

Inhaled Anticholinergics and the Long-Term Treatment of Chronic Obstructive Pulmonary Disease: Weighing Benefits and Risks

D. KYLE HOGARTH, MD, FCCP

Assistant Professor of Medicine
Director, Alpha One Antitrypsin Deficiency Clinical
Resource Center, Pulmonary Rehabilitation, and
Advanced Bronchoscopy Unit
University of Chicago
Chicago, Illinois

TERRY A. JACOBSON, MD, FACP, FAHA

Professor, Department of Medicine
Director, Office of Health Promotion and
Disease Prevention
Emory University School of Medicine
Atlanta, Georgia

A meta-analysis recently published in the *Journal of the American Medical Association* found an increased risk of nonfatal myocardial infarction, stroke, and cardiovascular death associated with inhaled anticholinergic use in patients with chronic obstructive pulmonary disease (COPD); however, inherent limitations in the meta-analysis and contradictory results from other studies cast uncertainty onto its conclusions. For example, the Understanding Potential Long-term Impacts on Function with Tiotropium trial, a large, prospective, 4-year outcome study in nearly 6000 patients with COPD, did not demonstrate an increase in cardiovascular events with anticholinergic therapy. Until more data are available, clinicians should always carefully weigh safety and efficacy data and help patients make informed decisions about their COPD care. (*Clinical Cornerstone*. 2009; 9[4]:45–49) © 2009 Elsevier. All rights reserved.

Treatment with bronchodilators, including anticholinergics, is an effective and essential component of chronic obstructive pulmonary disease (COPD) management.¹ Bronchodilators improve emptying of the lungs and exercise tolerance, and have a propensity for reducing dynamic hyperinflation both at rest and during exercise.¹ Because of their efficacy and convenience, inhaled anticholinergics are the most widely prescribed agents for COPD^{1,2} and they have been found to reduce the rate of exacerbations and improve the effectiveness of pulmonary rehabilitation.¹ Even in patients with moderate to severe COPD, meaningful increases in lung function can be achieved following administration of inhaled anticholinergic therapy, with a duration of up to 24 hours with tiotropium bromide.¹

The safety of inhaled anticholinergics in the management of COPD has been a focus for study, particularly when used over a long period of time. Most recently, a meta-analysis by Singh et al² published in the *Journal of the American Medical Association (JAMA)*, found an increased risk of nonfatal myocardial infarction (MI),

stroke, and cardiovascular death associated with inhaled anticholinergic use in patients with COPD. While the data from this analysis merit consideration, inherent weaknesses in the study's design and contradictory results from other studies cast uncertainty onto its conclusions.^{3,4} This underscores the need to gather prospective safety data for widely used therapies that provide needed relief to millions of patients. Large, prospective, randomized trials specifically designed to assess the cardiovascular risk of anticholinergic therapy in individuals with COPD are needed to decisively ascertain cardiovascular risk with anticholinergic therapy. One such study, the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial, included cardiovascular safety as an end point.³

Anticholinergics and Cardiovascular Risk: Weighing the Data

Consensus has never been established concerning the long-term safety of anticholinergic therapy. In a cohort study by Sin and Tu⁴ in 2000, no association was found between ipratropium use and all-cause mortality (relative

KEY POINT

Large, prospective, randomized trials specifically designed to assess the cardiovascular risk of anticholinergic therapy in individuals with COPD are needed to decisively ascertain cardiovascular risk.

risk [RR], 1.03; 95% CI, 0.98–1.08), whereas in a longitudinal cohort survey conducted by Ringbaek and Vislum⁵ in 2003, an increased risk for all-cause mortality was found with ipratropium use (RR, 1.6; 95% CI, 1.2–2.1). More recently, a nested case-control study performed by Lee et al⁶ examined the association between various respiratory medications (including ipratropium) and risk for death in 32,130 veterans with newly diagnosed COPD. In this study, ipratropium was associated with increased cardiovascular death (odds ratio, 1.34; 95% CI, 1.22–1.47), with consistent results being found across sensitivity analyses. Importantly, this study did not measure current smoking status and lung function—2 other important predictors of cardiovascular risk and mortality.⁶ All of these studies raise valid questions, but they also remind us of the limits of drawing conclusions from nonprospective, randomized data.

The latest controversy stems from the findings of a meta-analysis that were recently published in *JAMA*. This analysis, undertaken by Singh et al² to ascertain the cardiovascular risks of inhaled anticholinergics, including nonfatal MI, stroke, and cardiovascular death in patients with COPD, began with a systematic search for randomized controlled trials of any inhaled anticholinergic involving more than 30 days of follow-up. Other criteria for inclusion in the meta-analysis included a confirmed diagnosis of COPD of any severity in study participants; an inhaled anticholinergic as the intervention drug versus a control (a placebo or an active control, such as inhaled β -agonists or inhaled steroid/ β -agonist combinations); and reported data on the incidence of serious cardiovascular events, including MI, stroke, and cardiovascular death. Trials that recruited patients with asthma were excluded from the analysis.² Notably, patients with existing cardiovascular disease were not excluded.

The primary outcome was a composite of nonfatal MI,

nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). The secondary outcome was all-cause mortality.² After a rigorous screening of 103 trials encompassing 703 citations, 17 trials involving 14,783 patients were found that met the inclusion criteria.² The characteristics of the long-term trials included in the analysis can be seen in **Table I**.

In this meta-analysis, inhaled anticholinergics significantly increased the risk of MI, stroke, or cardiovascular death (1.8% vs 1.2% for control; RR, 1.58; 95% CI, 1.21–2.06; $P < 0.001$).² The results of the meta-analysis on individual end points of cardiovascular death, MI, stroke, and all-cause mortality can be seen in **Table II**.² Interestingly, statistically, there was no significant increase in the risk of all-cause mortality with inhaled anticholinergics (2.0% vs 1.6% for control; RR, 1.26; 95% CI, 0.99–1.61; $P = 0.06$).²

This meta-analysis was not without limitations. None of the trials studied were prospectively designed to specifically assess cardiovascular events, and consequently, these events were not adjudicated or defined in a similar fashion across the spectrum of trials; therefore, the reporting of such events may have been incomplete.² Also, cardiovascular end points were ascertained via routine adverse-event reporting within the individual trials.² Additionally, the majority of the trials studied were small and of short duration, which resulted in few events, and these small numbers cast uncertainty onto the exact magnitude of the observed risk.² Furthermore, the lack of available source data did not permit for more potent time-to-event analysis or assessment of dose-responsiveness, nor did it allow for stratified analysis based on factors such as forced expiratory volume in 1 second (which has been acknowledged as an independent predictor of cardiovascular death in COPD), current smoking, hypertension, diabetes, hypercholesterolemia, coronary artery disease, or the concomitant use of cardioprotective agents, such as statins, aspirin, and angiotensin-converting enzyme inhibitors.²

“Pooled analyses can provide early information about potential safety issues,” notes the US Food and Drug Administration (FDA). “However, these analyses have inherent limitations and uncertainty that require further investigation using other data sources.”⁷ Accordingly, the study authors acknowledge the need for adequately powered prospective trials with adjudication of cardiovascular events to assess the cardiovascular safety of inhaled anticholinergics in patients with COPD.²

TABLE I. CHARACTERISTICS OF LONG-TERM (>6 MONTHS–5 YEARS) RANDOMIZED CONTROLLED TRIALS OF INHALED ANTICHOLINERGICS INCLUDED IN THE ANALYSIS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS.

Source	Location and Duration	Primary Outcome	No. of Participants (% Male)	Age, Mean (SD), y	% Predicted FEV ₁ , Mean (SD)	Current Smokers, %*
Anthonisen et al, 2002 Inhaled ipratropium (2 puffs 3×/d) Placebo	10 centers; 280 wk	FEV ₁ , respiratory and cardiovascular morbidity	1961 (60.8)	48.4 (6.8)	74.8 (9.5)	40.4 pack-years
			1962 (64.0)	48.6 (6.8)	75.1 (9.5)	40.4 pack-years
Casaburi et al, 2002 Tiotropium, 18 µg Placebo	50 centers; 52 wk	FEV ₁	550 (66.5)	65 (9)	39.1 (13.7)	63 pack-years
			371 (62.8)	65 (9)	38.1 (14.1)	59 pack-years
Wedzicha et al, 2008 [†] Tiotropium, 18 µg Salmeterol, 50 µg 2×/d and fluticasone propionate, 500 g 2×/d	20 countries; 104 wk	Health care use, exacerbation	665 (84)	65 (NA)	39.4 (NA)	38
			658 (81)	64 (NA)	39.1 (NA)	38
Powrie et al, 2007 Tiotropium, 18 µg Placebo	Single United Kingdom center; 52 wk	Sputum inflammatory markers	69 (69.6)	66.3 (8.1)	50.9 (14.8)	59.4
			73 (56.2)	66.4 (9.8)	49.2 (15.6)	57.5
Chan et al, 2007 Tiotropium, 18 µg Placebo	Multicenter; 48 wk	FEV ₁	608 (59)	66.8 (8.7)	39.4 (13.4)	32
			350 (61)	66.9 (9.1)	39.4 (13.6)	30

FEV₁ = forced expiratory volume in 1 second; NA = not available.

*Unless otherwise indicated.

[†]Less than 2% of the study population had electrocardiogram abnormalities.

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

Less than 1 month after the publication of the Singh et al² meta-analysis, Tashkin et al³ published the results from the UPLIFT study, a large, prospective, 4-year, placebo-controlled clinical trial in nearly 6000 patients with COPD. In this study, tiotropium was associated with improvements in lung function, quality of life, and

COPD exacerbations throughout the 4-year study period.³ Importantly, there was no increased risk of adverse cardiovascular events with tiotropium in this study (3.56% vs 4.21% for tiotropium vs placebo; RR, 0.84; 95% CI, 0.73–0.98), which was a predefined secondary end point (**Table III**).³

TABLE II. RESULTS OF META-ANALYSIS ON INDIVIDUAL END POINTS OF CARDIOVASCULAR DEATH, MYOCARDIAL INFARCTION (MI), STROKE, AND ALL-CAUSE MORTALITY WITH INHALED ANTICHOLINERGICS.

Outcome	No. of RCTs	Patients Using Inhaled Anticholinergic (No./Total No.)	Controls (No./Total No.)	Relative Risk (95% CI)	P
Cardiovascular death	12	57/6156	31/6220	1.80 (1.17–2.77)	0.008
MI	11	68/5430	43/5168	1.53 (1.05–2.23)	0.03
Stroke	7	25/4548	18/4703	1.46 (0.81–2.62)	0.20
All-cause mortality	17	149/7472	115/7311	1.26 (0.99–1.61)	0.06

RCTs = randomized controlled trials.

Adapted from Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: A systematic review and analysis. *JAMA*. 2008;300:1439–1450.

TABLE III. INCIDENCE RATE OF SERIOUS ADVERSE EVENTS PER 100 PATIENT-YEARS IN THE UPLIFT TRIAL.*

Adverse Event	Tiotropium (N = 2986)	Placebo (N = 3006)	Relative Risk for Tiotropium vs Placebo (95% CI)
Cardiac arrest	3.56	4.21	0.84 (0.73–0.98) [†]
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96) [†]
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99) [†]
Lower respiratory	11.32	13.47	0.84 (0.77–0.92) [†]
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94) [†]
Dyspnea	0.38	0.62	0.61 (0.40–0.94) [†]
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92) [†]

UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; COPD = chronic obstructive pulmonary disease.

*Listed are serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

[†] $P < 0.05$.

From Tashkin DP, Celli B, Senn S, et al, for the UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.

The FDA is currently reviewing the complete data from the UPLIFT trial. It is expected that the full data from this trial will help address some of the safety issues raised about tiotropium in recent months by Singh et al.² In the meantime, until more data emerge, clinicians should continue to closely monitor their patients on anticholinergic therapy for the development of cardiovascular events.

“Certainly, patients with COPD who are taking long-term anticholinergics should be closely monitored for the development of the signs and symptoms of cardiovascular disease. However, this is best practice for almost all patients with COPD, since they are already at elevated risk for cardiovascular morbidity and mortality.”

—Terry A. Jacobson, MD, FACP, FAHA
Professor, Department of Medicine
Emory University, Atlanta, Georgia

Clinician Recommendations

Bronchodilators remain the most effective pharmacologic agents for the management of COPD. While the data revealed in some recent studies concerning potential safety concerns with anticholinergics merit consideration, contradictory results from other studies draw attention to the need for more conclusive analyses. Clinicians are advised to use prudence when making treatment decisions for their patients, taking care to weigh the risk:benefit ratio of effective therapies against each patient’s individual cardiovascular risk profile. Moreover, it is important that these patients be diligently treated for present cardiovascular risk factors, such as hypertension and dyslipidemia. For pulmonologists and other clinicians who do not routinely assess and treat cardiovascular risk, close collaboration with a patient’s primary care provider and/or cardiologist may be required.

Clinicians should always:

- **Discuss the potential risks and benefits of anticholinergic therapy with their patients and carefully as-**

sess the risk:benefit ratio of available therapies when making prescribing decisions. This is in keeping with best practice.

- **Be vigilant when prescribing anticholinergics for the long-term management of COPD, particularly in patients with established or unstable cardiovascular disease** or in those who are at elevated risk for cardiovascular events. While there is no indisputable evidence linking anticholinergics with cardiovascular risk, best practice again calls for due diligence.

—Routinely evaluate all patients with COPD for increased cardiovascular risk, including:

- Smoking
- Hypertension
- Premature family history of coronary heart disease
- Metabolic syndrome
- Hyperlipidemia
 - Increased low-density lipoprotein cholesterol
 - Increased triglycerides
 - Decreased high-density lipoprotein (HDL) cholesterol
 - Increased non-HDL cholesterol
- Diabetes
- Peripheral artery disease
- Coronary artery disease
- Valvular heart disease
- **Closely monitor patients receiving anticholinergic therapy** for the development of complications, including cardiovascular disease, and adverse effects, such as dry mouth, glaucoma, urinary retention, and constipation.

KEY POINT

Weigh risks and benefits of therapy, inform patients of risks and benefits of therapy, and be sure cardiovascular risk is properly managed.

Note: Terry A. Jacobson, MD, FACP, FAHA, is a founder and member of the Board of Trustees for the Cardiovascular & Metabolic Health Foundation. D. Kyle Hogarth, MD, FCCP, is a member of the Respiratory & Allergic Disease Foundation's Steering Committee.

Resources

The FDA is currently reviewing complete trial data from the UPLIFT study and is expected to issue its conclusions concerning the safety of anticholinergics in the coming months. To stay current on FDA decisions concerning emerging safety data for anticholinergics or to obtain updated guidelines for the treatment of COPD, please visit the following sites:

- <http://www.fda.gov/cder/drug>
- <http://www.goldcopd.org>

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Address correspondence to: D. Kyle Hogarth, MD, FCCP, Assistant Professor of Medicine, University of Chicago, 5841 South Maryland, MC 6076, Chicago, IL 60637. E-mail: dhogarth@uchicago.edu

Terry A. Jacobson, MD, FACP, FAHA, Professor, Department of Medicine, Emory University School of Medicine, Atlanta, GA 30303. E-mail: tjaco02@emory.edu