Visit-to-visit variability in low-density lipoprotein cholesterol is associated with adverse events in non-obstructive coronary artery disease

Original Investigation

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ABSTRACT

Objective: A higher visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) is associated with an increased frequency of cardiovascular events. We investigated the association between the visit-to-visit LDL-C variability and all-cause mortality, myocardial infarction (MI), and coronary revascularization in a population with non-obstructive coronary artery disease (CAD).

Methods: From this retrospective cohort of individuals who underwent coronary angiography from 2006 to 2010, a total of 2,012 consecutive patients with non-obstructive CAD, who underwent three or more LDL-C determinations during the first 2 years, were identified and followed up for 5 years. The variability in the visit-to-visit LDL-C was measured by standard deviation (SD) and coefficient of variation (CV). The risk of all-cause mortality and composite endpoints, MI, and coronary revascularization were evaluated by a multivariable Cox regression analysis.

Results: During a 5-year follow-up, a total of 99 (4.92%) mortality cases and 154 (7.65%) cases of composite endpoints were observed. The percentage of subjects who experienced mortality or composite endpoints was higher in those with a higher LDL-C-SD or LDL-C-CV level. The association between the LDL-C variability and clinical endpoints was regardless of possible confounding factors.

Conclusion: Among the patients with non-obstructive CAD, a higher visit-to-visit LDL-C variability is associated with increasing all-cause mortality or composite endpoints during the long-term follow-up. (Anatol J Cardiol 2019; 22: 117-24)

Keywords: coronary artery disease, low-density lipoprotein, cholesterol, variability, cardiovascular outcomes

Introduction

The intra-individual variability in multiple physiologic indicators has attracted increasing concern in recent years. A lower heart rate variability and higher blood pressure or glycemic variability have been reported to be associated with adverse clinical outcomes (1-6). Recently, a high visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) levels has also been identified as an independent predictor of adverse cardiovascular events (7-13).

Non-obstructive coronary artery disease (CAD) refers to the presence of coronary atherosclerosis without apparent coronary stenosis (14-17), and the progression and rupture of these lesions play a critical role in the pathogenesis of cardiovascular events (16). Prior studies have noted that non-obstructive CAD is associated with a higher risk of cardiovascular events than near-normal coronary artery (16). To date, optimal management strategies for this population have not yet been established (17). Hence, more information on non-obstructive CAD patients and their longitudinal clinical outcomes is required to understand their risks for major adverse cardiovascular events (MACEs) and latent therapeutic implications.

So far, to the best of our knowledge, no study has assessed the role of cholesterol variability as a determinant of cardiovascular events or mortality among the population with non-obstructive CAD. Therefore, we conducted a retrospective cohort
study involving more than 2,000 patients with non-obstructive CAD to investigate the prognostic significance of an increased LDL-C variability on all-cause mortality and composite endpoints [death, myocardial infarction (MI), coronary revascularization] during a 5-year follow-up.

Methods

Study population
We conducted a retrospective cohort study of adults with non-obstructive CAD, which was defined as a coronary artery stenosis ≥20% or more but <50% in the left main coronary artery or a stenosis ≥20% or more but <70% in any other epicardial coronary artery, as documented by the clinician in the coronary angiography (CAG) report (14). In brief, we identified a total of 2,012 patients with non-obstructive CAD among the cohort of 6,125 consecutive individuals from January 2006 to December 2010. The enrolled patients had undergone at least 3 LDL-C measurements during the first 2 years (baseline LDL-C variability), followed by a 5-year follow-up. Major exclusion criteria included heart failure; acute coronary syndrome; previous statin prescription; a history of MI, PCI, or CABG; and chronic kidney disease [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²]. Patients who experienced all-cause death, MI, or coronary revascularization during the period of baseline LDL-C variability (the first 2 years) were excluded. The medication possession ratio (MPR), known as the proportion of days covered, was calculated as the sum of days’ supply of medicine obtained between the first fill and the last fill divided by the total number of days in this period. The MPR was calculated using all statin fills during the study period. If patients were prescribed with statin, patients with statin MPR <80% were excluded. The research protocol was approved by the Local Ethics Committee, and written informed consent was obtained from all the participants.

Definition of LDL-C variability
The intra-individual mean (LDL-C-mean) was calculated according to the mean value of continuous measured LDL-C in each patient. The standard deviation of serial LDL-C measurements (LDL-C-SD) was measured as LDL-C variability. The coefficient of variation of LDL-C (LDL-C-CV) was used to correct the mean. Due to the lack of existing cutoffs for the LDL-C variability indices, we divided subjects into higher and lower groups, based on the median of each LDL-C variability indices.

Outcome measures
The primary outcome measure was an all-cause mortality during the follow-up period, and the secondary outcome was a composite of all-cause mortality, MI, and coronary revascularization. The study population was followed from baseline to the date of death or cardiovascular events, or the end of study, whichever came first. Most patients visited our clinic at least every 3 months. However, if the patients did not show up at their scheduled clinic, they were interviewed by telephone.

Statistical analysis
Statistical analysis was performed using the SPSS Statistical Software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean ± standard deviation (SD) and categorical variables as absolute number (n) and/or percent. An independent sample t-test and Chi-square test were used for between-group comparisons of quantitative or qualitative variables. The Cox proportional hazards regression model was used to explore the association between risk factors and the risk of all-cause mortality or composite endpoints. All predictors with a significance of p<0.10 in the univariable analysis and forced inclusion variables were entered into the multivariable model. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were reported. The Kaplan–Meier statistical analysis showed freedom from occurrence of all-cause mortality or composite endpoints at 5 years, and the log-rank test was used to assess differences between the groups. All p-values were two sided, and the alpha criterion was set to 0.05.

Results

Baseline characteristic
Characteristics of participants by the SD median for LDL-C are described in Table 1. The median value of LDL-C-SD or LDL-C-CV was 22 mg/dL, 24.49%, respectively. Subjects in the lower LDL-C-SD group used statin more frequently. No difference was found with regard the LDL-C-mean or number of LDL-C measurements between the two groups. Similar patterns of baseline characteristics were noted by the median of LDL-C-CV (Table 2).

All-cause mortality
There were 99 (4.92%) mortality cases during a 5-year follow-up in the entire cohort. The percentage of subjects who experienced all-cause mortality was lower in those with low LDL-C variability compared with high LDL-C variability [LDL-C-SD (low vs. high): 30/1006 vs. 69/1006, p<0.001; LDL-C-CV (low vs. high): 31/1007 vs. 68/1005, p<0.001]. The annualized mortality rate was 0.60% in the low LDL-C-SD group and 1.41% in the high LDL-C-SD group. Statistical analysis was performed using the SPSS Statistical Software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean ± standard deviation (SD) and categorical variables as absolute number (n) and/or percent. An independent sample t-test and Chi-square test were used for between-group comparisons of quantitative or qualitative variables. The Cox proportional hazards regression model was used to explore the association between risk factors and the risk of all-cause mortality or composite endpoints. All predictors with a significance of p<0.10 in the univariable analysis and forced inclusion variables were entered into the multivariable model. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were reported. The Kaplan–Meier statistical analysis showed freedom from occurrence of all-cause mortality or composite endpoints at 5 years, and the log-rank test was used to assess differences between the groups. All p-values were two sided, and the alpha criterion was set to 0.05.
associated with a decreased risk of all-cause mortality (Table 3). When using LDL-C-CV instead of LDL-C-SD in Model 2, LDL-C-CV was associated with an increased risk of all-cause mortality, and aspirin or statin therapies were associated with a decreased risk of all-cause mortality (Table 3).
risk of all-cause mortality (Table 3). When the interaction effects of LDL-C variability and statin or aspirin were further entered into the multivariable Cox regression model, the results indicated that LDL-C-SD (HR 2.032, 95% CI: 1.158–3.564, p=0.013) or LDL-C-CV (HR 1.779, 95% CI: 1.053–3.008, p=0.031) was still associated with an increased risk of all-cause mortality. The Kaplan–Meier plots for the occurrence of all-cause mortality between different LDL-C variability levels were in Figures 1a, 1b.

As for the relationship between the LDL-C variability and cardiovascular or non-cardiovascular death, a higher LDL-C-SD led to both increased cardiovascular [LDL-C-SD (low vs. high) 11/1006 vs. 33/1006, p=0.001] and non-cardiovascular death [LDL-C-SD (low vs. high) 19/1006 vs. 36/1006, p=0.020]. In addition, every 1-SD increase of LDL-C variability (LDL-C-SD) predicted a 44.6% greater likelihood of mortality (HR 1.446, 95% CI: 1.182–1.768, p<0.001).

**LDL-C variability and composite endpoints**

There were 154 (7.65%) cases of composite endpoints during the follow-up. The percentage of subjects who experienced combined endpoints was lower in those with a lower LDL-C variability group compared with a higher LDL-C variability group [LDL-C-SD (low vs. high): 56/1006 vs. 98/1006, p<0.001; LDL-C-CV (low vs. high): 59/1007 vs. 95/1005, p=0.002]. The annualized events rate was 1.14% in the low LDL-C-SD group and 2.02% in the high LDL-C-SD group. For the multivariable regression analysis in Model 3, variables (age, gender, medical history, medications, clinical status, laboratory variables) were entered into the univariate regression analysis, and variables with p<0.10 [age, LDL-C-SD (high or low), aspirin, statin] and forced inclusion variables that were considered as important predictors of clinical endpoints or associated with LDL-C variability (gender, eGFR, LDL-C-mean, baseline number of measurements) were entered into the multivariable regression analysis. The results indicated that LDL-C-SD (low vs. high) 1.758 (95% CI: 1.265–2.442, p=0.001) or LDL-C-CV (low vs. high) 1.634 (95% CI: 1.180–2.263, p=0.003) was still associated with an increased risk of composite endpoints. The Kaplan–Meier plots for the occurrence of composite endpoints between different LDL-C variability levels were in Figures 2a, 2b.

**Table 3. Multivariable Cox analysis for all-cause mortality**

|                | HR (Model 1) | 95% CI          | P value | HR (Model 2) | 95% CI          | P value |
|----------------|--------------|-----------------|---------|--------------|-----------------|---------|
| LDL-C-SD (high, low) | 2.272        | 1.479–3.491     | <0.001  | -            | -               | -       |
| LDL-C-CV (high, low)  | -            | -               | -       | 2.204        | 1.440–3.372     | <0.001  |
| Age             | 1.027        | 0.999–1.055     | 0.058   | 1.026        | 0.998–1.054     | 0.064   |
| Gender          | 0.935        | 0.617–1.418     | 0.752   | 0.992        | 0.608–1.398     | 0.702   |
| Aspirin         | 0.660        | 0.443–0.982     | 0.041   | 0.652        | 0.438–0.972     | 0.036   |
| Statin          | 0.643        | 0.426–0.976     | 0.036   | 0.635        | 0.420–0.959     | 0.031   |
| Baseline LDL-C   | 1.000        | 0.980–1.021     | 0.964   | 0.999        | 0.979–1.020     | 0.947   |
| number of measurements | 0.999       | 0.912–1.094     | 0.983   | 1.006        | 0.920–1.101     | 0.894   |

**Table 4. Multivariable Cox analysis for composite endpoints**

|                | HR (Model 3) | 95% CI          | P value | HR (Model 4) | 95% CI          | P value |
|----------------|--------------|-----------------|---------|--------------|-----------------|---------|
| LDL-C-SD (high, low) | 1.758        | 1.265–2.442     | 0.001   | -            | -               | -       |
| LDL-C-CV (high, low)  | -            | -               | -       | 1.634        | 1.180–2.263     | 0.003   |
| Age             | 1.108        | 0.996–1.400     | 0.110   | 1.017        | 0.996–1.400     | 0.117   |
| Gender          | 1.052        | 0.758–1.460     | 0.762   | 1.042        | 0.751–1.447     | 0.805   |
| Aspirin         | 0.690        | 0.502–0.949     | 0.023   | 0.686        | 0.499–0.943     | 0.020   |
| Statin          | 0.746        | 0.531–1.047     | 0.091   | 0.739        | 0.526–1.038     | 0.081   |
| Baseline LDL-C   | 1.001        | 0.985–1.018     | 0.880   | 1.001        | 0.984–1.017     | 0.948   |
| number of measurements | 0.999       | 0.924–1.069     | 0.874   | 0.999        | 0.930–1.074     | 0.979   |

eGFR - estimated glomerular filtration rate; CI - confidence interval; LDL-C-SD - standard deviation of low-density lipoprotein cholesterol; LDL-C-CV - coefficient of variation of low-density lipoprotein cholesterol
LDL-C, number of LDL-C measurements) were further entered into the multivariable Cox regression model. The result showed that LDL-C-SD (HR 1.758, 95% CI: 1.265–2.442, p=0.001) was associated with an increased risk of all-cause mortality, and aspirin therapy was associated with a decreased risk of all-cause mortality (Table 4). When using LDL-C-CV instead of LDL-C-SD in Model 3, LDL-C-CV was associated with an increased risk of all-cause mortality, and aspirin therapy was associated with a decreased risk of all-cause mortality (Table 4). When the interaction effects of LDL-C variability and statin or aspirin were further entered into the multivariable Cox regression model, and the results indicated that LDL-C-SD (HR 2.090, 95% CI: 1.334–3.273, p=0.001) or LDL-C-CV (HR 1.694, 95% CI: 1.103–2.603, p=0.016) was still associated with an increased risk of all-cause mortality. The Kaplan–Meier plots for the occurrence of composite endpoints between different LDL-C variability levels were presented in Figures 1c, 1d.

With respect to the association between the LDL variability and MI/coronary revascularization, separately, we found a decrease trend in lower LDL-C variability group [LDL-C-SD (low vs. high): 30/1006 vs. 46/1006, p=0.061].

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**Figure 1.** Kaplan–Meier curves of freedom from all-cause mortality (a, b) and composite endpoints (c, d) for low and high LDL-C variability after a 5-year follow-up in total HF patients. Numbers at the bottom of the figure are “numbers at risk.”
**Statin and LDL-C variability**

Taking statin can greatly affect the cholesterol variability (18-20). Therefore, we performed a detailed analysis according to the use of statin. Subjects receiving statin therapy showed a lower LDL-C mean (92±26 mg/dL vs. 95±29 mg/dL, p<0.001), as well as the LDL-C variability (LDL-C-SD: 21.2±3.9 mg/dL vs. 21.8±3.7 mg/dL p=0.009; LDL-C-CV: 25.6±9.1% vs. 26.6±9.6%, p=0.080) compared with subjects without statin treatment. Similarly, statin therapy led to a favorable prognosis in all-cause death (63/1490 vs. 36/522, p=0.015) or composite endpoints (104/1490 vs. 50/522, p=0.055).

**Discussion**

In this long-term retrospective cohort study, we investigated the association between the LDL-C variability and the risk of all-cause mortality, MI, and coronary revascularization in a population with non-obstructive CAD. The results indicate that visit-to-visit LDL-C variability is a powerful and independent predictor of all-cause mortality or composite endpoints, even after adjusting for possible confounding factors, including the LDL-C-mean level in this population.

The variability of biological indicators has been identified as a new biometric which has been shown to be associated with clinical outcomes in CAD patients (1-4, 21, 22). In patients with a history of MI, a depressed heart rate variability was found to be a sign of malignant arrhythmia and sudden cardiac death (22). The visit-to-visit blood pressure variability was considered to be a significant indicator of potential vascular dysfunction and adverse cardiovascular events in CAD (21). It was also indicated that higher hemoglobin A1c (HbA1c) variability was closely linked to greater left ventricular diastolic dysfunction and was an independent predictor of new-onset heart failure with preserved ejection fraction (HFpEF) in our previous study (5). In addition, increased HbA1c variability was significantly associated with future AF development in patients with type 2 diabetes mellitus (6). Our prospective longitudinal study showed that the HbA1c variability was independently and similarly predictive of death or combined endpoints in three heart failure phenotypes (23).

Recently, high cholesterol variability was considered as an independent predictor of MACES in CAD (7, 8, 13). The TNT trial showed that visit-to-visit LDL-C variability independently predicted cardiovascular event, death, MI, and stroke in stable CAD (7). Another study indicated that both elevated LDL-C variability and increased high-density lipoprotein cholesterol (HDL-C) variability were linked to the occurrence of a 5-year MACES in patients presenting with ST-segment elevation MI (STEMI) (13). Higher variability in LDL-C was also associated with both a lower cognitive performance and lower cerebral blood flow (8). Aforementioned studies raised an important question whether the LDL-C variability could be an additional risk factor in cardiovascular events.

It has been reported that the prevalence of non-obstructive CAD was 15%–30% in patients underwent elective CAG or coronary computed tomography angiography (CCTA) (14, 24-26). In patients with chest pain referring for CAG, those with non-obstructive CAD had elevated risks of all-cause mortality and MACES, compared to those without CAD (27). It has also showed that the risk of MI in non-obstructive CAD patients was 2 to 4.5 times higher than among those with no apparent CAD (14). Furthermore, the CONFIRM registry indicated that the presence of non-obstructive CAD led to an HR of 1.60 for all-cause mortality (24). These results indicate that non-obstructive CAD is associated with a significant risk for cardiovascular morbidity and mortality, and highlight the clinical importance of preventive strategies in this population. So, far no study has evaluated the role of cholesterol variability as a determinant of cardiovascular events and mortality among the non-obstructive CAD population. The present study showed that the visit-to-visit LDL-C variability is an independent predictor of all-cause mortality or composite endpoints after adjusting for possible confounding factors.

To date, the mechanism linking an increased LDL-C variability to an increased risk of cardiovascular events is unknown, but there are several hypotheses. The increase in the LDL-C variability might lead to instability at the vascular wall as a result of variability in the lipid efflux mechanism and thus enhance the risk for plaque vulnerability and rupture (28). Second, endothelial dysfunction predisposes vessels to atherosclerosis. It was reported that a higher LDL-C variability was associated with endothelial dysfunction (8, 29, 30).

Consistent with our results, it was reported that statin therapy was associated with a reduction in average LDL-C or visit-to-visit LDL-C variability (18-20), as well as favorable clinical prognosis in non-obstructive CAD (31). Besides, the variability in LDL-C levels might also reflect behavioral or clinical factors, such as inconsistent adherence to treatment, that weaken statins responsiveness (19). Statin withdrawal might lead to a rebound phenomenon by eliminating beneficial pleiotropic effects, such as cholesterol-lowering effect, plaque stabilization, endothelial function improvement, and anti-oxidative and anti-inflammatory effects (32). A strong positive and significant association was noted between increasing LDL-C variability and statin non-adherence (20). To avoid the effects of statin non-adherence in the present study, only patients with statin MPR ≥80% were enrolled.

In addition to all-cause mortality and composite endpoints, we also analyzed the associations of the LDL variability and MI/coronary revascularization, and the LDL variability and cardiovascular/non-cardiovascular death. We found a decrease trend in the incidence of MI/coronary revascularization in lower LDL-C variability. And a higher LDL-C variability led to both increased cardiovascular and non-cardiovascular death. The difference in cardiovascular death was more pronounced. These results suggested the clinical importance of LDL-C variability among non-obstructive CAD.

**Study limitation**

First, due to the nature of this retrospective cohort study, causality could not be determined. Furthermore, potential informa-
tion biases include changes in the sample examination method with time and differences in the number of LDL-C measurements. In particular, the intervals between LDL-C measurements varied for the enrolled patient. Second, we did not measure the markers of endothelial function, because it is widely recognized that the LDL-C variability causes endothelial dysfunction. Lastly, because only the Chinese population was included, our findings cannot be extrapolated to people of different ethnicities.

Conclusion

Overall, the LDL-C variability was related independently to the risk of all-cause mortality or composite endpoints (death, MI, and coronary revascularization) in a population with non-obstructive CAD. These findings suggest the clinical importance of LDL-C variability, and they warrant further investigation of interventions to improve outcomes among patients with non-obstructive CAD.

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