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COPD : A Modifiable Risk Factor for Cardiovascular Disease? - Main Session

Sunday, 18 August 2013 Start 11:30am Duration: 30mins Plenary



COPD A MODIFIABLE RISK FACTOR IN COPD?
South GPCME Meeting,Dunedin Sunday 18th August 2013

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DISCLAIMER

Professor Neil Barnes, has been appointed GSK Global Respiratory Medical Head effective 1st October 2013.

LEADING CAUSES OF DEATH

	1990		2020
Ischemic heart disease	1	→	1
Cerebrovascular disease	2	→	2
COPD	**6**	→	**3**
Lower respiratory infection	3	→	4
Lung cancer	10	→	5
Road traffic accidents	9	→	6
Tuberculosis	7	→	7
Stomach cancer	14	→	8

FEV1 AS A RISK FACTOR FOR CVS DISEASE

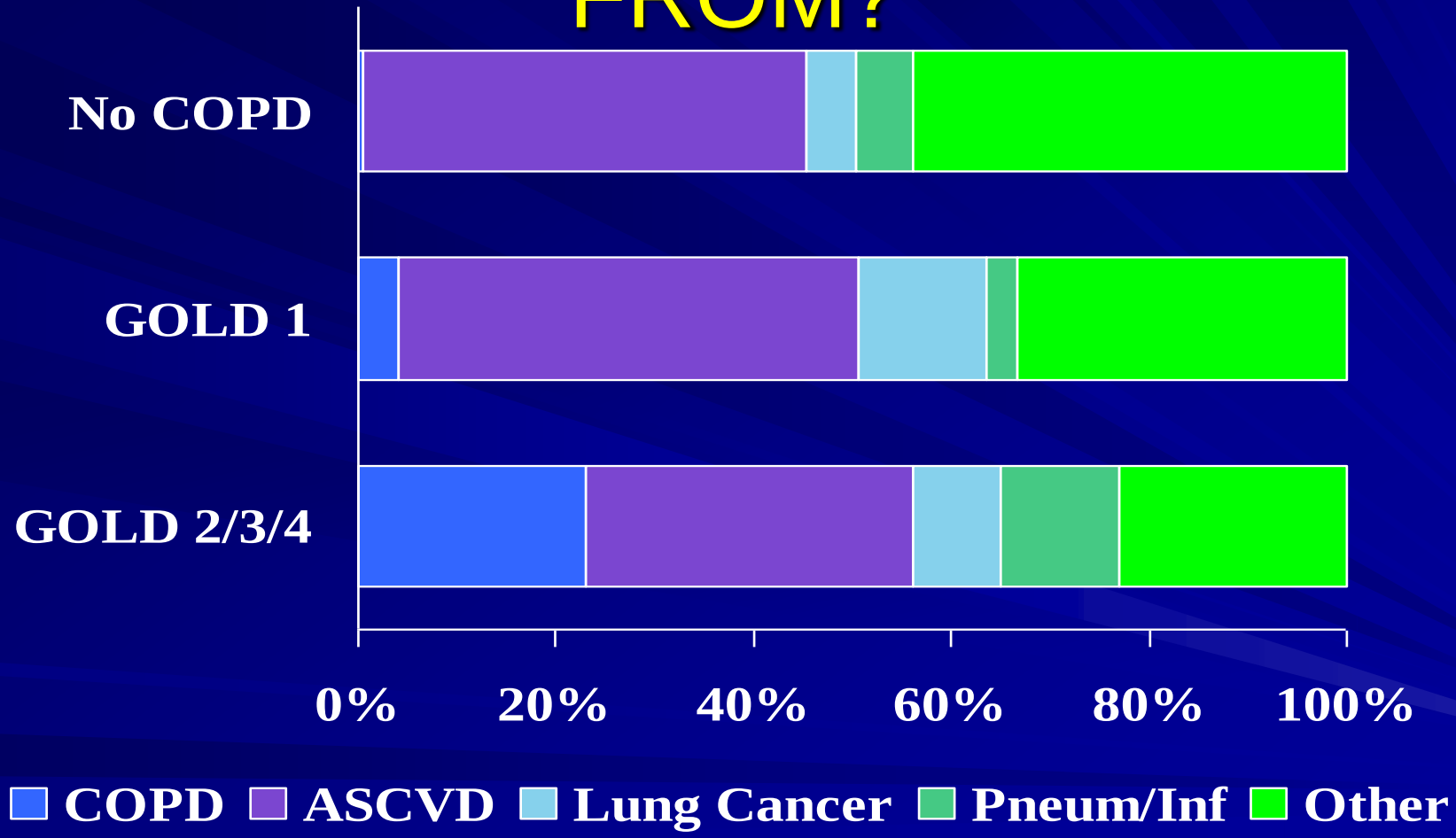
- Ranked second to smoking[1]
- 2 to 5 fold increase in cardiovascular mortality[2]
  - independent of smoking and other risk factors for coronary artery disease
- Incidence of ventricular arrhythmia[3]

1. Manino et al *ERJ* 2006
2. Friedman, *NEJM*, 1976
3. Gulsvik, *Scand J Respir Dis,* 1978

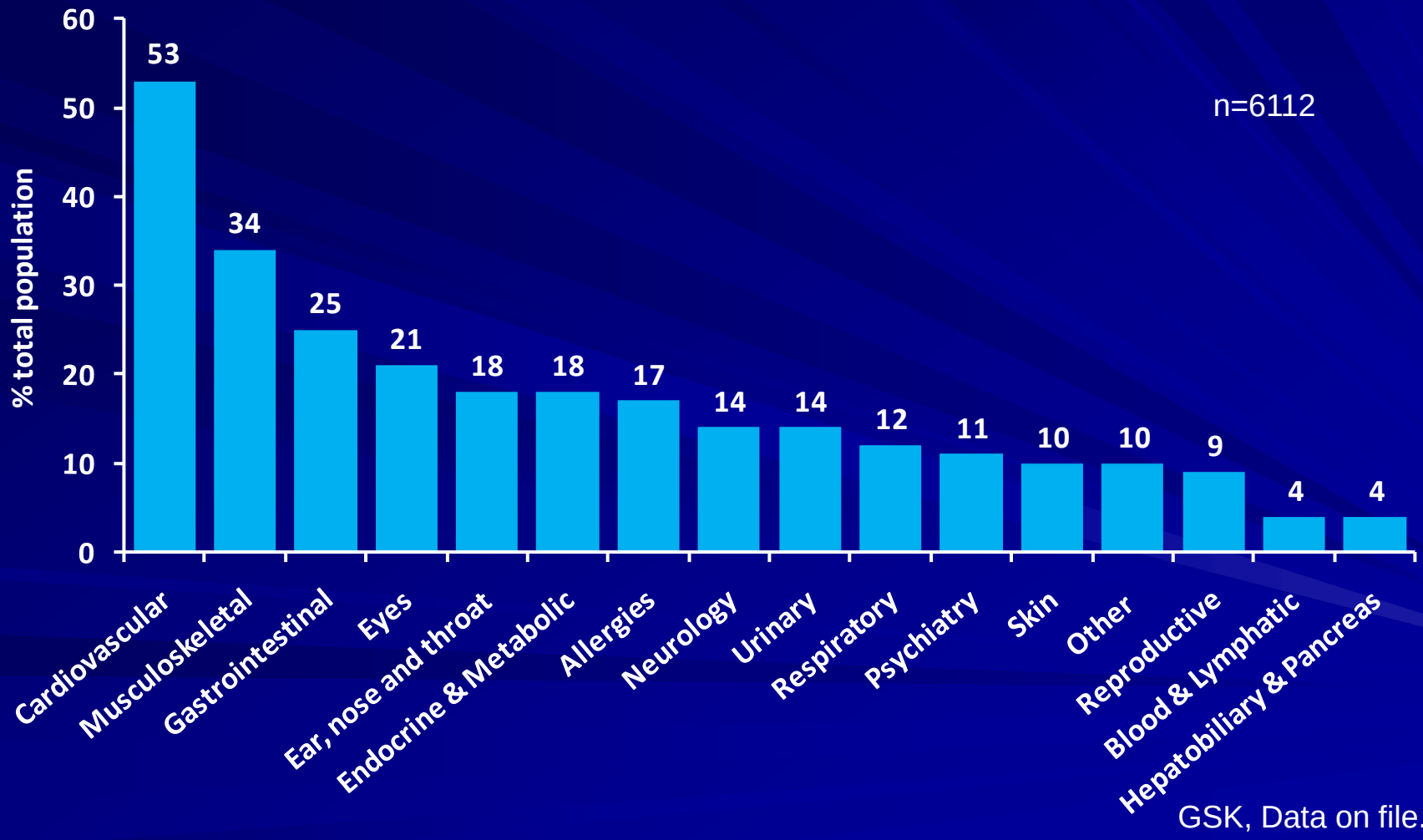
CO-MORBIDITIES

- Cardiac
- Hypertension
- Diabetes
- Metabolic syndrome
- Osteoporosis
- Muscle wasting
- Depression
- Anxiety
- Lung cancer

WHAT DO COPD PATIENTS DIE FROM?

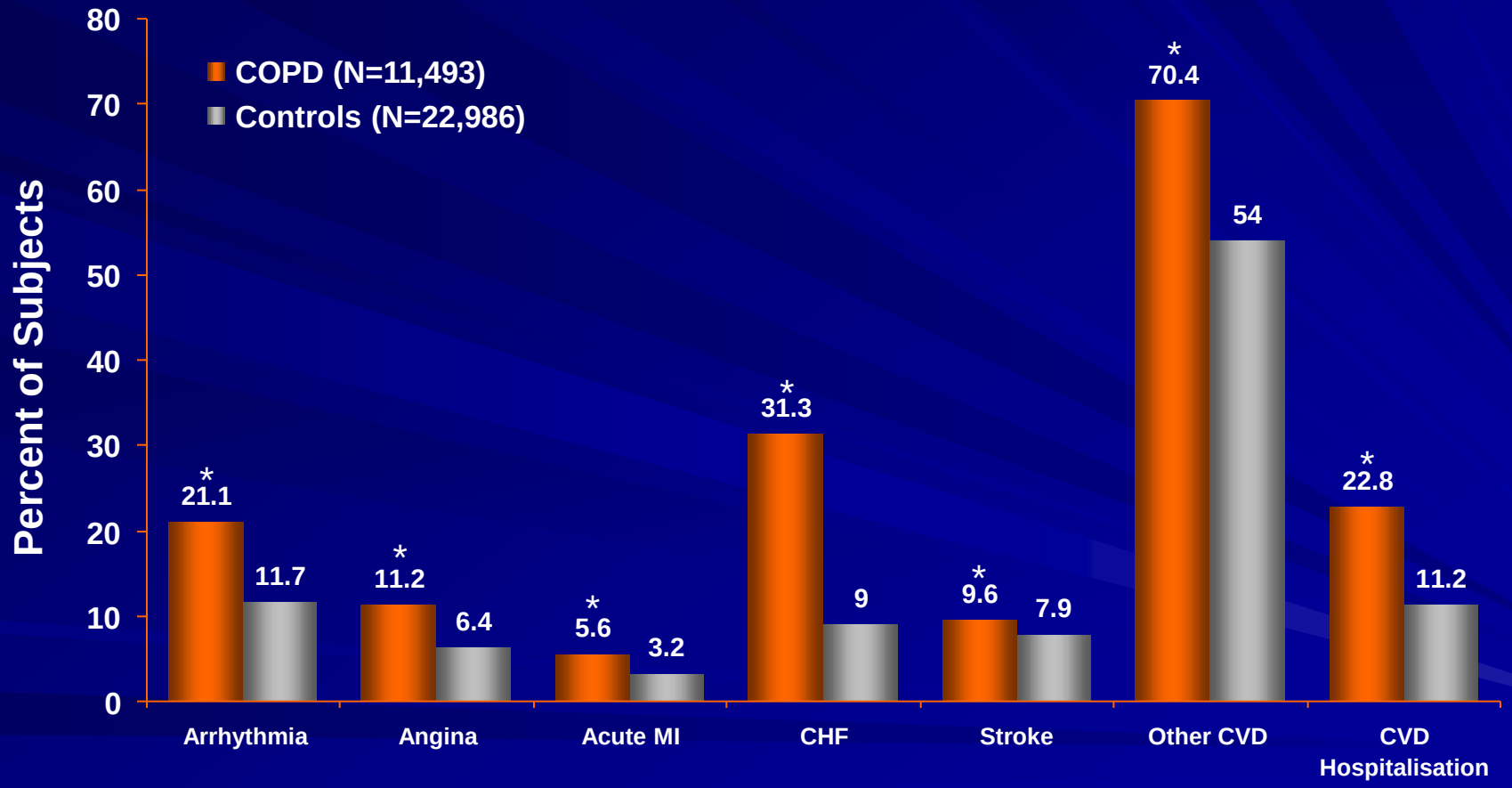


TORCH STUDY COMORBIDITIES



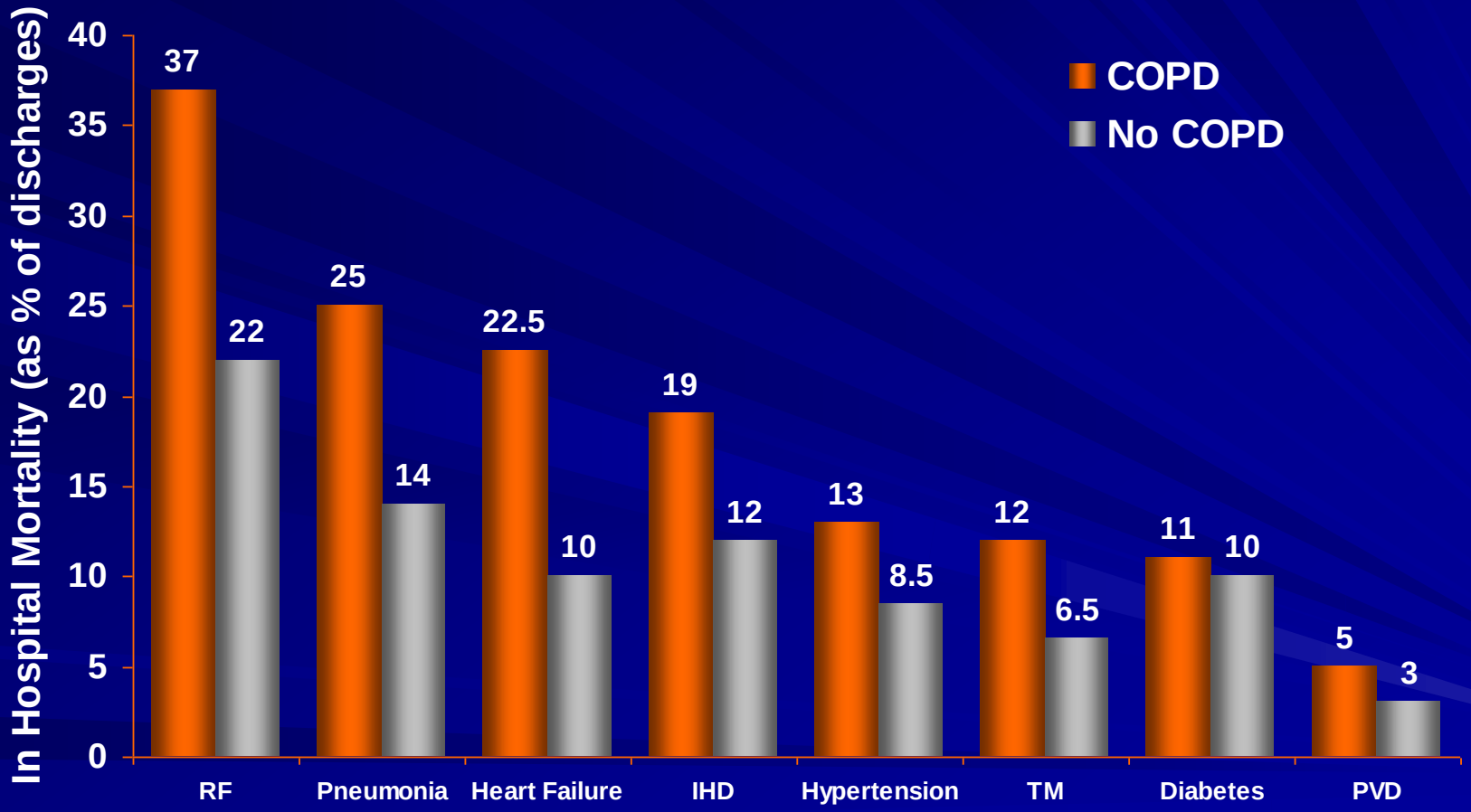
GSK, Data on file.

CARDIOVASCULAR DISEASE IN COPD AND CONTROLS



Curkendall SM, et al. *Am J Epidemiol.* 2006;16:63-70.

IN-HOSPITAL MORTALITY & COMORBIDITIES IN COPD



Holguin F, et al. Chest. 2005;128:2005

REDUCED LONG-TERM SURVIVAL OF PATIENTS WITH COPD AFTER ANGIOPLASTY

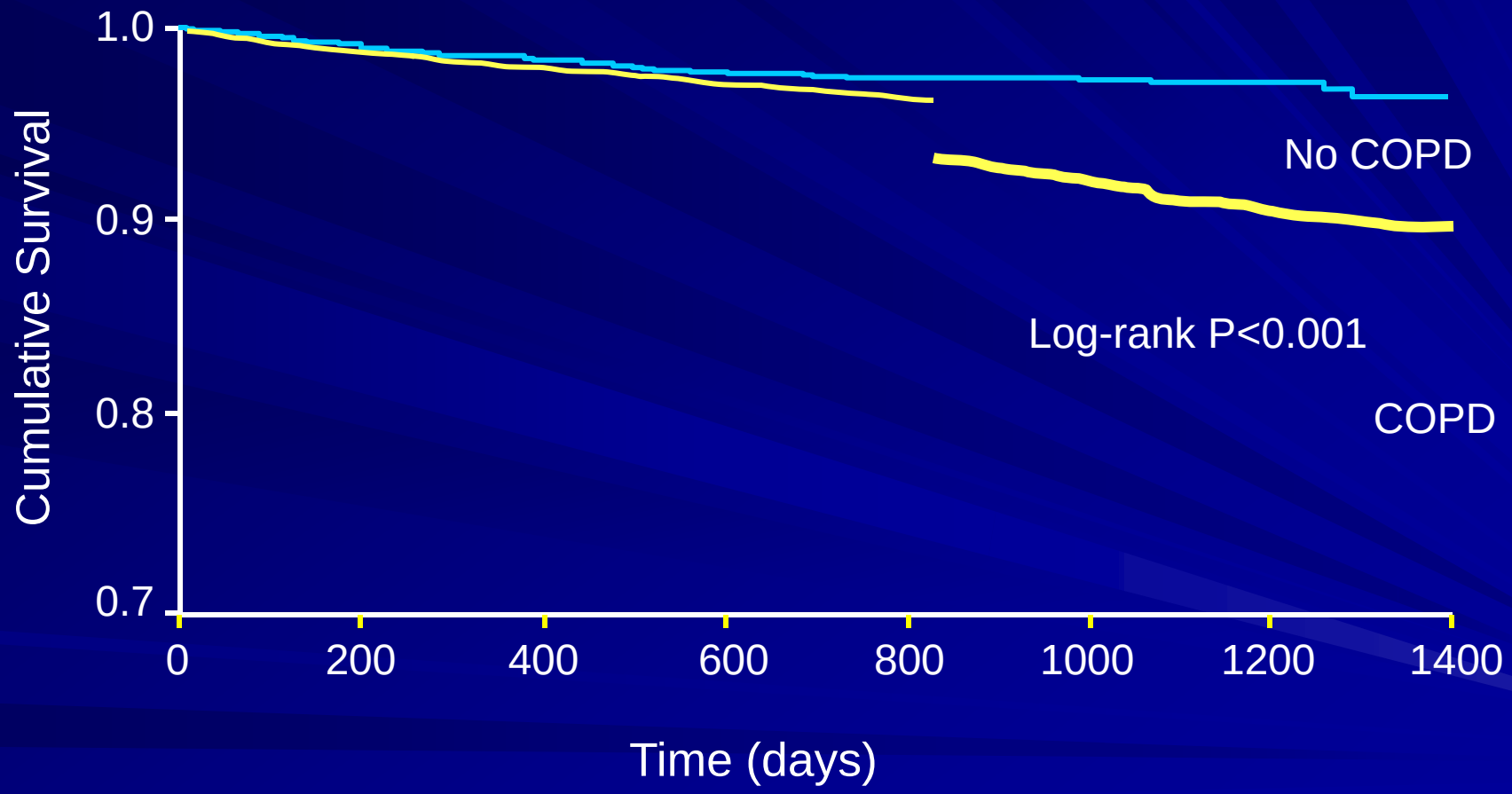
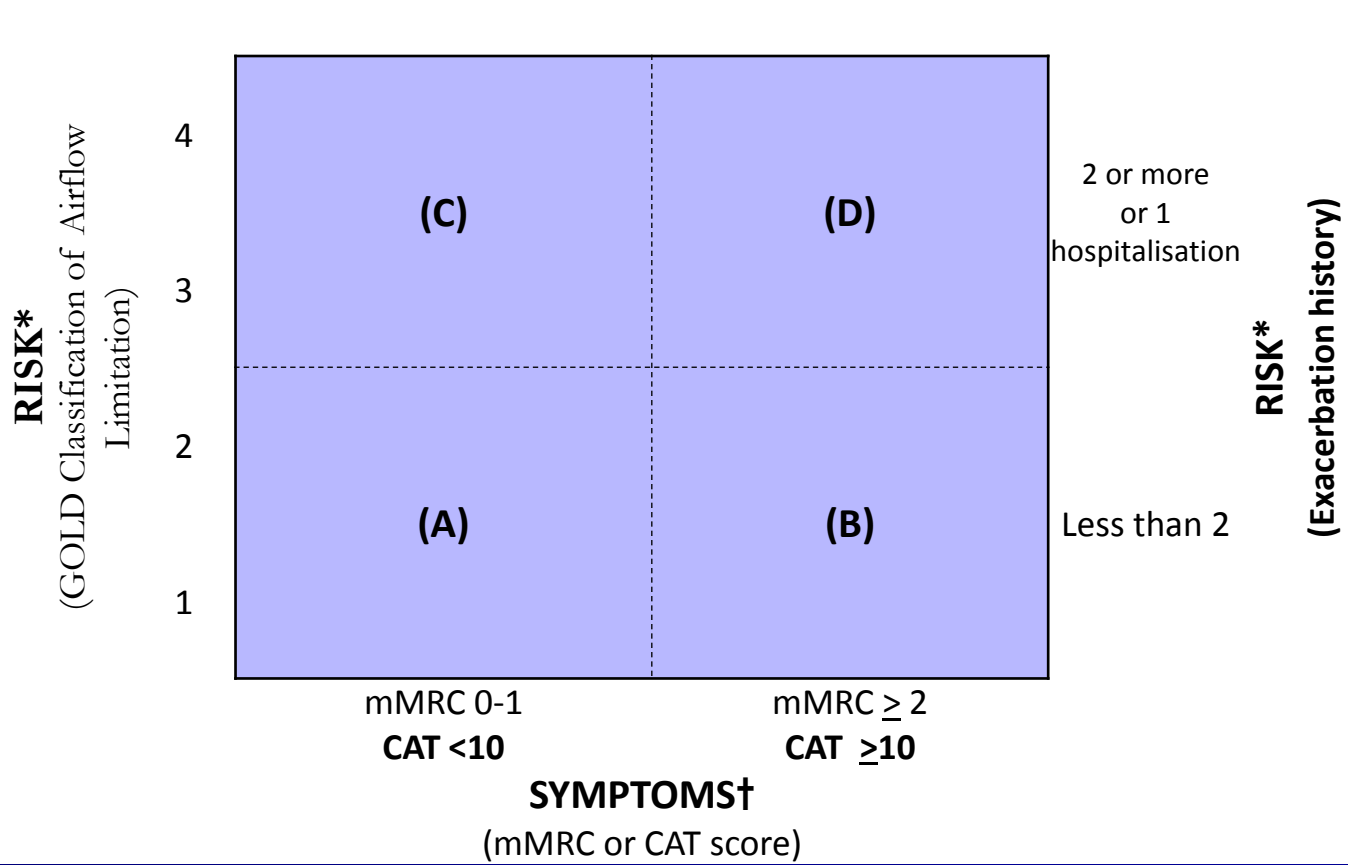


Figure 1. Kaplan-Meier curve for long-term survival in patients with and without COPD who underwent PCI.

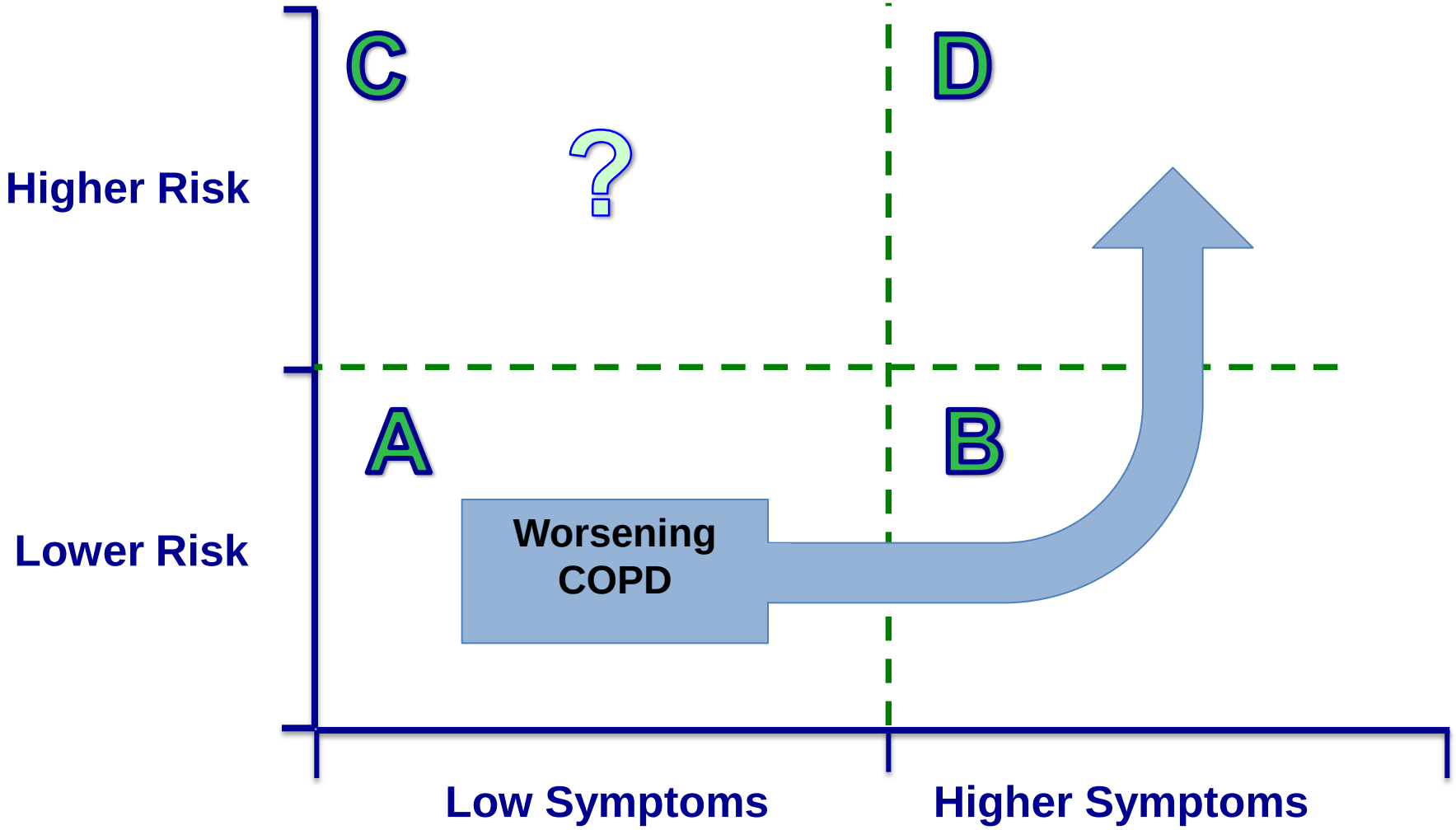
Berger J Am Card 2004

ASSESSMENT OF COPD GOLD 2013

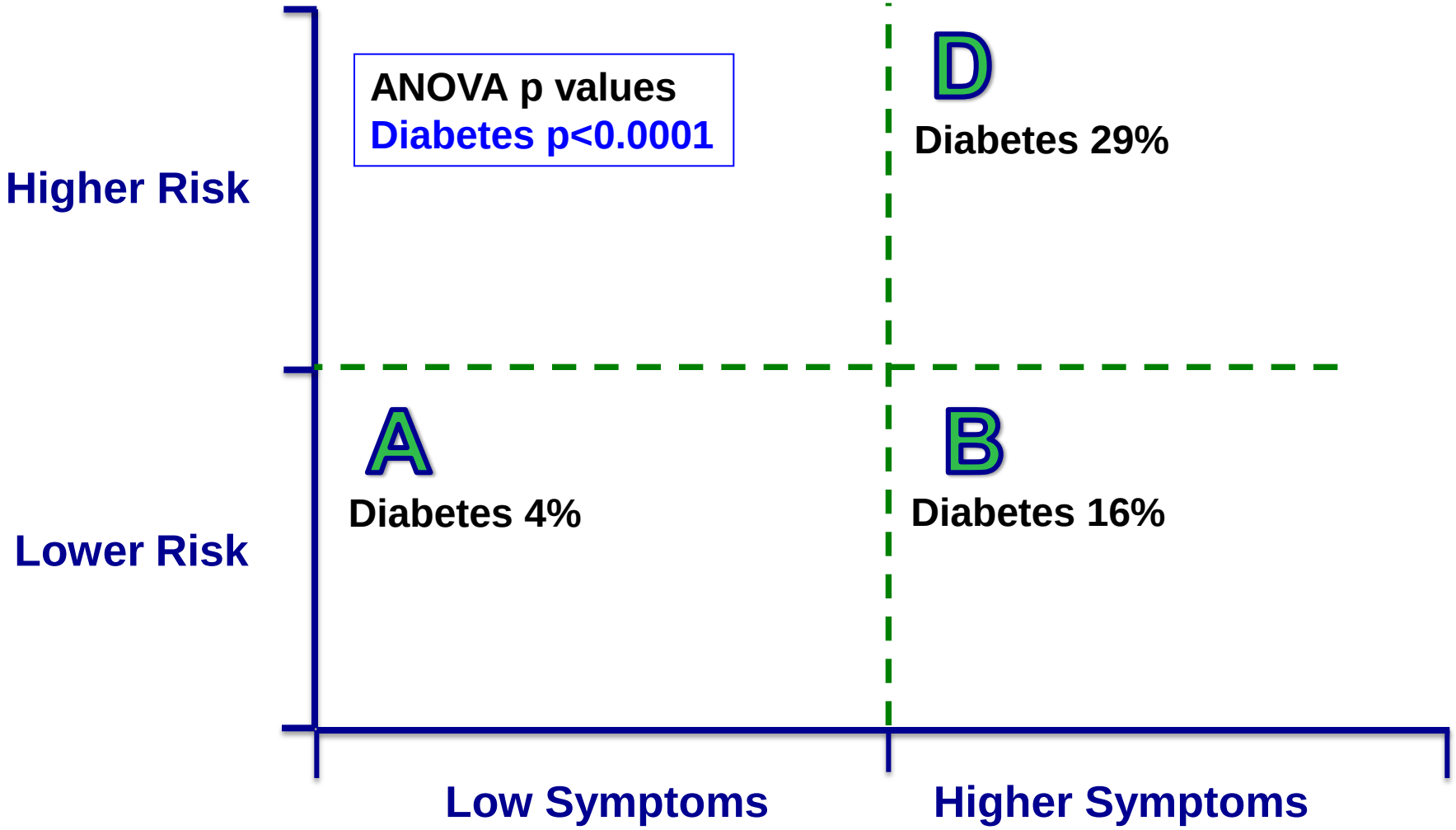


GOLD 2013; www.goldcopd.org

Severity assessed using the new system



Patients in European 1y and 2y care survey (n=1191)
'New' GOLD classified – co-morbidity



Jones et al ERS 2012

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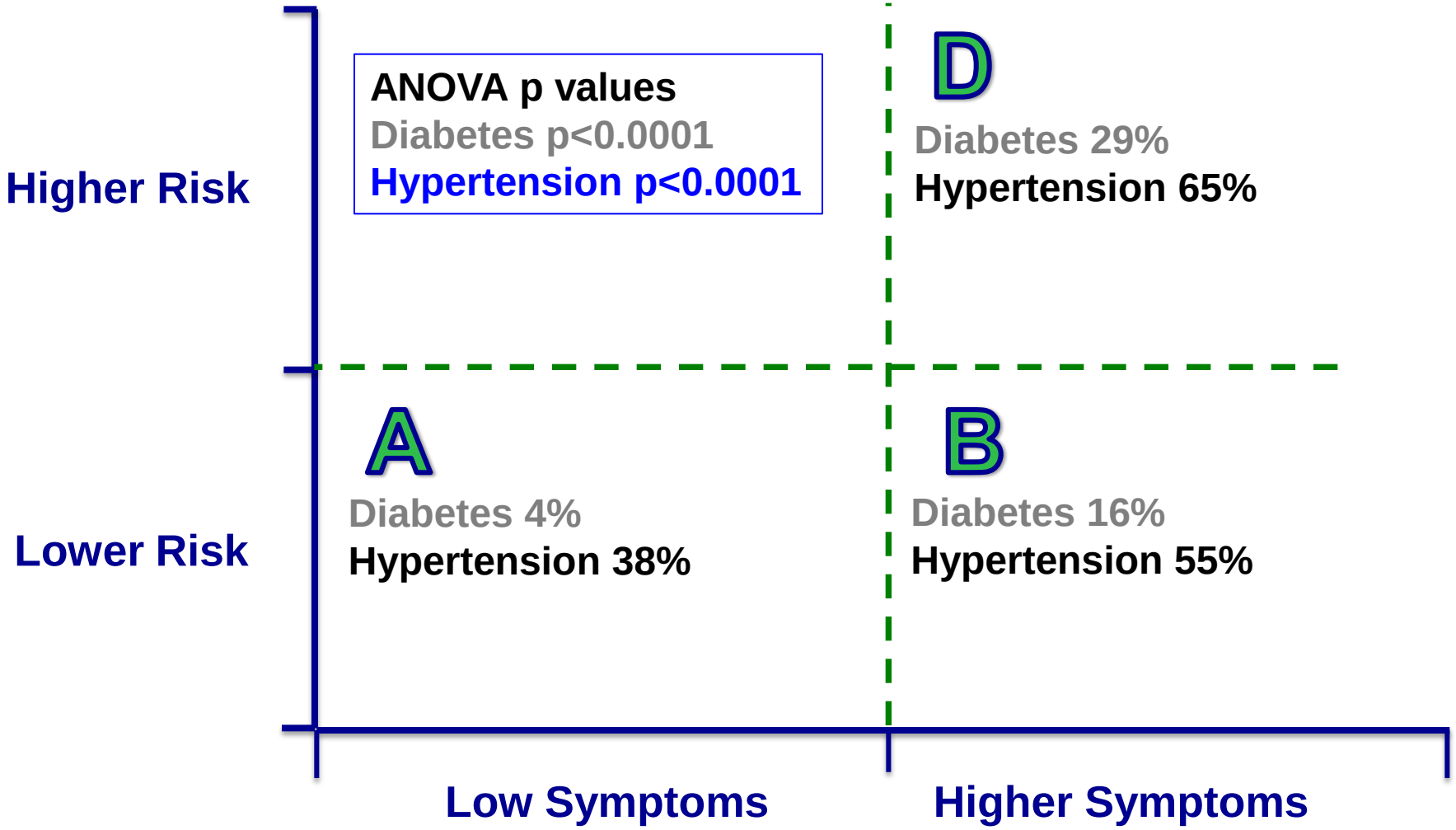

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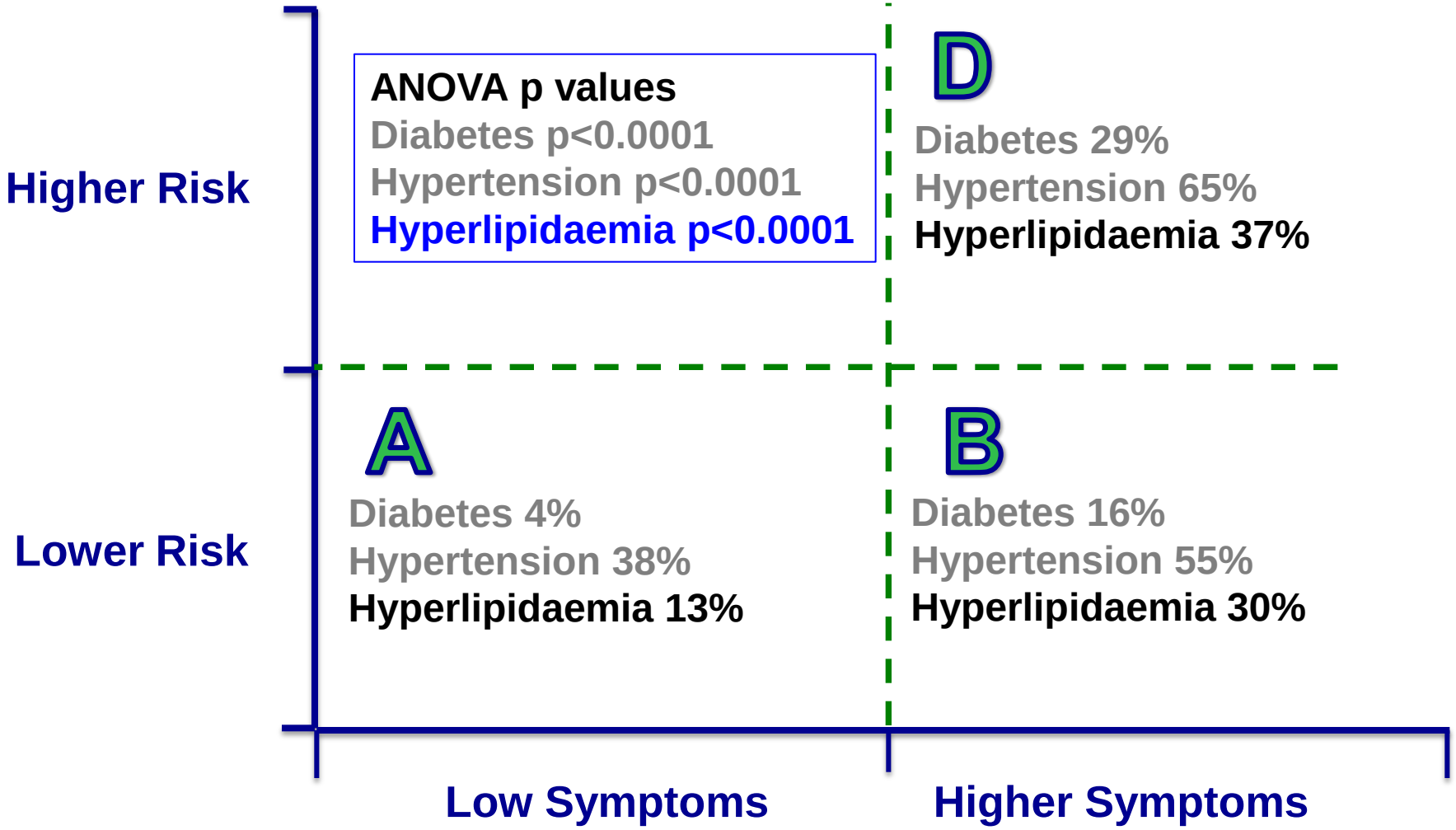

Jones et al ERS 2012

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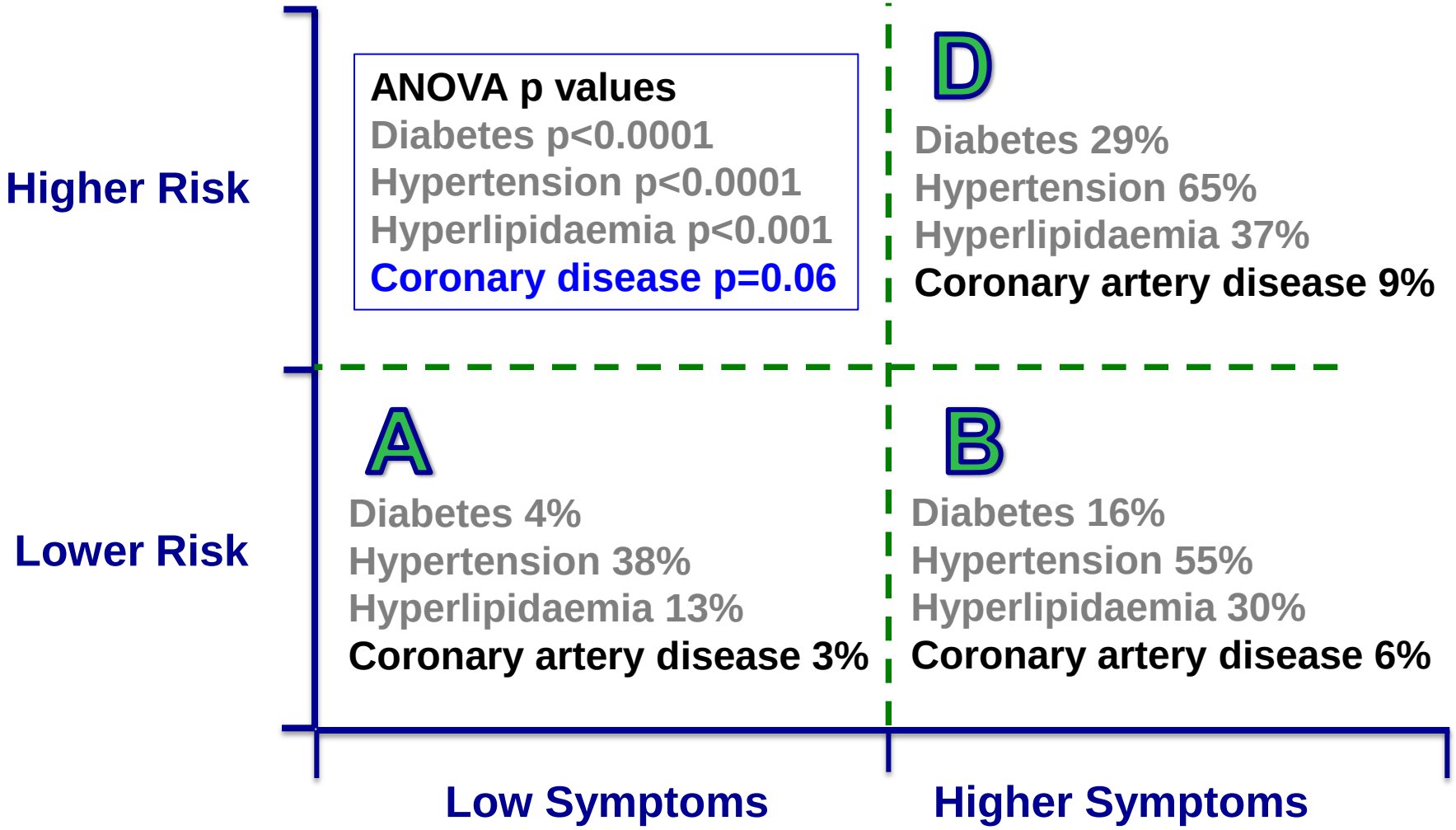

Jones et al ERS 2012

POSSIBLE MECHANISM OF LINK BETWEEN COPD AND CVS DISEASE

- Coincidence
- Smoking
- Hypoxia
- Shared genetic risk
- Hyperinflation
- Inflammation

POSSIBLE MECHANISM OF LINK BETWEEN COPD AND CVS DISEASE

- Coincidence
- Smoking

Can be ruled out

- Hypoxia
- Shared genetic risk
- Hyperinflation
- Inflammation

POSSIBLE MECHANISM OF LINK BETWEEN COPD AND CVS DISEASE

- Coincidence
- Smoking
- Hypoxia
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- Inflammation

SHARED GENETIC RISK

Table 3. Predicted Values for and Mean Change in Left Ventricular Structure and Function According to Percent Emphysema on CT.*

Variable	Percent Emphysema					Mean Change in LV Measure per 10-Percentage-Point Increase in Emphysema (95% CI)	P Value
	3.5% (N=563)	9.1% (N=563)	15.0% (N=564)	22.5% (N=564)	34.5% (N=562)		
LV end-diastolic volume — ml	124.9	121.8	118.8	115.8	111.2	–4.1 (–4.9 to –3.3)	<0.001
LV end-systolic volume — ml	37.8	36.7	35.4	34.3	32.9	–1.4 (–1.9 to –0.9)	<0.001
LV stroke volume — ml	87.1	85.1	83.4	81.5	78.3	–2.7 (–3.3 to –2.2)	<0.001
Cardiac output — liters/min	5.90	5.72	5.61	5.45	5.27	–0.19 (–0.23 to –0.14)	<0.001
LV ejection fraction — %	70.4	70.5	70.8	70.7	70.7	0.02 (–0.22 to 0.25)	0.89
LV mass — g	138.3	134.7	134.2	131.9	129.3	–2.5 (–3.4 to –1.6)	<0.001

* After multivariate adjustment, Increase in % emphysema was associated with a 4.1 ml decrease in LVEDV.

Barr et al , NEJM 2010

POSSIBLE MECHANISM OF LINK BETWEEN COPD AND CVS DISEASE

- Coincidence
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CONSEQUENCES OF HYPERINFLATION

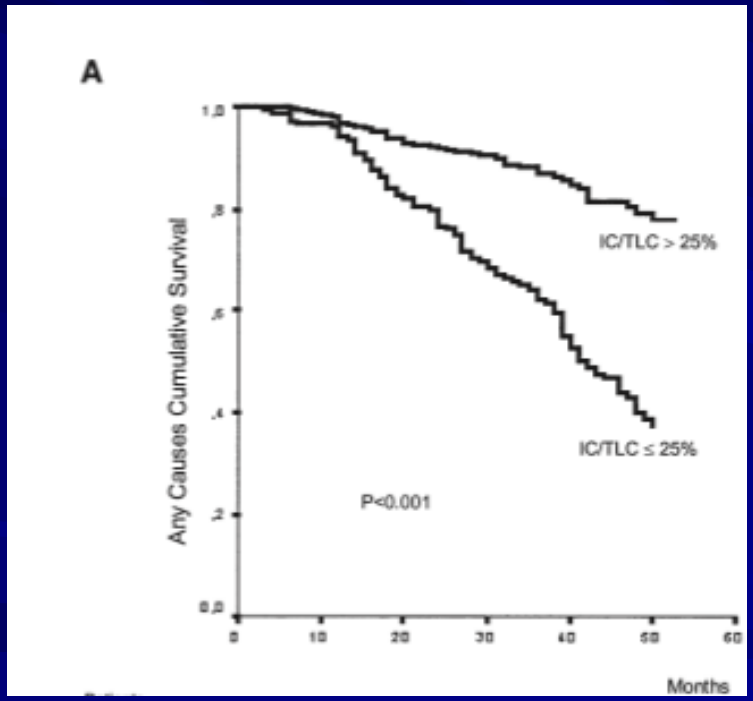
- Stiffness of the parietal pleura, the walls of the cardiac fossa.
  - ? contribute to left and right diastolic dysfunction in the absence of pulmonary hypertension[3]
- Reduction in intrathoracic blood volume related to increased PEEPi[4]

3. Butler J , Chest 1990
4. Jorgensen Chest 2007

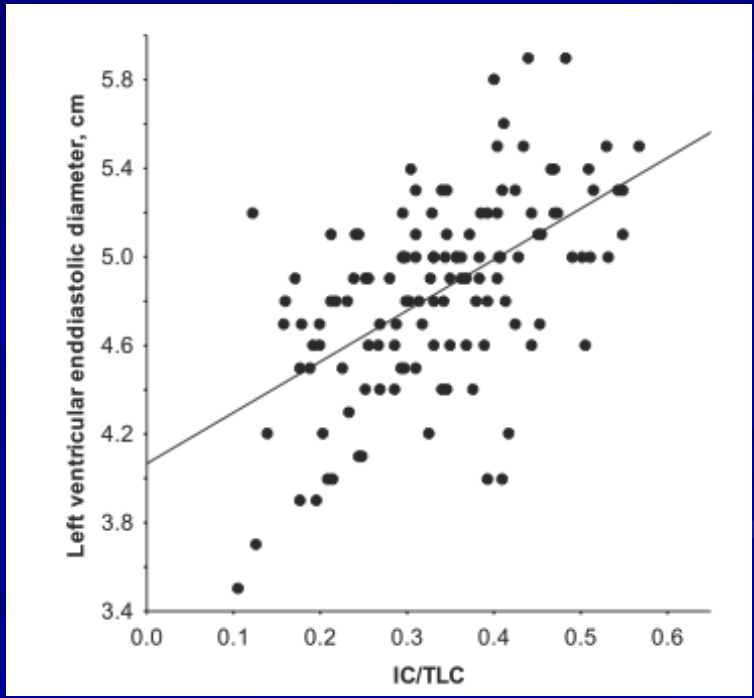
CONSEQUENCES OF HYPERINFLATION

- 2x all cause mortality[1]

  IC/TLC <0.25 vs IC/TLC > 0.25



- Significantly impaired LV diastolic filling pattern compared with a ratio of >0.25 [2]



1. Casanova et al AJRCCM 2005
2. Watz et al Chest 2010

POSSIBLE MECHANISM OF LINK BETWEEN COPD AND CVS DISEASE

- Coincidence
- Smoking
- Hypoxia
- Shared genetic risk
- Hyperinflation
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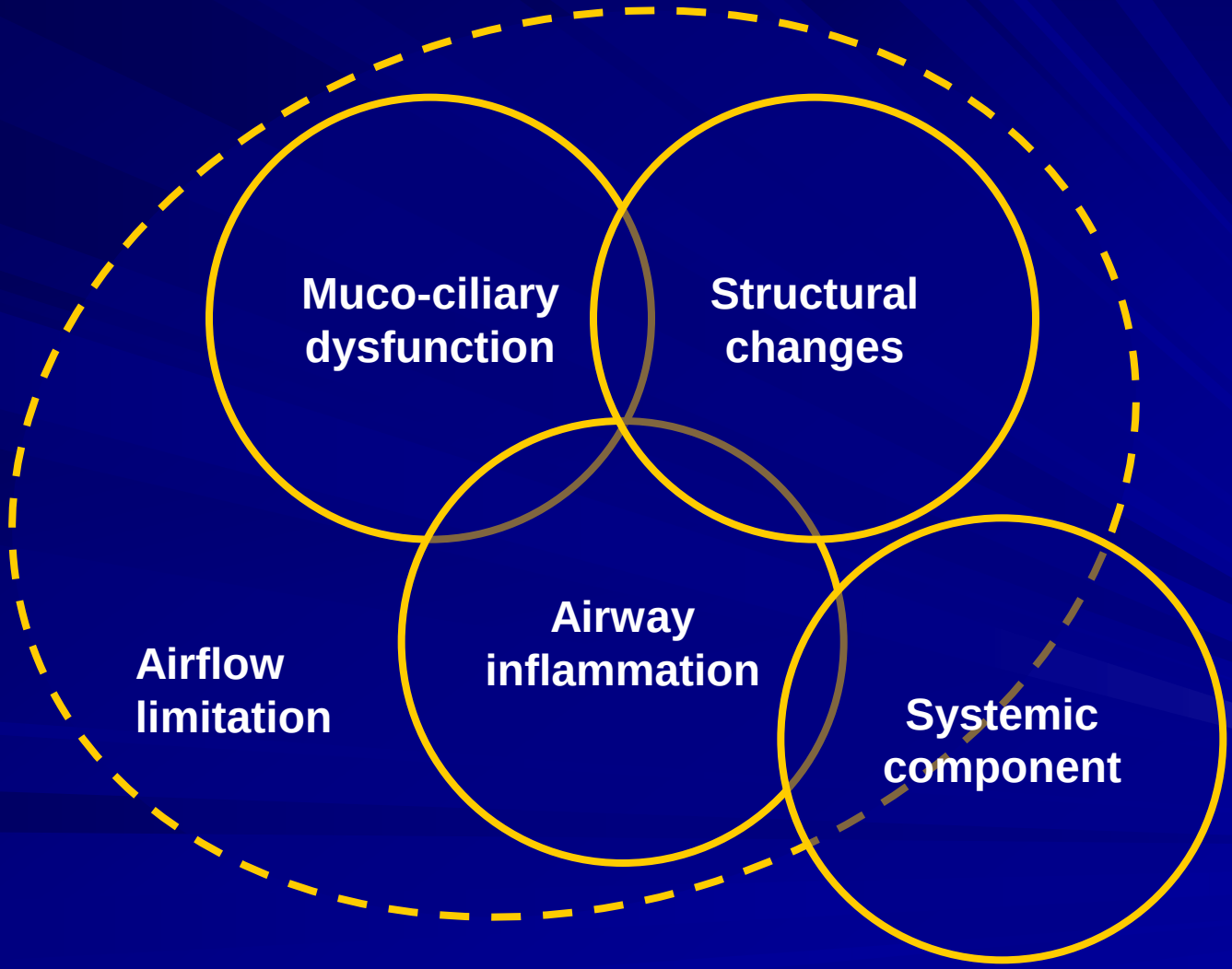
COPD DEFINITION GOLD 2006

COPD is a preventable and treatable disease with some extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal response of the lungs to noxious particles or gases.

MULTI-COMPONENT PATHOPHYSIOLOGY OF COPD



ARTERIAL STIFFNESS

- Pulse wave velocity

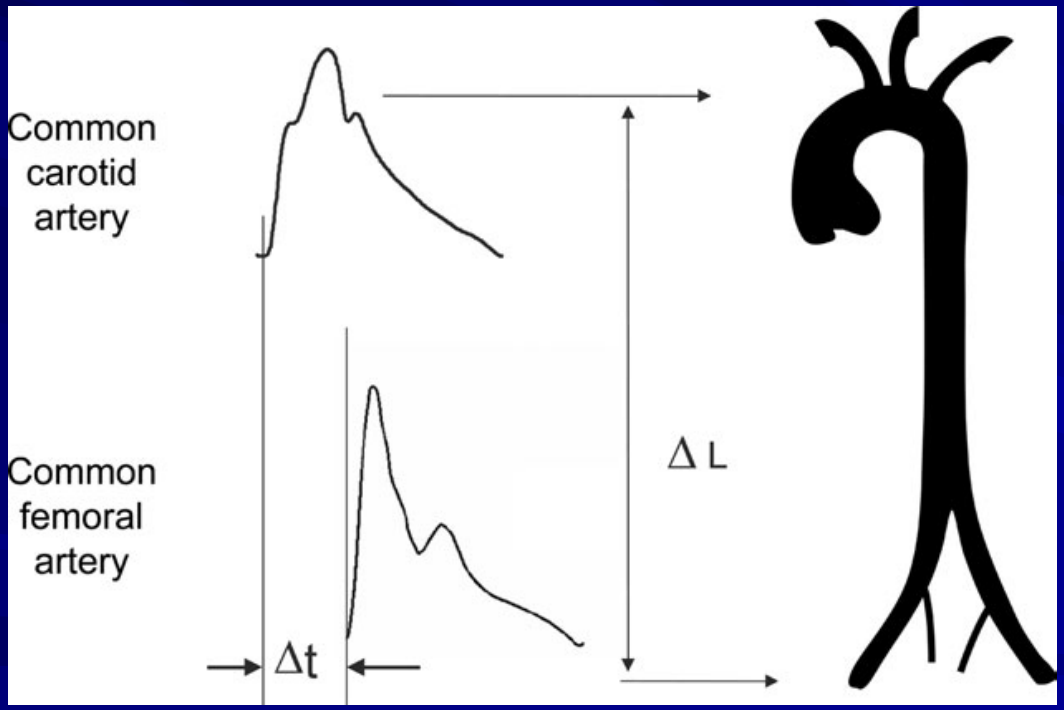


Figure 1 Measurement of carotid-femoral PWV with the foot to foot method.

SIGNIFICANCE OF PULSE WAVE VELOCITY

- Independent predictor of coronary artery disease
  - In hypertensive patients
  - In diabetic patients
  - In a general population including the elderly.
  - Associated with disease duration and the presence of inflammatory mediators CRP and interleukin (IL) 6

ARTERIAL STIFFNESS THE HEALTH ABC STUDY

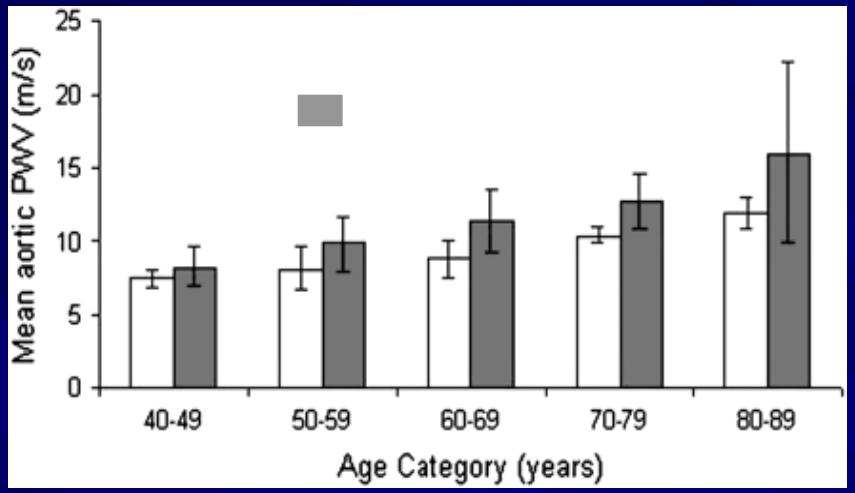
Associations between aPWV and events (aPWV Q2 vs Q1)

	Relative Risk	95 % CI
Total mortality	1.45	0.98 - 2.16
CV mortality	2.13*	1.07 – 4.24
Coronary HD	1.48*	1.05 – 2.09
Stroke	2.93*	1.37 – 6.27
CHF	0.99	0.62 – 1.58

Data adjusted for age, gender, race, systolic BP & other variables including smoking, cholesterol, HR, ankle/arm index etc.

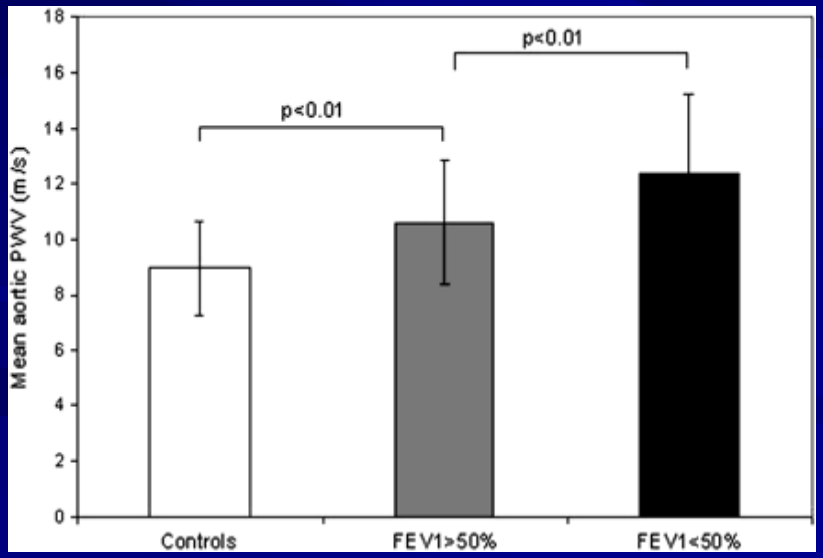
Sutton-Tyrrell et al Circulation 2005

INCREASED ARTERIAL STIFFNESS (APWV) IN COPD



In both Control & COPD groups:

- Age associated with aPWV
- aPWV greater in successive decades



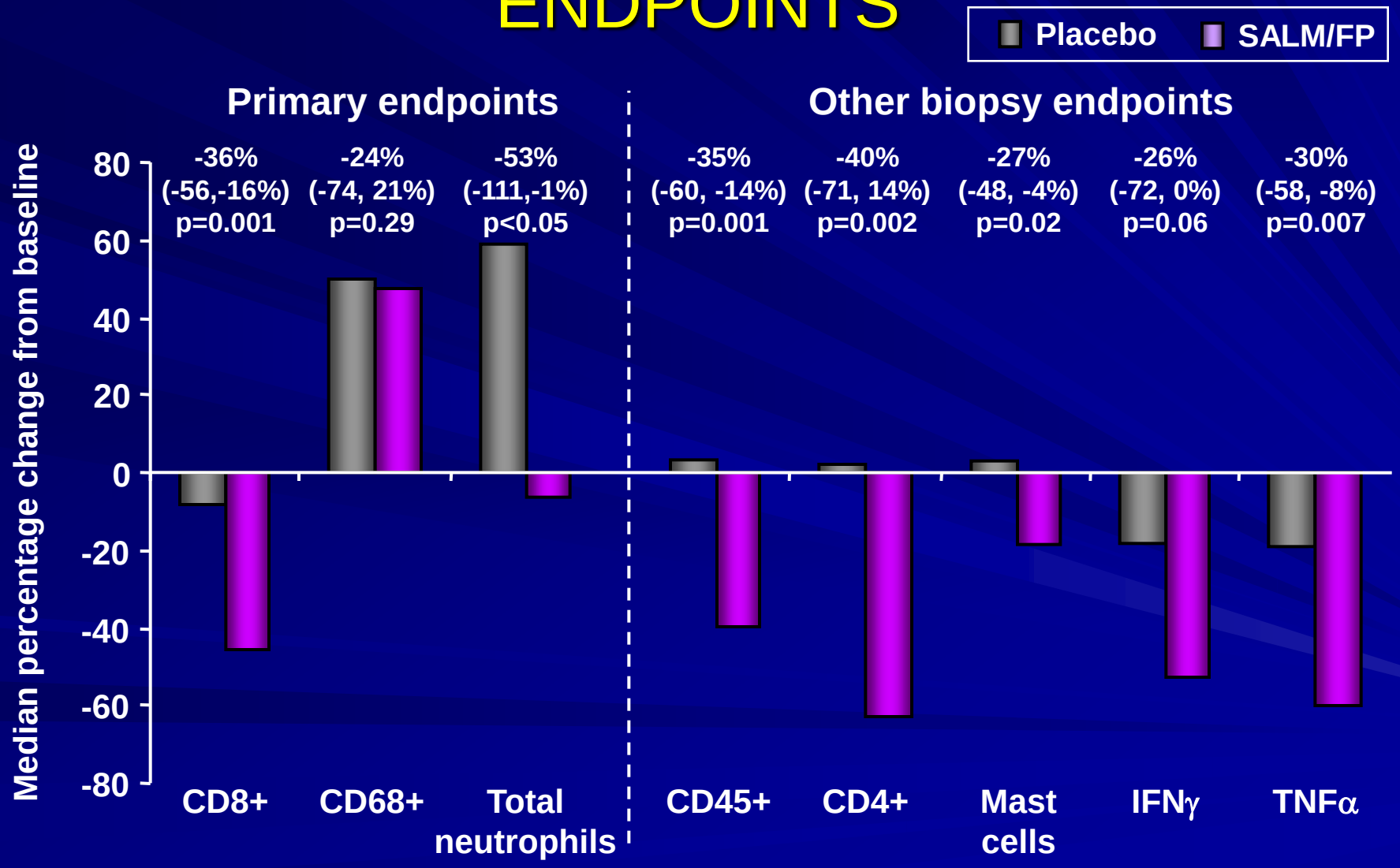
In all subjects:

An inverse relationship between aPWV & FEV

N = 75 patient (64.5 ± 9.5 y)
vs
N = 42 control (62.0 ± 10.5 y)

Sabit et al AJRCCM 2007

PERCENTAGE CHANGE FROM BASELINE IN BIOPSY AND SPUTUM ENDPOINTS



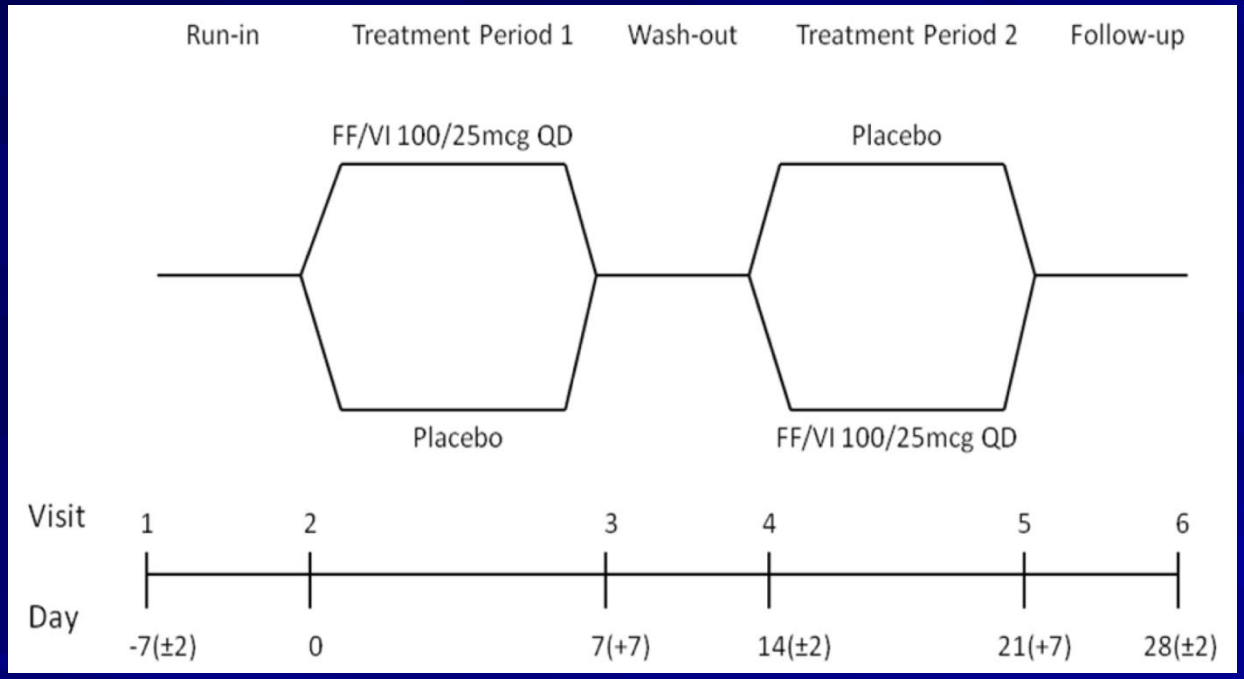
p-values relate to median difference between SALM/FP and placebo. No adjustments made for multiplicity

EFFECT OF TREATMENT ON PULSE WAVE VELOCITY

- Randomized Salm/FP 250 vs Placebo
- Primary endpoint change in PWV at 12/52
  - For those who remained on study treatment reduction of 0.49 m/s
    - p=0.045 CI:-0.098,-0.01
  - Post-hoc analysis in those with higher PWV
- Impact on cardiac function not known

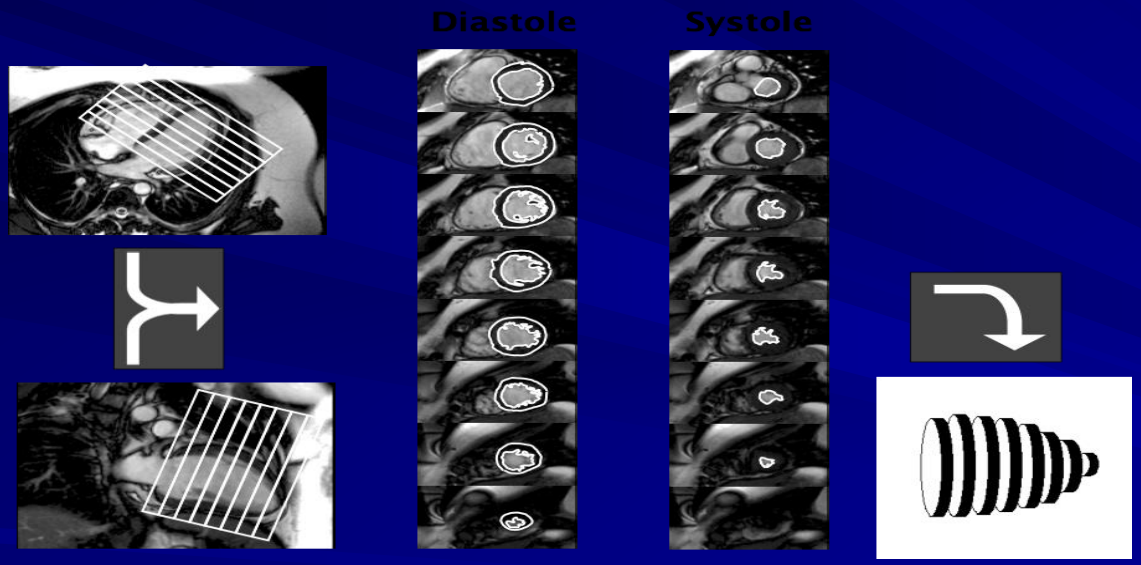
Dransfield et al, *Respiratory Medicine* 2010

A STUDY OF TREATMENT OF COPD ON CARDIAC FUNCTION



- 7 day run-in once washed out
- 2 x 7-14 day treatment periods
- 1 week washout period at cross-over
- Minimum of 4 visits (+ 2 telephone consults)

CARDIAC MRI



- No geometric assumptions
- Highly accurate and reproducible
- Limitations with ECHO due to emphysema do not apply

EFFECT OF TREATMENT ON CARDIAC MORBIDITY AND MORTALITY

- ICS/LABA
- Anticholinergics
- Phosphodiesterase 4 inhibitors
- Novel agents

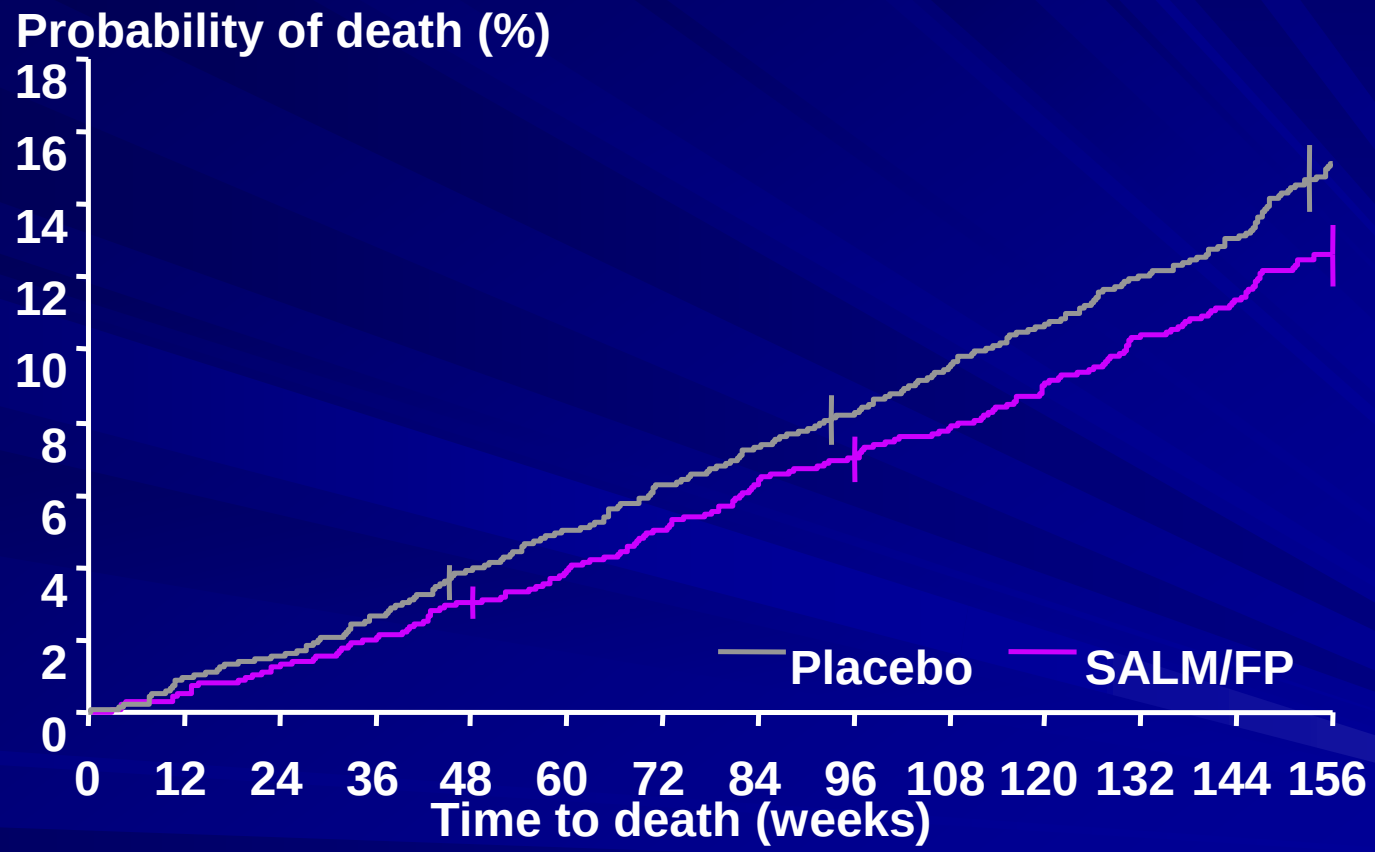
TORCH: STUDY DESIGN

*All ICS and inhaled LABA discontinued before run-in

ITT population

Calverley et al NEJM 2007

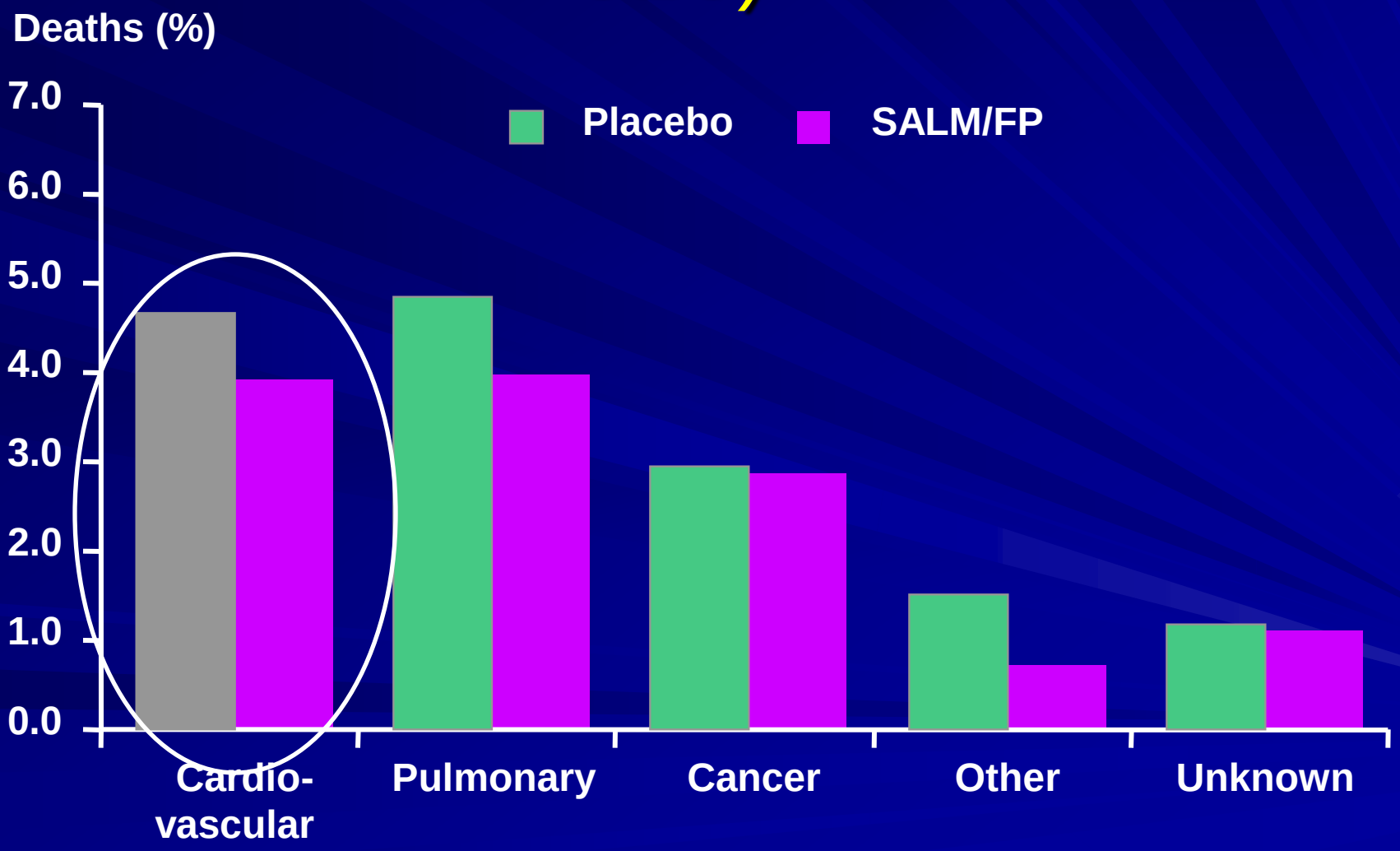
PRIMARY ANALYSIS: ALL-CAUSE MORTALITY AT 3 YEARS



Number	1524	1464	1399	1293
alive	1533	1487	1426	1339

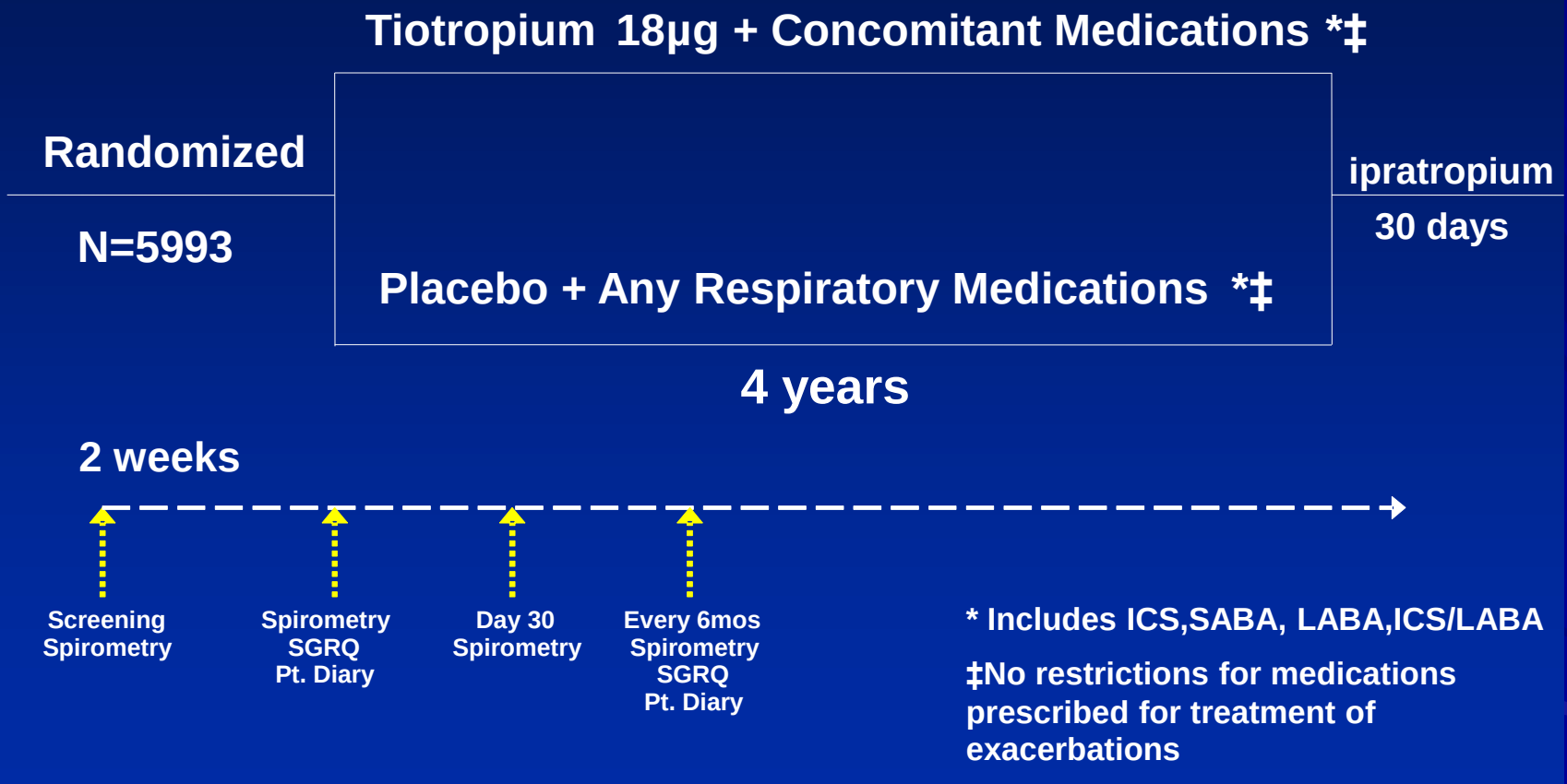
Calverley et al NEJM 2007

CAUSE OF DEATH ON TREATMENT (ADJUDICATED BY CEC)



UPLIFT: STUDY DESIGN

Four-year, randomized, double -blind, double-dummy

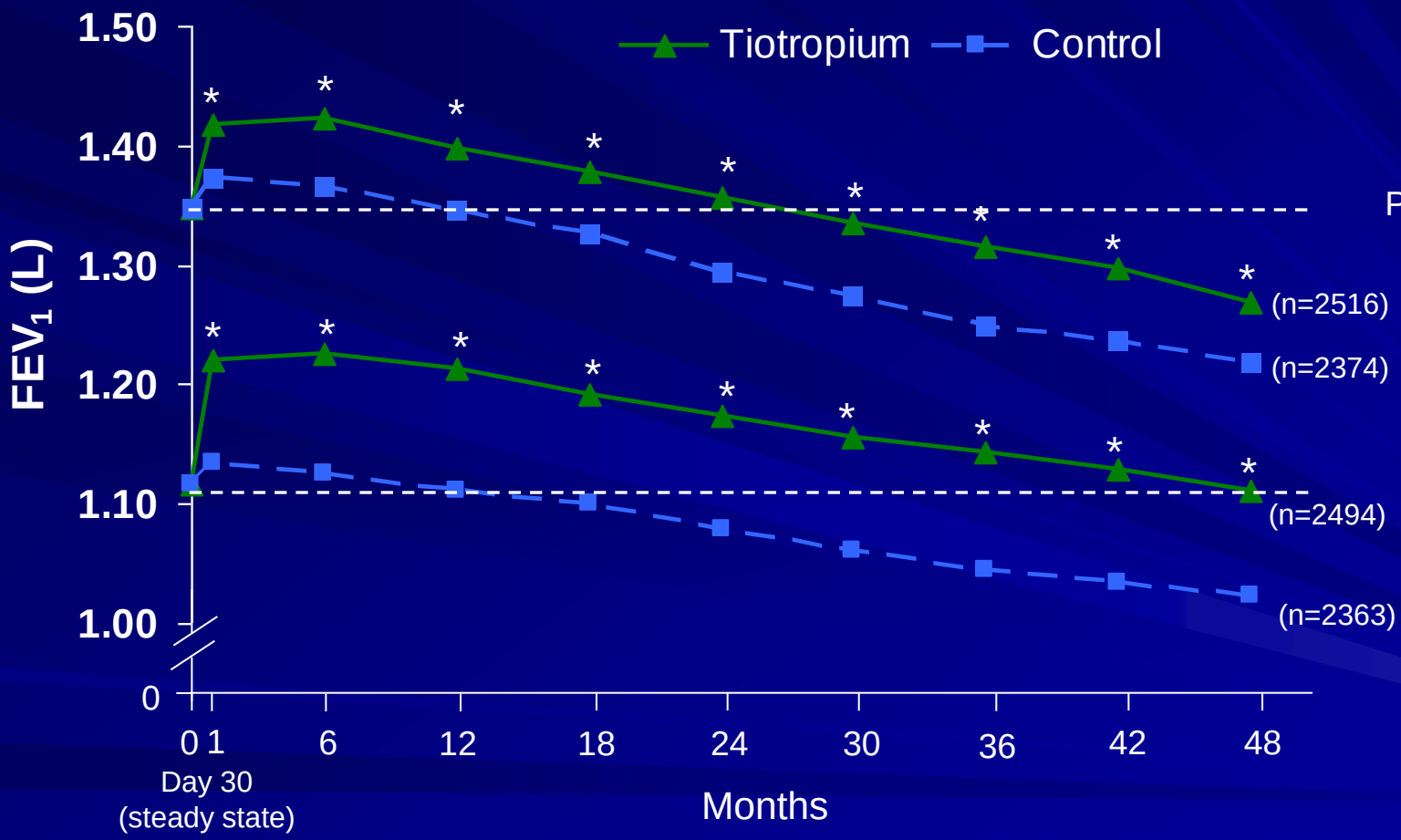


*** Includes ICS,SABA, LABA,ICS/LABA**

‡No restrictions for medications prescribed for treatment of exacerbations

Decramer M et al. J COPD 2004; 1: 303–312

IMPROVEMENT IN FEV1



N Eng J Med 2008: 359(Suppl 15):1543-1554.

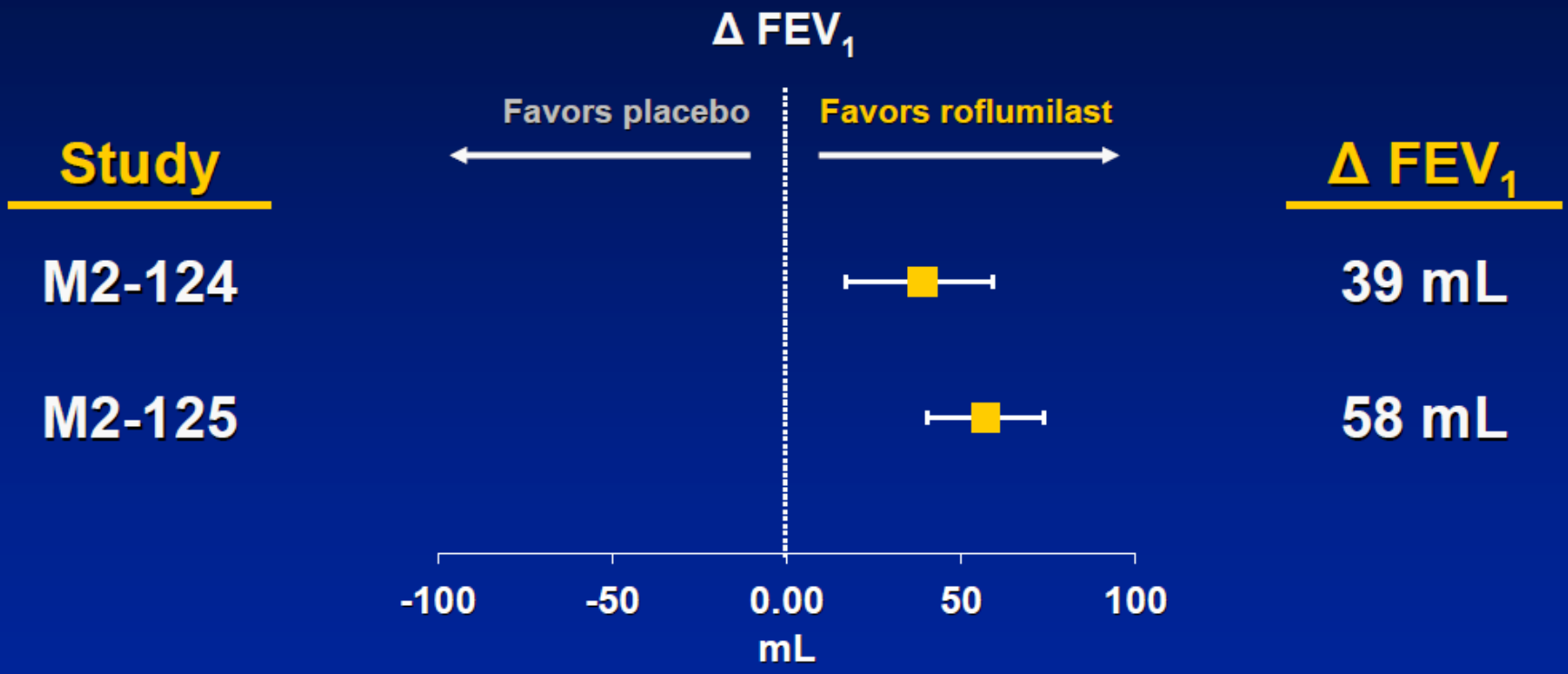
SERIOUS ADVERSE EVENTS

Incidence rate of serious adverse events per 100 patient-years*

Adverse Event	Tiotropium (n=2986)	Placebo (n=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.9	1.31	0.69 (0.52–0.92)†

M2-124 / M2-125

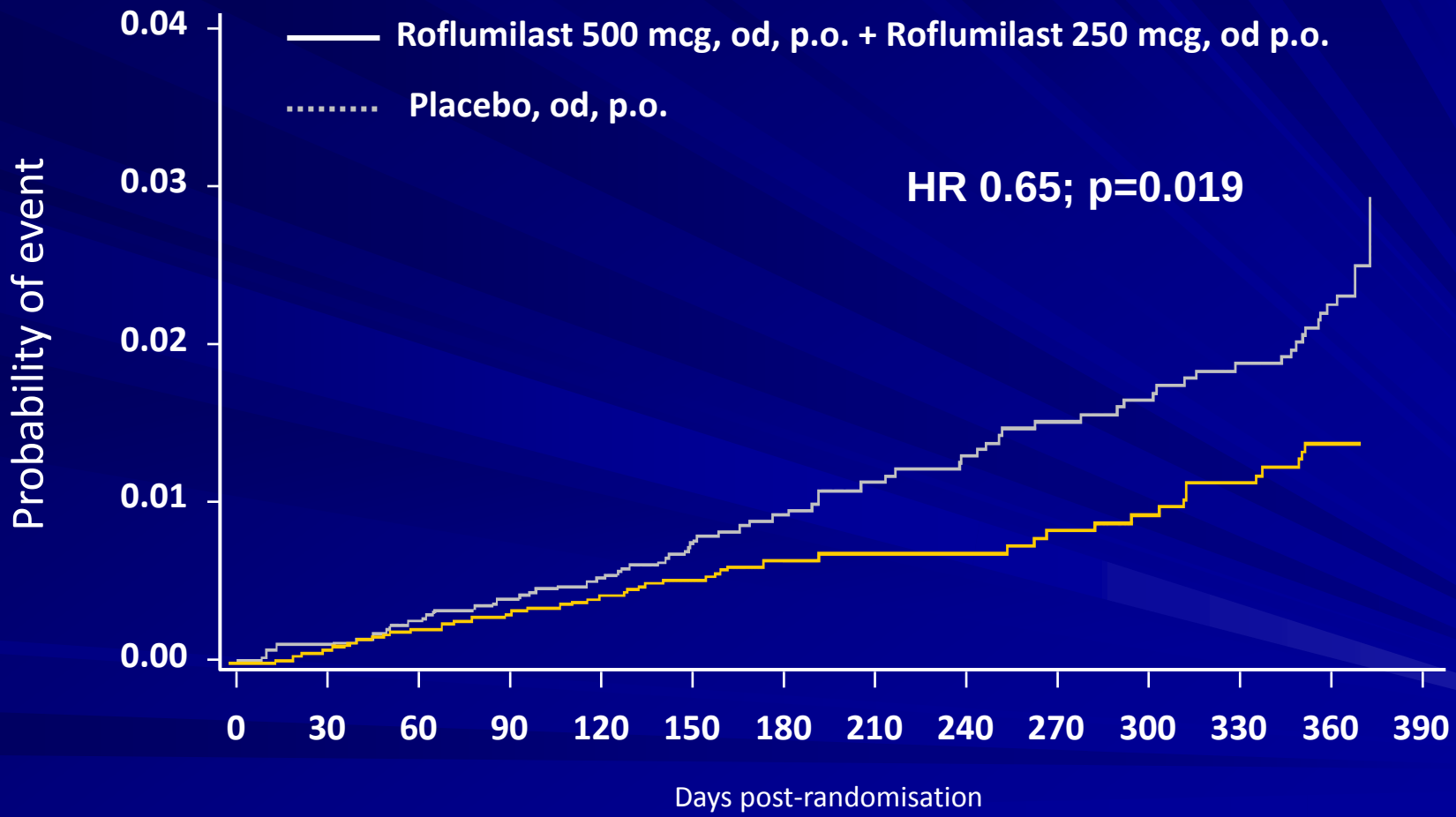
Primary End Point: Significant Improvement in Pre-bronchodilator FEV_1



Repeated measure ANCOVA was used with unstructured covariance matrix to estimate mean. Means are adjusted for baseline measurements

Calverley, et al. Lancet, 2009.

ROFLUMILAST: TIME TO ONSET OF FIRST MAJOR ADVERSE CV EVENT (MACE*)



White WB, et al. Am J Respir Crit Care Med 183;2011:A3092.

***MACE : CV death,** non-fatal **MI, non-fatal stroke**

EFFECT OF MAP KINASE INHIBITOR ON SERUM FIBRINOGEN & IL-8 IN COPD

Day 28	Estimate	95% CI	p
Fibrinogen Ratio SB/Plac	0.89	(0.81, 0.98)	0.020
IL-8 Ratio SB/Plac	1.22	(0.79, 1.89)	0.360

Fibrinogen Pbo baseline mean 3.45 d 14 3.57 day 28 3.64 g/L
‘323 baseline mean 3.59, d 14 3.27, day 28 3.32 g/L

IL-8 Pbo baseline mean 3312 d 14 3609 day 28 3205 ng/mL
‘323 baseline mean 2310, d 14 1849, day 28 2554 ng/mL

Barnes et al ERS 2009

SUMMARY

- COPD is an independent risk factor for cardiovascular disease
- There are multiple mechanisms which may link COPD and cardiovascular disease
- There is emerging evidence that treatment of COPD may reduce cardiovascular morbidity and mortality