Endpoints of Clinical Trials for COPD

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  - Physiologic marker: lung function decline
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  - Mortality
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- Future research about early intervention
- Summary

Goals for COPD treatment

Relieve symptoms

Improve exercise tolerance

Improve health status

→ **REDUCE SYMPTOMS**

Prevent disease progression

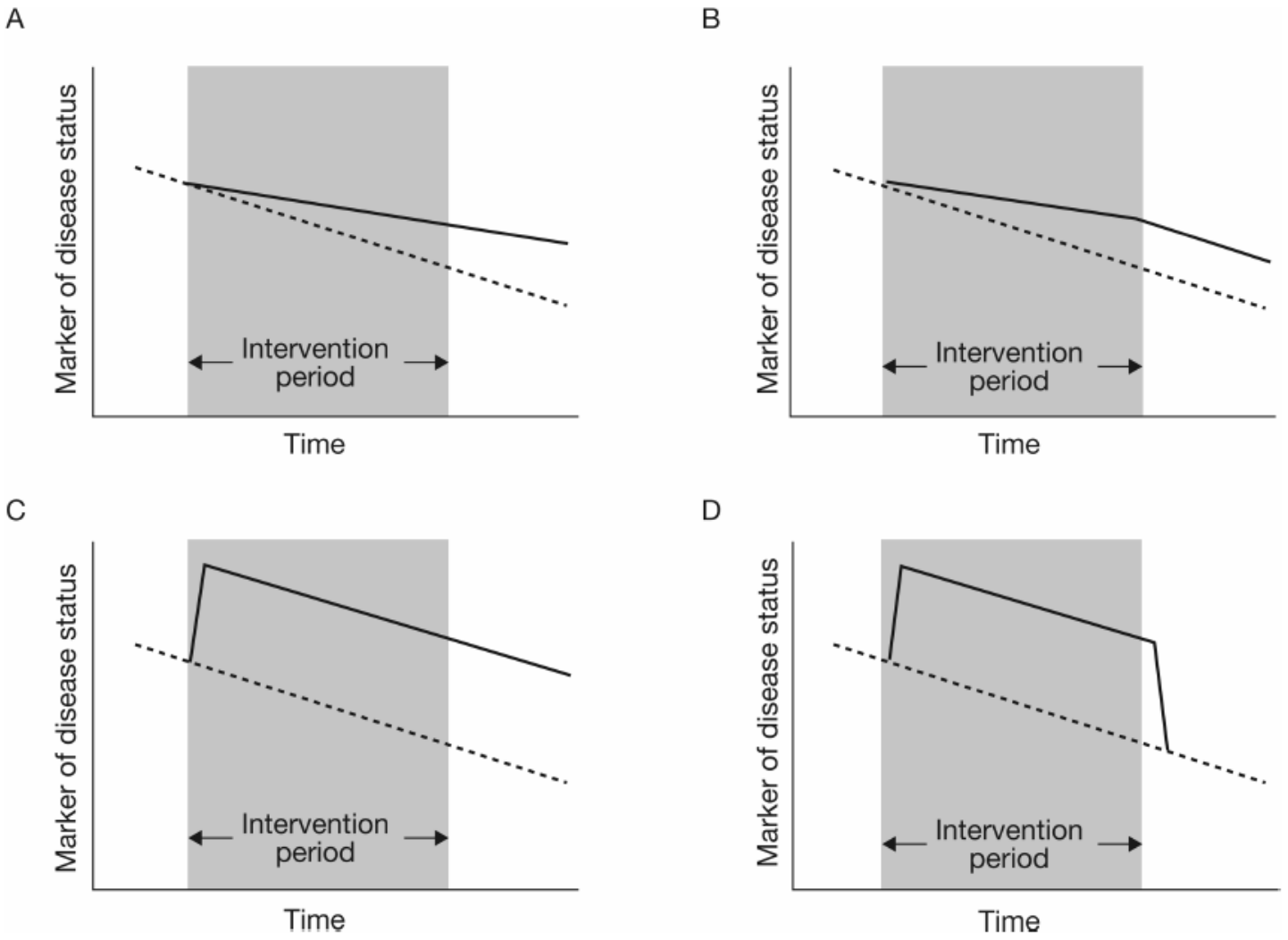
Prevent and Treat exacerbations

Reduce mortality

→ **REDUCE RISK**

→ Outcomes of clinical trials: Lung function, exacerbation, mortality, PRO

Effects of intervention on disease progression



David M.G.Halpin et al. COPD:J of COPD; 2009: 6: 211-225.

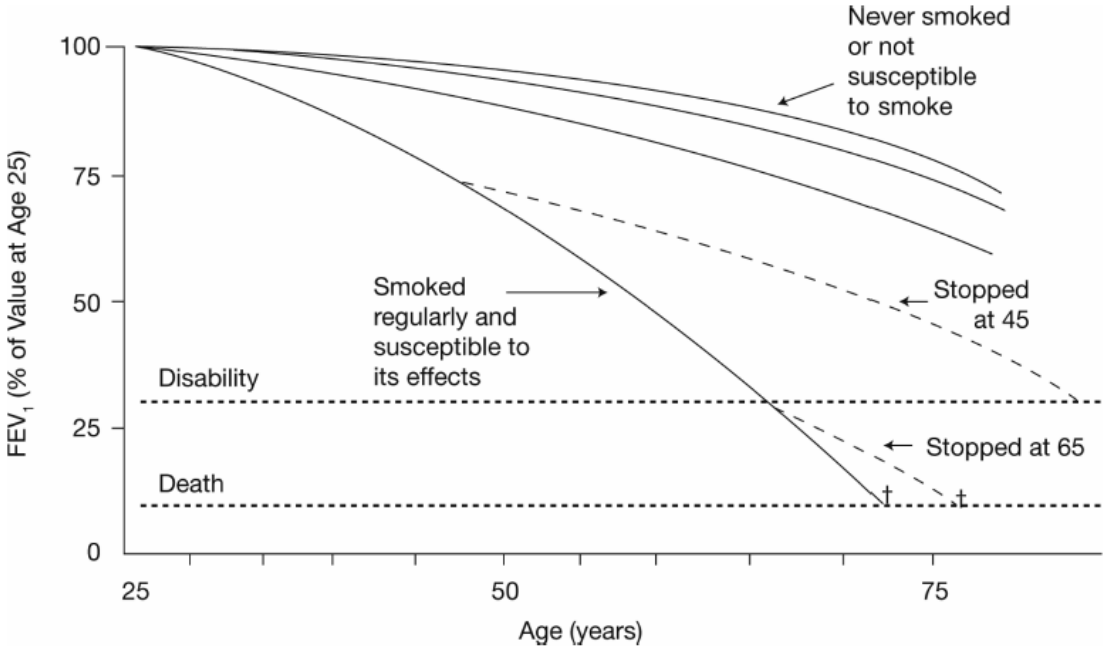
Key markers of disease modification in COPD

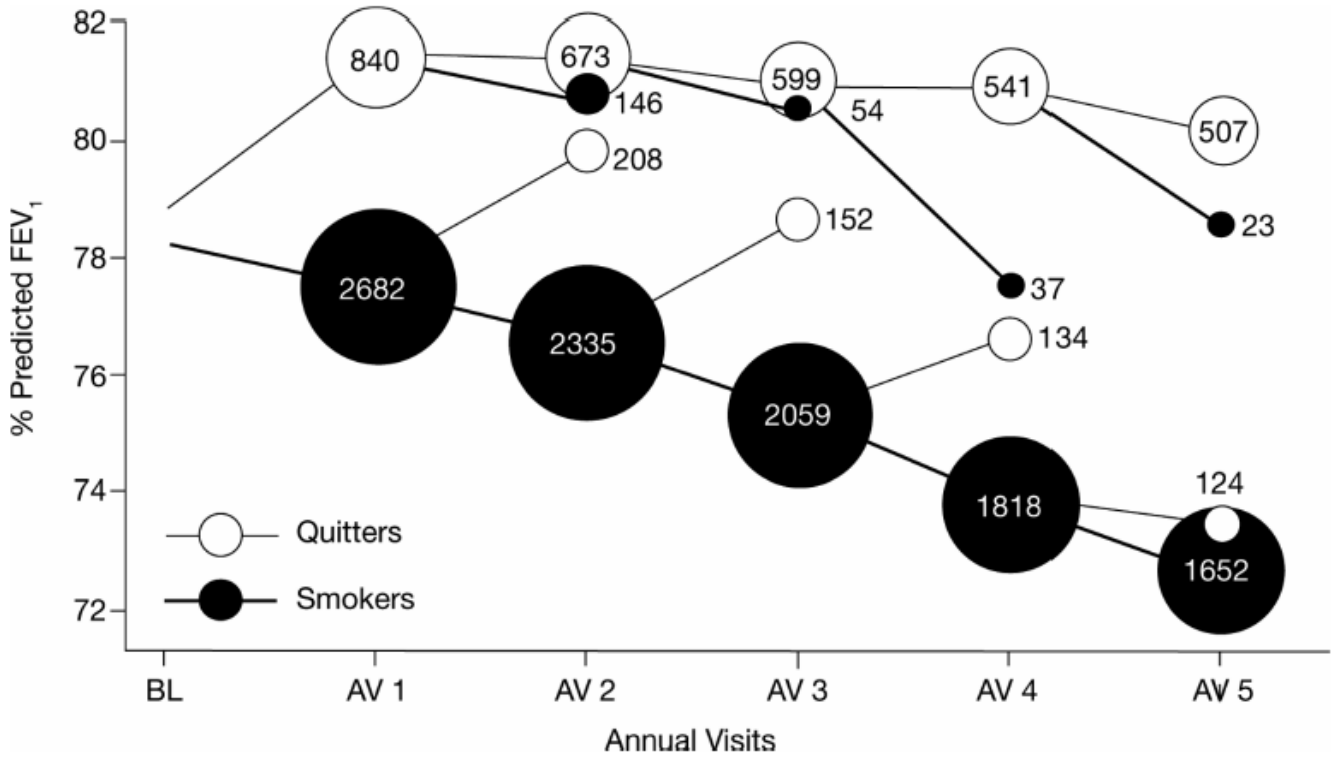
Outcome measures	Method	Outcome measures	Method
Pathophysiologic		**Patient-centered outcomes**	
Macrophages, neutrophils, CD4+ and CD8+, lymphocytes	BAL, endobronchial Bx.	Dyspnea	Baseline dyspnea index, TDI
Airway structural components	Transbronchial Bx.	Exercise capacity	6MWD
Cytokines, chemokines	Induced sputum	Health-related quality of life	SGRQ-c
NO, CO, Volatile hydrocarbons	Exhaled air	Exacerbations	Patient/physician report
Oxidative products, leukotrienes, cytokines, and pH	EBC	**Mortality**	
IL6, IL8, TNF-α, CRP	Plasma/serum sampling	Mortality rate	Physician report
Physiologic			
FEV1	Spirometry		

David M.G.Halpin et al. COPD:J of COPD; 2009: 6: 211-225.

Physiologic marker

Natural history of lung function decline & smoking



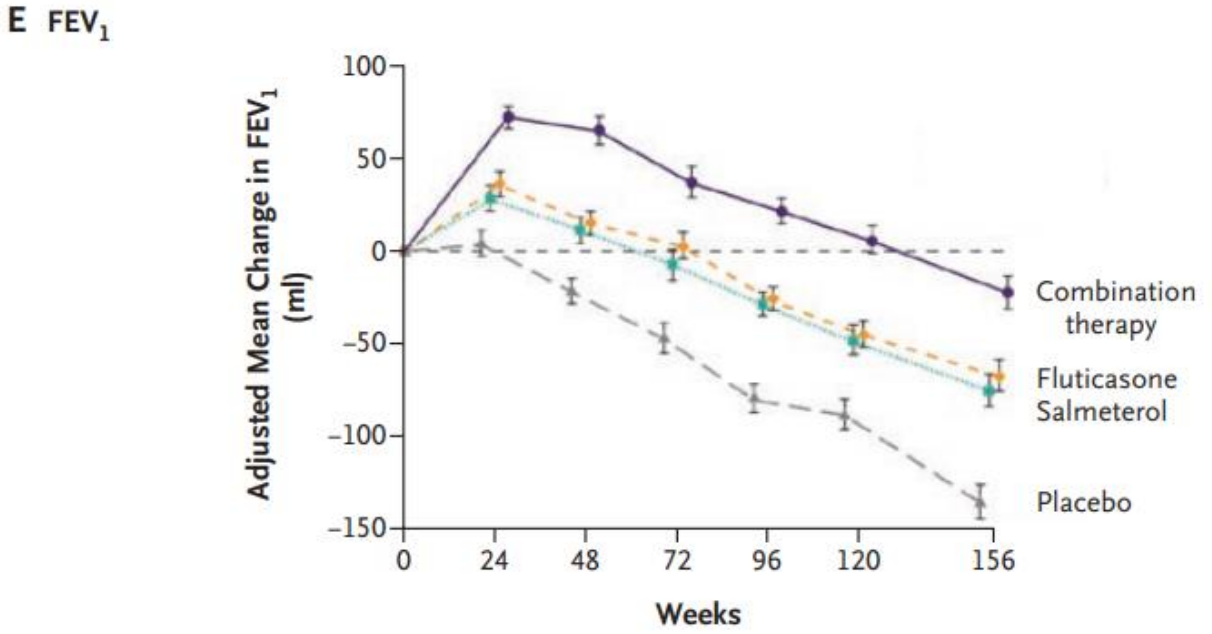


Smoking cessation ⇒ decrease the rate of lung function decline

Fletcher C, Peto R. BMJ. 1977; 1: 1645-1648.
Scanlon PD et al. Am J Respir Crit Care Med 2000; 161: 381-390.

Pharmacological intervention in TORCH study

- Randomized, double-blind trial comparing salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone **for a period of 3 years**.
- 40-80 yrs, at least 10yrs smoking history, FEV1 < 60% pred.
- **The primary outcome was death from any cause** for the comparison between the combination regimen and placebo
- The frequency of exacerbations, health status, and spirometric values were also assessed



No. of Patients							
Placebo	1524	1248	1128	1049	979	906	819
Salmeterol	1521	1317	1218	1127	1054	1012	934
Fluticasone	1534	1346	1230	1157	1078	1006	908
Combination therapy	1533	1375	1281	1180	1139	1073	975

-39mL/yr, p <0.001

-42mL/yr, p = 0.003

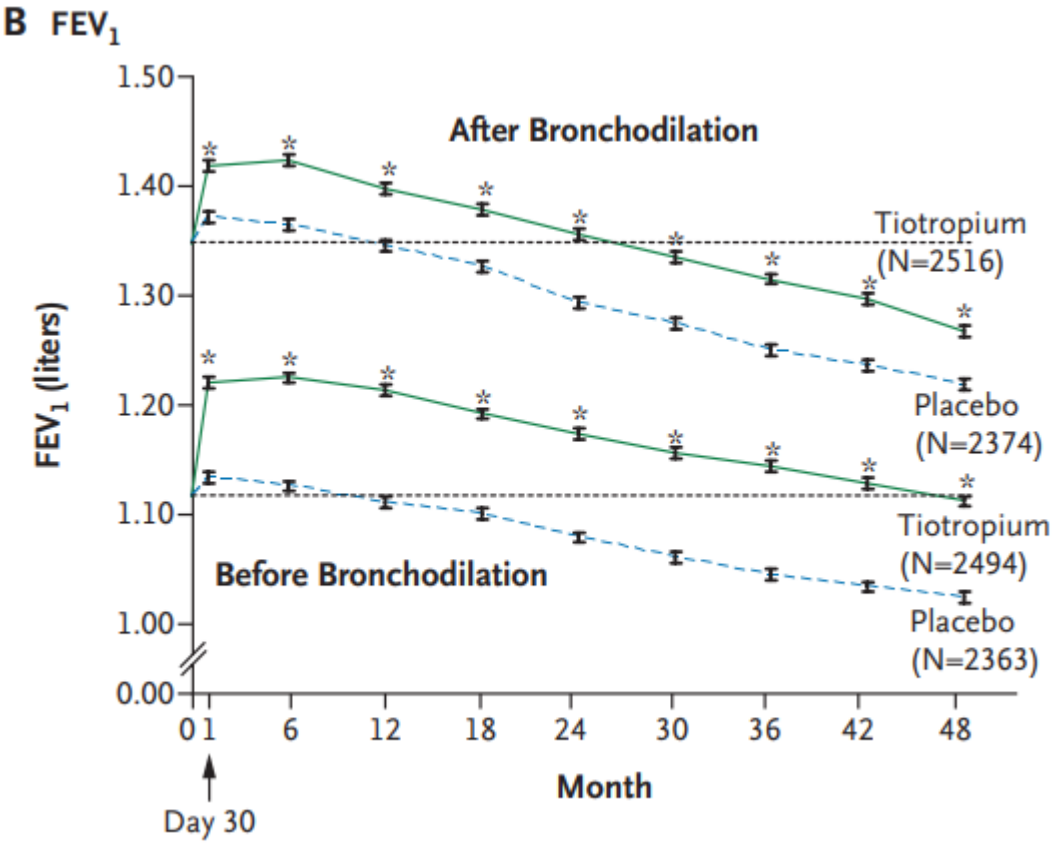
-42mL/yr, p = 0.003

-55mL/yr

Peter M.A. Calverley et al. N Engl J Med 2007;356:775-89.
Celli BR et al. Am J Respir Crit Care Med 2008; 178: 332-338.

Lung function change after 4-year tiotropium

- Randomized, double-blind trial, compare 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs.
- The patients were at least 40 yrs, with FEV1 < 70%, post BD FEV1/FVC < 70%
- **Coprimary end points** were the rate of decline in the mean FEV1 before and after bronchodilation beginning on day 30. **Secondary end points** included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality.



40±1 mL/yr

42±1 mL/yr

p = 0.21

30±1 mL/yr

30±1 mL/yr

p = 0.95

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

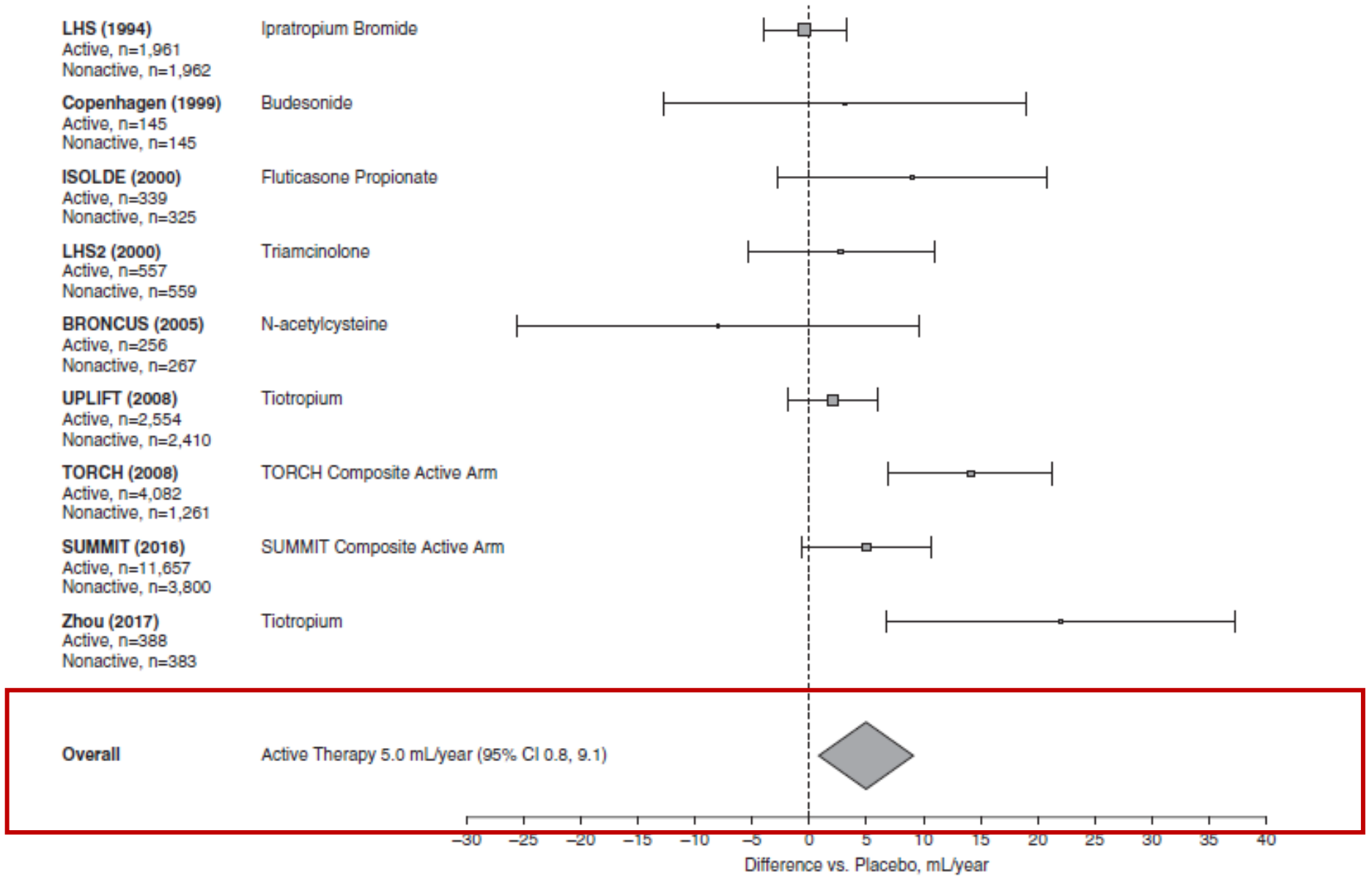
Pharmacotherapy and lung function decline from systematic review

- Systematic review of placebo-controlled pharmacological trials lasting >1 year to address the question of whether therapy alters FEV1 decline
- 33,051 patients in the analysis (active component, n = 21,941; placebo, n = 11,110 in nine studies)

	(1997–2003) BRONCUS* Ref 16	(1992–1998) ISOLDE* Ref 6	(2000–2005) TORCH* Refs 10 and 18	(2003–2008) UPLIFT* Ref 11	(1986–1994) Lung Health I* Ref 3	(2011–2015) Zhou *et al.** Ref 19	(2011–2015) SUMMIT* Refs 12 and 20	(1992–1994) Copenhagen City Lung Study* Ref 17	(1994–1999) Lung Health Triamcinolone* Ref 21
Treatment arms: placebo/**active intervention(s)**	Placebo/***N*-acetylcysteine**	Placebo/**fluticasone propionate**	Placebo/**salmeterol/fluticasone propionate/salmeterol + fluticasone propionate**	Placebo/**tiotropium**	Placebo/**ipratropium bromide**	Placebo/**tiotropium**	Placebo/**fluticasone furoate/vilanterol/fluticasone furoate + vilanterol**	Placebo/**budesonide**	Placebo/**triamcinolone acetonide**
Number of participants in study (*and in RoD analysis, if different*), (total) placebo/**total active intervention**	(523) 267/**256**	(751) 375/**376** *In RoD analysis*: (664) 325/**339**	(6,184) 1,545/**4,639** *In RoD analysis*: (5,343) 1,261/**4,082**	(5,992) 3,006/**2,986** *In RoD analysis*: (4,964) 2,410/**2,554**	(3,923) 1,962/**1,961**	(771) 383/**388**	(16,485) 4,111/**12,374** *In RoD analysis*: (15,457) 3,800/**11,657**	(290) 145/**145**	(1,116) 557/**559**
Age, mean, yr	62	64	65	65	48	64	65	59	56
Sex, F, *n* (%)	110 (21)	191 (25)	1,263 (24)	1,520 (25)	2,186 (37)	113 (15)	4,196 (25)	115 (40)	412 (37)
Smoking status current, %	46%	38%	44%	30%	NA	41%	47%	77%	90%
Previous year exacerbation hx, yearly rate	Placebo: 2.5 Active: 2.4	NA	0: 43% 1: 25% ⩾2: 32%	NA	NA	NA	0: 61% 1: 24% ⩾2: 15%	NA	NA
FEV_1, mean, L†	1.65	1.41	1.24	1.3	2.75	1.9	1.7	2.4	2.3
FEV_1, mean, % predicted	57	50	45	48	75	78	60	87	68
Study duration	3 yr	3 yr	3 yr	4 yr	5 yr	2 yr	1.8 yr‡	3 yr	40 mo§
Number of spirometric assessments	13	12	5	17	5	6	7‖	12	Every 6 mo¶
Completion of the study placebo/**total active intervention**	168/**186**	175/**212**	55%/**63%**	1,648/**1,887**	>94%**	282/**303**	2,919/**9,311**	94/**109**	92%

Celli BR et al. Am J Respir Crit Care Med 2020; 203(6): 689-698.

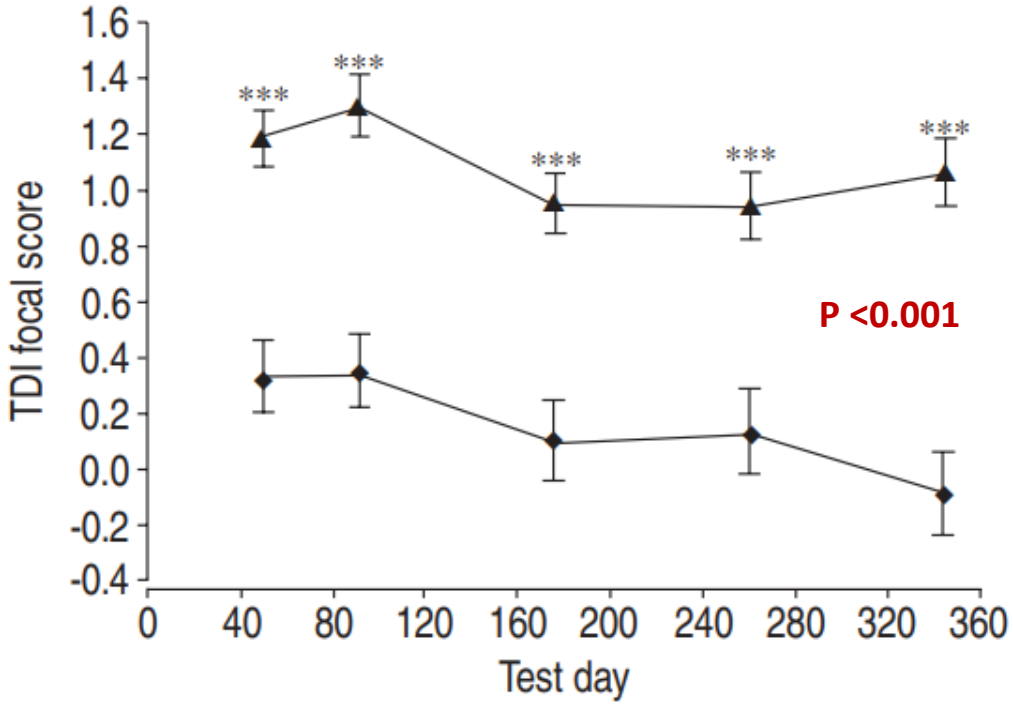
Physiologic marker

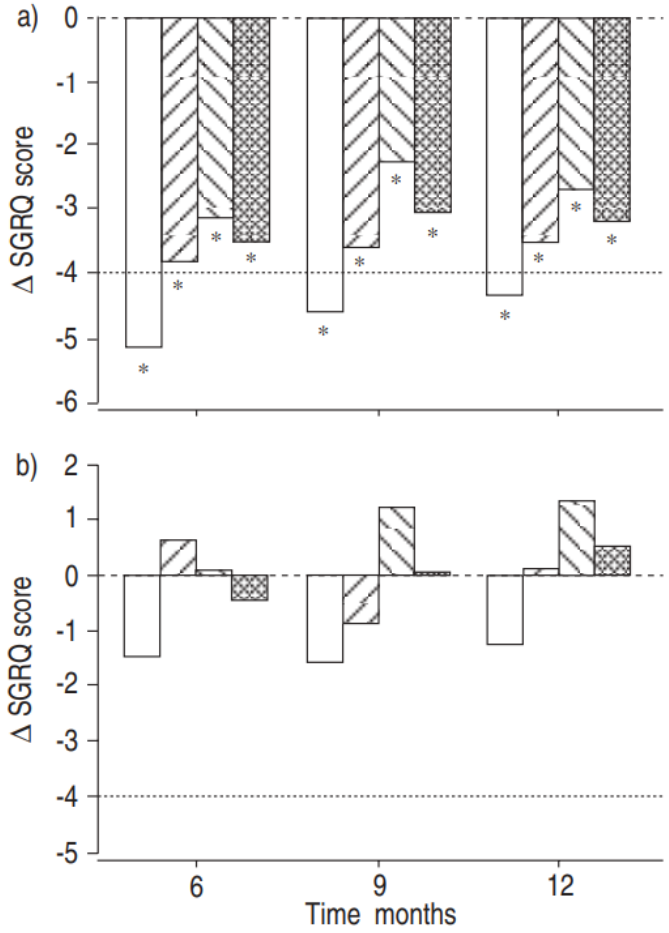


Celli BR et al. Am J Respir Crit Care Med 2020; 203(6): 689-698.

1yr with tiotropium and dyspnea improvement

- Two identical randomized double-blind placebo-controlled 1-yr studies. Patients inhaled tiotropium 18 mg or placebo.
- The primary spirometric outcome was trough FEV1 (i.e. FEV1 prior to dosing). Changes in dyspnoea were measured using the Transition Dyspnea Index, and health status with the disease-specific St. George9s Respiratory Questionnaire and the generic Short Form 36.





Casaburi R et al. Eur Respir J 2002; 19: 217-224.

Improvement in exercise performance with tiotropium

- A randomized, double-blind, placebo-controlled, parallel group study
- 261 COPD patients (189 men and 72 women)
- To address whether administration of tiotropium in the early morning will provide sustained improvements in exercise tolerance throughout the period of the day

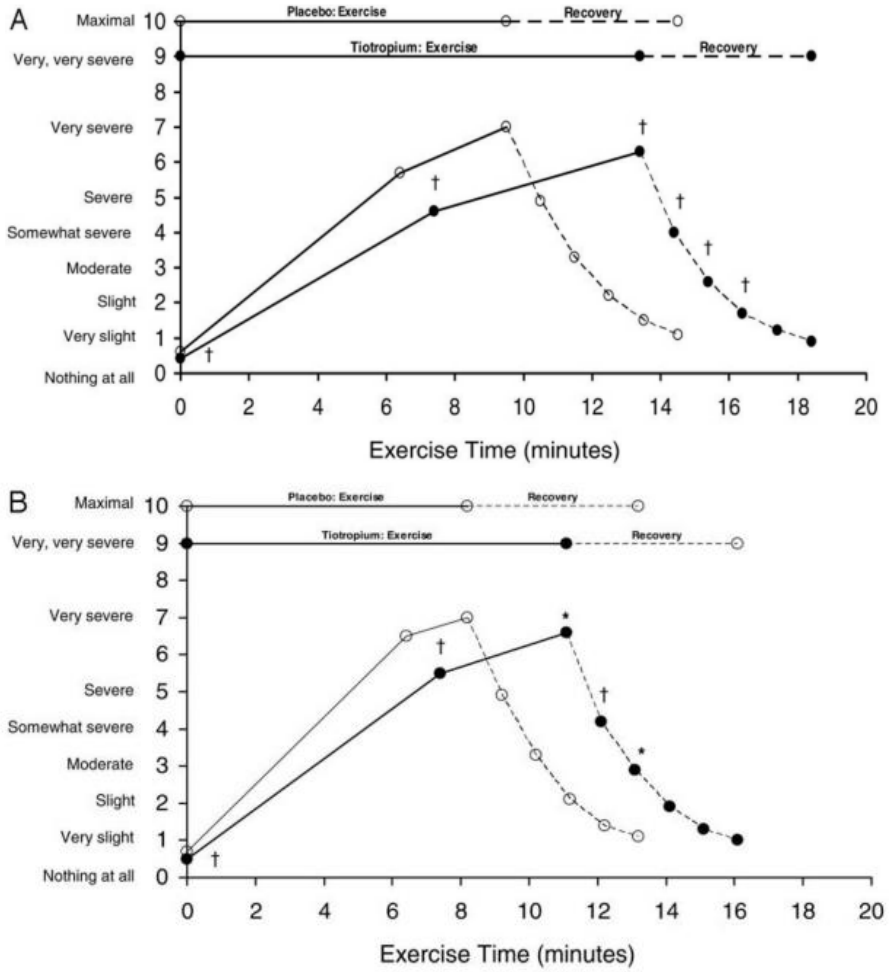


Table 4—*Perceived Symptom Limitation During Constant Work Rate Exercise at Baseline and on Day 42, 2.25 h After Dose*

	Tiotropium (n = 131), %		Placebo (n = 117), %	
Variables	Baseline	Day 42	Baseline	Day 42
Breathing discomfort	35.1	27.5*	46.2	41.9
Breathing discomfort/leg discomfort	48.9	41.2	37.6	38.5
Leg discomfort	13.7	29.8*	15.4	17.9
None	2.3	1.5	0.9	1.7

*$p < 0.01$ vs placebo, χ^2 test.

Maltais F et al. Chest 2005; 128:1168-1178.

PRO marker

Improvement in exercise tolerance with combination of tiotropium and pulmonary rehabilitation

- Randomized, double-blind, placebo-controlled trial (tiotropium, 18 µg qd, n =47; placebo, n=44) in COPD patients for 8 weeks of PR(treadmill training three times a week; > 30 min per session) at 17 sites
- Study drug was administered 5 weeks prior to, 8 weeks during, and 12 weeks following PR.
- The primary end point was treadmill walking (0% incline) endurance time at 80% of maximum speed attained in an initial incremental test.
- The transition dyspnea index (TDI), St. George's respiratory question-naire (SGRQ), and rescue albuterol use were secondary end points.

Characteristics	Tiotropium	Placebo	Total
Patients treated, No.	55	53	108
Male/female gender, %	54.5/45.5	58.5/41.5	56.5/43.5
Age, yr	65.9 (8.8)	67.3 (6.9)	66.6 (7.9)
Body mass index	25.0 (4.6)	26.8 (5.6)	25.9 (5.2)
Smoker/ex-smoker, %	29.1/70.9	18.9 /81.1	24.1 /75.9
Smoking history, pack-yr	58.7 (34.6)	58.8 (31.4)	58.7 (32.9)
COPD duration, yr	9.7 (7.6)	8.9 (6.6)	9.3 (7.1)
FEV_1, L	0.82 (0.31)	0.94 (0.40)	0.88 (0.36)
FEV_1, % predicted	32.6 (12.4)	36.2 (12.2)	34.4 (12.4)
FEV_1/FVC, %	41.5 (10.4)	44.6 (11.2)	43.0 (10.9)
FVC, L	2.01 (0.68)	2.14 (0.85)	2.08 (0.77)
Incremental treadmill test			
Duration, min	9.0 (2.8)	8.8 (3.6)	8.9 (3.2)
Maximum speed, mph	2.98 (0.87)	2.81 (0.98)	2.90 (0.92)

*Data are presented as mean (SD) unless otherwise indicated.

CasaBuri R et al. Chest 2005; 127:809-817.

PRO marker

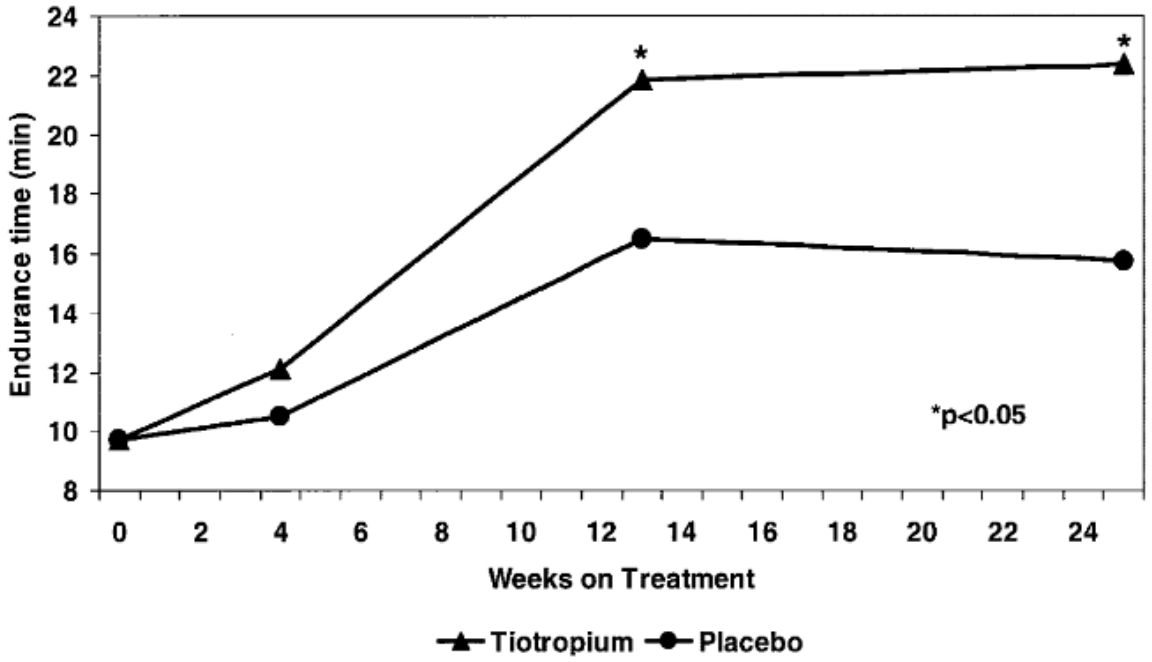


Table 3—*Endurance Time From the CWR Exercise Test on the Test Days

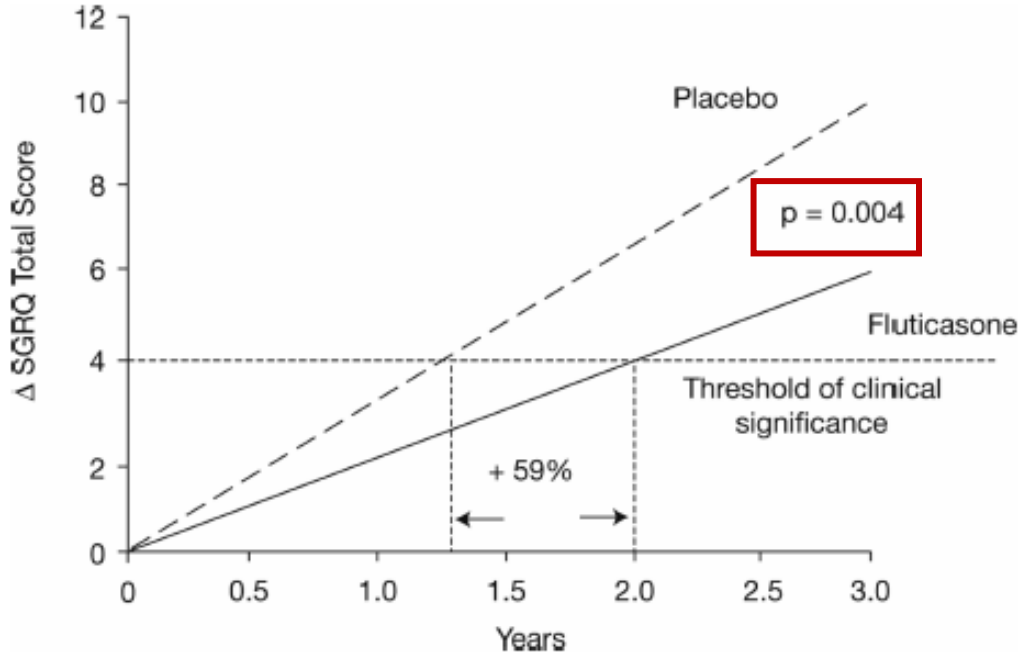
Variables	Time, min		Difference†		
	Tiotropium (n = 47)	Placebo (n = 44)	Mean (SE)	p Value	95% CI
Before PR (day 29)	12.14 (0.83)	10.50 (0.86)	1.65 (1.22)	0.183	− 0.79–4.09
After PR (day 92)	21.86 (1.58)	16.51 (1.64)	5.35 (2.34)	0.025	0.69–10.00
12 wk after PR (day 176)	22.36 (1.84)	15.76 (1.91)	6.60 (2.72)	0.018	1.18–12.02

*Data are presented as mean (SE). Mean adjusted baseline was 9.72 min.
†Analysis of covariance.

CasaBuri R et al. Chest 2005; 127:809-817.

Change of HRQoL and therapeutic intervention

- Correlations between decline in HRQoL and other aspects of COPD, such as exacerbations, FEV1 decline, and mortality.
- Data from the ISOLDE (Inhaled Steroids in Obstructive Lung Disease) trial
- SGRQ total scores in pts with moderate to severe COPD treated with fluticasone propionate 500 μg twice daily took longer to deteriorate by 4 points (the minimum clinically important difference) than patients treated with placebo (24 months versus 15 months)



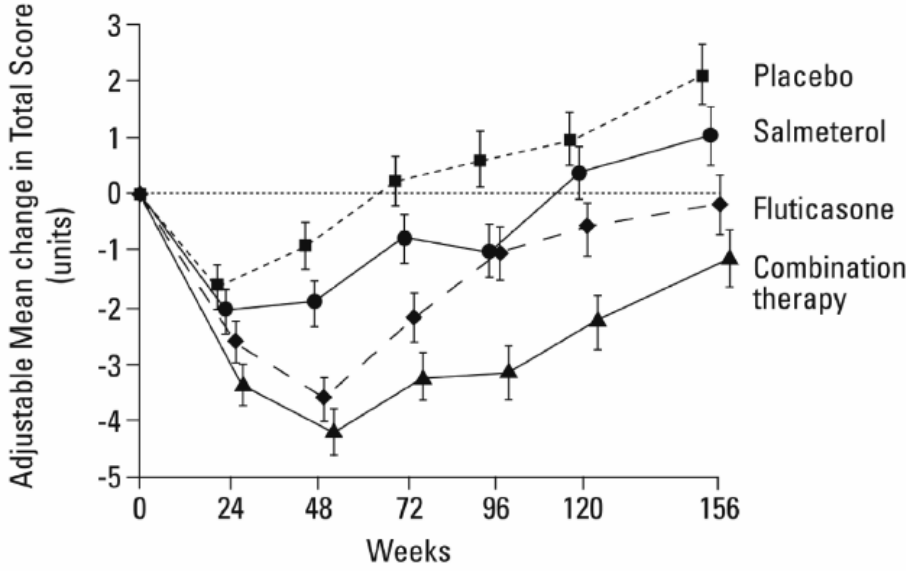
David M.G.Halpin et al. COPD:J of COPD; 2009: 6: 211-225.
Spencer S et al. Am J Respir Crit Care Med 2001; 163: 122-128.

PRO marker

Pharmacological intervention in TORCH study

- Randomized, double-blind trial comparing salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone **for a period of 3 years**.
- 40-80 yrs, at least 10yrs smoking history, FEV1 < 60% pred.
- **The primary outcome was death from any cause** for the comparison between the combination regimen and placebo
- The frequency of exacerbations, health status, and spirometric values were also assessed

Health Status



No. of Patients							
Placebo	1149	854	781	726	675	635	569
Salmeterol	1148	906	844	807	723	701	634
Fluticasone	1155	942	848	807	751	686	629
Combination therapy	1133	941	873	814	773	731	681

Peter M.A. Calverley et al. N Engl J Med 2007;356:775-89.
Celli BR et al. Am J Respir Crit Care Med 2008; 178: 332-338.

PRO marker

Impact of exacerbations on deterioration of health status

- Randomised, double-blind, placebo-controlled, parallel-group design and was conducted in 18 hospitals in the UK (ISOLDE study)
- To test whether the effect of FP on health status was attributable to its effect on exacerbations

	Number of exacerbations			Frequency of exacerbations		
	None	⩾1	p-value	<1.65·yr^{-1}	>1.65·yr^{-1}	p-value
Subjects n	93	520		291	286	
Sex M %	86	73	0.009	72	74	0.7
Age yrs	65±7	64±7	0.06	63±7	64±7	0.05
Current smokers %	52	48	0.6	48	48	0.9
SGRQ total score	42±17	50±17	<0.0001	48±18	52±15	0.03
FEV1 % pred	55±15	49±15	0.001	53±15	45±13	<0.0001

Spencer S et al. Eur Respir J 2004; 23: 698-702.

PRO marker

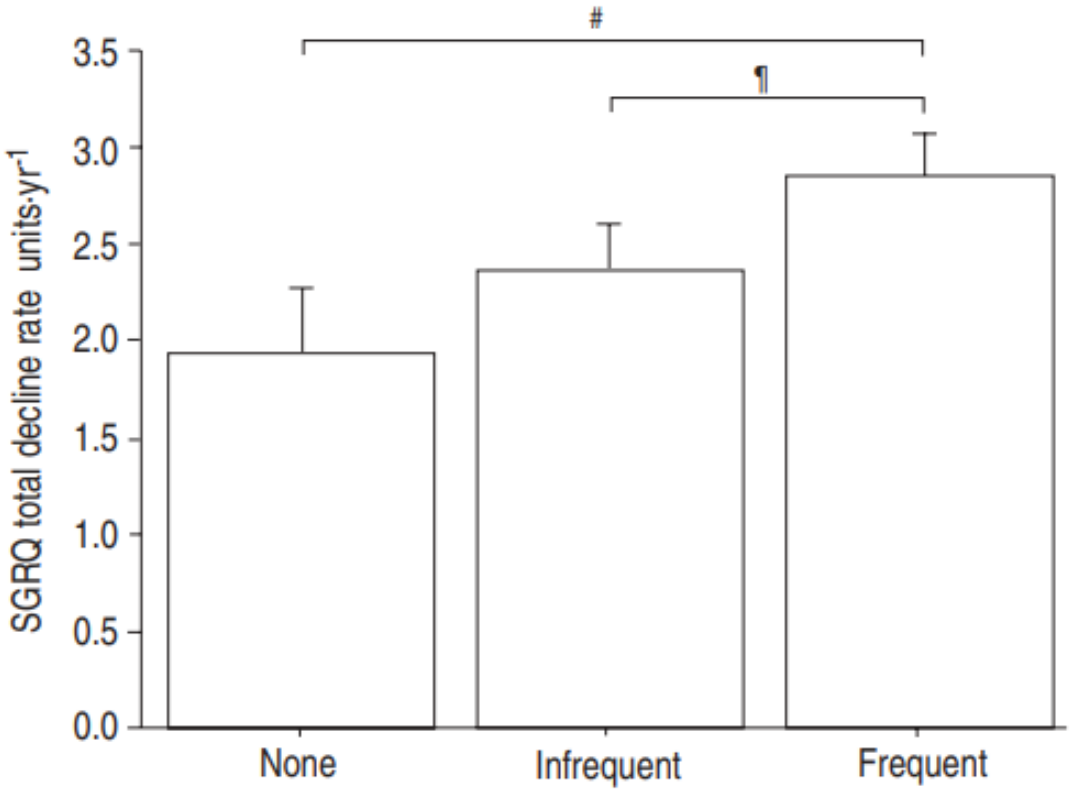


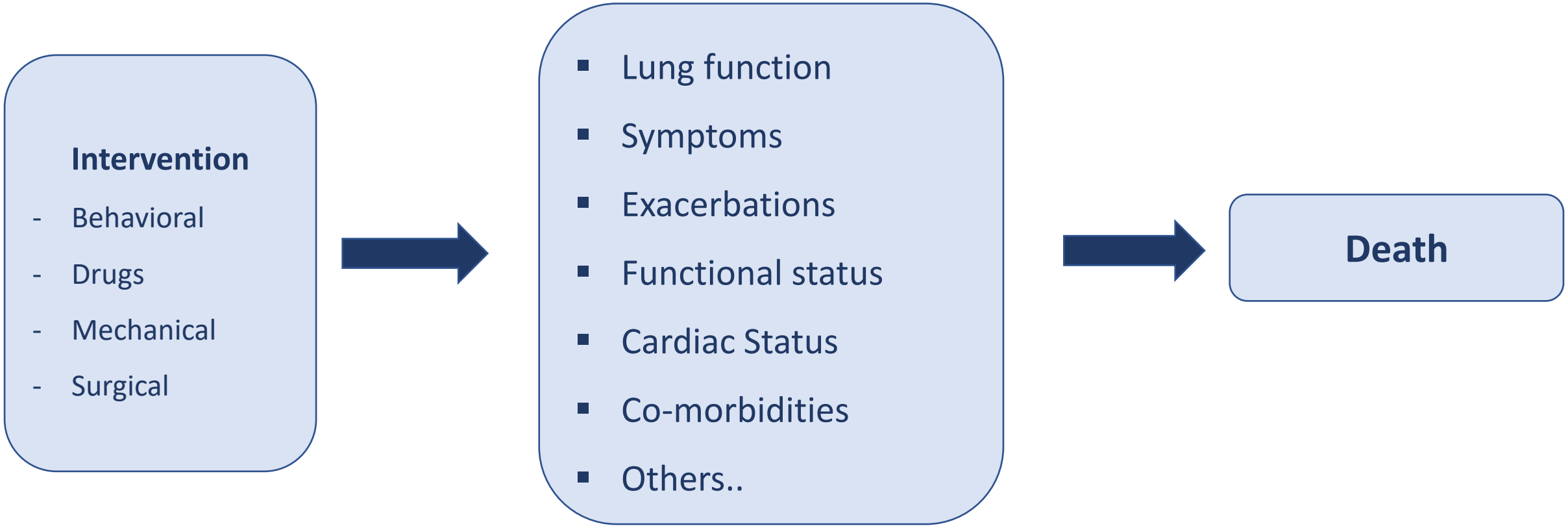
Table 2. – Effect of treatment and exacerbation frequency on change in St Georges Respiratory Questionnaire (SGRQ) score

	SGRQ score units·yr^{-1}	p-value
Exacerbation frequency		
None	2.0	0.0003
Infrequent	2.4	
Frequent	2.9	
Treatment		
FP	2.2	0.02
Placebo	2.6	

Data are presented as mean or as p-value. FP: fluticasone proprionate.

Spencer S et al. Eur Respir J 2004; 23: 698-702.

Death: ultimate consequence of disease progression

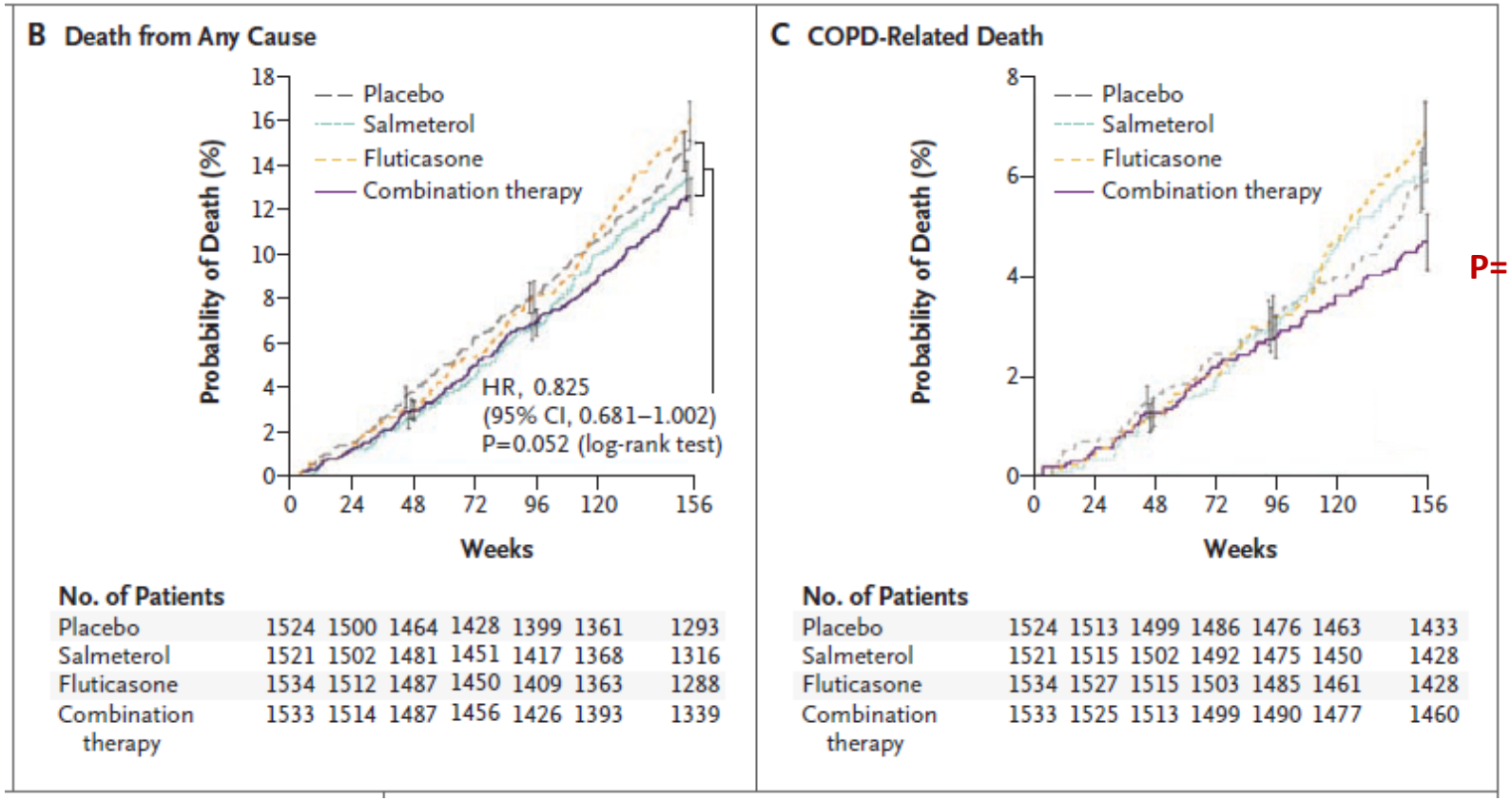


David M.G.Halpin et al. COPD:J of COPD; 2009: 6: 211-225.

PRO marker

Pharmacotherapy and survival in COPD

- Randomized, double-blind trial comparing salmeterol at a dose of 50 µg plus fluticasone propionate at a dose of 500 µg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone **for a period of 3 years**.
- 40-80 yrs, at least 10yrs smoking history, FEV1 < 60% pred.
- **The primary outcome was death from any cause** for the comparison between the combination regimen and placebo
- There were **875 deaths** within 3 years after randomization; combination therapy group (12.6%), placebo group (15.2%), salmeterol group (13.5%), and fluticasone group (16.0%).



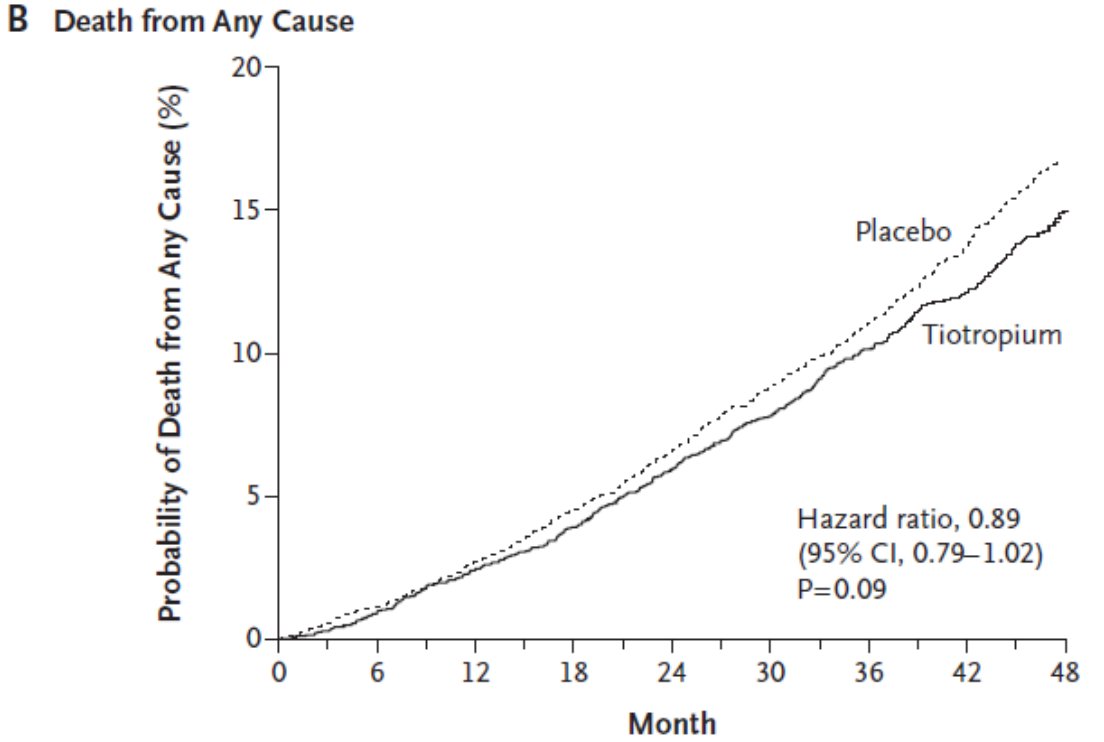
P= 0.007

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

PRO marker

Mortality from the UPLIFT trial

- Randomized, double-blind trial, compare 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs.
- The patients were at least 40 yrs, with FEV1 < 70%, post BD FEV1/FVC < 70%
- **Coprimary end points** were the rate of decline in the mean FEV1 before and after bronchodilation beginning on day 30. **Secondary end points** included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality.



No. at Risk									
Tiotropium	2986	2948	2899	2851	2785	2721	2646	2574	2306
Placebo	3006	2961	2903	2836	2772	2696	2624	2523	2249

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

Clinically important deterioration (CID)

- MCIDs are usually derived by one of two approaches: distribution- and anchor-based.
- **Distribution-based methods** use the frequency distribution of observed events, and 0.5 SD and 1 SEM have been suggested as MCIDs, indicates a statistical difference, but this may not be perceivable by a patient or clinician.
- **Anchor-based methods** examine the relationship between scores on the assessment instrument and other measures of impaired health (the anchors).

Mario Cazzola et al. Respiratory Medicine 2022; 205: 107054.

Endpoint	MCID (Improvement)	Method of Estimation	Reference
Lung function			
Trough FEV_1	100 ml	Anchor-based (exacerbations, patient perception, 2-yr decline in lung function)	9
Exacerbations	No validated MCID	—	—
Dyspnea			
TDI total score	1 unit	Anchor-based (physician's global evaluation score), distribution-based (SEM, 0.5 SD), expert preference	19
UCSD SOBQ	5 units	Anchor-based (CRQ dyspnea domain, TDI), distribution-based (SEM, Cohen's effect size), estimate by experienced users	20
Health status			
SGRQ total score	4 units	Anchor-based (MRC dyspnea grade, CRQ dyspnea domain, mortality rate), expert and patient preference	23
CRQ domain scores	0.5 units (average)*	Anchor-based (patient perspectives), distribution-based (SEM, Cohen's effect size), expert panel-based	24
Exercise capacity			
6-min walk distance	26 ± 2 m (patients with severe COPD)	Anchor-based (SGRQ, UCSD SOBQ), distribution-based (SEM, Cohen's effect size, empirical rule effect size)	31
Incremental shuttle walking test	47.5 m	Anchor-based (patient perception)	32
Endurance shuttle walking test	45–85 s	Anchor-based (patient perception), distribution-based (0.5 SD)	33
Constant-load cycling endurance tests	46–105 s	Distribution-based (0.5 SD)	8
Dyspnea during exercise tests			
Modified Borg scale	1 unit	Distribution-based (Cohen's effect size)	39
Visual analog scale	10–20 units	Distribution-based (Cohen's effect size)	39

Mario Cazzola et al. Respiratory Medicine 2022; 205: 107054.

Clinically important deterioration (CID)

- **Clinically important deterioration (CID)**

  - a composite tool that was developed to measure the progression of COPD

  - used to assess the early deterioration of acute worsening of COPD symptoms necessitating additional treatment

    - changes from baseline of FEV1 ≥100 mL

    - increase in total SGRQ score ≥4 units, increase in CAT score ≥2 units

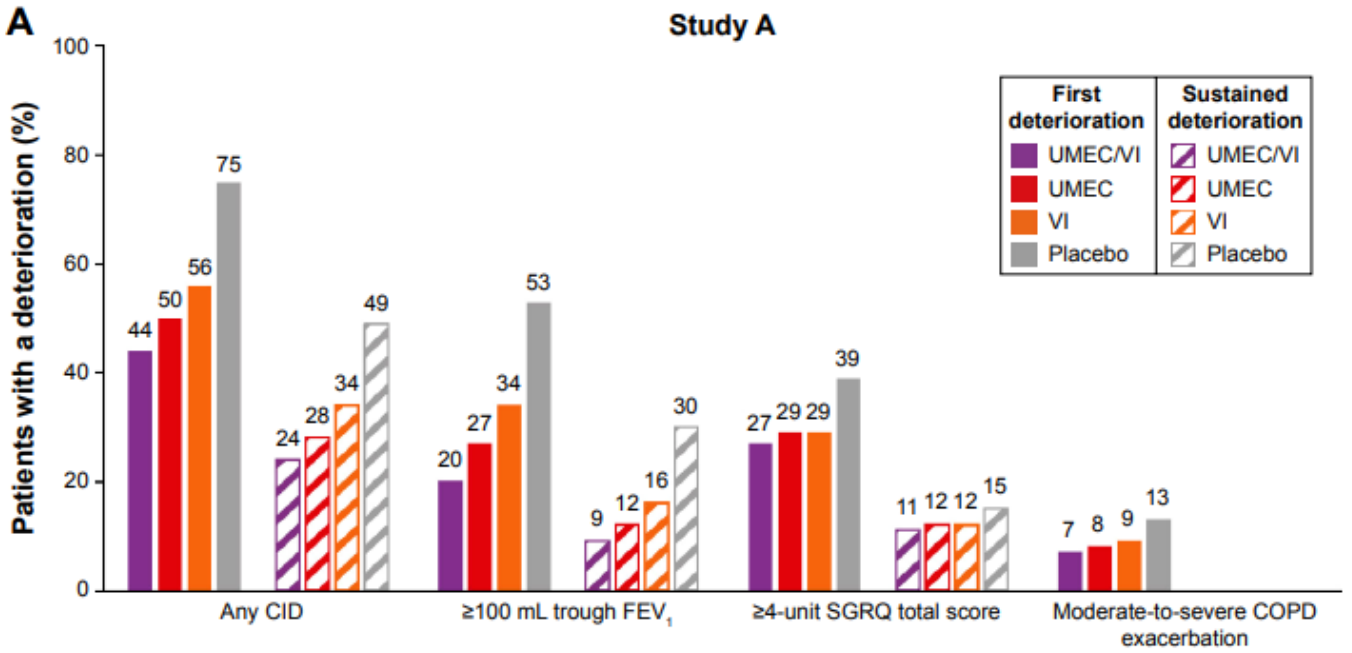
    - a moderate/severe exacerbation

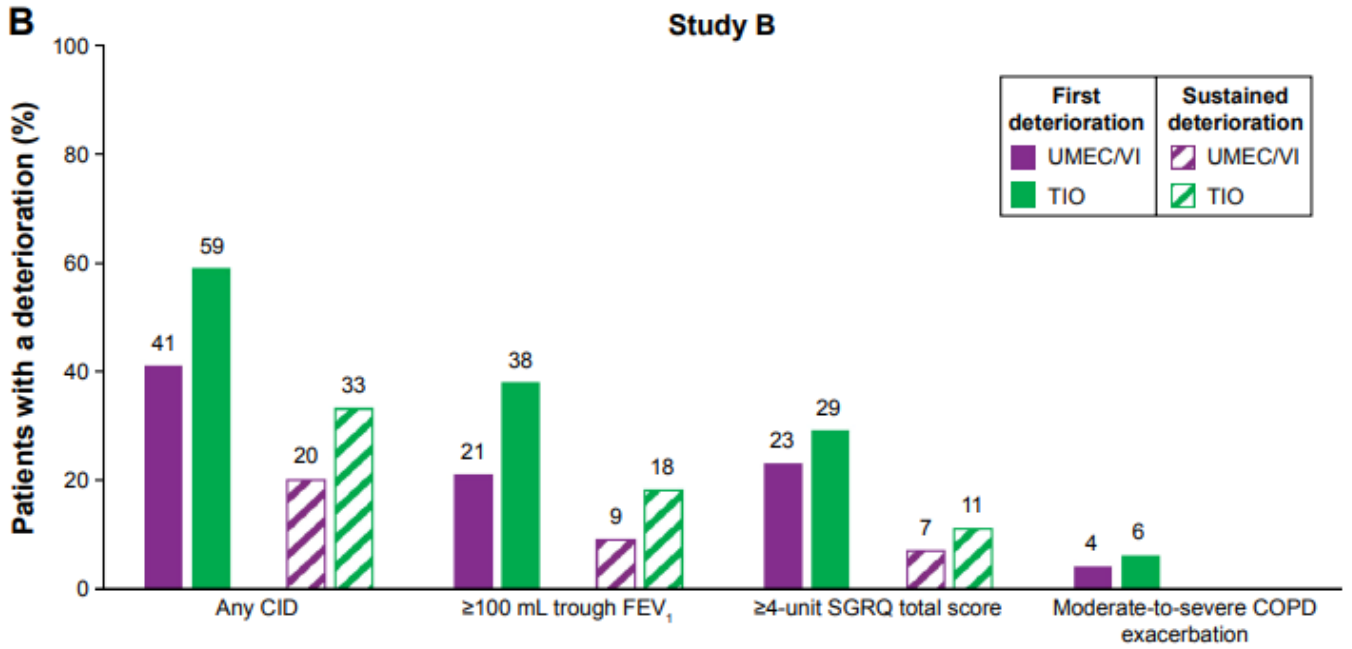
Paul W Jones et al. Am J Respir Crit Care 2014; 198: 250-255.

Prevention of CID in COPD with dual bronchodilator

- Post hoc analysis of two 24-week, Phase III, multicenter, randomized, double-blind, parallel-group trials comparing UMEC/VI 62.5/25µg with UMEC 62.5 µg, VI 25 µg, or placebo (Study A; NCT01313650), or UMEC/VI 62.5/25 µg with tiotropium (TIO) 18 µg
- Deterioration was assessed through CID of FEV1 decline, SGRQ score, and exacerbation.

Singh D et al. Int J Chron Obstruct Pulmon Dis 2016; 11: 1413-24.





Singh D et al. Int J Chron Obstruct Pulmon Dis 2016; 11: 1413-24.

Prognostic value of CID in COPD: IMPACT trial

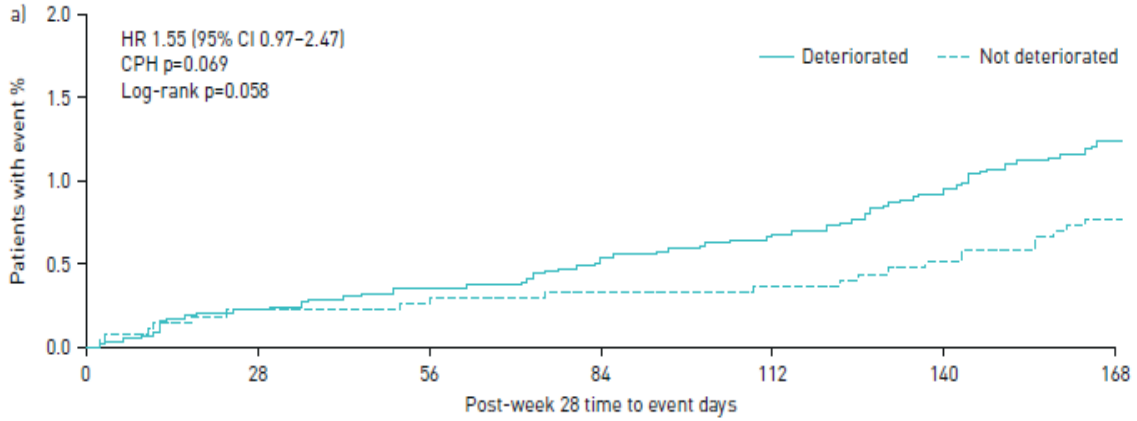
- Phase III, double-blind, 52-week, multicentre trial.
- Pts with symptomatic COPD and at least one moderate/severe exacerbation in the prior year were randomized 2:2:1 to fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25µg, FF/VI 100/25 µg or UMEC/VI 62.5/25 µg.
- Investigate the prognostic value of a CID event on future clinical outcomes and the effect of single-inhaler triple versus dual therapy on reducing CID risk in patients in the IMPACT trial.

M.K.Han et al. ERJ Open Res 2021; 7: 00663-2020.

	CID-positive	CID-negative	Difference (CID-positive *versus* CID-negative)
Definition including SGRQ	N=7008[#]	N=3055[#]	
	Annual rates (95% CI)		**% increase in rate (95% CI)**
Rate of exacerbations	n=5860[¶,+]	n=2729[¶,+]	
Moderate/severe exacerbations after week 28	0.94 (0.90–0.98)	0.54 (0.49–0.58)	75 (60–92)[§]
Severe exacerbations after week 28	0.14 (0.12–0.16)	0.07 (0.06–0.09)	96 (56–147)[§]
	Patients with event (%)		**% increase in risk (95% CI)**
Time to first exacerbation	n=5864[¶,+,f]	n=2732[¶,+,f]	
Moderate/severe exacerbations after week 28	1900 (32)	548 (20)	72 (56–89)[§]
Severe exacerbations after week 28	391 (7)	99 (4)	79 (43–123)[§]
Time to all-cause mortality	n=5887	n=2732	
All-cause mortality after week 28[##]	77 (1)	23 (<1)	55 (−3–147)[¶¶]
	LS mean CFB (95% CI)		**Difference (95% CI)**
Trough FEV_1 at week 52 mL	n=5359	n=2557	
	9 (2–15)	152 (143–162)	−143 (−155–−132)[§]
SGRQ total score at week 52	n=5298	n=2516	
	−2.4 (−2.7–−2.0)	−9.8 (−10.3–−9.3)	7.5 (6.8–8.1)[§]
CAT score at week 52	n=5218	n=2482	
	−1.2 (−1.3–−1.0)	−3.3 (−3.5–−3.0)	2.1 (1.8–2.4)[§]
Definition including CAT	N=7304[#]	N=2759[#]	
	Annual rates (95% CI)		**% increase in rate (95% CI)**
Rate of exacerbations	n=6150[¶,++]	n=2439[¶,++]	
Moderate/severe exacerbations after week 28	0.92 (0.88–0.96)	0.54 (0.49–0.58)	72 (56–89)[§]
Severe exacerbations after week 28	0.15 (0.13–0.17)	0.08 (0.06–0.10)	91 (50–142)[§]
	Patients with event (%)		**% increase in risk (95% CI)**
Time to first exacerbation	n=6153[¶,f,++]	n=2443[¶,f,++]	
Moderate/severe exacerbations after week 28	1959 (32)	489 (20)	68 (52–86)[§]
Severe exacerbations after week 28	402 (7)	88 (4)	78 (41–125)[§]
Time to all-cause mortality	n=6176	n=2443	
All-cause mortality after week 28[##]	82 (1)	18 (<1)	80 (8–200)[§§]
	LS mean CFB (95% CI)		**Difference (95% CI)**
Trough FEV_1 at week 52 mL	n=5632	n=2284	
	14 (7–20)	156 (146–167)	−142 (−155–−130)[§]
SGRQ total score at week 52	n=5565	n=2249	
	−3.2 (−3.6–−2.9)	−8.6 (−9.2–−8.0)	5.4 (4.7–6.0)[§]
CAT score at week 52	n=5502	n=2198	
	−0.9 (−1.1–−0.8)	−4.1 (−4.4–−3.9)	3.2 (2.9–3.5)[§]

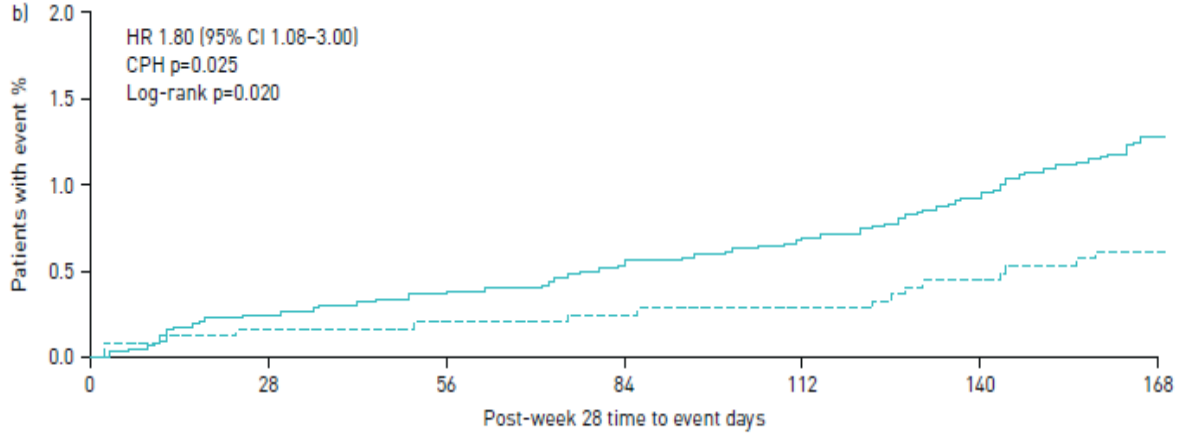
M.K.Han et al. ERJ Open Res 2021; 7: 00663-2020.

Three-component definition (+SGRQ)



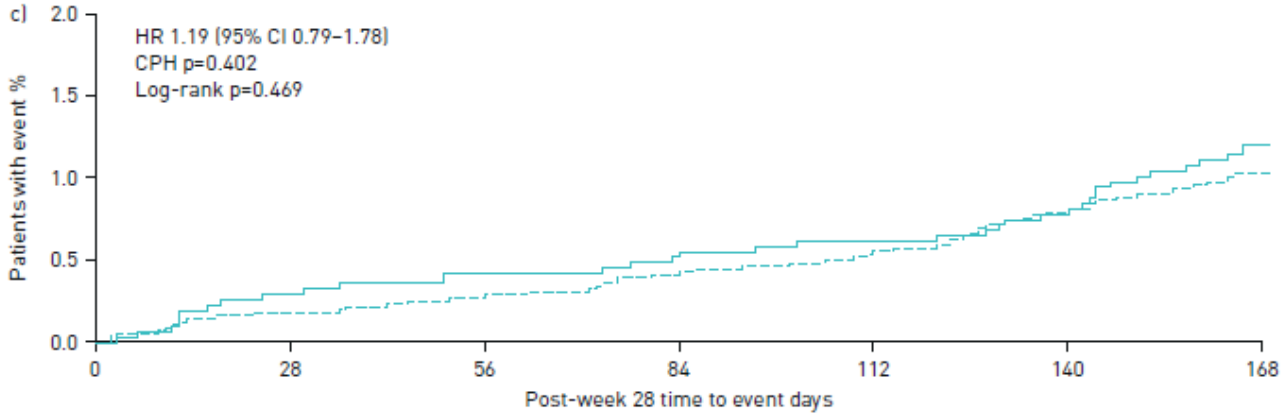
At risk n:							
Deteriorated	5887	5873	5864	5851	5841	5813	5280
Nondeteriorated	2732	2725	2724	2720	2716	2708	2494

Three-component definition (+CAT)



At risk n:							
Deteriorated	6176	6160	6151	6138	6127	6099	5530
Nondeteriorated	2443	2438	2437	2433	2430	2422	2244

Exacerbation component only

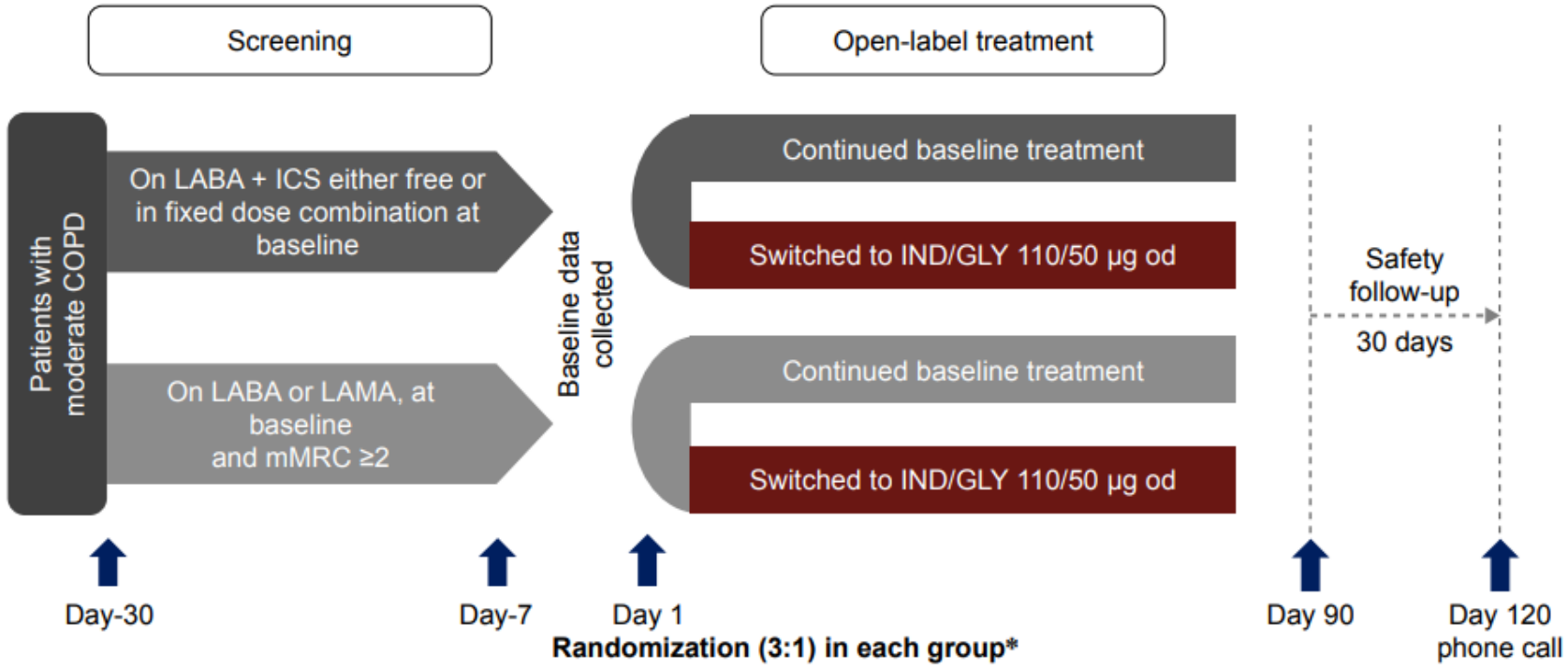


At risk n:							
Deteriorated	3068	3059	3055	3051	3048	3038	2729
Nondeteriorated	5551	5539	5533	5520	5509	5483	5045

M.K.Han et al. ERJ Open Res 2021; 7: 00663-2020.

The same in everyday practice as the RCT ?

- CRYSTAL was a 12-week, prospective, multicenter, randomized, open-label study conducted in clinical practice settings.
- Of the 2,159 patients analyzed, 1,622 switched to IND/GLY and 537 continued their baseline treatments.
- Three definitions of CID were used as FEV1 decline, TDI and/or CCQ and exacerbation.



T. Greulich et al. Int J Chronic Obstr Pulm Dis 2018; 13: 1229-12373

IND/GLY vs. LABA or LAMA

Outcome measures	IND/GLY[a] (n=811)	LABA or LAMA[a] (n=268)	IND/GLY versus LABA or LAMA odds ratio (95% CI)
Decrease in trough FEV_1 of ≥100 mL	100 (12.3)	74 (27.6)	0.37 (0.26–0.52)
Decrease in TDI of ≥1 point	72 (8.9)	42 (15.7)	0.55 (0.37–0.83)
Increase in CCQ of ≥0.4 point	93 (11.5)	51 (19.0)	0.55 (0.38–0.81)
Incidence of AECOPD[b]	44 (5.4)	19 (7.0)	0.75 (0.43–1.31)

IND/GLY vs. LABA + ICS

Outcome measures	IND/GLY (n=811)	LABA + ICS (n=269)	IND/GLY versus LABA + ICS odds ratio (95% CI)
Decrease in trough FEV_1 of ≥100 mL	126 (15.5)	61 (22.7)	0.66 (0.47–0.93)
Decrease in TDI of ≥1 point	91 (11.2)	39 (14.5)	0.81 (0.54–1.21)
Increase in CCQ of ≥0.4 point	113 (13.9)	48 (17.8)	0.79 (0.54–1.15)
Incidence of AECOPD[a]	63 (7.8)	16 (5.9)	1.33 (0.76–2.35)

T. Greulich et al. Int J Chronic Obstr Pulm Dis 2018; 13: 1229-12373

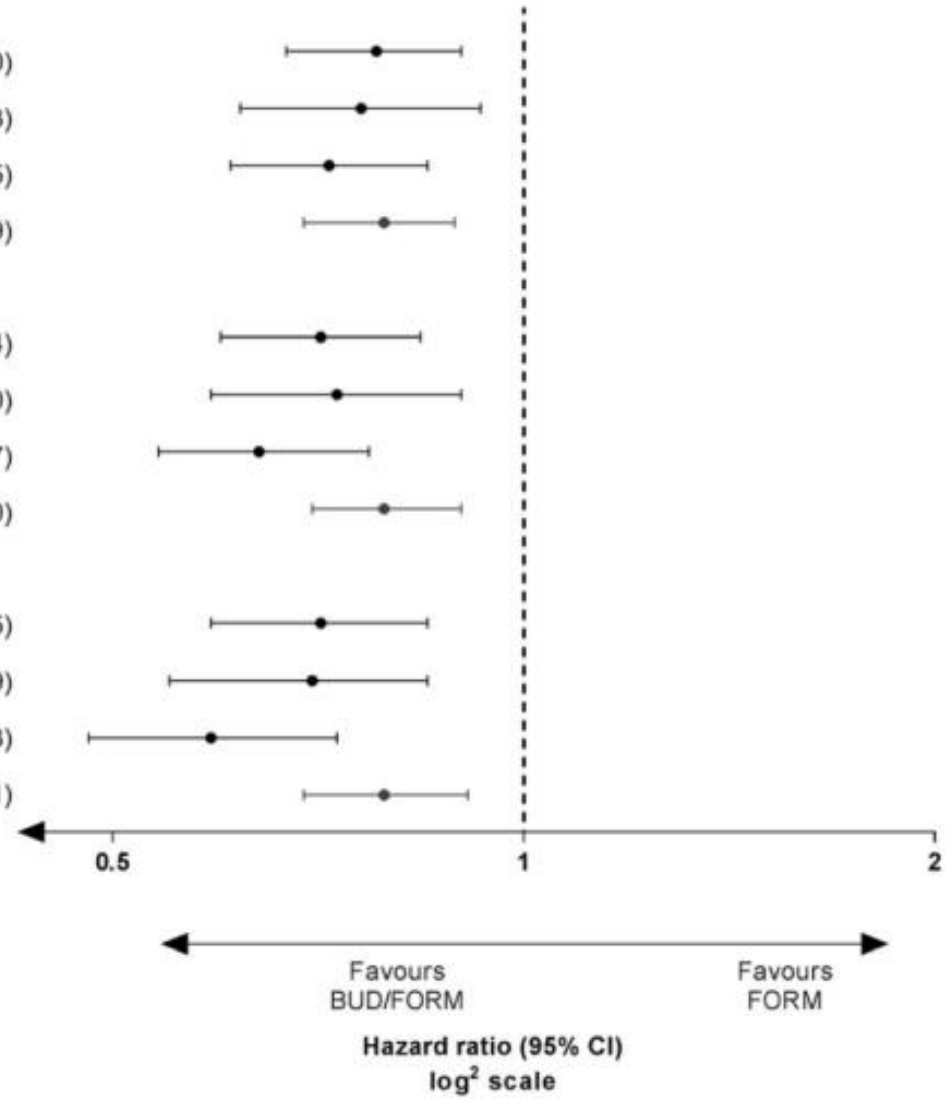
CID and adding ICS in COPD based on eosinophil

- Post-hoc analysis of four budesonide/formoterol (BUD/FORM) studies (SUN, SHINE, US3, RISE) comprised 3576 symptomatic moderate-to-very-severe COPD patients with a history of exacerbation.
- Examine the performance and utility of CID in assessing the effect of inhaled corticosteroids (ICS) in COPD.

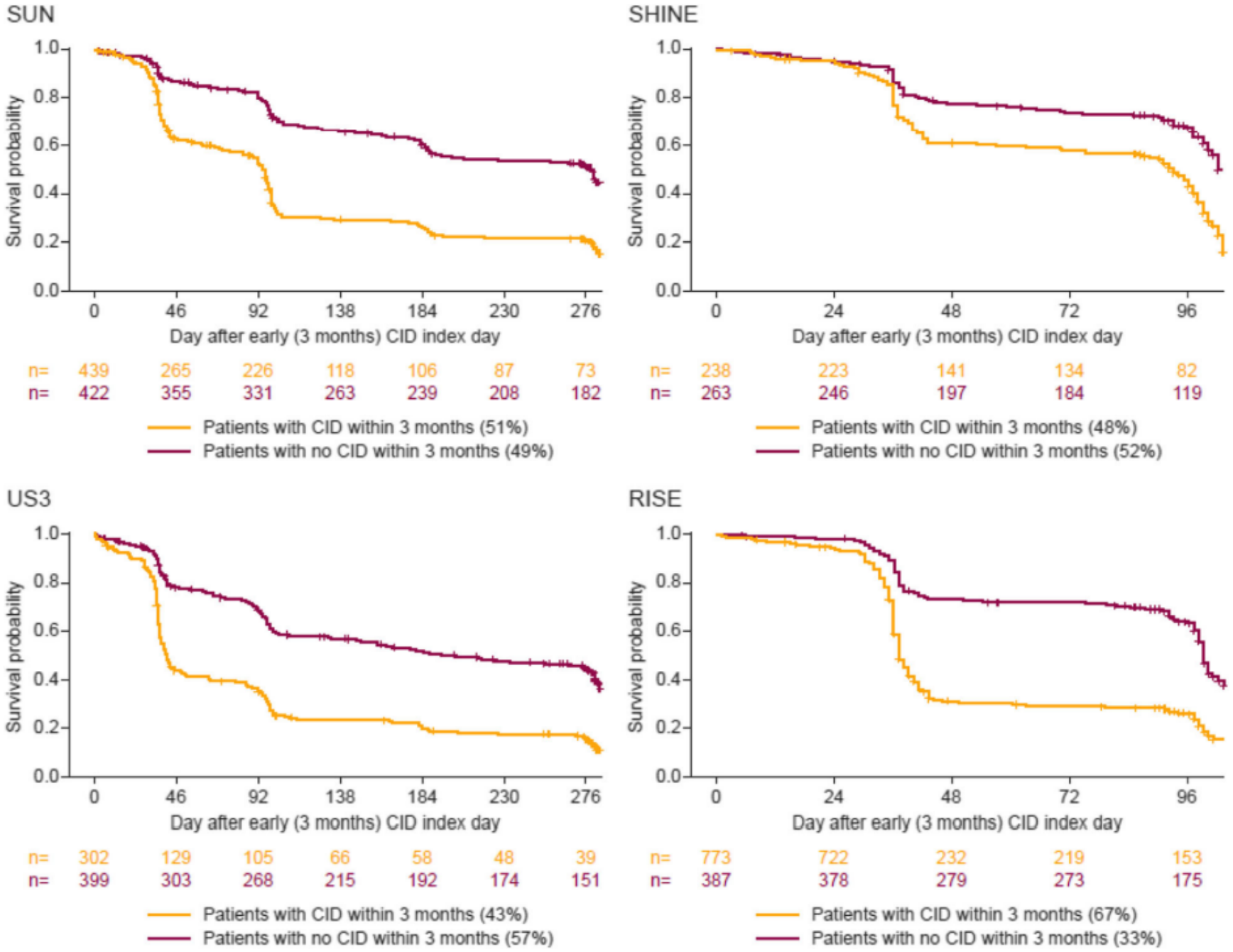
	SUN (n = 989)		SHINE (n = 561)		US3 (n = 807)		RISE (n = 1219)	
	BUD/FORM 160/4.5 μg bid (*n* = 494)	FORM 4.5 μg bid (*n* = 495)	BUD/FORM 160/4.5 μg bid (*n* = 277)	FORM 4.5 μg bid (*n* = 284)	BUD/FORM 160/4.5 μg bid (*n* = 404)	FORM 4.5 μg bid (*n* = 403)	BUD/FORM 160/4.5 μg bid (*n* = 606)	FORM 4.5 μg bid (*n* = 613)
Any CID	343 (69.4)	360 (72.7)	173 (62.5)	196 (69.0)	280 (69.3)	305 (75.7)	468 (77.2)	517 (84.3)
Subtypes of first CID								
Exacerbation alone	81 (23.6)	96 (26.7)	47 (27.2)	47 (24.0)	114 (40.7)	126 (41.3)	61 (13.0)	74 (14.3)
FEV_1 event alone	120 (35.0)	112 (31.1)	62 (35.8)	59 (30.1)	90 (32.1)	86 (28.2)	172 (36.8)	174 (33.7)
SGRQ alone	116 (33.8)	112 (31.1)	49 (28.3)	76 (38.8)	61 (21.8)	75 (24.6)	172 (36.8)	171 (33.1)
Exacerbation + FEV_1	3 (0.9)	5 (1.4)	0 (0.0)	2 (1.0)	6 (2.1)	8 (2.6)	5 (1.1)	7 (1.4)
Exacerbation + SGRQ	3 (0.9)	4 (1.1)	4 (2.3)	2 (1.0)	1 (0.4)	4 (1.3)	6 (1.3)	7 (1.4)
FEV_1 + SGRQ	20 (5.8)	30 (8.3)	10 (5.8)	10 (5.1)	7 (2.5)	5 (1.6)	51 (10.9)	79 (15.3)
Exacerbation + FEV_1 + SGRQ	0 (0)	1 (0.3)	1 (0.6)	0 (0)	1 (0.4)	1 (0.3)	1 (0.2)	5 (1.0)
Individual components								
Exacerbations	152 (30.8)	177 (35.8)	69 (24.9)	78 (27.5)	169 (41.8)	182 (45.2)	151 (24.9)	181 (29.5)
FEV_1 events	196 (39.7)	212 (42.8)	84 (30.3)	100 (35.2)	135 (33.4)	161 (40.0)	289 (47.7)	344 (56.1)
SGRQ events	188 (38.1)	202 (40.8)	81 (29.2)	116 (40.8)	143 (35.4)	164 (40.7)	312 (51.5)	357 (58.2)

M. Bafaddel et al. Respiratory Research 2020; 21: 17.

	BUD/FORM 160/4.5 µg Events/N (%)	FORM 4.5 µg Events/N (%)	HR (95% CI)
CID, full study duration			
SUN	343/494 (69.4)	360/495 (72.7)	0.78 (0.67–0.90)
SHINE	173/277 (62.5)	196/284 (69.0)	0.76 (0.62–0.93)
US3	280/404 (69.3)	305/403 (75.7)	0.72 (0.61–0.85)
RISE	468/606 (77.2)	517/613 (84.3)	0.79 (0.69–0.89)
CID, 6 months			
SUN	266/494 (53.8)	313/495 (63.2)	0.71 (0.60–0.84)
SHINE	161/277 (58.1)	191/284 (67.3)	0.73 (0.59–0.90)
US3	216/404 (53.5)	271/403 (67.2)	0.64 (0.54–0.77)
RISE	448/606 (73.9)	496/613 (80.9)	0.79 (0.70–0.90)
CID, 3 months			
SUN	222/494 (44.9)	269/495 (54.3)	0.71 (0.59–0.85)
SHINE	121/277 (43.7)	155/284 (54.6)	0.70 (0.55–0.89)
US3	146/404 (36.1)	213/403 (52.9)	0.59 (0.48–0.73)
RISE	378/606 (62.4)	433/613 (70.6)	0.79 (0.69–0.91)



M. Bafaddel et al. Respiratory Research 2020; 21: 17.



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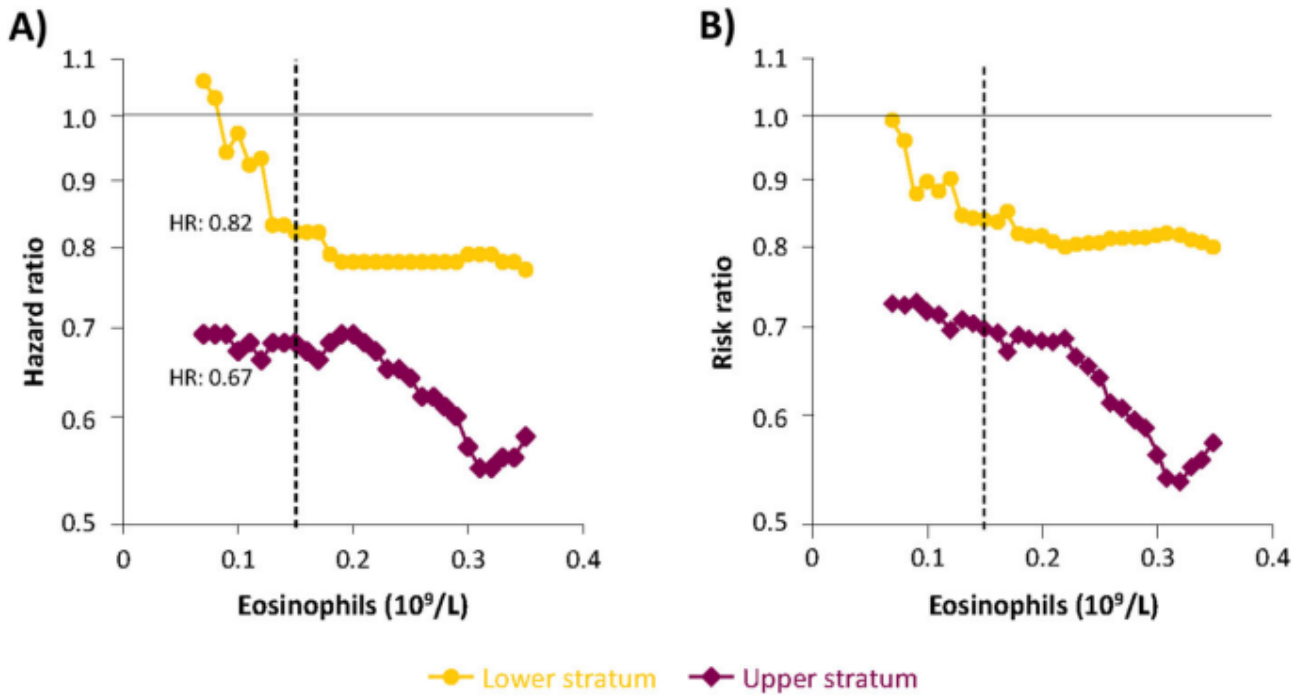


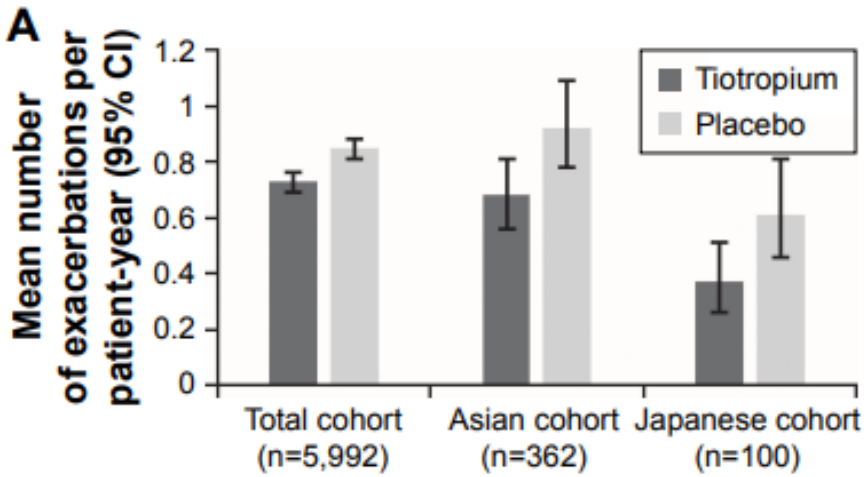
Cut-off, $\times 10^9$/L (% ≤)	Lower stratum			Upper stratum		
	BUD/FORM 160/4.5 µg bid	FORM 4.5 µg bid	HR (95% CI)	BUD/FORM 160/4.5 µg bid	FORM 4.5 µg bid	HR (95% CI)
0.10 (25.2)	201/285 (70.5)	199/291 (68.4)	0.97 (0.80–1.18)	569/857 (66.4)	633/853 (74.2)	0.67 (0.60–0.75)
0.15 (44.8)	350/503 (69.6)	373/520 (71.7)	0.82 (0.71–0.95)	420/639 (65.7)	459/624 (73.6)	0.68 (0.59–0.77)
0.20 (60.9)	466/675 (69.0)	519/718 (72.3)	0.78 (0.69–0.88)	304/467 (65.1)	313/426 (73.5)	0.69 (0.59–0.80)
0.25 (73.1)	560/818 (68.5)	613/852 (71.9)	0.78 (0.69–0.87)	210/324 (64.8)	219/292 (75.0)	0.64 (0.53–0.78)
0.30 (79.9)	616/896 (68.8)	670/931 (72.0)	0.79 (0.71–0.88)	154/246 (62.6)	162/213 (76.1)	0.57 (0.46–0.71)
0.35 (85.2)	659/965 (68.3)	708/983 (72.0)	0.77 (0.69–0.86)	111/177 (62.7)	124/161 (77.0)	0.58 (0.45–0.75)

M. Bafaddel et al. Respiratory Research 2020; 21: 17.

Limitations of CID evaluation

- PubMed searches to identify original research articles that were published up to May 15, 2017, using the search terms “COPD” AND “Japan” AND “exacerbation”.
- Finally, the full text of these 50 papers identified a total of 14 studies that met the following criteria

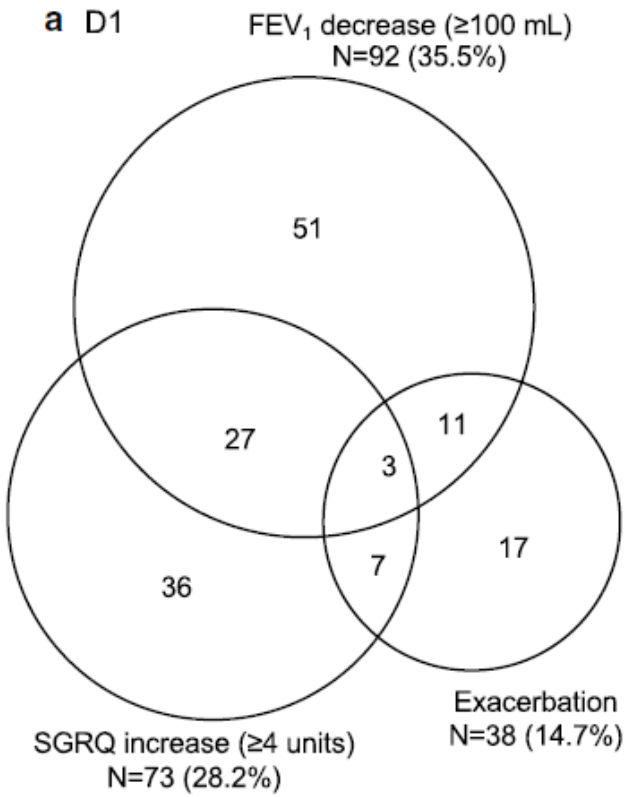
Study	Inclusion criteria relating to disease severity and exacerbation history	Definition of COPD exacerbation	Interventions	N	Patient baseline characteristics				Incidence of exacerbations (per person per year)[a]
					Age (years)[a]	Female (%)	GOLD stage III/IV (%)	ICS use (%)	
Furumoto et al (2008)[20]	• Patients with chronic lung disease including COPD, with sequelae of pulmonary tuberculosis • Previous exacerbations	Symptom-based	PV+IV IV alone	87 80	69.0±9.0	36.5	NR	NR	0.53 (COPD population; n=55)
Sasaki et al (2009)[21]	• Patients with COPD • No exacerbation criteria for inclusion or exclusion	Symptom-based	Lansoprazole 15 mg/day Placebo	50 50	74.9±8.9 74.8±7.5	6 4	34/6 40/2	26.0 24.0	0.34±0.72 1.18±1.4
Fukuchi et al (2011)[7]	• Patients with COPD • Post-FEV_1% pred: ≤70% • Post-FEV_1/FVC: ≤70% • No exacerbation 4 weeks before screening	Symptom-based	TIO Placebo	50 50	66.9±6.0 68.0±5.5	8 4	48/6 56/0	26.0 24.0	0.37 (95% CI: 0.26–0.51) 0.61 (95% CI: 0.46–0.81)
Fukuchi et al (2016)[19]	• Patients with COPD • Post-FEV_1% pred: <80% • Post-FEV_1/FVC: <70% • ≥1 exacerbations in the previous year • No exacerbation 7 days prior to drug administration	Symptom-based	Lysozyme 270 mg/day Placebo	202 204	68.8±9.3 70.3±7.2	9.4 8.8	36.1/5.0 29.4/5.4	8.4 7.4	1.4±1.5 1.2±1.4
Jones et al (2016)[9]	• Patients with COPD	Event-based, symptom-based	FP/SAL TIO	405	68.3±7.0	5	NR	NR	1.79 (95% CI: 1.56–2.05) (EXACT criteria) 0.33 (0.24–0.44) (physician reported)

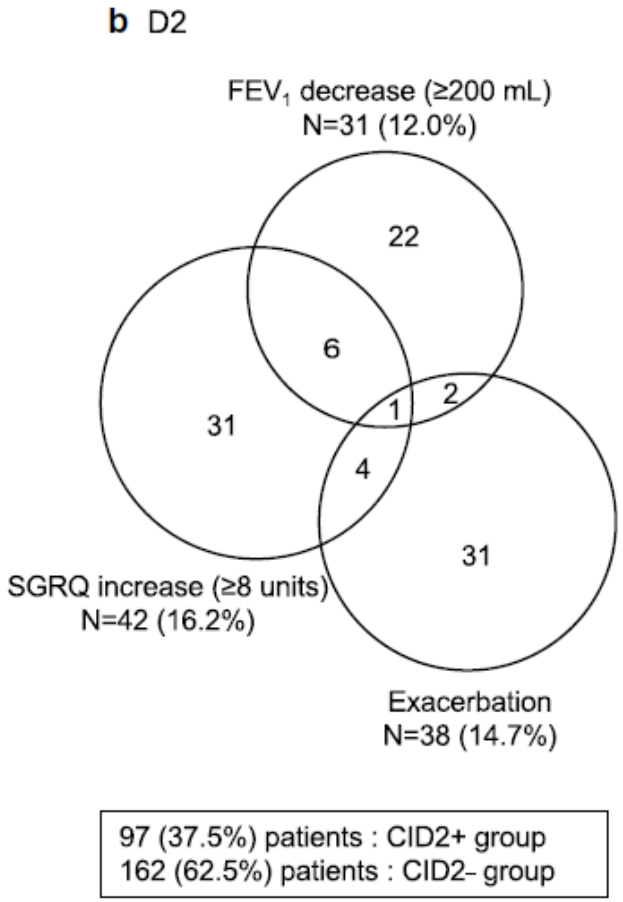


T Ishii et al. Int J Chronic Obstruct Pulm Dis 2018; 13: 3459-3471.

One year CID and long term clinical course in Japan

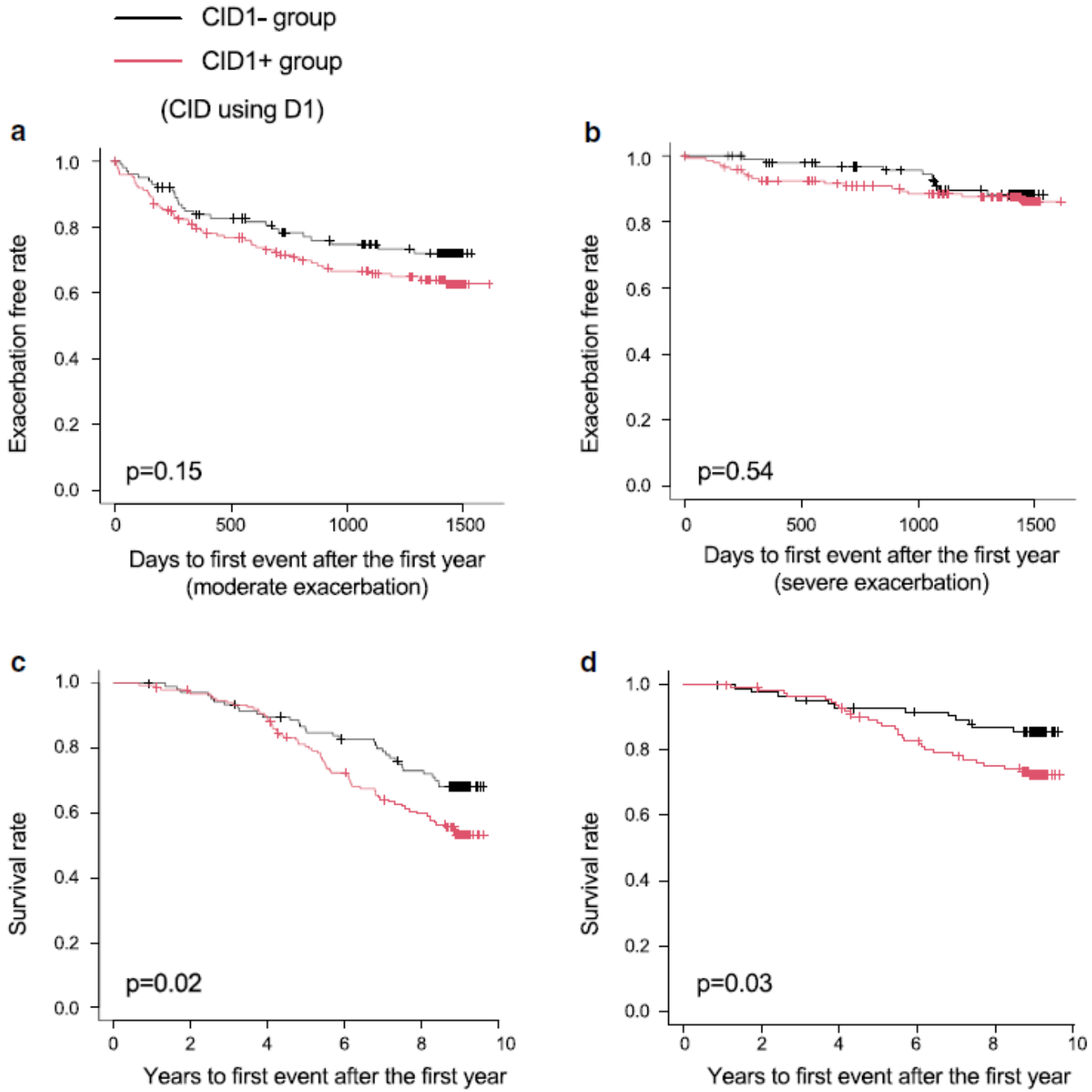
- Among Japanese COPD pts in the Hokkaido COPD cohort study, 259 patients who did not drop out within the first year were analyzed in this study.
- Two definitions of CID were used. Definition 1 comprised FEV1 ≥ 100 mL decrease, SGRQ≥ 4-unit increase from baseline, or moderate or severe exacerbation. For Definition 2, the thresholds for the FEV1 and SGRQ score components were doubled.





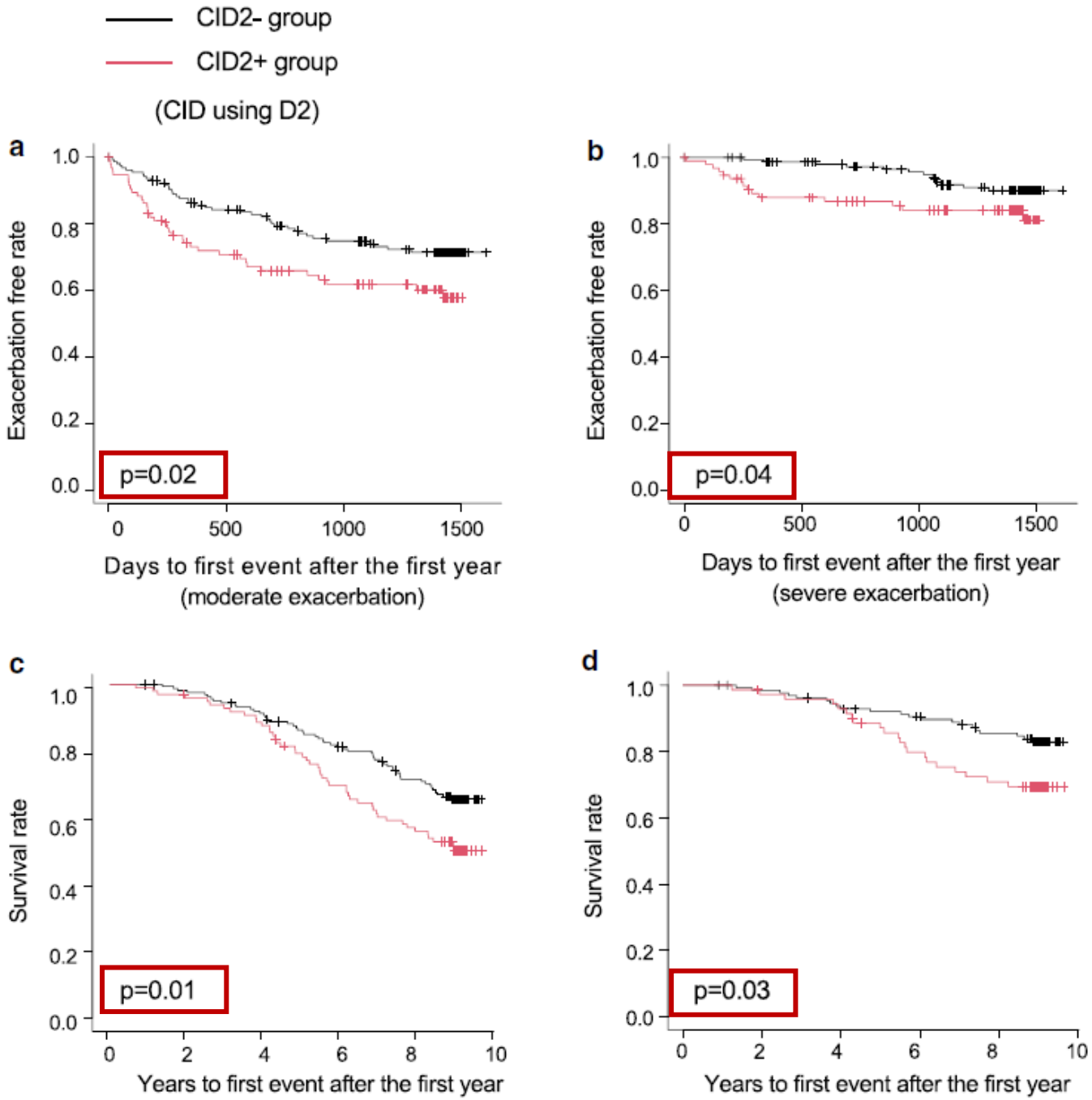
Y Abe et al. BMC Pulm Med 2021; 21: 159.

Definition 1



Y Abe et al. BMC Pulm Med 2021; 21: 159.

Definition 2



Y Abe et al. BMC Pulm Med 2021; 21: 159.

Future RCT for newly concept of COPD

- **Early COPD**

  : “early” means “near the beginning of a process”

  Biological “early” related to the initial mechanisms that eventually lead to COPD

- **Mild COPD**

  : “mild” should not be used to identify “early” COPD

  only describe the severity of airflow obstruction measured spirometrically

- **COPD in young people → Young COPD**

  : “Young COPD” for those patients included in the 20-50 years age range

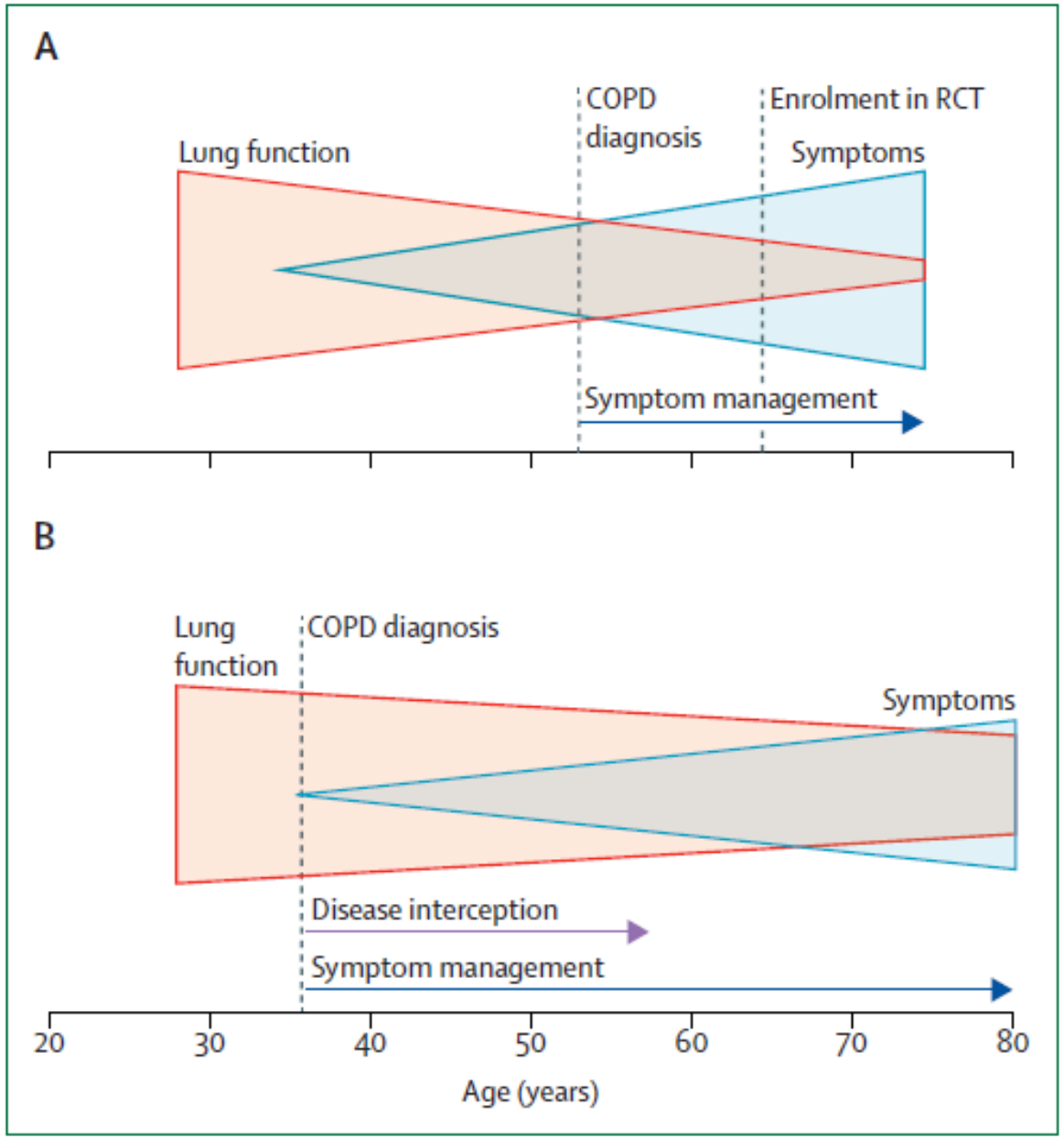
  Associated with significant structural and functional lung abnormalities.

- **Pre-COPD**

  : People who have respiratory symptoms with or without detectable structural and/or functional abnormality, in the absence of airflow limitation.

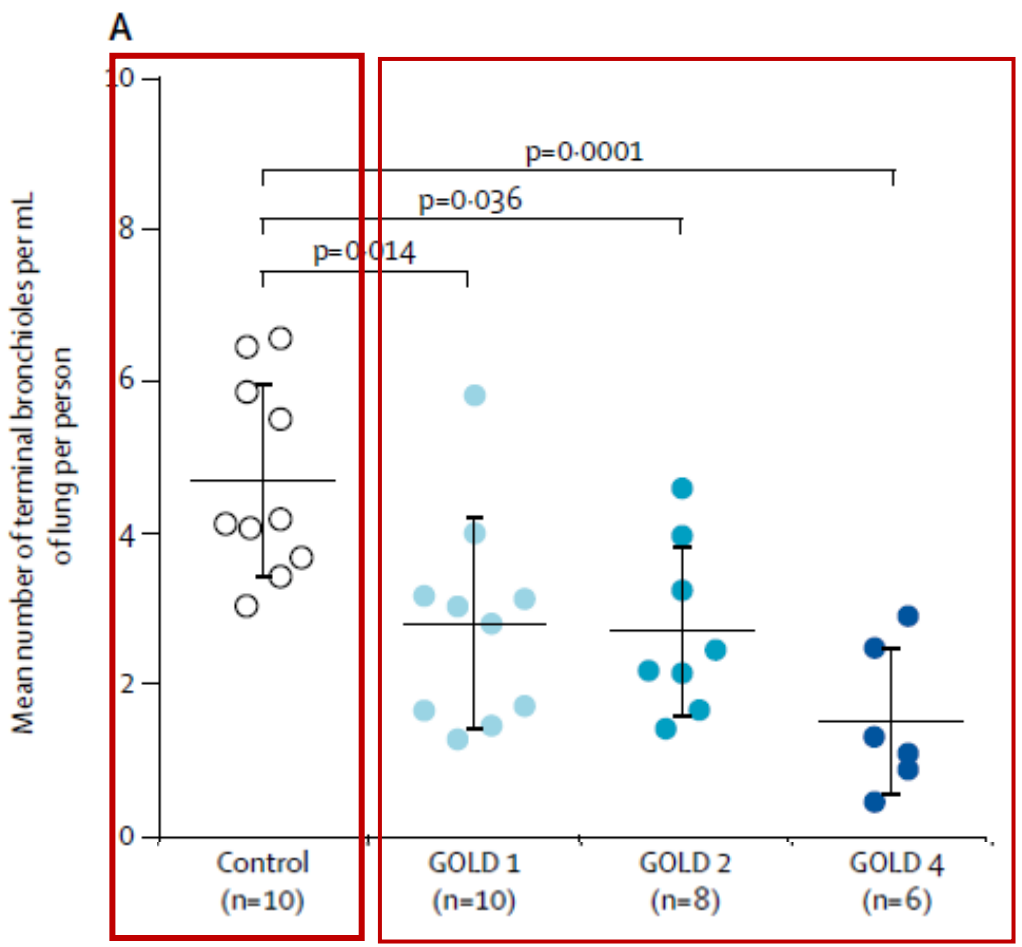
Global Initiative for Chronic Obstructive Lung Disease. Updated 2022 & 2023

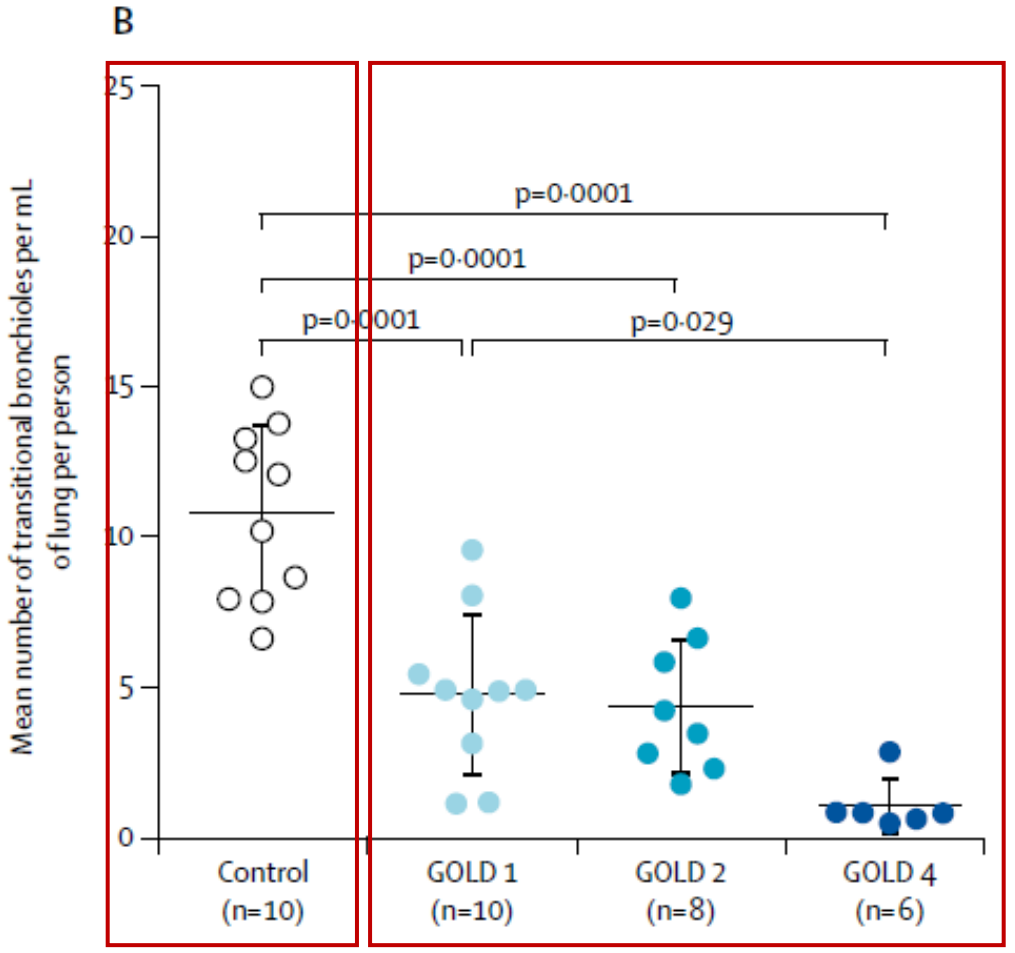
Importance of early diagnosis in COPD



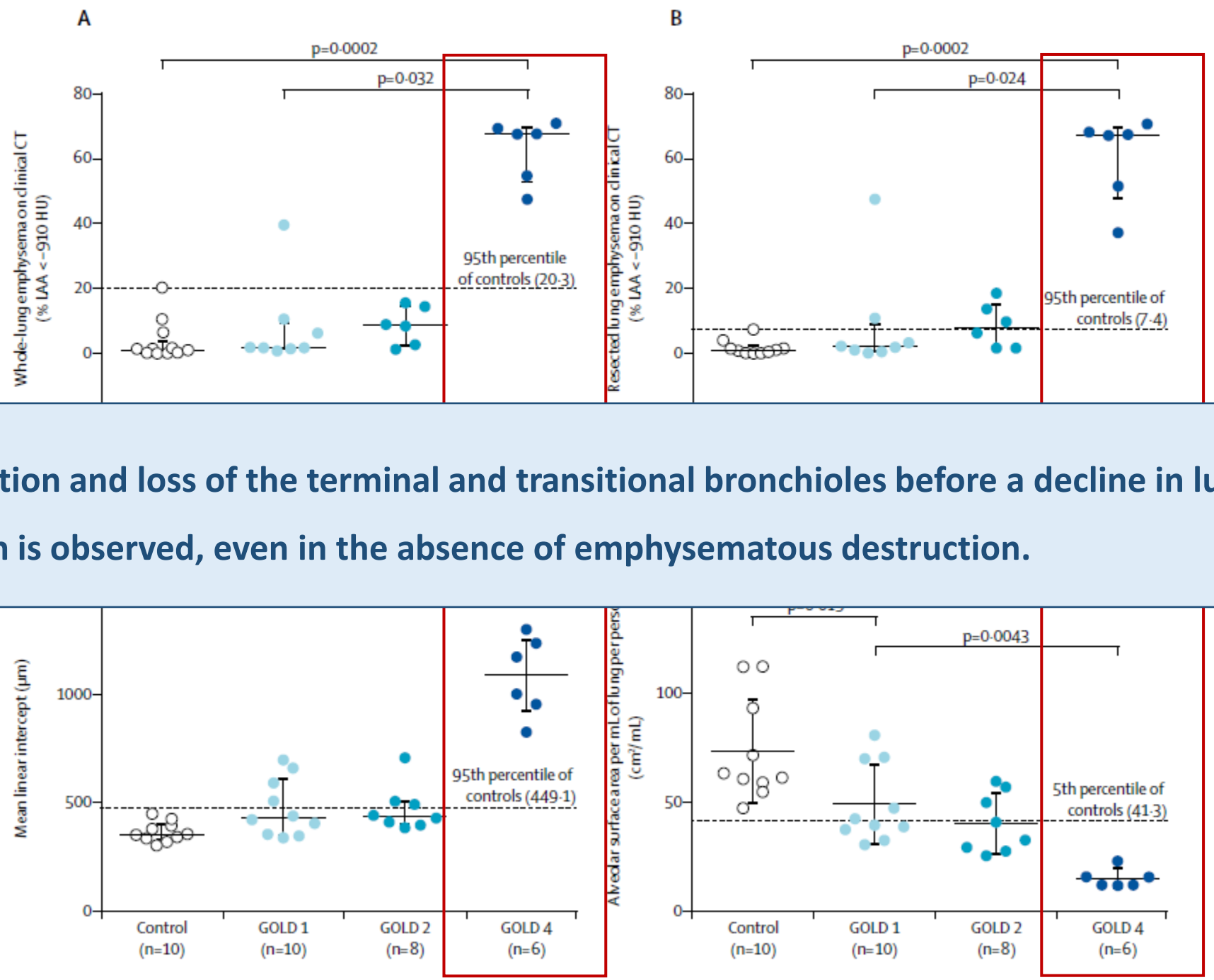
Daiana Stolz et al. Lancet 2022; 400: 921-72.

Quantification of small airways





Koo HK et al. Lancet Respir Med 2018; 6: 591-602.



Destruction and loss of the terminal and transitional bronchioles before a decline in lung function is observed, even in the absence of emphysematous destruction.

Koo HK et al. Lancet Respir Med 2018; 6: 591-602.

Summary

- Outcomes of clinical trials of COPD are lung function, exacerbation, PRO, and mortality.
- Endpoints of clinical trials are associated with disease modifications.
- Clinically important deterioration (CID) is a composite tool that was developed to measure the progression of COPD. It was used to assess the early deterioration of acute worsening of COPD symptoms necessitating additional treatment.
- Many clinical trials shows a good prognostic value of CID in treatment effect.
- The universal application along all ethnic populations is still not determined.
- Future action for finding the appropriate biomarkers of early COPD