Management of Chronic Obstructive Pulmonary Disease with Tiotropium Bromide

A. James Mamary and Gerard J. Criner

Division Pulmonary and Critical Care Medicine, Temple University School of Medicine, Philadelphia PA 19140, USA.

Email: albert.mamary@tuhs.temple.edu

Abstract: In COPD, pathologic upregulation and stimulation of muscarinic (M) receptors contribute to bronchospasm, mucus hypersecretion and possibly airway remodeling. Tiotropium bromide (brand name Spiriva; Boehringer Ingelheim/Pfizer) inhalational powder was approved by the US Food and Drug Administration in January 2004 for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is recommended by the Global initiative for Chronic Obstructive Lung Disease (GOLD) as a first-line therapeutic in treating chronic moderate and severe COPD and is the only long acting inhaled anti-muscarinic (anti-cholinergic) therapy available for the treatment of COPD in the USA. The primary functional effect of tiotropium is mediated through antagonism of M3 receptors and the decreased acetylcholine induced airway smooth muscle bronchoconstriction. Tiotropium is associated with increased lung function, health related quality of life, and exercise tolerance and reduced dyspnea and acute exacerbations of COPD (AECOPD). On November 19, 2009 the Pulmonary-Allergy Drugs Advisory Committee voted 11-1 for new product labeling about the benefits of tiotropium stating that the data provide “substantial and convincing evidence” that tiotropium decreases AECOPD. This indication “for reducing COPD exacerbations” was added to product labeling in December 2009. Tiotropium is safe and well tolerated with few side effects. The large multicenter UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial demonstrated the long-term safety of tiotropium over four years of continuous use showing no increase in stoke and all cause mortality. Serious adverse events including respiratory failure, congestive heart failure and myocardial infarction were significantly less in the tiotropium group. In a pre-specified subgroup analysis Tiotropium retarded FEV1 decline in milder COPD. Additional review of cholinergic pathobiology relevant to COPD and asthma provides context for future therapeutic and preventative roles for tiotropium.

Keywords: tiotropium, bronchodilator, chronic obstructive pulmonary disease (COPD), acute exacerbation of COPD (AECOPD), inhaled anticholinergic, muscarinic receptor antagonist, safety, health related quality of life, lung function, dyspnea, asthma
Introduction
Chronic obstructive pulmonary disease (COPD) is an international disease projected by the Global Initiative for Chronic Obstructive Lung Disease to be the fifth leading cause of disease worldwide and the third leading cause of death by 2020. COPD is caused by the inhalation of toxic fumes or particles of which tobacco smoke accounts for the majority of cases followed by occupational dust, biomass cooking fuel exhaust and air pollution. Annually, in the United States COPD causes 8 million office visits, 1.5 million emergency department visits, 726,000 hospitalizations and 119,000 deaths. This comes at an annual costs of $15 billion in direct health care costs and approximately $10 billion in lost work productivity. In addition to economic costs, COPD extracts a huge human toll. Exertional breathlessness and exercise limitation, cardinal features of COPD, become disabling as airflow obstruction worsens. COPD greatly diminishes health related quality of life. In advanced disease patients are rarely symptom free with daily symptoms nearly universal, including one or more element of cough, sputum, wheezing, chest tightness, nasal symptoms and sore throat. Acute exacerbations of COPD (AECOPD) account for substantial morbidity and mortality. Analogous to stroke or myocardial infarction, AECOPDs interrupt the daily symptom burden of COPD with acute, often trajectory changing deterioration of chronic disease. AECOPDs have been reported to cause frequent hospital admissions, relapses and readmissions, increased immediate and short-term mortality, reduced quality of life and accelerated decline of pulmonary function. Recently the aims of pharmacologic treatment of COPD have focused beyond the immediate relief of symptoms toward sustained improvement in FEV1 and the prevention of AECOPDs and their morbid consequences, the preservation of lung function, improved exercise tolerance and improved health related quality of life. Herein we will examine tiotropium bromide for the treatment of COPD.

Tiotropium bromide (brand name Spiriva; Boehringer Ingelheim/Pfizer) inhalational powder was approved by the US Food and Drug Administration in January 2004 for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is recommended by the Global initiative for Chronic Obstructive Lung Disease (GOLD) as a first-line therapeutic in treating chronic moderate and severe COPD and is the only long acting inhaled anti-muscarinic (anti-cholinergic) therapy available for the treatment of COPD. Tiotropium has joined inhaled corticosteroids and long acting beta agonists in the inhaled armamentarium to treat stable COPD.

Tiotropium is well studied in moderate and severe COPD. The search for optimal combinations of inhaled bronchodilators and corticosteroids has produced several recent, large, long-term randomized placebo controlled trials in moderate to severe COPD patients. Tiotropium is associated with increased lung function, health related quality of life, and exercise tolerance and reduced dyspnea and acute COPD exacerbations. Compared to combination long acting beta-agonist-inhaled corticosteroids (LABA-ICS) alone, the addition of tiotropium further reduced AECOPD. Post-hoc analysis of a recent, large, multicenter prospective, randomized trial demonstrated a tiotropium survival advantage during the study period. Tiotropium was shown not to increase cardiovascular morbidity or stroke risk as suggested by recent meta-analyses.

Pharmacology

Pulmonary muscarinic receptor physiology
Acetylcholine is the primary parasympathetic neurotransmitter in the human airway and is responsible for airway smooth muscle contraction. Excess vagal tone exists throughout the diseased COPD airway and provides the pathophysiologic basis for the use of anticholinergic therapy. In health, muscarinic (M) receptors regulate airway smooth muscle tone. In COPD, pathologic upregulation and stimulation of muscarinic (M) receptors contribute to bronchospasm, mucus hypersecretion and possibly airway remodeling. Exaggerated release of neuronal acetylcholine is associated with inflammation and increased expression of signaling molecules involved in M receptor functioning.

There are three known muscarinic acetylcholine receptor subtypes in the human lung, M1, M2 and M3. Stimulation of M1 and M3 receptors enhance cholinergic activity. Stimulation of M2 receptors decreases acetylcholine outflow from
vagal nerve pre-synaptic vesicles. Stimulation of \( M_1 \) receptors facilitates transmission of cholinergic neurotransmission through the parasympathetic ganglion. Cholinergic stimulation of \( M_2 \) muscarinic receptors on airway smooth muscle cells and submucosal mucus glands activates bronchoconstriction and mucus secretion.

The functional effects of tiotropium are mediated mainly through antagonism of \( M_1 \) receptors and the decreased acetylcholine induced airway smooth muscle bronchoconstriction and possibly submucosal mucus gland mucus secretion. Acetylcholine transmission is decreased through antagonism of \( M_1 \) mediated acetylcholine transmission. Tiotropium is a specific muscarinic receptor antagonist that binds the three \( M \) subtypes with similar affinity. However, tiotropium dissociates quickly from the \( M_2 \) receptors producing functional and kinetic selectivity for \( M_1 \) and \( M_3 \), \( M_1 \) and \( M_3 \) selectivity and \( M_2 \) avoidance is an important pharmacokinetic feature of tiotropium. \( M_2 \) receptor activity is autoregulatory and inhibitory and \( M_3 \) receptors remain functional in stable COPD.\(^{16}\) Tiotropium binds with 10 time’s greater affinity to the \( M_1 \) and \( M_3 \) receptors and dissociates 100 times more slowly than the short-acting anticholinergic ipratropium bromide.\(^{17}\)

Healthy airway smooth muscle expresses the \( M_2 \) and \( M_4 \) receptors in a 4 to 1 ratio. \( M_3 \) primarily mediates acetylcholine induced tracheal and bronchial smooth muscle contraction. Airway submucosal glands are innervated and express the \( M_1 \) and \( M_3 \) receptors in a 1:2 ratio. The \( M_4 \) receptor is the receptor predominantly involved in the regulation of mucus secretion while \( M_1 \) and \( M_3 \) receptor stimulation mediates electrolyte and water secretion.\(^{15}\) Acetylcholine induces mucus secretion in the central airways. The \( M_1 \) and \( M_3 \) receptors are likely the primary controller of this vagally mediated mucus production. Additionally, animal models suggest that submucosal mucus glands and some goblet cells respond to muscarinic receptor agonism at relatively high threshold concentrations of acetylcholine by releasing a mucus bolus.\(^{18}\) This observation may lead to future pharmaceutical targets in treating COPD-related mucus hypersecretion.

Preliminary evidence suggests a role for the non-neuronal cholinergic system in lymphocyte function, although its relative importance in normal airway physiology and in chronic airflow obstruction is not yet established.\(^{19}\)

**Pharmacokinetics**

Tiotropium and ipratropium are the only commercially available quaternary ammonium anticholinergic therapeutic compounds indicated for the treatment of COPD. These compounds are generally hydrophilic and do not easily cross biologic barriers such as the blood brain barrier that are easily crossed by the tertiary ammonium compounds like atropine. Quaternary ammonium compounds are poorly absorbed after oral administration further limiting central neurologic availability. Therefore, the drug side effects of dry mouth, urinary retention, constipation, flushing, blurred vision, mood changes, tachycardia that are associated with atropine are generally mild and infrequent.

Tiotropium is delivered as an orally inhaled dry powder using the HandiHaler proprietary inhalation device. After loading a capsule of tiotropium into the inhalational device the capsule is pierced and the patient inhales the powder contents through the plastic mouthpiece. Each capsule contains 18 mcg of tiotropium bromide blended with a lactose monohydrate carrier. The fraction of drug delivery is adequate even at very low inspiratory flow rates, a concern of many very severe COPD patients. At an inspiratory flow rate of 39 L/min for 3.1 seconds the device delivers a mean dose of 10.4 mcg of tiotropium. Effective delivery occurs at flow rates as low as 20 L/min.\(^{20}\) After tiotropium is deposited in the lung it becomes highly bioavailable (19.5%) with peak plasma concentrations attained at 5 minutes after inhalation of 17–19 pg/mL. Tiotropium binds extensively to plasma proteins (72%) and to tissues and has a large 32 L/kg volume of distribution.

Technetium radiolabeled gamma scintigraphy in healthy and COPD patients showed lung deposition to be 18 to 22% regardless of severity of airflow obstruction.\(^{21}\) A mean tiotropium spherical diameter of 4.0 ± 1.7 microns was derived from the distribution of radioactivity. The majority of properly orally inhaled tiotropium is deposited in the gastrointestinal tract where little of the drug is systemically absorbed. Absorbed tiotropium is largely excreted unchanged in the urine.\(^{22}\) Tiotropium has an absolute bioavailability and urinary excretion of 2%–3%.\(^{21}\)
Pharmacokinetic steady state is achieved at 2–3 weeks of daily administration without further accumulation.

Dosing
Tiotropium is dosed 18 mcg once-daily by oral inhalation. Doses ranging from 9 mcg to 36 mcg produced comparable improvement in peak and trough FEV$_1$, FVC and PEF. Steady-state therapeutic response was achieved by day 7 and maintained throughout a 29 day dose finding study conducted in 169 stable, moderate and severe COPD (mean FEV$_1$ = 1.08 L, 42% predicted) in which patients were randomized to placebo or tiotropium at doses of 4.5, 9, 18 and 36 mcg. Trough FEV$_1$ values of tiotropium treated patients averaged 7%–19% above the baseline and placebo values throughout the trial duration (P < 0.05). Spirometric improvements gradually returned to baseline in the 3 weeks after stopping treatment. The overall short-term safety profile for the 4 doses of tiotropium was similar to placebo. While there was no dose dependent increase in the incidence or severity of any adverse event, the 36 mcg dose had the largest proportion of patients with any adverse events.

Clinical Efficacy
Lung function and symptom relief
Casaburi and colleagues$^{23}$ evaluated lung function and symptom relief in the 2 parallel tiotropium efficacy and safety trials that involved 921 COPD patients randomized 3:2 to tiotropium vs. placebo. Spirometry was performed 1 hour before dosing, immediately prior to dosing and at 30, 60, 120 and 180 minutes after dosing on treatment day 1 and after study weeks 1, 7, 13, 25, 37 and 49. FEV$_1$ improved immediately with tiotropium compared to placebo at all time points and did not exhibit tachyphylaxis. Tiotropium improved FEV$_1$ relative to placebo by approximately 12% (110 ± 10 vs. –130 ± 10 ml, P < 0.001) at trough, 22% (120 ± 10 vs. –150 ± 20 ml, P < 0.001) at 3 hours postdose over the 12 month period. 81.3% and 72.2% of tiotropium and placebo patients completed the study with more withdrawing for side effects and lack of efficacy in placebo (13.7 and 7.0% vs. 9.6 and 204%; P < 0.05). Tiotropium improved dyspnea compared to placebo at all assessment points (day 50, 90, 180, 270 and 360). The proportion of patients who achieved a clinically important difference in Transitional Dyspnea Index (TDI) score was significantly greater in the tiotropium group at all five points of assessment (first at day 50, 40%–47% vs. 29%–34%, P < 0.01). Tiotropium treated patients reported significantly less wheezing. No tiotropium treatment effect occurred for cough or chest tightness compared to placebo.

Tiotropium is effective in improving lung function and dyspnea in COPD regardless of immediate bronchodilator response to a single dose of tiotropium. Tashkin and colleagues$^{25}$ showed that over one year tiotropium effectively increases FEV$_1$ regardless of pre-study immediate tiotropium bronchodilator response. Both the tiotropium responders (TIO-R) and the tiotropium poorly responsive group (TIO-PR) had significantly (P < 0.001) improved predose (trough) FEV$_1$ at one year relative to placebo (TIO-R 212 ± 17 mL TIO-PR 94 ± 17 mL). Both TIO-R and TIO-PR groups had significant one year improvements in dyspnea assessed by the Transitional Dyspnea Index and health status by the St. George Respiratory Questionnaire.

Dynamic hyperinflation and exercise
Dynamic hyperinflation (DH) is the major pathologic mechanism that produces dyspnea and limits exercise in COPD. DH occurs in the setting of increased airways resistance, decreased lung compliance and increased respiratory rate. With progressive exertion, end-expiratory lung volume increases and inspiratory capacity decreases. Patients are forced to breath closer to total lung capacity, at mechanical disadvantage and great energy expense. Tiotropium reduces static and dynamic hyperinflation, improves exercise tolerance and reduces perceived dyspnea in severe COPD.

O’Donnell and colleagues$^{26}$ first demonstrated the effect of tiotropium on lung hyperinflation and exercise tolerance in severely obstructed COPD patients with gas trapping and hyperinflation. In a 6 week multicenter, randomized, double-blind, placebo controlled trial 96 patients received once daily inhaled tiotropium and 100 received placebo. Other anticholinergic therapy and long acting beta agonist therapy were not permitted. Multiple peak and trough spirometry and plethysmography were obtained. Symptom-limited incremental and constant-load exercise testing with inspiratory capacity maneuvers were obtained at days –5, 0, 21 and 42. Residual volume, forced vital capacity and functional residual volume decreased at all time points.
(0, 21 and 42 days) in the group receiving tiotropium (P < 0.0001) with a corresponding increase in resting inspiratory capacity (P < 0.01). Compared with placebo, IC at rest, iso-time and peak exercise were significantly improved from baseline by 150–250 mL at all time points (P < 0.01; 0, 21 and 42 days). Dyspnea (measured in Borg units) at iso-time near-maximal exercise was reduced in the tiotropium group vs. placebo at 0, 21 and 42 days (0.5 ± 0.2, P = 0.042; 0.7 ± 0.3, P = 0.026; 0.9 ± 0.3, P = 0.0075). Exercise endurance at 75% Wmax was greater in tiotropium vs. placebo at days 21 and 42 compared to day −5 (67 ± 13%, P = 0.039 and 105 ± 21.4% P = 0.0098). Tiotropium therapy resulted in improved exercise capacity and time and decreased dyspnea.

The combination of tiotropium and pulmonary rehabilitation in severe COPD is superior to rehabilitation alone in improving endurance and perceived dyspnea. In a multicenter, randomized, double-blind, placebo-controlled trial, 108 patients (FEV1 34.4 ± 12.4%) received study drug 5 weeks prior, 8 weeks during and 12 weeks after 24 sessions of pulmonary rehabilitation. Endurance was assessed using a constant work rate treadmill test at 80% work maximum. After 13 weeks (including 8 weeks of PR) and 25 weeks the tiotropium group had longer exercise endurance times (5.35 ± 2.34 min, P = 0.025; 6.60 ± 2.72 min, P = 0.018).27 Gelb and colleagues28 demonstrated tiotropium’s influence on dynamic hyperinflation to be independent of radiographic extent of emphysema in a very small group of moderate COPD patients with relatively small amounts of emphysema. The authors studied 29 patients with mean post bronchodilator FEV1 of 61 ± 8% and a mean lung CT emphysema score of 23 ± 20 (scale 0–100). All received tiotropium for 30 days. Dynamic hyperinflation was measured after 20 seconds of metronome paced breathing at 30 breaths/minute. While there was a significant increase in FEV1, FVC and a decrease in dynamic hyperinflation (IC) at 30 days none correlated with lung CT emphysema score. A larger trial with a more heterogenous COPD cohort including disease severity and emphysema is required to thoroughly investigate a protective role of tiotropium by radiographic phenotype.

**Tiotropium vs. ipratropium**

Tiotropium’s convenient once daily dosing and superior peak, average and trough lung function29 vs. ipratropium are owed to its long muscarinic receptor-tiotropium bromide complex half life (34.7 ± 2.9 hours vs. 0.26 ± 0.02 hours). However, direct comparison of tiotropium and ipratropium is limited to one short-term, multi-center randomized, double blind, parallel group study. The spirometric effects of the two drugs were compared in a 13 week head to head trial. The study randomized 288 patients age 64 ± 8 years with moderate to severe COPD (FEV1 42 ± 11%) to treatment with tiotropium once daily or ipratropium four times daily. Spirometry was performed at 0.5, 1, 2, 3, 4, 5, 6 hours post drug on days 1, 8, 50 and 92 post enrollment. Tiotropium produced greater FEV1 response vs. ipratropium on days 8, 50 and 92 at all time points except 0.5 and 1 hours post dose (P < 0.005). Subsequently, tiotropium produced greater mean improvement in FEV1 vs. ipratropium over 6 hours on all study days (range of differences 0.06–0.11 liters, P < 0.005). One hour predose trough FEV1 was greater for tiotropium vs ipratropium on all days (approximate difference 0.13 ± 0.02 liters, P < 0.005). Similar changes in trough and mean FVC were demonstrated. Side effects were few and occurred with similar frequency in both groups.29 Non-spirometric outcomes such as exercise tolerance, dyspnea, health related quality of life and frequency of AECOPD were not assessed.

Tiotropium is more expensive than ipratropium. A retrospective cost-effectiveness analysis performed on two, 1 year, randomized, double-blind clinical trials in the Netherlands and Belgium demonstrated a small incremental increase in annual total health care cost mostly determined by about 5 fold higher cost of tiotropium. Medication cost was partially offset by a reduction in hospital admissions, hospital days and unscheduled visits to healthcare providers in the tiotropium group by 46% (P = 0.03), 42% (P = 0.07) and 36% (P = 0.04). In 2001 (3 years before US FDA approval) mean Dutch health care dollars, substituting tiotropium for ipratropium in moderate and severe COPD patients increased health care costs by approximately 180 Euros per patient year.30

**Acute exacerbation of COPD**

Acute exacerbations of COPD punctuate the chronic and progressive clinical course of COPD with increased dyspnea, cough and sputum which may be purulent. These events in the natural course of
the disease are beyond the day-to-day variation and may warrant a change in medication.31 Exacerbations account for most of the morbidity, mortality and cost associated with COPD. The risk for AECOPD increases with declining FEV₁ and previous exacerbation frequency.32 Estimates of the annual incidence of AECOPD vary with the population observed and the definition of exacerbation applied. Using a symptom-based definition, Miravitlles and colleagues32 described 1.6 ± 1.5 exacerbations/year in a group of ambulatory COPD patients with FEV₁ > 60% (mean 67 ± 5) and 2.3 ± 1.9 with FEV₁ < 40% (mean 32 ± 4). In total 1001 patients (mean FEV₁ 47 ± 13) were hospitalized infrequently for AECOPD at 0.24 per patient per year. Hospitalization from AECOPD is a marker of disease severity and is associated with high mortality.33,34 The SUPPORT trial7 described prognosis in severe COPD patients with mild hypercapnic respiratory failure (PaCO₂ > 50) hospitalized with AECOPD. The hospital mortality was 11%, 60 day 20%, 6 month 33% and 12 month 43%. An AECOPD is a serious life changing event from which patients may never fully recover. Soler-Cataluna and colleagues35 showed for the first time that severe AECOPDs negatively impact on prognosis with frequency of exacerbation particularly those requiring hospitalization increasing mortality. They studied 304 male patients age 71 ± 9 years with a mean FEV₁ 46.4 ± 17.2 over 5 years. Patients with greater than 3 AECOPDs had the highest mortality (HR 4.13; 95% CI 1.8–9.45). Those requiring hospitalization and readmission had an 80% 5 year mortality (HR 4.31; 95% CI 2.7–6.88).

The US Food and Drug Administration grants approval for inhaled COPD bronchodilator medications based solely upon change of FEV₁. However, tiotropium is repeatedly shown to reduce AECOPDs in registry trials as a secondary outcome and in large prospective trials as a primary outcome. Studies by Casaburi24 and Niewoehner26 and Dusser37 all show similar significant reductions in rates of AECOPD of approximately 14%. The methodology and results of these trials are reviewed in a previous publication.38 Reduction of hospitalization for AECOPD is a more difficult effect to demonstrate because hospitalizations have become relatively uncommon. Casaburi24 demonstrated a 41% relative reduction in hospital admissions. However, AECOPD requiring hospitalizations in the non-tiotropium group were rare. AECOPD reduction but not hospitalization was replicated most recently in the 4 year 5,993 patient UPLIFT trial. At 4 years and 30 days, tiotropium was associated with a reduction in the rate of exacerbations, time to first exacerbation and respiratory failure.25 On November 19, 2009 the Pulmonary-Allergy Drugs Advisory Committee voted 11–1 for new product labeling about the benefits of tiotropium stating that the data provide “substantial and convincing evidence” that tiotropium decreases AECOPD.1 The FDA changed the tiotropium product label on December 17th, 2009 to include this new indication “for reducing COPD exacerbations”.

The Uplift trial (described above) confirmed a tiotropium related reduction in AECOPD with tiotropium treated patients experienced 14% less than otherwise optimally treated patients (P < 0.001). The annual AECOPD rate was 0.73 ± 0.02 for tiotropium patients and 0.85 ± 0.02 for placebo patients (RR 0.86; 95% CI, 0.81 to 0.91, P < 0.001). These rates are lower than reported rates and may reflect the high proportion of UPLIFT patients receiving long-acting beta-agonists and inhaled corticosteroids. Tiotropium was associated with a 14% reduction in the average number of exacerbations (0.73 ± 0.02 vs. 0.85 ± 0.02 per patient year P < 0.001). Tiotropium was associated with delayed time to first AECOPD {median of 16.7 months (95% CI, 14.9 to 19.9) vs. 12.5 months (95% CI, 11.5 to 13.8)} and in a delay to time of first AECOPD hospitalization. AECOPD hospitalizations were rare and similar (0.15 ± 0.01 hospitalizations/patient/year vs. 0.16 ± 0.01).39

AECOPD tiotropium in combination with LABA and ICS

Combined use of tiotropium with long-acting beta agonists, and inhaled steroids is common practice. This practice is supported by results from a large multicenter trial with a primary endpoint of AECOPD requiring treatment with systemic steroids or antibiotics. Aaron and coworkers (for the Canadian Thoracic society/Canadian Respiratory Clinical Research Consortium) investigated the combined effect of tiotropium with LABA, ICS, BOTH or placebo.10 This multicenter, randomized, double-blind, placebo-controlled trial enrolled 449 patients with moderate to severe COPD, 27% current smokers and 12% used
home oxygen at enrollment. Treatment with tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone-salmeterol was administered for 1 year. Participant dropout was a significant finding and study limitation with highest study completion in the triple therapy group. 47% and 43% of patients discontinued in the tiotropium plus placebo and tiotropium plus salmeterol, many for perceived lack of efficacy vs. 26% in the tiotropium plus salmeterol plus fluticasone group (P < 0.001). AECOPD did not differ by treatment group (tiotropium 62.8%, tiotropium + salmeterol 64.8%, tiotropium + salmeterol + fluticasone 60.0%). Many patients discontinued from study protocol were crossed over to the open-label inhaled steroid and long acting B2 agonist inhaler on the advice of their physicians. High discontinuation rates and relatively small group sizes have reduced the power of the study to detect a therapeutic effect in AECOPD outcomes.

Secondary outcomes of lung function, quality of life and hospitalization rates for AECOPD and all causes were improved by combined therapy with tiotropium plus fluticasone and salmeterol vs. tiotropium. Patients treated with tiotropium plus fluticasone and salmeterol had lower rates of severe AECOPD requiring hospitalization vs. tiotropium plus placebo (incidence ratio 0.53; CI, 0.33 to 0.86, P = 0.01). All cause hospitalization was also reduced (P = 0.04).

Clinically meaningful improvements in disease specific health related quality of life (measured by a greater than 4 point reduction on the St. George Respiratory Questionnaire) were seen in all therapeutic groups with the greatest improvement in the tiotropium plus salmeterol and fluticasone group (~8.6 points).

Another recent large trial examined AECOPD as a primary endpoint. The INSPIRE trial (Investigating New Standards for Prophylaxis in Reducing Exacerbations) compared the effect of tiotropium 18 mcg to the inhaled combination of salmeterol/fluticasone propionate (50/500 mcg) (SFC) on the rate of moderate to severe AECOPD during a 2-year treatment period.13 1,323 patients from 179 centers were randomized 1:1 to the two treatment groups. During the study period patients were permitted short acting beta-agonists and standardized short courses of oral systemic steroids and/or antibiotics to treat AECOPD. Patient withdrawal was high and limiting in this trial, 35.3% and 42% of the SFC and tiotropium treated patients withdrew. INSPIRE showed no difference between tiotropium and SFC on rates of AECOPD or number of patients with at least one AECOPD. AECOPD per year were similar for SFC 1.28 and tiotropium 1.32 (ratio 0.967; 95% CI, 0.836 to 1.119).

The 52% reduction mortality in the SFC group 21(3%) vs. tiotropium 38(6%) (P = 0.032) is of uncertain validity because of large study withdrawal rates (35%–42%) particularly in the tiotropium without SFC group.

### Tiotropium and prevention of death

There is no direct evidence that any inhaled medication improved survival in any COPD trial measured as a primary outcome. It is intuitive to speculate that drugs that have been shown to reduce COPD exacerbation frequency have real potential to modify the natural course of illness and perhaps reduce mortality. The recently completed TORCH trial raised the possibility that pharmacotherapy could reduce mortality.40 Three years of treatment with salmeterol and fluticasone seemed to reduce mortality but fell just short of significance. Recent analysis of data from the UPLIFT trial in which tiotropium was added to standard therapy showed a reduction in mortality as a secondary endpoint.41

Celli and Colleagues41 examined the effect of tiotropium on survival in the 4 year UPLIFT trial (described above). Tiotropium had been shown to improve lung function; health related quality of life and decreased exacerbation compared with usual medications (LABA-ICS) except inhaled anticholinergics. Mortality and its causes were predetermined secondary outcomes. At study termination (approximately day 1,440) all patients were instructed to stop taking the study drug or placebo and to take ipratropium two oral inhalations (40 ug) four times daily for 30 days (the washout period) and return for final assessment (day 1470). Baseline medication use was common: approximately 62% ICS, 60% LABA, theophylline 23%. At randomization 45% stopped anticholinergics. 44.6% of patients receiving placebo dropped out before the end of the study compared to 36.2% of patients receiving tiotropium. An intention to treat at 1440 and 1470 days and on “On-treatment” analysis was performed. “On-treatment” analysis attributes the event (death) to the treatment or placebo.
if the patient was taking that treatment within 30 days of death. The rational for this type of analysis considers the high dropout rate in the placebo group and the wide commercial availability of tiotropium during the 4 years of UPLIFT. Deaths of placebo-drop-out patients who went on to treatment with commercial tiotropium were attributed to placebo narrowing the true treatment affect. On-treatment analysis showed a 0.9% reduction in mortality (12.8 vs. 13.7; HR 0.84, p = 0.016). Intention to treat analysis showed a 1.9% reduction in mortality (14.4 vs. 16.3; HR 0.87, P = 0.34). Significance was lost at day 1470 after the 30 day washout period (P = 0.086). The most common causes of death were “lower respiratory” including pneumonia, followed by “other respiratory” including lung cancer. Investigator reported and blinded adjudicated analysis showed no intergroup difference in death caused by myocardial infarction or stroke.

**Smoking status and tiotropium**

The relatively large sample size enrolled in UPLIFT (n = 5993) permitted subgroup analysis of the impact of cigarette smoking status on the efficacy of maintenance therapy with tiotropium on lung function and patient reported outcomes. At baseline 70% of patients were ex-smokers and 30% active smokers. Over the 4 year trial 60% of the patients were continued ex-smokers, 14% continuing smokers and 26% intermittent smokers equally distributed between the tiotropium and placebo treatment groups. At baseline pre- and post-bronchodilator FEV₁ was lowest in the continued ex-smokers. All three categories of smokers had a similar degree of broncho-reversibility (22%–24% improvement in FEV₁) and statistically significant tiotropium associated improvement in FEV₁: this was numerically greatest in the group that continued smoking at 1 month and 48 months. Treatment assignment had no effect on rate of loss of FEV₁. Loss of FEV₁ was most rapid in continued smokers and least in continued ex-smokers.

Tiotropium was associated with a significant increased time to first exacerbation in all groups, an effect most pronounced in the continued smokers. However, only tiotropium treated continued ex-smokers had significant reduction in AECOPD frequency compared to placebo (16%, Rate Ratio 0.83; 95% CI, 0.77–0.90). Tiotropium was associated with improved SGRQ scores (health related quality of life at 6 and 48 months in all patients, with the largest effect in the continuing smokers. Continued ex-smokers in the tiotropium treatment group achieved a significant reduction in mortality compared to placebo during the treatment period. Continued and intermittent smokers did not.

Tiotropium was associated with significant improvement in pre- and post-bronchodilator lung function and health related quality of life in smokers and ex-smokers. For ex-smokers, tiotropium was associated with a reduced rate of AECOPD and reduced rate of all-cause mortality.

**Maintenance of lung function**

Smoking cessation is the only intervention shown to slow the loss of lung function in COPD. Clinical pharmacologic trials of inhaled corticosteroids (ICS) and combination salmeterol-ICS have failed to demonstrate efficacy to retard the loss of lung function in COPD. The UPLIFT trial is the largest, multicenter, controlled study of a single therapeutic agent with the primary outcome of preservation of lung function. Its underpinnings come from a retrospective analysis of two 1-year placebo controlled trials suggested that tiotropium had the potential to slow the rate of loss of FEV₁ in COPD.

The 4-year UPLIFT trial (described above) of tiotropium vs. placebo (mostly optimal care) failed to demonstrate an influence on loss of lung function compared with placebo. The rate of decline in mean annual postbronchodilator FEV₁ was 55 ± 4 ml in the tiotropium group and 57 ± 4 in the placebo group compared to 38 ± 1 and 40 ± 1 in those completing the study. A prespecified subgroup analysis of GOLD class 2 patients receiving tiotropium achieved a significant reduction in post bronchodilator annual loss of FEV₁ compared to placebo {43(SE = 2), n = 1218 vs. 49(2), n = 1158; P = 0.024}. The mean loss of prebronchodilator FEV₁ did not differ between groups (35 ± 2 ml/year vs. 37 ± 2 ml/year; P = 0.38). The clinical significance of this small numerical difference is uncertain. The effect may be magnified with time and may suggest a therapeutic role for tiotropium as a preventative therapy in early stages of COPD.

**Tiotropium compared to LABA and placebo**

A head to head study compared the influence of tiotropium, salmeterol or matching placebo on
AECOPD frequency, hospitalization, dyspnea, and health related quality of life in moderate and severe COPD. Tiotropium but not salmeterol delayed the time to first AECOPD vs. placebo (P ≤ 0.01). This study included 1,207 COPD patients in 2, parallel, 6 month, placebo controlled double-dummy trials randomized to tiotropium 18 mcg via oral Handi-Haler, salmeterol 50 mcg twice daily via a metered dose inhaler or placebo. No patients received inhaled corticosteroids.

Patients treated with tiotropium experienced fewer AECOPDs per patient year and total exacerbation days than placebo (1.07/year vs. 1.49 and 17.2 days vs. 25; P < 0.05 for both). However, salmeterol did not differ from placebo. Tiotropium treated patients required fewer all cause hospital admissions than salmeterol and placebo (12% vs. 16% vs. 22.5%; P < 0.05). There was no difference in hospitalizations for AECOPD between groups but rates were low (0.1 to 0.17 per patient per year). Tiotropium treated patients achieved a clinically meaningful 4 point improvement in the SGRQ and were significantly better than placebo (P < 0.05). Both tiotropium and salmeterol groups experienced reduced dyspnea at 6 months. In the combined study TDI score improved 1.1 ± 0.3 and 0.7 ± 0.3 vs. placebo (P < 0.001 and P < 0.05).48

The combination of tiotropium and formoterol produces a greater improvement in lung function than either drug alone. A study in 2006 compared daily tiotropium to twice daily formoterol and to the combination of daily tiotropium plus daily formoterol in a 6 week, three-way, crossover double-dummy, cross-over design. Seventy-one moderate to severe COPD patients were randomized to a double-blind, three-way, crossover study each arm for 6 weeks. The mean baseline FEV₁ at the start of the treatment was 1.019 ± 0.03 L. Inhaled corticosteroids and low dose oral corticosteroids were permitted but not theophylline. The combination of tiotropium plus formoterol produced a greater increase in predose FEV₁ than formoterol (P < 0.05). Tiotropium maintained elevations in FEV₁ throughout the 24 post dose interval and significantly out-performed formoterol at hours 8–12 after formoterol daytime dosing and at hour 12 after nighttime dosing. There was no difference among tiotropium, and formoterol predose FEV₁. This is the first evidence of the superiority of combined therapy to either single agent.49

**Tiotropium in asthma with COPD**

Some asthmatic patients may benefit from chronic tiotropium treatment. Those with nocturnal symptoms, a component of fixed airway obstruction, and non-atopic asthma of long duration have been suggested. In patients with COPD and concomitant asthma the addition of tiotropium to conventional therapy resulted in spirometric improvement, symptomatic improvement and reduction in short acting rescue medication use over 12 weeks. 472 patients (m = 90, age = 59 ± 6, FEV₁ = 53 ± 13) with COPD and physician diagnosed asthma prior to age 30 were randomized to tiotropium or placebo in addition to conventional medical therapy minus anticholinergic medications and oral steroids glucocorticoids limited to ≤10 mg per day equivalent of prednisone. Spirometry was measured pre treatment and hourly for 6 hours post treatment. Tiotropium was associated with significant placebo corrected improvements at 12 weeks in pre-dose FEV₁ (difference 98 ± 23 ml, P < 0.001) and FVC (128 ± 34 ml, P < 0.001) and post dose FEV₁ (AUC 0–6 hours) (186 ± 24 ml, P < 0.001) and FVC (AUC 0–6 hours) (232 ± 35 ml, P < 0.001).

**Sleep**

Tiotropium improves REM sleep oxygenation measured by pulse oximetry but not sleep quality or architecture in advanced COPD. A 4 week, placebo-controlled, double-blind study of tiotropium vs. placebo50 analyzed 47 of 95 severe COPD patients who were randomized to study protocol. Thirty-six patients received tiotropium, pre-specified to either morning or evening dosing. Eleven patients received placebo. The primary outcome was the absolute values of SaO₂ measured during overnight polysomnography recorded at baseline and after 4 weeks. The dose timing of tiotropium did not change the mean improvement in nocturnal SaO₂. The pooled mean increase in REM SaO₂ for tiotropium compared to placebo treated subjects was 2.4% (P = 0.008).

**Inflammation, remodeling and tiotropium**

The recent observation that tiotropium slows the decline in expiratory airflow over four years in
patients with moderate (COPD GOLD class 2) patients suggests that cholinergic mechanisms may contribute to long term structural injury and remodeling in the lung. Parasympathetic activity is increased in asthma and COPD. Acetylcholine is the primary parasympathetic neurotransmitter in the human airways and an autocrine and paracrine hormone that is secreted from non-neural origins, including the airway epithelium and inflammatory cells. Acetylcholine, its synthesizing enzyme choline acetyltransferase (ChAT) and muscarinic receptors are nearly ubiquitous in the mammalian airways including parasympathetic innervations, epithelial, endothelial and smooth muscle cells. Acetylcholine is also released from non-neural origins in bronchial epithelial cells and circulating blood cells in the lung including lymphocytes, macrophages, mast cells, eosinophils and neutrophils. The significance of the acetylcholine activity at many anatomic sites and circulating cells is uncertain.

There is evidence that tiotropium blocks in vitro carbachol (a muscarinic agonist) stimulation of cultured human lung fibroblasts. Collagen synthesis increases in a shows a dose-dependent response to carbachol that is blocked by tiotropium at an inhibitory concentration of 50%: 110 pM. Prolonged muscarinic receptor stimulation increases cultured airway smooth muscle contractile protein expression, pro-mitogenic signaling and cell proliferation. Animal studies have demonstrated the protective effects of tiotropium in inhibiting aerosolized ovalbumin induced guinea pig airway smooth muscle thickening, contractile protein expression, mucus gland hyperplasia, increase in mucin 5 subtypes A and C goblet cells and eosinophilia an effect similar to inhaled glucocorticoids.

Tiotropium may alter elastin degradation in moderate to severe COPD. Ma and colleagues examined the elastin degradation products desmosine and isodesmosine (D/I) in the sputum, plasma and urine of 12 COPD patients treated with daily tiotropium for two months. All patients were tiotropium naïve, none were currently smoking or on supplemental oxygen and none changed inhaled steroid status during the study. All had significant reduction in sputum D/I (measured by mass spectrometry) compared to baseline (58%, range 4%-98%, P < 0.005). Ten of twelve had reduction in urine and plasma D/I (15%, range 9%-38%; 27%, range 2%-65%, P < 0.005).

This preliminary data suggests a possible cholinergic mechanism of elastin degradation and stimulates hypothesis generation to explain tiotropium associated preservation of lung function in Gold stage 2 patients (see UPLIFT).

Safety
Tiotropium is safe and well tolerated with few side effects. The most common side effect dry mouth is generally mild and does not necessitate drug discontinuation. Cardiovascular safety data from a recent 4 year, large, multicenter, randomized, placebo controlled tiotropium trial alloyed earlier concern over cardiovascular side effects and increased stroke risk. In the previously described dose-finding study safety of all does of tiotropium (range 4.5 mcg to 36 mcg) was reported to be similar to placebo. There were no dose-dependent increases in the incidence or severity of any individual adverse events. The most common adverse event was dry mouth that occurred in 7 out of the 169 (4.1%) treated COPD patients. The highest prevalence of adverse events was seen with the 36 mcg tiotropium dose. There were no clinically significant effects of tiotropium on vital signs, ECG or clinical laboratory parameters.

Factual information regarding tiotropium prescribing and safety can be viewed at www.pfizerpro.com/product_info/spiriva_pi_clinical_pharmacology.jsp. Tiotropium is contraindicated in patients with a history of hypersensitivity to tertiary or quaternary amines such as atropine, its derivatives or ipratropium. Tiotropium is not intended to treat acute symptoms related to an exacerbation of COPD. Tiotropium presents no known risk of serious drug-drug interaction.

Use of tiotropium in human pregnancy is unstudied, however studies in animals showed no evidence of mutagenicity or clastogenicity. As a result, tiotropium is listed as pregnancy category C. Breastfeeding mothers should use caution as tiotropium is likely excreted in human milk. Boehringer-Ingelheim, states “SPIRIVA (tiotropium) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus”. The safety and efficacy of tiotropium in pediatric patients has not been established.

Tiotropium may aggravate acute-narrow angle glaucoma, prostatic hyperplasia and bladder-neck obstruction and should be used with caution in any
of these conditions. There is no indication for age, renal or hepatic dose adjustment. Careful observation is recommended for geriatric patients or patients that have impaired hepatic or renal function.

Casaburi and colleagues evaluated the long-term safety and efficacy of tiotropium 18 mcg once daily oral inhalation from the two identically designed, one-year, randomized, placebo-controlled, multi-center tiotropium registry trials. In total 921 COPD patients were randomized 3:2 to tiotropium 18 mcg oral inhalation daily (n = 550) vs. placebo (n = 371).

Patients were permitted albuterol, theophylline, inhaled glucocorticosteroids and the equivalent of ≤10 mg/day of oral prednisone. The study completion rate for the tiotropium group was greater than for the placebo group (81.3% vs. 72.2%, P < 0.05). More frequent placebo group dropout occurred due to adverse events and lack of efficacy vs. tiotropium (13.7 and 7.0% vs. 9.6 and 2.4%, P < 0.05).

Only dry mouth occurred more frequently with tiotropium (16% vs. 2.7%). Dry mouth was generally mild and lead to <1% of the tiotropium treated patients to withdraw from the study. Serious adverse events (SAE) and SAEs leading to study withdrawal or death were no different between the study groups.

Concern about the safety of inhaled anticholinergic therapy for COPD originated before tiotropium. In 2002, 5 year follow-up data from the Lung Health Study showed that the inhaled ipratropium bromide was associated with a small unexpected increase in cardiovascular death in smokers with mild to moderate COPD. The Lung Health study showed that with unadjusted pairwise comparisons between the treatment groups there was a lower risk of cardiovascular death in the smoking intervention-placebo vs. smoking intervention-ipratropium group (0.36% vs. 0.96%; P = 0.027). There was no difference between the compliance rates with inhaled ipratropium vs. placebo with only about a third of patients in each group reporting 3 or more puffs a day at each annual visit. A post-hoc analysis of frequency of ipratropium use, smoking status and cardiovascular events by Lanes and colleagues (Boehringer Ingelheim Pharmaceuticals, Inc.) suggested that most cardiovascular deaths occurred in patients receiving the least ipratropium. Regardless, these findings prompted widespread concern and a recent Global Initiative for Chronic Obstructive Lung Disease guideline called for further investigation of the potential cardiovascular risks of inhaled anticholinergic medications.

On March 18, 2008 the US Food and Drug Administration issued an Early Communication about an ongoing safety review of tiotropium. Boehringer-Ingelheim the maker of the Spiriva HandiHaler (tiotropium bromide), had conducted a pooled analysis of 29 trials including approximately 13,500 COPD patients that suggested a 2 per 1000 patient year increased risk of stroke (8 per 1000 in patients treated for 1 year with tiotropium vs. 6 per 1000 for one year with placebo).

An additional meta-analysis of 17 studies was published in September 2008 involving 14,783 COPD patients using tiotropium, ipratropium bromide, placebo or an active non-anticholinergic control also suggested an anticholinergic related risk for cardiovascular death, stroke, and myocardial infarction (relative risk 1.58 P < 0.001). All cause mortality was not different. Serious adverse events occurred in 135 of 7,472 (1.8%) patients receiving anticholinergic therapy for more than 30 days (30 days to 5 years) vs. 86 of 7,311 (1.2%) in the control group.

A 2006 pooled clinical safety analysis of pre and post approval tiotropium randomized, placebo controlled studies found no increased risks associated with tiotropium. The analysis included 19 randomized, double-blind placebo controlled trials, 4,435 tiotropium assigned patients and 3,384 assigned to placebo totaling 2,159 tiotropium-person-years and 1,662 placebo-person-years.

SAEs such as AECOPD, myocardial infarction, and death and selected events such as dry mouth, sore throat and urinary retention were extracted by a blinded investigator from the clinical trial logs after study completion. Patients were included who received at least 30 days of tiotropium treatment or until they encountered the first event of interest. 90% of treated patients received tiotropium for 90 or more days. Study discontinuation prior to the anticipated end-date and withdrawal due to an adverse event was more common in patients receiving placebo vs. tiotropium (24% vs. 16%; χ² = 73.32, P < 0.0001 and 15% vs. 9%; χ² = 64.19, P < 0.0001). There was no difference in incidence of death, cardiovascular morbidity, or the development of myocardial infarction. Stroke was not recorded.
Tiotropium was associated with a lower relative risk of pneumonia and serious AECOPD (RR, 0.64; 95% CI, 0.42 to 0.98 and RR, 0.68; 95% CI, 0.54 to 0.85), although respiratory mortality was similar. Dry mouth was more common in the tiotropium treated patients (RR, 3.60; 95% CI, 2.56 to 5.05). The relative risk of urinary retention was 10.93 for tiotropium compared to placebo (95% CI, 0.59 to 48.33). The data suggests a trend toward reduced relative risk of left-heart failure with tiotropium but not of statistical significance (RR = 0.46; 95% CI, 0.21 to 1.00). Dysphagia, abdominal pain, constipation, nausea, glaucoma and prostatic disorders were observed at similar frequency.57

The UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial demonstrated the long-term safety of tiotropium over four years of continuous use. UPLIFT trial design was multicenter, prospective, placebo controlled and double blinded. 5,993 patients with moderate to very-severe COPD were treated with standard medications and randomized 1:1 to tiotropium vs. placebo for 4 years.12 Data collection included pre-specified secondary outcomes relevant to cardiovascular safety and mortality. During the 4-year treatment period plus 30 day follow up there was not difference in all-cause mortality; 941 patients died, 14.9% of the tiotropium group vs. 16.5% of placebo group (hazard ratio, 0.89; 95% CI, 0.79 to 1.02).

Serious adverse events including respiratory failure, congestive heart failure and myocardial infarction were significantly less in the tiotropium group | (RR, 0.67; 95% CI 0.51 to 0.89, P < 0.05), (RR, 0.59; 95% CI, 0.37 to 0.96, p < 0.05) and (RR, 0.71; 95% CI, 0.52 to 0.99, p < 0.05)). Of particular importance, there was no difference in the risk of stroke (n = 82) in the tiotropium vs. (n = 80) in the placebo groups (RR, 0.95; 95% CI 0.7 to 1.29).12 An FDA statement on October 7th 2008,58 based upon the recent publication of the UPLIFT trial, stated that there was no increase in stroke risk in patients receiving long term tiotropium therapy compared to placebo. The FDA plans to update the communication regarding tiotropium and stroke risk after completion a review of the data collected in UPLIFT and all available data regarding tiotropium. In November 2009 the FDA Pulmonary Allergy Drug Advisory Meeting completed its review concluding that tiotropium is safe, without an increased risk of stroke or adverse cardiovascular events.1 A definitive FDA communication is pending.

Celli and colleagues59 performed a meta-analysis (funded by Boehringer Ingelheim and Pfizer) of cardiovascular safety of tiotropium in patients with COPD. These results complement the prospectively obtained UPLIFT safety data confirming tiotropium’s cardiovascular safety. They included data from all randomized, double-blind, parallel-group, placebo-controlled trials of tiotropium of at least 4 weeks duration of patients ≥40 years with spirometry confirmed COPD. Incidence ratios (IR) for all patients and rate ratios (RR) for tiotropium/placebo were calculated. End points included all cause mortality and selected cardiovascular events including a composite CV endpoint of CV deaths, non-fatal myocardial infarction, non-fatal stroke, and sudden death. 19,545 patients were randomized, 10,846 tiotropium, from 30 trials with mean FEV$_1$ = 41% ± 14%, age 65 ± 9, male = 76%.

Incidence of all cause mortality was lower in tiotropium patients vs. placebo. There were 953 fatal cases (5%). The risk of death was approximately 12% less in the tiotropium group. The IR was 3.44 (tiotropium) vs. 4.10 (placebo) per 100 patient-years [RR (95% CI) = 0.88 (0.77, 0.999)]. The incidence of cardiovascular morbidity and mortality was lower in tiotropium patients. The IR for the composite CV endpoint was 2.15 vs. 2.67 per 100 patient years [RR (95% CI) = 0.83 (0.77–0.98)]. Incidence of myocardial infarction and stroke were no different in tiotropium vs. placebo [RR (95% CI) = 0.78 (0.59, 1.02) and 1.03 (0.79, 1.35)]. Incidence of cardiac failure was lower in tiotropium treated patients [RR (95% CI) = 0.82 (0.69, 0.98)].59

**Conclusion**

Inhaled tiotropium bromide is an important, safe and effective drug in the treatment of moderate to severe stable COPD. Tiotropium’s pharmacokinetic properties permit convenient daily dosing, functionally selective M$_1$ and M$_2$ receptor antagonism and superior predose trough and mean lung function compared to ipratropium. Tiotropium has repeatedly shown improvement in lung function, exercise tolerance, dyspnea, health related quality of life and reduction of AECOPD. The US FDA recently granted a new
tiotropium indication to reduce COPD exacerbations. Tiotropium is not associated with increased stroke or cardiovascular morbidity. Prespecified subgroup analysis of GOLD Stage 2 COPD patients in the 4 year UPLIFT trial demonstrated tiotropium’s association with a small but statistically significant reduction in annual loss of FEV\textsubscript{1}. These data may suggest a future role for earlier use of tiotropium in more mild COPD.

**Disclosures**

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

**References**


Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

http://www.la-press.com