DOI: https://doi.org/10.46354/i3m.2019.iwish.016

CONTINUOUS GLUCOSE MONITORING IN ACUTE STROKE

Aponte-Becerra, Laura MD. [a]*, Quispe, Rodrigo C. MD. [a]*, Mendez-Pino, Laura MD. [a], Novak, Vera MD. PhD. [a, b], Selim, Magdy MD. PhD. [b], Lioutas, Vasileios-Arsenios MD. [b]

[a] SAFE Laboratory, Department of Neurology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, MA, USA
[b]Stroke Division, Department of Neurology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, MA, USA

[a]laponte@bidmc.harvard.edu, [a]rquispe@bidmc.harvard.edu, [a]lmendez1@bidmc.harvard.edu, [a]vnovak@bidmc.harvard.edu, [b]mselim@bidmc.harvard.edu, [b]vlioutas@bidmc.harvard.edu

*These authors contributed equally to this paper.

ABSTRACT
Hyperglycaemia upon admission is a pathophysiological response to acute brain ischemia that has been independently associated with high mortality rate and poor prognosis. Glycaemic variability (GV) has also shown association with poor clinical outcomes among stroke patients. GV is best assessed by continuous glucose monitoring (CGM), which enables consecutives glucose measurements every 5 minutes. This pilot study aimed: 1) To describe safety, feasibility and tolerability of CGM in the acute stroke setting; and 2) To compare CGM and conventional FS glucose-based monitoring regimen in terms of their relationship with GUA and the accuracy of hypoglycaemic episodes detection. Safety, feasibility and tolerability of CGM was excellent in our cohort of 23 patients with acute stroke (61% ischemic and 39% intracerebral haemorrhage) and there were no adverse events. CGM recorded ten hypoglycaemic episodes that were not detected by conventional FS monitoring. GUA was associated with coefficient of variation (CV) of CGM (p=0.03), CV of FS (p=0.01), standard deviation (SD) of CGM (p-value=0.01) and mean amplitude of glucose excursions (MAGE) (p-value=0.001).

Keywords: acute stroke, glycaemic variability, continuous glucose monitoring, hypoglycaemia.

1. INTRODUCTION

Hyperglycaemia is a common phenomenon in critically ill patients (Kruyt et al. 2010). Both diabetic and non-diabetic acute ischemic stroke (IS) and intracerebral haemorrhage (ICH) patients commonly manifest high glucose levels upon admission (Siegelaar et al. 2011). Admission hyperglycaemia is independently associated with worse clinical outcomes, such as early neurological deterioration, IS haemorrhagic transformation, a more than threefold increase in the 30-day mortality rate, and poor 90-day functional status (Capes et al. 2001, Seners et al. 2015, Paciaroni et al. 2009). These associations remain true regardless of stroke subtype, stroke severity, or diagnosis of diabetes (Poppe et al. 2009). Peaks in glycaemia lead to an overproduction of superoxide radicals and activation of oxidative stress that result in neurodegeneration and endothelial dysfunction. Current glucose monitoring protocols used in acute stroke clinical practice and clinical trials consist of serum glucose upon admission (GUA) followed by finger-stick (FS) glucose every 6 hours (4 glucose measurements per day) during the first 1-2 days (Yoo et al. 2014, Fuentes et al. 2009) with reactive adjustment of glucose levels by insulin administration. Intensive glycaemic monitoring and corrective protocols with more frequent glucose measurements have also been tested in clinical trials, which have failed to achieve better clinical outcomes despite achieving their primary target of significantly lowering mean serum glucose (Godoy 2010, Gray et al. 2007, Staszewski et al. 2011, Kreisel et al. 2009,, Johnston et al. 2019). Additionally, all glucose-lowering trials in acute stroke resulted in substantial increase in hypoglycaemic episodes (Gray et al. 2007, Staszewski et al. 2011, Kreisel et al. 2009). Similarly to hyperglycaemia, hypoglycaemia adversely affects the acutely injured brain tissue (Rabinstein 2009). Glycaemic nadirs cause the release of counter-regulatory hormones such as norepinephrine and epinephrine inducing vasoconstriction and platelet aggregation (Eslami et al. 2011).

In addition to hyperglycaemia and hypoglycaemia, glycaemic variability (GV) has emerged as a third component of dysglycaemia (Monnier 2008). Glycaemic oscillations measured by blood glucose coefficient of variation (CV) are associated with high mortality rate in ICU patients. Detrimental effects are more profound in non-diabetics and are independent of age, illness severity, comorbidities, and hypoglycaemia (Lanspa et al. 2014). The mechanism of this association is unclear, but it is possible that diabetic patients receive insulin more frequently, which might confer benefits independent of glycaemic control (Falciglia et al. 2009).

Another hypothesis is that chronic diabetic patients may be conditioned to glucose fluctuations with periods of extreme hyperglycaemia (Graham et al. 2010). GV is best assessed by continuous glucose monitoring (CGM). For instance, area under the curve more than 144mg/dL of CGM glucose during the first 72 hours post-stroke was associated with death or dependency at 3 months (Wada Shinichi et al. 2018). CGM enables repeated measurements of interstitial glucose in 5-minute intervals. CGM offers more accurate and timely glycaemic monitoring as compared to even hourly glucose FS monitoring regimens that come with significant patient discomfort from repeated FS punctures and mobilization of resources and personnel (Egi et al. 2009).

Thus, CGM is an attractive glucose monitoring method that is already in use by community-dwelling diabetics.

However, CGM presents some technical limitations. Regarding the calibration of the device with 4 FS measurements per day, it is possible to introduce an error if the capillary glucose level is recorded after exercise or meals, where rapid changes in glucose levels (>2mg/dL/min) may occur. In addition, the accuracy of the CGM decreases during the first 24 hours after its insertion, due to reactive local inflammation (Zijlstra et al. 2013). Its safety, feasibility, tolerability in the acute stroke setting has not been thoroughly tested and it is not known whether its theoretical advantage over conventional glucose monitoring methods translates into a practical benefit.

This pilot study aimed to assess safety, feasibility and tolerability of CGM in the acute stroke setting and compared CGM and conventional FS glucose-based monitoring regimen in terms of their relationship with GUA and the accuracy of detecting hypoglycaemic events.

2. METHODS

This was a prospective, single centre observational study. Consecutive adults with acute IS or ICH presenting within 48 hours of symptom onset and admitted to the stroke service or NeuroICU at Beth Israel Deaconess Medical Centre (BIDMC) were included. Eligible participants signed an informed consent approved by the BIDMC Committee on Clinical Investigations and were enrolled. Informed consent was obtained by subject's surrogate if the subject was unable to consent. Diagnosis of IS or ICH was confirmed by appropriate clinical and imaging criteria. All consenting participants underwent CGM for 72 hours or until discharge (whichever occurred first). Demographic characteristics, past medical history, National Institute of Health Stroke Score (NIHSS) and laboratory tests including Haemoglobin A1c, lipid panel, white blood cells count (WBC), and blood glucose on admission were collected from medical records. For ICH patients, the haemorrhage volume (cm^3) was computed. All patients received the standard of care glucose FS monitoring every six hours with appropriate correction with sliding scale insulin according to hospital protocol. Feeding was started according to hospital guidelines and the judgement of treating physician and swallow therapist. Adverse events and CGM discontinuation were recorded.

2.1 Continuous glucose monitoring (CGM)

This study used CGM - Medtronic MiniMed, Northridge, CA, which is a portable and minimal invasive subcutaneous device that measures interstitial blood glucose every five minutes(Signal et al. 2010). CGM device requires to be calibrated with four glucose FS measurements per day. It utilizes an enzymatic technology using oxygen as a cofactor with subsequent release of an electron per glucose molecule. Electrons are transferred to an electrode generating an electric current, which is translated into a glucose value(Vaddiraju et al. 2010). Intra-day GV was assessed by the mean amplitude of glucose excursions (MAGE) and the standard deviation (SD) around the mean CGM glucose values. SD is considered the "gold standard" CGM metric and takes into account all fluctuations during CGM recording equally, whereas MAGE accounts only for major intra-day oscillations (Weber 2009). CGM indices were calculated using the EasyGV calculator version 9.0 (Hill 2010).

2.2 Glucose parameters

- **Mean FS**: is the mean of all glucose recordings by conventional FS glucose monitoring per subject.
- **Mean CGM**: is the mean of all glucose readings from the CGM per subject.
- **SD**: is a measure of the variability around the mean of all glucose values from the CGM per subject.
- **CV**: is the SD over the mean glucose value from CGM and FS, expressed as a percentage. A CV of less than 36% has been shown to distinguish stable from unstable glucose homeostasis(Monnier et al. 2017).
- **MAGE**: is the sum of the differences from peaks to nadirs divided by the total number of glucose values. The difference is only considered when greater than 1 SD of the mean in a 24-hour period (Weber and Schnell 2009).
- **Hypoglycaemic episode**: at least 4 consecutive measurements (15 minutes) (Danne et al. 2017) of glucose readings below 70 mg/dL using CGM (American Diabetes Association 2019).
- **Hyperglycaemia duration**: time period of glucose readings above 180 mg/dL over total recording time using CGM, expressed as a percentage.

2.3 Statistical analysis

Baseline contingency table was generated to describe demographic, clinical characteristics (past medical history, lipid panel, WBC, and severity of stroke upon admission) and glucose parameters (serum GUA, CGM indices and glucose FS). Continuous variables are expressed as mean ± SD and range, whereas categorical variables are expressed as total number (N) and percentages (%). Hypoglycaemic episodes and hyperglycaemia duration were calculated. Univariable

analysis using simple linear models was used to determine the unadjusted association between serum GUA as predictor and GV metrics such as CV of FS, CV of CGM, SD and MAGE as outcomes. Statistical significance was set at p-value <0.05 and all statistical analyses were performed using SAS 9.4 software.

3. RESULTS

Table 1 presents the baseline characteristics of our cohort. 23 acute strokes (14 IS, 9 ICH), 12 (52%) men, mean age 68±11.8 years. Most common comorbidities were hypertension (65%) and dyslipidaemia (65%). The majority of the cohort was classified as moderate stroke severity on admission (NIHSS median=10 and IQR=15). Mean GUA was 132mg/dL. CGM detected 10 hypoglycaemic episodes whereas none were detected with FS. Lowest glucose level detected by FS was 78mg/dL and lowest mean FS was 89.5mg/dL.

Table 1. Baseline characteristics

Demographics	**N=23**
Male	12 (52%)
Age, years	68.0 ± 11.8
	46.0 – 87.0
Past medical history	
Diabetes	4 (17%)
Hypertension	15 (65%)
Dyslipidaemia	15 (65%)
Laboratory	
Haemoglobin A1c, %	6.10 ± 1.42
	4.90 - 10.80
LDL cholesterol, mg/dL	99.70 ± 38.57
	29.00 – 164.00
HDL cholesterol, mg/dL	54.45 ± 17.94
	37.00 - 103.00
WBC, K/uL	9.23 ± 2.77
	5.60 – 14.70
Stroke Severity	
NIHSS, median (IQR)	10 (15)
	1.00 - 30.00
Glucose parameters	
GUA, mg/dL	132.09 ± 46.24
	94.00 – 325.00
Mean FS, mg/dL	128.91 ± 37.10
	89.50 - 246.50
Mean CGM, mg/dL	128.10 ± 33.78
	75.78 - 233.42
CV of CGM, %	15.60 ± 5.95
	8.12 - 30.25
CV of FS, %	14.89 ± 8.27
	3.73 - 33.52
SD of CGM	20.61 ± 12.99
	9.62 - 66.36
MAGE	45.62 ± 20.31
	16.04 - 104.22
Hypoglycaemic episodes	10
Hyperglycaemia duration, %	9.23 ± 23.03
	0.00 - 80.67

WBC, white blood cells; NIHSS, National Institutes of Health stroke scale, GUA, glucose upon admission, FS, finger-stick; CGM, continuous glucose monitoring; CV, coefficient of variation; SD, standard deviation; MAGE, mean absolute glucose excursions.

Linear models (Figure 1.) showed a significant association between GUA and CV of CGM (p-value=0.03, R^2=0.19), CV of FS (p-value=0.01, R^2=0.28), SD (p-value=0.01 and R^2=0.23) and MAGE (p-value=0.001 and R^2=0.38). Conversely, mean FS and mean CGM did not show a significant association with GUA. There were no significant associations of GUA with GV metrics when outliers where excluded from the sample.

3.1 Feasibility and safety of CGM

92 patients met eligibility criteria. Signed ICF was obtained for only 25 patients who underwent CGM. Limitations for CGM among the 67 patients that were eligible but not enrolled were patient or family decline participation (43%), missing 48-hour from symptom onset window period due to expected need of magnetic resonance imaging (MRI) scans or any other therapeutic procedure (23%), subject unable to consent and surrogate not reachable within enrolment period (16%), discharged the same day of admission (9%), treatment plan consisting of comfort measures only (7%) and seizures (2%). Of 25 enrolled subjects, 23 were able to complete the monitoring. One patient was discharged prematurely prior to inserting CGM; CGM malfunction led to loss of data on another patient. Mean of CGM recording period was 46.54±23.14 hours (range=12.25 – 84) among the 23 patients. There were no adverse events reported throughout the duration of the study. None of the enrolled patients dropped out of the study. CGM was well tolerated and did not lead to any disruption to patient care

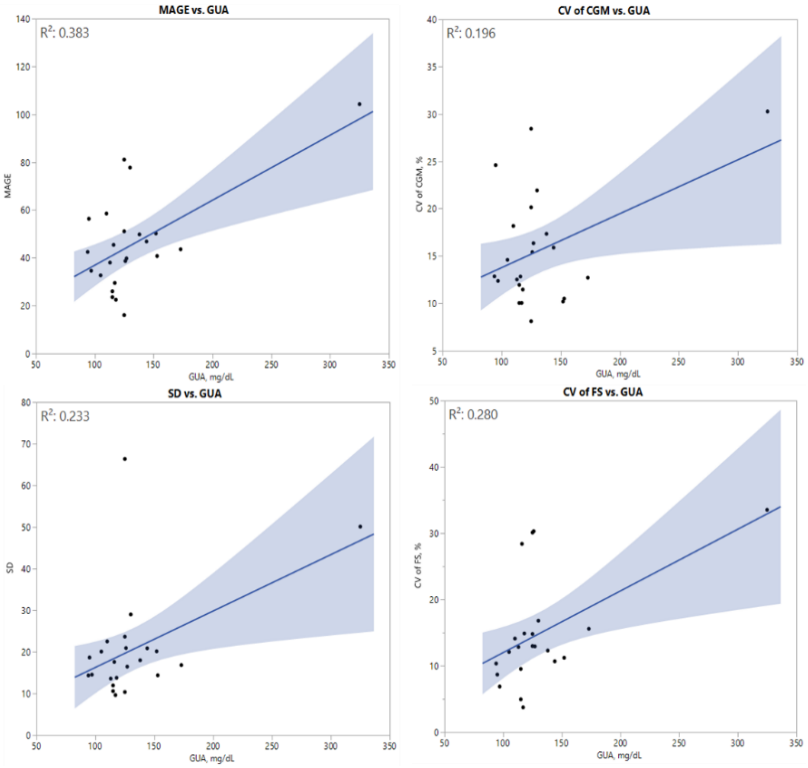

Figure 1. Linear regression models: GUA as predictor and MAGE, SD, CV of CGM and CV of FS as outcomes.
GUA, glucose upon admission, CV of FS, coefficient of variation of finger-stick; CV of CGM, coefficient of variation of continuous glucose monitoring; SD, standard deviation; MAGE, mean absolute glucose excursions.

4. DISCUSSION

In this prospective pilot study of CGM in acute stroke patients, we found excellent tolerability and safety. There were no reported side effects and none of the patients terminated the participation in the study prematurely. With regards to feasibility, in the pilot phase of the study only the principal investigator was involved in CGM insertion and monitoring. Due to the unpredictable nature of acute stroke and the time-sensitive of stroke physiology and outcomes, house staff and/or nursing would have to undergo training in CGM insertion and maintenance for this study to be performed at a larger scale. One additional potential layer of complexity is the need for brain MRI in this patient population which might occur in unpredictable hours, depending on scanner availability. Given incompatibility of CGM and MRI magnet, the monitor will need to be temporarily discontinued, re-inserted and recalibrated after the MRI scan.

Given the ease of use and the incorporation of alarm systems for hypoglycaemia of newer generation CGM, we anticipate that house staff and nursing training in these procedures will be feasible and the risk of inaccuracy due to repetitive calibrations will be optimized.

As reported above, hypoglycaemia can be particularly detrimental in the acute stroke phase and it is considered a potential reason for lack of clinical benefit in glucose-lowering trials in acute stroke. Despite best efforts and use of decision algorithms, these hypoglycaemic events could not be prevented. Blood glucose of 70mg/dL has been recognized as a threshold for neuroendocrine responses in non-diabetics and for impaired contra regulatory responses to hypoglycaemia in diabetics (American Diabetes Association 2019, Danne et al. 2017). In our study, CGM conferred a marked advantage over conventional, FS-based monitoring regimens: 10 hypoglycaemic episodes were detected with CGM, compared to none by FS. Hypoglycaemia was considered when glucose value was below 70mg/dL, also referred to as “level 1 hypoglycaemia” in medical literature (American Diabetes Association 2019).

This finding suggests that CGM confers a significantly more granular view of the glycaemic curve in acute stroke and allows capturing and potentially preventing clinically meaningful phenomena, such as hypoglycaemia.

This study did not find a statistically significant association between GUA and mean FS or mean CGM glucose, but found a statistically significant effect of GUA on GV in terms of CV of FS and CV of CGM. This might suggest that the pathophysiology involved in poor clinical outcomes of patients with hyperglycaemia on admission may be linked to the deleterious effect of GV.

Limitations of this study include a small sample size that does not allow safe assumptions regarding the association between GV and GUA neither control of the effect of outliers in the model. Also, there was lack of CGM recording in the very early stages of acute stroke due to limited resources in the pilot phase and MRI incompatibility device.

In summary, this pilot study demonstrated excellent safety and tolerability of CGM in the acute phase of stroke and suggests that CGM can provide clinically meaningful data, especially regarding hypoglycaemic episodes, which are not captured by conventional glucose monitoring methods. Future trials evaluating the feasibility and reliability of CGM in larger patient samples are needed in order to further implement measures of GV in acute stroke management.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Freddy J. Alfaro-Martinez and Daniela A. Pimentel while conducting the study.

REFERENCES

American Diabetes Association. 2019. "6. Glycaemic Targets: Standards of Medical Care in Diabetes—2019." *Diabetes Care* 42 (Supplement 1): S61–70.

Capes, S. E., D. Hunt, K. Malmberg, P. Pathak, and H. C. Gerstein. 2001. "Stress Hyperglycaemia and Prognosis of Stroke in Nondiabetic and Diabetic Patients: A Systematic Overview." *Stroke* 32 (10): 2426–32.

Danne, Thomas, Revital Nimri, Tadej Battelino, Richard M. Bergenstal, Kelly L. Close, J. Hans DeVries, Satish Garg, et al. 2017. "International Consensus on Use of Continuous Glucose Monitoring." *Diabetes Care* 40 (12): 1631–40.

Egi, Moritoki, Rinaldo Bellomo, and Michael C. Reade. 2009. "Is Reducing Variability of Blood Glucose the Real but Hidden Target of Intensive Insulin Therapy?" *Critical Care (London, England)* 13 (2): 302.

Eslami, Saeid, Zhila Taherzadeh, Marcus J. Schultz, and Ameen Abu-Hanna. 2011. "Glucose Variability Measures and Their Effect on Mortality: A Systematic Review." *Intensive Care Medicine* 37 (4): 583–93.

Falciglia, Mercedes, Ron W. Freyberg, Peter L. Almenoff, David A. D'Alessio, and Marta L. Render. 2009. "Hyperglycaemia-Related Mortality in Critically Ill Patients Varies with Admission Diagnosis." *Critical Care Medicine* 37 (12): 3001–9.

Fuentes, Blanca, José Castillo, Belén San José, Rogelio Leira, Joaquín Serena, José Vivancos, Antonio Dávalos, et al. 2009. "The Prognostic Value of Capillary Glucose Levels in Acute Stroke: The GLycemia in Acute Stroke (GLIAS) Study." *Stroke* 40 (2): 562–68.

Nathan R Hill. 2010. Glycaemic Variability Calculator: EasyGV. Oxford University Innovation. Retrieved from: https://innovation.ox.ac.uk/licence-details/glycaemic-variability-calculator-easygv/.

Godoy, Daniel A., Mario Di Napoli, and Alejandro A. Rabinstein. 2010. "Treating Hyperglycaemia in Neurocritical Patients: Benefits and Perils." *Neurocritical Care* 13 (3): 425–38.

Graham, Brian B., Angela Keniston, Ognjen Gajic, Cesar A. Trillo Alvarez, Sofia Medvedev, and Ivor S. Douglas. 2010. "Diabetes Mellitus Does Not Adversely Affect Outcomes from a Critical Illness*." *Critical Care Medicine* 38 (1): 16.

Gray, Christopher S., Anthony J. Hildreth, Peter A. Sandercock, Janice E. O'Connell, Donna E. Johnston, Niall E. F. Cartlidge, John M. Bamford, Oliver F. James, K. George M. M. Alberti, and GIST Trialists Collaboration. 2007. "Glucose-Potassium-Insulin Infusions in the Management of Post-Stroke Hyperglycaemia: The UK Glucose Insulin in Stroke Trial (GIST-UK)." *The Lancet. Neurology* 6 (5): 397–406.

Johnston, Karen C., Askiel Bruno, Qi Pauls, Christiana E. Hall, Kevin M. Barrett, William Barsan, Amy Fansler, et al. 2019. "Intensive vs Standard Treatment of Hyperglycaemia and Functional Outcome in Patients with Acute Ischemic Stroke: The SHINE Randomized Clinical Trial." *JAMA* 322 (4): 326–35.

Kreisel, Stefan H., Undine M. Berschin, Hans-Peter Hammes, Hans Leweling, Thomas Bertsch, Michael G. Hennerici, and Stefan Schwarz. 2009. "Pragmatic Management of Hyperglycaemia in Acute Ischaemic Stroke: Safety and Feasibility of Intensive Intravenous Insulin Treatment." *Cerebrovascular Diseases (Basel, Switzerland)* 27 (2): 167–75.

Kruyt, Nyika D., Geert Jan Biessels, J. Hans Devries, and Yvo B. Roos. 2010. "Hyperglycaemia in Acute Ischemic Stroke: Pathophysiology and Clinical Management." *Nature Reviews. Neurology* 6 (3): 145–55.

Lanspa, Michael J., Justin Dickerson, Alan H. Morris, James F. Orme, John Holmen, and Eliotte L. Hirshberg. 2014. "Coefficient of Glucose Variation Is Independently Associated with Mortality in Critically Ill Patients Receiving Intravenous Insulin." *Critical Care (London, England)* 18 (2): R86.

Monnier, Louis, Claude Colette, and David R. Owens. 2008. "Glycaemic Variability: The Third Component of the Dysglycemia in Diabetes. Is It Important? How to Measure It?" *Journal of Diabetes Science and Technology* 2 (6): 1094–1100.

Monnier, Louis, Claude Colette, Anne Wojtusciszyn, Sylvie Dejager, Eric Renard, Nicolas Molinari, and David R. Owens. 2017. "Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes." *Diabetes Care* 40 (7): 832–38.

Paciaroni, Maurizio, Giancarlo Agnelli, Valeria Caso, Francesco Corea, Walter Ageno, Andrea Alberti, Alessia Lanari, et al. 2009. "Acute Hyperglycaemia and Early Hemorrhagic Transformation in Ischemic Stroke." *Cerebrovascular Diseases (Basel, Switzerland)* 28 (2): 119–23.

Poppe, Alexandre Y., Sumit R. Majumdar, Thomas Jeerakathil, William Ghali, Alastair M. Buchan, Michael D. Hill, and Canadian Alteplase for Stroke Effectiveness Study Investigators. 2009. "Admission Hyperglycaemia Predicts a Worse Outcome in Stroke Patients Treated with Intravenous Thrombolysis." *Diabetes Care* 32 (4): 617–22.

Rabinstein, Alejandro A. 2009. "Hyperglycaemia in Critical Illness: Lessons from NICE-SUGAR." *Neurocritical Care* 11 (1): 131–32.

Seners, Pierre, Guillaume Turc, Catherine Oppenheim, and Jean-Claude Baron. 2015. "Incidence, Causes and Predictors of Neurological Deterioration Occurring within 24 h Following Acute Ischaemic Stroke: A Systematic Review with Pathophysiological Implications." *Journal of Neurology, Neurosurgery, and Psychiatry* 86 (1): 87–94.

Siegelaar, Sarah E, Maartje Hickmann, Joost BL Hoekstra, Frits Holleman, and J Hans DeVries. 2011. "The Effect of Diabetes on Mortality in Critically Ill Patients: A Systematic Review and Meta-Analysis." *Critical Care* 15 (5): R205.

Signal, Matthew, Christopher G. Pretty, J. Geoffrey Chase, Aaron Le Compte, and Geoffrey M. Shaw. 2010. "Continuous Glucose Monitors and the Burden of Tight Glycaemic Control in Critical Care: Can They Cure the Time Cost?" *Journal of Diabetes Science and Technology* 4 (3): 625–35. https://doi.org/10.1177/193229681000400317.

Staszewski, Jacek, Bogdan Brodacki, Jerzy Kotowicz, and Adam Stepien. 2011. "Intravenous Insulin Therapy in the Maintenance of Strict Glycaemic Control in Nondiabetic Acute Stroke Patients with Mild Hyperglycaemia." *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association* 20 (2): 150–54.

Vaddiraju, Santhisagar, Diane J Burgess, Ioannis Tomazos, Faquir C Jain, and Fotios Papadimitrakopoulos. 2010. "Technologies for Continuous Glucose Monitoring: Current Problems and Future Promises." *Journal of Diabetes Science and Technology* 4 (6): 1540–62.

Wada Shinichi, Yoshimura Sohei, Inoue Manabu, Matsuki Takayuki, Arihiro Shoji, Koga Masatoshi, Kitazono Takanari, et al. 2018. "Outcome Prediction in Acute Stroke Patients by Continuous Glucose Monitoring." *Journal of the American Heart Association* 7 (8): e008744.

Weber, Christian, and Oliver Schnell. 2009. "The Assessment of Glycaemic Variability and Its Impact on Diabetes-Related Complications: An Overview." *Diabetes Technology & Therapeutics* 11 (10): 623–33.

Yoo, Deok-Sang, Jane Chang, Joon-Tae Kim, Min-Ji Choi, Jina Choi, Kang-Ho Choi, Man-Seok Park, and Ki-Hyun Cho. 2014. "Various Blood Glucose Parameters That Indicate Hyperglycaemia after Intravenous Thrombolysis in Acute Ischemic Stroke Could Predict Worse Outcome." *PloS One* 9 (4): e94364.

Zijlstra, E., T. Heise, L. Nosek, L. Heinemann, and S. Heckermann. 2013. "Continuous Glucose Monitoring: Quality of Hypoglycaemia Detection." *Diabetes, Obesity & Metabolism* 15 (2): 130–35.