Glycemic variability of acute stroke patients and clinical outcomes: a continuous glucose monitoring study

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Abstract

Introduction: Glycemic variability (GV) has been associated with worse prognosis in critically ill patients. We sought to evaluate the potential association between GV indices and clinical outcomes in acute stroke patients.

Methods: Consecutive diabetic and nondiabetic, acute ischemic or hemorrhagic stroke patients underwent regular, standard-of-care finger-prick measurements and continuous glucose monitoring (CGM) for up to 96 h. Thirteen GV indices were obtained from CGM data. Clinical outcomes during hospitalization and follow-up period (90 days) were recorded. Hypoglycemic episodes disclosed by CGM but missed by finger-prick measurements were also documented.

Results: A total of 62 acute stroke patients [48 ischemic and 14 hemorrhagic, median NIHSS score: 9 (IQR: 3–16) points, mean age: 65 ± 10 years, women: 47%, nondiabetic: 79%] were enrolled. GV expressed by higher mean absolute glucose (MAG) values was associated with a lower likelihood of neurological improvement during hospitalization before and after adjusting for potential confounders (OR: 0.135, 95% CI: 0.024–0.751, p = 0.022). There was no association of GV indices with 3-month clinical outcomes. During CGM recording, 32 hypoglycemic episodes were detected in 17 nondiabetic patients. None of these episodes were identified by the periodic blood glucose measurements and therefore they were not treated.

Conclusions: Greater GV of acute stroke patients may be related to lower odds of neurological improvement during hospitalization. No association was disclosed between GV indices and 3-month clinical outcomes.

Keywords: acute stroke, clinical outcomes, continuous glucose monitoring, glycemic variability, hypoglycemic episodes, neurological improvement

Introduction

Poststroke hyperglycemia is a common phenomenon in the acute setting of stroke and has been considered an independent predictor of poor clinical outcomes in both ischemic and hemorrhagic stroke. Thus, hyperglycemia management with intensive treatment had been expected to improve clinical outcomes. Despite the initial enthusiasm, randomized controlled clinical trials did not confirm the safety and efficacy of such treatment approaches. On the contrary, aggressive protocols with intravenous insulin infusions significantly increased the risk of hypoglycemia, which has been related to adverse functional outcomes in patients with acute ischemic stroke.

By focusing strictly on hyperglycemia and hypoglycemia, however, we might have been overlooking a
third independent component of dysglycemia: glycemic variability (GV), which is defined as the degree of fluctuation in glucose values over time. GV has been correlated with higher mortality risk in critically ill patients, even when mean glucose values are within normal limits. GV has been consistently overlooked in relevant randomized controlled clinical trials, although it may be a key reason why intensive glycemic control has failed to demonstrate significant clinical benefit in stroke patients. In recent years, there has been a growing interest regarding the role of GV in stroke outcomes in several observational studies. Those studies, however, are relatively limited either by the lack of continuous glucose monitoring (CGM) data or by the assessment of only a proportion of the existing GV indices.

In this prospective, cohort study, we examined the association between GV and clinical outcomes in consecutive diabetic and nondiabetic, ischemic, and hemorrhagic acute stroke patients using CGM and calculated GV by measuring 13 different qualitative and quantitative indices. We hypothesized that increased GV in the acute stroke setting is associated with adverse short- and long-term clinical outcomes.

Methods
Consecutive patients with acute ischemic or hemorrhagic stroke were prospectively evaluated at two tertiary stroke centers (‘Attikon’ University Hospital, National and Kapodistrian University of Athens, Athens, Greece and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA) over a 3-year period. Patients were eligible for inclusion if they experienced acute neurological impairment within the last 48 h, attributable to acute ischemic or hemorrhagic stroke, as was confirmed by neuroimaging evaluation [brain computed tomography (CT) scan or magnetic resonance imaging (MRI) scan]. The patient cohort included both diabetic and nondiabetic patients. Patients with traumatic intracerebral hemorrhage, subarachnoid hemorrhage (aneurysmal or nonaneurysmal), or sub- or epidural hemorrhage were excluded from participation in the study. Other exclusion criteria were patients younger than 18 years old, symptoms onset >48 h from hospital admission, unwillingness to undergo subcutaneous CGM device insertion, or lack of informed consent.

All patients were treated according to standard of care. In addition, all patients underwent the following clinical laboratory and imaging examinations, as previously described: serial assessments of stroke severity using National Institute of Health Stroke Scale (NIHSS) score, brain CT scan or MRI scan, full blood count, biochemical blood analysis [baseline glucose values and Hemoglobin A1c (HbA1c) included], electrocardiogram, consecutive blood pressure measurements. In cases of ischemic stroke, cardiac ultrasound, 24-h Holter heart rhythm monitoring, carotid duplex ultrasound, and CT or magnetic resonance (MR) brain angiography or transcranial doppler ultrasound were also performed for the etiological classification according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, as previously described. Hemorrhagic strokes were also classified according to most probable etiology. In cases of intracerebral hemorrhage, hematoma volume was measured by two independent certified stroke neurologists according to the ABC/2 formula, as previously described.

Baseline characteristics, including demographics, various vascular risk factors with special interest to diabetes mellitus diagnosis, prestroke treatment, acute stroke treatment, the laboratory and imaging findings, were recorded, as previously described. Stroke severity at hospital admission and at discharge was documented using NIHSS score by certified vascular neurologists. Reduction of NIHSS score of 4 or more points between hospital admission and discharge was considered as neurological improvement during hospitalization. Increase by any point in NIHSS score at discharge compared with NIHSS at admission was considered as neurological deterioration during hospitalization. In-hospital complications were also recorded: fever, aspiration pneumonia, infection, intubation. Certified vascular neurologists also assessed functional outcomes at 3 months by patient examination, using the modified Rankin scale (mRS). Excellent functional outcome was defined as an mRS score of 0 or 1 and functional independence was defined as an mRS score between 0 and 2.

Glucose measurement and hyperglycemia management were performed according to current international recommendations. Each patient was evaluated 4 times daily by finger-prick glucose measurement and subcutaneous insulin was
administered accordingly, in order to achieve a mild hyperglycemic state (between 120 and 180 mg/dl). For hypoglycemia prevention and management, we implemented a nurse-initiated protocol when glucose values were below 70 mg/dl, according to American Diabetes Association recommendations.38

In all patients a CGM device (iPro2, Medtronic®, Northridge, CA, USA) was inserted subcutaneously in the lower abdomen within the first 48h of symptoms initiation. Glucose levels were recorded every 5 min for up to 96h and were saved in device memory. After the device was removed, data were uploaded and calibrated with the corresponding glucose values derived from finger-prick measurements. As an example, a diagram derived by CGM uploaded data is presented in Supplementary Figure S1. The final data set was edited anonymously in a macro-enabled Excel workbook using EasyGV© software (available free for noncommercial use at https://www.phc.ox.ac.uk/research/technology-outputs/easygv).39 The EasyGV© was used to calculate the following indices of GV: mean glucose value, standard deviation (SD), M-value, mean amplitude of glucose excursions (MAGE), average daily risk ratio (ADRR), lability index (LI), J-Index, low blood glucose index (LBGI), high blood glucose index (HBGI), continuous overlapping net glycemic action (CONGA), mean of daily differences (MODD), glycemic risk assessment in diabetes equation (GRADE), and mean absolute glucose (MAG).12,40–48 All definitions and formulas of the GV indices assessed are provided in the Supplementary Table S1.

In the case of continuous glucose measurements, hypoglycemic events were defined as four or more consecutive values of CGM-obtained glucose below 70 mg/dl, which amounted to a total duration of at least 20 min.49 The hypoglycemic episodes disclosed by CGM but missed by finger-prick measurements were also documented.

The primary outcome of interest was 3-month excellent functional outcome. Secondary outcomes were functional independence at 3 months, mortality at 3 months, in-hospital mortality, neurological deterioration, and neurological improvement during hospitalization. All endpoints’ assessments were performed by blinded independent neurologists during hospitalization and in the outpatient setting at 3-month follow-up. In addition, we sought to compare CGM and periodic finger-prick measurements in detecting asymptomatic hypoglycemic events.

The study protocol was approved by both local ethics committees (Protocol No. A.3/6th Committee Meeting/15-05-2018/Attikon’ University Hospital and Beth Israel Deaconess Medical Center Committee on Clinical Investigations, IRB Protocol No. 2014 P-000163) and signed informed consent was obtained from the patient or legal representative before enrollment in all cases. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statistical analysis
Continuous variables are presented as mean ± SD (normal distribution) and as median with interquartile range (IQR, skewed distribution). Categorical variables are presented as number of patients and the corresponding percentages. Statistical comparisons between two groups were performed using χ² test, or in case of small expected frequencies, Fisher’s exact test. Continuous variables were compared by the use of the unpaired t test or Mann–Whitney U test, as indicated.

Univariable and multivariable binary logistic regression models were used to evaluate the associations of different indices of GV with clinical outcomes before and after adjusting for potential confounders (demographic characteristics, stroke risk factors, stroke severity, in-hospital complications). A cutoff of p < 0.1 was used to select variables for inclusion in multivariable analyses that were conducted using backward stepwise selection procedure. In addition, age, sex, and index event were included in multivariable analysis, as they are considered significant potential confounders. To confirm the robustness of multivariable models, we repeated all multivariable analyses using a forward selection procedure. Associations are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was achieved if the p value was ≤0.05 in multivariable logistic regression analyses. The Statistical Package for Social Science (SPSS Inc, Armonk, NY, USA; version 23.0 for Windows) was used for statistical analyses.

Results
The CGM device was inserted successfully to a total of 62 stroke patients (mean age: 65 ± 10 years,
53% men, median NIHSS score on admission: 9, IQR: 3–16) after a median of 32 (IQR: 25–44) h from stroke onset. Thirteen (21%) patients were diabetic. The median duration of monitoring was 70 (IQR: 54–87) h and provided a total of 49,987 glucose measurements for analysis. The baseline characteristics of the study population are presented in Table 1. Forty-eight (77%) strokes were ischemic and 14 (23%) were hemorrhagic. Ischemic strokes were primarily cryptogenic (38%) and cardioembolic (33%), whereas hemorrhagic strokes were hypertension related in the majority of the cases (64%). Median HbA1c was 5.6% (IQR: 5.2–6.0%) and median blood glucose on admission was 118 (IQR: 105–131) mg/dl.

Patients were hospitalized for a median of 10 (IQR: 6–12) days. Three patients died during hospitalization and the in-hospital mortality rate was 5%. Death at 3 months was recorded in six patients (10%). All the rest completed follow-up clinical evaluation at 3 months. Clinical outcomes during hospitalization and at 3 months are presented in Table 2. Thirty patients (48%) presented neurological improvement during hospitalization and the median NIHSS score at discharge was 3 (IQR: 1–8). At 3 months, 34 patients (55%) were functionally independent and 24 patients (39%) presented an excellent functional outcome.

Analysis of CGM-derived data provided evaluation of GV by 13 different indices. Values of each index in all, nondiabetic and diabetic patients are presented in Supplementary Table S2. Diabetic patients had higher mean glucose value, SD, CONGA, J-index, HBGI, GRADE, and ADRR but lower LBGI value compared with nondiabetic patients (all \( p < 0.05 \)).

In the univariate analyses, no statistically significant association was found between GV indices and functional independence or excellent functional outcome at 3 months (all \( p > 0.1 \); Table 3). No further analysis was performed for death at 3 months and neurological deterioration during hospitalization due to infrequent events (Table 2). Higher ADRR and MAG values, however, were associated with lower likelihood of neurological improvement during hospitalization (Table 4). In multivariable models using backward selection procedure and adjusting for potential confounders (demographics, risk factors, baseline stroke severity, baseline neuroimaging and laboratory findings), MAG emerged as an independent predictor of the likelihood of neurological improvement during hospitalization with an inverse association (OR per 1-unit increase: 0.135, 95% CI: 0.024–0.751, \( p = 0.022 \); Table 4). We found identical results by repeating the multivariable analyses using forward selection procedure.

None of the GV indices were associated with neurological improvement during hospitalization at a corrected (for multiple comparisons) level of significance: \( p = 0.05 / 13 = 0.004 \) (unpaired \( t \) test after Bonferroni’s correction for multiple comparisons; Supplementary Table S3).

Asymptomatic hypoglycemic episodes were detected in 17 patients (27%) during CGM recordings; none of these had been identified with finger-prick measurements. In total, 32 hypoglycemic episodes had gone unrecognized by the standard finger-prick glucose measurements and left untreated in those patients. No symptomatic hypoglycemic episodes were detected by either CGM or finger-prick measurements. Up to six hypoglycemic episodes with a total duration of 18 h were recorded in a single nondiabetic patient, which remained hypoglycemic for more than 27% of the CGM recording. In this patient, the hypoglycemic episodes were recorded almost exclusively during sleep. The prevalence of hypoglycemic episodes was higher in nondiabetic patients (35%) than in diabetic individuals (0%, \( p = 0.013 \) by Fisher’s exact test). Those under-recognized hypoglycemic episodes were not associated with neither 3-month nor in-hospital clinical outcomes (Supplementary Table S4).

Discussion
Our pilot study showed that elevated GV expressed by higher MAG values was associated with a lower likelihood of neurological improvement during hospitalization. Clinical outcomes at 3 months, however, were not related to any of the GV indices measured in our study. This result can be explained by the fact that temporary oxidative stress and endothelial dysfunction promoted by GV may have contributed to short-term cerebrovascular damage and the corresponding lower likelihood of neurological improvement.50,51 This effect, however, appears not to interfere with long-term clinical outcomes at 3 months. Another potential explanation may be associated with the
Table 1. Baseline characteristics of the study population (\(N=62\)).

| Variable                                      | Overall       |
|-----------------------------------------------|---------------|
| **Demographics**                              |               |
| Age, years, mean ± SD                         | 65 ± 10       |
| Female sex, \(n\) (%)                        | 29 (47)       |
| **Index event**                               |               |
| NIHSS score, points, median (IQR)             | 9 [3–16]      |
| Ischemic stroke, \(n\) (%)                   | 48 [77]       |
| Large artery atherosclerosis, \(n\) [% IS]    | 9 [19]        |
| Cardio embolism, \(n\) [% IS]                | 16 [33]       |
| Small vessel occlusion, \(n\) [% IS]          | 2 [4]         |
| Other determined etiology, \(n\) [% IS]       | 3 [6]         |
| Undetermined etiology, \(n\) [% IS]           | 18 [38]       |
| Hemorrhagic stroke, \(n\) (%)                 | 14 [23]       |
| Hypertension related, \(n\) [% ICH]           | 9 [64]        |
| Oral anticoagulant related, \(n\) [% ICH]     | 4 [29]        |
| Vascular abnormalities related, \(n\) [% ICH]  | 1 [7]         |
| **Stroke risk factors**                       |               |
| Diabetes, \(n\) (%)                          | 13 [21]       |
| Noninsulin dependent, \(n\) [% DM]           | 11 [85]       |
| Insulin dependent, \(n\) [% DM]              | 2 [15]        |
| Hypertension, \(n\) (%)                      | 45 [73]       |
| Hyperlipidemia, \(n\) (%)                    | 47 [76]       |
| Current smoking, \(n\) (%)                   | 18 [29]       |
| Excessive alcohol intake, \(n\) [%]           | 8 [13]        |
| Coronary artery disease, \(n\) [%]           | 14 [23]       |
| Previous history of TIA or stroke, \(n\) [%]  | 10 [16]       |
| Heart failure, \(n\) (%)                     | 7 [11]        |
| Valvular disease, \(n\) (%)                  | 1 [2]         |
| Peripheral arterial disease, \(n\) [%]        | 9 [15]        |
| **Prestroke treatment**                       |               |
| Antiplatelet, \(n\) [%]                      | 23 [37]       |
| Anticoagulant, \(n\) [%]                     | 7 [11]        |

(Continued)
small sample size that may not have allowed the decreased odds of neurological improvement in patients with increased GV to translate into worse functional outcomes at 3 months.

GV has previously been shown to correlate well with oxidative stress, as it was estimated from 24-h urinary excretion rates of free 8-iso prostaglandin F2α.52 In fact, acute glucose fluctuations expressed by MAG were associated with higher production and urinary excretion of free 8-iso prostaglandin F2α, while no relationship was confirmed between oxidative stress and more traditional hyperglycemic markers, such as fasting plasma glucose, mean glucose, and HbA1c.52 Thus, increased oxidative stress may represent the link between increased GV during the first hours of ictus and early neurological deterioration occurring during hospitalization. MAG value represents the mean absolute glucose change, counting for all glycemic variations over time. It is calculated by the sum of all differences between consecutive glucose values (even when they are within normal range), divided by the total time of monitoring, measured in hours.12 MAG has been correlated with short-term outcomes, such as intensive-unit and in-hospital mortality, in critically ill patients.12

Clinical outcomes at 3 months were not associated with any of the GV indices measured in our study. On the contrary, Wada and colleagues20 showed that high mean glucose levels, distribution time with blood glucose values more than 8 mmol/L, and areas under the curve presenting blood glucose values more than 8 mmol/L during the initial 72 h of acute stroke were associated with death or dependency at 3 months. All of the associated factors, however, reflected a hyperglycemic state that has previously been correlated with adverse clinical outcomes in stroke.1,53–55 GV indices that reflected glucose fluctuations at both hyperglycemic and hypoglycemic values were not assessed in the Japanese study. Also difference in sample size (62 versus 100 patients), study population (Caucasians and African Americans versus Asians), and baseline stroke

| Variable                                      | Overall |
|-----------------------------------------------|---------|
| Antihypertensive, n (%)                       | 32 (52) |
| Statins, n (%)                                | 30 (48) |
| Acute stroke treatment                        |         |
| Intravenous thrombolysis, n (% IS)           | 21 (44) |
| Mechanical thrombectomy, n (% IS)             | 3 (6)   |
| Laboratory findings                           |         |
| Glucose on admission, mg/dl, median (IQR)     | 118 [105–131] |
| Hemoglobin A1c, %, median (IQR)               | 5.6 [5.2–6] |
| Low-density lipoprotein, mg/dl, mean ± SD     | 113 ± 38 |
| Systolic blood pressure, mmHg, median (IQR)   | 150 [140–165] |
| Diastolic blood pressure, mmHg, median (IQR)  | 85 [76–97] |
| Neuroimaging findings                         |         |
| Anterior circulation, n (%)                   | 54 (87) |
| Right hemisphere, n (%)                       | 31 (50) |
| Hematoma volume, mm³, median (IQR)            | 21 [12–30] |

DM, diabetes mellitus; ICH, intracerebral hemorrhage; IS, ischemic stroke; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.
severity (9 versus 6 points in NIHSS score) may account for the discrepant findings between our and the report by Wada and colleagues.20 Our pilot study suggests an excellent feasibility and tolerability of CGM in the acute stroke setting. CGM devices were successfully inserted in 62 patients without any adverse event, such as skin irritation or subcutaneous hematomas, even in the subgroup of patients that received intravenous thrombolysis (34%). Only few studies have implemented CGM recordings in order to measure GV and investigate its association with acute or short-term stroke outcomes.19,20,56 Those studies, however, calculated only a proportion of existing GV indices that are valid and widely used for GV assessment.57–59 In our study, we used EasyGV© software that provided 13 quantitative and qualitative GV markers.39 All of these markers were evaluated for possible associations with stroke outcomes during hospitalization and at 3 months.

GV indices were significantly different between diabetic and nondiabetic patients of our cohort. This should be expected because diabetic patients and patients with impaired blood glucose regulation have more pronounced glucose fluctuations and intraday glycemic excursions.38,60 In our cohort, nondiabetic patients had GV indices values within the proposed normal reference ranges for Caucasians patients.39 CGM, however, disclosed 32 hypoglycemic events that had gone unrecognized by the periodic finger-prick glucose measurements. All hypoglycemic episodes were recorded in the subgroup of nondiabetic patients. This finding could be partially attributed to dysphagia and food deprivation in the first days after stroke that may lead to hypoglycemia even in the absence of insulin treatment or history of diabetes mellitus.61 Despite that insulin treatment was not recorded in our study, such a finding would suggest for careful glycemia management in this patient subgroup. We also postulate that reactive endogenous hyperinsulinemia and insulin resistance may be a preexisting and predisposing factor for endothelial damage in this population. Characteristically, antidiabetic medications that do not increase GV, such as pioglitazone, have already proven beneficial for secondary stroke prevention in patients with diabetes mellitus, prediabetes, and insulin resistance as well.62

During those under-recognized hypoglycemic events, glucose values were below 70 mg/dl, but no patient exhibited severe hypoglycemia with glucose values below 40 mg/dl. Although this could be a potential explanation for hypoglycemic episodes being asymptomatic and without significant association with poststroke functional outcomes, it has been previously reported that glucose values lower than 67 mg/dL within the first 24h of ictus have been related to adverse functional outcomes in patients with acute ischemic stroke.9 Another reason for the lack of association between under-recognized hypoglycemic events and clinical outcomes may be attributed to the low sample size. The use of improved CGM sensors that do not require calibration and instantly provide glucose values may help identify hypoglycemic episodes and other glycemic excursions in real time and guide a more personalized hyperglycemia management in the acute stroke setting.63 Moreover, CGM has been

### Table 2. Clinical outcomes during hospitalization and at 3 months.

| Variable                                | Overall |
|-----------------------------------------|---------|
| **During hospitalization**              |         |
| Complications                           |         |
| Death, n (%)                            | 3 (5)   |
| Fever, n (%)                            | 20 (32) |
| Infection, n (%)                        | 19 (31) |
| Aspiration pneumonia, n (%)             | 10 (16) |
| Intubation, n (%)                       | 7 (11)  |
| **Clinical outcomes**                   |         |
| Exit NIHSS Score, points, median (IQR) | 3 (1–8) |
| Neurological deterioration, n (%)       | 7 (11)  |
| Neurological improvement, n (%)         | 30 (48) |
| **At 3 months**                         |         |
| Clinical outcomes                       |         |
| mRS score, median (IQR)                 | 2 (1–4) |
| Death, n (%)                            | 6 (10)  |
| Functional independence, n (%)          | 34 (55) |
| Excellent functional outcome, n (%)     | 24 (39) |

IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.
Table 3. Univariable logistic regression analyses depicting the associations of GV indices with functional outcomes at 3 months.

| Variable | Mean Glu | SD | CONGA | Li | J-index | LBGI | HBGI | GRADE | MODD | MAGE | ADRR | M-value | MAG |
|----------|----------|----|-------|----|---------|------|------|-------|------|------|------|---------|------|
|          | Odds ratio (95% CI) |          |       |    |         |      |      |       |      |      |      |         |      |
| Functional independence | 1.202 | [0.844–1.712] | 1.032 | [0.628–2.489] | 1.274 | [0.867–1.874] | 1.024 | [0.978–1.073] | 1.017 | [0.770–1.343] | 1.116 | [0.919–1.357] | 1.124 | [0.924–1.369] | 1.460 | [0.669–3.284] | 0.879 | [0.566–1.367] | 1.033 | [0.945–1.129] | 1.053 | [0.967–1.195] | 1.038 | [0.388–2.854] |
| Excellent functional outcome | 1.167 | [0.803–1.696] | 1.306 | [0.500–3.413] | 1.213 | [0.809–1.820] | 1.024 | [0.972–1.078] | 1.008 | [0.757–1.342] | 1.110 | [0.888–1.387] | 1.089 | [0.885–1.341] | 1.362 | [1.562–3.302] | 1.015 | [0.653–1.580] | 1.010 | [0.923–1.106] | 1.069 | [0.945–1.163] | 1.241 | [0.440–3.502] |

ADRR, average daily risk ratio; CI, confidence interval; CONGA, continuous overlapping net glycemic action; Glu, glucose; GRADE, glycemic risk assessment in diabetes equation; GV, glycemic variability; HBGI, high blood glucose index; LBGI, low blood glucose index; Li, lability index; MAG, mean absolute glucose; MAGE, mean amplitude of glucose excursions; MODD, mean of daily differences; SD, standard deviation.
Table 4. Univariable and multivariable logistic regression analyses depicting the associations of GV indices, baseline characteristics, and in-hospital complications with the likelihood of neurological improvement during hospitalization.

| Variable               | Univariable logistic regression analysis | Multivariable logistic regression analysisa |
|------------------------|-----------------------------------------|-------------------------------------------|
|                        | Odds ratio (95% CI)          | p         | Odds ratio (95% CI) | p         |
| GV indices             |                          |           |                          |           |
| Mean glucose           | 0.724 [0.487–1.079]       | 0.113     |                          |           |
| SD                     | 0.532 [0.193–1.473]       | 0.225     |                          |           |
| CONGA                  | 0.731 [0.481–1.110]       | 0.141     |                          |           |
| Li                     | 0.792 [0.448–1.4]         | 0.422     |                          |           |
| J-index                | 0.959 [0.906–1.016]       | 0.156     |                          |           |
| LBGI                   | 1.193 [0.877–1.623]       | 0.262     |                          |           |
| HBGI                   | 0.897 [0.731–1.101]       | 0.299     |                          |           |
| GRADE                  | 0.865 [0.7–1.069]         | 0.179     |                          |           |
| MODD                   | 0.590 [0.224–1.554]       | 0.286     |                          |           |
| MAGE                   | 0.759 [0.48–1.2]          | 0.238     |                          |           |
| ADRR                   | 0.843 [0.722–0.985]       | 0.032     | 0.924 [0.743–1.148]     | 0.160     |
| M-value                | 1.010 [0.938–1.087]       | 0.79      |                          |           |
| MAG                    | 0.333 [0.108–1.029]       | 0.056     | 0.135 [0.024–0.751]     | 0.022**   |
| Baseline characteristics|                          |           |                          |           |
| Age                    | 1.003 [0.956–1.053]       | 0.891     | 1.018 [0.949–1.091]     | 0.353     |
| Gender                 | 1.308 [0.481–3.558]       | 0.599     | 0.771 [0.195–3.041]     | 0.498     |
| Index event            | 0.338 [0.093–1.231]       | 0.1       | 0.301 [0.054–1.667]     | 0.312     |
| Diabetes               | 0.393 [0.107–1.449]       | 0.161     |                          |           |
| Hypertension           | 1.076 [0.352–3.290]       | 0.898     |                          |           |
| Hyperlipidemia         | 2.273 [0.673–7.674]       | 0.186     |                          |           |
| Smoking                | 1.5 [0.498–4.519]         | 0.471     |                          |           |
| Alcohol                | 1.933 [0.419–8.911]       | 0.398     |                          |           |
| Coronary artery disease| 1.087 [0.330–3.576]       | 0.891     |                          |           |
| Previous history of stroke | 1.080 [0.279–4.181]     | 0.911     |                          |           |
| Heart failure          | 1.487 [0.304–7.277]       | 0.624     |                          |           |
| Peripheral arterial disease | 0.831 [0.201–3.440]    | 0.798     |                          |           |
| Antiplatelet pretreatment | 0.551 [0.193–1.571]     | 0.265     |                          |           |

(Continued)
with neurological improvement during hospitalization at a corrected (for multiple comparisons) level of significance of $p=0.05/13 \approx 0.004$ (unpaired $t$ test after Bonferroni’s correction for multiple comparisons) and our results require further validation in larger studies.

**Conclusions**

GV was calculated during CGM recording in acute stroke patients and was expressed by 13 different indices. Elevated GV as indicated by higher MAG values was independently associated with lower likelihood of neurological improvement during hospitalization in acute stroke patients. ADRR index and HbA1c value were also associated with neurological improvement in the univariate analysis, but after adjusting for confounders they did not retain their statistical significance. No GV index was related to 3-month clinical outcomes, pointing to a more short-term impact of GV on early poststroke neurological status. CGM recording detected several hypoglycemic episodes in the nondiabetic stroke patients that were missed by the periodic blood glucose measurements, underscoring that glycemia management in the acute stroke setting should be further optimized. Larger multicenter studies are required to
further investigate the validity of these preliminary observations and determine the potential detrimental effects of increased MAG values on early clinical outcomes of acute stroke patients.

**Conflict of interest statement**
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**Ethics statement and data availability**
The study protocol was approved by the Ethics Committee of ‘Attikon’ University Hospital (Protocol No. A.3/6th Committee Meeting/15-05-2018) and the Beth Israel Deaconess Medical Center Committee on Clinical Investigations (IRB Protocol No. 2014 P-000163). Written informed consent was obtained from all participants before enrollment in the study. All procedures followed were in accordance with the Helsinki Declaration. The study data are available from the corresponding author upon reasonable request.

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**Supplemental material**
Supplemental material for this article is available online.

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