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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CRD summary
This review found that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction or stroke among patients with chronic obstructive pulmonary disease. The review was generally well conducted and the authors’ conclusions appear justified.

Authors’ objectives
To evaluate the cardiovascular risks associated with the long-term use of inhaled anticholinergics in patients with chronic obstructive pulmonary disease.

Searching
Two reviewers independently identified English language trials through a computerised bibliographic search of MEDLINE, Cochrane Database of Systematic Reviews, Web of Science, websites of the US Food and Drug Administration and regulatory authorities, clinicaltrials.gov and manufacturers product information sheets to March 2008. Published and unpublished trials in clinical trials registers of manufacturers, reference lists of previous systematic reviews and reference lists of included studies were also searched. Search terms used were reported.

Study selection
Randomised controlled trials (RCTs) comparing any inhaled anticholinergic (ipratropium bromide or tiotropium bromide) with more than 30 days of follow-up to a control, either placebo or active control, were eligible for inclusion. Trials were required to include participants with a diagnosis of chronic obstructive pulmonary disease of any severity and were also required to report data on the incidence of serious cardiovascular adverse events including myocardial infarction, stroke or cardiovascular death. Patients with asthma were excluded.

The primary outcome was a composite of non-fatal acute myocardial infarction, non-fatal stroke (including transient ischemic attack) and cardiovascular death (including sudden death). The mean age ranged from 48.4 years to 68.1 years and, on average, men accounted for 72% of patients. Follow-up duration ranged from six weeks to 280 weeks.

Two reviewers independently assessed eligibility and disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
Two reviewers independently assessed the quality of included studies for allocation concealment, blinding, loss to follow up and withdrawal rates. To determine the strength of adverse event monitoring, the frequency and type of monitoring during the follow-up period were evaluated using the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions.

Data extraction
Data on myocardial infarction, stroke, cardiovascular death and all-cause mortality among trial listings of serious adverse events. Because data is drawn from adverse events listings, rather than trial outcomes, it may mean the review is not powered to detect differences which could lead to underestimation of effects.

Two reviewers independently extracted data and discrepancies were resolved by consensus with a third reviewer.

Methods of synthesis
The pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated using a fixed-effect model where statistical heterogeneity was not present. The number-needed-to-harm was calculated by applying the relative risk estimates to the cardiovascular event rate in a large population based study. Statistical heterogeneity was assessed using the $I^2$ test, where 50% was considered substantial heterogeneity. Sensitivity analyses were conducted to test the influence of statistical models using a random-effects model, the influence of trial duration, completeness in
reporting individual end points, and influence of individual studies. Publication bias was assessed using the fail safe N, which indicates the number of non-significant studies needed to reverse an overall statistically significant result to non-significance.

**Results of the review**

Seventeen double blinded RCTs (n=13,645 patients) were included in the review. Quality was variable across included trials; allocation concealment was adequate in four trials (unclear in 13), withdrawal rates ranged from 6.1% to 42% and data on loss to follow-up was available for six trials (range 0% to 3.4%).

**Main outcomes**: Overall, inhaled anticholinergics significantly increased the risk of cardiovascular death, myocardial infarction or stroke (RR 1.60, 95% CI 1.22 to 2.10). Inhaled anticholinergics significantly increased the risk of myocardial infarction (RR 1.52, 95% CI 1.04 to 2.22) and cardiovascular death (RR 1.92, 95% CI 1.23 to 3.00) but did not significantly increase the risk of stroke (RR 1.46, 95% CI 0.81 to 2.62). No statistical heterogeneity was observed. Inhaled anticholinergics did not significantly increase the risk of all-cause mortality (RR 1.29, 95% CI 1.00 to 1.65). The number-needed-to-harm for myocardial infarction was estimated to be 174 per year (95% CI 75 to 1,835 per year) and for cardiovascular death 40 per year (95% CI 18 to 185 per year).

**Sensitivity analyses**: Results remained significant when a random-effects model was used; when limited to the six long-term trials (lasting over six months); when inhaled tiotropium and inhaled ipratropium were analysed separately in the long term trials; when five trials were excluded for which endpoint data was missing; and after excluding one trial which contributed to more than 50% of the weight in the fixed-effect model. Short-term trials did not show significantly increased risk.

**Fail safe N**: Sixteen non-significant long-term trials, each with a sample size of approximately 1,450, would be required to reverse the main outcomes.

It should be noted that the figures in this review are corrected from the original publication (cited in the Bibliographic Details field) using subsequently published errata (see Other Publications of Related Interest field).

**Authors’ conclusions**

Inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction or stroke among patients with chronic obstructive pulmonary disease.

**CRD commentary**

The review addressed a clear question in terms of inclusion criteria, study design and outcomes of interest. A number of relevant electronic databases and other sources were searched, the search terms were reported and efforts were made to retrieve unpublished data. However, the search was restricted to English language publications and important data might have been missed. Steps were taken to minimise bias and errors in searching for relevant trials, selection of included trials and data extraction. Quality of included trials was appropriately measured and the strength of adverse event monitoring was assessed using Cochrane criteria. The data appear to have been analysed using appropriate techniques and the rationale for sensitivity analyses was clear. Heterogeneity was investigated and discussed in the text. Reporting errors, which were in part due to a lack of information in the primary studies, were corrected in a subsequent publication of errata (see Other Publications of Related Interest field). Such errors do not appear to have detracted from the quality of the review. The authors’ conclusions are likely to be reliable given the evidence presented.

**Implications of the review for practice and research**

**Practice**: The authors stated that clinicians need to closely monitor patients with chronic obstructive pulmonary disease who are taking long-term anticholinergics for the development of cardiovascular events. The authors also stated that clinicians and patients should carefully consider whether the cardiovascular risks are an acceptable trade-off for the symptomatic benefits of inhaled anticholinergics in patients with chronic obstructive pulmonary disease.

**Research**: The authors stated that prospective, adequately powered trials with adjudication of cardiovascular events are needed to assess the cardiovascular safety of inhaled anticholinergics in patients with chronic obstructive pulmonary disease.
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