ΘΕΡΑΠΕΙΑ ΧΑΠ ΣΤΑΔΙΟΥ Ι-ΙΙ
ΟΔΗΓΙΕΣ - ΚΛΙΝΙΚΑ ΠΑΡΑΔΕΙΓΜΑΤΑ

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Αθήνα, 19 Νοεμβρίου 2011.

GOLD: Spirometric Classification of COPD Severity based on Post-Bronchodilator FEV_1

Stage I: Mild	FEV_1 / FVC < 0.70 $FEV_1 \geq 80\%$ predicted
Stage II: Moderate	FEV_1 / FVC < 0.70 $50\% \leq FEV_1 < 80\%$ predicted
Stage III: Severe	FEV_1 / FVC < 0.70 $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: Very Severe	FEV_1 / FVC < 0.70 $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

GOLD: Spirometric Classification of COPD Severity based on Post-Bronchodilator FEV_1

Stage I: Mild COPD ($FEV_1 \geq 80\%$ 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 ($50\% \leq FEV_1 < 80\%$ 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 Ήπια	Στάδιο II Μέτρια	Στάδιο III Σοβαρή	Στάδιο IV Πολύ σοβαρή
FEV_1/FVC <0.70 FEV_1 ≥80%pred	FEV_1/FVC <0.70 50% ≤ FEV_1 <80% pred	FEV_1/FVC <0.70 30% ≤ FEV_1 <50% pred	FEV_1/FVC <0.70 FEV_1 <30% pred ή FEV_1 <50% pred + Χρόνια αναπνευστική ανεπάρκεια (ΧΑΑ)

Αποφυγή των παραγόντων κινδύνου (κάπνισμα), αντιγριππικός εμβολιασμός

Προσθήκη βρογχοδιασταλτικού βραχείας δράσης (όταν είναι απαραίτητο)

Προσθήκη τακτικής αγωγής με ένα ή περισσότερα βρογχοδιασταλτικά μακράς δράσης (όταν είναι απαραίτητο). Πνευμονική αποκατάσταση

Προσθήκη εισπνεόμενων κορτικοστεροειδών εάν οι παροξυσμοί είναι επαναλαμβανόμενοι

Προσθήκη οξυγόνου σε μακροχρόνια βάση (ΧΑΑ)
Χειρουργικές θεραπείες (LVRS)

GOLD guidelines 2011, www.goldcopd.com

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 FEV1 than continued smoking (31 ml/year vs. 62 ml/year; $p < 0.001$).

Scanlon PD et al, Am J Respir Crit Care Med 2000;161:381-90.
GOLD guidelines 2011, www.goldcopd.com

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%

GOLD guidelines 2011, www.goldcopd.com

Θεραπεία Ήπιας ΧΑΠ (GOLD στάδιο Ι)

- Διακοπή καπνίσματος
- Αντιγριππικός εμβολιασμός

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

GOLD guidelines 2011, www.goldcopd.com

Θεραπεία Μέτριας ΧΑΠ (GOLD στάδιο II)

- Διακοπή καπνίσματος
- Αντιγριππικός εμβολιασμός

- Βρογχοδιασταλτική αγωγή μακράς δράσης (τακτική αγωγή)
  - Β2-αγωνιστές
  - Αντιχολινεργικά

  } Μονοθεραπεία ή συνδυασμός

  - Θεοφυλλίνη βραδείας αποδέσμευσης

- Βρογχοδιασταλτική αγωγή βραχείας δράσης (κατ'επίκληση)

GOLD guidelines 2011, www.goldcopd.com

Θεραπεία Μέτριας ΧΑΠ (GOLD στάδιο II)

- Εισπνεόμενα κορτικοστεροειδή
  - Σε ασθενείς με FEV_1 <60% pred βρέθηκε οτι 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

GOLD guidelines 2011, www.goldcopd.com

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 FEV1 60 - 80% predicted:
  - treatment with inhaled bronchodilators (anticholinergics or long-acting β-agonists) may be used
  - occasional use of short-acting inhaled bronchodilators for acute symptom relief.

Qaseem A et al, Ann Intern Med. 2011;155:179-191.

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

- For symptomatic patients with FEV1 <60% predicted:
  - treatment with inhaled bronchodilators is strongly recommended.
  - monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled b-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 β-agonists, or inhaled corticosteroids) may be administered.

Qaseem A et al, Ann Intern Med. 2011;155:179-191.

Rehabilitation

- Benefits of pulmonary rehabilitation
  - Improves exercise capacity
  - Reduces symptoms (breathlessnss)
  - 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

GOLD guidelines 2011, www.goldcopd.com

Rehabilitation

ACP Clinical Practice® American College of Physicians GUIDELINES

- Evidence supports the use of pulmonary rehabilitation for symptomatic patients who have severe COPD (FEV1 < 50% predicted) based on the fact that controlled trials of pulmonary rehabilitation have had a mean FEV1 of less than 50% predicted.

- Physicians may consider prescribing pulmonary rehabilitation for patients with an FEV1 >50% predicted if they remain symptomatic or have exercise limitation despite maximal medical therapy.

Qaseem A et al, Ann Intern Med. 2011;155:179-191.

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 Mölken, 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 (n=256)	Placebo (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 β2 agonists	182 (71%)	179 (67%)
Use of short-acting anticholinergics	90 (35%)	80 (30%)
Use of long-acting β2 agonists	161 (63%)	155 (58%)
Use of theophylline	87 (34%)	96 (36%)
VC (L)	3·43 (0·85)	3·44 (0·87)
FEV_1 (L)	1·65 (0·38)	1·65 (0·39)
Predicted FEV_1	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 characteristcs

- 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_1

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

- 1277 individuals with post-bronchodilator FEV1 50-100% predicted and FEV1/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 FEV1 in patients treated with budesonide compared with those receiving placebo

Pauwels RA et al (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease), N Engl J Med 1999; 340:1948-53.

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

- 1465 COPD patients with pre BD FEV1 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 FEV1 significantly more than placebo, salmeterol, or fluticasone alone ($p<0{\cdot}0001$).
  - produced a clinically significant improvement in health status and the greatest reduction in daily symptoms.

Calverley P et al, Lancet 2003; 361: 449–56.

2007: TOwards a Revolution in COPD Health (TORCH) study

- 6112 COPD patients with pre BD FEV1 <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)

Calverley P et al, N Engl J Med 2007;356:775-89

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.

Calverley P et al, N Engl J Med 2007;356:775-89

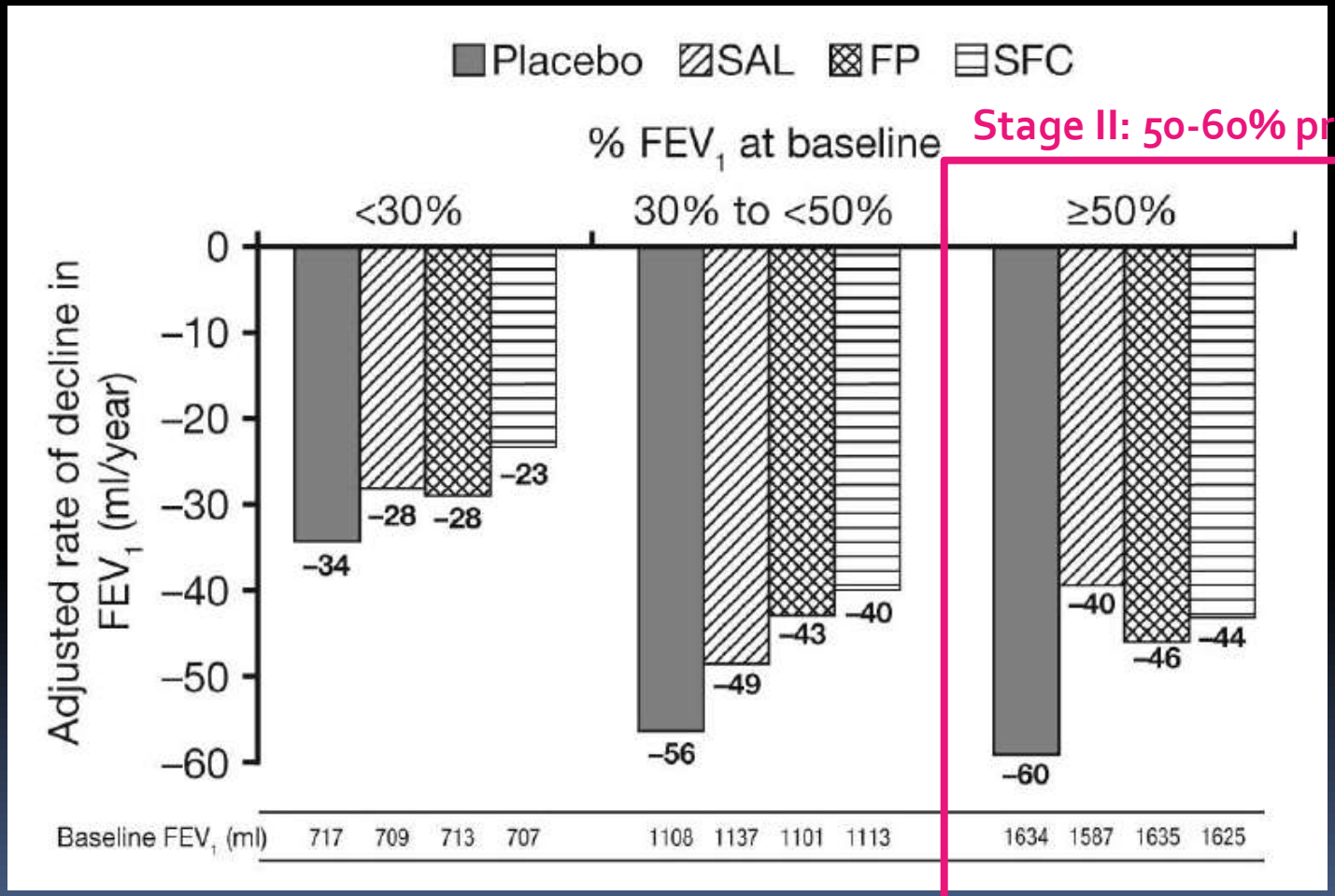
2009: Ανάλυση της Torch κατά στάδια

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

FEV_1, % predicted, n (%)	placebo (n = 1524)	SAL (n = 1521)	FP (n = 1534)	SFC (n = 1533)	total (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)
≥ 80%	5 (< 1)	2 (< 1)	9 (< 1)	12 (< 1)	28 (< 1)

Jenkins C et al, Res Research 2009, 10:59

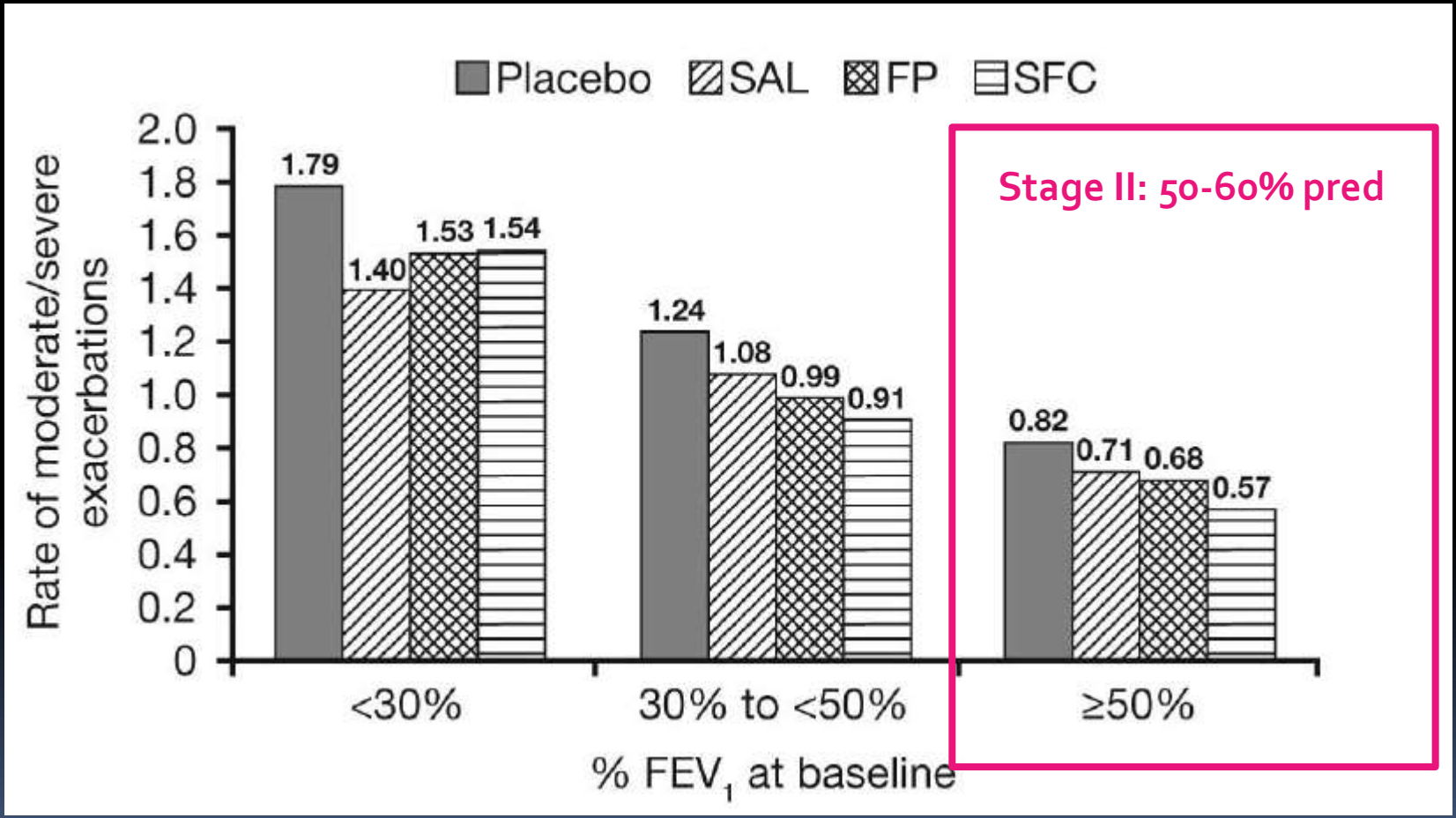
Ανάλυση της Torch κατά στάδια: FEV_1



Stage II: 50-60% pred

Jenkins C et al, Resp Res 2009;10:59

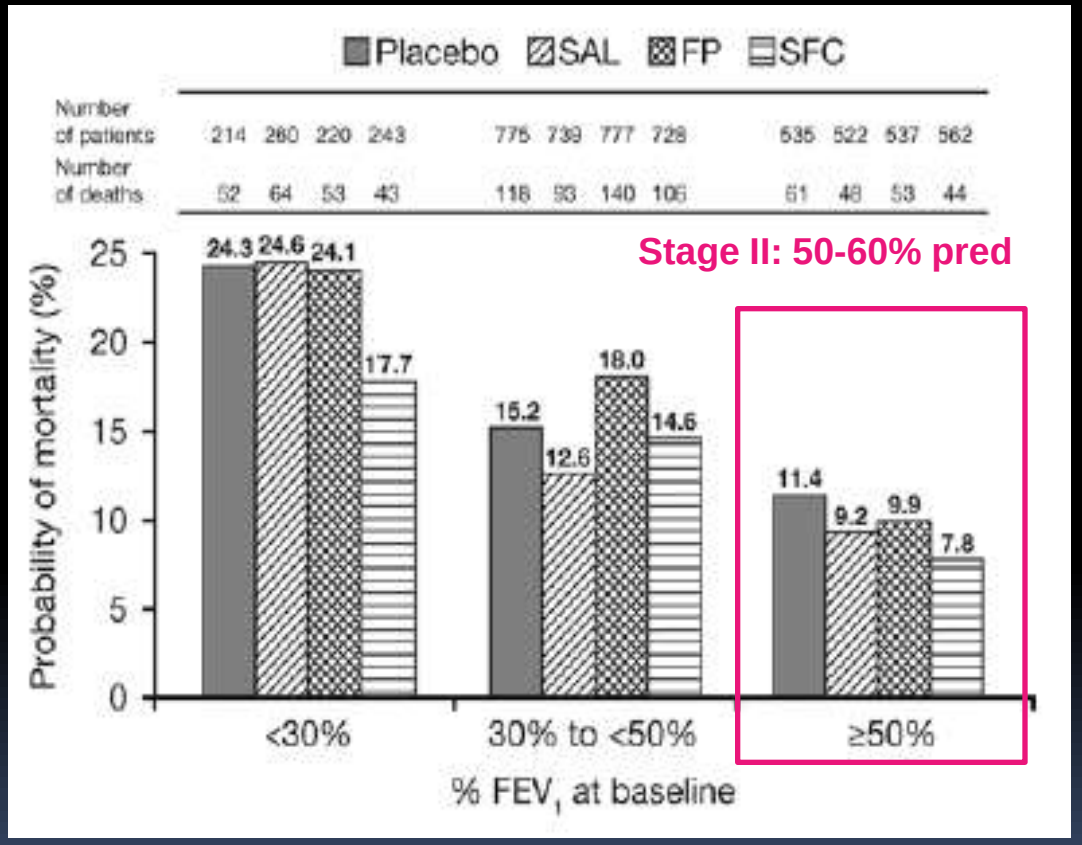
Ανάλυση της Torch κατά στάδια: παροξύνσεις



Jenkins C et al, Resp Res 2009;10:59

Torch conclusions

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



Jenkins C et al, Resp Res 2009;10:59

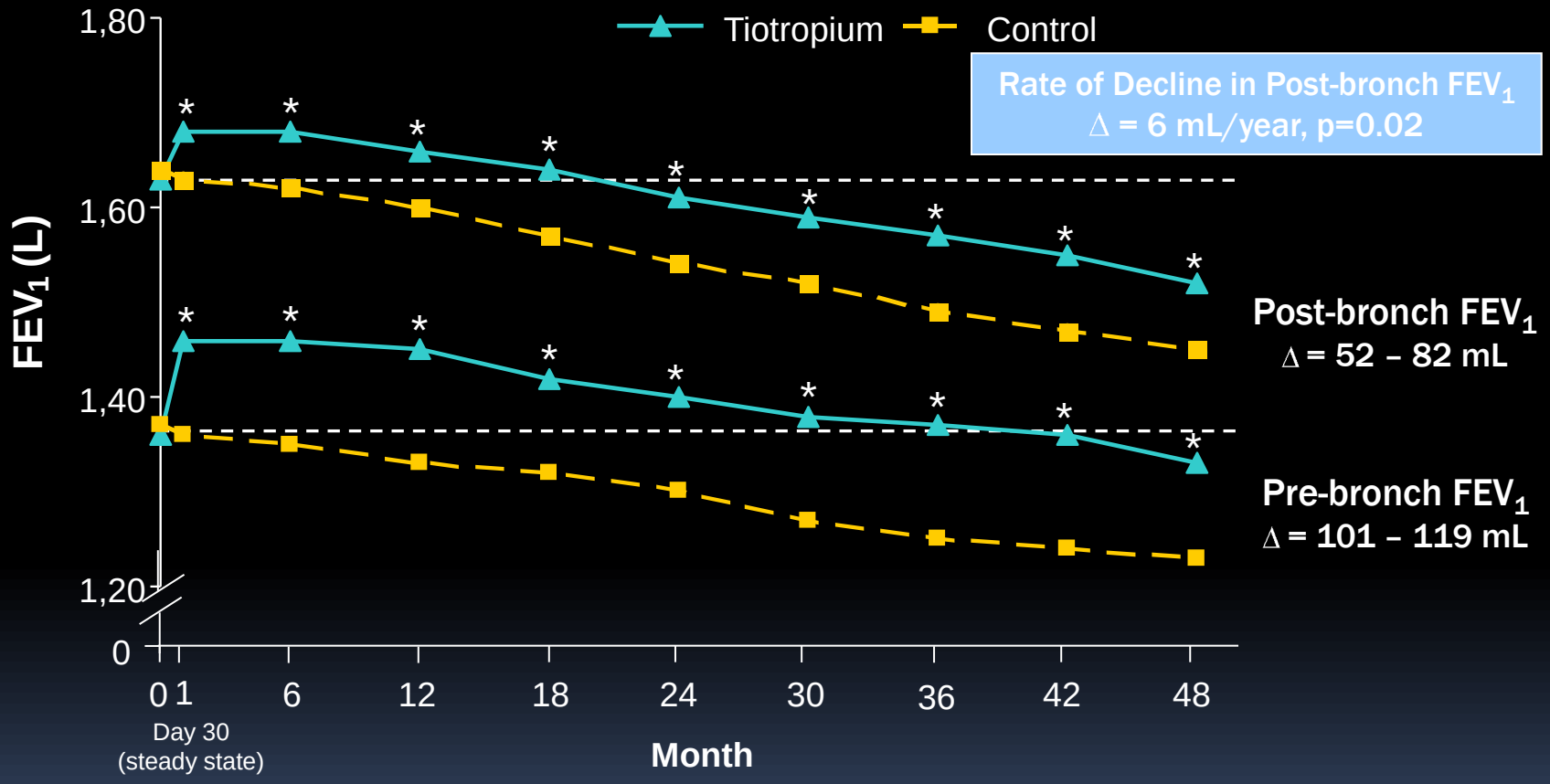
2008: Uplift trial

- 5,993 COPD patients with post BD FEV1 <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 FEV1

Tashkin DP et al, NEJM 2008;359:1543-54

GOLD Stage II: FEV_1



*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 ≥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

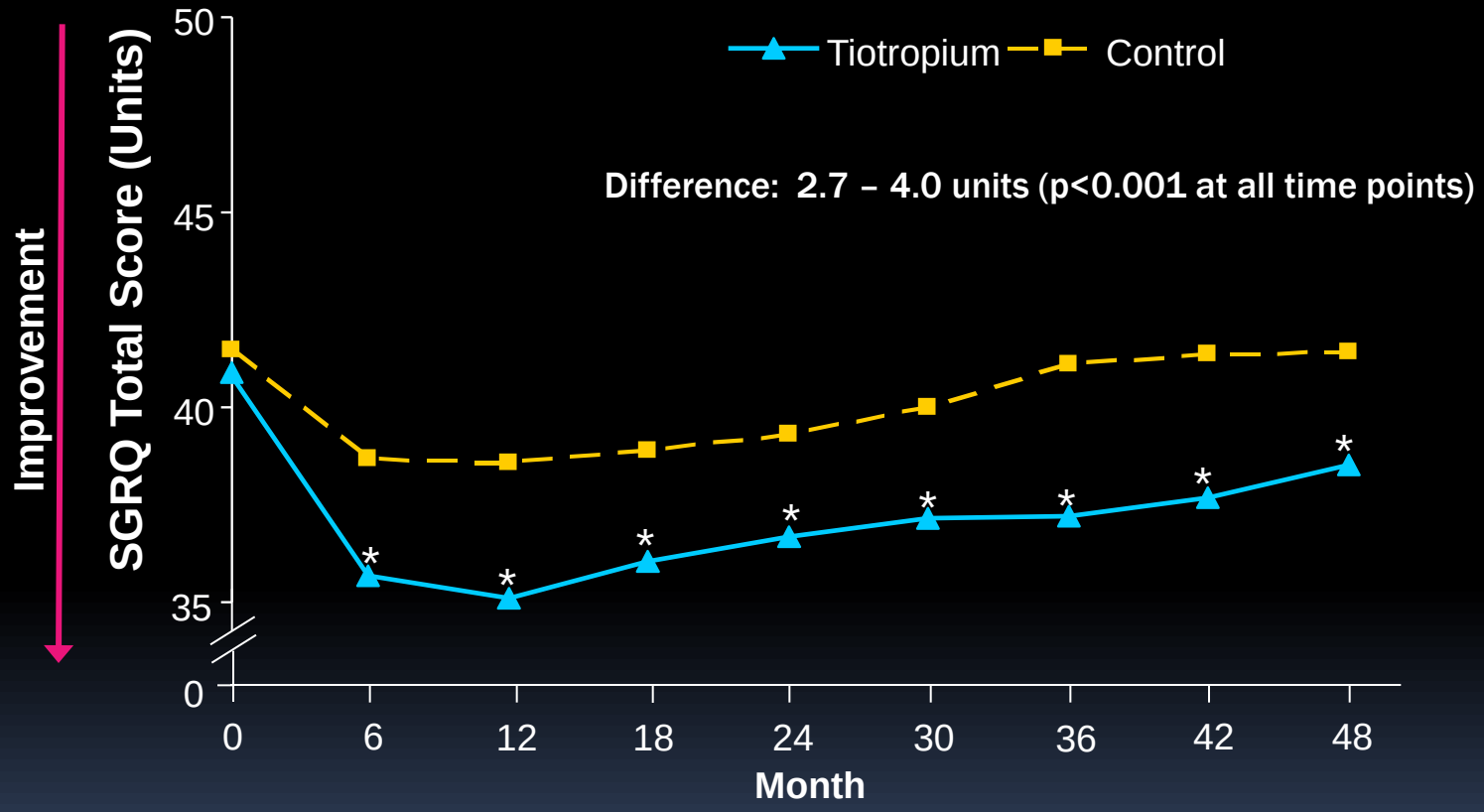
Decramer M et al, Lancet 2009;374:1171-8

Τι λάμβαναν οι ασθενείς σταδίου ΙΙ κατά τη μελέτη

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

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

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 ≥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

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

GOLD Stage II: Exacerbations

	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

GOLD Stage II: Mortality

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

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

Respiratory Medicine (2011) xx, 1–8

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

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

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 FEV1 (L) from baseline to week 24

Jung KS et al, Respiratory Medicine (2011), in press

Subgroup analysis with GOLD stage II patients (FEV1 50% to 65%)

- 266 (55.5%) of the 479 COPD patients randomized (FEV1 ≤65%)

  (2 weeks wash-out run-in period)
- Over 24 weeks, the pre-BD FEV1 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 SGRQ-C total score than tiotropium alone.

- In the overall rate of exacerbation, no significant difference was observed between the two groups.

Jung KS et al, Respiratory Medicine (2011), in press, doi:10.1016/j.rmed.2011.09.004

Κλινικό παράδειγμα

- Άνδρας 62 ετών
- Ενεργός καπνιστής (35 py)

- 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

S1, S2 ευκρινείς , ρυθμικοί

ΗΚΓ: φλεβοκομβικός ρυθμός

$SatO_2$ = 96% (fiO_2 = 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 ΙΙ

Σημαντικά σημεία

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

Θεραπευτική προσέγγιση

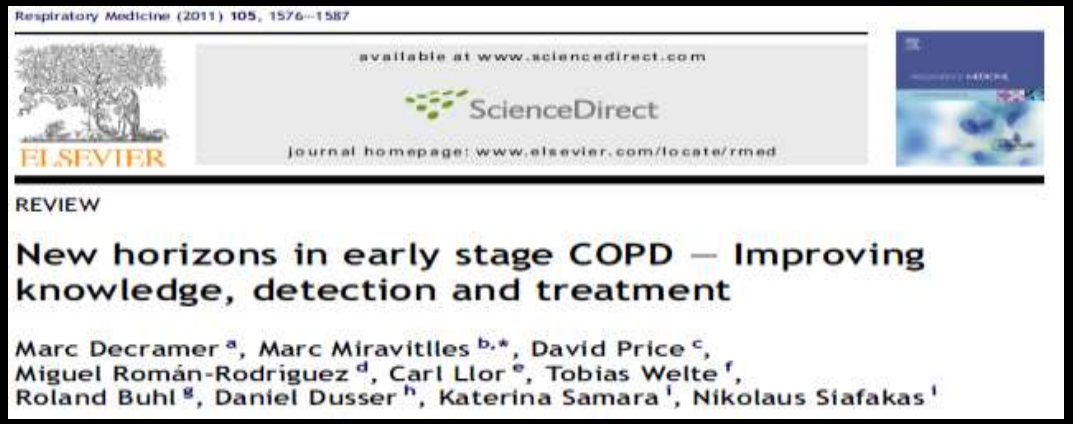
- Διακοπή καπνίσματος
- Αντιγριπικός εμβολιασμός
- Ηλικία < 65 έτη, και FEV_1 > 40% (δεν είναι απαραίτητος ο αντιπνευμονιοκοκκικός εμβολιασμός)

- 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



Respiratory Medicine (2011) 105, 1576–1587

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REVIEW

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

Marc Decramer [a], Marc Miravitlles [b,*], David Price [c], Miguel Román-Rodriguez [d], Carl Llor [e], Tobias Welte [f], Roland Buhl [g], Daniel Dusser [h], Katerina Samara [i], Nikolaus Siafakas [i]

"…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."

Decramer M et al, Resp Med 2011;105:1576-1587.