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Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK

Marion Kerr[1], Robert Pears[2], Zofia Miedzybrodzka[3], Kate Haralambos[4], Moyra Cather[5], Melanie Watson[6], and Steve E. Humphries[7]*

[1]Economics Department, Insight Health Economics Ltd., 16 Cambrian Road, Richmond, Surrey TW10 6JQ, UK; [2]Public Health Department, Hampshire County Council, Elizabeth II Court South, Winchester SO23 8UJ, UK; [3]Department of Medical Genetics, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK; [4]Wales Heart Research Institute, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; [5]Northern Ireland Regional Genetics Centre, Regional Genetics Laboratories, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK; [6]Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Princess Anne Hospital, Coxford Road, Southampton SO16 5YA, UK; and [7]Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, 5 University Street, London WC1E 6JJ, UK

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Aims Familial hypercholesterolaemia (FH) is a vastly under-diagnosed genetic disorder, associated with early development of coronary heart disease and premature mortality which can be substantially reduced by effective treatment. Patents have recently expired on high-intensity statins, reducing FH treatment costs. We build a model using UK data to estimate the cost effectiveness of DNA testing of relatives of those with monogenic FH.

Methods and results A Markov model was used to estimate the cost effectiveness of cascade testing, using data from UK cascade services. The estimated incremental cost effectiveness ratio (ICER) was £5806 and the net marginal lifetime cost per relative tested was £2781. More than 80% of lifetime costs were diagnosis-related and incurred in the 1st year. In UK services, 23% of 6396 index cases were mutation-positive. For each mutation-positive index case, 1.33 relatives were tested, resulting overall in a rate of 0.31 tested relatives per tested index case. If the number of relatives tested per tested index case rose to 3.2 (projected by National Institute for Health and Care Excellence in 2008) the ICER would reduce to £2280 and lifetime costs to £1092.

Conclusion Cascade testing of relatives of those with suspected FH is highly cost effective. The current Europe-wide high levels of undiagnosed FH, and associated morbidity and mortality, mean adoption of cascade services should yield substantial quality of life and survival gains.

Keywords Familial hypercholesterolaemia • Markov model • Cost effectiveness • Cascade testing

Introduction

Familial hypercholesterolaemia (FH) is an autosomal-dominant disorder associated with elevated low density lipoprotein cholesterol (LDL-C) and early development of atherosclerosis and coronary heart disease (CHD). Untreated, at least 50% of men with FH will develop CHD by age 50, and 30% of women by age 60.[1,2] The risk of CHD death at age 20–39 is increased 80–84-fold FH.[3] Treatment with statins reduces the risk of CHD to approximately general population levels.[4]

Historically it has been estimated that 1/500 people has FH, around 130 000 in the UK, 1.5 million in Europe and 15 million worldwide, although recent epidemiological data from Denmark[5] and next

* Corresponding author. Tel: +44 207 679 6962, Fax: +44 207 679 6212, Email: steve.humphries@ucl.ac.uk

generation sequencing data[6] suggest the frequency may be approximately 1/250. Although some countries such as the Netherlands have well established cascade testing programmes, most do not. The vast majority of those with FH, worldwide, are undiagnosed.[7]

In 2008, the National Institute for Health and Care Excellence (NICE) in England published guidelines for identification and management of FH.[8] These guidelines, like those elsewhere in Europe, recommended cascade testing of relatives of index cases, and estimated the cost-effectiveness of such testing. Testing programmes were set up in Scotland, Wales, and Northern Ireland. No national programme exists in England; commissioning responsibility is divided between 211 local organizations. In much of the country there is no FH testing programme at all.

Since the NICE guideline, much has changed. Patents have expired on some high-intensity statins used to treat FH, leading to substantial cost reductions, while next generation sequencing has reduced the cost of DNA tests. There is now convincing evidence that in patients with a clinical diagnosis of FH but no mutation in any of the three known FH-causing genes (*LDLR*, *APOB*, and *PCSK9*),[9,10] the most likely cause of elevated LDL-C is polygenic.[11] In polygenic FH the risk of relatives having significantly raised LDL-C is much lower[12] than the 50% observed for monogenic hypercholesterolaemia.[9] Finally, the establishment of FH cascade services in parts of the UK provides an opportunity to use real-life data rather than projections in economic modelling. UK audit data, combined with new evidence on the association between LDL-C reduction and CHD risk[13] allow for modelling based explicitly on observed LDL-C reductions in FH.

In this article, we use data from FH cascade services to inform an economic model re-examining the cost effectiveness in the UK of cascade testing for monogenic FH from known index cases, incorporating new study evidence, and changes in costs and clinical practice that have occurred since the 2008 guideline.

Methods

Data were collected from FH cascade services in Scotland, Wales and the Wessex region of England on people with clinically diagnosed FH who have had DNA tests, rates of monogenic FH diagnosis in this group (i.e. a detected FH-causing variant in *LDLR*, *APOB*, or *PCSK9*), and numbers of relatives DNA tested. Additional data were collected from Wales on the age-distribution and LDL-C levels at diagnosis of monogenic relatives, and resource use. Data on sections of the pathway were collected from Northern Ireland.

An economic model was developed to estimate the cost effectiveness of a cascade testing pathway with three steps: DNA testing of people who already have a clinical diagnosis of possible or definite FH (index cases), DNA testing of relatives of monogenic index cases, and treatment with high-intensity statins and, in some cases, ezetimibe for monogenic relatives, relative to no DNA tests, no cascade testing and no treatment of relatives (*Figure 1*).

It was assumed that, in both the intervention and non-intervention arms of the model, index cases are treated appropriately for FH. The outcome of the DNA test does not change the treatment of index cases. No costs or benefits were counted for identification or treatment of index cases, nor for treatment of relatives who do not carry the family mutation.

A Markov model was used to estimate the cost, adverse event, and Quality-adjusted-life-year (QALY) impacts of treatment for monogenic relatives, compared with no treatment.[14] The cycle length was one year. Markov states are shown in *Figure 2*.

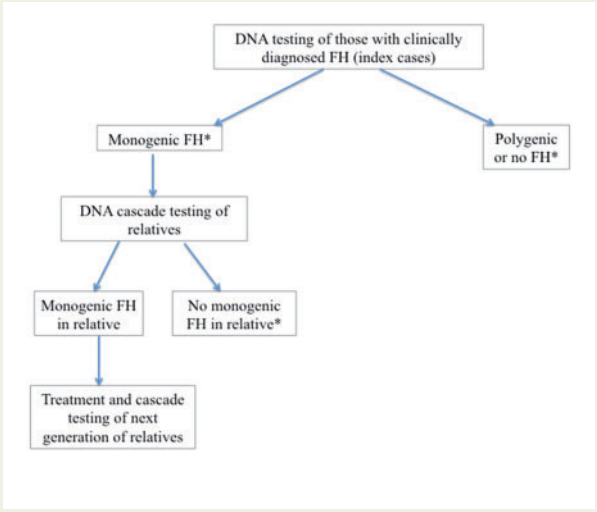

Figure 1 Structure of economic model.
*It is assumed that appropriate treatment is provided for index cases and, where applicable, for mutation-negative relatives. Any change to treatment for these groups as a result of DNA testing is outside the scope of the model.

Pooled data from cascade services in Scotland, Wales and Wessex were used in base case analysis to estimate monogenic diagnosis rates in index cases and the number of relatives tested per monogenic index case. Northern Ireland data were excluded from the pool, as they do not cover the entire pathway, but were used in sensitivity analysis.

It was assumed in the base case that, once diagnosed, 86.25% of monogenic adult relatives take statins, and 46.43% also take ezetimibe, as reported in a recent FH audit in the UK.[15] In sensitivity analysis, we modelled the impact of a 70% statin compliance rate, with a proportionate reduction in ezetimibe.

It was assumed that 72% of those treated take atorvastatin, 20% simvastatin and 8% rosuvastatin.[16] The distribution of adult daily dosages for each medication was taken from the 2010 audit.[15] In sensitivity analysis, we modelled the impact of a reduction in the price of rosuvastatin and ezetimibe when UK patent protection ends in 2017.

The model was run for seven representative patient groups, aged (at diagnosis) 20–24, 25–34, 35–44, 45–54, 55–64, 65–74, and 75+. The age distribution of patients at diagnosis was estimated from data supplied by the Welsh FH service. It was assumed that relatives diagnosed through cascade testing have no history of cardiovascular events.

Baseline (untreated) primary cardiovascular (CVD) risk by 5-year age-band and gender for the general population was estimated using the QRISK2-2016 calculator.[17] The general population risk of individual cardiovascular events (MI, angina, TIA, stroke, CVD death) was estimated by applying the estimates of the distribution of these events from the NICE Clinical Guideline on Cardiovascular Disease 181[18] to the QRSIK estimates. CHD death risk was estimated by examining the proportion of CVD deaths attributed to CHD in ONS 2014 mortality data for England and Wales[19] in each 5-year age-band, and applying this proportion to estimated CVD death risk. (CVD was identified by International Classification of Diseases-10 (ICD-10) codes G45, I20–25, I50, I60–64, and I73, and CHD by ICD-10 codes I20–25).

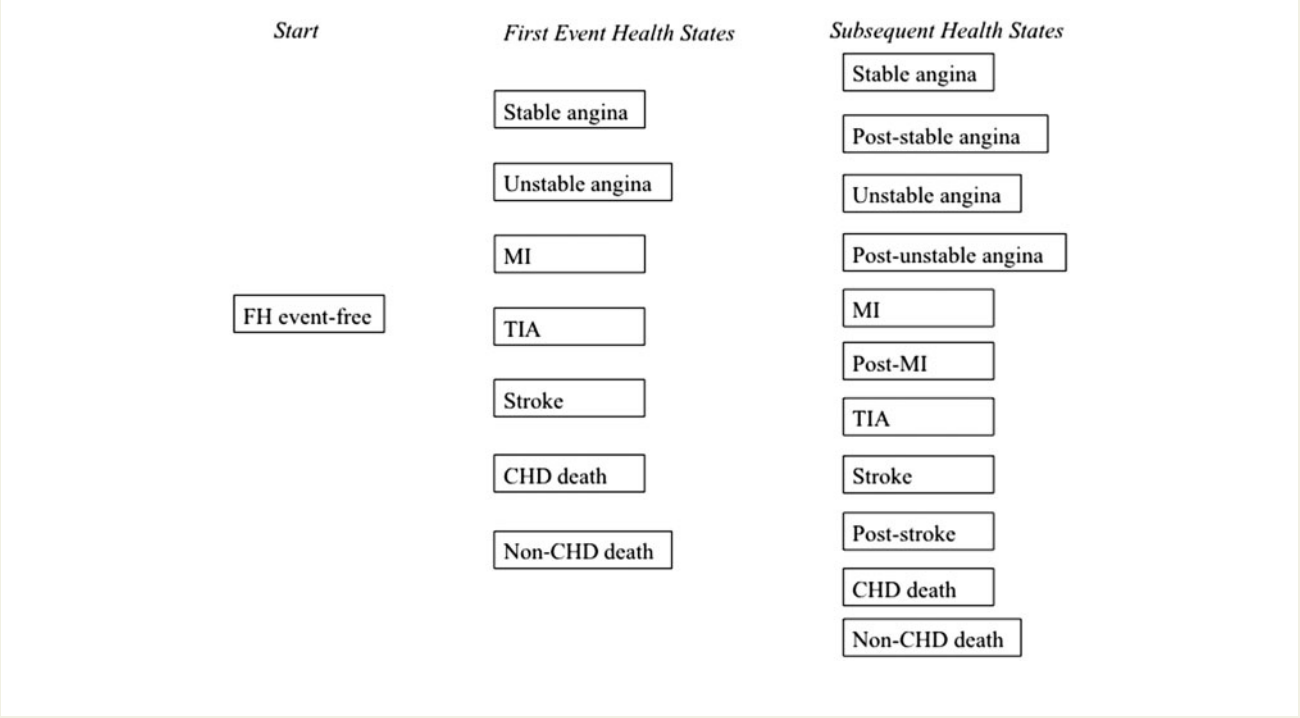

Figure 2 Markov model health states.

FH-specific primary risks of angina, MI and CHD death were estimated by applying the relative risks reported for the Simon Broome FH register population in 1980–92[3] to the general population baseline primary risks for each age-band (adjusting for the inclusion of the FH group in the general population figures). Simon Broome relative risks relate to CHD mortality rather than to total CHD events. They were used here as a proxy for CHD event relative risk. Simon Broome reported no increased risk of death from stroke or TIA in FH.[20] Unadjusted general population risks were therefore used for stroke, TIA and non-CHD CVD death. For age ≥80, it was assumed that the risk of cardiovascular events in FH is as for the general population. Estimated baseline risks are given in Supplementary material online.

Secondary risk was estimated for seven age-bands, 20–24, 25–34, 35–44, 45–54, 55–64, 65–74, and 75+. Secondary risks for those aged 45–74 were taken from NICE 181.[18] Risks for ages <45 and >74 were not provided in NICE 181. To estimate risk for ages 20–24, 25–34, and 35–44, we examined the per capita rate of hospital admissions with cardiovascular events as primary diagnoses, in hospital episode statistics (HES), for England in 2014–15, for each of these age-bands, relative to the per capita rate for age 45–54. Cardiovascular events were identified by ICD-10 codes as above. Population by age-band was taken from Office for National Statistics (ONS) 2014 mid-year population estimates for England.[21] The ratio of per capita events in each age-band relative to the per-capita rate for age 45–54 was applied as a scaling factor to the age 45–54 transition probabilities in NICE 181 to estimate risks for ages 20–24, 25–34, and 35–44. For ages 75+, the ratio of per capita events in this age group, relative to that for age 65–74 was applied as a scaling factor to the age 65–74 transition probabilities. It was assumed that, in general, secondary risks in FH do not differ from secondary risks in the general population. However, in cases where the general population secondary risk was lower than the FH primary risk, the primary risk estimate was used. Non-CVD mortality was estimated from ONS mortality data, by 5-year age-band.

Given that there are no large-scale studies of treatment effects in FH, treatment risk ratios were estimated using evidence from the cholesterol treatment trialists' collaborators (CTTC) study, which linked absolute reductions in LDL-C to cardiovascular relative risk.[13] While CTTC focused on primary events, we assumed that the relative risk reduction is the same for secondary events. Rate ratios for MI were applied also to angina, and those for stroke were applied also to TIA. Model outputs were sense-checked against existing small-scale FH studies.

It was assumed that mean baseline levels of LDL-C, for monogenic relatives by age-band, are as observed by the Welsh FH cascade service. In the base case it was assumed that the mean reduction in LDL-C for treated patients is 37%, as observed in the 2010 UK FH audit.[15] In sensitivity analysis we modelled the impact of a 50% reduction in LDL-C, the target recommended by NICE. In the base case it was assumed that the 37% reduction in LDL-C is achieved after cascade testing, for all treatment-compliant monogenic relatives. It is known, however, that some relatives are already taking cholesterol-lowering medication before receiving their DNA test results (though it is not known whether they started statins before the cascade-testing process began, or whether treatment was changed after monogenic diagnosis). In sensitivity analysis we modelled the impact of assuming no change in treatment after cascade testing for those already on statins before monogenic diagnosis (and thus no reduction in LDL-C associated with cascade testing). Some monogenic relatives are normocholesterolemic at diagnosis. In sensitivity analysis we modelled the impact of assuming no treatment and no health impact for this group.

The net cost and QALY impacts of testing and treatment, per relative participating in cascade testing, were estimated. The cost of DNA testing for index cases was apportioned across tested relatives.

Table 1 Costs of testing, treatment and adverse events

Test/Treatment/Event	Cost per person	Cost type	Source	Notes
Genetic scanning, index cases	£353	Non-recurring	UK Genetic Testing Network	Range £255-£450, mean used.
Genetic testing, relatives	£120			Range £65-£175, mean used.
Staff inputs, index case testing	Mutation-positive £371		Welsh FH service, PSSRU[22]	Costs are higher for those with positive results owing to family tree drawing, cascade test planning and (for relatives) treatment planning. See supplementary material online.
	Mutation-negative £174			
Staff inputs, relative testing	Mutation-positive £257			
	Mutation-negative £179			
Atorvastatin	£20	Recurring (annual)	Unit cost: NHS Electronic Drug Tariff.[23] Mean daily dose: National FH audit[15] Sensitivity analysis estimates for post-patent expiry.	Dose details, see supplementary material online.
Simvastatin	£12			
Rosuvastatin	£316			
	£20 sensitivity analysis			
Ezetimibe	£343			Daily dose: 10mg.[16]
	£34 sensitivity analysis			
Statin monitoring year 1	£120	Non-recurring	NICE CG181[18]	
Statin monitoring subsequent years	£101	Recurring (annual)		
MI	£3,731	Non-recurring (year 1 cost)		
Stable angina	£7,736			
Unstable angina	£3,313			
Stroke	£13,697		Saka 2009[24]	
TIA	£640		NICE CG181[18]	
Post-MI	£788	Recurring (annual)		
Post-stable angina	£240			
Post-unstable angina	£385			
Post-stroke	£3,301		Saka 2009[24]	
Post-TIA	£124		NICE CG181[18]	

See references [15, 16, 18, 22, 23] and [24].

Table 2 Age distribution and mean LDL-C (mmol/L) at diagnosis, mutation-positive relatives, Wales

Age	0–19	20–24	25–34	35–44	45–54	55+
% of all mutation-positive relatives	26.64%	8.30%	18.78%	19.21%	13.97%	13.10%
Mean LDL-C (95% CI)[a]	5.59 (5.33–5.86)	5.89 (5.13–6.64)	6.54 (6.04–7.03)	7.27 (6.62–7.92)	7.03 (6.26–7.79)	8.30 (7.35–9.25)
Normocholesterolemia, % of age group	13.11%	21.05%	11.63%	6.82%	15.63%	0.00%
Mean LDL-C (95% CI) excluding normocholesterolemic	5.82 (5.56–6.08)	6.36 (5.54–7.18)	6.90 (6.45–7.35)	7.51 (6.88–8.15)	7.57 (6.71–8.42)	8.30 (7.35–9.25)

LDL-C, low density lipoprotein cholesterol.
[a]Baseline LDL-C estimated from correction tables in 26% of cases.

Table 3 Estimated adverse events averted (cumulative) per 1000 relatives tested

Years after testing	Myocardial infarction	Stroke	Unstable angina	Stable angina	Deaths
5	10	1	3	12	2
10	22	3	8	22	7
20	46	8	14	36	16
30	67	13	17	42	23

Table 4 Lifetime net cost, ICER and QALY impacts of cascade testing per tested relative

Age	Lifetime cost	Lifetime QALY gain	ICER
20–34	£2722	0.56	£4889
35–44	£2943	0.46	£6369
45–54	£2789	0.48	£5770
55–64	£2732	0.36	£7587
65–74	£2495	0.31	£8056
75+	£2285	0.21	£11072
Cohort	£2781	0.48	£5806

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted-life-year.

A UK NHS perspective was used for costs. We examined costs and benefits over a lifetime perspective, and also their profile over time. All costs were expressed in 2014-15 UK pounds. Costs and benefits were discounted at 3.5% in the base case, and adjusted in sensitivity analysis. Cost sources are given in *Table 1*.

It was assumed that clinical effectiveness of statins continues undiminished throughout life. Health state utilities were taken from NICE 181. We assumed that statin treatment does not of itself reduce utility,[25] and that the same is true of ezetimibe.

Results

Since the Welsh, Scottish and Wessex FH services were established, 6,396 clinically diagnosed FH index cases have had DNA tests. Of these, 22.98% had an FH-causing monogenic mutation. On average, 1.33 relatives were tested per monogenic index case. In Northern Ireland, no data were available on index cases tested. The number of relatives tested per monogenic index case was 6.83 (Supplementary material online).

In Wales, mean baseline LDL-C in monogenic relatives was 6.67 mmol/L, and levels ranged from 5.59 in those aged ≤19, to 8.30 in those aged ≥55 (*Table 2*). Estimated relative risks associated with 37% and 50% reductions in LDL-C, respectively, based on CTTC estimates of the impact of absolute reductions in LDL-C on cardiovascular relative risk, and Welsh data on baseline LCL-C, are shown in Supplementary material online. In Wales, 41.66% of diagnosed monogenic relatives were taking cholesterol-lowering medication before receiving their DNA results. Of those aged ≥20, 8.89% were normocholesterolemic.

The economic model estimates that, for every 1,000 relatives tested, over 20 years 46 MIs, 50 cases of angina, 8 strokes and 16 deaths are averted (*Table 3*).

The estimated incremental cost effectiveness ratio (ICER) of DNA testing, cascade testing and treatment of relatives ranges from £4889 per relative tested in those aged 20-34, to £11 072 in those aged ≥75 (*Table 4*). For a cohort with the age-distribution observed in the Welsh cascade service the ICER is £5806 and the overall net marginal lifetime cost per relative tested is £2781.

The net annual cost per tested relative is £2268 in year 1. Net annual costs drop to £96 per tested relative in year 2, and are negative or <£2 from year 18 (Supplementary material online). Four fifths of total lifetime costs are for the initial tests, and almost two thirds are for DNA tests in index cases. The total cost per tested relative is highly sensitive to the ratio of relatives tested to index cases tested. If the number of relatives tested per tested index case rose from 0.31 (Scotland, Wales and Wessex mean) to 3.2 (projected by NICE in 2008) the ICER would reduce to £2280 and lifetime costs to £1092.

In sensitivity analysis, increasing the mean reduction in LDL-C to 50% reduces the ICER by 22%, and a reduction in treatment compliance to 70% increases it by 19%. Estimated reductions in the prices of rosuvastatin and ezetimibe, after patent expiry, reduce the net cost and ICER by 32%. A shift in the ratio of relatives to probands to the level observed in Northern Ireland reduces the net cost and ICER by 54%. Excluding treatment costs and effects for those taking statins before diagnosis reduces the net cost by 6% and increases the ICER by 71%. Reducing the discount rate to 1.5% reduces the ICER by 44%, and increasing the discount rate to 5% increases the ICER by 44%. Excluding treatment costs and effects for those with

Table 5 Sensitivity analyses: lifetime net cost, QALY and ICER impacts

Sensitivity analysis	Lifetime cost	Lifetime QALY gain	ICER
1: 50% LDL-C reduction	£2560	0.57	£4503
2: Northern Ireland relative: monogenic proband ratio	£1277	As base case	£2667
3: 70% compliance	£2672	0.39	£6874
4: Rosuvastatin and ezetimibe cost reduction	£1882	As base case	£3929
5: Discount rate 1.5%	£2773	0.85	£3278
6: Discount rate 5%	£2771	0.33	£8387
7: No treatment change if already on statins	£2615	0.26	£9954
8: No treatment change if normocholesterolemic	£2686	0.44	£6069

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted-life-year.

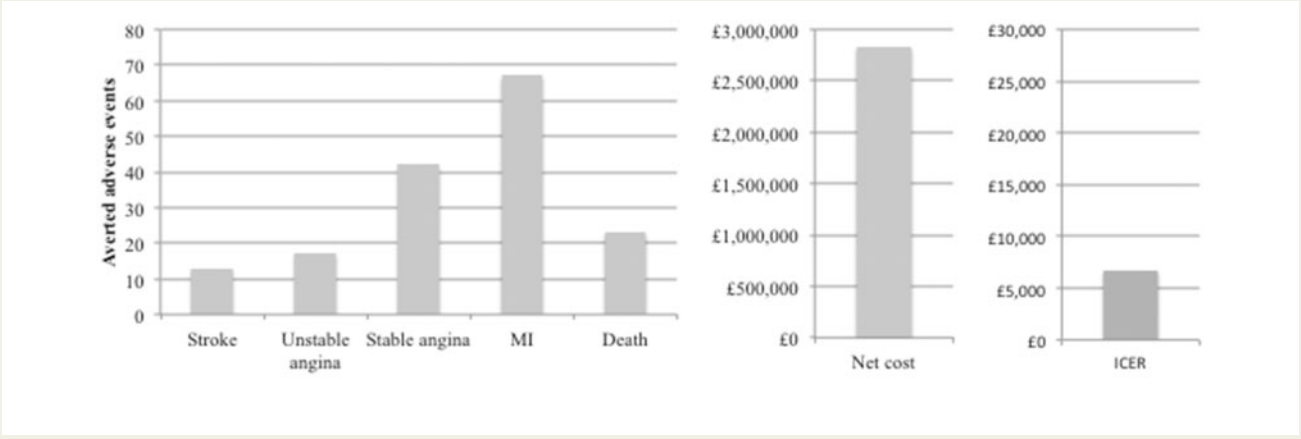

Figure 3 Adverse events averted, net cost and incremental cost effectiveness ratio after 30 years per 1000 relatives tested.

normocholesterolemia at DNA diagnosis increases the ICER by 5% (*Table 5* and Supplementary material online).

The reduction in CHD mortality in treated relatives is estimated at 44%, based on a mean LDL-C reduction of 37%, and 55% with a mean 50% LDL-C reduction. The Simon Broome study reported a 48% reduction in CHD mortality for those without prior CHD.[26] Our model estimates a 60.7% reduction in myocardial infarction (MI) over 8 years for treated relatives achieving a 37% reduction in LDL-C, and 68.6% for a mean 50% LDL-C reduction. Versmissen[4] did not report specifically on MI risk, but found an overall CHD risk reduction of 76% (hazard ratio 0.24 (95% CI 0.18-0.30), over mean follow-up time of 8.5 years.

Discussion

The reduction in unit costs for genetic testing and the expiry of patents for high-intensity statins make re-examination of the cost effectiveness of cascade testing for FH important for all countries. We were able to use data from UK FH cascade services to replace key assumptions of the NICE 2008 model, and to use the findings of recent clinical studies examining the link between cardiovascular risk and treatment-induced reductions in LDL-C, an approach which is likely to be more appropriate to FH than the use of population-level relative risks. However, in common with all economic studies of FH, we are restricted by the lack of large-scale studies on treatment effects in FH. We have assumed that FH patients respond to statins in the same way as non-FH patients, and also that treatment effects are undiminished over time. We have also assumed that compliance rates are the same across all age groups, and are sustained over a lifetime. We have sense-checked our model outputs against data from existing small-scale FH studies, and believe that our findings are compatible with those results. Exact comparison is not possible, as existing studies do not match the model in treatment regimes, achieved LDL-C reductions or patient characteristics. Our model excludes children because of lack of data to assess effectiveness.

Our economic model suggests that cascade testing in families with FH is highly cost effective. Our base case estimates the cost per QALY (ICER) of DNA cascade testing at £5806 per tested relative, considerably below the cost effectiveness threshold of £20 000-£30 000 commonly used in the English NHS. Over a 30-year perspective, we estimate that 139 adverse CVD events and 23 deaths are averted per 1,000 relatives tested, at a cost of £2.8 million (*Figure 3*). Health gains and cost effectiveness are negatively related to age at diagnosis. The cost per QALY is 57% higher in those aged ≥ 55 than in those aged 20-54.

These estimates are highly sensitive to the number of relatives tested per index case tested. Increasing the yield of monogenic diagnoses in index cases would significantly increase cost effectiveness, all other things equal. Currently 65% of lifetime costs are for index case testing and the monogenic detection rate is 22.98%. Increasing the number of relatives tested per monogenic index case would also increase cost effectiveness. Data from Northern Ireland indicate a considerably higher yield of tested relatives than elsewhere in the UK, with corresponding reductions in net costs, as shown in sensitivity analysis. In regions of Europe where there has been less family dispersion than in the UK, or where families are larger, cost effectiveness may be higher other things equal.

All the UK cascade services are relatively new, and it is likely that the yield of relatives will increase over time. It is also likely that the incompleteness of UK cascade services impacts testing rates for existing services; some relatives identified in the Welsh, Scottish and Northern Irish services live in England, where there is very little provision.

It is also important to note that many families with FH are completely undetected. There is a need for further study on the cost effectiveness of strategies for index case finding, and of approaches such as reverse cascade testing from children identified at immunization as having FH.[27]

The expiry of patents on atorvastatin and simvastatin has substantially reduced the cost of statin treatment since the NICE guidance of 2008. UK patents for ezetimibe and rosuvastatin will expire in 2017. We estimate that if, after patent expiry, the price of rosuvastatin were to fall to the same level as that of atorvastatin (a reduction of around 94%) and the price of ezetimibe were to fall by 90%, the lifetime cost of cascade testing would fall by a third.

Not all recent studies[28,29] have found cascade testing for FH to be as cost effective as we do here for the UK. For any programme, cost effectiveness depends on the choice of comparator and the cost structure of interventions, which may vary substantially from place to place.

Recent CVD risk management guidelines suggest that some statin-intolerant patients or those with high LDL-C on maximum tolerated statin dose should be considered for treatment with novel agents such as monoclonal antibodies to PCSK9.[30] We were unable to include these in our model, owing to the lack of robust RCT end point data and pricing data.

Any changes to the treatment of index cases or non-monogenic relatives are outside the scope of the model. It is likely, however, that in practice cascade testing would lead to changes in some cases and this could have an impact on overall cost effectiveness. Further work is needed on the impact of cascade testing on these groups.

It is hoped that the current study will lay the foundation for future work, and will support commissioning decisions on FH services in Europe and elsewhere.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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