Adv Ther (2011) 28(9):811-823.
DOI 10.1007/s12325-011-0056-7

ORIGINAL RESEARCH

Comparative Efficacy of Pitavastatin and Simvastatin in High-Risk Patients: a Randomized Controlled Trial

Mats Eriksson · Dragos Budinski · Neil Hounslow

Received: May 19, 2011 / Published online: August 25, 2011

ABSTRACT

Introduction: Despite the proven efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in lowering total and low-density lipoprotein cholesterol (LDL-C), many patients do not reach recommended lipid targets. This study compared pitavastatin, a new and highly effective statin, and simvastatin in patients at high risk of coronary heart disease (CHD). The primary objective was to demonstrate noninferiority of pitavastatin to simvastatin. ***Methods:*** The study was a phase 3, randomized, double-blind, double-dummy, parallel-group, active-controlled study conducted at 37 centers in five European countries. Following a dietary run-in period of 6-8 weeks, patients with primary hypercholesterolemia or combined dyslipidemia and at least two CHD risk factors were randomized 2:1 to receive pitavastatin 4 mg or simvastatin 40 mg once daily for 12 weeks. The primary efficacy variable was the change in LDL-C from baseline. ***Results:*** In total, 355 patients were randomized, 236 to pitavastatin and 119 to simvastatin; 330 patients (223 and 107, respectively) completed the study. In the pitavastatin group, mean (±SD) reduction in LDL-C concentrations from baseline was –44.0±12.8% compared with –43.8±14.4% in the simvastatin group. The adjusted mean treatment difference (simvastatin – pitavastatin) was 0.31% (95% confidence interval –2.47, 3.09; P=0.829), which was within the predefined noninferiority range. More than 80% of patients in each group reached recommended LDL-C targets. Pitavastatin provided a greater increase in high-density lipoprotein cholesterol (HDL-C; 6.8% vs. 4.5%; P=0.083) and a significantly greater decrease in triglycerides (–19.8% vs. –14.8%; P=0.044) than simvastatin. Both treatments were well tolerated. ***Conclusion:*** Pitavastatin 4 mg is as effective as simvastatin 40 mg in lowering LDL-C in dyslipidemic patients at high risk of CHD, with additional effects on HDL-C and triglycerides. Therefore, pitavastatin may be appropriate for the management of dyslipidemic patients at high cardiovascular risk.

Mats Eriksson (✉)
Department of Endocrinology, Metabolism & Diabetes, Karolinska University Hospital, M63 SE14186 Stockholm, Sweden. Email: mats.eriksson@ki.se

Dragos Budinski · Neil Hounslow
Kowa Research Europe Ltd, 105 Wharfedale Road, Winnersh Triangle, Wokingham, Berkshire, RG41 5RB, UK

Keywords: coronary heart disease; high-density lipoprotein cholesterol; lipid-modifying therapy; low-density lipoprotein cholesterol; pitavastatin; simvastatin; triglycerides

INTRODUCTION

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) occupy a central place in the management of dyslipidemia due to their documented efficacy in lowering elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations and reducing cardiovascular mortality and morbidity. In a meta-analysis of 14 studies involving over 90,000 patients who were followed for a mean of 5 years, statins were shown to reduce the risks of major vascular events, cardiac mortality, and overall mortality by 21%, 19%, and 12%, respectively, for each mmol/L decrease in LDL-C.[1] Nevertheless, a significant proportion of dyslipidemic patients do not meet the lipid targets recommended in current consensus guidelines, despite treatment with statins.[2-5] Thus, there is a need for more effective risk-management strategies to reduce the burden of cardiovascular mortality and morbidity associated with dyslipidemia. Such strategies could include the use of more aggressive initial therapy, more potent lipid-lowering agents, dose adjustment during treatment, or combination therapy using agents with different mechanisms of action.

Pitavastatin is a novel statin that has been shown to be more potent in lowering total cholesterol and LDL-C concentrations than simvastatin or pravastatin.[6-8] In contrast to other statins, it undergoes limited metabolism by cytochrome P450 isoenzymes[9,10] and, hence, the potential for interactions with drugs metabolized by these enzymes is low.[11]

The present study was performed to compare the efficacy of pitavastatin and simvastatin in lowering LDL-C concentrations in patients at high risk of coronary heart disease (CHD). The primary objective was to demonstrate noninferiority of pitavastatin 4 mg once daily compared with simvastatin 40 mg once daily in reducing LDL-C concentrations. Secondary objectives were to assess the long-term efficacy of the two drugs in achieving the LDL-C targets recommended by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III[12] and the European Atherosclerosis Society (EAS),[13] and to compare the effects of the two agents on other lipid measures and high sensitivity C-reactive protein (hs-CRP).

MATERIALS AND METHODS

Patients

Patients of either gender were eligible for inclusion in the study if they were aged 18-75 years and had primary hypercholesterolemia or combined dyslipidemia that was uncontrolled (LDL-C ≥3.4 mmol/L [130 mg/dL] and ≤5.7 mmol/L [220 mg/dL]; triglycerides ≤4.6 mmol/L [400 mg/dL]) despite dietary measures. In addition, patients were required to have at least two of the following cardiovascular risk factors: cigarette smoking; blood pressure of 140/90 mmHg or above or receiving antihypertensive therapy; a high-density lipoprotein cholesterol (HDL-C) concentration of 1 mmol/L (40 mg/dL) or below; a family history of CHD in a male or female first-degree relative below 55 or below 65 years of age, respectively; age above 45 years in men or above 55 years in women. An HDL-C concentration above 1.55 mmol/L (60 mg/dL) was considered to offset one risk factor. Patients who were receiving lipid-modifying therapies were eligible for inclusion if such treatment was withdrawn at least 8 weeks before randomization.

The principal exclusion criteria were homozygous familial hypercholesterolemia, unstable medical conditions, or conditions associated with secondary dyslipidemia, conditions that might affect drug pharmacokinetics, significant cardiovascular disease, or symptomatic heart failure (left ventricular ejection fraction <0.25) or cerebrovascular disease, uncontrolled or poorly controlled hypertension, uncontrolled diabetes (>8% glycated hemoglobin), impaired liver or kidney function, or other serious medical conditions. Women of childbearing potential were required to have a negative pregnancy test at the start of the dietary run-in period and before starting treatment, and to use adequate contraception throughout the study.

The study was performed in compliance with the Declaration of Helsinki, the draft Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders by the Committee for Proprietary Medicinal Products, and the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use - Harmonized Tripartite Guidelines for Good Clinical Practice. The protocol was approved by local institutional review boards or independent ethics committees at each center. All participants provided written informed consent before inclusion in the study.

Study Design

This was a phase 3, randomized, double-blind, double-dummy, parallel-group, active-controlled study conducted at 37 centers (predominantly in lipid clinics, cardiology clinics and university hospitals) in Denmark, the Netherlands, Spain, Sweden, and the United Kingdom. The study consisted of a 12-week initial treatment period (the core study) followed by a 44-week extension. This paper presents the results of the core study; the results of the extension phase will be reported separately.

Eligible patients entered a lead-in and wash-out phase of 8 weeks if they had previously received lipid-modifying therapy or 6 weeks if they had not previously received such therapy. During this phase, and for the duration of the study, they followed a fat- and cholesterol-restricted diet according to EAS guidelines. Patients received counseling to ensure that they adhered to this diet throughout the study. On completion of the run-in period, patients were randomized in a 2:1 ratio to receive pitavastatin 4 mg or simvastatin 40 mg once daily. Randomization was performed using an interactive voice recognition system at each center. Patients randomized to pitavastatin started treatment at a dose of 2 mg, and the dose was increased to 4 mg after 4 weeks. In patients randomized to simvastatin, the initial dose was 20 mg, which was increased to 40 mg after 4 weeks. Treatment was given once daily in the evening, and all other lipid-modifying therapies were prohibited for the duration of the study. Compliance was checked by counting unused tablets or capsules at each study visit.

Both patients and investigators were blinded to the treatment received. Because pitavastatin is given in tablet form, and simvastatin in capsule form, blinding was maintained by the use of placebo dummies, which were identical in appearance to the active medications. Pitavastatin tablets (2 and 4 mg) and matching placebos were supplied by SkyePharma Production (Saint Quentin-Fallavier, France), and over-encapsulated simvastatin tablets and matching placebos by ALMAC (Craigavon, UK).

Blood samples for lipid analyses were obtained after a 12-hour fast on three occasions during the run-in period and at weeks 0, 2, 4, 8, and 12 of the study.

Outcome Measures

The primary efficacy endpoint was the percentage change in LDL-C concentrations at 12 weeks compared with baseline. Secondary efficacy endpoints included the proportion of patients reaching NCEP and EAS LDL-C targets, percentage changes from baseline in concentrations of triglycerides, total cholesterol, HDL-C, non-HDL-C, apolipoprotein B (Apo-B) and apolipoprotein A1 (Apo-A1), and absolute changes from baseline in concentrations of oxidized LDL (measured using an enzyme-linked immunosorbent assay), and hs-CRP and ratios of total cholesterol:HDL-C, non-HDL:HDL-C, and Apo-B:Apo-A1. All lipid analyses were performed at a central laboratory.

Safety and Tolerability

Treatment-emergent adverse events (TEAE), defined as any event with onset on or after the first dose of study drug, and serious TEAE were recorded throughout the study. All such events were coded by system organ class preferred terms using the Medical Dictionary for Regulatory Activities. Clinical laboratory safety assessments included routine blood chemistry, hematology, urinalysis, liver enzymes (alanine aminotransferase and aspartate aminotransferase), and creatine kinase (CK). Other safety evaluations included physical examination, 12-lead electrocardiogram (ECG), and vital signs.

Statistical Analyses

The planned target size for the core study was 300 patients (200 randomized to pitavastatin and 100 randomized to simvastatin). It was calculated that this sample size would provide at least 99% power to reject the null hypothesis that the mean percentage decrease in LDL-C concentrations from baseline would be at least 6% greater in the simvastatin group than in the pitavastatin group, assuming a standard deviation (SD) of 12 (for percentage decrease from baseline LDL-C) and a one-tailed significance level of 2.5%.

The noninferiority analysis and other lipid assessments were performed on the full analysis set (FAS), which included all randomized patients who received at least one dose of study medication and had at least one lipid assessment during the study. Confirmatory analyses were performed on the per-protocol (PP) population, which included all patients in the FAS who had a lipid assessment at week 12 and no major protocol deviations. The primary efficacy variable was the change in LDL-C from baseline to endpoint for the FAS, or from baseline to week 12 for the PP population. The baseline measurement was defined as the mean of the three measurements made during the run-in period, while the endpoint was defined as the week 12 measurement or the last available measurement in patients who withdrew from the study prematurely. Differences in this primary efficacy endpoint between groups were analyzed by analysis of covariance (ANCOVA), with treatment and country as factors and baseline LDL-C as a covariate. The adjusted mean difference between treatments (simvastatin 40 mg minus pitavastatin 4 mg) and the corresponding 95% CI were calculated. Pitavastatin was considered noninferior (equivalent) to simvastatin if the lower limit of the 95% CI was greater than –6%. Prospectively planned subgroup analyses based on age, gender, race, body mass index (BMI), diagnosis, risk category, baseline LDL-C concentration, and presence of hypertension and diabetes were conducted using the same model. Secondary efficacy variables were also evaluated using

ANCOVA and 95% CIs on the adjusted mean differences in the absolute or percentage changes from baseline to endpoint for the FAS, and to week 12 for the PP population. Noninferiority margins for secondary variables were not defined. All analyses were performed using SAS® Version 8.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Flow and Baseline Characteristics

The first patient was enrolled on September 27, 2005 and the final patient visit took place on October 2, 2006. In total, 355 patients were randomized, of whom 236 received pitavastatin and 119 received simvastatin (Figure 1). Three patients in the pitavastatin group were excluded from the FAS and safety population because they did not receive any study medication: two patients withdrew consent and the third was withdrawn because of protocol violations. One patient in the simvastatin group was excluded from the FAS because of no on-treatment lipid assessment. Overall, 330 patients (223 in the pitavastatin group, 107 in the simvastatin group) completed the 12-week study.

The two groups were well matched in terms of their baseline characteristics (Table 1). The mean age of the patients was approximately 60 years, about two-thirds were male, and all except one were White. The majority of patients (>80%) had primary hypercholesterolemia, and approximately three-quarters were at moderate or high cardiovascular risk according to the NCEP criteria. Weight was similar between the pitavastatin and simvastatin groups at the screening visit and did not change significantly during the study (pitavastatin:

Figure 1. Patient disposition by treatment group and analysis population. *One patient excluded from the full analysis set and per protocol population completed the core study.

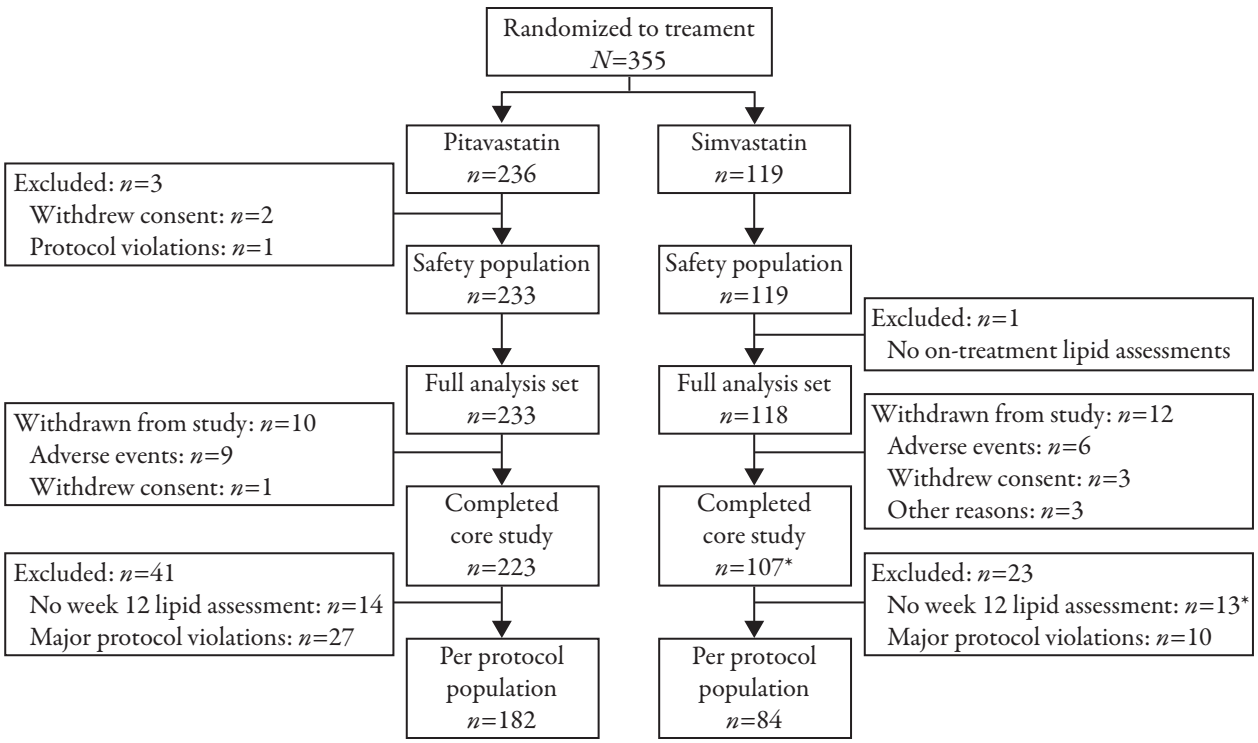


Table 1. Baseline demographic and clinical characteristics (safety population).

Characteristic	Pitavastatin 4 mg (*n*=233)	Simvastatin 40 mg (*n*=119)
Gender		
Male, *n* (%)	158 (67.8)	82 (68.9)
Female, *n* (%)	75 (32.2)	37 (31.1)
Age (years), mean ± SD	60.1±6.8	60.9±6.8
Age group, *n* (%)		
<65 years	184 (79.0)	88 (73.9)
≥65 years	49 (21.0)	31 (26.1)
Race, *n* (%)		
White	233 (100)	118 (99.2)
Black	0 (0.0)	1 (0.8)
Primary diagnosis, *n* (%)		
Primary hypercholesterolemia	194 (83.3)	102 (85.7)
Combined dyslipidemia	35 (15.0)	14 (11.8)
Heterozygous FH	4 (1.7)	3 (2.5)
Time since diagnosis (years), mean ± SD	3.7±5.4	4.5±6.0
Height (m), mean ± SD	1.7±0.1	1.7±0.1
Weight (kg), mean ± SD	80.8±13.5	80.9±12.8
Body mass index (kg/m^2), mean ± SD	27.6±3.5	27.6±3.2
NCEP risk category, *n* (%)		
High	59 (25.3)	35 (29.4)
Moderate	165 (70.8)	79 (66.4)
Low	9 (3.9)	5 (4.2)
Diabetes, *n* (%)	15 (6.4)	8 (6.7)
Hypertension, *n* (%)	123 (52.8)	70 (58.8)
Clinical CHD, *n* (%)	16 (6.9)	11 (9.2)
Concomitant medication, *n* (%)*	192 (82.4)	95 (79.8)
Total	26 (11.2)	12 (10.1)
ACE inhibitors (single)	9 (3.9)	4 (3.4)
ACE inhibitors (combination)	20 (8.6)	14 (11.8)
Angiotensin II antagonists (single)	16 (6.9)	10 (8.4)
Angiotensin II antagonists (combination)	41 (17.6)	17 (14.3)
Beta-blockers	29 (12.4)	22 (18.5)
Calcium channel blockers	34 (14.6)	21 (17.6)
Diuretics	39 (16.7)	26 (21.8)

*Total number of patients on concomitant medication and numbers on antihypertensive medications are listed.
ACE=angiotensin-converting enzyme inhibitor; CHD=coronary heart disease; FH=familial hypercholesterolemia; NCEP=National Cholesterol Education Program; SD=standard deviation.

screening=80.8±13.5 kg; week 12=79.9±13.7 kg; simvastatin: screening=80.9±12.8 kg; week 12=80.1±11.9 kg). Similar percentages of patients in each treatment group were receiving concomitant antihypertensive medication (Table 1).

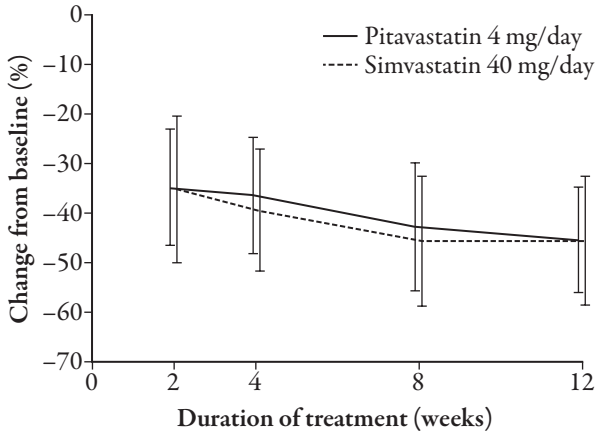
Efficacy

LDL-C Concentrations

In the pitavastatin group, mean (±SD) LDL-C concentrations decreased from 4.30±0.52 mmol/L at baseline to 2.40±0.61 mmol/L at endpoint, corresponding to a percentage decrease of –44.0±12.8%. In simvastatin-treated patients, LDL-C decreased from 4.32±0.61 mmol/L to 2.41±0.64 mmol/L, corresponding to a reduction of –43.8±14.4%. The adjusted mean treatment difference (simvastatin minus pitavastatin) was 0.31% (95% CI: –2.47, 3.09), which was within the predefined limits of noninferiority (*P*=0.829 for treatment difference). These results were confirmed in the PP analysis, which yielded a mean treatment difference of –0.61% (95% CI: –3.17, 1.94; *P*=0.637).

The mean reduction in LDL-C concentration was approximately 35% in both treatment groups after 2 weeks of treatment, and LDL-C continued to decrease throughout the study (Figure 2). Preplanned analyses were performed to compare the reductions in LDL-C concentration achieved with both treatments in different patient subgroups, based on age, gender, BMI, primary diagnosis, baseline LDL-C, NCEP CHD risk, and the presence of hypertension or diabetes (Figure 3). The only significant difference found in these analyses was a greater reduction in LDL-C concentration with simvastatin compared with pitavastatin in patients aged 65 years and over, who accounted for 23% of the overall study population.

Figure 2. Mean percentage reduction in low-density lipoprotein cholesterol (LDL-C) concentrations from baseline at weeks 2, 4, 8, and 12 of treatment with pitavastatin 4 mg or simvastatin 40 mg. Values are means ± standard deviation.



Attainment of EAS and NCEP Lipid Targets

NCEP targets for LDL-C concentrations were achieved by 203 of 233 (87.1%) patients in the pitavastatin group, and 101 of 118 patients (85.6%) in the simvastatin group. The numbers of patients achieving the EAS targets for LDL-C concentration were 203 (87.1%) and 96 (81.4%) for the pitavastatin and simvastatin groups, respectively. The mean treatment differences in the proportion of patients achieving LDL-C targets were –1.5% (95% CI: –9.2, 6.1; *P*=0.695) for the NCEP targets and –5.8% (95% CI: –14.0, 2.5; *P*=0.170) for the EAS targets.

Secondary Efficacy Variables

Mean percentage changes in secondary lipid variables (concentrations of triglycerides, total cholesterol, HDL-C, non-HDL-C, triglycerides, Apo-B, and Apo-A1) and absolute changes in oxidized LDL concentration, non-HDL:HDL-C ratio, Apo-B:Apo-A1 ratio, and hs-CRP level from baseline are summarized in Table 2. Pitavastatin provided a significantly greater reduction in triglycerides than simvastatin (–19.8% vs. –14.8%; *P*=0.044), and there was also a greater increase in HDL-C with pitavastatin (6.8% vs. 4.5%), which was not statistically significant (*P*=0.083). There were no other significant differences in secondary lipid measures between the two groups.

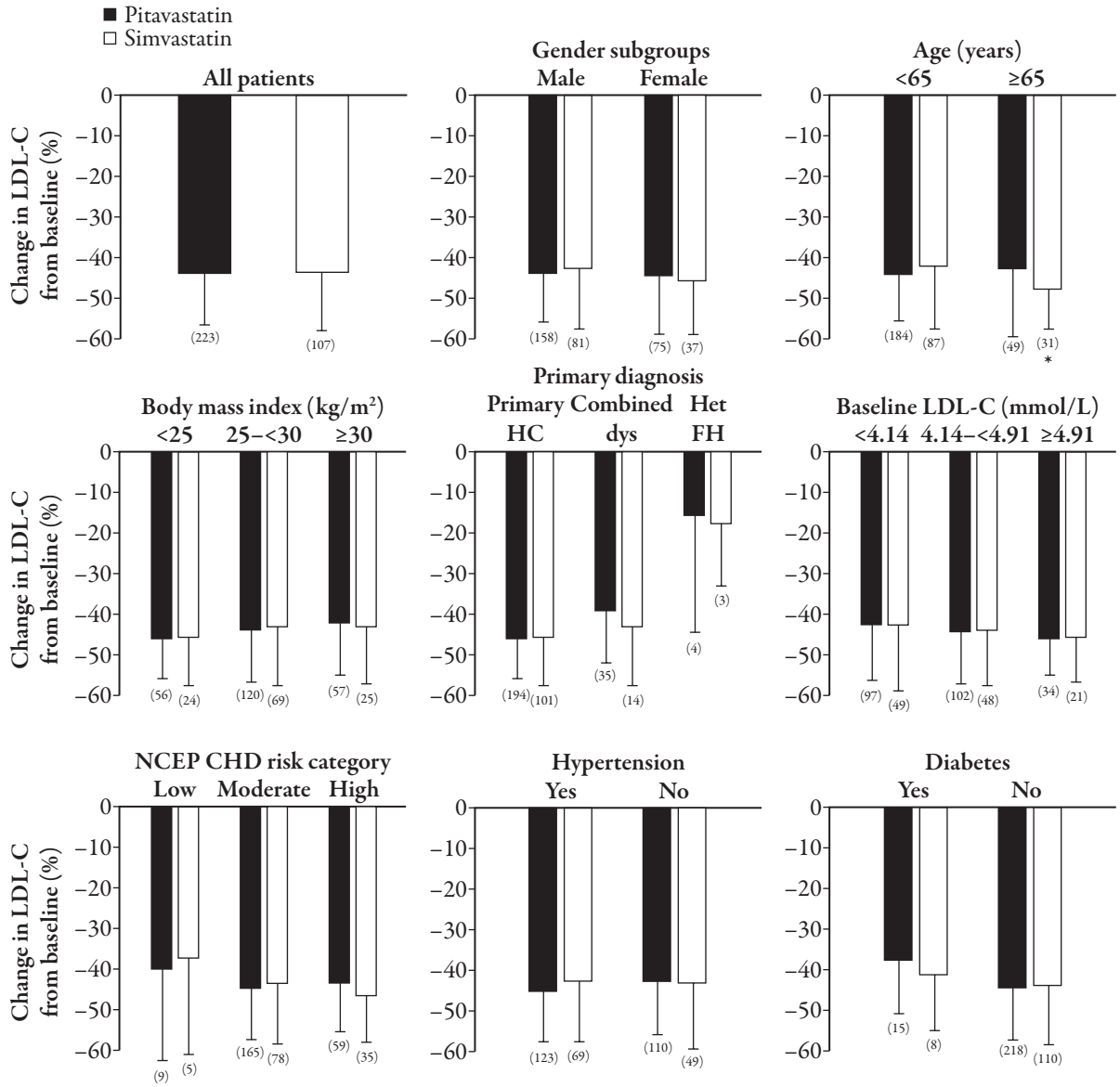
Safety and Tolerability

TEAE

TEAE were reported by 119 patients (51.1%) in the pitavastatin group and by 60 patients (50.4%) in the simvastatin group (Table 3). Adverse events that were considered to be treatment related occurred in 33 (14.2%) and 26 (21.8%) patients in the pitavastatin and simvastatin groups, respectively. The most common TEAE (those occurring in ≥2% of patients in either group) are summarized in Table 3. Constipation occurred in 4.3% of patients receiving pitavastatin and in 1.7% of those receiving simvastatin, and was considered to be treatment related in 3.9% and 0.8%, respectively. Myalgia was reported as a TEAE by seven pitavastatin-treated patients (3.0%) and by five simvastatin-treated patients (4.2%), and was considered to be treatment-related in four (1.7%) and three (2.5%) patients, respectively. Most TEAE were mild or moderate in severity. A total of 15 patients discontinued treatment because of TEAE; of these, nine (3.9%) were receiving pitavastatin and six (5.0%) were receiving simvastatin. The most common adverse event leading to treatment withdrawal was nausea, which occurred in three patients, all of whom were receiving simvastatin.

Four serious TEAE (gastritis, peritonsillar abscess, myocardial infarction, and acute coronary syndrome) occurred in patients in the pitavastatin group, and five serious TEAE (cholelithiasis, cystitis, aortic aneurysm, syncope, and lymphadenopathy) were reported in the simvastatin group. None of these events were considered to be treatment related.

Figure 3. Subgroup analysis of reductions in low-density lipoprotein cholesterol (LDL-C) concentrations from baseline to 12 weeks of treatment with pitavastatin 4 mg or simvastatin 40 mg. Values are means ± standard deviation for the number of patients in parentheses. *P=0.024 compared with pitavastatin. CHD=coronary heart disease; Combined dys=combined dyslipidemia; Het FH=heterozygous familial hypercholesterolemia; Primary HC=primary hypercholesterolemia; NCEP=National Cholesterol Education Program.



Laboratory Abnormalities

Three of the 12 patients in whom myalgia was reported as an adverse event showed elevated CK levels during the study. One patient in the simvastatin 40 mg group had elevated CK at baseline, which resolved during subsequent treatment, and one patient in each group developed elevated CK during treatment. Three patients in the pitavastatin group developed asymptomatic elevations of CK to more than five times the upper limit of the normal range (ULN), as did one simvastatin-treated patient. No patient showed elevations of liver enzymes above three times the ULN. There were no other clinically

Table 2. Changes from baseline in secondary lipid variables and high sensitivity C-reactive protein (hs-CRP) in patients treated with pitavastatin or simvastatin.

Parameter	Change from baseline (mean ± SD)*			
	Pitavastatin 4 mg (*n*=233)	Simvastatin 40 mg (*n*=118)	Adjusted mean treatment difference (95% CI)	*P*-value
Total cholesterol				
Baseline (mmol/L)	6.37±0.66	6.35±0.78		
Change (%)	−31.4±9.4	−31.2±11.1	0.28 (−1.79, 2.34)	0.793
HDL-C				
Baseline (mmol/L)	1.22±0.29	46.0±8.2		
Change (%)	6.8±12.6	4.5±12.1	−2.30 (−4.91, 0.30)	0.083
Non-HDL-C				
Baseline (mmol/L)	5.14±0.65	5.16±0.76		
Change (%)	−40.4±11.7	−39.2±13.4	1.35 (−1.17, 3.87)	0.293
Non-HDL-C:HDL-C ratio				
Baseline	4.45±1.25	4.50±1.09		
Change (%)	−1.9±0.9	−1.9±0.9	0.073 (−0.07, 0.22)	0.319
Total cholesterol:HDL-C ratio				
Baseline	5.45±1.25	5.50±1.09		
Change (%)	−1.9±0.9	−1.9±0.9	0.073 (−0.07, 0.22)	0.319
Triglycerides				
Baseline (mmol/L)	1.85±0.77	1.85±0.75		
Change (%)	−19.8±21.3	−14.8±29.7	5.23 (0.15, 10.30)	0.044
Apo-B				
Baseline (mg/dL)	152.5±20.9	153.3±24.6		
Change (%)	−33.7±12.3	−33.8±12.9	0.46 (−2.15, 3.07)	0.730
Apo-A1				
Baseline (mg/dL)	158.4±26.1	155.5±20.8		
Change (%)	7.6±12.7	6.9±12.1	−1.28 (−3.86, 1.30)	0.330
Apo-B:Apo-A1 ratio				
Baseline	0.99±0.24	1.00±0.20		
Change (%)	−0.4±0.2	−0.4±0.2	0.00 (−0.03, 0.04)	0.929
Oxidized LDL				
Baseline (U/L)	80.4±16.2	81.5±16.5		
Change (%)	−25.5±16.3	−25.9±17.1	0.40 (−2.21, 3.02)	0.761
hs-CRP				
Baseline (mg/L)	3.21±4.89	3.77±7.93		
Change (%)	−0.4±6.0	0.1±5.5	0.48 (−0.81, 1.78)	0.462

*Mean individual changes from baseline are given in terms of percentages or actual values as indicated.
Apo-A1=apolipoprotein A1; Apo-B=apolipoprotein B; CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; SD=standard deviation.

relevant findings on clinical laboratory evaluation, physical examination, vital signs, or ECG.

Mean plasma glucose levels did not change during the study in the groups treated with pitavastatin (baseline=98.4±14.5 mg/dL; week 12

Table 3. Summary of treatment-emergent adverse events (TEAE) in patients treated with pitavastatin or simvastatin.

	Number (%) of patients with a TEAE	
	Pitavastatin 4 mg (*n*=233)	**Simvastatin 40 mg (*n*=119)**
Any TEAE	119 (51.1)	60 (50.4)
Serious TEAE	4 (1.7)	5 (4.2)
Treatment-related TEAE	33 (14.2)	26 (21.8)
Discontinuations due to TEAE	9 (3.9)	6 (5.0)
TEAE occurring in ≥2% of patients in either group		
Headache	13 (5.6)	3 (2.5)
Nasopharyngitis	11 (4.7)	3 (2.5)
Constipation	10 (4.3)	2 (1.7)
Myalgia	7 (3.0)	5 (4.2)
Back pain	4 (1.7)	3 (2.5)

or last visit=98.4±15.9 mg/dL) or simvastatin (baseline=101.7±19.0 mg/dL; week 12 or last visit=101.1±18.0 mg/dL). Likewise, there was no indication of a treatment-related increase in urinary protein excretion (assessed by the protein:creatinine ratio) in either group.

DISCUSSION

This randomized trial has shown that pitavastatin 4 mg is noninferior to simvastatin 40 mg for lowering LDL-C concentrations in patients with primary hypercholesterolemia or combined (mixed) dyslipidemia who are at high risk of CHD. Simvastatin is a standard treatment in this patient population, based on studies such as the Heart Protection Study,[14] which showed that simvastatin 40 mg reduced the incidence of myocardial infarction, stroke, and revascularization by about one-third in high-risk patients. The present study is, therefore, consistent with other studies, which suggest that pitavastatin is an effective and well-tolerated statin that is potentially suitable for primary or secondary prevention of CHD in a broad range of patients.[8,9,15] Further studies to assess morbidity and mortality are currently underway in Japan to determine the long-term efficacy and safety of pitavastatin.

A high proportion (81%-87%) of patients in both treatment groups achieved the LDL-C targets recommended in the NCEP and EAS guidelines. This figure is considerably higher than those reported in observational studies in Europe, in which approximately 55% of patients did not attain recommended LDL-C targets despite receiving lipid-modifying therapy.[3,5,16] This commonly observed discrepancy suggests that more aggressive therapy or dose adjustment may be necessary to achieve lipid targets in routine clinical practice. The present findings suggest that a high proportion of patients can be brought to their cholesterol targets with pitavastatin. Moreover, the results of the extension study suggest that LDL-C concentrations are also maintained at target levels during long-term treatment, with little need for dose adjustment, in the majority of patients.[17]

Although pitavastatin and simvastatin had similar effects on LDL-C concentrations in this study, there were differences in their effects on secondary lipid measures. Pitavastatin 4 mg provided a larger increase than simvastatin in HDL-C concentrations, although the difference was not statistically significant. This is consistent with the results of other studies, showing that pitavastatin consistently increases HDL-C concentrations,[15] with other statins having more variable effects.[18] Whereas most statins increase HDL-C concentrations by inhibiting cholesteryl ester transfer protein and stimulating Apo-A1 synthesis,[18] there is evidence that pitavastatin increases HDL-C by increasing Apo-A1 and

ATP-binding cassette transporter (also known as cholesterol efflux regulatory protein) levels.[19,20] Further studies are needed to characterize the different effects of various statins on HDL-C concentrations, and their underlying molecular mechanisms.

Pitavastatin had a significantly greater effect than simvastatin on triglycerides, producing a mean reduction of approximately 20% from baseline. Triglycerides have been shown to be an independent risk factor for CHD,[21] and hence differences between statins in their ability to lower triglyceride concentrations may be clinically relevant. The potential importance of the effects of statins on HDL-C and triglyceride levels was highlighted by an analysis of secondary outcomes in the Scandinavian Simvastatin Survival Study (4S), which showed that the risk reductions in cardiovascular mortality and morbidity achieved with simvastatin were significantly greater (P=0.03) in patients with the lowest HDL-C and highest triglyceride levels, compared with patients with the highest HDL-C and the lowest triglyceride levels.[22]

Both treatments were well tolerated. The adverse event profiles of pitavastatin and simvastatin were similar, and there were no notable differences in the incidence of muscular adverse events (such as myalgia) and liver enzyme elevations. This is consistent with previous trials that have shown a favorable safety and tolerability profile of pitavastatin in a broad range of patients.[8,9,15]

The limitations of this study should be noted. The protocol was developed to compare pitavastatin 4 mg with simvastatin 40 mg (the most commonly prescribed statin regimen), and the effects of simvastatin 80 mg daily were not evaluated. The patient population was primarily White, and so caution should be exercised in extrapolating the results to, for example, Black patients, who were not represented in this study. Also, only four of the patients who were given pitavastatin, and three who were given simvastatin, were diagnosed with heterozygous familial hypercholesterolemia, making it difficult to interpret the increases seen in this small subgroup of patients. Finally, although pitavastatin 4 mg provided larger increases in HDL-C and reductions in triglyceride levels than simvastatin 40 mg in this study, large-scale studies with sufficient statistical power to evaluate effects on clinical outcomes are required to determine the clinical relevance of these differences.[9]

CONCLUSION

In conclusion, this study has shown that pitavastatin 4 mg is as effective as simvastatin 40 mg in lowering LDL-C concentrations in dyslipidemic patients at high risk of CHD, and also has effects on other lipid fractions, notably HDL-C and triglycerides. More than 80% of pitavastatin-treated patients reached the NCEP and EAS targets for LDL-C. These findings suggest that pitavastatin is an appropriate agent for the management of dyslipidemia in patients at high cardiovascular risk. Further outcome studies, however, with hard clinical endpoints, both in terms of cardiovascular events and safety – including liver and muscle toxicity – will be required to confirm the long-term benefits of pitavastatin.

ACKNOWLEDGMENTS

This study was supported by Kowa Research Europe Ltd. Editorial assistance in the preparation of this article was provided by Dr David Campbell of Oxford PharmaGenesis™ Ltd. Support for this assistance was provided by Kowa Research Europe Ltd. DB and NH

are employees of Kowa Research Europe Ltd. NH is the guarantor for this article, and takes responsibility for the integrity of the work as a whole. This study is registered at www.clinicaltrials.gov as NCT00309738.

REFERENCES

1. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681.

2. Phatak H, Wentworth C, Sazonov V, et al. Prevalence and predictors of lipid abnormalities in patients treated with statins in the UK general practice. Atherosclerosis. 2009;202:225-233.

3. Ferrières J, Gousse ET, Fabry C, et al. Assessment of lipid-lowering treatment in France – the CEPHEUS study. Arch Cardiovasc Dis. 2008;101:557-563.

4. García Ruiz FJ, Marín Ibáñez A, Pérez-Jiménez F, et al. Current lipid management and low cholesterol goal attainment in common daily practice in Spain. The REALITY Study. Pharmacoeconomics. 2004;22(suppl. 3):1-12.

5. Hermans MP, Van Mieghem W, Vandenhoven G, et al. Centralized pan-European survey on the undertreatment of hypercholesterolaemia (CEPHEUS). Acta Cardiol. 2009;64:177-185.

6. Aoki T, Nishimura H, Nakagawa S, et al. Pharmacological profile of a novel synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Arzneimittelforschung. 1997;47:904-909.

7. Morikawa S, Umetani M, Nakagawa S, et al. Relative induction of mRNA for HMG CoA reductase and LDL receptor by five different HMG-CoA reductase inhibitors in cultured human cells. J Atheroscler Thromb. 2000;7:138-144.

8. Saito Y, Yamada N, Teramoto T, et al. A randomized, double-blind trial comparing the efficacy and safety of pitavastatin versus pravastatin in patients with primary hypercholesterolemia. Atherosclerosis 2002;162:373-379.

9. Hayashi T, Yokote K, Saito Y, et al. Pitavastatin: efficacy and safety in intensive lipid lowering. Expert Opin Pharmacother. 2007;8:2315-2327.

10. Ando H, Tsuruoka S, Yanagihara H, et al. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. Br J Clin Pharmacol. 2005;60:494-497.

11. Sakaeda T, Fujino H, Komoto C, et al. Effects of acid and lactone forms of eight HMG-CoA reductase inhibitors on CYP-mediated metabolism and MDR1-mediated transport. Pharm Res. 2006;23:506-512.

12. Executive summary of the third report of the National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486-2497.

13. Assmann G, Lewis B, Mancini M, European Atherosclerosis Society. The recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. Eur Heart J. 1988;9:571-600.

14. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.

15. Yokote K, Bujo H, Hanaoka H, et al. Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). Atherosclerosis. 2008;201:345-352.

16. Alemao E, Yin D, Sintonen H, Salomaa V, Jousilahti P. Evaluation of lipid-lowering therapy and cholesterol goal attainment in Finland: the National FINRISK Study. Am J Cardiovasc Drugs. 2006;6:349-355.

17. Eriksson M, Budinski D, Hounslow N. A randomized study of long-term treatment with pitavastatin and simvastatin in high-risk dyslipidemic patients. Adv Ther. 2011. In press.

18. Sviridov D, Nestel P, Watts G. Statins and metabolism of high density lipoprotein. Cardiovasc Hematol Agents Med Chem. 2007;5:215-221.

19. Fukutomi T, Takeda Y, Suzuki S, Ito T, Joh T, Itoh M. High density lipoprotein cholesterol and apolipoprotein A-I are persistently elevated during long-term treatment with pitavastatin, a new HMG-CoA reductase inhibitor. Int J Cardiol. 2010;141:320-322.

20. Zanotti I, Potì F, Favari E, Steffensen KR, Gustafsson JA, Bernini F. Pitavastatin effect on ATP binding cassette A1-mediated lipid efflux from macrophages: evidence for liver X receptor (LXR)-dependent and LXR-independent mechanisms of activation by cAMP. J Pharmacol Exp Ther. 2006;317:395-401.

21. Morrison A, Hokanson JE. The independent relationship between triglycerides and coronary heart disease. Vasc Health Risk Manag. 2009;5:89-95.

22. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation. 2001;104:3046-3051.