Original Article

Visit-to-visit variability of metabolic parameters and progression of atherosclerosis in computed tomography: follow up of an asymptomatic cohort

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Background: We aimed to examine whether intra-individual variability in traditional risk factors affects the progression of atherosclerosis on subsequent coronary computed tomography angiography (CCTA).

Methods: We conducted a retrospective cohort study using asymptomatic health examination cohort data from Haeundae Paik Hospital in Korea collected between 2010–2020. A total of 387 adults met the inclusion criteria of having at least two CCTAs without specific symptoms with an interval of more than one year and having completed three or more health examinations. Visit-to-visit variability was evaluated using the average real variability (ARV) of body mass index, waist circumference, systolic and diastolic blood pressure, and plasma glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol. Progression of coronary artery atherosclerosis was defined as worsening of coronary artery stenosis from baseline to final CCTA. ARV values for various metabolic parameters were stratified into quartiles, and hazard ratios (HRs) and 95% confidence intervals (CIs) for coronary atherosclerosis progression were analyzed using multiple Cox proportional hazards models.

Results: There were 126 cases of coronary artery stenosis progression (32.56%) assessed using the Coronary Artery Disease Reporting and Data System during a mean follow up of 3.91 (range, 1–9) years. In the multivariate analysis comparing ARV quartiles for LDL-cholesterol after adjusting for covariates, individuals with higher variability showed an increased risk of stenosis progression: HR 2.23 (95% CI: 1.33–3.73) for the third quartile, HR 1.56 (95% CI: 0.91–2.66) for the fourth quartile (P for trend =0.005). Triglycerides also showed a significant linear trend (P for trend =0.04), and Q4 had a greater risk of stenosis progression (HR, 2.09; 95% CI: 1.24–3.52). Meanwhile, the risk of stenosis progression was significantly reduced as the ARV of HDL-cholesterol increased: HR 0.56 (95% CI: 0.35–0.89) for the third quartile, HR 0.47 (95% CI: 0.27–0.81) for the fourth quartile (P for trend =0.01).

Conclusions: High variability in LDL-cholesterol and triglyceride was an independent predictor of coronary artery stenosis progression on subsequent CCTA in our cohort. This finding highlights the importance of maintaining stable state to effectively prevent the progression of coronary artery stenosis in clinical settings.

Keywords: Coronary artery stenosis; low-density lipoprotein-cholesterol (LDL-cholesterol); high-density lipoprotein-cholesterol (HDL-cholesterol); variability

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Introduction

Traditional cardiovascular disease (CVD) risk factors, such as obesity, blood pressure (BP), fasting blood glucose level, and blood cholesterol levels, reflect the variability of risk factors between individuals. Recent studies have shown that the variability in these risk factors within individuals also contributes to CVD risk and related deaths (1-3). Variability in traditional risk factors within an individual, a measure of the instability of the risk factors over time, can occur for several environmental reasons, such as lifestyle changes, starting medications, or incomplete adherence to treatment. However, intra-individual variability itself may act as a novel risk factor. BP variability increased the risk of CVD in different body mass index (BMI) groups and affects prognosis even in patients undergoing percutaneous coronary interventions (4,5).

Since previous studies on variability were primarily epidemiological observational studies, little is known about the intermediate process by which risk factor variability affects the development of CVD and mortality. Greater variability in atherogenic lipoprotein levels is related to the progression of coronary atherosclerosis when intravascular ultrasound is serially performed in patients with coronary artery disease (6). There have been no studies on the association between the variability of metabolic risk factors and the progression of atherosclerosis using coronary computed tomography angiography (CCTA). We attempted to elucidate the mechanism by which risk factor variability increases CVD-related mortality by hypothesizing that this variability contributes to coronary artery stenosis. This study aimed to examine whether intra-individual variability of traditional risk factors affects the progression of stenosis or plaque in coronary arteries on subsequent CCTA in an asymptomatic Korean health examination cohort. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-75/rc).

Highlight box

Key findings

- High variability of low-density lipoprotein-cholesterol and triglyceride was an independent predictor of coronary artery stenosis progression on subsequent coronary computed tomography angiography.

What is known and what is new?

- Inter-individual differences in metabolic risk factors, such as blood pressure and serum cholesterol are well-known for cardiovascular disease risk factors.
- This study shows that intra-individual as well as inter-individual variability in traditional risk factors may contribute to the progression of coronary artery stenosis in an asymptomatic cohort.

What is the implication, and what should change now?

- It is important to maintain blood lipid profiles stable to prevent the progression of coronary artery stenosis in general clinical settings.

Methods

Data source and study population

This study has a retrospective cohort design. We reviewed the medical records of 764 individuals who underwent CCTA without specific symptoms for regular health examinations twice or more with an interval of more than one year between 2010–2020 at the Haeundae Paik Hospital in South Korea. Participants were excluded if they had already undergone coronary stenting (n=7), had missing values for personal history (n=3), were foreigners or Koreans residing abroad (n=73), or had fewer than three laboratory examinations during the study period (n=294). Ultimately, 387 individuals were included in the study. *Figure 1* shows the inclusion and exclusion criteria used to select the study subjects.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Haeundae Paik Hospital Institutional Review Board (No. HPIRB 2021-07-021). The requirement of informed consent was waived due to the retrospective nature of the analyses.

Definitions of measurements and variability

Participants answered a self-reported questionnaire on their lifestyle variables (smoking status, alcohol consumption, and physical activity), past medical history, and socioeconomic variables (marital status and educational attainment)

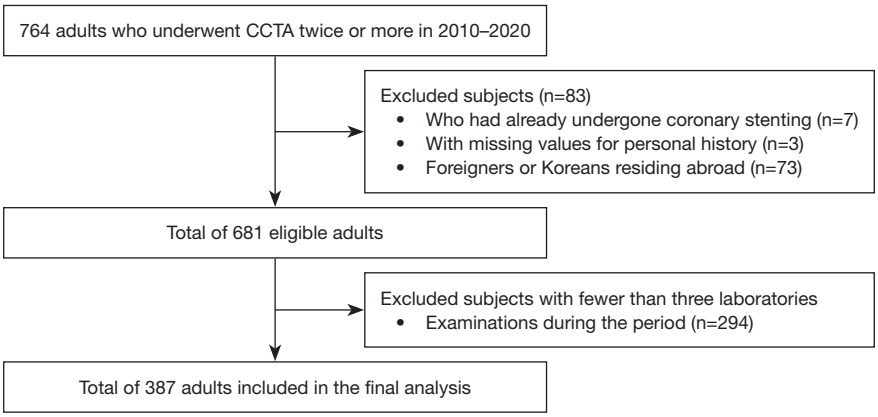

Figure 1 Inclusion and exclusion criteria used to select the study subjects. CCTA, coronary computed tomography angiography.

(Appendix 1). Smoking status was divided into non-smokers, past smokers, and current smokers. Problem drinking of alcohol was defined according to age and sex as follows; ≥14 cups per week for males under the age of 65, ≥7 cups per week for males over the age of 65 and females under the age of 65, ≥3 cups per week for females over the age of 65. Regular exercise was defined as moderate intensity exercise or walking performed at least five times per week or vigorous intensity exercise performed at least three times per week. Information on the diagnosis and medication for hypertension, diabetes mellitus, dyslipidaemia, stroke, and ischaemic heart disease was obtained using a questionnaire. We defined a medical history of each disease as being diagnosed by a doctor and taking medications in the questionnaire. Family history of these diseases was also recorded. Educational attainment and menopause in women were also confirmed using a questionnaire.

BMI was calculated as the weight in kilograms divided by the square of height in metres. Waist circumference (WC) was measured using flexible tape at the narrowest point between the uppermost lateral border of the iliac crest and the lowest border of the rib cage at the end of normal expiration. BP was measured in the upper arm by trained staff after the participants had been seated for more than five min. Plasma glucose, high-sensitivity C-reactive protein (hs-CRP), triglycerides, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol were measured using blood drawn after an 8–12 hour overnight fast.

Visit-to-visit variability was evaluated using at least three measurements of BMI, WC, systolic and diastolic BP, plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol values during the follow-up period. The average real variability (ARV) was calculated as the average of the absolute differences between consecutive measurements. The following formula was used to calculate the ARV, where N denotes the number of variable measurements.

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}\left|Value_{k+1} - Value_k\right| \quad [1]$$

Study outcome

All CCTA examinations were performed using a 320-slice multidetector CT scanner (Aquilion One, Toshiba, Japan). Patients with a heart rate >65 beats per minute received oral and intravenous metoprolol premedication if needed. We used prospective electrocardiogram (ECG)-gated CCTA with a single-breath-hold technique to minimise radiation exposure. Images were reconstructed with a slice thickness of 0.5 mm and reconstruction slice interval of 0.5 mm.

CCTA images were evaluated using axial, coronal, sagittal, cross-sectional, and curved multiplanar reformation images. One radiologist reviewed all CCTA images and was blinded to the patients' clinical information. Coronary atherosclerotic lesions were quantified for the degree of luminal diameter stenosis by visual estimation and graded using the Coronary Artery Disease Reporting and Data System (CAD-RADS™) as follows: no plaque or stenosis (0%), minimal stenosis or plaque with no stenosis (1–24%), mild stenosis (25–49%), moderate stenosis (50–69%), severe stenosis (70–99%), and occlusion (100%) (7). Progression of coronary artery atherosclerosis was defined as worsening of the degree of stenosis graded with CAD-RADS™ in any coronary artery on the final CCTA compared with the stenosis seen on CCTA at baseline.

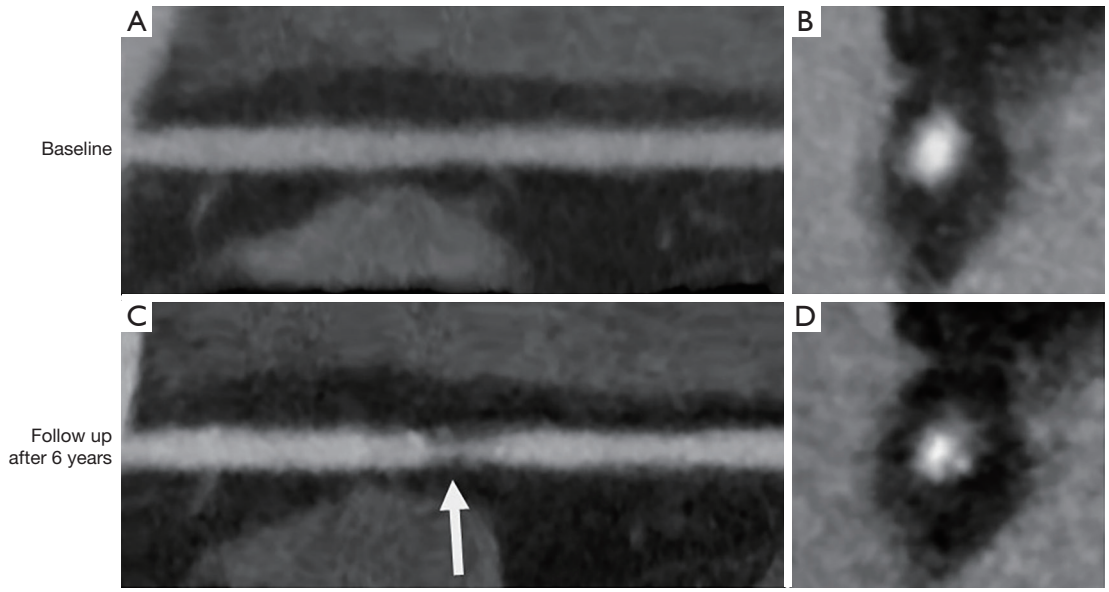

Figure 2 A case of normal coronary artery that progressed to significant stenosis after 6 years. Stretched MPR CT angiographic (A) and corresponding axial (B) CT images of a 38-year-old male reveal normal RCA with no atherosclerotic disease or stenosis at baseline (CAD-RADS category 0). After 6 years, stretched MPR CT angiographic (C) and corresponding axial CT (D) images show a focal plaque (arrow) with small calcification at the proximal RCA that is causing severe luminal stenosis (CAD-RADS category 4, 70–99%). No other lesion was identified. He did not have previous history of hypertension, diabetes, dyslipidemia, stroke or ischemic heart disease, and has smoked for 10 years. MPR CT, multi-planar reformatted computed tomography; RCA, right coronary artery; CAD-RADS, Coronary Artery Disease Reporting and Data System.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables or count (%) for categorical variables. We conducted the Wilcoxon rank sum test after the normality test and the chi-square test or Fisher's exact test, as appropriate. We stratified the study population into four groups according to the ARV values of the metabolic parameters. The incidence rate of coronary artery atherosclerosis progression was measured as the number of events during the follow-up period divided by 1,000 person-years. The hazard ratios (HR) and 95% confidence intervals (CI) for coronary artery atherosclerosis progression were analysed using multiple Cox proportional hazard models. Model 1 was adjusted for age, sex, smoking, alcohol consumption, exercise, and educational status. Model 2 was adjusted for baseline BMI, WC, systolic and diastolic BPs, plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol. Model 3 was further adjusted for a history of hypertension, diabetes, dyslipidaemia, ischaemic heart disease, and stroke. Statistical significance was set at a two-sided test $P<0.05$. We performed a sensitivity analysis after excluding participants who were taking medications for metabolic diseases at baseline, because adherence to medication can affect the variability of risk factors. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of participants

Of the 387 participants, 126 (32.56%) showed progression of coronary artery stenosis during a mean follow-up period of 3.91 (range, 1–9) years. During the follow-up period, four patients underwent coronary stent intervention. Nine patients demonstrated coronary atherosclerosis regression, exhibiting an improvement in the degree of stenosis as graded by CAD-RADS™ compared to the baseline measurements (for example, moderate to mild or severe to mild). A representative case of progression is illustrated in *Figure 2*. *Table 1* shows the baseline characteristics of the progression and non-progression groups. Participants with stenosis progression were more likely to be male

Table 1 Baseline characteristics of participants by the progression of coronary artery atherosclerosis

Characteristics	No progression	Progression	P value
Number	261 (67.44)	126 (32.56)	
Age, years	49.06±8.06	50.31±7.43	0.10
Female	59 (22.61)	14 (11.11)	0.007
Female with menopause	25 (42.37)	9 (64.29)	0.35
Current smoker	69 (26.44)	48 (38.10)	0.02
Problem drinking of alcohol	89 (34.10)	55 (43.65)	0.07
Regular exercise	132 (50.57)	58 (46.03)	0.33
Educational attainment (graduated from college/university or higher)	120 (45.98)	55 (43.65)	0.89
Medical history			
Hypertension	55 (21.07)	34 (26.98)	0.19
Diabetes	14 (5.36)	15 (11.90)	0.02
Dyslipidemia	37 (14.18)	26 (20.63)	0.11
History of stroke	2 (0.77)	1 (0.79)	0.98
History of ischemic heart disease	14 (5.36)	13 (10.32)	0.07
Family history			
Hypertension	74 (28.35)	41 (32.54)	0.40
Diabetes	55 (21.07)	41 (32.54)	0.01
Dyslipidemia	16 (6.13)	7 (5.56)	0.82
Stroke	44 (16.86)	25 (19.84)	0.56
Heart disease	56 (21.46)	26 (20.63)	0.85
BMI (≥25 kg/m^2)	105 (40.23)	61 (48.41)	0.13
50% or more stenosis of coronary arteries			
LAD	5 (1.92)	10 (7.94)	0.004
LCX	1 (0.38)	2 (1.59)	0.45
RCA	1 (0.38)	5 (3.97)	0.008

Data are presented as n (%) or mean ± standard deviation. BMI, body mass index; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

(88.89% *vs.* 77.39%; P=0.007) and current smokers (38.10% *vs.* 26.44%; P=0.02) than those in the no-progression group. The prevalence of diabetes was higher in patients in the progression group (11.90% *vs.* 5.36%; P=0.02). Family members with diabetes were more common in the progression group (32.54% *vs.* 21.07%; P=0.01). At baseline, there were more participants in the progression group with 50% or more stenosis of the left anterior descending artery (7.94% *vs.* 1.92%; P=0.004) and right coronary artery (3.97% *vs.* 0.38%; P=0.008).

Variability of metabolic parameters and risk of coronary artery stenosis progression

Table 2 shows the minimum and maximum values of multiple examinations for various metabolic risk factors of the participants. The ARV values of the risk factors are also presented. The minimum values of all metabolic risk factors showed no significant differences between the two groups, except for WC. However, the progression group had significantly higher maximum BMI

Table 2 Variability of metabolic risk factors by progression of coronary artery atherosclerosis

Factors	No progression (n=261)	Progression (n=126)	P value
BMI, kg/m^2			
ARV	0.78±0.67	0.77±0.57	0.44
Minimum†	23.94±2.62	24.48±2.75	0.11
Maximum†	24.88±2.68	25.60±2.84	0.02
Waist circumferences, cm			
ARV	3.83±3.08	3.76±2.59	0.54
Minimum†	80.92±7.75	82.91±7.07	0.02
Maximum†	85.43±7.68	88.37±7.77	<0.001
Systolic blood pressure, mmHg			
ARV	11.68±8.56	12.95±9.07	0.15
Minimum†	109.61±11.90	111.26±11.92	0.26
Maximum†	123.52±13.11	128.96±13.30	<0.001
Diastolic blood pressure, mmHg			
ARV	8.03±5.80	9.21±6.26	0.07
Minimum†	65.55±7.45	66.45±7.44	0.43
Maximum†	75.22±8.93	78.98±9.73	<0.001
Plasma glucose, mg/dL			
ARV	7.54±7.47	9.87±11.21	0.007
Minimum†	92.47±9.53	94.91±12.84	0.16
Maximum†	101.80±14.44	109.58±23.12	<0.001
Total cholesterol, mg/dL			
ARV	26.72±25.68	29.11±24.33	0.26
Minimum†	184.15±29.52	180.71±33.81	0.42
Maximum†	216.23±33.73	223.02±36.84	0.07
Triglyceride, mg/dL			
ARV	46.38±55.04	60.91±85.62	0.001
Minimum†	101.48±58.82	108.39±58.71	0.22
Maximum†	159.01±96.79	189.48±118.58	0.002
HDL cholesterol, mg/dL			
ARV	6.71±5.33	6.02±4.64	0.29
Minimum†	48.90±10.80	47.43±11.37	0.13
Maximum†	57.08±13.03	55.82±13.38	0.22
LDL cholesterol, mg/dL			
ARV	24.75±23.44	28.50±21.21	0.014
Minimum†	108.67±28.41	104.56±31.95	0.12
Maximum†	138.45±32.26	145.44±34.72	0.06
hs-CRP			
ARV	0.12±0.23	0.16±0.35	0.02
Minimum†	0.07±0.06	0.07±0.06	0.72
Maximum†	0.23±0.38	0.29±0.44	0.02

†, minimum and maximum values were obtained from three or more examinations for various metabolic risk factors performed on each individual. All values are mean ± standard deviation. BMI, body mass index; ARV, average real variability; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

(24.88±2.68 *vs.* 25.60±2.84 kg/m^2; P=0.02), WC (85.43±7.68 *vs.* 88.37±7.77 cm; P<0.001), systolic BP (123.52±13.11 *vs.* 128.96±13.30 mmHg; P<0.001) and diastolic BP (75.22±8.93 *vs.* 78.98±9.73 mmHg; P<0.001), plasma glucose (101.80±14.44 *vs.* 109.58±23.12 mg/dL; P<0.001), triglyceride (159.01±96.79 *vs.* 189.48±118.58 mg/dL; P=0.002), and hs-CRP levels (0.23±0.38 *vs.* 0.29±0.44 mg/dL; P=0.02). The ARVs of plasma glucose (7.54±7.47 *vs.* 9.87±11.21 mg/dL; P=0.007), triglyceride (46.38±55.04 *vs.* 60.91±85.62 mg/dL; P=0.001), LDL-cholesterol (24.75±23.44 *vs.* 28.50±21.21 mg/dL; P=0.014), and hs-CRP (0.12±0.23 *vs.* 0.16±0.35 mg/dL; P=0.02) were significantly higher in the progression group.

As shown in *Table 3*, the risk of progression to stenosis increased with the ARV quartile of blood lipid variables. Compared to the lowest variability for LDL-cholesterol, individuals with higher variability showed an increased risk of stenosis progression after adjusting for covariates: HR 1.07 (95% CI: 0.61–1.87) for Q2, HR 2.23 (95% CI: 1.33–3.73) for Q3, HR 1.56 (95% CI: 0.91–2.66) for Q4 (P for trend =0.005). Triglycerides also showed a significant linear trend (P for trend =0.04), and Q4 had a greater risk of stenosis progression (HR, 2.09; 95% CI: 1.24–3.52). Notably, the risk of stenosis progression was significantly reduced as

Table 3 Incidence and risk of coronary artery atherosclerosis progression by quartiles of metabolic parameters variability

Parameters	No.	Follow-up duration (person-years)	Incidence rate (/1,000)	Crude		Model 1		Model 2		Model 3	
				HR (95% CI)	P for trend	HR (95% CI)	P for trend	HR (95% CI)	P for trend	HR (95% CI)	P for trend
BMI											
Q1	84	322	74.53	ref	0.49	ref	0.31	ref	0.31	ref	0.49
Q2	110	440	81.82	1.05 (0.62, 1.76)		0.96 (0.57, 1.63)		0.96 (0.57, 1.63)		1.02 (0.60, 1.74)	
Q3	101	417	86.33	1.10 (0.66, 1.85)		1.17 (0.70, 1.98)		1.17 (0.70, 1.98)		1.13 (0.67, 1.91)	
Q4	92	430	69.77	0.77 (0.45, 1.32)		0.72 (0.42, 1.26)		0.72 (0.42, 1.26)		0.78 (0.45, 1.34)	
Waist circumference											
Q1	132	508	68.9	ref	0.04	ref	0.05	ref	0.05	ref	0.03
Q2	59	273	65.93	0.69 (0.39, 1.22)		0.71 (0.40, 1.27)		0.71 (0.40, 1.27)		0.65 (0.37, 1.17)	
Q3	114	475	107.37	1.28 (0.83, 1.98)		1.28 (0.82, 2.00)		1.28 (0.82, 2.00)		1.29 (0.83, 1.99)	
Q4	82	353	62.32	0.70 (0.41, 1.20)		0.69 (0.40, 1.19)		0.69 (0.40, 1.19)		0.67 (0.39, 1.16)	
Systolic BP											
Q1	100	352	79.55	ref	0.58	ref	0.40	ref	0.40	ref	0.44
Q2	97	429	69.93	0.69 (0.41, 1.17)		0.63 (0.37, 1.08)		0.63 (0.37, 1.08)		0.64 (0.37, 1.10)	
Q3	102	431	78.89	0.79 (0.48, 1.31)		0.73 (0.44, 1.22)		0.73 (0.44, 1.22)		0.73 (0.44, 1.23)	
Q4	88	397	85.64	0.80 (0.48, 1.33)		0.76 (0.46, 1.28)		0.76 (0.46, 1.28)		0.77 (0.46, 1.28)	
Diastolic BP											
Q1	108	414	67.63	ref	0.56	ref	0.72	ref	0.72	ref	0.57
Q2	89	393	76.34	0.93 (0.55, 1.56)		0.88 (0.52, 1.48)		0.88 (0.52, 1.48)		0.91 (0.54, 1.54)	
Q3	94	399	72.68	0.96 (0.57, 1.62)		0.88 (0.52, 1.48)		0.88 (0.52, 1.48)		0.96 (0.57, 1.62)	
Q4	96	403	96.77	1.26 (0.78, 2.06)		1.12 (0.67, 1.86)		1.12 (0.67, 1.86)		1.25 (0.76, 2.04)	
Plasma glucose											
Q1	106	441	54.42	ref	0.26	ref	0.52	ref	0.52	ref	0.34
Q2	93	386	77.72	1.24 (0.72, 2.13)		1.14 (0.66, 1.98)		1.14 (0.66, 1.98)		1.26 (0.73, 2.18)	
Q3	104	440	88.64	1.52 (0.91, 2.53)		1.36 (0.80, 2.30)		1.36 (0.80, 2.30)		1.49 (0.89, 2.51)	
Q4	84	342	96.49	1.62 (0.95, 2.75)		1.47 (0.84, 2.56)		1.47 (0.84, 2.56)		1.56 (0.91, 2.67)	
Total cholesterol											
Q1	99	388	77.32	ref	0.65	ref	0.65	ref	0.65	ref	0.69
Q2	98	441	72.56	0.79 (0.48, 1.30)		0.76 (0.46, 1.26)		0.76 (0.46, 1.26)		0.80 (0.48, 1.33)	
Q3	100	406	86.21	1.06 (0.65, 1.72)		0.98 (0.60, 1.60)		0.98 (0.60, 1.60)		1.06 (0.64, 1.76)	
Q4	90	374	77.54	0.98 (0.59, 1.64)		0.82 (0.48, 1.39)		0.82 (0.48, 1.39)		0.99 (0.58, 1.67)	
Triglyceride											
Q1	99	410	53.66	ref	0.06	ref	0.22	ref	0.22	ref	0.04
Q2	95	384	70.31	1.28 (0.73, 2.26)		1.27 (0.72, 2.23)		1.27 (0.72, 2.23)		1.35 (0.76, 2.39)	
Q3	97	428	84.11	1.42 (0.83, 2.42)		1.25 (0.72, 2.16)		1.25 (0.72, 2.16)		1.43 (0.84, 2.45)	
Q4	96	387	105.94	1.98 (1.18, 3.33)		1.75 (1.01, 3.05)		1.75 (1.01, 3.05)		2.09 (1.24, 3.52)	

Table 3 *(continued)*

Table 3 *(continued)*

Parameters	No.	Follow-up duration (person-years)	Incidence rate (/1,000)	Crude		Model 1		Model 2		Model 3	
				HR (95% CI)	P for trend	HR (95% CI)	P for trend	HR (95% CI)	P for trend	HR (95% CI)	P for trend
HDL-cholesterol											
Q1	116	431	92.81	ref	0.01	ref	0.03	ref	0.03	ref	0.01
Q2	86	326	95.09	0.95 (0.59, 1.52)		0.90 (0.55, 1.45)		0.90 (0.55, 1.45)		0.92 (0.57, 1.48)	
Q3	108	496	72.58	0.58 (0.36, 0.91)		0.59 (0.37, 0.95)		0.59 (0.37, 0.95)		0.56 (0.35, 0.89)	
Q4	77	356	53.37	0.49 (0.28, 0.85)		0.48 (0.27, 0.85)		0.48 (0.27, 0.85)		0.47 (0.27, 0.81)	
LDL-cholesterol											
Q1	100	419	57.28	ref	0.005	ref	0.03	ref	0.03	ref	0.005
Q2	102	442	61.09	1.04 (0.60, 1.81)		1.11 (0.64, 1.94)		1.11 (0.64, 1.94)		1.07 (0.61, 1.87)	
Q3	91	355	112.68	2.17 (1.30, 3.60)		2.00 (1.20, 3.34)		2.00 (1.20, 3.34)		2.23 (1.33, 3.73)	
Q4	94	393	89.06	1.57 (0.94, 2.65)		1.34 (0.78, 2.29)		1.34 (0.78, 2.29)		1.56 (0.91, 2.66)	

Model 1: adjusted by age, sex, smoking status, alcohol consumption, exercise, education. Model 2: further adjusted by baseline BMI, WC, systolic/diastolic BPs, plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol. Model 3: further adjusted by history of metabolic diseases (HT, DM, dyslipidemia, ischemic heart disease or stroke). HR, hazard ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference; HT, hypertension; DM, diabetes mellitus.

the ARV of HDL-cholesterol increased: HR 0.92 (95% CI: 0.57–1.48) for Q2, HR 0.56 (95% CI: 0.35–0.89) for Q3, HR 0.47 (95% CI: 0.27–0.81) for Q4 (P for trend =0.01).

Sensitivity analysis

Sensitivity analyses were performed after excluding participants taking medications for hypertension, diabetes mellitus, dyslipidaemia, stroke, and ischaemic heart disease at baseline (Table S1). Among the 300 individuals without medication at baseline, 92 (30.7%) showed progression of coronary artery stenosis. After adjusting for covariates, the risk of stenosis progression in individuals with higher LDL-cholesterol variability was still higher than that in Q1 (HR, 2.38; 95% CI: 1.28–4.40 for Q3; P for trend =0.007). Triglycerides also showed a significant linear trend (P for trend =0.03), and Q4 had a greater risk of stenosis progression (HR, 2.70; 95% CI: 1.38–5.28). The ARV of HDL-cholesterol showed an inverse relationship with stenosis progression: HR 0.56 (95% CI: 0.33–0.96) for Q3, HR 0.40 (95% CI: 0.20–0.79) for Q4 (P for trend =0.007).

Discussion

In this retrospective cohort study, we found that high variability in LDL-cholesterol and triglyceride levels within same individuals was associated with an increased risk of coronary artery stenosis progression during a mean 4-year follow-up period. HDL cholesterol variability is inversely associated with stenosis progression. The variability in BMI, WC, plasma glucose, and BP did not show any significant association with the outcome, even after adjusting for covariables. Several randomised controlled trials for patients taking lipid-lowering medications revealed that visit-to-visit variability in LDL cholesterol is a significant predictor of mortality and morbidity (1,8,9). The strength of our study is that it demonstrates that CAD stenosis is an intermediate link between intra-individual variability of traditional risk factors and increased mortality. Our study provides real-world evidence that high variability in LDL-cholesterol and triglyceride levels increases the risk of progression of coronary artery stenosis based on CCTA follow up.

Our study has some limitations. First, it had a retrospective cohort design and included only participants who had two or more CCTA scans from a health examination cohort in a single centre, making selection bias unavoidable. Of the subjects who had two or more CCTAs to confirm coronary atherosclerosis progression, 38% (294/764) were excluded because they had less than three laboratory studies. Second, we did not adjust for

the medication compliance of the participants which may influence the variability of risk factors. Patients with worse lipid profiles are most likely to have greater rates of CAD progression but also higher chances of being on medications; therefore, they are also more likely to have greater variation in lipid levels. However, considerable inter-individual variation exists in response to statin therapy, even with good compliance to statin therapy, and hypo-responders showed greater atheroma progression (10). Our sensitivity analysis, excluding those taking medications, also revealed that CAD stenosis progression was associated with variability in LDL cholesterol and triglyceride levels. Third, we identified the progression of coronary artery atherosclerosis according to the degree of stenosis, and CAD burden using high-risk plaque features or coronary artery calcium (CAC) score was not evaluated. It has been known that major adverse cardiac events were found to be linked to high-risk plaque including positive remodeling, low-attenuation plaque, and spotty calcification (11). However, baseline atheroma volume, and not the presence of high-risk plaque features, was the most important predictor of lesions developing into obstructive lesions in a multicentre longitudinal study evaluating serial CCTA (12). Most patients with detectable high-risk plaques on CCTA remained without acute cardiac ischaemic events or cardiac death in several cohort studies (13). The updated CAD-RADS classification follows an established framework of stenosis and plaque burden for patients with stable chest pain (14). Therefore, the degree of stenosis is an important and practical marker for evaluating and predicting the risk of progression of coronary artery atherosclerosis in clinical practice, especially when institutional protocols do not include CAC score to assess total coronary plaque burden.

The precise mechanism that can explain the association between blood lipid variability and the risk of cardiovascular events warrants further investigation. One possible explanation is that greater variability in LDL-cholesterol levels hinders lipid efflux from atheroma and finally leads to plaque vulnerability and progression at the vascular wall (1,6,15). Genetic variants may contribute the link of lipid variability and coronary artery stenosis. In a recent study of statin-naive Koreans, some single nucleotide polymorphisms (SNPs) related to LDL-cholesterol variability or HDL-cholesterol variability were found to be associated with advanced coronary artery stenosis (16). It is also unknown whether the same mechanism causes higher variability of LDL-cholesterol, HDL-cholesterol, and triglycerides, indicating that variability of one lipid measurement did not correlate well with the variability of the others in the Treating to New Targets (TNT) trial (8).

In comparison to LDL-cholesterol variability, the effect of HDL-cholesterol variability on coronary artery stenosis progression has not been studied. Our results suggest that greater HDL cholesterol variability may protect against stenosis progression. This contradicts the findings from the TNT trial, which showed that higher variability for HDL cholesterol was associated with an increased risk of coronary events (8). Although plasma HDL-cholesterol concentrations correlated negatively with atherosclerotic CVD risk, an increase in plasma HDL-cholesterol concentrations with pharmacological intervention did not reduce the risk of coronary heart disease events or related death (17). Moreover, recently, a U-shaped relationship has been found between plasma HDL cholesterol and all-cause mortality (18,19). Further research is needed to determine whether HDL variability is related to HDL functioning as an antioxidant and an acceptor of macrophage cholesterol efflux (20,21).

Meanwhile, the variability in BMI, WC, plasma glucose, and BP was not associated with coronary artery stenosis progression in our study. Previous studies in the general Korean population who did not have diabetes, hypertension, and dyslipidaemia showed that high variability in BMI, systolic BP, plasma glucose, and total cholesterol were independent predictors of all-cause mortality, myocardial infarction, stroke, heart failure, and atrial fibrillation (2,3,22). As the number of metabolic risk factors with higher variability increased, mortality and cardiovascular morbidity tended to increase further, but the correlation of variability between these risk factors was not high in the previous studies (3,23). Our results suggest that lipid variability may be more strongly associated with the progression of coronary artery stenosis than other risk factors. The variability of multiple cardiovascular risk factors eventually increases mortality and morbidity, but there appears to be no common mechanism at work among the factors, and various pathways are intricately linked; for example, body weight fluctuations are associated with diabetes, which increases the risk of CVD morbidity (24). In a recent study, BP variability influenced the morphology and composition of coronary plaques by inflammation and haemodynamics (25). On the one hand, it has been argued that BP variability is an early marker of epiphenomenon of frailty in older adults (26). Future research is needed on the mechanisms and interrelationships of the variability of each

risk factor on coronary artery atherosclerosis progression.

Conclusions

High intra-individual variability in LDL-cholesterol and triglyceride levels were independent predictors of coronary artery stenosis progression on CCTA follow up in an asymptomatic health examination cohort. These results highlight the importance of maintaining stable blood lipid profiles to prevent the progression of coronary artery stenosis in the general clinical setting. The mechanisms underlying these associations should be investigated in future studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-75/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-75/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Haeundae Paik Hospital Institutional Review Board (No. HPIRB 2021-07-021). The requirement of informed consent was waived due to the retrospective nature of the analyses.

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