Review: Varenicline for tobacco cessation does not increase CV serious adverse events

Prochaska JJ, Hilton JF. ***Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis.*** *BMJ. 2012;344:e2856.*

Clinical impact ratings: GM ★★★★★★☆ C ★★★★★☆☆

Question

Does use of varenicline for tobacco cessation increase risk for treatment-emergent, cardiovascular (CV) serious adverse events in adult tobacco users?

Review scope

Included studies compared varenicline with an inactive control in current adult tobacco users and reported adverse events. The primary outcome was treatment-emergent, CV serious adverse events defined as any ischemic or arrhythmic adverse CV event (myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmia, transient ischemic attack, stroke, sudden death or CV-related death, or congestive heart failure) occurring during drug treatment or within 30 days of drug discontinuation.

Review methods

MEDLINE, Cochrane Library, ClinicalTrials.gov, and Clinical Study Results registry (all 2005 to Sep 2011), reviews, and reference lists were searched for randomized controlled trials (RCTs). 22 RCTs (n = 9232, 49% to 100% men, median treatment duration 12 wk, median follow-up for adverse events 16 wk, median study duration 25 wk) met selection criteria. For 3 RCTs, the drug manufacturer (Pfizer) or study authors were contacted for data on timing of CV serious adverse events. 20 RCTs included cigarette smokers, and 2 RCTs included smokeless tobacco users. 13 RCTs included patients with current or past CV disease; 9 RCTs excluded patients with history of CV disease or did not specify timing of CV history for exclusion. Varenicline dose was 1 mg twice daily in 21 RCTs, and 3 of these RCTs also included lower doses. 1 RCT assessed varenicline, 1 mg, once daily. All RCTs were double-blind and had adequate descriptions of randomization, loss to follow-up, and CV serious adverse events.

Main results

Varenicline did not increase CV serious adverse events compared with placebo (Table).

Varenicline vs placebo for tobacco cessation in adult tobacco users*

Outcome	Number of trials (n)	Weighted event rates		At a median 16 wk	
		Varenicline	Placebo	RRI (95% CI)	Risk difference (CI)
CV serious adverse events†	22 (9232)	0.66%	0.47%	40% (–18 to 139)	0.27 (–0.10 to 0.63)

**CV = cardiovascular; other abbreviations defined in Glossary. Weighted event rate, RRI, and CI calculated from control event rate and relative risk in article using a fixed-effect model. 8 randomized controlled trials (n = 1596) with 0 events in both groups were included in the calculation of the control event rate but not in the calculation of the RRI.*

†Any ischemic or arrhythmic adverse CV event (myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmia, transient ischemic attack, stroke, sudden death or CV-related death, or congestive heart failure) occurring during drug treatment or within 30 days of drug discontinuation.

Conclusion

In adult tobacco users, varenicline for tobacco cessation did not increase treatment-emergent, cardiovascular serious adverse events compared with placebo.

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Commentary

Varenicline is effective for smoking cessation, but safety concerns about CV events have been reported. The review by Prochaska and Hilton responds to a request by the US Food and Drug Administration for a review of varenicline use and CV events. The authors used appropriate meta-analytic and review methods, with inclusion and exclusion criteria, independent ratings, quality coding, and bias and sensitivity analyses. The review identified 22 double-blind, placebo-controlled RCTs. Risk for CV events did not differ between the groups; the risk for a CV event was 0.66% with varenicline and 0.47% with placebo, a nonsignficant difference in an analysis that was highly powered, supporting with some confidence that varenicline does not increase risk for CV events.

The review has some limitations. First, the authors did not separately examine risk among the 13 studies that included only patients with a history of CV disease, thus reducing the applicability of the findings to patients with CV disease. Second, studies included mostly white men, restricting the generalizability of the results to other populations. Third, the authors combined studies with varying follow-up, which was necessary for the analysis but somewhat affects the accuracy of the risk estimates.

In summary, any increase in CV events with varenicline is probably small and would be overshadowed by the reduced risk associated with smoking cessation, particularly because the odds of successful smoking cessation with varenicline are higher than for any other monotherapy (1). It seems that varenicline is generally safe for patients with CV disease, and efforts to help patients stop smoking can ultimately reduce risk for CV events.

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Reference

1. **Fiore MC, Jaén CR, Baker TB, et al.** Treating tobacco use and dependence: 2008 update. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service; May 2008. www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf (accessed 28 Jun 2012).

