

REDUCING MORTALITY IN COPD – THE TORCH STUDY

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COPD STILL KILLS

- In 2002 the estimated annual mortality due to COPD in Europe was 260,000 - 2.7% of all deaths
- In the UK 30,000 people die from COPD each year
- Deaths due to COPD are under-diagnosed
- COPD contributes to death from other causes

FACTORS ASSOCIATED WITH DEATH

- Age
- Baseline FEV₁
- Smoking status
- BMI
- Exercise capacity
- Exacerbation frequency
- Health status

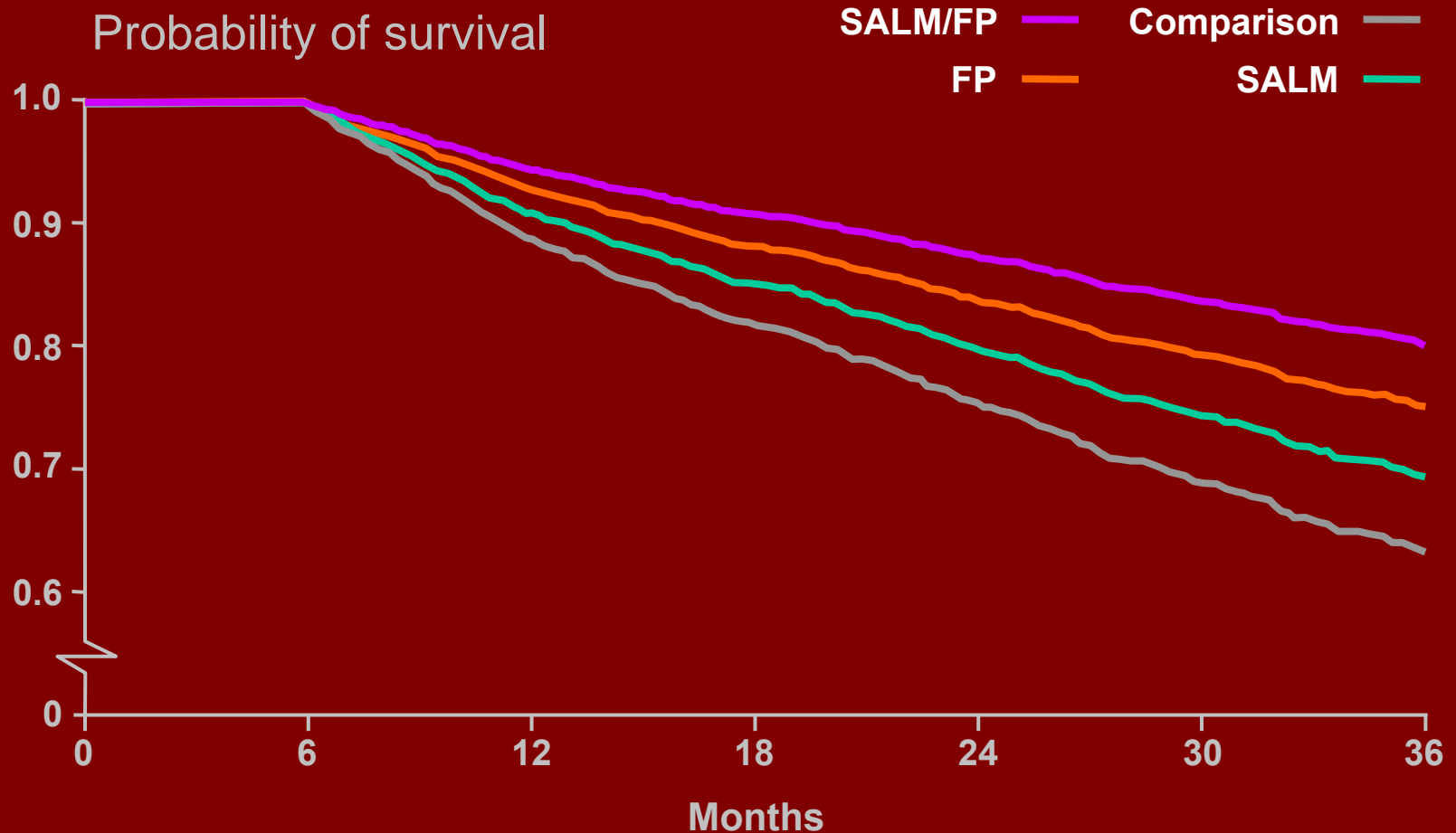
FACTORS YOU CAN MODIFY

- Age
- Baseline FEV1
- Smoking status
- BMI
- Exercise capacity
- Exacerbation frequency
- Health status

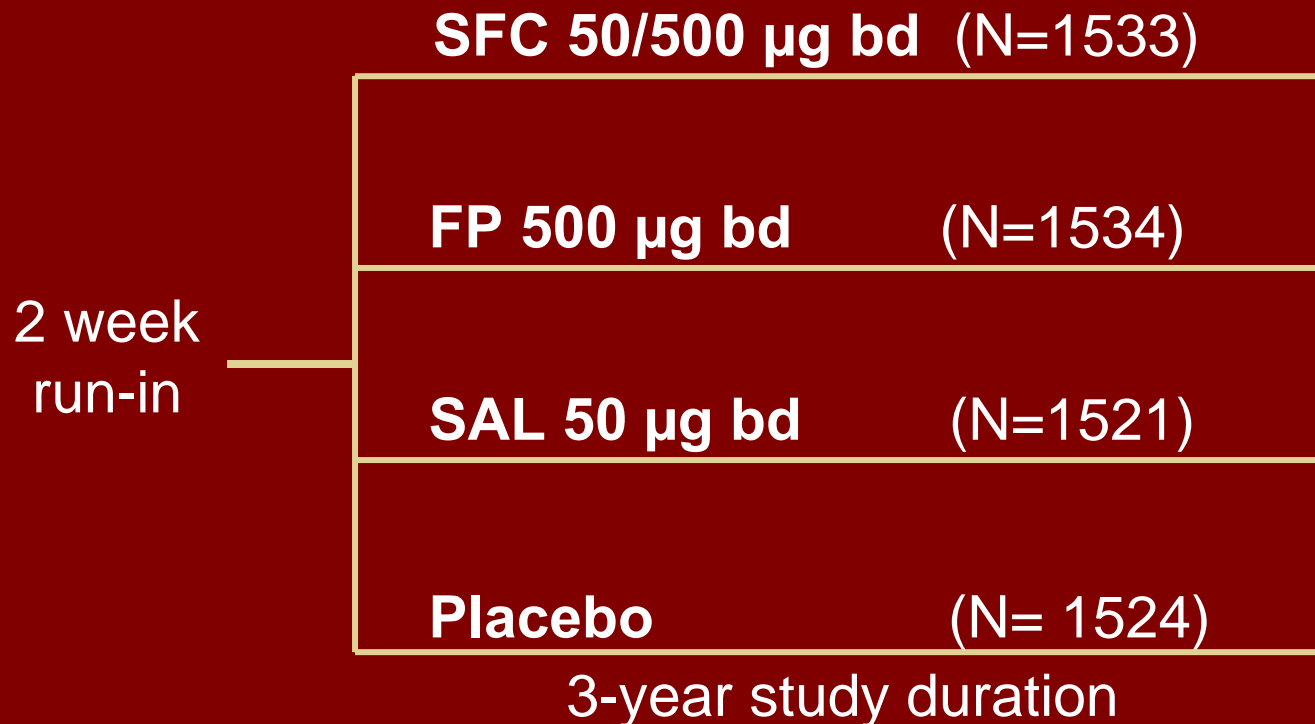
TREATMENT THAT REDUCES MORTALITY

- Smoking cessation – the earlier, the better
- LTOT if hypoxaemic
- LVRS in selected cases
- DRUGS – good or bad?

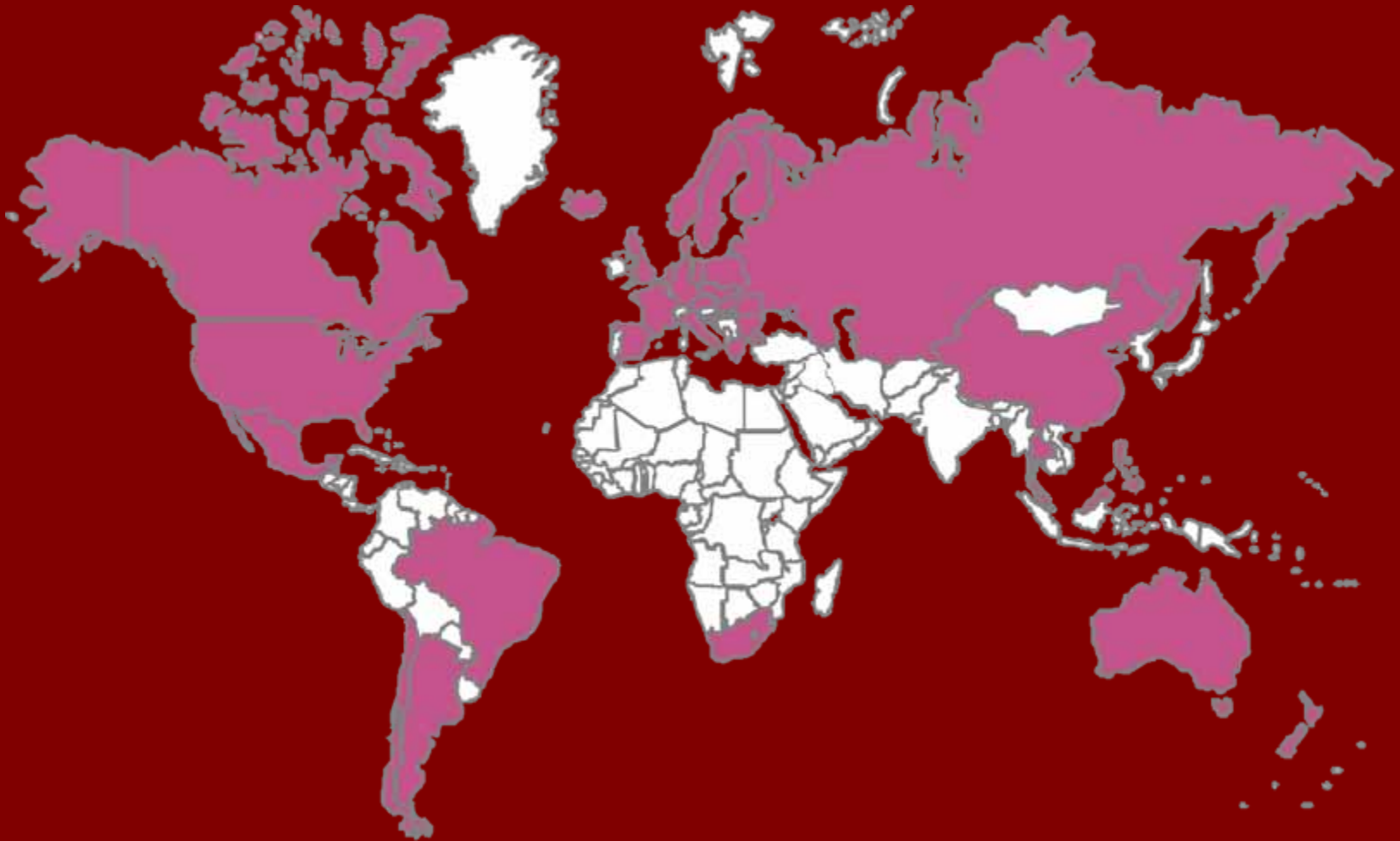
Adjusted Survival Function of COPD Patients by Therapy



TORCH: study design



Worldwide participation in 42 countries



TORCH: main objectives

- **Primary objective**
 - The effect of SFC 50/500 μg vs placebo on all-cause mortality over 3 years in patients with moderate-to-severe COPD
- **Secondary objectives**
 - The effect of SFC 50/500 μg on the rate of moderate and severe exacerbations
 - The effect of SFC 50/500 μg on health status (SGRQ)

Clinical Endpoint Committee (CEC)

- Independently review all fatal events (post randomisation) occurring during the course of the study and assign a primary cause of death
- Request all available documentation (e.g. clinical records, death certificates, and site investigator narratives)

Populations

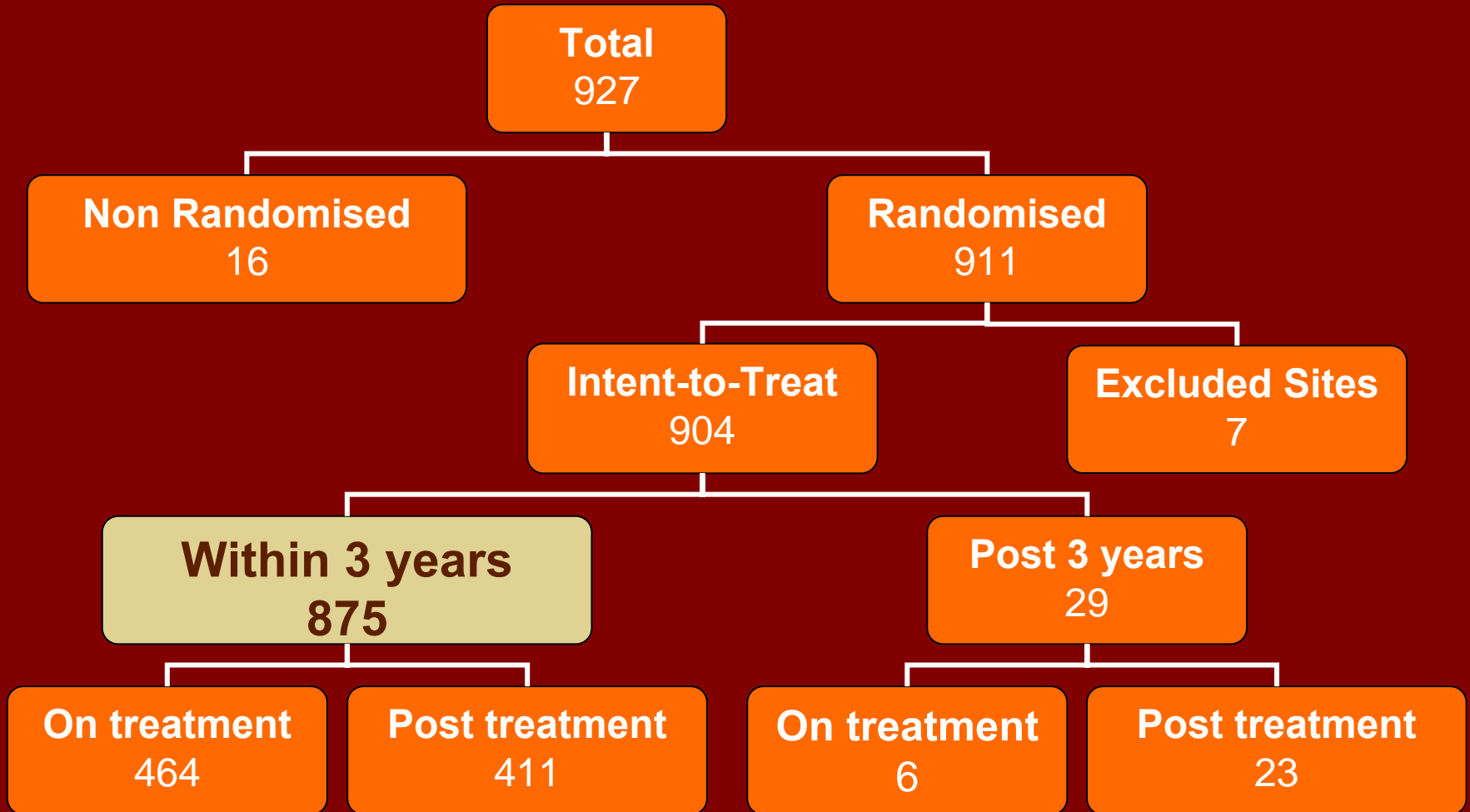
Population	Placebo	SAL	FP	SFC	Total
Safety	1544	1542	1552	1546	6184
Intent-to-treat (ITT) efficacy	1524	1521	1534	1533	6112

Demographics

ITT
N=6112
Mean (sd)

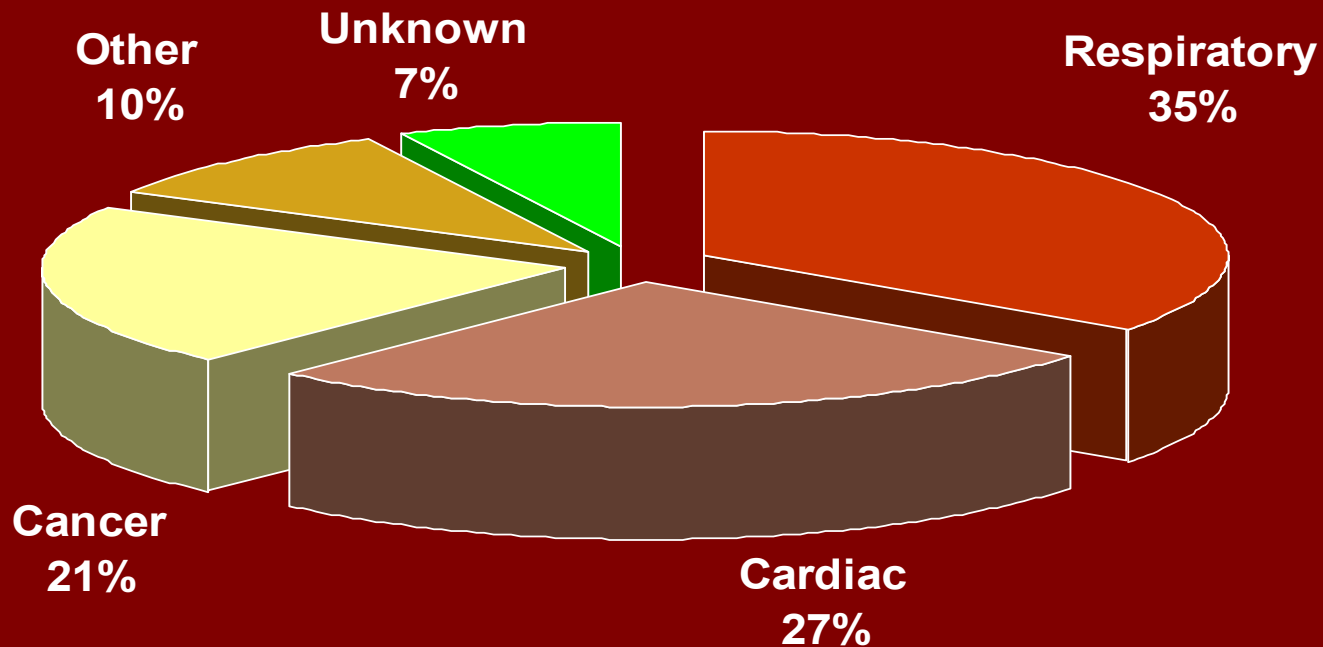
Age	65 (8)
Males	76%
Current smokers	43%
Pack years	49 (27)
% pred baseline FEV₁ (post bronc)	44 (13)
% pred reversibility	3.7 (3.7)
≥1 exacerbations in previous year	57%

Deaths

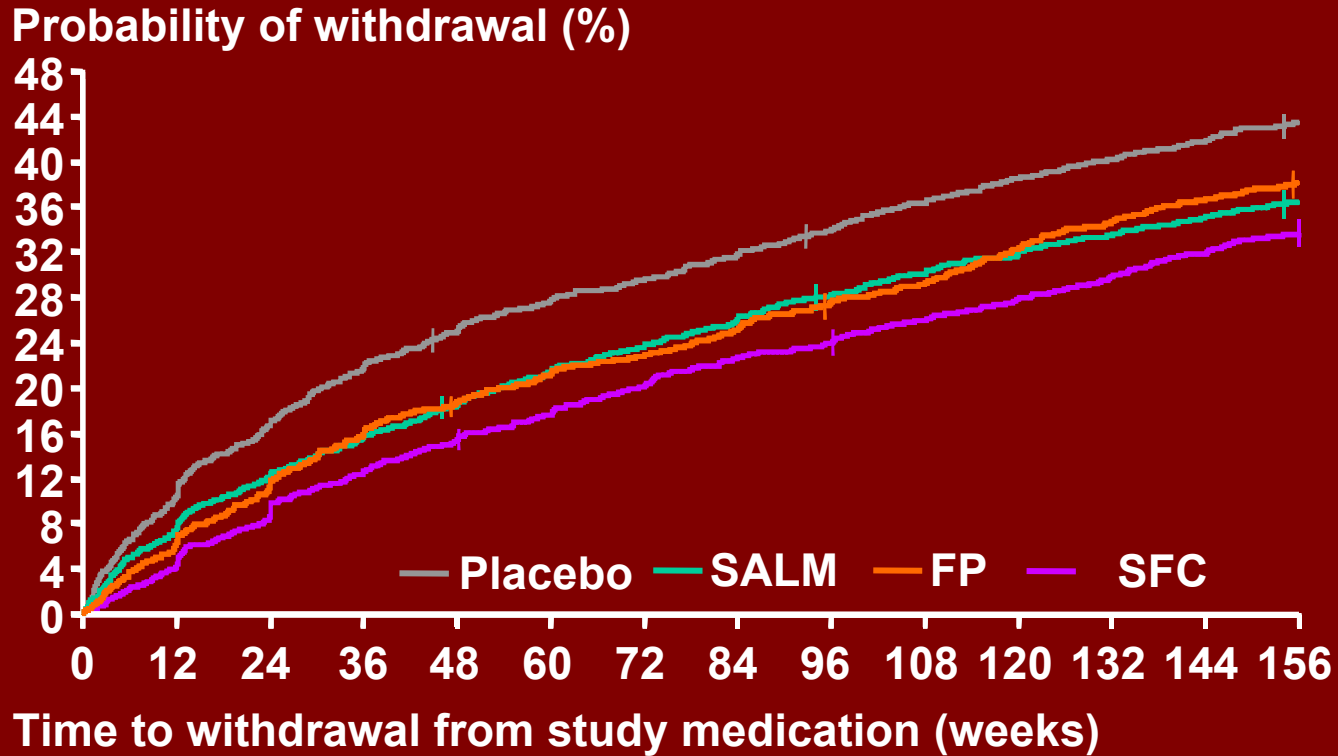


On Treatment = up to 14 days after treatment stop

Overall causes of death as adjudicated by the Clinical Endpoint Committee



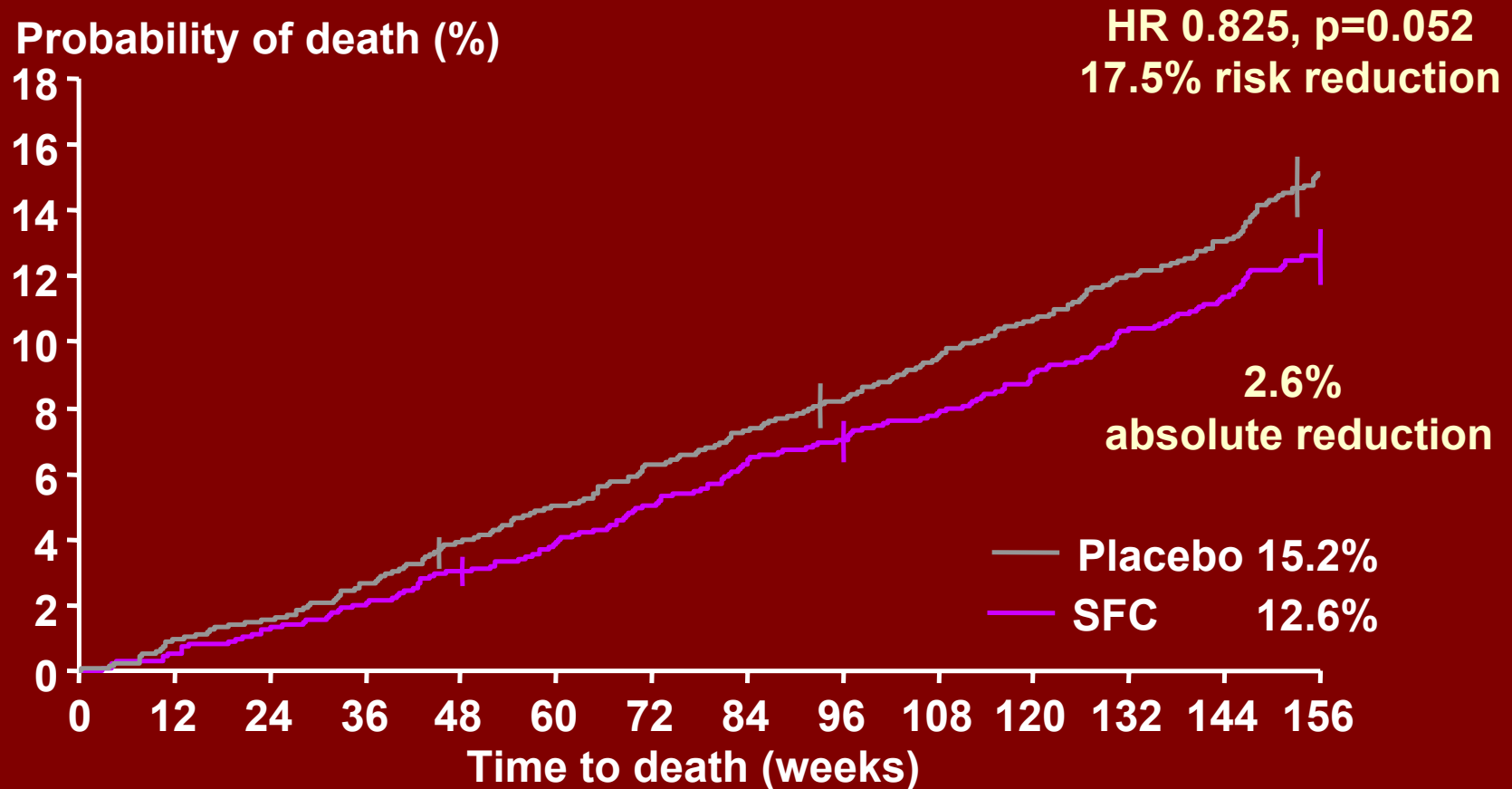
Premature study drug discontinuation



	Placebo	SALM	FP	SFC
Number	1524	1141	1005	884
at risk	1521	1240	1093	986
	1534	1247	1112	971
	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 $p = 0.001$
 Vertical bars are standard errors

Primary analysis: all-cause mortality at 3 years



1524
1533

1464
1487

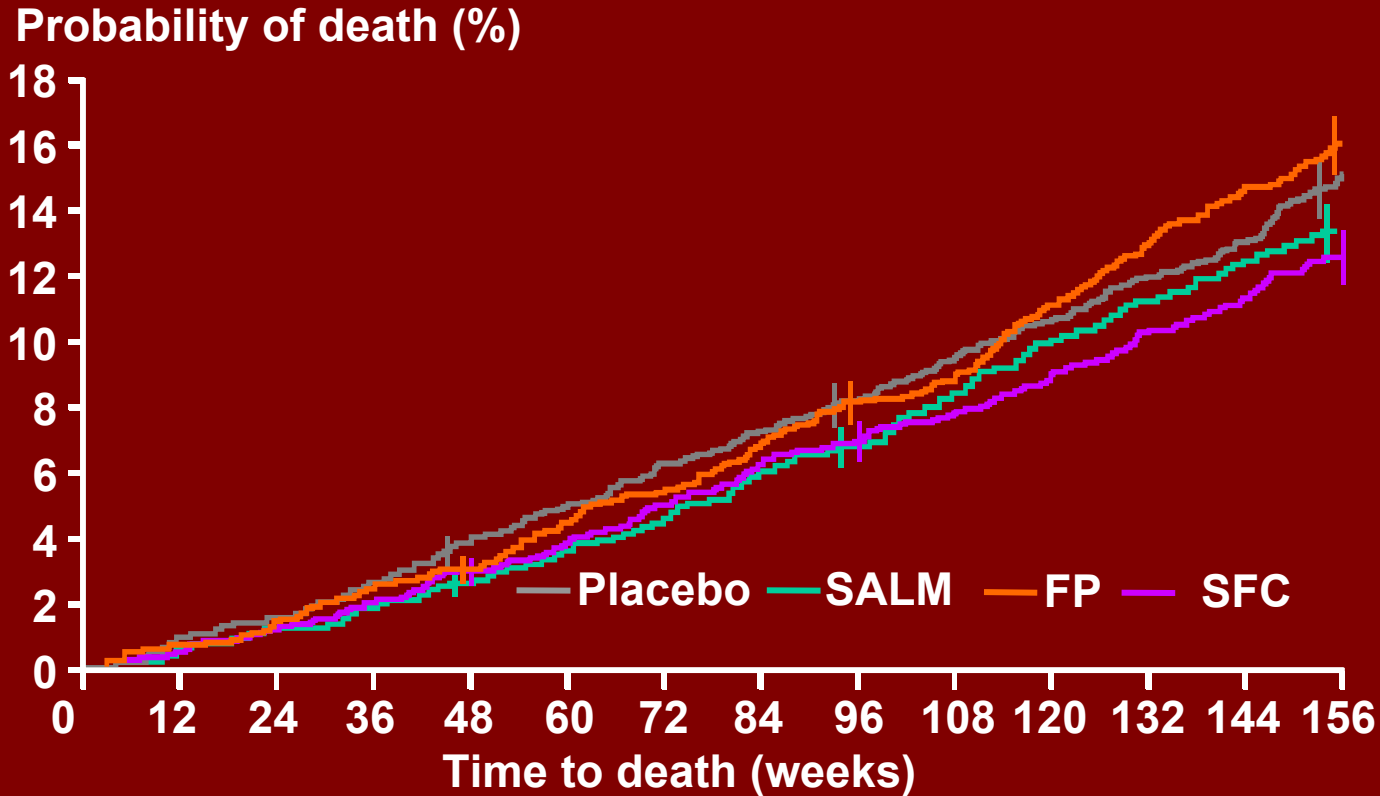
1399
1426

1293
1339

Supportive analysis: All-cause mortality at 3 years - Cox's proportional hazards

	Placebo (N = 1524)	SFC (N = 1533)
Number of deaths	231	193
Percentage of deaths by 3 years	15.2	12.6
HR (95% CI)[†]	0.811 (0.670, 0.982)	
p-value[†]	0.031	

All-cause mortality at 3 years



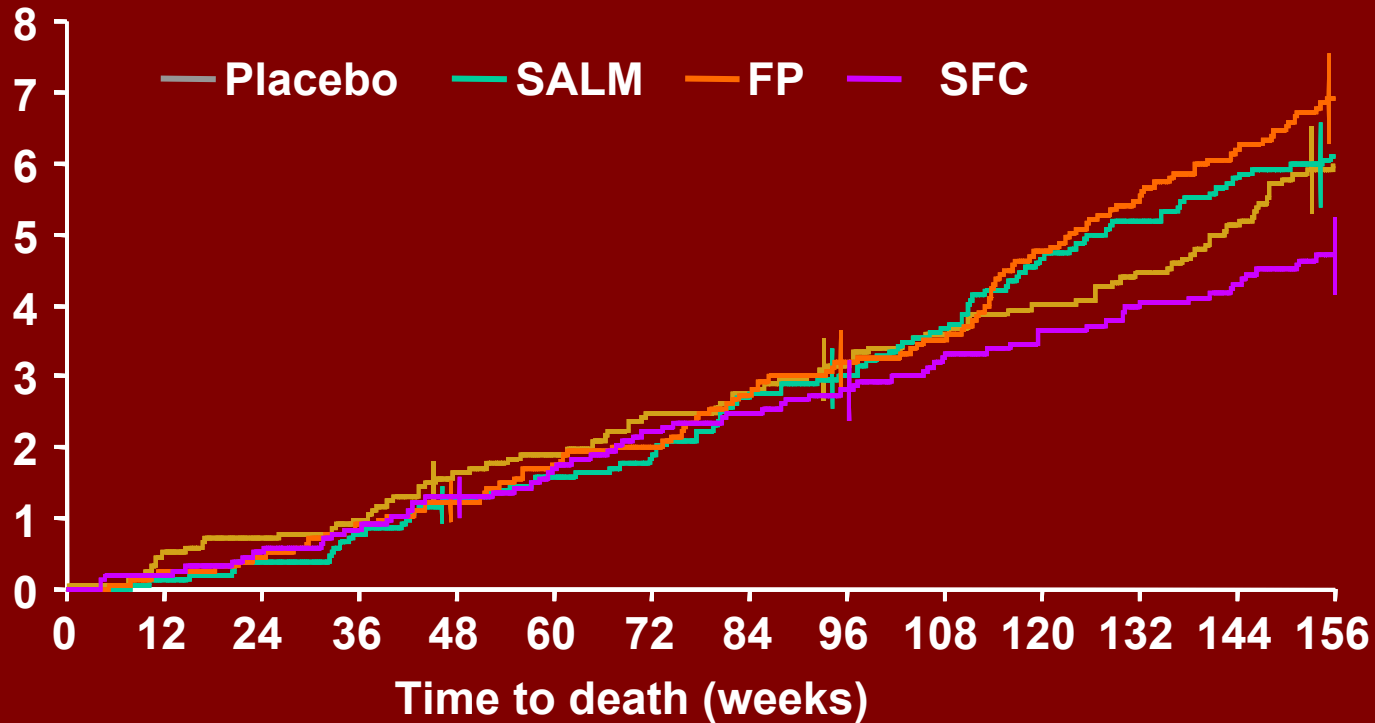
Number	1524	1464	1399	1293
alive	1533	1487	1426	1339
	1521	1481	1417	1316
	1534	1487	1409	1288

Vertical bars are standard errors

Calverley *et al.* NEJM 2007

COPD-related mortality by 3 years

Probability of death (%)

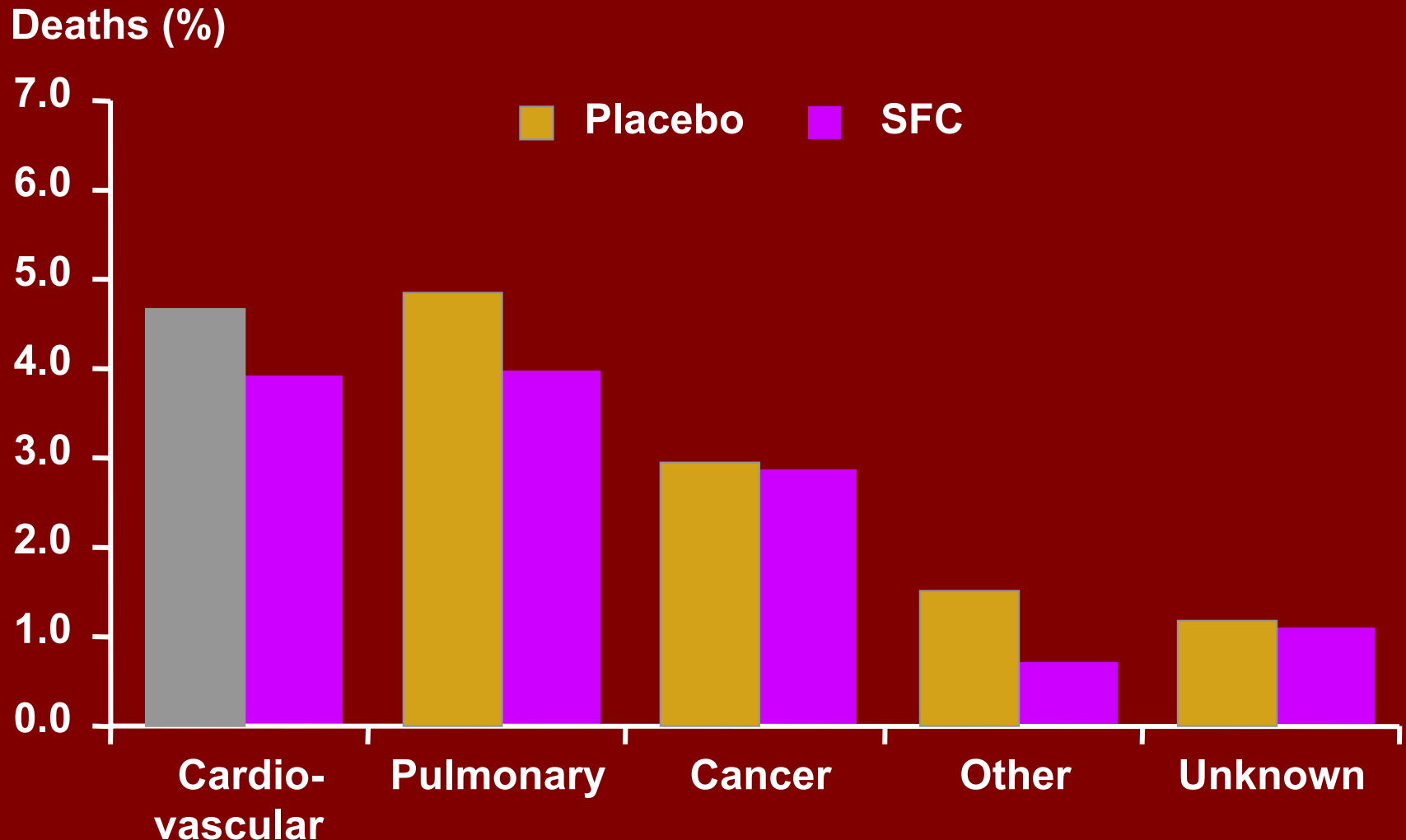


Number	1524	1499	1476	1433
alive	1533	1513	1490	1460
	1521	1502	1475	1428
	1534	1515	1485	1428

Vertical bars are standard errors

Calverley *et al.* NEJM 2007

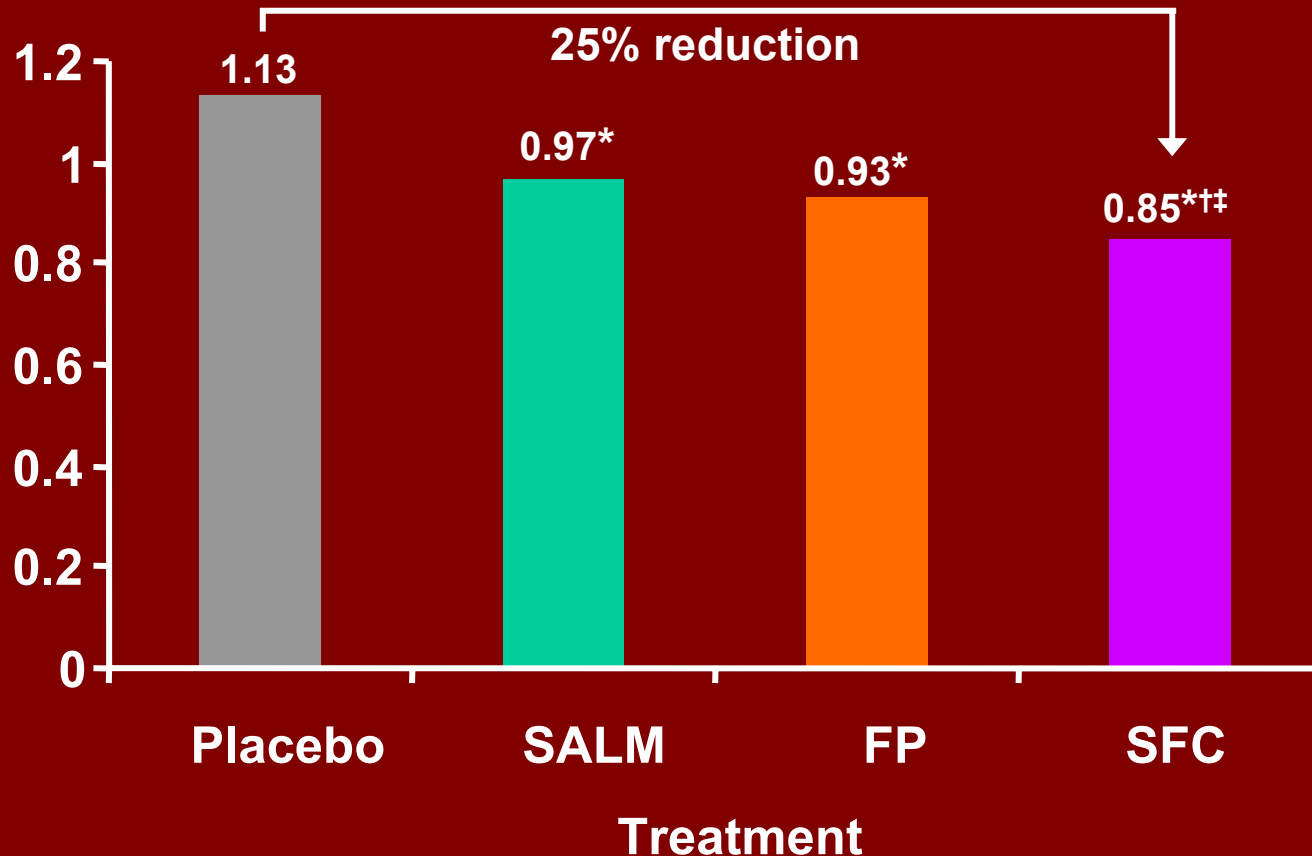
Cause of death on treatment (adjudicated by CEC)



Supportive evidence for a
significant effect

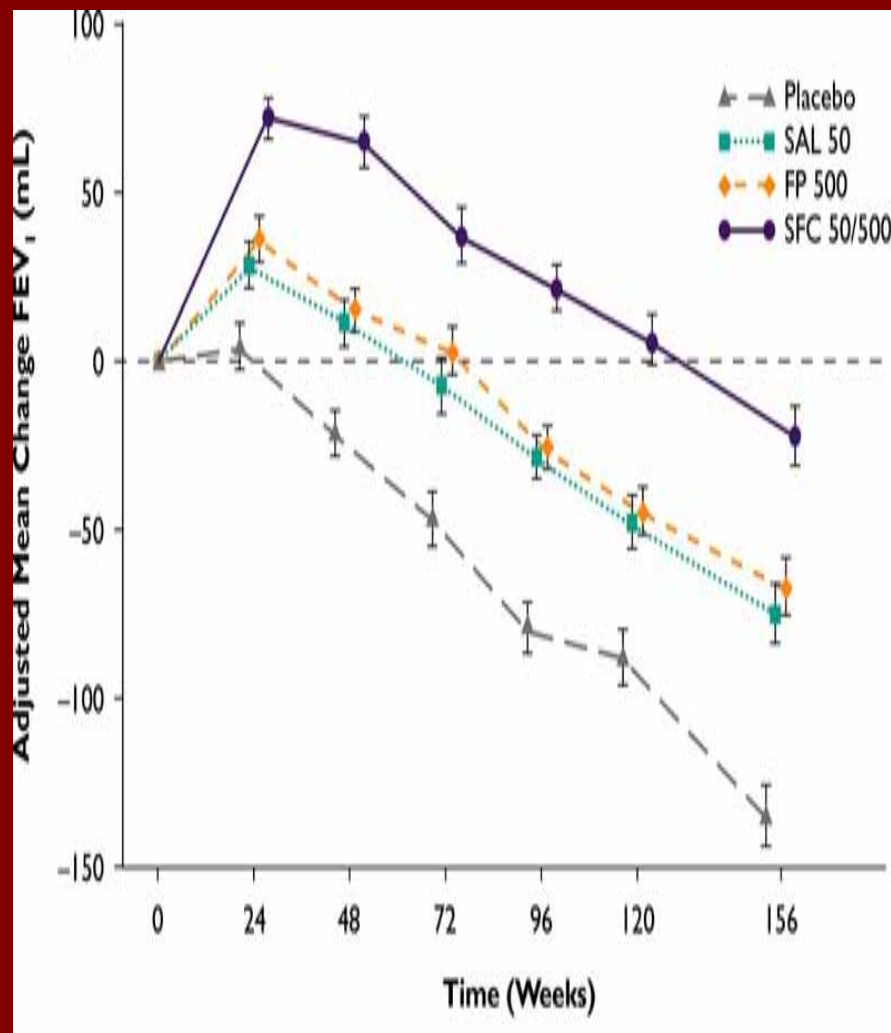
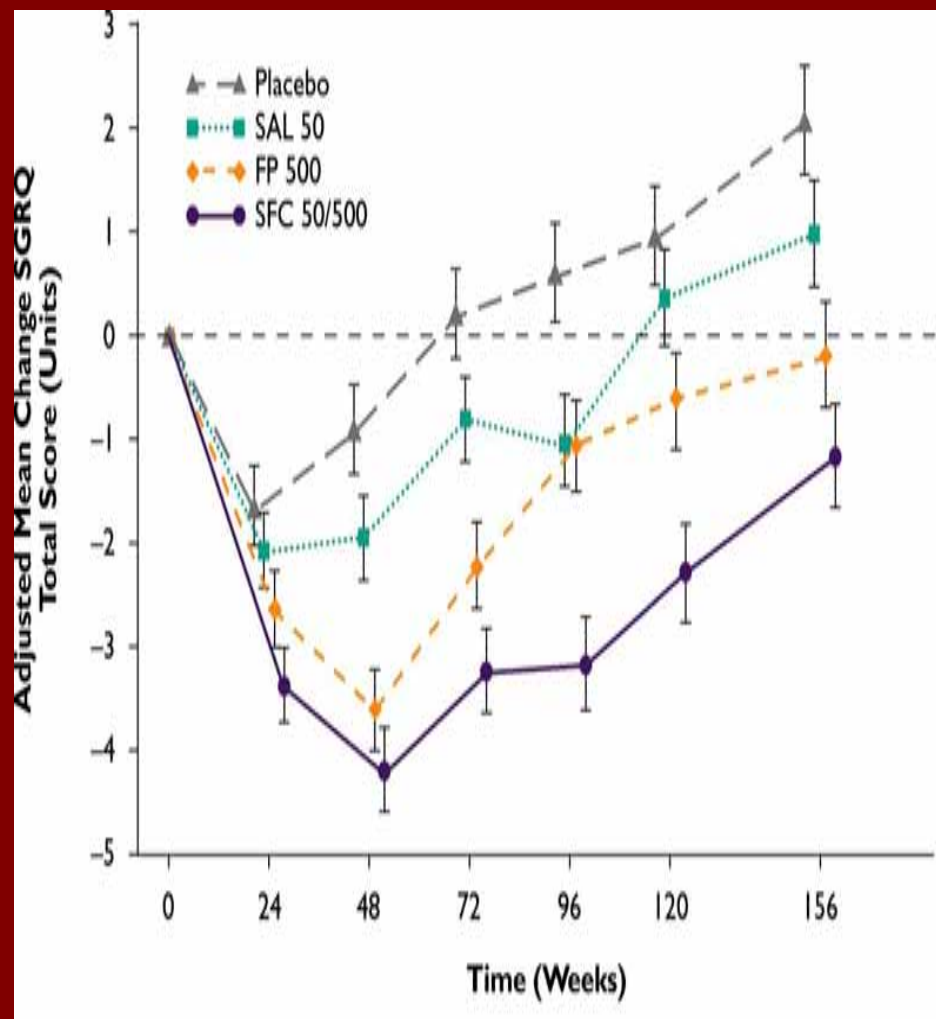
Rate of moderate and severe exacerbations over three years

Mean number of exacerbations/year



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

THE OTHER PREDICTORS OF MORTALITY



PUTTING THE MORTALITY EFFECT IN CONTEXT

RISK VS BENEFIT

- Health status data are encouraging
- No clear evidence for interaction with high background level of co-morbidity
- Fewer hospitalisations with salmeterol and SFC
- Pneumonia a new signal – not reflected in current markers of morbidity/mortality. More research is needed to understand this

Effect of statins on all-cause mortality in patients with coronary heart disease

- **Meta-analysis of 17 trials**
- **N = 40974**
- **Mean/median follow up 0.3–6.1 years**
- **Relative Risk Reduction = 16%**
- **Absolute Risk Reduction = 1.8%**

CONCLUSIONS

- Many COPD disease patents die from and with the disease
- Establishing the cause of death is difficult but not impossible.
- Pharmacotherapy reduces the risk of dying in moderate/severe COPD
- Statistical and methodological issues have a big effect on clinical trial design
- It is hard to test a readily available symptomatic therapy – contrast the original oxygen trials and TORCH
- Treatment can reduce COPD mortality....so we should tell people this!