**Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis**


**CRD summary**
This review evaluated the safety of inhaled tiotropium bromide (anticholinergic agent) in patients with chronic obstructive pulmonary disease. The authors concluded that tiotropium did not significantly increase the risk of adverse major cardiovascular events compared with placebo or salmeterol. The authors' conclusions reflected the evidence presented, but lack of clarity regarding included trial quality means that their reliability is unclear.

**Authors' objectives**
To evaluate the safety of regular use of inhaled tiotropium bromide in patients with any severity of chronic obstructive pulmonary disease.

**Searching**
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1966 to 2009. Search terms were reported. In addition, files from the clinical databases of the pharmaceutical company Boehringer Ingelheim and the US Food and Drug Agency (FDA) were searched; reference lists from reviews and texts were scanned; and the manufacturer of tiotropium was contacted to obtain data from their clinical trial database. There were no language restrictions. Unpublished studies were included.

**Study selection**
Randomised controlled trials (RCTs) that compared inhaled tiotropium bromide with placebo or long-acting beta agonists or long-acting beta agonists plus inhaled corticosteroid were eligible for inclusion in the review. Trials had to be more than four weeks duration. The patients of interest were adults, aged at least 35 years, with stable chronic obstructive pulmonary disease according to American Thoracic Society/European Respiratory Society or GOLD (Global Initiative for Chronic Obstructive Lung Disease) diagnostic criteria.

The primary eligible outcomes were: major adverse cardiovascular composite measurement including non-fatal myocardial infarction, stroke, and cardiovascular death during the treatment period. These individual components were also measured separately. All-cause mortality was eligible as a secondary outcome.

The mean age of included patients was 64.8 years, and 74% were men. In the majority of included trials, tiotropium was administered once a day and was compared with placebo. The other included comparators were salmeterol, or salmeterol/fluticasone. Trial duration ranged from two to 48 months.

All reviewers independently selected trials for inclusion, and disagreements were resolved by consensus.

**Assessment of study quality**
Two reviewers assessed trial quality according to the following criteria: sequence generation; allocation sequence concealment; blinding; incomplete outcome data; selecting outcome reporting; and other potential sources of bias according to the Cochrane Risk of Bias tool.

**Data extraction**
Two reviewers extracted data to enable the calculation of relative risks (RR) and 95% confidence intervals (CI).

**Methods of synthesis**
Relative risks and 95% confidence intervals were pooled in a meta-analysis by fixed-effect (Mantel-Haenszel) or random-effects models (DerSimonian and Laird) depending on the level of heterogeneity. Heterogeneity was measured using the Q and I^2 statistics, where values of more than 50% were considered to be high. Results were presented for composite scores and for their individual components. Where group differences for dichotomous outcomes were noted,
the number needed-to-harm (NNH) was also calculated.

Sensitivity analysis was conducted to explore the effect size for concealment allocation (adequate versus unclear), trial duration (long-term of six months to four years versus short-term of six weeks to six months), concomitant use of inhaled corticosteroids (55% of patients or above versus less than 55% of patients) and smoking history (55 pack-years and above versus less than 55 pack-years).

**Results of the review**

Nineteen RCTs (n=18,111 patients) were included in the review. Allocation concealment was adequate in four trials; this was unclear in the remaining trials. Withdrawal rate ranged from 0 to 45%.

**Primary outcomes**: There were no significant differences in the incidence of major composite adverse cardiovascular events (tiotropium group 3.6% versus control group 4%; 15 trials; n=15,695 patients). Sensitivity analysis including 13 placebo-controlled trials did not alter this result. A higher trend was noted in patients with a smoking history of 55 pack-years and above. A statistically significant higher incidence was reported in the tiotropium group when compared with salmeterol/fluticasone group (RR 1.94, 95% CI 1.06 to 3.55; two trials). There were no significant differences between groups on individual components of cardiovascular death (10 trials), non-fatal myocardial infarction (10 trials) and non-fatal stroke (four trials). There was no statistically significant heterogeneity in any analysis.

**Secondary outcome**: Tiotropium did not significantly increase the risk of all-cause mortality (16 trials). A higher incidence of all-cause mortality was reported in the tiotropium group when compared with salmeterol/fluticasone group (RR 1.87, 95% CI 1.07 to 3.28; one trial).

**Authors’ conclusions**

Compared with placebo or salmeterol, tiotropium did not significantly increase the risk of adverse major cardiovascular events among chronic obstructive pulmonary disease patients. Smoking history can modify the risks.

**CRD commentary**

The review question was clear and inclusion criteria were specified sufficiently to allow replication. Relevant sources were searched for trials, and adequate attempts were made to minimise language and publications biases. The review process was conducted with sufficient transparency to reduce error and bias.

The chosen quality assessment tool was relevant to the included study designs, but the absence of reporting on many aspects meant that the overall quality of included trials was unclear. The method of synthesis was appropriate; heterogeneity was assessed, and sensitivity analysis was conducted to validate the main findings. Trial details were provided, and the authors correctly acknowledged that the generalisability of the review findings may be limited to a comparison of tiotropium with placebo in the male population.

The authors’ conclusions reflected the evidence presented, but the lack of clarity regarding trial quality means that their reliability is unclear.

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

**Practice**: The authors stated that caution is advised in administering tiotropium in patients at risk for cardiovascular disease.

**Research**: The authors implied that adequately randomised trials prespecified on cardiovascular outcomes are needed to clarify evidence of safety for tiotropium.

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