First-degree relatives of individuals with premature coronary heart disease (CHD) bear an excess risk of CHD themselves that is 2 to 12 times that of the general population. Familial-clustered CHD accounts for 50% to 60% of total documented CHD before 60 years of age. Siblings of patients with CHD prior to 60 years also have an extremely high prevalence of elevated lipid levels, likely attributable to both shared sociocultural environment and heredity.

Elevated levels of serum cholesterol have been shown to be associated with high risk for CHD. Prior studies have shown that nearly 25% of these siblings have a low-density lipoprotein cholesterol (LDL-C) level above the 90th percentile relative to the general population. A high proportion have previously untreated elevations at the time of an index case event. Siblings also fail to lower LDL-C after there has been a premature event in the family even when they are seen by a physician for screening. Little is known about the effects of interventions to lower LDL-C in high-risk families identified from an index patient hospitalized with premature CHD. The Second Adult Treatment Panel (ATP II) Guidelines of the National Cholesterol Education Program are oriented to high-risk individuals. If applied to high-risk families, the guidelines offer a potentially powerful tool for reducing the projected number of subsequent premature CHD events.

This study was designed to: (1) determine whether goal ATP II levels of LDL-C lower than 3.36 mmol/L (130 mg/dL) can be attained with treatment in a population of apparently healthy siblings with high LDL-C levels of patients with documented CHD before 60 years of age and (2) determine whether nurse management (NURS) or enhanced primary care (EPC) resulted in a significant improvement in the proportion of siblings meeting the ATP II guidelines.
SUBJECTS AND METHODS

DESIGN AND SUBJECTS

Protocols for The Johns Hopkins Sibling Study have been previously described in detail. The overall design is presented in the Figure. Eligible index patients were younger than 60 years with any 1 of the following: (1) acute myocardial infarction with new pathologic Q waves on an electrocardiogram and elevation of creatine kinase levels to 2 times or more of the upper limit of normal, and an increase in the MB isoenzyme to 5% or more of the total creatine kinase concentrations, (2) revascularization including percutaneous transluminal angioplasty and coronary artery bypass surgery, or (3) angina with at least 1 angiographically documented lesion of 50% diameter stenosis or greater in 1 or more coronary arteries. Index case patients with collagen vascular disease, acute cocaine intoxication at the time of an acute myocardial infarction, long-term glucocorticosteroid therapy, or organ transplantation were excluded. All data were verified from the medical records at the time of hospitalization. Seven hospitals in Baltimore, Md, were used to access a socially, ethnically, and medically heterogeneous population.

Eligible siblings included those (1) between the ages of 30 and 59 years, (2) without known CHD, and (3) without major life-threatening comorbidity (cancer or acquired immunodeficiency syndrome). Siblings with organ transplantation, chronic glucocorticosteroid therapy, or comorbidity with a life expectancy of less than 3 years were excluded. Siblings with type 1 diabetes mellitus were excluded. Among index case patients with eligible siblings, less than 5% refused access to siblings. Identified siblings were sent a letter describing the study with a refusal postcard to return within 2 weeks. If the refusal was not received, siblings were called to verify medical history and to schedule risk factor screening. The absence of CHD was verified in the telephone interview by an experienced interviewer and verified with the primary care physician in the case of any potential CHD history. Refusal postcards were returned for less than 5% of eligible siblings; 267 eligible siblings of index case patients entered the screening portion of the study. Siblings were screened following informed consent in the Outpatient Clinical Research Center of the Johns Hopkins Medical Institutions after protocol approval by the Johns Hopkins Joint Committee on Clinical Investigation. A cardiovascular history taking and physical examination were conducted by a cardiologist. Dietary assessment and anthropometric measures were performed. Blood samples were drawn for lipid level determination after siblings fasted for 12 to 14 hours. Results of the screening were reviewed by a nurse and a cardiologist and a standardized feedback with recommendations based on ATP II guidelines was sent to all participants and their primary care physicians. The feedback was prepared by a nurse who entered the raw data into a computer program that used standard branching treatment algorithms developed from national ATP II guidelines. This computer program (SIB-ENABLE) was designed specifically for the Johns Hopkins Sibling Study. All feedback contained goal ranges and standardized computer-generated text based on screening results.

Siblings were randomized to either the EPC or to NURS intervention. Randomization was done by family using a computerized schema. Each family had a number with a corresponding sealed envelope containing the assignment. The envelopes were opened after all siblings from the same family had been screened. Siblings with LDL-C levels of 4.14 mmol/L (160 mg/dL) or higher were then randomized to NURS or EPC group, while those with LDL-C levels lower than 4.14 mmol/L (160 mg/dL) did not enter the trial.

INTERVENTIONS

Feedback and Recommendations

All siblings and their primary care physicians received the same feedback and recommendations after screening, including ATP II LDL-C goal levels and treatment guidelines. Dietary recommendations focused on consumption of less than 30% of total energy as fat and less than 300 mg/d of cholesterol. Physical activity recommendations followed those of the American College of Sports Medicine focusing on 30 minutes of moderate-intensity exercise, at leisure or at work, 3 days a week or more. Pharmaceutical companies provided free drugs for medically indigent patients on application who demonstrated both financial need and therapeutic indications. The process varied by company. Contact information for companies manufacturing specific agents are included in the Index Medicus. In this study, a protocol for pharmaceutical company application was generated. Pharmaceutical company indigent protocols were provided both to NURS and EPC groups based on siblings’ needs.

Specially Trained Nurses

Siblings randomized to the NURS group received care by a nurse for 2 years. Primary care providers of NURS siblings were explicitly asked not to intervene in the care of high LDL-C levels and to supply information to the study about the treatment of other nonlipid risk factors. Three study nurses received mentored training for 1 month at the Johns Hopkins Lipid Clinic and for 2 months at the Johns Hopkins Preventive Cardiology Clinic 2 to 3 days per week. All 3 nurses had a background in cardiovascular nursing (2, 6, and 10 years of experience). The LDL-C goal was lower than 3.36 mmol/L (130 mg/dL). After a 2-month trial of diet and exercise, pharmacologic recommendations were instituted for those whose LDL-C levels remained at 4.14 mmol/L (160 mg/dL) or higher. Prescriptions were

RESULTS

BASELINE CHARACTERISTICS

Index Case Patients

Index case patients (n = 171) corresponding to the 267 screened siblings had a mean ± SD age of 49 ± 6 years; 74% were men and 18% were African American. The majority experienced an invasive intervention at the time of hospitalization (37% had angioplasty and 39% had coronary artery bypass surgery), 9% had experienced a myocardial infarction without intervention, 14% were hospitalized for medical treatment of angiographically documented CHD, and 1% had sudden death on admission to the hospital. Risk factors were...
written by a study physician and drugs were managed at the discretion of the nurse, following the ATP II guidelines. For siblings whose levels decreased below 4.14 mmol/L (160 mg/dL) but not below 3.36 mmol/L (130 mg/dL), more aggressive measures included further adjustment of diet and exercise. Siblings met with a nurse approximately every 4 months and were contacted by telephone an average of 3 times per year for lipid therapy compliance monitoring and dietary counseling.

The NURS encounters used a health education framework to address factors known to be associated with behavior change. Barriers to implementation of diet, pharmacotherapy, exercise, and smoking cessation were discussed. Typically, encounters used standardized prompts that centered on readiness to change, support systems, and the sociocultural, work, and economic environment. Siblings in the NURS group in the same kindred were encouraged to come together for treatment. The ATP II guidelines were followed for monitoring of LDL-C blood levels and recommended laboratory tests were used to monitor safety during pharmacotherapy.

Enhanced Primary Care

Siblings randomized to EPC were encouraged to seek cardiovascular risk factor management from their primary health provider. Feedback and recommendations were sent to EPC siblings indicating that they should see their physicians within a month. Studies have demonstrated that the ATP II guidelines are often not followed in standard practice, although there has been a trend toward improvement over the last decade since the first National Cholesterol Education Program ATP guidelines were released. Usual care in this study was enhanced by providing primary care physicians with results of a full lipid profile, assessment of nonlipid cardiovascular risk factors, examination by a cardiologist, pharmaceutical company indigent protocols, and patient-specific recommendations based on algorithms from the ATP II guidelines.

ASSESSMENT OF NONLIPID RISK FACTORS

The threshold for implementing the ATP II guidelines is dependent on the presence of other nonlipid cardiovascular risk factors. More aggressive treatment and lower goal levels are sought for individuals with 2 or more risk factors. These include current cigarette smoking, hypertension, obesity, physical inactivity, age, sex, and family history of premature CHD. Cigarette smoking was assessed at baseline and defined as self-report of smoking in the past month and/or an expired carbon monoxide level of 8 ppm or higher. Blood pressure was measured using a standard mercury sphygmomanometer. Blood pressure used for all analyses was averaged from 3 auscultatory measurements taken over an 8-hour day using American Heart Association guidelines. Hypertension was defined as the presence of an average blood pressure of 140 mm Hg systolic or higher and/or 90 mm Hg diastolic and/or receiving treatment with antihypertensive agents. Obesity was defined as a body mass index (a measure of weight in kilograms divided by the square of the height in meters) higher than 27 kg/m². Physical inactivity was assessed by the questionnaire of Paffenbarger et al and defined as less than 30 minutes of moderate intensity 3 times per week or more. Diabetes mellitus was defined only as self-reported clinical type 2 diabetes, although 13 siblings were found to have a fasting blood glucose level higher than 7.8 mmol/L (140 mg/dL) in the absence of known diabetes. A questionnaire assessed age to the nearest birthday.

DIETARY ASSESSMENT

The Block Health Habits and History Questionnaire food frequency instrument was administered by the interviewer at baseline and at the 2-year follow-up to estimate total energy intake per day, percentage of total energy intake from fat, and cholesterol in milligrams per day. Frequency was estimated over the past month. Data were analyzed using the computerized Dietary Analysis System (National Cancer Institute, Bethesda, Md) for personal computers. All dietary information was verified and reviewed with the study diettian. This food frequency assessment method has demonstrated correlations of 0.70 or more with food records, diaries, and 2-day food recall methods.

ANTHROPOMETRIC MEASURES

Height in inches was measured using a stadiometer. Weight in pounds was determined on a balance scale without shoes and with light clothing, and body mass index was calculated.

LIPID MEASUREMENTS

Serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) levels were measured after a 12- to 14-hour overnight fast. Assays were performed using methods previously described by the Lipid Research Clinics program. The LDL-C was estimated using the equation by Friedewald et al:

\[
\text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5}
\]

This estimate is considered accurate for triglyceride levels up to 4.2 mmol/L (400 mg/dL). At baseline, siblings were eligible for randomization if their LDL-C level was 4.14 mmol/L (160 mg/dL) or higher. Goal levels at follow-up were lower than 3.36 mmol/L (130 mg/dL). Although the ATP II guidelines recommend 2 LDL-C measurements 1 to 8 weeks apart to make decisions for treatment, only 1 was used to characterize levels at baseline and follow-up. In the NURS group, measurements were made serially and monitored according to the frequency recommended by the ATP II guidelines.
tein profiles were generally less favorable in the EPC siblings. On average, eligible siblings were in their fifth decade of life and had been high school graduates.

Of siblings randomized after screening, few were consuming diets that were less than 30% of total energy as fat at baseline, with a mean fat intake of 82 g in the NURS group and 84 g in the EPC group. Daily energy intakes were similar at baseline between the NURS and the EPC groups (7941 kJ/d and 8146 kJ/d, respectively). Mean HDL-C levels increased modestly in both groups with similar ranges.

TWO-YEAR FOLLOW-UP

An intention-to-treat analysis was used. All individuals who failed to return for 2-year follow-up were considered not to have met goals and in the case of continuous variables were assigned a 0 for change scores or were assigned their original levels in multivariate analysis. Overall return rates were 77%, with a slightly higher return in the EPC group (82%).

Lipids

The average decline in levels of LDL-C was greater for the NURS group than the EPC group but each group showed a statistically significant decline at 2 years (Table 2). While not statistically significant, triglyceride levels decreased by a small amount in the NURS group (P = .56) and increased slightly in the EPC group (P = .48). Mean HDL-C levels increased modestly in both groups and nearly reached statistical significance in the NURS group (P = .10) but not the EPC group (P = .70). The most notable change was a marked difference in the proportion of siblings in the NURS group vs EPC group achieving LDL-C levels lower than 3.36 mmol/L (130 mg/dL) as per the ATP II recommendations: more than one quarter of siblings in the NURS group, 2.5 times that of the EPC group.

Diet

There was a clear trend toward improvement in dietary profiles in the NURS group with decrements in both total fat and energy intake. The EPC group had worse dietary fat and energy intake at follow-up, although there was considerable variation in both groups. In the NURS group, 33.8% achieved daily consumption of less than 30% of total energy as fat at 2 years, compared with 23.5% in the EPC group at 2 years (P = .18). The absolute change in proportion meeting the dietary total fat goal was 26.4% in the NURS group and 17.3% in the EPC group (P = .26). The NURS group reduced energy intake per day by 528 kJ (SD, ± 2519 kJ) while the EPC group increased energy intake per day by 263 kJ (SD, 2125 kJ; P = .07).
Anthropometrics

Mean body mass index stayed the same from baseline to 2 years: 28.1 and 28.2 kg/m², respectively, in the NURS group and 29.6 and 29.7 kg/m², respectively, in the EPC group. No changes were observed in body weight in either group.

Pharmacotherapy

At baseline, only 3 individuals in the NURS group and 6 individuals in the EPC group had pharmacotherapy prescribed. At follow-up, this increased to 41 individuals (n = 33) in the NURS group and 47 (n = 25) in the EPC group (P = .001). Of prescribed drugs, 82% were 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, 17% were nicotinic acid, and 5% were fibric acid derivatives in the NURS group; 75% were 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, 13% were nicotinic acid, and 5% were fibric acid derivatives in the EPC group. Most drugs in both groups were 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

Multivariate Analyses

To determine which factors contributed independently to achieving the goal LDL-C level lower than 3.36 mmol/L (130 mg/dL), multiple logistic regression analysis was used. Age, education, baseline LDL-C levels, and body mass index were entered as continuous variables. Sex, race (African American or white), and intervention contingency (NURS vs EPC) were entered as dichotomous variables. With regards to achieving goal LDL-C levels, no continuous variables had a statistically significant parameter estimate and no P value was less than .11, except for NURS compared with EPC (P = .005). The relative odds of achieving the goal LDL-C level in the NURS group was 4.10 times that of the EPC group (95% confidence interval, 1.55–10.86) controlling for other variables in this model. To determine the effects of pharmacotherapy and diet on achievement of goal LDL-C levels lower than 3.36 mmol/L (130 mg/dL), a logistic regression analysis was constructed adding new variables, including the prescription of a lipid-lowering agent and dietary total fat intake of less than 30% total fat at 2-year follow-up. In this model, only the presence of pharmacotherapy (P = .001) was a significant independent predictor. The relative odds of reaching the goal level independent of all other variables was 6.02 for individuals taking pharmacotherapy compared with those who did not (95% confidence interval, 2.24–16.18) (Table 3). The NURS intervention remained marginally statistically significant (P = .09).

This study reinforces a prior finding that high LDL-C levels are prevalent in apparently healthy siblings of patients with a recent hospitalization for documented premature CHD. Other nonlipid risk factors are also frequent. Much of the risk for premature CHD in childhood and adolescence stems from familial factors.17 Other nonlipid risk factors are also frequent. More siblings screened at baseline had high LDL-C levels according to ATP II guidelines and were eligible for treatment. After 2 years of treatment there was a significant increase in the percentage of siblings mea-

Table 2. Two-Year Lipid Changes Years Within and Between Groups Significance NURS and EPC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2 Years After Treatment Initiation</th>
<th>2 Years After Treatment Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, mg/dL†</td>
<td>0.05 ± 0.25</td>
<td>0.05 ± 0.25</td>
</tr>
<tr>
<td>HDL-C, mg/dL†</td>
<td>0.01 ± 0.19</td>
<td>0.01 ± 0.19</td>
</tr>
<tr>
<td>TG, mg/dL†</td>
<td>0.09†</td>
<td>0.09†</td>
</tr>
<tr>
<td>% LDL &lt; 3.36 mmol/L (130 mg/dL)</td>
<td>.008§</td>
<td>.008§</td>
</tr>
</tbody>
</table>

Table 3. Multiple Logistic Regression Analysis Predicting Achievement of LDL-C Levels Lower Than 3.36 mmol/L (130 mg/dL) 2 Years After Treatment Initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parameter Estimate/SE</th>
<th>Relative Odds</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>0.04/0.04</td>
<td>. . . . . . . .</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>Education, y†</td>
<td>0.03/0.10</td>
<td>. . . . . . . .</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>0.06/0.05</td>
<td>. . . . . . . .</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL†</td>
<td>0.05/0.01</td>
<td>. . . . . . . .</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Male sex§</td>
<td>0.55/0.51</td>
<td>1.73</td>
<td>0.63–4.71</td>
<td>.29</td>
</tr>
<tr>
<td>Black race‡</td>
<td>0.45/0.55</td>
<td>1.57</td>
<td>0.54–4.60</td>
<td>.41</td>
</tr>
<tr>
<td>Total fat % &lt; 30%¶</td>
<td>0.52/0.51</td>
<td>1.69</td>
<td>0.62–4.57</td>
<td>.30</td>
</tr>
<tr>
<td>NURS¶</td>
<td>0.92/0.54</td>
<td>2.51</td>
<td>0.87–7.23</td>
<td>.09</td>
</tr>
<tr>
<td>Lipid drug#</td>
<td>1.80/0.50</td>
<td>6.02</td>
<td>2.24–16.18</td>
<td>.40</td>
</tr>
</tbody>
</table>

* LDL-C indicates low-density lipoprotein cholesterol; BMI, body mass index (a measure of weight in kilograms divided by the square of the height in meters); TG, triglycerides; and LDL, low-density lipoprotein.
†Baseline levels, entered as continuous variables.
‡Compared with female sex.
§Compared with white race.
¶Compared with no lipid-lowering drug at 2 years.
#Compared with a diet at 2 years of less than 30% of total energy intake as fat.
*Compared with enhanced primary care.
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ing goal LDL-C levels in both interventions (NURS and EPC). However, siblings in the NURS model had significantly greater improvement in LDL-C levels and a greater proportion who reached LDL-C goal levels than siblings in the EPC strategy. No significant changes were observed in body mass index, body weight, or physical activity in either group. Multiple logistic regression analysis demonstrated that the primary independent factor in achieving goal LDL-C levels in siblings was pharmacotherapy, mainly with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. All lipid-lowering agents were prescribed more frequently for the NURS group. At follow-up, many siblings (95% of NURS and 92% of EPC) reported compliance with prescribed drug regimens. Compliance was based on self-report indicating that the drugs were taken “most or all of the time.” Among those who were considered noncompliant, most had initiated the drug but discontinued it due to adverse effects or disinterest.

Given that siblings are at a marked increase in risk for CHD and that they received individualized ATP II recommendations, it is disappointing that greater changes in diet and physical activity were not observed. This is congruent with our prior studies that indicate that siblings of individuals with premature CHD do not perceive their own high relative risk and that they do not make lifestyle changes to lower the risk. The greatest impact of intervention on LDL-C levels appears to be attributable to drug treatment. Since most siblings qualified for drug intervention, based on the presence of 2 or more other risk factors, it is surprising that more siblings requiring pharmacotherapy in both NURS and EPC groups did not receive it. There was no evidence that EPC siblings refused pharmacotherapy, suggesting the results were most influenced by prescribing patterns. The nurse interventionist was granted the same latitude for applying the ATP II guidelines as were EPC physicians. In the NURS group initiation of pharmacotherapy was negotiated with patients; many with high LDL-C levels did not receive therapy because they were reluctant or the nurse may have received feedback that discouraged therapy. Each encounter was complex and involved significant nurse/patient and family interactions. Rigid drug treatment protocols were not enforced but were encouraged in nurse management.

It is possible that denial of risk by siblings was a barrier to recommended lifestyle changes in both groups. Some siblings may have failed to make complex lifestyle changes since the use of lipid-lowering agents may have been far easier than recommended diets and exercise and may have also offered a sense of protection.

It remains unclear why ATP II guidelines are not applied more frequently by primary care providers. In this study, EPC providers were all physicians and most failed to apply the ATP II guidelines in this very high-risk population, even when prompted. The standard of care has markedly improved application of the ATP II guidelines among physicians.

Observational studies and randomized trials indicate that the NURS approach can effectively alter cardiovascular risk factors in high-risk populations. Nurse management has been shown to be a viable and effective alternative or complement to usual care, eminently reproducible across populations with a high prevalence of cardiovascular risk factors.

The intention-to-treat analysis might potentially obscure any additional attainment of goal LDL-C levels among dropouts, likely resulting in type II error. The characteristics of individuals who did not participate in the initial screening are not known, although this is unlikely to have had a major impact given the small number. We elected to define individuals with premature CHD as younger than 60 years for both men and women, while the ATP II guidelines specify individuals with premature CHD as younger than 65 years in women and 55 years in men. The bias resulting from this is not known. Siblings of individuals with sudden death were excluded. Again, the biases introduced by this remain unclear. It is likely, however, that this intervention trial produced a best-case scenario in both intervention groups. Virtually all siblings in the EPC group saw their health care provider at least once. Telephone calls did not occur often in the EPC group. It would have been helpful to examine the time spent with the sibling and the nature and number of visits, but this simply was not possible because of inadequate physician records and poor patient recall.

High LDL-C levels in siblings were more effectively treated by the NURS intervention than the EPC approach, probably related to stronger adherence to ATP drug and dietary guidelines. Nonetheless, most siblings with high LDL-C levels do not meet goal levels 2 years after an index case CHD event even with aggressive screening strategies. The failure to reach LDL-C goal levels in most high-risk siblings remains a concern.

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