The Role of Statin Therapy in Primary Hyperlipidemia and Mixed Dyslipidemia

Sergio Fazio, MD, PhD

Professor of Medicine and Pathology, Atherosclerosis Research Unit, Vanderbilt University Medical Center

Abstract

In the US, ischemic cardiovascular disease (CVD) and stroke combined are the major cause of death for all age groups older than 55 years. Preventive approaches are based on the management of all risk factors and co-morbidities. The management guidelines for the lipid risk factors focus on lowering low-density lipoprotein cholesterol (LDL-C) levels. Statins, which inhibit cholesterol synthesis via blockade of the enzyme 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase, are the drug of choice for LDL-C control. Currently, there are three generic and four branded statins. Pitavastatin, the latest statin to be approved by the US Food and Drug Administration (FDA) (2009), has the lipid indications of the other statins but is not indicated for CVD risk reduction. It is available in 1 mg, 2 mg, and 4 mg doses, with the recommended starting dose of 2 mg being equivalent to 20 mg of simvastatin and 10 mg of atorvastatin, and superior to 20 mg of pravastatin. Pitavastatin 2 mg reduces LDL-C levels by 39 %, apolipoprotein B by 31 %, total cholesterol by 28 % and triglycerides by 16 %, and raises high-density lipoprotein cholesterol (HDL-C) by 6 %. In phase III clinical trials, pitavastatin 4 mg decreases LDL-C by up to 45 %. Pitavastatin has a unique metabolism, with little processing by cytochrome P450 (CYP) and none by CYP3A4, and thus it may display less CYP-mediated drug interaction than other statins. However, the FDA has determined that pitavastatin should not be taken with cyclosporine. Pitavastatin should be limited to 1 mg daily with erythromycin and 2 mg daily with rifampin. Preliminary vascular investigations have suggested benefits in line with those obtained by other statins.

Keywords

LDL, atherosclerosis, statins, HDL, coronary artery disease, risk reduction, dyslipidemia

Disclosure: Over the last 12 months, Sergio Fazio, MD, PhD, has consulted for Merck, Takeda, Kowa, and Pfizer. He was compensated for planning and writing this manuscript.
Received: January 17, 2011 **Accepted:** May 16, 2011 **Citation:** *US Endocrinology*, 2011;7(1):23–9 *DOI: 10.17925/USE.2011.07.01.23*
Correspondence: Sergio Fazio, MD, PhD, Professor of Medicine and Pathology, Vanderbilt University Medical Center, Atherosclerosis Research Unit, 383 PRB – 2220 Pierce Avenue, Nashville, TN 37232-6300. E: sergio.fazio@vanderbilt.edu

Support: The publication of this article was funded by Kowa Pharmaceuticals. The views and opinions expressed are those of the author and not necessarily those of Kowa Pharmaceuticals.

Atherosclerosis is a degenerative process affecting large- and medium-caliber arteries, such as aorta, coronary, carotid, renal, and femoral arteries. The atherosclerotic lesion, or plaque, is a complex tissue dissecting the subendothelial layer and expanding first outwardly and eventually toward the lumen, causing occlusions ranging from minimal to complete. Ischemic consequences of plaque growth represent the major cause of disease, hospitalization, lost productivity, and death in both the industrialized and developing world.[1]

In the US (2006 data), ischemic cardiovascular disease (CVD) and stroke combined are a more common cause of death than accidents in people aged 45–54 years, and the major cause of death for all age groups older than 55 years of age.[2] It is interesting that the pathologic process so commonly identified in autoptic series of young people dying of unrelated causes appears unable to produce significant clinical consequences in the population until the fifth decade of life.[3] This long-held notion has informed our view of the atherosclerotic process as a slow burning event starting with lipoprotein infiltration in the subendothelium, leading to retention of lipoproteins, oxidative changes, endothelial dysfunction, recruitment of phagocytic elements, and activation of an inflammatory response self-perpetuated by bouts of cell death fueling chronic chemotaxis, volume expansion, and plaque instability.

Although the lipid factor is central to the current view of atherogenesis, it is established that a series of other factors and diseases contribute to CVD risk and predict event rates. Hypertension, cigarette smoking, and diabetes, among others, can induce or exacerbate endothelial dysfunction, thus facilitating and amplifying lipid entry in the intimal layer and the vascular response to lipid retention. Current risk assessment tools, such as the Framingham[4] and the Reynolds Risk Score[5] algorithms, consider age, lipid levels, blood pressure, smoking status, and high-sensitivity C-reactive protein (hsCRP) levels (Reynolds Risk Score only) to determine risk-appropriate lipid goal setting.[6]

There are two types of plasma lipoproteins, those that contain apolipoprotein B (apoB), which include chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), and low-density lipoprotein (LDL), and those that contain apolipoprotein AI (apoAI), namely high-density lipoprotein (HDL). The apoB lipoproteins are in general considered as causative of atherosclerosis via the delivery of lipid cargo to the vessel wall, whereas a protective value is attributed to apoAI lipoproteins because they can extract cholesterol out of the plaque. This is the main reason why preventive approaches focus on lowering LDL cholesterol (LDL-C) and increasing HDL cholesterol (HDL-C).

ApoB lipoproteins are produced by the liver (VLDL, IDL, LDL) or by the intestine (chylomicrons and their remnants, not present in the fasting serum). VLDL carries the bulk of fasting triglycerides (TG), whereas LDL is a cholesterol-rich particle derived from the complete TG hydrolysis of VLDL. ApoAI lipoproteins (HDL) are considered to be a protective agent against vascular degeneration because they can acquire cholesterol from peripheral tissues, including the atheroma (arterial plaque), and can carry it back into the liver.[7]

Epidemiology has provided strong evidence in support of a direct association between CVD rates and LDL-C levels. This association appears to be due to causation, as it is also found in Mendelian randomization studies where the LDL trait is set at birth by the presence of gene mutations.[8] Studies of LDL-C lowering have incontrovertibly confirmed the causative role of LDL in atherogenesis and its value as a target of therapy.[9] Epidemiology has also strongly linked HDL-C levels and CVD rates in an inverse correlation. However, genetic epidemiology studies have not clearly confirmed the causative nature of the association,[10,11] and clinical trials have yet to provide evidence that raising HDL-C levels reduces CVD rates.[12]

The current risk management guidelines support a multifaceted strategy of early initiation of lifestyle measures, appropriate control of diseases such as hypertension and diabetes, and targeting lipid goals. All guidelines endorse a primary goal of LDL-C reduction to a risk appropriate level, as low as 70 mg/dl in the highest-risk individuals (CVD patients with diabetes or multiple risk factors), and a secondary goal of TG and HDL management (as separate targets or as non-HDL cholesterol).[13]

Goal attainment strategies are additional to classic disease management paradigms that traditionally address severe genetic dyslipidemias such as familial hypercholesterolemia, familial combined dyslipidemia, familial hypertriglyceridemia, chylomicronemia, and low HDL syndromes.

Current Therapeutic Approaches

It is well established that interventions based on dietary changes, increased physical activity, smoking cessation, and weight loss cause only moderate LDL-C lowering—usually no more than 10 %—although more aggressive regimens such as the portfolio diet have shown stronger effects in the short term.[14] In addition, the use of dietary supplements (plant sterols, soy protein, almonds, green tea extract, red yeast rice, polycosanol, etc.) may cause a modest additional LDL-C reduction.[15] Beside lipid management, aggressive lifestyle modifications have been shown to prevent diabetes development in predisposed individuals, and to reduce incidence of CVD among diabetic patients. All lipid-modulating agents currently in use are approved as adjuvant to lifestyle and dietary changes.

Although statins represent more than 90 % of the lipid-lowering market, several other drugs are available for lipid modulation as monotherapy or combination in appropriate patients.

Intestinally Acting Agents

These include the bile acid binding resins, colestipol, cholestyramine, and colesevelam, and the intestinal absorption inhibitor, ezetimibe. These agents reduce LDL cholesterol by 15–20 % at full dose, and have minimal-to-no effects on TG and HDL-C levels. Since there is no redundancy of mechanism of action between the resins and ezetimibe, the two agents could be combined to maximize the non-systemic approach to cholesterol control in statin-resistant patients. Studies have been published on the effectiveness of combining resin therapy and ezetimibe on LDL-C levels,[16] but the resin may interfere with absorption of ezetimibe. Resins have provided evidence of CVD benefits in the general population,[17] whereas ezetimibe has recently been proven to reduce CVD risk in renal patients when used in combination with simvastatin.[18]

Niacin

There are at least 40 preparations of immediate-release, several formulations of slow-release, and one US Food and Drug Administration (FDA)-approved and patent-protected formulation of extended-release niacin. Niacin is vitamin B3 used in supra-physiologic doses. The lipid-modifying effects are seen for dosages above 500 mg/day, and the full dosage of 2,000 mg/day is needed to observe a significant effect on all lipid parameters. Niacin's effect on LDL-C is in the range of 15–20 % lowering for dosages of 2 g/day of slow- or extended-release formulations and 3 g/day of immediate-release formulations. At the same dosages, TG levels are lowered by 20–30 % and HDL-C levels raised by 25–35 %. Niacin can also reduce lipoprotein (a) [Lp(a)] concentrations by 30 % or more. The main obstacle to niacin utilization is the common occurrence of symptomatic side effects, most notably flushing of the face, neck and upper chest. This happens with immediate- and extended-release formulations, and less with slow-release formulations, which instead confer higher likelihood of liver toxicity. A formulation of extended-release niacin combined with an agent that reduces flushing (a prostaglandin receptor antagonist) is available in many countries but not yet in the US.[19] Niacin use has been shown to reduce CVD rates and total mortality.[20,21] In combination with simvastatin, it has proven superior to ezetimibe in reducing carotid intima-media thickness over a period of two years.[22] A large National Institutes of Health (NIH)-funded trial investigating the role of extended-release niacin in combination with simvastatin on CVD rates in a cohort of high-risk patients[23] has recently been halted due to lack of clinical efficacy.[24]

Fibrates

There are three fibrate agents on the US market: generic gemfibrozil, generic fenofibrate, and a patent-protected formulation of fenofibric acid. The fibrates activate the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)α, which causes the upregulation of several genes including some that control lipoprotein metabolism.

The effect of fibrates on LDL-C is highly variable because the majority of patients with high triglycerides have artificially low LDL-C and adjustment of TG produces compensatory elevations in LDL-C. By and large, only modest LDL-C reductions (10 %) are expected by fibrate therapy even in the absence of severe hypertriglyceridemia, and thus these agents are not commonly used for LDL-C management. Type A evidence of CVD risk reduction has been produced with gemfibrozil[25–27] but not with fenofibrate.[28,29] Fenofibric acid has not been studied in clinical trials of CVD risk reduction.

Omega 3 Fatty Acids

Although a staple of CVD risk reduction maneuvers, use of high-dose fish oils for lipid management is reserved for high TG levels. No LDL-C reduction is reported with formulations enriched in both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA),[30,31] whereas DHA-only containing agents claim a small but significant LDL-C reduction effect.[32] Omega 3 fatty acids have provided evidence of benefits on CVD rates, but not through lipid-lowering effects.[33,34]

Statin Therapy

Statins inhibit cholesterol synthesis via blockade of the enzyme 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase. Consequently, the inability of the liver to make its own cholesterol results in the upregulation of LDL receptor expression, which lowers plasma LDL cholesterol levels. Statins can lower LDL-C close to 50 %, and can also cause HDL-C elevations of around 5–10 % and triglyceride reductions of 15–30 %. For several years, there have been six different statins available: three generic (lovastatin, pravastatin, and simvastatin) and three branded (rosuvastatin [Crestor], atorvastatin [Lipitor], and fluvastatin [Lescol]). Three combination products are also available: lovastatin plus extended-release niacin (Advicor), simvastatin plus extended-release niacin (Simcor), and simvastatin plus ezetimibe (Vytorin). A new statin on the US market, pitavastatin (Livalo), is discussed separately below. Several statins have shown strong benefits in terms of CVD risk reduction in different populations,[35] including smokers, hypercholesterolemics, diabetics, metabolic syndrome patients, older subjects, and more recently patients with severe kidney disease.

Efficacy

It is beyond the scope of this short paper to review all the landmark trials that have led to the current acceptance of statins as mandatory agents for CVD risk reduction in most patients. Briefly, the story started in 1994 with the publication of the Scandinavian simvastatin survival study (4S) trial, which showed large mortality benefits from simvastatin 20/40 mg, versus placebo, in survivors of myocardial infarction (MI) with a baseline LDL-C around 190 mg/dl.[36] This was followed by the West-of-Scotland coronary prevention study (WOSCOPS) showing that pravastatin 40 mg, versus placebo, reduced risk of the first MI in healthy subjects with severe hypercholesterolemia (LDL-C around 190 mg/dl).[37] The Cholesterol and recurrent event (CARE) study[38] showed the benefits of pravastatin 40 mg, versus placebo, in reducing recurrent events in coronary artery disease (CAD) patients with mild hypercholesterolemia (LDL-C around 140 mg/dl), while the Air Force/Texas coronary atherosclerosis prevention study (AFCAPS/TexCAPS)[39] showed the value of lovastatin 40 mg in reducing the risk of first CVD event among healthy subjects with mild hypercholesterolemia (LDL-C around 150 mg/dl). The new millennium brought the Heart protection study (HPS),[40] showing that simvastatin 40 mg greatly reduces CVD event rate in high-risk patients, including patients with diabetes, even though baseline LDL-C was only about 120 mg/dl. This study introduced the concept of a lower therapeutic threshold for LDL-C control, as safety and benefits were obvious also for subjects reaching LDL-C below 70 mg/dl. This concept was confirmed and amplified by the Treatment to new targets (TNT) trial, which showed that atorvastatin 80 mg is superior to atorvastatin 10 mg in reducing CVD event rates among high-risk patients with stable coronary disease by virtue of on-treatment LDL-C levels close to the threshold of 70 mg/dl (compared with 100 mg/dl).[41] This same idea was also validated for patients with unstable plaques causing acute coronary syndromes in the Pravastatin or atorvastatin evaluation and infection therapy (PROVE-IT) trial (TIMI-22),[42] which showed the superiority of atorvastatin 80 mg compared with pravastatin 40 mg in reducing the risk of a combined outcome measure including hard endpoints, MI and death, as well as worsening angina and re-hospitalization. The importance of statin therapy in patients with hypertension and diabetes was spectacularly proven with atorvastatin 10 mg, versus placebo, in the Anglo-Scandinavian cardiac outcomes trial (ASCOT)[43] and the Collaborative atorvastatin diabetes study (CARDS)[44] trials, respectively. Both trials were terminated early because of evidence of benefits among the treatment group. This amazing journey ends with the recent publication of the Justification for the use of statins in primary prevention: an Intervention trial evaluating rosuvastatin (JUPITER),[45] showing that rosuvastatin 20 mg significantly reduces CVD risk in an apparently low-risk population characterized by hsCRP levels above the median and normal LDL-C. Interestingly, this study also was terminated early because of evidence of benefits in the treatment group, where nearly 25 % of the subjects reached an LDL-C below 50 mg/dl. Finally, the Study of heart and renal protection (SHARP) trial showed benefits in patients with end-stage renal disease (ESRD), some of them on dialysis, with a 40 mg/dl LDL-C reduction accomplished with the combination of simvastatin 20 mg and ezetimibe 10 mg.[18] The importance of this study lies in the fact that dialysis patients appeared to be the only group resistant to the beneficial effects of statin therapy, as both the Deutsche diabetes dialysestudie (4D) (with atorvastatin 20 mg versus placebo)[46] and A study to evaluate the use of rosuvastatin in subjects on regular hemodialysis: an assessment of survival and cardiovascular events (AURORA) (with rosuvastatin 10 mg versus placebo)[47] had failed to show reduced CVD risk in the treatment group. Meta-analyses encompassing all these trials and many more have confirmed the exceptional value and safety of LDL-C reduction in CVD risk management.[9,35]

Safety

Although not obvious from the results of randomized clinical trials, the use of statins in practice is severely limited by frequent development of muscle-based side effects, ranging from soreness to cramps, and from weakness to pain. These problems, which rarely are accompanied by creatine phosphokinase (CPK) elevations, drive the patient's, and in many instances the physician's, decision to discontinue the medication. For several years now, the most common referral reason to our lipid clinic has been history of intolerance to statins, without CPK elevation. The

Table 1: Effect of Co-administered Drugs on Pitavastatin Systemic Exposure[52]

Co-administered Drug	Dose Regimen	Change in AUC*	Change in C_{max}*
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on day 6	↑ 4.6-fold†	↑ 6.6-fold†
Erythromycin	Pitavastatin 4 mg single dose on day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8-fold†	↑ 3.6-fold†
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29 %	↑ 2.0-fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31 %	↑ 60 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45 %	↑ 31 %
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑ 18 %	↑ 11 %
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2 %	↓ 0.2 %
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6 %	↓ 7 %
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4 %	↓ 9 %
Grapefruit Juice	Pitavastatin 2 mg single dose on day 3 + grapefruit juice for 4 days	↑ 15 %	↓ 12 %
Itraconazole	Pitavastatin 4 mg single dose on day 4 + itraconazole 200 mg daily for 5 days	↓ 23 %	↓ 22 %

**Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e. one-fold = no change). Data presented as percent change represent percent difference relative to pitavastatin alone (i.e. 0 % = no change).*
†Considered clinically significant.
AUC = area under the curve; BID = twice a day; C_{max} = maximum concentration; QD = once a day.

disconnect between clinical trials and practice experience on statin safety is exemplary of the limits of evidence-based medicine on issues of symptomatic side effects, as trial patients, notoriously more engaged in health management and more positive about drug therapy compared with clinic patients, are often selected after run-in periods with the drug and enrolled only if tolerant. A typical scenario is offered by the HPS study, where there was no difference in the prevalence of muscle complaints between subjects taking 40 mg simvastatin and those taking placebo over a period of five years, and only 0.5 % of treatment-assigned subjects discontinued the drug because of muscle problems.[48] Real-world estimates of severe muscle complaints leading to discontinuation of the statin and undertreatment of at-risk subjects place that figure well above 10 %.[49] The other main toxicity problem with statin use is linked to liver function test (LFT) elevations. In people without pre-existing liver problems, elevations in transaminase levels of more than three times the upper limits of normal (>3xULN) sustained over time warrant discontinuation of the statin. In people with pre-existing liver disease, such as the fatty liver of insulin resistance, statin use is contraindicated and close monitoring of LFTs is warranted if decision to treat is made. This safety issue is likely predicted by randomized trials, which have consistently shown a rate of less than 1 % for LFT elevations >3xULN.

A New Statin—Pitavastatin

Pitavastatin was approved in Japan in 2003 and has since been approved in South Korea, Thailand, China, Europe, and the US. The FDA has approved pitavastatin at the doses of 1 mg, 2 mg, and 4 mg for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive to diet to reduce elevated total cholesterol, LDL-C, apoB, and TG, and to increase HDL-C. Pitavastatin has a novel structure (a synthetic cyclopropyl side group) that gives it unique properties to set it apart from other statins, including enhanced potency, minimal cytochrome P450 (CYP) metabolism, increased bioavailability, and reduced risk of CYP-mediated pharmacokinetic interactions. Pitavastatin is a more potent inhibitor of HMG-CoA reductase than simvastatin (>two-fold) and pravastatin (>six-fold), and causes increased LDL receptor mRNA expression, increased degradation of apoB, and reduced secretion of VLDL in human hepatoma HepG2 cells.[50] The effect of pitavastatin on HDL-C may be driven by induced expression of apoAI.[51] Pitavastatin is highly bioavailable (51 %), mostly protein bound (>99 %), and uniquely metabolized.[52] Whereas most statins use the CYP system as the predominant metabolic route, pitavastatin is mostly metabolized by glucuronidation via uridine 5'–diphosphate glucuronosyltransferase (UGT), isoforms 1A3 and 2B7.[52] Pitavastatin does not utilize the CYP3A4 pathway (which metabolizes lovastatin, simvastatin and atorvastatin) and only marginally utilizes CYP2C9 (which metabolizes fluvastatin and rosuvastatin) and, to a lesser extent, CYP2C8.[52,53] Pitavastatin is mostly excreted unchanged in the bile and undergoes entero-hepatic recirculation after intestinal re-absorption.[54] Only a small fraction (<3 %) of pitavastatin is excreted in the urine. In addition, pitavastatin peak plasma concentrations are achieved approximately one hour following oral administration and the mean plasma elimination half-life is approximately 12 hours.[52] Since pitavastatin undergoes only minimal metabolism by CYP, it has a unique drug–drug interaction profile compared with other statins.[53,55] Clinically significant increases in plasma levels of pitavastatin are seen only with cyclosporine (4.6-fold) and erythromycin (2.8-fold), while rifampin, atazanavir, and gemfibrozil have a modest effect (29 %, 31 %, and 45 %, respectively), and itraconazole decreases the area under the curve (AUC) of pitavastatin by 23 % (see *Table 1*).[50,52] Pitavastatin is transported by the organic anion-transporting polypeptides (OATP) 1B1, 1B3, and 2B1, and the sodium taurocholate co-transporting polypeptide (NTCP) from the plasma to the liver, and by breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2) and multidrug resistance protein 1 (MDR1) from the liver to the bile.[56–58] The 4.6-fold increase in AUC for pitavastatin compares to six- and seven-fold increases for atorvastatin and rosuvastatin, respectively.[59,60] Although pitavastatin undergoes minimal metabolism through the CYP system, it must be kept in mind that drug–drug interactions may involve the interaction of influx and/or efflux transporters. Pitavastatin is contraindicated in patients taking cyclosporine. Also, the FDA recommends a maximum dose of 1 mg and 2 mg, respectively, for patients taking erythromycin or rifampin.

Comparative Efficacy of Available Statins

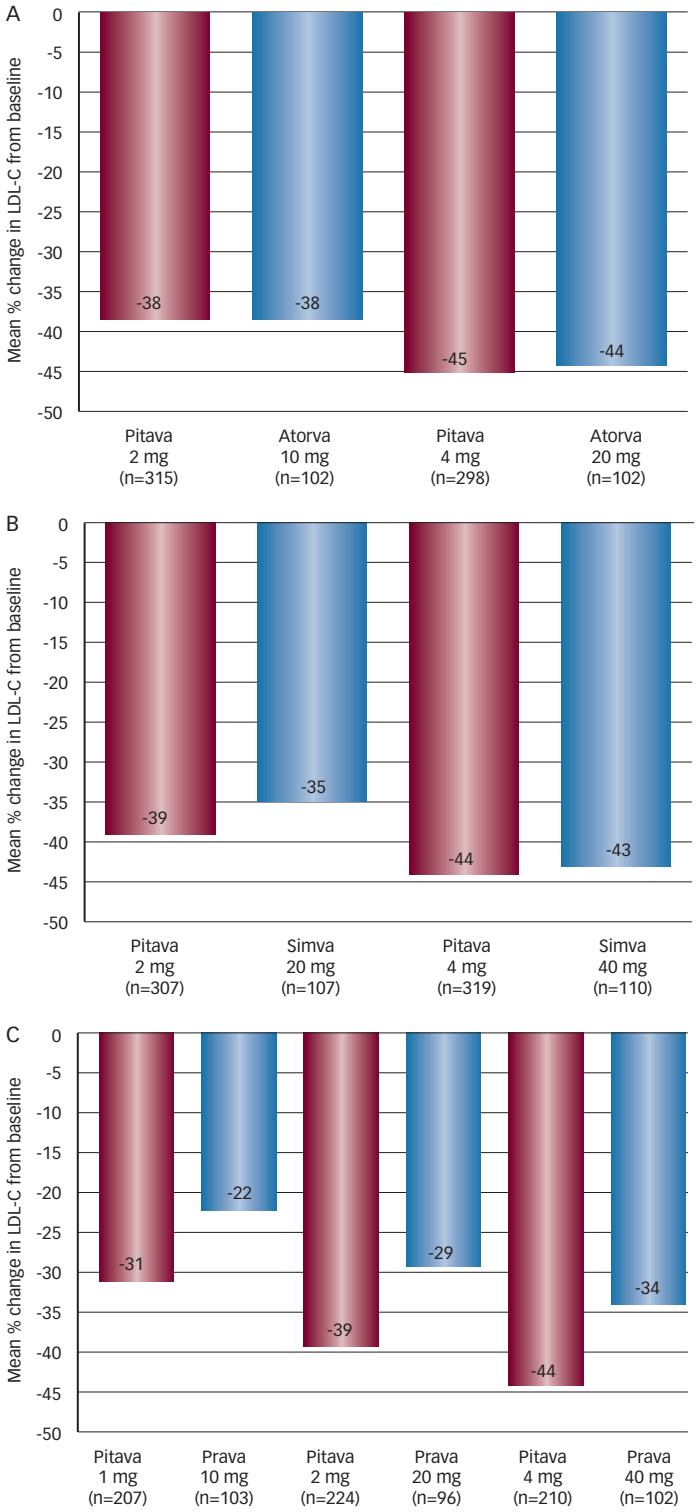
A series of phase III 12-week studies were performed to compare the lipid-lowering efficacy of pitavastatin with that of equipotent doses of

atorvastatin, simvastatin, and pravastatin based on LDL-C reduction. These studies aimed at testing the non-inferiority of pitavastatin versus the comparator on mean per cent change in LDL-C, defined as a differential of less than 6 % in LDL-C reduction in favor of the comparator.[61] Study drug comparisons were pitavastatin 1 mg versus pravastatin 10 mg; pitavastatin 2 mg versus atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 20 mg; and pitavastatin 4 mg versus atorvastatin 20 mg, simvastatin 40 mg, and pravastatin 40 mg. The studies confirmed that the mean per cent changes in LDL-C were not statistically different for the dose comparisons of pitavastatin 2 mg and 4 mg with atorvastatin 10 mg and 20 mg, and simvastatin 20 mg and 40 mg, whereas LDL-C reductions were superior to pravastatin, demonstrating approximately 10 % greater LDL-C reduction across all three pair-wise dose comparisons. Hence, studies demonstrated non-inferiority between pitavastatin and atorvastatin or simvastatin, and superiority for pitavastatin versus pravastatin (see *Figure 1*). The 1 mg dose of pitavastatin has lipid effects similar to those of pravastatin 40 mg. In these studies, the most common adverse reactions were constipation, back pain, diarrhea, pain in extremities and myalgia. Discontinuation rates were low with the most common reasons being elevated CPK (0.6 %) and myalgia (0.5 %) at the highest pitavastatin dose. In other studies performed outside the US, such as the Collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA) trial, subjects taking pitavastatin 2 mg or atorvastatin 10 mg were followed for 12 weeks for efficacy and safety parameters. There were no significant differences between the two regimens in non-HDL-C, total cholesterol, LDL-C, and TG changes, whereas HDL-C was significantly increased, though modestly, only by pitavastatin (p=0.033). There were no safety concerns with either drug, but LFT levels on average increased with atorvastatin and did not with pitavastatin.[62] Another study, a parallel group comparison of the tolerability and effects of pitavastatin and atorvastatin on HDL-C levels and glucose metabolism in Japanese patients with elevated levels of LDL-C and glucose intolerance (PIAT), compared pitavastatin 2 mg and atorvastatin 10 mg in 207 patients with pre-diabetes over a period of 52 weeks. Both statins produced significant lipid changes compared with baseline, but atorvastatin was superior to pitavastatin on LDL-C, non-HDL-C, and apoB reduction, whereas pitavastatin was superior to atorvastatin on HDL-C increases and increases in apoAI levels.[63] A recent *post hoc* analysis of the change in fasting glucose levels in patients with type 2 diabetes mellitus showed a significant increase with atorvastatin over 12 weeks versus no change with pitavastatin.[64] A surveillance study, LIVALO effectiveness and safety (LIVES), has followed nearly 20,000 patients on pitavastatin for two years. Most subjects were on the 1 mg or 2 mg dose. Lipid changes were in line with those obtained in the different phase III trials, and safety records showed a 0.14 % prevalence of serious adverse events and a 7.4 % discontinuation rate based on any adverse event. Increases in CPK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were reported in 2.7 %, 1.8 %, and 1.5 % of subjects, respectively.[65]

Pitavastatin and Clinical Endpoints

Pitavastatin has yet to show reduction in CV risk either in stable CAD patients, subjects with acute coronary syndrome (ACS), or in primary prevention settings. The Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS) study has,

Figure 1: Low-density Lipoprotein Cholesterol Reduction in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia After 12 Weeks—(A) Comparison with Atorvastatin, (B) Simvastatin, and (C) Patients 65 Years of Age or Older, Comparison with Pravastatin



Atorva = atorvastatin; LDL-C = low-density lipoprotein cholesterol; Pitava = pitavastatin; Prava = pravastatin; Simva = simvastatin.
Data from references 52, 77, and 78.

however, shown non-inferiority of pitavastatin 4 mg versus atorvastatin 20 mg in halting progression and inducing regression of non-culprit plaque volume after up to one year of therapy.[66,67] Both interventions induced significant regression, with coronary plaque volume reduced by 17–18 %. In a 52-week, open-label study of 90 ACS patients (TOGETHAR), pitavastatin 2 mg significantly decreased the degree of yellow plaque by angioscopy but had no effect on intravascular ultrasound (IVUS) parameters such as segment diameter. The grade of yellow plaque was significantly reduced from 2.9±0.8 (95 % confidence interval [CI] = 2.7–3.1) at baseline to 2.6±0.7 (95 % CI = 2.4–2.8, p<0.04) at week 52.[68] A randomized multicenter study comparing pitavastatin 1 mg and 4 mg doses, currently in the enrollment phase, will measure CVD outcomes after three–five years of treatment.[69]

An interesting link between pitavastatin and adipocyte biology may open a new area of investigation for this drug. A recent study has shown that pitavastatin upregulates expression of hormone-sensitive lipase, prevents TG accumulation, and reduces the expression of the adipocyte fatty acid binding protein 2 (aP2) in obese mice.[70] Since aP2 is a major transductor of the effects of insulin resistance on the vessel wall,[71–73] it is possible that pitavastatin may improve insulin sensitivity and exert an enhanced vascular protection in patients with diabetes. It is worth noting that two recent large meta-analyses of statin trials actually suggest a diabetogenic effect of statins.[74,75] Against this background, pitavastatin may show divergence of effects with other statins, an important clinical niche of use. In the LIVES surveillance program, average glycosylated hemoglobin (HbA_{1c}) decreased over two years in the 6,000 or so patients on pitavastatin.[65] This issue will be studied prospectively in the Japan prevention trial of diabetes by pitavastatin in patients with impaired glucose tolerance (J-PREDICT), where pitavastatin will be compared with lifestyle measures for preventive effects against the incidence of diabetes in a population with impaired glucose tolerance at baseline.[76]

Summary and Conclusions

Pitavastatin is the latest addition to the statin armamentarium. It has all the lipid indications of the other statins, but lacks indications for CVD risk reduction. Because it is more potent than the other statins, it is available in much lower doses. For LDL-C reduction, the recommended starting dose of 2 mg is comparable to 20 mg of simvastatin and 10 mg of atorvastatin, and more potent than 20 mg of pravastatin. Pitavastatin 2 mg is expected to reduce LDL-C by 39 %, apoB by 31 %, total cholesterol by 28 %, and TG by 16 %, while raising HDL-C by 6 %. In phase III clinical trials, pitavastatin 4 mg caused LDL-C reduction up to 45 %. The novel molecular structure of pitavastatin determines a unique metabolism, with little processing by the CYP system and none by CYP3A4. This translates into likely diminished pharmacokinetic interactions and a safety profile theoretically superior to that of other statins. Preliminary vascular investigations have provided suggestions of benefits in line with those obtained by other statins. A unique effect on adipocyte function with pitavastatin poses the basis to test a possible increased functionality to regulate glucose metabolism or protect patients with diabetes from vascular events. ■

1. Libby P, Ridker PM, Hansson GK, Inflammation in atherosclerosis: from pathophysiology to practice, *J Am Coll Cardiol*, 2009;54:2129–38.
2. Heron M, Hoyert DL, Murphy SL, et al., Deaths: final data for 2006, *Natl Vital Stat Rep*, 2009;57:1–134.
3. Tracy RE, Newman WP 3rd, Wattigney WA, et al., Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa Heart Study, *Am J Med Sci*, 1995;310(Suppl. 1):S37–41.
4. Vogel RA, Benitez RM, Noninvasive assessment of cardiovascular risk: from Framingham to the future, *Rev Cardiovasc Med*, 2000;1:34–42.
5. Ridker PM, Buring JE, Rifai N, et al., Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score, *JAMA*, 2007;297:611–9.
6. Linton MF, Fazio S, A practical approach to risk assessment to prevent coronary artery disease and its complications, *Am J Cardiol*, 2003;92:19i–26i.
7. Fazio S, Linton MF, High-density lipoprotein therapeutics and cardiovascular prevention, *J Clin Lipidol*, 2010;4:411–9.
8. Cohen JC, Boerwinkle E, Mosley TH Jr., et al., Sequence variations in PCSK9, low LDL, and protection against coronary heart disease, *N Engl J Med*, 2006;354:1264–72.
9. Baigent C, Keech A, Kearney PM, et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, *Lancet*, 2005;366:1267–78.
10. Fazio S, Linton MF, Sorting out the complexities of reverse cholesterol transport: CETP polymorphisms, HDL, and coronary disease, *J Clin Endocrinol Metab*, 2006;91:3273–5.
11. Fazio S, Linton MF, Elevated high-density lipoprotein (HDL) levels due to hepatic lipase mutations do not reduce cardiovascular disease risk: another strike against the HDL dogma, *J Clin Endocrinol Metab*, 2009;94:1081–3.
12. Barter P, Lessons learned from the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, *Am J Cardiol*, 2009;104:10E–5E.
13. Ali YS, Linton MF, Fazio S, Targeting cardiovascular risk in patients with diabetes: management of dyslipidemia, *Curr Opin Endocrinol Diabetes Obes*, 2008;15:142–6.
14. Gigleux I, Jenkins DJ, Kendall CW, et al., Comparison of a dietary portfolio diet of cholesterol-lowering foods and a statin on LDL particle size phenotype in hypercholesterolaemic participants, *Br J Nutr*, 2007;98:1229–36.
15. Houston MC, Fazio S, Chilton FH, et al., Nonpharmacologic treatment of dyslipidemia, *Prog Cardiovasc Dis*, 2009;52:61–94.
16. Bays H, Rhyne J, Abby S, et al., Lipid-lowering effects of colesevelam HCl in combination with ezetimibe, *Curr Med Res Opin*, 2006;22:2191–200.
17. Rifkind BM, Lipid Research Clinics Coronary Primary Prevention Trial: results and implications, *Am J Cardiol*, 1984;54:30C–4C.
18. Baigent C, Landray MJ, Reith C, et al., The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial, *Lancet*, 2011;377:2181–92.
19. Felts AS, Molecule of the Month. TREDAPTIVE (nicotinic acid/laropiprant): a new lipid-modifying therapy for the treatment of LDL-C, HDL-C and triglycerides, *Curr Top Med Chem*, 2008;8:1310.
20. Coronary Drug Project report on clofibrate and niacin, *Atherosclerosis*, 1978;30:239–40.
21. Canner PL, Berge KG, Wenger NK, et al., Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin, *J Am Coll Cardiol*, 1986;8:1245–55.
22. Taylor AJ, Villines TC, Stanek EJ, et al., Extended-release niacin or ezetimibe and carotid intima-media thickness, *N Engl J Med*, 2009;361:2113–22.
23. NCT00120289, Niacin Plus Statin to Prevent Vascular Events, Available at: www.clinicaltrials.gov/ct2/show/NCT00120289 (accessed June 16, 2011).
24. NHLBI, NIH stops clinical trial on combination cholesterol treatment. National Heart, Lung and Blood Institute. Press release 2011.
25. Frick MH, Elo O, Haapa K, et al., Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease, *N Engl J Med*, 1987;317:1237–45.
26. Robins SJ, Collins D, Wittes JT, et al., Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial, *JAMA*, 2001;285:1585–91.
27. Tenkanen L, Manttari M, Kovanen PT, et al., Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study, *Arch Intern Med*, 2006;166:743–8.
28. Ginsberg HN, Elam MB, Lovato LC, et al., Effects of combination lipid therapy in type 2 diabetes mellitus, *N Engl J Med*, 2010;362:1563–74.
29. Keech A, Simes RJ, Barter P, et al., Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial, *Lancet*, 2005;366:1849–61.
30. Barter P, Ginsberg HN, Effectiveness of combined statin plus omega-3 fatty acid therapy for mixed dyslipidemia, *Am J Cardiol*, 2008;102:1040–5.
31. Davidson MH, Stein EA, Bays HE, et al., Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study, *Clin Ther*, 2007;29:1354–67.
32. Milte CM, Coates AM, Buckley JD, et al., Dose-dependent effects of docosahexaenoic acid-rich fish oil on erythrocyte docosahexaenoic acid and blood lipid levels, *Br J Nutr*, 2008;99:1083–8.
33. Barzi F, Woodward M, Marfisi RM, et al., Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial, *Eur J Clin Nutr*, 2003;57:604–11.
34. Jacobson TA, Beyond lipids: the role of omega-3 fatty acids from fish oil in the prevention of coronary heart disease, *Curr Atheroscler Rep*, 2007;9:145–53.
35. Baigent C, Blackwell L, Emberson J, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet*, 2010;376:1670–81.
36. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), *Lancet*, 1994;344:1383–9.
37. Shepherd J, Cobbe SM, Ford I, et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group, *N Engl J Med*, 1995;333:1301–7.
38. Sacks FM, Pfeffer MA, Moye LA, et al., The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators, *N Engl J Med*, 1996;335:1001–9.
39. Downs JR, Clearfield M, Weis S, et al., Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study, *JAMA*, 1998;279:1615–22.
40. Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, *Lancet*, 2002;360:7–22.
41. LaRosa JC, Grundy SM, Waters DD, et al., Intensive lipid lowering with atorvastatin in patients with stable coronary

disease, *N Engl J Med*, 2005;352:1425–35.
42. Cannon CP, Braunwald E, McCabe CH, et al., Intensive versus moderate lipid lowering with statins after acute coronary syndromes, *N Engl J Med*, 2004;350:1495–504.
43. Sever PS, Dahlof B, Poulter NR, et al., Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial, *Lancet*, 2003;361:1149–58.
44. Colhoun HM, Betteridge DJ, Durrington PN, et al., Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial, *Lancet*, 2004;364:685–96.
45. Ridker PM, Danielson E, Fonseca FA, et al., Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, *N Engl J Med*, 2008;359:2195–207.
46. Wanner C, Krane V, Marz W, et al., Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis, *N Engl J Med*, 2005;353:238–48.
47. Fellstrom BC, Jardine AG, Schmieder RE, et al., Rosuvastatin and cardiovascular events in patients undergoing hemodialysis, *N Engl J Med*, 2009;360:1395–407.
48. Gotto AM Jr., Risks and benefits of continued aggressive statin therapy, *Clin Cardiol*, 2003;26:III3–12.
49. Harper CR, Jacobson TA, Evidence-based management of statin myopathy, *Curr Atheroscler Rep*, 2010;12:322–30.
50. Catapano AL, Pitavastatin – pharmacological profile from early phase studies, *Atheroscler Suppl,* 2010;11:3–7.
51. Maejima T, Yamazaki H, Aoki T, et al., Effect of pitavastatin on apolipoprotein A-I production in HepG2 cell, *Biochem Biophys Res Commun*, 2004;324:835–9.
52. Kowa, LIVALO [package insert]. Montgomery, AL: Kowa Pharmaceuticals America, Inc., 2010.
53. Fujino H, Yamada I, Kojima J, et al., Studies on the metabolic fate of NK-104, a new inhibitor of HMG-CoA reductase (5): In vitro metabolism and plasma protein binding in animals and human, *Xenobio Metabol Dispos*, 1999;14:415–24.
54. Kojima J, Ohshima T, Yoneda M, et al., Effect of biliary excretion on the pharmacokinetics of pitavastatin (NK-104) in dogs, *Xenobio Metabol Dispos*, 2001;16:497–502.
55. Fujino H, Yamada I, Shimada S, et al., Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: human UDP-glucuronosyltransferase enzymes involved in lactonization, *Xenobiotica*, 2003;33:27–41.
56. Fujino H, Saito T, Ogawa S, et al., Transporter-mediated influx and efflux mechanisms of pitavastatin, a new inhibitor of HMG-CoA reductase, *J Pharm Pharmacol*, 2005;57:1305–11.
57. Hirano M, Maeda K, Matsushima S, et al., Involvement of BCRP (ABCG2) in the biliary excretion of pitavastatin, *Mol Pharmacol*, 2005;68:800–7.
58. Hirano M, Maeda K, Shitara Y, et al., Drug-drug interaction between pitavastatin and various drugs via OATP1B1, *Drug Metab Dispos*, 2006;34:1229–36.
59. Asberg A, Hartmann A, Fjeldsa E, et al., Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients, *Am J Transplant*, 2001;1:382–6.
60. Simonson SG, Raza A, Martin PD, et al., Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine, *Clin Pharmacol Ther*, 2004;76:167–77.
61. Betteridge J, Pitavastatin – results from phase III & IV, *Atheroscler Suppl*, 2010;11:8–14.
62. Yokote K, Bujo H, Hanaoka H, et al., Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study), *Atherosclerosis*, 2008;201:345–52.
63. 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;30:1089–101.
64. Sponseller CA GJ, Zhu B, Yu CY, Hounslow N, Kryzhanovski VA, 60th Annual Scientific Sessions & Expo (ACC); New Orleans, LA, USA 2011.
65. Kurihara Y, Douzono T, Kawakita K, et al., A large-scale, long-term, prospective post-marketing surveillance of pitavastatin (LIVALO® Tablet) – LIVALO Effectiveness and Safety (LIVES) Study, *Jpn Pharmacol Ther*, 2008;36:709–31.
66. Hiro T, Kimura T, Morimoto T, et al., 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;54:293–302.
67. Miyauchi K, Kimura T, Morimoto T, et al., Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS): rationale and design, *Circ J*, 2006;70:1624–8. Erratum in *Cir J*, 2007;71:172.
68. Kodama K, Komatsu S, Ueda Y, et al., Stabilization and regression of coronary plaques treated with pitavastatin proven by angioscopy and intravascular ultrasound—the TOGETHAR trial, *Circ J*, 2010;74:1922–8.
69. NCT01042730, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD), Available at: www.clinicaltrials.gov/ct2/show/NCT01042730 (accessed June 16, 2011).
70. Ishihara Y, Ohmori K, Mizukawa M, et al., Beneficial direct adipotropic actions of pitavastatin in vitro and their manifestations in obese mice, *Atherosclerosis*, 2010;212:131–8.
71. Boord JB, Maeda K, Makowski L, et al., Combined adipocyte-macrophage fatty acid-binding protein deficiency improves metabolism, atherosclerosis, and survival in apolipoprotein E-deficient mice, *Circulation*, 2004;110:1492–8.
72. Erbay E, Babaev VR, Mayers JR, et al., Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis, *Nat Med*, 2009;15:1383–91.
73. Furuhashi M, Tuncman G, Gorgun CZ, et al., Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2, *Nature*, 2007;447:959–65.
74. Rajpathak SN, Kumbhani DJ, Crandall J, et al., Statin therapy and risk of developing type 2 diabetes: a meta-analysis, *Diabetes Care*, 2009;32:1924–9.
75. Sattar N, Preiss D, Murray HM, et al., Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, *Lancet*, 2010;375:735–42.
76. NCT00301392, Japan Prevention Trial of Diabetes by Pitavastatin in Patients With Impaired Glucose Tolerance (J-PREDICT). Available at: www.clinicaltrials.gov/ct2/show/NCT00301392 (accessed June 16, 2011).
77. Budinski D, Arneson V, Hounslow N, et al., Pitavastatin compared with atorvastatin in primary hypercholesterolemia or combined dyslipidemia, *Clin Lipidol*, 2009;4:291–302.
78. Ose L, Budinski D, Hounslow N, et al., Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia, *Curr Med Res Opin*, 2009;25:2755–64. Erratum in 2010;26:1046.