ABSTRACT

Anticholinergic drugs, a mainstay of treatment for chronic obstructive pulmonary disease, are generally considered to be very safe. There have been some new signals, however, of possible cardiovascular mortality with long-term use. Studies of these risks have yielded conflicting findings and warrant further assessment. Abrupt discontinuation of therapy could have serious clinical consequences. Much of the existing literature does not show an adverse impact on mortality and survival with anticholinergic treatment, and some studies support survival benefits. Some studies have demonstrated increased rates of pneumonia with combination therapy that includes inhaled corticosteroids, but these need to be weighed against the benefits of improved lung function and fewer exacerbations.

Increasingly, clinicians are prescribing combination therapy, and the medical literature supports this approach. This article summarizes key findings from selected studies.


Bronchodilator medications are central to symptom management in chronic obstructive pulmonary disease (COPD), and inhaled therapy is preferred. Inhaled anticholinergics are widely prescribed for COPD and include the short-acting muscarinic antagonists ipratropium and oxitropium, and the long-acting muscarinic antagonist (LAMA) tiotropium bromide. Due to their primarily localized effects, anticholinergic drugs are reported by the Global Initiative for Lung Disease (GOLD) to be “very safe,” with primarily nuisance side effects. However, reports of an unexpected small increase in cardiovascular events in patients with COPD who are regularly treated with ipratropium bromide prompted the GOLD committee to recommend additional study of these risks.

Initially, such concerns appeared to be unwarranted with the use of inhaled tiotropium bromide, as a pooled analysis of placebo-controlled trials of this treatment supported its safety profile. Conflicting results, however, were reported in another pooled analysis of 29 placebo-controlled clinical studies of approximately 13 500 patients with COPD. This study reported a small excess risk of stroke with tiotropium bromide over placebo (8 per 1000 vs 6 per 1000, respectively) following 1 year of treatment. These findings prompted the US Food and Drug Administration (FDA) to request further evaluation of this risk using other data sources.

In response to the FDA’s request for additional data surrounding the tiotropium cardiac safety profile, Boehringer Ingelheim pooled data from 30 trials, including 4-year safety results from the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial. Collectively, these trials represented 13 000 patient-years of drug expo-
Across studies, the analysis demonstrated:
(1) no increased risk of all-cause mortality (relative risk [RR] = 0.88; 95% confidence interval [CI], 0.77–0.99); (2) no increased risk of cardiac mortality (RR = 0.77; 95% CI, 0.55–1.03); (3) no increased risk of stroke (RR = 1.03; 95% CI, 0.79–1.35); and (4) no increased risk of myocardial infarction (MI; RR = 0.78; 95% CI, 0.59–1.02). A newly published report of 4-year UPLIFT data reveals that 67 patients in the tiotropium group experienced MI compared to 85 in the placebo group (RR = 0.73; 95% CI, 0.53–1) and stroke developed in 82 in the tiotropium group and 80 in the placebo group (RR = 0.95; 95% CI, 0.7–1.29).

Contrary findings are reported in a meta-analysis of the cardiovascular safety profile of inhaled anticholinergics by Singh et al. The meta-analysis of 17 trials that included 7472 patients with COPD who received inhaled anticholinergics reported that inhaled anticholinergics significantly increased the risk of cardiovascular death, MI, or stroke (1.8% vs 1.2% for control; RR = 1.58; 95% CI, 1.21–2.06; P < .001). The Table shows the number of events for each outcome. The increase in the risk of cardiovascular death, MI, or stroke occurred primarily in the long-term trials (>6 months) according to a sensitivity analysis of these 5 studies involving 7267 patients. This meta-analysis, however, might be criticized for including studies that had active control arms with combination inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) that may have reduced morbidity compared to tiotropium (see below).

Within the framework of these conflicting findings, clinicians should carefully weigh potential risks against demonstrated efficacy. Anticholinergics represent the basic platform for the treatment of COPD, and abrupt discontinuation of therapy could have serious clinical consequences. Additional analyses will likely elucidate whether or not cardiovascular risks exist, and whether they are significant enough to warrant treatment cessation.

**All-Cause Mortality and Survival**

Many people suffer from COPD for years and die prematurely. Increased mortality is associated with many symptoms of COPD, including acute exacerbations, reduced health status, and increased airway hyper-responsiveness. Treatments that impact favorably on symptoms and underlying disease mechanisms may increase survival.

A secondary outcome measure in the meta-analysis by Singh et al referenced earlier was all-cause mortality. The study found that inhaled anticholinergics did not significantly increase the risk of all-cause mortality (2% vs 1.6% for control; RR = 1.26; 95% CI, 0.99–1.61; P = .06). Other clinical trials have shown that ICSs may actually reduce mortality in patients with COPD. A study by Gershon et al suggests that tiotropium may in fact prolong survival. This longitudinal, population-based cohort study enrolled 7218 patients with COPD. Of these, 1046 (14.5%) died in the follow-up period. Patients who received tiotropium were 20% less likely to die than those receiving a LABA (hazard ratio = 0.80 [95% CI, 0.7–0.93]). A head-to-head study of salmeterol/fluticasone propionate and tiotropium given to 1323 patients with severe and very severe COPD demonstrated significantly fewer deaths in salmeterol/fluticasone propionate-treated patients as compared to those receiving tiotropium (21 [3%] vs 38 [6%], respectively [P = .032]). Outcomes for the study’s primary end point, healthcare utilization exacerbation rate, did not demonstrate a significant difference between the 2 treatments. Notably, salmeterol/fluticasone propionate reduced the rate of exacerbations requiring oral corticosteroids; conversely, tiotropium reduced those requiring antibiotics. Pneumonia was reported more frequently among patients receiving salmeterol/fluticasone propionate (P = .008).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCTs, n</th>
<th>Inhaled Anticholinergic</th>
<th>Controls</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>12</td>
<td>57/6156</td>
<td>31/6220</td>
<td>1.8 (1.17–2.77)</td>
<td>.008</td>
</tr>
<tr>
<td>MI</td>
<td>11</td>
<td>68/5430</td>
<td>43/5168</td>
<td>1.53 (1.05–2.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>25/4548</td>
<td>18/4703</td>
<td>1.46 (0.81–2.62)</td>
<td>.2</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>17</td>
<td>149/7472</td>
<td>115/7311</td>
<td>1.26 (0.99–1.61)</td>
<td>.06</td>
</tr>
</tbody>
</table>

CI = confidence interval; MI = myocardial infarction; RCT = randomized-controlled trial. Adapted with permission from Singh et al. JAMA. 2008;300:1439-1450.
In a post-hoc analysis of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study, researchers followed up deaths in all randomized patients, including withdrawn patients. Date and cause of death were established, and patients who withdrew from the trial were found to have a higher death rate from most causes compared with those who remained in the trial. Additionally, patients randomized to fluticasone propionate appeared to survive longer than those randomized to placebo ($P = .069$). However, because patients received other medication for their COPD after withdrawal from the study, a causal relationship to treatment cannot be confirmed.

The TORCH (Towards a Revolution in COPD Health) study was powered based on the results of ISOLDE and assumed there would be a death rate of 17% on placebo over 3 years and a 12.7% death rate on salmeterol/fluticasone. The primary end point of the TORCH trial was the effect of salmeterol/fluticasone propionate 50/500-µg combination versus placebo on all-cause mortality over 3 years in over 6000 patients with moderate-to-severe COPD. Patients who withdrew prematurely from the study were also followed up with regular contact for 3 years from the date of randomization in order to determine survival status. A lower probability of death was seen for the combination therapy group, compared with the other groups, although the rate did not quite reach statistical significance after adjustments were made for interim analyses. Specifically, the hazard ratio for death for the combination therapy group compared with placebo was 0.825 ($P = .052$). The mortality rates for salmeterol alone and fluticasone alone did not differ significantly from that for placebo. Treatment was associated with increased rates of pneumonia.

**Lung Function**

The annual rate in decline of forced expiratory volume in 1 second (FEV$_1$) has been used as a surrogate marker for the natural progression of COPD. Although smoking cessation improves this rate of decline,$^{17}$ historically airway medications have not been shown to significantly reduce the loss of lung function in patients with COPD.$^{6,18-22}$ These results suggest that decline in FEV$_1$ is not the best outcome for COPD, and future studies should be powered on mortality or composite outcomes, such as BODE (a composite for body-mass index, airflow obstruction, dyspnea, and exercise capacity).$^{23}$

Several recent reports, however, do suggest a modest benefit in FEV$_1$ in tiotropium-treated patients. A post-hoc analysis of data from 921 ambulatory patients with COPD participating in 2, 1-year, double-blind, tiotropium versus placebo-controlled trials revealed a mean decline in trough FEV$_1$ (ie, FEV$_1$ 23–24 hours after prior use of medication) of 59 mL/year in the placebo group and 19 mL/year in the tiotropium group ($P = .036$ vs placebo) between days 50 and 344. A second meta-analysis of 9 trials of 8002 patients reported a decline in FEV$_1$ of 30 mL or lower in tiotropium-treated patients. Four-year results from the UPLIFT trial, however, failed to show any significant differences in the rate of decline in the mean FEV$_1$ before and after bronchodilation.$^{4}$ In this trial, however, both the tiotropium and the placebo group who continued on study treatment had lower rates of decline of FEV$_1$ than had been observed in previous trials (38–40 mL/year).

**Combination Therapy**

Celli et al$^{26}$ investigated the effects of combined salmeterol plus fluticasone propionate, either component alone or placebo, on the rate of postbronchodilator FEV$_1$ decline in patients with moderate or severe COPD. The adjusted rate of decline in FEV$_1$ was 55 mL/year for placebo, 42 mL/year for salmeterol, 42 mL/year for fluticasone propionate, and 39 mL/year for salmeterol plus fluticasone propionate. Salmeterol/ fluticasone propionate reduced the rate of FEV$_1$ decline by 16 mL/year compared with placebo (95% CI, 7–25; $P < .001$). The difference was smaller for fluticasone propionate and salmeterol compared with placebo (13 mL/year; 95% CI, 5–22; $P = .003$; Figure 1).$^{26}$

Many physicians adopt a triple-therapy approach to COPD treatment, consisting of ICS, LABA, and LAMA therapy. The Canadian Optimal Therapy of COPD Trial$^{27,28}$ evaluated the efficacy and safety of salmeterol plus fluticasone plus tiotropium over 1 year in 449 patients with moderate-to-severe COPD. The 2 comparator groups were patients receiving salmeterol plus fluticasone and patients receiving tiotropium. For the primary end point, the percentage of patients experiencing at least 1 exacerbation that required treatment with systemic steroids or antibiotics, there was no significant difference between the triple combination therapy group and the other 2 groups. However, addition of salmeterol/fluticasone to tiotropium thera-
py did improve lung function \((P = .049)\) and quality of life \((P = .01)\).

A recent meta-analysis provides a broader perspective on the benefits and risks of adjunctive ICSs across 9 studies. Addition of an ICS to a LABA was associated with a reduced risk for exacerbations (rate ratio, 0.82; 95% CI, 0.72–0.92), but an increased risk for pneumonia and oral candidiasis (RR = 1.68; 95% CI, 1.28–2.21 and RR = 2.93; 95% CI, 1.94–4.42, respectively). Mortality was not affected (rate ratio, 0.86; 95% CI, 0.73–1.02). Another recent systemic review and meta-analysis of 11 randomized-controlled trials (14 426 participants) of ICSs in patients with stable COPD concluded that ICS therapy does not affect 1-year all-cause mortality. ICS therapy was associated with a higher risk of pneumonia (RR = 1.34; 95% CI, 1.03–1.75; \(P = .03\)). Subgroup analysis indicated an increased risk of pneumonia in the following: highest ICS dose; shorter duration of ICS use, lowest baseline FEV1; and combined ICS and bronchodilator therapy.

A recent study reported by Tashkin et al evaluated the efficacy and tolerability of budesonide/formoterol administered via 1 hydrofluoroalkane pressurized metered-dose inhaler (pMDI) in patients with COPD. This 6-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study of 1704 patients randomized patients to one of the following treatment groups: budesonide/formoterol pMDI 160/4.5 µg times 2 inhalations (320/9 µg); budesonide/formoterol pMDI 80/4.5 µg times 2 inhalations (160/9 µg); budesonide pMDI 160 µg times 2 inhalations (320 µg) plus formoterol dry powder inhaler (DPI) 4.5 µg times 2 inhalations (9 µg); budesonide pMDI 160 µg times 2 inhalations (320 µg); formoterol DPI 4.5 µg times 2 inhalations (9 µg); or placebo. The study’s primary outcomes were pre- and postdose FEV1. Budesonide/formoterol 320/9 µg demonstrated significantly greater improvements in predose FEV1 versus formoterol (\(P = .026\)) and 1-hour postdose FEV1 compared to budesonide (\(P < .001\)). Budesonide/formoterol 160/9 µg demonstrated significantly greater improvements versus budesonide (\(P < .001\)) for 1-hour postdose FEV1 but not versus formoterol for predose FEV1. Dyspnea and health-related quality-of-life scores were significantly improved with both dosage strengths of budesonide/formoterol compared with budesonide, formoterol, and placebo (\(P \leq .044\) for all). In contrast to previous studies of ICSs in COPD, this study did not produce a signal for increased pneumonia risks with treatment.

Although some physicians have adopted the LABA plus ICS combination as the preferred treatment program, results from a recent study may prompt some to reconsider that regimen. A 6-week, multicenter, randomized, double-blind, parallel-group study was conducted in 592 patients with COPD to compare tiotropium plus formoterol to salmeterol plus fluticasone. After 6 weeks, the 12-hour lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone (Figure 2). Peak responses favored tiotropium plus formoterol (difference in peak FEV1, 103 mL [\(P < .0001\)]; difference in peak forced vital capacity [FVC], 214 mL [\(P < .0001\)]), as were FEV1 and FVC at each individual time point after dose (\(P < .05\)). Predose FVC was significantly higher with the bronchodilator combination, but predose FEV1 was not.
CONCLUSIONS

With all of the conflicting data, what is the practitioner to do? Usually a well-designed prospective study such as UPLIFT is more persuasive than a meta-analysis performed on studies not initially powered to address different outcomes. Thus, in my opinion anticholinergics can be used safely in COPD. Nonetheless, because safety issues have been raised, additional data must be obtained and physicians must be vigilant and carefully monitor the use of long-acting antimuscarinic bronchodilators. ICSs seem to be associated with more frequent pneumonia events, but these must be taken in the context of reduced exacerbations, better lung function, and improved quality of life.

DISCUSSION

Dr Wise: The Singh et al meta-analysis of the cardiovascular safety profile of inhaled anticholinergics appears to be a study in the available population, though the results are dominated by the results of the Lung Health Study where the conclusion of the investigators was that ipratropium did not likely cause increased mortality because the excess deaths were in patients who were not using the drug. The other study that influenced the results was the INSPIRE (New Standards for Prophylaxis in Reduction of Exacerbations) study which compared tiotropium to ICS/LABA, which is suggested to lower mortality, including cardiovascular events. The UPLIFT trial, a very large, high-quality, 4-year trial, showed opposite findings. Are the exclusion criteria more rigorous in UPLIFT in order to avoid a signal of poor cardiovascular outcomes?

Dr Donohue: UPLIFT encouraged all comers; there were very few restrictions. Because they were looking for a mortality signal, they enrolled many very severe patients. So I do not think there was any enrollment bias.

Dr Rand: One possible explanation is that in studies in which adherence was more rigorously monitored patients may actually have received higher exposure to the drug compared to community-based studies. Perhaps different levels of drug exposure were a contributing factor to study outcomes.

Dr Donohue: Another important consideration is the number of patients who drop out of the control group and enter the treatment group. This is another factor that may contribute to the obvious discrepancies between the randomized-controlled trials and UPLIFT. It raises questions about compliance, and actual drug exposure. I think the bottom line is that physicians should just exercise some caution and wait to see what the emergent literature tells us about what the data, in totality, demonstrate.

Dr Rand: Data from the recent meta-analysis by Sobieraj et al shows an extremely modest survival benefit for drug therapies. Yet, the current smoker rate for people treated with drugs was high. What we know unequivocally is the benefit of smoking cessation in this population. If you were to compare the cost of proposed treatments versus the cost of aggressive cessation support that includes maintenance nicotine replacement, what would come out on top? Is the meta-analysis suggestive of an Alice in Wonderland proposition, in which our focus is totally misdirected? The target for intervention is clearly the behavior that is causing the risk.

Dr Donohue: Absolutely. Particularly with the study outcome of all-cause mortality, if you are continuing to smoke, treatment effects are minimal.

Dr Rand: From a therapeutic perspective, not a mortality perspective, should one actually be progressing with a treatment that you know will be less effective than intensive smoking cessation?

Dr Donohue: That is an extremely important point. Monotherapy with an inhaled steroid, for
example, has a very modest effect. For people who continued to smoke, there was nearly no benefit.

**Dr Rand:** I would also argue that drug interventions are much more costly than some other interventions that would address the original cause of the problem.

**REFERENCES**


