

# ΘΕΡΑΠΕΙΑ ΧΑΠ ΣΤΑΔΙΟΥ Ι-ΙΙ ΟΔΗΓΙΕΣ - ΚΛΙΝΙΚΑ ΠΑΡΑΔΕΙΓΜΑΤΑ



ΕΛΛΗΝΙΚΗ  
ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ  
ΕΤΑΙΡΕΙΑ



19-20 Νοεμβρίου 2011  
Αμφιθέατρο ΓΝΝΘΑ «Η Σωτηρία»

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Αθήνα, 19 Νοεμβρίου 2011.

# GOLD: Spirometric Classification of COPD Severity based on Post-Bronchodilator FEV<sub>1</sub>

Stage I: Mild

$$FEV_1 / FVC < 0.70$$

$$FEV_1 \geq 80\% \text{ predicted}$$

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Stage II: Moderate

$$FEV_1 / FVC < 0.70$$

$$50\% \leq FEV_1 < 80\% \text{ predicted}$$

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Stage III: Severe

$$FEV_1 / FVC < 0.70$$

$$30\% \leq FEV_1 < 50\% \text{ predicted}$$

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Stage IV: Very Severe

$$FEV_1 / FVC < 0.70$$

$FEV_1 < 30\% \text{ predicted}$  or  
 $FEV_1 < 50\% \text{ predicted}$  plus  
chronic respiratory failure

# GOLD: Spirometric Classification of COPD Severity based on Post-Bronchodilator FEV<sub>1</sub>

## Stage I: Mild COPD (FEV<sub>1</sub> ≥ 80% pred)

- Symptoms of chronic cough and sputum production may be present but not always
- The individual is usually unaware that his/her lung function is abnormal

## Stage II: Moderate COPD (50% ≤ FEV<sub>1</sub> < 80% pred)

- Worsening airflow limitation, shortness of breath typically developing on exertion
- Cough and sputum production sometimes present

# Management of COPD

- Disease prevention (ultimate goal)
- Effective management goals :
  - Relieve symptoms
  - Prevent disease progression
  - Improve exercise tolerance
  - Improve health status
  - Prevent/ treat complications
  - Prevent/ treat exacerbations
  - Reduce mortality

# Management of COPD: All patients

- Smoking cessation advice
- Assessment of comorbidities
- Exercise promotion
- Patient education / self management
- Annual influenza vaccination
- Pneumococcal vaccination
- Assess BMI
  - dietary advice if BMI >25
  - specialist referral if BMI <20



# Θεραπεία ΧΑΠ κατά στάδιο

| Στάδιο I<br>Ήπια  | Στάδιο II<br>Μέτρια   | Στάδιο III<br>Σοβαρή   | Στάδιο IV<br>Πολύ σοβαρή   |
|---|---|--|--|
| FEV <sub>1</sub> /FVC <0.70<br>FEV <sub>1</sub> ≥80%pred  | FEV <sub>1</sub> /FVC <0.70<br>50% ≤ FEV <sub>1</sub> <80% pred | FEV <sub>1</sub> /FVC <0.70<br>30% ≤ FEV <sub>1</sub> <50% pred                          | FEV <sub>1</sub> /FVC <0.70<br>FEV <sub>1</sub> <30% pred<br>ή FEV <sub>1</sub> <50% pred +<br>Χρόνια αναπνευστική<br>ανεπάρκεια (ΧΑΑ) |
| <p>Αποφυγή των παραγόντων κινδύνου (κάπνισμα), αντιγριππικός εμβολιασμός</p> <p>Προσθήκη βρογχοδιασταλτικού βραχείας δράσης (όταν είναι απαραίτητο)</p> |   |  |  |
| <p>Προσθήκη τακτικής αγωγής με ένα ή περισσότερα βρογχοδιασταλτικά μακράς δράσης (όταν είναι απαραίτητο).</p> <p>Πνευμονική αποκατάσταση</p>            |   |  |  |
|   |   | <p>Προσθήκη εισπνεόμενων κορτικοστεροειδών εάν οι παροξυσμοί είναι επαναλαμβανόμενοι</p> |  |
|   |   | <p>Προσθήκη οξυγόνου σε μακροχρόνια βάση (ΧΑΑ)</p> <p>Χειρουργικές θεραπείες (LVRS)</p>  |  |

# Management of COPD: Smoking Cessation

- Smoking cessation is the single most effective way to reduce exposure to COPD risk factors
- Quitting smoking
  - can prevent or delay the development of airflow limitation or reduce its progression
  - can have a substantial effect on subsequent mortality
- Sustained smoking cessation was associated with significantly lower declines in FEV<sub>1</sub> than continued smoking (31 ml/year vs. 62 ml/year;  $p < 0.001$ ).

# Management of COPD: Smoking Cessation

All COPD patients who are current smokers should be offered the most intensive smoking cessation intervention feasible

- Counseling
  
- Pharmacotherapy
  - Nicotine replacement products (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet)
  - Bupropion (Zyban)
  - Varenicline (Champix)



# Management of COPD: Vaccines

- Influenza vaccines can reduce serious illness and deaths in COPD patients by 50%
- Pneumococcal vaccine is recommended for COPD patients age >65 years
- It has been shown to reduce the incidence of community-acquired pneumonia in COPD patients <65 years with  $FEV_1 < 40\%$

# Θεραπεία Ήπιας ΧΑΠ (GOLD στάδιο I)

- Διακοπή καπνίσματος
- Αντιγριππικός εμβολιασμός
  
- Βρογχοδιασταλτική αγωγή βραχείας δράσης (κατ'επίκληση)
  - Β2-αγωνιστές
  - Αντιχολινεργικά
  - Θεοφυλλίνη βραδείας αποδέσμευσης ?

# Θεραπεία Μέτριας ΧΑΠ (GOLD στάδιο II)

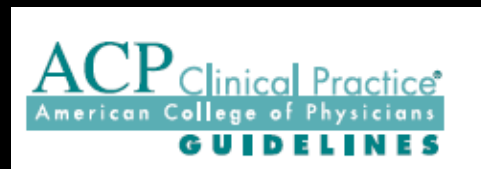
- Διακοπή καπνίσματος
- Αντιγριππικός εμβολιασμός
- Βρογχοδιασταλτική αγωγή μακράς δράσης (τακτική αγωγή)
  - Β2-αγωνιστές
  - Αντιχολινεργικά
  - Θεοφυλλίνη βραδείας αποδέσμευσης

} Μονοθεραπεία ή συνδυασμός
- Βρογχοδιασταλτική αγωγή βραχείας δράσης (κατ'επίκληση)

# Θεραπεία Μέτριας ΧΑΠ (GOLD στάδιο II)

- Εισπνεόμενα κορτικοστεροειδή
  - Σε ασθενείς με  $FEV_1 < 60\%$  pred βρέθηκε ότι μειώνει τον ρυθμό έκπτωσης της αναπνευστικής λειτουργίας  
(TORCH study, AJRCCM, 2008)
- Συνδυασμός εισπνεόμενου κορτικοστεροειδούς + βρογχοδιασταλτικής αγωγής
  - μεγαλύτερη αποτελεσματικότητα στην μείωση των παροξύνσεων, την βελτίωση της πνευμονικής λειτουργίας και της ποιότητας ζωής απο κάθε αγωγή ξεχωριστά

## 2011: ACP, ACCP, ATS and ERS guidelines on management of stable COPD



- Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction.
  
- For symptomatic patients with FEV<sub>1</sub> 60 - 80% predicted:
  - treatment with inhaled bronchodilators (anticholinergics or long-acting  $\beta$ -agonists) may be used
  
  - occasional use of short-acting inhaled bronchodilators for acute symptom relief.

## 2011: ACP, ACCP, ATS and ERS guidelines on management of stable COPD



- For symptomatic patients with FEV<sub>1</sub> <60% predicted:
  - treatment with inhaled bronchodilators is strongly recommended.
  - monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled  $\beta$ -agonists is recommended (clinicians should base their choice on patient preference, cost, and adverse effect profile)
  - combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled  $\beta$ -agonists, or inhaled corticosteroids) may be administered.

# Rehabilitation



- Benefits of pulmonary rehabilitation
  - Improves exercise capacity
  - Reduces symptoms (breathlessness)
  - Reduces number of hospitalizations
  - Improves quality of life
  - Increases survival
  - Reduces anxiety and depression related with COPD
  
- COPD patients at all stages of disease appear to benefit from exercise training programs

# Rehabilitation

- Evidence supports the use of pulmonary rehabilitation for symptomatic patients who have severe COPD ( $FEV_1 < 50\%$  predicted) based on the fact that controlled trials of pulmonary rehabilitation have had a mean  $FEV_1$  of less than 50% predicted.
- Physicians may consider prescribing pulmonary rehabilitation for patients with an  $FEV_1 > 50\%$  predicted if they remain symptomatic or have exercise limitation despite maximal medical therapy.



# Βλεννολυτικά (N-Acetylcysteine –NAC)

## Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial

Lancet 2005; 365: 1552–60

Marc Decramer, Maureen Rutten-van Milken, P N Richard Dekhuijzen, Thierry Troosters, Cees van Herwaarden, Riccardo Pellegrino, C P Onno van Schayck, Dario Olivieri, Mario Del Donno, Wilfried De Backer, Ida Lankhorst, Alfredo Ardia

|   | N-acetylcysteine<br>(n=256) | Placebo<br>(n=267) |
|---|-----------------------------|--------------------|
| Women   | 53 (21%)                    | 57 (21%)           |
| Age (years)   | 62 (8)                      | 62 (8)             |
| Current smokers   | 130 (51%)                   | 109 (41)           |
| GOLD II   | 190 (74%)                   | 199 (75%)          |
| GOLD III  | 66 (26%)                    | 68 (25%)           |
| Use of inhaled corticosteroids  | 182 (71%)                   | 183 (69%)          |
| Average daily dose of inhaled corticosteroids (mg equivalent fluticasone) | 579 (374)                   | 569 (372)          |
| Use of short-acting $\beta_2$ agonists                                    | 182 (71%)                   | 179 (67%)          |
| Use of short-acting anticholinergics                                      | 90 (35%)                    | 80 (30%)           |
| Use of long-acting $\beta_2$ agonists                                     | 161 (63%)                   | 155 (58%)          |
| Use of theophylline   | 87 (34%)                    | 96 (36%)           |
| VC (L)  | 3.43 (0.85)                 | 3.44 (0.87)        |
| FEV <sub>1</sub> (L)  | 1.65 (0.38)                 | 1.65 (0.39)        |
| Predicted FEV <sub>1</sub>  | 57% (9)                     | 57% (9)            |
| FRC (L)   | 4.43 (1.30)                 | 4.38 (1.22)        |
| Reversibility (% predicted)   | 4% (4)                      | 4% (4)             |
| Yearly exacerbation rate before study (events)                            | 2.4 (0.7)                   | 2.5 (0.9)          |
| St George's respiratory questionnaire total score                         | 39 (16)                     | 40 (15)            |
| Euroqol-5D score  | 0.76 (0.22)                 | 0.79 (0.19)        |

Data are number (%), mean (SD), or % (SD).

Table 1: Baseline characteristics

- Subgroup analysis suggested that the exacerbation rate might be reduced with N-acetylcysteine in patients not treated with inhaled corticosteroids
- Secondary analysis was suggestive of an effect on hyperinflation
- No difference in the rate of decline of FEV<sub>1</sub>

## 1999: European Respiratory Study on Chronic Obstructive Pulmonary Disease (EUROSCOP)

- 1277 individuals with post-bronchodilator FEV<sub>1</sub> 50-100% predicted and FEV<sub>1</sub>/FVC <70% who continued smoking were randomised to budesonide 400 mg or placebo twice daily
- After 3 years there was no difference in the rate of decline in FEV<sub>1</sub> in patients treated with budesonide compared with those receiving placebo

## 2003:Tristan study (TRial of Inhaled STeroids ANd long-acting 2 agonists)

- 1465 COPD patients with pre BD FEV<sub>1</sub> 25–70% predicted were randomised to either 50 µg salmeterol bid, 500 µg fluticasone bid, 50 µg salmeterol + 500 µg fluticasone bid, or placebo for 12 months.
- All active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations.
- Combination therapy
  - improved FEV<sub>1</sub> significantly more than placebo, salmeterol, or fluticasone alone ( $p < 0.0001$ ).
  - produced a clinically significant improvement in health status and the greatest reduction in daily symptoms.

## 2007: Towards a Revolution in COPD Health (TORCH) study

- 6112 COPD patients with pre BD FEV<sub>1</sub> <60% predicted were randomised to either 50 µg salmeterol bid, 500 µg fluticasone bid, 50 µg salmeterol + 500 µg fluticasone bid, or placebo for 3 years.
- The combination regimen compared with placebo,
  - reduced the annual rate of exacerbations including those exacerbations requiring hospitalization
  - improved health status
  - Improved spirometric values (p<0.001 for all arms vs. placebo)

## 2007: TOWARDS A REVOLUTION IN COPD HEALTH (TORCH) STUDY

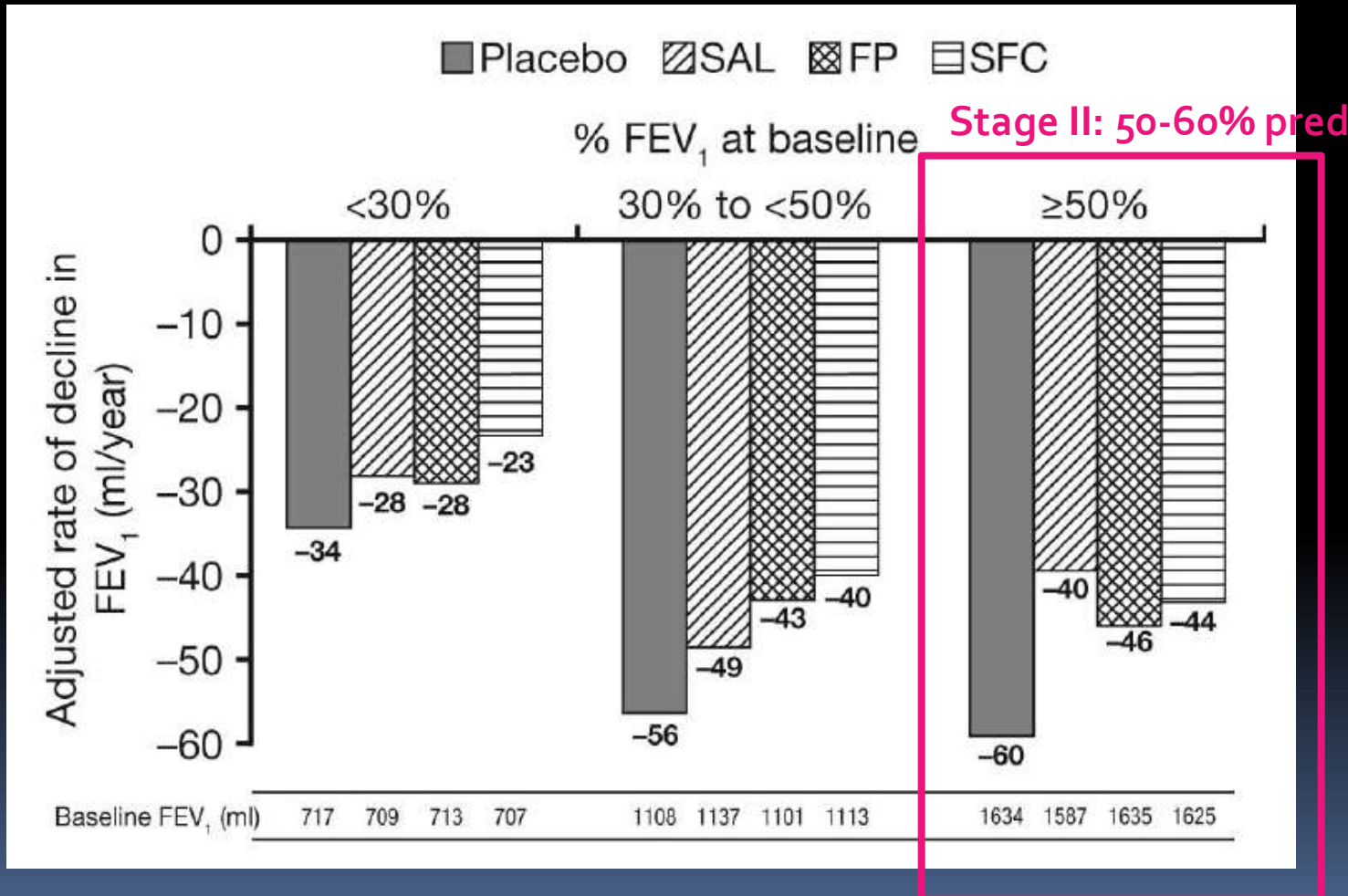
- The probability of having pneumonia as an adverse event was higher among patients receiving medications containing fluticasone propionate than in the placebo group
- Absence of a significant difference among the groups in bone mineral density among patients in the U.S. sub-study.

## 2009: Ανάλυση της Torch κατά στάδια

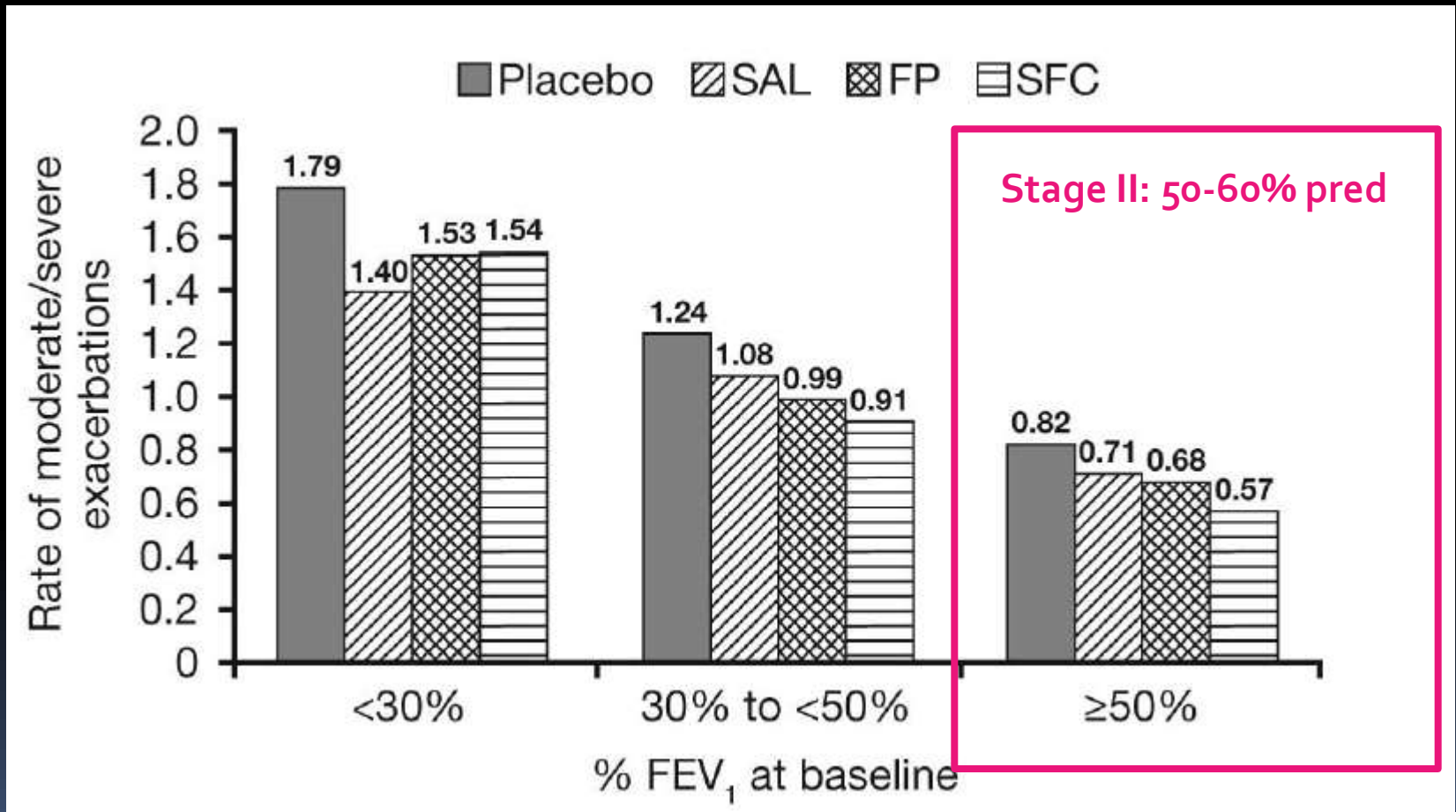
- 2,128 GOLD stage II patients ( $FEV_1 \geq 50\%$  predicted) of a total of 6,112 patients

| $FEV_1$ , % predicted, n (%) | placebo<br>(n = 1524) | SAL<br>(n = 1521) | FP<br>(n = 1534) | SFC<br>(n = 1533) | total<br>(n = 6112) |
|------------------------------|-----------------------|-------------------|------------------|-------------------|---------------------|
| < 30%                        | 214 (14)              | 260 (17)          | 220 (14)         | 243 (16)          | 937 (15)            |
| 30% to < 50%                 | 775 (51)              | 739 (49)          | 777 (51)         | 728 (47)          | 3019 (49)           |
| 50% to < 60%                 | 347 (23)              | 335 (22)          | 329 (21)         | 349 (23)          | 1360 (22)           |
| 60% to < 70%                 | 148 (10)              | 160 (11)          | 165 (11)         | 173 (11)          | 646 (11)            |
| 70% to < 80%                 | 35 (2)                | 25 (2)            | 34 (2)           | 28 (2)            | 122 (2)             |
| $\geq 80\%$                  | 5 (< 1)               | 2 (< 1)           | 9 (< 1)          | 12 (< 1)          | 28 (< 1)            |

# Ανάλυση της Torch κατά στάδια: FEV<sub>1</sub>



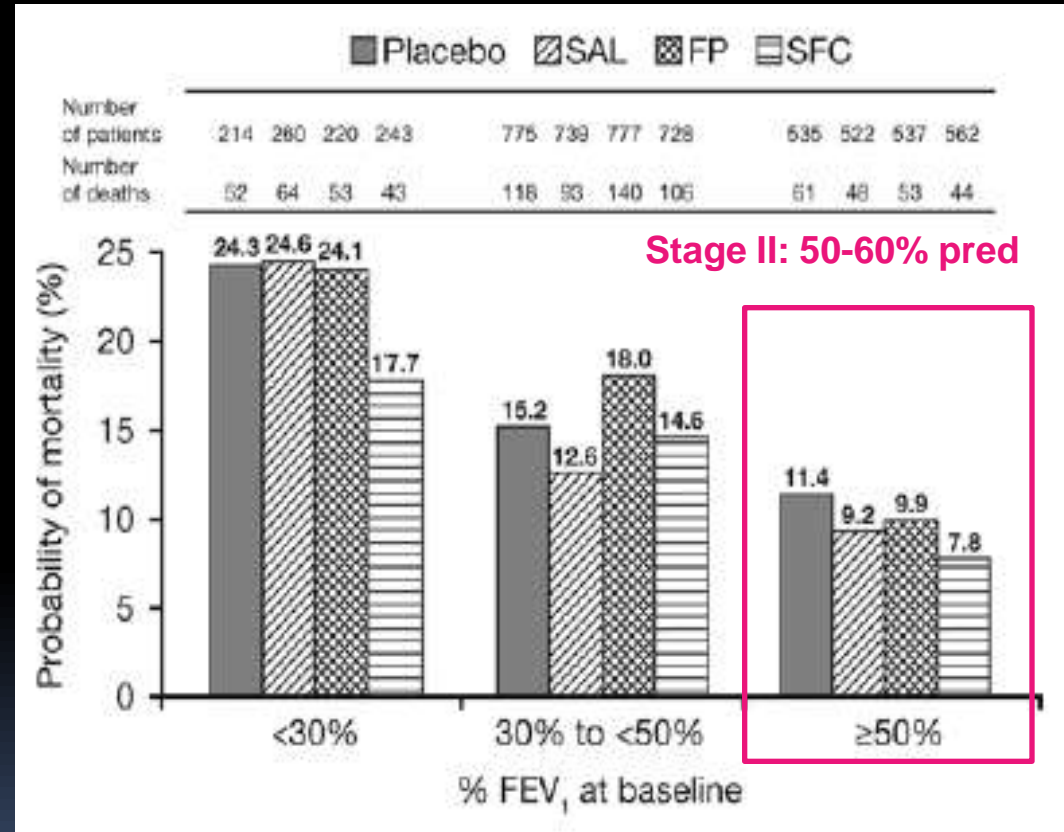
# Ανάλυση της Torch κατά στάδια: παροξύνσεις





# Torch conclusions

- SFC in GOLD stage II patients when compared with placebo
  - improved SGRO
  - reduced exacerbations
  - improved lung function
  - was associated with reduced mortality

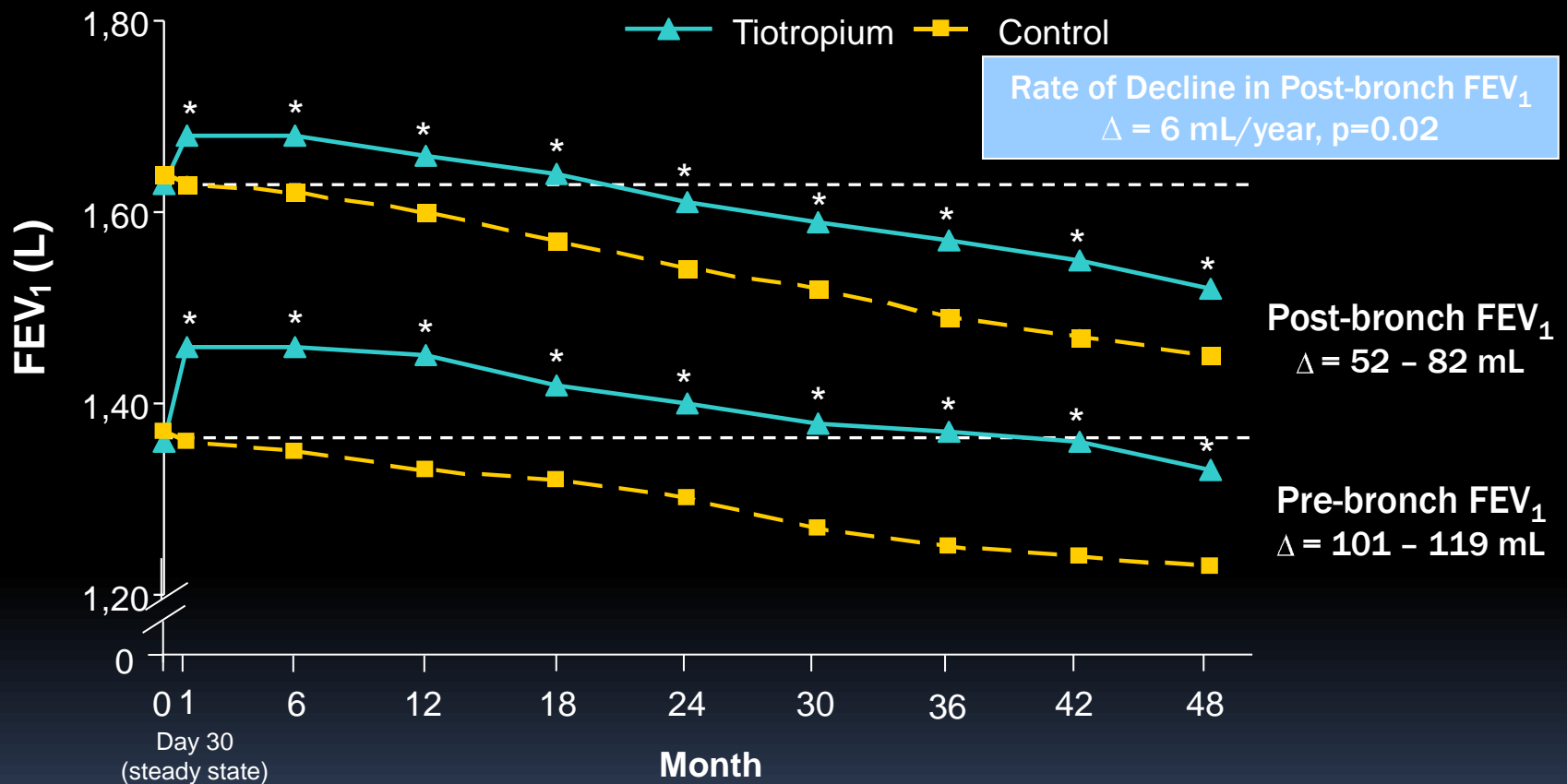


# 2008: Uplift trial



- 5,993 COPD patients with post BD FEV<sub>1</sub> <70% predicted were randomized to either tiotropium or placebo for 4 years
- 2,739 patients (46% of the randomized population) were GOLD stage II
- Patients were permitted to use all respiratory medications except inhaled anticholinergic drugs
- Therapy with tiotropium
  - was associated with improvements in lung function, quality of life, and exacerbations
  - did not significantly reduce the rate of decline in FEV<sub>1</sub>

# GOLD Stage II: FEV<sub>1</sub>

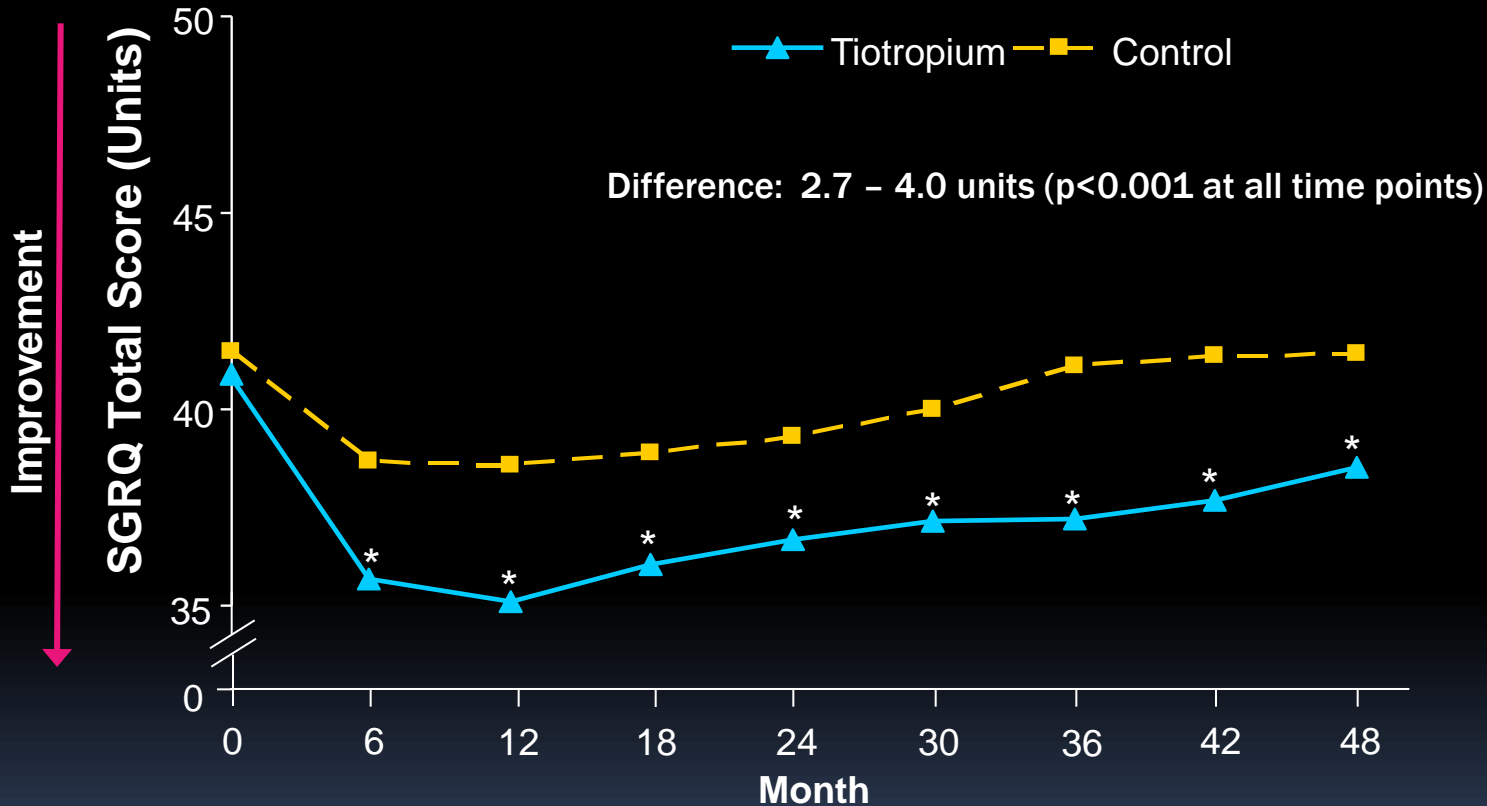


\*P<0.0001 vs. control. Repeated measure ANOVA was used to estimate means. Estimated means are adjusted for baseline measurements. Month 0 values are observed means. Patients with  $\geq 3$  acceptable PFTs after day 30 were included in the analysis. Tiotropium: Month 0 n = 1196, Month 48 n = 923; Control: Month 0 n = 1140, Month 48 n = 853

# Τι λάμβαναν οι ασθενείς σταδίου ΙΙ κατά τη μελέτη

|  | Baseline               |                     | During study           |                     |
|--|------------------------|---------------------|------------------------|---------------------|
|  | Tiotropium<br>(n=1384) | Control<br>(n=1355) | Tiotropium<br>(n=1384) | Control<br>(n=1355) |
| Longacting $\beta$ agonists*                                       | 771 (56%)              | 751 (55%)           | 955 (69%)              | 962 (71%)           |
| Inhaled corticosteroids*   | 810 (59%)              | 772 (57%)           | 996 (72%)              | 989 (73%)           |
| Combination longacting $\beta$ agonist and inhaled corticosteroids | 627 (45%)              | 598 (44%)           | 841 (61%)              | 827 (61%)           |
| Anticholinergic drugs†   | 542 (39%)              | 516 (38%)           | 484 (35%)              | 474 (35%)           |

# GOLD Stage II: SGRQ Total Score



\* $P < 0.0001$  vs. control. Repeated measure ANOVA was used to estimate means. Estimated means are adjusted for baseline measurements. Month 0 values are observed means. Patients with  $\geq 2$  acceptable SGRQ Total Scores after Month 6 were included in the analysis. Tiotropium: Month 0  $n = 1179$ , Month 48  $n = 908$ ; Control: Month 0  $n = 1119$ , Month 48  $n = 839$

# GOLD Stage II: Exacerbations

|  | <b>Tiotropium<br/>n = 1384</b> | <b>Control<br/>n = 1355</b> | <b>Ratio (95%<br/>CI)</b> | <b>P-value</b> |
|--|--------------------------------|-----------------------------|---------------------------|----------------|
| <b>Time to first<br/>exacerbation (month)</b>              | 23.1 (21.0,<br>26.3)           | 17.5 (15.9,<br>19.7)        | 0.82 (0.75,<br>0.90)*     | <0.0001*       |
| <b>Mean number of<br/>exacerbations/pt yr<br/>(95% CI)</b> | 0.56 (0.52,<br>0.60)           | 0.70 (0.65,<br>0.75)        | 0.80 (0.72,<br>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  $\geq 1$  dose of study medication were included in the analysis.

# GOLD Stage II: Mortality

|  | <b>Tiotropium<br/>N (%)</b> | <b>Control<br/>N (%)</b> | <b>Hazard Ratio*<br/>(95% CI)</b> | <b>P-<br/>value*</b> |
|--|-----------------------------|--------------------------|-----------------------------------|----------------------|
| <b>Total treated<br/>(GOLD Stage II)</b>       | 1384                        | 1355                     |                                   |                      |
| <b>On-treatment</b>                            |                             |                          |                                   |                      |
| All cause mortality                            | 117 (8.5)                   | 130 (9.6)                | 0.85 (0.66,<br>1.09)              | 0.19                 |
| <b>Including vital status (until day 1470)</b> |                             |                          |                                   |                      |
| All cause mortality                            | 134 (9.7)                   | 148 (10.9)               | 0.88 (0.69,<br>1.11)              | 0.26                 |

\*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. Observations were censored at 1470 days.



## Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomized controlled study<sup>☆</sup>

Ki Suck Jung<sup>a</sup>, Hye Yun Park<sup>b</sup>, So Young Park<sup>c</sup>, Se Kyu Kim<sup>d</sup>,  
Young-Kyoon Kim<sup>e</sup>, Jae-Jeong Shim<sup>f</sup>, Hwa Sik Moon<sup>g</sup>, Kwan Ho Lee<sup>h</sup>,  
Jee-Hong Yoo<sup>i,\*</sup>, Sang Do Lee<sup>j,\*\*</sup>

The study's aim was to assess whether tiotropium (18 mg once daily) plus FSC (250/50 mg twice daily) provides better clinical outcomes compared to tiotropium monotherapy.

The primary endpoint was the mean change in pre BD FEV<sub>1</sub> (L) from baseline to week 24



## Subgroup analysis with GOLD stage II patients (FEV<sub>1</sub> 50% to 65%)

- 266 (55.5%) of the 479 COPD patients randomized (FEV<sub>1</sub> ≤65%)  
  
(2 weeks wash-out run-in period)
- Over 24 weeks, the pre-BD FEV<sub>1</sub> increased significantly by 88 mL in the tio+FSC group compared to 30 mL in the tiotropium only group (p=0.011)
- In health-related quality of life, tio+FSC provided a greater improvement in the SGRO-C total score than tiotropium alone.
- In the overall rate of exacerbation, no significant difference was observed between the two groups.

# Κλινικό παράδειγμα



- Άνδρας 62 ετών
- Ενεργός καπνιστής (35 ργ)
- Αναφέρει δύσπνοια στην προσπάθεια το τελευταίο έτος
- Αναφέρει βήχα παραγωγικό με βλεννώδη απόχρεμψη και συχνές λοιμώξεις αναπνευστικού

# Κλινική εξέταση

Ακρόαση πνεύμονα: ήπια ελάττωση ΑΨ

BP = 120/65 mmHg

HR = 76/min

S<sub>1</sub>, S<sub>2</sub> ευκρινείς, ρυθμικοί

ΗΚΓ: φλεβοκομβικός ρυθμός

SatO<sub>2</sub> = 96% (fiO<sub>2</sub> = 21%)

# Λειτουργικός έλεγχος πνευμόνων

- $FEV_1 = 58\%$  predicted
- $FVC = 91\%$  predicted
- $FEV_1/FVC = 63.7\%$

- $FEV_1/FVC < 0.70$
- $FEV_1 > 50\%$  predicted

ΧΑΠ σταδίου II

# Σημαντικά σημεία

- Ο ασθενής είναι <65 ετών
- Είναι ενεργός καπνιστής
- Δεν έχει λάβει ποτέ θεραπεία
- $FEV_1 < 60\%$  predicted
- Εμφανίζει ήπια συμπτώματα αλλά συχνές λοιμώξεις (παροξύνσεις)

# Θεραπευτική προσέγγιση

- Διακοπή καπνίσματος
- Αντιγριπικός εμβολιασμός
- Ηλικία < 65 έτη, και  $FEV_1 > 40\%$  (δεν είναι απαραίτητος ο αντιπνευμονιοκοκκικός εμβολιασμός)
- Πνευμονική αποκατάσταση ?



# Φαρμακευτική αγωγή

- Έναρξη μονοθεραπείας με βρογχοδιασταλτικό μακράς δράσης (LAMA ή LABA)
- Βρογχοδιασταλτικά βραχείας δ κατ' επίκληση
- Θα μπορούσε να χορηγηθεί και συνδυασμός μακράς δράσης βρογχοδιασταλτικού (LAMA , LABA) και εισπνεόμενου κορτικοστεροειδούς



REVIEW

## New horizons in early stage COPD – Improving knowledge, detection and treatment

Marc Decramer <sup>a</sup>, Marc Miravittles <sup>b,\*</sup>, David Price <sup>c</sup>, Miguel Román-Rodríguez <sup>d</sup>, Carl Llor <sup>e</sup>, Tobias Welte <sup>f</sup>, Roland Buhl <sup>g</sup>, Daniel Dusser <sup>h</sup>, Katerina Samara <sup>i</sup>, Nikolaus Siafakas <sup>l</sup>

“...early stage COPD is under-recognised and under-diagnosed, yet has a substantial impact on patients’ lives that is out of proportion to measurable reductions in lung function. The tools to detect early stage COPD in primary and secondary care are widely available, and emerging evidence strongly suggests that we can improve patients’ lung function and quality of life, as well as reduce exacerbations, with early, intensive treatment.”