Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

META-ANALYSIS

Longbatu et al: HbA1c variability and HF risk

HbA1c variability and risk of incident heart failure: A systematic review and meta-analysis

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DOI: https://doi.org/10.17305/bb.2025.13376

ABSTRACT

Visit-to-visit variability in glycated hemoglobin (HbA1c) reflects long-term instability in glycemic control, potentially contributing to cardiovascular complications. However, the association between HbA1c variability and heart failure (HF) risk remains unclear. This meta-analysis aimed to quantify the relationship between HbA1c variability and the risk of incident HF in adults. A systematic search of PubMed, Embase, and Web of Science was conducted to identify relevant studies. Observational studies and post-hoc analyses of clinical trials evaluating the association between visit-to-visit HbA1c variability and incident HF were included. Random-effects models were employed to pool hazard ratios (HRs) with 95% confidence intervals (CIs), accounting for potential heterogeneity. A total of nine studies (n = 342,123) were included in the analysis. Overall, high HbA1c variability was associated with an increased risk of HF (pooled HR = 1.78, 95% CI: 1.39–2.27, p < 0.001; I^2 = 87%). Sensitivity analyses restricted to patients with type 2 diabetes (HR = 1.73, 95% CI: 1.35–2.22), high-quality studies (HR = 1.82, 95% CI: 1.32–2.50), or studies adjusting for mean HbA1c (HR = 1.68, 95% CI: 1.31–2.16) produced consistent results. Subgroup analyses indicated a stronger association in prospective cohorts (HR = 2.51) compared to retrospective or post-hoc studies (p for subgroup difference < 0.001). Meta-regression analysis revealed no significant modifying effects of age, sex, follow-up duration, or study quality (p all > 0.05). In conclusion, greater visit-to-visit HbA1c variability may be associated with an increased risk of incident HF, underscoring the prognostic importance of maintaining stable long-term glycemic control in patients with type 2 diabetes.

Keywords: Glycated hemoglobin, variability, heart failure, risk factor, meta-analysis.

INTRODUCTION

Heart failure (HF) is a major global health challenge, affecting more than 64 million people worldwide and representing a leading cause of hospitalization and mortality among older adults (1, 2). Despite advances in pharmacologic and device-based therapies, the prognosis of HF remains poor, with 5-year mortality rates approaching 50% (3). Conventional risk factors such as hypertension, diabetes mellitus, obesity, and coronary artery disease only partially explain the occurrence of HF, and a substantial proportion of cases develop in individuals without overt cardiac disease (4). Therefore, identifying novel and modifiable risk factors is essential to improve early prevention and risk stratification. Among these, metabolic dysregulation, particularly abnormal glucose metabolism, has been increasingly recognized as a key contributor to cardiac remodeling, fibrosis, and dysfunction (5). Chronic hyperglycemia is known to increase the risk of HF through mechanisms involving oxidative stress, endothelial injury, and myocardial fibrosis (6). However, recent evidence suggests that glycemic fluctuation may exert additional deleterious cardiovascular effects independent of sustained hyperglycemia, potentially through repetitive activation of oxidative and inflammatory pathways that impair myocardial energetics and vascular integrity (7, 8).

Long-term glucose fluctuations can be objectively assessed using serial measurements of glycated hemoglobin (HbA1c), which reflects average glycemia over the preceding 2 to 3 months (9). The variability of HbA1c across clinical visits—referred to as visit-to-visit HbA1c variability—has emerged as a reliable index of long-term glycemic instability (10). Several statistical measures are used to quantify HbA1c variability, including the standard deviation (SD), coefficient of variation (CV), average real variability (ARV), variability independent of the mean (VIM), and adjacent standard deviation (ASV), calculated from at least three separate HbA1c measurements during follow-up (11, 12). Unlike mean HbA1c, which reflects average exposure to hyperglycemia, these indices capture dynamic fluctuations that may better represent the biological stress imposed on the cardiovascular system (13). Although recent studies have reported that greater HbA1c variability is associated with an increased risk of adverse cardiovascular events, including myocardial infarction, stroke, and all-cause mortality, findings regarding its relationship with incident HF remain inconsistent (14, 15). Therefore, this meta-analysis was conducted to quantitatively evaluate the association between visit-to-visit HbA1c variability and the risk of

incident HF in adults, aiming to clarify the strength and consistency of this relationship and to provide further insights into the prognostic significance of long-term glycemic instability.

MATERIAL AND METHODS

This meta-analysis followed the PRISMA 2020 guidelines (16) and the Cochrane Handbook for Systematic Reviews and Meta-Analyses (17) for protocol design, data extraction, statistical analysis, and results reporting. The study protocol was also registered in PROSPERO under ID CRD420251167937. No methodological deviations occurred during the review process.

Literature search

Relevant studies for this meta-analysis were identified through a comprehensive search in PubMed, Embase, and Web of Science using a broad range of search terms, which included: (1) "glycosylated hemoglobin" OR "HbA1c"; (2) "variability" OR "variation" OR "fluctuation" OR "coefficient of variation" OR "standard deviation"; (3) "heart failure" OR "cardiac failure" OR "cardiac dysfunction"; and (4) "incidence" OR "risk" OR "cohort" OR "longitudinal" OR "prospective" OR "retrospective" OR "prospectively" OR "retrospectively" OR "followed" OR "follow-up". The search was limited to human studies and full-length articles published in English in peer-reviewed journals. Additionally, references from relevant original and review articles were manually screened for further eligible studies. The search spanned from database inception to August 30, 2025. The full search strategy for each database is shown in **Supplemental File 1**. Grey literature sources were not included because non–peer-reviewed materials may compromise data reliability in observational meta-analyses. Trial registries were not searched because our review focused on published cohort studies and post-hoc analyses rather than randomized trials.

Inclusion and exclusion criteria

The eligibility criteria for studies were established based on the PICOS framework:

P (patients): General adult population (≥18 years) without HF at baseline, both diabetic and non-diabetic population could be included.

I (exposure): Participants with a high visit-to-visit HbA1c variability at baseline, with the parameters and cutoff values for defining a high HbA1c variability consistent with the criteria used in the original studies;

C (comparison): Participants with a low visit-to-visit HbA1c variability at baseline.

O (outcome): Incidence of HF during follow-up, compared between participants with a high vs. a low HbA1c variability at baseline. The methods and criteria for the diagnosis of HF were also consistent with the criteria used in the original studies.

S (study design): Observational studies with longitudinal follow-up, such as cohort studies, nested case-control studies, or post-hoc analyses of clinical trials;

Studies were excluded if they were reviews, editorials, meta-analyses, preclinical research, or including pediatric patients, not involving an exposure of visit-to-visit HbA1c, or did not report the incidence of HF. Studies assessing short-term glycemic fluctuations, such as daily glucose variability not using HbA1c or metrics from continuous glucose monitoring, were also excluded. When population overlap occurred, the study with the largest sample size was selected for inclusion in the meta-analysis.

Study quality assessment and data extraction

Two authors independently conducted the literature search, study selection, quality assessment, and data extraction, resolving discrepancies through discussion with the corresponding author. Formal inter-rater agreement statistics were not recorded. Study quality was evaluated using the Newcastle–Ottawa Scale (NOS) (18), which assesses selection, confounding control, and outcome measurement, with scores ranging from 1 to 9, where 9 represents the highest quality. Studies with NOS scores of 8 or above are considered of high quality. Data extracted for analysis included study characteristics (author, year, country, and study design), participants characteristics (source of the population, number of participants, age, sex, and diabetic status), exposure characteristics (parameters for the evaluation of HbA1c variability, cutoffs, and times of HbA1c measured for evaluating the variability), follow-up durations, outcome characteristics (methods for validating HF outcomes and number of patients with newly developed HF during follow-up), and variables adjusted in estimating the relationship between HbA1c variability and the risk of HF. For each included study,

we extracted only the adjusted hazard ratio (HR) specific to incident HF, as defined in the original article or its supplemental materials. HF endpoints included adjudicated HF events, HF hospitalization, or ICD-based incident HF, depending on each study's protocol. Composite cardiovascular or mortality outcomes were not used. All outcome definitions, adjudication status, and extraction locations (table/figure) were independently cross-checked by two reviewers.

Statistical analyses

The association between HbA1c variability and HF in adults was presented as hazard ratio (HR) and corresponding 95% confidence intervals (CIs), compared between participants with a high versus a low HbA1c variability at baseline. When studies reported more than one validated metric of HbA1c variability, we extracted a single effect estimate per study to maintain statistical independence, following Cochrane recommendations (17). Because no universally accepted primary variability metric exists and different indices (e.g., SD, CV, ARV, VIM, ASV, HVS) reflect complementary aspects of long-term glycemic instability, we did not designate a single preferred metric a priori. Instead, we included one representative adjusted estimate per study and conducted predefined subgroup analyses by variability metric to evaluate consistency across measures. When a study reported multiple HbA1c-variability metrics, we applied a predefined rule: the adjusted HR associated with the largest reported effect size was selected. This rule was specified before data synthesis and applied consistently across all studies. HRs and their standard errors were calculated from 95% CIs or p-values and log-transformed to stabilize variance and normalize distribution (17). To assess heterogeneity, we used the Cochrane Q test and I^2 statistics (19), with $I^2 < 25\%$, 25~75%, and $> 75\%$ indicating mild, moderate, and substantial heterogeneity among the included studies. The primary analysis used the DerSimonian–Laird estimator, and between-study heterogeneity was quantified using the I^2 statistic and between-study variance (τ^2) (17). To enhance robustness, we additionally performed sensitivity analyses using restricted maximum likelihood (REML) random-effects models with Hartung–Knapp adjustment. Hazard ratios (HRs) were log-transformed prior to pooling (17). For each primary meta-analysis, a 95% prediction interval (PI) was calculated to reflect the expected range of effects in future comparable studies (17). A random-effects model was used to synthesize results while accounting for variability across studies (17). Sensitivity analysis was conducted by

sequentially excluding individual studies to assess the robustness of the findings (20). In addition, sensitivity analyses limited to diabetic patients, high-quality studies (NOS ≥ 8), and studies with the adjustment of mean HbA1c were also performed. Moreover, predefined subgroup analyses were also performed to evaluate the study characteristics on the results, such as study design (prospective vs. retrospective or post-hoc analyses), countries (Asian versus Western), different parameters for HbA1c variability, and mean follow-up durations. Subgroups were defined using the median values of continuous variables as cutoff points. Moreover, univariate meta-regression analyses were also performed to evaluate if study characteristics in continuous variables may affect the association between HbA1c variability and HF risk, such as mean ages of the population, proportions of men, mean follow-up durations, and NOS (17). All subgroup analyses and meta-regression models were prespecified but exploratory, performed as univariate analyses only, and no multiplicity correction was applied; therefore, these results should be interpreted cautiously. Publication bias was assessed through funnel plots, visual asymmetry inspection, and Egger's regression test (21). Small-study effects were assessed using Egger's regression test and Duval and Tweedie's trim-and-fill method (22). A p value < 0.05 indicates statistical significance. The statistical analyses were conducted using RevMan (Version 5.3; Cochrane Collaboration, Oxford, UK) and Stata software (version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study identification

Figure 1 outlines the study selection process. Initially, 979 records were identified across three databases, with 311 duplicates removed. After title and abstract screening, 647 articles were excluded for not meeting the meta-analysis criteria. The full texts of the remaining 21 studies were independently reviewed by two authors, leading to the exclusion of 12 for reasons detailed in **Figure 1**. Ultimately, nine studies were included in the quantitative analysis (23-31).

Overview of the study characteristics

Table 1 summarizes the main characteristics of the nine studies included in this meta-analysis, encompassing two prospective cohort studies (27, 30), five retrospective cohort studies (23, 25, 28, 29, 31), and two post-hoc analyses of clinical trials (24, 26).

These studies were published between 2018 and 2025 and were conducted across diverse geographic regions, including mainland China, Hong Kong (China), Taiwan (China), Thailand, Sweden, the United Kingdom, and the United States. Eight studies enrolled adult patients with type 2 diabetes (T2D) (23-29, 31), and another study included prediabetic or T2D patients with additional cardiovascular risk factors such as hypertension, obesity, or pre-existing atherosclerotic cardiovascular disease (30). Overall, 342,123 patients were included, with mean ages ranging from 58.4 to 65.3 years and the proportion of men ranging from 37.9% to 61.9%. HbA1c variability was assessed using various indices including SD, CV, VIM, ASV, ARV, and HbA1c variability score (HVS). The exposure contrast between high and low variability was commonly defined by quartiles (24, 29-31) or quintiles (26), though some studies used medians (23) or specific categorical cut-offs (25, 27). The number of HbA1c measurements used to compute variability ranged from at least 3 to a mean of 12.7 per participant, and the mean follow-up duration spanned 4.4 to 11.7 years. HF outcomes were identified through adjudicated clinical review processes (24, 26), validated diagnostic criteria from international guidelines (23), or HF related hospitalization in institutional or national administrative databases (25, 27-31). Across studies, the number of participants developing HF during follow-up ranged from 18 to 7,908. All studies performed multivariable-adjusted analyses, adjusting for key confounders such as age, sex, body mass index, blood pressure, lipid profiles, kidney function, comorbidities, medication use, and mean HbA1c levels, to a varying degree, thereby minimizing residual confounding.

Study quality evaluation

As shown in **Table 2**, the methodological quality of the included studies was assessed using the NOS. NOS scores ranged from 7 to 9, indicating overall high methodological quality. Most studies earned full scores for representativeness of the cohort, ascertainment of exposure, exclusion of baseline HF, and adjustment for major confounders (24-31). Two post-hoc analyses and one retrospective cohort (24, 26, 31) achieved the maximum NOS score of 9, reflecting robust design, standardized laboratory procedures, and adjudicated outcome assessment. Two large population-based registry studies (25, 27) and one single-center tertiary-hospital cohort with claims-based outcome ascertainment (28) scored 8, with minor limitations related to the use of registry-coded rather than clinically confirmed HF diagnoses. One

retrospective study also scored 8 because the possible bias in representativeness of the exposed cohort (23). Another two studies were scored 7 because HF was not diagnosed by clinical evaluation and the follow-up durations were short (< 5 years) (29, 30). Importantly, all studies had adequate follow-up and low attrition risk, supporting the reliability of pooled estimates linking long-term HbA1c variability to HF risk.

Meta-analysis results

Pooled results of nine studies (23-31) showed that overall, a high HbA1c variability was associated with an increased risk of HF during follow-up (HR: 1.78, 95% CI: 1.39 to 2.27, $p < 0.001$; $I^2 = 87\%$; **Figure 2**). The between-study variance was $\tau^2 = 0.09$. The 95% prediction interval ranged from 1.01 to 3.14, indicating that most future studies are expected to show a positive association. Sensitivity analysis using a REML random-effects model with Hartung–Knapp adjustment yielded a similar effect estimate (HR: 1.78, 95% CI: 1.35 to 2.35, $p < 0.001$; $I^2 = 86\%$; **Supplemental Figure 1**), confirming the robustness of the findings. Sensitivity analysis, excluding one study at a time, showed no significant impact on the results (HR: 1.57 to 1.90, p all < 0.05). In addition, further sensitivity analyses limited to patients with T2D only (23-29, 31) showed consistent results (HR: 1.73, 95% CI: 1.35 to 2.22, $p < 0.001$; $I^2 = 88\%$). Similar results were also obtained for sensitivity analyses limited to high quality studies with NOS ≥ 8 (23-28, 31) (HR: 1.82, 95% CI: 1.32 to 2.50, $p < 0.001$; $I^2 = 86\%$) or studies with the adjustment of mean HbA1c (23, 24, 26-31) (HR: 1.68, 95% CI: 1.31 to 2.16, $p < 0.001$; $I^2 = 87\%$). Interestingly, subgroup analyses showed stronger association between a high HbA1c variability and HF risk in prospective studies as compared to retrospective and post-hoc studies (HR: 2.51 vs. 1.42 and 2.02, p for subgroup difference < 0.001; **Figure 3A**). Similar results were observed in studies from Asian and Western countries (p for subgroup difference = 0.74; **Figure 3B**), in studies with variability of HbA1c measured by SD, CV, and ASV of HbA1c (p for subgroup difference = 0.74; **Figure 4A**), and in studies with follow-up duration < 6.5 years and ≥ 6.5 years (p for subgroup difference = 0.27; **Figure 4B**). The results of univariate meta-regression analysis are shown in **Table 3**. None of the predefined characteristics, including mean ages of the population, proportions of men, mean follow-up durations, or NOS could significantly modify the association between HbA1c variability and HF risk (p all > 0.05).

Publication bias

Figure 5 displays the funnel plots evaluating the publication bias underlying the meta-analysis of the association between HbA1c variability and the risk of HF. The funnel plots are symmetrical on visual inspection, suggesting a low risk of publication bias. The findings are further supported by Egger's regression analysis, which also did not suggest a significant publication bias (p = 0.35). Given the small number of studies (k = 9), Egger's test is underpowered, and the absence of statistical significance should be interpreted cautiously. The trim-and-fill procedure did not impute any additional studies, and the pooled HR remained unchanged, indicating no evidence of small-study effects.

DISCUSSION

This meta-analysis demonstrated that greater visit-to-visit variability in HbA1c may be significantly associated with a higher risk of developing HF, independent of mean HbA1c levels and other conventional risk factors. The findings were consistent across multiple sensitivity analyses restricted to patients with T2D, high-quality studies, and those adjusting for mean HbA1c, suggesting that long-term glycemic instability may have prognostic significance beyond average glycemic exposure. The strength of the association was more pronounced in prospective cohorts compared with retrospective or post-hoc analyses, underscoring the robustness of temporally assessed data. Collectively, these findings support the hypothesis that HbA1c variability reflects an additional dimension of glycemic burden that contributes to cardiovascular risk and highlight its potential role as a novel biomarker for identifying individuals at increased risk of HF.

Only one recent meta-analysis has examined HbA1c variability in relation to HF risk, but it did so as part of a broader synthesis of multiple glycemic risk factors and cardiovascular outcomes (15). Our review differs in that it provides a focused and updated estimate specifically for incident HF, incorporates additional recent cohorts, and applies comprehensive subgroup and REML–Hartung–Knapp sensitivity analyses. Clinically, HbA1c variability may serve as a complementary risk marker alongside mean HbA1c, diabetes duration, and renal function, and may help identify individuals with T2D who warrant closer monitoring, earlier initiation of HF-preventive therapies, or more stable glucose-lowering strategies. Several biological mechanisms may explain the link between long-term HbA1c variability and elevated HF risk. Repeated

oscillations in glucose levels have been shown to induce greater oxidative stress and endothelial dysfunction than sustained hyperglycemia, resulting in impaired nitric oxide bioavailability and microvascular inflammation (32-34). These fluctuations promote maladaptive cardiac remodeling through the accumulation of advanced glycation end-products (AGEs), mitochondrial dysfunction, and activation of pro-fibrotic pathways (35-37). In diabetic cardiomyopathy, intermittent hyperglycemia also triggers sympathetic overactivity and metabolic inflexibility, leading to impaired myocardial energy utilization and left ventricular diastolic dysfunction—key precursors of HF (38). Furthermore, HbA1c variability may reflect fluctuations in treatment adherence or medication responsiveness, which could exacerbate cardiovascular instability (39). Collectively, these mechanisms suggest that maintaining stable long-term glycemic control may be as important as lowering mean HbA1c for the prevention of HF.

The results of subgroup and sensitivity analyses provide additional insights into the robustness and potential heterogeneity of this association. The stronger relationship observed in prospective cohorts likely reflects the more rigorous data collection and outcome validation inherent to such designs, reducing the risk of measurement bias. Studies that adjusted for mean HbA1c retained a significant association, supporting the hypothesis that glycemic fluctuation exerts harmful cardiovascular effects beyond chronic hyperglycemia itself (40). Similarly, the consistent findings across high-quality studies and those with extended follow-up durations reinforce the temporal plausibility of the association. The absence of significant modifiers in the meta-regression analysis—including age, sex, study quality, and follow-up duration—suggests that the detrimental impact of HbA1c variability may be broadly consistent across populations, although subtle interactions may exist that cannot be detected without individual-level data.

From a clinical perspective, these findings emphasize the potential utility of incorporating measures of HbA1c variability into long-term risk assessment frameworks for patients with T2D. Current diabetes management guidelines primarily focus on mean HbA1c targets (41). However, these results indicate that minimizing long-term fluctuations in glycemia may confer additional cardiovascular benefits (41). Regular monitoring of HbA1c variability could help identify high-risk individuals who might benefit from more consistent glycemic control strategies, enhanced medication adherence, or early intervention for cardiovascular risk reduction.

Clinicians should also be aware that treatment regimens with a higher propensity for glycemic oscillation—such as those involving short-acting insulin secretagogues or intermittent insulin dosing—may increase the risk of adverse cardiac outcomes if glycemic variability is not adequately managed (42, 43).

This meta-analysis has several strengths that enhance the credibility of its findings. First, it represents the updated summary of the evidence, including nine longitudinal cohorts with over 340,000 participants and more than 10,000 incident HF events. Second, all included studies employed longitudinal designs with temporally defined exposure and outcome windows, ensuring that HbA1c variability preceded the onset of HF. Third, the analyses were based on multivariable-adjusted risk estimates, minimizing confounding by established cardiovascular risk factors. Furthermore, multiple sensitivity and subgroup analyses confirmed the stability of the results across diverse study settings, designs, and analytic approaches. Nevertheless, several limitations should be acknowledged. The majority of included studies involved patients with T2D, and thus the association between HbA1c variability and HF risk in individuals without diabetes or with type 1 diabetes remains uncertain. Although two post-hoc analyses were derived from randomized clinical trials (24, 26), most studies were observational and the possibility of residual and time-varying confounding cannot be excluded. Considerable heterogeneity was observed among studies, likely attributable to differences in definitions and metrics of HbA1c variability (e.g., SD, CV, ARV, VIM), population characteristics, comorbidity profiles, and concurrent medication use. Because individual participant data were unavailable, the influence of certain confounding variables—particularly antidiabetic treatment type, treatment adherence, and changes in therapy over time—could not be fully examined. In addition, as the included studies were based on observational data, causality cannot be established, and reverse causation remains possible despite efforts to exclude participants with preexisting HF. Moreover, definitions of HF varied across studies, with only a subset using fully adjudicated clinical endpoints while others relied on validated registry or administrative codes; because adjudicated outcomes were available in only a minority of cohorts, we could not perform a sensitivity analysis restricted to adjudicated HF, which should be considered when interpreting the findings. In addition, some studies used registry or administrative data to define HF outcomes, which may have introduced misclassification bias, although sensitivity analyses indicated overall robustness of the findings. Finally, a dose–response meta-

analysis could not be performed because most studies reported HbA1c variability in categorical form (e.g., quartiles or tertiles) without providing continuous effect estimates per SD or unit increase, limiting our ability to harmonize exposure thresholds. Accordingly, our clinical interpretation is based on relative hazards and the prediction interval, underscoring the need for future studies to report standardized absolute risk measures to facilitate clinical translation.

Given these limitations, the results should be interpreted cautiously. Future research should aim to validate these findings in non-diabetic and type 1 diabetic population and to explore the pathophysiological mechanisms underlying the observed relationship using longitudinal studies with standardized definitions of HbA1c variability. Individual participant data meta-analyses would allow more refined analyses adjusting for medication use, comorbidities, and time-dependent changes in glycemia. Randomized trials testing interventions designed to minimize long-term glycemic fluctuations may ultimately clarify whether reducing HbA1c variability can translate into improved cardiovascular outcomes, including the prevention of HF.

CONCLUSION

In conclusion, this meta-analysis suggests that greater visit-to-visit HbA1c variability may be independently associated with a higher risk of incident HF among adults, particularly those with T2D. These findings highlight the potential importance of maintaining stable long-term glycemic control, in addition to achieving optimal mean HbA1c levels, as part of comprehensive cardiovascular risk management. Given that all included data derive from observational studies, the overall certainty of evidence for this association should be regarded as low to moderate, and the findings should be interpreted accordingly. Further research is warranted to determine whether strategies aimed at reducing glycemic variability can effectively lower HF risk and improve long-term outcomes in diabetic populations.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: All data generated or analyzed during this study are included in this published article.

Submitted: October 15, 2025

Accepted: December 4, 2025

Published online: December 19, 2025

REFERENCES

1.Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2025;151(8):e41–e660.

2.Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272–87.
https://doi.org/10.1093/cvr/cvac013

3.Bozkurt B. Concerning Trends of Rising Heart Failure Mortality Rates. JACC Heart Fail. 2024;12(5):970–2.
https://doi.org/10.1016/j.jchf.2024.04.001

4.Triposkiadis F, Xanthopoulos A, Parissis J, Butler J, Farmakis D. Pathogenesis of chronic heart failure: cardiovascular aging, risk factors, comorbidities, and disease modifiers. Heart Fail Rev. 2022;27(1):337–44.
https://doi.org/10.1007/s10741-020-09987-z

5.Xie S, Xu SC, Deng W, Tang Q. Metabolic landscape in cardiac aging: insights into molecular biology and therapeutic implications. Signal Transduct Target Ther. 2023;8(1):114.
https://doi.org/10.1038/s41392-023-01378-8

6.Park JJ. Epidemiology, Pathophysiology, Diagnosis and Treatment of Heart Failure in Diabetes. Diabetes Metab J. 2021;45(2):146–57.
https://doi.org/10.4093/dmj.2020.0282

7.Alfieri V, Myasoedova VA, Vinci MC, Rondinelli M, Songia P, Massaiu I, et al. The Role of Glycemic Variability in Cardiovascular Disorders. Int J Mol Sci.

2021;22(16).
https://doi.org/10.3390/ijms22168393

8.Caturano A, Rocco M, Tagliaferri G, Piacevole A, Nilo D, Di Lorenzo G, et al. Oxidative Stress and Cardiovascular Complications in Type 2 Diabetes: From Pathophysiology to Lifestyle Modifications. Antioxidants (Basel). 2025;14(1).
https://doi.org/10.3390/antiox14010072

9.Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep. 2014;14(11):548.
https://doi.org/10.1007/s11892-014-0548-3

10.Sakamoto M. Type 2 Diabetes and Glycemic Variability: Various Parameters in Clinical Practice. J Clin Med Res. 2018;10(10):737–42.
https://doi.org/10.14740/jocmr3556w

11.Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol. 2019;7(3):221–30.
https://doi.org/10.1016/S2213-8587(18)30136-0

12.Umpierrez GE, B PK. Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes. Am J Med Sci. 2018;356(6):518–27.
https://doi.org/10.1016/j.amjms.2018.09.010

13.Li F, Zhang L, Shen Y, Liu HH, Zhang ZY, Hu G, et al. Higher glucose fluctuation is associated with a higher risk of cardiovascular disease: Insights from pooled results among patients with diabetes. J Diabetes. 2023;15(5):368–81.
https://doi.org/10.1111/1753-0407.13386

14.Qu F, Shi Q, Wang Y, Shen Y, Zhou K, Pearson ER, et al. Visit-to-visit glycated hemoglobin A1c variability in adults with type 2 diabetes: a systematic review and meta-analysis. Chin Med J (Engl). 2022;135(19):2294–300.
https://doi.org/10.1097/CM9.0000000000002073

15.Tabesh M, Sacre JW, Mehta K, Chen L, Sajjadi SF, Magliano DJ, et al. The association of glycaemic risk factors and diabetes duration with risk of heart failure in people with type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab. 2024;26(12):5690–700.
https://doi.org/10.1111/dom.15938

16.Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
https://doi.org/10.1136/bmj.n71

17.Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. The Cochrane Collaboration. 2021.
https://www.training.cochrane.org/handbook

18.Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2010.
http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

19.Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
https://doi.org/10.1002/sim.1186

20.Marušić MF, Fidahić M, Cepeha CM, Farcaș LG, Tseke A, Puljak L. Methodological tools and sensitivity analysis for assessing quality or risk of bias used in systematic reviews published in the high-impact anesthesiology journals. BMC Medical Research Methodology. 2020;20(1):121.
https://doi.org/10.1186/s12874-020-00966-4

21.Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
https://doi.org/10.1136/bmj.315.7109.629

22.Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455–63. https://doi.org/10.1111/j.0006-341X.2000.00455.x

23.Guo J, Fan YQ, Zhang JF, Wang CQ. Association of hemoglobin A1c variability and the incidence of heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus and arterial hypertension. Hellenic J Cardiol. 2018;59(2):91–7. https://doi.org/10.1016/j.hjc.2017.08.001

24.Kaze AD, Santhanam P, Erqou S, Ahima RS, Echouffo-Tcheugui JB. Long-term variability of glycemic markers and risk of all-cause mortality in type 2 diabetes: the Look AHEAD study. BMJ Open Diabetes Res Care. 2020;8(2). https://doi.org/10.1136/bmjdrc-2020-001753

25.Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-to-Visit HbA(1c) Variability Is Associated With Cardiovascular Disease and Microvascular Complications in Patients With Newly Diagnosed Type 2 Diabetes. Diabetes Care. 2020;43(2):426–32. https://doi.org/10.2337/dc19-0823

26.Segar MW, Patel KV, Vaduganathan M, Caughey MC, Butler J, Fonarow GC, et al. Association of Long-term Change and Variability in Glycemia With Risk of Incident Heart Failure Among Patients With Type 2 Diabetes: A Secondary Analysis of the ACCORD Trial. Diabetes Care. 2020;43(8):1920–8. https://doi.org/10.2337/dc19-2541

27.Wan EYF, Yu EYT, Chin WY, Ng FTY, Chia SMC, Wong ICK, et al. Age-specific associations of glycated haemoglobin variability with cardiovascular disease and mortality in patients with type 2 diabetes mellitus: A 10-year cohort study. Diabetes Obes Metab. 2020;22(8):1316–27. https://doi.org/10.1111/dom.14034

28.Lin YT, Huang WL, Wu HP, Chang MP, Chen CC. Association of Mean and Variability of HbA1c with Heart Failure in Patients with Type 2 Diabetes. J Clin Med.

2021;10(7).
https://doi.org/10.3390/jcm10071401

29.Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Franzen S, Svensson AM, et al. HbA1c variability predicts cardiovascular complications in type 2 diabetes regardless of being at glycemic target. Cardiovasc Diabetol. 2022;21(1):13.
https://doi.org/10.1186/s12933-022-01445-4

30.Manosroi W, Phimphilai M, Waisayanand N, Buranapin S, Deerochanawong C, Gunaparn S, et al. Glycated hemoglobin variability and the risk of cardiovascular events in patients with prediabetes and type 2 diabetes mellitus: A post-hoc analysis of a prospective and multicenter study. J Diabetes Investig. 2023;14(12):1391–400.
https://doi.org/10.1111/jdi.14073

31.Hsiao FC, Lin CP, Hsu TJ, Tung YC, Chan YH, Chen SW, et al. Glycohemoglobin Variations and Long-term Risk of Incident Heart Failure in Patients With Type 2 Diabetes. Mayo Clin Proc. 2025;100(8):1332–44.
https://doi.org/10.1016/j.mayocp.2024.12.022

32.Roy B. Pathophysiological Mechanisms of Diabetes-Induced Macrovascular and Microvascular Complications: The Role of Oxidative Stress. Med Sci (Basel). 2025;13(3).
https://doi.org/10.3390/medsci13030087

33.Liu TS, Pei YH, Peng YP, Chen J, Jiang SS, Gong JB. Oscillating high glucose enhances oxidative stress and apoptosis in human coronary artery endothelial cells. J Endocrinol Invest. 2014;37(7):645–51.
https://doi.org/10.1007/s40618-014-0086-5

34.Murata M, Adachi H, Oshima S, Kurabayashi M. Glucose fluctuation and the resultant endothelial injury are correlated with pancreatic β cell dysfunction in patients with coronary artery disease. Diabetes Res Clin Pract. 2017;131:107–15.
https://doi.org/10.1016/j.diabres.2017.07.007

35.Watanabe M, Kawai Y, Kitayama M, Akao H, Motoyama A, Wakasa M, et al. Diurnal glycemic fluctuation is associated with severity of coronary artery disease in

prediabetic patients: Possible role of nitrotyrosine and glyceraldehyde-derived advanced glycation end products. J Cardiol. 2017;69(4):625–31.
https://doi.org/10.1016/j.jjcc.2016.07.001

36.Mordel P, Fontaine F, Dupas Q, Joubert M, Allouche S. Glucose fluctuation promotes mitochondrial dysfunctions in the cardiomyocyte cell line HL-1. PLoS One. 2023;18(9):e0289475.
https://doi.org/10.1371/journal.pone.0289475

37.Zhang L, Liu HH, Yang F, Zhang ZY, Zhao XX, Qian LL, et al. Glucose fluctuations aggravate myocardial fibrosis via activating the CaMKII/Stat3 signaling in type 2 diabetes. Diabetol Metab Syndr. 2023;15(1):217.
https://doi.org/10.1186/s13098-023-01197-5

38.Brahma MK, Pepin ME, Wende AR. My Sweetheart Is Broken: Role of Glucose in Diabetic Cardiomyopathy. Diabetes Metab J. 2017;41(1):1–9.
https://doi.org/10.4093/dmj.2017.41.1.1

39.Vural Keskinler M, Takir M, Caklili OT, Oguz A. The Frequency and Determinants of HbA1c Variability in Type 2 Diabetic Patients. Metab Syndr Relat Disord. 2021;19(7):372–7.
https://doi.org/10.1089/met.2020.0131

40.Wu TE, Su YW, Chen HS. Mean HbA1c and HbA1c variability are associated with differing diabetes-related complications in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2022;192:110069.
https://doi.org/10.1016/j.diabres.2022.110069

41.Aroda VR, Eckel RH. Reconsidering the role of glycaemic control in cardiovascular disease risk in type 2 diabetes: A 21st century assessment. Diabetes Obes Metab. 2022;24(12):2297–308.
https://doi.org/10.1111/dom.14830

42.Huang Y, Heng C, Wei J, Jing X, Wang X, Zhao G, et al. Influencing factors of glycemic variability in hospitalized type 2 diabetes patients with insulin therapy: A

Strobe-compliant article. Medicine (Baltimore). 2017;96(36):e8021. https://doi.org/10.1097/MD.0000000000008021

43.Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: adverse clinical outcomes and how to improve it? Cardiovasc Diabetol. 2020;19(1):102. https://doi.org/10.1186/s12933-020-01085-6

TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Study design	Source of population	No. of participants	Mean age (years)	Men (%)	Parameters for HbA1c variability	Cutoffs of HbA1c variability	Times of HbA1c measured for variability	Mean follow-up duration (years)	Methods for validating HF outcome	No. of patients with HF	Variables adjusted
Gu 2018	China	RC	Patients with T2D and hypertension from a single institution	201	65.3	59.2	HbA1c-SD* and HbA1c-CV	Medians	Mean: 11.7	7.3	AHA/ACC diagnostic criteria for new-onset symptomatic HFpEF	18	Age, sex, SBP, DBP, HbA1c-mean, eGFR, BMI, duration of T2D and hypertension, AF, medical treatment (Calcium blocker, ACEI/ARB, Beta-

													blockers, Statin, Sulfonylurea, Metformin, α-GI, Thiazolidinedione, Insulin), LAD, LVMI, E/E', and LVEF
Kaze 2020	USA	Post-hoc Analysis of an RCT	Overweight or obese adults with T2D	3560	58.4	37.9	HbA1c-SD*, HbA1c-CV, HbA1c-VIM, and HbA1c-ASV	Q4:Q1	Mean: 4	6.8	Adjudicated incident HF events, as per the pre-defined process in the Look AHEAD trial	91	Age, sex, race/ethnicity, randomization arm, BMI, current smoking, alcohol drinking, use of antihypertensive

													medications, average ratio of total to HDL-c, eGFR, duration of diabetes, average SBP, and average HbA1c
Segar 2020	USA	Post-hoc Analysis of an RCT	Adults withT2D and high cardiovascular risk or established CVD	8576	62.4	61.9	HbA1c-SD, HbA1c-CV, and HbA1c-ASV*	Q5:Q1	Median: 8	6.4	Adjudicated incident HF hospitalization or death due to HF by an independent committee	388	Age, sex, race, education, intensive glycemic control treatment group, history of CVD, traditional cardiovascular risk factors

													(systolic BP, BMI, cigarette use, alcohol use, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (ARB, ACE inhibitor, β-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin, sulfonylurea,

													biguanide, meglitinide, α-glucosidase inhibitor), and mean HbA1c
Li 2020	UK	RC	Adults with newly diagnosed T2D	19059	63.3	54.6	HVS	HVS 80-100 vs. 0-20	Median: 12	6.8	Hospitalization or death from HF (as per electronic health records)	853	Age, sex, calendar year, Scottish Index of Multiple Deprivation, smoking, hypertension, BMI, HDL-c, eGFR, antiplatelet therapy, and CCI
Wan 2020	Hongkong (China)	PC	Hong Kong Hospital	147811	64.2	46.0	HbA1c-SD	≥3.0% vs. 0%-0.24%	Mean: 3.2	7.4	Hospital Authority electronic	7908	Age, sex, smoking status,

			Authority (HA) electronic health records; primary care patients with T2D								health records and Death Registry, using ICPC-2 and ICD-9/10 codes		duration of diabetes, BMI, systolic and diastolic BP, LDL-c, eGFR, use of metformin, sulphonylureas, other oral diabetic drugs, insulin, anti-hypertensive drugs, lipid-lowering agents, CCI, and mean HbA1c
Lin 2021	Taiwan (China)	RC	T2D patients from Diabetes Shared	3824	58.5	50.2	HbA1c-SD	T3:T1	At least 3 measurements within a 12-24	11.7	HF by National Health Insurance claim	315	Age, sex, diabetes duration, BMI, systolic BP, total

			Care Program at a tertiary hospital (China Medical University Hospital)						month baseline period		database using ICD-9-CM and ICD-10-CM codes		cholesterol, triglyceride, HDL-c, LDL-c, eGFR, CAD, hypertension, stroke, and use of sulfonylureas, metformin, thiazolinediones, insulin, statin, antiplatelet agents, warfarin, ACEIs, ARB, beta-blockers, CCB, diuretics, alpha-blockers, and

													mean HbA1c
Ceriello 2022	Sweden	RC	T2D patients from Swedish National Diabetes Register	101533	64.3	55.6	HbA1c-SD	Q4:Q1	At least 5 measurements during a 3-year exposure phase	4.4	National registry data using ICD-9 and ICD-10 codes (Hospitalization for HF)	NR	Age, sex, duration of diabetes, body weight, smoking, mean HbA1c, systolic and diastolic BP, total cholesterol, HDL-c, LDL-c, triglycerides, albuminuria, eGFR, retinopathy, treatment for diabetes, hypertension, dyslipidemia, and aspirin

Manosroi 2023	Thailand	PC	Thai patients aged >45 years with high atherosclerotic risk (Prediabetes or T2D)	3811	64.7	46.6	HbA1c-SD	Q4:Q1	Median: 3	4.5	Hospitalization for HF (as part of the 4P-MACE outcome)	109	Age, sex, educational level, BMI, established ASCVD status, systolic BP, smoking status, mean HbA1c, lipid profiles, creatinine level, number of HbA1c measurements, antihypertensive medications, diabetes medications, lipid-lowering

													agents, and antiplatelet/anticoagulants
Hsiao 2025	Taiwan (China)	RC	T2D patients from The Chang Gung Research Database	53748	63.7	50.7	HbA1c-ARV	Q4:Q1	Mean: 12.7	6.2	HF hospitalization, defined as a principal discharge diagnosis of HF plus at least one treatment during hospitalization (diuretics, nitrites, or inotropic agents)	1995	Age, sex, BMI, smoking, all comorbidities, baseline renal function, all medications, average lipid profiles, average vital signs (systolic/diastolic BP, heart rate), hypoglycemia, hyperglycemia, and the average

													HbA1c level

*, parameter used in the main meta-analysis.

Abbreviations: RC: Retrospective cohort; PC: Prospective cohort; RCT: Randomized controlled trial; T2D: Type 2 diabetes; HbA1c: Glycated hemoglobin; SD: Standard deviation; CV: Coefficient of variation; VIM: Variability independent of the mean; ASV: Adjacent standard deviation; HVS: HbA1c variability score; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; AHA/ACC: American Heart Association/American College of Cardiology; eGFR: Estimated glomerular filtration rate; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; AF: Atrial fibrillation; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; LAD: Left atrial diameter; LVMI: Left ventricular mass index; LVEF: Left ventricular ejection fraction; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; CAD: Coronary artery disease; CVD: Cardiovascular disease; ASCVD: Atherosclerotic cardiovascular disease; CCI: Charlson comorbidity index; CCB: Calcium channel blocker; ICD: International Classification of Diseases; ICPC: International Classification of Primary Care; NR: Not reported.

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale with reasons

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Gu 2018	0 point. The exposed cohort was drawn from a hospital medical record database. Unknown if the patients were consecutively or	1 point. The non-exposed cohort (low HbA1c variability group) was drawn	1 point. HbA1c was measured using a standardized, DCCT-aligned laboratory method (high-performance liquid chromatogr	1 point. Patients with symptomatic heart failure at baseline were explicitly excluded.	1 point. Both age and sex were included in the initial univariate analysis and considered for	1 point. The study adjusted for numerous important confounders, including blood pressure, mean HbA1c, renal function, BMI, comorbidities, and medications	1 point. The outcome (symptomatic HFpEF) was assessed using strict, pre-defined, and accepted (AHA/ACC) diagnostic criteria	1 point. The median follow-up was 7.3 years, which is >5 years	1 point. The study retrospectively enrolled patients who had been followed for at least 2 years, and follow-up	8

	randomly enrolled.	from the same source as the exposed cohort (high HbA1c variability group)	aphy)		the multivariable model		involving both clinical and echocardiographic evidence	and sufficient for the outcome to occur	information was obtained from a comprehensive medical record database, suggesting a low loss to follow-up	
Kaze 2020	1 point. The cohort was derived from a multi-center, randomized controlled trial (Look	1 point. The non-exposed cohort (low HbA1c	1 point. HbA1c was measured in a central laboratory using a standardized, high-	1 point. Participants with prevalent HF at baseline or during the first 36	1 point. Both age and sex were included in the multivariable	1 point. The model adjusted for numerous important confounders, including race, BMI, smoking, blood pressure, lipids, renal	1 point. The outcome (incident HF) was ascertained via a standardized and	1 point. The median follow-up was	1 point. As a post-hoc analysis of an RCT with a dedicated follow-up	9

	AHEAD) with a well-defined, prospective recruitment strategy	variability groups, e.g., Q1) was drawn from the same source as the exposed cohort (the trial population)	performance method (ion-exchange HPLC), ensuring reliable exposure assessment	months (the exposure assessment period) were explicitly excluded	regression models	function, diabetes duration, and crucially, the mean HbA1c level	adjudicated process within the clinical trial, which is a high-quality method	6.8 years, which is >5 years and sufficient for the outcome to occur	structure, the loss to follow-up is expected to be minimal	
Segar 2020	1 point. The cohort was	1 point. The	1 point. HbA1c was	1 point. Participant	1 point. Both age	1 point. The model adjusted for a	1 point. The outcome	1 point.	1 point. As a post-	9

	derived from a large, multicenter randomized controlled trial (ACCORD) with a well-defined, prospective recruitment strategy	non-exposed cohort (e.g., lower variability groups) was drawn from the same source as the exposed cohort (the trial	measured at a central laboratory using a standardized, NGSP-certified method at regular intervals, ensuring reliable exposure assessment	s with a history of HF or an HF event within the first 3 years of enrollment were explicitly excluded	and sex were included in the multivariable regression models	comprehensive set of confounders, including cardiovascular history, risk factors, medications, baseline HbA1c, and crucially, the mean change in HbA1c and other time-updated cardiometabolic parameters	(incident HF) was adjudicated by an independent, blinded clinical events committee using predefined criteria, which is a high-quality method	The median follow-up for the outcome was 6.4 years, which is >5 years and sufficient	hoc analysis of an RCT with a dedicated follow-up structure, the loss to follow-up is expected to be minimal	

		population)								
Li 2020	1 point. Population-based from SCI-DC database, includes all eligible newly diagnosed T2D patients	1 point. The non-exposed cohort was drawn from the same source as the exposed cohort	1 point. HbA1c measured extracted from electronic health records	1 point. Excluded patients with HF within first 3 years of diagnosis	1 point. Both age and sex were included in the multivariable regression models	1 point. Adjusted for multiple confounders (smoking, BMI, eGFR, deprivation, etc.)	0 point. HF defined by hospitalization or death, from validated records, not by clinically diagnosed HF	1 point. The median follow-up for the outcome was 6.8 years, which is >5 years and suffici	1 point. Low attrition due to use of national registry data	8

								ent		
Wan 2020	1 point. Population-based, using the Hong Kong HA database which covers >90% of local patients with chronic diseases	1 point. The non-exposed cohort was drawn from the same source as the exposed cohort	1 point. HbA1c measured from standardized laboratory tests within the HA system	1 point. Patients with a prior diagnosis of CVD at baseline were explicitly excluded	1 point. Both age and sex were included in the multivariable regression models	1 point. Comprehensively adjusted for numerous clinical and treatment-related confounders, including mean HbA1c	0 point. Outcomes determined via linkage with robust electronic health records and the official Death Registry, not by clinically diagnosed HF	1 point. The median follow-up for the outcome was 7.4 years, which is >5 years and sufficient	1 point. Low risk of attrition due to the use of a comprehensive, population-wide administrative database	8

Lin 2021	1 point. Consecutively enrolled from the hospital's Diabetes Shared Care Program, representing a real-world clinical cohort	1 point. The non-exposed cohort was drawn from the same source as the exposed cohort	1 point. HbA1c measured extracted from electronic health records	1 point. Patients with a history of HF were excluded, and those who developed HF within 1 year of enrollment were also excluded to mitigate reverse causality	1 point. Both age and sex were included in the multivariable regression models	1 point. Comprehensively adjusted for a wide array of clinical, laboratory, and medication-related confounders	0 point. Outcome determined via linkage with a national claims database, not by clinically diagnosed HF	1 point. The median follow-up for the outcome was 11.7 years, which is >5 years and sufficient	1 point. Used a national database, suggesting minimal loss to follow-up	8
Ceriel	1 point.	1 point.	1 point.	1 point.	1 point.	1 point.	0 point.	0	1 point.	7

lo 2022	Population-based, using the Swedish National Diabetes Register which includes ~90% of all patients with diabetes in Sweden	The non-exposed cohort was drawn from the same source as the exposed cohort	HbA1c measured by standard procedures as part of a national registry	Patients with prevalent macrovascular diseases (including HF) at baseline or during the exposure phase were excluded	Both age and sex were included in the multivariable regression models	Comprehensively adjusted for a very wide range of clinical, laboratory, and treatment-related confounders, including mean HbA1c	Outcomes determined via linkage with robust national registry data using standardized ICD codes, not by clinically diagnosed HF	point. The median follow-up for the outcome was 4.4 years, which is <5 years	Low risk of attrition due to the use of a comprehensive, national registry	
Manosroi 2023	1 point. The cohort is a multicenter, national registry	1 point. The non-exposed	1 point. Exposure (HbA1c variability) was	1 point. The study is a longitudinal analysis	1 point. Both age and sex were included	1 point. The model adjusted for numerous important confounders, including ASCVD	0 point. While not explicitly detailed, hospitalizati	0 point. The median	1 point. The description states patients	7

	(CORE-Thailand) designed to enroll patients with high atherosclerotic risk	cohort was drawn from the same source as the exposed cohort	ascertained from objective laboratory measurements (HbA1c SD) from patient records	of incident events. Patients were followed until they developed the outcome (HF hospitalization), died, or were censored	in the multivariable regression models	status, BMI, smoking, mean HbA1c, renal function, lipid levels, and medication use	on for HF recorded, not by clinically diagnosed HF	follow-up for the outcome was 4.5 years, which is <5 years	were followed until death, lost to follow-up, or censoring, suggesting a reasonable follow-up rate	
Hsiao 2025	1 point. The cohort is a large, multicenter, nationwide database (Chang	1 point. The "non-exposed" cohort (lowest	1 point. Exposure (HbA1c variability) was ascertained from	1 point. The study explicitly excluded patients with a history of	1 point. Both age and sex were included in the multivari	1 point. The model adjusted for a very extensive set of confounders, including comorbidities, renal function,	1 point. HF was defined by a primary hospital discharge diagnosis plus the	1 point. The median follow-up	1 point. The study used a comprehensive hospital database	9

	Gung Research Database) that systematically collects data from all treated patients with T2D in that system	quartile of HbA1c variability) was drawn from the same source population as the exposed cohort	objective, serial laboratory measurements (HbA1c ARV) recorded in the medical database	HF, myocardial infarction, or coronary intervention at baseline, ensuring the outcome was incident	able regression models	medications, lipid profiles, vital signs, hypoglycemia/hyperglycemia events, and crucially, the mean HbA1c level	requirement for specific HF treatments, with the information of LVEF	for the outcome was 6.2 years, which is >5 years	with a defined end-of-study date (Dec 31, 2018), suggesting minimal loss to follow-up	

Abbreviations: HbA1c: Glycated hemoglobin; SD: Standard deviation; ARV: Average real variability; T2D: Type 2 diabetes; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; AHA: American Heart Association; ACC: American College of Cardiology; HPLC: High-performance liquid chromatography; DCCT: Diabetes Control and Complications Trial; RCT: Randomized controlled trial; Look AHEAD: Action for Health in Diabetes trial; ACCORD: Action to Control Cardiovascular Risk in Diabetes trial;

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; CVD: Cardiovascular disease; ASCVD: Atherosclerotic cardiovascular disease; ICD: International Classification of Diseases; SCI-DC: Scottish Care Information–Diabetes Collaboration; HA: Hospital Authority; BP: Blood pressure; CAD: Coronary artery disease; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction.

Table 3. Results of univariate meta-regression analysis

Variables	HR for the association between HbA1c variability and the risk of heart failure			
	Coefficient	95% CI	*p* values	Adjusted R^2
Mean age (years)	0.056	-0.079 to 0.190	0.36	0%
Men (%)	-0.0026	-0.0532 to 0.0479	0.91	0%
Follow-up duration (years)	-0.043	-0.195 to 0.109	0.53	0%
NOS	0.17	-0.34 to 0.68	0.46	0%

Abbreviations: HR: Hazard ratio; HbA1c: Glycated hemoglobin; CI: Confidence interval; NOS: Newcastle–Ottawa Scale.

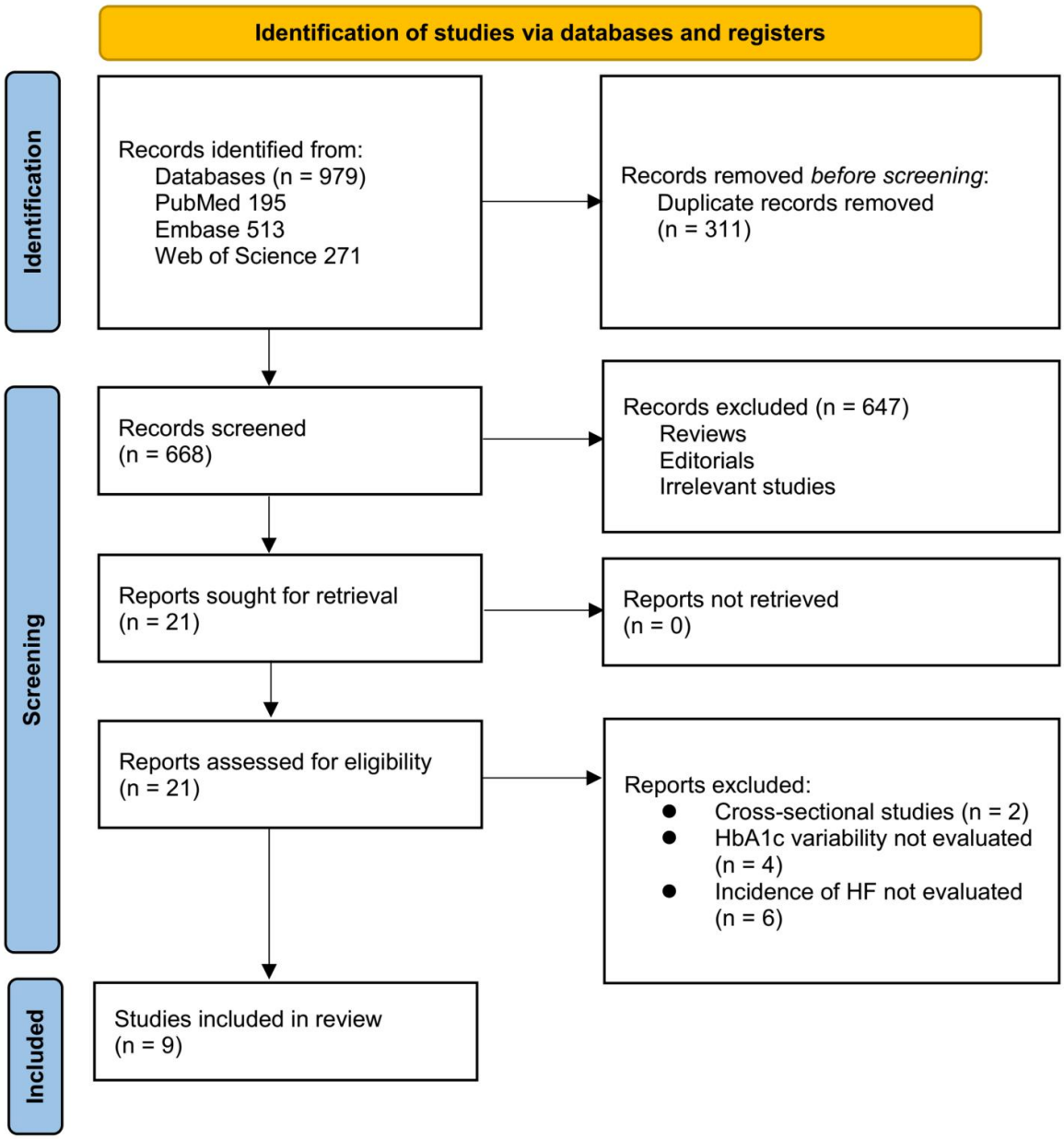

Figure 1. Flowchart of database search and study inclusion

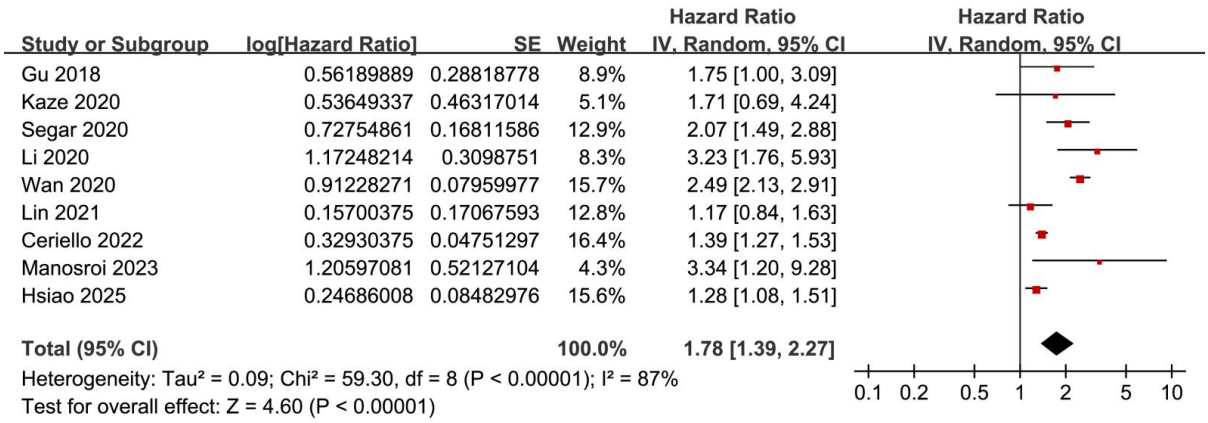

Figure 2. Forest plot illustrating the association between high and low visit-to-visit HbA1c variability and the incidence of HF. The adjusted HRs with 95% CIs from nine longitudinal studies were combined using an inverse-variance random-effects model. Squares denote individual study estimates, with their sizes proportional to study weight, while horizontal lines represent the 95% CIs. The diamond indicates the pooled effect (HR 1.78, 95% CI 1.39–2.27). The vertical line at HR = 1 signifies no association, and there was substantial between-study heterogeneity (I^2 = 87%; τ^2 = 0.09). Abbreviations: HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio; CI, confidence interval.

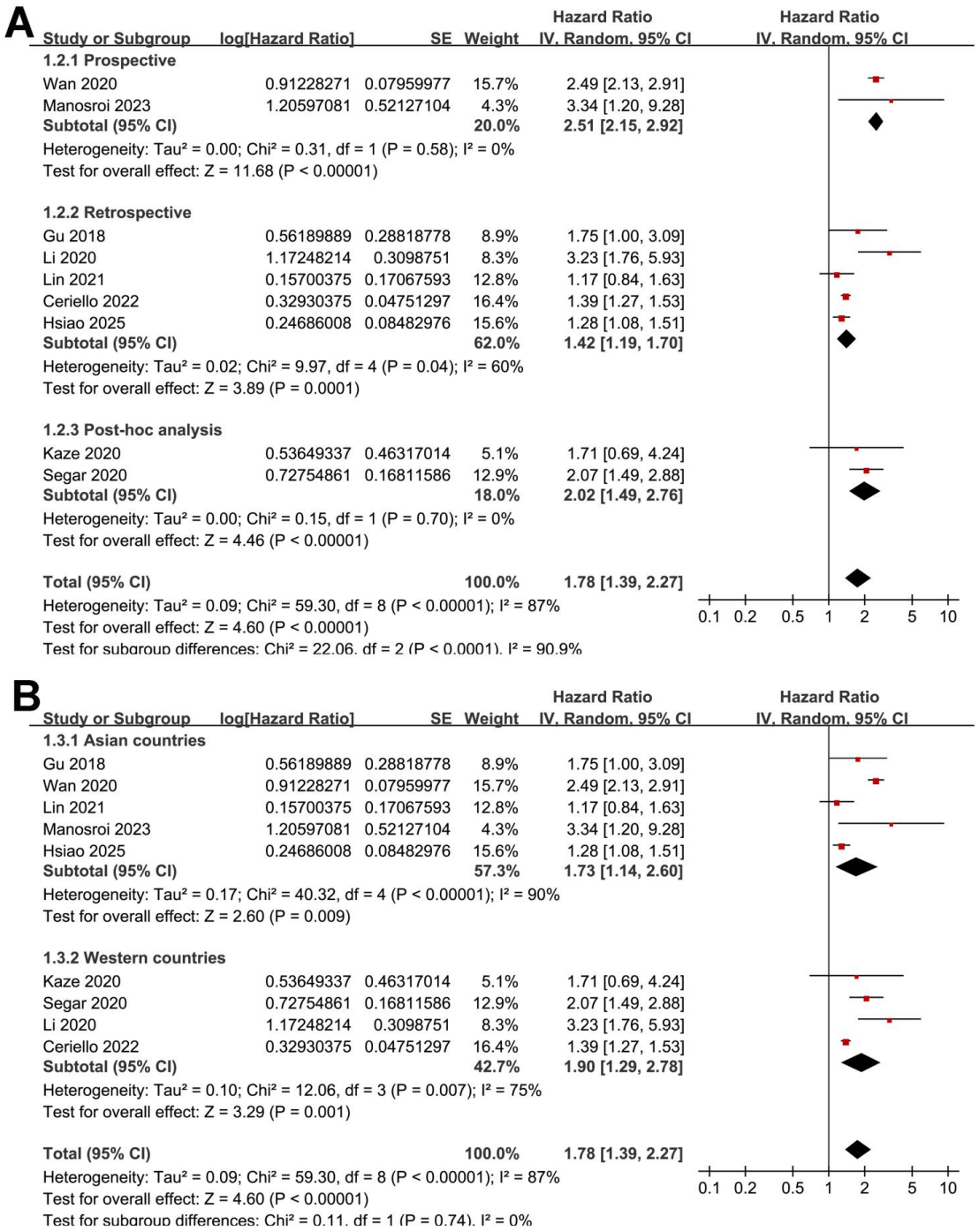

Figure 3. Forest plots illustrating subgroup analyses of the association between HbA1c variability and the risk of HF. (A) Subgroup analysis by study design. (B) Subgroup analysis by study country. Abbreviations: HbA1c, glycated hemoglobin; HF, heart failure.

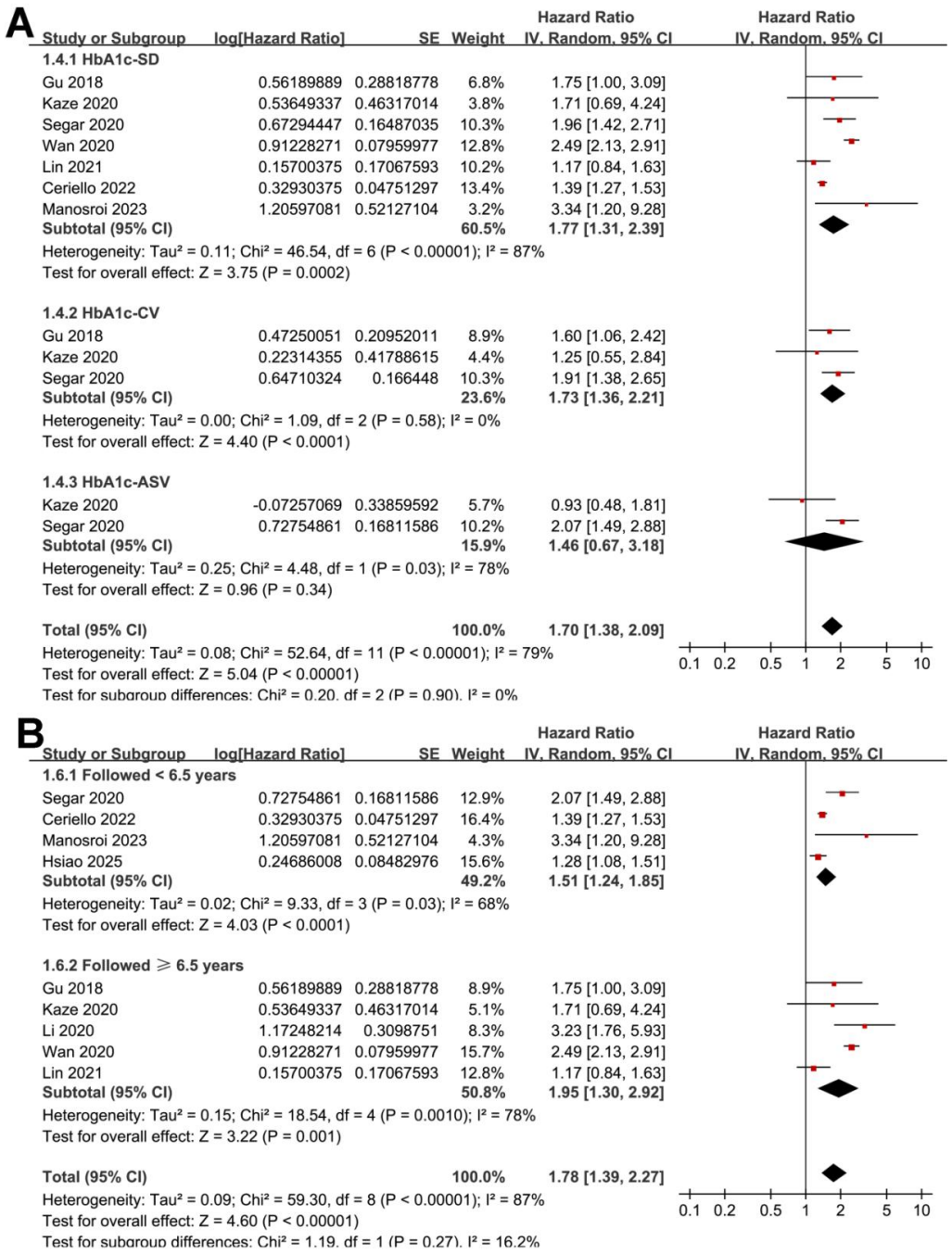

Figure 4. Forest plots of subgroup analyses for the association between HbA1c variability and the risk of HF. (A) Subgroup analysis by HbA1c-variability metric. (B) Subgroup analysis by follow-up duration. Panel A provides an exploratory, descriptive comparison of metric types; each study contributes one estimate within a given metric subgroup, whereas the primary meta-analysis (Figure 2) includes one independent estimate per study. Abbreviations: HbA1c, glycated hemoglobin; HF, heart failure.

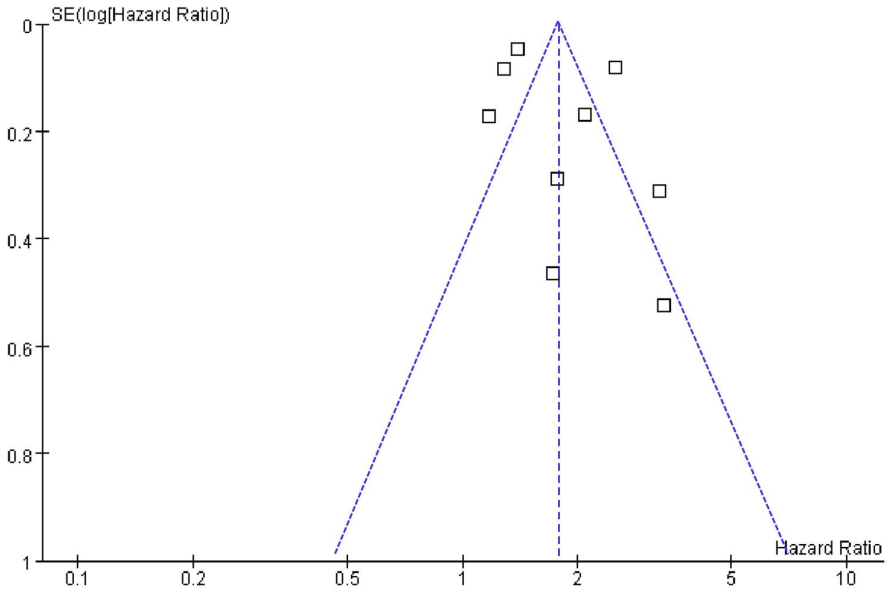

Figure 5. Funnel plots for assessing potential publication bias in meta-analyses of the associations between HbA1c variability and HF risk. Egger's test revealed no evidence of small-study effects; however, given the limited sample of only nine studies, the results should be interpreted with caution. Abbreviations: HbA1c, glycated hemoglobin; HF, heart failure.

SUPPLEMENTAL DATA

Supplemental file 1. Detailed search strategy for each database

PubMed

1. Population/Exposure (HbA1c / glycemic terms)

("Glycated Hemoglobin A"[Mesh] OR "Hemoglobin A, Glycosylated"[tiab] OR "Hemoglobin A1c"[tiab] OR HbA1c[tiab] OR A1c[tiab] OR "glycated hemoglobin"[tiab] OR "glycosylated hemoglobin"[tiab] OR glucose[tiab] OR glycemic[tiab])

2. Variability (visit-to-visit / dispersion metrics)

(variab*[tiab] OR fluctuat*[tiab] OR "visit-to-visit"[tiab] OR "visit to visit"[tiab] OR intervisit[tiab] OR intraindividual[tiab] OR "intra-individual"[tiab] OR "within-person"[tiab] OR "within person"[tiab] OR "coefficient of variation"[tiab] OR CV[tiab] OR "standard deviation"[tiab] OR SD[tiab] OR "average real variability"[tiab] OR ARV[tiab] OR "adjacent standard deviation"[tiab] OR ASV[tiab] OR "variability independent of the mean"[tiab] OR VIM[tiab])

3. Outcome (Heart failure)

("Heart Failure"[Mesh] OR "Ventricular Dysfunction, Left"[Mesh] OR "Heart Failure"[tiab] OR "cardiac failure"[tiab] OR "cardiac dysfunction"[tiab] OR "ventricular dysfunction"[tiab] OR "left ventricular dysfunction"[tiab])

4. Study design / incidence / risk

("Incidence"[Mesh] OR incidence[tiab] OR risk[tiab] OR hazard*[tiab] OR cohort*[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR "follow-up"[tiab] OR followed[tiab])

5. Combine and date limit

1 AND 2 AND 3 AND 4 AND ("0001/01/01"[Date - Publication] : "2025/08/30"[Date - Publication])

Embase

1. HbA1c / glycemic

'glycated hemoglobin a'/exp OR 'hemoglobin a1c'/exp OR (hba1c OR 'hemoglobin a1c' OR 'glycated hemoglobin' OR 'glycosylated hemoglobin' OR glucose OR glycemic):ti,ab,kw

2. Variability / metrics

(variab* OR fluctuat* OR 'visit-to-visit' OR (visit NEAR/2 visit) OR intervisit OR 'intra-individual' OR intraindividual OR 'within-person' OR 'within person' OR 'coefficient of variation' OR CV OR 'standard deviation' OR SD OR 'average real variability' OR ARV OR 'adjacent standard deviation' OR ASV OR 'variability independent of the mean' OR VIM):ti,ab,kw

3. Heart failure

'heart failure'/exp OR 'left ventricular dysfunction'/exp OR ('cardiac' NEAR/2 (failure OR dysfunction)):ti,ab,kw OR 'ventricular dysfunction'/exp

4. Study design / incidence / risk

'incidence'/exp OR 'risk'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'follow up'/exp OR (cohort* OR longitudinal OR prospective OR retrospective OR 'follow-up' OR followed):ti,ab,kw

5. Combine and years

1 AND 2 AND 3 AND 4, from inception to **2025-08-30**

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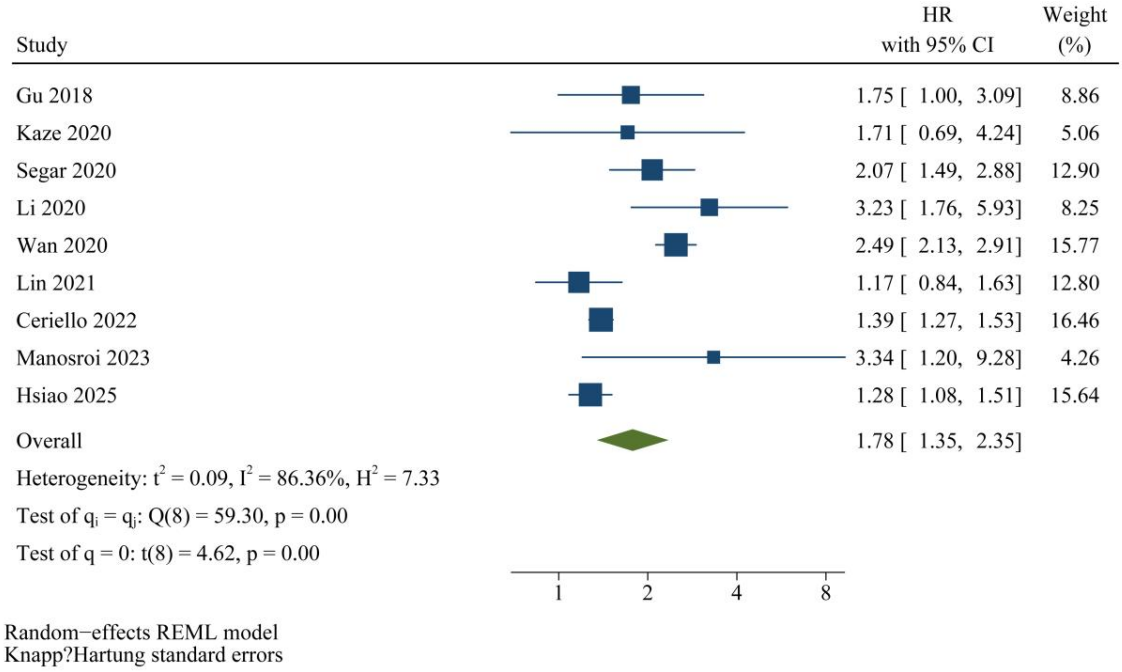
TS=(("hemoglobin a1c" OR HbA1c OR A1c OR "glycated hemoglobin" OR "glycosylated hemoglobin" OR glucose OR glycemic) AND (variab* OR fluctuat* OR "visit-to-visit" OR (visit NEAR/2 visit) OR intervisit OR "intra-individual" OR intraindividual OR "within-person" OR "within person" OR "coefficient of variation" OR CV OR "standard deviation" OR SD OR "average real variability" OR ARV OR "adjacent standard deviation" OR ASV OR "variability independent of the mean" OR

VIM) AND ("heart failure" OR ("cardiac" NEAR/2 (failure OR dysfunction)) OR "ventricular dysfunction" OR "left ventricular dysfunction") AND (incidence OR risk OR hazard* OR cohort* OR longitudinal OR prospective OR retrospective OR "follow-up" OR followed))

(Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI; Timespan: 1900–2025; Language: All)



Supplemental figure 1. Sensitivity analysis of the association between high vs. low visit-to-visit HbA1c variability and incident HF using a REML random-effects model with Hartung–Knapp inference. Pooled estimates are shown as HRs with 95% CIs, demonstrating results consistent with the primary analysis (HR 1.78, 95% CI 1.35–2.35; I^2 = 86%). Abbreviations: HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio; CI, confidence interval; REML, restricted maximum likelihood.