

Pitavastatin compared with atorvastatin in primary hypercholesterolemia or combined dyslipidemia

Aims: To demonstrate the equivalence of pitavastatin compared with the most commonly used doses of atorvastatin in the reduction of LDL-C in primary hypercholesterolemia or combined dyslipidemia. Secondary objectives included the comparison of pitavastatin against the most commonly used doses of atorvastatin in achieving National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III and European Atherosclerosis Society (EAS) LDL-C goals, changes in other lipid parameters and safety. **Method:** An 18- to 20-week, prospective, randomized, double-blind, double-dummy, controlled trial assessing noninferiority of presumed equipotent doses of pitavastatin and atorvastatin in 821 patients with primary hypercholesterolemia or combined dyslipidemia. After a 6- to 8-week dietary lead-in period, randomized patients received one of four treatment regimens for 12 weeks. Two groups received pitavastatin (2 mg/day) or atorvastatin (10 mg/day) and two groups received pitavastatin (2 mg/day) or atorvastatin (10 mg/day) for 4 weeks followed by forced titration to pitavastatin (4 mg/day) or atorvastatin (20 mg/day). **Results:** The primary efficacy analysis showed pitavastatin was comparable to atorvastatin in percent change of LDL-C from baseline to endpoint (week 12 or last observation carried forward [LOCF]). The majority of patients achieved NCEP and EAS LDL-C goals at all doses, and more patients reached NCEP targets at the higher doses (pitavastatin: 78%; atorvastatin: 71%) than at the lower doses (pitavastatin: 57%; atorvastatin: 66%). There were some interesting differences between treatments in the other lipid parameters but none were statistically significant. Adverse event profiles were similar in all groups, with no apparent dose-related adverse events. **Conclusion:** Pitavastatin is equivalent to atorvastatin in reducing LDL-C in primary hypercholesterolemia or combined dyslipidemia, in both the lower-dose (pitavastatin 2 mg vs atorvastatin 10 mg) and higher-dose (pitavastatin 4 mg vs atorvastatin 20 mg) comparisons. Pitavastatin can be considered an effective, first-line therapy for these patients and offers an alternative, simple treatment regimen in the long-term care of primary hypercholesterolemia and combined dyslipidemia.

KEYWORDS: atorvastatin ■ dyslipidemia ■ hypercholesterolemia ■ lipids ■ pitavastatin ■ statin

Compelling clinical evidence shows that statins are effective drugs for reducing cholesterol and achieving LDL-C treatment targets in patients at high risk of atherogenic events [1,2]. In everyday life, both achievement and maintenance of LDL-C targets are important for effective, safe, long-term therapy in patients with hyperlipidemia. However, as many as six out of ten statin patients are nonadherent to therapy 6 months after treatment initiation – with 10% reporting never having started their statin [3–7]. Poor statin compliance and discontinuation can be due to various factors. High-dose statins may induce more adverse events (AEs), as well as potential drug interactions with concurrent therapy [4,8–13]. Lack of titration, complex statin treatment regimens and sociodemographic factors may also play a part in noncompliance. For

example, women, ethnic minorities and the elderly are often undertreated for atherogenic problems [4,8–13]. Consequently, there is still a need for an effective, well-tolerated, low-dose statin therapy that provides beneficial changes in the atherogenic lipid profile over the long term, using a simple treatment regimen [13–17].

Pitavastatin was launched in Japan in 2003, South Korea in 2005 and Thailand in 2008. Following pitavastatin's clinical success and widespread use as a first-line statin in the Far East, larger Phase III clinical trials were recently completed in the west. Phase II randomized studies indicate that pitavastatin is efficacious in reducing LDL-C concentrations [18–20]. Pitavastatin doses of 2 mg and 4 mg were shown to safely lower LDL-C in patients with primary hypercholesterolemia and

Dragos Budinski^{1†},
Valerie Arneson²,
Neil Hounslow¹ &
Nikolai Gratsiansky³

[†]Author for correspondence:

¹Kowa Research Europe Ltd,
105 Wharfedale Road,
Winnersh Triangle,
Wokingham, Berkshire,
RG41 5RB, UK

Tel.: +44 118 922 9000 or +44
118 944 3802

Fax: +44 118 922 9001
dbudinski@kowa.co.uk

²PharmaNet Ltd, UK

³The State Research Institute of
Physical & Chemical Medicine,
Russia

future
medicine  part of

combined dyslipidemia after 3 months of treatment. Clinically relevant changes in other lipid parameters were also observed. These included reductions in total cholesterol (TC), triglycerides (TGs), ApoB and increases in HDL-C levels. Clinical and preclinical studies also show pitavastatin is taken up into the liver by multiple hepatic transporter mechanisms, and is minimally metabolized by cytochrome P450 (CYP); therefore, the risk of potential drug–drug interactions (DDIs) is reduced [18–22].

Based on this Phase II evidence, initial pitavastatin therapy with 2 mg or 4 mg was expected to have an LDL-C-lowering effect similar to the most common doses of first-line statins used in Europe and North America. The purpose of this Phase III study was to demonstrate the equivalence of pitavastatin (2 and 4 mg) by assessment of noninferiority at equipotent doses, compared with the most commonly prescribed doses of atorvastatin (10 mg and 20 mg) in reducing LDL-C in patients with primary hypercholesterolemia or combined dyslipidemia.

Patients & methods

■ **Study design**

This was a multicenter, prospective, randomized, double-blind, double-dummy, controlled trial, which was carried out by investigators at 39 clinical sites in India, Denmark, Russia and Spain, from 4 October 2005 to 8 November

2006. Subjects who qualified for the study were asked to follow a European Atherosclerosis Society (EAS) diet during a 6–8-week dietary lead-in period, to ensure adequate wash-out of prior therapy and establish stable baseline lipid values. This was followed by a 12-week treatment period (**Figure 1**).

The primary objective of the study was to demonstrate the equivalence of pitavastatin compared with commonly used doses of atorvastatin in reducing LDL-C levels in patients with primary hypercholesterolemia or combined dyslipidemia. Secondary objectives included comparing pitavastatin with commonly used doses of atorvastatin for achievement of National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III goals and EAS LDL-C goals, changes in other lipid parameters and safety [23,24].

Equivalence was assessed by demonstrating the noninferiority of presumed equipotent doses of pitavastatin and atorvastatin. The noninferiority margin of 6% used in this study approximates the treatment difference in percent reduction in LDL-C levels that might be expected from doubling a statin dose. This margin is also well within the difference in LDL-C reduction observed between pitavastatin and placebo in previous studies [25,26]. The treatment duration of 12 weeks was based on previously published trials in statins for hypercholesterolemia and combined dyslipidemia [27–29].

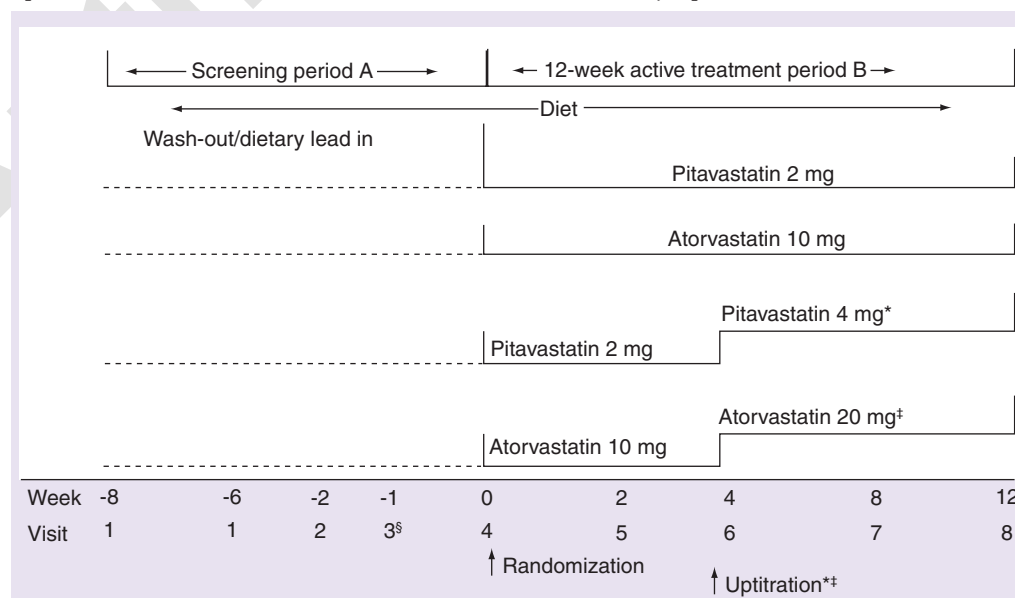


Figure 1. Study design. *Patients in the pitavastatin 4 mg group received pitavastatin 2 mg from weeks 0–4, and 4 mg from weeks 4–12.

†Patients in the atorvastatin 20 mg group received atorvastatin 10 mg from weeks 0–4, and 20 mg from weeks 4–12.

§Lipid panel may have been repeated (visit 3A) 1 week after visit 3 as required for qualification.

End points were selected with reference to the latest available guidelines issued by the Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders, amended July 2004). The target-attainment criteria for this study were based on LDL-C-reduction goals set by the NCEP ATP III (risk-adjusted), and the EAS general treatment goal of LDL-C less than 115 mg/dl (3.0 mmol/l).

A total of 800 randomized patients were planned to be recruited and randomized 3:1 between the two pitavastatin doses and the two atorvastatin doses. Patients randomized to the two higher doses were treated with the lower doses for the first 4 weeks and then force-titrated to the higher doses for 8 weeks. Assuming a standard deviation of 12 for percent reduction from baseline LDL-C, a noninferiority limit of 6% for the treatment difference and a 1-tailed test at 2.5% significance level, this sample size would provide 99% power to reject the null hypothesis for this study – that the mean percent decrease from baseline LDL-C is at least 6% greater in the atorvastatin groups than in the pitavastatin groups.

This trial was designed and conducted in accordance with the Declaration of Helsinki (version amended in October, 2000), the CHMP guidelines and the ethical principles of Good Clinical Practice. Appropriate review boards approved the trial, and informed consent was obtained from all participants after the purpose and nature of the investigation had been explained to them. Statistical analyses were performed by the Biostatistics Department at PharmaNet Ltd, Buckinghamshire, UK.

■ Patient population

Subjects eligible for inclusion were men and non-pregnant, nonlactating women, aged 18 to 75 years, diagnosed with primary hypercholesterolemia or combined dyslipidemia. Any previously prescribed lipid-regulating drugs were discontinued at screening and all patients were asked to follow an approved EAS diet during a lead-in/washout period of 6–8 weeks (8 weeks for those who had previously received lipid-regulating drugs and 6 weeks for those who had not). At each visit during the lead-in period, a 12-hour fasting blood sample was taken to determine qualifying lipid levels. Patients who were compliant with the diet, and had mean fasting LDL-C levels greater than or equal to 160 mg/dl (4.1 mmol/l) and less than or equal to 220 mg/dl (5.7 mmol/l),

and TG levels of less than or equal to 400 mg/dl (4.5 mmol/l) at the end of the lead-in period were eligible for randomization in the trial. All blood samples to assess efficacy and safety were assayed at a central laboratory (Global Central Laboratories PPD, Zaventem, Belgium). LDL-C was estimated using the Friedewald equation [30].

The main exclusion criteria for the trial included previous contraindications or intolerance to statin therapy, homozygous familial hypercholesterolemia, familial hypoalphalipoproteinemia, conditions that might have caused secondary dyslipidemia, uncontrolled diabetes mellitus, pregnancy, conditions affecting absorption, distribution, metabolism or excretion of drugs, symptomatic heart failure (New York Heart Association classification III or IV), significant cardiovascular disease, impaired pancreatic function, liver enzyme levels greater than 1.5 times the upper limit of normal, impaired renal function, impaired urinary tract function, uncontrolled hypothyroidism, symptomatic cerebrovascular disease, left ventricular ejection fraction less than 0.25, uncontrolled hypertension, muscular or neuromuscular disease, neoplastic disease, treatment with other lipid-lowering drugs and treatment that would interact with the pharmacokinetics of statins. Women of child bearing potential were only allowed to participate if they were using a reliable contraceptive method.

Patients who qualified for the trial were randomly assigned to one of four treatment groups: pitavastatin 2 mg/day, pitavastatin 4 mg/day (force-titrated from 2 mg/day), atorvastatin 10 mg/day or atorvastatin 20 mg/day (force-titrated from 10 mg/day) (**Figure 1**). An interactive voice response system randomized all patients to one of the groups at visit 4 (week 0) in the ratios 3:3:1:1, respectively. Investigators, their staff, patients and the sponsor were then kept blinded to lipid results and treatment information until the database was locked. Commercially available atorvastatin tablets were overencapsulated and a matching placebo capsule was produced so that a double-blind, double-dummy design could be used to maintain the blind in this study. Suitable analytical testing was conducted to confirm that overencapsulation had no impact on the oral delivery of test materials.

■ End points

The primary efficacy variable was calculated as the percent change in fasting LDL-C from baseline (mean of last three pretreatment values) to

end point (i.e., week 12 or the last observation while on treatment [Last Observation Carried Forward; LOCF]).

Target attainment was assessed against the NCEP LDL-C goal determined for each patient according to his/her risk category and the EAS LDL-C goal of less than 115 mg/dl (3.0 mmol/l).

The secondary efficacy variables were calculated as the percent change from baseline in TC, HDL-C, non-HDL-C, TG, ApoB, ApoA1, C-reactive protein measured using a

high-sensitivity assay (hs-CRP) and oxidized LDL; and the change in the TC:HDL-C, non-HDL-C:HDL-C, and ApoB:ApoA1 ratios at the end of 12 weeks of treatment were also calculated. No noninferiority limit was set for secondary end points.

Safety variables focused on the incidence of AEs and changes from baseline in safety laboratory values, with particular emphasis on elevations of liver (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and muscle

Table 1. Demographic and other baseline characteristics (whole study population).

| Demographic characteristic | Pitavastatin 2 mg/day (n = 316) | Atorvastatin 10 mg/day (n = 102) | Pitavastatin 4 mg/day (n = 300) | Atorvastatin 20 mg/day (n = 103) |
|--|---------------------------------|----------------------------------|---------------------------------|----------------------------------|
| Sex (n) | | | | |
| Male (%) | 142 (44.9) | 52 (51.0) | 136 (45.3) | 48 (46.6) |
| Female (%) | 174 (55.1) | 50 (49.0) | 164 (54.7) | 55 (53.4) |
| Age (years) | | | | |
| Mean (SD) | 58.4 (9.5) | 59.2 (8.6) | 57.9 (10.1) | 58 (9.1) |
| Diagnosis (n) | | | | |
| Primary hypercholesterolemia (%) | 250 (79.1) | 80 (78.4) | 236 (78.7) | 81 (78.6) |
| Combined dyslipidemia (%) | 65 (20.6) | 21 (20.6) | 62 (20.7) | 22 (21.4) |
| Familial hypercholesterolemia (%) | 1 (0.3) | 1 (1) | 2 (0.7) | 0 |
| Duration of current disease (years) | | | | |
| Mean (SD) | 3.4 (3.9) | 3.4 (4) | 3 (4.3) | 3.4 (3.7) |
| Hypertension (n) | | | | |
| Present (%) | 208 (65.8) | 67 (65.7) | 188 (62.7) | 65 (63.1) |
| Diabetes (n) | | | | |
| Present (%) | 26 (8.2) | 12 (11.8) | 14 (4.7) | 14 (13.6) |
| Weight range (kg) | | | | |
| | 40.0–108 | 31.5–111 | 45.0–124.3 | 48.0–102.8 |
| – Mean (SD) | 74.8 (11.4) | 75.9 (13) | 75.0 (12.6) | 75.5 (12.3) |
| Range BMI (kg/m²) | | | | |
| | 17–35.3 | 13.1–34.9 | 19.4–34.9 | 18.1–34.9 |
| – Mean (SD) | 27.3 (3.4) | 27.5 (3.7) | 27.5 (3.5) | 27.3 (3.8) |
| LDL-C (mg/dl) | | | | |
| – Mean (SD) | 183.5 (16.8) | 179.8 (16.8) | 181.8 (16.8) | 181.8 (16.7) |
| HDL-C (mg/dl) | | | | |
| – Mean (SD) | 48.5 (11.4) | 50.2 (11.7) | 49.9 (12.2) | 48.7 (12.9) |
| TC (mg/dl) | | | | |
| – Mean (SD) | 263.5 (22.7) | 261.3 (22.6) | 263.3 (22.1) | 262.6 (22.5) |
| TG (mg/dl) | | | | |
| – Mean (SD) | 157.7 (56) | 156.8 (60.7) | 157.4 (58) | 161 (66.4) |
| NCEP risk category (n) | | | | |
| High (%) | 160 (50.6) | 46 (45.1) | 133 (44.3) | 50 (49) |
| Moderate (%) | 77 (24.4) | 27 (27) | 52 (17.3) | 21 (20.4) |
| Low (%) | 79 (25) | 29 (28.4) | 115 (38.3) | 32 (31.1) |
| Major cardiovascular risk factors at week 0 (n) | | | | |
| Hypertension – treated (%) | 199 (63) | 60 (58.8) | 175 (58.3) | 65 (63.1) |

n: Number of patients; NCEP: National Cholesterol Education Program; SD: Standard deviation; TC: Total cholesterol; TG: Triglyceride.

creatine kinase (CK) enzymes. Other safety variables of interest included changes in 12-lead electrocardiogram and vital signs.

Data & statistical analyses

Following the treatment period, the 821 subjects in this trial were divided into the following populations for analysis, defined as:

- Safety population: all randomized patients who received at least one dose of the study drug;
- The full analysis set (FAS): all randomized patients who received at least one dose of study drug and who had at least one on-treatment lipid assessment;
- The per-protocol (PP) population: all patients in the FAS, who had no major protocol violations, and who had an on-treatment lipid assessment at week 12 (visit 8).

The FAS population was the principal population used for the efficacy analyses and the PP population was used for confirmatory analysis of the efficacy end points.

In the FAS and PP populations, the primary efficacy variable (percent change in LDL-C from baseline to week 12) was assessed using analysis of covariance (ANCOVA), including terms for treatment, country and baseline as covariates. Two-sided 95% confidence intervals (CI) were constructed on the adjusted mean difference between the following treatment groups: atorvastatin 10 mg minus pitavastatin 2 mg and atorvastatin 20 mg minus pitavastatin 4 mg. Pitavastatin was considered equivalent to atorvastatin if the lower bound on the 95% CI was greater than -6% for all doses tested.

Safety assessments involved the monitoring and recording of all spontaneously reported AEs and serious AEs. Blood test results were analyzed to evaluate the number and proportion of patients with serum transaminases (AST and ALT) or CK values greater than one-, three-, five- and 10-times the upper limit of the reference range (ULRR). Patients with CK elevations greater than or equal to 5 × ULRR but less than 10 × ULRR were reviewed weekly until they returned to within the normal range or the abnormality was considered chronic (30 days after first observation).

Investigators carried out electrocardiogram evaluations and physical examinations on each patient at the beginning of the dietary lead-in period (visit 1/week -6/8) and the end of the study (visit 8/week 12) or upon early treatment discontinuation.

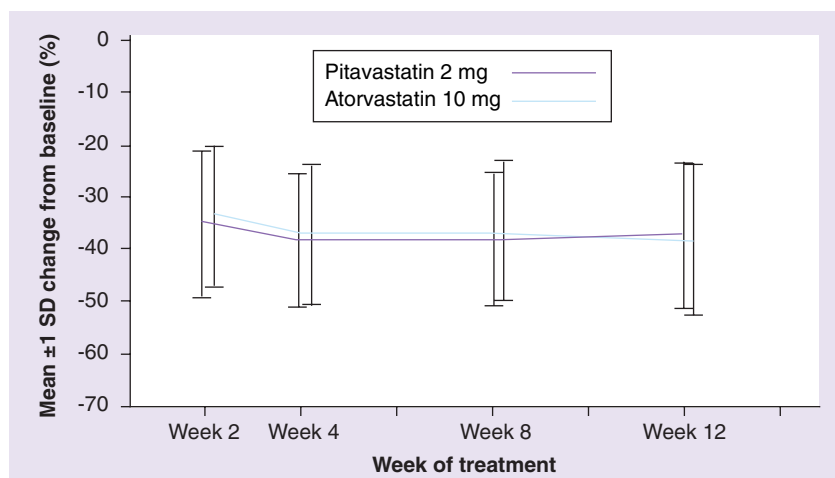


Figure 2. LDL-cholesterol mean percentage change from baseline (mg/dl; full analysis set).

Results

Baseline characteristics

Patient characteristics and lipid levels in each of the four randomized pitavastatin and atorvastatin groups at baseline are summarized in **Table 1**. The treatment groups were well matched in terms of age, vital statistics (height, weight and BMI) and disease diagnosis and duration. Approximately 79% of patients in each treatment group had primary hypercholesterolemia (78.4 to 79.1%) and most of the remainder had combined dyslipidemia. The groups were also well matched in diagnosis of hypertension and in baseline lipid values. Study subjects included slightly more women than men, and this balance was reflected across the treatment groups. Approximately half of the patients were classified as high risk according to NCEP criteria and there was an

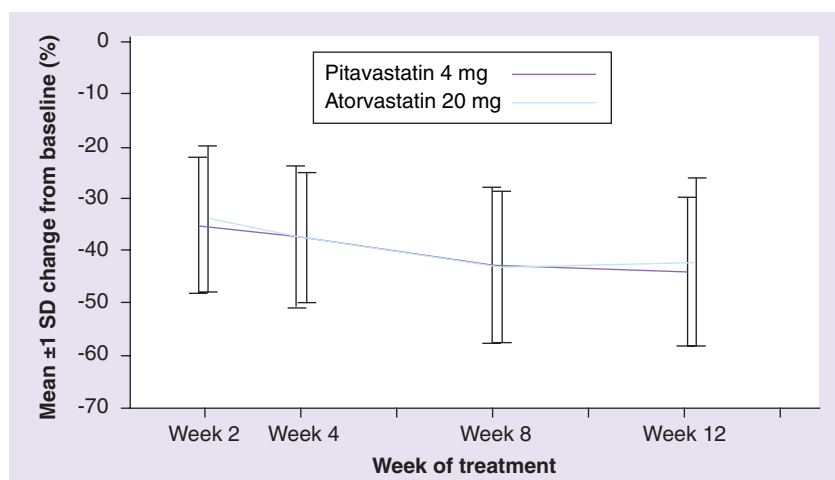


Figure 3. Mean percentage change from baseline in LDL-C (mg/dl; full analysis set). Pitavastatin 4 mg compared with atorvastatin 20 mg.

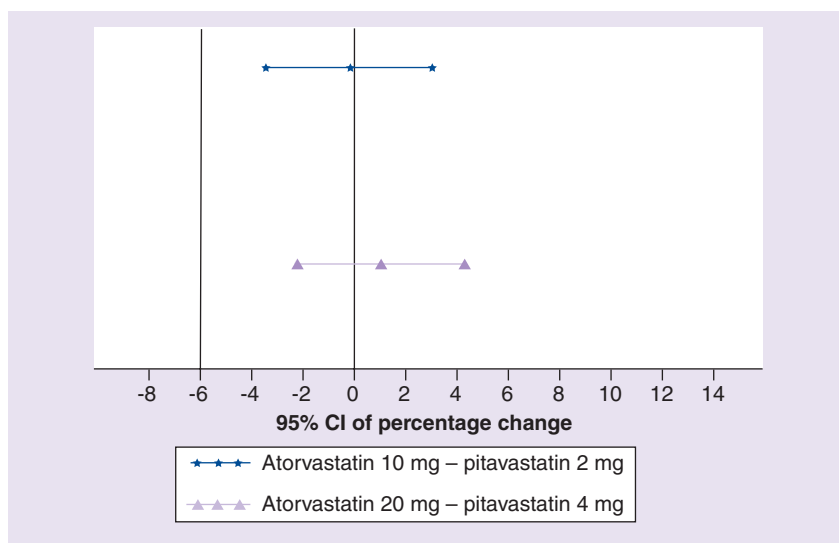


Figure 4. 95% confidence intervals on treatment difference in adjusted mean percentage change in LDL-C (full analysis set).

imbalance across treatment groups, with more high-risk patients in the pitavastatin 2 mg and atorvastatin 20 mg groups.

■ Primary efficacy analysis

The reductions in LDL-C from baseline to end point for the lower-dose study groups (pitavastatin 2 mg vs atorvastatin 10 mg) were 37.9 and 37.8%; respectively (Figure 2, Table 2), with an adjusted mean difference of -0.15 (Table 2). For the higher-dose study groups (pitavastatin 4 mg vs atorvastatin 20 mg), the LDL-C reductions were 44.6 and 43.5%, respectively, with a mean difference of 0.96 (Figure 3, Table 2). The lower 95% CI limits in the higher-dose and lower-dose comparisons were -2.32% and -3.42%, respectively – well clear of the noninferiority limit of -6% (Figure 4). These findings showed that the efficacy of pitavastatin in LDL-C reduction was

equivalent to atorvastatin in the principal patient population at these dosage levels. The analysis in the PP population confirmed these study findings.

The results also showed no significant treatment by subgroup interactions. Subgroups included age, sex, race, BMI, risk category, baseline LDL-C, hypertension, diabetes and primary diagnosis (primary hypercholesterolemia or combined dyslipidemia).

■ Secondary efficacy analysis

Attainment of LDL-C target levels

As presented in Table 3, using the NCEP criteria, the lower-dose comparison appeared to show an advantage for atorvastatin 10 mg over pitavastatin 2 mg (65.7% vs 56.8%), while the higher-dose comparison showed an apparent advantage for pitavastatin 4 mg over atorvastatin 20 mg (77.9% vs 70.6%). Neither of these differences was statistically significant. The observed treatment differences were smaller for the EAS criteria.

■ Other lipids

As seen in Table 4, reductions from baseline in TC, non-HDL-C, TC:HDL-C ratio, non-HDL-C:HDL-C ratio, ApoB, and ApoB:ApoA1 ratio were very similar between the two lower-dose treatment groups and between the two higher-dose groups. The higher-dose groups showed consistently greater decreases than the lower-dose groups. The increases from baseline in HDL-C were slightly greater in the pitavastatin lower-dose and higher-dose study groups (4 and 5%) than the corresponding atorvastatin groups (3 and 2.5%). The reductions in TG were somewhat greater in the two atorvastatin groups (17.7 and 22.3%) than in the corresponding pitavastatin groups (14 and 19%). None of the differences were statistically significant.

Table 2. Change from baseline to end point or week 12 in LDL-C (mg/dl) (full analysis set).

| | Pitavastatin 2 mg/day (n = 315) | Atorvastatin 10 mg/day (n = 102) | Pitavastatin 4 mg/day (n = 298) | Atorvastatin 20 mg/day (n = 102) |
|--|---------------------------------------|--|---------------------------------------|--|
| Baseline LDL-C | | | | |
| Mean (SD) | 183.6 (16.8) | 179.8 (16.9) | 182 (16.7) | 181.9 (16.7) |
| End point LDL-C | | | | |
| Mean (SD) | 113.9 (28) | 111.5 (28.2) | 100 (26.9) | 102.5 (31) |
| Change from baseline to end point (%) | | | | |
| Mean (SD) | -37.9 (14) | -37.8 (15.6) | -44.6 (15) | -43.5 (16.2) |
| Adjusted mean difference (95% CI) | -0.15 (-3.4–3.1) | | 0.96 (-2.3–4.2) | |
| p value | 0.93 | | 0.57 | |

CI: Confidence interval; n: Number of patients; (%). SD: Standard deviation.

Table 3. Patients with LDL-C target attainment (full analysis set).

| | Pitavastatin 2 mg/day (n = 315) | Atorvastatin 10 mg/day (n = 102) | Pitavastatin 4 mg/day (n = 298) | Atorvastatin 20 mg/day (n = 102) |
|--|------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|
| Target attained according to NCEP criteria (n, %) | | | | |
| Yes | 179 (56.8) | 67 (65.7) | 232 (77.9) | 72 (70.6) |
| No | 136 (43.2) | 35 (34.3) | 66 (22.1) | 30 (29.4) |
| Difference: | 8.9 | | -7.3 | |
| 95% CI | -1.9–19.6 | | -17.3–2.8 | |
| p value | 0.1 | | 0.1 | |
| Target attained according to EAS criteria (n, %) | | | | |
| Yes | 179 (56.8) | 61 (59.8) | 234 (78.5) | 78 (76.5) |
| No | 136 (43.2) | 41 (40.2) | 64 (21.5) | 24 (23.5) |
| Difference: | 3 | | -2.1 | |
| 95% CI | -8.0–14 | | -11.5–7.4 | |
| p value | 0.6 | | 0.7 | |

CI: Confidence interval; EAS: European Atherosclerosis Society; n: Number of patients (%); NCEP: National Cholesterol Education Program.

■ Safety

All treatments were well tolerated, as shown in **Table 5**. Although patients were randomized 3:1 between pitavastatin and atorvastatin in each treatment group, the overall incidence of treatment-emergent AEs was similar in each comparison. Most AEs were mild to moderate in intensity and considered unrelated to study medications. Rates of treatment discontinuation due to AEs were minimal, and only occurred in the pitavastatin groups (2%). The most commonly reported treatment-related AE (TRAE) leading to withdrawal was myalgia: 0.9% (three patients) in the pitavastatin 2 mg group and 0.7% (two patients) in the pitavastatin 4 mg group (**Table 6**). The majority of TRAEs seen in this study were also mild or moderate in intensity, with the most frequently reported TRAE being nasopharyngitis (3.2% in pitavastatin 2 mg; 2.7% in pitavastatin 4 mg; 3.9% in atorvastatin 10 mg; 2.9% atorvastatin 20 mg). Shift tables of laboratory values from baseline to week 12 did not indicate any treatment- or dose-related trends. In particular, there were no discernible trends in AST, ALT or CK.

Discussion

In large clinical studies, considerable evidence shows that first-line statin therapy effectively achieves LDL-C target levels in a wide range of patients [31,32]. In everyday life, effective maintenance of LDL-C targets is also important to reduce cholesterol risk on a long-term basis [33–35]. However, follow-up studies of established statins show that as many as six out of ten patients stop taking therapy during the first 6

months of treatment. Statin discontinuation and noncompliance may be due to a variety of factors, including high statin dosage, polypharmacy, lack of titration, intolerance and complicated treatment regimens [7,33–38]. Socioeconomic factors may also affect LDL-C target attainment and maintenance: women, the elderly and ethnic minorities are often undertreated for atherogenic problems [38–41]. As such, there remains a need for an effective, well-tolerated statin that can provide a good balance of cardioprotective benefits and improved multiple lipid parameters over the long-term, using a lower dosage and a simple treatment regimen.

Pitavastatin was launched in Japan in 2003, South Korea in 2005 and Thailand in 2008. Since then, it has been successfully used in these countries as a first-line statin therapy to treat primary hypercholesterolemia and combined dyslipidemia in a wide range of patients, including the elderly and those on concurrent medications [42]. Following the success of pitavastatin in the Far East, larger European Phase III trials were then carried out. Based on Phase II findings, the LDL-C lowering effect of pitavastatin at 2 mg and 4 mg was expected to compare well with the most commonly used doses of clinically established first-line statins in Europe, Canada and the USA.

This Phase III study set out to investigate this hypothesis by comparing the highest proposed doses of pitavastatin (2 and 4 mg) with the most commonly used doses of atorvastatin (10 and 20 mg). The atorvastatin 10 and 20 mg doses are also the recommended starting doses for patients with primary hypercholesterolemia

Table 4. Percent change from baseline in secondary lipids (full analysis set).

| | Pitavastatin 2 mg/day (n = 315) | Atorvastatin 10 mg/day (n = 102) | Pitavastatin 4 mg/day (n = 298) | Atorvastatin 20 mg/day (n = 102) |
|---|------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|
| Total cholesterol (mg/dl) | | | | |
| Baseline mean (SD) | 263.6 (22.7) | 261.3 (22.6) | 263.3 (22.2) | 262.7 (22.6) |
| Mean % change (SD) | -27.7 (10.5) | -28.1 (12.5) | -32.4 (11.5) | -32.7 (12.3) |
| p value | | 0.684 | | 0.773 |
| HDL-C (mg/dl) | | | | |
| Baseline mean (SD) | 48.5 (11.4) | 50.2 (11.7) | 49.9 (12.3) | 48.4 (12.8) |
| Mean % change (SD) | 4 (16.5) | 3 (16.9) | 5 (16.7) | 2.5 (13.7) |
| p value | | 0.840 | | 0.097 |
| Non-HDL-C (mg/dl) | | | | |
| Baseline mean (SD) | 215.1 (21.2) | 211.1 (22.6) | 213.3 (21) | 214.3 (22.9) |
| Mean % change (SD) | -34.7 (13) | -35.2 (15.2) | -41.1 (14.2) | -40.6 (15.1) |
| p value | | 0.688 | | 0.766 |
| Triglycerides (mg/dl) | | | | |
| Baseline mean (SD) | 157.8 (56.1) | 156.8 (60.7) | 156.8 (57.3) | 161.9 (66.1) |
| Mean % change (SD) | -14.1 (28.8) | -17.7 (29.9) | -19 (24.6) | -22.3 (24) |
| p value | | 0.236 | | 0.351 |
| Total cholesterol:HDL-C ratio | | | | |
| Baseline mean (SD) | 5.7 (1.2) | 5.5 (1.2) | 5.6 (1.3) | 5.8 (1.4) |
| Mean % change (SD) | -1.7 (1) | -1.6 (1.1) | -2.0 (1.0) | -2.0 (1.1) |
| p value | | 0.625 | | 0.461 |
| Non-HDL-C:HDL-C ratio | | | | |
| Baseline mean (SD) | 4.7 (1.2) | 4.5 (1.2) | 4.6 (1.3) | 4.8 (1.4) |
| Mean % change (SD) | -1.7 (1) | -1.6 (1.1) | -2 (1) | -2 (1.1) |
| p value | | 0.625 | | 0.461 |
| ApoB (mg/dl) | | | | |
| Baseline mean (SD) | 164.1 (21.6) | 161.3 (22.3) | 162.3 (22.3) | 163 (25.7) |
| Mean % change (SD) | -29.7 (13.7) | -29.1 (17.6) | -35.3 (14.9) | -35.5 (14.5) |
| p value | | 0.912 | | 0.961 |
| Apo-A1 (mg/dl) | | | | |
| Baseline mean (SD) | 155.2 (26.1) | 157.9 (25.6) | 158.5 (26.5) | 154.6 (26.4) |
| Mean % change (SD) | 6.5 (14.4) | 6.4 (14) | 5.6 (13.7) | 4.5 (13.9) |
| p value | | 0.894 | | 0.188 |
| ApoB:Apo-A1 ratio | | | | |
| Baseline mean (SD) | 1.1 (0.2) | 1.1 (0.2) | 1.1 (0.2) | 1.1 (0.3) |
| Mean % change (SD) | -0.4 (0.2) | -0.4 (0.2) | -0.4 (0.2) | -0.4 (0.2) |
| p value | | 0.648 | | 0.551 |
| High-sensitivity C-reactive protein (mg/l) | | | | |
| Baseline median | 1.8 | 1.5 | 1.7 | 2 |
| Median change | -0.3 | -0.2 | -0.1 | -0.4 |
| p value | | Not tested | | Not tested |
| Oxidized LDL (U/l) | | | | |
| Baseline mean | 82.1 (20.4) | 81.6 (19.8) | 80.2 (19.9) | 84.5 (21.6) |
| Mean change | -22.3 (20.6) | -22.8 (20.8) | -25.5 (21) | -29.3 (24.2) |
| p value | | 0.581 | | 0.683 |

Table 5. Overall summary of treatment-emergent adverse events (safety population) (n [%]).

| | Pitavastatin 2 mg/ day (n = 316) | Atorvastatin 10 mg/ day (n = 102) | Pitavastatin 4 mg/day (n = 300) | Atorvastatin 20 mg/ day (n = 103) |
|---------------------------------|-------------------------------------|--------------------------------------|------------------------------------|--------------------------------------|
| With any TEAE | 60 (19.0) | 17 (16.7) | 50 (16.7) | 23 (22.3) |
| With any serious TEAE | 3 (0.9) | 1 (1.0) | 1 (0.3) | 2 (1.9) |
| With any treatment-related TEAE | 20 (6.3) | 3 (2.9) | 16 (5.3) | 2 (1.9) |
| Discontinued due to TEAE | 5 (1.6) | 0 | 6 (2.0) | 0 |
| Death due to TEAE | 0 | 0 | 0 | 0 |

*TEAEs were defined as adverse events with onset on or after the first dose of study treatment. TEAEs related to study treatment were those with a relationship of possible, probable or definite.
n: Number of patients (%); TEAE: Treatment-emergent adverse event.*

and combined dyslipidemia [43]. This trial was not designed to be a coronary heart disease study. Target attainment was assessed against the NCEP LDL-C goal determined for each patient according to their risk category and the EAS LDL-C goal of less than 115 mg/dl (3.0 mmol/l) [23,24]. Atorvastatin is available at a range of doses up to 80 mg/day [43] and has end point studies to demonstrate the effect of LDL-C reduction on outcomes. Such studies have not been conducted with pitavastatin.

The trial findings indicate that pitavastatin doses (2 and 4 mg) were equivalent to the most commonly prescribed doses of atorvastatin (10 mg and 20 mg) in the reduction of LDL-C in patients with primary hypercholesterolemia and combined dyslipidemia. Pitavastatin was as effective as atorvastatin at bringing patients – nearly half of whom were higher-risk – to the NCEP and EAS LDL-C targets in this study.

While results showed these specific statin doses were matched for LDL-C reduction, there were some interesting differences in secondary lipids. The adjusted mean differences (statistically nonsignificant) in HDL-C favored pitavastatin in both the higher and lower-dose comparisons. A dose-response with pitavastatin and a reverse dose-response with atorvastatin indicated that the HDL-C increase with pitavastatin 4 mg was double that of the HDL-C elevation with atorvastatin 20 mg. The reverse dose response with atorvastatin on HDL-C has previously been observed [44].

The role of HDL-C is still being assessed in lipid-lowering therapy. A recent meta-analysis assessing 23 studies of cholesterol reduction by any means concluded that since HDL-C elevation and LDL-C reduction are statistically independent for moderate percentage changes, these could be considered additive [45]. Recent literature also reports the pro-atherogenic properties of low HDL-C concentrations in patients with diabetes or metabolic syndrome [46].

In this study, pitavastatin appeared to be as effective as atorvastatin in reducing TG levels, although atorvastatin produced slightly greater reductions. Other lipid analyses in this study also showed no significant differences between pitavastatin and atorvastatin regarding changes in the following lipid parameters: TC, non-HDL-C, ApoB, ApoA1, TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and ApoB:ApoA1 ratio and oxidized LDL. Other analyses also showed no apparent differences between pitavastatin and atorvastatin in treatment effects on hs-CRP.

Regarding safety and tolerability, the overall incidence of TRAEs was similar among all treatment groups, and the majority were mild to moderate in intensity and considered unrelated to study medications. In this trial, myalgia was the most common TRAE leading to withdrawal for 0.9% of patients in the pitavastatin 2 mg group and 0.7% of patients in the pitavastatin 4 mg group. The unbalanced randomization in the study population (300 patients in each pitavastatin group and 100 patients in each atorvastatin group) could account for the fact that no withdrawals due to AEs were observed in the atorvastatin groups [47]. In previous studies with atorvastatin, the rate of withdrawal due to AEs related to treatment has been approximately 2% compared with the 2% rate due to any adverse event, related or unrelated, seen with pitavastatin in this trial [48].

Throughout the trial, 61% of patients were on concurrent medication for hypertension, but the study excluded patients taking medications that might interact with atorvastatin, and no significant DDIs were identified in patients taking either pitavastatin or atorvastatin. In fact, pitavastatin has a favorable metabolic profile as it is minimally metabolized by CYP isoenzymes and, in particular, has no interaction with CYP 3A4. In addition, pitavastatin is not a substrate for P-glycoprotein (P-gp). This metabolic profile suggests that pitavastatin has less risk of potential DDIs in unselected patients on concurrent therapy [18–22].

Table 6. Incidence of treatment-emergent adverse events that led to withdrawal by system organ class (safety population).

| System organ class preferred term | Pitavastatin 2 mg/day (n = 316) | Atorvastatin 10 mg/day (n = 102) | Pitavastatin 4 mg/day (n = 300) | Atorvastatin 20 mg/day (n = 103) |
|---|---------------------------------|----------------------------------|---------------------------------|----------------------------------|
| Patients withdrawn due to TEAE | 5 (1.6) | 0 | 6 (2.0) | 0 |
| Cardiac disorders | 1 (0.3) | 0 | 0 | 0 |
| – Acute myocardial infarction | 1 (0.3) | 0 | 0 | 0 |
| Gastrointestinal disorders | 1 (0.3) | 0 | 1 (0.3) | 0 |
| – Constipation | 0 | 0 | 1 (0.3) | 0 |
| – Dyspepsia | 1 (0.3) | 0 | 0 | 0 |
| Infections and infestations | 1 (0.3) | 0 | 0 | 0 |
| – Furuncle | 1 (0.3) | 0 | 0 | 0 |
| Investigations | 0 | 0 | 1 (0.3) | 0 |
| – Liver function test abnormal | 0 | 0 | 1 (0.3) | 0 |
| Musculoskeletal and connective tissue disorders | 3 (0.9) | 0 | 2 (0.7) | 0 |
| – Arthralgia | 1 (0.3) | 0 | 0 | 0 |
| – Myalgia | 3 (0.9) | 0 | 2 (0.7) | 0 |
| Nervous system disorders | 1 (0.3) | 0 | 3 (1.0) | 0 |
| – Dizziness | 1 (0.3) | 0 | 3 (1.0) | 0 |
| – Headache | 0 | 0 | 1 (0.3) | 0 |
| – Migraine | 0 | 0 | 1 (0.3) | 0 |
| – Somnolence | 0 | 0 | 1 (0.3) | 0 |
| Psychiatric disorders | 1 (0.3) | 0 | 0 | 0 |
| – Insomnia | 1 (0.3) | 0 | 0 | 0 |

n: Number of patients (%); TEAE: Treatment-emergent adverse event.

Conclusion

In patients with primary hypercholesterolemia and combined dyslipidemia in a range of cardiovascular risk categories (nearly half with high cardiovascular risk), pitavastatin doses of 2 mg/day and 4 mg/day were as effective as atorvastatin doses of 10 mg/day and 20 mg/day in reducing LDL-C, TG, and TC, and increasing HDL-C concentrations. The majority of patients reached treatment targets on the lower dose, and this percentage was increased at the higher doses of pitavastatin and atorvastatin. The safety and tolerability profiles with each statin were similar, with no indications of any dose-related AEs. Overall, this study suggests that in patients who are controlled with atorvastatin at doses of 10 or 20 mg per day, pitavastatin could be considered an effective, first-line alternative that provides a simple, low-dose treatment regimen for primary hypercholesterolemia and combined dyslipidemia.

Future perspective

Patients at LDL-C treatment targets have a reduced risk of cardiovascular events but, as statin use becomes more widespread, there is an increasing need for broader protection from cardiovascular risk than that provided by LDL-C reduction alone, in a wider range of more complex-to-treat patients. Age, diabetes, ethnicity and add-on therapy for low HDL-C concentrations and other concurrent treatment should not preclude such patients from receiving effective, long-term statin therapy. A new statin that is appropriate as first-line therapy in a broad range of patients using a simple treatment regimen could have a valuable place in the future management of cardiovascular disease.

Acknowledgements

The authors would like to thank all the participating researchers, clinicians, healthcare professionals, personnel and patients who helped to complete the trial.

Financial & competing interests disclosure

Details of the trial can be found at www.clinicaltrials.gov NCT# NCT00249249. The trial was sponsored by Kowa Research Europe Ltd. The authors are responsible for the work described in this manuscript. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data, drafting the manuscript and/or revising the manuscript for important

intellectual content. All authors provided final approval of the version to be published. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors thank Corinne Swainger for help with the manuscript.

Executive summary

- An 18- to 20-week, prospective, randomized, double-blind, double-dummy, controlled trial in 821 patients comparing 12 weeks of therapy with proposed doses of pitavastatin versus equipotent doses of atorvastatin in primary hypercholesterolemia or combined dyslipidemia was conducted.
- The efficacy of pitavastatin 2 mg daily and 4 mg daily was equivalent to atorvastatin 10 mg daily and 20 mg daily, respectively, in LDL-C reduction.
- The majority of patients reached National Cholesterol Education Program (NCEP) treatment targets at the lower dose and the proportion of patients at these targets increased with the higher treatment doses.
- At doses that produced the same LDL-C reductions, there were no significant differences in secondary lipid parameters, although HDL-C concentrations increased as the dose of pitavastatin increased, but this was less in the higher atorvastatin dose (20 mg) compared with the lower atorvastatin dose (10 mg).
- Adverse effect profiles were similar in all treatment groups, with no apparent dose-related adverse effects.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

| | | |
|---|---|--|
| <p>1 Fonesca F, Ruiz A, Cardona-Muñoz E: The DISCOVERY PENTA study: a Direct Statin Comparison of LDL-C Value – an Evaluation of Rosuvastatin therapy compared with atorvastatin. <i>Curr. Med. Res. Opin.</i> 21(8), 1307–1315 (2005).</p> <p>2 McKenney J, Jones P, Adamczyk M <i>et al.</i>: Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. <i>Curr. Med. Res. Opin.</i> 19(9):689–698 (2003).</p> <p>3 Meyer J, Schultz J, O'Donnell J, Patel P, Sasane R: Patterns and effectiveness of lipid-lowering therapies in a managed care environment. <i>Value Health.</i> 8, 601–612 (2005).</p> <p>4 Foley K, Simpson R Jr, Crouse J 3rd <i>et al.</i>: Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. <i>Am. J. Cardiol.</i> 92, 79–81 (2003).</p> <p>5 Schuster H: Improving lipid management – to titrate, combine or switch. <i>Int. J. Clin. Pract.</i> 58(7), 689–694 (2004).</p> <p>6 Pearson T, Laurora I, Chu H, Kafoneck S: The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low density lipoprotein cholesterol goals. <i>Arch. Intern. Med.</i> 160, 459–467 (2000).</p> | <p>7 Liberopoulos E, Florentin M, Mikhailidis D, Elisaf M: Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. <i>Expert Opin. Drug Saf.</i> 7(6), 717–725 (2008).</p> <p>8 Bortorff C, Hourri J, Natarbartolo A <i>et al.</i>: Statin safety: what to know. <i>Am. J. Geriatr. Cardiol.</i> 13(3 Suppl. 1), 34–38 (2004).</p> <p>9 de Lemos J, Blazing M, Wiviott S <i>et al.</i>: Early intensive vs delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. <i>JAMA</i> 292(11), 1307–1316 (2004).</p> <p>10 Waters D: Safety of high-dose atorvastatin therapy. <i>Am. J. Cardiol.</i> 96(5A), F69–F75 (2005).</p> <p>11 Shitara Y, Sato H, Sugiyama Y: Evaluation of drug-drug interaction in the hepatobiliary and renal transport of drugs. <i>Annu. Rev. Pharmacol. Toxicol.</i> 45, 689–723 (2005).</p> <p>12 Rutishauser J: The role of statins in clinical medicine – LDL – cholesterol lowering and beyond. <i>Swiss Med. Wkly.</i> 136(3–4), 41–49 (2006).</p> <p>13 Ansell B: Not getting to goal: the clinical costs of noncompliance. <i>J. Manag. Care Pharm.</i> 14(Suppl. 6B), 9–15(2008).</p> <p>14 Watson K: What is the evidence in favor of low-dose statin therapy in 2008? <i>Curr. Atheroscler. Rep.</i> 10(1), 33–38 (2008).</p> <p>15 Murphy M, Wei L, Watson A, MacDonald T: 'Real-life' reduction in cholesterol with statins, 1993 to 2002. <i>Br. J. Clin. Pharmacol.</i> 65(4), 587–592 (2008).</p> <p>16 Stein E: Managing dyslipidemia in the high-risk patient. <i>Am. J. Cardiol.</i> 89, C50–C57 (2002).</p> | <p>17 Isley W: Pitavastatin (NK-104), a new HMG-CoA reductase inhibitor. <i>Drugs Today</i> 37, 587–594 (2001).</p> <p>18 Hayashi T, Yokote K, Saito Y, Iguchi A: Pitavastatin: efficacy and safety in intensive lipid lowering. <i>Expert Opin. Pharmacother.</i> 8, 2315–2327 (2007).</p> <p>19 Fujino H, Yamada I, Kojima J <i>et al.</i>: Studies on the metabolic fate of NK-104, a new inhibitor of HMG-CoA reductase (5): <i>in vitro</i> metabolism and plasma protein binding in animals and humans. <i>Xenobio. Metabol. Dispos.</i> 14, 415–424 (1999).</p> <p>20 Fujino H, Saito T, Tsunenari Y, Kojima J: Interaction between several medicines and statins. <i>Arzneimittelforschung</i> 53(3), 145–153 (2003).</p> <p>21 Sakaeda T, Fujino H, Komoto C: Effects of acid and lactone forms of eight HMG-CoA reductase inhibitors on CYP-mediated metabolism and MDR1 mediated transport. <i>Pharm. Res.</i> 23, 506–512 (2006).</p> <p>22 Hirano M, Maeda K, Shitara Y: Drug–drug interaction between pitavastatin and various drugs via OATP1B1. <i>Drug Metab. Dispos.</i> 34, 1229–1236 (2006).</p> <p>23 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): 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): final report. <i>Circulation</i> 106, 3143–3421 (2002).</p> |
|---|---|--|

- 24 European Atherosclerosis Society: The recognition and management of hyperlipidemia in adults: a policy statement of the European Atherosclerosis Society. *Eur. Heart J.* 9, 571–600 (1988).
- 25 Noji Y, Higashikata T, Inazu A *et al.*: Long-term treatment with pitavastatin (NK-104), a new HMG-CoA reductase inhibitor, of patients with heterozygous familial hypercholesterolemia. *Atherosclerosis* 163, 157–164 (2002).
- 26 Kajinami K, Koizumi J, Ueda K *et al.*: Effects of NK-104, a new hydroxymethylglutaryl-coenzyme reductase inhibitor, on low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia: Hokuriku NK-104 Study Group. *Am. J. Cardiol.* 85, 178–183 (2000).
- 27 Strandberg T, Feely J, Sigurdsson E: Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. *Clin. Ther.* 26(11), 1821–1833 (2004).
- 28 Yoshitomi Y, Ishii T, Kaneki M *et al.*: Efficacy of a low dose of pitavastatin compared with atorvastatin in primary hyperlipidemia: results of a 12-week, open label study. *J. Atheroscler. Thromb.* 13(2), 108–113 (2006).
- 29 Park S, Kang H-J, Rim S-J: A randomized, open-label study to evaluate the efficacy and safety of pitavastatin compared with simvastatin in Korean patients with hypercholesterolemia. *Clin. Ther.* 27, 1074–1082 (2005).
- 30 Friedewald W, Levy D, Fredrickson D: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the preparative ultracentrifuge. *Clin. Chem.* 18, 499–502 (1972).
- 31 LaRosa J, He J, Vupputuri S: Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled studies. *JAMA* 282, 2340–2346 (1999).
- 32 Heart Protection Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled study. *Lancet* 360(9326), 7–22 (2002).
- 33 Sasaki J, Ikeda Y, Kuribayashi T *et al.*: A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. *Clin. Ther.* 30, 1089–1101 (2008).
- 34 Grigioni F, Carigi S, Potena L *et al.*: Long-term safety and effectiveness of statins for heart transplant recipients in routine clinical practice. *Transplant Proc.* 38(5), 1507–1510 (2006).
- 35 Versmissen J, Oosterveer D, Yazdanpanah M *et al.*: Efficacy of statins in familial hypercholesterolemia: a long-term cohort study. *BMJ* 337, a2423 (2008).
- 36 Ratz Bravo A, Tchambaz L, Krähenbühl-Melcher A *et al.*: Prevalence of potentially severe drug–drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Saf.* 28(3), 263–275 (2005).
- 37 Sanossian N, Ovbiagele B: Drug insight: translating evidence on statin therapy into clinical benefits. *Nat. Clin. Pract. Neurol.* 4(1), 42–49 (2008).
- 38 Colleran K, Richards A, Shafer K: Disparities in cardiovascular disease risk and treatment: demographic comparison. *J. Investig. Med.* 55(8), 415–422 (2007).
- 39 Jacobson T: Overcoming ‘ageism’ bias in the treatment of hypercholesterolemia: a review of safety issues with statins in the elderly. *Drug Saf.* 29(5), 421–448 (2006).
- 40 Gotto A: Statin therapy and the elderly: SAGE advice? *Circulation* 115, 681–683 (2007).
- 41 Cauley J, McTiernan A, Roadbough R *et al.*: Statin use and breast cancer: prospective results from the Women’s Health Initiative. *J. Natl Cancer Inst.* 98(10), 700–707 (2006).
- 42 Kurihara Y, Douzono T, Kawakita K, Nagasaka Y: A large-scale, long-term, prospective post-marketing surveillance of pitavastatin (Livalo® Tablet): LIVALO Effectiveness and Safety (LIVES) Study. *Jpn Pharmacol. Ther.* 36(8), 709–731 (2008).
- 43 Joint Formulary Committee: British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary* 50, 135 (2005).
- 44 Jones P, Davidson M, Stein E *et al.*: Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STELLAR Trial). *Am. J. Cardiol.* 92, 152–160 (2003).
- 45 Brown B, Stukovsky K, Zhao X: Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr. Opin. Lipidol.* 17, 631–636 (2006).
- 46 Cardenas G, Lavie C, Cardenas V, Milani R, McCullough P: The importance of recognizing and treating low levels of high-density lipoprotein cholesterol: a new era in atherosclerosis management. *Rev. Cardiovasc. Med.* 9(4), 239–258 (2008).
- 47 Eypasch E, Lefering R, Kum CK, Troidl H: Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 311, 619–620 (1995).
- 48 Black D, Bakker-Arkema R, Nawrocki J: An overview of the clinical safety profile of atorvastatin (Lipitor™), a new HMG-CoA reductase inhibitor *Arch. Intern. Med.* 158, 577–584 (1998).