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Cardiovascular Events Associated With Smoking Cessation Pharmacotherapies A Network Meta-Analysis

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Abstract

Background—Stopping smoking is associated with many important improvements in health and quality of life. The 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 events associated within the quitting period. We aimed to examine whether the 3 licensed smoking cessation therapies—nicotine replacement therapy, bupropion, and varenicline—were associated with an increased risk of cardiovascular disease events using a network meta-analysis.

Methods and Results—We searched 10 electronic databases, were in communication with authors of published randomized, clinical trials (RCTs), and accessed internal US Food and Drug Administration reports. We included any RCT of the 3 treatments that reported cardiovascular disease outcomes. Among 63 eligible RCTs involving 21 nicotine replacement therapy RCTs, 28 bupropion RCTs, and 18 varenicline RCTs, we found no increase in the risk of all cardiovascular disease events with bupropion (relative risk [RR], 0.98; 95% confidence interval [CI], 0.54–1.73) or varenicline (RR, 1.30; 95% CI, 0.79–2.23). There was an elevated risk associated with nicotine replacement therapy that was driven predominantly by less serious events (RR, 2.29; 95% CI, 1.39–3.82). When we examined major adverse cardiovascular 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 nicotine replacement therapy (RR, 1.95; 95% CI, 0.26–4.30).

Conclusion—Smoking cessation therapies do not appear to raise the risk of serious cardiovascular disease events.

Keywords

bupropion; cardiovascular diseases; meta-analysis; smoking cessation; tobacco use cessation products; varenicline

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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 healthcare 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 United States recommend the use of smoking cessation pharmacotherapies with all adult smokers interested in quitting unless contraindicated.[5,6]

In North America, there are 3 approved first-line classes of therapies: nicotine replacement therapy (NRT); bupropion, an antidepressant, and; varenicline, a nicotine receptor partial agonist. Many randomized, clinical trials (RCTs) and systematic reviews have demonstrated these agents to be effective in promoting smoking cessation.[7,8] The medications have different mechanisms of action and side effect profiles. All underwent some scrutiny for potential cardiovascular effects when they came 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 that NRT was safe even with a high-dose patch, combination NRT, and concurrent smoking.[10–12] With bupropion, 3 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[16] involving 8216 participants reported that varenicline use may be associated with increased minor and major cardiovascular events (odds ratio, 1.72; 95% confidence interval [CI], 1.09–2.71), a finding at odds with the goal of smoking cessation that garnered a great deal of media attention. A follow-up meta-analysis found the difference between varenicline and placebo to be statistically and clinically nonsignificant.[17]

The large number of smokers attempting to quit by using pharmacotherapies and the widespread media reports of cardiovascular risks associated with pharmacotherapies make clear public health messages a priority. At the request of the Food and Drug Administration (FDA), the drug maker (Pfizer Inc) recently conducted a meta-analysis based on major adverse cardiovascular events (MACEs), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.[18] With the use of individual patient data from industry-sponsored RCTs, the hazard ratio was not significant (hazard ratio, 1.95; 95% CI, 0.79–4.82). The most recent FDA safety communication on varenicline from December 2012 indicates that the events were uncommon in both active and placebo drug conditions and that 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 bupro-pion (incidence rate ratio, 1.02; 95% CI, 0.71–1.47).[19]

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 (hazard ratio, 0.96; 95% CI, 0.67–1.39).[20] A meta-analysis examining only NRT found an increased risk for less

serious cardiovascular events such as tachycardia and nonspecific chest pain but did not examine MACEs.[21] Notably, few of the RCTs have been conducted within populations with secondary CVD risk profiles.[15,22] Most trials have compared an active medication with 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 all CVD events and MACEs reported in published RCTs and FDA reports in smokers with and without preexisting CVD.[23]

Methods

Eligibility Criteria

We included any RCT of NRT at any marketed dose or combination, bupropion at licensed doses, or varenicline at licensed doses. Studies had to enroll smokers at the initiation of therapy and report whether any CVD events occurred. We included studies of any duration as long as they reported a complete trial, defined as having provided the pre-planned duration of study drug. For varenicline RCTs, we obtained the individual-level data via a request about the confidential FDA report.[18]

Study End Points

We considered 2 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) MACEs using the same criteria as the FDA report.[18] They included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. In circumstances when 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 the online-only Data Supplement).[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. We also searched 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.

Study Selection

Two investigators (P.W., S.E.) 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 articles.

Data Collection

Two reviewers (P.W., S.E.) conducted data extraction independently using a standardized prepiloted form with the categories of CVD (available from the authors on request). Reviewers collected information about the smoking intervention, the population studied (age, sex, underlying conditions), treatment doses 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.[25]

Data Analysis

We assessed inter-rater reliability on inclusion of articles using the φ statistic, which provides a measure of interobserver agreement that is independent of chance.[26] Our analysis required 2 approaches: pairwise meta-analysis of all direct RCT evidence and 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 MACEs. For pairwise meta-analysis, we used the conventional DerSimonian-Laird approach to account for unexplained heterogeneity between studies.[27] We calculated the relative risk (RR) and 95% CIs of outcomes according to the number of events reported in the original studies or substudies. 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 >30% to be important and investigated the cause of heterogeneity using subgroup 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.[28,29] A detailed description of the underlying statistical model is provided in the online-only Data Supplement.

Results

Study Characteristics

Figure 1 displays the flow diagram documenting the search and inclusion of relevant studies. Table I in the online-only Data Supplement lists the excluded studies that did not report on CVD events. Our review identified 63 eligible RCTs[10,13–15,22,30–87] that reported cardiovascular events involving 30 508 patients. Table 1 displays the study characteristics. 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 as a result of dose differences, we pooled those arms for each treatment. Nineteen RCTs evaluated NRT versus placebo[10,30–34,36–38,40–46,49,53,68]; 27 RCTs evaluated bupropion versus placebo[13–15,47–49,51–71]; 18 RCTs evaluated varenicline versus placebo[22,54,55,72–79,81–87]; 1 RCT evaluated high-dose NRT versus placebo[39]; 1 RCT evaluated combination NRT versus control[35]; 2 RCTs evaluated bupropion versus varenicline[54,55]; 3 RCTs evaluated bupropion versus NRT[49,53,68]; and 1 RCT evaluated varenicline versus NRT.[80] Study quality was variable (Table II in the online-only Data Supplement).

The 63 RCTs collectively included 30 508 participants. Among RCTs examining specific CVD risk groups, 8 trials included patients with CVD,[10,13,15,22,46,47,61,87] 4 trials included

patients with chronic obstructive pulmonary disease,[53,59,64,77] and 1 trial included perioperative patients.[74] These RCTs were included in our analysis that was restricted to high-risk patients. The median duration of treatment across treatments was 12 weeks (interquartile range, 8–12 weeks), whereas the median duration of follow-up trial time was 12 months (interquartile range, 6–12 months). Attrition across the period of the trials was not importantly different by intervention or controls (NRT versus placebo, 23% versus 20%; bupropion versus placebo, 26% versus 31%; varenicline versus placebo, 28% versus 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 because I^2 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% credible interval [CrI], 1.35–2.43). When this was restricted to only MACEs, CIs 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 RR decreased and CIs became wider.

For bupropion, the results suggested a direction of effect that is protective against MACEs 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 CIs became slightly wider. When only MACEs were considered, the RR became almost identical to 1.00.

For varenicline, the RR was slightly larger than 1.00 (ie, no difference) for both outcome definitions and population groups, but CIs 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 compared with placebo and bupropion. However, when restricted to only MACE category of events, NRT was no longer significantly associated with harm.

Bupropion appears to protect against the risk of MACEs 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 MACEs from the NRT analysis to examine what end points were driving the harmful effect of NRT. When we removed all MACEs, 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 <12 months' duration to investigate potential effect modification by study duration. This analysis yielded results highly similar to the results of 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 1 addressing all CVD events that included more minor events such as tachycardia, and 1 that followed FDA definitions of MACEs.[18]

Our study demonstrates that all 3 evaluated therapies were not harmful for MACEs. 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 a 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 of this study to consider. Strengths include the comparative safety evaluation across pharmacotherapies, a strategy that, to the best of our knowledge, has not been applied previously. We evaluated 2 important definitions of CVD events, both all CVD events and the FDA definition of MACEs, considered to be a more stringent definition of patient important outcomes.[18] Because we applied 2 different categories of events, our findings can inform where previous evaluations of safety may have been limited. Limitations of our review are driven predominantly by the necessity that trial reports or the FDA reports provided information on the outcomes of interest. Because concern about CVD risk with smoking cessation is a relatively new issue, many trials that reported effectiveness outcomes did not report CVD safety outcomes.[24] Efforts to reduce this potential reporting bias by contacting study authors were hampered by nonresponse 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 MACEs, 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 MACEs across the 3 interventions, resulting in wide CrIs. It is possible that with a vastly larger data set, treatment outcomes would change.[18] However, we conducted post hoc power calculations to estimate the power of our comparisons for MACEs and found acceptable levels of power for all comparisons (see the online-only Data Supplement). Our varenicline analysis was hampered by lower power (online-only Data Supplement). For the most part, the findings

are largely limited to smokers without preexisting heart disease. We found similar rates of attrition across interventions, ranging from 20% to 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 it 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 CrIs. Although some analyses did not reach statistical significance, the possibility of risk still exists when CrIs 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 MACEs, the finding was no longer statistically significant. When we examined these findings in a sensitivity analysis, we found that the treatment effects were driven predominantly by lower-level CVD events (RR, 1.91), including tachycardia and arrhythmia, both well-known adverse events of NRT use,[9,21,89,90] 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 or 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 resulting from the 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] However, importantly, some research has documented more CVD events among patients with heart disease who smoked while on a placebo than on a nicotine patch.[10] Furthermore, equivalent proportions of palpitations or chest pain were found among those who smoked and 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 have 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.[92,93] 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,[94] whereas a US Surgeon General report (2010) advocates avoidance of NRT for 2 weeks after a major CVD event.[95] 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 in smokers hospitalized for ST-segment– elevation myocardial infarction.[95]

Our findings should be placed in the context of other available evidence. The concern about smoking cessation therapies increasing the risk of CVD events was most widely reported by

Singh et al[16] 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 CIs than random-effects models.[96] Applying a random-effects analysis to their data set yields an 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.[97] Prochaska and Hilton[17,98] have demonstrated this with the varenicline and CVD risk data. As a result of the controversy about varenicline and CVD risk, the FDA conducted its own meta-analysis using individual patient data addressing its definition of MACEs on 30-day posttreatment 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 finding that less clinically concerning events drove the signifi-cant finding of NRT for all CVD events is consistent with findings from our previously published meta-analysis that is based on RCTs and observational data on the outcome of chest pain and palpitations (RR, 1.66; 95% CI, 1.22–2.28).[21] Although the comparative effects of each therapy are, to the best of our knowledge, a new approach to evaluating the safety of smoking cessation therapies, a recent nationwide observational study in Denmark examined the comparative harms of bupro-pion and varenicline and did not demonstrate significant harm for either treatment.[20] Similar findings were reported in the United States.[19]

The potential cardioprotective 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 MACEs. It is possible that the antidepressant origins of bupropion reduce vascular stress.[99,100] However, at higher doses, bupropion also has sympathomimetic activity and can increase heart rate and blood pressure.[99,100] On the basis of our present findings, bupropion may be cardioprotective, likely through its effects on increasing smoking cessation and alleviating depression, although closer investigation of the cardiovascular effects of bupropion 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 the symptoms that may be attributable to existing diseases.

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CLINICAL PERSPECTIVE

Patients often use pharmacotherapies to aid in smoking cessation. Current licensed pharmacotherapies include nicotine replacement therapies, bupropion, and varenicline. Recently, there has been widespread public concern that varenicline may be associated with an increase in cardiovascular disease (CVD) events. Clinicians and the public are unsure about which smoking cessation therapies will offer the greatest likelihood of quitting with the safest adverse event profile. Using a statistical approach that permits the synthesis of direct and indirect randomized, clinical trial evidence, we compared the cardiovascular safety of nicotine replacement therapies, bupropion, and varenicline. We examined 2 categories of events: a composite of all CVD events that included both minor and major events and only major adverse CVD events. We included 63 randomized, clinical trials that reported CVD events. We found no increase in the risk of all CVD events with bupropion or varenicline. Nicotine replacement therapies had a statistically elevated risk that was driven predominantly by less serious events such as tachycardia. When the analysis was restricted to only major CVD events, we found a protective effect with bupropion and no clear evidence of harm with varenicline or nicotine replacement therapies. Our findings indicate that there is no clear evidence of major CVD events associated with smoking cessation. The increase in nicotine replacement therapy–associated CVD events was driven by well-known and largely benign events such as tachycardia and palpitations.

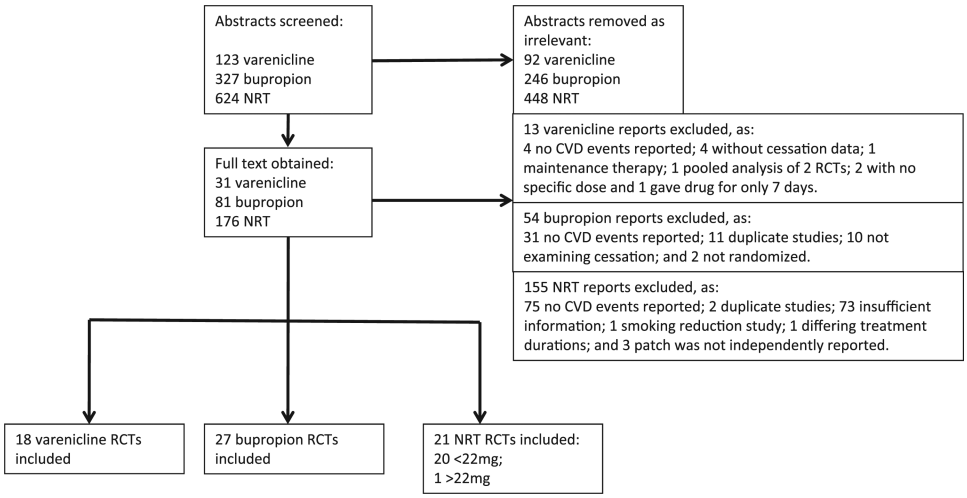

Figure 1.

Flow diagram of randomized, controlled trials (RCT) selected for the meta-analysis of cardiovascular (CV) events associated with smoking cessation therapies. NRT indicates nicotine replacement therapy.

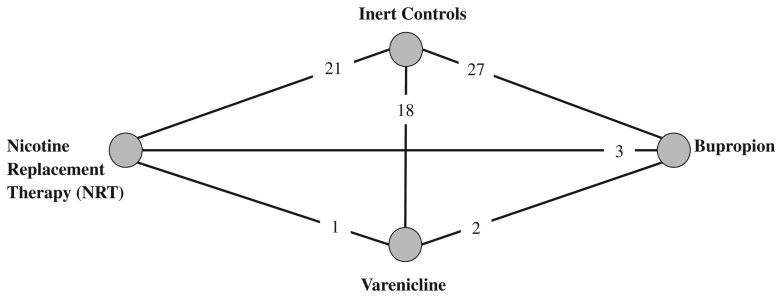

Figure 2.

Geometric distribution of the mixed treatment comparison analysis, including randomized trials of nicotine replacement therapy (NRT), bupropion, and varenicline. Nodes represent the study therapies. Links between the nodes represent direct comparisons from randomized, clinical trials (RCTs). The numbers beside the nodes represent the number of RCTs.

Table 1

Characteristics of Included Trials of Nicotine Replacement Therapy, Bupropion, and Varenicline

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
Nicotine Replacement Therapy											
Tønnesen et al,[30] 2012	Healthy	22.7 (8.8)	NR	52	NR	Placebo	Counseling	46.2 (11.3)	54.7	161	Myocardial infarction
						Spray 1 mg	Counseling	47.0 (10.9)	56.9	318	
Thomsen et al,[31] 2010	Breast cancer surgery	NR	NR	2	12	Placebo	Counseling	56.5 (36–82)	0.0	62	CVD event
						NRT	Counseling	57.5 (35–79)	0.0	58	
Shiffman et al,[32] 2009	Healthy	25 (8)	26 (12)	12	6	Placebo 2 mg	Counseling	42.2 (13.3)	34.5	817	Heart rate
						Gum 2 mg	Counseling	42.1 (13.0)	37.2	819	
						Placebo 4 mg	Counseling	46.3 (11.4)	47.8	830	
						Gum 4 mg	Counseling	46.1 (11.3)	52.4	830	
Oncken et al,[33] 2007	Postmenopausal women	21 (8)	33 (10)	12	12	Placebo	Group counseling	56.6 (6.9)	0.0	95	Hospitalized chest pain
						Patch 21 mg	Group counseling	54.0 (6.9)	0.0	57	
Wennike et al,[34] 2003	Healthy	24 (7)	29 (9)	52	24	Placebo 2 mg		44.0 (10.0)	41	68	Heart palpitations
						Gum 2 mg		45.0 (10.0)	35	65	
						Placebo 4 mg		44.0 (10.0)	41	138	
						Gum 4 mg		45.0 (10.0)	35	140	
Etter et al,[35] 2002	Healthy	30 (10)	≥3	24	6	Placebo		41.7	49	269	Stroke
						No treatment		42.9	44	389	
						NRT 2, 15, 0.5 mg		43.2	54	265	
Glover et al,[36] 2002	Healthy	29 (16)	25 (11)	12–24	12	Placebo		41.8 (11.6)	44.6	121	Atherosclerotic CVD
						Tablet 2 mg		43.9 (10.0)	47.5	120	
Wallström et al,[37] 2000	Healthy	19 (6)	26 (10)	12–24	12	Placebo		44.7 (11.4)	45.2	124	Atrial fibrillation
						Tablet 2 mg		44.5 (11.6)	36.6	123	
						Gum 4 mg		41.4 (11.7)	51.7	203	
Hays et al,[38] 1999	Healthy	≥15	26 (12)	6	6	Placebo		44.1 (11.6)	52.5	322	Acute myocardial infarction
						Patch 22 mg		43.5 (11.2)	48.6	321	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
						Patch 10–15 mg		28.2 (4.9)	0.0	124	
Tønnesen et al,[39] 1999	Healthy	27 (10)	23 (10)	8	12	Placebo	Advice brochure	41.0 (10.0)	52.0	714	Heart palpitations, tachycardia, acute myocardial infarction
						Patch 15 mg	Advice brochure	41.0 (10.0)	51.0	716	
						Patch 25 mg	Advice brochure	41.0 (10.0)	53.0	715	
Blöndal et al,[40] 1997	Healthy	25 (4–50)	2.7 (1–5)	12	24	Placebo		42 (21–67)	38.5	78	Heart palpitations
						Spray 1 mg		42.0 (22–67)	50.6	79	
Sønderskov et al,[41] 1997	Healthy	≥20	21 (11)	12	6	Placebo 14 mg		38.9 (13.7)	58.3	125	Heart palpitations, chest pain
						Patch 14 mg		38.2 (12.9)	41.7	119	
						Placebo 21 mg		39.9 (10.9)	49.2	142	
						Patch 21 mg		39.1 (10.8)	50.8	132	
Joseph et al,[10] 1996	Cardiac disease	28	44	10	6	Placebo	Behaviour counseling	60.0	98.6	290	Stroke, acute myocardial infarction, atrial fibrillation, heart failure, CVD
						Patch 7, 14, 21 mg	Behaviour counseling	61.0	98.6	294	
Gourlay et al,[42] 1995	Healthy	27 (10)	23 (10)	12	6	Placebo	Behavioral counseling	41.0 (10.4)	42.4	314	Heart palpitations, cardiac arrhythmia
						Patch 7–21 mg	Behavioral counseling	41.0 (10.4)	42.4	315	
Schneider et al,[43] 1995	Healthy	29 (10)	22 (10)	24	12	Placebo		39.7 (7.2)	58.0	127	Heart palpitations
						Spray 1 mg		39.9 (7.7)	52.0	128	
Hjalmarson et al,[44] 1994	Healthy	21 (10–70)	26 (10)	12	12	Placebo	Group counseling	44.9 (11.1)	43.1	123	Pounding heart
						Spray 1 mg	Group counseling	44.9 (11.5)	42.4	125	
						Gum 2 mg	Behavior modification program	38.1 (8.8)	76.0	76	
Sutherland et al,[45] 1992	Healthy	26 (10)	22 (10)	4	12	Placebo		40.4 (9.4)	34.2	111	Pounding heart
						Spray 1 mg		38.9 (9.4)	37.1	116	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
Tønnesen et al,[46] 1988	Healthy plus chronic disease	≥10	NR	6	24	Placebo	Counseling	45.5 (11.7)	42.0	53	Heart palpitations
						Gum 2 mg	Counseling	44.9 (10.4)	47.0	60	
Bupropion											
Eisenberg et al,[15] 2013	Acute myocardial infarction	23 (11)	33 (12)	9	12	Placebo	Counseling	53.4 (10.3)	83.2	200	Acute myocardial infarction, unstable angina, atrial fibrillation, cardiac arrest, tachycardia, cardiogenic shock, congestive heart failure, thrombo-endarterectomy
						Bupropion 300 mg	Counseling	54.5 (10.4)	83.8	192	
Planer et al,[47] 2011	Acute coronary syndrome	31 (16)	NR	8	12	Placebo	Counseling	51.5 (9)	82.7	75	Acute myocardial infarction, atrial fibrillation
						Bupropion 300 mg	Counseling	52.4 (11)	77	74	
McCarthy et al,[48] 2008	Healthy	22 (10)	25 (12)	8	12	Placebo	No counseling	39.4 (11.3)	46	116	Stroke, aneurysm
						Placebo	Counseling	37.8 (12.8)	47.9	121	
						Bupropion 300 mg	No counseling	41.0 (12.6)	50.9	116	
						Bupropion 300 mg	Counseling	36.8 (11.4)	54	113	
Covey et al,[49] 2007	Healthy	21 (9)	NR	20	12	Placebo	Placebo gum	42.5 (10.6)	53.5	71	Acute myocardial infarction
						Placebo	Nicotine gum	43.5 (10.8)	54.2	72	
						Bupropion 300 mg	Placebo gum	43.7 (10.8)	53.4	73	
						Bupropion 300 mg	Nicotine gum	40.3 (9.9)	57.5	73	
Evins et al,[50] 2007	Schizophrenia	26 (12)	26 (11)	12	6	Placebo	Nicotine patch and gum	43.6 (10.9)	NR	26	Heart palpitations
						Bupropion 300 mg	Nicotine patch and gum	44.8 (9.2)	NR	25	
Fossati et al,[51] 2007	Healthy	23 (9)	≥1	7	12	Placebo		48.5 (42–56) [IQR]*	55.4	193	Acute myocardial infarction
						Bupropion 300 mg		49.4 (40–57) [IQR]*	62	400	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
Muramoto et al,[52] 2007	Adolescent	11 (9) [IQR]*	4*	6	6	Placebo	Counseling	16*	58.3	103	Tachycardia
						Bupropion 150 mg	Counseling	16*	46.7	105	
						Bupropion 300 mg	Counseling	16*	57.7	104	
Uyar et al,[53] 2007	Pulmonary disease	≥10	≥1	6	6	Advice		36.0 (10.6)	70	31	Tachycardia
						Bupropion 300 mg		36.0 (10.5)	88	50	
						Patch 7–21 mg		36.3 (12.7)	80.0	50	
Gonzales et al, [54]	Healthy	21 (9)	24 (12)	12	12	Placebo	Counseling	42.6 (11.8)	54.1	344	Acute myocardial infarction, atrial fibrillation
						Bupropion 300 mg	Counseling	42.0 (11.7)	58.4	329	
						Varenicline 2 mg/d	Counseling	42.5 (11.1)	50	352	
Jorenby et al,[55] 2006	Healthy	22 (12)	25 (12)	12	12	Placebo	Counseling	42.3 (11.6)	58.1	341	Acute myocardial infarction, coronary artery occlusion
						Bupropion 300 mg	Counseling	42.9 (11.9)	60.2	342	
						Varenicline 2 mg/d	Counseling	44.6 (11.4)	55.2	344	
Rigotti et al,[13] 2006	CVD	22 (12)	38 (11)	12	12	Placebo	Counseling	54.9 (9.7)	69	124	Death in CVD
						Bupropion 300 mg	Counseling	56.7 (9.7)	69	124	
Puska et al,[56] 2005	Healthy	23 (8)	≥1	7	12	Placebo	Motivational support	40.3 (9.1)	36	170	Stroke
						Bupropion 300 mg	Motivational support	40.3 (8.9)	36	517	
Zellweger et al,[57] 2005	Healthy	23 (8)	26 (16)	7	12	Placebo		40.3 (9.1)	36	170	Stroke
						Bupropion 300 mg		40.3 (8.9)	36	517	
Dalsgareth et al,[58] 2004	Healthy	19 (6)	27 (13)	7	6	Placebo		44.3 (9.4)	25.4	114	Tachycardia, acute myocardial infarction (death)
						Bupropion 300 mg		42.5 (9.9)	25.3	221	
Tonstad et al,[14] 2003	CVD	25 (12)	50 (25)	7	12	Placebo		55.1 (9.0)	79	313	Angina pectoris, heart palpitations
						Bupropion 300 mg		55.6 (9.2)	74	313	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
ZYB40030,[59] 2003	COPD	NR	NR	9	9 wk	Placebo		55 (9.5)	63.4	159	Acute myocardial infarction, angina
						Bupropion 300 mg		55 (9.5)	63.4	155	
George et al,[60] 2002	Schizophrenia	24 (11)	NR	10	6	Placebo		40.9 (9.4)	50	16	Irregular heartbeat
						Bupropion 300 mg		45.4 (11.9)	62.5	16	
ZYB30011,[61] 2002	>1 CVD risk factor	≥10	≥1	7	6	Placebo		49.2 (9.9)	62.2	127	Heart palpitations
						Bupropion 300 mg		47.9 (9.7)	69.3	127	
Gonzales et al,[62] 2001	Healthy	≥15	NR	12	6	Placebo		45.5 (11.2)	45	224	Stroke, acute myocardial infarction, atrial fibrillation, coronary artery disorder
						Bupropion 300 mg		44.5 (11.8)	52	226	
Hays et al,[63] 2001	Healthy	27 (10)	≥1	45	24	Placebo		45.4 (9.2)	52.1	215	Angina, stroke, acute myocardial infarction (death)
						Bupropion 300 mg		47.0 (9.7)	45.3	214	
Tashkin et al,[64] 2001	COPD	28 (11)	51 (24)	12	6	Placebo		54.5 (9.5)	55.1	205	Stroke, cardiac arrest, myocardial infarction,
						Bupropion 300 mg		53.2 (9.0)	54.9	206	
ZYB40001,[65] 2001	Healthy	≥15	≥1 month	12	3	Placebo	Behavioural support	43.8 (22–68)	50.3	143	Stroke
						Bupropion 300 mg	Behavioural support	43.7 (19–67)	46.8	141	
ZYB40005,[66] 2001	NR	NR	NR	24	12	Placebo		41.8 (18–71)	53	304	Acute myocardial infarction, congestive heart failure
						Bupropion 300 mg		42.4 (19–69)	57.4	305	
SMK20001,[67] 2000	Healthy	≥15	≥1	7	12	Placebo		42.1 (10.2)	51	143	Stroke, acute myocardial infarction
						Bupropion 300 mg		42.9 (10.2)	52.4	143	
Jorenby et al,[68] 1999	Healthy	26 (11)	26 (11)	9	12	Placebo	None	42.7 (10.2)	41.2	160	Acute myocardial infarction (death)
						No treatment	Patch	44.0 (10.9)	48.4	244	
						Bupropion 300 mg	None	42.3 (10.2)	48.4	244	
						Bupropion 300 mg	Patch	43.9 (11.6)	50.6	245	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
Hurt et al,[69] 1997	Healthy	27 (10)	≥1	7	12	Placebo		43.0 (10.7)	40.5	153	Cardiac arrest (death)
						Bupropion 100 mg		44.1 (10.5)	41.8	153	
						Bupropion 150 mg		42.3 (11.3)	49.7	153	
						Bupropion 300 mg		45.0 (11.8)	49.4	156	
ZYBAK1A402,[70] 1994	Healthy	≥20	NR	12	12	Placebo	Counseling	54 (11.3)	86.3	95	Tachycardia
						Bupropion 300 mg	Counseling	51 (11.8)	82.1	95	
AKIA401,[71] 1992	Healthy	≥20	NR	12	12	Placebo	Counseling	58.0 (8.0)	100	25	Fatal hypotension (death)
						Bupropion 300 mg	Counseling	55 (9.3)	100	23	
Varenicline											
Tønnesen et al,[72] 2013	Healthy	23 (9)	NR	12	52	Placebo	Counseling	55.6 (9.1)	49.3	69	Stroke, myocardial infarction
						Varenicline 2 mg/d	Counseling	53.6 (8.2)	42.9	70	
Rennard et al,[73] 2012	Healthy	21 (10–70)	25 (2–57)	12	6	Placebo	Counseling	43.2 (12.2)	59.6	166	Carotid artery stenosis
						Varenicline 2 mg/d	Counseling	43.9 (12.5)	60	493	
Wong et al,[74] 2012	Perioperative	17 (8)	≥1	12	12	Placebo	Counseling	53.3 (11.4)	50.4	135	Myocardial infarction, ischemia, stroke, deep vein thrombosis, bradycardia
						Varenicline 0.5–2 mg/d	Counseling	51.9 (11.8)	55.0	151	
Garza et al,[75] 2011	Healthy	22 (10–50)	17 (3–49)	12	3	Placebo	Counseling	33.8 (8.8)	72.7	55	Heart palpitations
						Varenicline 2 mg/d	Counseling	33.4 (11.8)	60	55	
Steinberg et al,[76] 2011	Hospitalized Patients	≥10	NR	12	6	Placebo	Counseling	51 (22–78)	60	40	Heart palpitation, tachycardia, stroke, acute myocardial infarction
						Varenicline 2 mg/d	Counseling	51 (22–78)	59	39	
Tashkin et al,[77] 2011	Mild to moderate COPD	24 (10–99)	40 (11–67)	12	12	Placebo	Counseling	57.1 (9.0)	62.2	251	Angina pectoris, stroke, acute myocardial infarction
						Varenicline 2 mg/d	Counseling	57.2 (9.1)	62.5	248	
Bolliger et al,[78] 2010	Healthy	24 (10–90)	26 (1–58)	12	6	Placebo	Counseling	43.9 (10.8)	65.7	198	Tachycardia, atrial fibrillation

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
						Varenicline 2 mg/d	Counseling	43.1 (10.8)	57.7	390	
Fagerström et al,[79] 2010	Healthy	NR	22 (11)	12	6	Placebo	Counseling	43.9 (12.0)	89.9	218	Acute myocardial infarction
						Varenicline 2 mg/d	Counseling	43.9 (12.0)	88.7	214	
Rigotti et al,[22] 2010	CVD	23 (10–60)	40 (5–63)	12	12	Placebo	Counseling	55.9 (8.3)	82.2	359	Hospitalized angina pectoris, coronary revascularization, acute myocardial infarction, stroke
						Varenicline 2 mg/d	Counseling	57.0 (8.6)	75.2	355	
Aubin et al,[80] 2008	Healthy	23 (11–80)	25 (1–62)	12	9	Varenicline 2 mg/d	Counseling	42.9 (10.5)	48.4	376	Myocardial infarction
						Patch 7–21 mg	Counseling	42.9 (12.0)	50	370	
Niaura et al,[81] 2008	Healthy	22 (6–60)	25 (2–50)	12	12	Placebo	Education booklet	42.1 (11.7)	53.5	160	Acute myocardial infarction, atrial fibrillation,
						Varenicline 0.5–2 mg/d	Education booklet	41.5 (11.3)	50.3	160	
Nakamura et al,[82] 2007	Healthy	24 (10)	20 (11)	12	12	Placebo	Counseling	39.9 (12.3)	76	154	Angina pectoris
						Varenicline 0.5 mg/d	Counseling	40.2 (12.3)	72.7	153	
						Varenicline 1 mg/d	Counseling	39.0 (12.0)	71.1	156	
						Varenicline 2 mg/d	Counseling	40.1 (11.6)	79.2	156	
Tsai et al,[83] 2007	Healthy	23 (10–60)	21 (3–52)	12	6	Placebo	Counseling	40.9 (11.1)	92.7	124	Unstable angina
						Varenicline 2 mg/d	Counseling	39.7 (9.3)	84.9	126	
Williams et al,[84] 2007	Healthy	23 (10–90)	30 (4–57)	52	12	Placebo	Counseling	46.6 (12.1)	48.4	126	CVD, acute myocardial infarction
						Varenicline 2 mg/d	Counseling	48.2 (12.3)	50.6	251	
Nides et al,[85] 2006	Healthy	20 (8)	24 (11)	7	12	Placebo	Counseling	41.6 (10.4)	52	127	Stroke
						Varenicline 0.3 mg/d	Counseling	41.9 (10.6)	50	128	
						Varenicline 1 mg/d	Counseling	42.9 (10.5)	43.7	128	
						Varenicline 2 mg/d	Counseling	41.9 (9.8)	50.4	127	

Trial	Participant Characteristics	Cigarettes per Day, mean (SD or range); median*	Years Smoking, mean (SD or range); median*	Treatment Duration, wk	Whole Study Duration, mo	Arm	Cotreatment	Age, mean (SD or range); median*	Male, %	n	Reported CV Outcomes
Oncken et al,[86] 2006	Healthy	21 (9)	25 (10)	12	12	Placebo	Counseling	43.0 (9.4)	51.9	129	Unstable angina, tachycardia
						Varenicline 1 mg/d	Counseling	43.2	49.1	259	
						Varenicline 2 mg/d	Counseling	43	48.6	259	
Tonstad et al,[87] 2006	Healthy	21 (7)	28 (10)	12	12	Placebo		45.3 (10.4)	48.3	607	
						Varenicline 2 mg/d		45.4 (10.4)	50.2	603	

COPD indicates chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; IQR, interquartile range; and NRT, nicotine replacement therapy.

Table 2

Estimated RR and 95% CIs Produced by Random-Effects Pairwise Meta-Analysis for Cardiovascular Events in Smoking Cessation RCTs

		All CV Events			MACEs		
Studies, n	**Comparison**	**Events**	**RR (95% CI)**	**I^2, %**	**Events**	**RR (95% CI)**	**I^2, %**
All trials							
21 RCTs[10,30–46,49,53,68]	NRT vs placebo	202/6329 vs 83/5318	1.81 (1.35–2.43)	0	12/6329 vs 7/5318	1.38 (0.58–3.26)	0
27 RCTs[13-15,47–49,51–71]	Bupropion vs placebo	50/5947 vs 42/4455	1.03 (0.71–1.50)	0	15/5947 vs 25/4455	0.57 (0.31–1.04)	0
18 RCTs[22,54,55,72–79,81–87]	Varenicline vs placebo	63/5469 vs 41/3603	1.24 (0.85–1.81)	0	22/5469 vs 13/3603	1.44 (0.73–2.83)	0
2 RCTs[54,55]	Bupropion vs varenicline	1/686 vs 2/696	0.74 (0.05–10.5)		1/686 vs 0/696	3.07 (0.12–75.09)	
3 RCTs[49,53,68]	Bupropion vs NRT	4/367 vs 2/366	1.40 (0.25–7.82)	2	0/367 vs 1/366	0.34 (0.01–7.94)	
1 RCT[80]	Varenicline vs NRT	0/378 vs 2/379	0.20 (0.01–4.16)		0/378 vs 2/379	0.20 (0.01–4.16)	
High-risk patients only		*k=13*			*k=9*		
3 RCTs[10,46,53]	NRT vs placebo	33/454 vs 26/374	1.24 (0.77–2.02)		6/454 vs 4/374	1.48 (0.42–5.19)	NA
8 RCTs[13–15,47,53,59,61,64]	Bupropion vs placebo	27/1241 vs 25/1234	1.04 (0.59–1.83)	0	9/1241 vs 15/1234	0.63 (0.28–1.41)	0
3 RCTs[22,74,77]	Varenicline vs placebo	30/754 vs 26/745	1.15 (0.69–1.92)		14/754 vs 11/745	1.35 (0.61–3.01)	0
	Bupropion vs varenicline		NA			NA	
1 RCT[53]	Bupropion vs NRT	3/50 vs 0/50	7 (0.37–132.10)		0/50 vs 0/50	NA	
	Varenicline vs NRT		NA			NA	

CI indicates confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; NRT, nicotine replacement therapy; RCT, randomized, clinical trial; and RR, relative risk.

Table 3

Estimated RR and 95% CrI From Random-Effects Network Meta-Analysis for Cardiovascular Events in Smoking Cessation RCTs

Comparison	All CVD events	MACEs
All trials		
NRT vs placebo	2.29 (1.39–3.82)	1.95 (0.92–4.30)
Bupropion vs placebo	0.98 (0.54–1.73)	0.45 (0.21–0.85)
Varenicline vs placebo	1.30 (0.79–2.23)	1.34 (0.66–2.66)
Bupropion vs varenicline	0.76 (0.33–1.73)	0.33 (0.16–0.87)
Bupropion vs NRT	0.43 (0.19–0.91)	0.23 (0.08–0.63)
Varenicline vs NRT	0.56 (0.25–1.27)	0.67 (0.26–1.90)
High-risk populations (sensitivity analysis)		
NRT vs placebo	1.31 (0.58–3.32)	1.53 (0.38–6.24)
Bupropion vs placebo	1.06 (0.59–2.04)	0.48 (0.18–1.21)
Varenicline vs placebo	0.99 (0.45–1.88)	1.22 (0.44–2.90)
Bupropion vs varenicline	1.09 (0.46–2.92)	0.39 (0.11–1.49)
Bupropion vs NRT	0.81 (0.26–2.26)	0.31 (0.05–1.68)
Varenicline vs NRT	0.92 (0.34–2.19)	0.81 (0.13–4.20)

CrI indicates credibility interval; CVD, cardiovascular disease; MACE, major adverse cardiovascular event; NRT, nicotine replacement therapy; RCT, randomized, clinical trial; and RR, relative risk.