Familial hypercholesterolemia: the Dutch approach

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Chapter 18

Cascade Screening for Familial Hypercholesterolemia: 
Prevention of coronary artery disease in a 
large cohort of FH heterozygotes

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Submitted
ABSTRACT

Background: Familial hypercholesterolemia (FH) is associated with a substantially increased risk of coronary artery disease (CAD). Active screening for FH is ongoing in the Netherlands since 1994 and we previously showed that in this program 85% of FH patients were initiated on statin treatment. This treatment yields a clinically relevant 76% reduction of the risk of a first CAD event in FH patients referred to Lipid Clinics. We now set out to calculate the effectiveness of DNA testing followed by statin prescription on CAD risk reduction in FH patients identified by active screening, instead of by referral.

Methods: In a retrospective study, we assessed the incidence of non-fatal CAD events in 11,783 patients identified with FH by genetic screening before 1990. In the 6,936 patients, who were untreated and free of CAD at diagnosis, we subsequently estimated the number of CAD events after the FH diagnosis was established until expected age of death in order to determine the number of avoidable events.

Results: It was calculated that 3,389 CAD events would occur in 360,880 person years, if all 6,936 FH patients would remain undiagnosed and untreated. In contrast, 1,200 CAD events would occur, assuming that 85% would be treated with statins after FH diagnosis and that such treatment would be associated with a 76% risk reduction.

Conclusions: Genetic testing for FH is highly effective in the prevention of CAD with three untreated individuals to be diagnosed to avert one CAD event. Accordingly, genetic cascade testing for FH, as is currently being performed in the Netherlands, might also be an option for other countries.
INTRODUCTION

Familial hypercholesterolemia (FH) is a common autosomal dominant disorder and is caused by mutations in the low-density lipoprotein receptor (LDLR) gene. These molecular variants result in defective uptake of plasma low-density lipoprotein (LDL) cholesterol (LDL-C) by the liver cells. As a consequence, patients with FH have high plasma LDL-C levels and an increased risk of premature coronary artery disease (CAD). 1-4

In the vast majority of patients fulfilling the clinical criteria for FH, the causal LDLR mutation can be identified by DNA analysis. 5 Knowledge of the causal mutation enables testing of family members for the presence of the same LDLR mutation. In fact, recent guidelines recommend genetic cascade screening of family members of a patient in whom a molecular FH diagnosis is established. 6 Such a screening program for FH, at a national level, has been ongoing in the Netherlands since 1994. 7 Today approximately half of the FH patients that are estimated to be present in the Netherlands have been identified, i.e. 25,000 individuals.

Systematic follow-up of individuals diagnosed with FH through active cascade screening is lacking and the overall effectiveness of the FH screening program in terms of CAD prevention is not well established. This effectiveness was estimated previously on the basis of assumptions from older cohorts from other countries. 8 However, two recent publications on the percentage of statin use and efficacy of statins on CAD prevention allow a more accurate assessment. 9, 10

We aimed to calculate the effectiveness of active FH screening for the prevention of CAD, using data from the large Dutch cohort of FH patients.

METHODS

In order to construct a calculation of the effectiveness of genetic FH diagnosis on prevention of a first CAD event 5 elements are needed: 1 a cohort of FH patients who were treatment naïve and free of CAD at the time of their genetic diagnosis; 2 the incidence of CAD in untreated FH patients; 3 the proportion of FH patients initiating statin treatment after genetic diagnosis; 4 the CAD risk reduction associated with statin treatment in FH patients; 5 the expected average numbers of years to live based on gender and age at the moment of genetic diagnosis.
Study cohort
The study population consisted of unselected individuals that were actively recruited by cascade screening for FH between January 1994 and January 2010. Those identified with the \textit{LDLR} mutation were referred to as 'FH patients' and those without that mutation were referred to as 'Controls'. Index patients, i.e. the clinically diagnosed FH patient who served as the starting point for cascade screening, were excluded. Additionally, we excluded subjects tested for mutations in the Apolipoprotein B gene, which causes Familial Defective Apolipoprotein B, and those tested for \textit{LDLR} mutations that were later proven to be non-pathogenic.\cite{11, 12} Clinical information was obtained by specialised nurses at the time of blood collection. In particular, an extensive history of cardiovascular disease, risk factors and medication use was recorded. DNA was isolated from 10 ml of freshly collected blood. Mutation analysis of \textit{LDLR} was performed as described previously.\cite{13}

The primary outcome measure in this cohort is the calculated number of a first CAD event from genetic diagnosis until expected age of death. For that estimate, we specifically selected the FH patients that were untreated and free of CAD at diagnosis.

Incidence of CAD in untreated FH patients
CAD was defined as the occurrence of one of the following non-fatal cardiac outcomes: a) myocardial infarction; b) coronary artery bypass graft; c) percutaneous transluminal coronary angioplasty, or d) sudden cardiac arrest. For the assessment of CAD incidence, subjects with angina pectoris only were excluded from the analysis. CAD incidence was assessed in the period before statin treatment became available (1990) in order to better reflect the natural course of FH. Therefore, the observational period ended at January 1\textsuperscript{st} 1990.

The proportion of FH patients initiating statin treatment after genetic diagnosis
The assumptions on long-term statin treatment use after FH diagnosis and the efficacy of such treatment on CAD risk were derived from previous publications. The estimate on the proportion of patients to initiate statin treatment after FH diagnosis through DNA analysis was based on a recent survey on medication use two years after the FH diagnosis.\cite{9} For the current analysis, we only used the data of the participants with a proven \textit{LDLR} mutation.\cite{11, 12}
The CAD risk reduction associated with statin treatment in FH patients
In a large Dutch cohort of 2,400 clinically diagnosed FH patients it was shown that statin treatment reduced the CAD risk with 76% (point estimate of 0.24; 95% CI 0.18-0.30). We determined whether CAD risk due to FH mutation carriership was similar between those clinically diagnosed FH patients and the FH patients identified by active genetic screening (see supplemental data file 1). If so, we deemed it justifiable to extrapolate the reported 76% CAD risk reduction induced by statin treatment for the cohort of FH patients identified by genetic screening.

The life expectancy based on gender and age at the moment of genetic diagnosis
For each FH patient identified by genetic testing, we estimated the number of years until expected age of death. This estimate was based on the average life expectancy for individuals of the same age and sex in the general population in the Netherlands (Central Bureau for Statistics in the Netherlands: www.cbs.nl).

Estimate of the effect of genetic FH diagnosis on prevention of a first CAD event
The CAD incidences in the pre-statin era, calculated for 10 year age periods, were applied to the years after FH diagnosis for patients who were untreated and free of CAD at genetic testing, to estimate the number of expected events after diagnosis. At the beginning of each decade we entered all subjects at risk for a first CAD event, and for each subsequent decade, we removed the calculated number of individuals suffering from a first CAD event in the previous decade. The numbers of events that were expected to occur over the decades were added to estimate the overall incidence of first non-fatal CAD events.

Subsequently, we compared CAD incidence after genetic diagnosis in two scenarios: 1) if all would remain untreated and 2) if a proportion, estimated on the basis of observed clinical practice, would initiate treatment. Based on these outcomes, we calculated the number of subjects that would need to be identified with FH to prevent one CAD event during the average expected number of years of life after FH diagnosis. This number was calculated by taking the difference in the number of events expected, in case either none of the patients, or a large realistic proportion of patients would be treated.
Statistical analysis
General characteristics between the cohorts were compared using ANOVA and Chi-square tests. We compared survival of FH patients and controls using Kaplan-Meier survival analysis and the logrank test, stratified for sex. All data were analysed using SPSS software (version 16.0.2, SPSS, Chicago, IL, USA). A two-sided \( p \)-value of 0.05 was considered as significant.

RESULTS

The 5 elements that were needed to calculate the effectiveness of genetic FH diagnosis on prevention of a first CAD event were: 1 a cohort of FH patients who were treatment naïve and free of CAD at the time of their genetic diagnosis; 2 the incidence of CAD in untreated FH patients; 3 the proportion of FH patients initiating statin treatment after genetic diagnosis; 4 the CAD risk reduction associated with statin treatment in FH patients; 5 the life expectancy based on gender and age at the moment of genetic diagnosis. The first 3 elements were derived from the cohort that underwent genetic cascade screening for the proven FH mutation identified in a specific relative, i.e. the clinically diagnosed index patient.

Study cohort of FH patients identified by genetic screening
33,041 family members of genetically confirmed FH patients were actively screened for the specific \( LDLR \) mutation between January 1994 and January 2010. The median year of testing for family members was 2005 with an interquartile range of 2001 to 2006. From that cohort, 11,783 (35.7\%) family members were diagnosed with FH (‘FH patients’), whereas 21,259 (64.3\%) carried no mutation (‘controls’). The clinical characteristics at baseline of these two groups are shown in Table 1. FH patients had higher mean untreated total cholesterol levels than controls (9.7 ± 2.6 mmol/L vs. 6.2 ± 1.9 mmol/L; \( p <0.001 \)). On average, the FH patients were younger, had less hypertension and diabetes and smoked less than controls.

Among the 11,783 FH patients, 6,936 (59\%) did not receive any medication and had not experienced CAD at the moment of testing. These 6,936 patients form the cohort that we use later for calculation of the cumulative CAD incidence after diagnosis.
Effectiveness of FH screening in prevention of coronary artery disease

Table 1: General characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>FH patients</th>
<th>Controls</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>At testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>11,783</td>
<td>21,259</td>
<td>-</td>
</tr>
<tr>
<td>Median year of testing (IQR)</td>
<td>2005 (2001-2006)</td>
<td>2005 (2001-2006)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) (IQR)</td>
<td>37 (22-50)</td>
<td>44 (30-57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>5,636 (48)</td>
<td>10,001 (47)</td>
<td>0.171</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 5</td>
<td>25 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>937 (9)</td>
<td>2,461 (12)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>234 (2)</td>
<td>643 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>3,275 (29)</td>
<td>7,047 (35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)*</td>
<td>9.7 ± 2.6</td>
<td>6.1 ± 1.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cholesterol-lowering medication (%)</td>
<td>4,794 (41)</td>
<td>1,953 (9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>At 1st January 1990</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>9,620</td>
<td>18,440</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) (IQR)</td>
<td>28 (16-39)</td>
<td>33 (21-44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>227 (3)</td>
<td>175 (1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Continuous traits are given as mean ± SD or median (IQR). Abbreviation: FH=familial hypercholesterolemia. *Highest total cholesterol value without treatment.

CAD risk before the introduction of statins

To assess the incidence of CAD before the introduction of statins (set at 1990), 4,982 out of the 33,041 tested subjects had to be excluded because they were born after January 1st 1990. In total 401 CAD events occurred before 1990: 277 (2.9%) in 9,620 FH patients (269,932 person years), and 175 (0.9%) in the 18,440 control subjects (599,446 person years). The CAD incidence was higher for FH patients than for controls, with 10% suffering from a first CAD event by the age 51 and 71, respectively (p<0.001). The incidence of CAD was higher in males than in females, as shown by the Kaplan-Meier curves (Figure 2). The incidence of CAD per age decade in FH patients ranged from 0.6% between 20 and 30 years of age to 18% between 60 and 70 years of age. These incidences are the basis for calculating the incidence in untreated FH (Figure 1: assumption A).
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Figure 1: Flow diagram with used assumptions and the study outcomes.

**Abbreviations:** APOB = Apolipoprotein B gene, CAD = coronary artery disease, FH = familial hypercholesterolemia, HR = hazard ratio, LDLR = Low Density Lipoprotein Receptor gene.


**Assumptions:** A: CAD incidence for FH patients per 10 years of age in the pre-statin era. B: 85% will use statins after genetic FH diagnosis. C: statin treatment is associated with a hazard ratio of 0.24 for coronary artery disease in FH patients. D: life expectancy for Dutch inhabitants of certain gender and age.
Effectiveness of FH screening in prevention of coronary artery disease

Proportion of FH patients initiating statin treatment after genetic diagnosis
We retrieved the data of the responders of the previously published survey on medication use after the diagnosis of FH. In total 781 subjects, aged 18 to 65 years, participated in the survey, of whom 711 (91%) were identified with a proven LDLR mutation in 2006. Of these FH patients, 602 (85%) used statin therapy in 2008, on average two years after FH diagnosis. Therefore, we assumed that 85% of all patients would be on long-term statin treatment after FH had been diagnosed by genetic cascade testing. This figure is used as assumption B (Figure 1: assumption B).

CAD risk reduction associated with statin treatment in FH patients
CAD risk attributable to FH per se was comparable between referred FH index patients and family members identified with FH by genetic screening, as show in Supplemental data file 1. For example, both referred FH patients and FH patients identified by cascade DNA testing had a severely increased risk compared to controls during the age range of 20 to 50 years: HR 9.5, 95% CI: 6.5 to 13.8; p<0.001 and HR 7.3, 95% CI: 5.6 to 9.7; p<0.001, respectively. We used this observation for modelling in the subsequent steps, assuming that statin treatment can reduce the risk of a non-fatal CAD by approximately 76% for FH patients in general (Figure 1: assumption C).

Life expectancy at the moment of genetic diagnosis
The 6,936 FH patients, identified by genetic testing, who did not receive medication and who had not experienced a CAD event yet had an average age at testing of 29 years. We calculated that these subjects would live another 360,880 person years until estimated age of death (Figure 1, assumption D).

The estimated effect of treatment on incidence of CAD after genetic FH diagnosis
To calculate what the effect of DNA testing and subsequent statin prescription would be on cumulative CAD incidence, we first calculated what the consequences would be for these individuals if they remained undiagnosed and untreated. It was calculated that 3,389 events would occur in 360,880 person years, if all 6,936 FH patients would remain untreated, based on the incidence of CAD in the pre-statin era (Figure 1, assumptions A + D). Subsequently, the expected CAD incidence was calculated with the assumption that 85% would be treated after FH diagnosis (Figure 1, assumption B) and that this treatment would be associated with a hazard ratio of 0.24 (95% CI; 0.18-0.30) (Figure 1, assumption C). In that scenario, 1,200 CAD events would
occur. Hence, 2,189 of the 3,389 CAD events (65%) would be prevented (95% CI; 2016–2362) by DNA testing and subsequent statin prescription (Figure 1).

To calculate the number of subjects needed to be identified with FH to prevent one from experiencing CAD during the remaining years of life, it was assumed that without genetic testing all would remain untreated, whereas in contrast, the proportion of treated patients would increase to 85% after genetic diagnosis. With this increase in treatment, twelve family members need to be screened (26,035/2,189 = 11.9) and three FH patients need to be identified (6,936/2,189 = 3.2) to prevent one FH patient from experiencing a CAD event.

Figure 2: Cumulative coronary artery disease (CAD) event-free survival in familial hypercholesterolemia (FH) before 1990

Kaplan-Meier curves for cumulative CAD-event free survival for males and females. Log-rank tests: differences between controls and FH patients for both sexes: *p*<0.001. Abbreviation: CAD=coronary artery disease; FH=familial hypercholesterolemia.
DISCUSSION

This study confirms that the relative risk of CAD is severely increased in patients with FH compared to their unaffected relatives. We earlier showed that 85% of actively screened patients received statin treatment after genetic FH diagnosis \(^9\) and assumed that such cholesterol lowering intervention would yield a relative risk reduction of 76%.\(^10\) Based on all of the above, it was calculated that 65% of the untreated FH patients, who were free of CAD at diagnosis, would be protected against a first CAD event as a consequence of genetic testing followed by statin prescription.

In fact, the prediction model demonstrated that three untreated individuals free from CAD would need to be diagnosed with FH in order to protect one individual against a CAD event. Wonderling and colleagues estimated in 2004 that 100 FH patients would need to be identified and treated with statins between the ages of 18 and 60 to avoid 26 myocardial infarctions (approximately 4 FH patients identified to prevent 1 myocardial infarction).\(^8\) These authors based their findings on extrapolations from early data of the Dutch screening program, as well as from the Simon Broome Register in the United Kingdom.\(^1\), \(^8\), \(^14\) Based on those numbers, these authors concluded that the Dutch cascade testing program was cost-effective.\(^8\) The present findings in a much larger set of individuals outperform these past conservative assumptions.\(^8\), \(^15\)

Several limitations of our study merit discussion. First, the testing organization does not perform systematic follow-up on medication use and clinical outcomes of subjects diagnosed with FH. Therefore, we could only estimate use of medication in a random sample rather than making a direct observation. Similarly, the numbers of CAD events prevented were calculated using assumptions on CAD risk and medication use and compliance after FH diagnosis. Nonetheless, we feel that our estimates of this retrospective analysis are robust, based on the large number of patients both in this study as well as in the original studies that provided the data for our assumptions.\(^8\), \(^10\)

Second, two important aspects that could have biased our findings are selective survival and exclusion of angina pectoris. Standardized mortality was calculated during 10 years of follow up in the Simon and Broome Register, a cohort of 526 clinically diagnosed FH patients from the United Kingdom. The adult patients showed a 3.9 (95% CI 2.1-6.4) excess mortality due to coronary heart disease.\(^7\) In contrast, for the current analysis we did not have the opportunity to use data on the family members who died before FH testing was carried out, because data on cardiovascular history were collected at the time of testing. Second, subjects who only experienced angina
pectoris were excluded from the event free survival analysis. Angina was excluded, because such a symptom reported by tested family members proved unreliable when checked against the official diagnoses from medical records (data not shown). We have no reason to assume that the hazard ratio for angina pectoris free survival for unaffected family members and FH patients would be any different from the more severe CAD events. If we would have been able to include angina pectoris in our analyses, the overall incidence of cardiovascular disease would likely have been higher. Therefore, the absolute number of events prevented by statin treatment after diagnosis would be greater. Hence, both inclusion of living individuals and exclusion of subjects with angina pectoris has probably resulted in a underestimation of the CAD risk conferred by FH and therefore in a underestimation of the efficacy of active identification and statin prescription for the prevention of cardiovascular events.

Third, the estimate of the number of CAD events was restricted to subjects untreated at genetic diagnosis. The substantial proportion of FH patients that received some form of treatment before testing may limit the overall benefit of the program. However, we have previously shown that subjects who used cholesterol-lowering medication at testing received a significantly more intensive treatment regimen after DNA diagnosis of FH.9, 16 Such intensification of statin treatment has been reported to be cost-effective for CAD reduction in FH patients.17 However, clinical outcome studies in FH comparing the efficacy of intensive versus moderate statin therapy are lacking. Therefore, we were unable to quantify the effect of intensified therapy on CAD risk.

In conclusion, genetic cascade testing of family members of index patients with FH can identify subjects with a clearly increased risk of CAD. Genetic FH diagnosis and subsequent initiation or intensification of treatment contributes to the prevention of the majority of CAD events in these patients. Accordingly, genetic cascade testing for FH, as is currently being performed in the Netherlands, might also be an option for other countries.
Supplemental data file:

The estimate on efficacy of statin treatment in preventing CAD in FH was derived from a large cohort of FH patients with a clinical diagnosis of FH.\textsuperscript{10, 18} To determine if it was justified to extrapolate this estimate to the cohort of FH patients identified through genetic cascade screening, we compared the CAD risk in the cohort of clinically diagnosed FH patients with that of FH family members identified with FH through genetic cascade screening.

\textbf{METHOD}

The cohort of clinically diagnosed FH patients was described in detail previously.\textsuperscript{18} That cohort was recruited from 1989-2002 from 27 Lipid Clinics in the Netherlands. Out of 2,400 clinically diagnosed FH patients in this cohort, we selected patients in whom a pathogenic \textit{LDLR} mutation was identified.\textsuperscript{11, 12} The date of the first visit to the Lipid Clinic was set as the end of follow-up, since after the diagnosis of FH lifestyle changes and drug therapy might have modified the natural course of the disease, or conversely, may have lead to thorough screening for cardiac ischemia and earlier intervention than would have been done if FH had not been diagnosed. We refer to this cohort as ‘clinically diagnosed FH patients’.

The two other cohorts used in this study were derived from individuals that had been actively recruited by genetic cascade screening for FH between January 1994 and January 2010. These cohorts are described in detail in the main manuscript.

We determined risk in the period before statin treatment became available in order to estimate the CAD risk associated with the natural course of FH. Statins became available throughout the Netherlands in 1990. Therefore, we censored the analysis at the 1\textsuperscript{st} of January 1990, discarding all observations on CAD-event free survival after this date. Event-free survival was defined as the period from year of birth until the year of first CAD event or censor at the moment of screening or censor at 1\textsuperscript{st} January 1990, whichever came first. We compared survival of clinically diagnosed FH patients and FH family members and family members without FH using Kaplan-Meier survival analysis and the logrank test, stratified for sex. Subsequently, we compared CAD risk between clinically diagnosed FH patients and FH family members and family members without FH using a Cox-proportional hazard model. Unaffected family members served as reference group. We adjusted for sex, year of birth, hypertension, diabetes, smoking and body mass index and these variables included were fixed over time. The Cox-proportional hazard analyses were also repeated in R, taking also family ties into account.
RESULTS

From the cohort of 2,400 clinically diagnosed FH patients, 1,333 carried a pathogenic \textit{LDLR} mutation. Clinically diagnosed FH patients had higher mean total cholesterol levels (10.22 ± 2.10 mmol/L) than FH family members (9.72 ± 2.62 mmol/L; \(p <0.001\)) and, as expected, both FH cohorts had higher mean total cholesterol levels than family members without FH (6.15 ± 1.91 mmol/L; \(p <0.001\)). Other cardiovascular risk factors at the time of screening are shown in \textbf{Supplemental table 1}. In general, the clinically diagnosed FH patients had a more adverse risk profile than the family members identified with FH through genetic cascade screening.

When we censored in 1990, 4,982 out of the 33,041 family members were excluded because they were born after 1\textsuperscript{st} January 1990. In 918,256 person years, 492 CAD events occurred before 1990: 90 in 1,333 (6.8%) clinically diagnosed FH patients (48,878 person years), 277 (2.9%) in 9,620 FH family members (269,932 person years), and 175 (0.9%) in the 18,440 family members without FH (599,446 person years). As expected, traditional risk factors for CAD were significantly more prevalent in those who had experienced CAD than those who had not: patients with a history of CAD were older, had higher BMI, higher untreated cholesterol levels and showed a higher prevalence of diabetes, hypertension and smoking habit than those free of CAD (data not shown).

The CAD-event-free survival was shortest for the clinically diagnosed FH patients, slightly better for the FH family members and best for family members without FH (\textbf{supplemental figure 1}). To adjust for the cardiovascular risk factors, that significantly differed between the three groups (\textbf{supplemental table 1}), we performed Cox proportional hazard modelling. In the age range with the highest relative risk of CAD and sufficient numbers of observations, i.e. between 20 and 50 years, both clinically diagnosed FH patients and FH family members had an increased CAD risk compared to that in non carriers (HR 7.3, 95\%CI: 5.6 - 9.7; \(p<0.001\) and HR 9.5, 95\%CI: 6.5 - 13.8; \(p<0.001\) respectively). But the risk difference between the two FH cohorts was small and did not reach statistical significance in this age period: HR 1.3, 95\%CI: 0.9-1.8; \(p=0.14\). The analyses described above were also performed with \textit{R} statistics - also taking family ties into account – and these analyses yielded results that were in essence similar (data not shown).
Supplemental figure 1: Cumulative coronary artery disease (CAD) event-free survival in familial hypercholesterolemia (FH) before 1990

Kaplan-Meier curves for cumulative CAD-event free survival for males and females. Log-rank tests: differences between controls and FH patients for both sexes: \( p < 0.001 \). Abbreviation: CAD = coronary artery disease; FH = familial hypercholesterolemia.

CONCLUSION

We first demonstrated again that the relative risk of CAD is severely increased in patients with FH compared to their unaffected relatives, not only in referred and clinically diagnosed patients but to a similar extent affected in family members identified by cascade testing. In fact, CAD risk in FH family members found by proactive testing was very close to that of clinically diagnosed FH patients. We used this observation for modelling in the subsequent steps, assuming that for both FH groups CAD risk can be reduced by approximately 76% with statin treatment.\(^{10}\)
### Supplemental table 1: General characteristics of the study population

<table>
<thead>
<tr>
<th>clinically diagnosed FH patients</th>
<th>Family members without FH</th>
<th>relatives of FH patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At screening (N=34,375)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>1,333</td>
<td>11,783</td>
</tr>
<tr>
<td>Median year of screening</td>
<td>1995</td>
<td>2005</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 ± 12</td>
<td>37 ± 20</td>
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<tr>
<td>Male gender (%)</td>
<td>614 (46.1)</td>
<td>5,636 (47.8)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.5</td>
<td>23.7 ± 4.8</td>
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<tr>
<td>Hypertension (%)</td>
<td>99 (7.5)</td>
<td>937 (8.5)</td>
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<tr>
<td>Diabetes (%)</td>
<td>65 (4.9)</td>
<td>234 (2.1)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>395 (31.4)</td>
<td>3,275 (29.3)</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>10.22 ± 2.10</td>
<td>9.72 ± 2.62</td>
</tr>
<tr>
<td>Cholesterol-lowering medication (%)</td>
<td>622 (46.7)</td>
<td>4,794 (40.7)</td>
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<tr>
<td>Coronary artery disease (%)</td>
<td>175 (13.1)</td>
<td>829 (7.0)</td>
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<td><strong>At 1st January 1990 (N=29,393)</strong></td>
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<tr>
<td>N</td>
<td>1,333</td>
<td>9,620</td>
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<tr>
<td>Age (years)</td>
<td>38 ± 13</td>
<td>28 ± 17</td>
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<tr>
<td>Coronary artery disease (%)</td>
<td>90 (6.8)</td>
<td>227 (7.9)</td>
</tr>
</tbody>
</table>

Continuous traits are given as mean ± SD. Abbreviation: FH = familial hypercholesterolemia.
REFERENCES


