The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2019; 26: 805-820. http://doi.org/10.5551/jat.47597

Association between Prescription and Control Status of Dyslipidemia and Hypertension among Japanese Patients with Diabetes

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Aims: The proper management of atherosclerotic risk factors (ARFs) and attainment of target levels (TLs) for ARFs are crucial in preventing atherosclerotic cardiovascular disease (ASCVD). In this study, utilizing data from the "Specific Health Check and Guidance in Japan," which was conducted from 2008 to 2011, we examined TL attainment status of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) and prescription status of dyslipidemia and hypertension in patients with diabetes undergoing medical treatment, and analyzed the factors that affected prescription status.

Methods: Subjects receiving medical treatment for diabetes were selected from the database. Subjects were classified by prescription status for dyslipidemia and hypertension, and TL attainment status was assessed for each ARF.

Results: The percentage of subjects who did not attain TLs and were not under medication was higher for LDL-C than for BP. The un-prescribed rates among non-TL-attained subjects were 60%–75% for LDL-C, and around 30%–40% for BP. The un-prescribed rates to those who were qualified for prescription therapy were also higher for LDL-C than for BP. Logistic regression analyses revealed that the subjects who were prescribed for dyslipidemia had the following characteristics compared with the un-prescribed non-TL-attained subjects: older age, higher body mass index, lower estimated glomerular filtration rate, previous heart or cerebrovascular disease, and higher medication rate for other ARFs.

Conclusions: The present study revealed that, in Japan, the adequate prescription rate for dyslipidemia was lower than that for hypertension in patients with diabetes, suggesting the proper prescription therapy for dyslipidemia should be pursued to further prevent ASCVD.

Key words: Atherosclerotic risk factors, Prescription status, Cardiovascular high-risk patient, Japanese

Abbreviations: ARF: atherosclerotic cardiovascular risk factor, TL: target level, LDL-C: LDL-cholesterol, BP: blood pressure, DM: diabetes mellitus, HbA1c: glycated hemoglobin, BMI: body mass index, eGFR: estimated glomerular filtration rate, ASCVD: atherosclerotic cardiovascular disease, SHCG: Specific Health Check and Guidance in Japan, SBP: systolic blood pressure, pCVD: a past history of cerebrovascular disease, pHD: a past history of heart disease

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of mortality, both around the world and in Japan. Numerous epidemiological and interventional studies have clarified several risk factors and

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Received: October 15, 2018 Accepted for publication: December 26, 2018

high-risk conditions for ASCVDs[1], and medical societies have issued guidelines for the control of these atherosclerotic cardiovascular risk factors, with the goal of reducing the incidence of ASCVD. In these guidelines, the target level (TL) for each atherosclerotic cardiovascular risk factor has been set depending on the individual's clinical status and condition, because the absolute risk for ASCVD is different in each subject.

There are several clinical conditions that place an individual as very high or high-risk for ASCVD, and diabetes mellitus (DM) is classified as one of the high-risk conditions worldwide[2, 3], together with histories of ASCVD and chronic kidney disease (CKD). For individuals with these high-risk conditions, intensive and strict management of atherosclerotic cardiovascular risk factors has been strongly recommended in guidelines issued by Japanese medical societies[1, 4-7].

Despite the well-documented recommendations proposed by these guidelines, ASCVD reduction will be less effective if the TL for atherosclerotic cardiovascular risk factors is not attained. For example, poor statin adherence can lead to insufficiently controlled dyslipidemia, which is associated with an increased incidence of ASCVD[8]. Prior to this study, we used a database called the "Specific Health Check and Guidance in Japan (SHCG)"[9-11] to investigate how well major atherosclerotic cardiovascular risk factors, such as dyslipidemia, blood pressure (BP), and glycated hemoglobin (HbA1c), are controlled in Japanese subjects with high ASCVD conditions from 2008 to 2011[12]. Our findings showed that the rates of TL attainment for BP and low-density lipoprotein cholesterol (LDL-C) were lower than those for high-density lipoprotein cholesterol, triglycerides, and HbA1c, although those for both BP and LDL-C improved significantly during the study period.

Appropriate medical treatment must be combined with adequate lifestyle intervention in order to attain the TL, and this is particularly crucial in patients at high-risk for ASCVD. However, data on the relationship between prescription status and TL attainment status for major atherosclerotic cardiovascular risk factors in Japan are scarce. In this study, utilizing SHCG data from 2008 to 2011, we analyzed the relationship between prescription status for dyslipidemia and TL attainment status of LDL-C, and the relationship between prescription status for hypertension and TL attainment status of BP in patients with diabetes undergoing medical treatment, and then compared these findings between dyslipidemia and hypertension. We further analyzed patients' backgrounds to determine the factors that contributed to the status of insufficient prescription. In addition, we analyzed the relationship between control and prescription status of diabetes in subjects with a history of cardiovascular disease, in order to reference in comparison to the relationships observed for dyslipidemia or hypertension in subjects with diabetes undergoing medical therapy.

Methods

Study Population and Design

The population of this study is the same as that of our previous report[12]. Briefly, we utilized SHCG data from 2008 to 2011, collected from 16 prefectures whose data for that time period were already finalized and available by the end of 2014. Individual data were verified independently by the NPO Japan Clinical Support Unit (Tokyo, Japan). All participants remained anonymous, and the study was conducted according to Japanese privacy protection laws and ethical guidelines for epidemiological studies published by the Ministry of Education, Science, and Culture and the Ministry of Health, Labor, and Welfare.

The SHCG has been described previously[9-11]. In this system, each participant answers a self-administered questionnaire that covers medical history, including prescription status and current lifestyle. The data on height, weight, body mass index (BMI), etc. are collected by trained medical staff, and blood and urine samples are collected and analyzed for clinical characteristics.

Following the exclusion of subjects for whom sex data were unavailable or some answers to questionnaire entries were missing, we selected those for whom medication for DM was prescribed. The numbers of subjects in each year for each sex, along with mean age, are shown in **Table 1**. The rates of available data for the two analyzable atherosclerotic cardiovascular risk factors (BP and LDL-C) are also indicated in **Table 1**. We then analyzed the number and percentage of subjects who attained or did not attain the TL for the atherosclerotic cardiovascular risk factor, with or without medication each year. The TL for BP was set to less than 130/80 mmHg, and that for LDL-C was set to less than 120 mg/dL, as recommended by Japanese medical societies for patients with diabetes. The study subjects were classified into four categories (A, B, C, and D) as shown in **Table 2**, depending on whether they had attained the TL for the atherosclerotic cardiovascular risk factor and whether they had received a prescription for treatment of the atherosclerotic cardiovascular risk factor. Numbers and rates in each category were also calculated. The subjects for whom these atherosclerotic cardiovascular risk factor values were missing were excluded from the analyses.

Table 1. Numbers and mean age of the diabetic subjects under medication for each year, and numbers and percentages of available blood pressure and LDL-C data

Year		2008		2009		2010		2011	
		Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects in our SHCG database		113,618	155,827	126,400	168,357	126,326	165,157	126,372	163,340
No. of diabetic patients under medication (mean age)		8,035 (65.7)	6,269 (66.0)	9,325 (65.8)	7,160 (66.3)	9,810 (65.7)	7,180 (66.3)	10,563 (65.7)	7,483 (66.2)
No. (%) of available data on risk factor	BP	8,028 (99.9)	6,262 (99.9)	9,320 (99.9)	7,156 (99.9)	9,805 (99.9)	7,174 (99.9)	10,560 (100.0)	7,480 (100.0)
	LDL-C	8,032 (100.0)	6,264 (99.9)	9,324 (100.0)	7,159 (100.0)	9,806 (100.0)	7,180 (100.0)	10,561 (100.0)	7,479 (99.9)

Table 2. Categorization of the subjects depending on target level (TL) attainment status and prescription status

	TL attained	TL not-attained
Prescribed	B	C
Un-prescribed	A	D

Table 3. Numbers and mean age of those who had a past history of heart disease or cerebrovascular disease, and numbers and percentages of available HbA1c data for each year

A. Those who had a past history of heart disease								
Year	2008		2009		2010		2011	
	Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects (mean age)	6785 (66.7)	6138 (66.4)	7597 (66.9)	6331 (67.0)	7567 (66.8)	6000 (67.0)	7709 (66.9)	5931 (66.9)
No. (%) of available HbA1c data	6678 (98.4)	6035 (98.3)	7469 (98.3)	6169 (97.4)	7434 (98.2)	5864 (97.7)	7580 (98.3)	5801 (97.8)
B. Those who had a past history of cerebrovascular disease								
Year	2008		2009		2010		2011	
	Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects (mean age)	5366 (66.5)	4750 (66.4)	4864 (66.5)	3560 (66.2)	5091 (66.4)	3595 (66.3)	4931 (66.7)	3412 (66.9)
No. (%) of available HbA1c data	5048 (94.1)	4327 (91.1)	4814 (99.0)	3511 (98.6)	5039 (99.0)	3551 (98.8)	4879 (98.9)	3377 (99.0)

As the above analyses targeted subjects with diabetes receiving medication, the analysis to elucidate the association of glycemic control and prescription status for diabetes was unfeasible in these subjects; thus, in order to reference the association between prescription status for diabetes and control status of HbA1c, those who had a history of heart or cerebrovascular disease were selected from the same SHCG database. The numbers of these subjects in each year for each sex, along with their mean age, and the rates of available HbA1c data are shown in **Table 3**. The TL of HbA1c was set to less than 7.0%; the study subjects were classified into four categories, as shown in **Table 2**, depending on whether they had attained

Table 4. Ordinal values utilized for the logistic regression analyses

Variables	Ordinal Value	
	1	2
Dependent variables	Category D*	Categories B and C*
Smoking	Non Smoker	Smoker
pCVD	Without pCVD	With pCVD
pHD	Without pHD	With pHD
Medication	Un-prescribed	Prescribed

pCVD: a past history of cerebrovascular disease; pHD: a past history of heart disease.
*: Regarding categorization, please see Table 2.

the TL of HbA1c and whether they had received a prescription for DM, and the numbers and rates in each category were calculated. The subjects for whom the HbA1c value was missing were excluded from the analyses.

Statistical Analysis

We analyzed data separately by sex. After determining the category of each subject with regard to prescription status and TL attainment status, we used the Cochran–Armitage test to analyze the over-time trends in prevalence of un-prescribed subjects among those who qualified for prescription therapy, for each atherosclerotic cardiovascular risk factor. We also analyzed the over-time trends in prevalence of un-prescribed subjects among those who did not attain the TL with the Cochran–Armitage test. For subjects with diabetes receiving medication, we then applied the chi-squared test to compare this prevalence across LDL-C and BP, and performed independent *t*-tests to compare LDL-C or systolic BP (SBP) values between those who were prescribed and those who were un-prescribed. For subjects with diabetes receiving medication, we further applied logistic regression analysis to elucidate patient characteristics that contributed to under-prescribed status for dyslipidemia and hypertension. Continuous values were utilized for the calendar year of the data collected (year: 2008, 2009, 2010, and 2011), age (in years), BMI (in kg/m^2), and estimated glomerular filtration rate (eGFR) (in $mL/min/1.73\ m^2$); for dependent and independent variables, ordinal values were set as shown in **Table 4**.

The Cochran–Armitage test and chi-squared test were performed using Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Independent *t*-test and logistic regression analyses were done with the SPSS for Windows(version 22.0; SPSS, Chicago, IL, USA).

P-values less than 0.05 were deemed as statistically significant. The odd ratios indicate the probability for an increase in un-prescription when the independent variables increase by one or one unit.

Results

Analyses in Subjects with Diabetes Receiving Antidiabetic Medication

Fig. 1 and **Table 5** represent the percentage of each category (A, B, C, and D defined in **Table 2**) of subjects with diabetes receiving antidiabetic medication for LDL-C and BP in each year for each sex. **Table 5** also indicates the percentage of un-prescribed subjects among those for whom the TL was not attained (percentage of category D among categories C and D) and the percentage of un-prescribed subjects among those qualified for prescription therapy (percentage of category D among categories B, C, and D). The percentage of TL non-attainers who did not receive medication (category D) was higher for LDL-C than for BP in all 4 years in both genders; the 4-year average percentage of category D for LDL-C was 28.0% and 28.5%, and that for BP was 23.5% and 19.9% in male and female subjects, respectively. Furthermore, both the percentages of un-prescribed subjects among those for whom the TL was not attained and the percentages of un-prescribed subjects among those qualified for prescription therapy were higher for LDL-C than for BP in all the 4 years in both genders. The 4-year average percentages of un-prescribed subjects among TL non-attainers reached as high as 72.7% and 59.2% in males and females, respectively, for LDL-C, while they were 35.9% and 31.2% for BP, respectively. The 4-year average percentages of un-prescribed subjects among those qualified for prescription therapy were 47.5% and 36.7% in males and females, respectively, for LDL-C, while they were 29.4% and 24.9% for BP.

To examine the year by year changes in the un-prescription rate among TL non-attainers as well as the year by year changes in the un-prescription rate among those qualified for prescription, the Cochran–Armitage test was utilized to compare category C with

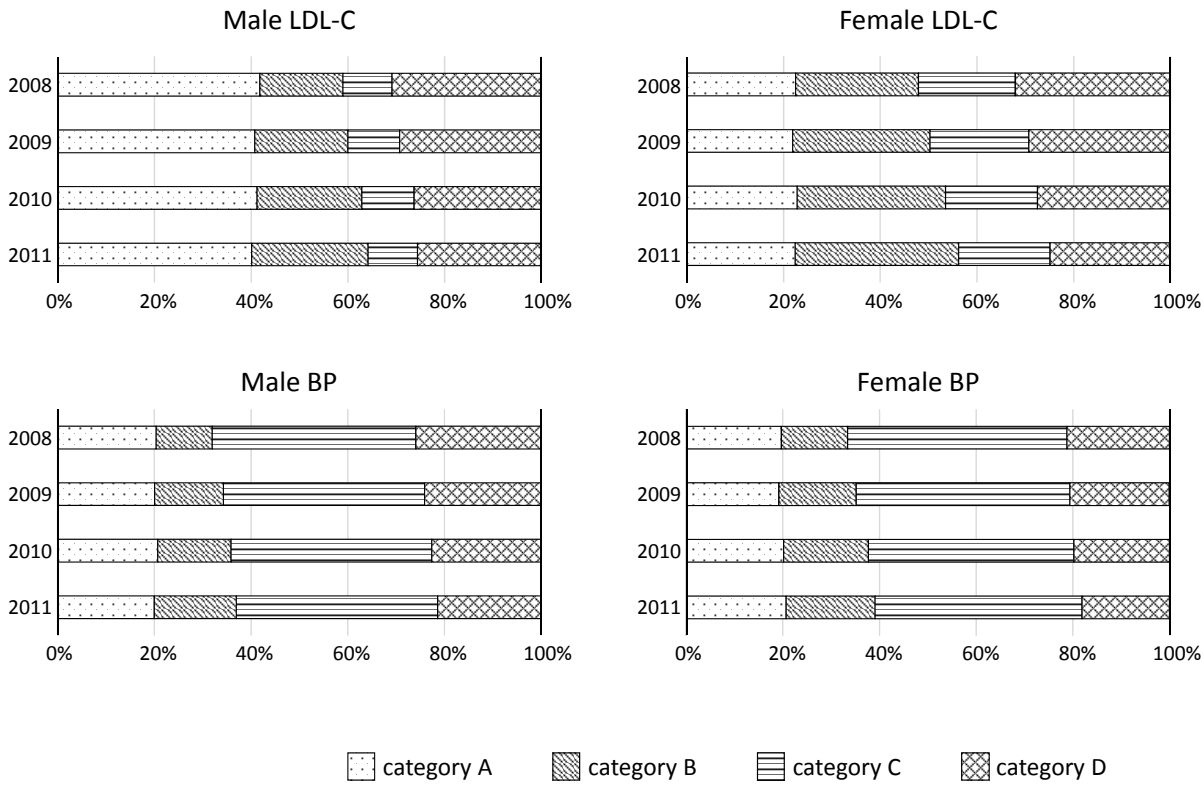

Fig. 1. Prescription status for and control status of LDL-C and BP in diabetic subjects under medication for each year for each sex

Subjects were categorized according to Table 2, and the percentages were calculated.

category D and to compare categories B and C with category D during the study period. As shown in **Table 5**, both the un-prescription rate among TL non-attainers and the un-prescription rate among those qualified for prescription therapy decreased significantly year by year for both LDL-C and BP.

As stated above, the un-prescription rates among TL non-attainers as well as among those qualified for prescription therapy were constantly higher for LDL-C than for BP for each sex for each year. To elucidate whether there were statistical differences in the insufficient prescription rate between LDL-C and BP controls, the prevalence of un-prescribed subjects among TL non-attainers as well as among those who qualified for prescription therapy was compared between LDL-C and BP with the chi-squared test for each year, and the P-values of these analyses are shown in **Supplementary Table 1**. As shown in **Supplementary Table 1**, the insufficient prescription rate was found to be significantly higher for LDL-C than for BP ($P<0.001$ for each) for each year for each sex.

The distributions of LDL-C and SBP values in those who were prescribed and un-prescribed are shown in **Fig. 2** (data of 2011) and **Supplementary Fig. 1** (data of 2008, 2009, and 2010). The comparison of these values between prescribed and un-prescribed groups revealed statistical significance for each sex all through the study period (**Table 6**). Notably, for LDL-C, the mean values were consistently higher in those who were un-prescribed; while for SBP, as was reported recently[13], they were consistently higher in the prescribed subjects.

We next analyzed the patient characteristics associated with under-prescribed status, designating subjects who were un-prescribed without attaining the TL (category D) as 1 and those were prescribed (categories B and C) as 2 (**Table 4**). Prescriptions for dyslipidemia were more commonly associated with older age, higher BMI, lower eGFR, and the presence of cardiovascular disease and prescriptions for other risk factors (**Table 7**). The same tendency was noted in prescriptions for hypertension.

Analyses of Subjects with a History of Heart Disease or Cerebrovascular Disease

Analyses on the association between prescription and control status for DM were performed in those who had a history of heart or cerebrovascular disease,

Table 5. Prescription status for and control status of LDL-C and BP in diabetic subjects under medication for each year in each sex

A. LDL-C

			2008		2009		2010		2011		Average percent of 4 years		*P*-Value
			Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	
Male	Prescribed	No. of Subjects (percent)	1356 (17.2%)	801 (10.1%)	1778 (19.3%)	984 (10.7%)	2114 (21.7%)	1053 (10.8%)	2523 (24.1%)	1072 (10.2%)	20.6%	10.5%	
	Un-prescribed	No. of Subjects (percent)	3300 (41.8%)	2438 (30.9%)	3757 (40.7%)	2703 (29.3%)	4006 (41.2%)	2559 (26.3%)	4199 (40.1%)	2683 (25.6%)	40.9%	28.0%	
	Un-prescription Rate among non-attainer (D/C + D)		75.3%		73.3%		70.8%		71.5%		72.7%		<0.001
	Inappropriate Prescription Rate (D/B + C + D)		53.1%		49.5%		44.7%		42.7%		47.5%		<0.001
Female	Prescribed	No. of Subjects (percent)	1564 (25.4%)	1228 (20.0%)	2013 (28.4%)	1447 (20.4%)	2192 (30.7%)	1351 (19.0%)	2508 (33.8%)	1399 (18.9%)	29.6%	19.5%	
	Un-prescribed	No. of Subjects (percent)	1386 (22.5%)	1976 (32.1%)	1557 (21.9%)	2081 (29.3%)	1622 (22.8%)	1964 (27.5%)	1663 (22.4%)	1847 (24.9%)	22.4%	28.5%	
	Un-prescription Rate among non-attainer (D/C + D)		61.7%		59.0%		59.2%		56.9%		59.2%		<0.001
	Inappropriate Prescription Rate (D/B + C + D)		41.4%		37.6%		35.7%		32.1%		36.7%		<0.001

B. BP

			2008		2009		2010		2011		Average percent of 4 years		*P*-Value
			Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	
Male	Prescribed	No. of Subjects (percent)	917 (11.6%)	3320 (42.1%)	1315 (14.2%)	3851 (41.6%)	1485 (15.2%)	4056 (41.5%)	1787 (17.0%)	4370 (41.6%)	14.5%	41.7%	
	Un-prescribed	No. of Subjects (percent)	1608 (20.4%)	2033 (25.8%)	1859 (20.1%)	2225 (24.1%)	2023 (20.7%)	2199 (22.5%)	2102 (20.0%)	2251 (21.4%)	20.3%	23.5%	
	Un-prescription Rate among non-attainer (D/C + D)		38.0%		36.6%		35.2%		34.0%		35.9%		<0.001
	Inappropriate Prescription Rate (D/B + C + D)		32.4%		30.1%		28.4%		26.8%		29.4%		<0.001
Female	Prescribed	No. of Subjects (percent)	839 (13.7%)	2793 (45.4%)	1139 (16.0%)	3145 (44.2%)	1252 (17.5%)	3040 (42.5%)	1369 (18.4%)	3186 (42.8%)	16.4%	43.8%	
	Un-prescribed	No. of Subjects (percent)	1209 (19.7%)	1305 (21.2%)	1365 (19.2%)	1461 (20.5%)	1443 (20.2%)	1413 (19.8%)	1541 (20.7%)	1346 (18.1%)	19.9%	19.9%	
	Un-prescription Rate among non-attainer (D/C + D)		31.8%		31.7%		31.7%		29.7%		31.2%		<0.05
	Inappropriate Prescription Rate (D/B + C + D)		26.4%		25.4%		24.8%		22.8%		24.9%		<0.001

Subjects were categorized according to Table 2, and the percentages were calculated. Un-prescription rates among non-attainer (D/C + D), inappropriate prescription rates (D/B + C + D), and the *P* values obtained with the over-time trends analysis of these values by Cochrane-Armitage test were also indicated.

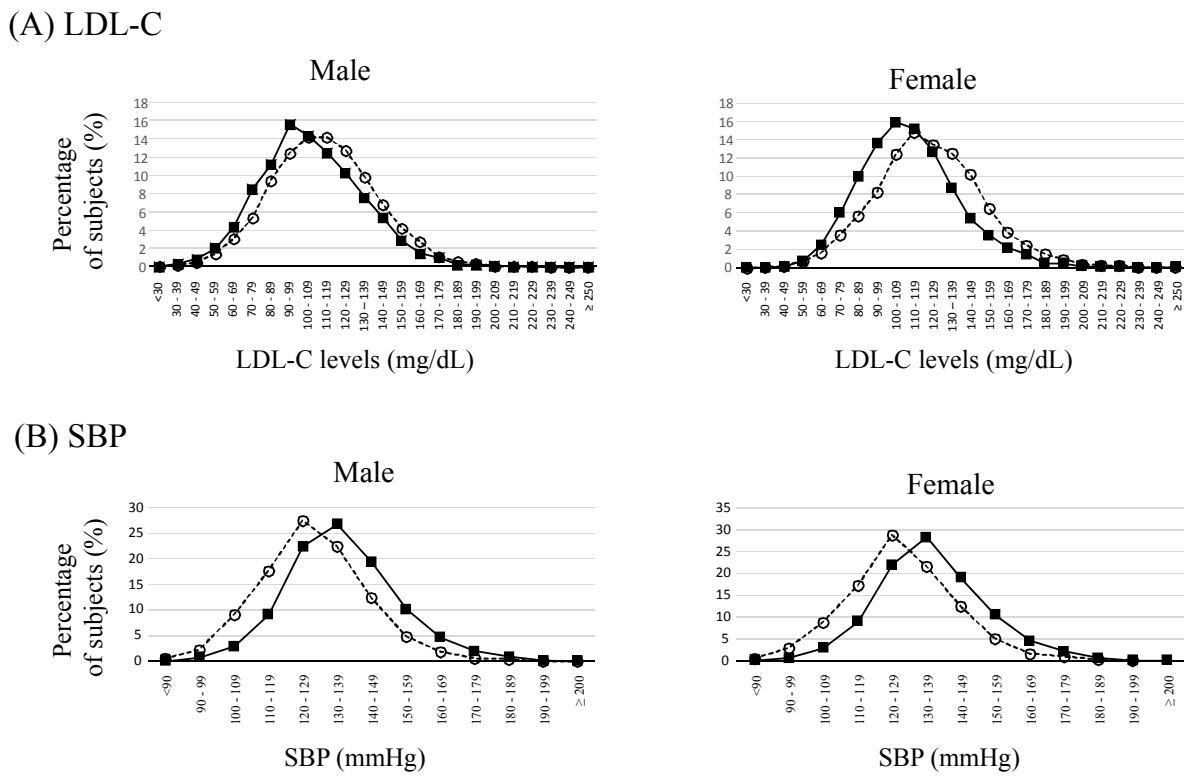

Fig. 2. Distribution of LDL-C and SBP levels in prescribed and un-prescribed subjects in 2011
Circles represent the values of un-prescribed subjects, and squares represent those of prescribed subjects.

Table 6. Comparison of the LDL-C or SBP values between those who were prescribed and those were not prescribed in each year using independent *t*-test

A. LDL-C							
		Male			Female		
Year	LDL-C (mg/dL)	Prescribed	Un-prescribed	*P* value	Prescribed	Un-prescribed	*P* value
2008	mean SD	112.1 28.1	114.9 29.1	<0.001	118.1 28.6	126.7 30.0	<0.001
2009	mean SD	110.8 28.7	114.4 28.7	<0.001	115.8 27.4	126.1 29.6	<0.001
2010	mean SD	109.3 28.1	113.0 28.7	<0.001	113.2 27.1	123.7 29.7	<0.001
2011	mean SD	106.3 28.0	112.7 28.0	<0.001	112.5 27.2	122.9 29.3	<0.001
B. BP							
		Male			Female		
Year	SBP (mmHg)	Prescribed	Un-prescribed	*P* value	Prescribed	Un-prescribed	*P* value
2008	mean SD	138.9 16.9	128.9 16.3	<0.001	138.8 16.7	128.2 16.7	<0.001
2009	mean SD	136.9 16.3	127.8 16.1	<0.001	137.2 16.0	128.1 16.3	<0.001
2010	mean SD	136.5 16.2	127.6 15.9	<0.001	136.3 16.6	127.6 16.1	<0.001
2011	mean SD	135.3 16.1	127.0 15.8	<0.001	135.5 15.9	126.9 15.8	<0.001

Table 7. Logistic regression analyses of the appropriate prescription statuses for atherosclerotic risk factors (ARFs)

A. LDL-C				
ARF	Male		Female	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Year	1.149 (1.115-1.184)	<0.001	1.139 (1.105-1.174)	<0.001
Age	1.009 (1.004-1.014)	<0.001	1.023 (1.017-1.029)	<0.001
BMI	1.019 (1.010-1.029)	<0.001	NA	0.455
eGFR	0.997 (0.995-0.999)	<0.001	0.995 (0.994-0.997)	<0.001
Smoking	1.153 (1.066-1.248)	<0.001	NA	0.342
pHD	2.202 (1.991-2.435)	<0.001	1.610 (1.412-1.836)	<0.001
pCVD	1.284 (1.139-1.447)	<0.001	1.308 (1.114-1.535)	<0.01
DrugBP	1.852 (1.729-1.985)	<0.001	1.471 (1.374-1.576)	<0.001
B. BP				
ARF	Male		Female	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Year	1.114 (1.083-1.146)	<0.001	1.077 (1.041-1.114)	<0.001
Age	1.033 (1.028-1.038)	<0.001	1.038 (1.032-1.045)	<0.001
BMI	1.092 (1.082-1.102)	<0.001	1.103 (1.092-1.113)	<0.001
eGFR	0.989 (0.987-0.991)	<0.001	0.990 (0.998-0.992)	<0.001
Smoking	NA	0.299	1.251 (1.056-1.483)	<0.05
pHD	1.482 (1.337-1.643)	<0.001	1.819 (1.555-2.128)	<0.001
pCVD	2.239 (1.958-2.561)	<0.001	2.113 (1.723-2.591)	<0.001
DrugLP	1.752 (1.633-1.880)	<0.001	1.576 (1.462-1.698)	<0.001

The independent effects of calendar year that the data were collected (year), age, BMI, eGFR, smoking, past histories, and medication for ARFs on the prescription status (categories B and C vs category D) were evaluated with logistic regression analyses. Odds ratios (OR) and p values are indicated. pHD: a past history of heart disease, pCVD: a past history of cerebrovascular disease, DrugBP: medication for hypertension, DrugLP: medication for dyslipidemia, NA: not applicable.

in the same way as performed for dyslipidemia and hypertension with subjects with diabetes receiving medication. As shown in **Table 8** and **Fig. 3**, the percentage of TL non-attainers who did not receive medication (category D) was less than 3% in all 4 years in both genders; the 4-year average percentage of category D was 2.2% and 1.4% in males and females, respectively, for those who had a history of heart disease, and 2.3% and 1.4% for those who had a history of cerebrovascular disease. Furthermore, both the percentage of un-prescribed subjects among those who did not attain the TL and the percentage of un-prescribed subjects among those qualified for prescription therapy were lower than the values observed for LDL-C and BP in subjects with diabetes receiving medication (**Table 5**) in all the 4 years in both genders. The 4-year average percentage of un-prescribed subjects among TL non-attainers were 26.5% and 25.5% in males and females, respectively, for those who had a history of heart disease, and 28.9% and 28.8% for those who had a history of cerebrovascular disease. The 4-year average percentage of un-prescribed subjects among those qualified for prescription therapy was 12.8% and 13.3% in males and females, respectively, for those who had a history of heart disease, and 14.3% and 14.1% for those who had a history of cerebrovascular disease.

The Cochran–Armitage test was utilized to examine the over-time trends in the un-prescription rate among TL non-attainers as well as those in the un-prescription rate among those qualified for prescription therapy. As shown in **Table 8**, statistical significance was not observed in these trends except for the un-prescription rate among those who qualified for prescription therapy in female subjects who had a history of cerebrovascular disease.

Discussion

The proper management of atherosclerotic cardiovascular risk factors is crucial in preventing ASCVDs. In cases where atherosclerotic cardiovascular risk factors routinely remain above the recommended TL, appropriate prescriptions for atherosclerotic car-

Table 8. Prescription status for DM and control status of HbA1c in those who had a past history of heart disease or cerebrovascular disease for each year in each sex

A. Those who had a past history of heart disease

			2008		2009		2010		2011		Average percent of 4 years		*P*-Value
			Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	
Male	Prescribed	No. of Subjects (percent)	645 (9.8%)	451 (6.8%)	606 (8.2%)	430 (5.8%)	610 (8.2%)	459 (6.2%)	717 (9.5%)	442 (5.8%)	8.9%	6.2%	
	Un-prescribed	No. of Subjects (percent)	5356 (81.1%)	149 (2.3%)	6209 (83.9%)	153 (2.1%)	6176 (83.3%)	172 (2.3%)	6235 (82.5%)	168 (2.2%)	82.7%	2.2%	
	Un-prescription rate among non-Attainer (D/C + D)		24.8%		26.2%		27.3%		27.5%		26.5%		0.256
	Inappropriate Prescription Rate (D/B + C + D)		12.0%		12.9%		13.9%		12.7%		12.8%		0.491
Female	Prescribed	No. of Subjects (percent)	348 (5.8%)	270 (4.5%)	277 (4.5%)	229 (3.8%)	270 (4.6%)	229 (3.9%)	276 (4.8%)	215 (3.7%)	4.9%	4.0%	
	Un-prescribed	No. of Subjects (percent)	5248 (88.2%)	83 (1.4%)	5502 (90.1%)	97 (1.6%)	5264 (90.2%)	71 (1.2%)	5222 (90.3%)	72 (1.2%)	89.7%	1.4%	
	Un-prescription rate among non-Attainer (D/C + D)		23.5%		29.8%		23.7%		25.1%		25.5%		0.989
	Inappropriate Prescription Rate (D/B + C + D)		11.8%		16.1%		12.5%		12.8%		13.3%		0.946

B. Those who had a past history of cerebrovascular disease

			2008		2009		2010		2011		Average percent of 4 years		*P*-Value
			Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	Attained	Not attained	
Male	Prescribed	No. of Subjects (percent)	353 (7.1%)	253 (5.1%)	366 (7.7%)	239 (5.0%)	400 (8.0%)	311 (6.2%)	462 (9.5%)	307 (6.3%)	8.0%	5.6%	
	Un-prescribed	No. of Subjects (percent)	4291 (85.8%)	106 (2.1%)	4044 (85.0%)	108 (2.3%)	4204 (83.6%)	114 (2.3%)	3981 (81.7%)	120 (2.5%)	84.0%	2.3%	
	Un-prescription rate among non-Attainer (D/C + D)		29.5%		31.1%		26.8%		28.1%		28.9%		0.410
	Inappropriate Prescription Rate (D/B + C + D)		14.9%		15.1%		13.8%		13.5%		14.3%		0.317
Female	Prescribed	No. of Subjects (percent)	183 (4.3%)	122 (2.8%)	183 (5.3%)	127 (3.7%)	181 (5.1%)	134 (3.8%)	207 (6.1%)	132 (3.9%)	5.2%	3.6%	
	Un-prescribed	No. of Subjects (percent)	3911 (91.3%)	66 (1.5%)	3112 (89.6%)	51 (1.5%)	3182 (89.9%)	43 (1.2%)	2978 (88.5%)	49 (1.5%)	89.8%	1.4%	
	Un-prescription rate among non-Attainer (D/C + D)		35.1%		28.7%		24.3%		27.1%		28.8%		0.055
	Inappropriate Prescription Rate (D/B + C + D)		17.8%		14.1%		12.0%		12.6%		14.1%		< 0.05

Subjects were categorized according to Table 2, and the percentages were calculated. Un-prescription rates among non-attainer (D/C + D), inappropriate prescription rates (D/B + C + D), and the *P* values obtained with the over-time trends analysis of these values by Cochrane-Armitage test were also indicated.

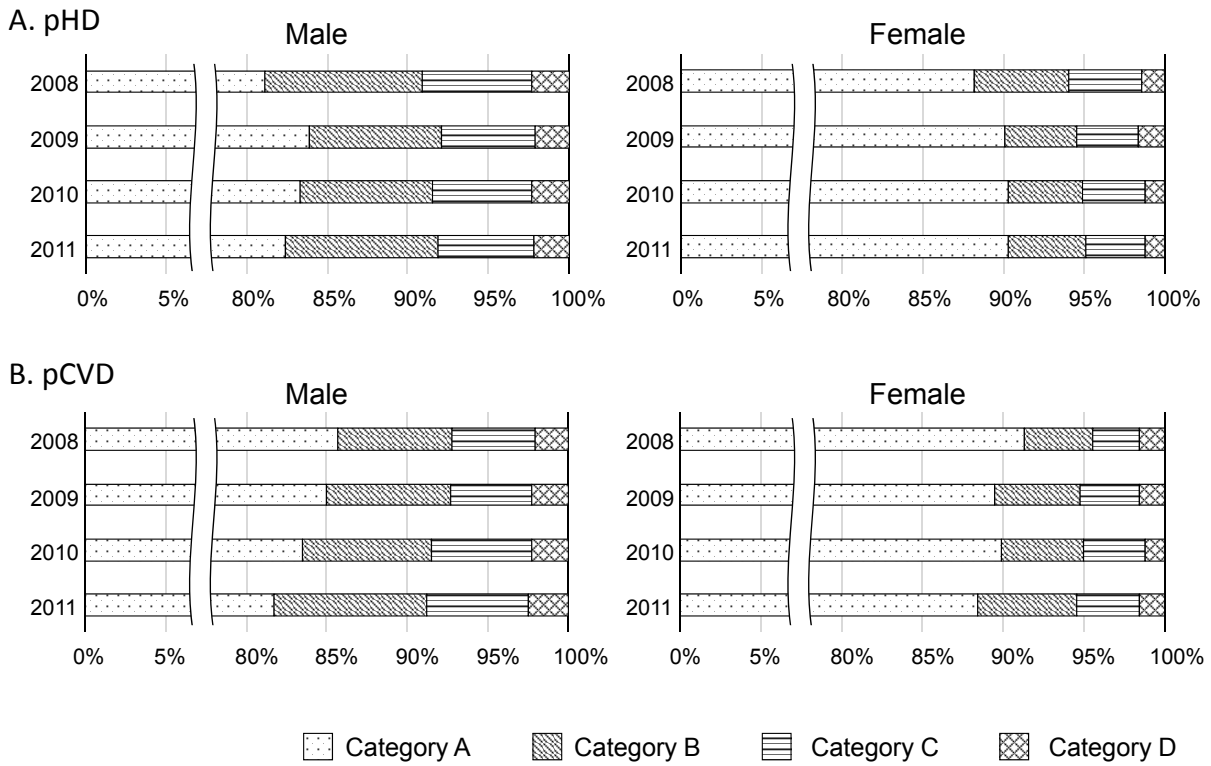

Fig. 3. Prescription status for diabetic treatment and control status of HbA1c in those who had a past history of heart disease or cerebrovascular disease for each year for each sex

Those who had a past history of heart disease (pHD) or cerebrovascular disease (pCVD) were selected from the database, and categorized according to the prescription status for diabetes and attainment status of TL (HbA1c less than 7.0%). Regarding categorization, please see Table 2.

diovascular risk factor drug therapy should be considered, especially in high-risk subjects. However, data on the status of atherosclerotic cardiovascular risk factor control and prescriptions in a real-world setting are scarce, and, as far as we know, no research has compared prescription status and control status among different atherosclerotic cardiovascular risk factors. In this study, after selecting patients with diabetes who were undergoing medical treatment for DM from the nationwide SHCG that was conducted from 2008 to 2011 in Japan, we analyzed the association of TL attainment status of LDL-C and prescription status of dyslipidemia as well as the association of TL attainment status of BP and prescription status of hypertension in these subjects. We also analyzed the association of TL attainment status of HbA1c and prescription status of DM, utilizing the data of those who had a history of heart or cerebrovascular disease.

The major finding of this study is that the rates of un-prescription for the atherosclerotic cardiovascular risk factor in subjects with diabetes receiving medication who qualified for prescription therapy for atherosclerotic cardiovascular risk factors, as well as in those who did not attain the TL of the atherosclerotic cardiovascular risk factor, were significantly higher for dyslipidemia than for hypertension, although these rates in both atherosclerotic cardiovascular risk factors decreased year by year during the study period (**Table 5**). Furthermore, among those who did not attain the TL of LDL-C, the percentage of un-prescribed subjects was around 60%–70% for both genders, while the equivalent percentages for BP were around 30%–40%. A previous report that analyzed data from 136 hospitals also found that around 70% of high-risk subjects who did not attain the TL of LDL-C were not receiving prescriptions for dyslipidemia[14], suggesting that this rate of 70% is likely to be valid in clinical practice across Japan.

The analyses of patients with diabetes undergoing medical treatment for DM do not make it possible to analyze the relationship between glycemic control and antidiabetic treatment. Thus, we performed analyses on the association between control and prescription status of DM utilizing the data of those who had suffered from heart disease or cerebrovascular disease (**Table 8**). These analyses disclosed that the un-prescription rates among those who did not attain the TL of HbA1c were around 25%–30%, which are almost

the same levels for BP in patients with diabetes receiving medication, but are lower than those for LDL-C. Furthermore, the rates of un-prescribed non-TL attained subjects among those who qualified for DM medication therapy (categories B, C, and D) were less than 18%, which were much lower than the rates for LDL-C in subjects with diabetes receiving medication. These data indicate that although aggressive LDL-C lowering is recommended for patients under high-risk conditions, less attention is paid to LDL-C lowering than to the control of hypertension and probably to glycemic control in real-world patient care in Japan.

Some reasons or factors possibly contribute to this phenomenon. One reason is that both the patients and physicians might pay less attention to LDL-C than to BP and glycemic control. Personal electronic sphygmomanometers are popular in Japan, and devices for self-monitoring blood glucose are readily available, but there are no devices for patient self-measurement of LDL-C levels. In addition, BP is measured on every visit to a clinic and the results are available on the same day, but the LDL-C level is not examined on every visit, and the results are usually reported on the next visit to the clinic. Moreover, serious uncontrolled hypertension and diabetes induce some symptoms, but dyslipidemia does not. As a consequence, the control of LDL-C might tend to be overlooked more commonly than the control of hypertension or diabetes. Another reason would be statin intolerance. A recent report[15] analyzed administrative claim databases in Japan, and the results showed that more than 20% of patients discontinued their medication for dyslipidemia within one year after the initiation of medication; for high-dose statin therapy, that amount exceeded 60%. Statin intolerance, including the nocebo effect[16], might somehow have contributed to this discontinuation. However, as the incidence of statin intolerance is thought to be around 5%–10%[17], other factors, such as those stated above, must surely contribute to discontinuation.

Previous works indicated that the attainment of the TL for dyslipidemia was easier than those for hypertension or DM[18, 19]. In our study, the comparison of the LDL-C and SBP values between prescribed and un-prescribed subjects (**Table 6**) also suggested that attainment of the TL with medication would be easier for LDL-C than for SBP. This suggests that an increased focus on dyslipidemia treatment could well lead to higher LDL-C TL attainment rates.

Finally, logistic regression analyses of the present data revealed that a higher prescription rate for dyslipidemia tended to be associated with older age, higher BMI, lower eGFR, and the presence of other high-risk diseases and the prescriptions for other risk factors (**Table 7**). These characteristics are generally classified as "high-risk states," and it is, in a sense, predictable and acceptable that subjects with these characteristics would receive more attention from physicians. However, as the subjects with diabetes undergoing medical therapy were at high-risk, and the younger the subjects the higher the lifetime risk, proper control through medication should be considered in younger subjects and before the subject's health is complicated by other risks.

This study had the following limitations. First, the data on medical treatment for diabetes and a history of heart or cerebrovascular disease were obtained from self-administered questionnaires, so the answers may include errors. Second, although the Specific Health Check is mandatory for all Japanese aged between 40 and 74 years, the response rate to health examinations is around 30%–40% in those who are covered by "National Health Insurance" or the "Japan Health Insurance Association." Thus, the self-selection bias would underlie in this study, and the results of this study might not always reflect the real Japanese medical situation. However, the utilization of the health check database for the analyses enables a larger scale analyses compared with the use of hospital databases. Third, the 16 targeted prefectures might be biased. There are differences in some aspects that affect health check data among prefectures; for example, differences in the salt intake or the medical situation among the prefectures affect the medical data, leading to bias. Thus, in order to minimize the bias caused by the lack of data of some calendar years in some prefectures, we utilized data from 16 prefectures that were fixed for all four calendar years when we began the analyses. However, the bias caused by the background of each prefecture analyzed in this study might affect our results.

In summary, by analyzing the data of the SHCG performed between 2008 and 2011, the prescription rate for dyslipidemia among those who qualified for medication was found to be lower than that for hypertension in Japanese patients with diabetes undergoing medical therapy. These results suggested that closer adherence to recommended guidelines for the proper treatment of dyslipidemia is crucial for a more efficient prevention of ASCVD in Japan.

Acknowledgement

This study was supported in part by a Health and Labor Sciences Research Grant for "Design of a comprehensive health care system for CKD based on individual risk assessment by Specific Health Checkup" (H24-intractible(renal)-ippan-006) from

the Ministry of Health, Labor, and Welfare of Japan, and was also supported in part by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease (REACH-J), Practical Research Project for Renal Diseases from the Japan Agency for Medical Research and Development, AMED.

Conflicts of Interest

Honoraria: Yasuo Ohashi: Chugai Pharmaceutical Co., Ltd., DAIICHI SANKYO COMPANY, LIMITED. Clinical Research Funds: Ichiei Narita: Teijin Pharma Co., Ltd., Baxter Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., DAIICHI SANKYO COMPANY, LIMITED, Sanofi K.K., Chugai Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., MSD K.K., Torii Pharmaceutical Co., Ltd., Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, Kissei Pharmaceutical Co., Ltd. Yasuo Ohashi: Eisai Co., Ltd.

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Supplementary Table 1. Comparison of the insufficient prescription rates among LDL-C and BP

A. Comparison between LDL-C and BP utilizing the numbers of categories B and C and that of category D

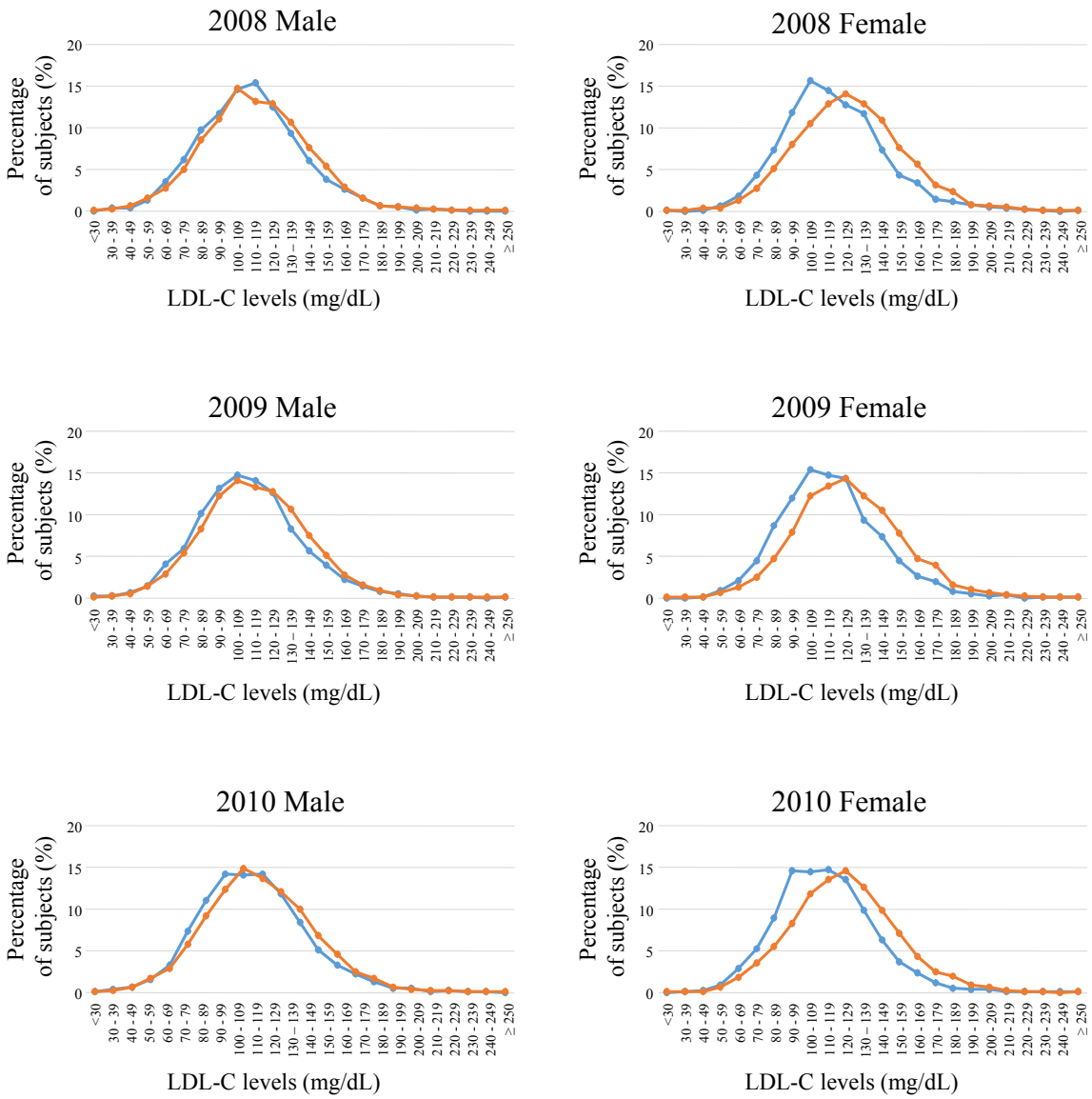
Compared Risk Factors	Sex	Year			
		2008	2009	2010	2011
LDL-C vs BP	Male	<0.001	<0.001	<0.001	<0.001
	Female	<0.001	<0.001	<0.001	<0.001

B. Comparison between LDL-C and BP utilizing the number of category C and that of category D

Compared Risk Factors	Sex	Year			
		2008	2009	2010	2011
LDL-C vs BP	Male	<0.001	<0.001	<0.001	<0.001
	Female	<0.001	<0.001	<0.001	<0.001

After counting the case numbers of categories B and C and that of category D for LDL-C and BP, comparisons of these numbers between LDL-C and BP were performed utilizing chi-square test for each year, and the P values were indicated (A). Similarly, after counting the case number of category C and that of category D for LDL-C and BP, comparisons of these numbers between LDL-C and BP were performed utilizing chi-square test for each year, and the *P* values were indicated (B).

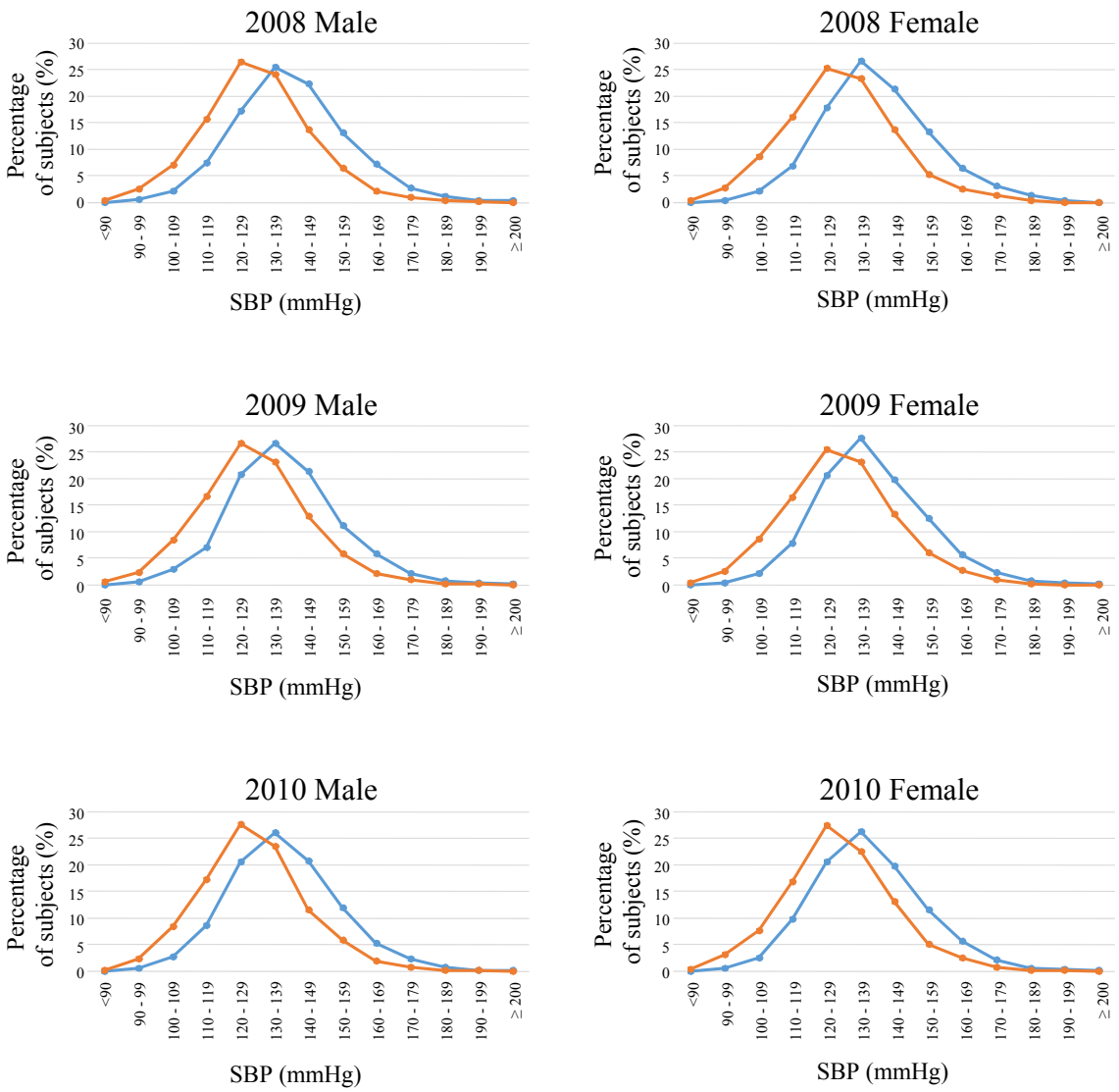
A. LDL-C



Supplementary Fig. 1A. Distribution of LDL-C and SBP levels in prescribed and unprescribed subjects in 2008, 2009 and 2010

A: LDL-C levels, B: SBP levels. Orange circles and lines represent the values of un-prescribed subjects, and blue circles and lines represent those of prescribed subjects.

B. SBP



Supplementary Fig. 1B. Distribution of LDL-C and SBP levels in prescribed and unprescribed subjects in 2008, 2009 and 2010

A: LDL-C levels, B: SBP levels. Orange circles and lines represent the values of un-prescribed subjects, and blue circles and lines represent those of prescribed subjects.