COPD Review

이화의대 이 진 화

순 서

- COPD의 발병
- ACOS
- COPD Microbiome
- COPD 기관지경 치료
- COPD Biomarker
- COPD 예후

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2015 VOL. 373 NO. 2

Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease

Peter Lange, M.D., Dr. Med. Sc., Bartolome Celli, M.D., Alvar Agustí, M.D., Ph.D., Gorm Boje Jensen, M.D., Dr. Med. Sc., Miguel Divo, M.D., Rosa Faner, Ph.D., Stefano Guerra, M.D., Ph.D., Jacob Louis Marott, M.Sc., Fernando D. Martinez, M.D., Pablo Martinez-Camblor, Ph.D., Paula Meek, R.N., Ph.D., Caroline A. Owen, M.D., Ph.D., Hans Petersen, Ph.D, Victor Pinto-Plata, M.D., Peter Schnohr, M.D., Dr. Med. Sc., Akshay Sood, M.D., M.P.H., Joan B. Soriano, M.D., Yohannes Tesfaigzi, Ph.D., and Jørgen Vestbo, M.D., Dr. Med. Sc.

배경

기존 가설 유전적 소인 → 흡연 → Rapid FEV_1 decline → COPD

ECLIPSE 등 연구 : **NOT** rapid FEV_1 decline

가설 성인기에 도달한 **FEV_1 최대치가 낮으면,**

정상 FEV_1 decline으로도 COPD가 발병

N Engl J Med 2015;373:111

방법

- Framingham Offspring Cohort
- Copenhagen City Heart Study
- Lovelace Smokers Cohort

- 연구개시: $FEV_1 \geq 80\%$ vs. $FEV_1 < 80\%$
- 연구종결: COPD 유무

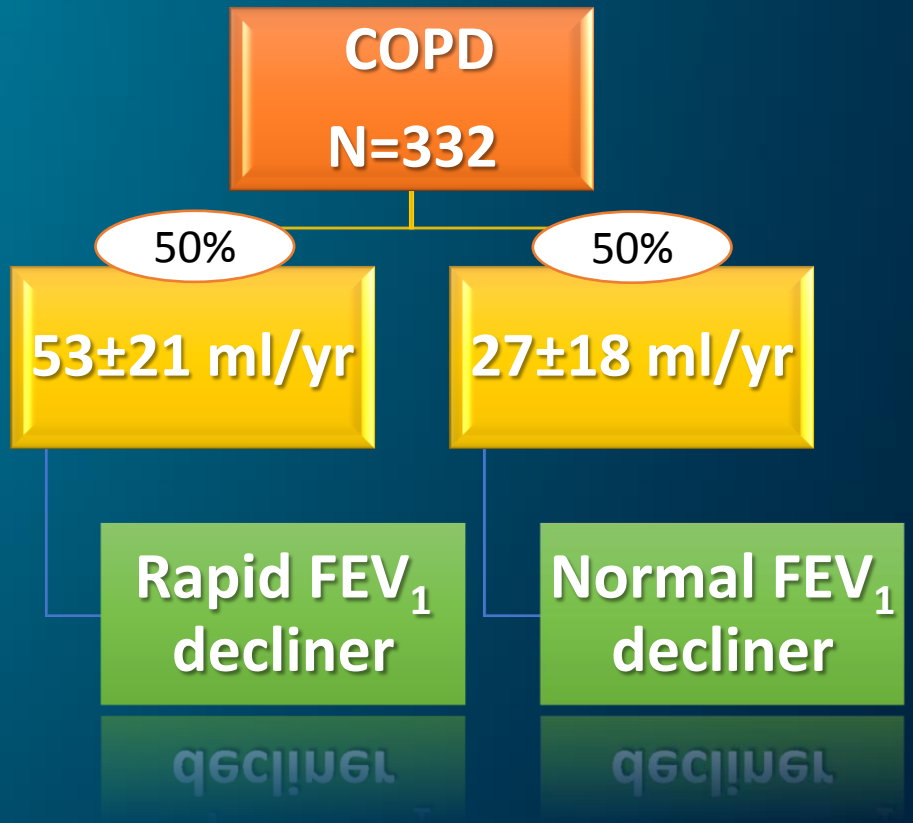
N Engl J Med 2015;373:111

결과

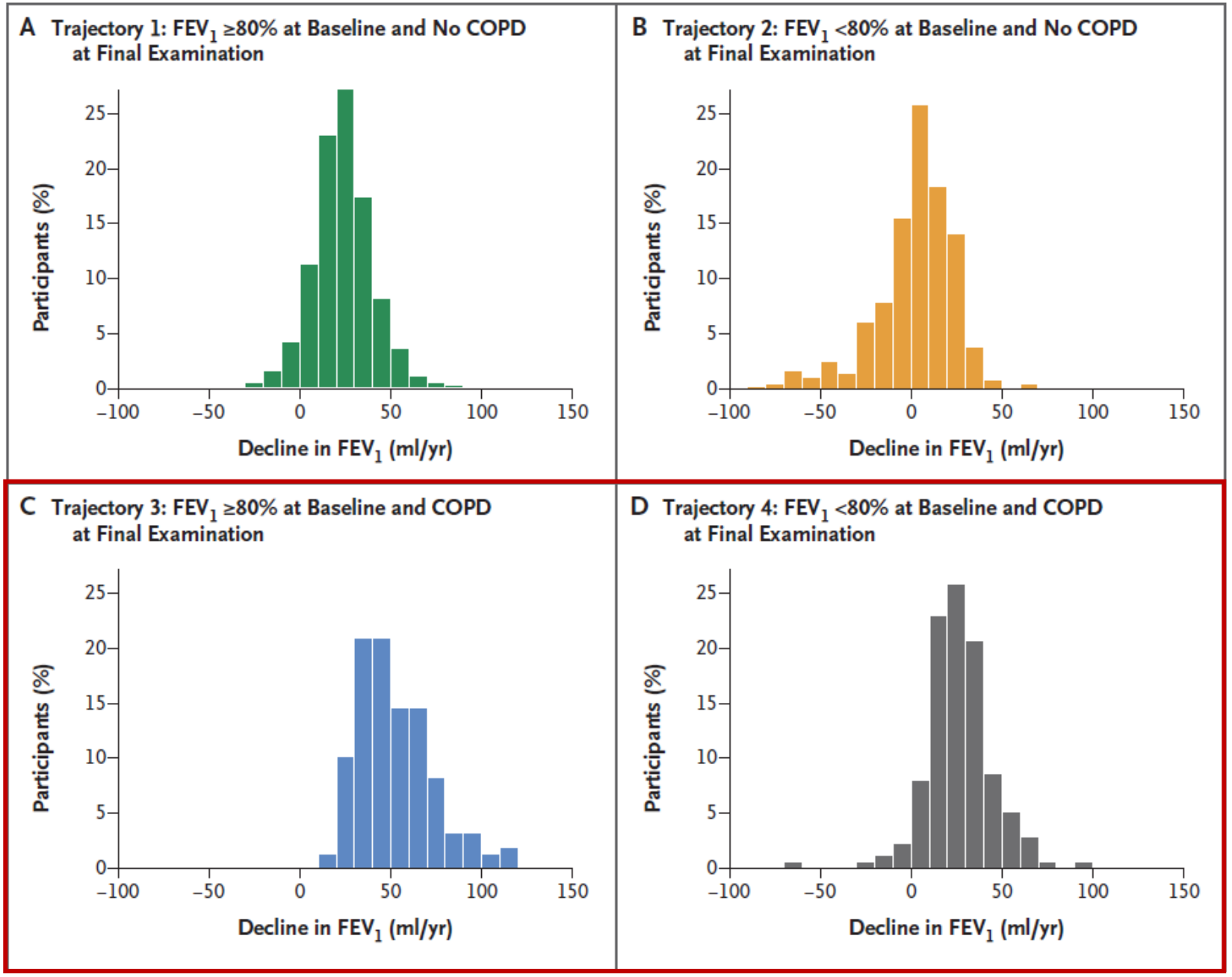
연구개시

FEV_1	≥80%	<80%
	2207	657
COPD	158 (7%)	174 (26%)

연구종결



N Engl J Med 2015;373:111



N Engl J Med 2015;373:111

결론

- 성인기 초기에 FEV_1 최대치가 낮으면, COPD가 발생할 수 있음
- Rapid FEV_1 decline: COPD 발병에 필수적인 요소는 아니다

N Engl J Med 2015;373:111

Long-Term Exposure to Traffic Emissions and Fine Particulate Matter and Lung Function Decline in the Framingham Heart Study

Mary B. Rice[1], Petter L. Ljungman[1,2], Elissa H. Wilker[1], Kirsten S. Dorans[1,3], Diane R. Gold[4], Joel Schwartz[4], Petros Koutrakis[4], George R. Washko[5,6], George T. O'Connor[6,7], and Murray A. Mittleman[1,3]

Am J Respir Crit Care Med 2015;191:656

목적

- 성인에서 장기간 미세먼지(fin particulate matter, $PM_{2.5}$) 노출과 폐기능 감소와의 상관관계: 연구 미흡

- 대기오염이 비교적 낮은, 미국 북동부의 인구집단코호트
- 차량배기가스와 $PM_{2.5}$에 대한 **노출**

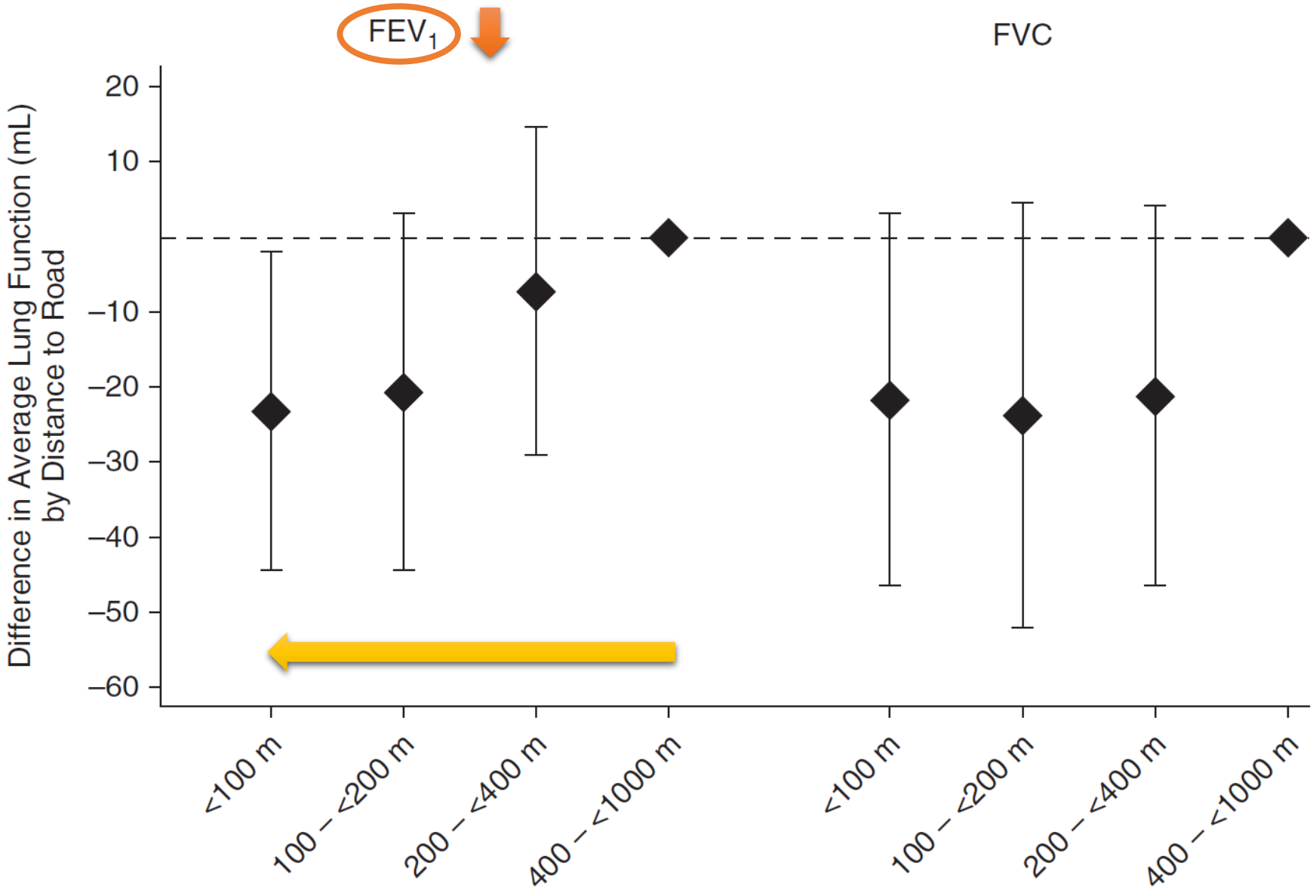
➢장기간에 걸친 **폐기능** 변화

Am J Respir Crit Care Med 2015;191:656

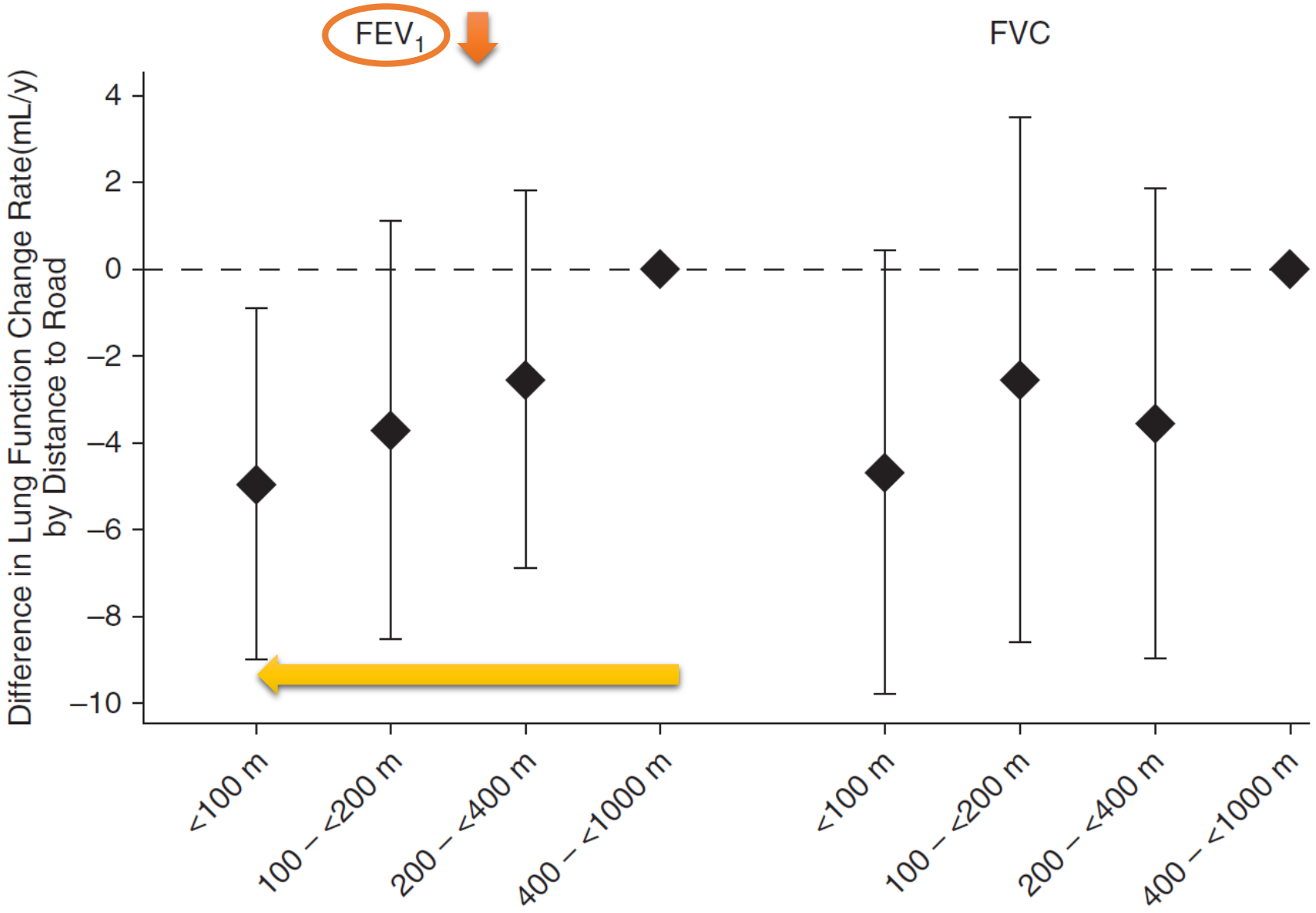
방법

- Framingham Offspring or Third Generation studies
- 6,339명
- FEV_1, FVC
- 1995년과 2011년 사이에 2회 측정

Am J Respir Crit Care Med 2015;191:656



Am J Respir Crit Care Med 2015;191:656



Am J Respir Crit Care Med 2015;191:656

$PM_{2.5}$

	Association with Average FEV_1		Association with Change in FEV_1	
	N	Difference in FEV_1, ml (95% CI)	N	Difference in FEV_1 change, ml/yr (95% CI)
$PM_{2.5}$*	4,872	**-13.5** (-26.6 to -0.3)	4,444	**-2.1** (-4.1 to -0.2)

*2 microg/m^3

결론

- 비교적 낮은 수준이더라도 장기간 자동차배기가스 및 $PM_{2.5}$ 노출은 **낮은 FEV_1**, FVC와 관련이 있었고 **폐기능 감소** 속도를 **가속화**했다.

Am J Respir Crit Care Med 2015;191:656

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Asthma–COPD Overlap

Clinical Relevance of Genomic Signatures of Type 2 Inflammation in Chronic Obstructive Pulmonary Disease

Stephanie A. Christenson[1,2], Katrina Steiling[3,4], Maarten van den Berge[5,6], Kahkeshan Hijazi[7], Pieter S. Hiemstra[8], Dirkje S. Postma[5,6], Marc E. Lenburg[3,4,9], Avrum Spira[3,4,9], and Prescott G. Woodruff[1,2]

Am J Respir Crit Care Med 2015;191:758

배경

- COPD: heterogenous
- COPD subgroup: biologically comparable to asthma
- COPD에서 asthma-associated gene expression을 조사
  - COPD pathogenesis
  - 스테로이드 반응성을 예측하는 biomarker

Am J Respir Crit Care Med 2015;191:758

목적

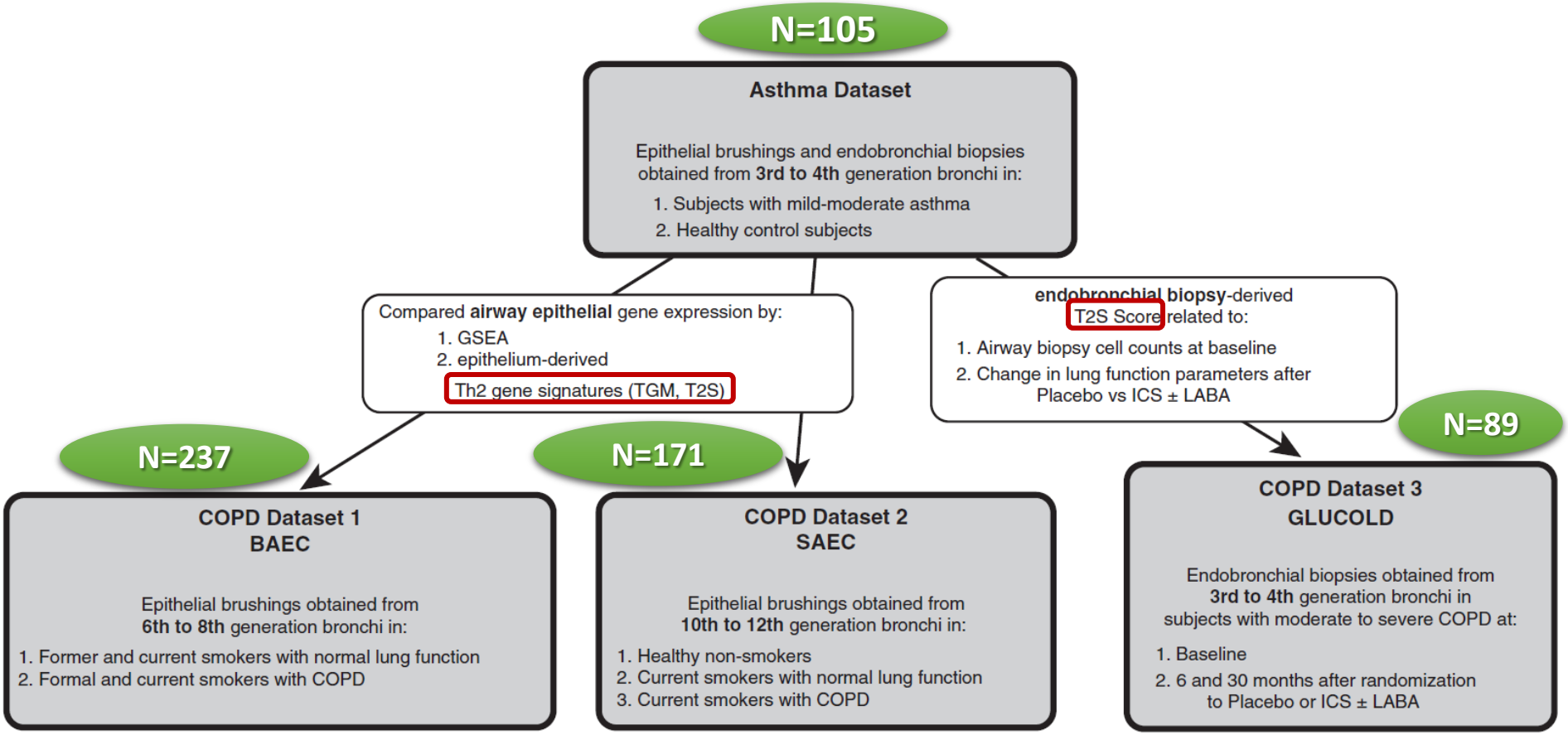
Asthma-associated gene signatures

1. COPD에서 증가되어 있는지

2. Asthma-related feature와 관련이 있는지

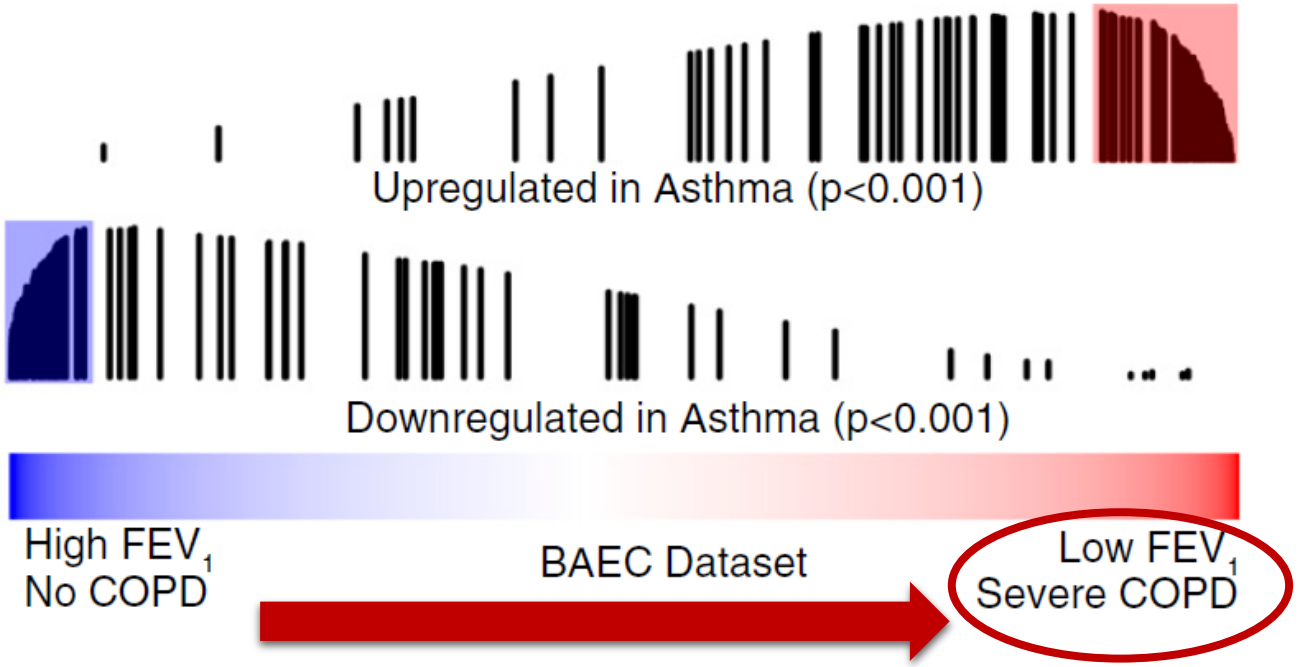
Am J Respir Crit Care Med 2015;191:758

방법

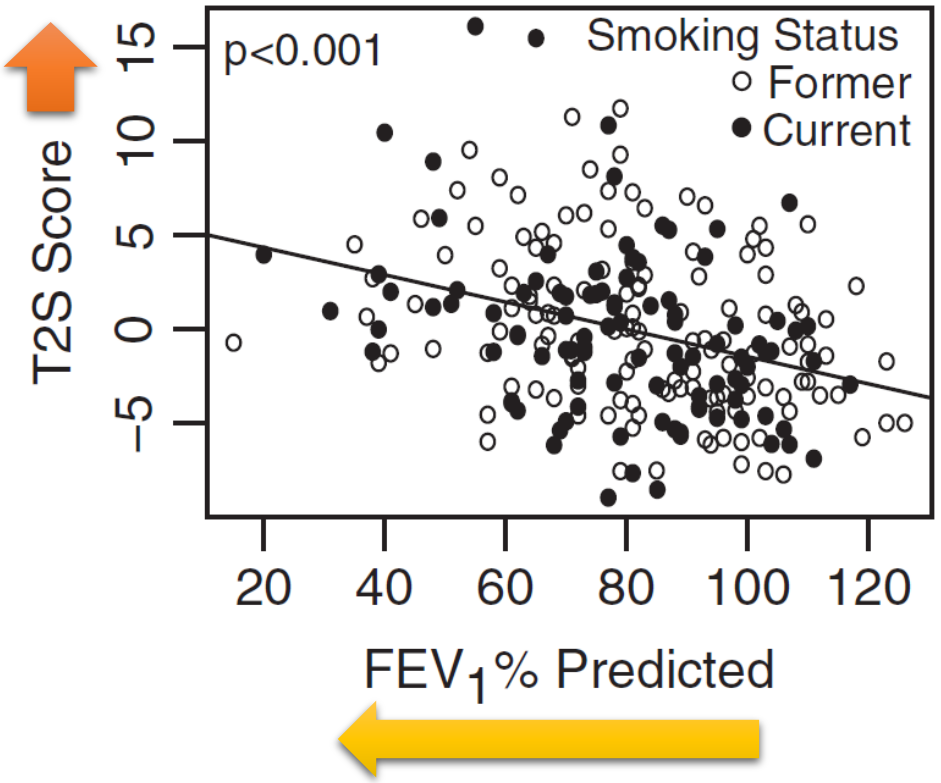


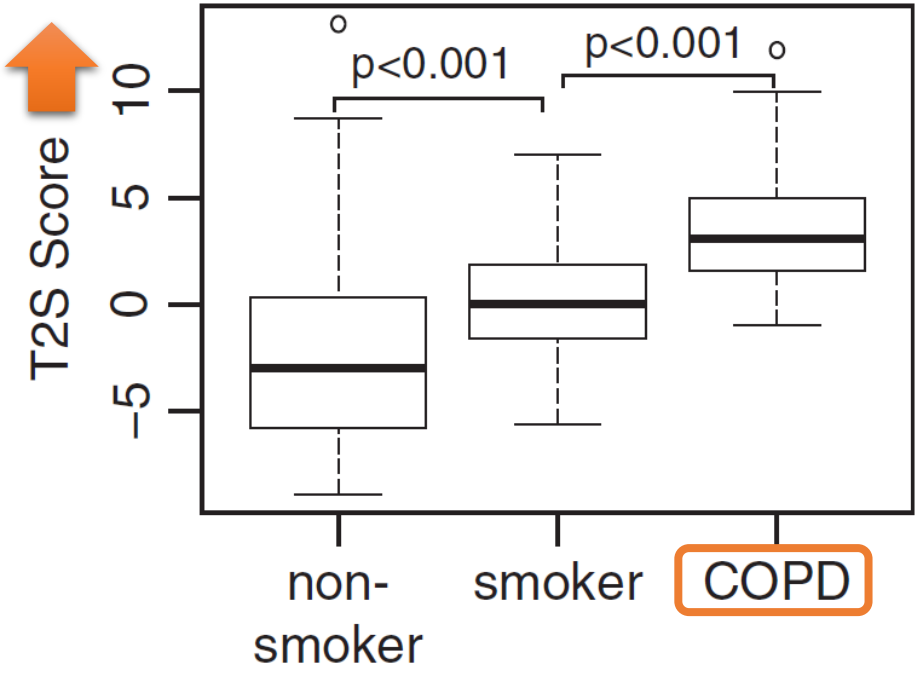
Am J Respir Crit Care Med 2015;191:758

Genes most altered in Airway Epithelium in Asthma evaluated in COPD



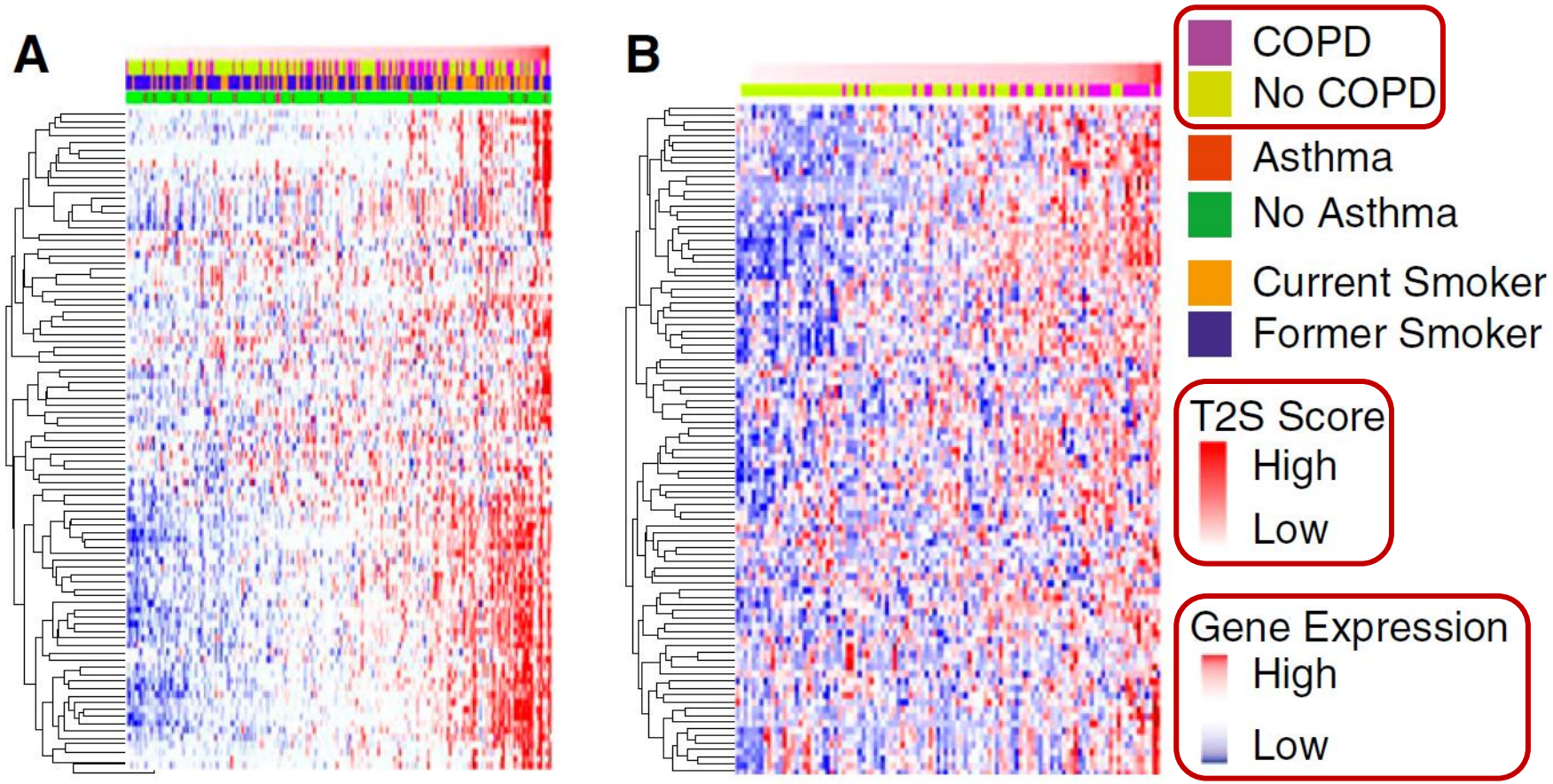
T2S Score





Am J Respir Crit Care Med 2015;191:758

Heatmap of 100-gene T2S score



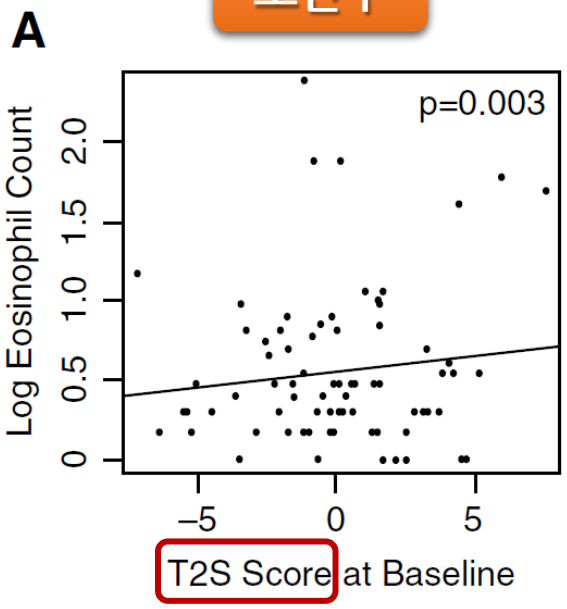
Bronchial airway epithelium

Small airway epithelium

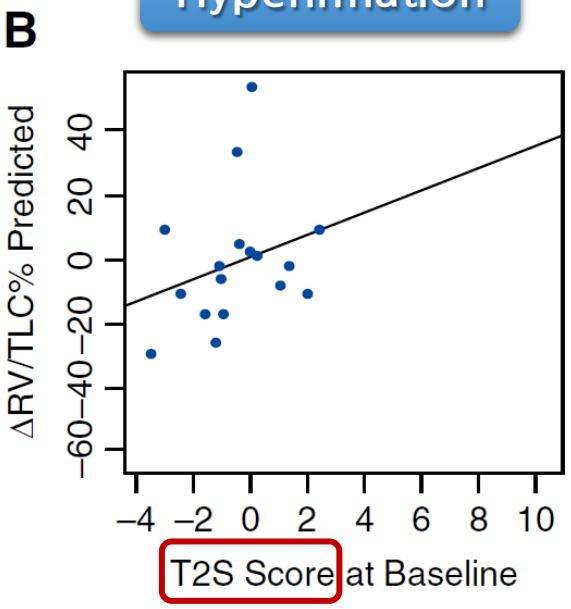
Am J Respir Crit Care Med 2015;191:758

T2S score in GLUCOLD cohort

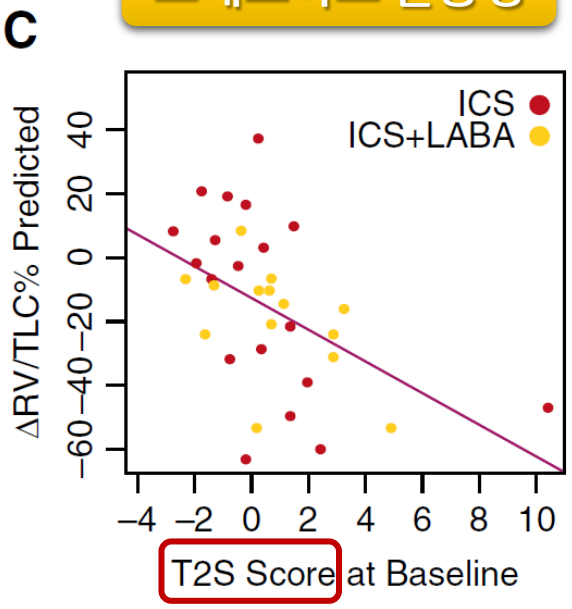
호산구



Hyperinflation



스테로이드 반응성



Am J Respir Crit Care Med 2015;191:758

결론

- 기도 유전자 발현 변이가 천식과 COPD에서 모두 발생
- T2S 점수가 중증기류폐쇄(스테로이드 반응성 포함)와 연관

Am J Respir Crit Care Med 2015;191:758

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Host Response to the Lung Microbiome in Chronic Obstructive Pulmonary Disease

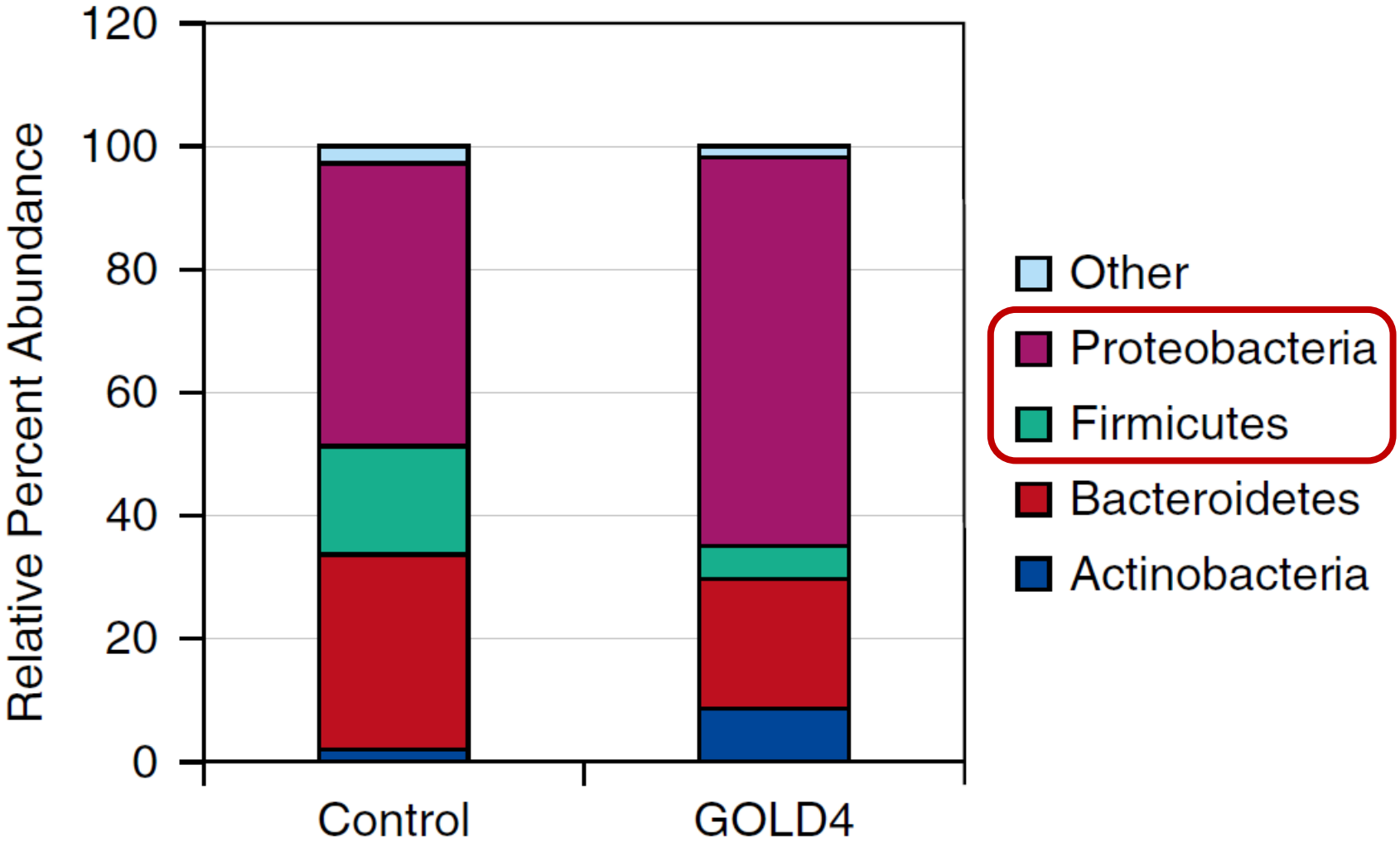
Marc A. Sze[1,2*], Pedro A. Dimitriu[3*], Masaru Suzuki[1,4], John E. McDonough[1,2], Josh D. Campbell[5], John F. Brothers[5], John R. Erb-Downward[6], Gary B. Huffnagle[6], Shizu Hayashi[1,4], W. Mark Elliott[1,2], Joel Cooper[7], Don D. Sin[1,2], Marc E. Lenburg[5], Avrum Spira[5], William W. Mohn[3], and James C. Hogg[1,4]

Am J Respir Crit Care Med 2015;192:438

Patient Demographics

	Control Subjects (*n* = 4)	GOLD Stage 4 (*n* = 5)
Age, yr	53.8±4.3	60.0±1.6
Sex, M:F	4:0	3:2
FEV_1/FVC	N/A	0.31±0.07
FEV_1% predicted	N/A	17.89±5.47
Samples per individual (n)	8 (3), 5 (1)	8 (5)

Phylum (문) relative % abundances



Am J Respir Crit Care Med 2015;192:438

8가지 주요 균
대조군 *vs.* GOLD 4

Prevotella oralis
Streptococcus
Prevotella oris
Porphyromonas
Flavobacterium succinicans
Haemophilus influenzae
Bacteroidales
Elizabethkingia meningoseptica
Dialister
Flavobacterium gelidilacus

Am J Respir Crit Care Med 2015;192:438

Microbiome &(Quantitative Histology & Micro-CT)

Comparison	Coefficient	*P* Value	FDR
Dialister and Vv of neutrophils	0.32	6.93×10^{-7}	9.01×10^{-5}
Elizabethkingia meningoseptica and Vv of elastin	0.23	1.58×10^{-4}	0.01
Haemophilus influenzae and number of terminal bronchioles	0.01	7.0×10^{-4}	0.02
Flavobacterium gelidilacus and surface area	3.0×10^{-4}	6.32×10^{-4}	0.02
Bacteroidales and Vv of neutrophils	0.62	1.24×10^{-3}	0.03
Dialister and number of terminal bronchioles	2.7×10^{-3}	2.49×10^{-3}	0.05
Streptococcus and Vv of neutrophils	1.35	3.65×10^{-3}	0.06
Flavobacterium succinicans and Vv of CD4 T cells	−2.58	3.96×10^{-3}	0.06
H. influenzae and Vv of neutrophils	0.48	4.35×10^{-3}	0.06
E. meningoseptica and Lm	0.02	4.40×10^{-3}	0.06
E. meningoseptica and Vv of CD4 T cells	1.00	5.03×10^{-3}	0.06
E. meningoseptica and Vv of total collagen	−0.08	8.00×10^{-3}	0.09

Definition of abbreviations: FDR = false discovery rate; Lm = mean linear intercept; Vv = volume fraction.

Am J Respir Crit Care Med 2015;192:438

ERJ Express. Published on February 25, 2016 as doi: 10.1183/13993003.01406-2015

ORIGINAL ARTICLE
IN PRESS | CORRECTED PROOF

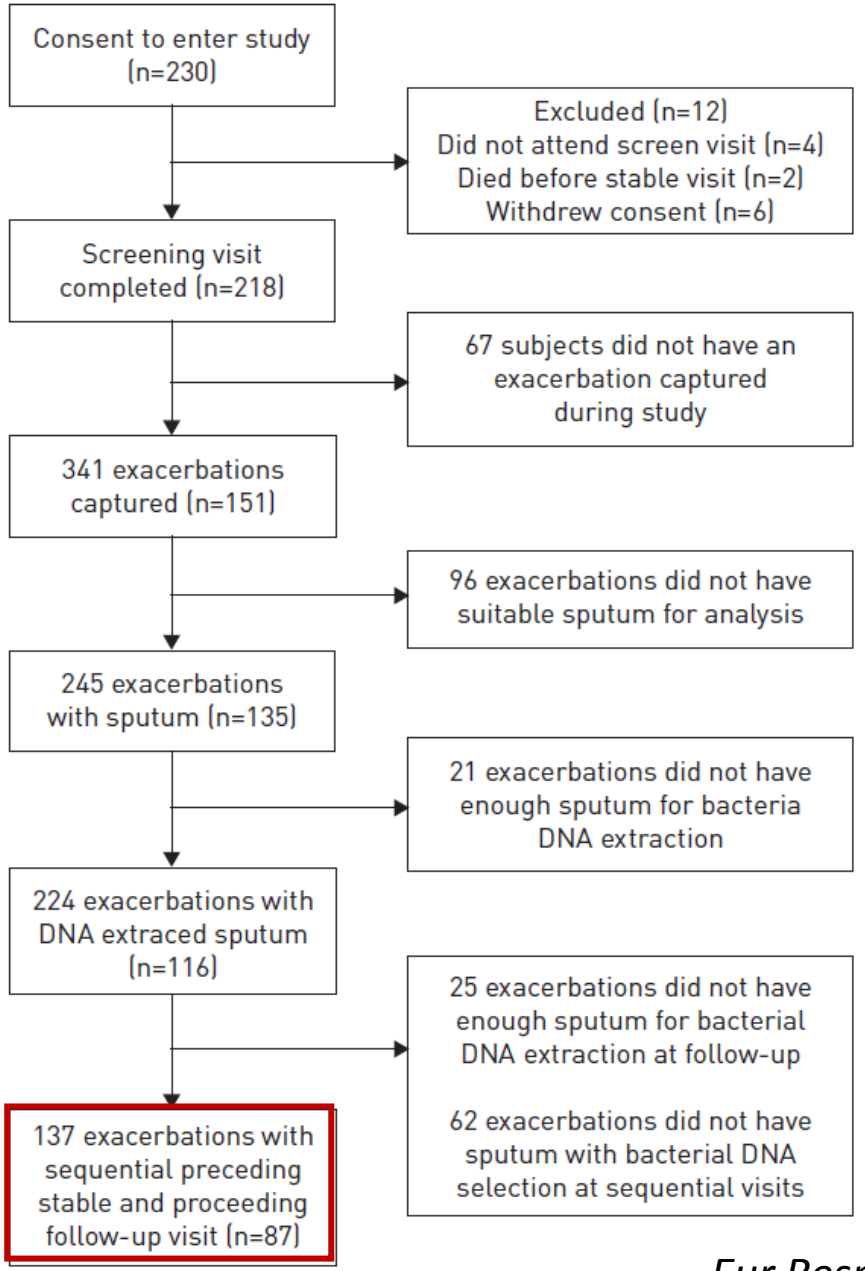
Lung microbiome dynamics in chronic obstructive pulmonary disease exacerbations

Zhang Wang[1,7], Mona Bafadhel[2,7], Koirobi Haldar[3,6], Aaron Spivak[1], David Mayhew[1], Bruce E. Miller[4], Ruth Tal-Singer[4], Sebastian L. Johnston[5], Mohammadali Yavari Ramsheh[3], Michael R. Barer[3], Christopher E. Brightling[3,6,8] and James R. Brown[1,8]

BEAT-COPD

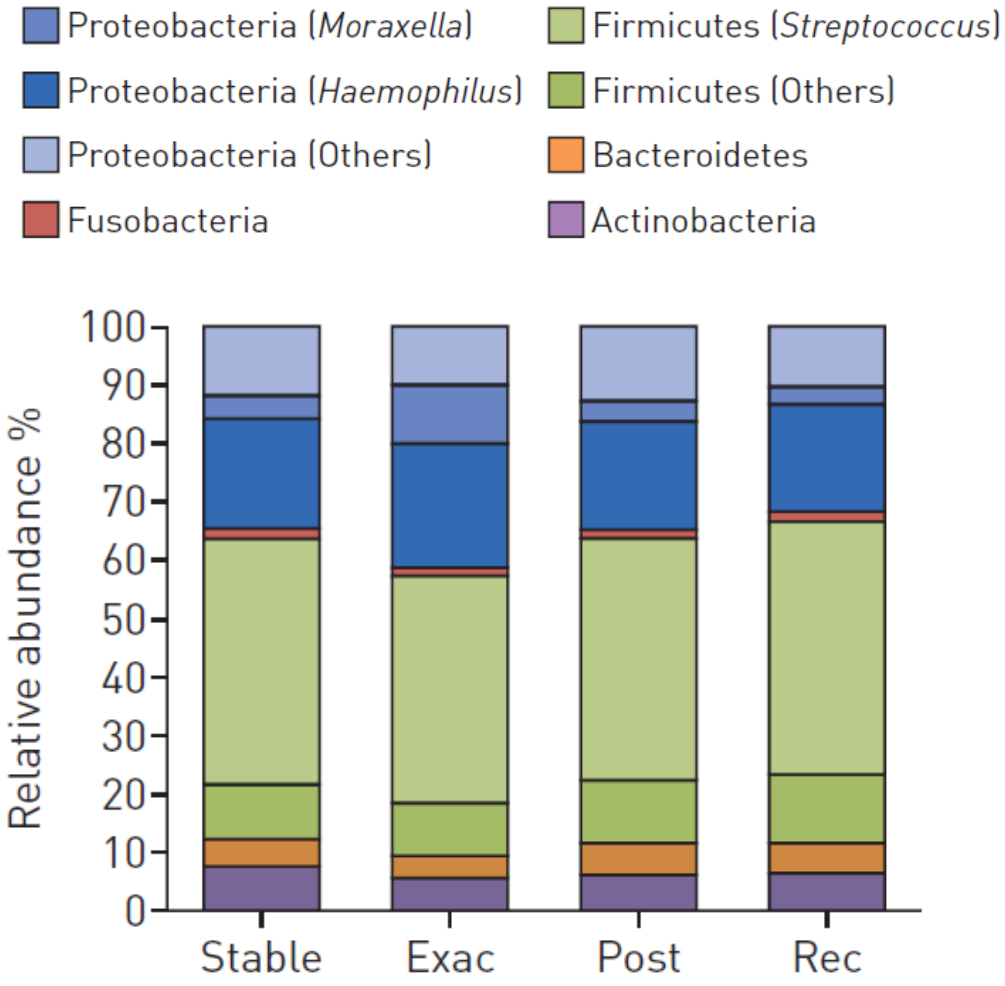
Biomarkers to Target Antibiotic and Systemic Corticosteroid Therapy in COPD Exacerbations

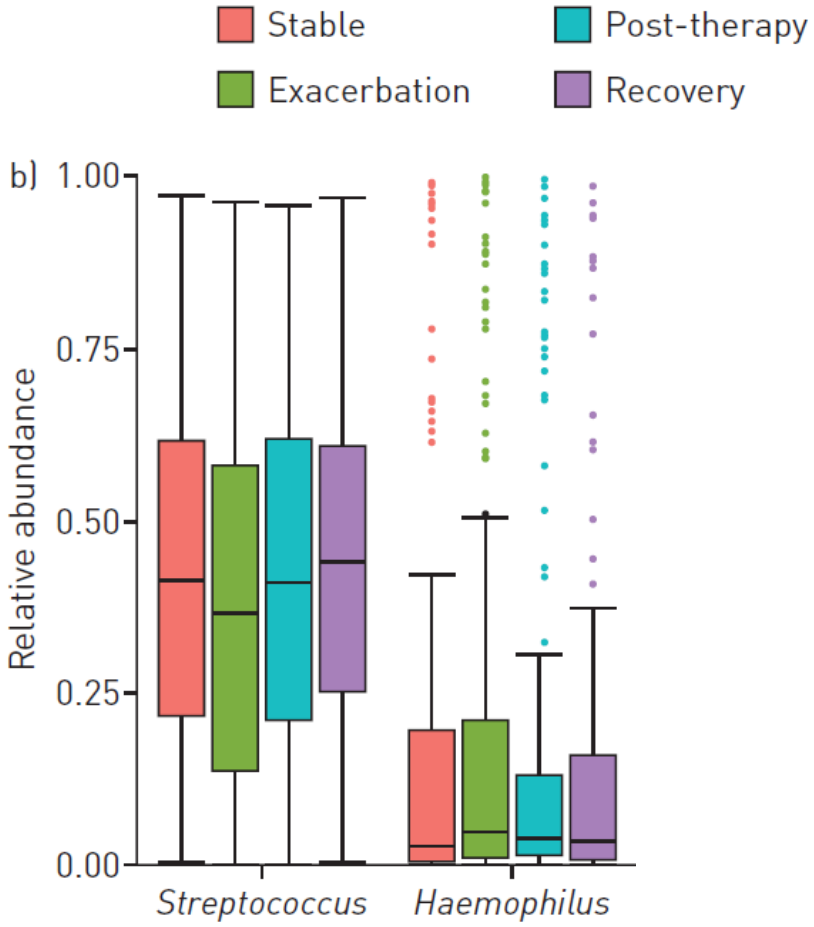
87명
476 **sputum**
① 안정 시
② 악화
③ 치료 후 2주
④ 회복기 6주
16S ribosomal RNA survey



Eur Respir J 2016

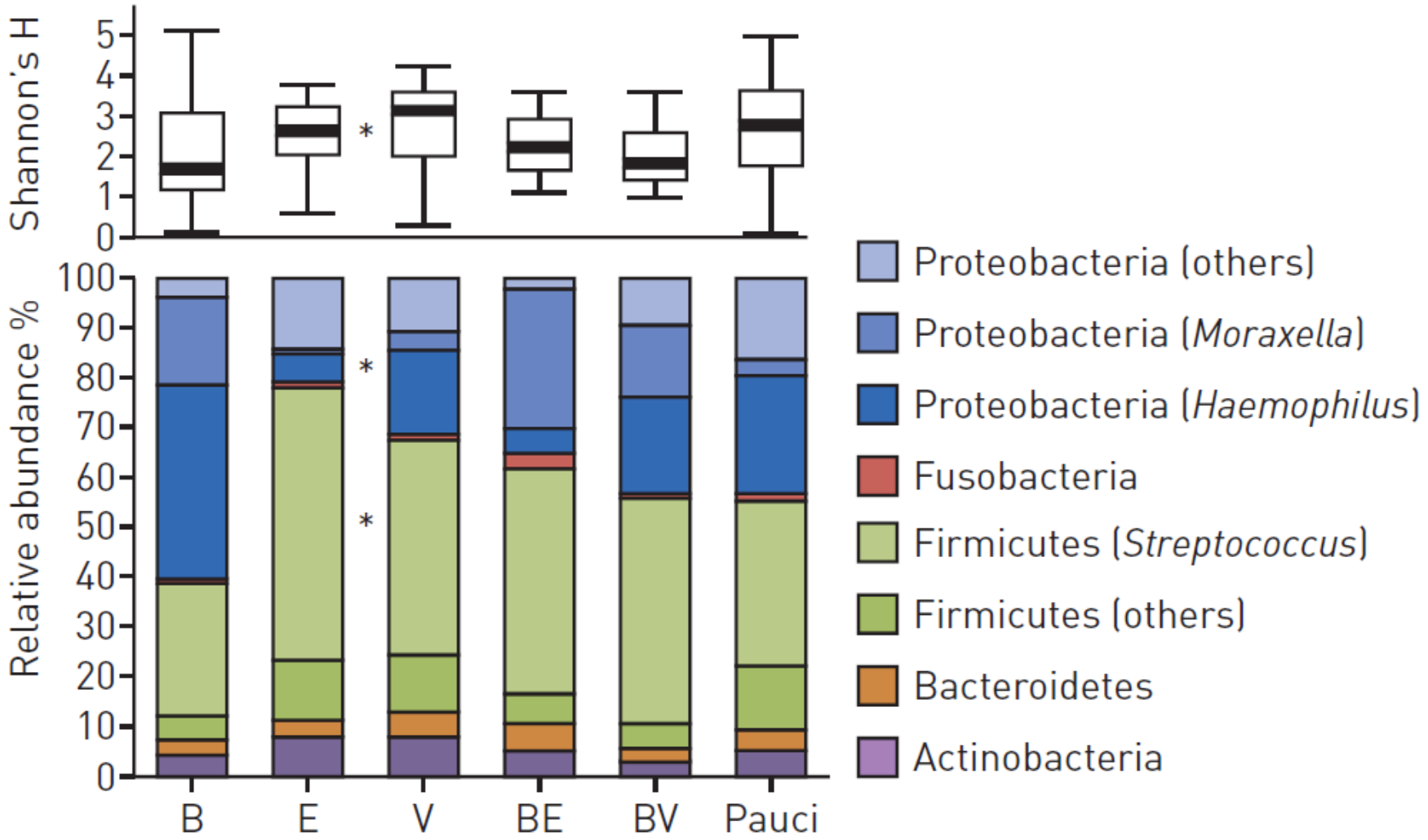
COPD 악화 동안 Microbiome 변화





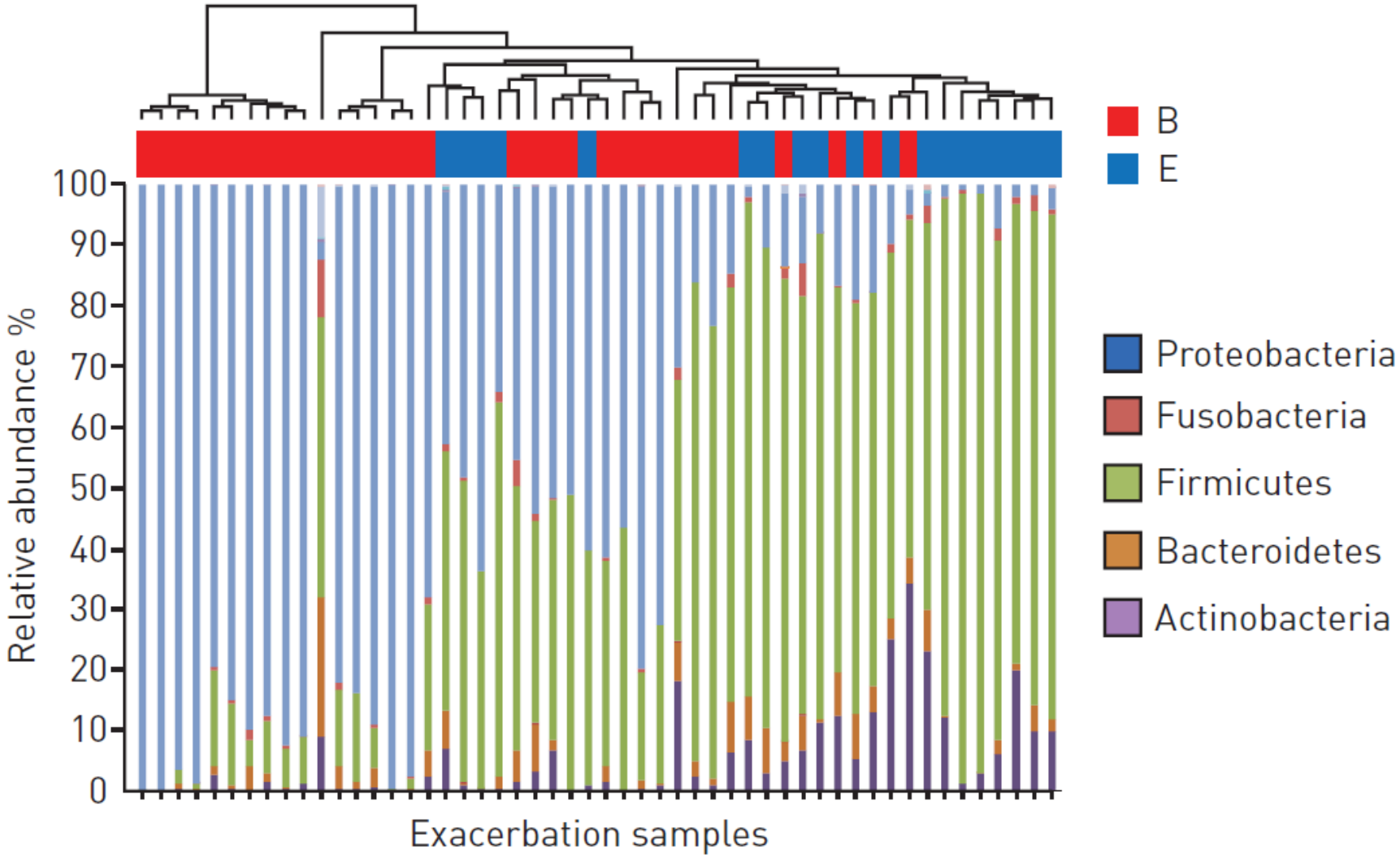
Eur Respir J 2016

Exacerbation Phenotypes

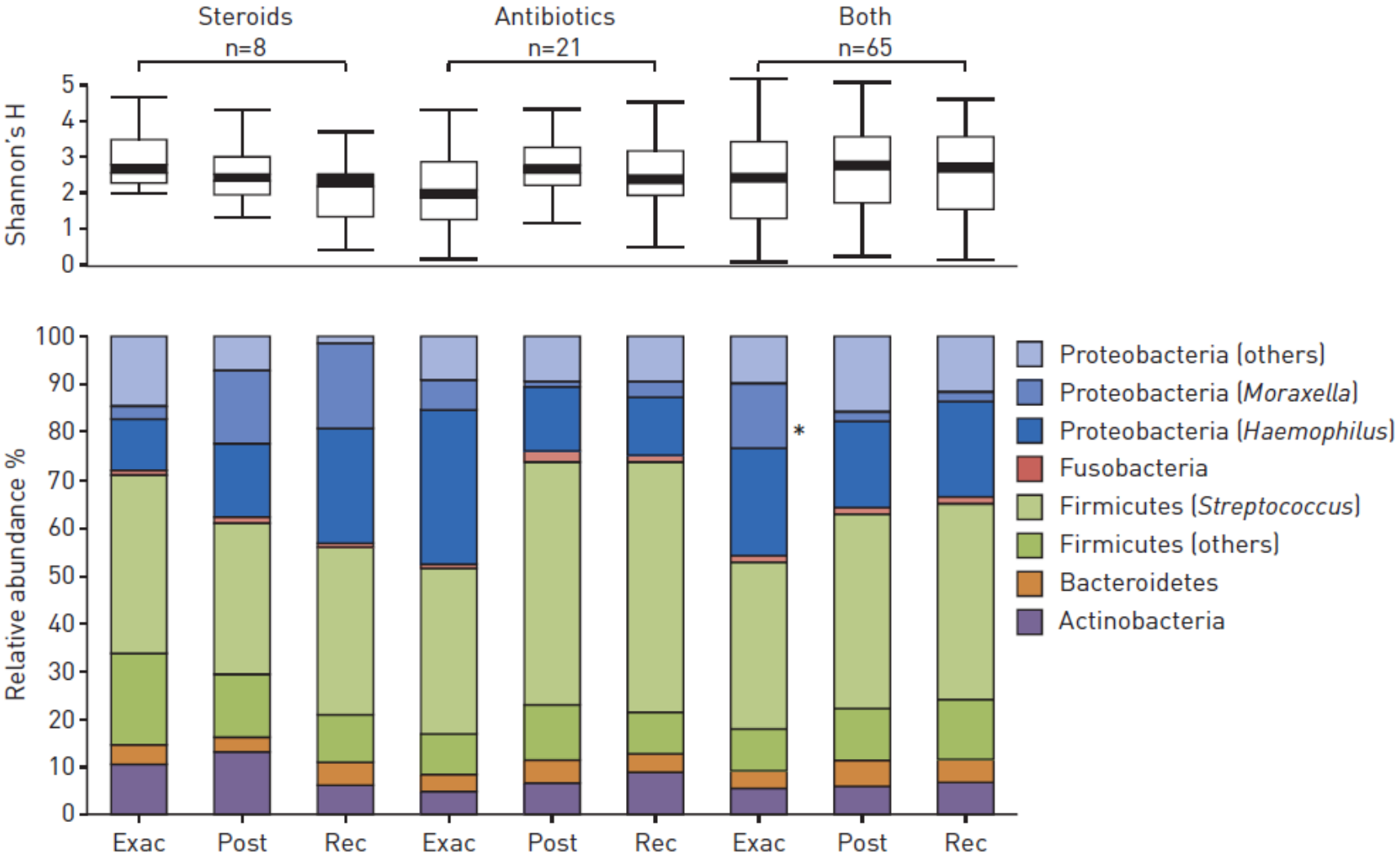


Eur Respir J 2016

세균성 악화 *vs.* 호산구성 악화



스테로이드와 항생제 투약에 따른 Microbiome 변화



Eur Respir J 2016

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

Karin Klooster, Nick H.T. ten Hacken, M.D., Ph.D., Jorine E. Hartman, Ph.D., Huib A.M. Kerstjens, M.D., Ph.D., Eva M. van Rikxoort, Ph.D., and Dirk-Jan Slebos, M.D., Ph.D.

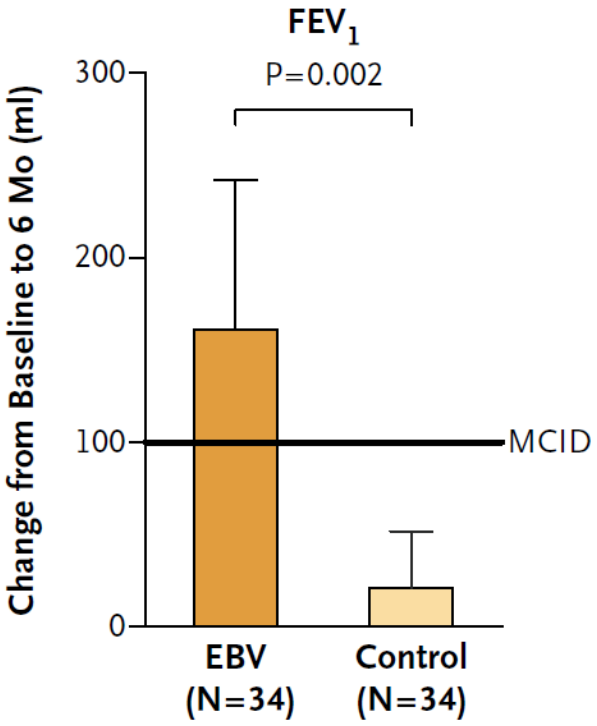
N Engl J Med 2015;373:2325

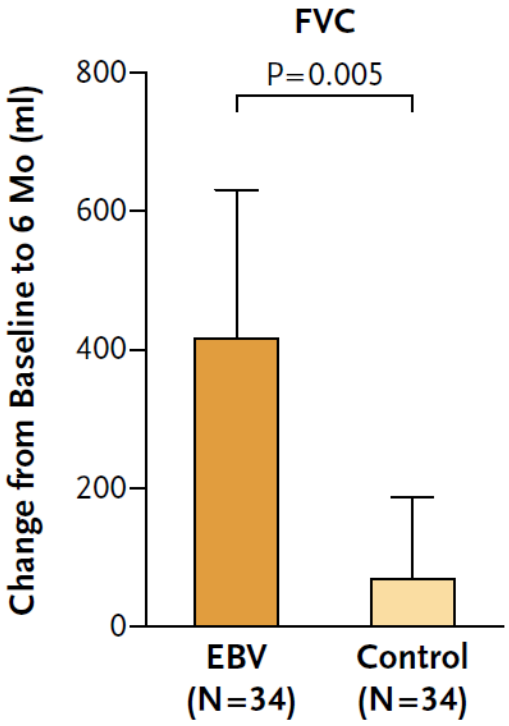
Baseline Characteristics

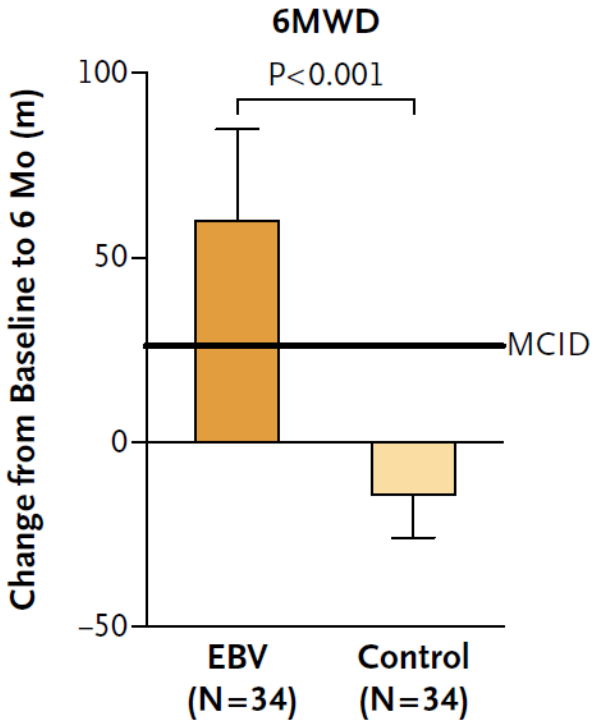
Characteristic	EBV (N = 34)	Control (N = 34)
Female – no. (%)	18 (53)	28 (82)
Age – yr	58±10	59±8
BMI – kg/m^2	24.1±3.5	24.2±4.0
Smoking – pack-yr	37±18	35±19
Lung function		
FEV_1 – L	0.86±0.30	0.79±0.27
FEV_1 % predicted	29±7	29±8
FVC – L	2.80±0.83	2.50±0.90
FVC % predicted	78±16	77±20
α-1 antitrypsin deficiency – no. (%)	4 (12)	3 (9)
Previous pneumothorax – no. (%)	2 (6)	1 (3)

N Engl J Med 2015;373:2325

Primary Outcomes







N Engl J Med 2015;373:2325

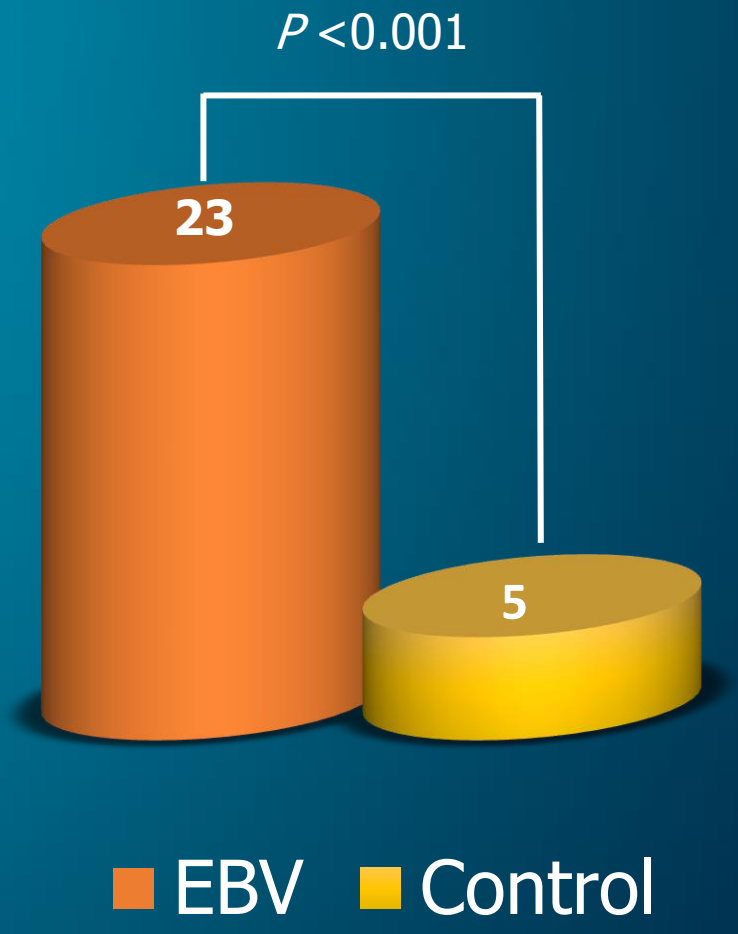
Serious Adverse Events

사망 1예

기흉 (18%)

밸브 교체 (12%)

밸브 제거 (15%)

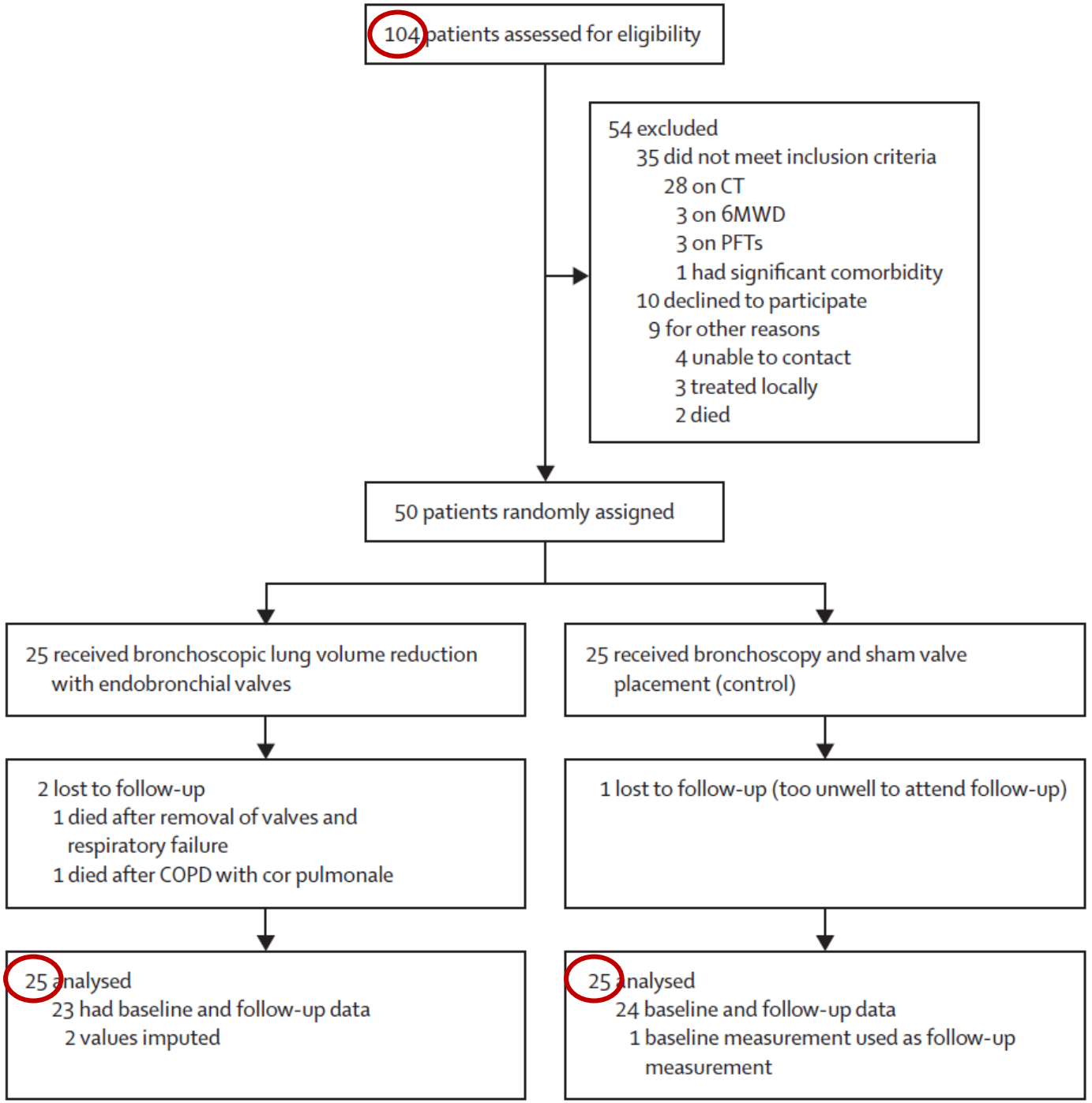


N Engl J Med 2015;373:2325

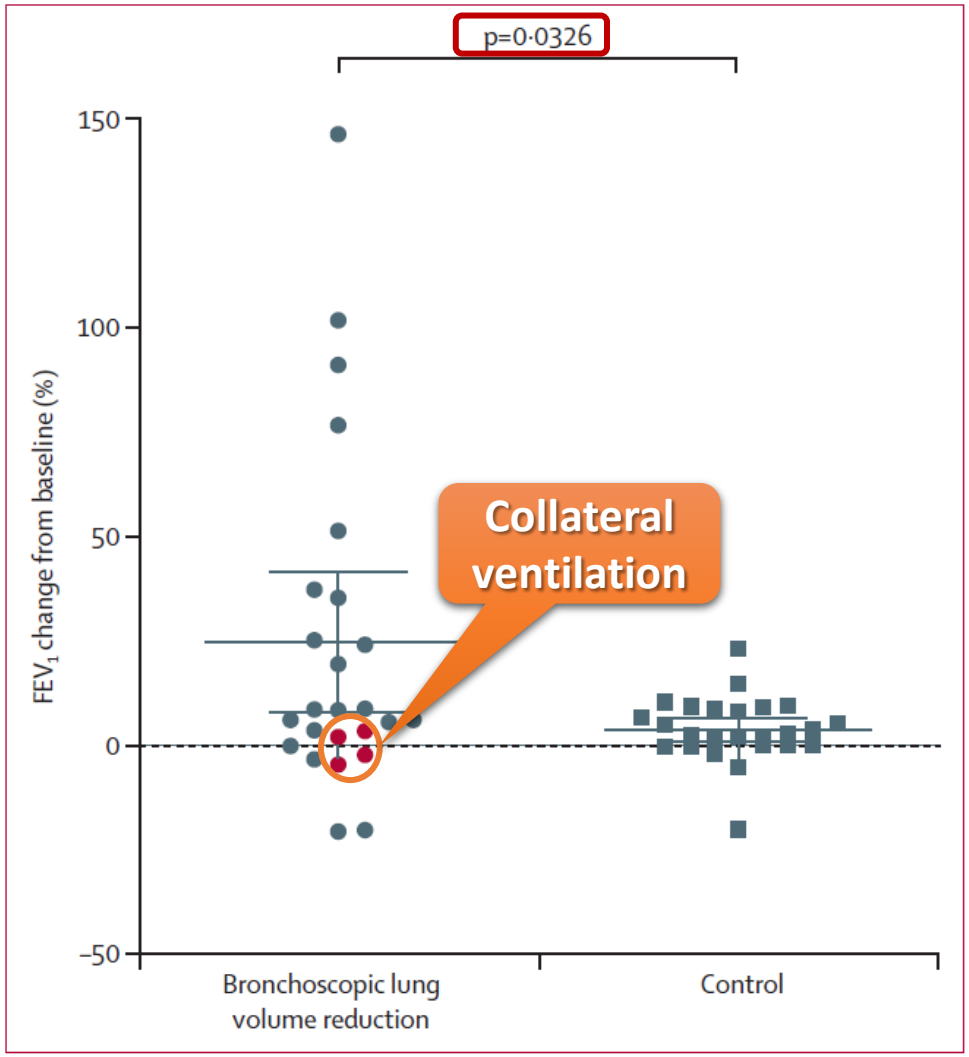
Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial

Claire Davey, Zaid Zoumot*, Simon Jordan, William H McNulty, Dennis H Carr, Matthew D Hind, David M Hansell, Michael B Rubens, Winston Banya, Michael I Polkey, Pallav L Shah, Nicholas S Hopkinson*

Lancet 2015; 386: 1066


104 patients assessed for eligibility
54 excluded
35 did not meet inclusion criteria
28 on CT
3 on 6MWD
3 on PFTs
1 had significant comorbidity
10 declined to participate
9 for other reasons
4 unable to contact
3 treated locally
2 died
50 patients randomly assigned
25 received bronchoscopic lung volume reduction with endobronchial valves
25 received bronchoscopy and sham valve placement (control)
2 lost to follow-up
1 died after removal of valves and respiratory failure
1 died after COPD with cor pulmonale
1 lost to follow-up (too unwell to attend follow-up)
25 analysed
23 had baseline and follow-up data
2 values imputed
25 analysed
24 baseline and follow-up data
1 baseline measurement used as follow-up measurement

3개월 후 FEV_1 변화



Lancet 2015; 386: 1066

Adverse Events

	BLVR (n=25)		Control (n=25)		p value
	Events	Patients	Events	Patients	
Exacerbation (total)	23	16	22	20	0·42*, 0·35†
Of which required hospitalisation	5	..	3	..	0·70
Pneumonia (respiratory tract infection with radiograph changes)	2	2	0	0	0·49
Pneumothorax	2	2	1	1	1·0
Deaths	2	..	0	..	0·49
Respiratory failure	1	..	0	..	1·0
COPD with cor pulmonale	1	..	0	..	1·0
Expectorated valve	5	4	0	0	..
Removal of valves	2	2	0	0	..
Seizure (unrelated)	0	0	1	1	1·0

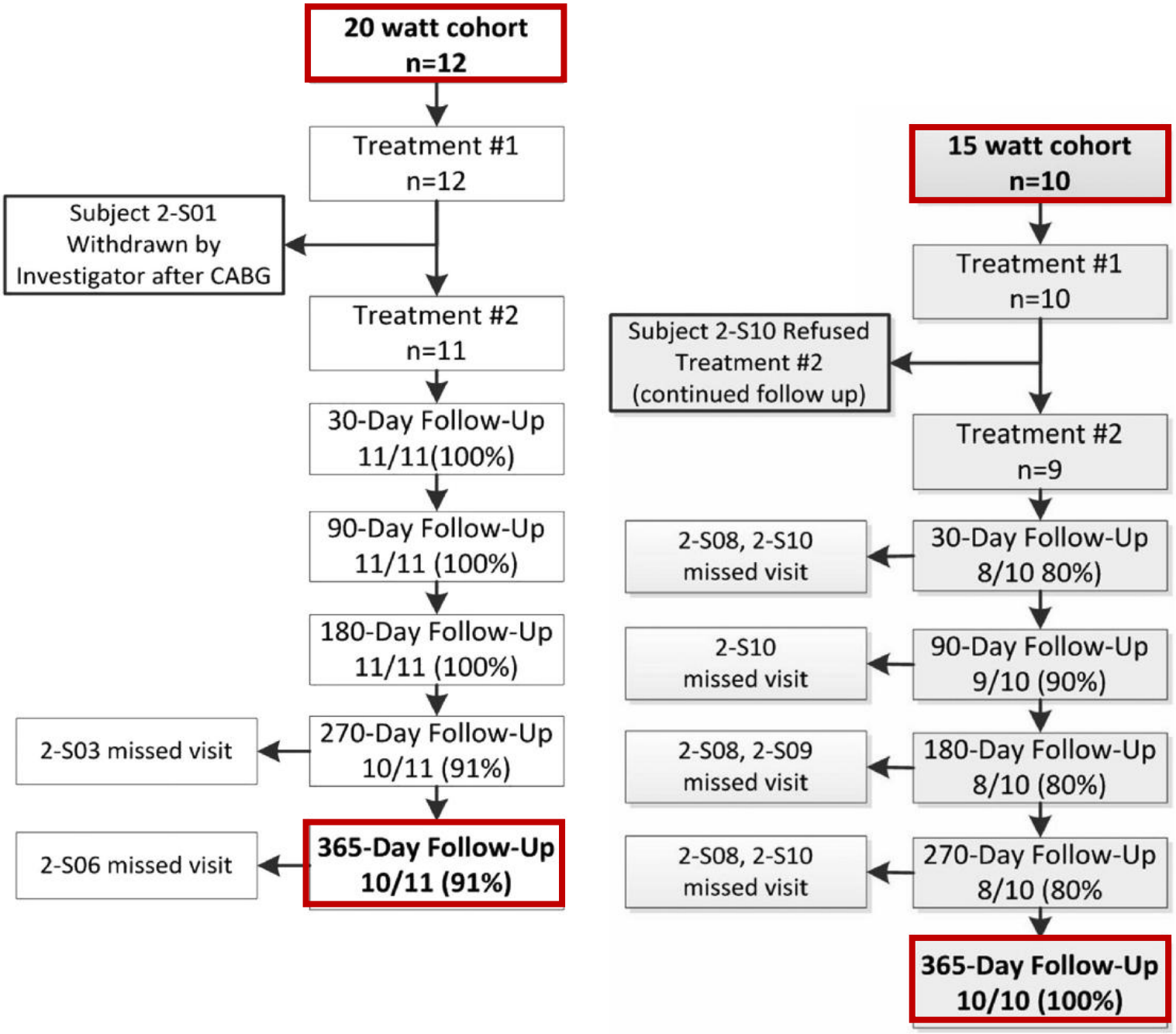
p value is for χ^2 test. BLVR=bronchoscopic lung volume reduction. COPD=chronic obstructive pulmonary disease.
*Comparison of patients. †Comparison of events.

Lancet 2015; 386: 1066

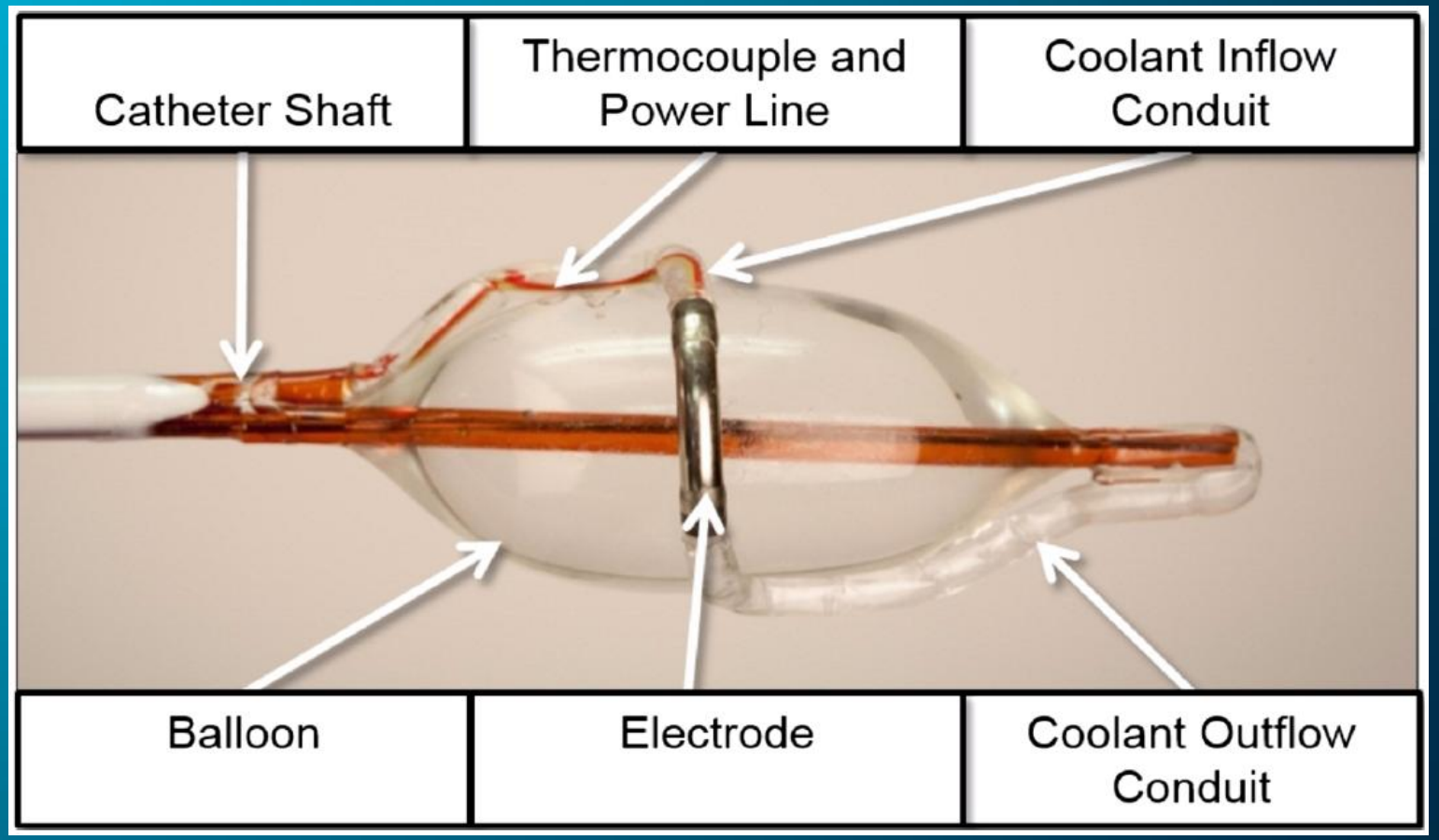
Targeted lung denervation for moderate to severe COPD: a pilot study

Dirk-Jan Slebos,[1] Karin Klooster,[1] Coenraad F N Koegelenberg,[2] Johan Theron,[3] Dorothy Styen,[2] Arschang Valipour,[4] Martin Mayse,[5] Chris T Bolliger[2,3]

Thorax 2015;70:411

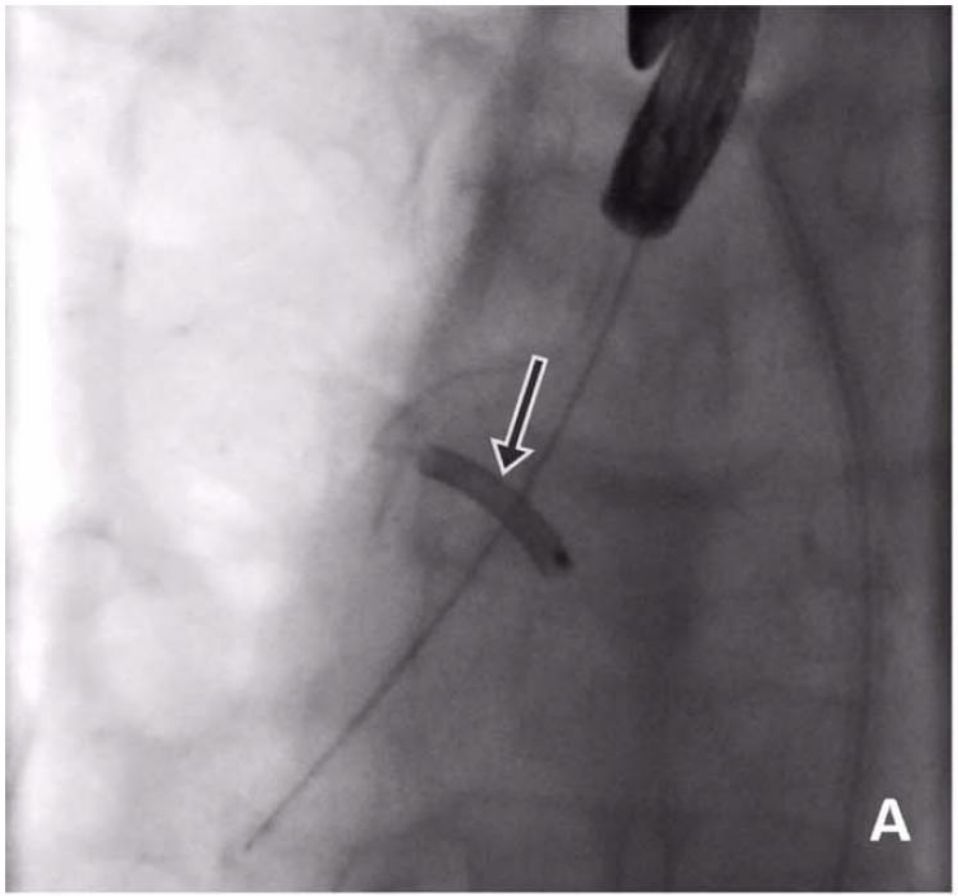

20 watt cohort
n=12
Treatment #1
n=12
Subject 2-S01
Withdrawn by
Investigator after CABG
Treatment #2
n=11
30-Day Follow-Up
11/11(100%)
90-Day Follow-Up
11/11 (100%)
180-Day Follow-Up
11/11 (100%)
270-Day Follow-Up
10/11 (91%)
2-S03 missed visit
365-Day Follow-Up
10/11 (91%)
2-S06 missed visit
15 watt cohort
n=10
Treatment #1
n=10
Subject 2-S10 Refused
Treatment #2
(continued follow up)
Treatment #2
n=9
30-Day Follow-Up
8/10 80%)
2-S08, 2-S10
missed visit
90-Day Follow-Up
9/10 (90%)
2-S10
missed visit
180-Day Follow-Up
8/10 (80%)
2-S08, 2-S09
missed visit
270-Day Follow-Up
8/10 (80%
2-S08, 2-S10
missed visit
365-Day Follow-Up
10/10 (100%)

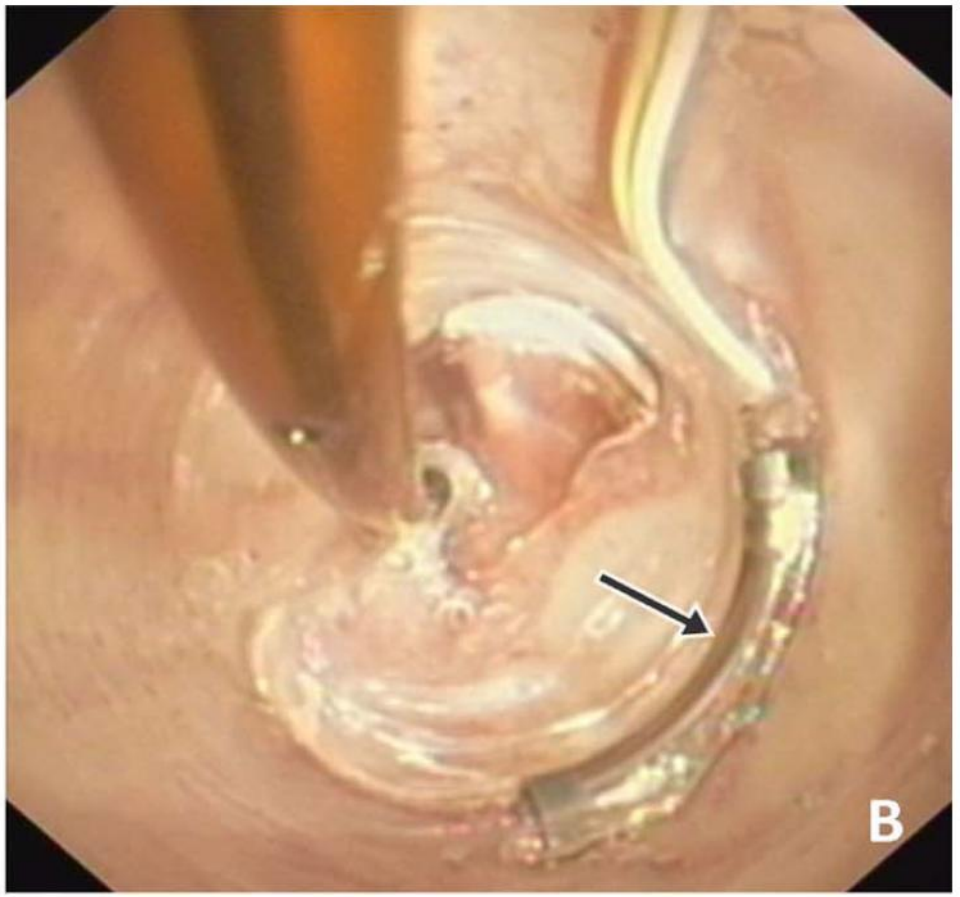
Targeted Lung Denervation (TLD) catheter



Thorax 2015;70:411

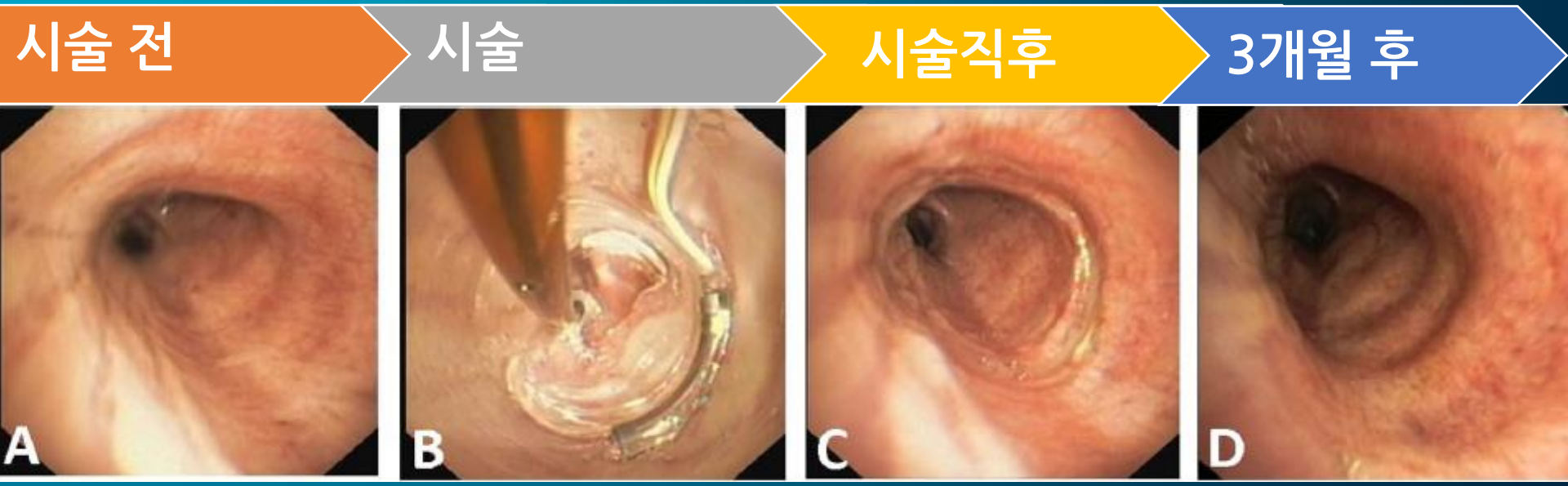
TLD procedure



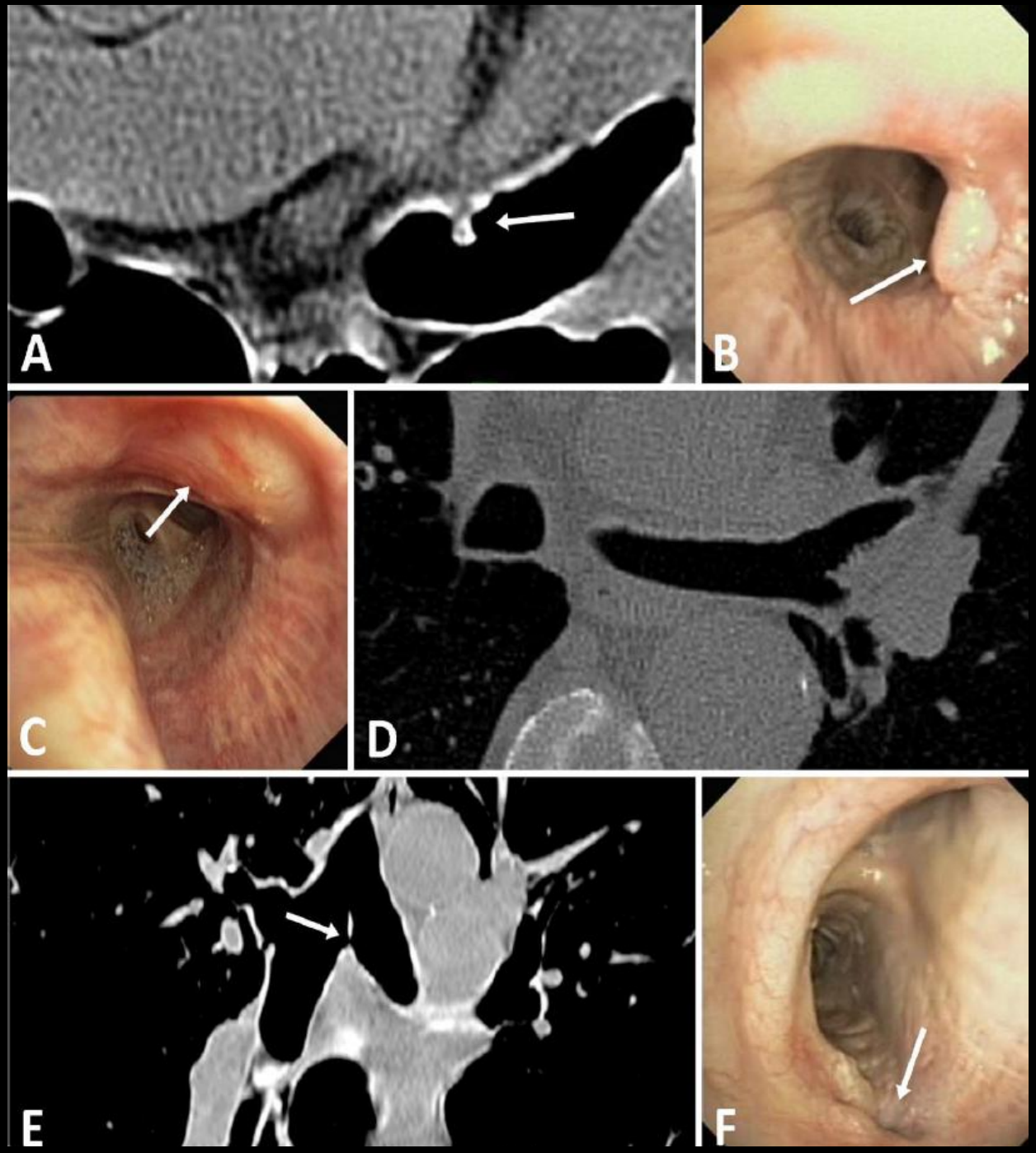


Thorax 2015;70:411

기도 치유 과정

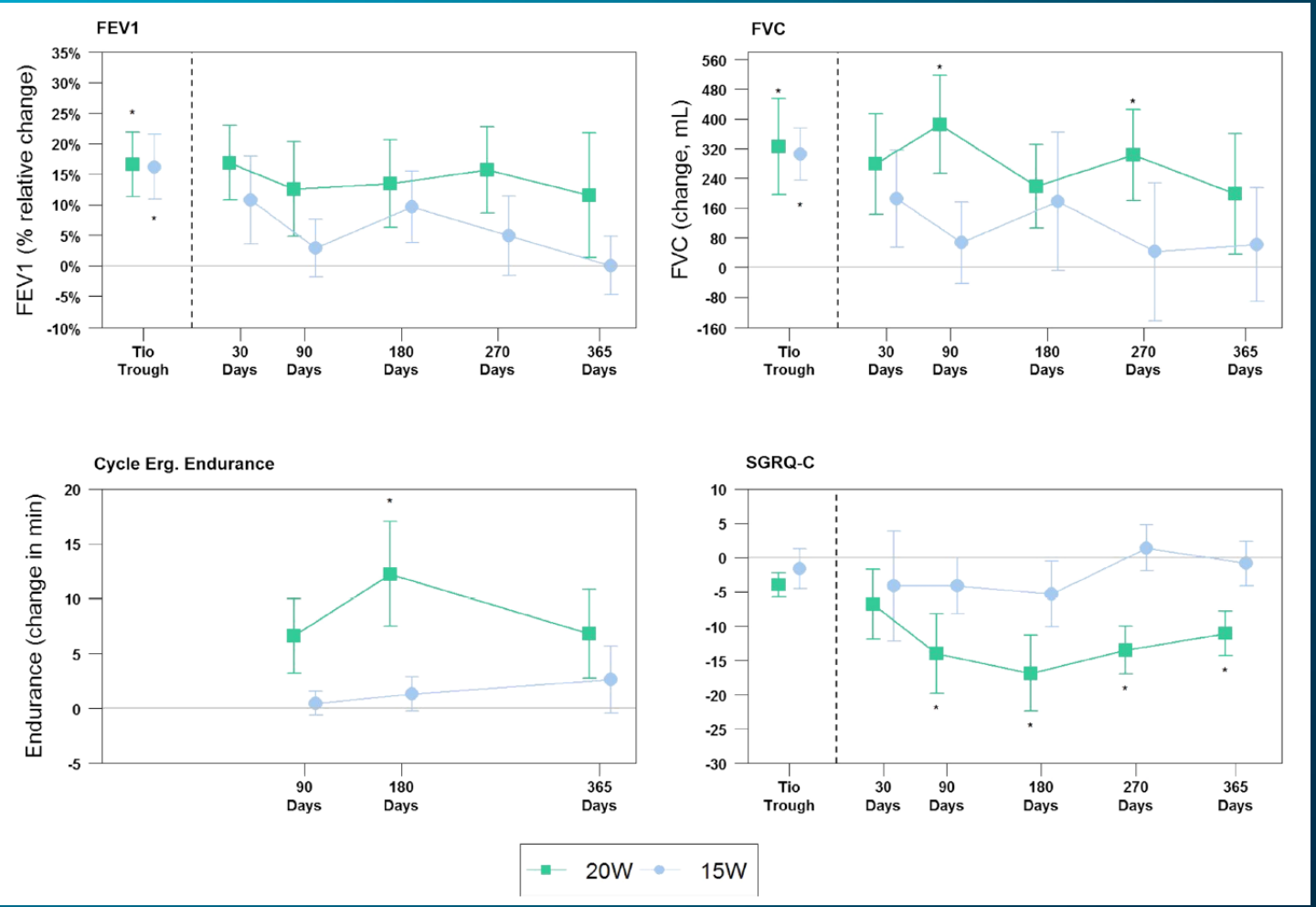


Thorax 2015;70:411



Thorax 2015;70:411

Secondary Efficacy Endpoints



Thorax 2015;70:411

순 서

- COPD의 발병
- ACOS
- COPD Microbiome
- COPD 기관지경 치료
- COPD Biomarker
- COPD 예후

[Original Research **COPD**]

CHEST

Serum Bilirubin and Disease Progression in Mild COPD

Scott Apperley, MD; Hye Yun Park, MD; Daniel T. Holmes, MD; S. F. Paul Man, MD; Donald Tashkin, MD; Robert A. Wise, MD; John E. Connett, PhD; and Don D. Sin, MD, FCCP

Chest 2015;148:169

배경

- COPD: 산화스트레스, 만성염증질환
- 혈청 빌리루빈: 강력한 항산화작용

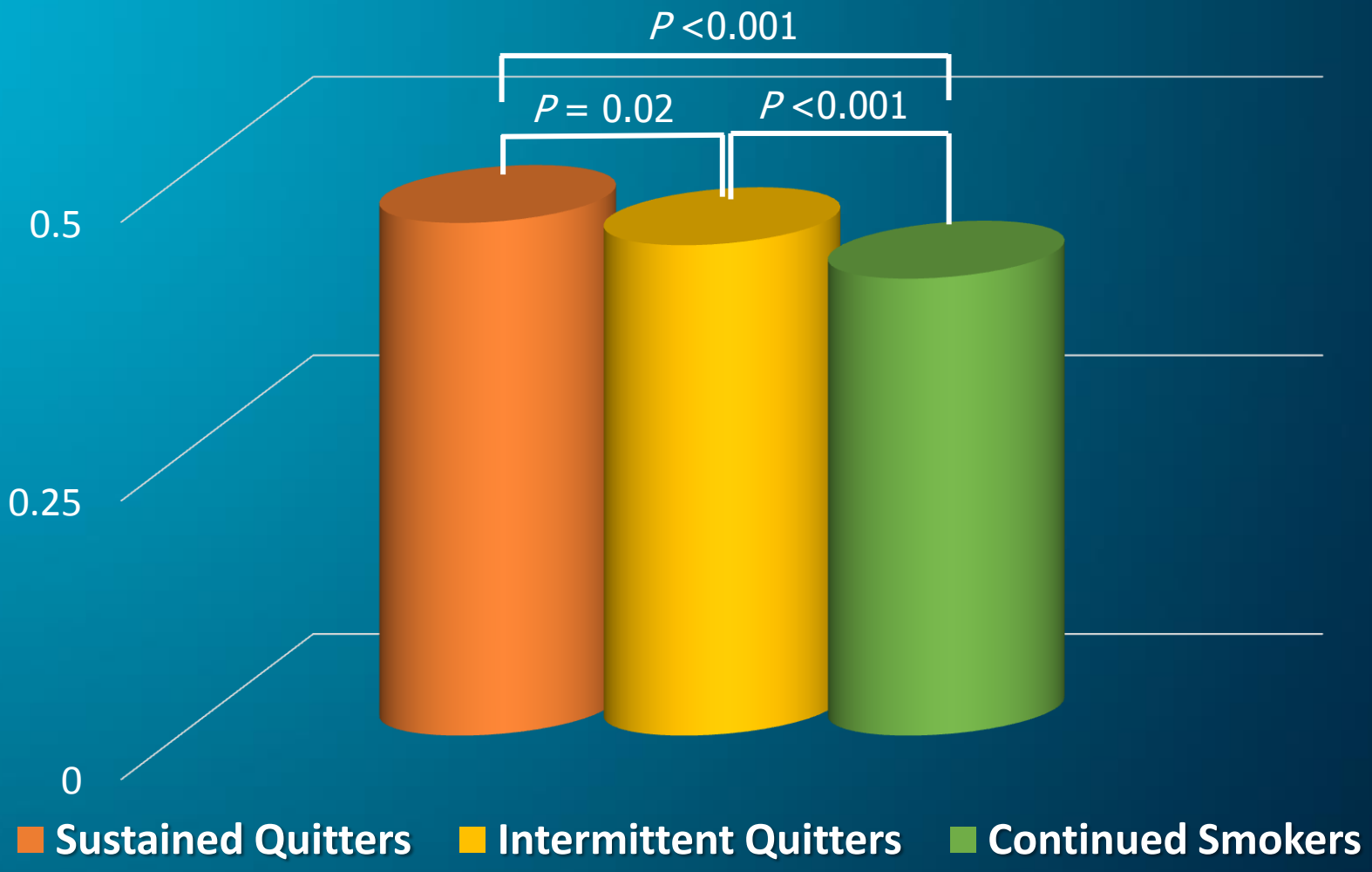
Chest 2015;148:169

방법

- Lung Health Study (LHS)
- 4,680 흡연자
- 35~60세
- Mild to moderate airflow limitation
- Bilirubin
- Post-BD FEV_1
- FEV_1 decline over 3~9 yrs
- Total and disease-specific mortality

Chest 2015;148:169

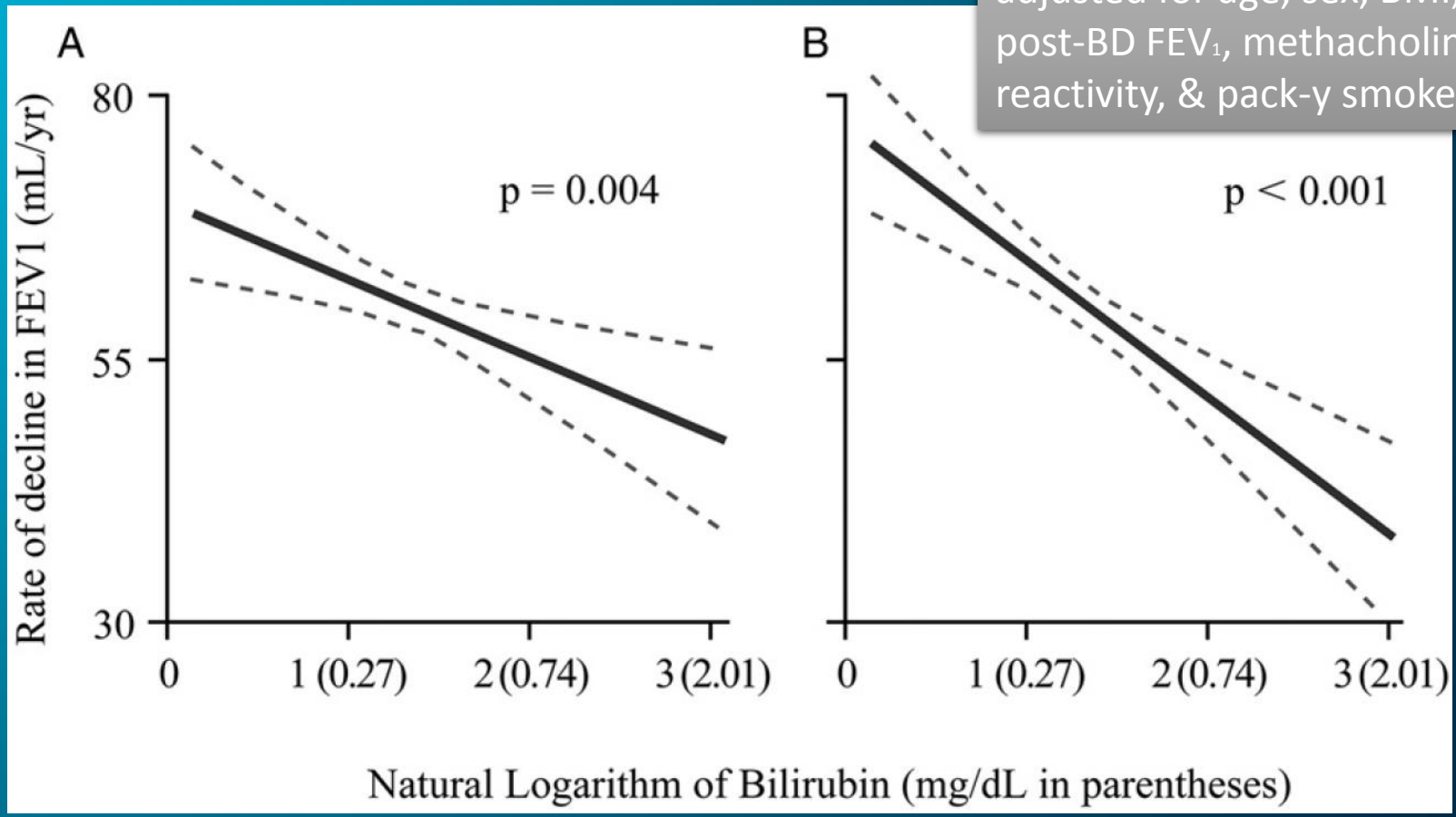
흡연 상태에 따른 빌리루빈 농도



Chest 2015;148:169

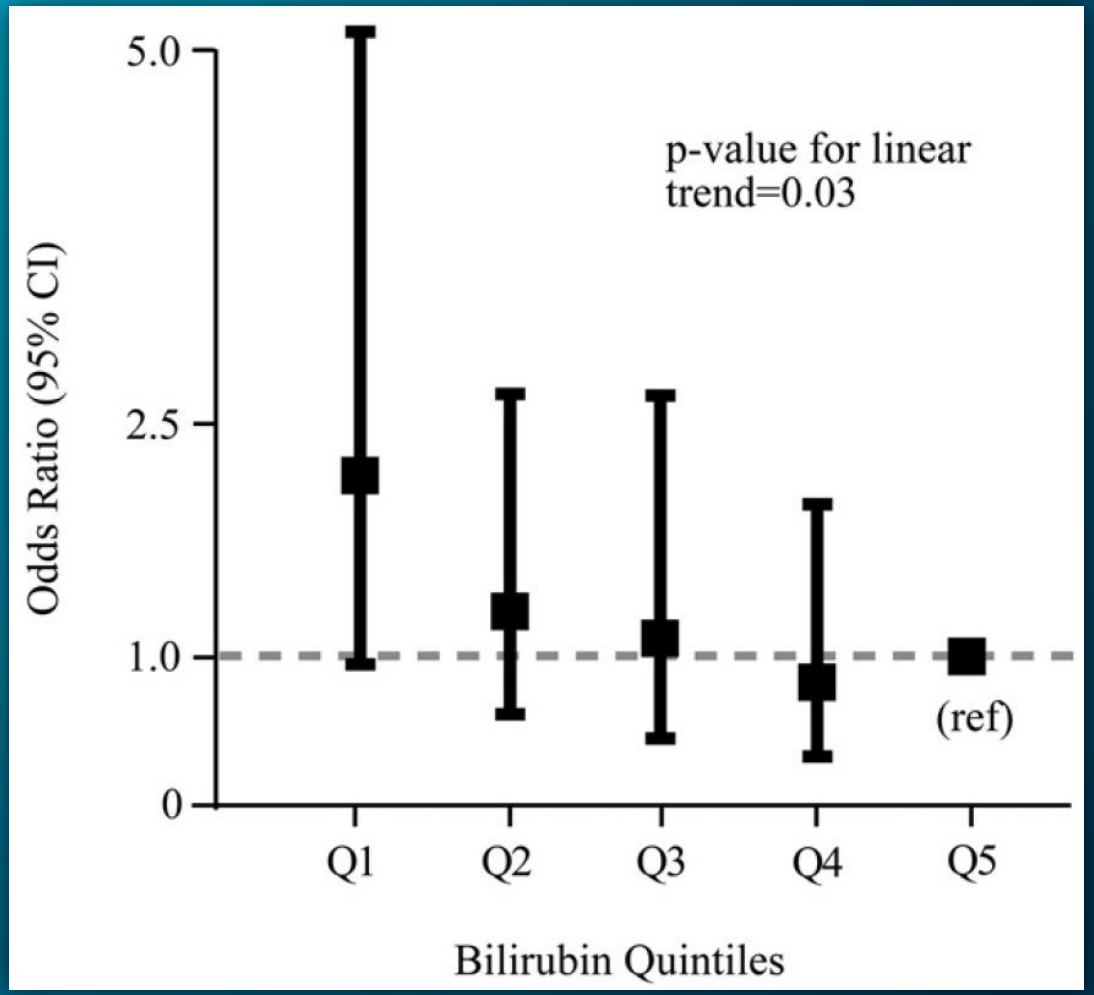
빌리루빈 농도에 따른 FEV_1 감소 속도

adjusted for age, sex, BMI, race, post-BD FEV_1, methacholine reactivity, & pack-y smoked



Chest 2015;148:169

빌리루빈 5분위에 따른 관상동맥질환 사망률



Chest 2015;148:169

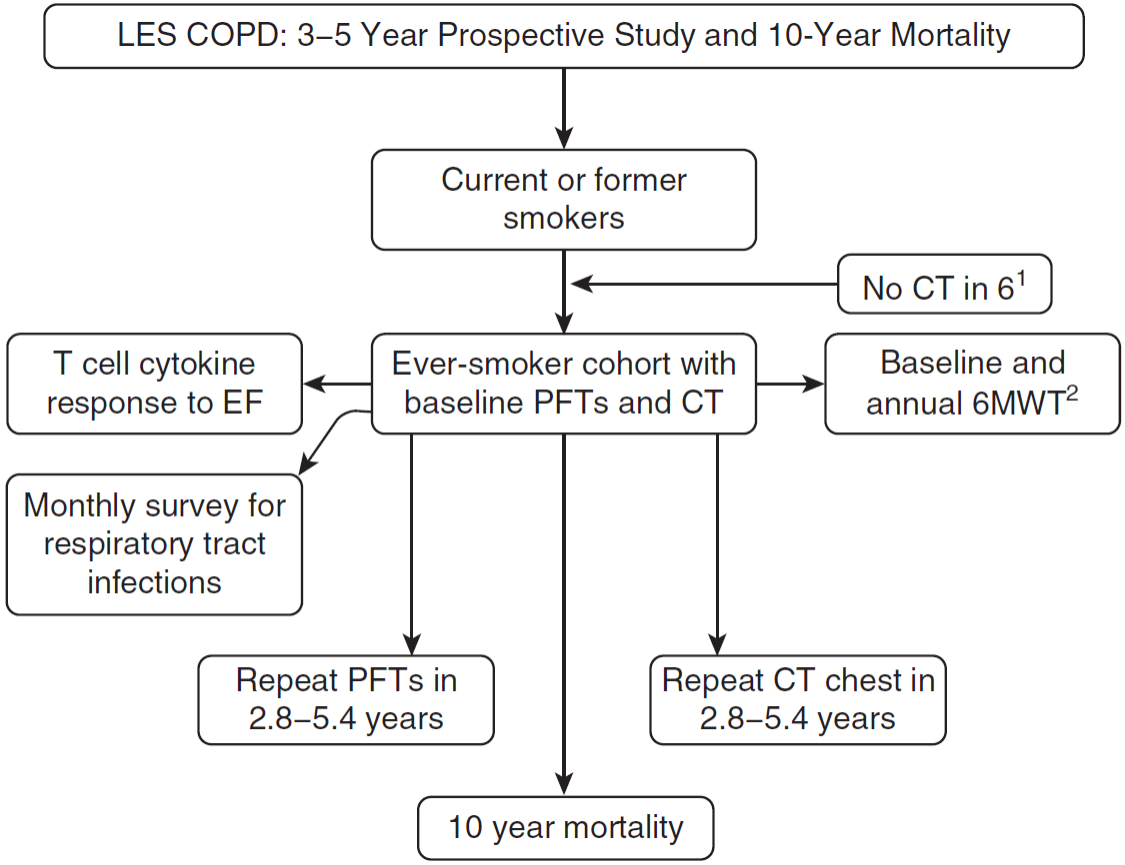
Clinical and Immunological Factors in Emphysema Progression

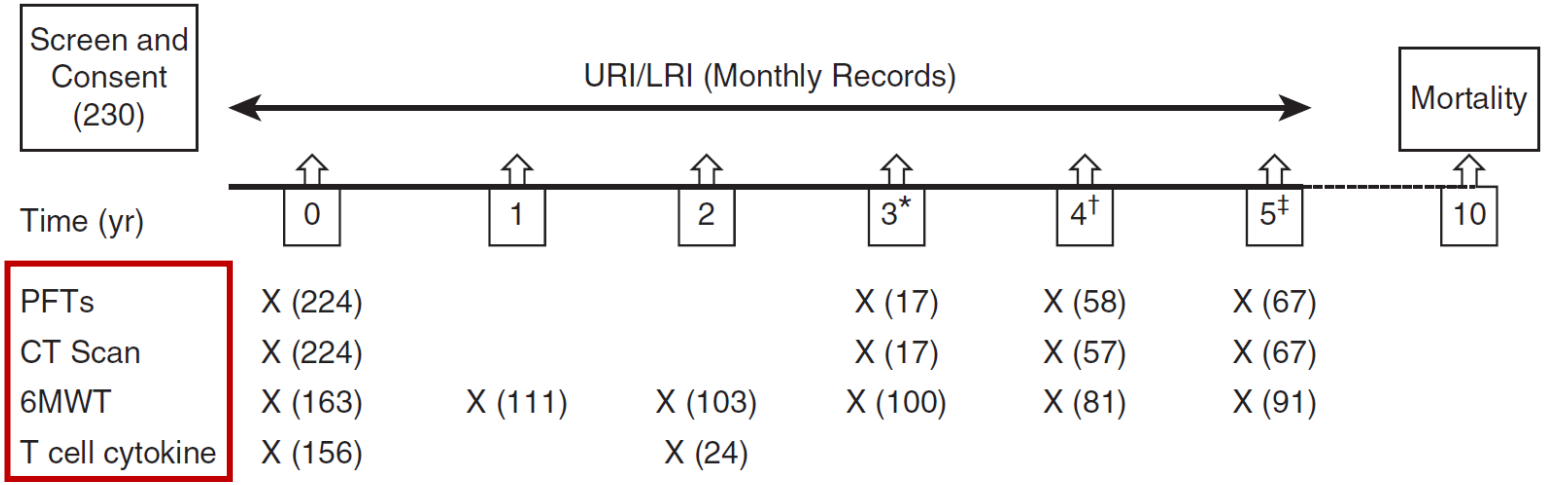
Five-Year Prospective Longitudinal Exacerbation Study of Chronic Obstructive Pulmonary Disease (LES-COPD)

Sivasubramanium Bhavani[1], Chu-Lin Tsai[2,3], Sarah Perusich[1], Sean Hesselbacher[1], Harvey Coxson[4], Lavannya Pandit[1,5], David B. Corry[1,5,6,7], and Farrah Kheradmand[1,5,6,7]

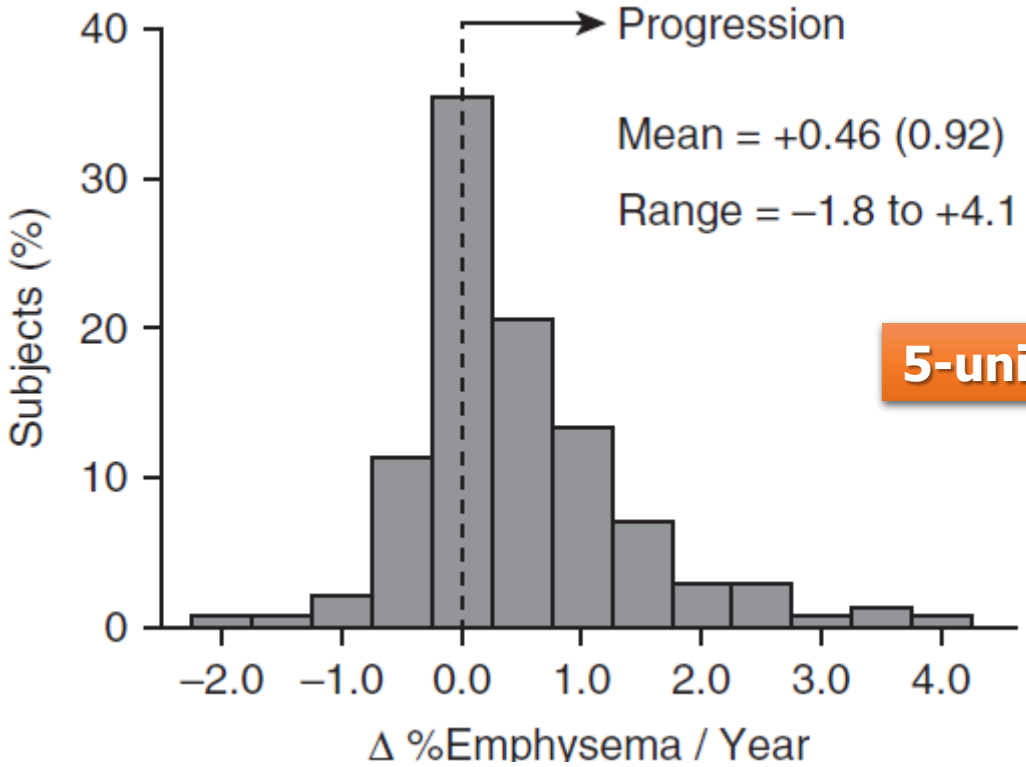
Am J Respir Crit Care Med 2015;192:1171

Longitudinal Exacerbation Study of COPD (LES-COPD)





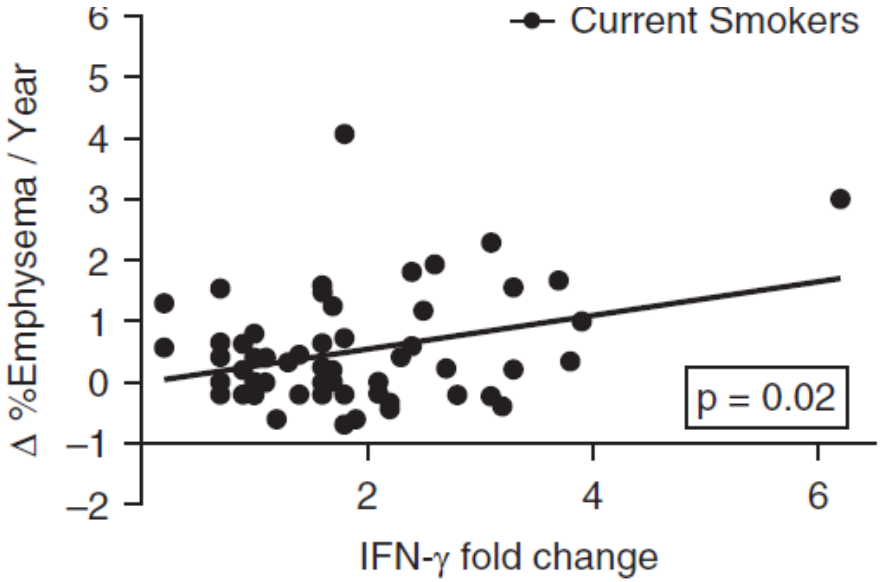
폐기종 진행 속도

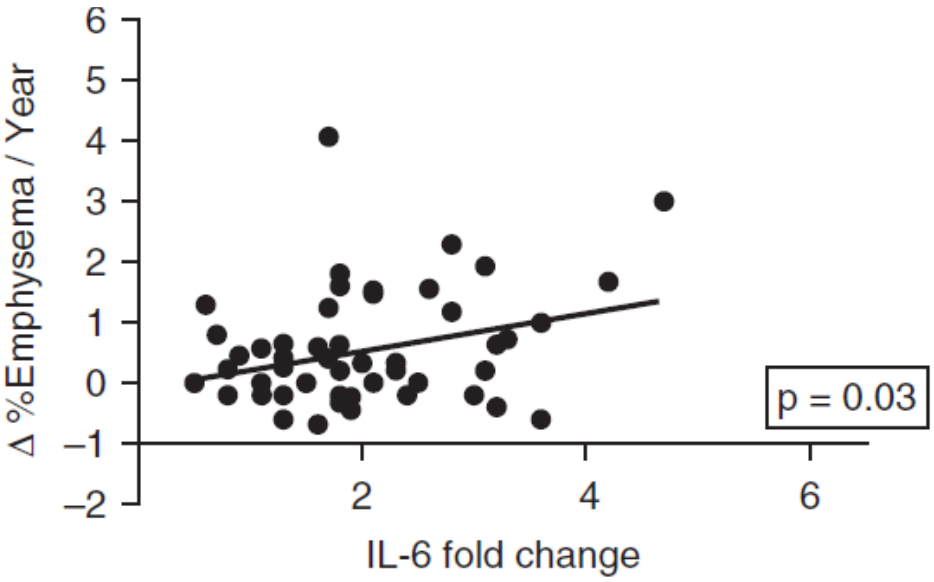


5-unit ↓ BMI → ↑+0.15 Emphysema

Am J Respir Crit Care Med 2015;192:1171

Autoreactive T-cell responses





Am J Respir Crit Care Med 2015;192:1171

순 서

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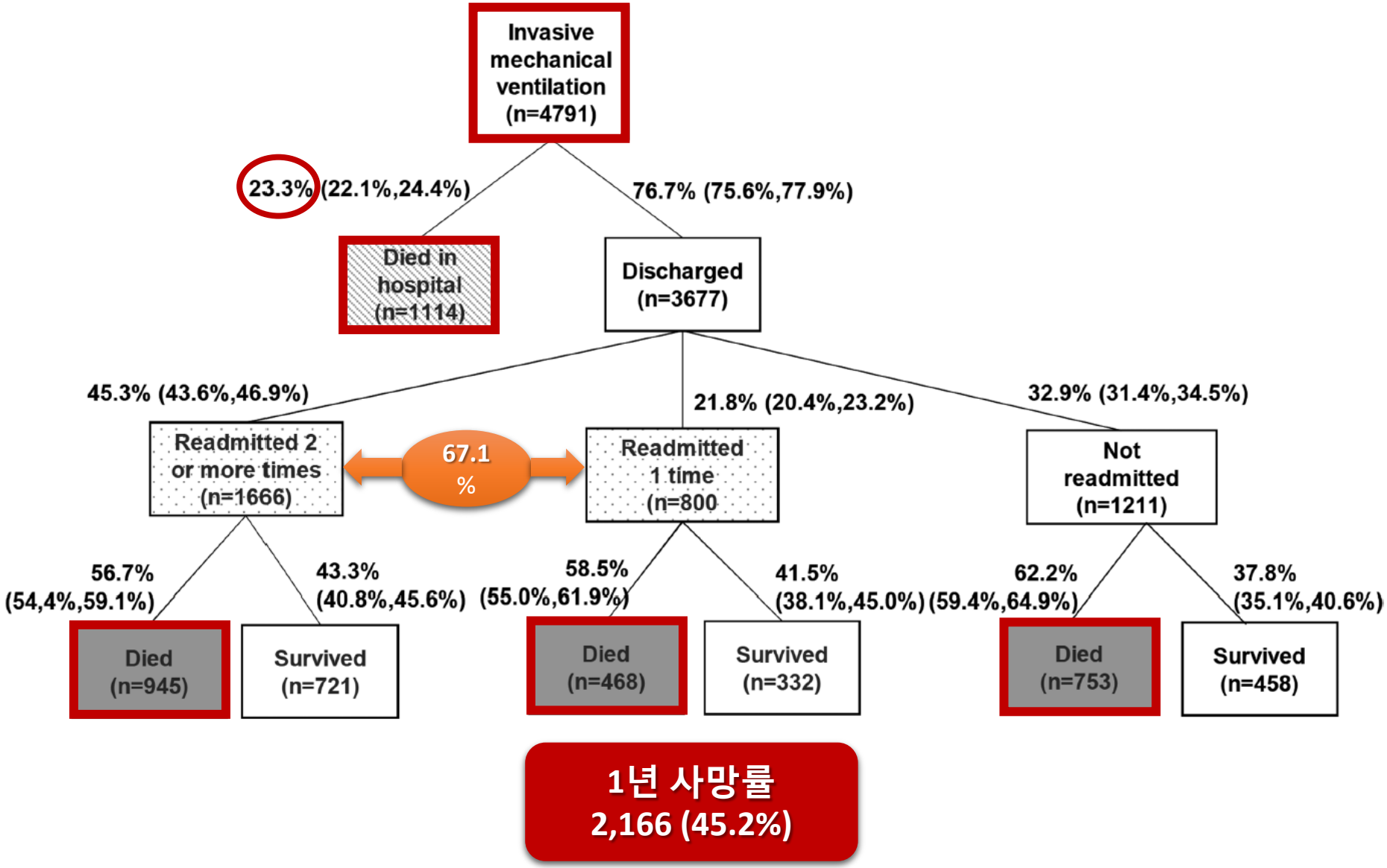
- COPD Biomarker
- COPD 예후

What happens to patients with COPD with long-term oxygen treatment who receive mechanical ventilation for COPD exacerbation? A 1-year retrospective follow-up study

Negin Hajizadeh,[1] Keith Goldfeld,[2] Kristina Crothers[3]

Thorax 2015;70:294–296



Thorax 2015;70:294–296

요약

- COPD의 발병: 낮은 FEV_1 최대치, $PM_{2.5}$
- ACOS의 Genomic Signature
- COPD의 Microbiome 특징, 악화에 따른 변화
- COPD 기관지경 치료: EBV, TLD
- COPD Biomarker: Bilirubin, 자가면역T세포
- COPD 예후: Home O_2 중인 환자의 중증악화


Thank
you!