Cholesterol lowering drugs and risk of age related maculopathy: prospective cohort study with cumulative exposure measurement

R van Leeuwen, J R Vingerling, A Hofman, P T V M de Jong, B H Ch Stricker

Recently, two studies have claimed that cholesterol lowering drugs, particularly statins, protect against age related maculopathy.[1 2] The end stage of this progressive retinal disorder is the commonest cause of untreatable blindness in elderly people in Western societies, and its prevalence is expected to rise with the ageing of the population. Thus, preventing this disorder would have an enormous public health impact.[3] The above mentioned studies used interview data on drug use and had a low statistical power. We therefore tested the hypothesis that cholesterol lowering drugs protect against age related maculopathy in a large cohort study with cumulative exposure measured.

Participants, methods, and results

This investigation was part of the Rotterdam study, a population based cohort study of people aged 55 years and more. After the baseline phase from 1990 to 1993, two follow up examinations were performed at mean intervals of 2 and 6.5 years. Of all the subjects at risk of age related maculopathy, 4822 (83%) participated at follow up. A diagnosis of age related maculopathy was based on stereoscopic colour fundus transparencies graded according to the international classification system.[4] The incidence of the disorder was defined as the development of soft distinct drusen with pigmentary irregularities, indistinct drusen, or the end stages of atrophic or neovascular age related macular degeneration.

A register of prescriptions filled by local pharmacies provided continuous data on use of cholesterol lowering drugs. These data were available for 99% of the cohort from 1 January 1991 onwards. We used Cox proportional hazards regression analysis to calculate hazard ratios, with age in days as the time axis to ensure optimal controlling for age. Cumulative exposure to drugs was represented as a time dependent covariate and was analysed both as a dichotomous and a categorical variable. The model compared each incident case of age related maculopathy with all subjects in the cohort who were alive and free of the disorder at the age when the case of maculopathy was diagnosed.[5]

During 26 781 person years of follow up, 457 patients used cholesterol lowering drugs for one or more days, and 419 cases of incident age related maculopathy were observed. Use of cholesterol lowering drugs at any time, defined as a binary variable, was not associated with the incidence of age related maculopathy (hazard ratio 1.0 (95% confidence interval 0.7 to 1.5)). Compared with patients who had never used cholesterol lowering drugs, cumulative exposure for less than one month, for one month to a year, or for more than a year did not have a protective effect on the risk of maculopathy (see table). Additional adjustment for body mass index, hypertension, smoking, and peripheral arterial disease (ankle:arm index <0.9) did not change the association. When we performed the same analysis with progression of age related maculopathy as the outcome variable, we obtained the same results.

Comment

Exposure to cholesterol lowering drugs did not change patients' risk of age related maculopathy. In contrast with the studies that reported a protective effect, we used a prospective design and assessed drug use by means of data registered by pharmacies. This minimised potential selection and information bias, and our data provided quantitative information for each patient's cumulative exposure to drugs. This prevented misclassification of the duration of drug use. Even though the total number of participants was high, the number of subjects using cholesterol lowering drugs who developed age related maculopathy was low, possibly leading to a type II error. With a two sided α of 0.05, we had a power of 80% to show a relative risk of 0.7 or lower. The fact that we did not find an association between cholesterol lowering drugs and age related maculopathy makes a protective effect of statins unlikely.

Contributors: RvL, PTVMdJ, and BHChS formulated the design of the study. RvL and JRV carried out the field work, and RvL and BHChS analysed the data. The paper was written by RvL and BHChS, and edited by JRV, AH, and PTVMdJ. AH, PTVMdJ, and BHChS are guarantors for the paper.

Funding: The Rotterdam study is supported by the Netherlands Organisation for Scientific Research (NWO), the Health and Development Research Council (ZON), the Netherlands Society for the Prevention of Blindness, and the Optimix Foundation.

Competing interests: None declared.

Department of Epidemiology and Biostatistics, Erasmus Medical Centre Rotterdam, PO Box 1738, 3000 DR Rotterdam, the Netherlands

R van Leeuwen *researcher*

A Hofman *professor*

P T V M de Jong *professor*

B H Ch Stricker *professor*

Department of Ophthalmology, Erasmus Medical Centre Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands

J R Vingerling *ophthalmologist*

Correspondence to: P T V M de Jong, Netherlands Ophthalmic Research Institute, KNAW, Meibergdreef 47, 1105 BA Amsterdam, the Netherlands p.dejong@ioi.knaw.nl

BMJ 2003;326:255–6

Hazard ratios of age related maculopathy (ARM) associated with the use of cholesterol lowering drugs

Exposure to cholesterol lowering drugs	No of subjects with incident ARM (n=419)	No of subjects in total cohort (n=4822)	Crude hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)†
All drugs:				
No exposure‡	391	4365	1.0	1.0
<1 month	2	26	1.1 (0.3 to 4.3)	1.2 (0.3 to 5.0)
1-<12 months	8	136	1.0 (0.5 to 2.1)	1.0 (0.5 to 2.0)
≥12 months	18	295	1.0 (0.6 to 1.6)	1.2 (0.7 to 1.9)
Statins:				
No exposure‡	394	4407	1.0	1.0
<1 month	2	21	1.5 (0.4 to 6.1)	1.6 (0.4 to 6.5)
1-<12 months	7	120	1.0 (0.5 to 2.1)	0.9 (0.4 to 2.1)
≥12 months	16	274	1.0 (0.6 to 1.6)	1.1 (0.7 to 1.9)

*Adjusted for age and sex.
†Additional adjustment for body mass index, smoking, hypertension, and peripheral arterial disease.
‡In this time dependent analysis, cumulative drug exposure of each case was compared with that for all other subjects in the cohort as controls, on the index date half way between the two examinations when the incident case occurred. Controls may contribute more than once. Hence, relative risks cannot be calculated with the numbers given in the table.

1 Hall NF, Gale CR, Syddall H, Phillips DI, Martyn CN. Risk of macular degeneration in users of statins: cross sectional study. *BMJ* 2001;323:375-6.
2 McCarty CA, Mukesh BN, Guymer RH, Baird PN, Taylor HR. Cholesterol-lowering medications reduce the risk of age-related maculopathy progression. *Med J Aust* 2001;175:340.
3 Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ* 2000;321:741-4.
4 Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, et al, for the International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol* 1995;39:367-74.
5 In t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, et al. Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001;345:1515-21.

(Accepted 20 August 2002)

RESEARCH POINTERS

Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women

Increased cardiovascular mortality more than 10 years after diagnosis of breast cancer is compatible with radiotherapy causing a substantial hazard

Clinical Trial Service Unit and Epidemiological Studies Unit, Radcliffe Infirmary, Oxford OX2 6HE
Sarah Darby *professor*
Paul McGale *statistician*
Richard Peto *codirector*
Department of Medical Epidemiology, Karolinska Institute, 171 77 Stockholm, Sweden
Fredrik Granath *statistician*
Per Hall *professor*
Department of Medicine, Karolinska Institute
Anders Ekbom *professor*
Correspondence to: S Darby sarah.darby@ctsu.ox.ac.uk

BMJ 2003;326:256–7

During radiotherapy for breast cancer there is often some irradiation of the heart and major blood vessels, which could increase cardiovascular mortality many years later.[1–3] The dose of radiation to the heart is generally higher when the left rather than the right breast is affected. Therefore, indirect evidence on the magnitude of any risk is available where the tumour laterality (left or right breast) can be linked to subsequent cardiovascular mortality.[1 2] Studies of the survivors of the atomic bombing of Japan who received single doses to the whole body of 0-4 Gy show that the cardiovascular disease risk is dose related and increases by about 14% per gray.[4]

Participants, methods, and results

Since 1970, the nationwide Swedish cancer registry has recorded the laterality of breast cancers but not the use of radiotherapy. Unpublished data from regional Swedish registries suggest that about 30% of women with early breast cancer during the 1970s and early '80s received radiotherapy. We linked registry records (1970-96) with national mortality records. The study was approved by the ethics committee of the Karolinska Institute.

After we excluded women whose cancer was diagnosed at autopsy or outside Sweden and those with previously registered cancers (except squamous cell skin cancer), 89 407 women aged 18-79 with unilateral breast cancer remained. We stratified analyses of subsequent mortality in groups of five years by calendar year of diagnosis, time since diagnosis, and age at diagnosis. Stratification by age was necessary because the proportion of left sided tumours increases with age.[5] Each woman's contribution to the person years at risk ran from the date of diagnosis until her date of death, date of emigration, 100th birthday, or 1 January 1997, whichever was earliest. We used Poisson regression to calculate mortality ratios, left versus right, from the numbers of deaths and person years. Ratios greater than one indicate greater mortality in women with left sided tumours than in women with right sided tumours.

Mortality from breast cancer was identical in women with left sided or right sided tumours (table). Mortality from cardiovascular diseases was higher in women with left sided tumours. Little excess occurred in the first 10 years after diagnosis (mortality ratio 1.01; 95% confidence interval 0.96 to 1.07), but later the ratio was 1.10 (1.03 to 1.18; P=0.004), 1.13 (1.03 to 1.25; P=0.01) for ischaemic heart disease (half of all cardiovascular mortality), and 1.08 (0.98 to 1.18) for other cardiovascular deaths (about 30% of which

Mortality ratio for women with left sided breast cancer versus women with right sided breast cancer during and after the first 10 years from diagnosis of breast cancer among 89 407 women registered during 1970-96 at the Swedish cancer registry

	All years	<10 years		≥10 years	
Cause of death (ICD-9 code)	Mortality ratio, left versus right (95% CI)	No of deaths	Mortality ratio, left versus right (95% CI)	No of deaths	Mortality ratio, left versus right (95% CI)
Breast cancer (174)	1.00 (0.98 to 1.03)	21 196	1.00 (0.97 to 1.03)	2714	1.00 (0.93 to 1.08)
Cardiovascular diseases:					
All (390-459, 785, and 798)	1.04 (1.00 to 1.09)*	5 739	1.01 (0.96 to 1.07)	3426	1.10 (1.03 to 1.18)†
Ischaemic heart disease (410-414)	1.06 (1.00 to 1.12)‡	3 078	1.02 (0.95 to 1.10)	1613	1.13 (1.03 to 1.25)§
Other cardiovascular diseases	1.03 (0.97 to 1.09)	2 661	1.00 (0.93 to 1.08)	1813	1.08 (0.98 to 1.18)
Remaining causes	0.97 (0.93 to 1.02)	4 446	0.96 (0.90 to 1.01)	2602	1.00 (0.92 to 1.07)

ICD-9=International classification of diseases, ninth revision.
*P=0.04
†P=0.004
‡P=0.05
§P=0.01