Six types of statins have been approved for clinical use in Japan (Table). Pravastatin and simvastatin are HMG-CoA reductase inhibitors derived from fungi; atorvastatin, fluvastatin, pitavastatin and rosuvastatin are fully synthetic.1,2 Atorvastatin, pravastatin, fluvastatin and simvastatin are relatively lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic because they have a polar hydroxyl group and a methane sulfonamide group, respectively.3 With the exception of pravastatin, all statins bind extensively to plasma proteins, and thus the amount of systemic exposure to unbound, pharmacologically active drug is relatively low. Although circulating levels of unbound pravastatin are higher than those of the other statins, widespread tissue distribution is prevented by its hydrophilic nature. Rosuvastatin and pravastatin are comparably hydrophilic, whereas the other statins are lipophilic.4 All statins are relatively hepatoselective with respect to HMG-CoA reductase inhibition, an important characteristic given that most of the endogenous cholesterol is produced in the liver. The passive diffusion of lipophilic statins through hepatocyte cell membranes is primarily responsible for efficient first-pass uptake, whereas extensive carrier-mediated uptake is the major mechanism for hydrophilic statins.4 Statins are predominantly metabolized by the cytochrome P450 (CYP450) family of enzymes, which comprises over 30 isoenzymes.2 Lipophilic drugs are highly susceptible to oxidative metabolism by the CYP450 family. Although statins share a common mechanism of action, they differ in terms of chemistry, pharmacokinetics, and relative abilities to improve lipid profiles.

Statin therapy reduces mortality and recurrent cardiac events across a wide range of cholesterol levels in patients with stable coronary artery disease (CAD) and acute coronary syndrome (ACS).5–7 The results of meta-analyses of many randomized controlled clinical trials (RCTs) indicate that the clinical effect of statins is directly related to the magnitude of the reduction and achieved levels of low-density lipoprotein cholesterol (LDL-C).8 These findings support a causal relationship that has consequently led to the mantra, ‘Lower is Better’ with regard to LDL-C-lowering to prevent CAD. For high-risk patients such as those with ACS, the ACC/AHA guidelines advocate LDL-C levels <70 mg/dl. However, most of the RCTs and almost all USA and European studies have compared statins with placebo or higher standard doses of statins. Additionally, whereas the previous ACC/AHA guidelines focused on therapy to decrease LDL-C and non-HDL-C to specific target levels, the new guidelines instead propose implementing cholesterol-lowering treatment using evidenced-based intensity of statin therapy without such targets.9 The Japan Atherosclerosis Society has recently recommended a target LDL-C level of <100 mg/dl for secondary prevention in patients with CAD. This is because RCTs have generated limited evidence supporting secondary prevention in Japanese patients with CAD.

The amount of clinical evidence generated within Japan related to a specific drug effect of statins in patients with CAD has gradually increased. Based on a subanalysis of their MUSASHI-AMI trial, Sakamoto et al demonstrated that hydrophilic pravastatin might be more effective than other lipophilic statins. Although pravastatin was less potent in lowering the LDL-C, it was more effective in preventing the appearance of new Q waves.

Table. Pharmacokinetic Properties of Commercially Available Statins in Japan2

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Pravastatin (Mevalotonin)</th>
<th>Rosuvastatin (Crestor)</th>
<th>Atorvastatin (Lipitor)</th>
<th>Pitavastatin (Livalo)</th>
<th>Fluvastatin (Locol)</th>
<th>Simvastatin (Lipovas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>18</td>
<td>20</td>
<td>12</td>
<td>80</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>1.8</td>
<td>19</td>
<td>14</td>
<td>11</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>~50</td>
<td>90</td>
<td>98</td>
<td>96</td>
<td>&gt;98</td>
<td>95–98</td>
</tr>
<tr>
<td>CYP450 metabolism and isoenzyme</td>
<td>No</td>
<td>Limited</td>
<td>Yes 3A4</td>
<td>Limited</td>
<td>Yes 2C9</td>
<td>Yes 3A4</td>
</tr>
</tbody>
</table>

CYP450, cytochrome P450. Reproduced with permission from Schachter M.2

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and reducing cardiovascular events in patients after acute myocardial infarction (AMI) than lipophilic statins.10 Chitose et al reported that hydrophilic rosuvastatin conferred significant benefits on myocardial salvage accompanied by a significantly greater decrease in BNP levels compared with lipophilic atorvastatin in patients with ST-elevated MI. They also found a significant difference in the effects of hydrophilic rosuvastatin and lipophilic atorvastatin on co-enzyme Q10 levels. The ratios of co-enzyme Q10 and LDL-C levels were significantly higher after 6 months in patients with AMI treated with rosuvastatin compared with acute-phase levels, but atorvastatin exerted no such changes.11 On the other hand, a subgroup analysis of a large observational study (the ICAD study) suggested a lipid-independent effect of statins on all cardiovascular events, and that these favorable effects were comparable between hydrophilic and lipophilic statins.12 From the CREDO-Kyoto registry cohort-2, Natsuaki et al found that therapy mainly with lipophilic atorvastatin was associated with a trend towards lower cardiovascular risk compared with standard therapy mainly with hydrophilic pravastatin in patients who underwent their first coronary revascularization.13 Furthermore, 1-year intensive lipid-lowering treatment with hydrophilic rosuvastatin was more effective in slowing progression of carotid intima–media thickness than conventional lipid-lowering treatment with hydrophilic pravastatin in the JART Study.14 The latter also found that long-term intensive therapy with hydrophilic rosuvastatin was well tolerated.15

As reported in this issue of the Journal, a 2-year comparison between hydrophilic pravastatin and lipophilic atorvastatin by Izawa et al (ALPS-AMI trial) did not reveal a significant difference in the prevention of secondary cardiovascular outcomes in patients with AMI.16 Furthermore, they did not find any significant differences in adverse effects or changes in metabolic effects, including HbA1c and BNP, after therapy with these 2 statins. Importantly, each statin was started at 10 mg/day and the treatment target was to reduce LDL-C to <100 mg/dL based on the Japanese guidelines. The mean LDL-C reduction in both groups during the study period was 30–40%. Although the final dose of each statin was not evaluated, significantly more patients given pravastatin than atorvastatin required ezetimibe therapy (P<0.001). Therefore, to argue the value of high-intensity statin therapy (>50% LDL-C reduction) or statin/ezetimibe combination therapy might be difficult. Further study is warranted to determine whether high-intensity statin therapy can reduce cardiovascular events more effectively and exert more powerful pleiotropic effects, regardless of the LDL-C-lowering effects, in Japanese patients with CAD. The present findings also suggested that hydrophilic pravastatin therapy might confer pleiotropic benefits that could prevent secondary events beyond LDL-C-lowering. Therefore, because these effects might differ among races, more clinical evidence of the specific drug effects of statins, rather than class and dose effects, is needed from Japan.

References

4. Nezasa K, Higaki K, Takeuchi M, Nakano M, Koike M. Uptake of co-enzyme Q10 and LDL-C levels were significantly higher after 6 months in patients with AMI treated with rosuvastatin compared with acute-phase levels, but atorvastatin exerted no such changes.11 On the other hand, a subgroup analysis of a large observational study (the ICAD study) suggested a lipid-independent effect of statins on all cardiovascular events, and that these favorable effects were comparable between hydrophilic and lipophilic statins.12 From the CREDO-Kyoto registry cohort-2, Natsuaki et al found that therapy mainly with lipophilic atorvastatin was associated with a trend towards lower cardiovascular risk compared with standard therapy mainly with hydrophilic pravastatin in patients who underwent their first coronary revascularization.13 Furthermore, 1-year intensive lipid-lowering treatment with hydrophilic rosuvastatin was more effective in slowing progression of carotid intima–media thickness than conventional lipid-lowering treatment with hydrophilic pravastatin in the JART Study.14 The latter also found that long-term intensive therapy with hydrophilic rosuvastatin was well tolerated.15

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Disclosures

None.

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