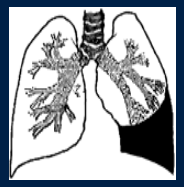

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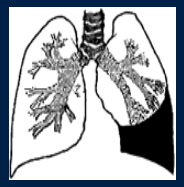
COPD Management in an evolving COPD landscape

John Wrightson

Oxford Centre for Respiratory Medicine

John.Wrightson@orh.nhs.uk



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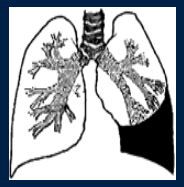
Structure

- Pathology
- Guidelines
- Historical trials
- Recent ‘mega’ trials



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Pathology

- Causes
  - smoking
  - some alpha-1-antitrypsin deficiency
  - biomass fuels in developing nations
- **Chronic** lung disease
- Airflow **obstruction**
  - airway and parenchymal damage
  - chronic inflammation

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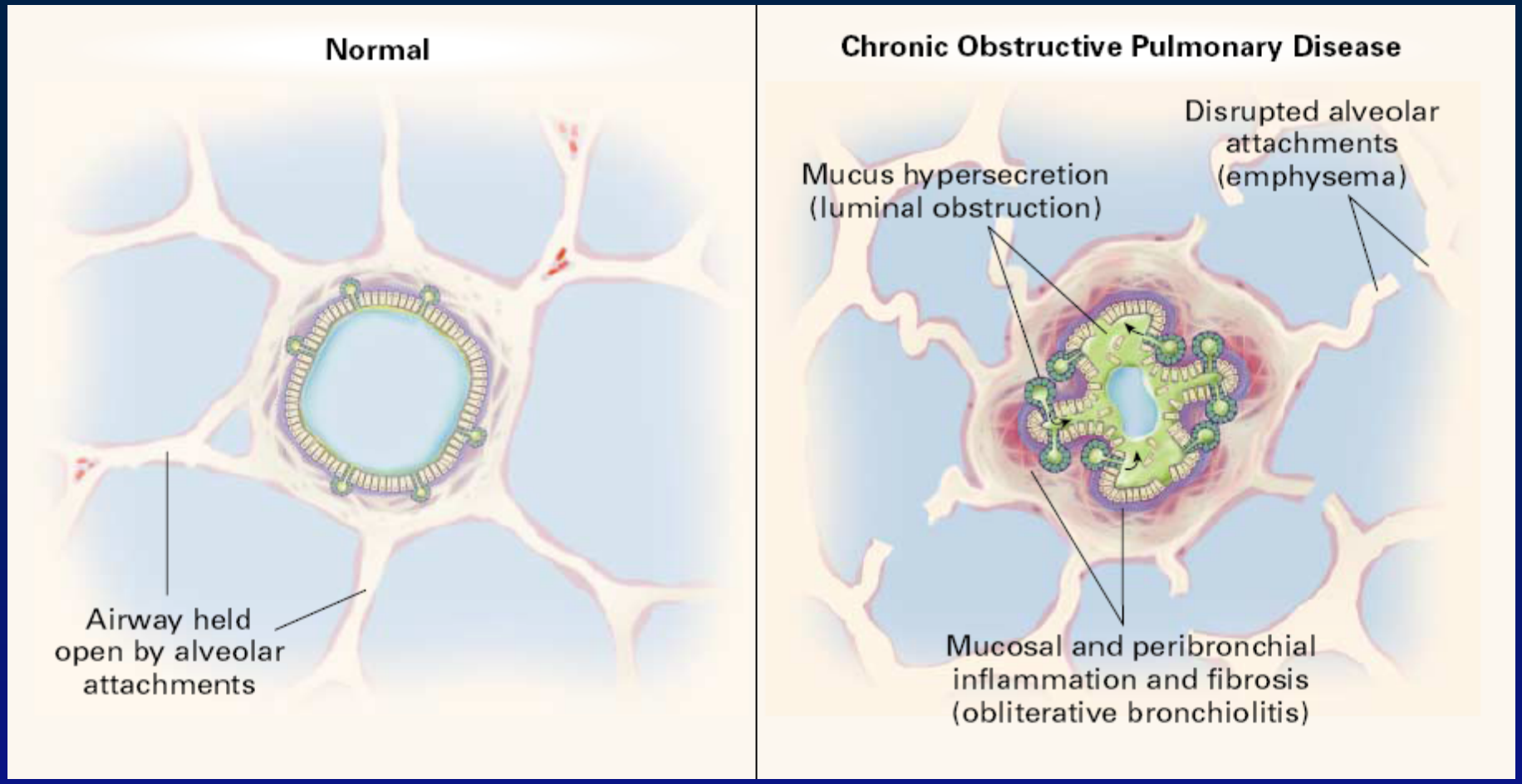
Pathology



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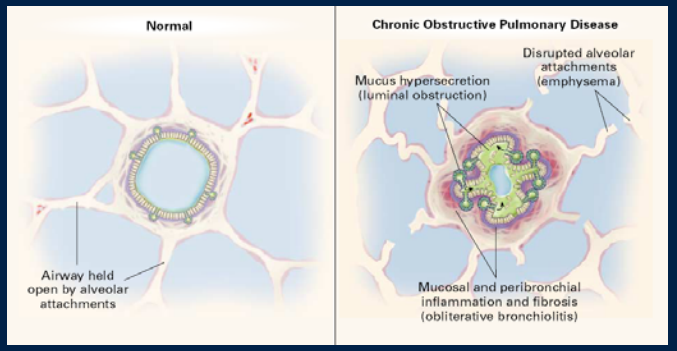


Pathology

- Smoke/Pollution irritants →
  - Mucous gland hypertrophy
  - Increased mucus
  - Increased polymorphs in airways

→ increase elastase

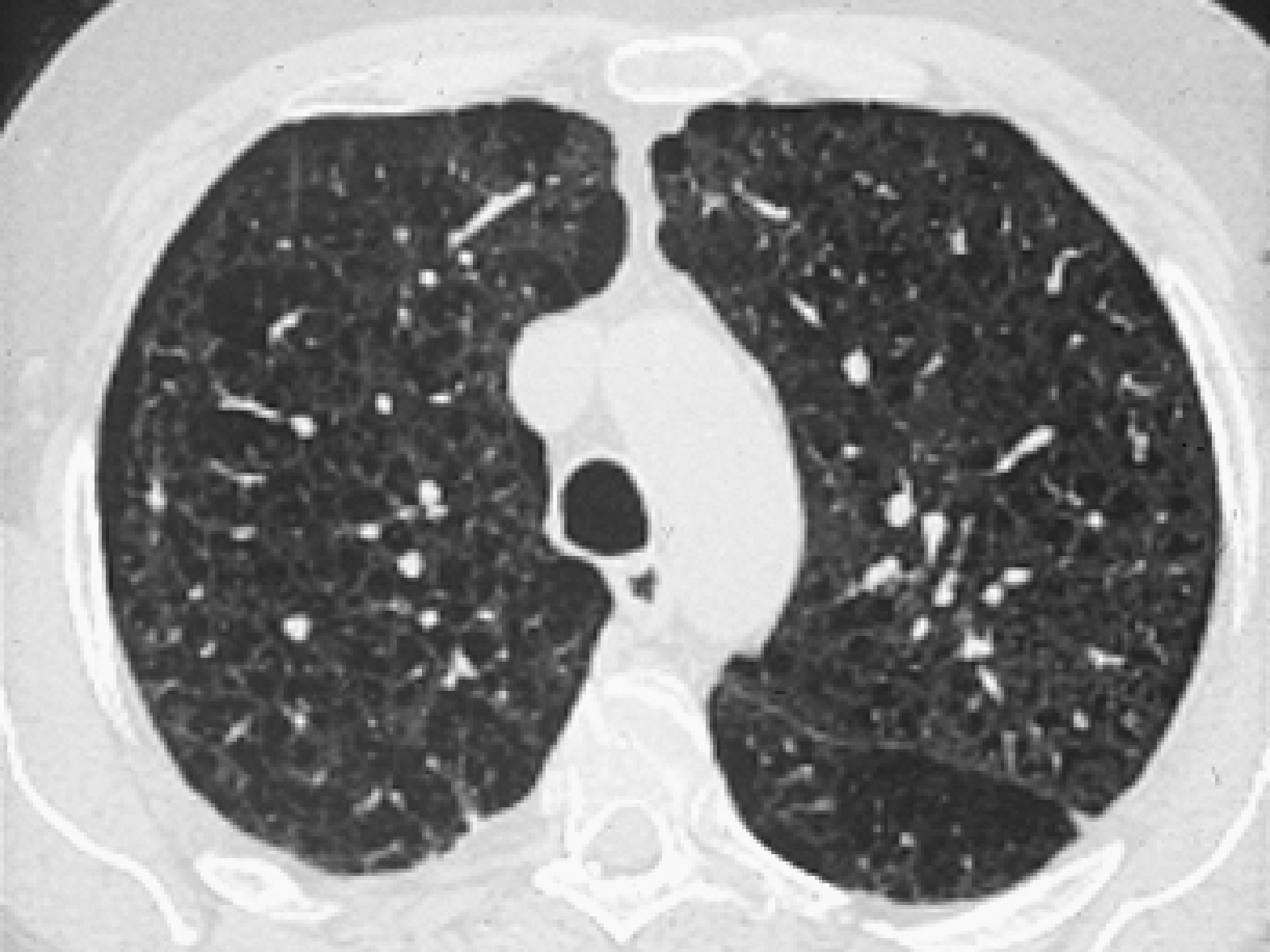
→ loss of alveoli / pulmonary vasculature

→ decreased area for gas exchange

→ loss of elastic supporting tissue

→ early expiratory airway collapse

→ hyperinflation



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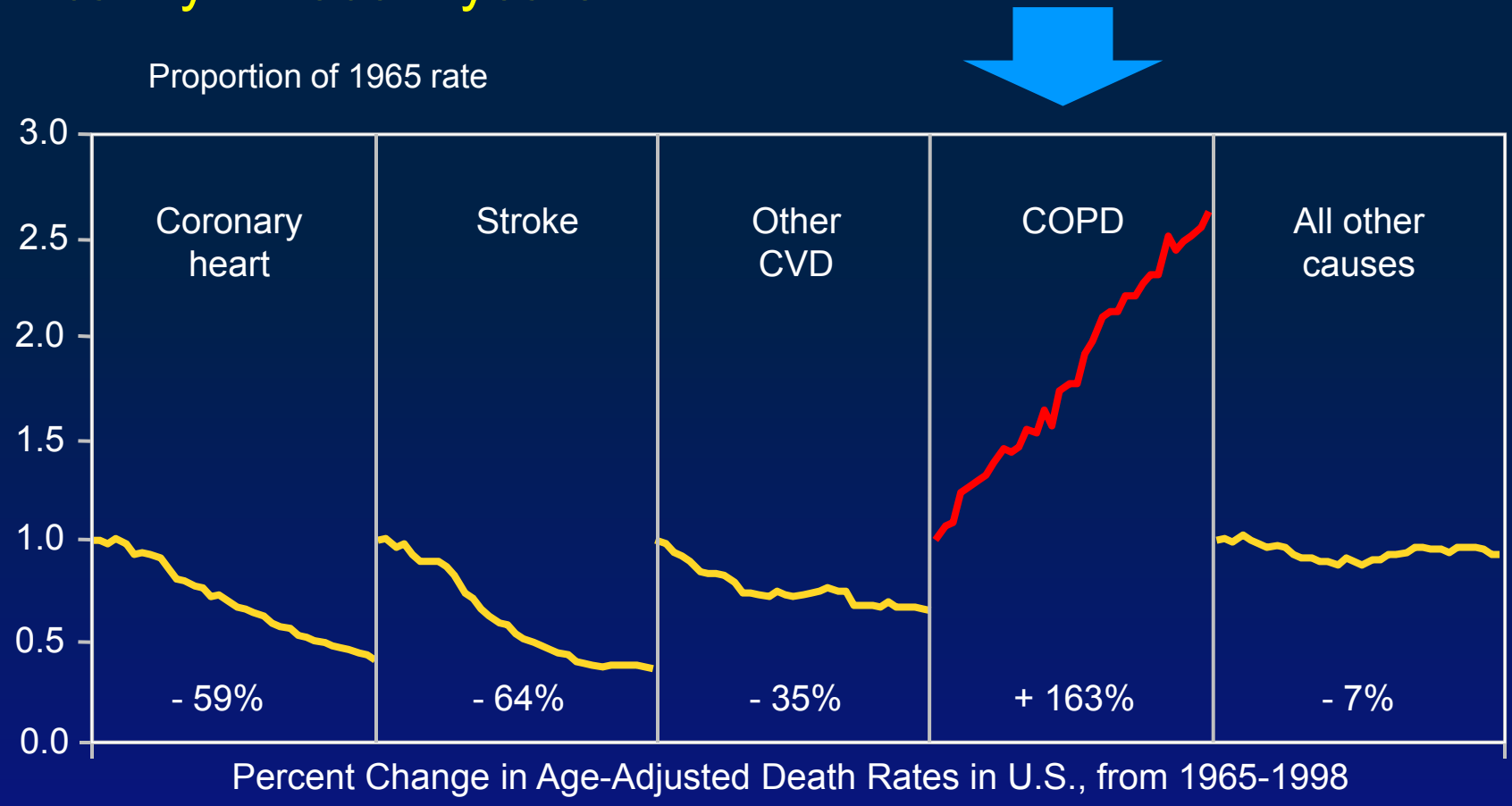
COPD is the only major cause of death that has increased significantly in recent years



GOLD Guidelines. http://www.goldcopd.com

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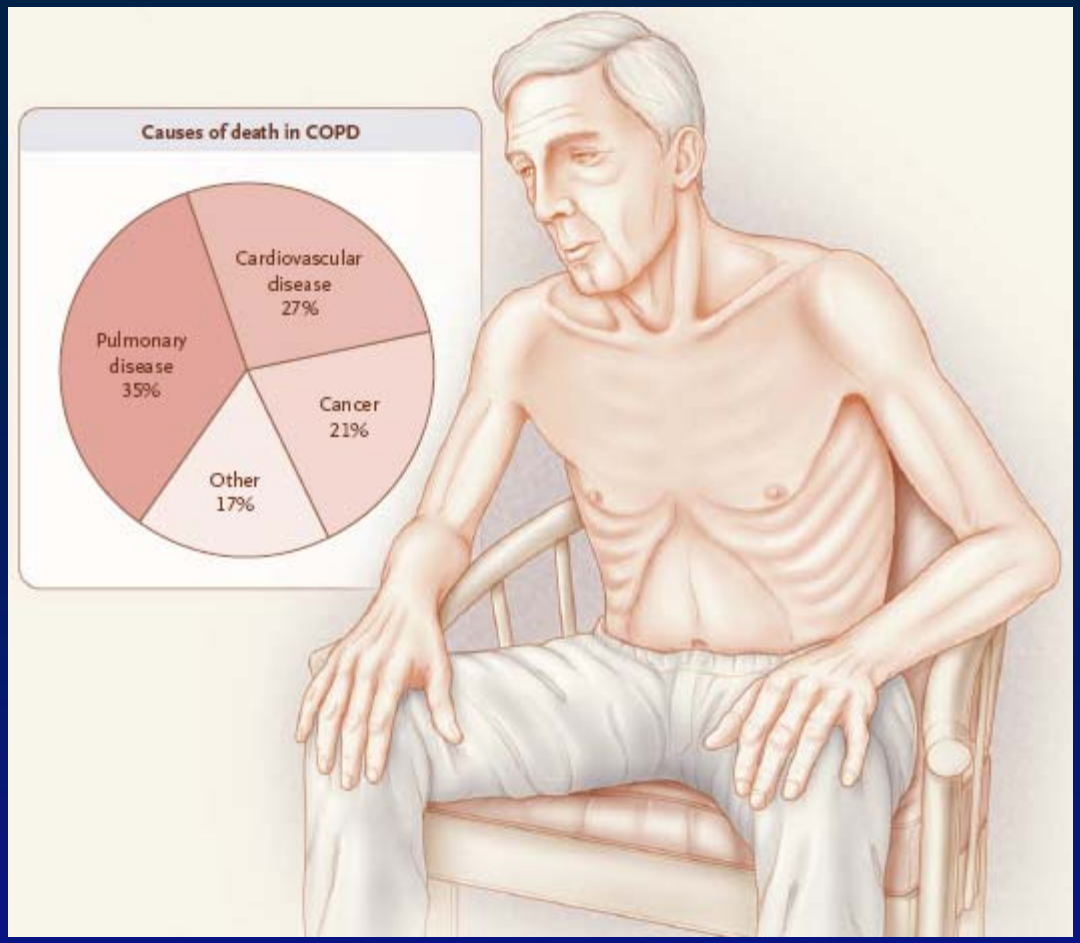
Not just respiratory

- Cardiovascular
- Lung cancer
- Osteoporosis
- Cachexia
- Depression



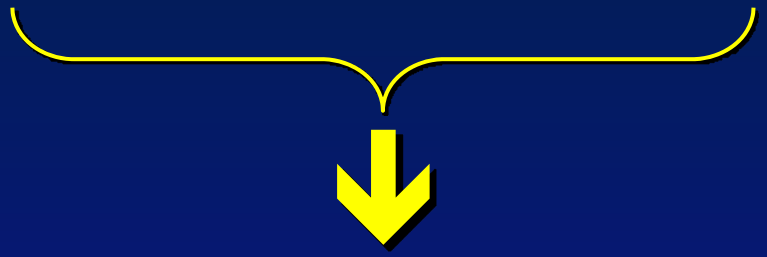
Think COPD

SYMPTOMS

Cough
Sputum
Dyspnoea

RISK FACTORS

>35 years old
Smoker
Occupation
Pollution



SPIROMETRY

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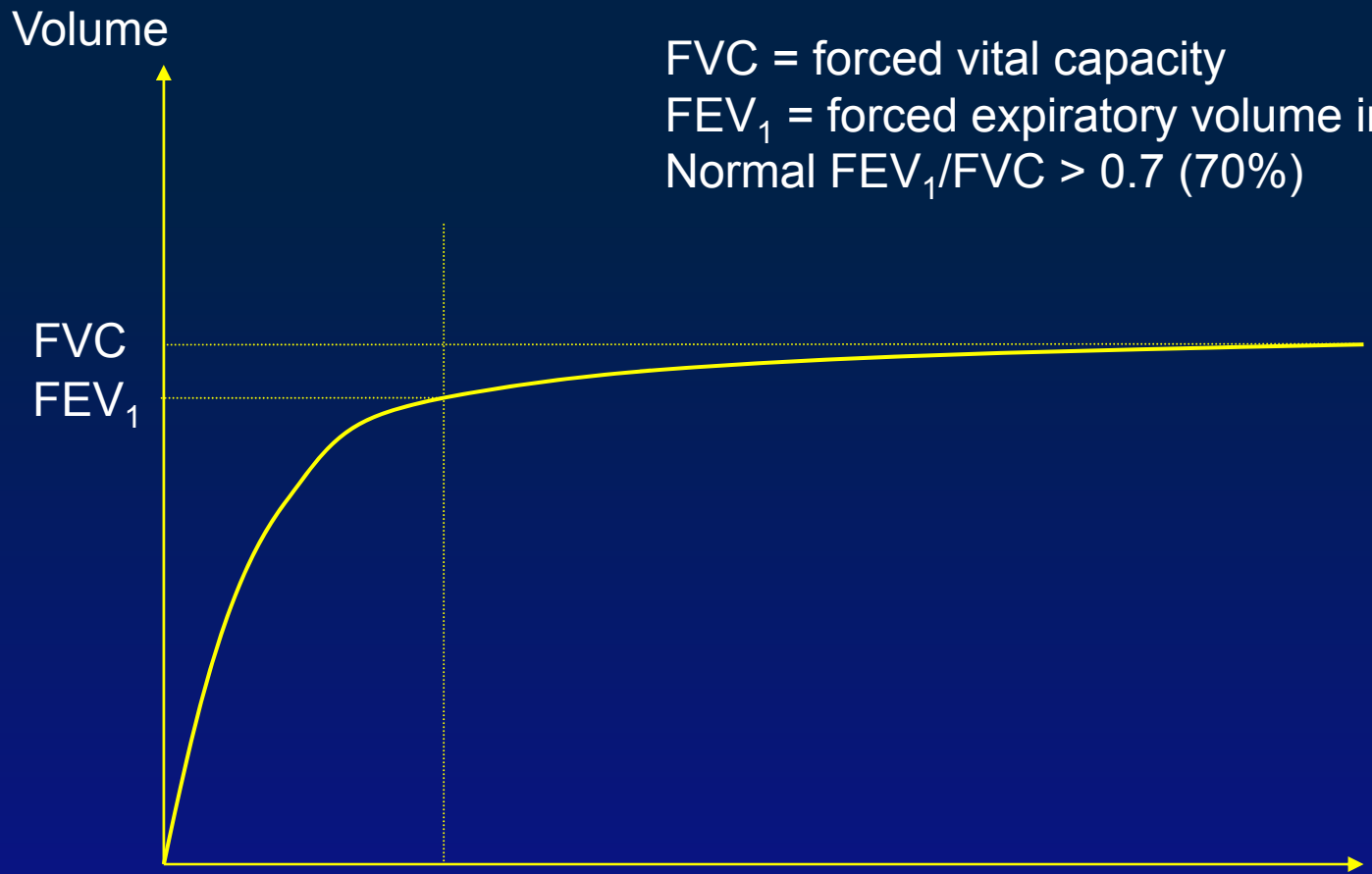
Spirometry



FVC = forced vital capacity

FEV_1 = forced expiratory volume in 1 second

Normal $FEV_1/FVC > 0.7$ (70%)

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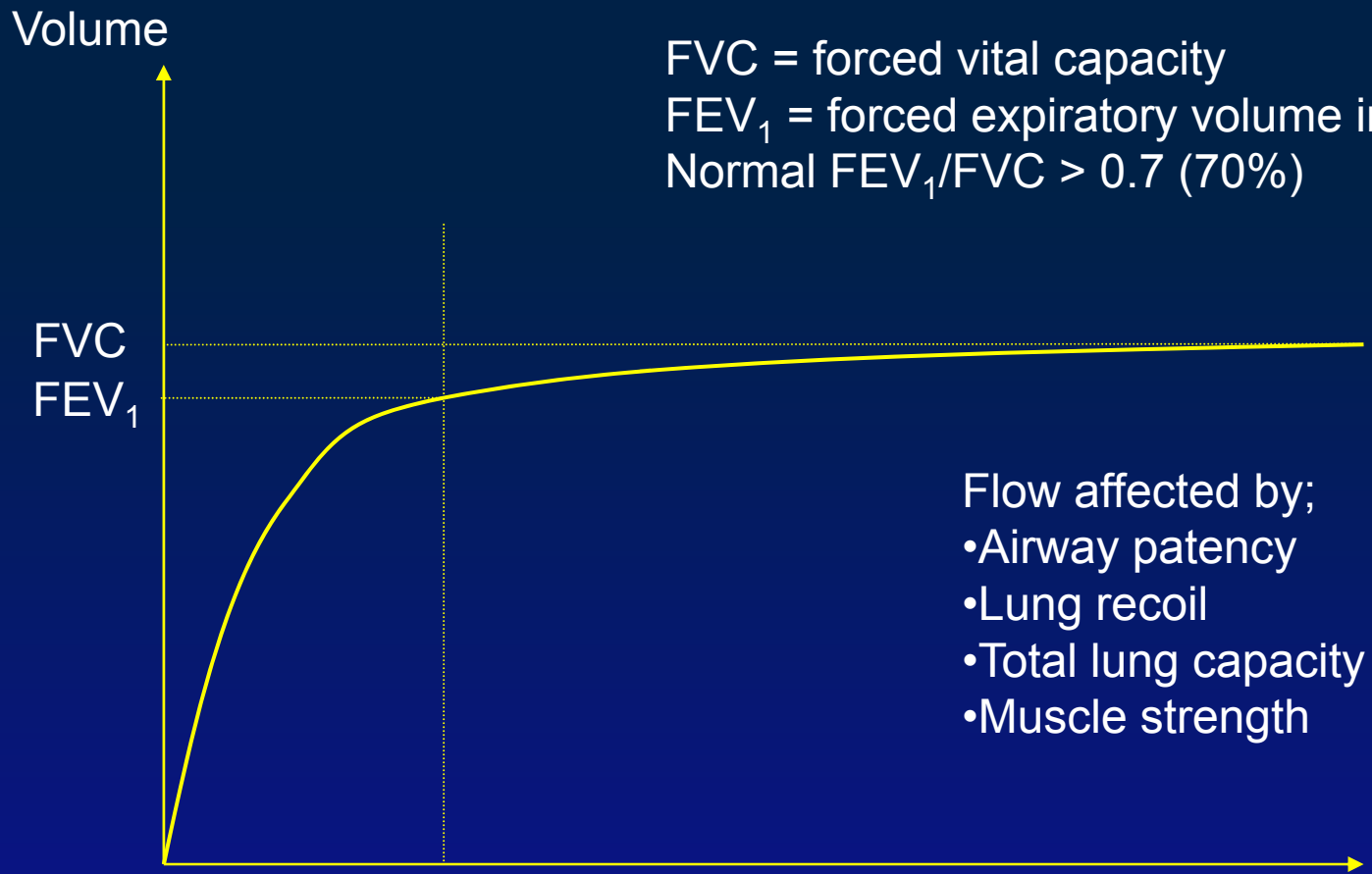
Spirometry



FVC = forced vital capacity
FEV_1 = forced expiratory volume in 1 second
Normal FEV_1/FVC > 0.7 (70%)

Flow affected by;
- Airway patency
- Lung recoil
- Total lung capacity
- Muscle strength

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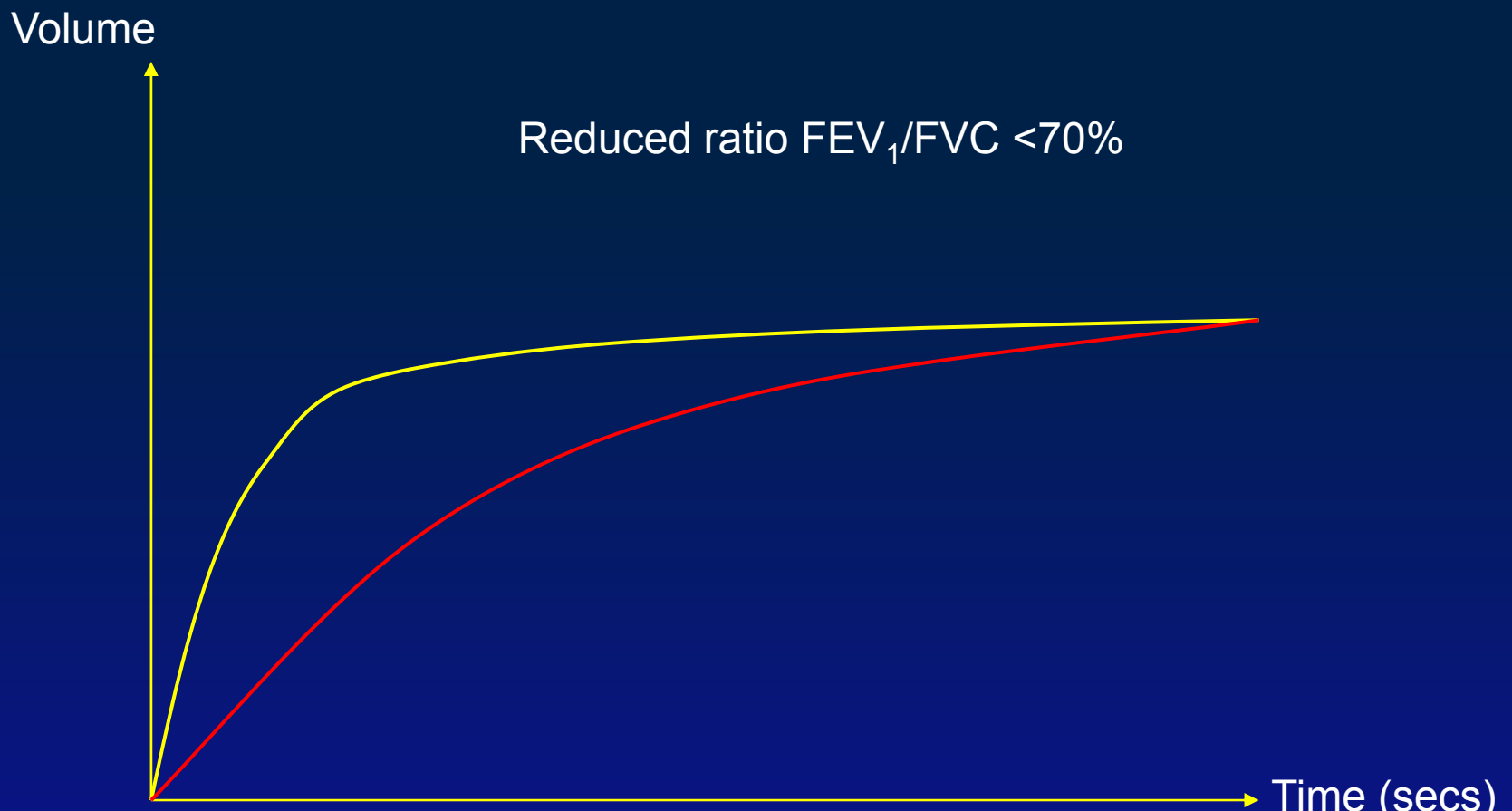
Airflow obstruction



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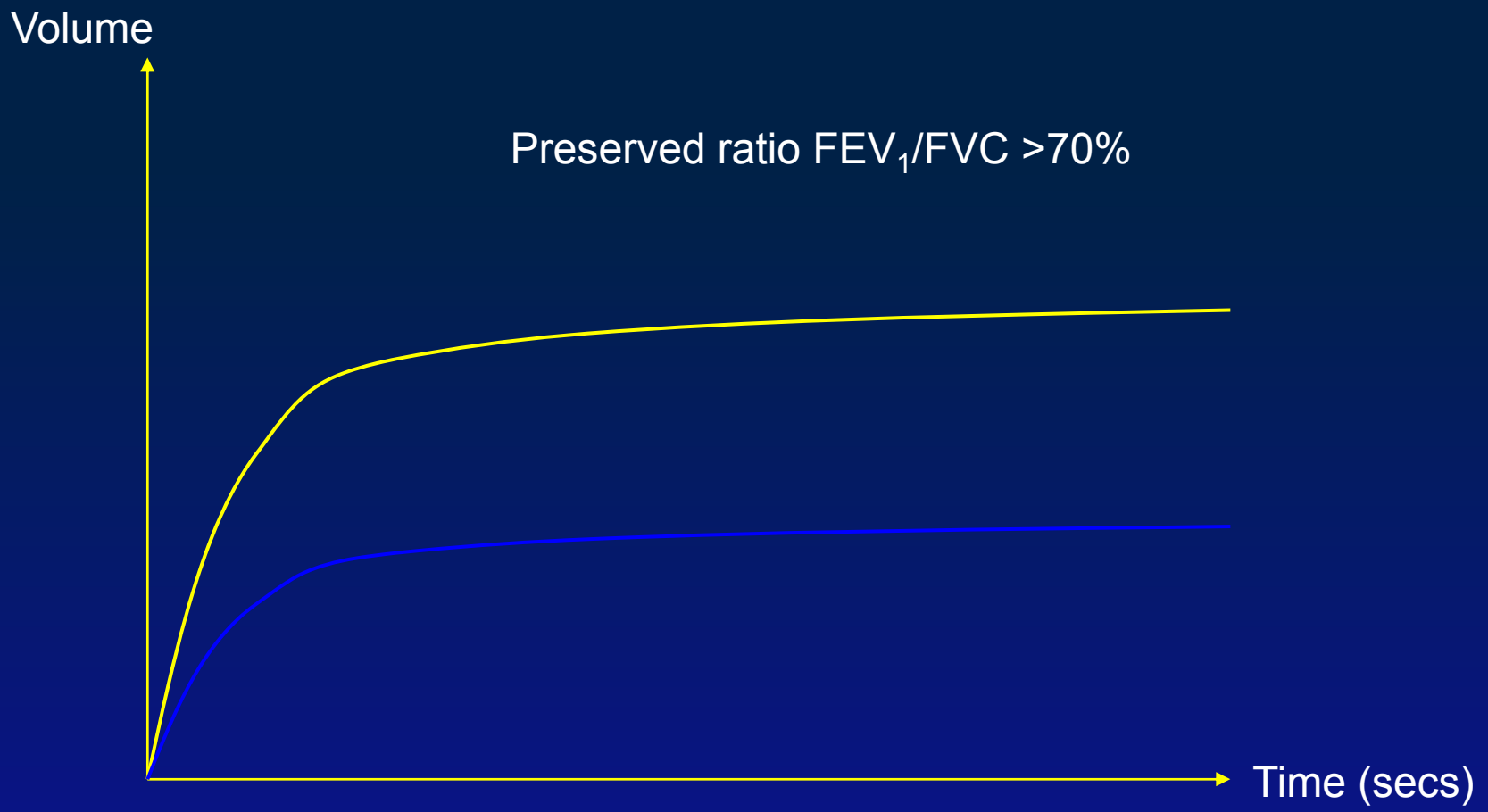
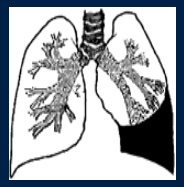
Restrictive defect

e.g. intrinsic lung diseases, thoracic wall disorders





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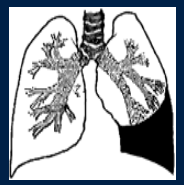
Severity of COPD

		NICE clinical guideline 12 (2004)	ATS/ERS 2004[3]	GOLD 2008[4]	NICE clinical guideline 101 (2010)
Post-bronchodilator FEV_1/FVC	FEV_1 % predicted		Post-bronchodilator	Post-bronchodilator	Post-bronchodilator
< 0.7	≥ 80%		Mild	Stage 1 – Mild	Stage 1 – Mild*
< 0.7	50–79%	Mild	Moderate	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30–49%	Moderate	Severe	Stage 3 – Severe	Stage 3 – Severe
< 0.7	< 30%	Severe	Very severe	Stage 4 – Very severe**	Stage 4 – Very severe**



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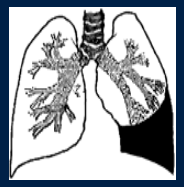
GOLD goals

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent & treat complications
- Prevent & treat exacerbations
- Reduce mortality

- … with minimum side-effects



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GOLD goals

- Prevent disease progression
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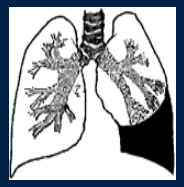
- Prevent & treat complications
- Prevent & treat exacerbations
- Reduce mortality

Not just FEV_1

- … with minimum side-effects

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)



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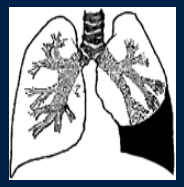
Impact of exacerbations

- Major cause of morbidity, mortality and hospital admissions[1,2]

- Higher exacerbation rate linked to[3,4]
  - More rapid decline in health status
  - More rapid decline in lung function
  - More chronic respiratory symptoms

1. Rodriguez-Roisin *Chest* 2000
2. Wedzicha *Novart Fdn Symp* 2001
3. Seemungal *AJRCCM* 1998
4. Donaldson *Thorax* 2002



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Impact of exacerbations

- In-patient mortality 7.4%
- Mortality 90 days 15.3%
- Re-admission rate 31.4%

Roberts *Thorax* 2003

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NICE guidelines - 2004

Smoking	Breathlessness & Exercise Limitation	Frequent Exacerbations	Respiratory Failure	Cor Pulmonale	Abnormal BMI	Chronic Productive Cough	Anxiety & Depression
• Offer help to stop smoking at every opportunity • Combine pharmaco-therapy with appropriate support as part of a programme	Stop therapy if ineffective • Use short-acting bronchodilator prn ($beta_2$-agonist or anticholinergic) • If still symptomatic try combined therapy with a short-acting $beta_2$-agonist and a short-acting anticholinergic • If still symptomatic use a long-acting bronchodilator ($beta_2$-agonist or anticholinergic) • **In moderate or severe COPD:** If still symptomatic consider a trial of combination of a long-acting $beta_2$-agonist and inhaled corticosteroid. **Discontinue if no benefit after 4 weeks** • If still symptomatic consider adding theophylline • Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled (usually MRC grade 3 and above) • Consider referral for surgery: bullectomy, LVRS, transplantation	• Offer annual influenza vaccination • Offer pneumococcal vaccination • Give self management advice • Optimise bronchodilator therapy with one or more long-acting bronchodilator ($beta_2$-agonist or anticholinergic) • Add inhaled corticosteroids if FEV_1 <50% and 2 or more exacerbations in a 12 month period. (N.B. These will usually be used with long-acting bronchodilators)	• Assess for appropriate oxygen: - LTOT - ambulatory - short burst • Consider referral for assessment for long-term domiciliary NIV	• Assess need for oxygen • Use diuretics	• Refer for dietetic advice • Give nutritional supplements if the BMI is low	• Consider trial of mucolytic therapy • Continue if symptomatic improvement	• Be aware of anxiety and depression and screen for them in those most physically disabled • Treat with conventional pharmaco-therapy

Palliative Care

Opiates can be used for the palliation of breathlessness in patients with end stage COPD unresponsive to other medical therapy
Use benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen when appropriate
Involve multidisciplinary palliative care teams

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NICE guidelines - 2004

Just updated

Smoking	Breathlessness & Exercise Limitation	Frequent Exacerbations	Respiratory Failure	Cor Pulmon	Abn…al …MI	Chronic Productive Cough	Anxiety & Depression
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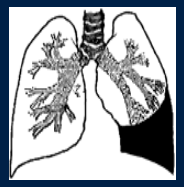

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Mortality improvements

- Existing treatments
  - Smoking cessation
  - LTOT (long term oxygen therapy)
  - LVRS (lung volume reduction surgery)

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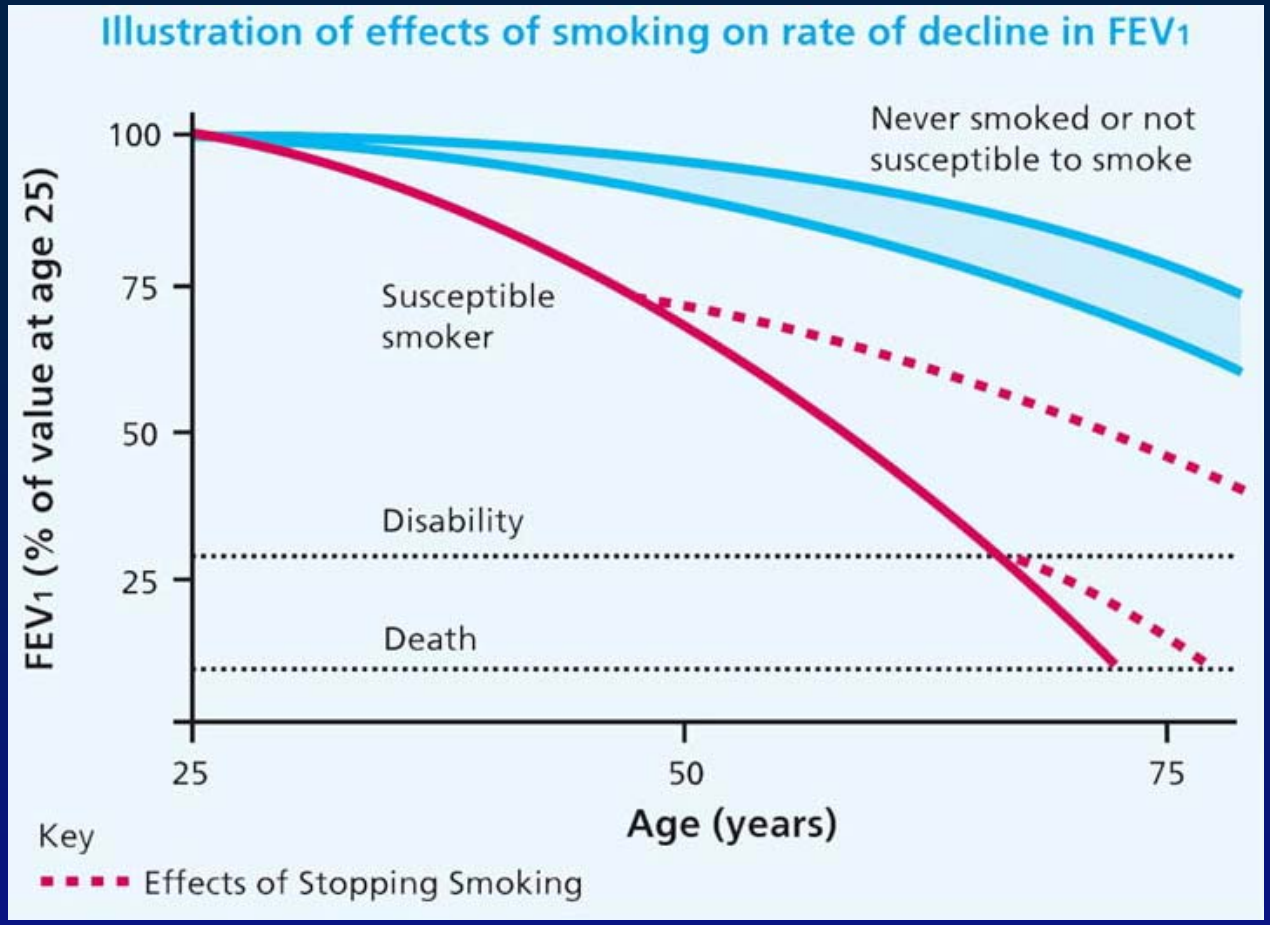
Smoking



Fletcher and Peto *BMJ* 1977

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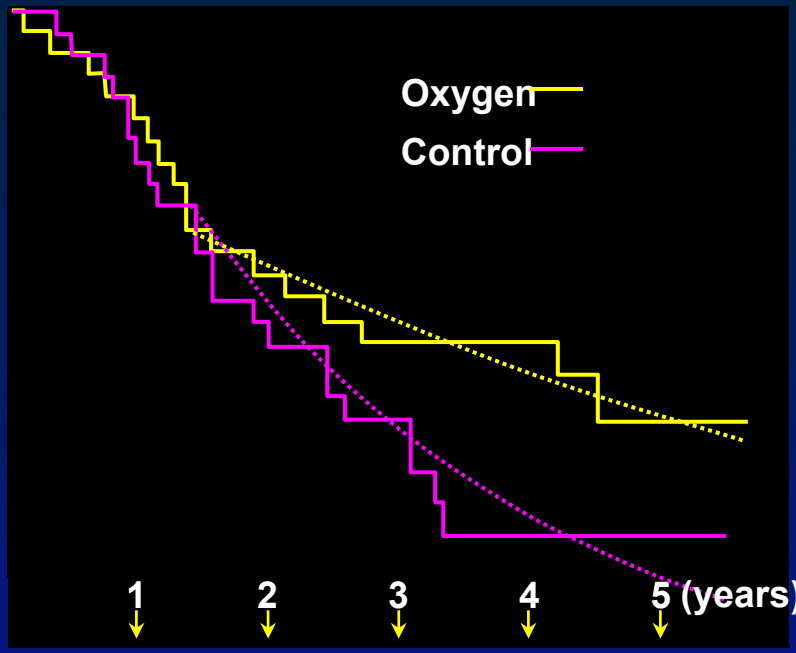
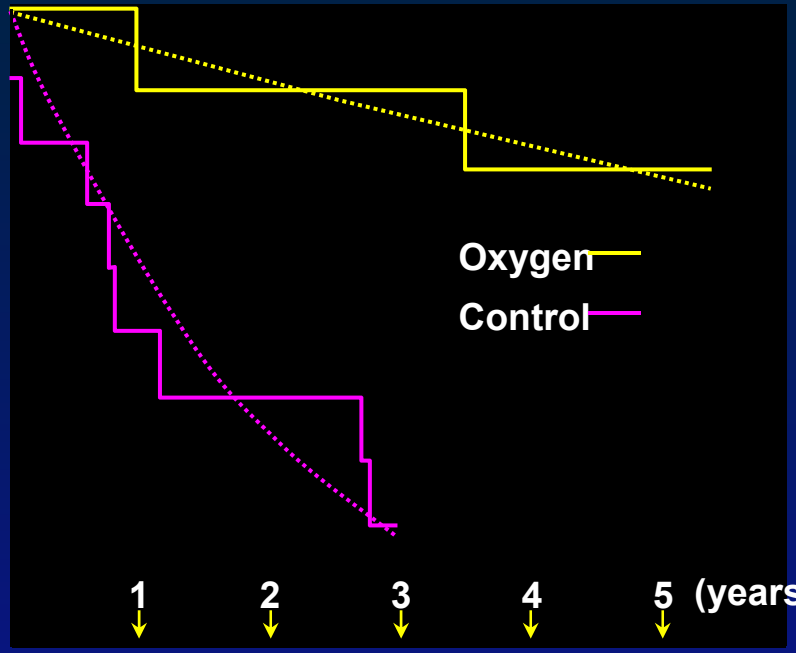
LTOT and mortality

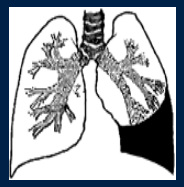
Mortality in male patients



Mortality in female patients



Medical Research Council Working Party *Lancet* 1981



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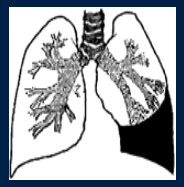
Lung Volume Reduction Surgery

- National Emphysema Treatment Trial (NETT)

- 1218 patients with severe emphysema
- compared LVRS to maximal medical therapy
- 6 to 10 weeks of pulmonary rehabilitation
- LVRS vs continued medical therapy

- Bilateral procedures removing 25-30% of most diseased portion of each lung

NETT trial *NEJM* 2003



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Lung Volume Reduction Surgery

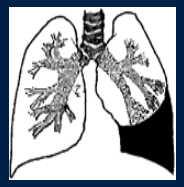
- Higher 90 day mortality post-LVRS than placebo due to peri-operative deaths

- Lower 5 year mortality in patients with upper lobe predominantly emphysema and low exercise capacity

NETT trial *NEJM* 2003

Patients	Total Mortality					
	Surgery Group		Medical-Therapy Group		Risk Ratio	P Value
	no. of deaths/ total no.	*no. of deaths/ person-yr*	*no. of deaths/ total no.*	*no. of deaths/ person-yr*		
All patients	157/608	0.11	160/610	0.11	1.01	0.90
High-risk†	42/70	0.33	30/70	0.18	1.82	0.06
Other	115/538	0.09	130/540	0.10	0.89	0.31
Subgroups‡						
Patients with predominantly upper-lobe emphysema						
Low exercise capacity	26/139	0.07	51/151	0.15	0.47	0.005
High exercise capacity	34/206	0.07	39/213	0.07	0.98	0.70
Patients with predominantly non–upper-lobe emphysema						
Low exercise capacity	28/84	0.15	26/65	0.18	0.81	0.49
High exercise capacity	27/109	0.10	14/111	0.05	2.06	0.02

NETT trial *NEJM* 2003



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Lung Volume Reduction Surgery

- Improved exercise capacity and QoL post-LVRS
- Trials with endobronchial valve insertion underway

NETT trial *NEJM* 2003

Drug trials

Short acting anticholinergics

Inhaled Corticosteroids (ICS)

N-Acetylcysteine

Long Acting Beta$_2$ Agonists/ICS

Long Acting Anticholinergic

LHS1 -1994
Ipratropium

EUROSCOP-1999
Budesonide

ISOLDE-2000
Fluticasone

BRONCUS -2005
N-Acetylcysteine

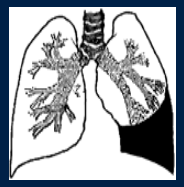
CCLS-1999
Budesonide

LHS II-2000
Triamcinolone

TORCH -2007
SALM + FP

UPLIFT-2008
Tiotropium

INSPIRE-2008
SALM + FP
v tiotropium



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TORCH – 2007

- Towards a revolution in COPD health

- Double blind, multinational RCT
- n=6112 over 3 years
- FEV1 <60%

- 4 arms
  - Seretide 500 bd (Salmeterol & Fluticasone)
  - Salmeterol 50 bd
  - Fluticasone 500 bd
  - Placebo

Calverley *NEJM* 2007

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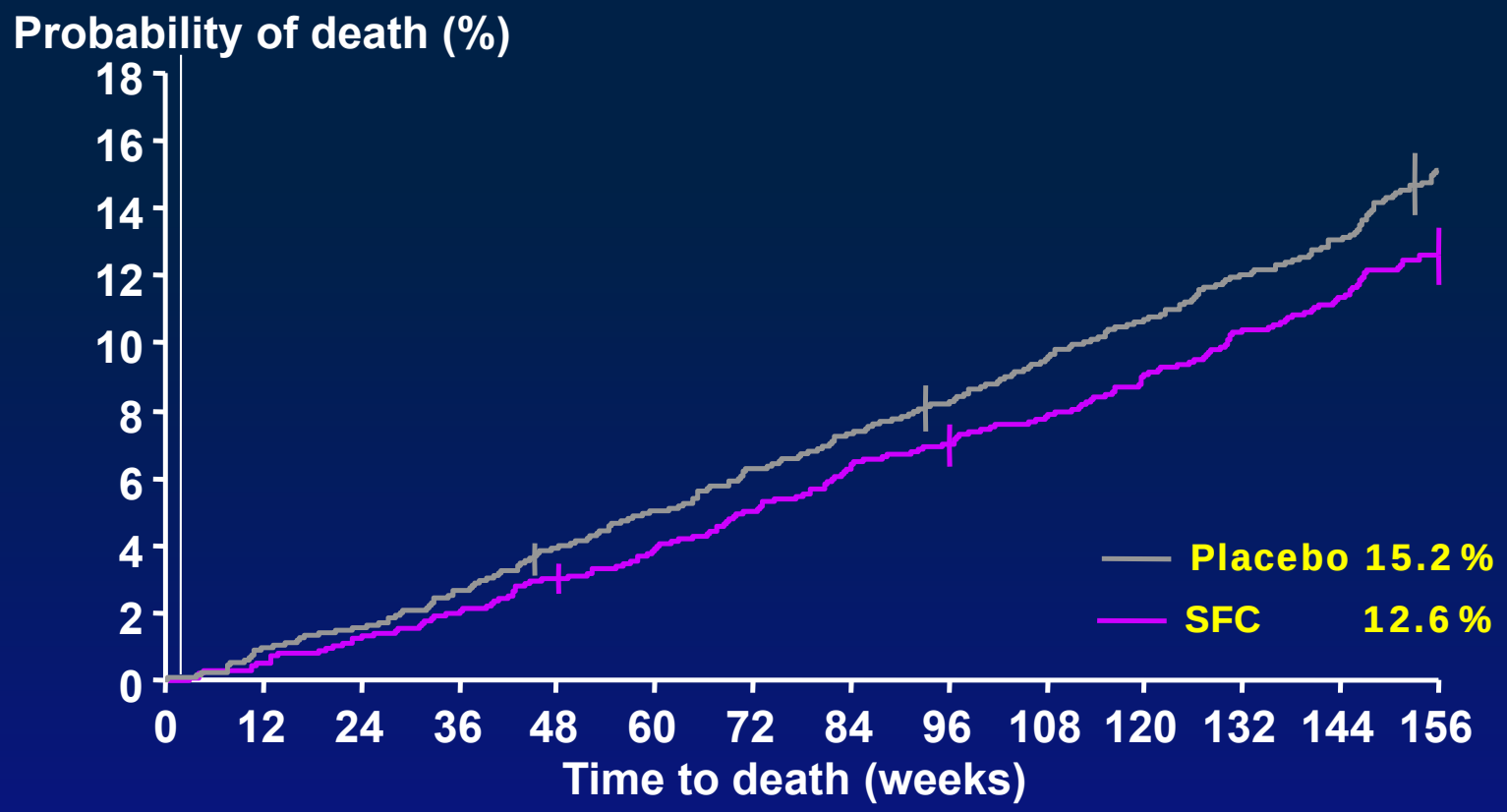
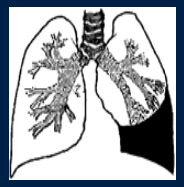
TORCH – primary endpoint



Vertical bars are standard errors

Calverley *NEJM* 2007



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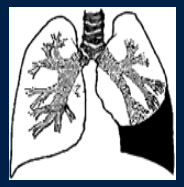
TORCH – primary endpoint

- Primary endpoint – mortality
  - 12.6% combination
  - 15.2% placebo
  - 13.5% salmeterol
  - 16.0% fluticasone

Not significant
(p=0.052)

- Deaths
  - 35% pulmonary causes
  - 27% cardiovascular
  - 21% cancer

Calverley *NEJM* 2007



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TORCH – secondary endpoints

- COPD exacerbations per annum
  - Exacerbation rate 1.13 cf 0.85 (25% decrease, $p < 0.001$)
  - Hospital admission rate reduced ($p<0.03$)

Calverley *NEJM* 2007
Celli *AJRCCM* 2008

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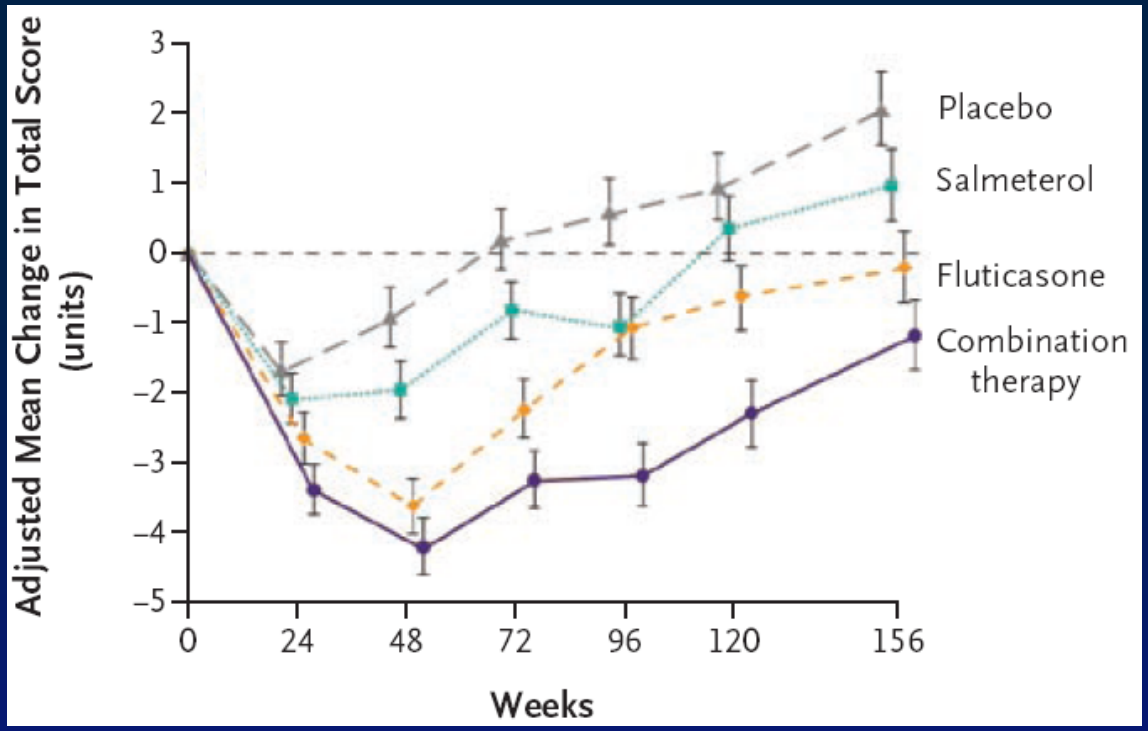
TORCH – secondary endpoints

- Health related quality of life
  - Improved SGRQ ($p < 0.001$)
  - ?clinically meaningful



Calverley *NEJM* 2007
Celli *AJRCCM* 2008

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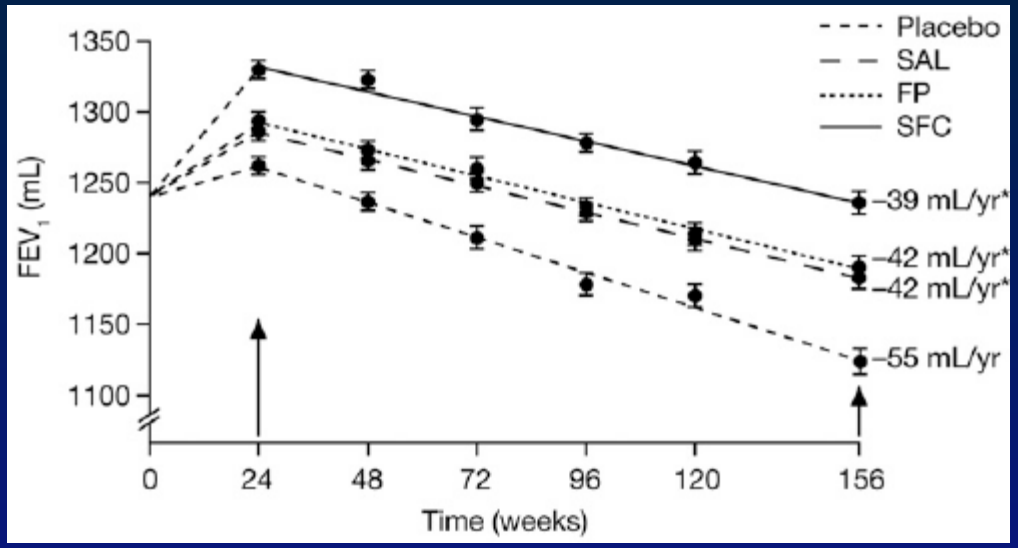
TORCH – secondary endpoints

- Lung function
  - Reduced decline in FEV1 in all active groups vs. placebo

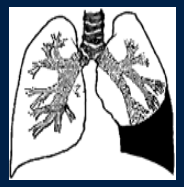
Combined 39ml/yr

Monotherapy 42ml/yr

Placebo 55ml/yr



Calverley *NEJM* 2007
Celli *AJRCCM* 2008



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TORCH – adverse events

- No difference in bony or ocular complications
- Pneumonia
  - Placebo 12.3%
  - Fluticasone 18.3%
  - Seretide 19.6%

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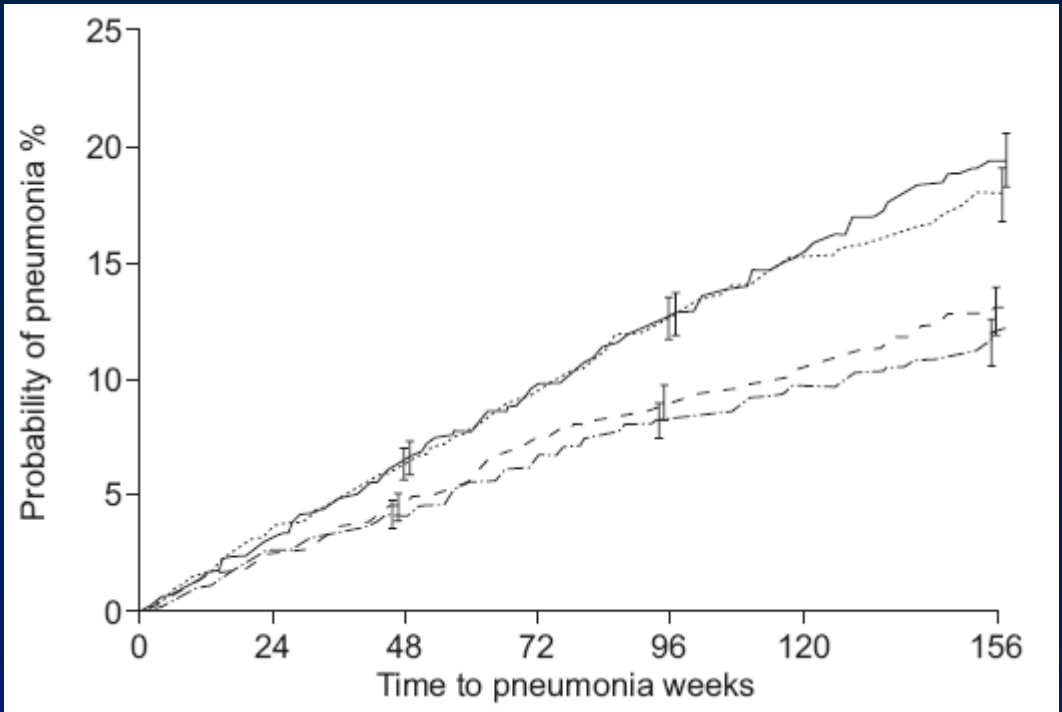
TORCH - time to pneumonia

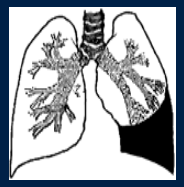


Seretide
Fluticasone

Salmeterol
Placebo

	SAL 50 µg	FP 500 µg	SFC 50 µg/500 µg	ICS overall
Hazard ratio¶	1.09	1.53	1.64	1.52+
95% CI¶	0.87–1.37	1.24–1.89	1.33–2.02	1.32–1.76+
p-value¶	0.465	<0.001	<0.001	<0.001+

Crim *ERJ* 2009



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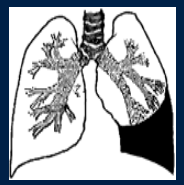
TORCH – conclusions

- Monotherapy with LABA seems safe
- Monotherapy with ICS should not be advocated
- Stepwise approach

- Trial issues;
  - Interim analysis reduced power
  - Lower overall death rate in placebo meant that number of patients recruited had to be increased
  - 40% subjects dropped out – problem of placebo for 3 years



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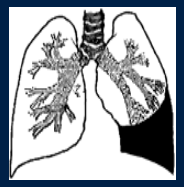
UPLIFT – 2008

- Understanding potential long term impacts on function with Tiotropium

- Double blind, multinational RCT
- n=5993 over 4 years

- 2 arms Tiotropium
  Placebo in COPD patients (46% mild)

Tashkin *NEJM* 2008



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UPLIFT – endpoints

- Primary endpoint
  - Rate of decline of FEV_1
- Secondary endpoints
  - FVC
  - Quality of life (SGRQ)
  - Exacerbations, hospitalisations
  - Mortality

Tashkin *NEJM* 2008

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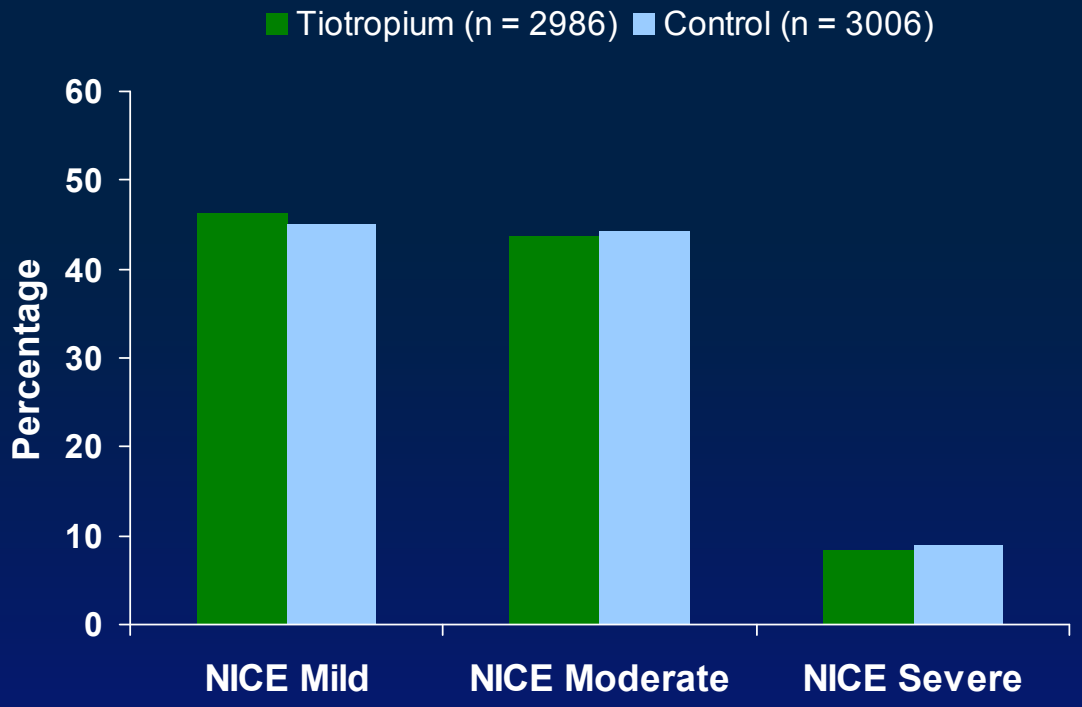
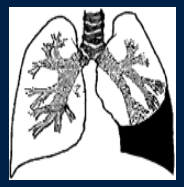
Design considerations vs. TORCH

- COPD severity



GOLD		NICE	
Patient classification	FEV_1 value	Patient classification	FEV_1 value
Mild	70-80%	Mild	50-80%
Moderate	50-80%	Moderate	30-49%
Severe	30-50%	Severe	<30%
Very Severe	≤30%		



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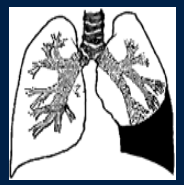
Design considerations vs. TORCH

- Placebo component of TORCH (no treatment) attracted criticism

- UPLIFT placebo arm were allowed all usual respiratory medications (apart from inhaled anticholinergics)



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UPLIFT maintenance drugs

Medication (%)	Tiotropium (n=2985)	Placebo (n=3006)
Long-acting beta agonists*	72	72
Inhaled steroids*	74	73
Xanthines (i.e. Theophylline compounds)	35	35

*alone or in combination

Tashkin *NEJM* 2008

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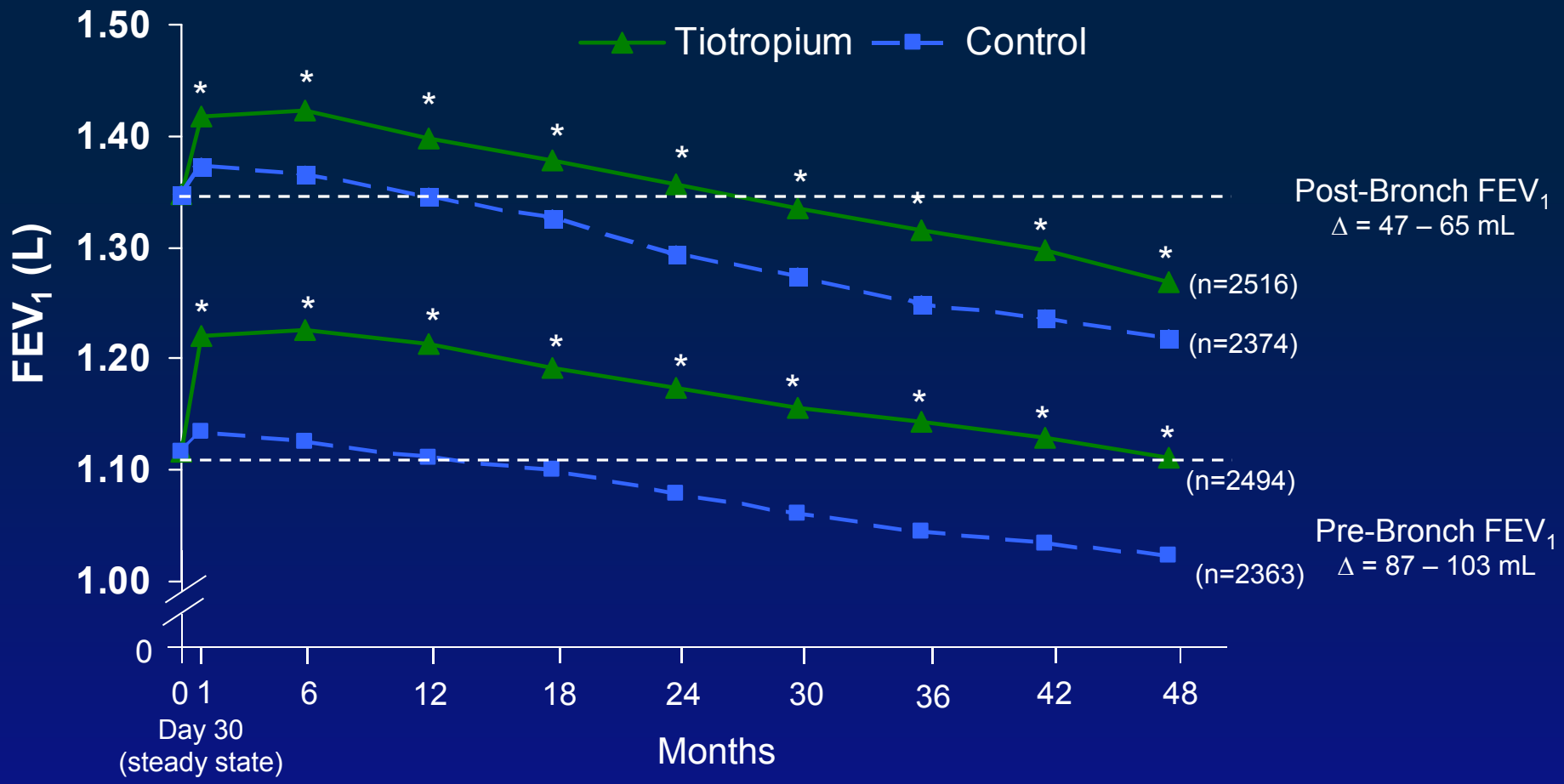
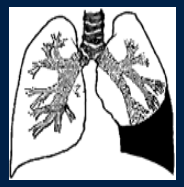
UPLIFT – primary endpoint



Tashkin *NEJM* 2008



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UPLIFT – primary endpoint

- No reduction in rate of decline FEV_1
- FEV_1 consistently improved while on tiotropium

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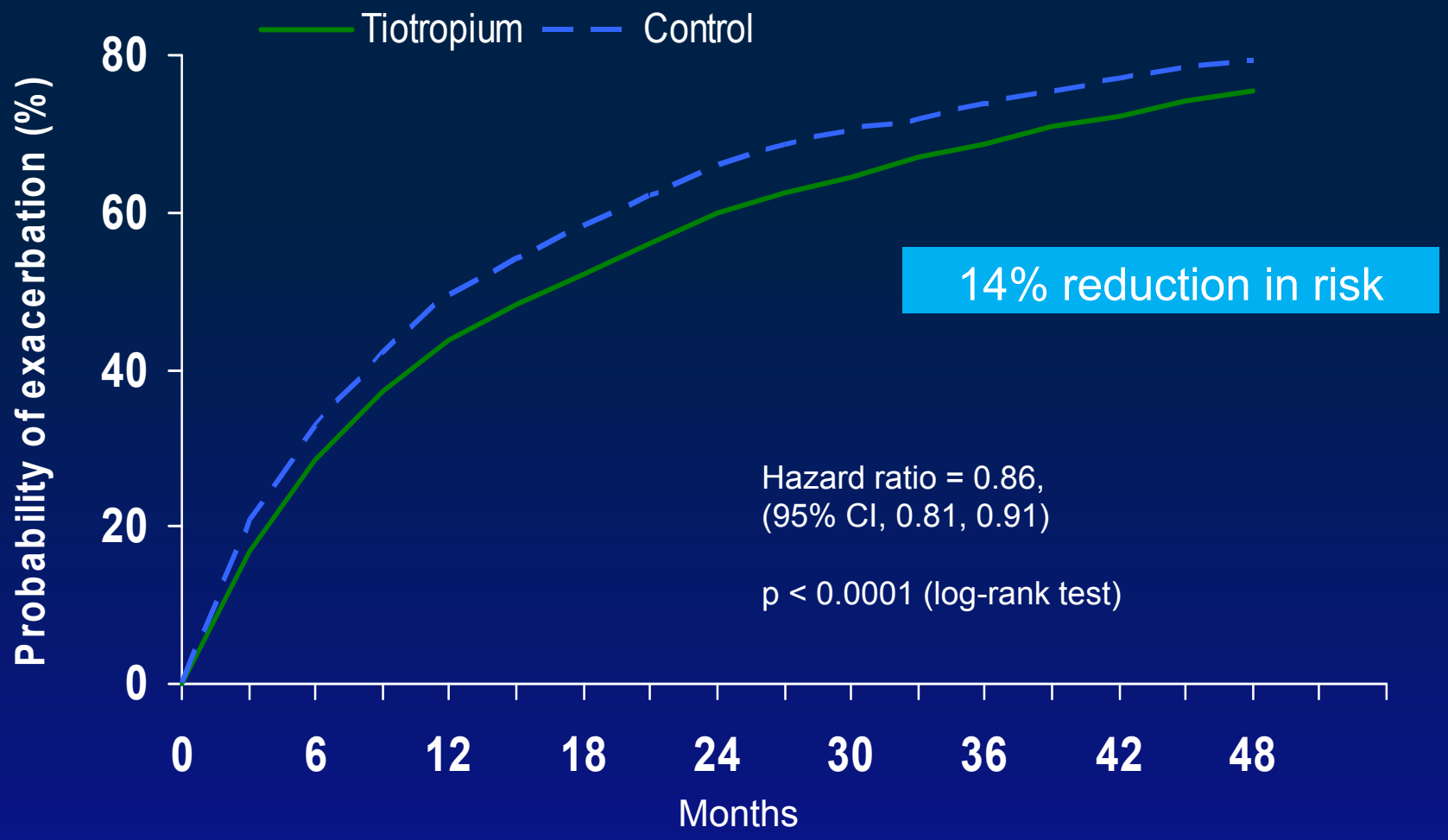
Exacerbations



Tashkin *NEJM* 2008

First exacerbation

	Tiotropium (N=2986)	Control (N=3006)	Δ Contol – Tiotropium (months)
	Median (95% CI)	Median (95% CI)	
Median time to first exacerbation (month)	16.7 (14.9, 17.9)	12.5 (11.5, 13.8)	-4.2

33% delay in time to first exacerbation = 4.2 months

$p < 0.001$

Tashkin *NEJM* 2008

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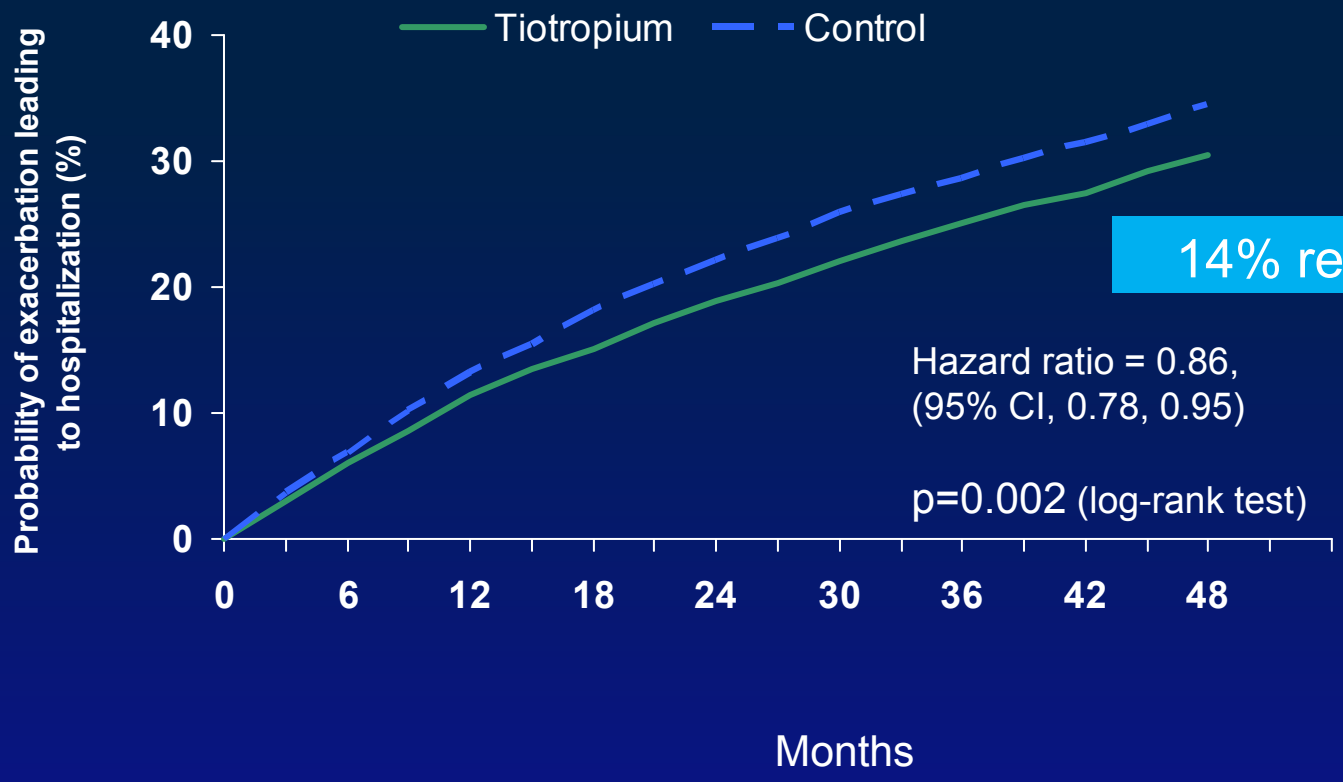
Hospitalisations



Tashkin *NEJM* 2008

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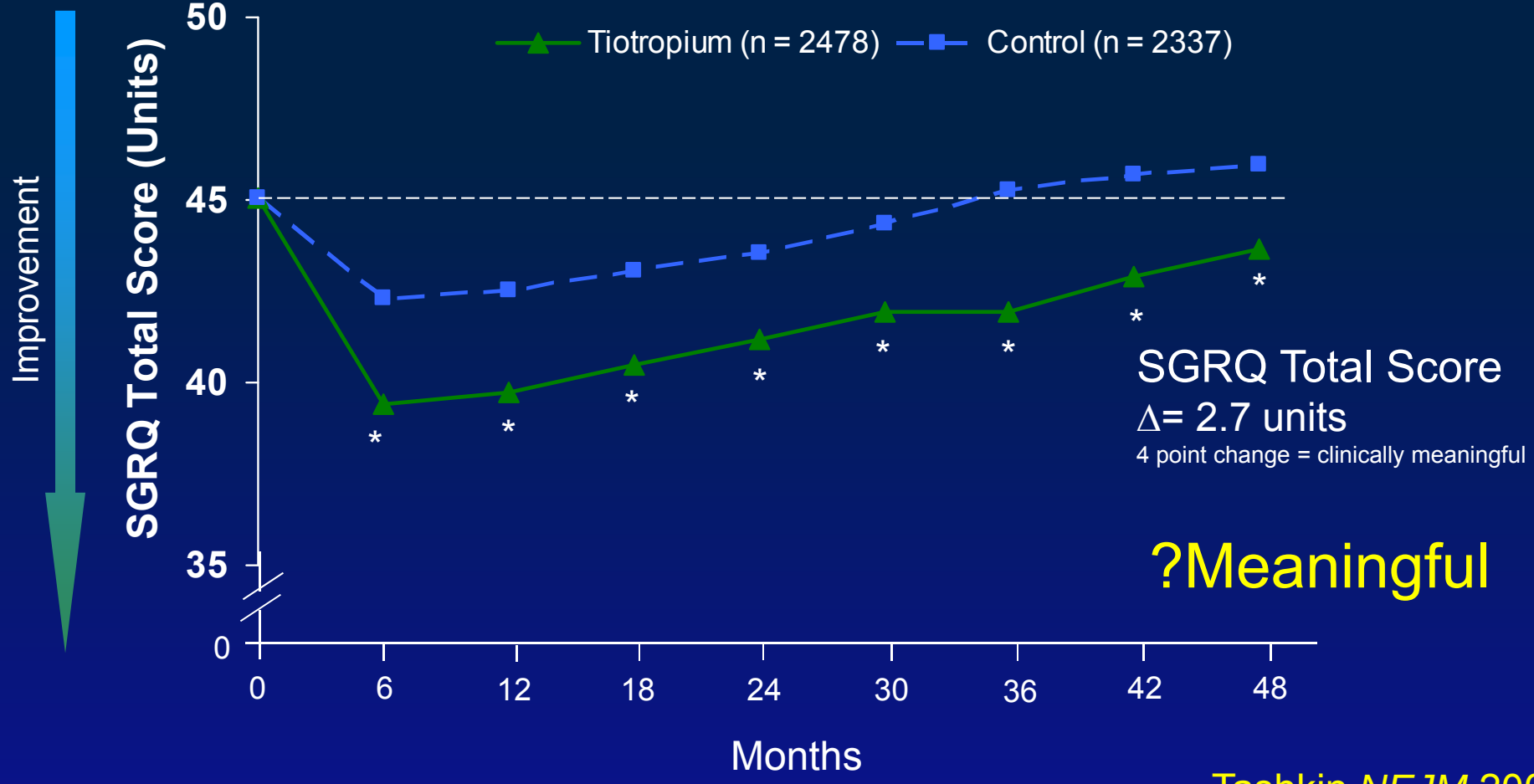
Quality of Life



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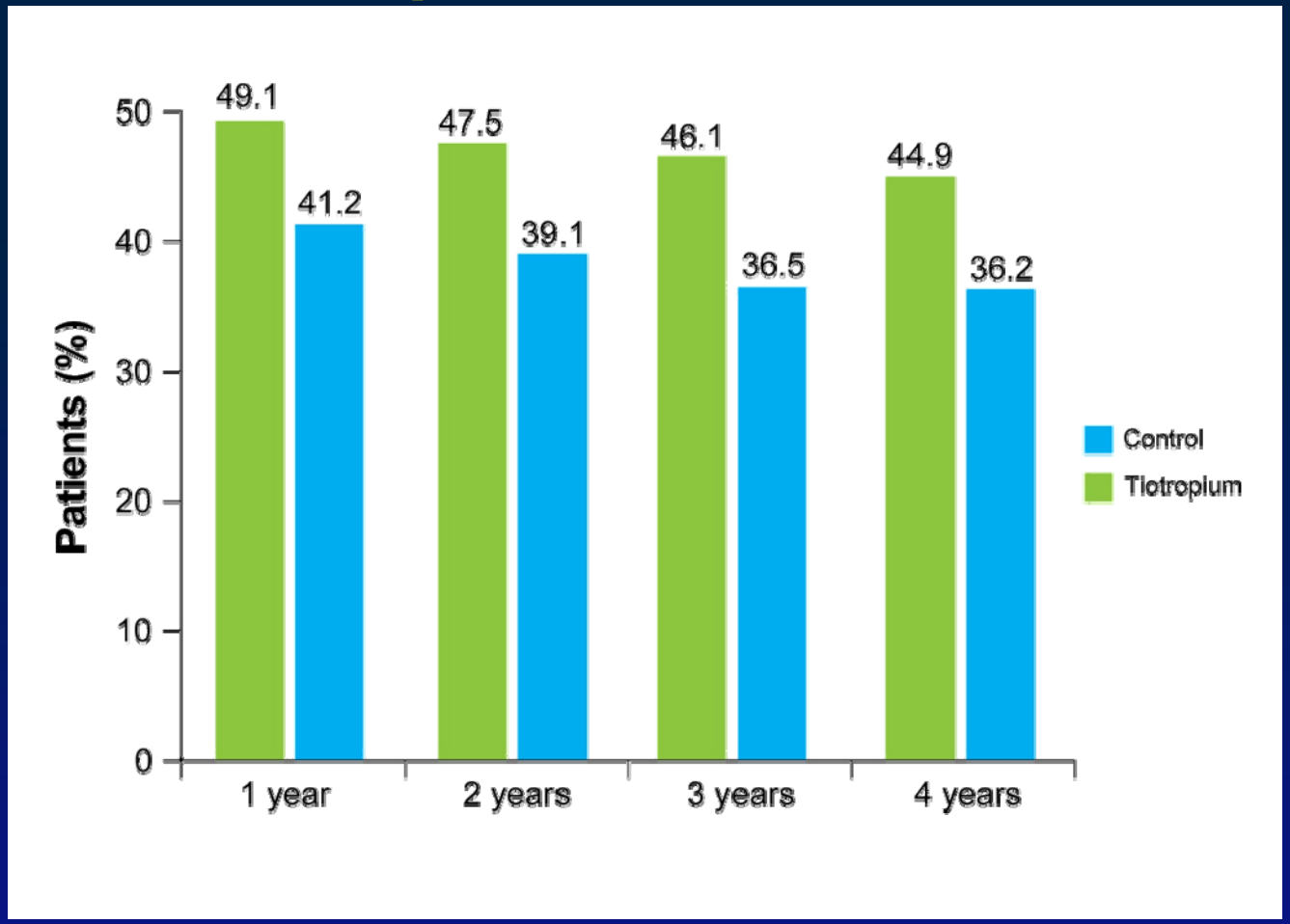
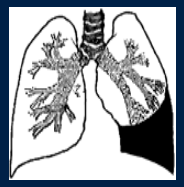
≥4 unit improvement in SGRQ



All p-values at all time points <0.001; *compared to Day 1

Tashkin *NEJM* 2008



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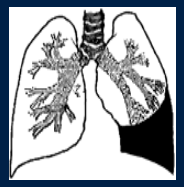
Mortality

	Control	Tiotropium	ΔRates	Hazard ratio Tiotropium vs. control		
	N (%)	N (%)		HR	95% CI	P-value
On-treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital status (Day 1470)	495(16.5)	446 (14.9)	1.9%	0.89	0.79, 1.02	0.086

Tashkin *NEJM* 2008



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Causes of death

	Tiotropium n=2986	Control n=3006	Rate Ratio (Tio/Con)	95% CI
Cardiac	3.56	4.21	0.84	0.73, 0.98*
Angina	0.51	0.36	1.44	0.91, 2.26
Atrial fibrillation	0.74	0.77	0.95	0.68, 1.33
Cardiac failure	0.61	0.48	1.25	0.84, 1.87
Cardiac failure congestive	0.29	0.48	0.59	0.37, 0.96*
Coronary artery disease	0.21	0.37	0.58	0.33, 1.01
Myocardial infarction	0.69	0.97	0.71	0.52, 0.99*
Respiratory (lower)	11.32	13.47	0.84	0.77, 0.92*
Bronchitis	0.37	0.31	1.20	0.73, 1.98
COPD exacerbation	8.19	9.70	0.84	0.76, 0.94*
Dyspnea	0.38	0.62	0.61	0.40, 0.94*
Pneumonia	3.28	3.46	0.95	0.81, 1.11
Respiratory failure	0.90	1.31	0.69	0.52, 0.92*

*p<0.05;

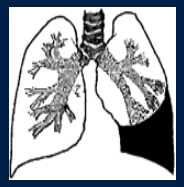
Tashkin *NEJM* 2008

UPLIFT NICE mild COPD subgroup

- Tiotropium maintained significant improvements in
  - lung function (including post-bronchodilator rate of decline in FEV1)
  - health-related quality of life
  - reduced exacerbations
  - over 4 years in patients with GOLD Stage II disease.

- ?Treat patients earlier in their disease

Decramer *Lancet* 2009



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Putting it all together!

- FEV_1 is not the whole picture
- Exacerbations may be best predictor of natural history

- TORCH (Fluticasone/Salmeterol)
  - Improvement in lung function decline
  - No change in mortality
- UPLIFT (Tiotropium)
  - Reduced exacerbations, hospitalisations and respiratory failure
  - Improved mortality and cardiovascular morbidity

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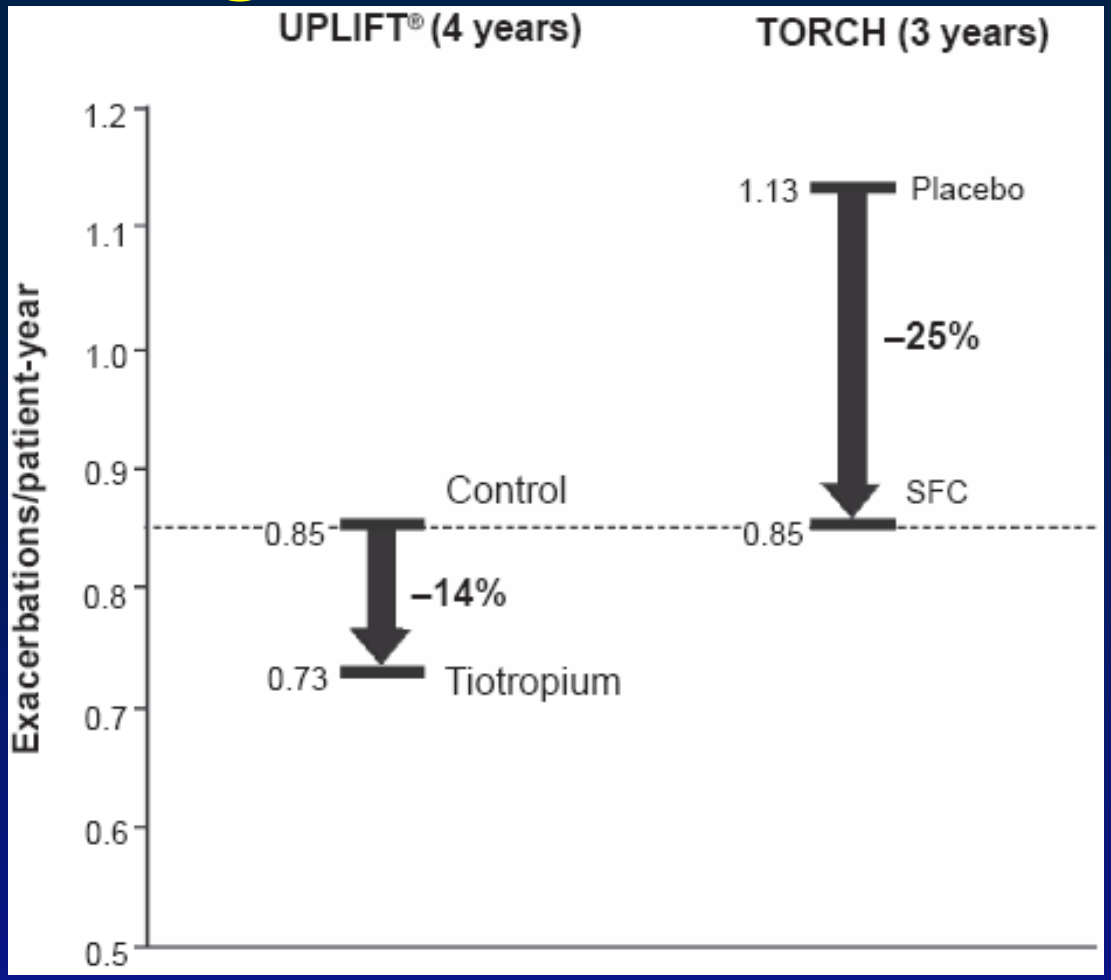
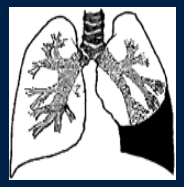
Putting it all together!

Exacerbations



Miravitlles *IJCOPD* 2009



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Putting it all together!

Exacerbations

- INSPIRE compared Seretide vs. Tiotropium for exacerbation rate (primary outcome)
- No significant difference

- n=1323, 2 year RCT

Wedzicha *AJRCCM* 2008

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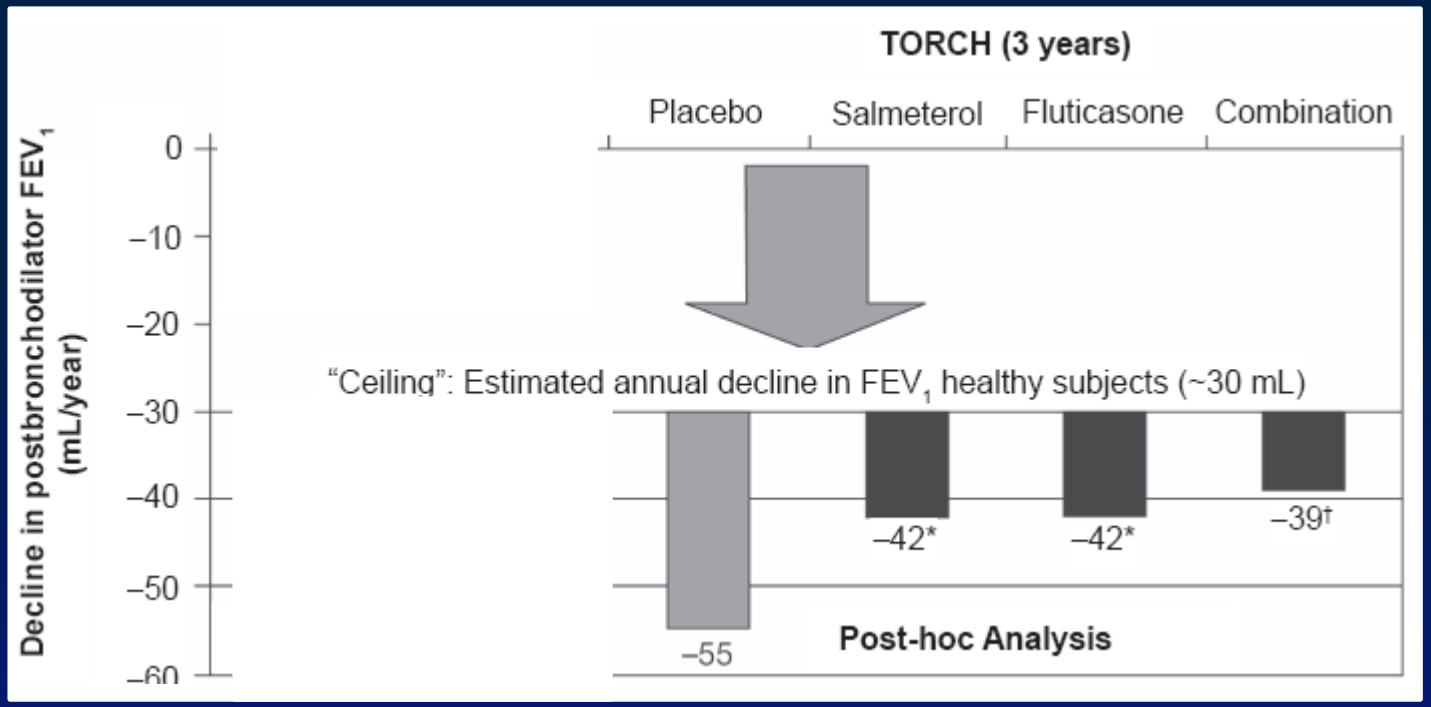
Putting it all together!



Ceiling effect in FEV_1 decline

Miravitlles *IJCOPD* 2009

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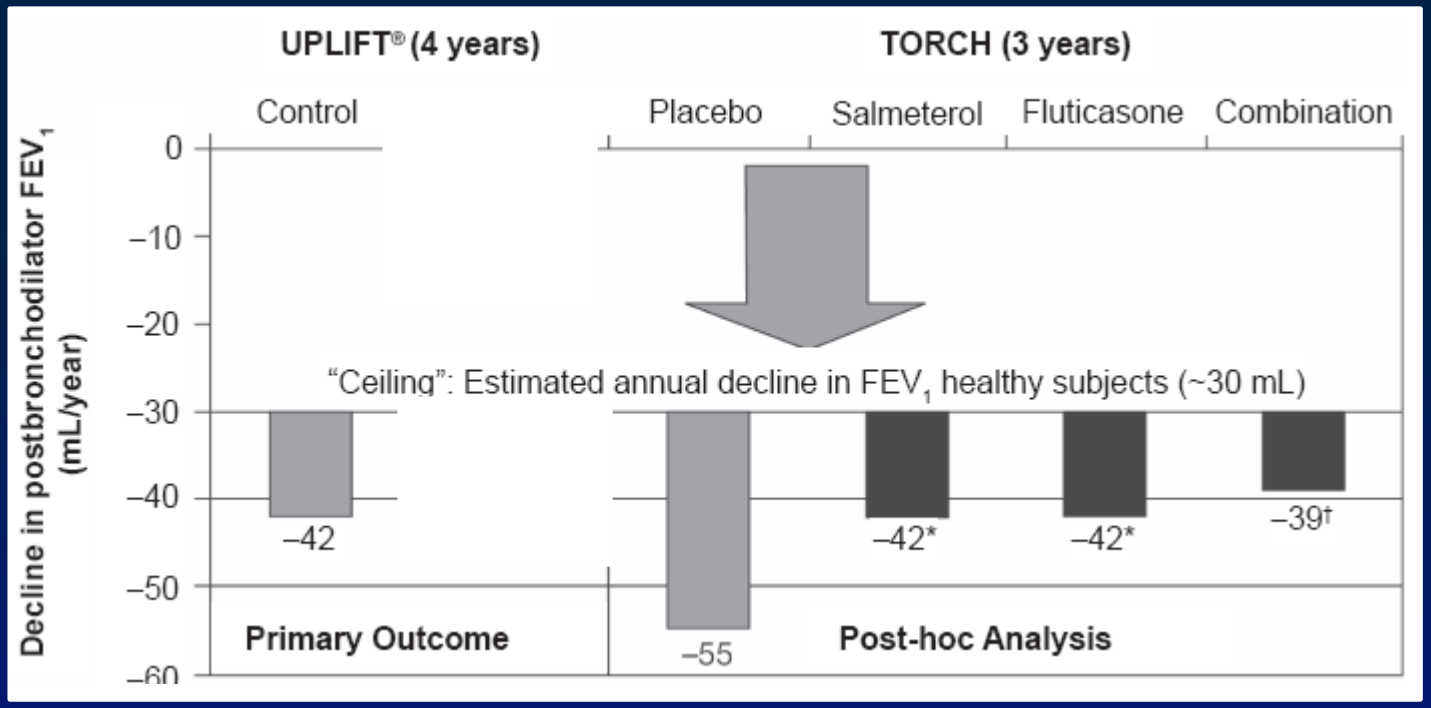

Ceiling effect in FEV_1 decline

Miravitlles *IJCOPD* 2009

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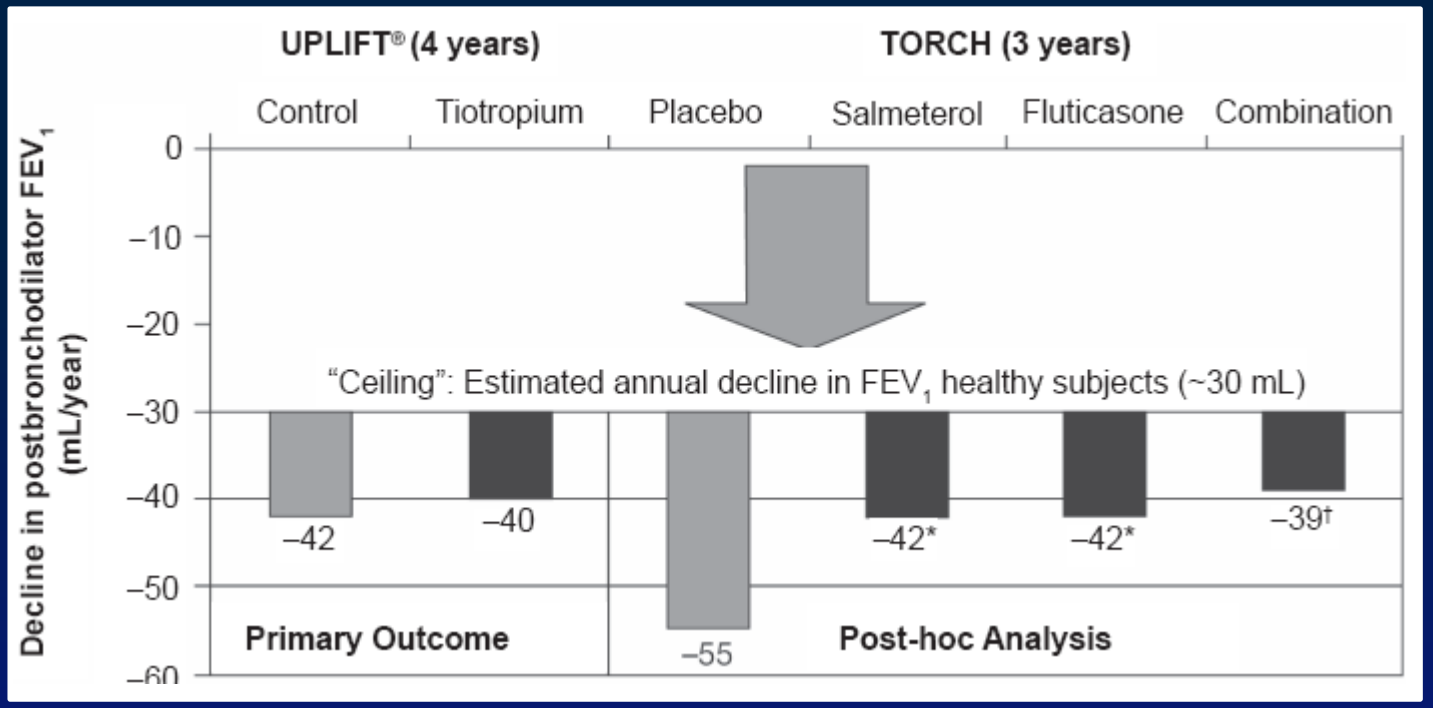
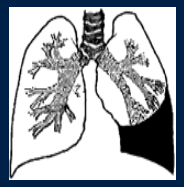
Putting it all together!



Ceiling effect in FEV_1 decline

Miravitlles *IJCOPD* 2009



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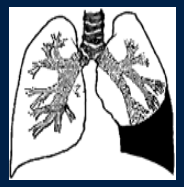
Implications

- Intervention really does make a difference
  - Smoking cessation
  - Striking mortality benefit with appropriate long term oxygen therapy
    - Home oxygen assessment service
  - Lung volume reduction surgery may confer QoL and mortality improvements for appropriate patients



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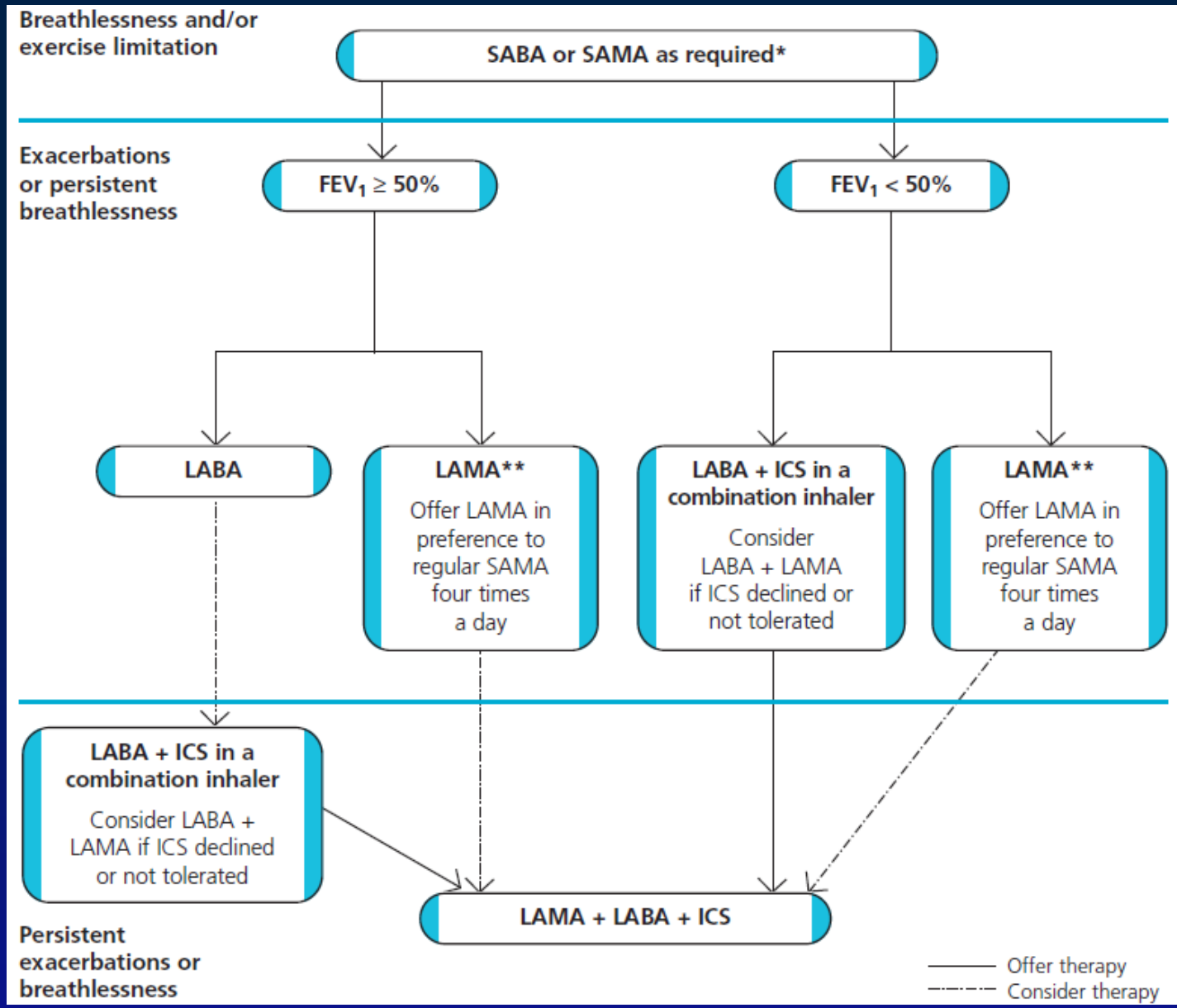
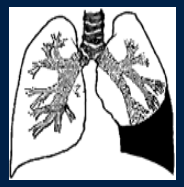
Implications

- Interventions really does make a difference
  - Treating COPD early improves exacerbation rate and QoL indices even for mild disease.
    - Treat earlier?
    - Tiotropium may have an effect on rate of decline of FEV_1 at early stage
  - Avoid ICS monotherapy
  - Adverse event profile
  - Effects additive
    - Stepwise approach reasonable


Breathlessness and/or exercise limitation
SABA or SAMA as required*
Exacerbations or persistent breathlessness
FEV1 ≥ 50%
FEV1 < 50%
LABA
LAMA**
Offer LAMA in preference to regular SAMA four times a day
LABA + ICS in a combination inhaler
Consider LABA + LAMA if ICS declined or not tolerated
LAMA**
Offer LAMA in preference to regular SAMA four times a day
LABA + ICS in a combination inhaler
Consider LABA + LAMA if ICS declined or not tolerated
LAMA + LABA + ICS
Persistent exacerbations or breathlessness
Offer therapy
Consider therapy



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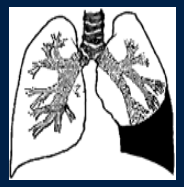
- Pathology
- Guidelines
- Historical trials
- Recent ‘mega’ trials



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Thank you

- Questions?

- John.Wrightson@orh.nhs.uk