Cardiovascular Events Associated with Smoking Cessation
Pharmacotherapies: A Network Meta-Analysis

Running title: Mills et al.; Cardiovascular events and stop smoking therapies

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Abstract

Background—Stopping smoking is associated with many important improvements in health and quality of life. Use of cessation medications is recommended to increase the likelihood of quitting. However, there is historical and renewed concern that smoking cessation therapies may increase the risk of cardiovascular disease (CVD) events associated within the quitting period. We aimed to examine whether the three licensed smoking cessation therapies: nicotine replacement therapy (NRT); bupropion, and; varenicline and were associated with an increased risk of CVD events using a network meta-analysis.

Methods and Results—We searched ten electronic databases, and made communication with authors of published randomized clinical trials (RCT), and accessed internal US Food and Drug Administration (FDA) reports. We included any RCT of the 3 treatments that reported on CVD outcomes. Among 63 eligible RCTs involving 21 NRT RCTs, 28 bupropion RCTs and 18 varenicline RCTs, we found no increase in the risk of all-CVD events with bupropion (RR 0.98, 95% Confidence Intervals [CIs], 0.54-1.73) or varenicline (RR 1.30, 95% CI, 0.79-2.23). There was an elevated risk associated with NRT that was predominantly driven by less serious events (2.29, 95% CI, 1.39-3.82). When we examined major adverse cardiovascular events (MACE) events, we found a protective effect with bupropion (RR 0.45, 95% CI, 0.21-0.85) and no clear evidence of harm with varenicline (RR 1.34, 95% CI, 0.66-2.66) or NRT (RR 1.95, 95% CI, 0.26-4.30).

Conclusions—Smoking cessation therapies do not appear to raise the risk of serious CVD events.

Key words: meta-analysis, statistical analysis, smoking, Smoking cessation, Bayesian, Meta-analysis, Pharmacotherapies, Randomized trials
Introduction

Smoking is the leading preventable cause of death around the world.\(^1\) Approximately 50% of long-term smokers will die a smoking-related death.\(^2\) Early cessation of smoking is associated with important increases in life expectancy, improved quality of life and reduced health care costs for smoking associated conditions.\(^2\) Chief among the benefits of smoking cessation are improved cardiovascular health.\(^3, 4\) For these reasons, clinical practice guidelines in the US recommend the use of smoking cessation pharmacotherapies with all adult smokers interested in quitting unless contraindicated.\(^5, 6\)

In North America, there are three approved first-line classes of therapies: nicotine replacement therapy (NRT); bupropion, an antidepressant, and; varenicline, a nicotine receptor partial agonist. Many randomized clinical trials and systematic reviews have demonstrated these agents as effective for promoting smoking cessation.\(^7, 8\) The medications have different mechanisms of action and side effect profiles. All have undergone some scrutiny for potential cardiovascular effects when coming onto the market. When NRT first came onto the market, there were concerns in the literature and popular press about its safety profile with regard to cardiovascular events, particularly among users who continued to smoke.\(^9\) Clinical trials and laboratory research that followed indicated NRT was safe even with high dose patch, combination NRT, and concurrent smoking.\(^10-12\) With bupropion, three trials consisting of 792 total smokers with cardiovascular disease (CVD) reported greater cardiovascular events among participants assigned to active versus placebo drug; the differences were not statistically significant, however, the trials were not powered for safety.\(^13-15\) Similar concerns have been raised about varenicline. In 2011, a meta-analysis by Singh et al. involving 8216 participants reported that varenicline use may be associated with increased minor and major cardiovascular
events (odds ratio [OR] 1.72, 95% confidence intervals [CIs], 1.09-2.71), a finding at odds with the goal of smoking cessation that garnered a great deal of media attention.\(^1^6\) A follow-up meta-analysis found the difference between varenicline and placebo to be statistically and clinically nonsignificant.\(^1^7\)

Recognizing the large number of smokers attempting to quit by using pharmacotherapies, and the widespread media reports of cardiovascular risks associated with pharmacotherapies, making clear public health messages remains a priority. At the request of the FDA, the drug maker (Pfizer Inc) recently conducted a meta-analysis based on major adverse cardiovascular events (MACE), that were defined as cardiovascular death, nonfatal MI, and nonfatal stroke.\(^1^8\) Using individual patient data from industry sponsored randomized clinical trials (RCTs), the Hazard ratio [HR] was not significant (HR=1.95, 95% CI 0.79, 4.82). The most recent FDA safety communication on varenicline from December 2012 indicates the events were uncommon both in active and placebo drug conditions and the increased risk was not statistically significant. Similarly, an FDA mini-sentinel evaluation evaluating CVD events among 89,519 varenicline users and 113,378 bupropion users found no difference in CVD event risk between varenicline and bupropion (incidence rate ratio 1.02, 95% CI, 0.71-1.47).\(^1^9\)

The concern about varenicline has led investigators to more closely examine the other pharmacotherapies. A large cohort study found no difference in CVD events between varenicline and bupropion among a nationwide study in Denmark (HR, 0.96, 95% CI, 0.67 to 1.39).\(^2^0\) A meta-analysis examining only NRT found an increased risk for less serious cardiovascular events, such as tachycardia and non-specific chest pain, but did not examine MACE.\(^2^1\) Notably, few of the RCTs have been conducted within populations with secondary CVD risk profiles.\(^1^5,^2^2\) Most trials have compared an active medication to a placebo, with few trials evaluating head-to-
head comparisons of cessation medications. Using a statistical technique called network meta-
analysis we can examine both direct (head-to-head RCTs) and indirect evidence and thus
increase the power and interpretability of a comparative analysis.23 We aimed to examine the
comparative safety of NRT, bupropion and varenicline, evaluating both all-CVD events and
MACE reported in published RCTs and FDA reports in smokers with and without pre-existing
CVD.23

Methods

Eligibility Criteria

We included any randomized clinical trial (RCT) of: NRT at any marketed dose or combination;
bupropion at licensed doses, or; varenicline at licensed doses. Studies had to enroll smokers at
initiation of therapy and report on whether or not any CVD events occurred. We included studies
of any duration as long as they reported on a complete trial, defined as having provided the
preplanned duration of study drug. For varenicline RCTs, we obtained the individual level data
via a request about the confidential FDA report.18

Study endpoints

We considered two definitions of cardiovascular events: 1) all-cardiovascular events, defined as
clinical diagnoses of any cardiovascular event considered in previous systematic reviews on risk
of cardiovascular events associated with smoking cessation therapies;16, 17, 24 and 2) major
adverse cardiovascular events (MACE) using the same criteria as the FDA report.18 These
included cardiovascular death, non-fatal MI, and non-fatal stroke. In circumstances where an
event is reported but not attributed to a group, we contacted the study authors for clarification.

Search strategy

In consultation with a medical librarian, we established a previously published search strategy
(available in appendix).\textsuperscript{24} We searched independently, in duplicate, the following 10 databases (from inception to March 20, 2013): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, and databases including the full text of journals (OVID, ScienceDirect, and Ingenta, which includes articles in full text from 1993). In addition, we searched the bibliographies of published systematic reviews and health technology assessments and contacted the authors of individual RCTs. Searches were not limited by language, sex or age.

\textbf{Study selection}

Two investigators (PW, SE) independently and in duplicate scanned abstracts and then obtained the full text reports of RCTs evaluating the interventions of interest. After obtaining full reports of the candidate trials the same reviewers independently assessed eligibility from full text papers.

\textbf{Data collection}

Two reviewers (PW, SE) conducted data extraction independently using a standardized pre-piloted form with the categories of CVD, available from the authors upon request. Reviewers collected information about the smoking intervention, the population studied (age, sex, underlying conditions), treatment dosages and dosing schedules, CVD events and loss to follow up. Study evaluation included general methodological quality features using a modified Cochrane risk of bias tool.\textsuperscript{25}

\textbf{Data analysis}

We assessed inter-rater reliability on inclusion of articles using the $\Phi$ statistic, which provides a measure of inter-observer agreement independent of chance.\textsuperscript{26} Our analysis required two approaches: first pair-wise meta-analysis of all direct RCT evidence, and secondly, a network
meta-analysis that includes both the direct RCT evidence, and indirect comparisons of those treatments. We evaluated the major outcomes as all-CVD events and MACE. For pair-wise meta-analysis we used the conventional DerSimonain-Laird approach to account for unexplained heterogeneity between studies.\textsuperscript{27} We calculated the Relative Risk [RR] and 95% Confidence Intervals [CIs] of outcomes according to the number of events reported in the original studies or sub-studies. We calculated the $I^2$ statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity. We considered an $I^2$ value greater than 30\% to be important and investigated the cause of heterogeneity using sub-group analysis and random effects meta-regression.

In the absence of many head-to-head trials evaluating all interventions, we conducted a Bayesian random-effects network meta-analysis.\textsuperscript{28,29} A detailed description of the underlying statistical model is provided in the appendix.

Results

Study Characteristics

Figure 1 displays the flow-diagram documenting the search and inclusion of relevant studies. Supplemental table 1 lists the excluded studies, as they did not report on CVD events. Our review identified 63 eligible RCTs\textsuperscript{10,13-15,22,30-87} that reported on cardiovascular events involving 30,508 patients. Table 1 displays the study characteristics. Out of these 63 trials, there were 58 two-armed trials, 3 three-armed trials and 2 four-armed trials. For trials that had multiple arms due to dosage differences, we pooled those arms for each treatment. 19 RCTs evaluated NRT versus placebo\textsuperscript{10,30-34,36-38,40-46,49,53,68}; 27 RCTs evaluated bupropion versus placebo\textsuperscript{13-15,47-49,51-71}; 18 RCTs evaluated varenicline versus placebo\textsuperscript{22,54,55,72-79,81-87}; 1 RCT evaluated high-dose
NRT versus placebo, 1 RCT evaluated combination NRT versus control, 2 RCTs evaluated bupropion versus varenicline, 3 RCTs evaluated bupropion versus NRT, and 1 RCT evaluated varenicline versus NRT. Study quality was variable (Supplemental table 2).

The 63 RCTs collectively included 30,508 participants. Among RCTs examining specific CVD risk groups, eight trials included patients with cardiovascular disease, four trials included patients with chronic obstructive pulmonary disease (COPD), and one trial included perioperative patients. These RCTs were included in our analysis that was restricted to high-risk patients. The median duration of treatment across treatments was 12 weeks (IQR = 8-12 weeks) while the median duration of follow-up trial time was 12 months (IQR = 6-12 months). Attrition across the period of the trials was not importantly different by intervention or controls (NRT vs placebo 23% vs 20%; bupropion vs placebo 26% vs 31%; varenicline vs placebo 28% vs 29%).

Pairwise comparisons
We examined pairwise comparisons of all interventions with available head-to-head data. The results are reported in Table 2. We found no major evidence of heterogeneity as I² values were equal or close to 0% at all times.

For NRT, the risk of any CVD event was statistically significantly increased compared with placebo (RR 1.81, 95% CrI, 1.35-2.43). When this was restricted to only MACE, confidence intervals became wide and thus, did not suggest statistical evidence of harm (RR, 1.38, 95% CrI, 0.58-3.26). When this was restricted to high-risk patients, the relative decreased and confidence intervals became wider.

For bupropion, the results suggested a direction of effect that is protective against MACE for the entire study population (RR 0.57, 95% CrI, 0.31-1.04). When the population was
restricted to high-risk patients, the trend remained, but confidence intervals became slightly wider. When looking only at MACE the relative risk became closely identical to 1.00.

For varenicline, the relative risk was slightly larger than 1.00 (i.e., no difference) for both outcome definitions and population groups, but confidence intervals were wide in all instances.

Network Meta-analysis

Figure 2 displays the trial network. The network meta-analysis results are reported in Table 3. The findings are similar to the pairwise findings and demonstrate that NRT was significantly associated with increased risk of all-CVD events. In particular, risk of events with NRT was statistically increased versus placebo and bupropion. However, when restricted to only MACE category of events, NRT was no longer significantly associated with harm.

Bupropion appears to protect for the risk of MACE relative to both NRT and varenicline. Varenicline was not associated with either benefit or harm in the network meta-analysis, but had a significantly higher risk of harm compared with bupropion (Table 2).

High-risk populations

When we examined only RCTs that enrolled high-risk populations, the direction of effect was similar to the complete trials analysis, but none of the comparisons reached statistical significance (Table 2).

Sensitivity analysis

We removed the MACE events from the NRT analysis to examine what endpoints were driving the harmful effect of NRT. When we removed all MACE events, the RR of NRT was 1.89 (95% CrI, 1.31-2.73). The most commonly reported NRT adverse events were heart palpitations. When we included only events we considered to be well-known lower severity adverse events associated with NRT (ie. palpitations, bradycardia, and arrhythmia), the pooled RR was 2.08...
(95% CrI, 1.35-3.19).

We also removed studies with shorter than 12 months duration to investigate potential effect-modification by study duration. This analysis yielded highly similar results to the main analysis for bupropion versus placebo, RR=0.97 (95% CrI, 0.56-1.59), and for varenicline versus placebo RR=1.45 (95% CrI, 0.86-2.62). However, for NRT the increased risk of all CVD was more pronounced and statistically evident RR=3.03 (95% CrI 2.04-4.67). Further, varenicline was significantly less likely than NRT to cause CVDs, RR=0.48 (95% CrI, 0.24-0.96).

Discussion

Our study addressed whether smoking cessation therapies increase the risk of CVD events using two definitions, one addressing all-CVD events that included more minor events, such as tachycardia, and one that followed FDA definitions of MACE.18

Our study demonstrates that all three evaluated therapies were not harmful for MACE events. Bupropion appears to have a protective effect, whereas varenicline, was not significantly associated with harm. NRT, the most widely used pharmacotherapy for smoking cessation was associated with an increase in CVD events that was driven by lower risk events, typically tachycardia, a well-known and largely benign effect of NRT.21 When our analysis was restricted to individuals with a higher risk-profile of having an event, because of previous history of predisposing conditions, we did not find evidence of increased risk with any pharmacotherapy, although this was based on a smaller sample.

There are several strengths and limitations to consider in this study. Strengths include the comparative safety evaluation across pharmacotherapies, a strategy that, to our knowledge, has not been applied previously. We evaluated two important definitions of CVD events, both all-
CVD events, and the FDA definition of MACE, considered to be a more stringent definition of patient important outcomes.\(^{18}\) Because we applied two different categories of events, our findings can inform where previous evaluations of safety may have been limited. Limitations of our review are predominantly driven by the necessity that trial reports or the FDA report provided information on the outcomes of interest. Because concern about CVD risk with smoking cessation is a relatively new issue, many trials that reported on effectiveness outcomes did not report on CVD safety outcomes.\(^{24}\) Efforts to reduce this potential reporting bias by contacting study authors were hampered by non-response and the long period of time since the trials were published, particularly for NRT trials. Given the heterogeneous reporting of CVD events in RCTs, we used a composite outcome of MACE events, as used by the FDA.\(^{18}\) It is possible that individual components of the composite would find differing effects, but we acknowledge that any analysis of these would be hampered by lower power to detect a signal of harm. We found low rates of MACE events across the three interventions resulting in wide credible intervals. It is possible that with a vastly larger dataset, treatment outcomes would change.\(^{18}\) However, we conducted post-hoc power calculations to estimate the power of our comparisons for MACE and found acceptable levels of power for all comparisons (see appendix 3). Our varenicline analysis was hampered by lower power. Appendix For the most part, the findings are largely limited to smokers without pre-existing heart disease. We found similar rates of attrition across interventions, these ranged from 20-29%, yet it is possible that attrition reflects intolerability of the intervention and thus misses some events. We did not report the Bayesian probability of risk because these are not widely understood and because the probability ranking can vary widely depending on the sparseness of the data.\(^{88}\) Throughout this analysis, we present the point estimates with credible intervals. Although some analyses did not reach statistical
significance, the possibility of risk still exists when credible intervals include an estimate that would be considered clinically important.

Our study found statistically significant evidence of all-CVD events associated with NRT use. However, when we restricted this to MACE events, the finding was no longer statistically significant. When we examined these findings in a sensitivity analysis, we found that the treatment effects were predominantly driven by lower level CVD events (RR 1.91), including tachycardia and arrhythmia, both well-known adverse events of NRT use,9,21,89 and occurred primarily in studies with longer periods of follow-up.

There are several possible explanations why NRT use may increase some CVD events and this has been recognized for some time, although it is not well understood, nor a major clinical concern.9,21,89,90 Chiefly, many smokers have a long history of smoking that may have established coronary artery disease. Those patients with unstable coronary syndrome, may be exhibiting coronary vasoconstriction associated with plaque ruptures due to increased strain of quitting and palpitations associated with NRT.89 Second, for those patients receiving NRT and continuing to smoke, high nicotine serum concentrations may stimulate the sympathetic nervous system response, thereby increasing blood pressure, stroke volume, and heart output.89 Yet, importantly, some research has documented more CVD events among patients with heart disease who smoked on a placebo than on a nicotine patch.10 Further, equivalent proportions of palpitations or chest pain were found among those who smoked or did not smoke during nicotine patch therapy.91

Only a few years on market, electronic cigarettes or e-cigarettes are a relatively new, and unregulated, approach to nicotine delivery. Consequently, the safety of these products and their use for quitting cigarette smoking has not been well evaluated. At this time, they are not
considered cessation devices, and their contents and risk profiles are just beginning to be explored. Different guidelines and algorithms exist on the choice of cessation pharmacotherapy according to patient history of smoking, substance abuse, and chronic disease risk profiles. For example, both the Mayo Clinic and the Ottawa model for smoking cessation recommend the use of NRT among at-risk CVD patients, while the US Surgeon General report (2010) advocates avoidance of NRT for two weeks post major CVD event. Given the current findings of low risk of serious CVD events attributed to smoking cessation pharmacotherapies, combined with the well-established CVD and mortality risks of continued smoking, the benefits of use would seem to outweigh the risks; however, further study is needed, particularly investigation of the use of cessation medications with smokers hospitalized for ST-elevation myocardial infarction.

Our findings should be placed in the context of other available evidence. The concern about smoking cessation therapies increasing risk of CVD events was most widely reported by Singh et al in 2011 in an evaluation of varenicline versus placebo RCTs. Using data from 14 RCTs, the study authors reported a Peto odds ratio for all-CVD events of 1.72 (95% CI, 1.09-2.71). The Peto odds ratio is an artifact of a fixed effects analysis and therefore has tighter confidence intervals than random-effects models. Applying a random-effects analysis to their dataset yields a RR of 1.43 (95% CI, 0.91-2.25), which is not very different from the findings in our analysis of 16 RCTs (RR 1.24, 95% CI, 0.85-1.81). Much has been written about the choice of effect measure for RCTs and it is well understood that odds ratios can be perceived as inflating the treatment effects. Prochaska has demonstrated this with the varenicline and CVD risk data. As a result of the controversy about varenicline and CVD risk, the FDA conducted their own meta-analysis using individual patient data addressing their definition of MACE on 30-
day post-treatment outcomes and found a hazard ratio of 1.95 (95% CI, 0.79, 4.82), which is not very different from the findings of our analysis based on additional aggregate data (RR 1.57, 95% CI, 0.67-3.17). Our findings that less clinically concerning events drove the significant finding of NRT for all-CVD events is consistent with findings from a meta-analysis we previously published based on RCTs and observational data on the outcome of chest pain and palpitations (RR 1.66, 95% CI, 1.22-2.28). While the comparative effects of each therapy is, to our knowledge, a new approach to evaluating safety of smoking cessation therapies, a recent nation-wide observational study in Denmark examined the comparative harms of bupropion and varenicline and did not demonstrate significant harm from either treatment. Similar findings were reported in the US.

The potential cardio-protective role of bupropion is not well understood. We did not find bupropion protective against all-CVD events, however, we did find a statistically significant protective effect for MACE. It is possible that the antidepressant origins of bupropion anti-depressant origins reduce vascular stress. However, at higher doses also has sympathomimetic activity and can increase heart rate and blood pressure. Based on our current findings, bupropion may be cardio-protective, likely through its effects on increasing smoking cessation and alleviating depression, though closer investigation of bupropion's cardiovascular effects are warranted.

Physicians often weigh the benefits and risks of available treatments including cessation pharmacotherapies. Concerns about adverse events need to be balanced with the consistent evidence for the benefit of smoking cessation and patients should be counseled about what adverse events may be associated with smoking cessation therapies, the symptoms associated with the withdrawal period from cigarettes, and symptoms that may be due to existing diseases.
Conflict of Interest Disclosures: Edward Mills and Kristian Thorlund have consulted to Merck & Co Inc, Pfizer Ltd, Novartis, Takeda, or GlaxoSmithkline on MTC issues. However, no funding was received from any of these entities for this manuscript. Judith Prochaska has received an Investigator Initiated Research award from Pfizer Inc (WS981308). Pfizer Inc has had no role in this manuscript. Ping Wu and Shawn Eapen declare no conflicts of interest. Edward Mills receives salary support from the Canadian Institutes of Health Research through a Canada Research Chair. Kristian Thorlund receives salary support from the Canadian Institutes of Health Research via the Drug and Safety Evaluation Network to develop methods for assessing harms using network meta-analysis. Judith Prochaska receives research and salary support from the National Institute on Drug Abuse (P50 DA09253 and R34DA030538), the National Institute of Mental Health (R01 MH083684), and the State of California Tobacco-Related Disease Research Program (17RT-0077 and 21BT-0018).

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1941.


Table 1. Characteristics of included trials of nicotine replacement therapy, bupropion, and varenicline.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participant characteristics</th>
<th>Cigarettes per day (mean (SD); median*)</th>
<th>Years Smoking (mean (SD); median*)</th>
<th>Duration of the treatment (wks)</th>
<th>Whole Study Duration (mth)</th>
<th>Arm</th>
<th>Co-Treatment</th>
<th>Age mean (SD or range); median*</th>
<th>Male (%)</th>
<th>n</th>
<th>Reported CV Outcomes</th>
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<tbody>
<tr>
<td>Tonnesen et al 2012</td>
<td>Healthy</td>
<td>22.7(8.8)</td>
<td>NR</td>
<td>52</td>
<td>NR</td>
<td>Placebo</td>
<td>Counseling</td>
<td>46.2(11.3)</td>
<td>54.7</td>
<td>161</td>
<td>Myocardial Infarction</td>
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<td>Thomsen et al 2010</td>
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<td>NR</td>
<td>NR</td>
<td>2</td>
<td>12</td>
<td>Placebo Spray 1 mg</td>
<td>Counseling</td>
<td>47.0(10.9)</td>
<td>56.9</td>
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<td>Healthy</td>
<td>25(8)</td>
<td>26(12)</td>
<td>12</td>
<td>6</td>
<td>Placebo 2mg</td>
<td>Counseling</td>
<td>42.2(13.3)</td>
<td>34.5</td>
<td>817</td>
<td>Heart Rate</td>
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<td>Oncken et al 2007</td>
<td>Post Menopausal Women</td>
<td>21(8)</td>
<td>33(10)</td>
<td>12</td>
<td>12</td>
<td>Placebo Group Counseling</td>
<td>Counseling</td>
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<td>29(9)</td>
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<td>25(11)</td>
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<td>52.0</td>
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*Note: SD = standard deviation; CV = cardiovascular; 3mg = 3 milligrams; 4mg = 4 milligrams; 5mg = 5 milligrams; 10mg = 10 milligrams; 15mg = 15 milligrams; 20mg = 20 milligrams; 25mg = 25 milligrams; 30mg = 30 milligrams; 45mg = 45 milligrams; 50mg = 50 milligrams; 60mg = 60 milligrams.
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<th>Group 2</th>
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**Notes:**
- IQR: Interquartile Range
- *: Significantly different from placebo

**Statistical Tests:**

- **CVD**: Coronary artery disease
- **Infarction**: Myocardial infarction
- **Aneurysm**: Aneurysm
- **Death**: Death
- **Support**: Motivational Support
- **Heart**: Heart Pulitations
- **Atrial Fibrillation**: Atrial fibrillation
- **Tachycardia**: Tachycardia
- **Infarction, Coronary Artery Occlusion**: Acute myocardial infarction, coronary artery occlusion
- **Infarction, Atrial Fibrillation**: Acute myocardial infarction, atrial fibrillation

**References:**
- Covey et al (2007)
- Zellweger et al (2005)
- Fossati et al (2007)
- Muramoto et al (2007)
- Uyar et al (2007)
- Puska et al (2005)
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<td>Placebo, Varenicline 2 mg/d Counseling</td>
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<td>21(3-52)</td>
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<td>28(10)</td>
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<td>12</td>
<td>Placebo</td>
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CVD, Acute Myocardial Infarction
Stroke
Unstable Angina, Tachycardia
Table 2. Estimated relative risk (RR) and 95% confidence intervals (CIs) produced by random effects pair-wise meta-analysis for cardiovascular events in smoking cessation RCTs.

<table>
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<th>Number of Studies</th>
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<th>All CV Events</th>
<th>MACE Events</th>
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<td>21 RCTs</td>
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<td>202/6329 vs. 83/5318</td>
<td>1.81 (1.35-2.43)</td>
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<td>27 RCTs</td>
<td>Bupropion vs placebo</td>
<td>50/5947 vs. 42/4455</td>
<td>1.03 (0.71-1.50)</td>
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<tr>
<td>18 RCTs</td>
<td>Varenicline vs placebo</td>
<td>63/5469 vs. 41/3603</td>
<td>1.24 (0.85-1.81)</td>
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<tr>
<td>2 RCTs</td>
<td>Bupropion vs varenicline</td>
<td>1/686 vs. 2/696</td>
<td>0.74 (0.05-10.5)</td>
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<td>3 RCTs</td>
<td>Bupropion vs NRT</td>
<td>4/367 vs. 2/366</td>
<td>1.40 (0.25-7.82)</td>
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<tr>
<td>1 RCT</td>
<td>Varenicline vs NRT</td>
<td>0/378 vs. 2/379</td>
<td>0.20 (0.01-4.16)</td>
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<td><strong>High risk patients only</strong></td>
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<tr>
<td>3 RCTs</td>
<td>NRT vs placebo</td>
<td>33/454 vs. 26/374</td>
<td>1.24 (0.77-2.02)</td>
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<td>Bupropion vs placebo</td>
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<td>1.04 (0.59-1.83)</td>
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<td>Bupropion vs NRT</td>
<td>3/50 vs. 0/50</td>
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<td>Varenicline vs NRT</td>
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Table 3. Estimated relative risk (RR) and 95% credibility intervals (CrI) from random effects network meta-analysis for cardiovascular events in smoking cessation RCTs.

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<th>MACE</th>
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<td>NRT vs placebo</td>
<td>2.29 (1.39-3.82)</td>
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<td>Bupropion vs placebo</td>
<td>0.98 (0.54-1.73)</td>
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<td>Varenicline vs placebo</td>
<td>1.30 (0.79-2.23)</td>
<td>1.34 (0.66-2.66)</td>
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<td>Bupropion vs varenicline</td>
<td>0.76 (0.33-1.73)</td>
<td>0.33 (0.16-0.87)</td>
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<td>Bupropion vs NRT</td>
<td>0.43 (0.19-0.91)</td>
<td>0.23 (0.08-0.63)</td>
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<tr>
<td>Varenicline vs NRT</td>
<td>0.56 (0.25-1.27)</td>
<td>0.67 (0.26-1.90)</td>
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</tbody>
</table>

**High risk populations (sensitivity analysis)**

<table>
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<tr>
<th>Comparison</th>
<th>All-CVD events</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT vs placebo</td>
<td>1.31 (0.58-3.32)</td>
<td>1.53 (0.38-6.24)</td>
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<td>Bupropion vs placebo</td>
<td>1.06 (0.59-2.04)</td>
<td>0.48 (0.18-1.21)</td>
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<td>Varenicline vs placebo</td>
<td>0.99 (0.45-1.88)</td>
<td>1.22 (0.44-2.90)</td>
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<td>Bupropion vs varenicline</td>
<td>1.09 (0.46-2.92)</td>
<td>0.39 (0.11-1.49)</td>
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<tr>
<td>Bupropion vs NRT</td>
<td>0.81 (0.26-2.26)</td>
<td>0.31 (0.05-1.68)</td>
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<tr>
<td>Varenicline vs NRT</td>
<td>0.92 (0.34-2.19)</td>
<td>0.81 (0.13-4.20)</td>
</tr>
</tbody>
</table>

**Figure Legends:**

**Figure 1.** Flow diagram of randomized controlled trials selected for the meta-analysis of cardiovascular events associated with smoking cessation therapies.

**Figure 2.** Geometric distribution of the MTC analysis, including randomized trials of nicotine replacement therapy, bupropion, and varenicline. Nodes represent the study therapies. Links between the nodes represent direct comparisons from RCTs. The numbers beside the nodes represent the number of RCTs.
Abstracts screened:
123 varenicline
327 bupropion
624 NRT

Full text obtained:
31 varenicline
81 bupropion
176 NRT

Abstracts removed as irrelevant:
92 varenicline
246 bupropion
448 NRT

13 varenicline reports excluded, as:
4 no CVD events reported; 4 without cessation data; 1 maintenance therapy; 1 pooled analysis of 2 RCTs; 2 with no specific dose and 1 gave drug for only 7 days.

54 bupropion reports excluded, as:
31 no CVD events reported; 11 duplicate studies; 10 not examining cessation; and 2 not randomized.

155 NRT reports excluded, as:
75 no CVD events reported; 2 duplicate studies; 73 insufficient information; 1 smoking reduction study; 1 differing treatment durations; and 3 patch was not independently reported.

18 varenicline RCTs included
27 bupropion RCTs included
21 NRT RCTs included:
20 <22mg;
1 >22mg

Figure 1
Figure 2
Cardiovascular Events Associated with Smoking Cessation Pharmacotherapies: A Network Meta-Analysis
Edward J. Mills, Kristian Thorlund, Shawn Eapen, Ping Wu and Judith J. Prochaska

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http://circ.ahajournals.org/content/early/2013/11/25/CIRCULATIONAHA.113.003961

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/11/25/CIRCULATIONAHA.113.003961.DC1

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SUPPLEMENTAL MATERIAL

Appendix 1. Description of Bayesian Network meta-analysis.

We modeled log odds ratios using the conventional logistic regression network meta-analysis setup. From this logistic regression model we produced relative risks for all comparisons, utilizing the pooled control group proportions (and pooled log odds). We accounted for unexplained variance by employing a random-effects approach. With rare event data, as was the case for the data, the between-study (heterogeneity) variance estimation can become upward biased in the Bayesian framework as the elicited prior variance distribution carries high probability mass for large values. For this reason, we decided to use an empirically informed approach previously shown to be reliable. Sensitivity analyses examined what endpoints were driving the harmful events and whether the duration of the trials were associated with larger effect sizes. We estimated the posterior densities for all unknown parameters using Markov chain Monte Carlo methods for each model. We assessed convergence based on the Brooks-Gelman-Rubin criteria using three Markov chains and found that 20000 iterations were enough for reliable burn-in. All results for the network analysis are reported as posterior means with corresponding 95% credibility intervals (CrIs). Credibility intervals are the Bayesian equivalent of classical confidence intervals. We assessed the fit of our model using the Deviance Information Criterion (DIC), a measure of model fit that penalizes model complexity. The network results were assessed for consistency by comparing them with an adjusted indirect comparison and with the pair-wise meta-analyses results. We evaluated incoherence between direct estimates and indirect estimates for statistical
differences. As ORs are statistically superior to RRs,\textsuperscript{5} we conducted the network with OR as the effect size and converted the OR to RRs.

Analyses were conducted using Comprehensive Meta-analysis (version 2, \url{http://www.meta-analysis.com}) and WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge).

**Appendix 2. Search strategy**

**(Ovid syntax)**

1. random:.tw,sh,pt. OR placebo:.tw,sh.

2. (clinical trial OR controlled clinical trial).pt.

3. ((single or doubl: or tripl: or treb:) AND (blind: or mask:)).tw,ab

4. OR/1 – 3

5. Tobacco Use Cessation Products [mesh]

6. nicotine OR NRT OR nicotine replacement

7. bupropion OR zyban

8. varenicline OR champix OR chantix

9. OR/5 – 8

10. smoking [mesh]

11. AND 9 AND 10
### Supplemental Table 1. List of publications excluded due to non-reporting of CVD events.

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<th>Intervention</th>
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<td>Brown et al 2007&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>Cox et al 2012&lt;sup&gt;10&lt;/sup&gt;</td>
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## Supplemental Table 2 - Risk-of-bias assessment of randomized controlled trials of nicotine replacement therapy, bupropion, and varenicline included in the analysis of serious adverse cardiovascular events

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Appendix 3. Retrospective power calculation for detection of harm or protection of harm

We conducted a post-hoc retrospective power calculation to examine our power to detect differences between interventions for MACE. The meta-analysis pooling all control group risks yields pooled proportion of 0.4% (95% confidence interval 0.3% to 0.6%). That is 4 out of 1,000 patients who are attempting to quit smoking, but do not receive any pharmacotherapy to aid smoking cessation, are expected to suffer from a major adverse cardiovascular event (MACE). The uncertainty interval is 3 to 6 patients out of 1,000.

The estimated relative risk for NRT versus control was 1.95, and so, one would expect approximately 8 out of 1,000 patients on NRT will suffer from a MACE.

The estimated relative risk for bupropion was 0.45, and so, one would expect that approximately 2 out of 1,000 patients on bupropion will suffer from a MACE.

The estimated relative risk for varenicline was 1.34, and so, one would expect that approximately 5-6 out of 1,000 patients on varenicline will suffer from a MACE.

The power to demonstrate these expected differences between the considered smoking cessation interventions can be retrospectively estimated using conventional post hoc power calculations for binary outcomes. A retrospective power calculation requires the following inputs:

- The sample size (i.e. number of patients) of the data set
- Some realistic assumption of a control group risk
- Some realistic assumption of an intervention group risk. This can be derived from multiplying the control group with a relative risk.

Below we provide retrospective power estimates based on the assumptions that the control group risk is 0.4%, 0.3%, or 0.6%, and based on the assumptions that the relative risks are exactly that of the primary network meta-analysis results, or other reasonable relative risk estimate assumptions for power calculations. The total number of patients in the network meta-analysis of MACE was 29,413.

For varenicline, the RR is relatively small, and thus, the retrospective power to demonstrate harm is low. However, the retrospective power to demonstrate non-inferiority to upper harm limits is considerable. For example, the power to demonstrate that varenicline causes no more harm than what corresponds to a RR of 1.95 (i.e., the NRT RR) is 95%. By the same token, the power of bupropion to demonstrate superiority (protective effect) to both varenicline and NRT is higher than the power to demonstrate superiority to control.
Retrospective power calculation to demonstrate harm for NRT

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Retrospective power calculation to demonstrate harm for Varenicline

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Retrospective power calculation to demonstrate non-inferiority of Varenicline vs NRT (the Varenicline RR was assumed to be 1.34)

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Retrospective power calculation to demonstrate protective effect of bupropion

<table>
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<tr>
<th>Assumed control risk</th>
<th>Assumed relative risk</th>
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<tr>
<td></td>
<td>RR=0.60</td>
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<tr>
<td>P&lt;sub&gt;c&lt;/sub&gt;=0.3%</td>
<td>55.7%</td>
</tr>
<tr>
<td>P&lt;sub&gt;c&lt;/sub&gt;=0.4%</td>
<td>68.1%</td>
</tr>
<tr>
<td>P&lt;sub&gt;c&lt;/sub&gt;=0.6%</td>
<td>84.6%</td>
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