Risk of Fatal Stroke in Patients With Treated Familial Hypercholesterolemia
A Prospective Registry Study

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Background and Purpose—Although it is recognized that in heterozygous familial hypercholesterolemia, large extracranial carotid vessels are affected by atherosclerosis, the risk of fatal stroke after treatment with cholesterol-lowering therapy remains uncertain. The goal of this study was to determine the risk of fatal stroke in patients with treated familial hypercholesterolemia.

Methods—A cohort of 1405 men and 1466 women with definite or possible heterozygous familial hypercholesterolemia was recruited from 21 outpatient lipid clinics in the United Kingdom. Patients were followed up prospectively from 1980 to 1998 for 22,992 person-years for a median duration of 7.9 years (interquartile range, 4.9 to 12.0 years). The mortality rate was calculated, and the standardized mortality ratio for men and women 20 to 79 years of age was derived from the ratio of the observed deaths to the number expected in the general population of England and Wales (standardized mortality ratio = 100 for the standard population).

Results—A total of 169 deaths occurred; 9 (5.3%) were a result of stroke. The mortality rate from stroke was 0.39 per 1000 person-years (95% confidence interval, 0.18 to 0.74), and the standardized mortality ratio for fatal stroke was nonsignificantly lower than in the general population (79; 95% CI, 36 to 150).

Conclusions—The results suggest that patients with treated familial hypercholesterolemia are not at increased risk of fatal stroke. However, the possibility cannot be excluded that untreated individuals are at increased risk, which would be consistent with the evidence that familial hypercholesterolemia is a panvascular disease. (Stroke. 2003;34:22-27.)

Key Words: hypercholesterolemia, familial ■ mortality ■ stroke

Heterozygous familial hypercholesterolemia is an autosomal dominant monogenic disorder of lipoprotein metabolism that affects ~1:500 of the population.1 In most patients, it is caused by mutations in the gene for the low-density lipoprotein (LDL) receptor, resulting in an accumulation of LDL cholesterol in the plasma and a substantial excess mortality from coronary heart disease.1 The cumulative risk of a fatal or nonfatal coronary event by 60 years of age without effective treatment is at least 50% in men and ~30% in women,2,3 and the relative risk of a fatal event has been reported to be increased ≈100-fold in young adults 20 to 39 years of age, although patients who survive through middle age appear to no longer be at substantially increased relative risk.4 The prognosis, however, has improved substantially since the introduction and widespread use of lipid-lowering drug therapy with HMG-CoA reductase inhibitors (statins).5

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The incidence of clinical manifestations of peripheral and cerebrovascular atherosclerotic disease in familial hypercholesterolemia remains unclear. A small increase in prevalence of peripheral vascular disease has been reported in some studies,6,7 although in a recent case-control study, nearly a third of patients without intermittent claudication had evidence of hemodynamically significant peripheral vascular disease.8 Large extracranial carotid vessels are also affected by atherosclerosis,9,10 and severity has been reported to be related to age and the level of hypercholesterolemia.11 There are few reported data on the incidence of stroke,10,12,13 and these conflict, with 1 study suggesting an excess risk12 while another found no increase compared with the general population.13 In this article, we report stroke mortality in the largest published cohort of 2871 men and women with treated familial hypercholesterolemia.
familial hypercholesterolemia followed up prospectively for up to 18 years.

**Patients and Methods**

The methods have been described in detail elsewhere. Recruitment of patients to the Simon Broome Hyperlipidemia Register began in 1980 and is continuing. The 21 participating outpatient lipid clinics registered patients referred to them by either general practitioners or hospital specialists, and a subsample of 6 clinics provided further detailed clinical information on 458 patients followed up between 1997 and 1999. A fasting venous blood sample was taken, and LDL cholesterol concentration was calculated with the Friedewald equation. Patients were classified as having either definite or possible familial hypercholesterolemia through the use of the Simon Broome Register diagnostic criteria, which were amended in June 1994 to include a DNA-based diagnosis. Definite familial hypercholesterolemia is defined in adults as (1) total cholesterol concentration >7.5 mmol/L (290 mg/dL) or an LDL cholesterol concentration >4.9 mmol/L (189 mg/dL) in adults (measurements either pretreatment or highest on treatment) plus (2) tendon xanthomas in the patient or a first- or second-degree relative or (3) DNA-based evidence of an LDL receptor mutation or familial defective apolipoprotein B-100. A possible diagnosis of familial hypercholesterolemia required the first definition above plus 1 of the following: (1) family history of myocardial infarction before 50 years of age in a second-degree relative or before 60 years of age in a first-degree relative or (2) family history of raised total cholesterol concentration >7.5 mmol/L in a first- or second-degree relative.

The names of registered patients were flagged by the National Health Service Central Registry, and in the event of death, a copy of the death certificate was supplied. The underlying cause of death was coded by an investigator using the International Classification of Disease, Ninth Revision (ICD-9). The diagnosis of stroke was based on ICD-9 codes 430 through 438: 430, subarachnoid hemorrhage; 431, intracerebral hemorrhage; 432, other unspecified hemorrhage; 433, occlusion and stenosis of precerebral arteries; 434, occlusion of cerebral arteries; 435, transient cerebral ischemia; 436, acute but ill-defined cerebrovascular disease; 437, other and ill-defined cerebrovascular disease; and 438, late effects of cerebrovascular disease.

**Statistical Analysis**

To determine whether patients with definite or possible familial hypercholesterolemia are at increased risk of fatal stroke, a life-table analysis was undertaken with a computer program that applies standard methods for cohort studies. The expected number of deaths was calculated by applying the 5-year age and 5-year calendar-specific death rates for men and women in the general population of England and Wales to the person-years accumulated by men and women in this cohort. Subjects were censored on reaching 80 years of age, and patients who emigrated were censored at the date of embarkation. The measure of risk derived was the ratio of the number of deaths observed to the number expected. This was expressed as a percentage to give the standardized mortality ratio (SMR; SMR = 100 for the reference population). The 95% confidence intervals (CIs) for the SMR were calculated assuming a Poisson distribution for the observed frequency in the numerator. The test of significance used was a 2-sided Poisson probability of observing the number of deaths that occurred given the expected number of deaths. To assess the effect of the introduction and widespread use of more effective lipid-lowering drug therapy with statins, separate analyses for stroke mortality were performed for the periods up to and from January 1, 1992.

**Results**

Patients were registered between January 1, 1980, and December 31, 1998. After exclusion of 22 patients whose vital status was unknown, the cohort consisted of 1569 patients with definite and 1302 patients with possible familial hypercholesterolemia who were followed up for 12,754 and 10,238 person-years, respectively. The median duration of follow-up was 7.9 years (interquartile range, 4.9 to 12.0 years). Table 1 shows the clinical characteristics of patients at registration. The median age was 45.0 years, and women were ≈7 years older than men. A total of 37 patients (1.3%) had a history of previous stroke. The mean ± SD total cholesterol concentration before treatment (calculated from all available measurements for each patient) for men was 9.5 ± 1.9 mmol/L (367 ± 74 mg/dL) and for women was 9.9 ± 2.0 mmol/L (382 ± 77 mg/dL). Table 2 shows the lipid and lipoprotein concentrations at registration, by which time 94.2% (2705 of 2871) had received dietary advice and 54.6% (1568 of 2871) had already been prescribed lipid-lowering drug therapy. A

**TABLE 1. Clinical Characteristics of Patients at Registration**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 1405)</th>
<th>Women (n = 1466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (interquartile range), y</td>
<td>42.3 (31.9, 52.2)</td>
<td>49.2 (32.9, 59.5)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>217 (13.7%, n = 1388)</td>
<td>110 (7.6%, n = 1451)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>18 (1.3%, n = 1385)</td>
<td>19 (1.3%, n = 1451)</td>
</tr>
<tr>
<td>Current or past angina</td>
<td>297 (15.6%, n = 1388)</td>
<td>247 (17.1%, n = 1448)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.7 (19.0, n = 1311)</td>
<td>135.2 (22.9, n = 1376)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.8 (11.2, n = 1310)</td>
<td>81.2 (11.7, n = 1375)</td>
</tr>
<tr>
<td>Diagnosed diabetes</td>
<td>23 (1.7%, n = 1386)</td>
<td>17 (1.2%, n = 1457)</td>
</tr>
<tr>
<td>Body mass index (SE), kg/m²</td>
<td>24.9 (3.9, n = 1193)</td>
<td>24.6 (4.2, n = 1263)</td>
</tr>
<tr>
<td>Body mass index &gt;30, kg/m²</td>
<td>105 (8.8%, n = 1193)</td>
<td>146 (11.7%, n = 1263)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>393 (28.0%, n = 1405)</td>
<td>332 (22.6%, n = 1466)</td>
</tr>
</tbody>
</table>

Differences in denominators are because of missing values.

**TABLE 2. Mean (SD) Lipid and Lipoprotein Concentrations (mmol/L) [mg/dL] at Registration**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>8.0 (1.7)</td>
<td>8.2 (1.8)</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>1.7 (0.5, 5.0)</td>
<td>1.4 (0.5, 4.0)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>LDL cholesterol†</td>
<td>5.6 (1.5)</td>
<td>5.7 (1.7)</td>
</tr>
</tbody>
</table>

*Values are geometric means (range).
†LDL cholesterol concentrations were calculated according to Friedewald et al.
TABLE 3. Standardized Mortality Ratio for Stroke by Calendar Period

<table>
<thead>
<tr>
<th>Period</th>
<th>Person Years</th>
<th>Observed</th>
<th>Expected</th>
<th>Standardized Mortality Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1992</td>
<td>7,435</td>
<td>1</td>
<td>2.9</td>
<td>35</td>
<td>1–192</td>
</tr>
<tr>
<td>From 1992</td>
<td>15,557</td>
<td>8</td>
<td>8.6</td>
<td>93</td>
<td>40–183</td>
</tr>
</tbody>
</table>

stain had been prescribed for 88.9% (407 of 458) followed up in 1997 through 1999, by which time the prevalence of cigarette smoking had fallen to 15.3% (70 of 485).

There were 169 deaths, including 102 (60%) from coronary heart disease. Fatal coronary disease was increased 2.5-fold (SMR = 2.5; 95% CI, 2.10 to 3.10) compared with the general population. There were 9 fatal strokes (5 occurred in patients with definite and 4 in patients with possible familial hypercholesterolemia), and 3 of the deaths occurred in patients who had a history of previous stroke at registration. The stroke mortality rate was 0.39 per 1000 person-years (95% CI, 0.18 to 0.74), and the SMR was nonsignificantly lower than that for the general population (79; 95% CI, 36 to 150). After exclusion of the 3 patients with a history of previous stroke, the SMR for stroke was 53 (95% CI, 19 to 115). Table 3 shows that there was no difference in the ratio of observed to expected number of strokes in the cohort for the periods up to and from January 1, 1992.

Discussion

Our study strongly suggests that patients with treated familial hypercholesterolemia are not at increased risk of fatal stroke. However, although this is the largest published cohort of patients followed up for ~23,000 person-years, there were only 9 fatal strokes, and we cannot exclude the possibility of a small excess risk. Because ischemic strokes are more likely to occur at older ages, it is possible that we may have underestimated the risk; some potentially susceptible individuals may have died beforehand of coronary artery disease, which has a much earlier age of onset, particularly in familial hypercholesterolemia.2–5 Our results need to be interpreted with some care and are of most direct relevance to patients referred for specialist lipid clinic care, which in the United Kingdom probably includes most patients in the community with diagnosed familial hypercholesterolemia.15

There are no entirely satisfactory diagnostic criteria for familial hypercholesterolemia. We used the diagnostic criteria of the Simon Broome Register, which place more emphasis on clinical than on DNA-based criteria. The reason is that a small number of LDL receptor mutations appear not to be associated with elevated cholesterol concentrations,17 and conversely, receptor mutations cannot be identified in all patients with xanthomatus (ie, definite) familial hypercholesterolemia with detection rates in case series ranging from ~30% to 80%.18,19 It is not clear whether differences in detection rates relate to the genetic heterogeneity of the particular case series, the accuracy of the clinical examination for xanthonoma, or differences in DNA methodology. Using the Simon Broome clinical criteria, we have reported identifying LDL receptor mutations in 32% of patients with definite and 14% of patients with possible familial hypercholesterolemia.19 In the United Kingdom, ~5% of patients with definite familial hypercholesterolemia have the apolipoprotein B mutation,19 and a proportion of the remainder may have a mutation in the yet-to-be-identified FH3 gene located on chromosome 1.20 Therefore, a DNA-based diagnosis currently has limited sensitivity and will not become widely available in routine clinical practice until low-cost, high-throughput laboratory methods are available.

The diagnosis of stroke was based on ICD-9, which may have introduced some inaccuracy.21 However, this would apply to both the study cohort and the reference population of England and Wales and consequently is unlikely to have biased the comparison. No adjustment was made for other cardiovascular risk factors because familial hypercholesterolemia is not associated with other risk factors such as hypertension, diabetes, or obesity,22 and in our cohort, their prevalence at registration was similar to that of the general population.23

The few published reports of the incidence of stroke in patients with heterozygous familial hypercholesterolemia20,12,13 were of smaller cohorts of patients. A Finnish study followed up for an average of 10 years a younger cohort of 54 patients with a mean serum cholesterol concentration at entry as high as 13.5 mmol/L (>500 mg/dL).12 It reported a 20-fold excess risk of a transient ischemic attack and fatal or nonfatal stroke. This substantially increased risk may be explained by ~75% of patients having coronary disease at entry to the study, but direct comparison with our results is not possible because we have no data on the incidence of nonfatal stroke and transient ischemic attack. An earlier study of 527 Japanese patients estimated that stroke accounted for ~10% of all deaths13 (based on 4 of a total of 41 deaths after 10 years of follow-up), which was a similar proportion to the general population. The Japanese results are consistent with our present study of 2871 treated familial hypercholesterolemia patients followed up for 22,992 person years. Our findings suggest that fatal stroke in treated patients accounts for ~5% of all deaths, which is comparable to rates in the general population of England and Wales.

The results are reassuring in demonstrating no increase in mortality from stroke. This may be in part because patients were given advice to stop smoking, which resulted in a significantly lower prevalence of cigarette smoking in our cohort at follow-up (based on a subsample) than in the general population.23 In addition, blood pressure is likely to have been more closely monitored than in the general population, hypertension may have been more aggressively treated, and antiplatelet agents may have been more widely prescribed, which would have further reduced the risk of fatal stroke. Cholesterol-lowering drug treatment for familial hypercholesterolemia is likely to have substantially reduced the risk of fatal and nonfatal stroke. Although epidemiological evidence from the Prospective Studies Collaboration24 of 45 prospective observational studies using individual patient data on 13,000 strokes showed no association between stroke and serum cholesterol concentration, the lack of an overall association may have concealed a positive relation with ischemic stroke and a negative association with hemorrhagic stroke. Conclusive evidence of a reduction of about one third
in the incidence of stroke with statin therapy has been provided by the recent findings of the Heart Protection Study,25 which randomized 20,536 patients to placebo or simvastatin 40 mg/d with a mean duration of follow-up of 5 years. Although it has been suggested that the mechanism underlying the reduction of cerebrovascular events is through a cholesterol-independent effect of statins, this remains speculative,26 and we found no excess mortality from stroke either before or after the introduction and widespread use of statins. This is consistent with the results of an earlier study of patients with familial hypercholesterolemia that showed that treatment with clofibrate and nicotinic acid for up to 6 years was associated with a benign course in 34 patients with extracranial carotid artery disease.10

The results from this large prospective cohort study strongly suggest that patients with familial hypercholesterolemia treated with cholesterol-lowering therapy are not at increased risk of fatal stroke. This needs to be confirmed in future studies when a substantially larger number of events have accumulated. Our results cannot exclude the possibility that untreated individuals are at increased risk, which would be consistent with the evidence that familial hypercholesterolemia is a panvascular disease.8–12,27

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References
Heterozygous familial hypercholesterolemia (Online Mendelian Inheritance in Man, no. 143890) is a disorder caused by a mutation in the low-density lipoprotein (LDL) receptor gene and has an average population frequency of 1 per 500. More than 350 different mutations of the LDL receptor gene have been identified. Missense, nonsense, frameshift, and splice-site mutations have all been described. Responses to statins are similar among some mutations and different among others. The phenotype consists of tendon xanthomas, corneal arcus, and coronary artery disease presenting in the fourth or fifth decade of life. Affected patients typically have a total cholesterol level in the range of 250 to 450 mg/dL and an LDL cholesterol level in the range of 200 to 400 mg/dL.

The study by Huxley and colleagues provides unique insight into the cerebrovascular implications of treated familial hypercholesterolemia. Their study population consisted of men and women with familial hypercholesterolemia followed up for 22 992 person-years at 21 lipid clinics in the United Kingdom. The principal finding was that patients with familial hypercholesterolemia did not have a significantly greater risk of fatal stroke than the general population. Future studies should assess both fatal and nonfatal stroke and should distinguish hemorrhagic from ischemic stroke. Such additional information on cerebrovascular events would enrich our understanding of the biology of treated familial hypercholesterolemia and permit direct comparison with studies done in the prestatin era.

Although the prognosis regarding cerebrovascular disease may be good for patients treated in lipid clinics relative to the general population, familial hypercholesterolemia is by no means benign. There is no room for complacency regarding its detection and treatment. An earlier analysis of the Simon Broome Register showed the relative risk for death from coronary artery disease to be increased by 50-fold for men and 125-fold for women 20 to 39 years of age. The relative risk for coronary death decreased with age so that by 60 to 79 years of age, men had no excess mortality from coronary artery disease and women had just higher than a 2-fold increased risk. This suggests that patients should be screened for familial hypercholesterolemia early in life, perhaps as early as the second decade.

Placebo-controlled trials of statins for familial hypercholesterolemia would not be ethical at this point. It does appear that aggressive lipid lowering with statins is superior to conventional lipid lowering. The Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study was a randomized, double-blind clinical trial comparing aggressive and conventional lipid-lowering therapy in 325 patients with familial hypercholesterolemia. Not surprisingly, the aggressively treated group achieved lower cholesterol levels, but 2 years into therapy, the aggressively treated group also showed greater favorable changes in carotid intima-media thickness, a predictor of coronary artery disease and ischemic stroke.

So where does this leave physicians who treat patients with stroke? First, it is important to diagnose familial hypercholesterolemia in affected patients. Cardiologists have been accused of not diagnosing familial hypercholesterolemia because of a preoccupation with acute events. I wonder whether neurologists might similarly be accused in the post–tissue plasminogen activator era. On many stroke services, physicians may be more likely to percuss an Achilles tendon than palpate it for xanthomas. Second, patients with hyperlipidemia should be followed up long term in a lipid clinic so that suitably aggressive lipid-lowering therapy can be initiated and maintained. Third, stroke patients with familial hypercholesterolemia should be informed of implications for family members and advised that family members, especially younger family members, may wish to be screened for the disease.

Controversy surrounds the issue of screening populations for genetic disorders. However, much good could come from early detection of familial hypercholesterolemia. Diverse population screening methods are being studied with variable results. For example, screening heel prick blood spot samples from 9673 neonates in a multiethnic population in London detected 7 families (14 individuals) with lipid profiles consistent with familial hypercholesterolemia. Cascade screening with DNA diagnostics shows even more promise. In the Netherlands, patients with familial hypercholesterolemia were tested for LDL receptor gene mutations, and those with an identified mutation became index cases. First-degree relatives of an index case were tested for the mutation harbored by the index case. Investigators identified an average of 20 relatives per index case, and they diagnosed familial hypercholesterolemia in an average of 8 relatives per index case. Investigators informed all participants of their DNA test results and referred carriers of a mutation to lipid specialists. Only 39% of adult patients with familial hypercholesterolemia were receiving some form of cholesterol-lowering therapy at the time of their initial examination. One year later, the proportion of adult patients with familial hypercholesterolemia who were receiving cholesterol-lowering therapy had risen to 93%. Cascade screening with DNA diagnostics can be effective, but it remains to be seen whether the approach will be adopted as a routine practice in many countries.

Progress in human genetics currently outpaces progress in protecting individuals from the risk of adverse social consequences that can come from knowing that they harbor a mutation. Of the patients who applied for insurance after being screened for familial hypercholesterolemia in the Netherlands study, 37% (17 of 46) encountered problems. Investigators concluded that patients needed further education about existing legislation. Unfortunately, patients in
many countries lack the legislative protections against misuse of genetic information that are afforded to citizens of the Netherlands. Familial hypercholesterolemia is an object lesson in the challenges that can be encountered when trying to improve public health by applying genetic discoveries.

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References
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