

RAPID APPRAISAL

Name of Trial: Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients with Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review and Meta-analysis

Reference: Singh S, Loke YK & Furberg CD. JAMA 2008; 300:1439-50 (doi: 10. 1001/jama.300.12.1439)

Question: Do inhaled anticholinergics increase the risk of cardiovascular events in patients with COPD?

Summary: This meta-analysis of 17 studies (n = 14,783) suggests that use of inhaled anticholinergics for more than 30 days is associated with a small (0.6%) increase in the absolute risk of cardiovascular events (cardiovascular death, myocardial infarction or stroke) in patients with COPD. However, this study has several methodological problems, and the results should be interpreted with caution. Many of the trials were small and short-term, and consequently the confidence intervals were wide, resulting in some uncertainty as to the precise magnitude of the observed risk. The quality and duration (six weeks to over five years) of the trials included were variable. The trials were not designed to monitor the risk of cardiovascular events, which were not adjudicated, so cardiovascular outcome event reporting may have been incomplete. The small increase in cardiovascular risk needs to be balanced against the potential benefits of inhaled anticholinergics. More prospective, robust studies are needed to establish whether inhaled anticholinergics are associated with an increase in cardiovascular risk in patients with COPD. Until such time, a change in prescribing practice is not recommended.

Did the study ask a clearly focussed question?

Yes – The main objective of this study was to ascertain the risks of serious cardiovascular events [cardiovascular death, myocardial infarction (MI) and stroke], associated with the long term use of inhaled anticholinergics in patients with COPD.¹ The secondary objective was to ascertain the risk of all-cause mortality in these patients.¹

Did the reviewers look for the appropriate sort of papers?

Yes – Specific inclusion criteria for trials were clearly defined: (1) randomised controlled trials (RCTs) for any inhaled anticholinergic (tiotropium or ipratropium) with > 30 days of follow-up; (2) study participants had a diagnosis of COPD of any severity; (3) an inhaled anticholinergic as the intervention drug vs a control, which could be placebo or active; and (4) data on the incidence of serious cardiovascular adverse events, including cardiovascular death, MI or stroke, had to be reported.¹

During data collection, the proportion of participants with pre-existing cardiac disease or cardiovascular risk factors was recorded, if available; however it was not included in the meta-analysis.¹

Trial duration ranged from six to 280 weeks, but the duration of active anticholinergic treatment was not recorded.¹

Were the important relevant studies included?

Probably – The reviewers searched MEDLINE through PubMed, the Cochrane database of

Systematic Reviews, websites of the US Food and Drug Administration and European regulatory authorities, clinicaltrials.gov, and the manufacturer's product information sheets.¹ Trial reports of all published or unpublished trials with inhaled ipratropium bromide and tiotropium bromide in the clinical trials register of the manufacturers were evaluated. Unpublished studies were included.¹

The reviewers did not however (never start a sentence with however!) search EMBASE; therefore relevant articles may have consequently been omitted.

Of 703 potentially relevant citations identified, 17 trials involving 14,783 patients fulfilled the inclusion criteria.¹ Tiotropium and ipratropium were evaluated in 12 and five studies, respectively.¹

Was the quality of the studies assessed?

Yes – Two reviewers assessed each study independently for the reporting of allocation, concealment, the use of blinding, loss to follow-up and withdrawal rates.¹ Adverse event monitoring, including frequency and type of adverse events were evaluated based on the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions.¹

Trial quality was reported as variable. Although all trials were double blind, allocation concealment was adequate in only four RCTs and unclear in the remaining 13.¹

Information on withdrawal rates was available for all but one trial and ranged from 6.1% to 42%. Reporting of loss to follow-up was variable, only available for six RCTs and ranged from 0% to 3.4%.¹

Trial duration ranged from six to 280 weeks (over five years).¹ The inclusion of short-term studies are likely to have influenced the overall results.

Was it reasonable to combine the results of the review?

Yes – With respect to the main outcomes of cardiovascular death, MI, or stroke there was no evidence of heterogeneity between the studies¹ and therefore combining the data for a meta-analysis is probably justified. With respect to the secondary outcome of death from any cause, there was evidence of a low level of heterogeneity between the studies.¹

Trial characteristics (duration, primary outcome, number of participants, age, % predicted FEV₁ and % current smokers), and trial quality assessment (allocation concealment, adverse event monitoring, withdrawal rates and loss to follow up), were clearly shown for the 17 trials included in the meta-analysis.¹

What is the overall result of the review?

Use of inhaled anticholinergic drugs for more than 30 days significantly increases the risk of MI, cardiovascular death or stroke from 1.2% to 1.8% (RR 1.58 [95% CI, 1.21-2.06]; P <0.001),¹ representing an absolute risk increase of 0.6%.

There was a non significant increase in all cause mortality within the anticholinergic group (2.0% vs 1.6% for control; RR 1.26 [95% CI, 0.99-1.61]; P = 0.06).¹

Meta-analyses of each individual component of the primary outcome was also reported (control vs. inhaled anticholinergic drug respectively). This identified an increased risk of MI from 0.8% to 1.2% (RR 1.53 [95% CI, 1.05-2.23]; P=0.03) in 11 trials involving 10,598 patients, and an increased risk of cardiovascular death from 0.5% to 0.9% (RR 1.80 [95% CI, 1.17-2.77]; P = 0.008) in 12 trials involving 12,376 patients.¹ No significant increase in risk of stroke was identified (0.4% vs. 0.5%, RR 1.46 [95% CI, 0.81-2.62]; P = 0.20) in seven trials involving 9,251 patients.¹

The random-effects analysis of the primary composite outcome of cardiovascular death, MI and stroke from the 17 trials yielded effect sizes (RR 1.57 [95% CI 1.19-2.06]; P = 0.001) similar in magnitude and direction to those obtained from the fixed dose analysis.¹ A sensitivity analysis limited to the five long-term (> 6 months) trials (n = 7,267) showed that inhaled anticholinergics significantly increased the risk of cardiovascular death, MI and stroke from 1.8% to 2.9% (RR 1.73 [95% CI, 1.27-

2.36]; P < 0.001).¹ A sensitivity analysis of the 12 short-term (< 26 weeks) trials (n = 7,516) failed to demonstrate a significant difference in the risk of this composite end point.¹

How precise are the results?

Many of the trials were small and short-term; resulting in few events. Consequently, the 95% confidence intervals were wide, resulting in some uncertainty as to the precise magnitude of the observed increase in risk.¹ Only five of the 17 trials were long-term; duration range six months to over five years.¹

The trials were not designed to monitor the risk of cardiovascular events, which were not adjudicated, so cardiovascular outcome event reporting may have been incomplete.¹

Drop out rates were high in some trials (up to 42%)¹ which may have reduced the statistical power and overestimated the potential risk of cardiovascular events associated with inhaled anticholinergics.

Can the results be applied to the local population?

Can't tell – The reviewers did not report enough patient demographics to enable the results to be applied to the local population.

During original data collection, reviewers recorded the proportion of participants with pre-existing cardiac disease or cardiovascular risk factors if available, but this was not included in the meta-analysis.¹ Other possible confounding comorbidities such as hypertension; diabetes, hypercholesterolaemia, coronary artery disease were not reported. Details of the countries included in the trials were not fully described, nor was the socioeconomic background or ethnicity of the participants in the trial reported.

The reported characteristics of the participants included in the studies were: mean age (range 48.4 - 66.9 years), % of male participants (range 49% - 95.8%), and mean % predicted FEV₁ (range 35.6% - 75.1%). Smoking status was not reported for all studies.¹

Were all important outcomes considered?

Yes – Studies were only included in the meta-analysis if they included data on cardiovascular adverse events.¹

Should policy or practice change as a result of the evidence contained in this review?

No - Given the methodological problems with this meta-analysis, the conclusions reached by the reviewers should be interpreted cautiously.

The absolute risk increase for the primary composite end point was only 0.6% and this needs to be balanced against the potential benefits of inhaled anticholinergics. These include increased

exercise capacity, reduction in the frequency of exacerbations, fewer hospitalisations because of exacerbations, improvements in dyspnoea sensation and statistically significant improvement in health related quality of life measurements.¹

It is plausible that ipratropium and tiotropium might give rise to arrhythmias by virtue of their anticholinergic properties.² The summary of product characteristics for ipratropium inhaler lists palpitations, supraventricular tachycardia and atrial fibrillation as rare adverse effects ($\geq 1/10,000 < 1/1,000$) and tachycardia as an uncommon adverse effect ($\geq 1/1,000 < 1/100$).³ For tiotropium tachycardia and palpitations are listed as rare adverse effects ($>1/10,000, < 1/1,000$).⁴

Current evidence surrounding cardiovascular risk associated with inhaled anticholinergics in patients with COPD is inconsistent. This meta-analysis, and the recently published case controlled study by Lee et al, examining the association between various respiratory medications and risk of death in U.S veterans, have both concluded that ipratropium alone was associated with an increased risk of cardiovascular death.⁵

However, the results from the "Understanding Potential Long Term Impacts on Function with Tiotropium" (UPLIFT) trial; a 4 year trial involving 5,993 patients from 37 countries, do not support the

findings of this meta-analysis.⁶ The results indicate a reduction in cardiac adverse events associated with tiotropium. Myocardial infarction developed in 67 patients in the tiotropium group compared to 85 in the placebo group, stroke developed in 82 in the tiotropium group and 80 in the placebo group, and respiratory failure occurred in 88 patients in the tiotropium group compared to 120 in the placebo group.⁶

The US Food and Drug Administration (FDA) are currently working to evaluate the potential association between tiotropium and stroke. The FDA have announced they were reviewing post-marketing adverse event reports with tiotropium, and will make a recommendation to the public once the complete results of the UPLIFT study had been reviewed.⁷

More prospective, robust studies are needed to establish whether inhaled anticholinergics are associated with an increased risk of stroke, MI or cardiovascular death in patients with COPD. Until such time, a change in prescribing practice is not recommended.

All suspected adverse reactions should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

REFERENCES

1. Singh S et al. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. JAMA 2008; 300:1439-50 (MA)
2. Anthonisen NR et al. Hospitalizations and mortality in the lung health study. Am J Respir Crit Care Med 2002; 166: 333-9 (RCT)
3. Boehringer Ingelheim Limited. Summary of product characteristics for Atrovent®▼ Inhaler CFC-Free. www.medicines.org.uk. Last updated 04.07.08
4. Boehringer Ingelheim Limited. Summary of product characteristics for Spiriva® 18 microgram inhalation powder, hard capsule. www.medicines.org.uk. Last updated 22.09.08
5. Lee TA et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Int Med 2008; 149; 380–90 (CCT)
6. Tashkin DP et al. A 4 year Trial of Tiotropium in chronic obstructive pulmonary disease. NEJM 2008; 359; 1543–54 (RCT)
7. Centre for Drug Evaluation and Research. Early communication about ongoing safety review of tiotropium. US Food and Drug Administration; 2008. Updated 07/10/2008. Accessed online 09/10/08 http://www.fda.gov/cder/drug/early_comm/tiotropium.htm

KEY: MA - meta-analysis, RCT - randomised controlled trials, G – guidance, CCS – case control study

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