Appendix 3: Risk-of-bias assessment and methodologic details of randomized controlled trials of varenicline included in the analysis of serious adverse cardiovascular events

Study*	Sequence generation	Allocation concealment	Adequate monitoring of adverse events	Drug and dose	Withdrawal rate, %	Loss to follow-up, %
Protocol A3051080, 2010[16]	Unclear	Unclear	Adequate; adverse events, vital signs, electrocardiogram (screening and end of treatment), physical examination and laboratory tests at wk 1, 2, 3, 4, 6, 8, 10, 12, 13, 16, 20, 24	Varenicline 1 mg bid	13.8	2.3
				Placebo	22.2	2.5
Protocol A3051095, 2010[17]	Unclear	Unclear	Adverse events, vital signs, electrocardiogram, physical examination, laboratory tests	Varenicline 1 mg bid	12.6	1.9
				Placebo	14.5	6.1
Fagerstrom et al., 2010[18]	Adequate; telephone interactive voice response system	Adequate	Adverse event monitoring and baseline laboratory tests, physical examination and vital signs	Varenicline 1 mg bid	20.2	4.2
				Placebo	22.0	2.8
Gonzales et al., 2006[19]	Centralized; computer-generated randomization	Adequate	All observed or self-reported adverse events were documented; those resulting in hospital admission, disability or death within 7 d of last drug dose were classified as serious	Varenicline 1 mg bid	25.5	12.2
				Bupropion 150 mg bid	31.6	10.9
				Placebo	37.5	14.2
Jorenby et al., 2006[20]	Centralized; computer-generated list	Adequate	All observed or self-reported adverse events were documented; electrocardiogram and urinalysis repeated at 2 and 12 wk	Varenicline 1 mg bid	24.1	9.5
				Bupropion 150 mg bid	29.2	11.4
				Placebo	34.6	12.6
Nakamura et al., 2007[21]	Computer-generated list of random numbers	Adequate	Physical examination, blood pressure, body weight, adverse and serious adverse events, and AES and SAEs and electrocardiogram at each clinic visit from baseline to 52 wk	Varenicline 1 mg bid	20.5	NA
				Varenicline 0.5 mg bid	17.4	NA
				Varenicline 0.25 mg bid	17.6	NA
				Placebo	14.3	NA
Niaura et al., 2008[22]	Centralized	Adequate	No safety assessments in follow-up period; adverse events resulting in hospital admission, disability or death within 7 d of last drug dose were classified as serious	Varenicline 1 mg/d	22	NA
				Placebo	29	NA
Nides et al., 2006[23]	Computer-generated randomization	Adequate	Adverse events, laboratory tests, vital signs, 12-lead electrocardiogram and physical examination. Serious adverse events recorded through 30 d after last study dose; adverse events after 30 d were reported if investigator considered them related to study medication	Varenicline 0.3 mg/d	31.7	9.5
				Varenicline 1 mg/d	29.4	7.1
				Varenicline 1 mg bid	31.2	11.0
				Bupropion 150 mg bid	28.6	3.9
				Placebo	33.3	12.6
Oncken et al., 2006[24]	Unclear	Unclear	Vital signs, weight and adverse events collected at each visit; electrocardiogram at screening baseline and at 1, 4, 7 and 12 wk	Varenicline 1 mg bid titrated	23.1	0
				Varenicline 1 mg bid nontitrated	26.4	16.2
				Varenicline 0.5 mg bid titrated	29.2	21.5
				Varenicline 0.5 mg bid nontitrated	25.6	20.9
				Placebo	44.2	28.6
Rigotti et al., 2010[9]	Computer-generated list	Adequate	Adverse events resulting in hospital admission, disability or death, or congenital anomaly or birth defect were classified as serious. Reported or observed cardiovascular events or deaths were reviewed and adjudicated under blinded conditions by an independent event committee that used a standard events manual	Varenicline 1 mg bid	16.9	1.7
				Placebo	17.8	0.8
Tashkin et al., 2010[25]	Unclear	Unclear	Adverse events, vital signs, physical examination, body weight and height, electrocardiograms and laboratory tests. Serious adverse events collected 28 d after last dose of study drug	Varenicline 1 mg bid	16.5	11.7
				Placebo	23.1	12.4
Tonstad et al., 2006[26]	Centralized; computer-generated randomization	Adequate	Physical examination at screening and at 12 and 24 wk; electrocardiogram at 2, 12 and 24 wk	Varenicline 1 mg bid	7.7	1.9
				Placebo	15.5	5.1
Tsai et al., 2007[27]	Randomized; permuted block via Web and telephone	Adequate	Adverse events, vital signs, physical examination, body weight and height, electrocardiograms and laboratory tests at study visits	Varenicline 1 mg bid	3.2	1.5
				Placebo	3.2	0
Williams et al., 2007[28]	Unclear	Unclear	Adverse events and vital signs at each visit; urine and blood tests at 2, 12, 24, 36 and 52 wk; physical examination and electrocardiogram at screening and at 24 and 52 wk	Varenicline 1 mg bid	46.2	10.0
				Placebo	53.2	15.1
Aubin et al.,† 2008[29]	Centralized; computer-generated randomization	Unclear	Laboratory tests, vital signs, physical examination and electrocardiogram during treatment period. Adverse events resulting in hospital admission, disability or death were classified as serious	Varenicline 1 mg bid	17.3	5.9
				Nicotine transdermal patch	20.3	4.9

Note: NA = not available.
*All trials except Aubin et al.[29] were double blind. Citations of the studies are available in the reference list of the main article (www.cmaj.ca/lookup/doi/10.1503/cmaj.110218).
†Open-label trial.