A maintenance ICS in severe COPD

: Can reduce exacerbation of COPD?

(severe to very severe COPD patient)

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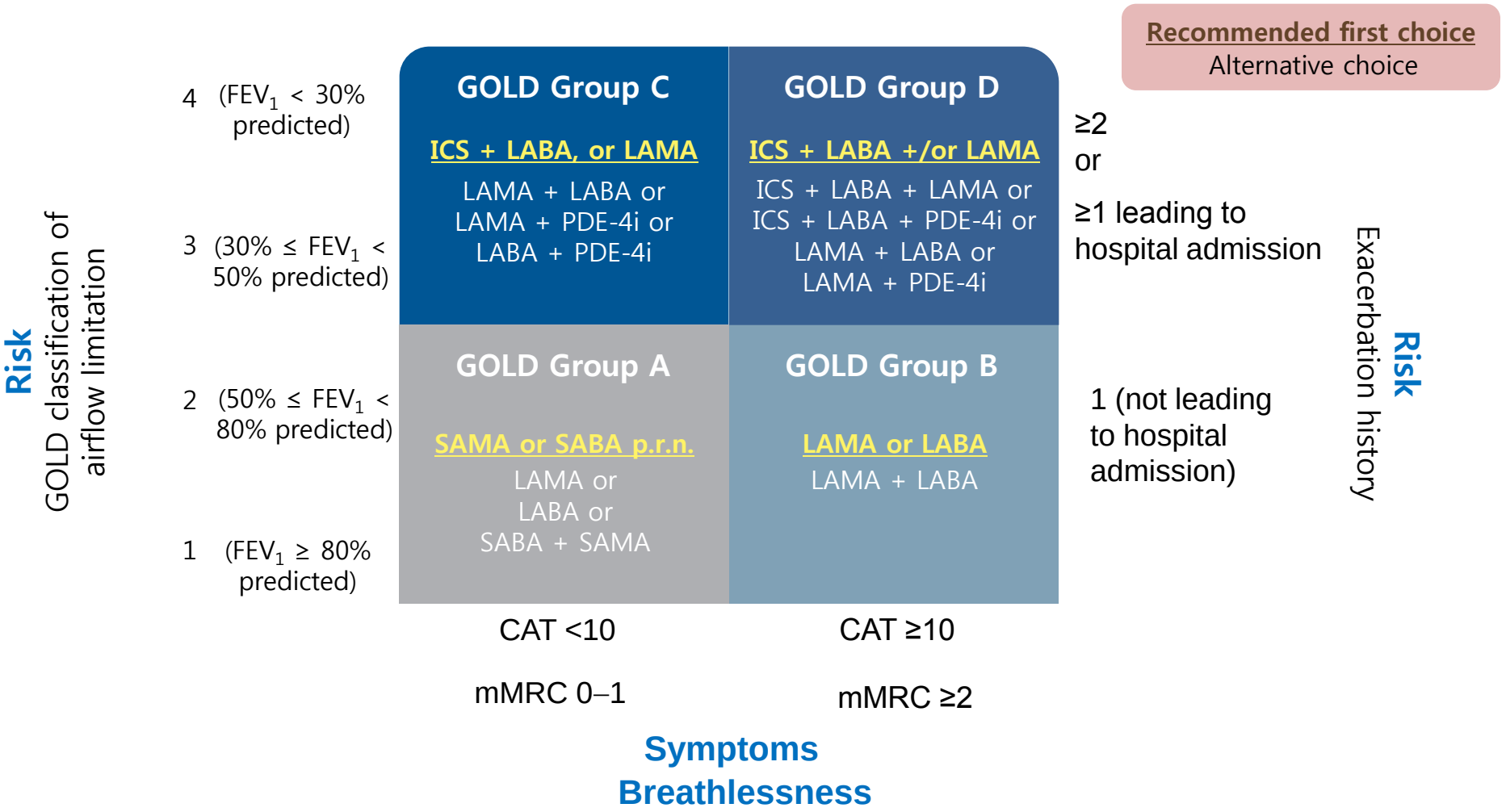
GOLD 2015
Initial pharmacological management of COPD

Based on combined assessment of airflow limitation, symptoms and exacerbation risk



GOLD 2015 (http://www.goldcopd.org/)

Janus

Inhaled corticosteroids in COPD

- ICS
  - Highly effective for the Tx of asthma (early 1980s)
  - Adopted in COPD with no scientific evidence of their benefit
  - Current guidelines recommend (ICS+LABA combination)
    - Severe to very severe COPD
    - History of frequent exacerbations

GOLD 2015

Inhaled corticosteroids in COPD

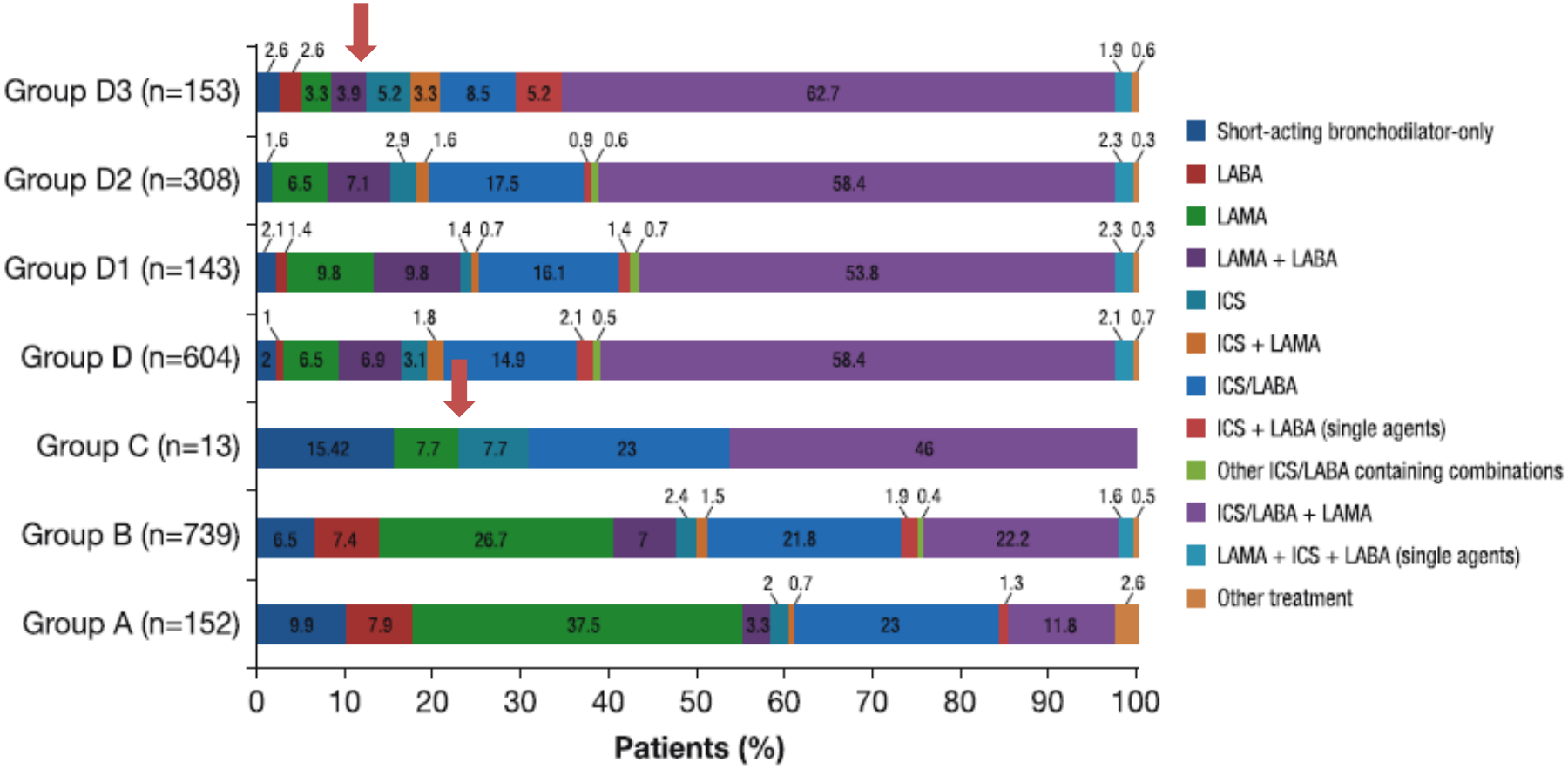
- Long term treatment of ICS
  - Reduced frequency of exacerbations
  - Improved lung function (little)
  - Improved symptoms, quality of life
  - Reduced mortality ?

- ICS monotherapy is not recommended in COPD (Evidence A)
    - Less effective than the combination ICS/LABA

- Withdrawal from treatment with ICS may lead to exacerbations in some patients

- Inhaled corticosteroid therapy is associated with an increased risk of pneumonia

Proportions of patients receiving different treatment regimens in each of the GOLD groups



ICS Group A = 41.4%
Group B = 52.4%
Group C = 76.95
Group D = 83.6%

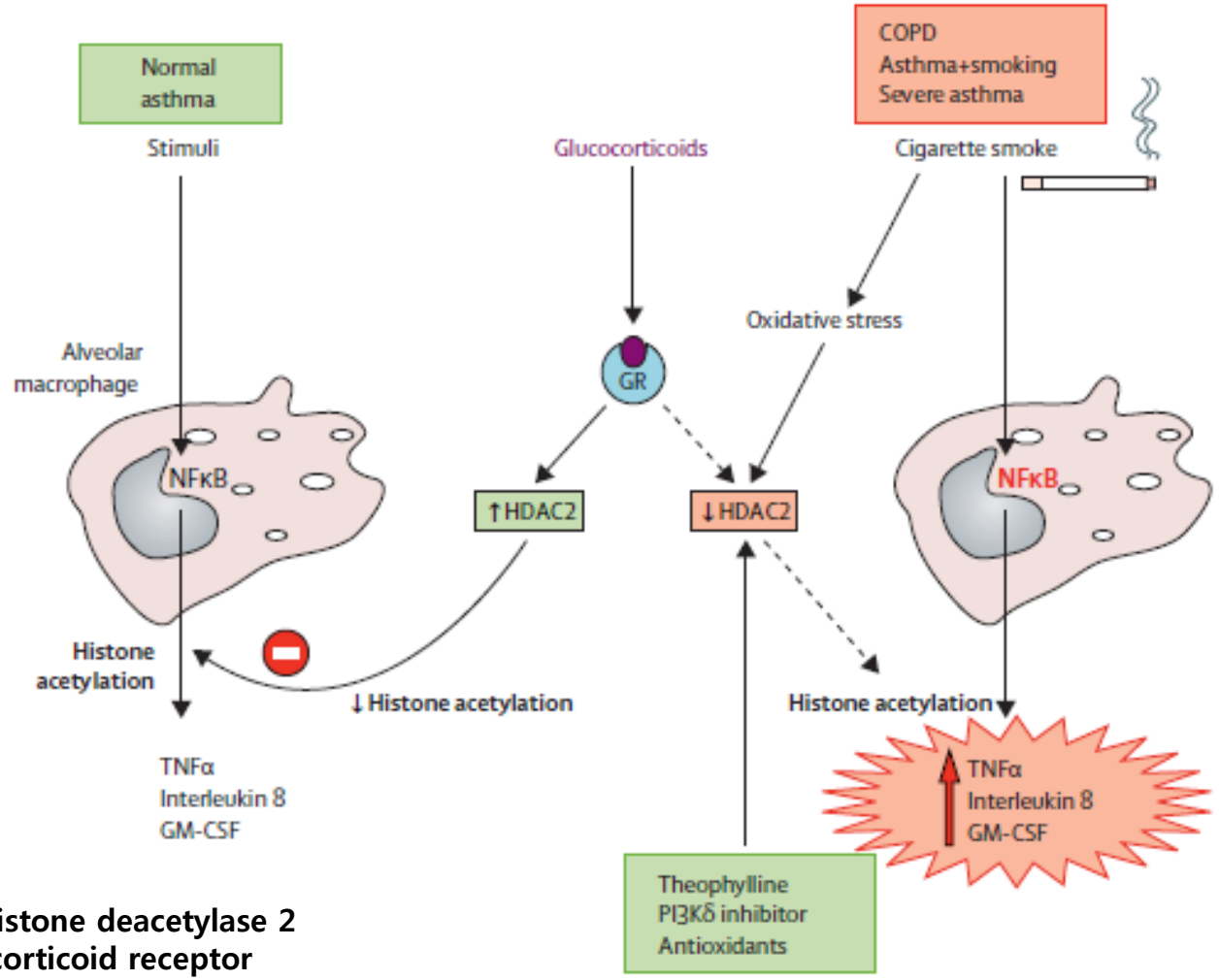
Vestbo J et al, Respiratory Medicine (2014) 108, 729-736

Inflammation is a key pathological process in COPD.

But, why do ICS not work in COPD ?

Glucocorticoid resistance in COPD

Mechanism of glucocorticoid resistance in COPD and asthma

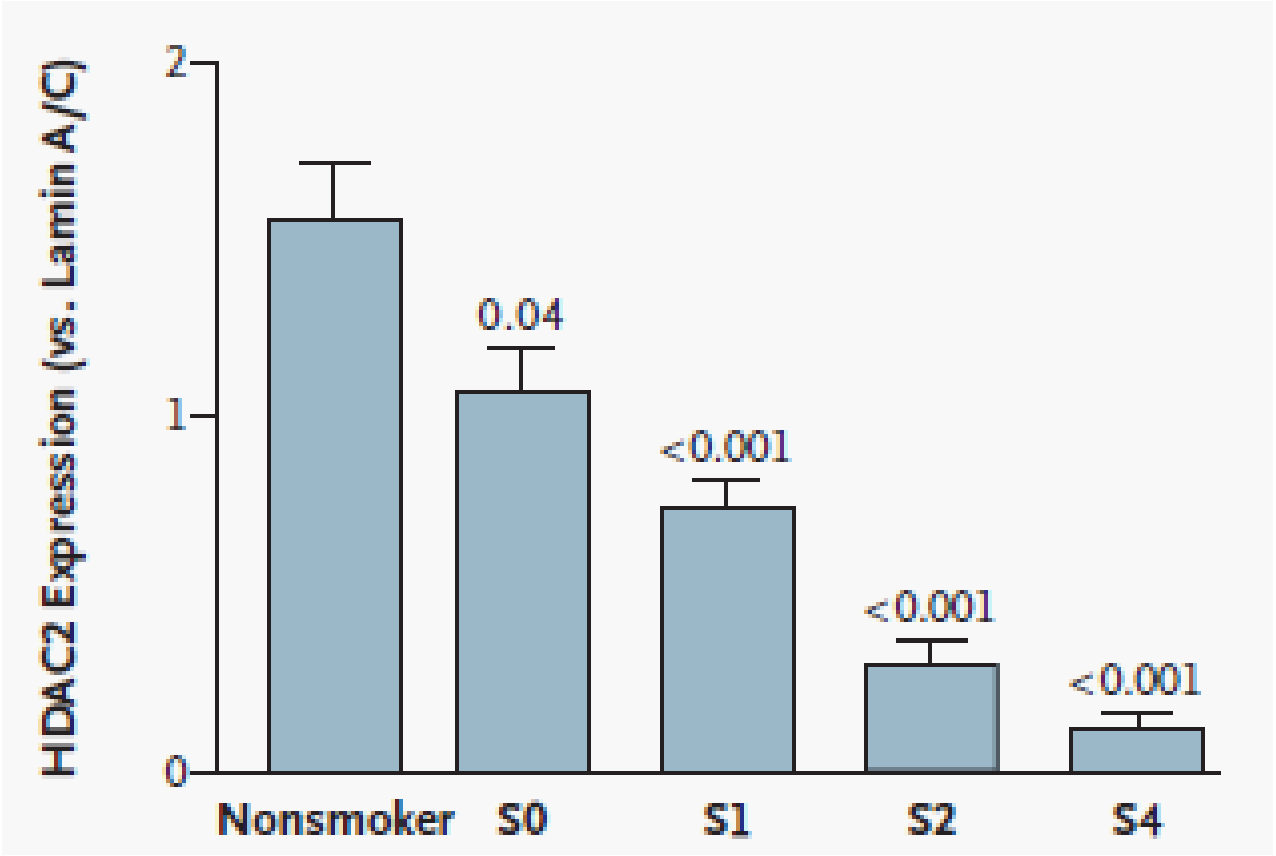


HDAC2 : histone deacetylase 2
GR=glucocorticoid receptor
PI3Kδ=phosphoinositide-3-kinase-δ

Lancet 2009; 373: 1905–17

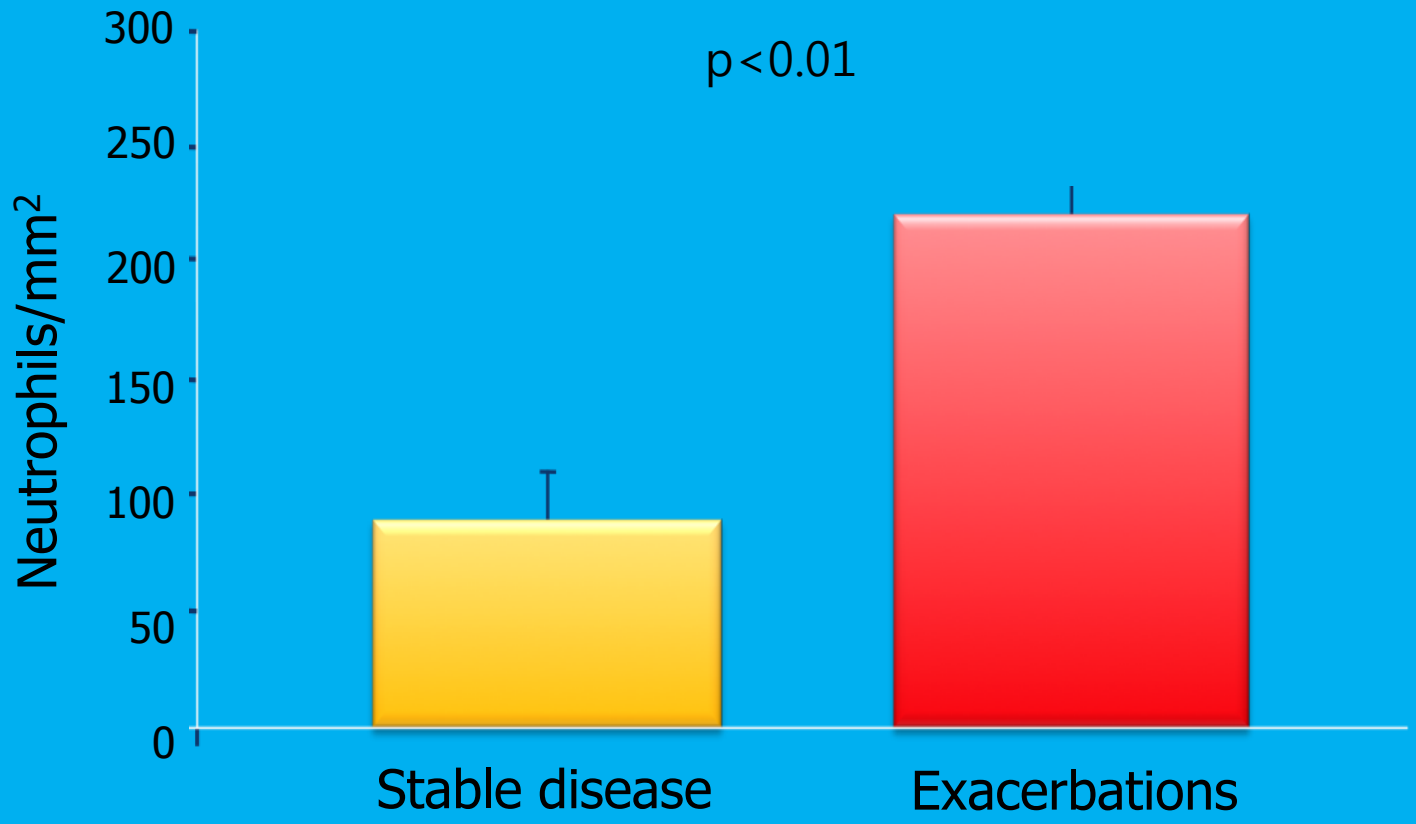
Histone Deacetylase (HDAC2) Expression in Peripheral Lung Tissue

COPD stage 0 (S0), stage 1 (S1), stage 2 (S2), and stage 4 (S4)



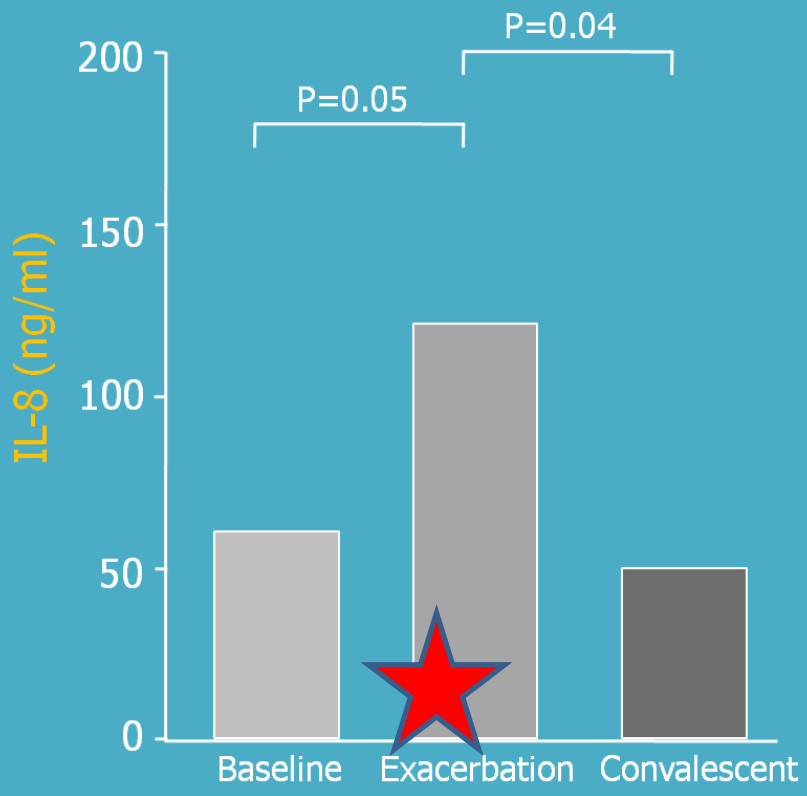
N Engl J Med 2005;352:1967-76.

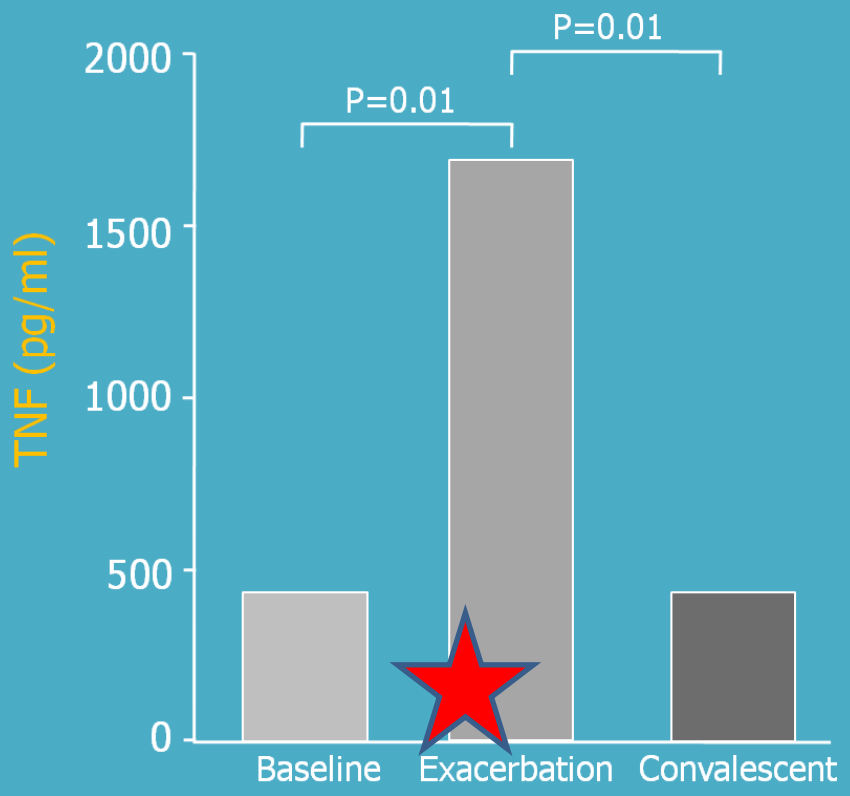
Sputum Neutrophil



Saetta M et al. Am J Respir Crit Care Med 1994;150:1646

Sputum IL-8 and TNF-α





Aaron DS et al. AJRCCM 2001:163;349

Inflammatory Indices in Induced sputum in COPD

2-wk course of inhaled budesonide (800 μg twice daily for 2 wk)
13 patients with severe COPD

	Baseline	Placebo	Budesonide	p Value
Total cell count/ml	6.3 ± 2.0	5.7 ± 2.0	4.8 ± 1.9	NS
Macrophages, %	28.5 ± 6.0	27.6 ± 3.7	27.5 ± 5.1	NS
Neutrophils, %	67.9 ± 6.3	69.9 ± 4.5	69.9 ± 5.1	NS
Eosinophils, %	2.7 ± 1.2	2.0 ± 1.1	1.0 ± 0.4	NS
Lymphocytes, %	0.9 ± 0.6	1.4 ± 0.1	1.6 ± 0.3	NS
TNF-α, pg/ml	760.2 ± 119	463.5 ± 35.7	715.5 ± 90.8	NS
IL-8, nM	3.3 ± 1.6	3.5 ± 2.0	2.1 ± 1.1	NS
ECP, μg/L	835.8 ± 0.40	730.3 ± 0.29	910.5 ± 0.21	NS
EPO, μg/L	262.4 ± 53.2	85.4 ± 15.1	41.9 ± 5.1	NS
MPO, mg/L	8.05 ± 1.49*	4.17 ± 0.58	2.97 ± 0.39	NS
HNL, mg/L	10.48 ± 1.02	8.98 ± 0.67	8.47 ± 0.68	NS

TNF-a = tumor necrosis factor-a / IL-8= interleukin-8 / ECP = eosinophil cationic protein
EPO = eosinophil peroxidase / MPO = myeloperoxidase / HNL = human neutrophil lipocalin.

Keatings VM, et al. AJRCCM 1997;155:542-548

FLUTICASONE PROPIONATE IN INDUCED SPUTUM

fluticasone propionate (500 μg twice a day) for 4 wk

Sputum Parameter	Baseline	FP
Total cell counts	1.9 (0.6–4.3)	1.4 (0.3–3.3)
Cell viability, %	85 (82–89)	86 (82–91)
Neutrophils, %	85% (39–95%)	76% (28–95%)
Absolute neutrophils	1.6 (0.3–6.9)	1.3 (0.3–2.9)
Macrophages, %	15% (4–60%)	22% (4–69%)
Absolute macrophages	0.27 (0.11–1.71)	0.23 (0.02–2.49)
IL-8, ng/ml	10.9 ± 3.4	6.9 ± 1.8
SLPI, μg/ml	5.7 ± 0.8	5.3 ± 1.0
Total elastase activity, μg/ml	4.2 ± 0.3	5.2 ± 0.5
MMP-1, ng/ml	19.1 ± 2.0	20.5 ± 2.8
MMP-9, ng/ml	13.7 ± 3.5	13.2 ± 3.8
TIMP-1, ng/ml	14.7 ± 5.1	15.1 ± 4.0

matrix metalloproteinase (MMP)-1 / antiproteases secretory leukoprotease inhibitor (SLPI)
tissue inhibitor of metalloproteinase (TIMP)-1

protease-antiprotease imbalance

Culpitt SV, et al. AJRCCM 1999;160:1635–1639.

Oral prednisolone & inhaled budesonide in induced sputum

long-term inhaled budesonide (800 μg daily, 6 months)
vs 3 weeks oral prednisolone (30 mg daily)

	Start prednisolone	3 Weeks prednisolone	Wash-out	*p*-value Start vs 3 weeks	*p*-value 3 weeks vs wash-out
Non-squamous TCC (10^6/g)	0.96 (0.47–3.67)	2.19 (0.68–4.52)	1.36 (0.75–4.15)	0.41	0.51
Neutrophils (%)	74.5 (64.2–85.4)	82.6 (68.5–89.0)	74.4(61.5–83.5)	0.26	0.22
Neutrophils (10^6/g)	0.67 (0.25–2.72)	1.25 (0.46–4.03)	0.86 (0.46–3.14)	0.26	0.38
Eosinophils (%)	1.6 (0.8–3.4)	0.2 (0.0–0.7)	1.0 (0.3–2.4)	0.007	0.033
Eosinophils (10^3/g)	15.2 (4.3–53.4)	15.2 (5.7–40.1)	14.6 (8.6–37.3)	0.21	0.12
MPO (μg/g)	7.2 (1.8–22.6)	10.2 (4.0–42.8)	7.0 (1.7–69.0)	0.72	0.97
IL–8 (ng/g)	4.6 (1.6–13.7)	3.1 (1.6–15.0)	4.7 (1.6–35.8)	0.43	0.81
ECP (ng/g)	287 (33–431)	140 (98–460)	220 (42–1921)	0.39	0.70

	3 months budesonide	6 months budesonide	3 months placebo	6 months placebo	*p*-value 3 months budesonide vs placebo	*p*-value 6 months budesonide vs placebo
Non-squamous TCC (10^6/g)	1.71 (0.68–3.78)	1.98 (0.85–3.53)	1.72 (1.32–3.81)	1.32 (0.95–4.63)	0.70	0.80
Neutrophils (%)	81.0 (68.7–86.6)	77.4 (64.5–88.1)	71.8 (62.2–88.4)	82.1 (64.2–87.1)	0.15	0.71
Neutrophils (10^6/g)	1.40 (0.50–2.80)	1.40 (0.63–2.63)	1.20 (0.70–3.60)	0.90 (0.60–4.08)	0.75	0.73
Eosinophils (%)	1.1 (0.30–1.75)	1.1 (0.25–3.45)	1.9 (0.60–6.65)	1.6 (0.20–4.20)	0.036	0.78
Eosinophils (10^3/g)	37.6 (16.2–44.2)	26.6 (10.6–103)	53.6 (18.1–159)	29.1 (16.0–75.9)	0.093	0.78
MPO (μg/g)	11.1 (3.5–19.7)	18.2 (4.0–47.5)	10.1 (4.3–32.4)	8.3 (2.5–24.4)	0.88	0.21
IL-8 (ng/g)	6.6 (2.4–32.7)	10.7 (3.2–19.1)	5.9 (3.1–31.2)	6.1 (2.0–13.8)	0.72	0.21
ECP (ng/g)	200 (113–699)	421 (78–1039)	470 (122–924)	412 (211–738)	1.00	0.87

TCC: Total Cell Count; % neutrophils and eosinophils as % of non-squamous cells; MPO: Myeloperoxidase; IL-8: Interleukin-8; ECP: Eosinophil Cationic Protein

Boorsma M, et al. COPD 2008;5:97-104

salmeterol/fluticasone propionate on airway inflammation in COPD

50 μg salmeterol & 500 μg FP twice daily For 3 months

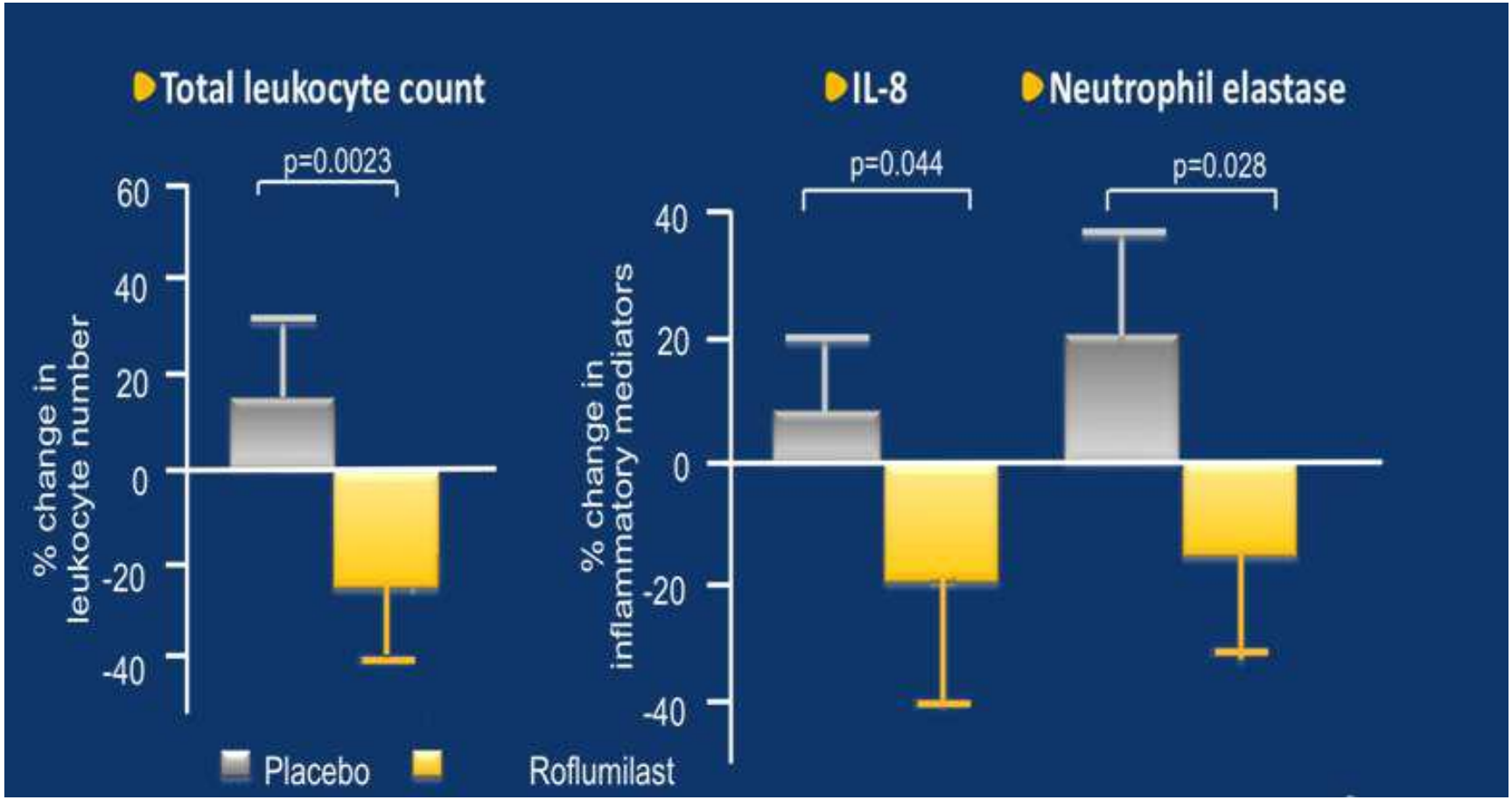
Table 2 Biopsy cell counts (cells/mm^2) according to treatment allocation

	SFC (n=19)	FP (n=17)	Placebo (n=15)
CD8+ T lymphocytes			
Baseline mean	191 (79)	195 (69)	187 (43)
Post-treatment mean	107 (31)	164 (67)	201 (48)
Mean change from baseline	−84 (67)	−31 (47)	14 (41)
Median change from baseline	−75 (−110 to −34)	−24 (−51 to −15)	11 (−4 to 41.50)
p Value for mean change from baseline	<0.001	0.20	0.42
CD68+ macrophages			
Baseline mean	102 (37)	122 (49)	135 (53)
Post-treatment mean	74 (24)	122 (49)	136 (40)
Mean change from baseline	−29 (22)	0 (33)	2 (49)
Median change from baseline	−30 (−41 to −10)	−2 (−15 to 30)	20 (−38 to 34)
p Value for mean change from baseline	0.008	0.98	0.88
Neutrophils			
Baseline mean	50 (19)	53 (20)	41 (26)
Post-treatment mean	41 (19)	67 (24)	36 (21)
Mean change from baseline	−9 (18)	14 (12)	−4 (15)
Median change from baseline	−11 (−19 to 0.5)	18 (6 to 21)	−4 (−11 to 7.5)
p Value for mean change from baseline	0.16	0.07	0.62
Eosinophils			
Baseline mean	5 (5)	9 (7)	7 (4)
Post-treatment mean	5 (4)	8 (7)	9 (5)
Mean change from baseline	−0.4 (5)	−1 (6)	3 (7)
Median change from baseline	0 (−3 to 3)	−1 (−2 to 3)	1 (0.5 to 7)
p Value for mean change from baseline	0.80	0.61	0.09

SFC, salmeterol xinafoate/fluticasone propionate; FP, fluticasone propionate.
Data expressed as mean (SD) or median (interquartile ranges).

Bourbeau J, et al. Thorax 2007;62:938–943

Roflumilast reduced levels of inflammatory markers in sputum samples

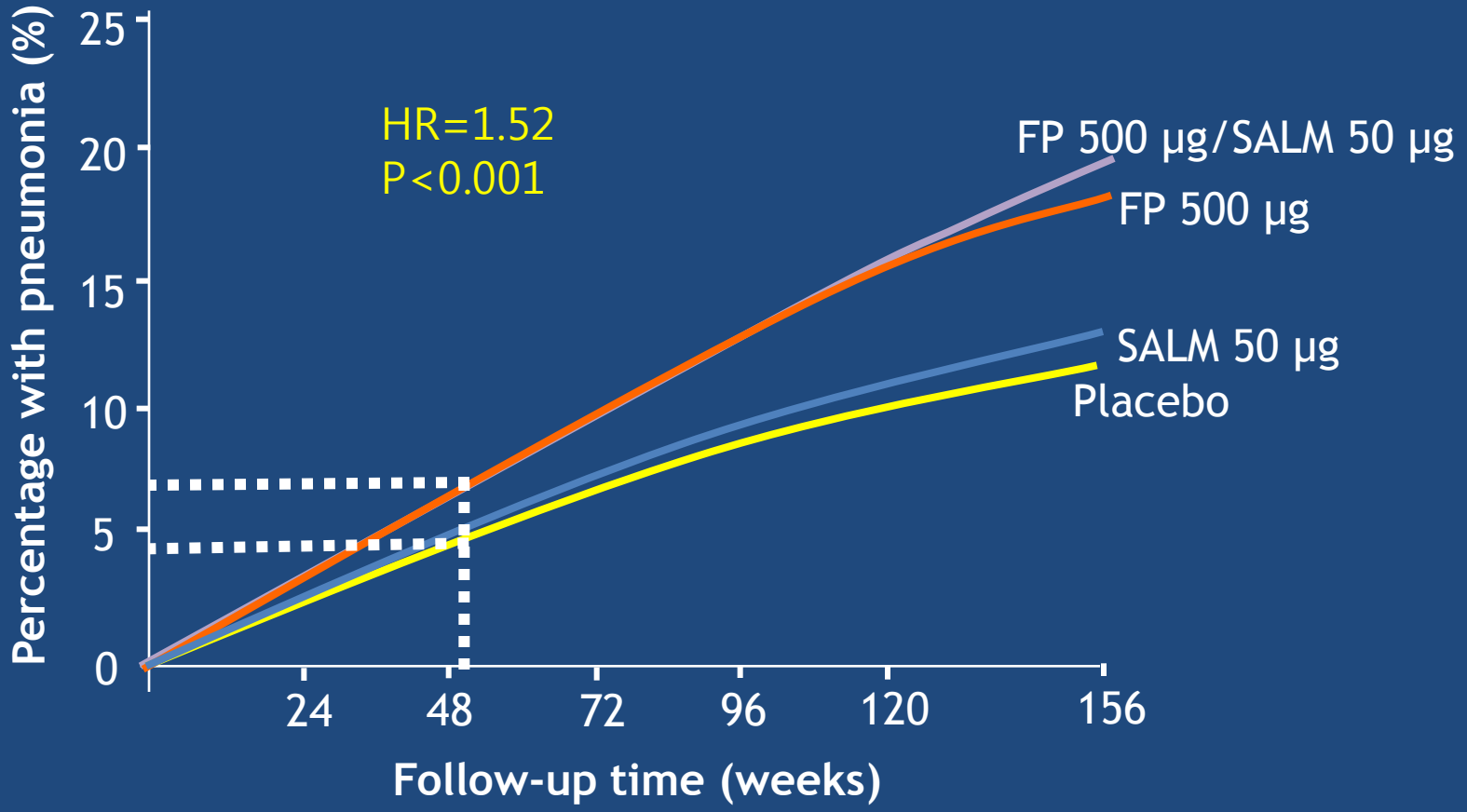


Grootendorst et al. Thorax 2007;62:1081–1087

THE RECENT ISSUE
Safety concerns

- ICS use : increased risk of side effects
  - Pneumonia
  - Diabetes
  - Tuberculosis
  - Cataracts (posterior subcapsular and nuclear cataracts)
  - Osteoporosis

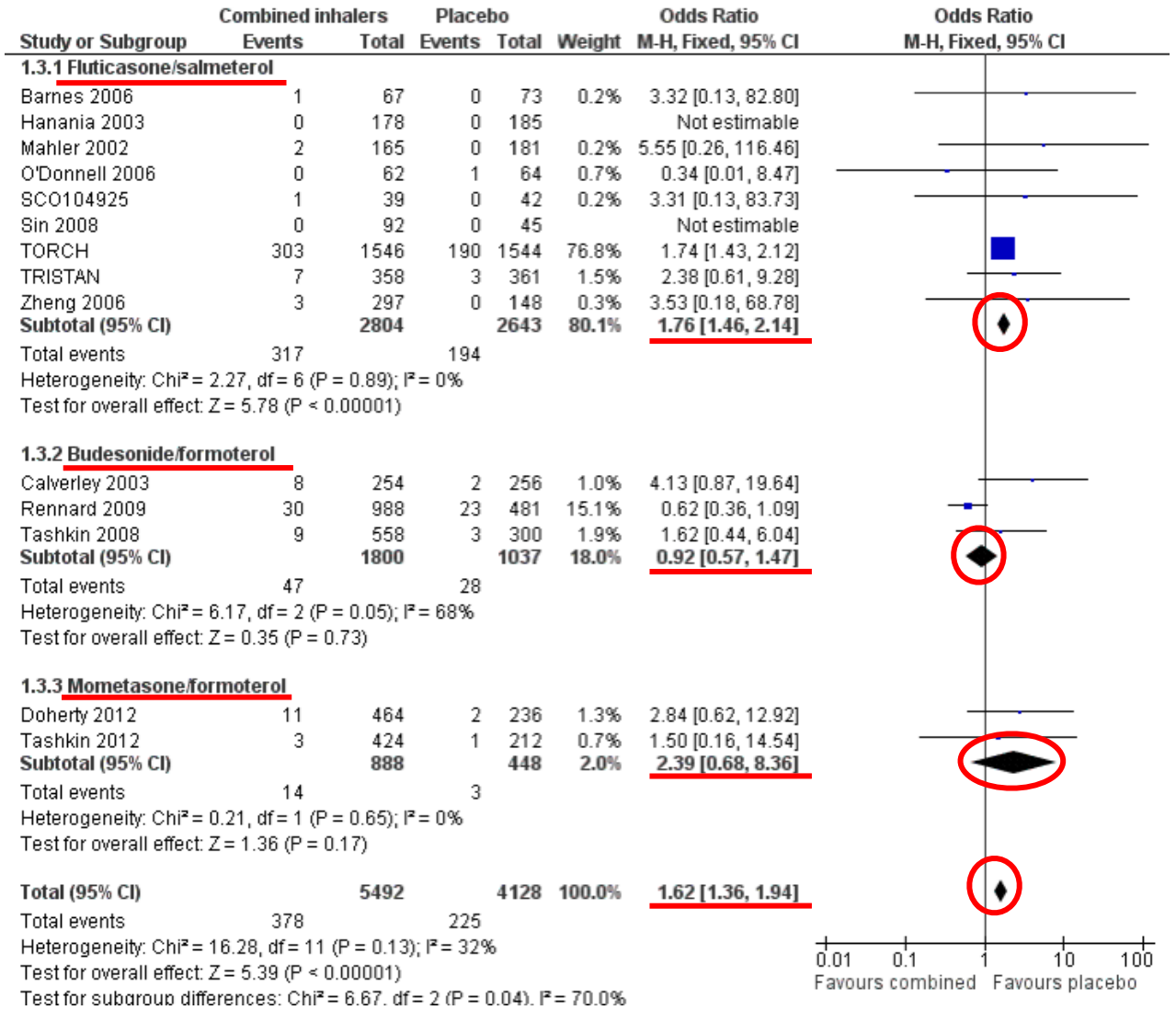
TORCH
ICS & PNEUMONIA



FP/SALM	1546	1231	1034	631
FP	1552	1189	992	574
SALM	1542	1214	1024	645
Placebo	1544	1117	947	587

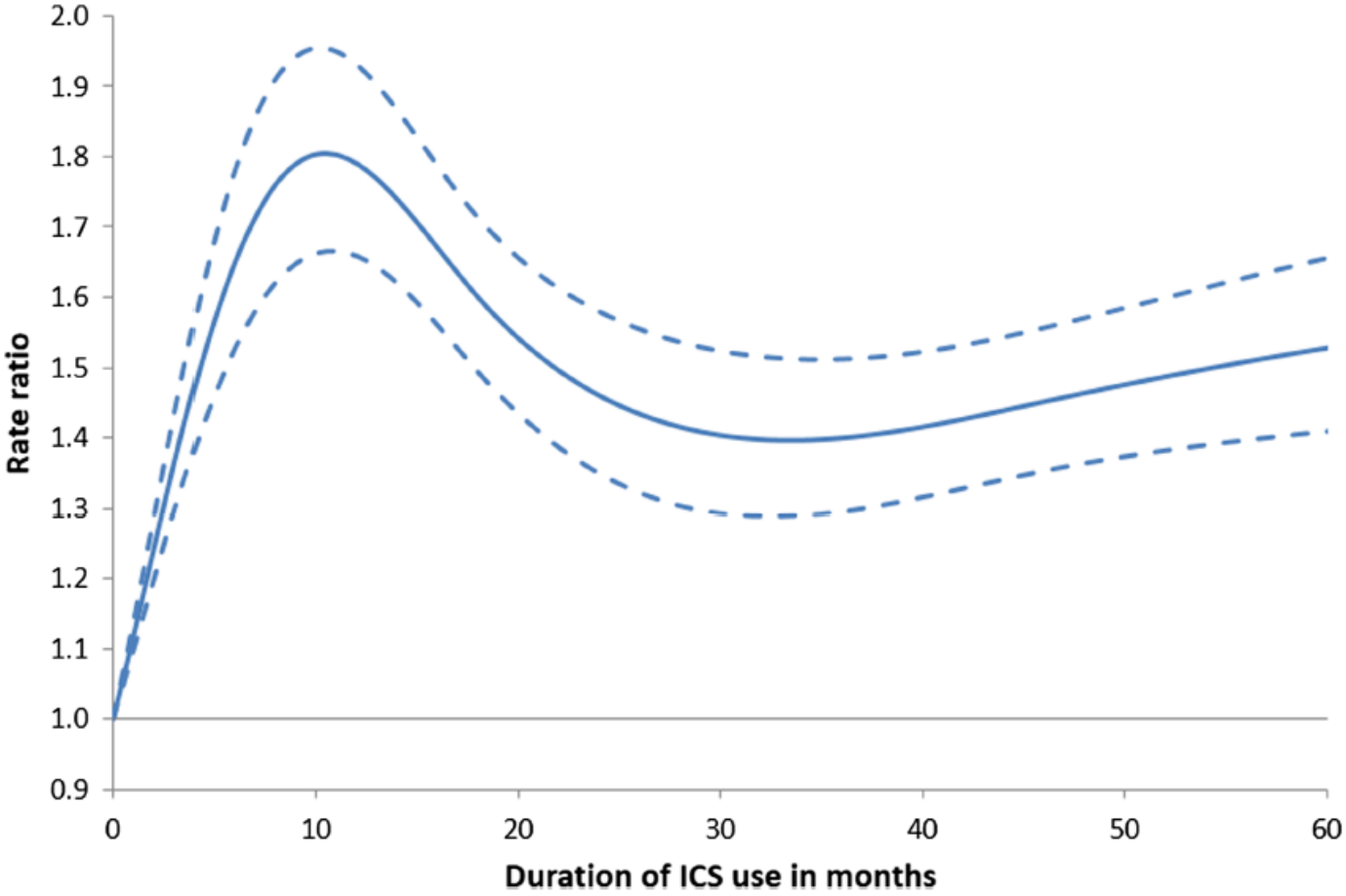
Crim C et al. Eur Respir J 2009; 34:641-647.

ICS/LABA vs Placebo Pneumonia



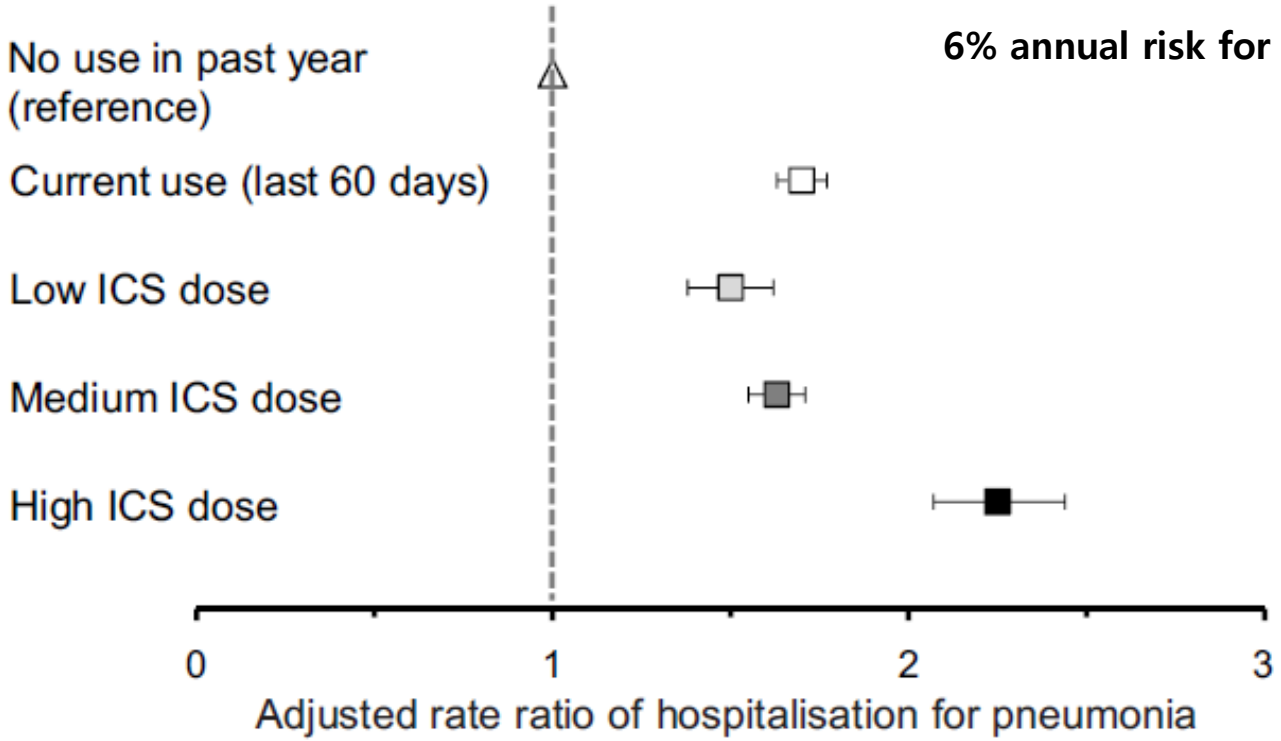
Nannini LJ, et. al. Cochrane Database Syst Rev 2013; 11: CD003794.

Pneumonia & duration of current ICS



Suissa S, et al. Thorax 2013;68:1029–1036

Adjusted rate ratios of hospitalisation for pneumonia associated with ICS



6% annual risk for ICS/LABA

converted to fluticasone equivalents
high (fluticasone >1,000µg/day)
moderate (fluticasone 500–999µg/day)
low (fluticasone <500µg/day)

Price D, et al. Prim Care Respir J 2013; 21(1): 92-100

INSPIRE study
Reported pneumonia events

Pneumonia Events	SFC (n = 658)	Tio (n = 665)
All pneumonia		
Patients	50 (8)	24 (4)
Events[a]	62	25
Serious pneumonia		
Patients	41 (6)	19 (3)
Events[a]	52	19
Fatal pneumonia		
Patients	3 (<1)	0
Events	3	0
All pneumonia	62	25
Duration, mean (SD), d	19.4 (19.8)	23.0 (21.7)
<1 wk	4 (6)	0
1 to <2 wk	26 (42)	9 (36)
2 to <3 wk	15 (24)	10 (40)
3 to <4 wk	5 (8)	1 (4)
≥4 wk	12 (19)	5 (20)

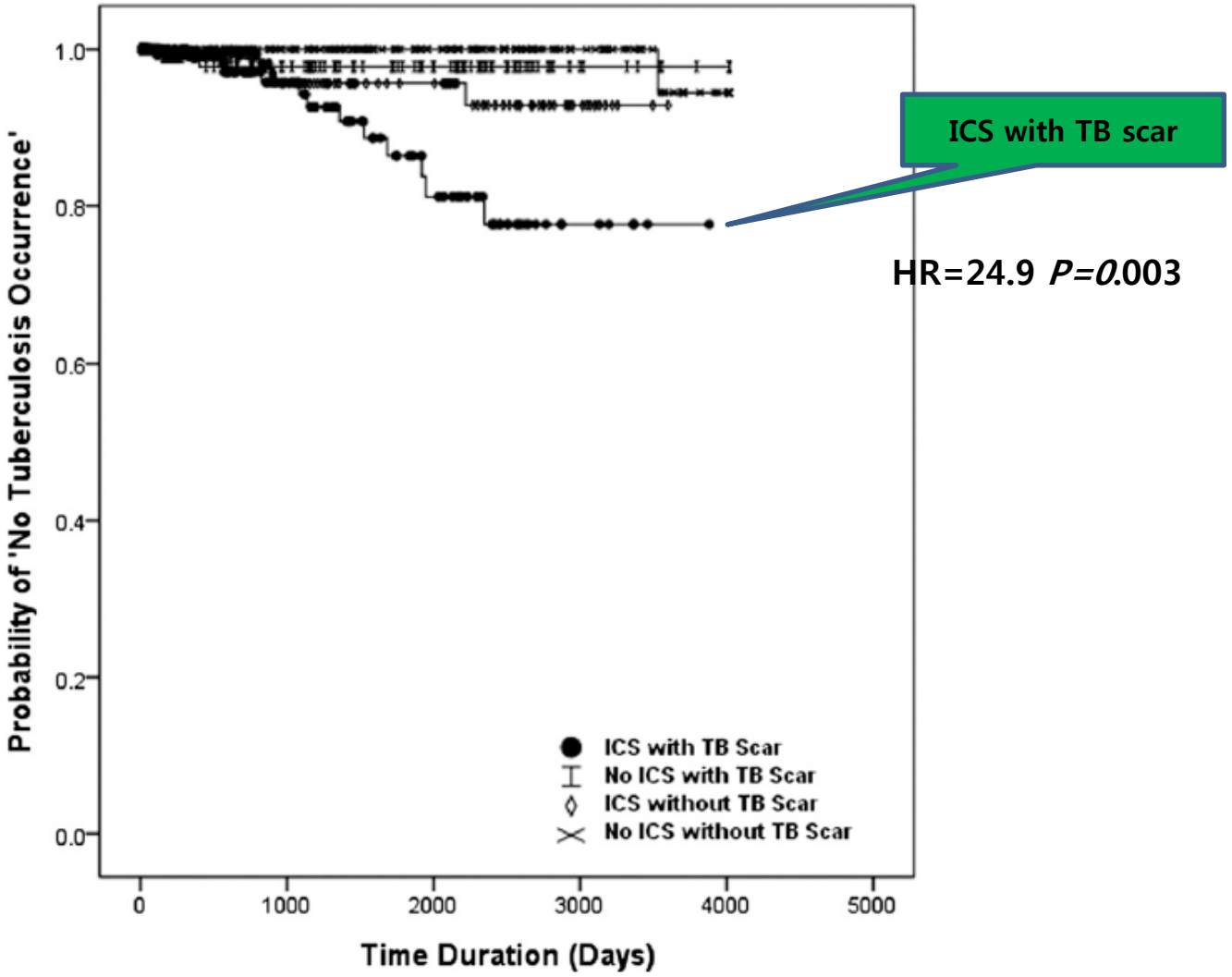
Data are expressed as No. (%) unless otherwise noted. SFC = salmeterol/fluticasone propionate 50/500 μg bid; Tio = tiotropium bromide 18 μg once daily.

[a]Patients can have more than one event.

INSPIRE study, 2-year treatment
SFC 50/500 mcg twice daily
Tiotropium bromide 18 mcg

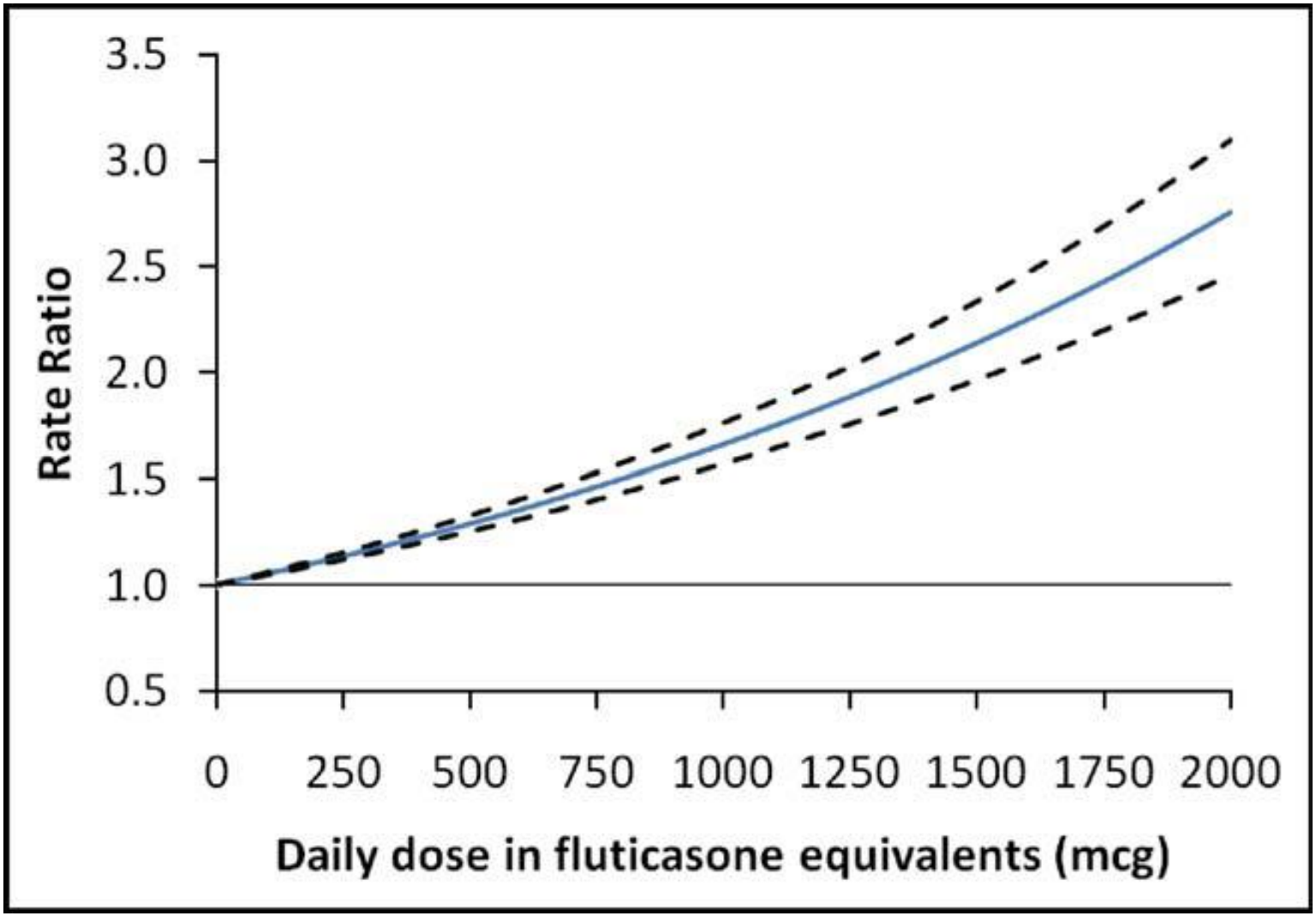
Calverley PM, et al. CHEST 2011;139(3):505

Occurrence of pulmonary tuberculosis



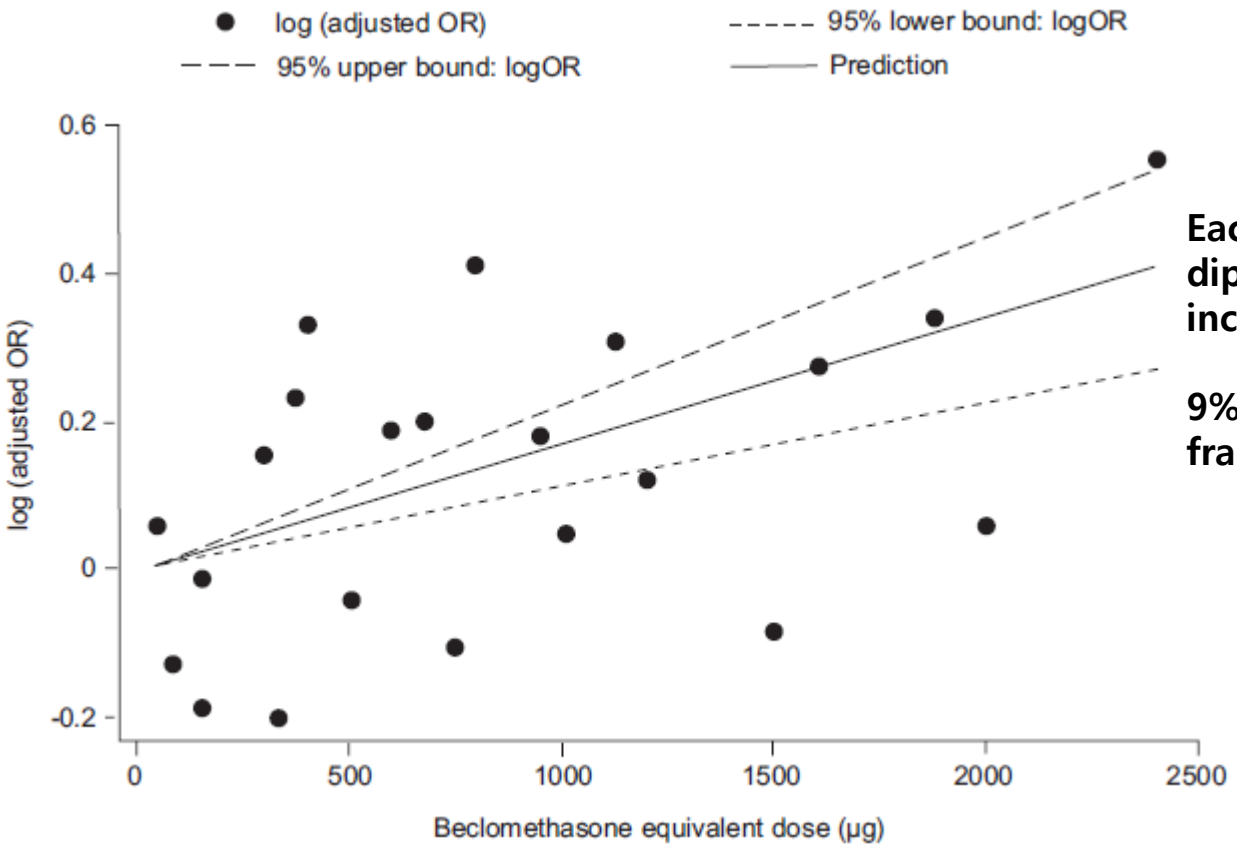
Kim JH et al. CHEST 2013; 143(4):1018–1024

Risks of Diabetes Onset and Progression - ICS



The American Journal of Medicine, Vol 123, No 11, November 2010

Risk of fractures with increasing dose of inhaled corticosteroid



Each 500µg (beclometasone dipropionate equivalent) increase in ICS dose

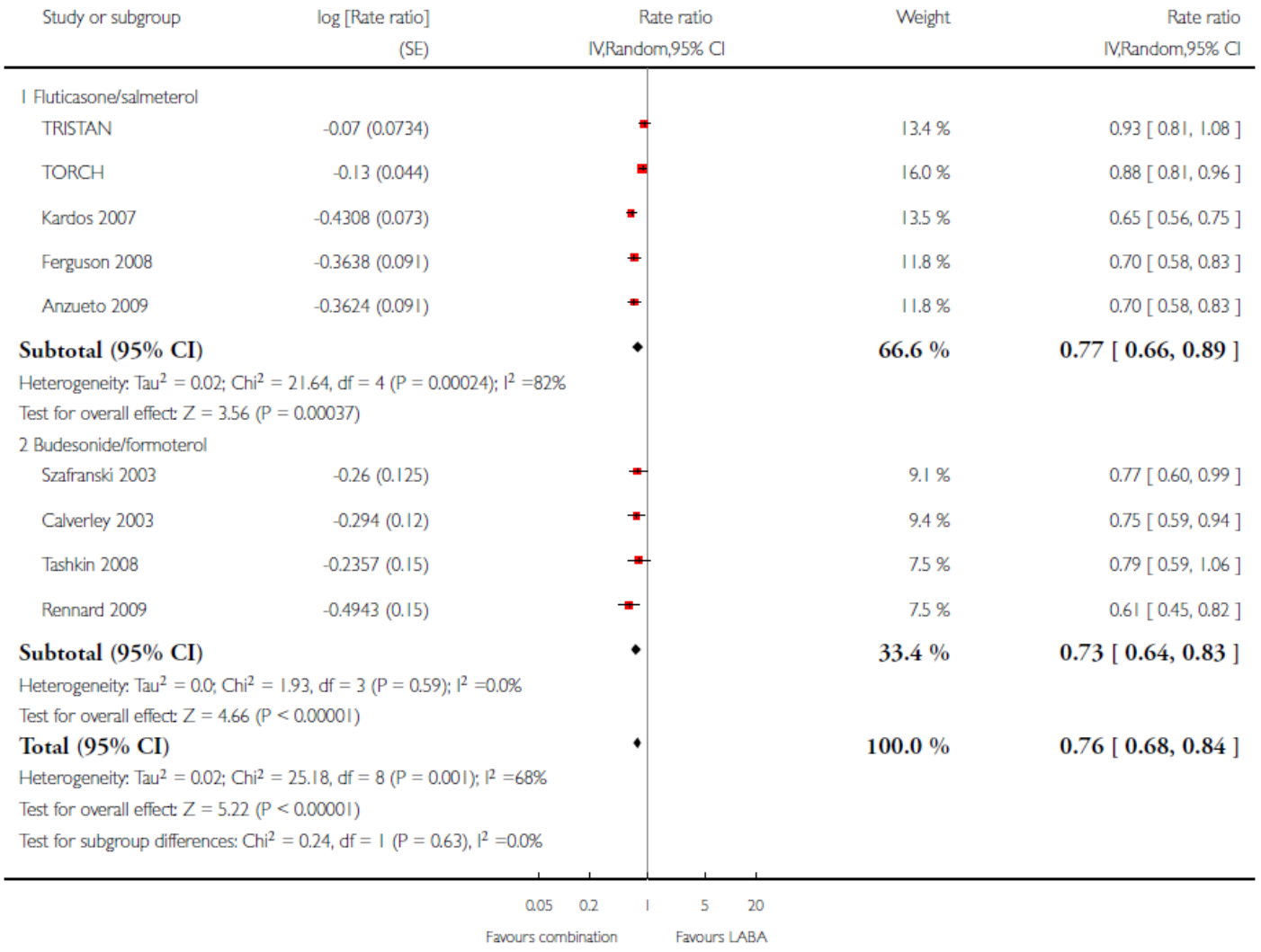
9% increase in risk of fractures

Price D, et al. Prim Care Respir J 2013; 21(1): 92-100

Clinical Trials for ICS

ICS/LABA vs LABA alone

Exacerbation rates (per person per year)



Cochrane Database Syst Rev. 2013;8

Influence of ICS on annual exacerbation rates

Table 3. Influence of inhaled corticosteroids (ICS) on annual exacerbation rates.

Study	*n*	Age (years)	Medication	Treatment period	Exacerbation rate (no./patient/year)			
					Placebo	LABA	ICS	ICS + LABA
ISOLDE [21]	751	64	FP/PLAC	3 years	1.32	–	0.99*	–
TORCH [12]	6112	65	SFC/FP/SAL/PLAC	3 years	1.13	0.97*	0.93*	0.85*
TRISTAN [16]	1465	63	SFC/FP/SAL/PLAC	1 year	1.30	1.04*	1.05*	0.97*‡
Calverley *et al.* [15]	1022	64	BF/BUD/FT/PLAC	1 year	1.80	1.85	1.60	1.38*
Szafranski *et al.* [39]	812	64	BF/BUD/FT/PLAC	1 year	1.87	1.84	1.59	1.42*
Kardos *et al.* [40]	994	64	SFC/PLAC	44 weeks	–	1.40	–	0.92‡

*$p < 0.05$ compared to placebo.

‡$p < 0.05$ compared with LABA.

– Group not present in study.

BDP: Beclomethasone; BF: Budesonide/formoterol; BUD: Budesonide; FP: Fluticasone propionate; FT: Formoterol; LABA: Long-acting β2-agonist; PLAC: Placebo; SAL: Salmeterol; SFC: Salmeterol/fluticasone.

Telenga ED, et al. Expert Opin. Pharmacother. 2010;11(3):405

Withdrawal ICS – ISOLDE

Clinically stable for at least 6 weeks
mean FEV, 42.8% predicted
38% of those previously treated with ICS
Withdrawn in the first week of the study & 7 weeks F/U

	No exacerbations		Exacerbations	
	Not on IS (105)	On IS (100)	Not on IS (7)	On IS (60)
Age, median (SEM)	64 (0·7)	64 (0·7)	66 (4)	66 (0·8)
Sex (M:F)	73:32	72:28	6:1	45:15
Pack year cigarette smoking, median (range)	50 (10–183)	40 (7–127)	45 (30–60)	47 (4–153)
Post-salbutamol FEV_1 mean % predicted (SD)	49 (12)	45 (12)	41 (4)	46 (12)
Reversibility of FEV_1 to salbutamol (%), mean (SD)	4·4 (3·1)	4·1 (30)	4·2 (3·1)	4·3 (3·2)
T_LCO (mmol min^{-1} kPa^{-1})	5·1 (1·9)	5·0 (1·9)	5·4 (2·5)	4·8 (2·1)
KCO (mmol min^{-1} kPa^{-1} l^{-1})	1·0 (0·5)	1·0 (0·4)	1·2 (0·8)	1·1 (0·6)
Baseline plasma cortisol (nmol l^{-1})	363 (146)	341 (126)	370 (98)	339 (46)

odds ratio 9.5 (C.I. 4.0-23.8) P<O.OOl

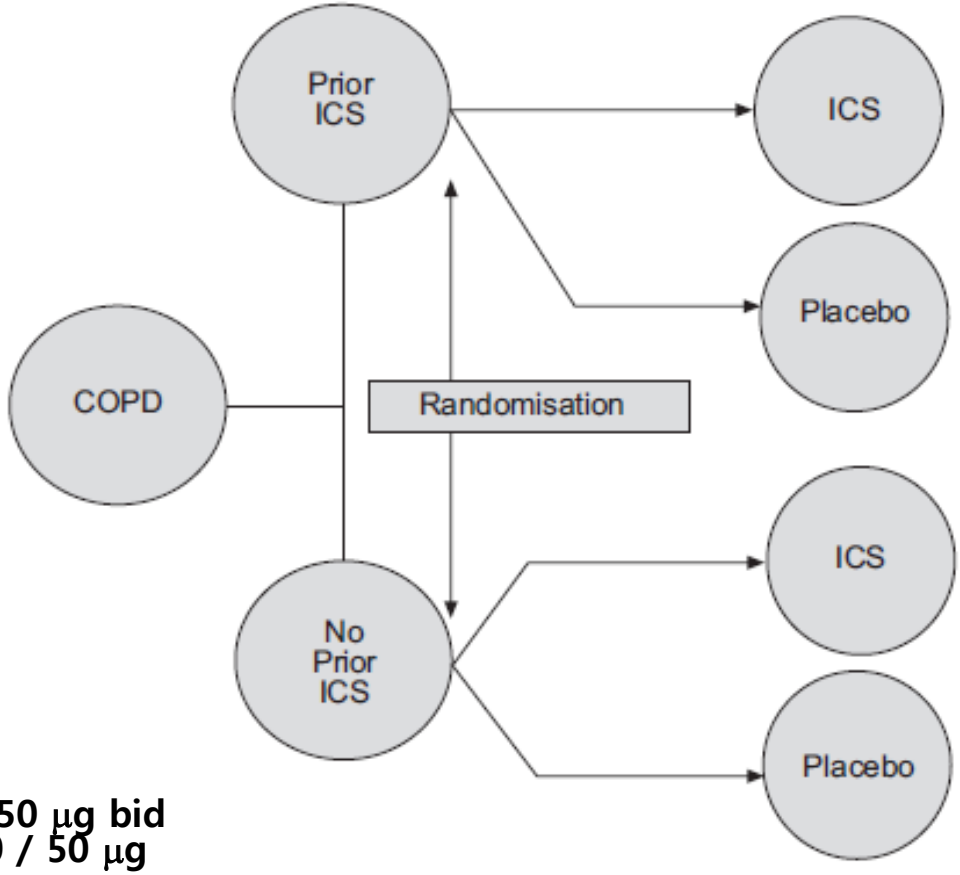
Abrupt withdrawal of inhaled corticosteroids should be monitored carefully

Jarad NA, et al. Respir Med 1999;93:161

Canadian OPTIMAL study

Canadian Optimal trial

Three-arm randomised trial
449 patients
with moderate or severe COPD
Mean FEV1: 39%
ICS use at recruitment 77%



Treatment arm
1. **Tiotropium 18 μg od**
2. **Tiotropium 18 μg od and Salmeterol 50 μg bid**
3. **Tiotropium 18 μg od and Flu/ Sal 500 / 50 μg bid**

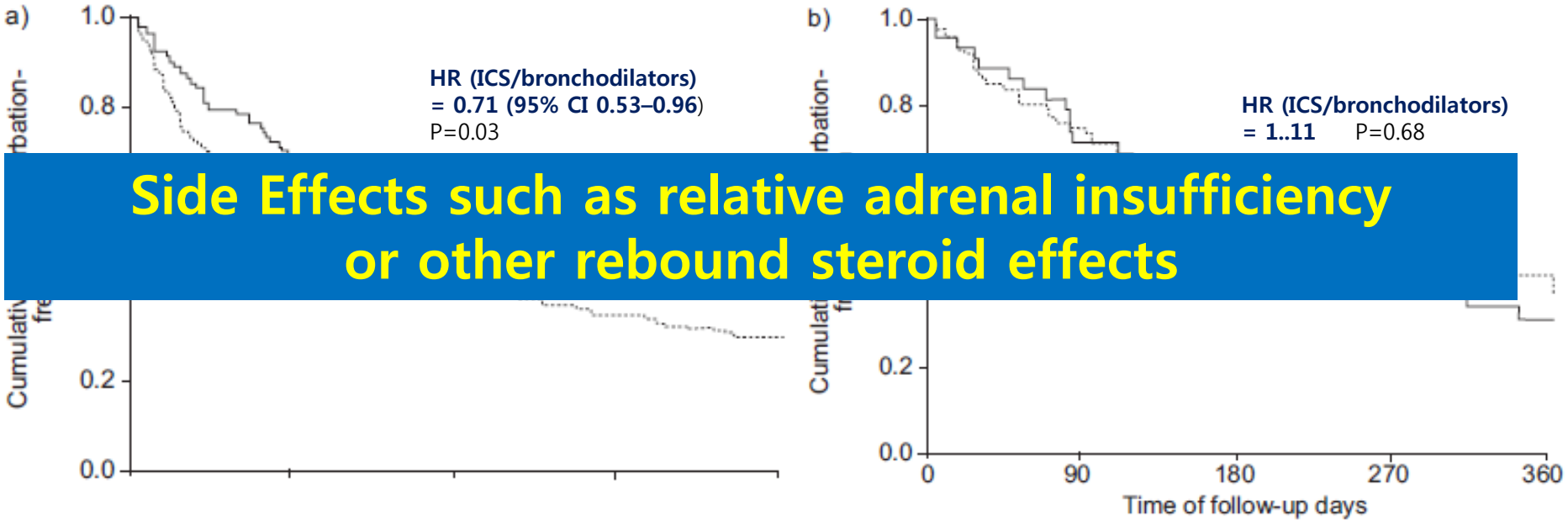
Aaron SD, et al. Ann Intern Med 2007;146:545
Suissa S, et al. Eur Respir J 2008; 31: 927–933

Canadian Optimal study

the time to the first exacerbation

Previous users of ICS

Naïve to ICS



Side Effects such as relative adrenal insufficiency or other rebound steroid effects

——— : inhaled ICS users

----- : bronchodilator users.

Suissa S, et al. Eur Respir J 2008; 31: 927–933

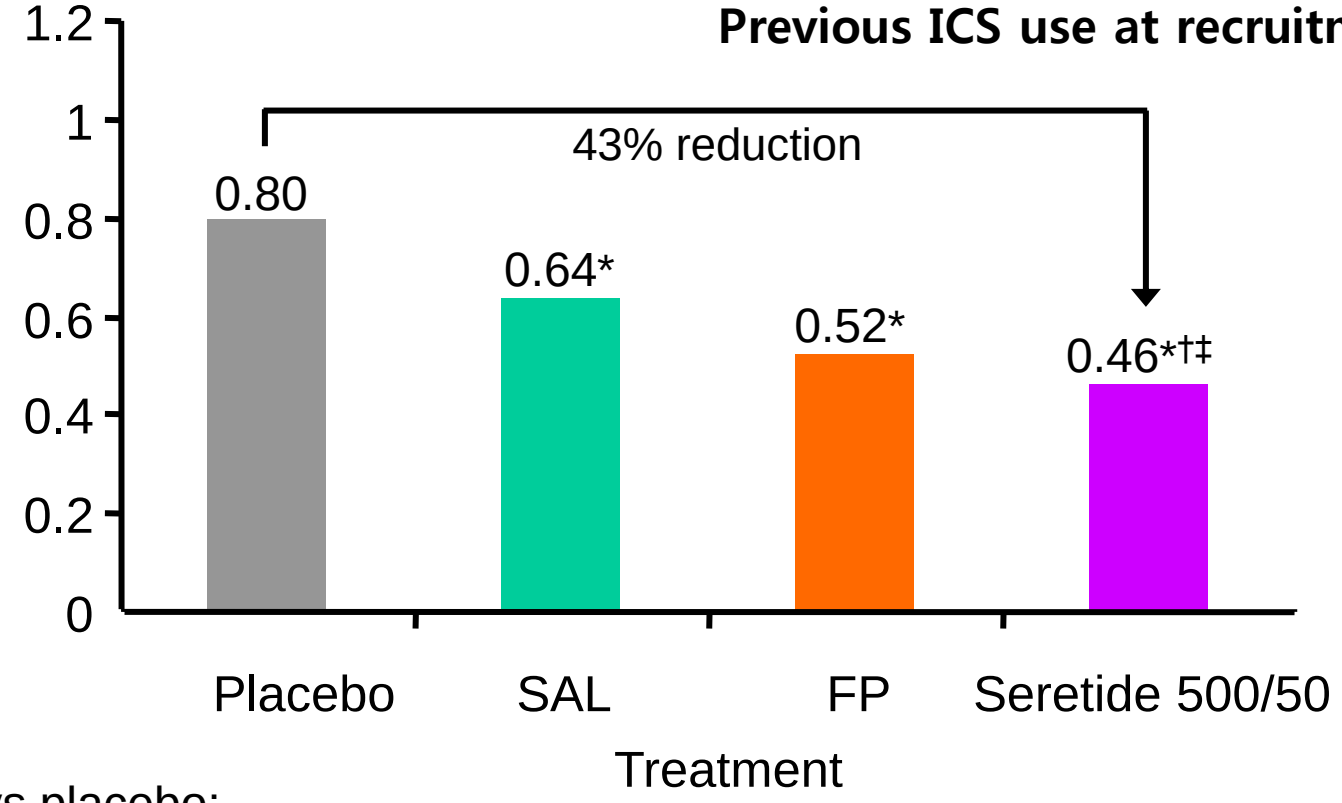
TORCH
ICS + LABA vs LABA alone

Rate of exacerbations requiring systemic corticosteroids

Mean number of exacerbations/year

Mean FEV1 ≈ 44%

Previous ICS use at recruitment 48%



*p < 0.001 vs placebo;
†p < 0.001 vs SAL; ‡p = 0.017 vs FP

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

2X2 Factorial analysis of the TORCH data

The independent effects of fluticasone & salmeterol 3-yr incidence of all-cause mortality

	Medication allocated		Crude RR	Adjusted RR (95% CI)
	Yes deaths/total n	No deaths/total n		
Medication				
Fluticasone	439/3067	436/3045	1.00	1.00 (0.89–1.13)
Salmeterol	398/3054	477/3058	0.83	0.83 (0.74–0.95)

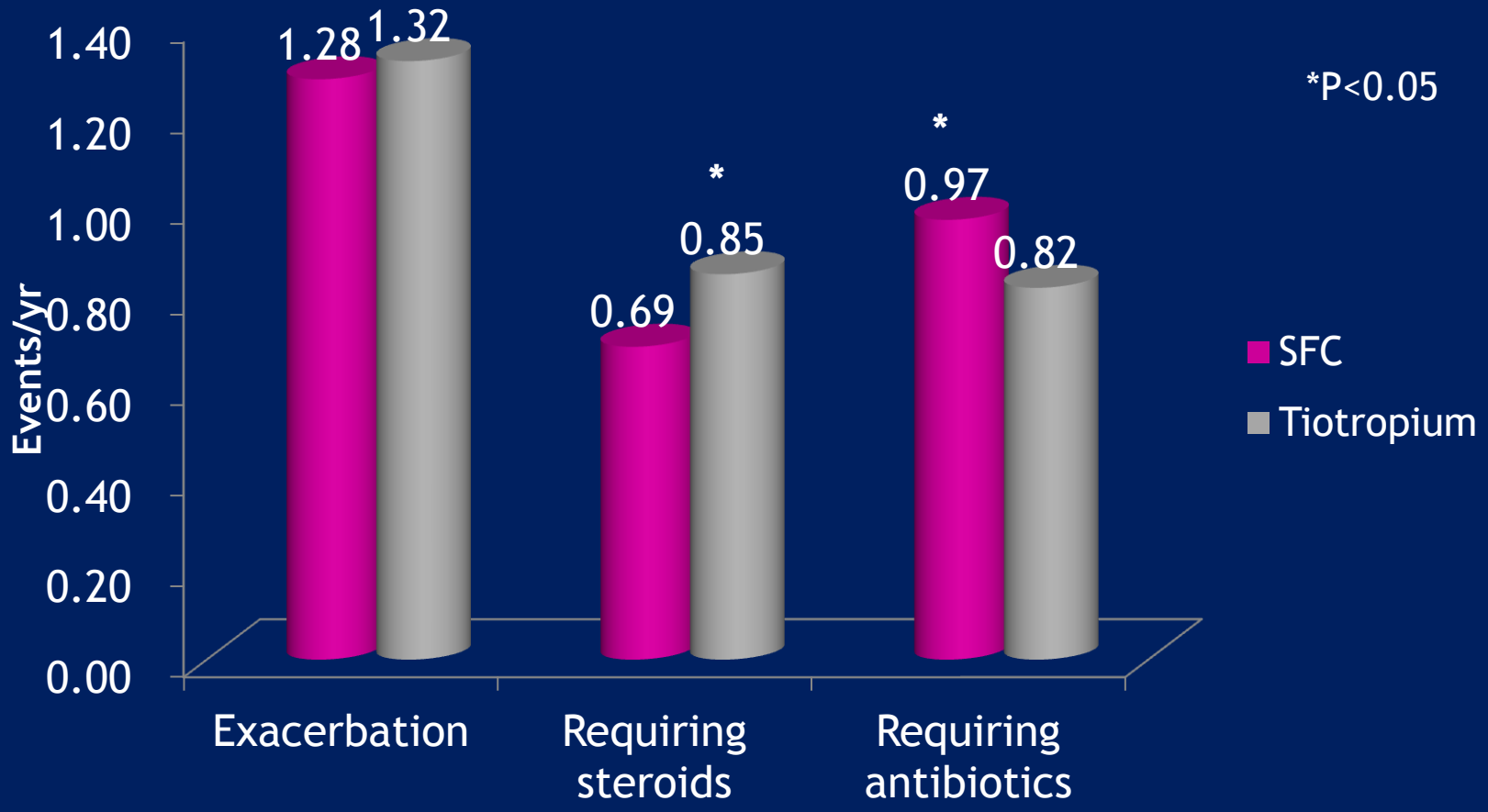
RR: relative rate ratio; CI: confidence interval.

Salmeterol component : 17% reduction in mortality

Suissa S, et al. Eur Respir J 2008; 31: 927–933

INSPIRE
ICS/LABA vs LAMA

Estimated overall rates of HCU exacerbations p=0.656

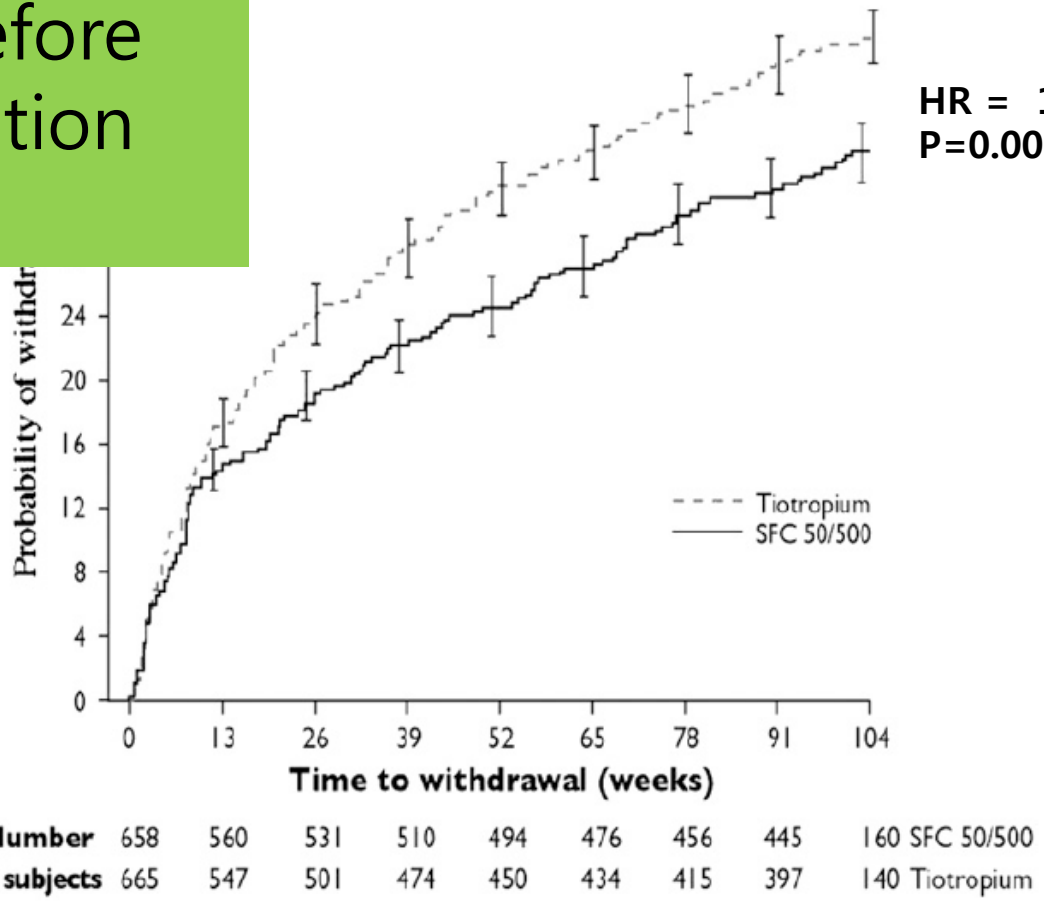


FEV1 <50% predicted, 2 years

Wedzicha et al. AJRCCM 2008;177:19-26

Time to withdrawal on treatment SFC Vs tiotropium

ICS use before randomization 50%

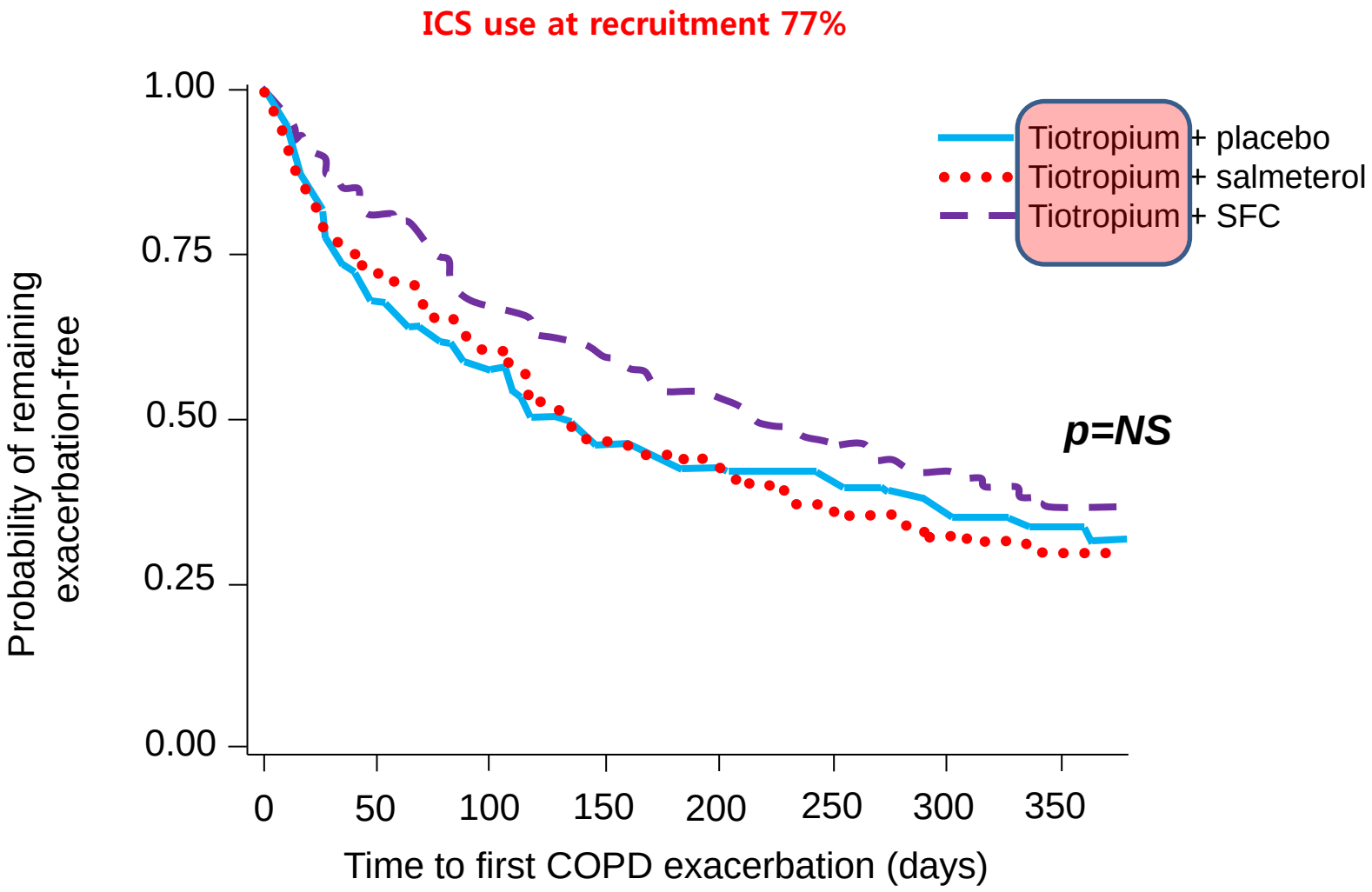


HR = 1.29 (95% CI, 1.08–1.54)
P=0.005

Wedzicha et al. AJRCCM 2008;177:19-26

Canadian OPTIMAL study

COPD exacerbation - ICS/LABA to LAMA

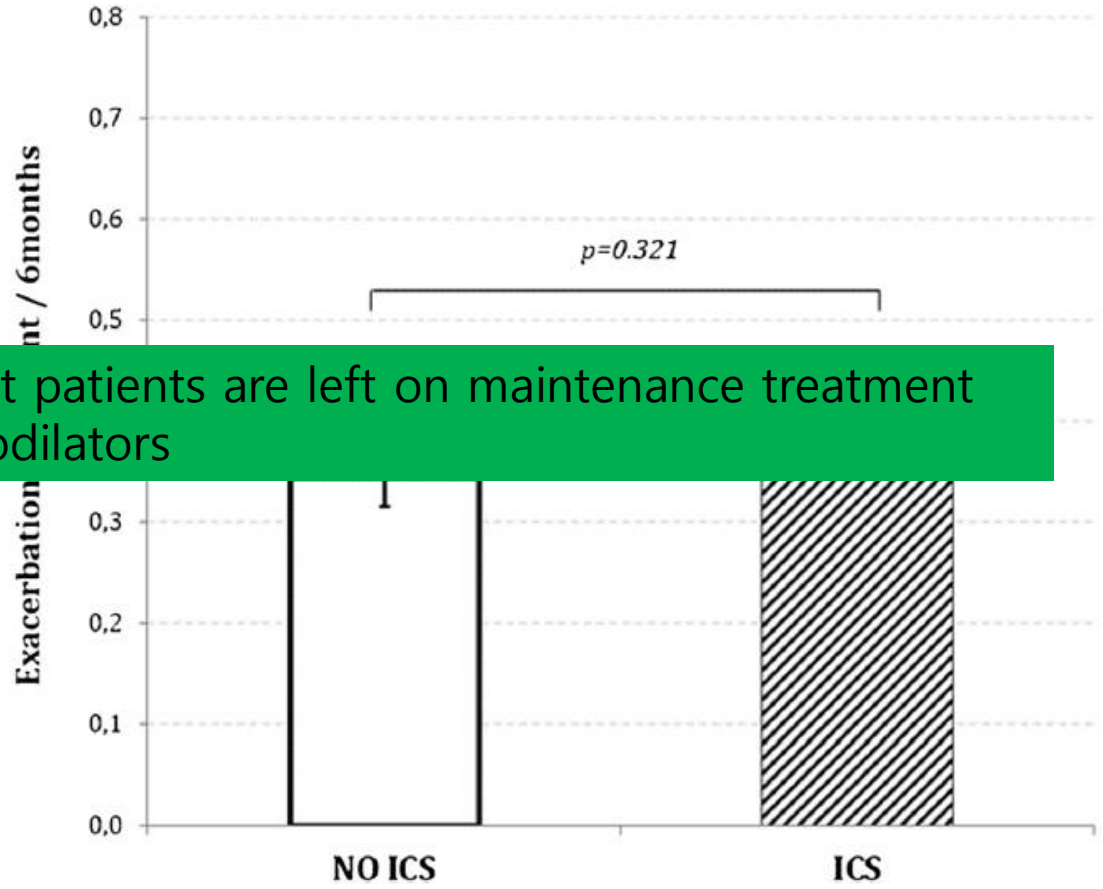


Aaron et al. Ann Int Med 2007;146:545-55

Withdrawal of ICS - OPTIMO

FEV1>50% predicted
no history of frequent exacerbations, (< 2 / year)

Mean (SE) exacerbation rate



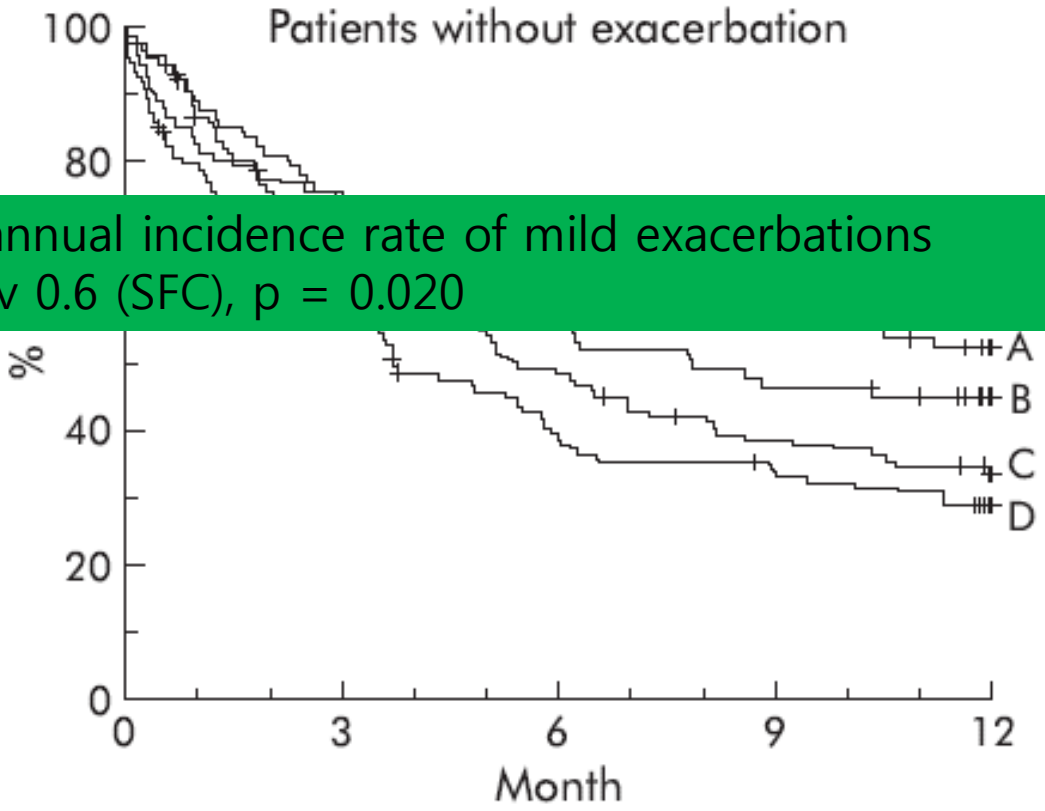
can be safe provided that patients are left on maintenance treatment with long-acting bronchodilators

Rossi A et al. Respiratory Research 2014, 15:77

Withdrawal ICS – COSMIC

Time to first moderate or severe exacerbation

Withdrawal of the ICS (FP) after a 3 month run-in treatment period with FP/salmeterol FEV1 30-70%



mean annual incidence rate of mild exacerbations
1.3 (S) v 0.6 (SFC), p = 0.020

A v B: p = 0.30

C v D: p = 0.57

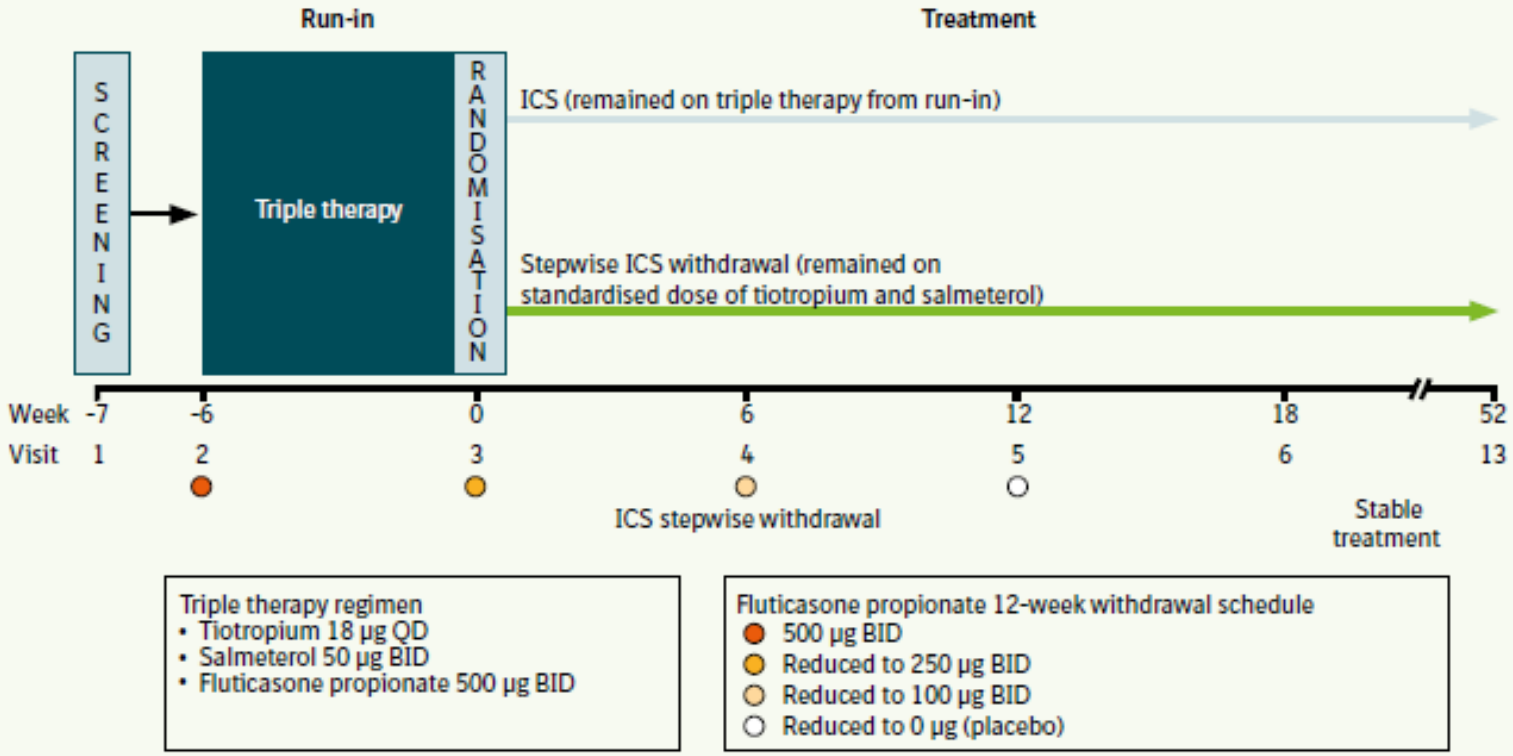
(A) salmeterol and FEV1 >50% (n = 75);
(B) salmeterol/fluticasone and FEV1 >50% (n = 75)
(C) salmeterol/fluticasone and FEV1 <50% (n = 114)
(D) salmeterol and FEV1<50% (n = 109)

Wouters EFM, et al. Thorax 2005;60:480–487.

WISDOM

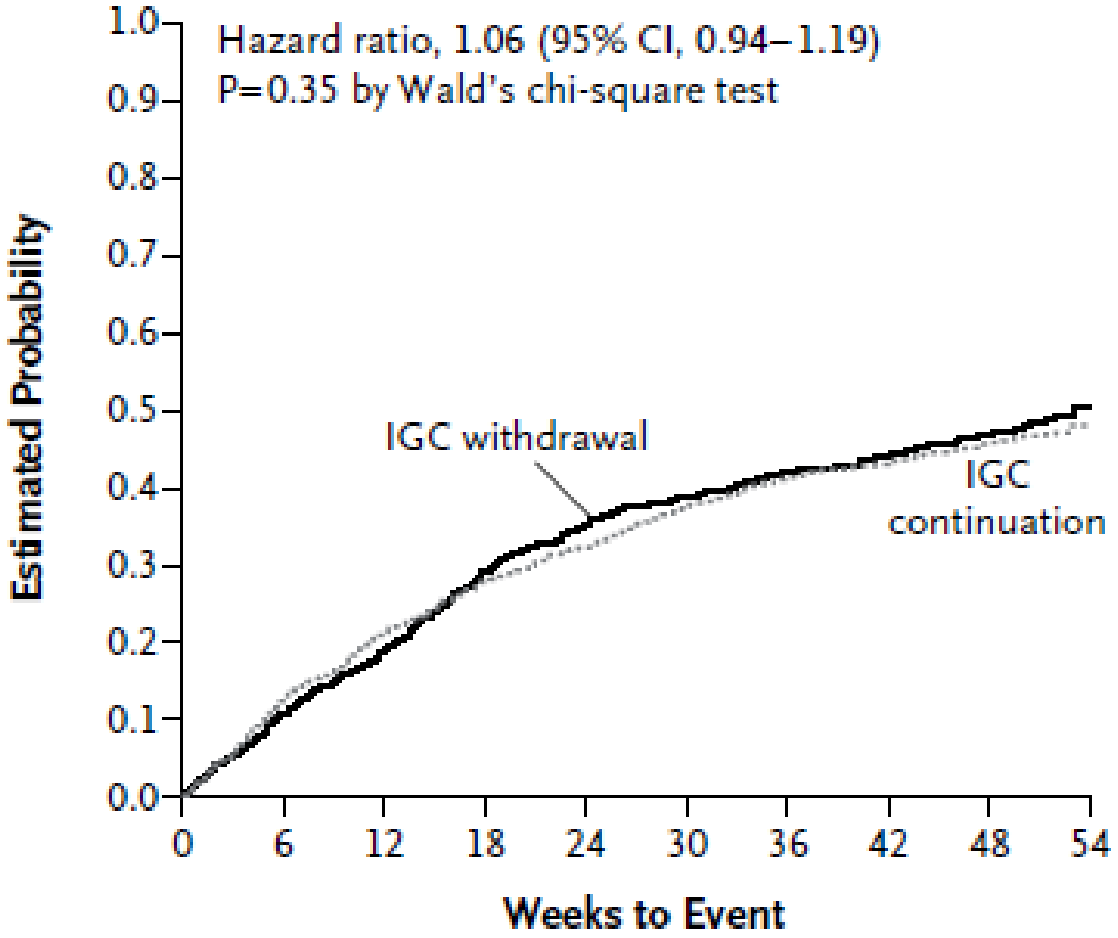
◆Severe to very severe COPD (Post BD FEV_1<50% and FEV_1/FVC<70%)
◆History of ≥1 exacerbation in year prior to screening

Figure 1. Study design.



Magnussen H, et al. NEJM 2014;371:1285-94

Time to moderate or severe exacerbations

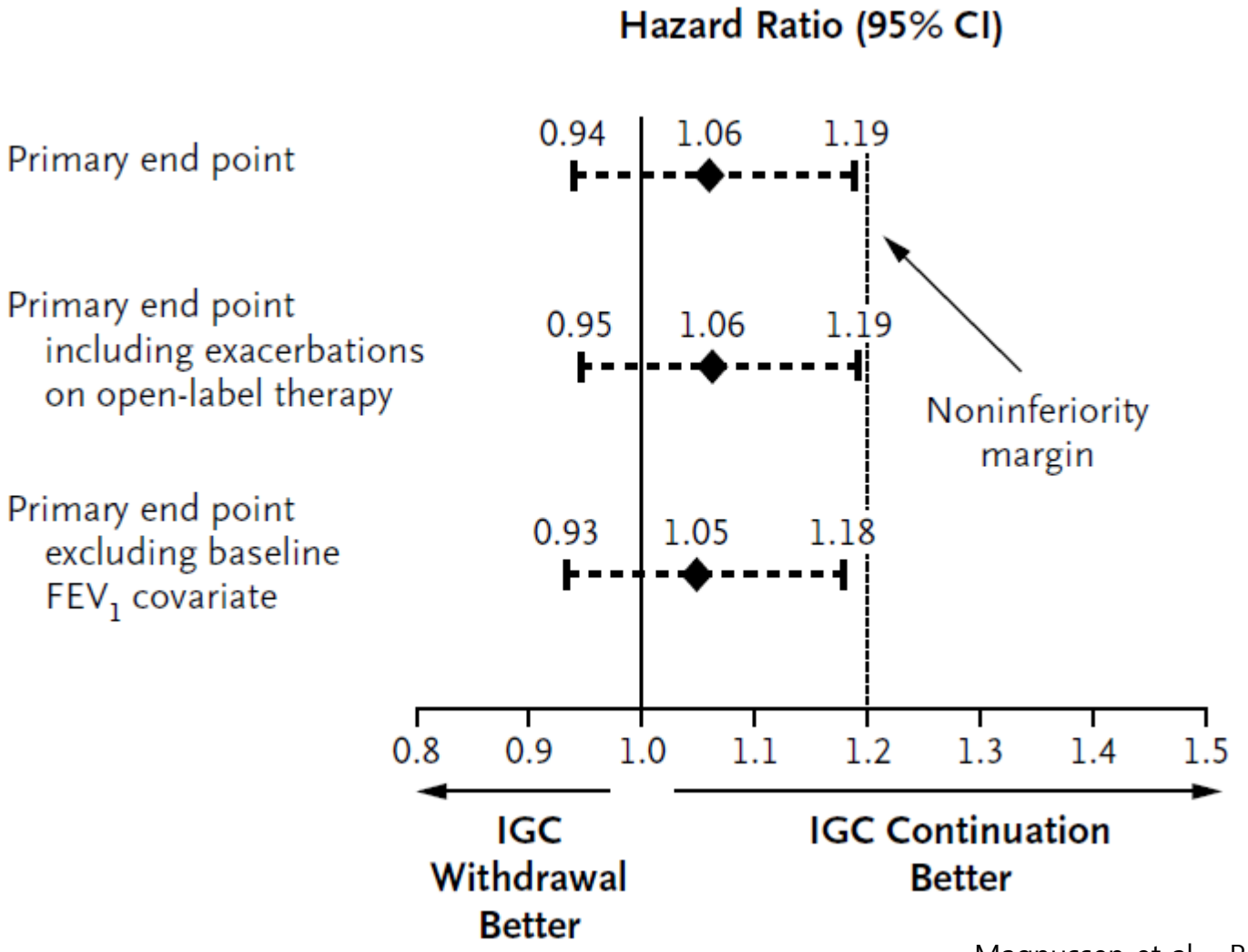


No. at Risk

IGC continuation	1243	1059	927	827	763	694	646	615	581	14
IGC withdrawal	1242	1090	965	825	740	688	646	607	570	19

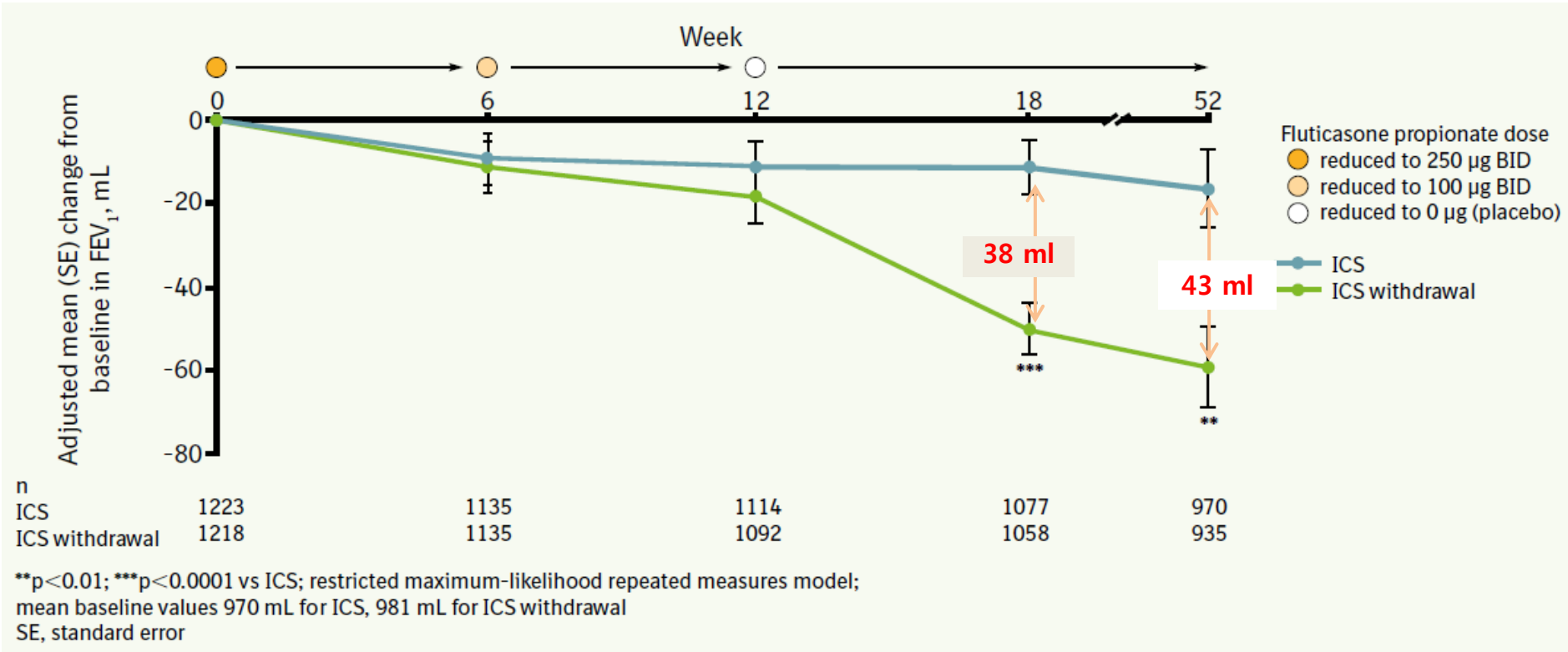
Magnussen H, et al. NEJM 2014;371:1285-94

Primary Endpoint was Met: Similar time to moderate or severe exacerbations



Magnussen et al – Resp Med 2014

WISDOM
Change from baseline in trough FEV1

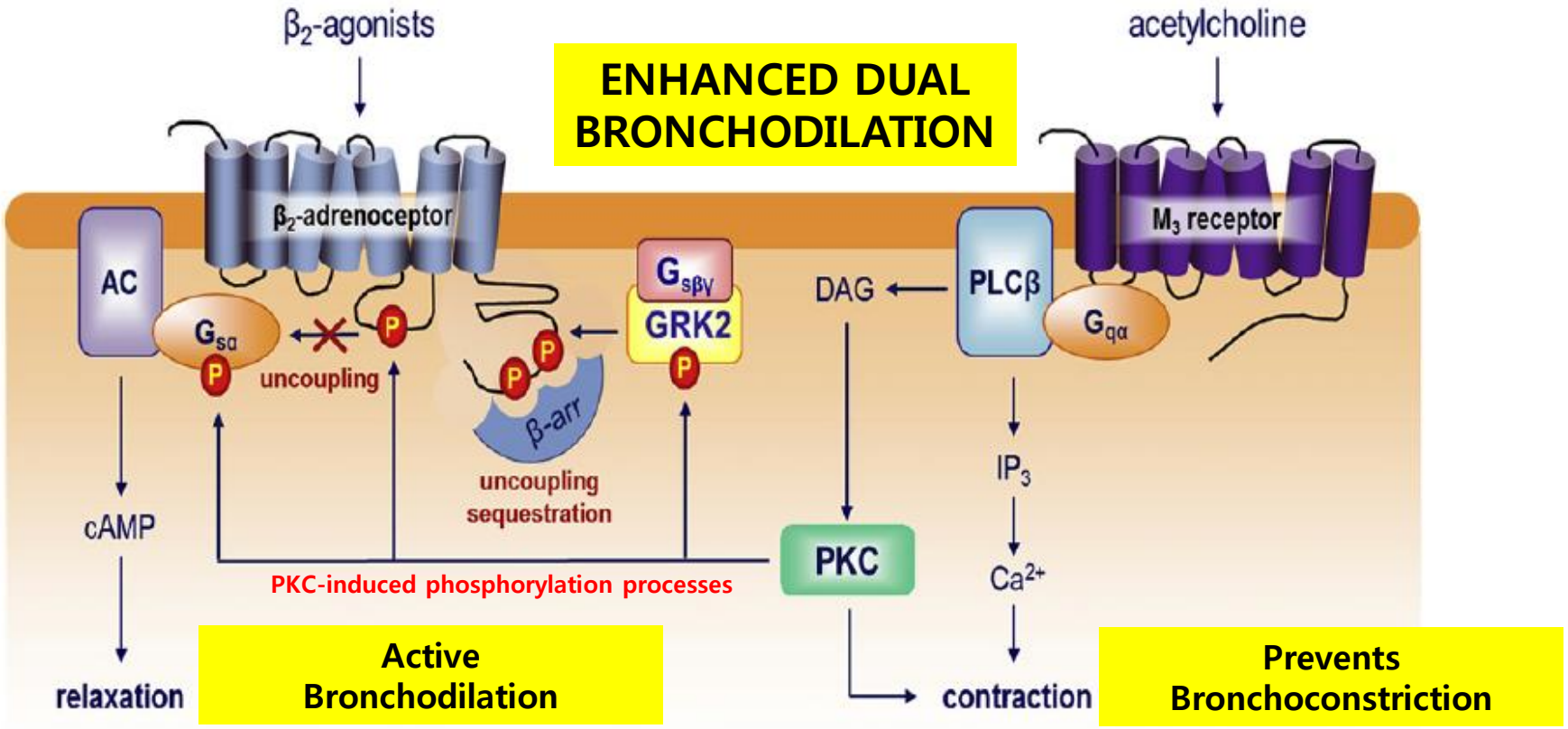


**p<0.01; ***p<0.0001 vs ICS; restricted maximum-likelihood repeated measures model;
mean baseline values 970 mL for ICS, 981 mL for ICS withdrawal
SE, standard error

Magnussen et al, N Engl J Med 2014;371:1285-94

WHY SO SERIOUS ?

Crosstalk between M_3R and β2-adrenoceptors in airway smooth muscle



AC, adenylyl cyclase
cAMP, cyclic adenosine-30,50-monophosphate
DAG, diacylglycerol;
IP3, inositol 1,4,5-trisphosphate;

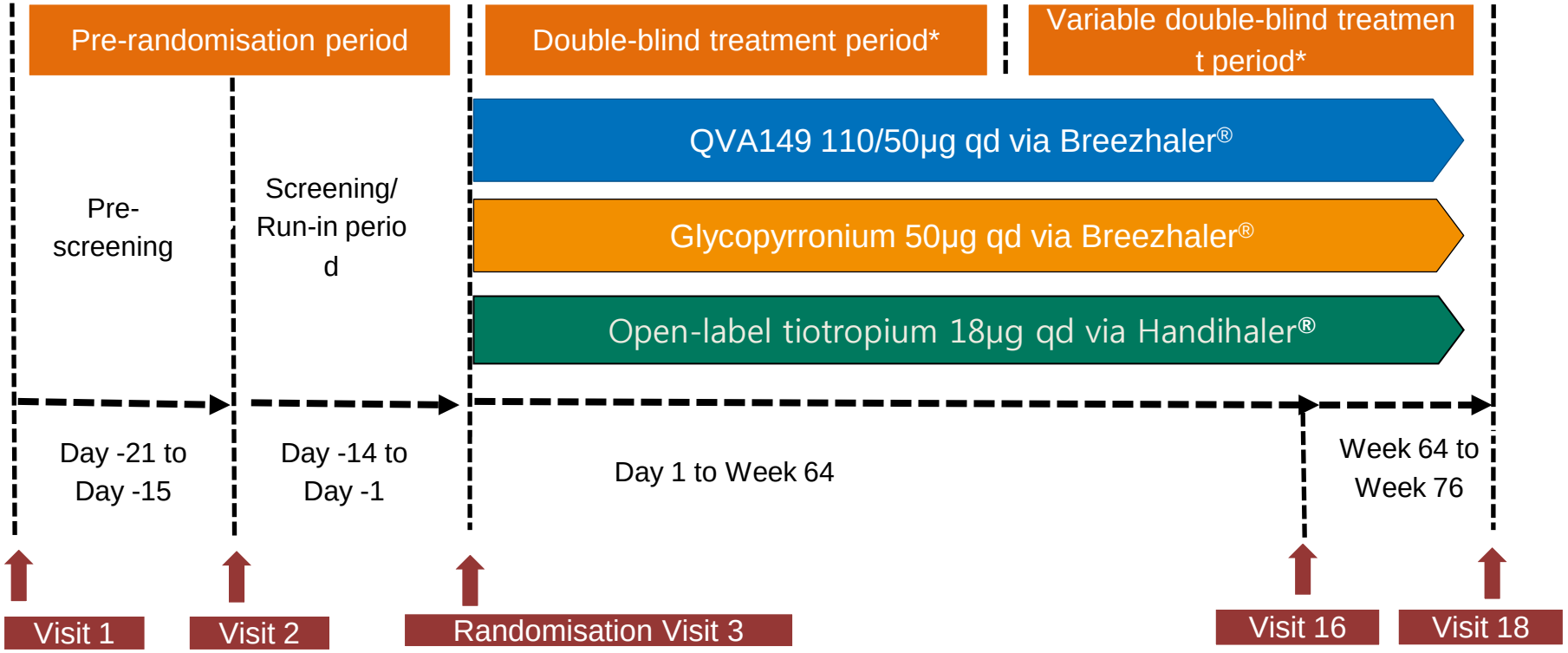
PLCb, phospholipase Cb
GRK2, G-protein-coupled kinase 2;
PKC, protein kinase C;

H. Meurs et al. Pulm Pharma Thera 26 (2013) 145-155

SPARK

Post-bronchodilator FEV_1<50%, mean FEV1 ≈ 37%
History of at least one COPD exacerbation in the previous 12 months

64-week, multicentre, randomised, double-blind, parallel-group and active cont rolled study

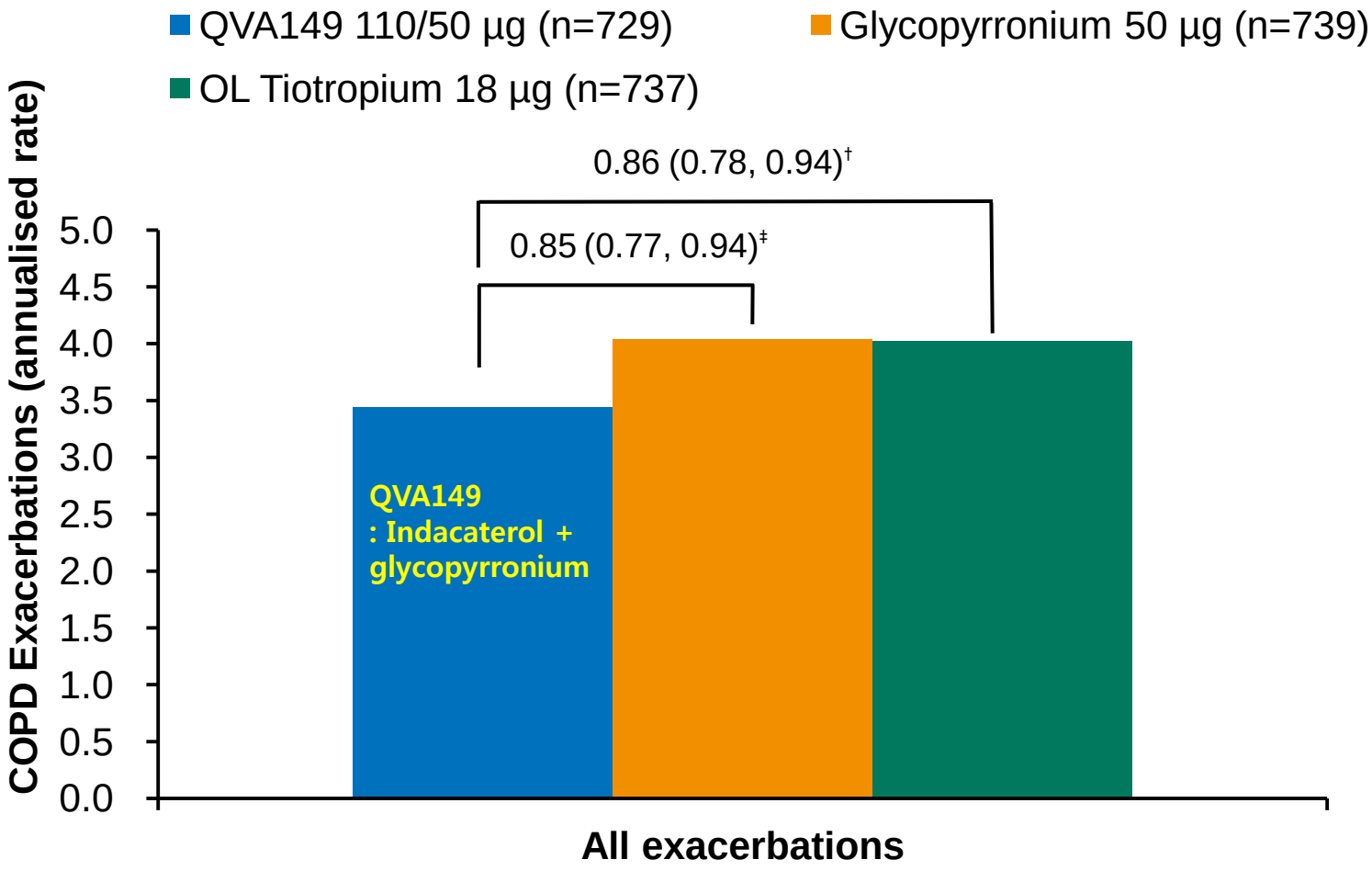


*QVA149 (indacaterol and glycopyrronium) and glycopyrronium both were double-blind treatments, while tiotropium was open-la bel; The double-blind treatment period could be extended to a total of 76 weeks; this extension period was designed to increase t he number of exacerbation events to ensure the study achieved the exacerbation rate prespecified for analysis; Handihaler® is a r egistered device and trademark of Boehringer Ingelheim to deliver tiotropium

Lancet Respir Med. 2013 May;1(3):199-209

QVA149 Vs glycopyrronium Vs tiotropium 18 µg

All (mild, moderate, and severe) exacerbations

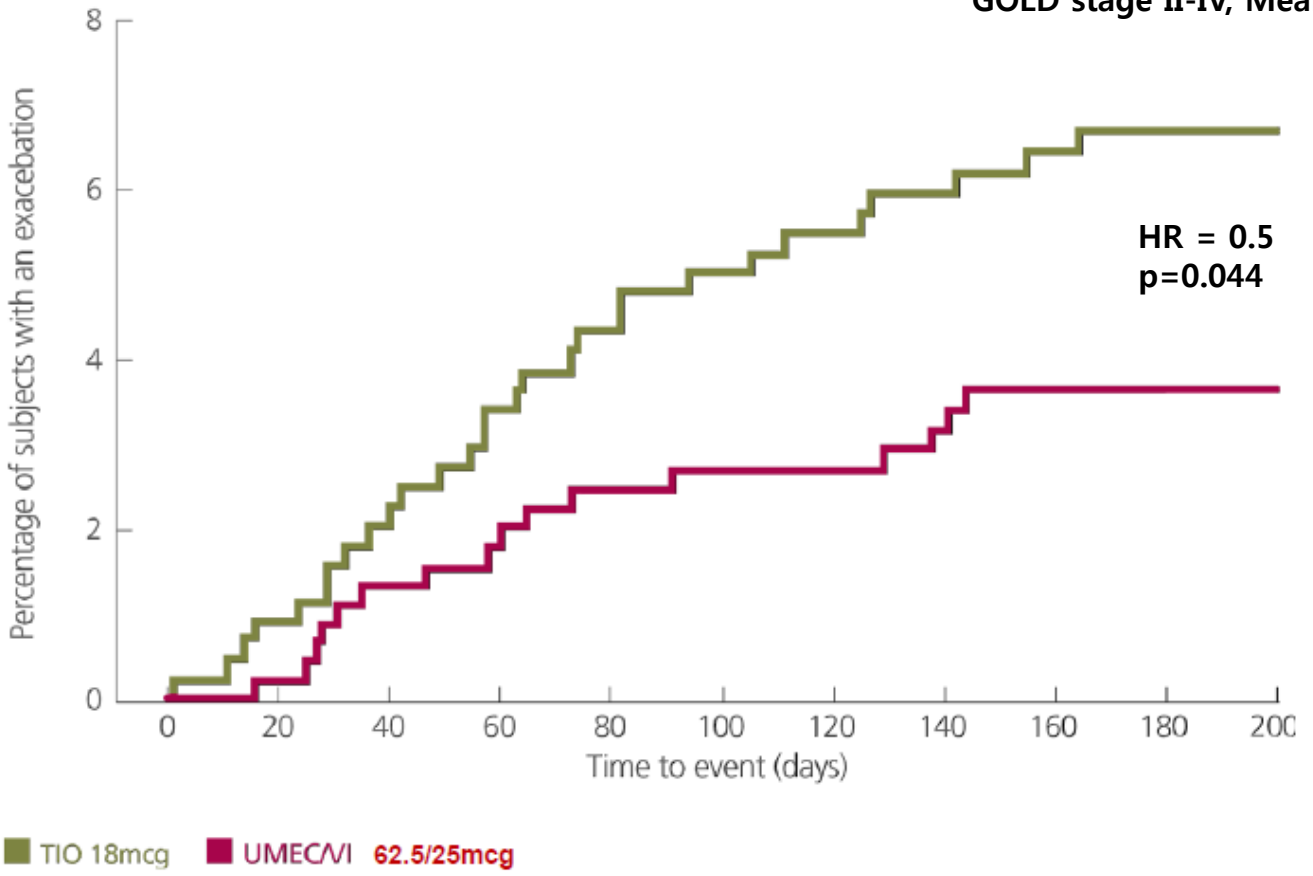


Values are rate reduction (95% CI); n=numbers per treatment group
‡p=0.0012 QVA 149 vs glycopyrronium, †p=0.0017 QVA 149 vs tiotropium

Lancet Respir Med. 2013 May;1(3):199-209

Umeclidinium+vilanterol Vs tiotropium Exacerbations

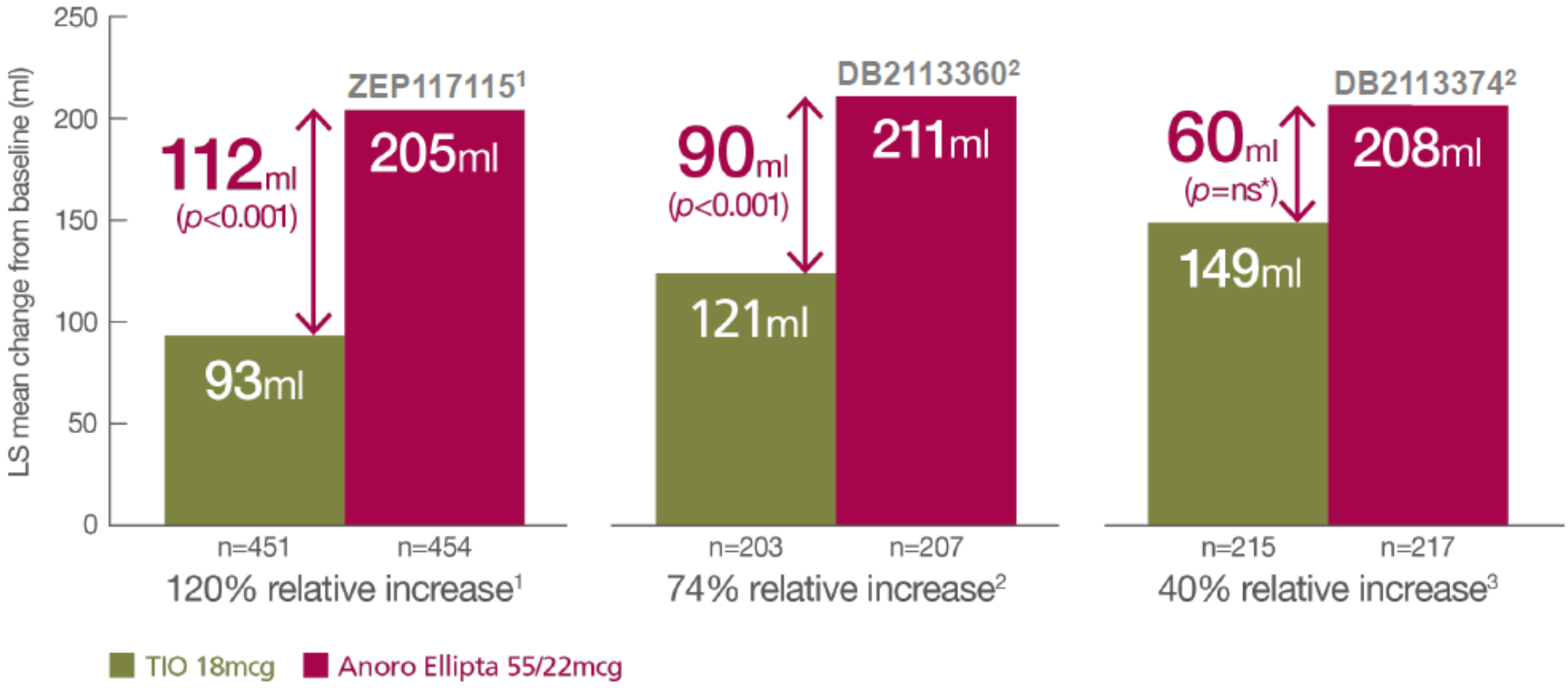
GOLD stage II-IV, Mean FEV1 ≒ 46%



Maleki-Yazdi M, et al. Respiratory Medicine 2014;108:1752

Anoro® Ellipta® 55/22mcg improves lung function compared with TIO

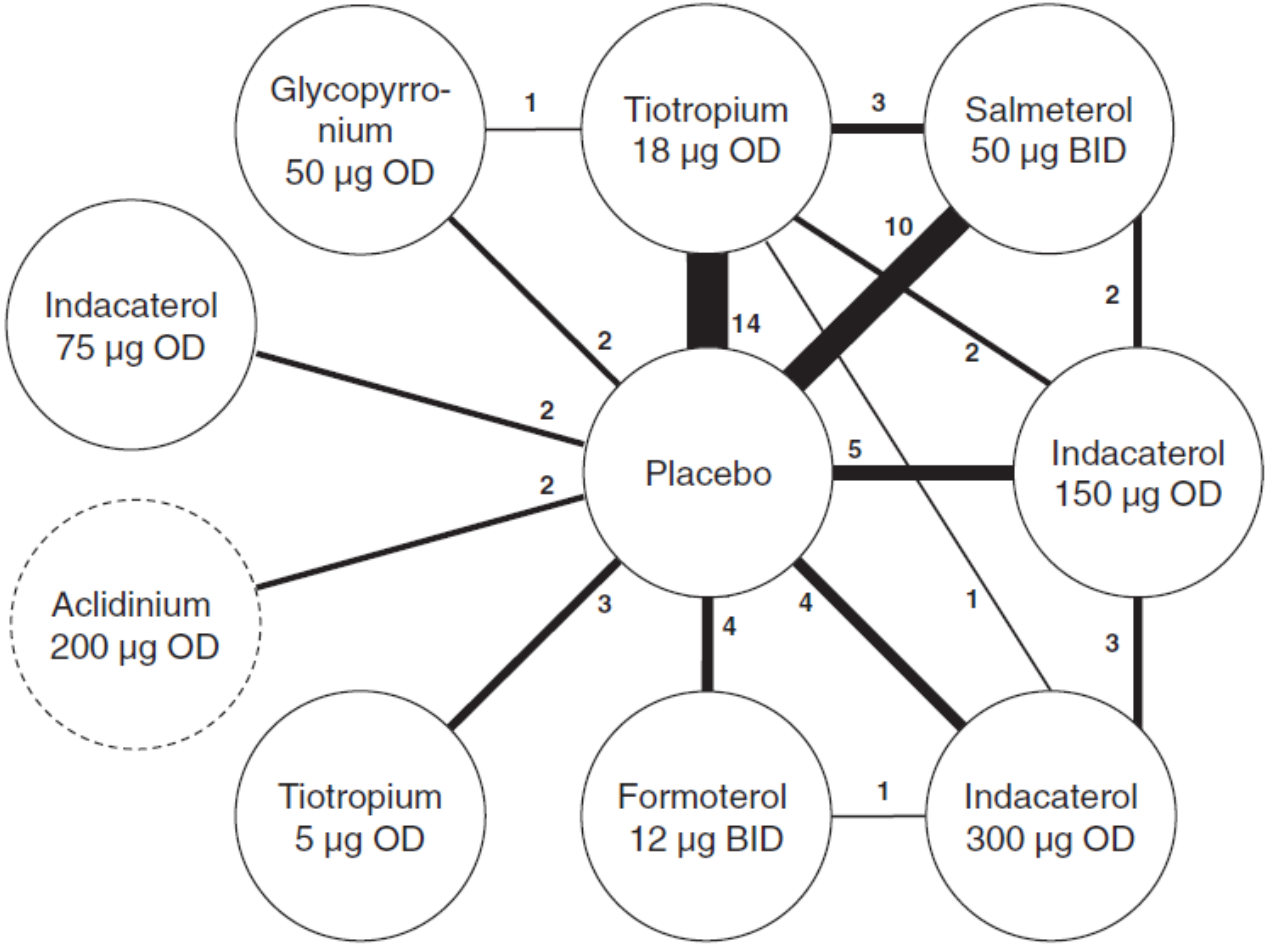
Primary endpoint: Trough FEV_1 at day 169



***Not statistically significant due to hierarchical testing**

1. Maleki-Yazdi et al. Respir Med. 2014;108(12):1752-1760 2. Decramer *et al. Lancet Resp Med* 2014 ; Vol 2 No. 6 pp 472-4486

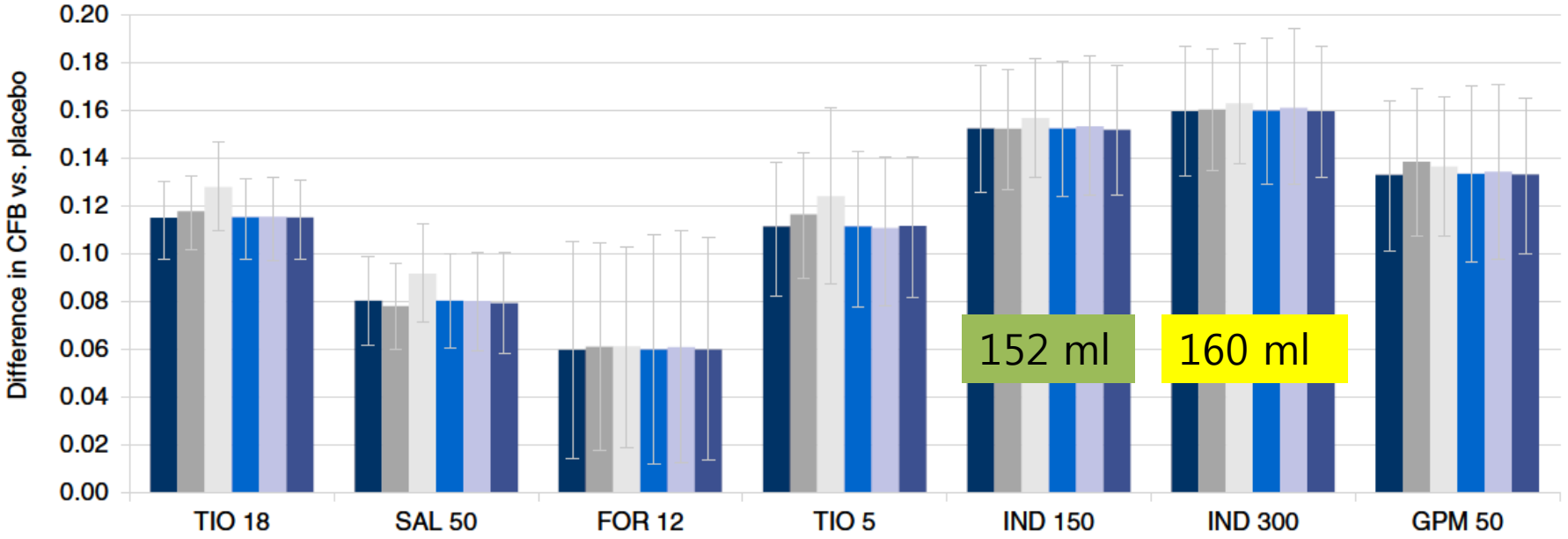
Network of RCTs included in the network meta-analysis



Cope S, et al. Respiratory Research 2013;14:100

Network meta-analysis
Trough FEV1 at 6 months

severe or very severe COPD



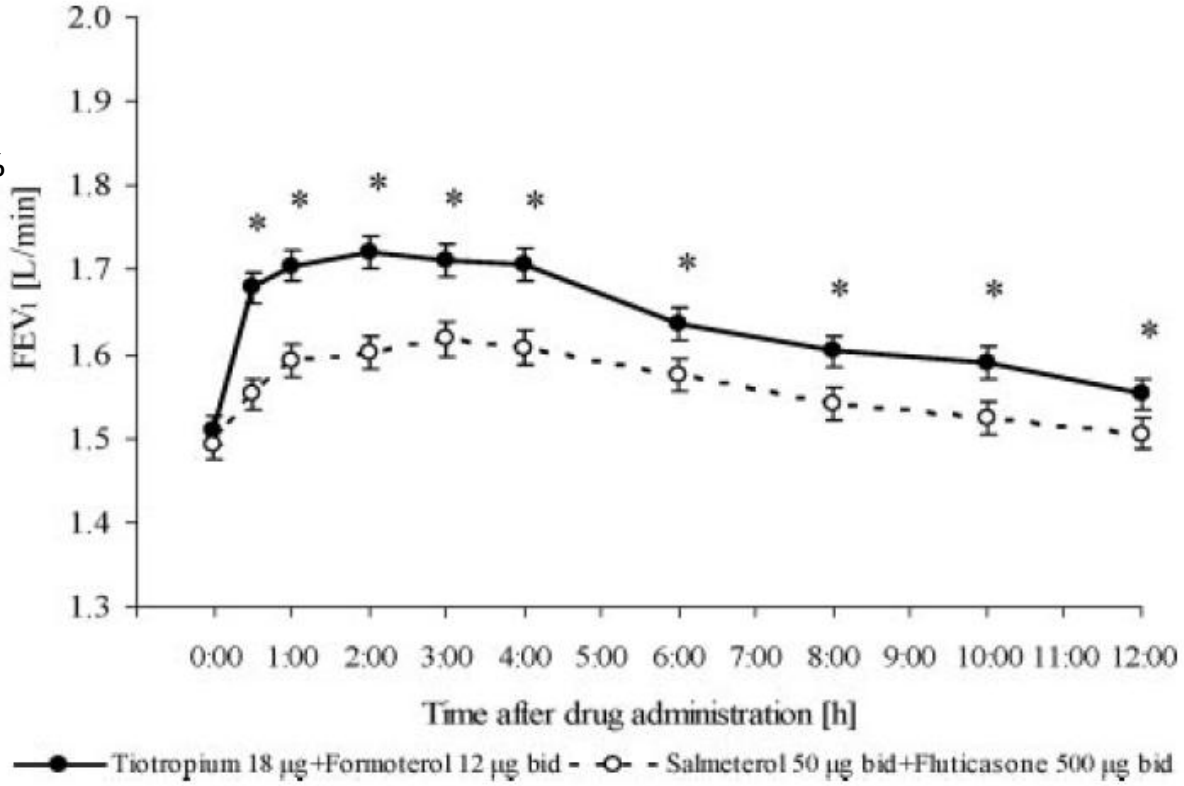
CFB=Change from baseline

Cope S, et al. Respiratory Research 2013;14:100

Tiotropium+Formoterol vs Salmeterol+Fluticasone

6-week, multicenter, randomized, double-blind, parallel-group study

FEV1/FVC 70%
predose FEV1≤ 65%

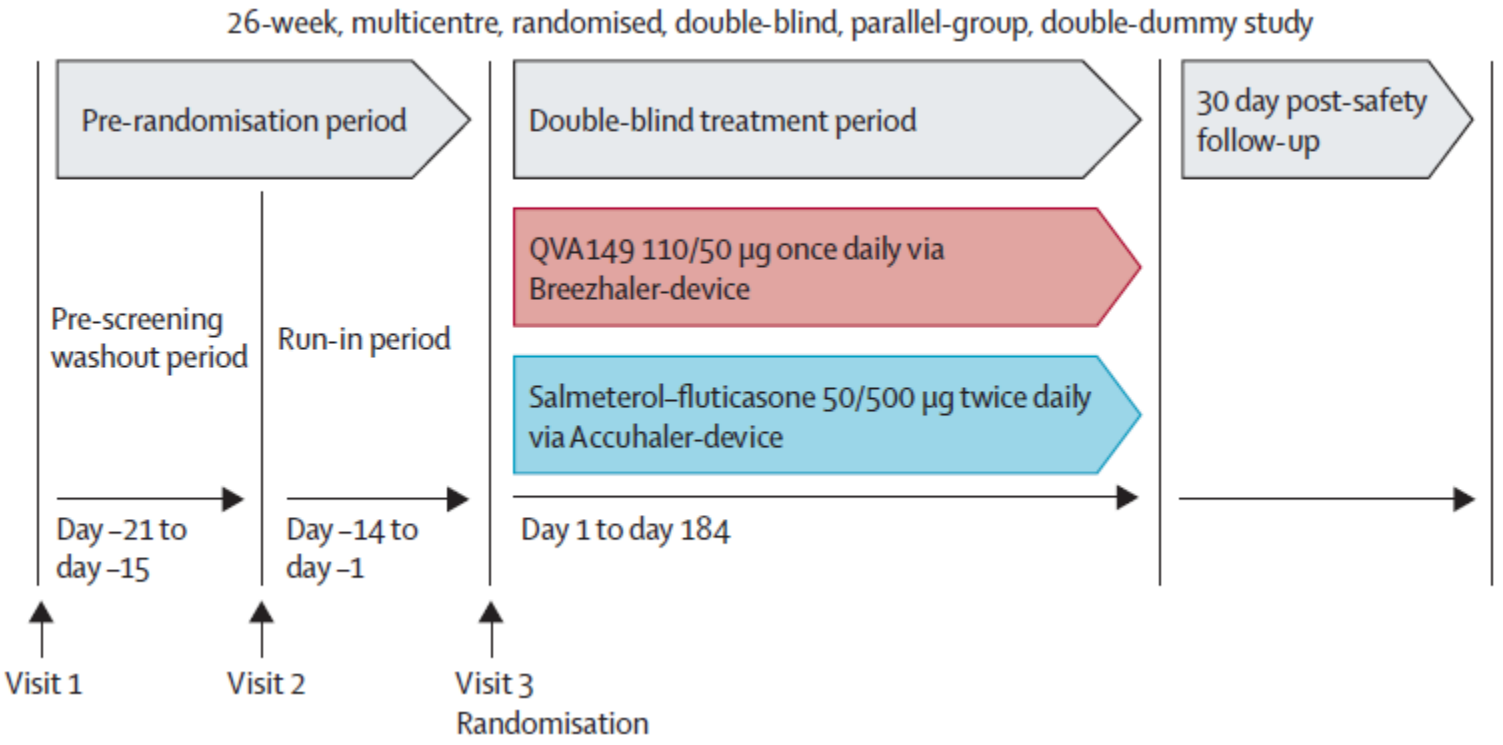


***p < 0.05**

Rabe KF et al. CHEST 2008;134:255-262

ILLUMINATE

post-bronchodilator FEV_1 ≥40% and <80%

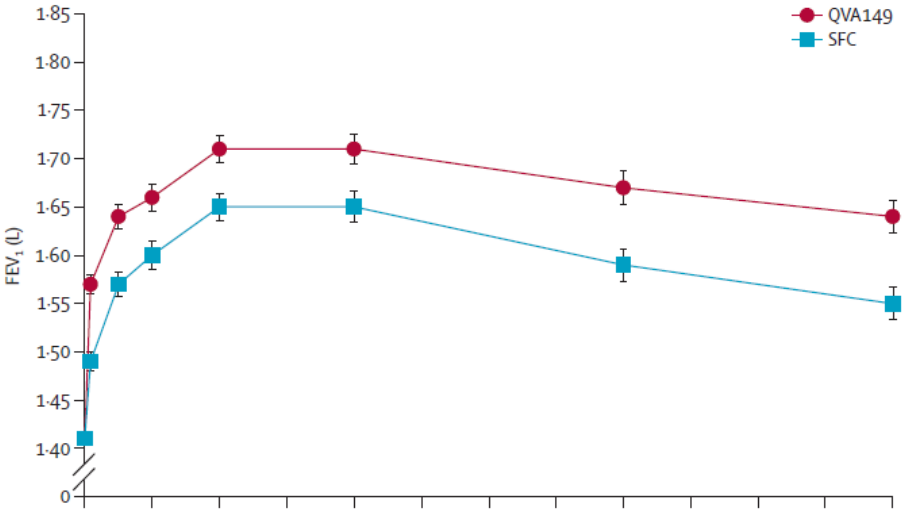


Vogelmeier CF, et al. Lancet Resp Med. 2013;1:51-60

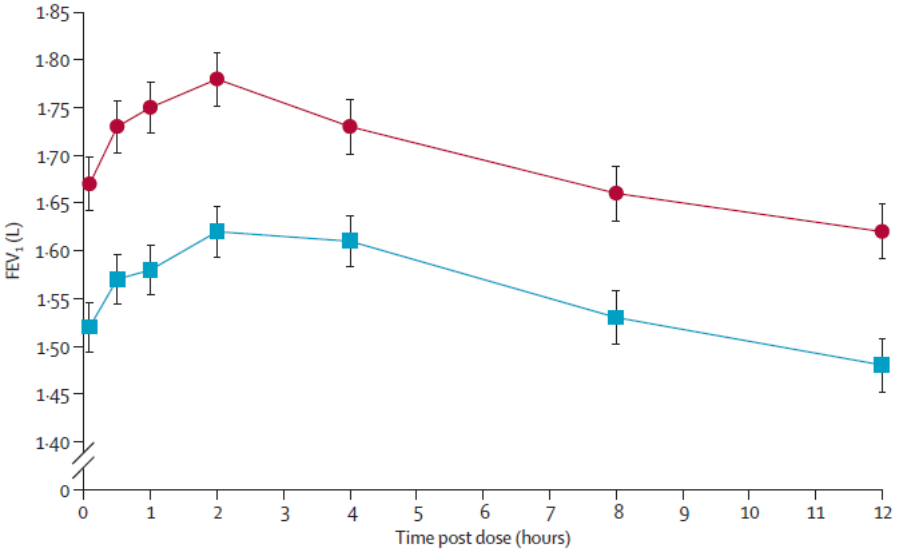
Serial measurements of FEV1

from 0−12 h post dose

Day 1

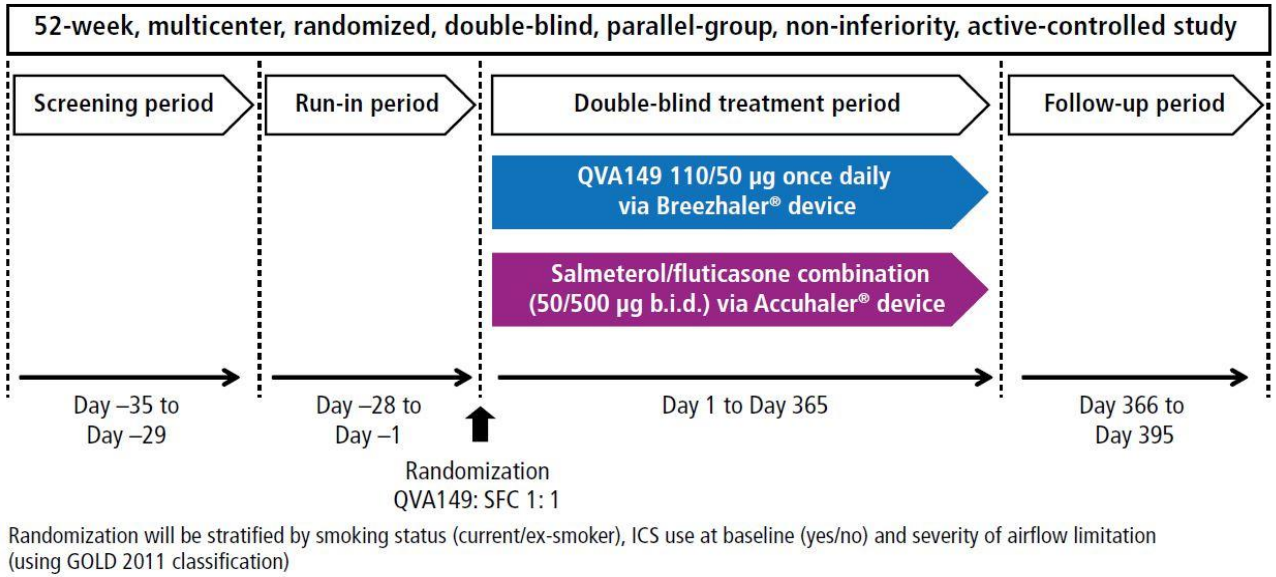


Week 26



Vogelmeier CF, et al. Lancet Resp Med. 2013;1:51-60

FLAME study design



Randomization will be stratified by smoking status (current/ex-smoker), ICS use at baseline (yes/no) and severity of airflow limitation (using GOLD 2011 classification)

moderate to very severe COPD (GOLD 2011)
history of at least 1 COPD exacerbation requiring systemic corticosteroids and/or antibiotics in the previous 12 months
Post-bronchodilator FEV1 ≥25 and <60% of the predicted normal value

Primary objective

Non-inferiority to SFC in terms of rate of all COPD exacerbations (mild/moderate/severe) during 52 weeks of treatment

Conclusion

- The effectiveness of ICS in treating COPD remains doutful, while the benefit observed with combination therapy may be due exclusively to the beneficial effects of the long-acting bronchodilator alone

- Corticosteroid resistance in COPD
  - may be the reduced expression and activity of the HDAC2
- ICS use : increased risk of side effects

Conclusion

- The stepwise withdrawal of glucocorticoids
  - Severe COPD receiving tiotropium + salmeterol
  - Risk of moderate or severe exacerbations was similar among those who discontinued ICS & those who continued glucocorticoid therapy
  - Decreased in lung function during the final step of glucocorticoid withdrawal
  - But, we have new weapons Now !

감사합니다