



## Timeline of Epidemiological Studies Involving VIOXX or NSAIDs<sup>1</sup>

Jan 2002 A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to measure the effects of non-aspirin NSAIDs, including naproxen, on risk of serious coronary heart disease (CHD). Study concludes that in a high-risk patient population of people 50 years and older, non-selective non-aspirin NSAIDs neither increased nor decreased risk of serious CHD. Analysis evaluated 6,362 cases from the Tennessee Medicaid program during 181,441 periods of new NSAID use in 128,002 people and the same number of periods of non-use of NSAIDs among 134,642 people.

May 2002 Three separate case-control studies are published in *Archives of Internal Medicine*. Each showed that use of naproxen reduced the risk of heart attacks. These studies were first presented at the American College of Rheumatology meeting in 2001.

**Solomon et al:** Objective was to determine whether NSAIDs have a similar effect or whether they differ in their effects on the risk of acute myocardial infarction (AMI). Study concludes that the findings do not support a relationship between the use of NSAIDs as a group and risk of heart attacks. However, use of naproxen was associated with a significant reduction in the risk of AMI (adjusted odds ratio, 0.84; 95% confidence interval, 0.72-0.98; P =.03). Analysis evaluated 4,425 cases from the N.J. Medicare/ Medicaid Program against a control group of 17,700 subjects.

**Watson, et al:** Objective of the study was to examine the risk of acute thromboembolic cardiovascular events (heart attack, sudden death and stroke) with naproxen use among patients with rheumatoid arthritis. The study concludes that patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major thromboembolic CV events relative to those who did not take naproxen in the past year. Analysis evaluated 809 cases from British General Practice Research Database against a control group of 2,285 subjects. Study sponsored by Merck.

**Rahme, et al:** Objective of the study was to compare the effect of naproxen to other NSAIDs in the prevention of acute myocardial infarction (AMI) in an elderly population. The study concludes that compared to other NSAIDs, concurrent use of naproxen has a protective effect against AMI. Analysis evaluated 4,163 cases from Canadian RAMQ and Med-Echo databases against a control group of 14,160 subjects. Study sponsored by Merck.

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<sup>1</sup> **Editor's Note:** Timeline is not an exhaustive list of every study ever conducted to evaluate the safety of NSAIDs and COX-2 inhibitors; selected studies have been identified to illustrate the wide divergence of results from observational studies.

- Oct 2002 A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to assess occurrence of serious coronary heart disease (CHD), specifically acute myocardial infarction (AMI) and cardiac death, in patients taking Vioxx, celecoxib or other NSAIDs. Study concludes use of Vioxx at doses greater than 25 mg could be associated with an increased risk of serious CHD; in contrast, there was no evidence of increased risk among users of Vioxx at doses of 25 mg or less, celecoxib, naproxen or ibuprofen. Analysis evaluated 5,316 events from the Tennessee Medicaid program among 251,046 NSAID users and 202,916 non-users.
- Oct 2002 A database cohort analysis by **Levy et al** is presented at the American College of Rheumatology meeting. Objective was to assess the correlation between COX-2 use and heart attacks among persons prescribed a COX-2 inhibitor, ibuprofen, or naproxen for at least 50 consecutive days. Study concludes long-term use of either of the COX-2 inhibitors (Vioxx and celecoxib) separately is not associated with an increase risk of heart attack compared with naproxen or ibuprofen. When users of COX-2 inhibitors were combined, there was an increased risk compared with users of ibuprofen or naproxen combined. Analysis evaluated 645 events from the Kaiser Permanente database among 172,260 subjects.
- Feb 2003 A population-based, retrospective cohort study by **Mamdani et al** is published in *Archives of Internal Medicine*. Objective was to compare the rates of acute myocardial infarction (AMI) among elderly patients taking COX-2 inhibitors, naproxen and non-aspirin NSAIDs. Study concludes no increased short-term risk of AMI among users of COX-2 inhibitors and no short-term reduced risk of AMI with naproxen. Analysis evaluated 701 events from administrative health care databases in Ontario among 66,964 users and 100,000 non-users.
- Nov 2003 A case-control study by **Kimmel et al** is presented at the American Heart Association annual meeting. Objective was to determine the risk of nonfatal heart attacks in users of COX-2 inhibitors compared with users of non-aspirin NSAIDs. Study concludes there was no increased risk of heart attacks overall from COX-2 inhibitors, or from VIOXX separately and that nonselective, non-aspirin NSAIDs were associated with a reduced risk of heart attack. Analysis evaluated 1,718 cases against 6,800 controls from the Delaware Valley Case-Control Network. Study sponsored by Merck and Pharmacia.
- Mar 2004 A population-based analysis by **Whelton et al** is presented at the American College of Cardiology meeting. Objective was to determine the risk of acute myocardial infarction (AMI) or stroke with Vioxx, celecoxib, and non-selective NSAIDs in hypertensive patients. Study concludes Vioxx significantly increases the risk of AMI or stroke compared with non-users of NSAIDs and there was no increased risk among users of celecoxib or non-selective NSAIDs. Analysis evaluated 3,723 users against 1,798 users from a private medical insurance healthcare claims database. Study sponsored by Pfizer.
- Mar 2004 A case-control study by **Kimmel et al** is published in the *Journal of the American College of Cardiology*. Objective was to determine the risk of nonfatal heart attacks in users of non-selective, non-aspirin NSAIDs and the interaction between non-aspirin NSAIDs and aspirin. Study concludes non-selective, non-aspirin NSAIDs are associated with a reduced risk of heart attack. Analysis

evaluated 581 events from the Philadelphia community among 4,153 control subjects.

- Apr 2004 A case-control study by **Solomon et al** is published in *Circulation*. Objective was to assess the risk of acute myocardial infarction (AMI) among users of Vioxx, celecoxib, and NSAIDs in an elderly population. Study concludes Vioxx all doses combined was associated with a significant increased risk of AMI compared to celecoxib. Non-significant differences were found comparing Vioxx to ibuprofen, naproxen, other NSAIDs and to those not taking NSAIDs. The risk was higher in persons taking greater than 25 mg of Vioxx and during the first 90 days of use but not thereafter. Analysis evaluated 10,895 cases from two state-sponsored pharmaceutical benefits program in the U.S. among 54,475 patients 65 years and older. This study was first presented at the American College of Rheumatology meeting in 2003. Study sponsored by Merck.
- May 2004 A population-based retrospective cohort study by **Mamdani et al** is published in *The Lancet*. Objective was to compare the rates of admission for congestive heart failure (CHF) in elderly patients who were given COX-2 inhibitors or non-selective NSAIDs. Study concludes there is a higher risk of admission for CHF in users of Vioxx and non-selective NSAIDs (diclofenac, naproxen and ibuprofen) but not celecoxib in comparison to non-users of NSAIDs. Analysis evaluated 654 events from administrative healthcare databases in Ontario among 45,097 users of NSAIDs/COX-2 inhibitors and 100,000 non users.
- June 2004 A cohort study by **Garcia Rodriguez et al** is published in *Circulation*. Objective was to estimate the effect of non-aspirin NSAIDs on the occurrence of AMI and death from CHD. Study concludes there was no risk reduction of NSAIDs on the occurrence of MI. Analysis evaluated 4,975 cases from the General Practice Research Database in the U.K. against a control of 20,000 subjects.
- Aug 2004 A case-control study by **Graham et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to determine if NSAID use increases the risk of AMI or sudden cardiac death (SCD) and if the risk is similar among COX-2 selective agents. Study concludes Vioxx use at doses greater than 25 mg increases the risk of AMI and SCD; Vioxx at 25 mg or less had an increased risk compared with celecoxib; and that several other NSAIDs increased the risk of AMI and SCD. Analysis evaluated 8,199 cases from Kaiser Permanente against a control group of 32,796 subjects. Funding provided by FDA.
- Aug 2004 A retrospective cohort study by **Rahme et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to assess the rates of hospitalizations for acute myocardial infarction (AMI) in an elderly cohort. 52,029 patients were taking non-selective NSAIDs and 71,543 patients were taking rofecoxib, with 14,056.4 and 37,371.0 person-years of exposure, respectively. Based on the regression model, the adjusted hazard ratios of hospitalizations for MI was 1.03 (0.83-1.27) for rofecoxib vs. ibuprofen/diclofenac. Study concludes there was no difference in the rate of hospitalizations for AMI among Vioxx and the non-selective NSAIDs ibuprofen and diclofenac. Study sponsored by Merck.

Aug 2004      A retrospective cohort study by **Shaya et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to examine the cardiovascular risk of COX-2 inhibitors compared to non-specific NSAIDS in a high risk Medicaid population. Analysis evaluated medical and prescription claims for Maryland Medicaid enrollees, COX-2 users numbered 1208 and non-naproxen NSAID users numbered 5274. Study concludes that COX-2 inhibitors did not increase cardiovascular risk over non-naproxen NSAIDs in a high risk population.

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### **Forward-Looking Statement**

This document contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any) which the company incorporates by reference.