

**Appendix 2: Characteristics of varenicline randomized controlled trials included in the analysis of serious adverse cardiovascular events (part 1 of 2)**

Source*	Phase	Location	Duration of treatment, wk	Duration of study, wk	Population	Primary outcome	Cardiac exclusions at enrolment	Drug and dose	No. of participants	Age, yr, mean (SD or range)	Males, %	White, %	No. of years of smoking, mean (SD or range)	Behavioural co-intervention
<b>Double-blind RCTs</b>														
A3051080, 2010 <sup>16</sup>	4	South Africa, SA, Middle East	12	26	Smokers	CAR	Clinical significant CVD in last 6 mo, BP > 150 mm Hg	Varenicline 1 mg bid	394	43.1 (18–69)	60.4	30.3	NA	NA
								Placebo	199	43.9 (20–71)	60.4†	7.6	NA	
A3051095, 2010 <sup>17</sup>	4	Multinational	12	24	Smokers	CQR, CAR	No serious or unstable disease in last 6 mo	Varenicline 1 mg bid	493	43.9 (18–75)	60.3	NA‡	NA	Smoking cessation counselling according to AHRQ guideline
								Placebo	166	43.2 (18–72)	60.0	NA‡	NA	
Fagerstrom et al, 2010d <sup>18</sup>	4	Sweden, Norway	12	26	Smokeless tobacco users	CQR	Any serious medical condition	Varenicline 1 mg bid	214	43.9 (12.0)	88.7	99.1	20.3 (11.0)	Brief behavioural support
								Placebo	218	43.9 (12.0)	89.9	99.5	21.7 (11.8)§	
Gonzales et al, 2006 <sup>19</sup>	3	US	12	52	Smokers	CQR	CVD within last 6 mo	Varenicline 1 mg bid	352	42.5 (11.1)	50.0	79.5	24.3 (11.5)	Brief counselling
								Bupropion 150 mg bid	329	42.0 (11.7)	58.4	80.2	24.1 (11.5)	
								Placebo	344	42.6 (11.8)	54.1	76.2	24.7 (12.1)	
Jorenby et al, 2006 <sup>20</sup>	3	US	12	52	Smokers	CQR	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	344	44.6 (11.4)	55.2	85.5	27.1 (11.5)	Smoking cessation counselling according to US Public Health guideline
								Bupropion 150 mg bid	342	42.9 (11.9)	60.2	82.7	25.4 (12.0)	
								Placebo	341	42.3 (11.6)	58.1	85.0	24.4 (11.6)	
Nakamura et al, 2007 <sup>21</sup>	2	Japan	12	52	Smokers	CAR	Unstable CVD	Varenicline 1 mg bid	156	40.1 (11.6)	79.2	NA	21.5 (11.3)	Smoking cessation counselling according to AHRQ guideline
								Varenicline 0.5 mg bid	156	39.0 (12.0)	71.1	NA	20.1 (11.3)	
								Varenicline 0.25 mg bid	153	40.2 (12.3)	72.7	NA	20.9 (11.5)	
								Placebo	154	39.9 (12.3)	76	NA	20.9 (11.4)	
Niaura et al, 2008 <sup>22</sup>	2	US	12	52	Smokers	CAR	History of CVD	Varenicline	160	41.5 (11.3)	50.3	93.0	24.9 (4–50)	Brief counselling
								Placebo	160	42.1 (11.7)	53.5	88.4	25.7 (2–46)	
Nides et al, 2006 <sup>23</sup>	2	US	7	52	Smokers	CAR	History of CVD	Varenicline 0.3 mg daily	128	41.9 (10.6)	50.0	88.1	24.6 (10.9)	Standardized smoking cessation counselling
								Varenicline 1 mg daily	128	42.9 (10.5)	43.7	88.1	25.4 (11.1)	
								Varenicline 1 mg bid	127	41.9 (9.8)	50.4	85.6	23.4 (10.0)	
								Bupropion 150 mg bid	128	40.5 (10.8)	45.2	88.3	23.4 (10.9)	
								Placebo	127	41.6 (10.4)	52.0	87.8	23.9 (10.6)	

**Appendix 2: Characteristics of varenicline randomized controlled trials included in the analysis of serious adverse cardiovascular events (part 2 of 2)**

Source	Phase	Location	Duration of treatment, wk	Duration of study, wk	Population	Primary outcome	Cardiac exclusions at enrolment	Drug and dose	No. of participants	Age, yr, mean (SD or range)	Males, %	White, %	No. of years of smoking, mean (SD or range)	Behavioural co-intervention
Oncken et al, 2006 <sup>24</sup>	2	US	12	52	Smokers	CAR	History of CVD	Varenicline 1 mg bid, titrated	130	42.2 (10.7)	48.5	80.8	24.0 (11.1)	Brief counselling
								Varenicline 1 mg bid, nontitrated	129	43.7 (10.0)	48.8	83.7	25.7 (10.6)	
								Varenicline 0.5 mg bid, titrated	130	43.5 (10.5)	53.1	80.8	25.0 (10.8)	
								Varenicline 0.5 mg bid, not titrated	129	42.9 (10.1)	45.0	85.3	26.0 (10.8)	
								Placebo	129	43.0 (9.4)	51.9	72.1	25.3 (9.5)	
Rigotti et al, 2010 <sup>6</sup>	3b	North America, Europe, Asia	12	52	Smokers	CAR	Excluded if unstable CVD in last 2 mo; included with stable CVD**	Varenicline 1 mg bid	355	57.0 (8.6)	75.2	80.3	40 (5–63)	Brief counselling
								Placebo	359	55.9 (8.3)	82.2	80.8	39 (12–60)	
Tashkin et al, 2010 <sup>25</sup>	3b	US, Europe	12	52	Smokers with COPD	CAR	Unstable CVD or history of CVD in last 6 mo	Varenicline 1 mg bid	250	57.2 (35–83)	62.5	81.9	40.4 (11–67)	Brief counselling according to US Public Health Service guideline
								Placebo	254	57.1 (34–77)	62.2	84.1	40.6 (18–64)	
Tonstad et al, 2006 <sup>26</sup>	3	Multinational	12	52	Smokers	Long-term quit rate	CVD within last 6 mo	Varenicline 1 mg bid	603	45.4 (10.4)	50.2	96.7	28.2 (10.4)	10 min of smoking cessation counselling
								Placebo	607	45.3 (10.4)	48.3	97	28.1 (10.5)	
Tsai et al, 2007 <sup>27</sup>	3b	Taiwan, Korea	12	24	Smokers	CAR	Unstable CVD	Varenicline 1 mg bid	126	39.7 (9.3)	84.9	NA	20.2 (3–45)	10 min of counselling according to AHRQ guideline
								Placebo	124	40.9 (11.1)	92.7	NA	22.1 (3–52)	
Williams et al, 2007 <sup>28</sup>	3	US, Australia	52	52	Smokers	Long-term safety	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	251	48.2 (12.3)	50.6	86.9	30.7 (4–57)	Brief counselling according to AHRQ guideline
								Placebo	126	46.6 (12.1)	48.4	92.1	29.9(6–57)	
<b>Open-label RCT</b>														
Aubin et al, 2008 <sup>29</sup>	3	US, Europe	12	52	Smokers	CAR	Serious or unstable disease in last 6 mo	Varenicline 1 mg bid	378	42.9 (10.5)	48.4	92.6	25.9(2–58)	Counselling according to US Public Health Service guideline
								Nicotine transdermal patch	379	42.9 (12.0)	50.0	93.5	25.2(1–62)	
<p>Note: CAR = continuous abstinence rates, COPD = chronic obstructive pulmonary disease, CQR = continuous quit rate, CVD = cardiovascular disease, SBP= systolic blood pressure, SD = standard deviation.                      *Citations of the studies are available in the reference list of the main article (<a href="http://www.cmaj.ca/lookup/doi/10.1503/cmaj.110218">www.cmaj.ca/lookup/doi/10.1503/cmaj.110218</a>).                      †Males in this study were reported for overall study population, not by treatment assignment.                      ‡Majority were white.                      §No of years of smokeless tobacco use.                      **The proportion of participants with cardiac disease in varenicline v. placebo was angina (53.2% v. 47.9%), myocardial infarction (45.9% v. 52.4%), prior coronary revascularization (46.2% v. 51.5%), stroke (4.5% v. 6.7%).</p>														