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Do Inhaled Anticholinergics Increase or Decrease the Risk of Major Cardiovascular Events?

A Synthesis of the Available Evidence

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Abstract

There has been recent uncertainty about whether the inhaled anticholinergic agents ipratropium bromide and tiotropium bromide increase or decrease cardiovascular risk in the treatment of patients with chronic obstructive pulmonary disease (COPD). This article synthesizes the available data in order to understand the controversy.

COPD is a common cause of hospitalizations and is a rapidly increasing cause of mortality worldwide. Despite the heavy burden of COPD-related illness, the leading cause of hospitalization in COPD patients is cardiovascular disease. This link between COPD and cardiovascular disease is in part due to the fact that both diseases share common risk factors, such as tobacco smoking and advanced age. It is also hypothesized that systemic inflammation in COPD increases the risk for cardiac events such as myocardial infarction.

Inhaled anticholinergics reduce COPD-related hospitalizations and respiratory deaths compared with placebo, and tiotropium bromide is more effective than ipratropium bromide. In randomized trials, patients receiving tiotropium bromide have lower discontinuation rates than those receiving placebo and, therefore, contribute more person-years to the analyses. In a recent large 4-year tiotropium bromide trial, the proportion of patients who died was similar in the tiotropium bromide and placebo groups, whereas the death rate per person-years was lower with tiotropium bromide, indicating longer overall survival.

There has been conflicting evidence concerning cardiovascular risk associated with inhaled anticholinergics. One meta-analysis found that the risk for major cardiovascular events was higher with anticholinergics compared with placebo or active comparator controls, whereas two subsequent meta-analyses that included new trial data found no difference in risk. In a recent pooled safety analysis, when incidence rates of events over time were evaluated, tiotropium bromide was associated with a lower rate of major cardiovascular events and cardiovascular deaths compared with placebo. This risk reduction was mainly because of a reduction in serious cardiac events such as myocardial infarction and congestive heart failure.

In conclusion, inhaled anticholinergics, especially tiotropium bromide, reduce COPD-related hospitalizations and deaths, and may improve total survival over time. Many COPD patients have concomitant cardiovascular disease processes. Thus, trials may observe more cardiovascular events associated with anticholinergics than with placebo, but this differential is eliminated when evaluating the rate of events per person-years of exposure. New evidence indicates that tiotropium bromide may actually reduce the incidence of cardiovascular events and deaths over time. It is possible that the reduction in respiratory morbidity could improve functional status and reduce adverse cardiac outcomes over time. Further studies are needed to address this important issue.

Chronic obstructive pulmonary disease (COPD) is considered to be a preventable and treatable disease characterized by airflow limitation that is not fully reversible, an abnormal inflammatory response in the lungs and significant extrapulmonary effects that may contribute to the severity of disease.[1] COPD is a common cause of hospitalization in adults, especially in the elderly, and is currently the fourth leading cause of death in the US.[2,3]

Bronchodilators, including β-adrenoceptor agonists and anticholinergics, are widely used in the treatment of COPD and can improve some of the symptoms associated with airflow obstruction.[1] However, potential safety concerns have arisen about possible cardiovascular adverse effects of these drugs. COPD patients often have co-morbid illnesses, such as ischaemic heart disease, hypertension and arrhythmias, so potential cardiac toxicity poses serious risk.[4,5]

Observational studies and a meta-analysis of randomized trials have provided evidence over the years that β-adrenoceptor agonists may increase adverse cardiac events through β-adrenergic stimulation, possibly by inducing ischaemia, congestive heart failure, arrhythmias or sudden death.[6-11] The cardiac risk associated with β-adrenoceptor agonist use appears to be greatest upon initiation of therapy, when treatment is associated with an increase in heart rate and a reduction in potassium concentrations.[6,7] In contrast, there is some evidence that inhaled corticosteroids may reduce major cardiovascular events, possibly through their anti-inflammatory effects.[5,12-14]

More recently, conflicting evidence has surfaced concerning cardiovascular risk associated with anticholinergic inhalers. Observational studies and a meta-analysis of randomized trials have found an association between inhaled anticholinergics and cardiovascular events, similar to that found with β-adrenoceptor agonists.[11,14-16] There are inherent difficulties in interpreting observational studies because of potential confounding variables that may not have been adequately adjusted for. Therefore, this review concentrates mainly on randomized trial evidence. Recently, there has been evidence from a large, randomized, placebo-controlled trial that the long-acting anticholinergic tiotropium bromide may reduce the rate of serious cardiovascular events.[17] This review article examines the available evidence in order to understand the cardiovascular effects of inhaled anticholinergics in patients with COPD. The evidence is presented chronologically according to date of publication so that we can better understand how our knowledge has evolved.

1. Co-Morbidity of Chronic Obstructive Pulmonary Disease (COPD) and Cardiovascular Disease

1.1 Burden of Cardiovascular Disease

COPD frequently exists with other co-morbid conditions, which can adversely affect outcomes.[3,5,12] In patients with mild to moderate COPD, who make up the vast majority of all cases, hospitalizations and deaths are three times

more likely to be due to cardiovascular events than respiratory causes.[18] In more severe COPD, respiratory and cardiovascular events occur with equal frequency.[19] The increased risk of cardiovascular disease in COPD patients is in part due to shared risk factors, such as tobacco smoking and advanced age.[13] It has also been hypothesized that underlying systemic inflammation associated with COPD plays a prominent role in increasing cardiovascular risk.[13]

2. Inhaled Anticholinergics in COPD

2.1 Respiratory Effects of Inhaled Anticholinergics

Inhaled anticholinergic bronchodilators inhibit bronchoconstriction and mucus secretion, improve respiratory symptoms and reduce COPD exacerbations without producing tolerance to their effects over time.[20] Meta-analyses of randomized trials have shown that anticholinergics reduce COPD hospitalizations by 30% and respiratory deaths by 70%, compared with placebo.[21,22] When trials that compared the long-acting tiotropium bromide with the short-acting ipratropium bromide were pooled together, tiotropium bromide was associated with 40% less severe exacerbations than ipratropium bromide.[23,24] Observational studies and randomized trials have compared the respiratory effects of inhaled anticholinergics with β-adrenoceptor agonists and have found that inhaled anticholinergics are associated with significantly fewer COPD hospitalizations and total mortality compared with inhaled β-adrenoceptor agonists.[24,25]

In a recent large trial, the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study, 6000 patients with moderately severe COPD were randomized to tiotropium bromide or placebo and followed for 4 years.[17] The discontinuation rate was significantly lower in the tiotropium bromide group (36%) compared with the placebo group (45%), in part because tiotropium bromide delayed the time to first exacerbation (17 vs 13 months).[17] Tiotropium bromide did not reduce the proportion of patients who died of any cause (odds ratio 0.92 [95% CI 0.80, 1.07]).[26] However, the annualized rate of fatal events was evaluated during the period when patients were on treatment, and tiotropium bromide was shown to reduce mortality by 15% (hazard ratio 0.84 [95% CI 0.73, 0.97]).[17]

2.2 Cardiovascular Effects of Inhaled Anticholinergics

Inhaled anticholinergics are relatively poorly absorbed from the gastrointestinal tract and lung, so it has been believed that systemic adverse effects are rare and mild.[20] However, treatment has been shown to substantially increase the risk of the development of dry mouth, urinary retention and sinus tachycardia, indicating significant systemic effects of inhaled anticholinergics.[27,28] For this reason, it is possible that inhaled anticholinergics can exert adverse systemic cardiovascular effects.

Inhaled anticholinergics increase the incidence of sinus tachycardia, which is a supraventricular arrhythmia that can signal severe underlying pathology and is associated with poor prognosis in the presence of cardiac conditions.[27,29] Elevated heart rate can contribute to cardiac work and strain, and has consistently been associated with an increased risk of congestive heart failure, fatal myocardial infarction and sudden cardiac death.[30-33]

2.2.1 Lung Health Study with Ipratropium Bromide, 2002

In 2002, the morbidity and mortality results of the 5-year Lung Health Study[18] were published, which showed that the short-acting anticholinergic ipratropium bromide had no significant effect on respiratory or total mortality compared with placebo. A surprising finding was a higher proportion of patients with cardiovascular hospitalizations and deaths in the ipratropium bromide group compared with placebo, a result that approached statistical significance (see table I).[18] Of note, there was a preponderance of arrhythmias, particularly supraventricular tachycardia, as a cause of hospitalization in the ipratropium bromide group.[18]

Table I. Risk of major cardiovascular events associated with inhaled anticholinergics

Study	Outcome	Results (95% CI)	Statistical significance
Lung Health Study[18]	Incidence rates of cardiovascular deaths, IPR and PL	IPR: 0.92% PL: 0.36%	p = NS
Singh et al.[15] (meta-analysis)	Proportion of major cardiovascular events, ACH vs PL/AC	Relative risk 1.58 (1.21, 2.06)	p < 0.05
UPLIFT trial[17]	Rate ratio of serious cardiac events, TIO vs PL	Rate ratio 0.84 (0.73, 0.98)	p < 0.05
Oba et al.[26] (updated meta-analysis)	Proportion of major cardiovascular events, ACH vs PL/AC	Relative risk 1.07 (0.95, 1.21)	p = NS
Reanalysis of data from Singh et al.[15] and Oba et al.[26]	Proportion of major cardiovascular events, ACH vs PL	Relative risk 1.05 (0.92, 1.18)	p = NS
Rodrigo et al.[34] (updated meta-analysis)	Proportion of major cardiovascular events, TIO vs PL	Risk ratio 0.91 (0.77, 1.07)	p = NS
	Proportion of cardiovascular deaths, TIO vs PL	Risk ratio 0.84 (0.64, 1.10)	p = NS
	Proportion of nonfatal myocardial infarction, TIO vs PL	Risk ratio 0.82 (0.62, 1.08)	p = NS
Updated pooled TIO safety analysis[35,36]	Rate ratio of total mortality, TIO vs PL	Rate ratio 0.88 (0.77, 0.999)	p < 0.05

AC = active control; **ACH** = anticholinergics; **IPR** = ipratropium bromide; **NS** = not significant; **PL** = placebo; **TIO** = tiotropium bromide; **UPLIFT** = Understanding Potential Long-term Impacts on Function with Tiotropium.

In a *post hoc* analysis of the Lung Health Study data reported in a letter to the editor by investigators from Boehringer Ingelheim, the incidence of cardiovascular outcomes were evaluated according to compliance with inhaler use, in order to assess plausibility of a true association.[37] There was a statistically significant trend between the risk for supraventricular tachycardia and the degree of compliance with inhaler use, which is understandable based on the pharmacology of anticholinergic agents.[37] In contrast, for overall cardiovascular morbidity and mortality there was no evidence of an association with these outcomes in the most compliant patients. In fact, a significant increase in risk for cardiovascular death was seen only in those subjects who reported no ipratropium bromide inhaler use at all, indicating that there may have been another confounding difference between study groups.[37]

2.2.2 Pooled Safety Analysis of Tiotropium Bromide, 2006

The long-acting tiotropium bromide was introduced in 2002 for once-daily administration, and a pooled safety analysis of 19 short-term, randomized, placebo-controlled trials was published in 2006.[27] In the pooled analysis there were statistically significant reductions in the rate of pneumonia and serious COPD exacerbations, and a nonsignificant trend towards reduced cardiovascular, respiratory and total mortality for tiotropium bromide compared with placebo.[27] When the rate of individual cardiovascular outcomes was evaluated, there was no significant effect of tiotropium bromide on any serious cardiac event or cardiovascular death.[27] Of note is that 24% of participants receiving placebo discontinued treatment prior to the end of the study compared with 16% of those receiving tiotropium bromide ($p < 0.0001$), indicating longer cumulative exposure to tiotropium bromide.

2.2.3 Meta-Analysis of Inhaled Anticholinergics, 2008

In 2008, Singh et al.[15] published a meta-analysis on the risk for major adverse cardiovascular events associated with the inhaled anticholinergic agents ipratropium bromide and tiotropium bromide, compared with placebo or active comparator controls. The pooled analysis of 17 trials evaluated proportions of patients in each group with events and did not measure annual rates per person-years, which could control for longer

exposure time with anticholinergics. Active comparator groups included salmeterol, salmeterol plus fluticasone propionate, and salbutamol (albuterol). The results found an increased risk for the composite outcome of myocardial infarction, stroke or cardiovascular death for anticholinergics compared with the control group (relative risk 1.58 [95% CI 1.21, 2.06; see table I]).[15] These major cardiovascular events occurred in 1.8% of the tiotropium bromide group and 1.2% of the placebo group, indicating an absolute increase in risk of 0.6% over the course of the mean trial duration. In subgroup analysis, a significant increase in risk was seen for myocardial infarction and cardiovascular death, but not for stroke or all-cause mortality. Of note, over 50% of the weight of the analysis came from the Lung Health Study.[18,37]

Singh et al.[15] chose to perform one analysis to compare anticholinergics with placebo, as well as with active comparators such as β-adrenoceptor agonists and corticosteroids. This may have introduced bias into the results concerning anticholinergics, as there is some evidence that β-adrenoceptor agonists could increase adverse cardiovascular events and that inhaled corticosteroids could decrease events.[5,6,12-14] However, if the pooled data were reanalyzed using only placebo-controlled trials, there would still be a statistically significant increase in cardiovascular events for anticholinergics compared with placebo (relative risk 1.63 [95% CI 1.2, 2.23]), with 70% of the weight coming from the Lung Health Study.

The conclusion from this meta-analysis was that inhaled anticholinergics increased the risk for adverse cardiovascular events. It is also possible that inhaled anticholinergics have no significant effect on cardiovascular events, but instead, the reduced withdrawal rate in the anticholinergic groups over time could result in significantly longer exposure times, allowing for a greater proportion of cardiovascular events to occur with this treatment. This hypothesis is supported by subgroup analysis of the pooled data from Singh et al.,[15] which showed a signifsicant increase in the risk for major cardiovascular events in long-term, but not short-term, trials. This could also explain why no increase in cardiovascular risk was seen in the aforementioned (section 2.2.2) pooled safety analysis of tiotropium bromide, which measured rates per person-years of exposure.[27] In addition, it is also possible that premature discontinuation of patients in the placebo groups could be associated with adverse events occurring immediately after discontinuation, as was seen in one of the trials included in the analysis.[38]

2.2.4 Long-Term Trial of Tiotropium Bromide, 2008

Since the publication of the meta-analysis by Singh et al.,[15] the results of the 4-year UPLIFT trial have been released.[17] In this trial, which was sponsored and conducted by Boehringer Ingelheim, approximately 6000 participants with moderate to very severe COPD were followed, with 64% of those receiving tiotropium bromide finishing the trial compared with 55% of those in the placebo group ($p < 0.001$).[17] Of note is that this was a long-term trial of patients with relatively severe COPD compared with those studied in previous trials. The UPLIFT trial reported deaths in 16% of participants compared with only 2% in the meta-analysis by Singh et al.[15,17] The UPLIFT investigators evaluated the annualized rate of events while patients were receiving the study drug, including the last day of study drug plus 30 days, and tiotropium bromide was shown to reduce COPD exacerbations by 15%, respiratory failure by 35% and total mortality by 15%.[17]

The incidence of cardiovascular events was not a primary outcome in the UPLIFT trial. However, serious adverse events were evaluated, and it was found that tiotropium bromide significantly reduced the rate of serious cardiac events by 15% (see table I), including a 30% reduction in myocardial infarction and a 40% reduction in congestive heart failure.[17] No increase in stroke rate was seen (relative risk 0.95 [95% CI 0.7, 1.29]). In a subsequent report on the trial, it was noted that tiotropium bromide did not have a significant effect on cardiovascular mortality or death from stroke or myocardial infarction.[39] As was noted in a letter to the editor of the *New England Journal of Medicine* by Singh et al.,[40] the UPLIFT trial classified deaths from sudden

death, unknown causes and stroke to be deaths from general disorders and not cardiovascular causes. In the author's response, Dr Tashkin of the UPLIFT investigators reported that inclusion of these nonspecific events in the category of cardiovascular causes still results in a significant reduction in major cardiovascular events for tiotropium bromide compared with placebo (relative risk 0.81 [95% CI 0.68, 0.97]).[40]

2.2.5 Updated Meta-Analyses of Inhaled Anticholinergics, 2008 and 2009

Since the publication of the UPLIFT trial, there have been two more meta-analyses evaluating the risk for cardiovascular events associated with inhaled anticholinergics[26] and specifically tiotropium bromide.[34] In 2008, Oba and colleagues[26] updated the meta-analysis of Singh et al.[15] in order to evaluate the cardiovascular safety of inhaled anticholinergics after the inclusion of new trial data. As with Singh et al., Oba et al. evaluated the proportion of participants with major cardiovascular events, defined as myocardial infarction, stroke or cardiovascular death. In this analysis, inhaled anticholinergics had no significant effect on major cardiovascular events compared with placebo or active comparator controls (see table I).[26] Of note, the UPLIFT trial provided 80% of the weight of the analysis and the Lung Health Study provided another 10%.

As with the previous meta-analysis by Singh et al., Oba and colleagues[26] pooled data on placebo and active comparator controls. If the analyses were performed only with placebo-controlled data, the results would be similar, with no significant effect on cardiovascular outcomes (see figure 1 and table I). The UPLIFT trial now provides 85% of the weight of the analysis.

More recently, in 2009, Rodrigo et al.[34] performed a subsequent meta-analysis evaluating the risk of fatal and nonfatal cardiovascular events associated with tiotropium bromide, separately evaluating placebo and active comparator controls. Pooled data from 13 placebo-controlled trials showed that tiotropium bromide had no significant effect on the proportion of patients with major cardiovascular events, with a risk ratio of 0.91 (95% CI 0.77, 1.07). As with the meta-analysis of Oba et al.,[26] the pooled effect evaluated dichotomous outcomes and did not take into account longer durations of treatment in the anticholinergic group.

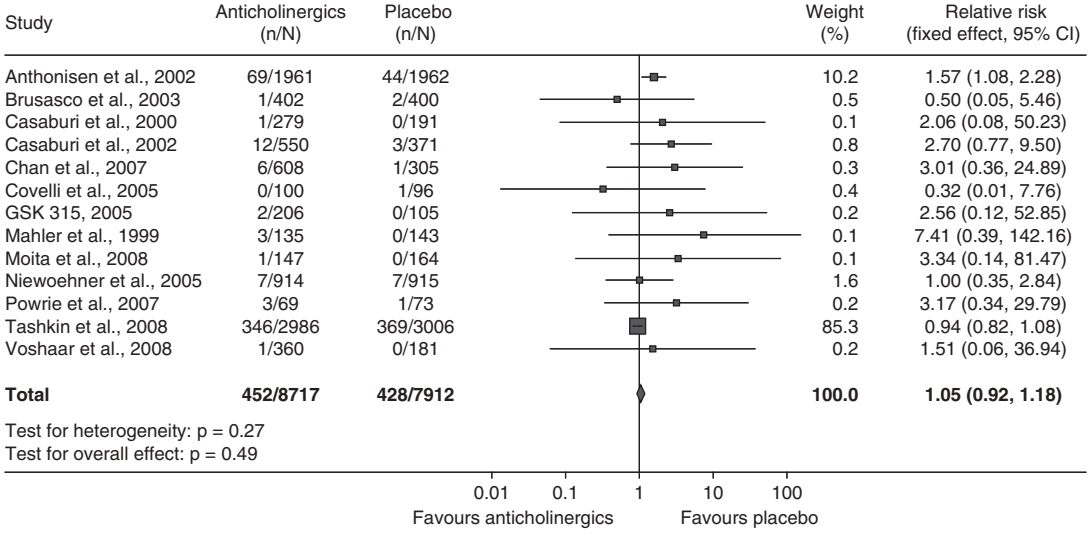

Fig. 1. Inhaled anticholinergics and the proportion of major cardiovascular events.[18,41-52] Relative risk of myocardial infarction, stroke or cardiovascular death for inhaled anticholinergics compared with placebo. Reanalysis of data from Singh et al.[15] and Oba et al.[26]

In a *post hoc* subgroup analysis of the pooled data, there were no statistically significant differences in results according to duration of treatment, allocation concealment, concomitant use of inhaled corticosteroids or smoking history.[34] Individual components of the composite cardiovascular outcome were evaluated separately, and tiotropium bromide did not significantly increase the risk for myocardial infarction, stroke, cardiovascular mortality or total mortality, compared with placebo or active comparator controls.[34] In a sensitivity analysis there was no significant difference in results when the large UPLIFT trial was excluded from the meta-analysis.

2.2.6 Updated Pooled Safety Analysis of Tiotropium Bromide, 2009

The pooled clinical trial safety analysis of tiotropium bromide has recently been updated by Boehringer Ingelheim; it evaluated almost 20 000 patients with COPD in 30 trials, with 13 146 patient-years of tiotropium bromide and 11 095 patient-years of placebo use.[35,36] The preliminary results indicate that tiotropium bromide was associated with a small reduction in the rate of cardiovascular events and total mortality compared with placebo, with borderline statistical significance (see table I).[35,36] The reduction in cardiovascular events was in large part due to reduced cardiac events such as myocardial infarction and congestive heart failure, whereas tiotropium bromide had no effect on stroke risk.[35,36]

3. Conclusion

Pooled trial data show that inhaled anticholinergics significantly reduce COPD-related hospitalizations, respiratory failure and respiratory deaths, compared with placebo. The long-acting tiotropium bromide has greater efficacy compared with the short-acting ipratropium bromide and may prolong total survival over time. Most of the trial data available to date are on tiotropium bromide, so most of our conclusions can be made about that agent. Because trials consistently report a substantial reduction in adverse events with tiotropium bromide, patients in the tiotropium bromide group have lower discontinuation rates than those in the placebo group, and therefore provide greater accumulated time in the analysis.

COPD patients have a high risk of cardiovascular events, probably because of shared cardiovascular risk factors and underlying systemic inflammation. In patients with COPD, hospitalizations and deaths are more often due to cardiovascular causes than respiratory events. A meta-analysis of randomized trials observed that a higher proportion of participants receiving inhaled anticholinergics had major cardiovascular events compared with those receiving placebo, but this differential is eliminated when the large UPLIFT trial is included in the meta-analysis or when evaluating the rate of events per total person-years of exposure. In fact, updated pooled trial data indicate that tiotropium bromide may actually reduce the incidence rates of major cardiovascular events and total mortality over time.

In conclusion, there have been conflicting data concerning the cardiovascular risk associated with the inhaled anticholinergic agents ipratropium bromide and tiotropium bromide. Observational studies and some randomized trials have shown an increase in adverse cardiovascular events, whereas pooled data from all available trials show no significant effect on the proportion of patients with adverse cardiovascular events and a trend towards reduced incidence of events over time. Anticholinergic agents may increase adverse cardiac events as a result of an increase in heart rate. However, it is also possible that the reduction in respiratory morbidity seen with tiotropium bromide could improve functional status and reduce the stress on the myocardium from hypoxaemia, thus reducing adverse cardiac events over time. Further studies are needed to address this important issue.

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