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Association of HbA1c variability and major adverse cardiovascular events among type 2 diabetes mellitus patients: A multicentre prospective cohort study

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ABSTRACT

Background: Glycaemic variability has emerged as a candidate risk marker for cardiovascular complications in patients with type 2 diabetes mellitus (T2DM), independent of mean glycaemic control. This study aimed to evaluate the association between visit-to-visit HbA1c variability and the incidence of major adverse cardiovascular events (MACE) in adults with T2DM.

Methods: A prospective cohort study was conducted across three tertiary hospitals in Indonesia between January 2021 and December 2024. Adult patients with T2DM and at least four HbA1c measurements during the first year were included. HbA1c variability was expressed as the coefficient of variation. MACE was defined as a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHR).

Results: A total of 1,248 patients were enrolled and followed for a median of 32 months. The cumulative incidence of MACE was 11.4%. Compared with the lowest tertile of HbA1c variability, the highest tertile was independently associated with an increased risk of MACE (aHR 1.78; 95% CI 1.32–2.41; $p<0.001$) after adjustment for age, sex, baseline HbA1c, hypertension, dyslipidaemia, and smoking status.

Conclusion: Higher HbA1c variability is independently associated with an increased risk of major adverse cardiovascular events in patients with type 2 diabetes mellitus. Long-term glycaemic stability, rather than mean control alone, should be considered when stratifying cardiovascular risk in this population.

Keywords: *HbA1c variability, Type 2 diabetes mellitus, Major adverse cardiovascular events, Cohort study, Glycaemic control*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains one of the most prevalent non-communicable diseases worldwide, with cardiovascular disease accounting for the majority of associated mortality.[1] Traditional management has focused on achieving target mean glycaemic levels, typically expressed as glycated haemoglobin (HbA1c). However, accumulating evidence suggests that fluctuations in glycaemic control over time may exert pathophysiological effects beyond those of sustained hyperglycaemia alone.[2,3]

Visit-to-visit HbA1c variability has been proposed as a clinically accessible marker that captures the long-term instability of glycaemic control.[4] Mechanistic studies indicate that recurrent glycaemic swings can promote oxidative stress, endothelial dysfunction, and accelerated atherosclerosis, potentially increasing the risk of major adverse cardiovascular events (MACE).[5,6] Despite this biological rationale, data from Southeast Asian populations remain limited, and the magnitude of risk attributable to HbA1c variability in routine clinical practice is not well characterised.

Therefore, the aim of this study was to evaluate the association between HbA1c variability, measured as the coefficient of variation, and the incidence of MACE in an Indonesian cohort of patients with T2DM, independent of mean HbA1c and conventional cardiovascular risk factors.

METHODS

Study design and setting

This was a multicentre prospective cohort study conducted at three tertiary teaching hospitals in Indonesia (Sanglah General Hospital, Cipto Mangunkusumo Hospital, and Dr. Soetomo General Hospital) between January 2021 and December 2024. The study protocol was approved by the institutional ethics committees of each participating centre (Approval No. ORM/2020/1184), and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Participants

Adults aged 18 years or older with an established diagnosis of T2DM according to the American Diabetes Association criteria were eligible. Inclusion required at least four HbA1c measurements during the first 12 months of enrolment, separated by intervals of no less than two months. Patients were excluded if they had type 1 diabetes, a history of MACE within six months prior to enrolment, end-stage renal disease requiring dialysis, active malignancy, or pregnancy.

Exposure and outcome assessment

HbA1c variability was operationalised as the coefficient of variation (HbA1c-CV), calculated as the standard deviation divided by the mean of all HbA1c values during the first year. The primary outcome was the first occurrence of MACE, defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Outcomes were adjudicated by an independent committee blinded to the exposure status.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as numbers and percentages. Participants were stratified into tertiles based on HbA1c-CV. Cumulative incidence of MACE was estimated using the Kaplan–Meier method. Cox proportional hazards regression was used to estimate hazard ratios with 95% confidence intervals, adjusting for age, sex, baseline HbA1c, hypertension, dyslipidaemia, and current smoking. All analyses were performed using R version 4.3.1.

Sensitivity and subgroup analyses

Pre-specified subgroup analyses were performed by age (<60 vs ≥60 years), sex, and baseline HbA1c (<7.0% vs ≥7.0%). Sensitivity analyses included alternative metrics of variability and exclusion of MACE events occurring within the first 12 months of follow-up.

RESULTS

Of 1,512 patients initially screened, 1,248 met the eligibility criteria and were included in the analysis. The mean age was 58.6 ± 9.4 years, and 54.2% were women. Baseline characteristics across HbA1c-CV tertiles are summarised in Table 1. Patients in the highest tertile of

HbA1c-CV were more likely to have a longer duration of diabetes and a higher baseline HbA1c.

During a median follow-up of 32 months (interquartile range, 26–38 months), 142 patients (11.4%) experienced a MACE. The crude incidence rates were 2.8, 4.1, and 6.9 events per 100 person-years across the lowest, middle, and highest tertiles of HbA1c-CV, respectively. After adjustment for confounders, the highest tertile remained independently associated with an increased risk of MACE compared with the lowest tertile (aHR 1.78; 95% CI 1.32–2.41; p<0.001). Subgroup and sensitivity analyses produced consistent findings.

Table 1: *Baseline characteristics of participants by HbA1c variability tertile.*

Variable	T1 (Low)	T2 (Mid)	T3 (High)
Age, y (mean ± SD)	57.2 ± 9.1	58.8 ± 9.3	59.7 ± 9.6
Female, n (%)	232 (55.8)	227 (54.1)	217 (52.5)
Baseline HbA1c, %	7.1 ± 1.0	7.6 ± 1.1	8.3 ± 1.4
Hypertension, n (%)	248 (59.6)	263 (62.6)	281 (68.0)
Dyslipidaemia, n (%)	189 (45.4)	208 (49.5)	232 (56.2)
Current smoker, n (%)	71 (17.1)	84 (20.0)	98 (23.7)
MACE, n (%)	32 (7.7)	44 (10.5)	66 (16.0)

SD: standard deviation; HbA1c: glycated haemoglobin; MACE: major adverse cardiovascular events.

DISCUSSION

In this multicentre prospective cohort of Indonesian adults with T2DM, higher HbA1c variability was independently associated with a markedly increased risk of MACE, even after adjustment for mean glycaemic control and established cardiovascular risk factors. The magnitude of association observed in the highest tertile (aHR 1.78) is consistent with prior reports from East Asian and European populations,[4,7] and extends those findings to a Southeast Asian setting where data have been relatively scarce.

The biological plausibility of these findings is supported by mechanistic studies demonstrating that fluctuating glucose levels can promote endothelial dysfunction, accelerate atherogenesis, and trigger pro-inflammatory pathways more strongly than stable hyperglycaemia.[5,8] Our results add to the growing body of evidence that HbA1c variability is not merely a statistical artefact of mean control, but rather a distinct prognostic marker.

Several strengths should be noted, including the prospective design, blinded outcome adjudication, and the inclusion of multiple tertiary centres. Limitations include possible residual confounding by unmeasured variables such as dietary patterns and adherence, as well as the relatively short follow-up duration. Future studies should evaluate whether interventions specifically targeting glycaemic stability can reduce cardiovascular risk independently of mean HbA1c reduction.

CONCLUSION

Higher HbA1c variability is independently associated with an increased risk of major adverse cardiovascular events in patients with type 2 diabetes mellitus, beyond the contribution of mean glycaemic control and traditional risk factors. These findings support the incorporation of glycaemic stability metrics into long-term cardiovascular risk assessment.

Author contributions: MAP and RHW conceptualised and designed the study. MAP and SKW conducted patient recruitment and data collection. RHW performed the statistical analysis. MAP drafted the manuscript, and all authors critically revised the manuscript and approved the final version.

Availability of data and materials: De-identified data are available from the corresponding author upon reasonable request.

Ethical approval: Approved by the Joint Institutional Review Boards of the three participating hospitals (Approval No. ORM/2020/1184).

Declaration of patient consent: Written informed consent was obtained from all participants.

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