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COPD update – how to avoid exacerbations and hospital admissions

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Structure

- Pathology
- Admission and exacerbation avoidance
- Evidence

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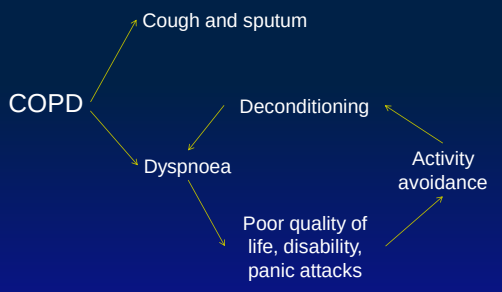
Cycle of decline



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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

Post bronchodilator spirometry

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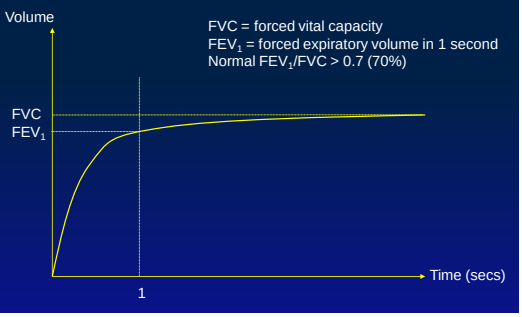
Spirometry



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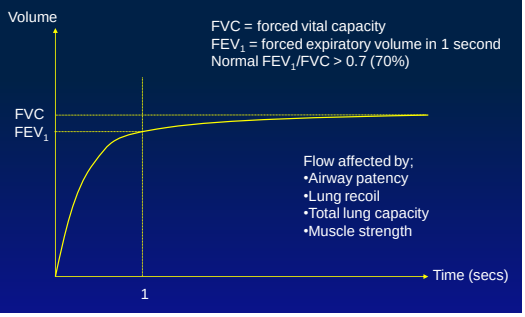
Spirometry



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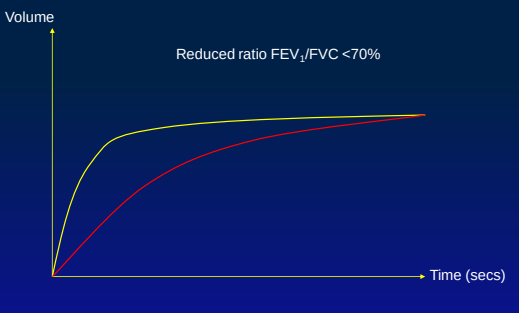
Airflow obstruction



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Severity of COPD

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

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Severity of COPD

		NICE clinical guideline 12 (2004)	ATS/ERS 2004[3]	GOLD 2008[4]	NICE clinical guideline 101 (2010)
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< 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

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)

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GOLD goals

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- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent & treat complications
- Prevent & treat exacerbations
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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 guidance

Smoking	Breathlessness & exercise limitation	Frequent exacerbations	Respiratory failure	Cor pulmonale	Abnormal BMI	Chronic productive cough	Anxiety and depression
Offer help to stop smoking at every opportunity	Optimise inhaled therapy using algorithm	Influenza vaccination	Assess for oxygen: •LTOT •Ambulatory •Short burst	Assess need for oxygen	Dietetic advice	Mucolytic trial	Screen for anxiety and depression
Combine pharmaco-therapy with support programme	Consider theophylline if still symptomatic	Pneumococcal vaccination	Consider long-term domiciliary NIV	Diuretics	Nutritional supplements for low BMI	Continue if improvement	
	Pulmonary rehabilitation to all those functionally disabled including those who have had a recent hospitalisation	Self-management advice					
	Consider bullectomy, LVRS, transplantation	Optimise inhaler therapy using algorithm					

Palliative care
Opiates when appropriate for end-stage COPD unresponsive to other therapy
Use benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen when appropriate.
Involve multidisciplinary palliative care teams.

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Exacerbation & admission avoidance

- Patient identification
  - Measured prevalence 1%
  - Estimated prevalence 2.4%
  - 10% of COPD admissions previously undiagnosed

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Exacerbation & admission avoidance

- Patient identification
- Vaccination

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Exacerbation & admission avoidance

- Patient identification
- Vaccination
- Smoking cessation

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Smoking

Fletcher and Peto *BMJ* 1977

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Exacerbation & admission avoidance

- Patient identification
- Vaccination
- Smoking cessation
- Self management advice
  - Appropriate involvement of respiratory nursing team

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Exacerbation & admission avoidance

- Patient identification
- Vaccination
- Smoking cessation
- Self management advice
- Pulmonary rehabilitation
  - Functional impairment
  - Recent discharge from hospital

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Pulmonary rehabilitation

	Pre rehabilitation	**Post rehabilitation**	***p***
n	186	186	
Admissions	90	49	<0.001
Days in hospital	723	398	<0.01
Average stay (days)	8.0	8.1	NS

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Exacerbation & admission avoidance

- Patient identification
- Vaccination
- Smoking cessation
- Self management advice
- Pulmonary rehabilitation
- Consideration of LTOT
  - Referral to HOAS if saturations <92%

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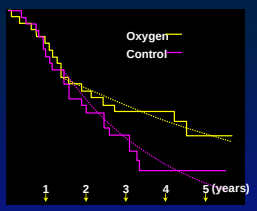
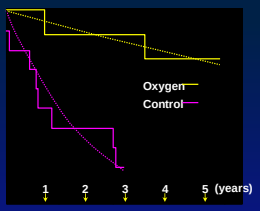
LTOT and mortality

Mortality in male patients



Mortality in female patients



Medical Research Council Working Party *Lancet* 1981

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Exacerbation & admission avoidance

- Patient identification
- Vaccination
- Smoking cessation
- Self management advice
- Pulmonary rehabilitation
- Consideration of LTOT
- Consideration of outpatient referral

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Outpatient referral

- Medical, nursing, lung function, physiotherapy, imaging
  - Diagnostic uncertainty
  - Severe COPD, cor pulmonale, rapid decline
  - Consideration of surgery
    - Bullectomy
    - LVRS
    - Lung transplantation

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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

NETT trial *NEJM* 2003

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Lung Volume Reduction

- Non-surgical techniques
  - Valves
  - Coils
  - Gel
  - Airway bypass tract

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Outpatient referral

- Medical, nursing, lung function, physiotherapy, imaging
  - Diagnostic uncertainty
  - Severe COPD, cor pulmonale, rapid decline
  - Consideration of surgery
    - Bullectomy
    - LVRS
    - Lung transplantation
  - Fitness to fly assessment

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Fitness to fly

- Healthy – saturations in flight 85-91%

- Saturations >95% — OK
- Saturations 92%-95% with FEV_1 ≥50% — OK
- Saturations 92%-95% with FEV_1 <50% — Assess
- Saturations <92% — Oxygen

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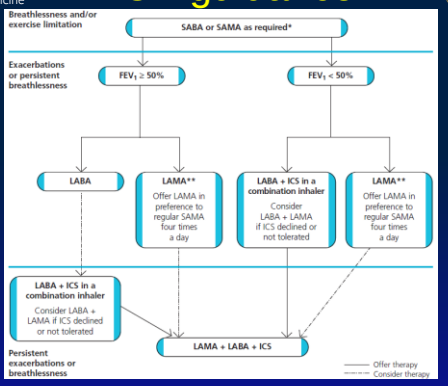
NICE guidance



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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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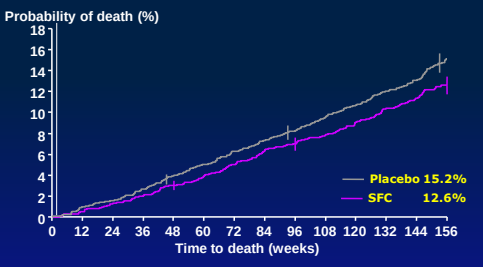
TORCH – primary endpoint



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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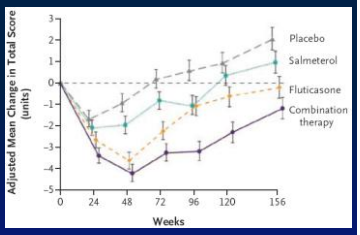
TORCH – secondary endpoints

- Health related quality of life
  - Improved SGRQ (p< 0.001)



Calverley *NEJM* 2007
Celli *AJRCCM* 2008

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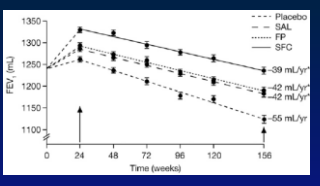
TORCH – secondary endpoints

- 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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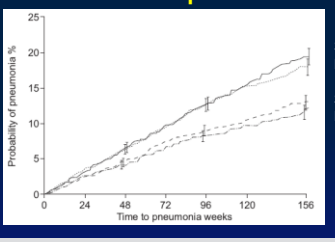
TORCH - time to pneumonia



Seretide
Fluticasone

Salmeterol
Placebo

	SAL 50 µg	FP 500 µg	SFC 50 µg/500 µg	ICS overall
Hazard ratio[1]	1.09	1.53	1.64	1.52*
95% CI[1]	0.87–1.37	1.24–1.89	1.33–2.02	1.32–1.76*
p-value[1]	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

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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

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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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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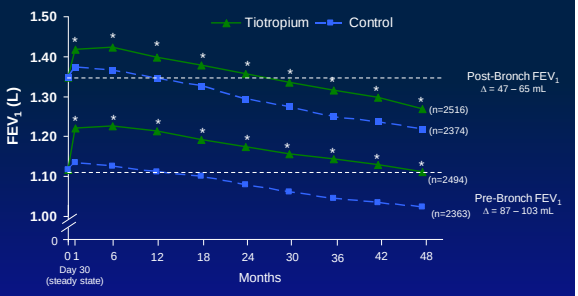
UPLIFT – primary endpoint



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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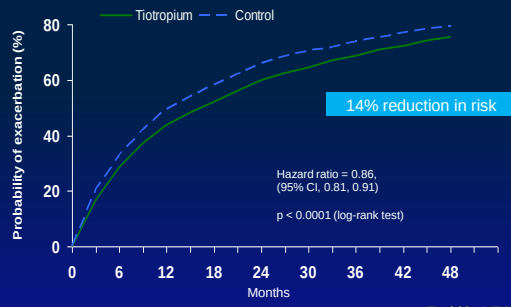
Exacerbations



Tashkin *NEJM* 2008

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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

p < 0.001

33% delay in time to first exacerbation = 4.2 months

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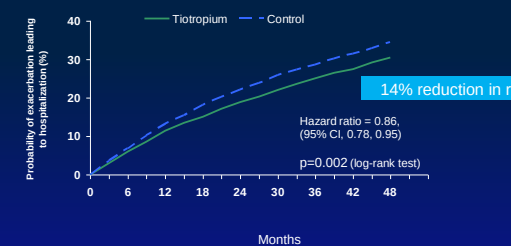
Hospitalisations



Tashkin *NEJM* 2008

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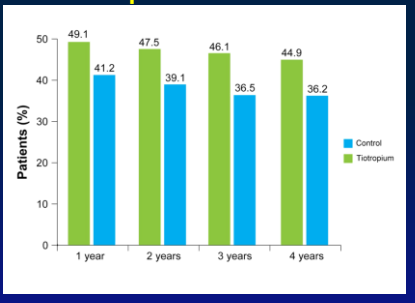
≥4 unit improvement in SGRQ



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

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UPLIFT NICE moderate 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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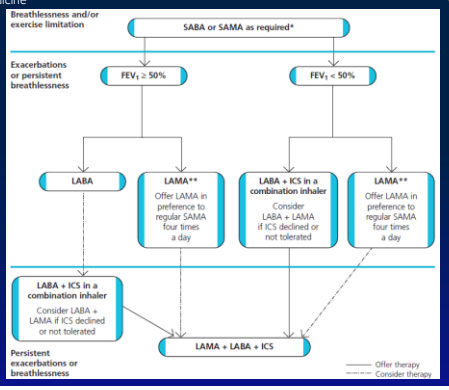

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LABA vs LAMA

- POET-COPD – Prevention of exacerbations with Tiotropium in COPD
- Double blind, multinational RCT
- n=7376 over 1 year
- 2 arms Tiotropium Handihaler
  Salmeterol

Vogelmeier *NEJM* 2011

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LABA vs LAMA

- Moderate to very severe COPD
- Primary endpoint – time to first exacerbation
  - Increasing symptoms
  - Requirement for oral steroids or antibiotics or admission
  - Improved with Tiotropium (187 vs. 145 days)
  - 17% reduction in risk over one year

Vogelmeier *NEJM* 2011

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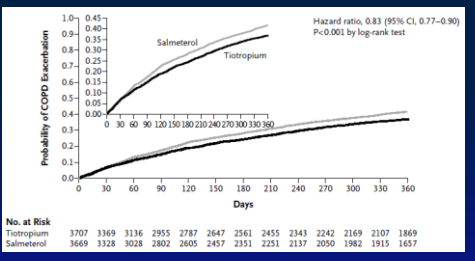
LABA vs LAMA



Vogelmeier *NEJM* 2011

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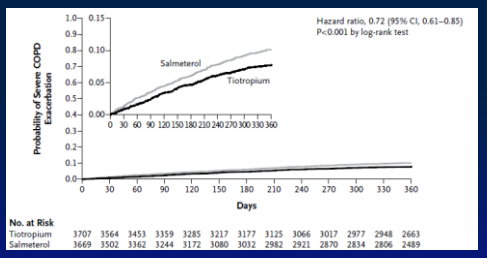
LABA vs LAMA



Vogelmeier *NEJM* 2011

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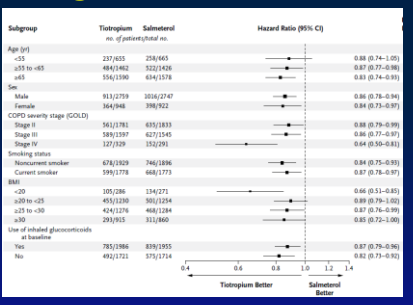
LABA vs LAMA



Vogelmeier *NEJM* 2011

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Implications

- Interventions really do 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 do 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

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- Pathology
- Guidelines
- Evidence

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Thank you

- Questions?
- John.Wrightson@orh.nhs.uk