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Statistical challenges of meta-analyses of randomised clinical trials in a regulatory setting

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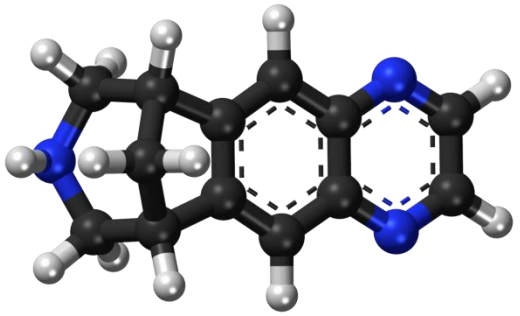
Outline

- Motivating example: cardiovascular risk with varenicline
- General reflections on challenges in meta-analyses, on opportunities with individual patient meta-analyses and on estimands in clinical trials for safety

Motivating Example

- Several **meta-analyses** of **cardiovascular adverse events** in trials for varenicline (Champix, approved in the EU and US in 2006). **Two in particular**:
  - Meta-analysis from an academic group (Singh et al) gave a signal of increased cardiovascular (CV) risk.
  - In response to this and upon request from the FDA, the MAH (Pfizer) performed a meta-analysis of their Phase II-IV trials.
- **Varenicline:**
  - Highly selective neuronal α4β2 nicotinic acetylcholine receptor partial agonist.
  - Reduces craving / withdrawal of smoking cessation.



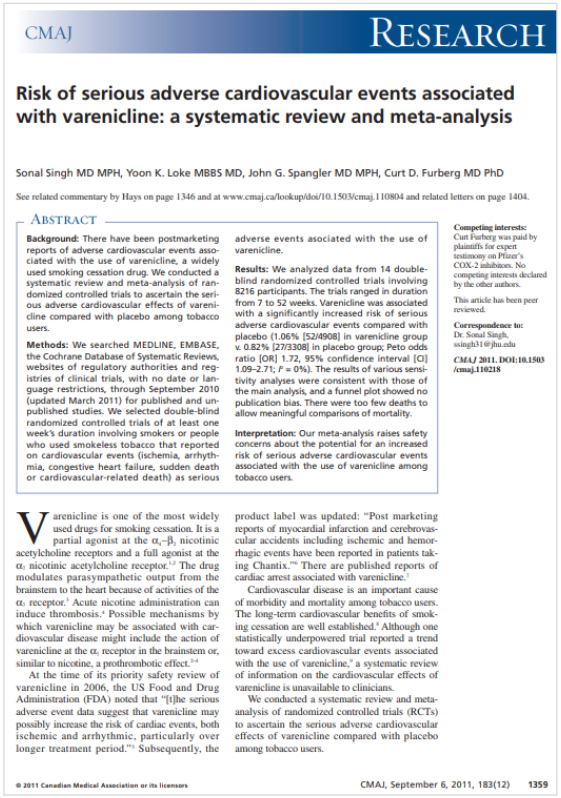
Singh et al. meta-analysis: studies [1]

(CMAJ, epub July 2011)

14	randomised clinicial trials (4908 varenicline, 3308 placebo)
13	in smokers, 1 in smokeless tobacco
13	with no clinically significant CV disease within 6 months prior to entry, 1 stable CV disease at least 2 months prior entry
7-52	weeks of treatment duration
24-52	weeks of study duration

Singh et al. meta-analysis: endpoints [1]

- **Primary endpoint:** any ischemic or arrhythmic adverse event:
  - Myocardial infarction, stroke, sudden or CV death, unstable angina, coronary revascularization, coronary artery disease, arrythmias, transient ischemic attacks, congestive heart failure
- *Of interest*: definition of serious AE (requiring intervention, hospitalisation) not standardised over studies
- **Secondary endpoint:** all-cause mortality



CMAJ RESEARCH

Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis

Sonal Singh MD MPH, Yoon K. Loke MBBS MD, John G. Spangler MD MPH, Curt D. Furberg MD PhD

See related commentary by Hays on page 1346 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.110804 and related letters on page 1404.

ABSTRACT

Background: There have been postmarketing reports of adverse cardiovascular events associated with the use of varenicline, a widely used smoking cessation drug. We conducted a systematic review and meta-analysis of randomized controlled trials to ascertain the serious adverse cardiovascular effects of varenicline compared with placebo among tobacco users.

Methods: We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, websites of regulatory authorities and registries of clinical trials, with no date or language restrictions, through September 2010 (updated March 2011) for published and unpublished studies. We selected double-blind randomized controlled trials of at least one week's duration involving smokers or people who used smokeless tobacco that reported on cardiovascular events (ischemia, arrhythmia, congestive heart failure, sudden death or cardiovascular-related death) as serious adverse events asociated with the use of varenicline.

Results: We analyzed data from 14 double-blind randomized controlled trials involving 8216 participants. The trials ranged in duration from 7 to 52 weeks. Varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] in varenicline group v. 0.82% [27/3308] in placebo group; Peto odds ratio [OR] 1.72, 95% confidence interval [CI] 1.09–2.71; $P = 0\%$). The results of various sensitivity analyses were consistent with those of the main analysis, and a funnel plot showed no publication bias. There were too few deaths to allow meaningful comparisons of mortality.

Interpretation: Our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse cardiovascular events associated with the use of varenicline among tobacco users.

Competing interests: Curt Furberg was paid by plaintiffs for expert testimony on Pfizer's COX-2 inhibitors. No competing interests declared by the other authors.

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Varenicline is one of the most widely used drugs for smoking cessation. It is a partial agonist at the $\alpha_4\beta_2$ nicotinic acetylcholine receptors and a full agonist at the α_7 nicotinic acetylcholine receptor.[2,3] The drug modulates parasympathetic output from the brainstem to the heart because of activities of the α_7 receptor.[2] Acute nicotine administration can induce thrombosis.[4] Possible mechanisms by which varenicline may be associated with cardiovascular disease might include the action of varenicline at the α_7 receptor in the brainstem or, similar to nicotine, a prothrombotic effect.[3,4]

At the time of its priority safety review of varenicline in 2006, the US Food and Drug Administration (FDA) noted that "[t]he serious adverse event data suggest that varenicline may possibly increase the risk of cardiac events, both ischemic and arrhythmic, particularly over longer treatment period."[5] Subsequently, the product label was updated: "Post marketing reports of myocardial infarction and cerebrovascular accidents including ischemic and hemorrhagic events have been reported in patients taking Chantix."[6] There are published reports of cardiac arrest associated with varenicline.[7]

Cardiovascular disease is an important cause of morbidity and mortality among tobacco users. The long-term cardiovascular benefits of smoking cessation are well established.[8] Although one statistically underpowered trial reported a trend toward excess cardiovascular events associated with the use of varenicline,[9] a systematic review of information on the cardiovascular effects of varenicline is unavailable to clinicians.

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to ascertain the serious adverse cardiovascular effects of varenicline compared with placebo among tobacco users.

CV: Cardiovascular AE: Adverse event

Singh et al. meta-analysis: results [1]

Study	Cardiovascular events, *n/N* Varenicline	Cardiovascular events, *n/N* Placebo	Weight, %	Peto OR (95% CI)
Protocol A3051080[16]	1/394	0/199	1.2	4.50 (0.07–285.96)
Protocol A3051095[17]	1/493	0/166	1.0	3.81 (0.04–347.82)
Fagerstrom et al.[18]	0/214	1/218	1.4	0.14 (0.00–6.95)
Gonzales et al.[19]	2/352	2/344	5.4	0.98 (0.14–6.97)
Jorenby et al.[20]	1/344	1/341	2.7	0.99 (0.06–15.88)
Nakamura et al.[21]	1/465	0/154	1.0	3.79 (0.04–352.44)
Niaura et al.[22]	2/160	0/160	2.7	7.44 (0.46–119.40)
Nides et al.[23]	1/383	0/127	1.0	3.79 (0.04–352.09)
Oncken et al.[24]	2/518	0/129	1.7	3.49 (0.11–112.44)
Rigotti et al.[9]	25/355	20/359	57.3	1.28 (0.70–2.34)
Tashkin et al.[25]	5/250	2/254	9.4	2.42 (0.55–10.74)
Tonstad et al.[26]	4/603	0/607	5.4	7.48 (1.05–53.20)
Tsai et al.[27]	1/126	0/124	1.4	7.27 (0.14–366.57)
Williams et al.[28]	6/251	1/126	8.3	2.40 (0.49–11.67)
Overall	**52/4908**	**27/3308**	**100.0**	**1.72 (1.09–2.71)**
Heterogeneity: $I^2 = 0\%$				

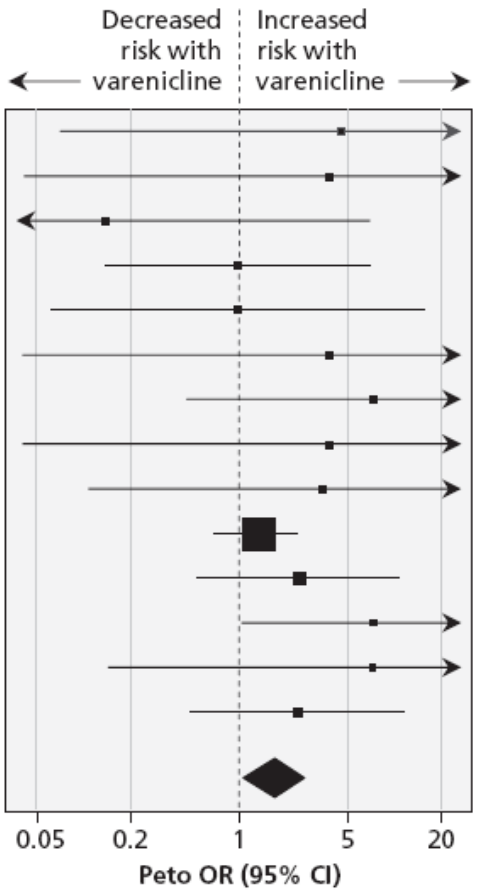

Figure 2: Meta-analysis of double-blind placebo-controlled randomized trials of the risk of serious adverse cardiovascular events associated with the use of varenicline. An odds ratio (OR) greater than 1.0 indicates an increased risk of a serious adverse cardiovascular event. CI = confidence interval.

CHMP assessment, November 2011 [2]

Champix marketing-authorisation holder should:

- Introduce **changes in SmPC**
  - **Include more information on cardiovascular events** → appropriate warnings on risk of cardiovascular events (section 4.4 - Special warnings and precautions for use)
  - The text has been made **more factual** by including information on the **frequency of cardiovascular events** in general and specific events such as myocardial infarction in each treatment group.

SmPC: Summary of Product Characteristics

Ware et al meta-analysis: studies [3]

- Done by the MAH (marketing authorisation holder)
- Included all Pfizer **Phase II-IV randomised clinical trials**
  - Blinded, ≥ 12weeks, with report before 30th June 2011
  - And two open-label, active-controlled, RCT
  - No non-Pfizer trials (allowed access to individual patient data)

American Journal of Therapeutics 20, 235–246 (2013)

Cardiovascular Safety of Varenicline: Patient-Level Meta-Analysis of Randomized, Blinded, Placebo-Controlled Trials

James H. Ware, PhD,[1]* George W. Vetrovec, MD,[2] Alan B. Miller, MD,[3] Andrew Van Tosh, MD,[4] Michael Gaffney, PhD,[5] Carla Yunis, MD,[5] Carmen Arteaga, PhD,[5] and Jeffrey S. Borer, MD[6]

Smoking is a major modifiable risk factor for cardiovascular (CV) disease. Varenicline is a pharmacological aid for smoking cessation. To explore the CV safety of varenicline, we investigated the incidence of CV events in varenicline-treated subjects across all phase 2-4 randomized placebo-controlled clinical trials of ≥12-week treatment duration conducted in smokers aged ≥18 years and sponsored by the drug manufacturer. This manuscript reports a subject-level meta-analysis of time to major adverse cardiovascular events (MACE; defined as CV-related death, nonfatal myocardial infarction, nonfatal stroke) and time to MACE+ (defined as MACE plus worsening or any procedure for peripheral vascular disease, hospitalization for angina, or performance of coronary revascularization). All events were adjudicated by an independent adjudication committee, blind to treatment assignment. Events were assessed during treatment and up to 30 days after the last treatment dose. The primary analytical method was a stratified logrank time-to-event analysis; secondary analyses were meta-analyses of incidence rate ratios and rate differences. Overall, 7002 subjects were included (varenicline: 4190; placebo: 2812) from 15 studies. MACE were reported by 13 varenicline subjects (0.31%) and 6 placebo subjects (0.21%) [hazard ratio, 1.95; 95% confidence interval (CI): 0.79–4.82; $P = 0.15$; risk difference, 0.006 events per subject-year; 95% CI: −0.003, 0.015, $P = 0.19$]. MACE+ were reported by 26 varenicline subjects (0.62%) and 12 placebo subjects (0.43%) (hazard ratio, 1.74; 95% CI: 0.91–3.34, $P = 0.10$; risk difference, 0.010; 95% CI: −0.002, 0.022, $P = 0.11$). This subject-level meta-analysis of MACE or MACE+ up to 30 days posttreatment in placebo-controlled clinical trials of varenicline found a trend toward increased incidence of these events in varenicline-treated patients that did not reach statistical significance. The overall number of events was low and the absolute risk of CV events with varenicline was small.

Keywords: varenicline, cardiovascular, adverse events, safety, risk

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Ware et al meta-analysis: endpoints [3]

- **Endpoints**
  - MACE (Major Adverse Cardiovascular Events): CV death, non-fatal myocardial infarction, non-fatal stroke
  - MACE+: MACE plus new onset or worsening peripheral vascular disease (PVD) requiring intervention; hospitalization for unstable angina; coronary revascularization
- **Summary measures:** time-to-event + incidence rates

Ware et al meta-analysis: results [3]

Study	Varenicline events	Varenicline cumulative time (year)	Placebo events	Placebo cumulative time (year)	Study weight	Risk difference
Oncken et al[16]	0	135.417	0	29.739	24.4	0.000
Niaura et al[17]	2	43.540	0	41.038	21.1	0.046
Gonzales et al[14]	0	94.042	1	86.396	45.0	−0.012
Jorenby et al[15]	0	91.890	0	87.324	44.8	0.000
Williams et al[24]	2	185.224	0	87.025	59.2	0.011
Tsai et al[21]	0	38.754	0	38.628	19.3	0.000
Nakamura et al[10]	0	141.782	0	47.165	35.4	0.000
Rigotti et al[8]	6	102.259	3	102.240	51.1	0.029
Tashkin et al[20]	3	73.224	2	71.619	36.2	0.013
Wang et al[22]	0	50.886	0	51.877	25.7	0.000
Williams et al[23]	0	22.804	0	12.600	8.1	0.000
Bolliger et al[11]	0	117.396	0	58.801	39.2	0.000
Rennard et al[19]	0	143.786	0	47.127	35.5	0.000
Fagerström et al[12]	0	58.861	0	59.754	29.7	0.000
Garza et al[13]	0	15.042	0	16.649	7.9	0.000
Total	**13**	**1314.908**	**6**	**837.979**	–	**0.006 (95% CI: −0.002, 0.015)**

Z value=1.414 (P-value=0.157)
Q heterogeneity test=4.930; Chi² P-value=0.988
F (%)=0; Number of studies with zero events=10

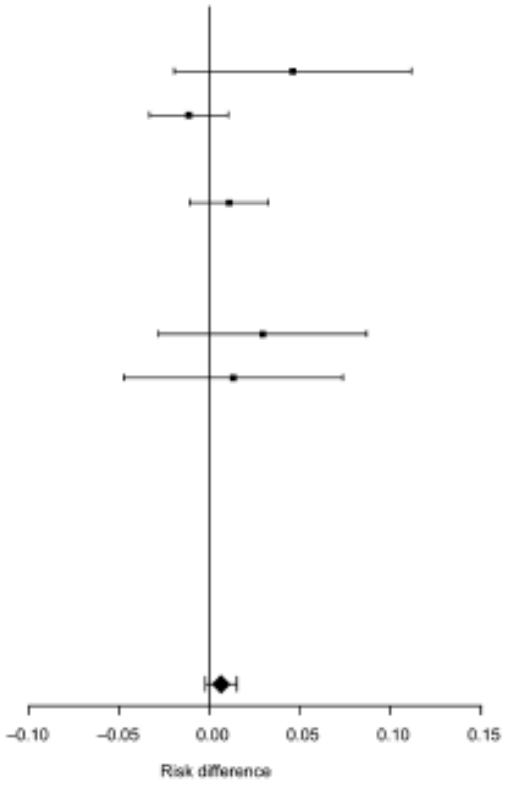


FIGURE 1. RD analysis for MACE for treatment plus 30 days.

Note: **many studies with 0 events**

Methodological questions on meta-analysis (1)

- Are the **'appropriate' studies included**?
  - Is the search strategy adequate?
  - (publication) bias?
  - Quality of study (allocation concealment, blinding of personel/patients, reporting withdrawals, ability to capture/report adverse events)
- Are the **endpoints adequate** (for the safety question)?

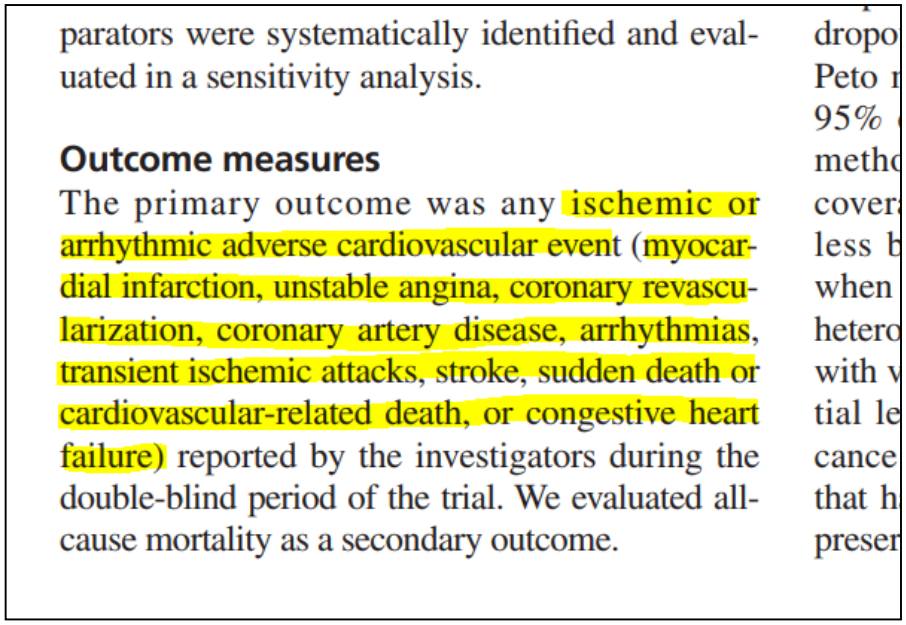
Methodological questions on meta-analysis (2)

- Are the studies similar enough to be combined (**heterogeneity**)?
  - Assessment bias
  - Different populations
  - Treatment duration, follow-up
- Is the **statistical method of combining** appropriate?
- Is the **interpretation** of the meta-analysis correct?

Singh et al meta-analysis: search strategy [1]

MEDLINE (OvidSP) using Haynes optimized filter: search March 2011	Varenicline.mp AND (randomized controlled trial.pt. OR randomized.mp. OR placebo.mp.)
EMBASE using OvidSP with randomized controlled trial filter applied: search March 2011	Varenicline.mp
Cochrane Controlled Trials Register: search March 2011	(varenicline)
CLINICALTRIALS.GOV: search September 2010	(varenicline [Limits: Completed Studies])
CLINICALSTUDYRESULTS.ORG: search September 2010	(varenicline)

Singh et al meta-analysis: endpoints



parators were systematically identified and evaluated in a sensitivity analysis.

Outcome measures

The primary outcome was any ischemic or arrhythmic adverse cardiovascular event (myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke, sudden death or cardiovascular-related death, or congestive heart failure) reported by the investigators during the double-blind period of the trial. We evaluated all-cause mortality as a secondary outcome.

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Different studies had **different definitions of serious adverse events**

Singh et al meta-analysis: endpoints

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[46]	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[47]	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	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[48]	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[49]	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	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
[50]			at each visit; electrocardiogram at screening baseline and at 1, 4, 7 and 12 wk	Varenicline 1 mg bid titrated	23.1	8
				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[5]	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[45]	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[18]	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[17]	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[16]	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[20]	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: = not available.
*All trials except Aubin et al. 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.

Gonzales et al., 2006[19]

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

Niaura et al., 2008[22]

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

Nides et al., 2006[23]

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

Singh et al meta-analysis: endpoints

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

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				Bupropion 150 mg bid	31.6	10.9
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				Placebo	14.3	NA
Niaura et al., 2008[49]	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[50]	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	17.6
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	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
[illegible] et al., 2006[51]	[illegible]	[illegible]	[illegible] 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[52]	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[29]	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	Varenicline 1 mg bid	46.2	10.0
				Placebo	53.2	15.1
Aubin et al.,† 2008[30]	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. 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.

Rigotti et al., 2010[9]

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

Tashkin et al., 2010[25]

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

Aubin et al.,† 2008[29]

Laboratory tests, vital signs, physical examination and electrocardiogram during treatment period. Adverse events resulting in hospital admission, disability or death were classified as serious

Singh et al. meta-analysis: naïve pooling

- **Naïve pooling:** Varenicline 1.06% vs. placebo 0.82% (52/4908 vs 27/3308).
  - 3 trials with multiple arms.
- **Limitations:**
  - Small number of CV events;
  - Differences in length of follow-up;
  - Non-inclusion of trials with no serious AEs;
  - Lumping CV events with different pathophysiological pathways and different degree of clinical importance.

CV: Cardiovascular AE: Adverse event

Singh et al meta-analysis: method to combine studies [1]

- **Peto odds ratio:**

  ".. provides best confidence interval coverage and is more powerful and relatively less biased than the random-effects analysis when dealing with low event rates."

- **Comments:**
  - Biased when **treatment groups of different size**
  - Not accounting for differences in **follow-up times** (alternative: time to event analysis)
  - Does not include **0-0 event** studies (alternative: risk difference)
  - Other **weighting** methods available

OR: Odds Ratio

Ware et al meta-analysis: endpoints [3]

Table 2. Distribution of first MACE+ occurring in 38 unique subjects during and 30 days after blinded treatment.

	Varenicline, n	Placebo, n
n (subject-years)	4190 (1314)	2812 (838)
Event		
CV death	1	1
Nonfatal MI	8	3
Nonfatal stroke	4	2
Unstable angina	6	2
Peripheral vascular disease	4	1
Coronary revascularization	3	3
Total	**26**	**12**
All-cause mortality	1	2

MACE+, major CV events plus worsening or any procedure for peripheral vascular disease, hospitalization for angina, or performance of coronary revascularization.

- **Homogeneous** definition
- Event **adjudication**:
  - Post hoc, based on trial data
  - Could decrease power to detect a difference (adding non-CV related events or conversely)
  - Changes due to adjudication need to be clear and transparent

CV: Cardiovascular MACE: Major Adverse Cardiac Events

Ware et al meta-analysis: method to combine studies [3]

- Time-to-event
- Risk difference allows inclusion of the 0 event studies
- Modified Peto odds ratio (Peto-type observed minus expected method for incidence rate ratio) – needs to be explained and justified when method not conventional

General considerations on meta-analysis

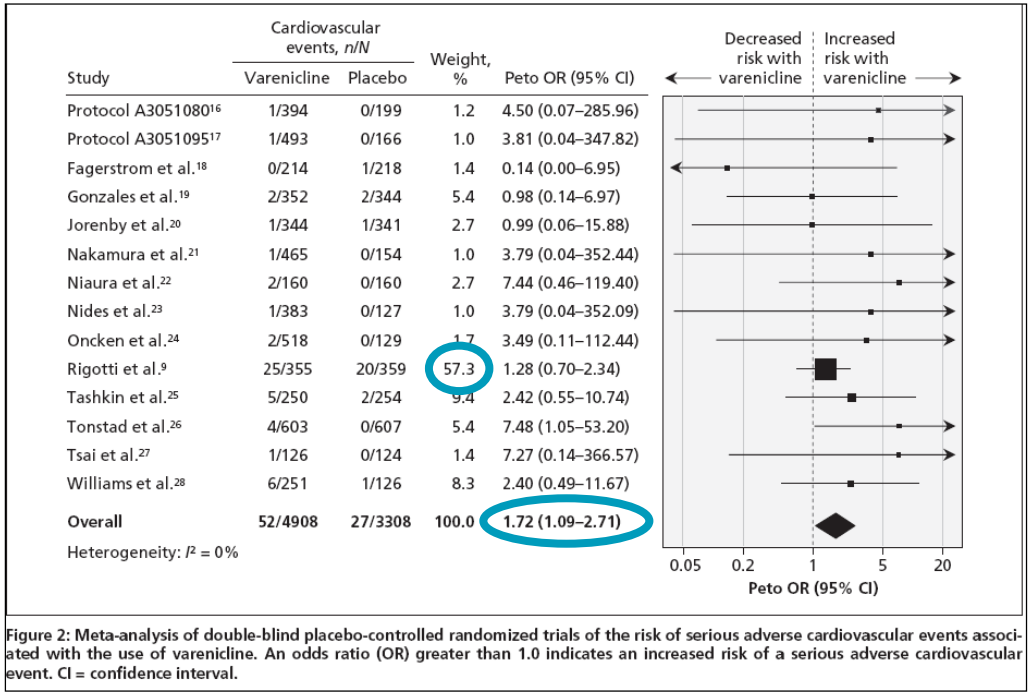
- One large study but different characteristics vs. other studies;
  - Results of the meta-analysis **driven by the one large study**
  - Only solution may be one large trial (as opposed to a large meta-analysis)
- Issue of **unequal randomisation** (when 0 events)
- Issue of **0 events** for calculation of summary measures
- Contrast issues with meta-analyses depending on **data sources** (CT, GP data)
- **Early phase studies won't have SAEs**, otherwise development would have stopped, so funnel plot not useful, other data presentations needed

CT: Clinical Trial GP: general practice
SAEs: Serious Adverse Events

General considerations on meta-analysis

- **Figure 2 from *Singh et al*:** look at the weight the one study has, and then look at the rate in all the other studies. It's extremely different, due to the patient characteristics being so different in this study. The question then arises:

  is it sensible to pool all studies if/when patient populations are so different?

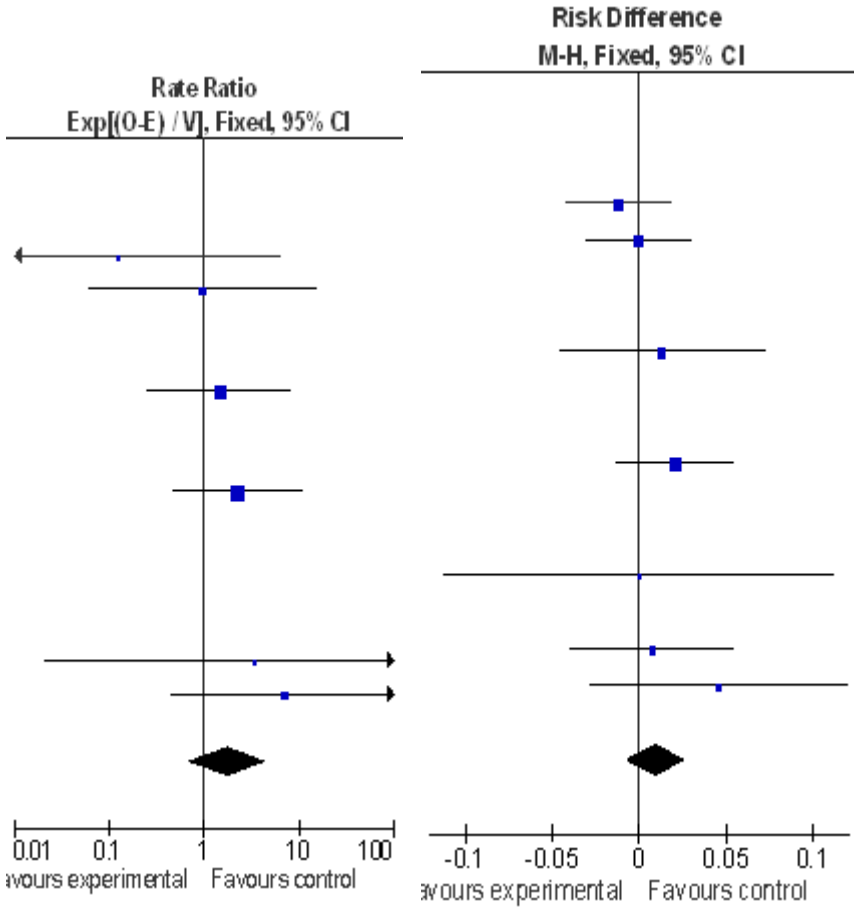


Study	Cardiovascular events, *n/N* Varenicline	Placebo	Weight, %	Peto OR (95% CI)
Protocol A3051080[16]	1/394	0/199	1.2	4.50 (0.07–285.96)
Protocol A3051095[17]	1/493	0/166	1.0	3.81 (0.04–347.82)
Fagerstrom et al.[18]	0/214	1/218	1.4	0.14 (0.00–6.95)
Gonzales et al.[19]	2/352	2/344	5.4	0.98 (0.14–6.97)
Jorenby et al.[20]	1/344	1/341	2.7	0.99 (0.06–15.88)
Nakamura et al.[21]	1/465	0/154	1.0	3.79 (0.04–352.44)
Niaura et al.[22]	2/160	0/160	2.7	7.44 (0.46–119.40)
Nides et al.[23]	1/383	0/127	1.0	3.79 (0.04–352.09)
Oncken et al.[24]	2/518	0/129	1.7	3.49 (0.11–112.44)
Rigotti et al.[9]	25/355	20/359	57.3	1.28 (0.70–2.34)
Tashkin et al.[25]	5/250	2/254	9.4	2.42 (0.55–10.74)
Tonstad et al.[26]	4/603	0/607	5.4	7.48 (1.05–53.20)
Tsai et al.[27]	1/126	0/124	1.4	7.27 (0.14–366.57)
Williams et al.[28]	6/251	1/126	8.3	2.40 (0.49–11.67)
Overall	**52/4908**	**27/3308**	**100.0**	**1.72 (1.09–2.71)**
Heterogeneity: $I^2 = 0\%$				

Figure 2: Meta-analysis of double-blind placebo-controlled randomized trials of the risk of serious adverse cardiovascular events associated with the use of varenicline. An odds ratio (OR) greater than 1.0 indicates an increased risk of a serious adverse cardiovascular event. CI = confidence interval.

General considerations on meta-analysis: removal of trials with 0-0 events

- Particularly problematic when **randomisation is unbalanced**, e.g. 0/400 vs. 0/200
- In general, when there is unbalanced randomisation it is in favour of the active arm, so excluding these trials (almost) always goes against active and bias the results.
- Using the **risk difference**, a raised risk may disappear.



Individual patient meta-analysis

- Individual patient data **allows** investigation of:
  - Types of events
  - Observation periods
  - Subgroups
- Analysis - individual patient data **needed for:**
  - Time-to-event (which takes into account different lengths of follow-up between arms)
  - Covariate adjustment
- Quality of meta-analysis increased with IPD vs. aggregate data?

Comments on estimands in CTs for safety

MACE in placebo-controlled studies

Observation period	Varenicline (n=4566)	Placebo (n=2812)	Hazard ratio	Risk incidence difference	Risk incidence ratio
Treatment	7	2	2.83 (0.76, 10.55) P-value=0.12	0.007 (-0.002, 0.015) P-value=0.12	2.82 (0.76, 10.52) P-value=0.12
Treatment + 30 days	13	6	1.95 (0.79, 4.82) P-value=0.15	0.006 (-0.002, 0.015) P-value=0.16	1.92 (0.78, 4.75) P-value=0.16
Study	18	10	1.66 (0.79, 3.49) P-value=0.18	0.006 (-0.003, 0.015) P-value=0.19	1.65 (0.78, 3.47) P-value=0.19

*patients as denominator, calculated from the data deduced from Tech Report Pfizer. The hazard ratio for MACE during treatment in the PCS (=placebo controlled trial set) is primary analysis.

- Here, the intercurrent event is **treatment discontinuation**
- Choice of **while on treatment** vs. **treatment policy** strategy

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