# Varenicline and cardiovascular adverse events: a perspective review

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***Abstract*:** Smoking is a leading preventable cause of mortality and morbidity. Varenicline, a first-line smoking cessation aid, is used widely to achieve successful quit rates in smokers. A number of studies and systematic reviews have evaluated the safety profile of the drug. To date, three systematic reviews by Singh and colleagues, Prochaska and Hilton, and Ware and colleagues, published between 2011 and 2013, have evaluated serious cardiovascular adverse events with varenicline use. Even though all three reviews demonstrated that serious cardiovascular adverse events were nominally more frequent in varenicline-treated patients when compared with placebo, a significantly increased event rate was found only in the review by Singh and colleagues. The three reviews included similar trials but differed in the evaluation of outcomes and performance of summary statistic computation. Though the evidence from the two most recent systematic reviews demonstrated that risk of serious cardiovascular events might not be increased with varenicline use, the US Food and Drug Administration has advised prescription with caution combined with close monitoring and education of patients until more conclusive evidence is available. Results of these reviews cannot be generalized to patients with unstable cardiac conditions.

***Keywords:*** adverse events, cardiovascular, Champix, Chantix, review, varenicline

## Introduction

Smoking is the foremost preventable cause of death and disease in the United States. The ill effects of smoking are widespread within the human body, sparing no tissue or organ. According to the Surgeon General's Report 2004, smoking is identified to have a causal relationship in the development of many cancers, cardiovascular, respiratory and reproductive illnesses [US Surgeon General, 2004].

The benefits of smoking cessation are immediate and multifold. Patients with coronary heart disease experienced a reduction in rates of mortality and non-fatal myocardial infarction on quitting smoking [Critchley and Capewell, 2003, 2004]. National and international healthcare agencies have advocated for smoking cessation programs to be made readily available to motivated smokers. In 2008, the US Public Health Service published clinical practice guideline recommendations for smoking cessation. Counseling, social support, quit lines, nicotine and non-nicotine medications formed the nucleus of these recommendations [US Public Health Service, 2008].

Varenicline (trade name Chantix® and Champix®) is a first-line medication used in smoking cessation. It is derived from cytisine, a naturally occurring compound that has been utilized for smoking cessation in Bulgaria and other European countries. This compound acts as partial agonist at the α4-β2 nicotinic acetylcholine receptors, thereby preserving the rewarding effects caused by smoking and simultaneously eliminating the addictive potential [Rollema *et al.* 2007; Fagerstrom and Hughes, 2008]. A number of clinical trials and reviews have assessed the effectiveness of varenicline in achieving smoking cessation. In a recent systematic review by Mills and colleagues, the effectiveness of high dose or combination nicotine replacement therapies was compared to standard dose patch, varenicline and buproprion [Mills *et al.* 2012]. When compared with other interventions, varenicline was associated with a statistically significant quit rate at 3 and 12 months.

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**Table 1.** Studies included in the three systematic reviews.

| Singh *et al*. [2011] | Prochaska and Hilton [2012] | Ware *et al*. [2013] |
|---|---|---|
| Gonzales (2006) | Gonzales (2006) | Gonzales (2006) |
| Jorenby (2006) | Jorenby (2006) | Jorenby (2006) |
| Oncken (2006) | Oncken (2006) | Oncken (2006) |
| Tonstad (2006) | Tonstad (2006) | Tonstad (2006) |
| Nakamura (2007) | Nakamura (2007) | Nakamura (2007) |
| Niaura (2007) | Niaura (2007) | Niaura (2007) |
| Tsai (2007) | Tsai (2007) | Tsai (2007) |
| Williams (2007) | Williams (2007) | Williams (2007) |
| Fagerstrom (2010) | Fagerstrom (2010) | Fagerstrom (2010) |
| Rigotti (2010) | Rigotti (2010) | Rigotti (2010) |
| Tashkin (2010) | Tashkin (2010) | Tashkin (2010) |
| Nides (2006) | Nides (2006) | Wang (2009) |
| Protocol A3051080 (2010) | Wang (2009) | Bollinger (2011) |
| Protocol A3051095 (2010) | Bollinger (2011) | Garza (2011) |
| | Garza (2011) | Rennard (2012) |
| | Rennard (2012) | Williams (2012) |
| | Protocol A3051072 | |
| | Steinberg (2011) | |
| | Ebbert (2011) | |
| | Hong (2011) | |
| | Hughes (2011) | |
| | Poling (2010) | |

The US Food and Drug Administration (FDA) approved varenicline in May 2006. The priority safety review published in 2006 found that varenicline treated patients experienced serious cardiovascular adverse events more commonly than placebo patients [Pfizer, 2006]. In 2010, a post-marketing experience report published by the FDA highlighted the case reports of myocardial infarctions and cerebrovascular accidents that occurred in patients treated with varenicline; however the role of smoking itself contributing to these events in smokers could not be ruled out [Pfizer, 2010]. In 2011 and 2013, further revisions to the marketing label highlighted results of individual studies and reviews that studied cardiovascular events in patients using varenicline [Pfizer, 2011, 2013].

## Methods

Systematic reviews of cardiovascular adverse events of varenicline were identified using the keyword 'varenicline' in MEDLINE and Cochrane Central Register of Controlled Trials databases through October 2013. We identified three systematic reviews and a Cochrane report that evaluated cardiovascular adverse events with varenicline use for smoking cessation. The three systematic reviews exclusively studied the association of varenicline with serious cardiovascular adverse events [Singh *et al.* 2011; Prochaska and Hilton, 2012; Ware *et al.* 2013]. The individual studies included in these systematic reviews are listed in Table 1. Results of the systematic reviews are illustrated in Table 2. The Cochrane review published in 2013 assessed safety of pharmacological smoking cessation aids in addition to efficacy in quit rates [Cahill *et al.* 2013]. In this review, we discuss systematic reviews that evaluated serious cardiovascular adverse events associated with use of varenicline as a smoking cessation aid.

## Systematic reviews of cardiovascular adverse events with varenicline

### *Singh and colleagues, 2011*

In 2011 Singh and colleagues conducted a systematic review and meta-analysis of 14 double blinded placebo-controlled randomized controlled trials (RCTs) [Singh *et al.* 2011]. An open label trial was included only for sensitivity analysis comparing placebo with active medications. The primary outcome of this review was any ischemic or arrhythmic cardiovascular event reported by investigators of the individual studies during the study period. All-cause mortality was evaluated as a secondary outcome.

**Table 2.** Systematic reviews of varenicline.

| Study | Studies included | Duration of treatment | No. of participants (varenicline) | No. of participants (placebo) | No. of participants with events (varenicline) | No. of participants with events (placebo) | Outcome for serious cardiovascular adverse event: varenicline vs. placebo |
|---|---|---|---|---|---|---|---|
| Singh *et al.* [2011] | 14 double-blind placebo-controlled RCTs | Range: 7–52 weeks | 4908 | 3308 | 52 | 27 | Peto OR (95% CI) 1.72 (1.09–2.71) |
| Prochaska and Hilton [2012] | 22 double-blind placebo-controlled RCTs | Median: 12 weeks | 5431 | 3801 | 34 | 18 | Risk difference: 0.27% (–0.10% to 0.63%, $p = 0.15$, $I^2 = 0\%$) Relative risk of at least one event (14 studies): 1.40 (0.82–2.39, $p = 0.22$, $I^2 = 0\%$) Mantel-Haenszel OR: 1.41 (0.82–2.42, $p = 0.22$, $I^2 = 0\%$) Peto OR: 1.58 (0.90–2.76, $p = 0.11$, $I^2 = 0\%$). |
| Ware *et al.* [2013] | 15 double-blind placebo-controlled RCTs | Range: 12–52 weeks | 4190 | 2812 | MACE+: 26 MACE:13 | MACE+: 12 MACE: 6 | MACE+: HR: 1.951 (95% CI: 0.789–4.823) Risk difference: 0.010 (95%CI: -0.002 to 0.022) MACE+: HR: 1.740 (95% CI: 0.905–3.343) Risk difference: 0.006 (95%CI: -0.002 to 0.015) |

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; OR, odds ratio; RCT, randomized controlled trial.

A total of 8216 participants were included in the 14 double-blinded RCTs; 4908 participants received varenicline and 3308 received placebo. The duration of treatment in these studies ranged from 7 weeks to 52 weeks, and the follow up period from 24 to 52 weeks. All 14 trials excluded participants with unstable cardiovascular disease. Nine trials were at low risk of bias. Trials suffered losses to follow up, which was consistently higher in the placebo group.

Overall, 52 serious cardiovascular events occurred in the varenicline groups. The corresponding number for the placebo group was 27. The meta-analysis demonstrated that varenicline use was associated with a significant increase in serious cardiovascular events compared with placebo [Peto odds ratio (OR) 1.72, 95% confidence interval (CI) 1.09–2.71; $I^2$= 0%]. Sensitivity analyses were conducted for the reciprocal of the treatment arm with a continuity correction, including active comparator in analysis, excluding Rigotti and colleagues which contributed 57.3% of weight in the meta-analysis, excluding trials with varenicline doses of less than 1 mg twice daily. None of the sensitivity analyses differed from the results of primary analysis. A funnel plot was conducted to exclude the possibility of publication bias.

### *Prochaska and Hilton, 2012*

In 2012 Proschaska and Hilton published the results of their systematic review which included 22 double-blinded and placebo-controlled RCTs with 9232 participants [Prochaska and Hilton, 2012]. Only events occurring during the treatment period or within 30 days of stopping

treatment were considered. Varenicline was prescribed at a dose of 1 mg twice daily in 21 trials. The median duration of treatment was 12 weeks and follow up for serious events was 16 weeks. Of the 21 trials, 11 excluded participants with a history of cardiovascular disease.

The crude rates of serious cardiovascular event were 0.63% in varenicline group and 0.47% in the placebo group. In eight trials there were zero events in both groups. The risk difference was 0.27% which was nonsignificant (-0.10% to 0.63%, $p = 0.15$, $I^2 = 0\%$). The relative risk (RR) carried out in 14 studies with at least one event was 1.41 (0.82–2.42, $p = 0.22$, $I^2 = 0\%$) and Peto OR was 1.58 (0.90–2.76, $p = 0.11$, $I^2 = 0\%$). Sensitivity analysis after excluding participants with active cardiovascular disease did not differ from the final conclusions.

### *Ware and colleagues, 2013*

In 2013 Ware and colleagues, in consultation with the FDA, conducted a systematic review of all phase II, III and IV clinical trials sponsored by Pfizer [Ware *et al.* 2013]. A total of 15 blinded, placebo-controlled RCTs were included. Studies had varying exclusion criteria with regard to the presence of cardiovascular disease in the participants. The treatment period was 12 weeks in all but one study. The follow-up duration ranged between 4 months and 52 weeks.

Two endpoints were defined as outcomes of interest in this review: major adverse cardiovascular event (MACE) that included death, nonfatal myocardial infarction and stroke; and MACE+ which was defined as 'MACE plus new onset, worsening or procedure for peripheral vascular disease, hospitalization for unstable angina, and performance of coronary revascularization'. Baseline cardiovascular risk was also assessed in all participants. An independent committee was set up to adjudicate all cardiovascular events and deaths.

There were 4190 participants in the varenicline group and 2812 in the placebo group. Time-to-event meta-analysis was conducted for MACE and MACE+ outcomes individually. The hazard ratio (HR) for MACE+ and MACE were 1.74 (95% CI: 0.91–3.34; $p = 0.10$) and 1.95 (95%CI: 0.79–4.82; $p = 0.15$) respectively. Risk difference calculated for MACE+ was 0.01 events per subject-year (95% CI: -0.002 to 0.002, $p = 0.11$) and that for MACE was 0.006 events per subject-year (95% CI: -0.002 to 0.015; $p = 0.16$). Three deaths were observed during the treatment period, one in the varenicline group and two in the placebo group. When stratified by baseline risk score, the occurrence of MACE+ events were increased in participants with a high baseline cardiovascular risk score. However, the risk interaction was not statistically significant.

### *Cochrane, 2013*

Cochrane recently published a systematic review on the efficacy and safety of pharmacological interventions for smoking cessation [Cahill *et al.* 2013]. Randomized controlled trials and post-marketing surveillance data were included for the assessment of harm. A total of 15 placebo-controlled RCTs, 2 trials of maintenance of quit rates and 2 open-label trials of varenicline *versus* nicotine patches were included in this review. A cardiovascular adverse event subgroup analysis demonstrated that there was no difference in event rates between varenicline and placebo arms, RR 1.26 (95% CI 0.62–2.56); 0.6% of participants treated with varenicline experienced a cardiovascular adverse event compared with 0.5% in placebo participants.

## Discussion

Three independent systematic reviews have consistently demonstrated that serious cardiovascular adverse events occurred more frequently in the varenicline treated group compared with placebo [Singh *et al.* 2011; Prochaska and Hilton, 2012; Ware *et al.* 2013]. Individual studies included in the three reviews were similar; the trial by Rigotti and colleagues that contributed most in terms of weight to the meta-analyses was included in all three reviews [Rigotti *et al.* 2010]. Nevertheless, the difference in event rates was not significant in two reviews.

Singh and colleagues studied the occurrence of serious adverse events throughout treatment and follow-up periods. This aspect of the review allowed the inclusion of events occurring not only during the duration of the trial but also during periods in which participants were not on varenicline. In addition, many trials included in this review are at risk of attrition bias as the dropout rate in placebo groups was high compared with treatment arms, thus compromising the validity of study results. None of the trials included in this

review were adequately powered, thus contributing to imprecision in effect estimates. This review used the Peto OR approach which gives zero weight to trials that do not report on cardiovascular events. The authors of the review identified important limitations that challenged the strength of their conclusions. They identified imprecision in their estimates of effect sizes due to low event rates and inadequately powered studies. The results of this review were deemed invalid in patients with unstable cardiovascular diseases.

Prochaska and Hilton and Ware and colleagues tried to address a limitation in the earlier review by capturing treatment emergent adverse events alone, i.e. serious cardiovascular adverse events occurring during the treatment phase or within 30 days of discontinuation. A sensitivity analysis conducted by the Ware and colleagues showed no difference in risk difference when events occurring 30 days post-treatment phase were included in the meta-analysis. Another interesting aspect of the review by Ware and colleagues was adjudication of adverse events. Out of 173 probable serious cardiovascular events from the included 15 placebo-controlled trials, only 93 were arbitrated to be a MACE or MACE+. The 2013 Cochrane review evaluated the risk of all cardiovascular adverse events with varenicline use, hence its results cannot be compared with the other three reviews that estimated serious cardiovascular events as their outcomes of interest.

The choice of summary statistic plays a crucial role in the estimation of effect sizes [Keus *et al.* 2009]. The three reviews were different in their measurement of outcomes and choice of summary statistics. Singh and colleagues with their estimation of OR concluded that there was a significant increase in risk of serious cardiovascular events in the varenicline group. In contrast, Prochaska and Hilton estimated the risk difference for treatment emergent adverse events. They also reported the OR and RR estimates for studies with events and none of the estimates achieved statistical significance. Ware and colleagues also adopted estimation of risk difference in addition to HR. The choice of summary statistic plays a crucial role in the estimation of effect. According to the Cochrane Hepato-Biliary Group review in 2009, the choice of summary statistic, inclusion or exclusion of zero events, type and size of continuity correction, fixed-or-random effect models would influence the conclusions of the meta-analysis [Keus *et al.* 2009].

Varenicline is a highly effective first-line smoking cessation aid. But in the light of evidence showing increased risk of cardiovascular adverse events, it is advised that clinicians exert caution when prescribing varenicline particularly in patients with cardiovascular disease. While Prochaska and Hilton claimed that risk of cardiovascular events was minimal and that undue caution and alarm among physicians and patients may be unwarranted, Singh and colleagues recommended clinicians to be cautious in prescription of varenicline. Some points in favor of wielding caution in prescription of varenicline are increase in cardiovascular event rates in varenicline-treated patients in all three reviews and risk of other known serious neuropsychiatric events such as depression, agitation and suicidal behavior. The FDA has also advised careful monitoring and education of patients on varenicline.

## Conclusion

The available evidence from the meta-analyses raises the possibility but do not prove that varenicline is associated with increased risk of cardiovascular events. Health risk to benefit assessment should guide clinicians in decision making. Caution and careful monitoring of patients is warranted.

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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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