

## Hopes come to reality in Chronic Obstructive Pulmonary Disease patient

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COPD

What can we do ???



### Goal of COPD treatment

- ◆ Relieve symptoms
  - ◆ Improve exercise tolerance
  - ◆ Improve health status
  - ◆ Prevent and treat exacerbations
- Short term
- ↓
- Prevent and treat complications
  - Prevent disease progression
  - Reduce mortality
- Long term
- Better living and longer life

GOLD 2007 updated

## Can we change COPD ?

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- ◆ COPD is a progressive disease !!
- ◆ Can we impact COPD progression ?
- ◆ UPLIFT Study - results
- ◆ So...what is next ??

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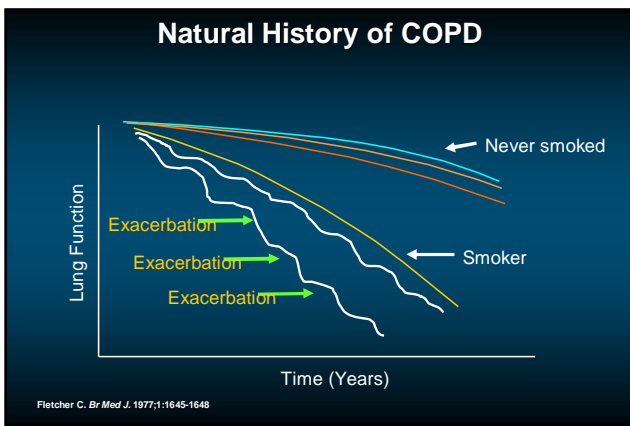
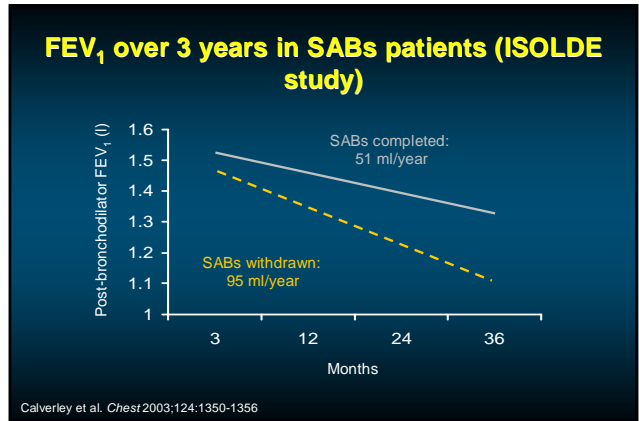
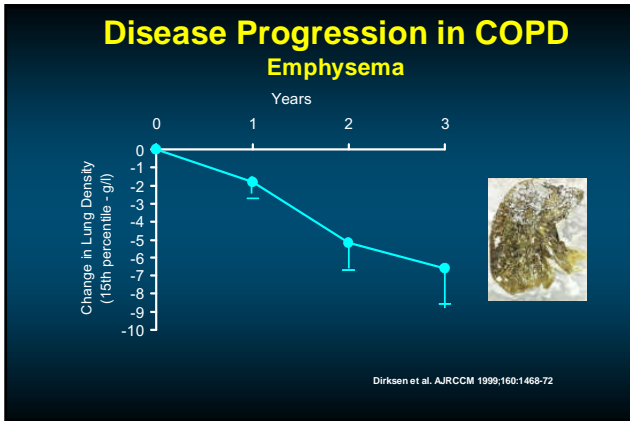
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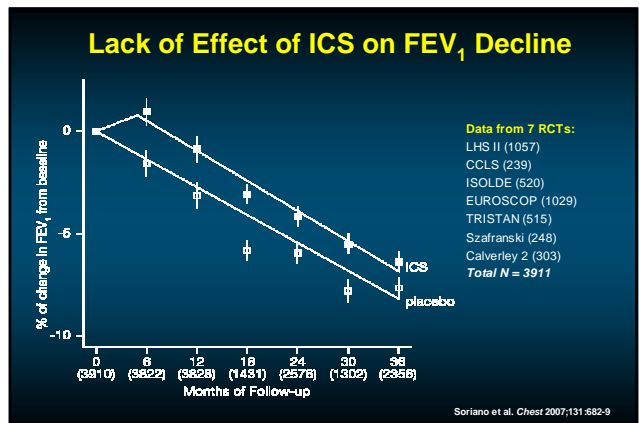
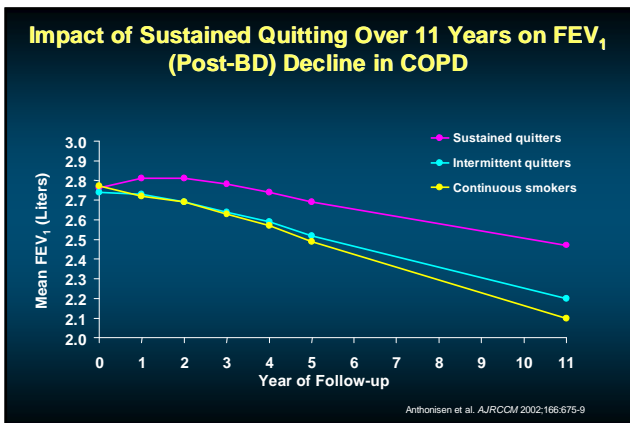
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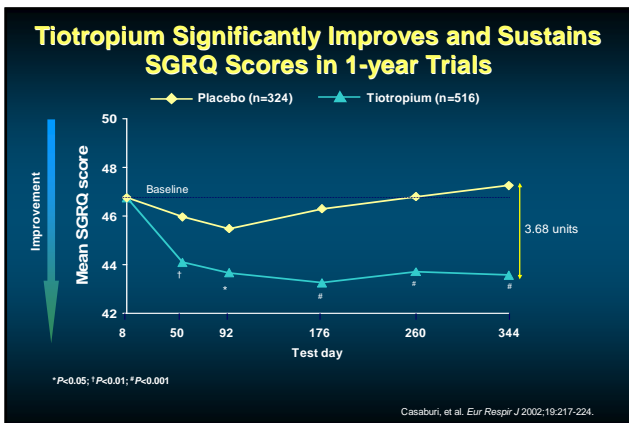
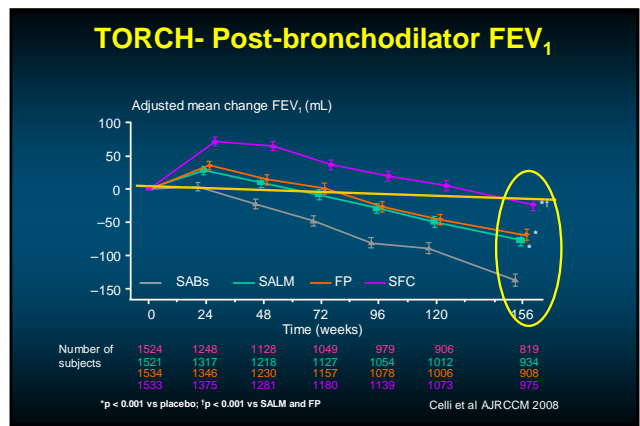
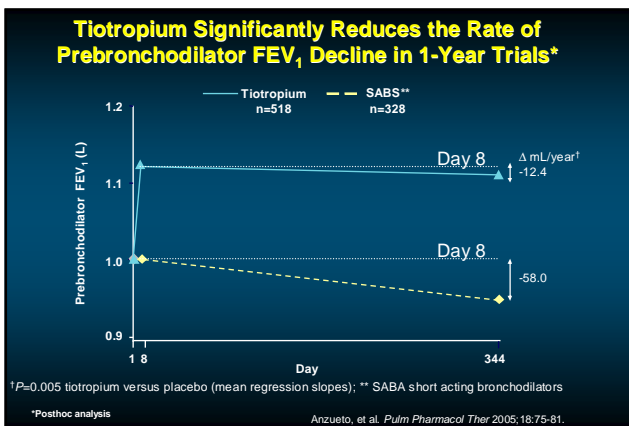
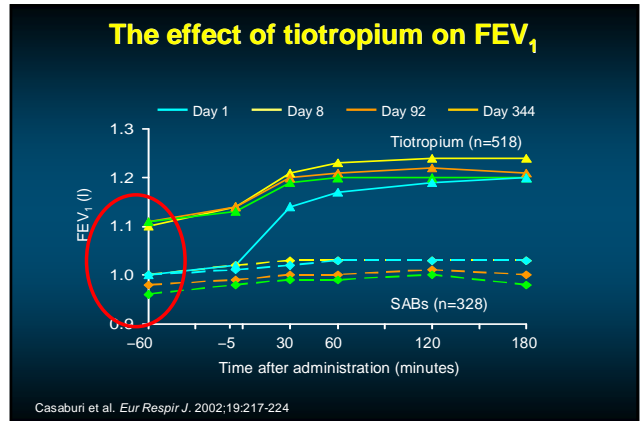
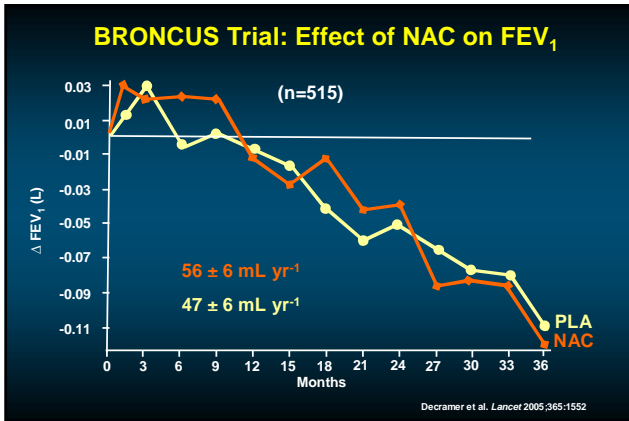
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### Tiotropium Significantly Reduces Exacerbation Rate and Delays Onset of First Exacerbation

	Versus	Patient Number	Duration	Exacerbation Number	Patients with >1 Exacerbation	Time to First Exacerbation
Brusasco 2003	Placebo	1207	6 months	-28% P=0.025	-18% P=0.06	P<0.01
Newoehner 2005	Placebo	1829	6 months	-19% P=0.031	-15% P=0.04	P=0.03
Casaburi 2002	Placebo	921	1 year	-20% P=0.045	-14% P=0.05	P=0.01
Vincken 2002	Ipratropium	535	1 year	-24% P=0.006	-11% P=0.01	P=0.008
Dusser 2006	Placebo	1010	1 year	-35% P=0.001	-17% P=0.01	P<0.001
Powrie 2007	Placebo	142	1 year	-52% P=0.001	-33% P=0.01	P=0.01
Freeman 2007	Placebo	395	12 weeks	n/a	-47% P=0.01	n/a
Chan 2007	Placebo	913	1 year	-4% P=0.599	+ 6% P=0.4	n/a

\*Primary endpoint: exacerbation

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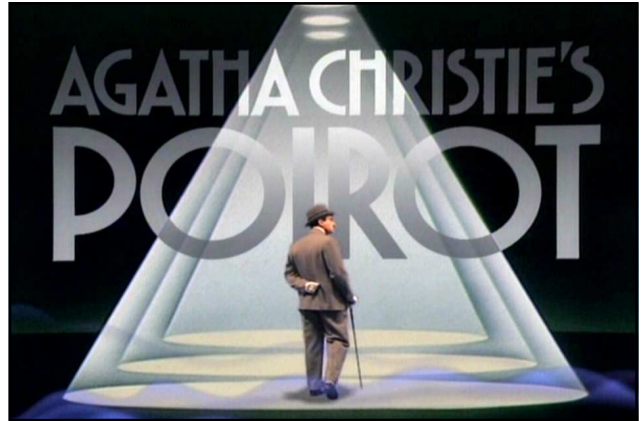
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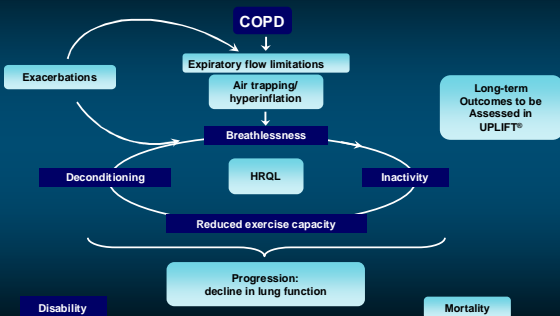
## Understanding the Potential Long-term Impacts on Function with Tiotropium

## UPLIFT® Study Hypothesis

### Tiotropium can impact the clinical course of COPD By

- Improve lung function and reduce rate of decline
- Improve health status
- Reduce exacerbations and hospitalizations
- Reduce mortality

## The Clinical Course Of COPD



HRQL = health-related quality of life  
Ferro T. *Clinical Pulmonary Medicine* 2005; Decramer M. *Eur Respir Rev* 2006

## Trial Design

- ◆ Multinational, multicenter, double-blind, randomized, placebo-controlled, parallel-group design
- ◆ Prospective comparison of 2 groups over a 4-year treatment period
  - First patient randomized – Jan 2003
  - Last patient out – Feb 2008
- ◆ COPD patients randomized to receive
  - Tiotropium (18 mcg) or placebo once daily via HandiHaler® inhalation device
  - Plus usual care, except for inhaled anticholinergics

Tashkin DP et al. *N Engl J Med*. 2008;359:1543-1554.

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## Study Endpoints

### Coprimary endpoints

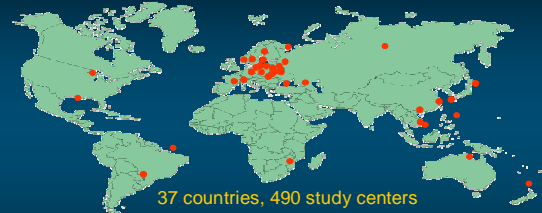
- Yearly rate of decline (from Day 30 [steady state] until completion of double-blind treatment) in predose FEV<sub>1</sub> and postbronchodilator FEV<sub>1</sub>

### Secondary endpoints

- Mean yearly rate of decline in:
  - Pre- and postbronchodilator FEV<sub>1</sub>
  - Pre- and postbronchodilator forced vital capacity (FVC), slow vital capacity (SVC)
  - Rate of decline in health-related quality of life (SGRQ)
  - Exacerbations, hospitalizations, and mortality (respiratory and all-cause) were also examined

Tashkin DP et al. *N Engl J Med*. 2008;359:1543-1554.

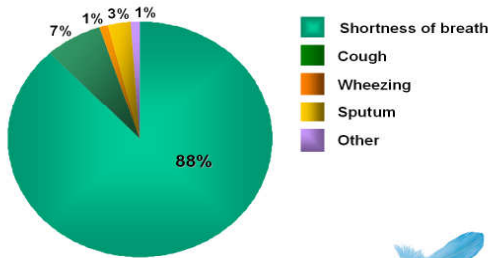
## Worldwide Distribution of UPLIFT Study Centers



37 countries, 490 study centers

Argentina	France	Lithuania	Portugal	Taiwan
Australia	Germany	Malaysia	Russia	Thailand
Austria	Greece	Mexico	Singapore	Turkey
Belgium	Hong Kong	Netherlands	Slovakia	United Kingdom
Brazil	Hungary	New Zealand	Slovenia	US
Czech Republic	Ireland	Norway	South Africa	
Denmark	Italy	Philippines	Spain	
Finland	Japan	Poland	Switzerland	

## Most Troublesome COPD Symptom



UPLIFT

## Baseline Characteristics

Characteristic	Tiotropium (n=2986)	Control (n=3006)
Male (%)	75.4	73.9
Age (yrs)*	64.5 ± 8.4	64.5 ± 8.5
Body Mass Index (kg/m <sup>2</sup> )*	26.0 ± 5.1	25.9 ± 5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yrs)*	49.0 ± 28.0	48.4 ± 27.9
Duration of COPD (yrs)*	9.9 ± 7.6	9.7 ± 7.4
GOLD stage (II / III / IV) (%)	46 / 44 / 8	45 / 44 / 9
SGRQ total score (units)*	45.7 ± 17.0	46.0 ± 17.2

\*Mean ± SD.  
Tashkin DP et al. *N Engl J Med*. 2008;359:1543-1554.

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## Baseline Spirometry

Characteristic	Tiotropium (n=2986)	Control (n=3006)
Before bronchodilation*		
FEV <sub>1</sub> (liters)	1.10 ± 0.40	1.09 ± 0.40
FEV <sub>1</sub> (% of predicted value)	39.5 ± 12.0	39.3 ± 11.9
FVC (liters)	2.03 ± 0.61	2.03 ± 0.63
Ratio of FEV <sub>1</sub> to FVC	42.4 ± 10.5	42.1 ± 10.5
After bronchodilation*		
FEV <sub>1</sub> (liters)	1.33 ± 0.44	1.32 ± 0.44
FEV <sub>1</sub> (% of predicted value)	47.7 ± 12.7	47.4 ± 12.6
FVC (liters)	3.09 ± 0.86	3.09 ± 0.90
Ratio of FEV <sub>1</sub> to FVC	43.6 ± 10.8	43.3 ± 10.7

\*Mean ± SD.  
Tashkin DP et al. *N Engl J Med*. 2008;359:1543-1554.

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## Baseline and On Treatment\* Respiratory Medications

Medication (% of patients)	Tiotropium (n = 2986)		Control (n = 3006)	
	Baseline	On Treatment	Baseline	On Treatment
Any respiratory medication	93	93	93	93
Short-acting anticholinergic	45	45	44	44
Short-acting beta-agonist	69	69	68	68
Long-acting beta-agonist*	60	60	60	60
Inhaled steroid*	62	62	62	62
Theophylline	23	23	23	23
Systemic steroids	8	8	8	8
Mucolytics	7	7	7	7
Leukotriene receptor antagonists	3	3	3	3
Supplemental O <sub>2</sub>	2	2	2	2

\*Used alone or in combination

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## Baseline and On Treatment\* Respiratory Medications

Medication (% of patients)	Tiotropium (n = 2986)		Control (n = 3006)	
	Baseline	On Treatment*	Baseline	On Treatment*
Any respiratory medication	93	96	93	94
Short-acting anticholinergic	45	17	44	17
Short-acting beta-agonist	69	81	68	79
Long-acting beta-agonist*	60	72	60	72
Inhaled steroid*	62	74	62	74
Theophylline	23	35	23	35
Systemic steroids	8	53	8	55
Mucolytics	7	27	7	27
Leukotriene receptor antagonists	3	5	3	5
Supplemental O <sub>2</sub>	2	12	2	12

\*Used alone or in combination + At any time during treatment including short-term treatment of exacerbations

## Concomitant Illness Top 5 by Organ System

Organ System	N (% of patients)	
	Tiotropium n=2986	Placebo n=3006
<b>Total with any concomitant diagnoses</b>	2644 (88.6)	2619 (87.1)
Vascular disorders*	1353 (45.3)	1367 (45.5)
Musculoskeletal and connective tissue disorders	945 (31.7)	929 (30.9)
Gastrointestinal disorders	861 (28.8)	870 (28.9)
Metabolism and nutrition disorders	823 (27.6)	803 (26.7)
Cardiac disorders	790 (26.5)	765 (25.5)

\*Included hypertension

\*Mean ± SD. Tashkin DP et al. *N Engl J Med* 2008;359:1543-1554.

## Annual Rates of Decline in FEV<sub>1</sub>

Annual rates of decline in FEV<sub>1</sub> from Day 30 until end of study (including 30 days after discontinuation of treatment). Patients with ≥3 measurements postrandomization were included in the analysis.

Variable	Tiotropium (mL/yr)		Control (mL/yr)		Δ Tio - Con	P Value*
	n	Mean (SE)	n	Mean (SE)		
Pre-BD	2557	30 (1)	2413	30 (1)	0 (2)	0.95
Post-BD	2554	40 (1)	2410	42 (1)	-2 (2)	0.21

\*Unadjusted P value. Pre-BD= prebronchodilator; Post-BD=postbronchodilator

Tashkin DP et al. *N Engl J Med* 2008;359:1543-1554.

## Annual Decline in Post-Bronchodilator FEV<sub>1</sub> in Major Long-Term COPD Trials

Study (Duration) (order-year of publication)	Current smokers	Baseline FEV <sub>1</sub> % predicted	Study drug	Annual decline in FEV <sub>1</sub> (mL/year)	
				Study drug	SA BD only
EUROSCOP (3 years)	100%	~ 79%	Budesonide	57	69
ISOLDE (3 years)	36 - 39%	~ 50%	Fluticasone	50	59
LHS II (3.3 years)	90%	~ 68%	Triamcinolone	44	47
BRONCUS (3 years)	41-51%	~ 57%	NAC	54	47
TORCH (3 years) post hoc analysis	43%	~ 48%	S/F/SFC	42/42/39	55

\* All respiratory medications permitted throughout the trial, other than inhaled anticholinergics

## Annual Decline in Post-Bronchodilator FEV<sub>1</sub> in Major Long-Term COPD Trials

Study (Duration) (order-year of publication)	Current smokers	Baseline FEV <sub>1</sub> % predicted	Study drug	Annual decline in FEV <sub>1</sub> (mL/year)		
				Study drug	SA BD only	ICS+LABA
EUROSCOP (3 years)	100%	~ 79%	Budesonide	57	69	-
ISOLDE (3 years)	36 - 39%	~ 50%	Fluticasone	50	59	-
LHS II (3.3 years)	90%	~ 68%	Triamcinolone	44	47	-
BRONCUS (3 years)	41-51%	~ 57%	NAC	54	47	-
TORCH (3 years) post hoc analysis	43%	~ 48%	S/F/SFC	42/42/39	55	-
UPLIFT (3 years)	30%	~ 47%	Tiotropium	37	-	42
UPLIFT (4 years)	30%	~ 47%	Tiotropium	40	-	42

\* All respiratory medications permitted throughout the trial, other than inhaled anticholinergics

## Rate of Decline in FEV<sub>1</sub> No Baseline LABA or ICS Post-Hoc Analysis

Mean slope from day 30 until completion of double-blind treatment

— treated set with ≥3 post-randomization measurements

	Tiotropium (mL/yr)		Control (mL/yr)		P-value
	n	Mean (SE)	n	Mean (SE)	
Pre-bronch	789	33 (2)	767	38 (3)	0.085
Post-bronch	787	40 (3)	764	47 (3)	0.048

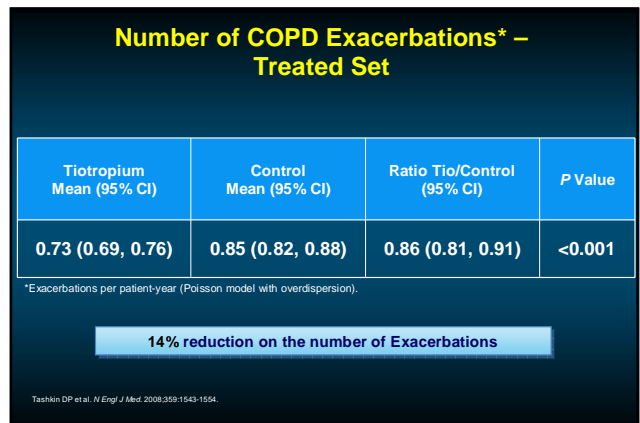
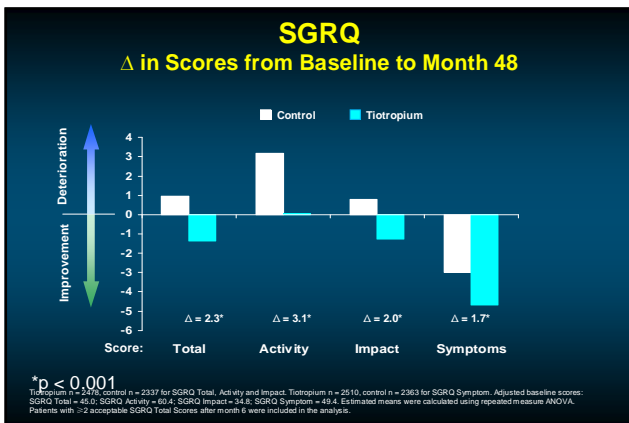
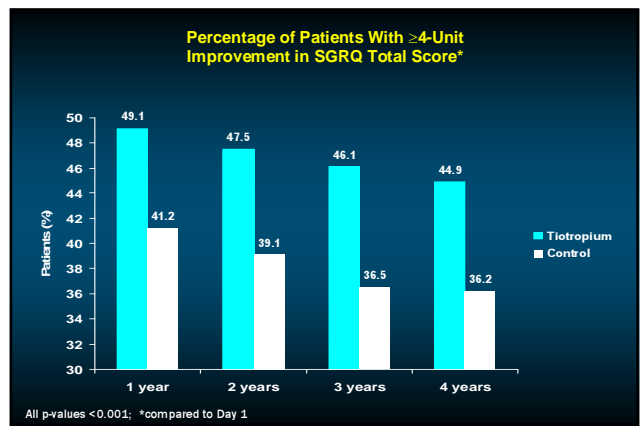
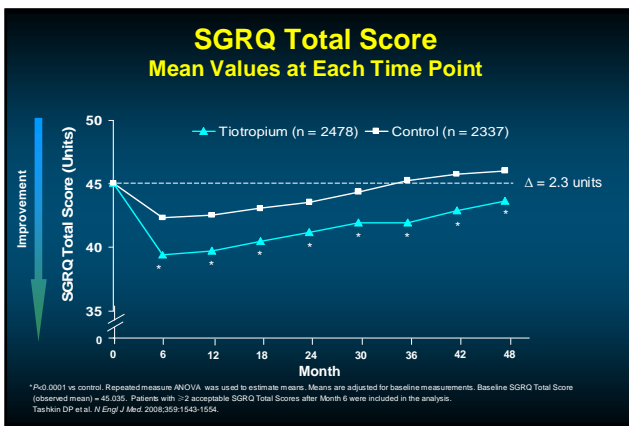
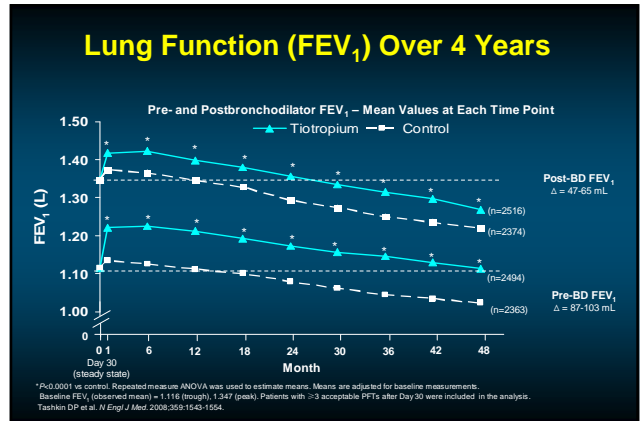
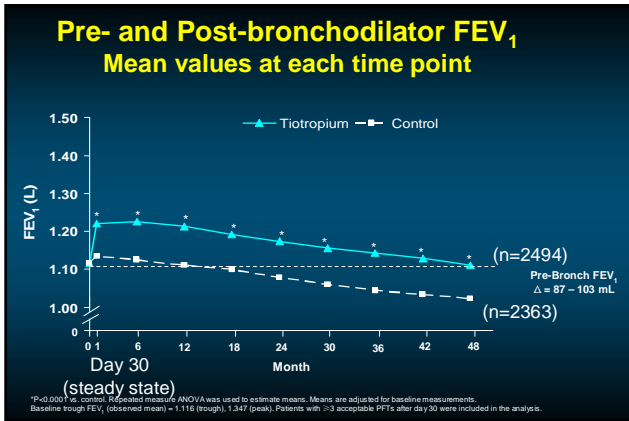
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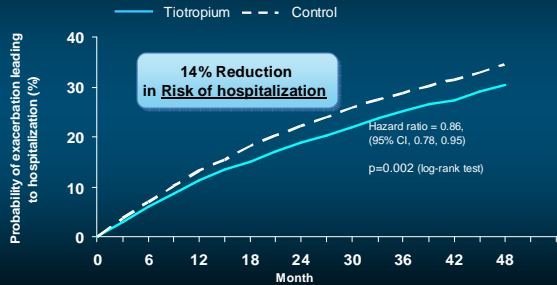
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## Probability of COPD Exacerbation Leading to Hospitalization



What about survival and safety ?

## Singh et al Meta-analysis Limitations

- Looks at the Cardiovascular risk of inhaled Anticholinergics
  - Cardiovascular Deaths
  - MI
  - Stroke
- Based only on select number of previously published trials (17)

Singh S, Loke YK, Furberg CD. Inhaled anticholinergic and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. A systemic review and meta-analysis. JAMA. 2008;300:1439-1450.

## Singh et al. meta-analysis Limitations

- Combined study summaries rather than analyzing individual patient data.
- No corrections for patients who dropped out of trials early
- Certain studies might have been included in the analysis twice
- Conclusions drawn from combined data of two different medications (tiotropium and ipratropium)
- Combined placebo and active comparator drugs in the control group

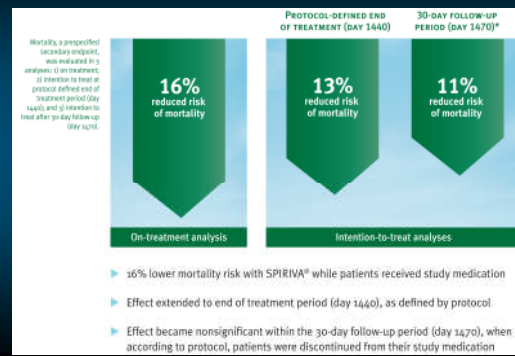
Singh S, Loke YK, Furberg CD. Inhaled anticholinergic and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. A systemic review and meta-analysis. JAMA. 2008;300:1439-1450.

## Mortality Results

	Tiotropium	Control	Hazard Ratio (HR) Tiotropium vs Control		
	N (%)	N (%)	HR	95% CI	P Value
<b>On-Treatment</b>	381 (12.8)	411 (13.7)	0.84	0.73, 0.97	0.016
<b>Vital Status (Day 1440)</b>	430 (14.4)	491 (16.3)	0.87	0.76, 0.99	0.034
<b>Vital Status (Day 1470)</b>	446 (14.9)	495 (16.5)	0.89	0.79, 1.02	0.086

Tashkin DP et al. N Engl J Med. 2008;359:1543-1554.

## Tiotropium Reduced Mortality



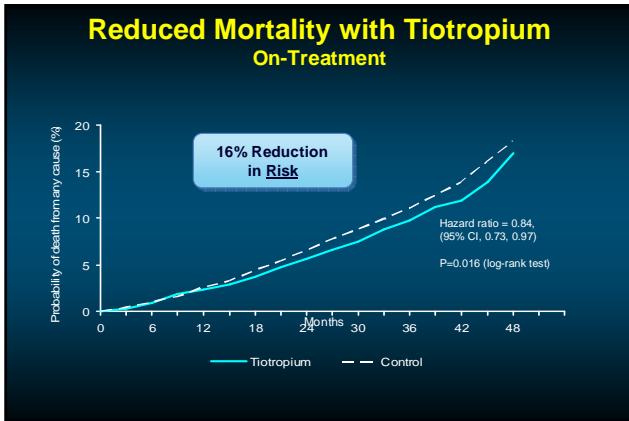
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### Incidence Rate of SAEs per 100 Patient-Years\*

Adverse Event	Tiotropium (n=2986)	Control (n=3006)	Relative Risk (Tio/Con)	95% CI
<b>Cardiac</b>	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
Congestive heart failure	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†
<b>Lower respiratory</b>	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	0.28	0.63	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†

Tashkin DP et al. *N Engl J Med.* 2008;359:1543-1554.

### Stroke

Adverse Event	Tiotropium (N = 2986)		Placebo (N = 3006)		Risk Ratio	95% CI	
	N with event	Rate / 100pt-yrs	N with Event	Rate / 100pt-yrs		Lower	Upper
Adverse Event	82	0.88	80	0.93	0.95	0.70	1.29
Serious Adverse Event	66	0.70	63	0.73	0.97	0.69	1.37
Fatal (on treatment-adj.)	12	0.13	13	0.15	0.85	0.39	1.87

Tashkin DP et al. *N Engl J Med.* 2008;359:1543-1554.

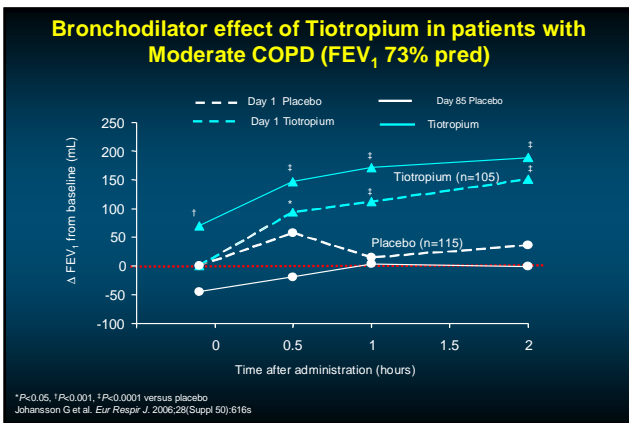
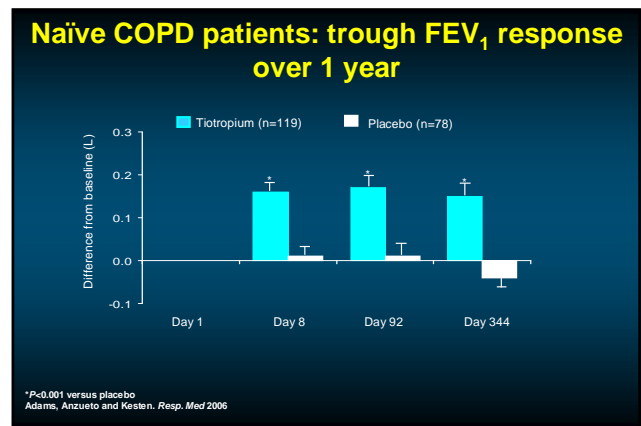
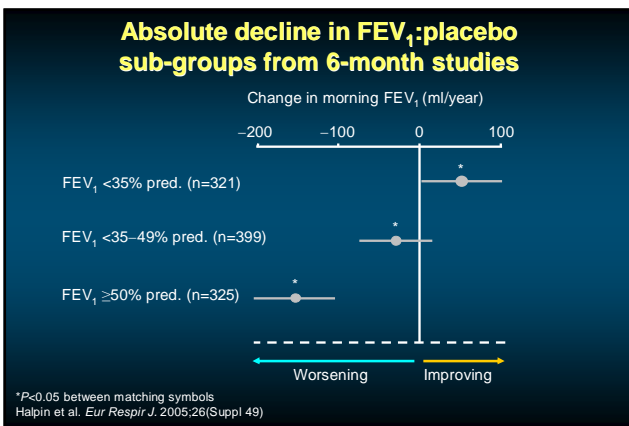
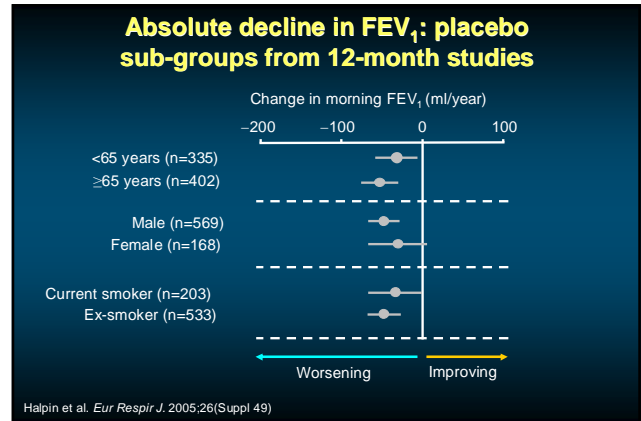
### Myocardial Infarction

Adverse Event	Tiotropium (N = 2986)		Placebo (N = 3006)		Risk Ratio	95% CI	
	N with event	Rate / 100pt-yrs	N with Event	Rate / 100pt-yrs		Lower	Upper
Adverse Event	67	0.71	85	0.93	0.73	0.53	1.00
Serious Adverse Event	65	0.69	84	0.97	0.71	0.52	0.99
Fatal (on treatment-adj.)	9	0.10	8	0.09	1.04	0.40	2.29

Tashkin DP et al. *N Engl J Med.* 2008;359:1543-1554.

- ### Summary
- There was no significant difference between tiotropium and control groups in the annual rate of FEV<sub>1</sub> decline
  - UPLIFT demonstrated Tiotropium vs control over 4 year period
    - Significant and sustained increases in Lung function
    - Improvement in SGRQ
    - A significant reduction in exacerbations
    - Reduced mortality
    - Reduced cardiac morbidity
    - Reduced lower respiratory morbidity
- Tashkin DP et al. *N Engl J Med.* 2008;359:1543-1554.

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- ◆ COPD is a progressive disease !!
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### Rate of Decline in FEV<sub>1</sub> by GOLD Stage

Post-bronchodilator FEV<sub>1</sub>

GOLD Stage	Tiotropium (mL/yr)		Control (mL/yr)		Δ Tio - Con Mean (SE)	P-value
	n	Mean (SE)	n	Mean (SE)		
II	1218	43 (2)	1158	49 (2)	6 (3)	0.02
III	1104	39 (2)	1031	38 (2)	0 (3)	0.87
IV	194	32 (5)	185	23 (5)	-9 (7)	0.24

P-value for subgroup by treatment interaction = 0.07

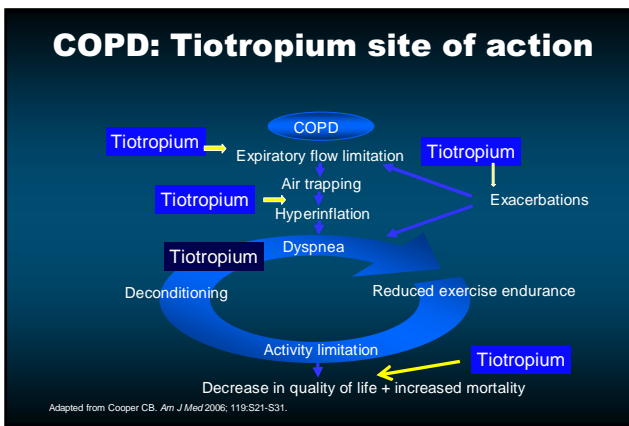
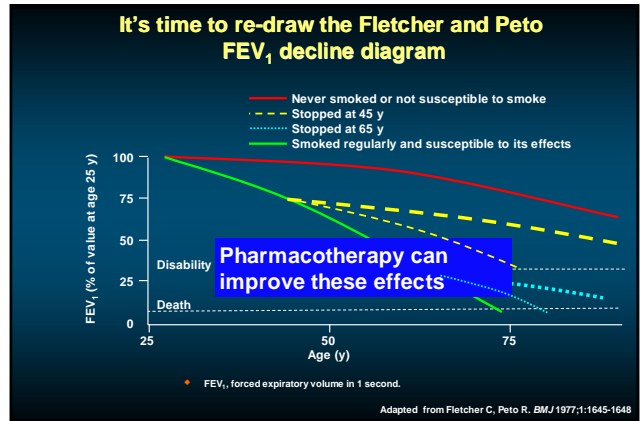
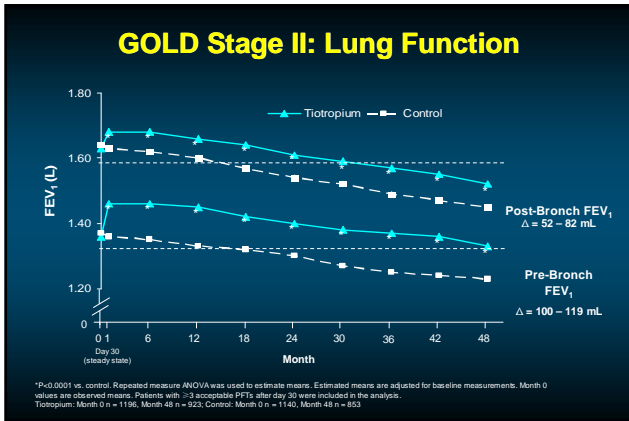
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### Take home message...

- ♦ Impacting the clinical course of COPD, as evidenced by sustained improvements in multiple clinical outcomes is consistent with disease modification.
- ♦ **UPLIFT**® demonstrated sustained improvement in lung function, quality of life, exercise capacity, decreased frequency of exacerbations and mortality.
- ♦ Tiotropium has significant impact on patients with moderate (GOLD II) disease.





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