menting cardiovascular risk reduction before the start of HAART, as well as for patients already taking HAART, deserves our attention in an era when we become more and more concerned with the long term side effects of HAART.[10]

Filip Moerman *head of HIV/STI outpatient department*
Alfons Van Gompel *associate professor*

Institute of Tropical Medicine, Unit of HIV/AIDS and STIs, Nationalestraat 155, 2000 Antwerp, Belgium (fmoerman@itg.be)

Jan Nimmegeers *consultant cardiologist*

Academic Hospital Saint-Lucas, 9000 Ghent, Belgium

Johan Moerman *general medical officer*

Bromeliastreet 91, 9040 Ghent, Belgium

Competing interests: None declared.

1 Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 × $10^9$ cells/L. *Ann Intern Med* 2003;139:810-6.
2 The writing committee of the D:A:D Study Group. Cardio- and cerebrovascular events in HIV-infected persons. *AIDS* 2004;18:1811-7.
3 Bergerson BM, Sandvik L, Bruun JN, Tonstad S. Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. *Eur J Clin Microbiol Infect Dis* 2004;23:625-30.
4 Bergersen BM, Sandvik L, Dunlop O, Birkeland K, Bruun JN. Prevalence of hypertension in HIV-positive patients on highly active antiretroviral treatment (HAART) compared with HAART-naïve and HIV-negative controls: results from a Norwegian study of 721 patients. *Eur J Clin Microbiol Infect Dis* 2003;22:731-6.
5 Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. Data collection on adverse events of Anti-HIV Drugs (DAD) Study Group. *N Engl J Med* 2003;349:1993-2003.
6 Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *J Antimicrob Chemother* 2004; 53:696-9.
7 Special communication. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486-97.
8 Calza L, Manfredi R, Chiodo F. Dislipidaemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrob Chemother* 2004;53:10-4.
9 Egger M, May M, Chene G, Phillips AN, Lederberger B, Dabis F, et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-29.
10 Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE Collaboration). Is the time from HIV seroconversion a determinant of the risk of AIDS after adjustment for updated CD4 cell counts? *J Acquir Immun Defic Syndr* 2001;28:158-65.
11 Gluckman Ty J, Baranowski B, Ashen D, Henrikson C, McAllister M, Braunstein JB, et al. A practical and evidence-based approach to cardiovascular risk reduction. *Arch Intern Med* 2004;164:1490-1500.
12 Adams MR. Prevention of myocardial infarction. *Intern Med J* 2002;32: 595-600.
13 Phillips A, Cozzi Lepri A, Lampe F, Johnson M, Sabin C. When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. *AIDS* 2003;17:1863-9.
14 Bonnet F, Morlat P, Chene G, Mercie P, Neau D, Chossat I, et al. Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy. *HIV Med* 2002;3:195-9.

# COX 2 inhibitors, traditional NSAIDs, and the heart

*Adverse event data from clinical trials must inform decision making*

*Primary care*
pp 1366, 1370

These are trying times for patients with chronic musculoskeletal pain. Worrying data about the drugs they regularly use keep emerging. In September 2004 rofecoxib (Vioxx) was withdrawn by Merck after the adenomatous polyp prevention on Vioxx (APPROVe)[1] trial showed an increase in major cardiovascular events in patients with a history of colorectal adenomas who were randomised to receive Vioxx, compared with those in the placebo group. [w1] Rofecoxib had been marketed as the non-steroidal anti-inflammatory drug (NSAID) of choice because selective inhibition of the isoform 2 of the cyclo-oxygenase (COX 2) enzyme made it highly effective but free from gastrointestinal toxicity.

More unwelcome data from placebo controlled trials of rofecoxib's competitors followed: valdecoxib (Bextra, Pfizer) taken after coronary artery bypass grafting was shown to be associated with an increased incidence of cardiovascular events[2]; and the adenoma prevention with celecoxib (APC) trial[3] reported an increased risk of cardiovascular events associated with use of celecoxib (Celebrex, Pfizer), a drug known to be less selective for COX 2 than rofecoxib or valdecoxib.[4] A small increase in the risk of myocardial infarction was also observed for the highly selective lumiracoxib (Prexige, Novartis).[5] No data on the cardiovascular safety of etoricoxib (Arcoxia, MSD) from large trials have been published so far, but no news is no longer good news: patients and doctors are anxious to know whether cardiotoxicity is a class effect applicable to any COX 2 inhibitor, or even to NSAIDs in general.

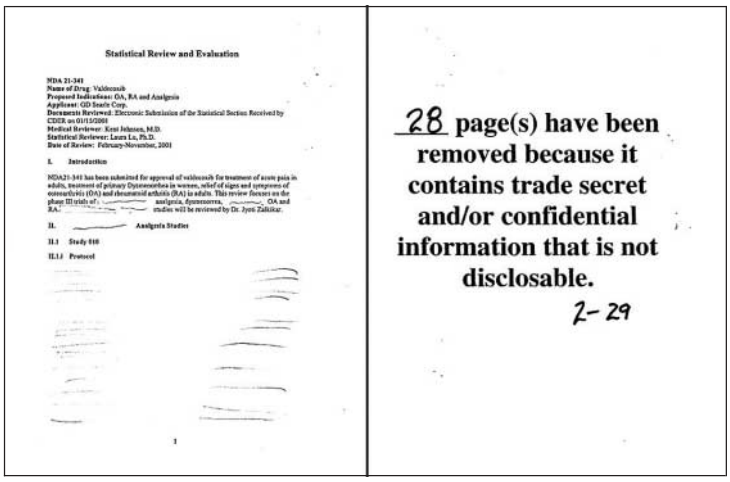
In this week's *BMJ* two observational studies address this question. A retrospective cohort study (page 1370)[6] in patients with congestive heart failure found lower mortality in patients treated with celecoxib than with rofecoxib or traditional NSAIDs. A case-control study nested in a UK general practice database (page 1366)[7] found a similar risk of myocardial infarction for celecoxib, rofecoxib, ibuprofen and naproxen, but a somewhat higher risk with diclofenac.

We believe that these results should be interpreted with caution. For example, the similar risk of myocardial infarction for naproxen and rofecoxib found in the case-control study[7] is incompatible with the trial data[8] and could be explained by confounding by indication if patients with a history of heart disease were more likely to receive naproxen than rofecoxib or other NSAIDs. The quality of the data on cardiovascular risk factors and other potential confounders was poor in both studies, and the ability to control for confounding therefore limited. For example, information on smoking was unrecorded in 13% of cases and 20% of controls in the case-control study[7] and entirely unavailable in the retrospective cohort study.[6]

What are the alternatives? We have argued that all unbiased data on serious adverse events from clinical trials should be made available to independent researchers and the public and analysed in a timely fashion.[9] Indeed, in the case of rofecoxib, cumulative meta-analysis of clinical trial data showed that an increased risk of myocardial infarction was evident from 2000 onwards.[8] Similar analyses are now required for the other COX 2 inhibitors.

*Additional references w1 and w2 are on bmj.com*

*BMJ* 2005;330:1342–3




Facsimile of pages 1 and 2 of the Food and Drug Administration (FDA) statistical review and evaluation of valdecoxib.[w2] Publicly available at www.fda.gov/cder/foi/nda/2001/21-341_Bextra_statr_P1.pdf (accessed 20 May 2005)

The US Food and Drug Administration (FDA) and other licensing authorities are an important source of relevant data. The FDA reviews clinical trials worldwide before approval and labelling, and again before relabelling of approved drugs. As part of the 1966 Freedom of Information Act, the agency is required to make available its reports on all drugs that are approved. Unfortunately, these reports are not as useful as they could be. We found that the criteria for including trials in reports were often unclear. For example, only 16 out of at least 27 trials of celecoxib that were performed up to 2002 in patients with musculoskeletal pain were included in the relevant reports. In any event, reporting on study characteristics and adverse events was not always transparent, and complete data on cardiovascular safety were available for only three trials. In the case of valdecoxib, we found that many pages and paragraphs had been deleted because they contained "trade secret and/or confidential information that is not disclosable" (figure).[w2]

Surely, the protection of the public's health justifies full access to the safety data submitted by industry to the FDA and other drug licensing authorities, and mandates transparent reporting on harms, in accordance with international guidelines.[10] Meta-analyses of adverse events might not resolve controversies, but will help decision making about issues such as the need for additional trials.

Observational studies "simply cannot test definitely whether there are small to moderate risks or benefits of a class of drugs when the factors associated with prescription of a particular drug are difficult to control and perhaps even uncontrollable."[11] This statement referred to postulated adverse events of calcium antagonists in the treatment of hypertension, a controversy finally resolved by large pragmatic trials, including the seminal antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT).[12] Such large trials might be required, ultimately, to establish the best and safest treatment for patients with musculoskeletal pain.

Peter Jüni *senior research fellow in clinical epidemiology*

Department of Social and Preventive Medicine, University of Berne, Finkenhubelweg 11, 3012 Berne, Switzerland (juni@ispm.unibe.ch)

Stephan Reichenbach *research fellow in rheumatology*

Department of Rheumatology, University Hospital Berne, 3010 Berne, Switzerland

Matthias Egger *visiting professor of clinical epidemiology*

MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol BS8 2PR

Competing interests: None declared.

1 Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
2 Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352:1081-91.
3 Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
4 Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *Faseb J* 2004;18:790-804.
5 Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004;364:675-84.
6 Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ* 2005;300:1370-3.
7 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005;300:1366-9.
8 Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021-9.
9 Dieppe PA, Ebrahim S, Martin RM, Jüni P. Lessons from the withdrawal of rofecoxib. Patients would be safer if drug companies disclosed adverse events before licensing. *BMJ* 2004;329:867-8.
10 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004;141:781-8.
11 Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction. A hypothesis formulated but not yet tested. *JAMA* 1995;274:654-5.
12 Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002;288:2981-97.

# Alcohol misuse, public health, and public policy

## *A comprehensive and evidence based approach is needed*

Alcohol misuse continues to be associated with as many as 22 000 deaths each year in England, with cumulative economic, health, and social costs estimated at £20bn annually.[1] While people in many other parts of Europe may have consumed a greater amount of alcohol in the past—although varying definitions of categories of consumption hamper accurate cross national comparisons[2]—the situation in England is one of increasing concern. According to recent figures, 38% of men and 23% of women in England exceed recommended maximum levels for the heaviest drinking day of the week,[3] and alcohol related illness mortality is on the rise.[4] Drinking patterns vary between England's regions in a predictable manner that reflects persistent health inequalities,[5] notably with the highest rates of binge drinking found in the north-

*BMJ* 2005;330:1343–4