

Treatment Options for Hypercholesterolemia and Combined Dyslipidemia: Focus on Pitavastatin

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Abstract: The progression of atherosclerosis and thus risk of cardiovascular disease is influenced by a variety of risk factors, including high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C). Lowering the serum cholesterol level with diet or drug therapy slows the progression of angiographically documented coronary atherosclerosis in patients with arterial bypass grafts. Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, are the most potent pharmacologic agents for lowering total cholesterol (TC) and LDL-C.

We conducted a review analyzing clinical efficacy and safety of pitavastatin, the latest statin to be commercialized, including the most important studies about pitavastatin published in the last ten years. Pitavastatin proved to be as effective as atorvastatin, and a little inferior to rosuvastatin in improving lipid profile, it also proved to be safe and well tolerated. Because of its positive pleiotropic effects on coronary plaque volume and fibro-fatty composition, pitavastatin could be a valid option for the treatment of hypercholesterolemia and combined dyslipidemia.

Keywords: pitavastatin, lipid profile, hypercholesterolemia, combined dyslipidemia

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Introduction

The progression of atherosclerosis and thus risk of cardiovascular disease is influenced by a variety of risk factors, including high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C).^{1,2} In particular elevated LDL-C plays a pivotal role in atheromatous plaque development and in progression and rupture of the plaque which causes most of the acute symptoms of acute coronary heart disease.³ The other risk factors, such as hypertension, diabetes, smoking, male gender, and possibly inflammatory markers appear to accelerate the disease driven by atherogenic lipoproteins, the first of which being low-density lipoprotein (LDL). The association between serum cholesterol levels and the risk of coronary heart disease is continuous;^{4,5} it has also already been proved that familial hypercholesterolemia causes premature coronary heart disease.^{6,7}

Familial hypercholesterolemia is a disorder characterized by the presence of high levels of cholesterol in the blood caused by an absent or defective LDL receptor.⁸ There is evidence that decreasing serum cholesterol levels with cholesterol-lowering drugs or dietary modification slows or reverses the progression of coronary atherosclerosis and reduces coronary events as showed by many randomized trials that include more than 40,000 subjects.^{9–11} Lowering the serum cholesterol level with diet or drug therapy also slows the progression of angiographically documented coronary atherosclerosis in patients with arterial bypass grafts.⁹ Aggressive lowering of the serum cholesterol level in patients with recent myocardial infarction results in a rapid decrease in the risk of subsequent ischemic cardiac complications, the need for surgical revascularization, and death rates.^{12,13} The overall guidelines on cardiovascular disease prevention in clinical practice strongly recommend modulating the intensity of the preventive intervention according to the level of the total cardiovascular risk. Therefore, the targets should be less demanding when the total cardiovascular risk decreases from very high to high or moderate.¹⁴

Statins, or inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are the most potent pharmacologic agents for lowering TC and LDL-C. They have become an accepted standard of care in the treatment of patients with known

atherosclerotic cardiovascular disease (secondary prevention) and also those at increased risk of cardiovascular events. Until 2009 there were six statin drugs commercially available in the US; although they were chemically similar and had the same primary mechanism of action in lowering TC and LDL-C, there were differences in their efficacy or potency, metabolism, drug-drug interactions, and individual tolerability. Of the six statins available, three were isolated from fungi (lovastatin, simvastatin, pravastatin) and three were synthesized in the laboratory (fluvastatin, atorvastatin, rosuvastatin).¹⁵ In August 2009, Food and Drug Administration approved another statin, pitavastatin, for the primary treatment of hypercholesterolemia and combined dyslipidemia in patients where diet and exercise failed to lower their cholesterol levels.

We have already written a review about HMG-CoA reductase inhibitors, in particular about the effect of a combination therapy with atorvastatin plus amlodipine, observing that the combination of amlodipine plus atorvastatin is more effective than the single drugs alone in reducing blood pressure and in improving lipid profile.¹⁶ Furthermore, the combination of amlodipine plus atorvastatin also improved small-artery compliance, inflammatory markers, left ventricular hypertrophy and reduced uric acid faster and more effectively than the single drugs taken alone.

However, as already noted by Alagona, even if statins are all HMG-CoA reductase inhibitors, each one is unique and can exhibit significant differences in chemical structure, bioavailability, enzyme-binding characteristics, tissue penetration and retention, half-life, metabolism and elimination, potency, dosage and efficacy, drug-drug interactions, and safety.¹⁷

For this reason we decided to conduct a review to test the efficacy and safety of pitavastatin in clinical practice, both compared to placebo and to other HMG-CoA reductase inhibitors.

Material and Methods

A systematic search strategy was developed to identify randomised controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 2010 through July 2011), and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, United Kingdom). The terms “pitavastatin”,



“HMG-CoA reductase”, “statins”, “treatment of hypercholesterolemia”, “treatment of combined dyslipidemia”, “adverse events” were incorporated into an electronic search strategy that included the Dickersin filter for randomised controlled trials.¹⁸ The bibliographies of all identified randomised trials and review articles were reviewed to look for additional studies of interest. We reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions evaluated, and outcome measured. Studies were required to be randomised trials comparing pitavastatin at any dosage with any other anti-hypercholesterolemic drugs for the treatment of hypercholesterolemia and combined dyslipidemia. Eligible trials had to present results on lipid profile variations or adverse events. Variations of total cholesterol (TC), triglycerides (Tg), HDL-C, and LDL-C that occurred during various trials were primary outcomes of interest, as was the frequency of patients having one or more adverse events such as myalgia. The following data were abstracted onto standardized case report forms: authors, year of publication, country of study, source of funding, study goal, means of randomisation and blinding, duration of treatment, treatment characteristics, sex, quantity of and reasons for study withdrawal, age characteristics of the treatment and control groups, outcomes, and adverse event data. A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomisation (0–2 points), double-blinding (0–2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5, and scores 3 indicated a study of high quality,¹⁹ and study selection was restricted to randomised controlled trials to ensure the inclusion of only high quality evidence.

Mechanism of Action, Including Key PK/PD Data

Pitavastatin belongs to the class of statins or HMG-CoA reductase inhibitors. The enzyme HMG-CoA reductase plays a central role in the production of cholesterol in the liver. About 20%–25% of total

daily cholesterol production, in fact, occurs in the liver; other sites of higher synthesis rates include the intestines, adrenal glands, and reproductive organs. Synthesis within the body starts with one molecule of acetyl CoA and one molecule of acetoacetyl-CoA, which are dehydrated to form HMG-CoA. This molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase. This passage is the regulated, rate-limiting and irreversible step in cholesterol synthesis and is the site of action for the statin drugs. Pitavastatin has a characteristic structure with a quinoline ring at the core, a cyclopropyl moiety, and a fluorophenyl group, similar to other statins, especially fluvastatin and rosuvastatin.²⁰ This structure improves pharmacokinetics, with better absorption and activity.²¹ After oral administration of C14-labeled pitavastatin, the concentration is 54 times greater in the liver than in serum. The unique cyclopropyl group on the base structure contributes to a more effective inhibition of the HMG-CoA reductase enzyme to inhibit cholesterol production, and potentially affords greater LDL-C clearance and reduction of plasma cholesterol. Pitavastatin is only minimally metabolized by the liver through the cytochrome P450 pathway, through which many other medications are metabolized, reducing the risk of interactions with other drugs.

The pKa values of pitavastatin were 5.36 (nitrogen of quinoline ring), and 4.40 (carboxyl moiety of side chain); its empirical formula is $C_{25}H_{24}FNO_4$.

Clinical Recommendations

Food and Drug Administration approved pitavastatin for the primary treatment of hypercholesterolemia and combined dyslipidemia in patients where diet and exercise fail to lower their cholesterol levels.

Pitavastatin is available in three different dosages: 1, 2 and 4 mg daily administered at any time of the day without regard to meals. Therapy is usually initiated at 2 mg daily and increased after 4 weeks up to a maximum dose of 4 mg daily if the LDL-C target is not reached. Doses greater than 4 mg daily are associated with severe muscle toxicity. The recommended dose for individuals with moderate renal dysfunction or on dialysis is 1–2 mg daily.

Pitavastatin is contraindicated in patients with a known hypersensitivity to any component of this product, in patients with acute liver disease which



may include unexplained persistent elevations of hepatic transaminase levels, and during pregnancy.

Adverse Events

Common side effects of pitavastatin are similar to the ones related to other statins and include back pain, muscle pain, joint pain, constipation, diarrhea, and abnormal liver function tests. In particular, according to several large databases, the incidence of myopathy is reported to be 0.08% with lovastatin and simvastatin, while elevations of creatine kinase greater than ten times the upper limit of normal have been reported in 0.09% of people treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect. Elevated hepatic transaminases, instead, are more frequent, and generally occur in 0.5%–2.0% of cases and are dose-dependent.^{22,23} Liver function tests should be performed before, and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically (for example, semiannually) thereafter. Like other statins, pitavastatin may cause fatal rhabdomyolysis at any dose, but most often at higher doses, or when used in combination with other drugs that increase its blood levels. All patients should promptly report unexplained muscle pain, tenderness, or weakness, especially if associated with malaise or fever. Pitavastatin should be discontinued if rhabdomyolysis is diagnosed or suspected.

Clinical Practice Evidences

For a summary of all the following studies, see Tables 1 and 2.

Pitavastatin Compared to Placebo

Nakamura et al conducted a prospective, randomised, placebo-controlled study to determine time course of stabilization of echolucent carotid plaques by statin therapy in patients with acute coronary syndrome (ACS).²⁴ The study enrolled 65 patients with ACS, the presence of carotid plaque [intima-media thickness (IMT) ≥ 1.1 mm], and hypercholesterolemia. Treatment with pitavastatin 4 mg/die or placebo was initiated within 3 days after onset of ACS in 65 patients with echolucent carotid plaque. Vulnerable carotid plaques were assessed by measuring plaque echolucency using carotid ultrasound with integrated backscatter (IBS) analysis before, and 1 month after treatment in all patients. The levels of TC, Tg, LDL-C, C-reactive protein (CRP), vascular endothelial growth factor, and tumor necrosis factor- α were significantly decreased, and the HDL-C levels were increased during treatment with pitavastatin ($P < 0.05$ vs. baseline, and $P < 0.01$ vs. placebo for all), but not with placebo. The fasting insulin and glucose levels, and BMI did not change during treatment in either group. The calibrated IBS value of vulnerable carotid plaques did not change

Table 1. Summary of the studies cited in the review where pitavastatin is compared to placebo.

Study	Duration	Drugs involved	Aim	Results
Nakamura et al ²⁴	1 month	Pitavastatin 4 mg/day or placebo	To determine time course of stabilization of echolucent carotid plaques by statin therapy in patients with acute coronary syndrome.	Pitavastatin improved carotid plaque echolucency, in association with decrease in the inflammatory biomarkers related to vulnerable plaques.
Takashima et al ²⁵	6 months	Pitavastatin 2 mg/day or placebo	To investigate the effect of pitavastatin on regression of human coronary plaque.	Pitavastatin induced significant coronary plaque regression, associated with a significant reduction in the LDL-C level.
Yoshida et al ²⁶	1 month	Pitavastatin 2 mg/day or placebo	To investigate if pitavastatin may improve endothelial function in chronic smokers via its antioxidant properties.	Pitavastatin restores endothelial function, even in chronic smokers, possibly through its antioxidative properties.
Nagashima et al ²⁷	2 weeks	Pitavastatin 2 mg/day or placebo	To determine whether pitavastatin might have an effect on post-prandial hypertriglyceridemia, and thereby on endothelial function in obese subjects.	Pitavastatin might prevent endothelial dysfunction caused by post-prandial hypertriglyceridemia within 2 weeks of therapy in obese subjects.

**Table 2.** Summary of the studies cited in the review where pitavastatin is compared to other statins.

Study	Duration	Drugs involved	Aim	Results
Lee et al ²⁸	2 months	Pitavastatin 2 mg/day or atorvastatin 10 mg/day	To compare the efficacy and tolerability of pitavastatin and atorvastatin in hypercholesterolemic Korean adults.	Pitavastatin and atorvastatin did not differ significantly in terms of the proportions of patients achieving the LDL-C goal; reductions in LDL-C, TC, and Tg; or increases in HDL-C. Both drugs were well tolerated.
Toi et al ²⁹	2–3 weeks	Pitavastatin 2 mg/day or atorvastatin 10 mg/day	To evaluate the quantitative and qualitative early effects of 2 statins on coronary lesions using VH-IVUS.	Fibro-fatty composition and plaque volume decreased significantly following treatment with pitavastatin, which suggests that pitavastatin might have a higher affinity for fibro-fat compared with atorvastatin.
Kawashiri et al ³⁰	5 months	Pitavastatin 4 mg/day or atorvastatin 20 mg/day	To compare pitavastatin and atorvastatin efficacy and safety, especially regarding plasma levels of coenzyme Q10.	Pitavastatin and atorvastatin caused significant and almost comparable reductions in serum levels of TC, LDL-C, and Tg and significantly increased serum levels of HDL-C. Plasma levels of CoQ10 were reduced by atorvastatin, but not by pitavastatin.
JAPAN trial ³²	8–12 months	Pitavastatin 4 mg/day or atorvastatin 20 mg/day	To evaluate the effects of aggressive lipid-lowering therapy with atorvastatin or pitavastatin on coronary plaque volume in patients with acute coronary syndrome.	The administration of pitavastatin or atorvastatin in patients with acute coronary syndrome equivalently resulted in significant regression of coronary plaque volume.
Shimabukuro et al ³³	6 months	Pitavastatin 2 mg/day or atorvastatin 10 mg/day	To evaluate the effects of pitavastatin and atorvastatin on the lipid profile and lipoprotein subclasses in patients with type 2 diabetes with dyslipidemia.	Between the pitavastatin and atorvastatin groups, changes in TC, LDL-C, non-HDL-C, LDL-C/HDL-C ratio were equivalent after 1, 3 and 6 months, but only pitavastatin increased cholesterol of medium HDL subclass. Serum triglyceride and triglyceride contents in VLDL and LDL subclasses were decreased only by atorvastatin.
CHIBA trial ³⁴	3 months	Pitavastatin 2 mg/day or atorvastatin 10 mg/day	To compare the efficacy and safety of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia	Pitavastatin and atorvastatin were equally effective in improving the lipid profile and were well tolerated in Japanese patients with hypercholesterolemia.

(Continued)

**Table 2.** (Continued)

Study	Duration	Drugs involved	Aim	Results
Sasaki et al ³⁵	13 months	Pitavastatin 2 mg/day or atorvastatin 10 mg/day	To compare the effects of pitavastatin and atorvastatin on HDL-C and other lipids and glucose metabolism in Japanese patients with elevated LDL-C levels and glucose intolerance.	Pitavastatin was associated with significantly greater increases in HDL-C and Apo A-I levels than atorvastatin. Both treatments were well tolerated.
Maruyama et al ³⁶	19 months for placebo, 39 for pravastatin, 26 for atorvastatin, 27 for pitavastatin.	Pravastatin (average dose: 10.3 mg), or atorvastatin (average dose: 11.3 mg), or pitavastatin (average dose: 2.3 mg), or placebo	To compare the efficacy of statins on serum lipid levels and to explore the association between those changes and cardiac events in patients after percutaneous coronary intervention.	Each statin significantly prevented major adverse cardiac events compared with no statin, and pitavastatin was the most effective of all.
PATROL trial ³⁷	4 months	Atorvastatin 10 mg/day, or rosuvastatin 2.5 mg/day, or pitavastatin 2 mg/day.	To compare the safety and efficacy of atorvastatin, rosuvastatin and pitavastatin head to head in patients with hypercholesterolemia.	The safety and efficacy of these 3 strong statins are equal.
Yanagi et al ³⁸	8 months	Pitavastatin (2 mg daily) or rosuvastatin (2.5 mg daily)	To evaluate the percentage changes in LDL-C, HDL-C, Tg, and LDL-C/HDL-C ratio in patients with type 2 diabetes.	Both statins improved lipid profile, and reduced pro-inflammatory responses; however, 2.5 mg of rosuvastatin have a potent LDL-C-lowering and hs-CRP lowering effect compared with 2 mg of pitavastatin in patients with diabetes.

at 1 week, but it was favorably changed at 1 month after treatment in both groups ($P < 0.05$ in both). The echolucency at 1 month decreased more in the pitavastatin than in the placebo group ($P < 0.01$). In contrast, the IMT max did not significantly change during treatment in either groups. In conclusion, pitavastatin improved carotid plaque echolucency within 1 month of therapy in patients with ACS, in association with decrease in the inflammatory biomarkers related to vulnerable plaques.

Similar results were recorded by Takashima et al:²⁵ eighty-two patients undergoing intravascular ultrasound (IVUS) guided percutaneous coronary intervention were retrospectively assigned to either pitavastatin 2 mg/day, or diet only. Serial volumetric IVUS analyses of a matched left main coronary arterial site were performed. The pitavastatin group

showed significantly lower values of TC (-21.8% vs. baseline), and LDL-C (-33.2% vs. baseline) compared with the control group at follow-up ($P < 0.001$, for both). No significant changes in these variables were observed in the control group. Plaque volume index was significantly reduced in the pitavastatin group ($-10.6\% \pm 9.4\%$) compared with the control group ($+8.1\% \pm 14.0\%$, $P < 0.001$ vs. pitavastatin). Furthermore there were positive correlations between the percent change in the plaque volume index and follow-up LDL-C level ($r = 0.500$, $P < 0.001$), and the percent change in LDL-C level ($r = 0.479$, $P < 0.001$). This study demonstrates that lipid-lowering therapy with pitavastatin induced a significant regression of the coronary atherosclerotic plaque burden in the left main coronary artery, as assessed by serial 3D-IVUS analysis.



Yoshida et al enrolled 30 male chronic smokers, with newly diagnosed mild hypercholesterolemia and randomised them to take 2 mg once daily of pitavastatin or to only continue lifestyle management for 4 weeks (control group).²⁶ In the pitavastatin group, the percent reductions in TC and LDL-C levels and oxidative stress markers, such as the malondialdehyde-LDL-C (MDA-LDL-C) level, and serum free radical activity, were significantly larger compared with the control group: there was a decrease of TC of $-24.4\% \pm 2.9\%$ with pitavastatin vs. $-1.9\% \pm 2.7\%$ with diet; a decrease of LDL-C of $-32.3\% \pm 3.6\%$ vs. $-3.9\% \pm 4.1\%$; a decrease of MDA-LDL-C of $-16.6\% \pm 8.5\%$ vs. $+7.5\% \pm 7.2\%$; and a decrease of serum free radical activity of $-1.8\% \pm 3.1\%$ vs. $+9.7\% \pm 4.5\%$ in the pitavastatin vs. the control group.

Nagashima et al enrolled twenty-four obese male subjects and randomized them to receive pitavastatin 2 mg/day or placebo for 2 weeks.²⁷ An oral fat loading test was performed pre- and post-treatment, in which the lipid profile and flow-mediated dilation (FMD) were assessed before and 4 h after the oral fat load. In the pitavastatin group, significant decreases of the serum TC (-16.4%), LDL-C (-19.5%), and Tg (-17.6%) were observed. In addition, FMD increased significantly from $10.4\% \pm 2.4\%$ to $11.2\% \pm 2.1\%$. Significant decreases of the post-prandial serum TC and LDL-C by pitavastatin treatment were observed, similar to the case in the fasting state. Post-prandial serum Tg was markedly decreased (-36%), indicating that the increase in post-prandial serum Tg was attenuated by pitavastatin treatment ($P < 0.001$). Concomitantly, the decrease in post-prandial FMD noted pre-treatment was also completely abolished following pitavastatin treatment ($-1.1\% \pm 1.2\%$ vs. $0.1\% \pm 1.0\%$, $P < 0.001$). No significant changes were noted in the placebo group.

Pitavastatin Compared to Other Statins

Pitavastatin vs. atorvastatin

Lee et al compared the efficacy and tolerability of pitavastatin and atorvastatin in hypercholesterolemic Korean adults for 8 weeks.²⁸ Two hundred and sixty eight patients were randomised to receive either pitavastatin 2 mg/daily or atorvastatin 10 mg/daily. Patients who had not reached the LDL-C goal by week 4 received a double dose of the assigned medication

for an additional period of 4 weeks. At week 8, there was no significant difference between the pitavastatin and atorvastatin groups in the proportion of patients achieving the LDL-C goal (92.7% with pitavastatin and 92.0% with atorvastatin). In addition, there were no significant differences between the pitavastatin and atorvastatin groups in terms of the percent change in LDL-C at the end of the study (-42.9 ± 12.7 vs. -44.1 ± 11.1 mg/dl), or in the percent changes in TC (-28.2 ± 10.7 vs. -29.6 ± 8.4 mg/dl), Tg (-9.9 ± 41.7 vs. -11.0 ± 56.9 mg/dl), and HDL-C (7.1 ± 17.4 vs. 6.7 ± 15.9 mg/dl). Regarding high sensitivity C-reactive protein (hs-CRP), at week 8, mean hs-CRP concentrations decreased of -32.9% in the pitavastatin group and of -15.4% in the atorvastatin group; the between-group difference was not statistically significant. Both pitavastatin and atorvastatin were well tolerated.

Toi et al compared the effects of atorvastatin compared to pitavastatin in patients with ACS who underwent emergency percutaneous coronary intervention (PCI).²⁹ Patients were randomised to receive pitavastatin ($n = 80$; 2 mg/day) or atorvastatin ($n = 80$; 10 mg/day) immediately after PCI for 2- to 3-weeks. The levels of TC and LDL-C were significantly reduced after drug administration in both groups ($P < 0.001$ in each). Both baseline and follow-up TC and LDL-C were lower in the pitavastatin group, but the percentage changes did not differ significantly between the two groups. Tg was also lower in the pitavastatin group at baseline and follow up, but there was also no significant difference in the percentage change between the two groups. HDL-C did not change significantly after treatment in either group. Plaque volume index, and fibro-fatty volume index were significantly reduced in the pitavastatin group, but not in the atorvastatin group. This study showed that the plaque fibro-fatty composition was significantly reduced and plaque volume was also reduced by pitavastatin compared to the respective values found with atorvastatin, suggesting that fibro-fat is more sensitive to pitavastatin than to atorvastatin in the early stage.

Kawashiri et al conducted an open, randomised, crossover study using 4 mg of pitavastatin or 20 mg of atorvastatin to compare their efficacy and safety, especially regarding plasma levels of coenzyme Q10 (CoQ10) in 19 Japanese patients with heterozygous



familial hypercholesterolemia.³⁰ Both pitavastatin and atorvastatin significantly decreased the serum levels of TC (−35.4% with pitavastatin, $P < 0.0001$; −33.8% with atorvastatin, $P < 0.0001$), LDL-C (−42.8% with pitavastatin, $P < 0.0001$, −40.7% with atorvastatin, $P < 0.0001$), and Tg (−26.1% with pitavastatin $P < 0.0001$, −29.4% with atorvastatin, $P < 0.0004$), and significantly increased the serum levels of HDL-C (+12.1% with pitavastatin, $P < 0.0001$, and +11.4% with atorvastatin, $P < 0.002$). Similarly, serum levels of apolipoprotein A-I and A-II were significantly increased, and those of apolipoprotein B, C-II, C-III, and E were significantly decreased by both pitavastatin and atorvastatin. However, there was no significant difference in the changes in serum lipids and apolipoproteins between pitavastatin and atorvastatin treatment. Regarding CoQ10, it is an essential cofactor in the mitochondrial electron transport chain and exists in almost all human tissues. Ubiquinol-10, the reduced form of CoQ10, is a potent lipophilic antioxidant, and the ratio between ubiquinol-10 and ubiquinone-10 is considered to be a good marker of oxidative stress.³¹ Administration of pitavastatin did not change plasma levels of total CoQ10 significantly (838.6 to 737.3 nmol/l (−7.7%, $P < 0.39$), whereas atorvastatin significantly reduced plasma levels of total CoQ10 (864.6 to 599.9 nmol/l (−26.1%, $P < 0.0007$). The reduction rate of plasma CoQ10 by atorvastatin treatment was significantly greater than that by pitavastatin treatment ($P < 0.03$). Plasma levels of the reduced form of CoQ10, ubiquinol-10, showed similar changes as total CoQ10 after pitavastatin and atorvastatin treatment: from 659.9 to 572.2 nmol/l (−7.4% $P < 0.14$) by pitavastatin and from 692.9 to 467.2 nmol/l (−23.0%, $P < 0.006$) by atorvastatin. Interestingly, the reduction rate of plasma levels of the oxidized form of CoQ10, ubiquinone-10, by pitavastatin (15.4%) was not significantly different from that by atorvastatin (8.3%) ($P < 0.4$). No adverse events or abnormalities of liver and muscle enzyme were observed after either statin treatment.

The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) trial evaluated the effect of intensive statin therapy on regression of coronary atherosclerosis in patients with ACS.³² In this prospective, randomised, open-label, parallel group study, 252 patients were randomly assigned to receive either 4 mg/day of pitavastatin

or 20 mg/day of atorvastatin. LDL-C decreased from 130.9 ± 33.3 mg/dl (3.39 ± 0.86 mmol/l) at baseline to 81.1 ± 23.4 mg/dl (2.10 ± 0.61 mmol/l, $P < 0.001$) in the pitavastatin group and from 133.8 ± 31.4 mg/dl (3.47 ± 0.81 mmol/l) to 84.1 ± 27.4 mg/dl (2.18 ± 0.71 mmol/l, $P < 0.001$) in the atorvastatin group. HDL-C, as well as Tg, showed comparable increase between the two groups. The percent change in coronary plaque volume showed a significant regression for both groups (−16.9% \pm 13.9% in the pitavastatin group, −18.1% \pm 14.2% in the atorvastatin group, and −17.5% \pm 14.0% for total patients). Non-inferiority of pitavastatin to atorvastatin and also atorvastatin to pitavastatin in terms of percent change in plaque volume was proved showing that pitavastatin provided a comparable benefit to reduce plaque volume in such patients.

Shimabukuro et al randomised patients with type 2 diabetes mellitus with hypercholesterolemia and/or hypertriglyceridemia to receive pitavastatin 2 mg or atorvastatin 10 mg for 6 months.³³ As compared with baseline, serum levels of TC, LDL-C, non-HDL-C and LDL-C/HDL-C ratio were decreased after 1, 3, and 6 months of treatment in the atorvastatin and pitavastatin groups. Serum levels of Tg were decreased after 1, 3, and 6 months of treatment with atorvastatin and after 3 months of treatment with pitavastatin. Serum levels of HDL-C were increased after 1, 3, and 6 months of pitavastatin treatment, while HDL-C was not changed in the atorvastatin group after 1, and 3 months of treatment, and even decreased after 6 months. Between the pitavastatin and atorvastatin groups, changes in TC, LDL-C, non-HDL-C, and LDL-C/HDL-C ratio were equivalent after 1, 3, and 6 months. By contrast, a significant difference was seen in change of HDL-C after 6 months of treatment (+0.09 mmol/l with pitavastatin vs. −0.06 mmol/l with atorvastatin, $P = 0.006$), and in apolipoprotein A1 levels (+0.10 g/l with pitavastatin vs. +0.06 g/l with atorvastatin, $P < 0.05$). Cholesterol levels of most VLDL and LDL subclasses were decreased equally in both groups, however, only pitavastatin increased cholesterol of medium HDL subclass. Serum Tg and Tg contents in VLDL and LDL subclasses were decreased only by atorvastatin.

In the CHIBA study, 251 Japanese patients with $TC \geq 220$ mg/dL were randomised to receive



pitavastatin 2 mg or atorvastatin 10 mg for 12 weeks.³⁴ Both pitavastatin and atorvastatin significantly reduced non-HDL-C levels after 12 weeks of treatment by $39.0\% \pm 11.1\%$ ($P < 0.001$) and $40.3\% \pm 11.3\%$ ($P < 0.001$), respectively. Both drugs similarly and significantly reduced TC, LDL-C and Tg. HDL-C significantly increased in the pitavastatin group ($+3.2\% \pm 13.0\%$, $P = 0.033$), but not in the atorvastatin group ($+1.7\% \pm 12.7\%$, $P = 0.221$), without significant intergroup differences. The efficacy of the two statins in a subgroup of patients with metabolic syndrome (28 patients on pitavastatin, 25 patients on atorvastatin) was further compared. Percent change from baseline in LDL-C was significantly greater in the pitavastatin ($-45.8\% \pm 8.8\%$) compared to the atorvastatin group ($-39.1\% \pm 12.1\%$, $P = 0.0495$ vs. pitavastatin). There were no significant differences between pitavastatin and atorvastatin in Tg and HDL-C, but pitavastatin significantly reduced Tg ($-25.2\% \pm 22.1\%$, $P < 0.001$), and increased HDL-C ($+6.7\% \pm 13.1\%$, $P = 0.019$) compared to baseline. Both pitavastatin and atorvastatin were well tolerated, with a similar low incidence of treatment-emergent adverse events.

Sasaki et al conducted a study where 207 patients with LDL-C levels ≥ 140 mg/dL and glucose intolerance were randomly assigned to receive either pitavastatin 2 mg/daily or atorvastatin 10 mg/daily for 52 weeks.³⁵ Levels of serum lipids, lipoproteins and measures of glucose metabolism [fasting insulin, fasting glucose, glycated hemoglobin (HbA_{1c}), and homeostasis model assessment for insulin resistance (HOMA-IR)] were obtained at baseline, and at 8, 26, and 52 weeks of treatment. The percent increase in HDL-C levels was significantly greater in the pitavastatin group than in the atorvastatin group ($+8.2$ vs. $+2.9$, respectively; $P = 0.031$). The percent change in Apo A-I was also significantly greater in the pitavastatin group compared with the atorvastatin group ($+5.1$ vs. $+0.6$; $P = 0.019$). The atorvastatin group had significantly greater reductions compared with the pitavastatin group in terms of the percent change in LDL-C (-40.1 vs. -33.0 , respectively; $P = 0.002$), non-HDL-C (-37.4 vs. -31.1 ; $P = 0.004$), Apo B (-35.1 vs. -28.2 ; $P < 0.001$), and Apo E (-28.1 vs. -17.8 ; $P < 0.001$). HDL-C levels were significantly higher in the pitavastatin group compared with the atorvastatin group at 8 weeks ($P = 0.013$) and 52 weeks ($P = 0.034$). Pitavastatin was associated with consistently higher

levels of Apo A-I compared with the atorvastatin group at each time point evaluated (8 weeks: $P = 0.026$; 26 weeks: $P = 0.013$; 52 weeks: $P = 0.031$). There was no significant difference between pitavastatin and atorvastatin in the percent changes in fasting plasma insulin, fasting plasma glucose, HbA_{1c} , or HOMA-IR. No differences regarding adverse events were recorded between the two groups.

Pitavastatin vs. atorvastatin or pravastatin

Maruyama et al retrospectively investigated 743 consecutive patients who underwent PCI from 2001 to 2008.³⁶ The patients had received pravastatin (average dose: 10.3 mg), atorvastatin (average dose: 11.3 mg), pitavastatin (average dose: 2.3 mg), or no statin; the endpoint was a composite of cardiac sudden death, fatal or nonfatal myocardial infarction (MI), death from worsening of chronic heart failure (CHF), bypass surgery, target lesion revascularization (TLR) and repeated PCI for de novo lesion. As expected, compared with the no statin treatment, each statin treatment showed a significant reduction in LDL-C: $-23.7\% \pm 15.7\%$ with pravastatin ($P < 0.001$), $-32.8\% \pm 14.4\%$ with atorvastatin ($P < 0.001$), and $-34.2\% \pm 16.6\%$ with pitavastatin ($P < 0.001$). On the other hand, the HDL-C level was increased of $+13.4\% \pm 22.9\%$ in the pitavastatin group ($P = 0.010$, compared with the no statin group, and $P = 0.029$ vs. atorvastatin). A total of 88 major adverse cardiac events occurred in the no statin group; among the patients treated with a statin, a total of 41 events were recorded in the pravastatin group, 31 events in the atorvastatin group and 15 events in the pitavastatin group.

Pitavastatin vs. atorvastatin or rosuvastatin

The PATROL (Randomised Head-to-Head Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy (Quantity and Quality of LDL) Trial compared the safety and efficacy of atorvastatin, rosuvastatin and pitavastatin head to head in patients with hypercholesterolemia.³⁷ Three hundred and two patients with risk factors for coronary artery disease and elevated LDL-C levels were randomised to receive atorvastatin (10 mg/day), rosuvastatin (2.5 mg/day), or pitavastatin (2 mg/day) for 16 weeks. Pitavastatin was non-inferior to both atorvastatin and rosuvastatin with



regard to efficacy in lowering LDL-C. There were no differences in the rate of adverse drug reactions among the 3 groups, but CRP decreased in the atorvastatin and pitavastatin groups ($P < 0.01$); HbA_{1c} was significantly increased in the atorvastatin and rosuvastatin groups ($5.68\% \pm 1.06\%$ to $5.75\% \pm 1.01\%$, $5.52\% \pm 0.91\%$ to $5.58\% \pm 0.80\%$, $P < 0.01$, respectively), but there was no change in the pitavastatin group. Uric acid was decreased in the atorvastatin and rosuvastatin groups (5.19 ± 1.23 mg/dl to 4.99 ± 1.12 mg/dl, 5.42 ± 1.48 mg/dl to 5.24 ± 1.54 mg/dl, $P < 0.05$, respectively). Serum creatine kinase was increased in the atorvastatin group (116 ± 64 mg/dl to 132 ± 113 mg/dl, $P < 0.05$), and estimated glomerular filtration rate was increased only in the rosuvastatin group, while urine albumin and α -microglobulin did not change statistically. The changes of CRP, HbA_{1c}, creatine kinase, uric acid, and estimated glomerular filtration rate, however, were not clinically significant.

Pitavastatin vs. rosuvastatin

Yanagi et al enrolled a total of 90 Japanese type 2 diabetic patients with hyperlipidemia LDL-C (≥ 140 mg/dL) and randomly assigned them to four groups with open-label treatment with rosuvastatin 2.5 mg daily or pitavastatin 2 mg daily; two groups were sequentially treated with both drugs, with crossover of medication after 12 weeks, and the other two groups underwent treatment with either rosuvastatin or pitavastatin for 24 weeks.³⁸ A significantly greater decrease in serum LDL-C levels from the baseline occurred with rosuvastatin (-44.1%) than with pitavastatin (-36.9% , $P < 0.01$) in the rosuvastatin-pitavastatin group, and a significantly greater decrease with rosuvastatin (-44.7%) than with pitavastatin (-34.8% , $P < 0.01$) in the pitavastatin-rosuvastatin group. A significant reduction in serum LDL-C levels from the baseline was also observed with rosuvastatin (-44.6% at 12 weeks and -5.5% at 24 weeks) in the rosuvastatin-rosuvastatin group and there were no significant differences between data at 12, and 24 weeks. A significant reduction in serum LDL-C levels from the baseline was also observed with pitavastatin (-38.8% at 12 and 24 weeks) in the pitavastatin-pitavastatin group and there were no significant differences between data at 12 and 24 weeks. The proportion of patients achieving LDL-C levels

< 120 mg/dL during the first 12-week period of rosuvastatin treatment was significantly greater (76.7%) than that with pitavastatin (51.2%, $P = 0.02$). Both rosuvastatin and pitavastatin significantly increased serum HDL-C levels, and decreased Tg levels without significant differences between the four groups. Regarding inflammatory parameters, both drugs significantly decreased plasma tumor necrosis factor- α ($P < 0.01$), and plasminogen activator inhibitor-1 levels ($P < 0.01$) from baseline and there were no significant differences between the four groups. A significantly greater decrease in plasma hs-CRP levels occurred with rosuvastatin (-20.1%) than with pitavastatin (-12.3% , $P < 0.01$) in the rosuvastatin-pitavastatin group, and significantly greater decreases with rosuvastatin (-28.8%) than with pitavastatin (-11.9% , $P < 0.01$) in the pitavastatin-rosuvastatin group. A significant reduction in plasma hs-CRP levels was observed with rosuvastatin (-28.1% at 12 weeks [$P < 0.01$ vs. baseline] and -29.8% at 24 weeks [$P < 0.01$ vs. baseline]) in the rosuvastatin-rosuvastatin group.

Discussion

The studies reported above proved that, as expected, pitavastatin was more effective than placebo in improving lipid profile.²⁴⁻²⁷ Compared to other previously commercialized statins, pitavastatin proved to be as effective as atorvastatin in terms of the proportions of patients achieving the LDL-C goal, reductions in LDL-C, TC, and Tg,²⁶⁻³⁴ but to be inferior to rosuvastatin in lowering LDL-C, and hs-CRP in patients with type 2 diabetes mellitus,³⁸ placing between atorvastatin and rosuvastatin in terms of effectiveness (Table 3). Moreover, compared to other statins, pitavastatin treatment was also associated with a significant greater increase in HDL-C levels (Table 3).³⁵ The effects of statins on levels of HDL-C have become a focus of research interest, because it has been reported that individuals with a $\geq 7.5\%$ increase in HDL-C levels had a statistically significant regression in coronary atherosclerosis ($P < 0.001$), independent of LDL-C levels.³⁹ In a post hoc analysis of the Treating to New Targets study,⁴⁰ HDL-C levels during statin treatment were inversely related to the risk of cardiovascular events, even among patients with LDL-C levels < 70 mg/dL. Giving a major increase of HDL-C³⁵ and of apolipoprotein A1,³³



Table 3. Effects of various statins on LDL-C, HDL-C, and their features.

Statin	Dosage	Average expected LDL-C reduction	Average expected HDL-C increase	Reduction of the risk of heart attack	Mortality reduction	Metabolism
Fluvastatin	20 mg	22%		Likely	Likely	CYP2C9
	40 mg	25%				
	80 mg	35%	10%			
Lovastatin	10 mg	21%		Likely	Likely	CYP3A4
	20 mg	24%–27%				
	40 mg	31%	5–8%			
Pravastatin	80 mg	30%–37%	10%	Yes	Yes	NonCYP
Simvastatin	10 mg	20%–30%	4.2%	Yes	Yes	CYP3A4
	20 mg	30%–40%	5.0%			
	40 mg	35%–45%	5.0%			
	80 mg	40%–50%	5.3%			
Atorvastatin	10 mg	30%–40%	5.5%	Yes	Yes	CYP3A4
	20 mg	42%–46%	6.0%			
	40 mg	47%–51%	6.0%			
	80 mg	46%–54%	8.0%			
Pitavastatin	1 mg	30%–35%		Yes	Yes	CYP2C9
	2 mg	35%–40%	10%–15%			
	4 mg	40%–48%				
Rosuvastatin	5 mg	30%–40%	5.5%	Yes	Likely	CYP2C9 and CYP2C19
	10 mg	43%–50%	6.1%			
	20 mg	52%–55%	7.0%			
	40 mg	55%–60%	8.0%			

pitavastatin has a further positive effect on reducing coronary atherosclerosis. This was confirmed by Maruyama et al that observed that, despite giving a similar reduction of LDL-C, pitavastatin resulted superior to atorvastatin in reducing major adverse cardiac events, due to their differing HDL-C raising ability.³⁶

Furthermore, differently from the majority of other statins, pitavastatin appears to be a substrate of CYP2C9, and not CYP3A4; as a result, pitavastatin is less likely to interact with drugs that are metabolized via CYP3A4, which might be important for elderly patients who need to take multiple drugs.⁴¹ A big advantage of pitavastatin regards also the use in patients with type 2 diabetes mellitus: in the JUPITER trial, in fact, rosuvastatin significantly prevented vascular events in men and women with elevated hs-CRP, but increased the incidence of new-onset diabetes more than the placebo,⁴² and a previous published meta-analysis showed that statin therapy was associated with a significantly increased risk (9%) of the development of diabetes;⁴³ differently from other statins, pitavastatin proved to not affect glycemic control, or insulin resistance in patients with

diabetes.^{35,44} No differences regarding adverse events were recorded between the various statins.

Other than these advantages, pitavastatin also proved to have many pleiotropic effects: several studies, in fact, have shown that echolucent plaques are histologically rich of lipids and macrophages, and, for this reason, are unstable;^{45–47} pitavastatin proved to improve carotid plaque echolucency, in association with a decrease in the inflammatory biomarkers related to vulnerable plaques such as vascular endothelial growth factor and CRP.²⁴ Vascular endothelial growth factor is an angiogenic growth factor, has pro-inflammatory action and it is intimately associated with plaque echogenicity and the extent of stenosis in the carotid artery.^{48,49}

Similar results were obtained by Takashima et al²⁵ that demonstrated that lipid-lowering therapy with pitavastatin induced a significant regression of the coronary atherosclerotic plaque burden in the left main coronary artery, as assessed by serial 3D-IVUS analysis. A previous observational study showed a relationship between left main coronary artery plaque progression and adverse cardiac events; based on these data, we can assert that plaque volume index



regression by pitavastatin has the potential to reduce cardiovascular events.⁵⁰ Furthermore in a study by Mizuguchi et al pitavastatin treatment improved not only carotid arterial stiffness, but also regional left ventricular systolic and diastolic function in patients with hypercholesterolemia and preserved left ventricular ejection fraction.⁵¹

Another pleiotropic effect is that pitavastatin did not significantly reduce plasma CoQ10, whereas atorvastatin did, despite the fact that changes in serum lipid and apolipoprotein parameters, including detailed lipoprotein lipid distribution analysis and the short-term safety after both statin treatments, were almost comparable.³⁰ CoQ10 is an essential cofactor in the mitochondrial electron transport chain, and 60% of plasma CoQ10 is endogenous. Although statins are generally well tolerated and safe, myopathy and an asymptomatic increase in hepatic enzymes are relatively frequent.³¹ It has been speculated that depletion of tissue levels of CoQ10 may be at least a potential cause of myositis or liver toxicity in humans, so, not changing CoQ10, pitavastatin could be also better tolerated compared to other statins.

Moreover, other than reducing hs-CRP, pitavastatin also reduced resistin secreted by macrophages, that is associated with high risk in patients with atherosclerosis.⁵² Pitavastatin also increased the plasma adiponectin levels after 6 months of treatment.⁵³ Adiponectin is exclusively expressed in and secreted by the adipose tissue, it suppresses the attachment of monocytes to endothelial cells, and also stimulates nitric oxide production in vascular endothelial cells, which ameliorates endothelial function and occurs in abundance in the circulation,^{54,55} suggesting the possibility of preventing the progression of atherosclerosis by pitavastatin. Moreover, pitavastatin also proved to be safe in patients with chronic kidney disease, giving a significant increase of the estimated glomerular filtration rate (+5.4 mL/min/1.73 m²) after 104 weeks of pitavastatin treatment ($P < 0.001$).⁵⁶

Conclusion

Pitavastatin proved to be as effective as atorvastatin, and a little inferior to rosuvastatin in improving lipid profile, it also proved to be effective in reducing major adverse cardiac events, and to be safe and well tolerated. Promising effects, such as reductions of

coronary plaque volume and fibro-fatty composition that may translate to better clinical outcomes, make pitavastatin a valid option for the treatment of hypercholesterolemia and combined dyslipidemia.

Conflicts of Interest

The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References

1. NCEP. 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. *Circulation*. 2002;106(25):3143–4216.
2. Gordon DJ, Probstfield JL, Garrison RJ, et al. High Density Lipoprotein Cholesterol and Cardiovascular Disease: Four Prospective American Studies. *Circulation*. 1989;79:8–15.
3. Kruth HS. Lipoprotein Cholesterol and Atherosclerosis. *Curr Mol Med*. 2001;1(6):633–53.
4. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum Cholesterol, Blood Pressure, and Mortality: Implications from a Cohort of 361,662 men. *Lancet*. 1986;2(8513):933–6.
5. Stamler J, Wentworth D, Neaton JD. Is Relationship Between Serum Cholesterol and Risk of Premature Death from Coronary Heart Disease Continuous and Graded? Findings in 356,222 Primary Screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256(20):2823–8.
6. Schaefer EJ, Levy RI. Pathogenesis and Management of Lipoprotein Disorders. *N Engl J Med*. 1985;312(20):1300–10.
7. Brown MS, Goldstein JL. A Receptor-Mediated Pathway for Cholesterol Homeostasis. *Science*. 1986;232(4746):34–47.
8. Durrington P. Dyslipidaemia. *The Lancet*. 2003;362(9385):717–31.
9. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial Effects of Combined Colestipol-Niacin Therapy on Coronary Atherosclerosis and Coronary Venous Bypass Grafts. *JAMA*. 1987;19(23):3233–40.
10. Brensike JF, Levy RI, Kelsey SF, et al. Effects of Therapy with Cholestyramine on Progression of Coronary Arteriosclerosis: Results of the NHLBI Type II Coronary Intervention Study. *Circulation*. 1984;69(2):313–24.



11. Yusuf S, Wittes J, Friedman L. Overview of Results of Randomized Clinical Trials in Heart Disease. II. Unstable Angina, Heart Failure, Primary Prevention with Aspirin, and Risk Factor Modification. *JAMA*. 1988;260(15):2259–63.
12. Kjekshus J, Pedersen TR. Reducing the Risk of Coronary Events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol*. 1995;76(9):64C–8.
13. Sacks FM, Pfeffer MA, Moye LA, et al. The Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients with Average Cholesterol Levels. *N Engl J Med*. 1996;335(14):1001–9.
14. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the Management of Dyslipidaemias. *Atherosclerosis*. 2011;217 Suppl 1:1–44.
15. Istvan ES, Deisenhofer J. Structural Mechanism for Statin Inhibition of HMG-CoA Reductase. *Science*. 2001;292:1160–4.
16. Derosa G, Maffioli P. Effects of Amlodipine plus Atorvastatin Association in Hypertensive Hypercholesterolemic Patients. *Expert Rev Cardiovasc Ther*. 2010;8(6):835–43.
17. Alagona P. Pitavastatin: Evidence for its Place in Treatment of Hypercholesterolemia. *Core Evidence*. 2010;5:91–105.
18. Dickersin K, Scherer R, Lefebvre C. Identifying Relevant Studies for Systematic Reviews. *BMJ*. 1994;309:1286–91.
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the Quality of Randomized Controlled Trials: is Blinding Necessary? *Control Clin Trials*. 1996;17:1–12.
20. Saito Y. Critical Appraisal of the Role of Pitavastatin in Treating Dyslipidemias and Achieving Lipid Goals. *Vasc Health Risk Manag*. 2009;5:921–36.
21. Kimata H, Fujino H, Koide T, et al. Studies on the Metabolic Fate of NK-104, a New Inhibitor of HMG-CoA Reductase (1): Absorption, Distribution, Metabolism and Excretion in Rats. *Drug Metab Pharmacokinet*. 1998;13:484–98.
22. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results. I. Efficacy in Modifying Plasma Lipoproteins and Adverse Event Profile in 8245 Patients with Moderate Hypercholesterolemia. *Arch Intern Med*. 1991;151(1):43–9.
23. Hsu I, Spinler SA, Johnson NE. Comparative Evaluation of the Safety and Efficacy of HMG-CoA Reductase Inhibitor Monotherapy in the Treatment of Primary Hypercholesterolemia. *Ann Pharmacother*. 1995;29(7–8):743–59.
24. Nakamura T, Obata JE, Kitta Y, et al. Rapid Stabilization of Vulnerable Carotid Plaque Within of Pitavastatin Treatment in Patients with Acute Coronary Syndrome. *J Cardiovasc Pharmacol*. 2008;51(4):365–71.
25. Takashima H, Ozaki Y, Yasukawa T, et al. Impact of Lipid-Lowering Therapy With Pitavastatin, a New HMG-CoA Reductase Inhibitor, on Regression of Coronary Atherosclerotic Plaque. *Circ J*. 2007;71(11):1678–84.
26. Yoshida O, Kondo T, Kureishi-Bando Y, et al. Pitavastatin, an HMG-CoA Reductase Inhibitor, Ameliorates Endothelial Function in Chronic Smokers. *Circ J*. 2010;74(1):195–202.
27. Nagashima H, Endo M. Pitavastatin Prevents Postprandial Endothelial Dysfunction Via Reduction of the Serum Triglyceride Level in Obese Male Subjects. *Heart Vessels*. 2011;26(4):428–34.
28. Lee SH, Chung N, Kwan J, et al. Comparison of the Efficacy and Tolerability of Pitavastatin and Atorvastatin: an 8-Week, Multicenter, Randomized, Open-Label, Dose-Titration Study in Korean Patients with Hypercholesterolemia. *Clin Ther*. 2007;29(11):2365–73.
29. Toi T, Taguchi I, Yoneda S, et al. Early Effect of Lipid-Lowering Therapy with Pitavastatin on Regression of Coronary Atherosclerotic Plaque. Comparison with Atorvastatin. *Circ J*. 2009;73(8):1466–72.
30. Kawashiri MA, Nohara A, Tada H, et al. Comparison of Effects of Pitavastatin and Atorvastatin on Plasma Coenzyme Q10 in Heterozygous Familial Hypercholesterolemia: Results from a Crossover Study. *Clin Pharmacol Ther*. 2008;83(5):731–9.
31. Bliznakov EG, Wilkins DJ. Biochemical and Clinical Consequences of Inhibiting Coenzyme Q 10 Biosynthesis by Lipid-Lowering HMG-CoA Reductase Inhibitors (Statins): a Critical Overview. *Adv Ther*. 1998;15:213–28.
32. Hiro T, Kimura T, Morimoto T, et al; for the JAPAN-ACS Investigators. Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients with Acute Coronary Syndrome: a Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin versus Atorvastatin (JAPAN-ACS [Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome] Study). *J Am Coll Cardiol*. 2009;54(4):293–302.
33. Shimabukuro M, Higa M, Tanaka H, Shimabukuro T, Yamakawa K, Masuzaki H. Distinct Effects of Pitavastatin and Atorvastatin on Lipoprotein Subclasses in Patients with Type 2 Diabetes Mellitus. *Diabet Med*. 2011;28(7):856–64.
34. 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(2):345–52.
35. 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*. 2008;30(6):1089–101.
36. Maruyama T, Takada M, Nishibori Y, et al. Comparison of Preventive Effect on Cardiovascular Events with Different Statins. *Circ J*. 2011;75(8):1951–9.
37. Saku K, Zhang B, Noda K; PATROL Trial Investigators. Randomized Head-to-Head Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy (Quantity and Quality of LDL): the PATROL Trial. *Circ J*. 2011;75(6):1493–505.
38. Yanagi K, Monden T, Ikeda S, Matsumura M, Kasai K. A Crossover Study of Rosuvastatin and Pitavastatin in Patients with Type 2 Diabetes. *Adv Ther*. 2011;28(2):160–71.
39. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, High-Density Lipoprotein Cholesterol, and Regression of Coronary Atherosclerosis. *JAMA*. 2007;297(5):499–508.
40. Barter P, Gotto AM, LaRosa JC, for the Treating to New Targets Investigators. HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events. *N Engl J Med*. 2007;357(13):1301–10.
41. Mukhtar RYA, Reid J, Reckless JPD. Pitavastatin. *Int J Clin Pract*. 2005;59:239.
42. Ridker PM, Danielson E, Fonseca FA, et al; for the JUPITER Study Group. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N Engl J Med*. 2008;359(21):2195–207.
43. Sattar N, Preiss D, Murray HM, et al. Statins and Risk of Incident Diabetes: a Collaborative Meta-Analysis of Randomised Statin Trials. *Lancet*. 2010;375(9716):735–42.
44. Kawai T, Tokui M, Funae O, et al. Efficacy of Pitavastatin, a new HMG-CoA Reductase Inhibitor, on Lipid and Glucose Metabolism in Patients with Type 2 Diabetes. *Diabetes Care*. 2005;28(12):2980–1.
45. Grønholdt ML, Nordestgaard BG, Bentzon J, et al. Macrophages are Associated with Lipid-Rich Carotid Artery Plaques, Echolucency on B-Mode Imaging, and Elevated Plasma Lipid Levels. *J Vasc Surg*. 2002;35(1):137–45.
46. Takiuchi S, Rakugi H, Honda K, et al. Quantitative Ultrasonic Tissue Characterization Can Identify High-Risk Atherosclerotic Alteration in Human Carotid Arteries. *Circulation*. 2000;102(7):766–70.
47. Shepard RK, Miller JG, Wickline SA. Quantification of Atherosclerotic Plaque Composition in Cholesterol-Fed Rabbits with 50-MHz Acoustic Microscopy. *Arterioscler Thromb*. 1992;12(10):1227–34.
48. Celletti FL, Waugh JM, Amabile PG, Brendolan A, Hilfiker PR, Dake MD. Vascular Endothelial Growth Factor Enhances Atherosclerotic Plaque Progression. *Nat Med*. 2001;7(4):425–9.
49. Papalambros E, Georgopoulos S, Sigala F, et al. Changes in Circulating Levels of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-2 After Carotid Endarterectomy. *Int J Mol Med*. 2004;14(1):133–6.



50. Von Birgelen C, Hartmann M, Mintz GS, et al. Relationship Between Cardiovascular Risk as Predicted by Established Risk Scores versus Plaque Progression as Measured by Serial Intravascular Ultrasound in Left Main Coronary Arteries. *Circulation*. 2004;110:1579–85.
51. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T. Impact of Statin Therapy on Left Ventricular Function and Carotid Arterial Stiffness in Patients with Hypercholesterolemia. *Circ J*. 2008;72(4):538–44.
52. Nomura S, Shouzu A, Omoto S, et al. Effects of Pitavastatin on Monocyte Chemoattractant Protein-1 in Hyperlipidemic Patients. *Blood Coagul Fibrinolysis*. 2009;20(6):440–7.
53. Ouchi N, Kihara S, Arita Y, et al. Novel Modulator for Endothelial Adhesion Molecules: Adipocyte-Derived Plasma Protein, Adiponectin. *Circulation*. 1999;100:2473–6.
54. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin Stimulates Production of Nitric Oxide in Vascular Endothelial Cells. *J Biol Chem*. 2003;278:45021–6.
55. Hattori Y, Suzuki M, Hattori S, Kasai K. Globular Adiponectin Upregulates Nitric Oxide Production in Vascular Endothelial Cells. *Diabetologia*. 2003;46:1543–9.
56. Kimura K, Shimano H, Yokote K, Urashima M, Teramoto T. Effects of Pitavastatin (LIVALO tablet) on the Estimated Glomerular Filtration Rate (eGFR) in Hypercholesterolemic Patients with Chronic Kidney Disease. Sub-Analysis of the LIVALO Effectiveness and Safety (LIVES) Study. *J Atheroscler Thromb*. 2010;17(6):601–9.