Woods and Caswell have implied in the previous letter.[2]

On the basis of an article by Hutton,[3] I believe that the interpretation of NNH would be better stated as the average number of comparable patients, which, if they received varenicline rather than placebo for the same period of time, would result in *one* patient being harmed who otherwise would not have been harmed. Since NNH is the inverse of the ARE, its correct value is 1/0.0024, or 417 patients, not 28 patients, as Singh and colleagues propose. By choosing to use the latter figure as the correct NNH, they have greatly overestimated the risk produced by varenicline. The failure to use 417 from their own data as the correct NNH contributes to a flawed analysis, interpretation and, probably, conclusion.

In the data Singh and colleagues cite from an FDA (US Food and Drug Administration) licensure submission,[4] they report that the risk with varenicline was 2.32 per 100 patient years of exposure and with placebo, 1.63 per patient years of exposure. However, the authors stop at this point and do not calculate the ARE of these data (i.e., the difference between these two incidence rates, which equals 0.69 patients per 100 patient years of exposure to varenicline, which again, like the NNH of 417, is an exceedingly small number).

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The meta-analysis by Singh and colleagues tries to quantify the risk of serious adverse cardiovascular events with varenicline.[1] Many representations of this risk have been disseminated, including a large increase (number needed to harm [NNH] 28) extrapolated from applying the odds ratio from an overall meta-analysis to a high-risk group and a small increase (NNH 417) extrapolated from using the absolute numbers (pooled numerators and denominators) from the overall meta-analysis.

The method of interpreting the data can give widely discrepant results. Simple pooling of absolute numbers is inaccurate because it does not account for the variations in the distribution of patients between the varenicline and placebo groups, so results are more affected by how the populations of different trials were distributed rather than the varenicline–placebo difference. However, with the formal meta-analysis, it is not clear that a single trial with a high rate of cardiovascular adverse events (about 6% in a trial of patients with cardiovascular disease) and 13 trials with very low rates of cardiovascular events should be combined in a single meta-analysis.

To estimate the risk of serious adverse cardiovascular events in patients with stable cardiovascular disease, the best estimate may come from an analysis that is based on patients with cardiovascular disease at baseline from across these trials. Until that can be accomplished, the best estimate may be from a single trial in this population,[2] in which the rates of cardiovascular adverse events were 7.04% with varenicline and 5.57% with placebo. The NNH would be 68, but it was not statistically significant.

A meta-analysis of the other 13 trials found a pooled cardiovascular event rate of 0.593% with varenicline and 0.237% with placebo. The Peto odds ratio was 2.54 with a 95% confidence interval (CI) of 1.26 to 5.12. This translates into an NNH range of 103 to 1627 across the 95% CI, using a control event rate of 0.237%.

The risk of serious neuropsychiatric symptoms may be of more concern, with hundreds of reported instances, including 272 completed suicides,[3] but comparative evidence is limited, and no differences were found when compared with other smoking cessation medications.[4]

Of course, risks must be weighed against benefits, with number needed to treat (NNT) of nine for continuous smoking cessation at one year in the trial with the higher cardiovascular event rate[2] and an NNT of six to nine at 24 weeks in a Cochrane review of 10 trials.[5]

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Authors' response

We largely agree with Blankfield[1] that the known elevation of blood pressure seen with varenicline could be one explanation for the increase in serious adverse cardiovascular events.[2] Other possible mechanisms include the vasoconstrictive effects of varenicline because it is a nicotinic acetylcholine receptor agonist.

Takagi and Umemoto argue about the choice of the appropriate method for pooling uncommon events.[3] However, they fail to realize that RevMan automatically adds a 0.5 continuity correction to zero event studies, and this continuity correction biased their reported Mantel–Haenszel estimates toward the null, which is bordering on statistical significance (odds ratio [OR] 1.56, 95% confidence interval 0.99–2.44). They interpret the lack of statistical significance as proof of the cardiovascular safety of varenicline. We chose the Peto–OR estimate because it is the recommended approach for uncommon events, particularly when there are trials with zero events.[4] Sensitivity analyses

using the fixed Mantel–Haenszel approach with appropriate continuity corrections showed similar results with the software package Stats Direct.

Woods and Caswell argue about the choice of reporting relative versus absolute risks.[5] There is scientific and regulatory consensus that uncommon events should be modelled with the relative approach. We reported both relative and absolute risks. Because relative risks are transmitted equally across populations, we applied the pooled OR from our meta-analysis to the baseline event rate among smokers with stable cardiovascular disease to estimate the annual number needed to harm (NNH) among this group. Although our estimated NNH of 28 is applicable only to smokers with stable cardiovascular disease, the meta-analytic OR estimates could be applied to the lower baseline risk among smokers without cardiovascular disease to generate their NNH, which is likely higher.

Squire questions our choice of a population with stable cardiovascular disease when computing the NNH and recalculates the NNH as a reciprocal of the proportion of events in each group.[6] Such an approach treats the summary estimate as a single trial and fails to leverage the benefits of randomization.

We partly agree with Alper that the method of interpreting the data can give discrepant results.[7] However, all these results demonstrate the presence of a cardiovascular risk with varenicline. We also agree that boxed warnings about the serious neuropsychiatric effects of varenicline such as depression, suicidal behaviour, suicidal ideation, hostility and aggression should be factored into a risk–benefit assessment. Data from randomized controlled trials would be ideal, but the proposed 12-week post-marketing safety trial to assess these serious risks of varenicline among smokers with psychiatric problems will not be completed until 2016, about 10 years after regulatory approval.[8]

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Varenicline: cardiovascular safety

Serious methodologic issues limit the reliability and relevance of the results of the analysis by Singh and colleagues, in which they reported an "increased risk of serious adverse cardiovascular events" associated with varenicline based on a meta-analysis of 14 studies.[1]

First, the authors did not use a composite endpoint that is typically used in the medical literature to evaluate cardiovascular safety by, for example, including arrhythmias like atrial fibrillation. Such arrhythmias are not included in conventional definitions of major cardiovascular events because they generally are not associated with hemodynamic instability. The inclusion of atrial arrhythmias allowed Singh and colleagues to add seven events to the varenicline group but only one to the placebo group.

Second, the authors selected cardiovascular events in a manner that was inconsistent with their own methods. For example, they stated that they would include only patients with unstable angina, but they included patients who had any report of angina. Ischemic peripheral vascular events were not part