Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis
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CRD summary
This review concluded that the use of beta2-agonists in individuals with obstructive airway disease increases the risk for adverse cardiovascular events. While the authors' conclusions are reasonable, the magnitude of the risk may have been overestimated due to the inclusion criteria of the review or underestimated due to the characteristics of the primary studies.

Authors' objectives
To evaluate the cardiovascular safety of beta2-agonists for patients with obstructive airway disease.

Searching
MEDLINE, EMBASE and CINAHL were searched from inception to June 2003 without any language restrictions; the search terms were provided. The references of identified articles and review articles were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing a beta2-agonist (either a single dose or longer duration of treatment) with placebo were eligible for inclusion. Trials were included if they allowed open-label rescue beta2-agonist in both the treatment and placebo groups. The included studies were of formoterol, fenoterol, terbutaline, salmeterol, salbutamol, albuterol, procaterol, levalbuterol and isoproterenol, either alone or in combination. There were studies of single-dose treatment and studies of longer treatment duration (mean 4.7 months, range: 3 days to 1 year). Rescue beta2-agonist use for treatment and placebo groups was permitted in all but one of the included studies.

Participants included in the review
Studies of participants with obstructive airway disease, defined as asthma or chronic obstructive pulmonary disease (COPD), were eligible for inclusion. Apart from one study of both asthma and COPD participants, the included studies were of either asthma or COPD participants alone. The mean age of the participants was 56.6 years in single-dose studies and 52.2 years in studies of longer duration.

Outcomes assessed in the review
Single-dose studies were eligible for inclusion if they provided extractable data on heart rate or potassium concentrations. Longer duration trials were eligible for inclusion if they reported at least one adverse cardiovascular effect. A cardiovascular event was defined as sinus or ventricular tachycardia, atrial fibrillation, syncope, myocardial infarction, congestive heart failure, cardiac arrest, or sudden death. Adverse events such as palpitations, chest pain, hypertension were classified as minor and were not included.

How were decisions on the relevance of primary studies made?
Two investigators independently assessed studies for inclusion. Inter-rater agreement was 98% (95% confidence interval, CI: 96, 100).

Assessment of study quality
Studies were assessed for quality in relation to randomisation, blinding, and whether a crossover or parallel group design was used. A rating of A, B or C was applied. Two investigators independently assessed study quality. The kappa statistic for inter-rater agreement was 1.0.
Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. The mean difference between treatment and placebo was calculated, along with the 95% CI, for the heart rate and potassium concentration outcomes. The relative risk (RR) and 95% CI were calculated for cardiovascular adverse events.

Methods of synthesis
How were the studies combined?
The single-dose studies were pooled in a meta-analysis using a random-effects model to obtain a weighted mean difference and 95% CI. Studies of longer duration were pooled using a fixed-effect model to obtain a RR and 95% CI. A random-effects model was also applied to the latter for comparison purposes. For the studies of longer duration, data on sinus tachycardia and all other cardiac adverse events combined were pooled separately.

How were differences between studies investigated?
The chi-squared test was used to investigate heterogeneity. The analysis of overall risk of cardiovascular events was rerun with one trial, which had contributed half of the adverse cardiac events, excluded.

Results of the review
Thirteen RCTs (n=232) of a single-dose intervention and 20 trials (n=6,623) of longer treatment duration were included.

The single-dose studies were all double- or single-blinded crossover trials (quality rating B). Fifteen of the longer duration studies were double-blind parallel-group trials (quality rating A) and 5 were single- or double-blind crossover trials.

Compared with placebo, a single-dose beta2-agonist was associated with a statistically significant increase in heart rate (9.12 beats per minute, 95% CI: 5.32, 12.92) and a decrease in potassium concentration (0.36 mmol/L, 95% CI: 0.18, 0.54). There was evidence of statistically significant heterogeneity for both analyses.

Compared with placebo, longer duration treatment with a beta2-agonist was associated with a statistically significant increased risk for adverse cardiovascular events (RR 2.54, 95% CI: 1.59, 4.05). The exclusion of one trial which contributed half of the cardiac events to the analysis did not alter the findings (RR 2.15, 95% CI: 1.26, 3.65). The subgroup analysis indicated a statistically significant increased risk of sinus tachycardia (RR 3.06, 95% CI: 1.7, 5.5), but no statistically significant difference between treatment and placebo for other major cardiovascular events combined (RR 1.61, 95% CI: 0.76, 3.42). The tests for statistical heterogeneity were not significant.

Authors' conclusions
The use of beta2-agonists in individuals with obstructive airway disease increased the risk for adverse cardiovascular events.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Relevant databases were searched without language restrictions, thereby reducing the risk of language bias. However, some relevant studies might have been missed as no specific attempts to identify unpublished studies were made. The review methods were well described and included measures to avoid the introduction of bias. The methodological quality of the studies was assessed, though it was unclear whether allocation concealment was considered. Since there can be considerable variability in how adverse event data are gathered, more detail on this aspect of the studies would have been useful.

Given the clinical heterogeneity of the studies, it is arguable whether it was appropriate to pool the longer duration studies despite there being no evidence of statistical heterogeneity. The authors’ conclusions are appropriate for the evidence available, but they cannot be regarded as definitive because of the problems outlined. In addition, the
absolute risk of a cardiovascular event in this patient group remains unclear as studies that did not report an event were not included in the review. This might have led to an overestimation of the risk, though the possibility of an underestimation due to studies allowing beta2-agonist rescue treatment in the placebo group also needs consideration.

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

Practice: The authors stated that the results of the study should heighten concern over the cardiovascular safety of using beta2-agonists in individuals with obstructive airway disease.

Research: The authors stated that long-term trials comparing the safety and efficacy of beta2-agonists with treatment such as ipratropium, corticosteroids or beta-blockers for patients with obstructive airway disease are required.

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