

Hemoglobin A1c Levels Affect Visit-to-visit Variability of Lipid Profiles in Patients Undergoing Elective Percutaneous Coronary Intervention: A Retrospective Study

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Research

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Abstract

Background

Both hemoglobin A1c (HbA1c) levels and visit-to-visit variability of lipid profiles are risk factors for cardiovascular disease (CVD). We conducted a retrospective cohort study to explore the relationship between HbA1c and lipid variability.

Methods

We retrospectively collected baseline and follow-up data on patients who underwent elective percutaneous coronary intervention (PCI) from January 2009 to April 2019. Univariate and multivariate linear regression analyses were performed to assess the association between HbA1c and lipid variability. Subgroup analyses employed multivariate linear regression analyses.

Results

A total of 4,445 patients were enrolled in the study. The median age and value of HbA1c were 64yrs old and 5.9%, respectively, 64% had hypertension and 25.5% diabetes. The variability of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and triglyceride (TG) was each significantly higher in patients with HbA1c \geq 6.5% than those with HbA1c $<$ 6.5% group. Multivariate linear regression indicated that HbA1c level was a potential risk factor for the variability of LDL-C, non-HDL-C, TC and TG, which was independent of the mean values of lipids. Subgroup analyses demonstrated that the relationship between HbA1c and the variability of LDL-C, non-HDL-C, TC, and TG did not importantly vary across several subgroups. These results remained consistent when lipid variability was represented by the standard deviation (SD), coefficient of variation (CV) and variability independent of the mean (VIM), respectively.

Conclusion

HbA1c is a potential risk factor for the variability of LDL-C, non-HDL-C, TC and TG in patients undergoing elective PCI.

Background

Cardiovascular disease (CVD) remains the leading cause of death globally and is one of the most common complications of diabetes mellitus (DM)[1, 2]. Hemoglobin A1c (HbA1c) is usually regarded as an indicator representing the average blood glucose levels over the past 2-3 months and is often employed to assess glycemic control[3]. Several epidemiological studies[4, 5] have demonstrated associations between elevated HbA1c levels and adverse CVD outcomes in patients with type 2 DM. Moreover, even within the normal reference range, increased blood glucose levels are associated with an increased risk of CVD[6].

Traditionally, mean values of indicators or exposures are often employed to estimate the prognostic risk for CVD. For example, higher low-density lipoprotein cholesterol (LDL-C) levels and lower high-density lipoprotein cholesterol (HDL-C) levels are associated with an increased risk of CVD[7, 8]. However, if there is wide variability in the exposure, the mean value will no longer be reliable. In recent years, more attention is being focused on the variability of these exposures. With particular emphasis on lipid profiles, the visit-to-visit variability of LDL-C, HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC) and triglyceride (TG) has each been demonstrated to be a potential risk factor for CVD[9-13]; these associations are independent of the mean levels of the exposures and traditional cardiovascular risk factors. Based on intravascular ultrasound examination, elevated variability of LDL-C has been shown to independently promote the progression of atherosclerosis, which is the crucial underlying pathology of CVD^[14]. In general, lipid variability, an independent risk factor for CVD, is attracting considerable attention.

Both HbA1c and the variability of blood lipids are risk factors for CVD. However, whether there is any relationship between HbA1c and the variability of lipids is still unclear. Therefore, the purpose of this study is to investigate the relationship between HbA1c and lipid variability in patients undergoing elective percutaneous coronary intervention (PCI).

Methods

Study subjects

The study population comprised all consecutive patients who attended the Sir Run Run Shaw Hospital, Zhejiang University in China, from January 2009 to April 2019. Eligibility criteria for inclusion into the study were: (1) patients who underwent elective PCI, (2) sufficient clinical information such as HbA1c and lipid profiles were available at baseline and follow-ups, (3) patients were followed up at 1, 3, 6, 9, and 12 months following PCI according to the prescribed follow-up procedures. Patients with acute myocardial infarction (MI), active cardiopulmonary diseases, heart failure, severe liver and/or renal insufficiency, cancer, acute or chronic infection and other serious diseases were excluded from the study. A total of 4,445 patients were finally enrolled in the study. All PCI procedures were performed by experienced interventional cardiologists using the recommended guidelines[15]. Baseline and follow-up measurements of exposures were ascertained from fasting venous blood samples (at least 8 hrs overnight). Levels of HbA1c, LDL-C, HDL-C, non-HDL-C, TC and TG were determined at each follow-up. Standard follow-up procedures and examinations were employed for all patients who had undergone elective PCI. The Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University approved the study (20200803-34).

Assessment of variability in lipid profiles

Baseline and follow-up values of lipids were measured by a blood chemistry analyzer (Hitachi 747; Hitachi, Tokyo, Japan). The variability of lipids reflected the degree of fluctuation of individual blood lipid levels during the 1-year follow-up period. To assess the lipid variability more comprehensively, the

following 3 indicators were used:(1) standard deviation (SD); (2) coefficient of variation (CV): The CV of blood lipids was defined as follows, $CV=(SD/mean)\times 100$ (%); and (3) variability independent of the mean (VIM): VIM was calculated as $(SD/mean^\beta)\times 100$ (%), in which β was derived from the fitting of the curve and was the regression coefficient based on the natural logarithm of SD and the natural logarithm of the mean[16].

Definitions

The level of HbA1c was defined as the mean value during a 1-year follow-up period and was calculated using values of HbA1c measured at follow-up. Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dL, a history of diabetes or the current use of antidiabetic medications. Hypertension was defined as blood pressure $\geq 140/90$ mmHg, a documented history of hypertension or on anti-hypertensive medications. Regular statin therapy was defined as atorvastatin ≤ 20 mg or rosuvastatin ≤ 10 mg per day. Intensive statin therapy was defined as atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg per day. Particular attention was paid to patients' compliance with statin use. Heart failure was defined by ejection fraction (EF) $< 40\%$ or N-terminal pro B-type natriuretic peptide (NT-pro BNP) > 2000 pg/ml without renal failure. Body mass index (BMI) was calculated as weight in kilograms, divided by height in meters squared. Glomerular filtration rate (GFR) was estimated using the Japanese Society of Nephrology equation as follows: estimated GFR (eGFR) (mL/min/1.73 m²) = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for women)[17].

Statistical analysis

Continuous variables were presented as median (interquartile range) or mean (standard deviation). Categorical variables were represented as frequency (%). Baseline characteristics were compared between patients with HbA1c $< 6.5\%$ and HbA1c $\geq 6.5\%$ using chi-square tests for categorical variables and nonparametric tests for continuous variables. Univariate and multivariate linear regression analyses were used to evaluate the relationship between HbA1c and lipid variability. Subgroup analyses employed multivariate linear regression analyses. A value of $P < 0.05$ (2 sided) was considered statistically significant. Statistical analysis was performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA).

Result

Patient characteristics

The 4,445 patients who had undergone elective PCI at the Sir Run Run Shaw Hospital between January 2009 and April 2019 comprised 3,538 males and 907 females. Overall, the median age of subjects was 64 (58-70) years old, with a median BMI of 24.73 (22.77-26.18) kg·m⁻², 64% had hypertension and 25.5% had type 2 diabetes mellitus. The median value of HbA1c was 5.9%, with the interquartile range from 5.5% to 6.7% for all subjects. The variability of LDL-C, non-HDL-C, TC and TG was each significantly higher in patients with HbA1c $\geq 6.5\%$ than in those with HbA1c $< 6.5\%$. Patients with HbA1c $\geq 6.5\%$

appeared to have higher BMI (24.73[23.38-26.67] vs. 24.62[22.48-26.00]); $p < 0.001$), more likely to have hypertension (70.0% vs. 62.5%; $p < 0.001$) than those with HbA1c $\geq 6.5\%$. Table 1 summarizes the baseline characteristics of the enrolled patients categorized by HbA1c levels.

Table 1 Baseline characteristics of patients

Characteristics	Total (n=4445)	HbA1c$\lt; 6.5\%$ (n=3538)	HbA1c$\geq 6.5\%$ (n=907)	P-value
Demographic information				
Age (Years)	64.00(58.00-70.00)	64.00(58.00-70.00)	64.00(58.00-71.00)	0.158
Male, N (%)	3187(71.7)	2549(72.0)	638(70.3)	0.391
BMI, (kg/m ²)	24.73(22.77-26.18)	24.62(22.48-26.00)	24.73(23.38-26.67)	\square 0.001
Current smoking, N (%)	1102(24.8)	890(25.2)	212(23.4)	0.388
Hypertension, N (%)	2845(64.0)	2210(62.5)	635(70.0)	\square 0.001
Type 2 diabetes, N (%)	1133(25.5)	327(9.2)	806(88.9)	\square 0.001
Previous MI, N (%)	164(3.7)	129(3.6)	35(3.9)	0.786
Previous PCI, N (%)	342(7.7)	278(7.9)	64(7.1)	0.581
LDL-C$\lt; 1.8\text{ mmol/L}$, N (%)	3729(83.9)	2984(84.3)	745(82.1)	0.127
Laboratory examination				
HbA1c (%)	5.9(5.50-6.70)	5.7(5.40-6.00)	7.6(6.90-8.70)	\square 0.001
LDL-C (mean, mmol/L)	1.78(1.49-2.13)	1.78(1.50-2.12)	1.77(1.47-2.18)	0.834
HDL-C (mean, mmol/L)	1.02(0.88-1.20)	1.05(0.90-1.22)	0.97(0.83-1.14)	\square 0.001
non-HDL-C (mean, mmol/L)	2.46(2.10-2.90)	2.47(2.10-2.87)	2.44(2.08-2.95)	0.806
TC (mean, mmol/L)	3.66(3.21-4.16)	3.67(3.25-4.12)	3.62(3.15-4.23)	0.219
TG (mean, mmol/L)	1.36(1.04-1.82)	1.35(1.04-1.78)	1.38(1.05-1.95)	0.051
LDL-C (SD)	0.47(0.27-0.75)	0.45(0.25-0.74)	0.50(0.29-0.76)	0.014
HDL-C (SD)	0.13(0.08-0.18)	0.13(0.08-0.18)	0.13(0.08-0.18)	0.577
non-HDL-C (SD)	0.43(0.25-0.70)	0.42(0.25-0.70)	0.47(0.27-0.73)	0.004
TC (SD)	0.59(0.35-0.93)	0.56(0.33-0.90)	0.66(0.39-1.00)	\square 0.001
TG (SD)	0.33(0.19-0.55)	0.32(0.19-0.52)	0.37(0.20-0.65)	\square 0.001
	89.25(75.22-	89.22(75.96-	89.19(70.65-	0.848

eGFR (mL/min/1.73 m ²)	98.11)	97.70)	99.01)	
Baseline medication				
ACEI, N (%)	1102(24.8)	876(24.8)	226(24.9)	0.897
ARB, N (%)	1565(35.2)	1180(33.4)	385(42.4)	□ 0.001
Beta blocker, N (%)	2614(58.8)	2092(59.1)	522(57.6)	0.429
CCB, N (%)	1325(29.8)	1020(28.8)	305(33.6)	0.007
Aspirin, N (%)	4294(96.6)	3424(96.8)	870(95.9)	0.244
Clopidogrel, N (%)	3592(80.8)	2889(81.7)	703(77.5)	0.007
Ticagrelor, N (%)	805(18.1)	613(17.3)	192(21.2)	0.008
Statin, N (%)	4401(99.0)	3507(99.1)	894(98.6)	0.151
Intensive statin, N (%)	845(19.0)	660(18.7)	185(20.3)	0.064
Statin combined with ezetimibe, N (%)	956(21.5)	764(21.6)	192(21.2)	0.818

Data are expressed as median (25%-75%) or n (%). Total indicates total group; SD, standard deviation; BMI, body mass index; MI, myocardial infarction; LDL-C < 1.8 mmol/L, LDL-C < 1.8 mmol/L at the first-month follow-up after percutaneous coronary intervention (PCI); LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

Results of univariate and multivariate linear regression for the variability of lipid profiles

Based on clinical considerations and differences in baseline characteristics according to HbA1c categories, the following factors were included in the univariate analysis: HbA1c, age, gender, BMI, current smoking, hypertension, eGFR, types of statin, intensive statin treatment, statin combined with ezetimibe and the corresponding mean values of lipids. Factors that were significant in the univariate analyses ($p < 0.05$) were included in multivariate linear regression analysis.

Multivariate analysis for the effect of HbA1c on lipid variability was conducted in all patients and demonstrated that HbA1c was a potential risk factor for the variability of lipids, which included LDL-C (regression coefficients of HbA1c on SD [β] 0.014, standard error [SE] 0.004, P-value \square 0.001), non-HDL-C ([β] 0.023, [SE] 0.004, P-value \square 0.001), TC ([β] 0.041, [SE] 0.005, P-value \square 0.001), and TG ([β] 0.033, [SE] 0.005, P-value \square 0.001). Besides, HbA1c remained a potential risk factor for the variability of LDL-C, non-

HDL-C, TC and TG when CV and VIM were employed to represent lipid variability, respectively (see Table 2 to 5).

Table 2 Results of univariate and multivariate linear regression for the variability of LDL-C

	SD						CV						VIM					
	Univariate regression			Multiple regression			Univariate regression			Multiple regression			Univariate regression			Multiple regression		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
HbA1c	0.019	0.005	<0.001	0.014	0.004	<0.001	0.010	0.002	<0.001	0.009	0.002	<0.001	0.003	0.001	<0.001	0.003	0.001	<0.001
Age	-0.003	0.001	<0.001	-0.001	0.001	0.076	-0.001	<0.001	<0.001	-0.001	<0.001	0.089	<0.001	<0.001	<0.001	<0.001	<0.001	0.122
Male	-0.044	0.012	<0.001	-0.022	0.012	0.055	-0.013	0.005	0.019	-0.001	<0.001	0.087	-0.004	0.002	0.018	-0.003	0.002	0.076
BMI	0.007	0.002	<0.001	0.001	0.002	0.438	0.002	0.001	0.052				<0.001	<0.001	0.049	<0.001	<0.001	0.467
Current smoking	0.018	0.013	0.158				0.002	0.006	0.754				0.001	0.002	0.787			
Hypertension	-0.047	0.012	<0.001	-0.024	0.011	0.030	-0.018	0.005	<0.001	-0.015	0.006	0.009	-0.005	0.001	<0.001	-0.004	0.002	0.008
eGFR	0.001	<0.001	<0.001	<0.001	<0.001	0.889	0.001	<0.001	0.014	<0.001	<0.001	0.646	<0.001	<0.001	0.014	<0.001	<0.001	0.694
Types of statins	0.001	0.007	0.958				0.003	0.003	0.318				0.001	0.001	0.321			
Intensive statin treatment	0.116	0.017	<0.001	0.088	0.016	<0.001	0.037	0.007	<0.001	0.050	0.008	<0.001	0.010	0.002	<0.001	0.014	0.002	<0.001
Statin combined with ezetimibe	0.322	0.013	<0.001	0.264	0.013	<0.001	0.131	0.006	<0.001	0.143	0.007	<0.001	0.037	0.002	<0.001	0.040	0.002	<0.001
LDL-C (mean)	0.317	0.008	<0.001	0.270	0.009	<0.001												

β indicates regression coefficients; SE, standard error; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; Other abbreviations, refer to Table 1. Significance was set to $P < 0.05$ and highlighted in bold

Table 3 Results of univariate and multivariate linear regression for the variability of non-HDL-C

	SD						CV						VIM					
	Univariate regression			Multiple regression			Univariate regression			Multiple regression			Univariate regression			Multiple regression		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
HbA1c	0.029	0.005	<0.001	0.023	0.004	<0.001	0.009	0.002	<0.001	0.009	0.002	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001
Age	-0.004	0.001	<0.001	-0.002	0.001	0.006	-0.001	<0.001	<0.001	-0.001	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.003
Gender	-0.042	0.013	0.001	-0.013	0.013	0.314	-0.003	0.004	0.416				-0.001	0.001	0.307			
BMI	0.010	0.002	<0.001	0.001	0.002	0.686	0.002	0.001	0.013	<0.001	0.001	0.573	<0.001	<0.001	0.007	<0.001	<0.001	0.464
Current smoking	0.025	0.013	0.067				0.008	0.004	0.057				0.001	0.001	0.082			
Hypertension	-0.046	0.012	<0.001	-0.025	0.013	0.045	-0.015	0.04	<0.001	-0.010	0.005	0.029	-0.002	0.001	<0.001	-0.001	0.001	0.035
eGFR	0.001	0.001	<0.001	<0.001	<0.001	0.660	<0.001	<0.001	<0.001	<0.001	<0.001	0.661	<0.001	<0.001	<0.001	<0.001	<0.001	0.690
Types of statins	0.015	0.007	0.035	0.026	0.009	0.005	0.006	0.002	0.011	0.008	0.003	0.016	0.001	<0.001	0.017	0.001	<0.001	0.014
Intensive statin treatment	0.032	0.017	0.068				0.007	0.006	0.199				0.001	0.001	0.356			
Statin combined with ezetimibe	0.232	0.015	<0.001	0.167	0.014	<0.001	0.069	0.005	<0.001	0.069	0.005	<0.001	0.009	0.001	<0.001	0.009	0.001	<0.001
non-HDL-C (mean)	0.264	0.007	<0.001	0.247	0.008	<0.001												

β indicates regression coefficients; SE, standard error; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; Other abbreviations, refer to Table 1. Significance was set to $P < 0.05$ and highlighted in bold

Table 4 Results of univariate and multivariate linear regression for the variability of TC

	SD						CV						VIM					
	Univariate regression			Multiple regression			Univariate regression			Multiple regression			Univariate regression			Multiple regression		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
HbA1c	0.048	0.006	<0.001	0.041	0.005	<0.001	0.012	0.001	<0.001	0.011	0.001	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001
Age	-0.005	0.001	<0.001	-0.003	0.001	0.001	-0.001	<0.001	<0.001	-0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Gender	-0.071	0.016	<0.001	-0.001	0.015	0.930	-0.005	0.004	0.153				<0.001	<0.001	0.159			
BMI	0.011	0.002	<0.001	0.006	0.002	0.006	0.002	0.001	<0.001	0.002	0.001	0.007	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Current smoking	0.012	0.016	0.438				0.005	0.004	0.151				<0.001	<0.001	0.322			
Hypertension	-0.036	0.015	0.014	-0.007	0.015	0.642	-0.006	0.003	0.073				<0.001	<0.001	0.134			
eGFR	0.002	0.001	<0.001	<0.001	<0.001	0.923	<0.001	<0.001	0.001	<0.001	<0.001	0.956	<0.001	<0.001	<0.001	<0.001	<0.001	0.880
Types of statins	0.004	0.009	0.672				0.001	0.002	0.456				<0.001	<0.001	0.410			
Intensive statin treatment	0.104	0.021	<0.001	0.306	0.017	<0.001	0.024	0.005	<0.001	0.031	0.005	<0.001	0.002	<0.001	<0.001	0.002	<0.001	<0.001
Statin combined with ezetimibe	0.379	0.017	<0.001	0.240	0.009	<0.001	0.080	0.004	<0.001	0.085	0.004	<0.001	0.006	<0.001	<0.001	0.006	<0.001	<0.001
TC (mean)	0.279	0.008	<0.001	0.240	0.009	<0.001												

β indicates regression coefficients; SE, standard error; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; Other abbreviations, refer to Table 1. Significance was set to $P < 0.05$ and highlighted in bold

Table 5 Results of univariate and multivariate linear regression for the variability of TG

	SD						CV						VIM					
	Univariate regression			Multiple regression			Univariate regression			Multiple regression			Univariate regression			Multiple regression		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
HbA1c	0.070	0.008	<0.001	0.033	0.005	<0.001	0.018	0.002	<0.001	0.018	0.002	<0.001	0.004	<0.001	<0.001	0.004	<0.001	<0.001
Age	-0.009	0.001	<0.001	0.001	0.001	0.378	-0.002	<0.001	<0.001	-0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Male	-0.002	0.023	0.948				0.008	0.005	0.128				0.002	0.001	0.081			
BMI	0.024	0.003	<0.001	-0.008	0.002	<0.001	0.004	0.001	<0.001	0.001	0.001	0.134	0.001	<0.001	<0.001	<0.001	<0.001	0.103
Current smoking	0.051	0.024	0.034	0.001	0.016	0.967	0.014	0.006	0.013	0.003	0.007	0.613	0.002	0.001	0.023	0.001	0.001	0.533
Hypertension	-0.002	0.022	0.932				-0.008	0.005	0.127				-0.001	0.001	0.317			
eGFR	0.002	<0.001	<0.001	0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.901	<0.001	<0.001	<0.001	<0.001	<0.001	0.498
Types of statins	0.009	0.013	0.503				-0.002	0.003	0.489				<0.001	0.001	0.619			
Intensive statin treatment	0.015	0.032	0.641				0.020	0.007	0.007	0.017	0.009	0.055	0.003	0.001	0.013	0.003	0.002	0.070
Statin combined with ezetimibe	0.083	0.027	0.002	0.031	0.017	0.066	0.022	0.006	<0.001	0.019	0.007	0.007	0.004	0.001	0.001	0.003	0.001	0.040
TG (mean)	0.622	0.008	<0.001	0.560	0.008	<0.001												

β indicates regression coefficients; SE, standard error; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; Other abbreviations, refer to Table 1. Significance was set to $P < 0.05$ and highlighted in bold

Results of the multivariate linear regression in subgroups

In multivariate subgroup analyses, the relationship between HbA1c and the variability of LDL-C, non-HDL-C, TC, and TG did not significantly vary across several subgroups such as non-diabetes, diabetes, atorvastatin, rosuvastatin, regular statin, intensive statin and statin-ezetimibe combined therapy.

Figures 1-3 present the results of subgroup analyses when lipid variability was represented by SD. Similarly, when CV and VIM were employed to represent lipid variability, respectively, subgroup analysis results were consistent with results when using SD. (see Table 6).

Table 6 Results of multivariate linear regression for the effect of HbA1c on variability in subgroups

	non-DM (n=3306)			DM (n=1139)			Atorvastatin (n=2687)			Rosuvastatin (n=1559)			RS (n=2681)			IS (n=764)			RS+E (n=875)		
	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
LDL-C (CV)	0.008	0.000-0.017	0.002	0.010	0.004-0.017	0.003	0.009	0.004-0.014	<0.001	0.011	0.004-0.019	0.002	0.010	0.005-0.014	<0.001	0.012	0.002-0.022	0.019	0.012	0.003-0.021	0.015
LDL-C (VIM)	0.002	0.000-0.005	0.039	0.003	0.001-0.005	0.003	0.002	0.001-0.004	<0.001	0.003	0.001-0.005	0.002	0.003	0.001-0.004	<0.001	0.004	0.001-0.007	0.014	0.003	0.000-0.007	0.023
non-HDL-C (CV)	0.014	0.007-0.021	<0.001	0.009	0.004-0.014	0.001	0.006	0.002-0.010	0.001	0.014	0.008-0.020	<0.001	0.009	0.005-0.012	<0.001	0.008	0.002-0.014	0.012	0.012	0.003-0.020	<0.001
non-HDL-C (VIM)	0.002	0.001-0.003	<0.001	0.001	0.000-0.002	0.001	0.001	0.000-0.001	0.002	0.002	0.001-0.003	<0.001	0.001	0.001-0.002	<0.001	0.001	0.000-0.002	0.009	0.002	0.001-0.003	<0.001
TC (CV)	0.017	0.012-0.022	<0.001	0.011	0.007-0.015	<0.001	0.009	0.006-0.012	<0.001	0.016	0.012-0.021	<0.001	0.01	0.007-0.013	<0.001	0.015	0.006-0.024	<0.001	0.015	0.008-0.023	<0.001
TC (VIM)	0.001	0.001-0.002	<0.001	0.001	0.000-0.001	<0.001	0.001	0.000-0.001	<0.001	0.001	0.001-0.002	<0.001	0.001	0.000-0.001	<0.001	0.001	0.000-0.002	<0.001	0.001	0.001-0.002	<0.001
TG (CV)	0.031	0.023-0.040	<0.001	0.013	0.006-0.021	0.001	0.014	0.009-0.020	<0.001	0.026	0.018-0.033	<0.001	0.015	0.009-0.020	<0.001	0.033	0.017-0.049	<0.001	0.02	0.012-0.033	<0.001
TG (VIM)	0.006	0.004-0.008	<0.001	0.003	0.001-0.005	<0.001	0.003	0.002-0.004	<0.001	0.006	0.004-0.007	<0.001	0.003	0.002-0.004	<0.001	0.008	0.004-0.011	<0.001	0.005	0.003-0.007	<0.001

The table collects regression coefficients of HbA1c on lipid variability in multivariate linear regression when lipid variability is represented by CV and VIM respectively. RS indicates regular statin therapy without ezetimibe; IS, intensive statin therapy without ezetimibe; RS+E, regular statin therapy combined with ezetimibe; β , regression coefficients; SD, standard deviation; CI, confidence interval; CV, coefficient of variation; VIM, variability independent of the mean. Other abbreviations, refer to Table 1.

Discussion

The main findings of this study are summarized as follows: (1) HbA1c level was a potential risk factor for the variability of LDL-C, non-HDL-C, TC and TG. The results were consistent when SD, CV, and VIM were used to represent lipid variability, respectively; (2) Subgroup analysis demonstrated that the effect HbA1c on the variability of LDL-C, non-HDL-C, TC, and TG remained similar in several relevant subgroups. In patients without diabetes, the significant positive correlations between HbA1c and lipids variability remained, including LDL-C, non-HDL-C, TC and TG.

Elevated visit-to-visit variability of blood lipids is associated with different adverse outcomes or organ dysfunction, including CVD, obstructive sleep apnea, renal function decline and cognitive decline[18-20]. Based on the Treating to New Targets (TNT) trial, the visit-to-visit variability of LDL-C, HDL-C and TG was demonstrated to be an independent predictor of cardiovascular events[21, 22]. Moreover, Lee *et al.*[12] confirmed that the visit-to-visit variability of non-HDL-C was associated with major adverse cardiovascular and cerebrovascular events (MACCE) in patients who had undergone PCI. Furthermore, a study based on 3.6 million people in the general population showed that the variability of TC was associated with the risk of all-cause mortality, MI and stroke[23]. A wealth of data suggests that the visit-to-visit variability of lipid profiles is independently associated with the risk of CVD. However, the underlying mechanisms for the association are still unclear. Similarly, HbA1c has been identified as a risk factor for CVD and confirmed by many epidemiological studies[4, 5, 24, 25]. The current study has demonstrated the potential role of HbA1c as a risk factor for the variability of LDL-C, non-HDL-C, TC, and TG. To further explore the relationship between HbA1c and blood lipid variability, we postulate the following underlying mechanisms based on findings from previous studies.

Insulin resistance (IR) is considered one of the underlying mechanisms, which play an essential role in glucose and lipid metabolism. In this study, IR may be ubiquitous among subjects. A quarter of the patients had a history of type 2 DM, which is very likely to be accompanied by IR[26]. Besides, within the normal range of glucose tolerance, patients with CVD have more IR compared to those without CVD, which suggests that patients without type 2 DM in this study may also have IR[27]. IR not only affects HbA1c levels by reducing glucose transport into cells and glycogen synthesis, but is also closely related

to dyslipidemia[28]. Although the existing evidence is not sufficient to ultimately demonstrate the effect of IR on lipid variability, the evidence for the role of IR in lipid metabolism appears to suggest this possibility. IR leads to dyslipidemia via the following ways: (1) increased TG, (2) decreased HDL-C, and (3) the appearance of small dense LDL particles[29]. Moreover, hyperinsulinemia, which is the response of insulin resistance, stimulates the synthesis and secretion of very LDL and promotes LDL-C transport into arterial smooth muscle cells[30, 31]. In general, given the high prevalence of IR in our patients and its effects on glucose and lipid metabolism, IR could be the potential mechanism behind our findings[32].

Based on analyses of baseline characteristics, the variability of LDL-C, non-HDL-C, TC and TG showed significant differences between categories of HbA1c. However, this finding was not observed for the variability of HDL-C. Unlike other blood lipids, HDL-C is often called “good cholesterol,” which exerts multiple beneficial functions within the cardiovascular system[33]. There is a negative correlation between HbA1c and HDL-C levels. Reduced HDL-C levels often accompany elevated HbA1c[34]. To some extent, it is possible that this negative correlation weakened the influence of HbA1c on the variability of HDL-C, hence the null findings.

Both HbA1c and blood lipid variability are risk factors for adverse CVD outcomes. Based on the data of patients undergoing elective PCI, this study clarified the relationship between HbA1c and blood lipid variability. First, insights on the relationships promote the understanding of the role of HbA1c and lipid variability in CVD development. Second, these findings provide new perspectives for further understanding the relationship between glucose metabolism and lipid metabolism, which are closely related in vivo.

Limitations

There are a number of limitations to consider. First, being a single-center retrospective study, it is limited by inherent biases. Second, we had no data on antidiabetic medications, which may affect lipid metabolism or improve insulin sensitivity. Third, this study examined the effect of long-term blood glucose levels on lipid variability. Indicators of short-term blood glucose levels or glucose tolerance such as random glucose, fasting plasma glucose and 2h post-OGTT glucose, were not included in this study,

Conclusion

HbA1c is a potential risk factor for the variability of LDL-C, non-HDL-C, TC, and TG in patients undergoing elective PCI.

Abbreviations

HbA1c: hemoglobin A1c; CVD: cardiovascular disease; PCI: percutaneous coronary intervention; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: and triglyceride; SD: standard deviation; CV: coefficient of variation; VIM: variability

independent of the mean; DM: diabetes mellitus; MI: myocardial infarction; EF: ejection fraction; BMI: Body mass index; eGFR: estimated Glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blocker.

Declarations

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Authors' contributions

WB Z and ZY C conceived and designed the study. DB L organized these data and drafted the manuscript with the help of C Y, LD Z and Yi L. DB L analysed the data. Ya L drew the pictures. WB Z, ZY C and GS F detected any errors in the whole process. All authors have read and approved the manuscript for submission.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was given approval by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

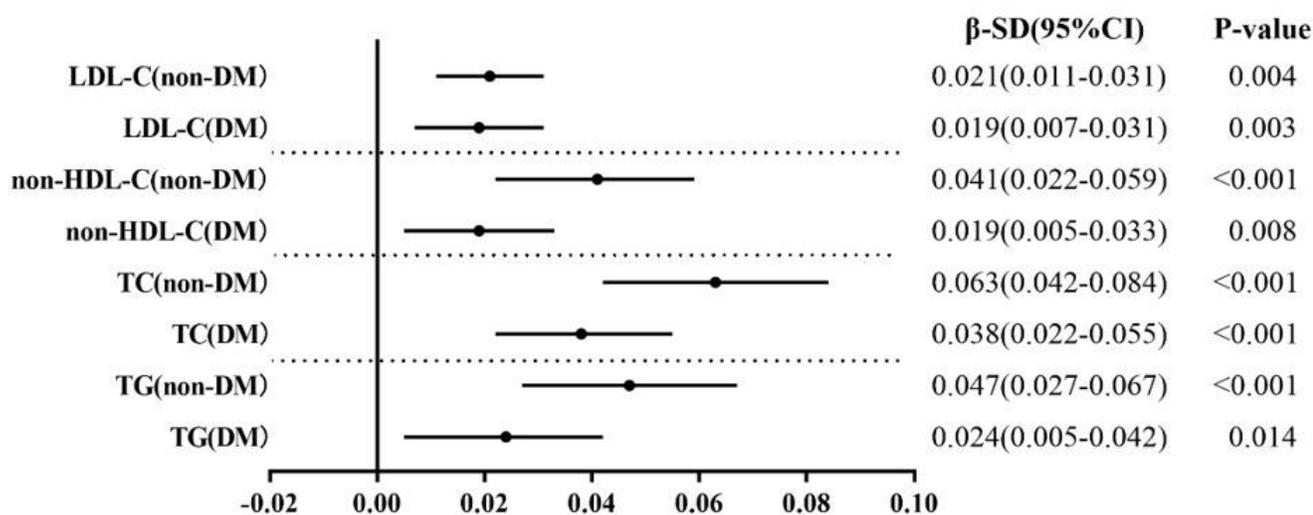


Figure 1

Multivariate analysis for the effect of HbA1c on lipid variability in patients with and without diabetes. Multivariate linear regression results for the effect of HbA1c on lipid variability, which was represented by

SD, non-DM indicates group without diabetes; DM, patients with diabetes; β -SD, regression coefficients of HbA1c on SD; CI, confidence intervals.

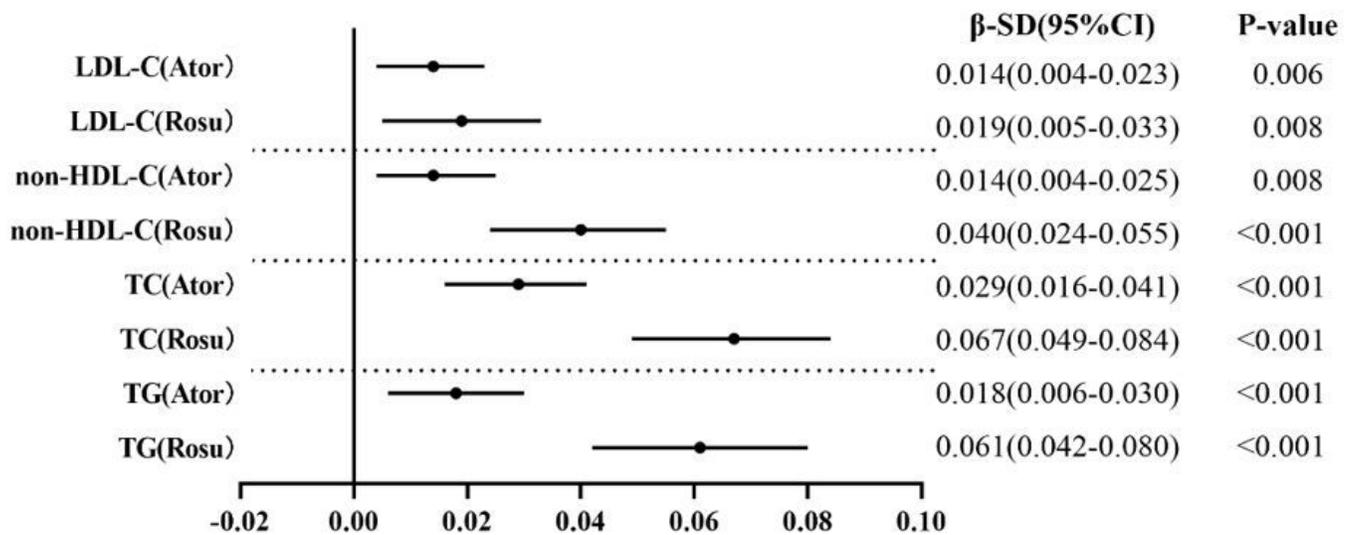


Figure 2

Multivariate analysis for the effect of HbA1c on lipid variability in Atorvastatin and Rosuvastatin therapy groups. Multivariate linear regression results for the effect of HbA1c on lipid variability, which was represented by SD. Ator indicates atorvastatin therapy group; Rosu, rosuvastatin therapy group; β -SD, regression coefficients of HbA1c on SD; CI, confidence intervals.

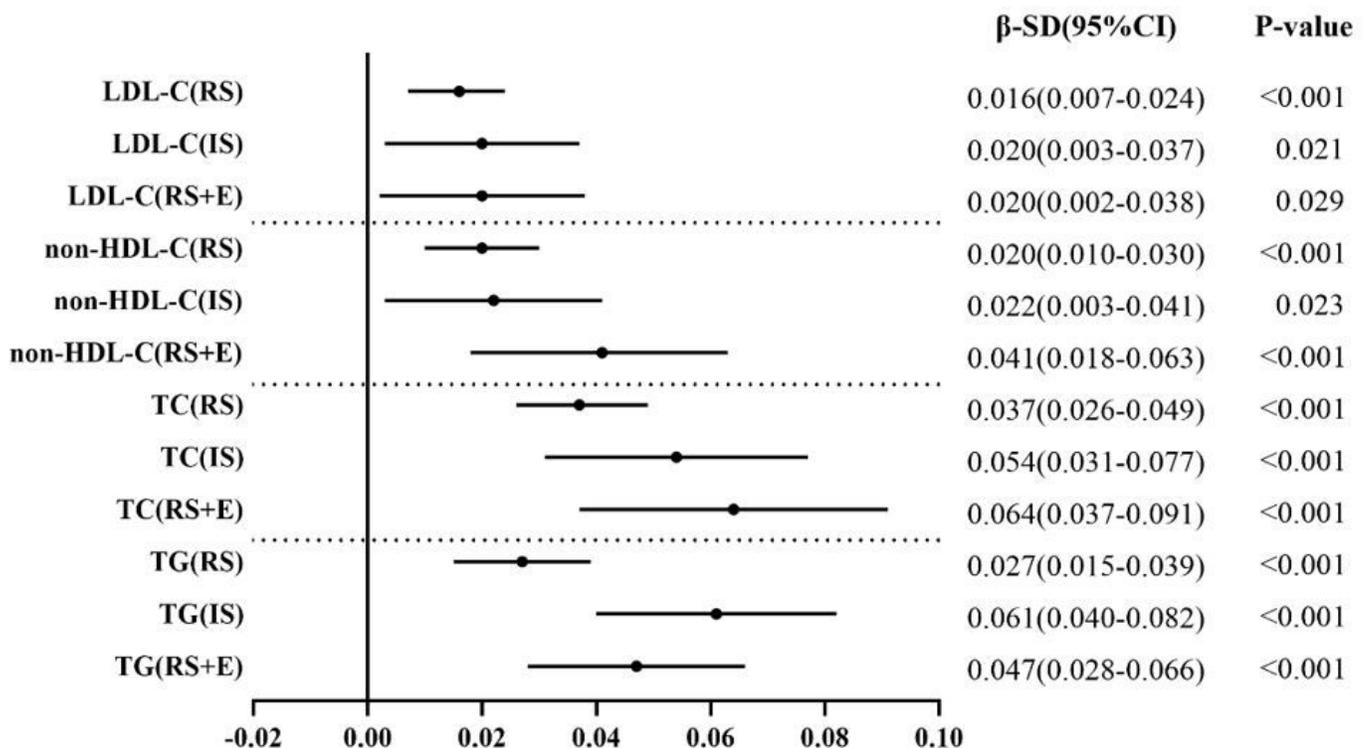


Figure 3

Multivariate analysis for the effect of HbA1c on lipid variability in the regular statin, intensive statin, and statin-ezetimibe combined therapy groups. Multivariate linear regression results for the effect of HbA1c on lipid variability, which was represented by SD. RS indicates regular statin therapy without ezetimibe; IS, intensive statin therapy without ezetimibe; RS+E, regular statin therapy combined with ezetimibe; β -SD, regression coefficients of HbA1c on SD; CI, confidence intervals.