Varenicline: quantifying the risk

The finding by Singh and colleagues that varenicline is associated with an increased risk of serious adverse cardiovascular events[1] is not surprising because varenicline is frequently associated with hypertension.[2,3] An elevation in blood pressure, however small, increases the risk of adverse cardiovascular outcomes.[4] Before approving varenicline, the US Food and Drug Administration (FDA) should have mandated that the manufacturer provide the FDA with data on cardiovascular safety.

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References

1. Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;183:1359-66.
2. *Physician's desk reference*. 64th ed. Montvale (NJ): Thomson; 2010. p. 2715.
3. *Drug facts and comparisons*. St. Louis (MO): Facts and Comparisons; 2011. p. 1115.
4. Weber MA. The ALLHAT report: a case of information and misinformation. *J Clin Hypertens (Greenwich)* 2003;5:9-13.

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Singh and colleagues found that varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] in the group receiving varenicline v. 0.82% [27/3308] in that receiving placebo (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.09–2.71).[1] They used the Peto method to calculate ORs and 95% CI, stating that the Peto method provides the best CI coverage and is more powerful and relatively less biased than the random-effects analysis when dealing with low event rates.

The approximation used to calculate the log OR works well when the effects of intervention are small (i.e., ORs are close to 1.0), events are not particularly common and the studies have similar numbers in the experimental and control groups.[2] As these criteria are not always fulfilled, the Peto method is not recommended as a default approach for analysis because it has been shown to give biased answers. On the other hand, when data are sparse (event rates are low or study size is small), Mantel–Haenszel methods have been shown to have better statistical properties.[2]

Sensitivity analyses by Singh and colleagues using the reciprocal of the treatment arm with a continuity correction (fixed Mantel–Haenszel OR 1.67, 95% CI 1.06–2.64) or without a continuity correction (fixed Mantel–Haenszel OR 1.77, 95% CI 1.09–2.88) showed results similar to those in the preliminary analysis using the Peto method. However, our recalculation of the same dataset as those in Figure 2 in Singh and colleagues' article using RevMan showed a statistically insignificant increase in serious adverse cardiovascular events with varenicline compared with placebo (fixed Mantel–Haenszel OR 1.56, 95% CI 0.99–2.44).

This should be a proper result of the primary analysis in the meta-analysis. Therefore, there are no safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with the use of varenicline among tobacco users.

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References

1. Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;183:1359-66.
2. Deeks JJ, Higgins JP, Altman DG, editors. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editors. *Cochrane handbook for systematic reviews of interventions version 5.1.0* (updated March 2011). Available: www.cochrane-handbook.org (accessed 2011 July 5).

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We agree that there is a lack of clarity in Singh and colleagues' article; it is very difficult for readers to follow how the various assumptions and extrapolations have been made.[1]

The rather alarming figure of a 72% increase in serious cardiovascular events has been picked up by the media. However, in absolute terms, the increase in risk is only 0.24%, which computes to an NNH (number needed to harm) of about 400. This is a very small increase in risk compared with the benefits of quitting smoking (number needed to treat 10 for varenicline).

Admittedly, Singh and colleagues' study may signal the need for caution when using varenicline in patients with a history of cardiovascular or active disease. The authors need to offer more explanation about how they reached the estimate of NNH of 28, which appears to be an extrapolation of their findings to a population at very high risk of cardiovascular disease.

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Reference

1. Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;183:1359-66.

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In their sophisticated review and meta-analysis, Singh and colleagues calculated the absolute risk for varenicline as 1.06% and that for placebo at 0.82%.[1] Hence, the correct absolute risk elevation (ARE) is the difference between the two percentages (0.24%, or 0.0024), which they also calculated correctly.

However, in their interpretation, Singh and colleagues chose to use pooled data in a way that was inconsistent with how NNH (number needed to harm) should have been calculated. They used a baseline cardiovascular risk of 5.57% — not the rate of cardiovascular events in the placebo groups of their meta-analysis — as the comparison group with varenicline. Doing so created problems with their subsequent analysis, interpretation and conclusion.

The problem was in part caused by their having combined their data with other data before coming to a conclusion. They used ARE as a summary statistic, then expressed it incorrectly. This highlights why NNH, as a summary statistic itself, is inferior to ARE, as