Does earlier intervention have better outcomes in COPD ?

Jae Seung Lee M. D. Associate Professor

Department of Pulmonary and Critical Care Medicine,

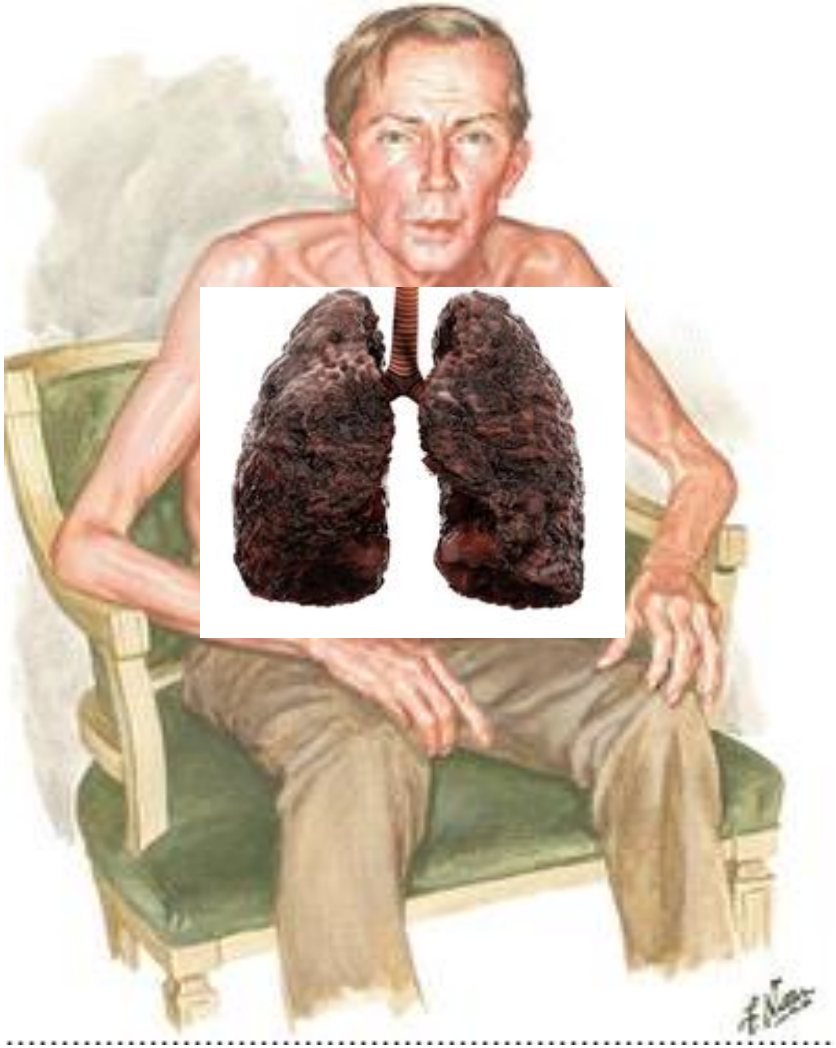
Astma•COPD center

Asan medical Center, University of Ulsan College of Medicine

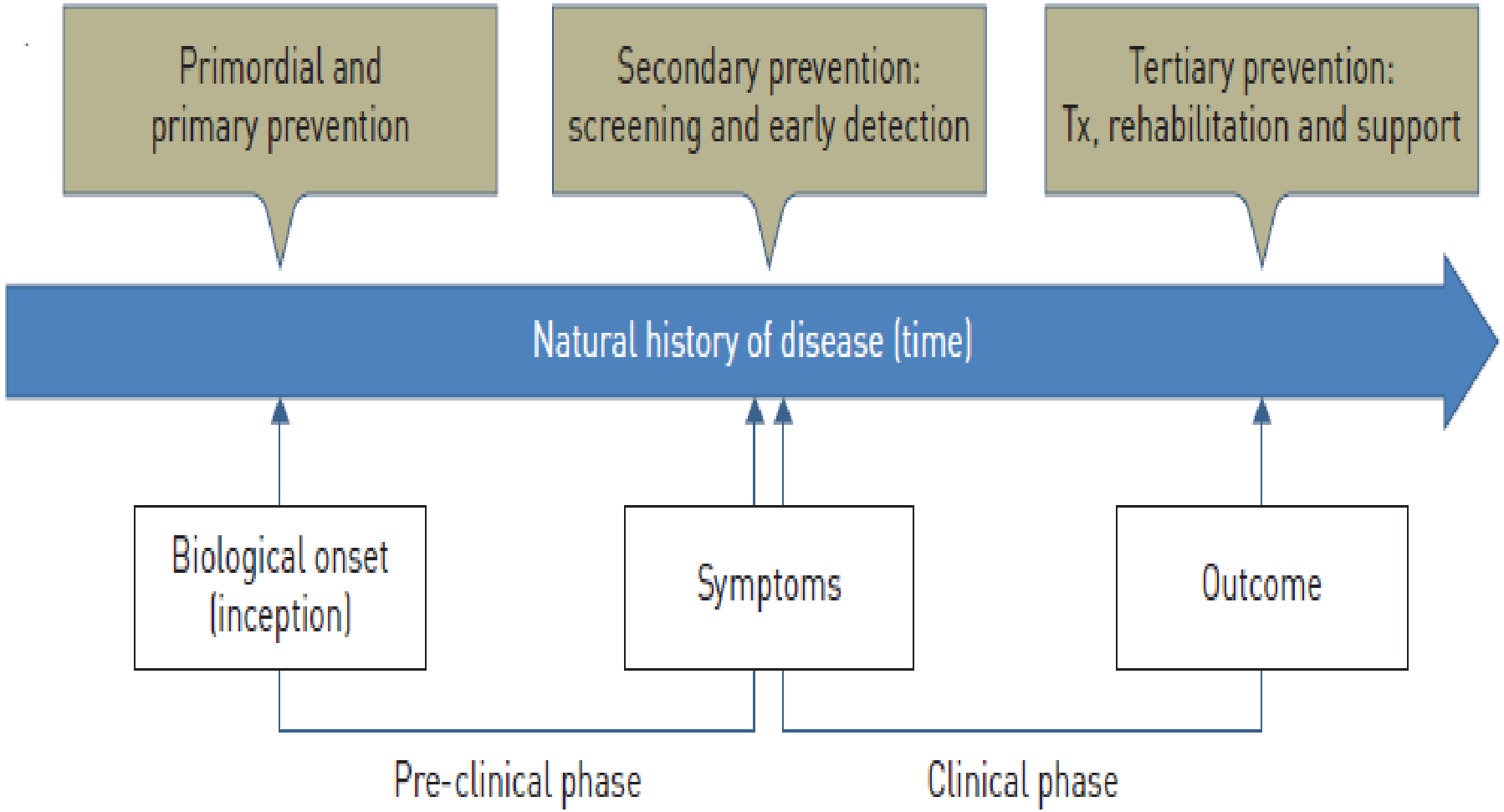
Current treatment of COPD

More pharmacotherapy in severe COPD patient who may have more irreversible pathologic changes

≥ 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



Preventive strategies and natural history of disease



Principles of early disease detection

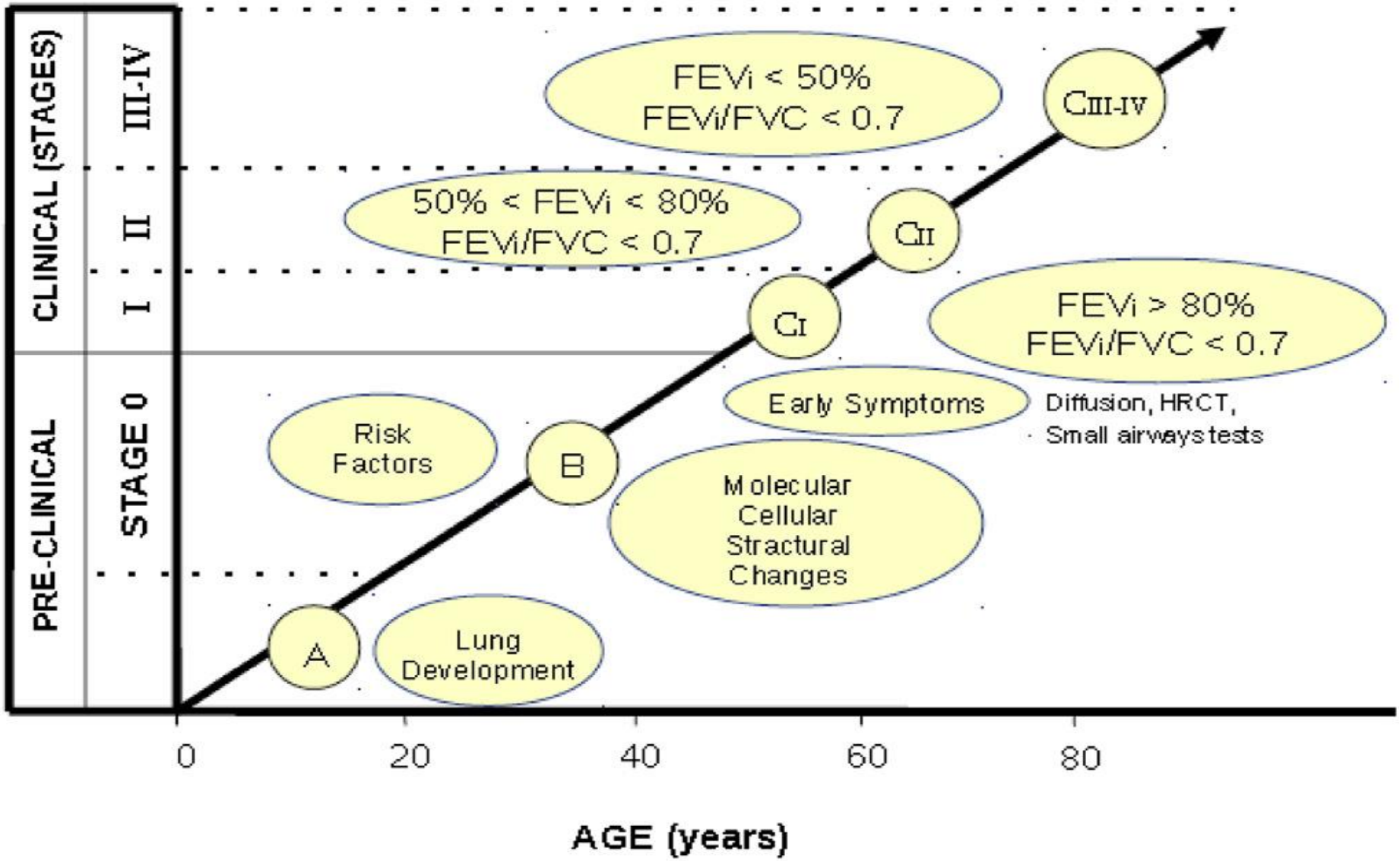
1. The condition sought should be an **important health problem**.
2. There should be an **accepted treatment** for patients with recognized disease. .
3. There should be a **recognizable latent or early symptomatic stage**.
4. There should be a **suitable test or examination**.

Wilson JMG & Jungner G. WHO report 1968

Rationale for early interventions

- **COPD is progressive and typically begins many years before a definite diagnosis is made.**
- **COPD remains under-diagnosed and under-treated,** even though it is now considered to be treatable .
- **The rate of decline in lung function is faster in the initial stages of the disease.**
- **The fast early decline in lung function may be accompanied by a substantial increase in morbidity and mortality.**

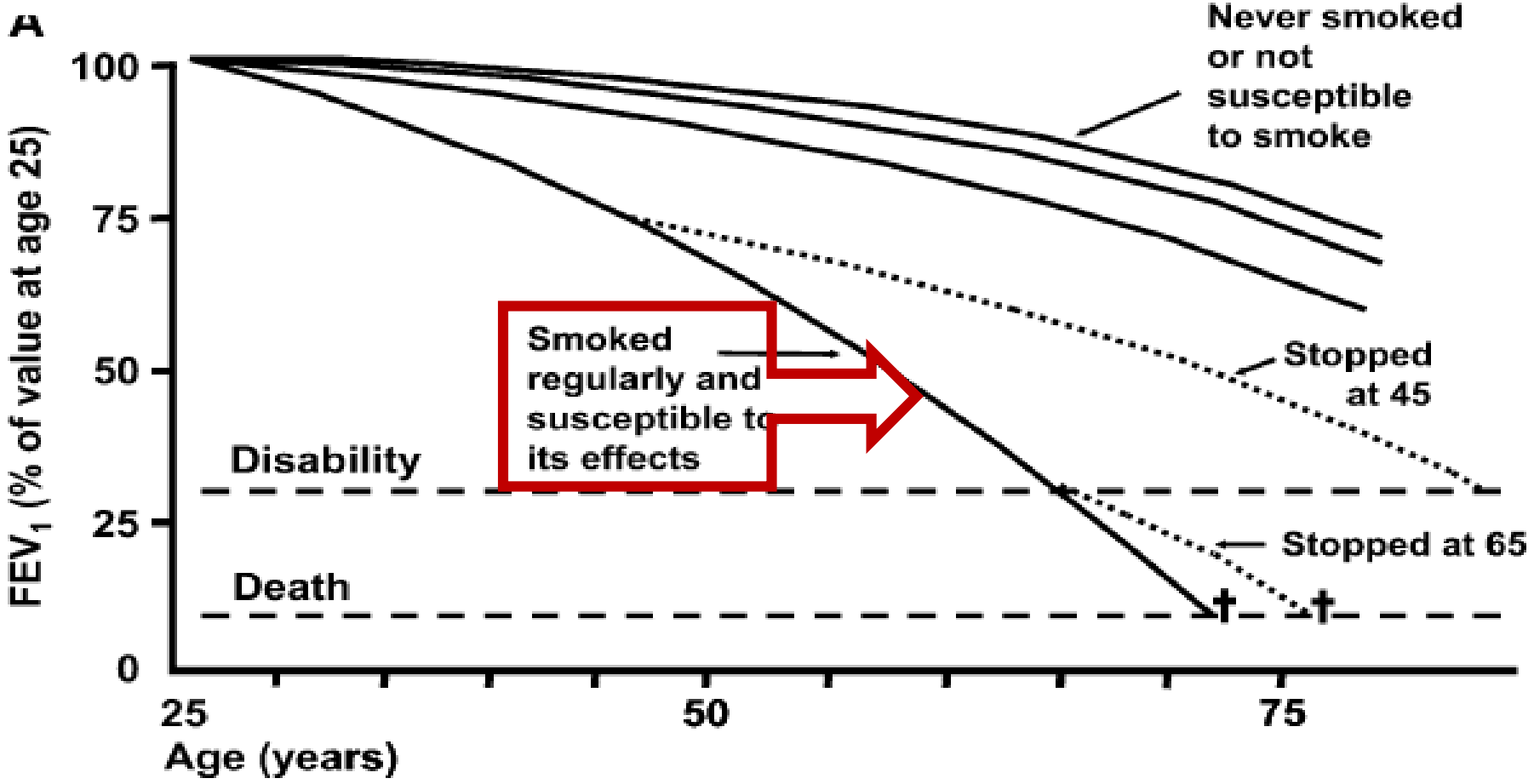
Natural history of COPD



Siafakas N, et a. Respir Med 2018;140:127-131.

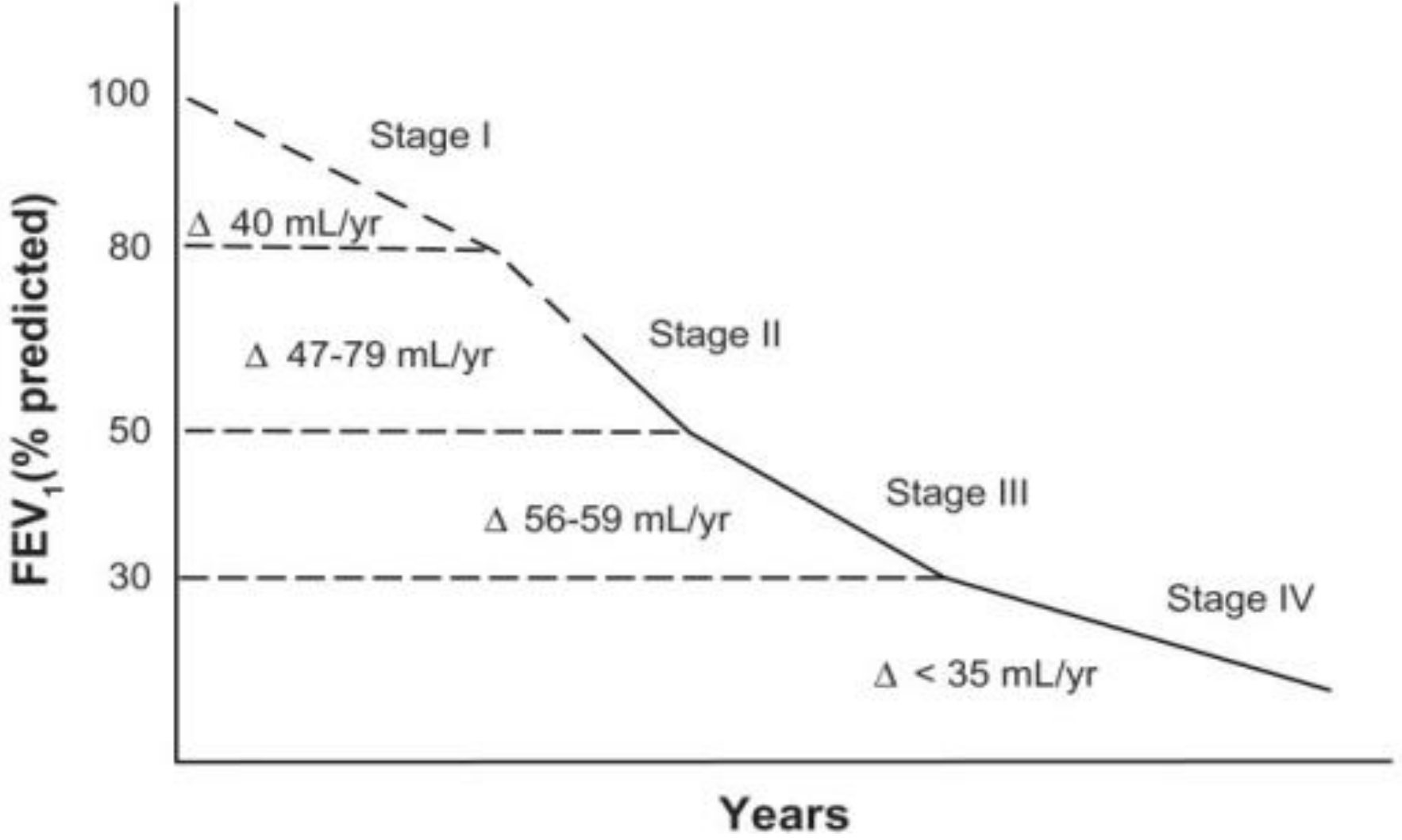
Natural history of chronic airflow obstruction: classic concept

A stratified random sample of 1136 men aged 30-59, 8-years follow up



Fletcher C. and Peto R. BMJ 1977;1645-1648

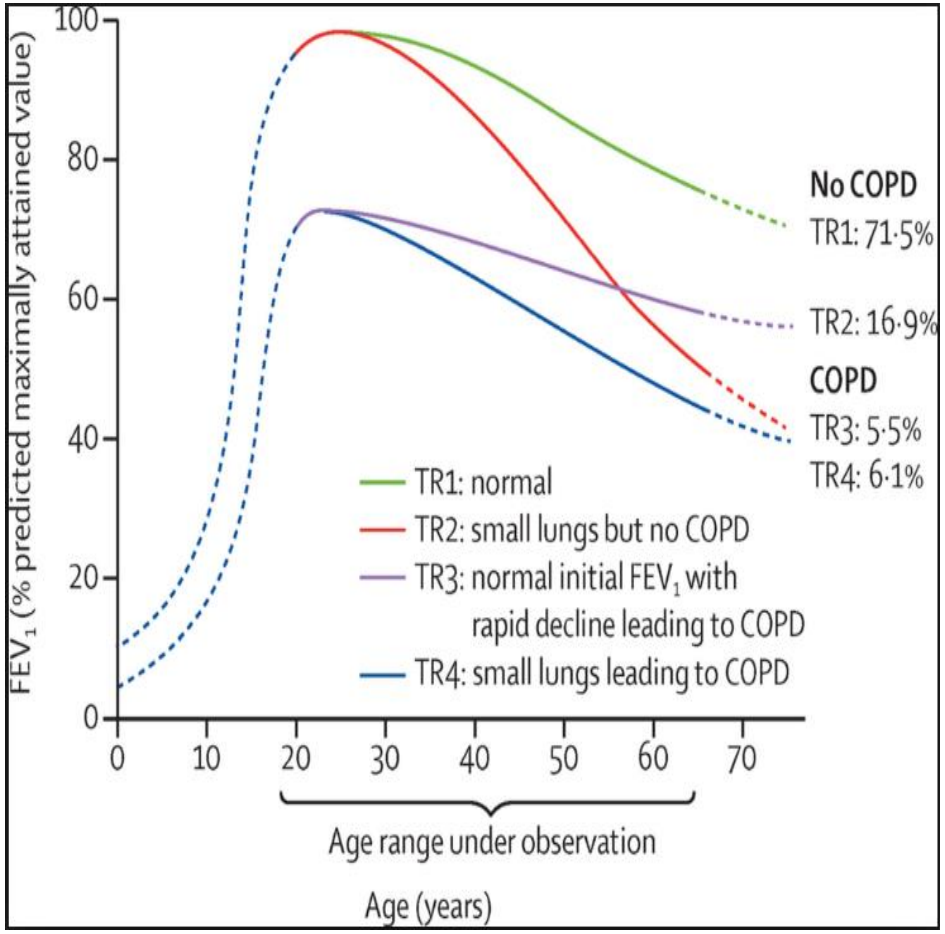
Lung function decline is faster in early stage COPD

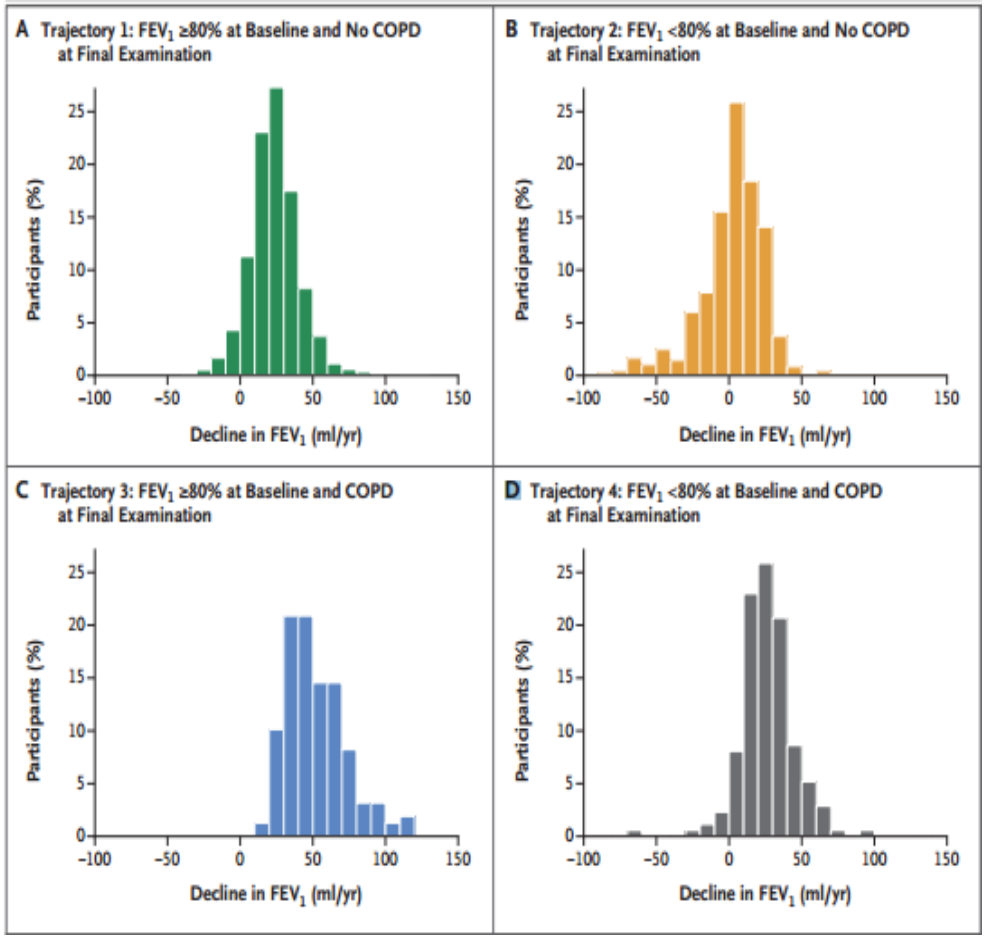


Tantucci C and Modina D. Int J COPD 2012;7:95-99

About half of COPD patients do not show accelerated decline in FEV_1

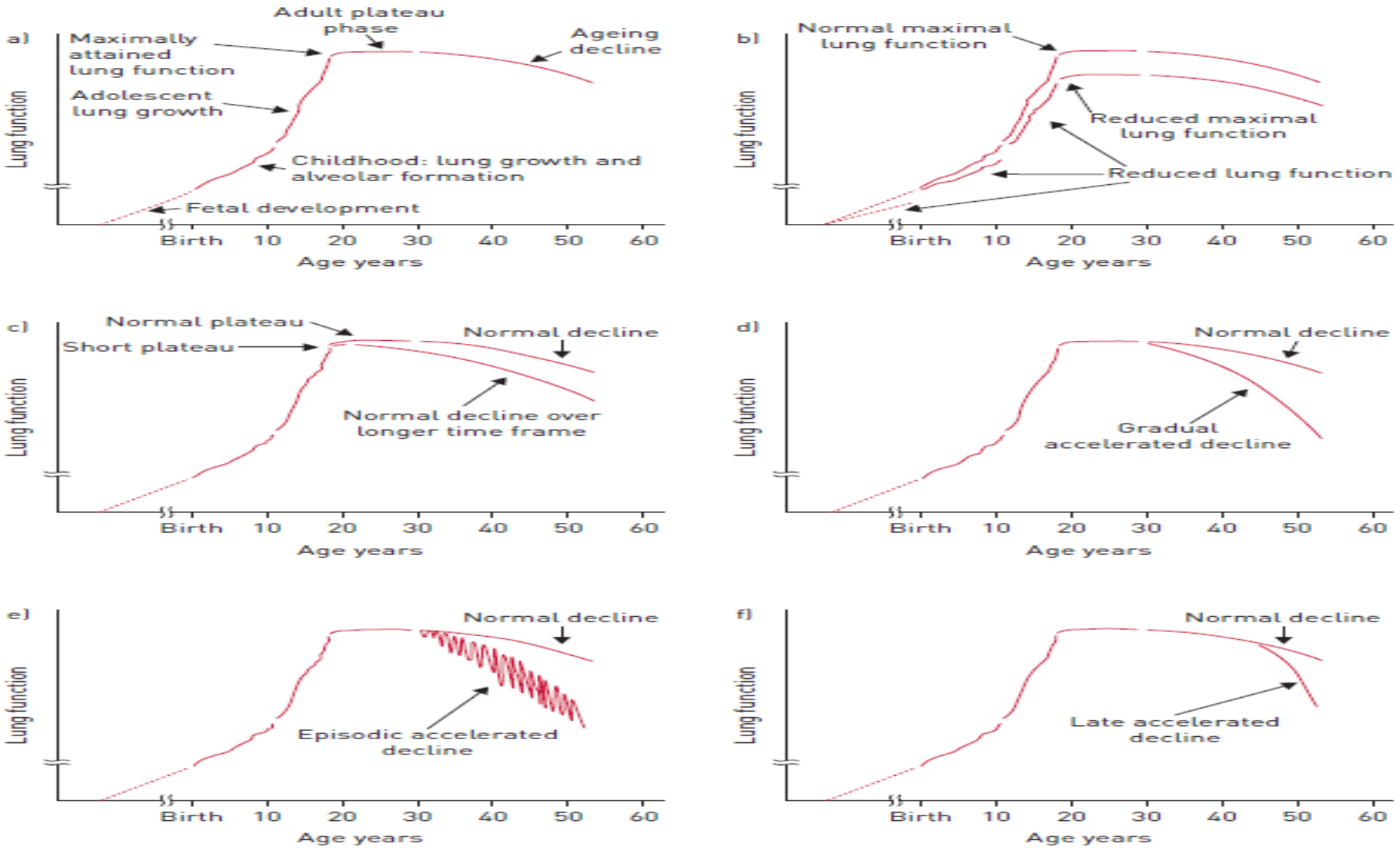
The Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort





Lange P et al. N Engl J Med 2015;373:111-22

Natural history of COPD: current concept

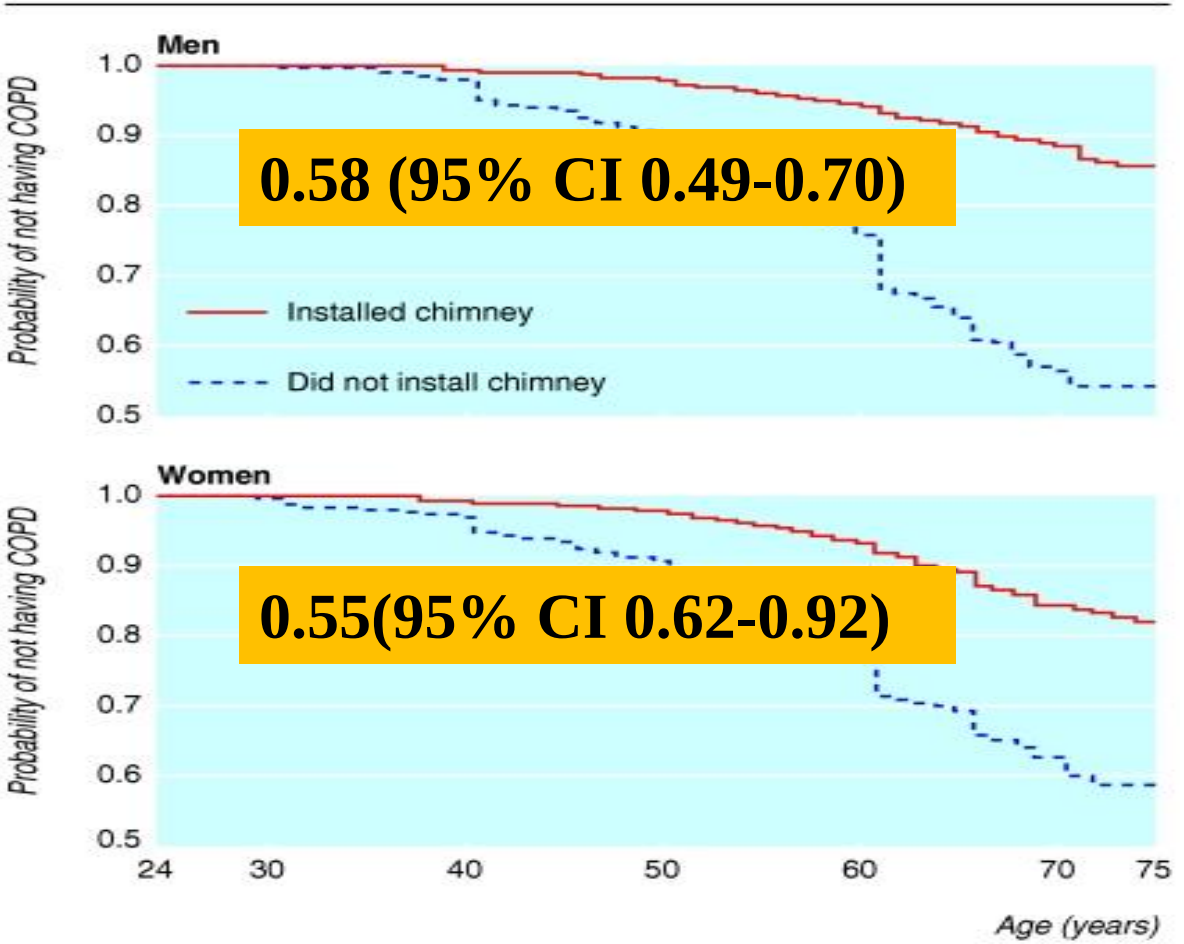


Rennard SI & Drummond MB. Lancet 2015;385:1778-1788

Primary prevention: smoking cessation

Primary prevention: environmental control

- **Retrospective cohort study (1976-1992) including 20,453 people who were born into homes with unvented coal stoves.**



Chapman RS, et al. BMJ 2005;331:1050

Secondary prevention: screening & early detection

- **The US Preventive Service Task Force recommends against screening for chronic obstructive pulmonary disease (COPD) in asymptomatic adults.**

- **GOLD advocates active case finding (performing spirometry in patients with symptoms and/or risk factors, but not screening spirometry.**

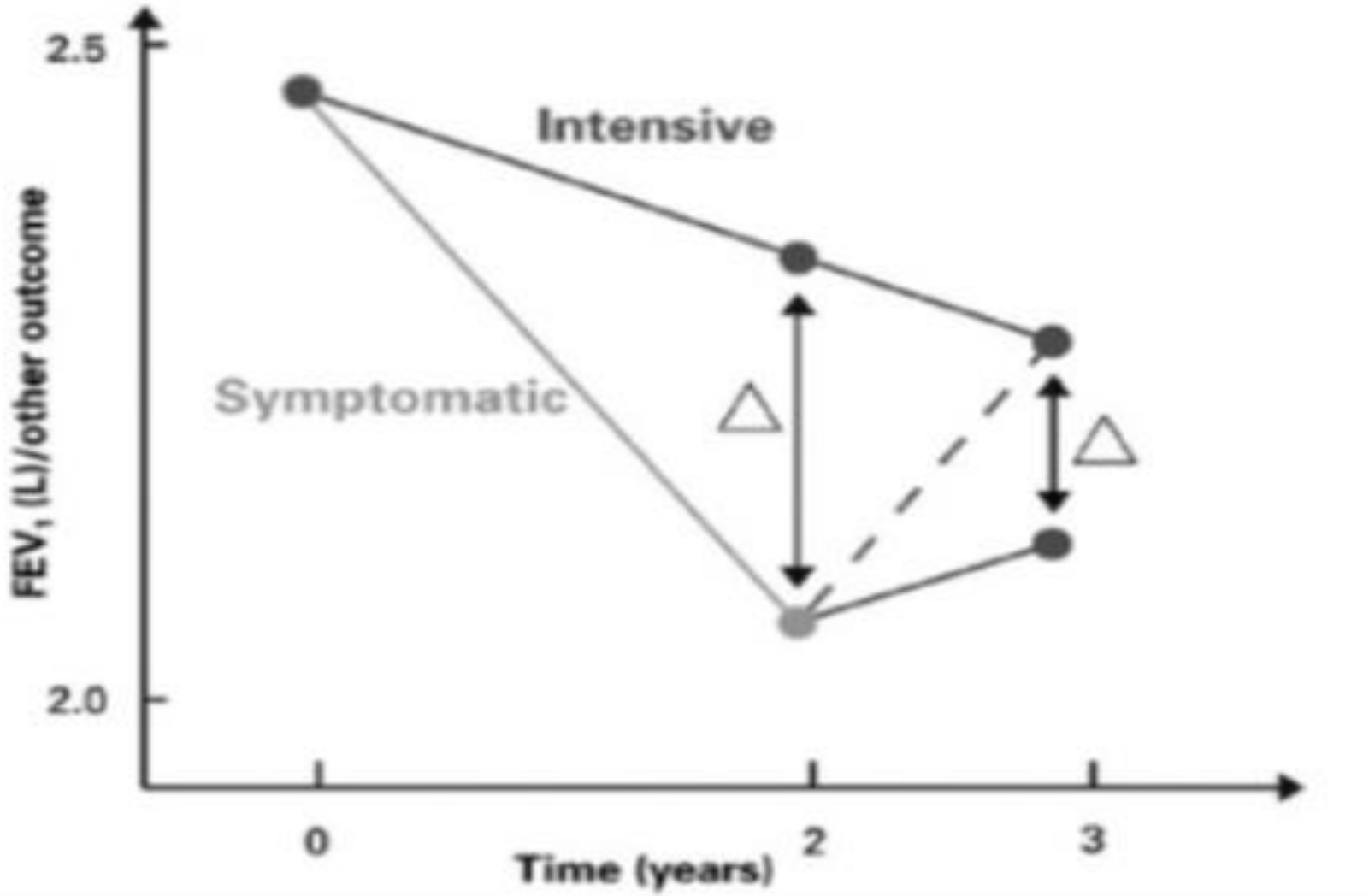
Key questions for early treatment

1. **Is there an effective treatment that can be shown either to halt or to reverse the early pathological changes ?**

2. **Does early treatment than late affect its course and prognosis?**

Wilson JMG & Jungner G. WHO report 1968

Evidence of early treatment COPD



Decramer M & Cooper CB. Thorax 2010;65:837-841

PICO for review

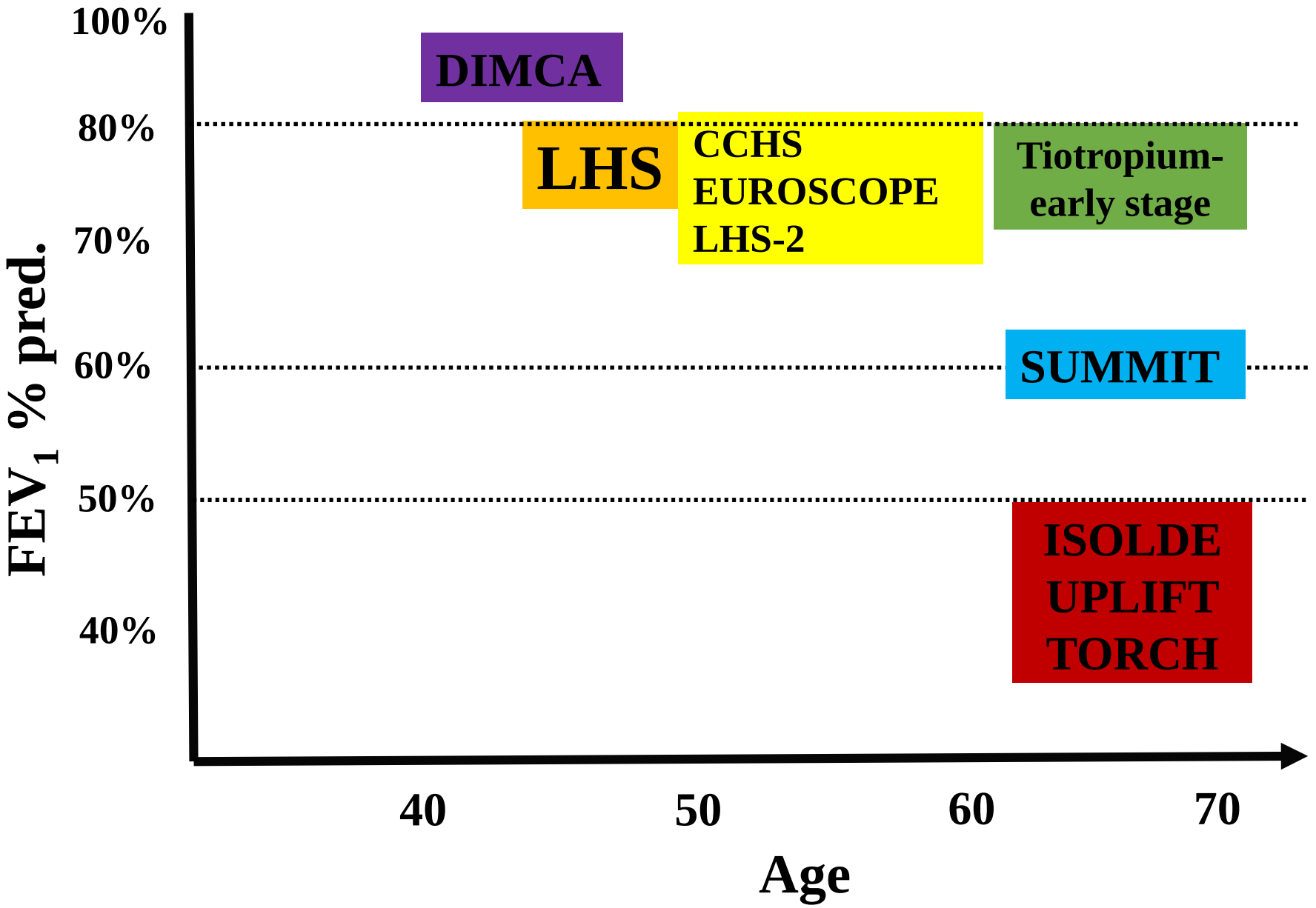
Participants	**Early COPD (?)** **COPD at risk (GOLD O)** **COPD (GOLD I-IV)**
Interventions	**Smoking cessation** **Pharmacotherapy (ICS, ICS/LABA, LAMA)**
Comparisons	**Special intervention** **versus usual care or placebo** **Early intervention (GOLD stage O, I, II)** **versus late intervention (GOLD stage III, IV)**
Outcomes	**Lung function (FEV1) decline** **Mortality**

Proposed operational definition of early COPD

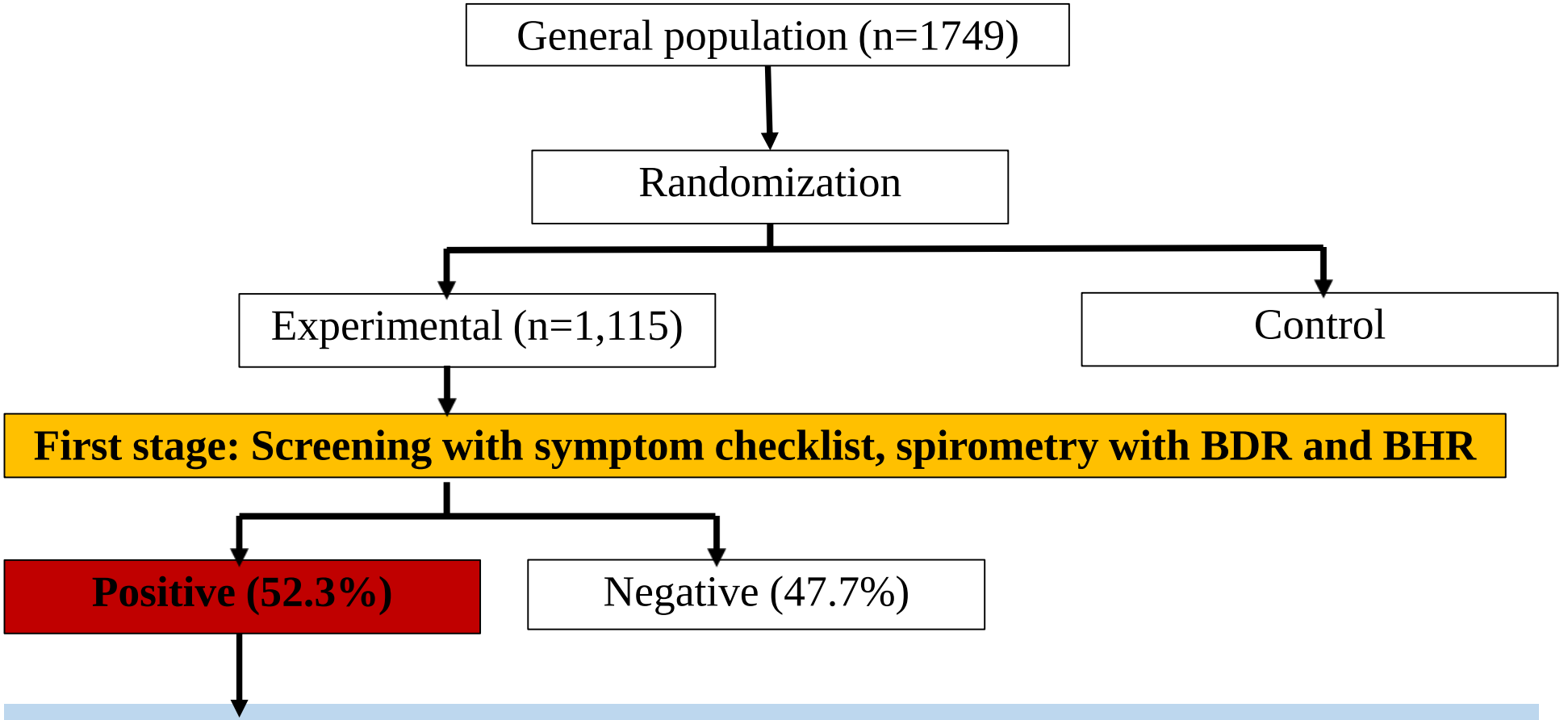
Required	One or more of the following:
< 50 year of age	**FEV_1/FVC less than lower limit of normal**
≥10 pack-years smoking history	**Compatible computed tomography abnormalities -Visual emphysema, air trapping, or bronchial thickening graded mild or worse**
	Evidence of accelerated FEV_1 decline (≥ 60 ml/yr)

Martinez FJ et al. Am J Respir Crit Care Med 2018;197(12):1540-1551

Mean FEV_1 and age in landmark clinical trials



DIMCA(Detection, Intervention and Monitoring of COPD and Asthma) program



Second stage: monitoring (n=384)

DIMCA 1 (7.7%) : COPD or asthma

DIMCA 2 (12.5%): rapid decline in lung function or signs of BHR

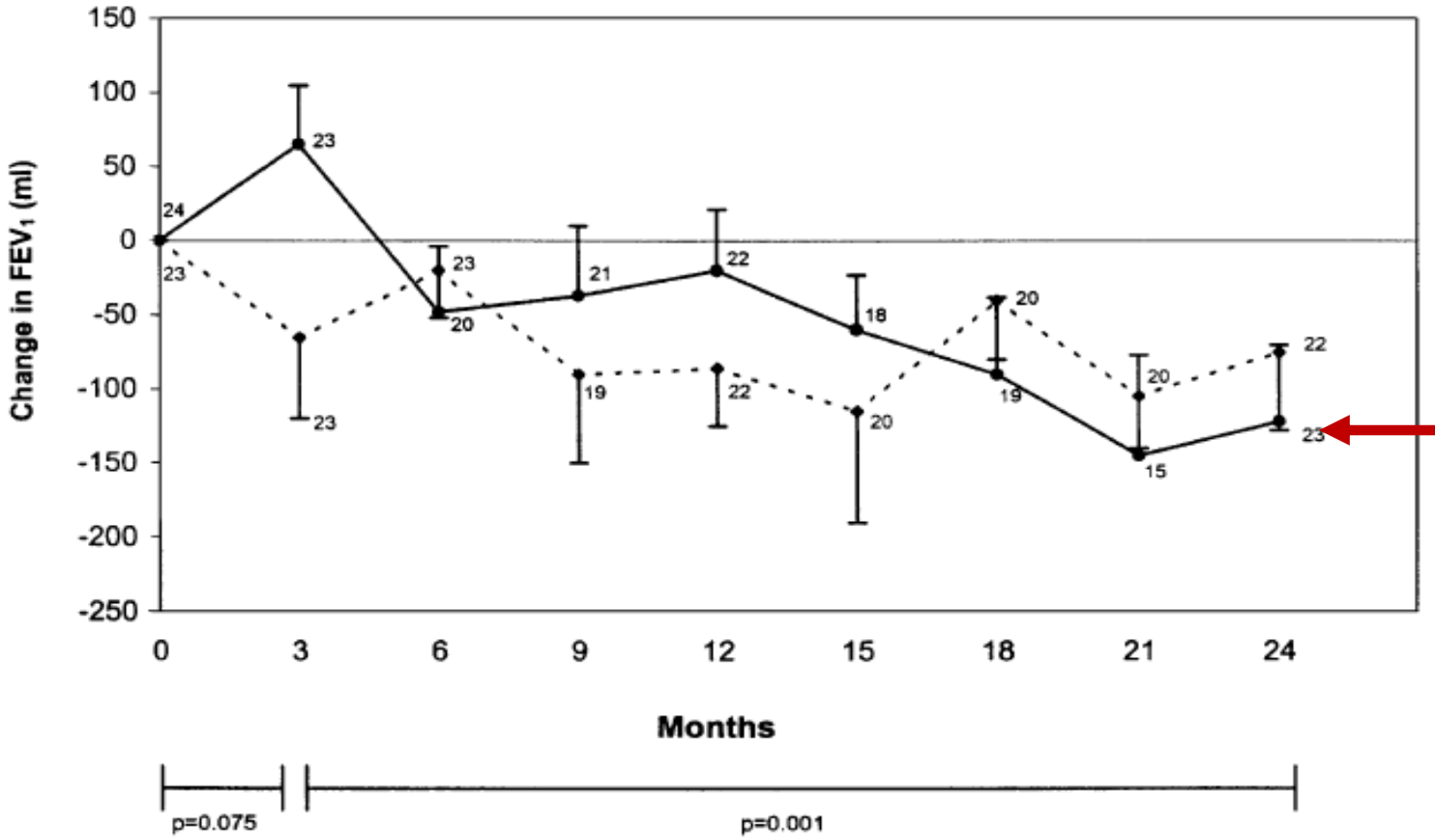
DIMCA 3 (19.4%): moderately increased decline in lung function or signs of BHR

False positive (12.7%)

BOM GVD, et al. AM J RESPIR CRIT CARE MED 1998;158:1730–1738

Short-and long-term efficacy of inhaled fluticasone in subjects with early signs and symptoms of COPD; the DIMCA study

48 subjects were randomized (24 fluticasone, 24 placebo)



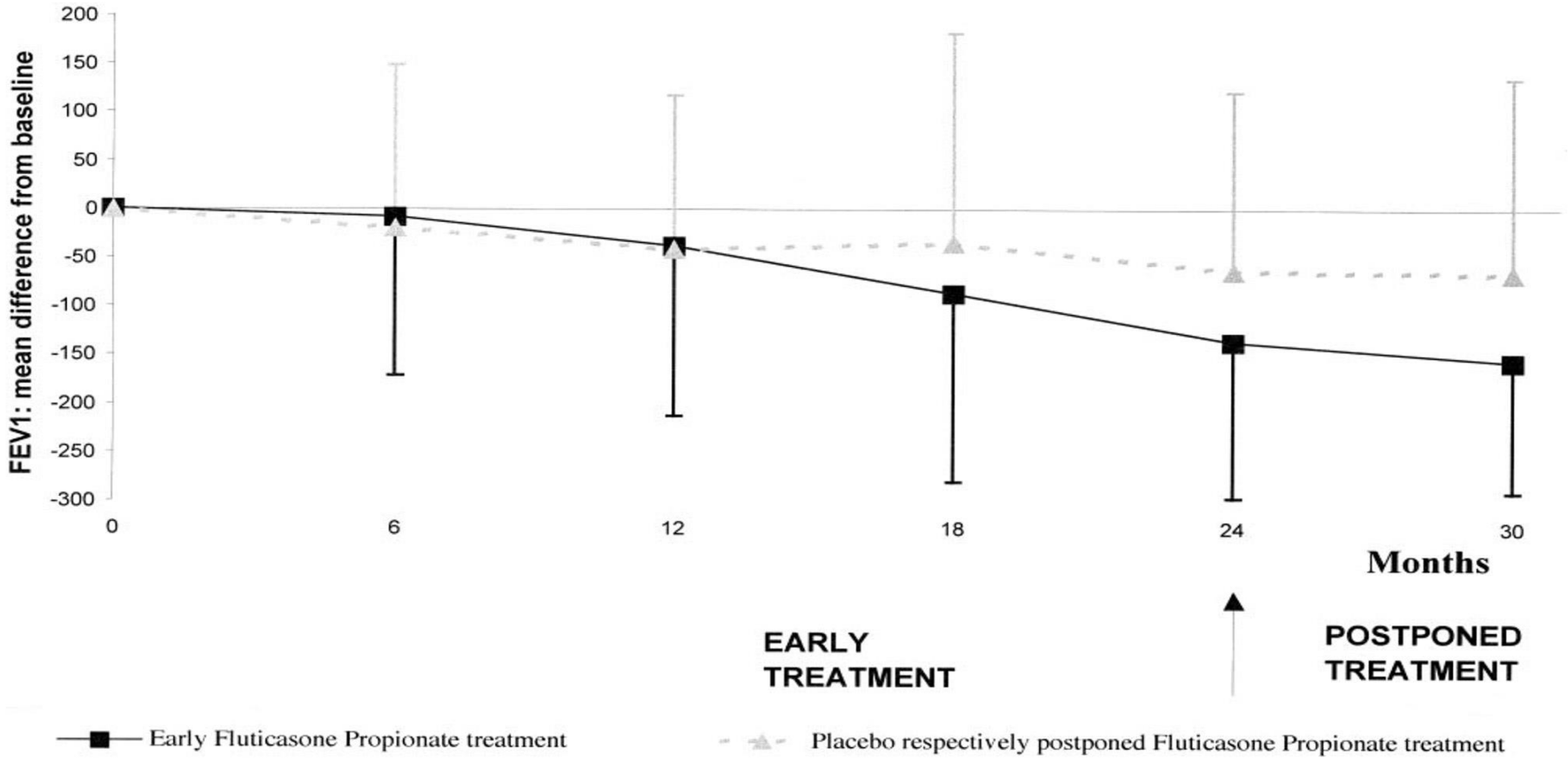
Placebo
-14ml/yr
Fluticasone
-93ml/yr
P=0.001

Grunsven PV et al. Respiratory Medicine 2003; 97:1303–1312

Inhaled steroid in undiagnosed subjects with a rapid decline in lung function

Design; 2-yr, DB, RCT of fluticasone (24 patients) or placebo (25 patients) followed by a 7-month open-label study

Primary outcome: post-BD FEV_1



Albers M, et al. CHEST 2004; 126:1815–1824

The US Lung Health Study

- **Design;** (1) **smoking intervention plus bronchodilator (ipratropium)**,
  (2) **smoking intervention plus placebo**,
  or (3) **no intervention**

- **Participant;** A total of 5887 male and female smokers, **aged 35 to 60 years,**
  with early COPD (FEV_1 55%- 90% pred.)

- **Primary end-point**; **annual rate of decline of maximum post-BD FEV_1**
  over 5-year period

Anthonisen NR, et al. JAMA. 1994;272:1497-1505

Baseline characteristics of LHS

	SIA (n=1961)	SIP (n=1962)	UC (n=1964)
Mean age, y	48.4	48.6	48.4
Male, %	60.8	64.0	63.8
Mean pack-years	31.2	31.5	31.1
Mean FEV_1, L (post-BD)	2.73	2.75	2.76
Mean post-BD FEV_1, % pred.	75.1	75.2	75.1

Anthonisen NR, et al. JAMA. 1994;272:1497-1505

Smoking cessation program in US LHS

(i) Strong physician message explaining the risk for symptomatic COPD

(ii) Group smoking cessation programs that met 12 times over 2 weeks and emphasized behavior modification techniques

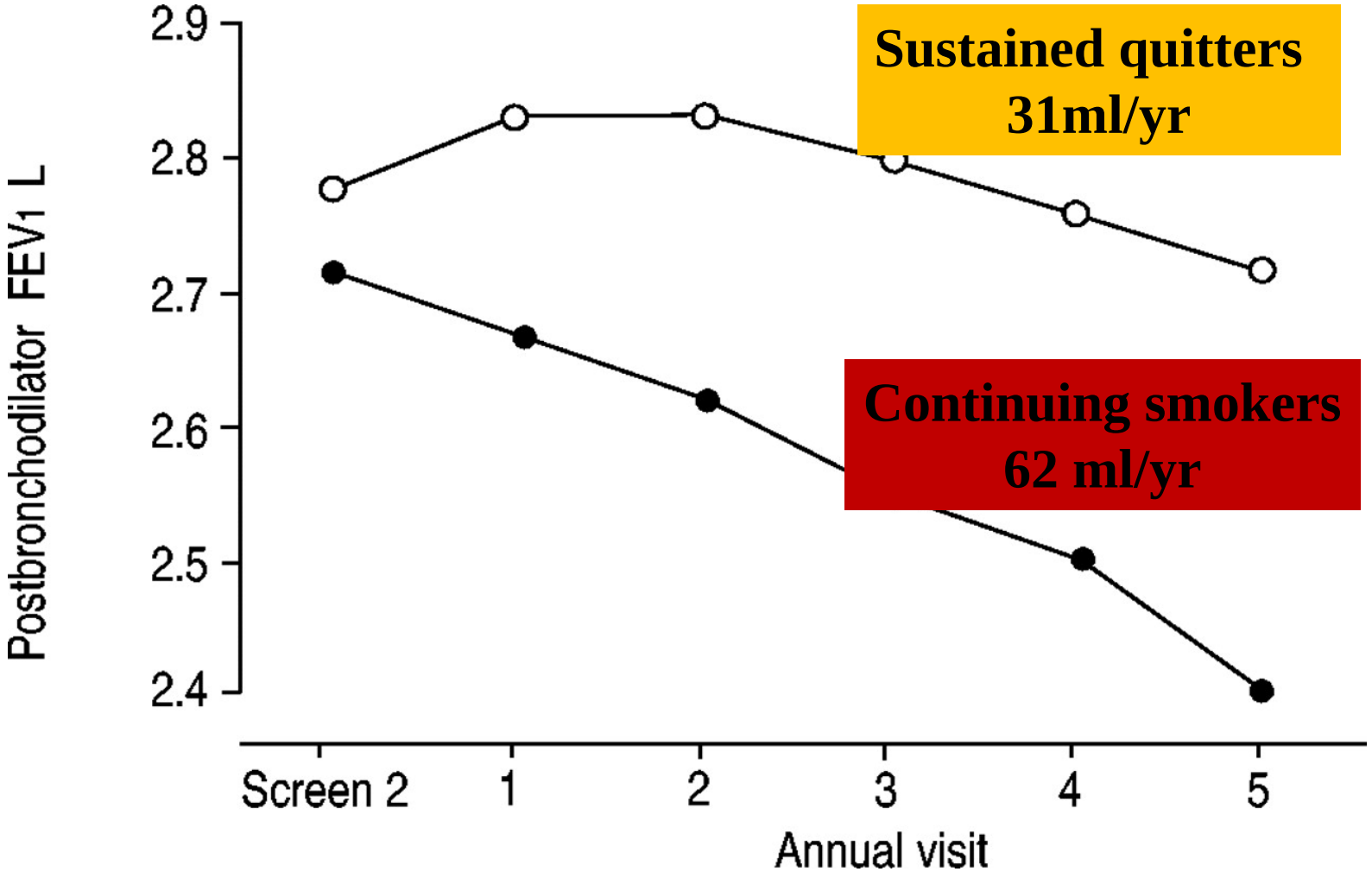
(iii) **Nicotine replacement therapy using Nicorette gum provided at no cost** to the participants

(iv) **Maintenance program aimed at preventing relapse** by teaching coping skills for problems such as stress and weight gain

(v) **individual intervention for relapse prevention**

Anthonisen NR, et al. JAMA. 1994;272:1497-1505

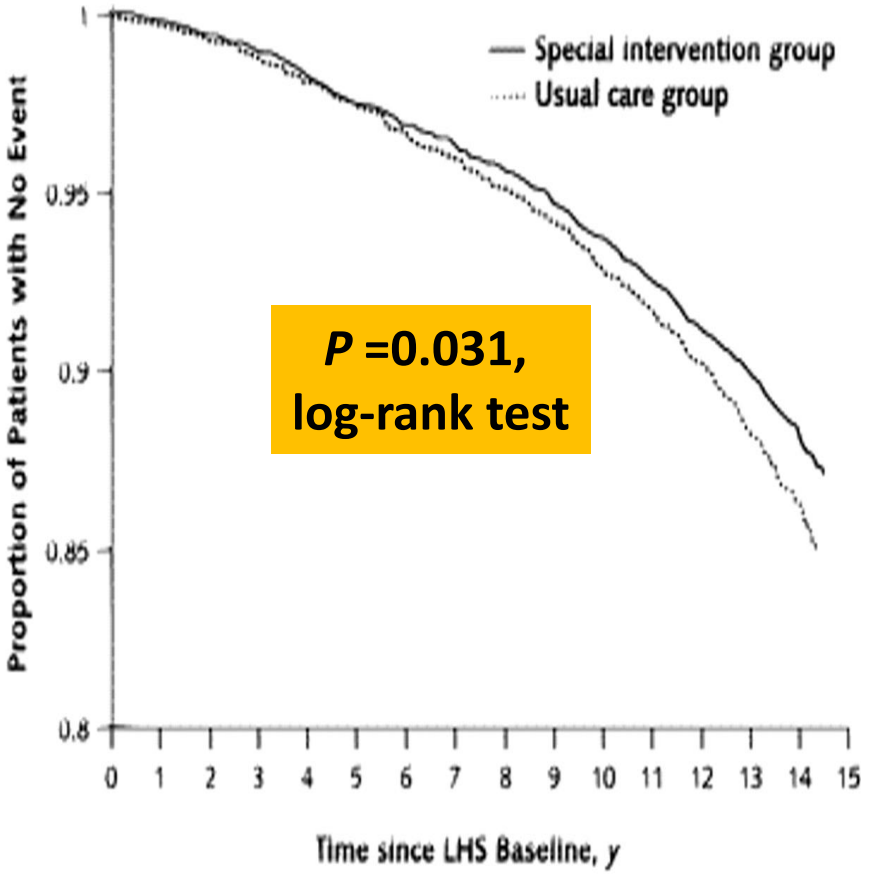
Smoking cessation and FEV_1 decline



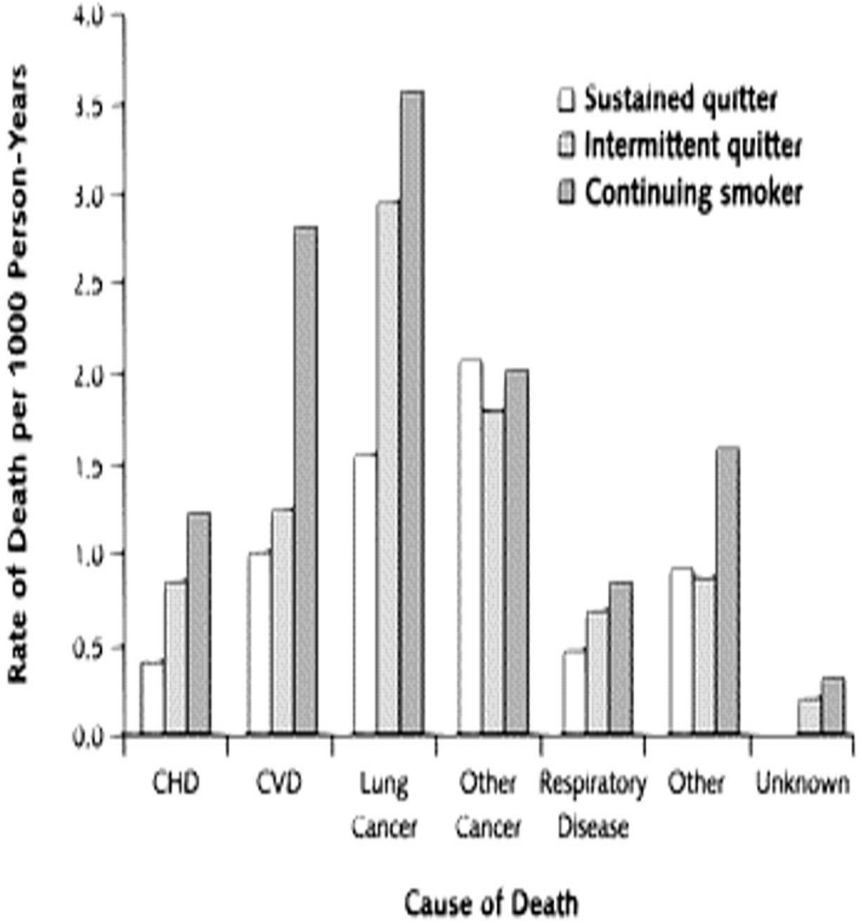
Anthonisen NR, et al. JAMA. 1994;272:1497-1505

Smoking cessation intervention and 14.5 year mortality

At 5 years, 21.7% of special intervention participants had stopped smoking since study entry compared with 5.4% of usual care participants.

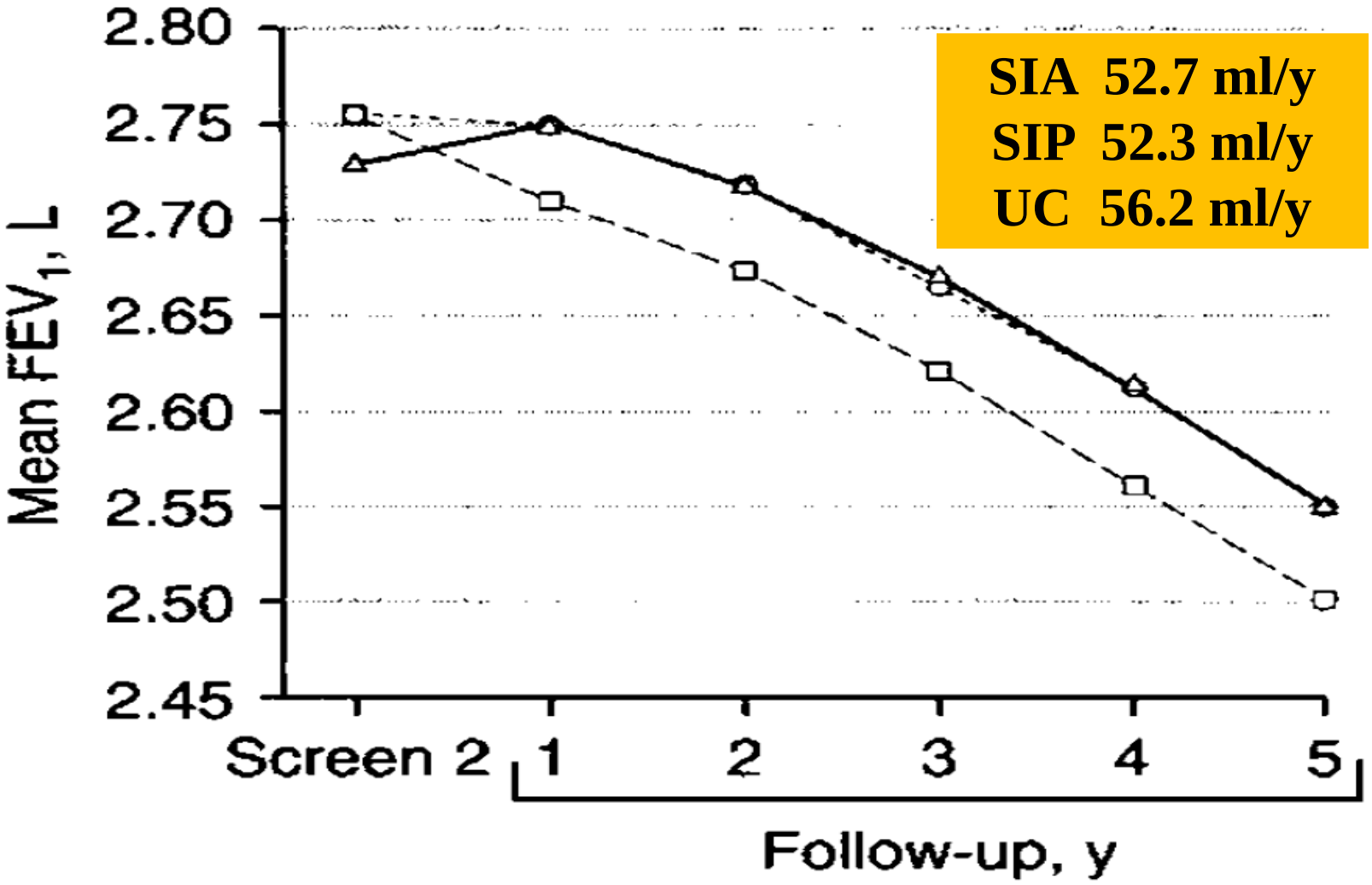


P **=0.031, log-rank test**



Anthonisen NR et al. Ann Intern Med 2005;142:233-239

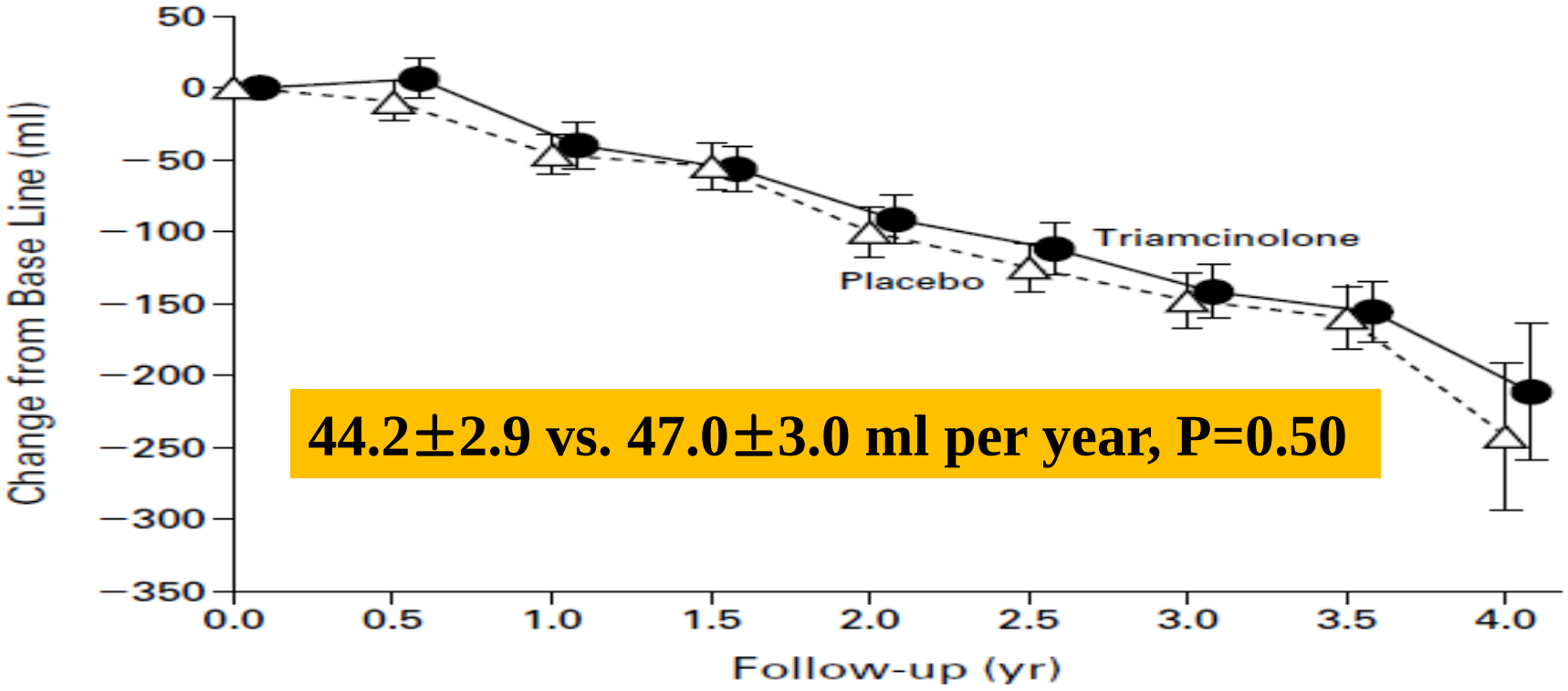
Ipratropium and FEV_1 decline: LHS



Anthonisen NR, et al. JAMA. 1994;272:1497-1505

Inhaled triamcinolone on lung function decline: the Lung Health Study-II

Participant: mean age 56 years, mean post-BD FEV_1 68% pred.
Primary outcome: the rate of post-BD FEV_1 decline



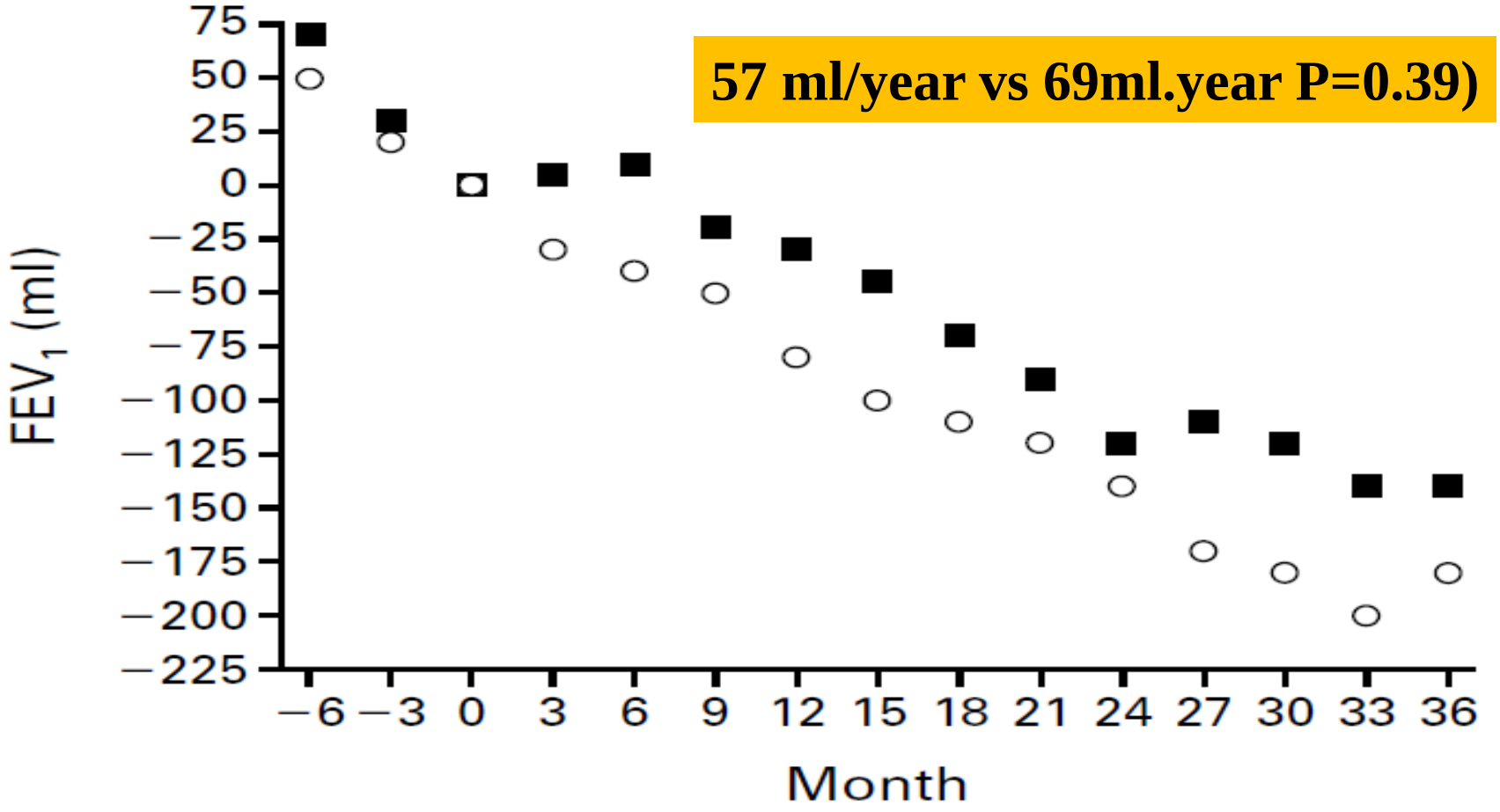
44.2±2.9 vs. 47.0±3.0 ml per year, P=0.50

No. of Participants									
Triamcinolone	556	511	513	490	499	485	479	388	81
Placebo	556	506	503	489	501	484	488	406	77

The LHS Group. N Engl J Med 2000;343:1902-9

Inhaled budesonide in persons with mild COPD who continue smoking: the EUROSCOP trial

Participant: mean age 52 years, mean pre-BD FEV_1 77% pred.
Primary outcome: the rate of post-BD FEV_1 decline

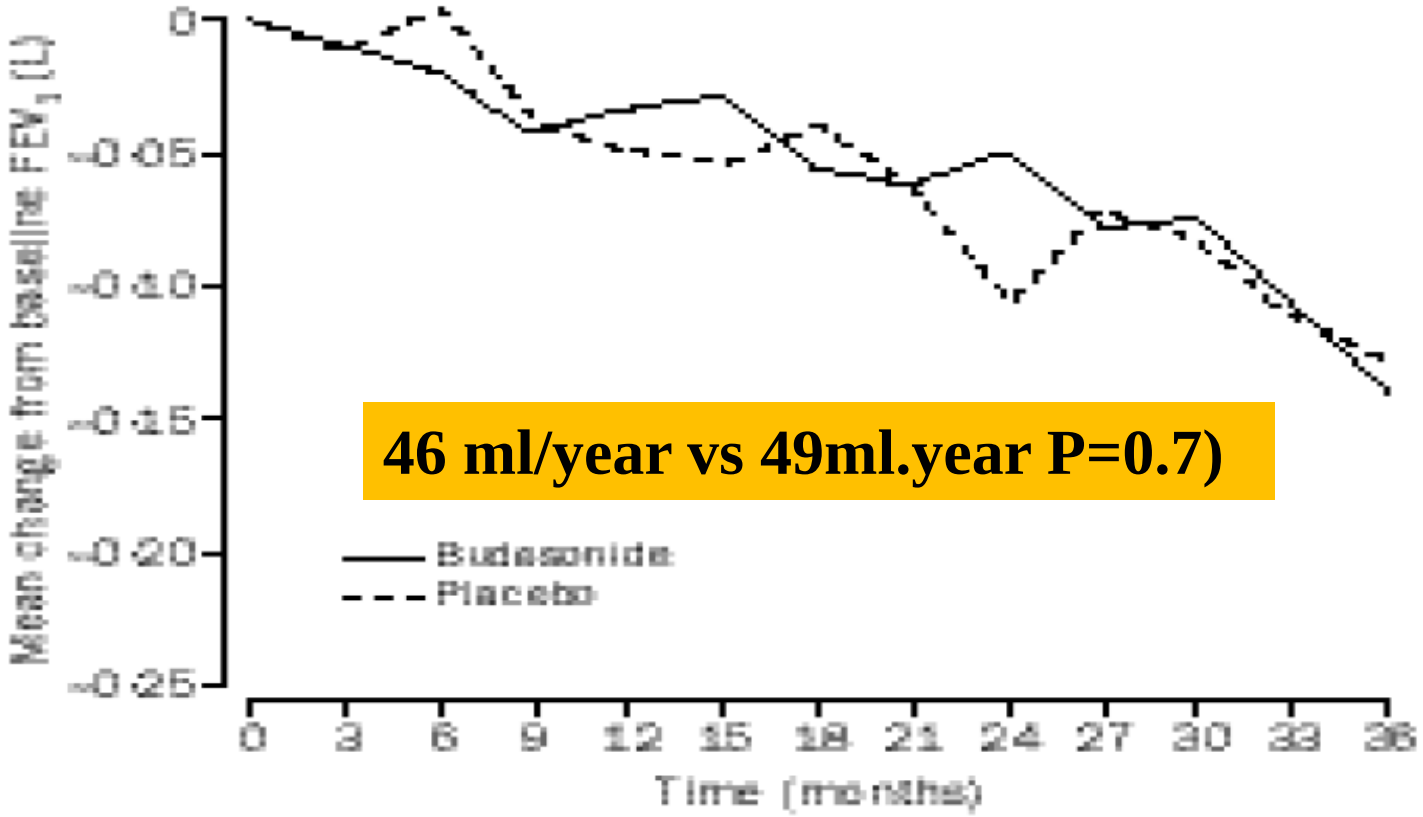


57 ml/year vs 69ml.year P=0.39)

Pauwels A, et al. N Engl J Med 1999;340:1948-53

Inhaled budesonide in mild& moderate COPD: the Copenhagen City Heart study

Participant: mean age 59 years, mean post-BD FEV_1 86% pred.
current smoker 76%
Primary outcome: the rate of post-BD FEV_1 decline

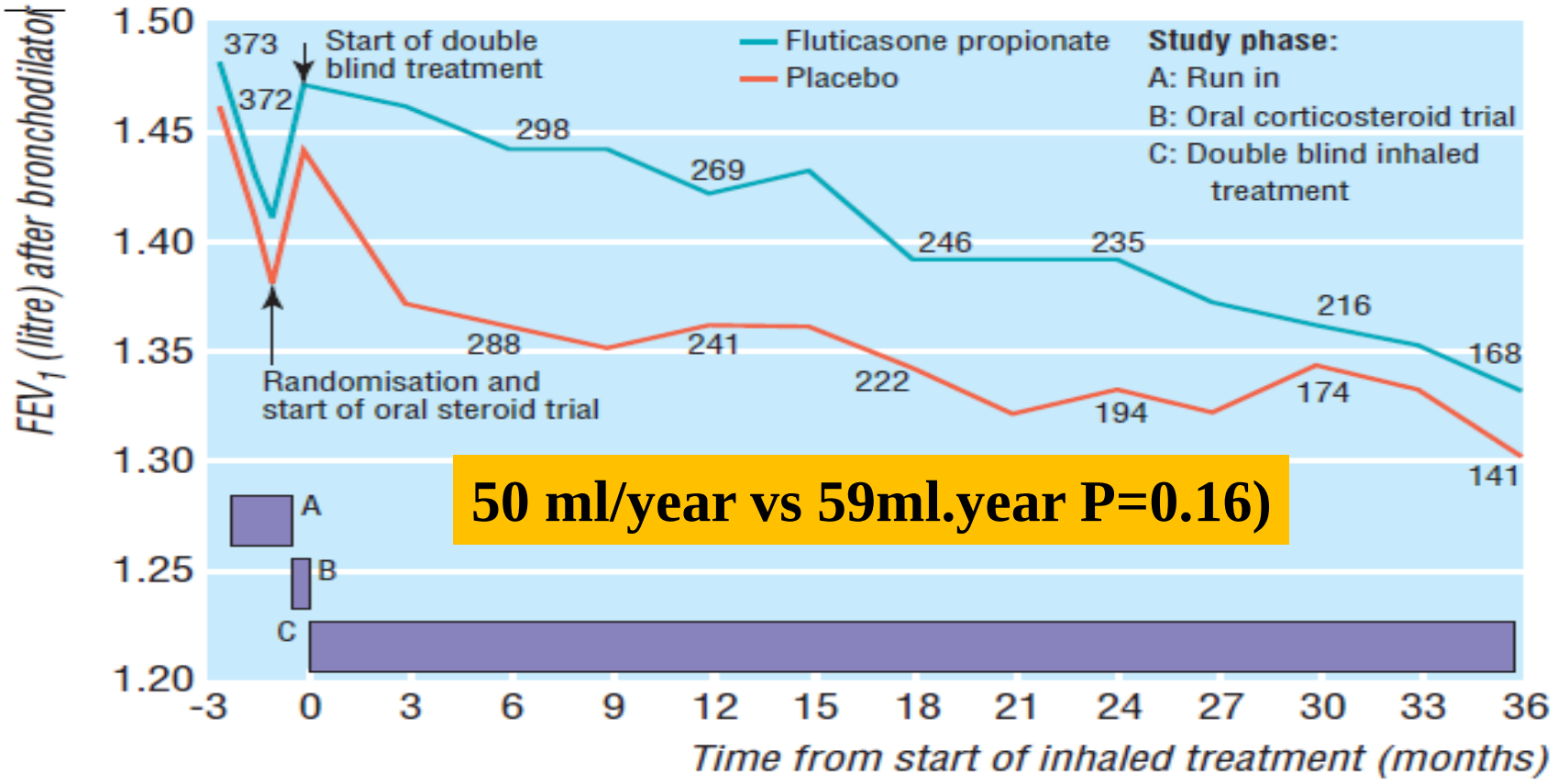


46 ml/year vs 49ml.year P=0.7)

Vestbo J, et al. L a n c e t 1999; 353: 1 8 1 9 – 2 3

Fluticasone propionate in patients with moderate to severe COPD: the ISOLDE trial

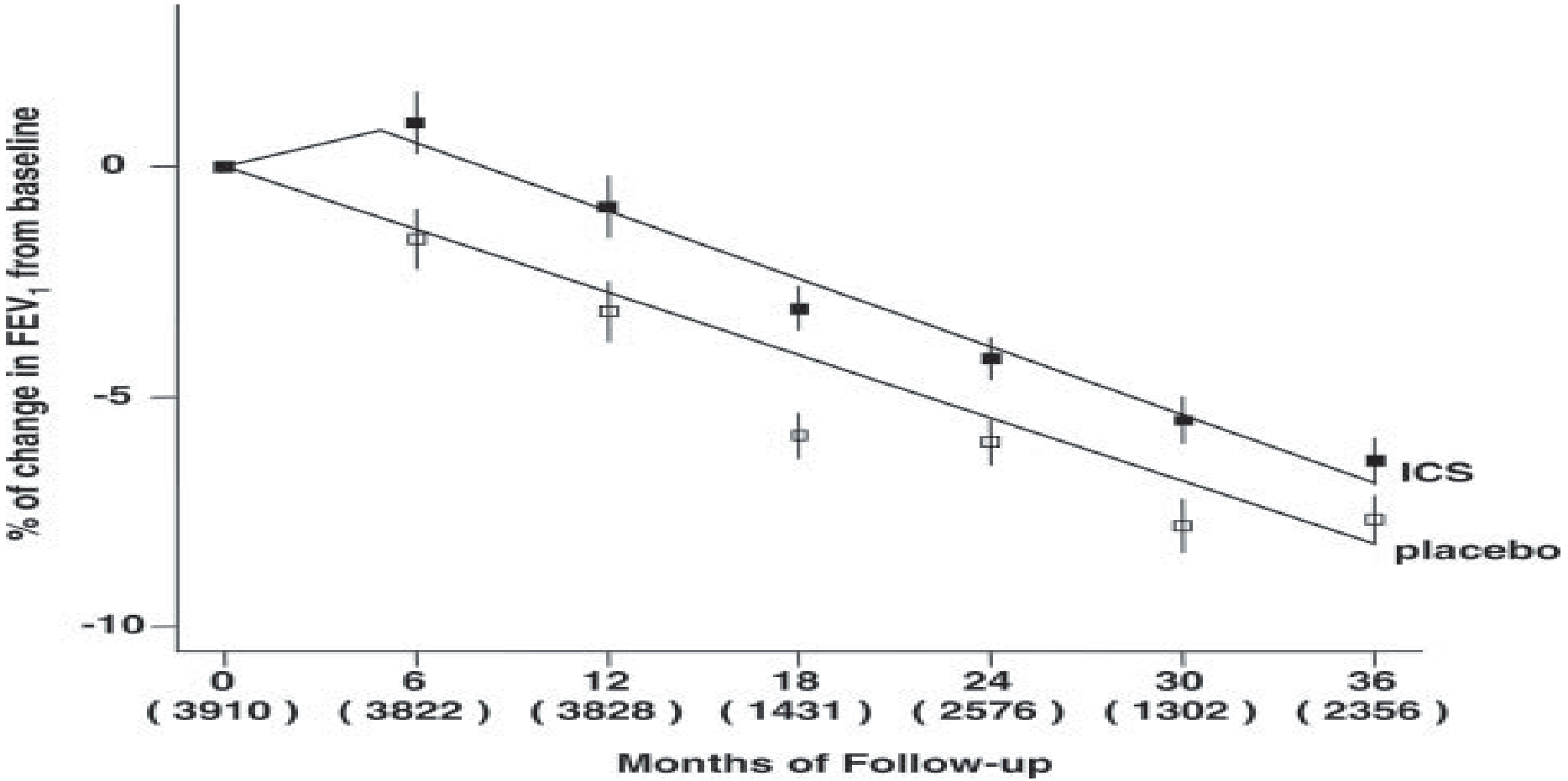
Participant: mean age 63 years, mean post-BD FEV1 50% pred.
Primary outcome: the rate of post-BD FEV_1 decline



Burge PS et al. BMJ 2000;320:1297-303

A pooled analysis of ICS and FEV_1 decline

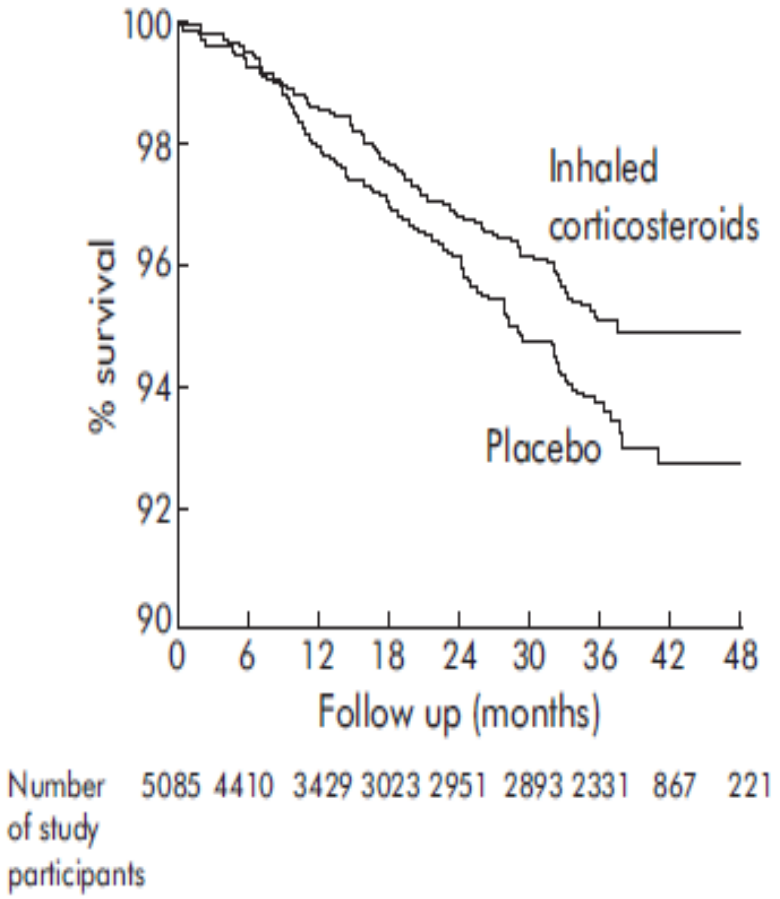
The Inhaled Steroid Effects Evaluation in COPD (ISEEC)
- 7 RCTs of ICS vs placebo lasting ≥12 months



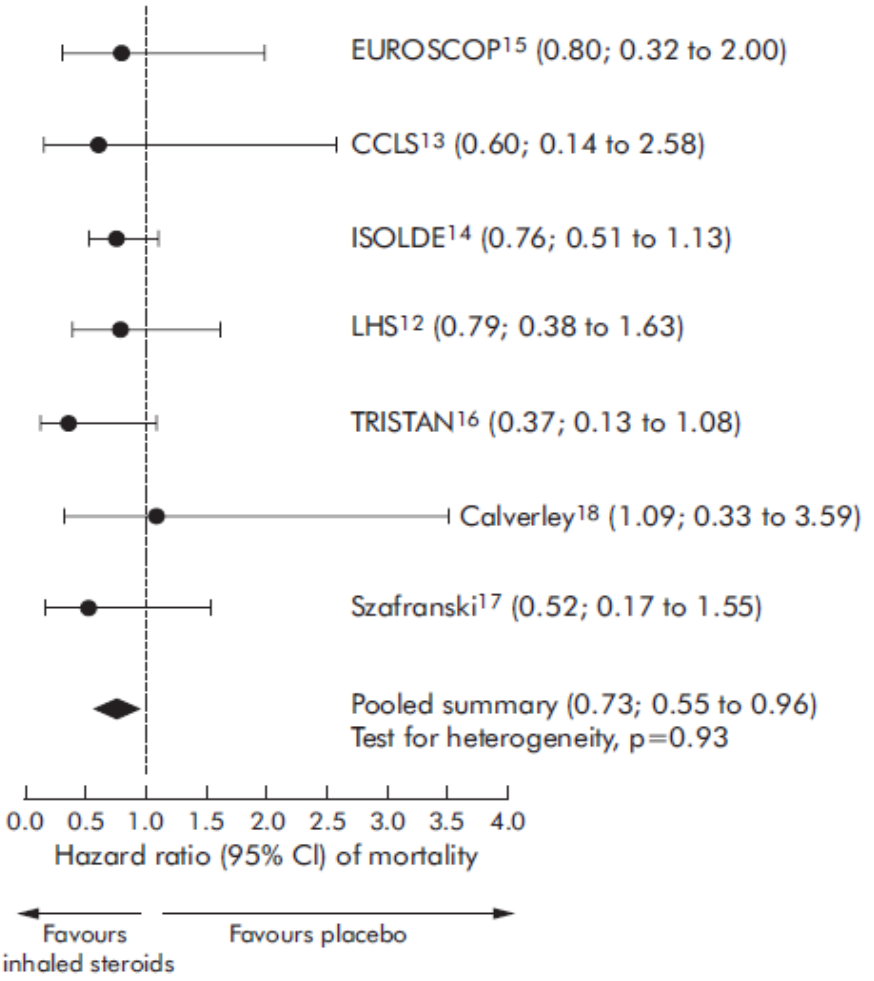
Soriano JB, et al. CHEST 2007; 131:682–689

A pooled analysis of ICS and mortality

HR 0.75; 95% CI 0.57 to 0.99

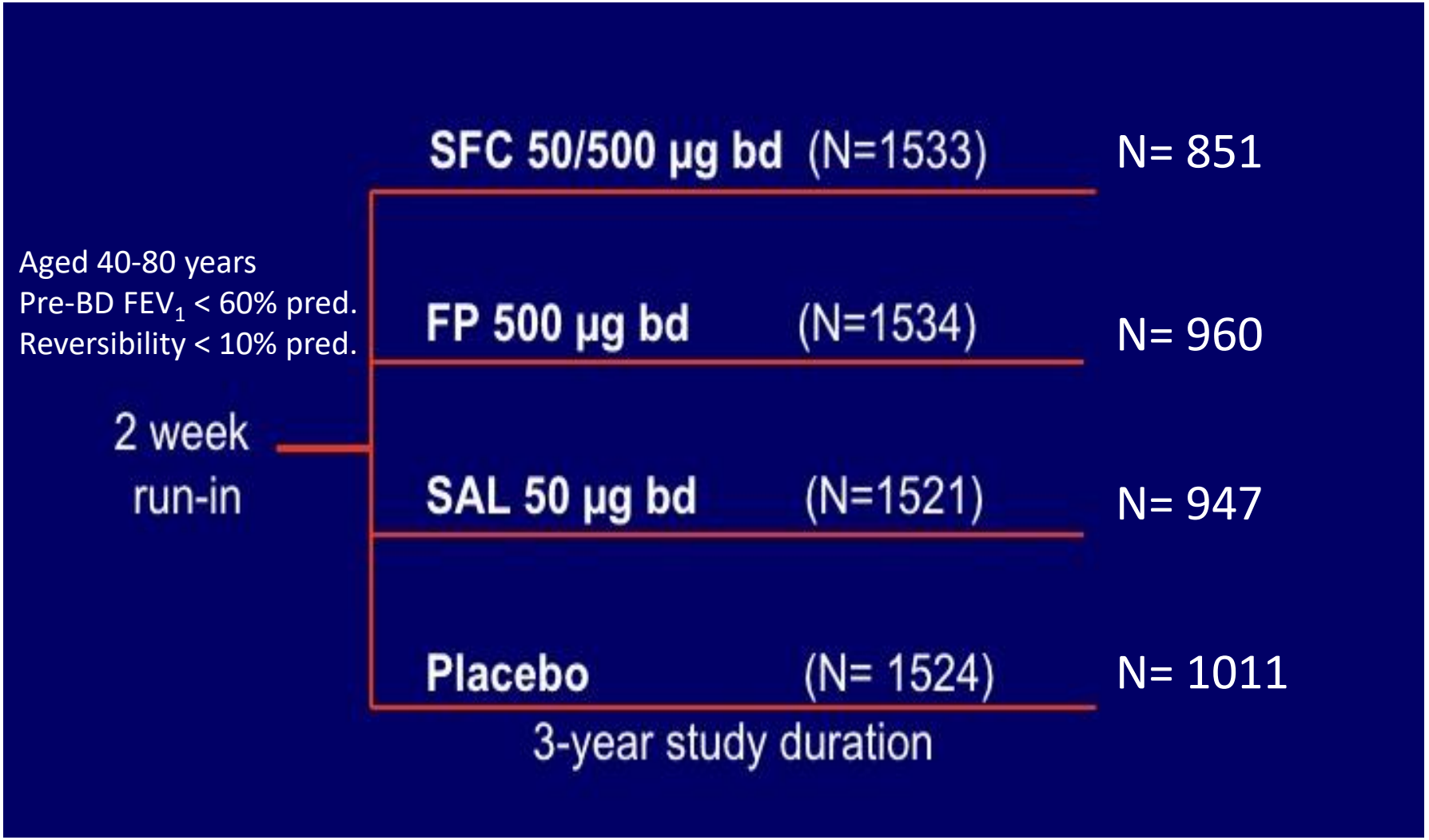


HR 0.73; 95% CI 0.55 to 0.96



Sin D D,e t al. Thorax 2005;60:992–997

Towards a Revolution in COPD Health (TORCH) study



Calverley et al. N Engl J Med 2007;356:775-89.

Baseline characteristics in TORCH study

	Placebo (n=1524)	Combination (n=1533)
Mean age, y	**65.0**	**65.0**
Male, %	76	75
Mean pack-years	48.6	47.0
Mean FEV_1, L (post-BD)	1.22	1.22
Mean FEV_1, % pred (post-BD)	**44.1**	**44.3**
Exacerbation-no.	1.0	1.0
SGRQ score	**49.0**	**48.9**

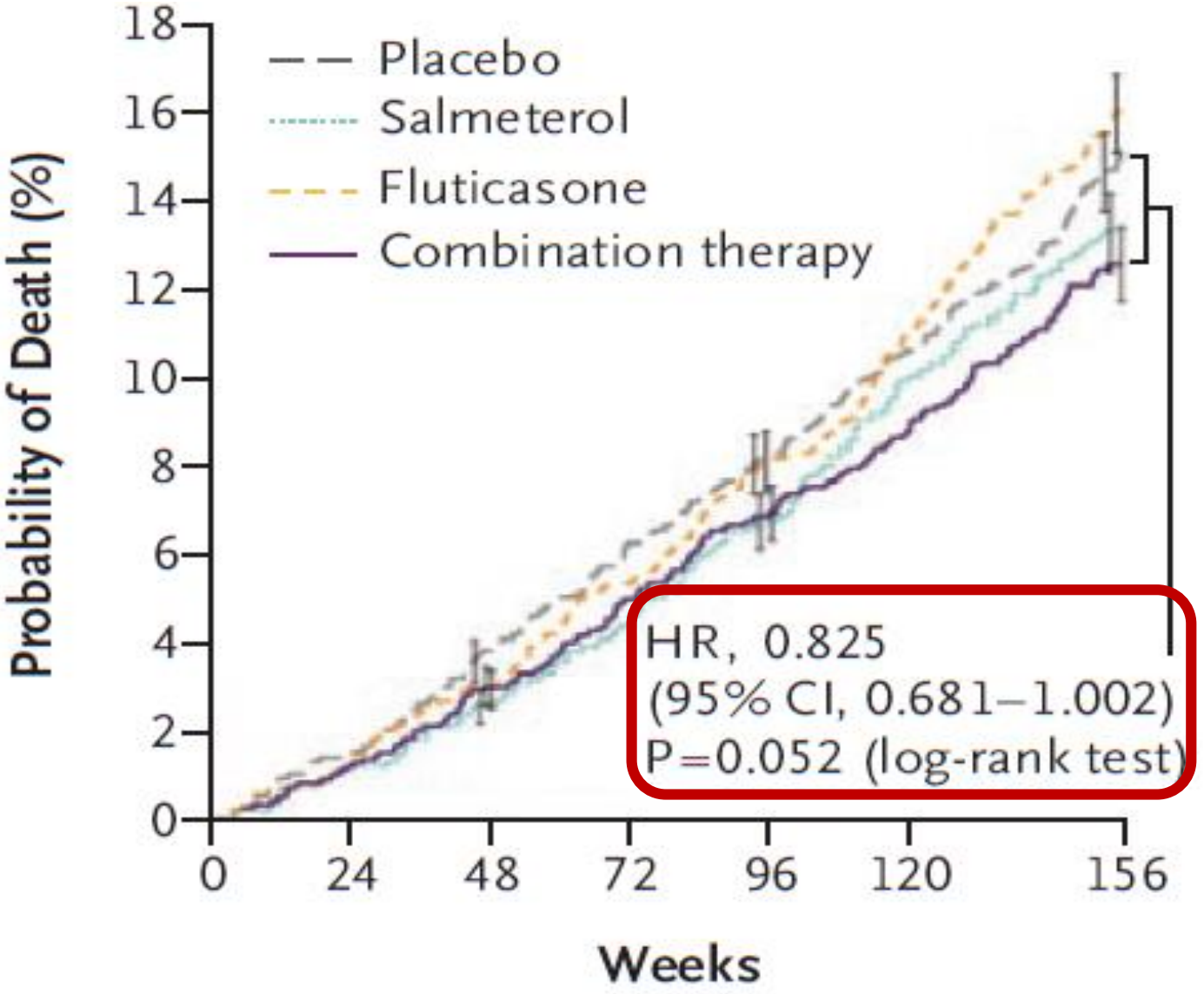
Calverley et al. N Engl J Med 2007;356:775-89.

Baseline post-BD FEV_1 % pred. In TORCH study

FEV_1, % predicted, n (%)	placebo (n = 1524)	SAL (n = 1521)	FP (n = 1534)	SFC (n = 1533)	total (n = 6112)
< 30%	214 (14)	260 (17)	220 (14)	243 (16)	937 (15)
30% to < 50%	775 (51)	739 (49)	777 (51)	728 (47)	3019 (49)
50% to < 60%	347 (23)	335 (22)	329 (21)	349 (23)	1360 (22)
60% to < 70%	148 (10)	160 (11)	165 (11)	173 (11)	646 (11)
70% to < 80%	35 (2)	25 (2)	34 (2)	28 (2)	122 (2)
≥ 80%	5 (< 1)	2 (< 1)	9 (< 1)	12 (< 1)	28 (< 1)

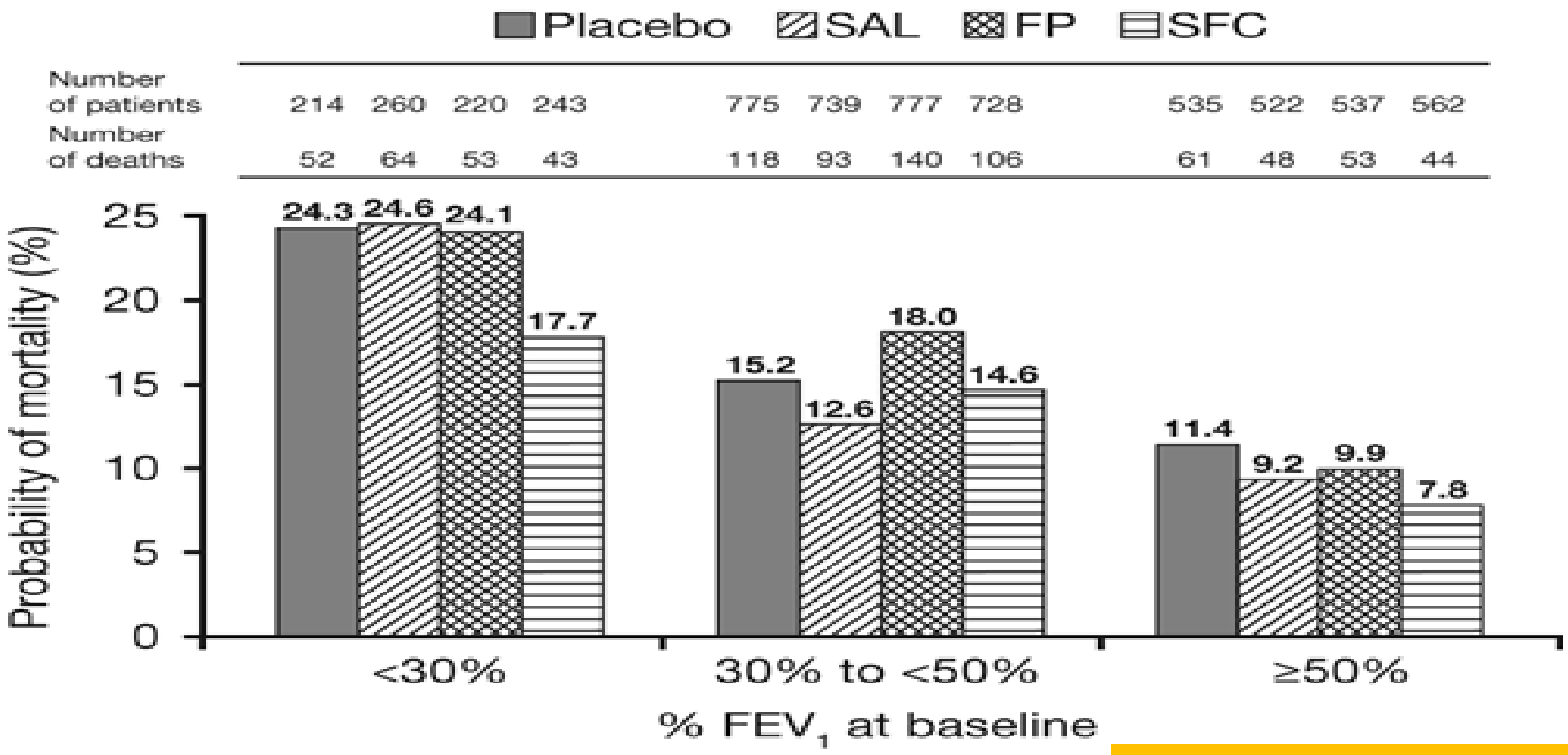
Jenkins CR,e t al. Respiratory Research 2009, **10:59**

Primary Outcome: all-cause mortality



Calverley et al. N Engl J Med 2007;356:775-89.

All cause mortality by baseline post-BD FEV_1 % predicted in TORCH study



HR 0.70
95% CI: 0.47-1.05

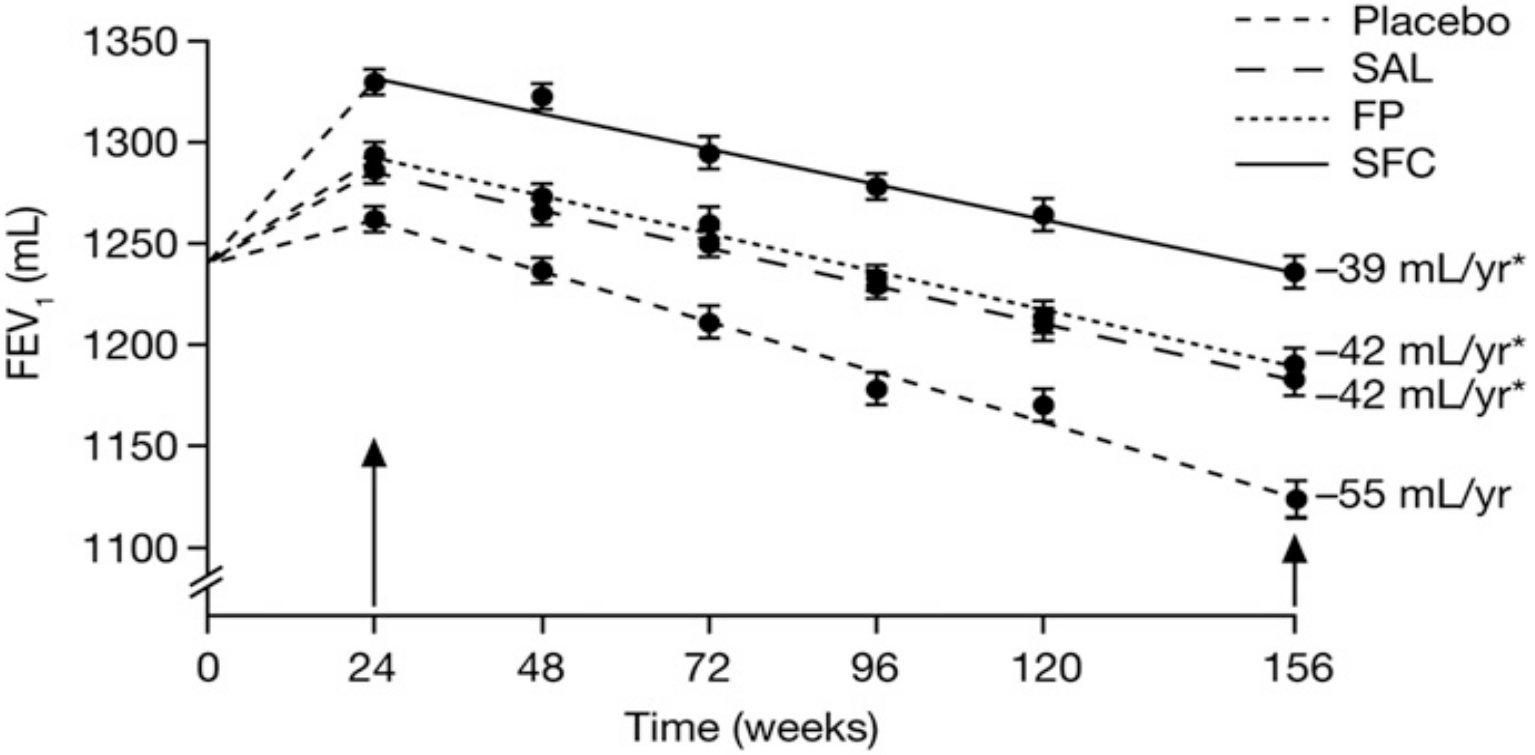
HR 0.95
95% CI: 0.73-1.24

HR 0.67
95% CI: 0.45-0.98

Jenkins CR,e tal. Respiratory Research 2009, **10:59**

A *post-hoc* analysis of TORCH study: Post-BD FEV_1 decline

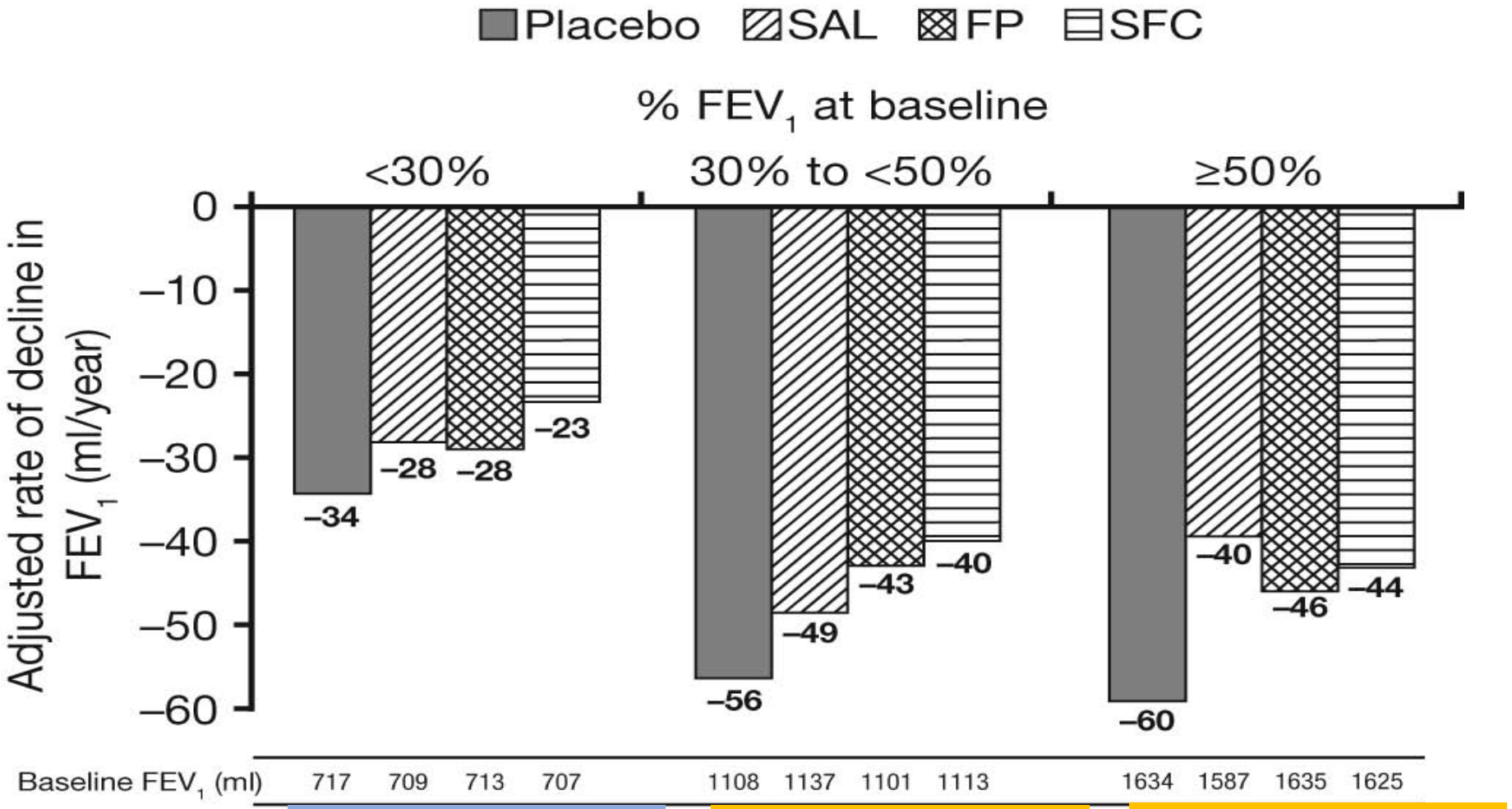
Δ16ml SFC compared with placebo *P < 0.003



No. of patients							
Placebo	1261	1248	1128	1049	979	906	819
SAL	1334	1317	1218	1127	1054	1012	934
FP	1356	1346	1230	1157	1078	1006	908
SFC	1392	1375	1281	1180	1139	1073	975

Celli BR, et al. Am J Respir Crit Care Med 2008; 178: 332–338

FEV_1 decline by baseline post-BD FEV_1 % predicted in TORCH study



Δ11ml
95% CI: -8~30

Δ16ml
95% CI: 5~28

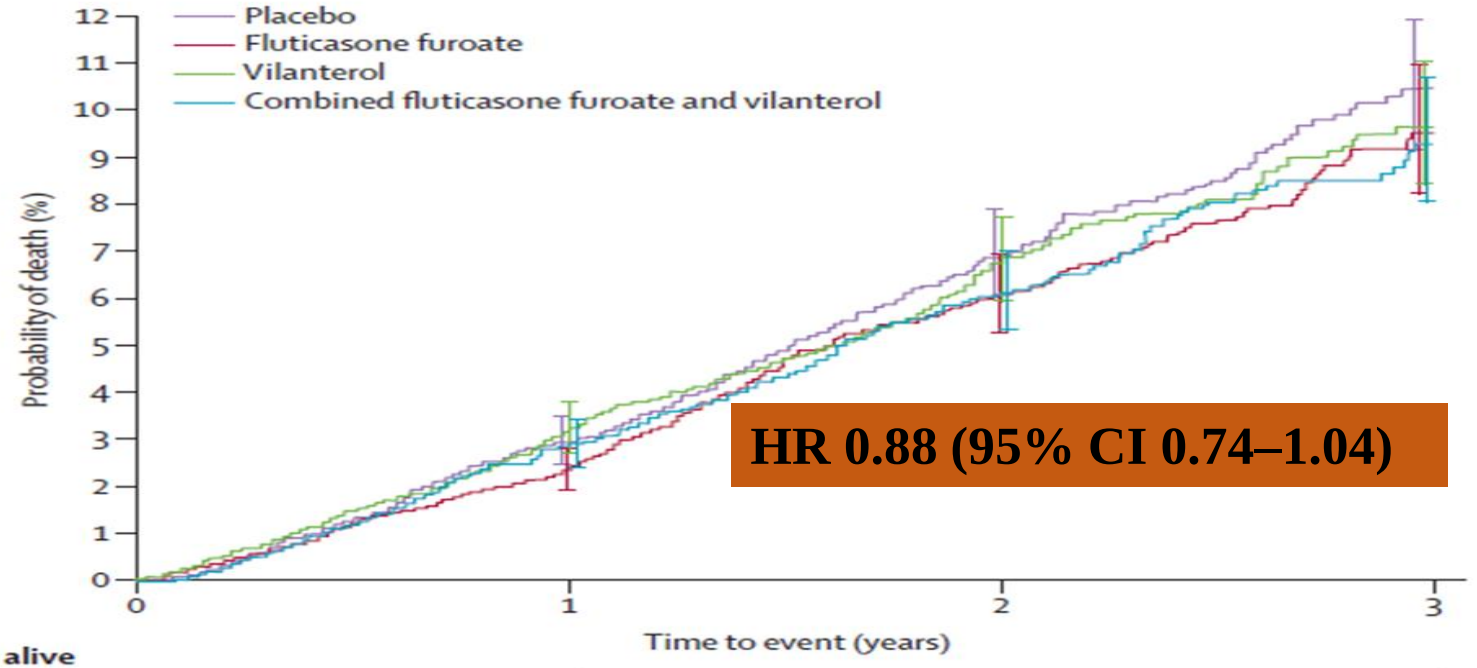
Δ16ml
95% CI: 0~32

Jenkins CR,e tal. Respiratory Research 2009, **10:59**

The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study

Participant: Patients had to have a history, or be at increased risk, of CVD mean age 65 years, mean post-BD FEV1 60% pred.

Primary outcome: all cause mortality

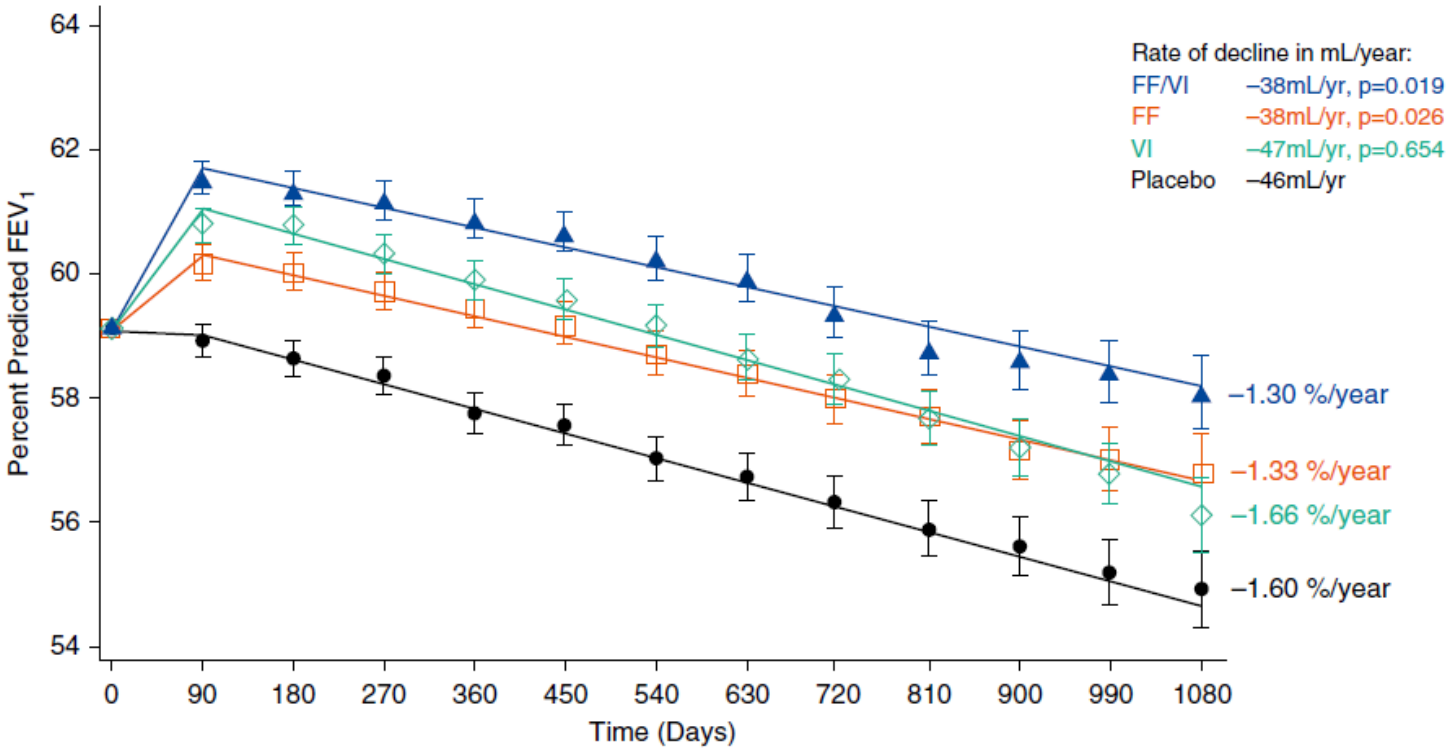


Number alive				
Placebo	4111	3465	1715	469
Fluticasone furoate	4135	3499	1734	490
Vilanterol	4118	3466	1734	486
Combined fluticasone furoate and vilanterol	4121	3484	1718	485

Vestbo J, et al. Lancet 2016; 387: 1817–26

The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study

Secondary outcome: Post-BD FEV_1 decline



N at visit:													
▲ FF/VI 100/25	3,912	3,883	3,731	3,610	3,505	2,864	2,391	1,997	1,633	1,290	1,035	827	545
□ FF 100	3,879	3,858	3,688	3,580	3,452	2,777	2,311	1,936	1,569	1,246	1,001	792	528
◇ V125	3,866	3,830	3,658	3,554	3,438	2,813	2,347	1,971	1,612	1,300	1,043	831	542
● Placebo	3,800	3,782	3,563	3,396	3,279	2,678	2,197	1,858	1,498	1,171	949	736	486

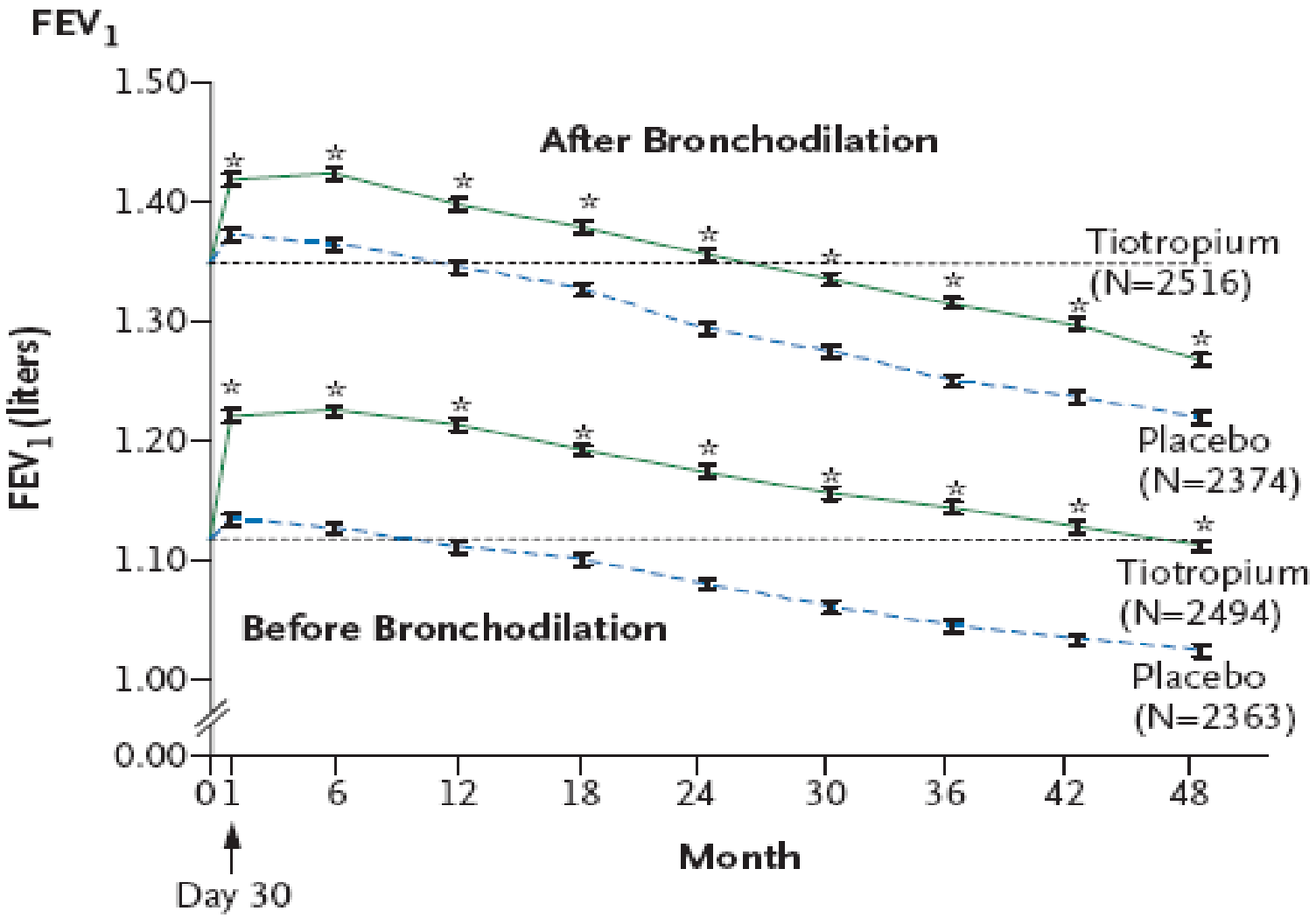
Calverley PMA, et al. AJRCCM 2018; 197: 47–55

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial:

	Tiotropium (n=2986)	Placebo (n=3006)
Mean age, y	64.5	64.5
Male, %	75	74
Mean pack-years	49	48
Mean FEV_1, L (post-BD)	1.33	1.32
Mean FEV_1, % pred (post-BD)	48	47
GOLD stage (%) **II** **III** **IV**	 **46** **44** **8**	 **45** **44** **9**
Withdrawal	**1099 (37%)**	**1358 (45%)**

Tashkin et al. N Engl J Med 2008;359:1543-54.

Co-primary outcomes of the UPLIFT trial



40m/yr
vs
42 ml/yr

30 ml/yr
vs
30 ml/yr

Tashkin et al. N Engl J Med 2008;359:1543-54.

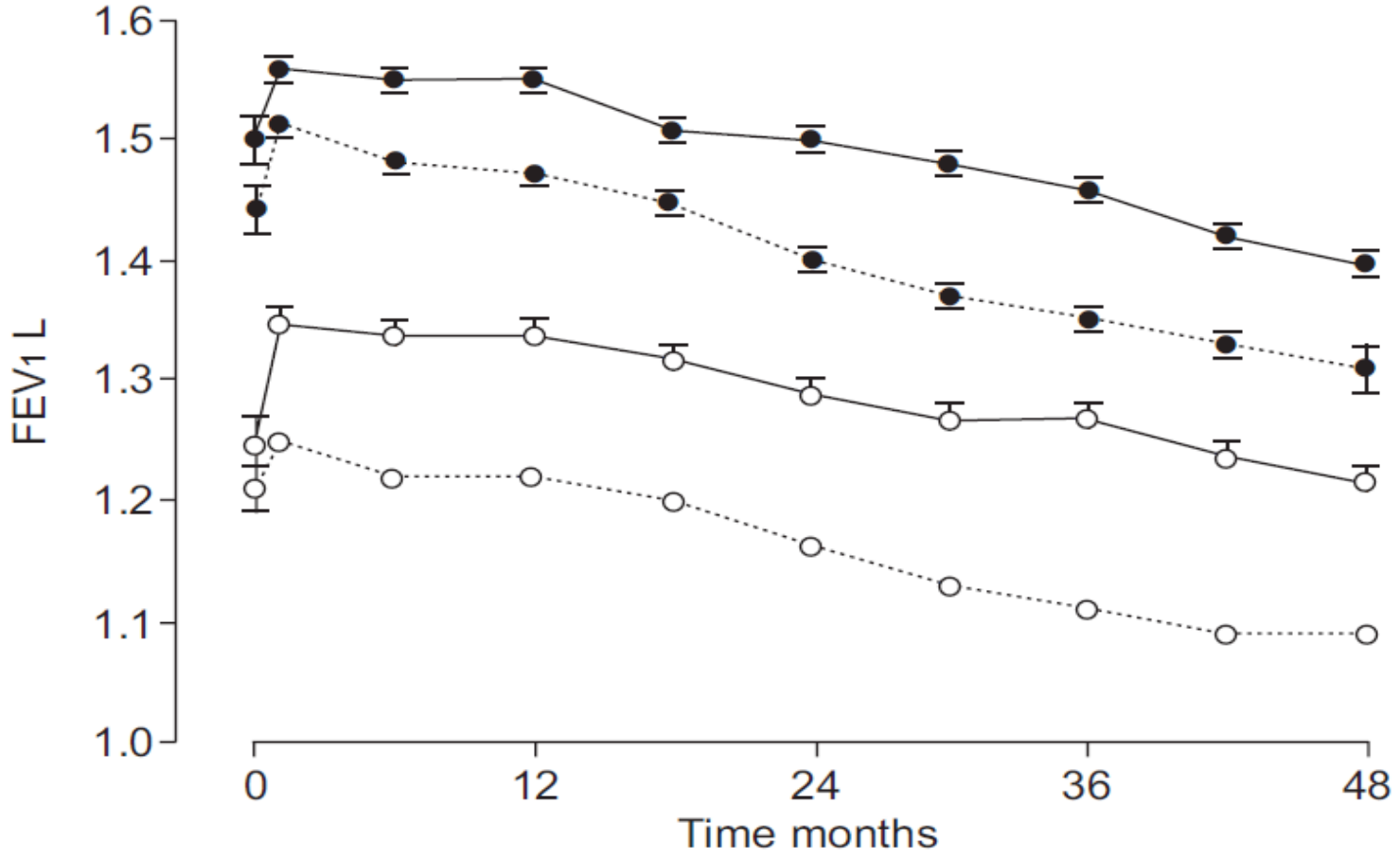
Baseline respiratory medications in UPLIFT trial

Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β_2-agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3

Tashkin et al. N Engl J Med 2008;359:1543-54.

Tiotropium as a first maintenance:

- **Secondary analysis of the UPLIFT trial**



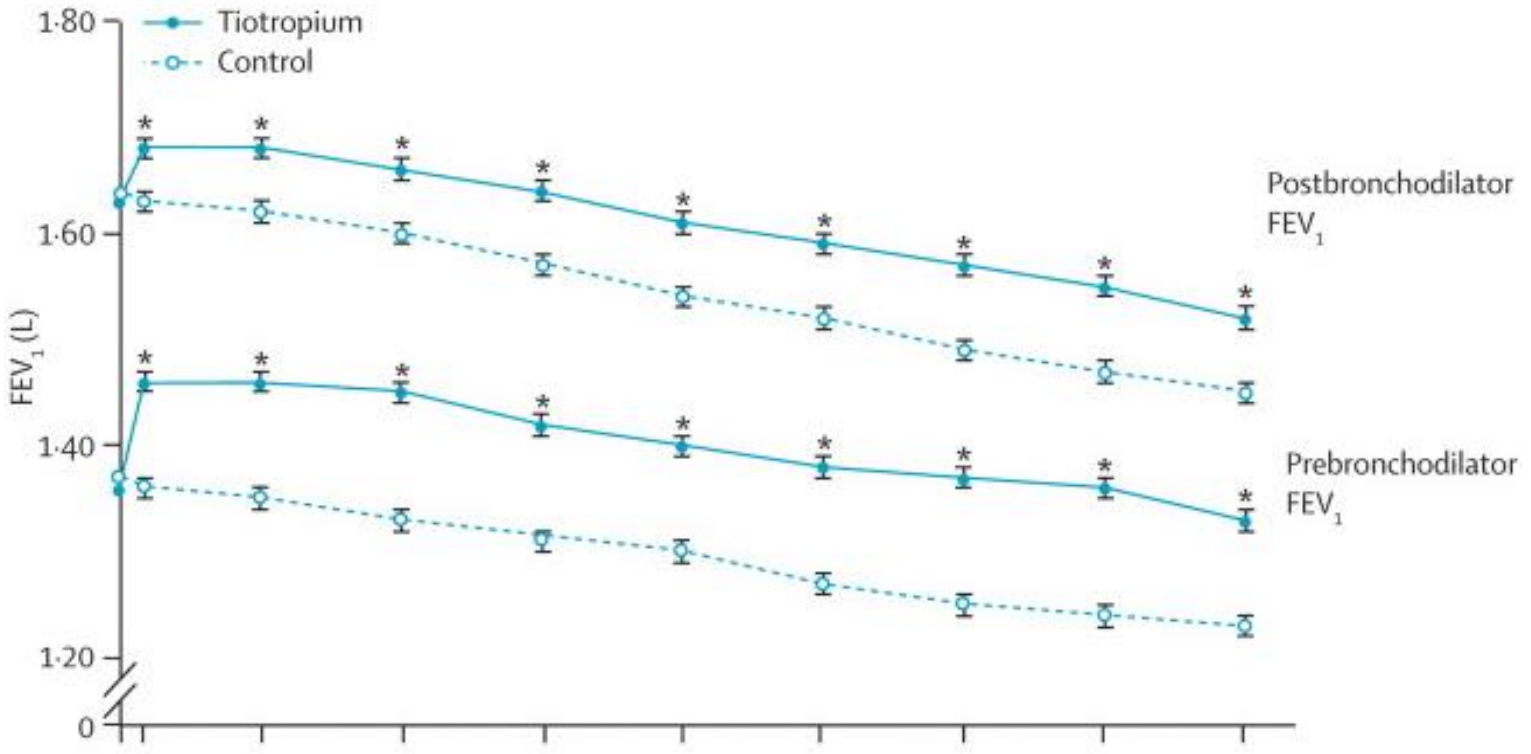
42m/yr
vs
53 ml/yr
(p=0.026)

35 ml/yr
45 ml/yr
(p=0.049)

Troosters T, et al. Eur Respir J 2010; 36: 65–73

Effect of tiotropium on outcomes in patients with moderate COPD(UPLIFT)

Pre-specified subgroup analysis on patients with GOLD stage II



Post-BD FEV_1 decline
Tiotropium: control = 43 mL/year : 49 mL/year (p=0.024)

Decramer M, et al. Lancet 2009; 374: 1171–78

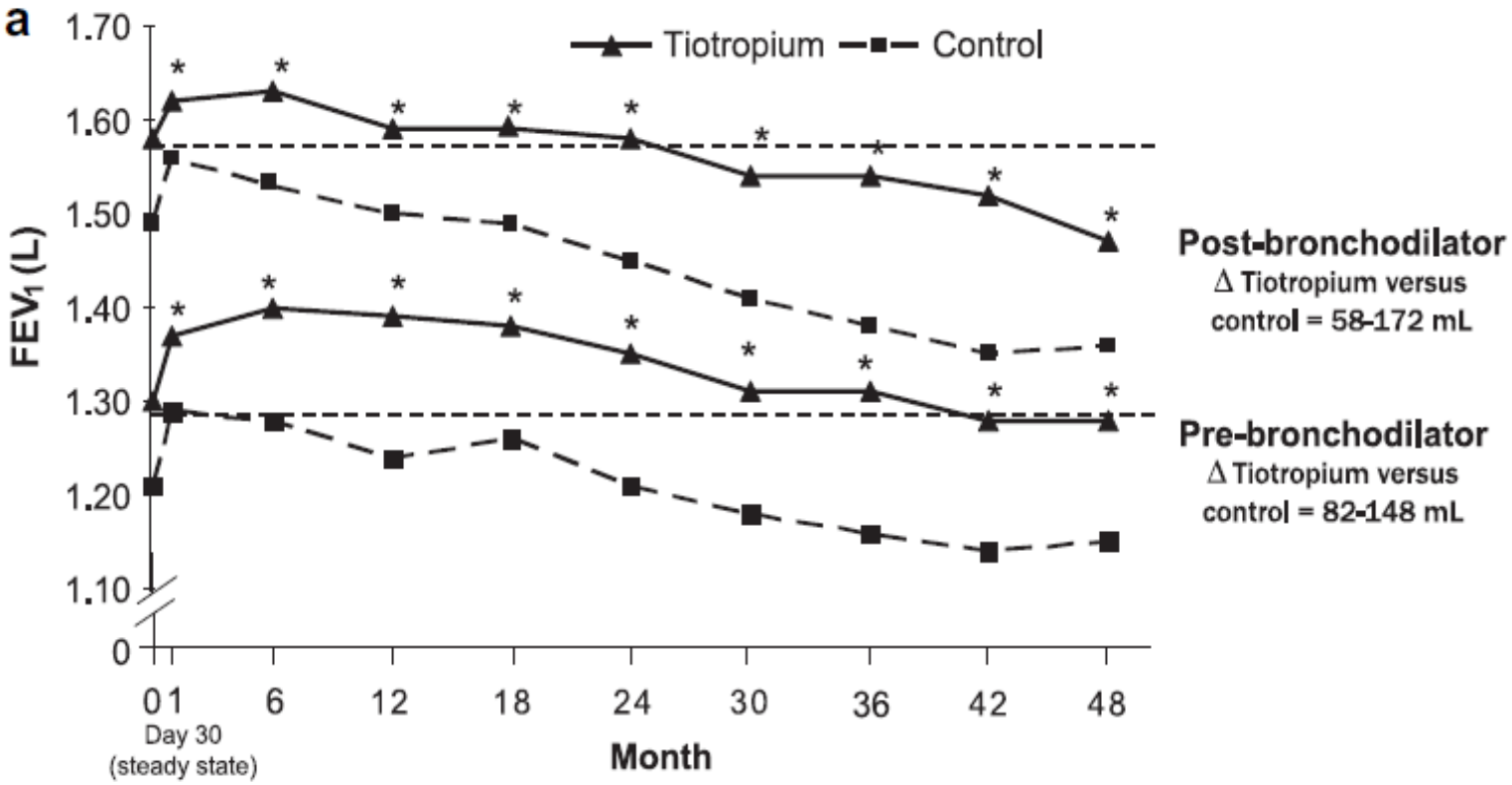
Effect of tiotropium on outcomes in patients with moderate COPD(UPLIFT)

Median time to first exacerbation (months [95% CI])				
GOLD stage II	**23·1 (21·0–26·3)**	**17·5 (15·9–19·7)**	**0·82 (0·75–0·90)**	**<0·0001**
GOLD stage III	13·2 (11·5–14·6)	9·8 (8·8–11·3)	0·87 (0·79–0·95)	0·002
GOLD stage IV	9·7 (8·2–12·0)	8·8 (6·9–11·7)	0·99 (0·81–1·21)	0·956
Mean number of exacerbations (per patient-year [95% CI])				
GOLD stage II	0·56 (0·52–0·60)	0·70 (0·65–0·75)	0·80 (0·72–0·88)	<0·0001
GOLD stage III	0·85 (0·80–0·90)	0·97 (0·91–1·03)	0·88 (0·80–0·95)	0·003
GOLD stage IV	1·05 (0·92–1·21)	1·15 (1·00–1·31)	0·92 (0·76–1·12)	0·397

Decramer M, et al. Lancet 2009; 374: 1171–78

Tiotropium in young COPD patients

- **Pre-specified post-hoc analysis**
- **356 patients with COPD ≤ 50 years old from the UPLIFT trial**



FEV_1, forced expiratory volume in 1 second
*p<0.05 versus control. Repeated measure analysis of variance was used to estimate means. Estimated means are adjusted for baseline measurements. Patients with ≥3 measurements after Day 30 were included in the analysis.

Morice AH et al. Respiratory Medicine 2010; 104:1659-1667

Tiotropium in early-stage COPD

Clinical diagnosis of GOLD Stage I/II COPD. Age 40-85 yrs

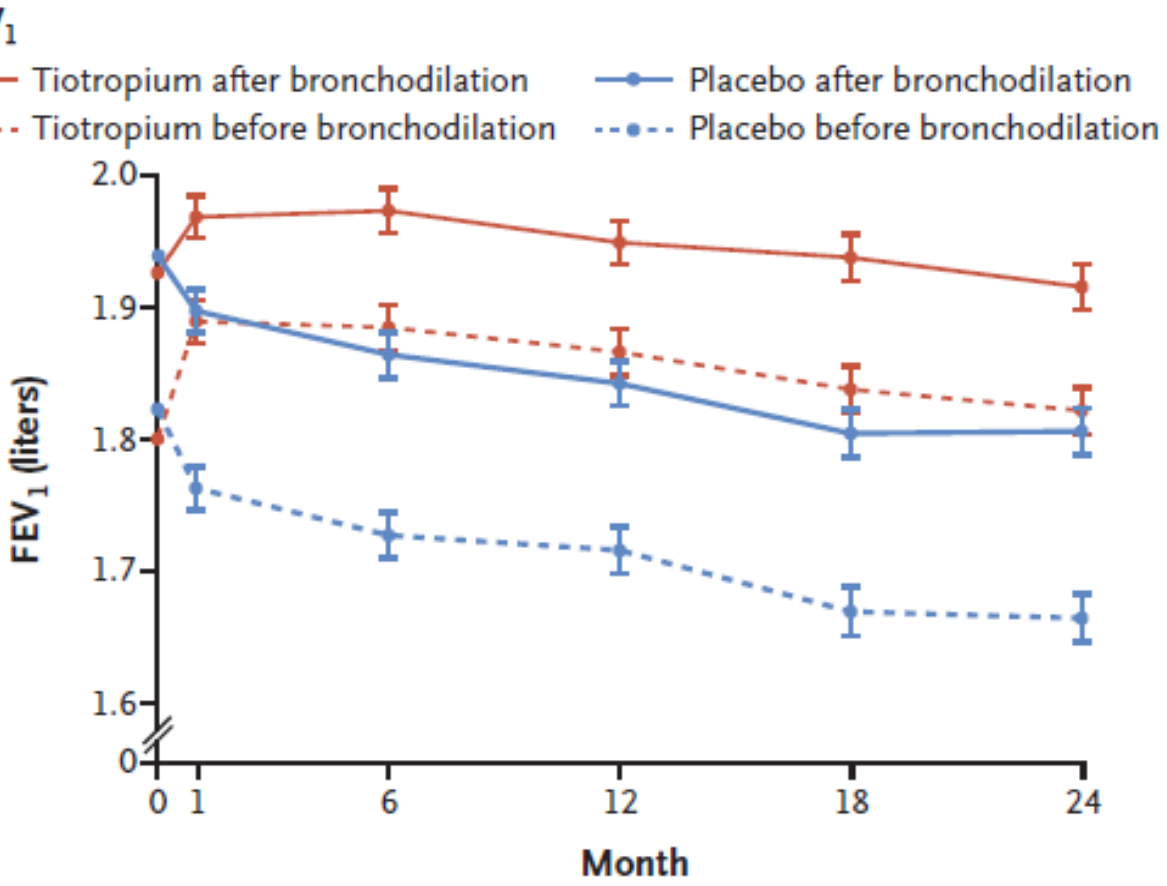
	Tiotropium (n=383)	Placebo (n=388)
Mean age, y	63.9	64.2
Male, %	86.2	84.5
Mean pack-years	55.1	50.6
Mean FEV_1, L (post-BD)	1.94	1.3
Mean FEV_1, % pred (post-BD)	**78.1**	**77.9**
GOLD stage (%)		
I	**43.1**	**44.6**
II	**56.9**	**55.4**
CAT score, Mean	**6.8**	**7.4**
< 10 (%)	**75.2**	**71.1**

Zhou Y, et al. N Engl J Med 2017;377:923-35

Tiotropium in early-stage COPD

Primary endpoint : Pre-BD FEV1 decline

Secondary endpoint : Post-BD FEV1 decline

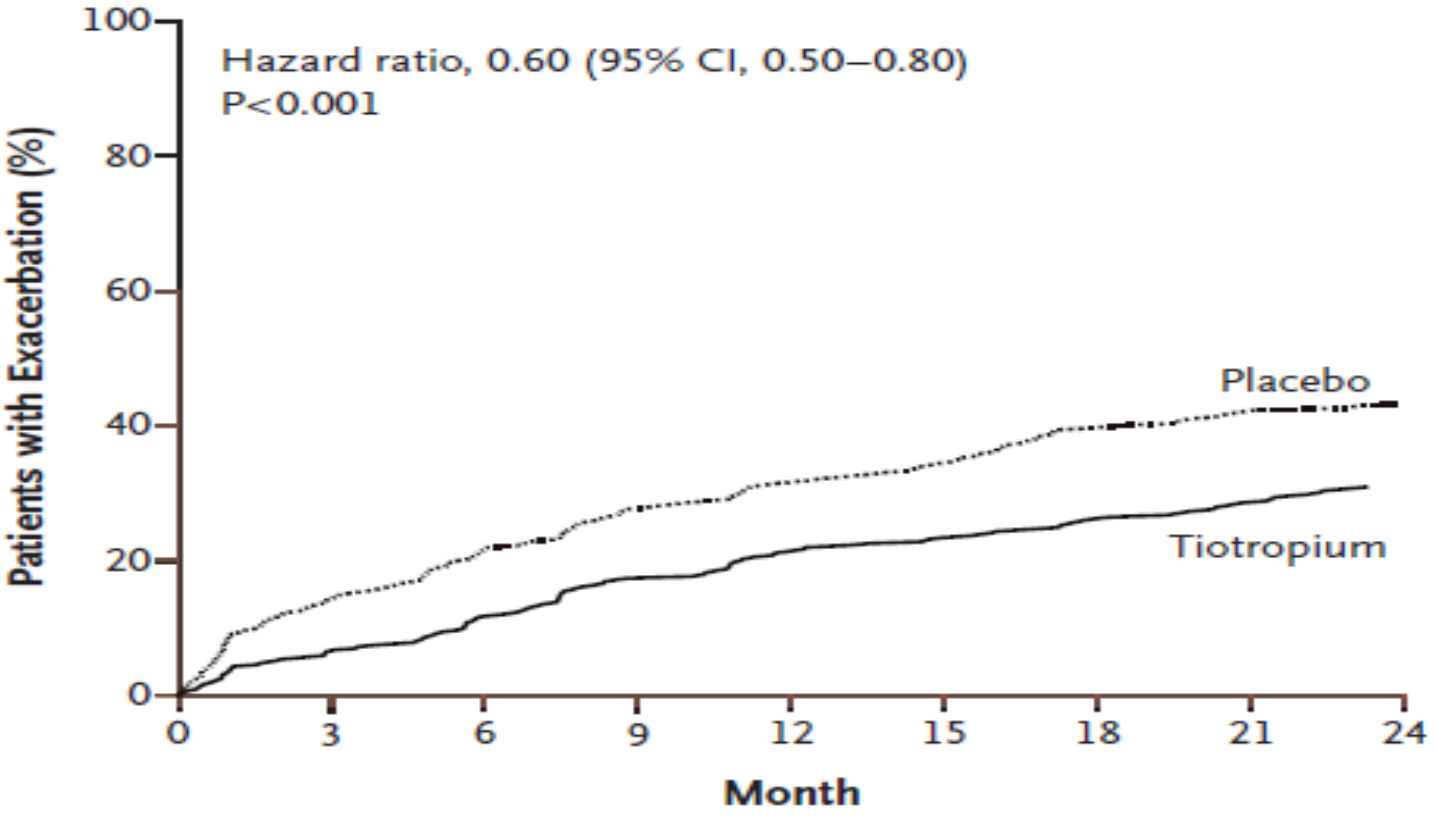


29m/yr
vs
51 ml/yr
(p=0.006)

38 ml/yr
vs
53 ml/yr
(p=0.06)

Zhou Y, et al. N Engl J Med 2017;377:923-35

Tiotropium in early-stage COPD: exacerbation



No. at Risk									
Placebo	383	314	273	244	227	211	188	178	161
Tiotropium	388	349	325	296	276	262	248	236	221

Zhou Y, et al. N Engl J Med 2017;377:923-35

Outcome of pharmacological treatment

- To date, there is **no conclusive clinical trial evidence** **that any existing medications for COPD modify the long term decline in lung function**.
- Post-hoc evidence of such an effect with long-acting bronchodilators and/or inhaled corticosteroids **requires confirmation in specifically designed trials.**

(GOLD 2019)

Does earlier intervention have better outcomes in COPD ?

Smoking cessation	**Yes**
Pharmacotherapy (ICS, ICS/LABA, LAMA)	**Probable but require confirmation study**