



Metabolic Syndrome Causes Cardiovascular Disease under Stable Statin Medication

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Objective: Statins are known to prevent only 30-50% of cardiovascular disease(CVD) by reducing low-density lipoprotein cholesterol (LDL-C). There is a controversy about whether metabolic syndrome(MS) can increase the risk of CVD. The aim of this study is to investigate whether MS can increase the risk of CVD, even after LDL-C is ideally controlled by taking statins.

Methods: As a retrospective observational study, we investigated CVD events of 909 patients (61.3 ± 10.2 years old) by reviewing medical records for at least 1 year before and after taking statins respectively, from June 2005 to February 2008, and analyzed the risk factors of CVD.

Results: During the study period (881.4 ± 232.8 days), 46 cases of CVD events occurred in patients with a very high risk of CVD and in patients with a high risk of CVD. In patients with a very high risk of CVD, 56.8% (21 cases over 37) of CVD events occurred in patients who achieved LDL-C goal (<70 mg/dL). A total of 9 events developed among high risk patients who reached LDL-C goal (<100 mg/dL). The patients with MS revealed significantly higher rates of CVD events [$p=0.015$; hazard ratio (HR) 3.033; 95% confidence interval (CI) 1.184-7.768]. Significantly higher rates of CVD events were also found in subgroup analysis of the patient with a past history of CVD events [$p=0.017$; HR 3.431; 95% CI 1.183-9.956]. Similar pattern was demonstrated in patients with diabetes [$p=0.049$; HR 2.738; 95% CI 0.963-7.782]. Cox regression analysis identified metabolic syndrome [$p=0.025$; HR 5.237; 95% CI 1.235-22.204], a past history of CVD events [$p=0.000$; HR 5.349; 95% CI 2.321-12.327], basal LDL-C level [$p=0.024$; HR 1.013; 95% CI 1.002-1.025] and total cholesterol level after statin therapy [$p=0.024$; HR 0.978; 95% CI 0.959-0.997] as independent predictors of CVD among LDL-C goal achieved patients.

Conclusion: Metabolic syndrome is the independent risk factor of CVD events in high risk patients with or without a past history of CVD events or diabetes. In these patients, statins could not prevent CVD events effectively. (J Lipid Atheroscler 2017 December;6(2):75-83).

Key Words: Statin, Cardiovascular disease, Metabolic syndrome

INTRODUCTION

Cardiovascular disease (CVD) is the second most common cause of death among Korean population.¹ Lowering low density lipoprotein cholesterol (LDL-C) through statin medication reduces the number of future CVD events as much as by 20% per 1 mmol/L LDL-C

reduction.^{2,3} In Korea, a previous report described that more than a million adult population is currently assumed to be under statin medication and 62.6% of high-risk patients including those with diabetes achieve the LDL-C target goal recommended by National Cholesterol Education Program-Adult Treatment Panel III (NCEP-III), i.e. <100 mg/dL.¹ Recently updated lipid management

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guidelines recommend more aggressive statin treatment, in which LDL-C levels should be maintained even <55 mg/dL in high risk group with history of acute coronary syndrome (ACS).^{4,5}

In Korea, the other phenotype of dyslipidemia showing high triglyceride or/and low high density lipoprotein cholesterol (HDL-C) levels is commonly found and is usually combined with abdominal obesity and elevated blood pressure and fasting glucose levels as co-morbidities for metabolic syndrome (MS). The prevalence of MS among Korean adult population is reported as high as 23.7% (male: 24.0%, female 23.4%) when NCEP-III diagnostic criteria is applied^{6,7} and keep increasing. Therefore, it is highly plausible that substantial number of Koreans with high risk for CVD is under MS condition and most of them have statin medication on a daily basis.

Although it was not independently proved whether statin prevents CVD in subjects with MS in a single trial, several reports described that MS increases the risk of future CVD^{8,9} and recent trials such as the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin The JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial)¹⁰ and the Heart Outcomes Prevention Evaluation HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial¹¹ included substantial number of MS subjects and showed the reduction of CVD events through statin medication. However, it is still unclear whether the risk of CVD elicited by complex dyslipidemic conditions in MS can be reduced by statin medication itself.

In this study, we tried to figure out whether the conventional statin treatment to Korean patients who were referred to tertiary hospital may achieve LDL-C target goals suggested by NCEP-III guideline. Additionally, the present study analyzed if MS may contribute to CVD events under well-maintained LDL-C condition with statin treatment.

MATERIALS AND METHODS

1. Study Subjects

This study is retrospectively designed study that included 909 subjects who visited outpatient clinic of cardiology department of Asan Medical Center, Seoul, Korea, between June, 2005 and February, 2009. All subjects had clear medical records for at least a year before the initiation of statin therapy, confirming that they did not have any serious co-morbidities other than CVD events to affect the clinical course during study period. And all subjects should have maintained fixed dose of specific statin for at least a year. The date of initiation of the statin was defined as 'baseline'. All study subjects were followed up until the development of first CVD episode or the change of statin regimen. The last follow-up date was defined as 'follow-up'.

CVD events in the present study were defined as follows; coronary angioplasty or stent insertion, development of ischemic stroke, admission due to coronary artery diseases (stable angina, ACS including myocardial infarction) or congestive heart failure due to ischemic heart disease. Ten-year risk for the development of CVD was calculated following NCEP-III guideline.¹² High risk for CVD is defined when the 10-year-risk exceeds 20 % and very-high risk is defined when the history of CVD is combined with any of risk factors such as smoking, diabetes, hypertension and/or MS. We also used NCEP-III diagnostic criteria for MS with slight modification as follows; abdominal obesity (body mass index (BMI) ≥ 25 kg/m²), blood pressure $\geq 130/85$ mmHg or anti-hypertensive medication, fasting blood glucose ≥ 100 mg/dL or hypoglycemic agents, triglyceride ≥ 150 mg/dL or lipid-lowering medication, HDL-C (<40 and <50 mg/dL in men and women, respectively). MS was diagnosed when any subjects had three or more of those criteria.^{12,13}

The collection of data was completed in February, 2009 and obtaining consent from subjects was not required

Table 1. Demographic characteristics and CVD risk factors at baseline

	Total (n=909)	Men (n=467)	Women (n=442)	<i>p</i> value
Age (yrs)	61.3±10.2	58.8±10.1	63.8±9.6	0.309
Total follow-up period (days)	881.4±232.8	882.5±237.1	880.2±228.6	0.292
CVD RISK FACTORS				
Hypertension	679 (74.7%)	337 (72.2%)	342 (77.4%)	0.071
HDL-C <40 mg/dL	231 (25.4%)	141 (30.2%)	90 (20.4%)	0.001
Cigarette smoking	151 (16.6%)	142 (30.4%)	9 (2.0%)	0.000
Age (Men ≥45, Women ≥55 yrs)	778 (85.6%)	417 (89.3%)	361 (81.7%)	0.001
FHx. for CHD (Men <55, Women <65 yrs)	20 (2.2%)	12 (2.6%)	8 (1.8%)	0.435
Diabetes mellitus	784 (86.2%)	384 (82.2%)	400 (90.5%)	0.000
CHD history	340 (37.4%)	210 (45.0%)	130 (29.4%)	0.000
Risk factors ≥3	699 (76.9%)	387 (82.9%)	312 (70.6%)	0.000
Hypertension medication	582 (64.0%)	299 (50.0%)	291 (65.8%)	0.268
Antiplatelet agent	294 (32.3%)	191 (50.9%)	103 (23.3%)	0.000

Values are expressed as mean±SD (standard deviation) or number (%)

CVD; Cardiovascular Disease, HDL-C; high-density lipoprotein cholesterol, FHx; family history among first degree relatives

Table 2. Changes of clinical parameters from baseline to follow-up

	Baseline		Follow-up		<i>p</i> value
BMI (kg/m ²)	25.3	3.00	25.3	3.00	0.872
HbA1c (%)	7.3	1.82	7.2	1.40	0.016
FBS (mg/dL)	127.4	48.44	123.2	43.36	0.029
SBP (mmHg)	130.3	17.16	125.8	15.20	0.000
DBP (mmHg)	79.3	10.93	76.7	9.31	0.000
TC (mg/dL)	223.4	39.68	159.5	34.55	0.000
HDL-C(mg/dL)	49.4	15.01	49.7	13.36	0.527
Triglyceride (mg/dL)	192.2	125.03	147.4	89.27	0.000
LDL-C (mg/dL)	137.4	38.01	81.2	30.00	0.000
nonHDL-C (mg/dL)	173.9	37.14	109.8	33.48	0.000

Values are expressed as mean±SD (standard deviation) or number (%)

BMI; body mass index (kg/m²), FBS; fasting blood sugar (mg/dL), SBP; systolic blood pressure (mmHg), DBP; diastolic blood pressure (mmHg), TC; total cholesterol (mg/dL), HDL-C; high-density lipoprotein cholesterol (mg/dL), LDL-C; low-density lipoprotein cholesterol (mg/dL), nonHDL-C; non-high density lipoprotein cholesterol (mg/dL)

p values were obtained by paired *t*-test

by Institutional Review Board for the retrospective study at that time. Otherwise, we strictly followed the World Medical Association Declaration of Helsinki revised at 59th General Assembly, Seoul, October 2008.

2. Statistics

All data were expressed as mean±standard deviation and the change of parameters at 'baseline' and 'follow-up' was analyzed by paired *t*-test. The multiple comparison

was analyzed by ANOVA and the impact of MS on the development of CVD was analyzed by Chi-square test. Cox regression analysis was used to identify factors associated with the development of CVD. The development of CVD during study period was expressed by Kaplan-Meier survival analysis. IBM SPSS Statistics 23 version was used and we considered as statistically significant if *p*<0.05.

Table 3. LDL cholesterol goal achievement and major cardiovascular events

Risk	LDL-C Goal (mg/dL)	Major CVD Events			<i>p</i> value
		Total	LDL-C Goal Achieved	LDL-C Goal Not-achieved	
		46/909 (5.1%)	30/602 (5.0%)	16/307 (5.2%)	
Very high	<70	37/340 (10.9%)	21/158 (13.3%)	16/182 (8.8%)	0.184
High	<100	9/508 (1.8%)	9/386 (2.3%)	0/122 (0.0%)	0.089
Moderate	<130	0/25 (0.0%)	0/23 (0.0%)	0/2 (0.0%)	NA
Low	<160	0/36 (0.0%)	0/35 (0.0%)	0/1 (0.0%)	NA

CVD; Cardiovascular disease, LDL-C; low-density lipoprotein cholesterol, NA; not applicable

p values were obtained by paired *t*-test

Table 4. Metabolic syndrome; the prevalence and distribution of diagnostic criteria

		Total (n=909)	Men (n=467)	Women (n=442)	<i>p</i> value
Metabolic syndrome (+)	Dx criteria ≥ 3	671 (73.8%)	324 (69.4%)	347 (78.5%)	0.002
DX CRITERIA FOR MS					
Body mass index	≥ 25 kg/m ²	450 (49.5%)	225 (48.2%)	225 (50.9%)	0.411
Triglyceride*	≥ 150 mg/dL	508 (55.9%)	264 (56.5%)	244 (55.2%)	0.687
HDL-C	(Men<40, Women<50 mg/dL)	400 (44.0%)	141 (30.2%)	259 (58.6%)	0.000
Blood pressure*	$\geq 130/85$ mmHg	749 (82.4%)	374 (80.1%)	375 (84.8%)	0.060
Fasting blood glucose*	≥ 100 mg/dL	813 (82.9%)	406 (86.9%)	407 (92.1%)	0.012

MS; metabolic syndrome, Dx; Diagnosis, HDL-C; high-density lipoprotein cholesterol

*; or with medication

p values were obtained by paired *t*-test

RESULTS

1. Demographic profiles

Of all subjects (n=909 ; mean 61.3±10.2 years old), 86.2% had diabetes, 37.4% had a history of CVD and 76.9% had 3 or more major CVD risk factors defined by NCEP-III guideline. Compare to women, more men were smokers, were older, had a history of CVD or ≥ 3 major risk factors, and showed low HDL-C levels (<40 mg/dL) while more women had diabetes than men (Table 1).

At "baseline", either atorvastatin (10-40 mg), rosuvastatin (5-20 mg), simvastatin (10-40 mg), pravastatin (20-40 mg), fluvastatin (40-80 mg), or simvastatin/ezetimibe (10/10 or 10/20 mg) was initiated and maintained for 881.4±232.8 days. In all subjects, blood pressure levels (*p*=0.000 for both systolic blood pressure (SBP) and diastolic blood pressure (DBP)) showed significant reductions after initiation of statin medication. The reduction

of fasting glucose (127.4±48.4 vs. 123.2±43.4 mg/dL; *p*=0.029) and HbA1c (7.3±1.8 vs. 7.2±1.4%; *p*=0.016) was also significant but modest. Unfortunately, BMI levels showed little changes during follow-up. Lipid parameters such as LDL-C (137.4±38.0 vs. 81.2±30.0 mg/dL; *p*=0.000), non HDL-C (174.0±37.1 vs. 109.8±33.5 mg/dL; *p*=0.000), triglyceride (192.2±125.0 vs. 147.4±89.3 mg/dL; *p*=0.000) showed significant reductions while HDL-C level showed little changes (49.4±15.01 vs. 49.7±13.36 mg/dL; *p*=0.527) (Table 2).

2. Development of CVD according to LDL-C goal achievement

Most subjects were turned out to be under high- (508/909; 55.9%) or very high risk (340/909; 37.4%) defined by status of 10-year CVD risk. The proportion who reached below target goal of LDL-C levels (less than 70, 100, 130 and 160 mg/dL for very high, high, moderate

Table 5. Demographic profiles by diagnostic criteria for metabolic syndrome

MS Dx criteria number	0 OR 1 (n=59)	2 (n=179)	3 (n=305)	4 (n=236)	5 (n=130)	<i>p</i> value
Age	59.5±9.51	61.7±9.93	60.7±9.94	61.5±10.66	62.0±10.45	0.553
Male	38 (64.4%)	105 (58.7%)	171 (56.1%)	113 (47.9%)	40 (30.8%)	0.000
Hypertension	15 (25.4%)	108 (59.8%)	232 (75.7%)	205 (86.9%)	121 (93.1%)	0.000
Diabetes Mellitus	30 (50.8%)	140 (78.2%)	265 (86.9%)	221 (93.6%)	128 (98.5%)	0.000
CVD history	21 (35.6%)	77 (43.0%)	104 (40.3%)	90 (38.1%)	46 (35.4%)	0.648
BASELINE						
Smoking (M/F)	11 (10/1)	36 (33/3)	50 (42/8)	44 (39/5)	11 (9/2)	0.000
BMI (kg/m ²)	22.2±1.71	23.4±2.30	24.9±2.95	26.0±2.89	27.7±2.43	0.000
FBS (mg/dL)	114.1±49.81	117.9±39.53	125.0±46.78	135.3±55.35	133.8±50.3	0.003
SBP (mmHg)	117.4±14.49	126.2±14.92	129.8±15.57	132.1±18.82	137.4±18.59	0.000
DBP (mmHg)	73.6±11.83	77.8±9.95	79.0±10.60	80.7±11.42	82.1±12.04	0.000
TC (mg/dL)	231.3±33.57	229.2±37.75	222.9±37.67	224.5±72.09	216.8±42.76	0.038
Triglyceride (mg/dL)	99.4±27.40	121.8±72.13	178.9±117.80	289.4±577.88	251.6±101.92	0.000
HDL-C (mg/dL)	62.7±17.68	57.4±16.28	50.7±15.69	43.5±8.68	39.9±6.50	0.000
LDL-C (mg/dL)	155.2±29.59	155.5±38.67	146.9±34.05	139.0±41.40	139.3±38.66	0.000
nonHDL-C (mg/dL)	168.6±30.83	171.8±36.70	172.1±34.04	181.0±69.94	176.9±40.70	0.322
FOLLOW-UP						
Smoking (M/F)	8 (8/0)	18 (16/2)	27 (27/0)	23 (22/1)	5 (5/0)	0.283
BMI (kg/m ²)	22.4±2.03	23.7±2.64	25.3±2.65	26.1±2.60	27.6±3.12	0.000
FBS (mg/dL)	108.2±41.32	111.2±35.80	126.8±48.42	125.3±39.03	135.0±42.63	0.000
SBP (mmHg)	116.9±12.98	122.9±13.91	125.9±14.61	127.7±15.44	130.3±14.93	0.000
DBP (mmHg)	72.8±9.20	76.5±9.04	76.7±8.59	77.5±9.69	77.3±9.45	0.020
TC (mg/dL)	166.2±33.77	161.6±31.78	158.9±34.75	160.3±39.35	154.2±30.59	0.300
Triglyceride (mg/dL)	97.7±39.21	120.1±65.26	145.7±96.76	175.1±107.25	164.5±73.19	0.000
HDL-C (mg/dL)	59.9±16.23	55.9±15.48	50.2±12.40	45.1±10.43	43.4±8.04	0.000
LDL-C (mg/dL)	92.7±27.65	87.1±29.93	86.7±32.06	88.6±32.03	85.2±27.00	0.585
nonHDL-C (mg/dL)	106.3±28.84	105.7±32.42	108.7±33.81	115.3±37.68	110.8±29.74	0.126

Values are expressed as mean±SD (standard deviation) or number (%)

MS; metabolic syndrome, BMI; body mass index (kg/m²), FBS; fasting blood sugar (mg/dL), SBP; systolic blood pressure (mmHg), DBP; diastolic blood pressure (mmHg), TC; total cholesterol (mg/dL), HDL-C; high-density lipoprotein cholesterol (mg/dL), LDL-C; low-density lipoprotein cholesterol (mg/dL), nonHDL-C; non-high density lipoprotein cholesterol (mg/dL) *p* values were obtained by paired *t*-test

and low risk, respectively) was 45.5, 76.0, 92.0, and 97.2 % for very high (n=340), high (n=508), and moderate (n=25) or low risk (n=36) groups, respectively (Table 3), during statin medication. During study period, total of 46 major CVD events were reported in very high risk (37/340) or high risk (9/508) group. The achievement of LDL-C goal did not significantly reduce the development of CVD (*p*=0.088 ; Chi-square test) (Table 3).

3. Clinical characteristics of MS

MS defined by NCEP-III with modification was diagnosed in 73.8% (671/909), more frequently in women (*p*=0.002

; *t*-test). Among five diagnostic criteria for MS, more women showed low HDL-C and higher fasting glucose levels compared to men (Table 4).

When the subjects were divided by the number of diagnostic criteria for MS at baseline, as the number is increasing, the prevalence of smoking, hypertension and diabetes was increasing (all *p*=0.000), and BMI (*p*=0.000), fasting blood glucose (*p*=0.003) and triglyceride (*p*=0.000) levels became higher as expected (ANOVA) while total cholesterol (TC) (*p*=0.038) and LDL-C levels (*p*=0.000) were getting lower. Statin medication significantly lowered TC, LDL-C and non-HDL-C levels in

Table 6. Metabolic syndrome and major CVD events

	Major CVD events		HR [95% CI]	<i>p</i> value
	MS (+)	MS (-)		
Overall	41/671 (6.1%)	5/238 (2.1%)	3.03 [1.184-7.768]	0.015
CVD Hx (+)	33/259 (12.7%)	4/98 (4.1%)	3.43 [1.183-9.956]	0.017
CVD Hx (-)	8/412 (1.9%)	1/140 (0.7%)	2.75 [0.341-22.204]	0.322
DM Hx (+)	38/614 (6.2%)	4/170 (2.4%)	2.74 [0.963-7.782]	0.049
DM Hx (-)	3/57 (5.3%)	1/68 (1.5%)	3.72 [0.376-36.807]	0.230

MS; metabolic syndrome, CVD; Cardiovascular disease, Hx; history, DM; diabetes mellitus

Table 7. Cox regression analysis for CVD risks among LDL-C goal achieved patients

	B	S.E.	Wald	DF	Sig	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Baseline LDL-C	0.013	0.006	5.068	1	0.024	1.013	1.002	1.025
CVD_Hx (+)	1.677	0.426	15.497	1	0.000	5.349	2.321	12.327
MS at baseline	1.656	0.737	5.407	1	0.025	5.237	1.235	22.204
Follow-up TC	0.023	0.010	5.063	1	0.024	0.978	0.959	0.997

Variable(s) Entered at Step Number 1: Sex, Smoking history, BMI, Hypertension, Diabetes history, CVD history, antiplatelet agent, MS, CVD 10yr-risk, LDL-C goal achievement, Basal TC, Basal HDL-C, Basal TG, Basal LDL-C, Basal nonHDL-C, F/U TC, F/U HDL-C, F/U TG, F/U LDL-C, F/U nonHDL-C

LDL-C; low density lipoprotein cholesterol, CVD; Cardiovascular disease, MS; metabolic syndrome, TC; total cholesterol, BMI; body mass index, HDL-C; high-density lipoprotein cholesterol, TG; triglyceride, F/U; follow up

all subgroup (Table 5). On the other hand, ANOVA showed that all five components of diagnostic criteria for MS such as BMI ($p=0.000$), fasting blood glucose ($p=0.000$), SBP ($p=0.000$) and DBP ($p=0.020$), triglyceride levels ($p=0.000$) and HDL-C level ($p=0.000$) still showed significant differences between subgroups at follow-up, suggesting the management of MS is not as efficient as LDL-C-related parameters (Table 4).

4. MS and CVD events

At “baseline”, the prevalence of CVD history was not associated with the presence and the severity of MS (Table 5). During study period, the developed major CVD events were more frequently reported in MS group (41/671 ; 6.1% vs. 5/238 ; 2.1%, $p=0.015$) The relationship between MS and CVD events was consistently observed in subgroups with diabetes ($p=0.049$) and previous CVD history ($p=0.017$) (Table 6).

Cox regression analysis showed that the history of CVD (HR:5.349, 95% CI 2.321-12.327, $p=0.000$) and the initial

diagnosis of MS (HR:5.237, 95% CI 1.235-22.204, $p=0.025$) were found to be related to the development of CVD among LDL-C goal achieved patients. Both LDL-C level (HR: 1.013, 95% CI 1.002-1.025, $p=0.024$) before statin treatment and total cholesterol level (HR: 0.978, 95% CI 0.959-0.997, $p=0.024$) at follow-up were also related to the development of CVD with lesser degree (Table 7). Kaplan-Meier survival analysis showed that the occurrence of CVD events during follow-up was observed more frequently in subjects with MS or previous history of CVD (Fig. 1).

DISCUSSION

The majority of our study subjects not only had diabetes (86.2%) but also had 3 or more CVD risk factors (76.9%) and previous CVD history (37.4%). Recent studies suggest that CVD-related morbidity and mortality of Asian and Korean population are not lower than other Caucasian ethnic groups at least for high- and very high CVD risk

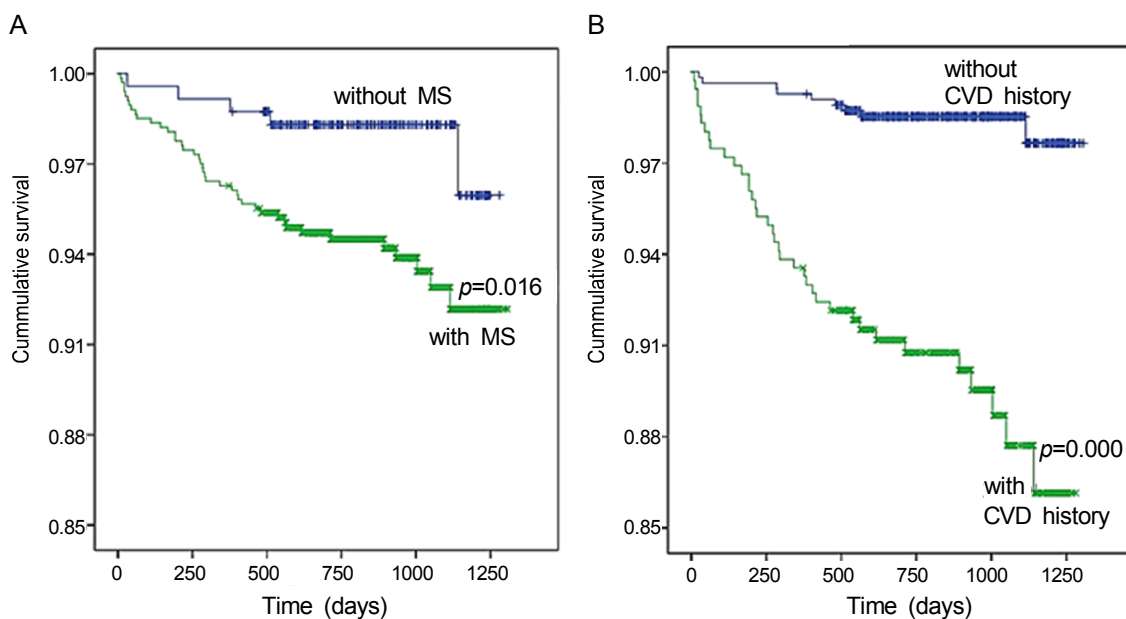


Fig. 1. Survival analysis of CVD events stratified by MS (A) or CVD history (B). MS; metabolic syndrome, CVD; Cardiovascular disease

groups as recruited in our study.^{14,15} Recently, Jung et al.¹⁶ analyzed over 2 million Korean patients with diabetes with and without history of previous coronary heart disease and showed that the annual incidence of coronary revascularization was 597.9 (without CHD history) and 4109.9 (with CHD history), respectively (per 100,000 person-years). A previous population-based study¹⁷ with Da Qing province in China described that the annual cardio-cerebrovascular death in newly-diagnosed diabetes group was 17.5 and 15.5/1000 person-years in men and women, respectively, during 23 years of follow-up.

The efficacy of statin management to patients with diabetes has been proved by Collaborative Atorvastatin Diabetes Study (CARDS),¹⁸ which proved the preventive effect of statin (atorvastatin 10 mg/day) on population with diabetes without CVD history. In this study, one-third of the subjects had history of CVD and basal LDL-C level was higher than CARDS trial, suggesting the absolute CVD risk in our subjects is presumed to be higher than subjects in CARDS trial. The statin medication in this study

significantly reduced LDL-C levels by 40.9 % to 81.2 ± 30.0 mg/dL, which is equal to or lower than CARDS trial and meets the minimal LDL-C target goal suggested by NCEP-III guideline,¹⁹ i.e. <100 mg/dL. Under these circumstances, the estimated annual incidence of CVD event during statin medication in this study was as low as 2.1%, which was comparable to the result of CARDS trial. Therefore, such results of this study highly suggest that the control of LDL-C through statin medication may have reduced CVD events in high-risk Korean subjects.

The strategy of statin use in the present study is less aggressive when compared to the updated 2013 ACC (American College of Cardiology) / AHA (American Heart Association) guideline recommending maximal-tolerable dose of statins (40 to 80 mg atorvastatin equivalent) especially to high- and very-high CVD risk groups. However, 75% of our subjects had reached <100 mg/dL LDL-C levels after statin medication, suggesting that Korean population may respond to statins more efficiently than Caucasian population^{1,3} in aspects of not only LDL-C reduction but also the prevention of CVD events. But it

has to be noted that ACS patients were not included in this study and all subjects were clinically stable at the “baseline”. Considering the fact that more aggressive statin management showed better CVD prevention within first year of medication,⁴ in ACS patients, such earlier benefit of statins may be inadvertently excluded in this study. Therefore, our study results are not applicable to patients under more severe forms of cardio- and cerebrovascular disease and are not contradictory to the most updated guidelines to use maximal tolerable doses of potent statins. It remains to be proved whether maximal tolerable dose of potent statins may improve the early outcome in Korean population with high- and very-high CVD risks.

Considering the fact that 73.6% of our study subjects were diagnosed as MS at baseline, optimal control of the components for MS as well as the reduction of LDL-C may be necessary for the prevention of CVD events. Unfortunately, our study results show that MS is under-recognized and poorly controlled when compared to LDL-C-related parameters. Most notably, HDL-C levels and obesity were not appropriately controlled and fasting glucose and HbA1c levels showed only mild reductions throughout the study period. Moreover, subjects diagnosed as MS at baseline persistently showed higher BMI, blood pressure, glucose profile, and triglyceride levels with lower HDL-C levels during follow up. Such poor control of MS may explain the results of multivariate analysis, in which the presence of MS had shown to affect the outcome of CVD events more heavily than the achievement of LDL-C goal. Kim et. al.²⁰ reported that active and persistent lifestyle intervention to Korean subjects with MS could lower the annual incidence of myocardial infarction by 50.5%. Therefore, if non-pharmacological as well as pharmacological intervention is actively applied to individuals with MS especially having CVD history, future development of CVD events could be further minimized in Korean population with high- and very-high CVD risks.

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REFERENCES

1. Roh E, Ko SH, Kwon HS, Kim NH, Kim JH, Kim CS, et al. Prevalence and management of dyslipidemia in Korea: Korea National Health and Nutrition Examination Survey during 1998 to 2010. *Diabetes Metab J* 2013;37:433-449.
2. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-1278.
3. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S1-S45.
4. Grundy SM, Cleeman JJ, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-239.
5. Schiele F, Farnier M, Krempf M, Bruckert E, Ferrières J. A consensus statement on lipid management after acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care*. Forthcoming 2016.
6. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-359.
7. Hong AR, Lim S. Clinical characteristics of metabolic syndrome in Korea, and its comparison with other Asian countries. *J Diabetes Investig* 2015;6:508-515.

8. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-1357.
9. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-1622.
10. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-2207.
11. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009-2020.
12. Fedder DO, Koro CE, L'Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. *Circulation* 2002;105:152-156.
13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.
14. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935-2959.
15. Ko MJ, Kim YJ, Park CM, Lee SM, Lee WJ, Pencina MJ, et al. Applicability and potential clinical effects of 2013 cholesterol guidelines on major cardiovascular events. *Am Heart J* 2015;170:598-605.e7.
16. Jung CH, Seo GH, Suh S, Bae JC, Kim MK, Hwang YC, et al. The Population-based risk of need for coronary revascularization according to the presence of type 2 diabetes mellitus and history of coronary heart disease in the Korean population. *PLoS One* 2015;10:e0128627.
17. An Y, Zhang P, Wang J, Gong Q, Gregg EW, Yang W, et al. Cardiovascular and all-cause mortality over a 23-year period among chinese with newly diagnosed diabetes in the Da Qing IGT and Diabetes Study. *Diabetes Care* 2015;38:1365-1371.
18. Owen OG. The collaborative atorvastatin diabetes study: preliminary results. *Int J Clin Pract* 2005;59:121-123.
19. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
20. Kim D, Yoon SJ, Lim DS, Gong YH, Ko S, Lee YH, et al. The preventive effects of lifestyle intervention on the occurrence of diabetes mellitus and acute myocardial infarction in metabolic syndrome. *Public Health* 2016; 139:178-182.