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Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study

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Aims To examine the changes in coronary, all-cause, and cancer mortality in patients with heterozygous familial hypercholesterolaemia (FH) before and after lipid-lowering therapy with statins.

Methods and results A total of 3382 patients (1650 men) aged <80 years were recruited from 21 lipid clinics in the United Kingdom and followed prospectively between 1980 and 2006 for 46 580 person-years. There were 370 deaths, including 190 from coronary heart disease (CHD) and 90 from cancer. The standardized mortality ratio (compared with the population in England and Wales) was calculated before and from 1 January 1992. In patients aged 20–79 years, CHD mortality fell significantly by 37% (95% CI = 7–56) from 3.4- to 2.1-fold excess. Primary prevention resulted in a 48% reduction in CHD mortality from 2.0-fold excess to none, with a smaller reduction of nearly 25% in patients with established disease. Coronary mortality was reduced more in women than in men. In patients without known CHD at registration, all-cause mortality from 1992 was 33% (21–43), lower than in the general population, mainly due to a 37% (21–50) lower risk of fatal cancer.

Conclusion The results emphasize the importance of early identification of FH and treatment with statins.

Keywords Familial hypercholesterolaemia • Coronary heart disease • All-cause mortality • Cancer mortality

Introduction

Familial hypercholesterolaemia (FH) is an autosomal co-dominant disorder.[1] Defects in at least three different genes that code for proteins involved in hepatic clearance of low-density lipoprotein-cholesterol (LDL-C) can cause FH. These include, most commonly, mutations in the gene coding for the LDL-receptor that removes LDL,[2] much less commonly in the gene for Apolipoprotein B which is the major protein of the LDL particle, and rarely in the gene coding for an enzyme called PCSK9

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involved in degrading the LDL receptor.[3] In all cases, this results in an accumulation of LDL in the plasma from birth, and to subsequent development of tendon xanthomas, xanthelasmas, and atheroma.[1]

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 ~30% in women. Coronary disease occurs ~10 years earlier in men than in women, with a marked increase in women post-menopausally.[4–6] Before effective treatment with HMG-Co reductase inhibitors (statins) became available, mortality from coronary disease was increased nearly 100-fold in young adults aged 20–39 years, and ~4-fold for patients aged 40–59 years, but in those surviving through middle age risk was similar to the high rates of CHD in the general population of England and Wales.[7,8]

In most European populations, heterozygous FH affects about one in 500 individuals, but no randomized placebo-controlled clinical outcome trials of statin treatment have been conducted for ethical reasons. Clinical management is therefore largely based on extrapolation from the results of cholesterol-lowering trials conducted in patients with polygenic hypercholesterolaemia;[8] from evidence using carotid intima-medial thickness as a surrogate outcome;[9] and from a small number of prospective observational studies. The latter include the Simon Broome Register of Familial Hyperlipidaemia, which is a register of patients with heterozygous FH recruited from 21 lipid clinics in Great Britain.[7] Earlier results from the register suggested that the prognosis for the heterozygous condition had improved since the introduction and widespread use of statins.[10]

The aim of this paper was to extend our previous reports[7,10–13] by studying an enlarged cohort of 3382 heterozygous patients followed for up to 26 years until the end of 2006, by when the exposure had more than doubled to 46 580 person-years. This has allowed us to examine more informatively the changes in mortality compared with the general population both before and after the routine use of statins.

Methods

Patients and study design

The methods have been described previously.[7] Recruitment to the Simon Broome Register of patients with heterozygous familial hypercholesterolamia began since 1980s. Homozygous patients were excluded. The 21 participating clinics registered patients referred to them by either general practitioners or hospital specialists. Patients were classified as having either 'definite' or 'possible' familial hypercholesterolaemia. A diagnosis of definite familial hypercholesterolaemia in adults was defined as a pre-treatment or on treatment total cholesterol >7.5 mmol/L (or, when available, an LDL-C of >4.9 mmol/L) together with the presence of tendon xanthomata either in the patient or in a parent, child, grandparent, sibling, uncle, or aunt. Possible familial hypercholesterolaemia was defined using the same cholesterol criteria together with either a family history of myocardial infarction before age 50 in second degree relative or before age 60 in first degree relative or, alternatively, a family history of raised the total cholesterol concentration >7.5 mmol/L in the first or second degree relative. The original definition was subsequently amended so that definite familial hypercholesterolaemia could be defined by the elevated cholesterol concentration and evidence of an LDL-receptor, an ApoB or PCSK9 mutation, but for this analysis the clinical criteria were used exclusively.

Registration and follow-up

The demographic and clinical characteristics of patients, including the presence of tendon xanthomas, were recorded on a standard registration form. A fasting venous blood specimen was taken at the registration visit and serum total cholesterol, triglycerides, and high-density lipoprotein were measured by the laboratories routinely used by the participating clinics. Serum low-density lipoprotein concentrations were calculated using the Friedewald formula.[14] The names of registered patients were flagged by the National Health Service Central Registry and, in the event of death, a copy of the death certificate was provided. The underlying cause of death was coded by one investigator using the International Classification of Disease (ICD), 9th revision.

Statistical methods

The analysis was undertaken using a computer program for cohort studies that applies standard methods.[15] Person-years of risk were accumulated within 5 year age groups and 5 year calendar periods to estimate the expected number of deaths from specified causes. A total of 199 subjects were censored on reaching the age 80 years, and a further 27 patients who had emigrated were censored at the date of embarkation. The expected number of deaths from coronary heart disease (CHD) (ICD codes 4100-4149), stroke (4300-4389), non-coronary causes (10-4099 and 415-9999), cancers (1400-2089), site-specific cancers, accidents and violence (8000-9999), and total mortality were calculated by applying the age- and calendar-specific death rates for men and women in the general population of England and Wales to the person-years accumulated by men and women in the cohort. The standardized mortality ratio (SMR) was derived from the ratio of the number of deaths observed to those expected, which was expressed as a percentage (SMR = 100 for the reference population), and the exact 95% confidence intervals were calculated. The test of significance used was a two-sided Poisson probability of observing the number of deaths that occurred given the expected number of deaths. Separate analyses for mortality were undertaken for the periods up to and from 1 January 1992 by which date statins were being widely prescribed.

Results

A total of 3413 patients were registered between 1 January 1980 and 31 December 2006. We excluded 28 (0.8%) patients whose vital status was unknown and three patients aged >80 years at registration. The resulting cohort of 3382 patients (1650 men) was followed for 46 580 person-years with a median duration of follow-up of 14.5 years for men and 14.1 years for women. It consisted of 1842 patients (908 male) with definite familial hypercholesterolaemia and 1540 patients (742 male) with possible familial hypercholesterolaemia who were followed for 25 504 and 21 076 person-years, respectively.

Patient characteristics

Table 1 describes the clinical characteristics, and reports the mean serum lipid and lipoprotein concentrations at registration for men and women (denominators differ because of missing measurements). By registration, 94.7% of patients (3184/3361) had received dietary advice and 54.6% (1568/2871) had already been prescribed lipid-lowering drug therapy. However, before treatment, the mean total cholesterol concentration was 9.5 (SD 2.0) mmol/L for men

Table 1 Clinical characteristics at registration

	Men ($n = 1650$)	Women ($n = 1732$)
Median age (inter-quartile range)	43.1 (31.9, 52.2)	49.0 (32.7, 59.7).
Previous myocardial infarction	247 (15.1%, $n = 1632$)	119 (6.9%, $n = 1716$)
Current or past angina	330 (20.3%, $n = 1623$)	283 (16.5%, $n = 1716$)
Diagnosed coronary heart disease	462 (28.0%, $n = 1649$)	338 (19.5%, $n = 1732$)
Previous stroke	21 (1.3%, $n = 1629$)	22 (1.3%, $n = 1718$)
Diagnosed diabetes	24 (1.5%, $n = 1630$)	20 (1.2%, $n = 1717$)
Current cigarette smoker	269 (16.6%, $n = 1622$)	340 (19.6%, $n = 1732$)
Systolic blood pressure (mmHg)	129.8 (18.8, $n = 1535$)	134.2 (22.6, $n = 1632$)
Diastolic blood pressure (mmHg)	79.6 (11.2, $n = 1535$)	80.5 (11.7, $n = 1632$)
Body mass index (kg/m^2)	25.2 (4.4, $n = 1424$)	24.79 (4.6, $n = 1525$)
Body mass index (kg/m^2) ≥ 30	143 (10.0%, $n = 1424$)	194 (12.7%, $n = 1525$)
Total cholesterol (mmol/l)	7.9 (1.9, $n = 1592$)	8.2 (2.1, $n = 1678$)
Triglycerides (mmol/L, geometric mean and inter-quartile range)	1.5 (1.0, 2.3, $n = 1555$)	1.3 (0.9, 1.9, $n = 1639$)
High-density lipoprotein-cholesterol (mmol/L)	1.2 (0.3, $n = 1341$)	1.4 (0.38, $n = 1429$)
Low-density lipoprotein-cholesterol[a] (mmol/L)	5.8 (1.9, $n = 1268$)	6.1 (2.1, $n = 1388$)

Results are presented as mean (SD) unless otherwise stated.
Diagnosed CHD defined as a previous myocardial infarction, angina, coronary artery by-passgraft, or angioplasty.
[a]LDL-cholesterol concentrations were calculated according to Friedewald *et al.*[14]

Table 2 Observed and expected deaths by major cause and time period

	From 1 January 1980 to 31 December 1991 (person-years exposure = 6640 years)					From 1 January 1992 (person-years exposure = 37 726 years)				
	Observed	Expected	SMR	95% CI	*P*-value	Observed	Expected	SMR	95% CI	*P*-value
Coronary heart disease	37	10.93	339	238–467	<0.0001	153	71.68	213	181–250	<0.0001
Stroke	1	2.81	36	1–198	0.46	20	24.59	80	47–128	0.43
Non-coronary heart disease	18	29.27	61	36–97	0.04	162	262.34	62	53–72	<0.0001
Accidents and violence	1	2.32	43	1–240	0.65	7	9.38	75	30–154	0.56
All cancers	14	14.56	96	53–161	1	76	120.44	63	50–79	<0.0001
All-causes of death	55	40.2	137	103–178	0.03	315	334.02	94	84–105	0.31

($n = 1409$) and 9.8 (2.1) mmol/L for women ($n = 1515$). At registration, 28% of men and 19.5% of women had known CHD defined as either a history of a previous myocardial infarction, angina, a coronary artery by-pass graft, or angioplasty.

Deaths by major cause and time period

Table 2 shows the observed and expected number of deaths by major cause and time period. In total, there were 370 deaths from all causes. There was a significant excess in mortality from all causes before, but not after, 1 January 1992. There were no differences in the observed and expected numbers of deaths from stroke or from accidents and violence in either period, but non-coronary mortality was significantly lower than the expected in both time periods (SMR 61 and 62, respectively). There were 90 deaths from cancer with no significant reduction in the first time period, but a 37% (95% CI = 21–50) lower than the expected cancer mortality in the second period. In total, there were 190 coronary deaths, and the SMR fell significantly by 37% (95% CI = 7–56; $P = 0.01$) in the second period from 3.4 - to 2.1-fold excess.

Standardized mortality ratio for coronary heart disease

Table 3 gives the observed and expected number of deaths from CHD by age group and time period for patients with and without known coronary disease at registration. No data are shown for patients aged <20 years (2223 person-years exposure) because no fatal events were observed. For secondary prevention, there was a reduction in SMR of 25% from a 5.2 (95% CI = 3.4–7.6) to a 3.9-fold excess (95% CI = 3.2–4.7) with a larger reduction in women than in men (51 vs. 8%, data not shown). For primary prevention, there was a 48% reduction in SMR from a 2-fold excess in mortality to none. There was a large reduction in coronary mortality in patients aged 20–39 years from a 37-fold excess to an 11.5-fold excess, and for those aged 40–59 years there was a reduction of

Table 3 Observed and expected deaths from coronary heart disease by age group and time period for patients with and without known coronary disease at registration

Attained age (years)	Person-years observation	1 January 1980 to 31 December 1991						Person-years observation	1 January 1992 to 31 December 2006					
		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000
Primary prevention														
20–39	2031	3	0.08	3750	773–10 959	<0.001	148	8227	3	0.26	1153	238–3372	<0.01	37
40–59	2181	8	2.34	342	148–674	<0.01	367	13123	13	9.19	141	75–242	0.28	99
60–79	686	1	3.63	27	1–153	0.25	146	8219	29	34.33	84	57–121	0.41	353
20–79	4898	12	6.05	198	102–346	0.04	212	29 569	45	43.78	103	75–138	0.89	145
Secondary prevention														
20–39	178	5	0.01	50000	16 235–116 683	<0.0001	2816	229	1	0			0	436
40–59	1016	9	1.58	570	260–1081	<0.0001	886	3419	34	3.83	888	615–1241	<0.0001	995
60–79	539	11	3.24	340	169–607	<0.001	2038	4509	73	24.01	304	238–382	<0.0001	1619
20–79	1733	25	4.83	515	335– 764	<0.0001	1442	8157	108	27.84	388	318–468	<0.0001	1324

Table 4 Observed and expected deaths from coronary heart disease for men and women without known coronary disease at registration from 1 January 1992 until 31 December 2006

Attained age (years)	Person-years observation	Men						Person-years observation	Women					
		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000
20–39	4120	2	0.23	870	105–3141	0.045	49	4107	1	0.03	3333	84–18 572	0.059	24
40–59	7068	12	7.56	159	82–277	0.17	170	6054	1	1.63	61	2–342	1	17
60–79	2529	11	15.98	69	34–123	0.26	435	5690	18	18.35	98	58–155	1	316
20–79	13 717	25	23.77	105	68–155	0.85	172	15 851	20	20.01	100	61–154	1	121

59% from a 3.4-fold significant excess to a 1.4-fold non-significant excess mortality. Overall, for primary and secondary prevention combined, for women there was a 60% reduction in SMR from 4.2- to 1.7-fold excess ($P = 0.001$), and for men an 18% reduction from 3.0 to 2.4-fold excess ($P =$ ns). The SMR fell significantly by 34% (from 384 to 255) in patients with definite familial hypercholesterolaemia ($P = 0.05$) and non-significantly by 37% (from 270 to 171) in patients with possible familial hypercholesterolaemia (data not shown). *Table 4* shows that for primary prevention there was no longer a statistically significant excess coronary mortality for either men or women aged 40 years or more.

Standardized mortality ratio for all-causes and cancer

Table 5 shows the observed and expected numbers of deaths from all-causes by age group and time period for patients with and without known coronary disease at registration. It demonstrates that for primary prevention from 1992 there was no excess all-cause mortality under the age of 60 years and a 43% significantly lower mortality in patients aged 60–79 years. For secondary prevention, the all-cause mortality was elevated in both time periods.

Table 6 presents a combined analysis for men and women of all cancer and site-specific cancer mortality. There was a statistically significant 37% reduction in all cancer mortality (95% CI = 21–50) after, but not before, 1 January 1992. A site-specific analysis showed that after this date there were significant reductions of 73% for fatal cancers of the respiratory and intrathoracic organs; 78% for lymphatic and haemopoetic cancer, 49% for genitourinary cancers, and a borderline significant reduction of 39% for digestive and peritoneal cancers. A record of past cigarette smoking was available for 97% (3266/3382) of patients, and 71% of those dying of cancer (62/87) compared with 43% (1366/3179) of the remainder had ever smoked (hazard ratio 3.47; 95% CI = 2.2–5.7; $P < 0.0001$). From 1992, deaths from respiratory causes other than cancer (ICD codes 460-519) were 63% (95% CI = 37–80; $P < 0.0001$) lower than in the general population (data not shown).

Discussion

Principal findings

This large long-term prospective registry study of 3382 patients with heterozygous familial hypercholesterolaemia demonstrates a statistically significant reduction in coronary mortality of about one-third since the widespread use of statins. Primary prevention resulted in a halving in risk of fatal coronary events, with a smaller reduction of nearly one-quarters in patients with established disease. Mortality was reduced more in women than in men for both primary and secondary prevention. Importantly, in patients without known coronary disease at registration, all-cause mortality was significantly lower than in the general population, mainly due to a reduction of more than one-thirds in the risk of fatal cancer. The data also confirm our earlier findings that FH patients are not at a higher risk of fatal stroke.[11]

Table 5 Observed and expected deaths from all causes by age group and time period for patients with and without known coronary disease at registration

Attained age (years)	Person-years observation	1 January 1980 to 31 December 1991						Person-years observation	1 January 1992 to 31 December 2006					
		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000
Primary prevention														
20–39	2031	3	1.58	190	39–555	0.42	147	8227	8	6.55	122	53–241	0.67	97
40–59	2181	12	9.23	130	67–227	0.44	550	13 123	46	48.33	95	70–127	0.81	351
60–79	686	6	12.58	48	18–104	0.07	874	8219	91	159.79	57	46–70	<0.0001	1107
20–79	4898	21	23.64	89	55–136	0.68	371	29 569	145	215.12	67	57–79	<0.0001	467
Secondary prevention														
20–39	178	5	0.18	2778	902–6482	<0.0001	2816	229	1	0.24	417	11–2322	0.43	436
40–59	1016	14	5.31	264	144–442	<0.01	1378	3419	40	16.49	242	173–330	<0.0001	1170
60–79	539	15	11.04	136	76–224	0.30	2780	4509	129	102.17	126	105–150	<0.01	2861
20–79	1733	34	16.53	206	142–287	<0.001	1961	8157	170	118.90	143	122–166	<0.0001	2084

Table 6 Observed and expected deaths for all cancers and site-specific cancers by time period

Specified site	ICD 9 codes	Before 1 January 1992 (person-years exposure = 6631)					From 1 January 1992 (person-years exposure = 37 726)				
		Observed	Expected	SMR	95% CI	*P*-value	Observed	Expected	SMR	95% CI	*P*-value
All cancers	1400–2089	14	14.56	96	53–161	1	76	120.40	63	50–79	<0.0001
Lip, oral cavity and pharynx	1400–1499	1	0.16	625	16–6482	0.30	2	1.58	127	15–457	0.94
Digestive organs and peritoneum	1500–1599	3	3.66	82	17–240	1	22	32.17	68	43–104	0.08
Respiratory and intrathoracic organs	1600–1699	1	3.76	27	1–148	0.22	7	30.31	23	9–48	<0.0001
Bone, connective tissue, skin and breast	1700–1759	1	2.21	45	1–252	0.67	19	14.34	133	80–207	0.27
Genitorurinary	1790–1899	2	2.01	100	12–359	1	9	17.80	51	23–96	0.03
Other solid cancers	1900–1999	3	1.44	208	43–609	0.35	14	9.86	142	78–238	0.25
Lymphatic and haemopoetic tissue	2000–2089	3	0.84	357	74–1044	0.11	3	13.39	22	5–65	0.002

Comparison with other studies

Few comparable data are available, with the exception of a much smaller prospective study from the Netherlands that used similar diagnostic criteria.[16] It followed 345 statin-treated patients for up to 8 years between 1988 and 1997. Among the 214 patients without a history of cardiovascular disease, there were five ischaemic heart disease deaths and mortality was increased 2.6-fold for patients of all ages with wide confidence intervals (95% CI = 1.1–6.3) and 7.6-fold for patients aged 40–59 years (95% CI = 2.9–20). In contrast, for the period 1992 to 2006, we found no excess coronary mortality for patients of all ages without known coronary disease at registration and only a 1.4-fold non-significant increase for patients aged 40–59 years (95% CI = 0.7–2.4). Overall, in a combined analysis for primary and secondary prevention, for men and women of all ages, coronary mortality was reduced by 37% ($P = 0.01$) when comparing the periods before and after 1992, which is similar to the reduction in major coronary events observed in randomized placebo-controlled trials of statin therapy. However, the Cholesterol Treatment Trialists' Collaborators systematic prospective meta-analysis,[8] which reported the efficacy of cholesterol-lowering treatment using individual patient data for 90 056 participants in 14 randomized trials of statins, found a similar proportional reduction in major coronary events irrespective of age, sex, or previous coronary disease. This differs from the pattern of mortality evident in different sub-groups in our study.

Coronary mortality

We found that, before and after statins became widely available, there was no excess coronary mortality in patients aged >60 years without known coronary disease at registration. This may be explained by selective survival, with earlier death occurring in those individuals most susceptible to the atherogenic effects of raised LDL-C, and a correspondingly lower risk among survivors. There is a strong intra-familial correlation for age of coronary death[17] and differences in susceptibility will be related partly to the particular mutation present.[18] A higher risk of coronary disease in patients with LDL receptor null allele mutations and in those with the *PCSK9* (D374Y) mutation is well documented.[19,20] Other genetic polymorphisms, including apolipoprotein E, are also associated with risk,[21] while some loss of function common variants in the *PCSK9* gene are associated with lower risk in the general population[22] and possibly also in FH patients.[23] Conventional cardiovascular risk factors such as gender, smoking, hypertension, and high-density lipoprotein cholesterol are recognized to influence the age of onset and severity of coronary disease in heterozygous patients.[24–26] Patients surviving into older age before statins became available were therefore likely to be a highly selected group at lower risk of coronary disease. In contrast, middle-aged patients were probably at more representative levels of coronary risk and the observed 59% reduction in the SMR for primary prevention in our cohort is consistent with the expected benefit of statin treatment. In the youngest group, aged 20–39 years, the number of events was small and the estimated mortality ratios are imprecise but suggest that the relative reduction in events may possibly be even larger.

The benefit of secondary prevention after the introduction and widespread use of statins appeared to be greater in women than in men with a 51 and 8% reduction, respectively, in the SMR. However, prior to 1992, these findings were based on only 15 events in men and 10 in women, and need to be interpreted with caution, particularly since the estimated reductions in risk from 1992 were imprecise and not statistically significant. It is possible, however, that the benefits of treatment were less in men, because the onset of coronary disease occurs ~10 years earlier than in women[4–6] and consequently men will have had more extensive atheroma that may involve the coronary ostia and aortic root, as well as the coronary arteries.[27] Furthermore, the intensity of statin treatment may have been sub-optimal, since evidence that reducing LDL-C by at least 50% in heterozygous FH prevents the progression of carotid intima medial thickness was not published until 2001.[9] Achieving substantial reductions in LDL was difficult before the introduction of more potent statins,[28] which are now often used in combination with a cholesterol absorption inhibitor to reduce LDL further, although the clinical benefit of combination therapy has yet to be demonstrated.[29] The more widespread use of post-infarction cardioprotective therapy with ACE inhibitors, beta-blockers, and aspirin and coronary interventions over the last 10–15 years would also be expected to have improved the prognosis, but in our cohort men showed little apparent benefit.

All-cause and cancer mortalities

All-cause mortality was significantly reduced by about one-third in patients without known coronary disease at registration, which was mainly due to a reduction in cancer mortality. This is probably attributable to close adherence to advice given as part of routine clinical care to be physically active, make dietary changes,[30] avoid obesity,[31] and stop smoking. The reduction in cancer mortality observed may also, in part, reflect earlier detection and treatment of cancer among patients undergoing regular medical surveillance, resulting in a better prognosis. It cannot be explained by competing mortality from premature coronary disease since the reduction in cancer mortality was only evident from 1992 onwards from when there was no excess coronary mortality for patients without known coronary disease at registration. The delay in the reduction in mortality may be due to the prolonged lead-time between exposure to carcinogens, pre-clinical incident disease, and subsequent mortality. We cannot, however, entirely exclude the possibility that statins have anti-cancer activity.[32] Indeed, a recent Canadian retrospective study of 30 076 patients started on a lipophilic statin after a myocardial infarction reported a reduction of one-quarter in the hazard ratio for cancer incidence with high-dose statin treatment.[33] However, the findings from observational studies are not supported by the results of a meta-analysis of clinical outcome trials conducted by the Cholesterol Treatment Trialists' Collaboration which reported no reduction in cancer incidence.[8] Nevertheless, their results cannot completely exclude longer term effects of statins as the mean duration of these trials was only 5 years.

Study limitations

Some care is needed in interpreting our findings. Although this is the largest published cohort of patients with heterozygous familial hypercholesterolaemia with over 44 000 person-years exposure in adulthood, it has limited statistical power to examine differences in mortality between the two time periods for multiple age- and sex-specific sub-groups. Furthermore, although statin treatment has been used routinely after 1991, some patients are likely to have been prescribed statins earlier, although most received less efficacious treatment with bile acid sequestrants, fibrates, and occasionally niacin. Our results are therefore likely to under-estimate the maximum potential benefits of statin treatment. It should also be recognized that the cohort comprised patients referred to specialist lipid clinics and cannot be entirely representative because at least three-quarters of affected cases in the United Kingdom remain undiagnosed.[34] The results are, therefore, of most direct relevance to patients referred for specialist care which, in practice, includes most patients in the community with diagnosed familial hypercholesterolaemia.[34] There are, however, no entirely satisfactory clinical diagnostic criteria and some misclassification of polygenic hypercholesterolaemia as familial will have occurred,[35,36] particularly among patients with possible familial hypercholesterolaemia, which will result in an under-estimate in absolute rates of coronary mortality. In contrast, DNA testing offers a definitive, highly specific diagnosis, which will be adopted in routine clinical practice as the speed and sensitivity of mutation testing increases and cost decreases using kits to test for common mutations[37] and systems such as those based on a DNA microarray.[38] As this study has shown, the prevalence of other cardiovascular risk factors in this monogenic disorder is no higher, and is probably lower, than in the general population, and our analyses made no adjustment for them.

Clinical implications

Our findings have a number of clinical implications. The study confirms the importance of early identification and treatment of affected heterozygous individuals since the major benefit of statin treatment appears to be in the primary prevention of fatal coronary disease. This suggests that with earlier diagnosis it should be possible to prevent any excess coronary mortality in early adulthood. It supports a strategy of cascade testing to identify the affected relatives of probands and, since LDL-C levels are elevated from soon after birth, testing must include children who have the highest rates of under-diagnosis.[34] Recent guidelines from the American Academy of Pediatrics recommend treatment with a statin from 8 years of age for children with a family history of early heart disease and an LDL-C level of >4.1 mmol/L,[39] although there is no clear evidence for this particular treatment threshold.[40] Our results also indicate that more intensive treatment may be needed to reduce the coronary mortality in patients with established disease, especially in men. In addition, the findings strongly suggest that lifestyle factors are associated with a large reduction in mortality from cancer, which in primary prevention results in the overall mortality being lower than in the general population. Lifestyle advice, therefore, remains an important aspect of care. Longer term follow-up will be needed to assess the prognosis into older age of patients treated with statins from early adulthood,

but expansion of the cohort would be needed to examine the long-term safety and efficacy of statin treatment started in childhood.

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CLINICAL VIGNETTE

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Uncommon variation in the papillary muscles presenting with ST elevation and T-wave inversion

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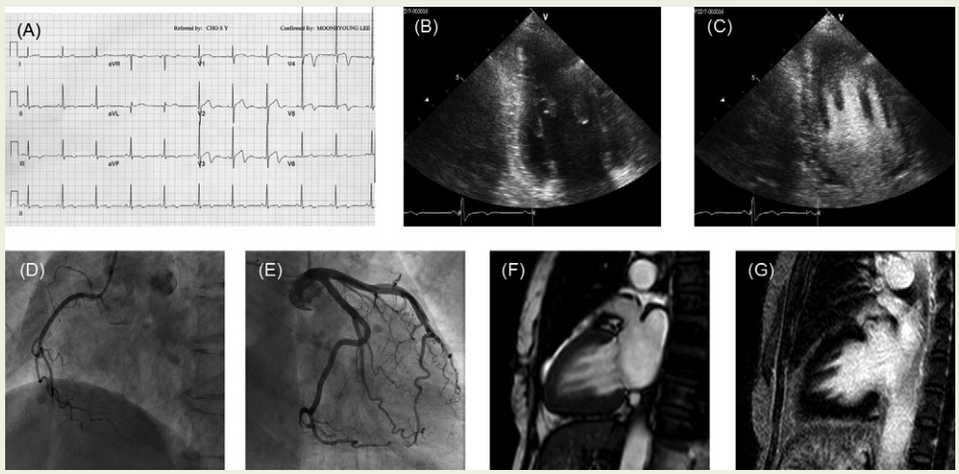

A 61-year-old woman was admitted for intermittent chest discomfort that had been present for 2 months. She was normotensive and denied any past history of medical illness. On physical examination, grade 2 systolic click murmur at the left ventricular (LV) apex was auscultated. A routine electrocardiogram (Panel A) revealed ST-segment elevation and T-wave inversion in V_2 to V_5 precordial leads with high voltage of QRS complex which made us suspect possible hypertrophic cardiomyopathy. Two-dimensional echocardiography showed no evidence of LV hypertrophy in all segments. However, unexpectedly, unusual structures of papillary muscles were detected. The papillary muscles were interlinked each others with numerous fine tendons and formed parallel arrangement without hypertrophies (Panel B). The anterior mitral leaflet was mildly prolapsed without significant mitral regurgitation. To clarify the structures of papillary muscles, perflurocarbon-exposed sonicated dextrose albumin (PESDA), a pulmonary circulation passing contrast agent, was injected via an antecubital vein. Contrast echocardiogram with PESDA showed contrast filling and opacification of the LV cavity showed more clearly the unusual variation of papillary muscles with four parallel bellies (Panel C). Coronary angiography showed no significant luminal narrowing (Panels D and E). A contrast-enhanced image obtained by magnetic resonance imaging showed consistent findings in structures (Panel F) and no delayed hyperenhancement of four papillary muscles, so there was no evidence of fibrosis in the papillary muscles (Panel G). This case illustrates that the variations of the papillary muscles should be considered for differential diagnosis of abnormal electrocardiographic findings such as ST elevation and T-wave inversion.