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Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease

A Systematic Review and Meta-analysis

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CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease worldwide.^{1,2} Inhaled anticholinergics include the short-acting muscarinic agonist ipratropium bromide, and the M1 and M3 selective long-acting muscarinic agonist tiotropium bromide. Inhaled tiotropium is the most widely prescribed agent for COPD.³ More than 8 million patients worldwide have used inhaled tiotropium since its approval in 2002,³ with net sales of €1792 million (approximately US \$2.4 billion) in 2007.³

According to the recent COPD Global Initiative for Lung Disease guidelines, inhaled tiotropium is indicated for the long-term, once daily maintenance treatment of bronchospasm associated with COPD.¹ The quaternary ammonium structure of inhaled anticholinergic agents limits their systemic bioavailability, and the only commonly recognized adverse effects include the development of anticholinergic effects, such as dry mouth and urinary retention.¹

Cardiovascular disease is an important cause of morbidity and mortality in COPD. According to the recent COPD

Context Inhaled anticholinergics (ipratropium bromide or tiotropium bromide) are widely used in patients with chronic obstructive pulmonary disease (COPD) but their effect on the risk of cardiovascular outcomes is unknown.

Objective To ascertain the cardiovascular risks of inhaled anticholinergics, including cardiovascular death, myocardial infarction (MI), and stroke.

Data Sources Systematic searches were conducted on March 19, 2008, of relevant articles in MEDLINE, the Cochrane Database of systematic reviews, regulatory authority Web sites in the United States and the United Kingdom, and manufacturers' trial registries with no date restrictions.

Study Selection Randomized controlled trials of any inhaled anticholinergic for treatment of COPD that had at least 30 days of treatment and reported on cardiovascular events.

Data Extraction The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. Relative risks (RRs) were estimated using fixed-effects models and statistical heterogeneity was estimated with the I^2 statistic.

Data Synthesis After a detailed screening of 103 articles, 17 trials enrolling 14 783 patients were analyzed. Follow-up duration ranged from 6 weeks to 5 years. Cardiovascular death, MI, or stroke occurred in 135 of 7472 patients (1.8%) receiving inhaled anticholinergics and 86 of 7311 patients (1.2%) receiving control therapy (RR, 1.58 [95% confidence interval {CI}, 1.21-2.06]; $P < .001$, $I^2 = 0\%$). Among individual components of the primary end point, inhaled anticholinergics significantly increased the risk of MI (RR, 1.53 [95% CI 1.05-2.23]; $P = .03$, $I^2 = 0\%$) and cardiovascular death (RR, 1.80 [95% CI, 1.17-2.77]; $P = .008$, $I^2 = 0\%$) without a statistically significant increase in the risk of stroke (RR, 1.46 [95% CI, 0.81-2.62]; $P = .20$, $I^2 = 0\%$). All-cause mortality was reported in 149 of the patients treated with inhaled anticholinergics (2.0%) and 115 of the control patients (1.6%) (RR, 1.26 [95% CI, 0.99-1.61]; $P = .06$, $I^2 = 2\%$). A sensitivity analysis restricted to 5 long-term trials (> 6 months) confirmed the significantly increased risk of cardiovascular death, MI, or stroke (2.9% of patients treated with anticholinergics vs 1.8% of the control patients; RR, 1.73 [95% CI, 1.27-2.36]; $P < .001$, $I^2 = 0\%$).

Conclusion Inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

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Global Initiative for Lung Disease guidelines: "an unexpected small increase in cardiovascular adverse events

was noted with inhaled ipratropium bromide which deserves further investigation."^{1,4} A pooled analysis of 19 short-

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 and questions on p 1472.

term placebo-controlled trials revealed no significant increase in the risk of cardiovascular adverse events with inhaled tiotropium bromide in 2006.⁵ However, in an early communication in 2008, the US Food and Drug Administration reported that patients in the inhaled tiotropium group experienced a “possible increased risk of stroke” based on a pooled analysis of 29 trials involving 13 500 patients with COPD.⁶ The risk of stroke was 8/1000 per year in the tiotropium group compared with 6/1000 per year in the placebo group.

It is important to establish the complete cardiovascular safety profile of inhaled anticholinergics in patients with COPD due to the widespread use of these agents. Our primary objective was to systematically ascertain the cardiovascular risks (myocardial infarction [MI], stroke, and cardiovascular death) associated with the long-term use of inhaled anticholinergics (ipratropium bromide and tiotropium bromide) compared with control therapies in patients with COPD in randomized controlled trials (RCTs).

METHODS

Eligibility Criteria

Our specific inclusion criteria for trials were (1) study design consisting of an RCT for any inhaled anticholinergic (ipratropium bromide or tiotropium bromide) with more than 30 days of follow-up; (2) study participants with a diagnosis of COPD of any severity; (3) an inhaled anticholinergic as the intervention drug vs a control, which could be placebo or active control (eg, inhaled β -agonists or inhaled steroid β -agonist combinations); and (4) the trial had to report data on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death. All RCTs that recruited patients with asthma were excluded.

Search Strategy

On March 19, 2008, 2 reviewers (S.S. and Y.K.L.) independently and in duplicate searched MEDLINE through PubMed with the clinical trial filter using the search terms *ipratropium and tiotropium* and *chronic and obstructive* with no date

restrictions. In addition, trials were retrieved from the Cochrane Database of systematic reviews, Web sites of the US Food and Drug Administration and European regulatory authorities, clinical trials.gov, and manufacturers' product information sheets. Trial reports also were evaluated of all published or unpublished trials with inhaled ipratropium bromide and tiotropium bromide in the clinical trials register of the manufacturers.⁷ We searched the included and excluded trials' lists from systematic reviews and meta-analysis of inhaled anticholinergics in COPD,^{5,8-12} checked for relevant data on adverse events within these systematic reviews, searched the bibliographies of included studies, and used the Web of Science Citation Index to identify relevant cited and citing articles. Our search was limited to English-language articles and included unpublished studies.

Study Selection

Two reviewers (S.S. and Y.K.L.) independently and in duplicate scanned all titles and abstracts that indicated whether a study was an RCT evaluating inhaled anticholinergics in patients with COPD. After obtaining full reports of potentially relevant trials, the same reviewers independently assessed eligibility from full-text articles. Disagreements regarding eligibility were resolved with a third reviewer (C.D.F.) through consensus.

Study Characteristics

A standard protocol was used to record the following properties of each study: the dose and frequency of the inhaled anticholinergic and control interventions, location and duration of the study (in weeks), primary outcome, mean age and sex of participants, percentage of current smokers enrolled, severity of COPD in the participants as mean predicted forced expiratory volume in the first second of expiration (FEV₁), and proportion of participants with preexisting cardiac disease or cardiovascular risk factors if available.

Validity Assessment

Two reviewers (S.S. and Y.K.L.) independently and in duplicate assessed each in-

cluded study for the reporting of allocation concealment, the use of blinding, loss to follow-up, and withdrawal rates. To determine the strength of adverse event monitoring, the frequency and type of adverse event monitoring during the follow-up period were evaluated based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* on assessing adverse effects.¹³

Outcome Measures

The primary outcome measure was prespecified as a composite of nonfatal MI, nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). These major adverse cardiovascular events represent serious ischemic events and are a widely used end point in cardiovascular outcome trials.¹⁴ Because none of the trials were prospectively designed to assess the cardiovascular risk of inhaled anticholinergics in patients with COPD, cardiovascular end points may not have been prospectively defined in a uniform fashion across the trials but were ascertained through routine serious adverse event reporting within each trial. The risk of all-cause mortality also was determined in the included trials as a secondary outcome.

Data Extraction

Two reviewers (S.S. and Y.K.L.) independently and separately extracted data (including 0 events) on MI, stroke, cardiovascular death, and all-cause mortality among trial listings of serious adverse events; a third reviewer (C.D.F.) adjudicated in the event of discrepancies. Data in the clinical trials register and the regulatory documents were reconciled with that of the published journal article when possible. If there were multiple reports for a particular study, data from the most recent version were extracted. When specific aspects of the data required clarification, the authors of the original articles were contacted.

Quantitative Data Synthesis and Sensitivity Analysis

Review Manager (RevMan) version 5.04 (Nordic Cochrane Center, Copenha-

gen, Denmark) was used to calculate relative risk (RR) and 95% confidence intervals (CIs) for the primary composite outcome (cardiovascular death, MI, and stroke), the individual end points of the composite, as well as all-cause mortality. All reported *P* values are 2-sided with significance set at less than .05. Statistical heterogeneity was assessed using the I^2 statistic.¹⁵ I^2 values of 50% or more indicate a substantial level of heterogeneity. We planned to pool data across studies using the fixed-effects models if substantial statistical heterogeneity was not present.

A predefined sensitivity analysis was performed to explore the influence on the effect size for statistical models (fixed and random effects), trial duration, and completeness in reporting of individual end points of the primary outcome, and the influence of the individual studies. The fail-safe number, using the Rosenberg method,¹⁶ was calculated to evaluate the potential impact of unpublished studies on the meta-analysis. The fail-safe number indicates the number of nonsignificant unpublished studies that would need to be added to a meta-analysis to reverse an overall statistically significant result to nonsignificance.¹⁶

The number needed to harm (NNH) (and 95% CI) with inhaled anticholinergics was calculated by applying the RR estimates to the cardiovascular event rate in a large population-based study using Visual Rx, version 2.0.¹⁷ The NNH varies when inhaled anticholinergics are used in a general population outside highly selected trial participants.¹⁸ The NNH is the number of patients with COPD who need to be treated with inhaled anticholinergics rather than with placebo or comparators for 1 additional patient to be harmed by a cardiovascular adverse event.

RESULTS

Of the 703 potentially relevant citations identified, 17 trials fulfilled the inclusion criteria after a detailed review of 103 studies.^{4,19-34} The flow of the trial is shown in FIGURE 1. Trial characteristics are shown in TABLE 1.

The trials included 14 783 participants, in which 7472 received inhaled anticholinergics and 7311 received control therapy. Twelve trials evaluated inhaled tiotropium vs control therapy,¹⁹⁻³⁰ and 5 trials evaluated inhaled ipratropium vs control therapy.^{4,31-34} Nine trials evaluated inhaled anticholinergics vs placebo.^{4,19,21-23,26,27,29,30} The remaining trials used active comparators, including inhaled salmeterol,^{24,25,32-34} a combination inhaler containing salmeterol and fluticasone,^{20,28} or inhaled albuterol.³¹ There were 5 long-term trials ranging from 48 weeks to 5 years,^{4,19-22} and 12 short-term trials ranging from 6 weeks to 26 weeks.²³⁻³⁴ The mean predicted FEV₁ of participants was less than 50% for all trials, except 1 trial⁴ in which the mean predicted FEV₁ was 75%.

The quality assessment of included trials is shown in TABLE 2. Trial quality was variable. All trials were double-blinded. Allocation concealment was adequate in 4 RCTs,^{4,20,23,27} and unclear in the remaining 13 RCTs.^{19,21,22,24-26,28-34} Information on withdrawal rates was available for all RCTs except 1 trial,²⁸ and ranged from 6.1%²³ to as high as 42%.²⁰ Reporting of loss to follow-up was variable and only available for 6 RCTs^{4,20,27,29,31,34} and ranged from 0%³⁴ to 3.4%.²⁹

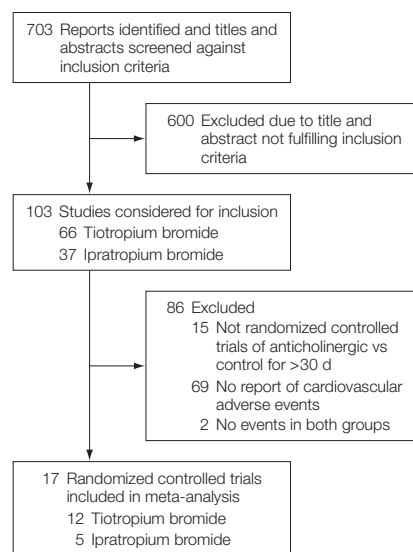
Data on MI, stroke, cardiovascular death, the major adverse cardiovascular event composite, and all-cause mortality are shown in TABLE 3.

Primary Outcome

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) in a meta-analysis of 17 trials involving 14 783 patients (FIGURE 2).^{4,19-34} There was no evidence of statistical heterogeneity among the included trials ($I^2=0\%$).

Among individual components of the primary outcome, inhaled anticholinergics significantly increased the risk of MI (1.2% vs 0.8% for control; RR, 1.53 [95% CI, 1.05-2.23]; *P* = .03) in a meta-analysis of 11 trials involving 10 598 pa-

Figure 1. Study Selection



tients.^{4,19-22,24,26,28,31-33} Inhaled anticholinergics also significantly increased the risk of cardiovascular death (0.9% vs 0.5% for control; RR, 1.80 [95% CI, 1.17-2.77]; *P* = .008) in a meta-analysis of 12 trials involving 12 376 patients.* Inhaled anticholinergics did not significantly increase the risk of stroke (0.5% vs 0.4% for control; RR, 1.46 [95% CI, 0.81-2.62]; *P* = .20) in a meta-analysis of 7 trials involving 9251 patients.^{4,19,20,24,32-34} There was no evidence of statistical heterogeneity among the included trials for any of these end points ($I^2=0\%$ for MI, cardiovascular death, and stroke) (TABLE 4).

Secondary Outcome

Inhaled anticholinergics did not significantly increase the risk of all-cause mortality (2.0% vs 1.6% for control; RR, 1.26 [95% CI, 0.99-1.61]; *P* = .06) in a meta-analysis of 17 trials involving 14 783 patients.^{4,19-34} There was evidence of low statistical heterogeneity among the included trials ($I^2=2\%$) (Table 4).

Sensitivity Analysis

The random-effects analysis of the primary composite outcome of cardiovascular death, MI, and stroke from the 17

*References 4, 19-21, 23-25, 27, 29-31, 33.

Table 1. Characteristics of 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, % ^a
Long-Term (>6 mo-5 y)						
Anthonisen et al, ⁴ 2002 Inhaled ipratropium (2 puffs 3 times/d)	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
Placebo			1962 (64.0)	48.6 (6.8)	75.1 (9.5)	40.4 pack-years
Casaburi et al, ¹⁹ 2002 Tiotropium, 18 µg	50 centers; 52 wk	FEV ₁	550 (66.5)	65 (9)	39.1 (13.7)	63 pack-years
Placebo			371 (62.8)	65 (9)	38.1 (14.1)	59 pack-years
Wedzicha et al, ²⁰ 2008 ^b Tiotropium, 18 µg	20 countries; 104 wk	Health care use, exacerbation	665 (84)	65 (NA)	39.4 (NA)	38
Salmeterol, 50 µg twice daily and fluticasone propionate, 500 µg twice daily			658 (81)	64 (NA)	39.1 (NA)	38
Powrie et al, ²¹ 2007 Tiotropium, 18 µg	Single UK center; 52 wk	Sputum inflammatory markers	69 (69.6)	66.3 (8.1)	50.9 (14.8)	59.4
Placebo			73 (56.2)	66.4 (9.8)	49.2 (15.6)	57.5
Chan et al, ²² 2007 Tiotropium, 18 µg	Multicenter; 48 wk	FEV ₁	608 (59)	66.8 (8.7)	39.4 (13.4)	32
Placebo			350 (61)	66.9 (9.1)	39.4 (13.6)	30
Short-Term (6 wk-6 mo)						
Casaburi et al, ²³ 2000 Tiotropium, 18 µg	25 centers; 13 wk	FEV ₁	279 (66.6)	65.0 (8.6)	39 (13.8)	65 pack-years
Placebo			191 (63.4)	65.5 (9.0)	38 (14.1)	61 pack-years
Brusasco et al, ²⁴ 2003 ^c Tiotropium, 18 µg	18 countries; 24 wk	Exacerbations, health use, dyspnea	402 (77.4)	63.8 (8.0)	39.2 (11.6)	44 pack-years
Salmeterol, 50 µg twice daily			405 (75.1)	64.1 (8.5)	37.7 (11.7)	44 pack-years
Placebo			400 (76.3)	64.6 (8.6)	38.7 (12.1)	42 pack-years
Donohue et al, ²⁵ 2002 Tiotropium, 18 µg	Multicenter; 26 wk	FEV ₁ , transition dyspnea index, and health-related quality of life	209 (74)	64.5 (7.9)	43.6 (9.8)	47 pack-years
Salmeterol, 50 µg twice daily			213 (75)	64.6 (8.1)	42.0 (9.5)	48 pack-years
Placebo			201 (75)	65.6 (7.8)	41.3 (8.7)	46 pack-years
Covelli et al, ²⁶ 2005 ^d Tiotropium, 18 µg	12 centers; 12 wk	Electrocardiogram	100 (66)	65.8 (8.9)	40.2 (13)	40
Placebo			96 (49)	63.3 (9.2)	38.6 (13.8)	36.5
Niewoehner et al, ²⁷ 2005 ^e Tiotropium, 18 µg	26 VA centers; 26 wk	COPD exacerbations	914 (98)	67.6 (8.7)	35.6 (12.6)	29
Placebo			915 (99)	68.1 (8.5)	35.6 (12.6)	30
Bateman et al, ²⁸ 2008 Tiotropium, 18 µg	12 SA centers; 6 wk	FEV ₁	56 (67.9)	62.4 (8.0)	45.9 (12.6)	57.1
Salmeterol, 50 µg twice daily and fluticasone, 250 µg twice daily			51 (74.5)	62.5 (8.3)	48.8 (12.3)	45.1
Moita et al, ²⁹ 2008 Tiotropium, 18 µg ^f	31 Portuguese centers; 12 wk	FEV ₁	147 (95.8)	65.7 (8.6)	38.4 (12.8)	27.7
Placebo ^g			164 (94.3)	65.7 (9.0)	42.3 (15.3)	25
Voshaar et al, ³⁰ 2008 Tiotropium, 5 µg	Multinational; 12 wk	FEV ₁	180 (69)	64 (9)	40 (12)	37
Tiotropium, 10 µg			180 (72)	64 (9)	39 (12)	37
Ipratropium, 36 µg			178 (67)	65 (8)	41 (13)	40
Placebo			181 (69)	63 (9)	42 (12)	43
Combivent Inhalation Aerosol Study Group, ³¹ 1994 Ipratropium (21 µg) and albuterol (120 µg) 2 puffs 4 times/d	24 centers; 12 wk	FEV ₁	182 (63.7)	63.4 (NA)	37.4 (NA)	NA
Albuterol, 120 µg 4 times/d			173 (64.7)	63.6 (NA)	36.8 (NA)	NA
Ipratropium, 21 µg 4 times/d			179 (67.0)	63.3 (NA)	36.6 (NA)	NA

(continued)

Table 1. Characteristics of Randomized Controlled Trials of Inhaled Anticholinergics Included in the Analysis of Major Adverse Cardiovascular Events (cont)

Source	Location and Duration	Primary Outcome	No. of Participants (% Male)	Age, Mean (SD), y	% Predicted FEV ₁ , Mean (SD)	Current Smokers, % ^a	
Short-Term (6 wk-6 mo)							
GlaxoSmithKline study SMS40315, ³² 2005 Ipratropium, 36 µg 4 times/d and salmeterol, 42 µg twice daily	56 centers; 8 wk	FEV ₁	213 (60.6)	64.3 (9.9)	41.5 (12.5)	39	
			Salmeterol, 42 µg twice daily	211 (63)	63.1 (9.2)	42.0 (13.2)	42
			Ipratropium, 36 µg 4 times/d	206 (56.7)	63.8 (8.4)	42.5 (13.3)	42
			Placebo	105 (64.7)	64.4 (10.2)	43.8 (12.8)	51
GlaxoSmithKline study SMS40314, ³³ 2005 Ipratropium, 36 µg 4 times/d and salmeterol, 42 µg twice daily	55 centers; 8 wk	FEV ₁	213 (61.9)	65.5 (8.8)	41.5 (11.6)	41	
			Salmeterol, 42 µg twice daily	205 (56.1)	64.2 (9.6)	42.4 (11.8)	35
			Ipratropium, 36 µg 4 times/d	205 (58.5)	64.5 (9.6)	42.1 (13.8)	37
			Placebo	108 (69.4)	64.8 (10.1)	42.1 (13.5)	32
Mahler et al, ³⁴ 1999 Ipratropium, 36 µg 4 times/d	30 centers; 12 wk	FEV ₁	133 (72.9)	64.0 (NA)	37.0 (NA)	68.3 pack-years	
			Salmeterol, 42 µg twice daily	135 (71.9)	63.2 (NA)	42.1 (NA)	60.2 pack-years
			Placebo	143 (76.2)	63.2 (NA)	40.8 (NA)	60.2 pack-years

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second of expiration; NA, data not available; SA, South Africa; VA, Veterans Affairs; UK, United Kingdom.

^aUnless otherwise indicated.

^bLess than 2% of the study population had electrocardiogram abnormalities.

^cExcluded patients who had heart failure within 3 years, myocardial infarction within 1 year, or arrhythmia.

^dThe study population included patients with hypertension (43%), diabetes mellitus (10%), and hyperlipidemia (16%). Excluded patients who had myocardial infarction within 6 months, or arrhythmias or heart failure within 1 year.

^eThirty-eight percent of the patients assigned to tiotropium had cardiac risk factors compared with 39% of the patients assigned to placebo.

^fFor smokers, the mean (SD) age was 61.6 (9.8) years and the mean (SD) FEV₁ was 44.4 (13.9).

^gFor smokers, the mean (SD) age was 64.0 (7.2) years and the mean (SD) FEV₁ was 40.4 (14.5).

trials^{4,19-34} yielded effect sizes (RR, 1.57 [95% CI, 1.19-2.06]; $P=.001$) similar in magnitude and direction to those obtained from the fixed-effects analysis.

Inhaled anticholinergics significantly increased the risk of cardiovascular death, MI, and stroke in a sensitivity analysis limited to the 5 long-term trials (>6 months) involving 7267 patients (2.9% vs 1.8% for control; RR, 1.73 [95% CI, 1.27-2.36]; $P<.001$) (FIGURE 3).^{4,19-22} There was no evidence of statistical heterogeneity among the trials ($I^2=0\%$).^{4,19-22} The significantly increased risk of cardiovascular death, MI, and stroke was demonstrated even when we separately analyzed inhaled tiotropium vs control therapy (RR, 2.12 [95% CI, 1.22-3.67]; $P=.008$),¹⁹⁻²² and inhaled ipratropium vs control therapy (RR, 1.57 [95% CI, 1.08-2.28]; $P=.02$)⁴ in the long-term trials. Although, there was no statistically significant increase in the risk of cardiovascular death, MI, and stroke in a sensitivity analysis of the 12 short-term trials (<26 weeks) involving 7516 patients (0.6% for anticholinergics vs 0.6% for con-

trol; RR, 1.16 [95% CI, 0.67-2.01]; $P=.60$), the direction of the drug effect was similar to that of the long-term trials (FIGURE 4).²³⁻³⁴ There was no evidence of statistical heterogeneity among the trials ($I^2=0\%$).

After excluding 5 trials for which data on some individual end points of the composite were unavailable,^{22,23,25,27,31} the sensitivity analysis limited to 12 trials, which provided complete reporting on individual end points of the primary composite outcome of cardiovascular death, MI, and stroke,[†] yielded effect sizes (RR, 1.63 [95% CI, 1.22-2.16]; $P<.001$) similar in magnitude and direction to those obtained from 17 trials.

After excluding the trial that contributed to more than 50% of the weight in the fixed-effects model (and the largest sample size and longest duration of follow-up),⁴ the sensitivity analysis limited to the remaining 16 trials on the primary composite outcome of cardiovascular death, MI, and stroke¹⁹⁻³⁴ yielded effect sizes (RR, 1.58 [95% CI,

1.08-2.33]; $P=.02$) similar in magnitude and direction to those obtained from the 17 trials. There was no evidence of statistical heterogeneity among the trials ($I^2=0\%$).

Fail-Safe Number

According to Rosenberg method, 16 non-significant long-term trials of inhaled anticholinergics each with a sample size of approximately 1450 participants (the mean sample size of the 5 long-term trials) would be required to reverse the significantly increased risk of cardiovascular death, MI, and stroke seen with long-term inhaled anticholinergic use in the 5 long-term trials.^{4,19-22}

Estimated NNH With Inhaled Anticholinergics for MI and Cardiovascular Death

Assuming a baseline MI event rate of 10.9/1000 person-years in adult patients with COPD from a population-based observational study (nearly 54% male and 75% >65 years),³⁵ the NNH for MI with inhaled anticholinergics is estimated to be approximately 174 per

[†]References 4, 19-21, 24, 26, 28-30, 32-34.

year (95% CI, 75-1835 per year). Assuming a baseline cardiovascular mortality event rate of 31.9/1000 person-years in adult patients with COPD from a population-based observational study,³⁵ the NNH for cardiovascular death with inhaled anticholinergics is

estimated to be approximately 40 per year (95% CI, 18-185 per year).

COMMENT

Inhaled anticholinergic use for more than 30 days significantly increases the risk of cardiovascular death, MI, or stroke in

patients with COPD by approximately 58%. This increase in the risk of cardiovascular death, MI, or stroke is particularly manifest in the long-term trials. However, in the short-term trials, inhaled anticholinergics do not significantly increase the risk of cardiovascu-

Table 2. Quality Assessment of Included Trials

Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
Anthonisen et al, ⁴ 2002 Ipratropium	Adequate	Cardiovascular deaths reviewed and participants followed up every 3 mo	23.1	0.03
Placebo			21.5	0.02
Casaburi et al, ¹⁹ 2002 Tiotropium	Unclear	Adverse events detected at regular intervals (first d, first wk, Q3 wk up to 13 wks; Q6 wks until study end)	18.7	NA
Placebo			27.8	NA
Wedzicha et al, ²⁰ 2008 Tiotropium	Adequate	Serious adverse events recorded up to 30 d poststudy	41.9	1.9
Salmeterol and fluticasone			35.2	2.2
Powrie et al, ²¹ 2007 Tiotropium	Unclear	Adverse event, vital signs, laboratory results, and examination recorded during the study at 4, 16, 32 and 52 wk and 30 d poststudy	30.4	NA
Placebo			28.8	NA
Chan et al, ²² 2007 Tiotropium	Unclear	Adverse events monitored throughout treatment period	22.2	NA
Placebo			27.5	NA
Casaburi et al, ²³ 2000 Tiotropium	Adequate	Adverse events recorded every 3 wk	6.1	NA
Placebo			11	NA
Brusasco et al, ²⁴ 2003 Tiotropium	Unclear	Adverse events tracked through baseline and 24 wk	15.4	NA
Salmeterol			18.8	NA
Placebo			25.7	NA
Donohue et al, ²⁵ 2002 Tiotropium	Unclear	Adverse events tracked through 24 wk	12	NA
Salmeterol			17	NA
Placebo			28	NA
Covelli et al, ²⁶ 2005 Tiotropium	Unclear	Electrocardiography and Holter performed at entry and 12 wk	10	NA
Placebo			17.7	NA
Niewoehner et al, ²⁷ 2005 Tiotropium	Adequate	Serious adverse events included if occurred within 30 d of study medication	16	0.07
Placebo			27	0.04
Bateman et al, ²⁸ 2008 Tiotropium	Unclear	Adverse events and vital signs, physical examination at each visit	NA	NA
Salmeterol and fluticasone			NA	NA
Moita et al, ²⁹ 2008 Tiotropium	Unclear	Adverse events and vital signs, physical examination at each visit	7.5	3.4
Placebo			6.7	2.4
Voshaar et al, ^{29,30} 2008 Tiotropium, 5 µg	Unclear	Adverse event, vital signs, 12-lead electrocardiographic routine laboratories, and physical examination	8.8	NA
Tiotropium, 10 µg			10	NA
Ipratropium			17.4	NA
Placebo			12.1	NA
Combivent Inhalation Aerosol Study Group, ³¹ 1994 Ipratropium and albuterol	Unclear	Adverse events monitored every 2 wk	13.2	2.7
Albuterol			12.7	2.3
Ipratropium			14.5	3.4

(continued)

Table 2. Quality Assessment of Included Trials (cont)

Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
GlaxoSmithKline study SMS40315, ³² 2005 Salmeterol and ipratropium	Unclear	NA	12	NA
Salmeterol			16	NA
Ipratropium			17	NA
Placebo			16	NA
GlaxoSmithKline study SMS40314, ³³ 2005 Salmeterol and ipratropium	Unclear	NA	15	NA
Salmeterol			11	NA
Ipratropium			11	NA
Placebo			19	NA
Mahler et al, ³⁴ 1999 Ipratropium	Unclear	Adverse events and vital signs at 2 wk, laboratory examinations, and physical examination at beginning and end of treatment; electrocardiography at regular intervals	13.5	1.5
Salmeterol			6.6	0
Placebo			16	1.3

Abbreviation: NA, data not available.

lar death, MI, or stroke, although the direction of the effect is similar to that of the long-term trials. Inhaled anticholinergics also significantly increase the risk of the individual end points of MI and cardiovascular death without a statistically significant increase in the risk of stroke and all-cause mortality.

The significant increase in the risk of cardiovascular death, MI, or stroke, without a significant increase in all-cause mortality with inhaled anticholinergics, may have 2 possible explanations—lack of statistical power to detect differences in all-cause mortality or an off-setting reduction of respiratory mortality with inhaled anticholinergics. It is more likely that the trials were inadequately powered to detect differences in all-cause mortality because inhaled anticholinergics have not been shown to reduce respiratory-related mortality in a clinical trial. The increased risk of cardiovascular death, MI, or stroke with inhaled anticholinergics cannot be attributed to the protective effects of comparators because neither inhaled β -agonists nor inhaled steroid and β -agonist combination inhaler reduce cardiovascular outcomes in patients with COPD. On the contrary, there are concerns about an excess risk of cardiovascular adverse events with β -agonists in patients with obstructive lung disease.³⁶

Our findings need to be distinguished from other meta-analyses of short-term trials. We specifically evaluated the risk of cardiovascular death, MI, and stroke with both inhaled anticholinergic agents, restricted our analysis to patients with COPD, and incorporated unpublished data from several recently published long-term trials of inhaled tiotropium.¹⁹⁻²² A meta-analysis of several short-term placebo-controlled trials reported that inhaled tiotropium use had no significant effect on the risk of MI (RR, 0.72 [95% CI, 0.26-2.07]), cardiovascular mortality (RR, 0.57 [95% CI, 0.26-1.26]), respiratory mortality (RR, 0.71 [95% CI, 0.29-1.74]), and all-cause mortality (RR, 0.76 [95% CI, 0.5-1.16]).⁵ Other meta-analyses also have failed to discern any effect of inhaled anticholinergics on all-cause mortality.⁸⁻¹⁰

The increased risk of cardiovascular death, stroke, or MI associated with inhaled anticholinergic use seen in our meta-analysis should be interpreted in the context of the evidence from recent population-based studies.³⁷⁻⁴⁰ However, these database studies are susceptible to residual confounding, misclassification bias, and channeling bias. A nested case-control study among patients with COPD, using the Manitoba health database, reported an increased risk of hospitalization for MI (odds ra-

tio [OR], 1.42 [95% CI, 1.24-1.63]), heart failure (OR, 3.07 [95% CI, 2.82-3.34]), and stroke (OR, 1.18 [95% CI, 1.04-1.33]) among those who had used inhaled ipratropium bromide 60 days prior to the event compared with controls.³⁷ Another observational cohort study in the Veterans Affairs database reported that inhaled ipratropium exposure was associated with a nearly 34% significant increase in the risk of cardiovascular death (OR, 1.34 [95% CI, 1.22-1.47]) with an estimated annualized NNH at 261.³⁸ Another industry-funded cohort study using the Health Information Network database in the United Kingdom among a broad population of users reported a nonsignificant higher risk of MI with inhaled tiotropium (hazard ratio, 1.29 [95% CI, 0.45-3.66]), without any difference in the risk of overall mortality (hazard ratio, 0.93 [95% CI, 0.59-1.44]), compared with long-acting β -agonists.³⁹ Another industry-funded, population-based cohort study in Denmark among 10 603 predominantly elderly (75% >60 years) participants with COPD and a mean follow-up of 18 months, also reported a nonsignificant higher risk of hospitalization for MI with inhaled tiotropium users (RR, 1.25 [95% CI, 0.49-3.17]) with a significant reduction in overall mortality (RR, 0.77 [95% CI, 0.65-0.91]) compared with nonusers.⁴⁰

Table 3. Cardiovascular Events and All-Cause Mortality in Randomized Controlled Trials of Inhaled Anticholinergics

Study	Total No. of Participants	No. of Participants				
		MI	Stroke	Cardiovascular Death	All-Cause Mortality	Major Adverse Cardiovascular Event ^a
Long-Term (>6 mo-5 y)						
Anthonisen et al, ⁴ 2002						
Ipratropium	1961	44	12	18	54	69
Placebo	1962	31	9	7	44	44
Casaburi et al, ¹⁹ 2002 ^b						
Tiotropium	550	3	4	6	7	12
Placebo	371	1	1	1	7	3
Wedzicha et al, ²⁰ 2008 ^c						
Tiotropium	665	6	4	19	38	23
Salmeterol and fluticasone	658	3	3	9	21	13
Powrie et al, ²¹ 2007 ^c						
Tiotropium	69	3	0	1	1	3
Placebo	73	1	0	1	2	1
Chan et al, ²² 2007 ^c						
Tiotropium	608	6	NA	NA	17	6
Placebo	350	1	NA	NA	4	1
Short-Term (6 wk-6 mo)						
Casaburi et al, ²³ 2000						
Tiotropium	279	NA	NA	1	1	1
Placebo	191	NA	NA	0	0	0
Brusasco et al, ²⁴ 2003 ^b						
Tiotropium	402	1	1	1	1	3
Salmeterol	805	5	4	3	11	12
Donohue et al, ²⁵ 2002						
Tiotropium	209	NA	NA	0	0	0
Placebo or salmeterol	414	NA	NA	3	7	3
Covelli et al, ²⁶ 2005						
Tiotropium	100	0	0	0	0	0
Placebo	96	1	0	0	0	1
Niewoehner et al, ²⁷ 2005						
Tiotropium	914	NA	NA	7	22	7
Placebo	915	NA	NA	7	19	7
Bateman et al, ²⁸ 2008 ^c						
Tiotropium	56	1	0	0	0	1
Salmeterol and fluticasone	51	0	0	0	0	0
Moita et al, ²⁹ 2008 ^c						
Tiotropium	147	0	0	1	2	1
Placebo	164	0	0	0	0	0
Voshaar et al, ³⁰ 2008 ^{c,d}						
Tiotropium	360	0	0	1	2	1
Placebo	181	0	0	0	0	0
Combivent Inhalation Aerosol Study Group, ³¹ 1994						
Ipratropium	182	1	NA	1	2	1
Albuterol	173	0	NA	0	0	0
GlaxoSmithKline study SMS40315, ³² 2005 ^c						
Ipratropium	419	1	1	0	1	2
Placebo or salmeterol	316	0	0	0	0	0
GlaxoSmithKline study SMS40314, ³³ 2005 ^c						
Ipratropium	418	2	0	1	1	2
Placebo or salmeterol	313	0	1	0	0	1
Mahler et al, ³⁴ 1999 ^c						
Ipratropium	133	0	3	0	0	3
Salmeterol or placebo	278	0	0	0	0	0

Abbreviations: MI, myocardial infarction; NA, data not available.

^aIndicates cardiovascular death, nonfatal MI, or nonfatal stroke or transient ischemic attack.

^bCardiovascular adverse event data were extracted from the US Food and Drug Administration submission as unavailable in the published article.

^cCardiovascular adverse event data were extracted from the manufacturer's clinical trials register as unavailable in the published article.

^dAlso had ipratropium group with no cardiovascular adverse event data hence ipratropium group could not be included in analysis.

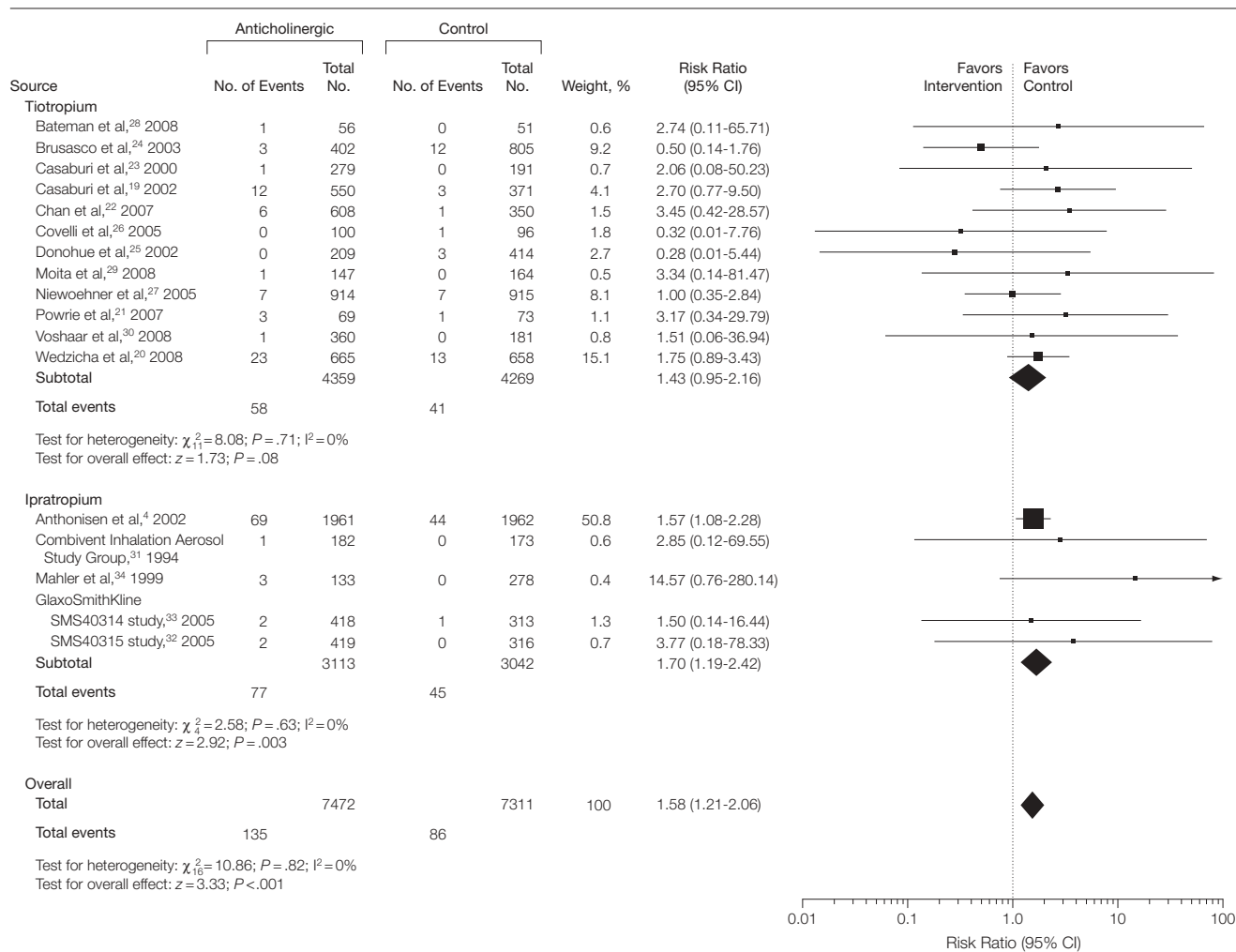
The precise biological mechanisms by which inhaled anticholinergics increase the risk of cardiovascular death, MI, or stroke among patients with COPD are uncertain. In the Lung Health Study,⁴ there was an increase in the incidence of supraventricular tachycardia with inhaled ipratropium consistent with the vagolytic nature of the drug. Chronic obstructive pulmonary disease is increasingly being recognized as a systemic inflammatory disease and inflammatory cytokines may potentially play a role in mediating the systemic cardiovascular effects of COPD.⁴¹ Inhaled tiotropium significantly increased the risk of sputum IL-8 ($P=.04$) compared

with placebo in a year-long placebo-controlled trial, without any significant difference in the levels of serum C-reactive protein and IL-6 levels.²¹ Serum IL-8 also may increase the risk of cardiovascular events by destabilizing existing atherosclerotic plaque.⁴² It needs to be investigated whether this increased risk of cardiovascular events is mediated via inflammatory cytokines.

Our study has limitations, which mainly stem from the quality of reported data. Many of these trials were small and short-term, resulting in few events. As a result of small numbers, the 95% CIs are wide, resulting in some un-

certainty as to the precise magnitude of the observed risk. None of these trials were specifically designed to monitor the risk of cardiovascular events, which were not adjudicated. The reporting of cardiovascular outcomes may have been incomplete. The lack of availability of source data did not allow the use of more statistically powerful time-to-event analysis or assessment of dose-responsiveness or stratified analysis based on FEV₁ (an independent predictor of cardiovascular death in COPD),⁴³ current smoking, hypertension, diabetes, hypercholesterolemia, coronary artery disease, and the concomitant use of cardioprotec-

Figure 2. Meta-analysis of Randomized Controlled Trials of Inhaled Anticholinergics vs Control for Major Adverse Cardiovascular Outcomes Composite



Cardiovascular outcomes composite indicates cardiovascular death, myocardial infarction, and stroke. Size of the data markers indicates weight of the study. CI indicates confidence interval.

tive agents (statins, angiotensin-converting enzyme inhibitors).⁴⁴ We did not have data to determine intraclass differences in the risk of cardiovascular events. A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest.

Prospective, adequately powered trials with adjudication of cardiovascular events are needed to assess the cardiovascular safety of inhaled anticholinergics in patients with COPD. These trials should provide evidence on the comparative effectiveness and safety of the currently available long-acting bronchodilators. A randomized, double-blind, placebo-controlled, 4-year trial involv-

ing more than 6000 patients with COPD, the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study, is evaluating the effect of tiotropium on the long-term decline in lung function and overall mortality in patients with COPD.⁴⁵ However, this trial has not been specifically designed to address cardiovascular adverse events, and may not provide information on nonfatal cardiovascular adverse events, as well as the cardiovascular adverse effects of inhaled ipratropium. Sixteen negative long-term trials with an average sample size of 1450 participants would be required to render non-significant the results from our meta-analysis of long-term trials.

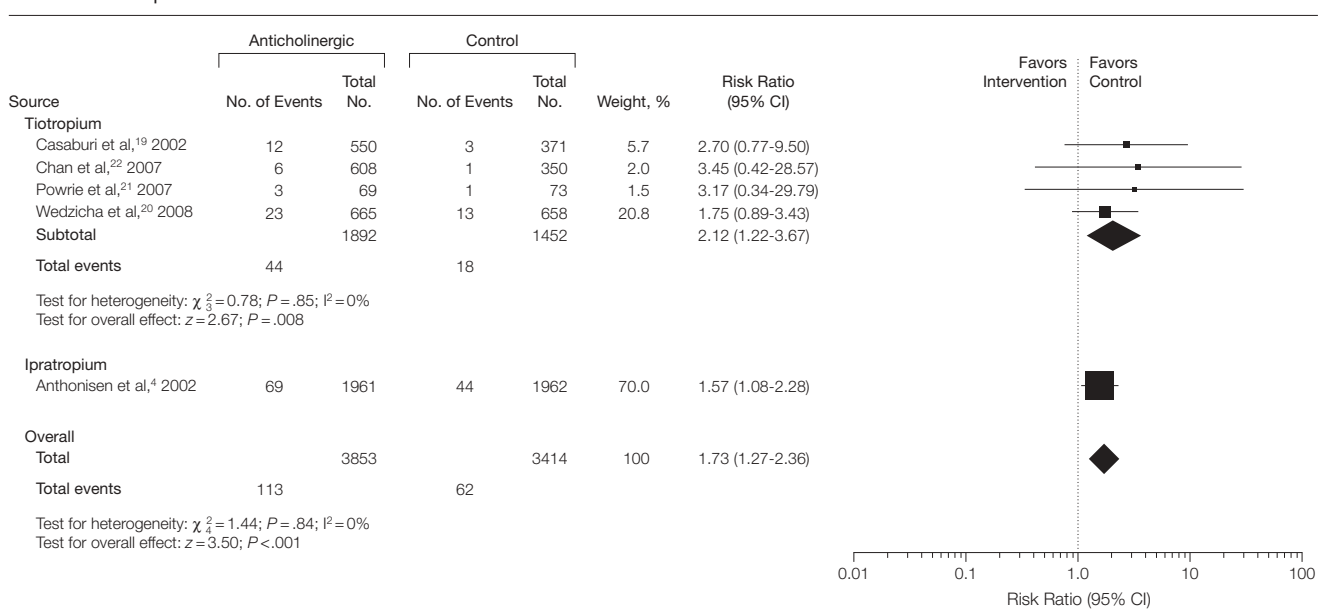
These risks of inhaled anticholinergics should be balanced against their benefits. The benefits of inhaled anticholinergics, such as tiotropium bromide, include symptomatic improvements seen in an increase in exercise capacity, reduction in the frequency of exacerbations (13%-25%),¹⁰ fewer hospitalizations because of exacerbations, improvements in dyspnea sensation as measured by the transition dyspnea index, and statistically significant improvement in health-related quality-of-life measures such as the St George Respiratory questionnaire.¹ The number needed to treat for tiotropium to prevent 1 COPD exacerbation is around 21 (95% CI,13-50),¹¹ or COPD-related hospitalization is around 20 (95% CI,

Table 4. 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	Reference No.	No./Total No.		RR (95% CI)	P Value	I ² ,% ^a
			Inhaled Anticholinergic	Controls			
Cardiovascular death	12	4, 19-21, 23-25, 27, 29, 30, 31, 33	57/6156	31/6220	1.80 (1.17-2.77)	.008	0
MI	11	4, 19-22, 24, 26, 28, 31-33	68/5430	43/5168	1.53 (1.05-2.23)	.03	0
Stroke	7	4, 19, 20, 24, 32-34	25/4548	18/4703	1.46 (0.81-2.62)	.20	0
All-cause mortality	17	4, 19-34	149/7472	115/7311	1.26 (0.99-1.61)	.06	2

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.
^aTest for statistical heterogeneity.

Figure 3. Meta-analysis of Long-Term Randomized Controlled Trials of Inhaled Anticholinergics vs Control for Major Adverse Cardiovascular Outcomes Composite



Cardiovascular outcomes composite indicates cardiovascular death, myocardial infarction, and stroke. Long-term indicates longer than 6 months to 5 years. Size of the data markers indicates weight of the study. CI indicates confidence interval.

14-34) compared with placebo.¹¹ This should be weighed against the NNH of 40 for cardiovascular death and 174 for MI with inhaled anticholinergics in a typical US COPD population. Clinicians should evaluate the baseline cardiovascular risk status when considering inhaled anticholinergic therapy because patients with lower baseline cardiovascular risk will have higher and more favorable NNH for cardiovascular events associated with inhaled anticholinergics.

Unfortunately, alternative effective therapeutic options for patients with COPD are limited. The other long-acting bronchodilator, such as the inhaled β -agonist, and steroid combinations have similar efficacy,¹⁰ but a different adverse effect profile. An inhaled combination of

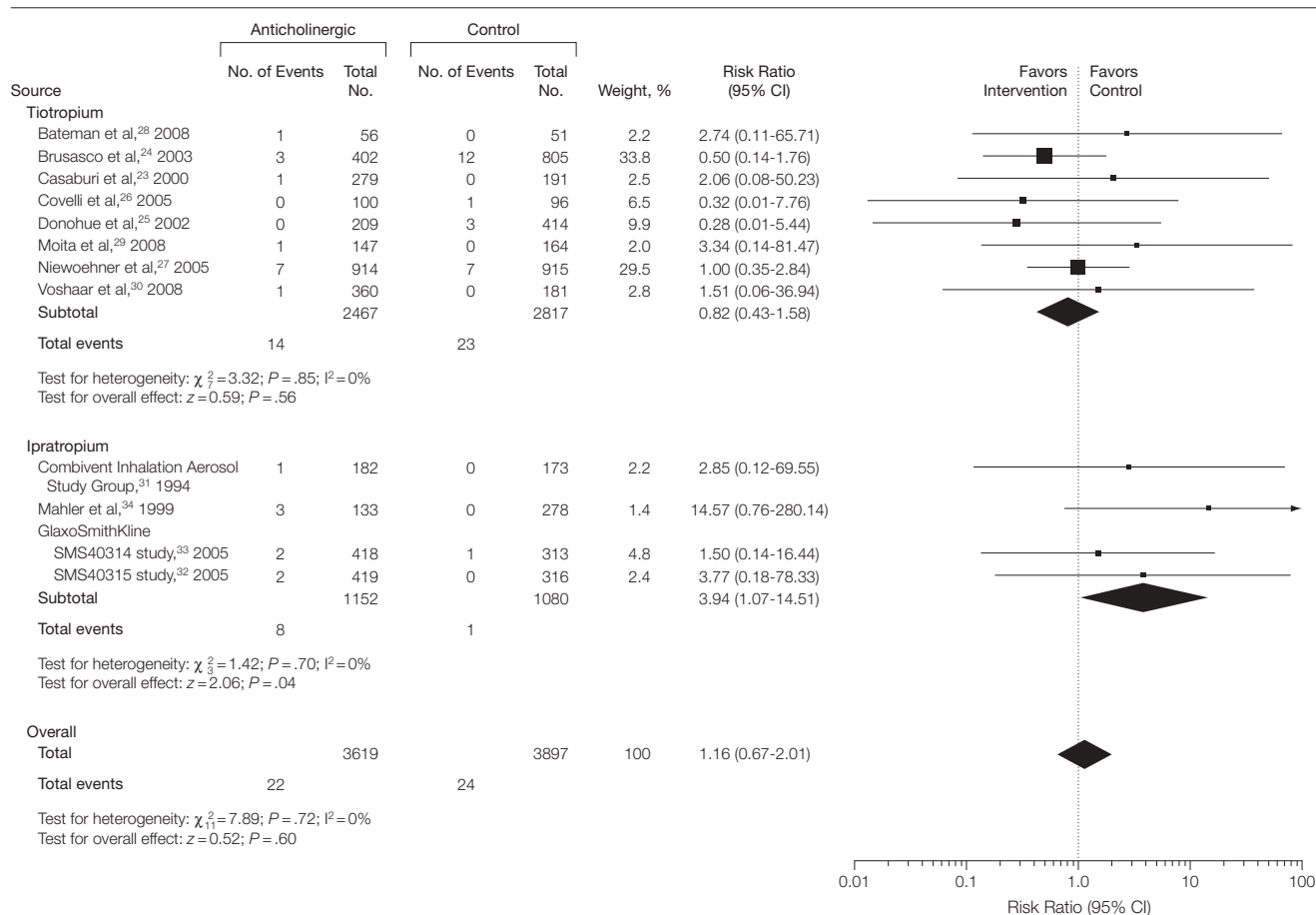
salmeterol and fluticasone failed to significantly reduce mortality (HR, 0.83 [95% CI, 0.68-1.00]; $P = .052$) compared with placebo, but was associated with a significantly increased probability of pneumonia (19.6% vs 12.3%; $P < .001$) compared with placebo in the Toward a Revolution in COPD Health (TORCH) trial.⁴⁶

Despite certain limitations, our findings have potential implications. Our findings indicate an increased risk of cardiovascular death, MI, or stroke with inhaled anticholinergic agents in patients with COPD. Chronic obstructive pulmonary disease is an independent risk factor for cardiovascular hospitalization and cardiovascular death.⁴⁷ Cardiovascular death is a more frequent cause of death in patients with

COPD than respiratory causes,⁴⁸ with the proportion of cardiovascular deaths increasing with the severity of the disease.⁴⁹ Clinicians need to closely monitor patients with COPD who are taking long-term anticholinergics for the development of cardiovascular events. Clinicians and patients should carefully consider these potential long-term cardiovascular risks of inhaled anticholinergics in the treatment of COPD, and decide whether these risks are an acceptable trade-off in return for their symptomatic benefits.

Author Contributions: Dr Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Singh, Loke.
Acquisition of data: Singh, Loke.

Figure 4. Meta-analysis of Short-Term Randomized Controlled Trials of Inhaled Anticholinergics vs Control for Major Adverse Cardiovascular Outcomes Composite



Cardiovascular outcomes composite indicates cardiovascular death, myocardial infarction, and stroke. Short-term indicates 6 weeks to 6 months. Size of the data markers indicates weight of the study. CI indicates confidence interval.

Analysis and interpretation of data: Singh, Loke, Furberg.

Drafting of the manuscript: Singh, Loke.

Critical revision of the manuscript for important intellectual content: Singh, Loke, Furberg.

Statistical analysis: Singh, Loke.

Administrative, technical, or material support: Singh.

Study supervision: Singh, Furberg.

Financial Disclosures: None reported.

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