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# Comparison of Efficacy and Safety after Administering High Potency Statin to High Risk Patients: Rosuvastatin 10 mg versus Atorvastatin 20 mg

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**ABSTRACT**

**Background and Objectives :** Although the rate of prescribing hydroxylmethyglutaryl-CoA reductase inhibitors (statin) has recently increased, there is a large treatment gap between the guidelines and actual clinical practice. We studied the effect of high potency statin on the percentage of patients who achieve the target low density lipoprotein (LDL) cholesterol level, and we determined the changes of lipid profiles with using 10 mg of rosuvastatin and 20 mg of atorvastatin. **Materials and Methods :** 222 consecutive patients with acute coronary syndrome or acute ischemic stroke were randomly assigned to either the group treated with rosuvastatin 10 mg (Group I) or atorvastatin 20 mg (Group II). We compared the percentage of patients who achieved the target LDL cholesterol level, and the percent change of the serum lipid profile from baseline to the 40th week between the two groups. **Results :** 117 (52.7%) patients completed this study. When the target LDL cholesterol level was <100 mg/dL, there was no significant difference in the target attainment rate between the two groups (86.7% vs. 77.2%; respectively, p=0.182). When the target LDL cholesterol level was <70 mg/dL, 48.3% of Group I and 29.8% of Group II reached the goal (p=0.040). The LDL cholesterol level was reduced by 46.8% in Group I (p<0.001), and by 40.1% in Group II (p<0.001). However, the final level showed a trend to be lower in the rosuvastatin group (p=0.077). There were no serious side effects in both groups. The study drug was discontinued due to adverse events in 2 patients (2.6%) of Group I, and in 3 patients (3.8%) of Group II (p=0.523). **Conclusion :** This study showed that the reduction of LDL cholesterol was not statistically different between rosuvastatin 10 mg and atorvastatin 20 mg. However, fewer than half of the patients achieved the goal in both groups despite of high potency statin therapy. This suggests that more aggressive statin therapy is preferred for high risk patients. **(Korean Circulation J 2007;37:154-160)**

**KEY WORDS :** Hydroxylmethyglutaryl-CoA reductase inhibitors ; Cholesterol ; Guideline.

## Introduction

The recent large-scale lipid-lowering trials have suggested that hydroxylmethyglutaryl-CoA reductase inhibitors(statins) have benefits for primary and secondary prevention of coronary artery disease.[1-4] Previous angiographic studies have also demonstrated that intensive lowering of lipid can retard the progression of coronary atherosclerosis.[5-8] Moreover, most recent studies that have used intravascular ultrasound showed that intensive statin therapy can cause regression of the atheroma volume.[9]

Despite the proved benefits of statin, there still exists a 'treatment gap' in statin therapy. According to the guidelines for the therapy, it is recommended to lower the low density lipoprotein(LDL) cholesterol in high risk patients below 100 mg/dL and ideally below 70 mg/dL, but according to several studies, fewer than half of such patients achieved the goal.[10-12] The reason for this treatment gap is that drugs are often not prescribed to patients who need treatment or that the treatment is not sufficient to reach the goal. With physicians' recent changing ideas, the number of statin

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prescriptions is increasing, but because statin itself varies in potency, even if patients take statin, they are not very likely to reach the target LDL cholesterol level.

Recently developed rosuvastatin is one of several powerful drugs that can effectively reduce LDL cholesterol. According to the Statin Therapies for Elevated Lipid Levels compared Across Doses to Rosuvastatin (STELLAR) trial, 10 mg of rosuvastatin reduced LDL cholesterol by 45%, and 82% of the study patients reached the target LDL cholesterol level of the National Cholesterol Education Program(NCEP) Adult Treatment Panel III(ATP III).[13] This effect is comparable with that of 40 mg of atorvastatin and 80 mg of simvastatin. Thus, we purposed to examine the percentage of patients who reach the target LDL cholesterol level by administering 10 mg of rosuvastatin to high risk patients. In addition, we studied the effect of early administration of high potency statin on the safety and changes of blood lipid profiles with using a control group that was administered 20 mg of atorvastatin.

## Materials and Methods

### Subjects

From July 2005 to December 2005, we studied 222 consecutive patients who had acute coronary syndrome (128 patients) or ischemic stroke(94 patients). Acute coronary syndrome was defined as the patients who had ischemia-like chest pain lasting for over 20 minutes and significant stenosis(a diameter stenosis of >50%) on diagnostic coronary angiography. Ischemic stroke was defined as the patients who showed neurological signs and symptoms of a cerebrovascular accident within 24 hours and they had lesions proved by brain CT or MRI. We excluded those cases that had undergone previous statin therapy within 6 weeks before this study, those with a history of sensitivity to statin, aspirin and other antiplatelet agents, and those patients with severe hepatic(a history of liver cirrhosis or an alanine aminotransferase level >2.5 times the upper normal limit) and renal diseases(serum creatinine >2.0 mg/dL).

The patients were randomly assigned to the group that was administered rosuvastatin 10 mg(Group I) or to the group that was administered atorvastatin 20 mg (Group II) during the hospital period. Randomization was performed at a 1 : 1 ratio. All the patients gave an informed consent according to a protocol approved by the Ethical Committee of Wonkwang University Hospital. The flow chart of this study is described in Fig. 1.

### Treatment and follow up

The treatment strategy was decided upon according to current clinical practice at the physician's discretion. All patients received antiplatelet agents immediately after admission.

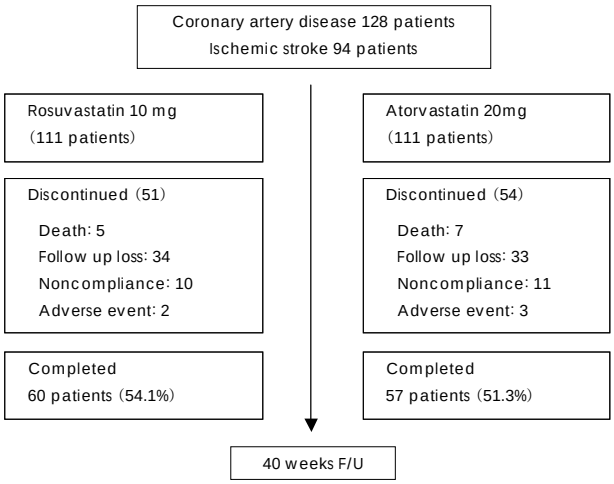


**Fig. 1.** The flow chart of the study.

Blood samples were collected before randomization. In addition to routine blood chemistry, the lipid profiles, including total cholesterol, triglyceride, high density lipoprotein(HDL) -cholesterol and lipoprotein(a) were measured from plasma samples. LDL cholesterol was calculated by Friedewald's formula[14] for the patients with triglyceride levels <400 mg/dL and those patients who revealed a triglyceride level >400 mg/dL were excluded.

The patients were observed for 40 weeks. As long as no particular side effect was observed, the initial drugs were maintained and the statin type and dose was not changed. Blood samples were collected in the 40th week, and the patients' serum lipid profiles were followed up.

Safety assessments included recording of treatment-emergent adverse events(adverse events that started or worsened during the randomized treatment), clinical chemistry measurements at 4th and 24th week, and a physical examination at every 4 weeks. Additional monitoring was performed for those patients who had creatinine kinase values >3 times the upper limit of normal or elevated ALT and AST values. All the patients who received any study drugs were included in the safety analysis.

### Primary and secondary end points

The primary end point was the percentage of patients who reached the target LDL cholesterol level in the 40th week. The target LDL cholesterol level was below 100 mg/dL and below 70 mg/dL according to the NCEP ATP III guidelines. Secondary end points included: (1) the percent change in the serum lipid profiles from baseline to the 40th week; (2) adverse events related to statin treatment.

### Statistical analysis

All measurements were represented as means±stand-

ard deviations. Inter-group analysis was done using independent t-tests and $\chi^2$ tests with using SPSS 11.0 for Windows(SPSS inc., Chicago, IL). To compare the change of lipid profiles before and after the medication, we used paired t tests. Statistical significance was set at $p<0.05$.

## Results

### Baseline characteristics

Of the 222 patients, 117(52.7%) patients completed this study. The average age of the subjects was 63.5±11.24 years, and 70(59.8%) of the subjects were male. 71(60.7%) patients presented with acute coronary syn-

**Table 1.** Baseline clinical characteristics

| | Group I (n=60) | Group II (n=57) | p |
|---|---|---|---|
| Age (years) | 63.5±11.67 | 63.4±10.88 | 0.964 |
| Male (%) | 41 (68.3) | 29 (50.9) | 0.054 |
| Hypertension (%) | 28 (46.7) | 33 (57.9) | 0.224 |
| Diabetes (%) | 15 (25.0) | 18 (31.6) | 0.429 |
| Smoker (%) | 17 (28.3) | 20 (35.1) | 0.432 |
| Diagnosis (%) | | | 0.823 |
| Coronary artery disease | 37 (61.7) | 34 (59.6) | |
| Cerebrovascular disease | 23 (38.3) | 23 (40.4) | |
| Total cholesterol (mg/dL) | 198.3±43.24 | 202.4±45.48 | 0.616 |
| Triglyceride (mg/dL) | 138.3±70.68 | 140.2±83.99 | 0.896 |
| HDL-cholesterol (mg/dL) | 50.1±13.76 | 48.8±13.39 | 0.617 |
| LDL-cholesterol (mg/dL) | 139.1±37.64 | 137.7±40.92 | 0.855 |
| Lipoprotein (a) (mg/dL) | 35.3±31.37 | 30.6±26.90 | 0.407 |
| Homocysteine (μM/L) | 13.1±5.39 | 12.9±6.94 | 0.878 |
| Creatinine (mg/dL) | 0.97±0.27 | 0.97±0.46 | 0.991 |
| CK (IU/L) | 168.6±138.68 | 166.9±130.76 | 0.964 |
| ALT (IU/L) | 26.4±29.61 | 27.8±23.17 | 0.624 |
| Concomitant medication (%) | | | |
| Aspirin | 52 (86.7) | 51 (89.5) | 0.640 |
| Clopidogrel | 47 (78.3) | 45 (78.9) | 0.935 |
| ACEI/ARB | 49 (81.7) | 49 (86.0) | 0.529 |
| Beta blocker | 34 (56.7) | 35 (61.4) | 0.603 |
| Calcium antagonist | 28 (46.7) | 27 (47.4) | 0.939 |

HDL: high density lipoprotein, LDL: low density lipoprotein, CK: creatinine kinase, ALT: alanine aminotransferase, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker

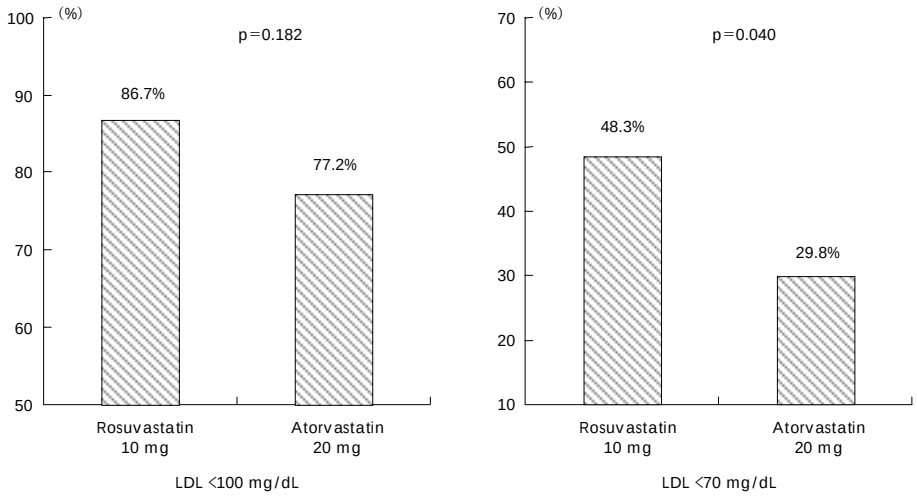


**Fig. 2.** Goal attainment rate. When the target LDL cholesterol level was <100 mg/dL, there was no significant difference in the target attainment rate between the two groups (86.7% vs. 77.2%; respectively, p=0.182). When the target LDL cholesterol level was <70 mg/dL, 48.3% of Group I and 29.8% of Group II reached the goal (p=0.040). LDL: low density lipoprotein

drome, including 25 patients of myocardial infarction; 46(49.3%) patients presented with acute ischemic stroke, including 18 patients of large artery atherosclerosis. There was no significant difference in most of the relevant clinical characteristics between the two groups (Table 1). Fifteen patients(12.8%) had a baseline LDL cholesterol level <100 mg/dL.

### Rate of attaining the goal

When the target LDL cholesterol level was below 100 mg/dL, there was no significant difference in the target attainment rate between the two groups(86.7% vs. 77.2%; respectively, p=0.182)(Fig. 2). When the target LDL cholesterol level was below 70 mg/dL, 48.3% of the rosuvastatin 10 mg group and 29.8% of the atorvastatin 20 mg group reached the goal(p=0.040). However, fewer than half of the patients in both groups achieved the goal.

### Changes of the serum lipid profile

The two statins both significantly reduced the level of total cholesterol, LDL cholesterol and apolipoprotein B(Table 2). The total cholesterol level was reduced by 27.8% in the rosuvastatin 10 mg group(p<0.001) and by 22.3% in the atorvastatin 20 mg group(p<0.001), the LDL cholesterol level was reduced by 46.8% in the rosuvastatin 10 mg group(p<0.001) and by 40.1% in the atorvastatin 20 mg group(p<0.001). However, the final levels were lower in the rosuvastatin group(p=0.026 for the total cholesterol, p=0.077 for the LDL

**Table 2.** Changes of the serum lipid profile after 40 weeks of statin treatment

| | Rosuvastatin 10 mg | Atorvastatin 20 mg | p |
|---|---|---|---|
| Total cholesterol | | | |
| Baseline (mg/dL) | 198.3±43.24 | 202.4±45.48 | 0.616 |
| After 40 weeks (mg/dL) | 143.4±33.17 | 157.7±34.77 | 0.026 |
| % change | -27.8 | -22.3 | |
| p by paired t test | <0.001 | <0.001 | |
| Triglyceride | | | |
| Baseline (mg/dL) | 138.3±70.68 | 140.2±83.99 | 0.896 |
| After 40 weeks (mg/dL) | 128.4±92.15 | 126.6±65.24 | 0.500 |
| % change | -7.2 | -10.6 | |
| p value by paired t test | 0.325 | 0.051 | |
| HDL-cholesterol | | | |
| Baseline (mg/dL) | 50.1±13.76 | 48.8±13.39 | 0.617 |
| After 40 weeks (mg/dL) | 45.4±10.77 | 47.1±13.19 | 0.466 |
| % change | -10.0 | -2.3 | |
| p by paired t test | 0.011 | 0.356 | |
| LDL-cholesterol | | | |
| Baseline (mg/dL) | 139.1±37.64 | 137.7±40.92 | 0.855 |
| After 40 weeks (mg/dL) | 74.4±22.08 | 82.08±24.45 | 0.077 |
| % change | -46.8 | -40.1 | |
| p by paired t test | <0.001 | <0.001 | |
| Lipoprotein (a) | | | |
| Baseline (mg/dL) | 35.3±31.37 | 30.6±26.90 | 0.407 |
| After 40 weeks (mg/dL) | 46.1±41.25 | 36.2±37.69 | 0.172 |
| % change | +31.1 | +16.1 | |
| p by paired t test | <0.001 | 0.154 | |
| Apolipoprotein A1 | | | |
| Baseline (mg/dL) | 142.5±28.92 | 137.9±27.25 | 0.400 |
| After 40 weeks (mg/dL) | 149.8±32.51 | 153.8±31.59 | 0.518 |
| % change | +4.3 | +11.6 | |
| p by paired t test | 0.156 | 0.003 | |
| Apolipoprotein B | | | |
| Baseline (mg/dL) | 102.9±30.49 | 108.8±29.73 | 0.307 |
| After 40 weeks (mg/dL) | 76.6±25.53 | 86.9±25.56 | 0.087 |
| % change | -26.9 | -21.1 | |
| p by paired t test | <0.001 | <0.001 | |

HDL: high density lipoprotein, LDL: low density lipoprotein

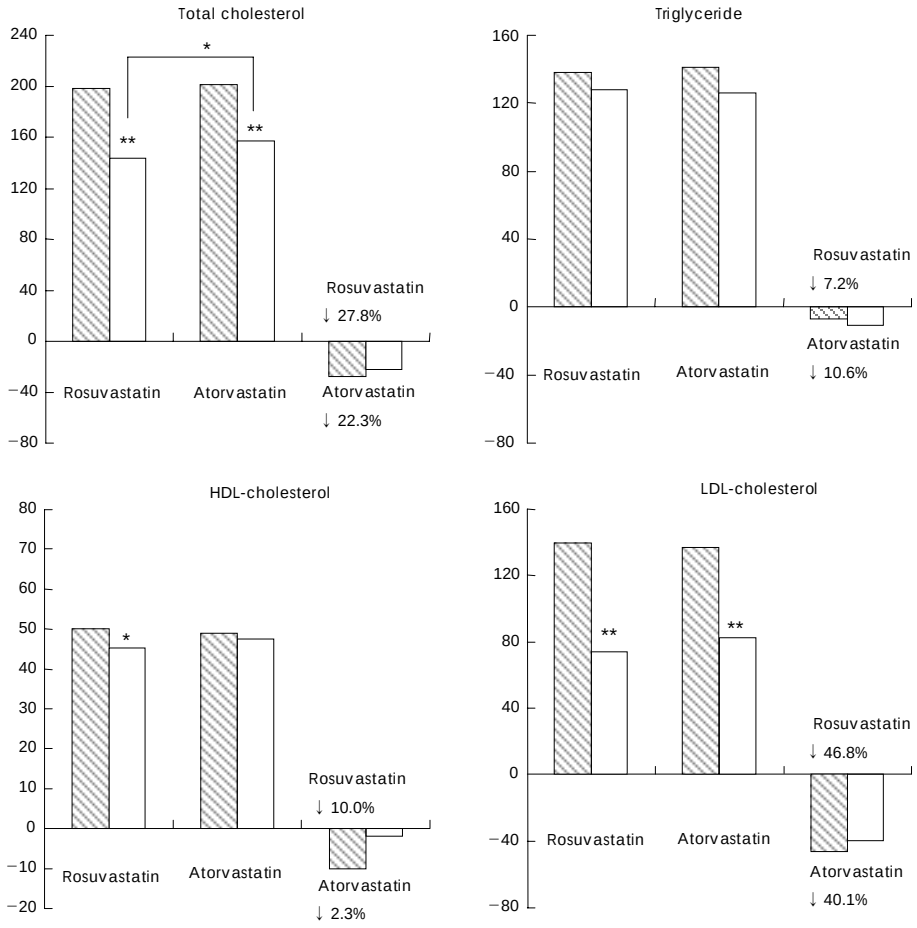


**Fig. 3.** Changes of the lipid profiles before and after high potency statin therapy. The total cholesterol level was reduced by 27.8% in the rosuvastatin 10 mg group, and by 22.3% in the atorvastatin 20 mg group ($p<0.001$), the LDL cholesterol level was reduced by 46.8% in the rosuvastatin 10 mg group, and by 40.1% in the atorvastatin 20 mg group ($p<0.001$). However, the final level showed a trend to be lower in the rosuvastatin group ($p=0.026$ in total cholesterol, $p=0.077$ in LDL cholesterol). *: $p<0.05$, **: $p<0.01$. HDL: high density lipoprotein, LDL: low density lipoprotein.

cholesterol)(Fig. 3). The apolipoprotein B level was reduced by 26.9% in the rosuvastatin 10 mg group($p<0.001$) and by 21.1% in the atorvastatin 20 mg group ($p<0.001$). For the rosuvastatin 10 mg group, the HDL cholesterol level was significantly reduced(-10%, $p=0.011$), and the lipoprotein (a) level was significantly elevated(+31.1%, $p<0.001$).

### Adverse effects of statin

Muscle side effects were infrequently observed, with no episode of rhabdomyolysis being observed during the study period(Table 3). There were no serious side effects in both groups with high potency statin therapy. Abdominal pain and headache occurred in 6 patients among the study patients. The study drug was discontinued due to adverse events in 2 patients(2.6%) in Group I, and in 3 patients(3.8%) in Group II($p=0.523$).

## Discussion

In this study, we showed the similar efficacy of rosuvastatin 10 mg for reducing LDL cholesterol, as compared with atorvastatin 20 mg. However, fewer than half of the patients in both groups achieved the goal despite the high potency statin therapy.

Statin has been shown to consistently reduce cardiovascular events in patients with elevated cholesterol levels. These benefits were observed in the major primary prevention and secondary prevention trials for stable patients with progressively lowered baseline cholesterol levels.[1)4)15-17)] The Heart Protection Study showed the benefit of treatment with simvastatin compared with placebo, regardless of the baseline cholesterol level, in the high risk patients. Treatment benefits were observed for the patients who had a baseline LDL cholesterol level <100 mg/dL.[17)] More recently, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22(PROVE IT-TIMI 22) trial showed that intensive therapy that achieved a median LDL cholesterol level of 62 mg/dL was superior, for reducing clinical events, to standard therapy that achieved a median LDL cholesterol level of 95 mg/dL

**Table 3.** Adverse events among the study population

| | Group I (n=77) | Group II (n=78) | p |
|---|---|---|---|
| Muscle side effect | | | |
| Myalgia | 1 (1.3) | 1 (1.3) | 0.739 |
| CK >3X ULN | 0 | 1 (1.3) | 0.487 |
| CK >10X ULN | 0 | 0 | |
| Rhabdomyolysis | 0 | 0 | |
| Liver side effect | | | |
| ALT >3X ULN | 1 (1.3) | 1 (1.3) | 0.739 |
| Peak AST (IU/L) | 31.9±17.55 | 29.4±15.74 | 0.342 |
| Peak ALT (IU/L) | 31.0±17.06 | 27.2±17.28 | 0.297 |
| Discontinuation because of LFT | 0 | 1 (1.3) | 0.487 |
| Other side effect | | | |
| Abdominal pain | 2 (2.6) | 1 (1.3) | 0.519 |
| Headache | 2 (2.6) | 1 (1.3) | 0.519 |
| Hemorrhagic stroke | 0 | 0 | |
| Discontinuation because of any side effects | 2 (2.6) | 3 (3.8) | 0.524 |

CK: creatinine kinase, ULN: upper limit of normal, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LFT: liver function test

after patients had experienced acute coronary syndrome.[18]

This "lower is better" hypothesis is consistent with the results of other trials. The Treating to New Targets (TNT) trial showed fewer major adverse cardiac events in stable patients who were treated with 80 mg of atorvastatin compared with 10 mg of atorvastatin.[19] The Z phase of the Aggrastat to Zocor(A to Z) trial showed a trend of reduced events after 6 months treatment for patients with final LDL levels of 66 mg/dL compared to patients with final LDL levels of 81 mg/dL.[20] Thus, the NCEP ATP III and the recent ACC/AHA guidelines recommend that the target LDL cholesterol levels should be below 70 mg/dL for patients with coronary artery disease or for patient with the equivalent of coronary artery disease.[21][22]

However, there is a large treatment gap between the guidelines and actual medical practice. According to the studies in Korea and other countries, only 24-38% of high risk patients reached the target LDL cholesterol level.[10-12] The reason for the treatment gap is that drugs are often not prescribed to patients who need treatment or that treatment is not sufficient to reach the goal. However, statin was prescribed to 80-90% of the high risk patients in these studies, and although the prescription rate was high, most patients taking statin failed to achieve the goal.

Rosuvastatin is one of several powerful drugs that are effective in reducing LDL cholesterol. The STELLAR trial reported that 10 mg of rosuvastatin reduced LDL cholesterol by 45%, and 82% of patients achieved the target LDL cholesterol level of the NCEP ATP III guideline after 6 weeks treatment.[13] In our study, 86% of the patients reached a LDL cholesterol level below 100 mg/dL, which was similar to the previous reports. However, when the target LDL cholesterol level was adjusted below 70 mg/dL, only 48% of the patients achieved the goal. Moreover, the attainment rate was lower in the cases treated with atorvastatin 20 mg. This suggests that a high potency statin is preferred for high risk patients.

Statins are highly effective in reducing LDL cholesterol and they are modestly effective in raising HDL cholesterol. Statins do not lower the lipoprotein(a) concentration.[23-25] In our study, however, the HDL cholesterol level did not change(atorvastatin 20 mg), or rather, it was reduced(rosuvastatin 10 mg). In addition, the lipoprotein(a) level was elevated in both groups, and the elevation was particularly significant in the rosuvastatin 10 mg group(31%). The possible reasons for the difference in results are as follows. First, in the previous studies, the HDL cholesterol level tended to be reduced by high dose statin therapy.[13][26][27] Accordingly, it is possible that our study's result was similar to that of previous studies done with high dose statin because reosuvastatin works with very high potency on Koreans. Second, there is the problem in our study's protocol that diet therapy was not actively applied to the patients. That is, the previous studies on the efficacy of statin applied diet therapy first and then they enrolled the patients, but our study did not have a lead-in period because the subjects were high risk patients. So, diet control for our patients might have been done improperly. Finally, the results of our study might have been just incidental due to the small number of patients and high follow up loss of data. Further study is needed on the efficacy of statins.

Our study has several limitations. The study was not a blinded study, and the sample size was small. Another major limitation was the low follow up rate. However,

a significant difference was observed in the goal attainment rate between the two groups. Further study is needed to generalize our result.

In conclusion, there was a statistical difference for LDL cholesterol reduction between rosuvastatin 10 mg and atorvastatin 20 mg. These high potency statin therapies were safe and effective in high risk patients. However, fewer than half of the patients in both groups achieved the goal despite of high potency statin therapy. This suggests that more aggressive statin therapy is preferred for high risk patients.

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