Serum Lipid Goal Attainment in Chronic Kidney Disease (CKD) Patients under the Japan Atherosclerosis Society (JAS) 2012 Guidelines

A Single-Center Study

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Aim: According to the Japan Atherosclerosis Society 2012 guidelines (JAS2012-GL), chronic kidney disease (CKD) has newly been added to the high-risk group in terms of atherosclerotic cardiovascular diseases. We therefore explored the lipid target level achievement rates under the JAS2012-GL in real-world clinical practice.

Methods: We retrospectively reviewed the medical charts of patients who were hospitalized at the Nephrology Department at Kobe City Medical Center General Hospital in the period from April 1, 2012 to May 31, 2013 and explored the serum lipid target level achievement rates. Patients without lipid data or those undergoing regular dialysis because of chronic renal failure were excluded. In this study, the CKD group (CKD-G) did not include CKD patients under secondary prevention for coronary heart disease (CHD) or diabetes mellitus (DM).

Results: The CKD-G included 146 (81.1%) of the 180 enrolled patients. According to the JAS2012-GL, 100% of the CKD-G patients were categorized into the high-risk group, although only 12.1% of the CKD-G subjects were at high risk according to the JAS2007-GL. Under the JAS2012-GL, the LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) target level achievement rates for CKD-G were 71.4% and 68.1%, respectively. According to the JAS2007-GL, these rates were 81.3% and 79.1%, respectively, and, under both guidelines, these rates were 71.7% and 72.1% for primary prevention DM and 66.7% and 66.7% for CHD, respectively.

Conclusions: After the revision of the JAS-GL in 2012, the LDL-C and non-HDL-C target level achievement rates for CKD-G were reduced by approximately 10%; however, they remained similar to those for DM and higher than those for CHD.


Key words: Guidelines, Risk stratification, Chronic kidney disease, Lipoproteins

Introduction

Atherosclerotic cardiovascular disease (ACVD) is the major cause of premature death in Western countries. In Japan, where demographic aging is proceeding at an unprecedented speed, the incidence of ACVD is also predicted to be increasing. Dyslipidemia, especially the high LDL cholesterol (LDL-C) level, is one of the most important risk factors for ACVD. Therefore, managing the LDL-C level is extremely important for preventing ACVD, and the target LDL-C level for a patient should be determined...
based on a comprehensive consideration of the relevant coronary heart disease (CHD) and diabetes mellitus (DM) history and other risk factors for ACVD when treating dyslipidemia.

In 2002, the Japan Atherosclerosis Society 2002 guidelines (JAS2002-GL) for the diagnosis and treatment of ACVD were published taking into account the results of the Japan Lipid Intervention Trial (J-LIT)\(^1\). Cut-off values for the total cholesterol (TC), LDL-C, triglyceride (TG) and HDL-cholesterol (HDL-C) levels for the diagnosis of dyslipidemia were 220 mg/dL, 140 mg/dL or 150 mg/dl and 40 mg/dL, respectively. The target management LDL-C level differs from the diagnostic cut-off value and depends on the patient's risk profile, such as CHD and the number of ACVD risk factors.

The JAS-GL was revised twice in 2007 (JAS2007-GL)\(^2\) and 2012 (JAS2012-GL)\(^3\). In 2007, the diagnostic criteria for hyperlipidemia were changed to the diagnostic criteria for dyslipidemia, taking into account the presence of low HDL-C and high TG levels, which make LDL-C particles smaller and more atherogenic. Due to the prevalence of subjects with a high HDL-C level, the TC level was removed from the diagnostic criteria. The major revised points in the JAS2012-GL were as follows. Emphasis was placed on the importance of providing comprehensive management of ACVD, including the adoption of the concept of absolute risk. Therefore, patients were classified into categories based on the absolute risk assessment chart developed in the NIPPON DATA 80 epidemiological study in Japan\(^4,\,5\). Chronic kidney disease (CKD) was newly classified as a high risk factor, similar to DM\(^6\). Furthermore, the non-HDL cholesterol level (non-HDL-C) was introduced as a treatment goal, secondary to the LDL-C goal, in cases of hypertriglyceridemia\(^5\).

Aim

The aim of this study was to examine compliance with the new guidelines, JAS2012-GL, compared to the old guidelines, JAS2007-GL, in real-world clinical practice. In the present study, the lipid target level achievement rates in CKD patients were assessed compared with those observed in DM and CHD subjects, as all CKD patients are newly categorized into the high-risk group, similar to DM.

Methods

Study Population

The medical charts of all patients hospitalized at the Department of Nephrology at Kobe City Medical Center General Hospital, Kobe, Japan in the period from April 1, 2012 to May 31, 2013 were retrospectively reviewed. Subjects who underwent regular dialysis because of chronic renal failure or those without lipid data were excluded. CKD of stage III or higher, according to the guidelines from the Japanese Society of Nephrology, was regarded as a high risk factor for ACVD. CHD was defined as myocardial infarction, angina pectoris or a history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, as described in the medical charts. We confirmed these findings based on a careful reading of the medical charts. The LDL-C levels were calculated using the Friedewald formula. If the serum TG level was above 200 mg/dL, the LDL-C level measured using a direct LDL-C measurement kit from Sekisui Medical Co. Ltd. was utilized. If the lipid levels were evaluated more than once, the steady state levels after admission were utilized. In this study, the CKD group (CKD-G) did not include CKD patients with CHD or DM, and the DM group (DM-G) did not contain DM subjects with CHD, due to the risk stratification assessment under the JAS-GL. The study protocol was approved by the ethics committees at Kobe City Medical Center General Hospital and Kobe Gakuin University.

Statistical Analysis

Continuous variables are presented as the mean ± standard error of mean (SEM), and categorical variables are shown as numbers and percentages. Based on their distribution, continuous variables were compared using Student's \(t\)-test and categorical variables were compared with the \(\chi^2\) test. All statistical analyses were carried out using the IBM SPSS Statistics software program (SPSS Inc.). \(P\) values below 0.05 (\(p < 0.05\)) were considered to be statistically significant.

Results

Patient Enrollment

The medical charts of all the 315 patients who were hospitalized at the Department of Nephrology, Kobe City Medical Center General Hospital in the period from April 1, 2012 to May 31, 2013 were reviewed retrospectively. Eighty-six (86) subjects without lipid data, as well as 49 patients who underwent regular dialysis because of chronic renal failure, were excluded. As a result, a total of 180 patients were enrolled (Fig. 1).

Characteristics of the Enrolled Patients

The characteristics of the enrolled patients are
Subjects admitted to Nephrology Department in Kobe City Medical Center General Hospital from April 2012 to May 2013 (n=315)

Subjects with complete lipid data (n=229)

Subjects without complete lipid data (n=86)

Enrolled patients (n=180)

Subjects on dialysis for chronic renal failure (n=49)

Fig. 1. Schematic illustration of patient exclusion and enrollment

Table 1. Characteristics of the enrolled patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count Value</th>
<th>Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.8 ± 1.4</td>
<td>(180)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>22.6 ± 0.3</td>
<td>(173/180)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47.8 (86)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52.2 (94)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>69.8 (125)</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>81.1 (146)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>30.6 (55)</td>
<td></td>
</tr>
<tr>
<td>Lipid profiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>106.4 ± 3.0</td>
<td>(180)</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>128.0 ± 5.2</td>
<td>(180)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>57.1 ± 1.7</td>
<td>(180)</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL</td>
<td>132.1 ± 3.5</td>
<td>(177/180)</td>
</tr>
<tr>
<td>CHD</td>
<td>10.0 (18)</td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as the percent (n) or mean ± SEM (n).

HT, hypertension; CKD, chronic kidney disease, DM, diabetes mellitus; LDL-C, LDL cholesterol; TG, triglycerides; HDL-C, HDL cholesterol; non-HDL-C, non-HDL cholesterol.

summarized in Table 1. The mean age of the study population was 61.8 years, and 47.8% of the subjects were men. The prevalence (number) of cases of hypertension (HT), CKD, DM and CHD was 69.8% (125), 81.1% (146), 30.6% (55) and 10.0% (18), respectively. The mean (± standard error) levels of LDL-C, TG, HDL-C and non-HDL-C were 106.4 ± 3.0, 128.0 ± 5.2, 57.1 ± 1.7 and 132.1 ± 3.5 mg/dL, respectively.

Comparison of Risk Stratification in the CKD-G Group between the JAS2012-GL and JAS2007-GL

The majority (87.9%) of CKD-G patients were stratified into moderate or low risk groups according to the JAS2007-GL. In contrast, all (100%) of the subjects were categorized into the high-risk group under the JAS2012-GL (Fig. 2).

LDL-C and Non-HDL-C Target Level Achievement Rates in the CKD-G Group According to the JAS2012-GL and JAS2007-GL

The LDL-C and non-HDL-C target level achievement rates according to the JAS2007-GL in the CKD-G group were 81.3% and 79.1%, respectively (Table 2). Under the JAS2012-GL, in contrast, these rates were 71.4% and 68.1%, respectively (Table 2). The differences (9.9% in LDL-C and 11.0% in non-HDL-C) in the target lipid level achievement rates between the JAS2007-GL and JAS2012-GL were much smaller than we had expected based on the large difference in the prevalence of patients categorized into the high-risk group (12.1% versus 100%, Fig. 2).
Comparison of the LDL-C and Non-HDL-C Levels between the CKD-G and DM-G Groups

In addition, according to the JAS2012-GL, the LDL-C and non-HDL-C target level achievement rates in the CKD-G group (71.4% and 68.1%) were comparable to those in the DM-G group (71.7% and 72.1%, Table 2) and higher than those in the CHD group (66.7% and 66.7%, Table 2).

Comparison of Lipid-Lowering Medication Prescription Rates between the CKD-G and DM-G Groups

Fig. 4 compares the prescription rates for lipid-lowering medications between the CKD-G and DM-G groups. The lipid-lowering medication prescription rates were 29.7% and 45.7% in the CKD-G and DM-G groups, respectively. Lipid-lowering drugs were significantly less frequently prescribed in the CKD-G group than in the DM-G group. This difference was statistically significant \((p = 0.049)\).
Comparison of the LDL-C and Non-HDL-C Target Level Achievement Rates According to the JAS2012-GL between the CKD-G and DM-G Groups among the Patients Treated with or without Lipid-Lowering Medications

In the patients treated with lipid-lowering medications, the LDL-C target level achievement rates in the CKD-G and DM-G groups were 85.2% and 81.0%, respectively (\( p = 0.495 \), Fig. 5, panel A). In the patients treated without lipid-lowering medications, these rates in the CKD-G and DM-G groups were 65.6% and 64.0%, respectively (\( p = 0.536 \), Fig. 5, panel B). In the patients treated with lipid-lowering medications, the non-HDL-C target level achievement rates in the CKD-G and DM-G groups were 81.5% and 80.0%, respectively (\( p = 0.593 \), Fig. 5, panel A). Meanwhile, these rates in the patients treated without lipid-lowering medications were 62.5% and 65.2% in the CKD-G and DM-G groups, respectively (\( p = 0.512 \), Fig. 5, panel B). In both the CKD-G and DM-G groups, the LDL-C and non-HDL-C target level achievement rates were higher in
the patients treated with lipid-lowering medications than in those treated without lipid-lowering medications. The LDL-C and non-HDL-C target level achievement rates in the CKD-G group appeared to be comparable to those observed in the DM-G group among both patients treated with and without lipid-lowering medications.

**Comparison of the Lipid-Lowering Medication Prescription Rates between the Patients who did and did not Achieve the Lipid Goals in the CKD-G and DM-G Groups**

The lipid-lowering medication prescription rates were compared between the patients who did and did not achieve the LDL-C and non-HDL-C goals in the CKD-G and DM-G groups. As shown in Fig. 7, the lipid-lowering medication prescription rates were 35.4% and 15.4% in the CKD-G patients who did and did not achieve the LDL-C target level, respectively ($p=0.048$), and 51.5% and 30.8% in the DM-G patients who did and did not achieve the LDL-C target level, respectively ($p=0.173$). As shown in Fig. 8, these rates were 35.5% and 17.2% in the CKD-G patients who did and did not achieve the non-HDL-C target level, respectively ($p=0.060$), and 51.6% and 33.3% in the DM-G patients who did and did not achieve the non-HDL-C target level, respectively ($p=0.232$). In addition, the LDL-C ($p=0.010$) and non-HDL-C ($p=0.019$) levels were significantly lower in the patients treated with lipid-lowering drugs than in those treated without these drugs in the CKD-G group, but not the DM-G group ($p=0.063$ and $p=0.062$, respectively).

**Discussion**

Atherosclerosis is a chronic disorder that develops insidiously throughout life and usually progresses to an advanced stage until clinical symptoms become apparent as ACVD. CKD is a common disorder in Japan and is associated with an increased risk of ACVD. Similar to that observed in Western countries, effective lipid-lowering therapy has been reported to delay the onset of ACVD in Japan. In the JAS2012-GL, CKD is newly classified as a high-risk condition, in accordance with the ESC/EAS guidelines in Europe and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines in the U.S. In Japan, all patients with CKD are now categorized into the high-risk group, whose target serum LDL-C level is the same as that for patients with DM. In the ESC/EAS and K/DOQI guidelines, the target LDL-C levels of moderate to severe CKD patients are 70 and 100 mg/dL, respectively. In the JAS2012-GL, the treatment goal for LDL-C is 120 mg/dL, which is higher than that seen in Europe and the U.S. In the present study, compliance with the new guidelines, JAS2012-GL, in
enrolled patients were hospitalized at a department of nephrology, and patients with dyslipidemia treated without lipid-lowering medications were also included. Likely for this reason, the LDL-C target level achievement rates in our study were lower than those in the above two studies. However, the LDL-C target level achievement rates in the present study were higher than those observed in the JL-GAP and J-LAP studies, in both the primary prevention high-risk and secondary prevention groups.

The LDL-C target level achievement rates, according to the JAS2007-GL, were also examined based on the Japan Society of Ningen Dock database. The results showed that, in the primary prevention high-risk group, the LDL-C target level achievement rates were 62.9% and 42.3% among the patients treated with and without lipid-lowering medications, respectively. The LDL-C target level achievement rate is 44.7% in the secondary prevention patients treated with lipid-lowering drugs. Therefore, the serum lipid goal attainment rates in the present chart survey appear to be superior to those in other previous studies in Japan.

In a large-scale cross-sectional survey in Japan conducted in 2003, namely the Japan Lipid Assessment Program (J-LAP), the LDL-C target level achievement rates were highest in the patients treated with atorvastatin, and the values were approximately 65% and 40% for primary prevention high-risk patients and patients under secondary prevention for CHD, respectively, according to the JAS2002-GL. In the Japan Lipid Guideline Achievement Program (JL-GAP) performed in 2010, the LDL-C target level achievement rates with statin monotherapy for primary prevention high-risk patients and patients treated with secondary prevention for CHD were 56.5% and 24.5%, respectively, according to the JAS2007-GL, despite the emergence of two additional strong statins, pitavastatin and rosuvastatin, after the J-LAP. In the JL-GAP and J-LAP, importantly, all enrolled patients had been prescribed lipid-lowering medications, mostly statins, for at least three months before the survey. In the present study, in contrast, the real-world clinical practice, was explored and compared to that for the former guidelines, JAS2007-GL, focusing on CKD patients in comparison with DM patients. To the best of our knowledge, this is the first report to show the serum lipid goal attainment rates in CKD patients under the new guidelines, JAS2012-GL.

Fig. 7. Comparison of the lipid-lowering medication prescription rates between the patients who did and did not achieve the LDL-C goal in the CKD-G and DM-G groups

The lipid-lowering medication prescription rates were compared between the patients who did and did not achieve the LDL-C goal in the CKD-G group (left two bars, $p=0.048$) and the DM-G group (right two bars, $p=0.173$). The values are expressed as percentages. The $p$ values were derived from the $\chi^2$ statistics.

Fig. 8. Comparison of the lipid-lowering medication prescription rates between the patients who did and did not achieve the non-HDL-C goal in the CKD-G and DM-G groups

The lipid-lowering medication prescription rates were compared between the patients who did and did not achieve the non-HDL-C goal in the CKD-G group (left two bars, $p=0.060$) and the DM-G group (right two bars, $p=0.232$). The values are expressed as percentages. The $p$ values were derived from the $\chi^2$ statistics.
as CHD risk equivalent, as recommended in the K/DOQI guidelines, 59.2 million persons were above the target LDL-C goals, indicating a 4.1 million increase in the number of patients who did not achieve the target LDL-C goals. A table in that manuscript shows that the number of CKD (stage 3-5) subjects was 13.9 million; therefore, 29.5% of the CKD (including CHD and DM) patients were additionally above the target LDL-C goals. In our study, 9.9% of the CKD (without CHD and DM) patients were newly above the target LDL-C goal. This difference may be derived from the difference in the levels of the LDL-C goals between the Japan and U.S. guidelines, as well as the serum LDL-C levels.

As compared to CKD, to our surprise, lipid management in CHD and DM patients remains unsatisfactory. This may result from the fact that typical lipid abnormalities in CKD subjects appear to include high TG and low HDL-C levels and that the LDL-C levels are relatively lower in CKD patients than in DM patients, as indicated in this study. In any case, more aggressive treatment is needed for secondary prevention and in both DM and CKD patients. In fact, the lipid-lowering drug prescription rate was much lower in the CKD-G group than in the DM-G group in the current study. In the CKD-G group, furthermore, lipid-lowering medications were much less frequently prescribed in the patients above the lipid goal than in those achieving the goal.

Limitations of the present study include the single-center retrospective cross-sectional study design with a relatively small sample size conducted only at a nephrology department. In addition, the lipid management status was not repetitively evaluated in the same subjects, especially before and after the release of the new guidelines. Hence, future studies with larger sample sizes are needed to confirm the findings of the present study.

Conclusion

The present data indicate that lipid goal attainment is insufficient in CKD patients because of the low prevalence of lipid-lowering drug prescriptions and suggest that lipid management in patients with high risks, such as those receiving secondary prevention for CHD and primary prevention with DM, in addition to CKD, remains to be improved.

Acknowledgments

We thank Yuki Maruyama, Ayano Kobayashi, Mari Seiki, Mao Morimoto, Aina Kitaoka and Yurina Omiya for their assistance in the medical chart survey at Kobe City Medical Center General hospital.

COI

Toru Kita received honoraria from Daiichi-Sankyo, Kowa and MSD.

References


