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Association of perioperative glucose profiles assessed by continuous glucose monitoring (CGM) with prognosis in Chinese patients with non-ST-elevation acute coronary syndrome: a cohort study protocol

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ABSTRACT

Introduction Non-ST-elevation acute coronary syndrome (NSTE-ACS) remains a significant clinical concern, accounting for over 70% of acute coronary syndrome cases. One well-established risk factor for NSTE-ACS is abnormal glucose metabolism, which is associated with a poor prognosis postpercutaneous coronary intervention. Effective monitoring of blood glucose is crucial in diabetes care, as it helps identify glucose metabolic imbalances, thereby guiding therapeutic strategies and assessing treatment efficacy. Continuous glucose monitoring (CGM) provides comprehensive glucose profiles. Therefore, the study aims to use CGM to track perioperative glucose variations in NSTE-ACS patients and to determine its prognostic implications.

Methods and analysis This is a multicentre, prospective observational study in a sample of patients (aged >18 years) with NSTE-ACS. A total of 1200 eligible patients will be recruited within 1 year at 6 sites in China. The primary composite endpoint will be determined as major adverse cardiovascular events (MACE) at 3 years. MACE includes all-cause mortality, non-fatal myocardial infarction, non-fatal stroke and target vessel revascularisation. Employing the CGM system, glucose levels will be continuously monitored throughout the perioperative phase. Prespecified cardiovascular analyses included analyses of the components of this composite and outcomes according to CGM-derived glucometrics at baseline.

Ethics and dissemination This study has received approval from the Medical Research Ethics Committee of The First Affiliated Hospital of the University of Science and Technology of China (No. 2022KY357) and will adhere to the moral, ethical and scientific principles outlined in the Declaration of Helsinki. All participants will provide written informed consent prior to any study-related procedures. Findings from the study will be shared at conferences and published in peer-reviewed scientific journals.

Trial registration number ChiCT2300069663.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multicentre, prospective study design.
⇒ Integration of continuous glucose measurements during the percutaneous coronary intervention procedure.
⇒ A continuous glucose monitoring (CGM) wear duration is set at 14 days.
⇒ Characterisation of CGM data collected from 1200 non-ST-elevation acute coronary syndrome individuals.
⇒ The initial phase of CGM sensor implantation necessitates tissue fluid saturation to ensure accurate data readings, leading to a preliminary gap in data acquisition.

INTRODUCTION

In recent years, while the incidence of ST-segment elevation myocardial infarction (STEMI) has seen a decline, the incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) has surged. Currently, NSTE-ACS accounts for over 70% of ACS diagnoses, marking it as a prevalent clinical emergency.[1] NSTE-ACS, divided into non-STEMI (NSTEMI) and unstable angina (UA) based on myocardial injury biomarkers, encompasses conditions such as resting angina, incipient angina, worsening and variant angina. Although NSTEMI and UA share similar pathogenesis and clinical manifestations, their severity varies, mainly determined by the extent of ischaemia causing myocardial injury detectable through biomarkers.[2 3] Although hospital mortality for NSTE-ACS patients is reportedly lower than for those with STEMI, there exists a

heightened risk of recurrent myocardial infarction, rehospitalisation and long-term mortality.[4 5]

Disturbances in glucose metabolism are a well-estabolished risk factor for NSTE-ACS. Persistent hyperglycaemia, stress-induced hyperglycaemia, hypoglycaemia and erratic glucose shifts not only undermine vascular endothelial cell function and instigate apoptosis but also correlate with a bleak prognosis postpercutaneous coronary intervention (PCI) in NSTE-ACS patients.[6–8] Elevated mortality rates are observed among NSTE-ACS patients undergoing hyperglycaemic events.[9] Post-PCI, the prognosis of NSTE-ACS patients with poor glycaemic control is worse than their well-regulated counterparts.[8 10] Furthermore, hypoglycaemic episodes during hospital stays escalate mortality risks and major complications.[11] Emphasising the urgency, prompt identification and remediation of abnormal glucose metabolism in NSTE-ACS patients become paramount.

Abrupt glucose level swings amplify reactive oxygen species generation via the protein kinase C pathway by activating nicotinamide adenine dinucleotide phosphate oxidase activation, which in turn exacerbates endothelial apoptosis, endothelial dysfunction and oxidative stress.[12–15] Underlying mechanisms contributing to perioperative hyperglycaemia during cardiac procedures encompass insulin resistance and disrupted insulin efficacy. Concomitantly, surgical stress elevates stress hormone concentrations, including cortisol, glucagon, epinephrine, norepinephrine and growth hormone. In addition, factors such as intraoperative haemodynamic maintenance of epinephrine and perioperative medication like low molecular heparin and β-blockers further compound hyperglycaemic conditions. The state of acute hyperglycaemia impairs the diastolic function of vascular, impedes the synthesis of nitric oxide in endothelial cells and hampers complement activity. Furthermore, there is an upsurge in lymphocyte and endothelial adhesion molecules and cytokines expression, bolstered neutrophil chemotaxis and phagocytosis, and intensified inflammatory response, predisposing individuals susceptible to infection and multiorgan dysfunction.

In addition to the adverse effects of hyperglycaemia, hypoglycaemia also contributes to vascular endothelial damage by promoting the upregulation and release of vasoactive substances, initiating inflammatory responses and stimulating the autonomic nervous system, further exacerbating myocardial ischaemia and potentially inducing arrhythmias.[16] Existing microvascular and macrovascular disease in patients with diabetes can affect outcomes related to tight glycaemic control.[17] For instance, patients experiencing cardiac autonomic dysfunction have a heightened risk of developing arrhythmias in the presence of hypoglycaemia, while those with diabetes coupled with endothelial dysfunction exhibit a more pronounced response to hypoglycaemia.[18] Consequently, the management of diabetes should not only focus on the average glucose concentration and glycated haemoglobin but also on the fluctuation of blood glucose.

Blood glucose monitoring is one of the core elements of diabetes management. Recently, guidelines, both national and international, have emphasised the use of the continuous glucose monitoring system (CGMS) as a complementary tool,[19] addressing limitations inherent to conventional glucose monitoring. CGMS measures glucose concentration in subcutaneous interstitial fluid, offering a comprehensively view of daily glucose variations, including extreme values and responses to factors like diet or medication. It uniquely identifies postprandial hyperglycaemia, hidden night hypoglycaemia and the dawn phenomenon often overlooked by self-monitoring of blood glucose and glycated haemoglobin A1c. Additionally, its software calculates metrics like time in target range (TIR), time in above range or time in below range, coefficient of variation and mean amplitude of glycaemic excursion (MAGE). These insights enhance clinicians' understanding of patient glucose trends, informing evidence-based decisions and bolstering the quality of patient care.

Objectives

The purposes of this study are to (1) evaluate the relationship between CGM-derived glucometrics and the incidence of MACE; (2) characterise the data collected from the CGM; (3) assess the impact of stress conditions on perioperative glucose levels; (4) identify microvascular complications and (5) probe into potential genetic, metabolic, behavioural and environmental risk factors, as well as their interplay, in relation to NSTE-ACS.

METHODS AND ANALYSIS

Study design

This is a multicentre, prospective observational study that aims to explore the relationship between CGM-derived glucometrics and the incidence of MACE in a sample of adults with NSTE-ACS. The study will be conducted across six sites: the First Affiliated Hospital of the University of Science and Technology of China, the First Affiliated Hospital of Anhui Medical University, the Anhui Provincial Maternal and Child Health Hospital, the First Affiliated Hospital of Wannan Medical College, the First Affiliated Hospital of Bengbu Medical College and the Bozhou People's Hospital.

Patient and public involvement

Patients were not directly involved in developing research questions, study design, intervention designs, outcome measures, recruitment and conducting of the study.

Study population

Patients admitted with NSTE-ACS are currently being recruited. This includes patients with NSTEMI and UA. In this prospective cohort study, the inclusion and exclusion criteria are as follows.

Inclusion criteria (all must be present)

1. Age ≥18 years.

2. Hospitalised with an incident NSTE-ACS.
3. Patients with NSTE-ACS with very high-risk features require immediate PCI if indicated, patients with NSTE-ACS and high-risk features should undergo PCI within 24 hours.
4. Able to provide informed consent.

Exclusion criteria (all must be absent)

1. Presence of severe disease including malignancy, cirrhosis, human immunodeficiency virus (HIV) positivity or a life expectancy <1 year.
2. Presence of severe hepatic or renal insufficiency (aspartate aminotransferase (AST) or alanine aminotransferase (ALT)>3 times the upper reference limit; estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2).
3. Preoperative haemoglobin levels <100 g/L, having received erythropoietin or a blood transfusion in the preceding 3 months, or exhibiting severe coagulation disorders (platelet count <100×10^9/L or international normalised ratio >1.7) and hypercoagulable states (such as erythrocytosis, platelet count ≥ 450×10^9/L).
4. Recent use (within the last 3 months) of glucocorticoids or cyclosporine.
5. Diagnosis of connective tissue diseases.
6. Presence of a history of heart transplantation, pacemaker implantation, cardiomyopathies or congenital/valvular heart diseases.
7. Pregnant, planning pregnancy or breastfeeding women.
8. Presenting with a fever.
9. Engagement in other drug or medical device studies within 1 month preceding this study's enrolment.
10. Inability to cooperate with follow-up visits.

Participants are systematically assessed for eligibility, and those who meet the specified criteria are invited to participate in the current study. All patients who provide consent are then enrolled. On admission, patients receive reperfusion therapy via PCI, consistent with the clinical guidelines in effect at the time of the study. The PCI is performed either through the radial or femoral artery, following standard techniques employed by cardiologists at catheterisation laboratory. Prior to the PCI, patients will administer a loading dose of 300 mg of aspirin in combination with either 300 mg of clopidogrel or 180 mg of ticagrelor.

Sample size

Referring to a previous study,[20] the observed incidence of MACE was 26.9% in the higher glucose group compared with 14.9% in the control group. A priori analysis used G*Power software, wherein the significance level α=0.01, test efficacy power (1−β)=0.99, and the sample ratio of the exposed group to the control group was established at 1:1, resulting in a sample size of 1008 cases. Accounting for a 15% drop-out rate, the necessary sample size was adjusted to 1186 participants, with a plan to include 1200 individuals.

Data collection

Sociodemographic variables will include age, sex, educational level and employment status (table 1). Clinical data related to the index cardiac admission will include NSTE-ACS type (UA or NSTEMI), Killip classification and ECG changes. Laboratory tests will include cardiac biomarkers (initial and peak), initial creatinine and lipid profile. Other variables will include in-hospital interventions, thrombolysis in myocardial infarction flow, left ventricular ejection fraction (LVEF) and major in-hospital events. Discharge data will include medication. Selected variables will be used to calculate the Global Registry of Acute Coronary Events 3.0 risk score,[21] which has been validated as a predictor of death in patients with NSTE-ACS. Variables related to medical history include prior cardiac history, risk factors and comorbidities. These data will be collected at baseline from standard questionnaire and hospital medical records.

Definition of NSTEMI and UA

Patients presenting with acute chest pain or equivalent signs and symptoms but without persistent ST-segment elevation or its equivalents on the ECG are provisionally diagnosed with NSTE-ACS.[22] These patients may exhibit various ECG alterations, including transient ST-segment elevation, persistent or transient ST-segment depression and T-wave abnormalities such as hyperacute T waves, T wave inversion, biphasic T waves, flat T waves and pseudonormalisation of T waves. Alternatively, the ECG may be normal. The majority of patients in this category who subsequently display a typical rise and fall in cardiac troponin levels (ie, fulfilling MI criteria as per the fourth universal definition of MI) will receive a final diagnosis of NSTEMI.[22] Conversely, in other patients, the troponin level will remain below the 99th percentile, leading to a final diagnosis of UA.[22] UA is characterised as myocardial ischemia at rest or during minimal exertion, without the presence of acute cardiomyocyte injury or necrosis. Specific clinical manifestations include prolonged angina (>20 min) at rest; newly onset, severe angina; increased frequency, duration or decreased threshold of angina or angina following a recent MI episode.[22]

Continuous glucose monitoring

A CGM device will be used to monitor the subcutaneous interstitial glucose levels. Concisely, the sensor of the CGM system will be inserted into the abdomen immediately on hospital admission and will be maintained in position for a duration of 14 days. This procedure culminates in a thorough daily record, encompassing 288 consecutive sensor readings. Subsequently, the data are retrieved from the system, culminating in the generation of an ambulatory glucose profile. Several crucial parameters (table 2), collectively referred to as glucometrics, associated with glycaemic control, can be deduced from the CGM, including TIR, MAGE and GV.

Table 1 Summary of measurements at baseline and follow-up in the cohort

Item	Measurements	Baseline survey and resurvey	Follow-up
Sociodemographic information	Age, gender, education level, insurance marital status, occupation, income	X	
Health behaviour	Frequency of smoking, alcohol consumption	X	X
Disease history	Hypertension, diabetes mellitus, MI, PCI, CABG, stroke, COPD, dyslipidaemia, angina pectoris, Angina pectoris, HF, VHD, arrhythmia, hypercholesterolaemia, CKD, PAD	X	X
Medication history	Antihypertensive, lipid-lowering, antidiabetic, antiplatelet, traditional Chinese medicine	X	X
Family history of disease	CHD, stroke, diabetes mellitus	X	
Physical measurements	Blood pressure, heart rate, height, weight, BMI	X	X
Laboratory tests	TC, TG, HDL-C, LDL-C glucose urine protein, ketone body, occult blood	X	X
CGM metric	TIR, TAR, TBR, MAGE, CV	X	X
Imaging examinations	ECG, carotid ultrasound echocardiogram	X	X

'X' indicates the procedure/item is conducted at that visit. This schedule would be adjusted based on the latest guidelines and the specific requirements of the study.
BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, coefficient of variation; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MAGE, mean amplitude of glycaemic excursion; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TAR, time in above range; TBR, time in below range; TC, total cholesterol; TG, triglyceride; TIR, time in target range; VHD, valvular heart disease.

Follow-up and endpoint definitions

The study is scheduled to commence in January 2024 and conclude in December 2027. Subjects will be monitored at designated intervals of 1, 3, 6, 12, 24 and 36 months subsequent to discharge through telephone interviews, outpatient consultations or a comprehensive review of medical records. The events corresponding to these endpoints will be rigorously evaluated by proficient physicians.

Primary outcome

The primary outcome will be MACE at 3 years post-PCI, which includes all-cause death, non-fatal myocardial infarction, non-fatal stroke and unplanned target vessel revascularisation (TVR).

Secondary outcome

1. An expanded composite cardiovascular outcome is defined as all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, revascularisation (coronary and peripheral) and hospitalisation for heart failure or UA at 3 years.
2. An additional composite outcome is defined as cardiac death, non-fatal myocardial infarction and TVR at 3 years.
3. Incidence of individual MACE components at 3 years.
4. The cumulative MACE rate at 5 years.

All-cause mortality is delineated as death resulting from any origin, encompassing both cardiac and non-cardiac causes. Cardiac death refers to fatalities resulting from any cardiac-related ailment. Reinfarction is characterised by chest pain persisting for ≥20 min and accompanied by new electrocardiographic alterations (Q waves >0.04 s or ST-segment elevation >0.1 mV) and/or an additional rise in biomarkers (creatine kinase, creatine kinase-MB or cardiac troponin).[23] TVR is defined as a repeat revascularisation of the infarct-related vessel, driven either by ischaemia or clinical necessity. Participants will be monitored for a minimum duration of 3 years, irrespective of the attainment of the primary endpoint, unless circumstances involve death, loss of contact or voluntary withdrawal from the research.

Statistical analysis

The analysis and presentation of results will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines specifically designed for observational studies.[24] Descriptive statistics will be used to compare the baseline characteristics of patients by CGM-derived glucometrics. Adjustment will be undertaken for baseline differences in potential confounding variables. Associations between each of the potential mediators with glucose profiles and the various health outcomes will be explored using regression methods. Adjusted analyses will be undertaken to consider any potential confounders of these associations. A sensitivity analysis will also be conducted to evaluate the model's stability. Statistical analyses will be performed using the R software (V.4.3.1 or later).

Table 2 Key metrics for CGM data analysis and reporting

CGM metric	Short description	Reference
TIR	Measures the percentage of time spent in consensus target glucose range 70–180 mg/dL (3.9–10.0 mmol/L)	Battelino *et al*[25]
TBR	Measures the percentage of time spent with glucose <70 mg/dL (<3.9 mmol/L), including readings <54 mg/dL (<3.0 mmol/L)	Battelino *et al*[25]
TAR	Measures the percentage of time spent with >180 mg/dL (>10.0 mmol/L), including readings >250 mg/dL (>13.9 mmol/L)	Battelino *et al*[25]
eA1C	A linear transformation of the mean glucose value, meant to estimate the HbA1C blood test. Calculated by the following formula: (46.7+mean (glucose))/28.7	Nathan *et al*[26]
J_index	This index was designed to stress the importance of the two major glycaemia components: the mean level and the variability of glycaemia. Calculated by the following formula: $0.001\times(\text{mean (Glucose)}+\text{SD(Glucose)})^2$	Wójcicki[27]
MAGE	Mean amplitude of glycaemic excursions (MAGE), an index for glycaemic variability. This index is focused on the amplitude of blood glucose changes, and as such it takes into account only changes in the blood glucose (either upward or downward) that are large enough to be considered significant responses—exceeding one SD of the blood glucose for the same 24 hours period.	Service *et al*[28]
MODD	Mean difference between glucose values obtained at the same time of day (MODD). This is a measure of glycaemic variability that is calculated by taking the mean of the absolute differences between glucose values measured at the same time, a day apart.	Service *et al*[28]
CV	A measure of dynamic glucose variability expressed as percentage CV and calculated as 100 × (SD divided by mean glucose); CV is correlated with time below range	Rodbard[29]
HBGI	High blood glucose index (HBGI) is a measure used to assess the variability and magnitude of high blood glucose levels in individuals with diabetes. It provides a quantitative indication of how often and how severely blood glucose levels exceed the target range. Prior to calculation, the blood glucose levels are transformed using a nonlinear transformation to create a symmetric distribution around the 'clinical centre' and create equal-sized intervals for hyperglycaemic and hypoglycaemic ranges (without this transformation the range of hyperglycaemia is much larger than the range for hypoglycaemia).	Kovatchev *et al*[30]
LBGI	Low blood glucose index (LBGI) is a numerical metric used to assess the extent of low blood glucose levels or hypoglycaemia in individuals with diabetes. It quantifies the risk and severity of hypoglycaemic events.	Kovatchev *et al*[30]

CGM, continuous glucose monitoring; CV, coefficient of variation; eA1C, estimated A1C; HbA1C, haemoglobin A1c; TAR, time above range; TBR, time below range; TIR, time in range.

Strengths and limitations

There are several strengths in our study. It is a multicentre study that incorporates continuous glucose measurements during the intervention and boasts a 14-day CGM wear period. Furthermore, we will examine novel risk factors, including gene mutations and multiomics-derived biomarkers. However, this study also has inherent limitations. First, during the initial implantation of CGM sensors, a tissue fluid saturation phase is essential for ensuring optimal sensor adhesion and accurate glucose readings. This phase, unfortunately, may impede immediate data collection, resulting in a brief lack of glucose data. Second, although CGM devices provide critical insights into glucose dynamics, their prolonged wear time poses potential challenges, such as issues with device adhesion, adverse skin reactions and mechanical disruptions. Situations such as device detachment or sensor malfunction can lead to discontinuities in the glucose record. Third, due to the study's observational nature, establishing a direct causal relationship between CGM-derived glucometrics and MACE is speculative, leaving room for potential residual confounding. Fourth, our participant pool is restricted to Chinese patients, which might limit the generalisability of our findings. Lastly, as our cohort includes only hospitalised patients, one should exercise caution when extrapolating these results to other demographics.

In summary, the study will elucidate the comprehensive glucometabolic state using a CGM device administered following the onset of NSTE-ACS by establishing a cohort

study. Additionally, it will illuminate the impact of perioperative glucose profiles, assessed by CGM, on the short-term and long-term prognosis of NSTE-ACS patients, thereby providing crucial evidence.

ETHICS AND DISSEMINATION

This study was approved by the Medical Research Ethics Committee of the first affiliated hospital of USTC (N0.2022KY357). The study will be performed in compliance with applicable local legislation and in accordance with the ethical principles in the Declaration of Helsinki. Eligible patients will be well informed of the purpose and schedule of this study. Written informed consent will be obtained by research physicians or nurses if patients decide to participate. All clinical data will be confidentially collected by research members. Findings of the study will be disseminated through publication in peer-reviewed scientific journals as well as relevant medical conferences.

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Contributors The study concept and design were conceived by SL, XZ and HH. HZ, JS, JW and XW will conduct data collection. Project administration and governance will be conducted by YD and JW. Analysis will be performed by JS and HZ. JS and HZ prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

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