Ο ρόλος του τιοτροπίου στην αντιμετώπιση των παροξύνσεων της ΧΑΠ

Θεόδωρος Βασιλακόπουλος

Πνευμονολόγος

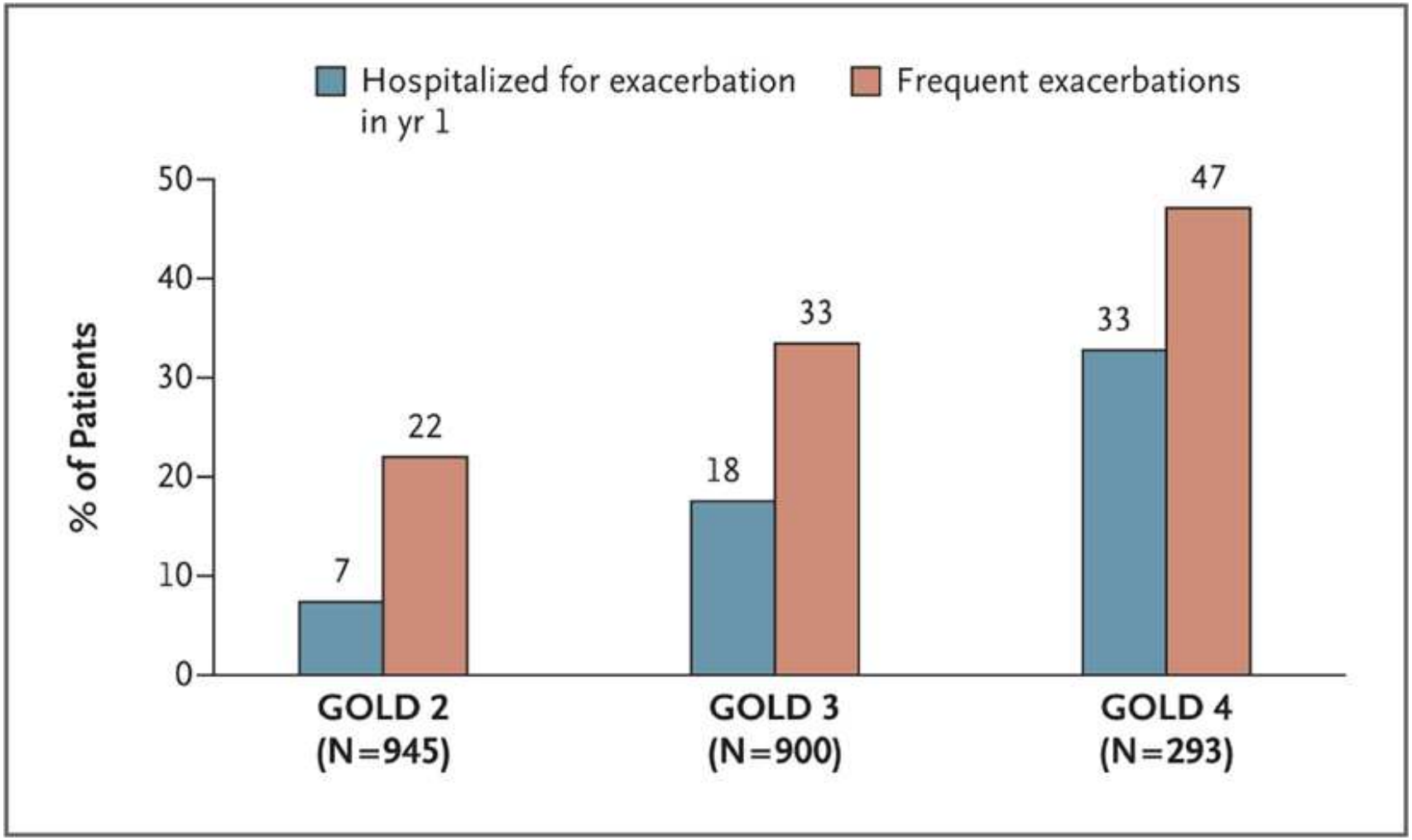
Αναπληρωτής Καθηγητής

Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

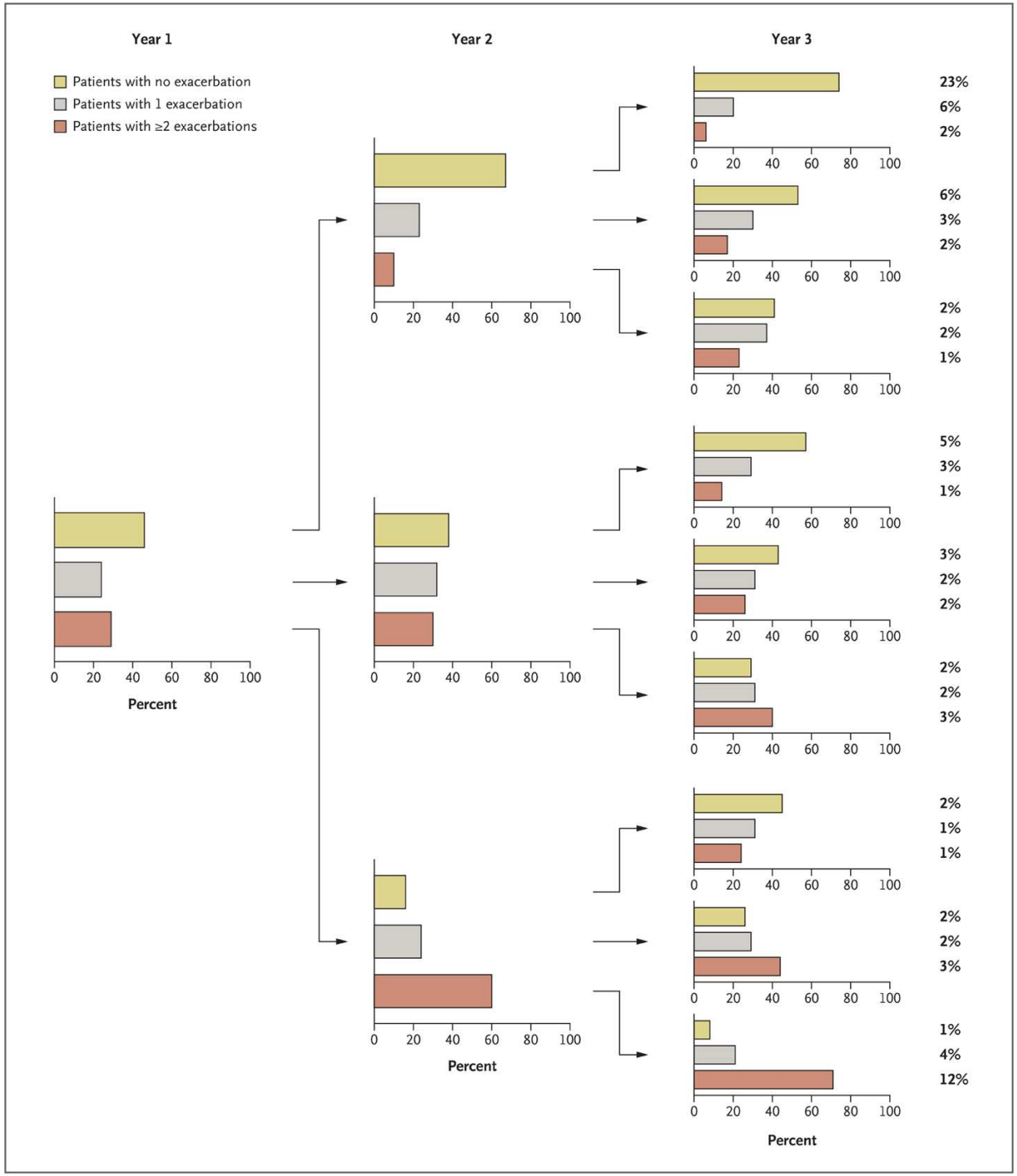
Ειδικός Γραμματέας ΕΠΕ

Γιατί μας ενδιαφέρουν οι παροξύνσεις της ΧΑΠ;

Παροξύνσεις ΧΑΠ κατά στάδιο ΧΑΠ



Hurst JR et al. N Engl J Med 2010;363:1128-1138


Year 1
Year 2
Year 3
Patients with no exacerbation
Patients with 1 exacerbation
Patients with ≥2 exacerbations
0 20 40 60 80 100
Percent
23%
6%
2%
6%
3%
2%
2%
2%
1%
5%
3%
1%
3%
2%
2%
2%
2%
3%
2%
1%
1%
2%
2%
3%
1%
4%
12%

Παράγοντες σχετιζόμενες με συχνές παροξύνσεις στη ΧΑΠ

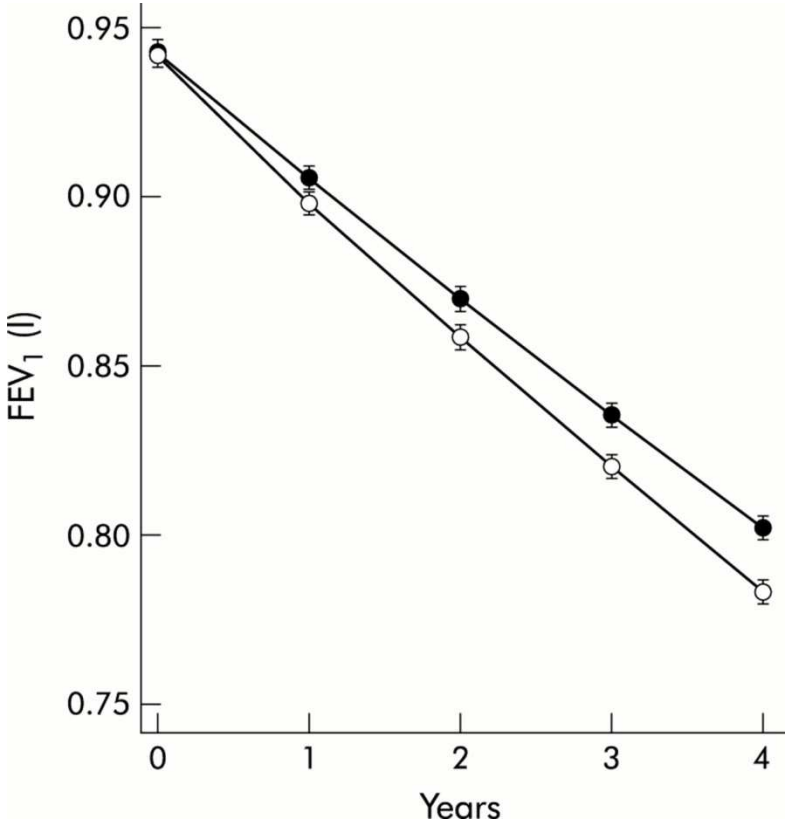
Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.*

Factor	Number of Exacerbations						P Value for Overall Model
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	1.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007

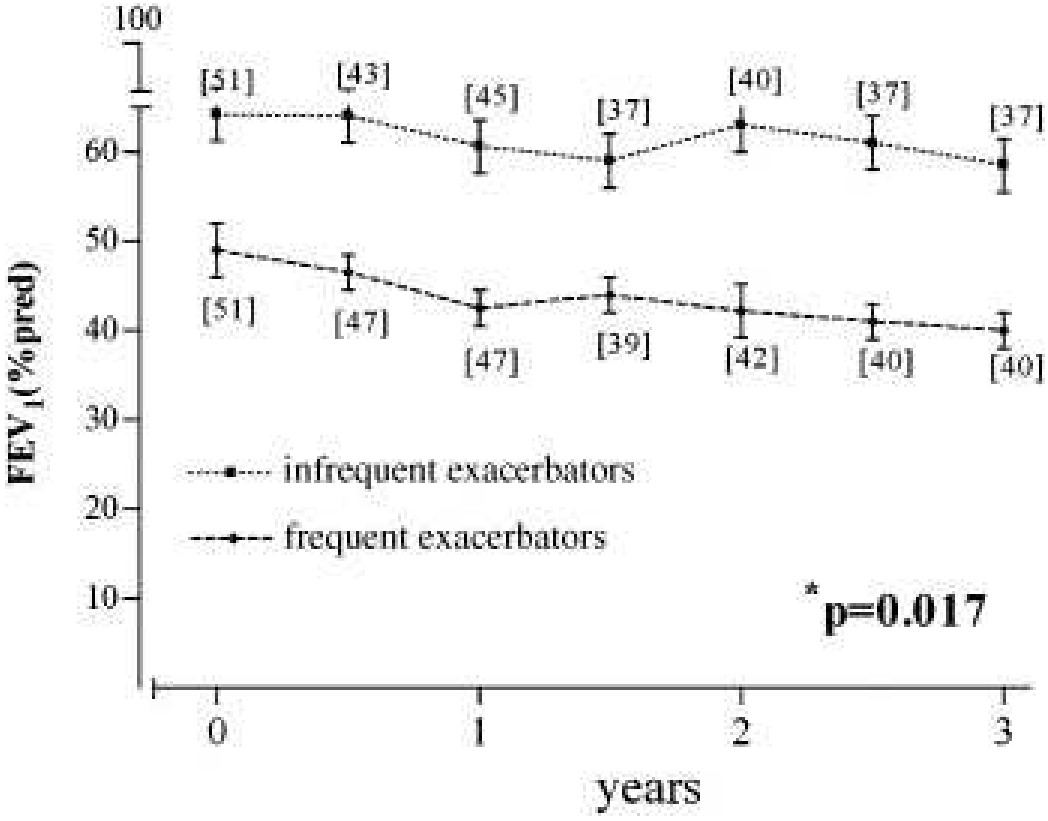
* FEV_1 denotes forced expiratory volume in 1 second, and SGRQ St. George's Respiratory Questionnaire.

Hurst JR et al. N Engl J Med 2010;363:1128-1138

Ο ρυθμός πτώσης του FEV_1 αυξάνει με τις συχνές παροξύνσεις



Donaldson G C et al. Thorax 2002;57:847-852



Makris D et al. Respiratory Medicine 2007;101:1305-1312

Τι προβλέπει τη θνητότητα;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease

Bartolome R. Celli, M.D., Claudia G. Cote, M.D., Jose M. Marin, M.D., Ciro Casanova, M.D., Maria Montes de Oca, M.D., Reina A. Mendez, M.D., Victor Pinto Plata, M.D., and Howard J. Cabral, Ph.D.

N Engl J Med 2004;350:1005-12

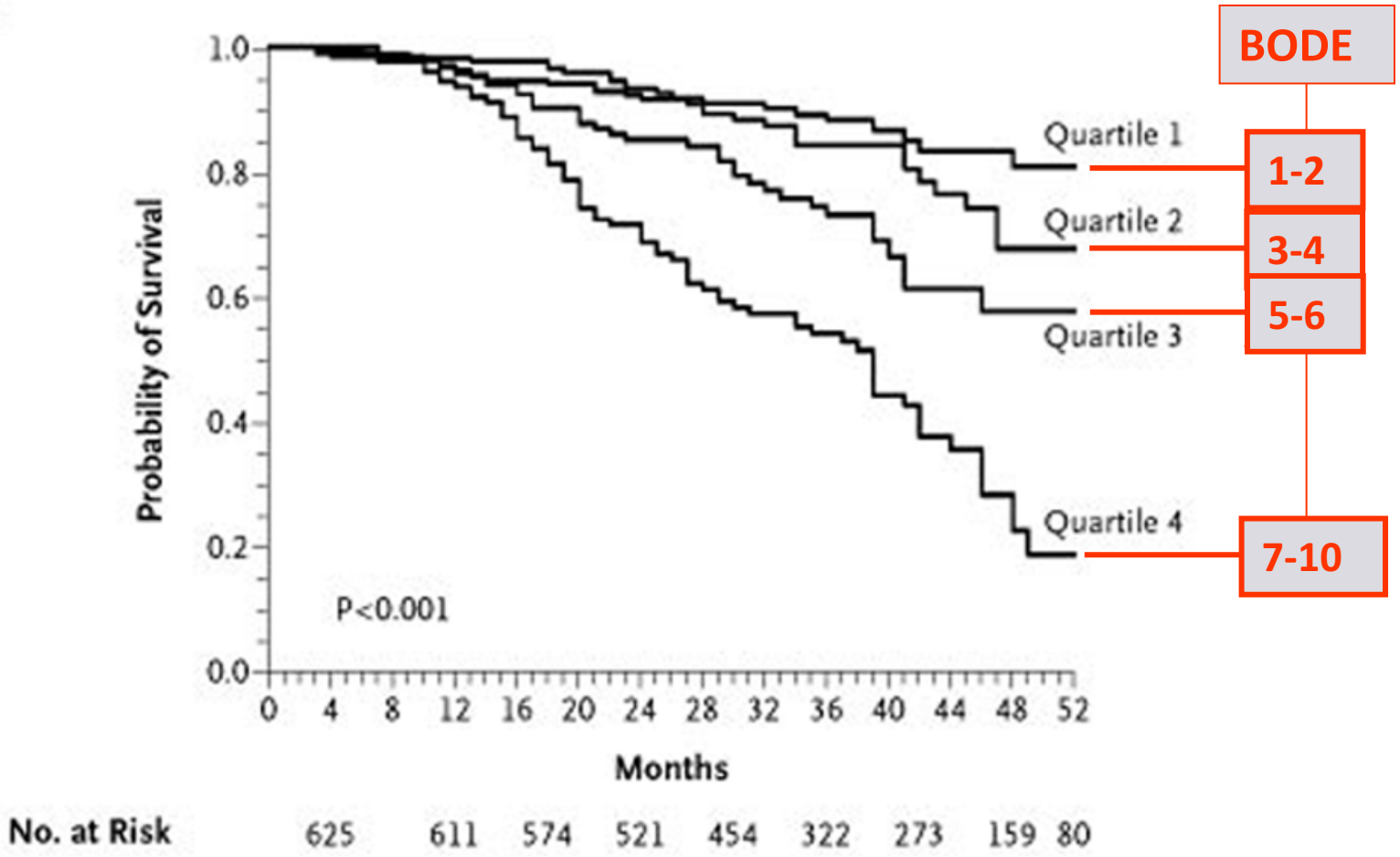
Τι προβλέπει τη θνητότητα;
BODE index

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

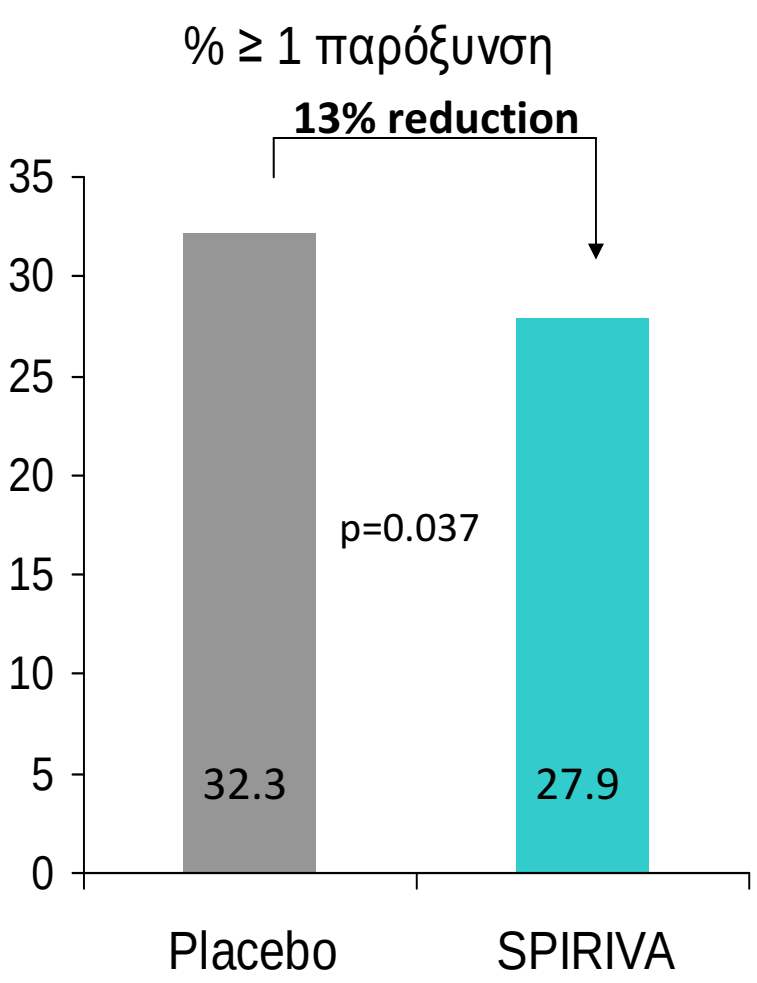
Celli et al, N Engl J Med 2004;350:1005-12

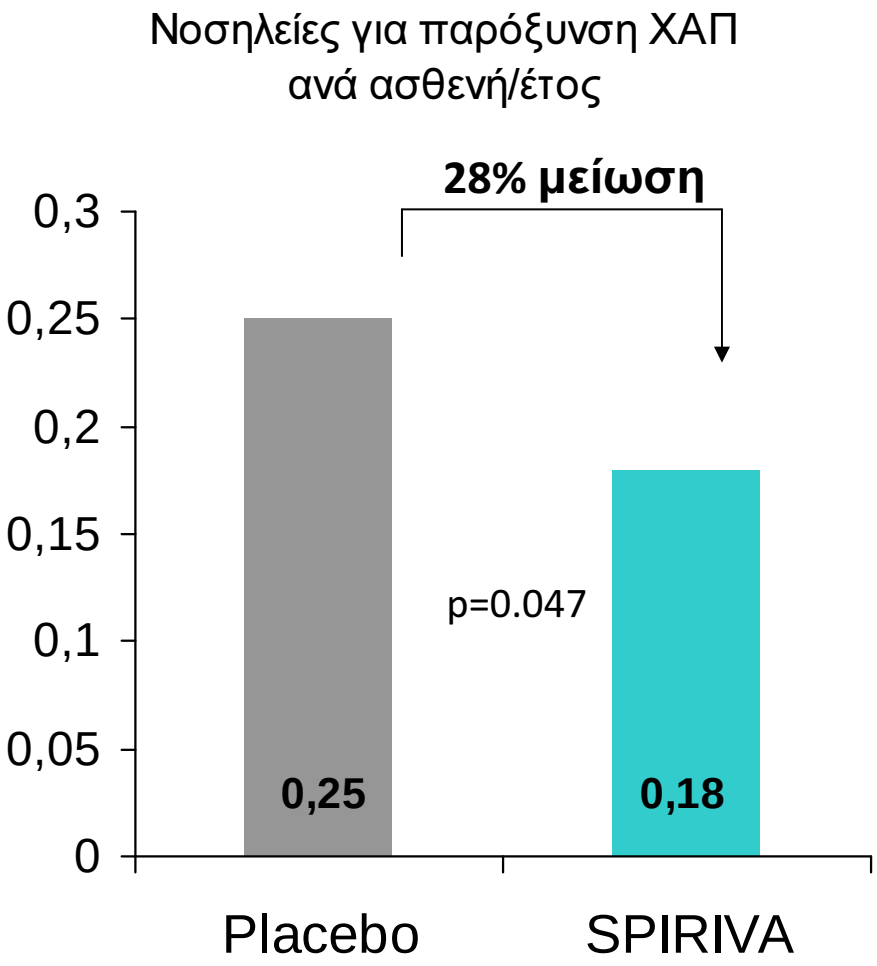
Τι προβλέπει τη θνητότητα;



Celli et al, N Engl J Med 2004;350:1005-12

Τιοτρόπιο: Μείωση των Παροξύνσεων





Niewoehner et al. Ann Intern Med 2005

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

Claus Vogelmeier, M.D., Bettina Hederer, M.D., Thomas Glaab, M.D., Hendrik Schmidt, Ph.D., Maureen P.M.H. Rutten-van Mölken, Ph.D., Kai M. Beeh, M.D., Klaus F. Rabe, M.D., and Leonardo M. Fabbri, M.D., for the POET-COPD Investigators*

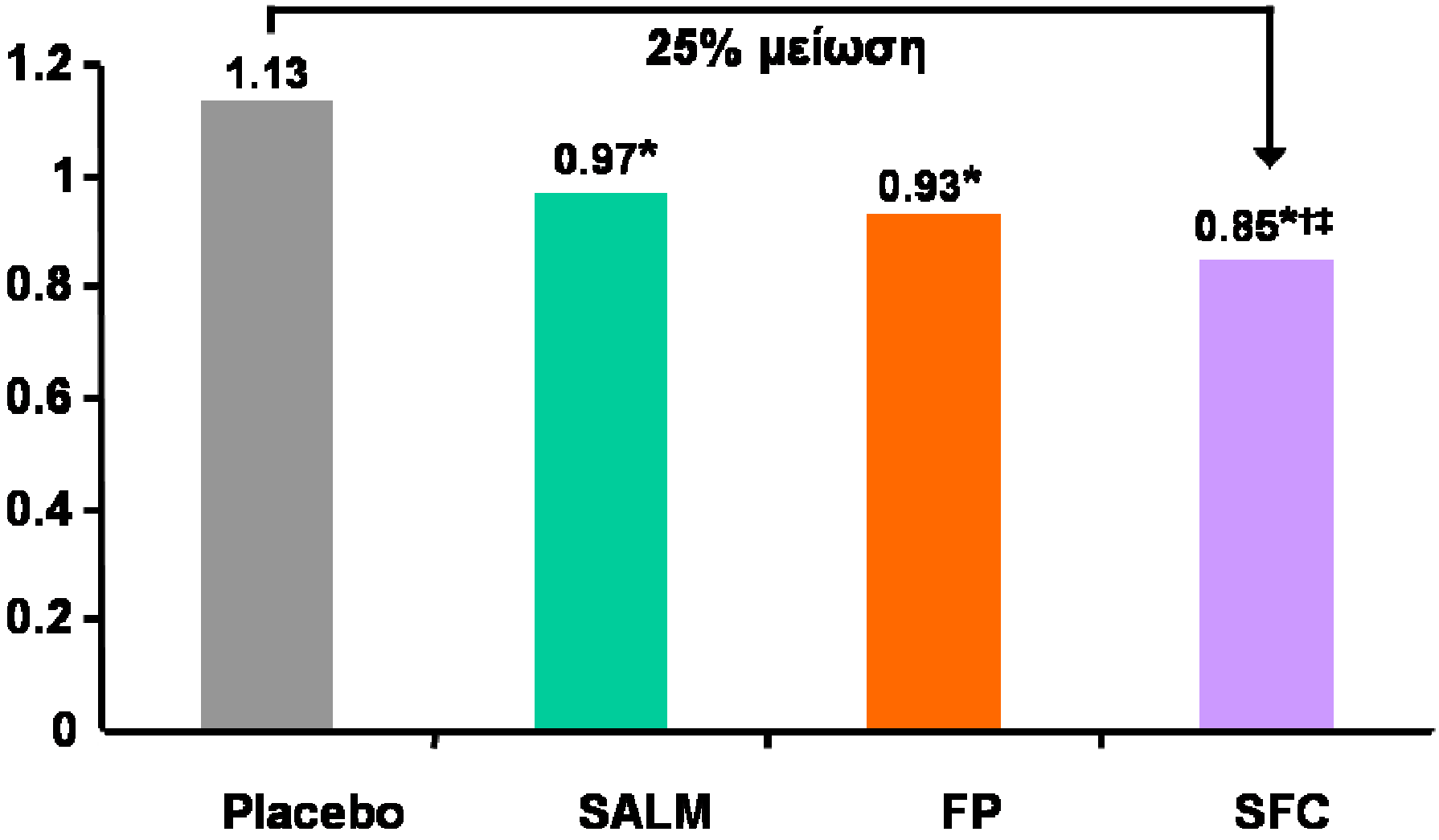
Prevention Of Exacerbations with Tiotropium

Characteristics of POET-COPD® Trial

- First head-to-head trial comparing a long-acting anticholinergic bronchodilator with a LABA on exacerbations outcomes
- Strict focus on exacerbations
- History of exacerbations required
- All concomitant medications permitted except for anticholinergics or LABAs

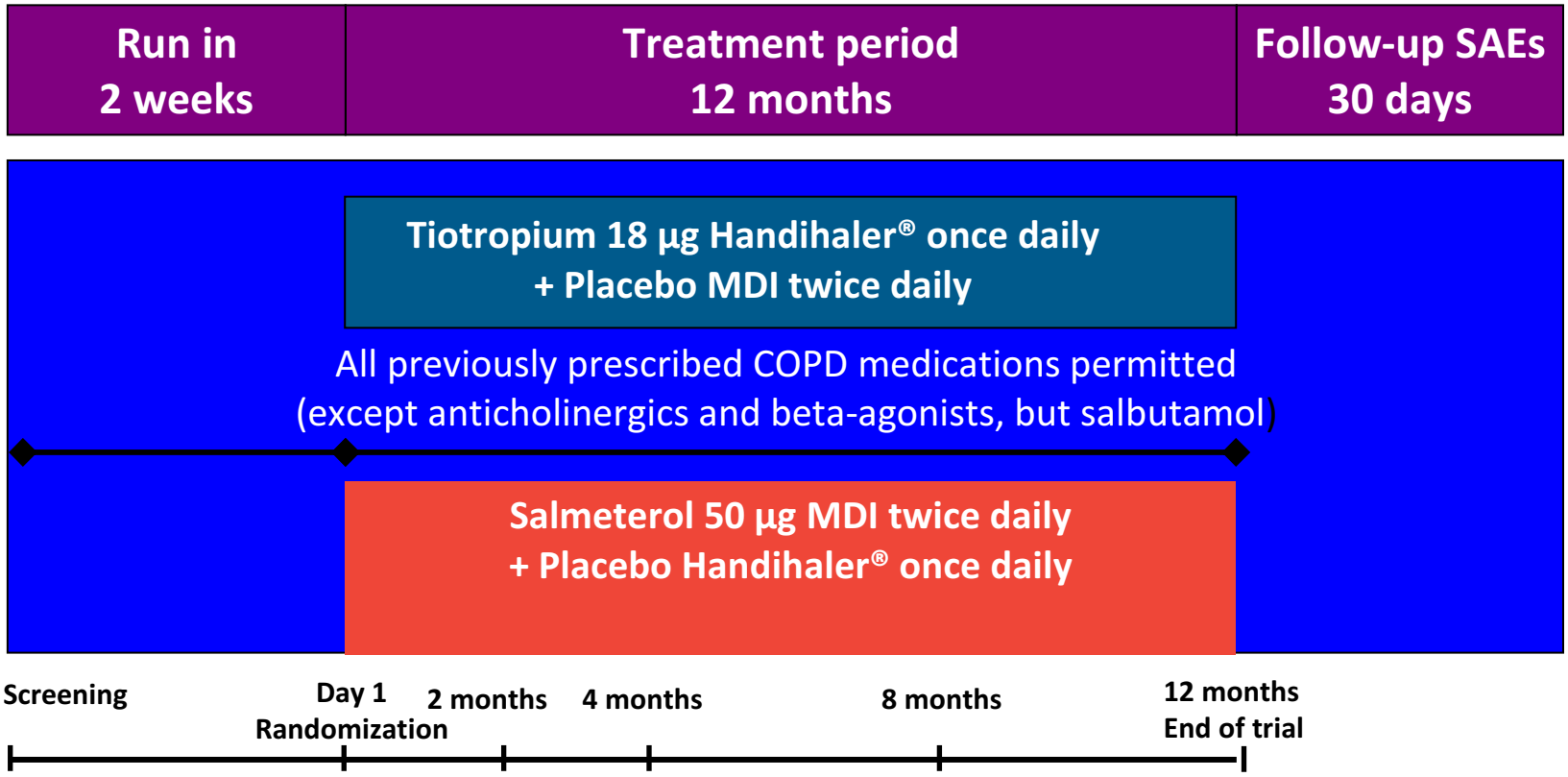
Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

TORCH:Παροξύνσεις ΧΑΠ



Calverley PMA et al. N Engl J Med 2007;356:775-789

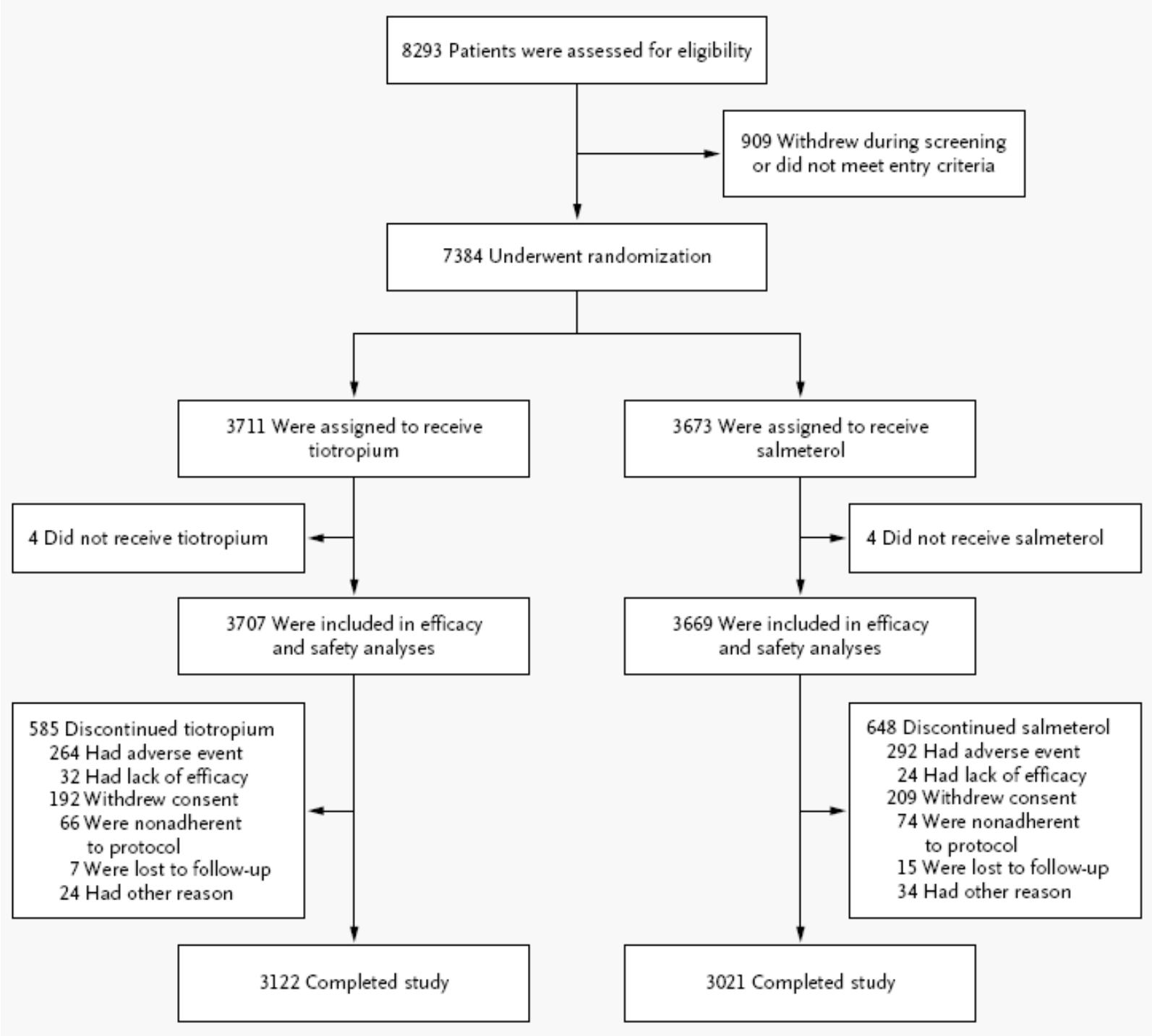
POET-COPD®: A Double-Blind, Double-Dummy Study



Exacerbations at Clinic Visits/Vital Status

MDI=metered-dose inhaler; SAE=serious adverse event.

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.


8293 Patients were assessed for eligibility
909 Withdrew during screening or did not meet entry criteria
7384 Underwent randomization
3711 Were assigned to receive tiotropium
3673 Were assigned to receive salmeterol
4 Did not receive tiotropium
4 Did not receive salmeterol
3707 Were included in efficacy and safety analyses
3669 Were included in efficacy and safety analyses
585 Discontinued tiotropium
264 Had adverse event
32 Had lack of efficacy
192 Withdrew consent
66 Were nonadherent to protocol
7 Were lost to follow-up
24 Had other reason
648 Discontinued salmeterol
292 Had adverse event
24 Had lack of efficacy
209 Withdrew consent
74 Were nonadherent to protocol
15 Were lost to follow-up
34 Had other reason
3122 Completed study
3021 Completed study

POET-COPD®: Primary Endpoint

- Time to first COPD exacerbation

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

POET-COPD®: Ορισμός της παρόξυνσης

- Symptoms
  - ≥2 of the following symptoms:
    - Cough
    - Sputum
    - sputum purulence
    - Wheezing
    - Dyspnea
    - chest tightness
- Duration
  - At least 1 symptom for at least 3 days
- Intervention
  - Antibiotics and/or systemic steroids (moderate exacerbation)
  - And/or hospital admission (severe exacerbation)

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

POET-COPD® Endpoints: Secondary (I)

- Time-to-event:
  - First COPD exacerbation leading to hospitalization (i.e. severe COPD exacerbation)
  - First moderate COPD exacerbation
  - Premature discontinuation of trial medication
  - First COPD exacerbation or discontinuation of study medication because of worsening of underlying disease (whichever came first)
  - First exacerbation treated with systemic steroids
  - First exacerbation treated with antibiotics
  - First exacerbation treated with systemic steroids and antibiotics

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

POET-COPD®: Κριτήρια εισόδου

- Μέτρια έως πολύ σοβαρή ΧΑΠ
    - Μετά βρογχοδιαστολή FEV_1 ≤70% προβλεπόμενης
    - FEV_1/FVC ≤70%
- Ηλικία ≥40 years
- Καπνιστικό ιστορικό ≥10 pack-years
- ≥1 παρόξυνση το τελευταίο έτος που απαιτούσε θεραπεία με
  – Συστηματικά κορτικοειδή
  – Αντιβιοτικά
  – Νοσηλεία σε νοσοκομείο

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N = 3707)	Salmeterol (N = 3669)
Male sex (%)	74.4	74.9
Age (yr)	62.9±9.0	62.8±9.0
Smoking status		
Current smoker (%)	48.0	48.3
Smoking history (pack-yr)	38.8±20.0	37.8±19.2
Duration of COPD (yr)†	8.0±6.7	7.9±6.5
GOLD stage (%)‡		
II	47.8	49.6
III	43.1	42.1
IV	8.9	7.9
Spirometry after bronchodilation§		
FEV_1 (liters)	1.41±0.47	1.41±0.45
FEV_1 (% of predicted value)	49.2±13.3	49.4±13.1
FVC (liters)	2.71±0.81	2.75±0.82
Ratio of FEV_1 to FVC (%)	52.5±10.8	52.4±11.2
Pulmonary medications (%)		
Any	90.0	89.9
Anticholinergic drug		
Tiotropium	30.5	30.3
Short-acting	29.3	29.6
β_2-Agonists		
Long-acting¶	51.5	51.5
Short-acting	52.5	53.4
Glucocorticoids		
Inhaled¶	53.6	53.3
With tiotropium	18.7	18.2
With long-acting β_2-agonists	43.3	43.5
Oral	2.4	2.3
Methylxanthines	23.0	21.2

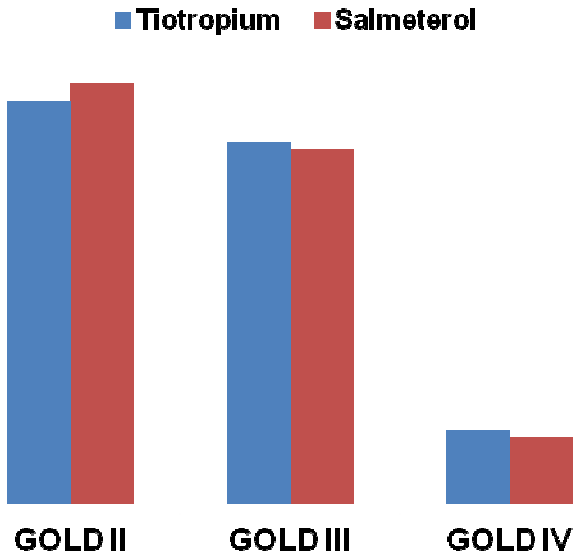
POET-COPD®: Baseline Characteristics

Characteristic	Tiotropium (N=3707)	Salmeterol (N=3669)
Male, %	74.4	74.9
Age, years*	62.9 (9.0)	62.8 (9.0)
Smoking status		
Current smoker, %	48.0	48.3
Smoking history, pack-years*	38.8 (20.0)	37.8 (19.2)
Duration of COPD, years*,†	8.0 (6.7)	7.9 (6.5)
GOLD stage, %‡		
II	47.8	49.6
III	43.1	42.1
IV	8.9	7.9

*Mean (standard deviation).
†Data on duration of COPD missing for 15 and 5 patients in tiotropium and salmeterol groups, respectively.
‡23 patients had GOLD stage I disease (tiotropium 0.2%; salmeterol 0.4%).
GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

POET-COPD®: GOLD Stages and Spirometry at Baseline



	Tiotropium (N=3707)	Salmeterol (N=3669)
FEV_1, L	1.41 (0.47)	1.41 (0.45)
FEV_1, % predicted	49.2 (13.3)	49.4 (13.1)
FVC, L	2.71 (0.81)*	2.75 (0.82)
FEV_1/FVC, %	52.5 (10.8)*	52.4 (11.2)

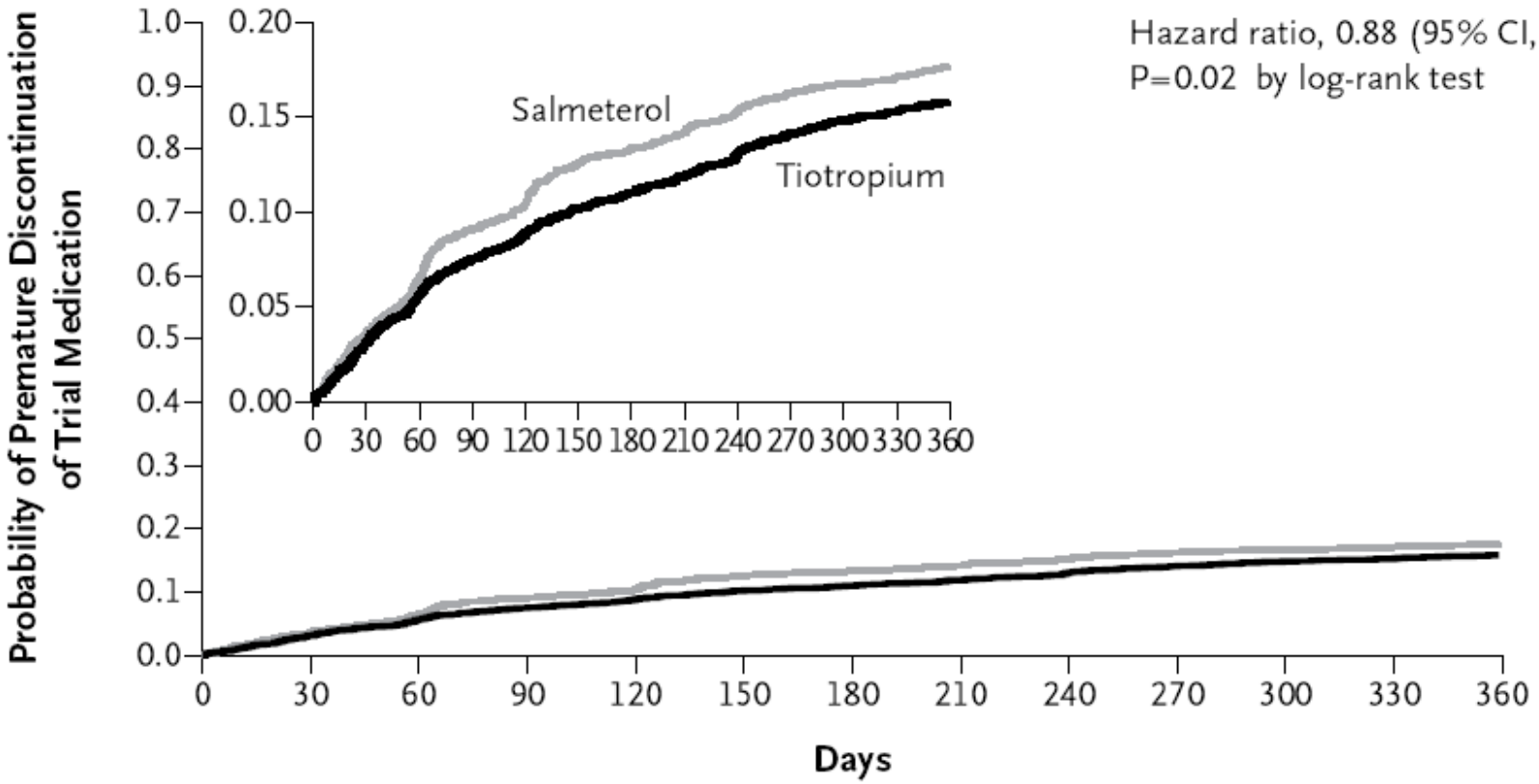
Data are post-bronchodilator, mean (standard deviation)
*Based on 3706 patients (FVC data missing for 1 patient).

GOLD=Global Initiative for Chronic Obstructive Lung Disease;
FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Vogelmeier C et al. *N Engl J Med* 2011;364:1093-1103.

αποτελέσματα

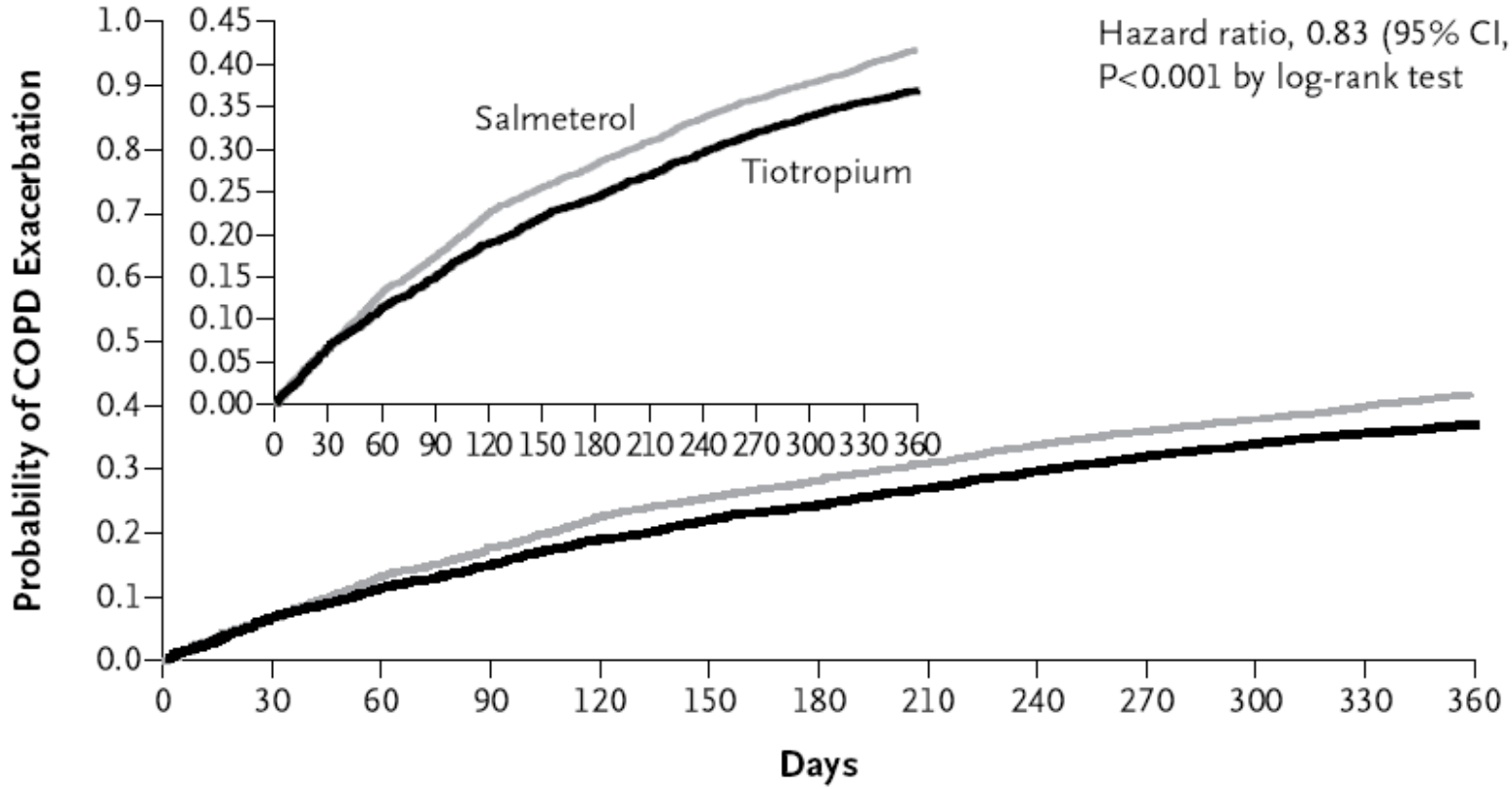
Πιθανότητα απόσυρσης από τη μελέτη



No. at Risk

Tiotropium	3707	3592	3501	3429	3382	3330	3299	3268	3225	3186	3158	3138	2841
Salmeterol	3669	3541	3436	3337	3291	3209	3181	3151	3111	3074	3054	3037	2703

Παροξύνσεις: Τιοτρόπιο vs Σαλμετερόλη

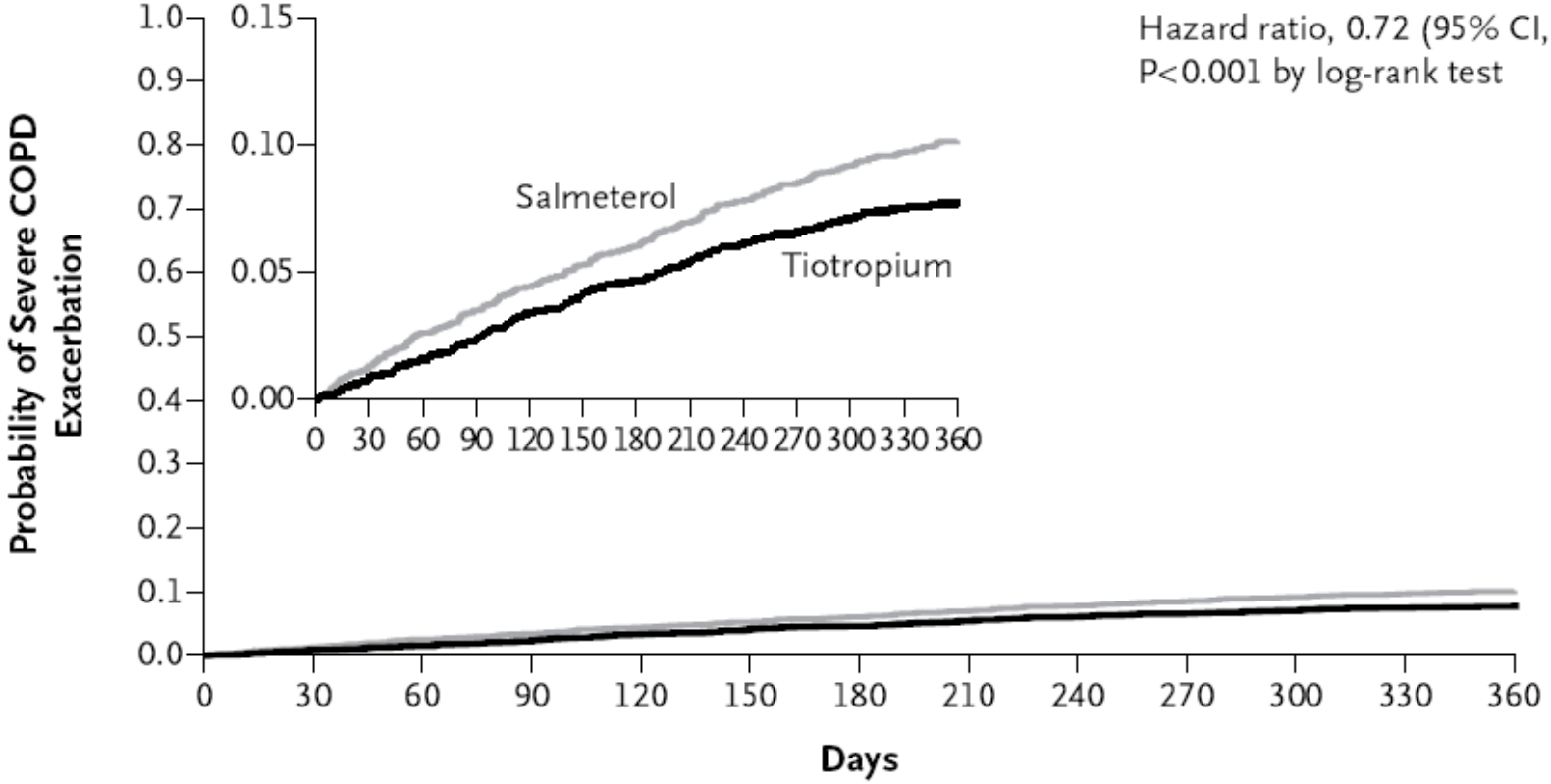


No. at Risk

Tiotropium	3707	3369	3136	2955	2787	2647	2561	2455	2343	2242	2169	2107	1869
Salmeterol	3669	3328	3028	2802	2605	2457	2351	2251	2137	2050	1982	1915	1657

Vogelmeier et al N Engl J Med 2011;364:1093-1103

Σοβαρές παροξύνσεις: Τιοτρόπιο vs Σαλμετερόλη



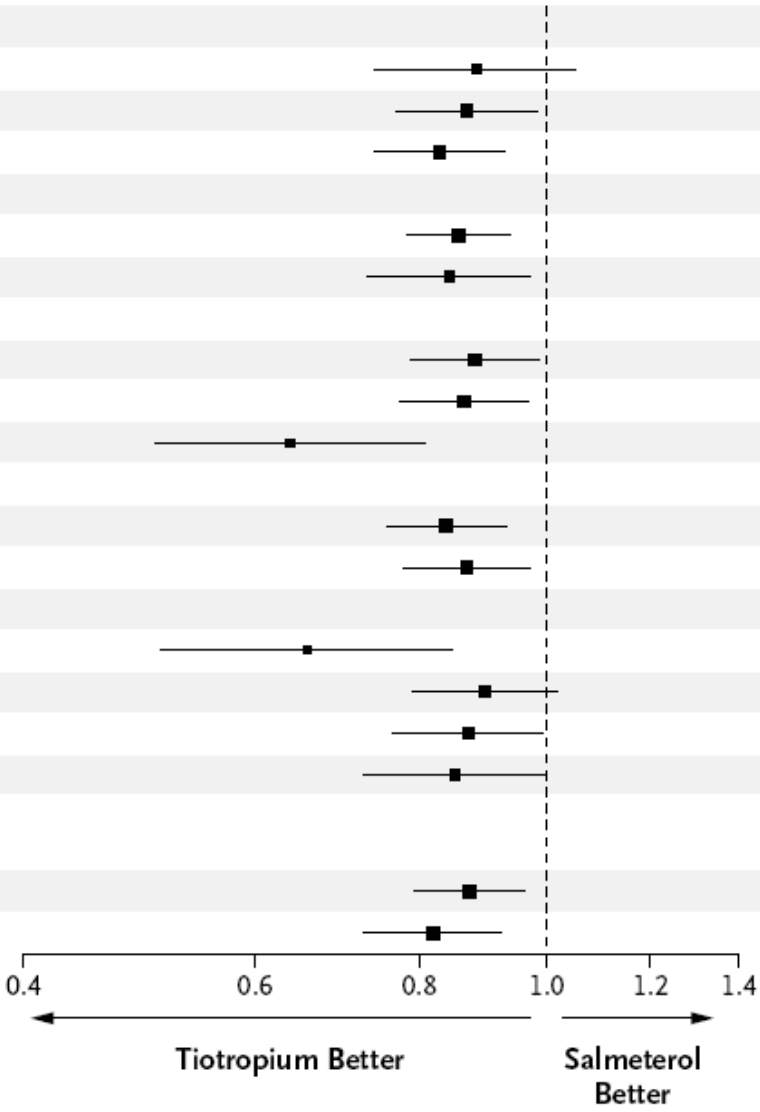
No. at Risk

Tiotropium	3707	3564	3453	3359	3285	3217	3177	3125	3066	3017	2977	2948	2663
Salmeterol	3669	3502	3362	3244	3172	3080	3032	2982	2921	2870	2834	2806	2489

Vogelmeier et al N Engl J Med 2011;364:1093-1103

Ανάλυση υποομάδων

Subgroup	Tiotropium	Salmeterol	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.			
Age (yr)				0.76
<55	237/655	258/665	0.88 (0.74–1.05)	
≥55 to <65	484/1462	522/1426	0.87 (0.77–0.98)	
≥65	556/1590	634/1578	0.83 (0.74–0.93)	
Sex				0.83
Male	913/2759	1016/2747	0.86 (0.78–0.94)	
Female	364/948	398/922	0.84 (0.73–0.97)	
COPD severity stage (GOLD)				0.05
Stage II	561/1781	635/1833	0.88 (0.79–0.99)	
Stage III	589/1597	627/1545	0.86 (0.77–0.97)	
Stage IV	127/329	152/291	0.64 (0.50–0.81)	
Smoking status				0.64
Noncurrent smoker	678/1929	746/1896	0.84 (0.75–0.93)	
Current smoker	599/1778	668/1773	0.87 (0.78–0.97)	
BMI				0.17
<20	105/286	134/271	0.66 (0.51–0.85)	
≥20 to <25	455/1230	501/1254	0.89 (0.79–1.02)	
≥25 to <30	424/1276	468/1284	0.87 (0.76–0.99)	
≥30	293/915	311/860	0.85 (0.72–1.00)	
Use of inhaled glucocorticoids at baseline				0.41
Yes	785/1986	839/1955	0.87 (0.79–0.96)	
No	492/1721	575/1714	0.82 (0.73–0.92)	



Vogelmeier et al N Engl J Med 2011;364:1093-1103

Table 2. Incidence Rates of Serious Adverse Events, According to System Organ Class.*

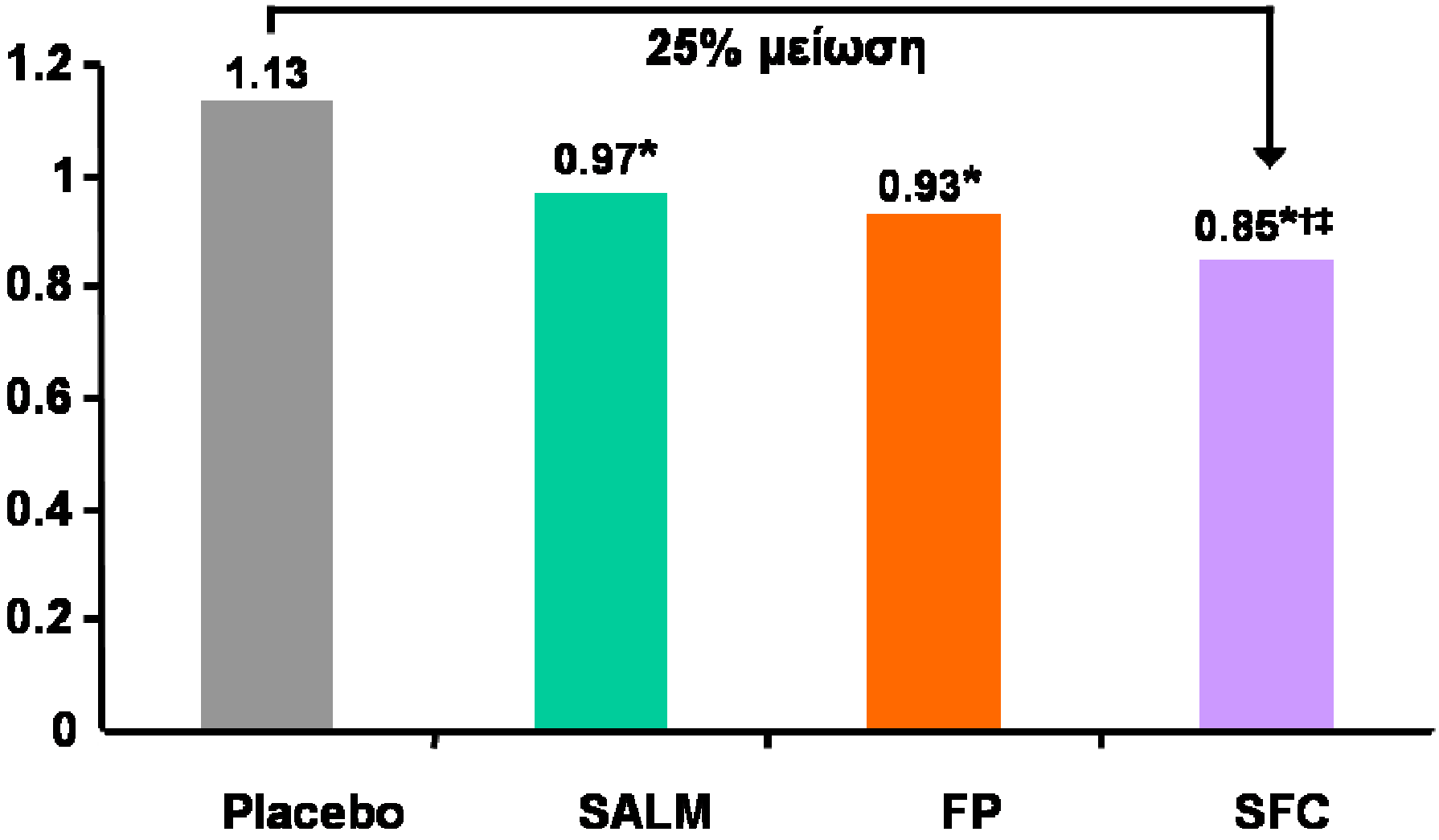
Serious Adverse Events	Tiotropium (N=3707)		Salmeterol (N=3669)		Rate Ratio for Tiotropium vs. Salmeterol (95% CI)
	no. (%)	*rate/100 patient-yr*	*no. (%)*	*rate/100 patient-yr*	
Respiratory, thoracic, and mediastinal events	300 (8.1)	8.66	366 (10.0)	10.99	0.79 (0.68–0.92)
Infections	96 (2.6)	2.69	109 (3.0)	3.15	0.85 (0.65–1.12)
Cardiac events	98 (2.6)	2.73	85 (2.3)	2.44	1.12 (0.84–1.50)
Neoplasms	51 (1.4)	1.42	43 (1.2)	1.23	1.15 (0.77–1.73)
Vascular events	37 (1.0)	1.03	25 (0.7)	0.71	1.44 (0.87–2.39)
Gastrointestinal events	32 (0.9)	0.89	32 (0.9)	0.92	0.97 (0.59–1.58)
Nervous system events	28 (0.8)	0.78	29 (0.8)	0.83	0.94 (0.56–1.58)
General events†	16 (0.4)	0.44	27 (0.7)	0.77	0.57 (0.31–1.07)
Injury, poisoning, and procedural complications	22 (0.6)	0.61	19 (0.5)	0.54	1.13 (0.61–2.08)
Musculoskeletal and connective-tissue events	10 (0.3)	0.28	22 (0.6)	0.63	0.44 (0.21–0.93)

Vogelmeier et al N Engl J Med 2011;364:1093-1103

Αποτελέσματα POET

Το τιοτρόπιο μειώνει τις παροξύνσεις της ΧΑΠ αποτελεσματικότερα από τη σαλμετερόλη

TORCH:Παροξύνσεις ΧΑΠ



Calverley PMA et al. N Engl J Med 2007;356:775-789

INSPIRE: τιοτρόπιο vs σαλμετερόλη/φλουτικαζόνη

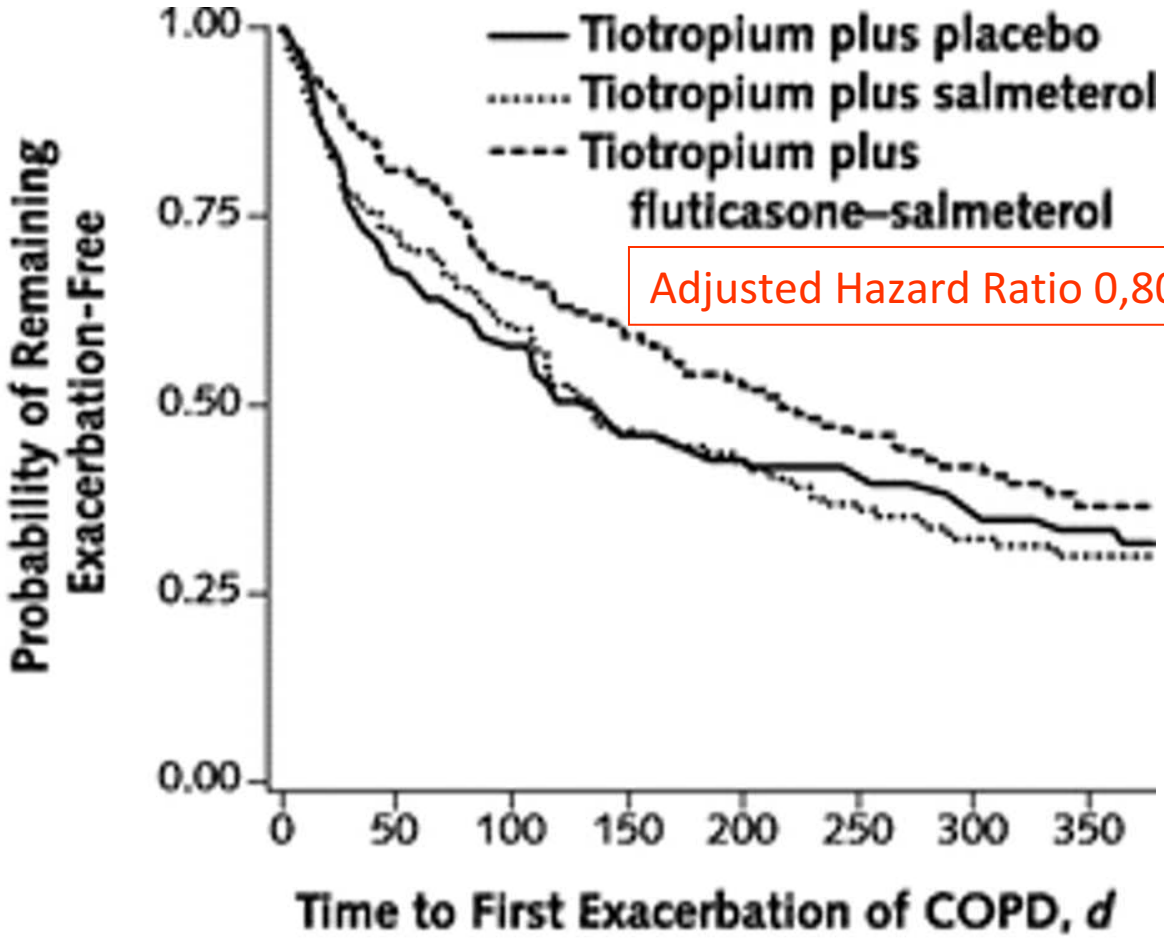
TABLE 3. SUMMARY OF EFFICACY RESULTS

Variable	SFC 50/500 (*n* = 658)	Tiotropium (*n* = 665)	Rate Ratio*	95% CI	*P* Value
		Exacerbations (*mean no./yr*)			
HCU	1.28	1.32	0.97	0.84 to 1.12	0.656
Requiring oral corticosteroids	0.69	0.85	0.81	0.67 to 0.99	0.039
Requiring antibiotics	0.97	0.82	1.19	1.02 to 1.38	0.028
		SGRQ (*adjusted mean change at 2 yr [units]*)			
			Treatment Difference (*units*)*		
Total score	−1.70	0.37	−2.07	−4.02 to −0.12	0.038
Activity score	−0.38	−0.18	−0.56	−2.67 to 1.56	0.605
Impact score	−2.65	0.56	−3.20	−5.36 to −1.05	0.004
Symptom score	−2.94	−0.57	−2.37	−5.02 to 0.28	0.080
		SGRQ (*no. of patients [%] with a change from baseline ≥4 units*)			
			Odds Ratio*		
Week 32	211 (35%)	190 (30%)	1.24	1.01 to 1.54	0.045
Week 56	194 (32%)	180 (29%)	1.29	1.04 to 1.60	0.021
Week 80	198 (33%)	171 (27%)	1.34	1.08 to 1.67	0.008
Week 104	193 (32%)	169 (27%)	1.29	1.04 to 1.60	0.021
		Post-bronchodilator FEV_1 (*adjusted mean change over 2 yr [L]*)			
			Treatment Difference (*L*)*		
Adjusted mean change	−0.01	0.01	−0.02	−0.06 to 0.01	0.218

Definition of abbreviations: CI = confidence interval; HCU = health care utilization; SFC = salmeterol + fluticasone propionate; SGRQ = St. George's Respiratory Questionnaire.

* SFC versus tiotropium.

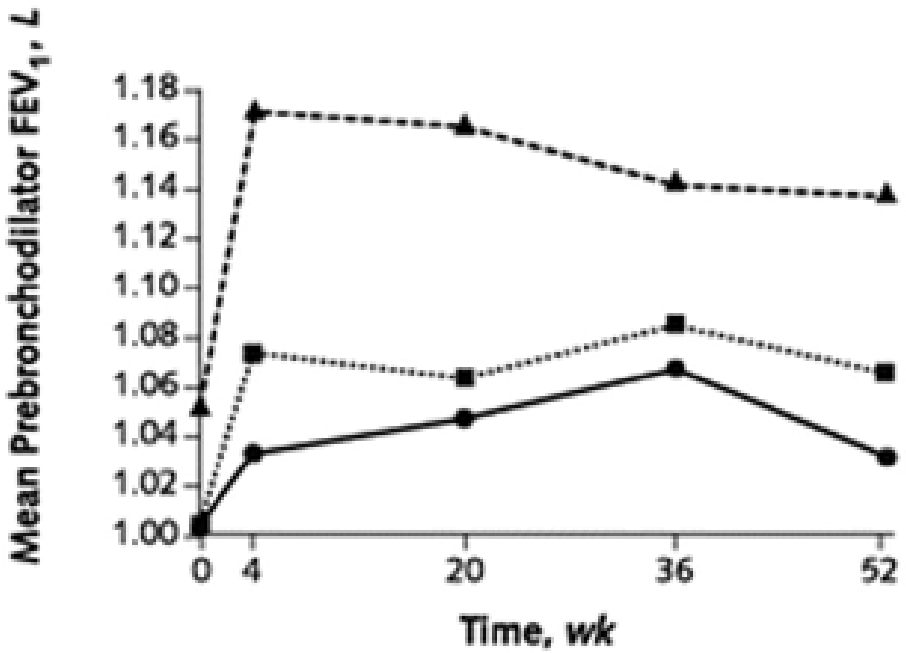
Wedzicha et al, Am J Respir Crit Care Med 2008:177:19-26



Adjusted Hazard Ratio 0,80, p=0,15

Patients at risk, *n*								
Tiotropium plus placebo	156	102	84	65	59	57	50	45
Tiotropium plus salmeterol	148	100	81	61	55	48	41	38
Tiotropium plus fluticasone–salmeterol	145	116	94	82	72	62	55	48

FEV_1



Patients with valid observations at each time point, *n*					
Tiotropium plus placebo	152	141	128	123	120
Tiotropium plus salmeterol	146	137	117	117	115
Tiotropium plus fluticasone–salmeterol	142	141	129	125	122

Tiotropium plus placebo — Tiotropium plus salmeterol — Tiotropium plus fluticasone–salmeterol

Aaron S D et al. Ann Intern Med 2007;146:545-555

UPLIFT Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

Σχεδιασμός μελέτης

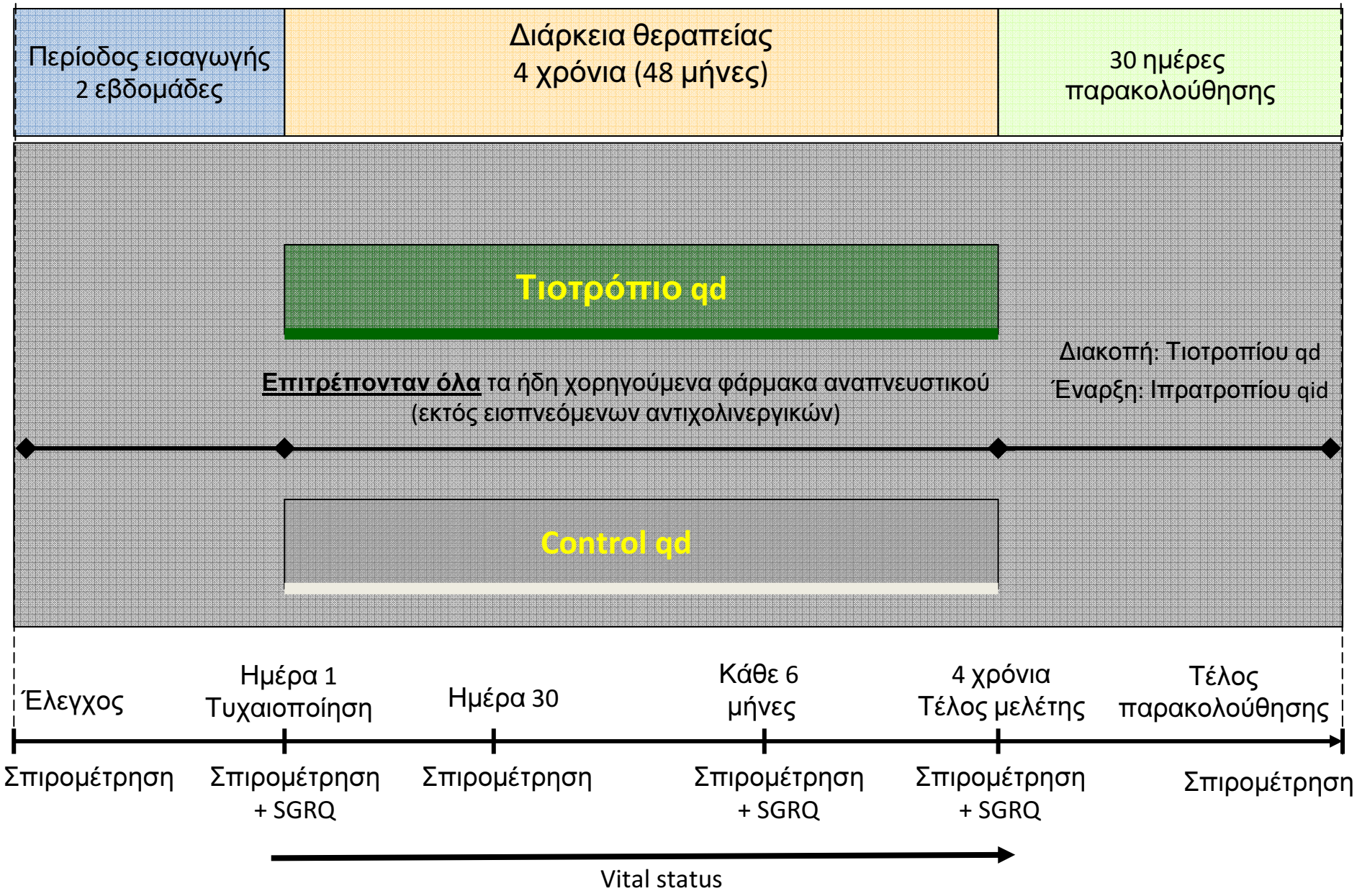


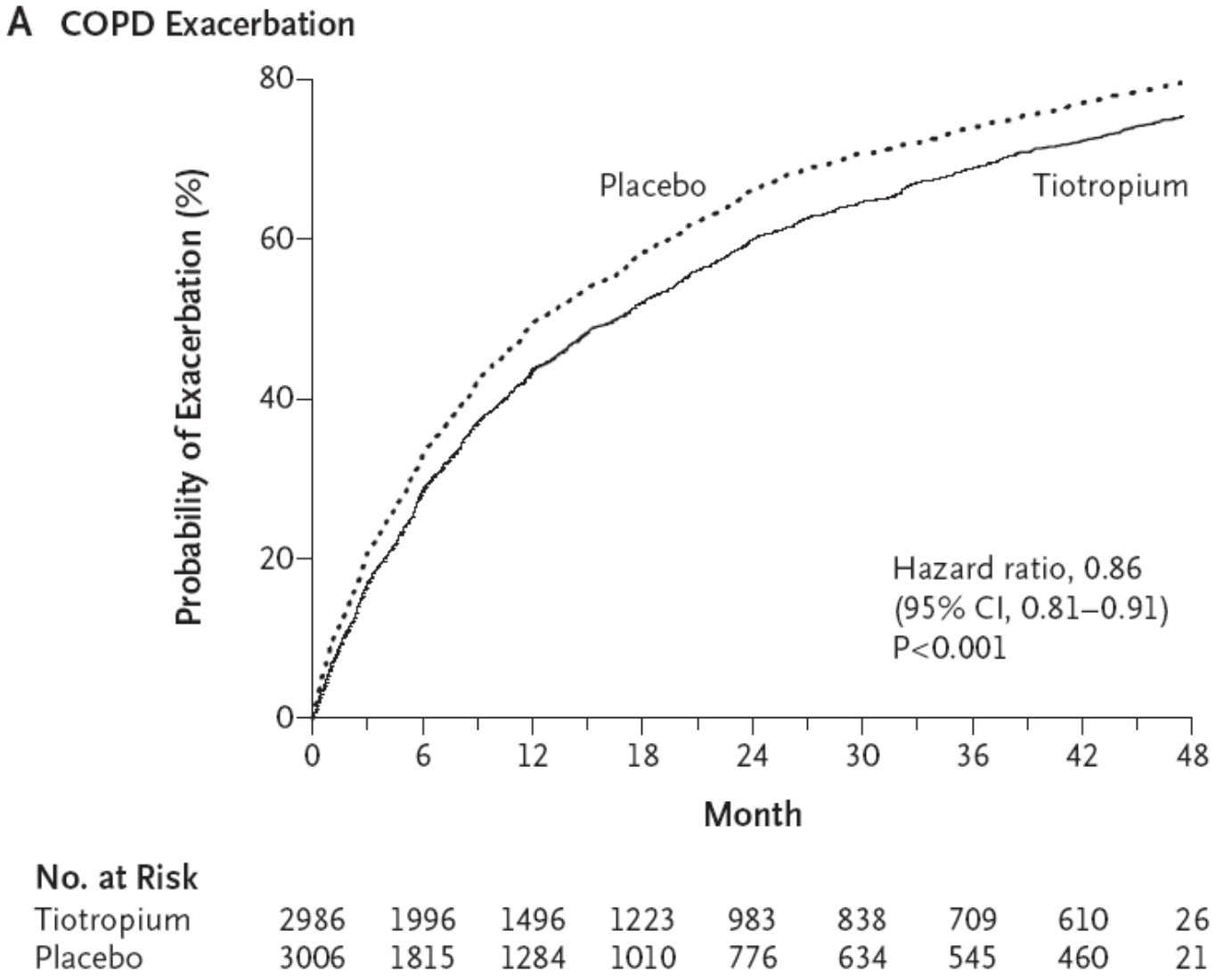
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=2986)	Placebo (N=3006)
Male sex (%)	75.4	73.9
Age (yr)	64.5±8.4	64.5±8.5
Body-mass index	26.0±5.1	25.9±5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yr)	49.0±28.0	48.4±27.9
Duration of COPD (yr)	9.9±7.6	9.7±7.4
Baseline spirometry		
Before bronchodilation		
FEV_1 (liters)	1.10±0.40	1.09±0.40
FEV_1 (% of predicted value)	39.5±12.0	39.3±11.9
FVC (liters)	2.63±0.81	2.63±0.83
Ratio of FEV_1 to FVC	42.4±10.5	42.1±10.5
After bronchodilation		
FEV_1 (liters)	1.33±0.44	1.32±0.44
FEV_1 (% of predicted value)	47.7±12.7	47.4±12.6
FVC (liters)	3.09±0.86	3.09±0.90
Ratio of FEV_1 to FVC	43.6±10.8	43.3±10.7
GOLD stage (%)†		
II	46	45
III	44	44
IV	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β_2-agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	2.3	1.9

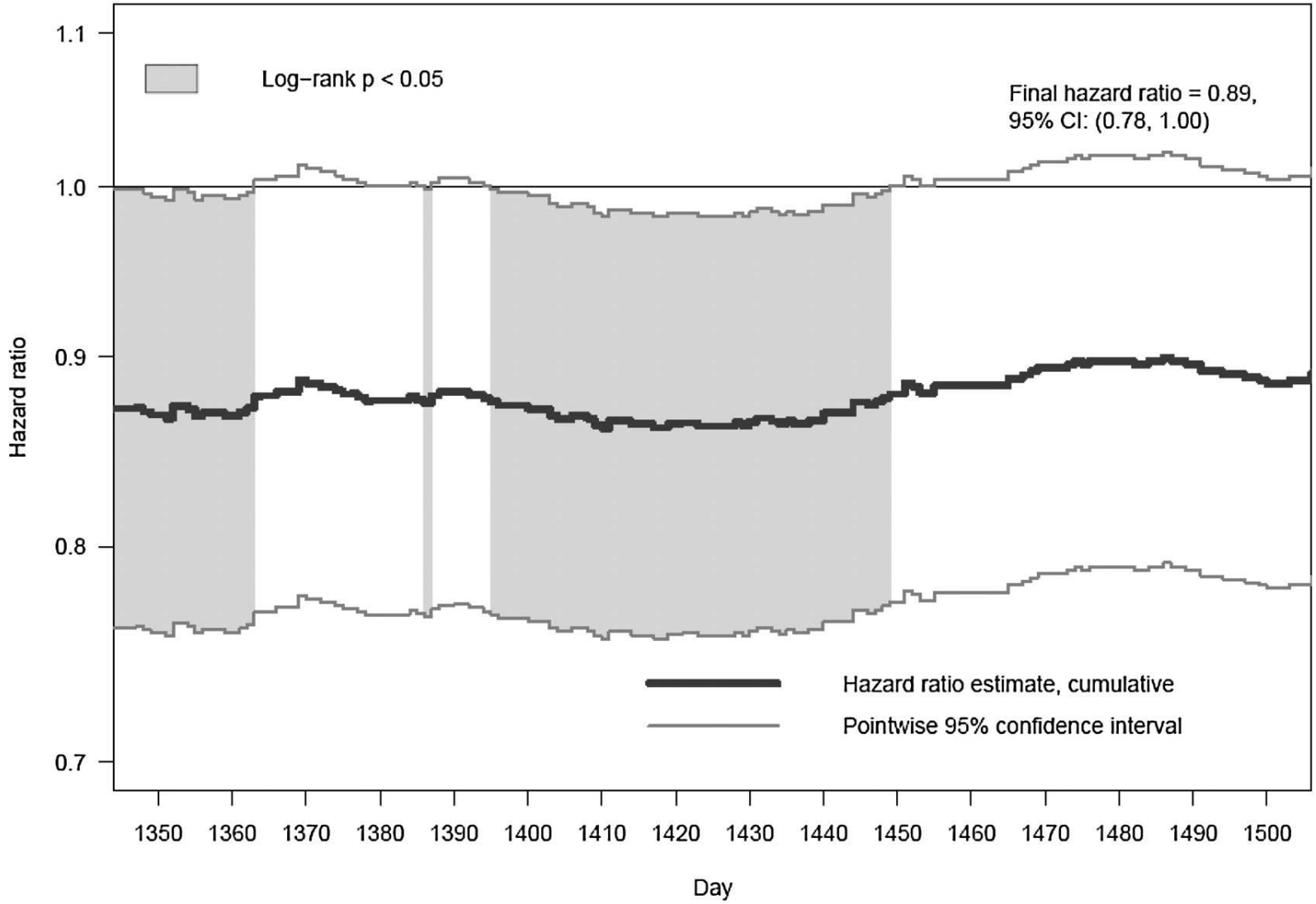
Δημογραφικά χαρακτηριστικά ασθενών

Characteristic	Tiotropium (n=2986)	Placebo (n=3006)
GOLD stage II (%)†	46	45
GOLD stage III (%)†	44	44
GOLD stage IV (%)†	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Short-acting inhaled anticholinergic §	44.9	44.1
Long-acting inhaled anticholinergic §	2.0	1.6
Short-acting inhaled $ß_2$-agonist §	68.5	68.1
Long-acting inhaled $ß_2$-agonist §	60.1	60.1
Inhaled corticosteroids §	61.6	61.9
Oral corticosteroids	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	2.3	1.9

Το τιοτρόπιο μειώνει τις παροξύνσεις της ΧΑΠ



Το τιοτρόπιο μειώνει τη Θνητότητα στη ΧΑΠ

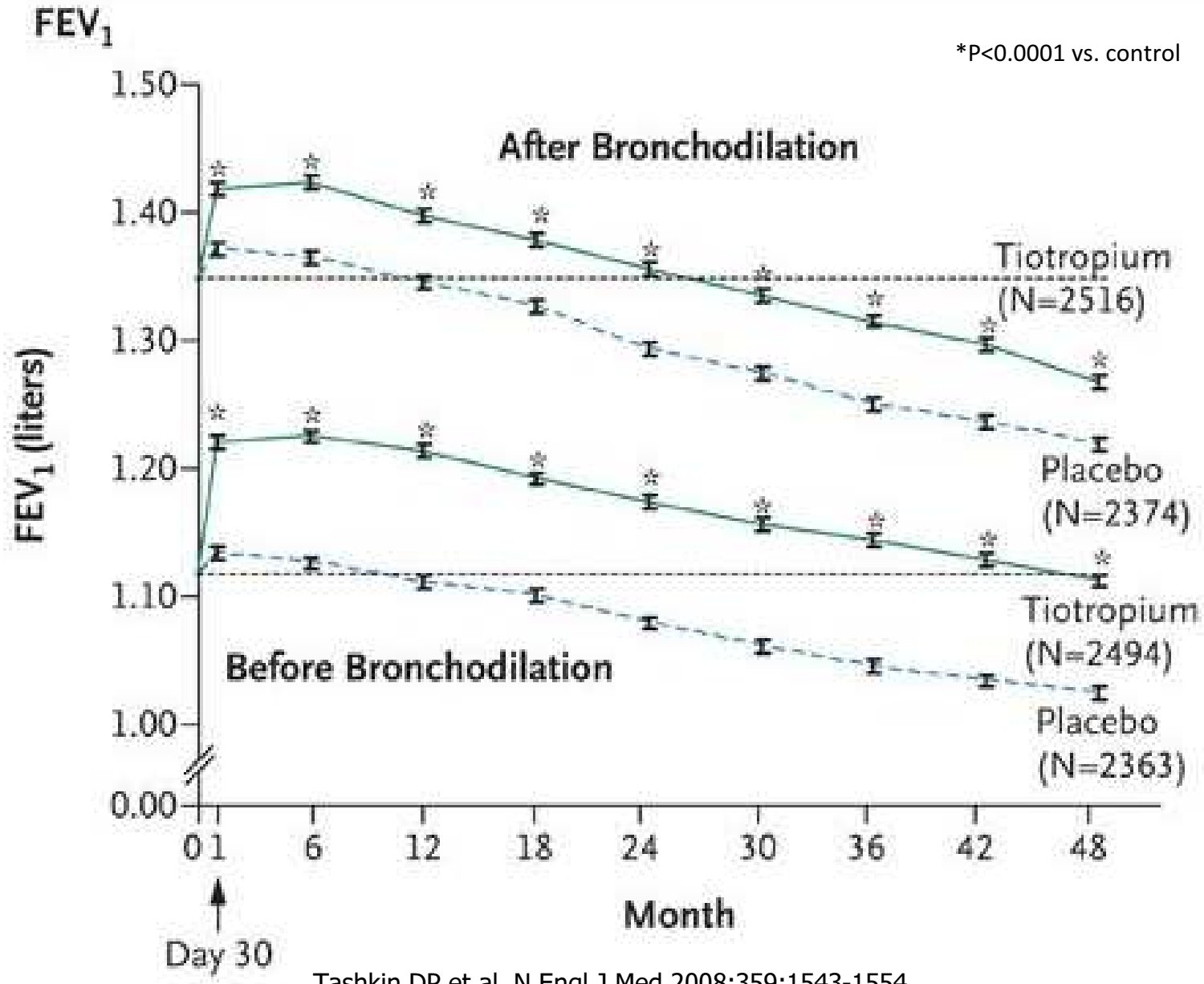


mulative censoring:

Tiotropium	59	61	61	62	62	73	86	97	112	137	178	225	736	2006	2187	2322
Control	83	84	84	84	88	95	117	129	145	164	196	249	741	2024	2187	2289

Celli B et al, Am J Respir Crit Care Med 2009;180:948-55

Το τιοτρόπιο βελτιώνει τον προ και μετά βρογχοδιαστολή FEV_1



Tashkin DP et al. N Engl J Med 2008;359:1543-1554

Θεραπεία της ΧΑΠ σε πρώιμα στάδια

(stage II)

UPLIFT

- Η UPLIFT περιλαμβάνει μεγάλο αριθμό ασθενών GOLD stage II (2,739 ασθενείς, 46% των ασθενών της μελέτης).

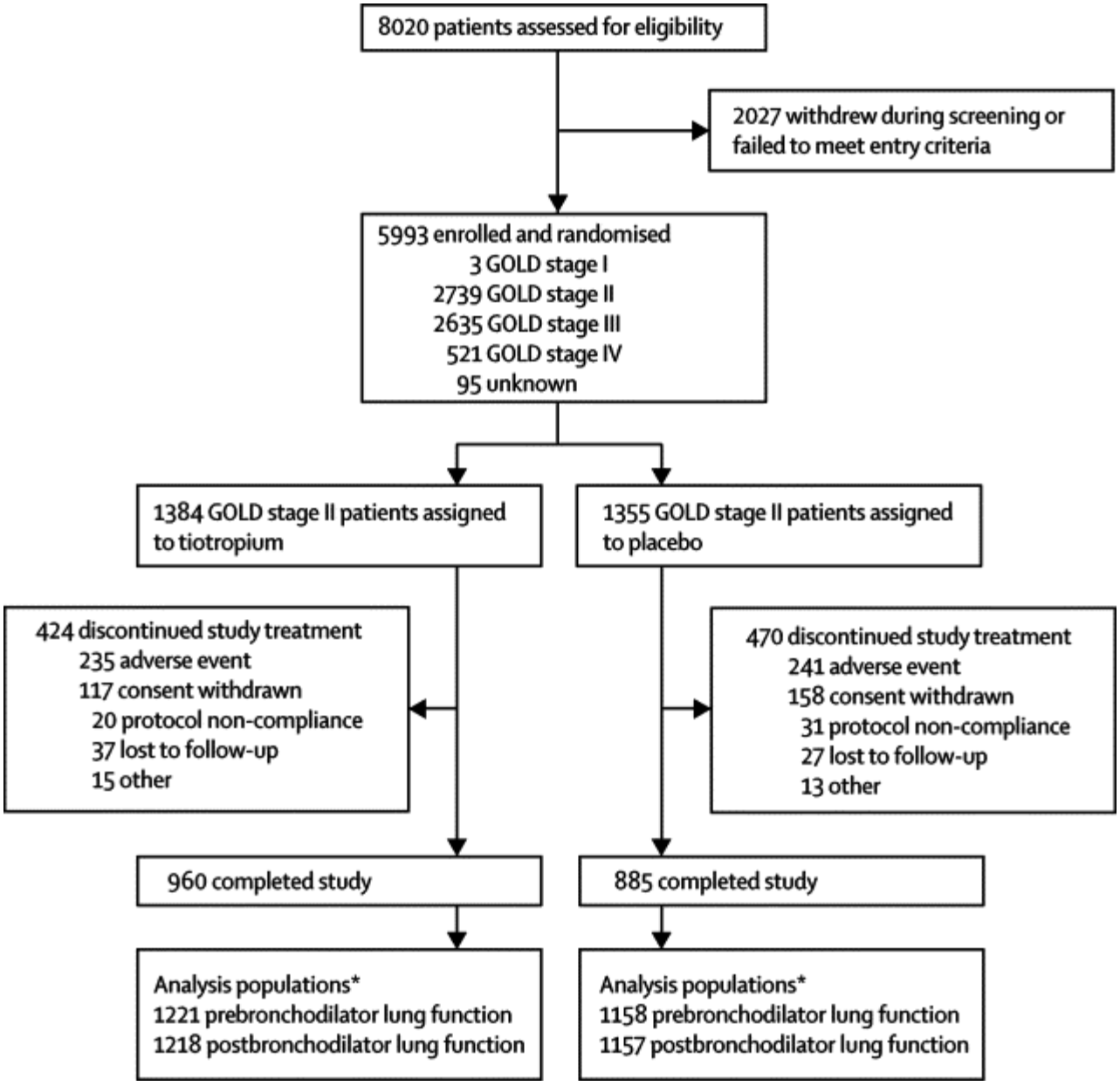
- Ο μεγαλύτερος αριθμός ασθενών που έχει λάβει μακράς δράσης αντιχολινεργικό (τιοτρόπιο) σε κλινική μελέτη με περίοδο παρακολούθησης 4 έτη.

UPLIFT :Προσχεδιασμένη ανάλυση

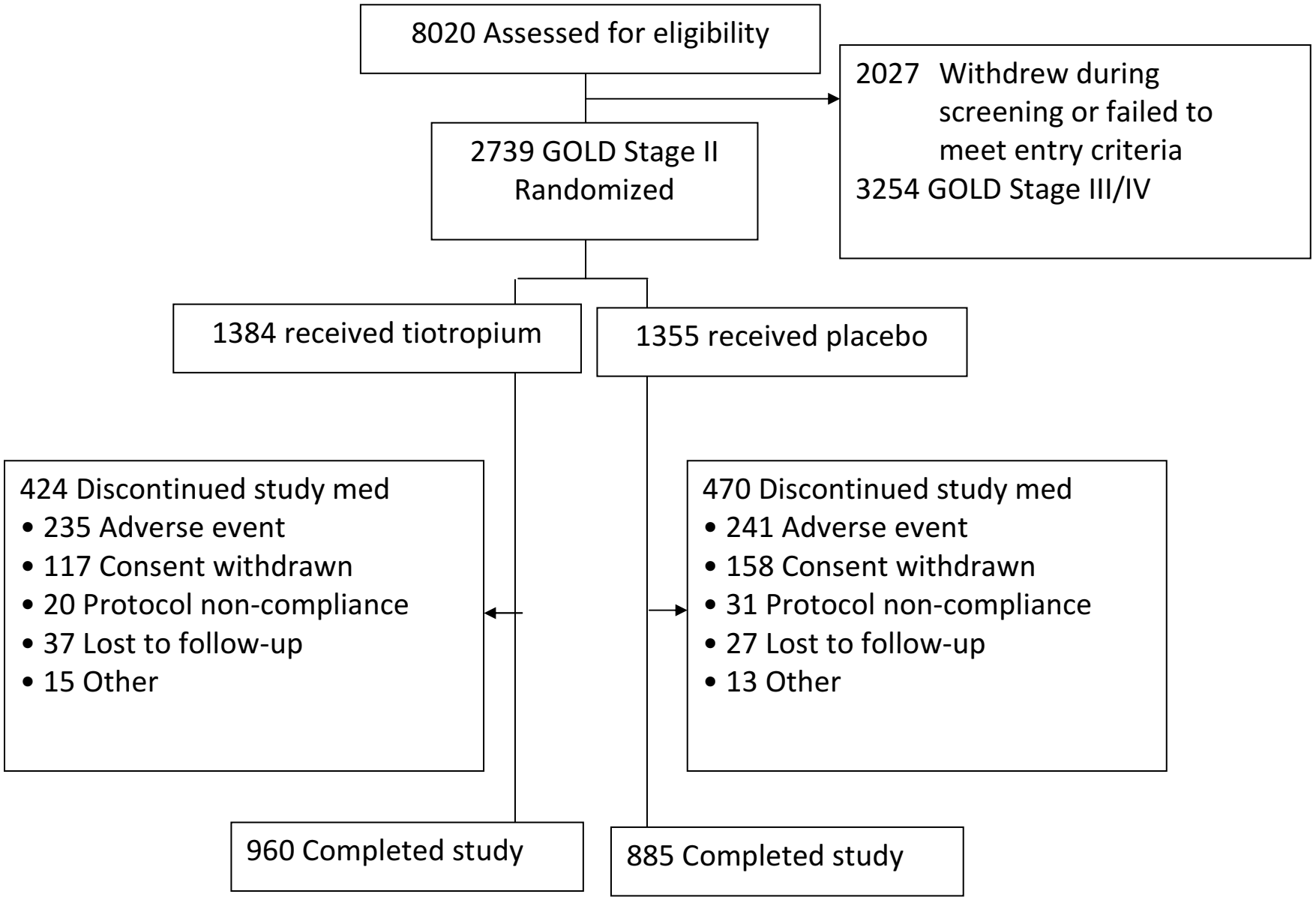
- Στόχος: Ανάλυση των μακροχρόνιων αποτελεσμάτων του τιοτροπίου σε ασθενείς με ΧΑΠ GOLD στάδιου II*.

*The analyses by GOLD stage were pre-specified before database lock.

Decramer M et al, Lancet 2009;374:1171-8



Decramer M et al, Lancet 2009;374:1171-8



Decramer M et al, Lancet 2009;374:1171-8

Δημογραφικά

Characteristic		Tiotropium (n = 1384)	Control (n = 1355)
Male (%)		72	72
Age (yrs)		64.5 ± 8.6 (range 40-85)	64.1 ± 8.7 (range 40-88)
Body Mass Index		26.7 ± 5.1 (range 11.0-53.6)	26.5 ± 5.0 (range 14.5-50.0)
Smoking status	Current smoker (%)	30.7	35.0
	Smoking history (pack-yrs)	47.9 (range 10-225)	47.5 (range 10-180)
Duration of COPD (yrs)		9.5 ± 7.5 (range 0.08-55.0)	9.3 ± 7.3 (range 0.08-51.0)
SGRQ total score (units)		41.3 ± 16.7	42.1 ± 17.2
Baseline LABA use* (%)		55.7	55.4
Baseline ICS use* (%)		58.5	56.9
Baseline combination LABA/ICS use (%)		45.3	44.1
Baseline anticholinergic use† (%)		39.2	38.1

Data are mean ± SD.

*Used alone or in combination. † Includes short- or long-acting anticholinergics

Decramer M et al, Lancet 2009;374:1171-8

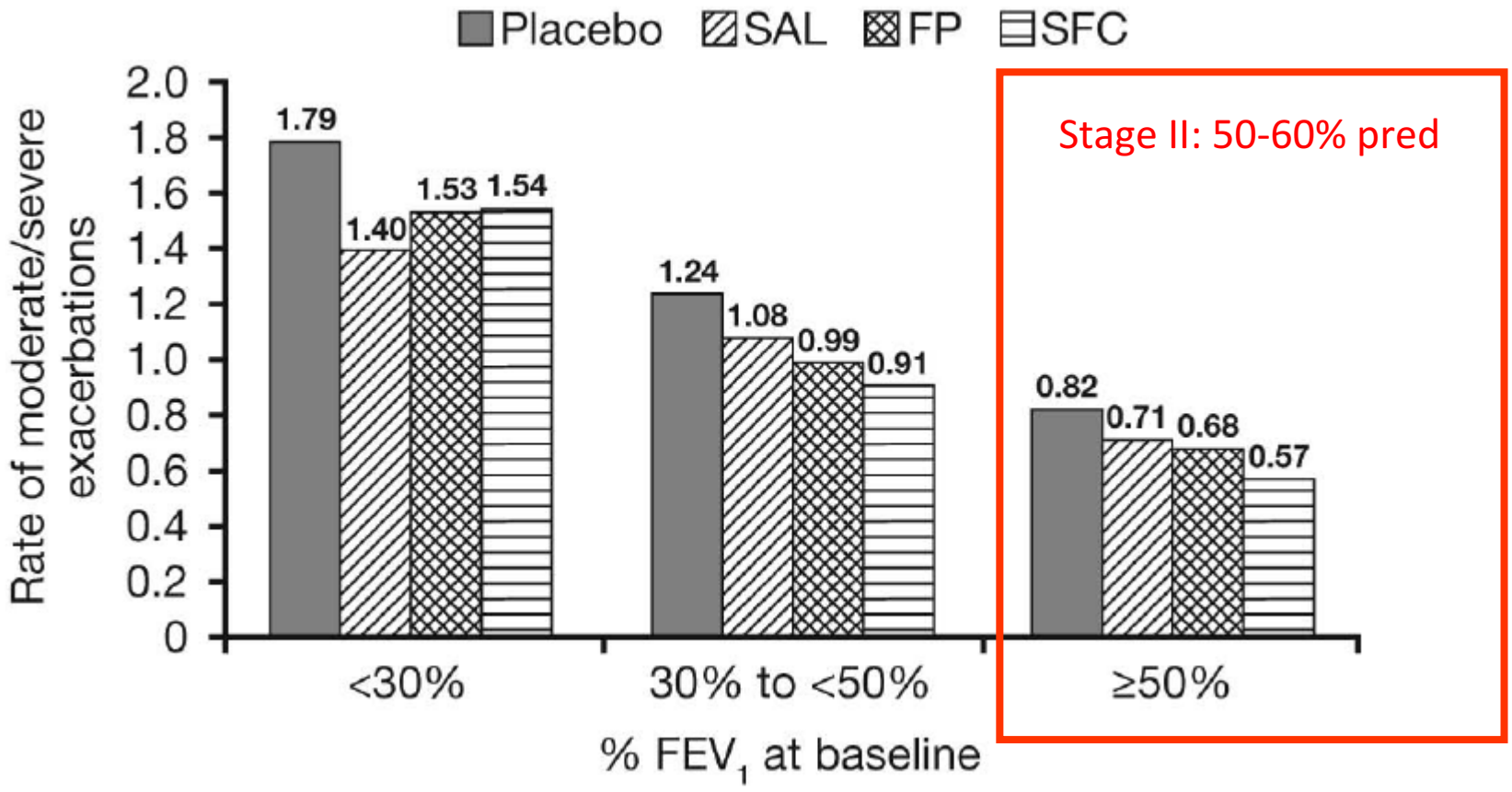
GOLD Στάδιο II: Παροξύνσεις

	Tiotropium n = 1384	Control n = 1355	Ratio (95% CI)	P-value
Time to first exacerbation (month)	23.1 (21.0, 26.3)	17.5 (15.9, 19.7)	0.82 (0.75, 0.90)*	<0.0001*
Mean number of exacerbations/pt yr (95% CI)	0.56 (0.52, 0.60)	0.70 (0.65, 0.75)	0.80 (0.72, 0.88)†	<0.0001†

*Hazard ratio (control vs. tiotropium) and p-value were estimated using Cox regression with treatment, GOLD stage, and treatment by GOLD stage interaction as covariates.
†Ratio (tiotropium/control) and p-value were estimated using the Poisson with Pearson overdispersion model adjusting for treatment exposure.
Randomized patients taking ≥1 dose of study medication were included in the analysis.

Decramer M et al, Lancet 2009;374:1171-8

Ανάλυση της Torch κατά στάδια: παροξύνσεις



Jenkins et al, Resp Res 2009;10:59

ΧΑΠ GOLD Στάδιο II: Εισαγωγή στο νοσοκομείο

	Tiotropium n = 1384	Control n = 1355	Ratio (95% CI)	P-value
Time to first hospitalization (month)	NE	NE	0.74 (0.62, 0.88)*	<0.001*
Mean number of hospitalizations/pt yr (95% CI)	0.08 (0.07, 0.09)	0.10 (0.08, 0.12)	0.80 (0.63, 1.03)†	0.082†

*Hazard ratio (control vs. tiotropium) and p-value were estimated using Cox regression with treatment, GOLD stage, and treatment by GOLD stage interaction as covariates.
†Ratio (tiotropium/control) and p-value were estimated using the Poisson with Pearson overdispersion model adjusting for treatment exposure.
Randomized patients taking ≥1 dose of study medication were included in the analysis.

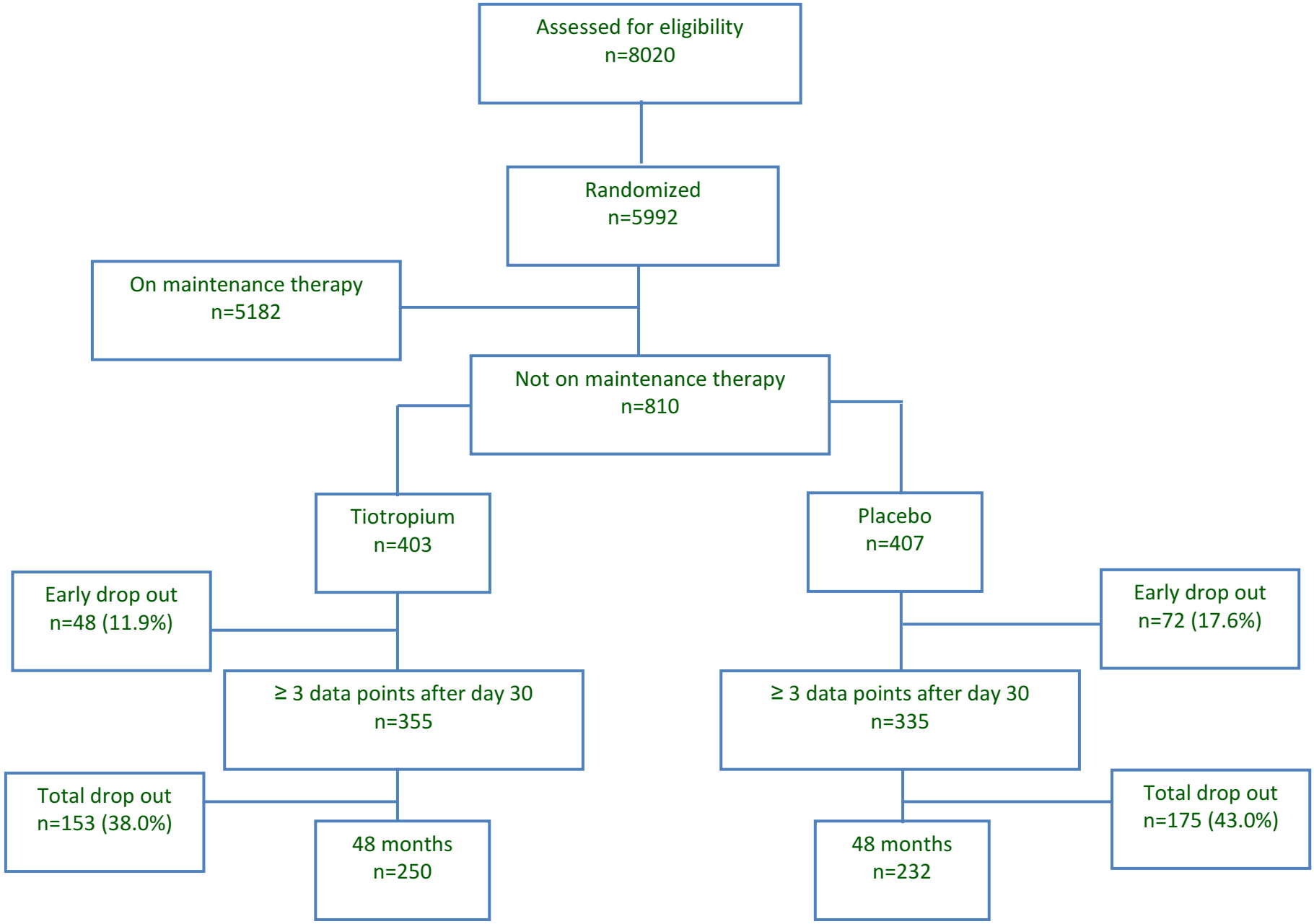
Decramer M et al, Lancet 2009;374:1171-8

Ασθενείς με ΧΑΠ
που δεν έχουν ποτέ λάβει θεραπεία

Naive patients

	Tiotropium (n=403)	Placebo (n=407)
Mean age (years)	63	64
Males (%)	73	74
Active smokers (%)	42	44
Body mass index (kg/m^2)	26	26
COPD duration (years)	8.6	8.5
Mean prebronchodilator		
FEV_1 (L)	1.25	1.22
FEV_1 (% predicted)	44	43
FVC (% predicted)	77	77
Mean postbronchodilator		
FEV_1 (L)	1.49	1.45
FEV_1 (% predicted)	53	51
FVC (% predicted)	90	90
GOLD Stage (%)		
II	61	59
III	34	35
IV	4	6

Troosters, T et al, ERJ 2010;36:65-73

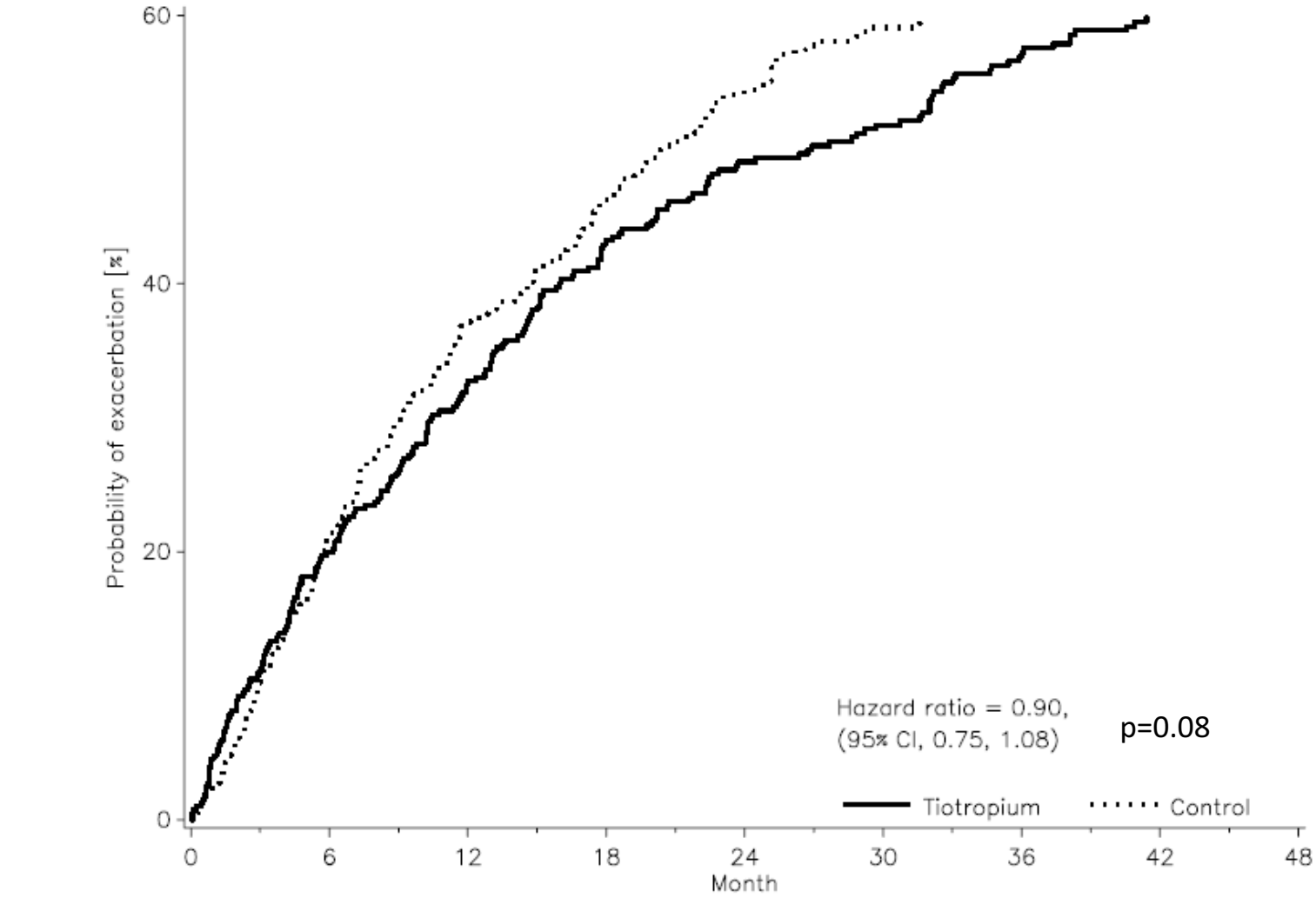


Troosters, T et al, ERJ 2010;36:65-73

	Tiotropium (n=403)	Pl (n=407)
Mean age (years)	63	
Males (%)	73	
Active smokers (%)		44
Body mass index (kg/m^2)		26
COPD duration (years)		8.5
Mean preb		
	1.25	1.22
	44	43
	77	77
ostbronchodilator		
FEV$_1$ (L)	1.49	1.45
FEV$_1$ (% predicted)	53	51
FVC (% predicted)	90	90
GOLD Stage (%)		
II	61	59
III	34	35
IV	4	6

60% των ασθενών που δεν έχουν λάβει ποτέ θεραπεία ήταν στο GOLD Stage II

Παροξύνσεις



No. of patients:									
Tiotropium	403	301	242	196	169	154	134	120	4
Control	407	288	213	175	139	122	112	96	6

Troosters, T et al, ERJ 2010;36:65-73

Ο ρόλος του τιοτροπίου στην αντιμετώπιση των παροξύνσεων της ΧΑΠ

Το τιοτρόπιο στη ΧΑΠ

- Μειώνει τις παροξύνσεις
  - Σε ασθενείς που δεν έχουν λάβει ποτέ θεραπεία
  - Σε ασθενείς όλων των σταδίων βαρύτητας
    - Ακόμα και σε στάδιο II (FEV1>50%)
  - Οι παροξύνσεις μειώνονται ανεξάρτητα από την ταυτόχρονη λήψη LABA/ICS
  - Η μείωση των παροξύνσεων παρατηρείται και σε μονοθεραπεία με τιοτρόπιο