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Comparison of lipid parameters to predict cardiovascular events in Japanese mild-to-moderate hypercholesterolemic patients with and without type 2 diabetes: Subanalysis of the MEGA study

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ABSTRACT

Aims: To determine whether specific lipid parameters are better predictors of cardiovascular disease (CVD) in Japanese mild-to-moderate hypercholesterolemic patients with and without diabetes.

Methods: Mildly or moderately hypercholesterolemic patients with no history of CVD received diet therapy or diet therapy plus pravastatin. In this post-hoc subanalysis, 5-year data from 3170 patients (668 diabetes, 2502 non-diabetes) on diet therapy alone were used to compare lipid parameters as predictors of CVD. We examined the data by tertiles, using hazard ratio (HR) per one-standard deviation (SD) increment (decrease for high-density lipoprotein cholesterol, HDL-C), χ^2 value, receiver operating characteristic curve analysis, and spline analysis.

Results: In mild-to-moderate hypercholesterolemic patients with diabetes, increased total cholesterol (TC)/HDL-C, low-density lipoprotein cholesterol (LDL-C)/HDL-C and decreased HDL-C were strongly associated with increased incidence of CVD (tertile analysis). In non-diabetes, increased non-HDL-C, and LDL-C/HDL-C were significantly associated with increased incidence of CVD. A one-SD decrease in HDL-C and a one-SD increment in non-HDL-C, TC/HDL-C, and LDL-C/HDL-C were significantly associated with increased HRs for CVD in both diabetes and non-diabetes. Linear CVD risk increases were found for non-HDL-C in diabetes and for non-HDL-C and HDL-C in non-diabetes (spline analysis).

Conclusions: In mild-to-moderate hypercholesterolemia, CVD risk prediction by stratifications of single or combination of traditional lipid parameter values illustrates various patterns. Parameters including HDL-C are better predictors of cardiovascular risk than only

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using TC or LDL-C alone. Non-HDL-C could be the most useful lipid parameter to assess CVD risk, considering it is easy to calculate and less affected by food intake.

1. Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is a major cause of death worldwide. Cardiovascular risk depends on the presence of comorbidities such as dyslipidemia, hypertension, overweight, and smoking [1]. Hypercholesterolemia is a particularly important risk factor and is managed by lipid-modifying therapies.

The assessment and management of cardiovascular risk is required for patients with diabetes mellitus, who often have hypercholesterolemia [2–4]. Patients with type 2 diabetes have an abnormal atherogenic lipid profile (low high-density lipoprotein cholesterol, HDL-C; high small dense low-density lipoprotein cholesterol, LDL-C; and high triglycerides, TGs) and double the cardiovascular risk of patients without diabetes [5].

Serum concentrations of lipids are used to assess cardiovascular risk and guide lipid-modifying therapies in patients with and without diabetes. A serum lipid profile commonly measured comprises total cholesterol (TC), HDL-C, LDL-C, and TGs. The ratios of TC/HDL-C and LDL-C/HDL-C also are useful. Recent guidelines have added non-HDL-C to the list of recommended variables for assessing cardiovascular risk [6,7]. Non-HDL-C (calculated as TC minus HDL-C) is widely used.

However, there is a lack of consensus on how to assess cardiovascular risk in patients with type 2 diabetes [8]. Few studies have compared the relative value of different lipid variables in predicting cardiovascular events in patients with diabetes especially in comparison with subjects without diabetes. It could be potentially important with respect to whether cardiovascular risk assessment and lipid-lowering therapy should be modified according to diabetes status. Furthermore, most of the key studies were done in Western countries, which have a higher incidence of CHD than in Japan. In Western countries, CHD causes the greater majority of deaths of patients with diabetes [9]. In contrast, cancer is the leading cause of death in Japanese patients with diabetes [10].

We conducted a subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study [11] to evaluate which lipid parameters best predict cardiovascular events in mild-to-moderate hypercholesterolemia patients with and without diabetes in the diet alone group.

2. Methods

2.1. Patients

The details of the MEGA study have been described elsewhere [11]. Briefly, 7832 patients (2476 men and 5356 postmenopausal women) aged 40–70 years with mild-to-moderate hypercholesterolemia (TC, 5.7–7.0 mmol/L [220–270 mg/dL]) and no history of CHD or stroke were randomly allocated to diet therapy alone or diet therapy plus pravastatin (10–20 mg/day, the approved dose in Japan) for a mean follow-up period of 5.3 years. Patients in both groups were counseled to follow the National Cholesterol Education Program step I diet [12] throughout the study period. Concomitant treatment for complications was unrestricted in both groups.

The primary composite endpoint was the first occurrence of CHD events, that is, fatal or nonfatal myocardial infarction, angina pectoris, cardiac or sudden death, and coronary revascularization. Secondary endpoints included all strokes, CHD plus stroke, all CVD events, and total mortality. Patients were evaluated by their attending physicians at 1, 3, and 6 months after the start of follow-up and every 6 months thereafter. Health checks at each clinic visit included biochemical tests and assessment of patient adherence to treatment. For each event, detailed information was evaluated by the Endpoints Committee under blinding according to established criteria [11,12].

Throughout the study period, non-fasting TC, HDL-C, TGs, and lipoprotein (a) were measured centrally at the same laboratory using methods standardized by the Centers for Disease Control and Prevention (Atlanta, GA, USA). LDL-C was estimated using the Friedewald formula [13].

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 patients for being included in the study.

2.2. Tertile analysis

The present study was a post-hoc subanalysis using 5-year follow-up data to reduce potential bias from the high drop-in rate for statin use in patients allocated to diet therapy alone, which was caused by an additional follow-up period. The 3170 patients with type 2 diabetes ($n = 668$) and without diabetes ($n = 2502$) who received diet therapy alone were divided into tertiles according to their baseline data for each lipid parameter to compare the incidence of CHD, CHD plus stroke, and all CVD events in patients with and without diabetes. Diabetes was defined as a baseline fasting glucose $\geq$7.0 mmol/L, $HbA_{1c} \geq 6.5\%$ (48 mmol/mol; National Glycohemoglobin Standardization Program, NGSP) [14], or taking an oral hypoglycemic agent.

2.3. Hazard ratios

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the multivariate Cox proportional hazards model adjusted by sex, age, body mass index (BMI), smoking status (current/past/never), alcohol intake, aspirin use, oral

hypoglycemic agent use, and hypertension, using the first tertile of each variable as the reference group.

2.4. Pearson's chi-squared test (χ^2)

We used the χ^2 likelihood ratio test to evaluate the strength of associations between lipid variables and the incidence of CHD, CHD plus stroke, and all CVD events.

The corresponding *P* values were estimated from the regression coefficient based on the Cox proportional hazards model adjusted by sex, age, smoking, and hypertension.

2.5. Receiver operating characteristic curve analysis

The discriminatory power of the lipid variables for CVD was compared using the receiver operating characteristic (ROC) curve analysis, applying various thresholds to the predicted probability obtained from the multiple logistic regression model. The area-under-the-curve (AUC) was calculated by integrating the area between the ROC curve and the diagonal line where sensitivity is equal to one specificity based on the trapezoidal rule.

2.6. Spline analyses

Multivariable Cox proportional hazards models with a restricted quadratic spline based on three knots for the quartiles were also used to explore potential nonlinear relations [15]. The multivariable models were simultaneously adjusted by sex and age, smoking status, and hypertension. All *P* values were two-sided, and the significance level was 0.05. All statistical analyses were done using SAS package version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient baseline characteristics

Table 1 shows the baseline characteristics of the patients with and without diabetes. The patients in the two groups were similar in age. However, the diabetes group contained a significantly higher percentage of men, as well as patients with a history of smoking or drinking alcohol. Patients with diabetes also had significantly higher values for body mass index, systolic blood pressure, and some lipid variables (LDL-C/HDL-C, non-HDL-C, and TGs). HDL-C was significantly lower in patients with diabetes.

3.2. Tertile analysis of lipid variables and cardiovascular events

There were 70 CVD events (34 CHD events, 24 strokes, and 12 other CVD events) in 668 patients with diabetes. Table 2 shows hazard ratios of all cardiovascular events according to lipid variables (for individual CVD events, see Supplemental Table 1). Patients with higher values for lipid variables other than HDL-C had higher cardiovascular risk. Conversely, higher HDL-C was associated with lower cardiovascular risk.

Diabetes was associated with higher cardiovascular risk. Patients with diabetes had 13.00 events/1000 person-years for CHD, 17.60 events/1000 person-years for CHD plus cerebral infarction, and 20.14 events/1000 person-years for all CVD. These values are over three times higher than the respective values for patients without diabetes (3.00 events/1000 person-years for CHD, 4.34 events/1000 person-years for CHD plus cerebral infarction, and 6.23 events/1000 person-years for CVD).

The tertile analysis, demonstrated that decreased HDL-C and increased TC/HDL-C and LDL-C/HDL-C were the significant predictor for CVD events in patients with diabetes (Table 2). A similar relationship was found in CHD and CHD plus cerebral infarction (Supplement Table 1). In contrast, in patients without diabetes, increased non-HDL-C and LDL-C/HDL-C were identified as significant risk predictors for CVD events. All these lipid variables were more predictive than LDL-C for any type of events and regardless of presence and absence of diabetes.

3.3. Hazard ratios for cardiovascular events

Table 3 shows the HRs of all cardiovascular events per one-standard deviation (SD) increment for the lipid variable and decrease for HDL-C (for individual CVD events, see Supplemental Table 2). In this analysis, HDL-C and non-HDL-C were significantly associated with increased HRs for each event in patients with and without diabetes compared with other lipid variables including LDL-C.

3.4. χ^2 values

In patients with diabetes, there were no apparent differences in the χ^2 values for the HDL-C, non-HDL-C, TC/HDL-C, and LDL-C/HDL-C and were higher than those for the other lipid variables (Table 2 and Supplemental Table 2). The χ^2 values were highest for HDL-C.

3.5. Receiver operating characteristic curve analysis

For patients with diabetes, AUC values were similar for CVD events (Table 3, range, 0.71–0.74). For HDL-C, non-HDL-C, TC/HDL-C, and LDL-C/HDL-C a one-SD increment was associated with a significant change in the incidence of CVD events. Meanwhile, in patients without diabetes, a one-SD increment in addition to above parameters, TGs/HDL-C for CVD events significantly increased the incidence of these events and had higher χ^2 values. AUC values were similar for CVD events (range, 0.77–0.78; Table 3). Similar results were found for CHD, and CHD plus cerebral infarction (Supplemental Table 2).

3.6. Spline analyses

Spline analyses were conducted to assess the sensitivity of lipid parameters for assessing cardiovascular risk. Spline analyses were performed for the lipid variables that showed visible associations with the incidence of all three groups of cardiovascular events. The non-HDL-C in patients with diabetes (Fig. 1a) and non-HDL-C and HDL-C in patients without diabetes (Fig. 1b) were seen to be almost linear.

Table 1 – Patient baseline characteristics.

	Patients without diabetes (n = 2502)	Patients with diabetes (n = 668)	Total (N = 3170)	P
Age (years)[§]	58.32 ± 7.14	58.66 ± 6.97	58.39 ± 7.10	0.24
Sex [n (%)]				
Male	720 (28.8)	295 (44.2)	1015 (32.0)	<0.01
Female	1782 (71.2)	373 (55.8)	2155 (68.0)	
BMI (kg/m^2)[§]	23.68 ± 2.96	24.27 ± 3.32	23.80 ± 3.05	0.01
BMI ≥ 25 (%)	756 (30.2)	250 (37.4)	1006 (31.2)	<0.01
Hypertension [n (%)]	1032 (41.2)	285 (42.7)	1317 (41.5)	0.51
Systolic blood pressure (mmHg)[§]	131.73 ± 16.41	135.03 ± 17.48	132.43 ± 16.69	0.01
Diastolic blood pressure (mmHg)[§]	78.65 ± 9.91	79.13 ± 10.49	78.76 ± 10.04	0.28
TC (mmol/L)[§]	6.28 ± 0.31	6.27 ± 0.32	6.27 ± 0.31	0.57
LDL-C (mmol/L)[§]	4.05 ± 0.43	4.05 ± 0.49	4.05 ± 0.45	0.62
HDL-C (mmol/L)[§]	1.50 ± 0.38	1.41 ± 0.40	1.48 ± 0.39	0.01
Non-HDL-C (mmol/L)[§]	4.77 ± 0.48	4.86 ± 0.49	4.79 ± 0.48	0.01
LDL-C/HDL-C	2.89 ± 0.87	3.08 ± 0.91	2.92 ± 0.89	<0.01
TGs (mmol/L) [median (min-max)]	1.4 (0.5–10.6)	1.6 (0.5–14.9)	1.4 (0.5–14.9)	<0.01
TGs (log transformed)	0.37	0.52	0.4	0.01
Fasting blood glucose (mmol/dL)[§]	5.30 ± 0.60	8.40 ± 2.20	6.00 ± 1.70	0.01
HbA_{1c} (%)[§,†]	5.7 ± 0.79	7.5 ± 1.64	6.3 ± 1.48	0.01
Diabetes therapy [n (%)]				
Diet therapy		214 (32.0)		
Insulin		72 (10.8)		
Sulfonylureas		290 (43.4)		
α-Glucosidase inhibitors		145 (21.7)		
Others		24 (3.6)		
Hypertension therapy [n (%)]				
No medication	954 (38.1)	259 (28.8)	1213 (38.3)	0.76
ACE inhibitor	281 (11.2)	102 (15.3)	383 (12.1)	0.004
ARB	22 (0.9)	6 (0.9)	28 (0.9)	0.96
α-Blocker	55 (2.2)	26 (3.9)	81 (2.6)	0.01
β-Blocker	208 (8.3)	41 (6.1)	249 (7.9)	0.06
αβ-Blocker	47 (1.9)	10 (1.5)	57 (1.8)	0.51
Calcium channel blocker	632 (25.3)	187 (28.0)	819 (25.8)	0.15
Diuretic	78 (3.1)	23 (3.4)	101 (3.2)	0.67
Others	27 (1.1)	7 (1.0)	34 (1.1)	0.94
Smoking status [n (%)]				
Non-smoker	2054 (82.1)	474 (71.0)	2528 (79.7)	0.01
Former or current	448 (17.9)	193 (28.9)	641 (20.2)	
Alcohol consumption [n (%)]				
No	1783 (71.3)	442 (66.2)	2225 (70.2)	0.01
Yes	719 (28.7)	225 (33.7)	944 (29.8)	
Hypertension	1032 (42.7)	258 (41.2)	1317 (41.5)	0.51

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides; HbA1c, glycated hemoglobin; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

[§] Mean ± SD.

[†] HbA1c values were converted from Japan Diabetes Society (JDS) values to National Glycohemoglobin Standardization Program (NGSP) values using the following formula: HbA1c (NGSP equivalent value) (%) = 1.02 × HbA1c (JDS value) (%) + 0.25%.

4. Discussion

Diabetes has been identified as a strong independent risk factor for CHD [16]. Nevertheless, it is well known that Japan is a country that has low incidence of CHD, although the prevalence of diabetes in Japan is proportionally higher than in Western countries [17]. On the other hand, Japanese have proportionally higher HDL-C levels than Western populations [18–21], which may be associated with lower incidence of CHD. Therefore, to elaborate the relationship between lipids, especially with combination of HDL-C, and CVD in diabetes will provide additional information to establish the optimal lipid management strategy in diabetic patients.

The present subanalysis revealed differences in the ability of lipid parameters to predict cardiovascular events in patients with and without diabetes. Although a total 7832 patients were included in the main analysis of the MEGA study, the present analysis was conducted using only the data from the diet alone group, and excluding patients who started statins during follow-up to eliminate any possible confounding effects because of pleiotropic effects of the statin on CVD which were suggested previously [22].

Table 2 – Hazard ratios of all cardiovascular events according to lipid variable stratified by tertile.

	Patients without diabetes				Patients with diabetes			
	Range	No. of events (/1000 person-years)	Hazard ratio (95% CI)	P (P for all)	Range	No. of events (/1000 person-years)	Hazard ratio (95% CI)	P (P for all)
TC (mmol/L)	5.7–6.1	18/833 (4.83)		(0.18)	5.7–6.1	22/224 (22.3)		(0.79)
	6.1–6.4	23/827 (6.18)	1.35 (0.73–2.50)	0.34	6.1–6.4	17/225 (18.0)	0.83 (0.44–1.56)	0.56
	6.4–7.0	29/842 (7.65)	1.75 (0.97–3.15)	0.06	6.4–7.0	19/219 (20.1)	1.02 (0.54–1.90)	0.96
LDL-C (mmol/L)	1.1–3.9	18/834 (4.80)		(0.16)	0.2–3.8	15/222 (15.2)		(0.14)
	3.9–4.2	22/829 (5.94)	1.30 (0.69–2.43)	0.41	3.8–4.3	21/222 (22.2)	1.79 (0.91–3.51)	0.09
	4.2–5.2	30/839 (7.94)	1.76 (0.97–3.20)	0.06	4.3–5.3	22/224 (23.3)	1.89 (0.96–3.73)	0.07
HDL-C (mmol/L)	1.6–3.7	11/836 (2.91)		(0.05)	1.5–4.2	10/221 (10.2)		(0.03)
	1.3–1.6	23/843 (6.06)	1.75 (0.84–3.62)	0.13	1.2–1.5	24/226 (25.1)	2.53 (1.18–5.43)	0.02
	0.6–1.3	36/823 (9.85)	2.37 (1.17–4.82)	0.02	0.7–1.2	24/221 (25.5)	2.68 (1.25–5.77)	0.01
TGs (log transformed)	−0.8–0.1	15/834 (3.97)		(0.50)	−0.7–0.3	17/222 (17.5)		(0.70)
	0.1–0.5	22/833 (5.90)	1.13 (0.58–2.20)	0.71	0.3–0.7	21/224 (21.7)	1.33 (0.69–2.55)	0.40
	0.5–2.4	33/835 (8.88)	1.43 (0.75–2.73)	0.27	0.7–2.7	20/222 (21.3)	1.20 (0.60–2.39)	0.61
Non-HDL-C (mmol/L)	2.6–4.6	11/838 (2.91)		(0.02)	2.2–4.7	16/222 (16.3)		(0.07)
	4.6–5.0	23/829 (6.21)	1.88 (0.91–3.90)	0.09	4.7–5.1	16/224 (16.7)	1.09 (0.54–2.23)	0.81
	5.0–6.1	36/835 (9.62)	2.75 (1.37–5.53)	0.00	5.1–5.9	26/222 (27.8)	1.94 (1.02–3.71)	0.04
TC/HDL-C	1.70–3.86	11/834 (2.91)		(0.06)	1.52–4.26	11/222 (11.3)		(0.04)
	3.87–4.81	24/834 (6.39)	1.79 (0.87–3.70)	0.11	4.26–5.09	22/223 (22.9)	2.28 (1.08–4.82)	0.03
	4.81–10.93	35/834 (9.46)	2.35 (1.15–4.80)	0.02	5.10–9.23	25/223 (26.5)	2.52 (1.20–5.30)	0.01
LDL-C/HDL-C	0.62–2.45	11/834 (2.93)		(0.02)	0.29–2.70	9/222 (8.98)		(0.00)
	2.45–3.19	23/834 (6.11)	1.87 (0.90–3.88)	0.09	2.70–3.36	26/223 (27.6)	3.64 (1.68–7.86)	0.00
	3.19–8.16	36/834 (9.70)	2.65 (1.32–5.33)	0.01	3.36–6.25	23/223 (24.6)	2.98 (1.36–6.56)	0.01
TGs/HDL-C	0.16–0.74	12/834 (3.18)		(0.18)	0.19–0.90	17/222 (17.3)		(0.72)
	0.74–1.29	23/834 (6.11)	1.46 (0.72–2.97)	0.30	0.90–1.60	20/223 (20.9)	1.29 (0.67–2.50)	0.45
	1.30–9.43	35/834 (9.47)	1.91 (0.95–3.83)	0.07	1.61–19.57	21/223 (22.3)	1.26 (0.63–2.52)	0.51

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

In mild-to-moderate hypercholesterolemic patients, there were some differences in risk profile between diabetes and non-diabetes, although HDL-C, non-HDL-C, TC/HDL-C, and LDL-C/HDL-C were similarly associated with the incidence of each category of cardiovascular events. In non-diabetes patients, TGs/HDL-C were additionally identified as significant predictors. In addition, our ROC analysis suggested that predictability for CVD is not so different among those

Table 3 – Hazard ratio per one-SD increment (decrease for HDL-C): all cardiovascular events and area under the curve.

	Hazard ratio (95% CI)	χ^2	P	AUC (95% CI)
Patients without diabetes				
TC	1.02 (1.00–1.04)	3.51	0.06	0.77 (0.72–0.82)
LDL-C	1.01 (1.00–1.02)	1.78	0.18	0.77 (0.71–0.82)
HDL-C	0.97 (0.96–1.00)	5.90	0.02	0.77 (0.72–0.82)
TGs (log transformed)	1.65 (0.97–2.81)	3.41	0.06	0.77 (0.71–0.82)
Non-HDL-C	1.02 (1.01–1.04)	9.94	<0.01	0.78 (0.72–0.83)
TC/HDL-C	1.35 (1.09–1.66)	7.77	0.01	0.77 (0.72–0.82)
LDL-C/HDL-C	1.36 (1.04–1.77)	5.09	0.02	0.77 (0.72–0.82)
TGs/HDL-C	1.13 (1.04–1.23)	9.26	<0.01	0.77 (0.72–0.82)
Patients with diabetes				
TC	1.01 (0.99–1.03)	0.38	0.54	0.71 (0.65–0.78)
LDL-C	1.01 (1.00–1.02)	2.94	0.09	0.72 (0.66–0.79)
HDL-C	0.97 (0.95–0.99)	7.84	0.01	0.74 (0.68–0.81)
TGs (log transformed)	1.19 (0.72–1.96)	0.46	0.50	0.72 (0.65–0.78)
Non-HDL-C	1.02 (1.01–1.04)	7.20	0.01	0.73 (0.67–0.80)
TC/HDL-C	1.30 (1.07–1.58)	6.83	0.01	0.74 (0.68–0.80)
LDL-C/HDL-C	1.39 (1.07–1.82)	5.86	0.02	0.73 (0.67–0.80)
TGs/HDL-C	1.05 (0.99–1.11)	2.71	0.10	0.72 (0.66–0.79)

SD, standard deviation; AUC, area-under-the-curve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

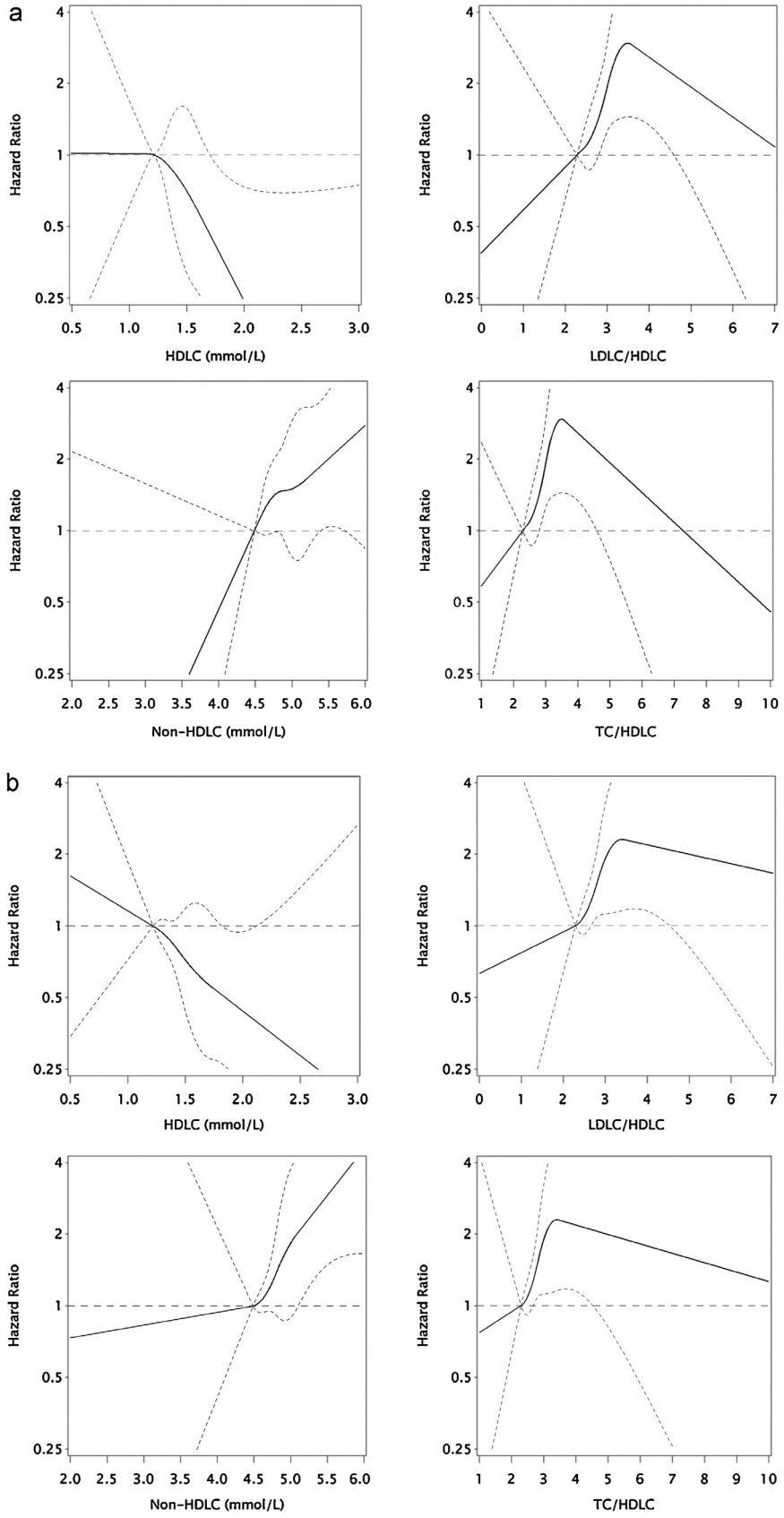

Fig. 1 – Spline curves for cardiovascular disease by lipid variable in (a) patients with diabetes and (b) patients without diabetes. Solid lines, relative risk; broken lines, 95% CIs. HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol.

parameters. In a subanalysis of the Tehran Lipid and Glucose Study [23], HRs stratified by the SD of TC, LDL-C, non-HDL-C, and TC/HDL-C were determined by the Cox proportional hazards model in patients with no history of diabetes. As in the present subanalysis, they showed that non-HDL-C and TC/HDL-C were significant predictors of cardiovascular events. Furthermore, more recent results showed that LDL-C/HDL-C and TC/HDL-C were significant predictors of CVD (evaluated by intima-media thickness) in Japanese patients with type 2 diabetes [24].

In the population in this analysis, no difference in LDL-C between patients with and without diabetes was found, probably due to the narrow range of TC for study enrollment (5.7–7.0 mmol/L). However, a difference in TGs and non-HDL-C level and incidence of CVD between diabetes and non-diabetes was observed in the present analysis. In particular, in patients with diabetes, hyperlipidemia is characterized by very low density lipoprotein cholesterol (VLDL-C), increased levels of small dense LDL-C and TGs, and decreased levels of HDL-C. Non-HDL-C includes LDL-C, intermediate-density lipoprotein cholesterol, and VLDL-C, chylomicron remnants, and lipoprotein (a), which are known risk factors for CVD as well as LDL-C [25] may enhance the ability to predict CVD. Therefore, to use non-HDL-C would be more appropriate in cardiovascular risk prediction for patients with diabetes [26–28]. The clear linear relationship between non HDL-C and CVD that was found in our spline analysis also supports the usefulness of non-HDL-C. Other advantages to using non-HDL-C to assess cardiovascular risk are the lesser effect of food intake and its ease of calculation [29,30], and these are also supported by previous studies [26–28] as well as recent guidelines [6].

Different lipid parameters may predict cardiovascular risk in patients with high and low HDL-C. A novel finding of the present analysis was the high sensitivity of HDL-C to predict cardiovascular events in patients with and without diabetes. In the MEGA study, low HDL-C (<1.04 mmol/L [40 mg/dL]) was the only lipid parameter identified as a risk factor for CHD [31]. The mean baseline HDL-C level in patients with diabetes in the present analysis was 1.41 mmol/L (54.6 mg/dL), which is higher than the baseline HDL-C of patients in similar studies done in Western countries. This difference in baseline HDL-C level of Japanese and Western patients may mean that any decrease in HDL-C is associated with a greater increase in cardiovascular risk in Japanese patients.

Hypoglycemia agents have been reported to modify lipid parameters in patients with diabetes [32]. In the MEGA study, almost 70% of the patients received one or more hypoglycemia agent. Sulfonylureas were used by 43.4% of patients, and 21.7% of patients received α-glucosidase inhibitors. Previous reports have suggested that all hypoglycemic agents are associated with decrease in TC, but different effects were observed in TGs and HDL-C with different hypoglycemic agents. α-Glucosidase inhibitors increased HDL-C and decreased TGs, while sulfonylurea decreased HDL-C and had no effect on TGs. A significant relationship was observed between each lipid parameter and the risk of CVD in patients with diabetes in relation to the lipid modifications which included the lipid modification effect caused by the hypoglycemic agents. In the present analysis, nearly 40% of the patients with and without diabetes had hypertension. The ratio of hypertensive patients was numerically higher and the average systolic blood pressure was significantly higher in patients with diabetes than those without diabetes. However, because the presence of hypertension and the type of antihypertensive medication would not affect lipid levels, it seems these do not need to be considered in the present analysis. Indeed, the blood pressure levels were similar throughout the entire study in the diet alone group and diet + pravastatin group [33].

A limitation of the present analysis is the limited number of patients with diabetes (n = 668) in the MEGA study. Our study population contained about four times as many patients without diabetes as those with diabetes. We believe that the issue of the small number of patients with diabetes had no influence on the present results, because this finding was based on the adjusted hazard ratio. Fewer cardiovascular events occurred in the MEGA study than in previous Western studies. Studies including more patients with diabetes should be performed.

Another limitation is that apolipoprotein was not measured. A recent metaanalysis of clinical studies of statins showed that the apolipoprotein (apo)-B/apo-A1 ratio is closely associated with the LDL-C/HDL-C ratio and is a better predictor of cardiovascular risk than other lipid parameters routinely used in clinical practice [34]. Furthermore, the importance of measuring the apo-B/apo-A1 ratio in addition to traditional lipid ratios to assess cardiovascular risk was shown by a subanalysis of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, which evaluated the efficacy of fenofibrate to prevent cardiovascular events in patients with type 2 diabetes. This showed the importance of measuring apo-B/apo-A1 ratio as well as traditional lipid ratios to assess cardiovascular risk [35]. However, our present results may support the findings of the metaanalysis and the FIELD study subanalysis, because the LDL-C/HDL-C ratio may reflect the apo-B/apo-A1 ratio (apo-B and apo-A1 are the primary apolipoprotein components of LDL-C and HDL-C, respectively).

This analysis included only patients with hypercholesterolemia; there was no comparison group consisting of patients with diabetes without hypercholesterolemia, which may be considered a limitation.

5. Conclusion

In summary, the presence or absence of diabetes should guide the lipid parameters the clinician uses to predict cardiovascular risk and guide lipid-modifying therapies. Non-HDL-C may be more sensitive than LDL-C in this regard. In Japanese patients with type 2 diabetes and mild-to-moderate hypercholesterolemia, non-HDL-C and the ratios of LDL-C/HDL-C and TC/HDL-C ratios may be better predictors of cardiovascular risk than traditional lipid parameters. In Japanese mild-to-moderate hypercholesterolemic patients without diabetes, LDL-C/HDL-C and TC/HDL-C best predict cardiovascular risk. Non-HDL-C is a particularly useful lipid parameter to assess cardiovascular risk, because it is easy to calculate and is less affected by food intake.

Conflict of interest statement

MEGA Study funds were provided by the Japanese Ministry of Health, Labour and Welfare for the first 2 years of the study, and thereafter the study was funded by Daiichi Sankyo Co., Ltd (Tokyo, Japan). The sponsor had no role in the design and conduct of the study. Medical editorial assistance was provided by Nature Japan KK (Macmillan Medical Communications, Tokyo, Japan) and funded by Daiichi Sankyo Co., Ltd.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.12.002.

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