2013 춘계 workshop
Apr. 6th, 8:30-9:00AM

Respiratory review of 2013; COPD

전남의대 호흡기내과
김유일

Introduction

- Published article in 2012
  - NEJM, Lancet
  - AJRCCM, Thorax

Contents

- **Risk factors**
- Phenotype
- Assessment
- Exacerbation
- Treatment
- Prognosis

- **Occupational Exposure to Dusts, Gases, and Fumes and Incidence of COPD in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults**

  – *Mehta et al. Am J Respir Crit Care Med. Jun 15, 2012. 185 (12), 1292–1300.*

Introduction

- **cigarette smoke**
  - **the most important cause of COPD**
- **15–30% of COPD**
  - **Related to occupational exposures**
- **Prospective study for environmental factor : rare**

Objectives

- **Association between occupational exposures and incidence of COPD ?**
  - **using the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).**

Methods

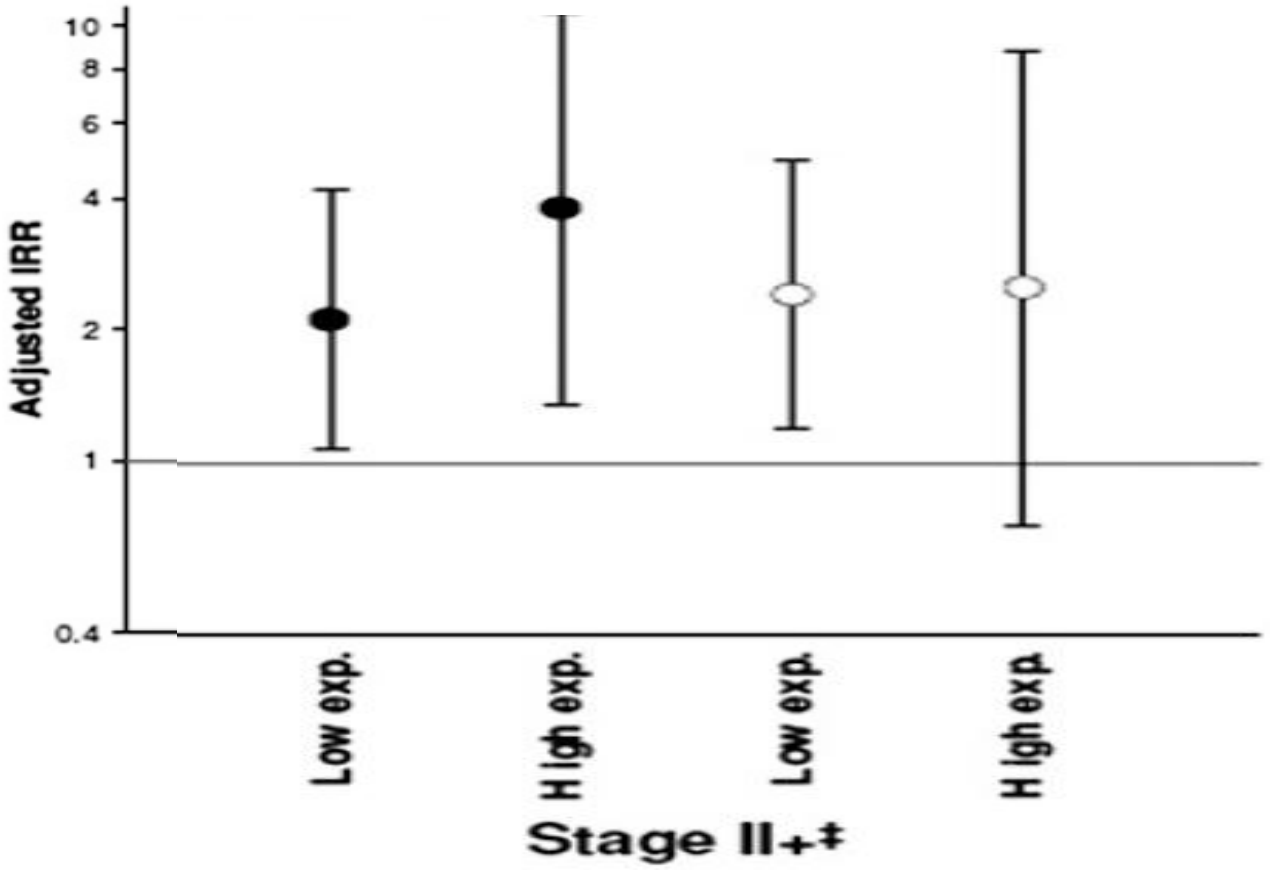
- 4,267 nonasthmatic SAPALDIA participants, ages 18–62
  - Prebronchodilator FEV1/FVC
    - at baseline in 1991
    - at follow-up in 2001–2003.

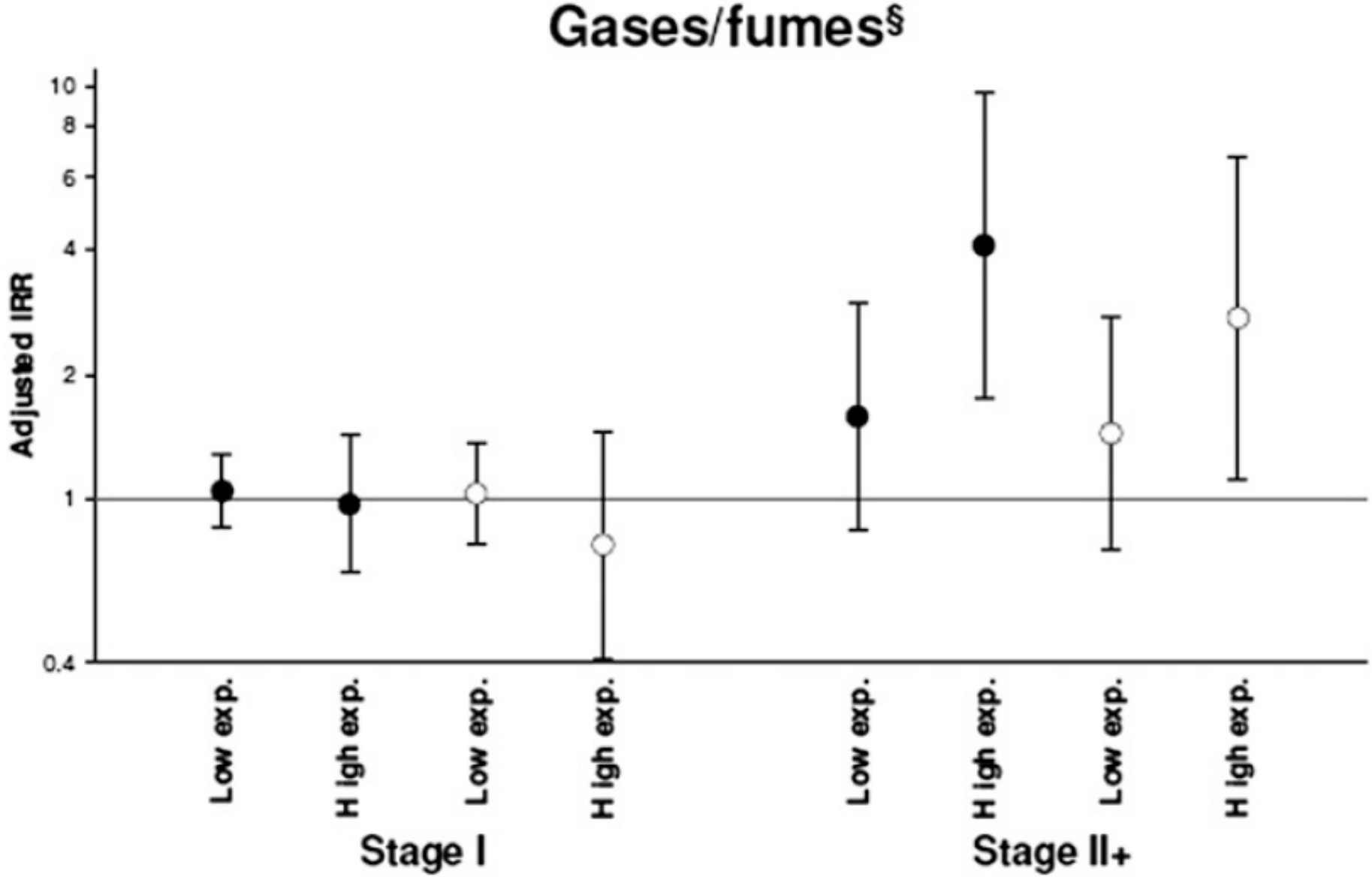
- COPD was defined
  - by GOLD criterion(FEV1/FVC,0.70)
  - by Quanjer reference equation (FEV1/FVC, lower limit of normal [LLN])

- job-exposure
  - biological dusts, mineral dusts, gases/fumes, and vapors, gases, dusts, or fumes (VGDF)
  - high, low, or unexposed

Results

Incidence rate of COPD for occupational exposure; biologic dust




Gases/fumes§
Adjusted IRR
10
8
6
4
2
1
0.4
Low exp.
High exp.
Low exp.
High exp.
Low exp.
High exp.
Low exp.
High exp.
Stage I
Stage II+

Distribution of baseline exposures

	GOLD*		
	Noncases (*n = 3,321*)	Stage I† (*n = 520*)	Stage II+† (*n = 57*)
Unexposed‡, n (%)	1,819 (54.8)	291 (56.0)	19 (33.3)
Exposure to biological dusts‡, n (%)			
Low	618 (18.6)	95 (18.3)	16 (28.1)
High	134 (4.0)	20 (3.9)	5 (8.8)

	LLN*		
	Noncases (*n = 3,724*)	Stage I (*n = 248*)	Stage II+ (*n = 51*)
Unexposed‡, n (%)	2,037 (54.7)	138 (55.7)	19 (37.5)
Exposure to biological dusts‡, n (%)			
Low	685 (18.4)	51 (20.6)	14 (27.5)
High	158 (4.2)	8 (3.2)	3 (5.9)
Cumulative exposure (years)§			
Mean (SD)	23.1 (30.8)	23.2 (37.0)	26.2 (26.5)
Median (IQR)	13 (6, 25)	10 (5, 21)	15 (8, 36)
Exposure to mineral dusts‡, n (%)			
Low	574 (15.4)	41 (16.5)	11 (21.6)
High	202 (5.4)	12 (4.8)	6 (11.8)
Cumulative exposure (years)§			
Mean (SD)	29.3 (36.1)	26.1 (31.7)	42.9 (41.2)
Median (IQR)	18 (7, 31.5)	15 (7, 31)	30 (15, 42)
Exposure to gases/fumes‡, n (%)			
Low	1,204 (32.3)	84 (33.9)	21 (41.2)
High	226 (6.1)	11 (4.4)	8 (15.7)
Cumulative exposure (years)§			
Mean (SD)	23.0 (28.8)	19.5 (25.5)	33.6 (31.1)
Median (IQR)	15 (6, 27)	12 (6, 24)	24 (14, 42)
Exposure to VGDF‡, n (%)			
Low	1,221 (32.8)	85 (34.3)	18 (35.3)
High	466 (12.5)	25 (10.1)	14 (27.5)
Cumulative exposure (years)§			
Mean (SD)	28.5 (35.8)	26.7 (37.2)	43.4 (39.7)
Median (IQR)	16 (6, 30)	12 (6, 25)	29 (12.5, 70)

Conclusions

- Occupational exposures to biological dus ts, mineral dusts, gases/fumes, and VGDF

→ associated with incidence of COPD of at least moderate severity.

Discussion

- 직업 및 환경적인 요인이 COPD의 중요한 위험인자로 작용할 수 있음을 시사

- 흡연뿐만 아니라, COPD 진단과 치료시 직업 및 유해 환경에 대한 병력 청취와 대처 필요

.

Contents

- Risk factors
- **Phenotype**
- Assessment
- Exacerbation
- Treatment
- Prognosis

- **Annual Change in Pulmonary Function and Clinical Phenotype in Chronic Obstructive Pulmonary Disease**

  – *Nishimura M et al. Am J Respir Crit Care Med. 2012 Jan 1;185(1):44-52.*

Introduction

- **Airflow limitation in COPD is caused**
  - **by airway narrowing &**
    parenchymal destruction (emphysema)

- **effect of emphysema severity on annual decline in FEV_1 ?**

Objectives

- **To examine the independent effects of emphysema severity on the annual decline in FEV1.**

Methods

- **279 COPD patients (GOLD I-IV: 26, 45, 24, 5%)**

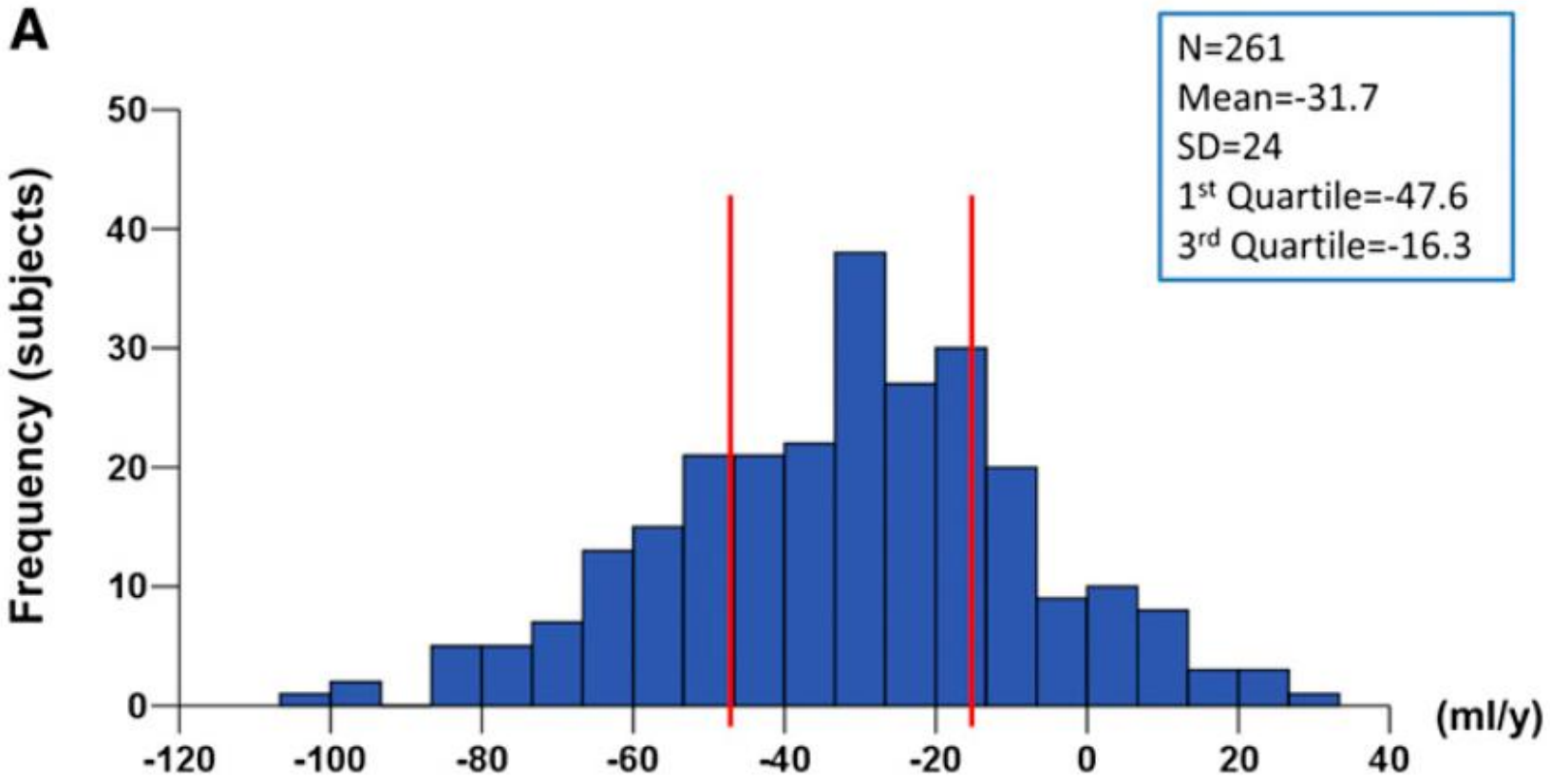
- **at baseline: pulmonary function and Chest CT**
- **spirometry every 6 months**
- **annual measurements of K_{CO}**

- **Emphysema severity**
  - **by CT & visual assessment**

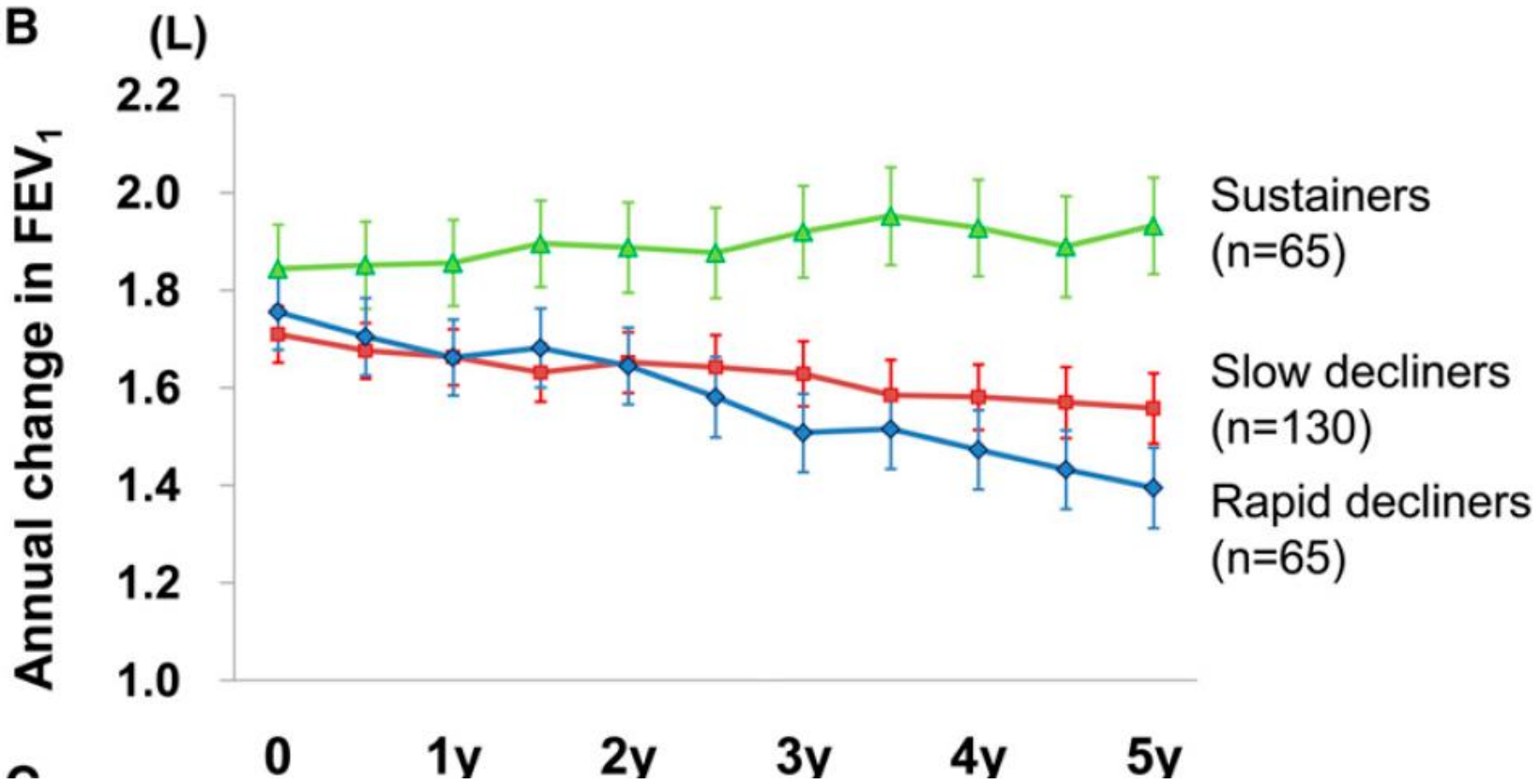
- **5-year observational cohort study**

Results

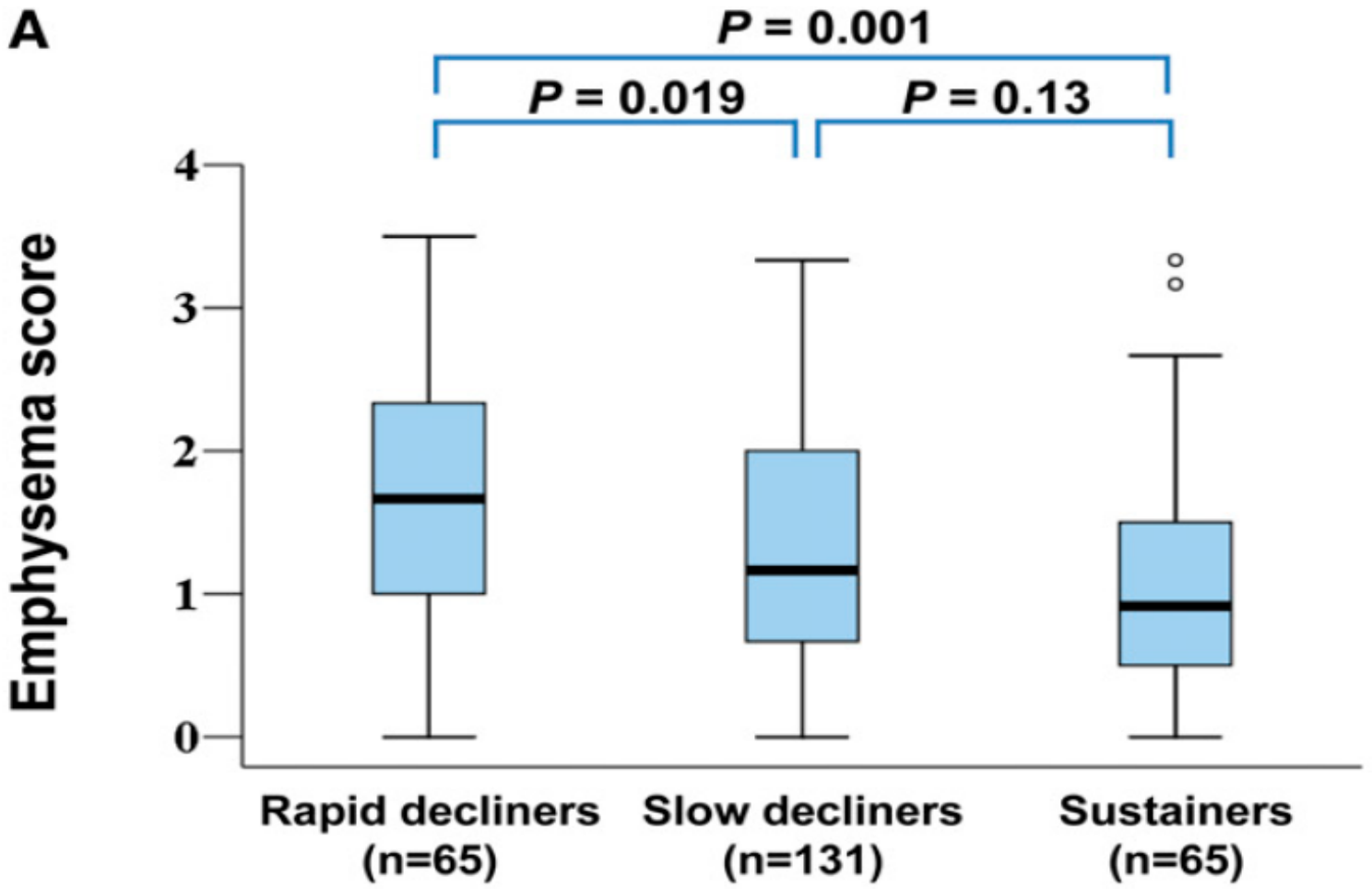
Annual change in postBD FEV1

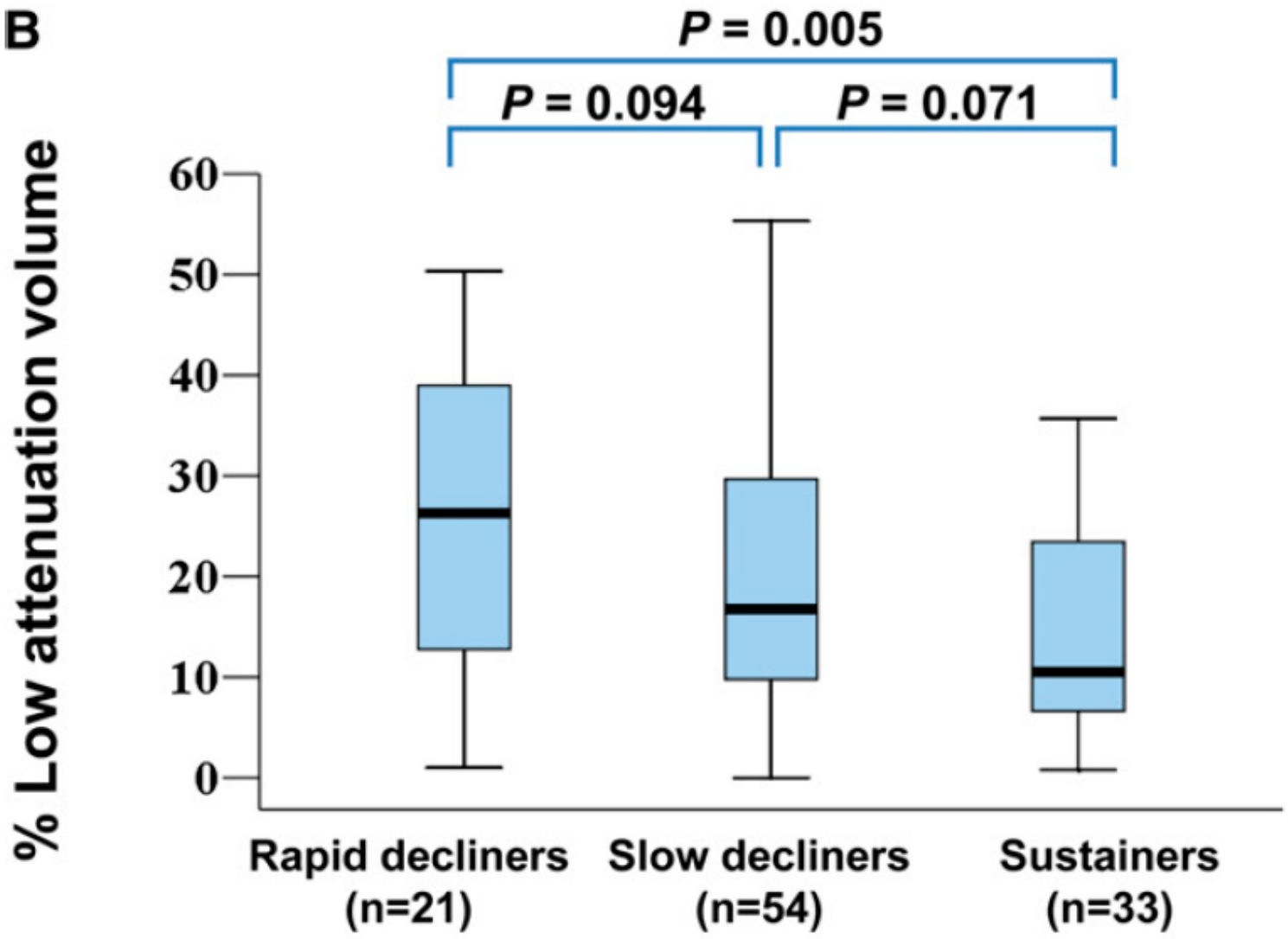


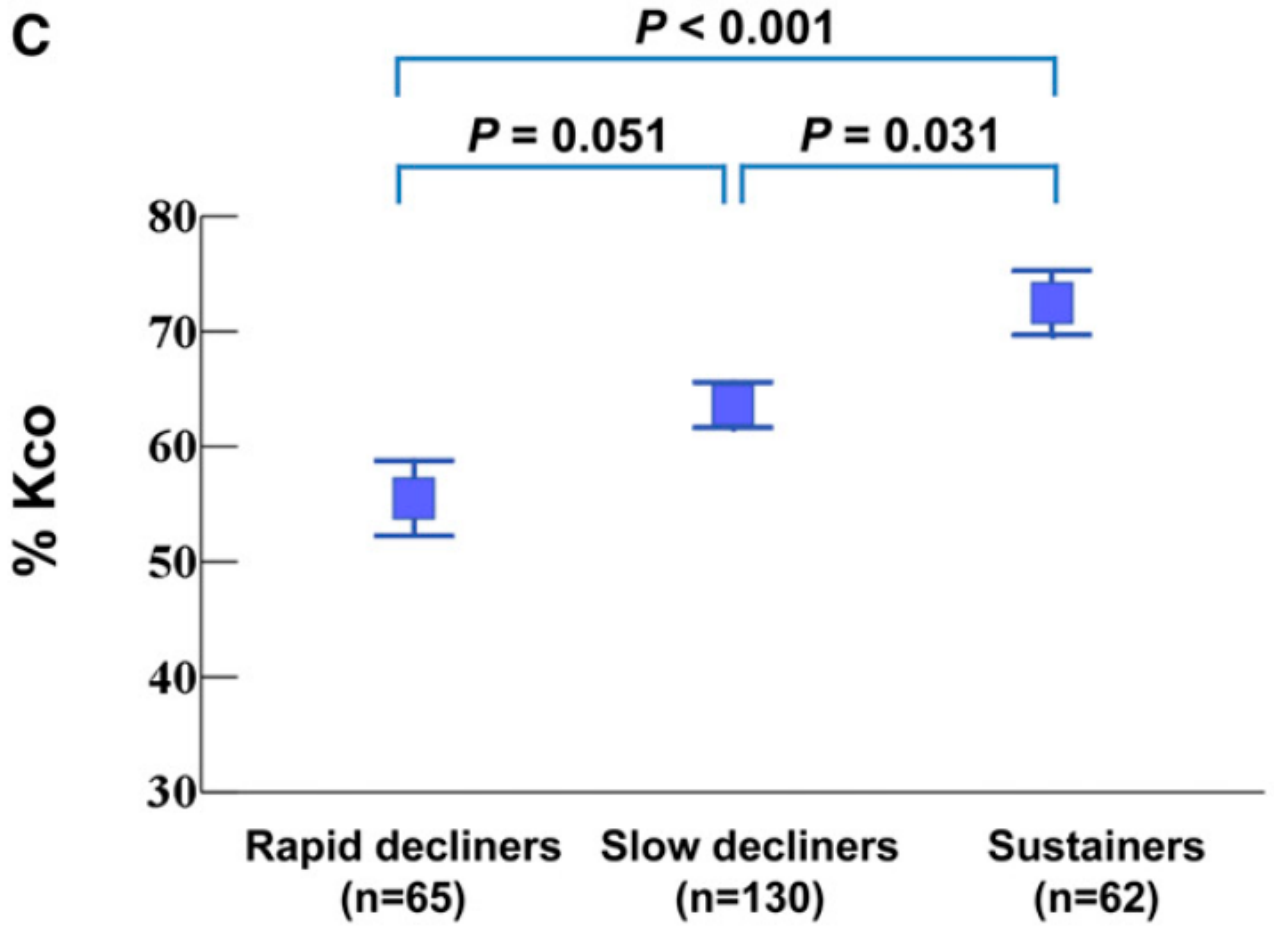
Annual change in postBD FEV1



Emphysema severity at baseline among three groups




B
P = 0.005
P = 0.094
P = 0.071
% Low attenuation volume
60
50
40
30
20
10
0
Rapid decliners
(n=21)
Slow decliners
(n=54)
Sustainers
(n=33)


C
P < 0.001
P = 0.051
P = 0.031
% Kco
80
70
60
50
40
30
Rapid decliners
(n=65)
Slow decliners
(n=130)
Sustainers
(n=62)

Relative risk for rapid decliners vs slow decliners

	%Kco Excluded		
	Odds Ratio	95% CI	*P* Value
Emphysema score	1.46	1.01–2.11	0.047
%Kco, 10%			
Post-bronchodilator FEV_1, % predicted	1.00	0.99–1.02	0.66
Reversibility of airflow limitation	1.01	0.98–1.05	0.45
Blood neutrophil count, 100 cells/μl	1.03	1.00–1.07	0.036
Blood eosinophil count, 10 cells/μl	0.98	0.95–1.01	0.12
Chronic bronchitis symptom	1.47	0.50–4.36	0.49
MRC dyspnea scale ⩾2	0.85	0.33–2.23	0.75
Continuous vs. noncontinuous smokers	0.84	0.35–1.98	0.68
Exacerbation frequency, events/yr	1.17	0.54–2.54	0.69
Age, yr	0.99	0.94–1.03	0.52
Female sex	0.20	0.02–1.67	0.14

Conclusions

- **Emphysema severity is independently a ssociated with a rapid annual decline i n FEV1 in COPD.**

- **Sustainers and Rapid decliners warrant specific attention in clinical practice.**

Discussion

- 폐기종이 심한 환자는 초기 폐기능 (FEV1)이 정상범위 일지라도, 향후 폐기능 저하가 빨리 나타날 수 있으므로 주의해서 추적해야 할 것이다.

- 폐기종 정도에 따라 치료 결과가 어떻게 나타나는지 평가하는 연구가 필요하겠다.

Contents

- Risk factors
- Phenotype
- **Assessment**
- Exacerbation
- Treatment
- Prognosis

- **GOLD 2011 disease severity classificati on in COPDGene: a prospective cohort study**

  – *M. Han et al. The Lancet respiratory medicine, Published Online August 18, 2012*

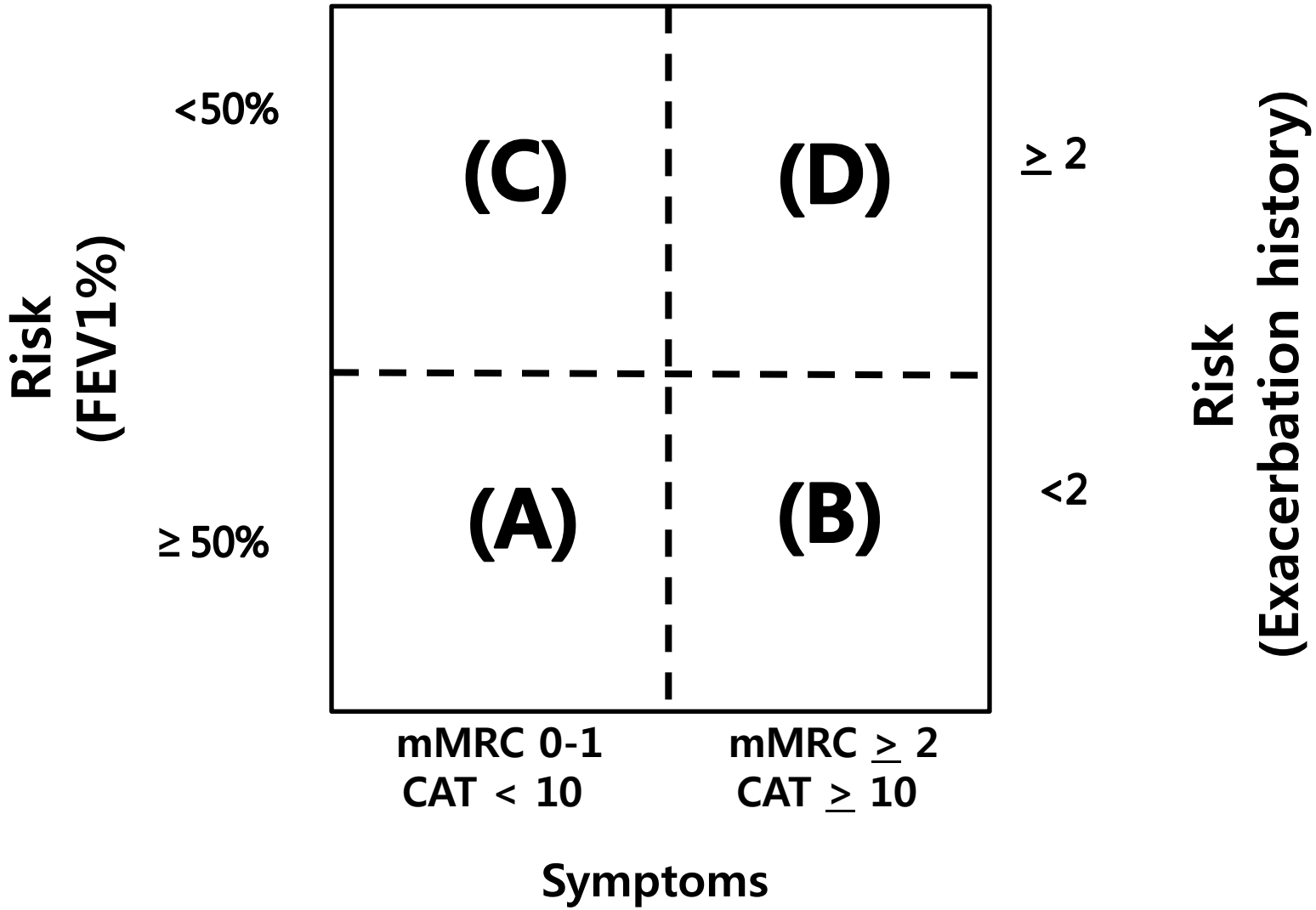
Introduction

- **Assessment of COPD in GOLD 2011**

  : symptoms & risk

  → categorise COPD patients

Assessment of COPD in GOLD 2011



Objectives

- **influence of symptom instrument choice on patient category assignment**

- **prospective exacerbation risk by category**

Methods

- **4,484 patients from 21 centers, COPDGene study, USA**
  - **45–80 years, >10 pack-years**
  - **FEV1/FVC<0.7**

- **Sx assessments**
  - **mMRC dyspnoea scale (score 0–1 *vs* ≥2)**
  - **SGRQ; ≥25 *vs* <25 (as a surrogate for CAT≥10 *vs* <10)**

Results

Distribution of patients into GOLD 2011 categories by symptom measure (mMRC *vs SGRQ)*

mMRC assignment

SGRQ assignment

	A	B
A	921	396
B	137	972

(κ coefficient for agreement, 0.77).

Exacerbation frequency according to GOLD risk groups (categorised using SGRQ)

	A	B	C1	C2	C3	D1	D2	D3
Number of patients	1317 (29%)	1109 (25%)	173 (4%)	38 (1%)	10 (<1%)	1182 (26%)	252 (6%)	403 (9%)
Total exacerbation rate in the year before enrolment (events/year)	0·07 (0·26; 0·06–0·08)	0·27 (0·44; 0·24–0·29)	0·18 (0·39; 0·13–0·24)	2·45 (0·80; 2·19–2·71)*	2·50 (0·71; 2·00–3·01)*	0·35 (0·48; 0·32–0·38)	2·90 (1·26; 2·74–3·05)	3·10 (1·36; 2·96–3·23)
Prospective total annual exacerbation rate (events/year)	0·17 (0·60; 0·13–0·20)	0·55 (1·4; 0·46–0·64)	0·58 (1·7; 0·31–0·84)*	0·52 (1·2; 0·08–0·97)*	1·39 (2·1; 0·0–3·0)*	0·89 (1·9; 0·78–1·0)	1·34 (2·2; 1·0–1·6)*	1·86 (2·5; 1·6–2·1)

Conclusions

- **The choice of symptom measure influences category assignment.**

- **Differences in exacerbation rates for the highest risk category D**
  - **by lung function, exacerbation history, or both.**

Discussion

- 개정된 GOLD 지침을 이용한 연구시 어떤 증상 지표를 이용할지 명확히 해야 될 것이며,

- 적용 지표에 따라 달라지는 환자군 분류를 어떻게 개선할지에 대해서는 연구가 더 필요하겠다.

Contents

- Risk factors
- Phenotype
- Assessment
- **Exacerbation**
- Treatment
- Prognosis

- **Pulmonary Arterial Enlargement & Acute Exacerbations of COPD**

  - *-JM Wells, et al. N Engl J Med 2012;367:913-21*

Introduction

- **Pulmonary hypertension**
  - **a complication of advanced COPD**
  - **predicts acute exacerbations**

Objectives

- **Pulmonary artery enlargement on CT**

→ severe COPD exacerbations ?

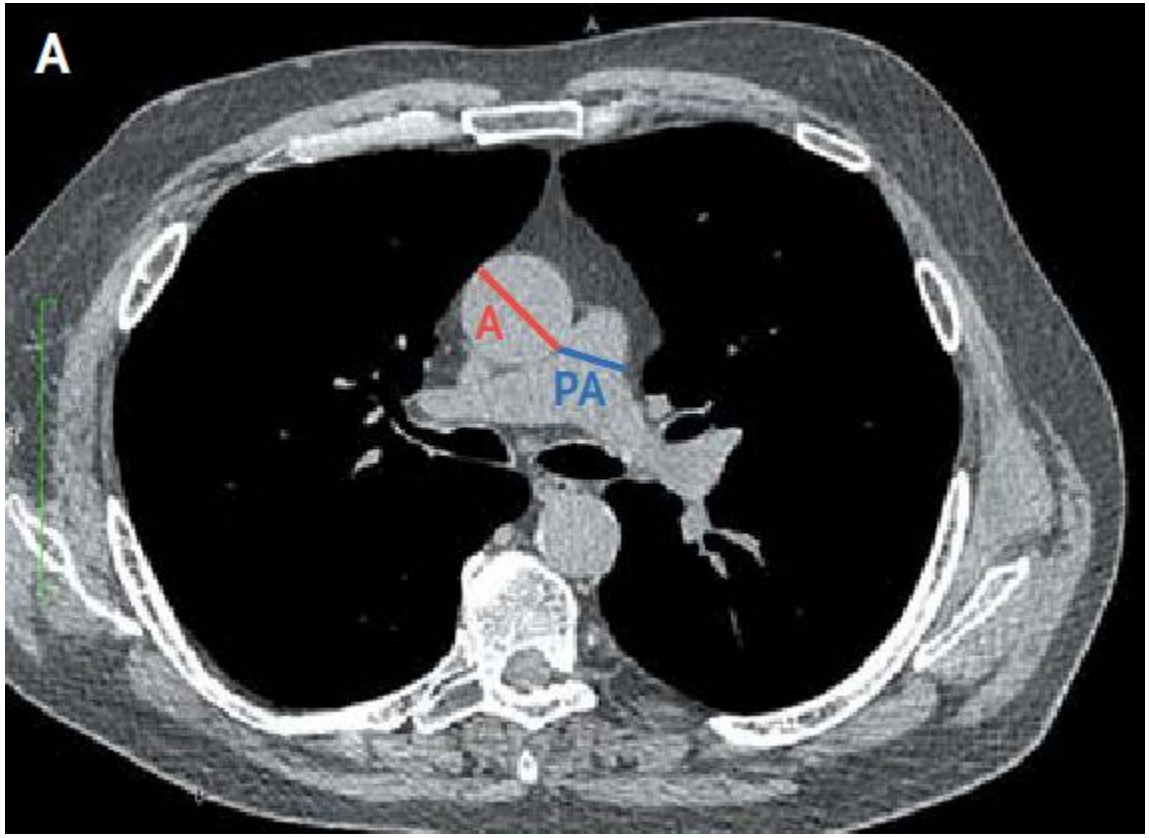
Methods

- a multicenter, COPDGene subjects
  - 3690 patients with GOLD II-IV
- pulmonary artery enlargement
  - a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1)
- PA:A ratio >1

  → a history of hospitalization d/t exacerbations

  → a predictor of severe AE in a longitudinal follow-up

Measurement of the Diameters of Pulmonary Artery and Aorta



Results

Factors Independently Associated with Exacerbations at Enrollment

Time Period and Factor	Odds Ratio (95% CI)	P Value
History of severe exacerbations at enrollment		
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	0.001
SGRQ, per 1-point increase	1.03 (1.02–1.04)	<0.001
Age, per 1-year increase	0.97 (0.95–0.99)	0.002
PA:A ratio >1	4.78 (3.43–6.65)	<0.001

Factors Independently Associated with Exacerbations at Follow-up

Severe exacerbations during longitudinal follow-up		
Exacerbation in previous yr	2.01 (1.61–2.49)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	<0.001
SGRQ, per 1-point increase	1.02 (1.01–1.02)	<0.001
GERD	1.22 (0.98–1.52)	0.08
Age, per 1-yr increase	0.99 (0.99–1.01)	0.74
PA:A ratio >1	3.44 (2.78–4.25)	<0.001

Conclusions

- **Pulmonary artery enlargement (a PA:A ratio of >1) detected by CT**

→severe exacerbations of COPD

Discussion

- 국내 COPD 지침(2012) & GOLD 2013
  - 이전 악화력, 심한 폐기능 저하, 입원 필요한 중증 악화

    +) 폐동맥/대동맥 직경>1
    (위의 기존 위험인자들보다 더 중요)

- 폐동맥/대동맥 직경>1 환자군
  - 급성악화 예방 치료, 임상 연구 필요

Contents

- Risk factors
- Phenotype
- Assessment
- Exacerbation
- **Treatment**
- Prognosis

- **Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bron chodilation compared with tiotropium alone: a randomised, double-blind comparison**

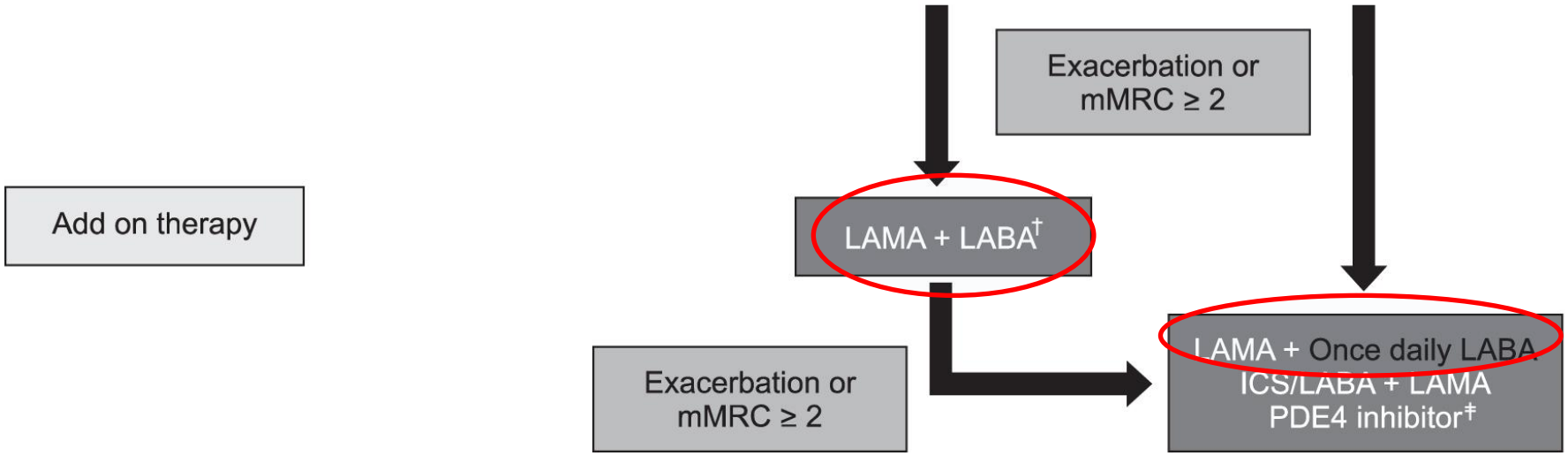
  - Mahler DA et al. Thorax 2012;67:781-788

Introduction

- one or more long-acting bronchodilators are recommended for moderate to severe COPD

Korean 2012: Pharmacologic Therapy

	$FEV_1 \geq 60\%$ and 0-1 exacerbation/year		$FEV_1 < 60\%$ or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0-1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or Once daily LABA or ICS/LABA



GOLD 2013: Pharmacologic Therapy

Patient	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		**Theophylline**
B	LAMA *or* LABA	**LAMA and LABA**		SABA *and/or* SAMA **Theophylline**
C	ICS + LABA *or* LAMA	**LAMA and LABA** *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA **Theophylline**
D	ICS + LABA ***and/or*** LAMA	ICS + LABA and LAMA *or* ICS+LABA and **PDE4-inh**. *or* **LAMA and LABA** *or* LAMA and **PDE4-inh.**		*C*arbocysteine *SABA and/or* SAMA **Theophylline**

Objectives

- Dual bronchodilation
  (once-daily LABA: indacaterol + LAMA: tiotropium)

VS

- LAMA (tiotropium) alone

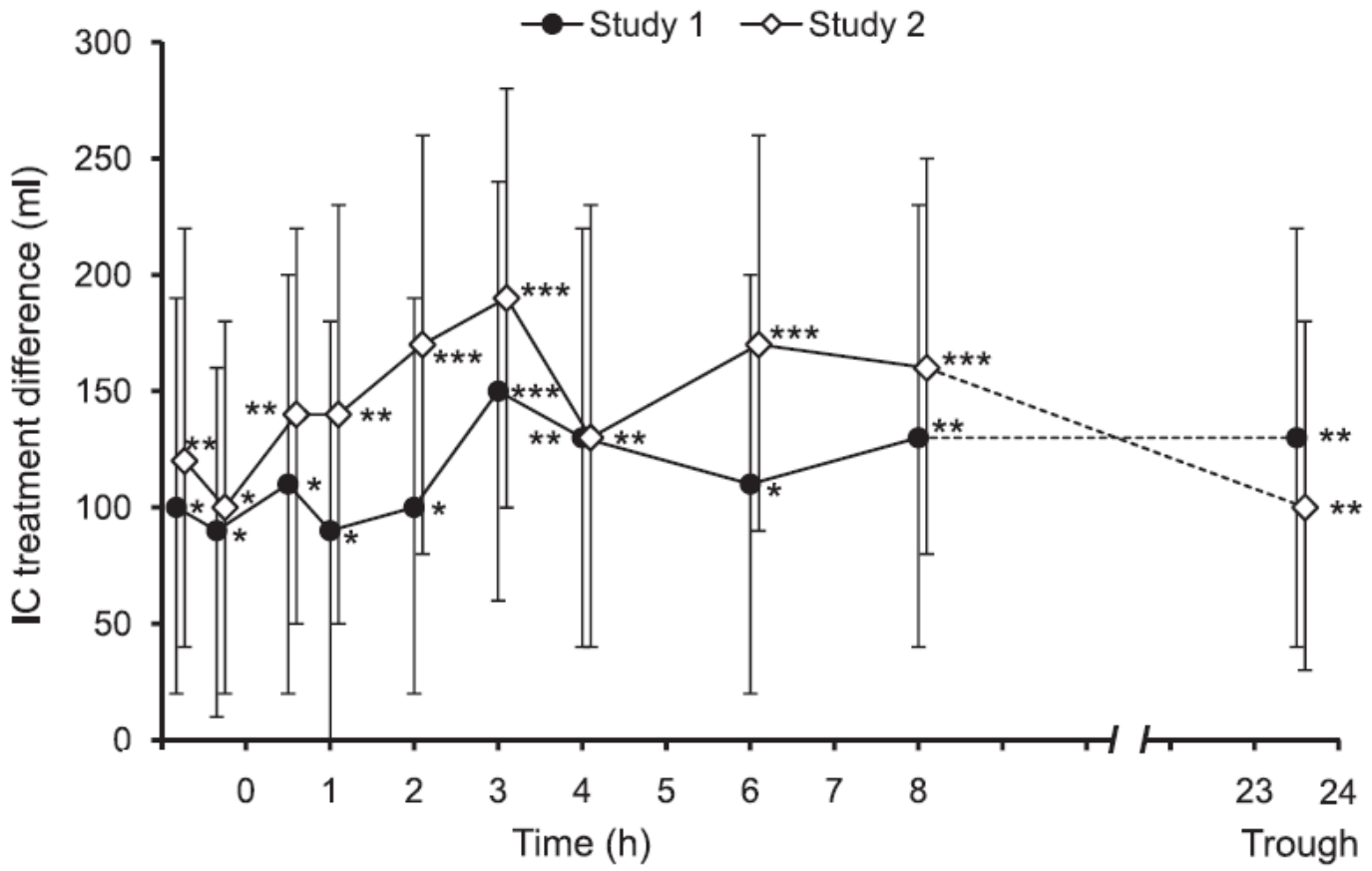
Methods

- **double-blind, 12-week studies, moderate to severe COPD**
  - indacaterol 150 μg once daily or placebo
  - All patients ;tiotropium 18 μg once daily
- primary outcome
  - standardised area under the curve of **FEV_1** from **5 min to 8 h** post dose at week 12.
- secondary outcome
  - 24 h post-dose **('trough') FEV_1** at week 12.
  - Resting **inspiratory capacity (IC)**

Differences between treatments (indacaterol plus tiotropium vs tiotropium only) in FEV1 AUC5min-8h and trough FEV1

	FEV_1 $AUC_{5min-8h}$	Trough FEV_1
	Study 1	Study 1
COPD severity†		
Moderate‡	120 ml (90 to 160) (n=233/237)§	90 ml (50 to 130) (n=259/260)
Severe or very severe	130 ml (100 to 160) (n=272/267)	70 ml (30 to 110) (n=302/289)
Smoking status		
Ex-smoker	120 ml (90 to 150) (n=300/324)	70 ml (40 to 110) (n=335/350)
Current smoker	130 ml (90 to 170) (n=205/180)	80 ml (40 to 130) (n=226/199)
ICS use		
ICS non-users	120 ml (90 to 160) (n=242/236)	70 ml (30 to 110) (n=271/260)
ICS users	130 ml (100 to 160) (n=263/268)	80 ml (50 to 120) (n=290/289)

Effects of indacaterol+ tiotropium on IC at week 12 compared to tiotropium alone



Adverse events

	Study 1	
	Indacaterol + tiotropium (n=570)	Tiotropium + placebo (n=561)
Any adverse event (% of patients)	45.4	41.2
COPD worsening	9.5	10.7
Cough	10.4	3.7
Nasopharyngitis	4.2	3.6
Muscle spasms	2.3	0
Dyspnoea	2.1	2.3
Headache	1.9	3.2
Upper respiratory tract infection	1.8	2.0
Dry mouth	1.6	1.6

Conclusions

- **indacaterol plus tiotropium**
  - **greater bronchodilation and lung deflatio n** (increased IC).
  - Adverse events were similar except mild co ugh
- These results support COPD guideline to combine bronchodilators with different mechanisms.

Contents

- Risk factors
- Phenotype
- Assessment
- Exacerbation
- Treatment
- **Prognosis**

- **Long-term natural history of COPD**

: severe exacerbations and mortality

  - *Samy Suissa et al. Thorax. 2012 Nov;67(11):957-63*

Introduction

- severe COPD exacerbations
  - long-term natural history ?
  - Association with mortality ?

Methods

- **73,106 patients** from their first hospitalisation for COPD **during 1990–2005**
  - Using healthcare databases from the province of Quebec, Canada.
  - **F/U until March 2007**

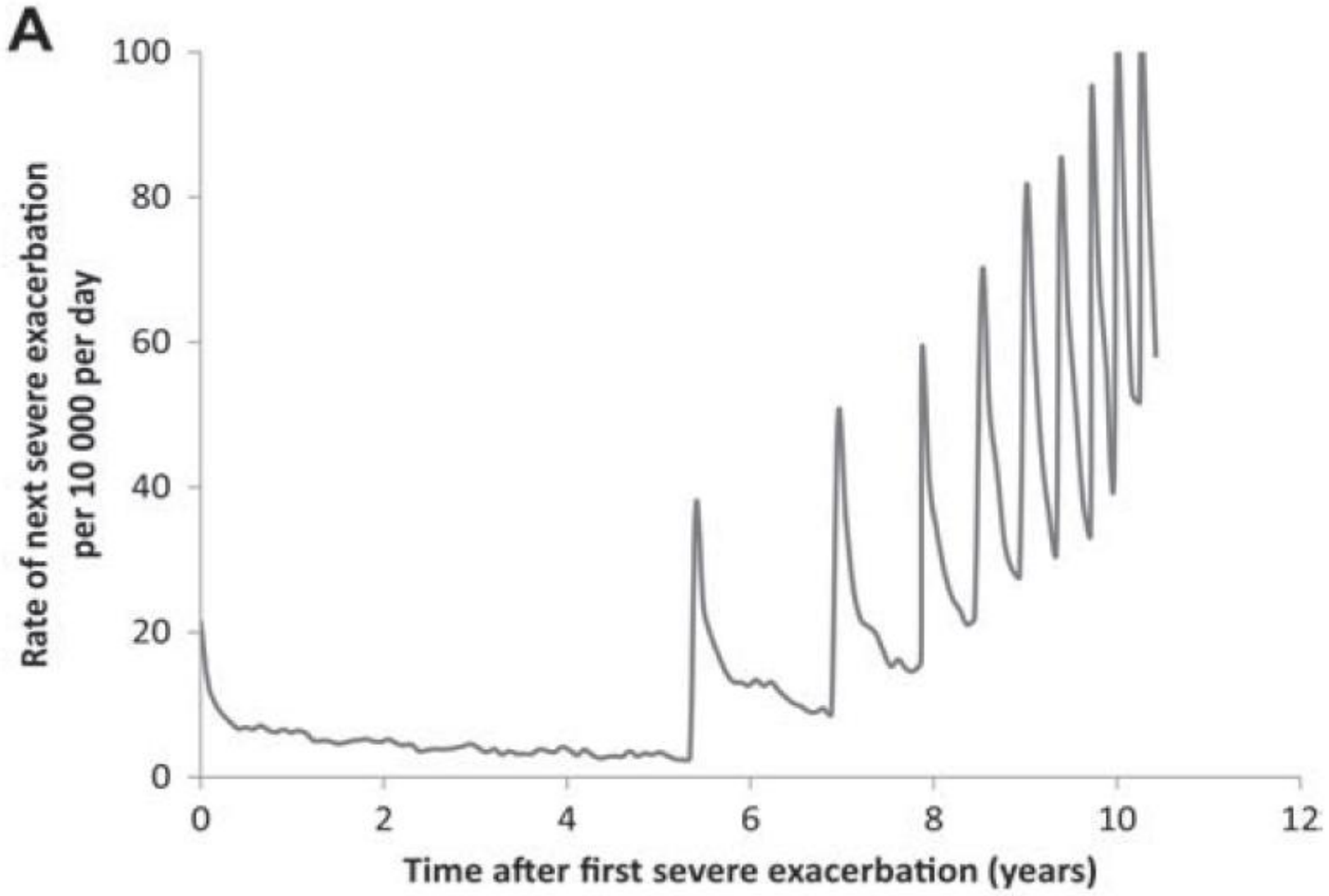
- Hazard functions of **successive hospitalised** COPD exacerbations and **all-cause mortality** over time

Results

Subject Characteristics

	Entire Cohort	At Least One Subsequent Exacerbation	Deaths
Number	73,106	33,166	50,580
Age at cohort entry (years; mean±SD)	76.4±8.4	73.9±7.9	76.4±8.1
Men (%)	54.5	56.7	59.0

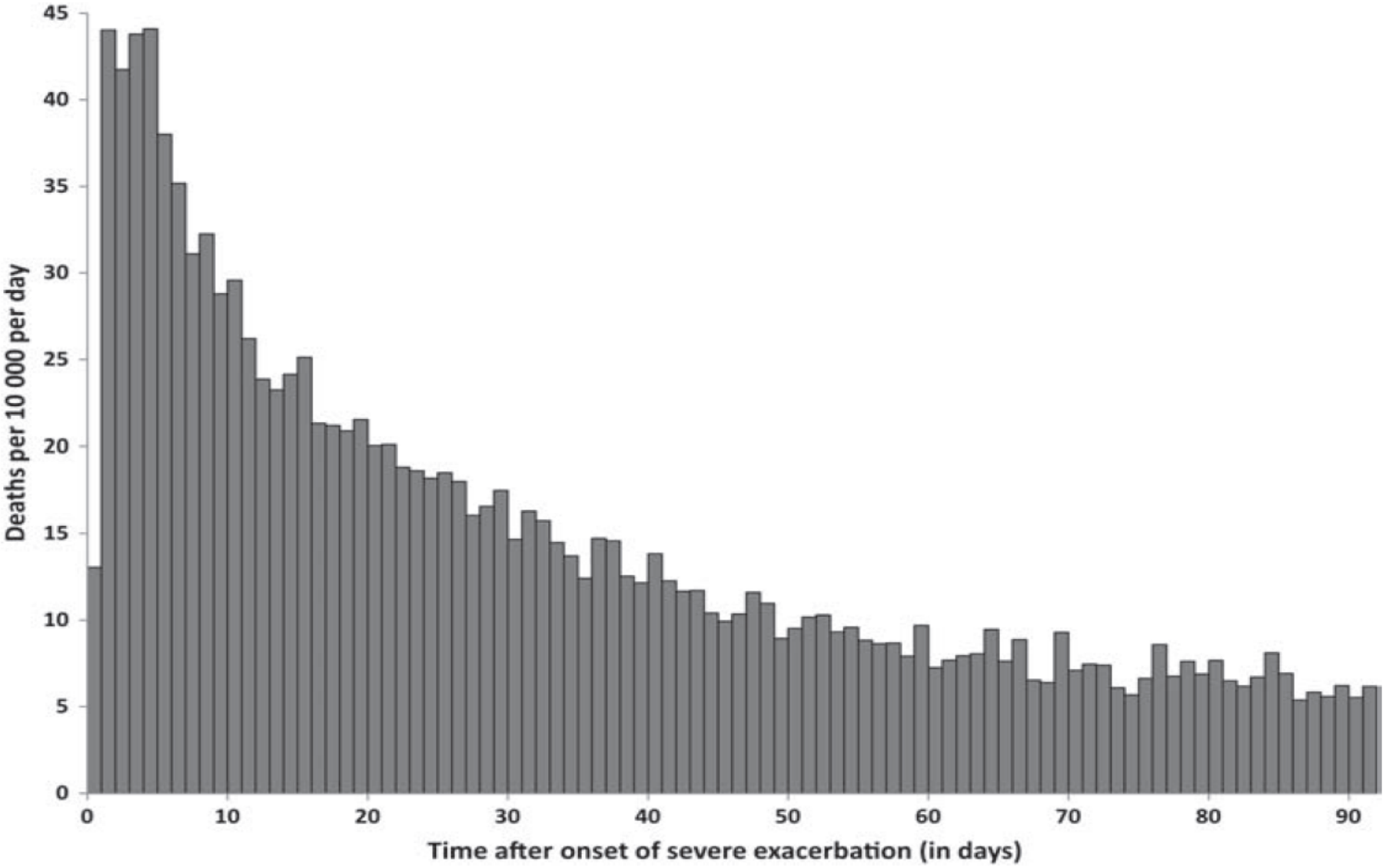
Rate of next severe AE after 1st AE



Hazard ratio (HR) of a subsequent exacerbation and death

Exacerbation sequence number	Number of deaths	Crude HR	Adjusted* HR (95% CI)
First (reference)	25 953	1.0	1.0 (reference)
Second	9828	1.8	1.9 (1.8 to 1.9)
Third	5203	2.4	2.4 (2.3 to 2.5)
Fourth	3078	2.8	2.9 (2.8 to 3.0)
Fifth	1879	3.0	3.2 (3.0 to 3.4)
Sixth	1207	3.1	3.3 (3.1 to 3.5)
Seventh	872	3.4	3.6 (3.4 to 3.9)
Eighth	645	3.9	4.2 (3.9 to 4.5)
Ninth	470	3.8	4.3 (3.9 to 4.7)
Tenth or greater	1445	4.5	5.2 (4.9 to 5.5)

Daily rates of death (per 10,000 per day) in the 90-day period after onset of severe AE

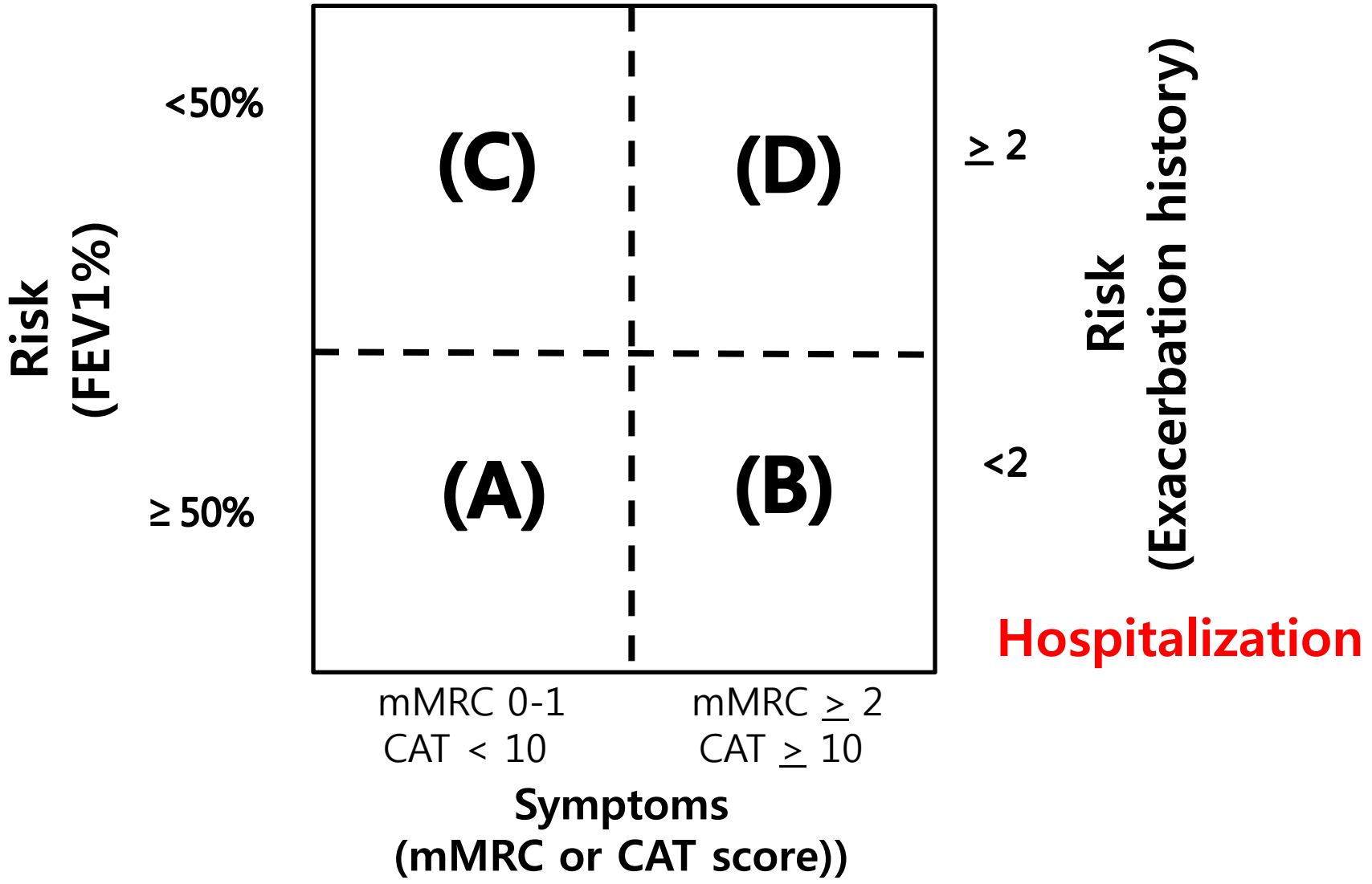


Conclusions

- **a rapid decline in health status after the second exacerbation**
- **high mortality in the weeks** following ev ery exacerbation

- **Two strategic targets for COPD Tx**
  - **delaying the second severe exacerbation**
  - **improving treatment of severe exacerbation s to reduce early mortality**

Assessment of COPD in GOLD 2011



Take home messages

- **Risk factors**
  - **occupational exposure**
- **Phenotype**
  - **emphysema severity → FEV1 declines**
- **Assessment**
  - **mMRC vs CAT, Excerbation risk (FEV1 vs Hx)**
- **Exacerbation**
  - **PA/A ratio>1 → AE risk**
- **Treatment**
  - **LABA+LAMA > LAMA single**
- **Prognosis**
  - **Prevention of 2nd admission, 1st week during admission**