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

Sonal Singh MD MPH

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Yoon K. Loke MBBS MD

School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

John G. Spangler MD MPH

Department of Family and Community Medicine

Curt D. Furberg MD PhD

Division of Public Health Sciences
Wake Forest University School of Medicine, Winston-Salem, NC

References

1. Blankfield R. Varenicline: quantifying the risk. *CMAJ* 2011;183:1404.
2. 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.
3. Takagi H, Umemoto T. Varenicline: quantifying the risk. *CMAJ* 2011;183:1404.
4. 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 Aug. 2).
5. Woods DJ, Caswell MD. Varenicline: quantifying the risk. *CMAJ* 2011;183:1404.
6. Squire EN. Varenicline: quantifying the risk. *CMAJ* 2011;183:1404-5.
7. Alper BS. Varenicline: quantifying the risk. *CMAJ* 2011;183:1405.
8. US Food and Drug Administration. *Postmarket requirements and commitments*. Available: www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=3&StepSize=1&Paging=Yes (accessed 2011 Aug. 2).

CMAJ 2011. DOI:10.1503/cmaj.111-2072

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

of their defined endpoint, yet in their counts for the Rigotti study,² Singh and colleagues included such events. They also planned to include only events reported during the double-blind period of each trial, but they included a number of events that occurred during the follow-up phase when the patients were no longer receiving drug treatment.

Third, Singh and colleagues failed to address potential statistical biases in their analysis. For example, the rate of patients lost to follow-up in most studies was greater in the placebo arm than in the varenicline arm. Furthermore, the authors excluded zero-event trials. Although this does not affect the relative risk, doing so distorts risk estimates, especially when the trials with zero events were designed to allocate more patients to varenicline than to placebo (e.g., 2:1 or 3:1 randomization).

In a July 2011 press release, the European Medicines Agency also noted “a number of limitations” in Singh and colleagues’ meta-analysis, including “the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which no-one had an event.”³

Pfizer is working with the US Food and Drug Administration to conduct a meta-analysis that will address many of the methodologic deficiencies in the meta-analysis by Singh and colleagues. This analysis will ensure that investigator-reported events are adjudicated by a committee of cardiovascular experts who are blinded to treatment to ensure correct diagnosis. We will publicly disclose the results when the analysis is completed.

Larry Samuels PhD

Senior Medical Director, Pfizer Inc., New York, NY

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. Rigotti NA, Pipe AL, Benowitz NI, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation* 2010;121:221-9.
3. European Medicine Agency Press Release. *European Medicines Agency confirms positive benefit-risk balance for Champix. Benefits as a smoking-cessation medicine outweigh slight reported*

increase in cardiovascular events. Available: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001314.jsp&mid=WC0b01ac058004d5c1&url=menus/news_and_events/news_and_events.jsp&jsearch=true (accessed 2011 July 25).

CMAJ 2011. DOI:10.1503/cmaj.111-2073

Authors’ response

In response to the sponsor’s (Pfizer’s) comments¹ about our analysis,² we reiterate the statement in the safety review by the US Food and Drug Administration (FDA): “The serious adverse event data suggest that varenicline may increase the risk of cardiac events, both ischemic and arrhythmic, particularly over longer treatment periods.”³ Because the sponsor never conducted adequately powered trials to determine whether varenicline increases the risk of cardiovascular events, a meta-analysis was conducted using available data.

It is true that the numbers of events in our analysis were small. However, that is because most of the trials were small and therefore underpowered to determine drug safety. Nevertheless, in spite of the small numbers, the difference in treatment groups was statistically significant. When statistically significant differences exist, the number of events is less relevant. A small number of events requires a larger difference to reach statistical significance.

We adhered to the intention-to-treat (ITT) analysis and counted events throughout the scheduled duration of each trial. This is in accordance with FDA regulations and established and generally accepted scientific principles. Although pharmaceutical companies might prefer to analyse data by treatment level, such an analysis would allow exclusion of events occurring in randomized patients. This practice to make unfavourable findings appear more favourable is subject to potentially serious bias. In addition, by adhering to the ITT principles, noncompliance becomes a nonissue. Thus, the higher drop-out rate in the placebo group is irrelevant.

Our statistical analysis dealt with the trials with no events. According to the Cochrane handbook, “The standard practice in meta-analysis of odds ratios and risk ratios is to exclude studies from the

meta-analysis where there are no events in both arms. This is because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect.”⁴ Sensitivity analyses with the fixed Mantel-Haenszel approach showed similar results.

We wanted to analyse the serious adverse event data by time after randomization. This was not possible because most trials failed to report time to the event. If the harmful effects of varenicline are limited to the period of active treatment, the data from the post-treatment phase would dilute these effects. In addition, any reduction in cardiovascular risk attributed to varenicline would also lead to an underestimation of the on-treatment harm. Post-hoc adjudication of investigator-reported cardiovascular events can only lead to reduction in events and statistical power.

It would be unfortunate if the FDA’s proposed review of the safety of varenicline³ were to be handled by the sponsor or its paid consultants. The scientific literature is replete with examples in which such conflicts of interest have impeded independent and fair analysis of drug safety.

Sonal Singh MD MPH

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Yoon K. Loke MBBS MD

School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

John G. Spangler MD MPH

Department of Family and Community Medicine

Curt D. Furberg MD PhD

Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

References

1. Samuels L. Varenicline: cardiovascular safety. *CMAJ* 2011;183:1407-8.
2. 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.
3. US Food and Drug Administration. *Postmarket requirements and commitments*. Available: www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=3&StepSize=1&Paging=Yes (accessed 2011 Aug. 2).
4. 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 Aug. 2).

CMAJ 2011. DOI:10.1503/cmaj.111-2074