Comparative analysis of the efficacy of low- and moderate-intensity statins in Korea

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Key words

Abstract. Purpose: The American College of Cardiology/American Heart Association (ACC/AHA) guidelines are based on studies with a limited number of Asian subjects; therefore, they are difficult to apply to Asian patients, including Korean patients. Materials and methods: Data were extracted from the clinical data warehouse system of Seoul St. Mary’s hospital (January 2010 – December 2012) to determine the percent change in low-density lipoprotein cholesterol (LDL-C) levels at an average 3 and 6 months from baseline. Statins with statistically similar lowering effects were placed in one group (group A, B, or C). The proportions of patients who achieved LDL-C < 100 mg/dL were compared between baseline LDL-C levels: low (< 130 mg/dL), medium (130 – 160 mg/dL), and high (> 160 mg/dL). Results: The majority of the 9 statins of various dosages (2,349 patients) were effective at 3 months, with additional, smaller decreases at 6 months. The LDL-C lowering effect of group A (atorvastatin (20 mg), rosuvastatin (10 mg)) was ~ 45%; that of group B (atorvastatin (10 mg), pitavastatin (2 mg), pravastatin (40 mg), simvastatin (20 mg)) was 35 – 37%. Groups A and B contained only moderate-intensity statins (ACC/AHA guidelines). With baseline LDL-C ≥ 130 mg/dL, greater proportions of patients achieved LDL-C < 100 mg with atorvastatin (20 mg) and rosuvastatin (10 mg). Conclusion: Because of the documented LDL-C lowering effects and target achievement rates, the ACC/AHA guidelines might not apply to Korean patients. Korean treatment guidelines should consider statins with relatively low potency. Additional studies regarding appropriate statin doses should be conducted with Asian populations.

Introduction

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) published updated guidelines for the treatment of hyperlipidemia based on the accumulating research conducted to reduce low-density lipoprotein cholesterol (LDL-C) levels [1], owing to its contribution to atherosclerosis and complications of cardiovascular disease. The new version emphasizes the prevention of atherosclerotic cardiovascular disease and recommends the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors as first line treatment. Statins decrease LDL-C and triglyceride levels and increase high-density lipoprotein cholesterol levels [2, 3, 4, 5]. Target LDL-C levels, which are typically used as treatment goals for statins, have been removed from this latest version of the guidelines; instead, the LDL-C lowering effect (as a % change from the baseline value) of statins has been emphasized, based on various randomized clinical trials. While some believe that the guidelines reflect the true clinical situation [6, 7], others do not.

In many Asian countries that have been using the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) guidelines [8], such as Korea, the updated ACC/AHA guidelines are likely to be controversial. Although previous treatment strategies that were based on the former NCEP-ATP III guidelines should be updated based on the new ACC/AHA guidelines,
use of statins at high doses is still very controversial in Korea because the ACC/AHA guidelines are based on studies that included a limited number of Asian subjects. Furthermore, it has been suggested that initiation of treatment with low-dose statins is sufficient [9]. Compared with previous guidelines such as the 2011 European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines, the 2013 ACC/AHA guidelines include considerable differences in treatment methods and assessment of high-risk groups [10]. Thus, in Korea, a number of controversies regarding these guidelines exist, and many issues need to be resolved before the guidelines are applied.

Moreover, the prescription of statins should be based on the absolute risk of developing symptomatic coronary heart disease that reflects the classic risk factors as well as a recalibration according to the prevalence within that population, as recommended by the ESC/EAS [10]. This is also true for Asian populations [10], including recalibration of the absolute risk in specific populations in Asia. Therefore, large-scale research should be conducted in Asian populations to determine the appropriate statin classifications and advantages/disadvantages of statin use, with the aim of establishing guidelines specific to Asian patients, rather than applying hyperlipidemia treatment guidelines that have been developed for Western populations. However, data to evaluate the cardiovascular risk in Korean patients are lacking. Therefore, the present study aimed to classify statins based on their effects in patients previously administered statins to provide a basic dataset for use in future large-scale studies.

Material and methods

We established the study dataset using prescription and laboratory data based on a Clinical Data Warehouse (CDW) system, which is a database that is optimized for mass storage and complex query processing for clinical research [11]. The Seoul St. Mary's hospital implemented a CDW system on a centralized Oracle database server (Oracle, CA, USA) in 2012. This study was approved by the institutional review board of the Catholic University of Korea. Owing to the anonymity of the data and retrospective nature of the study, informed consent was not required.

Extraction of the study sample and study design

Data for patients who were prescribed a statin for the first time at Seoul St. Mary's hospital between January 1, 2010 and December 31, 2012 were extracted from the CDW. Cases were identified as those who did not have a statin prescription for at least 6 months before a statin was prescribed for the first time. The date on which the initial statin prescription occurred was defined as visit 0 (baseline). Visit 1 (average 3 months later) was defined as the next occurrence of a laboratory test and subsequent renewal of the statin prescription within 2–4 months of baseline, and visit 2 was defined as the next visit that occurred within 5–7 months after baseline (average 6 months later). Patients were excluded if they had terms 4–5 months from baseline; were missing an LDL-C value at baseline, visit 1, or visit 2; had a change in the prescription to a different statin type; or had the statin prescription suspended during the study period. To determine the LDL-C lowering effect of each statin, the changes in the LDL-C value at visit 1 and visit 2, from baseline, were calculated: LDL-C lowering effect (%) = mean percent change (‰) = 100 × (visit 2 (or visit 1) – visit 0)/visit 0. We also calculated the proportion of the patients who achieved the LDL-C goal (<100 mg/dL) at visit 2; this value was compared between the statin types and between those with low (LDL-C < 130 mg/dL), medium (130–160 mg/dL), and high (≥160 mg/dL) baseline LDL-C levels.

Statin types and classification

Six types of statins currently available at Seoul St. Mary's hospital were selected for this study and classified into 15 categories based on dose: atorvastatin (10 mg, 20 mg, and 40 mg), fluvastatin (40 mg and 80 mg), pitavastatin (2 mg), pravastatin (10 mg, 20 mg, and 40 mg), rosuvastatin (5 mg,
Figure 1. Trial profile. Patients in the clinical data warehouse database that were prescribed a statin for the first time during the study period (January 1, 2010 – December 21, 2012).

10 mg, and 20 mg), and simvastatin (10 mg, 20 mg, and 40 mg). Combination treatments (simvastatin plus ezetimibe, atorvastatin plus amlodipine, or pravastatin plus fenofibrate) were excluded.

The ACC/AHA guidelines [1] categorize statins into three groups based on the LDL-C lowering effect from baseline: high-intensity statin, ≥ 50% LDL-C reduction; moderate-intensity statin, 30 – 50% reduction; and low-intensity statin, ≤ 30% reduction. Similarly, depending on the LDL-C lowering effect in the present study, the statins were divided into three groups: groups A, B, and C. The statins within each group had statistically similar average percent changes (p > 0.05).

**Statistical analysis**

The primary analysis examined the effect of the statins on the average LDL-C change from the baseline value using an ANOVA and the Student-Newman-Keuls (SNK) test for post-hoc analysis owing to the fact that the SNK test is more powerful than the Tukey test [12]. An ANOVA was also performed to compare statin equivalent doses [13] between visit 1 and visit 2. The secondary analysis determined the proportion that achieved LDL-C levels < 100 mg/dL at visit 2 for the total sample and for each of the following subsets: low (< 130 mg/dL), medium (130 – 160 mg/dL), and high (> 160 mg/dL) LDL-C levels at baseline. The proportions that achieved the goal LDL-C level were compared between statins using two sample proportion tests. The Holm test or Hochberg method was used to adjust for multiple comparisons. For unequal and heterogeneous variance, the Games-Howell procedure was used. The statistical software SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for analysis.

**Results**

Of the patients in the database, 4,449 people were prescribed a statin for the first time, and 1,290 cases without LDL-C blood test results from visit 1 and visit 2 were excluded. A baseline LDL-C level < 100 mg/dL was assumed to indicate that the patient was treated with statins at another hospital (n = 404), and irregular adherence to the statin prescription was assumed when the LDL-C level at visit 2 was higher than the baseline level (n = 267). These patients were also excluded. An additional 57 patients who had their prescription changed during the study period were excluded, leaving 2,431 patients that were included in the initial analysis (Figure 1). In this sample, 14 different types of statin were prescribed: rosuvastatin (10 mg), n = 717; atorvastatin (10 mg), n = 442; pitavastatin (2 mg), n = 275; pravastatin (40 mg), n = 263; simvastatin (20 mg), n = 235; and pravastatin (20 mg), n = 170. Patients who were prescribed the following statins were then excluded due to the small proportion of each (n < 50 each): atorvastatin (40 mg), fluvastatin (80 mg), rosuvastatin (5 mg), rosvastatin (20 mg), and simvastatin (40 mg). The final sample size was 2,349 patients (Figure 1).

The baseline characteristics of the sample are provided in Table 1. The average interval from baseline to visit 1 was 88 ± 16 days and from baseline to visit 2 was 181 ± 20
days. The average age of the patients was 57.6 ± 12.7 years, and 27.1% of the patients were aged ≥ 65 years. The mean baseline LDL-C values ranged from 141 to 177 mg/dL for the different statins. There was a tendency for higher doses of atorvastatin and pravastatin with higher baseline LDL-C levels.

**LDL cholesterol reduction rates**

The average percent changes in LDL-C values from baseline were 36.3% at visit 1 and 38.6% at visit 2. The largest decrease in LDL-C levels was observed at visit 1 with all of the statins, and the levels were maintained or reduced slightly more at visit 2. The ability of the different statins to lower LDL-C values was significantly different at both visit 1 (F = 36.1, p < 0.001) and visit 2 (F = 30.5, p < 0.001).

Atorvastatin (20 mg) and rosuvastatin (10 mg) resulted in the greatest decreases in LDL-C; the percent changes were 43.0% at visit 1 and 45.4% at visit 2 with atorvastatin (20 mg) and 44.3% at visit 1 and 45.1% at visit 2 with rosuvastatin (10 mg). These statins comprised group A and were considered moderate-intensity statins according to the ACC/AHA guidelines. There were no significant differences in the reduction in LDL-C with atorvastatin (10 mg), pitavastatin (2 mg), pravastatin (40 mg), and simvastatin (20 mg), analyzed using the SNK test (p > 0.05) (Table 2). These comprised group B and were considered moderate-intensity statins according to the ACC/AHA guidelines. Fluvastatin (40 mg), pravastatin (10 mg), and pravastatin (20 mg) comprised group C and were considered low-intensity statins according to the ACC/AHA guidelines.

Although the change with pravastatin (10 mg, 20 mg, and 40 mg) was not as pronounced at visit 1 as with the other statins, the average change at visit 2 was similar to the other statins; the percent change with pravastatin between visits 1 and 2 was 4.7 – 11.5%, compared to 0.7 – 2.7% with the remainder of the statins (Table 2). The use of pravastatin resulted in significantly lower LDL-C values at visit 2 compared to the values at visit 1, analyzed using a t-test (p < 0.001).
Table 2. Average change in the LDL-C value from the baseline LDL-C value, compared by statin type.

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Statin classification</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Group A*</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (20 mg)</td>
<td>100</td>
</tr>
<tr>
<td>Rosuvastatin (10 mg)</td>
<td>717</td>
</tr>
<tr>
<td>Group B*</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (10 mg)</td>
<td>442</td>
</tr>
<tr>
<td>Pitavastatin (2 mg)</td>
<td>275</td>
</tr>
<tr>
<td>Pravastatin (40 mg)</td>
<td>263</td>
</tr>
<tr>
<td>Simvastatin (20 mg)</td>
<td>235</td>
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<td>Group C*</td>
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<td>Fluvastatin (40 mg)</td>
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<tr>
<td>Pravastatin (10 mg)</td>
<td>88</td>
</tr>
<tr>
<td>Pravastatin (20 mg)</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>2349</td>
</tr>
</tbody>
</table>

LDL-C = low density lipoprotein cholesterol; ACC/AHA = American College of Cardiology/American Heart Association. The values are reported as mean ± SD with the percent change (Δ) from the baseline value. The LDL-C lowering effect of each statin was calculated as the following: LDL-C lowering effect (%) = mean percent change (%) = 100 × (visit 2 (or visit 1) – visit 0)/visit 0. *Groups A, B, and C include statins that had statistically similar average percent changes (p > 0.05). Pravastatin (10 mg) and pravastatin (40 mg) were marginally significant with p > 0.05 for the overall ANOVA effect and p < 0.1 in the SNK post-hoc test. 1The use of pravastatin resulted in significantly reduced LDL-C values at visit 2 compared to the values at visit 1 (p < 0.001). Pravastatin resulted in a change of 4.7 – 11.5% between visit 1 and visit 2.

Table 3. The proportion of the patients who achieved the LDL-C goal (< 100 mg/dL) at visit 2, compared between the statin types and between those with low, medium, and high baseline LDL-C levels.

<table>
<thead>
<tr>
<th>Baseline LDL-C</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=2,349)</td>
<td>&lt;130 mg/dL (n=656)</td>
<td>130–160 mg/dL (n=1,052)</td>
</tr>
<tr>
<td>Atorvastatin, 20 mg</td>
<td>76/100 (76%)</td>
<td>11/14 (78.6%)</td>
<td>36/43 (83.7%)</td>
</tr>
<tr>
<td>Rosuvastatin, 10 mg</td>
<td>555/717 (77.4%)</td>
<td>173/192 (90.1%)</td>
<td>251/322 (78.0%)</td>
</tr>
<tr>
<td>Atorvastatin, 10 mg</td>
<td>316/442 (71.5%)</td>
<td>135/150 (90.0%)</td>
<td>139/206 (66.8%)</td>
</tr>
<tr>
<td>Pitavastatin, 2 mg</td>
<td>191/275 (69.5%)</td>
<td>79/87 (90.8%)</td>
<td>85/120 (70.8%)</td>
</tr>
<tr>
<td>Pravastatin, 40 mg</td>
<td>122/263 (47.5%)</td>
<td>36/49 (73.5%)</td>
<td>58/113 (51.3%)</td>
</tr>
<tr>
<td>Simvastatin, 20 mg</td>
<td>147/235 (62.6%)</td>
<td>62/81 (76.5%)</td>
<td>66/103 (64.1%)</td>
</tr>
<tr>
<td>Fluvastatin, 40 mg</td>
<td>28/59 (44.1%)</td>
<td>10/15 (66.7%)</td>
<td>12/26 (50.0%)</td>
</tr>
<tr>
<td>Pravastatin, 20 mg</td>
<td>87/170 (51.2%)</td>
<td>35/39 (89.7%)</td>
<td>38/74 (51.4%)</td>
</tr>
<tr>
<td>Pravastatin, 10 mg</td>
<td>41/88 (46.6%)</td>
<td>16/29 (55.2%)</td>
<td>22/43 (51.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,573/2,349 (67%)</td>
<td>557/656 (84.9%)</td>
<td>708/1,052 (67.3%)</td>
</tr>
</tbody>
</table>

LDL-C = low density lipoprotein cholesterol. The values are presented as n (%). *Groups A, B, and C include statins that had statistically similar average percent changes (p > 0.05). Pravastatin (10 mg) and pravastatin (40 mg) were marginally significant with p > 0.05 for the overall ANOVA effect and p < 0.1 in the SNK post-hoc test.

**Target achievement rate (< 100 mg/dL)**

When comparing the proportion who achieved the LDL-C goal (< 100 mg/dL) (Table 2), of the patients prescribed rosuvastatin (10 mg), the LDL-C goal (< 100 mg/dL) was achieved by 78.0% (LDL-C 130 – 160 mg/dL) and 90.1% (LDL-C < 130 mg/dL); however, this decreased to 64.5% in the patients with baseline LDL-C levels > 160 mg/dL. Unlike rosuvastatin, atorvastatin (20 mg) resulted in the highest number of patients who achieved the goal LDL-C level regardless of baseline LDL-C levels; the rate was 72.1% in the patients with a baseline LDL-C level
> 160 mg/dL. In the patients with baseline LDL-C > 160 mg/dL, the proportion who achieved LDL-C < 100 mg/dL with atorvastatin (20 mg) was higher than with rosuvastatin (10 mg) (72.1% and 64.5%, respectively, p = 0.381). With a baseline LDL-C level of 130 – 160 mg/dL, the proportion of patients who achieved the goal LDL-C level with atorvastatin (20 mg) also tended to be higher than with rosuvastatin (10 mg) (83.7% and 78.0%, respectively, p = 0.343). In the patients with a baseline LDL-C < 130 mg/dL who were prescribed pravastatin (20 mg and 40 mg), the rate was 73.5 – 89.7%; however, this rate dropped to 24.6 – 37.6% in those with a baseline LDL-C ≥ 160 mg/dL (Table 3).

**Discussion**

In the present study, the majority of patients were prescribed moderate- or low-intensity statins (ACC/AHA guidelines). In addition, all of the statins within groups A and B were classified as moderate-intensity statins; however, we found significant differences in the efficacy of the statins between groups A and B, indicating that the guidelines provided by the ACC/AHA might not apply to the Korean population. Furthermore, we detected that the ability to achieve the target LDL-C level (< 100 mg/dL) significantly differed based on the baseline LDL-C level (Table 3). Even with the same statin, there were considerable differences in the proportion of patients who achieved the < 100 mg/dL target based on the baseline LDL-C value. The use of rosuvastatin (10 mg), atorvastatin (10 mg), and pitavastatin (2 mg) resulted in a greater proportion of patients reaching the target when the baseline LDL-C values were lower, compared to those in the highest LDL-C bracket. For the patients in the lowest LDL-C bracket, > 70% of the patients achieved the LDL-C target value with the use of all of the statins, except fluvastatin (40 mg) and pravastatin (10 mg). Furthermore, when baseline LDL-C values were > 130 mg/dL, there were marked differences between the statins.

Based on the LDL-C lowering effects and target achievement rate observed in the present study, the treatment guidelines for Korea should include the use of relatively low-intensity statins, compared with the guidelines developed for Western populations. In Korea, treatment initiation with low-dose statins is still suggested to be sufficient and remains very controversial. Similarly, a study conducted in Japan resulted in positive effects of a comparably low-dose statin for the prevention of cardiovascular disease [25], and treatment initiation with a low-dose statin was also suggested to be sufficient [9, 26]. Therefore, we recommend that physicians select a statin and dose according to the base-
line LDL-C level, desired LDL-C level, and LDL-C lowering effect.

This study has certain limitations. First, certain cofactors and confounders could not be accessed from the database, including socio-demographic variables, compliance with medication prescription, and the severity of potential diseases. However, we utilized a standardized study plan that was identified early to minimize confounding factors, which can have a significant impact on the results. We made certain assumptions about medication compliance and prescriptions from other centers, resulting in a substantial reduction in the sample size. Second, this study was conducted over a short period of 6 months in a single center. With an increase in the amount of and the variation in clinical or biochemical data, additional biochemical variables could become available that would identify people who respond well to a statin compared to those who do not respond well. Third, we arbitrarily defined LDL-C goals (<100 mg/dL) and did not base them on the risk categories identified in the NCEP-ATP III guideline. Nevertheless, all of the groups achieved a high target achievement rate. Finally, the present study lacked analysis of baseline characteristics that could affect the outcomes such as height, weight, and body mass index.

This study is electronic medical records-based clinical research and reflects real practice. Despite a lack of considerable differences from previous findings, we argue, based on the present findings, that the moderate-intensity statins in the ACC/AHA guidelines should be divided into two groups. To conclude, additional work is required to determine the application of the 2013 ACC/AHA guidelines in Korea for the following reasons: a target LDL-C concentration is lacking, the recommendations are general (moderate- or high-intensity statin), and the guidelines do not reflect differences between Asian and Western patients. Because large-scale studies regarding the efficacy and advantages/disadvantages of statins are lacking in Asia, studies should be conducted in Asian countries, including Korea, to determine appropriate statin doses, target LDL-C concentrations, and potential risk factors. The present study should provide a sufficient baseline dataset for further research.

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Conflict of interest

None declared.

References


