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Visit-to-visit lipid variability on long-term major adverse cardiovascular events: a prospective multicentre cohort from the CORE-Thailand registry

Chutithep Teekaput[1,2,4], Kitti Thiankhaw[1,2,4], Wanwarang Wongcharoen[3], Narawudt Prasertwitayakij[3], Siriluck Gunaparn[3] & Arintaya Phrommintikul[3]✉

Lipid variability (LV) has been studied and proposed as a potential predictor for cardiovascular disease (CVD), and increased LV may contribute to adverse clinical outcomes. This study aimed to investigate the association of various LV parameters with the risk of long-term major adverse cardiovascular events (MACE) among the Thai population. The study used data from the CORE-Thailand Registry, a prospective multicentre study of adults with high cardiovascular risk or established CVD. The primary outcome was 4-point MACE, including non-fatal myocardial infarction, non-fatal stroke, heart failure hospitalisation, and all-cause mortality. LV was defined as visit-to-visit variability in individual and combined lipid parameters using the coefficient of variation (CV), and patients were stratified into four groups according to CV quartiles. The hazard ratio (HR) and 95% confidence interval (CI), adjusted for potential confounders, were calculated using the Cox proportional hazards model. In a total of 9,390 patients, 6,041 patients with data of intra-individual LV were included. After adjusting covariates in the Cox proportional hazards model, higher LV was independently associated with an increased risk of 4-point MACE (HR for quartiles 2, 3, and 4 of the CV of total cholesterol, compared to first quartile, were 3.63 (95% CI 3.20–4.06, $P < 0.001$), 6.85 (95% CI 6.23–7.47, $P < 0.001$), and 8.91 (95% CI 8.18–9.64, $P < 0.001$), respectively). The present study demonstrated that higher visit-to-visit LV, particularly in the higher quartiles, was independently associated with MACE, MI, and all-cause mortality in the Thai population at high cardiovascular risk or established atherosclerotic CVD, indicating that LV might be useful as a potential risk indicator.

Keywords Lipid variability, Total cholesterol, Coefficient of variation, Major adverse cardiovascular events

Cardiovascular diseases (CVD) are among the most clinically significant public health problems associated with increased morbidity and mortality worldwide[1]. Clinical management in order to either primary or secondary prevention is an ongoing challenge for healthcare providers to deal with all potentially modifiable CVD risk factors[2,3]. Dyslipidemias has been recognized as associated with CVD and major adverse cardiovascular events (MACE) across all general and specific populations, including young adults, elderly, and diabetes[4,5]. Previous studies have demonstrated a causal relationship between dyslipidemias and various adverse clinical outcomes, including stroke and myocardial infarction (MI)[6,7]. In addition, according to the global stroke fact sheet of the World Stroke Organisation (WSO), a high level of low-density lipoprotein cholesterol (LDL-C) is a contributing behavioural factor to stroke risk at 10% (5.9–16.7)[8] .IDEAL and SPARCL trials established the benefit of high-intensity statin therapy as secondary prevention in those individuals with a definite history of recent or prior MI and stroke, respectively[9,10]. This clinical importance and evidence-based medicine result in strong

[1]Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [2]The Northern Neuroscience Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [3]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110, Inthawaroros Road, Sriphum, Chiang Mai, Chiang Mai 50200, Thailand. [4]Chutithep Teekaput and Kitti Thiankhaw contributed equally. ✉email: arintaya.p@cmu.ac.th

recommendations from major clinical practice guidelines on the treatment of abnormal blood cholesterol to reduce atherosclerotic cardiovascular risk[11,12].

Lipid variability (LV), variation in individual lipid parameters between visits, is an emerging lipid parameter as a novel biomarker for CVD and MACE prediction[13–15]. These biomarkers comprised of LV of individual lipid parameters, including standard deviation (SD) and coefficient of variation (CV) of each lipid aberration, and LV of combined lipid parameters, namely SD and CV of non-high-density lipoprotein cholesterol (non-HDL-C) and the ratio of total cholesterol (TC) or triglyceride (TG) to HDL-C (TC/HDL-C or TG/HDL-C, respectively)[16]. Conceivably, lipid variability can cause alterations in the atherosclerotic plaque's structure and composition, which may also consequently lead to plaque instability and rupture and, finally, clinical events related to plaque. As a result, lipid variability may be significantly connected with the likelihood of developing atherosclerotic cardiovascular diseases (ASCVD)[17]. As growing scientific evidence, several lipid variability parameters have been heightened as an increased incidence of cardiovascular events in short- and long-term follow-up in the population at risk or diabetic patients[15,18]. However, longitudinal studies to establish the diagnostic role of various LV parameters, especially for a long-period follow-up in Asian populations, are limited. Therefore, the present study aims to investigate the association of visit-to-visit lipid variability and long-term major adverse cardiovascular events in a large prospective cohort of Asian patients with high cardiovascular risk.

Methods

Study design and population

This study used the database from the Cohort Of patients with high Risk for cardiovascular Events (CORE-Thailand) registry, a prospective, multicentre, observational, longitudinal study conducted between April 2011 and March 2014 in twenty-five centres across all regions of Thailand, ranging from secondary-care to university-affiliated hospitals[19]. Initial assessment suggested no significant difference between cohorts from different centres. The details of the CORE-Thailand registry have been published previously[19].

Patients aged 45 years or over with high cardiovascular risk or established cardiovascular diseases were initially enrolled. Participants with high cardiovascular risk were defined by the presence of at least three atherosclerotic risks, including type 1 or 2 diabetes or impaired fasting glucose (IFG), hypertension, chronic kidney disease (CKD), dyslipidemias (TC > 200, smoking, aged 55 years or older in men and 65 years or older in women or having a family history of premature atherosclerosis. Established ASCVD included one of the following: stroke or transient ischemic attack (TIA) hospitalisation, coronary artery disease (CAD), or peripheral arterial diseases (PAD). Individuals diagnosed with a recent stroke or acute MI within the past three months, suffering from other serious medical illnesses (non-cardiovascular diseases) with a life expectancy of less than three years, currently enrolled in other clinical trials with concealment, or difficulty in obtaining follow-up appointments were excluded from the study.

Data collection at baseline and follow-up assessments

Baseline characteristics and medical history with medication used were obtained at enrollment. These demographics included age, sex, waist circumference, body mass index (BMI), smoking status, family history of CVD, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and ankle-brachial index (ABI). Laboratory variables were fasting and random blood glucose, glycated haemoglobin (HbA1C), creatinine, and estimated glomerular filtration rate (eGFR). Participants were monitored for at least five years since the enrollment for a total of seven visits, at enrollment, every six months in the first year, and then every twelve-month intervals (6, 12, 24, 36, 48, and 60 months). The assessment of risk factor control was conducted on patients who possessed accessible data in accordance with prevailing guidelines[20–22]. Dyslipidemia was defined as TC > 200 mg/dL or low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL or TG > 150 mg/dL or HDL-C < 40 mg/dL or current treatment with lipid-lowering agents.

Lipid variability definition and measurement

In the CORE-Thailand Registry, fasting plasma lipid profiles were collected and measured at baseline, 6 and 12 months, and yearly thereafter until five years. The maximal, mean, median, and minimal values of individual lipid parameters were calculated. Different lipid variability indices, including CV and SD for individual and combined lipid parameters, were computed using values measured during the follow-up period. To investigate the association between LV and clinical outcomes, the study population was stratified into quartiles (Q1–Q4) based on the CV of TC. This categorization allowed for a clear comparison of outcomes across groups with varying levels of LV and facilitated primary outcome analysis as well as Cox proportional hazards regression to assess the cumulative hazard of all-cause mortality and myocardial infarction (MI). The use of quartiles aligns with established methodologies in prior research, ensuring consistency and comparability with previously published findings[23–25].

Study outcomes

Cardiovascular events and mortality were prospectively documented throughout five years after the participants' enrolment. Data was locally gathered using a standardised case record form and forwarded to the data management team. Prior to data analysis, the data management team conducted quality inspections of the data, and the annual site monitoring was performed randomly. The primary outcomes of the study were long-term major adverse cardiovascular events, which is the composite of all-cause mortality, non-fatal MI, non-fatal stroke, and non-fatal heart failure hospitalisation (4-point MACE) during five years of the study period.

Statistical analysis

Descriptive statistics were displayed as numbers with percentages for categorical variables and mean with SD or median with interquartile range (IQR) for continuous variables depending on data distribution, which were determined by the Shapiro-Wilk statistical test. Comparisons of demographic data and clinical characteristics between groups were performed using the Pearson χ^2 test, Fisher's exact test, Student's *t*-test, Mann-Whitney U (Wilcoxon rank sum) test, analysis of variance (ANOVA) or the Kruskal-Wallis test as appropriate.

After statistical testing for proportional hazard assumption using goodness-of-fit by Schoenfeld's residual, Cox proportional hazards models were used to ascertain the association of variability in lipid profiles with the risk of 4-point MACE. A time-dependent model was conducted for the non-linear associations. Hazard ratio (HR) and 95% confidence interval (CI) were presented in an unadjusted HR from univariable analysis, and variables with *P* value < 0.10 from the univariable analysis were tested in multivariable analysis using Cox proportional hazards regression to calculate adjusted HR (aHR) and 95% CI. The Cox proportional hazards regression curves for the cumulative hazard were used to express the risk of developing all-cause mortality and MI among participants stratified across lipid variability quartiles. The differences in the study endpoints were compared using the log-rank test. Two-sided *P* values < 0.05 were set as statistical significance. We applied the Bonferroni correction for the non-linear associations with six comparisons to adjust for multiple comparisons. The adjusted significance level remains at 0.008, ensuring the overall Type I error rate is controlled. All statistical analyses were performed using licensed Stata statistical software version 16.1 (Stata Statistical Software: Release 16.1, Stata Corporation, College Station, TX, 2019).

Ethical approval and consent to participate

The Joint Research Ethics Committee and the Ministry of Public Health, Thailand, approved the study protocol (Certificate Number COA-JREC 004/2011). The study was registered at thaiclinicaltrials.org, identification number TCTR20130520001. Informed consent was obtained from all participants before the commencement of the study, and the data were anonymised or maintained with confidentiality. All methods in the study were conducted ethically in accordance with the Declaration of Helsinki.

Results

Baseline characteristics

The study included 9,390 participants, of whom 6,041 possessed follow-up lipid profiles. Table 1 summarises the characteristics of participants classified by quartiles (Q) of CV of TC. The mean age of the participants was 65.3 ± 9.5 years. The mean values and SD of TC in Q1–Q4 were 165.2 ± 31.9, 164.3 ± 30.3, 168.5 ± 36.9, and 181.5 ± 53.4 mg/dL, respectively. Compared to lower quartiles, patients in the higher quartiles of the CV of TC have exhibited a significantly higher prevalence of comorbidities such as hyperlipidaemia, diabetes, CKD, CAD, and PAD, which corresponded with high baseline TC, fasting plasma glucose, and eGFR. Statin was prescribed in 88.8% of patients and significantly higher in the Q2 group. There was no statistical difference regarding age, sex, BMI, smoking status, family history of CVD, or other comorbidities, including hypertension, congestive heart failure (CHF), and prior stroke or TIA among the participants.

During a median follow-up of 54 months, a total of 1,364 individuals (14.5%) developed MACE. Compared to the individuals without MACE, those with MACE were characterised by older age and a higher prevalence of comorbidities, including hypertension, CHF, CAD, CKD, PAD, and prior stroke or TIA. The individuals with MACE demonstrated a lower statin prescription than those without MACE (83.6% vs. 88.5%, $P < 0.001$).

Association of lipid variability with MACE

Table 2 demonstrates the association between MACE and quartiles of CV for individual and combined lipid parameters. When analyzing stratified data from an unadjusted model, we observed a significant association between the higher quartiles of lipid parameters and MACE. Compared to the lowest quartile (Q1), the highest quartile (Q4) of individual lipid parameters demonstrated a significant association with MACE. The HR and 95% CI for TC, TG, HDL-C, and LDL-C were 9.35 (8.72–9.98), 8.20 (7.62–8.77), 9.77 (9.10–10.44), and 8.98 (8.38–9.58), respectively, all *P* values < 0.001. Similarly, the combined lipid parameters also showed a significant association with MACE: HR 9.42 (95% CI 8.77–10.08) for TC/HDL-C, 9.21 (8.57–9.86) for TG/HDL-C, and 8.87 (8.25–9.49) for non-HDL-C, all *P* values < 0.001. After adjusting for age, sex, diabetes, hypertension, baseline TC, CKD, history of atherosclerotic cardiovascular disease (stroke, CAD, and PAD), high risk for atherosclerotic CVD, smoking, use of antiplatelet, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and statin (model 1), the highest quartiles independently correlated with increased MACE compared to reference Q1. The adjusted HR (aHR) and 95% CI for TC, TG, HDL-C, and LDL-C were 8.91 (8.18–9.64), 7.93 (7.26–8.60), 9.03 (8.28–9.78), and 8.56 (7.86–9.26), respectively, all *P* values < 0.001. The tendency was also seen across combined lipid parameters: aHR 8.90 (95% CI 8.16–9.64) for TC/HDL-C, 8.71 (7.98–9.43) for TG/HDL-C, and 8.62 (7.90–9.34) for non-HDL-C, all *P* values < 0.001. Additionally, the *P* for trends across quartiles was significant ($P < 0.001$) for all parameters, indicating a consistent and significant increase in risk associated with higher quartiles of lipid variability. The trends remained consistent in model 2 after further adjustment for mean TC. Interestingly, after including the interaction term between time and lipid parameters, the coefficients for these interaction terms were all negative, indicating that the aHRs associated with MACE decrease over time (Table 2). Fig. S1 demonstrates the distribution of the outcomes across the quartiles of LV.

Association of lipid variability and all-cause mortality and myocardial infarction

During the five-year follow-up, there were 973 deaths (10.4%). When focusing on CV, the highest quartiles, compared to the lowest quartiles, carried a higher risk of mortality. The aHR and 95% CI for TC, TG, HDL-C, and LDL-C were 10.27 (9.12–11.42), 8.51 (7.48–9.53), 9.91 (8.74–11.08), and 9.84 (8.74–10.95), respectively, all

Characteristic	Total cohort ($n=6,041$)	Quartile of CV of total cholesterol				*P* value
		Q1 ($n=1,511$)	Q2 ($n=1,510$)	Q3 ($n=1,510$)	Q4 ($n=1,510$)	
Demographics						
Age, mean (SD), year	65.3 (9.5)	65.5 (9.4)	65.3 (9.6)	65.1 (9.7)	65.4 (9.5)	0.69
Male , No. (%)	5,144 (54.8)	801 (53.0)	788 (52.2)	834 (55.2)	794 (52.6)	0.34
BMI, mean (SD), km/m^2	25.6 (4.2)	25.5 (4.2)	25.6 (4.3)	25.6 (4.1)	25.7 (4.3)	0.66
Smoking, No. (%)	497 (5.3)	63 (4.2)	53 (3.5)	81 (5.4)	72 (4.8)	0.08
Family history of CVD, No. (%)	736 (7.8)	121 (8.0)	107 (7.1)	99 (6.6)	122 (8.1)	0.31
Medical history, No. (%)						
Hypertension	5,737 (95.0)	1,437 (95.1)	1,433 (94.9)	1,432 (94.8)	1,435 (95.0)	0.99
Diabetes	3,706 (61.4)	841 (55.7)	944 (62.5)	953 (63.1)	968 (64.1)	<0.001
Hyperlipidaemia	5,450 (90.2)	1,335 (88.4)	1,393 (92.3)	1,359 (90.0)	1,363 (90.3)	0.004
Congestive heart failure	458 (7.6)	109 (7.2)	103 (6.8)	108 (7.2)	138 (9.1)	0.07
Coronary artery disease	2,411 (39.9)	635 (42.0)	563 (37.3)	575 (38.1)	638 (42.3)	0.005
Chronic kidney disease	1,156 (19.1)	262 (17.3)	266 (17.6)	271 (18.0)	357 (23.6)	<0.001
Peripheral arterial disease	91 (1.5)	17 (1.1)	15 (1.0)	25 (1.7)	34 (2.3)	0.02
Prior stroke or TIA	540 (8.9)	133 (8.8)	115 (7.6)	145 (9.6)	147 (9.7)	0.15
Medication, No. (%)						
Beta-blocker	3,091 (51.2)	797 (52.8)	756 (50.1)	744 (49.3)	794 (52.6)	0.13
ACEi/ARB	4,007 (66.3)	998 (66.1)	1,016 (67.3)	1,007 (66.7)	986 (65.3)	0.69
Statin	5,363 (88.8)	1,340 (88.7)	1,373 (90.9)	1,333 (88.3)	1,317 (87.2)	0.01
Laboratory results, mean (SD)						
Total cholesterol, mg/dL	169.9 (39.9)	165.2 (31.9)	164.3 (30.4)	168.5 (36.9)	181.5 (53.4)	<0.001
Fasting blood glucose, mg/dL	125.9 (44.9)	121.5 (38.0)	125.0 (46.1)	126.6 (42.6)	130.2 (51.2)	<0.001
eGFR, mL/min/1.73m^2	69.3 (25.0)	70.8 (24.6)	71.3 (24.1)	69.5 (24.4)	65.5 (26.5)	<0.001

Table 1. Patient characteristics by quartiles of coefficient of variation of total cholesterol. **Abbreviations**: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker, ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, coefficient of variation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Q, quartile; SD, standard deviation; TIA, transient ischaemic attack.

P values < 0.001. The aHR of combined lipid parameters also demonstrated significant association: aHR 9.65 (95% CI 8.51–10.79) for TC/HDL-C, 9.76 (8.61–10.92) for TG/HDL-C, and 9.15 (8.05–10.24) for non-HDL-C, all *P* values < 0.001. All parameters had significant P for trends across quartiles ($P<0.001$). A negative time-dependent interaction was also observed for each lipid parameter ($P<0.001$) (Fig. 1A-G and Supplementary Table S1).

On the other hand, 168 cases (1.8%) developed non-fatal MI. The incidence of MI was higher in the highest CV quartile for TC, HDL-C, LDL-C, TC/HDL-C, and non-HDL-C levels compared to the lower quartiles (2.9% vs. 1.6%, $P=0.003$; 2.8% vs. 1.6%, $P=0.01$; 2.9% vs. 1.5%, *P* 0.001; 2.7% vs. 1.6%, $P=0.01$; and 2.6% vs. 1.7%, $P=0.03$, respectively). After adjusting for confounding factors in multivariable regression analysis, the highest CV quartile of all lipid parameters was associated with an increased risk of MI: aHR 3.60 (95% CI 2.94–4.25) for TC, 2.69 (2.05–3.33) for TG, 3.06 (2.43–3.69) for HDL-C, 3.01 (2.40–3.61) for LDL-C, 3.33 (2.66–4.00) for TC/HDL-C, 2.89 (2.26–3.51) for TG/HDL-C, and 3.26 (2.60–3.93) for non-HDL-C, all *P* values < 0.001. The trend analysis across quartiles showed significant results for all parameters ($P<0.001$). Furthermore, each lipid parameter exhibited a significant negative interaction with time ($P<0.001$) (Fig. 2A-G and Supplementary Table S1).

Association of lipid variability with MACE in early follow-up

The association between lipid variability and the risk of MACE at 6 and 12 months showed a stepwise increase in risk across quartiles. In the TC CV group, participants in Q4 had a 19.42-fold increased risk at 6 months (95% CI: 12.32–26.52, $P<0.001$) and a 10.18-fold increased risk at 12 months (95% CI: 8.14–12.22, $p<0.001$) compared to Q1. The trend was similarly observed in other lipid parameters. Significant time interactions indicated that the impact of lipid variability diminished slightly over time. The trend analysis ($P<0.001$) confirmed a strong association between increasing lipid variability and higher cardiovascular risk across all lipid measures. (Supplementary Table S2)

Association of lipid variability and MACE in patients with and without prior ASCVD

The association between lipid variability and the risk of MACE was significantly stronger across all lipid measures in higher quartiles compared to the reference group (Q1), with a more pronounced effect observed in patients without ASCVD. In the TC CV group, Q4 was associated with a 7.78-fold increased risk in ASCVD patients and an 11.84-fold increased risk in those without ASCVD ($P<0.001$ for both). Similar trends were observed across

Parameters	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI) Model 1	*P* value	Adjusted HR (95% CI) Model 2	*P* value
TC CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.75 (3.39–4.12)	< 0.001	3.63 (3.20–4.06)	< 0.001	3.75 (3.38–4.12)	< 0.001
Q3	7.07 (6.53–7.60)	< 0.001	6.85 (6.23–7.47)	< 0.001	7.00 (6.47–7.54)	< 0.001
Q4	9.35 (8.72–9.98)	< 0.001	8.91 (8.18–9.64)	< 0.001	9.10 (8.47–9.74)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001
TG CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.21 (2.87–3.56)	< 0.001	3.21 (2.81–3.62)	< 0.001	3.25 (2.90–3.60)	< 0.001
Q3	6.35 (5.86–6.84)	< 0.001	6.26 (5.69–6.83)	< 0.001	6.33 (5.84–6.82)	< 0.001
Q4	8.20 (7.62–8.77)	< 0.001	7.93 (7.26–8.60)	< 0.001	8.08 (7.50–8.65)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.06)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001
HDL-C CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.76 (3.38–4.15)	< 0.001	3.47 (3.04–3.91)	< 0.001	3.71 (3.33–4.09)	< 0.001
Q3	7.30 (6.74–7.86)	< 0.001	6.74 (6.11–7.38)	< 0.001	7.16 (6.60–7.71)	< 0.001
Q4	9.77 (9.10–10.44)	< 0.001	9.03 (8.28–9.78)	< 0.001	9.47 (8.80–10.13)	< 0.001
Time interaction	−0.08 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001
LDL-C CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.54 (3.19–3.89)	< 0.001	3.49 (3.08–3.91)	< 0.001	3.64 (3.29–4.00)	< 0.001
Q3	6.84 (6.33–7.35)	< 0.001	6.69 (6.09–7.29)	< 0.001	6.90 (6.38–7.42)	< 0.001
Q4	8.98 (8.38–9.58)	< 0.001	8.56 (7.86–9.26)	< 0.001	8.86 (8.25–9.47)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001
TC/HDL-C CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.75 (3.36–4.13)	< 0.001	3.53 (3.09–3.97)	< 0.001	3.69 (3.31–4.07)	< 0.001
Q3	7.21 (6.66–7.77)	< 0.001	6.86 (6.23–7.48)	< 0.001	7.08 (6.53–7.63)	< 0.001
Q4	9.42 (8.77–10.08)	< 0.001	8.90 (8.16–9.64)	< 0.001	9.12 (8.47–9.77)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	0.006	-	0.002	-	0.002
TG/HDL-C CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	3.77 (3.40–4.15)	< 0.001	3.75 (3.38–4.12)	< 0.001	3.76 (3.38–4.13)	< 0.001
Q3	7.03 (6.49–7.58)	< 0.001	6.94 (6.40–7.49)	< 0.001	6.95 (6.41–7.50)	< 0.001
Q4	9.21 (8.57–9.86)	< 0.001	8.97 (8.33–9.61)	< 0.001	8.97 (8.33–9.61)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.06)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001
Non-HDL-C CV						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Continued						

Parameters	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI) Model 1	*P* value	Adjusted HR (95% CI) Model 2	*P* value
Q2	3.77 (3.41, 4.14)	< 0.001	3.74 (3.38, 4.11)	< 0.001	3.75 (3.38, 4.12)	< 0.001
Q3	6.91 (6.38, 7.44)	< 0.001	6.81 (6.28, 7.35)	< 0.001	6.83 (6.30, 7.36)	< 0.001
Q4	8.87 (8.25, 9.49)	< 0.001	8.64 (8.02, 9.27)	< 0.001	8.69 (8.06, 9.31)	< 0.001
Time interaction	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001	−0.07 (−0.08, −0.07)	< 0.001
P for trend	-	< 0.001	-	< 0.001	-	< 0.001

Table 2. Crude and adjusted hazard ratios for Major Adverse Cardiovascular Events Using Cox Proportional Hazards Models with Time-Dependent covariates. **Abbreviations**: CI, confidence interval; CV, coefficient of variation; HR, hazard ratio; HDL-C; high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quartile; TC, total cholesterol; TG, triglyceride. **Adjusted models: Model 1**: age, sex, diabetes, hypertension, baseline total cholesterol, chronic kidney disease, history of atherosclerotic cardiovascular disease (stroke, coronary artery disease, and peripheral arterial disease), high risk for atherosclerotic cardiovascular disease, smoking, use of antiplatelet, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and statin. **Model 2**: age, sex, diabetes, hypertension, average cholesterol level, chronic kidney disease, history of atherosclerotic cardiovascular disease (stroke, coronary artery disease, and peripheral arterial disease), high risk for atherosclerotic cardiovascular disease, smoking, use of antiplatelet, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and statin. *P* for trend was calculated across quartiles using the multivariable Cox regression model. The significant level was 0.05. Note: The *P* values were adjusted to the threshold for interpreting *P* values using the Bonferroni correction. The Cox proportional hazards model was fitted with time-dependent covariates. Lipid parameters, including TC, TG, HDL-C, LDL-C, TC/HDL-C ratio, TG/HDL-C ratio, and non-HDL-C, were modeled as time-dependent variables to capture changes over time. The time interaction term indicates how the hazard ratios for these variables change over the follow-up period. All other covariates (e.g., age, sex, baseline cardiovascular risk factors) were treated as time-independent.

other lipid measures. Time interaction terms indicated that the impact of lipid variability diminished slightly over time. The trend analysis ($P < 0.001$) further confirmed a strong, dose-dependent relationship between lipid variability and cardiovascular risk, with individuals without ASCVD showing greater vulnerability to lipid fluctuations, likely due to less aggressive lipid management compared to those with established ASCVD. (Supplementary Table S3)

Association of lipid variability and MACE stratified by baseline total cholesterol

Supplementary Table S4 presents the aHRs for lipid variability across quartiles of baseline TC in relation to major adverse cardiovascular events. For total cholesterol variability (TC CV), there was no statistically significant increase in risk across quartiles, with Q4 showing an HR of 2.29 (95% CI: 0.42–12.61, $P = 0.34$) compared to the reference group (Q1). In contrast, for TC/HDL-C variability, participants in Q4 had a significant 3.55-fold increased risk (95% CI: 1.54–8.20, $P = 0.003$), and for TG/HDL-C variability, Q4 was associated with a 1.89-fold increased risk (95% CI: 1.09–3.29, $P = 0.02$). Notably, for non-HDL-C variability, Q4 also showed a marginally significant increase in risk (aHR = 2.50, 95% CI: 1.01–6.15, $P = 0.05$). Other lipid variability measures, including TG CV and LDL-C CV, did not show statistically significant associations across quartiles. (Supplementary Table S4)

Sensitivity analysis

The sensitivity analysis outcomes for the imputed data are displayed in Supplementary Table S5. These results illustrate the link between visit-to-visit lipid variability, assessed through SD, and the occurrence of long-term MACE. Following adjustments for confounding factors, it was observed that all LV parameters were individually associated with a heightened risk of 4-point MACE.

Discussion

This study included 6,041 patients with documented lipid variability profiles from the CORE-Thailand Registry, which prospectively recruited participants with high cardiovascular risks or established ASCVD from 25 centres across Thailand, reflecting real-world data and varying levels of healthcare. The findings from the primary analysis of this study demonstrated that visit-to-visit lipid variability using the coefficient of variation (CV) of individuals (TC, TG, HDL-C, and LDL-C) and combined lipid parameters (TC/HDL-C, TG/HDL-C, and non-HDL-C) was independently associated with an increased risk of long-term major adverse cardiovascular events among the Thai population after adjusting for confounding variables. In addition, patients with a higher CV, particularly in the highest quartile (Q4) of all lipid parameters, showed an increased risk for all-cause mortality and the incidence of MI compared to those in the lower quartiles. Our findings were consistent with previous cohort studies, which established the association between lipid variability and the risk of mortality, myocardial infarction, stroke, and atherosclerotic progression[23,24]. The amplified effect of lipid variability in our study may be attributed to the higher rate of statin use and the inclusion of a high-risk population. Notably, patients without ASCVD showed a greater impact of lipid variability on MACE, likely due to fewer receiving statins compared

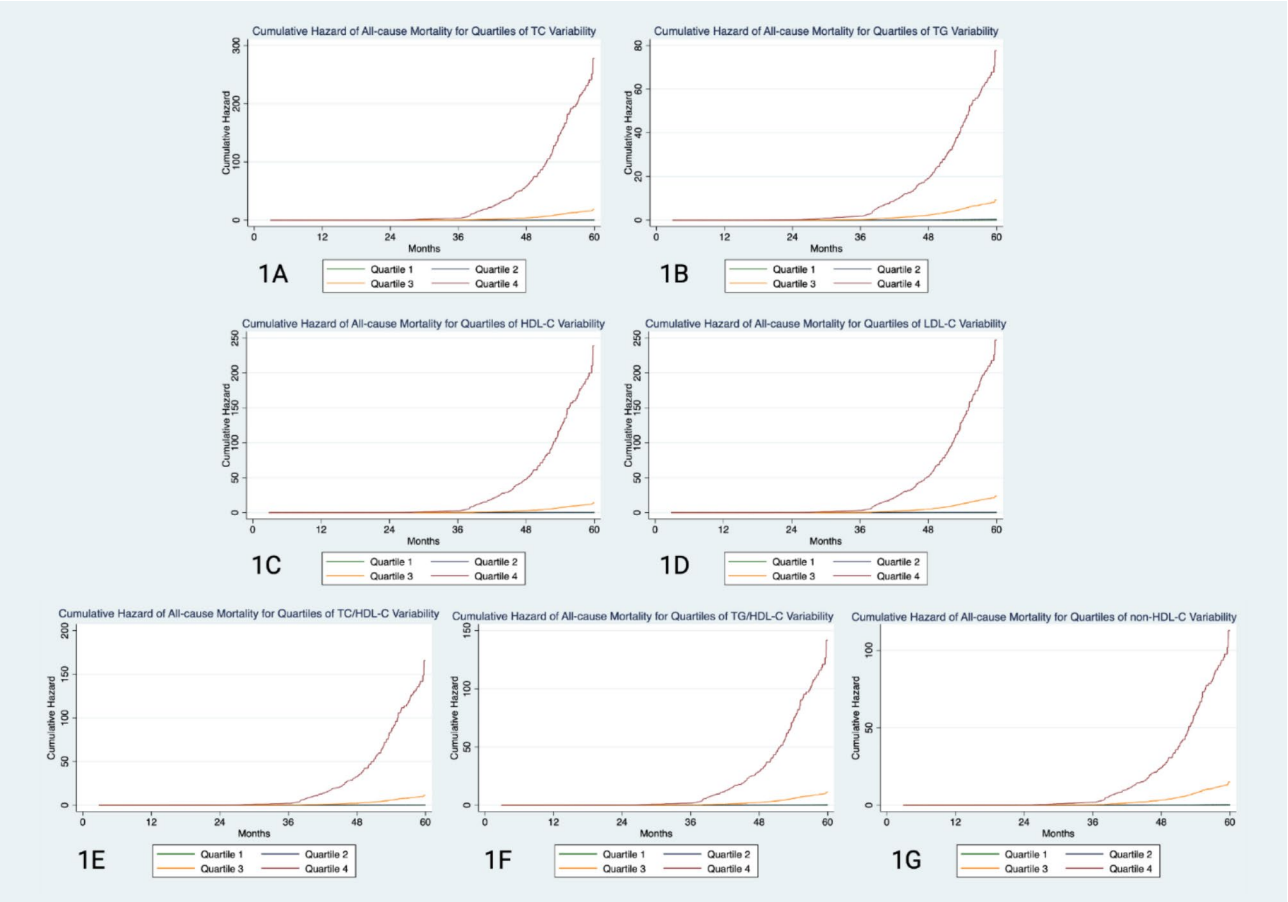

Fig. 1. Cox proportional hazards regression curves for the cumulative hazard of all-cause mortality stratified by quartiles of coefficient of variation of TC (**A**), TG (**B**), HDL-C (**C**), LDL-C (**D**), TC/HDL-C (**E**), TG/HDL-C (**F**) and non-HDL-C (**G**). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, total triglyceride.

to those with ASCVD (83.8% vs. 91.5%, $P<0.001$). In non-ASCVD patients, higher variability may reflect less controlled lipid levels, fewer preventive therapies, or unrecognized cardiovascular risk, leading to a greater increase in MACE risk[26]. Additionally, the early phase of follow-up saw increased MACE risk, potentially due to treatment adjustments contributing to higher lipid variability[27].

A large population-based study in the Korean population without a history of MI or stroke who were follow-up for 8.3 years showed a linear correlation between TC variability, as measured by CV, and all-cause mortality, MI, and stroke when comparing the highest to the lowest quartiles with an approximate risk of 1.3-fold, 1.1-fold, and 1.1-fold, respectively[23]. The findings suggest that a high visit-to-visit cholesterol variability might be an independent predictor of MACE in the general population without established ASCVD. A study by E Boey et al. in patients presenting with ST-segment elevation myocardial infarction (STEMI) found that compared to the non-MACE group, patients in the MACE group had more significant visit-to-visit variability in LDL-C levels, using corrected variation independent of the mean (cVIM) in 5-year follow-up. After controlling for confounding factors, it was observed that for every 0.01 cVIM increase in LDL-C and HDL-C variability, the incidence of major adverse cardiovascular events increased by 3.4% and 6.8% correspondingly[28] . The study results provided evidence supporting the correlation between visit-to-visit LDL-C and HDL-C variability and the occurrence of long-term MACE in individuals who were known to have ASCVD. A systematic review and meta-analysis of 11 articles using various matrics of lipid variability, including CV, SD, VIM, or average real variability (ARV), of individual lipid parameters (TC, HDL-C, LDL-C, and TG) illustrated that people in the highest quartile of TC, HDL-C, and LDL-C had an increased risk of all-cause mortality and CVDs, whilst the association between TG variability and the risk of cardiovascular diseases and all-cause mortality remains uncertain when considering various metrics[16].

Focus on a particular outcome, our findings demonstrated considerable effects of intra-individual variability in TC, TG, LDL-C, HDL-C, and other combined lipid parameters on myocardial infarction outcome and all-cause death. A study of acute coronary syndrome (ACS) patients whose morphologies of the culprit lesion were determined by optical coherence tomography (OCT) demonstrated that ACS patients with plaque rupture exhibited a notably higher intra-individual variability of LDL-C using cVIM compared to the group referred to as non-plaque rupture ACS, whilst having similar average LDL-C levels. Moreover, they also found that

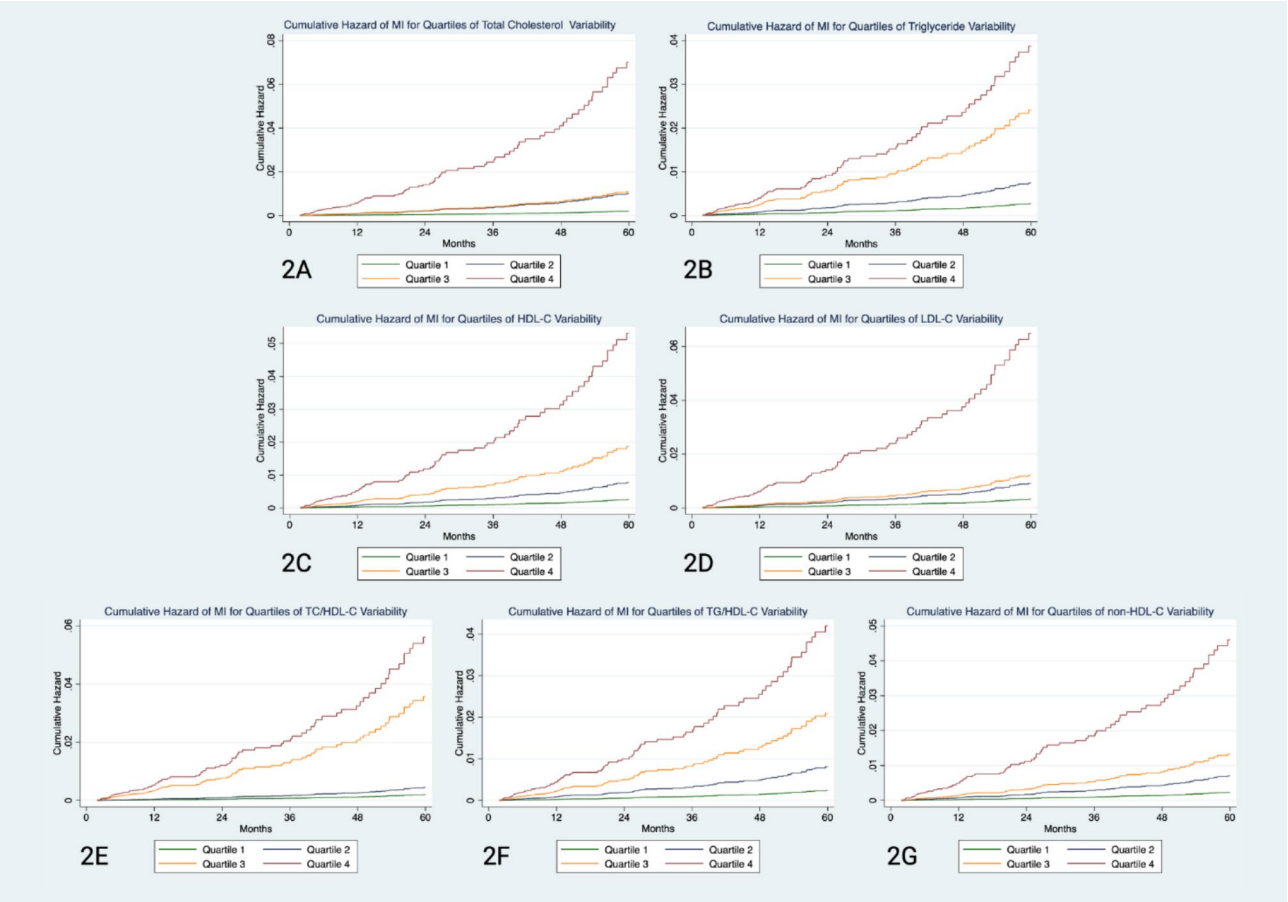

Fig. 2. Cox proportional hazards regression curves for the cumulative hazard of incidence of myocardial infarction stratified by quartiles of coefficient of variation of TC (**A**), TG (**B**), HDL-C (**C**), LDL-C (**D**), TC/HDL-C (**E**), TG/HDL-C (**F**) and non-HDL-C (**G**). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TG, total triglyceride.

higher cVIM of LDL-C was an independent risk factor of plaque rupture and might elucidate the underlying mechanism of the association of blood lipids variability with cardiovascular disease[17]. These might lead to the prognostic significance of elevated LV, especially LDL-C and HDL-C, on all-cause mortality for the community population and those with high cardiovascular risk[18,25].

Various hypotheses have been postulated pertaining to the underlying mechanism through which blood lipid variability contributes to the development and progression of cardiovascular disease[29]. A combination of nonatherosclerotic mechanisms and atheromatous lesion formation due to lipid variability might explain the underlying pathogenesis. In patients with established CAD, abrupt withdrawal of simvastatin therapy results in a rebound effect, characterised by a substantial increase in serum levels of TC and LDL-C, as well as a notable reduction in the expression of endothelial nitric oxide synthase (eNOS) mRNA[30]. This endothelial dysfunction-related finding was associated with poorer outcomes in patients with ACS and proved a causal relationship between cardiovascular diseases and statins as endothelium-dependent effects[31,32].

The formation of atheromatous lesions and consequent plaque instability secondary to fluctuation or intermittent hypercholesterolemia is a promising explanation for the association with cardiovascular outcomes. Atherogenic lipoprotein variability, measured using SD of LDL-C, HDL-C, non-HDL-C, and TC/HDL-C, in CAD patients was significantly associated with progression in percent atheroma volume (ΔPAV), finding that suggested decreased HDL efflux capacity as a consequent of increased LDL-C variability[24]. Clinical outcomes were also correlated with intra-individual cholesterol variability and confirmed by a study of acute discontinuation of statin therapy in patients following non-STEMI in which patients whose statin was stopped in the first 24 h of hospitalisation are associated with hospital death[33]. Recent research has demonstrated that the reduction of cholesterol levels has the potential to inhibit cell-mediated immunity. Conversely, an increase in cholesterol levels can potentially enhance innate immunity, leading to increased activation of macrophages and subsequent destabilization of plaque[34,35].

However, some contradictory findings regarding prognostic values of lipid variability still remained, especially in the general population. Masrouri S. et al. studied the association between mean lipid levels or lipid variability and the risk of CVD in middle-aged adults and found a significant correlation between the average lipid levels during a six-year follow-up and an elevated risk of developing CVD. However, no such association was

observed with lipid variability measurements through SD, CV, ARV, and VIM of individual and combined lipid parameters[15]. Although the general population exhibited average increases in risks of MACE that ranged from 6 to 11% in relation to LDL-C variability, the plausibility for the use as a risk predictor in a healthy population needs further investigation, and average lipide levels might be an optional measurement method[23,36]. Apart from the studied population, differences in dietary or culinary habits across other countries might underline the effects of LV on MACE or cardiovascular outcomes. In Thailand and most other Asian countries, high-salt and carbohydrate diets are the main dietary intake, but lipid-rich consumption of products is considered a central cuisine in most Western countries[37,38]. A systematic analysis including 266 country-specific nutrition surveys demonstrated the trend of consumption of saturated fat, dietary cholesterol, and trans fat at a global level that remained unchanged from 1990 to 2010[39]. Culinary habits, therefore, like unhealthy diets, combining lipid-rich and high-salt food, could influence the cardiovascular outcomes of our study.

The study possessed several notable advantages and strengths. Firstly, we enrolled a very large number of participants from various regions and levels of care to ensure a comprehensive representation of the Thai population or others who encounter similar health challenges. Additionally, the study had an extended observation period of at least five years of follow-up, allowing for a thorough examination of the variables under investigation and ensuring the accuracy of LV assessment because it has been recognised that a precise evaluation of individuals LV requires multiple measurements at specific intervals[40]. Significant findings obtained from the present study concerning the association between LV and MACE point toward its application as a potential therapeutic target for primary and secondary prevention in populations with high cardiovascular risk or established CVD, respectively. However, we acknowledge some limitations to our study. First, the generalizability of our study findings to individuals with CVD and PAD may be limited due to the small sample size of these patient categories (1.5%). Second, different laboratory investigations were conducted at various research centres. Serum lipid levels were not assessed using a validated centralised laboratory. Finally, despite including various healthcare levels, the study did not include primary care services. The knowledge gap regarding the practical use of LV in primary care settings remains unclear and needs further investigation.

Conclusions

In patients with high cardiovascular risk or established atherosclerotic cardiovascular diseases, visit-to-visit lipid variability, utilising the coefficient of variation of the individual or combined lipid parameters (TC, TG, HDL-C, LDL-C, a ratio of TC or TG to HDL-C, and non-HDL-C) in the higher quartiles were significantly associated with long-term major adverse cardiovascular events, the incidence of myocardial infarction and all-cause mortality compared to the lower quartiles, suggesting that LV might be a potential surrogate marker for risk of cardiovascular events. Our findings heightened the significance of maintaining consistent lipid levels as another therapeutic goal for eligible patients apart from achieving individual lipid targets.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Author contributions

C.T. and K.T. contributed equally to this work. C.T. and K.T.: conceptualisation, data curation, formal analysis, investigation, methodology, visualisation, and writing – original draft. S.G.: data curation, funding acquisition, project administration, and resources. W.W., N.P. and A.P.: conceptualization, data curation, funding acquisition, methodology, project administration, supervision, and writing – review & editing. All authors read and approved the manuscript and met the criteria for authorship.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to A.P.