Prognostic Significance of Visit-To-Visit Variability, Maximum and Minimum LDL Cholesterol in Diabetes Mellitus

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Abstract

BACKGROUND

Current guidelines for dyslipidemia management recommended that the LDL_C goal could be lower to less than 70 mg/dL. The present study was to investigate the prognostic significance of the visit-to-visit variability in LDL_C, and minimum and maximum LDL_C during follow-up in Diabetes mellitus.

METHODS

We studied the risk of outcomes in relation to visit-to-visit LDL_c variability in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial. LDL_c variability indices were coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV). Multivariable Cox proportional hazards models were employed to estimate adjusted hazard ratio (HR) and 95% confidence interval (CI).

RESULTS

Compared with the placebo group (n=2667), Fenofibrate therapy group (n=2673) had significantly (P<0.01) lower mean of plasma triglyceride (152.5 *vs.* 178.6 mg/dl), total cholesterol (158.3 vs.162.9 mg/dl), but similar mean LDL_C during follow-up (88.2 *vs.*88.6 mg/dl, P>0.05). All three variability indices were associated with primary outcome, total mortality and cardiovascular mortality both in total population and in Fenofibrate therapy group, but only with primary outcome in the placebo group. The minimum LDL_C but not the maximum during follow-up was significantly associated with various outcomes in total population, fenofibrate therapy and placebo group. The minimum LDL_C during follow-up ≥70 mg/dl was associated with increased risk for various outcomes.

CONCLUSIONS

Visit-to-visit variability in LDL_C was a strong predictor of outcomes, independent of mean LDL_C. Patients with LDL_C be controlled to less than 70 mg/dl at least once during follow-up might have a benign prognosis.

Background

Increased low-density lipoprotein cholesterol (LDL_C) is an established risk factor for cardiovascular disease and events, and lipid-lowering therapy with statins has been proved to be an effective way in lowering the risk of future cardiovascular events (1–3). However, the role of monitoring the level of LDL_C using a target-oriental way in patients on lipid-lowering therapy remained controversial (4). In addition, most studies whether observational studies or clinical trials just focused on the level of LDL_C in initial of study or the end of study, rarely on the variability or the persistence of LDL_C through the process of trial (5, 6).

Previous observational studies in diabetes have raised concerns on visit-to-visit lipid variability in relation to long-term major adverse cardiac event. The post-hoc analysis of Treating to New Targets (TNT) trial showed that visit-to-visit LDL-C variability was an independent predictor of cardiovascular events in patients 35 to 75 years of age who had known coronary artery disease (7). However, no studies concerned the prognostic value of visit-to-visit LDL-C variability and persistence of LDL_C control in type 2 diabetes at high cardiovascular risk.

Recent Joint European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guidelines recommended that LDL_C levels should be lowered as much as possible to prevent cardiovascular disease, especially in high and very high-risk patients (8). In high-risk patients, such as general diabetes mellitus, the LDL_C goal is <70 mg/dl or at least

50% reduction from baseline LDL_C levels. Thus, the benefits of persistence of LDL_C controlled to below 70 mg/dl might be a hot topic nowadays.

In the present study, we employed data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial to investigate the associations between visit-to-visit variability in LDL_C and primary outcome, and total and cardiovascular mortality in patients with type 2 diabetes who were at high risk for cardiovascular disease (9). Furthermore, we would like to investigate both the minimum and maximum LDL_C during follow-up, whether **or not** below 70 mg/dl, as predictors of deaths and major cardiovascular events in diabetes mellitus.

Methods

Study Population

The rationale, design, inclusion criteria, subject characteristics, and main results of ACCORD trial have been described (online study protocols: https://biolincc.nhlbi.nih.gov/studies/accord/) (9–13). In brief, the participants had the age between 40 and 79 years, had type 2 diabetes mellitus and a glycated hemoglobin level of ≥7.5%, had previous evidence of clinical cardiovascular disease or at least two additionally risk factors, and did not have a history of frequent or recent serious hypoglycemic events. All patients were randomly assigned to receive either intensive glycemic control targeting a glycated hemoglobin level below 6.0% or standard therapy targeting a glycated hemoglobin level of 7.0 to 7.9%.

ACCORD Lipid trial was conducted in a subgroup of patients in the ACCORD study, and was also performed randomization, in a 2-by-2 factorial design. Open-label simvastatin treatment started at the randomization time and either fenofibrate or placebo was masked given one month later. Randomization occurred between January 11, 2001, and October 29, 2005. End-of-study visits were scheduled between March and June 2009.

Patients were specifically eligible to participate in the lipid trial if they also had the following: an LDL cholesterol level of 60 to 180 mg/dL, an HDL cholesterol level below 55 mg/dL for women and blacks or below 50 mg/dL for all other groups, and a triglyceride level below 750 mg/dL if they were not receiving lipid therapy or below 400 mg/dL if they were receiving lipid therapy. All patients provided written informed consent.

Data Analysis

SAS software (Version 9.4, SAS Institute Inc, Cary, NC) was used for database management and statistical analysis. Means and proportions were compared using the large-sample z test and the $\chi 2$ statistic, respectively. Characteristics of study population included in the present analyses were shown by therapy status (Fenofibrate vs placebo) and baseline LDL variability levels (high vs low VIM)

We evaluated the visit-to-visit LDL_C variability using at least 3 measurements from the initial to the end of study, and calculated individual coefficient of variation (CV), independent of the mean (VIM) (14), and average real variability (ARV) (15). CV is calculated as the standard deviation (SD) divided by the mean. VIM is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x, with x derived from curve fitting. VIM can diminish the tight correlation between the CV and mean. ARV was calculated as the average of the absolute differences between consecutive LDL_C measurements. The prognostic significance of LDL_C variability for various outcomes was performed in multivariable Cox proportional hazards models, while adjusting for sex, therapy group, and baseline age, education, waist circumference, body mass index, systolic and diastolic blood pressure, and fasting plasma glucose. Two models were conducted as if it was additionally adjusted for the mean of LDL_C during visits or not.

The variability, and maximum and minimum LDL_C was investigated as a continuous variable using Cox proportional hazards models, and the hazard ratios (HRs) for various outcomes of one SD increment in LDL_C variability indices were reported. The maximum and minimum LDL_C was also investigated as a categorical variable and the HRs for various outcomes of ≥70 vs. <70 mg/dl were reported. In addition, HRs and 95% confidence intervals (CIs) for each decile relative to the first decile in the

placebo group and for each 10-percentile point increase in variability were estimated in a single model. Significance was a 2-tailed α-level of ≤0.05.

Results

Characteristics Of The Study Participants

Of all 5518 participants, 5340 performed LDL_C measurement on at least 3 visits during the study and were included in this analysis. The 5340 participants included 1632 women (30.6%), and had mean age was 62.8 (±6.6) years old. Key baseline characteristics were similar in the two therapy groups (Table 1).

Table 1
Characteristics of the Patients at Baseline or during follow-up

	All patients (n=5340)	Therapy Status[a]		LDL variability[b]		
		Fenofibrate(n=2673)	Placebo (n=2667)	VIM <13.2 (n=2665)	VIM ≥13.2 (n=2675)	P
At baseline						
Age	62.8±6.6	62.8±6.5	62.8±6.7	62.9±6.6	62.6±6.5	0.06
Female sex (n, %)	1632 (30.6)	817 (30.6)	815 (30.6)	770 (28.9)	862 (32.2)	0.008
Weight	94.9±18.3	94.6±18.2	95.2±18.5	95.6±17.9	94.3±18.7	0.009
Body-mass index	32.3±5.3	32.2±5.3	32.4±5.3	32.4±5.3	32.2±5.4	0.28
Waist circumference (cm)	107.7±13.5	107.5±13.3	107.8±13.7	108.1±13.4	107.2±13.6	0.02
Systolic blood pressure (mmHg)	133.9±17.7	133.8±17.6	133.9±17.9	132.2±17.2	135.5±18.1	<0.0001
Diastolic blood pressure (mmHg)	74.0±10.8	73.8±10.6	74.1±10.9	73.1±10.6	74.8±10.9	<0.0001
Fasting serum glucose (mg/dl)	175.8±54.6	176.3±54.1	175.3±55.1	170.7±51.8	180.8±56.8	<0.0001
Total cholesterol (mg/dl)	175.3±37.4	174.9±36.8	175.7±38.0	162.8±28.2	187.8±41.1	<0.0001
LDL cholesterol (mg/dl)	100.6±30.7	100.0±30.2	101.2±31.0	91.5±24	109.6±33.8	<0.0001
HDL cholesterol (mg/dl)	38.1±7.8	38.0±7.8	38.2±7.7	38.5±7.7	37.7±7.8	0.0005
Plasma triglyceride (mg/dl)	188.0±113	189.7±111,5	186.3±114.6	167±91.1	208.9±127.9	<0.0001
Serum creatinine (mg/dl)	0.92±0.22	0.93±0.23	0.93±0.22	0.92±0.23	0.93±0.21	0.04
Lipids during follow-up						
Mean total cholesterol (mg/dl)	160.6±26.8	158.3±26.2	162.9±27.2*	156.9±23.6	164.3±29.1	<0.0001

Values were means (SD) or median (quartile). VIM indicates variability independent of the mean; ARV, average real variability; and MMD, the difference of maximum minus minimum LDL. [a]The Fenofibrate vs Placebo group, *P<0.001; †P<0.01; and ‡P<0.05. [b]High vs Low VIM, and the *P* value is given.

	All patients (n=5340)	Therapy Status[a]		LDL variability[b]		
		Fenofibrate(n=2673)	Placebo (n=2667)	VIM <13.2 (n=2665)	VIM ≥13.2 (n=2675)	P
Mean plasma triglyceride (mg/dl)	165.5±88.5	152.5±80.6	178.6±94.0*	151.4±72.6	179.5±100	<0.0001
Mean HDL cholesterol (mg/dl)	39.9±8.2	40.2±8.7	39.5±7.8*	40.5±8.3	39.2±8.1	<0.0001
Mean LDL cholesterol (mg/dl)	88.4±19.8	88.2±19.9	88.6±19.7	86.6±18.4	90.1±21.0	<0.0001
Maximum LDL cholesterol (mg/dl)	120.1±29.6	119.0±29.6	121.3±29.5*	107.4±22.7	132.8±30.2	<0.0001
Minimum LDL cholesterol (mg/dl)	64.2±17.8	64.7±17.5	63.7±18.0‡	68.2±17.1	60.1±17.5	<0.0001
LDL SD	19.3±8.8	18.7±8.8	19.9±8.8*	13.5±4.8	25.1±8.1	<0.0001
LDL CV (%)	22.1±9.2	21.4±9.0	22.7±9.4*	15.8±5.3	28.3±8.0	<0.0001
LDL VIM	13.9±6.0	13.8±6.0	14.1±5.9	9.3±2.5	18.5±4.8	<0.0001
LDL ARV	18.4±9.6	17.7±9.5	19.0±9.6*	13.7±5.8	23.0±10.3	<0.0001

Values were means (SD) or median (quartile). VIM indicates variability independent of the mean; ARV, average real variability; and MMD, the difference of maximum minus minimum LDL. [a]The Fenofibrate vs Placebo group, *P<0.001; †P<0.01; and ‡P<0.05. [b]High vs Low VIM, and the *P* value is given.

Compared with the placebo group, the Fenofibrate group had significantly (*P*<0.001) lower total cholesterol (158.3 *vs.* 162.9 mg/dl) and triglyceride levels (152.5 *vs.* 178.6 mg/dl), but higher HDL levels (40.2 vs. 39.5 mg/dl). For LDL_C levels, the Fenofibrate group showed similar mean LDL_C, higher maximum LDL_C (120.1 vs. 119.0 mg/dl), but lower minimum LDL_C (63.7 vs. 64.7 mg/dl). For LDL_C variability indices, the Fenofibrate group showed no difference in mean LDL level and LDL VIM, but lower SD and ARV (all *P*<0.001, Table 1).

Compared with low LDL_C variability (VIM<13.2), high LDL_C variability (VIM≥13.2) group had significantly greater baseline body weight and waist circumference, and significantly (*P*<0.0001) higher baseline systolic and diastolic blood pressure, fasting serum glucose, and total, HDL and LDL cholesterol, but lower triglyceride levels. Increased LDL_C variability group had significantly (P<0.0001) higher total and LDL cholesterol and triglyceride, but lower HDL cholesterol. As expected, increased LDL_C variability group had significantly (*P*<0.0001) higher various LDL_C variability indices, including SD, VIM, and ARV (Table 1).

Variability Indices And Outcomes

During the trial, the primary outcome, all-cause deaths and cardiovascular deaths occurred in 276, 179 and 87 subjects in the Fenofibrate, respectively, and in 294, 201 and 102 subjects in the placebo group, respectively. In multiple C ox regression analyses adjusted for sex and age, education, waist circumference, body mass index, systolic and diastolic blood pressure, and fasting plasma glucose at baseline, and additionally mean LDL_C during follow-up, all three LDL_C variability indices were significantly (*P*<0.001) associated with primary outcome, and all-cause and cardiovascular deaths in total population and the

Fenofibrate group. However, in the placebo group, only LDL_C ARV was significantly associated with total and cardiovascular deaths (Table 2).

Table 2
Association of mean and variability indexes of LDL cholesterol during follow-up with Outcomes

Outcomes	Model	Total population (n=5340)		Fenofibrate(n=2673)		Placebo (n=2667)	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Primary outcome							
Mean (+20 mg/dl)	None[a]	1.33 (1.22-1.45)	<0.0001	1.33 (1.17-1.51)	<0.0001	1.34 (1.19-1.51)	<0.0001
CV (+9.2%)	None[a]	0.93 (0.85-1.02)	0.13	1.05 (0.92-1.20)	0.44	0.83 (0.73-0.94)	0.004
	Mean[b]	0.97 (0.88-1.06)	0.47	1.09 (0.95-1.24)	0.21	0.86 (0.75-0.98)	0.023
VIM (+6 U)	None[a]	0.88 (0.71-1.09)	0.24	1.16 (0.87-1.56)	0.31	0.67 (0.50-0.90)	0.008
	Mean[b]	0.92 (0.74-1.14)	0.44	1.21 (0.89-1.62)	0.22	0.70 (0.52-0.95)	0.02
ARV (+10 mg/dl)	None[a]	1.51 (1.31-1.75)	<0.0001	1.64 (1.36-1.97)	<0.0001	1.35 (1.09-1.68)	0.006
	Mean[b]	1.27 (1.07-1.49)	0.005	1.20 (1.04-1.39)	0.01	1.32 (1.16-1.50)	<0.0001
Total mortality							
Mean (+20 mg/dl)	None[a]	1.32 (1.19-1.46)	<0.0001	1.25 (1.07-1.46)	0.004	1.37 (1.20-1.56)	<0.0001
CV (+9.2%)	None[a]	1.07 (0.97-1.18)	0.19	1.26 (1.10-1.44)	0.001	0.93 (0.81-1.07)	0.29
	Mean	1.12 (1.01-1.23)	0.03	1.29 (1.13-1.49)	0.0003	0.98 (0.85-1.13)	0.77
VIM (+6 U)	None[a]	1.15 (1.05-1.27)	0.004	1.26 (1.12-1.43)	0.0003	1.06 (0.92-1.22)	0.45
	Mean[b]	1.13 (1.03-1.25)	0.01	1.25 (1.10-1.42)	0.0007	1.04 (0.90-1.19)	0.63
ARV (+10 mg/dl)	None[a]	1.37 (1.26-1.49)	<0.0001	1.35 (1.21-1.52)	<0.0001	1.40 (1.24-1.59)	<0.0001
	Mean[b]	1.29 (1.17-1.42)	<0.0001	1.31 (1.15-1.51)	<0.0001	1.29 (1.12-1.48)	0.0006
Cardiovascular mortality							
Mean (+20 mg/dl)	None[a]	1.34 (1.16-1.54)	<0.0001	1.30 (1.05-1.62)	0.018	1.36 (1.13-1.64)	0.001
CV (+9.2%)	None[a]	1.04 (0.90-1.20)	0.59	1.33 (1.10-1.61)	0.003	0.83 (0.67-1.01)	0.07

Model indicates which LDL index was entered into the models in addition to the predictor variable per se. VIM indicates variability independent of the mean; ARV, average real variability; and MMD, the difference of maximum minus minimum LDL. All models were adjusted for mean of lipid during visits, therapy group (if applicable), sex, and baseline age, education, body mass index, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose. [a]None indicates that no LDL cholesterol index was entered in the model. [b]Mean indicates that the mean of LDL_C during visits was additionally entered in the model.

Outcomes	Model	Total population (n=5340)		Fenofibrate(n=2673)		Placebo (n=2667)	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
	Mean[b]	1.09 (0.94-1.26)	0.27	1.37 (1.13-1.66)	0.001	0.86 (0.70-1.07)	0.17
VIM (+6 U)	None[a]	1.17 (1.02-1.34)	0.02	1.38 (1.18-1.61)	<0.0001	0.96 (0.78-1.18)	0.68
	Mean[b]	1.15 (1.00-1.31)	0.047	1.35 (1.16-1.59)	0.0002	0.94 (0.76-1.15)	0.53
ARV (+10 mg/dl)	None[a]	1.37 (1.22-1.55)	<0.0001	1.44 (1.24-1.68)	<0.0001	1.29 (1.07-1.55)	0.008
	Mean[b]	1.28 (1.11-1.47)	0.0006	1.40 (1.17-1.68)	0.0003	1.15 (0.93-1.42)	0.19

Model indicates which LDL index was entered into the models in addition to the predictor variable per se. VIM indicates variability independent of the mean; ARV, average real variability; and MMD, the difference of maximum minus minimum LDL. All models were adjusted for mean of lipid during visits, therapy group (if applicable), sex, and baseline age, education, body mass index, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose. [a]None indicates that no LDL cholesterol index was entered in the model. [b]Mean indicates that the mean of LDL_C during visits was additionally entered in the model.

To allow for nonlinearity, all three LDL_C variability indices were split into deciles and HRs calculated in relation to the first decile in the placebo group. For the primary outcome, only the 10th decile of LDL_C VIM and ARV in both groups had significantly higher risk (**Figure 1B**). For all-cause deaths, only the 10th decile of LDL_C CV in the intensive-therapy group had marginally significantly higher risk (**Figure 1C**). For cardiovascular deaths, some deciles of LDL_C variability indices had significantly lower risk but not higher risk.

Maximum And Minimum Ldl_c During Follow-up And Outcomes

In multiple Cox regression analyses, the mean LDL_C during follow-up was significantly associated with primary outcome, total mortality, and cardiovascular mortality in total population, the Fenofibrate group, and the placebo group (Table 2). We further investigated the prognostic variability of maximum and minimum LDL_C during follow-up to look at the most benefits in the way of lipid control. In multivariate analysis adjusted for other covariates and mean LDL_C during follow-up, the minimum but not the maximum LDL_C were more frequently significantly associated with the primary outcome, and total and cardiovascular deaths in total population, as well as in the Fenofibrate and placebo groups analyzed separately. The hazard ratios of the 1-SD increase in minimum LDL_C were 1.54 (95%CI, 1.41-1.67), 1.41 (1.28-1.56), and 1.54 (1.34-1.77) for primary outcome, all-cause deaths and cardiovascular deaths, respectively in the total population (Table 3**).**

Table 3
Hazard ratios for top decile of maximum and minimum LDL cholesterol during follow-up for Outcomes

	Total population (n=5340)		Fenofibrate(n=2673)		Placebo (n=2667)	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Maximum LDL_C						
+1 SD (30 mg/dL)						
Primary outcome	1.10 (1.01-1.20)	0.04	1.15 (1.01-1.31)	0.03	1.15 (1.01-1.31)	0.03
All-cause deaths	1.12 (1.01-1.23)	0.04	1.16 (0.99-1.34)	0.06	1.08 (0.94-1.24)	0.30
Cardiovascular deaths	1.15 (0.99-1.33)	0.054	1.26 (1.02-1.56)	0.03	1.05 (0.87-1.28)	0.60
≥70 **vs. <70** mg/dL						
Primary outcome	0.85 (0.48-1.52)	0.59	0.75 (0.33-1.69)	0.49	0.98 (0.43-2.20)	0.95
All-cause deaths	0.61 (0.34-1.12)	0.11	0.50 (0.21-1.24)	0.13	0.70 (0.31-1.61)	0.40
Cardiovascular deaths	0.48 (0.23-1.03)	0.06	0.62 (0.15-2.56)	0.51	0.43 (0.17-1.07)	0.07
Minimum LDL_C						
+1 SD (18 mg/dL)						
Primary outcome	1.54 (1.41-1.67)	<0.0001	1.48 (1.31-1.68)	<0.0001	1.60 (1.42-1.80)	<0.0001
All-cause deaths	1.41 (1.28-1.56)	<0.0001	1.31 (1.13-1.53)	0.0005	1.50 (1.31-1.70)	<0.0001
Cardiovascular deaths	1.54 (1.34-1.77)	<0.0001	1.43 (1.15-1.78)	0.001	1.63 (1.36-1.96)	<0.0001
≥70 *vs.* <70 mg/dL						
Primary outcome	2.11 (1.77-2.52)	<0.0001	1.95 (1.51-2.52)	<0.0001	2.30 (1.79-2.94)	<0.0001
All-cause deaths	1.60 (1.31-1.97)	<0.0001	1.48 (1.10-1.99)	0.01	1.73 (1.30-2.28)	0.0001
Cardiovascular deaths	2.03 (1.52-2.70)	<0.0001	1.70 (1.11-2.60)	0.02	2.39 (1.61-3.53)	<0.0001

All models were adjusted for therapy group (if applicable), sex, and baseline age, education, body mass index, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose.

We further looked into the maximum and minimum LDL_C exceed 70 mg/dl, the threshold recommended by recent guideline, in relation to various outcomes. In similar adjusted analysis, the minimum but not the maximum LDL_C exceeded 70 mg/dl were significantly ($P \leq 0.01$) associated with the primary outcome, and total and cardiovascular deaths in total population, as well as in the Fenofibrate and placebo groups analyzed separately. The hazard ratios of minimum LDL_C≥ 70 mg/dl were 2.11 (95%CI, 1.77-2.52), 1.60 (1.31-1.97), and 2.03 (1.52-2.70) for primary outcome, all-cause deaths and cardiovascular deaths, respectively in the total population (Table 3).

Discussion

In the present study, three variability indices of LDL_C (CV, VIM and ARV) were analyzed in type 2 diabetes. The key findings can be summarized in 3 points: (1) visit-to-visit variability in LDL_C was an independent and powerful predictor of primary outcome, all-cause and cardiovascular deaths, independent of mean LDL_C and Fenofibrate treatment effect; (2) the minimum but not the maximum LDL_C were significantly associated with the various outcomes in both the Fenofibrate and placebo groups; (3) the minimum LDL_C exceed 70 mg/dl, the threshold recommended by recent guideline, was associated with various outcomes. These findings raised the issue that visit-to-visit LDL_C variability might be an important risk factor for outcomes, and the LDL_C able to control to less than 70 mg/dl at least once might have a benign prognosis.

Several observational studies confirmed the relationship between LDL_C variability and major adverse cardiac event in patients after ST-segment elevation myocardial infarction (16), or patients with previous myocardial infarction (17), or elderly patients at high risk of vascular disease (18). Analysis from the TNT (Treating to New Targets) trial showed that visit-to-visit LDL-C variability is an independent predictor of cardiovascular events in subjects with coronary artery disease (19). In this study, a 1-SD increase in LDL-C variability conferred higher risk of any coronary event, any cardiovascular event, death, myocardial infarction, and stroke by 10–23%. The results of the present study also indicate that visit-to-visit variability in LDL-C (SD, CV, and ARV) was lower in the Fenofibrate group compared with the placebo group, irrespective of the statins therapy status. However, the mean LDL_C level was similar between the two groups, which showed that Fenofibrate did not reduce LDL_C level, but did reduce the LDL_C variability. The LDL_C variability (CV and VIM) was only significantly associated with both total and cardiovascular mortality in the Fenofibrate group but not the placebo group. However, the ARV of LDL_C was associated with various outcomes in both the Fenofibrate and placebo groups.

To the best of our knowledge, the current analysis was the first to the study the prognostic significance for LDL_C variability in type 2 diabetes. In 864 patients with type 2 diabetes aged 62.7 (±11.8) years, with a median follow-up of 3.8 years, HDL_C rather than LDL_C variability was associated with higher risk of diabetic nephropathy progression (20). Another study investigated the association between the variability of LDL_C, systolic blood pressure, diastolic blood pressure, and total-, HDL- and LDL-cholesterol in Type 2 diabetic patients with the risk of diabetic kidney disease (21). The study found the combination of high variability in LDL_C and HDL-C conferred the highest risk of developing albuminuria (HR 1.47; 95% CI 1.17-1.84). The present study confirmed high LDL-C variability was a predictor of primary outcome and mortality in diabetes mellitus.

The exact mechanism concerning increased LDL-C variability to a high risk of primary outcome and total and cardiovascular deaths remains unknown. However, there are several possible explanations. Because greater LDL-C variability might increase the likelihood of plaque vulnerability and rupture, it may lead to instability at the vascular wall, as a result of variability in lipid efflux mechanism, thereby increase the risk of cardiovascular events (19). Under the conditions of high plasma glucose or diabetes mellitus, the detriment of atherosclerosis might be amplified. In fact, associations between diabetes and atherosclerosis are well established (22). Amount data on clinical trials and experimental experiment showing the onset of diabetes mellitus complications are associated with atherosclerosis, which means that the important role of diabetes mellites might induce damage on endothelium function, and then cause an instability on vascular homeostasis (23, 24).

Recent dyslipidemia management guidelines recommended that LDL_C levels should be lowered as much as possible to prevent cardiovascular disease, especially in high and very high-risk patients. In high-risk patients, such as general diabetes mellitus, the LDL_C goal is <70 mg/dl or at least 50% reduction from baseline LDL_C levels (8). Our study was the first to investigate the prognostic significance of minimum and maximum LDL_C during follow-up, and found that the minimum but not the maximum LDL_C were significantly associated with the primary outcome, and total and cardiovascular deaths in both the Fenofibrate and placebo groups and the minimum LDL_C exceed 70 mg/dl was associated with various outcomes. The results mean that the LDL_C able to control to less than 70 mg/dl at least once during follow-up might have a benign prognosis.

Our study should be interpreted within the context of its strengths and limitations. The main strengths of our study include a large number of LDL_C measures, which enable us to accurately calculate LDL_C variability. In addition, as many as three variability indices were used and those enable us to study LDL_C variability more comprehensively. Furthermore, for primary outcome analysis, we calculated time-dependent measures of variation before the events happened. The analyses also have

limitations. Because of the post hoc nature of the analysis and the highly selected study population, and the results should be investigated in other studies and extended to real world studies. Another limitation was that this study was fenofibrate rather than statins treatment trial, and information on the statins usage was lacking, which affect the stability of LDL_C.

In conclusion, visit-to-visit variability in LDL_C was a strong predictor of outcomes, independent of mean LDL_C. The LDL_C able to control to less than 70 mg/dl at least once during follow-up might have a benign prognosis.

Declarations

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Authors' contributions All authors participated in critical revision of the manuscript for important intellectual content. C.-S.S. and Y.M. contributed to the statistical analysis and wrote the manuscript. C.-S.S., Y.M., L.D., Y.C., D.W.; and Y.Y. participated in acquisition, analysis, or interpretation of data. C.-S.S., and J.T. reviewed and edited the manuscript. C.-S.S., and J.T. is the guarantor of the work and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request or the ACCORD trial group.

Disclosures of Interest No potential conflicts of interest relevant to this article were reported.

Ethics approval and consent to participate

The protocol was approved by the institutional review board or ethics committee at each center and by an independent protocol review committee appointed by the NHLBI.

Declaration of Helsinki The authors state that this study complies with the Declaration of Helsinki.

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Figures

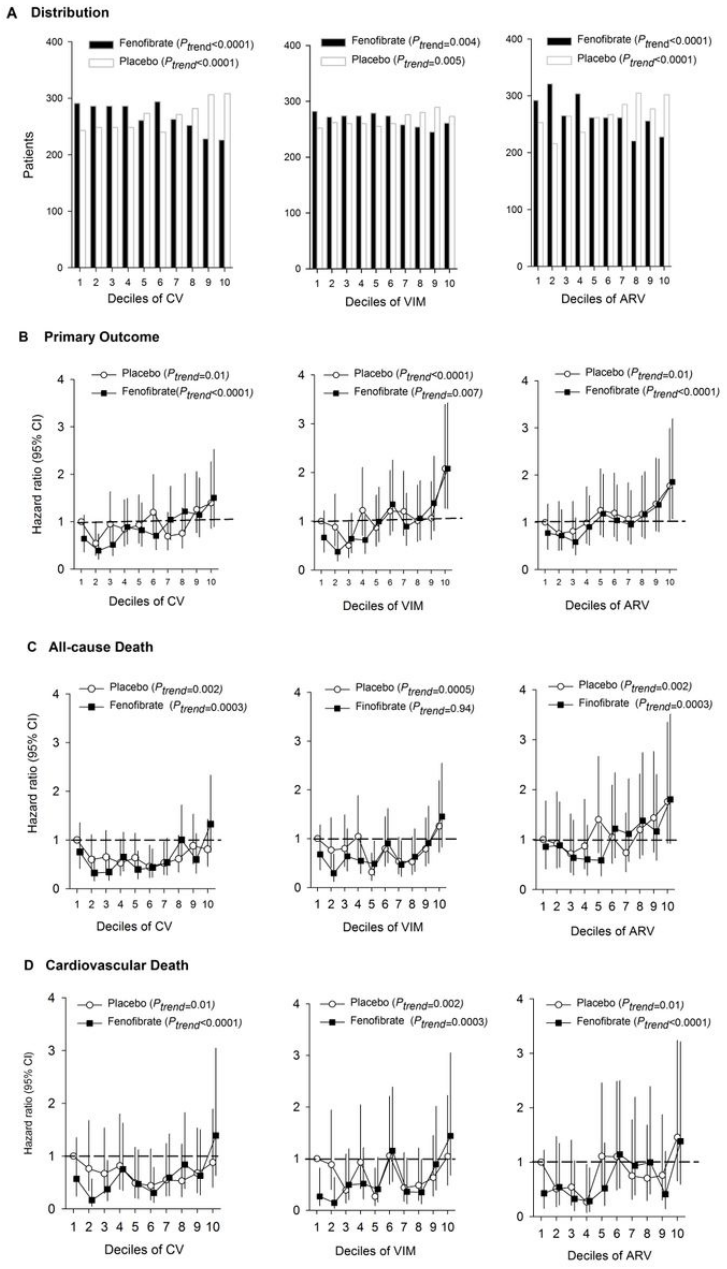

Figure 1

Hazard ratios for risk of outcomes by decile of LDL cholesterol variability indices. All Hazard ratios for primary outcome (B), all-cause death (C) and cardiovascular death (D) were adjusted for mean of lipid during visits, sex, and baseline age, education, body mass index, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose. Hazard ratios and 95% confidence intervals for each decile relative to the first decile in the placebo group and for each 10-percentile point increase in variability were estimated in a single model. The distributions of variability indices were also shown (A). VIM indicates variability independent of the mean (left); ARV, average real variability (middle); and MMD, the difference of maximum minus minimum LDL_C (right).

Supplementary Files

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- LHDSupplementalTables.docx