Cardiovascular disease and varenicline

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Executive Summary

In light of trials reporting on the incidence of cardiovascular serious adverse events among those using varenicline and a call to evaluate the association of cardiovascular serious adverse events with the use of varenicline, two recent meta-analyses have reviewed existing evidence. Whilst findings were not uniform, based on the findings of these reviews, the risk of cardiovascular events associated with the use of varenicline is judged to be minimal and clinically insignificant. Given the effectiveness of varenicline in helping people to stop smoking and the associated reduction in cardiovascular disease risk following smoking cessation, consensus recommendations indicate that the benefits of varenicline outweigh any potential slight increase in cardiovascular events. Patients on varenicline should, as should anyone, seek immediate medical attention if they experience symptoms of myocardial infarction and should contact their doctor if they experience new or worsening of any cardiovascular symptoms.

Key points

1. Background

- Smoking is a major risk factor for cardiovascular disease (CVD); the average person who smokes has about double the risk of developing heart disease prematurely than someone who doesn't smoke[1] and CVD is a leading cause of death among people who smoke[2] as well as a major comorbidity.[3]
- Varenicline is a highly effective smoking cessation aid, more than doubling the chances of stopping smoking.[4,5] When people stop smoking, the excess risk of CVD goes down by about 50% after the first year[6] and the risk of a recurrence of coronary events reverts to that of someone who doesn't smoke within three years.[7]
- Given the enormous benefits of smoking cessation in people with CVD, varenicline has been trialled in this population and shown to be effective.[8] However, given that a number of studies have reported cardiovascular serious adverse events in participants using varenicline, there have been calls for systematic reviews to estimate the potential for varenicline to increase cardiovascular risk.[9] Two such reviews have now been published,[10,11] reporting contradictory findings which are discussed below.

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2. The evidence

2.1 Review 2011[11]

- The authors reviewed 14 double-blind randomised controlled trials; these studies compared the effectiveness of varenicline and a placebo in helping tobacco users to stop smoking. Most of the trials excluded tobacco users with CVD within the last six months; one trial included those with stable CVD.
- A total of 8,216 tobacco users were included in these studies: 4,908 used varenicline and 3,308 used a placebo. The duration of treatment ranged from 7 to 52 weeks and participants were followed-up for between 24 and 52 weeks. In this time, 52 (1.06%) participants in the varenicline group experienced a cardiovascular event and 27 (0.82%) in the placebo group. These included any ischemic or arrhythmic adverse cardiovascular events. The difference between the groups was statistically significant which means that, if the authors only looked at this outcome and no others were considered and not reported, there is less than a 1 in 20 chance that it could have occurred without some real underlying difference (Figure 1).
- The authors conclude that 1 in 28 people who smoke who are treated with varenicline would experience an additional cardiovascular event. However, the difference in the occurrence of cardiovascular events between the varenicline and placebo groups was 0.24% (1.06–0.82) which translates into 1 in 417 people, not 1 in 28.
- An acknowledged source of bias is that the loss to follow-up rate was lower in the varenicline group than the placebo group; so there was more opportunity for adverse events to be detected in the varenicline group and a possibility that events were missed in the placebo group. It is also important to note that with events that are very rare, such as the cardiovascular events, and with imbalanced design, Peto odds ratios, which the main conclusions of this review were based upon, are likely to be biased.[12]

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2.2 Review 2012[10]

- A more recent systematic review and meta-analysis used a number of steps to address some of these concerns and provide a more accurate risk estimate:
  - Since it would be less plausible that varenicline had an effect if the cardiovascular events occurred substantially after the medication was no longer being used, the authors of this review restricted analysis to cardiovascular serious adverse events that occurred during treatment and within 30 days of discontinuation.
  - The authors used a more robust statistic, risk difference, which provides an estimate of absolute effect and has the advantage that (a) studies with no events can be included in analysis and (b) is unbiased when interpreting rare events.[13]
  - As this is a more recent analysis, several new trials of varenicline not covered in the previous review could be included in the meta-analysis.
- The authors reviewed 22 double-blinded and placebo-controlled trials of varenicline in current tobacco users which reported adverse events. Two of these included participants with active CVD and the remaining trials excluded participants with recent manifestation of CVD.
- Trials included a total of 9,232 tobacco users, 5,431 used varenicline and 3,801 were provided with a placebo. The duration of treatment ranged from 6 to 52 weeks with a median follow-up of 16 weeks. The review confirmed that the risk of cardiovascular events was extremely rare for users of both varenicline and the placebo. Within 30 days of discontinuation, 34 (0.63%) participants in the varenicline group experienced a cardiovascular event and 18 (0.47%) in the placebo group. These included any ischemic or arrhythmic adverse cardiovascular events.
- The risk difference in cardiovascular serious adverse events between the groups was very small (0.27%. 95% confidence interval -0.10–0.63, p=0.15) and not statistically significant or clinically meaningful, as the authors conclude. Thus, in contrast to the previous review, it is unlikely that there is real underlying difference in CVD risk between groups.
- Further sensitivity analysis, excluding studies on the basis of different methodology, confirmed this result as did the use of different risk estimates, including Peto odds ratio (see Figure 1).

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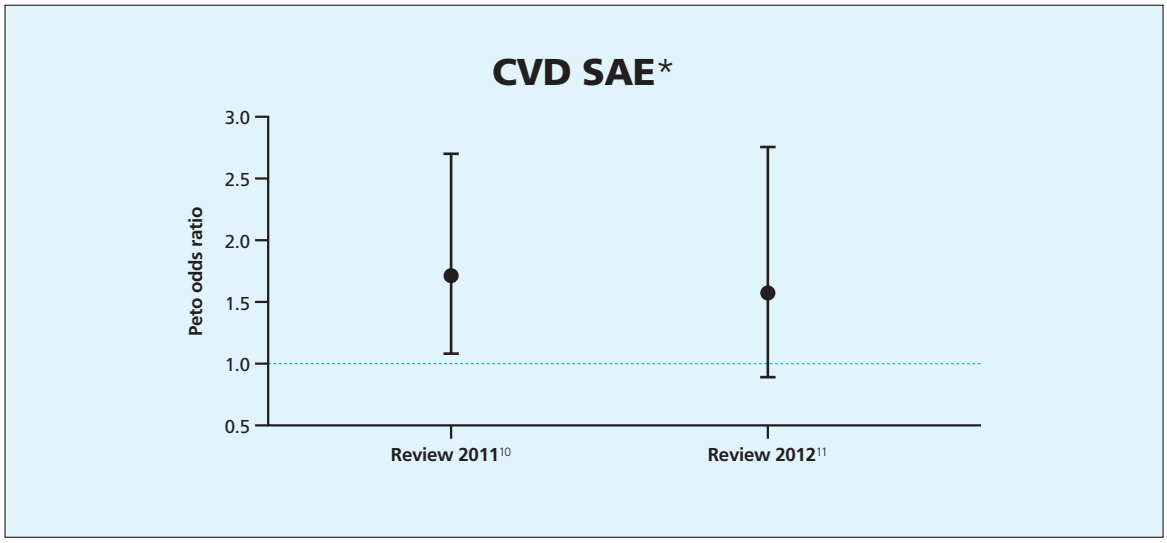
Figure 1: Risk of cardiovascular serious adverse events associated with varenicline use



SAE: Serious adverse event; Error bars indicated 95% confidence interval of estimate
(if error bars cross dotted line, the observed effect is not statistically significant)

2.3 Recent studies

Two studies that have been published since the second review support its conclusion. One of them[14] used data from trials of varenicline and calculated time to any major cardiovascular event in varenicline compared with placebo groups during treatment and up to 30 days after the last dose. There was a trend towards increased incidence of events in the varenicline group that did not reach statistical significance (events: 26/4,190=0.62% in varenicline and 12/2,812=0.43%; risk difference 0.010, 95% CI = -0.002 to 0.022, p=0.11). The overall number of events was low and the absolute risk of cardiovascular events with varenicline was small.

The second study[15] was a nationwide cohort study using Danish registry data on drugs dispensed, cardiovascular events and potential confounders. New users of varenicline and new users of bupropion (total n=35,924) were matched for demographic and medical characteristics. There was no significantly increased risk of any cardiovascular event associated with the use of varenicline compared with bupropion, and the risk of cardiovascular events was not significantly different for those with and without a history of cardiovascular disease.

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3. Conclusion

- Taking the findings of the reviews and the two more recent studies together, there is little reason to avoid this medication on the grounds that use of varenicline increases the risk of cardiovascular events. Based on a review that relied on a more robust methodology to mitigate the impact of biases in studying rare events, results indicate that the risk of such events is very small indeed and likely to be statistically and clinically insignificant.
- This view is in line with the European Medicines Agency that confirmed a positive benefit-risk balance for varenicline and concluded that its benefits as a smoking-cessation medicine outweigh any potential slight increase in cardiovascular events.[16]
- Nevertheless, the Summary of Product Characteristics for varenicline now includes a statement that patients should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke; advice that appears applicable to anyone, regardless of medication.

Conflict of interest statements

Leonie Brose and Eleni Vangeli have no conflicts of interest to declare. Lion Shahab has received an honorarium for a talk and travel expenses from a pharmaceutical company that makes smoking cessation products to attend meetings and workshops. Robert West undertakes research and consultancy for companies that develop and manufacture smoking cessation medications (Pfizer, J&J, McNeil, GSK, Nabi, Novartis and Sanofi-Aventis). He also is a trustee of QUIT, a charity that provides stop smoking support. Andy McEwen has received travel funding, honoraria and consultancy payments from manufacturers of smoking cessation products (Pfizer, GSK and Novartis). He also receives payment for providing training to smoking cessation specialists and receives royalties from books on smoking cessation. Robert West and Andy McEwen have shares in a patent for a novel nicotine delivery device.

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