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Comparative Drug Evaluation of Atorvastatin versus Rosuvastatin in Pharmacotherapy of Korean Patients with Dyslipidemia

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Abstract – Dyslipidemia is the multiple lipid metabolic disorders which is one of the high risk factors for the atherosclerotic diseases. It increases the morbidity and mortality and therefore, must be treated with antilipidemic agents. HMG-Co A reductase inhibitors (statins), one of many antidyslipidemic agents, have shown to be significant improvement from the various cholesterol levels. Especially, data from many comparative trials suggest that rosuvastatin is more effective than atorvastatin among many other statins. The aims of this study were to evaluate the efficacy and safety between rosuvastatin and atorvastatin in the treatment of Korean patients with dyslipidemia. Currently the Korean Society of Lipidology and Atherosclerosis based on the Korean health screening data suggests that Korean patients with dyslipidemia should be treated by the target cholesterol levels according to the Adult Treatment Panel III guidelines of the US National Cholesterol Education Program (NCEP-ATP III). We reviewed retrospectively all medical histories of the total 392 dyslipidemic patients with atorvastatin or rosuvastatin from June 1st, 2004 to August 31st, 2006 in Chungbuk National University Medical Center. Patients were classified as total 4 groups by the NCEP-ATP III Guidelines. The numbers of enrolled patients were each 5 mg atorvastatin (n=34), 10 mg atorvastatin (n=148), 5 mg rosuvastatin (n=94) and 10 mg rosuvastatin (n=82). In comparison between groups, rosuvastatin groups in the lowering LDL-C had better efficacies, and the results were each 22% (5 mg atorvastatin), 33.3% (10 mg atorvastatin), 35% (5 mg rosuvastatin) and 41.3% (10 mg rosuvastatin) with the dose relationship (P=0.000). Rosuvastatin groups also have shown to be more significantly reducing Total Cholesterol levels compared to atorvastatin groups with the no dose relationship (P=0.000). In the lowering of non-HDL cholesteroles, rosuvastatin groups showed significantly better efficacies than atorvastatin with the dose-relationship (P=0.000). Each medication groups did not demonstrate the differences in the changing of HDL cholesterol and triglyceride levels (P=0.096, 0.309, respectively). In conclusion, rosuvastatin was better efficacious than atrovastatin in reducing LDL-C Total Chol, and Tg. Therefore, rosuvastatin is a good antilipidemic agents for Korean patients with dyslipidemia and it can use to minimize the morbidity and mortality related to the cardiovascular diseases in Korean.

Key words □ dyslipidemia, atorvastatin, rosuvastatin, antilipidemic agents, TC, LDL-C, HDL-C, Tg

INTRODUCTION

Dyslipidemia is the abnormal pathologic serum lipid level which can cause multiple lipid metabolic disorders such as atherosclerotic diseases. Most of common forms are either elevations of serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) or triglyceride (Tg) associated with a reduction of high density of lipoprotein cholesterol (HDL-C) and they were usually showed the combined form (Sytkowski *et al.* 1996).

Since dyslipidemia along with smoking, diabetes mellitus or hypertension is one of major risk factors for coronary artery disease (CAD) or other arterial occlusive diseases, it must be controlled or treated by drugs or other nonpharmacological therapy in order to decrease the morbidity and mortality (Menottie *et al.*, 1996, Staamler *et al.,* 1986). Currently the Korean Society of Lipidology and Atherosclerosis based on the Korean health screening data suggests that Korean patients with dyslipidemia should be treated by the target cholesterol levels according to the Adult Treatment Panel III guidelines of the US National Cholesterol Education Program (NCEP-ATP III)(De

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Backer *et al.*, 2003, NCEP ATP III, 2001).

Statins, hydroxymethylglutaryl coenzyme A reductase inhibitors (HMG-co A reductase inhibitors) are the drug of first choice for the treatment of many lipid disorders due to their good efficacies. Currently atorvastatin, rosuvastatin, simbastain, pravastatin, lovastatins and fluvastatin are available. Recently the new statins such as atorvastatin and rosuvastatin are commonly more using for the treatment of dyslipidemia patients in Korea. However HMG-co A reductase inhibitors showed some serious adverse effects such as myopathy, hepatotoxicity or rhabdomyolysis for some patients, and therefore must be monitored those adverse drug effects during the pharmacotherapy. Also Statins in some clinical trials were showed different efficacy depending on the various race (Strutt *et al.*, 2004 Guidelines for Hyperlipidemia Therapy, 2006).

The aim of this study was to evaluate the efficacy and safety between rosuvastatin and atorvastatin and then the result of this study can apply for effective and safe pharmacotherapy of Korean dyslipidemic patients in the future. We reviewed retrospectively the total 392 medical records from the dyslipidemic patients either on atorvastatin or rosuvastatin from June 1st, 2004 to August 31st, 2006 in a university hospital of C City in Chungcheongbuk-do.

MATERIALS AND METHODS

The selected and excluded patients

This study was performed retrospectively by reviewing of medical records for total 392 patients over 18 years old who were on atorvastatin or rosuvastatin under the diagnosis of dyslipidemia in Cardiology and Endocrinology And Metabolism at a university hospital of C area from June 1st, 2004 thru August 31st 2006. The each selected patient was treated for dyslipidemia with only a drug from atorvastatin 5mg, atorvastatin 10mg, rosuvastatin 5mg, or rosuvastatin 10mg for 6weeks at least. Also, all selected patients should be undergone their a blood test for lipid profile in order to evaluate the efficacy at least during and after 6weeks treatment. The efficacies of atorvastatin and rosuvastatin were evaluated by TC, LDL-C, non-HDL-C, HDL-C and Tg. The safeties also were evaluated by any occurrence of any side effects during the drug therapy by reviewing of their medical records. If anyone did not meet the above conditions, they would be excluded. The 34 patients were excluded among total 392 patients in this study.

Target goal of dyslipidemic pharmacotherpy

The targeting of therapy and data collections were followed by NCEP-ATP III guidelines which the targeting of therapy was decided by the LDL-C levels. That is, all selected patients were classified and decided the target goal by NCEP-ATP III guideline. And then, each classified group was evaluated for sex, age (M >= 45 years, F >= 55 years), weight, height, Body Mass Index (BMI) of patients, positive risk factors as cigarette smoking, hypertension, diabetes mellitus, coronary artery disease (CHD), HDL-C (low < 40 mg/dl, high > 60 mg/dl), family history of premature CHD. After evaluating of all risk factors from the each patient, total risk factors were simply counted by addition or subtraction to apply for the therapy goal. Also if HDL-C level is more than 60 mg/dL, subtract number 1 from the total numbers of risk factors (NCEP ATP III, 2001)(table I).

Evaluation of the efficacy per each drug

1) Evaluations of changes for TC, LDL-C, HDL-C and Tg before and after each drug therapy

Evaluate each TC, LDL-C, HDL-C, and Tg levels before taking each medication as a baseline. And then re-evaluate each TC, LDL-C, HDL-C, and Tg serum levels after taking of either medication for 6weeks (atorvastatin 5mg, atorvastatin 10mg, rosuvastatin 5mg or rosuvastatin 10mg). After that, calculate the differences from both (before and after) values.

2) Evaluation of changes for non-HDL-C before and after drug therapy

Evaluate each HDL-C level before taking of each medication as a baseline. And then after 6weeks later, re-evaluate each HDL-C of patients who were taking either atorvastatin 5, atorvastatin 10, rosuvastatin 5 or rosuvastatin 10mg. And then calculates the differences of the both serum lipid levels by subtraction of HDL-C value from TC value of 1).

Evaluation of the safety per each drug

1) Evaluation of the adverse drug effects per drug therapy

Evaluate any occurrence of the adverse drug effects of each patients during the drug therapy by reviewing of the medical records. Also we evaluated for the levels of alanine aminotrasferase (ALT) and aspartate aminotransferase (AST) as liver function test, since both atorvastatin and rosuvastatin are metabolized by liver (Carrilho *et al.*,

1997, Gangne *et al.*, 2002).

Statistical analysis

The statistical differences between drugs were evaluated by ANOVA analysis. Student-Newmans-Keuls method applied for post hoc analysis with adjustments of sex, diabetes mellitus, CAD and any influencing factors. Data were judged by Statistical Package for the Social Science (SPSS), 10.0 edition with significance if p value is below 0.05.

RESULTS

Demographic characteristics and classifications of the selected and excluded patients

Only 358 patients among total 392 patients were selected and evaluated for this study after the reviewing of medical records (atorvastatin 5 mg: 34 patients, atorvastatin 10 mg: 148 patients, rosuvastatin 5 mg: 94 patients, rosuvastatin 10 mg: 82 patients. 34 patients among total 392 patients were excluded from this study. The reasons were that 14 patients were concurrently taking atorvastatin or rosuvastatin with other dyslipidemic drugs (atorvastatin 2 patients and rousuvastatin 12 patients) and 20 patients had insufficient laboratory data (atorvastatin 15 patients and rousuvastatin 5 patients).

Total 358 selected patients were classified as total 4 groups by the LDL-C target value according to the NCEP-ATP III guideline and all evaluated 358 patient's demographic characteristics were summarized in Table I(NCEP ATP III, 2002).

Evaluation of the efficacy for lipid profiles per each drug therapy

1) Evaluation of TC level before and after drug therapy

TC values before taking each drug were atorvastatin 5mg (201 mg/dL), atorvastatin 10 mg (211.4 mg/dL), rosuvastatin 5 mg (235.2 mg/dL) and rosuvastatin 10 mg (252.2 mg/dL). After the each drug therapy for 6weeks, both atorvastatin and rosuvastatin decrease TC serum levels and their results of TC levels were each atorvastatin 5 mg (-15.1%), atorvastatin 10 mg (-23.3%), rosuvastatin 5 mg (-28.7%) and rosuvastatin 10 mg (-28.3%)(Table II). Aa a results, both atorvastatin and rosuvastatin meaningfully decrease the TC serum level. However, we can also see that higher dose of atorvastatin had better efficacy compared that rosuvastatin had the similar good efficacy in all dose regimen(P=0.000)(Fig. 1).

Table I. Demographic characteristics of all selected patients for atorvastatin or rosuvastatin therapy according to the NCEP-ATP III Guideline

Patient Category (by NCEP-ATP III Guideline)		atorvastatin 5 mg (n=34)	atorvastatin 10 mg (n=148)	rosuvastatin 5 mg (n=94)	rosuvastatin 10 mg (n=82)
Group I (CHD(-), DM(-), Risk factors: 0~1, Target LDL-C goal: 160 mg/dL)		4	9	9	13
Group II (CHD(-), DM(-), Risk factors ≥ 2, Target LDL-C goal: 130 mg/dL)		5	8	8	11
Group III (CHD(+), DM(-), Risk factors ≥ 2, Target LDL-C goal: 100 mg/dL)		23	95	70	48
Group IV (CHD(+), DM(+), Risk factors ≥ 2, Target LDL-C goal: 70 mg/dL)		2	36	7	10
Age(years)	Mean(SD)	63(9.2)	61(9.9)	59(10.8)	60(9.7)
	65yr,n(%)	17(50)	62(41.9)	31(33)	33(40.2)
Sex,n(%)	male	21(61.8 %)	78(52.7 %)	37(39.4 %)	28(34.1 %)
	female	13(38.2 %)	70(47.3 %)	57(60.6 %)	54(65.9 %)
BMI (kg/m^2)	Mean(SD)	23.8(3.2)	24.5(3)	24.9(3)	25.7(4.2)
	>25(%)	27	43.7	48.3	52.3

NCEP-ATP-III: National Cholesterol Education Program-Adult Treatment Panel III
CHD: Coronary Heart Disease
DM: Diabetes Mellitus
BMI: Body Mass Index (kg/m^2)
Risk factors: cigarette smoking, hypertention, low LDL-C (<40 mg/dL), family history of premature CHD, age (men≥45 years, women ≥ 55 years)

Table II. Mean baseline values and least squares mean percent changes from baseline at first lab. test with Rosuvastatin 5 mg, 10 mg, Atorvastatin 5 mg, 10 mg by SPSS ANOVA Analysis with Student Newmans Keuls Method

	Atorvastatin 5 mg (n=34)		Atorvastatin 10 mg (n=148)		Rosuvastatin 5 mg (n=94)		Rosuvastatin 10 mg (n=82)	
	Base (mg/dL)	%Change (SE)	Base (mg/dL)	%Change (SE)	Base (mg/dL)	%Change (SE)	Base (mg/dL)	%Change (SE)
TC	201	15.1(3.3)	211.4	23.3(1.2)	235.2	28.7(1.5)	252.2	28.3(2)
LDL	123	22(4.5)	137.1	33.3(1.6)	152	36.6(2.2)	164.6	41.3(2.2)
N-HDL	155	20.2(4.3)	165	29.2(1.4)	187	35.8(1.9)	202.1	36.3(2.5)
HDL	46	-4.8(3)	46	-0.5(1.5)	47.8	-2.1(1.6)	50	-8.0(3.9)
Tg	161	-2.5(9.9)	159	-4(4.1)	189.4	10.5(4.3)	197	-4.8(11.2)

TC=total cholesterol (p=0.000), LDL=low density lipoprotein (p=0.000)
non-HDL=non-high density lipoprotein (p=0.000)
HDL=high density lipoprotein (p=0.096), TG=triglyceride (p=0.309), 95% CI (confidence interval)

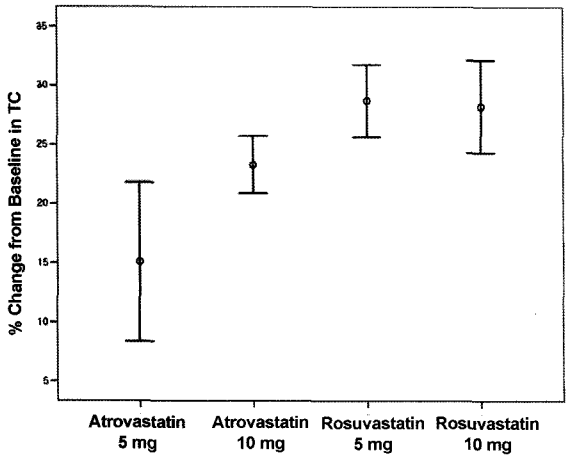

Fig. 1. Mean percent changes from baseline in Total Cholesterol (TC) at first lab. test with Atorvastatin 5 mg, 10 mg, Rosuvastatin 5 mg, 10 mg. by SPSS ANOVA Analysis with Student Newmans Keuls Method

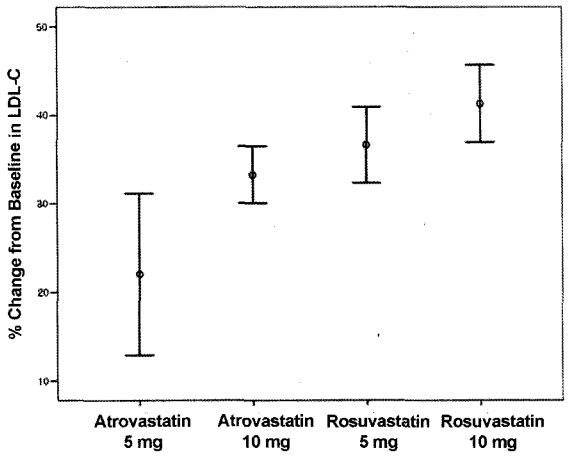

Fig. 2. Mean percent changes from baseline in Low Density Lipoprotein Cholesterol (LDL-C) at first lab. test with Atorvastatin 5 mg, 10 mg, Rosuvastatin 5 mg, 10 mg. by SPSS ANOVA Analysis with Student Newmans Keuls Method

2) Evaluation of LDL-C levels before and after drug therapy

LDL-C values before taking each drug were atorvastatin 5 mg (123.0 mg/dL), atorvastatin 10mg (137.1 mg/dL), rosuvastatin 5 mg (152 mg/dL) and rosuvastatin 10mg (164.6 mg/dL). After the each drug therapy for 6weeks, both atorvastatin and rosuvastatin decrease LDL-C serul levels and their results of LDL-C levels were each atorvastatin 5 mg (-22.0%), atorvastatin 10 mg (-33.3%), rosuvastatin 5 mg (-36.6%) and rosuvastatin 10 mg (-41.3%) (Table II). Aa a result, both atorvastatin and rosuvastatin, two drugs all showed the meaningfully high decrement of LDL-C level in high dose. Atorvastatin 10mg and rosuvastatin 5mg were showed the similar LDL-C levels that atorvastatin 10mg was showed for 33.3% and rosuvastatin 5 mg was showed for 36.6% (P=0.000)(Fig. 2).

3) Evaluation of HDL-C levels before and after drug therapy

Before initiating any drug therapy, each HDL-C level was evaluated. The evaluating levels were atorvastatin 5 mg (46.0 mg/dL), atorvastatin 10mg (46.0 mg/dL), rosuvastatin 5 mg (47.8 mg/dL) and rosuvastatin 10mg (50.0 mg/dL).

After for 6weeks each drug therapy, the results of both atorvastatin and rosuvastatin therapy improved of the decreasing of LDL-C serum levels. Their results of LDL-C levels were each atorvastatin 5mg (4.8%), atorvastatin 10mg (0.5%), rosuvastatin 5mg (2.1%) and rosuvastatin 10mg (8.0%)(Table II). In the levels of HDL-C for each drug also showed the improvement of increasing pattern but it was not meaningful statistically (p= 0.096)(Fig. 3).

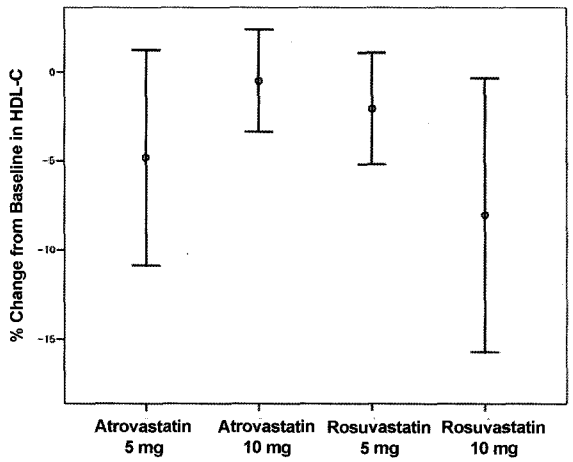

Fig. 3. Mean percent changes from baseline in High Density Lipoprotein Cholesterol (HDL-C) at first lab. test with Atorvastatin 5 mg, 10 mg, Rosuvastatin 5 mg, 10 mg. by SPSS ANOVA Analysis with Student Newmans Keuls Method

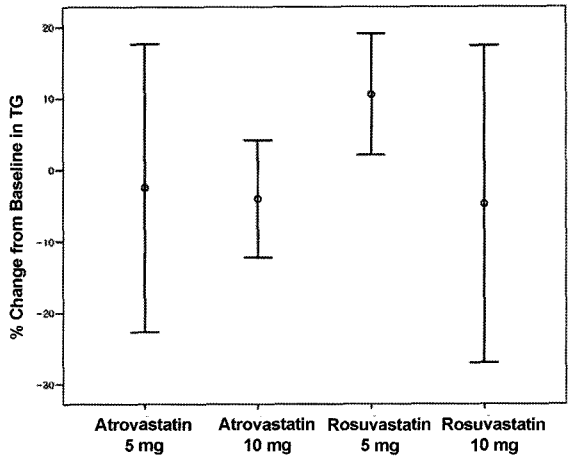

Fig. 5. Mean percent changes from baseline in Triglyceride (TG) at first lab. test with Atorvastatin 5 mg, 10 mg, Rosuvastatin 5 mg, 10 mg. by SPSS ANOVA Analysis with Student Newmans Keuls Method

4) Evaluation of non-HDL-C levels before and after drug therapy

Before initiating any drug therapy, each non-HDL-C value was evlauated. The evaluating levels were atorvastatin 5 mg (155.0 mg/dL), atorvastatin 10mg (165.0 mg/dL), rosuvastatin 5 mg (187.0 mg/dL) and rosuvastatin 10mg (202.1 mg/dL).

After for 6weeks each drug therapy, the results of both atorvastatin and rosuvastatin improved of the decreasing of non-HDL-C serum levels. Their results of LDL-C levels were each atorvastatin 5 mg (-20.0%), atorvastatin 10mg (-29.2%), rosuvastatin 5 mg (-35.8%) and rosuvastatin 10mg (-36.3%)(Table 3). In both atorvastatin and rosuvalstatin drugs were showed the improvement of non HDL-C levels and also showed meaningfully high decrements in a higher dose(P=0.000)(Fig. 4).

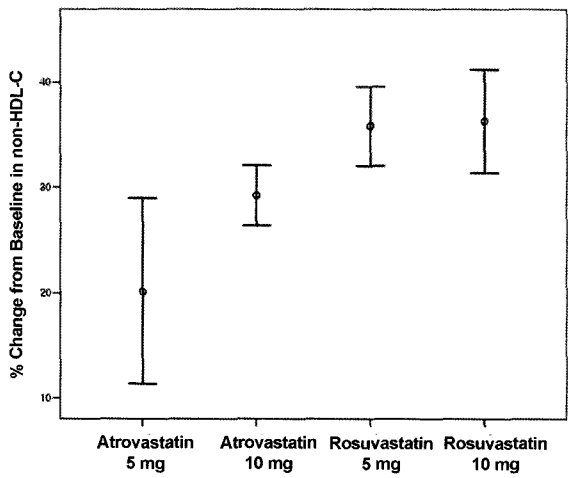

Fig. 4. Mean percent changes from baseline in non-High Density Lipoprotein Cholesterol (non HDL-C) at first lab. test with Atorvastatin 5 mg, 10 mg, Rosuvastatin 5 mg, 10 mg. by SPSS ANOVA Analysis with Student Newmans Keuls Method

5) Evaluation of Tg levels before and after drug therapy

Before initiating any drug therapy, each Tg level was evaluated. The evaluating levels of Tg were atorvastatin 5 mg (161.0 mg/dL), atorvastatin 10 mg (159.0 mg/dL), rosuvastatin 5mg (189.4 mg/dL) and rosuvastatin 10mg (197.0 mg/dL).

After for 6weeks each drug therapy, the results of both atorvastatin and rosuvastatin therapy improved of the decreasing of Tg serum levels. Their results of Tg levels were each atorvastatin 5 mg (-2.5%), atorvastatin 10 mg (-4.0%), rosuvastatin 5 mg (-10.5%) and rosuvastatin 10 mg (-4.8%), (Table II). Also the HDL-C serum level for each drug showed the increasing pattern with the decressing of Tg serum level but it was not meaningful statistically (p= 0.309)(Fig. 5).

Evaluation of adverse drug effects as the safety issue per drug therapy

The side effects were generally tolerable in the all doses of all drug therapy and any serious side effect was not documented at all in the medical records. A few patients showed some minor side effects such as headache or

dyspepsia. Among the total 358 patients, the profiles of side effect were like that the incidences of headache were atorvastatin 10 mg (1case) and rosuvastatin 10 mg (1 case), and also for the incidences of dyspepsia were atorvastatin 10 mg (1 case) and rosuvastatin 5 mg (1 case). Also the unusual liver functions were not documented neither.

DISCUSSION

Dyslipidemia is a condition which is unusually increasing of blood lipid concetration by disorders of lipoprotein which transport cholesterol. With the lipid concentration rises, athero-arteriosclerosis plaque is formed and it makes blood flow supply of each organ difficultly by occlusion of plaque. And eventually it causes CVD (Cardiovascular Diseases) such as ischemic heart diseases.

According to the current guidelines for dyslipidemic treatment, the occurrence of CVD can be prevented by the first prevention with non-pharmacologic treatments such as exercise or diet. The progress of and mortality from CAD diseases can be reduced by the second prevention with drug therapy (Endo *et al,* 1997, Davidson *et al.*, 2002, Olssonn *et al,*, 2002).

In many clinical trials, the second prevention by statins, HMG-CoA reductase inhibitor, showed the reducing results of the fatal cardiovascular diseases and sudden death compared to many other dyslipidemic agents (Shepherd *et al.* 1995 ; Sacks *et al.* 1998 ; LIPID Study Group, 1999 ; Heart Protection Study Collaborative Group, 2002; Mabuchi *et al.* 2002). The Scandinavian Simvastatin Survival Study(1994) is about the second prevention with simvastatin for CAD and this study showed that 35 % decrease of LDL cholesterol, 10 % decrease of Triglyceride, 8% increase HDL cholesterol and eventually it decreased 42% of the mortality. Therefore, the importance of statins in pharmacotherapy as the second prevention are emphasizing and using a lot in dyslipidemic disorders (Jones *et al,* 1998, Blasetto *et al.*, 2003, Strutt et al, 2004, Davidson *et al.* 2002, Olsson *et al.* 2002, Stein *et al.* 2001).

However, recent researches showed that each "statins" has a little different efficacy depending on the various races in some clinical trials. Therefore we performed on this study to evaluate the efficacy and safety of rosuvastatin and atorvastatin for the treatment of Korean dyslipidemic patients. So we can apply the results for effective and safe pharmacotherapy of Korean dyslipidemic patients with statins in the future.

In the result of this study, both atorvastatin and rosuvastatin showed the good improvements with decreasing of LDL-C. Howeverer, rosuvastatin showed meaningfully more decreasing rate compared with atorvastatin. Also both drugs showed meaningfully more decreasing rate in a higher dose. Particularly the result of decrements were similar with atorvastatin 10 mg (33.3%) and rosuvastatin 5 mg (36.6%) in Korean. Rosuvastatin showed meaningfully more decreasing rate compared with atorvastatin in TC and non-HDL-C. Both two drugs all showed meaningfully higher decreasing rate with a positive correlation of dose increasing.

The side effect profiles of both atorvastatin and rosuvastatin also very tolerable with minor symptoms such as headache or dyspepsia.

In conclusion, both atorvastatin and rosuvastatin were showed the improvements of lipid profiles with a few tolerable side effects in Korean. Therefore both atorvastatin and rosuvastatin among HMG-CoA reductase inhibitors have the benefit for the treatment of Korean dyslipidemia.

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