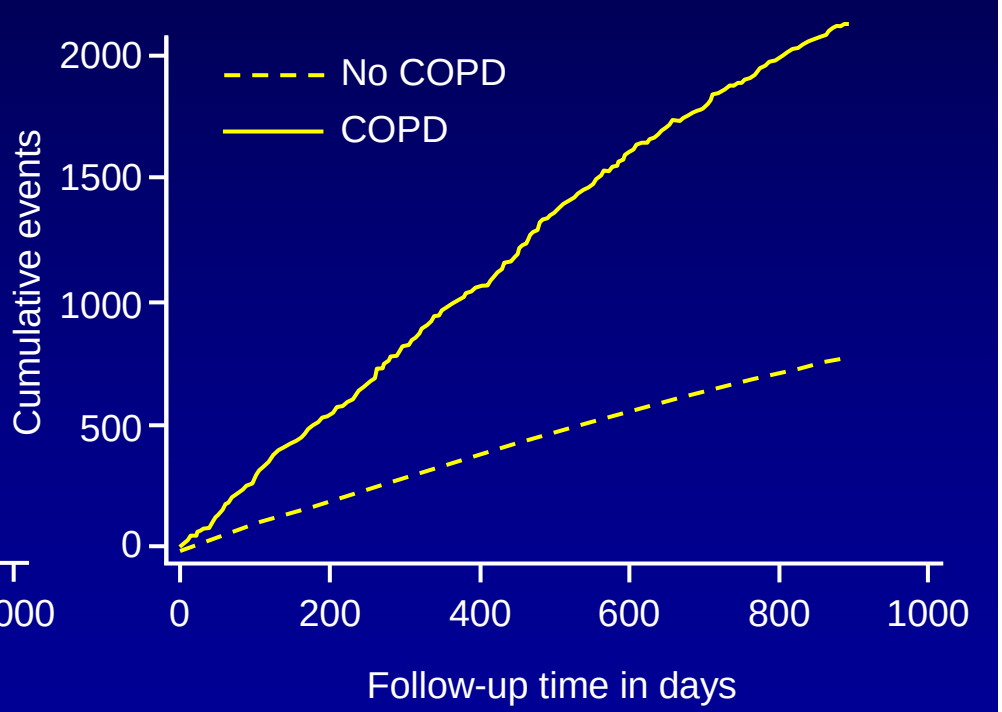
Thorax 2011;**66**:585–590.

COPD AND CARDIOVASCULAR DISEASE

Cumulative incidence of first MI



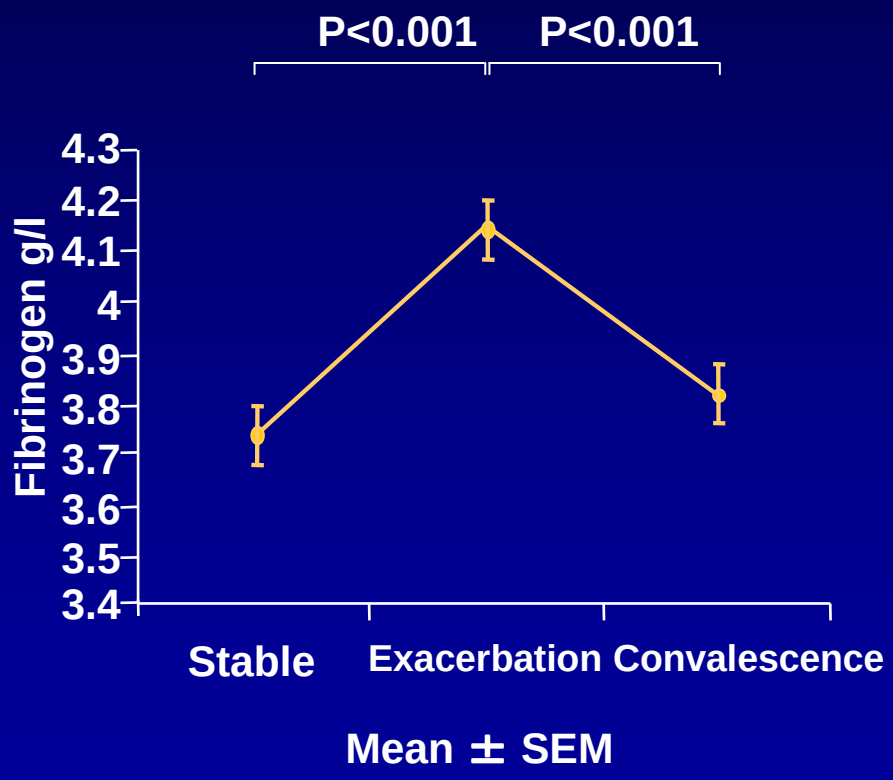
Cumulative incidence of first CVA



Thorax **2010**;**65**:956-962. doi:10.1136/thx.2009.128082.

PLASMA FIBRINOGEN AT EXACERBATION

N = 120 Exacerbations

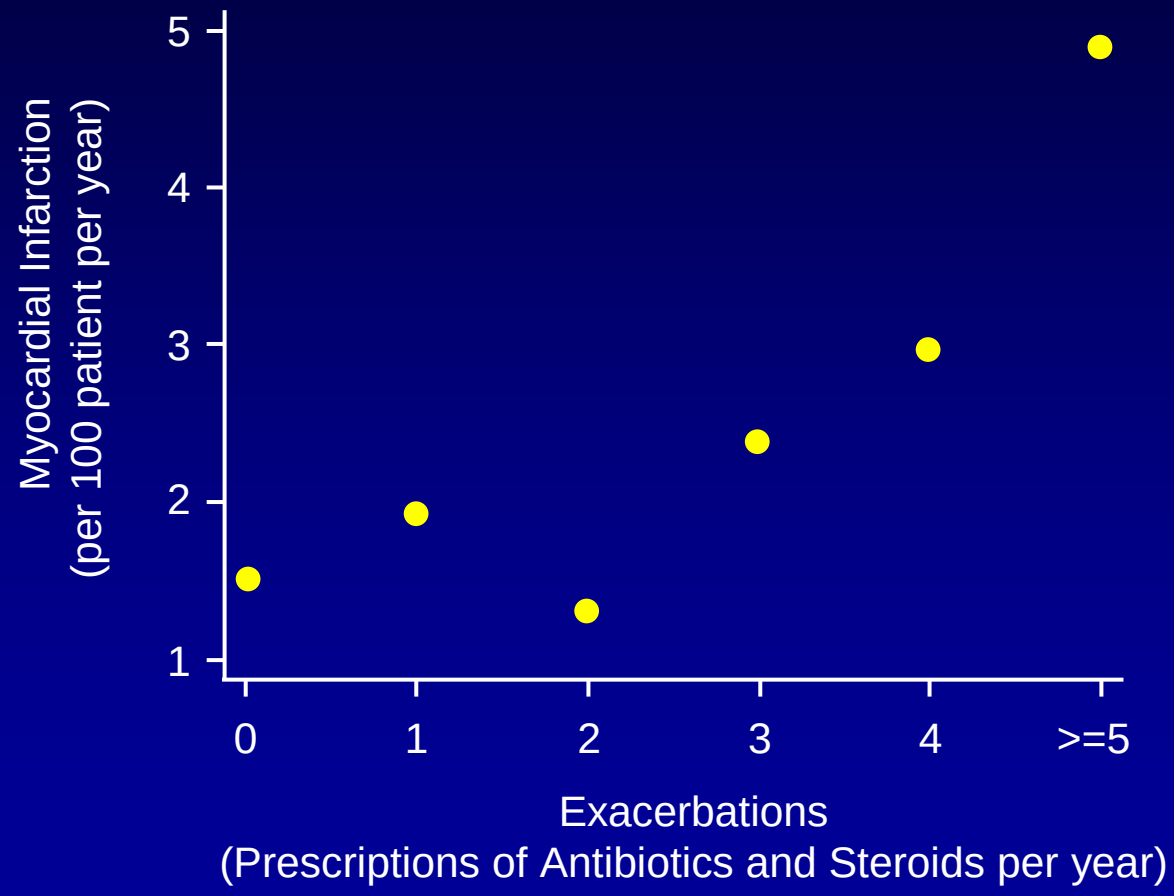


- Increased fibrinogen with colds P = 0.024
- Increased fibrinogen with sputum purulence P = 0.033
- Rise 0.56 g/l during viral Exs
- Rise in 0.27 g/l during non-viral Exs

p=0.056

Wedzicha, et al. *Thromb Haem* **2000.**

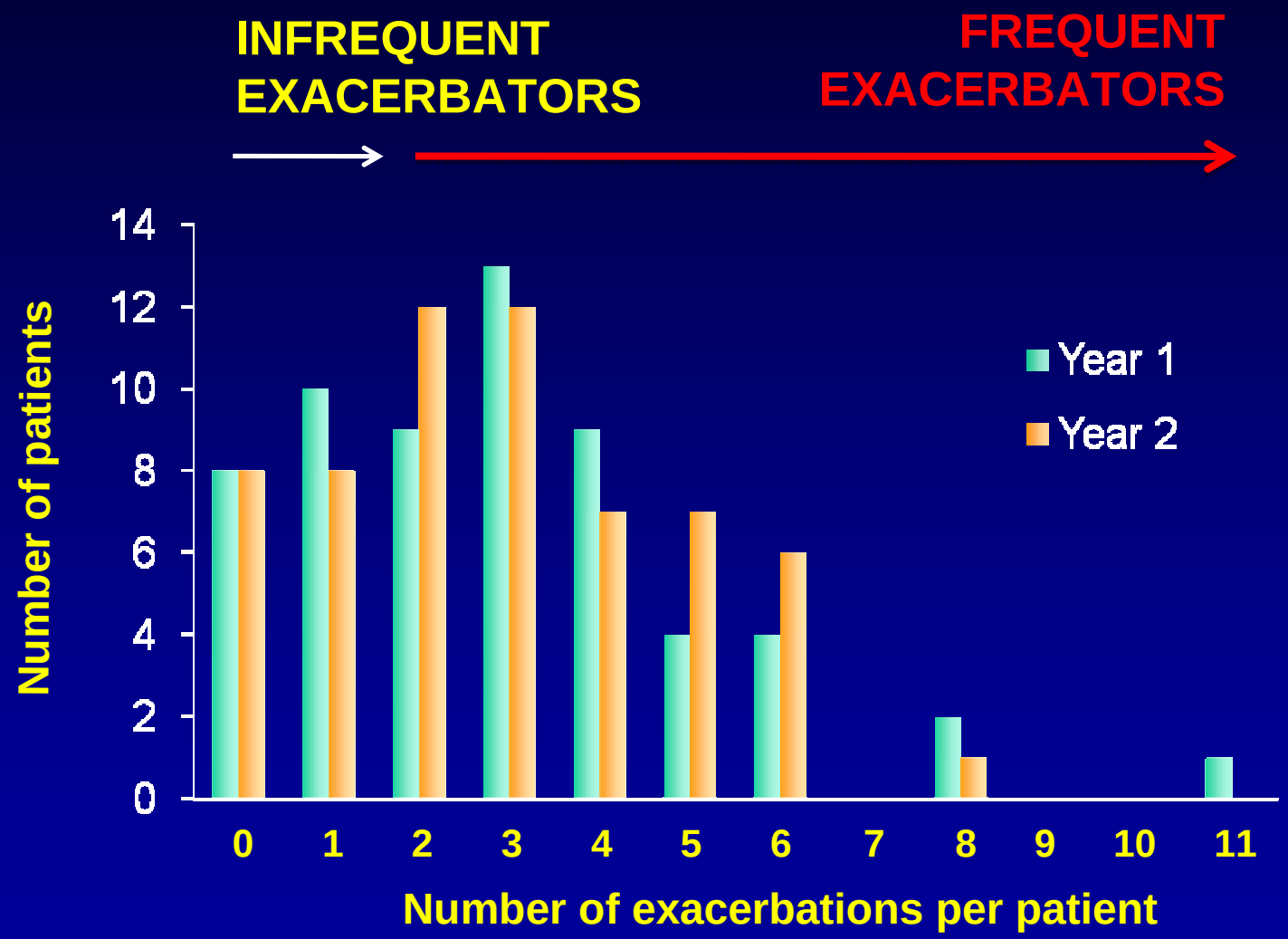
EXACERBATION FREQUENCY AND MYOCARDIAL INFARCTION



Donaldson, et al. *Chest* **2010.**

DATA FROM THIN GP DATABASE

EXACERBATION FREQUENCY



Data from London COPD cohort and
Seemungal TAR, et al. *AJRCCM* 1998;157:1418-1422.

Effect of Exacerbation on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease

TERENCE A. R. SEEMUNGAL, GAVIN C. DONALDSON, ELIZABETH A. PAUL, JANINE C. BESTALL, DONALD J. JEFFRIES, and JADWIGA A. WEDZICHA

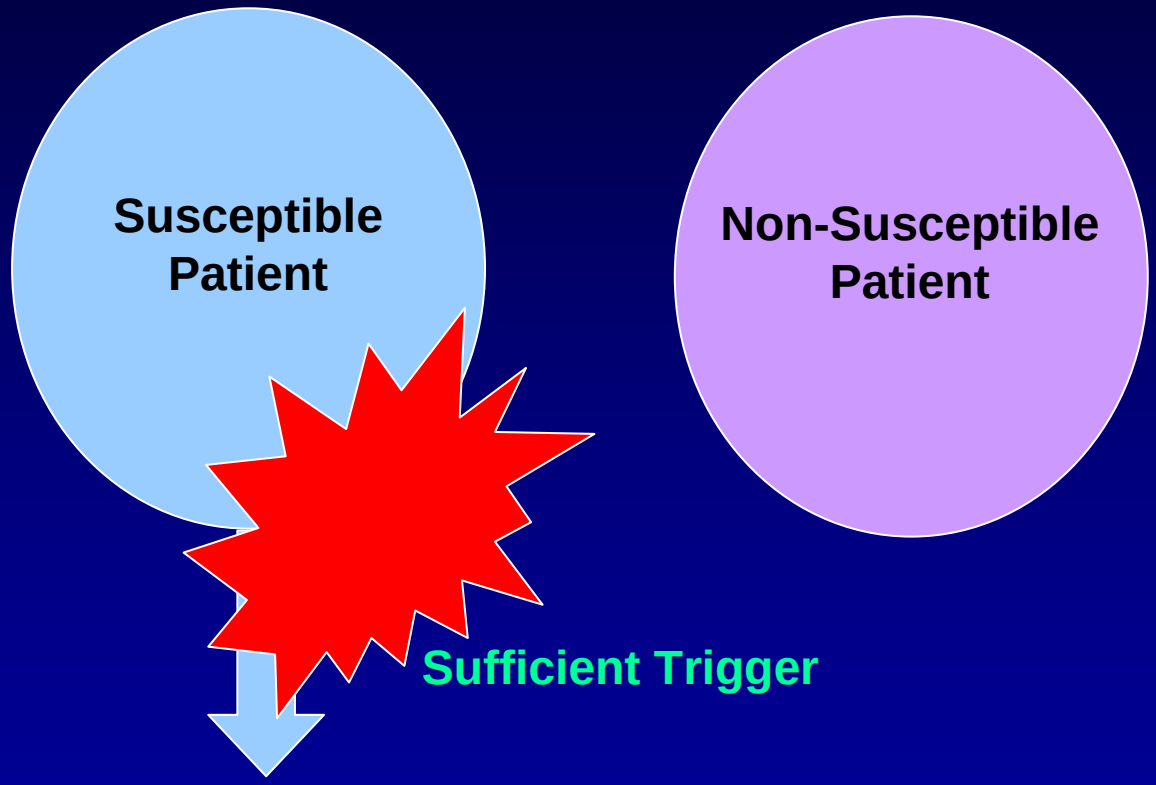
Academic Departments of Respiratory Medicine, Physiology, Environmental and Preventive Medicine, and Virology, St. Bartholomew's and Royal London School of Medicine and Dentistry, London, United Kingdom

FACTORS PREDICTING FREQUENT EXACERBATORS:

Number of exacerbations in previous year
Daily cough and sputum
Poor quality of life

Seemungal, et al. *AJRCCM* 1998.

EXACERBATION FREQUENCY IS A SUSCEPTIBILITY PHENOTYPE



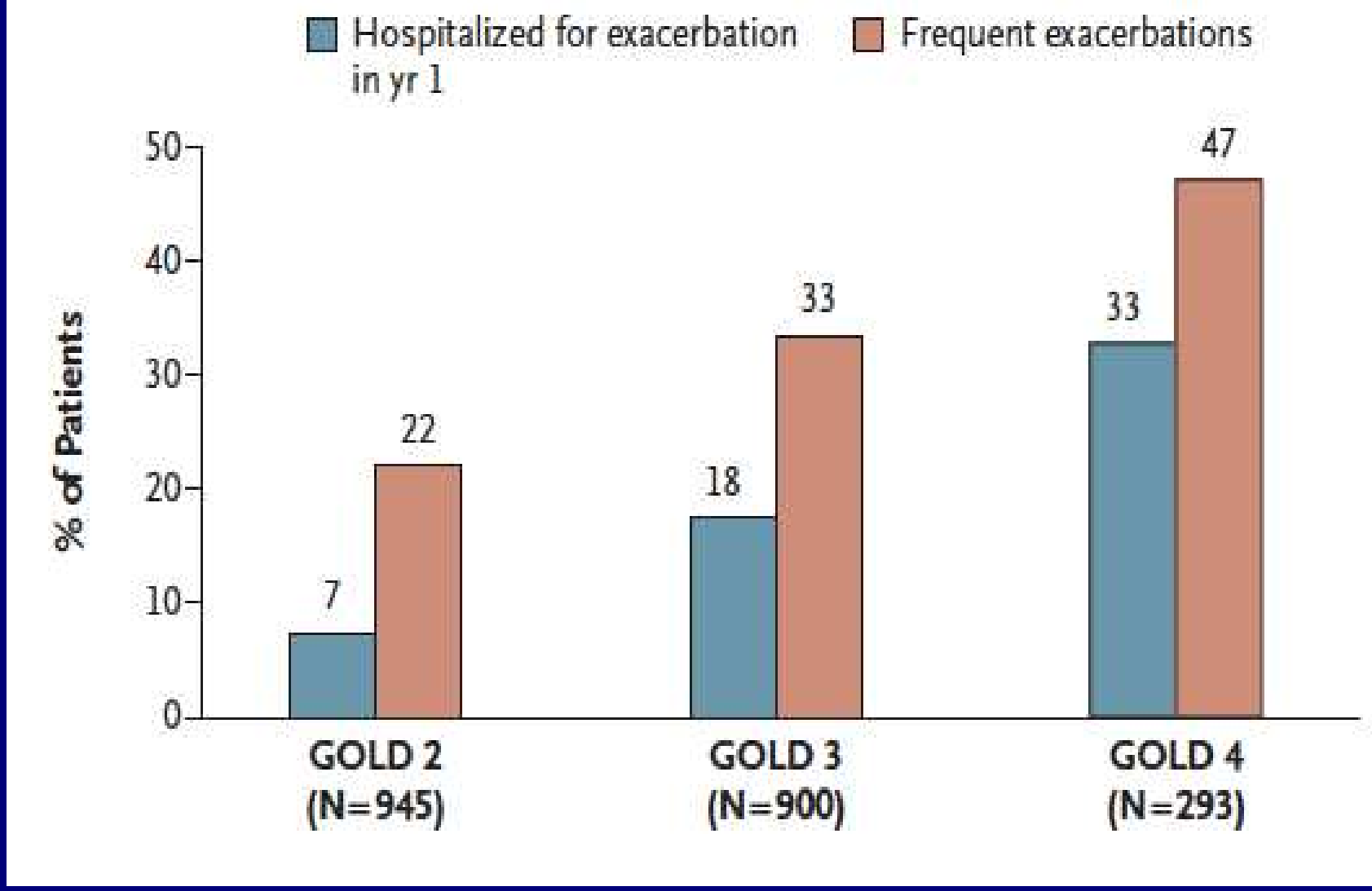
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

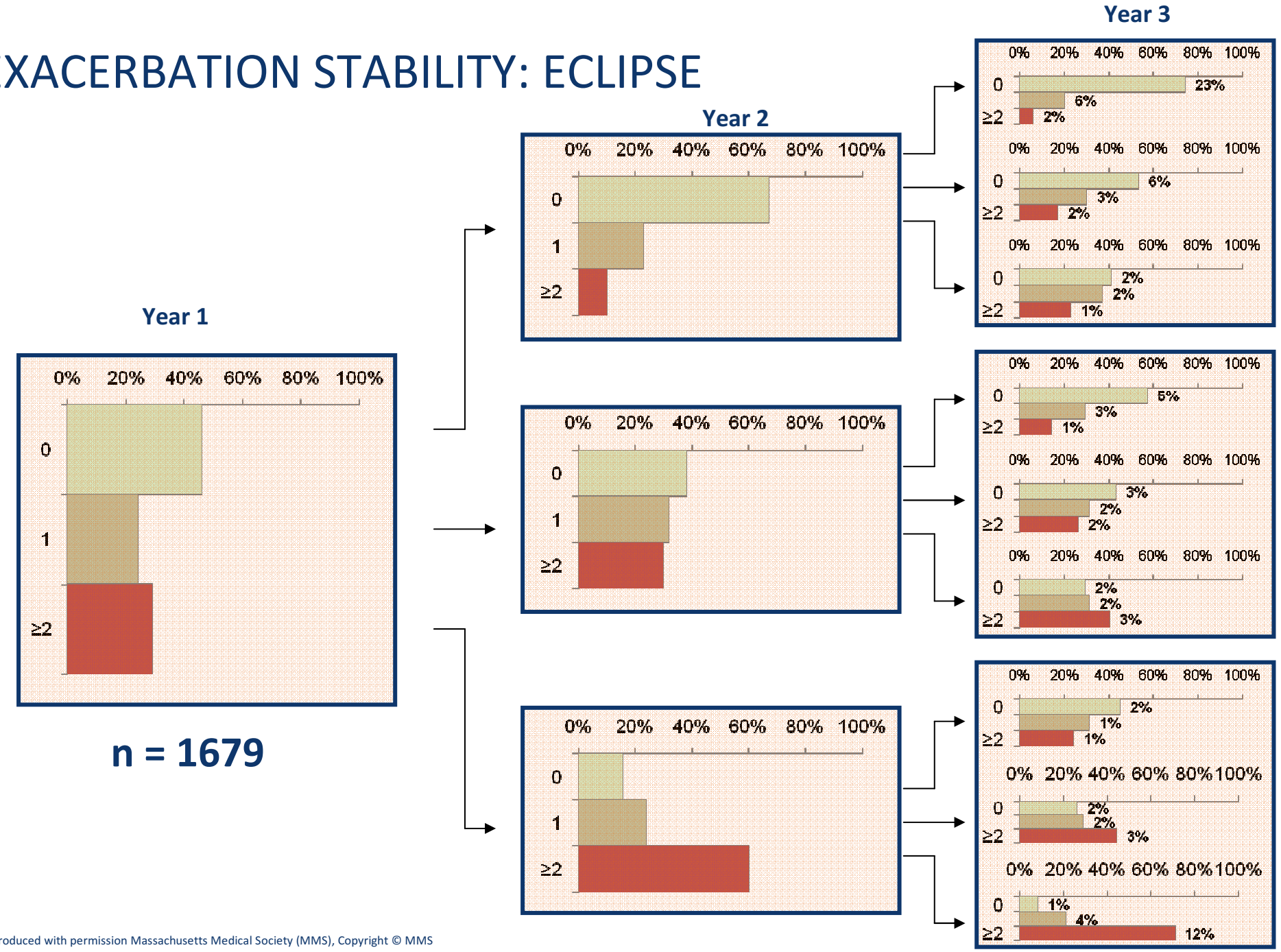
John R. Hurst, M.B., Ch.B., Ph.D., Jørgen Vestbo, M.D., Antonio Anzueto, M.D., Nicholas Locantore, Ph.D., Hana Müllerova, Ph.D., Ruth Tal-Singer, Ph.D., Bruce Miller, Ph.D., David A. Lomas, Ph.D., Alvar Agusti, M.D., Ph.D., William MacNee, M.B., Ch.B., M.D., Peter Calverley, M.D., Stephen Rennard, M.D., Emiel F.M. Wouters, M.D., Ph.D., and Jadwiga A. Wedzicha, M.D., for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators*

N Engl J Med 2010;363:1128-38.



N Engl J Med 2010;363:1128-38.

EXACERBATION STABILITY: ECLIPSE

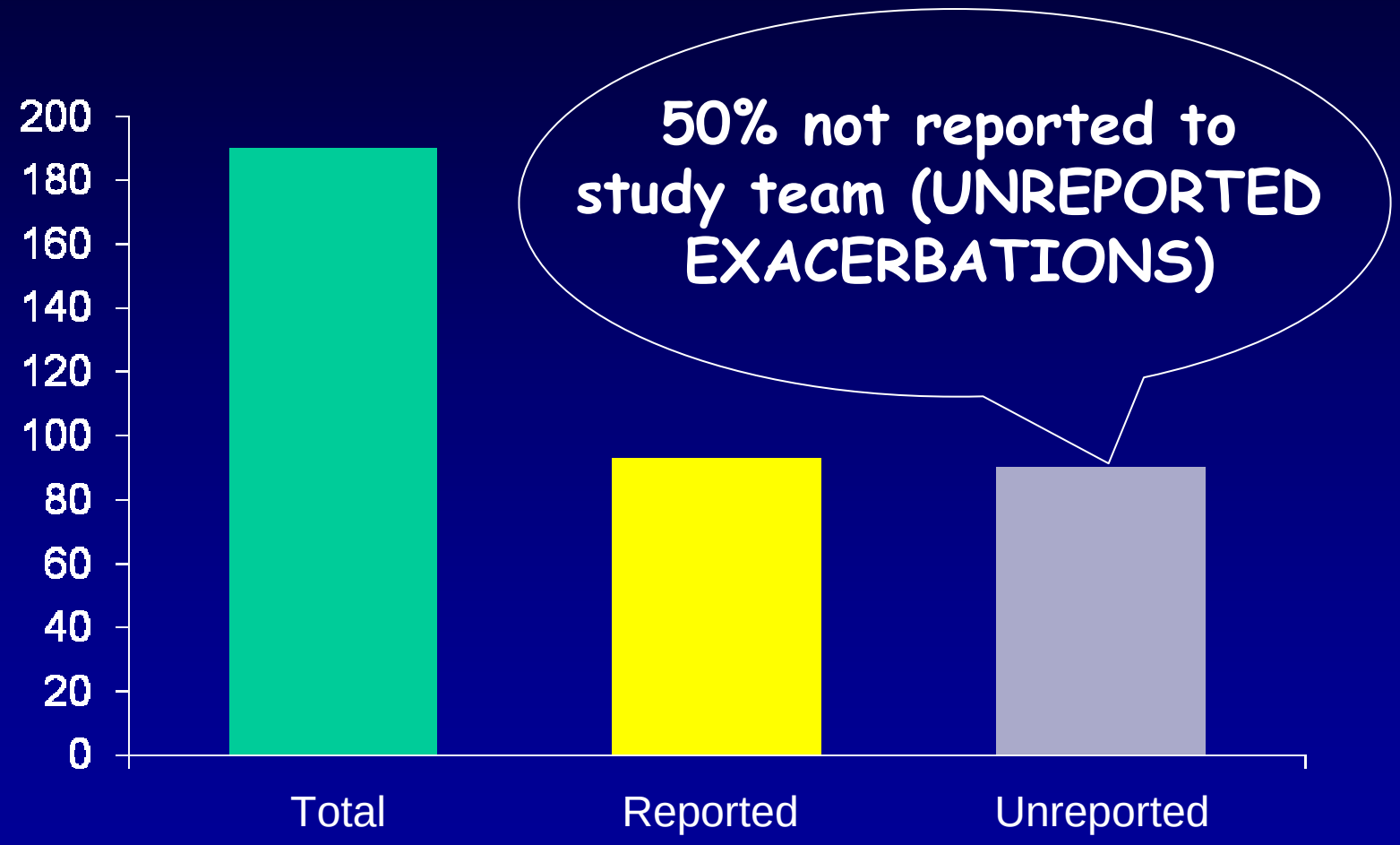


n = 1679

ECLIPSE 3 year data

Hurst JR, et al. N Engl J Med. 2010;363:1128-38

EXACERBATIONS: REPORTED AND UNREPORTED



Seemungal, et al. *AJRCCM* **1998.**

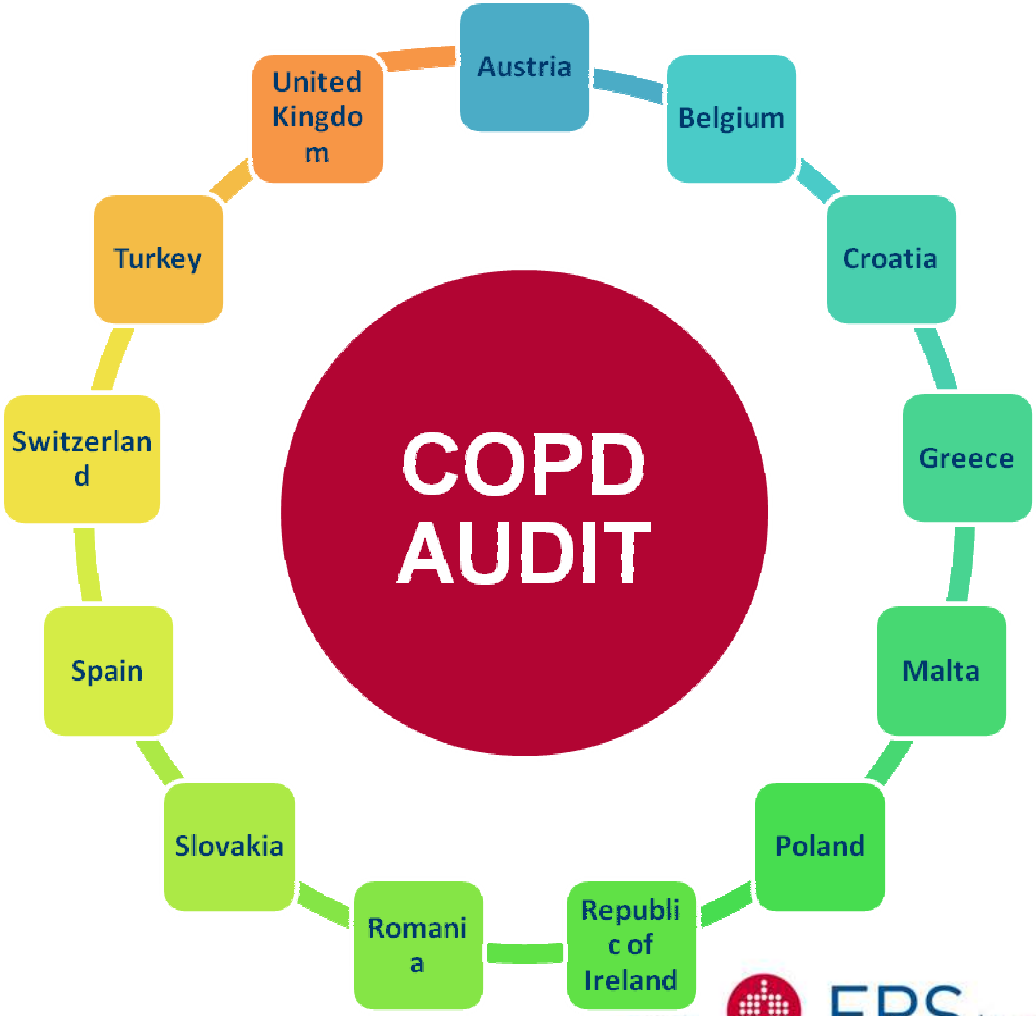
ONSET AND RESOLUTION OF COPD EXACERBATIONS - DATA FROM LONDON COPD COHORT

Aaron et al Thorax 2011

ERS | copdaudit

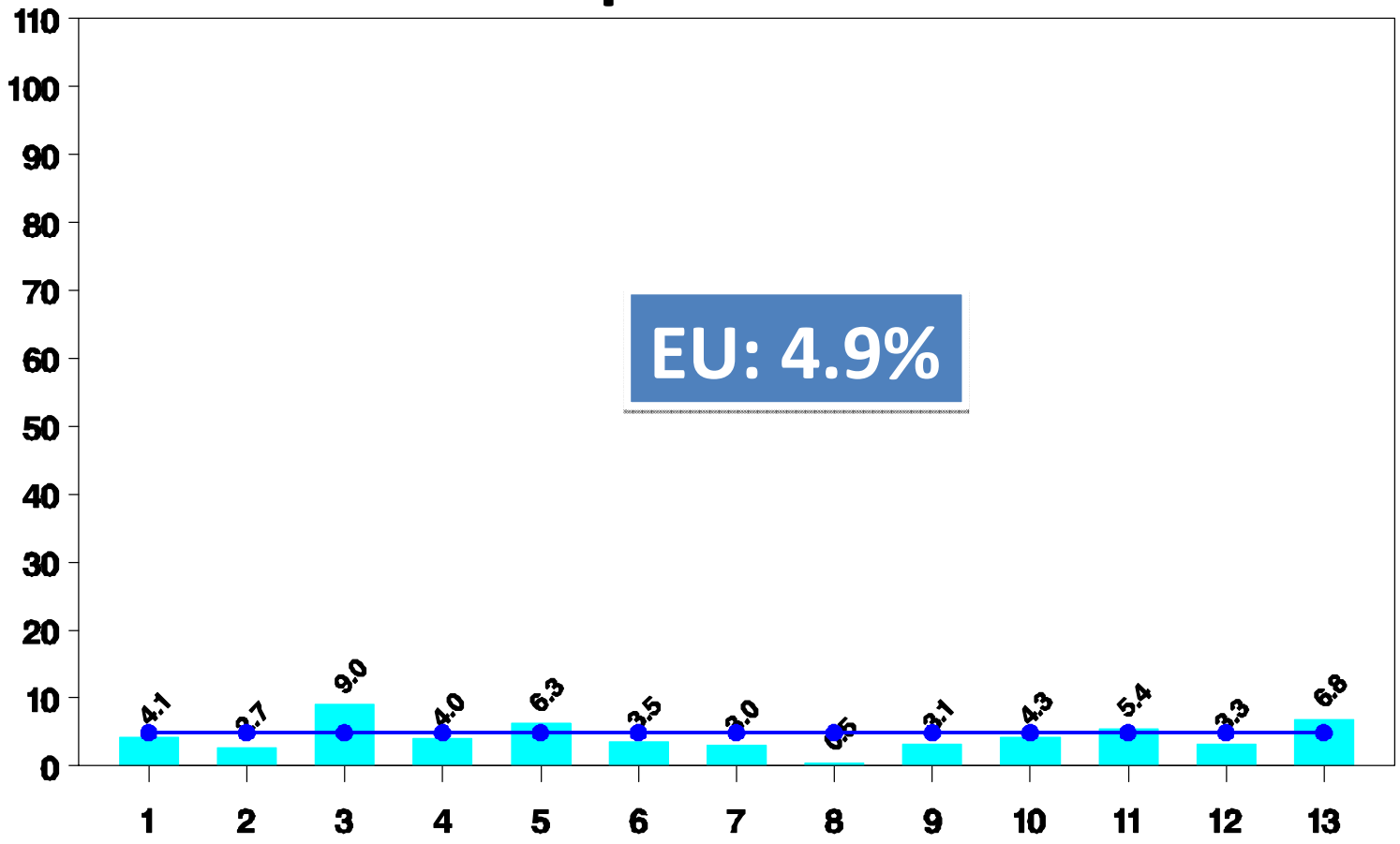
THE ERS COPD AUDIT

REDUCING INEQUALITIES IN COPD CARE ACROSS EUROPE



europ ERS ty every breath counts

In-hospital deaths



Results from the European COPD audit: outcomes

Patient-related factors associated to in-hospital mortality

Variables	Crude OR
Age	1.06 (1.05 – 1.07)
Gender female	1.17 (1.01 – 1.36)
Current smoker	0.52 (0.43 – 0.63)
Sputum colour change	0.84 (0.72 – 0.98)
Pack-years	1.004 (1.001 – 1.007)
Previous admissions 12 months	1.07 (1.03 – 1.10)
FEV1	0.978 (0.972 – 0.985)
BMI	0.95 (0.93 – 0.96)
pH	0.003 (0.001 – 0.007)
PaCO2	1.001 (1 – 1.002)

Organisational factors associated to in-hospital mortality

Variables	Crude OR
Number of respiratory specialists	0.98 (0.97 – 0.99)
Number of respiratory trainees	0.98 (0.97 – 0.99)
Number of physiotherapists	0.96 (0.93 – 0.99)
% seen by respiratory specialist	0.996 (0.994 – 0.999)
University hospital	0.80 (0.69 – 0.92)
Hospital with ICU	1.86 (1.24 – 2.7)
Respiratory Specialist on call everyday	0.76 (0.65 – 0.88)
Outpatient clinic	0.60 (0.41 – 0.89)
With HDU	1.40 (1.21 – 1.62)
Respiratory ward	0.67 (0.58 – 0.77)

Factors that predict failure in home management of an acute exacerbation of COPD

Dunican EM, et al. Thorax 2011 66(4)358-9

Multivariate analysis identified :

- **Hospitalisation in the previous year** (p<0.03, OR 2.26, CI 1.1 to 4.8) AND **Borg score ≥ 3** (p<0.04, OR 2.15, CI 1.0 to 4.6)

  Predicted readmission by day 14 in 75% of cases.

- **Longterm oxygen therapy** (p<0.001, OR 3.28, CI 1.6 to 6.5), **pack-year history ≥50** (p<0.008, OR 3.13, CI 1.4 to 7.3) AND **Borg score ≥ 3**(p<0.001, OR 3.31, CI 1.6 to 6.8)

  Predicted 6 week admission in 68.9%.

Antibiotic treatment is associated with reduced risk of a subsequent exacerbation in obstructive lung disease: an historical population based cohort study

B M Roede,[1,2] P Bresser,[3] P J E Bindels,[2] A Kok,[4] M Prins,[1,4] G ter Riet,[2,5] R B Geskus,[6] R M C Herings,[7] J M Prins[1]

Thorax 2008;63;968-973

Eur Respir J 2009; 33: 282–288
DOI: 10.1183/09031936.00088108

Reduced risk of next exacerbation and mortality associated with antibiotic use in COPD

B.M. Roede*,#, P. Bresser¶, J.M. Prins*, F. Schellevis+,§, T.J.M. Verheij^f and P.J.E. Bindels#

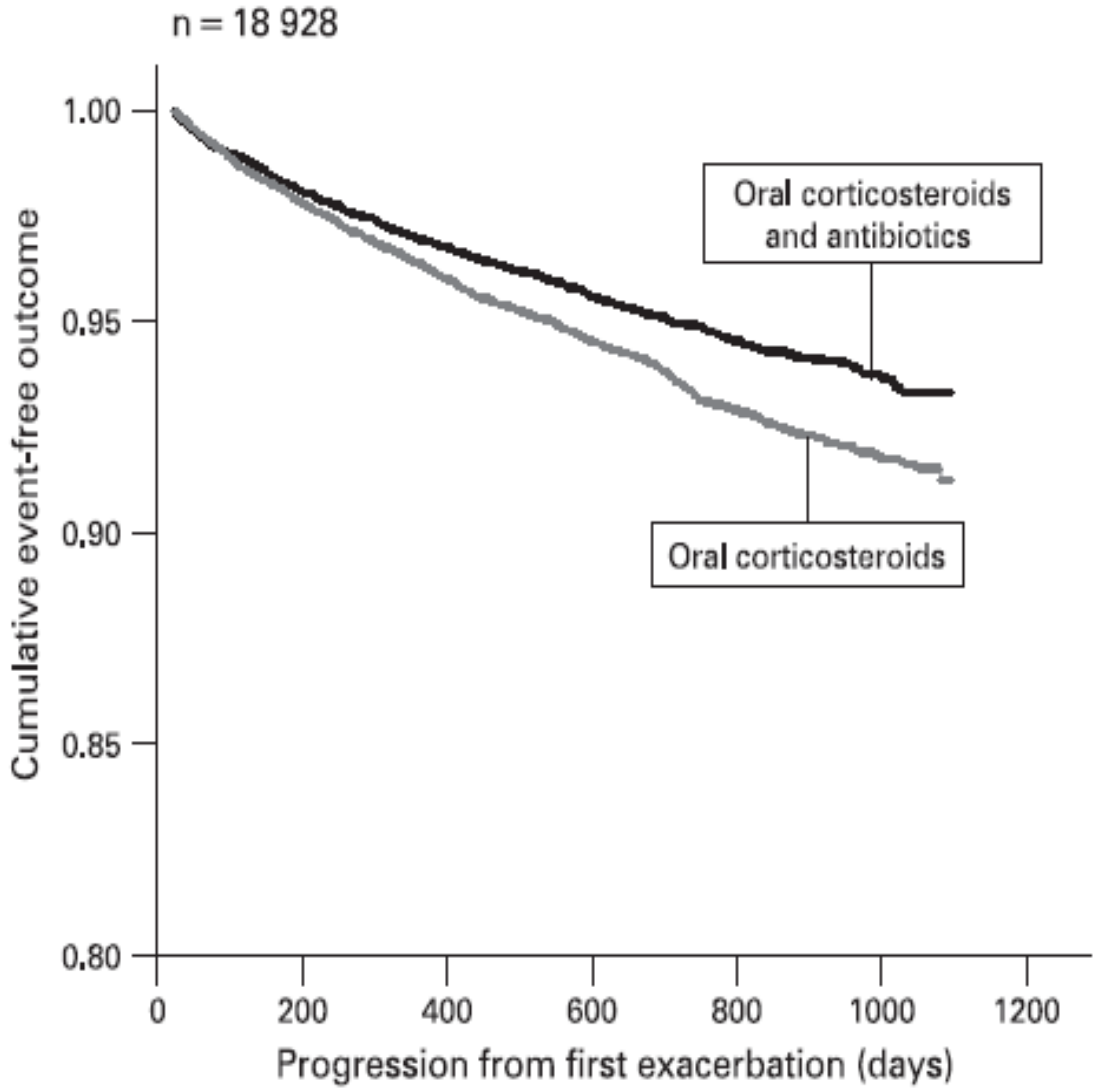


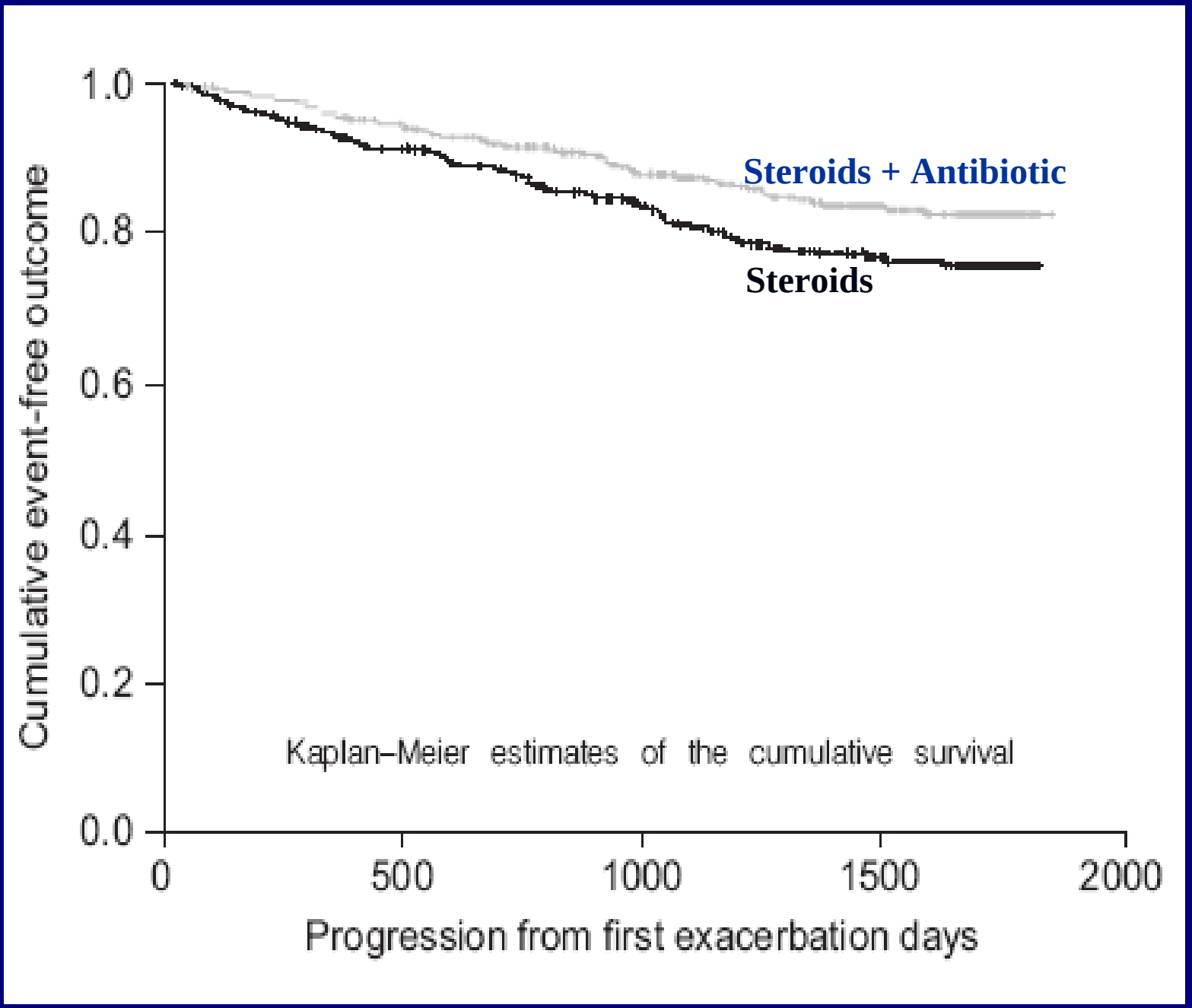
Figure 2 Kaplan–Meier estimates of the cumulative survival stratified according to treatment type.

Thorax 2008;63;968-973

Table 2 Hazard ratios of determinants of developing a next exacerbation after oral corticosteroids with antibiotics—compared with oral corticosteroids only—treatment in a multivariable Cox model

	HR of new exacerbation	99% CI for hazard ratio	
		Lower	Upper
Antibiotics added to treatment with oral corticosteroids			
0–3 months following treatment	0.62	0.60	0.65
3–6 months following treatment	0.68	0.65	0.73
6–12 months following treatment	1.03	0.96	1.12
>12 months following treatment	1.31	1.18	1.45
Exposure to antibiotics after previous exacerbation	0.82	0.78	0.87
Female sex	0.95	0.91	1.00
Inhaled corticosteroids as maintenance medication	0.91	0.84	0.98
Co-medication cardiovascular	1.16	1.10	1.23
Co-medication for diabetes	1.05	0.98	1.12
Hospitalisation* for COPD†	1.45	1.35	1.57
Hospitalisation for pneumonia	1.19	1.05	1.34

Thorax 2008;63;968-973



Eur Respir J 2009; 33: 282–288

TABLE 2 Hazard ratios (HRs) of developing a subsequent exacerbation, in a Cox proportional hazards model

	HR (95% CI) of subsequent exacerbation
OSA *versus* OS	
0–3 months after treatment	0.72 (0.62–0.83)
3–6 months after treatment	0.85 (0.70–1.04)
6–12 months after treatment	1.02 (0.80–1.30)
>12 months after treatment	1.22 (0.89–1.66)
Exposure to antibiotics after previous exacerbation	0.56 (0.45–0.71)
Female sex	0.91 (0.75–1.10)
Inhaled corticosteroids as maintenance medication#	0.87 (0.68–1.12)
Co-medication	
Cardiovascular#	1.37 (1.10–1.73)
Diabetes#	0.90 (0.68–1.19)

Eur Respir J 2009; 33: 282–288

JAMA®

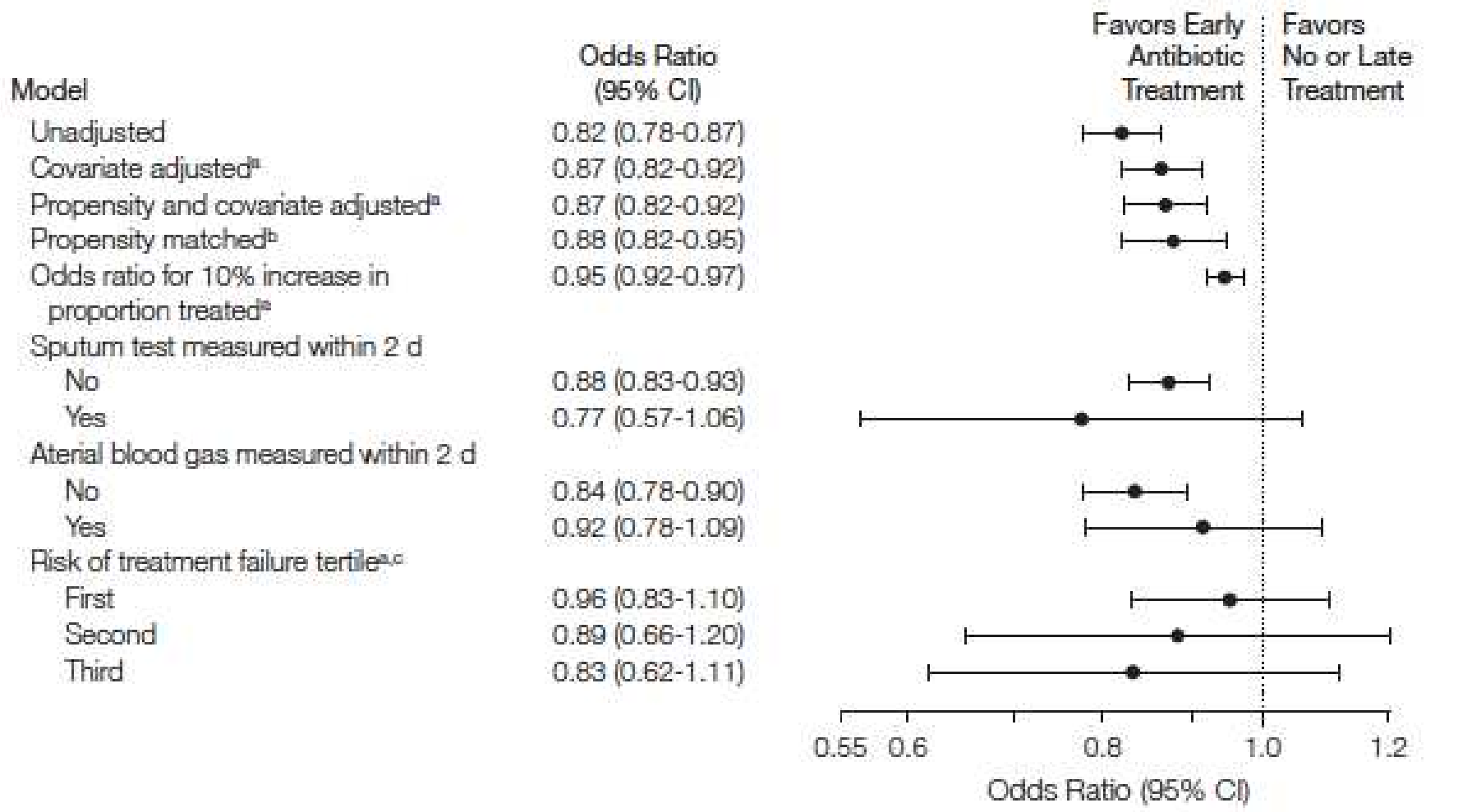
Online article and related content current as of June 29, 2010.

Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Michael B. Rothberg; Penelope S. Pekow; Maureen Lahti; et al.

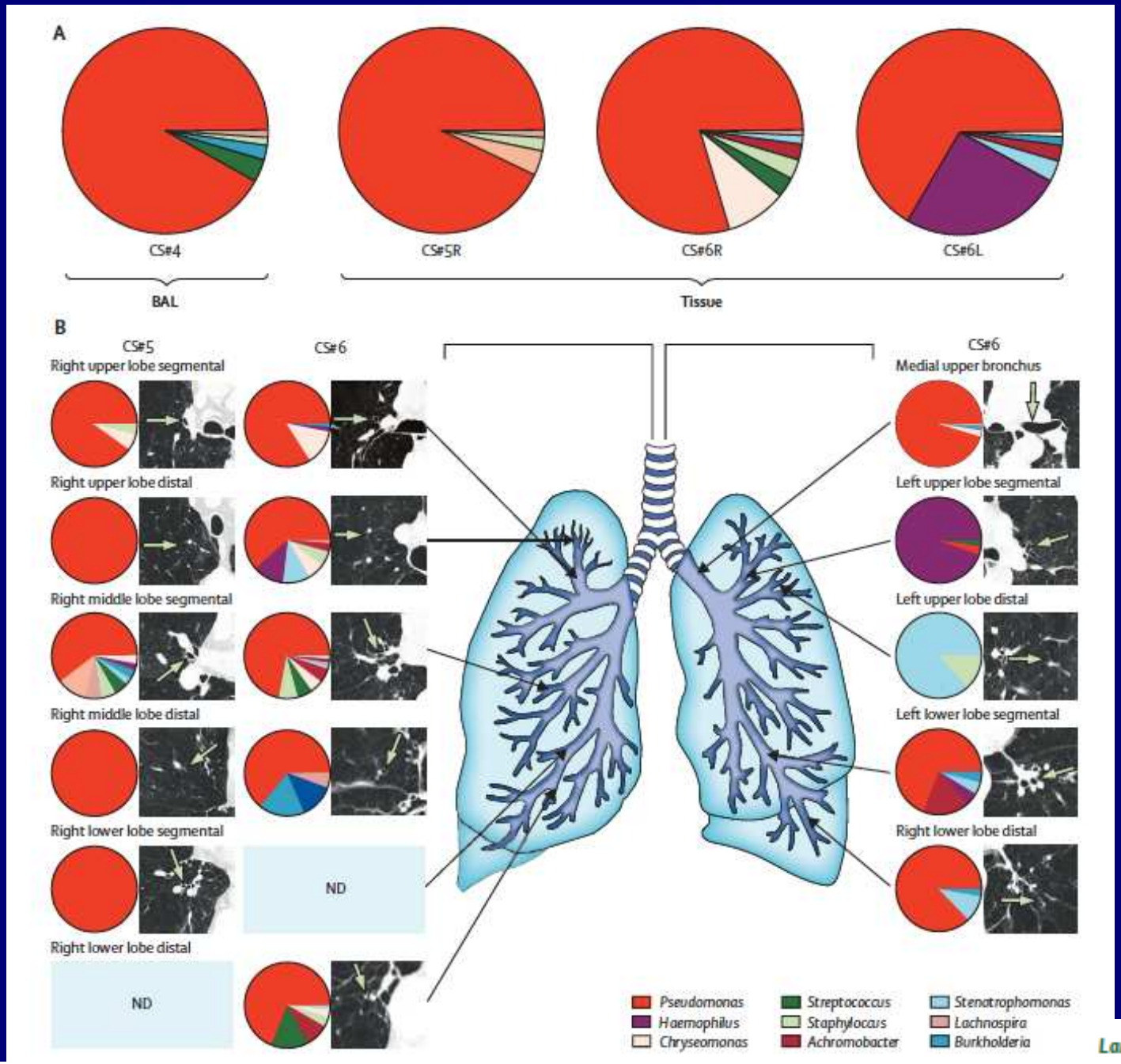
JAMA. 2010;303(20):2035-2042 (doi:10.1001/jama.2010.672)

Figure 1. Treatment Failure for Early Antibiotic Treatment vs Late or No Treatment



Rothberg MB et al. JAMA 2010

Bacterial community profiles for explanted lung from patients with severe COPD



Lancet 2011; 378: 1038-47

Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations

Am J Respir Crit Care Med Vol 178. pp 1139–1147, 2008

Terence A. R. Seemungal[1,2*], Tom M. A. Wilkinson[2*], John R. Hurst[2], Wayomi R. Perera[2], Ray J. Sapsford[2], and Jadwiga A. Wedzicha[2]

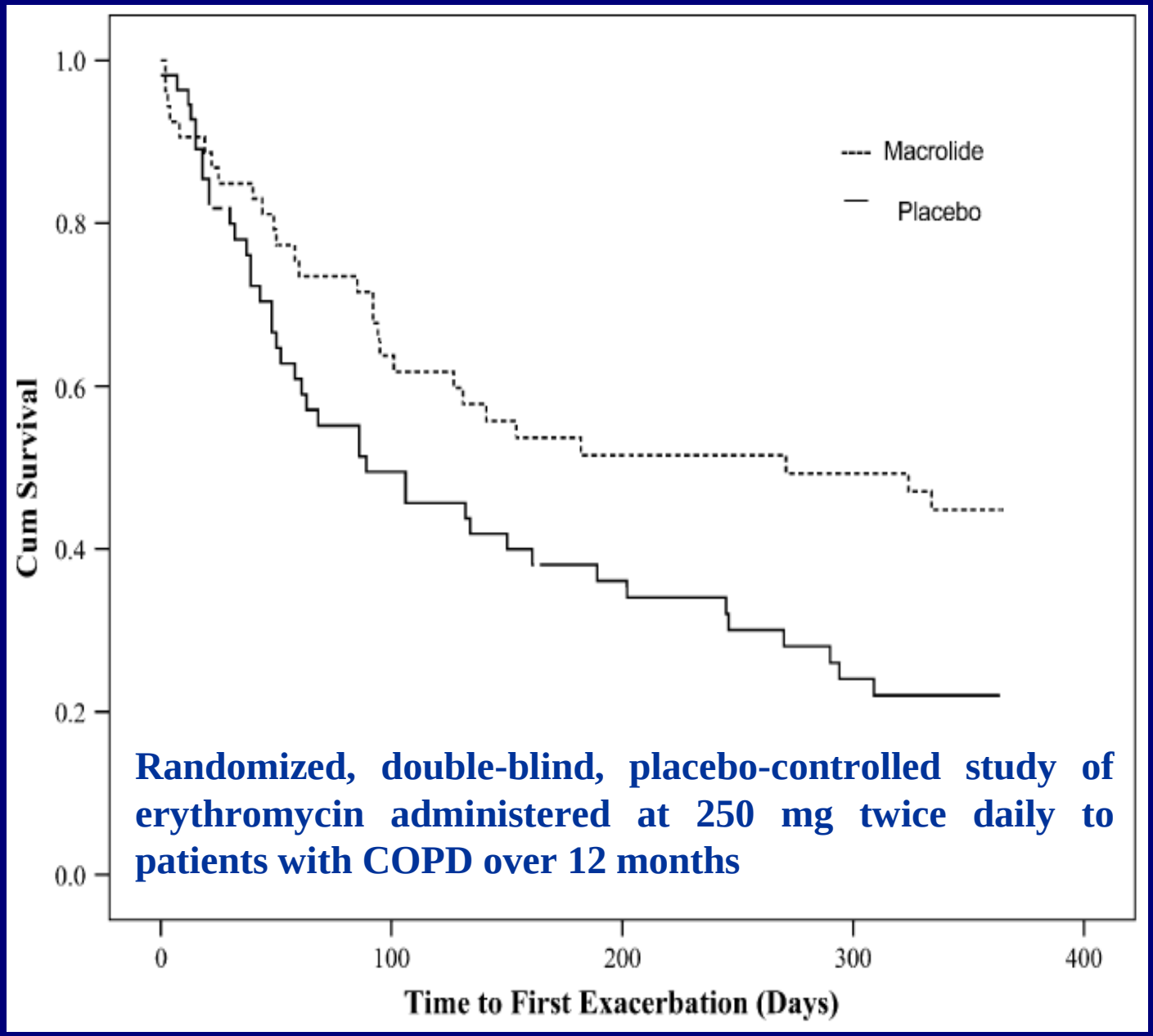
AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Frequent chronic obstructive pulmonary disease (COPD) exacerbations are a major cause of hospital admission and mortality and are associated with increased airway inflammation. Macrolides have airway antiinflammatory actions and may reduce the incidence of COPD exacerbations.

What This Study Adds to the Field

Macrolide therapy was associated with a significant reduction in COPD exacerbations compared with placebo and may be useful in decreasing the excessive disease burden in this patient population.



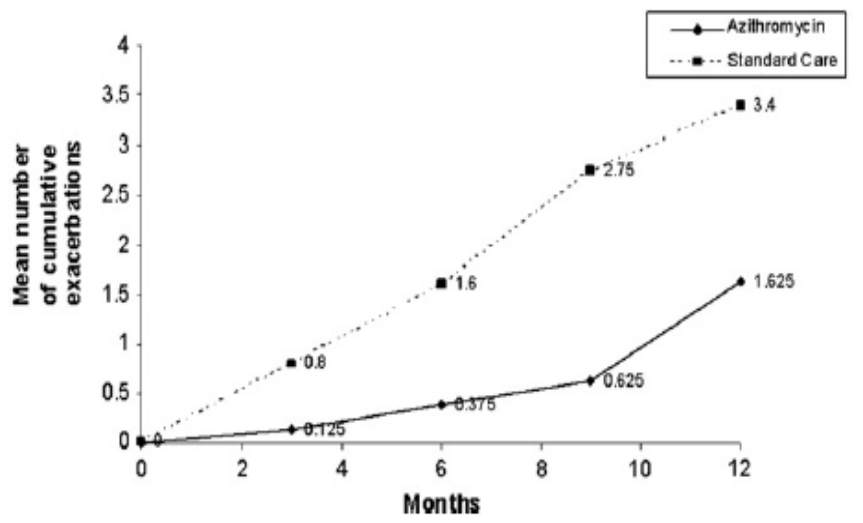
Randomized, double-blind, placebo-controlled study of erythromycin administered at 250 mg twice daily to patients with COPD over 12 months

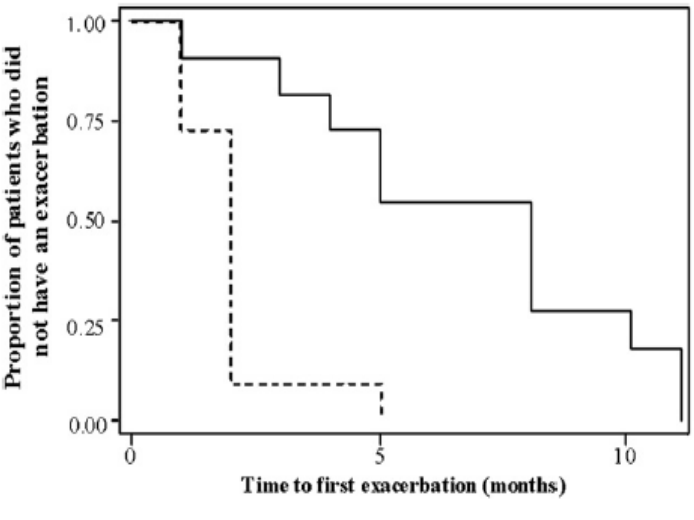
Am J Respir Crit Care Med Vol 178. pp 1139–1147, 2008

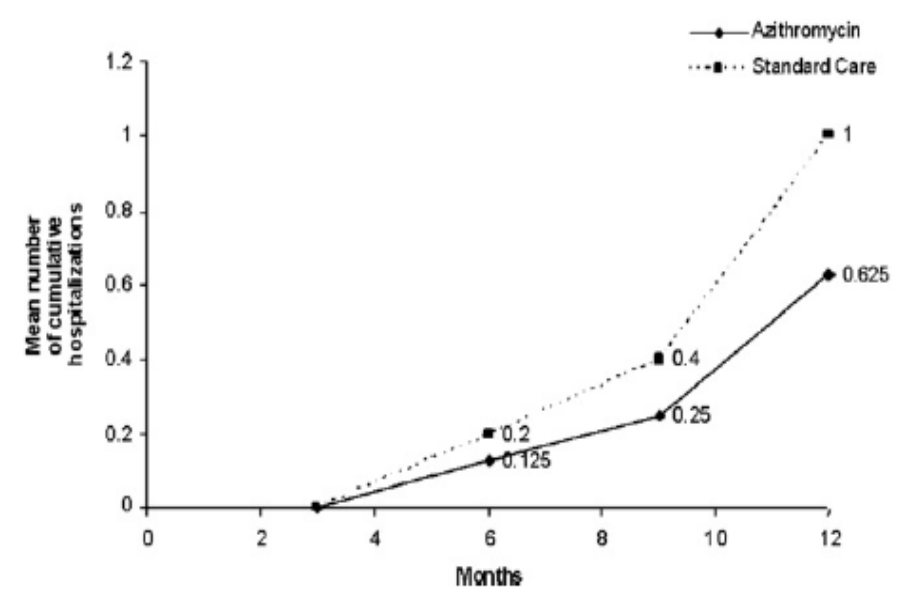
Long-term azithromycin use in patients with chronic obstructive pulmonary disease and tracheostomy☆

Pulmonary Pharmacology & Therapeutics 23 (2010) 200–207

Francesco Blasi [a,*], Daniela Bonardi [a], Stefano Aliberti [a], Paolo Tarsia [a], Marco Confalonieri [b], Omar Amir [c], Mauro Carone [d], Fabiano Di Marco [e], Stefano Centanni [e], Enrico Guffanti [f]







The NEW ENGLAND JOURNAL of MEDICINE

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

Azithromycin for Prevention of Exacerbations of COPD

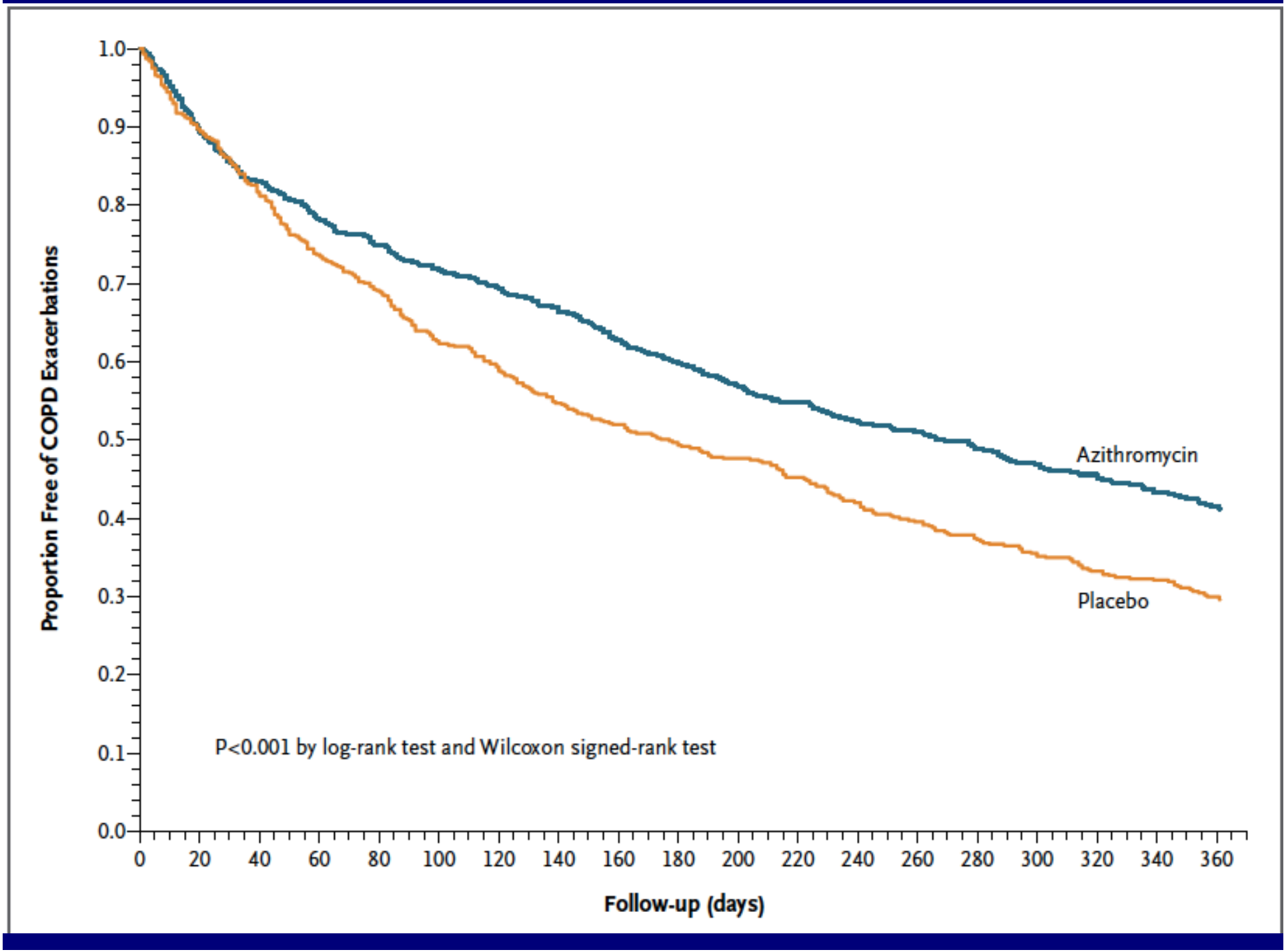
Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

METHODS

We performed a randomized trial to determine whether azithromycin decreased the frequency of exacerbations in participants with COPD who had an increased risk of exacerbations but no hearing impairment, resting tachycardia, or apparent risk of prolongation of the corrected QT interval.

RESULTS

A total of 1577 subjects were screened; 1142 (72%) were randomly assigned to receive azithromycin, at a dose of 250 mg daily (570 participants), or placebo (572 participants)


Proportion Free of COPD Exacerbations
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
Follow-up (days)
Azithromycin
Placebo
P<0.001 by log-rank test and Wilcoxon signed-rank test

The NEW ENGLAND JOURNAL of MEDICINE

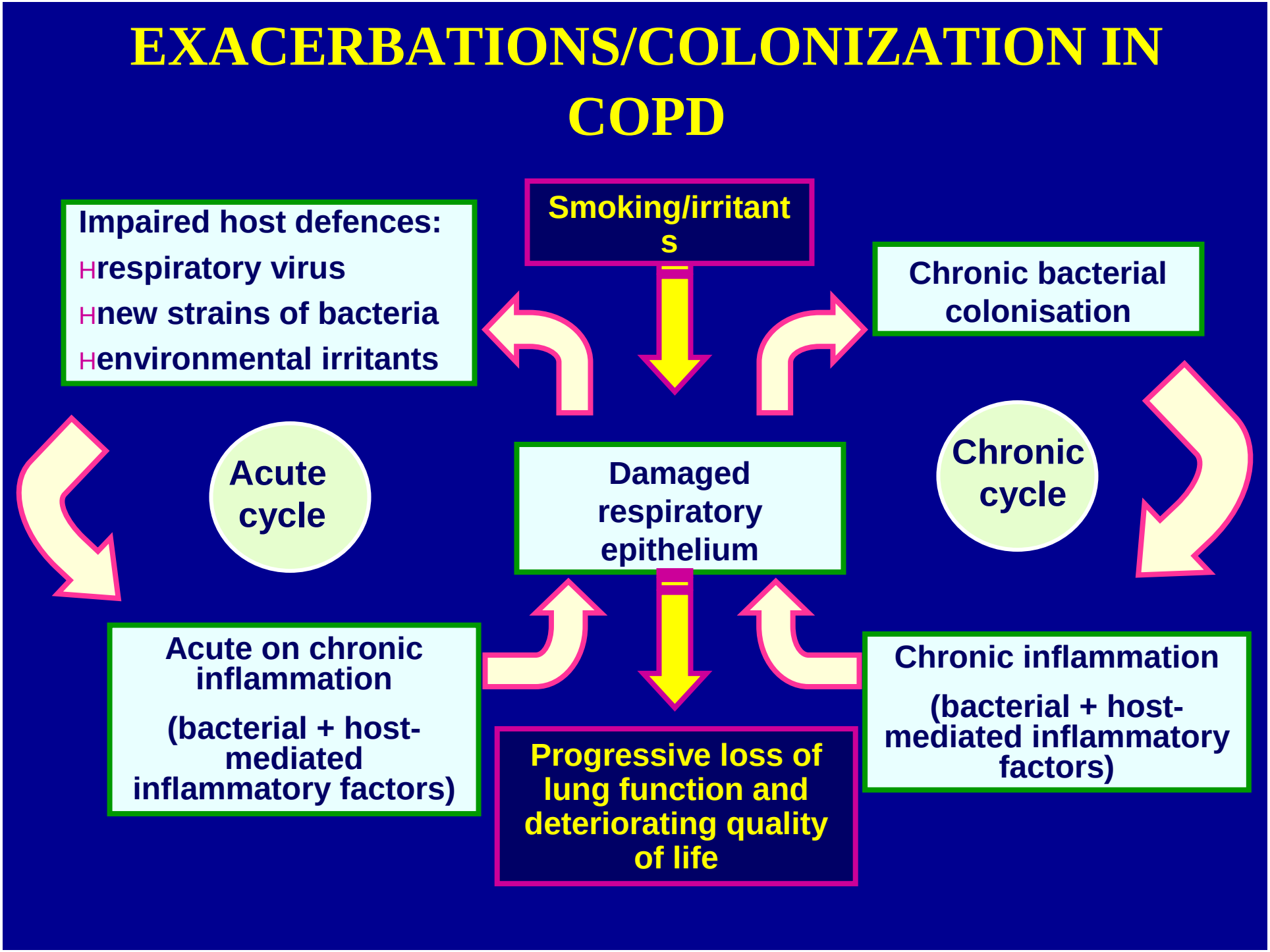
EDITORIALS

Preventing Exacerbations of COPD — Advice from Hippocrates

Nikolaos M. Siafakas, M.D., Ph.D.

However, if azithromycin is going to be used in patients who are known to have frequent exacerbations of COPD, then the local antibiotic resistance patterns should be closely monitored. It also makes sense to ask whether, in such patients, subsequent exacerbations should be treated empirically with a different class of antibiotics. On balance, however, the long-term use of azithromycin to prevent acute exacerbations of COPD would not seem to be at odds with the classical advice of Hippocrates, "Ωφελέειν ου Βλάπτειν" — "Do good, not harm."

EXACERBATIONS/COLONIZATION IN COPD



A new perspective on ‘optimal care’ for patients with COPD

Prim Care Respir J 2011; 20(2): 205-209

Primary Care RESPIRATORY JOURNAL www.thepcrj.org

DISCUSSION PAPER

A new perspective on optimal care for patients with COPD

***Dirkje Postma[a], Antonio Anzueto[b], Peter Calverley[c], Christine Jenkins[d], Barry J Make[e], Frank C Sciurba[f], Thomas Similowski[g], Thys van der Molen[h], Göran Eriksson[i]**

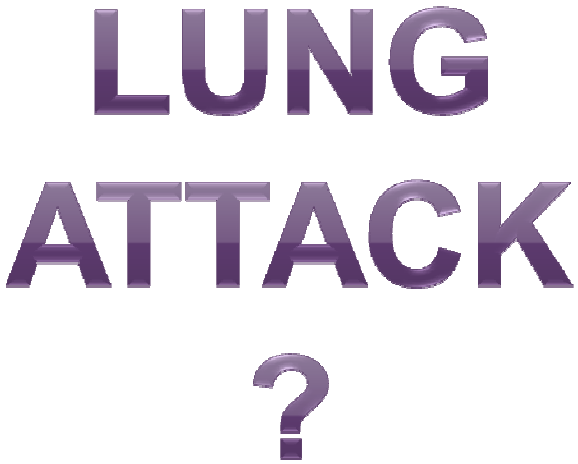
[a] Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, University of Groningen, The Netherlands
[b] Department of Pulmonology, University of Texas Health Sciences Center, San Antonio, Texas, USA
[c] Pulmonary and Rehabilitation Research Group, University Hospital Aintree, Liverpool, UK
[d] University of Sydney and Woolcock Institute of Medical Research, Camperdown, Australia
[e] Division of Pulmonary Sciences and Critical Care Medicine, National Jewish Health, University of Colorado, Denver, USA
[f] Emphysema/COPD Research Center, University of Pittsburgh, Pennsylvania, USA
[g] Service de Pneumologie et Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
[h] Department of General Practice, University Medical Center Groningen, University of Groningen, The Netherlands
[i] AstraZeneca R&D, Lund, Sweden

Received 4th February 2011; revised 29th March 2011; accepted 22nd April 2011; online 11th May 2011

- **The terminologies introduced in this concept paper are – ‘optimal COPD care’, ‘best current control’, and ‘future risk reduction’ reflecting the concept that , to a COPD patient, prevention of future risk is of equal importance to the immediate impact of treating symptoms.**
- **The impact an intervention may have on long-term disease progression is sometimes independent of any effect it may have on current symptoms.**
- **Clinicians already apply this broader approach to risk factors such as hypertension and hypercholesterolaemia. Treatments that reduce high blood pressure and serum cholesterol are nowadays prescribed independently of any acute effects on current symptoms. It has now been suggested that this approach should also be considered in COPD.**

Postma D, Anzueto A, Calverley P, et al. *Prim Care Respir J* **2011**; 20:205-209.

Make every exacerbation count – THORAX May 2011 EDITORIALS

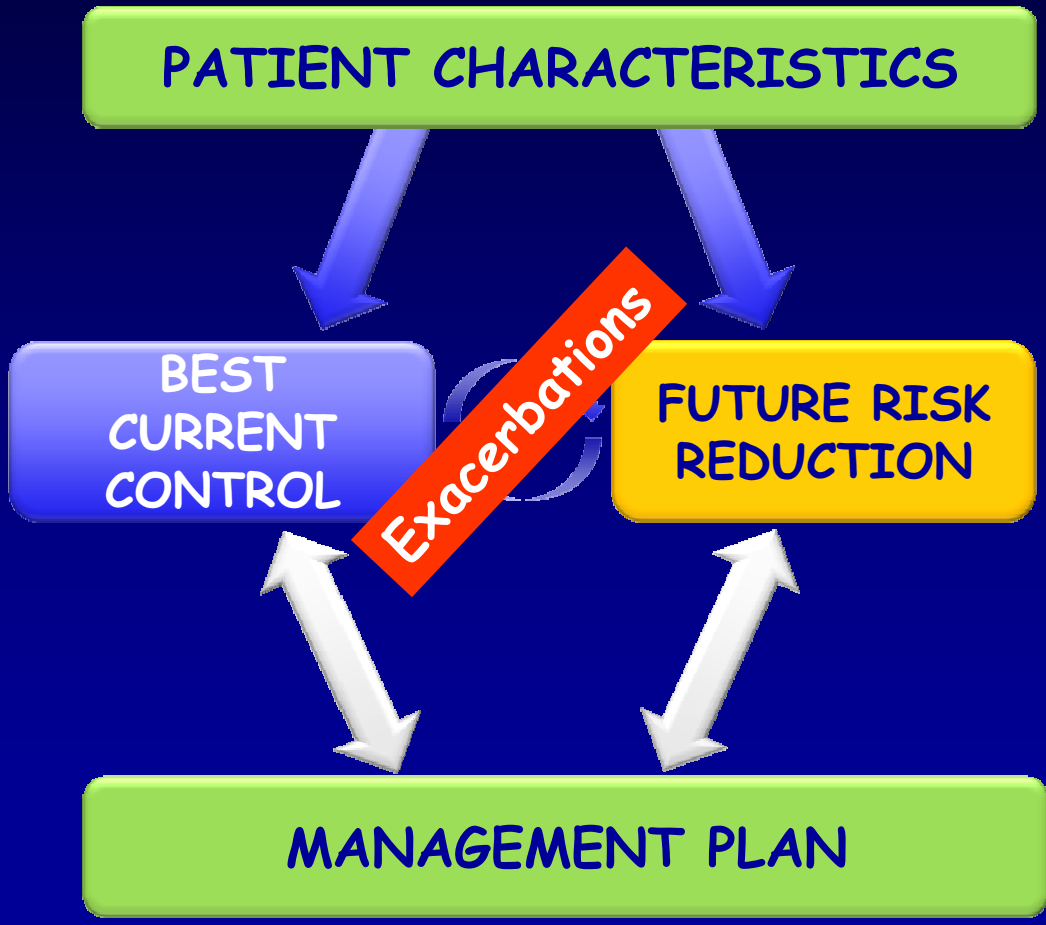


- **“We suspect that the generally accepted view of exacerbation is that it is like the exasperation of falling over on an icy road temporarily inconvenient, but reversible by dusting oneself down and taking paracetamol and whisky”**
- **“A lung attack is not a temporary inconvenience, it can be associated with permanent damage and is a sign of a worse outlook unless something is done**
- **In the case of an acute myocardial infarction initial management is much more aggressive, risk stratification is routine and patients are usually discharged on a medication bundle. In addition standard of care involves patients being enrolled in well-funded cardiac rehabilitation programs.**

Bush A & Pavord I. *Thorax* 2011;66:367

FitzGerald JM. *Thorax* 2011;66:365-66

A NEW PERSPECTIVE ON 'OPTIMAL CARE' FOR PATIENTS WITH COPD



Postma D, et al. *Prim Care Respir J* **2011**; 20:205-209.

CONCLUSIONS

- COPD phenotypes can be identified across COPD stages and will need different therapeutic approaches
- Frequent exacerbators are more likely to have chronic bronchitis
- Frequent exacerbations contribute to disease progression in COPD
- Important phenotype for targeting therapies

THANK YOU FOR YOUR ATTENTION