CARDIOVASCULAR MEDICINE

Established and emerging coronary risk factors in patients with heterozygous familial hypercholesterolaemia

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Objectives: To assess the clinical and biochemical factors associated with inter-individual variation in susceptibility to coronary artery disease (CAD) in treated heterozygous familial hypercholesterolaemia.
Design: A cross sectional study was conducted of 410 patients recruited from six lipid clinics in the UK.
Results: CAD was documented in 104 of the 211 men and in 55 of the 199 women with mean ages of onset of 43.1 and 46.5 years, respectively. CAD was significantly more common in men (49% *v* 28%, $p < 0.001$) and in patients who had smoked cigarettes versus patients who had never smoked (51% *v* 28%, $p < 0.001$). After adjusting for age, sex, and current smoking status, there were no significant differences between patients with or without CAD in lipoprotein(a), homocysteine, fibrinogen, plasminogen activator inhibitor-1, white blood cell count, body mass index, glucose, triglyceride or total cholesterol. However, high density lipoprotein (HDL) cholesterol concentrations were significantly lower in those with CAD (6%, 95% confidence interval (CI) 1% to 11%, $p = 0.03$) and this difference was greater in women than men (12% *v* 2%, $p = 0.041$).
Conclusions: These results indicate that emerging coronary risk factors appear not to be associated with CAD in adults with treated familial hypercholesterolaemia, but the strong association with smoking suggests that patients should be identified early in childhood and discouraged from ever starting to smoke.

Familial hypercholesterolaemia is an autosomal co-dominant disorder with an estimated frequency of 1 in 500 of the population. Most cases are caused by one of more than 700 different mutations of the low density lipoprotein (LDL) receptor[1] resulting in an accumulation of LDL cholesterol in the plasma from birth[2] and subsequent development of tendon xanthoma, xanthelasma, and atheroma.[2–4] In the heterozygous condition the cumulative risk of a coronary event by the age of 60 years without effective treatment is at least 50% in men and about 30% in women,[5 6] with coronary disease occurring earlier in men than women,[3–7] and a notable increase occurring in women post-menopausally.[4 5] The relative risk of a fatal coronary event is increased nearly 100-fold in young adults aged 20–39 years, although patients who survive through middle age appear no longer to be at substantially increased relative risk.[3] The factors influencing differences in susceptibility to coronary disease remain unclear.

Although there is a strong intra-family correlation with the age of coronary death in affected sibling pairs,[8] relatives with identical LDL receptor mutations and similar LDL concentrations may have different outcomes.[9] This suggests that both environmental factors and other genetic polymorphisms influence the susceptibility to coronary disease and explain the wide variability in phenotypic expression. Some established coronary risk factors are recognised to be associated with an increased risk of CAD in familial hypercholesterolaemia, but few studies have assessed the role of novel risk markers,[10 11] usually termed emerging coronary risk factors. We therefore examined the association of both established and emerging coronary risk factors with documented CAD in a large cohort of patients with treated xanthomatous familial hypercholesterolaemia.

METHODS

A cross sectional comparison was undertaken of white patients aged 18 years or more with treated heterozygous familial hypercholesterolaemia with and without clinically documented CAD. Eligible patients had been registered from 1980 onwards with the Simon Broome Familial Hyperlipidaemia Register by one of six outpatient hospital lipid clinics. The diagnostic criteria for familial hypercholesterolaemia were defined as a total cholesterol concentration above 7.5 mmol/l (treated or untreated), or a LDL cholesterol above 4.9 mmol/l, together with the presence of tendon xanthomas either in the patient or in a parent, child, grandparent, sibling, uncle, or aunt.[3] The names of registered patients had been flagged by the National Health Service central registry and, in the event of death, a copy of the death certificate was provided. Eligible patients were alive on 31 December 1996 and not known to have emigrated. They were invited to participate in the study and were recruited over a period of 2.5 years.

The clinical case notes of all participants were scrutinised to confirm eligibility and to identify cases with documented CAD. Patients with known diabetes, renal, or thyroid disorders were excluded. Clinical CAD was defined as patients with a definite myocardial infarction (new Q waves and/or ST elevation and/or new T wave inversion persisting in more than two leads together with creatine kinase > 400 iu/l or other equivalent enzyme changes) or having undergone coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, having angina with an ischaemic resting ECG, or an abnormal angiogram. We excluded from the analyses patients with acute coronary insufficiency, asymptomatic patients with an ischaemic ECG, and those with a suspicious episode of acute chest pain or angina of effort diagnosed by a physician but with no significant ECG changes at rest or on exercise.

Participants remained on their usual drug treatment and attended the clinic after an overnight fast of at least 12 hours

Abbreviations: ACE, angiotensin converting enzyme; HDL, high density lipoprotein; LDL, low density lipoprotein; Lp, lipoprotein

duration. Written consent was obtained before measurement of blood pressure, height, and weight. Currently prescribed drug treatment, alcohol consumption, and smoking habit were documented (smoking was defined as having smoked at least one cigarette a day for at least one year), and a venous blood sample was taken. Additional clinical and demographic information was obtained from the registration form completed on enrolment to the Simon Broome Register.[3] The study received approval from the local ethics committee of each participating centre.

Biochemical measurements

Venous blood specimens were collected into EDTA, fluoride, and citrate vacutainers and, except for a sample collected into EDTA for haematological measurements, centrifuged immediately to separate plasma for the measurement of lipids, lipoproteins, apolipoproteins, and lipoprotein Lp(a) by the Department of Chemical Pathology, University College Hospital, London. Total plasma cholesterol concentration was measured in fresh EDTA plasma by an enzymatic colorimetric method (CHOD/PAP: cholesterol esterase, cholesterol oxidase, and 4-aminoantipyrine enzymatic method, using Roche FAS calibrators with a Roche Integra 700 analyser) (Roche Diagnostics, Welwyn Garden City, Herts, UK). HDL cholesterol was measured on a plasma sample after pre-treatment with polyanions and detergent that selectively solubilises HDL cholesterol followed by direct CHOD/PAP assay for cholesterol using Roche HDL-direct calibrators. LDL concentrations were estimated using the Friedewald formula.[12] Triglyceride was measured by an enzymatic colorimetric method (GPO-PAP glycerophosphate oxidase, peroxidase, amino antipyrene) (Roche Diagnostics) with no correction for free glycerol and using Roche FAS calibrators. Glucose was measured by the hexokinase/glucose 6 phosphate dehydrogenase method on a Roche Integra 700 analyser and using Roche FAS calibrators. Apolipoprotein A1, apolipoprotein B and Lp(a) were measured by immunoturbidimetry on a Cobas-Bioanalyser (Roche Diagnostics), with kits obtained from DiaSorin using SPQ SPQ II test systems calibrators (DiaSorin Ltd, Wokingham, Berks, UK). Since about 20% of the measurements for Lp(a) were beneath the detectable range of the assay, they were divided into two groups for statistical analyses using a pre-specified cut off concentration of 0.3 g/l.[13]

Plasma samples for all other measurements were stored at −85°C until analysed. Fibrinogen concentrations were measured turbidometrically using Roche PreciChrom I/II standards (Fibrinogen Kinetic, Roche Diagnostics). Plasminogen activator inhibitor-1 was measured by a chromogenic assay (Spectrolyse (PL) PAI-1; Biopool, Ventura, California, USA). EDTA plasma for homocysteine analysis was separated within 15 minutes and frozen at −85°C until transport and analysis by the department of chemical pathology, Bristol Royal Infirmary. Total homocysteine (the sum of reduced and oxidised forms of homocysteine) was measured following liberation of thiols by borohydride, derivatisation by bromobimane and analysis by gradient elution using reversed phase high performance liquid chromatography (HPLC) with a fluorimetric detector.[14] The Department of Haematology, University College Hospital, London, undertook the haematological measurements on whole blood collected into EDTA vacutainers with a GEN-S haematological analyser (Beckmann-Coulter UK, High Wycombe, UK).

Statistical analysis

The study was designed to have 90% power at a 5% level of significance to detect differences of at least 8% between patients with and without CAD for continuously distributed variables on the basis of their known standard deviations and an assumption that at least 150 patients with and 250 patients without coronary heart disease would be recruited. It had the power to detect smaller differences for analytes with the least inter-individual variability.

The distributions of age, sex, and smoking status for the patients with and without CAD were compared but were not available for body mass index for 97 patients without a recorded height. Linear regression models were used to assess the significance of differences in established and emerging risk factors between the patients with and without CAD. The analyses were adjusted for sex and age at time of follow up. As smoking status (current cigarette smoker, ex-smoker or never smoked) affects a number of biochemical variables, the analyses also adjusted for this. The distributions of the biochemical variables were mostly skewed to the right and logarithmic transformation reduced the skewness for all variables except diastolic blood pressure. The analyses were, therefore, conducted on the transformed data and for consistency we used the transformed data for all variables including diastolic blood pressure (no major differences occurred between the analyses using the untransformed and transformed data). The use of logarithms meant that differences were measured on a geometric scale; means were consequently calculated as geometric means, and parameters from the fitted models were expressed as ratios. To aid in the interpretation of the results, the mean values for the patients with and without CAD were predicted from the fitted models for a male patient aged 49 years who had never smoked. A ratio of 1.0, or equivalently 100%, therefore represents no difference between patients with and without CAD. A ratio of 1.08, for example, indicates that patients with CAD had on average 8% higher values.

As HDL has been found to be a stronger coronary risk factor in the general population for women than for men, we tested for interaction by examining whether or not any difference in HDL between patients with and without CAD was greater for women than for men. Similarly, we tested the associations with other biochemical variables for any sex interactions. As data on Lp(a) were categorised into two, these were analysed using logistic regression and were adjusted for sex, age, and current smoking status as for other biochemical variables.

RESULTS

Between 1 January 1980 and 31 December 1996 the six participating clinics registered 851 patients with the Simon Broome Register, but only 710 were eligible for inclusion after excluding 141 ineligible patients (three had emigrated, 61 died, and 77 were no longer attending clinics). A total of 458 (64.5%) patients participated in the study and 48 patients (10.5%) with possible CAD were subsequently excluded because the diagnoses failed to meet the pre-specified diagnostic criteria for CAD. Among the remaining 410 participants, two patients with data missing on smoking status were excluded from the subsequent analyses, and seven patients who exclusively smoked a pipe or cigars were categorised as never having smoked cigarettes. The clinical and demographic characteristics of the 252 eligible patients not recruited to the study did not differ significantly from the participants—136 (55.5%) male, 66/204 (33.0%) documented CAD, and 40/212 (19.3%) current smokers—although the variable denominators were caused by missing data.

Table 1 shows the clinical characteristics of the participants. CAD was documented in 49% (104/211) of men and 28% (55/199) of women (difference 22%, 95% confidence interval (CI) 13% to 31%). Patients with CAD at the time of the study were nearly 12 years older than those without disease. Nevertheless, the mean age at diagnosis of CAD in

Table 1 Characteristics of participants by CAD status and sex

Characteristic	CAD status	Males (n = 211)	Females (n = 199)
*Age at entry to study (years)	CAD	56.0 (10.2)	56.6 (10.4)
	No CAD	44.2 (12.5)	44.8 (14.4)
*Age at onset of CAD			
All patients	CAD	43.1 (9.8)	46.5 (11.9)
Never smoker	CAD	45.7 (9.9)	48.4 (10.6)
Ever smoker	CAD	41.5 (9.4)	45.2 (12.6)
Ever cigarette smoker (%)	CAD	64 (62.1%)	32 (58.2%)
	No CAD	38 (35.5%)	57 (39.6%)
Current cigarette smoker (%)	CAD	11 (10.7%)	7 (12.7%)
	No CAD	13 (12.1%)	25 (17.4%)
BMI (kg/m^2)*†	CAD	25.4 (3.2)	25.0 (4.1)
	No CAD	24.1 (4.2)	23.6 (4.1)
Statin therapy	CAD	102 (99.0%)	52 (94.5%)
	No CAD	99 (92.5%)	107 (74.3%)
Duration of statin therapy (years)‡	CAD	7.0 (5.2–8.3)	7.2 (5.2–8.6)
	No CAD	5.0 (2.0–6.7)	4.0 (1.8–6.4)
Anion exchange resins	CAD	33 (32.0%)	13 (23.6%)
	No CAD	24 (22.2%)	16 (11.1%
Fibrates	CAD	12 (11.7%)	3 (5.5%)
	No CAD	5 (4.6%)	12 (8.3%)
β Blockers	CAD	33 (34.7%)	20 (38.5%)
	No CAD	5 (4.8%)	5 (3.6%)
ACE inhibitors	CAD	15 (15.8%)	5 (10.2%)
	No CAD	3 (2.9%)	10 (7.1%)
Calcium antagonists	CAD	25 (26.3%)	17 (35.4%)
	No CAD	3 (2.9%)	3 (2.2%)
Antiplatelet therapy	CAD	83 (83.0%)	38 (73.1%)
	NO CAD	20 (19.0%)	15 (10.9%)
Anticoagulant therapy	CAD	6 (6.1%)	5 (9.8%)
	No CAD	0 (0%)	0 (0%)
Paternal myocardial infarct <50 years of age	CAD	13 (12.5%)	12 (21.8%)
	No CAD	17 (15.9%)	25 (17.4%)
Maternal myocardial infarct <55 years of age	CAD	7 (6.8%)	4 (7.3%)
	No CAD	3 (2.8%)	4 (2.8%)

*Data are expressed as mean (SD); †excludes 97 missing values; ‡data are expressed as median (IQR).

men was 43.1 years and in women 46.5 years, which was similar to the age of patients without CAD at time of study. The age at diagnosis of CAD was earlier in men and among patients who smoked. After adjusting for sex, the age at diagnosis was significantly earlier in patients who smoked compared with those who had never smoked (3.8 years, 95% CI 0.48 to 7.2 years, p = 0.025), and this difference did not differ significantly between men and women. As shown in table 2, smoking was significantly associated with CAD (odds ratio (OR) 2.5). Table 1 also shows that cardioprotective drug treatment had been prescribed significantly more often to patients with CAD; β blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, or a combination of these drugs had been prescribed for 83 patients with CAD and 25 without CAD (52% *v* 10%, difference 42%; 95% CI 34% to 51%) and a higher proportion with CAD had also been prescribed antiplatelet or anticoagulant treatment. Similarly, a higher proportion of patients with CAD than those without had been prescribed two or more lipid lowering drugs, 35% (56/159) *v* 16% (40/251), difference 19%, 95% CI 11% to 28%.

Table 3 presents the geometric means of biochemical and haematological measurements by CAD status and sex. The mean total cholesterol concentration before diet or drug treatment, which was available for 295 patients, was 10.3 mmol/l (IQR 8.7–11.6). On treatment the mean total cholesterol for all patients was 6.6 mmol/l (IQR 5.8–7.5) and was lower in patients with CAD than patients without CAD (6.4 *v* 6.9 mmol/l). Univariate analysis showed significant but small differences in LDL cholesterol, blood pressure, and several biochemical variables between patients with CAD and patients without CAD, but these were largely accounted for by differences in age. After adjustment for age, sex, and smoking, the only difference to remain significant was HDL cholesterol concentration. Patients with CAD had, on average, 6% lower HDL concentrations than those without (1.28 *v* 1.36 mmol/l at 49 years of age). This reduction was significantly greater in females than males (12% and 2%,

Table 2 Proportion of patients with and without coronary heart disease who had ever or never smoked, and odds ratio of CAD

	CAD n = 158	No CAD n = 250	Odds ratio	95% CI	p Value
Male					
Never smoked	38% (39/103)	64% (68/106)	1		
Ever smoker	62% (64/103)	36% (38/106)	2.94	1.67 to 5.15	<0.001
Female					
Never smoked	42% (23/55)	60% (87/144)	1		
Ever smoker	58% (32/55)	40% (57/144)	2.12	1.13 to 3.99	0.02
Males and females					
Never smoked	39% (62/158)	62% (155/250)	1		
Ever smoked	61% (96/158)	38% (95/250)	2.53	1.67 to 3.83	<0.001

Table 3 Geometric means and the IQR for biochemical and physiological variables by CAD status in males and females separately and together; the ratios of the means in patients with CAD relative to those without CAD; the values predicted from the fitted regression models for patients with and without CAD; and the corresponding adjusted ratios with their 95% CI.

		Geometric mean (IQR)		Males and females			*Adjusted		
Risk factor (number missing)	CAD status	Males	Females	Geometric mean	Ratio	†p Value	‡Adjusted mean	Ratio (95% CI)	†p Value
Total cholesterol (mmol/l)	CAD	6.21 (5.4–7.2)	6.72 (5.9–7.4)	6.38	0.93	<0.001	6.29	0.97 (0.93–1.02)	0.22
	No CAD	6.54 (6.0–7.2)	7.14 (6.2–8.2)	6.88			6.47		
LDL (mmol/l)	CAD	4.14 (3.5–5.0)	4.45 (3.7–5.3)	4.24	0.90	<0.001	4.26	0.95 (0.90 to 1.02)	0.14
	No CAD	4.58 (4.0–5.3)	4.92 (4.0–5.9)	4.77			4.46		
HDL (mmol/l)	CAD	1.24 (1.1–1.5)	1.37 (1.2–1.6)	1.28	0.92	0.004	1.21	0.94 (0.89 to 0.99)	0.03
	No CAD	1.23 (1.1–1.4)	1.51 (1.3–1.8)	1.39			1.29		
Triglycerides (mmol/l)	CAD	1.44 (1.1–1.9)	1.45 (1.1–2.1)	1.44	1.16	0.001	1.33	1.08 (0.97 to 1.19)	0.16
	No CAD	1.27 (0.9–1.6)	1.22 (0.9–1.7)	1.24			1.24		
Apolipoprotein A 1 (g/l)	CAD	1.34 (1.2–1.6)	1.43 (1.2–1.7)	1.37	1.00	0.88	1.33	1.01 (0.96 to 1.06)	0.74
	No CAD	1.27 (1.1–1.4)	1.45 (1.3–1.7)	1.37			1.32		
Apolipoprotein B (g/l)	CAD	1.17 (1.0–1.4)	1.33 (1.1–1.6)	1.22	0.94	0.08	1.21	1.01 (0.94 to 1.09)	0.76
	No CAD	1.23 (1.1–1.5)	1.34 (1.1–1.6)	1.29			1.20		
Systolic blood pressure (mm Hg)[10]	CAD	128.3 (117–140)	135.5 (120–158)	130.7	1.05	<0.001	126.3	1.00 (0.97 to 1.03)	0.80
	No CAD	125.4 (118–135)	123.4 (110–135)	124.3			125.8		
Diastolic blood pressure (mm Hg)[10]	CAD	78.3 (70–89)	79.0 (70–89)	78.6	1.02	0.12	76.3	0.99 (0.95 to 1.02)	0.37
	No CAD	77.4 (70–80)	76.4 (70–84)	76.8			77.4		
Homocysteine (μmol/l)	CAD	11.40 (9.5–13.2)	11.84 (9.8–14.5)	11.55	1.09	0.006	11.05	1.03 (0.96 to 1.10)	0.47
	No CAD	11.01 (8.9–12.4)	10.32 (8.5–12.3)	10.60			10.77		
Fibrinogen (g/l)	CAD	3.04 (2.4–3.8)	3.18 (2.7–3.7)	3.09	1.11	0.001	2.81	1.03 (0.97 to 1.10)	0.34
	No CAD	2.64 (2.2–3.1)	2.88 (2.3–3.5)	2.78			2.72		
Plasminogen activator inhibitor-1 (IU/ml)	CAD	10.50 (6.8–18.8)	9.75 (4.9–17.2)	10.2	1.22	0.01	9.83	1.03 (0.87 to 1.22)	0.73
	No CAD	9.83 (6.2–18.9)	7.49 (4.1–12.8)	8.4			9.54		
White blood cells (number/nl)[1]	CAD	6.16 (5.4–7.2)	6.54 (5.3–8.0)	6.29	1.05	0.10	5.85	1.05 (0.99 to 1.11)	0.13
	No CAD	5.85 (5.0–6.8)	6.14 (5.1–7.5)	6.02			5.60		
Haematocrit[1]	CAD	0.44 (0.42–0.46)	0.40 (0.39–0.42)	0.43	1.02	0.07	0.44	0.99 (0.98 to 1.01)	0.35
	No CAD	0.44 (0.43–0.46)	0.40 (0.39–0.42)	0.42			0.44		
Glucose (mmol/l)	CAD	5.12 (4.7–5.5)	4.97 (4.6–5.4)	5.07	1.05	<0.001	5.00	1.00 (0.98 to 1.03)	0.87
	No CAD	5.00 (4.7–5.3)	4.71 (4.3–5.1)	4.83			4.99		

*Adjusted for sex, age and smoking status (never smoked, ex-smoker or current smoker); †p values are given for the tests of differences between both the unadjusted and adjusted means; ‡means estimated from the fitted models for male patients, who have never smoked at 49 years of age.

respectively, p = 0.041). Tests for interaction for other variables produced one more significant finding; systolic blood pressure was 4% higher for women with CAD but 5% lower for men with CAD (p = 0.013).

Table 4 shows that the proportion of patients with Lp(a) concentrations > 0.3 g/l was significantly higher among current smokers than never smokers (OR 1.9, 95% CI 1.03 to 3.50), and among patients with CAD compared to those without (OR 1.54, 95% CI 1.03 to 2.32), although this was no longer significant after adjusting for age, sex, and smoking status.

DISCUSSION

Main results

The results of the study unequivocally confirm the association of the established risk factors age, sex, and cigarette smoking with CAD in patients with treated familial hypercholesterolaemia. There was a 2.5-fold increased odds ratio of ever smoking among patients with CAD compared to those without documented disease. Furthermore, the mean age of onset of CAD was about four years earlier in men and women who had ever smoked. There was, however, no evidence of an association with the more recently suggested coronary risk factors: homocysteine, Lp(a), fibrinogen, haematocrit, plasminogen activator inhibitor-1 or white cell count, although prospective studies in the general population have shown associations with CAD in individuals with no more than average LDL cholesterol concentrations.

Strengths and limitations

The study was a large, statistically powerful, cross sectional comparison of patients with and without clinically documented CAD using pre-specified, rigorously defined, diagnostic criteria, and the results provide a more precise estimate of the effect size of emerging coronary risk factors than previously available. The findings are unlikely to be confounded by the inclusion of patients with polygenic hypercholesterolaemia since the diagnostic criteria used for

Table 4 Proportion of patients with Lp(a) ⩾ 0.3 g/l by CAD, sex, and smoking status

			Univariate			*Full model		
Factor	Total	% with Lp(a) ⩾0.3 g/l (n)	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
No CAD	249	48% (122)	1					
CAD	158	59% (92)	1.54	1.03 to 2.32	0.035	1.45	0.91 to 2.31	0.11
Females	198	53% (104)	1					
Males	207	52% (108)	0.99	0.67 to 1.46	0.99	0.91	0.61 to 1.37	0.65
Never smoked	204	47% (96)	1		0.066	1		0.11
Ex-smoker	147	56% (82)	1.41	0.92 to 2.17		1.24	0.79 to 1.99	
Current smoker	54	63% (34)	1.91	1.03 to 3.54		1.92	1.03 to 3.50	

*The model consists of terms for CHD, sex, smoking status, and age.

familial hypercholesterolaemia have been shown to have a high specificity.[15]

Some care is needed in interpreting the results as there are a number of limitations to the study. The cohort of patients from whom participants were recruited comprised patients referred to specialist lipid clinics and so was not entirely representative, although in practice it probably included most patients with diagnosed familial hypercholesterolaemia living in the areas served by the participating clinics.[16] The observation that patients with CAD were nearly 12 years older than those without suggests that we may have underestimated the impact of some risk factors since more susceptible individuals may have died of coronary disease beforehand. The dependence on the clinical documentation of CAD means that some apparently unaffected individuals with undiagnosed disease will have been misclassified, which again will result in an underestimate of effect size. Importantly, patients had to remain on prescribed drug treatment for ethical reasons and inferences for untreated patients should be made with caution. Treatment effects will have confounded some comparisons—for example, differences in systolic and diastolic blood pressure between patients with and without CAD could not be assessed accurately because 42% more patients with CAD had been prescribed either a β blocker, ACE inhibitor, or calcium antagonist. Nevertheless, among patients with CAD, we observed a significantly higher mean systolic blood pressure in women than men, which raises the possibility that women may have been treated less intensively.

Established coronary risk factors

Our results are consistent with accumulating evidence from a number of much smaller cross sectional[10 17] and case control[11] studies that have assessed the role of established and emerging coronary risk factors in adults with familial hypercholesterolaemia. These have confirmed earlier reports of the importance of the established risk factors: age,[6 7 18 19] sex,[6 7 18 19] cigarette smoking,[3 18 19] hypertension,[18 19] and diabetes.[19 20] However, as the prevalence of known diabetes is lower than in the general population,[4] we excluded these patients, and found fasting plasma glucose concentrations not to be associated with CAD. Studies conducted before effective lipid lowering drug treatment became available demonstrated that low concentrations of HDL were associated with CAD[7 18 21] and this was recently confirmed by a cross sectional study[17] and a case–control study in a molecularly defined group of patients,[22] both conducted after lipid lowering drug treatment had been withdrawn. We found HDL concentrations to be significantly lower among CAD cases after adjusting for age, sex, and smoking, and this effect was more notable in women than men. Similar findings were reported by the Utah MEDPED registry study, which assessed the role of both established and emerging coronary risk factors in a cross sectional study of 262 patients.[10]

Emerging coronary risk factors

There was no evidence from our study to suggest that emerging coronary risk factors are associated with CAD in patients with familial hypercholesterolaemia. However, in the general population prospective studies demonstrate a clear association of Lp(a) concentrations with coronary disease. Individuals in the top third of the baseline measurements compared with those in the bottom third have an increased risk ratio of 1.7.[23] Higher concentrations are also recognised to occur in patients with familial hypercholesterolaemia than in unaffected individuals.[24] In our study concentrations were higher in current smokers than non-smokers, and in patients with CAD than in those without CAD, although this latter difference was no longer significant after adjustment for age, sex, and smoking status. In the Utah MEDPED registry study Lp(a) only appeared to be associated with risk among the earliest onset cases.[10] More recently, long term statin treatment has been reported to lower Lp(a) in patients with familial hypercholesterolaemia, but the change in Lp(a) concentration was not correlated with change in carotid intima–medial thickness.[25] Some previous studies have reported that increased Lp(a) concentrations represent the best discriminator between patients with and without CAD,[12 26] but others have failed to confirm this.[10 17 23 27] This inconsistency may reflect differences in patient selection, differences in analytic methods, and the absence of standardised measurements.

None of the other emerging risk factors measured in our study were associated with CAD. Although a 25% lower homocysteine concentration is associated with a small reduction of 11% in CAD risk in the general population after adjustment for known cardiovascular risk factors,[28] in common with previous studies,[10 11 17] we found no increase in homocysteine concentrations in our patients with CAD. Nevertheless, the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene mutation has been reported to accelerate the onset of CAD through elevation of plasma homocysteine concentrations both in subjects with heterozygous familial hypercholesterolaemia[29] and in the general population.[30] Insulin was not measured in our patients, but the Utah MEDPED registry study reported no association between insulin concentrations and CAD,[10] nor did an earlier study.[11] Haematocrit is weakly associated with coronary disease in prospective studies in the general population with a risk ratio between the top and bottom tertile of 1.16,[31] and we and others[10] found no significant association in patients with familial hypercholesterolaemia. Fibrinogen is also a recognised risk factor in the general population,[32] but neither we nor the Utah group[10] found an association. Additionally, in the present study there was no association with plasminogen activator inhibitor-1, which together with Lp(a) and fibrinogen were previously found not to be related to carotid intima–media thickness in young patients.[33] A further study in adults reported no association with plasminogen activator inhibitor-1 and demonstrated that only LDL cholesterol and a cholesterol-years score were related to carotid intima–media thickness.[11] Although in the general population comparison of total blood leucocyte count in the top and bottom tertile of measurements independently predicts coronary disease in long term prospective studies with a risk ratio of 1.4,[32] we found no such association but, by contrast, the Utah MEDPED Registry Study[10] reported an increased OR of 1.3 (95% CI 1.05 to 1.59). This difference is unlikely to be related to the higher proportion of patients taking statins in our study since although statins reduce C reactive protein concentrations,[34] no effect on leucocyte count has been demonstrated.[35] MEDPED also found an association with smaller LDL cholesterol (OR 2.6, 95% CI 1.2 to 5.6), but this has not been assessed in other studies. Soluble adhesion molecules have not been measured in any studies to date, but these appear unlikely to add much predictive information to that provided by more established risk factors.[36] Overall, our findings are consistent in most respects with those of the MEDPED study[10] and together provide little evidence to suggest that emerging coronary risk factors are associated with CAD in adult patients with treated familial hypercholesterolaemia. Prospective cohort studies are now needed to confirm the findings of these cross sectional studies.

Clinical implications

Our results have a number of potential clinical implications. They suggest that extensive investigation of risk factors in

patients with familial hypercholesterolaemia is not warranted. LDL cholesterol concentration, duration of exposure to raised LDL concentrations,[11] hypertension, and cigarette smoking appear to be the most important modifiable determinants of coronary risk in these patients. Accumulating evidence suggests that aggressive lowering of LDL cholesterol in patients at high risk is required,[37] although our results indicate that despite treatment LDL concentrations remain substantially raised in many patients with familial hypercholesterolaemia, which reflects the high pre-treatment concentrations[3 4] and the limitations of monotherapy. Rigorous treatment with statins, however, can result in regression in carotid intimal thickness and this finding has led to the suggestion that LDL cholesterol should be reduced by at least 45% in routine clinical practice.[38] Most patients, nevertheless, remain undiagnosed and untreated until middle age when they may present with symptomatic coronary disease or be identified after the diagnosis of premature coronary disease or sudden death in a sibling. A recent UK study found that only a quarter of cases predicted on the basis of the carrier frequency had been diagnosed in routine clinical practice and the prevalence was lowest in subjects aged less than 20 years,[16] among whom only 5% of predicted cases had been diagnosed. This suggests that more effective methods of case ascertainment are needed, particularly to identify cases in early childhood and to discourage them from ever starting to smoke. Incorporating a case finding strategy into routine clinical practice, using either a DNA based[39] or a clinical diagnosis,[40] is a feasible and cost effective method[41 42] of identifying affected children and adult relatives of known patients.

In summary, there is little evidence to indicate that emerging coronary risk factors are associated with CAD among patients with treated familial hypercholesterolaemia, but the strong association with cigarette smoking suggests that patients should be diagnosed early in childhood and discouraged from ever starting to smoke.

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IMAGES IN CARDIOLOGY

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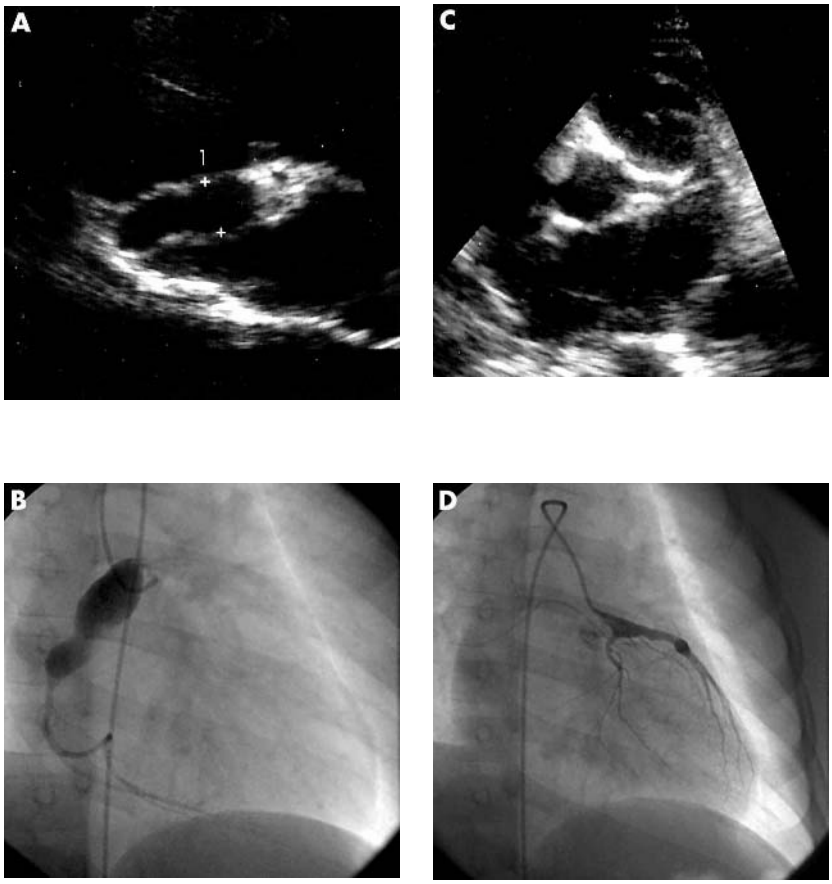
Giant and fusiform aneurysms of coronary arteries following early and adequate treatment of suspected Kawasaki disease

A boy aged 2 years 10 months was admitted to the hospital because of high fever for three days, a rash over the trunk, oedema, redness of the palms without peeling skin, conjunctivitis affecting both eyes, redness of the lips, reddened throat with strawberry-coloured tongue, and swollen lymph nodes in the neck region.

The diagnosis of acute Kawasaki disease was suspected and an early echocardiography was performed which initially showed normal sized coronary arteries, normal function and wall motion of both ventricles, no pericardial effusion, and no valvar dysfunction.

In spite of immediate treatment with intravenous γ globulin (using a single dose of 2 g/kg) and aspirin (10 mg/kg) daily, a giant aneurysm (12 mm in diameter) of the proximal right coronary artery (panels A and B), and three fusiform aneurysms of the left main coronary artery including the proximal part of the left anterior descending artery (panels C and D) developed, as seen on follow up echocardiography 10 days later. There were no wall motion disorders, no thrombus formation, and no other lesions. Coronary angiography confirmed these findings, and no significant coronary artery obstruction was visible.

Giant coronary artery aneurysms are seen in 0.5–1% of adequately treated children with Kawasaki disease. To avoid thrombus formation in the giant aneurysm of the right coronary artery we decided to treat the patient with long term aspirin together with coumadin.



The outcome following 20 months of follow up has been astonishing and favourable to date. Elective follow up catheterisation is planned in the ensuing months.

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