THE CASE FOR INHALED CORTICOSTEROIDS IN THE MANAGEMENT OF COPD

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NOT EVERYONE CAN COPE WITH ADVANCES IN MEDICINE

- Harvey was pilloried for his preposterous suggestion that blood circulated – The Misanthrope
- Semmelweiss was forced from Vienna for advocating hand washing in the delivery room
- Haldane was convinced that the lungs secreted oxygen by an active process
- Numerous chest doctors doubted that triple therapy could cure TB

and today?

CONSIDER THE EVIDENCE

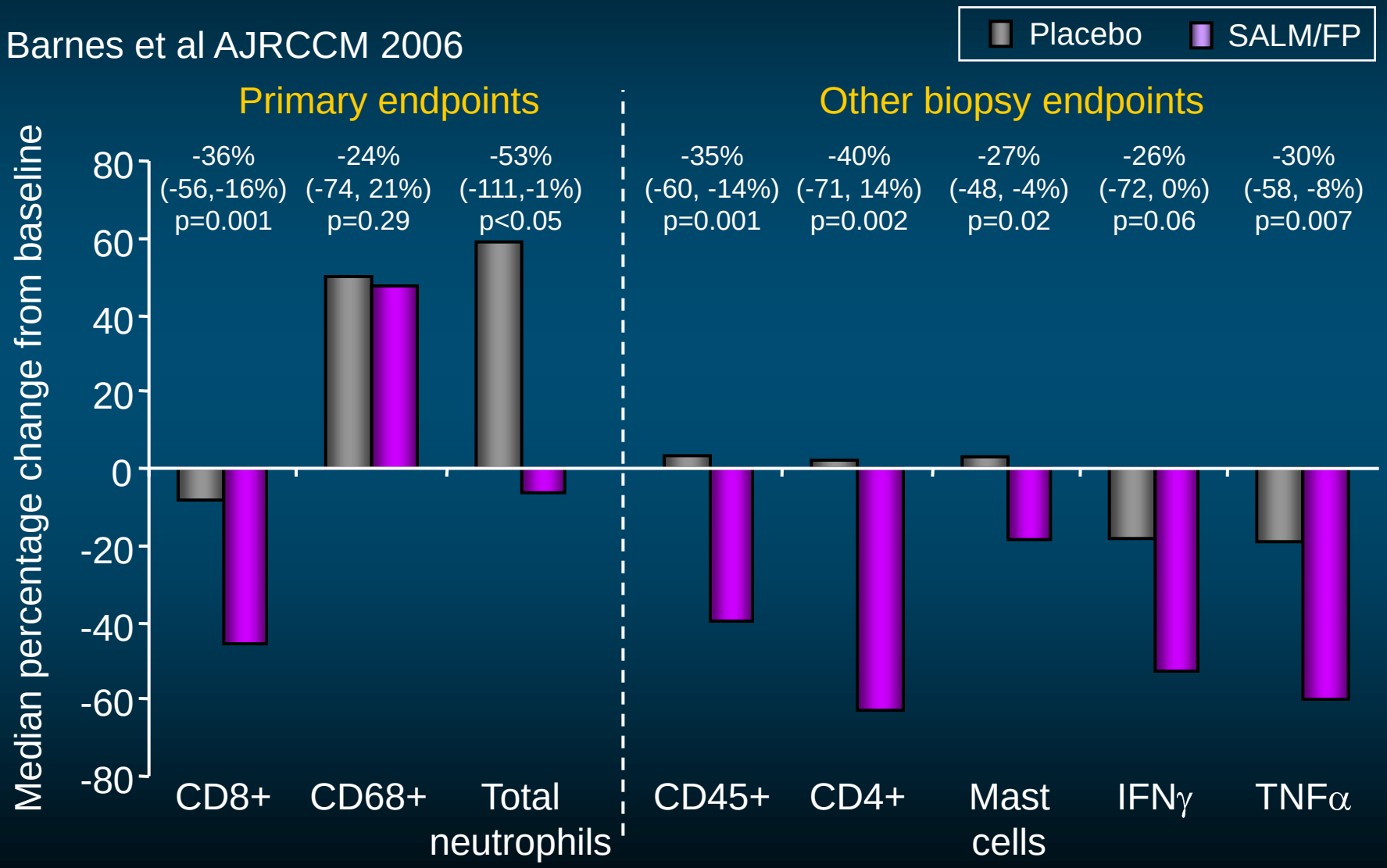
- Mechanism
- Clinical trials
- Comparative studies
- Risks

An anti-inflammatory effect of treatment?

- No convincing effect on inflammatory cells from COPD patients –HDAC2
- Difficult to establish with short (6 weeks) corticosteroid treatment in stable COPD
- Role of prior therapy, statistical power
- No effect on biopsy or induced sputum measures
- GLUCOLD in very selected patients with 3 year follow up suggests that there is an anti-inflammatory effect
- 3 studies with combinations of LABA/ICS were positive

PERCENTAGE CHANGE FROM BASELINE IN BIOPSY AND SPUTUM ENDPOINTS

Barnes et al AJRCCM 2006



p-values relate to median difference between SALM/FP and placebo. No adjustments made for multiplicity

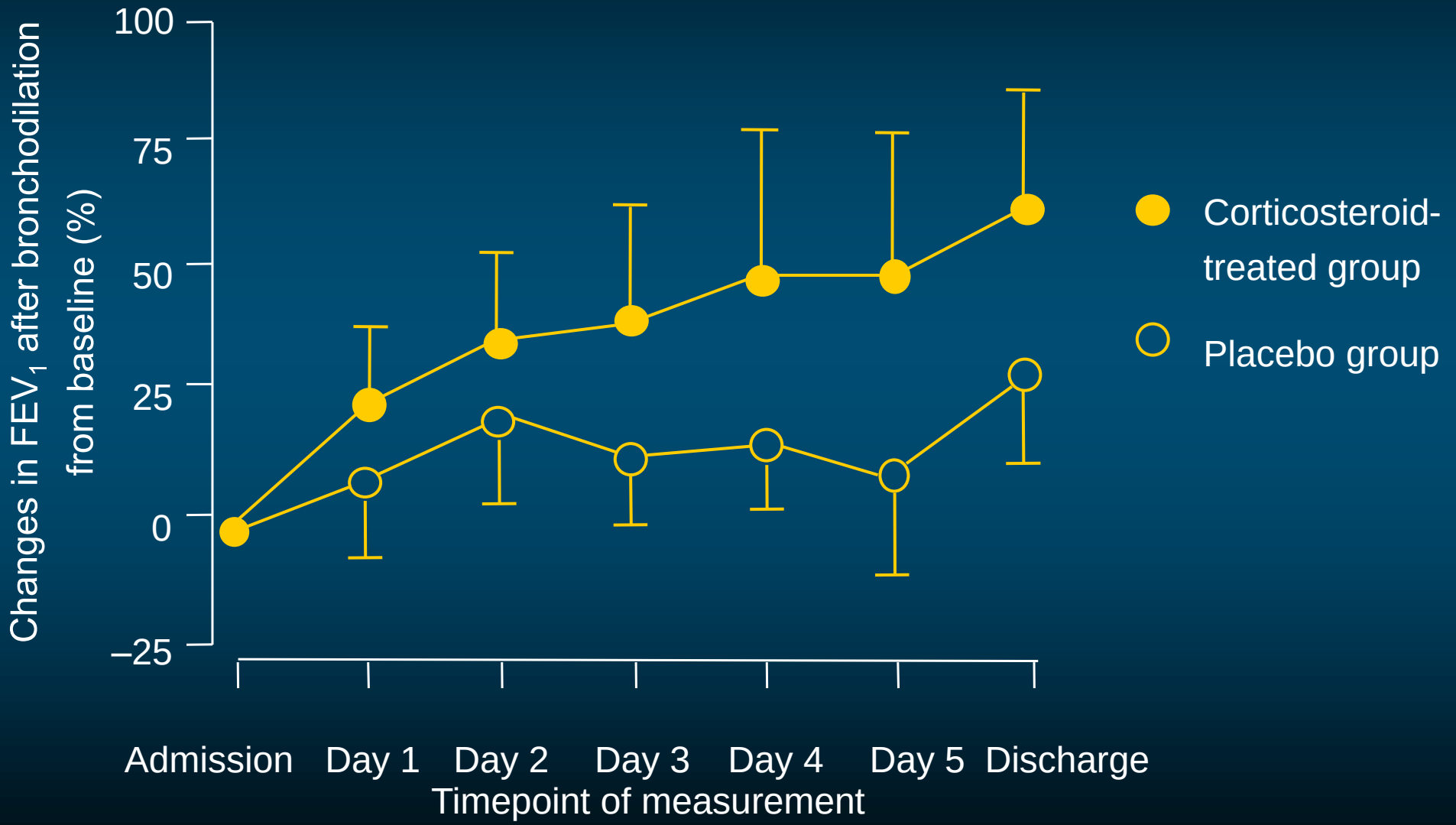
Inflammation may not be the only target

- Decrease in airway oedema –skin blanching for potency
- Up regulation of down –regulated beta-receptors: a role wit LAMAs

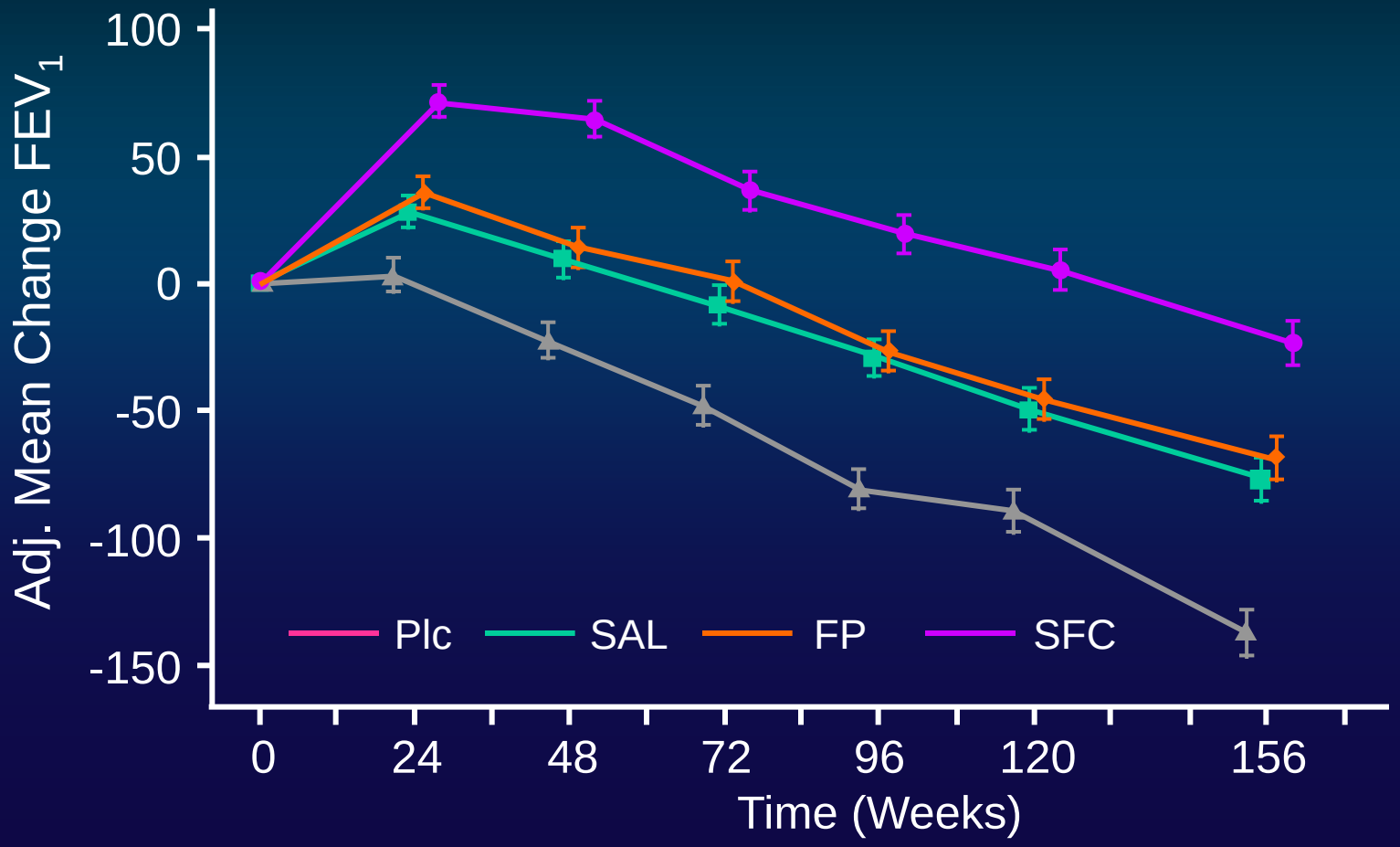
CLINICAL TRIALS –BENEFITS AND COMPARISONS

ORAL STEROIDS AT COPD EXACERBATION

Davies et al Lancet 1999



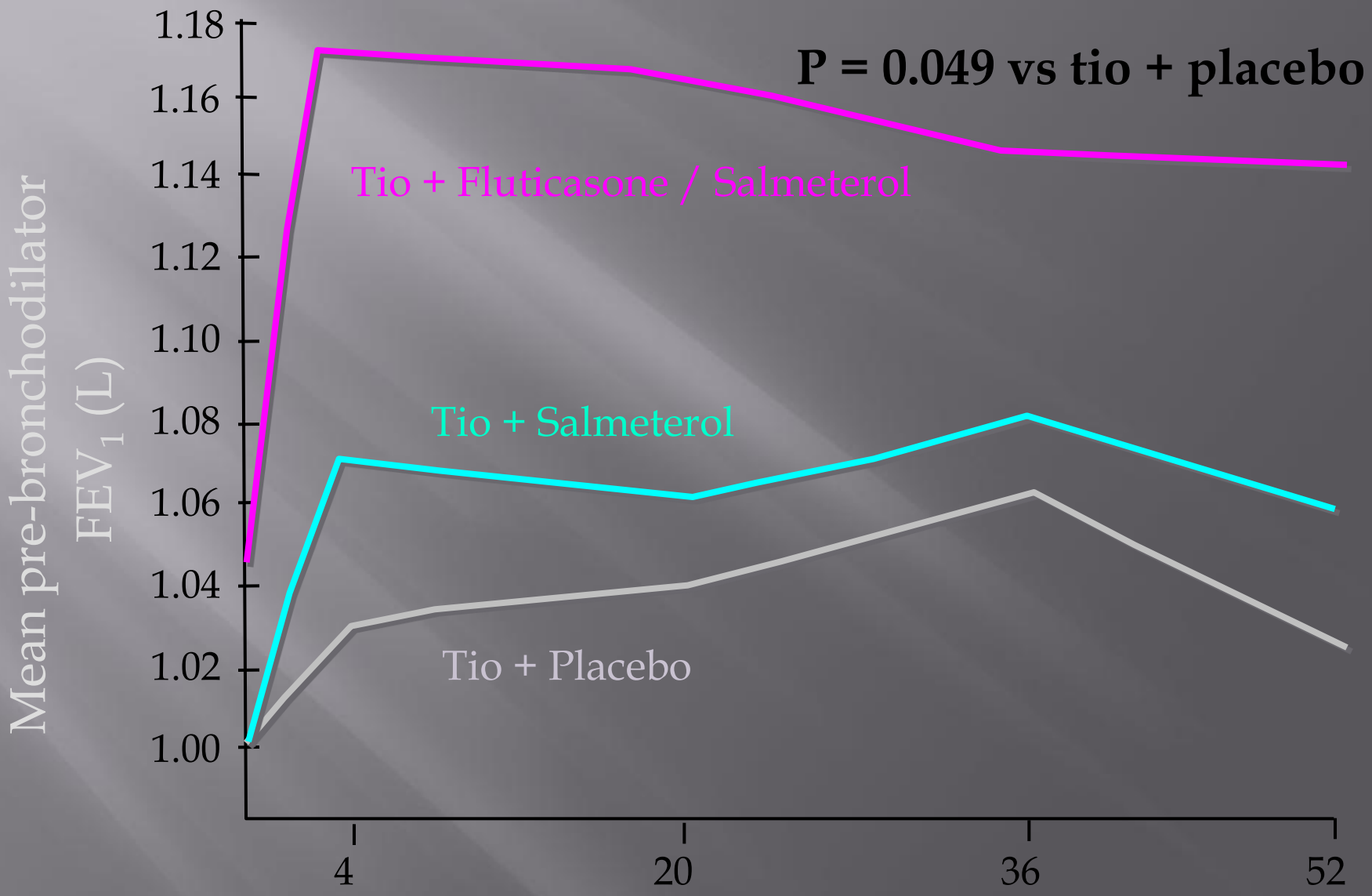
TORCH - Post Bronchodilator FEV_1 (mL)



Number of Subjects							
Plc	1524	1248	1128	1049	979	906	819
SAL	1521	1317	1218	1127	1054	1012	934
FP	1534	1346	1230	1157	1078	1006	908
SFC	1533	1375	1281	1180	1139	1073	975

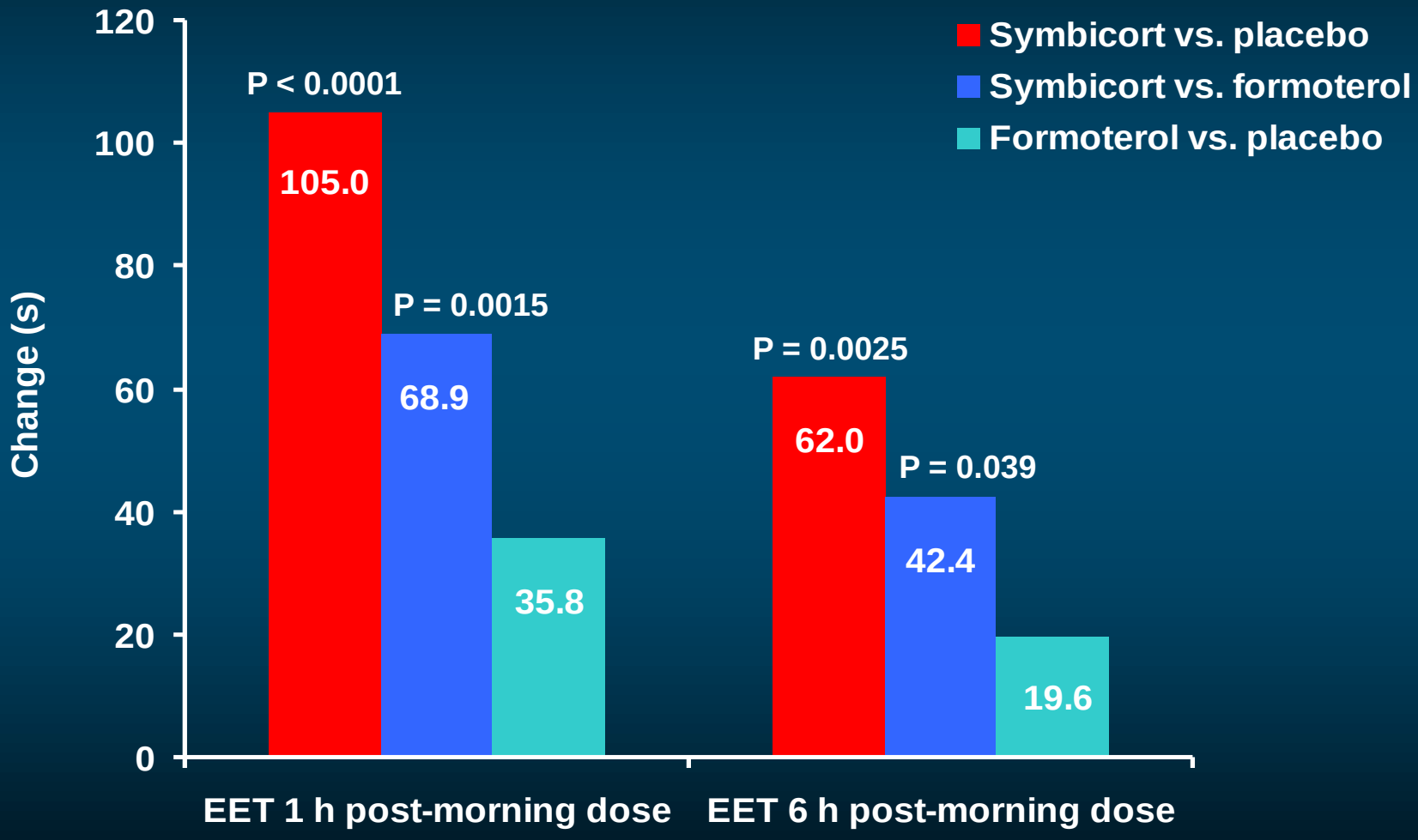
Vertical bars represent standard errors

One year changes in lung function:

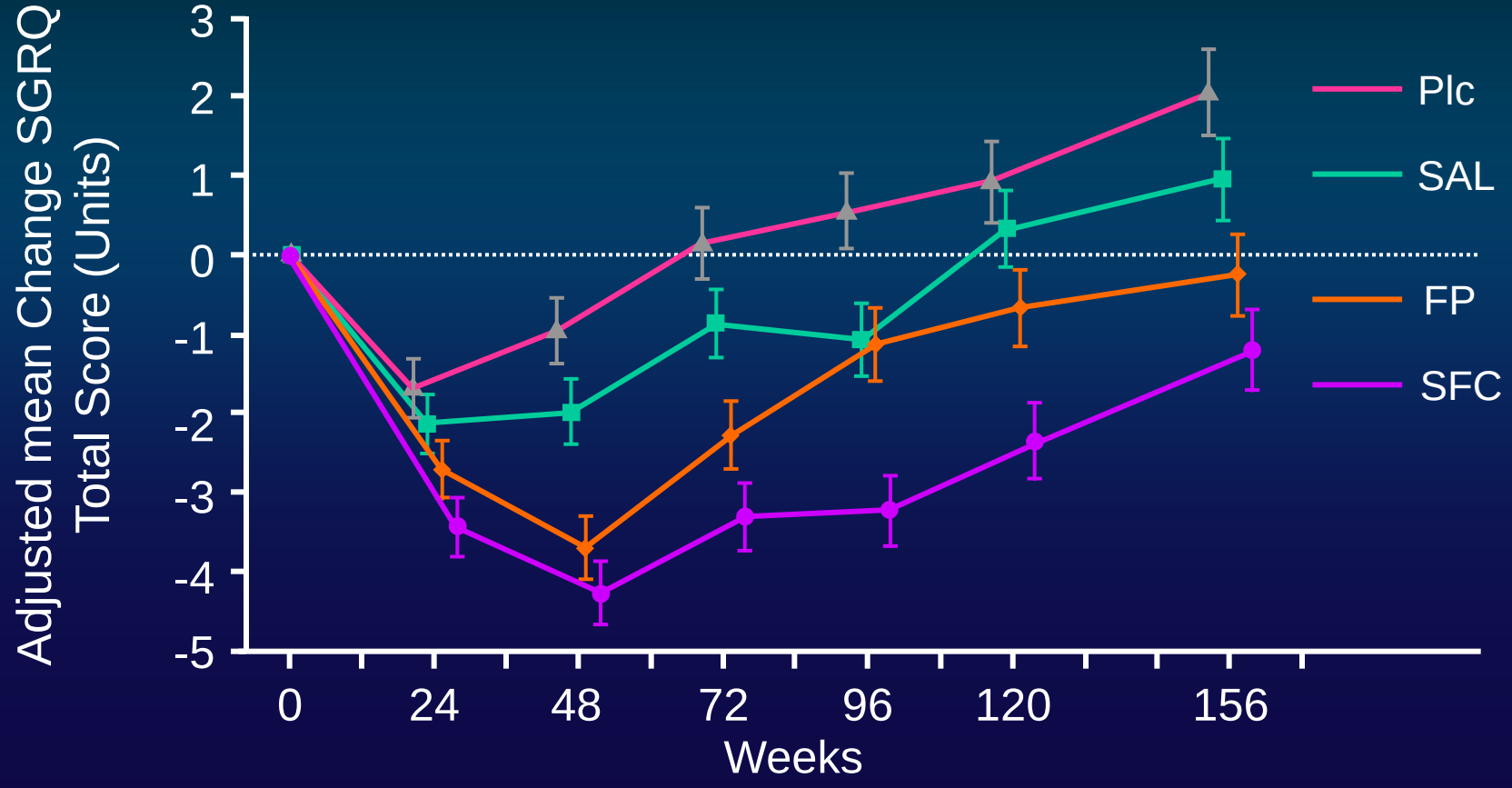


Aaron et al Ann Intern Med 2007

Treatment comparison for exercise endurance times (EET)



Results
SGRQ Total Score

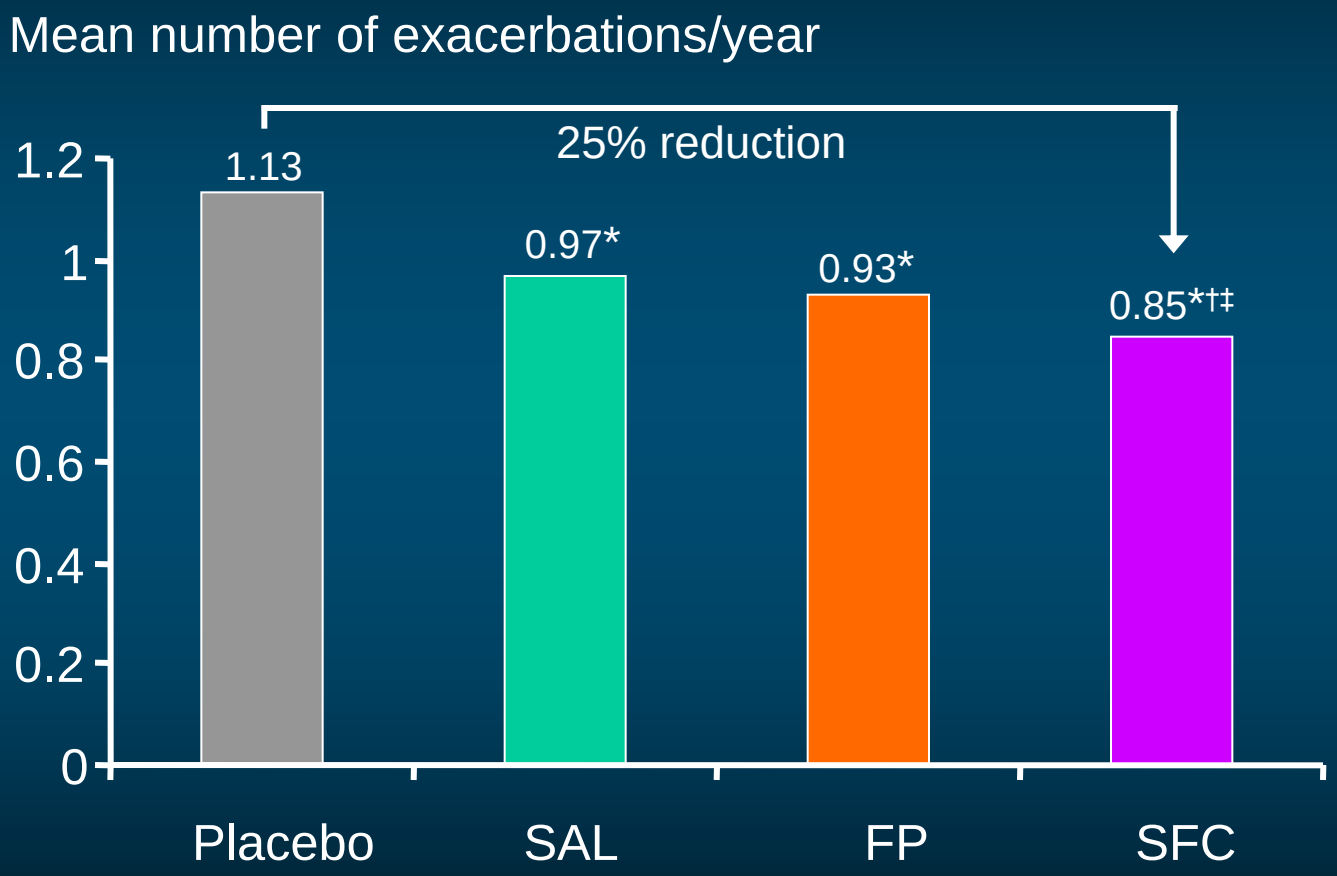


Number of Subjects							
	1149	854	781	726	675	635	569
	1148	906	844	807	723	701	634
	1155	942	848	807	751	686	629
	1133	941	873	814	773	731	681

Vertical bars represent standard errors

HO Pop Source Figure: 7.3.004

Rate of moderate and severe exacerbations over three years

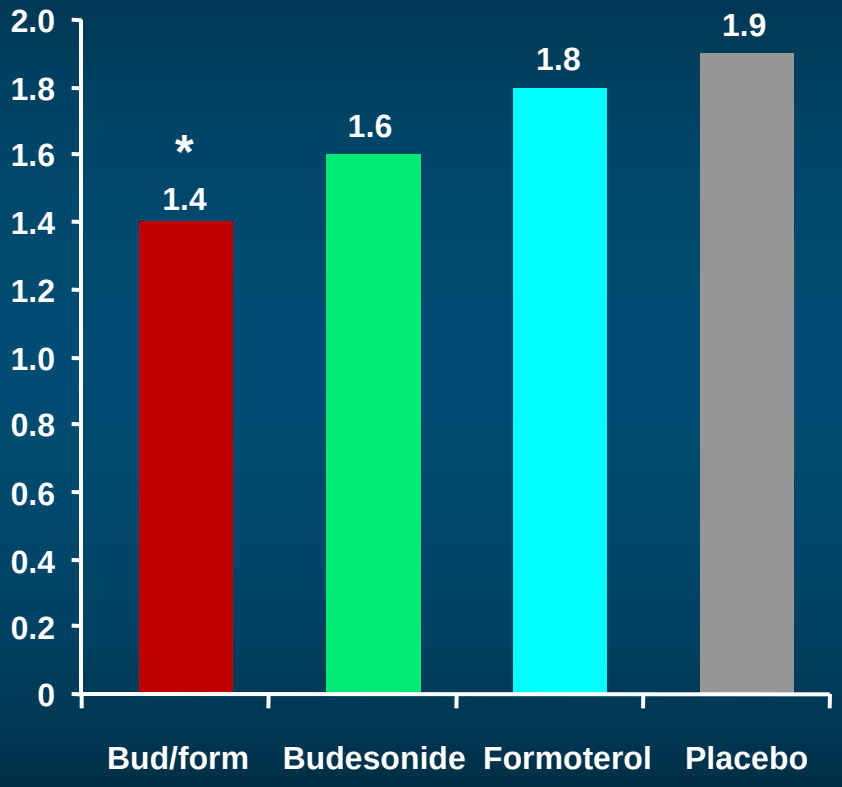


*p < 0.001 vs placebo; †p = 0.002 vs SAL; ‡p = 0.024 vs FP

Bud/form reduces moderate/ severe exacerbations

Mean no. of severe exacerbations/ patient/year

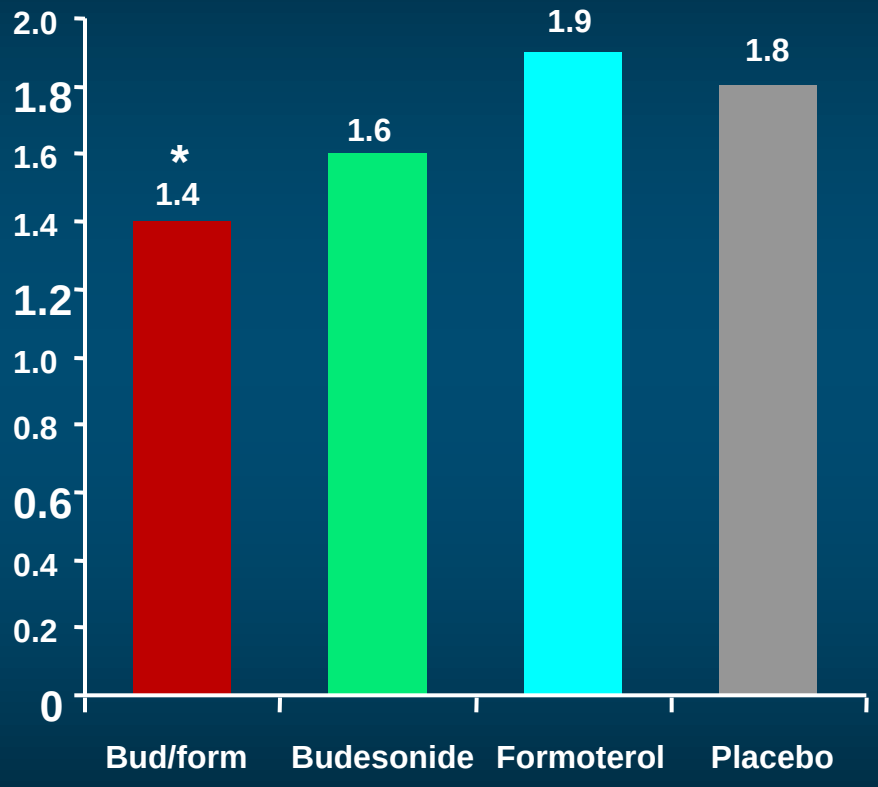
Szafranski



*p<0.05 vs placebo

p=0.043 Bud/form vs formoterol

Calverley

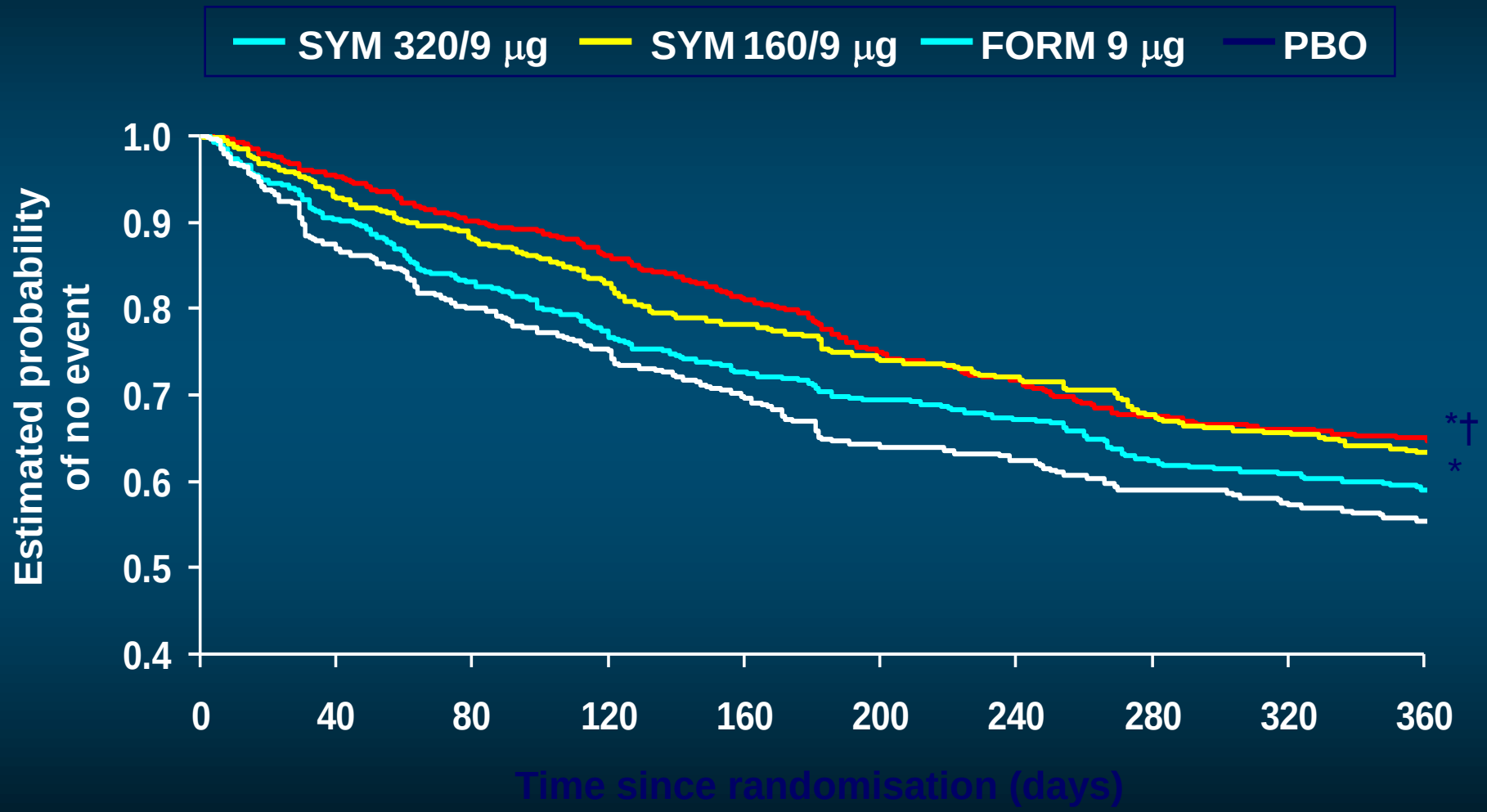


*p<0.05 vs placebo

p=0.015 Bud/form vs formoterol

Time to first COPD exacerbation

Kaplan–Meier probability curves



FORM = formoterol; PBO = placebo; SYM = Symbicort.;
* $P \leq 0.004$ vs. PBO; † $P = 0.026$ vs. FORM

Rennard SI, et al. Drugs 2009; 69: 549-565.

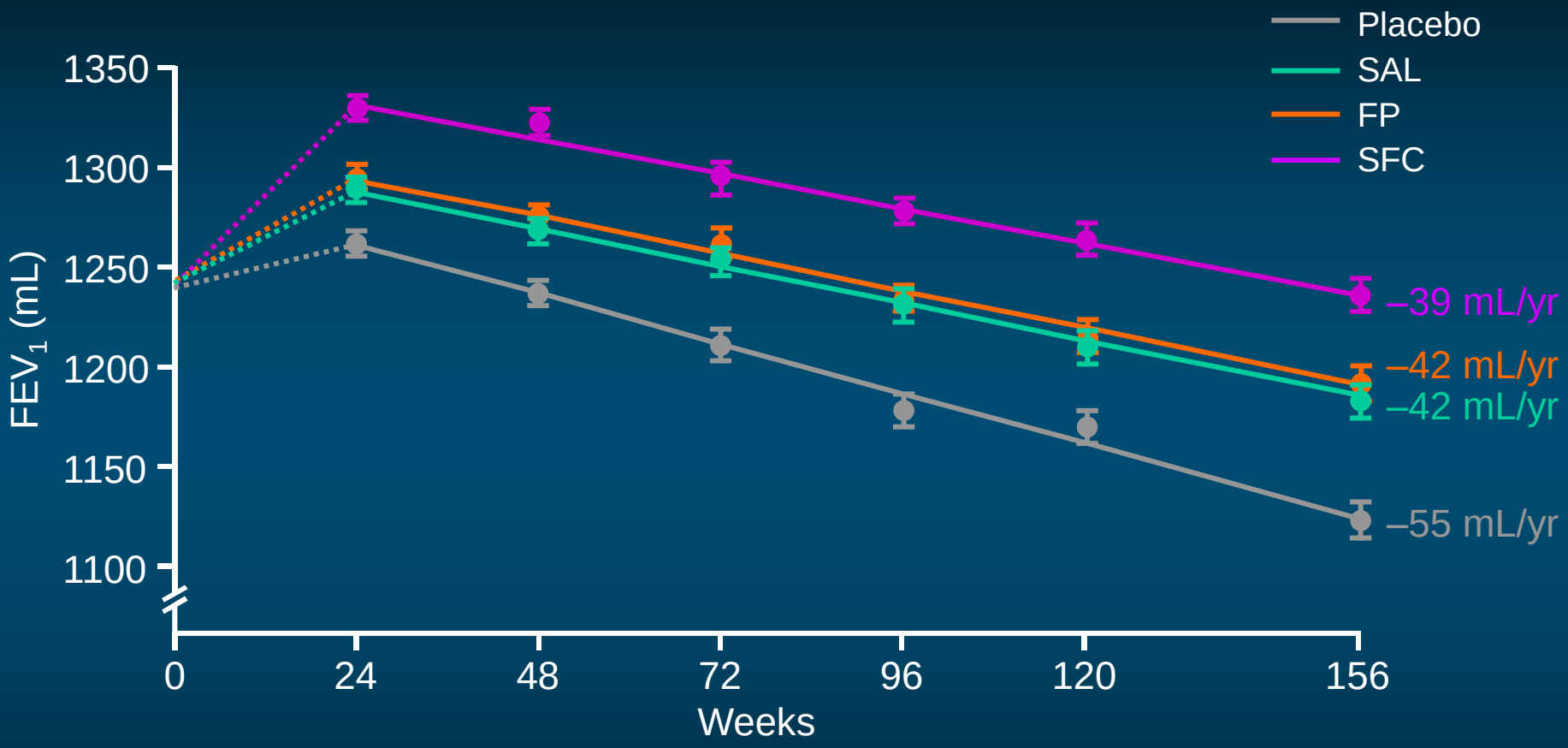
Rate of healthcare utilization exacerbations

	SFC 50/500 (n=658)	TIO 18 (n=665)	Rate Ratio (CI)	P value
Rate of all HCU exacerbations	1.28	1.32	0.97 (0.84 to 1.12)	0.656
HCU exacerbations requiring oral corticosteroids	**0.69**	**0.85**	**0.81 (0.67 to 0.99)**	**0.039**
HCU exacerbations requiring antibiotics	**0.97**	**0.82**	**1.19 (1.02 to 1.38)**	**0.028**

There is a shift in the character of the exacerbations: more antibiotics with SFC, more OCS with tiotropium

Wedzicha JA, *et al*. AJRCCM *2008*

Rate of decline in lung function: effect of treatment

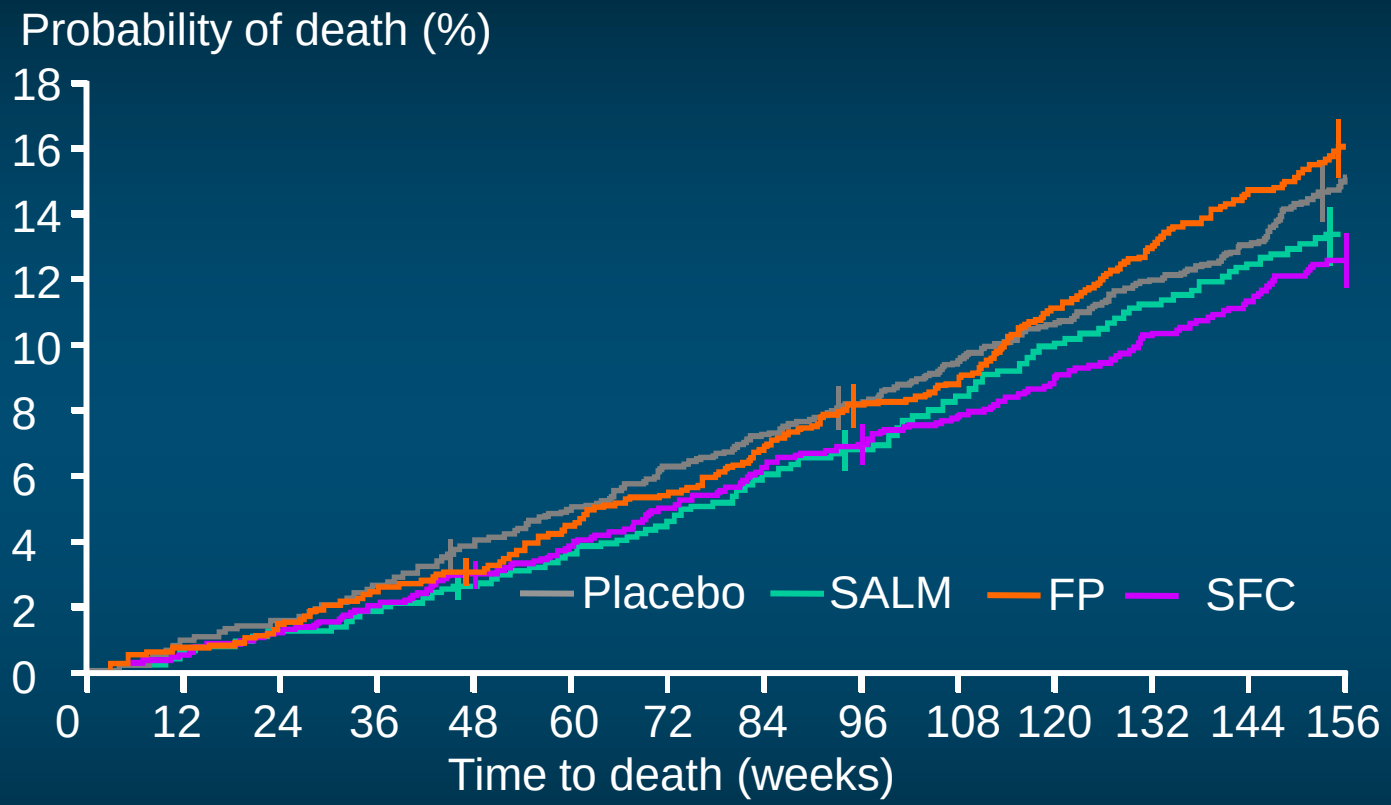


No. of patients						
1261	1248	1128	1049	979	906	819
1334	1317	1218	1127	1054	1012	934
1356	1346	1230	1157	1078	1006	908
1392	1375	1281	1180	1139	1073	975

Vertical bars are standard errors

Celli et al AJRCCM 2008

All-cause mortality at 3 years

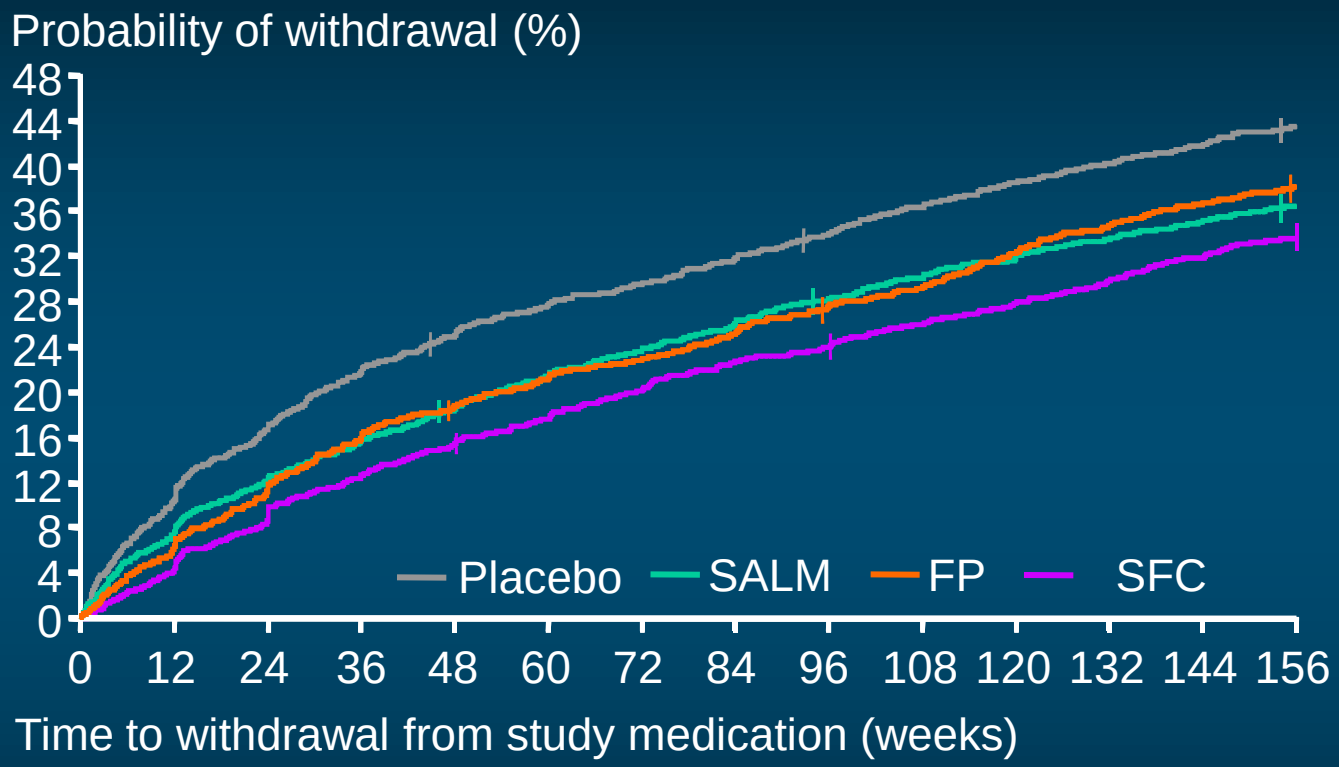


Number alive				
	1524	1464	1399	1293
	1533	1487	1426	1339
	1521	1481	1417	1316
	1534	1487	1409	1288

Vertical bars are standard errors

Calverley *et al.* NEJM 2007

Premature study drug discontinuation - TORCH

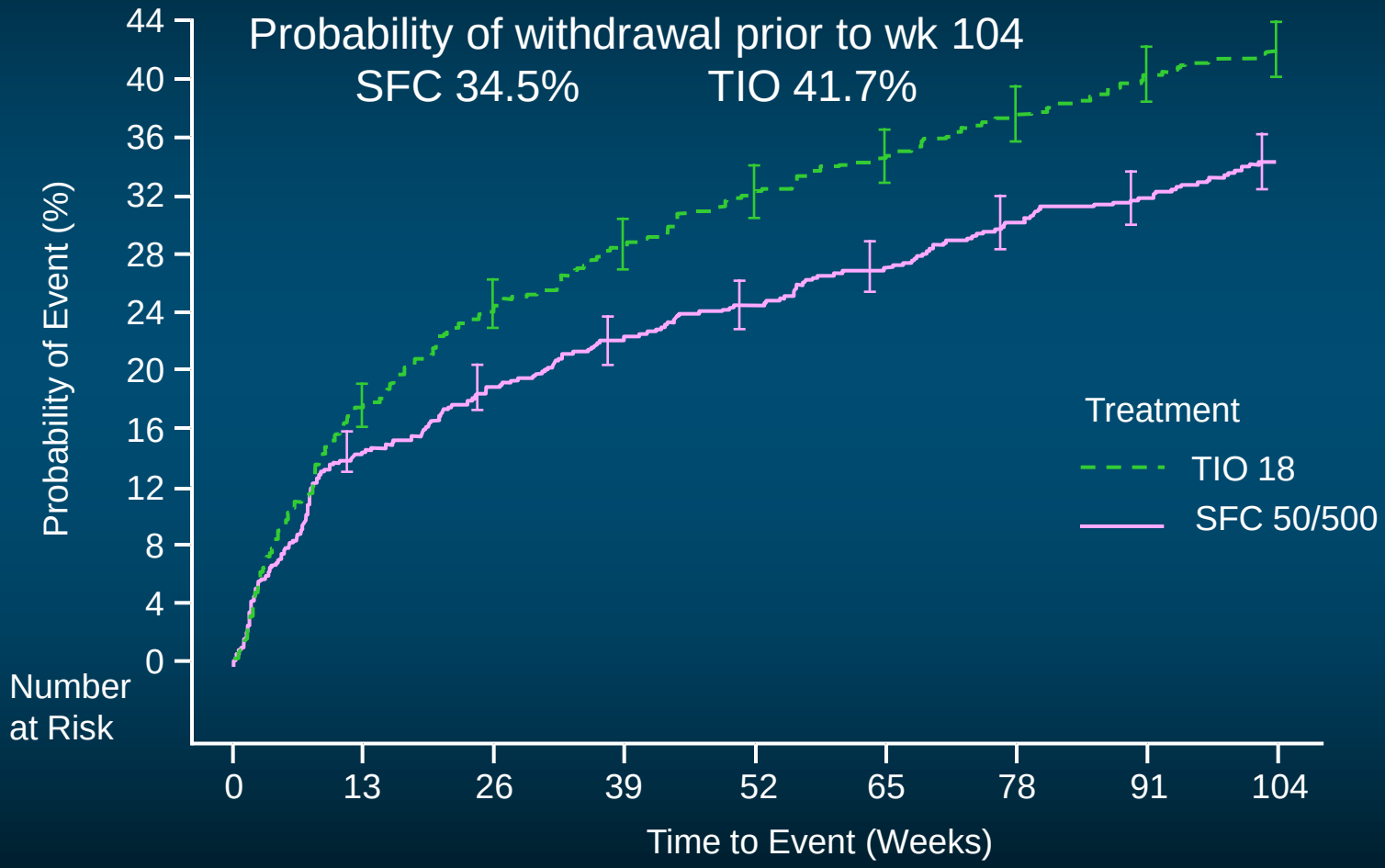


Number at risk				
Placebo	1524	1141	1005	884
SALM	1521	1240	1093	986
FP	1534	1247	1112	971
SFC	1533	1296	1164	1042

Statistical comparisons: SALM/FP, SAL & FP vs placebo $p < 0.001$; SALM/FP vs SAL $p = 0.048$; SALM/FP vs FP $p = 0.01$
Vertical bars are standard errors

Calverley *et al.* NEJM 2007

Time to withdrawal - INSPIRE



	Cox Hazard Ratio	95% CI	p-value
TIO vs SFC	1.29	(1.08 – 1.54)	0.005

Wedzicha JA, *et al*. AJRCCM *2008*

OPTIMAL study withdrawals

- 46% of patients in the TIO/placebo,
- 43% of patients in the TIO/salmeterol arm and
- 26% of patients in the SFC/TIO arm withdrew

Aaron et al Ann Intern Med 2007

ADVERSE EVENTS

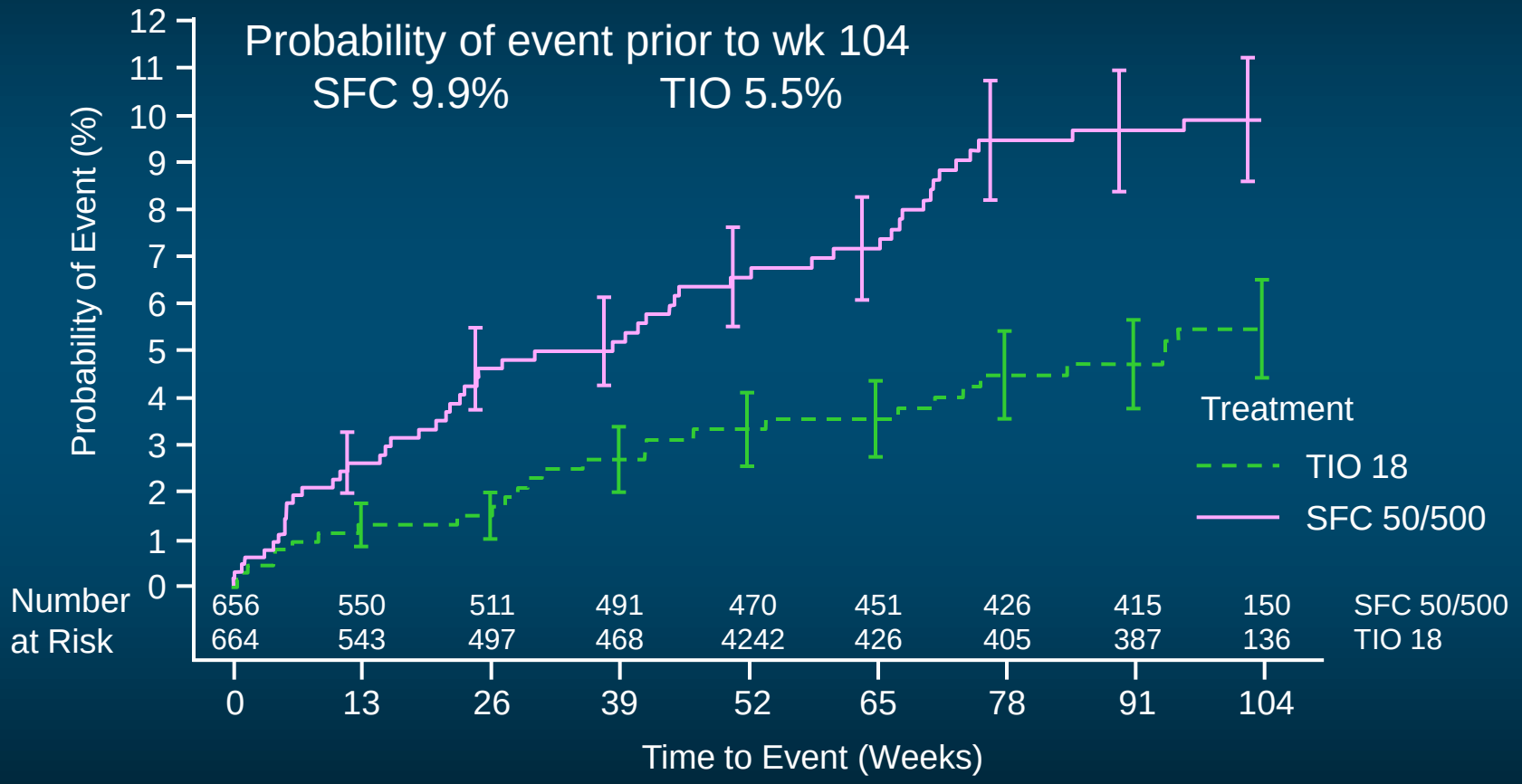
- No significant anticipated side effects in TORCH – bones, eyes etc.
-
- Prospective DEXA scanning did not identify increase in development of osteoporosis /osteopaenia
- Physician-reported pneumonia significantly more frequent with fluticasone
- Budesonide data over one year now available

Most common AEs beginning on treatment: Rate per treatment year

	Placebo (N = 1544)	SALM (N = 1542)	FP (N = 1552)	SFC (N = 1546)
COPD exacerbations	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02

Calverley *et al.* NEJM 2007

Time to First Pneumonia AE



	Cox Hazard Ratio	95% CI	p-value
SFC vs TIO	1.94	(1.19, 3.17)	0.008

Results: analysis of pneumonia reports according to treatment

Rule-based definition		
No. pneumonias	**SFC**	**Tio**
After HCU exacerbation	16	3
After untreated symptomatic exacerbation	20	4
De novo	22	16

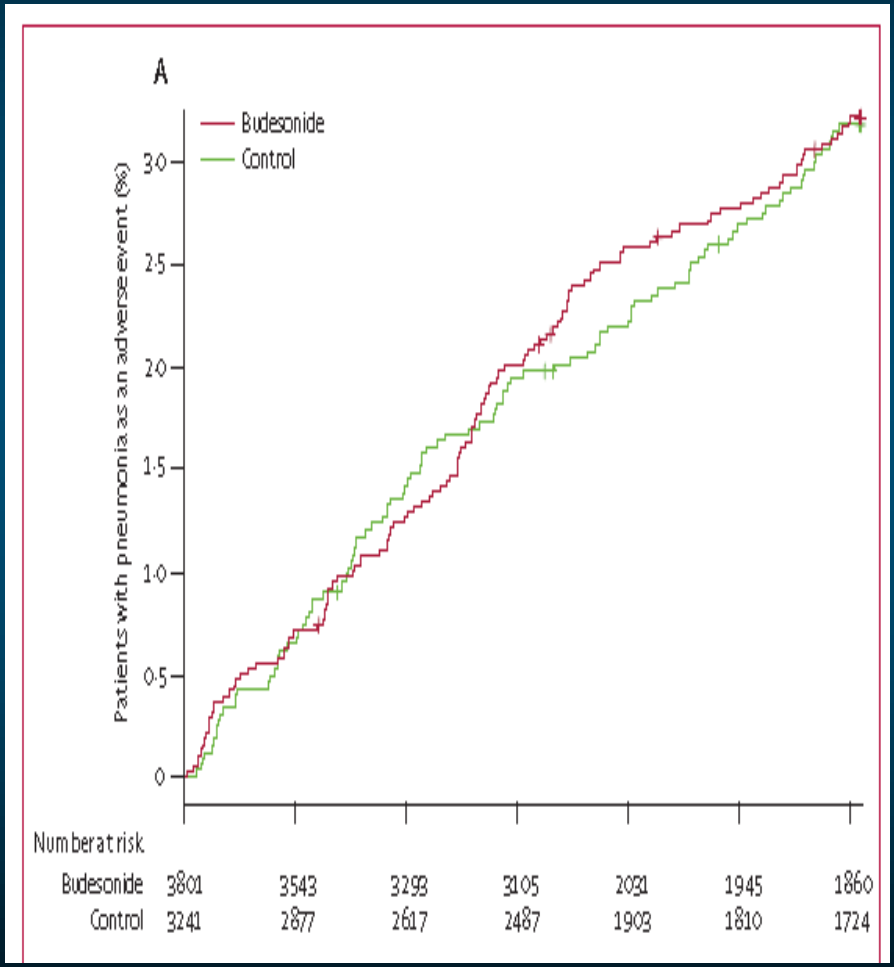
Calverley P *et al*, Chest 2010

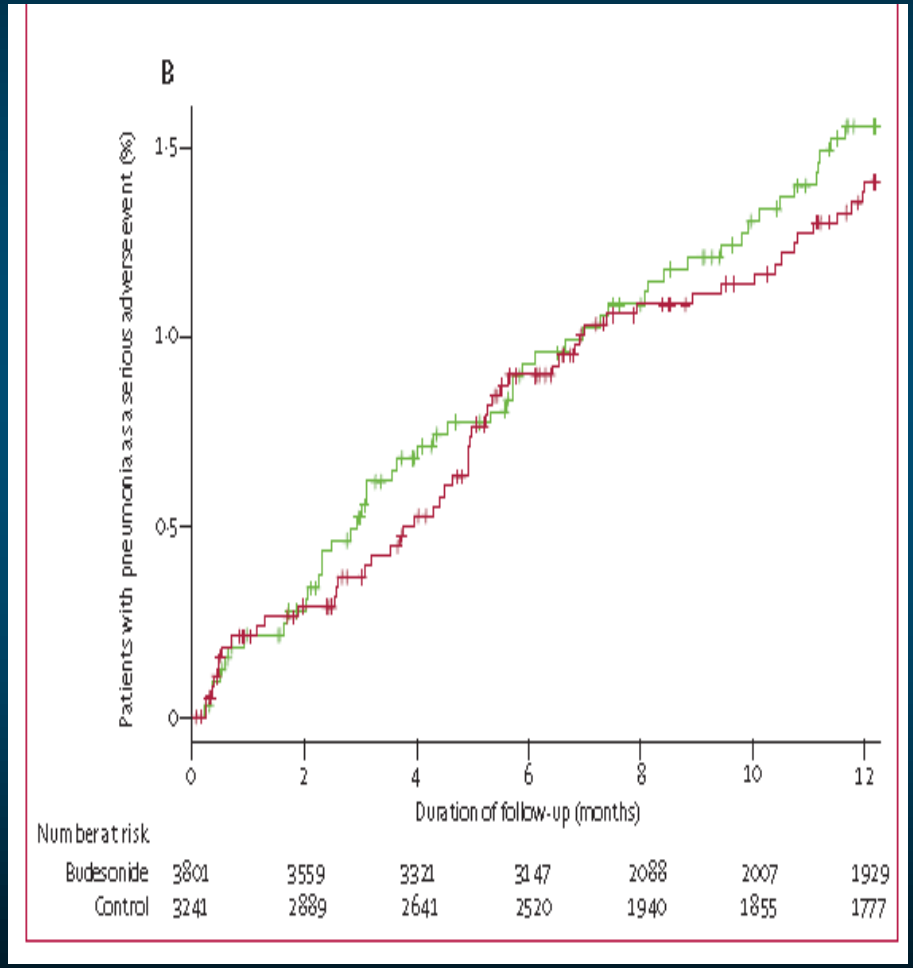
Budesonide and the risk of pneumonia: a meta-analysis of individual patient data

Don D Sin, Donald Tashkin, Xuekui Zhang, Finn Radner, Ulf Sjöbring, Anders Thorén, Peter M A Calverley, Stephen I Rennard

Lancet 2009; 374: 712–19

TIME TO FIRST PNEUMONIA AE OR SAE





Sin et al Lancet 2009

So what is the message?

- Are ICS the best drugs ever seen for COPD – **NO**
- Are they best used as monotherapy – **NO**
- Do they add significantly to existing therapy – YES
- Should we use ICS in COPD management – **YES, TILL SOMETHING BETTER COMES ALONG**