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Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands

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Abstract

Aims
To estimate the cost-effectiveness of the current screening programme on familial hypercholesterolaemia (FH) in relatives of diagnosed FH-patients in the Netherlands.

Methods and results
Data from 2229 screened FH-relatives, including age, sex, risk factor status and screening outcome, were combined with the Framingham risk function and national disease-specific cost data to arrive at a model-based comparison of survival and costs, with and without the screening programme. Cost-effectiveness ratios were computed for various treatment strategies, with no screening as reference. Costs per life year gained varied between 25,5 and 32 thousand Euros, depending upon the precise treatment strategy after a positive screen. The costs for screening (tracing the FH-positive individuals) were much lower than the follow-up costs (treatment), of which 80% were costs for statins. Consequently, the costs per life year gained of alternative screening programmes are about the same.

Conclusion
The cost-effectiveness ratio of FH screening is within the range requiring explicit political consideration in the Netherlands. As the costs of statin treatment are the single most important determinant of costs, policy decisions reduce to decisions on the acceptability of statin treatment for this risk group. Pending major changes in statin price, clear guidelines should be developed on how screen positive individuals should be treated, since not all of them have an elevated cholesterol level.
Introduction

Statin treatment is now widely used as lipid lowering therapy: the EUROASPIRE II study carried out in 15 European countries in 1999-2000, showed that the proportion of patients taking a statin varied from 30.7% (Greece) to 75.1% (the Netherlands) [1]. In recent years a number of cost-effectiveness analyses have been carried out regarding statin treatment in cardiovascular disease [2-5]. Assuming lifelong simvastatin treatment for individuals at risk, Pickin and others conclude that treatment is cost-effective for individuals with an annual CHD risk of 3% or higher, for whom the costs are £8200 per life year gained [5]. Studies so far covered patients with a general high risk for coronary heart disease (CHD). Only one study addressed patients with heterozygous familial hypercholesterolaemia (FH) [6]. Patients of this autosomal dominant genetic disease, with a prevalence of 1 in 500 in most Western countries [7-9], usually develop severe dyslipidaemia, characterised by elevated cholesterol levels (mainly the Low Density Lipoprotein (LDL) cholesterol), often in combination with the presence of tendon xanthomata, corneal arcus, xanthelasmata and a family (or personal) history of early CHD [10]. Patients experience a cholesterol-related increased risk for CHD and subsequent mortality especially at a young age [10;11]. From this, Goldman and others considered low to moderate doses of statins to be efficient for primary prevention in these patients [6].

The discovery of LDL receptor gene mutations in clinically diagnosed FH patients allowed for the subsequent development of DNA diagnostic tests, to be used for suspected FH patients. In view of the much higher risk and the availability of treatment, a family based genetic screening programme for familial hypercholesterolaemia was implemented in the Netherlands from 1994 onwards [12]. The programme targets first and second degree relatives of probands diagnosed with FH and a LDL receptor gene mutation at Lipid Research Clinics throughout the country. These relatives with a 50 and 25% prior probability of FH respectively, are tested for the same LDL receptor gene mutation as found in the FH proband. The screening extends further into the family if new patients are identified. Individuals with a mutation for FH are advised to contact their GP to be referred to a Lipid Research Clinic.

The above screening programme started with government approval in a provisional setting. To decide upon nation-wide implementation of the programme, an evaluation study was carried out including a cost-effectiveness analysis (from 1997 until 2000). This is relevant in particular since not all mutation carriers have an elevated cholesterol level [13], so that part of the screen positives are not likely to experience any health gain due to the screening programme but do account for part of the cost. In the absence of trial data, the effectiveness of the Dutch FH screening programme was estimated by combining data on risk factor status and screening outcomes for a large cohort of FH relatives with the Framingham risk function and national disease-specific cost data, to arrive at a comparison of survival and costs with and without the screening programme.
Methods

Population
Data were subtracted for a closed cohort of individuals screened for a LDL receptor gene mutation in the period 1994-1997, aged 16 years and older. In this period 2814 individuals were screened, of which 363 aged younger than 16 years and 222 who were screened on the apoB mutation, leaving 2229 individuals to be included in the present analysis. These individuals were found through 137 FH probands.

General structure of analysis
Primary outcomes of the analysis were life years gained and life time costs of the screened cohort of relatives, theoretically subjected to various strategies of treatment and to a strategy without screening. Life years gained were estimated assuming that all effects of screening and subsequent treatment are mediated by cholesterol level. Empirical data on the cholesterol level and on the treatment effects in terms of cholesterol reduction, were combined with the Framingham risk function to derive a CHD-specific mortality risk under various treatment strategies. All other causes of mortality were assumed to be unaffected. Life time costs were estimated by combining the empirical data on screening costs, with the estimated life years gained by screening, assuming that these will be years with treatment, and the available age and sex specific Dutch costs data [14]. Both computational procedures are presented in detail below. A lifetime horizon was chosen because 1) the start of statin treatment usually implies lifelong treatment, and 2) the life years gained of a preventive intervention (such as screening) are usually in the future (especially with young individuals) while costs are being made from the start onwards. Therefore the time horizon should be long enough to show the full effect regarding the life years gained.

Calculation of life years gained
The following disease model was assumed.
This model is supported by the following facts:
1. FH, defined as the presence of a LDL receptor gene mutation, is associated with an elevated LDL cholesterol and total cholesterol level [10].
2. An elevated cholesterol level causes CHD and thereby excess mortality [15-17].
The presence of a LDL receptor gene mutation is assumed to carry the increased risk through the elevated cholesterol level. Furthermore, we assumed that the screened population only differed from the general Dutch population on their cholesterol values, but not in any other CHD risk factor (blood pressure, obesity). As a consequence, we assumed that any impact of a screening programme would be observed in CHD mortality, leaving the non-CHD mortality unaltered.

The method used to calculate cumulative survival of the above cohort of individuals with and without screening, has been described before [18]. We first used the Framingham risk function [19] to estimate the CHD mortality risk in the general Dutch population, using the observed average CHD risk factor prevalences in the Netherlands [20-23]. The estimated CHD mortality was then compared with the observed CHD mortality [24], and the Framingham risk function was fitted on the observed CHD mortality by adjusting age. Subsequently, the observed total cholesterol / HDL cholesterol ratios from the screened population were entered in this fitted Framingham function, to estimate the (increased) CHD mortality in the screened population. This was done separately for men and women grouped into 5-year age groups as risk profiles and consequent mortality risks differ between each of these groups. The mortality risks calculated with the Framingham function were then added to the observed non-CHD mortality risk in the general Dutch population [24;25], and the resulting total mortality risk was entered into a life table to calculate the life expectancy at the time of screening. Calculations were repeated for the situation in which part of the population is treated with statins, causing a lowering of the cholesterol level in this group. The difference in the life years lived by the cohort in the untreated and the treated situation is the number of life years gained due to screening.

Cholesterol levels were known for 1295 individuals out of the 2229 screened. The lack of cholesterol data for other screenees was due to financial reasons (it was no longer covered by the programme), and we therefore could not see any reason why it would give rise to any systematic bias. We therefore applied the calculations regarding the years of life gained among the 1295 individuals, to the other screenees without cholesterol data, thereby assuming that the cholesterol distribution in these individuals would be the same.

Since no clear guidelines exist at this point with respect to eligibility for treatment for the screened population, different treatment strategies were considered:

1. All individuals with a mutation for FH are eligible for treatment.
2. All individuals with a mutation for FH and a cholesterol level above the 95th percentile of the general Dutch population are eligible for treatment.
3. All individuals with a mutation for FH that fulfil the treatment criteria in the national CBO consensus guideline on hypercholesterolaemia [26], are eligible for treatment.
4. See 1. but only if untreated at screening.
5. See 2. but only if untreated at screening.
6. See 3. but only if untreated at screening.

For all strategies we assumed that all persons with a mutation for FH were adequately treated, once traced by the screening programme, without side effects or non-compliance, causing a
proportional reduction in cholesterol level that persists lifelong (on average 21% reduction of total cholesterol level and 5% increase of HDL cholesterol level) [27]. This was done by using the observed (cross-sectional) cholesterol ratios in the screened population to calculate the difference in cholesterol ratio with the general Dutch population at screening. This difference was then assumed to remain throughout life (thus assuming lifelong treatment and 100% compliance). Lifelong treatment was defined as treatment until 85 years of age, since treatment at higher ages does not seem to be indicated.

**Calculation of costs**

We distinguished between the screening process (tracing the individuals) and the follow-up process, including the direct medical costs and the indirect medical costs during the life years gained due to treatment. We used actual costs when possible.

The cost components for the screening process are: a DNA test in FH probands to find the mutation for FH to enable the family based screening, the programme costs of the family based screening (administration, field work personnel), and DNA tests for all individuals screened for the mutation as found in the FH proband. For the FH probands the national tariff of a DNA test was assumed to reflect the actual costs.

The cost components for the follow-up process are: a single GP consult, a single consult at a Lipid Research Clinic, a single measurement of the lipid profile, treatment with cholesterol lowering drugs for part of the screenees, and control at the Lipid Research Clinic for part of the screenees. Consult costs and lab measurements were calculated assuming full compliance of FH-positives to the diagnostic and follow up protocol, and using published unit costs. Costs of FH-negatives who go to their GP, because they nevertheless have become worried, or because they wanted to have their cholesterol tested, were taken into account. Based on clinical practice we assumed 4 control visits during the first treatment year, 2 visits during the second treatment year, and 1 visit (for ¾ of the treated persons) and 2 visits (for ¼ of the treated persons) during consecutive treatment years.

The costs for statin treatment were calculated by multiplying the number of extra treatment years by the price of cholesterol lowering drugs per person per year. The number of extra treatment years was estimated from the life years gained due to screening, assuming that these will be years with treatment. To estimate the price of cholesterol lowering drugs, we used the observed frequency distribution of drugs in our study (50% atorvastatin, 45% simvastatin and 5% pravastatin). Similarly, we used the observed average dose as prescribed in 2 leading hospitals (45.9 mg atorvastatin, 30.7 mg simvastatin and 27.6 mg pravastatin). Since the average dose exceeded the Standard Daily Dose, which is reported annually in the Dutch formulary (Pharmaceutical Compass) issued by the insurance companies, we have assumed that a doubling in dose causes a 1,5 increase in price, based on the price data per tablet. The price is estimated including 4% administration costs and 4.97 Euros per prescription line, assuming 1 prescription per year.

To estimate the induced costs during the life years gained, the number of deaths prevented due to screening were multiplied by the average direct medical costs per death [14]. This was
done separately for men and women, and for each 5-year age group. Since screening may shift mortality to higher ages and to other causes of death, we distinguished between CHD mortality and non-CHD mortality. This shift may have consequences in terms of costs for CHD that are saved, but are spent on other diseases.

**Technical cost assumptions**
Cost data were collected in the period 1994-1998. Since both the costs of the programme and the number of individuals screened by the programme increased considerably in this period, we calculated the programme-related costs per screenee in 1998 and applied these costs to all screenees to standardize scale effects.

Costs are presented as differential costs (screening minus non-screening). Cost results are presented without discounting. Prices are expressed in Euros. One Euro equals 0,62 British pounds (currency exchange date 18-03-2002).

**Effect and cost estimations in an alternative screening programme**
The considered alternative screening programme differs from the current screening strategy by taking the lipid profile into account. The following treatment strategies will be considered:

1. All individuals with a cholesterol level above the 95th percentile of the general Dutch population, are eligible for treatment.
2. All individuals that fulfil the treatment criteria in the national CBO consensus guideline on hypercholesterolaemia [26], are eligible for treatment.
3. See 1. but only if untreated at screening.
4. See 2. but only if untreated at screening.

The calculation of effects and costs for this alternative screening is done in the same way as for the current screening programme.

**Sensitivity analysis**
The relative importance of our key assumptions was checked through sensitivity analysis.

1. Family history (first degree CHD death before age 60) was not systematically recorded in our study, and ignored in our baseline analysis. In a sensitivity analysis we assume that all screenees have a positive family history, which implies an increased absolute CHD risk and therefore a changed eligibility for treatment according to the Dutch cholesterol consensus.
2. Our Framingham based CHD survival estimates rest on a risk set of which cholesterol level is but one. In the absence of complete detailed data on other risk factors, our baseline analysis assumed the average risk factor levels as have been published for the general Dutch population. In a sensitivity analysis we assume all screenees to have a 20% higher blood pressure compared with the general Dutch population.
3. The baseline analysis assumed that treatment would lead to an average lowering of the cholesterol level as reported in the clinical trials. However, these trials did not include FH patients, so that the generalisation of this quantitative response to our cohort is uncertain.
In a sensitivity analysis we therefore assume that treatment leads to a reduction in the cholesterol level of 30% and an increase in the HDL cholesterol of 6% (instead of 21% and 5% respectively in the baseline analysis), which should be regarded as the most optimistic variant given the observed reductions in a trial [27].

Table 1 Costs of current screening programme

<table>
<thead>
<tr>
<th>Cost components</th>
<th>N</th>
<th>Unit price</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Programme</td>
<td>288 484</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA test on mutation</td>
<td>2229</td>
<td>125.70</td>
<td>280 179</td>
</tr>
<tr>
<td>Multiple DNA test</td>
<td>137</td>
<td>540</td>
<td>73 980</td>
</tr>
<tr>
<td>Total screening</td>
<td></td>
<td></td>
<td>642 642</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single consult GP FH+</td>
<td>759</td>
<td>16.59</td>
<td>12 596</td>
</tr>
<tr>
<td>Single consult GP FH-</td>
<td>121</td>
<td>16.59</td>
<td>2 000</td>
</tr>
<tr>
<td>Single consult specialist FH+</td>
<td>759</td>
<td>72.60</td>
<td>55 112</td>
</tr>
<tr>
<td>Single consult specialist FH-</td>
<td>50</td>
<td>72.60</td>
<td>3 629</td>
</tr>
<tr>
<td>Single lipid profile measurement FH+</td>
<td>759</td>
<td>14.79</td>
<td>11 229</td>
</tr>
<tr>
<td>Single lipid profile measurement FH-</td>
<td>213</td>
<td>14.79</td>
<td>3 153</td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td>29 119</td>
<td>714.46</td>
<td>20 804 347</td>
</tr>
<tr>
<td>Controls during treatment years</td>
<td>29 119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st year</td>
<td>3 036</td>
<td>72.60</td>
<td>220 447</td>
</tr>
<tr>
<td>2nd year</td>
<td>1 518</td>
<td>72.60</td>
<td>110 224</td>
</tr>
<tr>
<td>3rd year and onwards</td>
<td>34 501</td>
<td>72.60</td>
<td>2 504 929</td>
</tr>
<tr>
<td>Costs during life years gained</td>
<td></td>
<td></td>
<td>2 678 255</td>
</tr>
<tr>
<td>Total follow-up</td>
<td>26 405 920</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total screening + follow-up</td>
<td>27 048 563</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number screened: 2229
Number FH+: 759
Number treated: 759
Screening costs per screenee: € 288
Screening costs per FH+: € 847
Follow-up costs per treated individual: € 34 787

1 Costs for follow-up in case of strategy 1: treat all FH+
2 N refers to the number of treatment years for all individuals treated.
Price is calculated per treatment year.

Results

Cost-effectiveness of current screening

Table 1 shows the costs of the screening and the follow-up process in the current screening. The total screening costs are approximately 640 thousand Euros. Per individual screened the screening costs are 288 Euros.
Furthermore, the follow-up costs are shown according to the first screening strategy (treat all FH positives). In this strategy 26 million Euros are spent on treatment for the screened population, which considerably exceeds the screening costs. The costs per person treated are almost 35 thousand Euros. About 80% of the total costs are costs for cholesterol lowering drugs. The reason that additional costs are being made during the years of life gained is that although CHD events are prevented due to treatment, thereby saving CHD-related costs, these individuals survive and have other diseases at older ages, thereby increasing the on average more costly non-CHD related costs.

Table 2 shows the balance between costs and years of life gained for various treatment strategies.

### Table 2 Difference in cost-effectiveness between treatment strategies (current screening)

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>N treated</th>
<th>Costs</th>
<th>Years of life gained</th>
<th>Costs per year of life gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>All FH+</td>
<td>759</td>
<td>27 048 563</td>
<td>865</td>
<td>31 260</td>
</tr>
<tr>
<td>FH+ with elevated cholesterol level</td>
<td>461</td>
<td>18 247 529</td>
<td>610</td>
<td>29 918</td>
</tr>
<tr>
<td>FH+ as in cholesterol consensus</td>
<td>265</td>
<td>9 251 537</td>
<td>361</td>
<td>25 613</td>
</tr>
<tr>
<td>Untreated FH+</td>
<td>430</td>
<td>16 704 039</td>
<td>519</td>
<td>32 164</td>
</tr>
<tr>
<td>Untreated FH+ with elevated cholesterol level</td>
<td>303</td>
<td>12 554 834</td>
<td>407</td>
<td>30 843</td>
</tr>
<tr>
<td>Untreated FH+ as in cholesterol consensus</td>
<td>133</td>
<td>5 637 424</td>
<td>204</td>
<td>27 700</td>
</tr>
</tbody>
</table>

The costs per year of life gained vary between 25,5 and 32 thousand Euros. The lowest costs per year of life gained are made if treatment follows the Dutch cholesterol consensus guideline. These guidelines are based on a cut-off point of 18.151 Euros per year of life gained. The costs being higher here is due to 1) the costs during the years of life gained are not taken into account in the consensus calculations, and 2) relatively more young individuals in the screened population are eligible for treatment due to their highly elevated cholesterol level. The higher costs in the other strategies are due to more young individuals being treated. At these young ages the absolute mortality probabilities are small, so that the number of life years gained due to treatment (in absolute terms) is small, against the high costs of lifelong treatment.

### Cost-effectiveness of alternative screening

Additional cholesterol level measurement in the screening results in about similar cost-effectiveness (table 3).

### Table 3 Cost-effectiveness between treatment strategies in case of alternative screening

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>N treated</th>
<th>Costs</th>
<th>Years of life gained</th>
<th>Costs per year of life gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>All with elevated cholesterol level</td>
<td>658</td>
<td>25 030 932</td>
<td>836</td>
<td>29 957</td>
</tr>
<tr>
<td>All as in cholesterol consensus</td>
<td>406</td>
<td>12 368 034</td>
<td>507</td>
<td>24 376</td>
</tr>
<tr>
<td>Untreated with elevated cholesterol level</td>
<td>489</td>
<td>19 038 280</td>
<td>623</td>
<td>30 558</td>
</tr>
<tr>
<td>Untreated as in cholesterol consensus</td>
<td>263</td>
<td>8 555 188</td>
<td>337</td>
<td>25 360</td>
</tr>
</tbody>
</table>
Although more individuals are treated, resulting in higher costs, more life years are also gained, resulting in similar cost-effectiveness ratios. Note that the cost-effectiveness ratios of comparable treatment strategies are similar or better in table 3 compared with table 2, due to the fact that relatively more elderly individuals are being treated. The absolute mortality probabilities are higher at older ages, so that treatment leads to a greater increase in the total number of years of life gained. On average these individuals are treated for a shorter amount of time because of their shorter remaining life-expectancy, resulting in lower costs and thereby in a more favourable cost-effectiveness ratio.

**Sensitivity analyses**

Table 4 shows the results of the sensitivity analysis.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Baseline analysis</th>
<th>Sensitivity analysis (1)</th>
<th>Sensitivity analysis (2)</th>
<th>Sensitivity analysis (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH+ as in cholesterol consensus</td>
<td>25 613</td>
<td>25 312</td>
<td>19 636</td>
<td>19 328</td>
</tr>
<tr>
<td>Untreated FH+ as in cholesterol consensus</td>
<td>27 700</td>
<td>27 330</td>
<td>21 117</td>
<td>20 770</td>
</tr>
</tbody>
</table>

1 Assuming that all screened individuals have a positive family history

2 Assuming that all screened individuals have a 20% higher blood pressure than the general Dutch population

3 Assuming that treatment results in a 30% reduction of total cholesterol level and a 6% increase in the HDL cholesterol, causing a 35% reduction of the cholesterol ratio

The assumption regarding a positive family history does not affect our results. An assumed 20% higher blood pressure in the screened population (thereby increasing the baseline CHD-risk) results in a more favourable cost-effectiveness ratio, as with higher baseline risk the absolute mortality reduction will be greater. Combined with an on average smaller number of treatment years per person, due to the lower remaining life-expectancy, this results in a better cost-effectiveness ratio. An assumed greater effect of treatment on lowering the cholesterol level results in a lower, more favourable, cost-effectiveness ratio. More life years are gained due to the assumed greater effect of treatment. Although these life years will be years with treatment, thereby increasing costs, the relative increase in the number of life years gained is greater than the relative increase in the number of treatment years.

**Discussion**

The present study has shown that the cost-effectiveness of a family based screening programme for FH in the Netherlands is between 25,5 and 32 thousand Euros per year of life gained, depending on the treatment strategy after a positive screen. The screening costs were much smaller than the follow-up costs, of which 80% consisted of costs for cholesterol
lowering drugs. Consequently, the cost-effectiveness of an alternative screening including cholesterol level measurement is about the same. In the Netherlands systematic screening of serum cholesterol levels is not recommended by national guidelines [26]. Screening for the phenotype (increased serum cholesterol level in affected families) might be an alternative strategy for screening for the genotype (the affected gene). We limited our analysis of screening for the genotype to comparisons with the existing policy (no screening). No data exist about the efficiency of such alternative policies. Analysing costs and effects of these alternative screening policies require a separate analysis, going beyond the scope of this paper.

A model-based approach was used in this study because of lack of available longitudinal data concerning the screened population. The Framingham risk function that was used has been shown to be applicable to a European population [28]. Furthermore, this risk model was used since it contains the cholesterol level as one of the risk factors, and since the screened population mainly consists of asymptomatic carriers who for their cholesterol levels are at CHD risk much alike non-FH patients of similar age and lipid profile. Evidence is lacking concerning more damage and/or higher risks of FH mutation carriers compared with age and cholesterol matched counterparts without FH e.g. due to a greater number of cholesterol years. Jensen et al have shown that a model using the cholesterol-year score to predict the CHD risk in FH patients has the worst correlation with vessel damage [29]. A model with traditional risk factors did not predict the CHD risk very well, but gave a better prediction than the model with the cholesterol-year score. Therefore, the model we used containing all traditional risk factors seems to be the best alternative available.

However, extrapolating the Framingham function to younger and older ages may cause bias. The Framingham function was based on persons aged 30 to 55 years without pre-existing cardiovascular disease at the start of the study. Stamler et al have recently shown that the relationship between cholesterol level and CHD at younger ages is comparable to the relationship in the age group 30 to 55 years of age [30], so that the extrapolation of the Framingham function to younger ages seems justifiable. Extrapolation to older ages seems more hazardous since the relationship between the cholesterol level (or other risk factors) and CHD attenuates at older ages [31;32]. As a result we might have overestimated the life years gained due to screening.

Sensitivity analysis showed that the life years gained may have been underestimated if the effectiveness of treatment in the screened population exceeds the average effectiveness reported in clinical trials[27]. A greater reduction is found in trials carried out in populations with pre-existing cardiovascular disease and a higher baseline cholesterol level (e.g. 26% reduction in the 4S study), compared with trials carried out in populations mainly without cardiovascular disease and a lower baseline cholesterol level (e.g. 20% reduction in the WOSCOPS study). With respect to the presence of cardiovascular disease and baseline cholesterol level, the screened population resembles the latter population more, although the cause of an elevated cholesterol level in the screened population is likely to be quite different. Furthermore, the question is whether the effect of statin treatment as found in the trials is an
accurate estimate of the lifetime impact, given the limited follow-up of the trials (smaller than 10 years). No evidence exists on the effect of statin treatment beyond 10 years. From available knowledge on the way its effects are mediated, the extrapolation based on trial effects seems rational and defendable. In particular, no signs exist on attenuation of its effects. Therefore, it does not seem likely that we underestimated the life years gained.

An issue of general concern is the implicit assumption that the CHD risk is related to a certain cholesterol level, regardless of whether this cholesterol level is the result of treatment or not. We are not aware of any study that has investigated this issue directly. However, since the reduction in mortality risk as found in the trials is greater than the reduction expected based on observational studies [33], this might be regarded as indirect evidence that we have underestimated the risk reduction in the present study in this respect.

On the other hand, our compliance assumptions (100% follow-up, 100% treatment and 100% compliance) were probably too generous. In another study we found that 87% of the individuals with a mutation for FH consult a medical doctor due to the screening and 82% have their cholesterol level checked [34;35]. However, only 21% started taking cholesterol-lowering drugs after the screening, while the remainder was already taking these when they were screened. The compliance was estimated to be 90% rather than 100%. This will have overestimated the absolute number of life years gained. Furthermore, this compliance assumption may also have overestimated the costs if it would mean that individuals get fewer pills on a yearly basis (from the pharmacist) than prescribed because they sometimes forget taking them. The result of both effects on the cost effectiveness ratio is difficult to calculate since it will depend on how often individuals forget. Furthermore, assuming a different percentage of compliance brings up the question who is compliant and who is not. Are individuals at higher risks more compliant or not? And what is the effect on their cholesterol level if individuals are temporarily not compliant? Since we did not have individual data on compliance for the population studied, other assumptions could not be explored.

We assumed that the screened population only differed from the general population in their cholesterol levels, and not in e.g. other risk factors. This assumption followed from our main assumption that the increased CHD risk is entirely determined by the raised cholesterol level. In that context it seems likely that the average level of other risk factors is not different from that in the general population. For smoking this is supported by data from another study on the same screened population [34]. Since we did not have individual data on other cardiovascular risk factors, this could not be checked empirically. We have tested the effect of this assumption on the cost effectiveness ratio through sensitivity analyses, which showed a more favourable cost-effectiveness in case of a 20% higher average blood pressure in the screened population. Further research is needed to investigate to what extent the screened population has a different risk profile apart from the cholesterol level.

The results were presented without discounting. Discounting is appropriate if costs and effects show different flows in future time. However, in this cohort lifetable model, both costs and effects are determined by the same dimension: future life years gained. As this
same dimension is discounted both in numerator and denominator, the effect of discounting on the cost-effectiveness ratio is marginal. Other studies have shown different results with respect to cost-effectiveness. The study of Goldman did also use a model based on the Framingham risk function, but considered lovastatin rather than the newer statins used in this study, and defined FH patients as persons with an extremely elevated CHD risk (equivalent to the risk of persons with a cholesterol level of 15,6 mmol/l) [6]. Also lovastatin was added as primary prevention to already available secondary prevention measures. Pickin et al have shown more favourable cost-effectiveness ratios of lifelong treatment with statins than the present study [5]. Part of the explanation is that only the saved CHD-related health care costs were taken into account but not the shift of costs to older ages and non-CHD causes. When assuming lifelong treatment, the same perspective should also be applied when assessing the health care costs saved. Excluding the costs during the life years gained in our study, resulted in estimated costs of between 23 and 29 thousand Euros per year of life gained, depending on the treatment strategy. Although the difference is smaller, these estimates are still higher. This may have been caused by the younger average age in our screened population (38 years in case of the first treatment strategy compared with 55 to 58 years in the study of Pickin et al). Another reason may be that the screened individuals have fewer other CHD risk factors. Sensitivity analysis showed that a higher baseline CHD risk would lead to a more favourable cost-effectiveness ratio. Within a couple of years some statins will be out of patent, which would lower the costs of statins and would thereby result in a more favourable cost-effectiveness ratio. However, history has shown that pharmaceutical companies usually have a new drug (a statin in this case) ready, which is in fact more expensive than its predecessor. We therefore doubt that in the long run this would lower the statin costs. In conclusion, the cost-effectiveness ratio of this family based screening on FH exceeds the cut-off point of 18,151 Euros per year of life gained as set by the Dutch cholesterol consensus guideline. It therefore requires explicit political consideration. As the costs of statin treatment are the single most important determinant of costs, policy decisions reduce to decisions on the acceptability of statin treatment. Pending major changes in statin price, clear guidelines should be developed on how screen positive individuals should be treated, since not all of them have an elevated cholesterol level. If a mutation for FH does not add to the cholesterol-related CHD risk, mutation carriers should be treated depending on their cholesterol level. Since evidence is lacking in this respect, a final answer cannot be given. For now it seems best to treat screened individuals based on their cholesterol level. Following the guidelines from the Dutch cholesterol consensus and cost-effectiveness considerations, this may exclude many young individuals from treatment although their health gain due to treatment may be much higher than in many other screening programmes. A possibility may be to monitor their cholesterol level regularly and to start treatment when the risks become higher.
Reference List


[34] Marang-van de Mheen P.J., ten Asbroek AHA, van Maarle MC, Stouthard ME, Bonsel GJ, Klazinga NS. Screening on Familial Hypercholesterolemia in The Netherlands. An evaluation of costs, effects and psychosocial consequences [in Dutch]. Amsterdam: Department of Social Medicine, Academic Medical Centre, University of Amsterdam; 2000.