Meta-Analysis of Varenicline Use and Treatment-Emergent Cardiovascular Serious Adverse Events

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Stanford Prevention Research Center
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TRDRP Webcast

Acknowledgments

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UCSF Professor of Epidemiology & Biostatistics

Prochaska, J.J., & Hilton, J.F. (2012). Meta-analysis of varenicline use and treatment-emergent cardiovascular events . British Medical Journal, 344, e2856

Study Funding: TRDRP Research Award #17RT-0077

DISCLOSURES:

Grant funding: NIMH (RO1), NIDA (P50, R34), TRDRP (Pilot CARA, Res Award), FAMRI, Pfizer (IIR)

Mentor on training grants: NHLBI, NIDA, NCI

Grant review: NIH (NIDA-K, RPIA), Pfizer (GRAND)

Ad hoc scientific advisor: Pfizer

Board Member: Cooper Institute

PFIZER IIR
VARENICLINE INPATIENT STUDY

- **AIMS:**
  - Examine the acceptability & efficacy of varenicline use with hospitalized smokers for managing nicotine withdrawal and supporting cessation

JULY 4, 2011

FOX NEWS .com Fair & Balanced

Pfizer Drug Tied to Heart Risks

Pfizer Inc.'s smoking-cessation drug Chantix was linked to a 72 percent increase in risk of cardiovascular problems, including stroke and congestive heart failure, according to a new analysis of medical studies.

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USA TODAY | News

Study: Stop-smoking drug Chantix ups risk of heart problems

By Denise Mann, HealthDay

Updated 7/6/2011 12:22 PM

Comment 38

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Singh et al. (2011)

- Meta-analysis of varenicline use and cardiovascular serious adverse events (CV-SAEs)
- Coded CV-SAEs at any time during the trial
- Differential attrition (greater in placebo group) in 13 of 14 trials reviewed
- Summary statistic: Peto OR
- Concluded varenicline increased the risk of CV-SAEs by **72%** (absolute difference was **0.24%**)
  - 52/4908 (1.06%) on varenicline vs. 27/3308 (0.82%) on placebo

Media/Web Coverage

- Google search “Singh Chantix”
- 1+ million hits
- 2 staff independently coded articles for the first 100 hits
  - Report of relative (Peto OR, 72%) vs. absolute difference (0.24%) anywhere and within major sections (title, header, caption)

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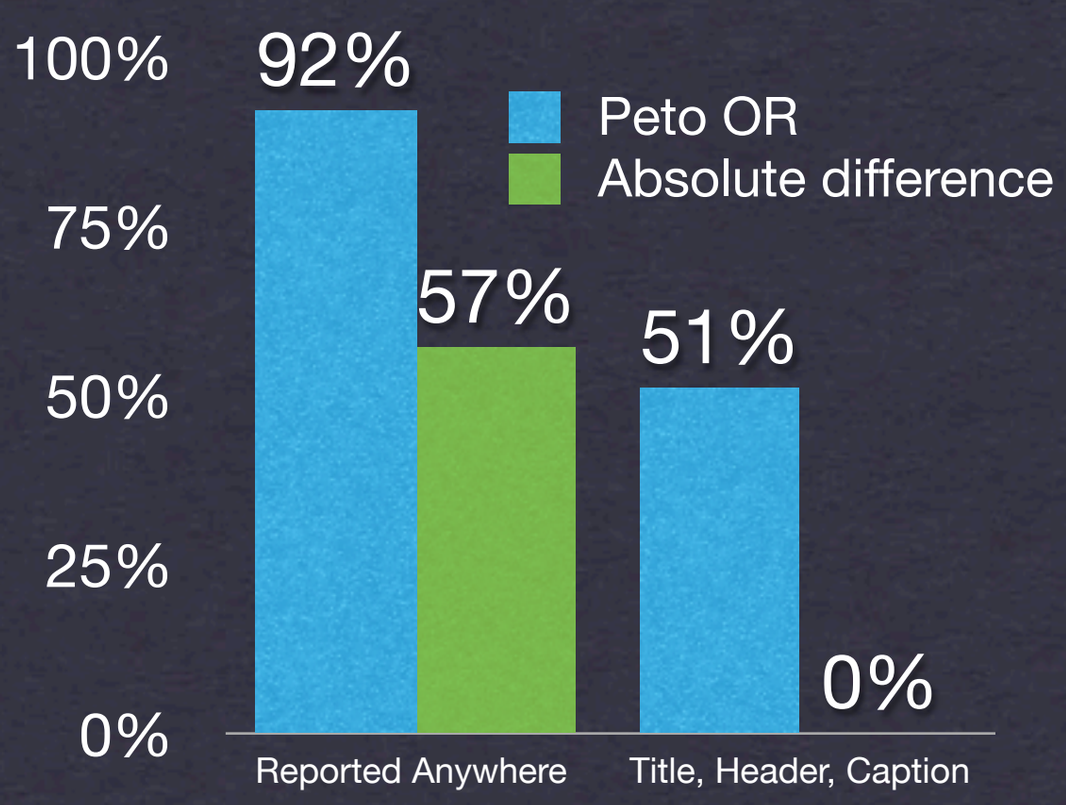

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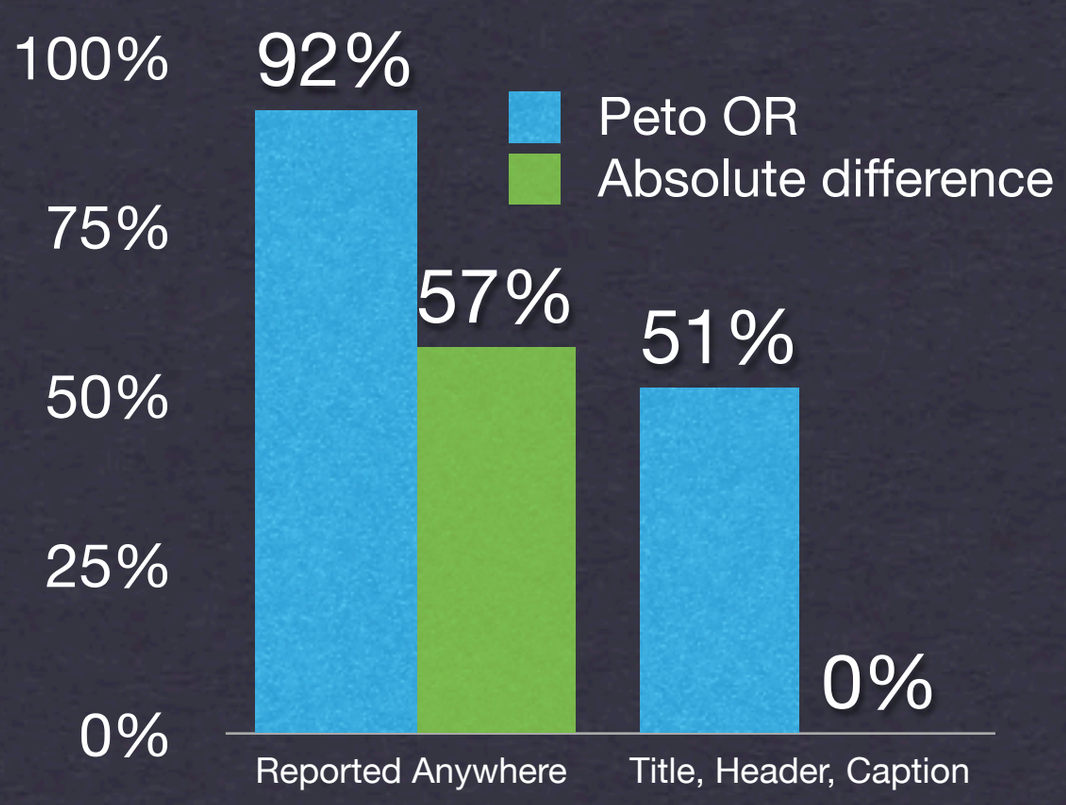

Meta-analysis: Chantix causes one heart attack for every three patients it helps quit smoking
-- Michael Siegel, MD
tobaccoanalysis.blogspot.com

Johns Hopkins Press Release

JOHNS HOPKINS
MEDICINE

Release Date: 07/04/2011
Popular antismoking drug increases chance of serious cardiac event by 72 percent compared to people on placebo, study finds

Healthy, middle-aged smokers who take the most popular smoking cessation drug on the market have a 72 percent increased risk of being hospitalized with a heart attack or other serious heart problems compared to those taking a placebo, a Johns Hopkins-led study suggests.

“People want to quit smoking to reduce the risk of cardiovascular disease but in this case they’re taking a drug that increases the risk for the very problems they’re trying to avoid,” says Sonal Singh, M.D., M.P.H., an assistant professor of general internal medicine at the Johns Hopkins University School of Medicine and the lead author of the research.

In the study, described in the Canadian Medical Association Journal, Singh and his colleagues reviewed and analyzed 14 double-blind, randomized, controlled clinical trials involving more than 8,200 healthy people who received either varenicline (made by Pfizer and sold in the United States under the brand-name Chantix) or a placebo. Whereas the number of people who died in each group was the same (seven), the increased risk of a major harmful cardiovascular event requiring hospitalization such as a heart attack or arrhythmia was 72 percent in the varenicline arms. None of the studies followed people for longer than a year. The average age of study participants was less than 45 years and the majority were men.

Varenicline has been shown to modestly increase the chances of a successful quit attempt, compared to unassisted smoking cessation attempts. But overall, the majority of smokers who quit do so without any pharmaceutical assistance at all.

Moreover, Singh noted, varenicline already carries a boxed warning — the Food and Drug Administration’s highest level of caution — because of its association with suicidal thoughts and behaviors. “We notified the FDA of our cardiovascular safety concerns with Chantix earlier this year,” Singh says.

On June 16, the FDA announced that on the basis of a 700-person study, people with existing heart disease who use varenicline have a slightly increased risk of a heart attack or other cardiovascular event. But Singh’s study found that varenicline substantially increased the risk of a serious cardiovascular event even among smokers without heart disease.

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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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Peto OR

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

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Interpretation

The use of varenicline among tobacco u
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Study	Cardiovascular events, *n/N*		Weight, %	Peto OR (95% CI)
	Varenicline	Placebo		
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)
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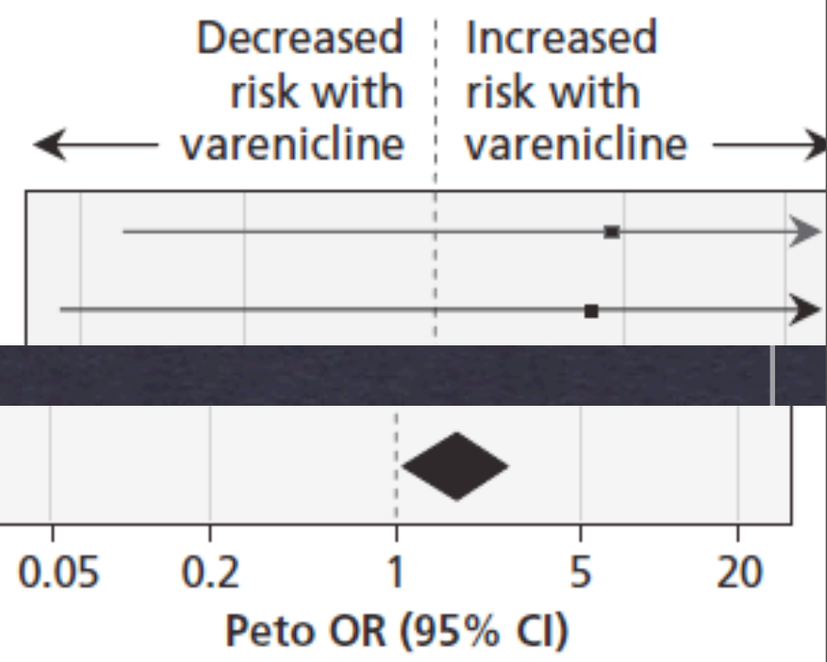
Heterogeneity: $I^2 = 0\%$				



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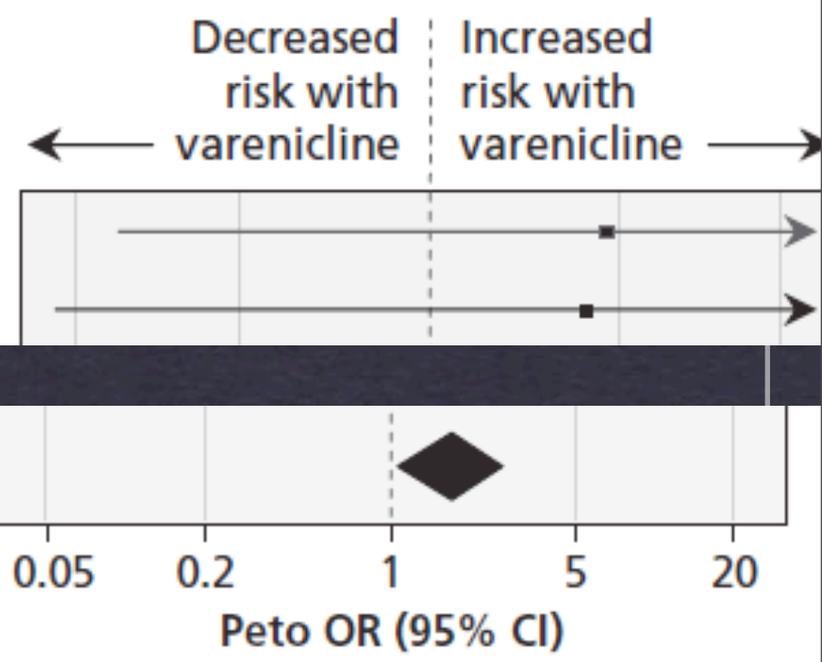

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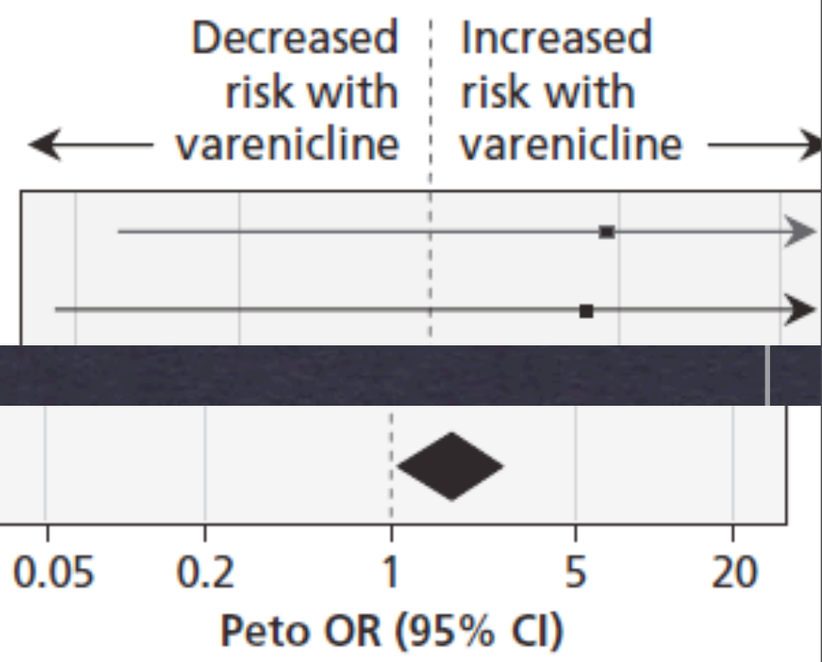

1.06% VS. 0.82%
ABSOLUTE DIFFERENCE OF 0.24%

Peto OR

- Known bias under conditions of imbalanced design and rare events, present in a majority of the reviewed trials
  - The Cochrane Handbook discourages use of the Peto OR when studies have unequal allocation, Section 9.4.4.2
- Excludes trials with no events
- Relative estimate -- unitless
  - Hides the fact that a low response rate remains very low even when scaled up by a seemingly large effect

scientific response

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- Bias in Peto OR -- *Takagi & Umemoto, 2011, CMAJ*
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European Medicines Agency confirms positive benefit-risk balance for Champix

Benefits as a smoking-cessation medicine outweigh slight reported increase in cardiovascular events

The European Medicines Agency has confirmed that the benefit-risk balance for Champix (varenicline) remains positive, despite the results of a recent meta-analysis of the medicine's side effects affecting the heart and blood vessels.

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- Meta-analysis of treatment-emergent CV-SAEs in all published, RCTs of varenicline use for tobacco cessation:

Treatment emergent CV-SAEs were defined as occurring during the drug treatment window or within 30 days of discontinuation

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CV-SAEs included "any ischemic or arrhythmic adverse cardiovascular event (MI, unstable angina, coronary revascularization, CAD, arrhythmias, transient ischemic attacks, stroke, sudden death or cardiovascular-related death, or CHF)"

Methods

Databases: MEDLINE, Cochrane, Clinicalstudyresults.org

Time Frame: Jan 2005 – Sept 2011 (including online pre-pubs)

Inclusion Criteria: (a) RCT, (b) current tobacco users, (c) adult age, (d) varenicline with comparison to placebo, (e) report of adverse events

Exclusion Criteria: quasi-experimental or cross-over design; lab studies with no follow-up; studies with teens or nonsmokers; studies where all participants received varenicline; and comparisons of varenicline to another active med (e.g., NRT)

Data Extraction: Two reviewers independently conducted article data extraction & quality assessment for each study meeting the inclusion criteria

Articles identified through literature search, N=241

MEDLINE, n=133
Cochrane Central Register of Controlled Trials, n=83
Clinicalstudyresults.org, n=25

Excluded, n= 219

Reviews, commentaries, letters, n=51
Secondary publications, n=24
Duplicates, n=101
Laboratory/dose tolerance study, n=10
Not an RCT, n=9
All participants received varenicline, n=8
Cross-over study, n=7
Active drug comparison (e.g., NRT), n=2
No varenicline in the study, n=2
Adolescent sample, n=2
Animal study, n=2
Nonsmokers, n=1

RCTs included in meta-analysis, N=22

Trials with smokers, n=20
Trials with smokeless tobacco users, n=2

Literature Search Results & Study Selection

Results

- **22 trials** were identified with **9232 participants**;
  - 2 trials enrolled participants with active CVD
  - 11 trials enrolled participants with a past history
  - 9 trials no history or unclear timeframe
- 8 trials had no treatment-emergent CV-SAEs
  - 3 with N>200 participants
- Rates of treatment-emergent CV-SAEs were:
  - 34/5431 (0.63%) on varenicline
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ABSOLUTE DIFFERENCE OF 0.16%

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Tx-Emerg CV-SAEs	**34/5431**	**18/3801**		**1.58 (0.90, 2.76)**	**1.41 (0.82, 2.42)**	**1.40 (0.82, 2.39)**	**0.27% (-0.10%, 0.63%)**

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4. Hong et al.[25]	0/20	0/21		UC	UC	UC	0 (-9.00%, 9.00%)
5. Ebbert et al.[30]	0/38	0/38		UC	UC	UC	0 (-4.99%, 4.99%)
6. Garza et al.[37]	0/55	0/55	1	UC	UC	UC	0 (-3.48%, 3.48%)
7. Hughes et al.[39]	0/107	0/111	1	UC	UC	UC	0 (-1.78%, 1.78%)
8. Wang et al.[47]	0/165	0/168	1	UC	UC	UC	0 (-1.17%, 1.17%)
9. Poling et al.[44]	0/13	0/18	0.7	UC	UC	UC	0 (-12.10%, 12.10%)
10. Steinberg et al.[24]	1/40	1/39	1	0.98 (0.06, 15.87)	0.97 (0.06, 16.15)	0.98 (0.06, 15.05)	-0.06% (-0.07%, 6.87%)
11. Jorenby et al.[40]	1/344	1/341	1	0.99 (0.06, 15.88)	0.99 (0.06, 15.91)	0.99 (0.06, 15.78)	0 (-0.81%, 0.81%)
12. Gonzales et al.[38]	2/352	2/344	1	0.98 (0.14, 6.97)	0.98 (0.14, 6.98)	0.98 (0.14, 6.90)	-0.01 (-1.14%, 1.11%)
13. Rigotti et al.[11]	10/355	10/359	1	1.01 (0.42, 2.46)	1.01 (0.42, 2.46)	1.01 (0.43, 2.40)	0.03% (-2.39%, 2.45%)
14. Oncken et al.[43]	2/518	0/129	4	3.49 (0.11, 112.44)	1.25 (0.06, 26.27)	1.25 (0.06, 25.93)	0.39% (-0.83%, 1.61%)
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BOLLIGER 1/394 0/199 PETO OR = 4.50 MH-OR = 1.52 MH-RR = 1.52 MH-RD = 0.25%

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Study	Events/Randomized		Allocation	Treatment Effect (95% Confidence Interval)			
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1. Fagerstrom et al.[23]	0/214	1/218	1	0.14 (0.00, 6.95)	0.34 (0.14, 8.34)	0.34 (0.01, 8.29)	-0.46% (-1.73%, 0.81%)
2. Protocol A3051095[36]	0/493	0/166	3	UC	UC	UC	0 (-0.87%, 0.87%)
3. Protocol A3051072[35]	0/85	0/43	2	UC	UC	UC	0 (-3.52%, 3.52%)
4. Hong et al.[25]	0/20	0/21	1	UC	UC	UC	0 (-9.00%, 9.00%)
5. Ebbert et al.[30]	0/38	0/38	1	UC	UC	UC	0 (-4.99%, 4.99%)
6. Garza et al.[37]	0/55	0/55	1	UC	UC	UC	0 (-3.48%, 3.48%)
7. Hughes et al.[39]	0/107	0/111	1	UC	UC	UC	0 (-1.78%, 1.78%)
8. Wang et al.[47]	0/165	0/168	1	UC	UC	UC	0 (-1.17%, 1.17%)
9. Poling et al.[44]	0/13	0/18	0.7	UC	UC	UC	0 (-12.10%, 12.10%)
10. Steinberg et al.[24]	1/40	1/39	1	0.98 (0.06, 15.87)	0.97 (0.06, 16.15)	0.98 (0.06, 15.05)	-0.06% (-0.07%, 6.87%)
11. Jorenby et al.[40]	1/344	1/341	1	0.99 (0.06, 15.88)	0.99 (0.06, 15.91)	0.99 (0.06, 15.78)	0 (-0.81%, 0.81%)
12. Gonzales et al.[38]	2/352	2/344	1	0.98 (0.14, 6.97)	0.98 (0.14, 6.98)	0.98 (0.14, 6.90)	-0.01 (-1.14%, 1.11%)
13. Rigotti et al.[11]	10/355	10/359	1	1.01 (0.42, 2.46)	1.01 (0.42, 2.46)	1.01 (0.43, 2.40)	0.03% (-2.39%, 2.45%)
14. Oncken et al.[43]	2/518	0/129	4	3.49 (0.11, 112.44)	1.25 (0.06, 26.27)	1.25 (0.06, 25.93)	0.39% (-0.83%, 1.61%)
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SUMMARY	**34/5431**	**18/3801**		**PETO OR = 1.58 (0.90, 2.76)**	**MH-OR = 1.41 (0.82, 2.42)**	**MH-RR = 1.40 (0.82, 2.39)**	**MH-RD = 0.27% (-0.10%, 0.63%)**

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8. Wa							%)
9. Pol							0%)
10. St							87%)
11. Jo							%)
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13. Ri							45%)
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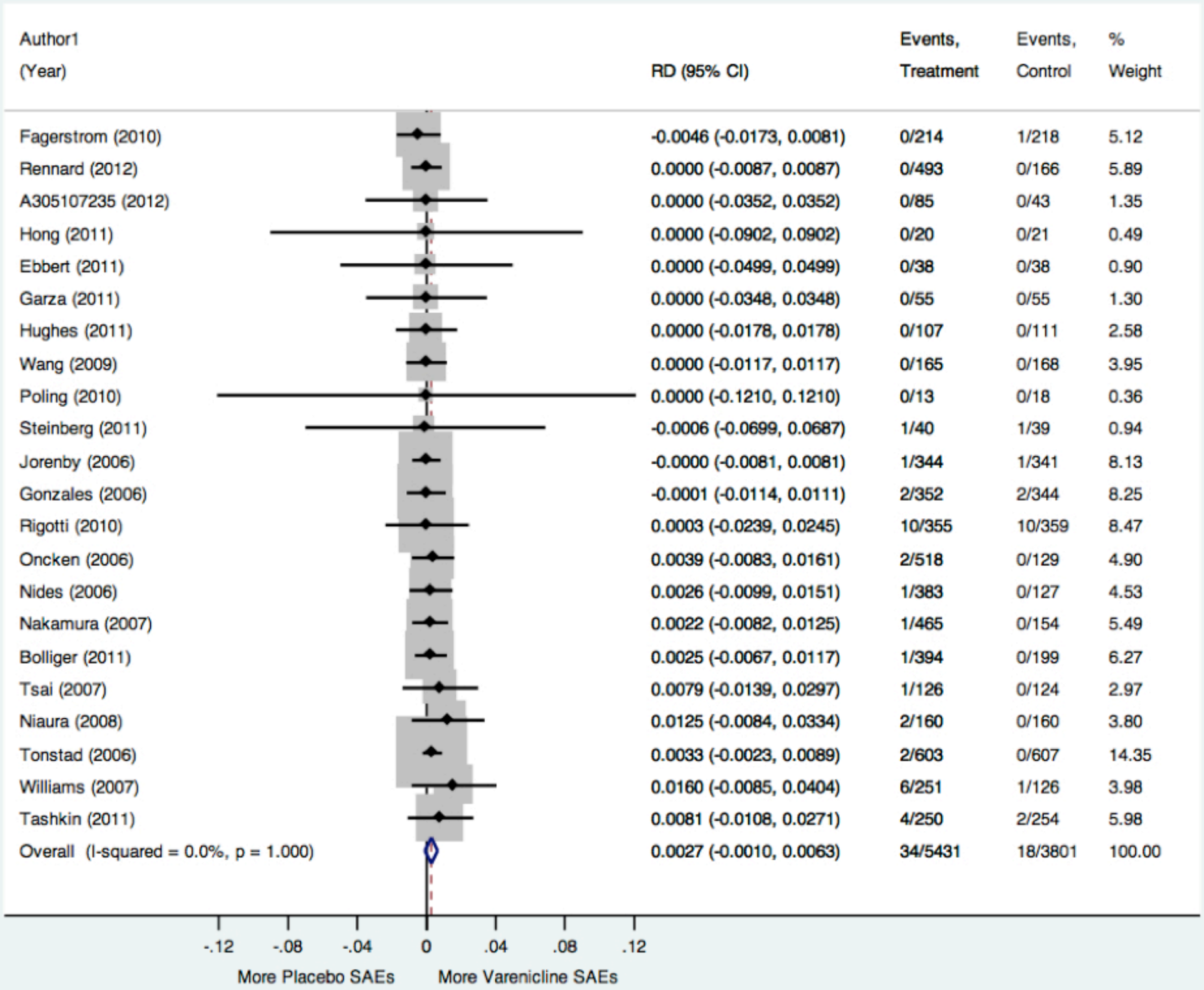
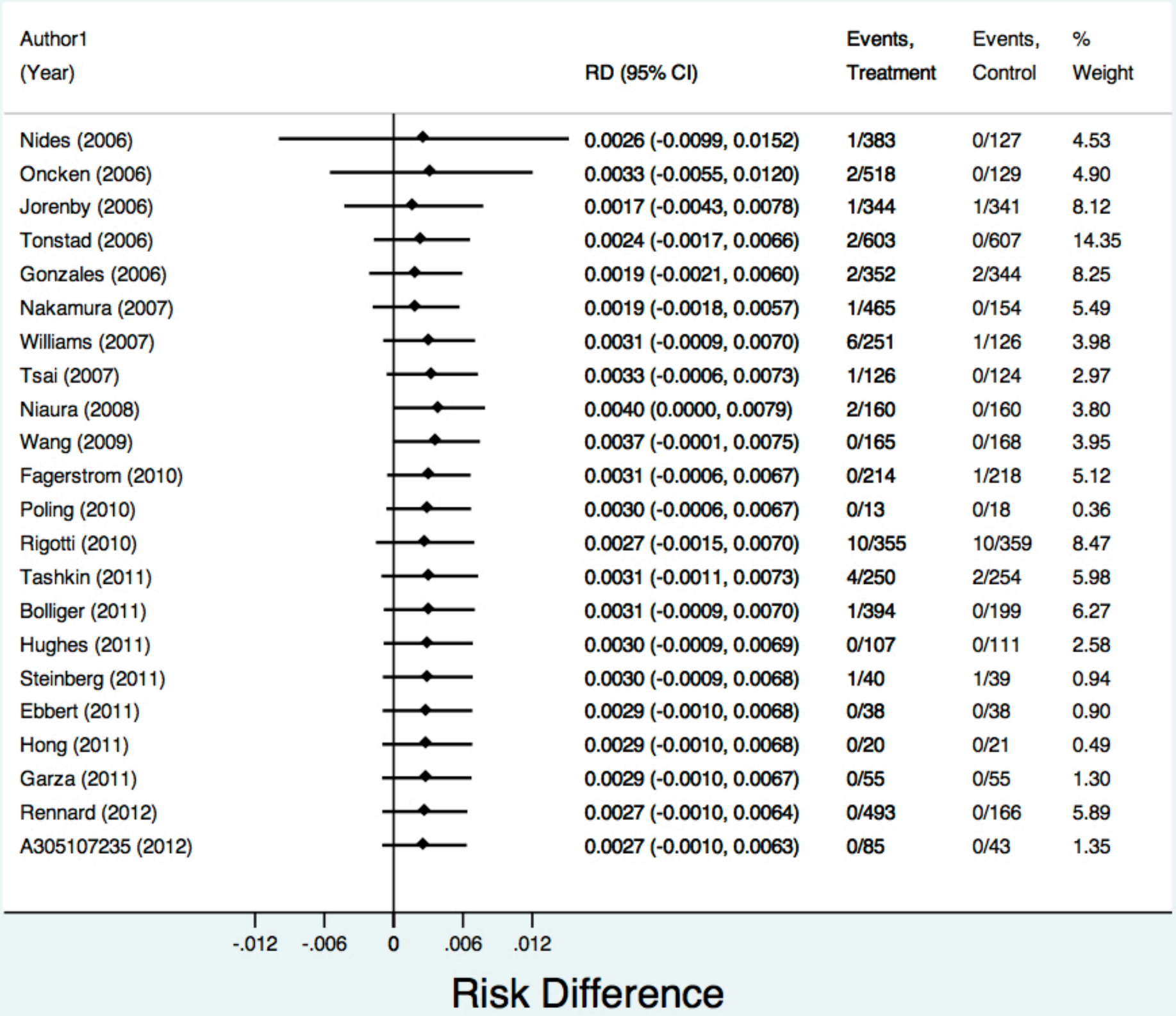
THE RISK OF CV-SAEs ASSOCIATED WITH VARENICLINE USE IS STATISTICALLY & CLINICALLY INSIGNIFICANT ABSOLUTE INCREASE OF 0.27% RELATIVE TO PLACEBO



Difference in Risk (x 100%) of Treatment-Emergent CV-SAEs Associated with Varenicline Use in 22 Double-Blind Placebo-Controlled Randomized Trials



Cumulative estimated risk difference effect of varenicline and treatment emergent CV-SAEs, studies sorted by publication year

NNT

number needed to treat

(# needed to treat to have 1 person quit smoking)

10 smokers

NNH

number needed to harm

(# needed to treat to observe one CV-SAE)

1/RD = 1/.0027 = 370

The bottom line...

✦ With few events, the evidence is limited, no matter what method one applies, so inferences need to be cautious

✦ In practice, risks & benefits need to be weighed

✦ Our analysis, with 4 summary estimates, is intended to provide transparent and comparative findings to inform decision making for tobacco dependence treatment

online commentary

- questioning disclosure of Pfizer funding
- claims that we didn’t follow intent-to-treat
- suggestions we didn’t include all CV-SAEs
- assertions of inadequate power

Conclusions

- Our meta-analysis:
  - Included **all** double-blind RCTs of varenicline vs. placebo
  - Focused on events occurring **during drug exposure or within 30 days after discontinuation**
  - Analyzed findings using **4 summary estimates**
  - Indicated **no significant increase in CV-SAEs** associated with varenicline use on any of the measures and
  - Found **negligible variation** in the evidence over 22 independent trials with >9,000 subjects