Lung function decline in COPD patients

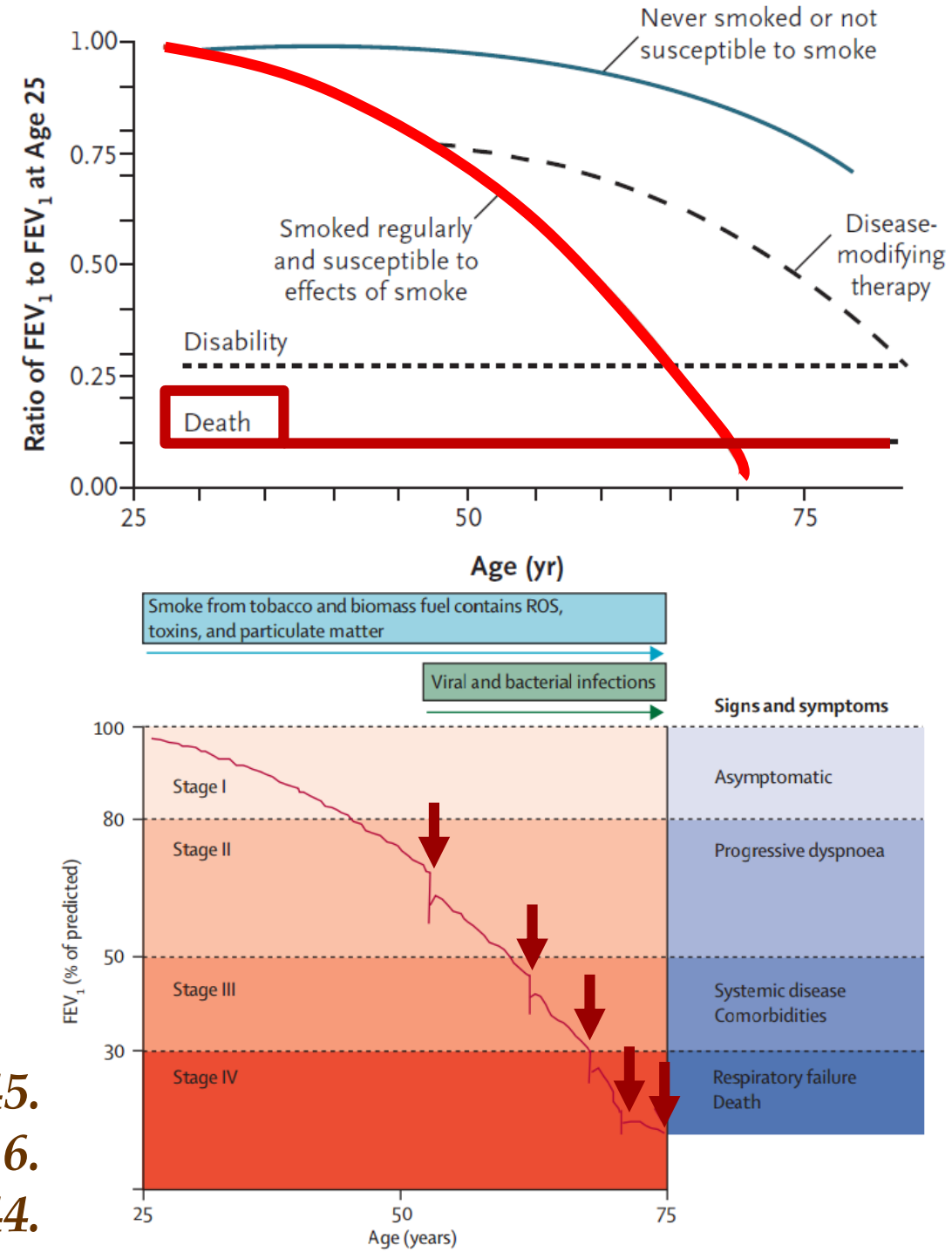
Improving inhaler adherence in patients

2015. 2. 14.

with airway disease

Chang-Hoon Lee, M.D.

The course of COPD



Fletcher C. Br Med J 1977;1:1645.
Reilly J. NEJM 2008;359:1616.
Hansel T. Lancet 2009;374:744.

Goals for treatment of stable COPD

- **Reduce symptom**
  - Relieve symptoms
  - (Improve lung function)
  - Improve exercise tolerance
  - Improve health status

- **Reduce risk**
  - Prevent and treat exacerbations
  - Prevent disease progression
  - Reduce mortality

Exacerbation

Lung function decline

Mortality

GOLD updated 2014.

Contents

- Why lung function declines
- Who shows faster lung function decline
- How to slow lung function decline

Contents

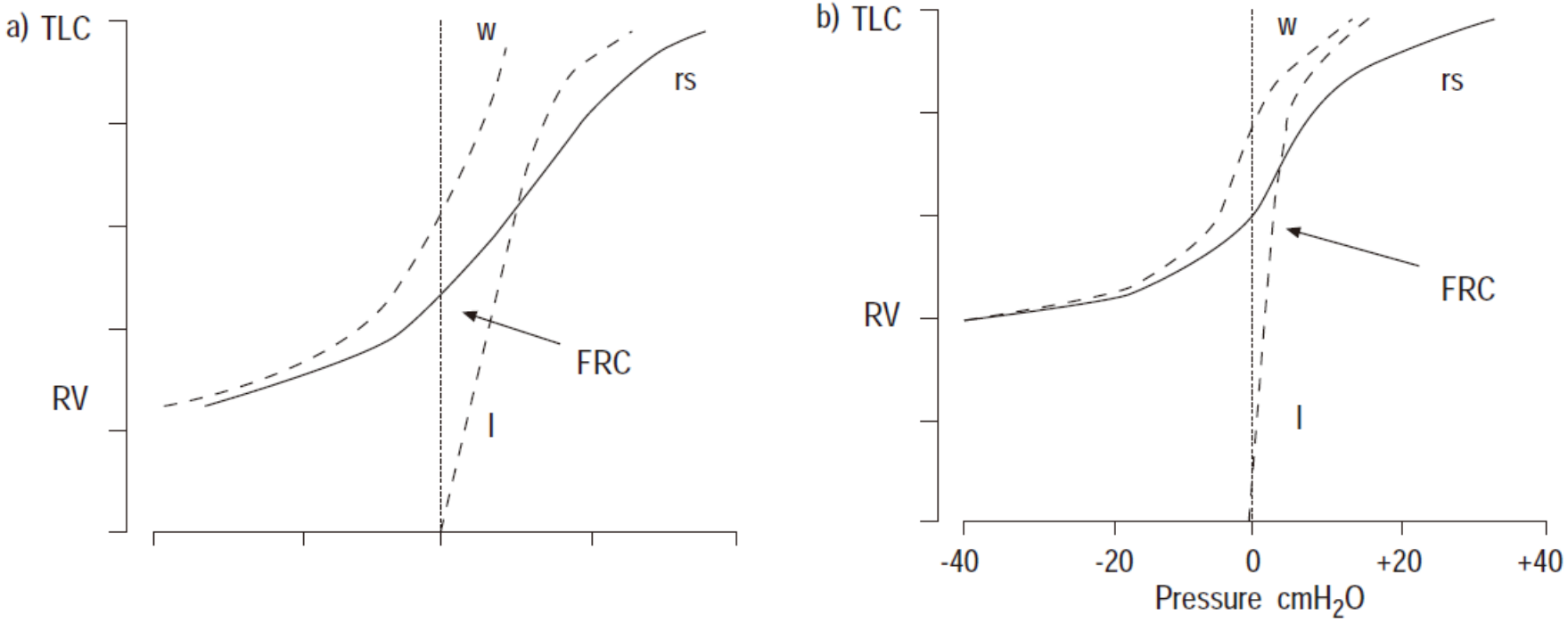
- **Why lung function declines**
- **Who shows faster lung function decline**
- **How to slow lung function decline**

Changes in respiratory system with ageing

- **Lung compliance↑**
  - **Lung elastic recoil ↓**
- **Airway resistance↑**
- **Respiratory muscle strength↓**
- **Chest wall compliance↓**

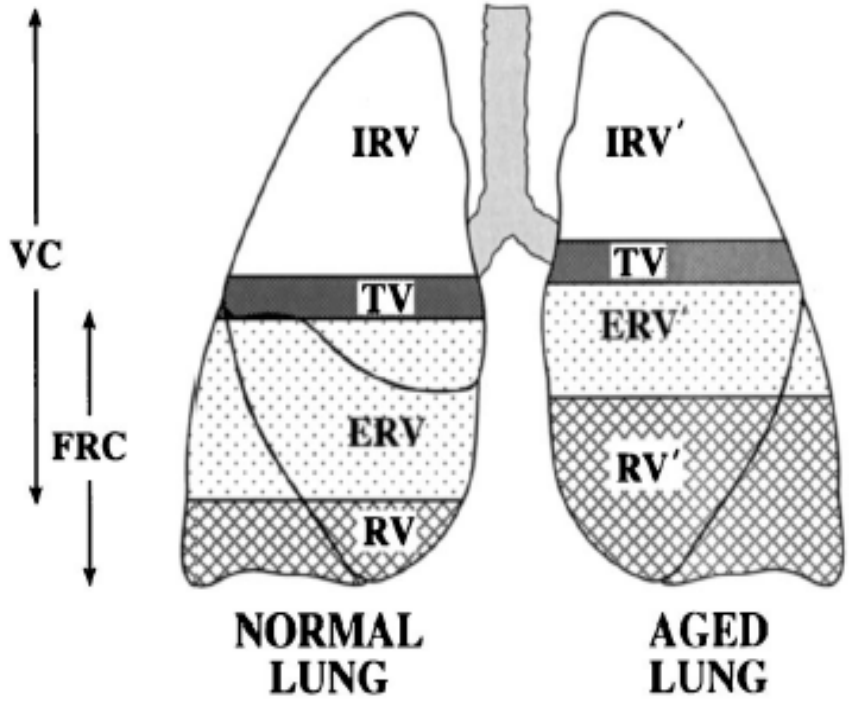
Janssens JP. Eur Respir J 1999;13:197.

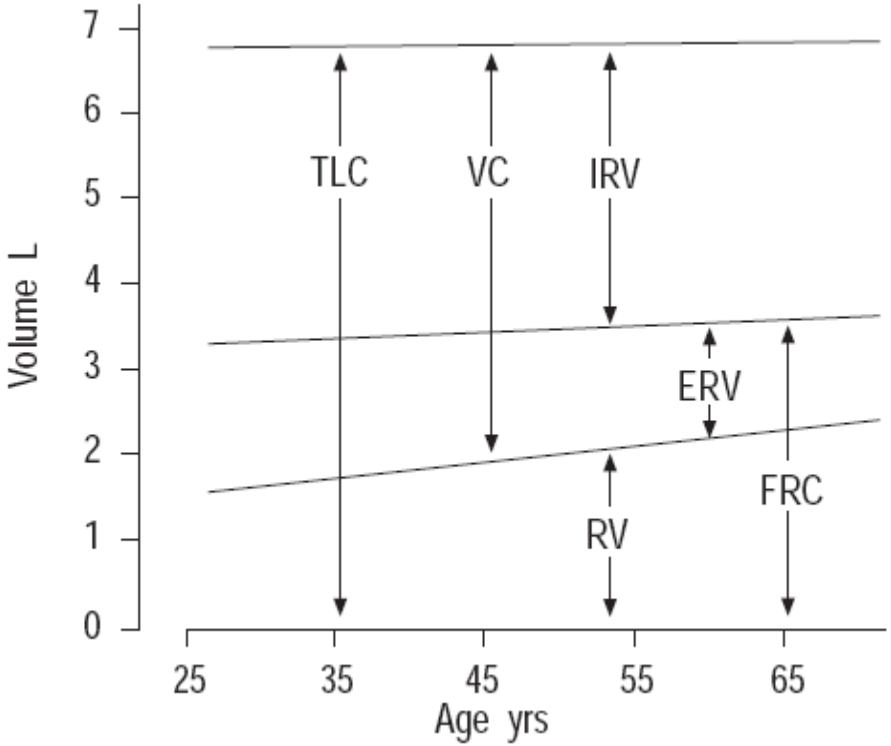
Lung compliance⇧,
Chest wall compliance ⇩ ⇨ FRC⇧



Janssens JP. Eur Respir J 1999;13:197.

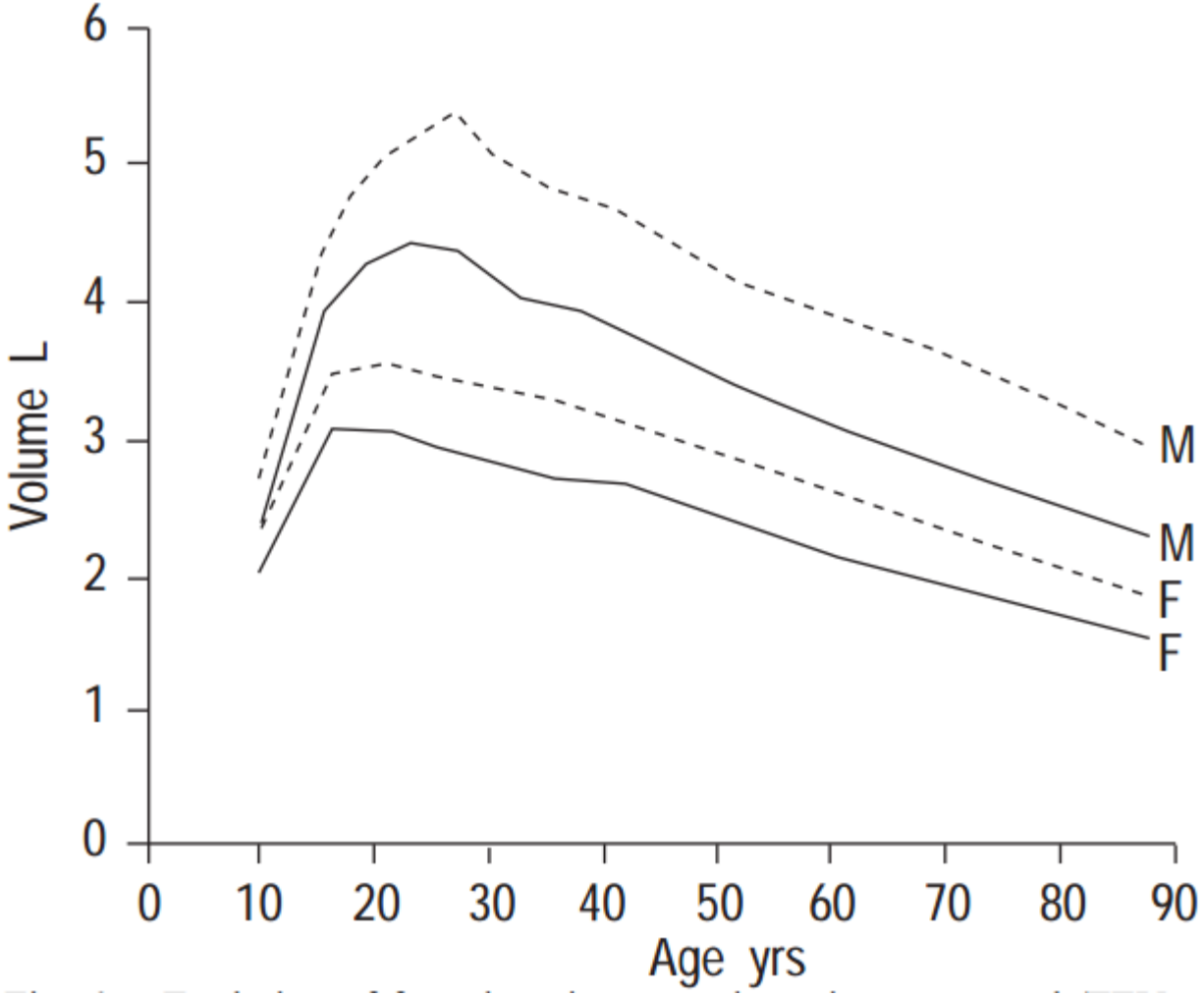
Changes in lung volume with ageing





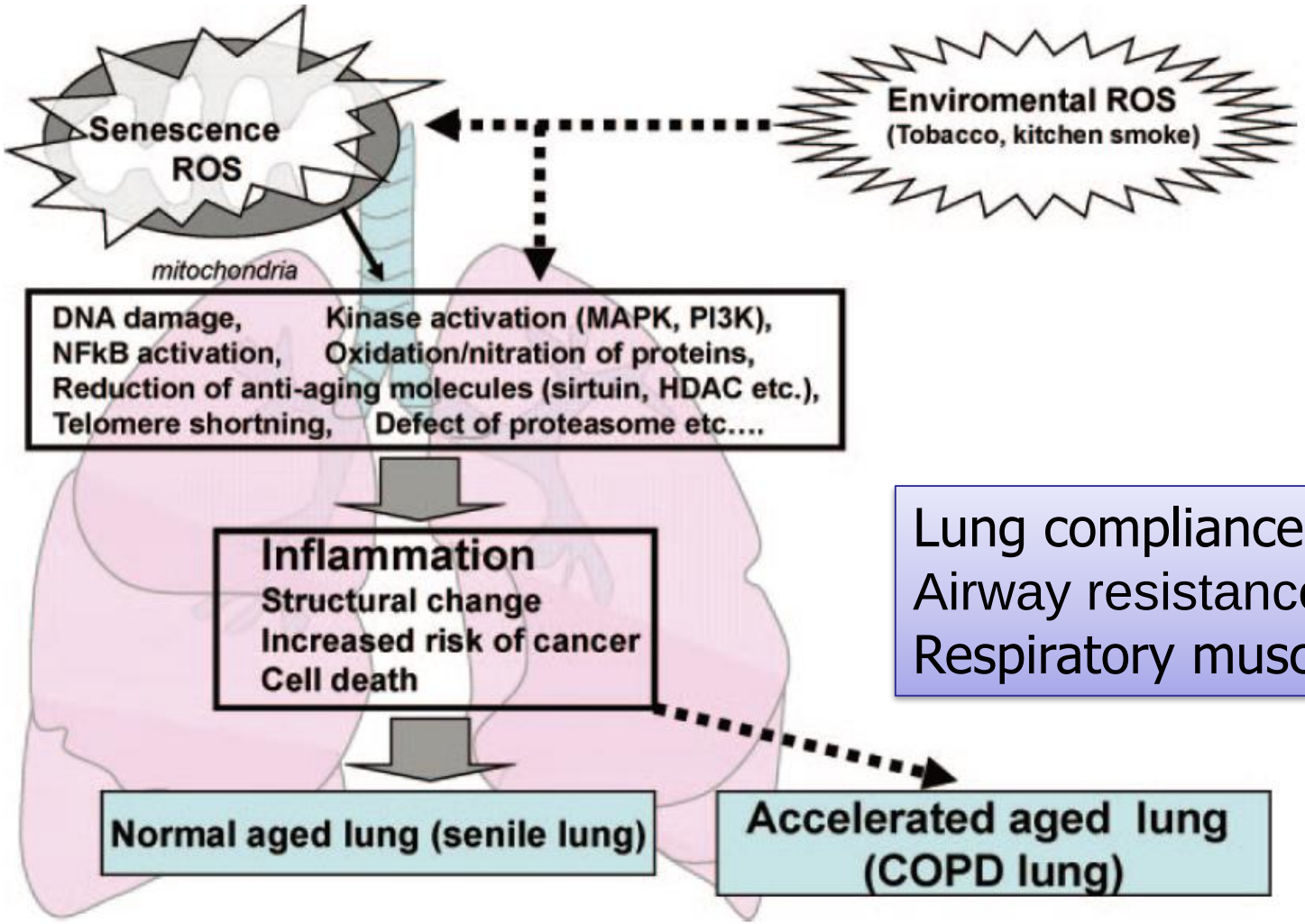
Janssens JP. Eur Respir J 1999;13:197.

FEV1 and FVC with ageing



Janssens JP. Eur Respir J 1999;13:197.

COPD: "a disease of accelerated lung ageing"



Lung compliance↑↑
Airway resistance↑↑
Respiratory muscle↓↓

Ito K. Chest 2009;135:173.

Physiologic aging *vs* COPD

Normal aging		COPD
↓(FEV_1: 20 ml/year)	Lung function	↓↓ (FEV_1: 50–100 ml/year)
↑	Alveolar spaces	↑↑ With alveolar wall destruction
↑	Neutrophils	↑↑
↑	IL-6, IL-8, TNFα, IL-1β, adhesion molecules (E, P, L selectin, VCAM, ICAM)	↑↑
↑	NF-κB activation	↑↑
↑	iNOS	↑↑
↑	Reactive oxygen species, NO	↑↑
↓	MnSOD, catalase	↑↓ → ?
	Nrf2 activity	↓
Slight reduction	Histone deacetylase 2	↓
ND	SIRT1/6	↓
↑	DNA damage/oxidation	↑↑
↑	Nitrated and oxidized proteins	↑↑
	Unfold proteins	
↓	Proteasome/autophagy	↓↓ (bronchial, macrophage cells) ↑ (Diaphragm, peripheral lung)

Ito K. Exp Gerontol 2014;59:21.

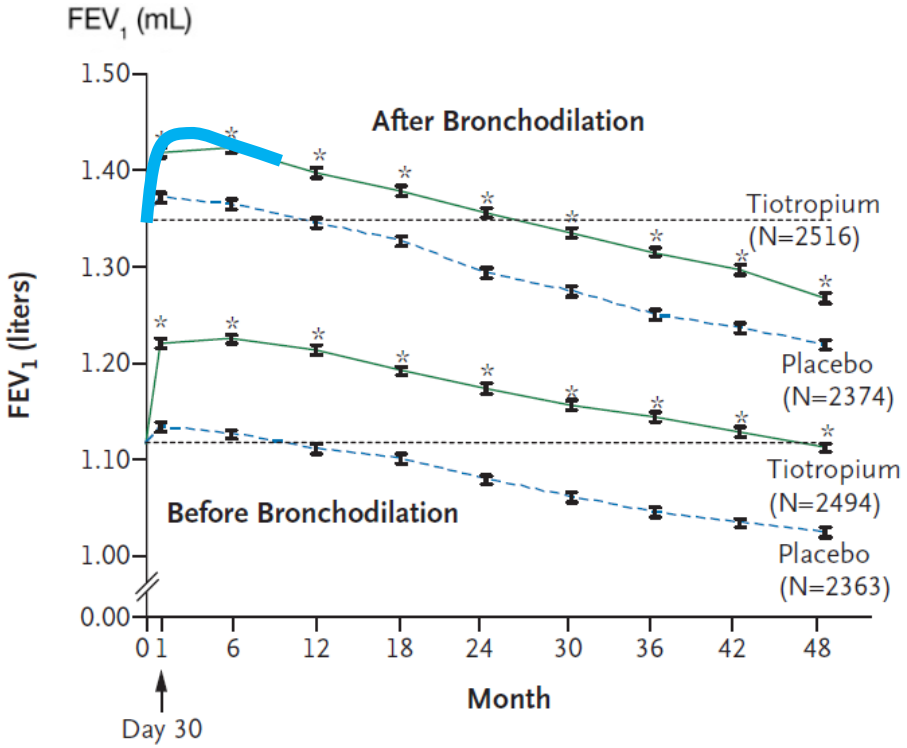
Summary I

- COPD: “a disease of accelerated lung ageing”

Contents

- Why lung function declines
- **Who shows faster lung function decline**
- How to slow lung function decline

Heterogeneity in lung function decline?



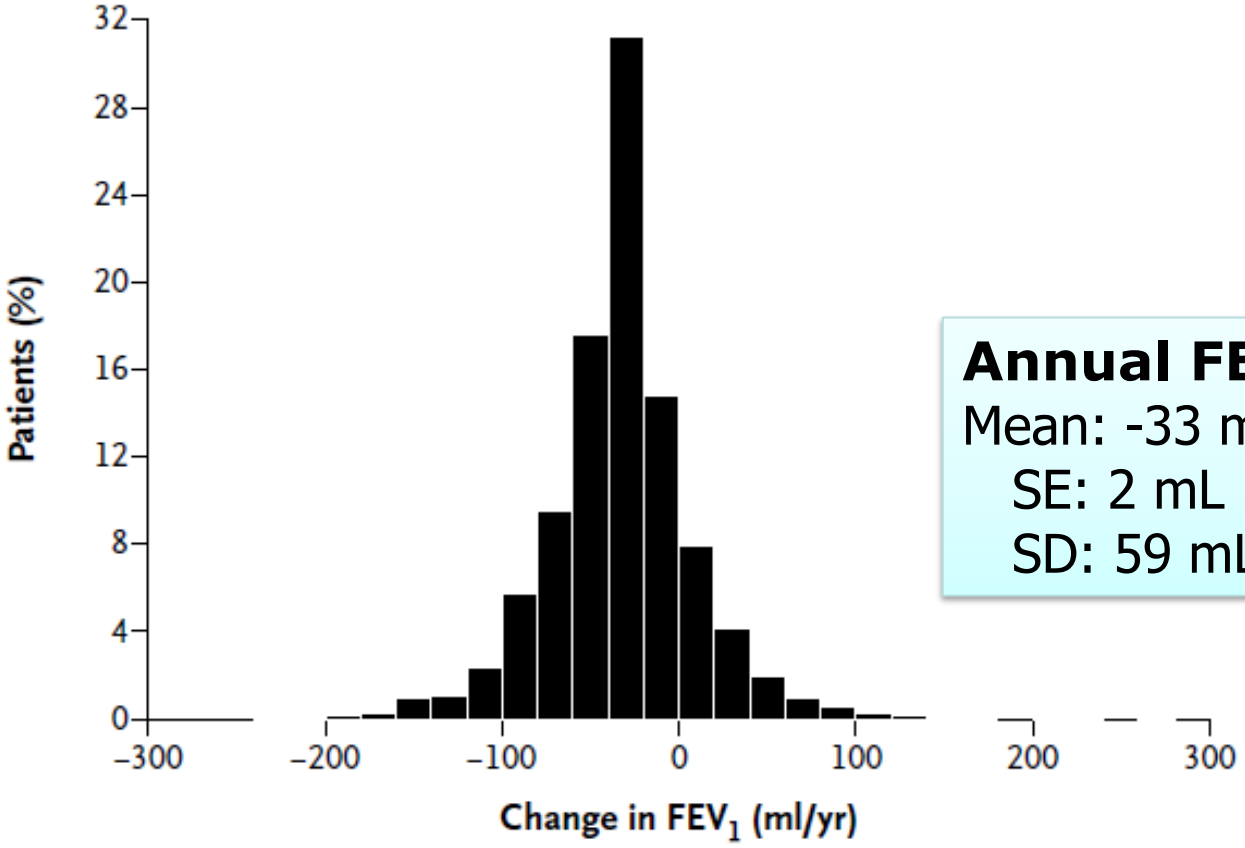
STATISTICAL ANALYSIS

The number of patients needed for the study was based on the assumption of a standard deviation of 90 ml in the rate of decline in the mean FEV_1 during the 4-year period to detect a difference of 15 ml between the tiotropium group and the placebo group, with a power of more than 90% at a significance level of 5% with the use of a two-sided test.

Tashkin DP. N Engl J Med. 2008;359:1543.

FEV1 change rates vary

Prospective cohort study (ECLIPSE).
COPD pts over 3yr (**N=2,163**).

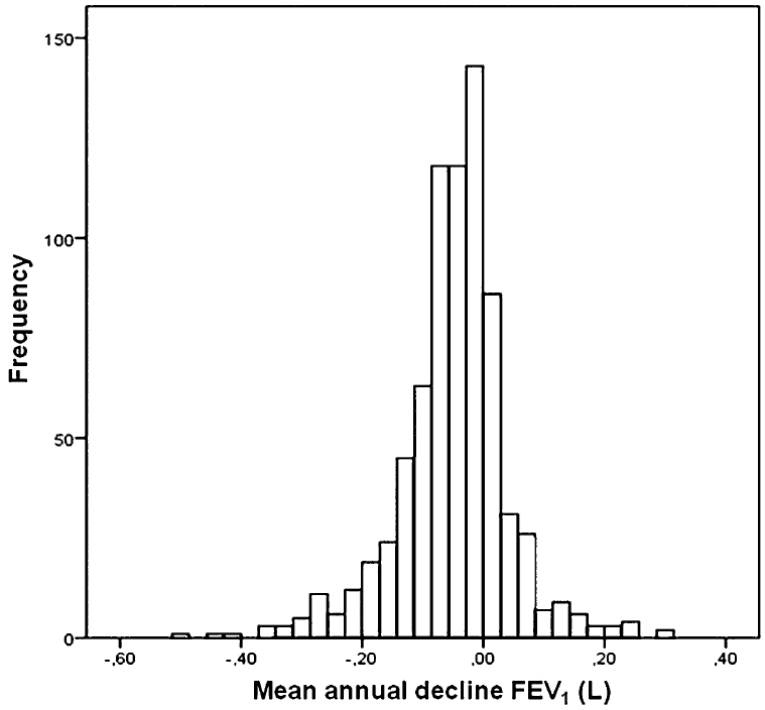


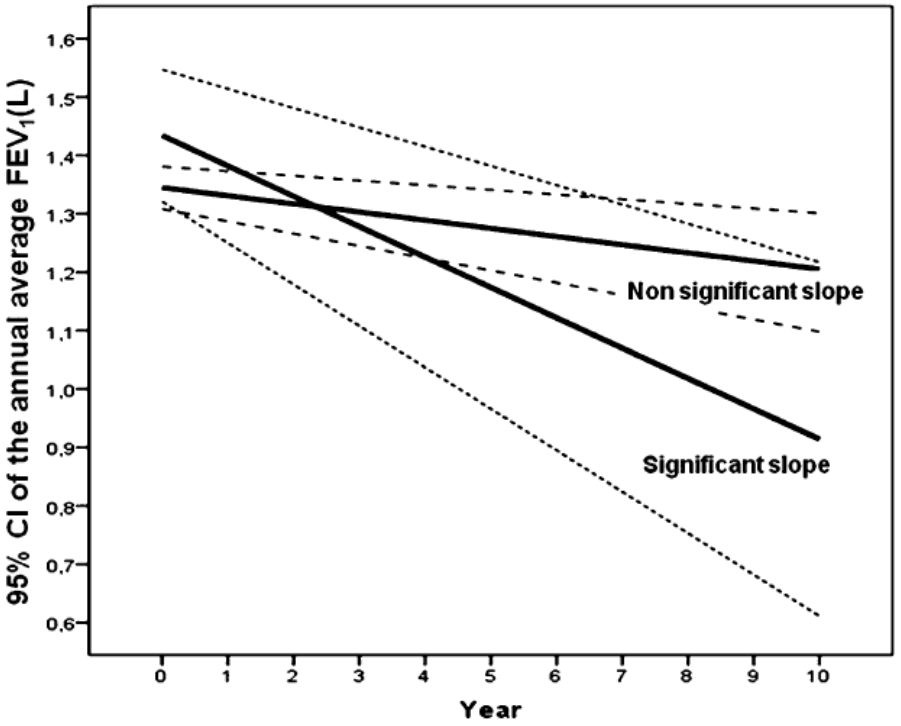
Annual FEV1 change rates
Mean: -33 mL
SE: 2 mL
SD: 59 mL

Vestbo J. NEJM 2011;365:1184.

Only 18% showed statistically significant annual FEV1 loss

Prospective cohort study (BODE). COPD pts with mean 5.4 times PFT (**N=751**).





Annual FEV1 change rates

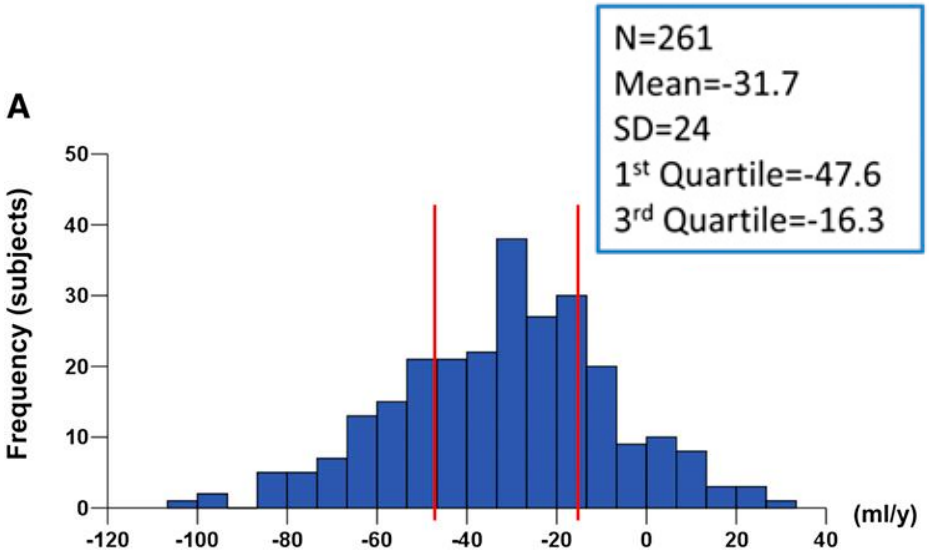
Significant slope group (18%): -86 mL/yr (-32 to -278 mL/yr)

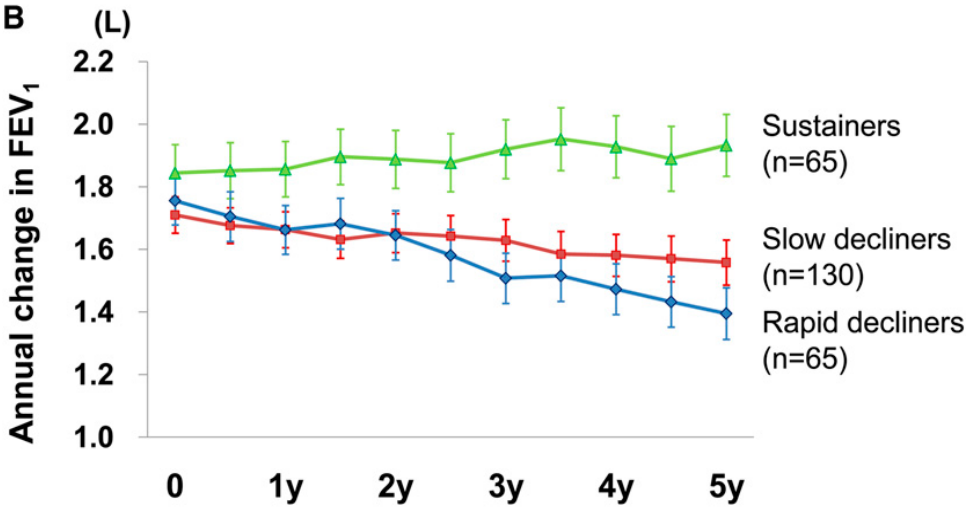
Non-significant slope group (82%): -28 mL/yr (+9 to -214 mL/yr)

Casanova C. Am J Respir Crit Care Med 2011;184:1015.

Majority of COPD patients did not experience rapid decline

Prospective cohort study in Japan. COPD pts with mean 5.4 times PFT (**N=279**).

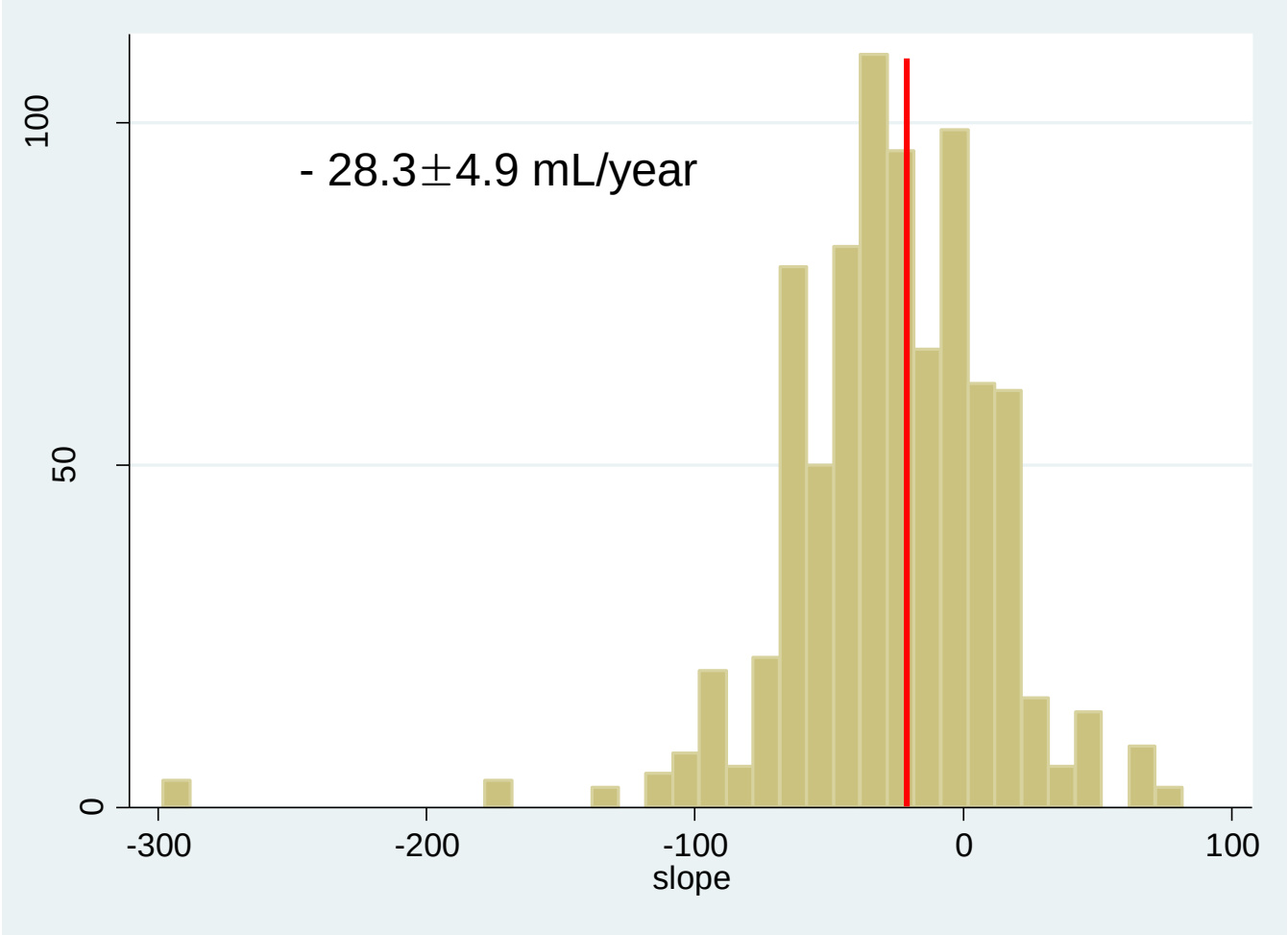




Nishimura M. AJRCCM 2012;185:44.

Annual FEV1 rate among Korean COPD pts

Prospective cohort study (KOLD). COPD pts with mean 4.7 times PFT (**N=175**).



Kim JH. (in submission)

Asian shows smaller lung function decline ?

Double-blind, multicenter RCT (TORCH).
COPD patients with FEV1<60% (**N=6,184**).
FP (ICS) vs **SAL (LABA)** vs **FP + SAL (ICS/LABA)** vs **PLA** for **3 years**.
Primary endpoint: **overall mortality.**

	Number of Subjects in Analysis	Baseline Mean FEV_1 (SD), ml	Adjusted Rate of FEV_1 Decline (SE), ml/yr	Effect of Covariates on Slopes
Region				$P < 0.001$
United States (n = 1,388)	1,172	1,205 (451)	−49.4 (3.4)	
Asia Pacific (n = 758)	697	1,045 (400)	−30.7 (4.2)	
Eastern Europe (n = 1,154)	1,070	1,341 (435)	−38.2 (3.3)	
Western Europe (n = 1,908)	1,642	1,307 (423)	−50.9 (2.8)	
Other (n = 904)	762	1,178 (441)	−48.4 (4.2)	
Ethnic Origin				$P < 0.001$
White (n = 5,006)	4,338	1,278 (439)	−48.1 (1.7)	
Black (n = 95)	83	1,139 (429)	−43.4 (13.1)	
Asian (n = 769)	705	1,046 (400)	−30.6 (4.2)	
American Hispanic (n = 193)	173	1,107 (468)	−22.4 (8.4)	
Other (n = 49)	44	1,121 (333)	−46.8 (17.4)	

Celli BR. Am J Respir Crit Care Med 2008;178:332.

Current smoker, AE during F/U, BDR, Emphysema ⇨ FEV1 decline⇧

Prospective cohort study (ECLIPSE). COPD pts over 3yr (**N=2,163**).

Characteristic	Effect on Baseline FEV_1	P Value	Effect on Annual Rate of Change in FEV_1	P Value
	ml		*ml/yr*	
Age (per yr)	−10±1.4	<0.001	0±0.3	0.21
Female sex	−55±26.0	0.04	3±3.8	0.42
Height (per cm)	19±1.5	<0.001		
Weight (per kg)	5±0.6	<0.001		
Smoking status				
Current smoker (yes vs. no)	102±20.7	<0.001	−21±3.8	<0.001
Smoking history (per pack-yr)	−1±0.4	0.02	0±0.1	0.20
Prior exacerbations				
≥3 vs. 0	−259±34.3	<0.001	−3±6.7	0.67
≥3 vs. 1	−107±37.1	0.004	2±7.2	0.83
≥3 vs. 2	−47±41.6	0.25	−5±8.1	0.57
Exacerbations during follow-up (per exacerbation)			−2±0.5	<0.001
Bronchodilator reversibility (yes vs. no)	220±22.4	<0.001	−17±4.2	<0.001
Emphysema (yes vs. no)	−327±21.2	<0.001	−13±4.2	0.002
Chronic bronchitis (yes vs. no)	−43±20.2	0.033	−2±3.8	0.67
Cardiovascular disease (yes vs. no)	11±19.7	0.57	1±3.6	0.77

Vestbo J. NEJM 2011;365:1184.

CC-16⇩ ⇨ FEV1 decline⇧

Prospective cohort study (ECLIPSE). COPD pts over 3yr (**N=2,163**).

Biomarker†	Effect on Baseline FEV_1 *ml*	P Value‡	Effect on Annual Rate of Change in FEV_1 *ml/yr*	P Value‡
Fibrinogen	−93±10.6	<0.001	−1±2.1	0.63
Interleukin-6	0±10.0	>0.99	1±2.3	0.52
Interleukin-8	20±9.9	0.04	−2±2.0	0.36
TNF-α	1±9.9	0.89	0±1.8	0.84
C-reactive protein	−23±10.3	0.037	4±2.1	0.07
CC-16	33±10.8	0.002	4±2.2	0.04
Surfactant protein D	0±10.3	0.96	−3±2.1	0.18

Vestbo J. NEJM 2011;365:1184.

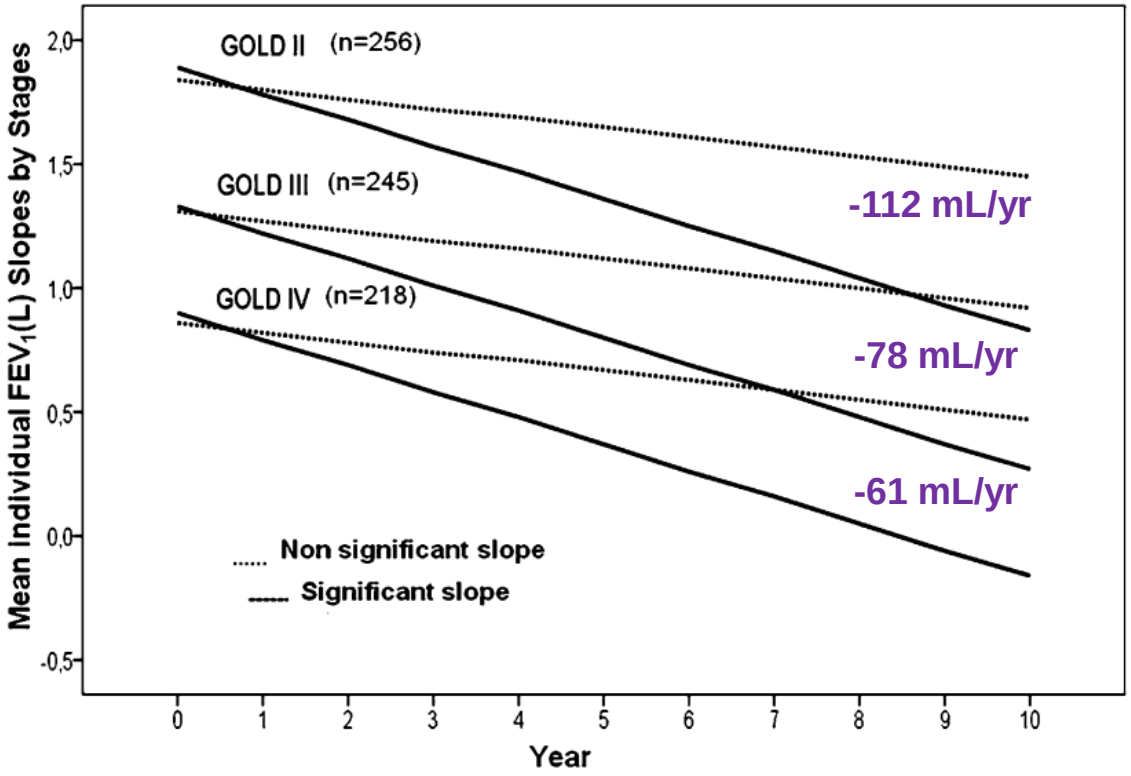
FEV1⇧, BMI⇩ ⇨ significant decline ⇧

Prospective cohort study (BODE). COPD pts with mean 5.4 times PFT (**N=751**).

TABLE 3. RELATIVE RISK OF THE DECLINE OF FEV_1 WITH SIGNIFICANT SLOPE CHANGE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING MULTIVARIATE LOGISTIC REGRESSION MODELING* INCLUDING AGE, SEX, PACK-YEARS, SMOKING HABIT, COMORBIDITY (CHARLSON INDEX), AND ANNUAL HOSPITAL EXACERBATION RATE

For Each	Relative Risk	95% Confidence Interval	*P* Value
FEV_1 (⩾1 ml)	1.857	1.322–2.610	<0.001
Body mass index (one point less)	1.071	1.035–1.106	<0.001

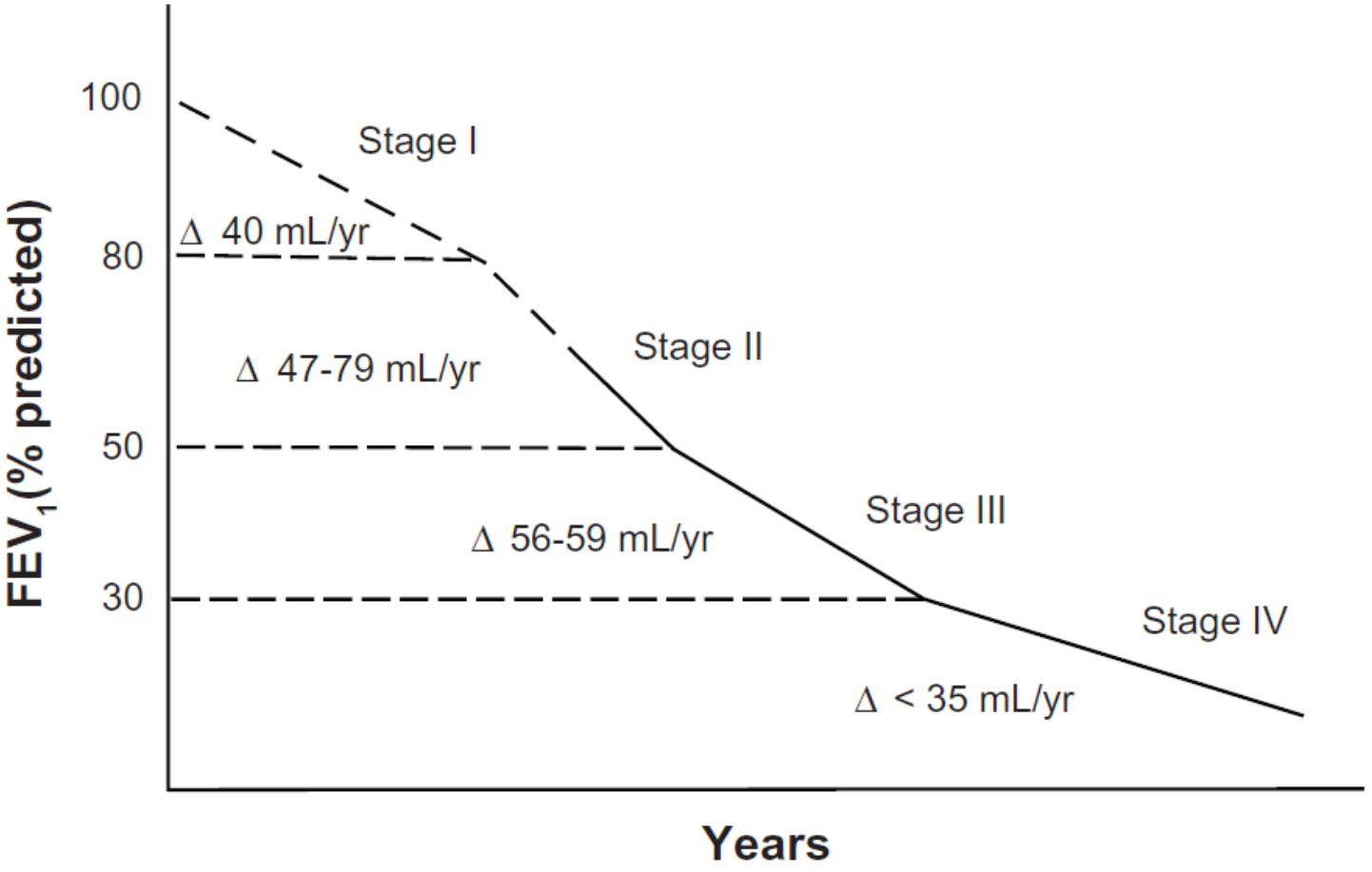
* With constant using backward stepwise method and Wald criteria per seven iterations.



Casanova C. Am J Respir Crit Care Med 2011;184:1015.

FEV1⇧ ⇨ significant decline ⇧

Pooled analysis for 15 RCTs. COPD pts (**N=9,976**).



Tantucci C. Int J Chron Obstruct Pulmon Dis 2012;7:95.

Emphysema⇧, blood neutrophil⇧ ⇨ FEV1 decline⇧

Prospective cohort study (Hokkaido COPD study).
COPD pts with mean 5.4 times PFT (**N=279**).

TABLE 3. RELATIVE RISK FOR RAPID DECLINERS VERSUS SLOW DECLINERS USING LOGISTIC REGRESSION ANALYSES

	%Kco Excluded			Emphysema Scores Excluded		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Emphysema score	1.46	1.01–2.11	0.047			
%Kco, 10%				0.84	0.73–0.96	0.014
Post-bronchodilator FEV_1, % predicted	1.00	0.99–1.02	0.66	1.00	0.99–1.02	0.75
Reversibility of airflow limitation	1.01	0.98–1.05	0.45	1.02	0.98–1.06	0.36
Blood neutrophil count, 100 cells/μl	1.03	1.00–1.07	0.036	1.04	1.01–1.07	0.021
Blood eosinophil count, 10 cells/μl	0.98	0.95–1.01	0.12	0.98	0.95–1.01	0.12
Chronic bronchitis symptom	1.47	0.50–4.36	0.49	1.34	0.44–4.11	0.61
MRC dyspnea scale ⩾2	0.85	0.33–2.23	0.75	0.77	0.30–2.02	0.60
Continuous vs. noncontinuous smokers	0.84	0.35–1.98	0.68	0.70	0.30–1.76	0.42
Exacerbation frequency, events/yr	1.17	0.54–2.54	0.69	1.16	0.54–2.52	0.70
Age, yr	0.99	0.94–1.03	0.52	0.98	0.94–1.03	0.39
Female sex	0.20	0.02–1.67	0.14	0.22	0.03–1.85	0.16

Definition of abbreviations: CI = confidence interval; %Kco = carbon monoxide transfer coefficient (% predicted); MRC = Medical Research Council.

Nishimura M. AJRCCM 2012;185:44.

GOLD 2011 groups and FEV1 decline

A prospective cohort study (ECLIPSE). COPD pts (**N=2,164**).

Distribution	2011 GOLD groups				p-value
	A	B	C	D	
Rate of annual FEV_1 decline mL per year	-33.4 (46.2)	-38.0 (47.0)	-30.2 (45.5)	-31.9 (34.6)	0.157

Agusti A. Eur Respir J 2013;42:636.

FEV1 decline according to GOLD subgroups in KOLD cohort

A prospective cohort study (KOLD). COPD pts (**N=175**).

		Unadjusted		Adjusted[1]	
	n	Rate (mL/year)	*P*-value	Rate (mL/year)	*P*-value
FEV1					
Total	175	-25.8 ± 3.8		-28.3 ± 4.9	
Group			0.474		0.794
A	58	-32.9 ± 6.3		-34.4 ± 7.9	
B	45	-27.4 ± 7.4		-26.2 ± 9.4	
C	15	-22.8 ± 12.9		-22.7 ± 16.0	
D	57	-18.3 ± 6.9		-24.0 ± 8.7	
Symptom group			0.255		0.444
Fewer	73	-30.9 ± 5.7		-32.3 ± 7.2	
Greater	102	-22.2 ± 5.1		-25.0 ± 6.5	
Risk group			0.145		0.443
Low	103	-30.6 ± 4.8		-31.0 ± 6.1	
High	72	-19.2 ± 6.1		-23.6 ± 7.7	

Kim JH. (in submission)

Summary II

- **Majority of COPD patients**
  - **did not experience rapid FEV1 decline**
- **Predictors of rapid FEV1 decline**
  - **ECLIPSE cohort: current smoking, AE during F/U, BDR(+), Emphysema, CC-16↓**
  - **BODE cohort: initial FEV1↕, BMI↓**
  - **Hokkaido cohort: Emphysema, blood neutrophil**

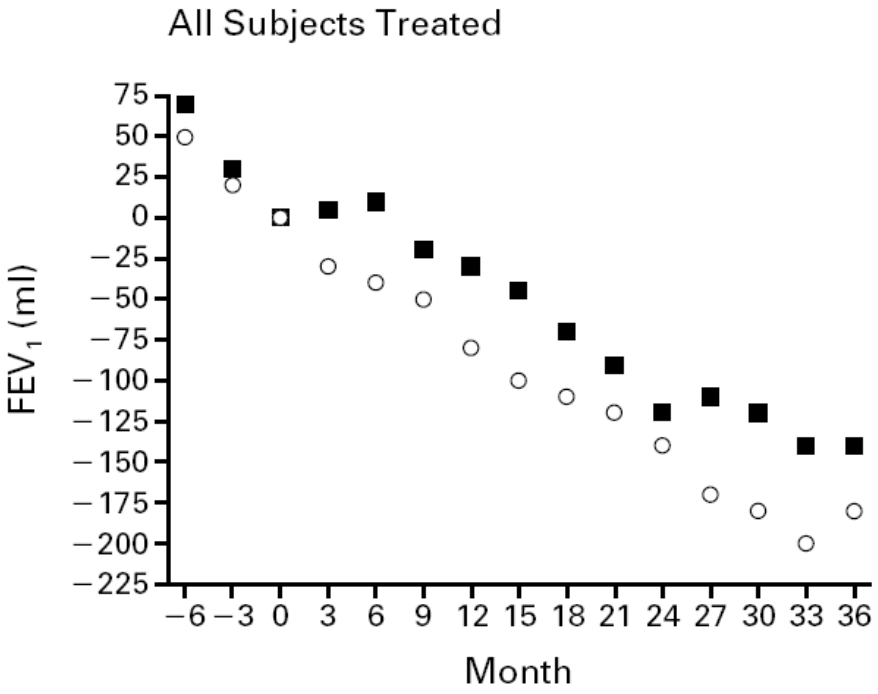
GOLD 2011 group
No difference in FEV1 decline

Contents

- Why lung function declines
- Who shows faster lung function decline
- **How to slow lung function decline**

BUD ⇨ FEV1 decline⇩ (x)

Double-blind RCT (EUROSCOP).
COPD with smokers > 5PY aged 30-65 FEV1/FVC<0.7, FEV1 50-100% (**N=1,277**)
BUD (ICS) 400µg bid *vs* **PLA** for **3yr**
Primary outcome: **annual post-BDR FEV1 decline rate**



Budesonide[1] -57mL/yr
Placebo -69mL/yr

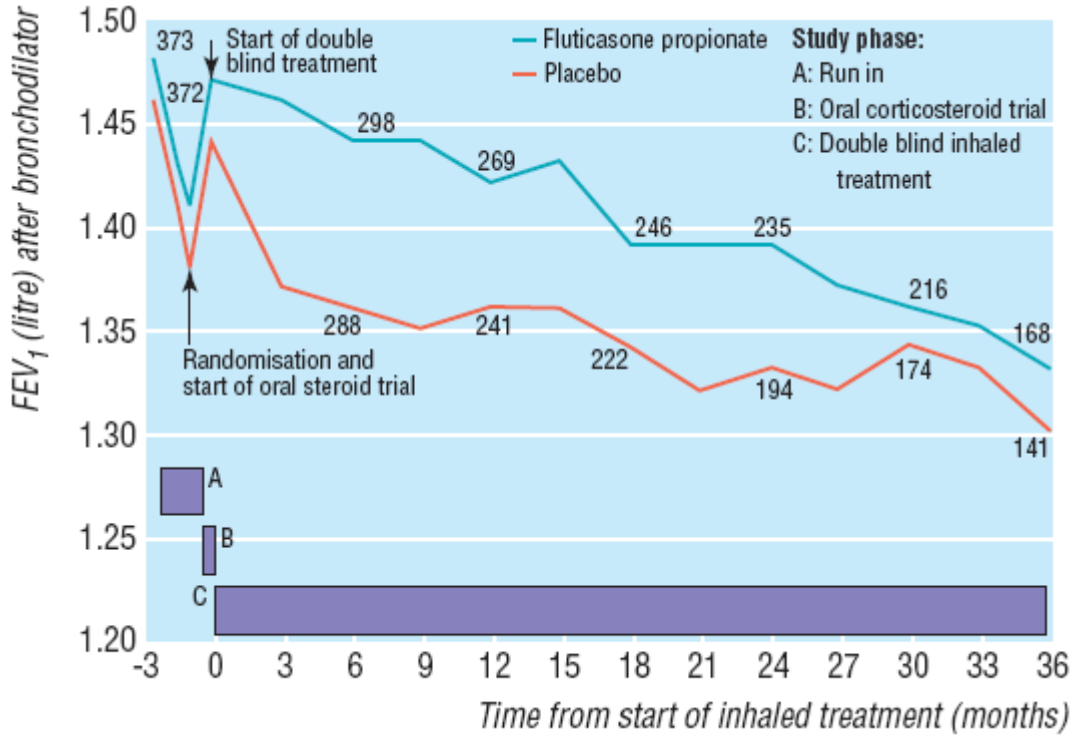
P=0.39

[1] **Inhaled corticosteroid (ICS)**

Pauwels RA. NEJM 1999;340:1948.

FP ⇨ FEV1 decline⇩ (x)

Double-blind RCT (ISOLDE).
COPD pts aged 40-75, FEV1/FVC<0.7, Post-FEV1<85%, BDR<10% (**N=751**)
FP 500µg bid *vs* **PLA** for **3yr**
Primary outcome: **annual post-FEV1 decline rate**.



Fluticasone[1] -50mL/yr
Placebo -59mL/yr

P=0.16

[1] **Inhaled corticosteroid (ICS)**

Burge PS. BMJ 2000;320:1297.

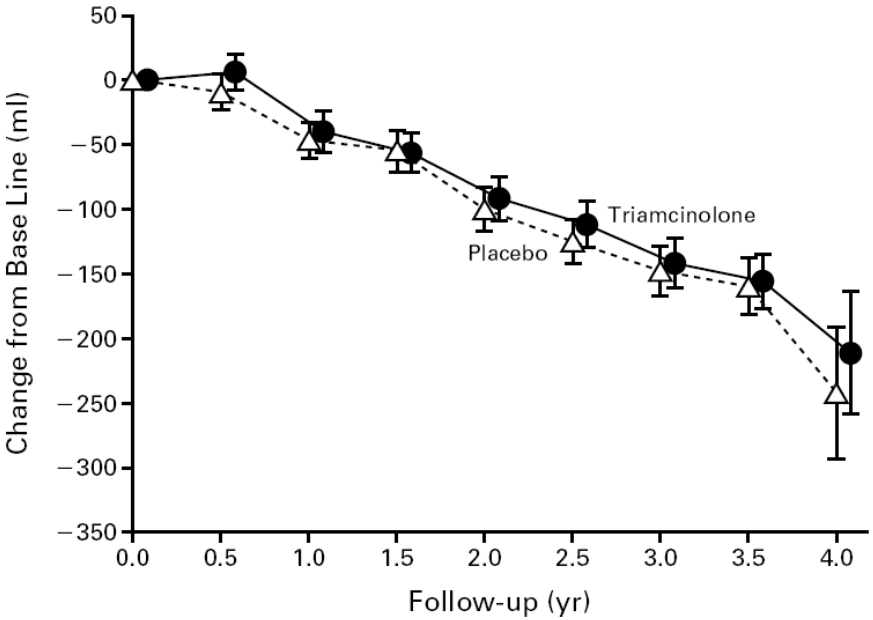
Triamcinolone ⇨ FEV1 decline⇩ (x)

Double-blind RCT (LHS II).

COPD pts with smokers aged 40-69 FEV1/FVC<0.7, FEV1 30-90%, BDR<10% (**N=1,116**)

Triamcinolone 600µg bid *vs* **PLA** for **mean 40 mo**

Primary outcome: **annual post-FEV1 decline rate**



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

● Triamcinolone[1] -44mL/yr

Δ Placebo -47mL/yr

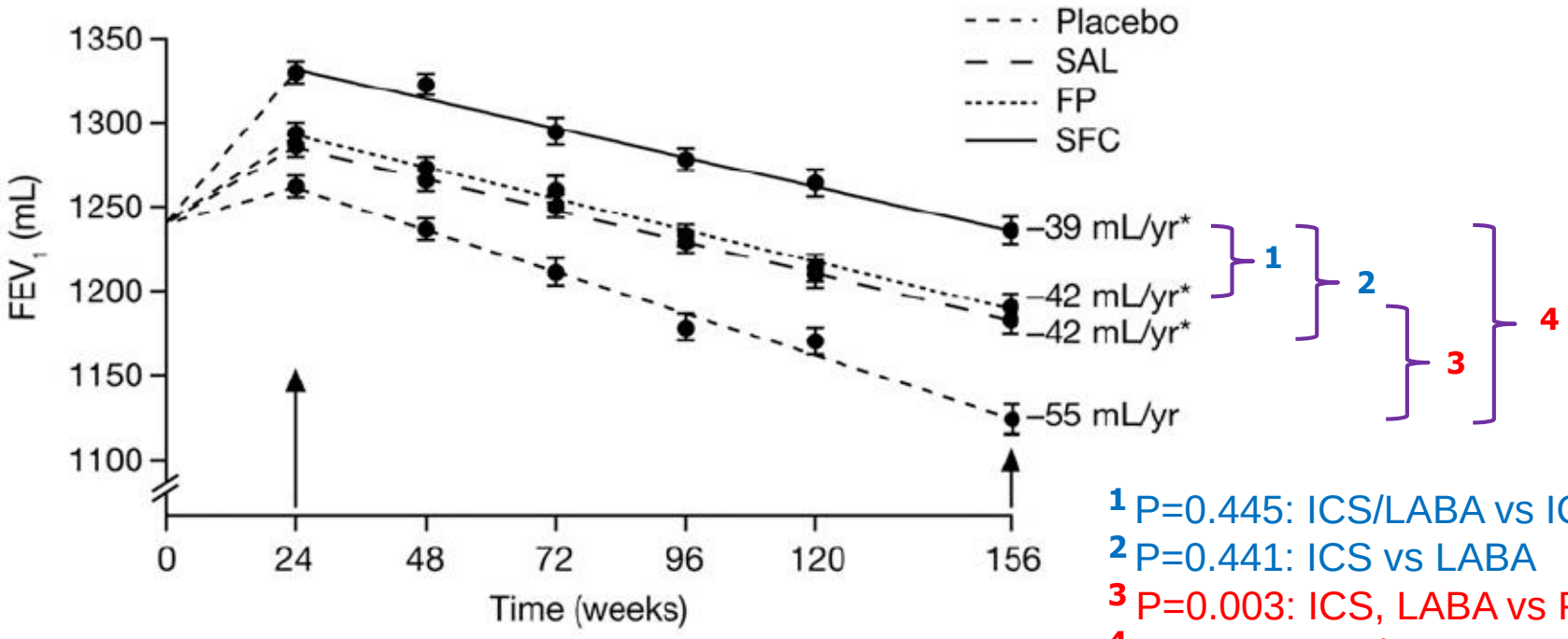
P=0.50

[1] **Inhaled corticosteroid (ICS)**

Lung Health Study Research Group. NEJM 2000;343:1902.

FP/SAL, SAL, FP ⇨ FEV1 decline⇩

Double-blind, multicenter RCT (TORCH).
COPD patients with FEV1<60% (**N=6,184**).
FP (ICS) vs **SAL (LABA)** vs **FP + SAL (ICS/LABA)** *vs* **PLA** for **3 years**.
Primary endpoint: **overall mortality.**

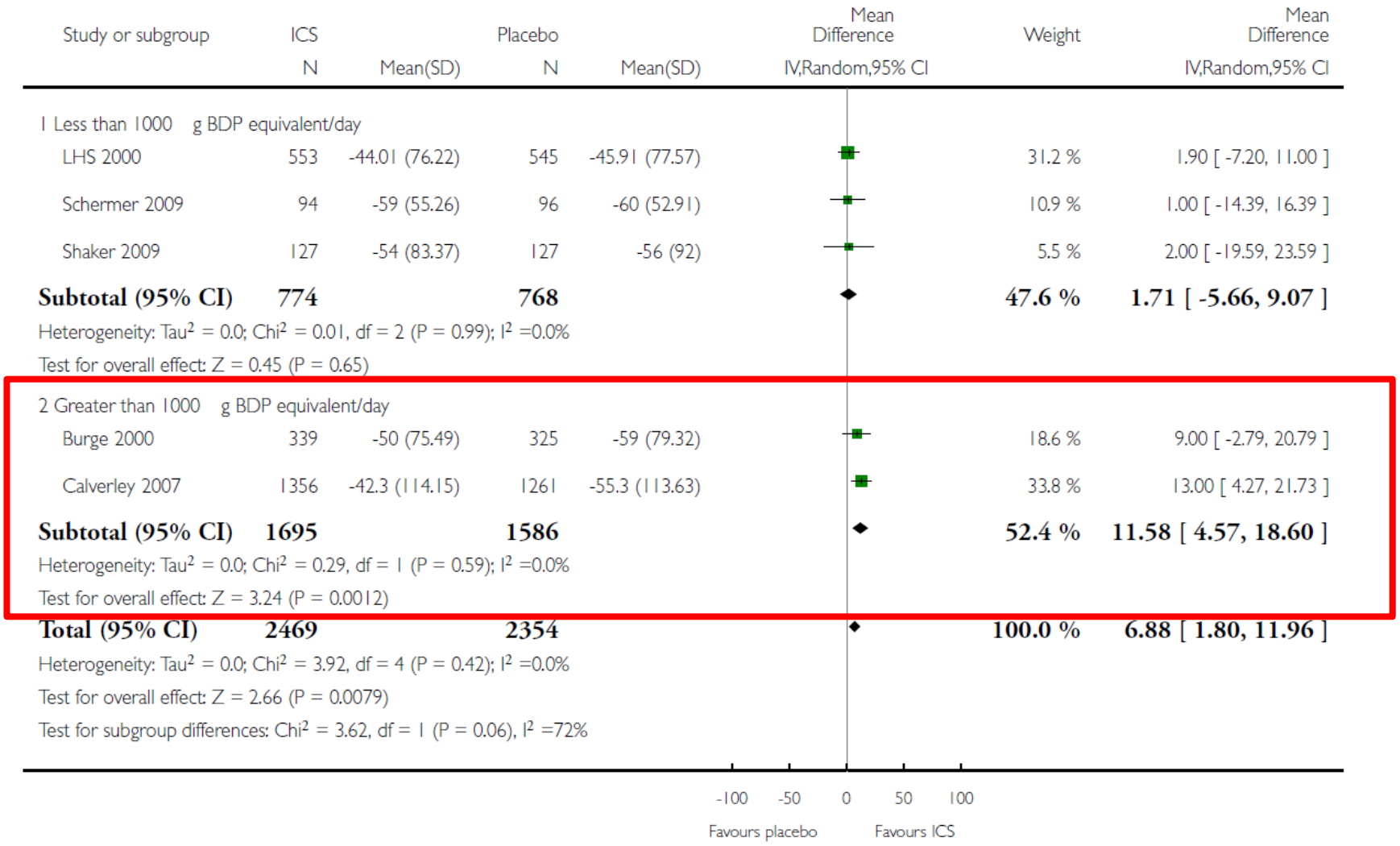


[1] P=0.445: ICS/LABA vs ICS
[2] P=0.441: ICS vs LABA
[3] P=0.003: ICS, LABA vs PLA
[4] P<0.001: ICS/LABA vs PLA

Celli BR. Am J Respir Crit Care Med 2008:178:332.

ICS ⇨ FEV1 decline⇩

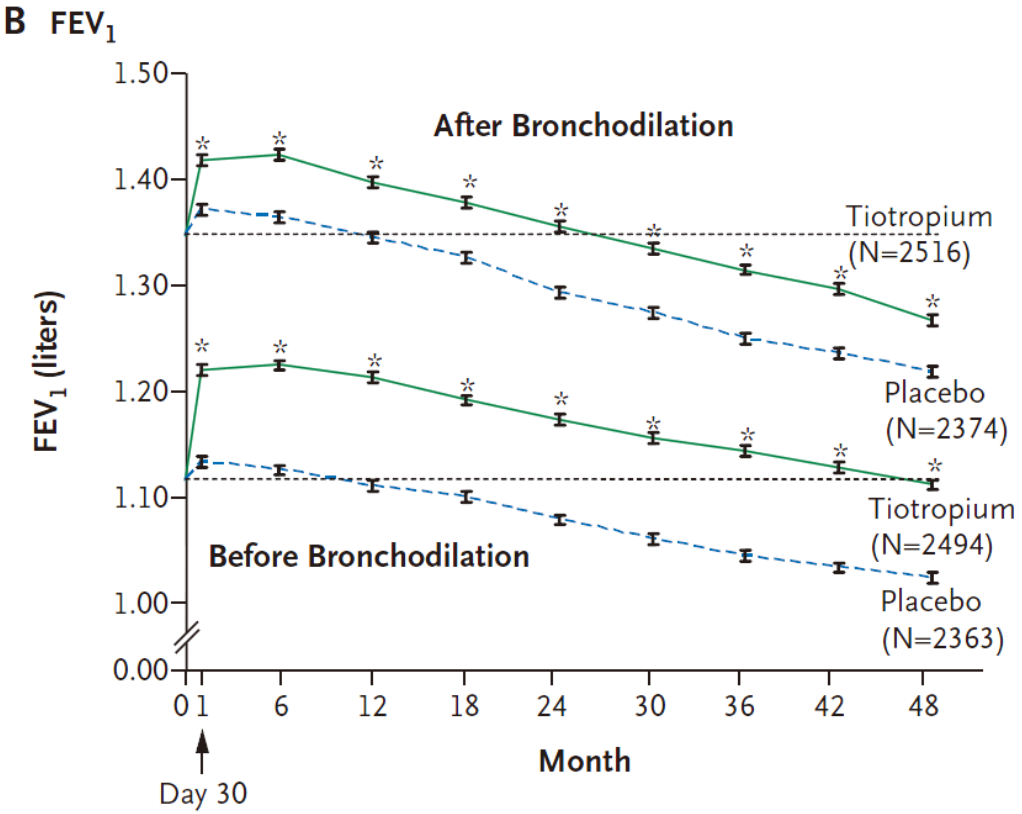
Meta-analysis for **55 RCTs (N=16,154)**



Yang IA. Cochrane Syst Rev 2012;CD002991.

TIO DPI ⇨ FEV1 decline⇩ (x)

Double-blind, multicenter RCT (UPLIFT).
COPD pts with **FEV1<70%** (**N=5,993**).
TIO HH (LAMA) *vs* **PLA** for **4 years**.
Primary endpoint: **the rate of decline in pre-, post-FEV1**



Tiotropium[1]	-40mL/yr
Placebo	-42mL/yr

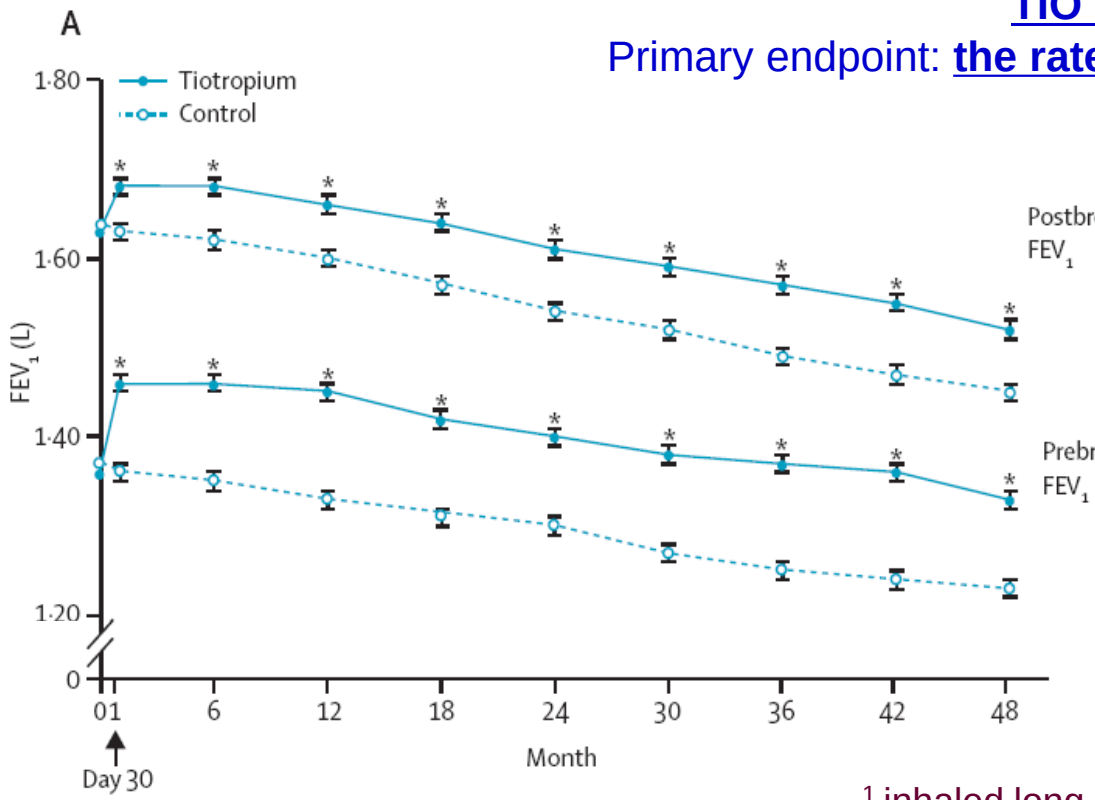
P=0.21

[1] **Inhaled long-acting muscarinic antagonist (LAMA)**

Tashkin DP. NEJM 2008;350:1543.

TIO DPI ⇨ FEV1 decline⇩ (in stage II)

Double-blind, multicenter RCT (UPLIFT).
COPD stage II pts (**subgroup n=2,739; pre-specified analysis**).
TIO HH (LAMA) *vs* **PLA** for **4 years**.
Primary endpoint: **the rate of decline in pre-, post-FEV1**



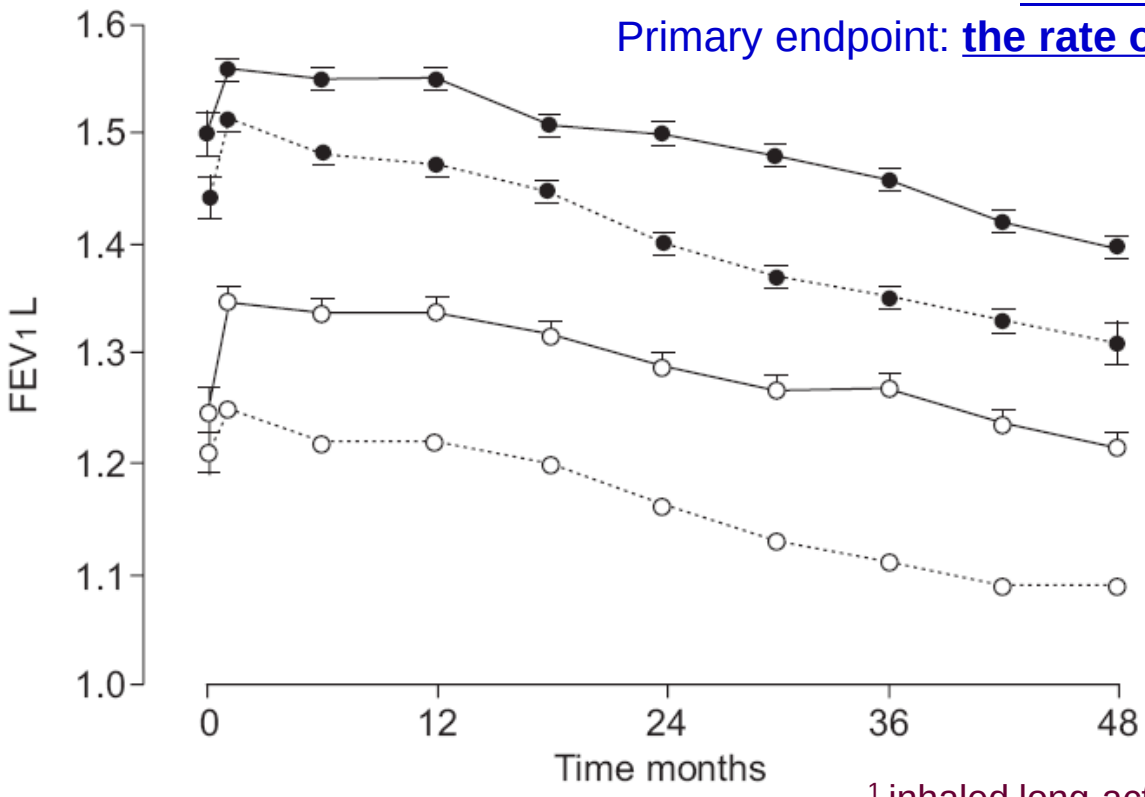
Tiotropium[1] -43mL/yr
Placebo -49mL/yr
P=0.024

[1] inhaled long-acting muscarinic antagonist (LAMA)

Decramer M. Lancet 2009;374:1171.

TIO DPI ⇨ FEV1 decline⇩ (as a 1st-line tx)

Double-blind, multicenter RCT (UPLIFT).
COPD pts not on other maintenance tx at randomization (**subgroup n=810**).
TIO HH (LAMA) *vs* **PLA** for **4 years**.
Primary endpoint: **the rate of decline in pre-, post-FEV1**



Tiotropium[1] -42mL/yr

Placebo -53mL/yr

P=0.026

[1] inhaled long-acting muscarinic antagonist (LAMA)

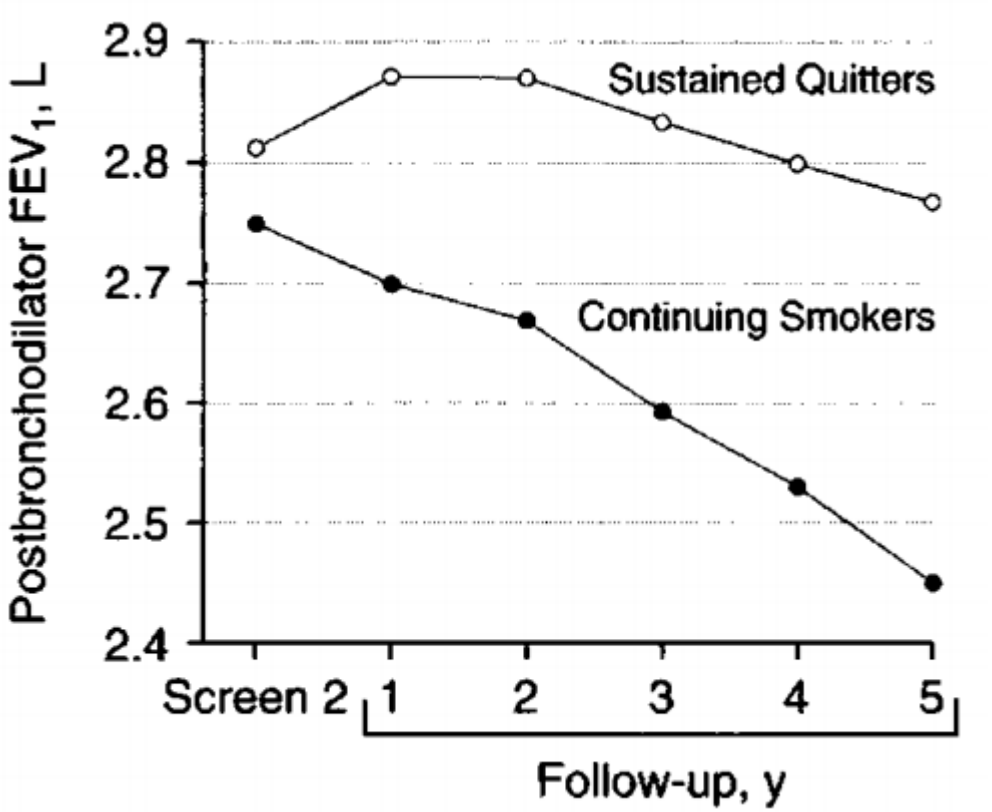
Troosters T. Eur Respir J 2010;36:65.

Stop smoking ⇨ FEV1 decline⇩

RCT (Lung Health Study I). COPD pts aged 35-60 with FEV1 55-90% (**N=5,887**)
Smoking intervention + Placebo (SIP) *vs*
Smoking intervention + Ipratropium (SIA) *vs* **Usual care (UC)** for 5yr
Primary outcome: **annual post-FEV1 decline rate**

SIP: -52.3mL/yr
SIA: -52.7mL/yr } *
UC: -56.2mL/yr } **

* P=0.02
** P=0.03



Anthonisen NR. JAMA 1994;272:1497.

Summary III

- **No drug**
  - **Surely reduce the FEV1 decline rate**
  - **Stop smoking can slow disease progression**
- **Hope**
  - **FP, SAL, FP/SAL: a post-hoc analysis of TORCH**
  - **TIO in Stage II: prespecified analysis of UPLIFT**
  - **TIO as 1st line therapy: a post-hoc analysis of UPLIFT**

Contents

- **Why lung function declines**

  COPD: Accelerated lung ageing

- **Who shows faster lung function decline**

  Current smoker, AE during F/U, Emphysema,
  BDR (+), Lower BMI, CC-16, Higher FEV1, Non-Asian

- **How to slow lung function decline**

  Stop smoking, Drug (TIO, FP/SAL)


Thank you

Random intercept model *vs* Random slope model