Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis

Iqbal Malik, John Danesh, Peter Whincup, Vinay Bhatia, Olia Papacosta, Mary Walker, Lucy Lennon, Andrew Thomson, Dorian Haskard

Summary

Background Previous studies have suggested that circulating concentrations of soluble adhesion molecules are useful predictors of risk of coronary heart disease (CHD). Larger studies are needed, however, to test this hypothesis.

Methods We measured serum concentrations of four soluble cell adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], E-selectin, and P-selectin) in the stored baseline serum samples of 643 men with coronary heart disease and 1278 controls nested in a prospective sutdy of 5661 men who were monitored for 16 years. We also did a meta-analysis of previous relevant studies to place our findings in context.

Results Concentrations of soluble adhesion molecules were significantly associated with one another, with other markers of inflammation, and with some classic coronary risk factors. For ICAM-1, the odds ratio for CHD was 1·68 (95% CI 1·32–2·14) in a comparison of men in the top third with those in the bottom third of baseline measurements after adjustments for age and town. This decreased to 1·11 (0·75–1·64) after adjustment for some classic coronary risk factors and indicators of socioeconomic status. For the three other cell adhesion molecules, the odds ratios for CHD, first adjusted for age and town only, and then additionally adjusted for other risk factors, were: VCAM-1: 1·26 (0·99–1·61) and 0·96 (0·66–1·40); E-selectin: 1·27 (1·00–1·61) and 1·13 (0·78–1·62); and P-selectin: 1·23 (0·96–1·56) and 1·20 (0·81–1·76).

Interpretation The measurement of these adhesion molecules is unlikely to add much predictive information to that provided by more established risk factors.

Lancet 2001; **358:** 971–75
See Commentary page 946

BHF Cardiovascular Medicine Unit, National Heart and Lung Institute, Imperial College School of Medicine, Hammersmith Hospital, London W12 0NN, UK (I Malik MRCP, V Bhatia MRCP, Prof D Haskard FRCP); **Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge** (Prof J Danesh DPhil); **Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE** (Prof P Whincup FRCP); **and Department of Primary Care and Population Sciences, Royal Free and University College London Medical School** (O Papacosta MSc, M Walker MA, L Lennon BA, A Thomson BSc)

Correspondence to: Prof Dorian Haskard (e-mail: d.haskard@ic.ac.uk)

Introduction

Atherosclerosis may, in part, be an inflammatory disease.[1] This suggestion is supported by the presence of mononuclear cells in arterial lesions and by the ability of various blood markers related to inflammation to predict major coronary events.[1-3] Previous meta-analyses of long-term prospective studies have reported that the risk of coronary heart disease (CHD) is about 40% (95% CI 30–50%) greater in people with raised total blood leucocyte counts, and about 90% (50–130%) greater in those with raised circulating concentrations of C-reactive protein (a sensitive acute-phase reactant), in comparisons between people in the top third of these factors and those in the bottom third of baseline measurements.[2,3]

Adhesion molecules facilitate the recruitment of circulating leucocytes to sites of inflammation.[4] Transient rolling of leucocytes along endothelium is mediated by selectins, including E-selectin and P-selectin.[5] Stronger attachment of white cells to endothelium is mediated by intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1).[4] These cell adhesion molecules are detected more commonly in human atherosclerotic lesions than in healthy arterial tissue.[6,7] Moreover, knock-out mice deficient in E-selectin, P-selectin, or ICAM-1 develop fewer arterial lesions than normal mice.[8-11] Although increased cell surface expression of these molecules is difficult to quantify in vivo, soluble forms can now be measured in serum.[12] Preliminary studies have reported strong associations between concentrations of particular soluble adhesion molecules and CHD.[13,14] For example, one study of about 200 cases reported that CHD risk is five times greater in people with raised values of soluble ICAM-1, and two times greater in those with raised E-selectin.[13]

We report a prospective study with a larger number of CHD cases and more extended follow-up than previous studies of this topic, and have done a meta-analysis to place our results in context. Whereas most previous epidemiological studies have measured only one or two soluble adhesion molecules, we have measured serum concentrations of four cell adhesion molecules: ICAM-1, VCAM-1, E-selectin, and P-selectin. To investigate to what extent various soluble adhesion molecules are related to one another and to processes known, or suspected, to be relevant to CHD, we examined inter-relations of adhesion molecules with one another as well as with smoking habits, blood pressure, circulating markers of lipid metabolism, low-grade systemic inflammation, persistent infection, haemostasis and thrombosis, and indicators of socioeconomic status.

Methods

Study participants

To establish the British Regional Heart Study, 7735 men aged 40–59 years (response rate 78%) were randomly selected from general practice registers in each of 24 British towns between 1978 and 1980.[15] Nurses administered questionnaires, took physical measurements, recorded an electrocardiogram, and, in 5661 men from 18

of the towns, collected non-fasting venous blood samples (which were centrifuged and then stored as aliquots of serum at –20°C).[15] Additional questionnaires on car ownership and childhood social circumstances (father's social class and childhood household amenities) were mailed 5 years (98% response among survivors) and 12 years (90% response among survivors) after entry, respectively.[16] All men have been monitored subsequently for all-cause mortality and for cardiovascular morbidity, with a follow up loss of less than 1% to date.

The 643 cases eligible for the present study were diagnosed with major CHD events (279 died from CHD and 364 had non-fatal myocardial infarction) before December, 1995, and comprise cases reported in two previous analyses of this cohort.[17,18] Men who had died from CHD were ascertained through National Health Service Central Registers on the basis of a death certificate with ICD-9 codes 410–414. The diagnosis of non-fatal myocardial infarction was based on reports from general practitioners, supplemented by regular reviews of general practice records, and diagnosed in accordance with WHO criteria.[18] Cases were frequency matched on town of residence and age in 5-year bands with controls who were randomly selected from among men surviving to the end of the study period free from incident CHD.

Laboratory analysis

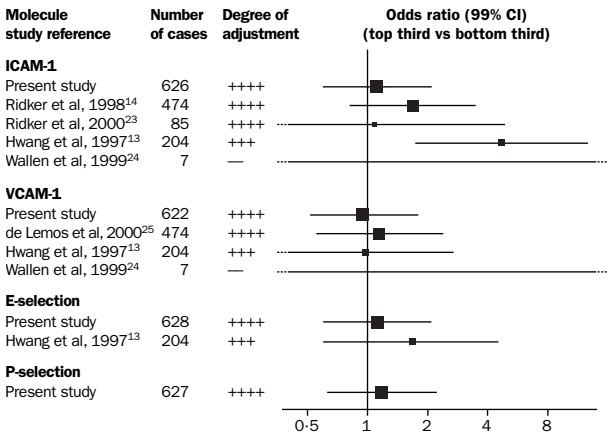
Two investigators (IM and VB), masked to the case-control status of participants, measured serum concentrations of ICAM-1, VCAM-1, E-selectin, and P-selectin with commercial enzyme immunoassays (R & D Systems, Abingdon, UK), with intra-assay and inter-assay coefficients for each factor of about 5% and about 10%, respectively. Assays for all four factors were done concurrently to minimise any effects of repeated freeze-thaw cycles. Immunoassays were also used to measure serum concentrations of C-reactive protein, amyloid A protein, fibrin D-dimer, and von Willebrand factor, as previously described.[3] Measurements were made of serum concentrations of IgG antibodies to *Helicobacter pylori* (Premier, Meridian Diagnostics, Cincinatti, Ohio, USA) and to *Chlamydia pneumoniae* (whole organism antigen, by means of time-resolved fluorimetry),[19] and of serum lipids, albumin, blood leucocyte count, homocysteine, glucose, insulin, and markers of renal function by means of standard assays.[15]

Statistical analysis

Case-control comparisons involved unmatched stratified logistic regression fitted by unconditional maximum likelihood (SAS version 6.12). Analyses for each adhesion molecule were pre-specified to be by thirds of the values in the controls. Adjusted analyses included, as explanatory variables: age; cigarette smoking habit (never, former, current); daily cigarette consumption; non-fasting blood concentrations of serum total cholesterol, HDL cholesterol, and triglyceride; current social class (by means of the Registrar General's 1980 classification and including a separate category for armed forces); housing tenure (owner, private rent, council rent); marital status; current car ownership; father's occupation (manual, non-manual), family car ownership; bathroom in house; hot water tap in house; and bedroom sharing. Various characteristics, including circulating markers of inflammation and infection, were investigated as correlates of adhesion molecules. Emphasis in these comparisons was given to results more extreme than 2·6 SD (p=0·01) to make some allowance for multiple comparisons. Skewed variables were log transformed to produce approximately symmetrical distributions. Comparisons of baseline characteristics of cases and controls involved standard χ^2 tests for discrete variables and Student's t-tests for continuous variables. Odds ratios are given with 95% CIs, and two sided probability (2p) values are used.

Systematic review

Prospective studies published before February 2001 with more than 1 year follow-up that reported on correlations between CHD and soluble values of ICAM-1, VCAM-1, E-selectin and P-selectin were sought by computer-assisted searches, scanning of relevant reference lists, hand searching of cardiology, haematology, and other relevant journals, and by correspondence with authors of such reports.[2] Searches used key words related to the disease (eg, coronary heart disease, myocardial infarction, atherosclerosis, vascular disease) and to each of the four soluble adhesion molecules. Studies were included that reported separate results for non-fatal myocardial infarction or CHD death (hence, one study of soluble E-selectin with 16 CHD cases and one study of P-selectin with 115 cases of stroke, coronary revascularisation, and CHD could not be included).[20,21] The following data were abstracted from published studies: location of study; size and type of cohort (ie, population based or selected on the basis of previous vascular disease); mean age and follow-up duration; assay methods; degree of adjustment for potential confounders (categorised as + for age and sex only; ++ for these plus smoking; +++ for these plus other standard vascular risk factors; ++++ for these plus markers of socioeconomic status [or for studies in socially homogenous populations]); cut-off values for comparisons of risk; and the relation between CHD risk and the baseline assay results. We compared cases directly only with controls within the same study to avoid potential biases. Combination of results involved inverse-variance-weighted averages of log odds ratios. In the figure, 99% CIs are used for the individual studies to make some allowance for the increased scope for random error in multiple comparisons. Heterogeneity was assessed by standard χ^2 tests.



Meta-analysis of prospective studies of soluble adhesion molecules and coronary heart disease risk

Odds ratios compare top and bottom thirds of baseline measurements. Black squares indicate the odds ratio in each study, with the square size proportional to the number of cases and the horizontal lines representing 99% CI. Degree of adjustment is denoted as: +, for age and sex only; ++, for these plus smoking; +++, for these plus some standard risk factors; ++++, for these plus markers of socioeconomic status.

Characteristic	Cases (n=643)	Controls (n=1278)	p
Questionnaire			
Age (years)	52·6 (5·3)	52·5 (5·3)	Matched
Current smoker	333 (52%)*	540 (42%)*	<0·0001
Evidence of coronary disease†	230 (36%)*	259 (20%)*	<0·0001
Diabetic	18 (3%)*	21 (2%)*	0·09
> 2 drinks alcohol/day	128 (20%)*	288 (23%*)	0·18
Non-manual occupation	196 (32%)*	481 (39%)*	0·003
Homeowner‡	344 (63%)*	823 (69%)*	0·02
Physical measurements			
Body mass index (kg/m^2)	26·0 (3·4)	25·4 (3·3)	0·0006
Systolic blood pressure (mm Hg)	152 (22)	147 (21)	<0·0001
Diastolic blood pressure (mm Hg)	86 (14)	83 (13)	<0·0001
FEV_1 (L/min)	308 (72)	323 (78)	<0·0001
Blood sample			
Total cholesterol (mmol/L)	6·62 (1·07)	6·19 (0·99)	<0·0001
HDL cholesterol (mmol/L)	1·09 (0·27)	1·16 (0·28)	<0·0001
Log_{10}triglyceride (mmol/L)	0·29 (0·23)	0·23 (0·24)	<0·0001

Data are mean (SD), unless otherwise indicated. *Data are numbers (%). †Evidence of ischaemia on baseline electrocardiogram or reported history of angina or myocardial infarction. ‡Information on home ownership was available for only 548 cases and 1200 controls.

Table 1: **Baseline characteristics of men with coronary heart disease and of age-matched and town-matched male controls**

Results

Measurements were available for: ICAM-1 (626 cases, 1253 controls), VCAM-1 (622 cases, 1249 controls), E-selectin (628 cases, 1253 controls), and P-selectin (627 cases, 1254 controls). The mean age at CHD event among cases was 62 years. There were significant differences between cases and controls with respect to established vascular risk factors, such as smoking, body-mass index, blood pressure, and blood lipids (table 1).

In control individuals without evidence of CHD at baseline, the correlation coefficients between circulating values of ICAM-1 and VCAM-1, E-selectin, and P-selectin were 0·23, 0·31, and 0·14 (p<0·0001 for each), respectively, and the correlation coefficients between VCAM-1 and E-selectin and P-selectin were 0·15 (p<0·0001) and −0·01 (p=0·73), respectively. The correlation coefficient between E-selectin and P-selectin was 0·19 (p<0·0001). Apart from the association between VCAM-1 and P-selectin, these associations remained significant after adjustment for age, town, smoking, body-mass index, and indicators of socioeconomic status (see webtables 1-4 on *The Lancet* website www.thelancet.co.uk).

There were highly significant associations between ICAM-1 and C-reactive protein, serum amyloid A protein, leucocyte count, von Willebrand factor, fibrin D-dimer, *C pneumoniae* IgG titres, low urea, and low forced expiratory volume (p<0·0001 for each) all of which remained largely unchanged after adjustments for age, town, smoking, and indicators of social class. There were also significant associations between ICAM-1 and age, cigarette smoking, low HDL cholesterol, and some markers of low socioeconomic status (p<0·01 for each: webtable 1). However, associations between ICAM-1 and creatinine, low albumin, and *H pylori* seropositivity weakened substantially after such adjustments. There were significant associations between VCAM-1 and von Willebrand factor (p<0·0001), which remained largely unchanged after adjustment for possible confounders. Such adjustment substantially weakened the association of VCAM-1 with fibrin D-dimer (webtable 2). Strong adjusted associations were seen between E-selectin and smoking, body-mass index, triglyceride, low urea, C-reactive protein, serum amyloid A protein (p<0·001 each: webtable 3) and between P-selectin and leucocyte count (p<0·001), fibrin D-dimer, and smoking (p<0·01: webtable 4). Possible associations of E-selectin were seen with diastolic blood pressure, urate, insulin, and von Willebrand factor, and similarly borderline associations

All cases and controls

Factor (tertile cut-offs ng/mL)	Cases			Control			Odds ratio (95% CI)			
	Top	Middle	Bottom	Top	Middle	Bottom	Age and town, only	Age, town, and smoking	Age, town, smoking, and risk factors*	Age, town, smoking, risk factors, and SES†
ICAM-1 (338 and 261)	274	185	167	418	418	417	1·68 (1·32–2·14)	1·52 (1·18–1·96)	1·49 (1·14–1·94)	1·11 (0·75–1·64)
VCAM-1 (516 and 37)	238	201	183	416	416	417	1·26 (0·99–1·61)	1·29 (1·01–1·64)	1·35 (1·05–1·75)	0·96 (0·66–1·40)
E-selectin (75 and 52)	244	190	194	418	418	417	1·27 (1·00–1·61)	1·23 (0·97–1·56)	1·08 (0·84–1·39)	1·13 (0·78–1·62)
P-selectin (150 and 95)	225	220	182	418	418	418	1·23 (0·96–1·56)	1·18 (0·93-1·51)	1·02 (0·79-1·32)	1·20 (0·81–1·76)

Participants without evidence of coronary heart disease at entry

Factor (tertile cut-offs, ng/mL)	Cases			Controls			Odds ratio (95% CI)			
	Top	Middle	Bottom	Top	Middle	Bottom	Age and town only	Age, town, and smoking	Age, town, smoking, and risk factors*	Age, town, smoking, risk factors, and SES†
ICAM-1 (338 and 261)	178	129	110	334	345	354	1·81 (1·35–2·41)	1·57 (1·16–2·12)	1·51 (1·10–2·08)	1·17 (0·74–1·84)
VCAM-1 (516 and 37)	141	141	132	344	346	339	1·01 (0·76–1·35)	1·04 (0·78–1·39)	1·09 (0·80–1·48)	0·89 (0·58–1·36)
E-selectin (75 and 52)	163	124	132	343	331	358	1·30 (0·99–1·72)	1·25 (0·95–1·66)	1·12 (0·83–1·51)	1·20 (0·80–1·82)
P-selectin (150 and 95)	151	147	121	328	350	355	1·35 (1·01–1·79)	1·30 (0·97–1·73)	1·09 (0·81–1·49)	1·20 (0·78–1·87)

*Risk factors were total cholesterol, HDL cholesterol, triglyceride, body-mass index, systolic and diastolic blood pressure. †SES=markers of socioeconomic status: occupation, housing tenure, marital status, car ownership; father's social class, family car ownership, bathroom in house, hot water tap in house, bedroom sharing.

Table 2: **Odds ratios of coronary heart disease in men who had values of the relevant cell adhesion molecule in the top third of the distribution of controls relative to those who had values in the bottom third of this distribution**

were seen between P-selectin and total cholesterol, triglyceride, and von Willebrand factor. So, although serum concentrations of P-selectin may have been overestimated by its release from platelets during clotting, any such effect did not obscure our ability to detect significant associations between P-selectin values and some markers of inflammation.

For ICAM-1, the age-adjusted and town-adusted odds ratio for CHD was 1·68 (95% CI 1·32–2·14) in men in the top third compared with those in the bottom third of baseline measurements (tertile cutoffs, >338 *vs* <261 ng/mL), which fell to 1·11 (0·75–1·64) after further adjustments for smoking, classical coronary risk factors, and indicators of socioeconomic status (table 2). Such comparisons for the other soluble adhesion molecules yielded the following odds ratios for CHD (reported first with adjustments for age and town only and then with adjustments for additional risk factors): VCAM-1 (>516 *vs* <371 ng/mL), 1·26 (0·99–1·61) and 0·96 (0·66-1·40); E-selectin (>75 *vs* <52 ng/mL), 1·27 (1·00-1·61) and 1·13 (0·78–1·62); and P-selectin (>150 *vs* <95 ng/mL): 1·23 (0·96–1·56) and 1·20 (0·81–1·76). Emphasis was placed on results that involved all cases and all controls since these findings were not materially different from analyses restricted to the 407 cases and 1010 controls with no evidence of CHD at baseline (table 2), or from analyses restricted to participants with complete information on childhood socioeconomic status. Varying the pre-specified cut-off levels for analysis of each adhesion molecule did not materially alter the odds ratios for CHD.

Discussion

The present long-term, community-based study assessed the predictive ability of baseline serum concentrations of four soluble adhesion molecules (ICAM-1, VCAM-1, E-selectin, and P-selectin) for fatal and non-fatal CHD. After making allowances for known risk factors, we found no strong associations of these adhesion molecules with CHD risk, and our findings have been reinforced by a meta-analysis of previously published prospective studies.

Our study adds considerable data to the available information on vascular risk factors and circulating values of adhesion molecules in people in the general population without CHD,[13,14,21–23] and it confirms that these factors are generally modestly associated with one another, the leucocyte count, and circulating concentrations of other acute-phase reactants such as C-reactive protein, serum amyloid A protein, and von Willebrand factor (which is also a marker of endothelial dysfunction and a haemostatic factor). These data support the view that soluble forms of adhesion molecules reflect inflammatory events, consistent with the regulation of their expression by pro-inflammatory cytokines.[4,5] Although these significant cross-sectional associations suggest that our assay methods were reasonably robust, serial measurements would be needed to quantify, and correct for, possible underestimation of associations due to fluctuations of soluble cell adhesion molecule values within individuals over time (ie, regression dilution) and any protein degradation with sample storage.[26]

Including the present study, we identified six relevant prospective studies of various soluble cell adhesion molecules and CHD. For ICAM-1, five studies included 1396 cases of non-fatal myocardial infarction or death from CHD; the weighted mean age at baseline was 55 years with a weighted mean follow-up of 11 years.[13,14,23,24] For VCAM-1, four studies included 1307 such cases, again with a weighted mean age at baseline of 55 years and a weighted mean follow-up of 11 years.[13,24,25] For E-selectin, two studies included a total of 832 major coronary events, with a weighted mean age at baseline of 54 years and a weighted mean follow-up of 13 years.[13] Only our study has reported on P-selectin values specifically in relation to CHD (although a previous study reported on results for a combination of cardiovascular endpoints, including stroke, coronary revascularisation procedures, and fatal and non-fatal CHD).[21] All published studies used commercial enzyme immunoassays, and all but one adjusted for smoking and some other classical coronary risk factors.

A combined analysis of the five studies on ICAM-1 yielded an odds ratio of 1·39 (1·11–1·73; figure) for CHD in those in the top third compared with those in the bottom third of baseline measurements. Most of the heterogeneity among these five studies was due to the report that generated the hypothesis (χ^2_4=10·4; p=0·04).[13] An analysis restricted to the four hypothesis-testing studies of ICAM-1 (1192 cases in total) yielded a non-significant odds ratio of 1·21 (0·95–1·55), and there was no significant heterogeneity among them (χ^2_3=3·0; p>0·1).[14,23,24] Hence, the present study, in the context of a meta-analysis of other hypothesis-testing studies, suggests that the original report of a 5-fold odds ratio for CHD in people with raised ICAM-1 was exaggerated by chance and selective reporting.[13] For E-selectin, there was no evidence of heterogeneity between the two available studies (χ^2_1=0·8; p>0·1), and a combined analysis yielded an odds ratio of 1·16 (0·87-1·55). Again, this finding argues against the hypothesis-generating suggestion of an odds ratio of about 2 for CHD in people with raised E-selectin.[13] For VCAM-1, there was no significant heterogeneity among the four studies (χ^2_3=0·4; p>0·1), and a combined analysis of them yielded an odds ratio of 1·02 (0·81–1·29) for CHD in those in the top third compared with those in the bottom third of baseline measurements. For P-selectin we found an odds ratio of 1·18 (0·63–2·21) for CHD, by contrast with a previous study of five times fewer cases that reported an odds ratio of about 2 for occurrence of a combination of stroke and various coronary events.[21] The present evidence, therefore, argues against strong associations between any of these adhesion molecules and CHD, but further data are needed to confirm or refute any modest effects. These data have not directly addressed the separate issue of adhesion molecules in acute coronary syndromes.[27–32]

Contributors

The study was designed and done by the British Regional Heart Study research group. All investigators contributed to analysis and interpretation of data and to writing the report.

Acknowledgments

A G Shaper established the British Regional Heart Study. G D O Lowe, A Rumley, K Craig, F Key, and L Oxford provided von Willebrand factor and fibrin D-dimer assays; M B Pepys and J R Gallimore provided C-reactive protein and serum amyloid A assays; H Refsum and P Ueland provided homocysteine assays; M Thomas, Yuk-ki Wong, and M Ward provided *C pneumoniae* serology; J Atherton and C Hawkey provided *H pylori* serology; and J John provided valuable assistance.

This study was supported by a British Heart Foundation project grant. The British Regional Heart Study is a British Heart Foundation research group and also receives support from the Department of Health. IM and VB are supported by British Heart Foundation Junior Research Fellowships. DH is supported by a professorial award from the British Heart Foundation. JD was supported by a Merton College fellowship, the Frohlich Trust, and the Raymond and Beverly Sackler Research Award in the Medical Sciences.

References

1 Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999; **340:** 115–26.

2 Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen,

C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998; **279:** 1477–82.
3 Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; **321:** 199–204.
4 Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 1994; **76:** 301–14.
5 Tedder TF, Steeber DA, Chen A, Engel P. The selectins: vascular adhesion molecules. *FASEB J* 1995; **9:** 866–73.
6 Poston RN, Haskard DO, Coucher JR, Gall NP, Tidey RR. Expression of the adhesion molecule ICAM-1 in atherosclerotic plaques: implications for positive-feedback monocyte recruitment in the pathogenesis of the plaque. *Am J Pathol* 1992; **140:** 665–73.
7 Davies MJ, Gordon JL, Gearing AJ, et al. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. *J Pathol* 1993; **171:** 223–29.
8 Johnson RC, Chapman SM, Dong ZM, et al. Absence of P-selectin delays fatty streak formation in mice. *J Clin Invest* 1997; **99:** 1037–43.
9 Nageh MF, Sandberg ET, Marotti KR, et al. Deficiency of inflammatory cell adhesion molecules protects against atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 1997; **17:** 1517–20.
10 Dong ZM, Chapman SM, Brown AA, et al. The combined role of P-and E-selectins in atherosclerosis. *J Clin Invest* 1998; **102:** 145–52.
11 Collins RG, Velji R, Guevara NV, et al. P-Selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *J Exp Med* 2000; **191:** 189–94.
12 Gearing AJ, Newman W. Circulating adhesion molecules in disease. *Immunol Today* 1993; **14:** 506–12.
13 Hwang SJ, Ballantyne CM, Sharrett AR, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. *Circulation* 1997; **96:** 4219–25.
14 Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998; **351:** 88–92.
15 Shaper AG, Pocock SJ, Walker M, et al. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *BMJ* 1981; **283:** 179–86.
16 Walker M, Shaper A G, Lennon L, Whincup P H. Twenty years of follow-up of a cohort based in general practice in 24 British towns. *J Public Health Med* 2000; **22:** 479–85.
17 Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between Helicobacter pylori infection, coronary heart disease, and stroke in middle aged men. *Heart* 1996; **75:** 568–72.
18 Whincup P, Danesh J, Walker M, et al. Prospective study of potentially virulent strains of *Helicobacter pylori* and coronary heart disease in middle-aged men. *Circulation* 2000; **101:** 1647–52.
19 Danesh J, Whincup P, Walker M, et al. Chlamydia pneumoniae IgG titres and coronary heart disease: prospective study and meta-analysis. *BMJ* 2000; **321:** 208–13.
20 Blann AD, Miller JP, McCollum CN. von Willebrand factor and soluble E-selectin in the prediction of cardiovascular disease progression in hyperlipidaemia. *Atherosclerosis* 1997; **132:** 151–56.
21 Ridker PM, Buring JE, Rifai N. Soluble P-Selectin and the risk of future cardiovascular events. *Circulation* 2001; **103:** 491–95.
22 Rohde LE, Hennekens CH, Ridker PM. Cross-sectional study of soluble intercellular adhesion molecule-1 and cardiovascular risk factors in apparently healthy men. *Arterioscler Thromb Vasc Biol* 1999; **19:** 1595 –99.
23 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342:** 836–43.
24 Wallen NH, Held C, Rehnqvist N, Hjemdahl P. Elevated serum intercellular adhesion molecule-1 and vascular adhesion molecule-1 among patients with stable angina pectoris who suffer cardiovascular death or non-fatal myocardial infarction. *Eur Heart J* 1999; **20:** 1039–43.
25 de Lemos J, Hennekens CH, Ridker PM. Plasma concentration of soluble vascular cell adhesion molecule-1 and subsequent cardiovascular risk. *J Am Coll Cardiol* 2000; **36:** 423–26.
26 Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; **150:** 341–53.
27 Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 1994; **331:** 417–24.
28 Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997; **349:** 462–66.
29 Rebuzzi AG, Quaranta G, Liuzzo G, et al. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. *Am J Cardiol* 1998; **82:** 715–19.
30 Ghaisas NK, Shahi CN, Foley B, et al. Elevated levels of circulating soluble adhesion molecules in peripheral blood of patients with unstable angina. Am J Cardiol. 1997; **80:** 617–19.
31 Kaikita K, Ogawa H, Yasue H, et al. Increased plasma soluble intercellular adhesion molecule-1 levels in patients with acute myocardial infarction. *Jpn Circ J* 1997; **61:** 741–48.
32 Shyu KG, Chang H, Lin CC, Kuan P. Circulating intercellular adhesion molecule-1 and E-selectin in patients with acute coronary syndrome. *Chest* 1996; **109:** 1627–30.

For further information see www.thelancet.com

Early report

Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial

*Andrew Robinson, David G Thompson, David Wilkin, Chris Roberts, for the Northwest Gastrointestinal Research Group**

Summary

Background Ulcerative colitis is managed mainly in secondary care by regular outpatient reviews done by specialist clinicians. Alternatives would be to discharge patients to primary care or to provide open-access clinics, but neither of these options reduce patients' dependency on doctors or allow patients' involvement in disease management. We did a randomised controlled trial to assess an alternative to traditional outpatient care.

Methods We randomly assigned 203 patients with ulcerative colitis who were undergoing hospital follow-up to receive patient-centred self-management training and follow-up on request (intervention group), or normal treatment and follow-up (control group). The main outcome was the interval between relapse and treatment, and secondary outcomes were rates of primary and secondary care consultation, quality of life, and acceptability to patients. Analysis was by intention to treat.

Findings Intervention patients had relapses treated within a mean of 14·8 h (SD 19·1) compared with 49·6 h (65·1) in controls (difference 34·8 h [95% CI 16·4–60·2]). Furthermore, intervention patients compared with controls made significantly fewer visits to hospital (0·9 *vs* 2·9 per patient per year, difference 2·0 [1·6–2·7]) and to the primary-care physician (0·3 *vs* 0·9 per patient per year, difference 0·6 [0·2–1·1], p<0·006). Only two patients in the intervention group preferred traditional management. Health-related quality-of-life scores were unchanged in both groups.

Interpretation Self-management of ulcerative colitis accelerates treatment provision and reduces doctor visits, and does not increase morbidity. This approach could be used in long-term management of many other chronic diseases to improve health-service provision and use, and to reduce costs.

Lancet 2001; **358:** 976–81

*Members listed at end of paper

Section of Gastrointestinal Science, University of Manchester, Clinical Sciences Building, Hope Hospital, Salford M6 8HD, UK (A Robinson MRCP, Prof D G Thompson MD); **and National Primary Care Research and Development Centre, University of Manchester, Manchester, UK** (Prof D Wilkin PhD, C Roberts PhD)

Correspondence to: Dr Andrew Robinson (e-mail: arobinson@fs1.ho.man.ac.uk)

Introduction

Ulcerative colitis is a chronic inflammatory disorder that affects more than 100 000 people in Britain.[1] Symptoms are usually intermittent, and are characterised by episodes of diarrhoea and rectal bleeding punctuated by periods of relative quiescence. A few patients require surgery and are thereby cured, but most are adequately managed with medical therapy. Regular outpatient follow-up by specialist clinicians in secondary care is the normal strategy for management of chronic diseases such as this one. Every year in England, more than 15 million outpatient follow-up consultations are made by patients who have attended clinics for longer than 6 months.[2] Most gastroenterologists follow up their colitic patients indefinitely in outpatient clinics.[3] Hospital doctors' reasons for long-term follow-up include: a perceived need for review of symptoms, medication, and blood tests; unwillingness to discharge to primary-care management; and a belief that patients expect hospital treatment.[4]

In addition to the cost of such an approach to health care, several other factors indicate that this might not be the most appropriate method of management: because chronic diseases such as ulcerative colitis, asthma, Parkinson's disease, and arthritis frequently run a relapsing or remitting course, prearranged clinic visits are unlikely to correspond with disease activity; access to clinicians when symptoms are exacerbated normally depends on clinic availability, which often results in delayed initiation of treatment; non-attendance rates are notoriously high in this group of patients (19% in study hospitals); and duplication of clinical activity in primary and secondary care is common.[5]

Until recently, the debate about reduction of long-term hospital follow-up has concentrated on discharge from hospital and transfer of follow-up to primary care as the main alternative.[6–8] Up to 48% of patients receiving long-term hospital follow-up could be discharged to their family practioners.[4] However, most primary-care physicians see few patients with uncommon chronic diseases such as ulcerative colitis (average of 3–4 per 2000 patients), and most are unwilling to take sole responsibility for managing them.[9] Open access to hospital clinics is preferred by patients and family practitioners, and can reduce routine hospital visits.[10] However, patients still need to see a doctor before treatment of relapse can begin, which inevitably delays onset of therapy.

Patients' participation in treatment of diabetes mellitus results in better metabolic control,[11–13] and reduces morbidity in asthmatic patients.[14–16] We have designed a patient-centred alternative to conventional management for patients with ulcerative colitis. We have produced personalised self-management plans that enable patients to monitor and treat their symptoms, and to refer themselves to hospital when they need additional advice or treatment outside agreed guidelines for care. Such an approach is consistent with the need for health services to provide