

### What is already known on this topic

Data on perinatal mortality in China rely on surveys and hospital based statistics

The perinatal mortality rate in urban China has been reported to be lower than in other developing countries and is inversely associated with socioeconomic status

There have been few reports on perinatal mortality for rural China

### What this study adds

Routine statistics collected by the Chinese family planning system were a reliable data source for the study of perinatal mortality

The perinatal mortality rate in rural China was much higher than previously reported rates from urban areas and was associated with parity in a different way than in other countries

In this cohort, in which most women were under 35 years of age and lived in a cultural context where smoking among women is rare, the rate of stillbirth increased strongly from first to second pregnancies, contrary to the situation in developed countries.<sup>15</sup> This might be due to the misclassification of some abortions as stillbirths.

The higher early neonatal mortality in second born compared with first born children, particularly in girls, was probably also a result of both the family planning policy and the preference for sons. This is reflected in the high male to female sex ratio among the liveborn

children in the cohort. We are currently investigating mortality by infant sex and the issue of sex ratio at birth.

We thank Duolao Wang for his helpful comments.

Contributors: See bmj.com

Funding: Academy of Finland.

Competing interests: None declared.

Ethical approval: The study was approved by the STAKES ethics committee, 11 January 1999.

- Zhang J, Cai WW, Chen H. Perinatal mortality in Shanghai 1986-1987. *Int J Epidemiol* 1991;20:958-62.
- Xu BZ. *Perinatal mortality in China and Finland with specific reference to sex differentials*. Oulu: Acta Universitatis Ouluensis Medica, 1995.
- Li XT, Yu YP, Shen YT. The perinatal mortality from 1983 to 1993 in Wuhu city. (In Chinese.) *Zhong Guo Fu You Bao Jian* 1995;10:246-8.
- Liu XH, Yi RT, Yao JR, Lei W. Perinatal mortality in the past 10 years in Chengdu, Sichuan province. (In Chinese.) *Zhong Guo Shi Yong Fu Chan Ke Za Zhi* 2001;17:111-2.
- Wei YZ, Cui HZ. Perinatal mortality in Guizhou province 1987. (In Chinese.) *Gui Yang Yi Xue Yuan Xue Bao* 1992;17:42-5.
- Yao JS, Chen YZ, Xi BL, Jiang YZ, Li WS, Wang H. Systematic prenatal care management in rural areas. (In Chinese.) *Zhonghua Fu Chan Ke Za Zhi* 1991;26:224-7.
- Zhu XL, Er XD. Maternal and child health status in Shanshan County. (In Chinese.) *Xin Jiang Yi Xue Yuan Xue Bao* 1996;19:83-5.
- Kane P, Choi CY. China's one child family policy. *BMJ* 1999;319:992-4.
- Chu JH. Prenatal sex determination and sex-selective abortion in rural central China. *Pop Dev Rev* 2001;27:259-81.
- Mu L. Appraisal of an infant mortality indicator used in evaluating primary health care services. (In Chinese.) *Zong Guo Chu Ji Wei Sheng Bao Jian* 1995;9:34-5.
- Shah D, Shroff S, Ganla K. Factors affecting perinatal mortality in India. *Int J Gynaecol Obst* 2000;71:209-10.
- Kulmala T, Vaahtera M, Ndekha M, Koivisto A-M, Cullinan T, Salin M, et al. The importance of preterm births for peri- and neonatal mortality in rural Malawi. *Paediatr Perinat Epidemiol* 2000;14:219-26.
- Shah NM, Shah MA, Khalaf AA, Mustafa MM, Al-Sayed A. Searching for socio-economic risk factors in perinatal mortality in Kuwait: a case control study. *Soc Sci Med* 2000;51:539-50.
- Banister J. *China's changing population*. Stanford: Stanford University Press, 1987.
- Raymond EG, Cnattingius S, Kiely JL. Effects of maternal age, parity, and smoking on the risk of stillbirth. *Br J Obstet Gynaec* 1994;101:301-6.

(Accepted 30 September 2003)

## Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study

Jeptha P Curtis, Yongfei Wang, Edward L Portnay, Frederick A Masoudi, Edward P Havranek, Harlan M Krumholz

Observational studies and in vivo experiments have raised concern that the cardioprotective effects of taking aspirin are blocked by ibuprofen, a non-steroidal anti-inflammatory drug that competitively inhibits aspirin's binding site on platelets.<sup>1,2</sup> We determined whether prescribing aspirin and ibuprofen to patients being discharged after myocardial infarction was associated with increased risk of death.

### Participants, methods, and results

The database compiled by the Cooperative Cardiovascular Project consisted of 234 769 Medicare patients in the United States who were hospitalised with a myocardial infarction between 1994 and 1996.<sup>3</sup> We identified patients aged  $\geq 65$  with myocardial infarction who were prescribed aspirin on discharge and

excluded patients who had repeat admissions, had terminal illness, had incomplete drug records, or had been transferred. The outcome measure was time to death within a year of discharge, which we ascertained from the Medicare enrolment database.<sup>4</sup> We compared the baseline characteristics of patients prescribed only aspirin, prescribed aspirin and ibuprofen, and prescribed aspirin and other non-steroidal anti-inflammatory drugs with  $\chi^2$  tests and analysis of variance. We compared Kaplan-Meier survival curves with the log rank test. We developed a Cox proportional hazards mortality model including demographics, medical history, admission presentation, hospital course, and discharge care. We did statistical calculations with SAS.

A total of 70 316 patients were prescribed aspirin at discharge from hospital; 66 739 were prescribed

Editorial by Kimmel and Strom

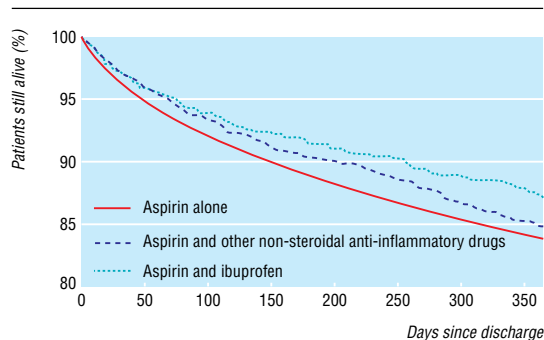
Correspondence to: H M Krumholz harlan.krumholz@yale.edu

continued over

BMJ 2003;327:1322-3



Table A on bmj.com gives baseline characteristics; a disclaimer also appears on bmj.com



Kaplan-Meier survival curves for elderly US survivors of myocardial infarction prescribed aspirin alone, aspirin and ibuprofen, or aspirin and a different non-steroidal anti-inflammatory drug on discharge from hospital

aspirin alone, 844 aspirin and ibuprofen, and 2733 aspirin and other non-steroidal anti-inflammatory drugs. Patients prescribed only aspirin had more comorbidity and had had more complications in hospital (see *bmj.com*). Totals of 11 546 (17.5%) patients who were prescribed only aspirin, 118 (14.0%) who were prescribed aspirin and ibuprofen, and 432 (15.8%) who were prescribed aspirin and other non-steroidal anti-inflammatory drugs died within a year after discharge (log rank  $P = 0.003$ ) (figure). Our multivariable model found that patients prescribed aspirin and ibuprofen on discharge had a risk of death that was comparable to that of patients prescribed aspirin alone (hazard ratio 0.84; 95% confidence interval 0.70 to 1.01) or prescribed aspirin and another non-steroidal anti-inflammatory drug (0.96; 0.86 to 1.06).

## Comment

Aspirin and ibuprofen did not adversely interact in this cohort of elderly patients discharged after myocardial infarction. The pharmacodynamic interaction of aspirin and ibuprofen may not have a significant impact on patient outcomes.

Recently, investigators reported that patients with established cardiovascular disease who were pre-

scribed aspirin and ibuprofen on discharge were at increased risk of death compared with patients discharged on aspirin alone.<sup>2</sup> The findings received extensive media attention and prompted recommendations against patients with coronary disease using ibuprofen.<sup>5</sup> However, their study included only 187 patients on both aspirin and ibuprofen and did not adjust for severity of cardiovascular disease. Conversely, we found that patients taking aspirin and ibuprofen have similar mortality to patients discharged on aspirin alone. In comparison, our analysis included four times as many patients prescribed both aspirin and ibuprofen and we could adjust for measures of severity of disease, such as shock, ejection fraction, and heart failure.

Because of the non-experimental design, our analysis may have allowed residual confounding. In particular, we had no information about patterns of use of ibuprofen after discharge from hospital. Because ibuprofen and other non-steroidal anti-inflammatory drugs are available over the counter, we have likely underestimated the overall use of ibuprofen, which could bias our results toward the null. Nevertheless, recommendations that patients with coronary artery disease should avoid taking both ibuprofen and aspirin may be unfounded.

Contributors: HMK and JPC conceived and designed the study and drafted the report. YW provided statistical expertise. ELP, FAM, and EPH did analysis and wrote the report. HMK is guarantor.

Funding: FAM is supported by NIH/NIA Research Career Award K08-AG01011.

Competing interests: EPH has received funds from Sanofi.

Ethical approval: Not needed.

- 1 Fitzgerald GA. Parsing an enigma: the pharmacodynamics of aspirin resistance. *Lancet* 2003;361:542-4.
- 2 MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;361:573-4.
- 3 O'Connor GT, Quinton HB, Traven ND, Ramunno LD, Dodds TA, Marciniak TA, et al. Geographic variation in the treatment of acute myocardial infarction: the cooperative cardiovascular project. *JAMA* 1999;281:627-33.
- 4 Fleming C, Fisher ES, Chang CH, Bubolz TA, Malenka DJ. Studying outcomes and hospital utilization in the elderly: the advantages of a merged database for Medicare and Veterans Affairs hospitals. *Med Care* 1992;30:377-91.
- 5 Associated Press. Ibuprofen may not be heart healthy. *USA Today* 2003 Feb 13:D1.

(Accepted 24 July 2003)

Section of Cardiovascular Disease, Department of Internal Medicine, Yale University School of Medicine, Room I-456 SHM, 333 Cedar Street, PO Box 208088, New Haven CT 06520-8088, USA

Jeptha P Curtis  
*clinical fellow*

Yongfei Wang  
*lecturer*

Edward L Portnay  
*clinical fellow*

Harlan M Krumholz

*professor of medicine*

Division of Cardiology, MC 0960, Denver Health Medical Center, 777 Bannock Street, Denver CO 80204, USA

Frederick A Masoudi  
*assistant professor of medicine*

Edward P Havranek  
*associate professor of medicine*

## Through the looking glass

A 37 year old man with a long history of bipolar affective disorder with type 1 diabetes presented in a hypomanic episode with a history of five days of blurred vision in both eyes. He was taking sodium valproate 750 mg orally twice daily, quetiapine 100 mg at night, metformin 500 mg orally twice daily, and insulin (Mixtard 50, 16 units in the morning and 6 units at night).

The patient's mental state was improving, and he was not a management problem on the unit. However, he still reported blurred vision in both eyes. Ophthalmological examination showed that both conjunctivae were bloodshot, but no other abnormalities were found. His last glucose measurement had been recorded at 6.8 mmol/l at 8 o'clock that morning. Physical examination showed mild obesity and no neurological deficits.

His blood results showed a normal white cell count, low albumin and total protein concentrations, and mildly raised alanine aminotransferase activity.

It seemed unlikely that this blurred vision was related to side effects from his medication, and re-examination before transfer to an ophthalmological unit identified the source of the problem: the patient had two sets of contact lenses in his eyes. The blurring resolved on removal of one set of lenses.

One never knows what one will see through one looking glass, but through two?

Paul Myhill *associate psychiatrist, Florence Nightingale Hospital, London*