Glycaemic variability is associated with adverse cardiovascular outcomes in patients hospitalised with an acute myocardial infarction

Thora Y. Chai\textsuperscript{a,b,*}, Mark McLean\textsuperscript{b,c,d}, Vincent W. Wong\textsuperscript{e}, N. Wah Cheung\textsuperscript{a,b}

\textsuperscript{a} Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, NSW, Australia
\textsuperscript{b} Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
\textsuperscript{c} Department of Diabetes and Endocrinology, Blacktown Hospital, Blacktown, NSW, Australia
\textsuperscript{d} School of Medicine, University of Western Sydney, Campbelltown, NSW, Australia
\textsuperscript{e} Department of Diabetes and Endocrinology, Liverpool Hospital, Liverpool, NSW, Australia

ARTICLE INFO

Keywords:
Glycaemic variability
Mean amplitude of glucose excursion
Acute myocardial infarction
Major adverse cardiovascular events

ABSTRACT

Unlike admission hyperglycaemia, there is significant controversy surrounding whether acute glycaemic variability is associated with major adverse cardiovascular events (MACE) in patients immediately after an acute myocardial infarction (AMI). We conducted a retrospective post-hoc analysis in an AMI population and determined fluctuating glycaemia is associated with a higher risk of 3-month MACE.

Introduction

Glycaemic variability, defined as fluctuations in the measurement of blood glucose levels (BGLs) over a given interval of time, has been associated with increased mortality, length of stay and infections in hospitalised patients with or without diabetes [1–3]. Whether glycaemic variability is an important predictor of adverse cardiovascular outcomes following acute myocardial infarction (AMI) remains controversial, with previous studies demonstrating conflicting results [4–9]. Glycaemic variability can deleteriously affect endothelial function and oxidative stress than constant hyperglycaemia, possibly impacting on the prognosis of patients during and after an AMI [10–12].

We hypothesise that in an AMI population, an increased risk of major adverse cardiovascular events (MACE) is associated with glycaemic variability, measured as mean amplitude of glucose excursion (MAGE) and standard deviation of glucose (SD). MAGE is the arithmetic average of all BGLs exceeding 1 standard deviation above the mean BGLs within an observed period [1].

Methods

We conducted a post-hoc analysis of data from the Hyperglycaemia: Intensive Insulin Infusion In Infarction (HI-5) Study, a prospective multicentre randomised controlled trial of insulin – dextrose infusion for glycaemic control amongst hyperglycaemic or diabetic patients admitted with an AMI between 2001 and 2005 [13]. The details of the protocol and the results of the study have previously been described [13]. In brief, patients with known diabetes or without diabetes with an admission BGL > 7.8 mmol/L who presented with an AMI at six hospitals in the state of New South Wales, Australia were randomised to intensive insulin therapy (received insulin – dextrose infusion therapy for at least 24 h to maintain their fingerprick BGLs between 4 and 10 mmol/L) or conventional therapy (received their usual diabetes therapy (excluding metformin) with supplemental subcutaneous short-acting insulin if fingerprick BGLs exceeded 16 mmol/L). The HI-5 study conformed with good clinical practice guidelines and the recommendations of the Declaration of Helsinki. Approval was obtained from all local ethics committees [13].

A post-hoc analysis was conducted on 121 patients from the intensive treatment arm of the HI-5 study. The systematic collection and recording of hourly capillary fingerprick BGLs in the intensive insulin therapy group provided us with the opportunity to calculate glycaemic variability and determine if any association existed with MACE. MAGE and SD were calculated using the EasyGV calculator from the University of Oxford [14] in patients with > 3 BGLs whilst on insulin – dextrose infusion. MAGE and SD values were dichotomised into HIGH (MAGE value > 2.8 mmol/L and SD value > 1.6 mmol/L) and LOW (MAGE value ≤ 2.8 mmol/L and SD value ≤ 1.6 mmol/L) groups. The values for dichotomising MAGE and SD were obtained from a prior study [2].
Patients were defined as having diabetes if they had a prior diagnosis or if their glycaemic variability could help improve clinical outcomes in patients with an AMI.

Table 1: Baseline characteristics of the AMI population categorised into high and low MAGE/SD (total n = 121).

| Variables                | HIGH (n = 61) | LOW (n = 60) | p-value |
|--------------------------|---------------|--------------|---------|
| Age (years)              | 62 (53–68)    | 64 (55–73)   | 0.26    |
| Males                    | 48 (78.7%)    | 48 (80.0%)   | 0.86    |
| Admission BGL (mmol/L)   | 11.5 (9.2–16.0) | 8.9 (7.4–9.8) | < 0.01* |
| Hypoglycaemic event(s)   | 9 (14.8%)     | 3 (5.0%)     | 0.07    |
| Length of hospital stay (days) | 7 (5–14) | 8 (5–10) | 0.97 |

Risk Factors

- Diabetes: 53 (86.9%) vs 21 (35.0%) < 0.01*
- HbA1c: 7.4% (6.6–9.0%) vs 5.9% (5.5–6.5%) < 0.01*
- mmol/mol: 57 (49–75) vs 41 (37–48) < 0.01*
- Prior AMI: 18 (29.5%) vs 11 (18.3%) 0.15
- Hyperlipidaemia: 35 (57.4%) vs 32 (53.3%) 0.66
- Hypertension: 35 (57.4%) vs 29 (48.3%) 0.32
- Current smoker: 14 (23.0%) vs 20 (33.3%) 0.16

Table 2: The effect of sequential adjustment for diabetes and AdBGL on MAGE and SD.

| Glucose Variability Metric | Adjusted for Diabetes Alone | Adjusted for Diabetes & AdBGL |
|----------------------------|------------------------------|-------------------------------|
| MAGE                       | OR (95% CI) p-value          | OR (95% CI) p-value           |
|                            | (1.39–1.73) p = 0.01*       | (0.98–1.63) p = 0.02*         |
| SD                         | 2.07                         | (1.34–3.18) < 0.01*          | (1.11–3.25) < 0.01* |

| n = 121.                  |

*p-value significant at < 0.05.

AdBGL, admission blood glucose levels; MAGE, mean amplitude of glucose excursion; SD, standard deviation of glucose; OR, odds ratio; CI, confidence interval.

Results

Baseline characteristics of the 121 subjects categorised into HIGH (n = 61) and LOW (n = 60) groups are outlined in Table 1. Sixty-one percent of the study subjects had diabetes and the mean number of fingerprick BGLs were 15 ± 4 per patient. A significantly higher proportion of subjects in the HIGH group had diabetes, an increased admission blood glucose level (BGL) and HbA1c level compared with the LOW group (Table 1). There was a trend towards an increased incidence of hypoglycaemia in the HIGH group compared with the LOW group (7.4% vs 2.5%, p = 0.07).

MACE within 3–months of hospital admission occurred in 41 patients (34%): 7 patients (5.8%) died, 14 patients (11.6%) had a cardiac arrest, 9 patients (7.4%) developed congestive cardiac failure, 6 patients (5.0%) had cardiogenic shock, 1 patient suffered a re–infarction (0.8%), 31 patients (25.6%) developed atrial/ventricular arrhythmia and 2 patients (1.7%) had a non–fattle stroke. On unadjusted analyses, no association was identified between MAGE and high MAGE (p = 0.23) or MACE and high SD (p = 0.14).

Subgroup analyses via stratification by diabetes status identified no difference in MACE outcomes (Diabetes 28.4% vs No diabetes 42.6%, p = 0.11). After separation into HIGH and LOW groups, a trend towards increased MACE occurred in subjects in the LOW group without diabetes compared to those with diabetes (38.5% vs 15.0%, p = 0.05). This was not statistically significant in the HIGH group between subjects without and those with diabetes (62.5% vs. 34.0%, p = 0.12).

When adjusted for diabetes in our regression model, an increased risk of MACE occurred with high MAGE (OR 1.37, 95% CI 1.09–1.73; p = 0.01) and SD (OR 2.07, 95% CI 1.34–3.18; p < 0.01). After adjusting for both diabetes and admission BGL in our regression model, an increased risk of MACE remained with SD (OR 1.89, 95% CI 1.11–3.25; p = 0.02). However, only a trend towards higher MACE with MAGE occurred when adjusted for diabetes and admission BGL (OR 1.27, 95% CI 0.98–1.63; p = 0.07) (Table 2).

Subgroup analyses between MACE and other risk factors for cardiovascular disease (hypertension, prior AMI, hypercholesterolaemia, smoking status) were also performed. There were no differences demonstrated in MACE among subjects with hypertension (39.1% vs 28.1%, p = 0.20), hypercholesterolaemia (31.3% vs 37.0%, p = 0.51), smoking status (36.7% vs 28.6%, p = 0.37) or a prior history of AMI (44.8% vs 30.4%, p = 0.15) and thus were not included in our adjusted regression model.

Discussion

Our study suggests that acute glycaemic variability in patients admitted immediately post AMI is associated with a higher risk of MACE. This is clinically important, as measuring and correcting inpatient glycaemic variability could help improve clinical outcomes in patients with an AMI.

It has been postulated in recent years that glycaemic variability is a determinant of vascular complications [10–12]. Fluctuating BGLs can increase oxidative stress more than sustained hyperglycaemia, particularly accelerating superoxide production in the mitochondria and vascular inflammation [12]. Vascular inflammation can occur through activation of the nuclear factor-κB and protein kinase C pathway, resulting in increased expression of adhesion molecules and excess formation of advanced glycation end products [15]. As such, reducing glycaemic variability may be a potential target to help safely reduce not only mean BGLs, but also its direct effects on vascular complications, which is particularly detrimental to patients immediately post AMI.

Both Lipska and colleagues [7] and Mellbin and colleagues [8] were unable to determine whether glycaemic variability had any association with MACE in patients admitted with an AMI. Unlike Lipska and colleagues [7], we did not adjust for hypoglycaemia in our multivariable logistic regression models, given the minimal frequency of hypoglycaemia occurring in our population. Mellbin and colleagues [8] used three differing glucose variability metrics (root mean square error, range of all BGLs within a 48 h period and best fitted regression line of BGLs over 24 h) which are not as reasonable a measure of glycaemic variability in patients with coronary artery disease, with MAGE and SD reported as independent risk factors for coronary stenosis [17,18].

Although this study has several limitations, our findings highlight the importance of monitoring and managing glycaemic variability in patients with AMI. Further research is needed to investigate the potential benefits of interventions aimed at reducing glycaemic variability in this patient population.
### Table 3

Summary of studies on the association of glycaemic variability with MACE outcomes in AMI patients.

| Study | Type of Study | Population | Diabetes | GV metric | MACE outcomes |
|-------|---------------|------------|----------|------------|---------------|
| Kosiborod et al. (2008) [5] | Retrospective | n = 16,871 | 29.0% | Mean BGL, Hyperglycaemic index, Time averaged BGL: S for ↑ mean BGL (mean BGL > 7.0) | S for ↑ mean BGL (mean BGL > 7.0) |
| Borg et al. (2011) [6] | Prospective | n = 427 | 100.0% (T2DM 37.2%) | MAGE, CONGA, SD | NS with GV metric |
| Lipska et al. (2012) [7] | Retrospective | n = 18,563 | 38.0% | Range, SD, MAGE, MAG, Average daily risk range | Unadjusted model: N S for ↑ average BGL and HbA1c |
| Mellbin et al. (2013) [8] | Retrospective | n = 578 | 100.0% (All T2DM) | Root mean square error, range, best fitted regression line over 24 h | Unadjusted model: N S; Adjusted model: N S |
| Su et al. (2013) [9] | Prospective | n = 222 | 53.6% | MAGE | Unadjusted model: S with ≥ 3.9 |
| Okada et al. (2015) [16] | Prospective | n = 57 | 49.1% | MAGE | Unadjusted model: S with MAGE (MAGE ≥ 3.3) |
| Akasaka et al. (2017) [17] | Prospective | n = 65 | 0.0% (no diabetes) | MAGE, RHI | Unadjusted model: MAGE and ↓ 3.5; Adjusted model: MAGE and ↑ RHI (MAGE ≥ 3.5) |
| Gerbaud et al. (2019) [18] | Prospective | n = 327 | 100.0% (T2DM 93.9%) | MAGE, SD | ↑ SD (SD > 2.7) |

*BGL, MAGE and SD measured in mmol/L. AMI, acute myocardial infarction; GV, glycaemic variability; MACE; major adverse cardiovascular events; BGL, blood glucose level; S, significant; NS, non-significant; T2DM, type 2 diabetes; MAGE, mean amplitude of glucose excursions; CONGA, continuous overlapping net glycemic action; SD, standard deviation of glucose; HbA1c, glycated haemoglobin; RHI, reactive hyperaemia index.

Despite a higher proportion of subjects with high MAGE/SD values having diabetes, there was no difference in MACE outcomes after stratification by diabetes status. This was a similar finding to the primary results of the HI-5 study, where no difference in mortality at any stage was demonstrated between subjects with diabetes and those without [13]. Interestingly, Kosiborod and colleagues [19] identified that subjects without diabetes had a higher proportion of MACE outcomes compared to those with recognised diabetes, although this was not found to be significant in our study. It was postulated by Kosiborod that a higher rate of MACE may have occurred in the non-diabetic cohort due to the presence of subjects with undiagnosed diabetes (particularly with admission BGLs ≥ 13.3 mmol/L) who had not received appropriate treatment for their hyperglycaemia during hospitalisation (i.e. with insulin therapy). As hyperglycaemia is toxic to the ischaemic myocardium, this therapeutic difference may have partially accounted for the disparity between diabetes status and MACE [19]. Through the HI-5 study though, stringent BGL control in patients immediately after an AMI did not improve short-term mortality [13], and as such, other factors may play a more significant role in mediating this disparity over hyperglycaemia alone.

Our study is limited by its retrospective nature. We were reliant on the BGLs recorded from the intensive insulin therapy arm of the HI-5 study only, which limited our sample size. As the HI-5 study was conducted prior to the advent of modern continuous BGL monitoring systems, we relied on hourly fingerprick BGLs, which was not present in the conventional therapy arm. Using patients only on the insulin – dextrose infusion post AMI may have reduced the degree of glycaemic variability, such as coefficient of variation or mean absolute change in glucose (MAG).

### Conclusion

Fluctuating glycaemia in AMI patients is associated with a higher risk of MACE. Further studies are needed to determine whether reducing glycaemic variability during the initial phase following AMI has therapeutic impact.

### Author contributions

TYC conceptualised the idea, carried out the post–hoc statistical analysis and contributed to the manuscript. MM & VW contributed to the Discussion section and made constructive criticism to the manuscript. NWC helped with post–hoc statistical analysis and contributed to the manuscript.

### Funding

The authors declare they have no funding source or support for this study.

### Declaration of Competing Interest

The authors declare they have no conflicts of interests.

### References

[1] Hans DeVries J. Glucose variability: Where it is important and how to measure it. Diabetes 2013;62(5):1405–8.
[2] Donati A, Damiani E, Domizi R, Boticelli L, Castagnani R, Gabbanelli V, et al.
Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. Crit Care Resusc 2014;16(1):13–23.

[3] Mendez CE, Mok KT, Ashar A, Tanenberg RJ, Calles-Escandon J, Umpierrez GE. Increased glycaemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. Diabetes Care 2013;36(12):4091–7.

[4] Hirakawa Y, Arima H, Zoungas S, Ninomiya T, Cooper M, Hamet P, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. Diabetes Care 2014;37(8):2359–65.

[5] Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalised with acute myocardial infarction: defining the optimal outcomes-based measures of risk. Circulation 2008;117(8):1018–27.

[6] Borg R, Kuenen JC, Carstensen B, Zheng H, Nathan DM, Heine RJ, Borch-Johnsen K, Witte DR. HbA1c and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. Diabetologia 2011;54(1):69–72.

[7] Lipska KJ, Venkitachalam L, Gosch K, Kovatchev B, Van den Berghe G, Meyfroidt G, et al. Glucose variability and mortality in patients hospitalized with acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2012;5(4):550–7.

[8] Mellbin LG, Malmberg K, Ryden L, Wedel H, Vestberg D, Lind M. The relationship between glycaemic variability and cardiovascular complications in patients with acute myocardial infarction and type 2 diabetes: a report from the DIGAMI 2 trial. Eur Heart J 2013;34(5):374–9.

[9] Su G, Mi SH, Tao H, Li Z, Yang HX, Zheng H, et al. Impact of admission glycaemic variability, glucose and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care 2013;36(4):1026–32.

[10] Okada K, Hibi K, Gohbara M, Kataoka S, Takano K, Akiyama E, et al. Association between blood glucose variability and coronary plaque instability in patients with acute coronary syndromes. Cardiovasc Diabetol 2015;14:111. https://doi.org/10.1186/s12933-015-0275-3.

[11] Akasaka T, Sueta D, Tabata N, Takashio S, Yamamoto E, Izuimiy Y, et al. Effects of the mean amplitude of glucose excursion and vascular endothelial dysfunction on cardiovascular events in nondiabetic patients with coronary artery disease. J Am Heart Assoc 2017;6(5):e004841. https://doi.org/10.1161/JAHA.116.004841.

[12] Gerbaud E, Darier R, Montaudo M, Beaufieux MC, Coffin-Boutreux C, Coste P, et al. Glycaemic variability is a powerful independent predictive factor of midterm major adverse cardiovascular events in patients with diabetes with acute coronary syndrome. Diabetes Care 2019;42(4):674–81. https://doi.org/10.2337/dc18-2047.

[13] Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek HV, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005;111(23):3078–86.