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Mean and Variability of Lipid Measurements and Risk for Development of Subclinical Left Ventricular Diastolic Dysfunction

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Background: Subclinical left ventricular diastolic dysfunction (LVDD) is an emerging consequence of increased insulin resistance, and dyslipidemia is one of the few correctable risk factors of LVDD. This study evaluated the role of mean and visit-to-visit variability of lipid measurements in risk of LVDD in a healthy population.
Methods: This was a 3.7-year (interquartile range, 2.1 to 4.9) longitudinal cohort study including 2,817 adults (median age 55 years) with left ventricular ejection fraction >50% who underwent an annual or biannual health screening between January 2008 and July 2016. The mean, standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apoB), non-HDL-C, and triglycerides were obtained from three to six measurements during the 5 years preceding the first echocardiogram.
Results: Among the 2,817 patients, 560 (19.9%) developed LVDD. The mean of no component of lipid measurements was associated with risk of LVDD. CV (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.10 to 1.67), SD (HR, 1.27; 95% CI, 1.03 to 1.57), and VIM (HR, 1.26; 95% CI, 1.03 to 1.55) of LDL-C and all the variability parameters of apoB were significantly associated with development of LVDD. The association between CV-LDL and risk of LVDD did not have significant interaction with sex, increasing/decreasing trend at baseline, or use of stain and/or lipid-modifying agents.
Conclusion: The variability of LDL-C and apoB, rather than their mean, was associated with risk for LVDD.

Keywords: Apolipoproteins B; Cholesterol, LDL; Diastole; Physiology; Ventricular dysfunction, left

INTRODUCTION

It is well known that elevated low-density lipoprotein cholesterol (LDL-C) increases atherosclerotic cardiovascular risk, and studies have reported that the variability of lipid measurements is related to atherosclerotic cardiovascular risk [1-3]. In addition, in patients with advanced coronary artery disease or myocardial infarction at baseline, variability of lipid measure-

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ments such as LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and non-HDL-C are associated with major adverse cardiovascular events and/or hospitalization for heart failure [4-6].

Despite the robust evidence on the association between visit-to-visit variability in lipid measurements and adverse cardiovascular outcomes in those with established atherosclerotic cardiovascular disease (ASCVD) at baseline, the impact of lipid variability on the risk of incident heart failure is less clear, especially in those without established ASCVD at baseline. Although a few studies have reported that increased baseline level of non-HDL-C, decreased level of HDL-C, ratio of apolipoprotein B (apoB) to apolipoprotein (apoA), and variability of total cholesterol (TC) were associated with a clinical diagnosis of heart failure [7-9], it has not been determined which components of these lipid measurements best describe the risk of incident heart failure. Therefore, it is unclear how to interpret the various lipid measurements in terms of risk of heart failure, even though dyslipidemia is one of its few correctable risk factors.

Subclinical left ventricular diastolic dysfunction (LVDD), an emerging metabolic consequence of increased insulin resistance, is one of the most important structural risk factors for heart failure with preserved ejection fraction (HFpEF) [10,11]. Early detection of LVDD and control of its associated risk factors are important for preventing and slowing the progression of HFpEF. However, no longitudinal cohort study specifically examined the variability of each component in lipid measurements and risk of incident LVDD in the general population.

The purpose of this longitudinal retrospective cohort study was to evaluate whether the mean and visit-to-visit variability of each component in lipid measurements is associated independently with increased risk of LVDD and to determine the relative contribution of each component to this association using serial echocardiography in a healthy population.

METHODS

Study population

This was a longitudinal retrospective cohort study that included subjects 20 years or older who underwent comprehensive health examinations including echocardiography between January 2008 and July 2016, at the Health Promotion Center at Samsung Medical Center (SMC, Seoul, Republic of Korea). The study population consisted of employees of various organizations and companies and subjects who voluntarily took part in annual or biennial comprehensive health screening examinations at the center. Of 9,809 patients who had two or more echocardiograms, those with fewer than three lipid measurements during the 5 years preceding the first echocardiogram and those who had missing data were excluded from the analyses (n=5,801). We also excluded subjects with indicators of early diastolic dysfunction that met the criteria of the primary endpoint, moderate to severe heart valve disease, and left ventricular ejection fraction (LVEF) less than 50% on the first echocardiogram (n=852). Subjects with a clinical diagnosis of heart failure, a history of ischemic heart disease, cardiomyopathy, valvulopathy, and chronic atrial fibrillation at baseline were excluded (n=144). We also excluded subjects with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 at the time of the first echocardiography (n=38), as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and those with any history of cancer (n=157). A total of 2,817 subjects was included in the final study population (Fig. 1). The study protocol was approved by the Institutional Review Board (IRB) of SMC (no. 2020-06-076), and the informed consent requirement was waived by the IRB because the study information was de-identified. The protocol for the study was in accordance with the guidelines of the Declaration of Helsinki.

Clinical variables, biochemical measurements, and definitions

Medical history, smoking status, alcohol status, exercise status, medication, anthropometric data, and laboratory data were collected during routine health examinations. Subjects completed self-administered questionnaires that covered their prior medical history, prescribed medications, smoking, and exercise history. Smoking status was categorized as never, past smoker, or current smoker. Exercise status was assessed as none or regular exercise (≥3 days/week). Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Blood pressure was measured using a mercury sphygmomanometer after at least 5 minutes of rest in a sitting position. Blood samples were collected after a 12-hour overnight fast. Plasma TC, TG, HDL-C, and LDL-C were measured using a Modular D2400 analyzer (Roche Diagnostics, Basel, Switzerland). ApoB level was measured by the immunoturbidimetric method using a Roche/Hitachi Modular P analyzer (Roche Diagnostics). Non-HDL-C was calculated by subtracting HDL-C from TC. Fasting plasma glucose (FPG) and insulin levels were

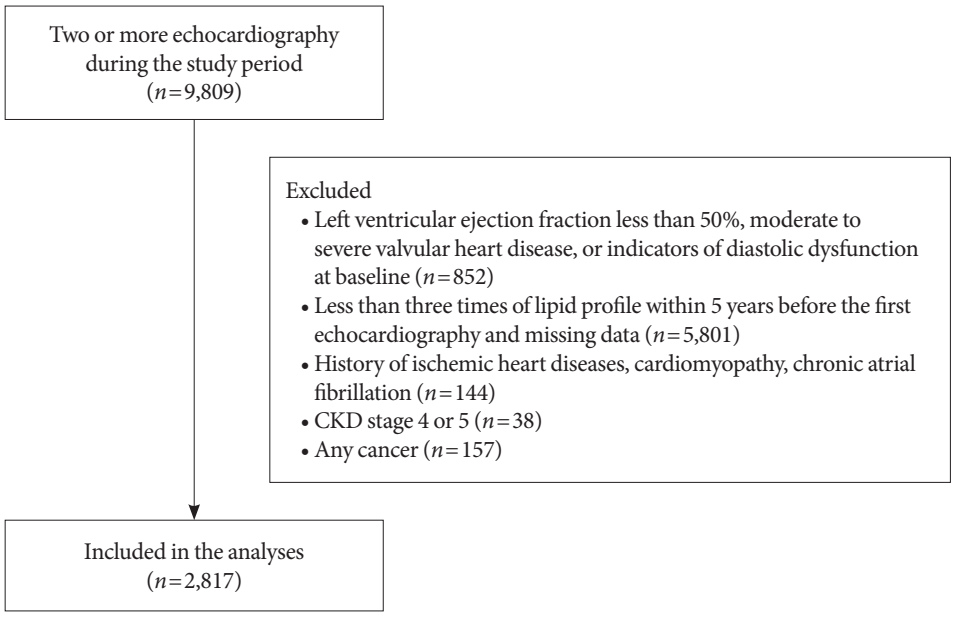

Fig. 1. Patient selection. CKD, chronic kidney disease.

measured using the hexokinase method with Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany) and an immunoradiometric assay (DIAsource Co., Louvain-la-Neuve, Belgium), respectively. The N-terminal fragment of pro-brain natriuretic peptide was determined using an Elecsys proBNP reagent kit and an Elecsys 2010 chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA). Glycosylated hemoglobin (HbA1c) level was determined by high-performance liquid chromatography on an HLC-723G8 automated glycohemoglobin analyzer (TOSOH, Yokkaichi, Japan). Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication [12]. Diabetes mellitus (DM) was defined as FPG of 126 mg/dL or greater, HbA1c of 6.5% or greater, or current use of diabetes medication [13].

Definition and measurement of lipid variability

The mean, standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV) of each lipid parameter were calculated from three to six consecutive measurements of LDL-C, TC, HDL-C, TG, and non-HDL-C during the 5 years preceding the first echocardiogram (three measurements, $n=1,183$; four measurements, $n=679$; five measurements, $n=752$; six measurements, $n=203$). Only the measurements during the 5 years preceding the first echocardiogram, but not those during the follow-up period, were included in the calculation of variability parameters. CV was defined as SD divided by the mean ×100, as described previously [14,15], VIM was calculated as SD divided by mean to the power χ ($SD/mean^{\chi}$), where χ is derived from curve fitting via nonlinear regression analysis as implemented in the PROC NLIN procedure of the SAS package (SAS Institute Inc., Cary, NC, USA). ARV was the average of the absolute differences between consecutive values and was calculated using the following formula, where N denotes the number of measurements of the lipid profile [1].

$$ARV = \frac{1}{N-1}\sum_{K=1}^{N-1}\left|Value_{K+1} - Value_{K}\right|$$

For 1,061 of 2,817 subjects in whom three or more apoB measurements during the 5 years preceding the first echocardiogram were available (three measurements, $n=582$; four measurements, $n=147$; five measurements, $n=224$; six measurements, $n=108$), the mean, SD, CV, VIM, and ARV of apoB level were calculated in the same manner as in other lipid measurements. Only the measurements during the 5 years preceding the first echocardiogram, but not during the follow-up period, were included in the calculation of variability parameters.

Echocardiographic data, definition of LVDD, and E/e' change

Standard two-dimensional transthoracic echocardiography and Doppler echocardiography using multiple windows were

conducted as part of a health promotion program using commercially available equipment (Vivid7, GE Medical Systems, Horten, Norway; and SC2000, Siemens Medical Solution, Mountain View, CA, USA). Image acquisition and measurements were performed according to the 2003 American Society of Echocardiography (ASE) guidelines and 2009 European Association of Echocardiography/ASE guidelines [16]. Echocardiographic parameters of LVEF, left atrial volume index (LAVI), left ventricular mass index (LVMI), transmitral early diastolic velocity (E), and mitral annulus early diastolic velocity (e') were assessed. LVEF was evaluated using biplane Simpson's rule by way of a manual tracing of digital images.

LVDD was defined as preserved LVEF (≥50%) and one or more of the following findings on screening echocardiography: (1) E/e' >15; (2) 8<E/e'≤15 and e' <7 cm/sec; or (3) 8<E/e'≤15 and left atrial enlargement (LAVI >34 mL/m^2) and left ventricular hypertrophy (LVMI >115 g/m^2 in males, >95 g/m^2 in females) [16,17]. The rate of change in E/e' over time was determined by subtracting baseline E/e' from E/e' measured at the last follow-up, divided by duration of follow-up in months.

Statistical analysis

Subjects were classified into three groups according to tertile of the mean and variability of each lipid parameter. The Kaplan-Meier analysis and log-rank test were used to compare survival between the three groups. The hazard ratio (HR) and 95% confidence interval (CI) for LVDD were calculated by multivariable Cox proportional hazard regression analysis. In multivariable analyses, a non-adjusted model (model 1); a model adjusted for age and sex (model 2); a model further adjusted for the presence of hypertension and DM, BMI, and mean of lipid measurements (model 3); and a model further adjusted for E/e' and HbA1c (model 4) were constructed. To determine the relative contributions of CV-HDL-C, CV-LDL-C, and CV-TG to the significant association in the fully adjusted models, we sequentially added the tertile of mean TG, CV-TG, and mean LDL-C and CV-LDL-C to a multivariable analysis model including mean HDL-C, CV-HDL-C, and other covariates.

Two separate subgroup analyses were conducted according to (1) statin therapy and (2) statin therapy and/or use of any lipid-modifying agents as identified by self-reported questionnaires. Statin therapy was confirmed by searching the institutional clinical data warehouse (CDW). However, as searching the institutional CDW is reliable for prescriptions inside the institution but can miss statin therapy outside the institution, we supplemented the analysis by including questionnaire-confirmed cases using any lipid-modifying agents. Statin therapy and use of lipid-modifying agent were defined as one or more prescriptions or positive responses to the questionnaire during the same period as used in the determination of the variability of lipid measurements prior to the first echocardiograph.

Subgroup analyses were conducted according to sex and the trend of each lipid parameter before study entry. An increasing or decreasing trend before study entry was determined by beta-estimate of the regression line generated from the consecutive measurements included in the calculation of variability parameters at baseline [18]. An increasing or decreasing trend was defined as slope ≥0 and <0, respectively.

All data are presented as mean±SD for continuous variables or as number with percentage for categorical ones. All *P* values were two-tailed, and *P* values <0.05 were considered statistically significant. All statistical analyses were performed using STATA version 16.0 (StataCorp., College Station, TX, USA) and SAS version 9.4.

RESULTS

Baseline characteristics and study population

Of the 2,817 participants included in this study, 2,336 were male and 481 were female. The mean age was 55 years (interquartile range, 50 to 60). Among these participants, 371 (13.2%) had diabetes at baseline. Clinical and echocardiographic characteristics of the study population are summarized in Table 1. The cut-off values for tertiles of mean, SD, and CV of lipid measurements are summarized in Supplementary Table 1.

Mean and variability of lipid measurements and risk of LVDD

Five hundred and sixty subjects (19.9%) developed LVDD during a median follow-up of 3.7 years (interquartile range, 2.1 to 4.9), comprising 459 of 2,336 male subjects and 101 of 481 female subjects (19.6% and 21.0%, respectively). Among the 560 patients who developed LVDD, three had regional wall motion abnormality consistent with ischemic heart disease in echocardiogram, and the remaining 557 patients had no sign of ischemic heart disease in echocardiogram.

Among the mean parameters, only the tertile of TG level was associated with incident LVDD in the unadjusted model and the age- and sex-adjusted model (Table 2, Fig. 2). However, the association between tertile of mean TG level and risk of LVDD

Table 1. Baseline clinical and echocardiographic characteristics of total subjects

Characteristic	Did not develop LV diastolic dysfunction (*n*=2,257)	Developed LV diastolic dysfunction (*n*=560)	*P* value
Age, yr	54.16±7.15	58.55±7.88	<0.001
Male sex	1877 (83.2)	459 (82.0)	0.500
Current smoker	497 (24.9) (*n*=1,995)	106 (23.1) (*n*=458)	0.713
Regular exercise	793 (56.7) (*n*=1,398)	203 (60.8) (*n*=334)	0.147
Hypertension	691 (30.6)	268 (47.9)	<0.001
DM	259 (11.5)	112 (21.8)	<0.001
FPG, mg/mL	97.41±16.63	102.37±17.89	<0.001
HbA1c, %	5.63±0.55	5.78±0.58	<0.001
NT-proBNP, pg/mL	29.68±28.47 (*n*=1,327)	34.90±35.08 (*n*=296)	0.116
hs-CRP, mg/dL	0.12±0.32 (*n*=2,240)	0.13±0.30 (*n*=556)	0.025
HOMA-IR	1.86±1.23 (*n*=1,597)	2.20±1.50 (*n*=397)	<0.001
BMI, kg/m^2	23.83±2.63 (*n*=2,255)	24.84±2.64 (*n*=559)	<0.001
LDL-C, mg/dL			
Mean	122.41±23.66	122.99±24.52	0.611
SD	12.67±8.30	14.09±9.34	0.002
CV	10.56±7.10	11.75±8.15	0.002
HDL-C, mg/dL			
Mean	53.86±13.03	52.41±11.44	0.063
SD	4.49±2.51	4.55±2.49	0.446
CV	8.37±4.18	8.75±4.35	0.078
TG, mg/dL			
Mean	128.78±63.05	138.29±64.73	<0.001
SD	37.67±24.27	30.79±25.71	0.004
CV	20.52±10.32	21.15±10.44	0.197
LVEF, %	64.68±5.21	65.98±5.22	<0.001
E/e'	7.09±1.62	8.05±1.78	<0.001
E, cm/sec	61.75±14.09	62.31±13.47	0.343
e', cm/sec	8.84±1.62	7.81±1.04	<0.001
LAVI, mL/m^2	25.42±5.11	25.84±5.09	0.087
LVMI, g/m^2	81.13±14.00	84.40±13.44	<0.001

Values are presented as mean±standard deviation or number (%).
LV, left ventricular; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; CV, coefficient of variation; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LVEF, left ventricular ejection fraction; E/e', ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LAVI, left atrial volume index; LVMI, left ventricular mass index.

was not significant in the fully adjusted model (Table 2). An incrementally higher risk of LVDD was observed with higher CV tertile for LDL-C and TC compared with the lowest tertile group in the unadjusted model (*P* for trend; CV-LDL-C 0.002, CV-HDL-C 0.108, CV-TC 0.009, CV-TG 0.083) (Fig. 2). In the fully-adjusted model, higher CV-LDL-C, CV-HDL-C, and CV-TG were associated with elevated risk for LVDD (for tertile 3 vs. tertile 1: CV-LDL-C [HR, 1.35; 95% CI, 1.10 to 1.67], CV-HDL-C [HR, 1.24; 95% CI, 1.01 to 1.52], CV-TG [HR, 1.25; 95% CI, 1.01 to 1.54]) (Table 2). Tertile 2 but not tertile 3 of CV-TC was associated with LVDD (for tertile 2 vs. tertile 1; HR, 1.28; 95% CI, 1.03 to 1.58) (Table 2).

Because the highest tertiles of CV-TG, CV-HDL-C, and CV-LDL-C were associated with risk of LVDD, we conducted an additional multivariable Cox regression analysis including CV-TG, CV-HDL-C, and CV-LDL-C as covariates. When tertile of mean TG, CV-TG, and mean LDL-C and CV-LDL-C were added sequentially to the fully adjusted model including tertiles of mean HDL-C and CV-HDL-C along with other covariates, the association between CV-LDL-C and LVDD remained significant (for tertile 3 vs. tertile 1 [HR, 1.30, 95% CI, 1.05 to 1.62]; for tertile 2 vs. tertile 1 [HR, 1.26; 95% CI, 1.01 to 1.56]) (Supplementary Table 2).

Although the highest tertiles of SD and VIM of all lipid measurements were associated with LVDD in unadjusted multivariate Cox analysis, only SD-LDL-C and VIM-LDL-C were associated with LVDD in fully adjusted Cox analysis (Table 2, Supplementary Table 3). ARV of LDL-C and of TC were associated with LVDD in unadjusted multivariate analysis. However, its significant association was lost in fully adjusted multivariate analysis (Supplementary Table 3).

Subgroup analyses

Two separate analyses were conducted according to use of statin therapy and to use of statin and/or any dyslipidemia medications. In these analyses, there was no significant interaction with statin therapy in the association between mean LDL-C, SD-LDL-C, and CV-LDL-C and risk of LVDD. Significant associations between SD-LDL-C and CV-LDL-C and risk of LVDD were observed in the group without statin therapy (Table 3). A similar trend was observed when the group was defined based on use of statin and/or any dyslipidemia medications, with no significant interaction with use of statin and/or any dyslipidemia medications in the associations between mean LDL-C, SD-LDL-C, and CV-LDL-C and risk of LVDD (Table 3).

Table 2. Results of multivariable Cox analysis in all subjects

Variable	Model 1			Model 2			Model 3			Model 4		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
LDL-C												
Mean	1 (reference)	0.84 (0.68–1.04)	0.94 (0.77–1.14)	1 (reference)	0.91 (0.74–1.12)	0.99 (0.81–1.20)	1 (reference)	0.93 (0.76–1.15)	1.01 (0.82–1.23)	1 (reference)	0.99 (0.80–1.22)	1.05 (0.86–1.28)
SD[a]	1 (reference)	1.19 (0.96–1.47)	1.61 (1.32–1.98)	1 (reference)	1.17 (0.95–1.45)	1.41 (1.15–1.73)	1 (reference)	1.19 (0.97–1.48)	1.25 (1.01–1.54)	1 (reference)	1.25 (1.01–1–54)	1.27 (1.03–1.57)
CV[a]	1 (reference)	1.24 (1.00–1.54)	1.68 (1.37–2.06)	1 (reference)	1.22 (0.98–1.51)	1.47 (1.20–1.80)	1 (reference)	1.23 (1.00–1.53)	1.33 (1.08–1.64)	1 (reference)	1.29 (1.04–1.60)	1.35 (1.10–1.67)
HDL-C												
Mean	1 (reference)	0.94 (0.77–1.15)	0.87 (0.71–1.07)	1 (reference)	0.88 (0.72–1.08)	0.75 (0.61–0.93)	1 (reference)	0.95 (0.78–1.16)	0.98 (0.79–1.22)	1 (reference)	0.97 (0.79–1.18)	0.98 (0.79–1.23)
SD[a]	1 (reference)	1.1 (0.89–1.35)	1.31 (1.07–1.60)	1 (reference)	1.08 (0.88–1.32)	1.16 (0.94–1.42)	1 (reference)	1.11 (0.90–1.36)	1.21 (0.98–1.50)	1 (reference)	1.16 (0.95–1.43)	1.24 (1.00–1.54)
CV[a]	1 (reference)	1.27 (1.04–1.57)	1.4 (1.14–1.72)	1 (reference)	1.22 (0.99–1.50)	1.33 (1.08–1.63)	1 (reference)	1.16 (0.94–1.42)	1.21 (0.98–1.48)	1 (reference)	1.17 (0.96–1.45)	1.24 (1.01–1.52)
TC												
Mean	1 (reference)	0.94 (0.77–1.16)	1.04 (0.85–1.27)	1 (reference)	1.03 (0.84–1.27)	1.08 (0.89–1.33)	1 (reference)	1.09 (0.88–1.34)	1.14 (0.92–1.40)	1 (reference)	1.11 (0.90–1.37)	1.15 (0.94–1.42)
SD[a]	1 (reference)	1.33 (1.08–1.64)	1.51 (1.23–1.86)	1 (reference)	1.24 (1.00–1.53)	1.27 (1.04–1.57)	1 (reference)	1.22 (0.99–1.51)	1.13 (0.91–1.40)	1 (reference)	1.24 (1.00–1.53)	1.15 (0.93–1.43)
CV[a]	1 (reference)	1.27 (1.03–1.56)	1.56 (1.27–1.91)	1 (reference)	1.2 (0.97–1.49)	1.31 (1.07–1.61)	1 (reference)	1.24 (1.00–1.53)	1.18 (0.96–1.46)	1 (reference)	1.28 (1.03–1.58)	1.22 (0.99–1.51)
TG												
Mean	1 (reference)	1.2 (0.97–1.49)	1.38 (1.12–1.70)	1 (reference)	1.23 (0.99–1.52)	1.5 (1.22–1.85)	1 (reference)	1.09 (0.88–1.35)	1.17 (0.94–1.45)	1 (reference)	1.08 (0.87–1.35)	1.15 (0.92–1.42)
SD[a]	1 (reference)	1.17 (0.95–1.44)	1.35 (1.10–1.65)	1 (reference)	1.09 (0.88–1.34)	1.4 (1.14–1.71)	1 (reference)	0.97 (0.78–1.21)	1.14 (0.89–1.45)	1 (reference)	0.97 (0.78–1.20)	1.13 (0.89–1.45)
CV[a]	1 (reference)	1.34 (1.09–1.64)	1.39 (1.13–1.72)	1 (reference)	1.26 (1.02–1.55)	1.29 (1.05–1.59)	1 (reference)	1.22 (0.99–1.50)	1.26 (1.03–1.60)	1 (reference)	1.22 (0.99–1.50)	1.25 (1.01–1.54)

Values are presented as adjusted hazard ratio (95% confidence interval). Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for covariates in Model 2 plus diabetes, hypertension, and body mass index; Model 4, adjusted for covariates in Model 3 plus baseline E/e' and glycosylated hemoglobin.
LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; CV, coefficient of variation; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
[a]Further adjusted for the mean of each lipid parameter in Models 3 and 4.

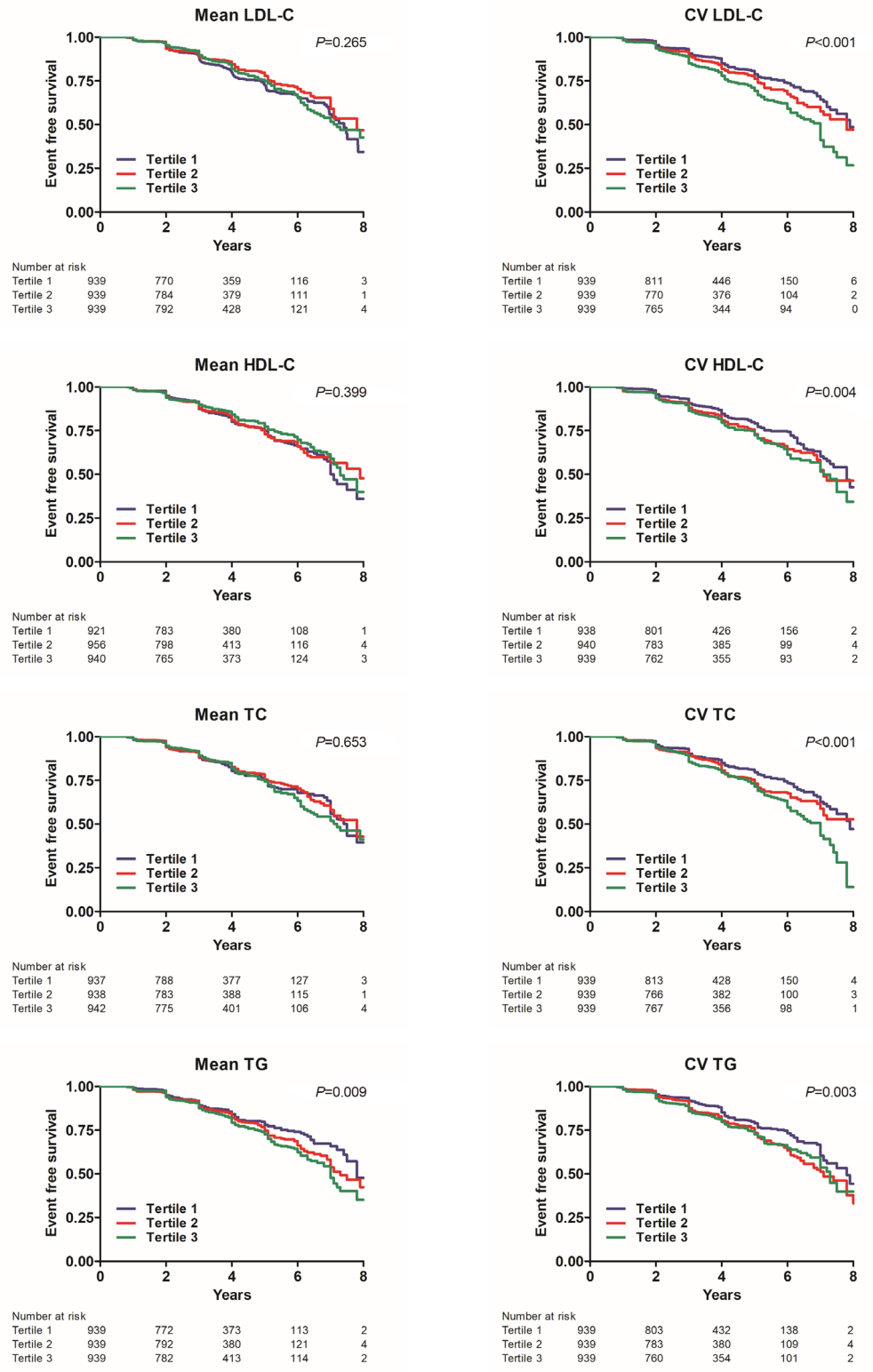

Fig. 2. Kaplan-Meier estimates of left ventricular diastolic dysfunction by tertiles of mean and coefficient of variation (CV) of lipid measurements. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 3. Subgroup analysis according to statin and any lipid-modifying agents before echocardiogram

Variable	HR (95% CI)			*P* for interaction
	Tertile 1	Tertile 2	Tertile 3	
With statin therapy (*n*=375)				
Mean LDL-C	1 (reference)	1.22 (0.76–1.95)	1.39 (0.86–2.24)	
SD-LDL-C[a]	1 (reference)	0.76 (0.49–1.19)	0.57 (0.35–0.93)	
CV-LDL-C[a]	1 (reference)	0.85 (0.54–1.33)	0.61 (0.37–1.01)	
Without statin therapy (*n*=2,442)				
Mean LDL-C	1 (reference)	0.94 (0.75–1.20)	1.12 (0.81–1.28)	0.604[b]
SD-LDL-C[a]	1 (reference)	1.21 (0.95–1.54)	1.38 (1.10–1.74)	0.086[b]
CV-LDL-C[a]	1 (reference)	1.26 (1.00–1.61)	1.36 (1.09–1.72)	0.079[b]
With statin and/or any lipid modifying agents (*n*=531)				
Mean LDL-C	1 (reference)	1.17 (0.78–1.74)	1.30 (0.86–1.94)	
SD-LDL-C[a]	1 (reference)	0.90 (0.59–1.12)	0.72 (0.48–1.08)	
CV-LDL-C[a]	1 (reference)	0.84 (0.57–1.23)	0.72 (0.48–1.08)	
Without statin and/or any lipid modifying agents (*n*=2,286)				
Mean LDL-C	1 (reference)	1.01 (0.79–1.30)	1.05 (0.83–1.34)	0.984[c]
SD-LDL-C[a]	1 (reference)	1.21 (0.94–1.55)	1.31 (1.03–1.67)	0.160[c]
CV-LDL-C[a]	1 (reference)	1.26 (0.98–1.62)	1.27 (1.00–1.62)	0.199[c]

Adjusted for age, sex, hypertension, diabetes, body mass index, baseline E/e', glycosylated hemoglobin.
HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; CV, coefficient of variation.
[a]Further adjusted for mean of LDL-C, [b]Versus those with statin therapy before echocardiogram, [c]Versus those with statin or any dyslipidemia therapy before echocardiogram.

When we explored if there was significant interaction with increasing and decreasing trend of each lipid parameter at baseline in the association between variability of each lipid parameter and risk of LVDD, there was a significant interaction with increasing and decreasing trend only in the association between CV-HDL-C and risk of LVDD, but not in the association between CV-LDL-C or CV-TC and risk of LVDD (Supplementary Table 4). The association between CV-HDL-C and risk of LVDD was significant only in the subgroup with increasing trend of HDL-C at baseline (Supplementary Table 4).

When stratified by sex, the association between highest tertile of CV-LDL-C and LVDD was significant in both male and female subjects (for males, *P*=0.048; for females, *P*=0.047) (Supplementary Table 5). The association between the highest tertile of CV-TC and LVDD was significant only in females. However, there was no significant interaction with sex in the association between each lipid parameter and risk of LVDD.

Mean and variability of apoB, non-HDL-C, and risk of LVDD

Mean apoB was not associated with development of LVDD. However, SD-apoB, CV-apoB, VIM-apoB, and ARV-apoB were all significantly associated with LVDD even in the fully adjusted multivariable model (Supplementary Table 6). Both mean and variability of non-HDL-C were not associated with development of LVDD in the fully adjusted multivariable model (Supplementary Table 6).

Rate of change in E/e' over time

The rate of change in E/e' during the follow-up period according to tertile of mean, SD, and CV of lipid measurements is presented in Supplementary Table 7. An incrementally higher risk of LVDD was observed with higher tertiles of SD-LDL-C (*P* for trend=0.045) and CV-LDL-C (*P* for trend=0.036).

DISCUSSION

In this study, there was no significant association between the mean of any component of lipid measurements and LVDD. However, the CV of LDL-C, HDL-C, and TG was significantly associated with LVDD. CV-LDL-C remained significantly associated with LVDD when CV-LDL-C tertile was included in

the multivariable model with established risk factors and the tertiles for CV-TG and CV-HDL-C. There was no significant interaction with sex, increasing/decreasing trend before study entry, or use of statin and/or lipid-modifying agents. Only VIM-LDL-C, but not VIM-TG or VIM-HDL-C, was associated with risk of LVDD. In addition, all the variability parameters of apoB including VIM and ARV, but not those of non-HDL-C, were associated with risk of LVDD.

The lack of a significant association between the mean of any component of lipid measurements and risk of LVDD was in contrast to previous studies. Several cross-sectional studies showed that low HDL-C and high TG, TC, or LDL-C levels are risk factors for diastolic dysfunction [19-21]. Two longitudinal cohort studies showed associations of baseline HDL-C, baseline TG, and longitudinal increases of TG with progression of diastolic dysfunction [22,23]. The discrepancy could be explained by differences in the study population, because the previous studies were conducted in a population with an increased risk of developing LVDD that included postmenopausal women, those with hypertension, and those with preexisting echocardiographic abnormalities that indicated early stages of LVDD.

The association between variability of LDL-C and apoB and risk for LVDD is in line with several recent studies suggesting the association between metabolic variability and cardiovascular outcomes [1,9,24], although the mechanism for this association cannot be explained fully in the current study. Because it has been suggested that non-adherence to statin increases LDL-C variability, which might explain the association between increased LDL-C variability and cardiovascular risk [25], we conducted subgroup analysis according to use of statin and/or any lipid-modifying agents. In this study, however, significant association between SD-LDL-C and CV-LDL-C and risk of LVDD was observed in the subgroup without statin therapy, in which non-adherence to statin cannot explain the significant association. This indicates that mechanisms other than non-adherence to statin are important for the association. Indeed, the significant association between metabolic variability and cardiovascular outcome observed in several recent studies was not confined to those who use statins [1,9]. One of the alternative explanations is that LDL-C variability causes plaque volume expansion by suppressing lipid efflux from atheromas, and this process causes subclinical ischemia and subclinical cardiac damage, which is an important mechanism of heart failure development [9,26,27]. Endothelial dysfunction is considered to play a crucial role in the pathogenesis of LVDD and HFpEF [28,29]. Higher LDL-C variability was associated with endothelial dysfunction [25,30], which alters paracrine signaling between endothelial cells and cardiomyocytes to affect signaling of left ventricular remodeling and dysfunction. This can result in HFpEF especially in the presence of hyperinsulinemia [31].

To further determine whether the association between variability of LDL-C and risk of LVDD is attributable to the variability in number or size of LDL-C particles, we examined the association between the mean and variability of apoB lipoprotein level and risk of LVDD. In this study, all the variability parameters of apoB were associated with LVDD. In contrast, neither mean nor variability of non-HDL-C was associated with risk of LVDD. The results indicated that the variability in number of apoB lipoprotein particles was the primary determinant of the increased risk.

Although we adjusted for sex in the multivariable Cox analyses, we additionally stratified the analyses by sex to explore interaction between the observed association and sex. The highest tertile for CV-LDL-C was associated with increased risk for LVDD in both male and female subjects, while CV-TC was associated only in female subjects. However, there was no significant interaction with sex for the association between any lipid parameter and LVDD.

The strength of the current study is a longitudinal analysis of serial echocardiography, which allowed analysis of the rate of change in echocardiographic parameters. We showed that the impact of LDL-C variability on progression of LVDD was measurable within several years of observation, which could be important information for designing future intervention studies. Several limitations of the current study should be considered. First, the possibility of selection bias is inevitable due to the retrospective study design. Second, although the subgroup analysis stratified by sex did not show significant interaction (Supplementary Table 5), the participants of this study were mostly employed men, suggesting that the results cannot be generalized to other populations. Third, the possibility of use of statin or lipid-modifying agents during the follow-up period could not be considered. Fourth, the duration of follow-up was not long enough to evaluate changes in LVDD parameters. Therefore, the lack of association between the mean of each lipid parameter and incident LVDD does not preclude the possibility of a long-term association. Finally, the echocardiographic parameters did not include measurements of strain.

In conclusion, the variability rather than the mean of LDL-C and apoB was a risk factor for the development of LVDD. Such associations could be measurable within several years of disease onset, without a significant interaction with sex, increasing/decreasing trend before study entry, or use of statin and/or lipid-modifying agents. In terms of risk stratification for incident LVDD, lipid parameters should be interpreted with a focus on variability, primarily that of LDL-C and apoB.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0080.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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