Reduction in Mortality in Subjects With Homozygous Familial Hypercholesterolemia Associated With Advances in Lipid-Lowering Therapy

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Background—Homozygous familial hypercholesterolemia is an inherited disorder caused by mutations in both low-density lipoprotein receptor alleles, which results in extremely elevated plasma low-density lipoprotein cholesterol concentrations and very early morbidity and mortality due to cardiovascular disease.

Methods and Results—To evaluate the impact of advances in lipid-lowering (predominantly statin) therapy on cardiovascular disease morbidity and mortality in a large cohort of patients with homozygous familial hypercholesterolemia, the records of 149 patients (81 females, 68 males) from 2 specialized lipid clinics in South Africa were evaluated retrospectively. homozygous familial hypercholesterolemia was diagnosed by confirmation of mutations in genes affecting low-density lipoprotein cholesterol or by clinical criteria. A Cox proportional hazard model with time-varying exposure was used to estimate the risk of death and major adverse cardiovascular events among statin-treated patients compared with statin-naive patients. The hazard ratio for benefit from lipid therapy, calculated with the Cox proportional hazards model for the end point of death, was 0.34 (95% confidence interval 0.14–0.86; P = 0.02), and for the end point of major adverse cardiovascular events, it was 0.49 (95% confidence interval 0.22–1.07; P = 0.07). This occurred despite a mean reduction in low-density lipoprotein cholesterol of only 26.4% (from 15.9±3.9 to 11.7±3.4 mmol/L; P<0.0001) with lipid-lowering therapy.

Conclusions—Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia. (Circulation. 2011;124:00-00.)

Key Words: hypercholesterolemia, familial ■ lipid-lowering therapy ■ statins ■ mortality

Familial hypercholesterolemia (FH) is an inherited, autosomal dominant disorder usually caused by mutations in the low-density lipoprotein (LDL) receptor gene or other genes that lead to defective or absent LDL receptor function, which results in reduced uptake and clearance of circulating LDL cholesterol (LDL-C) by the liver.1 Homozygous FH (HoFH), caused mainly by mutations in both LDL receptor alleles, is characterized by extremely high plasma LDL-C concentrations detectable at birth, cutaneous or tendinous xanthomas, and the onset of cardiovascular disease in early childhood.1 Untreated HoFH patients who are LDL-receptor-negative (<2% of normal LDL receptor activity in cultured fibroblasts) rarely survive beyond the second decade. LDL-receptor-defective patients (2%–25% residual LDL receptor activity) have a slightly better prognosis but, with few exceptions, develop clinically significant atherosclerotic vascular disease by the age of 30 years, if not earlier.2

Clinical Perspective on p 000

The frequency of FH throughout the world has been estimated at 1 in 500 people in the less severe heterozygous form and at 1 per 1 million people in the more severe homozygous form.3 In South African white Afrikaners, there is a much higher prevalence of heterozygous and homozygous FH, estimated at 1:100 and 1:30 000, respectively.3 This high prevalence is due to a founder effect that occurred when a limited number of LDL receptor mutations were introduced by Dutch families who settled in the Cape Province during the second half of the seventeenth century.4

Until the 1980s, treatment of FH was limited to a low-fat diet and minimally effective lipid-modifying agents. Lipid-lowering drug therapy changed radically in the 1990s with the introduction of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, a drug class that is remarkably effective in lowering LDL-C.5 Multiple ran-
domized, placebo-controlled studies in non-FH populations have demonstrated that statin therapy significantly reduces cardiovascular mortality and prolongs life.\textsuperscript{5-7} Clinical trials have shown that statins can lower LDL-C levels substantially in HoFH patients.\textsuperscript{8-10} They probably lower LDL-C by inhibiting hepatic cholesterol synthesis, thereby limiting cholesterol availability for the formation and secretion of apolipoprotein B–containing lipoproteins in receptor-negative HoFH patients, and by increasing residual LDL receptor activity in receptor-defective patients.\textsuperscript{9} In the early 2000s, further reductions in LDL-C were achievable in HoFH with cholesterol absorption inhibitors such as ezetimibe.\textsuperscript{11} However, because of the rarity of HoFH, data on the effect of advances in lipid-lowering therapy on clinical outcome and mortality are completely absent.

The aims of the present study were to assess the impact of modern lipid-lowering therapy, predominantly statin therapy, on all-cause and cardiovascular mortality in a large cohort of HoFH patients who have been followed up for up to 40 years at 2 specialized lipid treatment centers in South Africa.

Methods

Patients

This study was a retrospective cohort design that reviewed data from July 1972, the time of inception of the first specialized lipid clinics in South Africa, to March 2009. Medical records of HoFH subjects were reviewed to establish genetic and phenotypic data, anthropometric measures, and data on cardiovascular events and lipid-lowering drug therapy. Ethnic origins were recorded and family pedigrees examined. The study was approved by the Committees for Research on Human Subjects at the Universities of the Witwatersrand and Cape Town.

Criteria for the diagnosis of HoFH were (1) genetic confirmation of 2 mutant alleles at the LDL receptor gene locus or (2) an untreated LDL-C >13 mmol/L, together with either cutaneous or tendinous xanthoma before 10 years of age or evidence of elevated LDL-C >4.9 mmol/L before lipid-lowering therapy consistent with heterozygous FH in both parents. January 1, 1990, was selected as the delineation for modern lipid-lowering therapy because this was approximately the time the first statin, simvastatin, became available in South Africa.

Determination of HoFH Gene Mutations

Genotype determinations that had been performed as described previously\textsuperscript{4,9-10} were recorded. Individual base pair changes or deletions were verified against published DNA sequences and allele designations of the LDL receptor gene.\textsuperscript{12,13}

Lipid Profiles

To evaluate the efficacy of advances in lipid-lowering therapy, untreated lipid profiles at the time of initial presentation or the most recent untreated lipid profiles were compared with treated lipid profiles at the time nearest to study analysis (March 2009) or at the time of death. Fasting serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured with standard enzymatic assays at both centers. LDL-C concentrations were calculated with the Friedewald formula.\textsuperscript{14}

Major Adverse Cardiovascular Events

A major adverse cardiovascular event (MACE) was defined as death due to a cardiovascular cause (eg, fatal myocardial infarction, stroke, or death related to a vascular procedure) or nonfatal myocardial infarction, nonfatal stroke, or need for arterial revascularization (coronary angioplasty, stent insertion or bypass surgery, aortic valve repair or replacement, or other vascular procedure). The use of non–lipid-lowering pharmacological therapy to reduce cardiovascular risk (such as the use of β-blockers, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker therapy) and the use of aspirin and other antiplatelet agents were also recorded.

Statistical Analysis

Any patient who had survived beyond January 1, 1990, for longer than 6 months before an end point was reached was considered to have benefited from modern lipid-lowering therapy. Data analyses were performed with GB-STAT (Dynamic Microsystems, Inc) and R: A Language and Environment for Statistical Computation (R Foundation for Statistical Computing). \(P<0.05\) was considered significant. Differences between groups were determined by the paired or unpaired \(t\) test and the Wilcoxon signed rank test or Mann-Whitney \(U\) test for parametric or nonparametric data, respectively. Results are expressed as mean ± SD. We used the Cox proportional hazards model to estimate the risk of death and MACE among statin-treated patients compared with statin-naïve patients. Because HoFH is a condition present from birth, time of entry was defined as date of birth. The 2 end points evaluated were death and first MACE. Age of the patients (years since birth) was used as the time scale in the model. For the end point of death, patients still alive at the end of the study period, March 31, 2009, were censored on this date. For the end point of MACE, patients who had not had a MACE at the end of the study period were also censored on this date. Statin treatment was defined as a time-dependent variable equal to 0 for the time statins were not used and 1 from the start of statin therapy to the end point or censoring. The Cox proportional hazards model was adjusted for year of birth, and for those patients who received statin treatment, age at first treatment was considered as a covariate in a separate model. Patients lost to follow-up, defined as no contact for a 5-year period, and for whom no end-point data were available, were excluded from the Cox proportional hazards model. Another 2 patients for whom dates of death were unknown were excluded from the survival analysis. A small number of patients had undergone plasma exchange or LDL apheresis. Because these procedures can significantly lower LDL-C, a separate analysis was performed after exclusion of those patients who had undergone these procedures, even if the procedure had been performed only for a limited period of time.

Results

Clinical Characteristics

The study cohort of 149 HoFH subjects (111 subjects from the Johannesburg Hospital and 38 from the University of Cape Town lipid clinic) comprised 81 females and 68 males. The majority of patients were white Afrikaners (\(n=125; 84\%\)). The remainder included a small group of Indians who were descendants of migrants from the Indian subcontinent (\(n=13; 9\%\)); people of mixed, including Afrikaner ancestry (\(n=8; 5\%\)); and indigenous black Africans (\(n=3; 2\%\)). Eighty percent of patients had xanthomas that had appeared during the first decade of life.

At the time of study analysis, of the 16 patients who had ever smoked, most had stopped, and only 5 patients were current smokers. Only 4 patients were hypertensive (3\%), and none were diabetic. Mean age of the surviving patients was 26.8 ± 14.6 years, and mean body mass index was 24.3 ± 6.2 kg/m\(^2\). Cardiovascular morbidity and mortality characteristics of the 2 groups before and after 1990 are shown in Table 1.

Fifty individual patients experienced a total of 104 nonfatal cardiovascular events. Among the 65 patients who had died, the major cause of death was cardiovascular (\(n=50; 77\%\)). Eight patients succumbed to causes unrelated to HoFH, such
mutations. A single black African patient had autosomal mutation in the apoB gene in addition to having 2 LDL receptor recessive hypercholesterolemia.18

Lipid-Lowering Therapy (Statin With or Without Ezetimibe) and Percentage Change on Therapy

Table 2. Lipid Concentrations of Patients With Homozygous Familial Hypercholesterolemia According to Receipt of Modern Lipid-Lowering Therapy (Statin With or Without Ezetimibe) and Percentage Change on Therapy

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Pre-1990 (n=113)</th>
<th>Post-1990 (n=113)</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>17.3±3.8</td>
<td>13.1±3.3*</td>
<td>-24.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28±0.81</td>
<td>1.18±0.63</td>
<td>-7.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.89±0.33</td>
<td>0.91±0.25</td>
<td>2.2</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>15.9±3.9</td>
<td>11.7±3.4*</td>
<td>-26.4</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>21.4±10.9</td>
<td>13.5±5.9*</td>
<td>-36.9</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Results are expressed as mean±SD.
*P<0.0001.

as infections or accidents, and 7 patients died of unknown causes.

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Genetic Features and Mutations
Eighty-three families had 1 homozygote, and in 31 families there were 2 or more homozygous siblings. There were 5 consanguineous marriages. Twenty-one patients were examined before the availability of genetic testing, and for them, the diagnosis of HoFH was based on clinical criteria described previously.17–20 Of the patients who had undergone genetic testing (n=128), the majority had both LDL receptor gene mutations identified (n=123; 96%). Twenty-one different LDL receptor mutations were indentified, with 70 patients (55%) being true homozygotes (having the same mutation on both alleles) and 58 (45%) being compound heterozygotes (having a different mutation on each allele). The most frequent alleles in the LDL receptor gene were D206E (FH Afrikaner-1), V408M (FH Afrikaner-2), and D154N (FH Afrikaner-3), which were present in 90, 37, and 17 patients, respectively.15 Other mutated alleles included P664L, which occurred in 10 of the Indian patients.16 One patient was heterozygous for the R3005Q mutation in the apoB gene in addition to having 2 LDL receptor mutations.17 A single black African patient had autosomal recessive hypercholesterolemia.18

Therapy
Before January 1990, therapy for our HoFH patients consisted of a low-fat diet in conjunction with bile acid sequestrants, nicotinic acid, fibrates, and/or probucol. After January 1990, statins became the primary therapy for all HoFH patients, initially simvastatin, followed by atorvastatin and rosuvastatin. In view of the poor prognosis of HoFH, statin therapy was initiated at the time of presumptive diagnosis, the youngest patient being only 18 months of age when statin therapy was commenced. Patients <10 years of age were started on a lower dose (atorvastatin or rosuvastatin at a dose of 0.5–1 mg/kg body weight per day), with further dose escalation according to safety, tolerability, and weight gain. The majority of patients (88%) were taking a statin at the maximal dose of 40 mg of rosuvastatin or 80 mg of atorvastatin daily. Despite the use of high-dose statin therapy, even in very young HoFH children, this therapy has been remarkably well tolerated, with no serious adverse events ascribed to it in the patient cohort. The cholesterol absorption inhibitor ezetimibe became available in June 2006, and a daily dose of 10 mg was added to high-dose statin therapy; however, because of limited funding, only 50% of patients were receiving a statin-plus-ezetimibe combination.

In the entire study cohort, portacaval shunt operations had been performed in 21 patients before 2000, and 7 patients had undergone partial ileal bypass surgery, all before 1985. Twenty-three patients had undergone extracorporeal removal of LDL-C either by LDL apheresis or by plasma exchange. Approximately 45% of the cohort was receiving aspirin therapy at the time of study analysis. Other cardiovascular medications that also may have influenced cardiovascular mortality were used infrequently, with only 28 patients (19%) taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blocker therapy.

Lipid Profiles
Untreated lipid profiles were available for 122 patients, and mean lipid concentrations (in mmol/L) were total cholesterol 17.8±3.8, triglycerides 1.32±0.83, high-density lipoprotein cholesterol 0.82±0.34, and LDL-C 16.4±3.9. Paired lipid profiles before and after modern lipid-lowering therapy were available for 75 patients and demonstrated significant decreases in total cholesterol of 24.3% (from 17.3±3.8–13.1±3.3 mmol/L; P<0.0001) and decreases in LDL-C of 26.4% (from 15.9±3.9–11.7±3.4 mmol/L; P<0.0001). Mean triglyceride concentration decreased, and high-density lipoprotein cholesterol increased slightly, but these changes were not significant (Table 2).
We report the effect of modern lipid-lowering therapy, particularly statin therapy, on cardiovascular disease in the largest and longest-observed group of HoFH patients. All-cause mortality and time to first MACE were compared before and after the introduction of modern lipid-lowering therapy into the routine management of these patients. Despite not achieving LDL-C target and only achieving a mean reduction in LDL-C of 26%, patients who had received modern lipid-lowering therapy, particularly statin therapy, showed a significant reduction in mortality according to the Cox proportional hazards model. This compares favorably with recent studies that have reported significantly better event-free survival in statin-treated heterozygous FH patients. The data suggest that despite the fact that LDL-C remains significantly elevated, advances in lipid-lowering treatment, predominantly statin therapy, are associated with delayed cardiovascular events and prolonged survival in HoFH patients and have altered their disease spectrum of HoFH from a fatal disease in childhood to that seen in untreated heterozygous FH.

Other than lipid-lowering drug therapy, potential treatment options for HoFH include portacaval shunt, partial ileal bypass surgery, gene therapy, liver transplantation, and LDL apheresis. Portacaval shunt and partial ileal bypass do lower LDL-C, but the effect is variable and often transient. Partial ileal bypass may be complicated by malabsorptive gastrointestinal side effects, whereas portacaval shunting may lead to hepatic encephalopathy. Liver transplantation is restricted by a lack of donor organs and the need for continuous postoperative immunosuppression. LDL apheresis significantly lowers LDL-C and is considered the standard of care for patients with HoFH. This procedure reduces the risk of coronary heart disease in patients with heterozygous FH. However, drawbacks of apheresis include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access. There are also no prospective randomized studies demonstrating improved survival with apheresis, and despite apheresis, HoFH patients still develop extensive aortic calcification.

Prospective studies in non-HoFH populations have consistently shown a significant reduction in cardiovascular events and total mortality when LDL-C is reduced by 24% to 30%. Meta-analyses of more than 90,000 patients treated with placebo or statins have shown a 20% reduction in cardiovascular disease events in 5 years for every 1-mmol/L reduction in LDL-C. Clinical benefits in these studies were independent of the baseline LDL-C level. This relationship has been confirmed recently in a similar analysis in high-risk populations that compared more aggressive LDL-C reduction with more efficacious doses of statins to less LDL-C reduction with lower statin doses. The 4-mmol/L reduction in LDL-C seen in HoFH patients in the present study therefore probably explains the reduction observed in both cardiovascular events and total mortality. The use of other cardiovascular medications known to reduce cardiovascular mortality, such as angiotensin-converting enzyme inhibitors, was small and unlikely to have influenced the findings. However advances in access to routine cardiac care, such as thrombolytic therapy for acute coronary syndromes, which we could not evaluate, may have contributed to the improved survival.
A limitation the study is that it was not prospective or systematic in treatment options provided to HoFH patients, because patients were always treated with the current best available lipid-lowering therapy. Only patients who died before 1990 did not receive statin therapy. This creates a bias, because those patients who survived after 1990 all would have benefited from statin therapy for at least part of their lives.

The cohort comprised referred HoFH patients treated at specialized lipid clinics. It is possible that some patients with the more severe LDL-receptor–negative HoFH died prematurely, before benefiting from modern lipid-lowering therapy. In the pre-1990 group, none of those patients with known LDL receptor mutations had LDL-receptor–negative HoFH, compared with 6 patients in the post-1990 group. The small number of patients whose diagnosis of HoFH was based on clinical criteria alone was also unlikely to have influenced the results.

Detailed cardiovascular assessments such as echocardiography and coronary angiography were not performed routinely, because the approach to cardiac and coronary imaging was symptom driven rather than elective. However, it is well known that lesions identified on coronary angiography are usually not the lesions likely to cause future fatal coronary events, and percutaneous coronary intervention is therefore performed mainly for symptomatic relief.

The strength of the present unique review lies in the large number of patients; to the best of our knowledge, this is the largest cohort of HoFH patients described worldwide. This analysis of therapy in HoFH patients over the past 40 years highlights the importance of early diagnosis and initiation of modern lipid-lowering therapy, especially statin therapy, even in young children with HoFH, to delay life-threatening cardiovascular disease. This therapy has been well tolerated and remarkably safe and has prolonged their lives by several years. However, the clinical management of HoFH patients remains a challenge, because currently available lipid-lowering drug therapy is unable to achieve desirable LDL-C levels. New therapies under development, including apolipoprotein B antisense oligonucleotides, microsomal triglyceride transfer protein inhibitors, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, and thyroid hormone analogues, may be of added benefit but are also unlikely to achieve LDL-C targets in HoFH patients.

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Disclosures

Dr Raal has received research support for pharmaceutical trials of lipid-modifying agents and has received honoraria for consultations on lipid disorders; he has consulted or given lectures for Pfizer, Merck, AstraZeneca, and Genzyme. Dr Blom has received support for pharmaceutical trials with lipid-lowering agents and served as a member of the Merck Advisory Board for ezetimibe/simvastatin. Dr Marais has received a research grant from the Medical Research Council of South Africa and research support for a pharmaceutical trial with a lipid-lowering agent; he has also received honoraria for consultations on lipid management and has consulted for MSD, Parke-Davis, Pfizer, Bayer, and AstraZeneca. The other authors report no conflicts.

References

Homozygous familial hypercholesterolemia (HoFH) is an inherited disorder usually caused by mutations in both low-density lipoprotein receptor alleles, which results in extremely elevated plasma low-density lipoprotein cholesterol concentrations and very early morbidity and mortality due to cardiovascular disease. Untreated, HoFH patients rarely survive beyond the third decade. This retrospective study reports the effect of lipid-lowering treatment, mainly statin therapy, on survival and time to first major cardiovascular event in a large cohort of HoFH patients who have been followed up for up to 40 years. Despite achieving a mean reduction in low-density lipoprotein cholesterol of only 26%, lipid-lowering therapy was associated with delayed cardiovascular events and prolonged survival in patients with HoFH. This supports the mounting evidence of the remarkable benefit of lipid-lowering therapy, particularly statin therapy, and establishes that lowering low-density lipoprotein cholesterol can prolong life even in HoFH. This analysis also highlights the importance of early diagnosis and initiation of lipid-lowering therapy, especially in young children with HoFH, to delay the onset of cardiovascular disease.
Reduction in Mortality in Subjects With Homozygous Familial Hypercholesterolemia Associated With Advances in Lipid-Lowering Therapy
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지질 강하 약물 치료는 가족성 고콜레스테롤혈증 동종 접합체 환자의 사망률을 감소시켰다

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Summary

배경
가족성 고콜레스테롤혈증(familial hypercholesterolemia) 동종 접합체 환자는 저밀도지단백 콜레스테롤 수용체 유전자의 양쪽 염기 서열에 변이를 가지고 있다. 이에 따라 혈중 저밀도지단백 콜레스테롤 수치는 매우 높으며, 소년기나 청년기 등 조기에 심혈관질환이 발생하여 사망하는 경우가 예를 들며. 이 연구는 statin 등의 지질 강하 약물 치료가 가족성 고콜레스테롤혈증 동종 접합체 환자의 사망의 예후를 개선하였다.

방법 및 결과
지질 강하 약물 치료가 예후에 미친 영향을 알아보기 위해, 남아프리카 공화국에 있는 2개의 지질 치료 클리닉에서 가족성 고콜레스테롤혈증 동종 접합체 환자 149명 (남성 68명, 여성 81명)의 의무기록을 분석하였다. 가족성 고콜레스테롤혈증 동종 접합체 환자의 진단은 저밀도지단백 콜레스테롤 수용체 유전자의 돌연변이를 확인함으로써 또는 임상적인 진단 기준에 근거하여 시행하였다. Statin 투여군과 비투여군의 사망과 주요 심혈관사건 발생률을 비교하기 위해 시간변이 노출 분석 등의 통계분석을 시행하였다.
Statin 약물 치료에 따른 사망 위험도는 0.34(95% CI, 0.14-0.86, P=0.02)로서 유의한 감소 효과를 보였고, 주요 심혈관사건 발생 위험도는 0.49(95% CI, 0.22-1.07, P=0.07)로서 약물 치료에 따른 감소 효과를 볼 수 있었다. 가족성 고콜레스테롤혈증 동종 접합체 환자에서의 지질 강하 약물 치료는 혈중 저밀도지단백 콜레스테롤 수치를 26.4% 낮추었다 (620.1±152.1mg/dL에서 456.3±152.1mg/dL로 감소, P<0.0001).

결론
지질 강하 약물 치료는 가족성 고콜레스테롤혈증 동종 접합체 환자의 심혈관 사건 발생을 줄이고, 생존율을 유의하게 개선하는 효과를 보였다.
가족성 고콜레스테롤혈증의 유병률은 전 세계적으로 이
형 접합체는 1/500, 동종 접합체는 1/1,000,000이고, 남
아프리카 백인에서는 유병률이 높아서 이형 접합체는
1/100, 동종 접합체는 1/30,000의 수준이다. 이는 17세기
에 가족성 고콜레스테롤혈증 유전자를 지닌 네덜란드계
선조들이 남아프리카 공화국 케이프 지역에 정착하여 마
을 형성하였고, 후손들 간의 결혼으로 FH-Afrikaner 유
전자 발현 빈도가 증가하였기 때문이다.1 이 지역의 높은
유병률은 이 연구에서 남아프리카 공화국 2개의 지질대
사 이상 치료 클리닉의 환자 중에서 흔하지 않은 질병인
가족성 고콜레스테롤혈증 동종 접합체 환자를 100명 이
상 모아 자료를 분석할 수 있었던 이유이기도 하다.

이 연구에서 가족성 고콜레스테롤혈증 동종 접합체 환자
에서 지질 강하 약물 치료의 효과를 분석한 것은 대부분
statin의 역할을 평가하기 위함이다. 유전성질환이 아닌
고콜레스테롤혈증 환자들 대상으로 시행된 많은 연구
에서 statin이 저밀도지단백 콜레스테롤을 낮추는 등의
작용을 통해 심혈관질환 사건 발생과 사망을 감소시켜
저밀도지단백 콜레스테롤을 약 40mg/dL 감소시키면 심
혈관질환 사건 발생이 약 24% 감소한다고 보고하였다.2

가족성 고콜레스테롤혈증 동종 접합체 환자의 경우 대부
분 20대 이전에 심혈관질환을 겪다가 사망하며, 치료가
성공적으로 이루어지면 30대까지 생존할 수도 있다. 저밀
도지단백 콜레스테롤 수치는 매우 높아 정상인의 수 배에
이르며, 지질 강하 치료가 지질 수치를 목표치까지 낮추기
에는 효과가 부족하다. 이는 복합 약물 치료의 경우에도
마찬가지이고, 그나마 1990년대부터 널리 사용된 statin
이 주된 역할을 하였다. 이 연구에서 statin을 주축으로 한
복합약물 치료를 받은 1990년대 이후에는 심혈관질환 사
건 발생 및 사망률이 매우 감소하여 첫 번째 질환 발생
자가 10년 이상 연장된 것은 확고한 만한 성과이다.

하지만 이 연구의 해석에서 주의할 점을 보면, 이 연구는
후향적 분석 연구로서 어떤 자침에 의한 일괄적인 약물
치료가 적용된 것이 아니라, 당시 각 지역에서 치료 가능
한 수단으로 상황에 맞추어 시행한 기록을 분석한 자료
이다. 또한, 일부 고위험 환자들은 1990년 이전에 이미 사
망하여 statin 치료 군에 포함되지 않고, 상대적으로 저밀
도지단백 수용체 가리기가 좋은 환자들이 살아남아 statin
치료군에 포함되는 빈도가 현상이 내재되어 있을 수 있
다. 그럼에도 불구하고 가족성 고콜레스테롤혈증 동종 접
합체 환자군 연구에서 이 연구의 자료는 매우 중요하며,
별다른 전형적 연구가 불가능했던 상황을 잘 반영해준
d라고 생각한다.

1990년 이전에는 주로 저지방 식사, 담즙산 수지, 니아신
(niacin), 피브레이트(fibrate), 프로부콜(probucol) 등의 복
합 치료와 함께 일부 환자에서는 문맥-정맥 단락 수술, 회
장 우회로 수술, 체외방사 제거, 혈액투석 등이 이용되었
다. 1990년 이후에 statin이 투여되었는데, 대부분 statin
최대 용량을 투여하였고 약물에 대한 부작용은 많지 않
다고 보고되었다. 2006년부터는 ezetimibe 병용 투여가
가능하였으나, 이 연구에서는 약제 비용 문제로 50%의
환자에서만 시행되었다. 이 연구에서 적극적인 복합약물
요법이 동원되었고 기저 저밀도지단백 콜레스테롤 수치
가 정상인의 수 배에 해당함에도 불구하고 저밀도지단백
콜레스테롤이 26.4% 감소하였다는 것은 추가적인 지질
강하 효과 치료 방법의 개발이 필요함을 알 수 있다. 현재
개발 중인 많은 약제가 성공적인 효과와 안전성을 보인다
면, 향후 가족성 고콜레스테롤혈증 환자의 치료에 큰 도
움이 될 것이다.

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Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective
meta-analysis of data from 90,056 participants in 14 randomised trials of statins.
Reduction in Mortality in Subjects With Homozygous Familial Hypercholesterolemia Associated With Advances in Lipid-Lowering Therapy

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Background—Homozygous familial hypercholesterolemia is an inherited disorder caused by mutations in both low-density lipoprotein receptor alleles, which results in extremely elevated plasma low-density lipoprotein cholesterol concentrations and very early morbidity and mortality due to cardiovascular disease.

Methods and Results—To evaluate the impact of advances in lipid-lowering (predominantly statin) therapy on cardiovascular disease morbidity and mortality in a large cohort of patients with homozygous familial hypercholesterolemia, the records of 149 patients (81 females, 68 males) from 2 specialized lipid clinics in South Africa were evaluated retrospectively. Homozygous familial hypercholesterolemia was diagnosed by confirmation of mutations in genes affecting low-density lipoprotein cholesterol or by clinical criteria. A Cox proportional hazard model with time-varying exposure was used to estimate the risk of death and major adverse cardiovascular events among statin-treated patients compared with statin-naive patients. The hazard ratio for benefit from lipid therapy, calculated with the Cox proportional hazards model for the end point of death, was 0.34 (95% confidence interval 0.14–0.86; \(P = 0.02\)), and for the end point of major adverse cardiovascular events, it was 0.49 (95% confidence interval 0.22–1.07; \(P = 0.07\)). This occurred despite a mean reduction in low-density lipoprotein cholesterol of only 26.4% (from 15.9 ± 3.9 to 11.7 ± 3.4 mmol/L; \(P < 0.0001\)) with lipid-lowering therapy.

Conclusions—Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia. (Circulation. 2011;124:2202-2207.)

Key Words: hypercholesterolemia, familial ■ lipid-lowering therapy ■ statins ■ mortality

Clinical Perspective on p 162

The frequency of FH throughout the world has been estimated at 1 in 500 people in the less severe heterozygous form and at 1 per 1 million people in the more severe homozygous form.\(^1\) In South African white Afrikaners, there is a much higher prevalence of heterozygous and homozygous FH, estimated at 1:100 and 1:30 000, respectively.\(^2\) This high prevalence is due to a founder effect that occurred when a limited number of LDL receptor mutations were introduced by Dutch families who settled in the Cape Province during the second half of the seventeenth century.\(^3\)

Until the 1980s, treatment of FH was limited to a low-fat diet and minimally effective lipid-modifying agents. Lipid-lowering drug therapy changed radically in the 1990s with the introduction of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, a drug class that is remarkably effective in lowering LDL-C.\(^4\) Multiple ran-
domized, placebo-controlled studies in non-FH populations have demonstrated that statin therapy significantly reduces cardiovascular mortality and prolongs life. Clinical trials have shown that statins can lower LDL-C levels substantially in HoFH patients. They probably lower LDL-C by inhibiting hepatic cholesterol synthesis, thereby limiting cholesterol availability for the formation and secretion of apolipoprotein B–containing lipoproteins in receptor-negative HoFH patients, and by increasing residual LDL receptor activity in receptor-defective patients. In the early 2000s, further reduction in LDL-C was achievable in HoFH with cholesterol absorption inhibitors such as ezetimibe. However, because of the rarity of HoFH, data on the effect of advances in lipid-lowering therapy on clinical outcome and mortality are completely absent.

The aims of the present study were to assess the impact of modern lipid-lowering therapy, predominantly statin therapy, on all-cause and cardiovascular mortality in a large cohort of HoFH patients who have been followed up for up to 40 years at 2 specialized lipid treatment centers in South Africa.

Methods

Patients

This study was a retrospective cohort design that reviewed data from July 1972, the time of inception of the first specialized lipid clinics in South Africa, to March 2009. Medical records of HoFH subjects were reviewed to establish genetic and phenotypic data, anthropometric measures, and data on cardiovascular events and lipid-lowering drug therapy. Ethnic origins were recorded and family pedigrees examined. The study was approved by the Committees for Research on Human Subjects at the Universities of the Witwatersrand and Cape Town.

Criteria for the diagnosis of HoFH were (1) genetic confirmation of 2 mutant alleles at the LDL receptor gene locus or (2) an untreated LDL-C >13 mmol/L together with either cutaneous or tendinous xanthoma before 10 years of age or evidence of elevated LDL-C >4.9 mmol/L before lipid-lowering therapy consistent with heterozygous FH in both parents. January 1, 1990, was selected as the delineation for modern lipid-lowering therapy because this was approximately the time the first statin, simvastatin, became available in South Africa.

Determination of HoFH Gene Mutations

Genotype determinations that had been performed as described previously were recorded. Individual base pair changes or deletions were verified against published DNA sequences and allele designations of the LDL receptor gene.

Lipid Profiles

To evaluate the efficacy of advances in lipid-lowering therapy, untreated lipid profiles at the time of initial presentation or the most recent untreated lipid profiles were compared with treated lipid profiles at the time nearest to study analysis (March 2009) or at the time of death. Fasting serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured with standard enzymatic assays at both centers. LDL-C concentrations were calculated with the Friedewald formula.

Major Adverse Cardiovascular Events

A major adverse cardiovascular event (MACE) was defined as death due to a cardiovascular cause (eg, fatal myocardial infarction, stroke, or death related to a vascular procedure) or nonfatal myocardial infarction, nonfatal stroke, or need for arterial revascularization (coronary angioplasty, stent insertion or bypass surgery, aortic valve repair or replacement, or other vascular procedure). The use of non-lipid-lowering pharmacological therapy to reduce cardiovascular risk (such as the use of β-blockers, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker therapy) and the use of aspirin and other antiplatelet agents were also recorded.

Statistical Analysis

Any patient who had survived beyond January 1, 1990, for longer than 6 months before an end point was reached was considered to have benefited from modern lipid-lowering therapy. Data analyses were performed with GB-STAT (Dynamic Microsystems, Inc) and R: A Language and Environment for Statistical Computation (R Foundation for Statistical Computing). P<0.05 was considered significant. Differences between groups were determined by the paired or unpaired t test and the Wilcoxon signed rank test or Mann-Whitney U test for parametric or nonparametric data, respectively. Results are expressed as mean±SD. We used the Cox proportional hazards model to estimate the risk of death and MACE among statin-treated patients compared with statin-naive patients. Because HoFH is a condition present from birth, time of entry was defined as date of birth. The 2 end points evaluated were death and first MACE. Age of the patients (years since birth) was used as the time scale in the model. For the end point of death, patients still alive at the end of the study period, March 31, 2009, were censored on this date. For the end point of MACE, patients who had not had a MACE at the end of the study period were also censored on this date. Statin treatment was defined as a time-dependent variable equal to 0 for the time statins were not used and 1 from the start of statin therapy to the end point or censoring. The Cox proportional hazards model was adjusted for year of birth, and for those patients who received statin treatment, age at first treatment was considered as a covariate in a separate model. Patients lost to follow-up, defined as no contact for a 5-year period, and for whom no end-point data were available, were excluded from the Cox proportional hazards model. Another 2 patients for whom dates of death were unknown were excluded from the survival analysis. A small number of patients had undergone plasma exchange or LDL apheresis. Because these procedures can significantly lower LDL-C, a separate analysis was performed after exclusion of those patients who had undergone these procedures, even if the procedure had been performed only for a limited period of time.

Results

Clinical Characteristics

The study cohort of 149 HoFH subjects (111 subjects from the Johannesburg Hospital and 38 from the University of Cape Town lipid clinic) comprised 81 females and 68 males. The majority of patients were white Afrikaners (n=125; 84%). The remainder included a small group of Indians who were descendants of migrants from the Indian subcontinent (n=13; 9%); people of mixed, including Afrikaner ancestry (n=8; 5%); and indigenous black Africans (n=3; 2%). Eighty percent of patients had xanthomas that had appeared during the first decade of life.

At the time of study analysis, of the 16 patients who had ever smoked, most had stopped, and only 5 patients were current smokers. Only 4 patients were hypertensive (3%), and none were diabetic. Mean age of the surviving patients was 26.8±14.6 years, and mean body mass index was 24.3±6.2 kg/m2. Cardiovascular morbidity and mortality characteristics of the 2 groups before and after 1990 are shown in Table 1.

Fifty individual patients experienced a total of 104 nonfatal cardiovascular events. Among the 65 patients who had died, the major cause of death was cardiovascular (n=50; 77%). Eight patients succumbed to causes unrelated to HoFH, such
were present in 90, 37, and 17 patients, respectively. Other mutations included V408M (FH Afrikaner-2), and D154N (FH Afrikaner-3), which occurred when the same mutation was on each allele. The most frequent mutations, present in 55% of patients, were compound heterozygotes (having a different mutation on each allele) and 58 (45%) being compound heterozygotes (having the same mutation on both alleles) and 58 (45%) being true homozygotes (having the same mutation on each allele). The majority of patients (88%) were taking a statin at the maximal dose of 40 mg of rosuvastatin or 80 mg of atorvastatin daily. Despite the use of high-dose statin therapy, even in very young HoFH children, this therapy has been remarkably well tolerated, with no serious adverse events ascribed to it in the patient cohort. The cholesterol absorption inhibitor ezetimibe became available in June 2006, and a daily dose of 10 mg was added to high-dose statin therapy; however, because of limited funding, only 50% of patients were receiving a statin-plus-ezetimibe combination. Results are expressed as mean±SD.

### Genetic Features and Mutations

Eighty-three families had 1 homozygote, and in 31 families there were 2 or more homozygous siblings. There were 5 consanguineous marriages. Twenty-one patients were examined before the availability of genetic testing, and for them, the diagnosis of HoFH was based on clinical criteria described previously.\(^8\)–\(^10\) Of the patients who had undergone genetic testing (n=128), the majority had both LDL receptor gene mutations identified (n=123; 96%). Twenty-one different LDL receptor mutations were indentified, with 70 patients (55%) being true homozygotes (having the same mutation on both alleles) and 58 (45%) being compound heterozygotes (having a different mutation on each allele). The most frequent alleles in the LDL receptor gene were D206E (FH A frikaner-1), V408M (FH A frikaner-2), and D154N (FH A frikaner-3), which were present in 90, 37, and 17 patients, respectively.\(^15\) Other mutated alleles included P664L, which occurred in 10 of the Indian patients.\(^16\) One patient was heterozygous for the R3005Q mutation in the apoB gene in addition to having 2 LDL receptor mutations.\(^17\) A single black African patient had autosomal recessive hypercholesterolemia.\(^18\)

### Therapy

Before January, 1990, therapy for our HoFH patients consisted of a low-fat diet in conjunction with bile acid sequestrants, nicotinic acid, fibrates, and/or probucol. After January 1990, statins became the primary therapy for all HoFH patients, initially simvastatin, followed by atorvastatin and rosuvastatin. In view of the poor prognosis of HoFH, statin therapy was initiated at the time of presumptive diagnosis, the youngest patient being only 18 months of age when statin therapy was commenced. Patients <10 years of age were started on a lower dose (atorvastatin or rosuvastatin at a dose of 0.5–1 mg/kg body weight per day), with further dose escalation according to safety, tolerability, and weight gain. The majority of patients (88%) were taking a statin at the maximal dose of 40 mg of rosuvastatin or 80 mg of atorvastatin daily. Despite the use of high-dose statin therapy, even in very young HoFH children, this therapy has been remarkably well tolerated, with no serious adverse events ascribed to it in the patient cohort. The cholesterol absorption inhibitor ezetimibe became available in June 2006, and a daily dose of 10 mg was added to high-dose statin therapy; however, because of limited funding, only 50% of patients were receiving a statin-plus-ezetimibe combination.

In the entire study cohort, portacaval shunt operations had been performed in 21 patients before 2000, and 7 patients had undergone partial ileal bypass surgery, all before 1985. Twenty-three patients had undergone extracorporeal removal of LDL-C either by LDL apheresis or by plasma exchange. Approximately 45% of the cohort was receiving aspirin therapy at the time of study analysis. Other cardiovascular medications that also may have influenced cardiovascular mortality were used infrequently, with only 28 patients (19%) taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blocker therapy.

### Lipid Profiles

Untreated lipid profiles were available for 122 patients, and mean lipid concentrations (in mmol/L) were total cholesterol 17.8±3.8, triglycerides 1.32±0.83, high-density lipoprotein cholesterol 0.82±0.34, and LDL-C 16.4±3.9. Paired lipid profiles before and after modern lipid-lowering therapy were available for 75 patients and demonstrated significant decreases in total cholesterol of 24.3% (from 17.3±3.8–13.1±3.3 mmol/L; P<0.0001) and decreases in LDL-C of 26.4% (from 15.9±3.9–11.7±3.4 mmol/L; P<0.0001).

### Table 1. Cardiovascular Morbidity and Mortality

<table>
<thead>
<tr>
<th>Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990</th>
<th>Pre-1990 (n=36)</th>
<th>Post-1990 (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/males, n</td>
<td>24/12</td>
<td>58/55</td>
</tr>
<tr>
<td>Age at death, y, mean±SD</td>
<td>52.0±7.6</td>
<td>64.5±5.7</td>
</tr>
<tr>
<td>All causes</td>
<td>18.4±10.1 (n=27)</td>
<td>32.9±15.5 (n=38)*</td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>17.7±10.1 (n=22)</td>
<td>31.7±13.3 (n=23)*</td>
</tr>
<tr>
<td>Age at first nonfatal MACE, y, mean±SD</td>
<td>12.8±5.9 (n=6)</td>
<td>28.3±10.8 (n=44)†</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events, No. of patients</td>
<td>6 (14 Events)</td>
<td>44 (90 Events)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (7 Mls)</td>
<td>10 (11 Mls)</td>
</tr>
<tr>
<td>Coronary procedures (CABG, AVR, PTCA, stent)</td>
<td>5 (7 Procedures)</td>
<td>43 (69 Procedures)</td>
</tr>
<tr>
<td>Other vascular procedures (carotid surgery, aortoiliac bypass surgery)</td>
<td>None</td>
<td>5 (8 Procedures)</td>
</tr>
<tr>
<td>Cerebrovascular events (TIA, stroke)</td>
<td>None</td>
<td>2 (2 Events)</td>
</tr>
</tbody>
</table>

MACE indicates major adverse cardiac event; MIs, myocardial infarctions; CABG, coronary artery bypass surgery; AVR, aortic valve replacement; PTCA, percutaneous coronary angioplasty; and TIA, transient ischemic attack.

†P<0.0001.

### Table 2. Lipid Concentrations of Patients With Homozygous Familial Hypercholesterolemia According to Receipt of Modern Lipid-Lowering Therapy (Statin With or Without Ezetimibe) and Percentage Change on Therapy

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Pre-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>17.3±3.8</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28±0.81</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.89±0.33</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>15.9±3.9</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>21.4±10.9</td>
</tr>
</tbody>
</table>

LDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Results are expressed as mean±SD.

\*P<0.0001.
cause mortality and time to first MACE were compared before and after the introduction of modern lipid-lowering therapy into the routine management of these patients. Despite not achieving LDL-C target and only achieving a mean reduction in LDL-C of 26%, patients who had received modern lipid-lowering therapy, particularly statin therapy, showed a significant reduction in mortality according to the Cox proportional hazards model. This compares favorably with recent studies that have reported significantly better event-free survival in statin-treated heterozygous FH patients. The data suggest that despite the fact that LDL-C remains significantly elevated, advances in lipid-lowering treatment, predominantly statin therapy, are associated with delayed cardiovascular events and prolonged survival in HoFH patients and have altered their disease spectrum of HoFH from a fatal disease in childhood to that seen in untreated heterozygous FH.

Other than lipid-lowering drug therapy, potential treatment options for HoFH include portacaval shunt, partial ileal bypass surgery, gene therapy, liver transplantation, and LDL apheresis. Portacaval shunt and partial ileal bypass do lower LDL-C, but the effect is variable and often transient. Partial ileal bypass may be complicated by malabsorptive gastrointestinal side effects, whereas portacaval shunting may lead to hepatic encephalopathy. Liver transplantation is restricted by a lack of donor organs and the need for continuous postoperative immunosuppression. LDL apheresis significantly lowers LDL-C and is considered the standard of care for patients with HoFH. This procedure reduces the risk of coronary heart disease in patients with heterozygous FH. However, drawbacks of apheresis include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access. There are also no prospective randomized studies demonstrating improved survival with apheresis, and despite apheresis, HoFH patients still develop extensive aortic calcification.

Prospective studies in non-HoFH populations have consistently shown a significant reduction in cardiovascular events and total mortality when LDL-C is reduced by 24% to 30%. Meta-analyses of more than 90,000 patients treated with placebo or statins have shown a 20% reduction in cardiovascular disease events in 5 years for every 1 mmol/L reduction in LDL-C. Clinical benefits in these studies were independent of the baseline LDL-C level. This relationship has been confirmed recently in a similar analysis in high-risk populations that compared more aggressive LDL-C reduction with more efficacious doses of statins to less LDL-C reduction with lower statin doses. The 4 mmol/L reduction in LDL-C seen in HoFH patients in the present study therefore probably explains the reduction observed in both cardiovascular events and total mortality. The use of other cardiovascular medications known to reduce cardiovascular mortality, such as angiotensin-converting enzyme inhibitors, was small and unlikely to have influenced the findings. However advances in and access to routine cardiac care, such as thrombolytic therapy for acute coronary syndromes, which we could not evaluate, may have contributed to the improved survival.
A limitation the study is that it was not prospective or systematic in treatment options provided to HoFH patients, because patients were always treated with the current best available lipid-lowering therapy. Only patients who died before 1990 did not receive statin therapy. This creates a bias, because those patients who survived after 1990 all would have benefited from statin therapy for at least part of their lives.

The cohort comprised referred HoFH patients treated at specialized lipid clinics. It is possible that some patients with the more severe LDL-receptor-negative HoFH died prematurely, before benefitting from modern lipid-lowering therapy. In the pre-1990 group, none of those patients with known LDL receptor mutations had LDL-receptor-negative HoFH, compared with 6 patients in the post-1990 group. The small number of patients whose diagnosis of HoFH was based on clinical criteria alone was also unlikely to have influenced the results.

Detailed cardiovascular assessments such as echocardiography and coronary angiography were not performed routinely, because the approach to cardiac and coronary imaging was symptom driven rather than elective. However, it is well known that lesions identified on coronary angiography are usually not the lesions likely to cause future fatal coronary events, and percutaneous coronary intervention is therefore performed mainly for symptom relief.

The strength of the present unique review lies in the large number of patients; to the best of our knowledge, this is the largest cohort of HoFH patients described worldwide. This analysis of therapy in HoFH patients over the past 40 years highlights the importance of early diagnosis and initiation of modern lipid-lowering therapy, especially statin therapy, even in young children with HoFH, to delay life-threatening cardiovascular disease. This therapy has been well tolerated and remarkably safe and has prolonged their lives by several years. However, the clinical management of HoFH patients remains a challenge, because currently available lipid-lowering drug therapy is unable to achieve desirable LDL-C levels. New therapies under development, including apolipoprotein B antisense oligonucleotides, microsomal triglyceride transfer protein inhibitors, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, and thyroid hormone analogues, may be of added benefit but are also unlikely to achieve LDL-C targets in HoFH patients.

Acknowledgments

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Disclosures

Dr Raal has received research support for pharmaceutical trials of lipid-modifying agents and has received honoraria for consultations on lipid disorders; he has consulted or given lectures for Pfizer, Merck, AstraZeneca, and Genzyme. Dr Blom has received support for pharmaceutical trials with lipid-lowering agents and served as a member of the Merck A divisory Board for ezetimibe/simvastatin. Dr Marais has received a research grant from the Medical Research Council of South Africa and research support for a pharmaceutical trial with a lipid-lowering agent; he has also received honoraria for consultations on lipid management and has consulted for MSD, Parke-Davis, Pfizer, Bayer, and AstraZeneca. The other authors report no conflicts.

References


**Clinical Perspective**

Homozygous familial hypercholesterolemia (HoFH) is an inherited disorder usually caused by mutations in both low-density lipoprotein receptor alleles, which results in extremely elevated plasma low-density lipoprotein cholesterol concentrations and very early morbidity and mortality due to cardiovascular disease. Untreated, HoFH patients rarely survive beyond the third decade. This retrospective study reports the effect of lipid-lowering treatment, mainly statin therapy, on survival and time to first major cardiovascular event in a large cohort of HoFH patients who have been followed up for up to 40 years. Despite achieving a mean reduction in low-density lipoprotein cholesterol of only 26%, lipid-lowering therapy was associated with delayed cardiovascular events and prolonged survival in patients with HoFH. This supports the mounting evidence of the remarkable benefit of lipid-lowering therapy, particularly statin therapy, and establishes that lowering low-density lipoprotein cholesterol can prolong life even in HoFH. This analysis also highlights the importance of early diagnosis and initiation of lipid-lowering therapy, especially in young children with HoFH, to delay the onset of cardiovascular disease.