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Lipid Management in a Japanese Community: Attainment Rate of Target Set by the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012

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Aim: The Japan Atherosclerosis Society (JAS) guidelines for the prevention of atherosclerotic diseases 2012 (JAS2012) proposed lipid management targets; however, less data is available regarding the attainment rates of each target in community-based settings. Therefore, we assessed the attainment rates of lipid management targets among subjects who underwent Japanese specific health checkups.

Methods: A total of 85,716 subjects (male=29,282, 34.2%) aged 40–74 years who underwent specific health checkups from 2012 to 2014 in Kanazawa city, Japan, were included in this study. We evaluated the attainment rates of the lipid management targets according to the JAS2012 guideline and investigated the clinical characteristics of the subjects without achieving the targets.

Results: The target for LDL cholesterol (LDL-C) was the least attained in all risk categories, 89, 72, 50, and 34% for category I, II, III, and secondary prevention, respectively, in 2014. In addition, these rates inversely correlated with the grade of risk categories (p -value for trends <0.001). Attainment rate of the LDL-C target in the suspected chronic kidney disease (CKD) group was significantly lower than in the groups with diabetes, stroke, or absolute risk in category III (49.2, 60.3, 63.5, 54.4%, respectively, p -value <0.001 for each). Moreover, the attainment rate of the LDL-C target was significantly lower in subjects that did not receive lipid-lowering therapy than in those who received it in the secondary prevention (27.7 and 40.6%, respectively, p -value <0.001).

Conclusions: Lipid management is inadequate in community-based settings, particularly, in subjects with CKD and secondary prevention.

Key words: JAS guideline 2012, LDL cholesterol, Specific health checkup

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Introduction

The Japan Atherosclerosis Society (JAS) has proposed guidelines for the prevention of atherosclerotic

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diseases in 2012 (JAS 2012), including lipid management, dividing the subjects into four categories based on the absolute cardiovascular disease risk¹. JAS2012 has contributed to cardiovascular disease prevention in subjects with primary prevention as well as with secondary prevention. Several studies have shown that the attainment rates of lipid management targets were up to 50% in hospital-based settings^{2, 3}. However, not much data is available regarding attainment rates in community-based settings. Therefore, we aimed to assess the attainment rates of lipid management tar-

gets determined by JAS2012 among subjects who underwent specific health checkups initiated in community-based medical checkups in Japan.

Methods

Study Subjects

A total of 85,716 subjects (men = 29,282, 34.2%) aged 40–74 years who underwent specific health checkups from 2012 to 2014 in Kanazawa city, Japan, and who had no missing data were included in this study. Most of the subjects visited general practitioners in clinics in Kanazawa city. All data were collected and anonymized by the Kanazawa Medical Association.

Ethical Considerations

This study was approved by the Ethics Committee of Kanazawa Medical Association and Kanazawa University and carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all subjects for being included in the study.

Data collection in Specific Medical Checkup

Eligible participants visited a clinic and responded to a questionnaire regarding past history of stroke, cardiac disease, kidney disease, lifestyle habits, such as smoking, alcohol intake, walking, and medications for hypertension, diabetes, and dyslipidemia. Measurements included standard medical checks, such as measurement of height, weight, waist circumference, blood pressure, fasting blood glucose, hemoglobin A1c, total cholesterol, triglyceride, serum high-density lipoprotein (HDL) cholesterol (HDL-C), low-density lipoprotein (LDL) cholesterol (LDL-C), serum creatinine, dipstick urine test for proteinuria, hematuria, and urinary sugar. Proteinuria was coded as negative, plus and minus, 1 plus, 2 plus, and 3 plus. Serum creatinine levels were measured using the enzymatic method. Glomerular filtration rate was calculated using the formula of the Japanese Society of Nephrology⁴⁾. Hypertension was defined as a blood pressure of $\geq 140/90$ mmHg or if the subject was receiving hypotensive medication. Diabetes was defined as the patient having 1) hemoglobin A1c $\geq 6.5\%$ and blood glucose ≥ 126 at fasting, 2) hemoglobin A1c $\geq 6.5\%$ and blood glucose ≥ 200 at non-fasting, or 3) hypoglycemic medication. The presence of suspected chronic kidney disease (CKD) was defined according

to the CKD classification based on the combination of estimated glomerular filtration rate (eGFR) and dipstick proteinuria findings⁵⁾. We could not definitively determine the presence of CKD based on our cross-sectional design, although the definition of CKD includes a situation where kidney injury continues for over 3 months. Accordingly, we investigated the proportion of subjects fulfilling this CKD criteria at least twice for the subjects suspected as having CKD in 2012. Of these, only the subjects whose follow-up data were available either in 2013 or in 2014 were included to validate our inclusion criteria as CKD.

Risk Assessments and Categorization According to JAS Guideline 2012

Next, we classified subjects into four categories according to the JAS2012. The methodology of the risk classification procedure according to the JAS2012 has been described previously¹⁾. Briefly, subjects were assessed if they were secondary prevention cases with any histories of coronary artery disease (CAD). If not, then they were assigned to risk category III when the following criteria were fulfilled: (1) diabetes, (2) suspected CKD, and (3) non-cardiogenic cerebral infarction. After these assignments, remaining subjects were assigned to risk categories I, II, and III based on the absolute risk of CAD death estimated by NIPPON-DATA 80⁶⁾ and on the existence of an additional risk factor (hypo-HDL cholesterolemia).

Evaluations

We evaluated the attainment rates of the lipid management targets according to the JAS2012 guidelines for each risk category and compared these rates among each category. We employed LDL-C values calculated using the Friedewald formula if the measurements were of fasting and TG < 400 mg/dl. Otherwise, we used LDL-C values directly measured. In addition, we investigated the trends of those attainment rates from 2012 to 2014. Furthermore, we investigated the characteristics of the subjects who did not attain the LDL-C target.

Statistical Analysis

Jonckheere-Terpstra trend test was used to assess the trends of the attainment rates among each category. The chi-squared test was used to compare the attainment rates over time. *P*-value < 0.05 was considered statistically significant, and all tests were two-tailed. All analyses were performed with R statistical software.

Table 1. Characteristics of the study subjects (2012)

	All (N=27,370)	Category I (N=3,761)	Category II (N=12,144)	Category III (N=9,384)	Secondary prevention (N=2,081)
Age (yr)	64.3 ± 8.3	50.1 ± 6.2	67.2 ± 4.5	65.5 ± 7.4	68.0 ± 5.3
Male (%)	9312 (34.0)	640 (17.0)	3,419 (28.2)	4,191 (44.6)	1,062 (51.0)
Body mass index (kg/m ²)	22.8 ± 3.3	22.0 ± 3.4	22.5 ± 3.0	23.3 ± 3.5	23.5 ± 3.4
Waist circumference (cm)	82.5 ± 9.4	79.1 ± 9.5	81.9 ± 8.9	84.0 ± 9.7	85.2 ± 9.3
Total cholesterol (mg/dl)	202.2 ± 33.3	203.9 ± 33.7	205.7 ± 31.4	199.5 ± 34.6	191.4 ± 33.1
Triglyceride (mg/dl)	122.4 ± 82.4	107.6 ± 86.1	116.3 ± 67.2	134.3 ± 95.4	131.1 ± 85.7
HDL cholesterol (mg/dl)	60.2 ± 15.1	66.1 ± 14.8	61.9 ± 14.0	56.5 ± 15.5	56.3 ± 13.4
LDL cholesterol (mg/dl)	119.0 ± 29.8	118.5 ± 31.0	121.2 ± 28.7	118.1 ± 30.8	111.2 ± 28.6
Smoking (%)	3,366 (12.3)	544 (14.5)	1,189 (9.8)	1,380 (14.7)	253 (12.2)
Suspected CKD (%)	6,927 (25.3)	0 (0)	0 (0)	6,150 (65.5)	777 (37.3)
Stroke (%)	1,263 (4.6)	0 (0)	0 (0)	1,015 (10.8)	248 (11.9)
Coronary artery disease (%)	2,081 (7.6)	0 (0)	0 (0)	0 (0)	2,081 (100)
Hypertension (%)	9,272 (33.9)	395 (10.5)	3,860 (31.8)	3,912 (41.7)	1,105 (53.1)
Diabetes (%)	2,512 (9.2)	0 (0)	0 (0)	2,189 (23.3)	323 (15.5)
Lipid-lowering therapy (%)	6,504 (23.8)	348 (9.3)	3,086 (25.4)	2,394 (25.5)	676 (32.5)
Hypertriglyceridemia (%)	6,410 (23.4)	615 (16.4)	2,476 (20.4)	2,745 (26.4)	574 (27.6)
Low HDL cholesterolemia (%)	1,726 (6.3)	0 (0)	133 (0.1)	1,373 (14.6)	220 (10.6)
Hypertriglyceridemia and low HDL cholesterolemia (%)	1,082 (4.0)	0 (0)	95 (0.1)	860 (9.2)	127 (6.1)

CKD: Chronic kidney disease, Hypertriglyceridemia was defined as triglyceride ≥ 150 mg/dl. Low HDL cholesterolemia was defined as HDL cholesterol < 40 mg/dl

Results

Characteristics of Study Subjects

Clinical characteristics of study subjects are shown in **Tables 1-3**. As expected, category I comprises younger subjects than present in any other categories (p -value < 0.001). In addition, we observed significant trends in category I, II, III, and secondary prevention for other basic characteristics, such as, sex (the proportion of male=17.6, 28.1, 46.1, and 52.4%, respectively, in 2014, p -value for trend < 0.001), body mass index (mean=21.9, 22.4, 23.4, and 23.4 kg/m², respectively, in 2014, p -value for trend < 0.001), and waist circumference (mean=78.9, 81.9, 84.5, and 84.9 cm, respectively, in 2014, p -value for trend < 0.001). As much as a quarter of the subjects were classified as having suspected CKD.

Attainment Rates for Lipid Management Targets

Attainment rates for lipid management targets are illustrated in **Fig. 1-3**. In 2012, when the current guideline was introduced, the attainment rate of all four lipid management targets (LDL-C, TG, HDL-C, and non-HDL-C) for all the study subjects was 51.5%. When divided into four categories based on JAS2012, an inverse correlation was observed in the attainment rates of all four lipid management targets

according to the category (76.3, 60.7, 35.8, and 24.2%, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001). Among the four different targets, LDL-C management target was the least attained (67.3%). Similar to the overall trend, an inverse correlation was observed in the attainment rate of LDL-C management target according to the category (90.4, 75.7, 54.3, and 35.2%, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001). In 2013, the overall attainment rate of all the four lipid management targets was 52.0%. An inverse correlation was observed in the attainment rates of all the four lipid management targets according to the category (78.3, 60.0, 33.6, and 25.0%, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001) in 2012. Further, an inverse correlation was observed in the attainment rates of LDL-C management target according to the category (89.6, 74.3, 51.6, and 36.1, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001). In 2014, we observed the same overall trends (75.9, 57.3, 33.5, and 23.2%, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001), as well as in LDL-C (89.1, 71.5, 50.0, and 34.3%, in category I, II, III, and secondary prevention, respectively, p -value for trend < 0.001). We could not

Table 2. Characteristics of the study subjects (2013)

	All (N=29,002)	Category I (N=4,177)	Category II (N=13,819)	Category III (N=8,878)	Secondary prevention (N=2,128)
Age (yr)	64.3 ± 8.5	50.0 ± 6.2	67.3 ± 4.5	65.4 ± 7.9	68.2 ± 5.3
Male (%)	9,838 (33.9)	740 (17.7)	4,222 (30.6)	3,770 (42.5)	1,106 (52.0)
Body mass index (kg/m ²)	22.7 ± 3.4	21.9 ± 3.6	22.5 ± 3.2	23.2 ± 3.5	23.5 ± 3.5
Waist circumference (cm)	82.5 ± 9.6	79.0 ± 9.7	82.2 ± 9.1	83.9 ± 9.7	85.3 ± 9.6
Total cholesterol (mg/dl)	201.1 ± 33.5	201.9 ± 33.0	203.0 ± 32.1	200.1 ± 35.2	189.1 ± 33.0
Triglyceride (mg/dl)	118.5 ± 78.8	99.5 ± 66.0	114.1 ± 67.4	131.8 ± 95.5	128.4 ± 81.4
HDL cholesterol (mg/dl)	61.1 ± 15.5	66.6 ± 14.0	62.3 ± 14.3	57.5 ± 16.4	56.8 ± 15.4
LDL cholesterol (mg/dl)	120.3 ± 30.3	119.8 ± 31.1	121.8 ± 29.5	120.5 ± 30.9	111.1 ± 29.5
Smoking (%)	3,605 (12.4)	602 (14.4)	1,431 (10.4)	1,299 (14.6)	273 (12.8)
Suspected CKD (%)	7,715 (26.6)	0 (0)	0 (0)	6,903 (77.8)	812 (38.2)
Stroke (%)	1,349 (4.7)	0 (0)	0 (0)	1,079 (12.2)	267 (12.5)
Coronary artery disease (%)	2,128 (7.3)	0 (0)	0 (0)	0 (0)	2,128 (100)
Hypertension (%)	9,775 (33.7)	416 (10.0)	4,583 (33.2)	3,600 (40.5)	1,176 (55.3)
Diabetes (%)	2,664 (9.2)	0 (0)	0 (0)	1,024 (11.5)	331 (15.6)
Lipid-lowering therapy (%)	6,848 (23.6)	380 (9.1)	3,655 (26.4)	2,157 (24.3)	656 (30.8)
Hypertriglyceridemia (%)	6,375 (22.5)	584 (14.0)	2,721 (19.7)	2,513 (28.3)	557 (26.2)
Low HDL cholesterolemia (%)	1,709 (5.9)	0 (0)	159 (1.2)	1,318 (14.8)	232 (11.0)
Hypertriglyceridemia and low HDL cholesterolemia (%)	1,041 (3.6)	0 (0)	107 (0.8)	792 (8.9)	142 (6.7)

CKD: Chronic kidney disease, Hypertriglyceridemia was defined as triglyceride ≥ 150 mg/dl. Low HDL cholesterolemia was defined as HDL cholesterol < 40 mg/dl

Table 3. Characteristics of the study subjects (2014)

	All (N=29,344)	Category I (N=4,213)	Category II (N=12,911)	Category III (N=10,038)	Secondary prevention (N=2,182)
Age (yr)	64.5 ± 8.5	49.9 ± 6.1	67.6 ± 4.5	66.0 ± 7.5	68.3 ± 5.6
Male (%)	10,132 (34.5)	742 (17.6)	3,627 (28.1)	4,619 (46.1)	1,144 (52.4)
Body mass index (kg/m ²)	22.7 ± 3.4	21.9 ± 3.5	22.4 ± 3.1	23.4 ± 3.6	23.4 ± 3.5
Waist circumference (cm)	82.6 ± 9.6	78.9 ± 9.6	81.9 ± 9.0	84.5 ± 9.9	84.9 ± 9.8
Total cholesterol (mg/dl)	201.5 ± 34.1	202.3 ± 33.9	204.1 ± 33.0	200.8 ± 35.0	190.3 ± 33.0
Triglyceride (mg/dl)	120.0 ± 80.7	103.3 ± 69.3	115.3 ± 68.9	131.3 ± 92.5	128.1 ± 99.6
HDL cholesterol (mg/dl)	62.2 ± 15.7	67.6 ± 15.3	63.8 ± 14.7	58.7 ± 16.0	58.1 ± 16.0
LDL cholesterol (mg/dl)	122.0 ± 30.8	120.5 ± 31.3	124.3 ± 29.6	121.6 ± 31.9	113.1 ± 29.9
Smoking (%)	3,616 (12.3)	618 (14.7)	1,279 (9.9)	1,460 (14.5)	259 (11.9)
Suspected CKD (%)	7,486 (25.5)	0 (0)	0 (0)	6,681 (66.6)	805 (36.9)
Stroke (%)	1,396 (4.8)	0 (0)	0 (0)	1,104 (11.0)	292 (13.4)
Coronary artery disease (%)	2,182 (7.4)	0 (0)	0 (0)	0 (0)	2,182 (100)
Hypertension (%)	10,047 (34.2)	438 (10.4)	4,221 (32.7)	4,198 (41.8)	1,190 (54.5)
Diabetes (%)	2,812 (9.6)	0 (0)	0 (0)	2,443 (24.3)	369 (16.9)
Lipid-lowering therapy (%)	7,163 (24.4)	358 (8.5)	3,431 (26.6)	2,680 (26.7)	694 (31.8)
Hypertriglyceridemia (%)	6,662 (22.7)	672 (15.9)	2,575 (19.9)	2,828 (28.2)	587 (26.9)
Low HDL cholesterolemia (%)	1,462 (5.0)	0 (0)	115 (0.9)	1,129 (11.2)	218 (10.0)
Hypertriglyceridemia and low HDL cholesterolemia (%)	930 (3.2)	0 (0)	83 (0.6)	724 (7.2)	123 (9.6)

CKD: Chronic kidney disease, Hypertriglyceridemia was defined as triglyceride ≥ 150 mg/dl. Low HDL cholesterolemia was defined as HDL cholesterol < 40 mg/dl

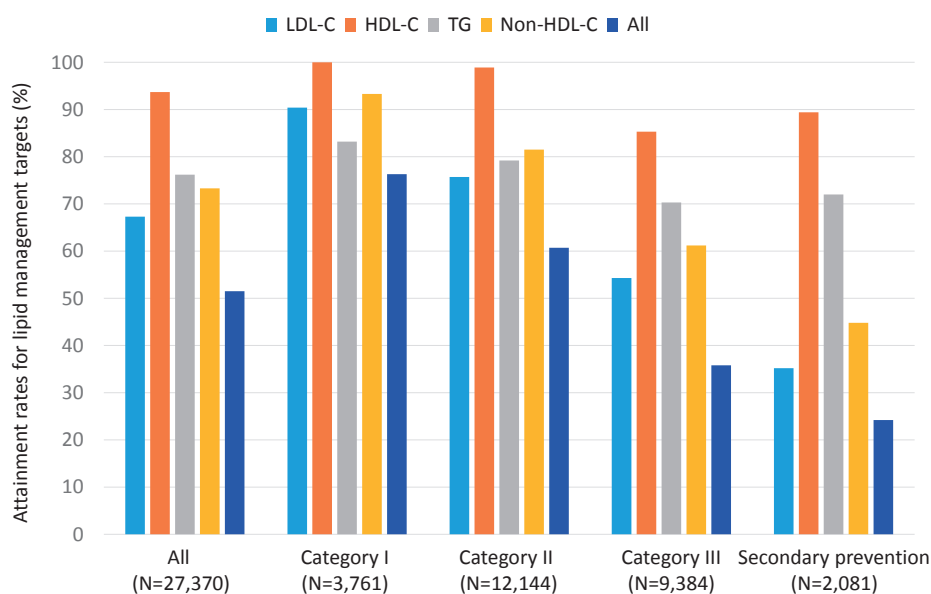


Fig. 1. Attainment rates for lipid management targets (2012)

Light blue: LDL-C, Orange: HDL-C, Gray: TG, Yellow: Non-HDL-C, Blue: All

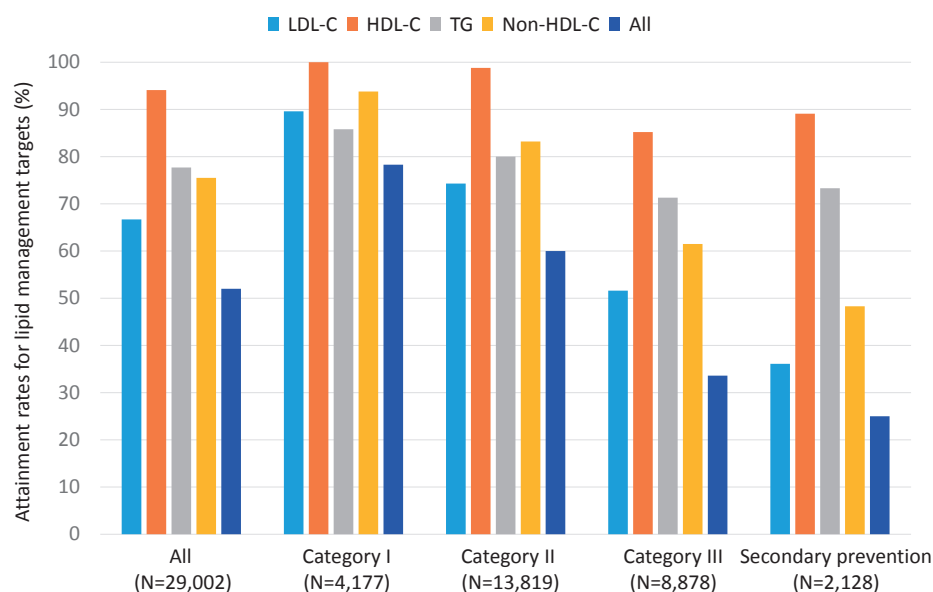


Fig. 2. Attainment rates for lipid management targets (2013)

Light blue: LDL-C, Orange: HDL-C, Gray: TG, Yellow: Non-HDL-C, Blue: All

observe any significant increases in attainment rates in all of lipid management targets (LDL-C, triglyceride, and HDL-C), from 2012 to 2014.

Characteristics of the Subjects that did not Achieve the Targets in Category III and Secondary Prevention Cases

Next, we investigated the characteristics of the

subjects who did not attain the management targets, particularly, LDL-C targets using data in 2014 that were the latest and the largest. In category III, the highest risk category in the primary prevention, as many as 5,018 subjects (50.0%) did not attain the LDL-C management target. Among them, as many as 3,392 (67.6%) subjects exhibited CKD (Table 4). The attainment rate of the LDL-C target in the sus-

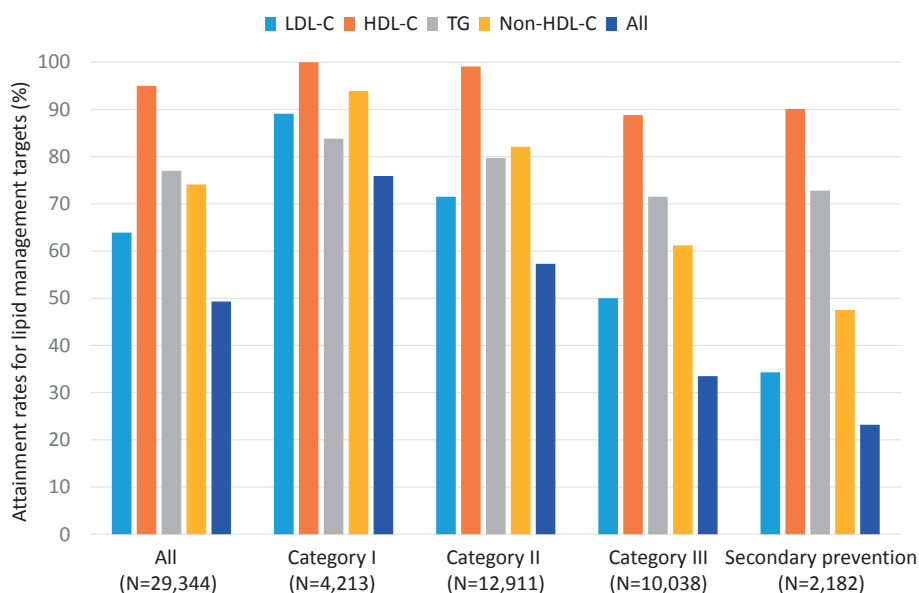


Fig. 3. Attainment rates for lipid management targets (2014)
 Light blue: LDL-C, Orange: HDL-C, Gray: TG, Yellow: Non-HDL-C, Blue: All

Table 4. Comparison of attainment rates of the LDL-C target among risks in category III

	All (N)	Attained LDL-C target (N, %)	Did not attain LDL-C target (N, %)	p-value
Suspected CKD	6,681	3,289 (49.2)	3,392 (50.8)	reference
Diabetes	2,443	1,472 (60.3)	972 (39.7)	<0.001
Stroke	1,104	701 (63.5)	403 (36.5)	<0.001
Absolute risk	3,204	1,744 (54.4)	1,460 (45.6)	<0.001

CKD: Chronic kidney disease, LDL-C: LDL cholesterol

Table 5. Comparison of attainment rates of the LDL-C target according to lipid-lowering therapy in secondary prevention cases

	All (N=2,182)	Attained LDL-C target (N, %)	Did not attain LDL-C target (N, %)	p-value
On lipid-lowering therapy	694	282 (40.6)	467 (59.4)	reference
No lipid-lowering therapy	1,488	412 (27.7)	1,021 (68.6)	<0.001

LDL-C: LDL cholesterol

pected CKD group was significantly lower than in the group with diabetes, stroke, or absolute risk in category III (49.2% vs. 60.3, 63.5, and 54.4%, respectively, p -value <0.001 for each comparison, **Table 4**). Moreover, the attainment rate of the LDL-C target was significantly lower in subjects who did not receive lipid-lowering therapy than in those who did as the secondary prevention (27.7 and 40.6%, respectively, p -value <0.001, **Table 5**).

Validation of Suspected CKD as a Substitute for CKD

Among the 6,927 subjects suspected of having CKD in 2012, 4,577 (66.1%) subjects were followed-up either in 2013 or in 2014. We found that 4,236 (92.5%) fulfilled the criteria of CKD diagnosis.

Discussion

Using a large dataset from the community-based

specific medical check-ups, we found that 1) the attainment rates of all the four lipid management targets were approximately 50%, 2) the targets of LDL-C were overall the least attained (65%), 3) there were significant inverse trends in the attainment rate of LDL-C management target according to the category, 4) the attainment rate of the LDL-C target in the group with CKD was significantly lower than in the group with diabetes, stroke, or absolute risk in category III, 5) the attainment rate of the LDL-C target was significantly lower in subjects who did not receive lipid-lowering therapy than in those who did as the secondary prevention, and 6) such trends did not change from 2012 to 2014.

In 1992, JAS proposed the initial guideline for the diagnosis and treatment of hyperlipidemia in adults, which is revised every 5 years. These revisions have adopted a number of updated clinical interventional trials and observational cohort studies⁷⁻⁹). On the other hand, only little data investigating the attainment rates of target established by such guidelines are available, most of which are from hospital-based settings^{2,3}). However, a larger proportion of Japanese population is treated by general practitioners in the community; thus, it is vital to expand such studies to community-based settings. Since 2008, community-based medical checkups named “specific health checkups” have been started in Japan considering our aging society and increases in lifestyle-related diseases. Specific health checkups have great advantages such as financial support provided from the government to a large number of participants and the uniformity of the investigated items^{10,11}). In this study, we used the dataset collected in Kanazawa city, Japan, which has a population of approximately 500,000.

The proportions of the subjects who attained the LDL-C targets seem to be lower than those previously investigated in hospital-based settings. It is reasonable to see such differences, since the subjects who are treated in hospitals should have much more complications than those treated in clinics in communities, leading to their more intensive therapies.

It is of note that the subjects with suspected CKD, classified into category III, were quite undertreated, although known to be highly associated with CAD¹²), and that the majority of secondary prevention cases without achieving LDL-C target did not receive any lipid-lowering therapies. Furthermore, such trends unchanged during the study period despite of the intensive effort of enlightenment of this guideline by JAS, at least in community-based settings. It seems that general practitioners in the community tended to treat patients aiming for the normal range (LDL-C=120 to 140 mg/dl), rather than to

attain the targets determined by the guideline. The concept of “the lower, the better” in LDL-C level has been widely accepted, and such a situation will be achievable using new drugs, such as proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitor¹³). However, awareness itself to attain the current target should be the first step in the prevention of CAD.

This study has several limitations. First, this study investigated the population living in Kanazawa area, not using nation-wide dataset, which could potentially affect the results. However, we believe that large sample size could dilute such bias. Second, information of peripheral artery disease, family history of premature CAD, and impaired glucose tolerance are lacking in our data, which could potentially underestimate the risk category. However, such underestimations of risk category do not likely to reduce the proportions of undertreated subjects in category III nor in secondary prevention cases. Third, the definition of diabetes includes only “definite” diabetes, leaving the possibility of missing subjects who require oral glucose tolerance and other diagnostic tests. In addition, we could not determine definite CKD because of the cross-sectional nature of the study design. However, we found that most subjects suspected as having CKD eventually fulfilled the criteria of CKD, and thus, the essential conclusions of this study would not change. Fourth, a fair proportion of subjects exhibited hyper LDL-cholesterolemia ≥ 180 mg/dl (~4% of the subjects), among whom there should be some patients with familial hypercholesterolemia (FH) whose lipid management targets are set more strictly. In this regard, we need to consider special notification of possibility for FH in the reports, since the prevalence of FH in general population has been shown to be more frequent than previously considered¹⁴). Fourth, large proportions of individuals were receiving checkups regularly (17,734 among 29,002 [61%] individuals were overlapped between 2012 and 2013, and 18,298 among 29,334 [62%] individuals were overlapped between 2013 and 2014), which could lead some potential bias. However, this fact rather makes us confident that the attainment rates of lipid management target unchanged during these periods. Finally, detailed information regarding lipid-lowering therapies is lacking in this study. However, we want to emphasize the fact that high-risk patients in category III or in secondary prevention group are not treated adequately, instead of the way of treatment.

In conclusion, lipid management is inadequate in the community-based settings, especially in the subjects with CKD and secondary prevention cases.

Conflict of Interest Statement

None.

Source of Finding

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