

Perioperative dilution and intraoperative blood salvage techniques (such as those described in this paper) are gaining credence, particularly for patients undergoing cardiac and orthopaedic surgery. But neither of these processes is suitable for patients with infection or malignant disease.

After surgery, devices are available to collect blood from wound drains, which can then be retransfused back into the patient. Such techniques reduce the formation of haematomas, but few studies of their efficacy are available, and the techniques are not in general use.⁴

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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.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 effective⁵⁻⁶ 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 history¹¹ or a genetic test.

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 review¹²: 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.

We developed a hypothetical care pathway. 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

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Table 1 Life expectancy (expected age at death, discounted at 1%) of people with familial hypercholesterolaemia with and without treatment

| Age at start of treatment (years) | Untreated | Treated | Increment |
|-----------------------------------|-----------|---------|-----------|
| Men | | | |
| 16 | 53.37 | 58.18 | 4.82 |
| 16-24 | 55.11 | 60.13 | 5.02 |
| 25-34 | 62.08 | 64.87 | 2.79 |
| 35-44 | 68.63 | 69.06 | 0.43 |
| 45-54 | 73.63 | 73.85 | 0.21 |
| Women | | | |
| 16 | 57.42 | 63.03 | 5.60 |
| 16-24 | 59.19 | 65.12 | 5.92 |
| 25-34 | 63.86 | 69.48 | 5.62 |
| 35-44 | 67.91 | 73.42 | 5.51 |
| 45-54 | 74.56 | 77.31 | 2.75 |

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.¹³ 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 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. We used population mortality in the life tables for ages 60 years and over.

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.

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% 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 £1544.¹⁴ 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%.¹⁵ We carried out sensitivity analyses by altering parameters in five areas to check the robustness of the model. Further details are given on bmj.com and in the full health technology report¹² (see also www.hta.nhsweb.nhs.uk/fullmono/mon429.pdf).

Results

Increase in life expectancy

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) (table 1).

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 2). A genetic confirmation of diagnosis requires greater numbers because currently a mutation is detected in only half of clinically diagnosed cases.¹⁶ 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

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 2).

Table 2 Comparison of number needed to be invited to screening and screening costs (ages 16-54 years) for different strategies using clinical and genetic confirmation of the diagnosis

| | No needed to screen to find one case | Screening cost per person invited for all stages | Screening cost per case detected | Life years gained (discounted at 1%) | Incremental drug costs | Incremental CHD event costs |
|---|--------------------------------------|--|----------------------------------|--------------------------------------|------------------------|-----------------------------|
| Clinical confirmation | | | | | | |
| Universal (16 year olds) | 1365 | £7.15 | £9754 | 5.2 | £4818 | -£200 |
| Universal | 1146 | £8.42 | £9645 | 3.5 | £3704 | -£171 |
| Opportunistic (GP)* | 938 | £9.67 | £9072 | 3.7 | £3707 | -£171 |
| Opportunistic (MI)† | 22 | £13.15 | £284 | 0.8 | £2599 | -£52 |
| Family tracing | 2.6 | £51.16 | £133 | 3.5 | £3704 | -£171 |
| Genetic confirmation | | | | | | |
| Universal (16 year olds) | 2729 | £26.43 | £72 140 | 5.2 | £4818 | -£200 |
| Universal | 2292 | £31.38 | £71 922 | 3.5 | £3704 | -£171 |
| Opportunistic (GP)* | 1876 | £37.72 | £70 776 | 3.7 | £3707 | -£171 |
| Opportunistic (MI)† | 43 | £86.16 | £3720 | 0.8 | £2599 | -£52 |
| Family tracing (relatives, including cost of finding mutation in proband) | 2.6‡ | £719.26 | £1873§ | 3.5 | £3704 | -£171 |

CHD=coronary heart disease.

*Patients attending general practitioner.

†Patients hospitalised for myocardial infarction.

‡Genetic testing of family members only if mutation is identified in proband.

§Including cost of testing proband.

Cost effectiveness ratios

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) (table 3). 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 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. If the genetic mutation was known within the family then the cost per life year gained was only slightly increased by genetic diagnostic confirmation.

Sensitivity analysis

The ranking of cost effectiveness between or within the strategies was not affected by any of the sensitivity analyses (see bmj.com). 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.

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.¹⁷ 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,¹⁸ and the success of a programme based on genetic testing in the Netherlands has recently been reported.¹⁹ 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 interventions²⁰ and suggests that pilot evaluation programmes should be conducted.

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

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.

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.

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

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Fluoroquinolones and risk of Achilles tendon disorders: case-control study

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Fluoroquinolones have been associated with tendon disorders, usually during the first month of treatment,¹⁻⁵ but the epidemiological evidence is scanty. We did a nested case-control study among users of fluoroquinolones in a large UK general practice database to study the association with Achilles tendon disorders.

Participants, methods, and results

We obtained data from the IMS Health database (UK MediPlus), which contains data from general practice on consultations, morbidity, prescriptions, and other interventions in a source population of 1.2 million inhabitants. The base cohort consisted of all patients aged 18 years or over who had received a fluoroquinolone. We excluded people with a history of Achilles tendon disorders, cancer, AIDS, illicit drug use, or alcohol misuse. We identified potential cases by reviewing patient profiles and clinical data and excluded tendon disorders due to direct trauma. We randomly sampled a group of 10 000 control patients from the study cohort.

We defined four categories of exposure to fluoroquinolones: current use, recent use, past use, and no use. We defined current use as when the tendon disorder occurred in the period between the start of the fluoroquinolone treatment and the calculated end date plus 30 days, recent use as when the calculated end

date was between 30 and 90 days before the occurrence of the disorder, and past use as when the calculated end date was more than 90 days before the occurrence of the disorder. We used unconditional logistic regression analysis to calculate adjusted relative risks and 95% confidence intervals for Achilles tendon disorders, using the no use group as the reference. We adjusted for age, sex, number of visits to the general practitioner, use of corticosteroid, calendar year, obesity, and history of musculoskeletal disorders.

The cohort included 46 776 users of fluoroquinolones between 1 July 1992 and 30 June 30 1998, of whom 704 had Achilles tendinitis and 38 had Achilles tendon rupture. Four hundred and fifty three (61%) of the cases were women, and the mean age was 56 years. Cases visited the general practitioner significantly more often than did controls (mean 20 v 17). Cases and controls were similar with respect to indications for use of fluoroquinolone. Age, number of visits to the general practitioner in the previous 18 months, gout, obesity, and use of corticosteroid were determinants of Achilles tendon disorders. The adjusted relative risk of Achilles tendon disorders with current use of fluoroquinolones was 1.9 (95% confidence interval 1.3 to 2.6). The risk for recent and past use was similar to that for no use. The relative risk with current use was 3.2 (2.1 to 4.9) among patients aged 60 and over and 0.9 (0.5 to 1.6) among patients aged under 60 (table). In patients aged 60 or over, concurrent use of