Pravastatin for Cardiovascular Event Primary Prevention in Patients With Mild-to-Moderate Hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study

Toshibo Kushiro, Kyoichi Mizuno, Noriaki Nakaya, Yasuo Ohashi, Naoko Tajima, Tamio Teramoto, Shinichiro Uchiyama, Haruo Nakamura; for the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group

Abstract—Lipid-lowering therapy in individuals with high risk of cardiovascular disease reduces the incidence of coronary heart disease. However, few studies have assessed the benefits of cholesterol lowering for primary prevention of coronary heart disease in hypertensive patients with mild dyslipidemia or without conventional dyslipidemia. The large, randomized Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study showed a 33% reduction in coronary heart disease incidence with pravastatin as the primary prevention in Japanese patients. We conducted an exploratory analysis of the effect of diet plus pravastatin therapy on the primary prevention of cardiovascular events (coronary heart disease, coronary heart disease plus cerebral infarction, and cardiovascular disease) in the 3277 patients with hypertension during the 5-year follow-up. There were no significant differences in mean baseline total cholesterol, blood pressure levels, or variation in blood pressure during the 5-year period between the diet (n=1664) and diet plus pravastatin (n=1613) groups. In the diet plus pravastatin group, the relative risk of coronary heart disease plus cerebral infarction was reduced by 35% (hazard ratio: 0.65; CI: 0.46 to 0.93; P=0.02), cerebral infarction by 46% (hazard ratio: 0.54; CI: 0.29 to 0.98; P=0.04), and cardiovascular disease by 33% (hazard ratio: 0.67; CI: 0.49 to 0.91; P=0.01). In patients without a history of cardiovascular disease who have hypertension and mildly elevated cholesterol, pravastatin was effective in reducing the incidence of cardiovascular disease, particularly cerebral infarction. Hence, in patients with hypertension with mildly elevated cholesterol levels, treatment with a statin is advisable to reduce the burden of cardiovascular disease. (Hypertension. 2009;53:135-141.)

Key Words: hypertension ■ hypercholesterolemia ■ diet ■ pravastatin ■ cardiovascular diseases

Epidemiological research has established hypertension as a common and prominent risk factor for the major cardiovascular diseases (CVDs), including coronary heart disease (CHD) and stroke.1 Several risk factors tend to accompany hypertension and thereby increase its risk, including glucose intolerance, obesity, left ventricular hypertrophy, and dyslipidemia (elevated total cholesterol [TC], low-density lipoprotein [LDL] cholesterol, and small-dense LDL cholesterol levels; raised triglyceride [TG] levels; and reduced high-density lipoprotein [HDL] cholesterol levels). Although the beneficial effect of statins on reducing the risk of stroke has been well demonstrated from previous large-scale trials, some concerns, such as an increased risk of hemorrhage or cancer, in relation to lower lipid levels have been raised. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the use of pravastatin versus usual care in patients with mild-to-moderate hypertension produced only nonsignificant reductions in cardiovascular events.2 However, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, in persons with hypertension and ≥3 cardiovascular risk factors and below average serum cholesterol levels, lipid-lowering therapy with atorvastatin reduced the incidence of CVD and stroke by 29% and 27%, respectively.3 It remains uncertain whether statin therapy is effective for the primary prevention of CVD, including stroke for persons with both hypertension and hyperlipidemia in Japan, where their incidence is different from Western countries. Of note, stroke is a major cause

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00211705).

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of death and disability in most populations of eastern Asia, including Japan. Therefore, we conducted a posthoc analysis to examine the effect of pravastatin in persons with hypertension, who accounted for 42% of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study patients, which evaluated the effects of pravastatin in Japanese adults with mildly elevated cholesterol levels.5,6

Methods

MEGA Study
The MEGA Study design and main results were reported previously.4,5 Briefly, diet plus pravastatin reduced mean LDL cholesterol by 18%, and this reduction was associated with a 33% lower incidence of CHD events compared with the diet group during 5.3 years of follow-up. In this prospective, randomized, open-labeled, blinded end point study conducted between 1994 and 2004, we compared the effect of diet versus diet plus pravastatin 10 to 20 mg daily on cardiovascular events in Japanese patients with mildly elevated TC (5.7 to 7.0 mmol/L [220 to 270 mg/dL]) and without CHD. Both postmenopausal women aged ≥70 years and men aged 40 to 70 years were included.

The primary end point was CHD defined as fatal/nonfatal myocardial infarction, angina, cardiac/sudden death, and revascularization. Myocardial infarction was defined by clinical symptom and enzyme level. Secondary end points included cerebral infarction (CI), stroke (CI+intracranial hemorrhage), composite of CHD+CI, all CVD events (CHD+stroke+transient ischemic attack+arterio-sclerosis obliterans), and total mortality. Stroke was discriminated by diagnostic imaging using computed tomography or MRI. For each stroke event, detailed information was obtained from physicians and evaluated by the blinded end point committee according to the established criteria for hemorrhagic and nonhemorrhagic stroke.

Follow-Up

After random assignment, patients were assessed at 1, 3, and 6 months, as well as every 6 months thereafter. At every visit, data on treatment compliance, concomitant use of other drugs, onset of events, occurrence of adverse events, and laboratory tests were gathered by the physicians. Blood pressure (BP) was measured by auscultatory method in each patient while seated at each visit. In addition, an ECG was obtained and assessed annually. The incidence of the end points in the treatment groups was determined in a blinded manner by an end point committee, using prespecified diagnostic criteria based on the clinical course and findings as reported by the attending physicians. The follow-up period was initially scheduled for 5 years; however, based on the recommendation of the data and safety monitoring committee, the study was continued for an additional 5 years to increase the number of events. Thus, patients who provided written consent at 5 years to continue the study were followed until the end of March 2004.

Statistical Analyses

In the main MEGA Study results, the observed risk reduction for stroke was different between the initially planned 5-year follow-up and the entire follow-up period that included the extended follow-up.5 This difference was attributed to the observation that consent to participate in the extended follow-up was obtained more frequently from patients who were in the diet plus pravastatin group than in the diet alone group at 5 years. This could cause an underestimation of the effect of treatment with diet plus pravastatin.6 Thus, the results based on the initial 5-year follow-up may more accurately reflect the potential effect of pravastatin treatment. Therefore, all of our posthoc analyses used the 5-year data, including the present analysis.

Baseline characteristics and lipid changes during each year of the 5-year study period were evaluated in patients with hypertension. Hypertension was defined as clinical diagnosis by physicians at baseline. Time-to-event curves for major events were estimated by the Kaplan–Meier method in patients with hypertension in both treatment groups. The effect of diet plus pravastatin on primary and secondary end points in patients with hypertension was examined. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by Cox proportional hazards model adjusted by sex and age.

Subgroup analyses of patients with known risk factors for CI, such as male sex, presence of diabetes, body mass index (BMI) ≥25 kg/m², current or past smoker, and BP ≥140/90 mm Hg were conducted by a Cox proportional hazards model with sex, age, diabetes mellitus, and HDL cholesterol level as covariates. The evaluation of safety, including severe adverse events and cancers that occurred during the 5-year follow-up, was based on the entire study period for each patient to determine the safety of long-term treatment.

All of the P values are 2 sided, and P values <0.05 were defined as significant. Statistical analyses were done with SAS 8.2 (SAS Institute, Inc.).

Results

The analysis set for the primary analysis, the results of which have already been reported, was composed of 7832 patients (diet therapy: n = 3966; diet plus pravastatin: n = 3866). The present posthoc analysis set was composed of 3277 patients with hypertension (diet group: n = 1664; diet plus pravastatin: n = 1613). Mean age was 3 years older in patients with hypertension than those without, and ECG abnormality was more frequent in patients with hypertension. Also, compared with patients without hypertension, the incidence of obesity and mean BMI were higher, HDL cholesterol was lower, and TG was higher in patients with hypertension at baseline (Table 1). In the patients with hypertension, the baseline characteristics and risk factors for both treatment groups were similar, including BP and serum lipids (Table 2).

Approximately 90% of patients in both treatment groups were taking antihypertensive drugs at baseline. The percentages of patients in the diet and the diet plus pravastatin groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No Hypertension (n=4555)</th>
<th>Hypertension (n=3277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±7</td>
<td>60±7</td>
</tr>
<tr>
<td>Age ≥65 y, %</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Men</td>
<td>1480 (33)</td>
<td>996 (30)</td>
</tr>
<tr>
<td>Women</td>
<td>3075 (67)</td>
<td>2281 (70)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126±15</td>
<td>141±16</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75±9</td>
<td>83±10</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Obesity, %*</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±2.9</td>
<td>24.6±3.2</td>
</tr>
<tr>
<td>ECG abnormality (resting), %</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>TC, mmol/L (mg/dL)</td>
<td>6.3±0.3 (243±12)</td>
<td>6.3±0.3 (242±12)</td>
</tr>
<tr>
<td>LDL-C, mmol/L (mg/dL)</td>
<td>4.1±0.5 (157±18)</td>
<td>4.0±0.4 (156±17)</td>
</tr>
<tr>
<td>HDL-C, mmol/L (mg/dL)</td>
<td>1.5±0.4 (59±15)</td>
<td>1.4±0.4 (56±14)</td>
</tr>
<tr>
<td>TG, mmol/L (mg/dL)</td>
<td>1.4 (121)</td>
<td>1.5 (137)</td>
</tr>
</tbody>
</table>

Values are means±SDs or n (%) unless otherwise indicated. SBP indicates systolic BP; DBP, diastolic BP; LDL-C, LDL cholesterol; HDL, HDL cholesterol. *BMI ≥25 kg/m².
Table 2. Baseline Characteristics, Lipid Parameters, and Antihypertensive Drug Use at Baseline in Patients With Hypertension in the MEGA Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diet (n=1664)</th>
<th>Diet + Pravastatin (n=1613)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±7</td>
<td>60±7</td>
</tr>
<tr>
<td>Age ≥65 y, %</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Women, %</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>141±16</td>
<td>141±15</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83±10</td>
<td>83±10</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Obesity, %*</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6±3.1</td>
<td>24.7±3.3</td>
</tr>
<tr>
<td>ECG abnormality (resting), %</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>TC, mmol/L (mg/dL)</td>
<td>6.3±0.3 (242±12)</td>
<td>6.3±0.3 (242±12)</td>
</tr>
<tr>
<td>LDL-C, mmol/L (mg/dL)</td>
<td>4.0±0.5 (155±18)</td>
<td>4.0±0.4 (156±17)</td>
</tr>
<tr>
<td>HDL-C, mmol/L (mg/dL)</td>
<td>1.5±0.4 (56±15)</td>
<td>1.4±0.4 (56±14)</td>
</tr>
<tr>
<td>TG, mmol/L (mg/dL) [median]</td>
<td>1.6 (138)</td>
<td>1.5 (137)</td>
</tr>
</tbody>
</table>

Values are means±SDs or n (%) unless otherwise indicated. SBP indicates systolic BP; DBP, diastolic BP; LDL-C, LDL cholesterol; HDL, HDL cholesterol. *BMI ≥25 kg/m².

who had taken calcium channel blockers were 63% and 62%, respectively; angiotensin-converting enzyme inhibitors were 28% for both; and β-blockers were 23% for both. α-Blockers were used in only 6% and 8% of diet and diet plus pravastatin patients, and diuretics were used in only 7% and 6%, respectively. Angiotensin II receptor blockers came to market in 1995; thus, their use was limited.

At 5 years, compared with baseline, the mean systolic BP was reduced by 1.9 mm Hg (baseline: 141.0 mm Hg; follow-up: 138.1 mm Hg) and the mean diastolic BP by 1.7 mm Hg (baseline: 82.9 mm Hg; follow-up: 79.3 mm Hg) in the diet group. In the diet plus pravastatin group, the reductions were 1.8 mm Hg (baseline: 140.9 mm Hg; follow-up: 138.6 mm Hg) and 1.7 mm Hg (baseline: 82.9 mm Hg; follow-up: 80.3 mm Hg), respectively. The variation in BP over the 5-year treatment period was similar in both groups (Figure 1).

Diet plus pravastatin, compared with diet alone, significantly decreased in TC (−12.8% [from 6.3 to 5.4 mmol/L] versus −2.2% [from 6.3 to 6.1 mmol/L]; P<0.001), LDL cholesterol (−20.0% [from 4.0 to 3.2 mmol/L] versus −3.6% [from 4.0 to 3.8 mmol/L]; P<0.001), and TG (−9.6% [from 1.5 to 1.3 mmol/L] versus −1.6% [from 1.6 to 1.3 mmol/L]; P<0.001) and significantly increased in HDL cholesterol (4.7% [from 1.4 to 1.5 mmol/L] versus 2.0% [from 1.5 to 1.5 mmol/L]; P=0.004; Figure 2).

The primary end point, CHD, was observed in 35 of 1613 patients in the diet plus pravastatin group (4.8/1000 person-years) and in 51 of 1664 patients in the diet-alone group (6.7 per 1000 person-years). Treatment with diet plus pravastatin was associated with a 29% lower relative risk of experiencing a primary end point event compared with diet alone, although this result was not statistically significant (Figures 3 and 4). The incidence of myocardial infarction in the diet plus pravastatin and diet-alone groups was 1.6 and 2.1 per 1000 person-years, respectively. Regarding the secondary outcome measures, better cardiovascular outcomes were observed in all of the categories of end point events in the diet plus pravastatin versus the diet-alone group (Figures 3 and 4). The incidence of CHD+CI, CI, and CVD events was significantly reduced by 35% (95% CI: 0.46 to 0.93; P=0.019), 46% (95% CI: 0.29 to 0.98; P=0.044), and 33% (95% CI: 0.49 to 0.91; P=0.012), respectively, in the diet plus pravastatin group compared with the diet-alone group (Figure 3). The diet plus pravastatin therapy reduced the incidence of stroke and all-cause death by 31% (95% CI: 0.42 to 1.12; P=0.13) and 22% (95% CI: 0.46 to 1.33; P=0.36), although these differences were not significant (Figure 4).
47 ischemic strokes (diet: n=31; diet plus pravastatin: n=16), 20 hemorrhagic strokes (diet: n=9; diet plus pravastatin: n=11), and 1 not classifiable (diet: n=1). There was no significant difference in the incidence of hemorrhagic stroke between treatment groups (P=0.58). Notably, pravastatin had an early effect on reducing the incidence of CI, with the Kaplan–Meier curves beginning to diverge soon after initiation of treatment (Figure 4).

The number needed to treat to prevent 1 incidence of CI over 5 years was 115 persons, for CHD or CI it was 61, and for CVD it was 50 persons. Subgroup analysis of risk factors for CI showed that pravastatin reduced the incidence of CI in men by 57%, in the presence of diabetes mellitus by 69%, in those with BMI $\geq 25$ kg/m$^2$ by 47%, in current/past smokers by 73%, in the BP-controlled group by 47%, and in the BP-uncontrolled group by 46% (Figure 5). No significant interaction was detected between patients with and without additional risk factors for CI or for BP control status.

Adverse events and laboratory findings are summarized in Table 3. No significant difference was seen between the 2 groups in terms of severe adverse events, all-site cancer, and abnormal laboratory parameters. No incidence of rhabdomyolysis was seen in either treatment group.

### Discussion

A number of epidemiological studies have investigated risk factors for stroke$^7$–$^10$ and established them to include hypertension,$^7$,$^8$ diabetes mellitus,$^8$,$^9$ smoking,$^7$,$^8$ and heavy alcohol intake.$^10$ Hypertension is the strongest risk factor for stroke, and stroke prevention has become one of the main objectives of BP control. However, although there appears to be no strong correlation between high serum cholesterol and incidence of stroke,$^11$ there is considerable evidence from many clinical trials that have demonstrated consistent benefits of lipid lowering by statins in reducing the incidence of stroke in the settings of both primary and secondary prevention.$^{12–15}$ In

### Figure 3.

Effect of pravastatin on cardiovascular end points. MI indicates myocardial infarction.

### Figure 4.

Kaplan–Meier plots showing the effects of pravastatin on (A) CHD, (B) CI, (C) CHD+CI, and (D) CVD events. NNT indicates numbers needed to treat.
addition, meta-analyses of these studies suggest that statins can reduce the risk of stroke in patients with coronary artery disease or hypercholesterolemia.16–23

Recent clinical trials were conducted specifically to assess the benefits of cholesterol-lowering therapy for the primary prevention of CHD in patients with hypertension without dyslipidemia (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm)3 and with risk factors for CHD events (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).2

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, there were significant reductions in CHD (36%), stroke (27%), and CVD (21%) in the atorvastatin group. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, no significant reductions were found in total mortality, CHD, or stroke with pravastatin. One reason for the different results from these trials seems to be the 9.6% difference in the TC level between the treatment groups at study end (pravastatin: /H11002 17.2%; usual care: /H11002 7.6%): less than half the average found in the other 8 long-term statin trials with /H11350 1000 participants.16,24–30 Despite the conflicting results in these previous studies, reductions were found in the present analysis: CHD by 29% (P=0.12), CHD + CI by 35% (P=0.019), CI by 46% (P=0.044), and CVD by 33% (P=0.012), with a differential in reductions of 10.6% in TC (diet: –2.2%; diet plus pravastatin: –12.8%) and in LDL cholesterol of 16.4% (diet: –3.6%; diet plus pravastatin: –20.0%). The sample size in the present analysis is too small to determine whether the beneficial effects are related to lower LDL level.

In this analysis, the risk reduction of each event in the patients with hypertension was similar to those without hypertension, and in some cases more effective compared with the total population,5 particularly for CI. This is despite the patients with hypertension being at higher risk (average age of 3 years older, more frequent ECG abnormality, higher incidence of obesity and greater mean BMI, lower HDL cholesterol, and higher TG) at baseline (Table 1). The present results indicate that diet plus pravastatin was an effective treatment for the primary prevention of cardiovascular events, especially CI, in Japanese patients with hypertension and moderate hyperlipidemia.

Observational studies and epidemiological research have shown associations between low cholesterol levels and hemorrhagic stroke. Therefore, there has been concern that statin treatment will increase the risk of hemorrhagic stroke, even while lowering the risk of ischemic stroke. This effect might counterbalance the overall assessment of statins on preventing stroke. In the Long-Term Intervention with Pravastatin in Ischemic Disease Study,31 pravastatin did not increase the risk of hemorrhagic stroke (incidence of 0.4% versus 0.2% for nonhemorrhagic stroke; P=0.28). In the MEGA Study and in a pooled analysis of the Cholesterol and Recurrent Events Study and the Long-Term Intervention with Pravastatin in Ischemic Disease Study participants, pravastatin was associated with a reduction of nonhemorrhagic stroke; no statistical difference between treatment groups was found for hemorrhagic strokes or unknown type. Therefore, the effect of pravastatin on reducing stroke risk over a wide range of

Table 3. Adverse Events and Laboratory Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diet Group (n=1664)</th>
<th>Diet + Pravastatin (n=1613)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe adverse events</td>
<td>206 (12.4)</td>
<td>212 (13.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>All-site cancer</td>
<td>51 (3.1)</td>
<td>51 (3.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>ALT &gt;1.67 μkat/L (100 IU)</td>
<td>57 (3.5)</td>
<td>47 (3.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>CK &gt;8.35 μkat/L (500 IU)</td>
<td>43 (2.6)</td>
<td>51 (3.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

ALT indicates alanine amino transferase; CK, creatine kinase; NA, not applicable.
lipid values was attributable to a reduction in nonhemorrhagic strokes.

In the present study of primary prevention, the incidence of CI began to diverge early, and a significant difference for the combined end point of CHD+CI was seen at 1 year. The Prospective Study of Pravastatin in Elderly at Risk was conducted in a large cohort of 70- to 82-year-old normal cholesterolemic men and women either with preexisting vascular disease or who were at risk of such disease because of smoking, hypertension, or diabetes. Although randomized assignment to pravastatin significantly reduced the primary combined end point, there was no discernible effect on cerebrovascular outcomes, transient ischemic attack, or decline of cognitive function, which may be related to vascular factors, during the 3.2 years of follow-up. This might have been because of the relatively short period, because it has been suggested that longer-term intervention may be necessary for statin therapy to show an effect on reducing stroke. For instance, in a subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm cohort to determine the timing of cardiovascular risk reduction, whereas for coronary artery disease events significant differences in the HR in CVD between active treatment and placebo became apparent at 30 days and significant within 3 months, a significant reduction in the risk for stroke was detected only after 2 years of follow-up. More data are required to assess whether statin therapy reduces the risk of stroke in the short term. An ongoing clinical trial of pravastatin, the Japan Statins Treatment to Prevent Stroke Study, is expected to provide more data on the timing of onset of action of pravastatin with regard to preventing stroke occurrence.

Perspectives

Diet plus pravastatin reduced all of the major cardiovascular events in patients with hypertension in this posthoc analysis of the MEGA Study. Although given at a mean daily dose as low as 8.3 mg daily (maximum allowable dose in Japan is 20.0 mg/d), our results indicate that diet plus pravastatin therapy was effective at reducing cardiovascular events in Japanese patients with hypertension and hyperlipidemia, similar to reductions in other large-scale clinical statin studies in Western countries. Notably, pravastatin was effective for the primary prevention of CI.

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References


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