Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia

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Abstract

Objectives To assess the cost effectiveness of strategies to screen for and treat familial hypercholesterolaemia.
Design Cost effectiveness analysis. A care pathway for each patient was delineated and the associated probabilities, benefits, and costs were calculated.
Participants Simulated population aged 16-54 years in England and Wales.
Interventions Identification and treatment of patients with familial hypercholesterolaemia by universal screening, opportunistic screening in primary care, screening of people admitted to hospital with premature myocardial infarction, or tracing family members of affected patients.
Main outcome measure Cost effectiveness calculated as cost per life year gained (extension of life expectancy resulting from intervention) including estimated costs of screening and treatment.
Results Tracing of family members was the most cost effective strategy (£3097 (€5066, $4479) per life year gained) as 2.6 individuals need to be screened to identify one case at a cost of £133 per case detected. If the genetic mutation was known within the family then the cost per life year gained (£4914) was only slightly increased by genetic confirmation of the diagnosis. Universal population screening was least cost effective (£13 029 per life year gained) as 1365 individuals need to be screened at a cost of £9754 per case detected. For each strategy it was more cost effective to screen younger people and women. Targeted strategies were more expensive per person screened, but the cost per case detected was lower. Population screening of 16 year olds only was as cost effective as family tracing (£2777 with a clinical confirmation).
Conclusions Screening family members of people with familial hypercholesterolaemia is the most cost effective option for detecting cases across the whole population.

Introduction

Familial hypercholesterolaemia is an autosomal dominant condition caused mainly by mutations of the low density lipoprotein receptor gene which result in substantially raised serum cholesterol concentrations.[1] Men with this condition have over a 50% risk of coronary heart disease by the age of 50 years. For women the risk is at least 30% at 60 years.[2 3] About 110 000 people in the United Kingdom are thought to be affected, and at least 75% of them are undiagnosed.[4] Treatment with hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is effective[5 6] and delays or prevents the onset of coronary heart disease.[7–10] Effective primary prevention, however, requires early diagnosis.

A diagnosis of familial hypercholesterolaemia is made on the basis of the plasma total and low density lipoprotein cholesterol concentrations combined with either a clinical examination and family history[11] or a genetic test. When a mutation is known within a family an unequivocal diagnosis can be made by DNA testing at any age.[12] A mutation is detected in only half of clinically identified cases, probably because of technical insensitivity, clinical misdiagnosis, or causes of familial hypercholesterolaemia not related to the low density lipoprotein gene.[13]

One report on the cost effectiveness of screening for familial hypercholesterolaemia was published in 1993[14] and updated in 1997.[15] This reported US data and did not present costs and effectiveness separately so it is not possible to adapt the findings to the United Kingdom. We carried out a modelling exercise to determine the costs and benefits of different screening strategies in the United Kingdom.

Methods

We identified potential screening strategies in a systematic literature review[16]: universal population screening; opportunistic screening of patients consulting for unrelated reasons in primary care; opportunistic screening of patients admitted to hospital with premature myocardial infarction; and systematic screening of first degree relatives of people with diagnosed familial hypercholesterolaemia. We added to these the option of screening all young people aged 16 years. With the exception of screening 16 year olds, outcomes were modelled for each sex within 10 year age bands from 16 to 54 years because there are no clinical endpoint data to support the effectiveness of statin treatment at later ages.

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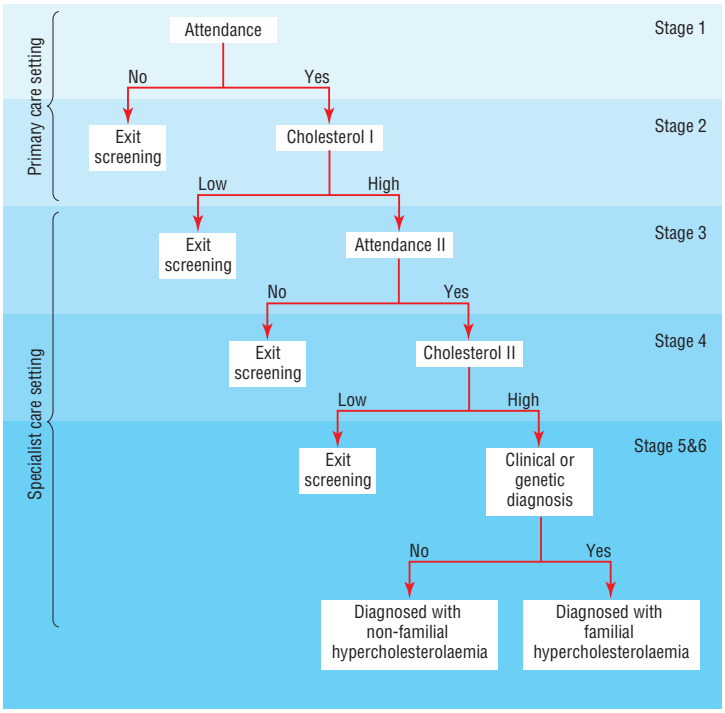

Probability	Screening strategy			
	Universal	Opportunistic at GP	Opportunistic after myocardial infarct	Family tracing
Attends for first blood test	0.650[17]	0.800[17]	0.600[17]	0.950[18]
Blood cholesterol concentration above cut off	0.050[17]	0.050[17]	0.290[19]	0.490[20]
Attends for second blood test	0.750[21]	0.750[21]	0.900[22]	0.900[22]
Blood cholesterol concentration above cut off[23]	0.935	0.935	0.935	0.935
Familial hypercholesterolaemia*[16]	0.038	0.038	0.160	0.950

*Data taken from Marks et al[16] and depend on prevalence of familial hypercholesterolaemia and probability of high cholesterol concentration in target population.

Decision tree used in the modelling

We developed a hypothetical care pathway (figure). In the universal and opportunistic strategies, people with a non-fasting total cholesterol concentration above the population 95th centile are invited for a fasting blood test. Those with a confirmed fasting total cholesterol concentration above 7.5 mmol/l and low density lipoprotein cholesterol above 4.9 mmol/l are referred for diagnostic confirmation by clinical examination with a lipid clinic consultant or by genetic testing on blood or buccal cells. For the family tracing strategy, a lipid clinic nurse approaches existing patients, collects family histories, and asks permission to approach relatives.[17] For each strategy we used a combination of decision analysis and life table analysis to estimate life years gained per case diagnosed as a result of screening and subsequent treatment with statins; number needed to screen, defined as the number of people who must be invited for screening for one case to be identified; cost of screening per case diagnosed; and cost effectiveness in terms of the cost per life year gained.

We calculated the life years gained that were attributable to the use of statins by patients with familial hypercholesterolaemia as the life expectancy (expected age at death) with statin treatment minus the life expectancy in the absence of treatment for each age and sex group. We constructed life expectancy tables using mortality data from a UK cohort of 1185 patients with heterozygous familial hypercholesterolaemia who have been followed prospectively since 1980. From 1992 treatment was mostly with statins; before 1992 treatment was with bile acid sequestrants.[5] This cohort study was the only published report of the effect of statins on mortality in familial hyperlipidaemia that we identified. We used population mortality in the life tables for ages 60 years and over because the cohort in this age range was small.

We calculated the number needed to screen and the screening cost per person invited using a decision analytic model. Unit cost data (including laboratory costs, staff time, letters, and overheads) and probabilities (including attendance rates and prevalence of familial hypercholesterolaemia) were taken from published sources where available (table 1).

We calculated screening cost per case diagnosed as the screening cost per person invited multiplied by the number needed to screen. We calculated the cost per life year gained (C/LYG) as the screening cost per patient diagnosed (ScreenCost) plus the additional drug costs arising from the new diagnoses ($StatinCost_{Screen}$–$StatinCost_{NoScreen}$) plus the cost savings due to reduced incidence of coronary events ($EventCost_{Screen}$–$EventCost_{NoScreen}$) divided by the life years gained (LY_{Screen}–$LY_{NoScreen}$): $C/LYG=(ScreenCost+(StatinCost_{Screen}–StatinCost_{NoScreen})+(EventCost_{Screen}–EventCost_{NoScreen}))/(LY_{Screen}–LY_{NoScreen})$.

We estimated the annual cost of treatment to be £411 (€672, $594) with a treatment regimen of statin therapy (70% simvastatin 40 mg daily and 30%

Table 1 Costs and probabilities assigned to each screening strategy for familial hypercholesterolaemia

Cost code*	Description	Price	Source
Stage 1,2,3,4	Invitation or results letter plus reminders	£0.50	Estimated cost of sending average of 1.5 letters
Stage 2-3	10 minute nurse appointment	£4.50	Netten et al[24]—£27 per hour of patient contact time (includes salary, on costs, overheads, capital overheads, training, and non-contact time)
Stage 2	Cholesterol test	£3.77	Total cholesterol (Diabetes Research Laboratory, Oxford)
Stage 4	30 minute nurse appointment	£13.50	Netten et al[24]
Stage 4	Lipid profile	£11.82	£3.77 for total cholesterol, £3.94 for high density lipoprotein cholesterol, £4.11 for triglycerides (Diabetes Research Laboratory, Oxford)
Stage 5-6	Outpatient appointment with consultant at lipid clinic	£67.00	Netten et al[24]
Stage 5-6	Genetic test (proband)	£1000	Clinical Molecular Genetics Laboratory, Institute of Child Health
Stage 5-6	Genetic test (family member)	£185	Clinical Molecular Genetics Laboratory, Institute of Child Health

*See figure.

Table 2 Life expectancy (expected age at death) of people with familial hypercholesterolaemia with and without treatment

Age at start of treatment (years)	Undiscounted			Discounted at 1%		
	Untreated	Treated	Increment	Untreated	Treated	Increment
Men						
16	65.64	72.76	7.11	53.37	58.18	4.82
16-24	66.09	73.05	6.97	55.11	60.13	5.02
25-34	70.72	74.42	3.70	62.08	64.87	2.79
35-44	75.05	75.62	0.57	68.63	69.06	0.43
45-54	77.92	78.18	0.26	73.63	73.85	0.21
Women						
16	71.87	81.04	9.17	57.42	63.03	5.60
16-24	72.01	81.14	9.13	59.19	65.12	5.92
25-34	73.35	81.51	8.16	63.86	69.48	5.62
35-44	74.51	81.84	7.33	67.91	73.42	5.51
45-54	79.44	82.85	3.41	74.56	77.31	2.75

atorvastatin 20 mg daily, based on data from a specialist lipid clinic) and an annual general practitioner appointment until the age of 60 years. We calculated drug costs after allowing for an 18% rate of non-adherence to treatment. The cost of a coronary event was taken as £1544.[25] We calculated the lifetime cost of drug and event treatment using the life tables.

We discounted life expectancy and life years gained at 1% and costs at 6% in accordance with Treasury and Department of Health guidelines.[26] We carried out sensitivity analyses by altering parameters in five areas to check the robustness of the model. Marks et al give further details of the modelling procedures and assumptions.[16] The full HTA report can be found at www.hta.nhsweb.nhs.uk/fullmono/mon429.pdf.

Results

Increase in life expectancy

Table 2 shows the change in life expectancy by sex after diagnosis and treatment. The gain in life years was highest when treatment was started earliest (7.0 years in men and 9.1 years in women aged 16-24 years) and decreased with increasing age (0.3 and 3.4 years at age 45-54 years).

Number needed to screen

The number needed to be invited for screening to result in the identification of one person with familial hypercholesterolaemia is determined by the prevalence of familial hypercholesterolaemia, the attendance rate in the care pathway, and by whether a clinical or genetic confirmation of diagnosis is made (table 3). A genetic confirmation of diagnosis requires greater numbers because currently a mutation is detected in only half of clinically diagnosed cases.[13] The number varied from 2292 people in the general population (confirmed by genetic screening) to 2.6 people in first degree relatives of identified cases (with clinical confirmation).

Cost per case detected

The cost per case detected is the number needed to screen multiplied by the cost per person invited. More targeted strategies are more expensive but fewer people need be invited to find one case. Costs per case detected ranged from £133 for a clinically diagnosed relative (family tracing) to £9645 in a population wide strategy (clinically confirmed) (table 3).

Cost effectiveness ratios

Table 4 shows cost effectiveness of the screening strategies with clinical or genetic confirmation of diagnosis together with undiscounted rates and results for cost and effectiveness data discounted at 3% for comparison. The earlier a diagnosis of familial hypercholesterolaemia is made the more cost effective the screening strategy becomes (£2777 per life year gained for 16 year olds). In addition, identification of relatives is the most cost effective for all age groups (£3097 to £4914 per life year gained).

Screening women was more cost effective than screening men because women gained more life years

Table 3 Comparison of overall cost per life year gained of different screening strategies using clinical or genetic confirmation of diagnosis

Strategy	Main results	Results with alternative discount rates	
	Baseline discount rates (effectiveness 1%; costs 6%)	Undiscounted effectiveness	Costs and effectiveness discounted at 3%
Clinical			
Universal (16 year olds)	£2777	£1798	£7 244
Universal	£13 029	£10 269	£21 289
Opportunistic (GP)*	£11 310	£8909	£18 578
Opportunistic (MI)†	£9281	£7513	£15 738
Family tracing	£3097	£2420	£6 084
Genetic			
Universal (16 year olds)	£14 842	£9610	£33 882
Universal	£78 060	£61 661	£120 841
Opportunistic (GP)*	£70 009	£55 283	£108 578
Opportunistic (MI)†	£21 106	£17 116	£32 833
Family tracing	£4914‡	£3856	£8 865

*Patients attending general practitioner.
†Patients hospitalised for myocardial infarction.
‡Including cost of finding mutation in proband.

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Table 5 Life years gained and cost per life year gained for men and women at different ages using family tracing strategy with clinical or genetic confirmation of diagnosis

Age-sex group	Life years gained discounted at 1%	Cost per life year gained
Clinical confirmation (family tracing age 16-54 years)		
Men:		
16-24	5.0	£870
25-34	2.8	£1468
35-44	0.4	£8278
45-54	0.2	£11 344
Women:		
16-24	5.9	£796
25-34	5.6	£766
35-44	5.5	£637
45-54	2.8	£838
All	3.5	£3097
Genetic confirmation (family tracing age 16-54 years, including cost of testing proband)		
Men:		
16-24	5.0	£1216
25-34	2.8	£2093
35-44	0.4	£12 298
45-54	0.2	£19 591
Women:		
16-24	5.9	£1090
25-34	5.6	£1075
35-44	5.5	£953
45-54	2.8	£1470
All	3.5	£4914

after treatment. Within each strategy it was more cost effective to screen younger men and women, although this trend was less pronounced in women. There was a 10-fold increase in the cost per life year gained between the oldest and the youngest age group in the family tracing strategy (table 5). If the genetic mutation was known within the family then the cost per life year gained was only slightly increased by genetic diagnostic confirmation (table 5).

Sensitivity analysis

In the analyses we altered the number of first degree relatives of the proband (which affects the cost effectiveness of a family tracing strategy—cascade screening); the proportion of identifiable mutations (which affects the cost of genetic confirmation of the diagnosis); drug costs (which are likely to decrease after the expiry of patents for some statins); attendance rates; discount rates for cost and effectiveness data; cost of a coronary event; and life years gained

The ranking of cost effectiveness between or within the strategies was not affected by any of the sensitivity analyses (table 6). When we modelled lower drug costs the cost effectiveness ratio improved most in those strategies where the drug costs were a larger proportion of the overall costs. This was particularly true of the family tracing strategy.

Discussion

This modelling exercise identified screening of relatives of people with familial hypercholesterolaemia as the most cost effective way of detecting cases across the whole population. Familial hypercholesterolaemia fulfils the World Health Organization criteria for screening programmes.[27] Clinical endpoint trials of lipid lowering drug treatment with statins have shown their effectiveness in the primary and secondary prevention of coronary heart disease risk,[7–10] especially in the groups at highest risk, although there are no trials specifically in patients with familial hypercholesterolaemia. Family tracing in a pilot study in the United Kingdom was acceptable and feasible,[28] and the success of a programme based on genetic testing in the Netherlands has recently been reported.[29] We estimated the cost effectiveness of family tracing to be £3097 per life year gained (or £4914 with genetic confirmation). This represents good value for money compared with common medical interventions[30] and suggests that pilot evaluation programmes should be conducted.

Screening of patients admitted to hospital with premature myocardial infarction may be worth considering but costs three times more per life year gained compared with family tracing though it ensures complete coverage. Universal screening restricted to 16 year olds and with clinical methods of diagnosis was even more cost effective than family tracing. However,

Table 6 Effect on estimates of cost effectiveness of changing paramaters used in model (sensitivity analysis)

	Universal (at 16 years old)	Universal	Opportunistic (GP)*	Opportunistic (MI)†	Case finding
Baseline cost per life year gained	£2777	£13 029	£11 310	£9281	£3097
Changed assumptions:					
1.31 relatives per proband	No change	No change	No change	No change	£3113
5.75 relatives per proband	No change	No change	No change	No change	£3092
37% reduction in drug cost	£2451	£11 972	£10 352	£6344	£2040
73% reduction in drug cost	£2134	£10 944	£9419	£3787	£1011
80% attendance	£2651	£12 461	£10 919	£9338	£3102
50% attendance	£3499	£17 043	£14 441	£9683	£3128
CHD event cost reduced by 50%	£2797	£13 059	£11 338	£9321	£3126
CHD event cost increased by 50%	£2757	£13 000	£11 282	£9242	£3067
Life years gained decreased by 50%	£5555	£26 058	£22 621	£18 563	£6194
Life years gained increased by 50%	£1852	£8686	£7540	£6188	£2065
Genetic					
Baseline cost per life year gained	£14 842	£78 060	£70 009	£21 106	£4914‡
30% identified mutations	£24 142	£128 128	£114 894	£29 670	£5990‡
70% identified mutations	£10 856	£56 602	£50 772	£17 448	£4453‡
50% reduction in cost of genetic testing	£9753	£50 580	£44 975	£15 682	£4065‡

CHD=coronary heart disease.
*Patients attending general practitioners.
†Patients hospitalised for myocardial infarction.
‡Including cost of testing proband.

What is already known on this topic

In the United Kingdom there are an estimated 110 000 men and women with familial hypercholesterolaemia, only a small percentage of whom have been identified to date

Without identification and treatment, over half of these people will have a fatal or non-fatal coronary heart disease event by the age of 50 (men) or 60 (women)

Effective treatment of high cholesterol concentrations reduces total and coronary heart disease mortality

No recommended screening strategy currently exists in the United Kingdom for familial hypercholesterolaemia

What this study adds

Computer modelling has shown that the earlier familial hypercholesterolaemia is diagnosed the more cost effective the screening strategy becomes

Identifying relatives of people with familial hypercholesterolaemia is the most cost effective screening option for all age groups

As technology improves and the cost of statins falls all strategies will become more cost effective

we assumed that 55% of 16 year olds would attend screening and that most of those diagnosed would adhere to statin treatment over many years. Neither of these assumptions can be currently validated and the ethical acceptability of such a strategy is unclear. Such a strategy would also, by definition, exclude the possibility of diagnosis for all those aged over 16 years and hence its full benefits in reducing population mortality from familial hypercholesterolaemia would not be seen for many years.

Accuracy of estimates

The estimates of life expectancy of people with familial hypercholesterolaemia were based on a UK familial hypercholesterolaemia register.[5 11] This may underestimate the true benefit of statins, which have been widely available for just over 10 years. Earlier identification and longer treatment are likely to give greater benefit. On the other hand, the register data may overestimate the gain in life expectancy because our model used mortality data before and after the introduction and widespread use of statins to estimate life years gained but did not take account of the underlying population trend of decreasing mortality. In addition, it is possible that clinics contributing to the register provided closer medical supervision and more aggressive statin treatment than elsewhere. As people with familial hypercholesterolaemia aged over 60 years in the Simon Broome cohort had a similar mortality and longevity to the general population neither the costs nor benefits of treatment were estimated beyond that age.[5] Nevertheless, we advocate continuing treatment at this age.

Awareness by general practitioners, accident and emergency staff, cardiology teams, and the general public of the signs of familial hypercholesterolaemia and the benefits of early treatment is important, and extra training would be needed. All screening strategies will become cheaper (and therefore more cost effective) as drug costs fall, which can be expected as the patents for some statins expire. The generic equivalent of a preparation can be between one third to two thirds of the cost of the proprietary product. As the technology improves (especially DNA diagnostic techniques) the cost effectiveness of all strategies will benefit.

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