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Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea

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ABSTRACT

Objective: The aim of this study was to evaluate under target rates of low-density lipoprotein-cholesterol (LDL-C) in Korean patients with stable coronary artery disease (CAD) or an acute coronary syndrome (ACS) in real world practice.
Methods: Dyslipidemia International Study II was an international observational study of patients with stable CAD or an ACS. Lipid profiles and use of lipid-lowering therapy (LLT) were documented at enrollment, and for the ACS cohort, 4 months follow-up was recommended. Rates of under target LDL-C as per European guidelines, were evaluated, and multivariate regression was performed to identify predictive factors of patients presenting under the target.
Results: A total of 808 patients were enrolled in Korea, 500 with stable CAD and 308 with ACS. Of these, 90.6% and 52.6% were being treated with LLT, respectively. In the stable CAD group, 40.0% were under target LDL-C, while in ACS group, the rate was 23.7%. A higher statin dose was independently associated with under target LDL-C in both groups (OR, 1.03; p=0.046 [stable CAD] and OR, 1.05; p=0.01 [ACS]). The mean statin dosage (atorvastatin equivalent) was 17 mg/day. In the 79 ACS patients who underwent the follow-up examination, the LDL-C under target rate rose to 59.5%.
Conclusion: Only a minority of patients with stable CAD or ACS were under their target LDL-C level at enrollment. The statin dose was not sufficient in the majority of patients. These results indicate a considerable LLT gap in Korean patients with established CAD.

Keywords: Cholesterol; Hydroxymethylglutaryl-CoA reductase inhibitors; Acute coronary syndrome; Coronary artery disease; Dyslipidemias

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Conflict of Interest

The authors have no conflicts of interest to declare.

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INTRODUCTION

It has been demonstrated that the 5-year incidence of major vascular events can be cut by approximately a fifth by reducing the level of low-density lipoprotein-cholesterol (LDL-C) by 39 mg/dL (1 mmol/L).[1] The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias recommend that an LDL-C level of <70 mg/dL (1.8 mmol/L) should be the aim in patients at very high cardiovascular risk, which includes those with documented cardiovascular disease.[2]

According to the lipid treatment assessment project (L-TAP) 2, a survey performed in >10,000 dyslipidemic patients in 9 countries (United States, Canada, Mexico, Brazil, Spain, Netherlands, France, Taiwan, and Korea) between 2006 and 2007, 75.7% of U.S patients and 67.3% of Canadian patients attained their LDL-C target (defined according to regional guidelines at the time).[3] The result in Spain was lowest, with 47.4% of patients reaching their LDL-C goal. These goal attainment figures are similar to those observed in the original Dyslipidemia International Study (DYSIS), with 63.2% of high-risk patients and 48.2% of total patients in Europe and Canada who were on statin treatment reaching their LDL-C target.[4]

Lipid-lowering therapy (LLT) is widely used in South Korea and one study suggested more intensive treatment use than in other Asian countries.[5] However, achievement of recommended LDL-C target levels remains suboptimal. In the Centralized Pan-Asian Survey of the Under treatment of Hypercholesterolemia (CEPHEUS), 31.5% of the very high-risk LLT patients from South Korea had reached their LDL-C target of <70 mg/dL.[5] Although this compares favorably with the 24.4% observed in the non-Korean Asian patients and the 22.8% found for the overall global CEPHEUS cohort,[6] it remains disappointingly low.

The aim of this study was to assess the rate of under-target LDL-C in Korean patients with stable coronary artery disease (CAD) or an acute coronary syndrome (ACS). The LLT regimen was also investigated.

MATERIALS AND METHODS

1. Study patients and design

DYSIS II was a multinational, observational, cross-sectional study that enrolled patients over 18 years of age with stable CAD or ACS. Data were collected from 21 countries across the Asia-Pacific region, Europe, and the Middle East and Africa.[7,8] The present article involves the patients enrolled in Korea between July 2013 and July 2014. Data of patients with CAD were collected at outpatient visit, whereas those of patients with ACS were obtained at hospital admission and by telephone interview or outpatient visit 4 months after discharge. Stable CAD was defined as coronary artery stenosis >50% by either coronary angiography or coronary CT, prior percutaneous coronary intervention, prior coronary artery bypass graft, or ACS >3 months prior to the outpatient visit. ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-STEMI or unstable angina. A lipid profile was collected for each patient. For the stable CAD group, this was constructed from by the last samples taken in the past 12 months, while for the ACS group, it was from samples taken in 24 hours of hospital admission. Individuals were excluded if they were currently participating in a clinical trial, and for the ACS group, if they died during the hospital stay. Patients were divided based on whether or not they were taking LLT at the time of enrollment. Patients in

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the LLT group needed to be treated for 3 months or longer. The study protocol was approved by ethics committee at each site (4-2013-0210) and study was conducted in accord with the Declaration of Helsinki.

2. Data collection

Baseline demographic and clinical characteristics were documented. These included age, sex, body mass index (BMI), lifestyle factors, and comorbidities. Obesity was defined as a BMI >30 kg/m^2. A sedentary lifestyle was defined as walking for <20–30 minutes on <3–4 days a week. Diabetes mellitus was defined as current treatment, previous diagnosis of diabetes mellitus, or a fasting plasma glucose level ≥126 mg/dL.[9] Hypertension was defined as current treatment, a previous diagnosis of hypertension, or a blood pressure >140/90 mm Hg.[10,11] Chronic kidney disease (CKD) was defined as stage 3, 4, or 5 when a glomerular filtration rate was 30–59, 15–29, or <15 mL/min/1.73m^2, respectively.[12]

The baseline lipid profile included total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), LDL-C and non-HDL-C. The cardiovascular risk level of the ACS patients prior to the ACS event was determined according to the 2011 ESC/EAS guidelines as very high, high, moderate, or low.[13] The corresponding target LDL-C levels for these groups were <70 mg/dL, <100 mg/dL, <115 mg/dL, and <130 mg/dL. The proportions of patients in each risk category that had achieved their specific LDL-C target were calculated. Target achievement was re-evaluated at the 4-month follow-up for ACS patients with a further lipid profile available.

LLT was classified as statin monotherapy, non-statin monotherapy, statin plus ezetimibe or statin plus other non-statin (fibrates, omega-3 fatty acids, or nicotinic acid). Statins included lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, and pitavastatin. Atorvastatin dose equivalents were based on a systematic review of clinical trial data on the LDL-C-lowering efficacy of various statins.[14]

3. Statistical analysis

SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for statistical analyses. Data are presented as means with standard deviations, medians with interquartile ranges, or absolute values with percentages. Statistical significance was determined using the Mann-Whitney-Wilcoxon test or the χ^2 test.

Multivariate regression analyses were performed in both groups to identify any determinants of LLT-treated patients achieving an LDL-C level of <70 mg/dL. The covariates included age, female gender, diabetes mellitus, hypertension, congestive heart failure, current smoking, sedentary lifestyle, stable angina, CKD and statin dose (i.e., atorvastatin equivalent dose). Mortality at follow-up was estimated using Kaplan–Meier analysis, with *p*-values calculated using a log-rank test. All statistical comparisons were 2-tailed, and results with a *p*-value of <0.05 were considered significant.

RESULTS

1. Patient characteristics

The stable CAD group consisted of 500 patients. The mean age was 64.4±10.3 years and 73.2% were male (**Table 1**). The majority of this group (90.6%) was under LLT. The mean

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Table 1. Patient characteristics: stable CAD group

	Total (n=500)	LLT (n=453)	No LLT (n=47)	*p*-value‡
Age (yr)	64.4±10.3	64.7±10.4	61.6±9.2	0.03
Male (sex)	366/500 (73.2)	328/453 (72.4)	38/47 (80.9)	0.21
BMI (kg/m^2)	24.9±3.2	25.0±3.2	24.3±3.0	0.18
BMI (>25 kg/m^2)	228/497 (45.9)	209/450 (46.4)	19/47 (40.4)	0.53
Cardiovascular risk factors and comorbidities				
Type 2 diabetes mellitus	198/500 (39.6)	188/453 (41.5)	10/147 (21.3)	0.007
Hypertension	343/500 (68.6)	314/453 (69.3)	29/47 (61.7)	0.28
CKD	16/500 (3.2)	16/453 (3.5)	0/47 (0.0)	0.19
Stroke*	43/498 (8.6)	40/451 (8.9)	3/47 (6.4)	0.56
PAD	9/500 (1.8)	8/453 (1.8)	1/47 (2.1)	0.86
Current smoker	92/500 (18.4)	83/453 (18.3)	9/47 (19.1)	0.89
Sedentary lifestyle	124/499 (24.8)	107/453 (23.6)	17/46 (37.0)	0.08
Family history of CAD	65/436 (14.9)	61/397 (15.4)	4/39 (10.3)	0.39
History of CAD				
Prior PCI	445/500 (89.0)	404/453 (89.2)	41/47 (87.2)	0.68
Prior CABG	22/500 (4.4)	21/453 (4.6)	1/47 (2.1)	0.42
History of ACS†	195/500 (39.0)	172/453 (38.0)	23/47 (48.9)	0.14

Data presented as mean±standard deviation or number (%).
LLT, lipid-lowering therapy; BMI, body mass index; CKD, chronic kidney disease; CAD, coronary artery disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome.
*Includes ischemic and hemorrhagic stroke; †>3 months prior to enrollment; ‡The *p*-values calculated using χ^2 test or Mann-Whitney-Wilcoxon test.

age was higher and type 2 diabetes mellitus was more common in the LLT group. The ACS group consisted of 308 patients. The mean age was 63.0±11.4 years and 73.1% were male (**Table 2**). Prior to their admission for ACS, 52.6% of these patients were being treated with LLT. Patients with prior LLT were older and more likely to have type 2 diabetes mellitus and a sedentary lifestyle. Conversely, current smoking was less common in this subgroup. In regard to clinical presentation of ACS, STEMI was less common, whereas unstable angina was more common in patients with prior LLT compared to those with no LLT.

Table 2. Patient characteristics: ACS group

Characteristics	Total (n=308)	LLT (n=162)	No LLT (n=146)	*p*-value†
Age (yr)	63.0±11.4	64.4±10.5	61.3±12.2	0.03
Male (sex)	225/308 (73.1)	112/162 (69.1)	113/146 (77.4)	0.10
BMI (kg/m^2)	24.7±3.2	25.0±3.2	24.4±3.2	0.10
BMI (>25 kg/m^2)	132/306 (43.1)	75/161 (46.6)	57/146 (39.0)	0.24
Cardiovascular risk factors and comorbidities				
Type 2 diabetes mellitus	94/306 (30.7)	66/162 (40.7)	28/144 (19.4)	<0.001
Hypertension	190/308 (61.7)	116/162 (71.6)	74/146 (50.7)	<0.001
CKD	7/308 (2.3)	3/162 (1.9)	4/146 (2.7)	0.60
Stroke*	25/304 (8.2)	17/161 (10.6)	8/143 (5.6)	0.12
PAD	4/306 (1.3)	3/162 (1.9)	1/144 (0.7)	0.37
Current smoker	90/308 (29.2)	26/162 (16.0)	64/146 (43.8)	<0.001
Sedentary lifestyle	80/291 (27.5)	54/158 (34.2)	26/133 (19.5)	0.005
ACS diagnosis				
STEMI	76/308 (24.7)	20/162 (12.3)	56/146 (38.4)	<0.001
NSTEMI	103/308 (33.4)	51/162 (31.5)	52/146 (35.6)	0.44
Unstable angina	129/308 (41.9)	91/162 (56.2)	38/146 (26.0)	<0.001

Data presented as mean±standard deviation or number (%).
LLT, lipid-lowering therapy; BMI, body mass index; CKD, chronic kidney disease; ACS, acute coronary syndrome; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.
*Includes ischemic and hemorrhagic stroke; †The *p*-values calculated using χ^2 test or Mann-Whitney-Wilcoxon test.

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2. Lipid profiles and under-target rate

The mean LDL-C level of the patients with stable CAD was 81±28 mg/dL, and 40.0% of the patients had LDL-C <70 mg/dL (**Table 3**). The LDL-C level in the LLT group was lower than that of no LLT group (78 and 110 mg/dL in the LLT and no LLT groups, respectively; p<0.001). Accordingly, the proportion of subjects under target LDL-C level was higher in the LLT group (43.0% and 10.6% for LLT and no LLT groups, respectively; p<0.001). In the multivariate analysis, diabetes mellitus (OR, 1.59; p=0.046) and statin dosage (OR, 1.03; p=0.046) were found to be associated with under-target LDL-C levels in stable CAD group with LLT (**Fig. 1A**).

In the ACS group, the mean LDL-C level was 101±39 mg/dL, and 23.7% of patients displayed an LDL-C level of <70 mg/dL (**Table 3**). The LLT group had a lower mean LDL-C value than the no LLT group (83 and 121 mg/dL in LLT and no LLT groups, respectively; p<0.001). The proportion of patients with under target LDL-C level of <70 mg/dL was greater in the LLT group than the no LLT group (38.3% and 7.5%, respectively; p<0.001). When the patients were sub-divided according to their pre-ACS risk status, under-target rates were 66.7%, 91.4%, 68.4%, and 42.9% for the low, moderate, high, and very high-risk groups, respectively (**Fig. 2**). In the ACS group with no LLT, the corresponding rates were 76.9%, 38.8%, 12.5%, and 5.3%, respectively. In the multivariate analysis, statin dosage (OR, 1.05; p=0.01) and sedentary lifestyle (OR, 0.36; p=0.01) were associated with under-target rate (**Fig. 1B**). For some of the ACS group, lipid levels were re-assessed at 4 months after discharge. For the ACS patients treated with LLT at admission (n=79), the proportion of patients with under-target LDL-C of <70 mg/dL increased from 50.0% to 64.3% in this period (**Fig. 3**). Whereas, in ACS patients with no LLT at admission (n=146) the proportion increased from 5.4% to 59.5%.

3. LLT

For patients with stable CAD being treated with LLT, statin monotherapy was the most commonly used (81.2%), followed by statin plus ezetimibe (13.0%) and statin plus other non-statin (5.3%) (**Table 4**). Atorvastatin (43.9%), rosuvastatin (27.7%) and simvastatin (14.6%) were frequently used (**Supplementary Table 1**). The mean daily statin dosage (atorvastatin-equivalent) was 17±10 mg.

For the ACS patients treated with LLT at admission, the predominant LLT regimen was statin monotherapy (84.6%), and a small proportion of subjects were receiving a statin plus ezetimibe (6.8%) or a statin plus other non-statin (6.2%). The mean daily statin dosage (atorvastatin equivalent) was 17±12 mg. At 4-month follow-up, 98.3% of patients were receiving LLT: statin monotherapy (83.4%), statin plus ezetimibe (9.0%). The mean daily statin dosage (atorvastatin-equivalent) was 21±14 mg at this time point (**Table 4**).

Table 3. Lipid profile at baseline

Variables	Stable CAD				ACS			
	Total (n=500)	LLT (n=453)	No LLT (n=47)	p-value	Total (n=308)	LLT (n=162)	No LLT (n=146)	p-value
TC (mg/dL)	148±33	145±32	178±33	<0.001	168±54	152±59	186±41	<0.001
Triglycerides (mg/dL)	148±101	146±100	163±111	0.42	138±138	149±146	126±129	<0.01
HDL-C (mg/dL)	45±11	45±11	42±10	0.19	41±11	41±11	41±11	0.11
LDL-C (mg/dL)	81±28	78±26	110±28	<0.001	101±39	83±30	121±38	<0.001
Non-HDL-C (mg/dL)	103±32	100±31	135±31	<0.0001	125±44	108±40	144±40	<0.0001
LDL-C (<70 mg/dL)*	200/500 (40.0)	195/453 (43.0)	5/47 (10.6)	<0.001	73/308 (23.7)	62/162 (38.3)	11/146 (7.5)	<0.001
Distance to LDL-C <70 mg/dL (mg/dL)†	27±24	24±23	45±24	<0.0001	45±33	29±26	57±34	<0.0001

Data presented as mean±standard deviation or number (%).
CAD, coronary artery disease; ACS, acute coronary syndrome; LLT, lipid-lowering therapy; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Target for very high-risk patients; †Difference between actual LDL-C value and the goal of LDL-C <70 mg/dL.

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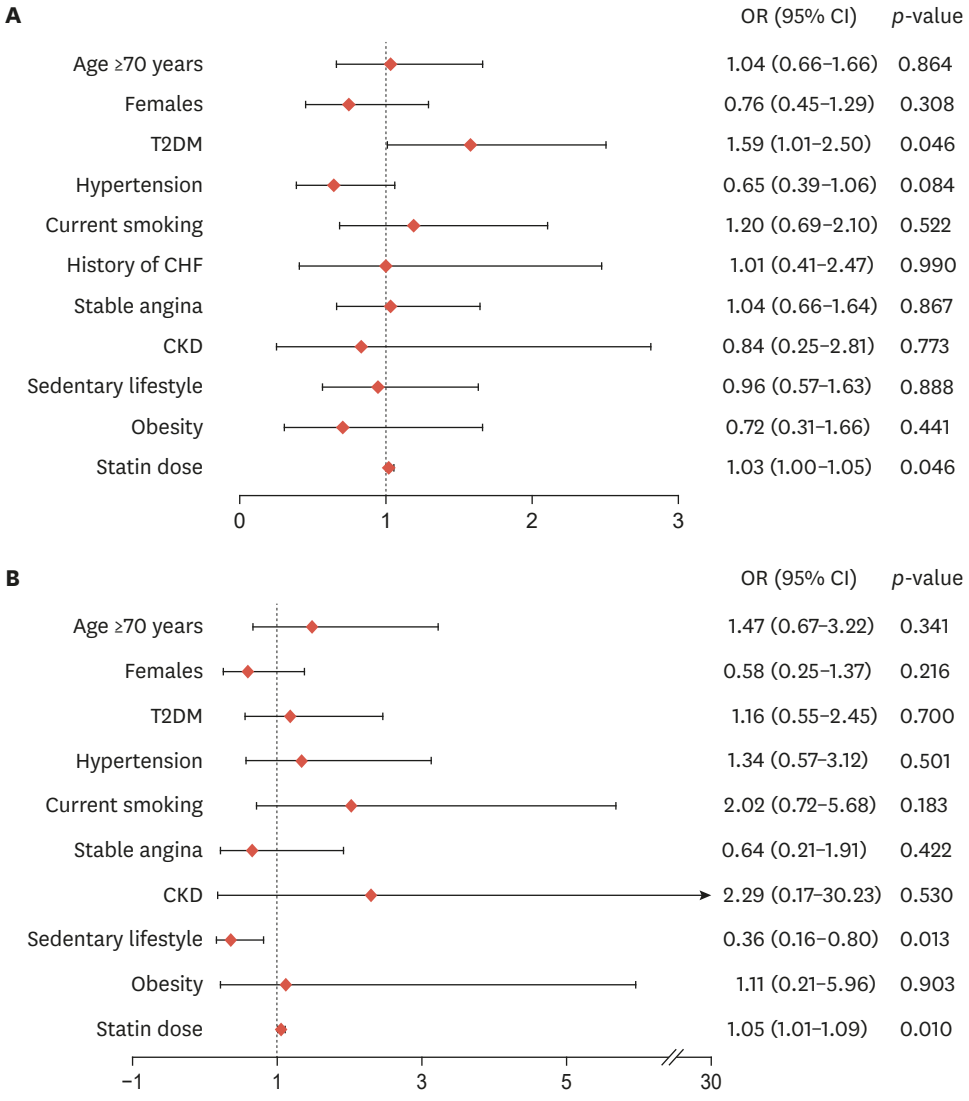

Fig. 1. Determinants of under low-density lipoprotein-cholesterol target of <70 mg/dL for patients treated with lipid-lowering therapy. (A) Determinants in stable coronary artery disease group, (B) Determinants in acute coronary syndrome group. ORs and 95% CIs calculated using logistic regression, with adjustment for all variables included in the figure.
CHF, congestive heart failure; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; OR, odds ration; CI, confidence interval.

Table 4. Use of LLT

Therapies	Stable CAD (n=500)	ACS	
		On admission (n=308)	4-month follow-up (n=307)
LLT	453 (90.6)	162 (52.6)	296 (98.3)
Statin monotherapy	368 (81.2)	137 (84.6)	251 (83.4)
Average statin dose (atorvastatin equivalent) (mg/day)*	17±10	17±12	21±14
Non-statin monotherapy	2 (0.4)	4 (2.5)	3 (1.0)
Statin+ezetimibe	59 (13.0)	11 (6.8)	27 (9.0)
Statin+other non-statin	24 (5.3)	10 (6.2)	15 (5.0)

Data are presented as number (%).
LLT, lipid-lowering therapy; CAD, coronary artery disease; ACS, acute coronary syndrome.
*Normalized according to atorvastatin potency.

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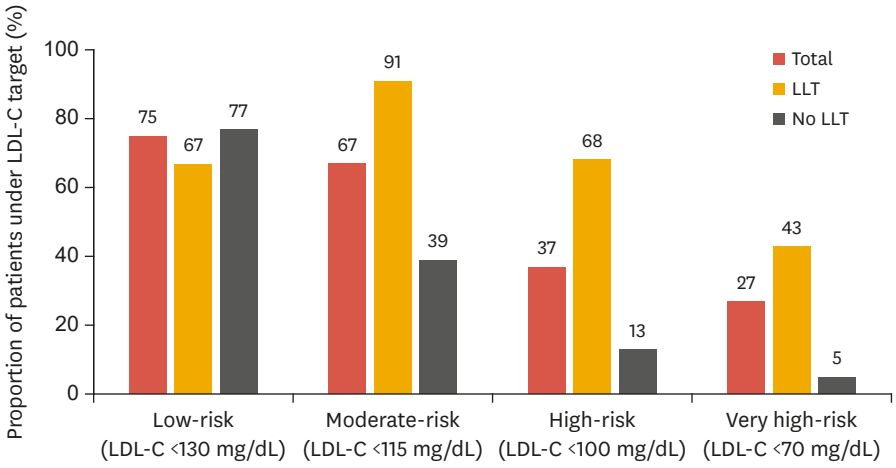

Fig. 2. Under-target rate of patients with ACS classified by pre-ACS risk status*.
LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein-cholesterol; ACS, acute coronary syndrome.
*Risk categories and corresponding LDL-C targets specified in the 2011 European Society of Cardiology/European Atherosclerosis Society guidelines.[10]

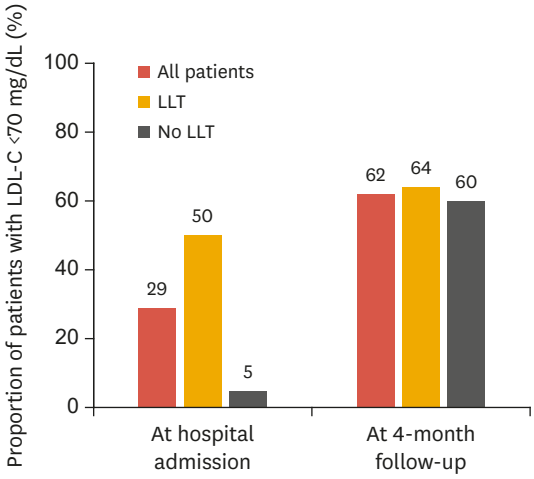

Fig. 3. Under-target rate of patients with acute coronary syndrome at hospital admission and 4-month follow-up*.
LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein-cholesterol.
*Includes only patients with lipid levels available from both baseline and 4-month follow-up.

DISCUSSION

In the present study, we found the mean LDL-C levels were 81 and 101 mg/dL in patients with stable CAD and those with ACS at enrollment. Only 40% and 24% of patients in each group had LDL-C levels under target of <70 mg/dL (for stable CAD and ACS, respectively). High statin dosage was identified as an independent determinant of under-target rate of LDL-C in both groups; however, the mean dosage at enrollment was not sufficiently high. Of the ACS patients who underwent the 4-month follow-up examination, 62% achieved the LDL-C target.

The Korean data from the Pan-Asian CEPHEUS study, one of several studies regarding achievement rates of LDL-C targets among patients with hypercholesterolemia who were receiving LLT, showed that 51.2% of patients had LDL-C levels below target according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.[5] In a

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separate study conducted in a primary care setting, only 28.6% of Korean patients with hypercholesterolemia at very high risk, 79.2% of those at high risk, and 87.4% of those at moderate risk achieved target LDL-C levels of <70 mg/dL, <100 mg/dL, and <130 mg/dL, respectively, despite the use of statin therapy.[15] Similarly, among the 2,093 diabetic patients who received LLT, only 34.2% of very high-risk and 68.6% of the high-risk patients attained target LDL-C level of <70 mg/dL and <100 mg/dL, respectively.[16] Even with increasing use of statins and improved management of LDL-C, the 2010 Korean National Health and Nutrition Examination Survey showed that only 47.7% of diabetic patients reached LDL-C target of <100 mg/dL.[17]

In the Return on Expenditure Achieved for Lipid Therapy in Asia study, less than 40% of patients with coronary heart disease and/or diabetes mellitus reached LDL-C <100 mg/dL, ranging from 56% in China to 16% in Taiwan.[18] Taiwan displayed improved LDL-C goal attainment in a recent study, with 54% of patients with cardiovascular disease reaching the LDL-C target of <100 mg/dL.[19] In the relatively large CEPHEUS Pan-Asian study, less than half of the patients (49.1%) reached their LDL-C goal, even though 85% were receiving statin treatment. Furthermore, the LDL-C goal of <70 mg/dL was attained by only 34.9% of the very high-risk patients.[20]

In L-TAP 2, a multinational study including LDL-C data from patients in American, European and Asian countries, LDL-C goal attainment was achieved in 73% of patients, with success rates varying from as low as 47% to as high as 84%.[3] It should be noted that LDL-C targets and risk categories varied between countries, and, unlike for DYSIS II, coronary heart disease was not an inclusion criterion. Substantial progress had been made since the original L-TAP study, which had a goal attainment rate of 38% for LDL-C.[21] L-TAP 2 showed a goal attainment rate of 30% in the very high-risk patient group.[3] These results are similar to those observed in the original DYSIS study from Europe and Canada, showing that overall 48.2% of patients did not achieve their LDL-C treatment goal.[4]

There were several known determinants of achievement of LDL-C targets. Use of potent LLT and patient compliance with therapy are important determinants, as well as baseline LDL-C, nationality, age, gender, smoking, concomitant diabetes, and systolic blood pressure.[5,16,19] A previous study including European and Canadian patients showed that potency of LLT was significantly correlated with goal attainment. It also showed that ischemic heart disease, diabetes, high blood pressure and obesity negatively impacted the treatment result.[4] Patients with more aggressive LLT showed better outcome, while more than half of the patients did not have any change in medication.[17]

Low rate of obtaining lipid profiles at 4 months follow-up in the ACS group is a limitation of our study. Obtaining lipid profile in more patients in this group might have provided clearer insight into the relationship between LDL-C reduction, LLT use, and cardiovascular events during the 4-month period. Furthermore, the short follow-up time resulted in occurrence of few events, making it difficult to draw definitive conclusions from the observed differences between groups.

In conclusion, only a minority of patients with stable CAD or ACS were under their target LDL-C levels at enrollment. Despite high statin dose being an independent determinant of under-target rate, statins were not used in sufficient dose in the majority of patients. Our current real-world survey suggests that there remains a considerable LLT gap in Korean patients with established CAD.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Use of statins in patients receiving lipid-lowering therapy

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