Ποιος είναι ο ρόλος των εισπνεομένων στεροειδών στη θεραπευτική αντιμετώπιση της ΧΑΠ το 2019;

Θεόδωρος Βασιλακόπουλος

Καθηγητής Πνευμονολογίας-Εντατικής Θεραπείας

Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Διευθυντής Γ’ Κλινικής Εντατικής Θεραπείας, Ευγενίδειο Θεραπευτήριο

Σύμβουλος Πνευμονολόγος, Λαϊκό Νοσοκομείο

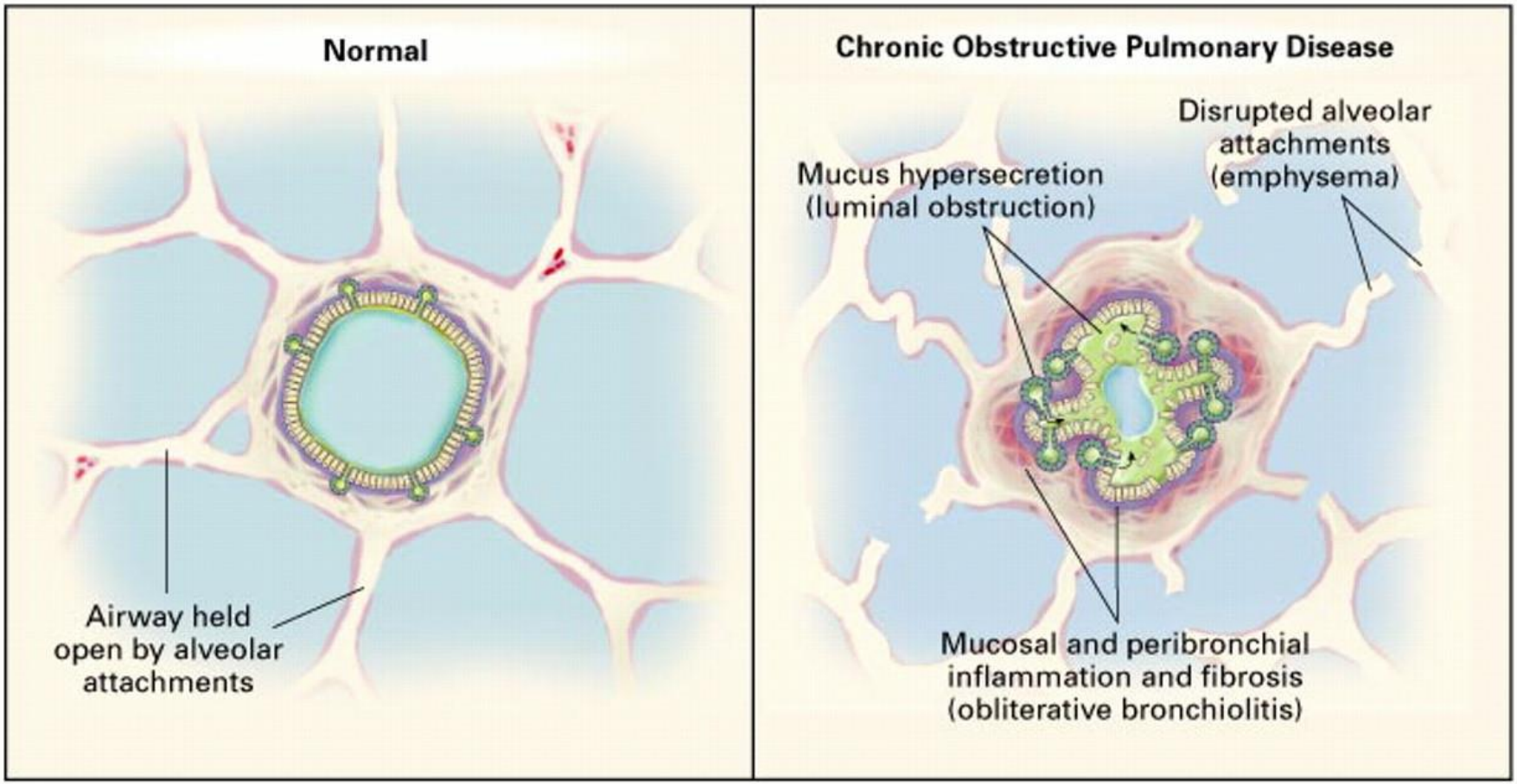
Adjunct Professor, McGill University, Montreal, Canada

Δήλωση συμφερόντων

Grants: Boehringer Ingeleim, GSK, Chiesi, Menarini, Pharmathen

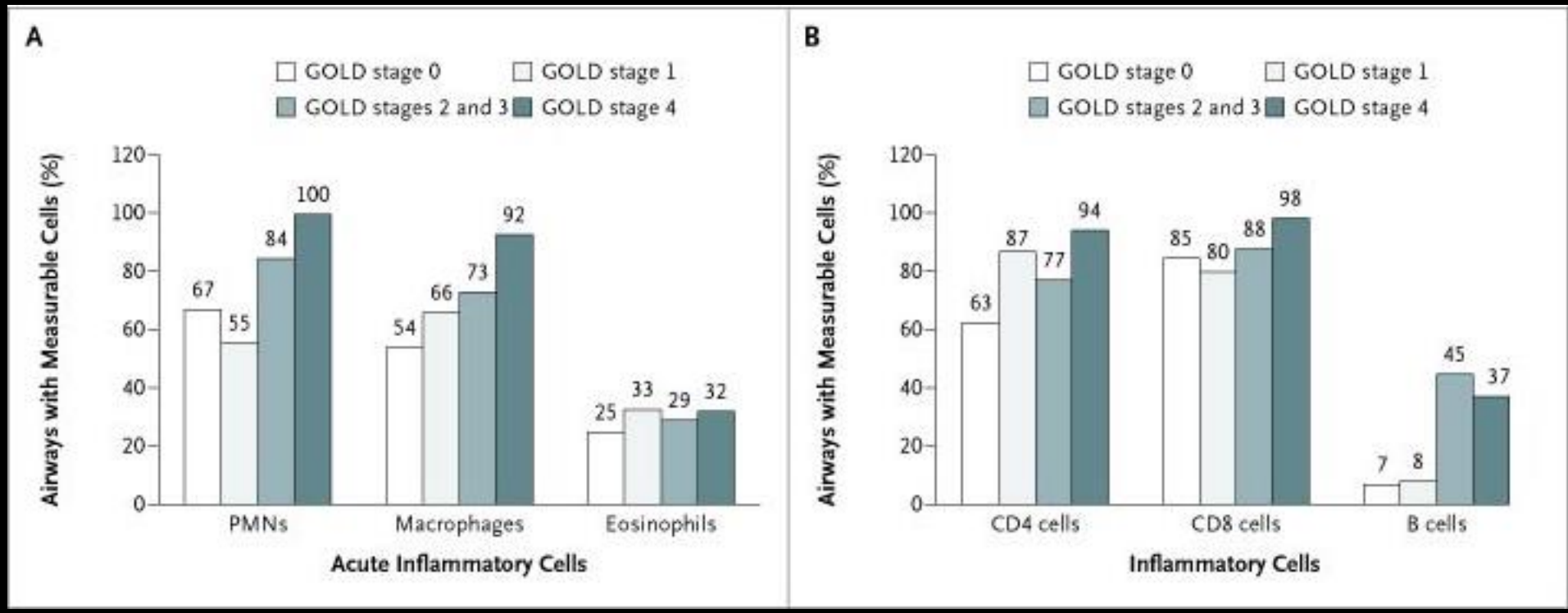
Honoraria: Astra Zaneca, Boehringer Ingeleim, GSK, Chiesi, Menarini, Pharmathen, Novartis, La Roche

ΧΑΠ: νόσος μικρών αεραγωγών



Barnes, P. J. N Engl J Med 2000;343:269-280

Φλεγμονή του πνεύμονα από τα αρχικά στάδια της ΧΑΠ



Hogg, J. et al. N Engl J Med 2004;350:2645-2653

Τι κάνει η μονοθεραπεία
με εισπνεόμενα κορτικοστεροειδή
στη ΧΑΠ;

ICS & φλεγμονή

GLUCOLD STUDY:
Βιοψίες βρόγχων σε μακροχρόνια χορήγηση εισπνεόμενων κορτικοειδών στη ΧΑΠ

Annals of Internal Medicine | ARTICLE

Effect of Fluticasone With and Without Salmeterol on Pulmonary Outcomes in Chronic Obstructive Pulmonary Disease

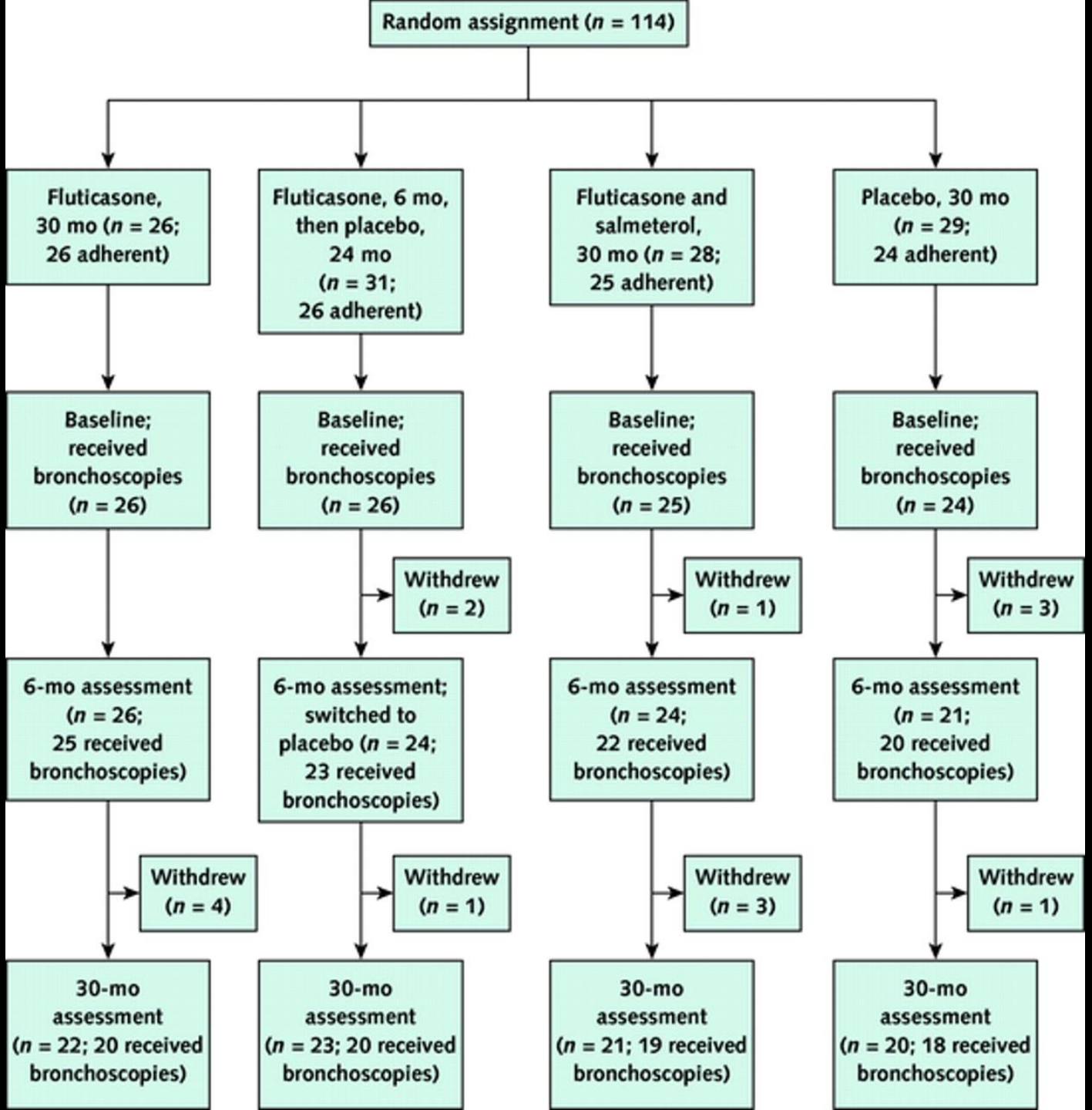
A Randomized Trial

Thérèse S. Lapperre, MD; Jiska B. Snoeck-Stroband, MD; Margot M.E. Gosman, PhD, MD; Désirée F. Jansen, PhD; Annemarie van Schadewijk, MSc; Henk A. Thiadens, PhD, MD; Judith M. Vonk, PhD; H. Marike Boezen, PhD; Nick H.T. ten Hacken, PhD, MD; Jacob K. Sont, PhD; Klaus F. Rabe, PhD, MD; Huib A.M. Kerstjens, PhD, MD; Pieter S. Hiemstra, PhD; Wim Timens, PhD, MD; Dirkje S. Postma, PhD, MD; Peter J. Sterk, PhD, MD; and the GLUCOLD (Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease) Study Group*

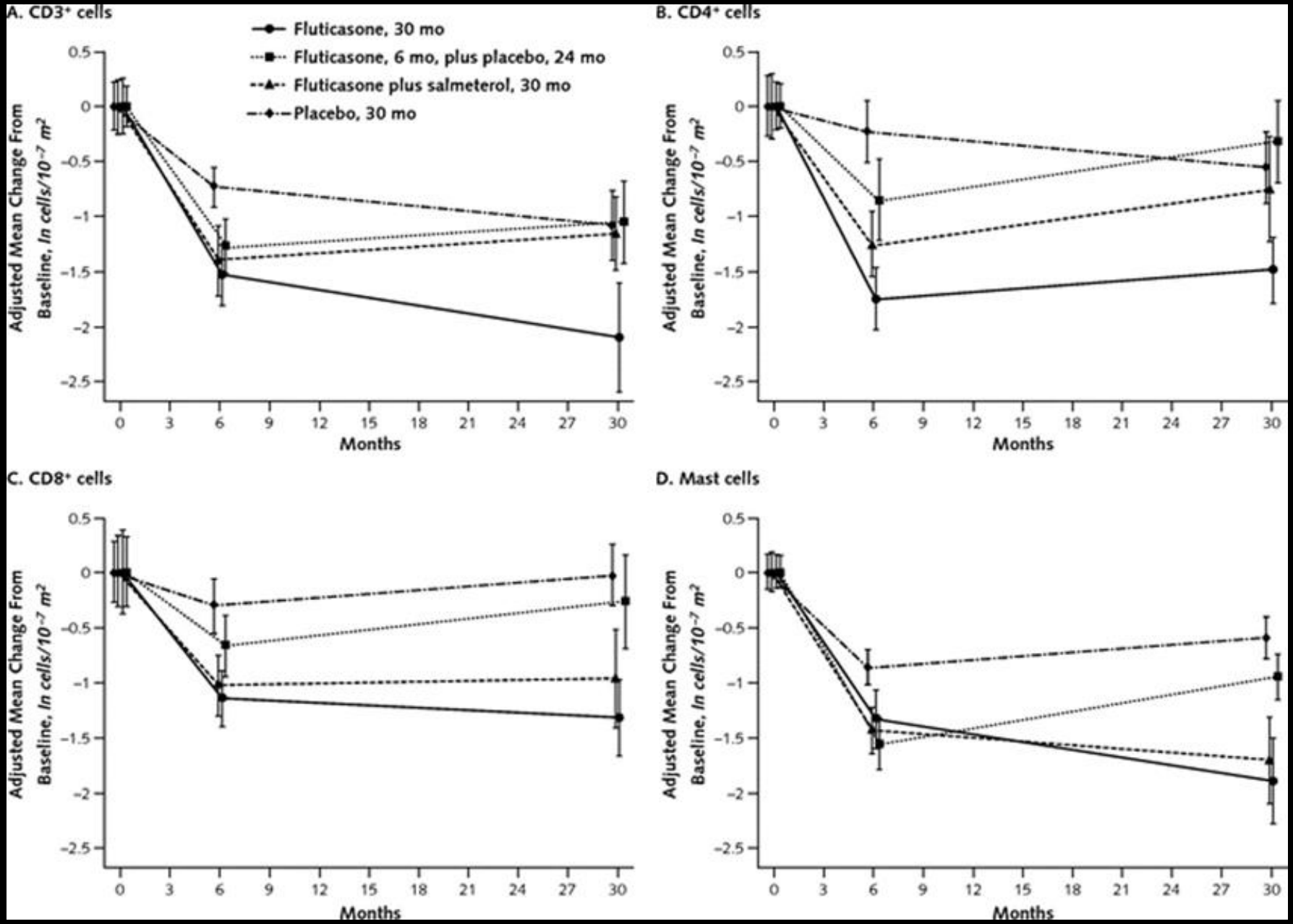
Ασθενείς με ΧΑΠ που δεν έχουν λάβει κορτικοειδή

Lapperre T S et al. Ann Intern Med 2009;151:517-527

30 μήνες

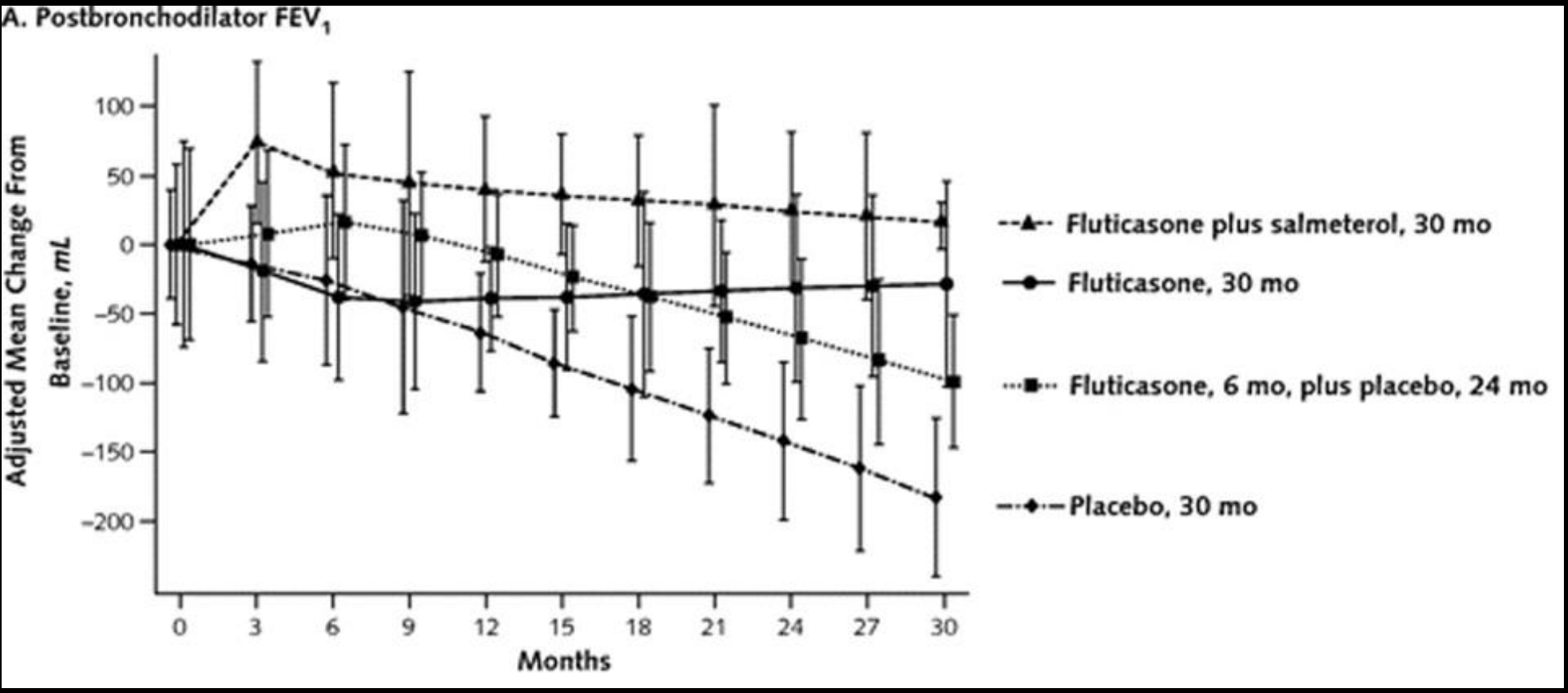

Random assignment (n = 114)
Fluticasone, 30 mo (n = 26; 26 adherent)
Fluticasone, 6 mo, then placebo, 24 mo (n = 31; 26 adherent)
Fluticasone and salmeterol, 30 mo (n = 28; 25 adherent)
Placebo, 30 mo (n = 29; 24 adherent)
Baseline; received bronchoscopies (n = 26)
Baseline; received bronchoscopies (n = 26)
Baseline; received bronchoscopies (n = 25)
Baseline; received bronchoscopies (n = 24)
Withdrew (n = 2)
Withdrew (n = 1)
Withdrew (n = 3)
6-mo assessment (n = 26; 25 received bronchoscopies)
6-mo assessment; switched to placebo (n = 24; 23 received bronchoscopies)
6-mo assessment (n = 24; 22 received bronchoscopies)
6-mo assessment (n = 21; 20 received bronchoscopies)
Withdrew (n = 4)
Withdrew (n = 1)
Withdrew (n = 3)
Withdrew (n = 1)
30-mo assessment (n = 22; 20 received bronchoscopies)
30-mo assessment (n = 23; 20 received bronchoscopies)
30-mo assessment (n = 21; 19 received bronchoscopies)
30-mo assessment (n = 20; 18 received bronchoscopies)

Φλεγμονώδη κύτταρα σε βιοψίες βρόγχων



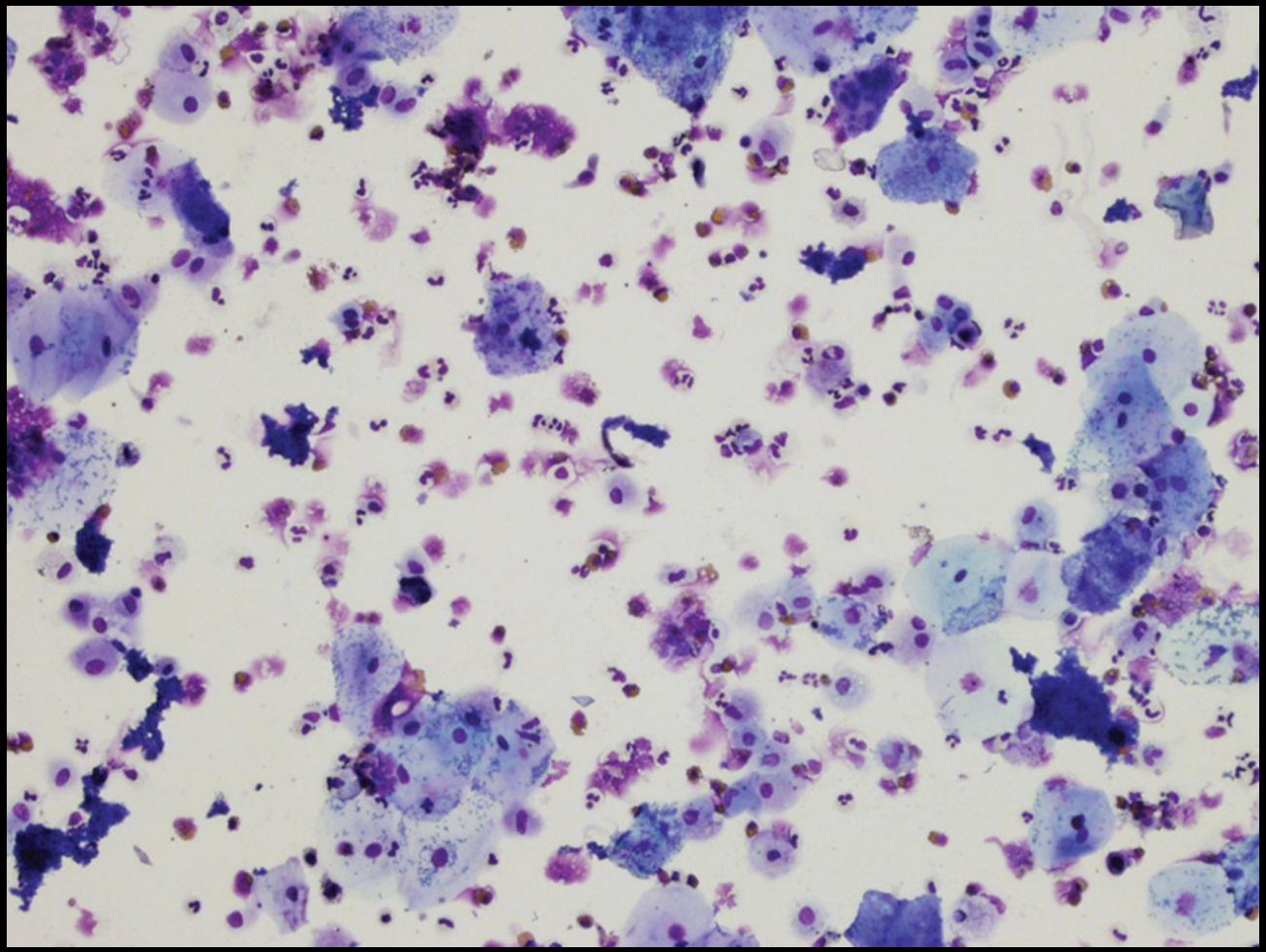
Lapperre T S et al. Ann Intern Med 2009;151:517-527

FEV_1



Lapperre T S et al. Ann Intern Med 2009;151:517-527

Απόσυρση ICS: Τι γίνεται με τη φλεγμονή;



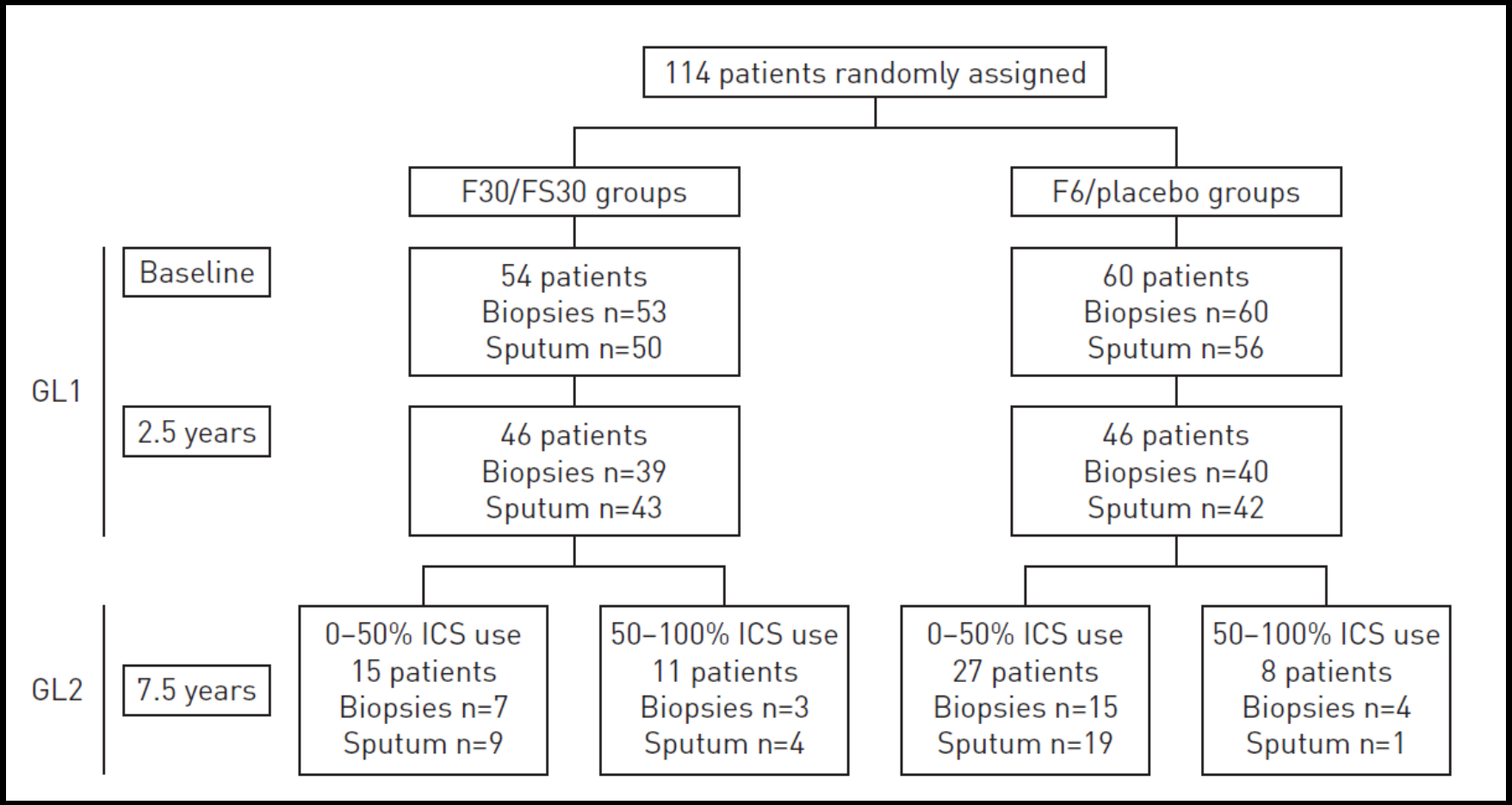
Airway inflammation in COPD after long-term withdrawal of inhaled corticosteroids

Lisette I.Z. Kunz[1], Nick H.T. ten Hacken[2], Thérèse S. Lapperre[1,3], Wim Timens[4], Huib A.M. Kerstjens[2], Annemarie van Schadewijk[1], Judith M. Vonk[5], Jacob K. Sont[6], Jiska B. Snoeck-Stroband[6], Dirkje S. Postma[2], Peter J. Sterk[7] and Pieter S. Hiemstra[1] the GLUCOLD Study Group[8]

***Eur Respir J* 2017**

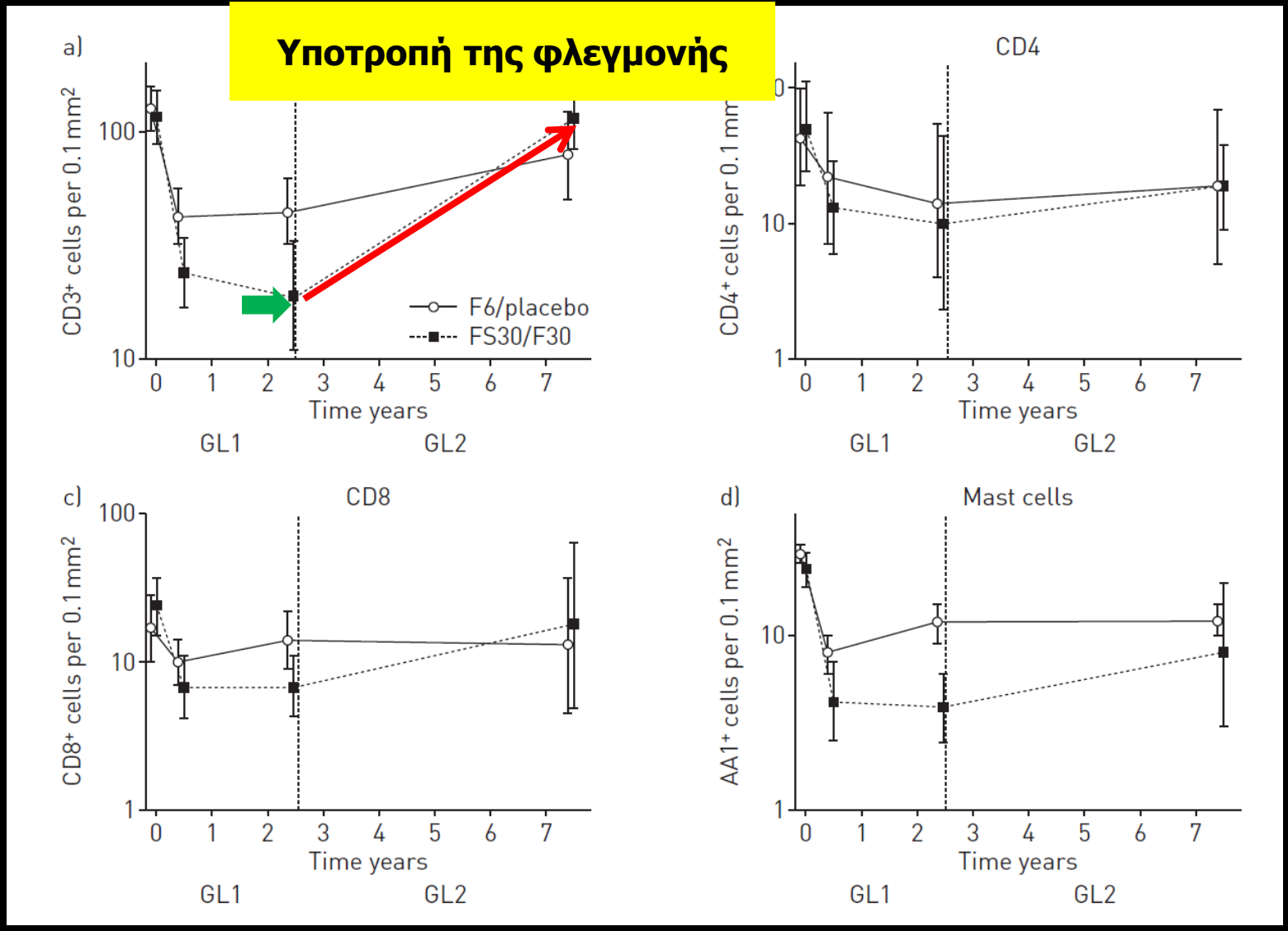
- Υλικό: Στην μελέτη GLUCOLD-1, 114 ασθενείς με μέτρια/σοβαρή ΧΑΠ τυχαιοποιήθηκαν να λάβουν θεραπεία με φλουτικαζόνη (500 μg Χ 2) για 6 ή 30 μήνες, με φλουτικαζόνη/σαλμετερόλη (500/50 μg Χ 2) για 30 μήνες ή placebo
- Παρακολούθηση: 5ετής (GL2) και θεραπεία σύμφωνα με τις οδηγίες
- Βρογχικές βιοψίες και προκλητά πτύελα: στην έναρξη, στους 30 μήνες (τέλος της GL1) και στα 7.5 χρόνια (τέλος της GL2)
- Πρωτεύον καταληκτικό σημείο: Η επίδραση στον αριθμό των φλεγμονωδών κυττάρων (βρογχικές βιοψίες) της απόσυρσης των ICS

Σχεδιασμός μελετών GL1/GL2: σύγκριση ασθενών που έλαβαν ICS κατά 0-50% vs όσων έλαβαν κατά 50-100% του χρόνου παρακολούθησης (GL2)



Βρογχικές βιοψίες: Ασθενείς με χρήση ICS κατά 0-50% του χρόνου από τα 2.5 στα 7 έτη

Υποτροπή της φλεγμονής



Kunz L, et al. *Eur Respir J* 2017; 49: 1600839

ICS & Εξέλιξη νόσου:
Ρυθμός απώλειας αναπνευστικής λειτουργίας

TORCH Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

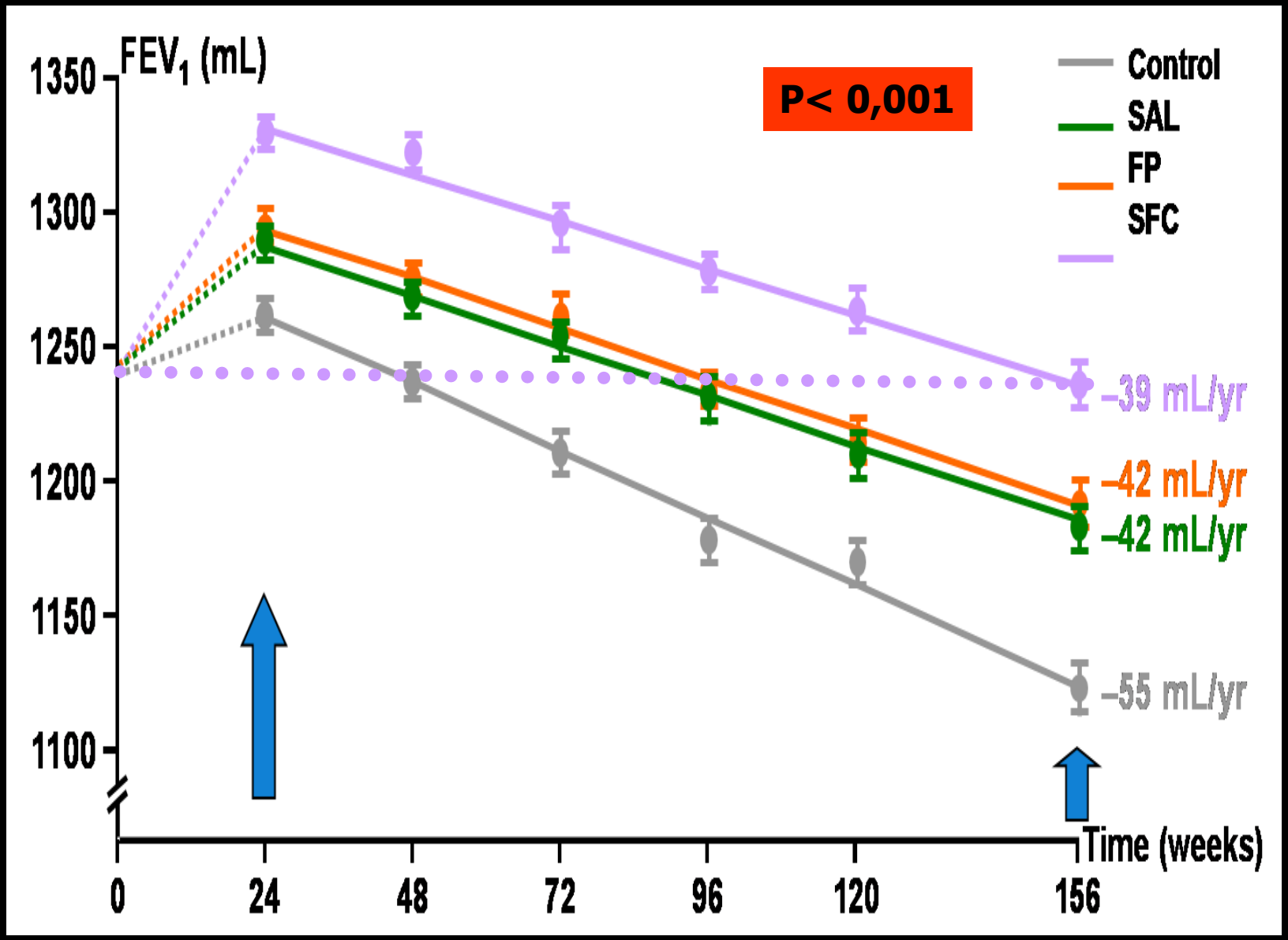
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

Διάρκεια:

Υλικό:

Ο συνδυασμός β2/ICS μειώνει το ρυθμό έκπτωσης του FEV_1



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

SUMMIT Study

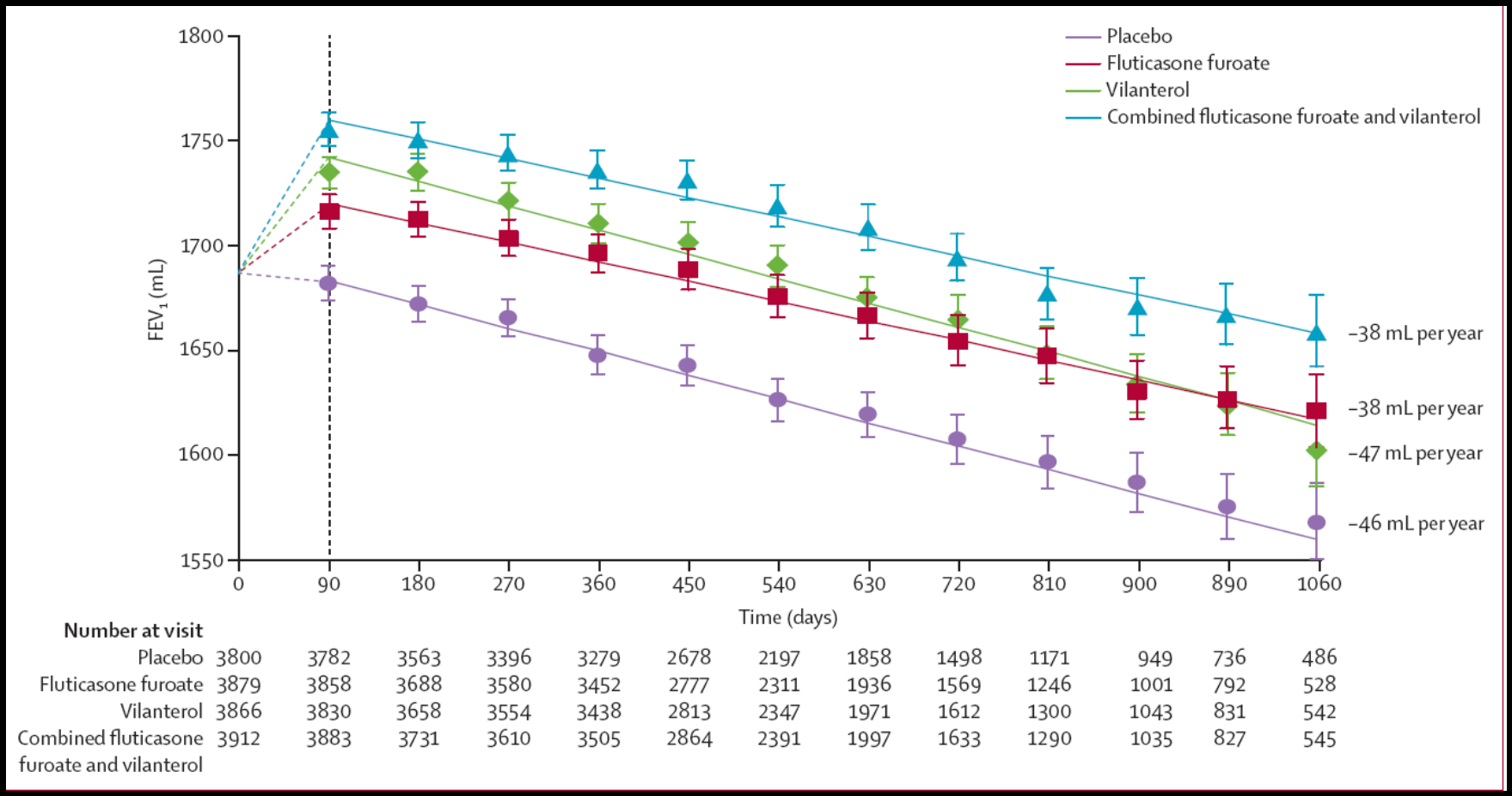
Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators

- Υλικό: Ασθενείς με ΧΑΠ, FEV_1 = 50-70% pred, καπνιστικό ιστορικό ≥ 10 py, mMRC ≥ 2, με ιστορικό καρδιαγγειακής νόσου ή σε υψηλό καρδιαγγειακό κίνδυνο
- Πρωτεύον καταληκτικό σημείο: Χρόνος έως τον θάνατο από οποιαδήποτε αιτία (θνητότητα)
- Δευτερεύοντα καταληκτικά σημεία: ρυθμός έκπτωσης FEV_1, καρδιαγγειακά συμβάματα, παροξύνσεις (μέτριες = ανάγκη λήψης αντιβιοτικών ή CS συστηματικά, σοβαρές = νοσηλεία)

Vestbo J, et al. *Lancet* 2016; 387: 1817–26.

Ρυθμός έκπτωσης FEV_1: 8 ml διαφορά από placebo για FF/V και FF

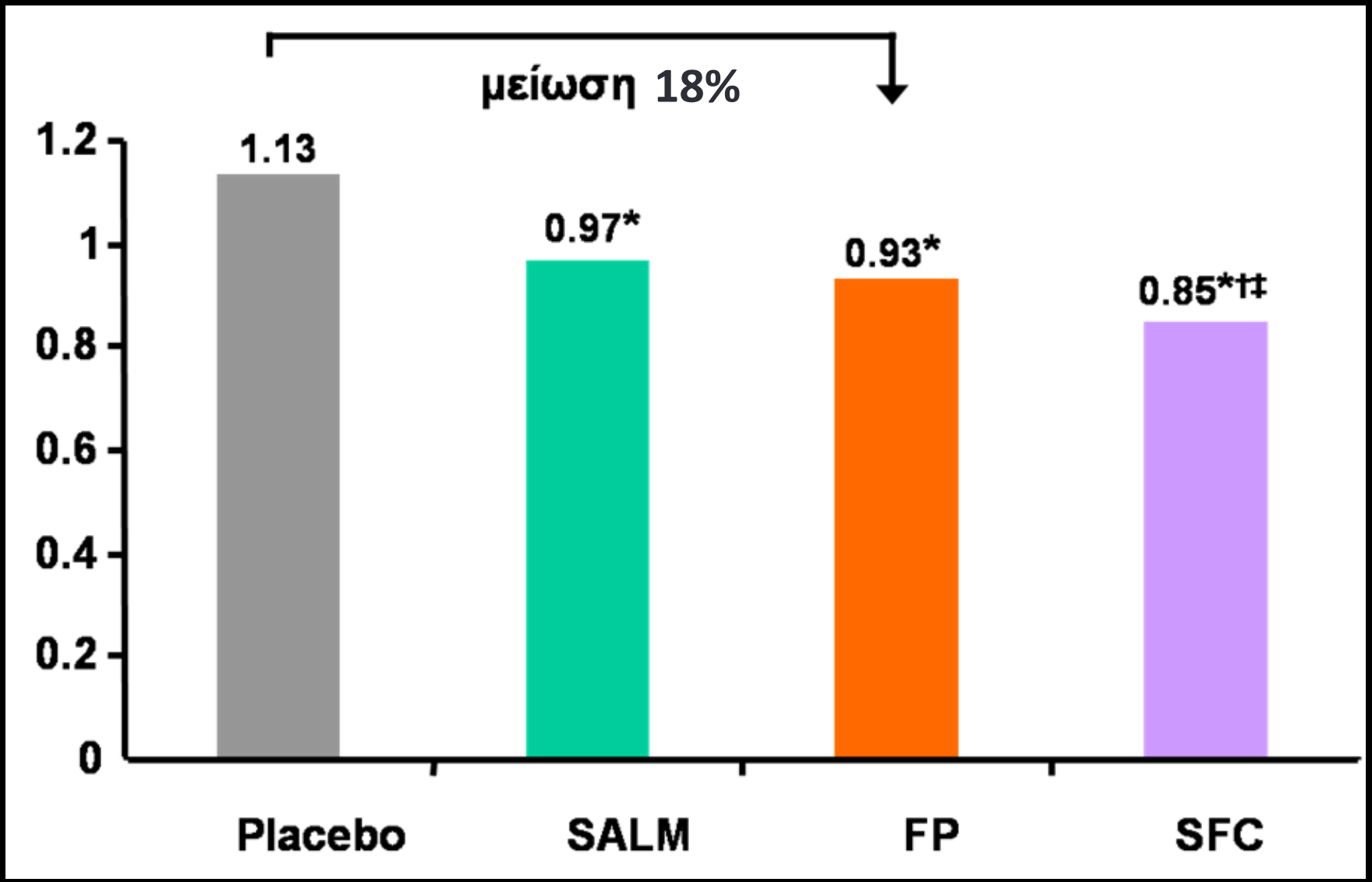


ICS: μειώνουν το ρυθμό έκπτωσης του FEV_1 σε πρώιμα στάδια της νόσου

Vestbo J, et al. *Lancet* 2016; 387: 1817–26.

ICS & Παροξύνσεις

TORCH Study: Παροξύνσεις ΧΑΠ



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

Τι γίνεται όταν
τα εισπνεόμενα κορτικοστεροειδή
προστίθενται σε LABA?

Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations

J.A. Wedzicha [a,*], D. Singh [b], J. Vestbo [d], P.L. Paggiaro [c], P.W. Jones [e], F. Bonnet-Gonod [f], G. Cohuet [f], M. Corradi [g], S. Vezzoli [h], S. Petruzzelli [h], A. Agusti [i], for the FORWARD Investigators[1]

A double-blind, randomised, study

- 1199 ασθενείς με ΧΑΠ
- και 30<FEV_1< 50% pred
- και τουλάχιστον μία παρόξυνση το προηγούμενο έτος

Διάρκεια: 48 εβδομάδες

Συμπρωτεύοντα καταληκτικά σημεία:

-Παροξύνσεις ΧΑΠ στις 48 εβδομάδες

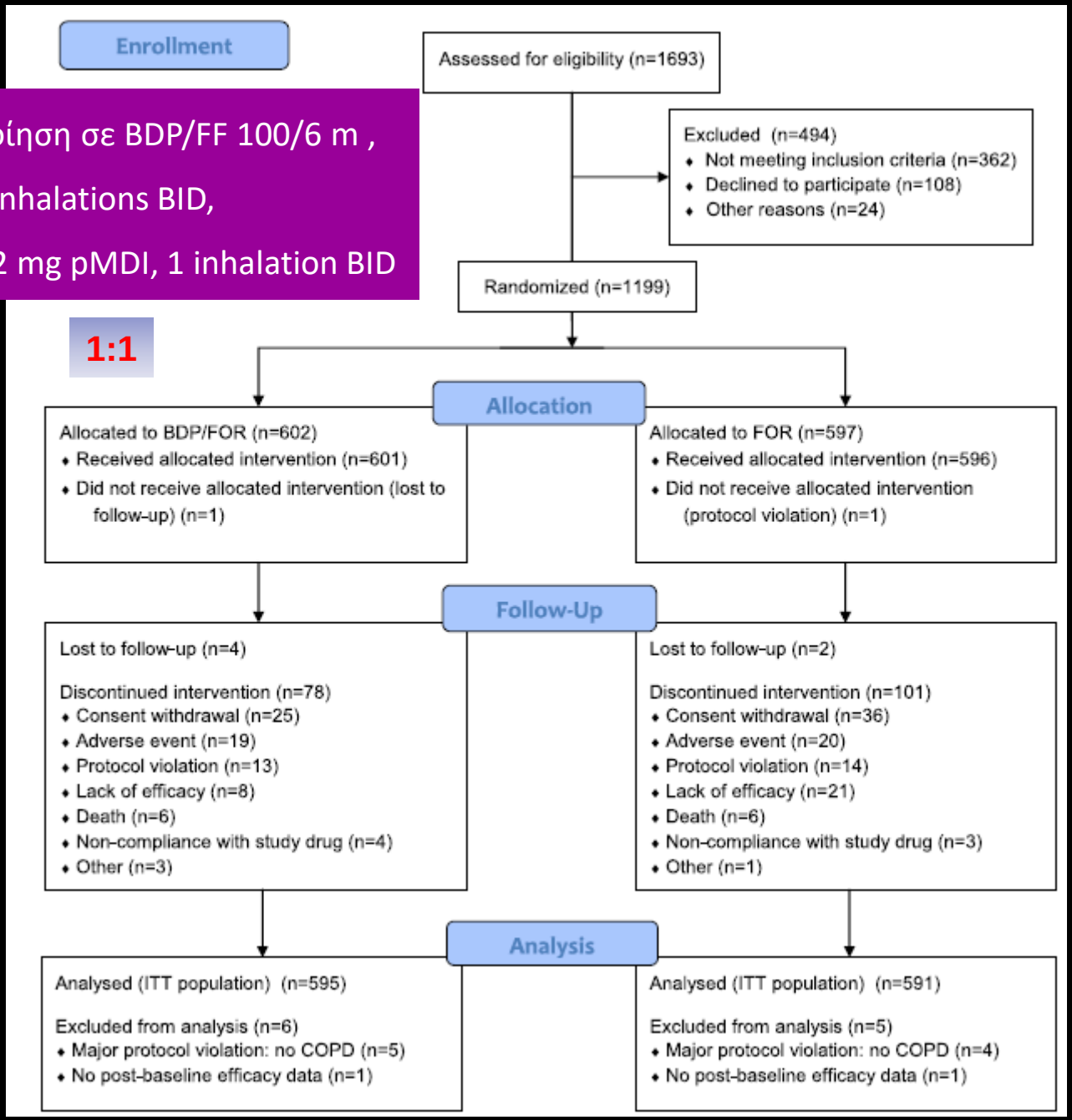
-πρωινός (πριν τη δόση) FEV_1 την 12η εβδομάδα

Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

Τυχαιοποίηση σε BDP/FF 100/6 m ,

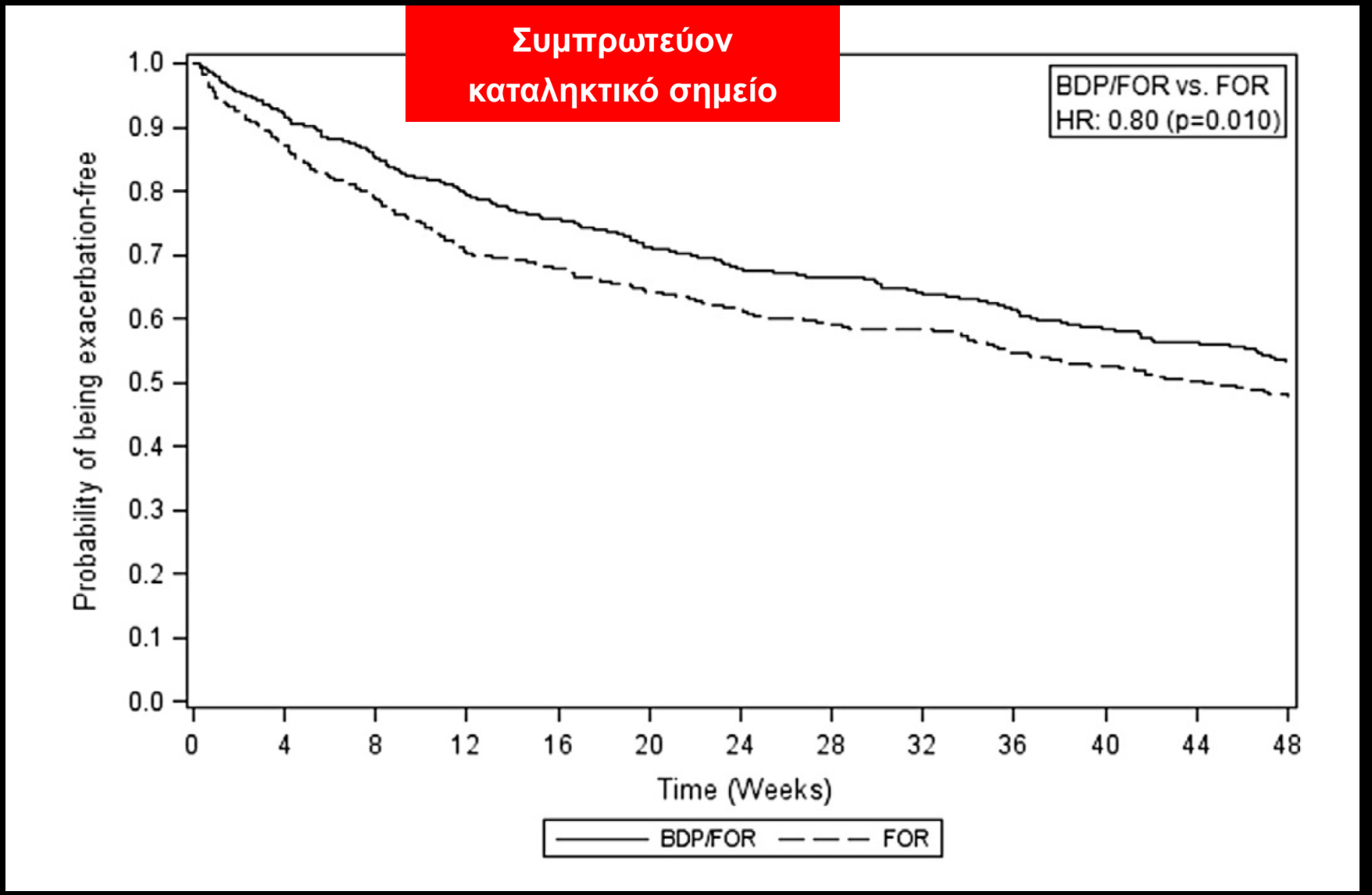
pMDI, 2 inhalations BID,

vs FOR 12 mg pMDI, 1 inhalation BID



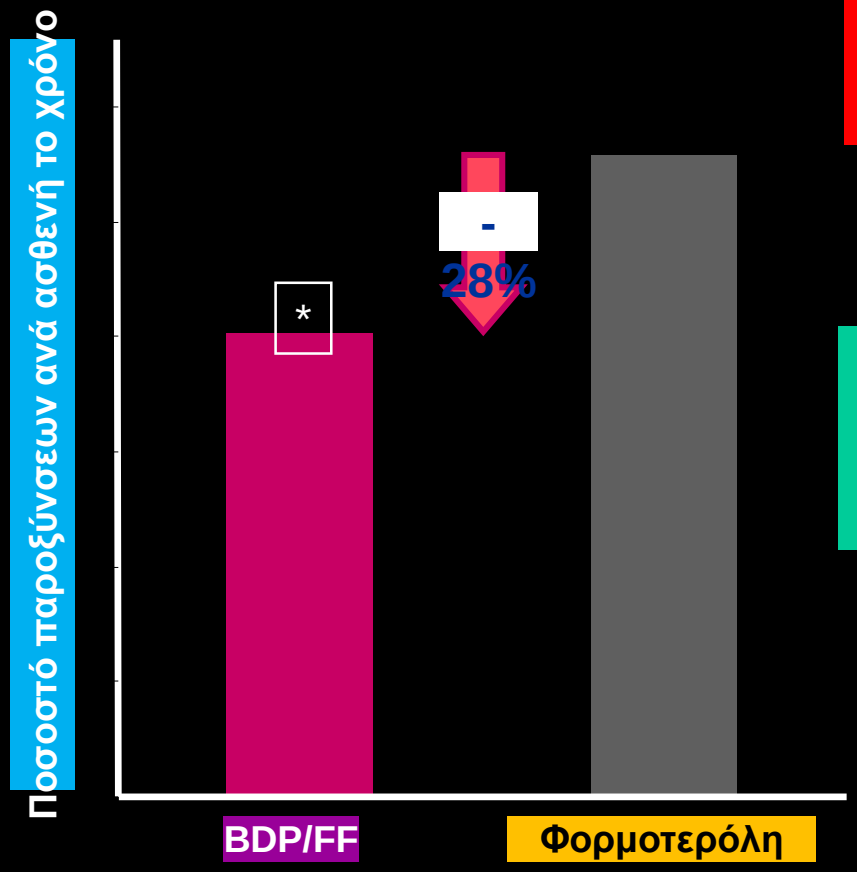
Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

Παροξύνσεις ΧΑΠ: Υπεροχή BDP/FOR έναντι FOR



Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

Παροξύνσεις ΧΑΠ:
↓ κατά 28% με BDP/FOR έναντι FOR



Συμπρωτεύον καταληκτικό σημείο

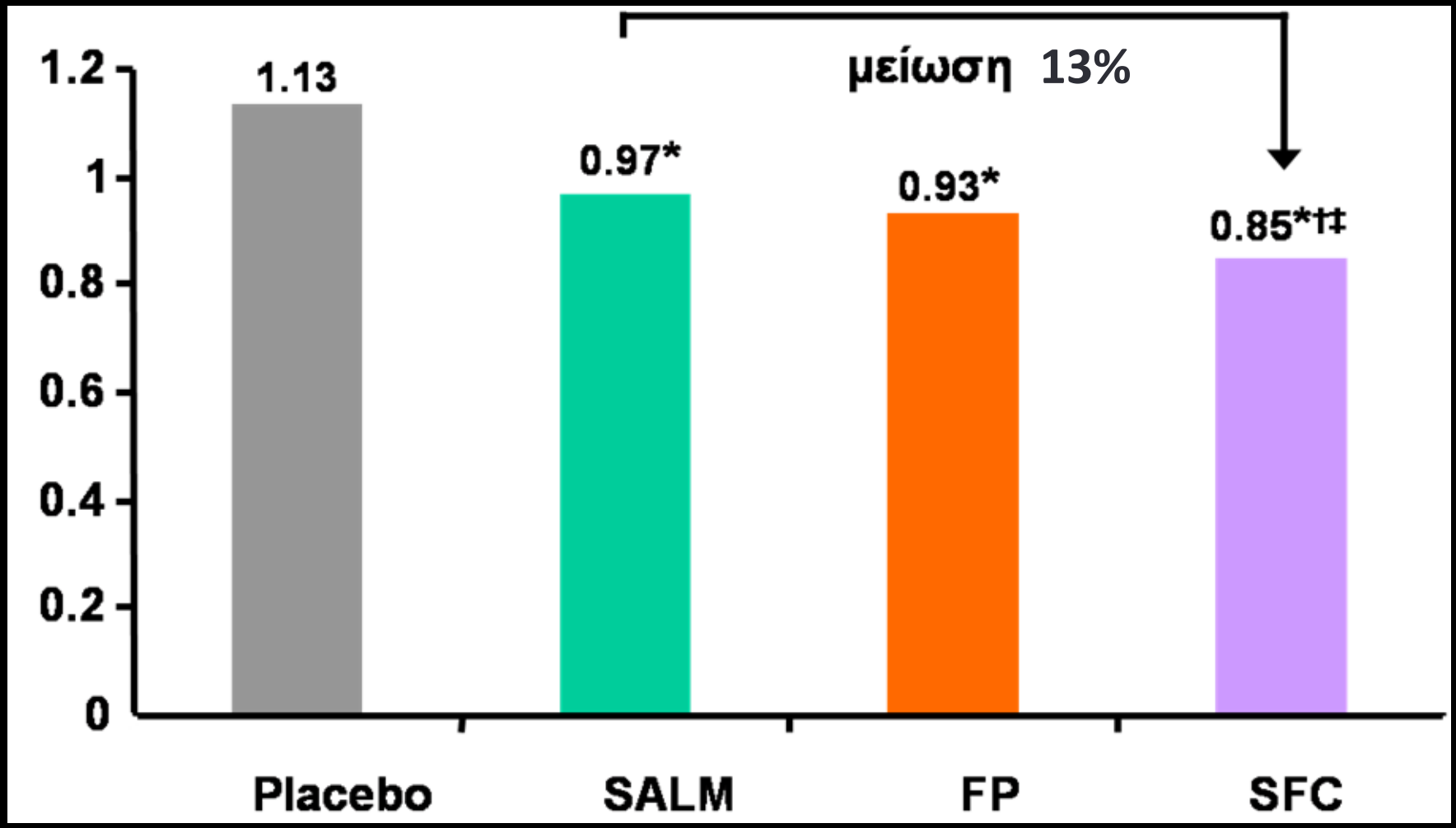
BDP/FOR έναντι φορμοτερόλης

0,719 (0,619, 0,837)

***p<0,001**

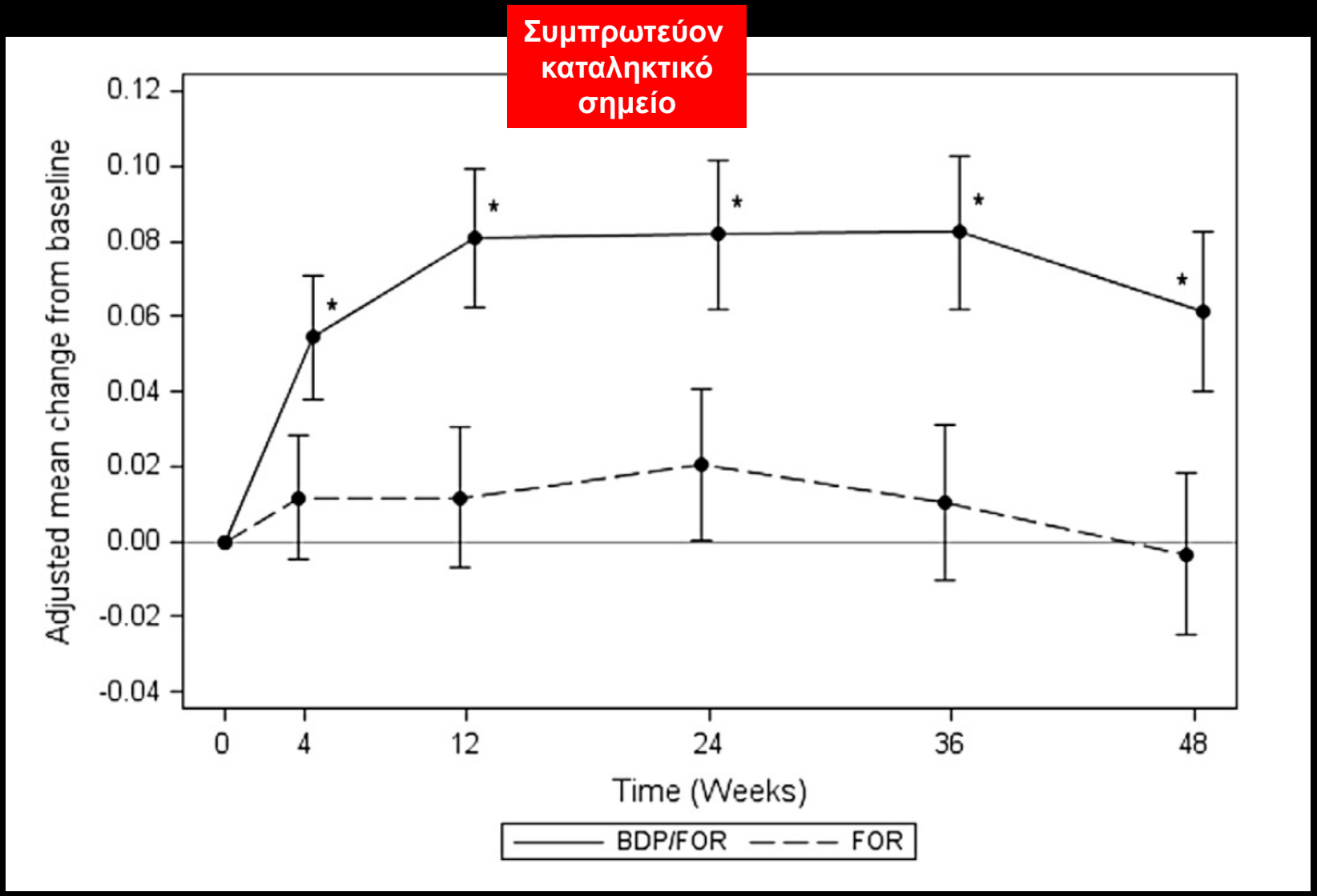
Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

TORCH Study: Παροξύνσεις ΧΑΠ



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

FEV_1: BDP/FOR υπεροχή έναντι FOR



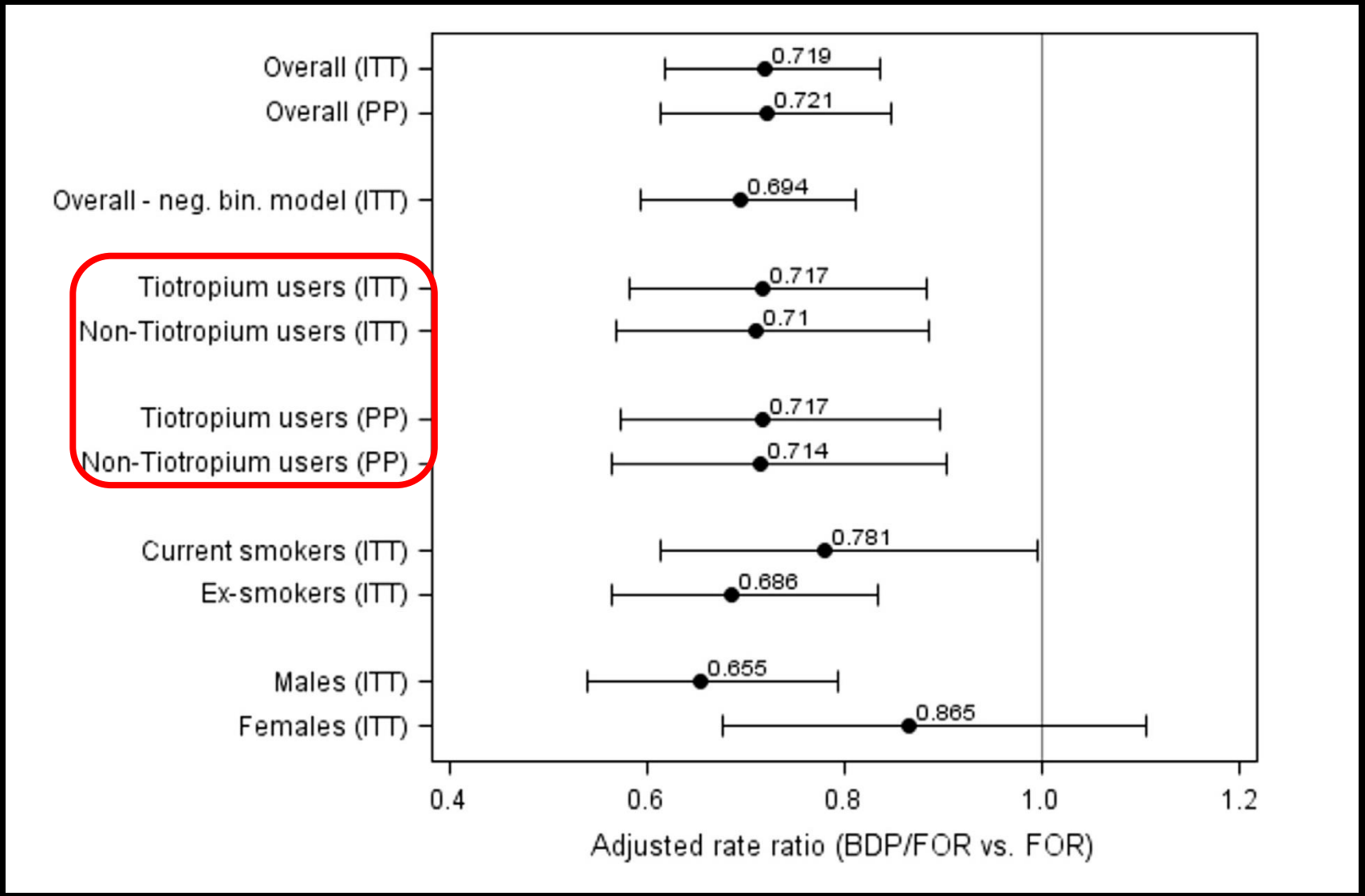
Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

Το 53% των ασθενών ελάμβανε BDP/FOR/TIO (τριπλή θεραπεία) και το 50% FOR/TIO (LABA/LAMA)

	(*N* = 595)	(*N* = 595)
Males, *n* (%)	408 (69%)	410 (69%)
Age, years, mean ± SD	64.6 ± 8.6	63.9 ± 8.6
BMI, Kg/m^2, mean ± SD	26.5 ± 5.4	26.5 ± 5.3
Current smokers, *n* (%)	231 (39%)	237 (40%)
Packs/year, mean ± SD	43.1 ± 23.5	42.7 ± 22.9
SGRQ total score, mean ± SD	47.3 ± 17.9	48.0 ± 17.2
Number of exacerbations in past year, mean ± SD	1.5 ± 0.9	1.4 ± 0.9
Tiotropium users, *n* (%)	318 (53%)	298 (50%)
Post-bronchodilator FEV_1, % of predicted, mean ± SD	41.9 ± 6.0	41.6 ± 6.0
Post-bronchodilator FEV_1, L, mean ± SD	1.15 ± 0.30	1.16 ± 0.30
Post-bronchodilator FEV_1/FVC, mean ± SD	0.48 ± 0.10	0.48 ± 0.10
Reversibility, L, mean ± SD	0.10 ± 0.12	0.10 ± 0.13
Reversibility, %, mean ± SD	10.8 ± 12.9	10.7 ± 14.1

Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

Παροξύνσεις ΧΑΠ: ανάλυση υποομάδων



Wedzicha JA, et al . *Respiratory Medicine* 2014; 108: 1153-62.

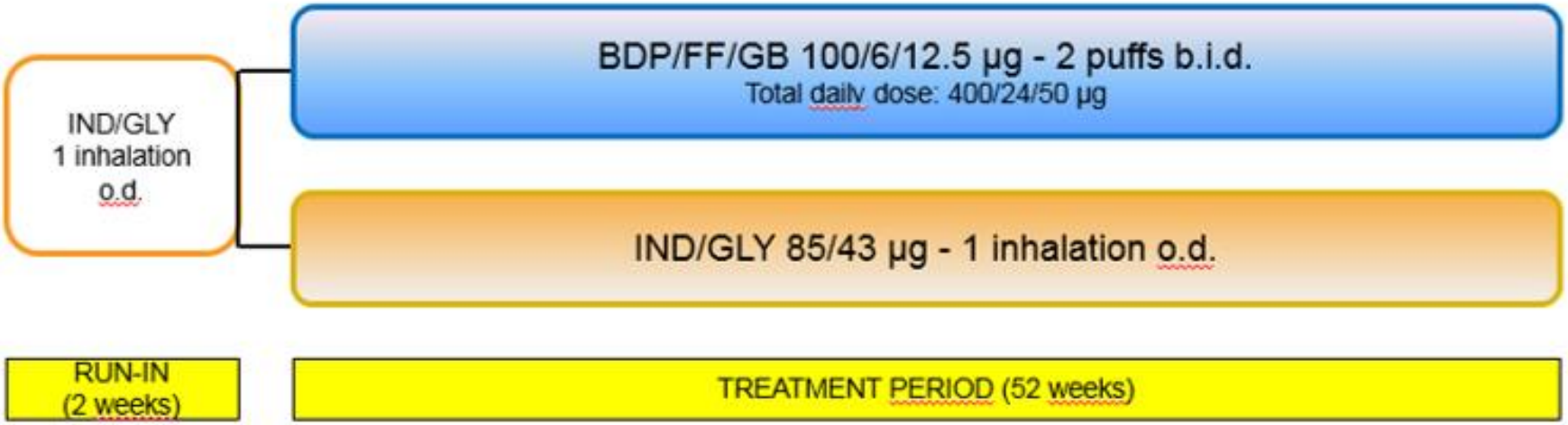
Τι γίνεται όταν
τα εισπνεόμενα κορτικοστεροειδή
προστίθενται σε LABA/LAMA?

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

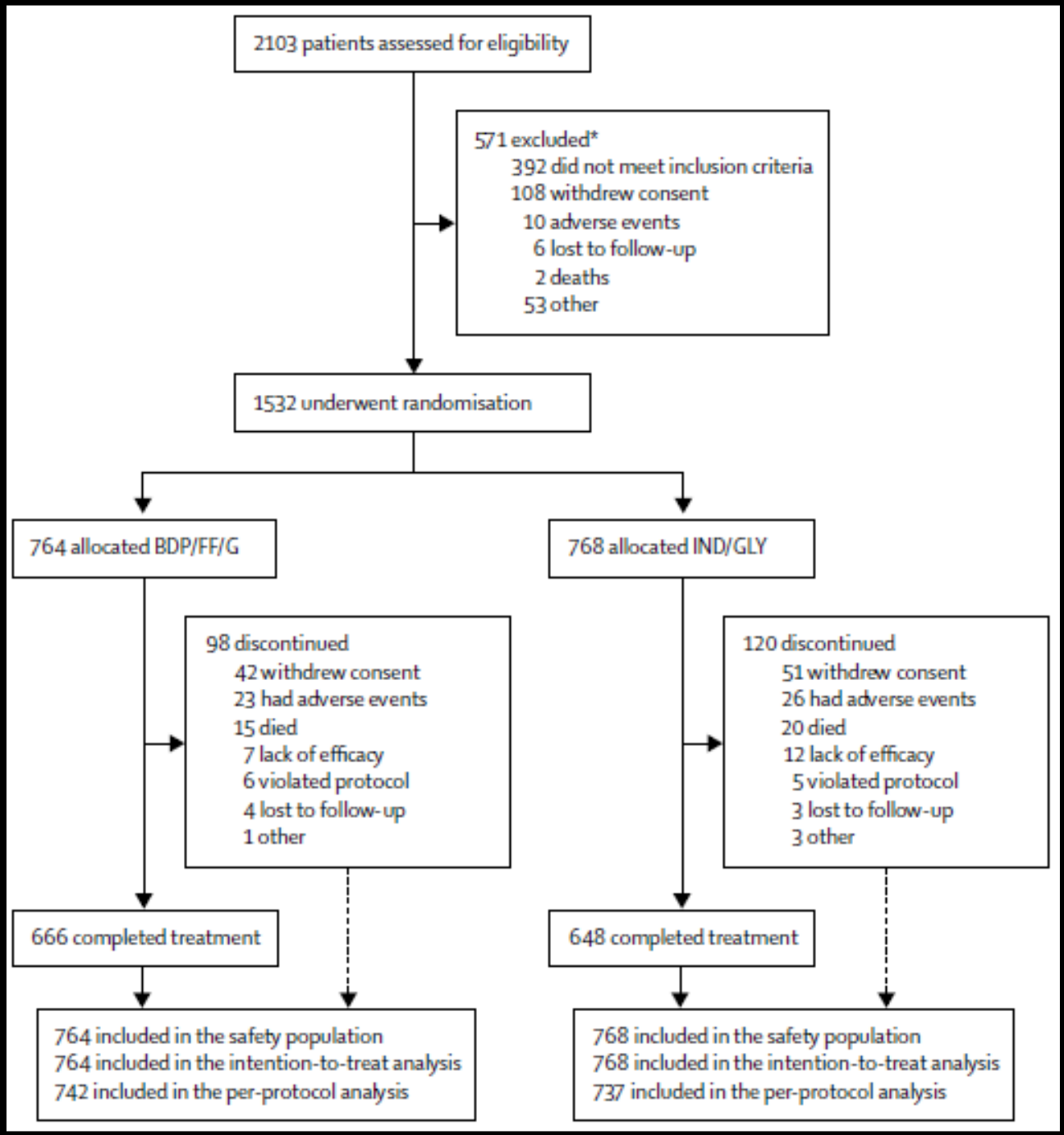
Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

Lancet 2018; 391: 1076–84

TRIBUTE: Study Design



- Same population as TRILOGY and TRINITY
- Blinded
- Aim: to demonstrate superiority of ICS/LABA/LAMA vs LABA/LAMA combination
- Primary Endpoint : exacerbations


2103 patients assessed for eligibility
571 excluded*
392 did not meet inclusion criteria
108 withdrew consent
10 adverse events
6 lost to follow-up
2 deaths
53 other
1532 underwent randomisation
764 allocated BDP/FF/G
768 allocated IND/GLY
98 discontinued
42 withdrew consent
23 had adverse events
15 died
7 lack of efficacy
6 violated protocol
4 lost to follow-up
1 other
120 discontinued
51 withdrew consent
26 had adverse events
20 died
12 lack of efficacy
5 violated protocol
3 lost to follow-up
3 other
666 completed treatment
648 completed treatment
764 included in the safety population
764 included in the intention-to-treat analysis
742 included in the per-protocol analysis
768 included in the safety population
768 included in the intention-to-treat analysis
737 included in the per-protocol analysis

Ποιοί ασθενείς με ΧΑΠ συμμετείχαν στη μελέτη;

- Ασθενείς με ΧΑΠ και FEV_1< 50% pred,
- 1 μέτρια σοβαρή παρόξυνση το προηγούμενο έτος,
- CAT score ≥10, BDI focal score ≤ 10

Διάρκεια: 52 εβδομάδες

Πρωτεύον καταληκτικό σημείο: συχνότητα μέτριων-σοβαρών παροξύνσεων

Δευτερεύοντα καταληκτικά σημεία:

- χρόνος μέχρι την πρώτη παρόξυνση
- pre-dose FEV_1
- SGRC

Papi A, et al. *Lancet* 2018; 391: 1076–84.

	BDP/FF/G (n=764)	IND/GLY (n=768)
Sex		
Male	548 (72%)	552 (72%)
Female	216 (28%)	216 (28%)
Race*		
White	705 (92%)	708 (92%)
Other	51 (7%)	52 (7%)
Age (years)	64·4 (7·7)	64·5 (7·7)
Body-mass index (kg/m²)†	25·7 (5·1)	26·6 (5·4)
Blood leukocyte count (10^9 cells per L)	8·05 (2·38)	8·00 (2·04)
Blood eosinophil count (10^9 cells per L)	0·24 (0·20)	0·23 (0·20)
Blood eosinophil	3·14% (2·47)	2·97% (2·30)
Smoking status		
Ex-smoker	413 (54%)	436 (57%)
Current smoker	351 (46%)	332 (43%)
Time since first COPD diagnosis (years)	8·16 (5·76)	7·99 (5·64)
FEV_1 (L)‡	1·07 (0·31)	1·07 (0·31)
Proportion of predicted normal FEV_1 value‡,§	36·4 (8·0)	36·4 (8·1)
<30%	154 (20%)	160 (21%)
≥30% to <50%	609 (80%)	608 (79%)
FVC (L)‡	2·70 (0·78)	2·64 (0·77)
FEV_1:FVC ratio‡	0·41 (0·10)	0·42 (0·10)
Reversibility (%)	8·4% (13·5)	8·8% (13·5)
Clinical COPD phenotype¶		
Chronic bronchitis	434 (57%)	421 (55%)
Emphysema	227 (30%)	235 (31%)
Mixed chronic bronchitis and emphysema	103 (13%)	112 (15%)
Moderate or severe exacerbations in the previous year (range)	1·2 (1–6)	1·2 (1–4)
1	612 (80%)	626 (82%)
≥2	152 (20%)	142 (18%)
COPD medication taken for at least 2 months before study entry		
ICS/LABA	467 (61%)	465 (61%)
ICS/LAMA	36 (5%)	24 (3%)
LABA/LAMA	183 (24%)	199 (26%)
LAMA	77 (10%)	80 (10%)

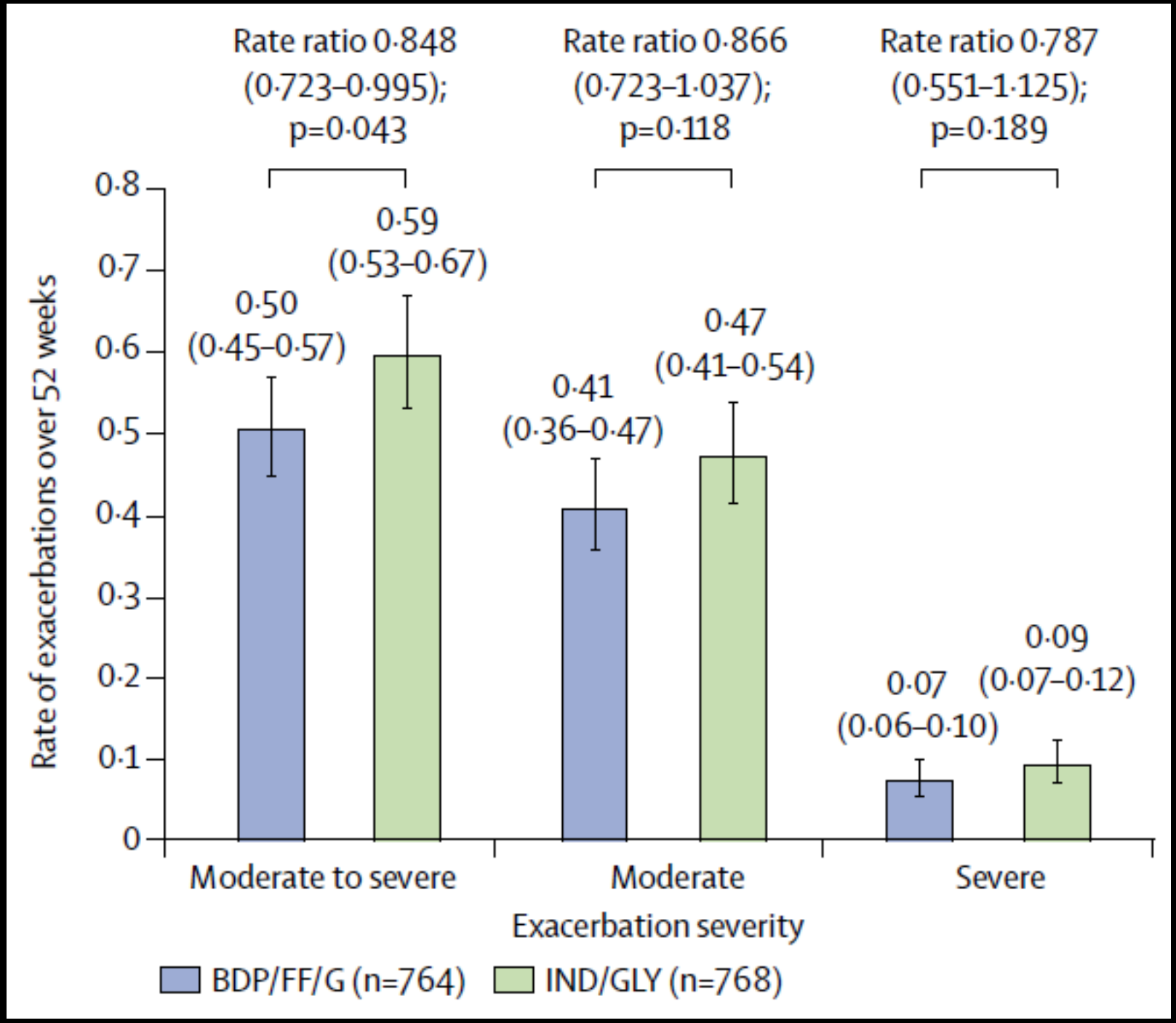
(Table 1 continues in next column)

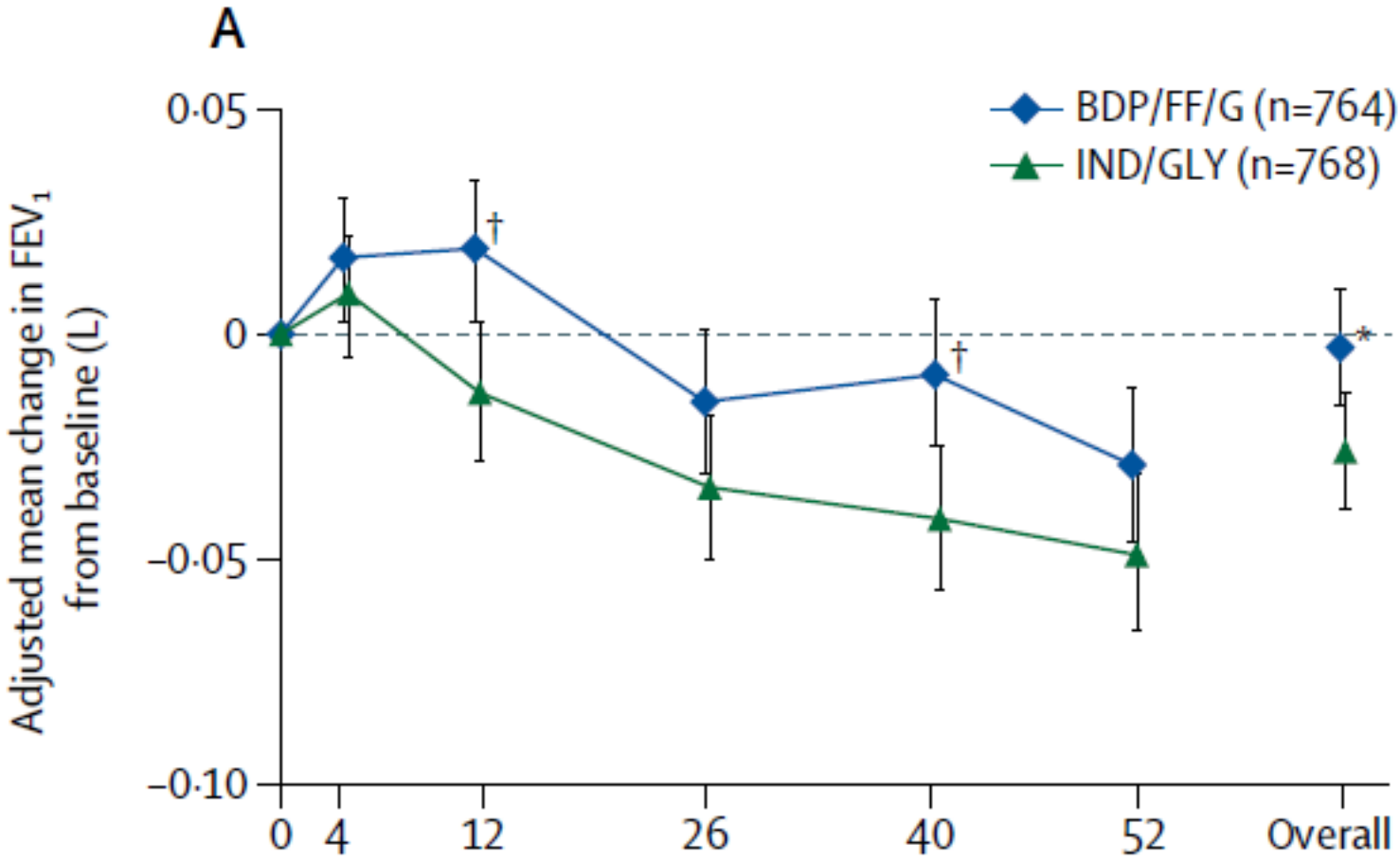
(Continued from previous column)

	BDP/FF/G (n=764)	IND/GLY (n=768)
Patients with at least one concomitant disease‖	644 (84%)	657 (86%)
Hypertension	437 (57%)	460 (60%)
Ischaemic heart disease	134 (18%)	156 (20%)
Myocardial ischaemia	69 (9%)	75 (10%)
Coronary artery disease	42 (5%)	63 (8%)
Angina pectoris	32 (4%)	27 (4%)
Myocardial infarction	3 (<1%)	0
Ischaemic cardiomyopathy	1 (<1%)	1 (<1%)
Diabetes	99 (13%)	108 (14%)
Cardiac failure	75 (10%)	75 (10%)
Hypercholesterolaemia	58 (8%)	65 (8%)
Dyslipidaemia	64 (8%)	56 (7%)
Benign prostatic hyperplasia	49 (6%)	35 (5%)
Obesity	33 (4%)	49 (6%)
Gastroesophageal reflux disease	35 (5%)	45 (6%)
Hyperlipidaemia	23 (3%)	47 (6%)

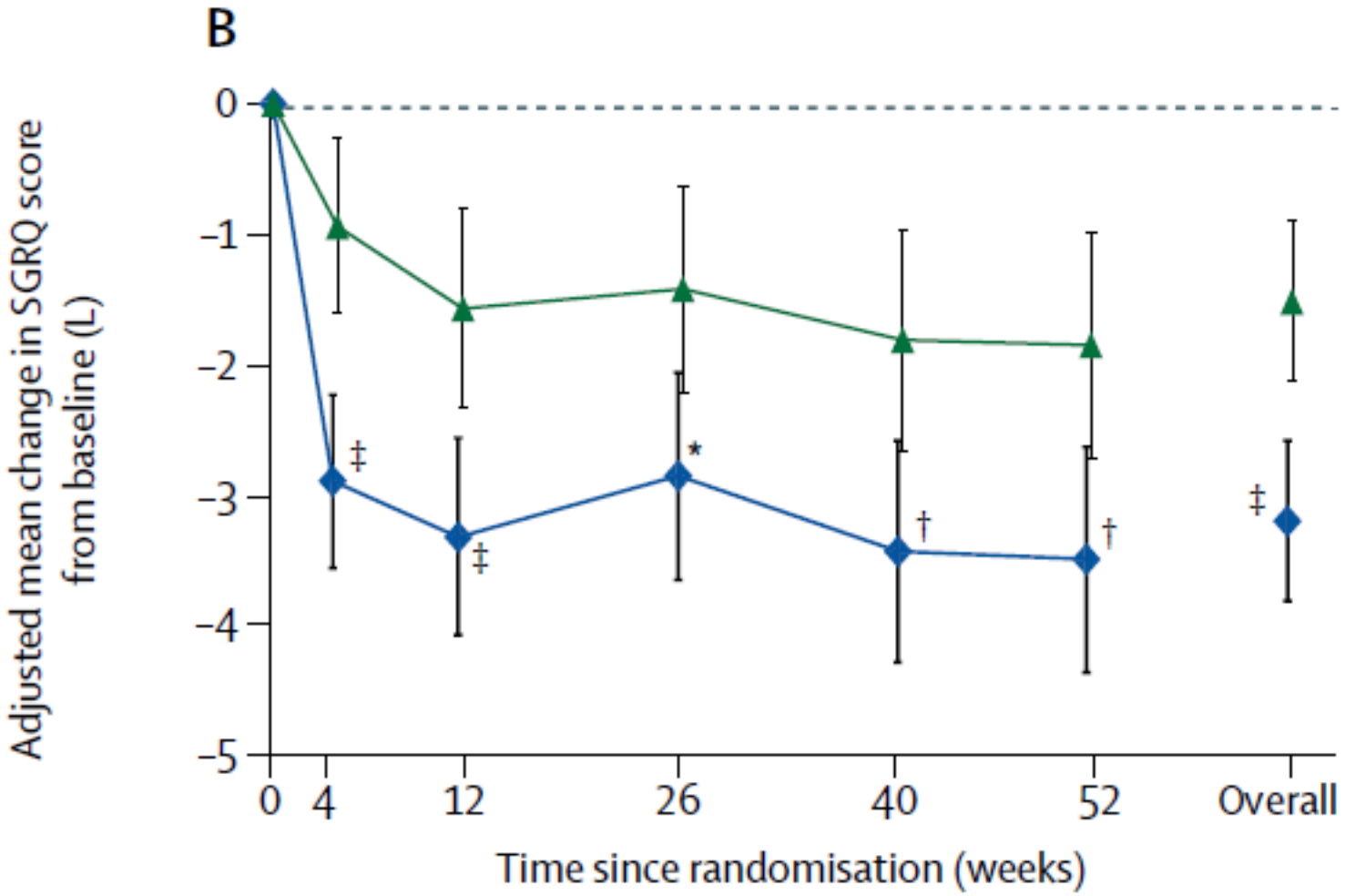
Data are n (%) or mean (SD) unless specified otherwise. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroid. LABA=long-acting β_2-agonist. LAMA=long-acting muscarinic antagonist. *Because of data collection restrictions, this information was not collected in Portuguese sites, and so data are missing from eight patients in each group. †At baseline (visit 2). ‡Measured at screening after salbutamol was given. §One patient in the BDP/FF/G group had an FEV_1 greater than 50% predicted—this patient was excluded from the per-protocol population. ¶Based on the clinical judgement of the investigator. ‖Most common concomitant diseases (≥5% in either group).

Table 1: **Baseline characteristics of the safety population**


Rate ratio 0·848
(0·723–0·995);
p=0·043
Rate ratio 0·866
(0·723–1·037);
p=0·118
Rate ratio 0·787
(0·551–1·125);
p=0·189
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
Rate of exacerbations over 52 weeks
0·50
(0·45–0·57)
0·59
(0·53–0·67)
0·41
(0·36–0·47)
0·47
(0·41–0·54)
0·07
(0·06–0·10)
0·09
(0·07–0·12)
Moderate to severe
Moderate
Severe
Exacerbation severity
BDP/FF/G (n=764)
IND/GLY (n=768)



Adjusted mean difference between treatments (mL)						
	8	32	20	32	19	22
Number with available measurements						
BDP/FF/G	761	754	737	718	694	688	757
IND/GLY	767	758	742	712	677	652	760



Adjusted mean difference between treatments (mL)						
	−1·96	−1·75	−1·43	−1·62	−1·64	−1·68
Number with available measurements						
BDP/FF/G	763	757	740	722	695	667	760
IND/GLY	768	762	744	716	679	654	763

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 3, 2018 VOL. 378 NO. 18

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D., Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S., for the IMPACT Investigators

STUDY PROTOCOL
COPD

A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol

Steven J. Pascoe[1], David A. Lipson[1,2], Nicholas Locantore[1], Helen Barnacle[3], Noushin Brealey[3], Rajat Mohindra[3], Mark T. Dransfield[4], Ian Pavord[5] and Neil Barnes[3,6]

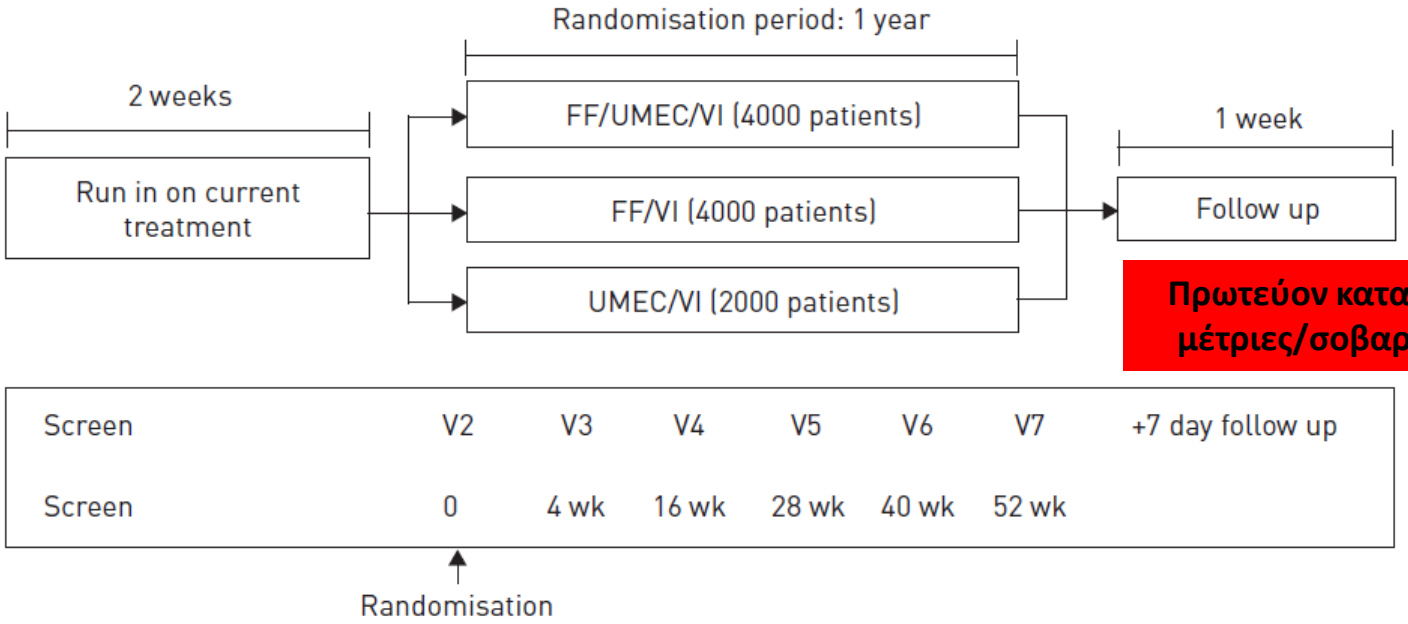


FIGURE 1 Study design. FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; V: visit; wk: week.

Πρωτεύον καταληκτικό σημείο: μέτριες/σοβαρές παροξύνσεις

Eur Respir J 2016; 48: 320–330

Κριτήρια ένταξης μελέτης IMPACT

Impact: InforMing the PAthway of COPD Treatment

- Ηλικία 40+ και διάγνωση ΧΑΠ (ορισμός κατά ATS/ERS)
- CAT ≥10
- FEV_1 <50% με ≥1 μέτρια/σοβαρή παρόξυνση το τελευταίο έτος
- **ή** FEV1 ≥50%, έως <80% με ≥2 μέτριες παροξύνσεις ή ≥1 σοβαρή παρόξυνση το τελευταίο έτος

- Η IMPACT συμπεριέλαβε έναν τυπικό πληθυσμό συμπτωματικών ασθενών με ΧΑΠ σε θεραπεία συντήρησης με ιστορικό παροξύνσεων τον προηγούμενο χρόνο

1. Pascoe SJ, et al. *Eur Respir J*. 2016;48:320–330; 2. Lipson DA, et al. *N Engl J Med*. 2018; May 3;378(18):1671-1680

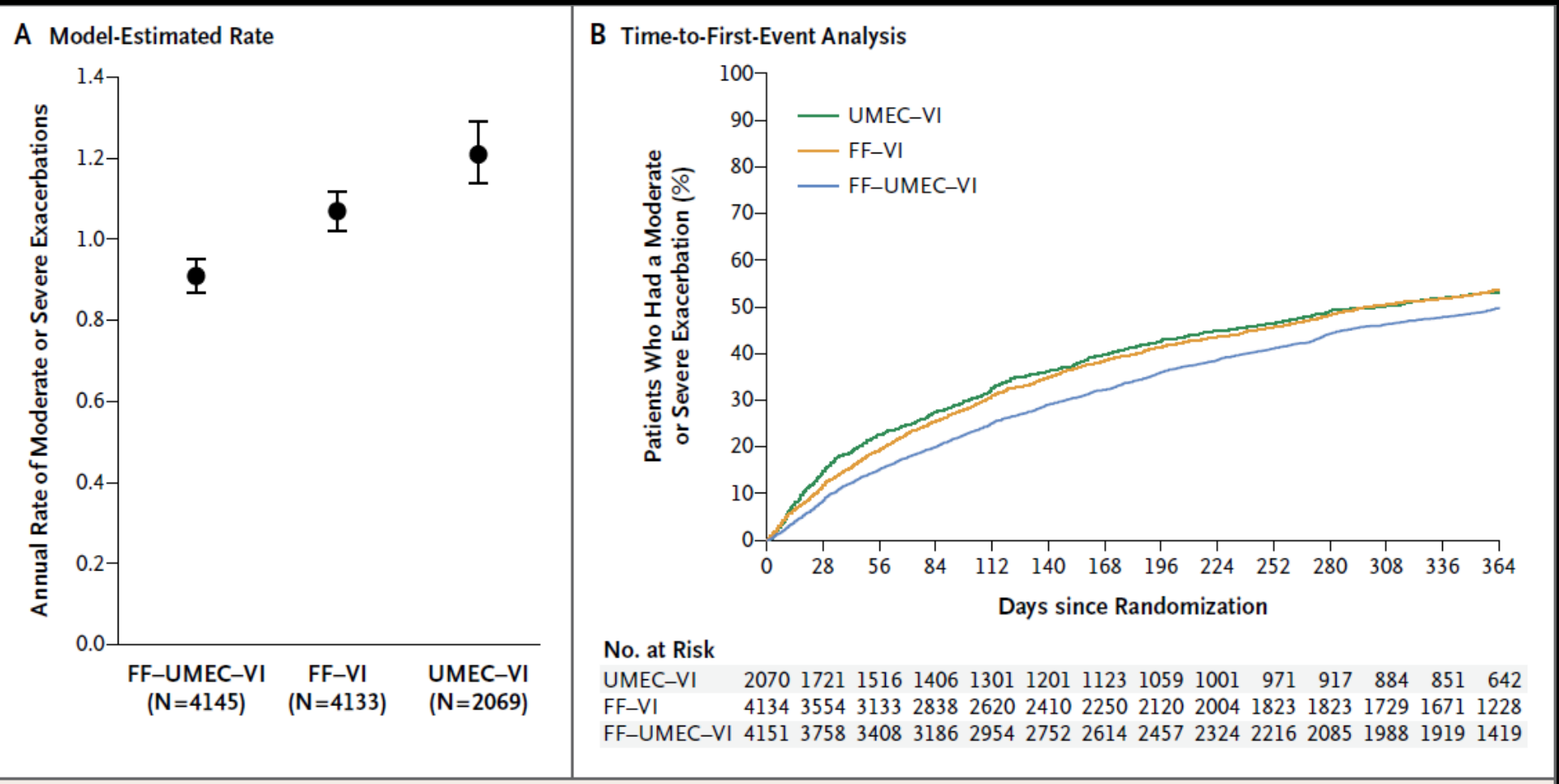
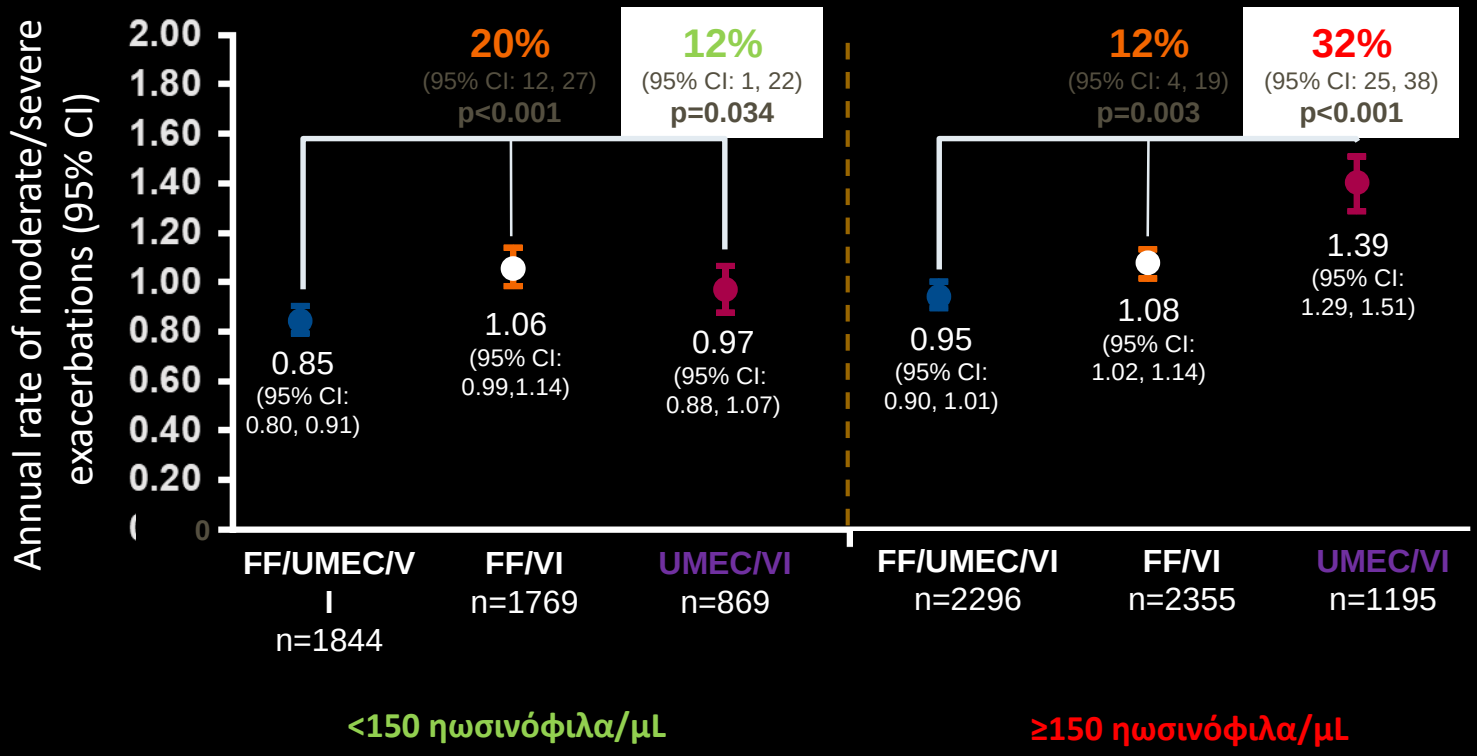


Figure 1. Moderate or Severe COPD Exacerbations (Intention-to-Treat Population).

I bars indicate 95% confidence intervals. COPD denotes chronic obstructive pulmonary disease, FF fluticasone furoate, UMEC umeclidinium, and VI vilanterol.

Ρυθμός μέτριων/σοβαρών παροξύνσεων με βάση των αριθμό των ηωσινοφίλων

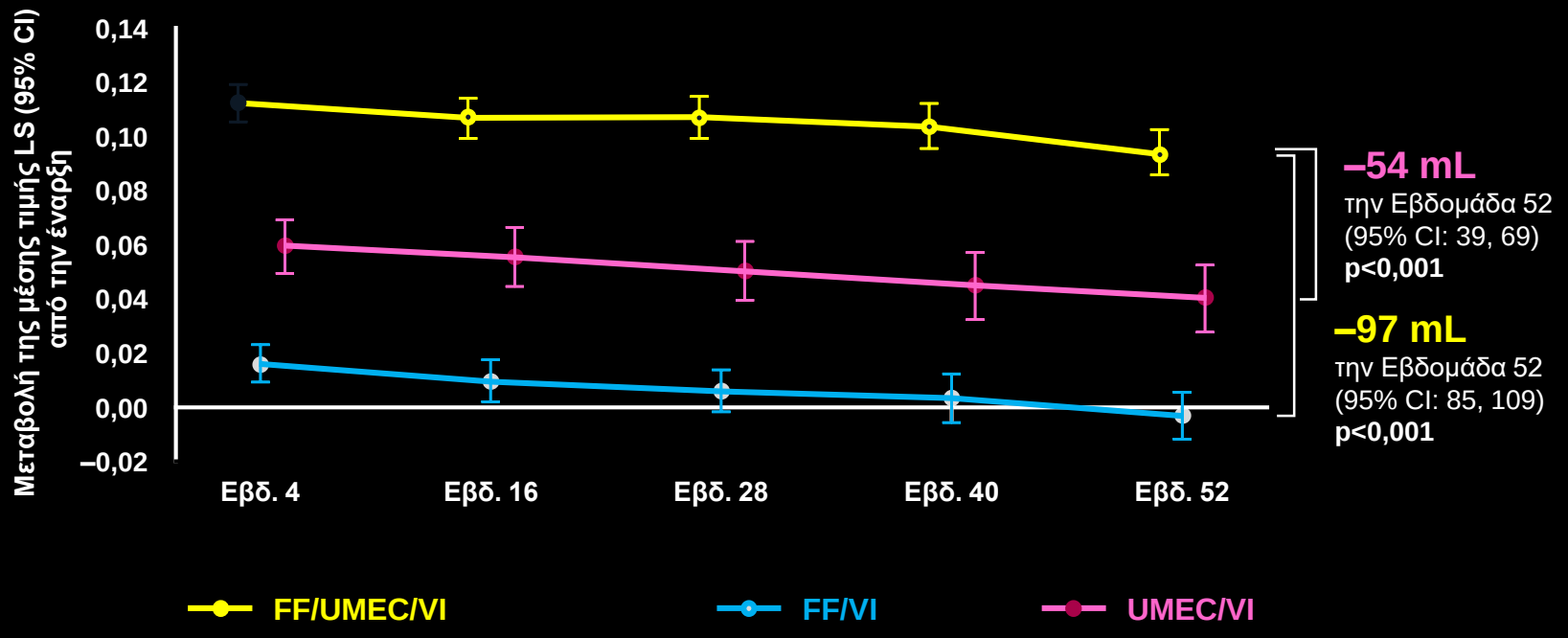


Σημαντική μείωση στο ρυθμό μέτριων/σοβαρών παροξύνσεων με FF/UMEC/VI σε ασθενείς με ηωσινόφιλα αίματος <150 και ≥150 κύτταρα/μL

Lipson DA, et al. *N Engl J Med*. 2018; May 3;378(18):1671-1680;

Πνευμονική λειτουργία (κατώτατος FEV_1)

Σημαντική βελτίωση του κατώτατου FEV_1 με την αγωγή FF/UMEC/VI έναντι των αγωγών FF/VI και UMEC/VI



IMPACT TRIAL

LS: ελάχιστα τετράγωνα.

Lipson DA, et al. *N Engl J Med*. 2018; May 3;378(18):1671-1680

Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

Gary T Ferguson, Klaus F Rabe, Fernando J Martinez, Leonardo M Fabbri, Chen Wang, Masakazu Ichinose, Eric Bourne, Shaila Ballal, Patrick Darken, Kiernan DeAngelis, Magnus Aurivillius, Paul Dorinsky, Colin Reisner

Lancet Respir Med 2018; 6:747-58

Κριτήρια ένταξης μελέτης KRONOS

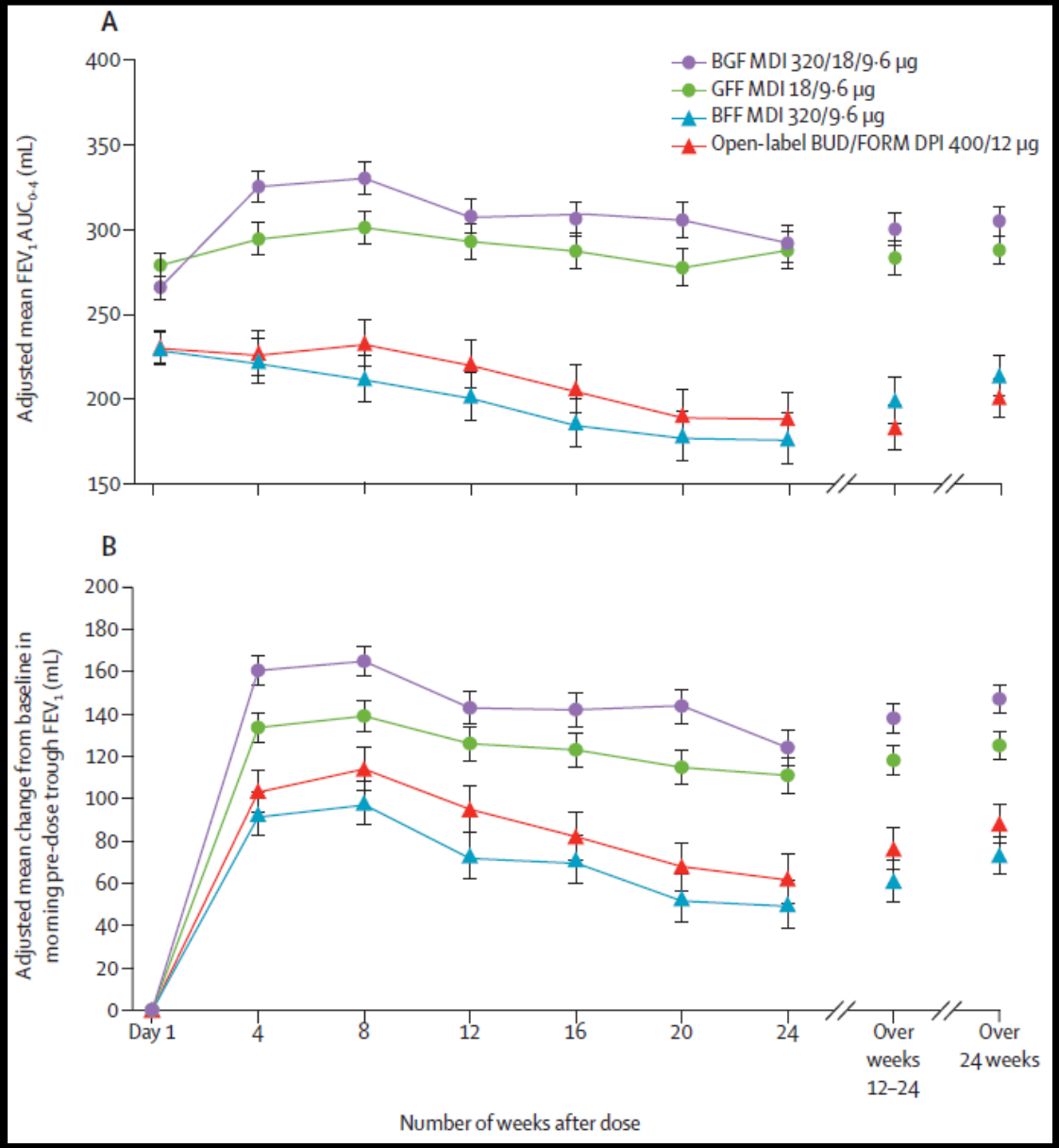
- Ηλικία 40-80 και διάγνωση ΧΑΠ (ορισμός κατά ATS/ERS)
- CAT ≥10
- FEV_1 25%-80% predicted
- Οι ασθενείς δεν απαιτείτο να είχαν ιστορικό παρόξυνσης το προηγούμενο έτος

- Η ΚΡΟΝΟΣ συμπεριέλαβε έναν πολύ ευρύ πληθυσμό συμπτωματικών ασθενών με ΧΑΠ σε θεραπεία συντήρησης

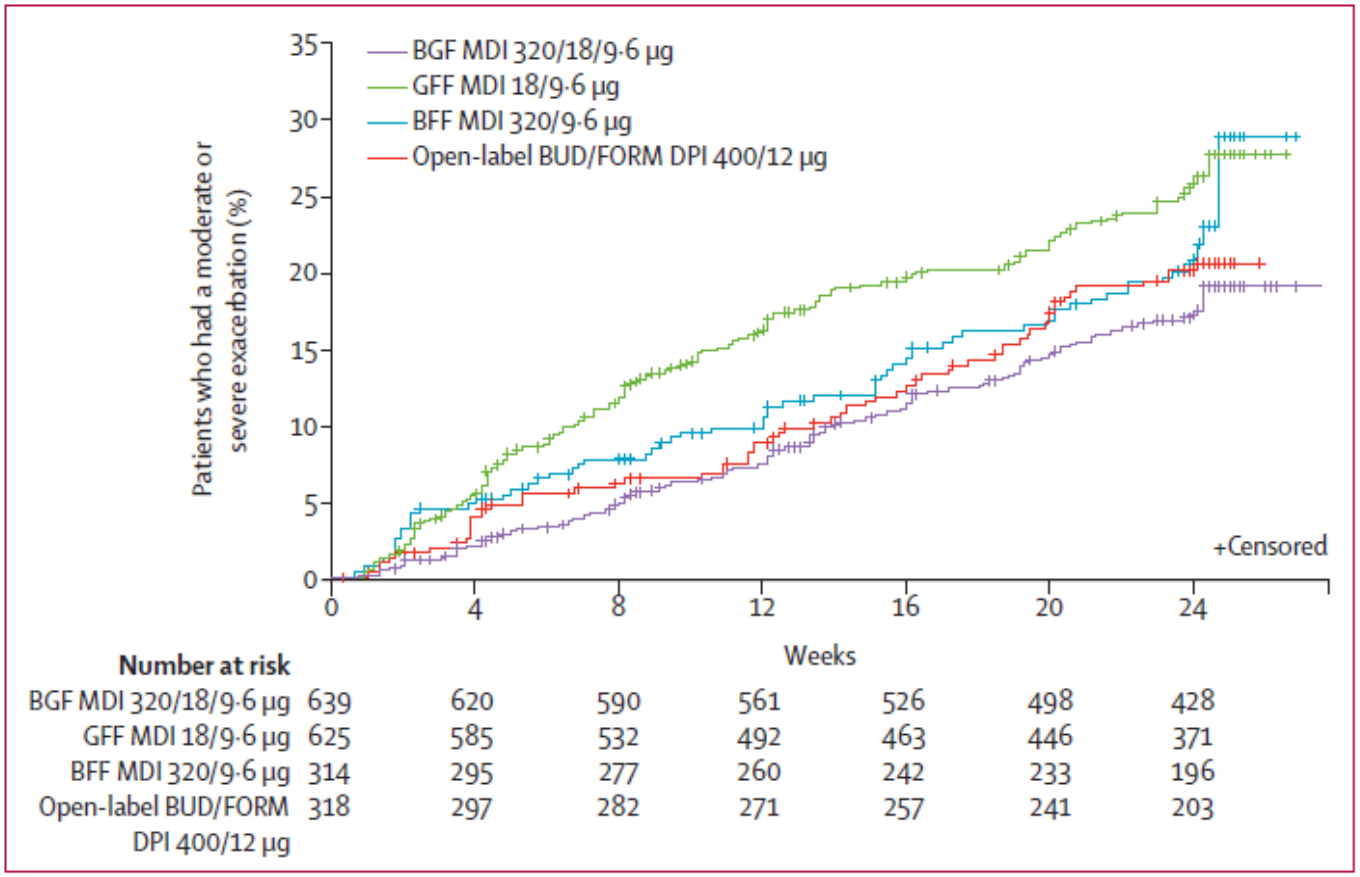
Πληθυσμός Kronos

	BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)	BFF MDI 320/9·6 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
COPD severity				
Mild	2 (0·3%)	0	1 (0·3%)	0
Moderate	310 (48·5%)	306 (49·0%)	154 (49·0%)	160 (50·3%)
Severe	275 (43·0%)	267 (42·7%)	133 (42·4%)	138 (43·4%)
Very severe	52 (8·1%)	52 (8·3%)	26 (8·3%)	20 (6·3%)
Moderate or severe COPD exacerbations in the past 12 months				
0	469 (73·4%)	473 (75·7%)	235 (74·8%)	234 (73·6%)
1	125 (19·6%)	108 (17·3%)	61 (19·4%)	59 (18·6%)
≥2	45 (7·0%)	44 (7·0%)	18 (5·7%)	25 (7·9%)
Moderate or severe exacerbation rate				
Mean	0·4 (0·8)	0·3 (0·7)	0·3 (0·6)	0·4 (0·8)
Median	0·0 (0–8)	0·0 (0–5)	0·0 (0–4)	0·0 (0–8)

KRONOS: Αναπνευστική Λειτουργία



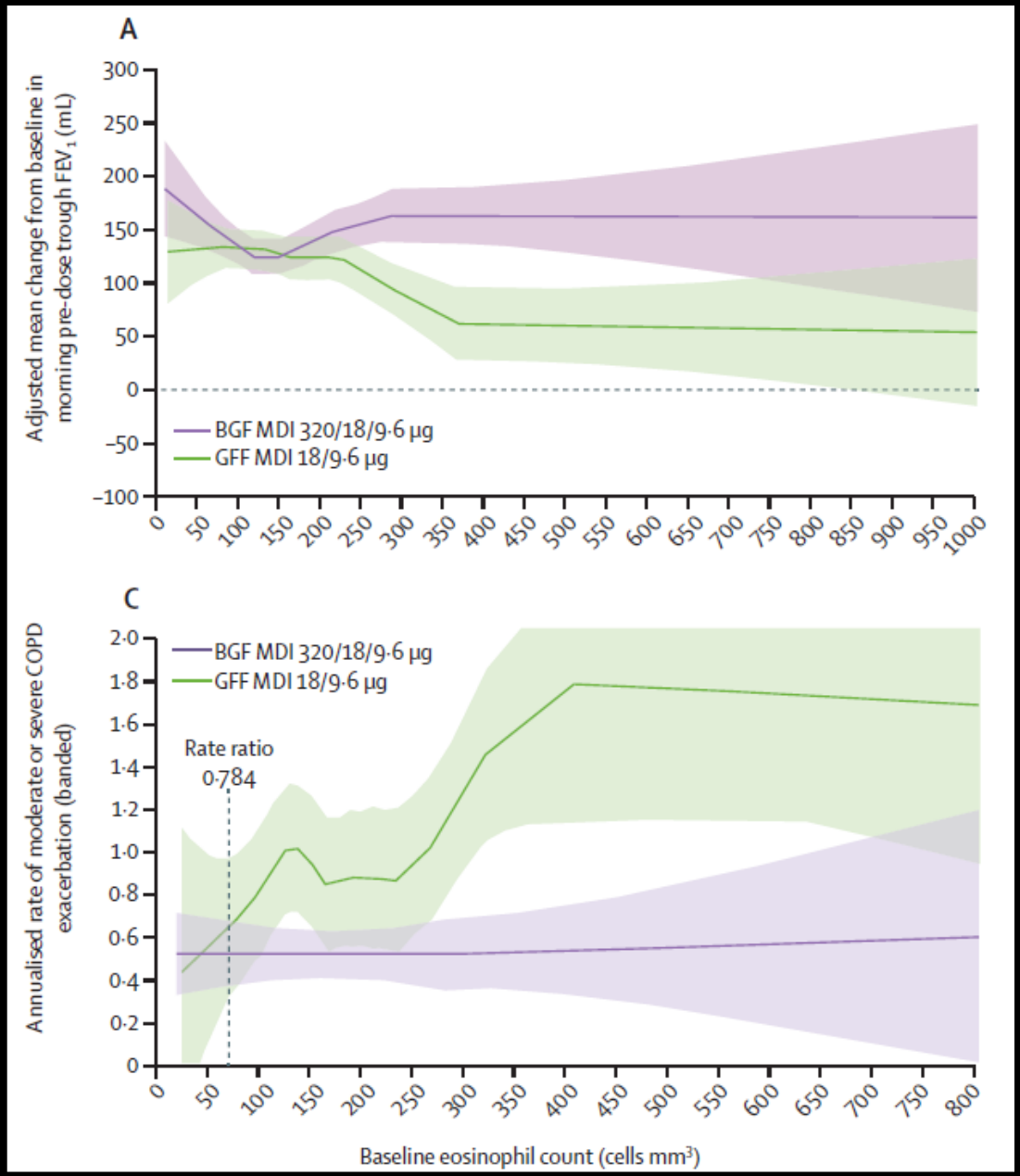
KRONOS: παροξύνσεις



Number at risk							
BGF MDI 320/18/9·6 µg	639	620	590	561	526	498	428
GFF MDI 18/9·6 µg	625	585	532	492	463	446	371
BFF MDI 320/9·6 µg	314	295	277	260	242	233	196
Open-label BUD/FORM DPI 400/12 µg	318	297	282	271	257	241	203

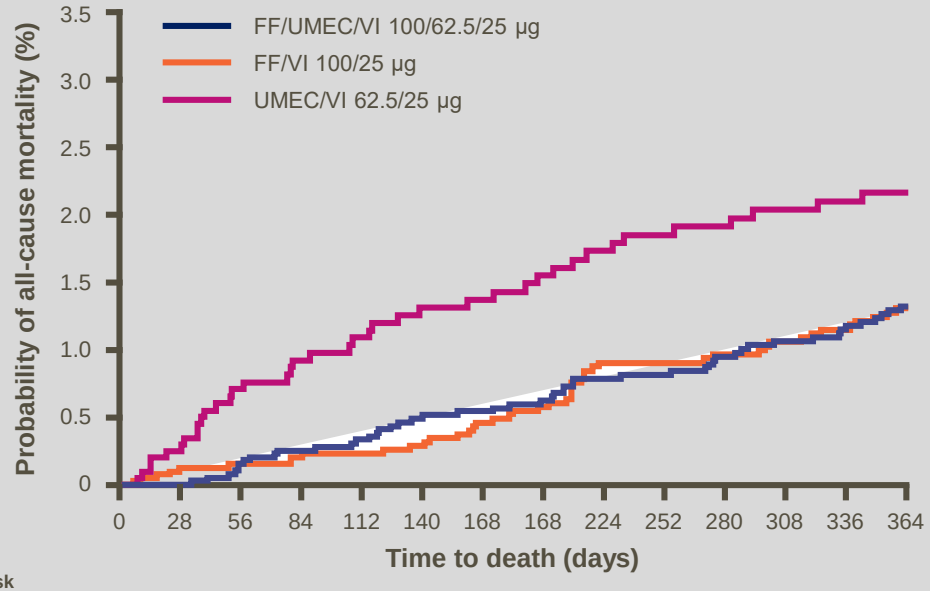
Figure 3: **Time to first exacerbation of chronic obstructive pulmonary disease**
BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered-dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry-powder inhaler.

KRONOS: ρόλος των ηωσινοφίλων



ACM findings in IMPACT: Pre-specified on-treatment ACM[1,2]

ACM benefit seen with both FF-containing regimens vs UMEC/VI



N at risk															% Mortality
FF/UMEC/VI	4,151	4,082	3,968	3,898	3,838	3,752	3,714	3,690	3,613	3,581	3,545	3,486	3,454	3,346	1.20 (n = 50)
FF/VI	4,134	3,984	3,798	3,694	3,619	3,496	3,443	3,391	3,291	3,258	3,230	3,182	3,152	3,044	1.19 (n = 49)
UMEC/VI	2,070	1,993	1,880	1,820	1,769	1,713	1,685	1,656	1,612	1,595	1,578	1,548	1,531	1,485	1.88 (n = 39)

Risk reduction (RR)

FF/UMEC/VI vs UMEC/VI

42%

(95% CI: 12, 62); *p* = 0.011

Absolute RR = 0.68%

FF/VI vs UMEC/VI

39%

(95% CI: 7, 60); *p* = 0.022

Absolute RR = 0.69%

IMPACT trial

ACM causes

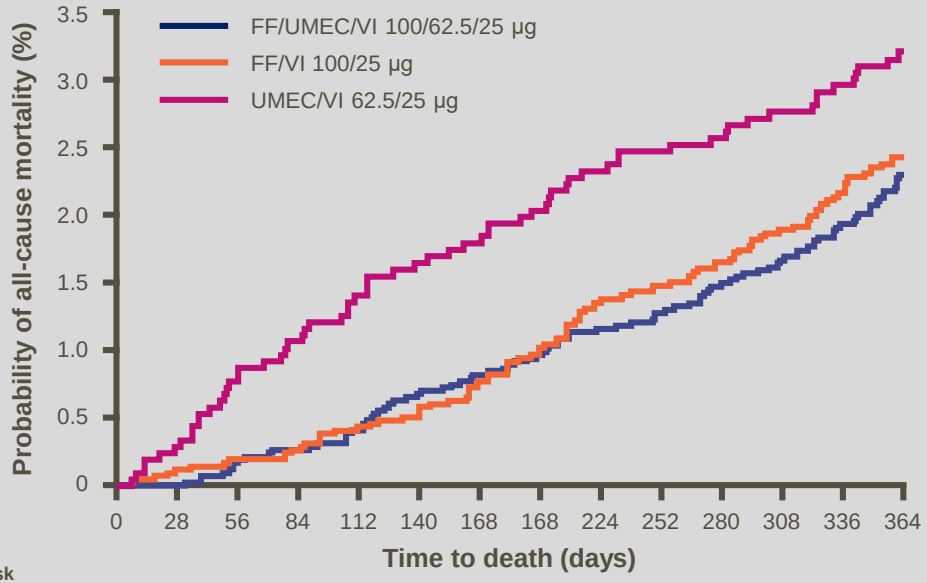
1. Lipson DA, et al. *N Engl J Med*. 2018;378:1671–1680; 2. GlaxoSmithKline. Data on file. RF/TLY/0096/17(1).

- The study was not designed to study ACM as a primary outcome; however, ACM was a pre-specified endpoint
- Patients who discontinued study treatment were encouraged to stay in the study; off-treatment analysis was derived from data obtained from these patients. Censored patients were those whose vital status was missing

- Preliminary on/off treatment sensitivity analyses continues to show a reduction in the risk of all cause mortality for FF/UMEC/VI vs UMEC/VI (p=0.043). However there are 5.5% of patients whose data was censored in this analysis, i.e. these patients did not have complete vital status follow-up at 52 weeks. Any data available would still be used in the analysis, but it is still considered as missing information. However, as 5.5% of patients in this analysis were censored prior to 52 weeks, these analyses will be repeated once the missing data has been collected

ACM findings in IMPACT: *Post hoc* on/off-treatment ACM[1]

ACM benefit with FF/UMEC/VI vs UMEC/VI (after 27 extra off-treatment deaths identified)



N at risk															% Mortality
FF/UMEC/VI	4,151	4,150	4,142	4,137	4,131	4,119	4,113	4,107	4,097	4,092	4,082	4,073	4,062	3,919	2.36 (n = 98)
FF/VI	4,134	4,129	4,123	4,118	4,111	4,106	4,095	4,082	4,065	4,060	4,050	4,040	4,027	3,848	2.64 (n = 109)
UMEC/VI	2,070	2,063	2,052	2,045	2,037	2,030	2,027	2,021	2,013	2,008	2,004	1,999	1,995	1,914	3.19 (n = 66)

Risk reduction (RR)

FF/UMEC/VI vs UMEC/VI

28%

(95% CI: 1, 47); $p = 0.042$

Absolute RR = 0.83%

FF/VI vs UMEC/VI[2]

18%

(95% CI: –11, 40); $p = 0.190$

Absolute RR = 0.55%

Collection of additional vital status data resulted in available data for an additional 27 off-treatment deaths (providing data for 99.6% of the study population [42 censored patients]), which are included in the ACM analyses presented here.

1. Lipson DA, et al. ATS 2019. Poster 221 (A7344);
2. GlaxoSmithKline. Data on file. DOF_2019N406509_00.

IMPACT trial

FF/UMEC/VI is currently the only COPD medication that has prospectively-defined All Cause Mortality (ACM) benefits

Reduced survival in COPD is linked to three baseline treatable risk factors: 1) severe airflow limitation, 2) increased dyspnoea and 3) a history of severe exacerbations. All can theoretically be ameliorated by optimal pharmacotherapy

For over a decade the respiratory community has debated the potential mortality benefit of ICS-containing treatments; but until now, this benefit has not been established prospectively, despite some suggestive evidence:

– *3-year TORCH trial (FP/SAL vs PBO; 17% risk reduction on and off treatment,* p = *0.052)*
– *2-year INSPIRE trial (FP/SAL vs TIO;* post hoc *52% risk reduction on treatment analysis,* p = *0.012)*

Based on the 1-year landmark IMPACT trial, performed in >10,000 patients with high symptoms and an exacerbation history, FF/UMEC/VI single inhaler triple therapy is currently the only COPD medication that has prospectively defined ACM benefits in both an on- and off-treatment analysis

The absolute mortality risk reduction with FF/UMEC/VI vs UMEC/VI (0.83% per annum) in the IMPACT full ACM dataset was greater than that found in corresponding data for sustained smoking cessation in the Lung Health Study, and similar, or greater than, several cardioprotective strategies in non-COPD survival trials

Τι γίνεται με τις πνευμονίες;

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

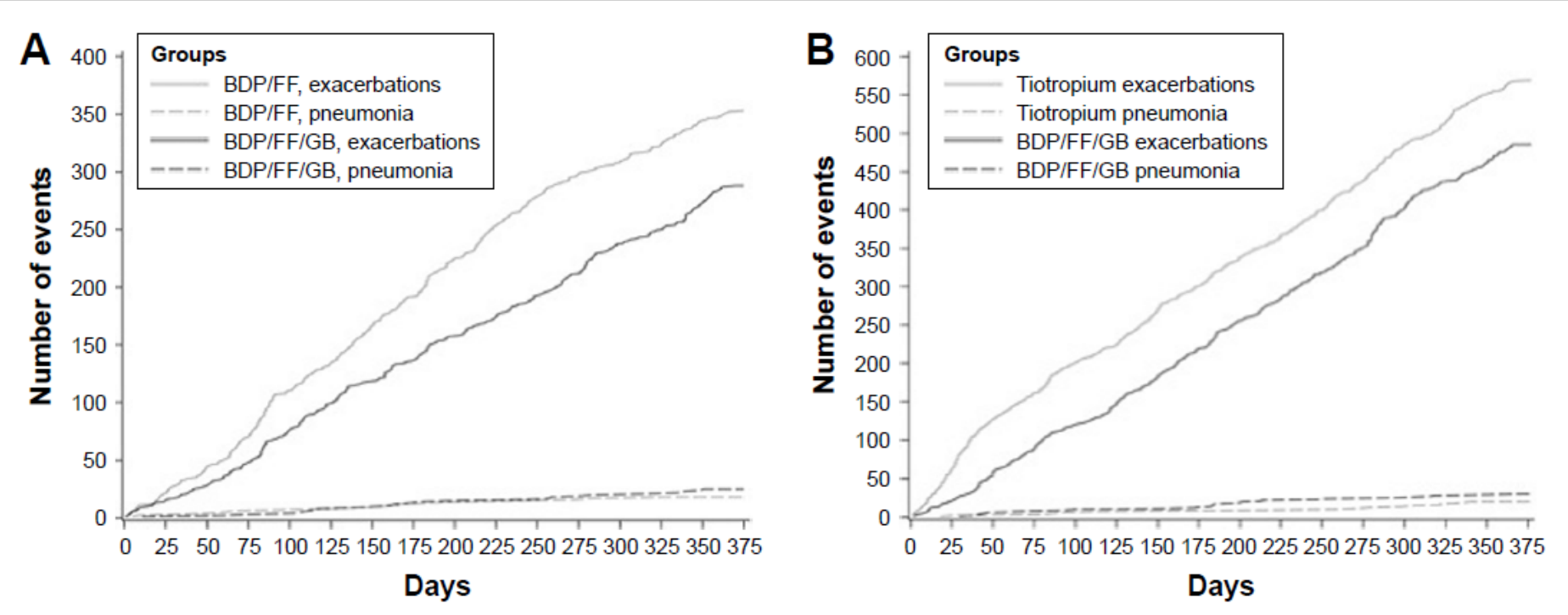
Lancet 2018; 391: 1076–84

Μήπως ο κίνδυνος πνευμονίας οφείλεται ειδικά στη φουροϊκή φλουτικαζόνη (FF);

Tribute

	BDP/FF/G (n=764)	IND/GLY (n=768)
Adverse events	490 (64%)	516 (67%)
COPD	273 (36%)	288 (38%)
Nasopharyngitis	43 (6%)	37 (5%)
Headache	44 (6%)	35 (5%)
Pneumonia	28 (4%)	27 (4%)
Respiratory tract infection	22 (3%)	28 (4%)
Dyspnoea	23 (3%)	24 (3%)
Back pain	21 (3%)	23 (3%)
Hypertension	15 (2%)	26 (3%)
Cough	13 (2%)	25 (3%)
Cardiac failure	15 (2%)	16 (2%)
Ischaemic heart disease	8 (1%)	16 (2%)
Myocardial infarction	1 (<1%)	8 (1%)
Angina pectoris	5 (1%)	1 (<1%)
Coronary artery disease	2 (<1%)	4 (1%)
Myocardial ischaemia	2 (<1%)	4 (1%)
Serious adverse events	117 (15%)	130 (17%)
COPD	61 (8%)	69 (9%)
Pneumonia	18 (2%)	17 (2%)

Κίνδυνος πνευμονίας vs παρόξυνσης



Trilogy

Trinity

International Journal of COPD

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REVIEW

Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide

Dave Singh[1]
Massimo Corradi[2]
Monica Spinola[3]
Alberto Papi[4]
Omar S Usmani[5]
Mario Scuri[3]
Stefano Petruzzelli[3]
Jørgen Vestbo[1]

International Journal of COPD 2017:12:2917-28

Πνευμονίες

Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

Gary T Ferguson, Klaus F Rabe, Fernando J Martinez, Leonardo M Fabbri, Chen Wang, Masakazu Ichinose, Eric Bourne, Shaila Ballal, Patrick Darken, Kiernan DeAngelis, Magnus Aurivillius, Paul Dorinsky, Colin Reisner

BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)
2%	2%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 3, 2018 VOL. 378 NO. 18

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

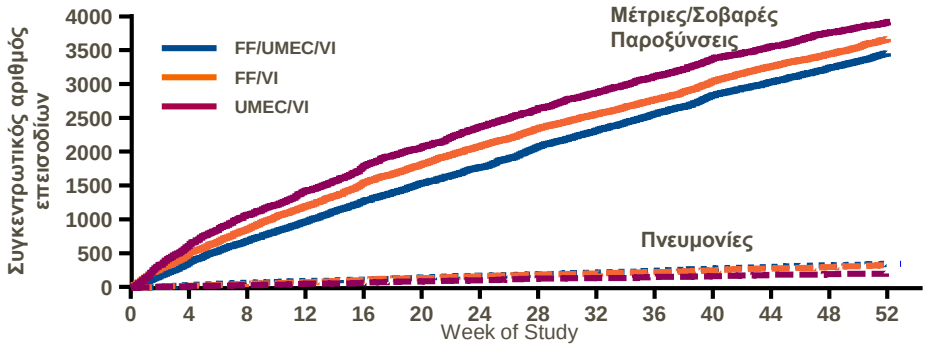
David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D., C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D., David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D., Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S., for the IMPACT Investigators

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

Μέτριες/σοβαρές παροξύνσεις σε αντιδιαστολή με τις πνευμονίες (κατά τη διάρκεια της θεραπείας)

Κλινικά σημαντική μείωση των μέτριων/σοβαρών παροξύνσεων με FF/UMEC/VI και UMEC/VI, σε σχέση με τον κίνδυνο εμφάνισης πνευμονίας



Διαφορά FF/UMEC/VI vs. UMEC/VI: **224.8**/1000 έτη ασθενή

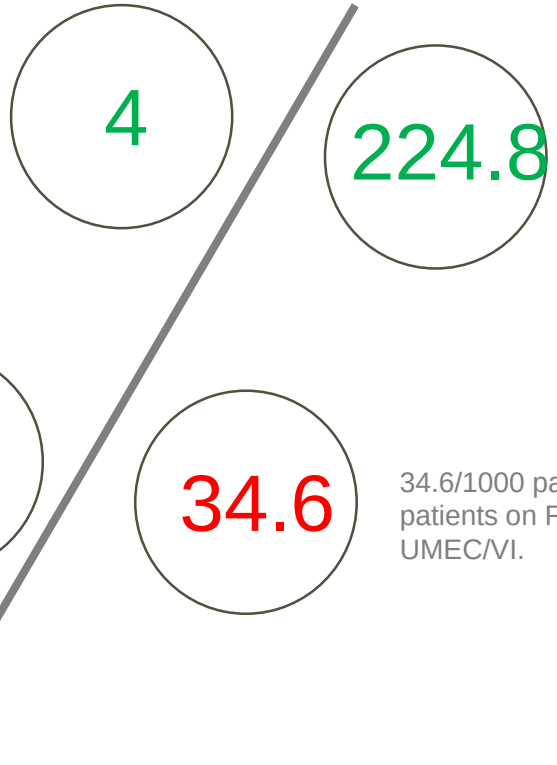
Διαφορά FF/UMEC/VI vs. UMEC/VI: **34.6**/1000 έτη ασθενή

	Μέτριες/Σοβαρές Παροξύνσεις				Ετήσιος ρυθμός εμφάνισης πνευμονιών κατά τη διάρκεια της θεραπείας
	Ετήσιος ρυθμός εμφάνισης παροξύνσεων	% μείωσης ρυθμού εμφάνισης παροξύνσεων με το FF/UMEC/VI	Αναλογία ετήσιου ρυθμού εμφάνισης παροξύνσεων με το FF/UMEC/VI (95% CI)	p value	
FF/UMEC/VI	0.91	–	–	–	0.09
FF/VI	1.07	15%	0.85 (0.80,0.90)	<0.001	0.09
UMEC/VI	1.21	25%	0.75 (0.70,0.81)	<0.001	0.06

1. Lipson DA, et al. *N Engl J Med*. 2018; May 3;378(18):1671-1680

Μέτριες/σοβαρές παροξύνσεις σε αντιδιαστολή με τις πνευμονίες (κατά τη διάρκεια της θεραπείας)

For every 4 subjects treated for one year, FF/UMEC/VI prevents one moderate/severe exacerbation compared with UMEC/VI.



224.8/1000 patient-years less exacerbations for the patients on FF/UMEC/VI compared with UMEC/VI.

For every 33 subjects treated for one year, FF/UMEC/VI caused 1 pneumonia AESI compared with UMEC/VI

34.6/1000 patient years more pneumonias for the patients on FF/UMEC/VI compared with UMEC/VI.

1. Lipson DA, et al. *N Engl J Med*. 2018; May 3;378(18):1671-1680

SALFORD Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*

N Engl J Med 2016;375:1253-60.

Table 2. Serious Adverse Events of Special Interest during Treatment in the Entire Trial Population.*

Event	Usual Care (N=1403)	Fluticasone Furoate–Vilanterol (N=1396)
	number (percent)	
Cardiovascular event		
Any event	107 (8)	108 (8)
Cardiac arrhythmia	54 (4)	52 (4)
Cardiac failure	28 (2)	28 (2)
Cardiac ischemia	33 (2)	34 (2)
Hypertension	1 (<1)	0
Stroke	25 (2)	21 (2)
Pneumonia	83 (6)	94 (7)
Lower respiratory tract infection, excluding pneumonia	58 (4)	64 (5)
Decreased bone mineral density and associated fracture	45 (3)	45 (3)
Effects on glucose level	16 (1)	23 (2)

Η θεραπεία με FF/V δεν αυξάνει τον κίνδυνο για πνευμονία και για καρδιαγγειακά συμβάματα

SUMMIT Study

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators

- Υλικό: Ασθενείς με ΧΑΠ, FEV_1 = 50-70% pred, καπνιστικό ιστορικό ≥ 10 py, mMRC ≥ 2, με ιστορικό καρδιαγγειακής νόσου ή σε υψηλό καρδιαγγειακό κίνδυνο
- Πρωτεύον καταληκτικό σημείο: Χρόνος έως τον θάνατο από οποιαδήποτε αιτία (θνητότητα)
- Δευτερεύοντα καταληκτικά σημεία: ρυθμός έκπτωσης FEV_1, καρδιαγγειακά συμβάματα, παροξύνσεις (μέτριες = ανάγκη λήψης αντιβιοτικών ή CS συστηματικά, σοβαρές = νοσηλεία)

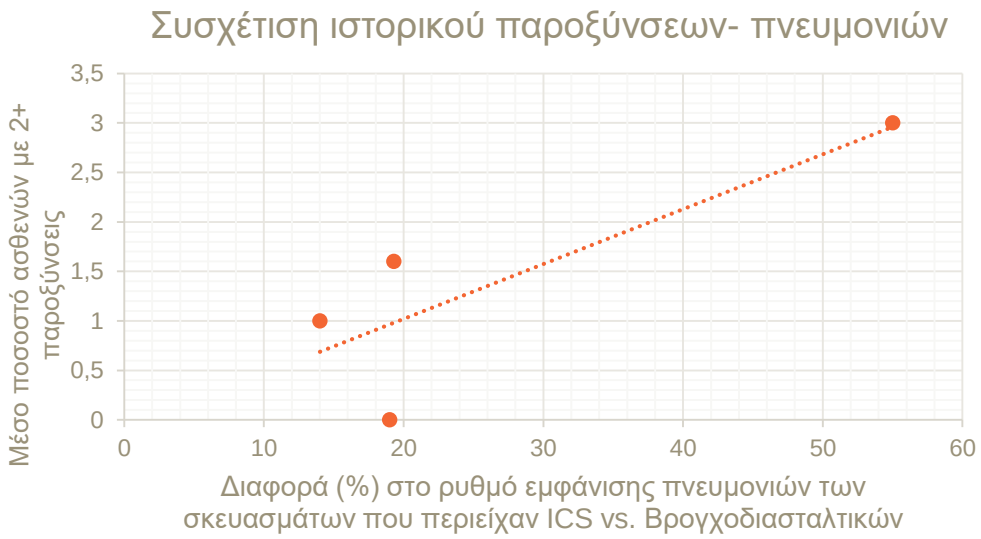
Vestbo J, et al. *Lancet* 2016; 387: 1817–26.

	Placebo (n=4131)	Fluticasone furoate (n=4157)	Vilanterol (n=4140)	Combination therapy (n=4140)
Any adverse event	2782 (67%)	2820 (68%)	2809 (68%)	2780 (67%)
Adverse event leading to discontinuation of study medication	397 (10%)	367 (9%)	370 (9%)	342 (8%)
Serious adverse event	918 (22%)	929 (22%)	972 (23%)	961 (23%)
Fatal adverse event	192 (5%)	183 (4%)	198 (5%)	182 (4%)
Total exposure to study medication (patient-years)	6614	6889	6955	7038
Adverse events of special interest*				
Local steroid events	146 (4%) [2·7, 2·3–3·1]	209 (5%) [3·9, 3·4–4·4]	152 (4%) [2·5, 2·1–2·9]	225 (5%) [4·2, 3·8–4·7]
All cardiovascular events	695 (17%) [16·4, 15·4–17·4]	699 (17%) [15·7, 14·8–16·7]	707 (17%) [15·7, 14·8–16·6]	735 (18%) [16·3, 15·4–17·3]
Cardiac arrhythmias	211 (5%) [4·1, 3·6–4·6]	229 (6%) [4·1, 3·6–4·6]	224 (5%) [3·9, 3·4–4·4]	209 (5%) [3·9, 3·4–4·3]
Lower respiratory tract infections excluding pneumonia	226 (5%) [4·7, 4·2–5·2]	238 (6%) [4·5, 4·0–5·0]	220 (5%) [4·2, 3·7– 4·7]	221 (5%) [4·2, 3·8–4·7]
Pneumonia	214 (5%) [3·8, 3·4–4·3]	228 (5%) [4·2, 3·8–4·8]	163 (4%) [2·8, 2·4–3·2]	237 (6%) [3·9, 3·5–4·4]
Hypersensitivity	143 (3%) [2·6, 2·2–3·0]	147 (4%) [2·7, 2·3–3·1]	160 (4%) [2·8, 2·5– 3·3]	175 (4%) [3·0, 2·6–3·4]
Bone disorders including fractures	78 (2%) [1·3, 1·1–1·6]	79 (2%) [1·5, 1·2–1·8]	88 (2%) [1·6, 1·3– 1·9]	96 (2%) [1·6, 1·3–1·9]
Hyperglycaemia/new onset diabetes mellitus	156 (4%) [2·7, 2·3–3·1]	153 (4%) [2·6, 2·2–3·0]	134 (3%) [2·3, 1·9– 2·7]	148 (4%) [2·3, 2·0–2·7]
Corticosteroid-associated eye disorder	43 (1%) [0·8, 0·6–1·0]	62 (1%) [1·0, 0·8–1·3]	59 (1%) [1·0, 0·8– 1·2]	57 (1%) [1·0, 0·8–1·3]

Η θεραπεία με FF, V, FF/V είναι καλά ανεκτή και δεν αυξάνει τον κίνδυνο για πνευμονία και για καρδιαγγειακά συμβάματα

Πνευμονίες & Παροξύνσεις: Υπόθεση

	SUMMIT[1]				TRIBUTE[2]		FLAME[3]		IMPACT[4]		
Exacerbations in the previous year (%)	pl	FF	VI	FF/VI	IND/GLY	BDP/FF/G	IND/GLY	SAL/FP	UMEC/VI	FF/VI	UMEC/FF/VI
0	60	62	61	61	-	-	-	-	<1	<1	<1
1	25	24	24	24	82	80	80.7	80.6	45	46	45
≥2	15	14	14	14	18	20	19.3	19.3	55	54	55
Pneumonia Incidence	5	5	4	6	4	4	3.2	4.8	5	7	8



Vestbo, J., et al., *The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol.* Eur Respir J, 2013. **41**(5): p. 1017-22. 2. Papi, A., et al., *Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic structive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.* Lancet, 2018. **391**(10125): p. 1076-1084. 3. Wedzicha, J.A., et al., *Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD.* Engl J Med, 2016. **374**(23): p. 2222-34. 4. Lipson, D.A., et al., *Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.* N Engl J Med, 2018. **378**(18): p. 1671-1680.

Ευχαριστώ για την προσοχή σας