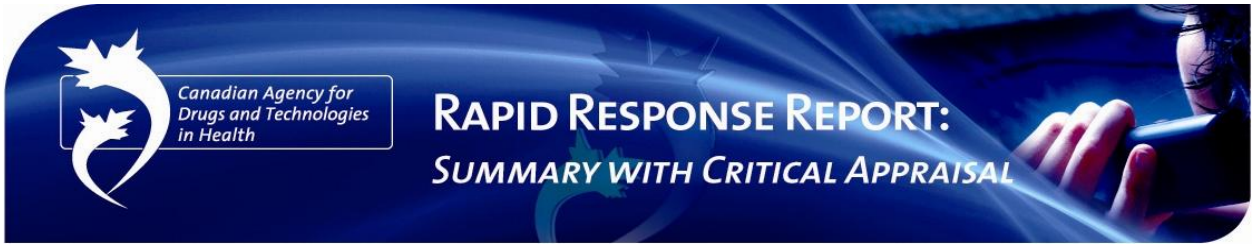

TITLE: Pharmacologic Smoking Cessation Interventions for Patients with Cardiovascular Conditions: A Review of the Safety and Guidelines

DATE: 16 May 2012

CONTEXT AND POLICY ISSUES

Cardiovascular disease (CVD) is a collective term referring to a group of diseases affecting the heart and blood vessels including: ischemic heart disease, stroke, peripheral vascular disease, heart failure, rheumatic heart disease, and congenital heart disease.[1] CVD is a leading cause of morbidity and mortality in adult Canadians accounting for 16.9% of all hospitalizations in 2005 and 29% of all deaths in Canada in 2008.[2,3] Tobacco smoking is an important modifiable risk factor for cardiovascular events and Canadian and international clinical practice guidelines unanimously recommend smoking cessation for patients with CVD.[4-6]

Strategies for health care professionals who are assisting patients attempting to quit smoking can include counseling and the use of pharmacotherapy. Commonly used pharmacotherapy for smoking cessation includes nicotine replacement therapy (NRT), bupropion hydrochloride (Zyban), and varenicline tartrate (Champix). NRT is available without a prescription in Canadian pharmacies and can be administered using a transdermal patch, an inhaler, chewing gum, or a combination of these devices. Bupropion and varenicline are two smoking cessation treatments that are currently only available with a prescription. Bupropion is available in 150 mg sustained release tablets and is taken daily for 7 to 12 weeks.[7] Varenicline is available in 0.5 mg and 1.0 mg tablets and is taken daily for 12 to 24 weeks.[8] It is recommended that patients planning to use bupropion and varenicline set a quit date and begin treatment one to two weeks prior to that date.[7,8]

CADTH has conducted a health technology assessment which evaluated the clinical and cost-effectiveness of pharmacologic-based strategies for smoking cessation.[9] Patients with CVD and smoking-related diseases were a subpopulation of interest in the CADTH review. The report suggested that nicotine gum, nicotine patch, bupropion, and varenicline were efficacious as an aid for smoking cessation compared with placebo for this patient population; however, harms data were not assessed in the review. In addition, Canadian and international regulatory agencies have recently updated the safety information for varenicline to include a warning regarding a potential increase in the risk of cardiovascular events in patents with CVD.[10-12] As a result of these changes, there is some uncertainty regarding the comparative safety of different

pharmacotherapies for smoking cessation in patients with CVD. The present review was conducted to summarize the available safety evidence for varenicline, bupropion, and NRT in patients with CVD. A search for evidence-based guidelines and recommendations on the use of these agents was also conducted to provide information regarding current practice.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the safety of pharmacologic smoking cessation interventions for patients with cardiovascular conditions?

2. What are the evidence-based guidelines regarding the use of pharmacologic smoking cessation interventions for patients with cardiovascular conditions?

KEY MESSAGE

The efficacy of bupropion, varenicline, and NRT in patients with CVD has been assessed in well-conducted RCTs and systematic reviews. However, the majority of these studies were not specifically designed to fully assess the safety of smoking cessation pharmacotherapy. There were no head-to-head trials or indirect comparisons of different active treatments for smoking cessation. Overall, there is uncertainty regarding the comparative safety of varenicline, bupropion, and NRT in patients with various forms of CVD.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, The Cochrane Library (2012, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and April 16, 2012.

The included systematic review was primarily focused on efficacy assessments and included only sparse descriptions of adverse events. Although the publication dates for many of the individual randomized controlled trials (RCTs) included the systematic review predated our search criteria, the results have been summarized in this report to address the paucity of harms data presented in the existing review.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection according to the criteria presented in Table 1.

Table 1: Selection Criteria

Population	Smokers with controlled or uncontrolled cardiovascular disease • Ischemic heart disease • Acute coronary syndrome • Stable angina • Unstable angina • Hypertension • History of stroke
Intervention	Pharmacologic smoking cessation interventions • Varenicline • Bupropion • Nicotine replacement therapy
Comparators	• Active treatments compared to each other • Placebo • Untreated controls
Outcomes	• Adverse events • Guidelines addressing utilization and administration
Study Designs	• Health technology assessments • Systematic reviews and meta-analyses • Randomized controlled trials • Controlled, non-randomized studies • Evidence-based guidelines and recommendations

Exclusion Criteria

Studies meeting any of the following criteria were excluded: uncontrolled studies, case series, case reports, and non-English language publications.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was performed according to study design. Appraisal of full-text publications for primary studies was performed using the criteria described by Downs and Black.[13] Systematic reviews and clinical practice guidelines were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR)[14] criteria and the Appraisal of Guidelines for Research and Evaluation (AGREE)[15] criteria, respectively. Numeric scores were not calculated. Instead, the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 189 citations. Upon screening titles and abstracts, 14 potentially relevant articles were retrieved for full-text review. Fourteen additional potentially relevant reports were retrieved from grey literature and hand searching. Of the 28 potentially relevant reports, five contained an irrelevant population, three contained irrelevant outcomes, two contained an irrelevant comparator, one was narrative review article, and one was a commentary. Sixteen publications were included in this review. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

One systematic review and meta-analysis was identified in the literature search that assessed the efficacy of pharmacotherapies for smoking cessation in patients with CVD.[16] A total of eight reports of seven placebo-controlled RCTs were identified which investigated the use of varenicline (one RCT),[17] bupropion (three RCTs reported in four publications),[18-21] and transdermal NRT (three RCTs)[22-24] in patients with CVD. One retrospective, non-randomized study was identified that compared the prescription of NRT against no NRT on in-hospital mortality in patients who had undergone CABG.[25] Five evidence-based guidelines and recommendations regarding the use bupropion, varenicline, and NRT for smoking cessation in patients with CVD were identified.[5,6,26-28] One National Guideline Clearinghouse summary of a selected guideline was also included.[29] Information regarding the use of bupropion, varenicline, and NRT in patients with CVD has also been summarized from Canadian product monographs (Appendix 2). Two additional meta-analyses[30,31] did not meet the inclusion criteria of this review due to the inclusion of non-CVD patients; however, the key findings of these reviews are summarized as additional information (Appendix 3).

Summary of Study Characteristics

A detailed summary of individual study characteristics is provided in Appendix 4.

Systematic Reviews

The systematic review and meta-analysis conducted by Eisenberg et al (2010)[16] had broad eligibility criteria including inpatients and outpatients with either stable or unstable CVD. The interventions in the included studies were limited to bupropion, nicotine patches, and nicotine gum. There were no studies which assessed the use of varenicline in patients with CVD.

Randomized Controlled Trials

All of the RCTs were double-blind and used a parallel-group design comparing an active treatment (i.e., varenicline,[17] bupropion,[18-21] or transdermal NRT[22-24]) against placebo. Five RCTs[17,21-24] included outpatients with stable CVD and two RCTs involved patients hospitalized for acute CVD (e.g., myocardial infarction or unstable angina). Eligibility criteria across trials varied with respect to smoking status at the time of screening, with RCTs requiring at least 10 cigarettes per day,[17,18,21] at least 15 cigarettes per day,[22,24] at least one pack per day,[23] or at least one cigarette during the past month.[19] Treatment periods ranged from two weeks[24] to 12 weeks[17,19] and the duration of follow-up ranged from two weeks[24] to 52 weeks.[17-19,21] All of the RCTs but one[24] specified some form smoking-cessation counseling that was offered in addition to the randomized interventions. Sample sizes ranged from 106[24] to 714.[17]

Non-randomized studies

The non-randomized study which met the inclusion of the review was a retrospective matched cohort study (N = 134). The assessed the impact of transdermal NRT on in-hospital mortality following coronary artery bypass graft. Patients who were prescribed transdermal NRT were compared with matched controls that were not prescribed NRT.

Evidence-based Guidelines and Recommendations

Included evidence-based guidelines were identified from the following agencies: the Canadian Cardiovascular Society;[5] the Australian National Prescribing Service Rational Assessment of Drugs and Research (NPS RADAR);[28] the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom;[27,29] and the New Zealand Ministry of Health.[6,26]

Summary of Critical Appraisal

Details of individual study critical appraisal are presented in Appendix 5.

Systematic Reviews

The systematic review by Eisenberg et al (2010)[16] was conducted using a comprehensive, well-reported literature search involving multiple databases. Article selection and data extraction were performed using a rigorous and well-reported methodology. Limitations with the review included poor reporting of adverse event data and pooling of efficacy data across different classes of pharmacotherapy (i.e., data for bupropion were pooled with NRT).

Randomized Controlled Trials

Overall, the included studies appear to have strong internal validity (i.e., the results do not appear to be influenced by systemic bias or confounding). All of the included RCTs had clearly stated objectives, methods, and eligibility criteria. All of the publications had a good description of the study interventions and all of the RCTs used a double-blind approach for administering the study treatments. Five RCTs[18,19,22-24] clearly stated that the active and placebo treatments were identical in appearance. Three of the RCTs[19,22,23] reported an appropriate and adequately-concealed method of randomization and four failed to fully report their methods for randomization and allocation concealment.[17,18,21,24] All of the studies reported that the baseline characteristics were similar between the active and placebo groups; therefore, there is no evidence of selection bias within the individual studies.

The external validity of the included RCTs (i.e., the degree to which the findings are generalizable to the broader population of patients with CVD) is limited by several important factors including limited statistical power, the exclusion of potentially relevant patient populations (e.g., those with unstable CVD), and extensive contact with health professionals. One RCT[22] provided a power calculation specifically for detecting differences in adverse events between the active and placebo treatment groups. All of the other studies were either powered for assessing smoking-cessation efficacy (i.e., quit rates)[17-19,21] or did not report a sample size calculation.[23,24] The included RCTs involved considerable contact with health professionals via telephone calls or clinic visits which may not be reflective of routine clinical practice in Canada. The trial population of one of the included RCTs[22] was almost exclusively male (98.6%), limiting the generalizability of the results to women.

Non-randomized studies

The non-randomized study by Paciullo et al (2009)[25] was generally well-reported. The objectives, eligibility criteria, and methods were clearly stated and well-described. The baseline characteristics were similar between the two groups and a logistic regression used to control for any differences between the groups. An important strength was the use of in-hospital mortality as the primary outcome. The most important limitations with the study are the lack of randomization and retrospective design. In addition, there were no sample size calculations provided and the number of patients assessed may be too limited to accurately assess differences in safety endpoints.

Evidence-based Guidelines and Recommendations

The guidelines prepared by NICE and the New Zealand Ministry of Health (MoH) were both prepared using rigorous methodologies to select and review evidence and both were generally well-reported. Both of these guidelines satisfied the majority the AGREE assessment criteria. The only limitation of the NICE guideline was the absence of clearly reported conflict of interest statements; however, this is mitigated by extensive peer-review and methodological rigor. The most important limitations with the New Zealand MoH guidelines was the poor reporting of methods used to select evidence and the absence of explicit links between the recommendations and the supporting evidence.

The shorter guidance documents from the CCS and NPS RADAR have numerous limitations with respect to the reporting of recommendations and methods. Limitations common to both documents included poor-reporting of the following: objectives, clinical questions, search strategy, methods for evidence selection and formulating recommendations, and a lack of clarity regarding patient input. Strengths common to both CCS and NPS RADAR guidance documents included explicit linkages between recommendations and supporting evidence, well-documented external review, and the consideration of both benefits and harms when formulating recommendations.

Summary of Findings

Systematic Reviews and Meta-Analyses

Eisenberg et al (2010)[16] conducted a systematic review and meta-analysis of RCTs to assess the efficacy of behavioural and pharmacological smoking cessation therapies in patients with cardiovascular disease. The review included four placebo-controlled RCTs that investigated the use of bupropion (two RCTs), nicotine gum (one RCT) and transdermal nicotine patch (one RCT). Data regarding adverse events were poorly reported in the systematic review. The report states that adverse events were similar in both the active groups (i.e., bupropion or NRT) and placebo groups of the included RCTs and that the safety data could not be pooled. Overall, the authors concluded that there is insufficient data regarding the safety of pharmacological therapies for smoking cessation in cardiac patients. Harms data from the individual trials included in this systematic review are described below.

Randomized Controlled Trials

Bupropion SR vs. Placebo

Three RCTs, reported in four publications, compared bupropion sustained-release (SR) against placebo in patients with CVD.[18-21] Planer et al (2011)[18] conducted a placebo-controlled, double-blind RCT to investigate the safety and efficacy of bupropion SR for smoking cessation in patients hospitalized with acute coronary syndrome (ACS). A total of 151 patients were randomized (1:1) to receive treatment with bupropion SR (150 mg twice daily) or placebo for eight weeks and were followed for up to one year. All patients received hospital and telephone-based smoking cessation counseling. The trial had initially planned to recruit approximately 250 patients; however, the study was stopped after an interim analysis failed to demonstrate superiority of bupropion SR over placebo in smoking abstinence after one year (P = 0.86).

Safety endpoints which were assessed during the trial are summarized in Table 2. No patients died in either treatment group during the one year follow-up period. Hospitalization occurred for 36% of bupropion-treated patients and 39% of placebo-treated patients (P = 0.70). A larger proportion of patients treated with bupropion SR reported experiencing dizziness during the trial compared with placebo (P = 0.005). All other adverse events occurred in a similar proportion of patients in each treatment group. Cardiovascular adverse events were relatively rare in both groups; however, the incidence of ACS was numerically greater in the placebo group compared to the bupropion SR group (7% vs. 3%; P = 0.44).

Table 2: Summary of Adverse Events for Bupropion SR vs. Placebo 2011[18]

Adverse Events – n (%)	Bupropion SR	Placebo	P Value
Death	0 (0)	0 (0)	0.99
Any hospitalization	26 (36)	29 (39)	0.70
Suicide attempt	0 (0)	0 (0)	0.99
Myocardial infarction	2 (3)	1 (1)	0.62
Acute Coronary Syndrome	2 (3)	5 (7)	0.44
Chest pain	11 (15)	14 (19)	0.66
Sleep disturbance	16 (22)	14 (19)	0.69
Headache	19 (26)	19 (26)	0.99
Mouth dryness	21 (29)	18 (24)	0.58
Nausea	4 (5)	6 (8)	0.74
Anxiety	4 (5)	4 (5)	0.99
Dizziness	10 (14)	1 (1)	0.005
Constipation	1 (1)	5 (7)	0.21
Rash	3 (4)	1 (1)	0.37

n=number of patients with event; **N**=total number of patients; **SR**=slow release

Rigotti et al (2006)[19] and Thorndike et al (2008)[20] reported the results of a double-blind, placebo-controlled RCT conducted to assess the efficacy and safety of bupropion SR in smokers admitted to hospital for acute CVD (N = 254). Patients were randomized to receive treatment with bupropion SR (150 mg twice daily) or placebo for 12 weeks and were followed for up to one year. In addition to the randomized treatments, all of the trial participants received cognitive-behavioral smoking cessation and relapse-prevention counseling.

At one year follow-up, there was no statistically significant difference between the two groups for all-cause mortality, cardiovascular mortality, new cardiovascular events, or other serious adverse events (Table 3). There was no statistically significant difference between the two groups for change in blood pressure (both systolic and diastolic), body weight, depressive

symptoms, or nicotine withdrawal symptoms. Based on the findings of this study, the authors suggested that bupropion SR was safe in the study population of smokers with acute CVD.

Table 3: Summary of Adverse Events for Bupropion SR vs. Placebo[19]

Adverse Events n (%)	Up to 3 months			Up to 12 months		
	B. SR	PLC	Rate Ratio (95% CI)*	B. SR	PLC	Rate Ratio (95% CI)*
All-cause mortality	—	—	—	0 (0)	2 (2)	—
CV mortality	—	—	—	0 (0)	1 (1)	—
CV events	20 (16)	17 (14)	1.22 (0.64, 2.33)	32 (26)	22 (18)	1.56 (0.91, 2.69)
Non-cardiac SAEs	25 (20)	24 (19)	1.02 (0.58, 1.79)	46 (37)	38 (31)	1.17 (0.76, 1.80)
New BP elevation	16 (13)	12 (10)	1.31 (0.62, 2.77)	16 (13)	12 (10)	1.34 (0.64, 2.83)

BP=blood pressure; **B. SR**=bupropion sustained-release; **CI**=confidence interval; **CV**=cardiovascular; **n**=number of patients with events; **PLC**=placebo; **SAEs**=serious adverse events

*Rate ratio presented as events per person-year of follow-up

Data from Rigotti et al, 2006[19]

Tonstad et al (2003)[21] conducted a double-blind, multicenter, placebo-controlled RCT to assess the efficacy and safety of bupropion SR in patients with smoking-related CVD (i.e., myocardial infarction or an interventional cardiac procedure at least three months prior to screening, stable angina pectoris, peripheral vascular disease or congestive heart failure). Eligible patients were randomized (1:1) to receive bupropion SR (150 mg twice daily) or placebo.

Adverse events of were reported for 64% of patients treated with bupropion and 58% of placebo-treated patients (Table 4). Statistical significance of the findings were not reported. Insomnia and dry mouth were more commonly reported with bupropion SR compared with placebo (24% vs. 12% and 18% vs. 10%, respectively). Cardiovascular adverse events were also slightly more common with bupropion SR compared with placebo (7.7% vs. 4.5%). Discontinuations due to adverse events were similar between the two treatment groups (5% vs. 6%). Serious adverse events (SAEs) during treatment were reported for five patients (1.6%) in the bupropion group compared with no events in the placebo group. None of the SAEs resulted in discontinuation of bupropion SR. Three additional SAEs occurred within one week of finishing treatment, one in the bupropion group and two in the placebo group. Two patients in each group died during the study. The authors reported that there was no overall treatment effect observed for blood pressure (both systolic and diastolic) or heart rate and that there were no clinically significant changes in vital signs for either treatment group during the 52-week follow-up period.

Table 4: Summary of Adverse Events for Bupropion SR vs. Placebo[21]

Summary of Adverse Events - n (%)	Bupropion SR (N = 313)	Placebo (N = 313)
At least 1 adverse event	201 (64.2)	181 (57.8)
Withdrawals due to adverse events	17 (5.4)	19 (6.1)
Serious adverse events	5 (1.6)	0 (0.0)
Cardiovascular events	24 (7.7)	15 (4.8)
Angina pectoris	7 (2.2)	4 (1.3)
Hypertension	2 (0.6)	3 (1.0)
Palpitations	4 (1.3)	1 (0.3)
Insomnia	75 (24.0)	37 (11.8)
Dry mouth	55 (17.6)	31 (9.9)
Nausea	40 (12.8)	19 (6.1)
Headache	35 (11.2)	34 (10.9)
Dizziness	24 (7.7)	17 (5.4)
Constipation	16 (5.1)	4 (1.3)
Sweating	16 (5.1)	10 (3.2)

n=number of events; **N**=total number of patients; **SR**=sustained release

Data from Tonstad et al, 2003[21]

Varenicline vs. Placebo

Rigotti et al (2010)[17] conducted a multicenter, double-blind, placebo-controlled RCT to assess the efficacy and safety of varenicline for smoking cessation in patients with stable CVD. In addition to smoking-cessation counseling, 714 smokers were randomized (1:1) to receive varenicline (1 mg BID) or placebo for 12 weeks. Patients were followed for up to one year. Reported or observed cardiovascular events or deaths resulting from any cause were independently adjudicated.

A summary of adverse events including mortality, vascular events, and psychiatric events reported in the trial is shown in

Table 5. The proportion of patients who experienced at least one adverse event of any severity was greater with varenicline compared with placebo [risk difference (RD) 16.7; 95% confidence interval (CI) 10.3 to 23.2]. Withdrawals due to adverse events were also more frequently reported for varenicline compared with placebo [RD 5.3; 95% CI 1.6 to 9.1]. The proportion of patients with at least one SAE was similar between the two groups. All-cause mortality, cardiovascular death, and non-cardiovascular death were rare in both groups; however, events of all three were numerically greater in the placebo group. Compared with placebo, a greater proportion of varenicline-treated patients experienced nausea, vomiting, insomnia, and abnormal dreams.

Cardiovascular events were reported for 7.1% of varenicline-treated patients compared with 5.7% of those in the placebo group [RD 1.4; 95% CI -2.3 to 5.0]. The numerical increase in cardiovascular events appears to be primarily due to a slightly higher incidence of non-fatal myocardial infarction (2.0% vs. 0.9%) and need for coronary revascularization (2.3% vs. 0.9%) in patients treated with varenicline compared with placebo. Psychiatric adverse events were similar between the two groups, with the exception of sleep disorders which occurred more frequently with varenicline compared with placebo [RD 12.4; 95% CI 7.1 to 17.7)]. No varenicline-treated patients reported suicidal ideation, a change in behaviour, or a cognitive or attention disorder.

Rigotti et al (2010) concluded that varenicline was well tolerated and did not increase cardiovascular events or mortality in patients with stable CVD; however, the finding that serious cardiovascular events were reported more frequently with varenicline compared to placebo has been included in the Warnings/Precautions section of the Canadian product monograph for varenicline (see Appendix 2). Both Rigotti et al (2010)[17] and the product monograph[8] state the findings of this RCT should be interpreted with caution as the limited size and duration of the study prevent definitive conclusions regarding the safety of varenicline in patients with stable CVD.

Table 5: Summary of Adverse Events for Varenicline vs. Placebo

Summary of Adverse Events – n (%)	Varenicline (N = 353)	Placebo (N = 350)	Risk Difference (95% CI)
≥1 Adverse event	288 (81.6)	227 (64.9)	16.7 (10.3, 23.2)
Withdrawals due to adverse events	34 (9.6)	15 (4.3)	5.3 (1.6, 9.1)
≥1 Serious adverse events	23 (6.5)	21 (6.0)	0.5 (-3.1, 4.1)
Most Common Adverse Events			
Nausea	104 (29.5)	30 (8.6)	20.9 (15.3, 26.5)
Headache	45 (12.7)	39 (11.1)	1.6 (-3.2, 6.4)
Insomnia	42 (11.9)	23 (6.6)	5.3 (1.1, 9.6)
Vomiting	29 (8.2)	4 (1.1)	7.1 (4.0, 10.1)
Abnormal dreams	28 (7.9)	6 (1.7)	6.2 (3.1, 9.4)
Fatigue	25 (7.1)	14 (4.0)	3.1 (-0.3, 6.5)
Nasopharyngitis	23 (6.5)	30 (8.6)	-2.1 (-6.0, 1.8)
Constipation	23 (6.5)	7 (2.0)	4.5 (1.6, 7.5)
Diarrhea	22 (6.2)	18 (5.1)	1.1 (-2.3, 4.5)
Dizziness	22 (6.2)	16 (4.6)	1.7 (-1.7, 5.0)
Dyspepsia	19 (5.4)	12 (3.4)	2.0 (-1.1, 5.0)
Mortality			
All-cause mortality	2 (0.6)	5 (1.4)	-0.8 (-2.3, 0.6)
Cardiovascular death	1 (0.3)	2 (0.6)	-0.3 (-1.3, 0.7)
Non-cardiovascular death	1 (0.3)	3 (0.9)	-0.6 (-1.7, 0.5)
Vascular Adverse Events			
Any cardiovascular event	25 (7.1)	20 (5.7)	1.4 (-2.3, 5.0)
Nonfatal myocardial infarction	7 (2.0)	3 (0.9)	1.1 (-0.6, 2.9)
Need for coronary revascularization	8 (2.3)	3 (0.9)	1.4 (-0.4, 3.2)
Hospitalization for angina pectoris	8 (2.3)	8 (2.3)	-0.02 (-2.2, 2.2)
Hospitalization for CHF	0 (0.0)	2 (0.6)	-0.6 (-1.5, 0.3)
Nonfatal stroke	2 (0.6)	1 (0.3)	0.3 (-0.7, 1.2)
Transient ischemic attack	1 (0.3)	1 (0.3)	-0.0 (-0.8, 0.8)
Diagnosis or admission for PVD	5 (1.4)	3 (0.9)	0.6 (-1.0, 2.1)
Psychiatric Adverse Events			
Sleep disorders	78 (22.1)	34 (9.7)	12.4 (7.1, 17.7)
Anxiety disorders	12 (3.4)	16 (4.6)	-1.2 (-4.1, 1.7)
Depressed mood disorders	11 (3.1)	8 (2.3)	0.8 (-1.6, 3.2)
Bipolar disorder	1 (0.3)	0 (0)	0.3 (-0.4, 1.0)
Other mood disorders	9 (2.5)	3 (0.9)	1.7 (-0.2, 3.6)

CHF=congestive heart failure; **CI**=confidence interval; **PVD**=peripheral vascular disease

Data from Rogotti et al, 2010[17] and ClinicalTrials.gov[32]

Transdermal NRT vs. Placebo

Joseph et al (1996)[22] conducted a double-blind, placebo-controlled, multicenter RCT to evaluate the efficacy and safety of transdermal NRT in smokers with at least one major cardiovascular disorder. The RCT was conducted at 10 Veterans Affairs medical centers in the United States where 584 outpatients with CVD were randomized (1:1) to 10 weeks of transdermal NRT or placebo. Patients were assessed for 14 weeks for the primary safety endpoints which included death, myocardial infarction, cardiac arrest, and admission to hospital for increased severity of angina, arrhythmia, or congestive heart failure. Secondary safety endpoints included hospitalization for other reasons, outpatient visits for increased severity of CVD, and adverse events.

A summary of serious and severe adverse events is shown in Table 6. Primary safety endpoints were reported for 5.4% of the NRT group compared to 7.9% of the placebo group with a risk difference (RD) of 2.5% (95% CI -1.6 to 6.5; P = 0.23). There were a larger number of deaths in

the placebo group compared with the NRT group; however, the difference was not statistically significant (P = 0.07). There was no statistically significant difference between the NRT group (11.9%) and the placebo group (9.7%) for the occurrence of secondary safety endpoints (RD 2.2%; 95% CI -2.2 to 7.4; P = 0.37). The authors reported that more patients in the NRT group had outpatient visits for chest pain, arrhythmia, or congestive heart failure compared to the placebo group; however, the difference was not statistically significant (P = 0.5).

Table 6: Summary of Adverse Events for Transdermal NRT vs. Placebo

Adverse Events	Nicotine (N = 294)		Placebo (N = 290)	
	n (%)	Events	n (%)	Events
Serious Adverse Events				
Death	1 (0.3)	1	6 (2.1)	6
Myocardial Infarction	0 (0.0)	0	1 (0.3)	1
Cardiac Arrest	1 (0.3)	1	1 (0.3)	1
Hospitalized for angina	7 (2.4)	8	10 (3.4)	12
Hospitalized for arrhythmia	5 (1.7)	6	3 (1.0)	6
Hospitalized for CHF	2 (0.7)	3	2 (0.7)	3
Hospitalized for PVD	3 (1.0)	5	5 (1.7)	5
Hospitalized for cerebrovascular	4 (1.4)	5	3 (1.0)	4
Hospitalized for other reason	16 (5.4)	21	13 (4.5)	16
Outpatient for atherosclerotic CVD	12 (4.1)	16	7 (2.4)	8
Severe Adverse Events				
Sleep disturbance	10 (3.4)	6	4 (1.4)	6
Skin reaction	6 (2.0)	3	3 (1.0)	4
Gastrointestinal	5 (1.7)	6	6 (2.1)	7
Other adverse events	15 (5.1)	12	12 (4.1)	13

CHF=congestive health failure; **CVD**=cardiovascular disease; **n**=number of patients with events; **N**=total number of patients; **PVD**=peripheral vascular disease

Data from Joseph et al, 1996[22]

Tzivoni et al (1998)[24] conducted a two-week, placebo-controlled RCT to assess the safety of transdermal NRT in patients with coronary artery disease who were attempting to quit smoking (i.e., enrolled in a smoking-cessation program). A total of 106 patients were randomized to receive transdermal NRT (n = 52) or placebo (n = 54) for a period of two weeks. The transdermal NRT was provided as 30 cm^2 patches for those smoking at least 20 cigarettes per day or 20 cm^2 patches for those smoking fewer than 20 cigarettes. Heart rate, blood pressure, and electrocardiogram recordings were unchanged in either group for the duration of the two-week study period. There was limited information regarding adverse events reported in the publication; however, the authors noted that SAEs were reported for two patients in the NRT group (angina at rest and unstable angina) and one patient in the placebo group (worsening of angina). No patients experienced worsening of palpitations or symptomatic arrhythmias.

The Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease conducted a five-week, double-blind, placebo-controlled RCT to assess the safety of transdermal NRT in patients with coronary artery disease (N = 156).[23] Patients were randomized to receive either transdermal NRT (14 to 21 mg/day) or placebo. Safety endpoints included adverse events, cardiac events, electrocardiographic changes, frequency of angina, cardiac symptoms, vital signs, and changes in body weight.

At least one adverse event was reported for approximately 50% of patients in each treatment group. Adverse events were not fully reported in the publication; however, the authors noted that the only event that was reported more often by patients in the NRT group was transient itching at the patch site (36% vs. 9%). Adverse events reported more frequently in the placebo group were dizziness, insomnia, diarrhea, body aches, nervousness, and angina. Withdrawals

due to adverse events were more common with placebo compared to NRT (10.1% vs. 3.9%); however, the difference was not statistically significant (P = 0.13). There was no statistically significant difference in the frequency of angina, cardiac symptoms, or electrocardiogram between the two groups. Mean body weight increased 2.2 kg for patients receiving transdermal nicotine and 1.3 kg for patients receiving placebo (P < 0.05). The authors concluded that transdermal nicotine was well tolerated by the patients with stable coronary artery disease included in the trial.

Controlled Non-randomized Studies

Paciullo et al (2009)[25] conducted a retrospective matched cohort study to assess the impact of transdermal NRT on in-hospital mortality following CABG. Patients who had CABG and were prescribed NRT (n = 67) were matched with controls who had not received NRT (n = 67) based on pack-year smoking history and disease severity measured by Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores.[33] The primary endpoint of the study was in-hospital mortality. Three patients (4.5%) in the NRT group died in-hospital compared with none in the placebo group (P = 0.080). The deaths were attributed to cardiac arrest (n = 2) and pneumonia (n = 1).

Evidenced-based Guidelines and Recommendations

Guidelines and recommendations which addressed the use of pharmacotherapies for smoking cessation were identified from the Canadian Cardiovascular Society (CCS);[5] the Australian National Prescribing Service Rational Assessment of Drugs and Research (NPS RADAR);[28] the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom;[27,29] and the New Zealand Ministry of Health (MoH).[6,26] Evidence statements from these organizations regarding the safety of varenicline, bupropion, and NRT in patients with CVD are provided in Table 7.

The CCS published a position paper titled: *Smoking Cessation and the Cardiovascular Specialist*.[5] The paper offers general guidance regarding smoking cessation stating that cardiovascular specialists should be familiar with the benefits, limitations, use, and prescription of smoking cessation therapies. The CCS recommends that smokers hospitalized with acute coronary artery disease should commence interventions for smoking cessation during the period of hospitalization. The paper also addresses the use of NRT, bupropion, and varenicline in patients with CVD stating that all three pharmacotherapies are effective when used appropriately. There is some uncertainty regarding the scope of the recommendations as the paper did not specifically differentiate between stable and unstable CVD.

The NPS RADAR has reviewed varenicline and issued evidence-based guidance regarding its use in patients with CVD (updated in 2011).[28] The NPS RADAR states that health care professionals should consider the medical and psychiatric history of a patient before prescribing varenicline and that they should consider other treatment options for people with CVD.

The New Zealand Ministry of Health (MoH) has produced evidenced-based recommendations regarding the use of pharmacotherapy for smoking cessation in patients with CVD. The recommendations were published in the following two guidelines: the New Zealand Smoking Cessation Guidelines (2007)[26] and the New Zealand Cardiovascular Guidelines (2009).[6] The recommendations addressing the use of NRT, bupropion, and varenicline in patients with CVD are summarized in Table 7.

NICE produced evidenced-based recommendations regarding the use of pharmacotherapy for smoking cessation in a range of patient populations including those with CVD.[27] The guideline was initially published by NICE in 2008 and a summary was subsequently published by the National Guideline Clearinghouse.[29] The guidance was directed at cardiac rehabilitation teams, healthcare professionals, and counsellors who advise on, prescribe or dispense pharmacotherapies (i.e., NRT, varenicline or bupropion) for smoking cessation. With respect to patients with CVD who smoke, NICE recommends that the patients be offered brief advice or behavioural support and prescriptions of NRT, varenicline or bupropion, according to clinical judgement. The recommendations state that varenicline or bupropion may be offered to people with unstable CVD, subject to clinical judgement. The risks and benefits of using NRT should be explained to people who have unstable CVD and to maximize the benefits of NRT, people in these groups should also be strongly encouraged to use behavioural support in their quit attempt.

Table 7: Summary of Statements and Recommendations for Patients with CVD

Treatment	Recommendations for Patients with CVD
Canadian Cardiovascular Society	
NRT	• The safety of NRT use in cardiac patients has been established in a variety of settings.[22,34] • Evidence that NRT is safe for smokers with acute coronary syndrome continues to accrue; it may be commenced during a hospital stay if the smoker is experiencing serious withdrawal symptoms and is unable to abstain from smoking.[35]
Bupropion	• Bupropion effectively doubles the rate of smoking cessation when compared with placebo; its safety and effectiveness have been clearly demonstrated in the treatment of smokers with cardiovascular disease.[19,21]
Varenicline	• Varenicline is effective in smokers with cardiovascular disease.[17]
New Zealand Guideline Group	
NRT	• NRT can be provided to people with cardiovascular disease; dosage adjustment is required. • Where people have suffered a serious cardiovascular event (e.g., myocardial infarction or stroke) in the past 2 weeks or have a poorly controlled disease, treatment should be discussed with a physician. Oral NRT products are recommended (rather than longer-acting patches) for such patients. *Grade B*
Bupropion	• Suitable treatment, if appropriate. • Bupropion can be used by those with stable cardiovascular and respiratory diseases. *Grade A*
Varenicline	• Suitable treatment, if appropriate. • There are no data regarding use of varenicline in people with acute CVD. • There is insufficient evidence to recommend for patients with unstable CVD.
National Institute for Health and Clinical Excellence	
NRT	• Patients with CVD who smoke, should be offered brief advice or behavioural support and prescriptions of NRT, varenicline or bupropion, according to clinical judgement. • The risks and benefits of using NRT should be explained to people who have unstable CVD and to maximize the benefits of NRT, people in these groups should also be strongly encouraged to use behavioural support in their quit attempt.
Bupropion	• Patients with CVD who smoke, should be offered brief advice or behavioural support and prescriptions of NRT, varenicline or bupropion, according to clinical judgement. • Bupropion may be offered to people with unstable CVD, subject to clinical judgement.

Treatment	Recommendations for Patients with CVD
Varenicline	• Patients with CVD who smoke, should be offered brief advice or behavioural support and prescriptions of NRT, varenicline or bupropion, according to clinical judgement. • Varenicline may be offered to people with unstable CVD, subject to clinical judgement.
NPS RADAR	
Varenicline	• Health care professionals should consider other treatment options (e.g., counseling alone, NRT) for patients with CVD who wish to stop smoking.
Grade A: The recommendation is supported by strong evidence Grade B: The recommendation is supported by reasonable evidence, but there may be minimal inconsistency or uncertainty	

Limitations

The literature review identified at least one well-conducted, placebo-controlled RCT for each of the pharmacological therapies of interest in this review (i.e., varenicline, bupropion, and NRT); however, all but one of the RCTs were designed for assessing smoking-cessation efficacy and may lack sufficient statistical power to detect differences in serious adverse events. There were no head-to-head studies which directly compared varenicline, bupropion, and NRT in patients with CVD; therefore, the comparative safety of the different pharmacotherapies has not been fully established in this patient population. This may be reflected in the evidence-based guidelines and recommendations identified in this review, as only the NPS RADAR specifically recommended that treatment options other than varenicline should be considered for patients with CVD.

The efficacy of bupropion SR has been studied in patients with stable and unstable CVD; however, the single RCT which investigated the use of varenicline in patients with CVD excluded patients with unstable CVD. Therefore, it is unclear if the findings of the RCT by Rigotti et al (2010)[17] would be generalizable to patients with unstable CVD. In addition, this RCT excluded patients with comorbid depression. The authors noted that smokers with CVD may be at a greater risk of depression than smokers without CVD, suggesting that this population may be of clinical relevance. The studies of NRT identified in this review also excluded patients with unstable CVD.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The efficacy of bupropion, varenicline, and NRT in patients with CVD has been assessed in well-conducted RCTs and systematic reviews. However, the majority of these studies were not specifically designed to fully assess the safety of smoking cessation pharmacotherapy, which typically requires a larger sample size, longer duration of follow-up, and more events. In addition, there were no head-to-head trials or indirect comparisons of different active treatments for smoking cessation. Overall, there is uncertainty regarding the comparative safety of varenicline, bupropion, and NRT in patients with various forms of CVD. Further study may be required in order to accurately determine if meaningful differences exist between the safety profiles of these treatment options. A four-arm, multicentre, double-blind RCT is currently being conducted that will directly compare the safety and efficacy of varenicline, bupropion, NRT, and placebo.[36] This trial is not excluding patients with CVD and has specified the time to a major cardiovascular event as the primary endpoint of a pre-planned extension phase.[37] With an estimated enrollment of 8000 patients this study may provide robust evidence regarding the comparative safety of the different smoking-cessation pharmacotherapies in patients with CVD.

Evidence-based guidelines and recommendations were reviewed from the CCS, NICE, New Zealand MoH, and NPS RADAR. The CCS, NICE, and the New Zealand MoH suggested that bupropion, varenicline, and NRT all have a place in therapy for patients with stable CVD. The NPS RADAR only reviewed varenicline and recommended that health care professionals should consider other treatment options for patients with CVD. Recommendations from NICE and the New Zealand MoH differed with respect to the use of varenicline and bupropion in patients with unstable CVD. The New Zealand MoH stated that there is insufficient evidence to recommend the use of these agents in patients with unstable CVD and NICE recommended that they may be used according to clinical judgement. The CCS position paper did not specifically separate recommendations for stable and unstable CVD; therefore, the scope of their recommendations is uncertain.

Regulatory authorities continue to monitor and assess safety data for smoking-cessation pharmacotherapy. Health Canada,[10] the FDA,[11] and the European Medicines Agency (EMA)[12] recently updated the label for varenicline with additional information regarding cardiovascular safety based on the RCT by Rigotti et al (2010).[17] In addition, both Health Canada and the FDA have stated that they will continue to evaluate new data on the cardiovascular safety of varenicline as it becomes available. Following publication of the meta-analysis presented in Appendix 3, the EMA re-evaluated the benefit-risk balance for varenicline and concluded that the slight increase in the risk of cardiovascular events reported by Singh et al (2010) does not outweigh the benefits of varenicline in assisting patients with smoking cessation.[38]

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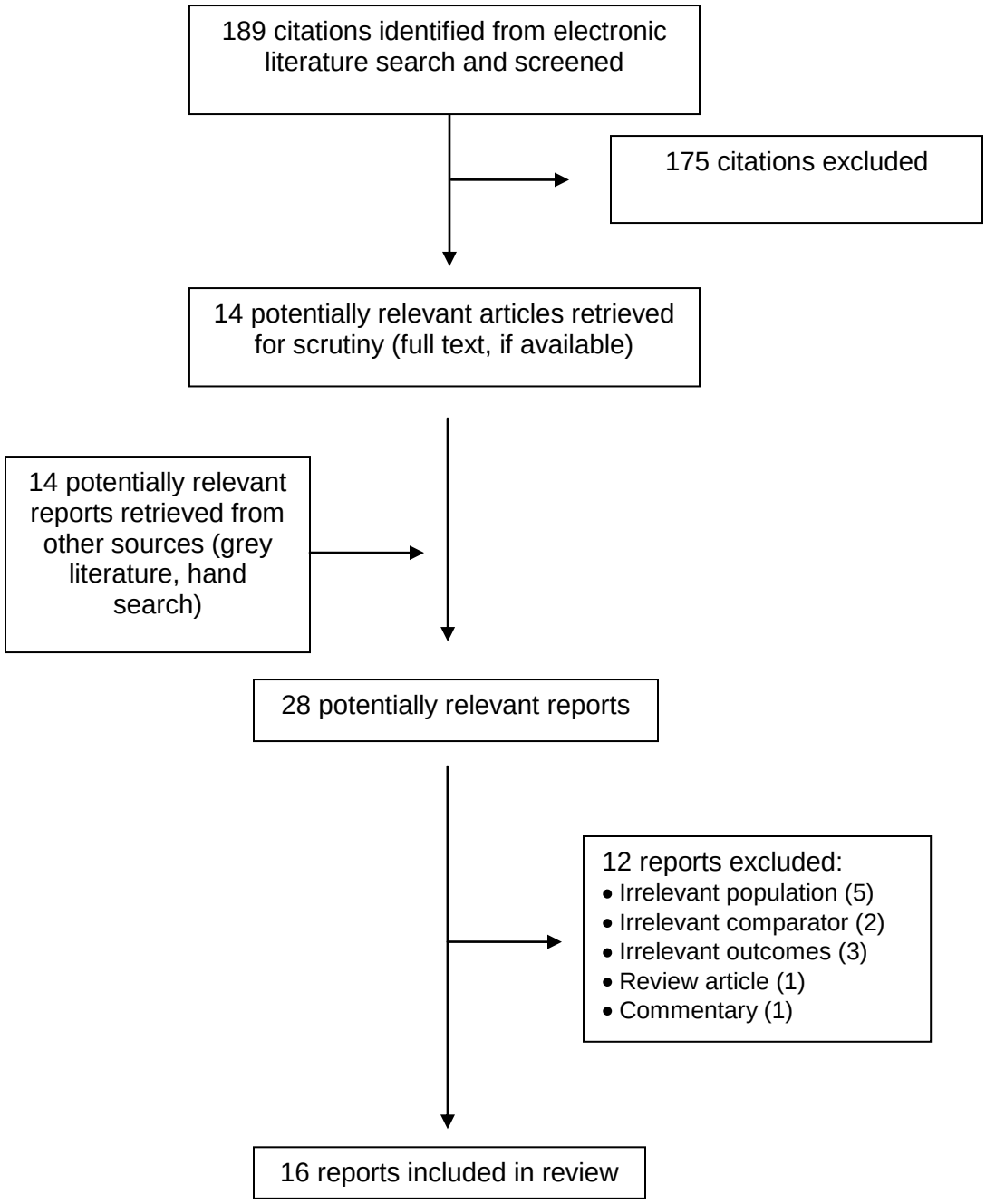
Appendix 1: Selection of Included Studies



Appendix 2: Information from Canadian Product Monographs

Table 8: Cardiovascular Warnings and Precautions from Canadian Product Monographs

Generic (Brand)	Information from Canadian Product Monograph	
	Indications	**Cardiovascular Warnings/Precautions**
Verenicline (Champix)	Smoking-cessation treatment in adults, in conjunction with smoking-cessation counselling	In a placebo-controlled smoking cessation clinical trial in patients with stable CVD, patients were treated with varenicline 1 mg BID or placebo for 12 weeks, and then followed for another 40 weeks. There were approximately 350 patients per arm. Serious CV events that were reported more frequently in varenicline compared to placebo (difference > 2 subjects) were: non-fatal MI (4 vs. 1, on-treatment phase) and need for coronary revascularization (7 vs. 2, post-treatment phase). The total number of patients that experienced serious CV events in varenicline compared to placebo was: 10 vs. 9 on treatment phase, 16 vs. 11 post-treatment phase, for a total of 25 vs. 20 over the 52 week duration. The serious CV events occurring during the treatment and post-treatment phases were adjudicated by an independent blinded committee. The study was powered for assessing efficacy but not for assessing differences in the occurrence of serious CV events between varenicline and placebo. Therefore, the study was not large enough to allow conclusions regarding the difference in the incidence of CV events reported in the two arms. Physicians are to inform patients with CVD of the symptoms of a heart attack and stroke, and instruct them to get emergency medical help right away if they experience any of these symptoms.[8]
Bupropion (Zyban)	Smoking-cessation treatment in conjunction with behavioural modification; NRT may be used in addition to bupropion	There is no clinical experience establishing the safety of bupropion in patients with a recent history of MI or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable heart failure. However, bupropion was associated with a rise in supine blood pressure in the study of patients with stable heart failure, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.[7]
NRT (Habitrol, Nicoderm, Nicorette)	As an aid to smoking cessation for partial relief of nicotine withdrawal symptoms	Contraindicated in patients during the immediate post-MI period, in patients with life-threatening arrhythmias, in patients with severe or worsening angina pectoris and in patients who have had a recent cerebral vascular accident.[39-42] The risks of NRT in patients with certain types CVD and PVD should be weighed against the benefits of including NRT in a smoking-cessation program for them. Specifically, patients with CHD, serious cardiac arrhythmias, or vasospastic diseases should be carefully screened and evaluated before NRT is prescribed.[39-42]
BID=twice daily; **CHD**=coronary heart disease; **CV**=cardiovascular; **CVD**=cardiovascular disease; **MI**=myocardial infarction; **NRT**=nicotine replacement therapy; **PVD**=peripheral vascular disease		

Appendix 3: Summary of Excluded Systematic Reviews

Singh et al (2010)[30] conducted a systematic review and meta-analysis of RCTs to investigate the risk of serious adverse cardiovascular events with varenicline compared to placebo. The meta-analysis included 14 double-blind placebo-controlled trials involving a total of 8216 patients (4908 received varenicline and 3308 were given placebo). Only one RCT (Rigotti et al, 2010)[17] included patients with cardiovascular disease (CVD), the remaining 13 RCTs excluded patients with a history of CVD. The results of the individual RCTs and the meta-analysis are summarized in Table 9.

The meta-analysis showed an increase in the number of cardiovascular events in patients treated with varenicline relative to placebo with a pooled odds ratio of 1.72 (95% CI: 1.09, 2.71). The effect size was largely driven by the RCT which involved patients with a history of CVD as this trial contributed 57% of the overall weighting. In general, cardiovascular events were much more common in this study compared with the RCTs involving non-CVD patients (48% of the total events in the varenicline and 74% of those in the placebo group occurred in Rigotti RCT).

Table 9: **Risk of Cardiovascular Events with Varenicline versus Placebo**

Study	Cardiovascular events, n/N		Peto OR (95% CI)
	Varenicline	Placebo	
Individual RCTs			
A3051080	1/394	0/199	4.50 (0.07, 285.96)
A3051095	1/493	0/166	3.81 (0.04, 347.82)
Fagerstrom 2010	0/214	1/218	0.14 (0.00, 6.95)
Gonzales 2006	2/352	2/344	0.98 (0.14, 6.97)
Jorenby 2006	1/344	1/341	0.99 (0.06, 15.88)
Nakamura 2007	1/465	0/154	3.79 (0.04, 352.44)
Niaura 2008	2/160	0/160	7.44 (0.46, 119.40)
Nides 2006	1/383	0/127	3.79 (0.04, 352.09)
Oncken 2006	2/518	0/129	3.49 (0.11, 112.44)
Rigotti 2010*	25/355	20/359	1.28 (0.70, 2.34)
Tashkin 2010	5/250	2/254	2.42 (0.55, 10.74)
Tonstad 2006	4/603	0/607	7.48 (1.05, 53.20)
Tsai 2007	1/126	0/124	7.27 (0.14, 366.57)
Williams 2007	6/251	1/126	2.40 (0.49, 11.67)
Meta-Analysis			
14 RCTs pooled	52/4908	27/3308	1.72 (1.09, 2.71)

CI=confidence interval; **n**=number of patients with cardiovascular events; **N**=number of patients in the safety analysis population; **OR**=odds ratio; **RCT**=randomized controlled trial

Data from Singh et al, 2011[30]

* Rigotti et al (2010) was the only RCT which included patients with CVD.[17]

Stead et al (2008)[31] conducted a systematic review and meta-analysis of RCTs to investigate the efficacy of NRT for smoking cessation compared to placebo and other pharmacotherapies. The systematic review included a total of 132 studies; however, only a single RCT (Joseph et al, 1996)[22] included patients with a history of CVD. There was no quantitative synthesis of adverse events in the review. The authors provided a brief qualitative summary of serious adverse events, noting the RCT reported by Joseph et al (1996) found no evidence that incidence of serious adverse events or events related to cardiovascular disease differed between the nicotine patch group and the placebo group. Overall, the authors concluded that NRT does not appear to lead to an increase in the risk of adverse CV events in patients with a history of CVD.

Appendix 4: Characteristics of Included Studies

Table 10: Summary of key study characteristics from the included studies

Author, Year	Description	Population	Comparators	Safety Endpoints
Systematic Reviews				
Eisenberg 2010 [16]	• Systematic review and meta-analysis • 4 RCTs with pharmacological interventions	• Stable CVD • Unstable CVD • Inpatient and outpatient	• Bupropion • Nicotine patch • Nicotine gum	• Adverse events • Not pooled and poorly reported
Randomized Controlled Trials				
Rigotti 2010 [17]	• DB RCT • 12 weeks treated • 52 weeks F/U • 15 countries • N = 714	• Stable CVD (angina, MI, revascularization, TIA, PVD) • >10 cigarettes/day	• Varenicline (1 mg BID) • Placebo Both groups received smoking-cessation counseling	• AEs, SAEs, WDAEs • Cardiovascular • Cerebrovascular • Psychiatric • Mortality
Planer 2011[18]	• DB RCT • 8 weeks treated • 52 weeks F/U • Israel (2 sites) • N = 151	• Hospitalized for ACS (including unstable angina and MI) • >10 cigarettes/day • Intention to quit	• Bupropion SR (150 mg OD for 3 days then BID for 2 months) • Placebo Both groups received smoking-cessation counseling	• All-cause mortality • Hospitalization • ACS, chest pain • AEs, SAEs • Change in BP • Change in BMI
Rogotti 2006[19] Thorndike 2008[20]	• DB RCT • 12 weeks treated • 52 weeks F/U • USA (5 sites) • N = 254	• Hospitalized for acute CVD (MI, unstable angina, CABG, CAD) • ≥1 cigarette/past month	• Bupropion SR (150 mg OD for 3 days then BID for 12 weeks) • Placebo Both groups received multi-component cognitive-behavioral smoking cessation and relapse prevention counseling	• CV mortality • All-cause mortality • CV events • Change in BP • Change in weight • Depressive symptoms
Tonstad 2003 [21]	• DB RCT • 7 weeks treated • 52 weeks F/U • 10 countries • N = 629	• Smoking-related CVD (MI, stable AP, PVD, CHF, or had a cardiac procedure) • >10 cigarettes/day	• Bupropion SR (150 mg OD for 3 days then BID for 2 months) • Placebo Both groups received smoking-cessation counseling	• AEs, SAEs • Vital signs • Change in weight
Joseph 1996[22]	• DB RCT • 10 weeks treated • 24 weeks F/U • USA (10 sites) • N = 684	• Major CV disorders (MI, CABG, angina, angioplasty, CHF, PVD, CBD, arrhythmia, stenosis ≥50%) • ≥15 cigarettes/day • ≥2 quit attempts	• Transdermal NRT (21 mg for 6 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks) • Placebo Both groups received brief smoking-cessation counseling	• Death • MI, cardiac arrest • Hospitalizations • Outpatient visits • AEs, SAEs

Author, Year	Description	Population	Comparators	Safety Endpoints
Tzivoni 1998[24]	• DB RCT • 2 weeks treated • 2 weeks F/U • Israel (2 sites) • N = 106	• Patients with CAD (≥70% stenosis, stable angina pectoris, MI) • ≥15 cigarettes/day • Enrolled in a smoking cessation program	• Transdermal NRT (14 mg for 1 week, 14-21 mg for 4 weeks) • Placebo	• SAEs • Heart rate • Change in BP • ECG changes
Working Group 1994[23]	• DB RCT • 5 weeks treated • 5 weeks F/U • USA (4 sites) • N = 156	• Patients with CAD (≥60% stenosis, MI, angina pectoris, CABG, angioplasty) • ≥1 pack/day	• Transdermal NRT (14 mg for 1 week, 14-21 mg for 4 weeks) • Placebo Both groups received brief smoking-cessation counseling	• AEs, WDAEs • Cardiac events • ECG changes • Angina • Cardiac symptoms • Vital signs • Change in weight
Controlled Non-randomized Studies				
Paciullo 2009[25]	• Case control • Retrospective • N = 134	• Post-CABG	• Prescribed NRT • Not prescribed NRT	• In-hospital mortality

AEs=adverse events; **BID**=twice daily; **BMI**=body mass index; **BP**=blood pressure; **CABG**=coronary artery bypass graft surgery; **CAD**=coronary artery disease; **CBD**=cerebrovascular disease; **CHF**=congestive heart failure; **CVD**=cardiovascular disease; **CV**=cardiovascular; **DB**=double-blind; **ECG**=electrocardiogram; **F/U**=follow-up; **MI**=myocardial infarction; **NRT**=nicotine replacement therapy; **PVD**=peripheral vascular disease; **RCT**=randomized controlled trial; **SAEs**=serious adverse events; **SR**=sustained-release; **TIA**=transient ischemic attack; **WDAE**=withdrawal due to adverse event

Appendix 5: Critical Appraisal of Included Studies and Guidelines

Table 11: Summary of Critical Appraisal

Author, Year	Strengths	Limitations
Systematic Reviews		
Eisenberg 2010 [16]	• Comprehensive literature search involving multiple databases. • Literature search methods were well reported. • Eligibility criteria were clearly stated. • Article selection was well documented including a list of included and excluded studies. • Data abstraction was performed by two independent reviewers. • Characteristics of the included studies were well reported. • Authors of RCTs were contacted when necessary for additional information. • Conflict of interest statement provided.	• No risk of bias assessment. • Search restricted to English language articles. • Unclear if grey literature was included in the literature search. • Unclear if study selection was performed in duplicate. • Publication bias was not formally assessed; however, the small number of studies would limit the statistical validity of such an assessment. • Adverse event data were poorly reported • Efficacy data were pooled across the different pharmacotherapies (i.e., data for bupropion were pooled with NRT).
Randomized Controlled Trials		
Rigotti 2010[17]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • The dose and duration of treatment with varenicline is consistent with recommendations in the Canadian product monograph. • Treatments were administered in a double-blind fashion. • Sample size calculation was provided. • Baseline characteristics were similar between the two groups. • Patient disposition was well reported and the proportion of patients who discontinued the study was reasonable. • CV events and deaths were independently adjudicated. • All pre-specified efficacy and safety assessments available in the peer-review publication or on ClinicalTrials.gov. • 98.5% of randomized patients were assessed in the safety analysis population.	• Methods for randomization and allocation concealment were not reported. • The study was powered for assessing efficacy (i.e., quit rates) but not for assessing differences varenicline and placebo in the occurrence of CV events between groups. • Findings may not be generalizable to patients with unstable CVD as these patients were excluded from the trial.

Author, Year	Strengths	Limitations
Planer 2011[18]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • The dose and duration of treatment with bupropion is consistent with recommendations in the Canadian product monograph. • Treatments were administered in a double-blind fashion and the active and placebo tablets were identical in appearance. • Baseline characteristics were similar between the two groups. • Compliance was assessed by pill count. • Sample size calculation was provided. • Patient disposition was well-reported and 99% of randomized patients completed the trial.	• Methods for randomization and allocation concealment were not reported. • The study was powered for assessing efficacy (i.e., quit rates) but not for assessing differences bupropion and placebo in the occurrence of CV events between groups. • Patients received weekly telephone-calls during the first two months and monthly calls thereafter. This may not be reflective of routine clinical practice in Canada.
Rogotti 2006[19] Thorndike 2008[20]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • The dose and duration of treatment with bupropion is consistent with recommendations in the Canadian product monograph. • Methods for randomization and allocation concealment were appropriate and well-reported. • Treatments were administered in a double-blind fashion and the active and placebo tablets were identical. • Sample size calculation was provided. • Baseline characteristics were similar between the two groups. • Patient disposition was well reported.	• The study was powered for assessing efficacy (i.e., quit rates) but not for assessing differences bupropion and placebo in the occurrence of CV events between groups. • Only 17% of eligible patients (N = 1516) agreed to participate in the study. • Discontinuations were high with only 67% of patients completing the one-year follow-up. • All patients received a multicomponent cognitive-behavioral smoking cessation and relapse prevention counseling program that began during hospitalization and was continued by telephone 5 times after discharge. This may not be reflective of routine clinical practice in Canada.
Tonstad 2003[21]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • The dose and duration of treatment with bupropion is consistent with recommendations in the Canadian product monograph. • Treatments were administered in a double-blind fashion. • Sample size calculation was provided. • Baseline characteristics were similar between the two groups. • Safety analysis population included 99.5% of randomized patients.	• Methods for randomization and allocation concealment were not reported. • The study was powered for assessing efficacy (i.e., quit rates) but not for assessing differences bupropion and placebo in the occurrence of CV events between groups. • At 52 weeks, discontinuations were high in both groups (38% with bupropion SR and 50% with placebo). • Patients received extensive contact with health professions (2 phone calls and 6 clinic visits). This may not be reflective of routine clinical practice in Canada.

Author, Year	Strengths	Limitations
Tzivoni 1998[24]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • Treatments were administered in a double-blind fashion and the active and placebo patches were identical in size, appearance, and odor. • Baseline characteristics were similar between the two groups.	• The treatment period and length of follow-up (i.e., 2 weeks) in the study was limited. This may be acceptable for assessing short-term effects of NRT but may be reflective of longer-term effects. • Methods for randomization and allocation concealment were not reported. • There were no sample size calculations provided, and the number of patients recruited may be too limited to detect differences in safety endpoints. • Patient disposition was poorly reported and there was no description of reasons for withdrawal. • All patients were taking part in a smoking cessation program which may not be reflective of routine clinical care in Canada.
Joseph1996 [22]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • Method of randomization was well-reported and appropriate. • Treatments were administered in a double-blind fashion and the active and placebo patches were identical in size, appearance, and odor. • Baseline characteristics were similar between the two groups. • Sample size calculation was provided and the study was powered to detect differences in adverse events between the groups.	• Methods for allocation concealment were not reported. • The study was powered for assessing efficacy (i.e., quit rates) but not for assessing differences NRT and placebo in the occurrence of safety events between groups. • Patient disposition was poorly reported and there was no description of withdrawals or reasons for withdrawal. • The trial population was 98.6% male, which may limit the generalizability of the results to women.
Working Group 1994[23]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • Method of randomization was well-reported, appropriate, and adequately concealed. • Sample size calculation was provided. • Treatments were administered in a double-blind fashion and the active and placebo patches were identical in size, appearance, and odor. • Baseline characteristics were similar between the two groups. • Compliance was greater than 90% for each treatment.	• There were no sample size calculations provided, and the number of patients recruited may be too limited to detect differences in safety endpoints. • Patient disposition was poorly reported for each of the individual treatment groups. • Discontinuations were relatively high for a trial of five weeks duration (20.5%). • Patients received weekly contact with health professionals which may not be reflective of routine clinical practice in Canada. • Transient itching at the site of the patch was more common in the active NRT group compared with placebo. This may have led to some inference of treatment allocation and patients and/or the investigators.
Non-randomized Studies		
Paciullo 2009[25]	• Objective and methods were clearly stated. • Eligibility criteria were clearly stated. • Interventions were well described. • Baseline characteristics were similar between the two groups. • Confounding factors (e.g., on-pump vs. off-pump) were clearly described. • Logistic regression used to control for differences between the groups. • Mortality was the primary outcome.	• Retrospective, non-randomized study design. • No description of how records were selected at random. • There were no sample size calculations provided, and the number of patients assessed may be too limited to accurately assess differences in safety endpoints.

Author, Year	Strengths	Limitations
Guidelines and Recommendations		
CCS, 2011[5]	• Explicit link between the recommendations and the supporting evidence. • The target users and patients to whom the position paper is meant to apply are specifically described. • The options for smoking cessation are clearly presented. • Health benefits and safety were considered in formulating the recommendations. • Key recommendations are easily identifiable. • The authors of the position paper included individuals from relevant professional groups. • The position paper was externally reviewed by experts prior to its publication. • COI statements were reported.	• The objectives and clinical questions were not specifically described in the position paper. • The publication states that the position paper was developed following a thorough consideration of medical literature, the best available evidence, and clinical experience; however, the methods used to search for and select evidence were not reported. • The publication states that the position paper represents the consensus of a Canadian panel comprised of multidisciplinary experts; however, the specific methods used for formulating the recommendations were not reported. • It is unclear if patient input and preferences were sought during the development of the guideline. • There was no discussion regarding organizational barriers or potential cost implications of applying the recommendations. • There were no criteria for auditing or monitoring the recommendations stated in the publication.
NPS RADAR, 2011[28]	• Explicit link between the recommendations and the supporting evidence. • The target users and patients to whom the guidance is meant to apply are specifically described. • Health benefits and safety were considered in formulating the recommendations. • Key recommendations are easily identifiable. • The options for smoking cessation are clearly presented. • The guidance document was externally reviewed by experts prior to its publication. • The guidance document has been updated since its original publication.	• The objectives and clinical questions were not specifically described in the guidance document. • The methods used to search for and select evidence were not reported. • The methods used for formulating the recommendations were not reported. • It is unclear if patient input and preferences were sought during the development of the guidance document.

Author, Year	Strengths	Limitations
NICE, 2008[27] NGC 2011[29]	• The objectives and clinical questions were not specifically described in the guideline. • The target users and patients to whom the guideline is meant to apply are specifically described. • The methods used to search for and select evidence were appropriate and well-reported. • The methods used to formulate recommendations were well-reported. • The options for smoking cessation are clearly presented. • The authors of the guideline included individuals from relevant professional groups. • The guidance document was externally reviewed by experts prior to its publication. • The NICE process allows patients to provide input on the recommendations. • The guideline is supported with tools for application. • A process for monitoring and updating the guideline was provided.	• No COI statements were reported. • There is not always and explicit link between the recommendations and the supporting evidence.
NZMH 2007[26] NZMH 2009[6]	• The guideline states that the development process has followed as closely as possible the steps recommended in the AGREE tool. • The target users and patients to whom the guideline is meant to apply are specifically described. • The evidence was derived from a comprehensive literature search which is publically available. • The options for smoking cessation are clearly presented. • The authors of the guideline included individuals from relevant professional groups. • The guidance document was externally reviewed by experts prior to its publication. • A process for monitoring and updating the guideline was provided. • COI statements were reported.	• The specific methods used to select evidence were not reported. • There is not always and explicit link between the recommendations and the supporting evidence.

AGREE=Appraisal of Guidelines for Research and Evaluation; **CCS**=Canadian Cardiovascular Society; **COI**=conflict of interest; **CV**=cardiovascular; **CVD**=cardiovascular disease; **NGC**=National Guideline Clearinghouse; **NICE**=National Institute for Health and Clinical Excellence; **NPS RADAR**=National Prescribing Service Rational Assessment of Drugs and Research; **NRT**=nicotine replacement therapy; **NZMH**=New Zealand Ministry of Health; **RCT**=randomized controlled trial