Could the NNH really be 28?

Risk of Serious Adverse Cardiovascular (CV) Events with Varenicline (Champix) Comment on Systematic Review and Meta-analysis[1]

Findings at a glance

- In 14 randomized placebo controlled trials with 8216 participants, varenicline was associated with an increase in serious adverse CV events.
  - **Varenicline vs Placebo – CV events:**   **52/4908 vs 27/3308**
    1.06% vs 0.82%
  - **Peto Odds Ratio (OR):**   **1.72**; 95% CI=1.09-2.71
    - CV events included: MI, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke, sudden death/CV death, congestive heart failure
    - Role of adjudication for events: unclear (CV events never part of 1° endpoint; thus rely on 2° endpoint data); ∴caution
    - Treatment duration: 7days – 12 weeks. Duration of total follow-up: 24-52 weeks.
    - Risk of bias: low 9 trials; unclear 5 trials. Sensitivity analysis: supportive of findings
    - A standard OR calculation (as opposed to the Peto OR method used) results in an OR=1.3 (95% CI 0.82-2.08)[2]

Questions about the extrapolated Number Needed to Harm (NNH) = 28

- Authors extrapolate the Peto OR to a population of smokers with stable CV disease:
  - **NNH=28** 52 weeks of follow up for 12 weeks of therapy; from authors' discussion
    (For every 28 patients treated with varenicline vs placebo, there is 1 extra serious CV event)
  - To get this NNH, the authors applied the OR to a baseline risk of 5.57% per 52 weeks[3]
    - The resulting projected CV event risk for varenicline vs placebo rounded off
      - $\cong$ 9.6% (1.72 x 5.6%) vs 5.6%
      - Absolute risk ↑ $\cong$ 4%; NNH $\cong$ 25 100/4%; on ≤ 1 year follow up of 1 treatment course
- CAUTION: There are some problems with this extrapolation
  - The actual meta-analysis only had an absolute risk increase of 0.24% (1.06% vs 0.82%)
    - Resulting **NNH would be 417** 100/0.24% overall for patients in trials
  - The baseline risk for smokers with stable CV disease was taken from the one trial that included this population.[4] However, in this trial the absolute risk only went up 1.4% (CV events: 7.1% vs 5.7%; OR=1.28 (0.7-2.34), not significant. Had the results been significant, the NNH would have been around 72). Of interest, this one trial was weighted to account for 57% of all CV events in the meta-analysis. {The OR =1.28 in this highest weighted study of CV disease patients is consistent with a non-Peto OR method =1.3 in the meta.}

Bottom Line – from our point of view

- Systematic review/meta-analysis was well done and provides hypothesis generating evidence for a potential small increase in CV risk with varenicline versus placebo within 1 year follow up of treatment.
- The extrapolated NNH=28 for CV risk in smokers with stable CV disease is quite questionable and may overstate the risk. Meta-analysis techniques can vary and may be open to criticism.
- One final over-riding point. Many patients stop smoking without the help of drug therapy. For those who may need a drug to stop, the benefit of stopping, especially long-term, is usually thought to outweigh the risks. Other pharmacotherapy alternatives[5,6], all with their own risk benefit profiles, include nicotine replacement therapy E.g, NICODERM, HABITROL, NICORETTE, THRIVE, bupropion ZYBAN and nortriptyline AVENTYL.
- If you will indulge me for a moment, I'd suggest one slightly humorous way to look at the results. ☺

> *In 14 trials that analysed 8216 patients on varenicline vs placebo, the NNH was 417. In 0 trials analysing 0 patients, but all of whom were at much higher risk, this extrapolated NNH would be 28, assuming that the proposed odds ratio holds true. Note that the absolute risk of continuing smoking would also be a major factor to consider in weighing the risk/benefit of therapy.*

Extras:

RxFiles Meta Q&A – July 2011:
> **Risk of Serious Adverse Cardiovascular (CV) Events with Varenicline (Champix, Chantix):**
> **Comment on Systematic Review and Meta-analysis**

> F**DA Drug Safety Communication link** (Aug 2011): http://www.fda.gov/Drugs/DrugSafety/ucm264436.htm
> **Health Canada (Jan 2012)** http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_07-eng.php

Additional articles:
July 2012: Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ. 2012 May 4;344:e2856.
> {Unlike the previous meta-analysis of the same studies, this one found no difference in CV events for varenicline vs placebo.}

Update...

References

[1] Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ. 2011 Jul 4.

[2] Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions* - Combining Studies. {Online discussion of PETO vs Mantel-Haenszel OR methods in meta-analysis.} Accessed at http://www.cochrane-net.org/openlearning/html/mod12-3.htm . Accessed online 13 July, 2011.

[3] **Calculation of NNT from OR:**
> NNT =((PEER*(OR-1))+1) / (PEER*(OR-1)*(1-PEER))
> =((0.0557*(1.72-1))+1) / (0.0557*(1.72-1)*(1-0.0557))
> =27.46
> Let OR=1.09, NNT= 12.18
> Let OR=2.71, NNT= 212.31

[4] Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010 Jan 19;121(2):221-9.

[5] Regier L, Jensen B, Chan W. Tobacco / Smoking Cessation Pharmacotherapy Chart. RxFiles Drug Comparison Charts. 8th Ed. Saskatoon, SK: Saskatoon Health Region; 2010. Available from: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Smoking-Cessation.pdf . Accessed online 12 July, 2011.

[6] Regier L, Jensen B. Smoking Cessation Pharmacotherapy. RxFiles. Saskatoon, SK: Saskatoon Health Region; Oct 2006. Available from: http://www.rxfiles.ca/rxfiles/uploads/documents/Smoking-Cessation-Newsletter-Header.pdf . Accessed online July 12, 2011.
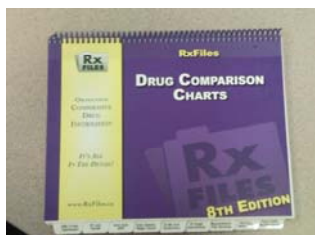
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