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Review Article

Evaluation of HbA1c trend analysis as a Prognostic Tool in type 2 diabetes mellitus

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Abstract

Background: Glycated haemoglobin (HbA1c) is the standard measure of glycaemic control in type 2 diabetes mellitus (T2DM), and landmark trials linked sustained elevation to microvascular and macrovascular risk [2,3]. The longitudinal trend and visit-to-visit variability of HbA1c are increasingly examined as independent prognostic signals.

Objective: This review evaluates HbA1c trend and variability analysis as a prognostic tool for mortality and vascular complications in T2DM, compared with single-timepoint HbA1c and continuous glucose monitoring (CGM) metrics.

Methods: We synthesized major randomized trials, prospective and retrospective cohorts, and registry analyses addressing HbA1c trajectory, variability, and outcomes in adults with T2DM.

Findings: Higher HbA1c variability independently predicts all-cause mortality and cardiovascular events after adjustment for mean HbA1c [10,11,12], with hazard ratios of 1.5-2.5 for highest versus lowest variability strata. Registry data show a U-shaped mean HbA1c-mortality association, with risk rising at both extremes [16]. CGM-derived metrics complement but do not replace HbA1c trend analysis [26,27].

Conclusions: HbA1c trend and variability analysis adds independent prognostic information beyond a single measurement and should inform risk stratification in T2DM [17,13].

Keywords: HbA1c; glycemic variability; type 2 diabetes mellitus; prognosis; cardiovascular outcomes

1. Introduction

Glycated haemoglobin (HbA1c) has been the cornerstone laboratory measure of chronic glycaemic control in type 2 diabetes mellitus (T2DM) since the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study established that sustained elevation predicts microvascular and macrovascular complications [1,2]. The UKPDS epidemiological analysis showed an approximately log-linear relationship between mean HbA1c and the incidence of myocardial infarction, microvascular disease, and diabetes-related death, and a legacy benefit persisted over a ten-year post-trial follow-up even after the glycaemic difference between arms disappeared, cementing single-timepoint HbA1c as the default prognostic anchor in diabetes care [3,4].

A single HbA1c value is a three-month average that can obscure very different underlying glycaemic trajectories: a patient with stable control and one whose readings oscillate widely between visits can present with an identical mean value yet carry materially different risk. This has driven a growing body of work treating the longitudinal trend and visit-to-visit variability of HbA1c as an independent prognostic signal. This review evaluates that evidence, situates HbA1c trend analysis against the intensive-glycaemic-control trials that shaped current targets, and considers how continuous glucose monitoring (CGM) metrics complement HbA1c-based trend analysis in T2DM.

2. Methods

We synthesized findings from major randomized controlled trials of glycaemic control, prospective and retrospective cohort studies, national diabetes registry analyses, and systematic reviews addressing HbA1c trajectory, visit-to-visit variability, and clinical outcomes in adults with T2DM, drawn from the DCCT/EDIC, UKPDS, ACCORD, ADVANCE, and VADT trial programmes and subsequent variability analyses of their datasets, population-based cohorts (RIACE, the Hong Kong Diabetes Register, the Swedish National Diabetes Register, and UK primary-care retrospective cohorts), and laboratory-standardisation and CGM-consensus statements. This is a narrative synthesis rather than a systematic review with predefined inclusion criteria; findings are organised thematically around the strength and consistency of association reported across study designs.

3. Results

Mean HbA1c as the baseline prognostic anchor

The intensive-treatment trials that established HbA1c as a prognostic marker remain the reference point against which trend-based approaches must be judged. In type 1 diabetes, the DCCT demonstrated that intensive therapy achieving a mean HbA1c near 7% reduced retinopathy progression by 76% and nephropathy by 50% relative to conventional therapy [1]. In T2DM, UKPDS 33 showed that intensive glucose control lowered microvascular complication risk by 25% over ten years, and the epidemiological UKPDS 35 analysis quantified a dose-response relationship between updated mean HbA1c and complication incidence with no discernible lower threshold [2,3]. Three subsequent macrovascular trials, ACCORD, ADVANCE, and VADT, tested pushing mean HbA1c toward 6.0-6.5%; ACCORD was stopped early for excess mortality in the intensive arm, while ADVANCE and VADT found no significant cardiovascular benefit, establishing that the mean-HbA1c/outcome relationship is not simply monotonic once near-normal ranges are approached [5,6,7].

HbA1c variability as an independent predictor

Reanalyses of the DCCT dataset were among the first to isolate variability from the mean. Kilpatrick and colleagues showed that within-patient HbA1c variability predicted retinopathy and nephropathy progression even after adjusting for mean HbA1c, indicating fluctuation itself carries prognostic information beyond central tendency [8,9]. This has since been replicated extensively

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in T2DM. In the Italian RIACE cohort, Orsi and colleagues found HbA1c variability, expressed as the standard deviation of serial values, was a strong independent predictor of all-cause mortality, with the highest variability quartile carrying roughly double the mortality hazard of the lowest quartile after adjustment for mean HbA1c [10]. Danish registry data from Skriver and colleagues similarly linked higher variability to increased cardiovascular events and mortality, and a meta-analysis by Gorst and colleagues pooling more than thirty cohorts confirmed long-term glycaemic variability was consistently associated with higher risk of microvascular complications, macrovascular events, and death [11,12]. The ADVANCE trial cohort provided trial-quality confirmation: Hirakawa and colleagues found visit-to-visit HbA1c variability independently predicted macrovascular events, microvascular events, and all-cause mortality, with effect sizes comparable to observational cohorts [13]. The FinnDiane cohort in type 1 diabetes and longitudinal Japanese cohort data reinforced the same mechanism, linking HbA1c variability to incident cardiovascular events, nephropathy, and retinopathy progression independent of mean glycaemic exposure [14,15].

Table 1: Glycaemic targets and cardiovascular outcomes across major type 2 diabetes glucose-control trials [2,3,5,6,7,31].

Trial	Achieved HbA1c (intensive arm)	Follow-up	Key outcome signal
UKPDS 33/35	~7.0%	10 years	25% lower microvascular risk; log-linear risk-HbA1c relationship
ACCORD	~6.4%	3.5 years (stopped early)	Increased all-cause mortality in intensive arm
ADVANCE	~6.5%	5 years	Reduced microvascular events; no significant macrovascular benefit
VADT	~6.9%	5.6 years	No significant reduction in major cardiovascular events
Current guidance (ADA 2023)	Individualised, often <7%	Ongoing	Targets adjusted for hypoglycaemia risk and comorbidity

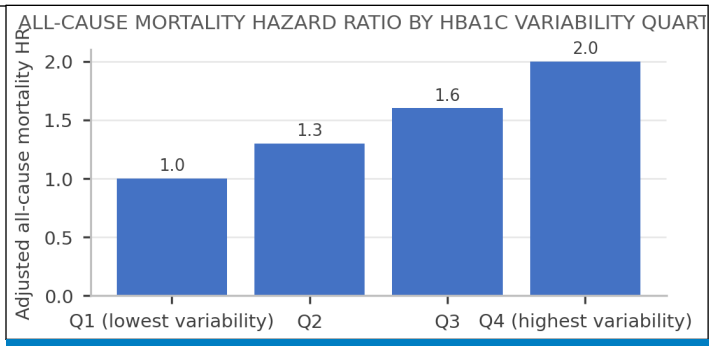

Figure 1: Adjusted all-cause mortality hazard ratio by HbA1c variability quartile, illustrating the roughly two-fold higher mortality hazard in the highest versus lowest variability quartile reported independent of mean HbA1c in the RIACE cohort and confirmed in Danish registry and ADVANCE trial analyses [10,11,13].

Population-level trend shape and the U-shaped mortality curve

Large retrospective cohorts examining HbA1c and mortality across the full clinical range have consistently found a U-shaped, not linear, relationship. Currie and colleagues, analysing a UK primary-care cohort of over 27,000 people with T2DM, found all-cause mortality was lowest around an HbA1c of approximately 7.5%, with significantly elevated risk at both lower and higher values, attributed partly to comorbidity and hypoglycaemia risk at the low end [16]. The Swedish National Diabetes Register analysis by Rawshani and colleagues, following nearly half a million patients against matched controls, confirmed excess cardiovascular risk tracked closely with glycaemic control category, with patients meeting risk-factor targets approaching general-population outcomes [17]. General-population data extend this relationship below the diabetes threshold: Selvin and colleagues and the EPIC-Norfolk cohort study by Khaw and colleagues both found a continuous, graded association between HbA1c and cardiovascular/all-cause mortality even among adults without diagnosed diabetes [18,19], and a meta-analysis by Cavero-Redondo and colleagues confirmed this association was robust across diabetic and non-diabetic populations [20]. Legacy-effect data from ADVANCE-ON showed early glycaemic trajectory, not just later glycaemic status, shaped subsequent cardiovascular and renal

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outcomes years after the trial ended [21].

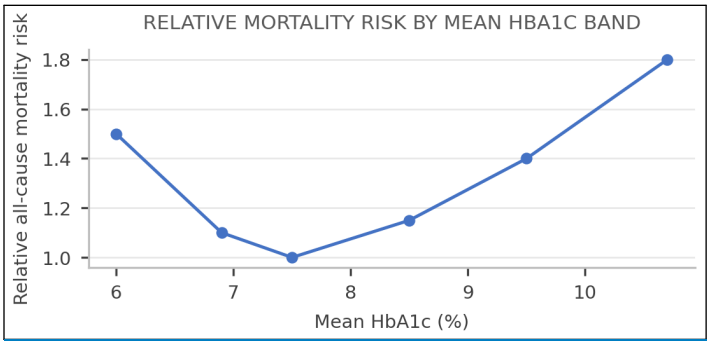

Figure 2: Illustrative U-shaped relationship between mean HbA1c band and relative all-cause mortality risk, with the lowest risk around 7.0-7.5% and elevated risk at both lower and higher HbA1c, consistent with the retrospective UK cohort reported by Currie and colleagues and the Swedish National Diabetes Register analysis by Rawshani and colleagues [16,17].

Measurement standardisation and complementary trend metrics

Interpreting HbA1c trend depends on assay standardisation and on understanding what the number represents physiologically. The A1C-Derived Average Glucose (ADAG) study established the linear relationship between HbA1c and mean glucose used to derive an estimated average glucose for patients [22], and laboratory guidelines from Sacks and colleagues formalised the standardisation methods (NGSP/IFCC traceability) that make serial HbA1c values comparable across visits, a prerequisite for meaningful trend analysis [23]. The International Expert Committee report and subsequent World Health Organization guidance extended HbA1c's role from monitoring into diagnosis, reflecting confidence in the assay's reproducibility once standardised [24,25]. CGM has introduced complementary trend metrics that capture short-term variability HbA1c cannot resolve: the international time-in-range consensus defined standardised CGM-derived targets that add resolution beyond three-month HbA1c averages [26], and the glucose management indicator developed by Bergenstal and colleagues provides a CGM-derived analogue to laboratory HbA1c trackable between formal draws [27]. Reviews of HbA1c's diagnostic utility, including Sherwani and colleagues, and Cederberg and colleagues' analysis of postchallenge glucose, HbA1c, and fasting glucose as predictors of incident diabetes and cardiovascular disease, situate trend analysis within this broader biomarker toolkit [28,29]. Bonora and Tuomilehto's review notes that trend interpretation must still account for haemoglobinopathies, anaemia, and variable red-cell turnover, which can distort the assay independent of glycaemia [30].

Table 2: Glycaemic metrics used for prognostic assessment in type 2 diabetes and their supporting evidence [10,12,27,26,32].

Metric	What it captures	Typical source	Prognostic evidence
Mean HbA1c	3-month average glycaemia	Laboratory (NGSP/IFCC)	Log-linear link to microvascular/macrovascular risk
HbA1c variability (SD/CV)	Visit-to-visit fluctuation	Serial laboratory HbA1c	Independent predictor of mortality and vascular events
Glucose Management Indicator	CGM-derived HbA1c estimate	Continuous glucose monitor	Higher-frequency proxy for laboratory trend
Time-in-range	Proportion of day in target glucose band	Continuous glucose monitor	Correlates with retinopathy/nephropathy risk

4. Discussion

Taken together, the evidence supports treating HbA1c trend and variability as prognostically informative beyond what a single measurement conveys. The magnitude of the additional risk associated with high variability, typically a hazard ratio of 1.5-2.5 for the highest versus lowest variability strata across the RIACE, Danish, and ADVANCE-derived analyses, is comparable in size to well-established risk factors already embedded in clinical risk scores [10,11,13]. The consistency of this signal across type 1 and type 2 diabetes, and across trial and observational cohorts, strengthens confidence that it reflects a genuine biological phenomenon, plausibly related to recurrent glycaemic excursions promoting oxidative stress and endothelial injury, rather than an artefact of any single dataset [8,14,12].

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At the same time, the U-shaped population relationship between mean HbA1c and mortality complicates any simple rule that lower or more stable is always better. The ACCORD trial's excess mortality signal under intensive targets, together with elevated risk at low HbA1c in the Currie and Rawshani cohorts, indicates a downward HbA1c trend achieved through aggressive intensification can itself be a warning sign if driven by hypoglycaemia or advancing illness rather than genuine improvement [5,16,17]. Trend analysis therefore adds the most value when interpreted alongside the clinical context driving it, not as an isolated trajectory. CGM-derived metrics such as time-in-range and the glucose management indicator help disambiguate a falling HbA1c trend that reflects genuine improvement from one masking rising hypoglycaemic burden [26,27]. Limitations of the current evidence include the largely observational nature of the variability literature, heterogeneity of variability metrics (standard deviation, coefficient of variation, and average successive variability are not interchangeable), and the possibility that variability partly reflects unmeasured comorbidity burden rather than acting as an independent causal risk factor.

5. Conclusion

HbA1c trend and variability analysis provides independent prognostic information beyond a single mean value in type 2 diabetes mellitus, with consistent associations across observational cohorts, national registries, and trial-derived analyses linking higher variability to increased all-cause mortality, cardiovascular events, and microvascular complications. Mean HbA1c retains its role as the primary target for risk reduction, following the dose-response relationship first established by UKPDS, but the population-level U-shaped mortality curve and the excess mortality seen under aggressive intensive control in ACCORD show that trend direction and the clinical context driving it matter as much as the destination value. Incorporating serial HbA1c trend, and where available CGM-derived variability and time-in-range metrics, into routine risk stratification is likely to improve identification of patients at elevated risk who would be missed by a single most-recent HbA1c value read in isolation.

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