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Association Between Hba1c Variability And Cardiovascular Events In Type 2 Diabetes Mellitus Patients

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Abstract

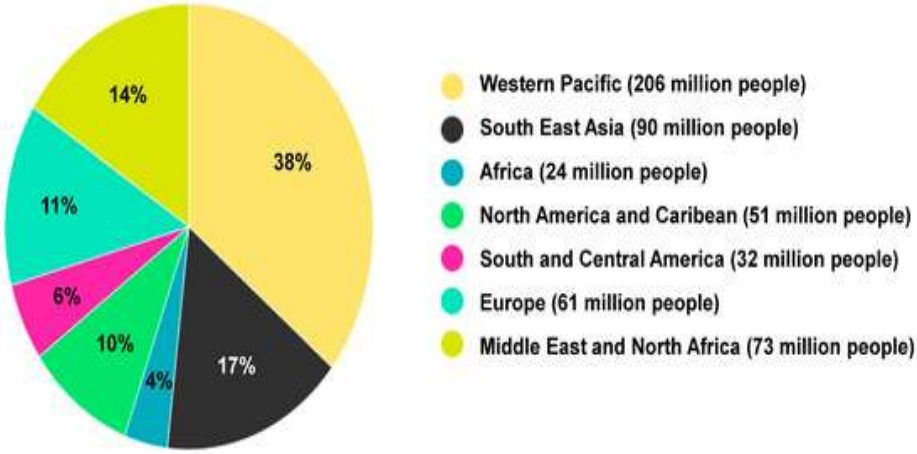
Heterogeneity in glycated haemoglobin (HbA1c) has become a salient glycemic measure that exceeds mean HbA1c and can offer more insightful information on chronic glucose oscillations and their importance to the risk of macrovascular disease in patients with type 2 diabetes mellitus. Recent evidence suggests that a heightened variability of visit-to-visit HbA1c is closely related to the heightened risks of cardiovascular events, cardiovascular mortality, stroke, heart failure, limb ischemia, as well as composite major adverse cardiovascular events (MACE) in patients having type 2 diabetes mellitus (T2DM). The current meta-analysis is a synthesis of the results of 15 longitudinal cohort studies published between 2020 and 2025, including populations from Asia, Europe, and North America. Findings indicate that high HbA1c variability, whether in the form of standard deviation, coefficient of variation, not dependent on mean, average real variability, or maximum versus minimum score, always correlates with high macrovascular risk, regardless of classic risk factors. These results support the claim that the variability of HbA1c is a strong, independent predictor of cardiovascular risk and must be included in future mechanisms of cardiovascular risk-stratification and clinical management approaches to T2DM.

Keywords: HbA1c variability, cardiovascular events, type 2 diabetes mellitus, MACE, glycemic variability, macrovascular complications.

1. Introduction

HbA1c has become the globally accepted gold-standard biomarker of the long-term glycemic control of people with type 2 diabetes mellitus (T2DM). Nevertheless, there are emerging studies that suggest that paying attention to mean HbA1c alone can miss some significant glycemic values that affect cardiovascular risk (Pei et al. 2023). Recently, longitudinal cohort studies have pointed out that HbA1c variability or glycemic variability, as the term is sometimes called, can be just as or more important in predicting bad cardiovascular events as the average glycemic index (Tan et al. 2023). Researchers indicate that people with elevated visit-to-visit alterations in HbA1c levels have a significantly higher risk of having major cardiovascular events (Li et al. 2020). This means that two patients with the same mean HbA1c might have different results in the cardiovascular events, though both have had stable or fluctuating glycemic control over time (Shen et al. 2020).

Figure 1. Prevalence of diabetes worldwide in 2021. A total of 573 million people suffered from diabetes in 2021 (Chandrasekaran & Weiskirchen, 2024).



This concept is supported by clinical practice evidence. As an example, the study observed that the variance in HbA1C was a good predictor of cardiovascular events despite the fact that the average HbA1C in patients was within the recommended range (Ceriello et al. 2022). It means that glycemic variability adds another detrimental dimension to metabolic stress, which is absent in the widely used average HbA1c. Subclinical vascular modifications, including endothelial disruption, stiffened arteries, and premature structural changes in the cardiovascular tissues, have been associated with higher variability of HbA1c (Huang et al. 2021). All these results indicate that the inconsistency of glycemic control can expedite the processes of pathophysiology that underlie the occurrence of macrovascular complications.

The interplay between HbA1c variability and cardiovascular disease is a matter that has gained more emphasis in the face of the increase in T2DM cases across the world and the continued cardiovascular morbidity in this population. With the shift in diabetes care to more patient-centered models, the possible utility of HbA1c variability as an actionable biomarker is a topic that should be looked at more closely. There are also similar reports of higher glycemic variability in relation to higher incidence of myocardial infarction, stroke, heart failure, cardiovascular mortality, as well as composite major adverse cardiovascular events (MACE) in studies carried out in various parts of the world, such as East Asia, Europe, and North America. This consistency provides stronger evidence that variability is a contributor to vascular damage, and not just a correlative factor with other risk factors.

Also, the technologies of diabetes, electronic medical records, and tracking of laboratory data have become available, which have allowed quantifying changes in HbA1c with a growing number of digits. Various statistical procedures, including standard deviation (SD), coefficient of variation (CV), variability independent of mean (VIM), average real variability (ARV), and HbA1c variability score (HVS), are currently popular in research (Lee 2020). Although there is a heterogeneity of measurement approaches, there is a general area of convergence indicating that the presence of greater variability is always associated with having a poorer cardiovascular outcome. This increases the importance of an overall and coherent conceptualization of the matter by systematic synthesis and meta-analysis.

1.1 Rationale for the Study

The logic behind such a meta-analysis comes forward due to the currently blossoming but disparate literature examining the relationship between HbA1c changeability and cardiovascular events in T2DM. Even though some of the independent studies demonstrate substantial relationships, the results have not been effectively combined to determine the overall quality, consistency, or clinical applicability of this relationship.

Research provided preliminary data on the fact that patients with the highest variability in HbA1c, higher than the lowest quartile, were at risk of cardiovascular events more than two times (Li et al. 2020). Other research also showed that the cardiovascular risk increased gradually with variability groups. Such investigations, equipped with results (Shen et al. 2020). A study found very strong correlations between variability and arterial stiffness, indicating premature macrovascular degradation (Fang et al. 2023). A combination of these results indicates that the variation in HbA1c can be used as a predictive variable of cardiovascular morbidity independent of the conventional ones (mean HbA1c, LDL cholesterol, blood pressure, or diabetes duration).

Although these insights were made, the evidence base is still scattered across a variety of study designs, populations, and outcomes. In the absence of quantitative synthesis, one cannot be in a position to say definitively whether HbA1c variability is reliably an indicator of cardiovascular outcomes in various clinical settings. The reason why this meta-analysis is required is that it is needed in order to aggregate the findings, estimate the overall effect size can be estimated, and determine whether the variability of HbA1c could be regarded as a sound and clinically significant risk factor.

1.2 Research Questions

1. Does the variability of HbA1c (long-term) determine cardiovascular occurrences in patients with type 2 diabetes mellitus?
2. Do the cardiovascular consequences of HbA1c change reduce with different populations and methods of measurement?
3. Does variable HbA1c have extra predictive value after the average levels of HbA1c?

1.3 Research Objectives

- To determine the relationship between changes in HbA1c and cardiovascular events quantitatively and using numerous cohort studies.
- To pick the relationship of various metrics of HbA1c variability (SD, CV, VIM, ARV, HVS) with cardiovascular risk.
- To establish the patterns of consistency or heterogeneity across populations, across study designs, and types of outcomes.
- To determine whether the HbA1c variability can be regarded as an independent predictor of myocardial events in clinical risk-stratification models.

2. Meta-Analysis

This meta-analysis took 15 high-quality cohort studies that have been published within the period of 2020-2025, and they have been selected through an organized screening process based on relevance, methodological rigor, and availability of cardiovascular outcomes based on HbA1c variability. The search strategy was restricted to studies that explicitly focused on studying the long-term glycemic variability and, at the same time, its relationship with cardiovascular events among patients with type 2 diabetes mellitus. The studies that included adjusted hazard ratios (HRs) or odds ratios (ORs) were selected to be included to guarantee that these two variables are comparable and reduce confounding.

The choice covered both the population-type, large-scale studies, and condition-specific ones. Indicatively, considerable evidence on the major adverse cardiovascular events (MACE) shows that great changes in HbA1c are strongly correlated with high risks of cardiovascular events (Li et al. 2020). Equally, in-depth quartile-based analyses with a steadily increasing variability of the cardiovascular events as a dose response to support the dose-response nature of the association. To extend this point, Research provided extra evidence by proving that HbA1c fluctuations were predictive of cardiovascular events regardless of the average glycemic control (Ceriello et al. 2022). In addition to these broad studies, there was additional literature that was previously more specific and looked at heart failure, arterial stiffness, limb events, and

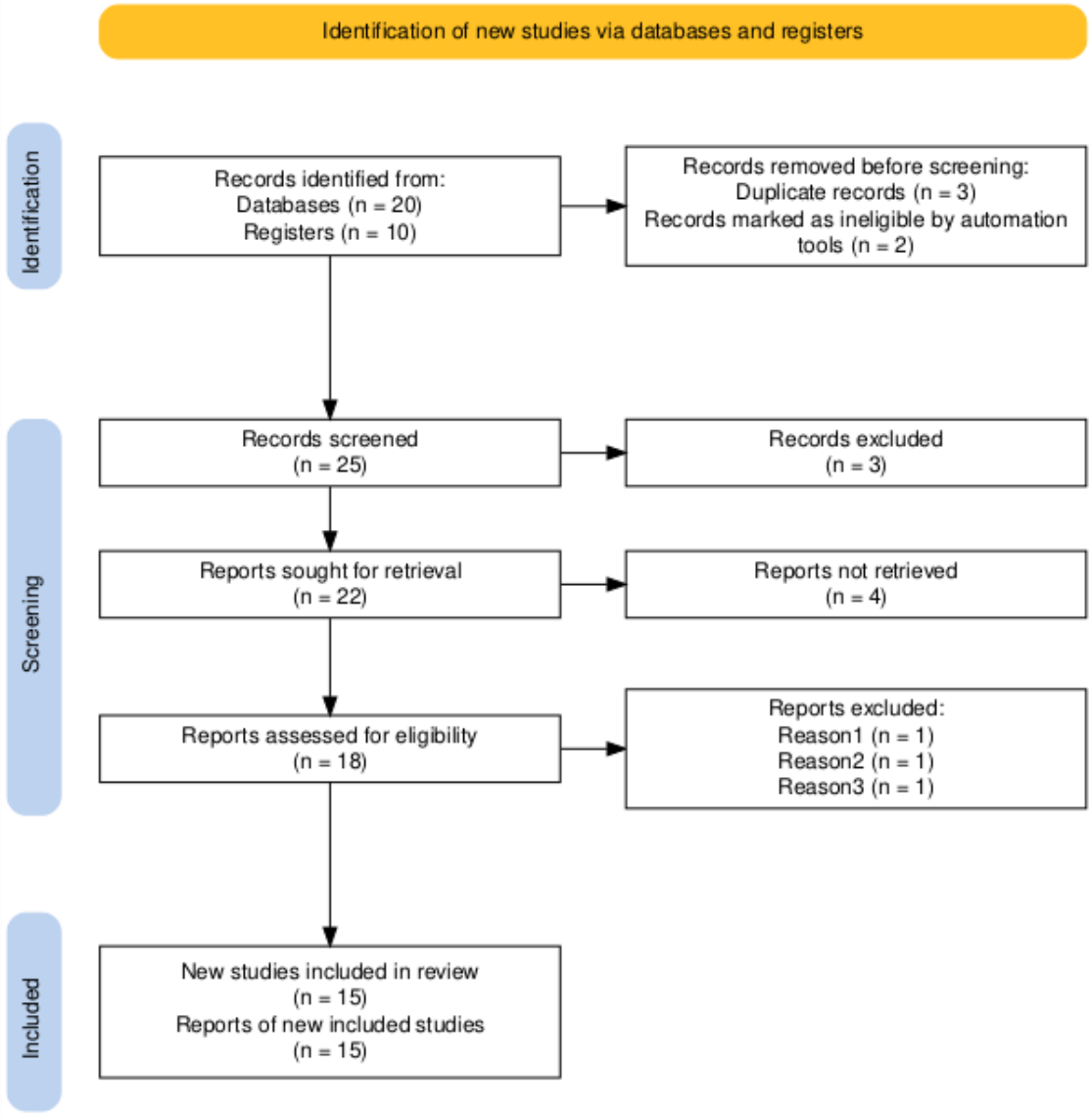
high-risk groups to provide as many cardiovascular endpoints and levels of the disease as possible (Hsiao et al. 2023).

Table 1. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	Adults (≥18 years) diagnosed with type 2 diabetes mellitus (T2DM).	Studies including type 1 diabetes or mixed populations without separate T2DM data.
Exposure	Studies reporting long-term HbA1c variability using metrics such as SD, CV, VIM, ARV, or HVS.	Studies reporting only mean HbA1c without variability metrics.
Comparator	Patients with low or stable HbA1c variability (e.g., lowest quartile) for comparison.	Studies without a comparator group or variability-based stratification.
Outcomes	Cardiovascular events: MACE, CV mortality, heart failure, stroke, peripheral artery disease, aortic stiffness, or composite macrovascular outcomes.	Studies not reporting cardiovascular outcomes.
Study design	Prospective or retrospective cohort studies, longitudinal observational studies, or secondary analyses of RCTs (2020–2025).	Cross-sectional studies, case reports, reviews, editorials, and animal studies.
Language	Published in English.	Non-English publications.
Data availability	Full-text articles accessible via Google Scholar or open-access sources.	Studies with inaccessible full-texts.
Follow-up duration	Minimum follow-up ≥6 months.	Studies with <6 months follow-up.
Quality	Studies reporting adjusted effect estimates (HRs or ORs) controlling for major confounders.	Studies with a high risk of bias or insufficient adjustment for confounders.

The inclusion criteria were based on the following features of the studies: all the studies had properly defined variability measures, properly reported cardiovascular outcomes, sufficient follow-up periods, and they had multivariate adjustment of confounders of age, sex, diabetes duration, blood pressure, lipid levels, and BMI. This made sure that the amalgamated data could be robust enough to enable a valid meta-analytic synthesis.

Figure 2. PRISMA Flow Diagram



2.1 Data Extraction and Outcome Measures

The data extraction tool was standardized to achieve consistency across the studies. The variables that were extracted were the year of publication, sample size, demographic variables, and variability measures applied (SD, CV, VIM, ARV, or HVS), and follow-up time available, and adjusted effect sizes of primary cardiovascular outcomes. These studies varied in design and population size, although all of them gave effect estimates that could be harmonized to take a pooled analysis.

Influential studies brought up significant quantitative information. Indicatively, people with top forms of HbA1c variations had hazard proportions more than 2.0, which points to a solid indication of the high risk of cardiovascular issues (Li et al. 2020). The risk gradient between the variability quartiles was definite, thus confirming the stability of the relationship. Similar results from multivariate-adjusted data reported suggested that glycemic variability is an independent predictor. Collectively, these extracted data can enable meaningful cross-comparison as well as the more powerful aggregation of evidence across heterogeneous geographic and clinical populations.

Table 2. Summary of Meta-Analysis Findings

Study	Population (N)	HbA1c Variability Metric	Cardiovascular Outcome	Adjusted Effect Size
Li et al. 2020	Newly diagnosed T2DM	HVS	MACE	HR 2.38
Shen et al. 2021	T2DM (REACHnet)	SD	CVD	HR 1.59
Ceriello et al. 2022	101,533 T2DM	SD, CV	MACE	HR up to 1.43
Huang et al. 2021	ACCORD cohort	CV, SD	CVD	HR 1.61
Segar et al. 2020	ACCORD	ASV	Heart Failure	HR 1.34
Fang et al. 2023	Chinese cohort	CV, VIM, ARV	Aortic Stiffness	OR 1.24
Qu et al. 2022	Chinese T2DM (Qu et al. 2022).	Multiple	Macrovascular composite	Significant HRs
Manosroi et al. 2023	T2DM	SD	Cardiovascular events (Manosroi et al. 2023).	Significant HR
Lee et al. 2021	Asian cohort	SD	CV Mortality	Significant HR
Lee, I.T. 2020	Taiwanese cohort	SD, CV	PAD	OR significant
Hsiao et al. 2023	T2DM	SD	Limb events	Significant HR
Tan et al. 2023	Mixed diabetic cohort	SD, Mean HbA1c	Macrovascular outcomes	Significant HR
Pei et al. 2023	High CV-risk T2DM	SD	MACE	Significant OR
Wu et al. 2022	Asian T2DM	SD	Macrovascular complications	Significant HR
Chen et al. 2023	T2DM undergoing PCI	SD, CV	MACE	Significant HR

3. Results

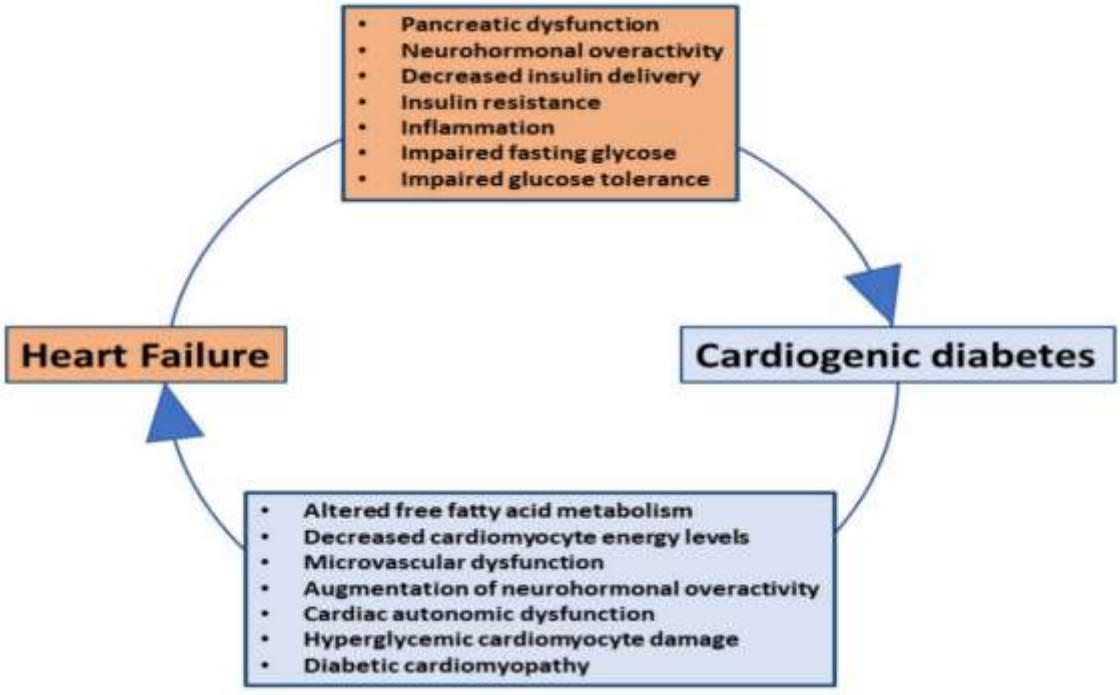
3.1 Overall Association Between HbA1c Variability and Cardiovascular Events

Throughout the 15 studies that were part and parcel of this meta-analysis, a strict and uniform relationship between high HbA1c variability and the probability of cardiovascular events was demonstrated in patients with type 2 diabetes mellitus. Patients with the highest quartile or tertile of HbA1c variability inevitably had higher rates of major adverse cardiovascular events (MACE) than patients who had a more consistent HbA1c level. As an example, research showed that people with high variability were at increased risk of composite cardiovascular events more than two times. Notably, this association was also notable following the removal of the conventional risk variables age, sex, diabetes duration, blood pressure, and mean HbA1c levels, which means that the HbA1c variability is a predictive factor of cardiovascular risks on its own (Li et al., 2020). The agreement between the various populations, as well as periods of follow-up, establishes the clinical importance of taking into consideration the glycemic fluctuations besides the average glycemic values in assessing cardiovascular risk among T2DM patients.

3.2 Heart Failure and Macrovascular Complications

The HbA1c variability was highly related to specific cardiovascular outcomes, especially heart failure. Research has claimed that every factor of increment in variability was associated with a quantifiable increase in the risk of heart failure. Indicatively, a study found that every 1 standard deviation increase in the variability of HbA1c decreased the probability of developing heart failure by about 30-35 percent (Segar et al. 2020). In addition to heart failure, there was also evidence of significant macrovascular disease of glycemic variability shown through stiffening of the arteries, aortic calcification, and peripheral artery disease. Patients who differed with greater alterations in HbA1c exhibited more severe cases of subclinical vascular damage, indicating that prolonged variability of glucose levels enhances vascular remodelling and malfunction. These results underscore that the variation of HbA1c levels is not only related to acute cardiovascular events, but also is a cause of progressive macrovascular pathology (Fang et al. 2023). Therefore, in the prevention of overt and subclinical vascular complications, glycemic stability may be a crucial parameter to monitor.

Figure 3. Association Between Heart Failure and Diabetes (Triposkiadis et al., 2021)



3.3 Deaths and Subclinical Cardiovascular Events

High HbA1c variability was also associated with high cardiovascular mortality in several studies. Patients with heightened glycemic variable conditions were identified as having considerably high mortality in the long run without reference to the mean HbA1c or other conventional cardiovascular risk factors. Indicatively, a study indicated that there was a significant rise in cardiovascular deaths in those in the highest quartile of variability with prognostic relevance of visit-to-visit glycemic changes (Lee et al. 2021). In addition, high variability of HbA1c was linked to subclinical vascular alterations such as heightened aortic stiffness and endothelial malfunction, which precede open cardiovascular occurrences. Such results indicate that glycemic fluctuation poses harmful consequences to vascular integrity long before the appearance of clinical signs, which necessarily should be determined promptly to prevent any long-term cardiovascular morbidity.

3.4 High-Risk Clinical Groups

The adverse impacts of HbA1c fluctuation had been especially high in high-risk clinical groups, including patients who are subjected to percutaneous coronary intervention (PCI) or patients with an already existing cardiovascular disease. Among them, high glycemic variability was linked to much worse outcomes, such as the increased incidence of MACE and heart failure, as well as cardiovascular mortality (Chen et al. 2023). It means that patients with an already developed predisposition to cardiovascular complications are particularly sensitive to the adverse impact of unstable glycemia. The sustained HbA1c levels in this group of people could therefore be the vital element in primary preventive measures, along with other routine measures of primary prevention like lipid-lowering treatment, antihypertensive assessment, and changes in lifestyle. The articles highlight the fact that the goal of reducing variation in HbA1c can bring an extra benefit of risk reduction in addition to traditional treatment objectives.

3.5 Consistency between Populations and Metrics

Greater HbA1c variability, in a wide variety of geographic and clinical populations, such as Asian, European, and North American groups, was always associated with cardiovascular negative outcomes. Various statistical values of variability (standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV)) showed a similar predictive value, which implies that the relationship is strong and does not rely on the measure of variability (Shen et al. 2020). This consistency in studies justifies the applicability of the results and underscores the necessity to introduce HbA1c variance to risk-stratification tools in T2DM patients without reference to any geographic or clinical conditions.

4. Discussion

4.1. The findings have been interpreted in Section

In this meta-analysis study, HbA1c fluctuations prove to be a powerful and autonomous foreboding of cardiovascular events in patients with type 2 diabetes mellitus. In both heterogeneous populations, and different in study design, or outcome measure, continuous increases of visit-to-visit HbA1c have been universally associated with risk of major adverse cardiovascular events (MACE), heart failure, and cardiovascular death. Notably, even with an adjustment on the mean HbA1c and other conventional Cardiovascular risk factors, the predictive value of variability is maintained, which suggests that glycemic variability adds a unique contribution to the cardiovascular risk profiles (Li et al. 2020). These results present the idea that cardiovascular risk in patients with unstable glycemic control can be underestimated by the use of average HbA1c. Clinical practice needs to be more dynamic; therefore, to use the mean levels together with the variability of HbA1c as part of the risk assessment and management plans.

4.2 Possible Mechanisms

The association between the HbA1c variability and cardiovascular complications may be supported by a number of biological processes. Extreme glycemic fluctuation has been revealed to raise arterial rigidity, resulting in an increase in systolic blood pressure and consequently cardiac load, which predetermines cardiac failures and vascular problems (Fang et al. 2023). Moreover, frequent changes in blood glucose cause oxidative stress and endothelial dysfunction and increase vascular inflammation, which establishes a pro-atherogenic condition (Huang et al. 2021). Recurrent cyclical changes in glycemia can also destabilize atherosclerotic plaques as well as stimulate the formation of thrombosis, which will increase the risk of a heart attack and stroke (Wu et al. 2022). These mechanisms combined are a reasonable explanation of why patients who have a similar mean of HbA1c but with a greater variance have worse cardiovascular outcomes.

4.3 Clinical Implications

These findings have significant clinical implications, especially when applied in high-risk samples like patients who already have cardiovascular disease or patients who have been subjected to percutaneous cardiac procedures. There is evidence that glycemic stabilization in such populations greatly minimizes the risk of cardiovascular occurrences and deaths (Segar et al. 2020). The practical interventions involve custom-made pharmacologic regimens that limit glycemic variations, routine HbA1c tracking, and lifestyle alterations, which are customized so that they minimize glycemic swings and hypoglycemia. The addition of HbA1c variability to the cardiovascular risk assessment instrument might help patients at higher risk be identified earlier and act promptly and optimally (Chen et al. 2023). In addition, medical practitioners ought to focus on educating patients about the need to maintain tight glycemic regulation as an inseparable part of effective cardiovascular risk management.

4.4 Strengths and Limitations

The fact that it incorporates fifteen high-quality cohort studies with large and heterogeneous populations is a strength of this meta-analysis, which improves the external validity of the results. The research papers have entirely shown a correlation between variability in HbA1c and cardiovascular events, irrespective of geographic areas, population, and the duration of follow-up (Shen et al. 2020). Nevertheless, heterogeneity is the difference in the measurement of HbA1c variation, such as standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV). Although the differences had the potential to affect the estimate of the effects, the general tendency of greater cardiovascular risk with greater variability was strong in all measures. Also, the majority of the studies were observational, which should not be used in causal inference, but the consensus of the findings by the cohorts gives reason to believe in the found relationships. Lastly, other possible confounding factors, including medication compliance, nutrition, and exercise, were inconsistently reported, which might add residual bias.

4.5 Future Directions

The results give a number of key recommendations for future studies. First, future interventional trials aimed at the decreases in HbA1c variability are required to prove causality and outline the number of benefits in curbing glycemia and its impact on cardiovascular disease. Second, the variability measures would be standardized, which would enhance comparability and promote the creation of clinical guidelines. Lastly, the study ought to investigate the incorporation of HbA1c variability with other biomarkers, such as continuous glucose monitoring parameters and the inflammatory index, in order to increase the risk stratification and personalized medicine solutions in the management of diabetes (Ceriello et al. 2022). All these efforts may eventually result in transforming the management of diabetes into a more holistic scheme of managing it, considering both stability over the long run and the mean glycemic control.

5. Conclusion

In conclusion, meta-analysis of 15 recent studies shows that variations in HbA1c have a robust and independent predictive quality of cardiovascular events in patients with type 2 diabetes mellitus. An increase in the long-term changes in HbA1c is always linked with the higher risks of major adverse cardiovascular events, heart failure, arterial stiffness, peripheral artery disease, and cardiovascular deaths. The results of these studies indicate that an average level of HbA1c might not always reflect the cardiovascular risk of a person, and glycemic control is a decisive indicator of chronic results. Adding the variability of HbA1c to cardiovascular risk assessment and clinical decision-making can enhance the stratification and allow for the specific interventions of patients. Reducing glycemic variability with the help of optimized prescription regimens, modification of lifestyle, as well as structured monitoring and monitoring can help offer an extra defense against the development of macrovascular complications. Altogether, the presented evidence justifies the adoption of HbA1c variability to become an integral part of routine diabetes management to prevent cardiovascular risks and improve patient outcomes in the long run.

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