



Role of PRO in evaluating COPD Patients

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Patients Reported Outcomes

환자자가보고성과 (Patient Reported Outcome, PRO)

: 제 3자의 해석 없이 환자가 직접 보고하는 환자의 건강상태

PRO
Patient Reported Outcome

Definition by FDA 2009

“**A**ny report of the status of a patient's health condition that comes **directly from the patient without interpretation** of the patient's response by a clinician or anyone else.”

✓ PROs can be assessed by taking the **patient's history or by questionnaires.**

CURRENT CONCEPTS

ASSESSMENT OF QUALITY-OF-LIFE
OUTCOMESMARCIA A. TESTA, M.P.H., PH.D.,
AND DONALD C. SIMONSON, M.D.

SINCE 1948, when the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being,¹ quality-of-life issues have become steadily more important in health care practice and research. There has been a nearly exponential increase in the use of quality-of-life evaluation as a technique of clinical research since 1973, when only 5 articles listed "quality of life" as a reference key word in the Medline data base; during the subsequent five-year periods, there were 195, 273, 490, and 1252 such articles. The growing fields of outcomes research and health-technology assessment² evaluate the efficacy, cost effectiveness, and net benefit of new therapeutic strategies to determine whether the associated increases in expenditures for health care are justified. Quality-of-life assessment measures changes in physical, functional, mental, and social health in order to evaluate the human and financial costs and benefits of new pro-

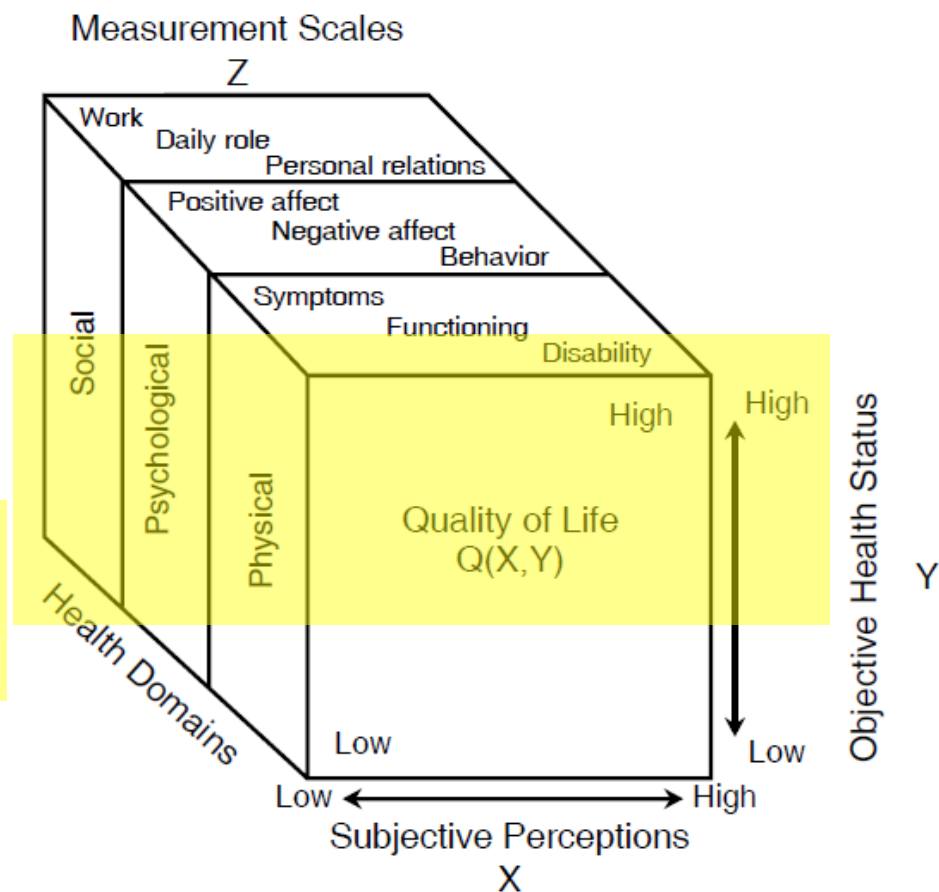


Figure 1. Conceptual Scheme of the Domains and Variables Involved in a Quality-of-Life Assessment.

The x axis represents subjective perceptions of health, the y axis objective health status, the coordinates $Q(X,Y)$ the actual quality of life, and Z the measurement of the actual quality of life associated with a specific component (e.g., positive affect) or domain (e.g., the psychological domain).

PRECISION MEDICINE INITIATIVE



*“Doctors have always recognized that **every patient is unique**, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. **What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?**”*

- President Obama, January 30, 2015



PRO

- ◆ **치료의 효과, 효율성 성과 지표**
 - ◆ 증상완화, 부작용, 기능, 삶의 질
- ◆ **치료 효과나 환자의 상태에 대한 Unique perspective 제공**
 - ◆ 폐활량측정을 통한 폐기능 평가 – 숨참 정도
- ◆ **특정 치료의 효과나 증상은 PRO로만 파악이 가능**
 - ◆ 피로, 통증
 - ◆ 환자의 전반적인 기분이나 상태
 - ◆ 환자의 function (일상 생활 영위 가능 정도)
 - ◆ 환자의 진료에 대한 만족도



COPD Outcomes



Exacerbation
frequency




Lung function
e.g. trough FEV₁

Quality of life
e.g. SGRQ



Exercise tolerance
e.g. ESWT

Symptoms
e.g. TDI score





Contents

PRO in GOLD guideline

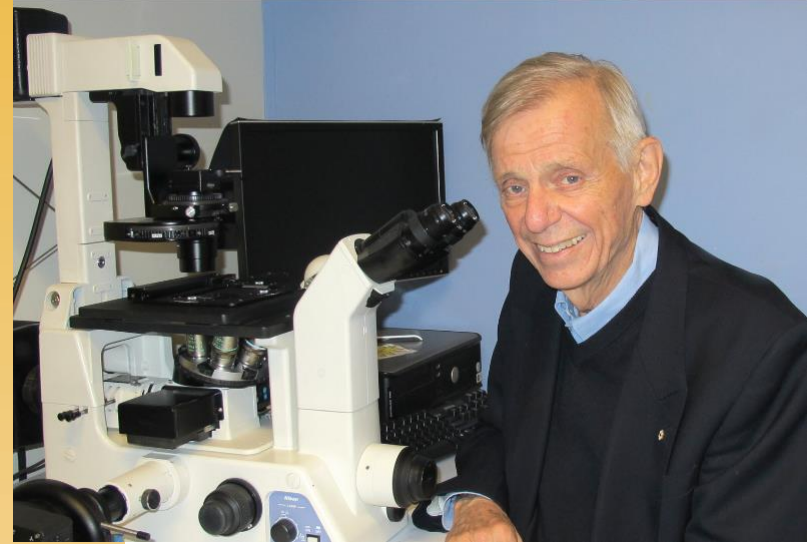
How to evaluate

What to expect?

Global Initiative for Chronic Obstructive Lung Disease



**GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE**



2001

**By expert panel
One of the main aim:
To promote research
into COPD**



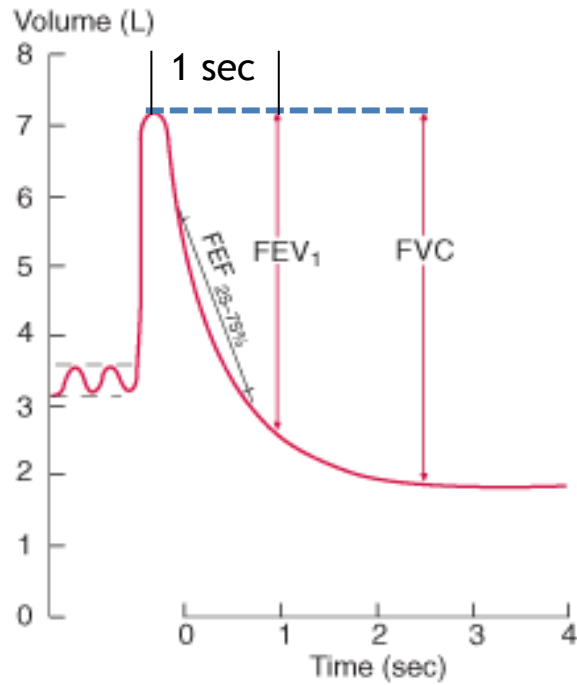
COPD Diagnosis

Lung Function Tests
(post BD $FEV_1/FVC < 0.7$)

2 puff



15mins



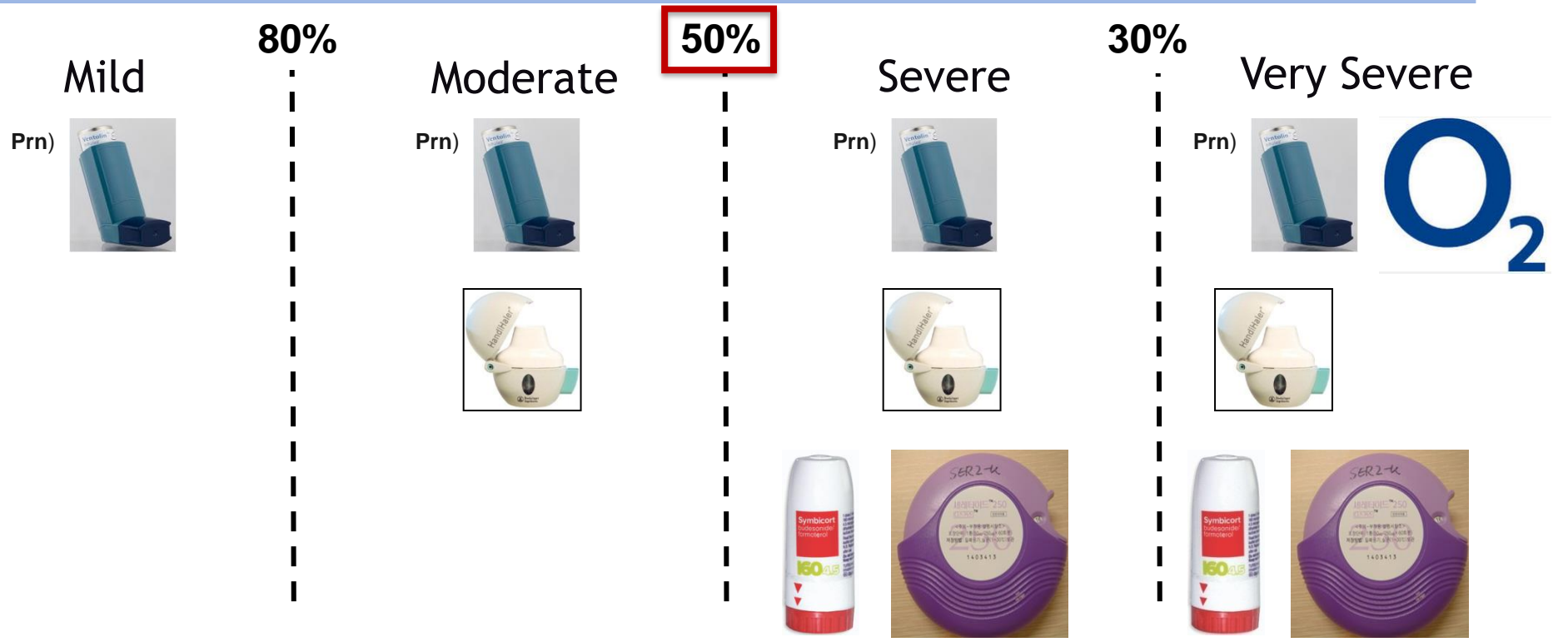


Before 2011



Post bronchodilator FEV₁/FVC < 0.7

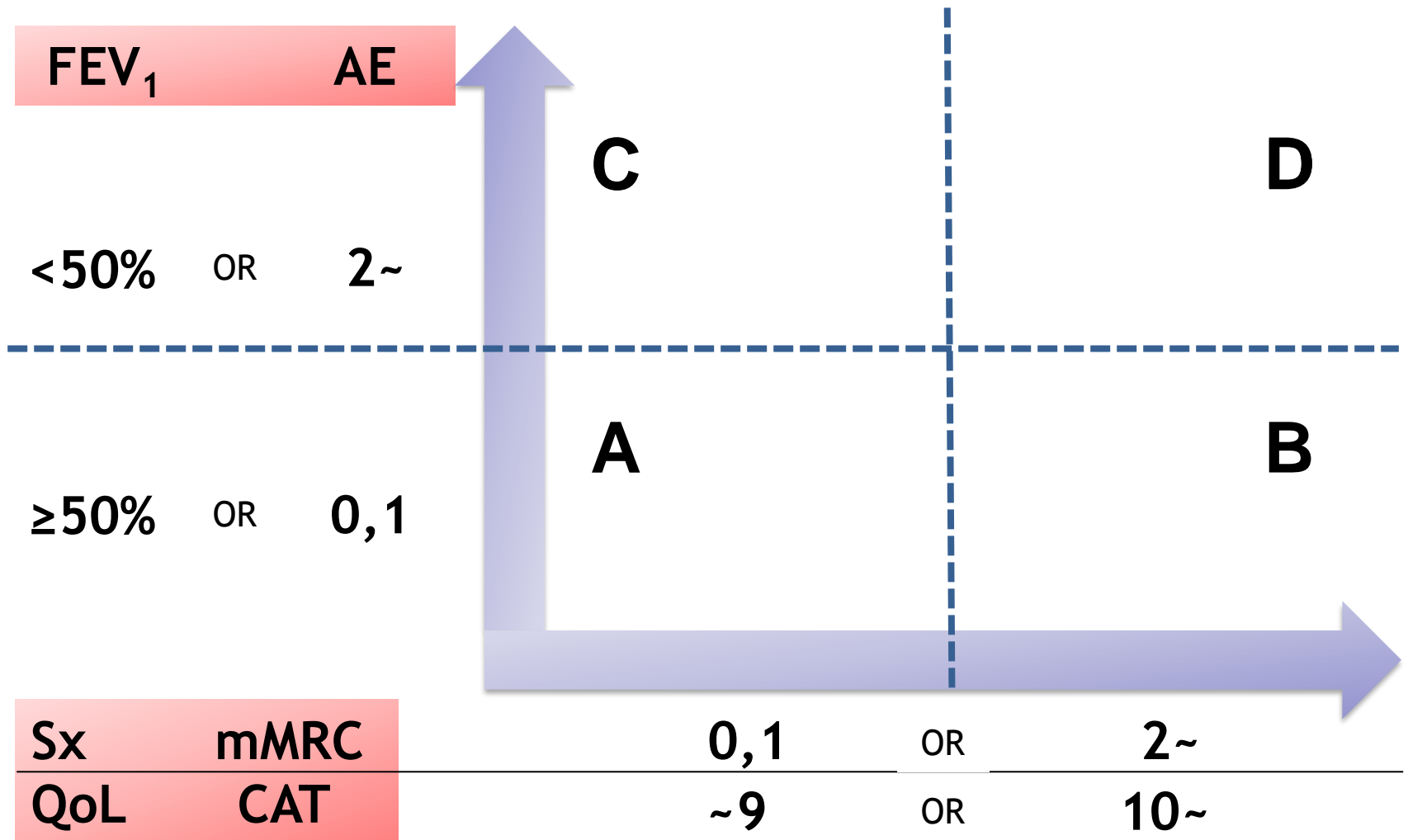
Post-BD FEV₁



Smoking Cessation/Vaccination/Rehabilitation*



2011, COPD



2011, COPD



폐기능

증상

급성 악화

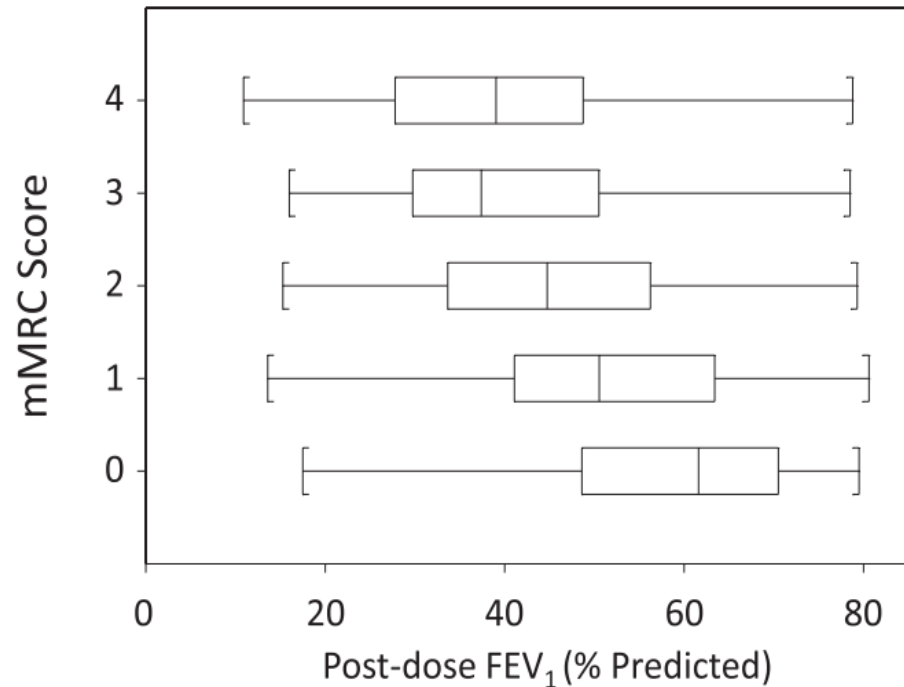
평가 및
치료 결정



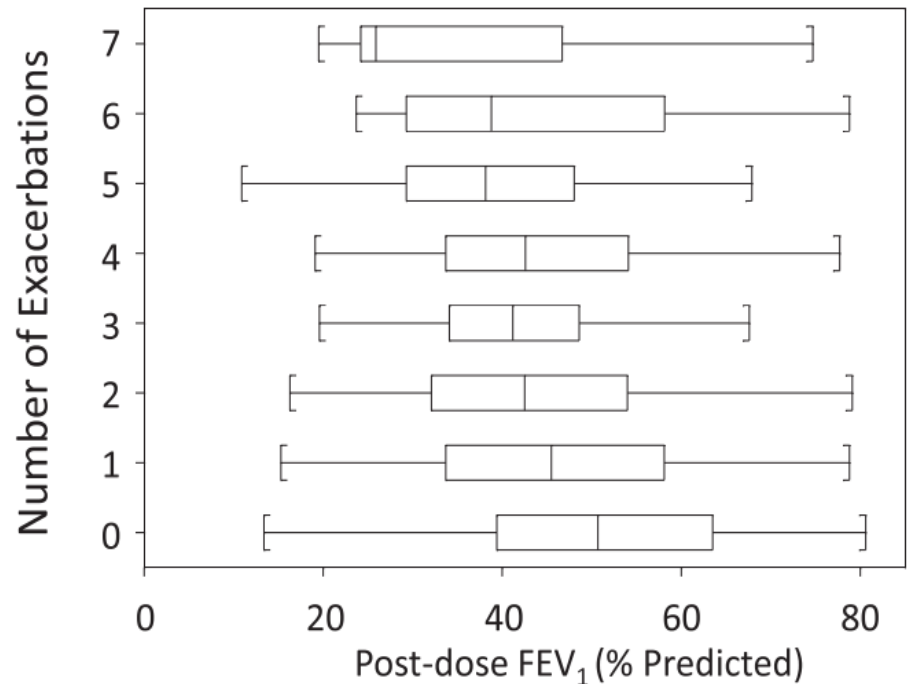
FEV₁ ? Dyspnea and AE

The clinical manifestations of COPD are highly variable and the degree of airflow limitation does not capture the heterogeneity of the disease.

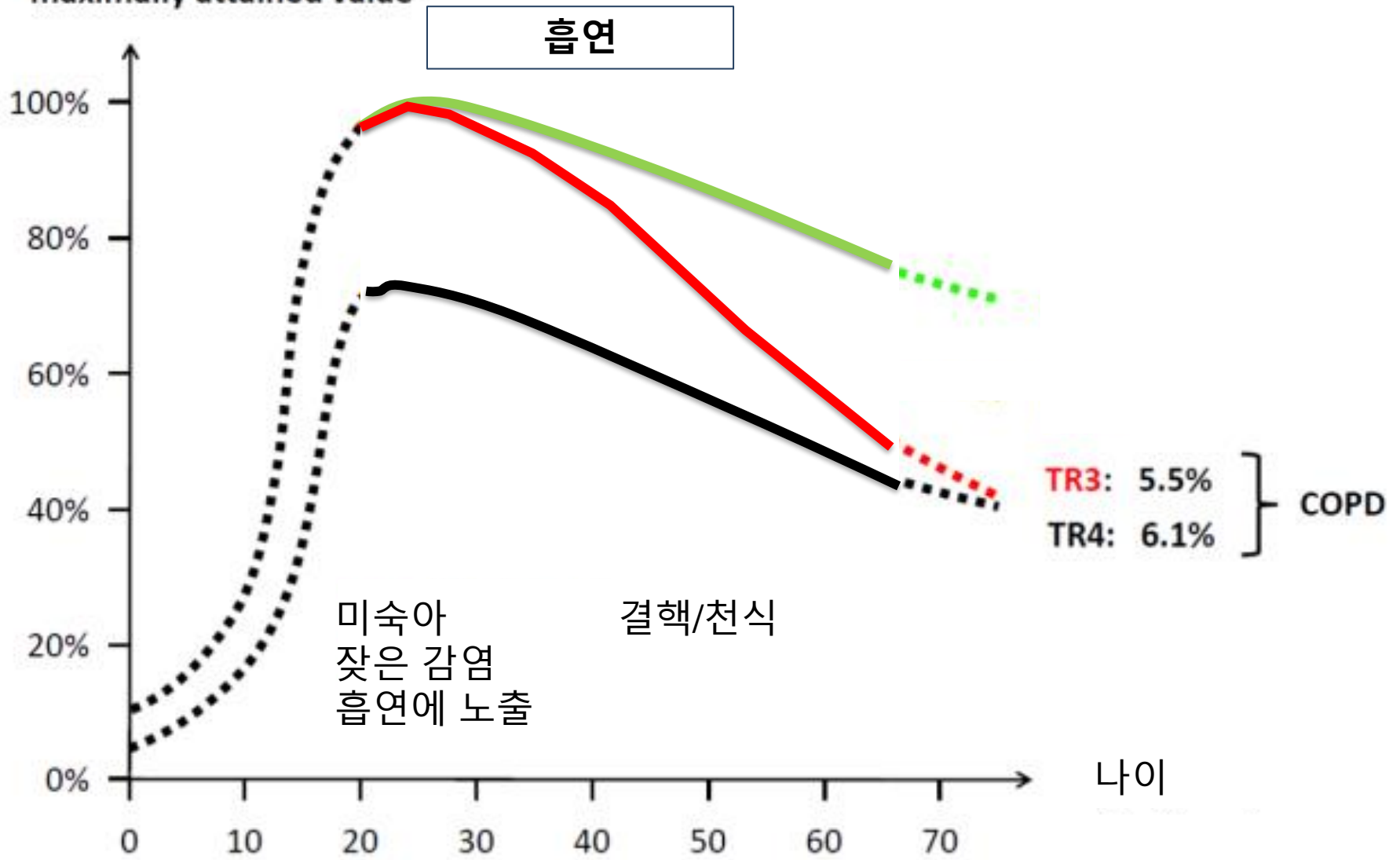
Rho=-0.36
p<0.001



Rho=-0.21
p<0.001



FEV₁ in percent of predicted
maximally attained value





2017, COPD

Spirometrically confirmed diagnosis



Assessment of airflow limitation



Assessment of symptoms/risk of exacerbations



	FEV ₁ (% pred)
GOLD 1	≥80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	<30

Exacerbation history

≥2 or ≥1 leading to hospital admission
0 or 1 (not leading to hospital admission)

C	D
A	B
mMRC 0-1 CAT <10	mMRC ≥2 CAT ≥10

Symptoms



2019 COPD Treatment

INITIAL PHARMACOLOGICAL TREATMENT

≥ 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

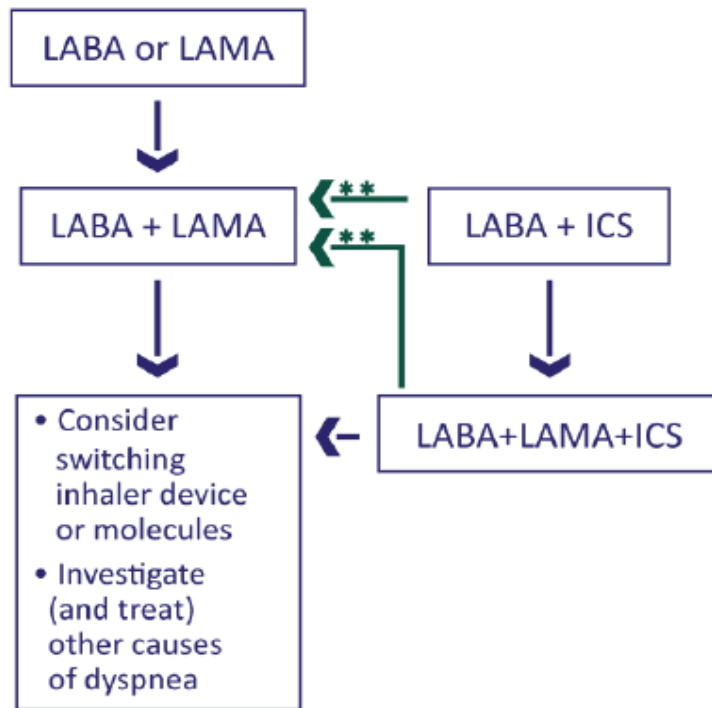
FIGURE 4.1

FOLLOW-UP PHARMACOLOGICAL TREATMENT

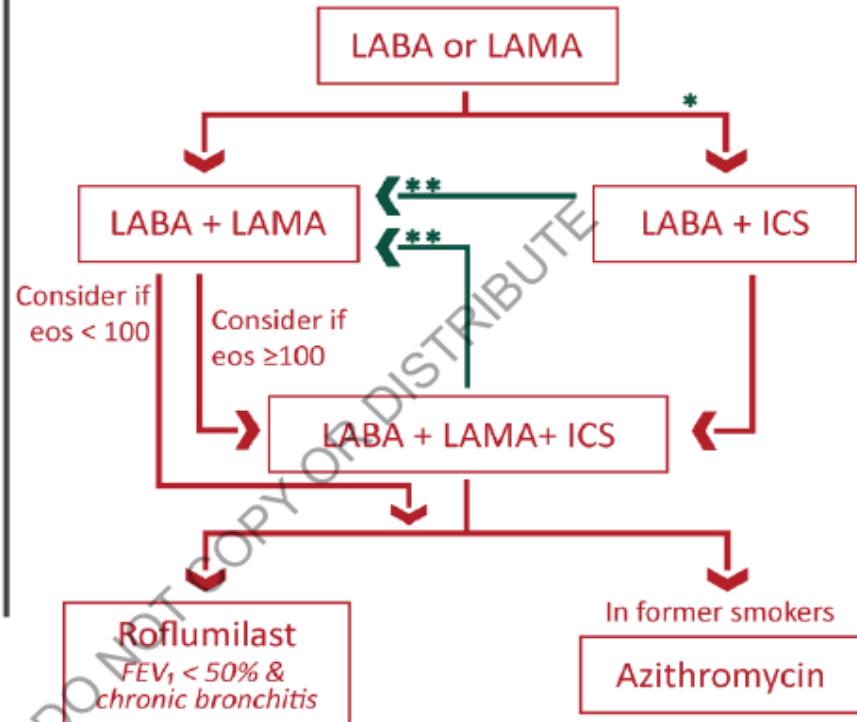
1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.

2. IF NOT:
- ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
 - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
 - ✓ Place patient in box corresponding to current treatment & follow indications
 - ✓ Assess response, adjust and review
 - ✓ These recommendations do not depend on the ABCD assessment at diagnosis

• DYSPNEA •



• EXACERBATIONS •



eos = blood eosinophil count (cells/ μ L)

* Consider if eos \geq 300 or eos \geq 100 AND \geq 2 moderate exacerbations / 1 hospitalization

** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS



2018 COPD 종합평가 우리 나라 지침

	FEV ₁ (% 정상예측치)	지난해 악화횟수
미만	(다)	≥2 또는 입원할 정도로 심한 악화 ≥1
60%		
이상	(가) (나)	0~1
	mMRC 0~1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
	증상 (mMRC 또는 CAT 점수)	

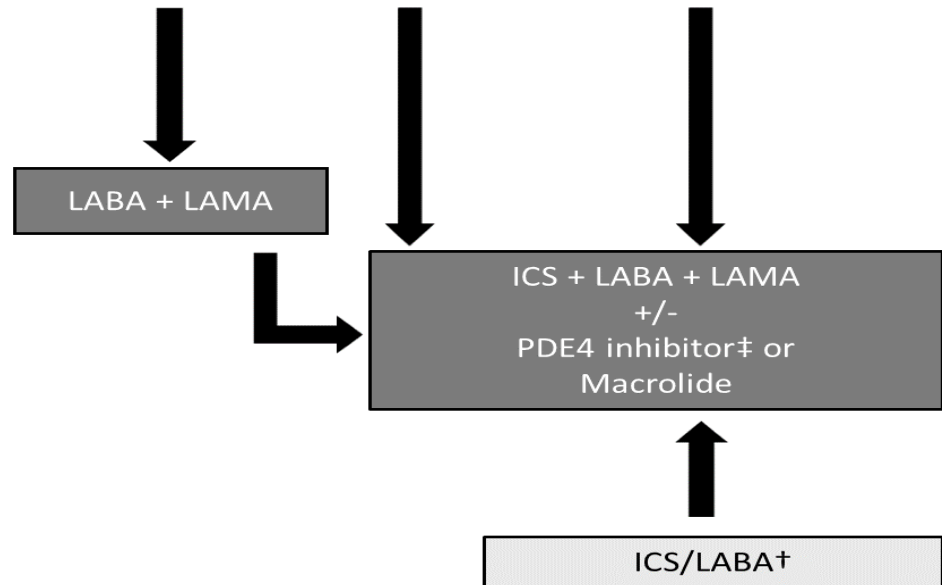
그림 2-3. COPD 종합평가(증상, FEV₁, 악화). **가군: 위험 낮음, 증상 경함.** FEV₁ 60% 이상이고 지난해 악화가 없었거나 한 번이며, mMRC 0~1 (또는 CAT 점수가 10 미만)인 경우이다. **나군: 위험 낮음, 증상 심함.** FEV₁ 60% 이상이고 지난해 악화가 없었거나 한 번이며, mMRC 2 이상(또는 CAT 점수가 10 이상)인 경우이다. **다군: 위험 높음.** mMRC 혹은 CAT 점수와 상관없이 FEV₁ 60% 미만에 해당하거나 또는 지난해에 2회 이상 급성악화가 있었거나 입원할 정도로 심한 악화가 1회 이상 있었던 경우이다. 참고. 악화(=급성악화)는 약제를 추가해야 할 정도로 호흡기증상이 나빠진 급성상태를 의미한다.



2018 COPD 종합평가 우리 나라 지침

	FEV ₁ ≥ 60% pred. and 0~1 exacerbation/year		FEV ₁ < 60% pred. 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-agonist as required		
First choice	SABA as needed	LABA or LAMA or LABA + LAMA	LABA + LAMA

Add on therapy:
exacerbation or mMRC ≥ 2



*AE COPD: Acute exacerbation of COPD.

†Asthma overlap or high blood eosinophil

‡급성악화 병력이 있고 만성기관지염을 수반한 COPD: 1) FEV1 < 50% 정상예측치 또는 흡입지속성베타-2작용제나 흡입지속성항콜린제 등의 지속 투여에도 연 2회 이상 급성악화가 발생한 경우



Contents

PRO in GOLD guideline

How to evaluate?

What to expect?



어떤 질문?

A general single question:

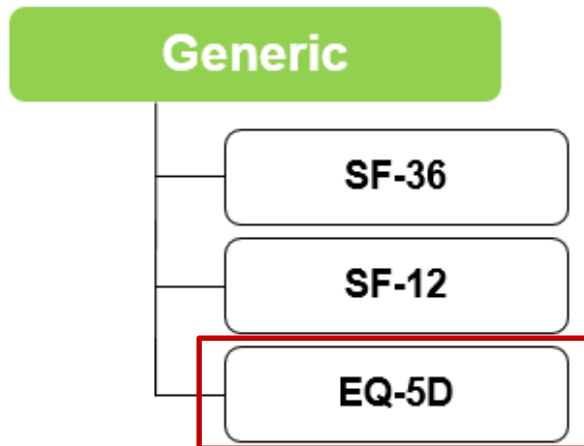
How are you doing?

will usually underreport patients' symptoms

PRO measures

Patient Reported Outcome Measures, PROM

- instruments that are used to measure the PROs
- most often **self-reported but standardized, validated questionnaires**
- **informative, reliable and consistent answers**



For mobility:

나는 걷는데
전혀 지장이 없다.
약간 지장이 있다.
중간정도의 지장이 있다.
심한 지장이 있다.
나는 걸을 수 없다.

-운동 능력
-자기 관리
-일상 활동
-통증/불편
-불안/우울

Article

Association of Ventilatory Disorders with Respiratory Symptoms, Physical Activity, and Quality of Life in Subjects with Prior Tuberculosis: A National Database Study in Korea




Bumhee Yang ^{1,†}, Hayoung Choi ^{2,†} , Sun Hye Shin ³, Youlim Kim ^{4,5}, Ji-Yong Moon ⁶, Hye Yun Park ^{3,*},  and Hyun Lee ^{6,*} 

Table 2. Comparison of symptoms, physical activity, and quality of life according to spirometric pattern.

	Total (<i>n</i> = 2669)	Normal Ventilation (<i>n</i> = 1466)	Obstructive Ventilatory Disorder (<i>n</i> = 783)	Restrictive Ventilatory Disorder (<i>n</i> = 420)	<i>p</i> Value
Any respiratory symptoms	16.4 (14.0–19.3)	12.4 (9.5–16.1)	22.9 (18.1–28.5) ^a	18.6 (12.6–26.6)	0.001
Cough	7.3 (5.7–9.2)	5.4 (3.5–8.3)	11.6 (8.5–15.8) ^a	5.1 (2.8–9.3)	0.004
Sputum	13.0 (10.8–15.5)	9.5 (7.0–12.8)	18.2 (13.9–23.5) ^a	15.1 (9.5–23.2)	0.004
Dyspnea	2.0 (1.3–3.1)	0.9 (0.3–2.5)	3.8 (2.1–6.7)	2.4 (0.9–5.9)	0.020
Physical activity limitations	15.6 (11.2–21.2)	5.1 (2.3–10.9)	27.7 (19.3–38.0) ^a	13.0 (6.2–28.4)	<0.001
EQ-5D component					
Mobility	18.3 (16.4–20.3)	14.0 (11.9–16.4)	24.1 (20.4–28.1) ^a	23.5 (18.1–29.8) ^b	<0.001
Self-care	5.2 (4.3–6.6)	3.6 (2.6–5.0)	7.7 (5.5–10.7) ^a	7.3 (4.3–12.4)	0.005
Usual activity	12.8 (11.1–14.6)	9.4 (7.7–11.5)	16.3 (13.1–20.1) ^a	19.1 (14.2–25.2) ^b	<0.001
Pain/discomfort	29.0 (26.6–31.5)	30.7 (26.5–35.2)	30.1 (26.5–35.2)	36.3 (29.8–43.4)	0.015
Anxiety/depression	13.6 (11.9–15.5)	13.5 (11.3–16.1)	13.5 (10.6–17.1)	13.7 (9.5–17.5)	0.999
EQ-5D index	0.93 (0.92–0.93)	0.94 (0.93–0.94)	0.91 (0.90–0.93) ^a	0.91 (0.89–0.93) ^{b,c}	0.002

Data are presented as weighted mean (95% confidence interval) or weighted percentage (95% confidence interval). *p* values are comparisons of three groups. EQ-5D, EuroQoL five dimensions. The results of Bonferroni correction with three comparisons are provided as superscripts in Table (a *p* value of 0.05 corresponds to 0.017 [0.05/3]). ^a Indicates statistical significance for the comparison of normal ventilation and obstructive ventilatory disorder. ^b Indicates statistical significance for the comparison of normal ventilation and restrictive ventilatory disorder. ^c Indicates statistical significance for the comparison of obstructive ventilatory disorder and restrictive ventilatory disorder.

Disease-specific PROM in COPD

**SGRQ/
SGRQ-C**

CRQ

CCQ

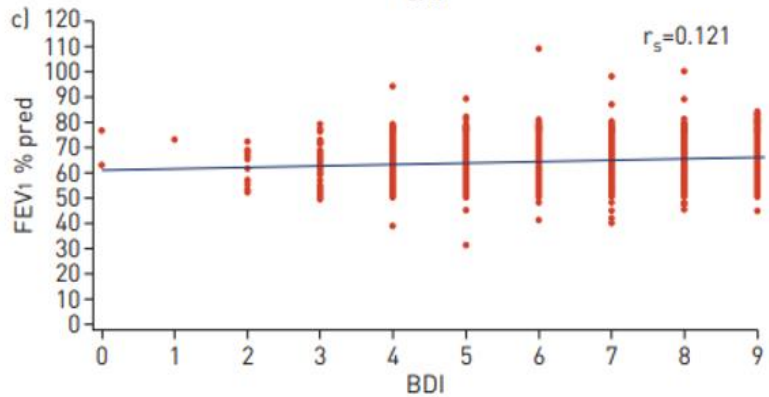
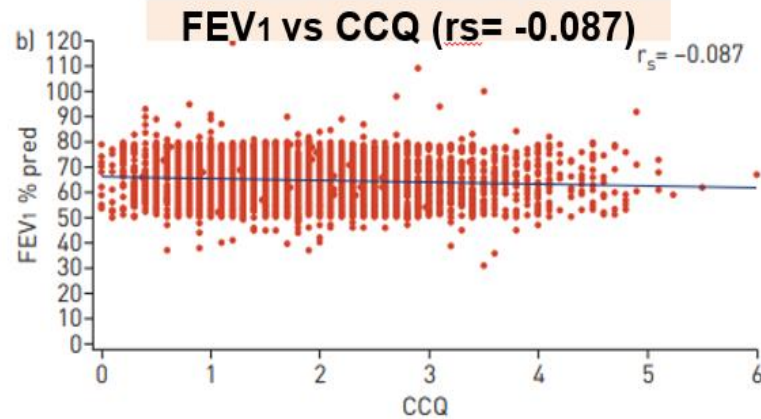
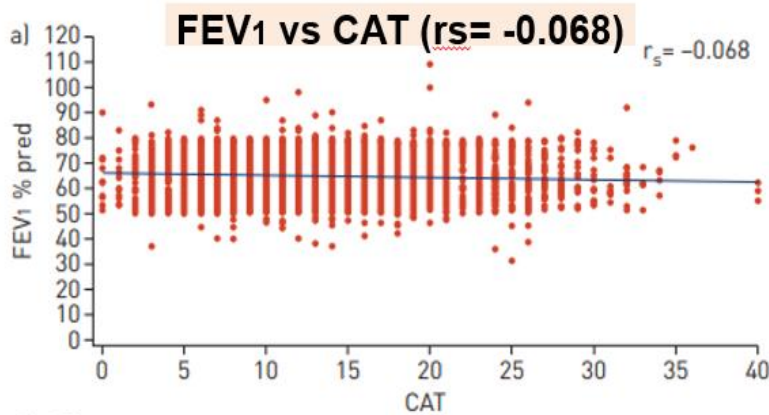
CAT

BDI/TDI



FEV₁ and PROM with no correlation

A post hoc analysis of CRYSTAL study



FEV₁ vs BDI ($r_s = 0.121$)

CAT : COPD Assessment Test
CCQ: Clinical COPD Questionnaire
BDI: Baseline Dyspnoea Index

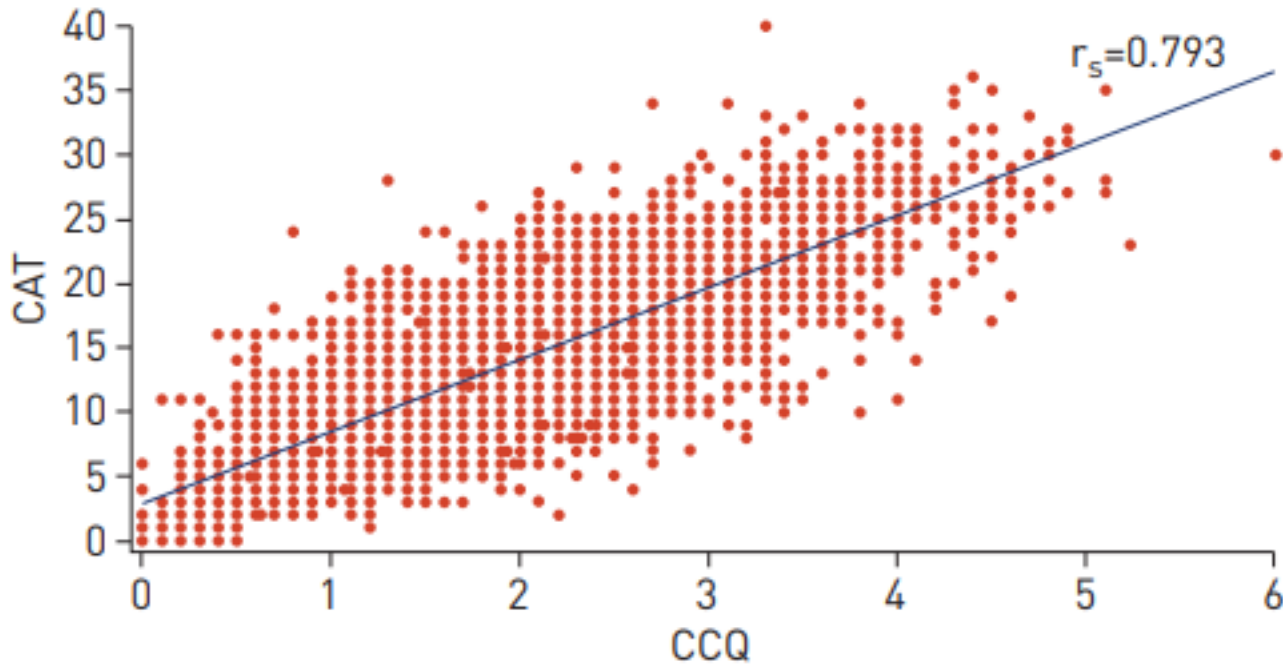
CRYSTAL study assessed the efficacy and safety of a direct switch from previous treatments to indacaterol/glycopyrronium 110/50 µg or glycopyrronium 50 µg once daily.



CAT and CCQ with very strong correlation

A post hoc analysis of CRYSTAL study

At baseline, a strong positive correlation between the CAT and CCQ



CRYSTAL study assessed the efficacy and safety of a direct switch from previous treatments to indacaterol/glycopyrronium 110/50 μg or glycopyrronium 50 μg once daily.



Clinical COPD Questionnaire

Clinical COPD Questionnaire (CCQ)

Please check the number of the response that best describes how you have been feeling during the **past week**. (Only one response for each question).

On average, during the past week, how often did you feel:

never hardly ever a few times several times many times A great many times Almost all the time

1. Short of breath **at rest?** 0 1 2 3 4 5 6

2. Short of breath **doing physical activities?** 0 1 2 3 4 5 6

3. **Concerned** about getting a cold or your breathing getting worse? 0 1 2 3 4 5 6

4. **Depressed (down)** because of your breathing problems? 0 1 2 3 4 5 6

In general, during the past week, how much of the time:

never hardly ever a few times several times many times A great many times Almost all the time

5. Did you **cough?** 0 1 2 3 4 5 6

6. Did you **produce phlegm?** 0 1 2 3 4 5 6

On average, during the past week, how limited were you in these activities because of your breathing problems:

not limited at all very slightly limited slightly limited moderately limited very limited extremely limited totally limited / or unable to do

7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)? 0 1 2 3 4 5 6

8. **Moderate physical activities** (such as walking, housework, carrying things)? 0 1 2 3 4 5 6

9. **Daily activities at home** (such as dressing, washing yourself)? 0 1 2 3 4 5 6

10. **Social activities** (such as talking, being with children, visiting friends/relatives)? 0 1 2 3 4 5 6

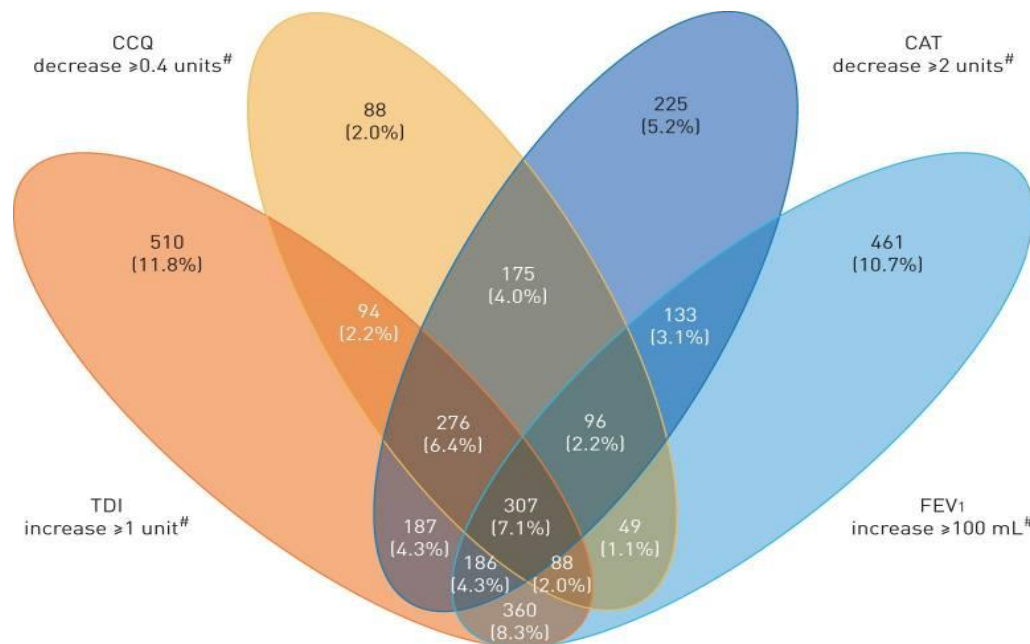
Total CCQ Score: 2.4
Symptom Score: 1.75
Mental state score: 3
Functional state score: 2.75

Add to Chart



Heterogeneous disease

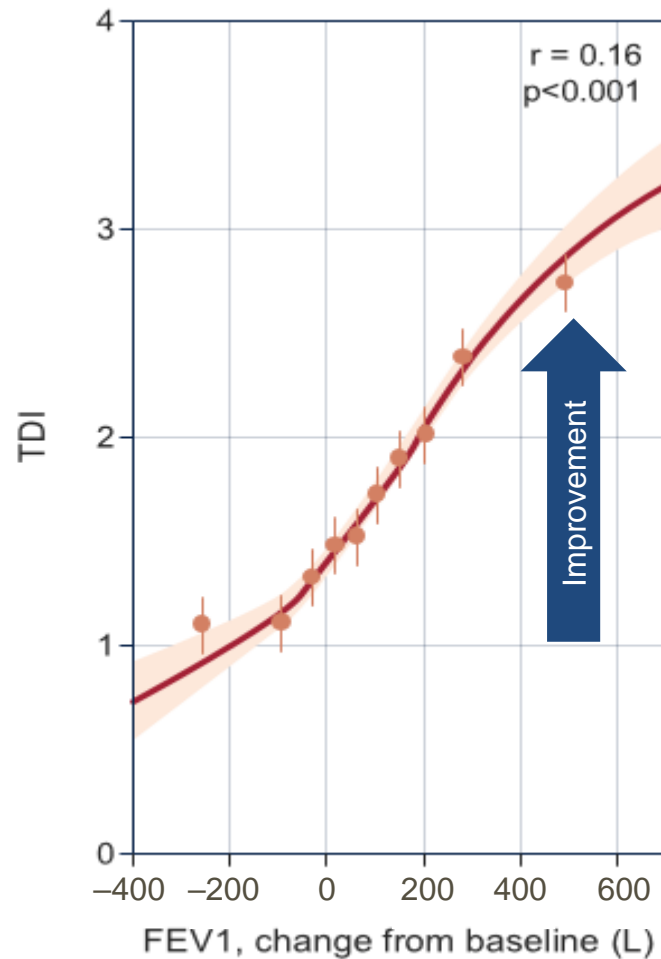
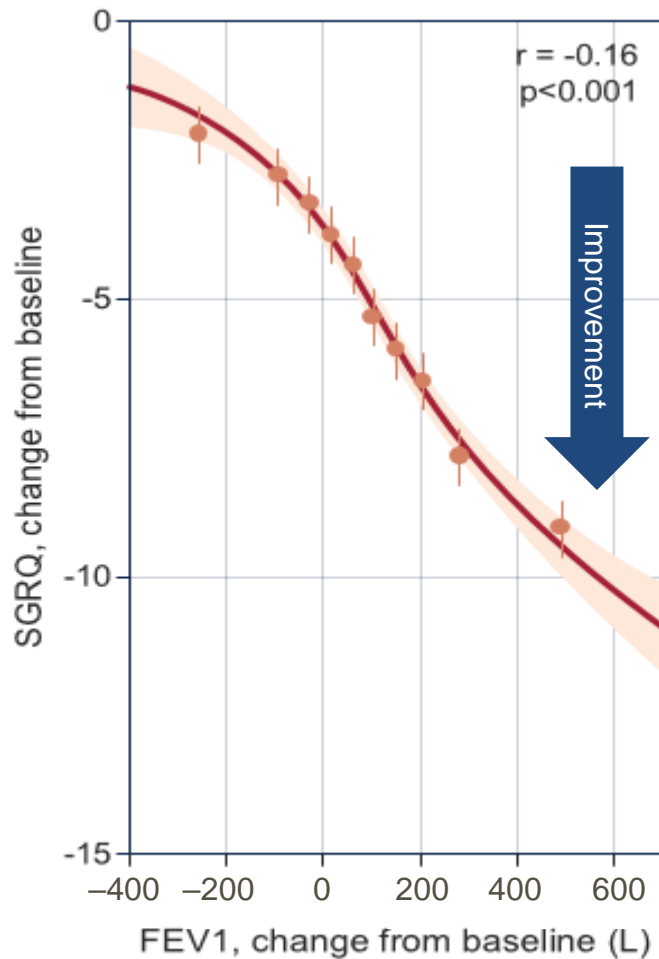
Responder analysis based on PROs and FEV₁ at week 12
 31.6%, 19.1% and 13.5% of patients showed a MCID improvement
 in one, two or all three PROs, respectively.



There were small overlaps among the patients who responded to PROs (TDI, CCQ and CAT)



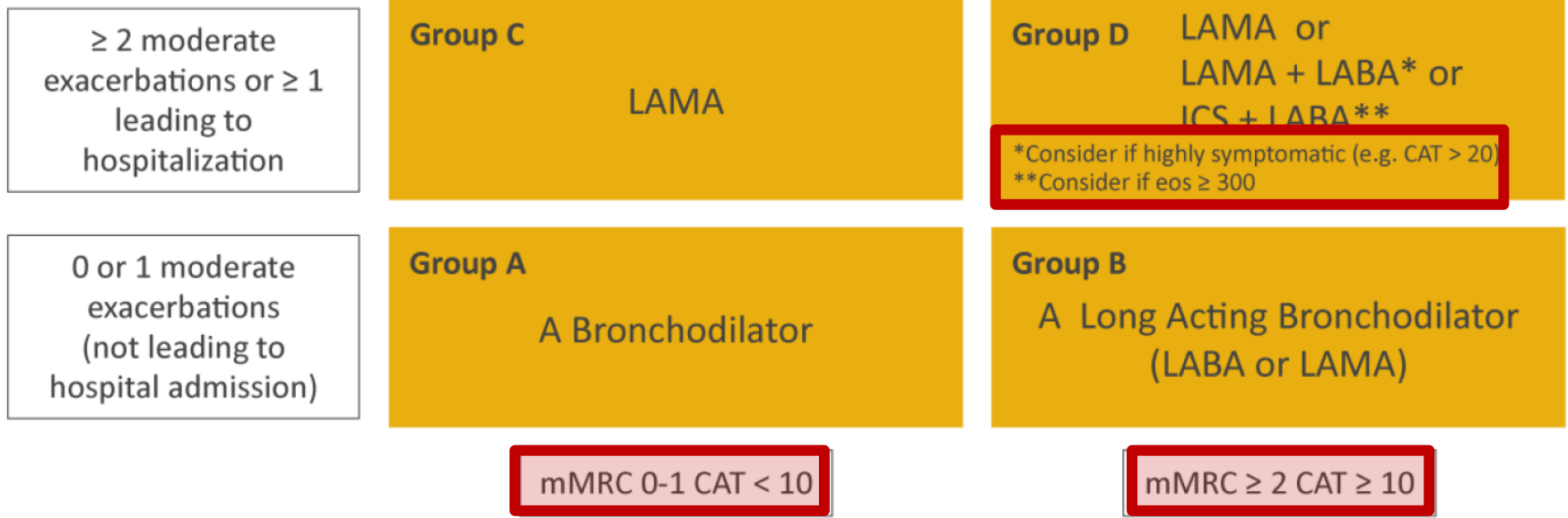
Correlations between FEV1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with COPD





COPD Assessment Test (CAT)

- Determinant of COPD disease severity
- Guide to choose initial treatment (CAT >20 dual bronchodilator)



Disease-specific PROM in COPD

호흡곤란

2

mMRC 호흡곤란점수	호흡곤란 내용
0	힘든 운동을 할 때만 숨이 차다.
1	평지를 빨리 걷거나, 약간 오르막길을 걸을 때 숨이 차다.
2	<u>평지를 걸을 때 숨이 차서 동년배보다 천천히 걷거나, 자신의 속도로 걸어도 숨이 차서 멈추어 쉬어야 한다.</u>
3	평지를 약 100m 정도 걷거나, 몇 분 동안 걸으면 숨이 차서 멈추어 쉬어야 한다.
4	숨이 너무 차서 집을 나설 수 없거나, 옷을 입거나 벗을 때도 숨이 차다.



Initial Visit (M/65)

- Chief Complaints:
 - Dyspnea with mMRC Gr II without previous Hx of AE

Validated 8 items
Questionnaire

상태 (Good)	점 수						상태 (Poor)
	0	1	2	3	4	5	
나는 전혀 기침을 하지 않는다.			2				나는 항상 기침을 한다.
나는 가슴에 전혀 가래가 없다.			2				나는 가슴에 가래가 가득 차 있다.
나는 전혀 가슴이 답답함을 느끼지 않는다.						5	나는 가슴이 아주 답답함을 느낀다.
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다.						5	나는 언덕이나 계단을 오를 때 아주 숨이 차다.
나는 집에서 활동하는데 전혀 제약을 받지 않는다.					4		나는 집에서 활동하는데 많은 제약을 받는다.
폐질환에도 불구하고 나는 외출에 자신이 있다.				3			폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다.
나는 잠을 깊이 잔다.				3			폐질환으로 인하여 나는 잠을 깊이 자지 못한다.
나는 기운이 왕성하다.						5	나는 전혀 기운이 없다.
CAT Score : 29							

- Cough
- Mucus
- Chest Tightness
- Breathless
- Activities
- Confidence
- Sleep
- Energy

Total score: 0-40

Example of an individual case is shared for scientific exchange only. Does not represent all patients



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How to evaluate?

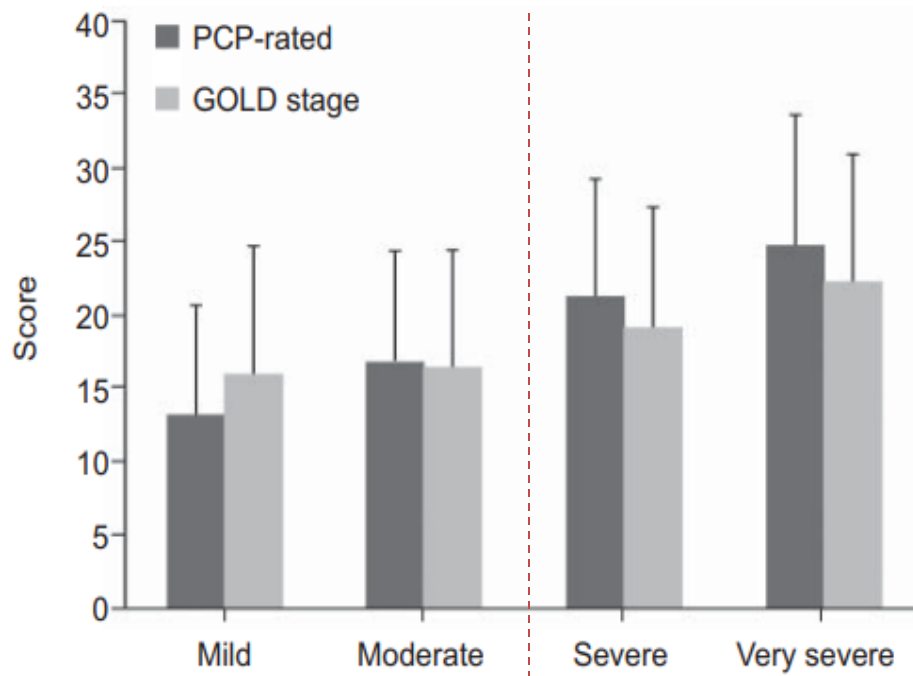
What to expect?



COPD Assessment Test (CAT)

1817 COPD patients from 7 European countries, cross-sectional study

There were no differences in CAT score: Female vs. Male; Younger vs. Older; Across the countries



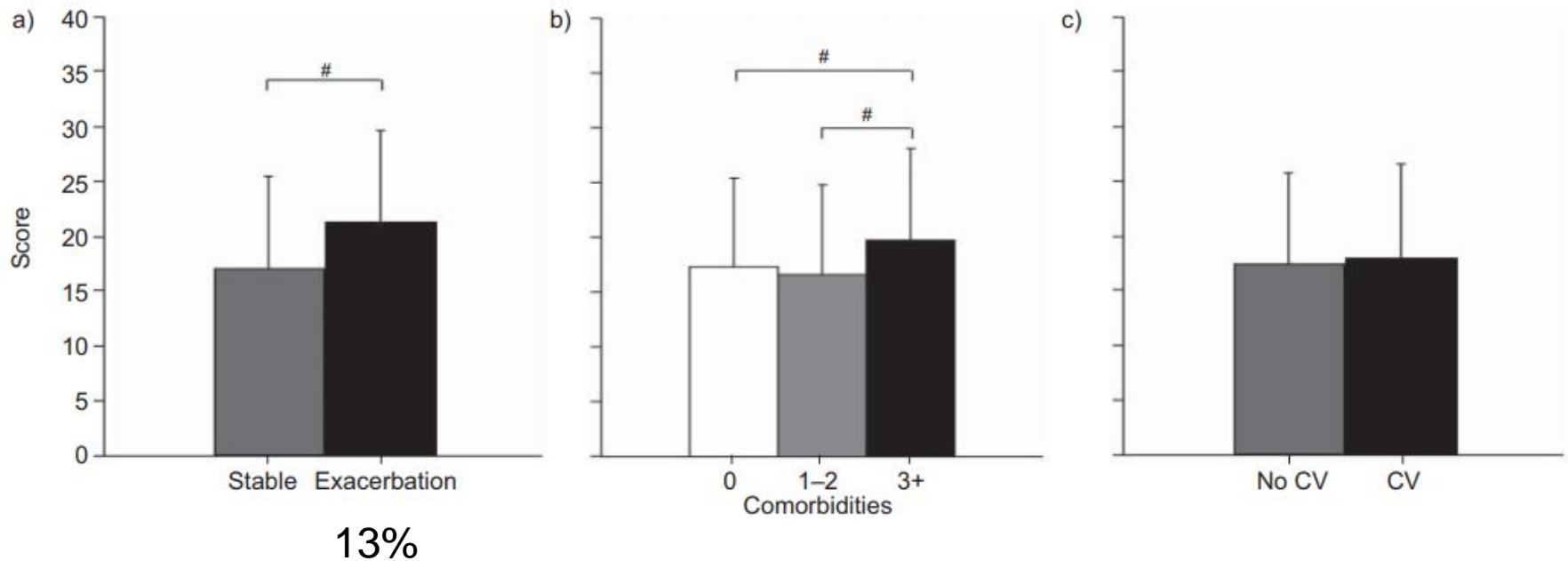
CAT scores showed significant impairment in health status across all COPD severities, even in patients with mild disease



COPD Assessment Test (CAT)

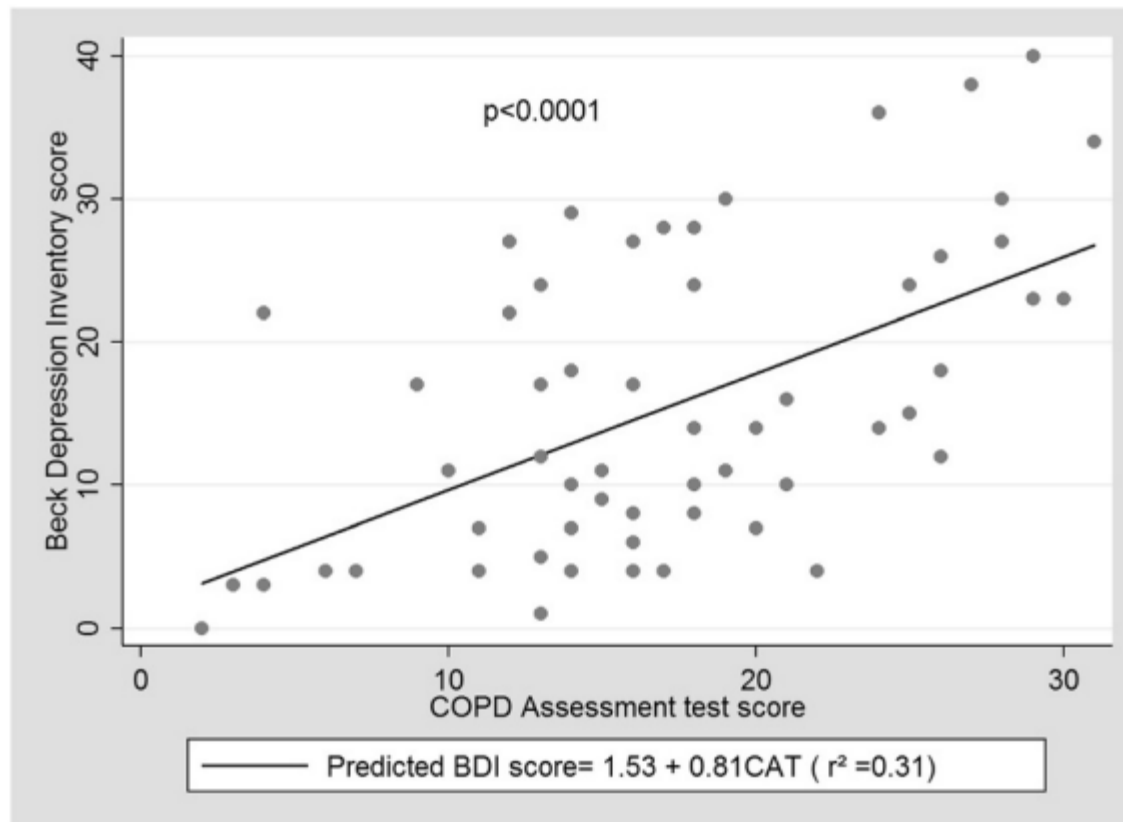
1817 COPD patients from 7 European countries

Worse health status in COPD patients with AE or 3+ comorbidities, but cardiovascular comorbidity did not influence the CAT score.



COPD Assessment Test (CAT) score as a predictor of major depression among subjects with chronic obstructive pulmonary disease and mild hypoxemia: a case-control study

José Laerte R Silva Júnior^{1,2*}, Marcus Barreto Conde³, Krislainy de Sousa Corrêa², Christina da Silva², Leonardo da Silva Prestes⁴ and Marcelo Fouad Rabahi^{1,2}

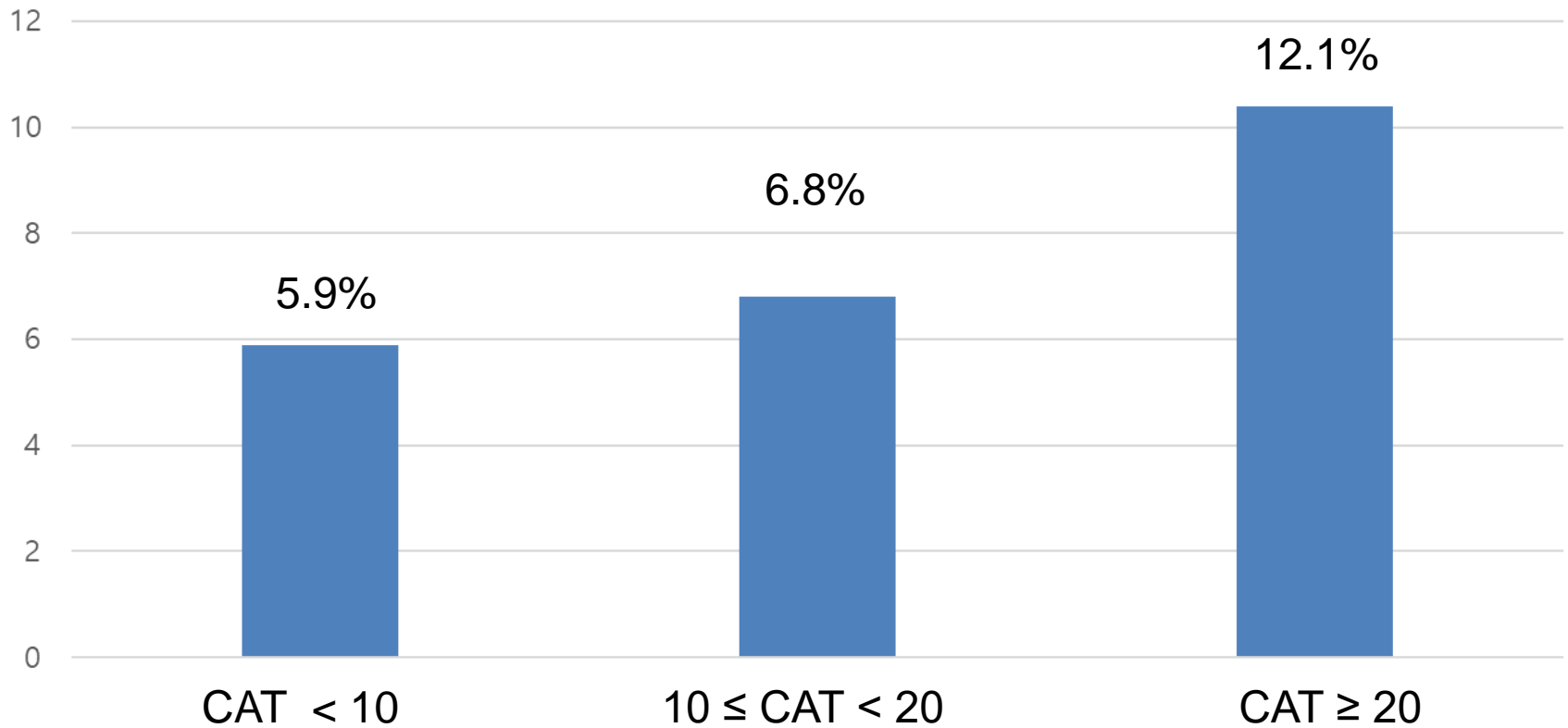




CAT and depression

BDI ≥ 16 ,
%

N=1,225, KOCOSS data





CAT & COPD exacerbations

545 COPD patients from 19 hospitals in Australia, China, Korea and Taiwan
 - 226 patients (46%) with at least one moderate-severe AE during study period (observational 6-month study)

Factor	Time to first exacerbation		Any exacerbation	
	Hazard ratio (95% CI)	p-Value	Relative risk (95% CI)	p-Value
Categorised CAT score (adjusted)		0.001		<0.001
0–9	1		1	
10–19	1.73 (1.23–2.43)	0.001	1.30 (1.09–1.56)	0.004
20–29	2.41 (1.62–3.58)	<0.001	1.37 (1.14–1.65)	0.001
30–40	4.16 (2.26–7.64)	<0.001	1.50 (1.24–1.81)	<0.001

Compared with the lowest baseline CAT score, the higher baseline CAT scores were associated with significantly higher exacerbation risks and shorter time to first exacerbations.



Following visit

Exacerbations!

mMRC Gr I

mMRC Gr III

상태 (Good)	점수						
	0	1	2	3	4	5	
Cough		1					나는 할
Mucus			2				나는 기
Chest Tightness				3			나는 기
Breathless				3			나는 일
Activities			2				나는 집
Confidence			2				폐질환
Sleep			2				폐질환
Energy				3			나는 진

CAT Score : 18

상태 (Good)	점수						상태 (Poor)
	0	1	2	3	4	5	
나는 전혀 기침을 하지 않는다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	나는 항상 기침을 한다.
나는 가슴에 전혀 가래가 없다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	나는 가슴에 가래가 가득 차 있다.
나는 전혀 가슴이 답답함을 느끼지 않는다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	나는 가슴이 아주 답답함을 느낀다.
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	나는 언덕이나 계단을 오를 때 아주 숨이 차다.
나는 집에서 활동하는데 전혀 제약을 받지 않는다	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	나는 집에서 활동하는데 많은 제약을 받는다.
폐질환에도 불구하고 나는 외출에 자신이 있다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다.
나는 잠을 깊이 잔다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	폐질환으로 인하여 나는 잠을 깊이 자지 못한다.
나는 기운이 왕성하다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	나는 전혀 기운이 없다.

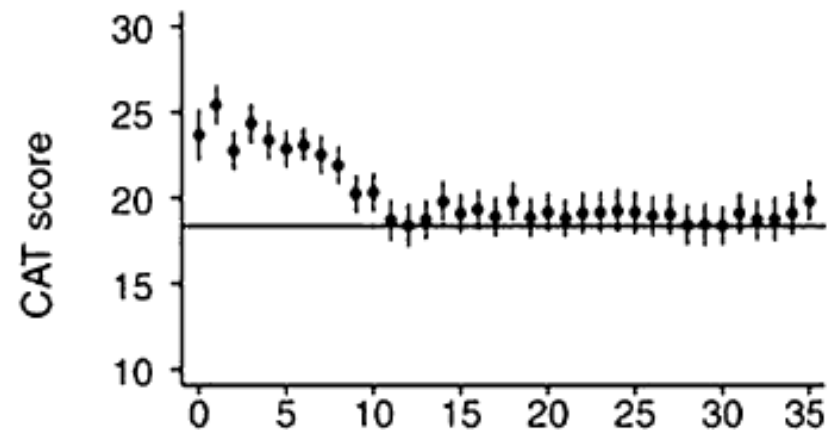
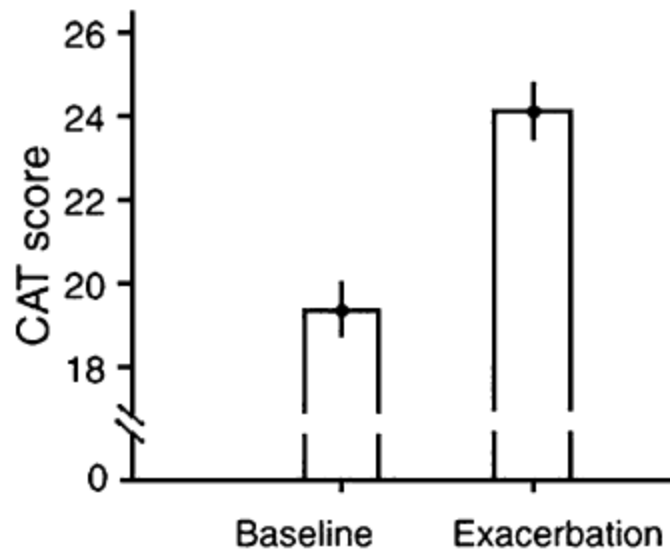
CAT Score : 36



Change of CAT during AE

161 COPD patients in the London COPD cohort

Fifty-two different patients completed the CAT questionnaire on at least 21 of 35 days during the recovery phase after an exacerbation

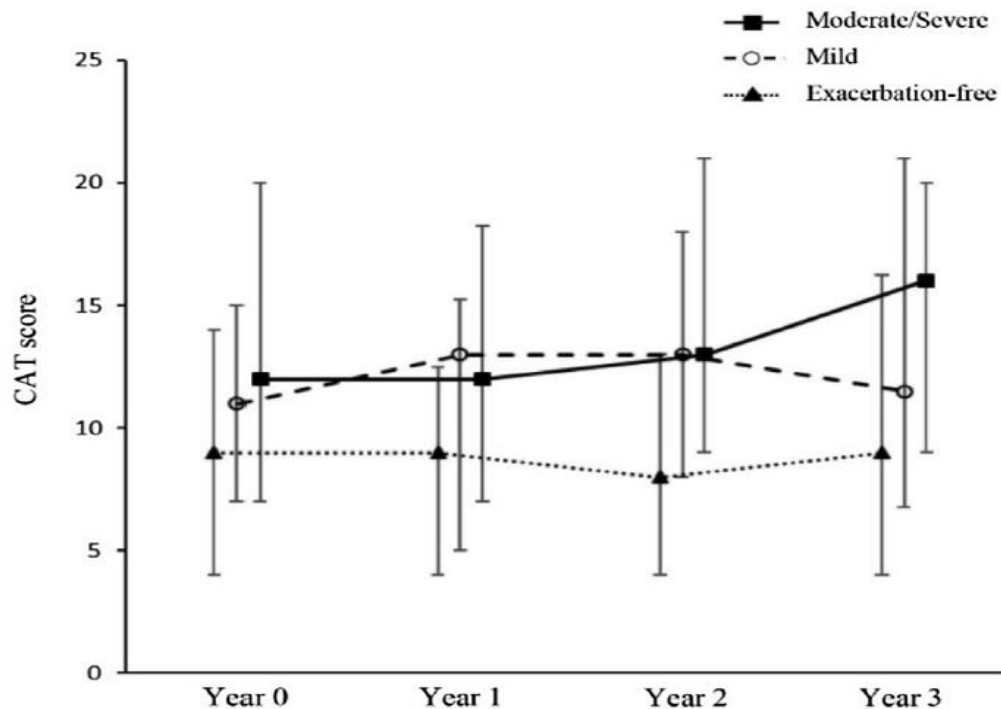




Annual change in CAT

315 COPD patients with at least 3 CAT scores over 3 years
: Gold grade 1,2: 71%

A significant positive association
between the evolution of the CAT over time and the risk of exacerbations.





COPD Assessment Test (CAT)

- Current studies focused on total CAT score.
- However, CAT items can be divided into 2 categories, pulmonary and extra-pulmonary (constitutional) symptoms.

예: 나는 매우 행복하다 (0) (1) (2) (3) (4) (5) 나는 매우 슬프다

Left Statement	Scale (0-5)	Right Statement	점수
나는 전혀 기침을 하지 않는다	0 1 2 3 4 5	나는 항상 기침을 한다	
나는 가슴에 전혀 가래가 없다	0 1 2 3 4 5	나는 가슴에 가래가 가득 차 있다	
나는 전혀 가슴이 답답함을 느끼지 않는다	0 1 2 3 4 5	나는 가슴이 아주 답답함을 느낀다	
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다	0 1 2 3 4 5	나는 언덕이나 계단을 오를 때 아주 숨이 차다	
나는 집에서 활동하는데 전혀 제약을 받지 않는다	0 1 2 3 4 5	나는 집에서 활동하는데 많은 제약을 받는다	
폐질환에도 불구하고 나는 외출하는데 자신이 있다	0 1 2 3 4 5	폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다	
나는 잠을 깊이 잔다	0 1 2 3 4 5	폐질환으로 인하여 나는 잠을 깊이 자지 못한다	
나는 기운이 왕성하다	0 1 2 3 4 5	나는 전혀 기운이 없다	

Pulmonary symptoms

- Cough
- Sputum
- Chest tightness
- Dyspnea

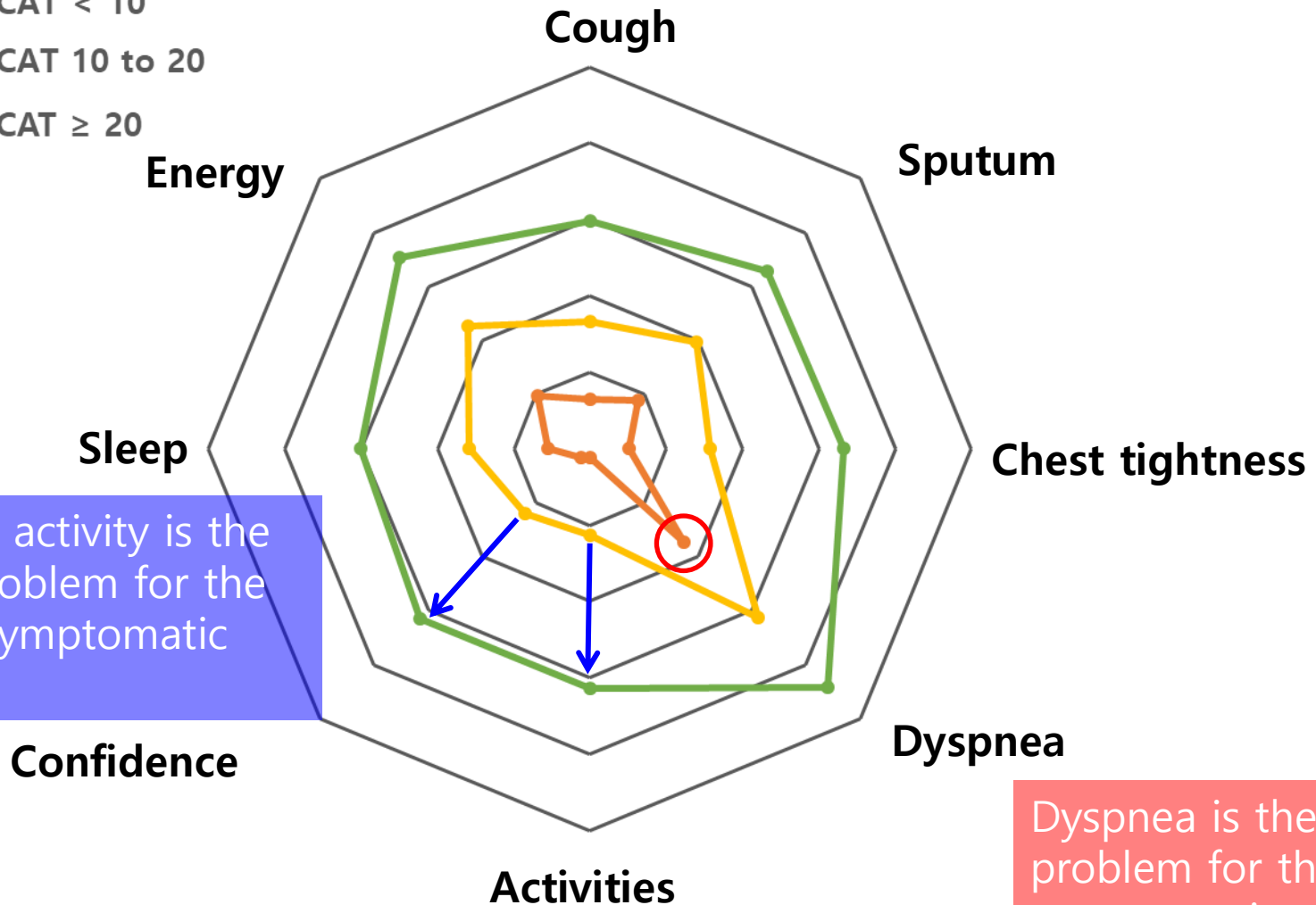
Extra-pulmonary symptoms

- Activities
- Confidence
- Sleep
- Energy



Distribution of each CAT item

- CAT < 10
- CAT 10 to 20
- CAT ≥ 20

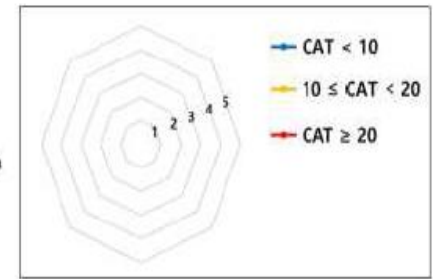
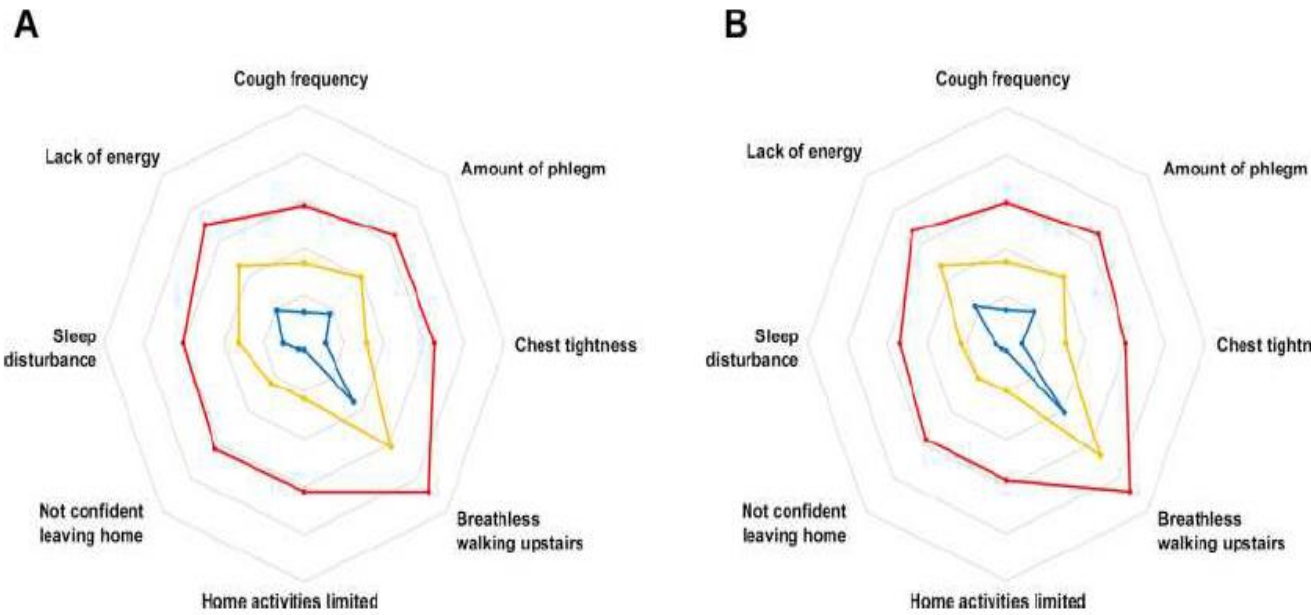


Physical activity is the main problem for the highly symptomatic patients

Dyspnea is the main problem for the less symptomatic patients



Distribution of each CAT item



Single center data

KOCOSS cohort



CAT

점수

나는 전혀 기침을 하지 않는다	0 1 2 3 4 5	나는 항상 기침을 한다	
나는 가슴에 전혀 가래가 없다	0 1 2 3 4 5	나는 가슴에 가래가 가득 차 있다	
나는 전혀 가슴이 답답함을 느끼지 않는다	0 1 2 3 4 5	나는 가슴이 아주 답답함을 느낀다	
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다	0 1 2 3 4 5	나는 언덕이나 계단을 오를 때 아주 숨이 차다	
나는 집에서 활동하는데 전혀 제약을 받지 않는다	0 1 2 3 4 5	나는 집에서 활동하는데 많은 제약을 받는다	
폐질환에도 불구하고 나는 외출하는데 자신이 있다	0 1 2 3 4 5	폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다	
나는 잠을 깊이 잔다	0 1 2 3 4 5	폐질환으로 인하여 나는 잠을 깊이 자지 못한다	
나는 기운이 왕성하다	0 1 2 3 4 5	나는 전혀 기운이 없다	

Cough

Mucus

Chest Tightness

Breathless

Activities

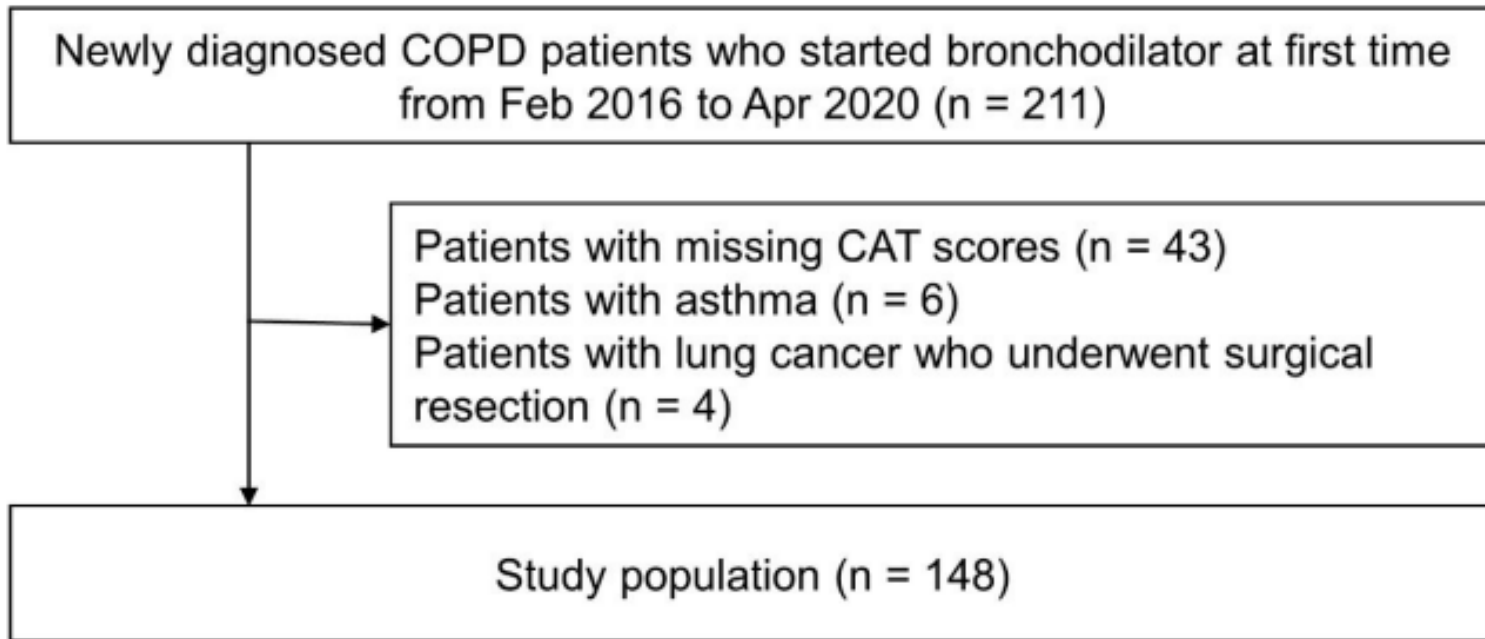
Confidence

Sleep

Energy



Change in CAT after short-tem bronchodilator therapy





Outcome changes after 6 months inhaler therapy

148 newly diagnosed COPD patients with bronchodilator initiation

	Baseline	After Bronchodilator therapy	<i>p</i> -value	Adjusted difference*
CAT total scores	16.0 ± 8.4	14.9 ± 8.3	0.13	-1.10 (-2.40, 0.20)
CAT individual item score				
Cough	1.9 ± 1.5	1.7 ± 1.3	0.13	-0.22 (-0.48, 0.04)
Phlegm	2.1 ± 1.4	1.9 ± 1.4	0.07	-0.22 (-0.44, -0.002)
Chest tightness	1.8 ± 1.5	1.5 ± 1.3	0.02	-0.30 (-0.56, -0.05)
Breathlessness	3.2 ± 1.5	2.8 ± 1.4	<0.001	-0.45 (-0.66, -0.23)
Activities	1.4 ± 1.6	1.4 ± 1.4	0.34	-0.09 (-0.32, 0.14)
Confidence	1.5 ± 1.5	1.5 ± 1.6	0.90	0.03 (-0.22, 0.28)
Sleep	1.6 ± 1.5	1.8 ± 1.5	0.20	0.17 (-0.11, 0.45)
Energy	2.4 ± 1.4	2.4 ± 1.4	0.64	-0.20 (-0.26, 0.22)
CAT pulmonary item score	9.1 ± 4.5	7.9 ± 4.1	0.003	-1.19 (-1.92, -0.46)
CAT extra-pulmonary item score	6.9 ± 4.9	7.0 ± 4.9	0.74	0.09 (-0.66, 0.84)
Lung function				
FEV1, mL	1810 ± 490	1990 ± 490	<0.001	170 (130, 220)
mMRC dyspnea grade ≥ 2	64 (43.2)	47 (31.8)	0.041	0.58 (0.39, 0.85)

Notes: Data presented as mean (SD) or n (%). Data were collected at two points in "Baseline" and "After Bronchodilator therapy (after median 5.8 [5.1-6.5] months)".

Outcome changes after 6 months inhaler therapy

Improved Group: a decrease of 2 points or more of the total CAT score

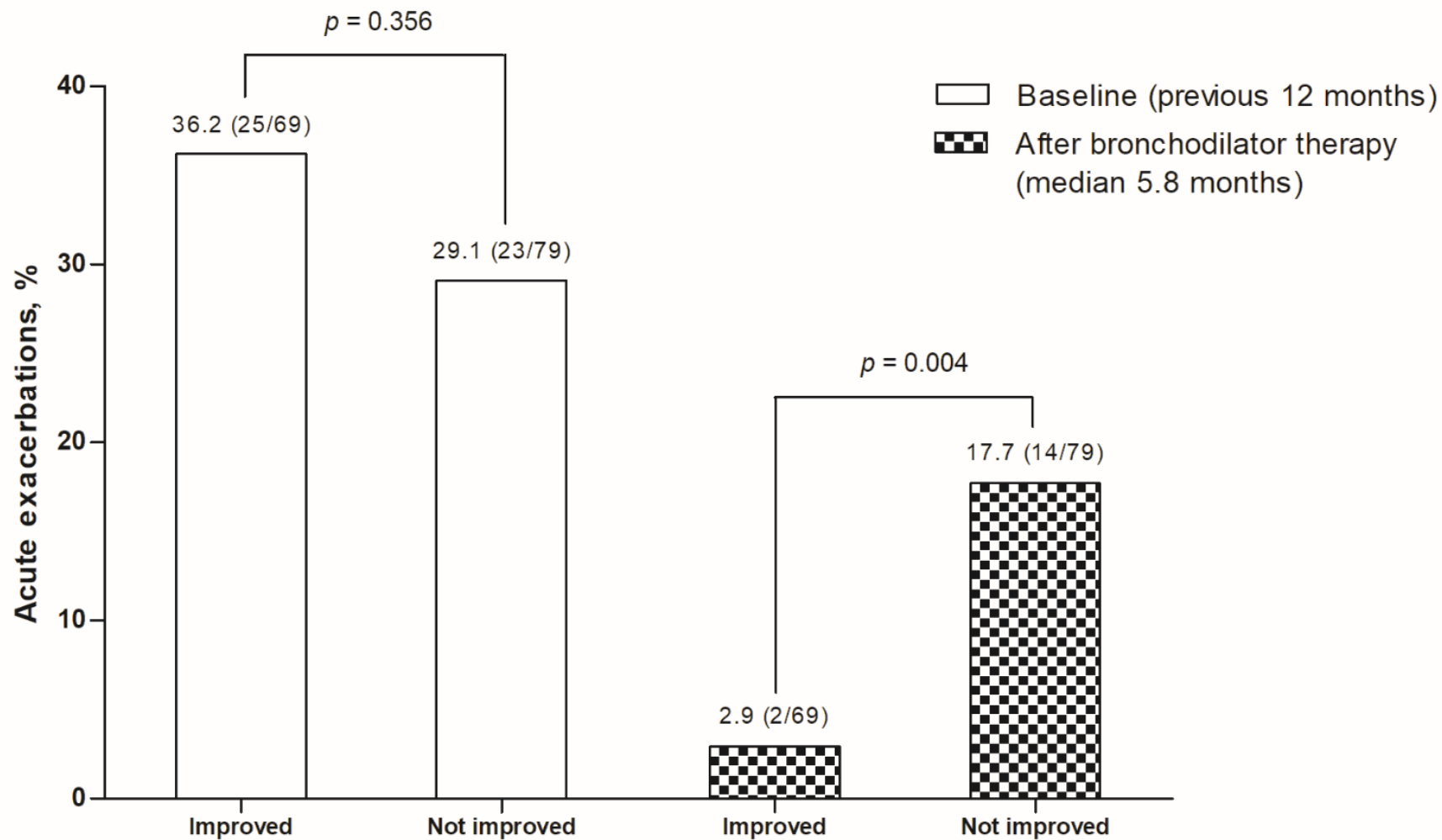
CAT Score	Improved* (N=69)	Not improved (N=79)
CAT total scores	-7.80 (-9.03, -6.58)	4.76 (3.64, 5.88)
CAT individual item score		
Cough	-1.10 (-1.44, -0.77)	0.56 (0.26, 0.86)
Phlegm	-1.06 (-1.34, -0.78)	0.51 (0.28, 0.74)
Chest tightness	-1.31 (-1.62, -0.99)	0.57 (0.30, 0.84)
Breathlessness	-1.09 (-1.36, -0.82)	0.12 (-0.16, 0.40)
Activities	-1.01 (-1.28, -0.73)	0.71 (0.47, 0.96)
Confidence	-0.80 (-1.12, -0.50)	0.75 (0.45, 1.06)
Sleep	-0.60 (-0.97, -0.22)	0.84 (0.49, 1.20)
Energy	-0.84 (-1.12, -0.56)	0.70 (0.41, 1.00)
CAT pulmonary item score	-4.57 (-5.33, -3.79)	1.75 (1.04, 2.47)
CAT extra-pulmonary item score	-3.25 (-4.06, -2.44)	3.01 (2.26, 3.76)
Lung function		
FEV ₁ , mL	190 (140, 240)	150 (80, 230)
mMRC dyspnea grade $\geq 2^{\dagger}$	0.36 (0.20, 0.64)	0.85 (0.52, 1.40)

Adjusted for age, smoking history, Global Initiative for Chronic Obstructive Lung Disease stage, pulmonary comorbidity, other comorbidities, and acute exacerbation history.

Data are presented as adjusted differences (95% confidence intervals).



AE after 6 months inhaler therapy





M/62

운동시 호흡곤란

mMRC Gr I, no previous AE, no BA

Current smoker 1 pack/day x 42 yrs

3개월 후

훨씬 나아졌다. 걷는 것도 많이 걷는다.

담배도 많이 줄었다.

상태 (Good)	점수						
	0	1	2	3	4	5	
Cough				3			나는
Mucus				3			나는 있다
Chest Tightness				3			나는 느낀
Breathless						5	나는 때
Activities		1					나는 제한
Confidence		1					폐 질 환 하 는
Sleep			2				폐 질 환 이
Energy				3			나는
CAT Score : 21							

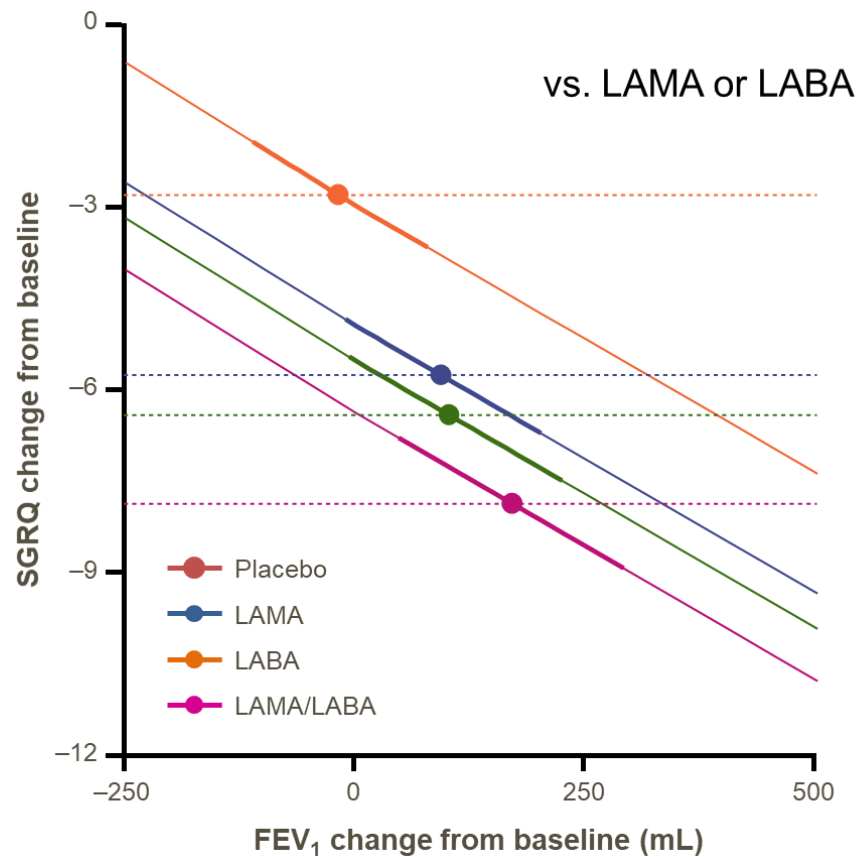
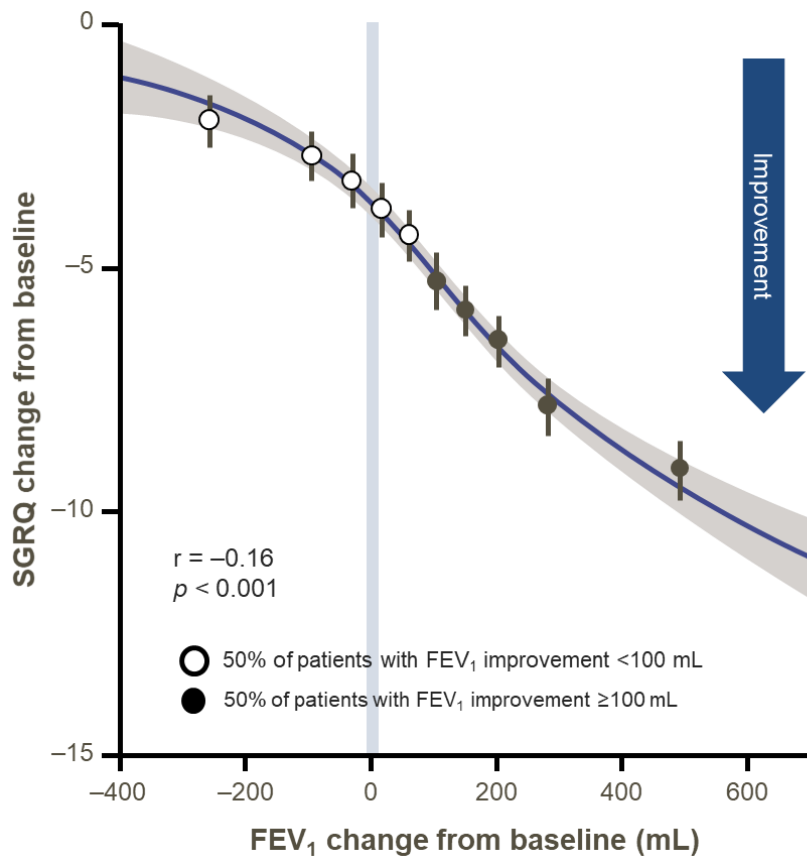
상태 (Good)	점수						상태 (Poor)
	0	1	2	3	4	5	
나는 전혀 기침을 하지 않는다.				3			나는 항상 기침을 한다.
나는 가슴에 전혀 가래가 없다.			2				나는 가슴에 가래가 가득 차 있다.
나는 전혀 가슴이 답답함을 느끼지 않는다.		1					나는 가슴이 아주 답답함을 느낀다.
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다.			2				나는 언덕이나 계단을 오를 때 아주 숨이 차다.
나는 집에서 활동하는데 전혀 제한을 받지 않는다		1					나는 집에서 활동하는데 많은 제한을 받는다.
폐질환에도 불구하고 나는 외출에 자신이 있다.		1					폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다.
나는 잠을 깊이 잔다.		1					폐질환으로 인하여 나는 잠을 깊이 자지 못한다.
나는 기운이 왕성하다.		1					나는 전혀 기운이 없다.
CAT Score : 12							

FEV₁: 1.94L, 54%/2.15L, 60% pred

FEV₁: 2.47L, 71% pred



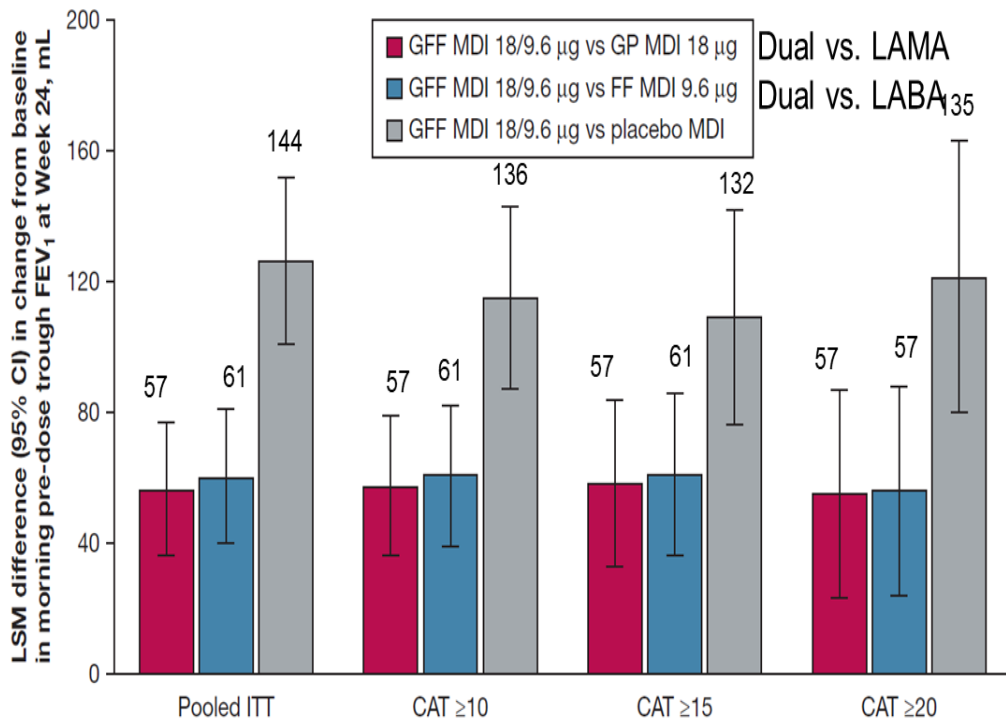
Correlations between FEV₁ and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with COPD



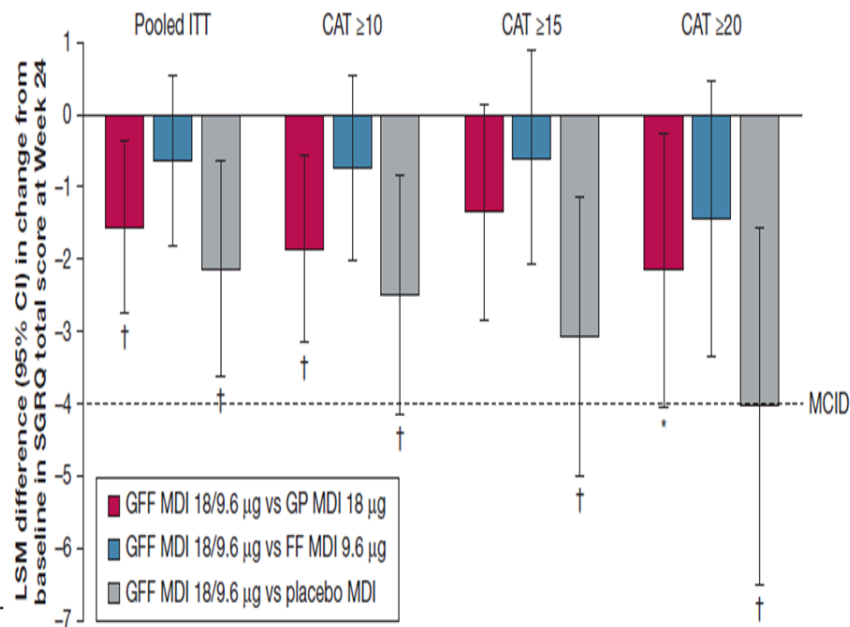


Baseline CAT & dual bronchodilators

FEV₁



SGRQ total



GFF glycopyrrolate/formoterol fumarate
GP glycopyrrolate
FF formoterol fumarate



Chronic bronchitis (CB)

Classic definition : chronic cough & sputum for at least 3 months/year for 2 consecutive years

Alternative definition using SGRQ definition : more sensitive, similar characteristics with classic definition

SGRQ chronic bronchitis

1. Over the last 4 weeks, I have coughed:

Almost every day
Several days a week

A few days a month
Only with lung/respiratory infections
Not at all

2. Over the last 4 weeks, I have brought up phlegm (sputum):

Almost every day

Several days a week

A few days a month
Only with lung/respiratory infections
Not at all

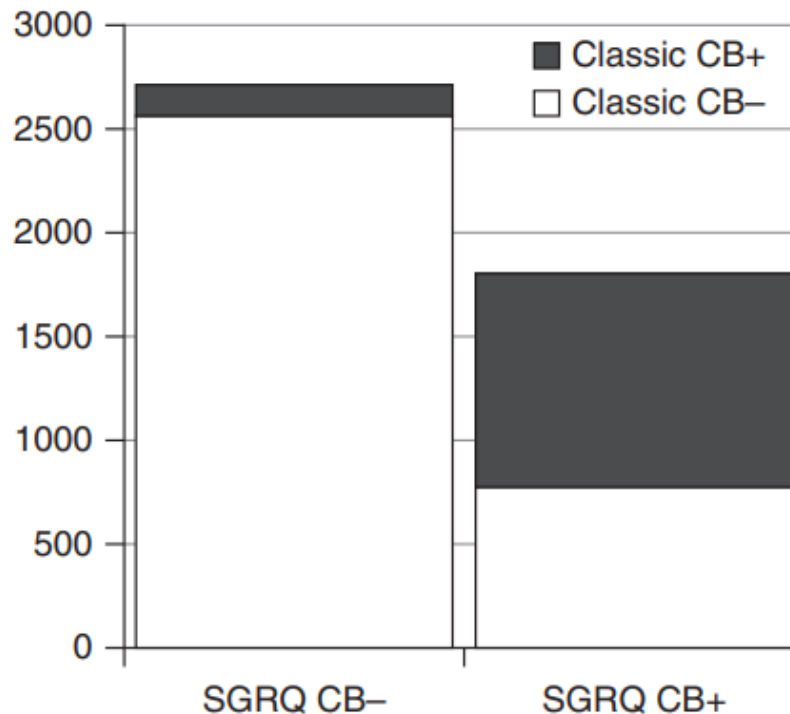
Chronic bronchitis = cough AND phlegm almost every day or several times a week



Chronic bronchitis (CB)

N= 4,513 from COPDGene cohort

The SGRQ CB definition had a sensitivity and specificity of 0.87 and 0.77. The SGRQ CB+ and Classic CB+ groups were strikingly similar, with more respiratory symptoms and exacerbations, worse lung function, and greater airway wall thickness.



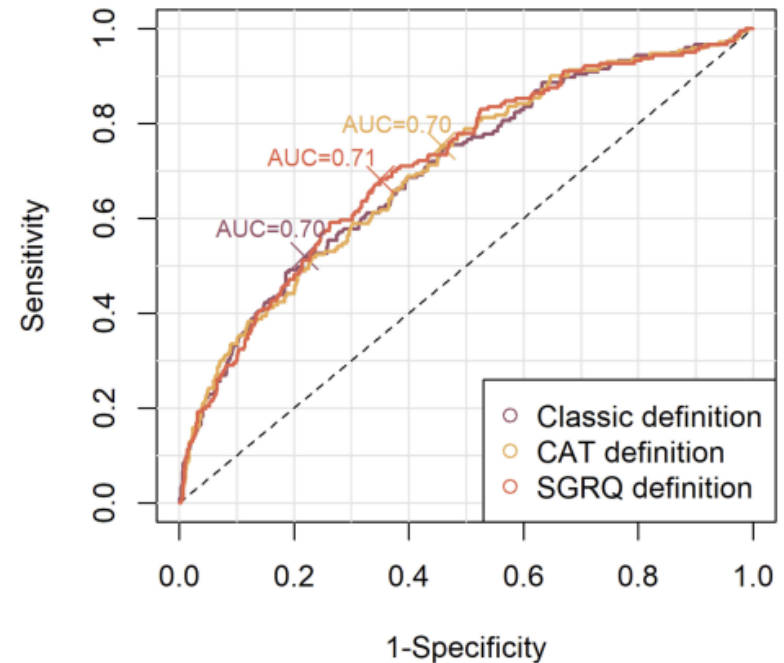


Chronic bronchitis (CB)

N=2,694 patients from KOCOSS

		점수					
나는 전혀 기침을 하지 않는다	0 1 2 3 4 5	나는 항상 기침을 한다					
나는 가슴에 전혀 가래가 없다	0 1 2 3 4 5	나는 가슴에 가래가 가득 차 있다					
나는 전혀 가슴이 답답함을 느끼지 않는다	0 1 2 3 4 5	나는 가슴이 아주 답답함을 느낀다					
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다	0 1 2 3 4 5	나는 언덕이나 계단을 오를 때 아주 숨이 차다					
나는 집에서 활동하는데 전혀 제약받지 않는다	0 1 2 3 4 5	나는 집에서 활동하는데 많은 제약을 받는다					
폐질환에도 불구하고 나는 외출하는데 자신이 있다	0 1 2 3 4 5	폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다					
나는 잠을 깊게 잔다	0 1 2 3 4 5	폐질환으로 인하여 나는 잠을 깊게 자지 못한다					
나는 기운이 왕성하다	0 1 2 3 4 5	나는 전혀 기운이 없다					

CAT 1 (cough) & 2 (sputum) scores ≥ 3





Summary

**PRO in GOLD
guideline**

Already

How to evaluate

**mMRC/CAT
Each item**

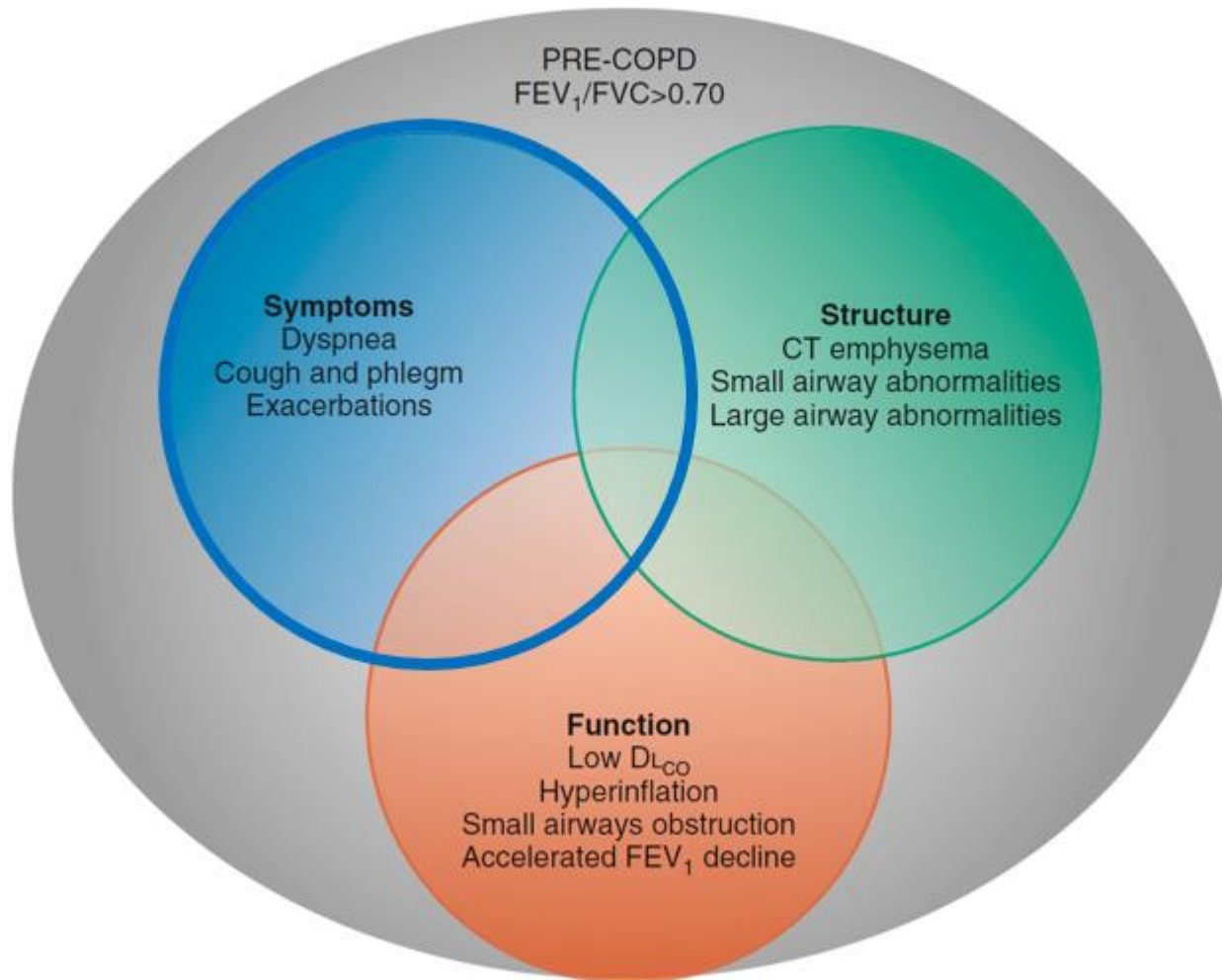
What to expect

Outcomes

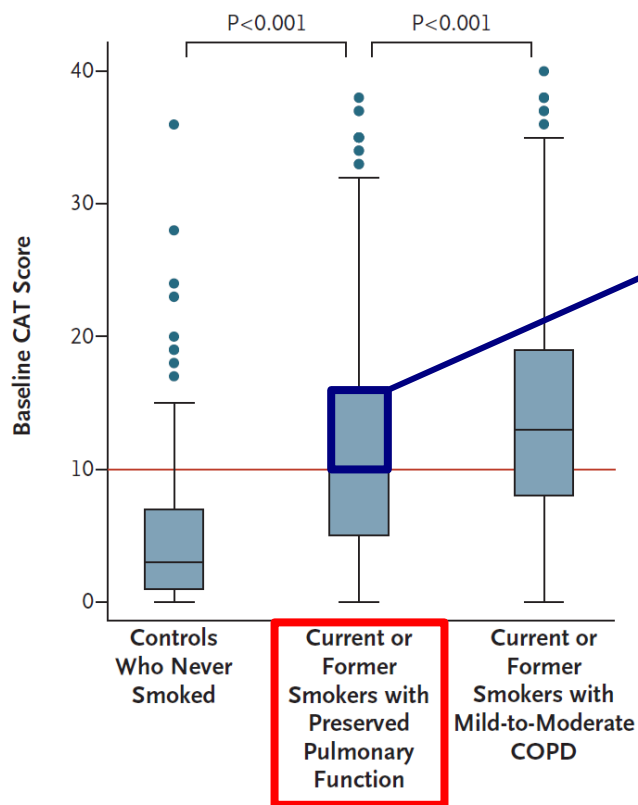
경청해 주셔서
감사합니다.



Concept of Pre-COPD



Symptomatic smoker with normal PFT



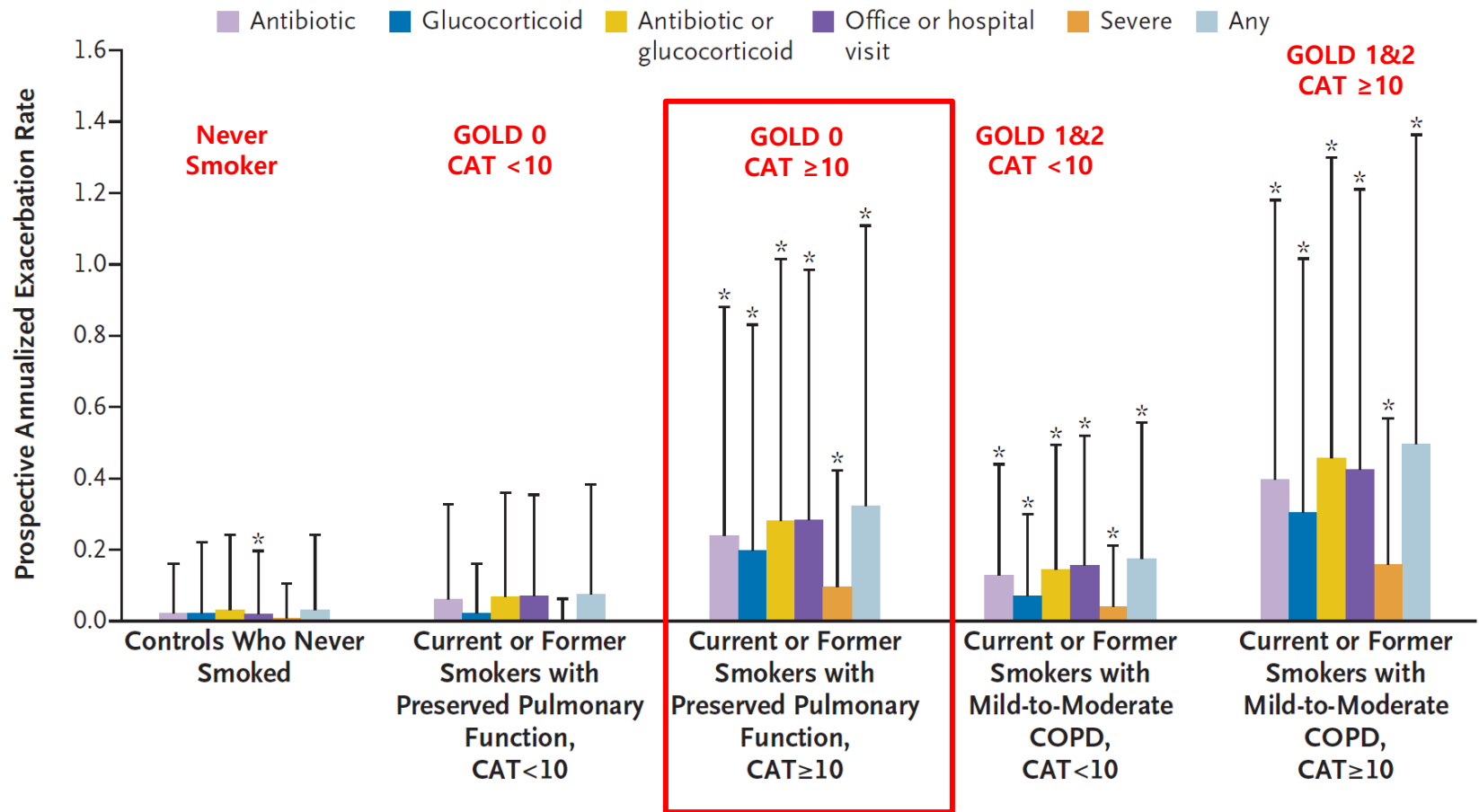
- SPIROMICS (N = 2,736) between 2010 – 2015

Smoker with preserved lung function
CAT ≥ 10 (vs. CAT < 10)

- ✓ More respiratory exacerbations
- ✓ Shorter 6MWD
- ✓ Evidence of occult airway disease (e.g., $FEV_1 \downarrow$, $FVC \downarrow$, and inspiratory capacity \downarrow)
- ✓ Airway wall thickening



Symptoms and Risk of Respiratory Exacerbations





Contents

PRO in GOLD guideline

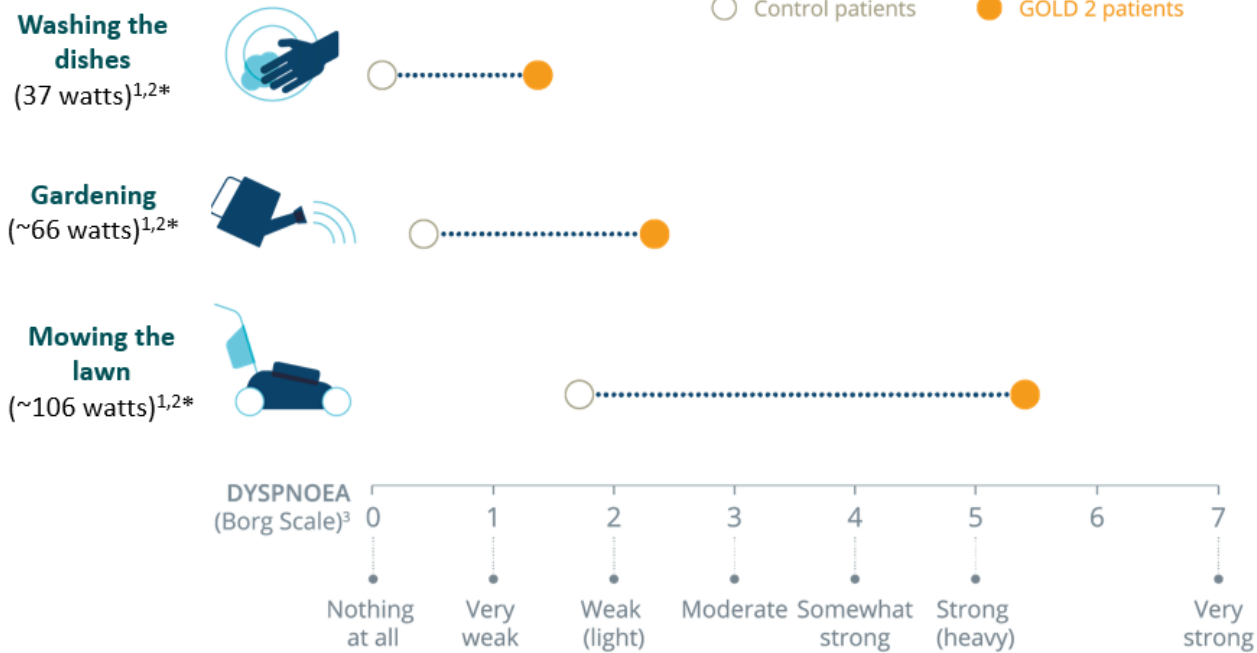
How to evaluate

How to improve



Dyspnea

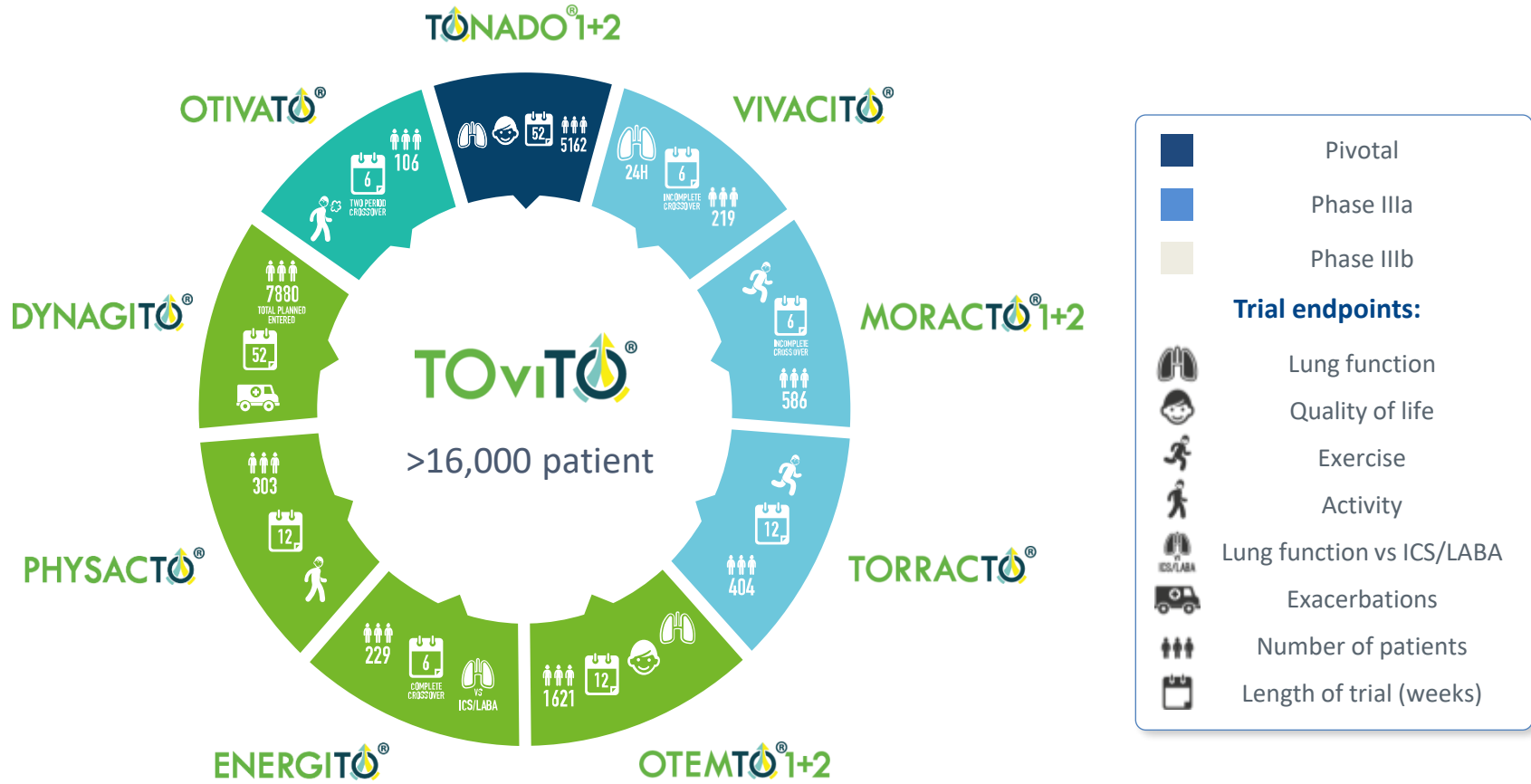
Dyspnea is a hallmark of COPD which impacts on day-to-day lives



The majority of patients with COPD experience **breathlessness, often to a severe degree**, and this impacts their ability to carry out daily activities^{4,5}



TOviTO[®] phase III clinical trial

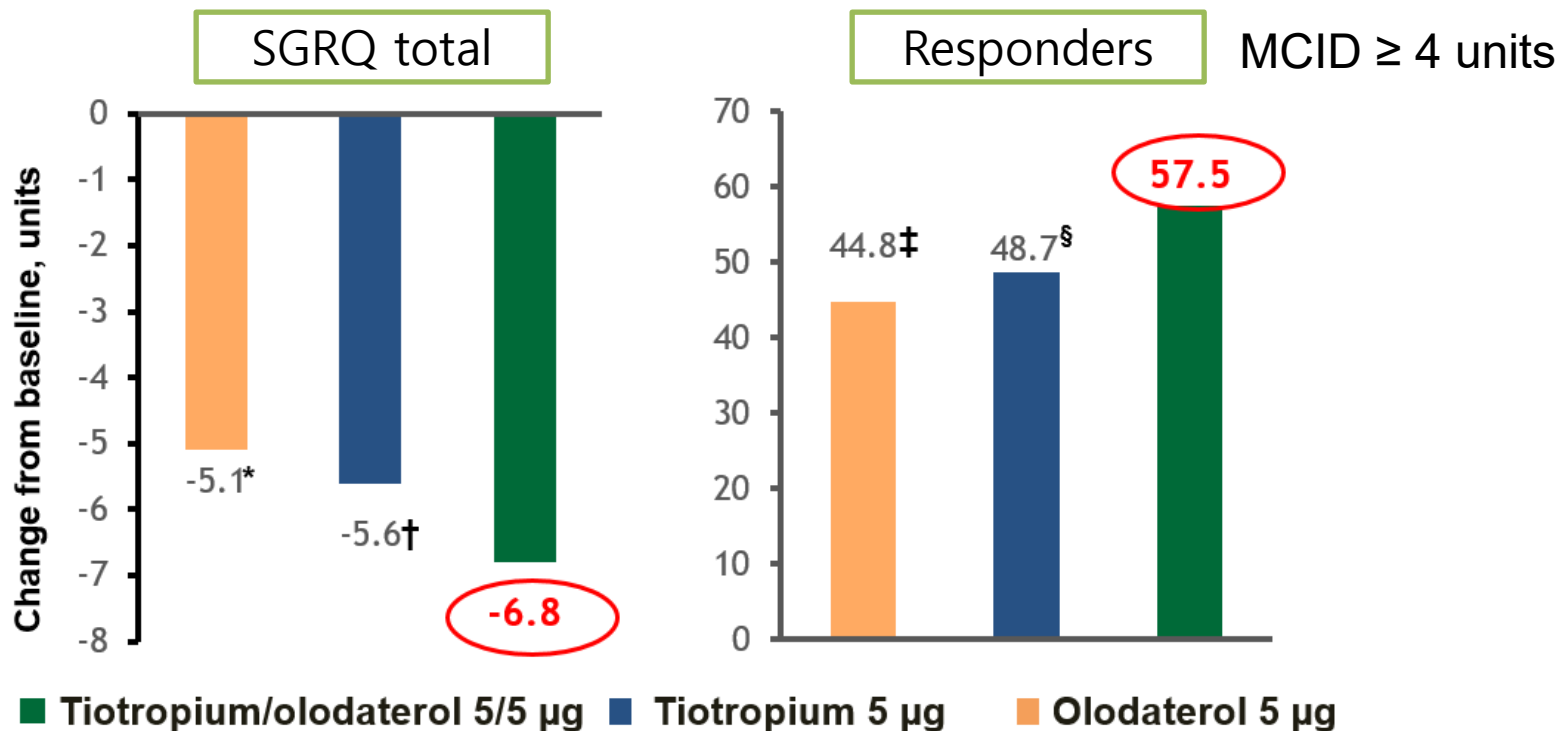


1. Buhl RM, et al. *Eur Respir J* 2015; 45: 969-979; 2. Ferguson GT, et al. *Adv Ther* 2015; 32: 523-536; 3. Beeh KM, et al. *Pulm Pharmacol Ther* 2015; doi:10.1016/j.pupt.2015.04.002; 4. Singh D, et al. *Respir Med* 2015; doi: 10.1016/j.rmed.2015.08.002



SGRQ at week 24

Significant improvements for tiotropium+olodaterol FDC 5/5 µg over corresponding individual component

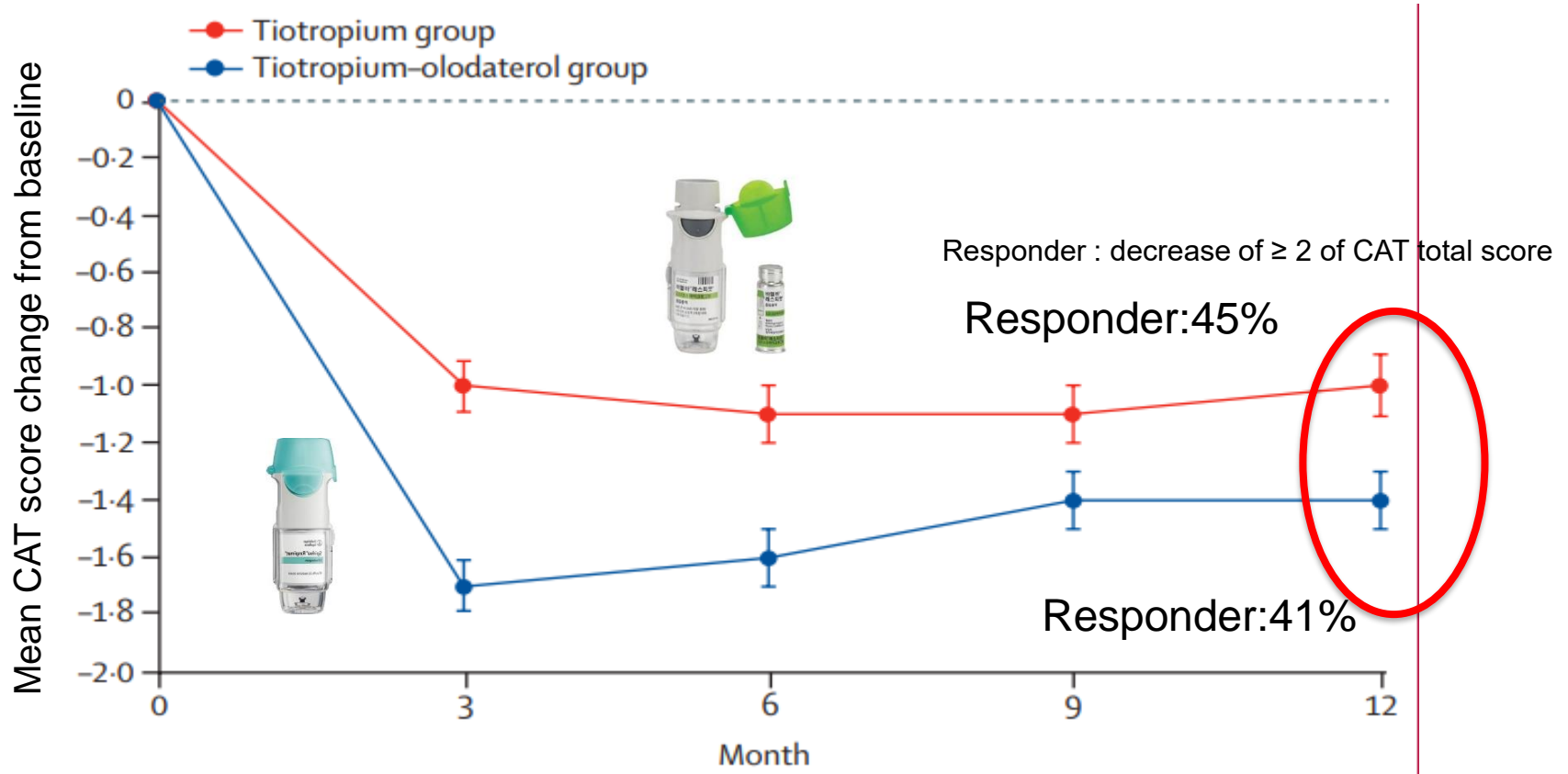


*p=0.0022 vs tiotropium/olodaterol 5/5 µg; †p=0.025 vs tiotropium/olodaterol 5/5 µg;
 ‡p<0.0001 vs tiotropium/olodaterol 5/5 µg; § p=0.001 vs tiotropium/olodaterol 5/5 µg.



CAT at week 52

COPD Assessment Test™ (CAT) score at clinic visits
– treatment comparison by visit

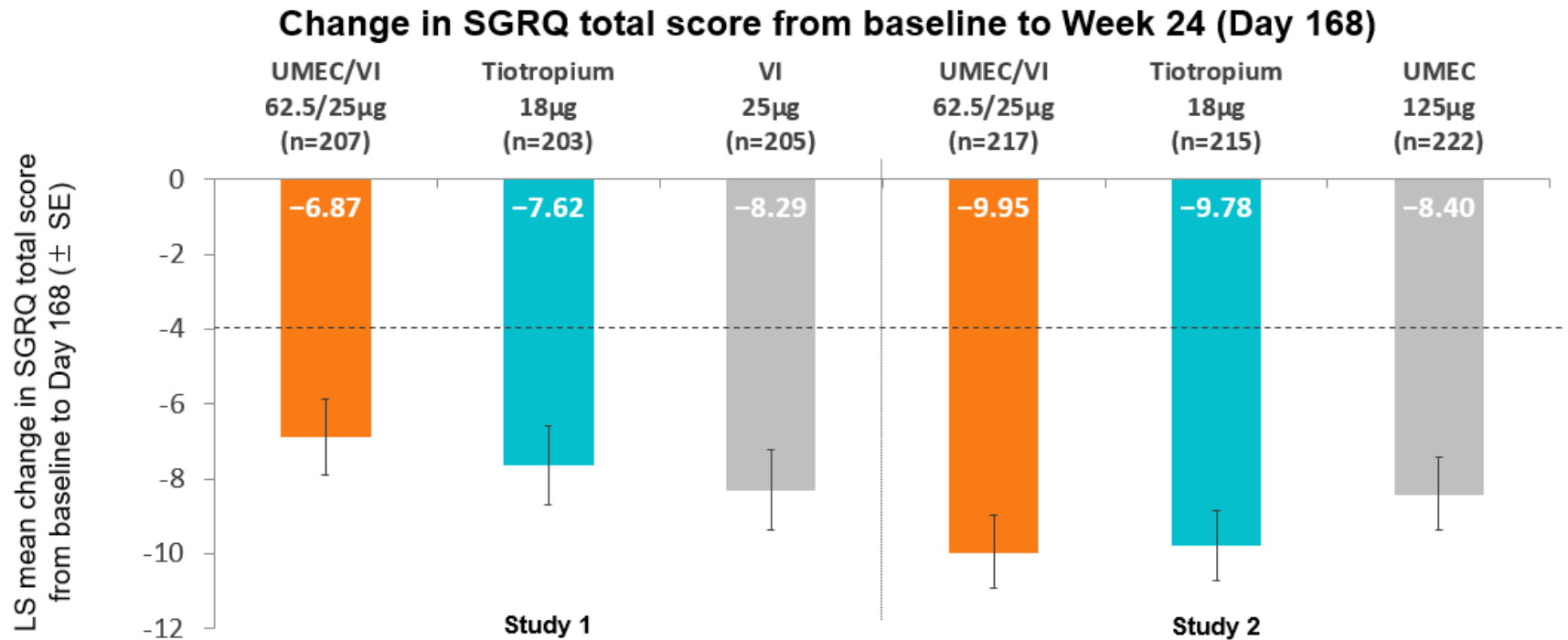




LAMA/LABA vs. TIOT

- 2,332 COPD patients & Primary outcomes: Trough FEV₁ response

No difference in improvement of SGRQ score with UMEC/VI vs TIO from Decramer study



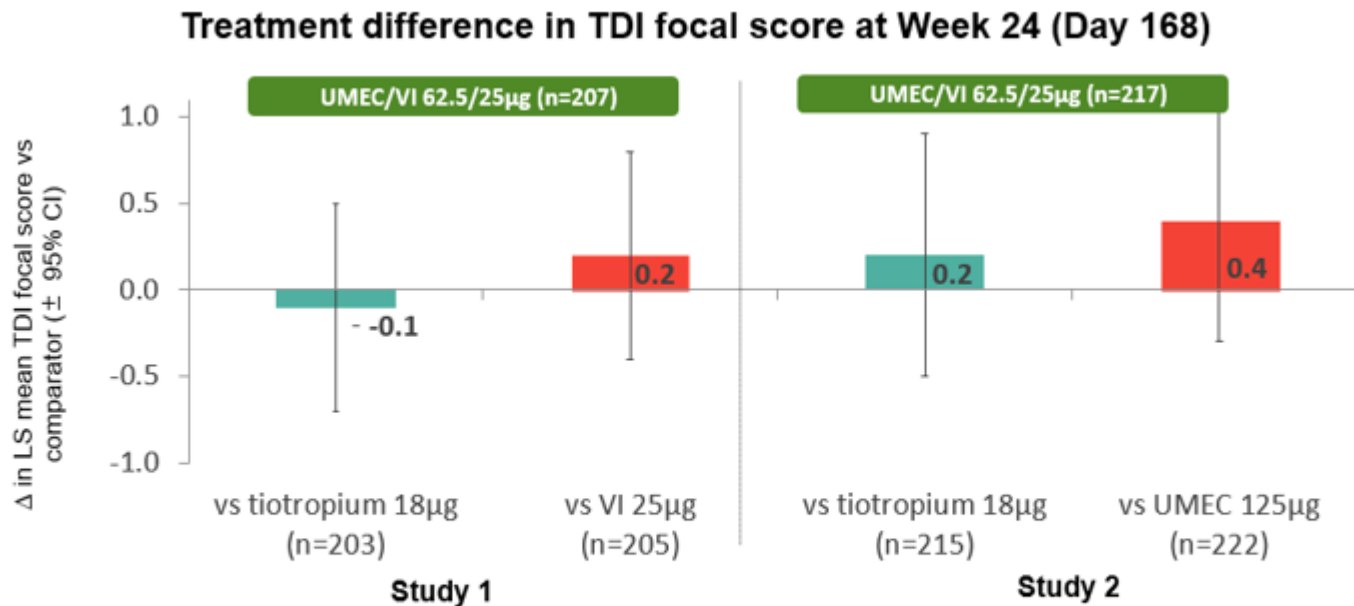
- The LS mean change from baseline for all treatments met or exceeded the MCID of -4.0 points at Week 24^{1,2}



LAMA/LABA vs. TIOT

- 2,332 COPD patients & Primary outcomes: Trough FEV1 response

No difference in TDI score between UMEC/VI vs TIO in Decramer study



- All treatments improved breathlessness, with an increase from baseline greater than the MCID of 1.0 unit
- The odds of being a TDI responder* were no different for UMEC/VI than for tiotropium monotherapy (OR: 0.9 and 1.3 in Study 1 and Study 2, respectively)



M/62

Initial visit for dyspnea on exertion
 mMRC Gr I, no previous AE, no BA
 Current smoker 1 pack/day x 42 yrs



3 months later

"I feel much better, I can walk further"
 0.5 pack/day

상태 (Good)	점수						
	0	1	2	3	4	5	
Cough				3			나는
Mucus				3			나는 있다
Chest Tightness				3			나는 느낀
Breathless						5	나는 때
Activities		1					나는 제한
Confidence		1					폐 질 환 하 는
Sleep			2				폐 질 환 이
Energy				3			나는
CAT Score : 21							

상태 (Good)	점수						상태 (Poor)
	0	1	2	3	4	5	
나는 전혀 기침을 하지 않는다.				3			나는 항상 기침을 한다.
나는 가슴에 전혀 가래가 없다.			2				나는 가슴에 가래가 가득 차 있다.
나는 전혀 가슴이 답답함을 느끼지 않는다.		1					나는 가슴이 아주 답답함을 느낀다.
나는 언덕이나 계단을 오를 때 전혀 숨이 차지 않는다.			2				나는 언덕이나 계단을 오를 때 아주 숨이 차다.
나는 집에서 활동하는데 전혀 제한을 받지 않는다		1					나는 집에서 활동하는데 많은 제한을 받는다.
폐질환에도 불구하고 나는 외출에 자신이 있다.		1					폐질환으로 인하여 나는 외출하는데 전혀 자신이 없다.
나는 잠을 깊이 잔다.		1					폐질환으로 인하여 나는 잠을 깊이 자지 못한다.
나는 기운이 왕성하다.		1					나는 전혀 기운이 없다.
CAT Score : 12							

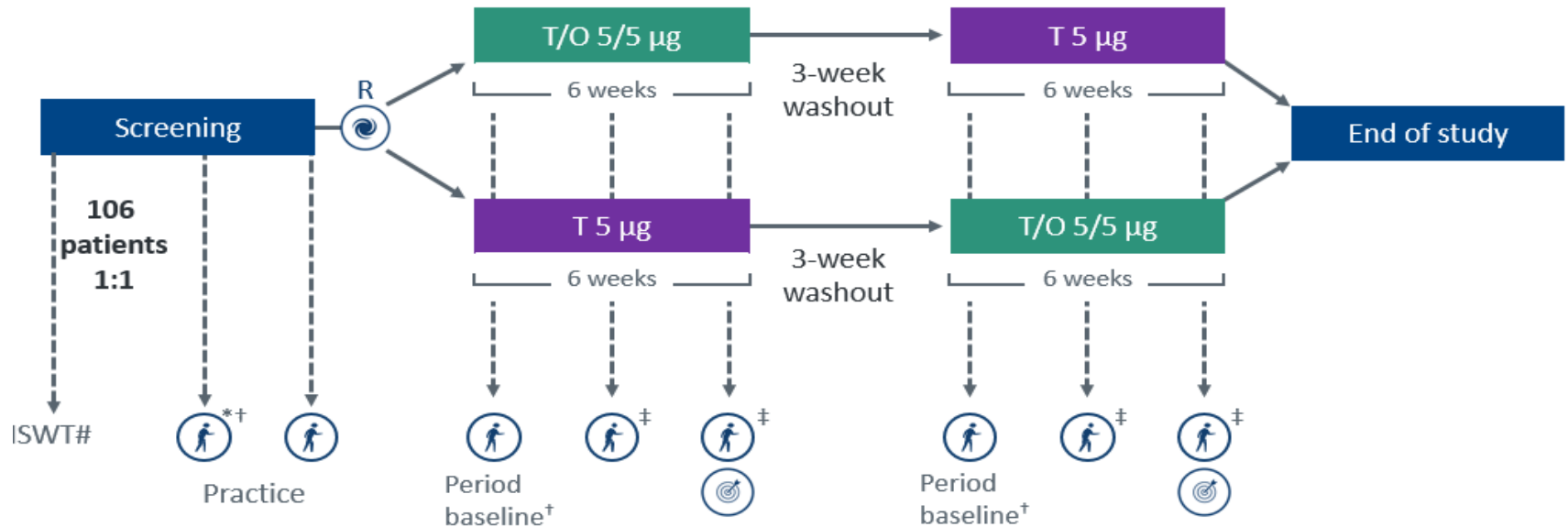
FEV₁: 1.94L, 54%/2.15L, 60% pred

FEV₁: 2.47L, 71% pred



OTIVATO®: Trial design

Double-blind, randomised, active comparator-controlled, two-period, crossover trial
 Primary outcome: Breathlessness at end of 3-min walking test (Borg scale)



LEGEND



3-min CSST (walking test)

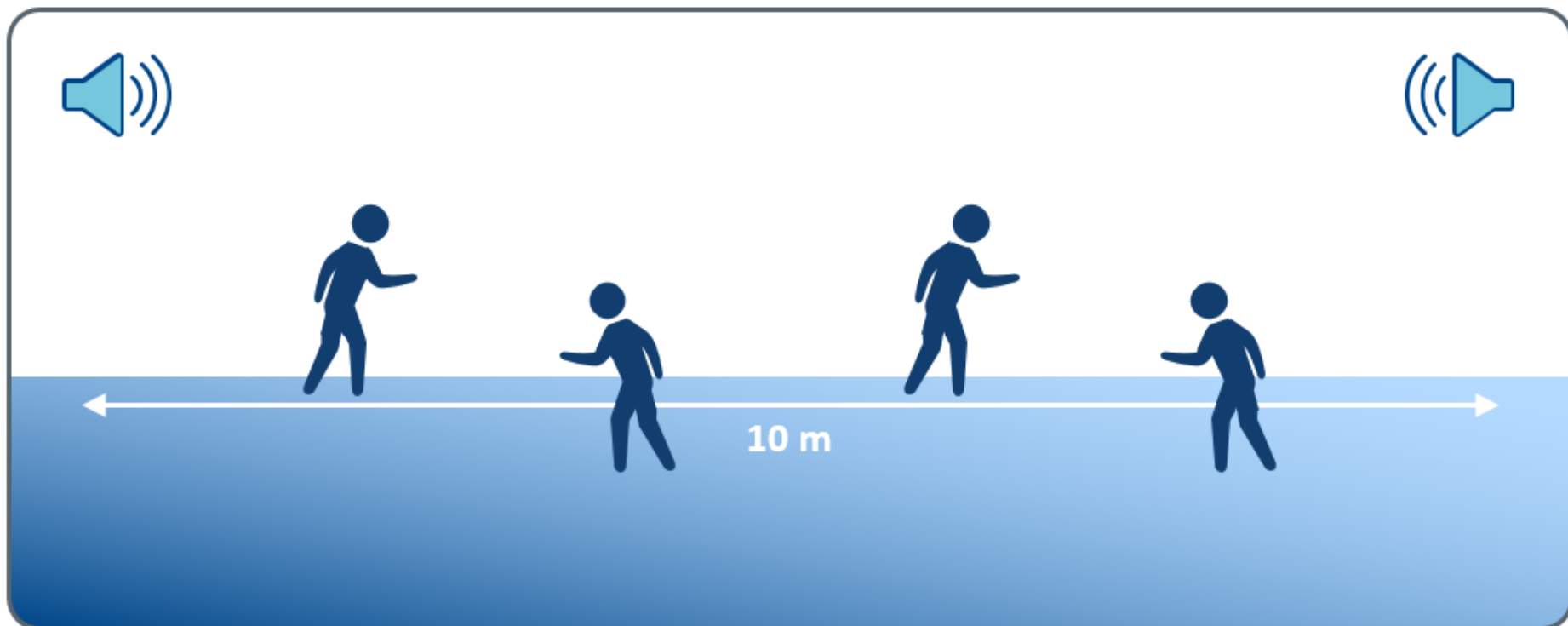


Primary endpoint (after 6 weeks)

Incremental Shuttle Walking Test, *Speed determination based on the individual level of each patient, ⁺prior to dosing. [‡]CSST was conducted 2 hours (+15 minutes) after inhalation of the study medication.



Method: 3-min constant speed shuttle test (walking test)

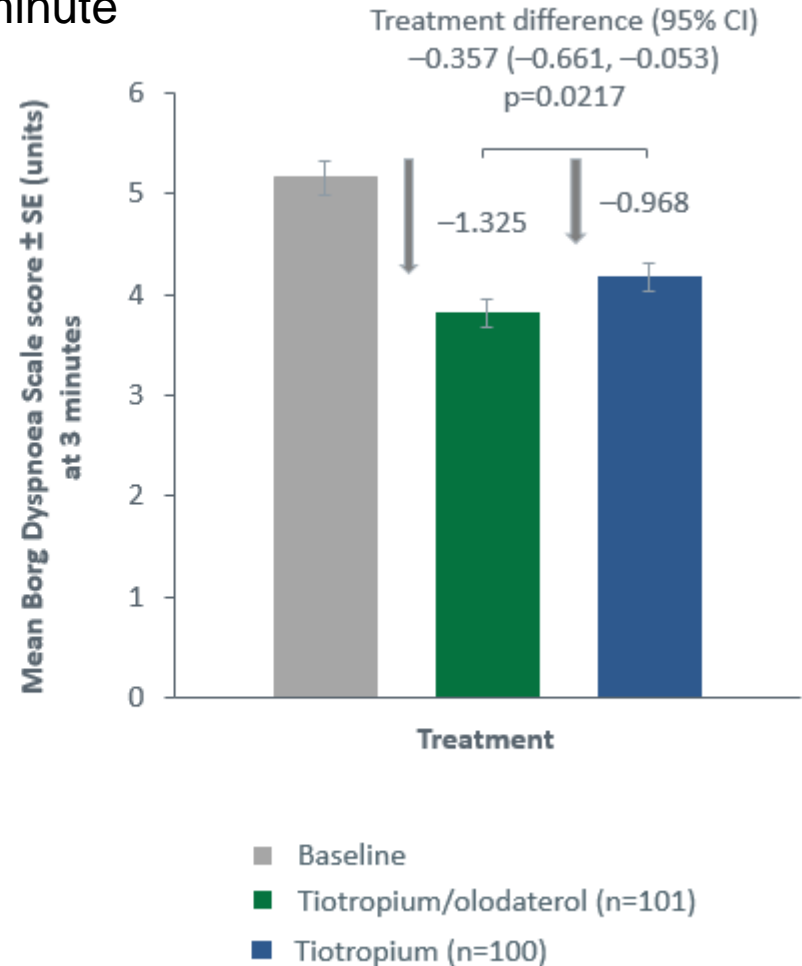
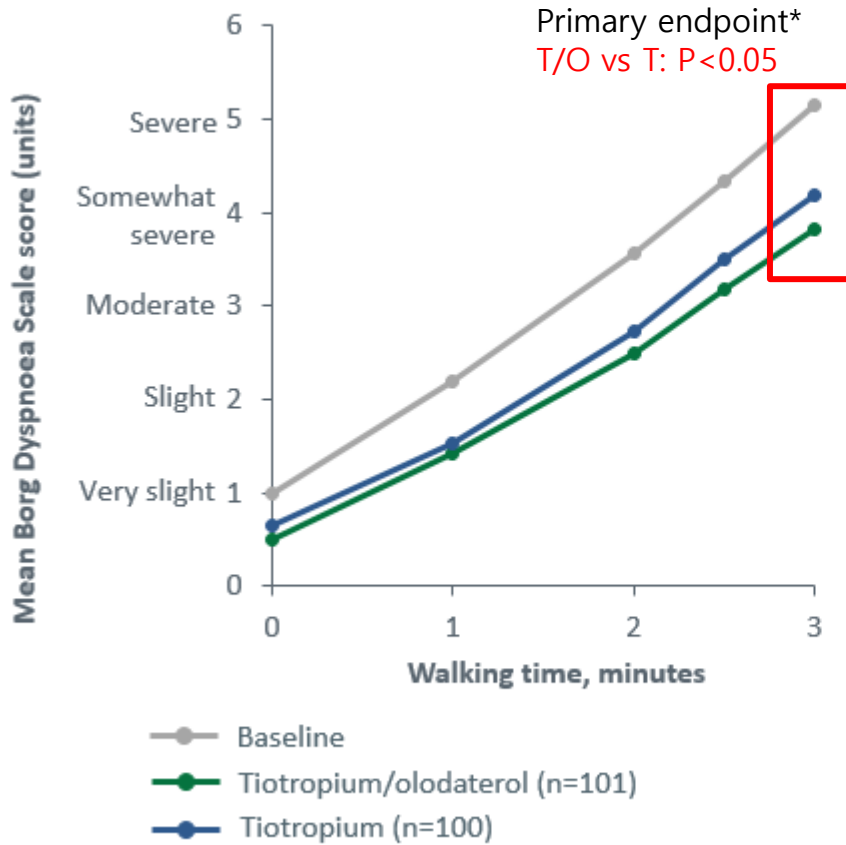


- Patients walk (or jog) back and forth for 3 minutes, keeping pace with the pre-recorded audio signal, completing a turn at each audio signal.
- Patients move at a speed that causes breathlessness, determined at baseline for each patient.
- Before, during and at the end of the test, patients report intensity of breathlessness.



OTIVATO®: Trial design

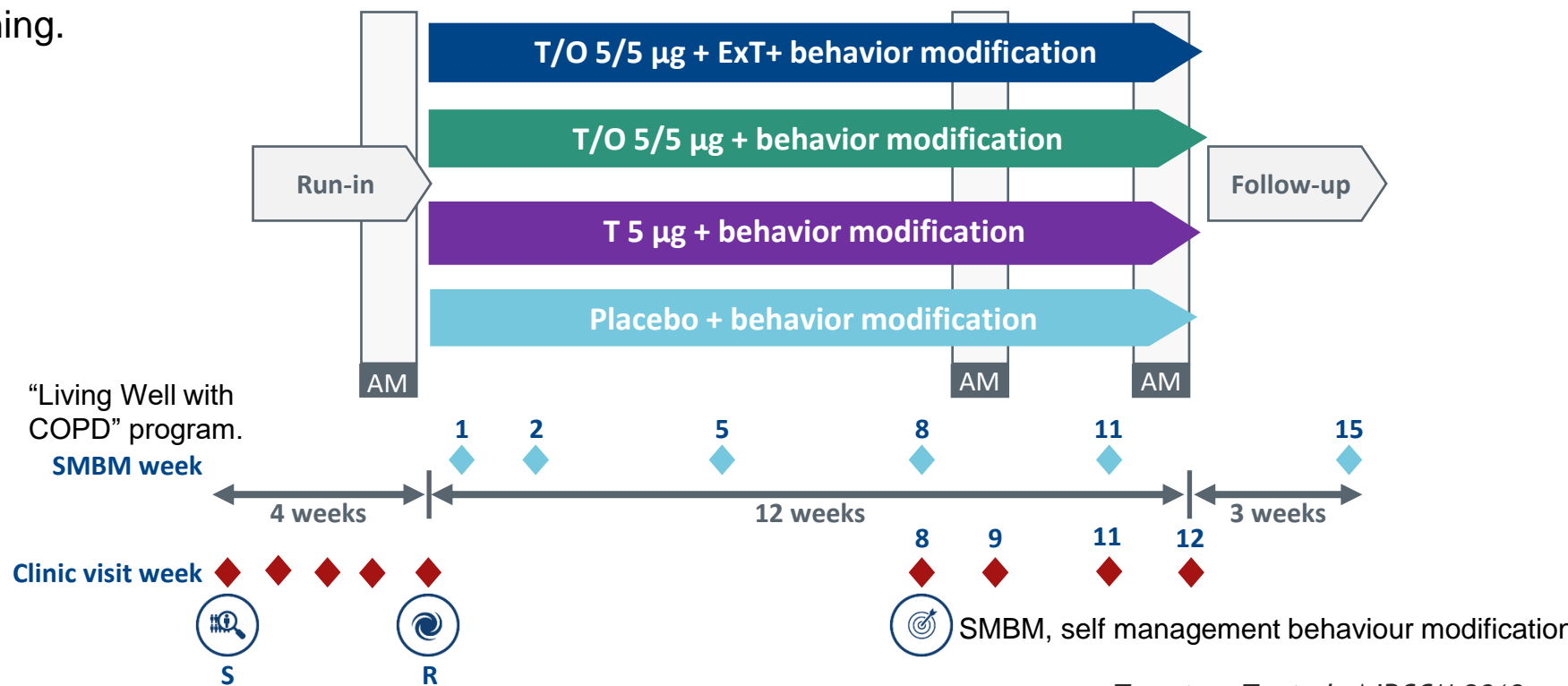
After 6 weeks, tiotropium/olodaterol reduced breathing discomfort during and after the 3-minute constant speed shuttle test vs tiotropium





Exercise: MORATO, TORRACTO, **PHYSACTO**, OTIVACTO

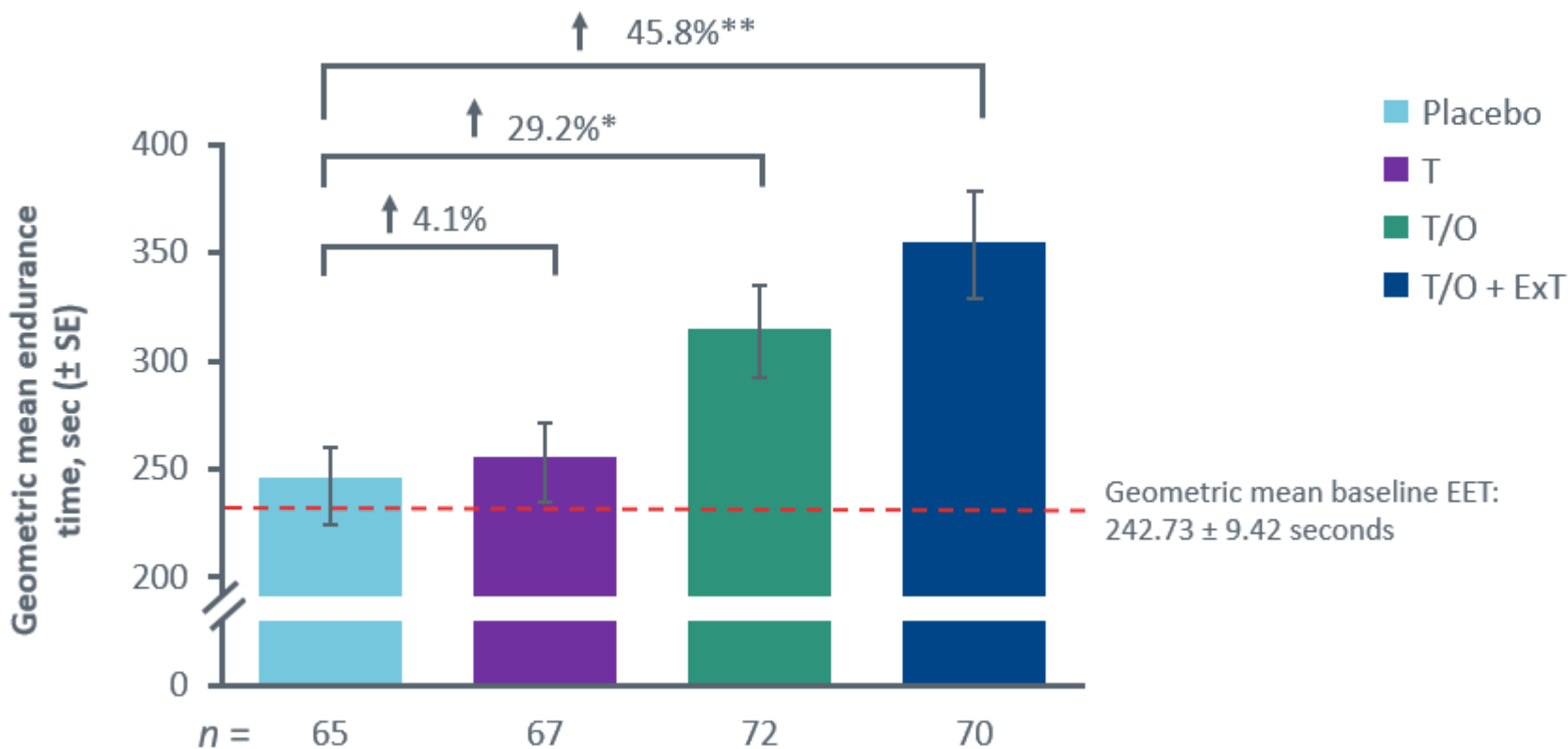
- 303 COPD Patients (post BD $30\% \leq FEV_1 < 80\%$ pred)
- Primary outcomes: **Exercise endurance time (EET) during endurance shuttle walk test at 8 wks**
- ExT arm was conducted three times per week for 8 weeks; each session included 30 minutes of aerobic exercise (cycling or walking) and 45 minutes of upper and lower limb resistance training.





Tiotropium/olodaterol plus behaviour modification increased EET vs placebo

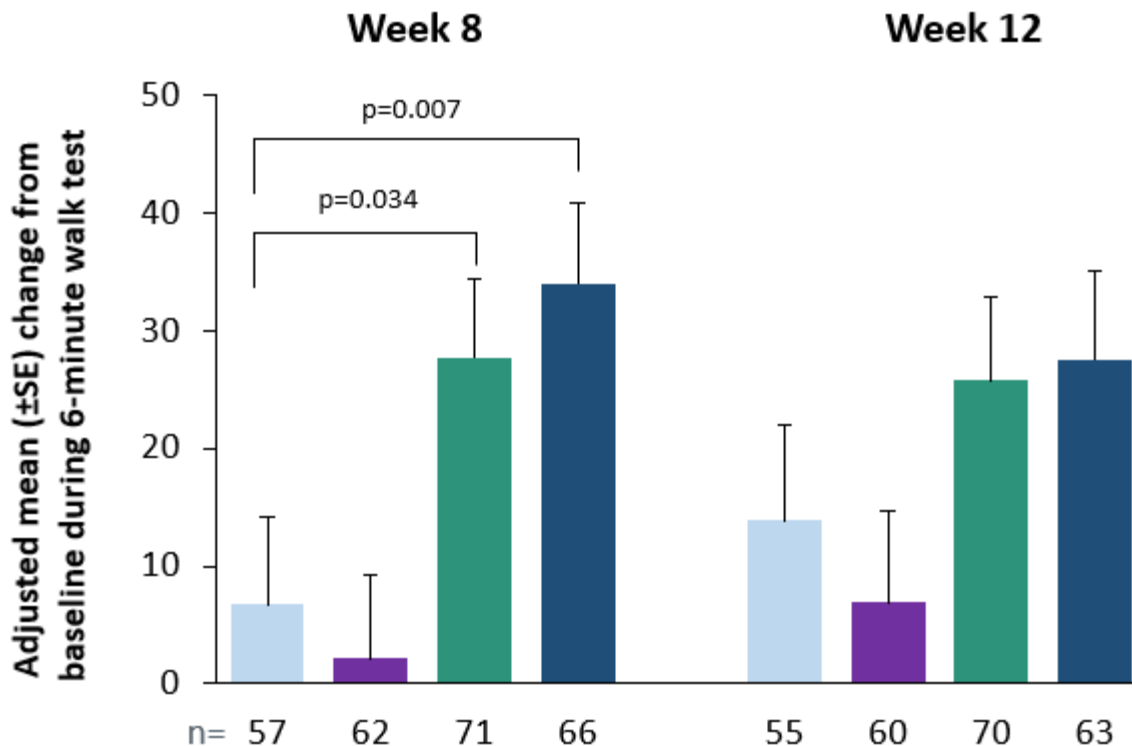
Mean exercise endurance time (EET) during Endurance shuttle walk test results after 8 weeks





Tiotropium/olodaterol plus behaviour modification increased EET vs placebo

Improvements in mean distance walked during the 6-minute walk test with tiotropium/olodaterol 5/5µg





Summary

PRO in GOLD
guideline

Already

How to evaluate

mMRC/CAT
Each item

How to improve

Tio/Olo+Ex

**Thank You
For Your Attention**





EXACT-PRO

Did your chest feel **congested** today

How **often** did you **cough** today?

How **much mucus** (phlegm) did you bring up when coughing today?

How **difficult** was it to bring up mucus (phlegm) today?

Did you have chest **discomfort** today?

Did your chest feel **tight** today?

Were you **breathless** today?

Describe **how breathless** you were today

Were you short of breath today when performing your usual **personal care activities** like washing or dressing?

Were you short of breath today when performing your usual **indoor activities** like cleaning or household work?

Were you short of breath today when performing your usual **activities outside** the home such yard work or errands?

Were you **tired** or **weak** today?

Last night, was your **sleep disturbed**?

How **scared** or **worried** were you about your lung problems, today?

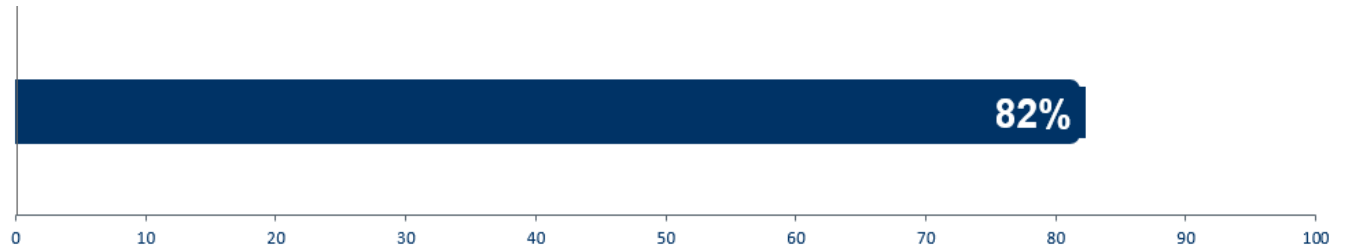


Dyspnea/Exacerbations

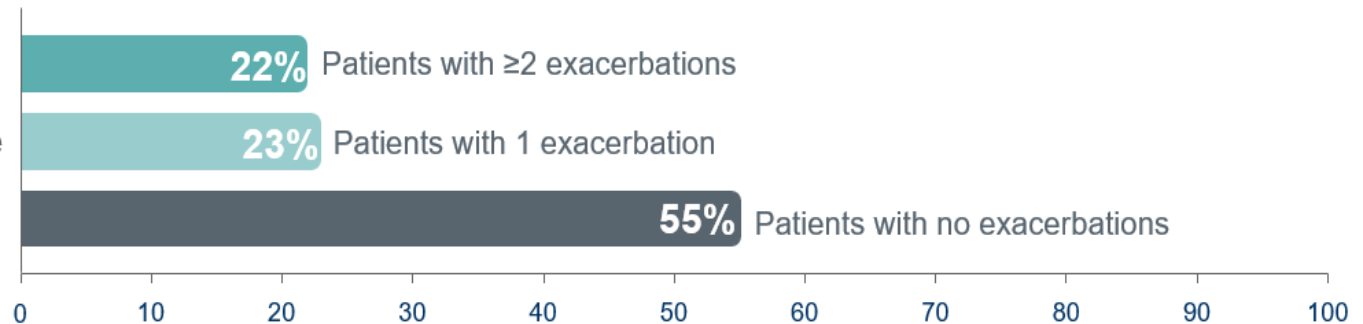
Dyspnea is a common experience in COPD patients whereas exacerbation rate may vary



Proportion of patients with any MRC dyspnoea grade recorded (N=40,425)¹



1-year exacerbation rates in GOLD stage 2 patients (N=945)²



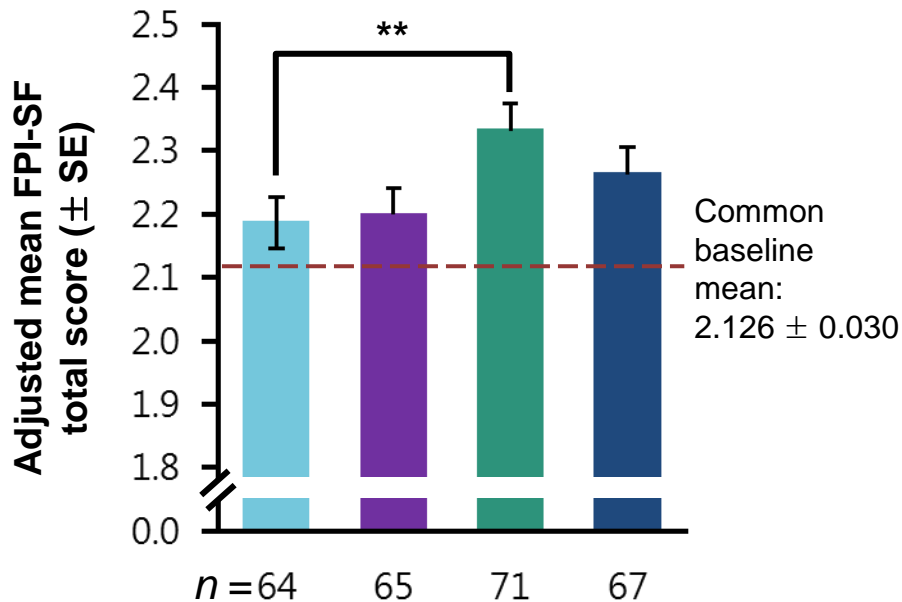
1. Müllerová H, et al. PLoS One 2014; 9: e85540; 2. Hurst JR, et al. N Engl J Med 2010; 363: 1128-1138

Activity-related breathlessness

T/O (\pm ExT) improved activity-related breathlessness and difficulty compared with placebo

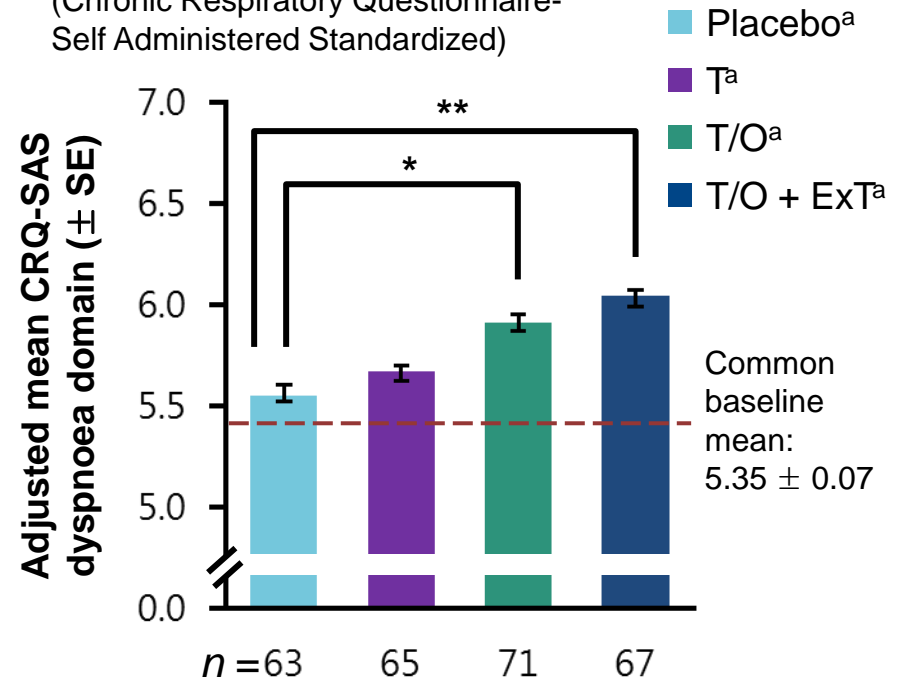
Secondary endpoint: Adjusted mean FPI-SF total score at Week 12

(Functional Performance Inventory Short Form)



Further endpoint: Adjusted mean CRQ-SAS dyspnoea domain at Week 12

(Chronic Respiratory Questionnaire-Self Administered Standardized)



Summary

T/O, alone or with ExT, reduced activity-related breathlessness and patient-reported difficulty more than placebo



T/O \pm ExT improved walking endurance time in patients with COPD



T/O compared with placebo reduced activity-related breathlessness and difficulty