

# Place of pitavastatin in the statin armamentarium: promising evidence for a role in diabetes mellitus

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**Abstract:** Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, known as statins, have revolutionized the treatment of hypercholesterolemia and coronary artery disease prevention. However, there are considerable issues regarding statin safety and further development of residual risk control, particularly for diabetic and metabolic syndrome patients. Pitavastatin is a potent statin with low-density lipoprotein (LDL) cholesterol-lowering effects comparable to those of atorvastatin or rosuvastatin. Pitavastatin has a high-density lipoprotein (HDL) cholesterol raising effect, may improve insulin resistance, and has little influence on glucose metabolism. Considering these factors along with its unique pharmacokinetic properties, which suggest minimal drug–drug interaction, pitavastatin could provide an alternative treatment choice, especially in patients with glucose intolerance or diabetes mellitus. Many clinical trials are now underway to test the clinical efficacy of pitavastatin in various settings and are expected to provide further information.

**Keywords:** HMG-CoA reductase inhibitor, pitavastatin, efficacy, safety, diabetes mellitus

## Introduction

Statins can competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, resulting in an effective decrease of low-density lipoprotein (LDL) cholesterol levels, and their use has been proved to reduce major cardiovascular events in both primary and secondary prevention.<sup>1</sup> Since 1973 when Akira Endo discovered the first statin, ML236B (compactin or mevastatin) in Japan, a variety of statins have been developed all over the world.<sup>2</sup> Pitavastatin (LIVALO® Tablet) is a synthetic statin developed by Nissan Chemical Industries Ltd (Tokyo, Japan), and Kowa Co Ltd (Nagoya, Japan). In Japan, the usual dose of pitavastatin is 1–2 mg/day, and the maximum dose is 4 mg/day. Pitavastatin appeared first on the Japanese market in September 2003, in Korea in July 2005, Thailand in January 2008, China in July 2009, and the US in June 2010. Pitavastatin will appear on the European market in 2011.

Recently, the prevalence of diabetes mellitus has greatly increased in Japan as well as in other industrialized countries, and prevention of coronary artery disease in diabetics has become an emerging issue to be resolved. One of the characteristics of patients with diabetes mellitus is impaired insulin secretion. Their beta cells cannot fully compensate for the insulin resistance caused by various environmental factors, and therefore they easily fall into chronic insulin insufficiency. In this article, we review clinical evidence for the use of pitavastatin in the treatment of hypercholesterolemia and in the prevention of atherosclerotic cardiovascular

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diseases, especially focusing on efficacy in patients with diabetes mellitus, who are an important target population for statin treatment.

## Pharmacokinetic and pharmacodynamic properties

### Pharmacokinetic properties

Pitavastatin is distributed selectively to the target organ, the liver, and pharmacokinetic studies in rats conducted using  $^{14}\text{C}$ -pitavastatin have confirmed approximately 54 times greater radioactivity in the liver than in the serum<sup>3</sup>. Pitavastatin is a lipophilic statin. Its bioavailability is about 60%,  $t_{\text{max}}$  is 0.5–0.8 hours,  $t_{1/2}$  is 11 hours, and the urinary excretion rate of both pitavastatin and its lactone form are less than 2%. Pitavastatin shows enterohepatic circulation and is excreted with the feces. Pitavastatin is minimally metabolized by liver cytochrome P450 (CYP), which seems a favorable feature in terms of CYP-mediated drug–drug interaction. The CYP metabolic properties of pitavastatin are similar to those of pravastatin and rosuvastatin, and it is classified as a non-CYP metabolizable type (Table 1).<sup>4</sup>

### Pharmacodynamic properties

Pitavastatin has a characteristic structure consisting of a heptenoate basic structure with a quinoline ring, moieties

of fluorophenyl and a cyclopropyl side chain (Figure 1),<sup>5</sup> which provides optimal activity as a HMG-CoA reductase inhibitor and better drug absorption. Figure 2 shows simulation imaging of the binding mode with the active site on the reductase.<sup>6</sup> Pitavastatin inhibits HMG-CoA reductase and synthesis of cholesterol in the liver like other statins, however, the  $\text{IC}_{50}$  for the inhibition of cholesterol synthesis from [ $^{14}\text{C}$ ] acetic acid in the cultured human hepatoma cell line HepG2 was found to be 5.8 nM, being 2.9-fold higher than that of simvastatin and 5.7-fold higher than that of atorvastatin.<sup>7</sup> The  $\text{ED}_{50}$  of oral pitavastatin for inhibition of sterol synthesis in the rat liver was 0.13 mg/kg, being 2.8-fold and 18-fold higher, respectively, than that of simvastatin and that of pravastatin.<sup>8</sup>

## Clinical studies of pitavastatin

### Efficacy

#### Improvement of dyslipidemia

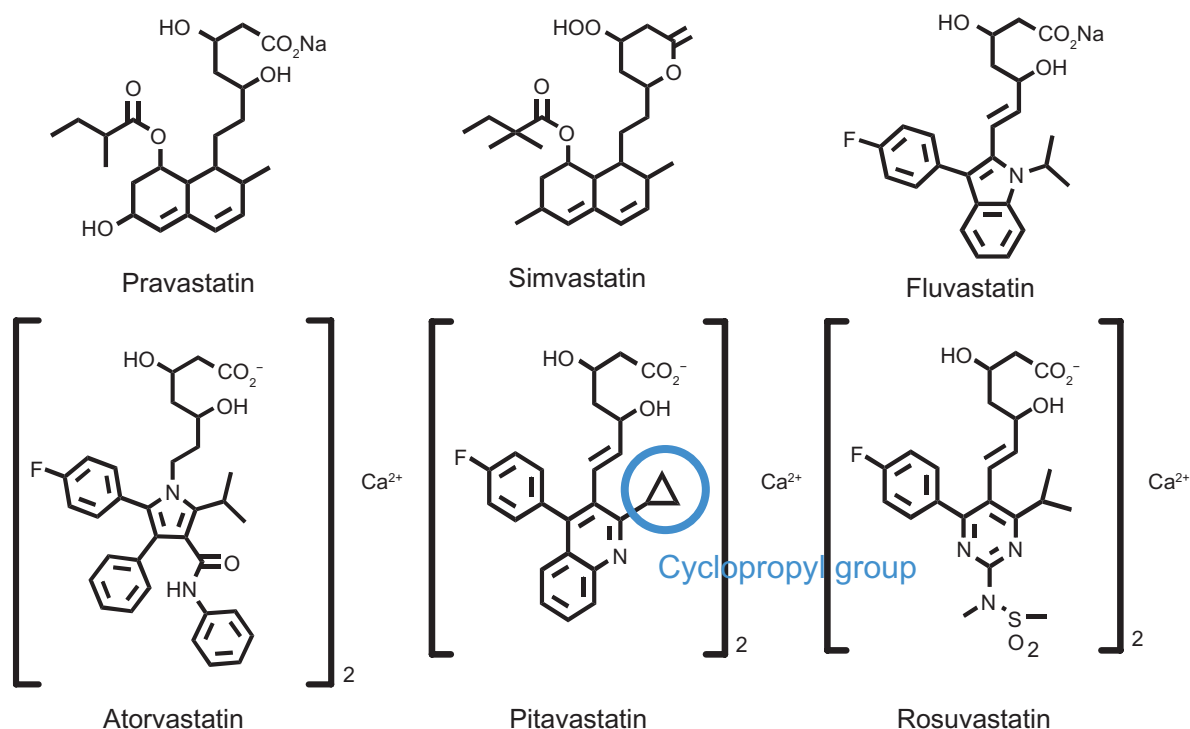
#### Effects on LDL cholesterol

In the Steno-2 Study, intensive, multifactorial care of patients with type 2 diabetes led to reduction of rates of death and cardiovascular disorders.<sup>9,10</sup> By contrast, in the ACCORD trial, intensive glucose lowering in type 2 diabetics increased mortality and did not significantly reduce major cardiovascular events.<sup>11</sup> In the ADVANCE trial, intensive glucose

**Table 1** Pharmacokinetic parameters of statins

Statin	Pitavastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Molecular weight	881	1209	433.5	405	446.5	1001	418.15
Origin	Synthetic	Synthetic	Synthetic	Microbial	Semi-synthetic (microbial origin)	Synthetic	Semi-synthetic (microbial origin)
Racemic	No	No	Yes	No	No	No	No
Prodrug	No	No	No	Yes	No	No	Yes
Log <i>P</i>	1.49	1.11	1.27	1.70	−0.84	−0.33	1.60
Absorption (%)	80	30	98	31	37	50	65–85
Hepatic excretion (%)	NA	>70	68	>70	66	90	78–87
Bioavailability (%)	>60	12	10–35	<5	17	20	<5
Effect of food on bioavailability (%)	No	Yes (↓ 13)	Yes (↓ 15–25)	Yes (↑ 50)	Yes (↓ 30)	No	No
Protein binding (%)	96	>98	>98	96–98.5	43–54	88	>95
$T_{\text{max}}$	0.5–0.8	2.0–4.0	0.5–1.5	2.8	0.9–1.6	3	1.3–2.4
$T_{1/2}$	11	11–30	0.5–2.3	2.5–3.0	0.8–3.0	20	1.9–3.0
Renal excretion	<2	2	6	30	60	10	13
50% inhibitory concentration (nmol/L)	6.8	15.2	17.9	2.7–11.1	55.1	12	18.1
Lipid-lowering	No	Yes, active	Yes, mainly inactive	Yes	Yes, mainly active	No	Yes
Metabolites							
Range of dose (mg)	1–4	10–80	20–80	10–80	5–40	5–80	5–80
CYP isoforms primarily involved with metabolic pathway	CYP2C9	CYP3A4	CYP2C9	CYP3A4	CYP3A4	CYP2C9	CYP3A4
	Minimally				Minimally	Minimally	

**Note:** Log *P*, logarithm of base 10 of the n-octanol/water partition coefficient of active hydroxy forms of statins. Adapted from Saito Y.<sup>4</sup>



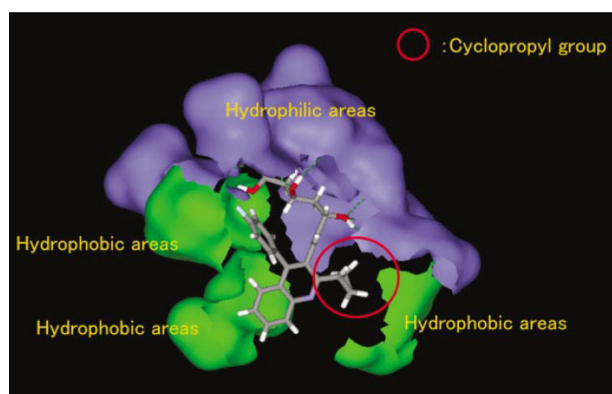
**Figure 1** Chemical structures of statins. The circled moiety on pitavastatin denotes the unique cyclopropyl group. Adapted from Catapano.<sup>5</sup>

lowering in type 2 diabetic subjects significantly reduced the composite outcome of major macrovascular or microvascular events, but there was no significant reduction in major macrovascular events.<sup>12</sup>

Contrary to this controversy over the effects of intensive glucose lowering on cardiovascular events, the importance of the management of LDL cholesterol in diabetes mellitus has already been shown by many. In the United Kingdom prospective diabetes study (UKPDS 23)<sup>13</sup> and the Japan Diabetes Complications Study (JDCS 9th),<sup>14</sup> LDL cholesterol was the top-ranked risk factor for coronary artery disease

in type 2 diabetes. The Cholesterol Treatment Trialists' (CTT) collaborators reported the importance of LDL cholesterol lowering therapy with statins in 18,686 people with diabetes.<sup>15</sup> Based on these findings, in the Japan Atherosclerosis Society (JAS) Guideline, diabetic patients are classified as Category III (high-risk group) and their LDL cholesterol treatment goal is less than 120 mg/dL, or less than 100 mg/dL if they have coronary artery disease.<sup>16</sup> In the United States, the consensus conference report from the ADA/ACC recommended that the LDL cholesterol goal of the highest-risk patients, with established diabetes with one or more additional major cardiovascular disease risk factor, should be less than 70 mg/dL.<sup>17</sup> In the prevention of coronary artery diseases in diabetic patients, it may be important to pay attention not only to glycemic control but also to lipid profile.

To achieve these LDL cholesterol goals, intensive medication in which statins play a pivotal role is required. Six statins are currently available in the Japanese market and pitavastatin is one of the three potent statins. In the Japanese dose-response trial, the LDL cholesterol lowering effect of pitavastatin after 12 weeks was 34% (n = 81) at a dose of 1 mg, 42% (n = 75) at a dose of 2 mg, and 47% (n = 76) at a dose of 4 mg.<sup>18</sup> In the LIVES Study, a large-scale, prospective post-marketing surveillance of pitavastatin<sup>19</sup> and the JAPAN-ACS study, a prospective, randomized, open-label,



**Figure 2** Pitavastatin in the complex with active site of human HMG-CoA reductase. Adapted from Yamazaki et al.<sup>6</sup>

parallel group study with blind endpoint evaluation at 33 centers in Japan,<sup>20</sup> the LDL cholesterol lowering effect among diabetic patients was almost the same as that in nondiabetic subjects. Nomura et al reported that 6 months administration of pitavastatin at 2 mg/day significantly reduced LDL cholesterol, from 155 to 88 mg/dL, in 45 diabetic patients (Figure 3).<sup>21</sup> In the CHIBA Study, a randomized, multicentered, open-label study comparing the efficacy and safety of pitavastatin with that of atorvastatin in Japanese patients with hypercholesterolemia, 12 weeks administration of pitavastatin 2 mg/day ( $n = 126$ ) significantly reduced LDL cholesterol by 42.6%, which was almost the same reduction produced by atorvastatin 10 mg/day ( $n = 125$ ).<sup>22</sup>

In Europe, a randomized, double-blind, 12-week study to compare pitavastatin and simvastatin reported that the administration of pitavastatin 2 mg/day reduced LDL cholesterol by 39.0% ( $n = 307$ ), which was significantly greater than that achieved with simvastatin 20 mg/day (35.0%,  $n = 107$ ), and that the administration of pitavastatin 4 mg/day reduced LDL cholesterol by 44.0% ( $n = 319$ ), which was comparable to that of simvastatin 40 mg/day (42.8%,  $n = 110$ ).<sup>23</sup> Another European randomized, double-blind, comparative study reported that 12-week administration of pitavastatin 2 mg/day reduced LDL cholesterol by 37.9% ( $n = 315$ ), which was comparable to that of atorvastatin 10 mg/day (37.8%,  $n = 102$ ), and that the administration of pitavastatin 4 mg/day reduced LDL cholesterol by 44.6% ( $n = 298$ ) which was comparable to that of atorvastatin 20 mg/day (43.5%,  $n = 102$ ).<sup>24</sup>

### High-density lipoprotein (HDL) cholesterol

Insulin resistance causes various dyslipidemic states such as increase of small dense LDL particles, remnant lipoprotein,

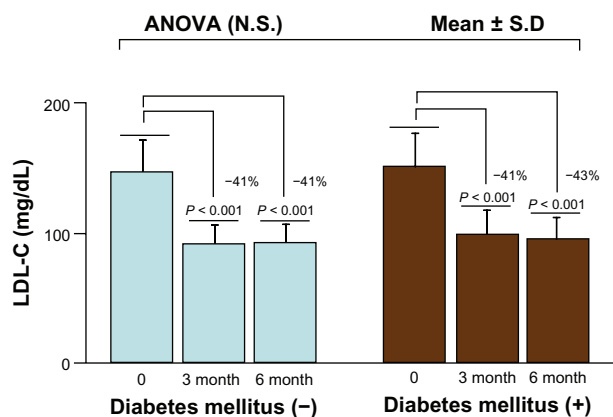
and decrease of HDL cholesterol. In diabetes mellitus, reduced activity of lipoprotein lipase (LPL) leads to low HDL cholesterol because of impaired catabolism of VLDL.<sup>25</sup> In addition, it has recently been reported that low HDL cholesterol in type 2 diabetic patients is associated with hypoapoproteinemia.<sup>26</sup> In diabetes mellitus, the management of low HDL cholesterol is important. In the subanalysis of the J-LIT study, an increase of 10 mg/dL in HDL cholesterol was associated with a 34.9% decrease in the risk of coronary events in type 2 diabetes.<sup>27</sup>

One of the most striking characteristics of pitavastatin is the HDL cholesterol increase which continues for about 2 years from the start of administration. Pitavastatin 1–4 mg/day significantly increased the serum HDL cholesterol levels in a long-term (52 weeks) administration study.<sup>28</sup> In the LIVES Study, 2-year treatment with pitavastatin 1–4 mg/day significantly increased serum HDL cholesterol levels from 58.8 to 60.8 mg/dL (+5.9%) in all subjects ( $n = 3427$ ) and from 35.1 to 43.3 mg/dL (+24.6%) in low HDL cholesterol (<40 mg/dL) subjects ( $n = 346$ ) (Figure 4).<sup>29</sup> In the PIAT Study to compare pitavastatin 2 mg/day ( $n = 88$ ) and atorvastatin 10 mg/day ( $n = 85$ ), pitavastatin gave greater increases in HDL cholesterol and ApoA-1 levels than atorvastatin after 1 year of treatment.<sup>30</sup> In the European 1-year trial ( $n = 1346$ ), pitavastatin 4 mg/day increased HDL cholesterol from 50.5 to 57.0 mg/dL (+14.3%).<sup>31</sup>

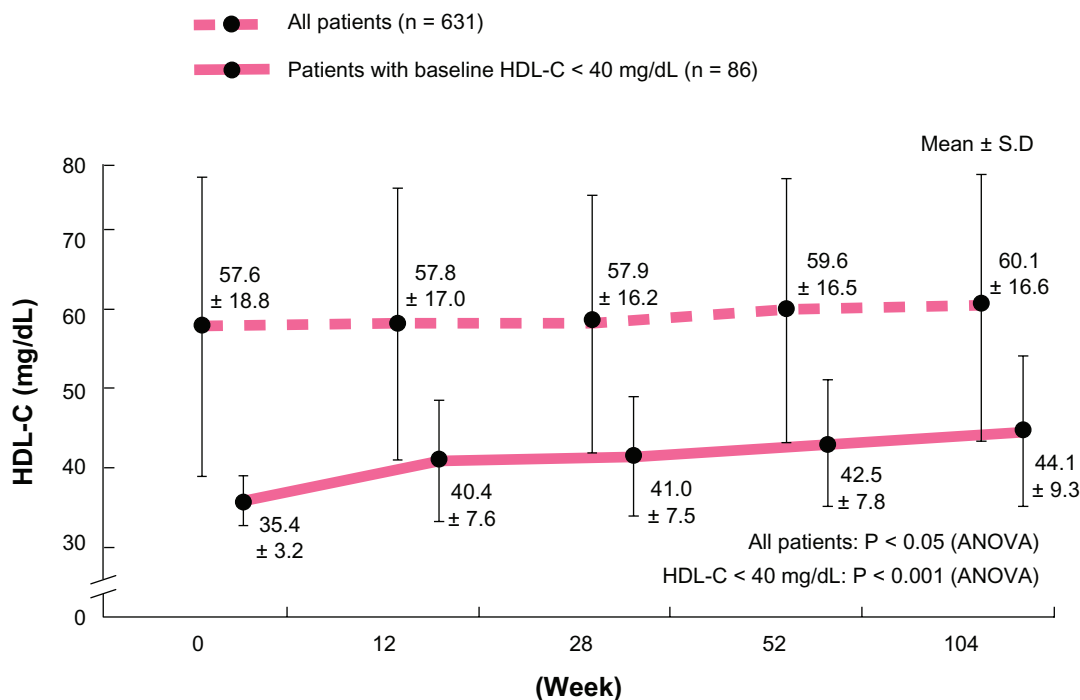
The mechanisms of the increase of HDL cholesterol caused by pitavastatin have been reported by several investigators. In hepatocytes, pitavastatin increases ApoA-1 gene expression through the activation of peroxisome proliferator-activated receptor (PPAR)- $\alpha$ ,<sup>32</sup> which is considered a major regulator of intra- and extracellular fatty acid metabolism, and also increases ApoA-1 secretion by elevating ATP binding cassette A1 (ABCA1) expression via activation of LXR $\alpha$ .<sup>33</sup> Although pitavastatin decreases circulating cholesteryl ester transfer protein (CETP) mass in hypercholesterolemic patients,<sup>34</sup> induction of ApoA-1 production may play a central role in increasing HDL cholesterol.<sup>30,35</sup>

### Non-HDL cholesterol

Non-HDL cholesterol is easily calculated as: total cholesterol minus HDL cholesterol. The measurement of non-HDL cholesterol is reliable even in the nonfasting sample and is noted as the secondary target after the achievement of LDL cholesterol goals. The goal for non-HDL cholesterol has been reported to be the level of LDL cholesterol plus 30 mg/dL.<sup>36</sup> In type 2 diabetics, several characteristics such as elevated triglycerides, decreased HDL cholesterol, and elevated small



**Figure 3** Changes in LDL cholesterol before and after administration of pitavastatin 2 mg/day in hyperlipidemic patients with and without type 2 diabetes mellitus. Adapted from Nomura et al.<sup>21</sup>



**Figure 4** The time course of HDL cholesterol for 104 weeks before and after administration of pitavastatin 1–4 mg/day in the LIVES study. Adapted from Teramoto et al.<sup>29</sup>

dense LDL, are well-known.<sup>25</sup> Because non-HDL cholesterol reflects all apolipoprotein B-containing atherogenic lipoproteins, non-HDL cholesterol may be useful in predicting cardiovascular disease in patients with type 2 diabetes mellitus. In the Strong Heart Study, non-HDL cholesterol was a strong predictor of coronary heart disease in men and women with diabetes.<sup>37</sup>

In the CHIBA Study, the reduction of non-HDL cholesterol by pitavastatin 2 mg/day (39.0%) was similar to that achieved with atorvastatin 10 mg/day (40.3%). However, in the atorvastatin group, the waist circumference, body weight and BMI were significantly correlated with percent reduction of non-HDL cholesterol, whereas pitavastatin showed consistent reduction of non-HDL cholesterol irrespective of these variables.<sup>22</sup>

#### Remnant lipoprotein, small dense LDL

Serum levels of remnant-like particle (RLP) cholesterol and small dense LDL are elevated in diabetic patients as a result of insulin resistance.<sup>38,39</sup> RLP and small dense LDL are more susceptible to oxidation and in turn more atherogenic relative to LDL particles. Effects of pitavastatin on these specific lipoprotein particles are as follows.

In 28 diabetic patients, all of whom were treated with pitavastatin 2 mg/day for 8 weeks, LDL cholesterol significantly decreased by 36.1% (from 168.4 to 105.4 mg/dL),

small dense LDL significantly decreased by 10.3% (from 29.9 to 19.7%), peak particle diameter of LDL significantly increased by 0.7 nm (from 26.363 to 27.095 nm), and RLP cholesterol significantly decreased by 2.49 mg/dL (from 6.62 to 4.13 mg/dL).<sup>40</sup> In another report, administration of pitavastatin 1 mg/day for 3 months significantly reduced small dense LDL from 37 to 25 mg/dL measured in type 2 diabetic patients.<sup>41</sup>

#### Vascular effect

In diabetics, vascular endothelial function can be impaired by hyperglycemia or oxidized lipoproteins.<sup>42,43</sup>

In Watanabe heritable hyperlipidemic myocardial infarction-prone rabbits (WHHL-MI rabbits), 8 week treatment with 0.5 mg/kg/day pitavastatin resulted in a significant increase in acetylcholine induced nitric oxide (NO) production.<sup>44</sup> The silent mating type information regulation 2 homolog 1 (SIRT1) gene has been recognized as a key regulator of vascular endothelial homeostasis, controlling angiogenesis, endothelial senescence, and dysfunction. Administration of pitavastatin increased endothelial nitric oxide synthase (eNOS), SIRT1, and catalase expression and decreased endothelial senescence in streptozotocin-diabetic mice.<sup>45</sup> In clinical settings, pitavastatin 2 mg/day (n = 37) increased flow-mediated dilatation (FMD) more in comparison with atorvastatin 10 mg/day (n = 34) after

2 weeks treatment (relative change 82% vs 40%,  $P < 0.05$ ).<sup>46</sup> In type 2 diabetic patients, administration of pitavastatin 2 mg/day for 12 months ( $n = 45$ ) significantly decreased vascular stiffness as assessed by cardio-ankle vascular index (CAVI), which was associated significantly with a decrease in malondialdehyde-LDL (MDA-LDL).<sup>47</sup> These results suggest that pitavastatin may produce beneficial effects on vasculature.

### Coronary artery

From the VH-IVUS analysis, coronary plaques in diabetic patients showed increased necrotic core and dense calcium, and VHD-TCFA (VH IVUS-derived thin-cap fibroatheroma) and VHD-FCA (VH IVUS-derived fibrocalcific atheroma) were more frequently observed in diabetic patients than in nondiabetic patients.<sup>48</sup> In another pooled analysis, coronary plaque build-up was more progressive in diabetic patients than in nondiabetic patients.<sup>49</sup>

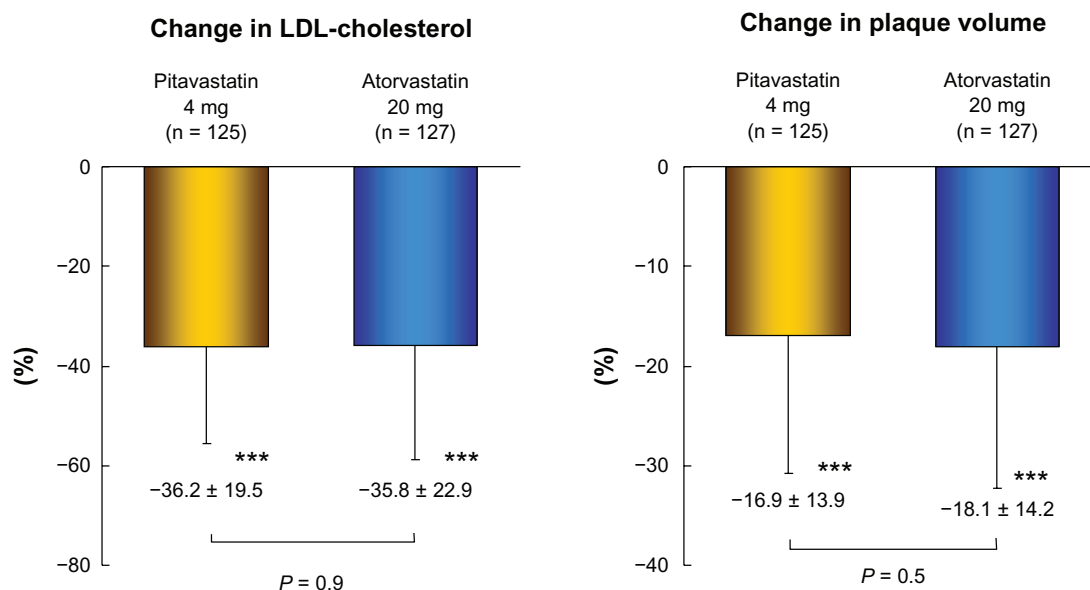
The JAPAN-ACS study was a randomized prospective study with blind endpoint evaluation in Japanese acute coronary syndrome (ACS) patients, to evaluate the effect of pitavastatin 4 mg/day ( $n = 125$ ) or atorvastatin 20 mg/day ( $n = 127$ ) on coronary artery plaques as assessed by intravascular ultrasound.<sup>50</sup> After 8–12 months treatment, the coronary plaque volume significantly decreased by 16.9% in the pitavastatin group and 18.1% in the atorvastatin group, suggesting pitavastatin was comparable to atorvastatin (Figure 5). In a subanalysis of the JAPAN-ACS study to

compare diabetic patients with nondiabetic patients, changes in coronary plaque volume were significantly associated with the reduction of LDL cholesterol in diabetic patients, whereas this relationship was not observed in nondiabetic patients.<sup>20</sup> In another subanalysis of JAPAN-ACS study, diabetic ACS patients showed greater coronary plaque regression than total ACS patients after intensive LDL cholesterol lowering therapy.<sup>51</sup> In another study to compare pitavastatin 2 mg/day ( $n = 80$ ) with atorvastatin 10 mg/day ( $n = 80$ ) in ACS patients, only pitavastatin 2 mg/day produced significant regression of coronary artery plaque volume in 2–3 weeks.<sup>52</sup>

In the prevention of coronary artery diseases, plaque stabilization is another therapeutic target in addition to plaque regression. Yellow color in coronary atheromas as assessed by angioscopy was reported to be an indicator of plaque rupture risk, and diabetic patients were reportedly more likely to have higher yellow color grades than nondiabetics.<sup>53</sup> In the TOGETHAR trial which evaluated the effects of pitavastatin on coronary plaque stabilization using angioscopy and IVUS, pitavastatin 2 mg/day ( $n = 46$ ) significantly reduced the yellow grade from 2.9 to 2.6 after 52 weeks' treatment.<sup>54</sup>

### Carotid artery

Effects of pitavastatin on carotid plaques were assessed by measuring plaque echolucency using carotid ultrasound with integrated backscatter (IBS) analysis.<sup>55</sup> In patients with ACS, pitavastatin 4 mg/day ( $n = 33$ ) significantly improved the carotid plaque echolucency within 1 month of therapy;



**Figure 5** Changes in LDL cholesterol and plaque volume for 12 months in the JAPAN-ACS study.

Adapted from Hiro et al.<sup>50</sup>

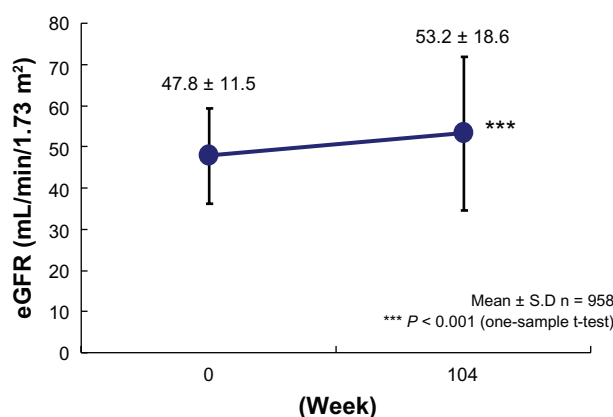
\*\*\* $P < 0.001$  mean  $\pm$  S.D.

pitavastatin improved the calibrated IBS value from  $-18.7$  to  $-12.7$  dB, which was almost the same value obtained in patients with stable coronary artery disease:  $-13.2$  dB ( $n = 32$ ). Echolucent carotid plaques with low IBS value were reported to be associated with future coronary events in patients with coronary artery disease<sup>56</sup> and pitavastatin may be useful in preventing coronary events by stabilizing plaques. In addition to plaque characteristics, two ongoing trials, PEACE (UMIN 000001229, NCT 00711919) and NTPP (UMIN C000000328), will clarify the effect of pitavastatin on carotid intima-media thickness, and another ongoing trial, EPOCH-CAS (UMIN 000004113), will examine the effect of pitavastatin on perioperative ischemic complications after carotid artery stenting.

### Kidney

Accumulating evidence suggests that renal dysfunction promotes the development of cardiovascular diseases. For example, from a recent meta-analysis, low estimated glomerular filtration rate (eGFR) of less than  $60$  mL/min/ $1.73$  m<sup>2</sup>, and high urine albumin-to-creatinine ratio (ACR) of  $10$  mg/g or more were independent predictors of all-cause mortality and cardiovascular mortality in the general population.<sup>57</sup> These findings have stimulated interest in the potential effects of statin treatment on kidney function, or other surrogate markers related to tubuloglomerular damage.

In the LIVES Study subanalysis, pitavastatin  $1-4$  mg/day significantly increased eGFR from  $47.8$  to  $53.2$  mL/min/ $1.73$  m<sup>2</sup> over 104 weeks in patients with a baseline eGFR less than  $60$  mL/min/ $1.73$  m<sup>2</sup> ( $n = 958$ ) (Figure 6). Using multivariate analysis in the LIVES Study, proteinuria and HDL cholesterol were negatively and positively associated with increased eGFR, respectively.<sup>58</sup> In the GREACE study, various statin



**Figure 6** Changes in eGFR before and after administration of pitavastatin  $1-4$  mg/day in the LIVES study. Baseline eGFR  $< 60$  mL/min/ $1.73$  m<sup>2</sup>. Adapted from Kimura et al.<sup>58</sup>

treatments (mainly atorvastatin) over 3 years significantly increased eGFR by  $9.8\%$  ( $P < 0.0001$ ,  $n = 880$ ). Multiple regression analysis showed that every  $5\%$  statin-induced HDL cholesterol increase significantly and independently contributed to eGFR improvement.<sup>59</sup> Furthermore, in patients with early diabetic nephropathy, pitavastatin  $1$  mg/day ( $n = 10$ ) significantly reduced urinary albumin excretion and urinary liver-type fatty acid-binding protein (L-FABP), which reflected the extent of tubulointerstitial damage.<sup>60</sup>

The precise mechanism underlying renal protection by statins remains unknown. Moorhead et al proposed that chronic progressive kidney disease may be mediated by abnormalities of lipid metabolism.<sup>61,62</sup> Several other reports have proposed potential explanations. Firstly, as observed in the LIVES Study, HDL cholesterol showed a positive association with increasing eGFR,<sup>58</sup> which suggests the possibility that the antioxidant properties of HDL cholesterol may play a role in eGFR increase. Paraoxonase 1 (PON1) is known to be located on HDL particles and to inhibit the oxidation of LDL and HDL.<sup>63</sup> Pitavastatin activates transcription of the *PONI* gene,<sup>64</sup> and this may lead to antioxidantization which improves endothelial function, and thus renal function. In Imai rats, used as a model of focal segmental glomerulosclerosis (FSGS), pitavastatin prevented renal injuries, and lag times for LDL and HDL oxidation were prolonged by the treatment of pitavastatin.<sup>65</sup> Secondly, pitavastatin suppresses glomerular mesangial cell proliferation by blocking Ras processing and MAP kinase activation.<sup>66</sup> Thirdly, pitavastatin is reported to cause upregulation of the SLCO4C1 transporter, which eliminates uremic toxins. This could provide a novel therapeutic potential for statins in chronic kidney disease (CKD) patients, if future studies support this idea.<sup>67</sup>

### Cardiovascular event

In the JAPAN-ACS study, major adverse cardiac events (MACE) were evaluated prospectively.<sup>50</sup> There was no significant difference in MACE;  $20.4\%$  in pitavastatin  $4$  mg/day group and  $22.8\%$  in atorvastatin  $20$  mg/day group. In the JAPAN-ACS subanalysis of patients with diabetes mellitus, the rate of MACE was  $29.9\%$  in diabetic patients, which was significantly greater than that in nondiabetic patients ( $18.2\%$ ).<sup>20</sup>

### Anti-inflammatory effect and antioxidant effect

C-reactive protein (CRP) is an important risk marker for atherosclerotic cardiovascular disease. In the PROVE IT-TIMI22 Study, ACS patients who have low CRP levels after statin therapy have better clinical outcomes than those

with higher CRP levels, regardless of the resultant level of LDL cholesterol.<sup>68</sup> In the Hisayama Study, in which a total of 2,589 Japanese participants aged 40 years or older were followed up for 14 years, the risk of coronary heart disease in the highest quartile group of high-sensitivity CRP (hsCRP) levels was 2.98-fold higher than that in the lowest group even after controlling for other cardiovascular risk factors.<sup>69</sup> In the JUPITER Trial, rosuvastatin significantly reduced the incidence of major cardiovascular events in healthy persons with elevated hsCRP.<sup>70</sup> Moreover, in some studies, elevated hsCRP was reported to be a predictor of the development of diabetes.<sup>71,72</sup> Anti-inflammatory effects may be important in preventing not only cardiovascular disease but also the onset of diabetes.

In the KISHIMEN Trial, administration of pitavastatin 1–2 mg/day for 12 months significantly decreased hsCRP by 34.8% (from 0.69 to 0.45 mg/L) in Japanese subjects with hypercholesterolemia ( $n = 31$ ).<sup>73</sup> In another small trial, administration of pitavastatin 4 mg/day for 1 month significantly decreased hsCRP from 0.64 to 0.28 mg/dL in Japanese ACS patients ( $n = 33$ ).<sup>55</sup>

Anti-oxidant effect is another important factor in preventing cardiovascular disease and diabetes mellitus. Oxidized LDL plays a key role in the initiation and development of atherosclerosis.<sup>74–76</sup> In Japanese type 2 diabetic patients, an inverse correlation between 8-hydroxydeoxyguanosine (8-OHdG) positive islet beta-cells and beta-cell volume density was observed.<sup>77</sup> Pitavastatin 2 mg/day for 12 months ( $n = 45$ ) significantly decreased urinary 8-OHdG excretion from 11.3 to 8.4 ng/mg Cr ( $P < 0.05$ ) and serum MDA-LDL levels from 170 to 114 U/L ( $P < 0.01$ ) in type 2 diabetic patients.<sup>47</sup> Also pitavastatin 2 mg/day for 6 months ( $n = 25$ ) significantly decreased circulating ligand for lectin-like oxidized LDL receptor-1 (LOX-1), a receptor for oxidized LDL expressing in vascular endothelial cells, from 867 to 435 ng/mL ( $P < 0.0001$ ).<sup>78</sup>

### Improving insulin resistance

In the WOSCOPS subanalysis, pravastatin reduced the onset of diabetes by 30%, suggesting its beneficial influence on glucose tolerance.<sup>79</sup> Some reports suggested that pitavastatin improved insulin resistance. Pitavastatin increased glucose uptake in KKA<sup>y</sup> mice,<sup>80</sup> and the response to intraperitoneal insulin was greater in the pitavastatin-treated mice than in the untreated KKA<sup>y</sup> mice.<sup>81</sup> Also, pitavastatin improved HOMA-R in type 2 diabetic patients ( $n = 31$ ) after 6 month treatment.<sup>82</sup> A recent study suggested that HDL particle improved glucose metabolism in patients with type

2 diabetes.<sup>83</sup> Thirteen patients with type 2 diabetes were treated for 4 hours with intravenous reconstituted HDL (rHDL) and placebo in a double-blind, placebo-controlled crossover study. Plasma glucose and plasma insulin were reduced and increased more, respectively, during the rHDL period than during the placebo period. Also, both HDL and ApoA-1 increased glucose uptake in primary human skeletal muscle cell cultures established from patients with type 2 diabetic patients. These findings suggest that HDL may be associated with improving insulin resistance. The potential of pitavastatin to increase HDL cholesterol and ApoA-1 in a long-term treatment may be useful not only in preventing cardiovascular disease but also in improving insulin resistance. From this viewpoint, the Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) study ( $n = 1240$ ), which examines the preventative effects of pitavastatin plus lifestyle modification on the development of new-onset diabetes in Japanese patients with impaired glucose tolerance (IGT), is now underway.

## Safety

### Effects on glucose metabolism

Effects of statins on glucose metabolism are an issue currently under debate.<sup>84,85</sup> For example, in the JUPITER trial, rosuvastatin significantly prevented vascular events in men and women with elevated hsCRP, but increased the incidence of new-onset diabetes more than the placebo.<sup>70</sup> A meta-analysis showed that statin therapy was associated with a significantly increased risk (9%) of the development of diabetes, and meta-regression analysis showed that the risk of development of diabetes with statins was highest in trials with older participants irrespective of baseline body-mass index or magnitude of LDL cholesterol reduction.<sup>86</sup> However, this study also suggested that the increment of risk remained small both in absolute value and in comparison with coronary event reduction, and that clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not be changed.

The advantage of pitavastatin for dyslipidemia in diabetic patients is that pitavastatin hardly influences glycemic control. In the CHIBA Study subanalysis of diabetic patients, atorvastatin 10 mg/day ( $n = 22$ ) significantly increased glycoalbumin, but pitavastatin 2 mg/day ( $n = 23$ ) had no significant influence on fasting plasma glucose, HbA1c, insulin, glycoalbumin, or HOMA-R.<sup>87</sup> In another retrospective analysis to compare the effects of atorvastatin 10 mg/day ( $n = 74$ ), pravastatin 10 mg/day ( $n = 70$ ), and pitavastatin 2 mg/day ( $n = 76$ ) on glycemic control during a 3-month



treatment period, only atorvastatin significantly increased plasma glucose (from 147 to 176 mg/dL) and HbA<sub>1c</sub> (from 7.0 to 7.4%). Neither pravastatin nor pitavastatin had any significant influence on plasma glucose and HbA<sub>1c</sub> (Figure 7).<sup>88</sup> Pitavastatin significantly decreased HbA<sub>1c</sub> in diabetic patients in the LIVES Study (n = 308) (Figure 8).<sup>89</sup> Although concomitant antidiabetic therapy was continued in the LIVES Study, pitavastatin at least produced no adverse effects on glycemic control in diabetic patients in real clinical settings.

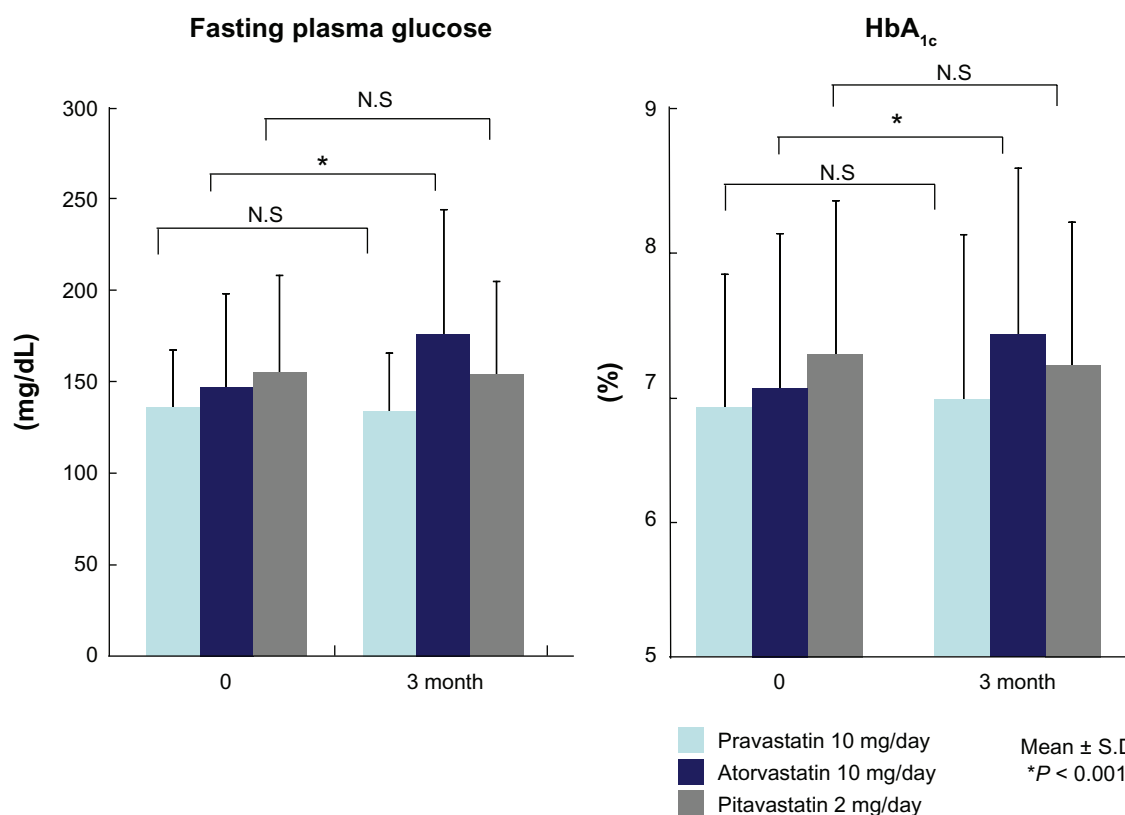
The mechanisms by which some statins have adverse effects on glycemic control remain uncertain, but one of the possible explanations is related to interference with glucose transporter-4 (GLUT4). In 3T3-L1 adipocytes, atorvastatin significantly prevented translocation of GLUT 4 into the plasma membrane, as compared to pravastatin.<sup>90</sup> Another study examined the effects of statins on glucose uptake using 3T3-L1 cells. Treatment with atorvastatin attenuated glucose transporter-4 (SLC2A4) and C/EBP $\alpha$  expressions in differentiated 3T3-L1 adipocytes. Also atorvastatin 1–10 ng/mL significantly decreased glucose uptake in differentiated 3T3-L1 cells, but pitavastatin 10<sup>2</sup> ng/mL did not produce

any influence.<sup>91</sup> These differences across several kinds of statins are of great interest and should be confirmed by further studies.

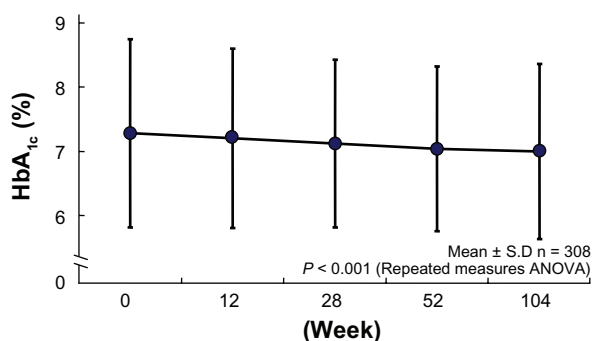
## Drug–drug interaction

Patients treated with statins usually take a number of drugs, and therefore the possibility of drug–drug interactions is an issue to be considered when they are prescribed. Atorvastatin and simvastatin are known to be metabolized by CYP3A4, but pitavastatin is hardly metabolized through this system at all (only slightly metabolized by CYP2C9).<sup>4,92</sup> For example, diabetic patients often have nail ringworm and take antifungal agents such as itraconazole. Combined administration of itraconazole with CYP3A4-metabolized statin may result in an increased concentration of statin due to strong inhibition of CYP3A4 by itraconazole.

One example is related to grapefruit juice (GFJ), which is known to inhibit CYP3A4. When atorvastatin was taken with GFJ, the mean AUC<sub>0–24</sub> of atorvastatin acid significantly increased by 83%, compared to taking atorvastatin with water. By contrast, AUC<sub>0–24</sub> of pitavastatin remained similar irrespective of concomitant GFJ or water,<sup>93</sup> which would be a



**Figure 7** Changes in fasting plasma glucose and HbA<sub>1c</sub> before and after administration of pravastatin 10 mg/day (n = 70), atorvastatin (n = 74), and pitavastatin (n = 76) in patients with type 2 diabetes mellitus. Adapted from Yamakawa et al.<sup>88</sup>



**Figure 8** Changes in HbA<sub>1c</sub> before and after administration of pitavastatin 1–4 mg/day in the LIVES study in patients with diabetes mellitus. Adapted from Teramoto et al.<sup>89</sup>

clinical advantage for pitavastatin. Warfarin is another drug that is of concern. CYP2C9 is the primary enzyme in S-warfarin metabolism. Assessing the effects of pitavastatin 4 mg/day on steady-state warfarin in healthy volunteers ( $n = 24$ ), the ratios of the least squares mean of prothrombin time (PT) and international normalized ratio (INR) between the monotherapy of warfarin and the concomitant treatment of warfarin and pitavastatin were 0.989 and 0.993, respectively, and the 90% confidence intervals (CIs) were 0.955 to 1.023 for PT and 0.956 to 1.029 for INR.<sup>94</sup> In this study, no drug–drug interaction between pitavastatin and warfarin was demonstrated.

## Adverse event rate

Statin treatment usually requires long-term administration, and therefore the safety profile is one of the most important factors when considering which kind of statins should be prescribed. In the LIVES Study, approximately 20,000 Japanese patients with hypercholesterolemia or familial hypercholesterolemia were treated for 2 years in order to analyze drug safety and effectiveness. The incidence of adverse drug reactions was 6.1% (1,206/19,921 patients) after 3 months of pitavastatin treatment,<sup>19</sup> 8.8% (1,753/19,925 patients) after 1 year of treatment,<sup>95</sup> and 10.4% (2,069/19,925 patients) after 2 years of treatment.<sup>96</sup> For other types of statin treatment used in Japan, the incidence of adverse drug reactions was 12.0% (576/4,805 patients) at 3 months of atorvastatin treatment,<sup>97</sup> and 11.1% (978/8,795 patients) at 3 months of rosuvastatin treatment,<sup>98</sup> both of which were about twice that of pitavastatin. Looking at laboratory data abnormalities during a 3 month post-marketing survey of each statin, the incidence of CK elevation was 1.41% (pitavastatin), 2.19% (atorvastatin), and 2.29% (rosuvastatin); the incidence of AST elevation was 0.71% (pitavastatin), 1.14% (atorvastatin), and 0.53% (rosuvastatin); the incidence of ALT elevation was 0.90% (pitavastatin), 1.83% (atorvastatin),

and 0.69% (rosuvastatin); and the incidence of myalgia was 0.66% (pitavastatin), 0.50% (atorvastatin), and 1.43% (rosuvastatin). In another report from the Japanese Society of Hospital Pharmacists, the incidence of suspicious myopathy was 0.38% (4/1040) for simvastatin, 0.53% (17/3229) for pravastatin, 0.50% (22/4440) for atorvastatin, 0.58% (2/347) for fluvastatin, 0.36% (3/838) for pitavastatin, and 1.01% (9/891) for rosuvastatin.<sup>99</sup>

One of the possible explanations why pitavastatin is associated with a lower incidence of adverse reactions than other potent statins is that pitavastatin can reduce LDL cholesterol effectively and safely without blocking the mevalonate pathway excessively and in turn inducing LDL receptors. When HepG2 cells were treated with a 200-fold excess of the IC<sub>50</sub> concentration of three HMG-CoA reductase inhibitors (pitavastatin, atorvastatin, and simvastatin), pitavastatin was able to induce LDL receptor mRNA most effectively.<sup>7</sup> This suggests that pitavastatin could have the additional capability to enhance LDL receptor gene expression, unrelated to HMG-CoA reductase inhibition. Interestingly, a crossover study comparing pitavastatin 4 mg/day with atorvastatin 20 mg/day showed that plasma levels of CoQ10 were reduced by atorvastatin (−26.1%,  $P = 0.0007$ ) but not by pitavastatin (−7.7%,  $P = 0.39$ ).<sup>100</sup>

The relationship between statin-related adverse effects and the hepatic drug transporter *SLCO1B1* genetic variants has been reported. In the SEARCH Study, common variants in *SLCO1B1* were associated with an increased risk of statin-induced myopathy, and the odds ratio for myopathy was 4.5 per copy of the rs4149056 C allele and 16.9 in CC as compared with TT homozygotes.<sup>101</sup> Also in the STRENGTH Study, *SLCO1B1*\*5 genotype and female sex were associated with mild statin-induced adverse effects.<sup>102</sup> The influence of this genetic variant on pitavastatin-related myopathy should be investigated in future studies.

## Ongoing pitavastatin trials

Additional trials to test the clinical efficacy of pitavastatin in various settings are now underway, and are expected to provide further data.

## REAL-CAD (n = 12,600)

REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease, NCT 01042730, UMIN 000002680) is a trial to evaluate the prevention of cardiovascular disease by standard cholesterol lowering (pitavastatin 1 mg/day) or aggressive cholesterol lowering (pitavastatin 4 mg/day) in patients with

stable coronary artery disease. Several large-scale trials such as TNT, A-to-Z, IDEAL and PROVE-IT elucidated the efficacy of aggressive cholesterol lowering for secondary cardiovascular event reduction, and a meta-analysis showed that intensive lipid lowering with high-dose statin therapy showed a significant (16%) reduction of odds ratio in the risk of coronary death or myocardial infarction.<sup>103</sup> Although target LDL cholesterol for patients with coronary artery disease is below 100 mg/dL in the guidelines of the Japan Atherosclerosis Society, REAL-CAD will provide important information about whether more aggressive cholesterol lowering therapy is beneficial, especially in diabetic subjects.

### PEARL study (n = 577)

PEARL Study (Pitavastatin Heart Failure Study, UMIN C00000428) is a comparative and randomized trial to evaluate the effects of pitavastatin 2 mg/day on cardiac death and hospitalization for worsening heart failure in patients with mild-to-moderate heart failure.<sup>104</sup> Although early studies suggested that statins improve cardiac function, CORONA and GISSI-HF failed to demonstrate the benefit of rosuvastatin therapy in primary endpoints in patients with heart failure,<sup>105,106</sup> and the effects of statins on cardiac function have remained controversial.

In a small study (n = 23), administration of pitavastatin 1–2 mg/day for 7.5 months significantly increased left ventricular ejection fraction (LVEF) from 42 to 48%, and significantly decreased the plasma brain natriuretic peptide (BNP) level from 94 to 70 pg/mL.<sup>107</sup> It has also been reported that there was an inverse correlation between atorvastatin-induced changes in CoQ10 and BNP,<sup>108</sup> that CoQ10 level was an independent predictor of mortality in chronic heart failure,<sup>109</sup> and that the CoQ10 level in myocardial tissue was lower in patients of NYHA class IV than in patients of NYHA class I.<sup>110</sup> Considering that pitavastatin does not reduce CoQ10 and is effective in improving vascular function, the results of PEARL Study may be expected to provide new evidence for heart failure treatment with statins.

### J-PREDICT (n = 1,240)

J-PREDICT (Japan Prevention Trial of Diabetes by Pitavastatin in Patients With Impaired Glucose Tolerance, NCT 00301392, UMIN C00000394) is a comparative and randomized trial to evaluate the prevention of new-onset diabetes using pitavastatin 1–4 mg/day in patients with impaired glucose tolerance (IGT). This will provide a new possibility for the use of statins to control glucose metabolism and the development of diabetes.

### DIALYSIS (n = 1,550)

DIALYSIS (Differential Intervention Trial by Standard Therapy Versus Pitavastatin in Patients With Chronic Hemodialysis, NCT 00846118) is a trial to evaluate the effects of pitavastatin 1–4 mg/day on all-cause mortality and the incidence of myocardial infarction in hemodialysis patients. In Japan, the primary reason for dialysis is diabetic nephropathy, but few trials have evaluated the effects of statins on cardiovascular diseases in dialyzed patients. In a 4D trial by atorvastatin<sup>111</sup> and AURORA by rosuvastatin,<sup>112</sup> statin therapy did not show any benefit on the primary endpoint such as cardiovascular disease or all-cause mortality. However, in 4D subanalysis, atorvastatin treatment led to a 46% risk reduction of all composite cardiovascular endpoints, a 52% decrease of sudden cardiac death, and a 28% decrease of all-cause mortality among patients in the highest LDL cholesterol quartile (greater than 145 mg/dL).<sup>113</sup> DIALYSIS is expected to provide the first evidence of statin use in Asian patients with hemodialysis.

### TOHO-LIP (n = 600)

TOHO-LIP (TOHO lipid intervention trial using Pitavastatin, UMIN 000001404) is a trial to evaluate the prevention of various macrovascular diseases by pitavastatin or atorvastatin in subjects at high risk of cardiovascular disease. Although pitavastatin 2 mg/day and atorvastatin 10 mg/day are generally considered to show similar LDL cholesterol lowering effects, it has also been reported that pitavastatin 2 mg/day is superior to atorvastatin 10 mg/day in LDL cholesterol lowering in metabolic syndrome patients.<sup>22</sup> Therefore, a comparative study using pitavastatin and atorvastatin in specific patient populations is of interest.

### Extended-JAPAN-ACS (n = 252)

The Extended-JAPAN-ACS (Extended Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome, NCT 01223586, UMIN 000003166) trial was carried out to verify the relationship between coronary plaque regression and cardiovascular events in long-term follow-up in ACS patients enrolled in JAPAN-ACS. There are few reports which elucidate the relationship between coronary artery plaque regression and cardiovascular event reduction,<sup>114</sup> and therefore the Extended-JAPAN-ACS trial could add further evidence useful for secondary prevention in the Japanese population.

### Prospects and conclusion

Based on these findings, pitavastatin has a number of favorable characteristics that are beneficial in patients with

diabetes mellitus, which are derived from its efficacy and safety; potency in LDL cholesterol reduction; sustained HDL cholesterol raising effect; beneficial vascular effects; anti-inflammatory and antioxidant effects; improvement of insulin resistance; minimal influence on glucose metabolism; minimal drug–drug interaction; and low incidence of adverse effects. The maximum dose of pitavastatin allowed in Japan is 4 mg/day, and it reduces LDL cholesterol by 47%. Judging from the unique characteristics of pitavastatin as reviewed in this article, this Japanese-oriented statin could provide alternative treatment choice especially in patients with glucose intolerance or diabetes mellitus.

Considering very recent publications about experimental studies using nanoparticle (NP)-mediated delivery of pitavastatin in limb ischemia models<sup>115,116</sup> and pulmonary artery hypertension models,<sup>117</sup> information is likely to be obtained from current clinical trials that will expand the possible applications of pitavastatin.

## Disclosure

The authors report no conflicts of interest in this work.

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