The association between HbA1c variability and strokes in patients receiving anticoagulants

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**Funding Acknowledgements:** Type of funding sources: Public hospital(s). Main funding source(s): Sanming Project of Medicine in Shenzhen, China

**Background:** Diabetes, higher glycaemic level, is associated with an increased risk of stroke in patients with atrial fibrillation (AF) and is integrated into the CHA2DS2-VASc score for stroke risk prediction. However, the association between glycaemic variability and stroke risk in AF patients remains unclear.

**Objective:** To evaluate the association between glycaemic variability and stroke among diabetic and non-diabetic patients with nonvalvular AF receiving anticoagulants.

**Methods:** Newly diagnosed AF from 2013-2018 (n=8,790) were divided by their diabetes status. Variability in glycaemic, represented by coefficient of variation (CV) on HbA1c (haemoglobin A1c), was assessed by at least three HbA1c measurements following enrollment to the end of the follow-up period. Participants with ischaemic stroke (IS)/systemic embolism (SE), haemorrhagic stroke (HS) or all-cause mortality at baseline or within 1 year of enrollment were excluded. Multivariate Cox regression was performed to evaluate the association between variability in HbA1c and subsequent incident IS/SE, HS and all-cause mortality. Sensitivity analyses included defining HbA1c variability using average successive variability (ASV) and variability independent of the mean (VIM).

**Results:** Diabetes status significantly modified the relationship between HbA1c variability and risk of IS/SE (Pinteraction = 0.36) and all-mortality (Pinteraction <0.01). Greater incidence rates were observed among individuals with diabetes, compared to those without diabetes (3.74 vs. 2.41 for IS/SE, 0.54 vs. 0.33 for HS and 4.89 vs. 2.42 for all-cause mortality per 100 person years). Among those with diabetes, greater HbA1c variability was significantly associated with increased risk of IS/SE (hazard ratio [HR] = 1.21, 95% confidence interval [CI]: 1.11-1.31), all-cause mortality (HR = 1.13, 95%CI: 1.05-1.20) and HS (HR = 1.10, 95%CI: 1.02-1.23). Similar patterns were found in individuals without diabetes (IS/SE: HR = 1.28, 95%CI: 1.08-1.52; all-cause mortality: HR = 1.50, 95%CI: 1.29-1.75). However, no significant association was observed between glycemia variability and HS among those without diabetes. Results were consistent with alternative measures of HbA1c variability.

**Conclusion:** Variability in HbA1c was independently associated with the risk of IS/SE and all-cause mortality among patients with AF, regardless of diabetes status.
Figure 1. Forest plot of the association of each SD increment of variability in HbAlc with risk of all-cause mortality, IS/SE, and HS.

Abbreviations: SD, standard deviation; HbAlc, haemoglobin Alc; IS, ischaemic stroke; N, number; SE, systemic embolism; HS, haemorrhagic stroke; CV, coefficient of variation; HR, hazard ratio; CI, confidence interval. Model 1 adjusted for: age at baseline, and sex; Model 2 adjusted for: variables in model 1 and baseline comorbidities, medications, and procedures; Model 3 adjusted for: variables in model 2 and mean HbAlc.

Figure 2.
A. Kaplan-Meier of CV tertile and all-cause mortality.
P < 0.0001

B. Kaplan-Meier of CV tertile and IS/SE.
P = 0.0061

C. Kaplan-Meier of CV tertile and haemorrhagic stroke.
P = 0.019

Abbreviations: CV, coefficient of variation; IS, ischaemic stroke; N, number; SE, systemic embolism; HS, haemorrhagic stroke.