Efficacy and Safety of Smoking Cessation Interventions in Patients With Cardiovascular Disease

A Network Meta-Analysis of Randomized Controlled Trials

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Background—Although the efficacy and safety of smoking cessation interventions are well established, their efficacy and safety in patients with cardiovascular disease (CVD) remain unclear. The objective of this study was to evaluate the efficacy and safety of pharmacological and behavioral smoking cessation interventions in CVD patients via a meta-analysis of randomized controlled trials.

Methods and Results—EMBASE, PsycINFO, MEDLINE, PubMed, and the Cochrane Tobacco Addiction Specialized Register were searched for randomized controlled trials evaluating the efficacy of smoking cessation pharmacotherapies and behavioral therapies in CVD patients. Outcomes of interest were smoking abstinence at 6 and 12 months, defined using the most rigorous criteria reported. Data were pooled across studies for direct comparisons using random-effects models. Network meta-analysis using a graph-theoretical approach was used to generate the indirect comparisons. Seven pharmacotherapy randomized controlled trials (n=2809) and 17 behavioral intervention randomized controlled trials (n=4666) met our inclusion criteria. Our network meta-analysis revealed that varenicline (relative risk [RR]: 2.64; 95% confidence interval [CI], 1.34–5.21) and bupropion (RR: 1.42; 95% CI, 1.01–2.01) were associated with greater abstinence than placebo. The evidence about nicotine replacement therapies was inconclusive (RR: 1.22; 95% CI, 0.72–2.06). Telephone therapy (RR: 1.47; 95% CI: 1.15–1.88) and individual counseling (RR: 1.64, 95% CI: 1.17–2.28) were both more efficacious than usual care, whereas in-hospital behavioral interventions were not (RR: 1.05; 95% CI, 0.78–1.43).

Conclusions—Our meta-analysis suggests varenicline and bupropion, as well as individual and telephone counseling, are efficacious for smoking cessation in CVD patients. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e002458. DOI: 10.1161/CIRCOUTCOMES.115.002458.)**

Key Words: behavior therapy ■ bupropion ■ cardiovascular disease ■ meta-analysis ■ smoking ■ tobacco use cessation products ■ varenicline

The efficacy and safety of pharmacological and behavioral smoking cessation interventions have been examined in multiple randomized controlled trials (RCTs), with subsequent meta-analyses showing that such interventions are efficacious at increasing quit rates.[1,2] However, participants in these trials were generally healthy, and the generalizability of these data to patients with cardiovascular disease (CVD) is unclear. This unclear generalizability is underscored by 3 trials that found that the smoking cessation drug bupropion did not increase the prevalence of abstinence when used in patients with acute manifestations of CVD.[3–5] This may be because of fundamental differences between such patients, who tend to have higher quit rates without therapy because of an increased motivation to quit and the teachable moment that occurs after an adverse event,[6] and the otherwise healthy smokers enrolled in previous RCTs.[6,7] Similarly, the generalizability of RCTs conducted in the general population to patients with stable CVD is also unknown. A thorough assessment of the effect of smoking cessation interventions in CVD patients is needed to develop tailored recommendations to increase abstinence in the CVD population. Consequently, we conducted a systematic review and network meta-analysis of RCTs to evaluate the relative efficacy and safety of pharmacological and behavioral smoking cessation interventions in CVD patients.

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WHAT IS KNOWN

- Several randomized controlled trials and subsequent meta-analyses have demonstrated that pharmacological and behavioral smoking cessation therapies are efficacious at increasing smoking abstinence in the general population.
- However, participants in these trials were generally healthy, and the generalizability of these data to patients with cardiovascular disease is unclear.

WHAT THE STUDY ADDS

- Our network meta-analysis of 24 trials of pharmacotherapies and behavioral therapies suggests that, among patients who are motivated to quit smoking, varenicline and bupropion are efficacious for smoking cessation in patients with cardiovascular disease, whereas available data about nicotine replacement therapies are inconclusive.
- Individual and telephone counseling also seem to be efficacious in this patient population.
- Available evidence suggests that varenicline is the most efficacious smoking cessation therapy in patients with cardiovascular disease who are motivated to quit smoking, although more safety data are needed.

Methods

Our systematic review and network meta-analysis was performed after a prespecified protocol and is reported using the guidelines described in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for reporting of systematic reviews incorporating network meta-analyses.[8]

Data Sources

We systematically searched Ovid EMBASE, Ovid PsycINFO, Ovid MEDLINE, PubMed, and the Cochrane Tobacco Addiction Group Specialized Register from inception to June 2015 to identify RCTs of pharmacological and behavioral smoking cessation interventions in CVD patients. The search strategy was designed and conducted by an experienced health librarian (G.C.G.). No language restriction was used in the search. A combination of text words, Medical Subject Headings (MeSH), EMTREE terms, and the Thesaurus of Psychological Index Terms was used for smoking cessation, interventions, and CVD (Tables I through V in the Data Supplement). Additionally, we scanned the references of previous reviews on smoking cessation in CVD and hospitalized populations[9–14] to retrieve studies that were not identified by our primary search.

Study Selection

The titles and abstracts of identified publications were screened by 2 independent reviewers, with those deemed relevant by at least one reviewer carried forward for full-text review, where disagreements were resolved by consensus. Included studies were RCTs that investigated the efficacy or safety of a smoking cessation intervention (pharmacological or behavioral) compared with an appropriate reference group (placebo for pharmacological interventions and usual care for behavioral interventions). Pharmacotherapies of interest were varenicline, bupropion, or nicotine replacement therapy (NRT), including patch, gum, inhaler, or spray, and behavioral therapies, including in-hospital counseling (inpatient counseling only), telephone counseling (≥2 telephone support sessions for outpatients), or individual counseling (≥1 outpatient counseling sessions). Inclusion was restricted to RCTs conducted in smokers with CVD or to RCTs where smoking cessation outcomes for this population were reported. CVD included the following conditions: angina pectoris, coronary artery disease, coronary artery bypass grafting, myocardial infarction, heart failure, peripheral artery disease, transient ischemic attack, and stroke. Included studies had to report smoking cessation either as continuous or point prevalence abstinence by treatment group at 6 or 12 months (allowing for a 6-week grace period). Biochemical validation of abstinence was not an inclusion criterion; however, subgroup analyses involving this study characteristic were performed.

Smoking reduction and maintenance studies were excluded, as were those that examined general lifestyle interventions not specifically aimed at smoking cessation (eg, multifactorial CVD prevention programs). Studies that randomized participants who were described as not motivated to quit or did not have a precise quit date were also excluded. Trials that included patients who were not motivated to quit were excluded because treatment effects for behavioral and pharmacological therapies are likely different in such patients and their inclusion would violate the consistency assumption if such patients were distributed differentially across treatment groups.[15] Importantly, only trials that explicitly stated that their population included patients who were not motivated to quit were excluded; with patients having given informed consent to participate in a smoking cessation trial, it was assumed that patients were motivated unless stated otherwise (Table VI in the Data Supplement). Observational studies, case reports, case series, letters to editors, editorials, reviews, conference abstracts, commentaries, and guidelines were excluded. Finally, studies published in a language other than English or French were excluded.

Data Extraction

Data extraction was performed independently by 2 reviewers with any disagreements resolved by consensus or by a third reviewer. Study characteristics were extracted, including study population (inpatient versus outpatient, acute versus stable) and intervention details. For pharmacotherapy RCTs, type and dosage were extracted. For behavioral therapy RCTs, intensity level, counseling type, duration and number of sessions, usual care definition, and adjunct pharmacotherapy use were extracted. Outcomes were point prevalence of abstinence and continuous abstinence from smoking at 6 and 12 months. Patient demographics, smoking habits, and use of biochemical validation were also extracted. Safety outcomes extracted included the number of patients with adverse events, serious adverse events, and cardiovascular events. Multigroup trials were treated as separate trials using the same reference group.

Classification of Outcomes

Outcomes were classified following the criteria from a previous systematic review on pharmacotherapies for smoking cessation.[1] Point prevalence of abstinence was defined as no smoking in the 7 days before the follow-up. Continuous abstinence was defined as a complete cessation from the quit date to the latest follow-up. Because of the heterogeneity of reported outcomes between studies, we analyzed smoking abstinence according to the most rigorous criterion provided by each trial: (1) continuous abstinence at 12 months; (2) continuous abstinence at 6 months; (3) point prevalence of abstinence at 12 months; and (4) point prevalence of abstinence at 6 months, with priority given to any biochemically validated outcome. All analyses were intention-to-treat, with all patients who were alive but lost to follow-up considered to have returned to smoking, a common assumption in smoking cessation trials.[16]

Quality Assessment

Quality assessment was performed by 2 independent reviewers using the Cochrane Collaboration's tool for assessing risk of bias,[17] with disagreements resolved by consensus or by a third reviewer. This tool assesses 6 potential sources of bias: sequence generation; allocation concealment; blinding of participants, outcome assessors, and personnel; incomplete outcome data; selective outcome reporting; and other potential sources of bias. A score of high, low, or unclear was

assigned for each domain. All RCTs that met our inclusion criteria were included, regardless of their quality.

Statistical Analysis

Relative risks (RRs) and 95% confidence intervals (CIs) were generated using DerSimonian and Laird random-effects models with inverse variance weighting. In our primary analysis, count data were pooled, and heterogeneity was estimated by the I^2 statistic. Stratified analyses were performed based on the nature of CVD (stable versus acute) and the presence of biochemical validation. Network meta-analysis was used to compare the efficacy of interventions that may or may not have been directly compared with each other using the graph-theoretical approach by Rücker.[18] This approach originated from the graph-theoretical methods that were developed for the electrical network theory. In the case of a pairwise meta-analysis with direct comparisons, this approach simplifies to the fixed-effect model estimate. The network geometry was explored graphically. The transitivity, homogeneity, and consistency assumptions were assessed via subgroup analyses (by type of therapy, CVD subtype, and the exclusion of behavioral trials in which the availability of pharmacotherapy was differential between treatment groups) and the I^2 statistic. Consistency was assessed by running inconsistency models and assessing the residuals in inconsistency plots. Treatment rankings and *P* scores were calculated, and rankogram curves were constructed. All statistical analyses other than inconsistency models were performed using R version 3.2.1; direct comparisons were analysed using the meta package, and network meta-analyses were performed with the netmeta package.[19] Inconsistency models were created using NetMetaXL and WinBUGS.[20]

Results

Search Results

Our initial electronic search identified 2967 potentially relevant publications (Figure 1). After the removal of 814 duplicates, the titles and abstracts of 2153 relevant publications were screened for eligibility, and 198 were selected for full-text review, 22 of which met our inclusion criteria. A list of the full texts that did not meet our inclusion criteria is presented in the Data Supplement. The handsearch of reference lists of previous reviews identified 2 additional RCTs[21,22] that had not been retrieved by our electronic search. Thus, a total of 24 RCTs[3–5,7,21–40] were included in our systematic review and meta-analysis. One RCT had 2 behavioral intervention arms; these 2 arms were treated as 2 separate trials and compared with the same usual care group.

Study and Patient Characteristics

In total, 6761 patients were randomized in the 24 included studies: 2095 in the 7 pharmacotherapy trials and 4666 in the 17 behavioral therapy trials (Tables 1 and 2), with sample sizes ranging from 40 to 643. The 7 pharmacotherapy trials examined 12-month continuous abstinence, with 6 biochemically validating abstinence. All 7 studies had a cointervention in the form of personalized counseling, with the number of sessions ranging from 3 to 25.

Of the 17 behavioral interventions trials, 5 examined 12-month continuous abstinence, with 15 biochemically validating abstinence. Seven trials did not provide any form of adjunct pharmacotherapy, 5 provided it for both the control and the intervention group, and 3 trials provided it only for the intervention group. The type of behavioral intervention was most often motivational support (10 trials), with only 3 trials offering cognitive behavioral therapy. On average, in-hospital counseling trials offered 44 minutes of intervention, telephone counseling trials 99 minutes, and individual counseling trials 233 minutes.

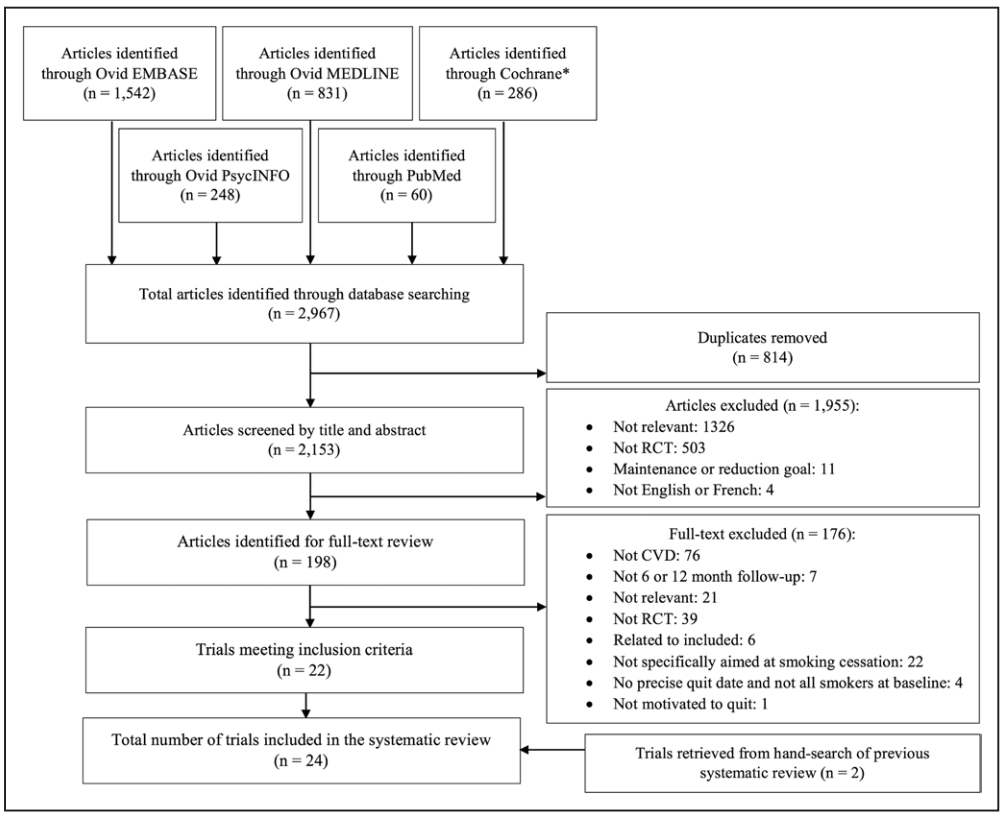

Figure 1. Flow diagram of randomized controlled trials (RCTs) included in the systematic review and meta-analysis. *Cochrane indicates Cochrane Tobacco Addiction Group Specialized Register.

Table 1. Characteristics of RCTs Examining the Efficacy of Smoking Cessation Pharmacotherapies in Patients With Cardiovascular Disease

First Author	Year	Population	No. of Patients (n)			Most Rigorous Outcome	Cointervention (No. of Sessions)
			Total Randomized	Efficacy Analysis			
				I	C		
NRTs							
Joseph et al[23]	1996	Outpatient-stable CVD	584	294	290	12 mo CA-BV	Individual counseling (3)
Campbell et al[22]	1991	Inpatient-CVD	85	44	41	12 mo CA-BV	Individual counseling (7)
Bupropion							
Tonstad et al[24]	2003	Outpatient-stable CVD	629	313	313	12 mo CA-BV	Individual counseling (19)
Eisenberg et al[3]	2013	Inpatient-acute CVD	392	183	194	12 mo CA-BV	Individual counseling (7)
Rigotti et al[5]	2006	Inpatient-acute CVD	254	124	122	12 mo CA-BV	Telephone counseling (6)
Planer et al[4]	2011	Inpatient-ACS	151	74	75	12 mo CA	Individual counseling (21)
Varenicline							
Rigotti et al[25]	2010	Outpatient-stable CVD	714	355	359	12 mo CA-BV	Individual Counseling (25)

ACS indicates acute coronary syndrome; BV, biochemically validated; C, control; CA, continuous abstinence; CVD, cardiovascular disease, I, intervention; and NRT, nicotine replacement therapy.

Quality Assessment

Overall, the pharmacotherapy trials had a low risk of bias (Table VII in the Data Supplement). Three studies had insufficient information about sequence generation and allocation concealment, and those were rated as having an unclear risk of bias. The studies had a low risk of bias for all other criteria, except one trial that had a high risk of bias for selectively reporting certain outcomes.

Among the 17 behavioral therapy RCTs that were included in this meta-analysis, 7 trials had insufficient information about sequence generation and 9 for allocation concealment, resulting in an unclear risk of bias for those domains. All behavioral trials had a high risk of bias for blinding of participants and personnel; this was expected given the nature of behavioral interventions. In addition, there were 2 studies with a high risk of having incomplete outcome data because of losses to follow-up that were not accounted for in the analysis. Four studies had a high risk of selective outcome reporting and 1 gave insufficient information for this domain. Seven studies had a high risk of other biases for issues related to missingness and imbalances in baseline characteristics between treatment groups.

Efficacy of Pharmacotherapies and Behavioral Therapies

In our direct comparisons of pharmacotherapies, the use of bupropion and NRTs for smoking cessation produced inconclusive results, although the possibility of some benefit is likely, particularly for bupropion (Figure 2; Table VIII in the Data Supplement). Interestingly, when data were stratified by stable and acute CVD populations, a difference in efficacy was observed (Figure I in the Data Supplement), with the one study conducted in stable CVD patients[24] finding bupropion to be highly efficacious compared with placebo (RR: 2.46; 95% CI, 1.63–3.71), whereas the pooled result for acute CVD patients suggested little to no benefit (RR: 1.16; 95% CI, 0.90–1.50). The efficacy of varenicline compared with placebo was only assessed in one study,[25] which found varenicline to be highly efficacious compared with placebo in stable CVD patients (RR: 2.64; 95% CI, 1.72–4.06; Figure 2).

In our direct comparison of behavioral therapies, we found that in-hospital counseling[7,26–28] was not efficacious at increasing smoking abstinence (Figure 3). However, as the intensity of the behavioral interventions increased, greater increases in smoking abstinence were observed; telephone counseling[26,29–36] was 50% more efficacious than usual care (RR: 1.50; 95% CI, 1.15–1.97), and individual counseling[21,37–40] was 68% more efficacious than usual care (RR: 1.68; 95% CI, 1.13–2.48; Figure 3). Stratified analyses according to stable and acute CVD subtypes were also performed for behavioral therapies (Figures II through IV in the Data Supplement). Telephone counseling was efficacious in both the stable and acute subgroups; however, the effect appeared greater in the patients with acute CVD (RR: 1.96; 95% CI, 1.17–3.29) than in those with stable CVD (RR: 1.24; 95% CI, 1.04–1.48).

Network Meta-Analysis

In indirect comparisons via network meta-analysis, we first compared all pharmacological and behavioral therapies to a single reference group consisting of placebo or usual care (Figure 4). This analysis suggests that bupropion is an efficacious smoking cessation therapy (RR: 1.42; 95% CI, 1.01–2.00). For all other therapies, results were similar to those obtained in direct comparisons, with varenicline being the most efficacious therapy (RR: 2.64; 95% CI, 1.34–5.21), followed by individual (RR: 1.64; 95% CI, 1.17–2.28) and telephone counseling (RR: 1.47; 95% CI, 1.15–1.88). We then compared each therapy to each other (Table 3). Because of the wide 95% CIs obtained, data are insufficient to definitively demonstrate that one therapy is superior to another. However, varenicline seems to be more efficacious when compared with the placebo/usual care group (RR: 2.64; 95% CI, 1.34–5.21) than all the other pharmacological and behavioral treatments. As with our direct comparisons, a trend was observed where increasing intensity of behavioral

Table 2. Characteristics of RCTs Examining the Efficacy of Smoking Cessation Behavioral Interventions in Patients With Cardiovascular Disease

First Author	Year	Population	Type of Intervention (Duration in Min/No. of Sessions)	Number of Patients (n)			Most Rigorous Outcome	Adjunct Pharmacotherapy
				Total Randomized	Efficacy Analysis			
					I	C		
In-hospital counseling								
Hajek et al[7]	2002	Inpatient-acute CVD	Basic (34/1)	540	274	266	12 mo CA-BV	Not provided
Miller et al[26]	1997	Inpatient-CVD	Motivational support (58/2)	448	138	310	12 mo CA-BV	…
Wiggers et al[27]	2006	Outpatient-stable CVD	Behavioral therapy (23/2)	384	188	188	12 mo PP-BV	Not provided
Rigotti et al[28]	1994	Inpatient-CABG	CBT (60/4)	89	44	43	12 mo CA-BV	Not provided
Telephone counseling								
Smith et al[29]	2011	Inpatient-CVD	Motivational support (53/8)	643	301	315	12 mo PP-BV	Not provided
Miller et al[26]	1997	Inpatient-CVD	Motivational support (88/5)	492	182	310	12 mo CA-BV	…
Sivarajan Froelicher et al[30]	2004	Inpatient-CVD	Motivational support (75/6)	277	121	125	12 mo PP-BV	All high relapse patients
Smith and Burgess[31]	2009	Inpatient-acute CVD	Motivational support (105/8)	276	135	137	12 mo PP	Free on-demand for all patients
Feeney et al[32]	2001	Inpatient-ACS	Motivational support (–/9)	198	96	102	12 mo CA-BV	Not provided
Taylor et al[33]	1990	Inpatient-ACS	CBT (210/8)	173	84	82	12 mo PP-BV	Free for IG only
Reid et al[34]	2007	Inpatient-CHD	Motivational support (60/4)	100	50	49	12 mo PP	Free on-demand for all patients
Cossette et al[35]	2012	Inpatient-acute CVD	Motivational support (102/8)	40	20	20	6 mo PP-BV	Free on-demand for all patients
Park et al[36]	2015	Inpatient-acute CVD	Motivational support (180/10)	62	30	32	12 mo PP-BV	Not provided
Individual counseling								
Ockene et al[37]	1992	Inpatient-CHD	Basic (73/6)	267	133	123	12 mo PP-BV	…
Quist-Paulsen et al[21]	2003	Inpatient-acute CVD	Behavioral therapy (150/12)	250	114	119	12 mo PP-BV	High relapse patients in IG
Mohiuddin et al[38]	2007	Inpatient-acute CVD	Behavioral therapy (510/9)	209	109	100	12 mo CA-BV	Free for IG only
Hennrikus et al[39]	2010	Outpatient-PAD	CBT (200/7)	124	61	59	6 mo PP-BV	Not provided
Brunner Frandsen et al[40]	2012	Inpatient-CVD	Motivational support (–/11)	94	49	45	6 mo PP-BV	Free on-demand for all patients

ACS indicates acute coronary syndrome; BV, biochemically validated; C, control; CA, continuous abstinence; CABG, coronary artery bypass grafting; CBT, cognitive behavioral therapy; CHD, coronary heart disease; CVD, cardiovascular disease; I, intervention; IG, intervention group; NRT, nicotine replacement therapy; PAD, peripheral vascular disease; and PP, point prevalence of abstinence.

therapy was associated with greater efficacy for smoking cessation. Surface under the cumulative ranking curve values and rankograms suggest that varenicline (*P* score=0.96) and individual counseling (*P* score=0.72) ranked as the most efficacious treatments (Table IX and Figure V in the Data Supplement).

The geometry of the treatment network was described using diagrams of all comparisons between treatments in a network (Figures VI and VII in the Data Supplement). The shape of the network is mainly star shaped. In addition, diversity and co-occurrence were assessed. First, when assessing diversity, we observed that the network is moderately complex, with 6 interventions studied for smoking cessation. These interventions seem to have been studied slightly disproportionately. Second, when examining the network for co-occurrence, we observed that not all pairs were studied equally. The behavioral interventions have been studied more often than the pharmacotherapy interventions. This irregularity is normal because pharmacotherapy trials are more difficult to conduct because of the more invasive nature of the therapy. Additionally, inconsistency plots for fixed- and random-effects models (Figures VIII and IX in the Data Supplement) did not show signs of important inconsistency between trials in the network.

Safety of Pharmacotherapies and Behavioral Therapies

Safety data extracted from the pharmacotherapy trials showed a slightly higher number of adverse cardiovascular events in the treatment arm of the studies (Table 4). However, given the insufficient number of RCTs reporting safety data and the varying definitions of adverse cardiovascular events, it was

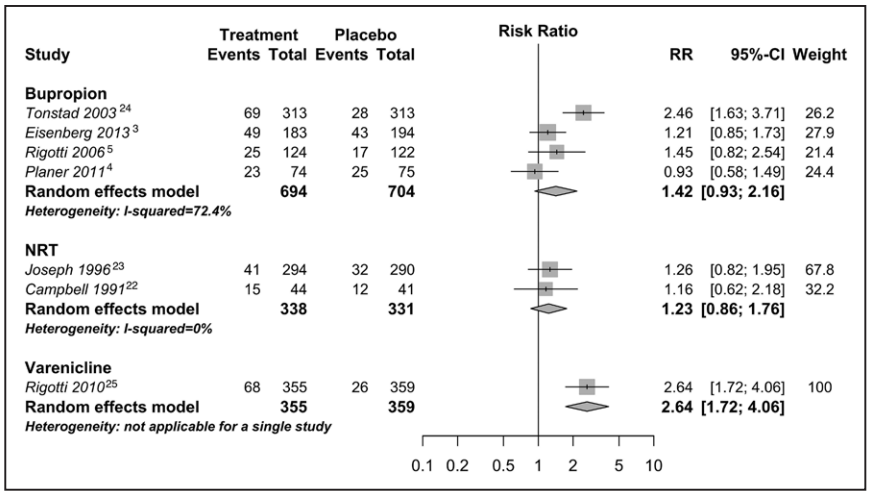

Figure 2. Forest plot describing the efficacy of pharmacotherapies using the most rigorous criterion of smoking abstinence reported relative to that of placebo in patients with cardiovascular disease. CI indicates confidence interval; NRT, nicotine replacement therapy; and RR, relative risk.

not possible to pool these data across trials or draw meaningful quantitative conclusions.

Sensitivity Analysis

We performed separate network analyses for pharmacotherapies and behavioral therapies, and the results were similar to those of our primary network analysis, supporting the assumption of homogeneity of comparison groups (Figures X and XI in the Data Supplement). In addition, we repeated our network meta-analyses excluding behavioral trials in which pharmacotherapies were only available to patients in the active treatment group; the results were consistent with those of our primary analysis (Table X in the Data Supplement). Analyses restricted to trials that biochemically validated abstinence were consistent for behavioral interventions (Figure XII in the Data Supplement). For bupropion, some differences existed, but this is likely because of sparse data, as only one RCT did not biochemically validate abstinence (Figure XIII and Tables XI and XII in the Data Supplement). Subgroup network analyses for acute CVD were inconclusive because of sparse data (Table XIII in the Data Supplement). For stable CVD, results were consistent with those of the primary analysis; however, bupropion had a stronger effect in this group (Table XIV in the Data Supplement).

Discussion

We designed this systematic review and network meta-analysis to determine the efficacy and safety of smoking cessation pharmacotherapies and behavioral therapies in patients with CVD who are motivated to quit smoking. Our results for NRTs were inconclusive because of wide CIs. However, available evidence suggests that bupropion is efficacious at increasing abstinence in patients with CVD. To date, only one study has assessed varenicline use in this population, and this study found that varenicline is highly efficacious in patients with stable CVD. We also observed that increasing intensity of the behavioral intervention was positively associated with increasing smoking abstinence, with telephone counseling

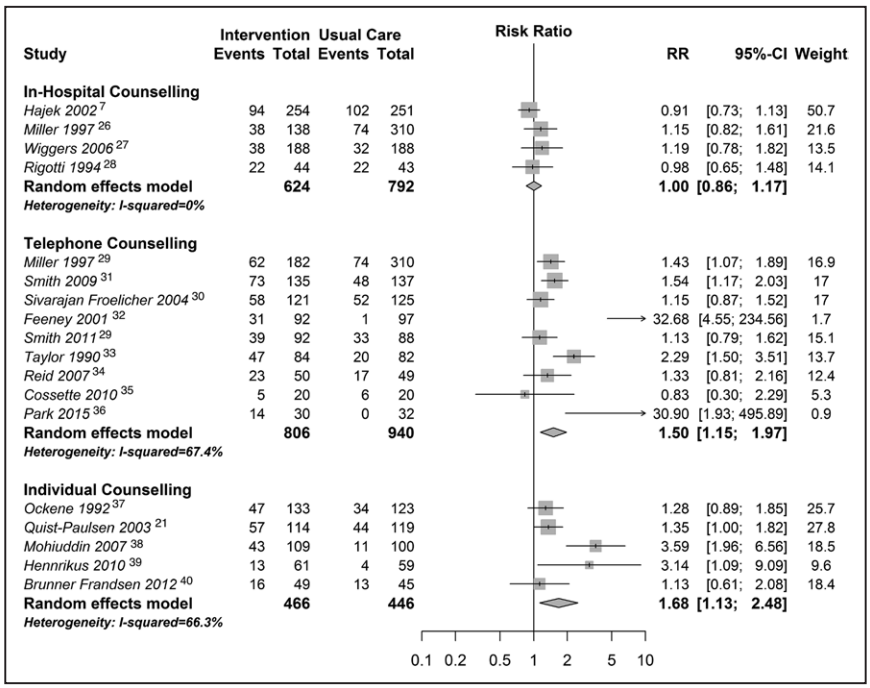

Figure 3. Forest plot describing the efficacy of behavioral therapies using the most rigorous criterion of smoking abstinence reported relative to that of usual care in patients with cardiovascular disease. CI, indicates confidence interval; and RR, relative risk.

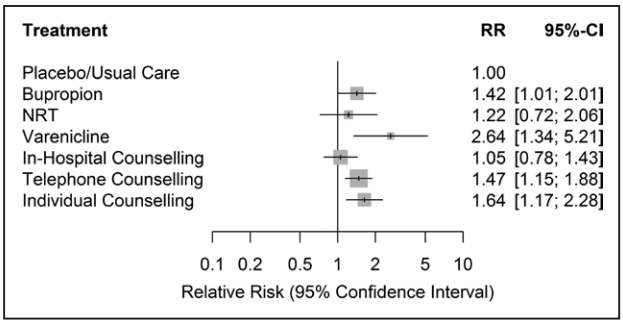

Figure 4. Forest plot describing the network meta-analysis of the efficacy of pharmacotherapies and behavioral therapies using the most rigorous criterion of smoking abstinence reported relative to that of placebo/usual care in patients with cardiovascular disease. Estimate of heterogeneity (I^2): 61.5%. CI indicates confidence interval; NRT, nicotine replacement therapy; and RR, relative risk.

and individual counseling both associated with increased smoking abstinence compared with in-hospital interventions. Our network meta-analysis ranked varenicline and individual counseling as the most efficacious smoking cessation treatments in this population.

Cardiac patients are at a higher risk for cardiovascular events compared with the general population, resulting in a greater motivation to quit smoking after a cardiac event.[11] It is, therefore, not surprising to observe different treatment effects in CVD patients and those from the general population. Trials studying the efficacy of pharmacotherapies in the CVD population remain scarce despite the well-established benefits of smoking cessation in this population, including decreased risks of stroke and myocardial infarction and lower mortality rates from CVD.[41] This may be related to safety concerns surrounding the use of smoking cessation pharmacotherapies during the acute period.[4] For example, there is a relative contraindication to NRT use in the 2 weeks post-myocardial infarction as NRT increases blood pressure and heart rate, particularly in cardiovascular patients.[42] Nonetheless, NRT is the most widely prescribed smoking cessation drug, and it is a central component of the Ottawa Heart Model[43] and the Clinical Practice Guidelines of 2008 for treating tobacco dependence,[44] standards of care in Canada and the United States, respectively.

Safety concerns also exist about the use of varenicline in patients with CVD. One RCT showed a higher number of cardiovascular adverse events in the group taking varenicline, but the 95% CI was wide (6.5 versus 6.0%; difference: 0.5%; 95% CI, −3.1 to 4.1%).[25] A meta-analysis found an increased risk of CVD with varenicline in all patients[45] including cardiovascular-related death, nonfatal myocardial infarction, and nonfatal stroke, but subsequent meta-analyses concluded that there was no association with varenicline[46] or any pharmacotherapy.[47] In addition, an observational study conducted by the US Mini-Sentinel system found no evidence of an increased risk.[48] On the basis of the available evidence, the US Food and Drug Administration has concluded that, although an increased risk of major cardiovascular events cannot be ruled out, the health benefits attributable to increased cessation with varenicline suggest that benefits likely outweigh potential harms.[49] Concerns of neuropsychiatric harms of varenicline and bupropion also exist, including changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.[50,51] With most trials excluding patients with a history of neuropsychiatric disease, neuropsychiatric adverse event data are limited. However, the recently completed the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial found no increase in neuropsychiatric adverse events among patients randomized to varenicline or bupropion relative to those randomized to nicotine patch or placebo.[52]

We identified 7 previous systematic reviews on the efficacy of smoking cessation interventions in CVD patients. Overall, the pharmacotherapy reviews found greater abstinence with active treatment.[11,12,53] The reviews that assessed the effect of the combination of pharmacotherapy and behavioral therapy had inconsistent results.[13,14] The 2 systematic reviews that examined only behavioral therapies found higher cessation rates with higher intensity behavioral interventions.[9,10] These systematic reviews are outdated; with at least 4 new RCTs meeting our inclusion criteria have been published since the searches for these previous reviews were conducted. The present study, thus, provides a more contemporary synthesis of the literature and is, to our knowledge, the first to include both

Table 3. Network Meta-Analysis of Pharmacotherapies and Behavioral Therapies for Smoking Cessation in Patients With Cardiovascular Disease

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counseling	Telephone Counseling	Individual Counseling
Placebo/usual care	1.00	0.70 (0.50–0.99)	0.82 (0.48–1.38)	0.38 (0.19–0.75)	0.95 (0.70–1.29)	0.68 (0.53–0.87)	0.61 (0.44–0.85)
Bupropion	1.42 (1.01–2.01)	1.00	1.16 (0.62–2.18)	0.54 (0.25–1.15)	1.35 (0.85–2.14)	0.97 (0.63–1.48)	0.87 (0.54–1.41)
NRT	1.22 (0.72–2.07)	0.86 (0.46–1.61)	1.00	0.46 (0.20–1.09)	1.16 (0.63–2.13)	0.83 (0.47–1.48)	0.75 (0.40–1.39)
Varenicline	2.64 (1.34–5.21)	1.86 (0.87–3.98)	2.16 (0.92–5.10)	1.00	2.51 (1.19–5.29)	1.80 (0.87–3.70)	1.62 (0.76–3.44)
In-hospital counseling	1.05 (0.78–1.43)	0.74 (0.47–1.17)	0.86 (0.47–1.58)	0.40 (0.19–0.84)	1.00	0.72 (0.50–1.03)	0.64 (0.41–1.01)
Telephone counseling	1.47 (1.15–1.88)	1.03 (0.68–1.58)	1.20 (0.67–2.15)	0.56 (0.27–1.14)	1.40 (0.97–2.02)	1.00	0.90 (0.59–1.36)
Individual counseling	1.64 (1.17–2.28)	1.15 (0.71–1.86)	1.34 (0.72–2.49)	0.62 (0.29–1.32)	1.55 (0.99–2.44)	1.11 (0.74–1.68)	1.00

RRs and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column. NRT indicates nicotine replacement therapy; and RR, risk ratio.

Table 4. Adverse Cardiovascular Events in Pharmacotherapy Trials Conducted in Patients With Cardiovascular Disease

Author	Year	Placebo		Treatment	
		Total (N)	n ≥1 CVD AE n (%)*	Total (N)	n ≥1 CVD AE n (%)*
NRT					
Campbell et al[22]	1991	…	…	…	…
Joseph et al[23]	1996	290	47 (16.2)	294	48 (16.3)
Bupropion					
Tonstad et al[24]	2003	313	14 (4.5)	313	24 (7.7)
Rigotti et al[5]	2006	124	22 (17.7)	124	32 (25.8)
Planer et al[4]	2011	75	14 (18.7)	74	11 (14.9)
Eisenberg et al[3]	2013	200	16 (8.0)	192	17 (8.9)
Varenicline					
Rigotti et al[25]	2010	350	20 (5.7)	353	25 (7.1)

AE indicates adverse events; CVD, cardiovascular disease; and NRT, nicotine replacement therapy.

*Number of patients with one or more cardiovascular adverse events.

direct and indirect comparisons of smoking cessation therapy use in this patient population. The results of this study, along with patient and physician preference, and consideration of the issue of polypharmacy in this population, should be considered when determining the most appropriate choice of smoking cessation therapy in CVD patients.

Our study has some potential limitations. First, some heterogeneity existed in the definition of smoking abstinence, and there were an insufficient number of included trials to conduct sensitivity analyses by abstinence definition. Second, in our network meta-analysis comparing all treatments, we made 2 key assumptions. The first was the transitivity assumption, which states that patients in the network had equal chances of getting the treatment. To assess whether this assumption was met, we conducted several subgroup and sensitivity analyses that suggested that no major violations were present. The I^2 statistic for our network also suggested the presence of only moderate heterogeneity. Nonetheless, with differences in dose, use of cointerventions, and inherent differences between pharmacotherapies and behavioral therapies, this assumption may not have been fully satisfied. However, analyses stratified by type of intervention (pharmacotherapy versus behavioral therapy), type of CVD, and biochemical validation produced consistent results, suggesting that mild violations of this assumption are unlikely to have impacted our conclusions. We also assumed that the comparison groups of pharmacotherapies (placebo) and behavioral therapies (usual care) were equivalent; the sensitivity analysis testing this assumption produced similar results to those of our primary analysis. The second was the consistency assumption; our assessment of inconsistency plots suggested the presence of moderate heterogeneity in the network. Third, concerning the network geometry, although the network is not entirely symmetrical, the asymmetry of the network is likely because of greater safety concerns with the pharmacotherapies than with the behavioral therapies. The asymmetry may also be because of publication bias. The selection forces that shape the network, called comparator preference bias, are practically inevitable in network meta-analysis.[54] Fourth, we excluded conference abstracts because their results are often not final, and they contain insufficient information to assess study quality. Although we attempted to contact the authors of full-length articles to seek additional information, no attempt was made to contact the authors of conference abstracts. The exclusion of such abstracts may increase the risk of publication bias, potentially affecting the results of our network meta-analysis. Fifth, the exclusion of trials published in a language other than English or French may have also resulted in language bias. Sixth, most of our head-to-head evidence was obtained via indirect comparison because of the small number of RCTs directly comparing smoking cessation therapies to each other conducted in this patient population. Seventh, some studies were excluded because of the inclusion of patients not motivated to quit because differences in the distribution of an effect modifier such as motivation to quit may result in a violation of the consistency assumption.[15] Unfortunately, we were restricted to the aggregate data presented in the published articles. If patient-level data had been available, we would have been able to use regression or stratification to account for differences in motivation to quit. Finally, we were unable to pool safety data from the pharmacotherapy trials because of inconsistent reporting of events and heterogeneous adverse event definitions.

Conclusions

Our network meta-analysis suggests that among patients who are motivated to quit smoking, varenicline and bupropion are efficacious for smoking cessation in patients with CVD, whereas available data about NRTs are inconclusive. Individual and telephone counseling also seem to be efficacious in this patient population. Overall, available evidence suggests that varenicline is the most efficacious smoking cessation therapy in patients with CVD who are motivated to quit smoking, although more safety data are needed. Given the small number of participants considered in these analyses, there remains a need for RCTs sufficiently powered to examine safety in this patient population as well as large, population-based observational studies to examine this issue.

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Efficacy and Safety of Smoking Cessation Interventions in Patients With Cardiovascular Disease: A Network Meta-Analysis of Randomized Controlled Trials

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Description of literature search on EMBASE (through Ovid) for trials of pharmacotherapy or behavioral therapy for smoking cessation in cardiac patients.

Search Number	Search Description	Number of Results
1	Smoking Cessation/	40,881
2	((cigarette* or tobacco or smoking or smoker*) and (cease$1 or cessation or quit* or stop*)).mp.	56,150
3	or/1-2	56,150
4	amfebutamone/	14,595
5	bupropion.mp.	4,613
6	zyban.mp.	1,003
7	amfebutamone.mp.	14,707
8	varenicline/	2,852
9	varenicline.mp.	2,975
10	champix.mp.	270
11	chantix.mp.	358
12	(nicotine and (patch or patches or lozenge$1 or inhaler$1 or nasal spray$1 or transdermal system* or gum or polacrilex or replacement)).mp.	9,192
13	nicotine patch/	1,472
14	nicotine lozenge/	149
15	nicotine replacement therapy/	3,508
16	nicotine gum/	2,458
17	nicoderm.mp.	402
18	nicorette.mp.	645
19	habitrol.mp.	173
20	exp Behavior Therapy/	38,566
21	(behavio?r* adj5 (therap* or intervention*)).mp.	74,885
22	cognitive therap*.mp.	37,882
23	exp Counselling/	118,436
24	counsel?ing.mp.	145,382
25	pharmacotherap*.mp.	39,586
26	(pharmaco* adj3 (therap* or intervention*)).mp.	51,813
27	physician attitude/	43,727
28	patient education/	91,014
29	(physician* adj3 advice).mp.	1,284
30	(physician* adj role*).mp.	1,639
31	patient education.mp.	96,233
32	minimal* invasive* intervention*.mp.	447
33	combined modality therap*.mp.	3,004
34	nrt.mp.	1,801
35	exp psychotherapy/	206,079
36	psychotherap*.mp.	106,176
37	psychoeducation*.mp.	6,815
38	(combination therap* or combination treatment*).mp.	62,119

39	("Electronics"/ or Electrical Equipment/ or Nebulizer/) and (tobacco/ or tobacco dependence/ or smoking cessation/ or exp smoking/ or nicotine/)	351
40	electronic cigarette/	809
41	(electronic adj3 cig*).mp.	961
42	(e cig* or ecig*).mp.	666
43	nicotine delivery.mp.	430
44	endd.mp.	11
45	non-cigarette.mp.	101
46	(vaper$1 or vape or vaping).mp.	83
47	(vapo?r adj3 cigarette*).mp.	81
48	(non-combustible or noncombustible).mp.	97
49	reduced exposure product*.mp.	74
50	personal vapo?ri?er*.mp.	3
51	nicotine vapo?ri?er*.mp.	5
52	electronic smok*.mp.	7
53	(nicotine adj (inhaler$1 or inhalator$1)).mp.	121
54	or/4-53	655,090
55	3 and 54	17,599
56	exp Cardiovascular Disease/	3,404.068
57	exp heart surgery/	290,046
58	exp Cardiovascular System/	1,662,860
59	coronar*.mp.	569,357
60	angina.mp.	99,895
61	aneurysm*.mp.	165,769
62	arrhythmi*.mp.	171,511
63	(atrium or atrial).mp.	254,917
64	cardia*.mp.	741,795
65	cardio*.mp.	1,237,403
66	cerebrovascular.mp.	191,901
67	heart*.mp.	2,057,984
68	revasculari*.mp.	82,066
69	CVD.mp.	30,199
70	myocard*.mp.	461,515
71	arter*.mp.	1,453,723
72	vascular.mp.	862,283
73	renovascular*.mp.	24,358
74	(stroke or strokes).mp.	297,648
75	isch?em*.mp.	566,367
76	endocardi*.mp.	71,467
77	ventric*.mp.	592,885
78	pericard*.mp.	65,192
79	embol*.mp.	213,476
80	thromb*.mp.	806,401

81	tachycardi*.mp.	127,043
82	bradycardi*.mp.	51,553
83	sick sinus.mp.	4,537
84	apople*.mp.	5,263
85	((brain or cerebral) adj2 (accident* or injur*)).mp.	129,432
86	((brain* or cerebral or lacunar) adj2 infarct*).mp.	54,568
87	or/56-86	5,566,774
88	55 and 87	4,544
89	Clinical trial/	854,019
90	Randomized controlled trial/	375,456
91	Randomization/	66,806
92	Single blind procedure/	20,364
93	Double blind procedure/	125,491
94	Crossover procedure/	43,422
95	Placebo/	274,199
96	Randomi?ed controlled trial$.tw.	117,631
97	Rct.tw.	17,336
98	Random allocation.tw.	1,497
99	Randomly allocated.tw.	22,825
100	Allocated randomly.tw.	2,058
101	(allocated adj2 random).tw.	884
102	Single blind$.tw.	16,223
103	Double blind$.tw.	161,116
104	((treble or triple) adj blind$).tw.	498
105	Placebo$.tw.	224,622
106	Prospective study/	294,074
107	or/89-106	1,498,033
108	88 and 107	1,542

Supplemental table 2. Description of literature search on PsycINFO (through Ovid) for trials of pharmacotherapy or behavioral therapy for smoking cessation in cardiac patients.

Search Number	Search Description	Number of Results
1	Smoking Cessation/	9,947
2	((cigarette* or tobacco or smoking or smoker*) and (cease$1 or cessation or quit* or stop*)).mp.	14,884
3	or/1-2	14,884
4	Bupropion/	827
5	bupropion.mp.	1,802
6	zyban.mp.	44
7	amfebutamone.mp.	6
8	varenicline.mp.	494
9	champix.mp.	13
10	chantix.mp.	31
11	(nicotine and (patch or patches or lozenge$1 or inhaler$1 or nasal spray$1 or transdermal system* or gum or polacrilex or replacement)).mp.	2,370
12	nicoderm.mp.	11
13	nicorette.mp.	33
14	habitrol.mp.	2
15	exp Behavior Modification/	39,136
16	(behavio?r* adj5 (therap* or intervention*)).mp.	64,133
17	cognitive therapy/	11,982
18	cognitive therap*.mp.	14,252
19	exp Counselling/	68,611
20	counsel?ing.mp.	86,591
21	pharmacotherap*.mp.	11,857
22	(pharmaco* adj3 (therap* or intervention*)).mp.	6,429
23	exp psychotherapist attitude/	1,182
24	exp psychologist attitude/	1,019
25	counselor role/	1.252
26	therapist role/	1,589
27	client education/	3,203
28	(physician* adj3 advice).mp.	303
29	(physician* adj role*).mp.	406
30	patient education.mp.	2,526
31	minimal* invasive* intervention*.mp.	6
32	combined modality therap*.mp.	3
33	nrt.mp.	626
34	exp psychotherapy/	184,046
35	psychotherap*.mp.	159,820
36	psychoeducation*.mp.	7,923
37	(combination therap* or combination treatment*).mp.	2,098

38	(electronic adj3 cig*).mp.	194
39	(e cig* or ecig*).mp.	194
40	nicotine delivery.mp.	208
41	endd.mp.	2
42	non-cigarette.mp.	19
43	(vaper$1 or vape or vaping).mp.	21
44	(vapo?r adj3 cigarette*).mp.	7
45	(non-combustible or noncombustible).mp.	13
46	reduced exposure product*.mp.	35
47	personal vapo?ri?er*.mp.	2
48	nicotine vapo?ri?er*.mp.	2
49	electronic smok*.mp.	1
50	(nicotine adj (inhaler$1 or inhalator$1)).mp.	40
51	or/4-50	390,735
52	3 and 51	4,822
53	exp cardiovascular disorders/	46,803
54	heart surgery/	1,291
55	exp cardiovascular system/	8,056
56	coronar*.mp.	10,017
57	angina.mp.	977
58	aneurysm*.mp.	1,261
59	arrhythmi*.mp.	2,419
60	(atrium or atrial).mp.	1,308
61	cardia*.mp.	14,385
62	cardio*.mp.	32,039
63	cerebrovascular.mp.	19,408
64	heart*.mp.	51,563
65	revasculari*.mp.	347
66	CVD.mp.	1,745
67	myocard*.mp.	5,037
68	arter*.mp.	16,488
69	vascular.mp.	14,603
70	renovascular*.mp.	42
71	(stroke or strokes).mp.	24,616
72	isch?em*.mp.	13,800
73	endocardi*.mp.	140
74	ventric*.mp.	8,014
75	pericard*.mp.	125
76	embol*.mp.	1,256
77	thromb*.mp.	3,394
78	tachycardi*.mp.	1,249
79	bradycardi*.mp.	840
80	sick sinus.mp.	10

81	apople*.mp.	77
82	((brain or cerebral) adj2 (accident* or injur*)).mp.	21,394
83	((brain* or cerebral or lacunar) adj2 infarct*).mp.	2,138
84	or/53-83	155,142
85	52 and 84	376
86	(control* or random*).tw. or exp treatment/	1,115,626
87	85 and 86	248

Supplemental table 3. Description of literature search on MEDLINE (through Ovid) for trials of pharmacotherapy or behavioral therapy for smoking cessation in cardiac patients.

Search Number	Search Description	Number of Results
1	exp Smoking Cessation/	21,477
2	((cigarette* or tobacco or smoking or smoker*) and (cease$1 or cessation or quit* or stop*)).mp.	38,216
3	or/1-2	38.216
4	Bupropion/	2,515
5	bupropion.mp.	3,840
6	zyban.mp.	118
7	amfebutamone.mp.	28
8	varenicline.mp.	1,214
9	champix.mp.	38
10	chantix.mp.	51
11	(nicotine and (patch or patches or lozenge$1 or inhaler$1 or nasal spray$1 or transdermal system* or gum or polacrilex or replacement)).mp.	5,320
12	nicoderm.mp.	25
13	nicorette.mp.	88
14	habitrol.mp.	9
15	exp Behavior Therapy/	55,320
16	(behavio?r* adj5 (therap* or intervention*)).mp.	52,648
17	cognitive therap*.mp.	18,124
18	exp Counselling/	34,469
19	counsel?ing.mp.	87,139
20	pharmacotherap*.mp.	24,970
21	(pharmaco* adj3 (therap* or intervention*)).mp.	28,835
22	Physician's Role/	26,451
23	Patient Education as Topic/	72,418
24	(physician* adj3 advice).mp.	980
25	(physician* adj role*).mp.	27,111
26	patient education.mp.	82,508
27	minimal* invasive* intervention*.mp.	309
28	Combined Modality Therapy/	146,897
29	combined modality therap*.mp.	147,611
30	nrt.mp.	1,406
31	exp Psychotherapy, Group/	23,302
32	psychotherap*.mp.	70,831
33	psychoeducation*.mp.	2,888
34	(combination therap* or combination treatment*).mp.	41,680
35	"Tobacco Use Cessation Products"/	920
36	("Electronics"/ or "Electrical Equipment and Supplies"/ or "Nebulizers and Vaporizers"/) and ("tobacco products"/ or "tobacco use cessation products"/ or "tobacco use disorder"/ or "smoking cessation"/ or	340

	smoking/ or nicotine/ or tobacco/)	
37	(electronic adj3 cig*).mp.	644
38	(e cig* or ecig*).mp.	577
39	nicotine delivery.mp.	395
40	endd.mp.	5
41	non-cigarette.mp.	115
42	(vaper$1 or vape or vaping).mp.	78
43	(vapo?r adj3 cigarette*).mp.	60
44	(non-combustible or noncombustible).mp.	51
45	reduced exposure product*.mp.	66
46	personal vapo?ri?er*.mp.	7
47	nicotine vapo?ri?er*.mp.	2
48	electronic smok*.mp.	6
49	(nicotine adj (inhaler$1 or inhalator$1)).mp.	88
50	or/4-49	555,528
51	3 and 50	11,872
52	exp Cardiovascular Diseases/	1,949,880
53	exp cardiac surgical procedures/	172,398
54	exp Cardiovascular System/	1,050,505
55	coronar*.mp.	413,556
56	angina.mp.	61,953
57	aneurysm*.mp.	124,220
58	arrhythmi*.mp.	114,619
59	(atrium or atrial).mp.	149,945
60	cardia*.mp.	608,701
61	cardio*.mp.	698,600
62	cerebrovascular.mp.	115,108
63	heart*.mp.	1,035,652
64	revasculari*.mp.	49,623
65	CVD.mp.	20,186
66	myocard*.mp.	476,311
67	arter*.mp.	944,128
68	vascular.mp.	611,636
69	renovascular*.mp.	9,782
70	(stroke or strokes).mp.	201,305
71	isch?em*.mp.	325,591
72	endocardi*.mp.	49,272
73	ventric*.mp.	384,522
74	pericard*.mp.	43,419
75	embol*.mp.	133,180
76	thromb*.mp.	408,654
77	tachycardi*.mp.	64,720
78	bradycardi*.mp.	23,767

79	sick sinus.mp.	3,215
80	apople*.mp.	3,165
81	((brain or cerebral) adj2 (accident* or injur*)).mp.	71,100
82	((brain* or cerebral or lacunar) adj2 infarct*).mp.	39,198
83	or/52-82	3,711,700
84	51 and 83	1,819
85	randomized controlled trial.pt.	397,503
86	controlled clinical trial.pt.	89,689
87	random*.ti.	133,948
88	randomized.ab.	323,376
89	randomised.ab.	64,025
90	placebo.ti.ab.	163,465
91	drug therapy.fs.	1,782,383
92	randomly.ab.	232,581
93	trial.ab.	334,859
94	groups.ab.	1,462,116
95	or/85-94	3,583,719
96	exp animals/ not humans.sh.	4,061,598
97	95 not 96	3,081,406
98	84 and 97	834

Supplemental table 4. Description of literature search on PubMed for trials of pharmacotherapy or behavioral therapy for smoking cessation in cardiac patients.

Search Number	Search Description	Number of Results
1	"smoking cessation"[MeSH Terms]	20,864
2	((((cigarette*[tiab] OR tobacco[tiab] OR smoking[mesh] OR smoking[tiab] OR smoker*[tiab]) AND (cease*[tiab] OR cessation[tiab] OR quit*[tiab] OR stop*[tiab]))))	29,656
3	(#1 OR #2)	36,353
4	"bupropion"[MeSH Terms]	2,456
5	bupropion[tiab]	3,245
6	zyban[tiab]	116
7	amfebutamone[tiab]	28
8	"varenicline"[Supplementary Concept]	770
9	varenicline[tiab]	1,041
10	champix[tiab]	34
11	chantix[tiab]	46
12	(((nicotine[tiab] AND (patch[tiab] OR patches[tiab] OR lozenge[tiab] OR lozenges[tiab] OR inhaler[tiab] OR inhalers[tiab] OR nasal spray[tiab] OR nasal sprays[tiab] OR transdermal system*[tiab] OR gum[tiab] OR polacrilex[tiab] OR replacement[tiab]))))	4,741
13	nicoderm[tiab]	25
14	nicorette[tiab]	86
15	habitrol[tiab]	9
16	"behavior therapy"[MeSH Terms]	54,336
17	(((behavior*[tw] OR behaviour*[tw]) AND (intervention*[tw] OR therap*[tw])))	248,646
18	cognitive therap*[tiab]	2,152
19	"counselling"[MeSH Terms]	33,988
20	counselling[tiab]	46,513
21	counselling[tiab]	19,084
22	pharmacotherap*[tiab]	24,663
23	((((pharmaco[tw] OR pharmacological[tw]) AND (therap*[tw] OR intervention*[tw]))))	76,445
24	"Physician's Role"[mesh]	26,319
25	"Patient education as topic"[mesh]	71,832
26	(((physician*[tw] AND advice[tw])))	5,969
27	patient education[tw]	82,024
28	"combined modality therapy"[MeSH Terms]	211,748
29	combined modality therap*[tiab]	1,787
30	nrt[tiab]	1,373
31	"Psychotherapy, Group"[Mesh]	23,138
32	psychotherap*[tiab]	33,709

33	psychoeducation*[tiab]	2,922
34	combination therap*[tiab]	33,810
35	"Tobacco use cessation products"[mesh]	1,020
36	((((("Electronics"[mesh:noexp] OR "Electrical Equipment and Supplies"[Mesh:noexp] OR "Nebulizers and Vaporizers"[Mesh:NoExp]) AND ("tobacco products"[mesh] OR "tobacco use cessation products"[mesh] OR "tobacco use disorder"[mesh] OR "smoking cessation"[mesh] OR "smoking"[mesh:noexp] OR "nicotine"[mesh] OR "tobacco"[mesh]))))	326
37	((electronic[tiab] AND cig*[tiab]))	821
38	((e cig*[tiab] OR ecig*[tiab]))	635
39	nicotine delivery[tiab]	360
40	endd[tiab]	5
41	non-cigarette[tiab]	76
42	vaper*[tiab]	22
43	vape[tiab]	28
44	vaping[tiab]	42
45	(((vapor[tiab] OR vapour[tiab]) AND cigarette*[tiab]))	264
46	combination treat*[tiab]	9,293
47	((non-combustible[tiab] OR noncombustible[tiab]))	53
48	reduced exposure product*[tiab]	64
49	((personal vaporizer*[tiab] OR personal vaporiser*[tiab] OR personal vapourizer*[tiab] OR personal vapouriser*[tiab]))	6
50	((nicotine vaporizer*[tiab] OR nicotine vaporiser*[tiab] OR nicotine vapourizer*[tiab] OR nicotine vapouriser*[tiab]))	9
51	electronic smok*[tiab]	5,836
52	((nicotine[tiab] AND (inhaler*[tiab] OR inhalator*[tiab])))	227
53	(physician*[tiab] AND role*[tiab])	27,612
54	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53	825,556
55	(#3 AND #54)	14,366
56	"Cardiovascular Diseases"[Mesh]	1,926,351
57	"cardiac surgical procedures"[Mesh]	171,145
58	"Cardiovascular System"[Mesh]	1,037,164
59	coronary[tw]	412,959
60	angina[tw]	62,061
61	aneurysm*[tw]	124,462
62	arrhythmi*[tw]	114,600
63	atrium[tw]	27,192
64	atrial[tw]	137,128
65	cardia*[tw]	603,948
66	((cardio[tw] OR cardiolog*[tw]))	58,278
67	cerebrovascular[tw]	113,541

68	heart[tw]	1,014,827
69	revasculari*[tw]	49,910
70	CVD[tw]	19,951
71	myocard*[tw]	474,373
72	((artery[tw] OR arteries[tw] OR arterial[tw] OR arterio*[tw]))	926,256
73	vascular[tw]	607,736
74	renovascular*[tw]	9,688
75	stroke[tw]	195,732
76	strokes[tw]	15,264
77	ischaem*[tw]	47,977
78	ischem*[tw]	294,923
79	endocardi*[tw]	49,292
80	ventric*[tw]	382,970
81	pericard*[tw]	43,485
82	embol*[tw]	133,266
83	(thrombo[tw] OR thrombotic[tw] OR thrombos*[tw] OR thromboe*[tw] OR thrombog*[tw] OR thrombol*[tw] OR thrombom*[tw])	250,621
84	tachycardi*[tw]	64,797
85	bradycardi*[tw]	23,776
86	"sick sinus"[tw]	3,217
87	apople*[tw]	3,057
88	(((brain[tiab] OR cerebral[tiab]) AND (accident*[tiab] OR injur*[tiab])))	82,423
89	((((brain*[tw] OR cerebral[tw] or lacunar[tw]) AND infarct*[tw])))	56,181
90	#56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89	3,485,334
91	(#55 AND #90)	2,107
92	randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo[tiab] OR drug therapy[sh] OR trial[tiab] OR groups[tiab]	3,733,798
93	(#91 AND #92)	948
94	(#93 NOT medline[sb])	60

Supplemental table 5. Description of literature search on Cochrane Tobacco Addiction Group for trials of pharmacotherapy or behavioral therapy for smoking cessation in cardiac patients.

Search Number	Search Description	Number of Results
1	MeSH descriptor: [Smoking Cessation] explode all trees	302
2	(cigarette* or tobacco or smoking or smoker*):ti,ab,kw and (cease* or cessation or quit* or stop*):ti,ab,kw	6,501
3	#1 or #2	6,501
4	MeSH descriptor: [Bupropion] explode all trees	532
5	bupropion:ti,ab,kw	1,023
6	zyban:ti,ab,kw	42
7	amfebutamone:ti,ab,kw	284
8	varenicline:ti,ab,kw	370
9	champix:ti,ab,kw	4
10	chantix:ti,ab,kw	11
11	(nicotine and (patch or patches or lozenge or lozenges or inhaler or inhalers or "nasal spray" or "nasal sprays" or transdermal next system* or gum or polacrilex or replacement)):ti,ab,kw	1,863
12	nicoderm:ti,ab,kw	18
13	nicorette:ti,ab,kw	38
14	habitrol:ti,ab,kw	4
15	MeSH descriptor: [Behavior Therapy] explode all trees	10,909
16	((behavio*r*) near/5 (therap* or intervention*)):ti,ab,kw	15,617
17	cognitive next therap*:ti,ab,kw	7,691
18	MeSH descriptor: [Counselling] explode all trees	3,455
19	counsel*ing:ti,ab,kw	8,947
20	pharmacotherap*:ti,ab,kw	5,194
21	(pharmaco* near/3 (therap* or intervention*)):ti,ab,kw	12,096
22	MeSH descriptor: [Physician's Role] explode all trees	186
23	MeSH descriptor: [Patient Education as Topic] explode all trees	6,723
24	(physician* near/3 advice):ti,ab,kw	133
25	(physician* next role*):ti,ab,kw	6
26	patient education:ti,ab,kw	8,422
27	minimal* next invasive* next intervention*:ti,ab,kw	23
28	MeSH descriptor: [Combined Modality Therapy] this term only	12,268
29	combined next modality next therap*:ti,ab,kw	12,832
30	nrt:ti,ab,kw	274
31	MeSH descriptor: [Psychotherapy, Group] explode all trees	2,508
32	psychotherap*:ti,ab,kw	7,542
33	psychoeducation*:ti,ab,kw	1,144
34	(combination next (therap* or treatment*)):ti,ab,kw	8,529
35	MeSH descriptor: [Tobacco Use Cessation Products] explode all trees	201
36	nicotine next replacement next therap*:ti,ab,kw	646
37	MeSH descriptor: [Electronics] this term only	66
38	MeSH descriptor: [Electrical Equipment and Supplies] this term only	30

39	MeSH descriptor: [Nebulizers and Vaporizers] explode all trees	1,907
40	MeSH descriptor: [Tobacco Products] explode all trees	146
41	MeSH descriptor: [Tobacco Use Cessation Products] explode all trees	201
42	MeSH descriptor: [Tobacco Use Disorder] explode all trees	770
43	MeSH descriptor: [Smoking Cessation] explode all trees	302
44	MeSH descriptor: [Smoking] explode all trees	4
45	MeSH descriptor: [Nicotine] explode all trees	1553
46	MeSH descriptor: [Tobacco] explode all trees	140
47	(#37 or #38 or #39) and (#40 or #41 or #42 or #43 or #44 or #45 or #46)	31
48	electronic near/3 cig*:ti,ab,kw	34
49	((e next cig*) or ecig*):ti,ab,kw	28
50	nicotine delivery:ti,ab,kw	162
51	endd:ti,ab,kw	1
52	non-cigarette:ti,ab,kw	1
53	(vaper* or vape or vaping):ti,ab,kw	2
54	((vapor or vapour) near/3 cigarette*):ti,ab,kw	1
55	((non next combustible) or (noncombustible)):ti,ab,kw	3
56	reduced next exposure next product*:ti,ab,kw	21
57	personal next vapo*ri?er*:ti,ab,kw	0
58	nicotine next vapo*ri?er*:ti,ab,kw	1
59	electronic next smok*:ti,ab,kw	2
60	(nicotine next (inhaler* or inhalator*)):ti,ab,kw	46
61	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #47 or #48 or #54 or #55 or #56	75,228
62	#3 and #61	3,333
63	MeSH descriptor: [Cardiovascular Diseases] explode all trees	77,237
64	MeSH descriptor: [Cardiac Surgical Procedures] explode all trees	11,928
65	MeSH descriptor: [Cardiovascular System] explode all trees	17,289
66	MeSH descriptor: [Cholesterol] explode all trees	8,484
67	coronar*:ti,ab,kw	33,029
68	angina:ti,ab,kw	8,921
69	aneurysm*:ti,ab,kw	2,846
70	arrhythmi*:ti,ab,kw	7,140
71	atrium:ti,ab,kw	2,614
72	atrial:ti,ab,kw	8,678
73	cardia*:ti,ab,kw	32,898
74	cardio*:ti,ab,kw	50,874
75	cerebrovascular:ti,ab,kw	7,204
76	heart:ti,ab,kw	73,371
77	revasculari*:ti,ab,kw	5,801
78	CVD:ti,ab,kw	1,670
79	myocard*:ti,ab,kw	26,061
80	arter*:ti,ab,kw	53,211
81	*vascular*:ti,ab,kw	64,613

82	stroke:ti,ab,kw	26,686
83	strokes:ti,ab,kw	1,251
84	isch*m*:ti,ab,kw	20,899
85	endocardi*:ti,ab,kw	579
86	ventric*:ti,ab,kw	18,061
87	pericard*:ti,ab,kw	718
88	embol*:ti,ab,kw	5,143
89	thromb*:ti,ab,kw	28,063
90	tachycardi*:ti,ab,kw	5,058
91	bradycardi*:ti,ab,kw	2,927
92	sick sinus:ti,ab,kw	201
93	apople*:ti,ab,kw	343
94	((brain* or cerebral) and (accident* or infarct*)):ti,ab,kw	3,599
95	((brain* or cerebral or lacunar) and infarct*):ti,ab,kw	3,706
96	#63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95	217,365
97	#62 and #96 with Tobacco Addiction Group in Review Groups	286

Supplemental table 6. Motivation to quit smoking for all studies included

Trial	Motivation	Additional Information
Rigotti 1994	Not specified	Excluded if not willing to quit
Miller	Not specified	Excluded if not willing to quit
Tonstad	Motivated	-
Joseph	Not specified	Included if made a minimum of 2 attempts to quit
Hajek	Motivated	-
Eisenberg	Motivated	-
Wiggers	Not specified	Excluded if not willing to quit
Smith 2009	Not specified	-
Ockene	Not specified	Excluded if not willing to quit
Froelicher	Not specified	Refused to participate because no desire to quit
Rigotti 2006	Motivated	Excluded if not willing to quit
Quist-Paulsen	Not specified	-
Mohiuddin	Motivated	Fagerstrom score >7
Feeney	Not specified	-
Smith	Not specified	Excluded if not willing to quit
Taylor	Not specified	-
Planer	Motivated	-
Hennrikus	Motivated	-
Reid	Not specified	-
Brunner	Not specified	-
Rigotti 2010	Motivated	-
Campbell	Motivated	Agreed to quit smoking
Cossette	Not specified	-
Park	Motivated	-

Abbreviations: "-" denotes not reported.

Supplemental table 7. Quality assessment of trials on smoking cessation therapies in patients with cardiovascular disease as defined by the Cochrane Risk of Bias tool.

Lead Author	Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel, and Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
NRTs							
Campbell	1991	Unclear	Unclear	Low	Low	Low	Unclear
Joseph	1996	Low	Low	Low	Unclear	Low	Low
Bupropion							
Tonstad	2003	Unclear	Unclear	Low	Low	Low	Low
Rigotti	2006	Low	Low	Low	Low	Low	Low
Planer	2011	Unclear	Low	Low	Low	High	Low
Eisenberg	2013	Low	Low	Low	Low	Low	Low
Varenicline							
Rigotti	2010	Low	Unclear	Low	Low	Low	Low
In-hospital counselling							
Rigotti	1994	Unclear	Unclear	High	Low	Low	Low
Hajek	2002	Unclear	Unclear	High	Low	Low	High
Wiggers	2006	Unclear	Unclear	High	Low	Unclear	Low
Telephone counselling							
Taylor	1990	Low	Low	High	Low	High	High
Miller	1997	Unclear	Low	High	Low	High	High
Feeney	2001	Low	Low	High	High	Low	High
Froelicher	2004	Low	Low	High	Low	Low	High
Reid	2007	Low	Unclear	High	Low	High	Low
Smith	2009	Low	Low	High	Low	High	Low
Cossette	2012	Unclear	Low	High	High	Low	High
Park	2015	Low	Unclear	High	Low	Unclear	Unclear
Smith	2011	Low	Unclear	High	Low	Low	Low
Individualized counselling							
Ockene	1992	Unclear	Unclear	High	Low	Low	Low
Quist-Paulsen	2003	Low	Low	High	Low	Low	Low
Mohiuddin	2007	Unclear	Unclear	High	Low	Low	Low
Hennrikus	2010	Low	Unclear	High	Low	Low	Low
Brunner	2012	Low	Low	High	Low	Low	Low

Supplemental table 8. Effectiveness of different treatments in terms of abstinence rate after one year.

Treatment	RR*	Expected Abstinence Rate† (%)
Bupropion	1.33	25.7
NRT	1.19	23.0
Varenicline	2.36	45.5
In hospital	1.03	19.9
Telephone	1.31	25.3
Individual	1.42	27.4

* From network meta-analysis.

† Assuming an abstinence rate of 19.3% in the placebo/usual care group (the mean abstinence rate among patients randomized to placebo/usual care across all trials).

Supplemental Table 9. Network meta-analysis treatment rankings.

Treatment	P-Score
Varenicline	0.9557
Individual Counselling	0.7174
Telephone Counselling	0.6033
Bupropion	0.5565
NRT	0.3765
In-Hospital Counselling	0.1867
Placebo/Usual Care	0.1040

*The p-score indicates the probability that the treatment ranks the highest in terms of efficacy

Supplemental Table 10. Network meta-analysis of pharmacotherapies and behavioral therapies for smoking cessation in patients with cardiovascular disease excluding behavioral RCTs in which pharmacotherapy was available differentially across groups[*].

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counselling	Telephone Counselling	Individual Counselling
Placebo/Usual Care	1.00	0.70 (0.51, 0.96)	0.82 (0.50, 1.33)	0.38 (0.20, 0.70)	0.96 (0.73, 1.27)	0.73 (0.58, 0.93)	0.72 (0.47, 1.10)
Bupropion	1.42 (1.04, 1.95)	1.00	1.16 (0.65, 2.08)	0.54 (0.27, 1.08)	1.37 (0.90, 2.09)	1.05 (0.70, 1.55)	1.02 (0.60, 1.74)
NRT	1.22 (0.75, 1.99)	0.86 (0.48, 1.53)	1.00	0.46 (0.21, 1.02)	1.18 (0.67, 2.06)	0.90 (0.52, 1.55)	0.88 (0.46, 1.68)
Varenicline	2.64 (1.42, 4.92)	1.86 (0.93, 3.73)	2.16 (0.98, 4.76)	1.00	2.55 (1.29, 5.03)	1.94 (1.00, 3.77)	1.90 (0.89, 4.04)
In-Hospital Counselling	1.04 (0.79, 1.37)	0.73 (0.48, 1.11)	0.85 (0.49, 1.48)	0.39 (0.20, 0.77)	1.00	0.76 (0.54, 1.07)	0.75 (0.45, 1.24)
Telephone Counselling	1.36 (1.07, 1.73)	0.96 (0.64, 1.42)	1.11 (0.65, 1.91)	0.52 (0.26, 1.00)	1.31 (0.93, 1.84)	1.00	0.98 (0.60, 1.60)
Individual Counselling	1.39 (0.91, 2.14)	0.98 (0.57, 1.66)	1.14 (0.59, 2.17)	0.53 (0.25, 1.12)	1.34 (0.81, 2.23)	1.02 (0.63, 1.67)	1.00

Abbreviations: NRT: nicotine replacement therapy

* Risk ratios (RRs) and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column.

Supplemental Table 11. Network meta-analysis of pharmacotherapies and behavioral therapies for smoking cessation in patients with cardiovascular disease restricted to the trials that biochemically validated abstinence [*].

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counselling	Telephone Counselling	Individual Counselling
Placebo/Usual Care	1.00	0.61 (0.40, 0.93)	0.82 (0.47, 1.42)	0.38 (0.18, 0.78)	0.94 (0.68, 1.31)	0.64 (0.47, 0.88)	0.61 (0.43, 0.86)
Bupropion	1.63 (1.07, 2.47)	1.00	1.33 (0.67, 2.66)	0.62 (0.27, 1.41)	1.53 (0.90, 2.60)	1.04 (0.62, 1.76)	0.99 (0.57, 1.70)
NRT	1.22 (0.70, 2.12)	0.75 (0.38, 1.50)	1.00	0.46 (0.17, 1.14)	1.15 (0.60, 2.18)	0.78 (0.41, 1.48)	0.74 (0.38, 1.42)
Varenicline	2.64 (1.29, 5.42)	1.63 (0.71, 3.73)	2.17 (0.88, 5.35)	1.00	2.48 (1.13, 5.47)	1.69 (0.77, 3.71)	1.60 (0.72, 3.57)
In-Hospital Counselling	1.06 (0.77, 1.48)	0.65 (0.38, 1.11)	0.87 (0.46, 1.66)	0.40 (0.18, 0.89)	1.00	0.68 (0.45, 1.04)	0.65 (0.40, 1.04)
Telephone Counselling	1.56 (1.14, 2.15)	0.96 (0.57, 1.63)	1.28 (0.68, 2.42)	0.59 (0.27, 1.30)	1.47 (0.96, 2.24)	1.00	0.95 (0.59, 1.52)
Individual Counselling	1.65 (1.16, 2.35)	1.01 (0.59, 1.75)	1.35 (0.70, 2.60)	0.62 (0.28, 1.39)	1.55 (0.96, 2.51)	1.06 (0.66, 1.70)	1.00

Abbreviations: NRT: nicotine replacement therapy

* Risk ratios (RRs) and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column.

Supplemental Table 12. Network meta-analysis of pharmacotherapies and behavioral therapies for smoking cessation in patients with cardiovascular disease restricted to the trials that did not biochemically validate abstinence [*].

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counselling	Telephone Counselling	Individual Counselling
Placebo/Usual Care	1.00	1.07 (0.67, 1.71)	-	-	-	0.69 (0.55, 0.88)	-
Bupropion	0.93 (0.58, 1.49)	1.00	-	-	-	0.65 (0.38, 1.09)	-
NRT	-	-	1.00	-	-	-	-
Varenicline	-	-	-	1.00	-	-	-
In-Hospital Counselling	-	-	-	-	1.00	-	-
Telephone Counselling	1.44 (1.14, 1.82)	1.55 (0.92, 2.61)	-	-	-	1.00	-
Individual Counselling	-	-	-	-	-	-	1.00

Abbreviations: NRT: nicotine replacement therapy. "-" denotes no trials that did not biochemically validated abstinence examined this intervention.

* Risk ratios (RRs) and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column.

Supplemental Table 13. Network meta-analysis of pharmacotherapies and behavioral therapies for smoking cessation in patients with cardiovascular disease restricted to the trials that assessed patients with acute CVD [*].

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counselling	Telephone Counselling	Individual Counselling
Placebo/Usual Care	1.00	0.86 (0.54, 1.37)	-	-	1.06 (0.63, 1.80)	0.54 (0.36, 0.82)	0.59 (0.36, 0.95)
Bupropion	1.17 (0.73, 1.87)	1.00	-	-	1.24 (0.61, 2.52)	0.63 (0.34, 1.18)	0.69 (0.35, 1.35)
NRT	-	-	1.00	-	-	-	-
Varenicline	-	-	-	1.00	-	-	-
In-Hospital Counselling	0.94 (0.56, 1.59)	0.80 (0.40, 1.63)	-	-	1.00	0.51 (0.26, 0.99)	0.55 (0.27, 1.13)
Telephone Counselling	1.84 (1.22, 2.78)	1.58 (0.85, 2.94)	-	-	1.96 (1.01, 3.83)	1.00	1.09 (0.58, 2.04)
Individual Counselling	1.70 (1.05, 2.75)	1.45 (0.74, 2.85)	-	-	1.81 (0.88, 3.69)	0.92 (0.49, 1.73)	1.00

Abbreviations: NRT: nicotine replacement therapy. "-" denotes no trials that examined this intervention among patients with acute CVD.

* Risk ratios (RRs) and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column.

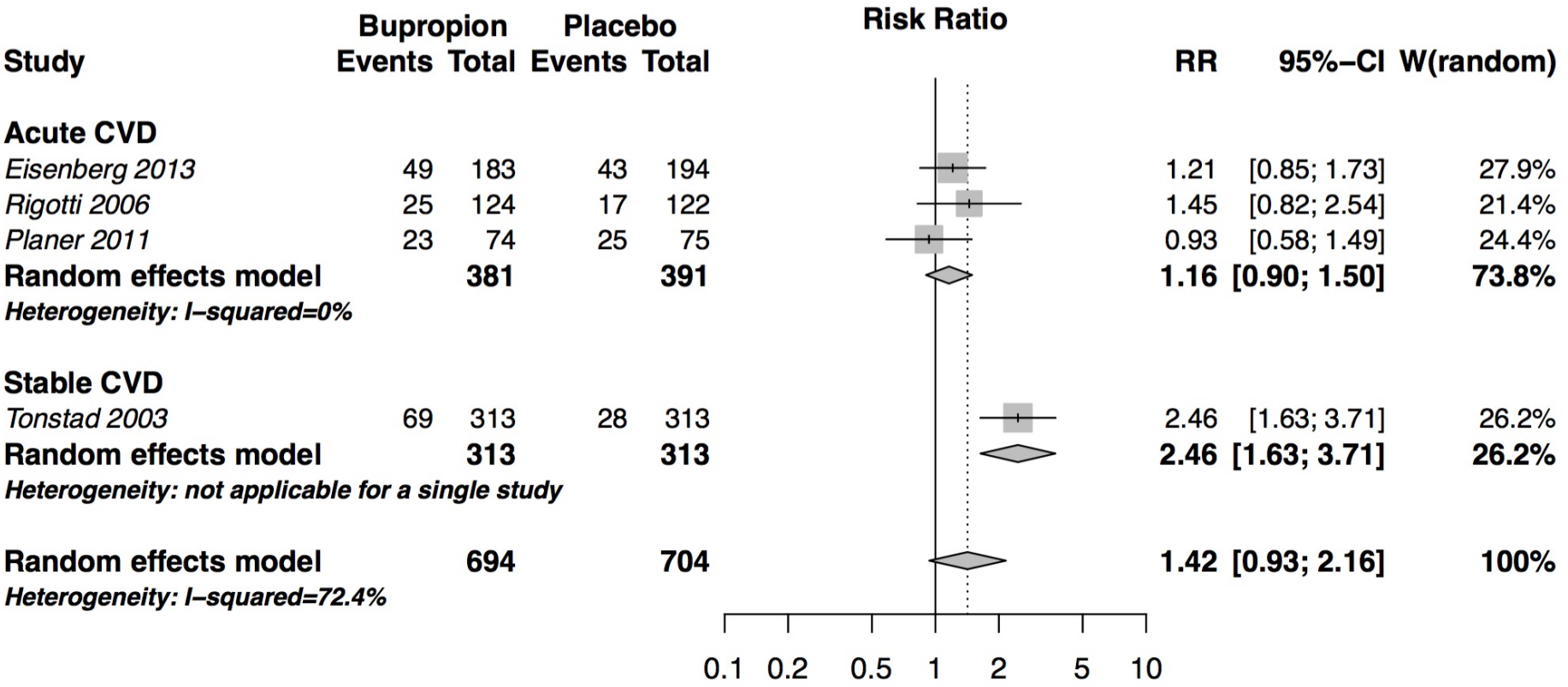
Supplemental Table 14. Network meta-analysis of pharmacotherapies and behavioral therapies for smoking cessation in patients with cardiovascular disease restricted to the trials that assessed patients with stable CVD [*].

Treatment	Placebo/Usual Care	Bupropion	NRT	Varenicline	In-Hospital Counselling	Telephone Counselling	Individual Counselling
Placebo/Usual Care	1.00	0.41 (0.27, 0.61)	0.81 (0.57, 1.16)	0.38 (0.25, 0.58)	0.90 (0.70, 1.16)	0.80 (0.67, 0.95)	0.71 (0.50, 1.01)
Bupropion	2.46 (1.64, 3.71)	1.00	2.00 (1.16, 3.45)	0.93 (0.52, 1.69)	2.21 (1.36, 3.58)	1.97 (1.26, 3.08)	1.75 (1.02, 3.00)
NRT	1.23 (0.86, 1.76)	0.50 (0.29, 0.86)	1.00	0.47 (0.27, 0.81)	1.10 (0.71, 1.71)	0.99 (0.66, 1.46)	0.87 (0.53, 1.44)
Varenicline	2.64 (1.72, 4.06)	1.07 (0.59, 1.94)	2.15 (1.23, 3.75)	1.00	2.37 (1.44, 3.90)	2.12 (1.34, 3.35)	1.88 (1.08, 3.26)
In-Hospital Counselling	1.12 (0.87, 1.44)	0.45 (0.28, 0.73)	0.91 (0.59, 1.40)	0.42 (0.26, 0.69)	1.00	0.89 (0.68, 1.17)	0.79 (0.52, 1.22)
Telephone Counselling	1.25 (1.05, 1.48)	0.51 (0.33, 0.79)	1.02 (0.68, 1.51)	0.47 (0.30, 0.75)	1.12 (0.85, 1.47)	1.00	0.89 (0.60, 1.31)
Individual Counselling	1.41 (0.99, 1.99)	0.57 (0.33, 0.98)	1.14 (0.70, 1.88)	0.53 (0.31, 0.92)	1.26 (0.82, 1.94)	1.13 (0.76, 1.66)	1.00

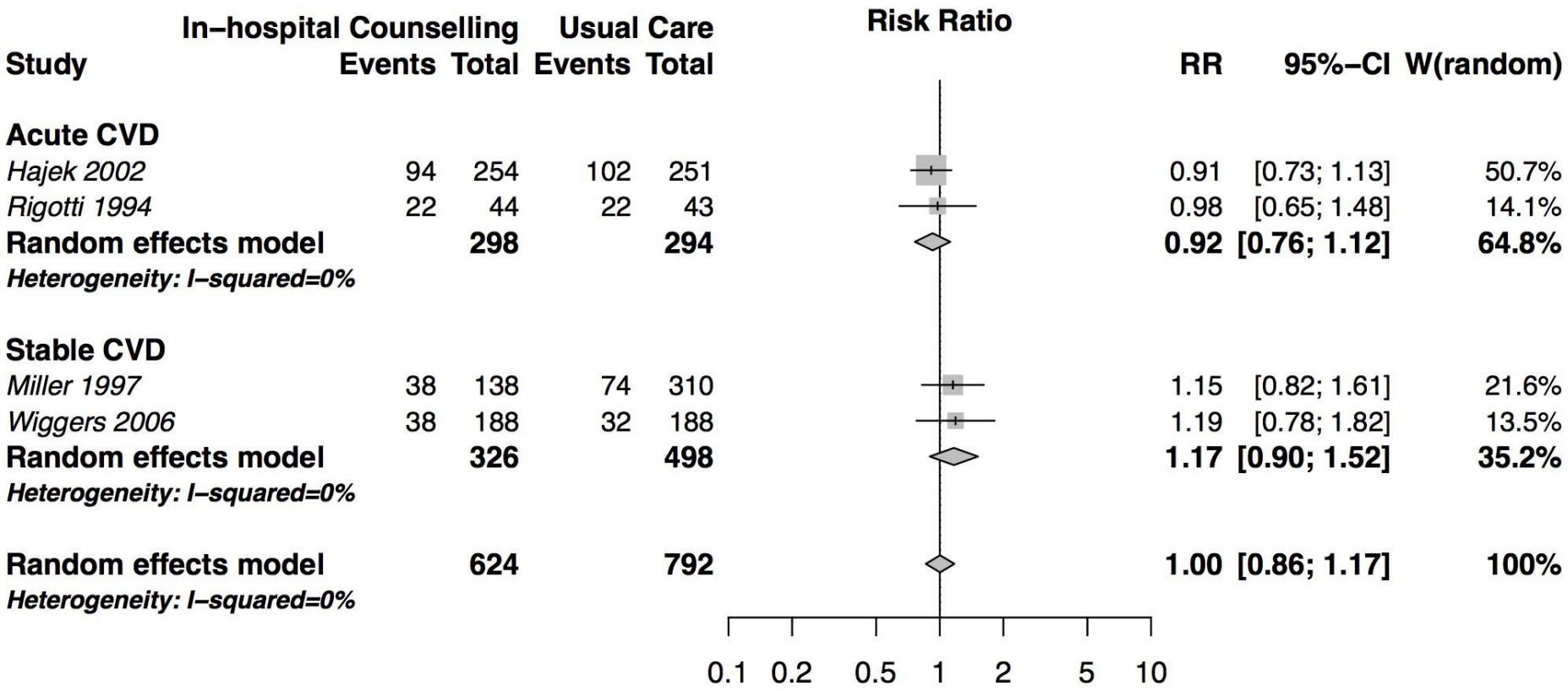
Abbreviations: NRT: nicotine replacement therapy.

* Risk ratios (RRs) and 95% confidence intervals were estimated using random-effects models. RRs are comparing the treatment in the far left column to that listed at the top of the column.

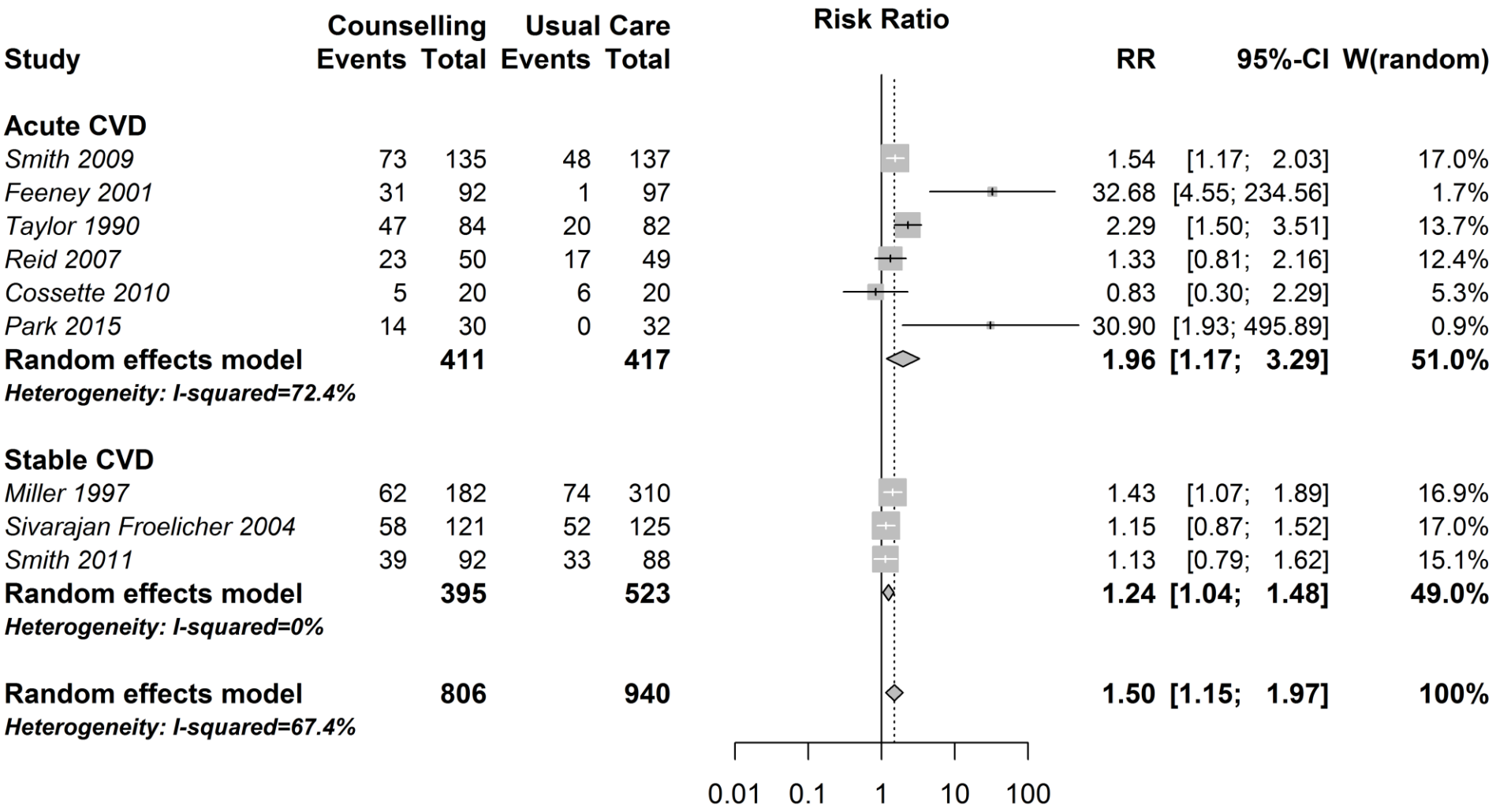
Supplemental Figure 1. Forest plot presenting the results comparing the efficacy of bupropion for smoking cessation to that of placebo, stratified by CVD subtype.



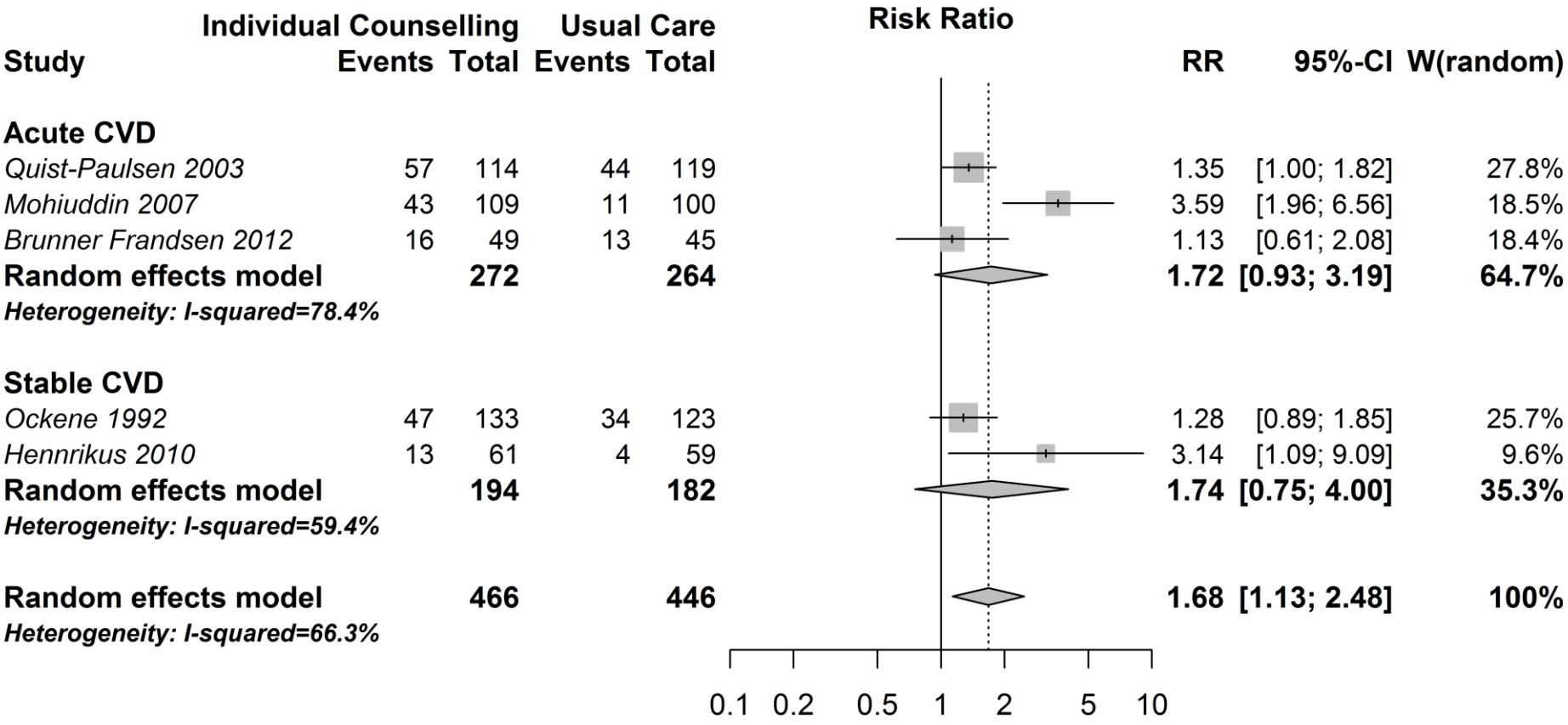
Supplemental Figure 2. Forest plot presenting the results comparing the efficacy of in-hospital counselling for smoking cessation to that of usual care stratified by CVD subtype.



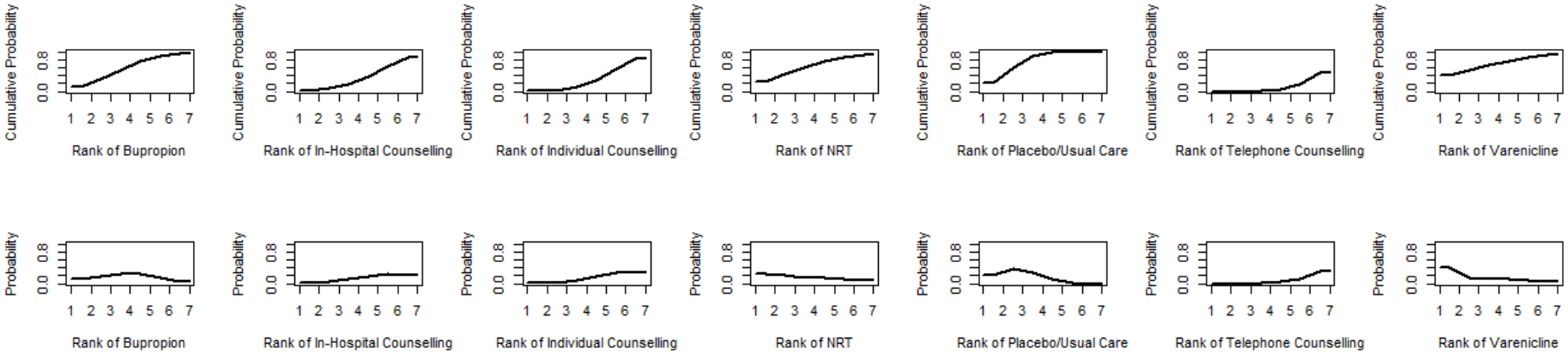
Supplemental Figure 3. Forest plot presenting the results comparing the efficacy of telephone counselling for smoking cessation to that of usual care stratified by CVD subtype.



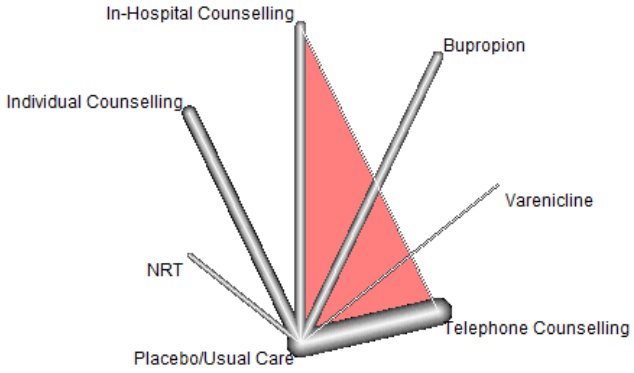
Supplemental Figure 4. Forest plot presenting the results comparing the efficacy of individual counselling for smoking cessation to that of usual care stratified by CVD subtype.



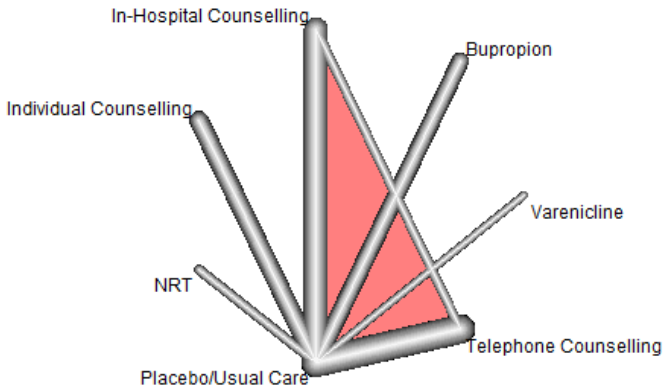
Supplemental Figure 5. Network meta-analysis SUCRA treatment rankograms.



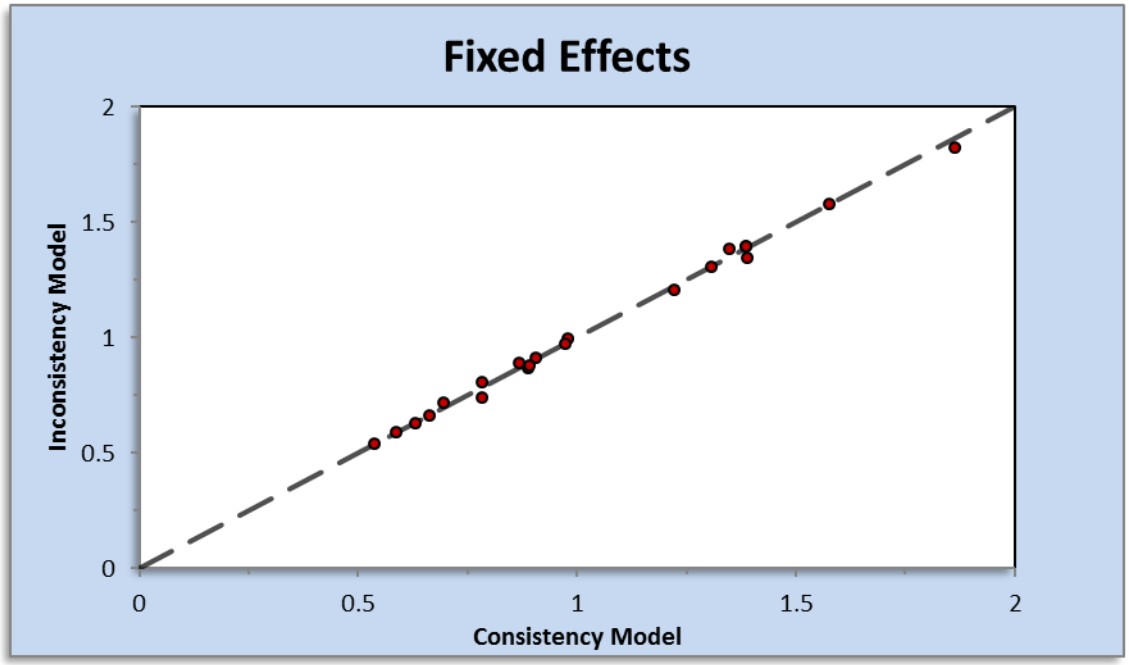
Supplemental Figure 6. Network meta-analysis diagram by number of studies.



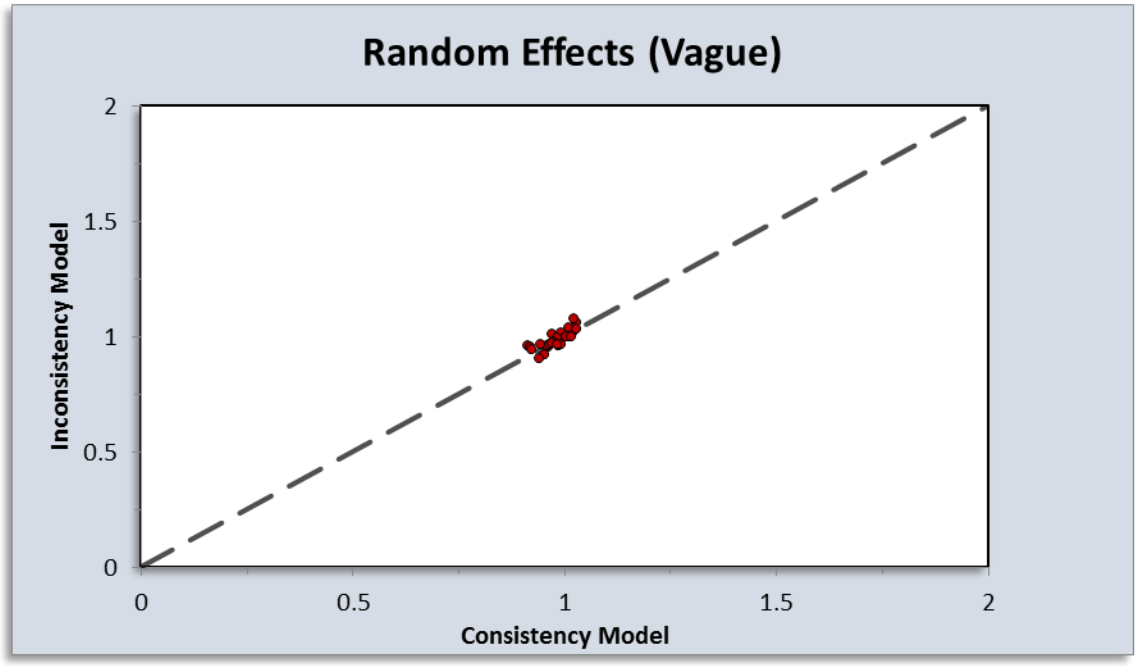
Supplemental Figure 7. Network meta-analysis diagram by number of studies using random standard error.



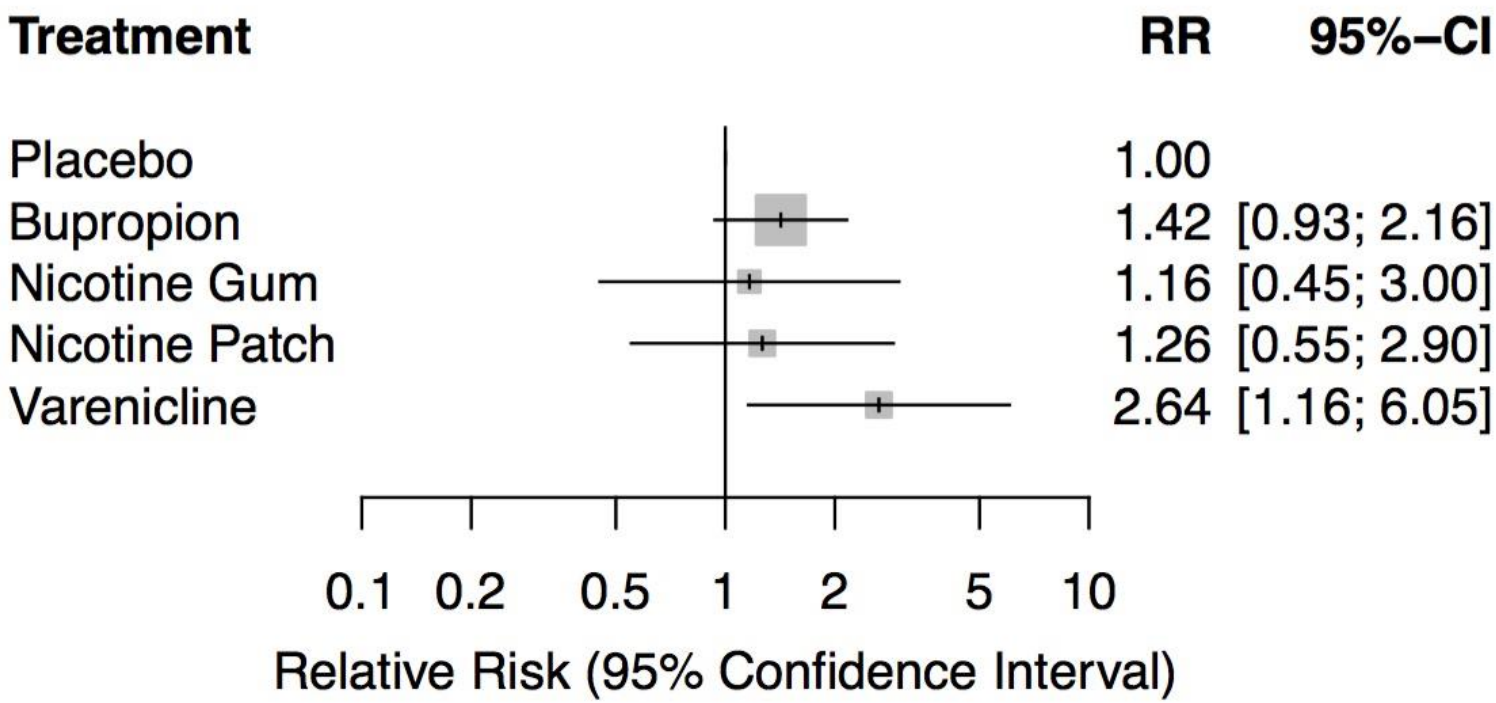
Supplemental Figure 8. Inconsistency plot of the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model using fixed effects models.



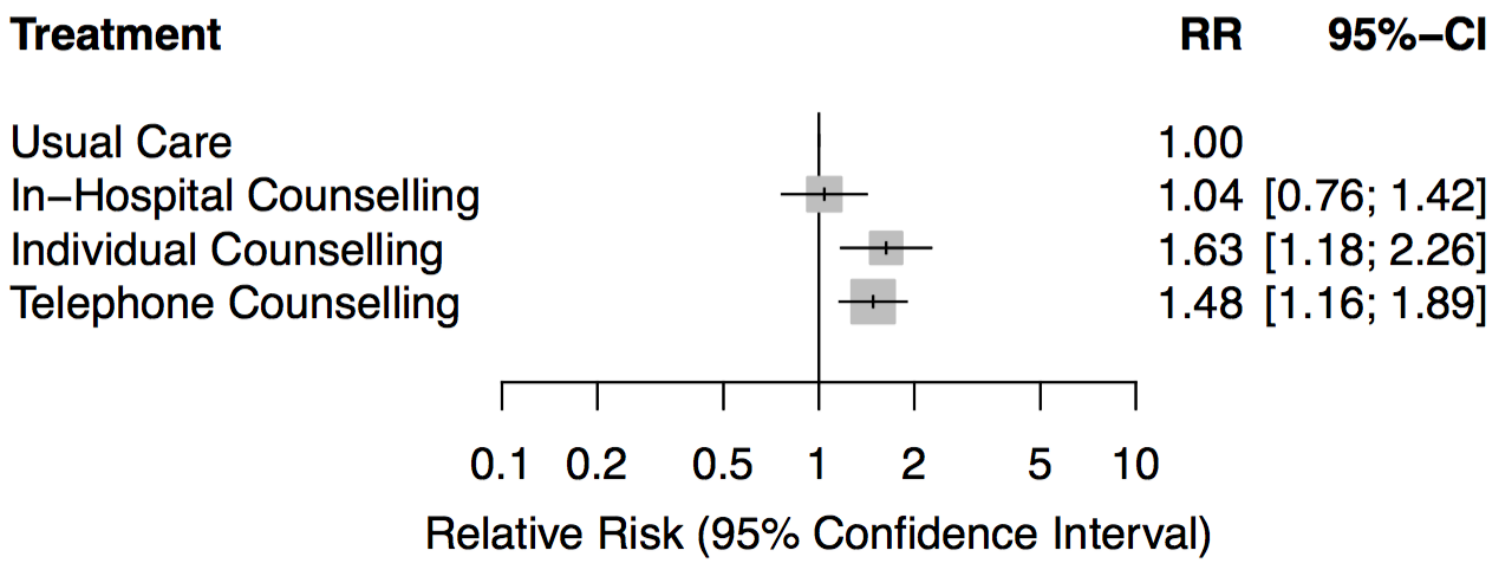
Supplemental Figure 9. Inconsistency plot of the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model using random effects models.



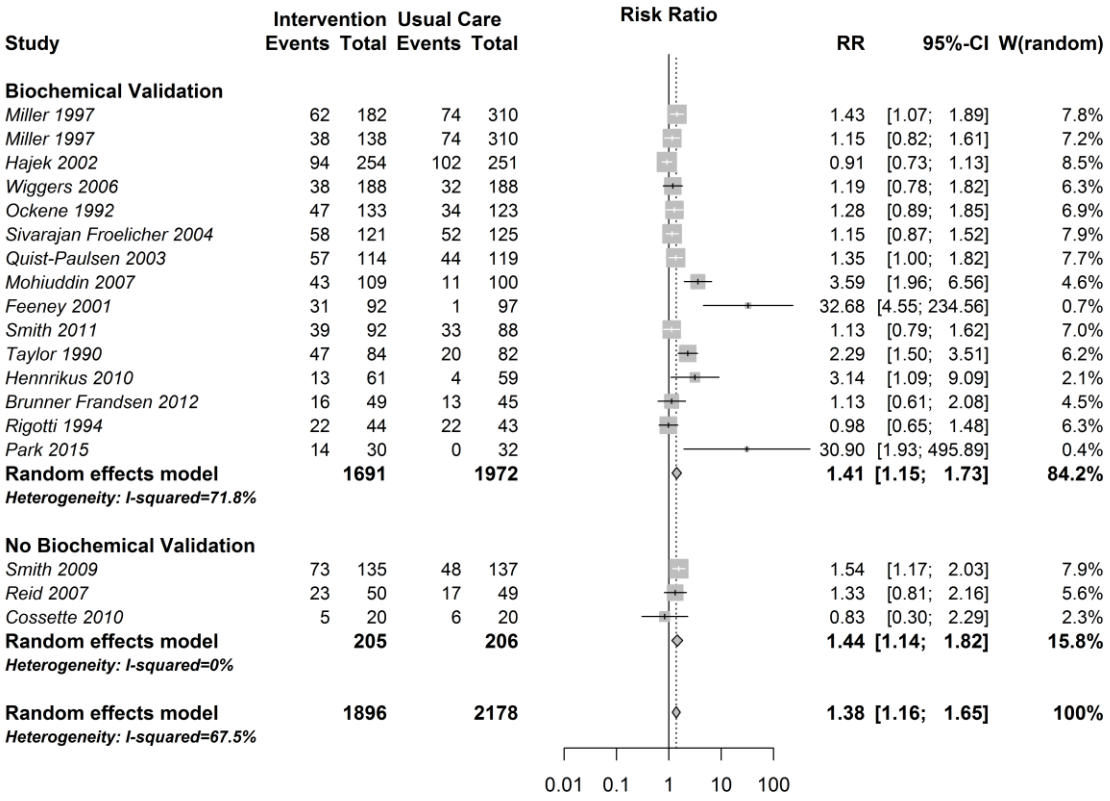
Supplemental Figure 10. Forest plot presenting the network analysis comparing the efficacy of pharmacotherapies for smoking cessation to that of placebo/usual care in patients with cardiovascular disease.



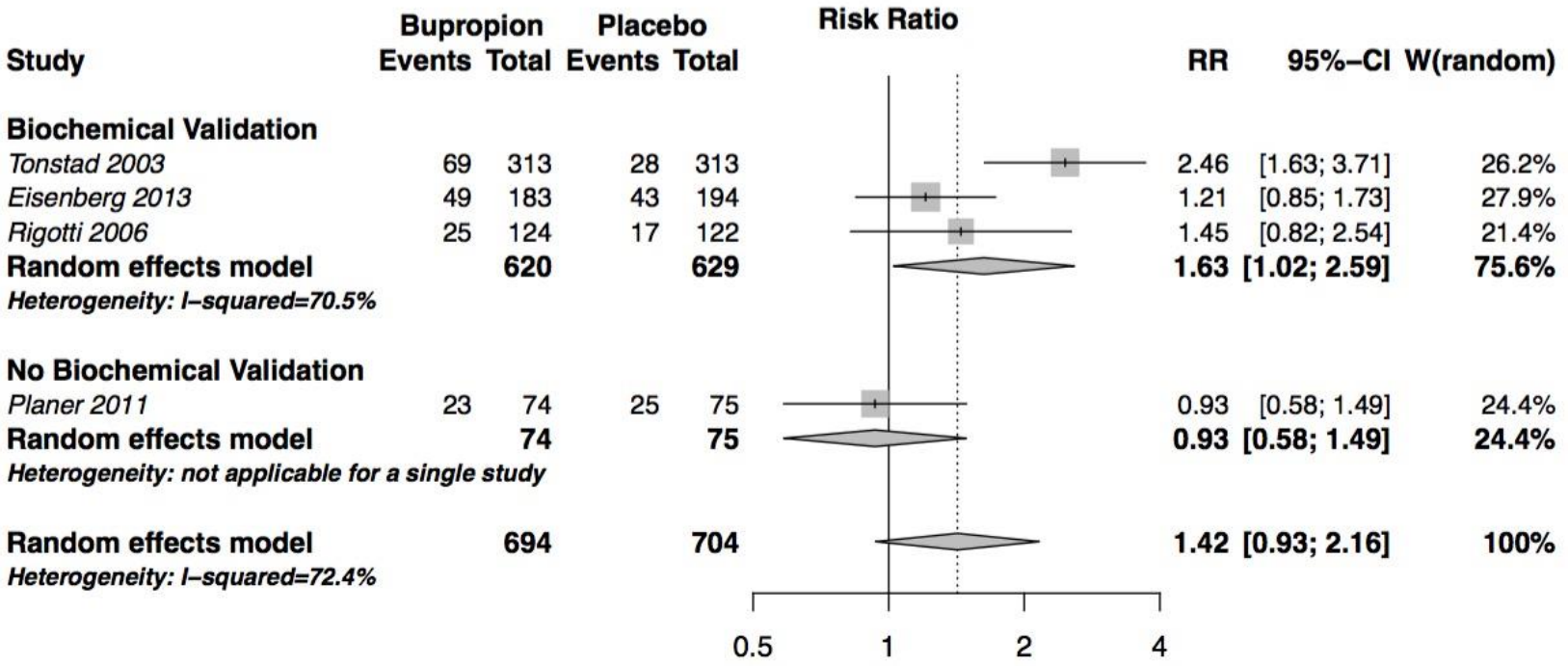
Supplemental Figure 11. Forest plot presenting the network analysis comparing the efficacy of behavioral therapies for smoking cessation to that of placebo/usual care in patients with cardiovascular disease.



Supplemental Figure 12. Forest plot presenting the sensitivity analysis comparing the efficacy of behavioral therapies for smoking cessation to that of usual care in patients with cardiovascular disease stratified by biochemical validation of abstinence.



Supplemental Figure 13. Forest plot presenting the sensitivity analysis comparing the efficacy of bupropion for smoking cessation to that of placebo in patients with cardiovascular disease stratified by biochemical validation of abstinence.



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