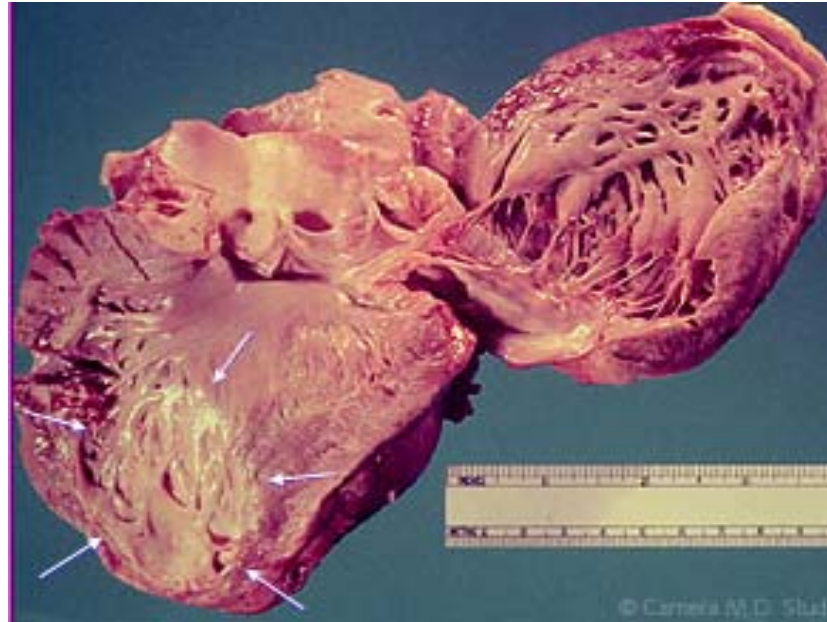


Was Vioxx™ the Culprit?



(Arrows show necrosis from coronary heart disease (CHD).)

Jack K. Horner

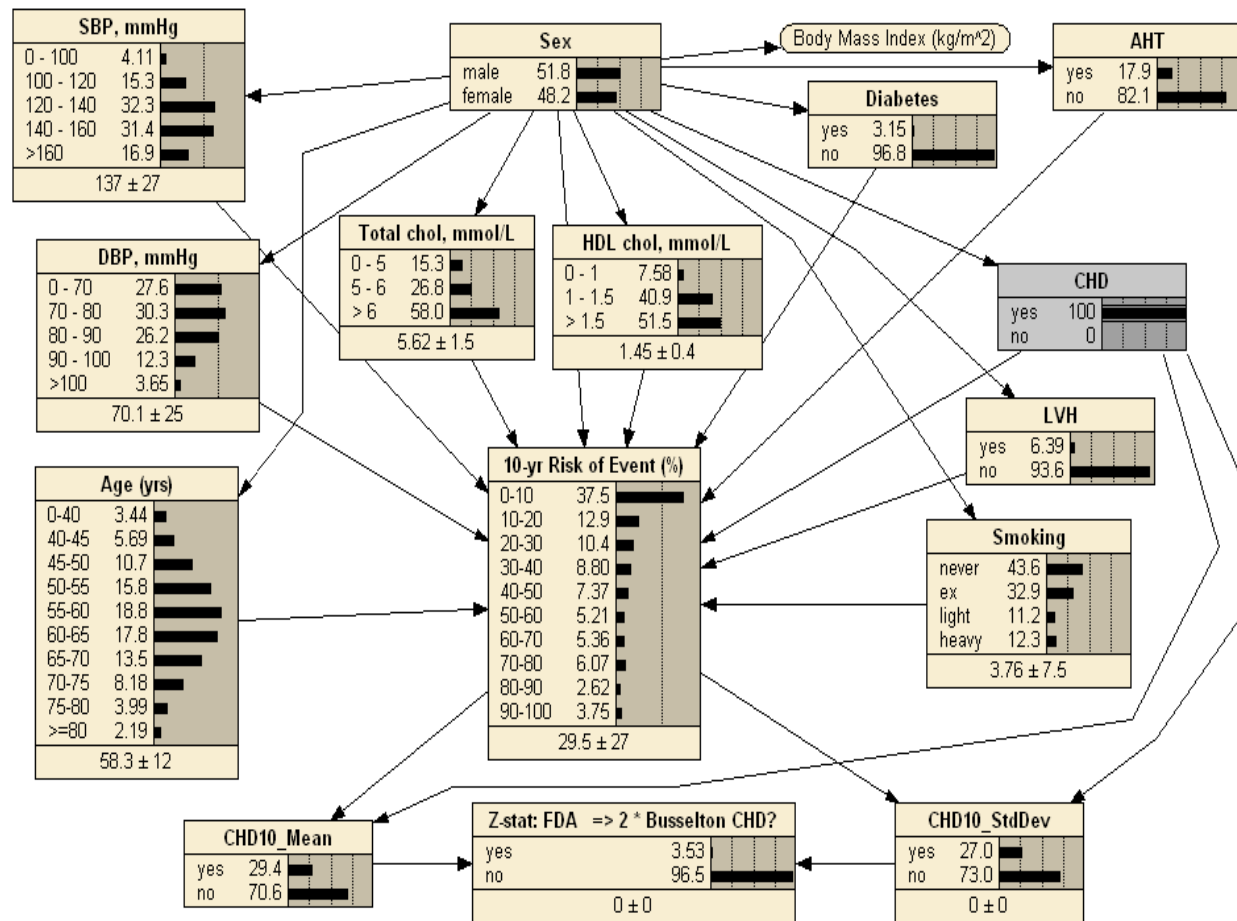
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Problem statement

- On 30 September 2004
 - the Food and Drug Administration (FDA)
 - claimed a **4-fold increase** due to the non-steroidal anti-inflammatory drug (NSAID) Vioxx™ of “serious” coronary heart disease (CHD) cases (hospitalized acute myocardial infarction (AMI), or sudden cardiac death (SCD) wherever it occurred), in patients with a history of CHD, compared to a control group which was administered the NSAID naproxen (e.g., Aleve™)
 - was prepared to issue a restriction (“black”) label order for Vioxx™ for patients with “serious” CHD
 - Merck withdrew Vioxx™ from the market
- Did the medical evidence support the withdrawal?

Method: Extend the Bayesian network of Twardy et al. with a Z-statistic large two-sample difference-of-means CI test
 FDA-“serious” CHD vs. Busselton CHD
 (Boxes are observables; an arrow from Box A to Box B means B is dependent on A)



Results

- The hypothesis test (two-sample difference-of-means CI test) and control (pre-Vioxx™ Busselton CHD cohort) used in the current study *reject* the hypothesis
 **H_0 : Vioxx at least doubled the “serious”
CHD frequency in patients with a
history of CHD**
at the 95% confidence level
- The standard deviation of the CHD data in the control alone is sufficient to ensure rejection of H_0

Discussion

- The FDA results were based on
 - a cohort of “serious” CHD cases; the Busselton CHD cohort presumably includes both “serious” and “non”-serious CHD cases
 - a post-1999 NSAID regime; the Busselton CHD cohort is based on a pre-2000 NSAID regime
- The Busselton CHD data are therefore not an exact control for the FDA study

Discussion

- The FDA study assumes a standard of safety defined in terms of the safety of comparable therapeutics *at the time of the test*. *Aspirin would not meet this standard if compared to today's NSAIDs*.
- The FDA study uses a likelihood ratio CI test whose reliability is problematic when the variances of the test and control populations are not equal. In the FDA study, the variances of the test and control populations differ by a factor of two. There is *no* discussion of this problem in the FDA's publications about Vioxx™.
- Even if the variances in the test and control populations in the FDA study were equal
 - the CI test in the FDA study would be equivalent to a two-sample, equal-variances *t*-statistic test
 - the two-sample, equal-variances *t*-statistic test is equivalent to special case of the difference-of-means test used in the current study, which rejects H_0