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Literature Review of Visit to Visit Lipid Variability as a Predictor of Cardiovascular Events

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Abstract

Cardiovascular disease remains a major global health problem due to its substantial contribution to morbidity and mortality. The World Health Organization reports that cardiovascular disease is the leading cause of death worldwide, accounting for approximately 17.9 million deaths each year. In Indonesia, reports from the Ministry of Health show a persistent increase in cardiovascular disease prevalence. Dyslipidemia, defined as an imbalance in blood lipid levels, is a major modifiable risk factor associated with cardiovascular events, making lipid control a key focus of preventive strategies. Visit to visit lipid variability (VLV) refers to fluctuations in lipid parameters such as total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides across different clinical visits over a certain period. Recent studies indicate that higher variability in lipid levels is independently associated with an increased risk of coronary heart disease, stroke, and cardiovascular mortality. This study adopted a literature review design to examine the role of VLV as a predictor of cardiovascular events. Ten national and international journal articles were selected based on predefined inclusion and exclusion criteria. The reviewed evidence consistently shows that high variability in lipid levels, particularly LDL-C and HDL-C, is linked to a greater risk of myocardial infarction, stroke, acute coronary syndrome, and cardiovascular-related death in various populations, including patients with diabetes mellitus and familial hypercholesterolemia. Conversely, maintaining stable lipid levels over time is associated with a reduced risk of adverse cardiovascular outcomes. These findings highlight the importance of continuous lipid monitoring and long-term lipid stability as essential components in efforts to prevent and control cardiovascular disease.

Introduction

Cardiovascular disease is one of the major health problems in the world that requires special attention due to its widespread impact on morbidity and mortality rates. According to data from the World Health Organization (WHO), this disease is the leading cause of death globally, with approximately 17.9 million deaths each year (Alanzi et al., 2025; Karnan et al., 2025; Liu et al., 2025). The causes of cardiovascular disease include genetic, environmental, and lifestyle factors. Among these factors, dyslipidemia plays an important role in triggering the development of this disease. In Indonesia, the Ministry of Health (2023) reports that the prevalence of cardiovascular disease continues to increase, in line with changes in lifestyle,

urbanization, and increased life expectancy (Wazir et al., 2023; Formichi et al., 2025; Kang et al., 2025).

Dyslipidemia has long been recognized as one of the major risk factors for cardiovascular disease, and prevention efforts have generally focused on lowering lipid levels in the body. However, recent research reveals that fluctuations in lipid levels between visits are also associated with an increased risk of coronary heart disease (CHD), stroke, and death, regardless of average lipid levels, both in high-risk individuals and in the general population (Yum et al., 2024; Ahlers et al., 2025; Tang et al., 2025).

Visit-to-visit lipid variability (VLV) describes fluctuations in lipid levels (such as total cholesterol, LDL, HDL, and triglycerides) between visits over a given period. Unlike average lipid values, which describe long-term status, inter-visit variability reflects metabolic stability and patient adherence to therapy over time. Recent studies have shown that increased VLV is associated with an increased risk of cardiovascular events, even after adjusting for average lipid levels and other conventional risk factors (Zhang et al., 2025; Grinspoon et al., 2025; Campbell et al., 2025).

Elevated serum cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), have long been recognized as a major risk factor in the development of atherosclerosis and related cardiovascular diseases (Kamrani et al., 2025; Stoicescu et al., 2025; Sosnowska et al., 2025). In addition to high total cholesterol (TC) and LDL-C levels, low high-density lipoprotein cholesterol (HDL-C) levels are also known to be an important risk factor for atherosclerotic cardiovascular disease. Various studies have consistently shown that high LDL-C levels and low HDL-C levels contribute to poor cardiovascular health outcomes. Therefore, careful monitoring and achieving target cholesterol levels are very important in primary and secondary prevention of this disease (Park et al., 2022; Hodeda et al., 2025; Rodriguez et al., 2025).

Previous epidemiological studies have shown that high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are major risk factors for cardiovascular disease. Results from previous studies also reveal that high variability in HDL-C and LDL-C levels between visits is associated with an increased incidence of ischemic stroke and hemorrhagic stroke, respectively (Liu et al., 2020).

Recent studies have shown that intra-individual variability from one visit to the next in various traditional risk factors can be a potentially useful new prognostic marker for predicting clinical outcomes, regardless of the average value. For example, increased blood pressure (BP) variability between visits and decreased heart rate variability have been associated with various negative outcomes, including cognitive impairment, stroke, and increased risk of death from various causes. Although the main guidelines for dyslipidemia management still focus on controlling average lipid levels, lipid level fluctuations have gained increasing attention in recent years. Several retrospective studies from randomized controlled trials have also shown a positive association between high LDL-C level variability between visits and worse cardiovascular outcomes (Cao et al., 2021; Sun et al., 2025).

Research conducted by Wan et al. (2020) revealed that high lipid variability is significantly associated with an increased risk of cardiovascular disease and mortality in patients with type 2 diabetes mellitus (Wan et al., 2020). Meanwhile, research by Cao et al. (2021) reported that lipid level variability between visits is associated with an increased incidence of major adverse cardiovascular events (MACE) in patients with familial hypercholesterolemia or genetic disorders that cause very high LDL levels in the blood (Cao et al., 2021; Hosseini, 2025; Kindborg et al., 2025).

Thus, from an epidemiological perspective, VLV can be considered a new biological marker with the potential to predict the onset of cardiovascular disease. Therefore, studying VLV patterns in various population groups is very important to strengthen the scientific basis for its use in medical practice and in heart disease prevention efforts.

Methods

The design used in this study was literature review because it was used in order to provide a systematic study of the role of visit to visit lipid variability as a predictor of cardiovascular events. The literature review method was chosen due to the possibility of an extensive synthesis of the available empirical data of different populations and clinical scenarios, especially in the sphere where the results are scattered over observational cohort and case control studies. This review was aimed at determining patterns, methodological consistency and clinical implications of lipid variability as opposed to the production of new primary data.

Three large electronic databases, i.e. PubMed MEDLINE, ScienceDirect, and Google Scholar were used as the literature search. These databases were chosen to make sure that their coverage was wide on peer reviewed biomedical and clinical studies. Keywords that were combined to do the search included visit to visit lipid variability, lipid fluctuation, LDL cholesterol variability, HDL cholesterol variability, triglyceride variability, and cardiovascular events. Boolean operators were used to narrow the search strategy and to include studies that specifically covered lipid variability among several clinical visits.

To ensure that the study is methodologically rigorous, the articles were chosen according to preset inclusion and exclusion criteria. The inclusion criteria were original research articles, cross sectional, cohort or case controls, and published in 2020-25, included human subjects who had repeated lipid measurements on more than one visit, and explicitly measured lipid variability as an exposure or predictor variable. Those studies were eliminated in case there was no access to full text, the study was released prior to 2020, or the lipid measurement procedures or variability assessment were not described clearly in the methods section.

In the first search of the database, 124 articles were found. Once the duplicate records had been eliminated, 90 distinct articles were left and filtered using titles and abstracts. In this process of screening, the research which did not involve the study of lipid variability or cardiovascular outcome were eliminated. The number of articles to be seen in a full text reached 28. After a thorough review of the eligibility criteria, 18 articles were excluded due to the lack of specific analysis on visit to visit lipid variability in the study, absence of information about the cardiovascular outcomes in the studies or incomplete information on the methodology. Finally, 10 studies were evaluated that fitted all the requirements of inclusion and were added to the final analysis.

Each eligible study underwent a systematic approach in terms of data extraction. Some of the information gathered was the design of the study, the characteristics of the population, the lipid parameters measured, methods of measuring the lipid variability, the duration of follow up and cardiovascular outcomes reported. Visit to visit lipid variability was mainly determined by the coefficient of variation of repeated measurements of lipids, which often had a minimum of three measures per individual. Parameters of lipids that were examined in studies were; low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides and in some studies, the total cholesterol.

In order to promote clear conceptualization, operational definitions were created to indicate visit to visit lipid variability depending on variability thresholds that were reported in the included studies. These thresholds were descriptively applied to make cross study comparisons and not to simply set a universal cut off. Findings synthesis was done in a narrative manner by

paying attention to the consistency of the associations, between lipid variability and cardiovascular events, variations in lipid parameters applied and the clinical implications.

This methodological strategy presented a systematic and clear synthesis of recent evidence on visit to visit lipid variability and its prognostic value to cardiovascular disease but also recognised variations in study design, population, and variability measurement methods across the literature that was included.

Table 1. Operational Definitions

Variable	Operational Definition	Indicator/ Parameter	Measurement Method	Cut-off/category
Visit-to-Visit Lipid Variability	Fluctuations in blood lipid levels between visits in the same individual over a certain period of time	LDL, HDL, Triglycerides	Calculation of **the Coefficient of Variation (CV)** from repeated lipid test results (≥3 times) reported in research articles	HDL: - CV: > 12.8% (High variability) - CV: 12.8% (Moderate-high variability) - CV: < 12.8% (Low variability) LDL: - CV: > 13.2% (High variability) - CV: 13.2% (Moderate-high variability) - CV: < 18.7% (Low variability) Triglycerides - CV: >18.7% (Low variability) - CV: 18.7% (Moderate-high variability) - CV: <13.2% (Low variability) -

Results and Discussion

This study was conducted through a literature review, which involved collecting data from several sources on VLV (Visit to Visit Lipid Variability) as a predictor of cardiovascular events. A total of ten references were obtained, which were then discussed and related to the title of this study. The most relevant references are presented in the table below:

Table 2. Literature Review

No.	Title	Method	Author and Year	Results
1	Visit-to-Visit Variability of Lipid Measurements and the Risk of Stroke- , and Stroke Types: A Prospective Cohort Study	Prospective Cohort	(Wang et al., 2020)	In this study, the total sample consisted of 1,189 stroke cases (1,036 ischemic strokes and 160 hemorrhagic strokes). The results of the study stated that the variability of LDL-C and HDL-C levels over time was proven to be associated with an increased risk of stroke, both ischemic and hemorrhagic strokes.
2	Association Between Visit-to-Visit Variability in Low-Density Lipoprotein Cholesterol and	Case-Control Observational Multicenter Retrospective Study	(Nakano et al., 2021)	In this study, the total sample size was 3,075 ACS patients, but 74 met the exclusion and inclusion criteria. The results of this study show that significant variability in LDL-C levels

	Plaque Rupture That Leads to			over time is associated with a higher risk of acute coronary syndrome due to plaque rupture in the heart's blood vessels, even if the average LDL-C level is not particularly high.
3	Associations of visit-to-visit variabilities and trajectories of serum lipids with the future probability of type 2 diabetes mellitus	Retrospective Cohort	(Sun et al., 2021)	In this study, the total sample size was 5,769 patients. The results showed that visit-to-visit variability in triglyceride (TG) levels over a specific period, as well as the pattern of changes in TG and HDL-C levels over time, were significantly associated with the occurrence of type 2 diabetes mellitus.
4	Joint effect of visit-to-visit variability in LDL cholesterol, HDL cholesterol, and HbA1c on cardiovascular and total mortality in patients with diabetes	Retrospective Cohort	(He et al., 2022)	In this study, the total sample consisted of 5,194 patients with cardiovascular disease. The results showed that the variability of LDL-C, HDL-C, and HbA1c levels together increased the risk of cardiovascular death and mortality in patients with type 2 diabetes.
5	Prognostic significance of visit-to-visit variability in , and maximum and minimum LDL cholesterol in diabetes mellitus	cohort	(Sheng et al., 2022)	In this study, a total of 5,518 participants underwent LDL-C level measurements during 3 visit . The study showed that LDL-C level variability was associated with a 10–23% increase in the risk of coronary heart disease. High LDL-C variability can also lead to increased mortality rates in diabetes mellitus patients.
6	Variability in Lipid Levels and Risk for Cardiovascular Disease: An Electronic	EHR-Based Cohort	(Manemann et al., 2023)	In this study, the total sample size was 19,652 people who underwent lipid testing. The results showed that high variability in total

	Health Record–Based Population Cohort Study			cholesterol, HDL-C, and LDL-C levels was associated with an increased risk of cardiovascular disease, regardless of the influence of traditional risk factors such as hypertension, diabetes mellitus, and smoking.
7	LDL Cholesterol Variability Impacts the Prognosis of Patients with Chronic Ischemic Heart Disease: A Real-World Italian Experience	retrospective observational	(Faggiano et al., 2023)	In this study, a total of 3,398 patients were considered eligible for inclusion in this retrospective analysis with a median follow-up of 56 months. The study found that if LDL-C levels continue to decrease consistently, this is beneficial as it can reduce the risk of heart disease and death. Conversely, if there is variability in LDL-C levels between visits, this is detrimental as it can worsen the prognosis in patients who already have stable coronary artery disease (stable CAD).
8	Visit-to-visit variability of metabolic parameters and progression of atherosclerosis in computed tomography: follow-up of an asymptomatic cohort	Retrospective Cohort	(Lim et al., 2023)	In this study, a total of 764 patients from medical records were examined. The results showed that significant variability in LDL cholesterol and triglyceride levels over time in the same individuals could predict worsening coronary artery stenosis, as seen on coronary CT angiography (CCTA).
9	Visit-to-visit variability in multiple biological measurements and cognitive performance and risk of	Cohort	(Sherlock et al., 2024)	In this study, the total sample size was 5,897. The results showed that high visit-to-visit lipid variability was associated with an increased risk of adverse health outcomes,

	cardiovascular disease: A cohort study			such as heart attack, stroke, heart failure, or even death.
10	Visit-to-visit lipid variability on long-term major adverse cardiovascular events: a prospective multicenter cohort from the CORE-Thailand registry	Cohort	(Teekaput et al., 2025)	In this study, the total sample size was 6,041 people who had advanced lipid profiles and were at high risk of cardiovascular disease. The results showed that variability in cholesterol and triglycerides between visits significantly increased the risk of heart attack, severe heart complications, and death. Conversely, stable lipid levels over time tended to protect against risks such as heart attack, severe heart complications, and death. [16]

Hyperlipidemia has long been recognized as one of the major risk factors for cardiovascular disease. However, in recent years, researchers have increasingly focused on the variability of lipid levels in individuals obtained from repeated tests. This lipid variability reflects metabolic stability and patient response to long-term therapy. Several studies have shown that high lipid level fluctuations, particularly in LDL and HDL, can significantly increase the risk of major cardiovascular events. Therefore, lipid variability is considered a potential indicator that is relatively cost-effective and easy to apply in clinical practice to estimate future cardiovascular risk. However, further research is still needed to confirm its prognostic value and clinical utility in a broader population and to determine the most representative variability parameters (Faggiano et al., 2023).

Based on various explanations in the literature, fluctuations in lipid levels, or known as lipid variability, are known to increase the risk of cardiovascular disease. This has been proven through a number of literature reviews conducted by Wang et al., Shinsuke et al., Qian et al., He Panpan et al., Le et al., Sheng et al., Sheile et al., Pompilio et al., Yun et al., Laura et al., and Chutitep et al.. The results of these studies indicate that inter-visit lipid variability is closely related to the occurrence of cardiovascular disease, even though each study used different parameters and disease focuses.

Research conducted by He Panpan et al., Sheng et al., Sheile et al., Laura et al., and Chutitep et al. generally shows that inter-visit lipid variability can increase the risk of death and cardiovascular disease, even though each study used different parameters. In the study by Sheng et al., the parameters used were limited to LDL-C levels. In contrast, Laura et al. used total cholesterol and triglyceride (TG) parameters in their study. However, the advantage of Sheng et al.'s study lies in its broader scope of analysis, as it not only links LDL-C variability to cardiovascular disease events but also to an increased risk of mortality in patients with diabetes mellitus (He et al., 2022; Manemann et al., 2023; Sheng et al., 2022; Sherlock et al., 2024; Teekaput et al., 2025).

Unlike the studies conducted by Qian et al and He Panpan et al., both studies used more than one lipid parameter. He Panpan et al. examined the variability of LDL-C, HDL-C, and HbA1C, the results of which showed that increased lipid variability can increase the risk of death from

cardiovascular disease and type 2 diabetes mellitus. The study by He Panpan et al. is consistent with the study by Qian et al., but uses different parameters. Qian et al. only used triglyceride (TG) and HDL-C parameters (He et al., 2022; Sun et al., 2021).

The study conducted by Chutitep et al. differs in the parameters used, namely total cholesterol and triglycerides. The results of this study indicate that high lipid variability can increase the risk of heart attack and death. Furthermore, this study also confirms that stable lipid levels act as a protective factor that can reduce the risk of heart attack and death (Teekaput et al., 2025).

Research conducted by Shinsuke et al. and Pompilio et al. shows that lipid variability plays a role in increasing the risk of coronary heart disease, with both studies using the same parameter, namely HDL-C levels. The study by Shinsuke et al. revealed that high lipid variability can increase the incidence of acute coronary syndrome, which is an emergency manifestation of coronary heart disease (Faggiano et al., 2023; Nakano et al., 2021).

Meanwhile, research conducted by Pompilio et al. shows that fluctuations in lipid levels can worsen the condition of patients with coronary heart disease. However, this study not only discusses the effects of lipid fluctuations, but also emphasizes that a consistent decrease in lipid levels without significant variability can be a good indicator because it has the potential to reduce the risk of coronary heart disease. These findings are consistent with the results of research by Chutitep et al., which also shows that stable lipid levels have a protective effect against cardiovascular events (Faggiano et al., 2023; Teekaput et al., 2025).

Visit-to-visit lipid variability not only plays a role in increasing the risk of cardiovascular disease and diabetes mellitus, but also has the potential to cause cancer and stroke, both hemorrhagic and ischemic stroke.

The study by Lim et al. used broader parameters, including LDL-C, triglycerides, and total cholesterol. The study proved that fluctuations in lipid levels not only cause cancer but can also cause narrowing of the coronary arteries, commonly known as coronary artery stenosis (Lim et al., 2023).

Patients who regularly take medication and receive high-intensity therapy usually have the lowest risk of heart disease. Results from the large Treating to New Targets (TNT) study show that in patients with stable coronary heart disease, changes in LDL cholesterol levels over time (LDL-C variability) can be a factor that influences the incidence of cardiovascular disease, regardless of average LDL levels or the type of medication used. The study found that the greater the change in LDL-C levels between visits, the higher the risk of patients experiencing a heart attack, stroke, or death. Specifically, increased LDL-C variability was associated with a 16% increase in the risk of coronary events, an 11% increase in cardiovascular events, a 23% increase in mortality, a 10% increase in heart attacks, and a 17% increase in strokes. Therefore, it is not only important to achieve target LDL-C levels but also to maintain stable LDL levels over time to improve the outcomes of coronary heart disease treatment (Sherlock et al., 2024).

Visit-to-visit lipid variability describes changes in lipid levels that occur over time. These fluctuations can affect the stability of atherosclerotic plaques in blood vessels. Repeated changes in LDL-cholesterol and total cholesterol levels can cause cholesterol to dissolve in plaques, which then promotes the formation of cholesterol crystals. These crystals are sharp and can damage the fibrous cap of the plaque. This damage makes the plaque more prone to rupture, which can trigger thrombus formation and cause acute cardiovascular events, such as myocardial infarction and ischemic stroke (Li et al., 2022).

In addition, lipid level fluctuations can cause endothelial dysfunction through increased oxidative stress. Impaired endothelium loses its protective function, increasing blood vessel permeability and allowing LDL to more easily penetrate the intima layer. Inter-visit lipid variability is also associated with increased systemic inflammation. Overall, lipid variability

reflects metabolic instability that affects various disease mechanisms, including plaque instability, endothelial dysfunction, vascular inflammation, and atherosclerosis progression. This explains why lipid variability is a strong predictor of cardiovascular events, even when average lipid levels are within normal limits. Therefore, maintaining long-term lipid stability is increasingly viewed as an important target in cardiovascular disease prevention (Frąk et al., 2022; Li et al., 2022).

Overall, evidence from various studies shows that lipid level stability is as important as achieving lipid level targets in the management of dyslipidemia. Therefore, doctors need to consider longitudinal monitoring of patients' lipid levels over a certain period of time, rather than just the results of a single examination. This strategy is especially important in patients with chronic metabolic or cardiovascular diseases (Nakano et al., 2021).

The limitation of this study is that not all journals reviewed explain in detail the lipid variability threshold values, so there is no consistency in determining the threshold for when lipid levels are categorized as high and when they are categorized as low. Differences in the definitions and methods of assessing lipid variability between studies, including variations in the parameters used, such as LDL-C, HDL-C, triglycerides, and total cholesterol, have the potential to cause differences in the interpretation of results and make direct comparisons between studies difficult. This situation can affect the strength of the conclusions drawn, as the absence of a standard for determining lipid variability can lead to differences in the assessment of the risk of cardiovascular events associated with fluctuations in lipid levels between visits.

Conclusion

Based on the results of the literature review, it was found that visit-to-visit lipid variability (VLV), particularly in LDL-C and HDL-C levels, is significantly associated with an increased risk of major cardiovascular events. e lipid variability over time reflects metabolic instability and poor treatment adherence, which can accelerate the atherosclerosis process and worsen patient prognosis. Conversely, lipid level stability over time has been shown to provide a protective effect against cardiovascular events. Therefore, regular and continuous monitoring of lipid levels should be an important part of cardiovascular disease prevention and control strategies.

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