Usefulness of Hydrophilic vs Lipophilic Statins After Acute Myocardial Infarction

Subanalysis of MUSASHI-AMI

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Background Statins are widely used to reduce blood levels of low-density lipoprotein-cholesterol (LDL-C). Each statin has unique pharmacokinetic properties; lipophilicity is one such property and relates to tissue selectivity.

Methods and Results The Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction (MUSASHI-AMI) trial evaluated the effect of discreetional statin treatment initiated within 96h after onset of acute myocardial infarction (AMI) in Japanese patients. To clarify whether statin lipophilicity affects prognosis, a post hoc analysis of the MUSASHI-AMI database was performed. Patients who were assigned to receive statin were separated into 2 groups according to the lipophilicity of the statins they were administered: lipophilic statins (atorvastatin, fluvastatin, pitavastatin and simvastatin; LS group; n=131) or hydrophilic statins (pravastatin; HS group; n=110). There was no difference in baseline LDL-C concentrations between the 2 groups. Although LDL-C was decreased more potently in the LS than HS groups (–34% vs –19%; p=0.0069), acute coronary syndrome events tended to occur less frequently (3.6% vs 9.9%; p=0.0530) and the incidence of new Q-wave appearance in electrocardiogram was significantly lower (75% vs 89%; p=0.0056) in the HS than LS groups.

Conclusions In normocholesterolemic Japanese patients after AMI, hydrophilic pravastatin could be superior to lipophilic statins at preventing new Q-wave appearance and reducing cardiovascular events. (Circ J 2007; 71: 1348–1353)

Key Words: Acute myocardial infarction; HMG-CoA reductase inhibitors; Hydrophilicity; Lipophilicity; Pravastatin

In the 1970s, an HMG-CoA reductase inhibitor, ML-236B (compactin), was isolated for the first time from the culture broth of Penicillium citrium by Endo and colleagues.1,2 This compound was shown to be a potent competitive inhibitor of HMG-CoA reductase.3 Since then, a variety of HMG-CoA reductase inhibitors (statins) were developed and clinically approved.4 Now many statins (pravastatin, atorvastatin, fluvastatin, pitavastatin, rosuvastatin and simvastatin) are clinically available worldwide. Each statin has different pharmacokinetic properties and bioavailability. Solubility in water or alcohol (hydrophilicity or lipophilicity) is one such property related to tissue selectivity of statins.5 Among clinically available statins, pravastatin and rosuvastatin, have been categorized as hydrophilic statins; other statins are lipophilic.6 Although there is overwhelming evidence that statins are equally effective for primary and secondary prevention of cardiovascular disease,7–11 in experimental animal models it has been reported that each statin has different effects according to its water solubility.12,13 Lipophilic statins enhanced myocardial stunning in association with adenosine triphosphate (ATP) reduction after ischemia–reperfusion injury as compared with hydrophilic pravastatin. This suggests that hydrophilic statins potentially might be cardio-protective, especially in patients undergoing reperfusion therapy for acute myocardial infarction (AMI). Indeed, hydrophilic pravastatin has been shown substantially to reduce the risk of cardiovascular disease even when it causes only relatively mild lipid lowering.8–11 However, it remains unknown whether lipophilicity of statins affects clinical events and/or cardiac function after AMI.

The Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction (MUSASHI-AMI) was a PROBE-design trial conducted in 486 normocholesterolemic patients who were randomly assigned to receive either lipid-lowering treatment with any available statins or no statin within 96 h of AMI onset.14 At a mean follow-up of 416 days randomization to discreetional, statins were associated with significantly less recurrent cardiovascular
Lipophilicity of Statins Affects Outcome After AMI

events as compared with standard therapy without statins. In the MUSASHI-AMI trial, frequency of hydrophilic or lipophilic statin use was almost equal. Therefore, we reanalyzed the MUSASHI-AMI database to investigate whether the specific statin used influenced the outcome of early statin therapy in patients with AMI, focusing on their hydrophilicity and lipophilicity.

**Methods**

**Study Design**

The design and main results of the MUSASHI-AMI trial have already been reported. Briefly, between February 2002 and September 2004, a total of 486 consecutive eligible AMI patients who were admitted to 54 medical centers throughout Japan were recruited. Serum total cholesterol (TC) concentrations were required to be 180–240 mg/dl. On admission to hospital, patients underwent acute reperfusion therapy, including percutaneous coronary interventions (PCI) and/or thrombolysis as required. Within 96h after symptom onset they were randomly assigned to receive lipid-lowering therapy, including treatment with any available statin (pravastatin, atorvastatin, fluvastatin, simvastatin or pitavastatin) or standard therapy without statins and monitored for ≤2 years. During the study period, all patients were advised to adopt the Japan Atherosclerosis Society Step 1 diet. In this re-analysis of the MUSASHI-AMI data, based on octanol–water partition coefficients, which measure lipophilicity of compounds by determining their equilibrium distribution between water and the organic solvent octanol as surrogate for natural organic matter, patients who were assigned to the statin treatment group

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**Table 1 Baseline Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hydrophilic statins group (n=110)</th>
<th>Lipophilic statins group (n=131)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>64 (11)</td>
<td>63 (10)</td>
<td>0.7465</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>88 (80)</td>
<td>103 (79)</td>
<td>0.8737</td>
</tr>
<tr>
<td>Time from onset to admission, mean (SD), h</td>
<td>6.8 (10.0)</td>
<td>5.2 (7.2)</td>
<td>0.1631</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>6 (5)</td>
<td>4 (3)</td>
<td>0.5190</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>70 (64)</td>
<td>83 (63)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>55 (50)</td>
<td>67 (51)</td>
<td>0.8975</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>45 (41)</td>
<td>39 (30)</td>
<td>0.0787</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dl</td>
<td>205 (17)</td>
<td>209 (16)</td>
<td>0.0486</td>
</tr>
<tr>
<td>Low-density lipoprotein-cholesterol, mean (SD), mg/dl</td>
<td>132 (22)</td>
<td>136 (23)</td>
<td>0.1865</td>
</tr>
<tr>
<td>High-density lipoprotein-cholesterol, mean (SD), mg/dl</td>
<td>46 (13)</td>
<td>47 (12)</td>
<td>0.8830</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dl</td>
<td>137 (90)</td>
<td>137 (101)</td>
<td>0.9744</td>
</tr>
<tr>
<td>Killip II–IV, n (%)</td>
<td>13 (12)</td>
<td>14 (11)</td>
<td>0.8391</td>
</tr>
<tr>
<td>Anterior myocardial infarction, n (%)</td>
<td>54 (49)</td>
<td>60 (46)</td>
<td>0.6977</td>
</tr>
<tr>
<td>ST-segment elevation, n (%)</td>
<td>96 (87)</td>
<td>115 (88)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Left ventricular ejection fraction at hospital discharge, mean (SD), %</td>
<td>56 (10)</td>
<td>57 (10)</td>
<td>0.4724</td>
</tr>
<tr>
<td>Emergent coronary angiography performed, n (%)</td>
<td>107 (97)</td>
<td>130 (99)</td>
<td>0.3338</td>
</tr>
<tr>
<td>Reperfused by percutaneous coronary intervention, n (%)</td>
<td>104 (95)</td>
<td>119 (91)</td>
<td>0.3309</td>
</tr>
<tr>
<td>Coronary stents implanted, n (%)</td>
<td>92 (84)</td>
<td>106 (81)</td>
<td>0.6159</td>
</tr>
</tbody>
</table>
were further subdivided into 2 groups according to whether they received lipophilic statins (atorvastatin, fluvastatin, simvastatin, or pitavastatin; LS group) or hydrophilic statin (pravastatin; HS group). In this subanalysis, the primary endpoint was a composite of acute coronary syndrome (ACS) events, such as cardiovascular death, non-fatal myocardial infarction (MI) and recurrent acute myocardial ischemia requiring emergency hospitalization. A combination of the primary endpoint events, and congestive heart failure requiring emergent rehospitalization and non-fatal stroke was defined as the secondary endpoint. Besides the primary and secondary endpoints, appearance of a new Q-wave was settled as a surrogate endpoint. Q-wave was defined as follows: Q-wave >3 mm in depth and/or >0.04 s in duration in at least 2 leads except aVR.\textsuperscript{16}

Statistical Analysis
Differences in the characteristics of patients between the 2 treatment groups were evaluated by Student’s t-test in the case of continuous variables and chi-squared test for absolute categorical variables. Cumulative event curves of the study endpoint were plotted by the Kaplan–Meier method. Differences with a p-value of <0.05 were considered statistically significant. All statistical analyses were conducted with SAS 8.2 software (SAS Institute, Cary, NC, USA).

Results
In the MUSASHI-AMI trial a total of 241 normocholesterolemic Japanese patients were randomized to receive statin therapy within 96 h of symptom onset. Lipophilic statins were used in 131 patients and hydrophilic statins in 110 patients (Fig 1). Baseline demographic characteristics were similar between the 2 groups (Table 1). Baseline lipids profiles were almost the same except for TC concentrations, which were slightly but significantly higher in the LS than in the HS group; LDL-C concentrations were the same in the 2 groups (Table 1). ST-elevation MI was seen in approximately 90% of patients in both groups. Severity of MI as indicated by Killip class II–IV and anterior location of ischemia was the same in the 2 groups. Emergency coronary angiography was performed in almost 100% of
the study population (Table 1). Primary PCI was performed as reperfusion therapy in >90% and bare metal coronary stents were implanted in most (>80%) of the patients. Left-ventricular ejection fraction at hospital discharge was the same in the 2 groups (Table 1).

Unsurprisingly, at 24 months, patients in the LS group showed a 2-fold reduction of TC (209 to 162 mg/dl, –22%) and LDL-C (136 to 90 mg/dl, –34%) as compared with those in the HS (205 to 185 mg/dl, –10% in TC; 132 to 107 mg/dl, –19% in LDL-C) (Figs 2a,b). Changes in HDL-C and TG were the same in the 2 groups (Figs 2c,d). In a similar way, changes in C-reactive protein were not different between the 2 groups (Fig 3). Kaplan–Meier estimates of combined primary outcomes are shown in Fig 4. In comparison with those on LS therapy, treatment with HS was associated with fewer tendency of ACS events (3.6% vs 9.9%; p=0.0530). The secondary endpoints events occurred equally between the 2 groups (9.0% vs 10.7%; p=0.3390) (Fig 5). Fig 6 shows the incidence of new Q-wave appearance on electrocardiogram in the 2 groups. Although the rates of ST-segment elevation and primary PCI done were similar in the 2 treatment groups at enrollment, during follow-up incidence of new Q-wave appearance was significantly lower in the HS than LS groups (75% vs 89%; p=0.0056).

Discussion

Although in the statin treatment arm of MUSASHI-AMI the choice of statin was made at each treating physician’s discretion, in this re-analysis the numbers of patients in the LS and HS groups turned out to be closely matched at 131 and 110, respectively. There was no difference in baseline LDL-C concentrations between the 2 groups, and a significantly greater reduction of LDL-C was achieved in those patients on lipophilic statins as compared with patients taking hydrophilic pravastatin. Despite a less reduction of lipid levels in the HS group, this group exhibited a signifi-
stantly lower incidence of new Q-wave appearance and a tendency of a lower ACS events rate than the LS group. For reference, the primary endpoint events of the present study occurred in 8.8% and the incidence of new Q-wave appearance was 88% of non-statin treatment group in the MUSASHI-AMI trial being equal to those of the LS group of this subanalysis.

In the present study, pravastatin was the only hydrophilic statin used, whereas several lipophilic statins were administered: atorvastatin, fluvastatin, simvastatin and pitavastatin. Hydrophilic statins are distributed much more selectively in hepatocytes compared with lipophilic statins. Liver cellular membranes contain organic anion transporters that mediate uptake of hydrophilic substances into the cell. However, because extrahepatic cellular membranes consist of lipid bilayers, hydrophilic statins cannot penetrate these cellular membranes and thus cannot inhibit intracellular HMG-CoA. Hence, whereas hydrophilic statins are prevented from entering extrahepatic tissues, lipophilic statins might inhibit not only cholesterol synthesis in the liver but also production of essential substances by HMG-CoA reductase reaction, such as farnesylated proteins, heme A, dolichol and ubiquinone (coenzyme Q10; CoQ10), in peripheral compartments.17 CoQ10, an essential factor in oxidative energy-generating systems in mitochondria, is synthesized from mevalonic acid in many organs including the heart.18 The mitochondrial inner membrane of heart muscle has high activity of polypropenyltransferase, which attaches isoprenoids to quinone bodies and is a key enzyme in CoQ10 biosynthesis.19 It has been also reported that upregulated CoQ10 biosynthesis in the heart is associated with increased activity of HMG-CoA reductase.20 Lipophilic statins that can enter easily myocardial cells inhibit isoprenoid expression and thereby prevent CoQ10 biosynthesis in the heart. This process could slow down mitochondrial generation of ATP and affect myocardial contraction. Ichihara et al reported that in a canine experimental myocardial ischemia model, lipophilic statins worsened myocardial contractile dysfunction during reperfusion, whereas pravastatin did not.12-13 They also noted that worsening of myocardial contraction was associated with reduction of myocardial concentrations of CoQ10 and mitochondrial respiratory function.21 Taken together, these mechanisms could explain the superiority of hydrophilic vs lipophilic statins observed in the present study.

Statins as a class have been shown to exert multiple lipid lowering-independent, so-called pleiotropic effects. These include anti-inflammation, antioxidation, stabilization of vascular endothelial function, reduction of lipid component of coronary plaques and inhibition of platelet thrombus formation. In the present study, anti-inflammatory effects indicated by decreasing C-reactive protein concentrations were the same between the lipophilic and hydrophilic statin groups. However, there are a number of pleiotropic effects that seem unique to pravastatin, such as increasing plasma adiponectin23 improving insulin resistance24 and stabilization of vulnerable atheroma.25 It is possible that beneficial effects unique to pravastatin might have preserved viable myocardium as indicated by lower incidence of new Q-wave and thereby improved prognosis in the present study.

Our results appear at variance with those of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial26 which suggested that in normocholesterolemic patients with ACS aggressive lipid lowering with high-dose atorvastatin 80 mg/day provided greater protection against death and cardiovascular events than moderate lipid lowering using pravastatin 40 mg/day as early as 30 days after therapy was started. This timeframe within which recurrent cardiac events most commonly occur after an ACS was 27 It was proposed that high-dose atorvastatin exerted cardioprotective effects by a combination of coronary plaque stabilization and rapid cholesterol lowering, thereby preventing subsequent plaque rupture. However, several differences exist between the PROVE-IT trial and our study. First, PROVE-IT was a head-to-head comparison of intensive lipid-lowering therapy vs standard medical care. In MUSASHI-AMI, patients were randomized to any available statin or control: the present retrospective re-analysis aimed to establish whether there are any observable differences between patients allocated to standard treatment with hydrophilic or lipophilic statins including not only atorvastatin but also fluvastatin, simvastatin and pitavastatin. Second, the MUSASHI-AMI cohort included far fewer patients than PROVE-IT, and the possibility that our results were because of chance is consequentially greater. Third, ethnic differences between patients enrolled in the 2 studies might have influenced the results, with US and Japanese patients known to have distinct patterns of dyslipidemia and possibly different responses to statin therapy. Hence, the manifold differences between PROVE-IT and MUSASHI-AMI hinder any useful attempts to compare the results of these 2 trials. Prospective studies of lipophilic vs hydrophilic statins given at their most clinically effective doses are needed to identify any differences between the cardioprotective effects of these drugs in patients with ACS.

In conclusion, our preliminary results suggest that hydrophilic pravastatin prevents new Q-wave appearance and might reduce cardiovascular events to a greater extent than lipophilic statins in Japanese patients post-AMI. To confirm the superiority of pravastatin, a large-scale prospective randomized comparative trial with lipophilic statins is needed.

Acknowledgment

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References


Appendix

The MUSASHI-AMI investigators are listed below in alphabetical order. Amakusa Medical Center: Nartisugakakuma, Shotanakamura, Shinichi Nakamura; Arai City Hospital: IkkoMitsumori; Asahikawa Medical College Hospital: Naozukikasebe, Masaru Yamaki, Kenjiro Kikuchi; Chikamori Hospital: Naohisa Hamashige; Dokkyo University Koshigaya Hospital: ToshikiroUchida, HiroshiKobayashi; Fukuoka University Hospital: KojiKoga, HidetakaShimodaira, NishiharuOgata, ToruYamamuro; Fukuoka University Hospital: KenjiSakata; Gunma Prefectural Cardiovascular Center: ShigeruOhshima, Health Insurance Hirosho General Hospital: KenjiObata, HidekiOka; Hiroshi University Hospital: Ken Okumura, ToshiroMatsunaga; Hiroshima City Hospital: Masaharu Ishihara; Izumi City Hospital: ShigenobuTateishi; Japanese Red Cross Kumamoto Hospital: HitoshiSumida, RyusukeTsunoda, YasuhitoOgata; Kagoshima City Hospital: HiroshiToda; Kagoshima Medical Association Hospital: HiroyukiTorii; Kagoshima University Hospital: ChuaTei; Karatsu Red Cross Hospital: TakanobuNi; Kiihara Cardiovascular Clinic: HajimeKihara; Kitasato University Hospital: NaotoFukuda, ToruIzumi, KohseikaiHospital: YoshihiroIwasa; Kumamoto Central Hospital: ShuichiOshima; Kumamoto City Hospital: YoshihiroKimura; Kumamoto Kino Hospital: JujiMizuno; Kumamoto Regional Medical Center: NobutakaHirai; Kumamoto Rosai Hospital: ToshiiroMatsumura, HidekiOri; Kumamoto University Hospital: HisaoOgawa, TomohiroSakamoto, SunaoKojima, KoichiKakita; Mie University Hospital: TakeshiNakano, NaokiIsaka; Minamata City General Hospital and Medical Center: HidekiMaruyama; Miyazaki Medical Association Hospital: YoshihitoShibata; Miyazaki University Hospital: TakuroImamura, TanenaoEto; Miyazaki Prefectural Nobekoa Hospital: YasushiMoriyama, NobuyasuYamamoto; Nagasaki Municipal Medical Center: KazuakiYakabe; Nagasaki University Hospital 2nd Internal Medicine: YoshihikoMiyahara, ShigeruKohno; Nagasaki University Hospital 3rd Internal Medicine: KatsusukeYano, YujiKoide; Nara Medical University Hospital: YoshihikoSaito, ShiroUemura; National Hospital Organization Kumamoto Medical Center: KazuteruFujimoto, YujiMiyao; National Hospital Organization Kyushu Cardiovascular Center: TatsuruMatsuda, National Hospital Organization Oita Medical Center: TatsuhikoOoie; Oji General Hospital: HitoshiOoiwa; Okayama Public General Hospital: MotoyukiMatsui; Saiseikai Kumamoto Hospital: TakashiHonda, KoichikuNakao; Satsuma Medical Center: NobuoYoshimoto; Sapporo Medical University Hospital: KazufumiTsukishima, KazuakiShimamoto; Sasebo City General Hospital: ToshikiroYamasu; Shimane Medical Center: YuzuruOgasahara; Kumamoto Chuo Hospital: TakakuniWakamatsu; University of the Ryukyu Hospital: MichioShimabukuro; Urasoe General Hospital: ToruHiga; Yamagata University Hospital: IssaKubota; Yokohama City Medical Center: KiyoshiHibi, MasamiKosuge, KazuKimura.