Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis

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CRD summary
This generally well-conducted review concluded that there were safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with varenicline treatment for tobacco users. This conclusion seems reliable, but the included evidence had limitations that need to be kept in mind.

Authors' objectives
To determine the incidence of serious adverse cardiovascular events associated with varenicline, compared with placebo, for tobacco use cessation.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restrictions, for articles from inception to March 2011; search terms were reported. ClinicalTrials.gov and the industry-sponsored Clinical Study Results Database, and websites of the US Food and Drug Administration, and the European Medicines Agency were searched to identify unpublished studies. Bibliographies of systematic reviews and included trials were scanned.

Study selection
Double-blind randomised controlled trials (RCTs), with at least one week of follow-up, that reported on cardiovascular events (including no events) with varenicline use, compared with placebo, among tobacco users, were eligible for inclusion. Open-label trials and trials of varenicline compared with active treatments were also eligible. The primary outcome was any ischaemic or arrhythmic adverse cardiovascular event (details provided). All-cause mortality was a secondary outcome.

Across the trials, mean age ranged from 39 to 57 years and the percentage of males from 44% to 93%. Where reported, the mean number of years of smoking ranged from 20 to 41. Most trials used a 1mg twice daily dose of varenicline. The duration of treatment ranged from seven to 52 weeks, and study duration ranged from 24 to 52 weeks. One trial enrolled non-smoking tobacco users, whilst the others recruited smokers. Most of the trials excluded patients with a history of cardiovascular disease. Where these patients were included, they had stable cardiovascular disease. The majority of trials did not use an objective definition of cardiovascular events.

Two independent reviewers selected trials for the review; disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
Two reviewers independently assessed trial quality in terms of adequacy of randomisation, allocation concealment, blinding of participants and personnel, reporting of withdrawals and loss to follow-up, and reporting of adverse outcomes. Disagreements were resolved by consensus with a third reviewer.

Data extraction
Data to calculate odds ratios and 95% confidence intervals were extracted by two independent reviewers. Disagreements were resolved by consensus including a third reviewer.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using the Peto method on an intention-to-treat basis. Heterogeneity was assessed using $I^2$ and 50% or more was considered to be substantial. The primary analysis was of the double-blind placebo-controlled RCTs; the open-label trials and trials with active comparators were included in sensitivity analyses. Sensitivity analyses were conducted using the fixed-effect Mantel-Haenszel method, with adjusted
and unadjusted data, and the role of individual trials was investigated by excluding the most influential trial. Publication bias was investigated using a funnel plot.

**Results of the review**

Fourteen double-blind placebo-controlled trials met the primary inclusion criteria (8,216 participants, range 250 to 1,210) and one open-label trial of varenicline versus nicotine replacement therapy was included in the sensitivity analysis (n=757). Nine RCTs were judged to be at low risk of bias, with adequate randomisation, allocation concealment, and double blinding, and clear reporting of withdrawal rates; the remainder were at an unclear risk of bias. Loss to follow-up across trial arms ranged from zero to 28.6%.

There was a significant increase in the risk of serious adverse cardiovascular events associated with varenicline, compared with placebo (OR 1.72, 95% CI 1.09 to 2.71; I²=0%; 14 RCTs). Across the trials seven participants out of 4,908 died in the varenicline groups and seven out of 3,308 in the placebo groups; these data could not be pooled. All the sensitivity analyses showed results similar to those of the primary analysis. There was no significant impact of varenicline on myocardial infarction, stroke, and cardiovascular-related death. There was no evidence of publication bias.

**Authors' conclusions**

This meta-analysis raised safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with varenicline treatment for tobacco users.

**CRD commentary**

The authors addressed a clear research question, supported by appropriate inclusion criteria. Several relevant sources were searching, and a specific attempt was made to locate unpublished trials. Each stage of the review process was conducted in duplicate, reducing the risk of error and bias. Trial quality was assessed, using appropriate criteria, and the results were reported in full in an online appendix. The analysis seems to have been appropriate. The authors acknowledged the limitations of the included trials in terms of small samples with inadequate power, some methods, and restricted populations, impacting on the generalisability of the results.

This was a generally well-conducted review and the conclusions seem reliable, but the included evidence had limitations that need to be kept in mind.

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

**Practice**: The authors stated that, until more robust evidence was available, clinicians should carefully balance the risk of serious cardiovascular events and serious neuropsychiatric adverse events, associated with varenicline, against the known benefits of the drug for smoking cessation.

**Research**: The authors stated that an adequately powered safety trial was required.

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