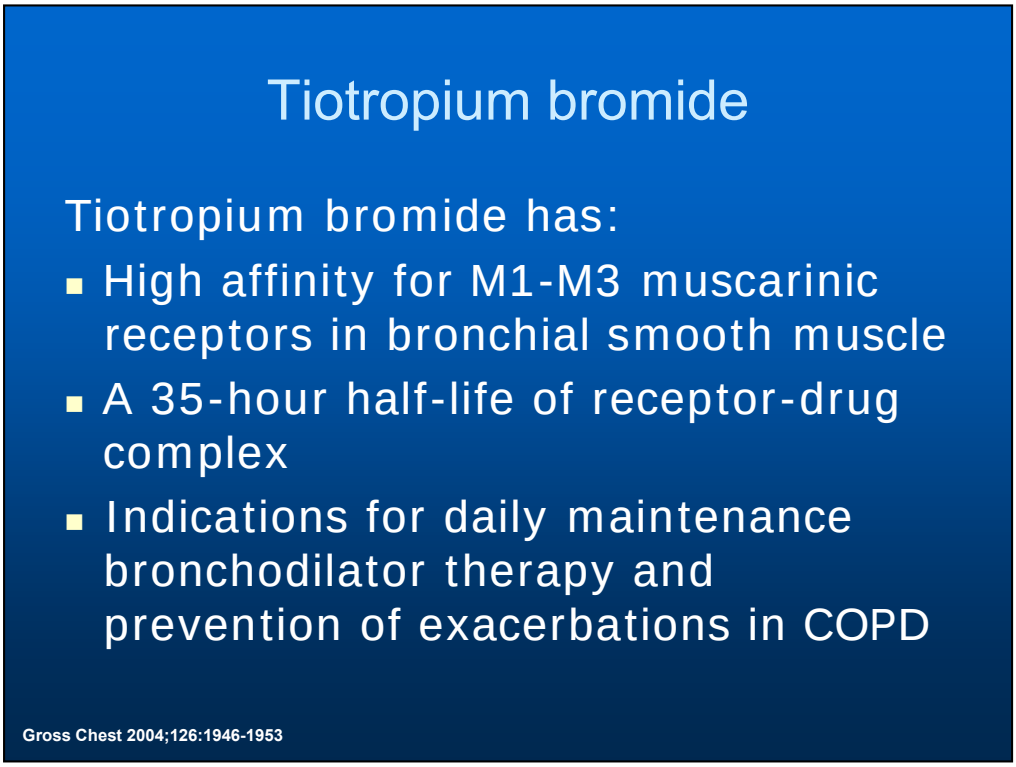
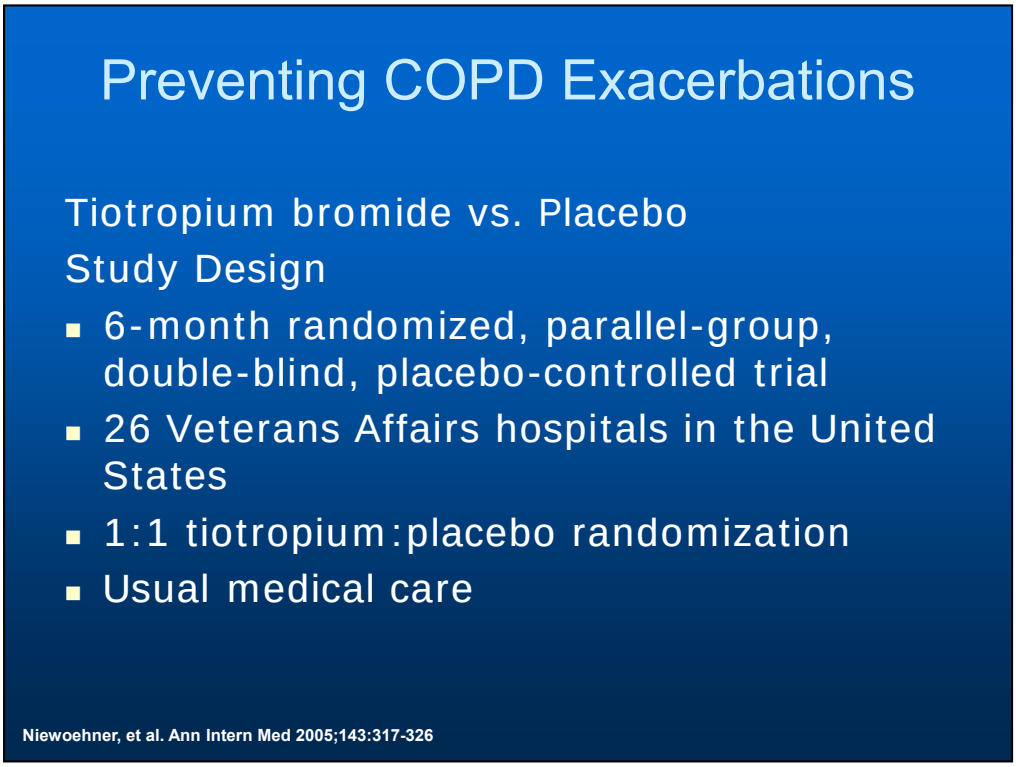
Use of Tiotropium bromide in the Management of COPD

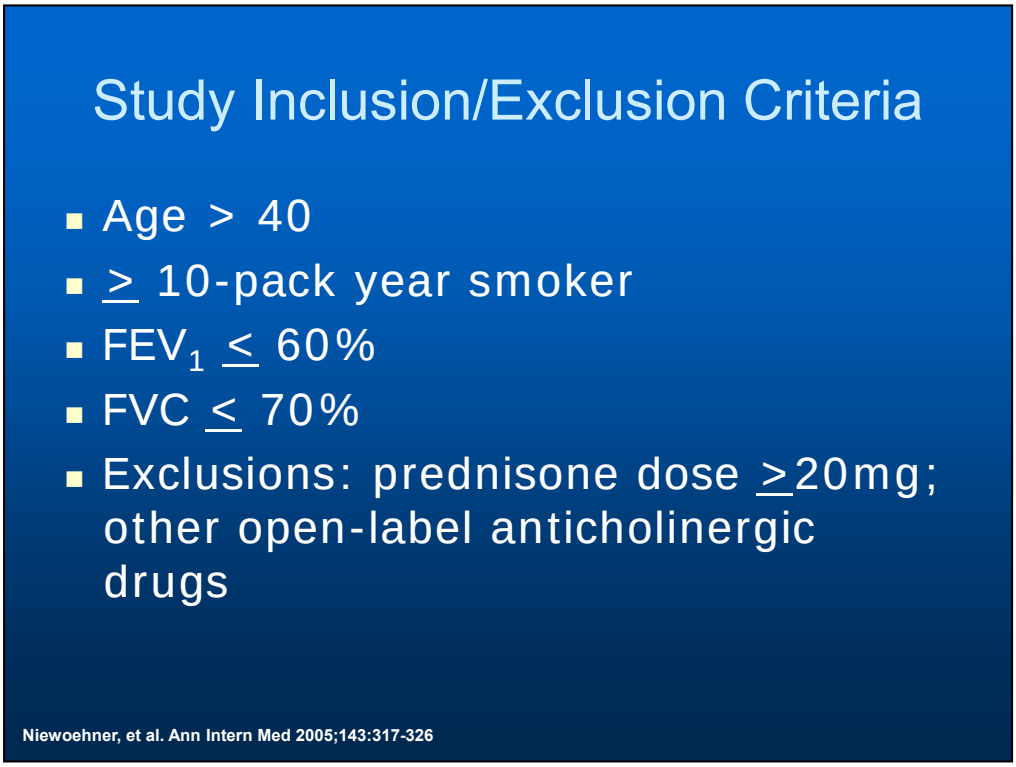
Title Page



1. Inhibiting parasympathetic drive to bronchial smooth muscle results in bronchodilation. (Gross)
2. Tiotropium bromide is a synthetic quaternary ammonium compound and anticholinergic agent functionally selective for M1-M3 muscarinic receptors mediating bronchial smooth muscle contraction in the lung. (Gross)
3. Tiotropium bromide improves lung function, reduces symptoms, improves health status, and reduces exacerbations. (Gross)



1. This study was a randomized, parallel-group, double-blind, placebo-controlled trial conducted over 6 months at 26 Veterans Affairs (VA) hospitals in the US.
2. Patient were allowed to continue usual medical care including antibiotics, corticosteroids as long as the dose was < 20mg, and oxygen therapy.

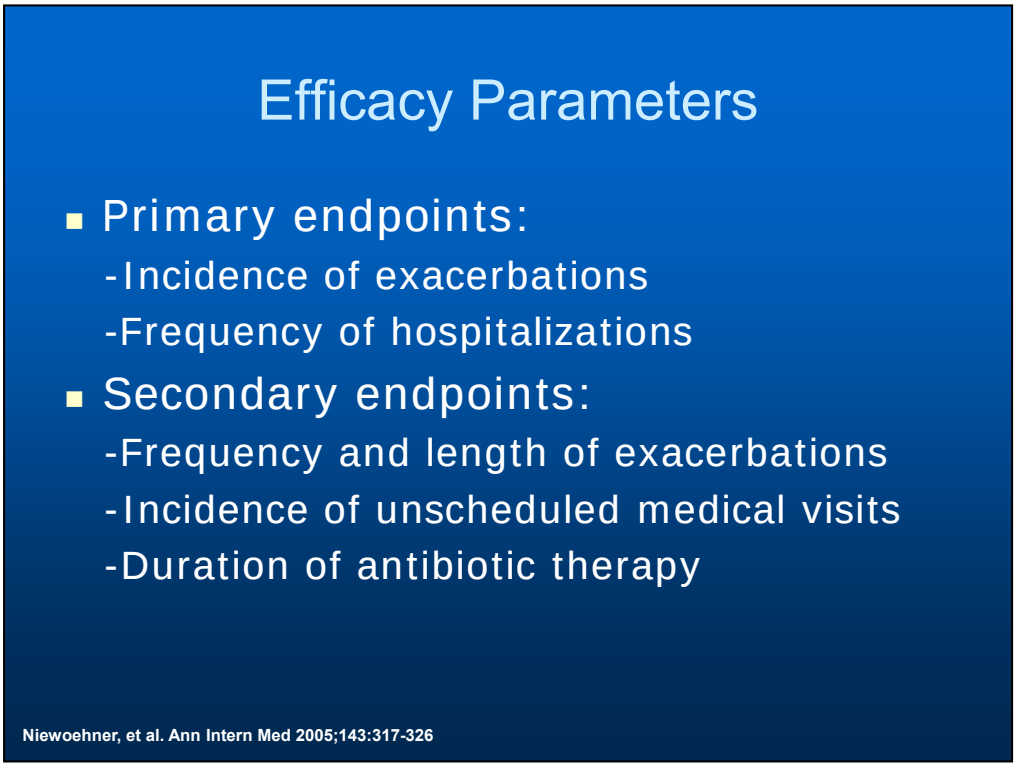


1. A total of 1829 patients were enrolled 915 to placebo and 914 to tiotropium. Patients were eligible if they were ≥ 40, ≥ 10-pack year smoking history, had clinical criteria for COPD with an FEV_1 ≤ 60% predicted, and FVC ≤ 70%. 99% of study population was male.
2. Exclusion criteria included:

- diagnosis of asthma or MI 6 months prior to study enrollment
- hospitalization 1 year prior to study enrollment for serious cardiac arrhythmia or heart failure
- moderate to severe renal impairment
- moderate to severe prostate hypertrophy or bladder neck obstruction
- narrow angle glaucoma
- current treatment for cancer
- receiving unstable doses of corticosteroids or had an exacerbation 30 days prior to study onset and were not fully recovered.

3. The tiotropium and placebo groups had similar demographics: 99% male, with a mean age of 67.8, were majority Caucasian, 30% still smoked with a mean pack year smoking history of 68.4 years. Mean FEV_1 was similar at 1.04 L and 35.6% of predicted with a FEV_1/FVC ratio of 47.8%. For existing medication, 94% were on an inhaled beta agonist, 80% on ipratropium bromide, and 59% were on corticosteroids. The most common co-existing illnesses were cardiovascular in

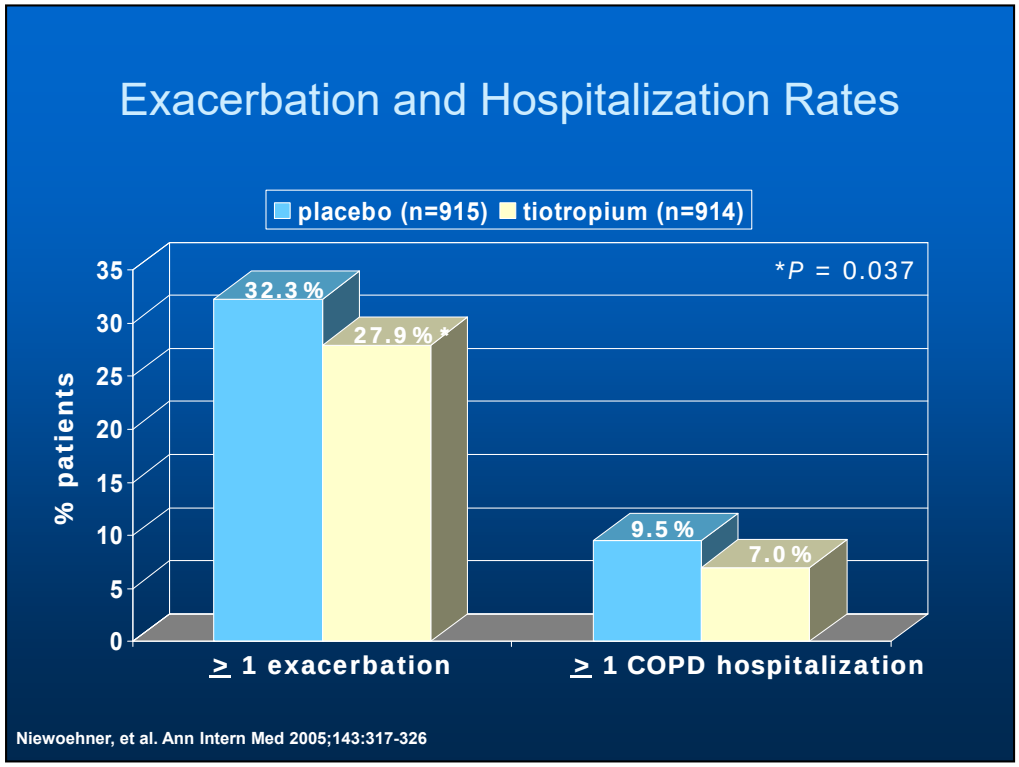
nature.



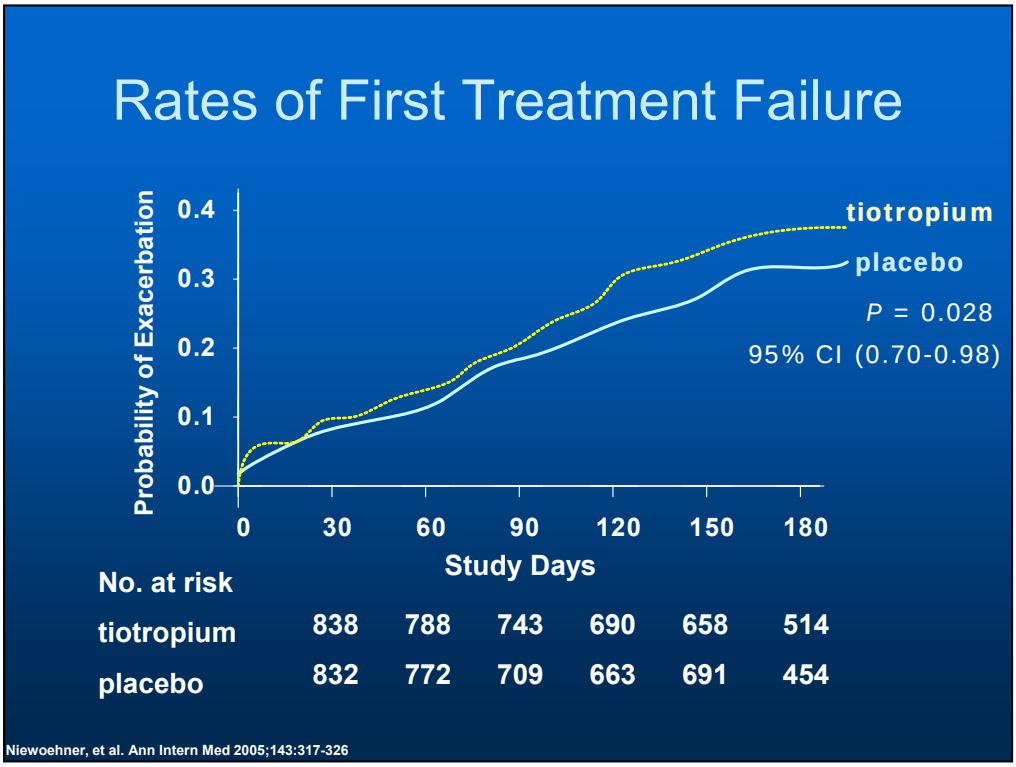
1. Primary outcomes were the percentage of patients with a COPD exacerbation and/or hospitalization due to a COPD exacerbation.
2. Exacerbations were defined as two or more of the following:

- Cough
- Sputum
- Wheezing
- Shortness of breath
- Chest tightness
- Symptoms lasting a minimum of 3 days and required treatment with antibiotics or systemic steroids, hospitalization, or both
- Any patient kept in an observation unit for more than 24 hours was considered a hospitalization.

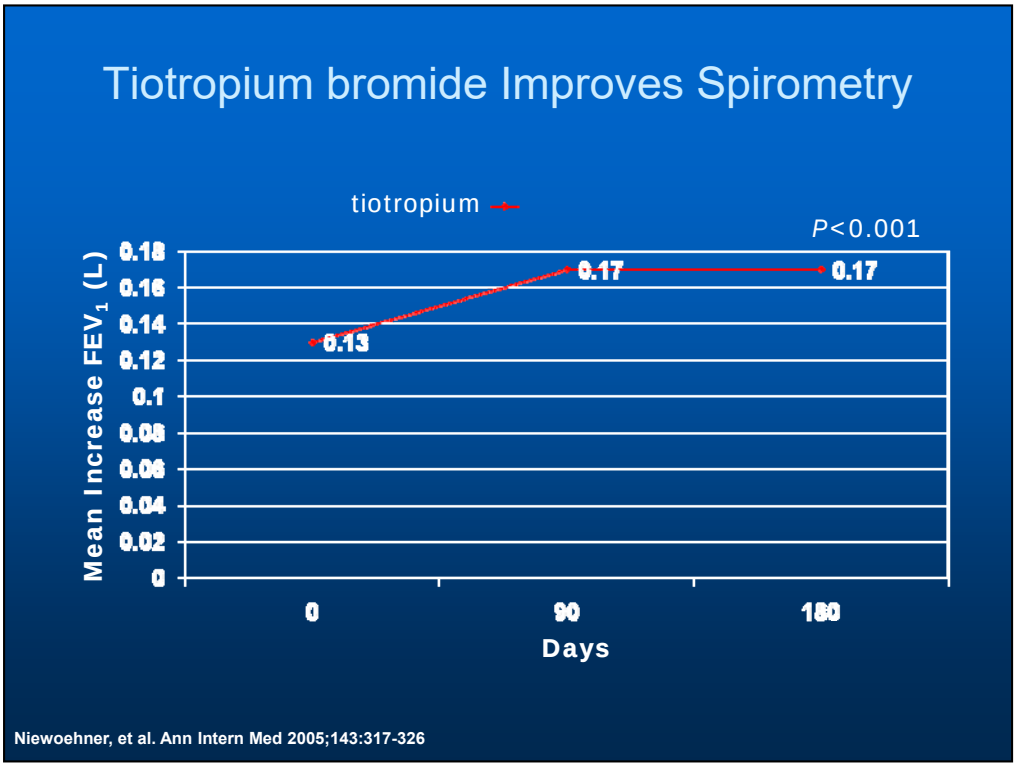
3. Secondary outcomes were time to first exacerbation or hospitalization due to COPD and use of healthcare facilities as measured by hospitalizations, hospitalization days, unscheduled clinic visits, length of treatment with antibiotics, and results of spirometry.



1. Of patients on tiotropium, 27.9% had one or more exacerbations of COPD as compared to 32.3% of patients who received placebo. This reached significance at a *p* value = 0.037.
2. For hospitalizations, patients on tiotropium were hospitalized 7% of the time compared to 9.5% of the time for placebo. This number did not reach significance.
3. For this study, significance was assessed at a P value = 0.050.
4. Time to first exacerbation and time to first hospitalization were also extended.
5. The asterisk for exacerbations and hospitalization rates indicates that 5.1% or 47 of the tiotropium and 7.2% or 66 of the placebo group patients withdrew from the study before either an exacerbation or hospitalization and were counted as not having an event.



1. Tiotropium bromide extended the time to the first exacerbation as noted previously and this value reached significance at 0.028.



1. FEV_1 at 90 minutes increased from a mean of 0.13 L at day 0 to a mean of 0.17 at days 90 and 180 in the tiotropium group as compared to placebo.
2. Morning trough FEV_1 prior to drug administration was higher for the tiotropium group as compared to placebo
3. This reached significance at $P < 0.001$ for all comparisons

Secondary Outcomes

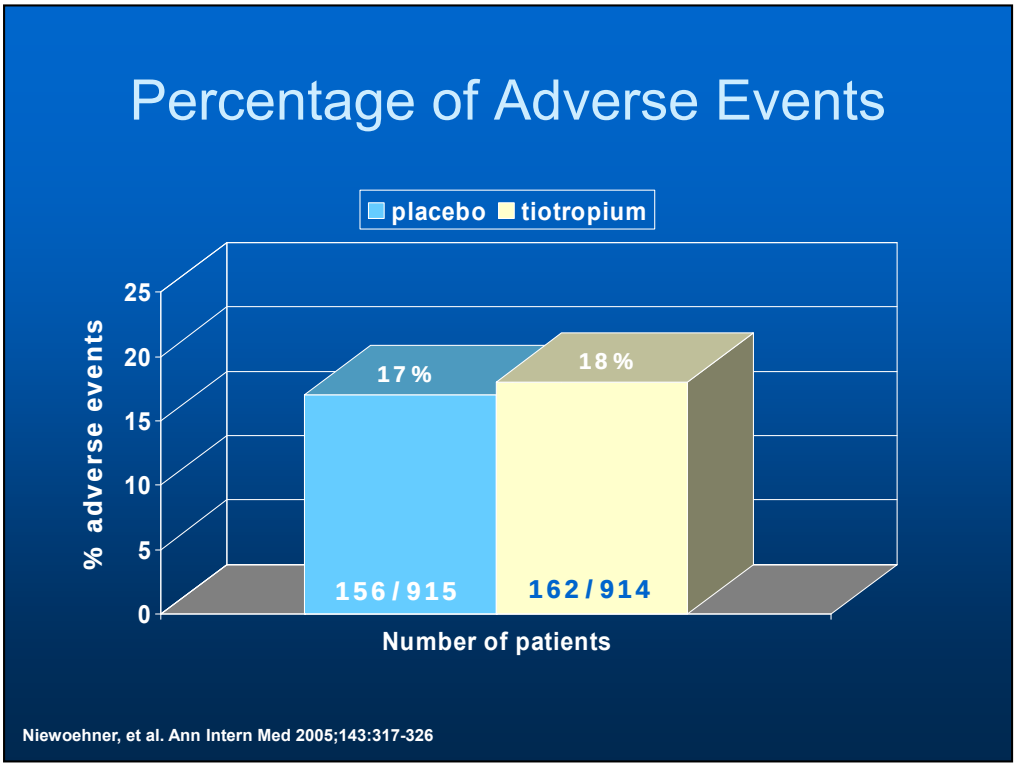
Outcomes	Placebo (n=915)	Tiotropium (n=914)	Difference	*P* Value
Exacerbations	1.05	0.85	-0.20	0.031
#Exacerbation days	16.0	12.6	-3.35	0.019
#Antibiotic days	9.8	8.1	-1.71	0.015
#Steroid days	7.4	6.3	-1.15	0.25
Unscheduled visits	0.49	0.39	-0.11	0.019
Hospitalizations	0.25	0.18	-0.08	0.047
#Hospitalization days	1.7	1.4	-0.27	0.054

Niewoehner, et al. Ann Intern Med 2005;143:317-326

1. In looking at tiotropium and measuring secondary outcomes, tiotropium reduced

- Exacerbations
- Length of exacerbations in days
- Length of time on antibiotics during an exacerbation
- Length of time on steroids
- Unscheduled clinic visits for increased symptoms
- Frequency of hospitalizations and length of hospitalization.

2. Not shown are all-cause hospitalizations which tiotropium also reduced compared to placebo; however, length of hospitalizations for all causes was no different between the tiotropium and placebo groups.



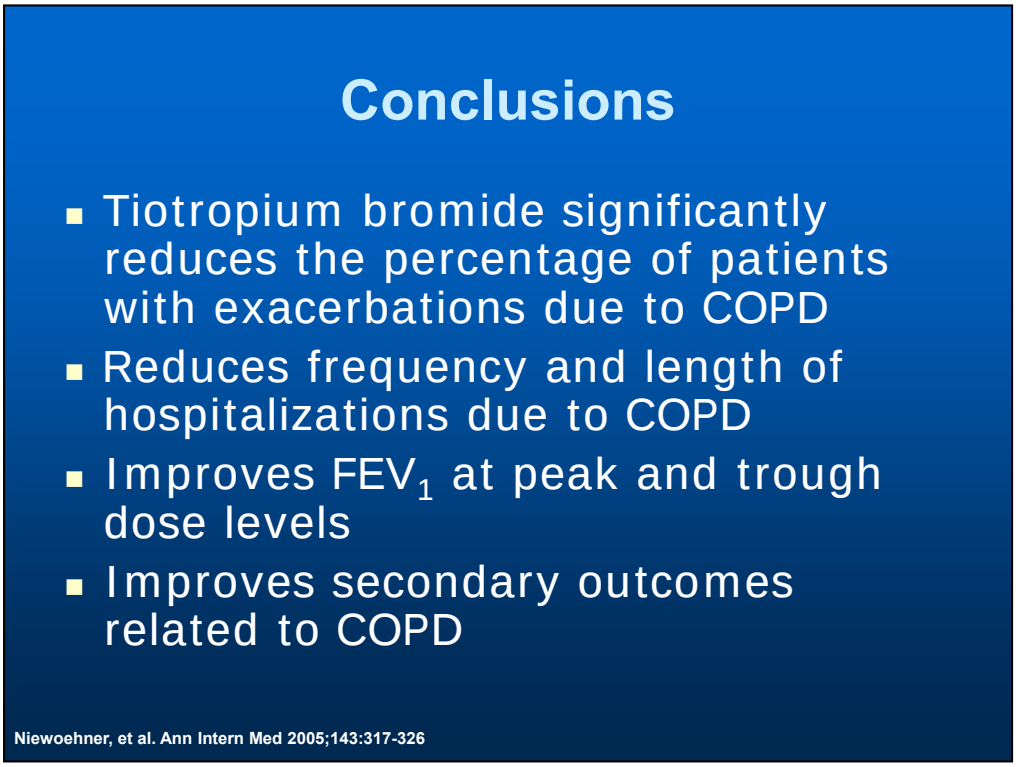
1. Adverse events were similar in both groups at 17% for placebo and 18% for tiotropium respectively.
2. Any adverse event that occurred within 30 days of the last dose of medication was assigned to the appropriate treatment group.
3. 27% (245) of placebo and 16% (149) of tiotropium patients withdrew from the study; however, time to withdrawal was longer for those in the tiotropium group and was significant at P < 0.001. The most common reason given for withdrawal was worsening of COPD.`

Types of Adverse Events

Adverse Event	Tiotropium	Placebo
Lower Respiratory System Disorder	7.8%	9.9%
Congestive heart failure	1.09%	1.09%
Atrial fibrillation	0.2%	0.9%
Deaths	2.1%	2.4%

Niewoehner, et al. Ann Intern Med 2005;143:317-326

1. Lower respiratory tract disorders were the most common adverse event reported for both groups though the tiotropium group had a lower percentage.
2. Cardiac system disorders were the next most frequent as noted. Ischemic events were similar for both groups
3. There were fewer deaths due to lower respiratory system disorders in the tiotropium group, 2 as compared to 7 deaths for placebo.
4. There were a total of 7 cardiac deaths for the two groups and 13 deaths due to cancer, 8 in the tiotropium and 5 in the placebo group.



In conclusion:

1. Tiotropium bromide significantly reduces the percentage of patients with exacerbations due to COPD
2. Reduces frequency and length of hospitalizations due to COPD as well as reduces other healthcare utilization factors such as days on antibiotics, days on systemic corticosteroids, and unscheduled clinic visits
3. Tiotropium bromide improved spirometry at both peak and trough dose levels.

References

- Gross N. Tiotropium bromide. Chest 2004;126:1946-1953.
- Niewoehner D, Rice K, Cote C, et al. Prevention of exacerbations of COPD with tiotropium, a once-daily inhaled anticholinergic bronchodilator. Ann Intern Med 2005;143:317-326.