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Two-Year Efficacy and Safety of *Simvastatin* 80 mg in Familial Hypercholesterolemia (The Examination of Probands and Relatives in Statin Studies With Familial Hypercholesterolemia [ExPRESS FH])

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Conventional doses of statins rarely achieve targeted reductions of low-density lipoprotein (LDL) cholesterol in patients with familial hypercholesterolemia (FH). Our study was designed to evaluate the efficacy and safety of high-dose (80 mg) simvastatin in >500 patients with FH.

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For this open-label multicenter study, patients with FH were recruited from 37 lipid clinics in The Netherlands. Patients were included if they met the following criteria: all patients had to have either a molecular diagnosis for FH or were diagnosed with definite FH and had to have ≥6 points according to an algorithm (to allow standardization of the diagnosis of FH based on clinical findings, personal and familial clinical history, and biochemical parameters)[1]; at least 18 years of age and patients with a history of myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty could be included if the physician thought it was medically allowed for the patient to have a washout period. Patients were excluded if they: were pregnant or nursing, or premenopausal and not taking adequate contraceptives; had acute liver disease, hepatic dysfunction, or persistent elevations in serum transaminases; had hypersensitivity or intolerance to simvastatin or any of its components; had hypercholesterolemia type I, IV, or V or homozygous FH; had a recent history of alcohol or drug abuse; had secondary hypercholesterolemia due to any cause; had inadequately controlled diabetes, unstable angina, or intermediate coronary syndrome, or clinically significant ventricular arrhythmia at study entry or myocardial infarction within the past 3 months; or if they were on concurrent use of erythromycin and similar drugs affecting the cytochrome P450 enzyme or had a history of cancer.

The ethics committees of all 37 centers approved the protocol and written informed consent was obtained from all participants.

After a washout period of 6 weeks, patients were begun on monotherapy with simvastatin 80 mg, 1 tablet once daily, for 2 years. No other lipid-lowering medication was allowed. Medical history, physical examination, and additional risk factors for cardiovascular disease as well as laboratory analysis of lipid and lipoprotein levels and routine safety parameters were obtained in all patients. Biochemical analyses of lipid

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TABLE 1 Demographic and Clinical Baseline Characteristics of 508 Patients With FH

Characteristics	Men (n = 285)	Women (n = 223)
Age (yrs)	45.3 ± 11.5	50.0 ± 14.7
Cardiovascular disease	38.6%	35.4%
Mean age of onset (yrs)	43.4 ± 8.1	50.9 ± 9.9
Coronary artery disease	93.6%	87.3%
Peripheral artery disease	15.5%	27.8%
Both	9.1%	15.2%
Smoking		
Current	27.4%	24.2%
Nonsmoking	72.6%	75.8%
Family history of premature coronary artery disease	64.2%	66.8%
Diabetes mellitus	1.8%	2.2%
Systemic hypertension	16.5%	14.3%
Weight (kg)	83.9 ± 11.9	70.1 ± 11.4
Height (m)	1.79 ± 0.07	1.65 ± 0.06
Body mass index (kg/m^2)	26.0 ± 3.1	25.6 ± 4.0
Xanthomas	39.6%	49.3%
Arcus cornealis	35.4%	25.1%

All values are expressed as mean ± SD or percentages.

levels and safety parameters were performed in the hospitals themselves at each of 8 clinic visits (at weeks −6, 1, 6, 12, and 24; and at years 1, 1½, and 2) and were standardized by a virtual central laboratory. The apolipoprotein determinations were performed in the Academic Medical Center in Amsterdam.

The primary efficacy end point was the percent change in LDL cholesterol level relative to baseline. Secondary end points included percent change in total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and the apolipoproteins A-I and B, all relative to baseline values. Safety and tolerability were evaluated with adverse event reporting, laboratory studies, and vital sign recording. Patients were questioned about the occurrence of adverse events using nonleading questions. Vital signs were measured at each visit. A physical examination was performed at baseline visit. Fasting samples for serum chemistry were taken at each visit. The proportion of patients with values of alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal confirmed on repeat measurements, and the proportion of patients withdrawn from therapy due to these elevations at any time during the study, were tabulated. Any elevations in creatine kinase of >5 times the upper limit of normal that were confirmed on repeat measurements and accompanied by clinical signs or symptoms of myopathy, or creatine kinase elevations >10 times the upper limit of normal (even if asymptomatic) were considered safety end points for the study. All drug-related clinical and laboratory adverse experiences as well as discontinuations due to these events were recorded. The drug relatedness was scored as definitely not, probably not, possibly, probably, or definitely. Those adverse events scored as possibly, probably, and definitely were considered drug related.

Blood samples were obtained in the morning after an overnight fast. Total cholesterol, HDL cholesterol, triglycerides, and safety parameters were routinely determined in the different laboratories and standardized by a virtual central laboratory. LDL cholesterol was calculated using the Friedewald formula.[2] Apolipoprotein A-I and B were determined by an immunologic rate-nephelometric procedure using a polyclonal goat antihuman antibody (Array protein system, Beckman Coulter, Mijdrecht, The Netherlands).[3]

Mean values in lipids and lipoproteins before and after treatment were compared using the paired sample *t* test, and the statistical significance of the relative change (for patients with lipid levels at baseline and 2 years of treatment) compared with baseline, was tested using the 1-sample *t* test. Triglyceride levels were compared by the nonparametric Wilcoxon test because they had a skewed distribution. All statistical analyses were performed using the SPSS package (version 10.0.7, Chicago, Illinois). A p value <0.05 was considered statistically significant.

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In all, 546 patients were considered for inclusion. Of these, 508 met the inclusion criteria and received simvastatin 80 mg. Of all patients, 341 had a molecular diagnosis of FH, whereas 167 patients received the diagnosis of FH based on the algorithm. All patients were eating a modest lipid-lowering diet, comparable to the National Cholesterol Education Program step I, and during the study considerable attention was focused on dietary adherence. Baseline characteristics for men and women separately are listed in Table 1.

Mean baseline lipid and lipoprotein levels of all patients are listed in Table 2. Mean total cholesterol (10.50 mmol/L or 404 mg/dl) and LDL cholesterol (8.37 mmol/L or 322 mg/dl) levels were, as can be expected in patients with FH, severely elevated. In comparison, total cholesterol and LDL cholesterol levels were 5.49 mmol/L (211 mg/dl) and 3.56 mmol/L (137 mg/dl), respectively, in 3,403 Dutch controls.[4]

After 2 years of treatment, total cholesterol levels were reduced by 39.2% to mean levels of 6.31 mmol/L (243 mg/dl) and LDL cholesterol levels by 48.0% to mean levels of 4.29 mmol/L (165 mg/dl). Triglyceride levels were reduced by 26.1% to median levels of 1.20 mmol/L (106 mg/dl). HDL cholesterol levels increased by 12.7% to mean levels of 1.35 mmol/L (52 mg/dl). All these changes from baseline were highly statistically significant.

In Figure 1, short- and long-term efficacy of lipids and lipoproteins is presented. Mean LDL cholesterol levels were reduced by 45% to 48% at different time intervals during the 2 years of treatment. Over the same period, the 80-mg dose was also effective in reducing total cholesterol (mean changes from 37% to 39%) and triglycerides (median changes from 26% to 31%), and in

TABLE 2 Treatment Effects of Simvastatin 80 mg on Fasting Lipid and Lipoprotein Levels

Variable	Baseline (n = 508)	Year 2 (n = 445)	% Change	95% CI	p Value
Total cholesterol					
mmol/L	10.50 ± 2.16	6.31 ± 1.42	−39.2 ± 11.8	−40.3–−38.1	<0.0001
mg/dl	404 ± 83	243 ± 55			
LDL cholesterol					
mmol/L	8.37 ± 2.12	4.29 ± 1.32	−48.0 ± 13.5	−49.2–−46.7	<0.0001
mg/dl	322 ± 82	165 ± 51			
HDL cholesterol					
mmol/L	1.22 ± 0.35	1.35 ± 0.36	12.7 ± 21.8	+10.7–+14.8	<0.0001
mg/dl	47 ± 13	52 ± 14			
Triglycerides					
mmol/L	1.80 (1.20/2.40)	1.20 (0.90/1.70)	−26.1 (−46.2/−5.6)		<0.0001
mg/dl	159 (106/212)	106 (80/150)			
Apolipoprotein A-I (g/L)	1.22 ± 0.21	1.29 ± 0.22	7.0 ± 20.9	+4.8–+9.2	<0.0001
Apolipoprotein B (g/L)	1.98 ± 0.44	1.20 ± 0.31	−38.2 ± 13.9	−39.7–−36.8	<0.0001

All values are expressed as mean ± SD. Only triglycerides are given as median (interquartile range in parentheses).
CI= confidence interval.

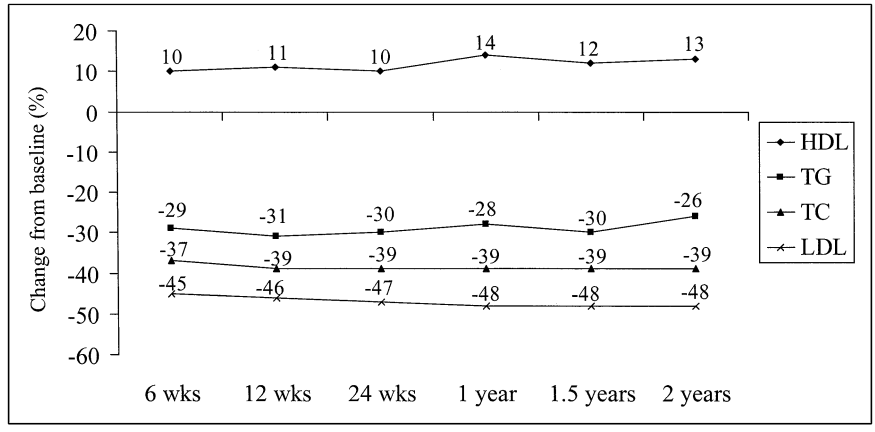

FIGURE 1. Short- and long-term efficacy of simvastatin 80 mg at different points in time. TC = total cholesterol; TG = triglycerides.

raising HDL cholesterol (mean changes from 10% to 14%).

A total of 29 patients discontinued therapy due to clinical adverse events (5.7%). Of these, 6 patients died. No deaths were considered drug related and 4 were due to cardiovascular events. One patient died suddenly of unknown causes. The other patient had a history of myocardial infarction and mitral valve insufficiency and he died in the washout period. He was admitted with unstable angina, and a coronary bypass procedure was performed combined with a mitral valve repair. The patient died from an aortic dissection during the procedure. From the total of 29 patients, 22 discontinuations (4.3%) were classified as drug related (Table 3). The most common drug-related adverse events leading to discontinuation were musculoskeletal (1.8%) and gastrointestinal (1.0%) complaints, fatigue (0.6%), and headache (0.4%).

Only 5 patients discontinued therapy because of laboratory adverse events, 4 of which were drug related (0.8%). Drug-related myalgia was observed in 45 patients (8.9%) and 7 of these patients discontinued therapy (1.4%). Myopathy is traditionally defined as muscle pain or weakness accompanied by creatine kinase levels >10 times above the upper limit of normal. Three patients had creatine kinase elevations >10 times the upper limit, but only 1 patient had accompanying muscle pain. However, this was local back pain after a sporting event and creatine kinase levels returned to normal at retest within 1 week while treatment was continued. The other patient continued treatment and creatine kinase levels returned to normal within 7 days, but the third patient discontinued the study due to drug-related aspartate aminotransferase and creatine kinase elevations.

Consecutive elevations in liver function tests of >3 times the upper limit of normal are regarded as clinically significant. Only 3 patients had consecutive liver function elevations. Importantly, 1 of the 3 patients continued therapy and another patient interrupted therapy during 4 weeks after which he started again with the study medication. In both patients, the levels returned to normal. The third patient withdrew from the study because of bad compliance and was lost to follow-up. In 3 other patients, elevated levels of liver transaminases were measured once while on therapy. Two of these patients discontinued therapy because they were considered to have a drug-related adverse event. These 2 patients are presumed to have had consecutive elevations as well, because their levels were not checked again while on the drug. In the third patient, therapy was interrupted after which the

TABLE 3 Safety During Two Years of Treatment With Simvastatin 80 mg

Variable	No.
Discontinued because of drug-related clinical AE	22 (4.3%)
Discontinued because of drug-related laboratory AE	4 (0.8%)
Discontinued because of drug-related myalgia	7 (1.4%)
Myopathy*	0 (0.0%)
Consecutive ALT or AST increases >3 × ULN	5 (1.0%)

*Myopathy was defined as muscle pain accompanied by >10 × the upper limit of normal in creatine kinase.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

levels returned to normal and remained normal after therapy was restarted. The total incidence of consecutive transaminase elevations was 1.0%.

A total of 29 patients discontinued therapy for other reasons during the 2 years of follow-up.

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Mean LDL cholesterol levels were reduced by 48.0% after 2 years of therapy and more importantly, this reduction was maintained at different time points during these 2 years. Therefore, tachyphylaxis to simvastatin did not occur. Recently, a retrospective study reported that tachyphylaxis may occur with atorvastatin but not with simvastatin.[5] Reductions in total cholesterol and triglyceride levels were maintained throughout the study as well. HDL cholesterol increased by 12.9%, which was maintained during 2 years of treatment. A recent report has summarized most studies performed with simvastatin 80-mg treatment.[6] In a total of 1,936 hypercholesterolemic (non-FH) patients, the 80-mg dose reduced LDL cholesterol by 45.7% and showed excellent safety and tolerability. However, in those studies, follow-up ranged from 36 to 48 weeks. In our study, we showed that patients with FH had a more pronounced LDL cholesterol reduction, which was maintained over a 2-year period.

This cohort provided the opportunity to collect long-term safety and tolerability data in a large cohort of FH patients who required high-dose statin therapy. No unexpected adverse events were observed. The incidence of discontinuations due to drug-related clinical (4.3%) or laboratory (0.8%) adverse events was very low. Only 3 patients had creatine kinase elevations >10 times the upper limit of normal, and only 1 of these had accompanying muscle pain. The incidence of sustained elevations in hepatic liver enzymes >3 times the upper limit of normal was also low (1.0%). These safety and tolerability data are in line with the results of other studies performed with simvastatin 80 mg.[6] In those 1,586 patients, the incidence of clinical and laboratory drug-related discontinuations was 2.5% and 1.6%, respectively, whereas that of consecutive elevations in liver function tests was 1.5% and of myopathy 0.6%.

In summary, high-dose (80 mg) simvastatin is efficacious in both reducing LDL cholesterol (−48%) and triglyceride (−26%) levels, and in elevating HDL cholesterol (+13%) levels in a large cohort of patients with FH. No tachyphylaxis was seen during a 2-year treatment period and therapy with simvastatin 80 mg was well tolerated.

APPENDIX

The following investigators participated in the Dutch ExPRESS study: Almelo: R.J. Lionarons; Amersfoort: A. van de Wiel; Amsterdam: J.J.P Kastelein, P.R.W. de Sauvage Nolting, MD Trip; Assen: A.A.M. Franken, R.K. Gonera; Breda: P.J. Stijnen; Brunssum: R. Bianchi, W.J.R.R. Venekamp; Delft: A.J. Spanjersberg, A.M. Vollaard, A.J.A.M. Withagen; Delfzijl: P. van Hoogdalem, A. Sijperda; Den Bosch: R.J.J. Claessens; Den Helder: W.W. Meijer, R.J. Timmerman; Dokkum: L.J. de Vries; Drachten: M.C. Snoep; Eindhoven: J.P.M. van Asseldonk, J.J.R.M. Bonnier, H.R. Michels; Emmen: J. Westenburg; Enschede: M.A. Galjee, K. Huisman; Goes: A.H. Liem; Groningen: J.J. van Doormaal; Haarlem: W.T. van Dorp; Hardenberg: B.L.S. Borger van der Burg, J.T.A. te Gussinklo; Heerenveen: O. de Vries; Heerlen: R.J.C.T. Feld, J.A. Kragten, J. deWarrimont-Henquet; Hoorn: D.C.G. Basart, C.L. Janus, R. Zwertbroek; Leiden: A.H.M. Smelt; Meppel: J.C. Ogterop; Purmerend: F.D. Slob; Rotterdam: M.G.A Baggen, I.I.L. Berk-Planken, N. Hoogerbrugge, J.J.C. Jonker, B. van Leeuwen; Utrecht: M. Castro Cabezas, D.W. Erkelens, J.M. Hartog, Th.B. Twickler, H.W. de Valk; Veldhoven: M. Beganovicz, A.H. Bosma, H.T. Droste, L.C. Slegers; Venlo: R.P.T. Troquay; Weert: H.J.A.M. Penn; Winschoten: H. Pothoff; Winterswijk: J.V.C. Stevens; Zwolle: J.E. Heeg.

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