The Prognostic Value of Capillary Glucose Levels in Acute Stroke
The GLycemia in Acute Stroke (GLIAS) Study

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Background and Purpose—Evidence is accumulating regarding the prognostic influence of hyperglycemia in patients with acute ischemic stroke. However, the level associated with poor outcome is unknown. Our objectives were to establish the capillary glucose threshold with the highest predictive accuracy of poor outcome and to evaluate its hypothetical value in influencing functional outcome by adjusting for other well-known prognostic factors in acute stroke.

Methods—The authors conducted a multicenter, prospective, and observational cohort study of 476 patients with ischemic stroke within less than 24 hours from stroke onset. Capillary finger-prick glucose and stroke severity were determined on admission and 3 times a day during the first 48 hours. Poor outcome (modified Rankin Scale >2) was evaluated at 3 months.

Results—The receiver operating characteristic curves showed the predictive value of maximum capillary glucose at any time within the first 48 hours with an area under the curve of 0.656 (95% CI, 0.592 to 0.720; P<0.01) and pointed to 155 mg/dL as the optimal cutoff level for poor outcome at 3 months (53% sensitivity; 73% specificity). This point was associated with a 2.7-fold increase (95% CI, 1.42 to 5.24) in the odds of poor outcome after adjustment for age, diabetes, capillary glucose on admission, infarct volume, and baseline stroke severity and with a 3-fold increase in the risk of death at 3 months (hazard ratio, 3.80; 95% CI, 1.79 to 8.10).

Conclusions—Hyperglycemia ≥155 mg/dL at any time within the first 48 hours from stroke onset, and not only the isolated value of admission glycemia, is associated with poor outcome independently of stroke severity, infarct volume, diabetes, or age. (Stroke. 2009;40:562-568.)

Key Words: acute stroke ■ hyperglycemia ■ outcome ■ stroke care

Recently, evidence has been accumulating about the prognostic influence of hyperglycemia in patients with acute ischemic stroke (IS), and it is becoming an important issue in stroke management.1,2 Several studies have demonstrated that hyperglycemia on admission is a common characteristic in acute stroke, involving more than 50% of patients and which affects all stroke subtypes.3 High glucose levels on admission have been related to poor outcome independent of age, stroke severity, or stroke subtype4 and may counterbalance the beneficial effect of tissue plasminogen activator-induced recanalization.5,6 Most previous studies have focused on admission hyperglycemia rather than on a prospectively recorded glucose level profile. However, glycemia is a continuous physiological parameter that can increase in stressful situations, thereby exerting a deleterious effect on stroke outcome due to sustained increased levels within the first hours from stroke onset. In fact, persistent hyperglycemia on serial glucose monitoring was associated with infarct expansion and poor functional outcome.7 The majority of previous studies have used predefined cutoff levels of glycemia.3,4,6,7 Although a linear relationship between hyperglycemia and stroke outcome is possible, from a clinical point of view, it would be interesting to identify a capillary glucose threshold predicting poor outcome that could serve as a reference for starting corrective treatment.

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562
Our primary objective was to establish the capillary glucose threshold with the highest predictive accuracy of poor outcome, and the secondary objective was to evaluate its hypothetical value in influencing functional outcome by adjusting for other well-known prognostic factors in acute IS.

Methods

Study Design

The GLIAS Study (GLycemia In Acute Stroke) is a multicenter, prospective, observational study promoted by the Stroke Project of the Cerebrovascular Disease Study Group of the Spanish Society of Neurology conducted from January 2002 to December 2003 in 7 university hospitals, all with a Stroke Unit in the Department of Neurology (see participant list in the “Acknowledgments”). Consecutive patients with acute IS of less than 24 hours from symptom onset were included. Exclusion criteria were transient ischemic attack, coma at admission, prior functional dependency (modified Rankin Scale [mRS] >2), and comitant disease with life expectancy <3 months.

All patients were managed following current international guidelines. During the first 24 hours, patients were not allowed to be fed and maintenance intravenous fluids with 0.9% normal saline were provided. After the first 24 hours, feeding was initiated. Those patients with good consciousness levels and no hypoglycemia were orally fed; otherwise, continuous nasogastric tube feeding was initiated. Glucose-lowering therapy was at the discretion of the treating physician and consisted of titrated intravenous or subcutaneous insulin and/or oral hypoglycemic agents.

The following parameters were recorded in a specific data bank: (1) demographic characteristics (age, sex); (2) vascular risk factors such as hypertension (defined as the existence of a previous clinical diagnosis of arterial hypertension, regular treatment with antihypertensive drugs, or the existence of ≥2 prestroke readings ≥140 and/or 90 mm Hg), diabetes mellitus (previous diagnosis and/or current treatment with insulin or oral hypoglycemic medications), hypercholesterolemia (previous diagnosis and/or current treatment with lipid-lowering drugs), and (3) coronary artery disease, arrhythmic heart failure, symptomatic peripheral vascular disease (intermittent claudication, critical leg ischemia or previous intervention by amputation, reconstructive vascular surgery or angioplasty in one or both legs due to atherosclerotic disease), renal disease (previous diagnosis of renal failure or diabetic or hypertensive nephropathy), obesity, and cigarette smoking (current or in the last year). Patient information regarding prior vascular risk factors and previous diseases was collected from medical charts and confirmed by patient interviews by the physician in charge; (3) previous stroke history; (4) prior antiplatelet treatment; (5) time from stroke onset to emergency department arrival; (6) stroke etiologic subtype, classified following published criteria as large vessel disease, cardioembolic, small vessel disease, cerebral infarction of uncommon etiology, or cerebral infarction of undetermined etiology; and (7) stroke severity, which was evaluated by an experienced neurologist using the Canadian Neurological Scale (CNS) admission, at arrival at the Neurology Ward or Stroke Unit, and 3 times a day during the first 2 days. The CNS measures level of consciousness (alert 3.0; drowsy 1.5), orientation (oriented 1.0, disoriented/not applicable 0.0), speech (normal 1.0; expressive deficit 0.5; receptive deficit 0.0), and weakness (score 0 to 5) in face, arms, hands, and legs with a total score ranging from 1.5 (maximum deficit) to 10 (absence of deficit). This scale can be categorized as ≤6 (severe stroke) and >6 (mild–moderate stroke).

Capillary finger-prick glucose (mg/dl), blood pressure (mm Hg), body temperature (°C), and stroke severity (CNS) were determined on admission (emergency room), at arrival at the Neurology Ward or Stroke Unit, and 3 times a day during the first 2 days. Regarding capillary glucose levels, 2 variables were considered for the analysis (admission values and the point of maximum capillary levels within the first 48 hours for each patient, which also included the admission value). A brain CT was performed on all patients on admission and was repeated within the first week in 344 patients according to physician criteria. The volume of hypodensity (mL) was calculated in the second scan according to the formula \(0.5 \times a \times b \times c\) (where \(a\) and \(b\) are the largest perpendicular diameters measured on CT and \(c\) is the slice thickness).

The mRS was used to evaluate the outcome of patients at 3 months (±15 days) in a follow-up visit at an outpatient clinic. This scale is defined with 7 different grades (0 indicates no symptoms; 1, no disability despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death). Dichotomization (mRS of ≤2 good outcome, mRS of >2 poor outcome) has been extensively used in stroke studies. Recently, analyses across the distribution of scores rather than dichotomization have been reported to improve the statistical power for detection of clinically meaningful differences. For the purpose of our study, the principal outcome measure was poor outcome defined as mRS of >2 at 3 months. Further analyses across the distribution of scores considering capillary glucose levels were also developed. Because it is expected that an equal proportion of patients will lie above and below the cut off point of mRS ≤2, a sample of 400 patients will allow CIs of sensitivity and specificity of overall amplitude <14%.

Statistical Analysis

Statistical analysis was performed by 2 independent professional statisticians in SPSS 12.0 and the R Development Core Team (Version R.2.2.0, 2005) with the rpart software package. Continuous data are presented as mean±SD or median and interquartile range (interquartile range, 25th to 75th percentile) in the case of distributions that were not normal. Discrete data are given as counts and percentages. Proportions between groups were compared using the \(\chi^2\) test. The role of capillary glucose levels on stroke prognosis was analyzed in several steps. First, a receiver operating characteristic curve analysis was conducted to determine the predictive value of the area under the curve as well as a cut point of admission glycaemia and maximum glucose levels within the first 48 hours that better distinguish between favorable and unfavorable outcomes. We considered the point at which the sum of specificity and sensitivity was highest and then gave the same weight to false-positives and false-negatives. Second, univariate and multivariate-adjusted forward stepwise logistic regression models were constructed to adjust for the effect of admission and maximum glucose levels on outcome for factors that showed significant differences in the univariate analysis. Significance was tested by the likelihood ratio. Variables with a value of \(P<0.2\) on univariate testing were included. Those continuous variables that were not normally distributed were categorized and included in the logistic regression analysis as follows: body temperature on admission ≥37.5°C and CNS on admission ≤6. Infarct volume was categorized using the median value as a cut point. Third, an exploratory classification tree was built with those independent prognostic factors to assess the prognostic role of hyperglycemia. This theoretical approach does not make the assumption that the coefficient estimate for one variable is the same independent of the specific value of the other prognostic variables and could be considered a tool to explain the prognostic weight of factors adjusted for the other variables. Finally, survival time was estimated from Kaplan-Meier survival curves and tested for statistical significance with a log rank test. Estimated hazard ratios and 95% CIs were calculated by fitting a Cox proportional hazards survival model. For all tests, a probability value <0.05 was considered statistically significant.

Results

A total of 476 inpatients with acute IS admitted during the study period who fulfilled the inclusion criteria were included. No data about patients screened during the study period who met exclusion or no inclusion criteria were collected. Demographic data, risk factors, and stroke diagnosis is shown in Table 1. The median time from stroke onset to emergency department arrival was 5 hours (interquartile...
range, 2 to 10). Mean glucose levels on admission were 137.2±57.2 mg/dL. Patients with diabetes had higher mean glucose levels within the first 48 hours than those without diabetes (228.9±66.45 mg/dL versus 134.2±35.9 mg/dL). Median infarct volume was 32.42 mL (interquartile range, 4.75 to 91.07). Four hundred eleven patients (83% of the total) completed the 3-month (±15 days) follow-up period. Of those, 156 patients (38%) had poor outcome at 3 months.

The receiver operating characteristic curves for maximum capillary glucose within the first 48 hours showed an area under the curve of 0.656 (95% CI, 0.592 to 0.720; P<0.01) and pointed to 155 mg/dL admission capillary glucose (34.6% sensitivity; 80.3% specificity) and 155 mg/dL (8.5 mmol/L) maximum capillary glucose within the first 48 hours (53% sensitivity; 73% specificity) as the optimal cutoff levels for poor outcome at 3 months (Figure 1). The adjusted forward stepwise multiple logistic regression analysis showed that maximum capillary glucose within the first 48 hours ≥155 mg/dL was an independent predictive factor (OR, 2.734; 95% CI, 1.425 to 5.244) of poor outcome after adjustment for age, diabetes, admission capillary glucose levels, stroke severity on admission, and infarct volume (Table 2). One hundred thirteen (23.9%) patients had admission capillary glucose levels ≥155 mg/dL, but 27 of them maintained normal levels within the next 48 hours. From the 359 patients with admission glucose levels <155 mg/dL, the repeated capillary measurements allowed the identification of 64 patients (17.8%) who developed glucose levels ≥155 mg/dL within the first 48 hours. Differences in the distribution of mRS scores at 3 months using this cutoff point of capillary glucose are shown in Figure 2. Patients with diabetes had higher frequency of poor outcome at 3 months than those without diabetes (47.6% versus 34.8%; P=0.013). However, when analyzing those patients with maximum capillary glucose within 48 hours ≥155 mg/dL, there were no differences in outcome regarding the diagnosis of diabetes (51.6% versus 56.7%; P=0.319).

A new receiver operating characteristic curve analysis including those variables independently related to poor outcome in the logistic regression model (age, CNS on admission ≥6, infarct volume >32 mL, and maximum glucose within the first 48 hours ≥155 mg/dL) showed improvement in the predictive value for poor outcome for this combination with an area under the curve of 0.88 (95% CI, 0.840 to 0.921; P<0.001; Figure 1, dotted line). An exploratory classification tree (Figure 3) with those variables independently related to poor outcome in the logistic regression model (age, CNS on admission ≥6, infarct volume >32 mL, and maximum glucose within the first 48 hours ≥155 mg/dL) was built to test the stability of the prognostic role of maximum glucose at any time within the first 48 hours ≥155 mg/dL, if the statistical modeling assumptions are changed. The predictive role of this value of capillary glucose was clear not only in patients with more severe strokes and infarct volume >32 mL.
but also in patients with lower infarct volumes but older than 69 years of age (predicted class probability 0.7).

Of the total 411 who completed the 3-month follow-up period, 51 died (12.4%). The mortality rate was greater in the group of patients with maximum capillary glucose within the first 48 hours \( \geq 155 \, \text{mg/dL} \) (23.2% versus 5.9%; \( P < 0.001 \)).

Kaplan-Meier survival curves showed a higher risk of death for patients with maximum capillary glucose \( \geq 155 \, \text{mg/dL} \) at any time within the first 48 hours from stroke onset (log rank \( P < 0.01 \); Figure 4). The Cox proportional hazards survival model confirmed that maximum capillary glucose \( \geq 155 \, \text{mg/dL} \) within the first 48 hours from stroke onset was independently associated with a higher risk of death at 3 months (hazard ratio, 3.80; 95% CI 1.02–13.50).

![ROC curve Glu-max24h, AUC=0.656 (0.592-0.720)](image)

![ROC curve LR, AUC=0.880 (0.840-0.921)](image)

**Table 2. Logistic Regression Analysis of Poor Outcome at 3 Months (mRS >2)**

<table>
<thead>
<tr>
<th></th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( P )</td>
<td>OR</td>
</tr>
<tr>
<td>Age</td>
<td>(&lt;0.001)</td>
<td>1.051</td>
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<tr>
<td>Female gender</td>
<td>0.028</td>
<td>1.567</td>
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<td>Heart disease</td>
<td>(&lt;0.001)</td>
<td>2.169</td>
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<td>Hypertension</td>
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<td>1.547</td>
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<tr>
<td>Diabetes mellitus</td>
<td>0.020</td>
<td>1.707</td>
</tr>
<tr>
<td>Renal disease</td>
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<td>2.677</td>
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<tr>
<td>Cigarette smoking</td>
<td>0.053</td>
<td>0.642</td>
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<tr>
<td>CNS on admission ( \geq 6 )</td>
<td>(&lt;0.001)</td>
<td>10.941</td>
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<tr>
<td>Systolic blood pressure on admission</td>
<td>0.190</td>
<td>1.005</td>
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<tr>
<td>Body temperature on admission ( \geq 37.5 , ^\circ \text{C} )</td>
<td>0.030</td>
<td>2.604</td>
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<tr>
<td>Admission glycemia ( \geq 155 , \text{mg/dL} )</td>
<td>0.015</td>
<td>1.708</td>
</tr>
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<td>Capillary glucose ( \geq 155 , \text{mg/dL} ) within the first 48 hours</td>
<td>(&lt;0.001)</td>
<td>2.985</td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>(&lt;0.001)</td>
<td>3.755</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>(&lt;0.001)</td>
<td>4.647</td>
</tr>
<tr>
<td>Infarct volume ( &gt;32 , \text{mL} )</td>
<td>(&lt;0.001)</td>
<td>10.742</td>
</tr>
<tr>
<td>Corrective treatment of hyperglycemia within the first 48 hours</td>
<td>0.023</td>
<td>1.644</td>
</tr>
</tbody>
</table>

*Forward stepwise (likelihood ratio) multivariate logistic analysis, variables included in the analysis but not in the final equation, number of subjects. at risk for each variable is shown parentheses: female gender (144), heart disease (104), hypertension (130), diabetes (73), renal disease (15), cigarette smoking (67), systolic blood pressure on admission, body temperature on admission \( \geq 37.5 \, ^\circ \text{C} \) (20), admission glycemia \( \geq 155 \, \text{mg/dL} \) (77), large vessel disease (89), cardioembolism (101), and corrective treatment of hyperglycemia within the first 48 hours (211). Number of subjects at risk for variables included in the final equation: CNS on admission \( \geq 6 \) (138), capillary glucose \( \geq 155 \, \text{mg/dL} \) within the first 48 hours (107), infarct volume \( >32 \, \text{mL} \) (140).
Our study demonstrates that capillary glucose \( \geq 155 \text{ mg/dL} \) (8.5 mmol/L) at any time within the first 48 hours is associated with a higher risk of poor outcome in patients with IS independent of age, stroke severity, or infarct volume. It also shows the superiority of capillary glucose within the first 48 hours over isolated admission determination in predicting outcome. The predictive value of capillary glucose \( \geq 155 \text{ mg/dL} \) for poor outcome was modest (sensitivity 53%; specificity 73%), which could be related, at least in part, to the high proportion of patients with acute stroke with hyperglycemia in the acute phase. However, further analyses such as multivariate regression logistic and the regression tree models confirmed the importance of this cutoff level.

The majority of previous studies carried out blood glucose analysis on admission, but it must be taken into account that blood glucose is a dynamic biological variable, so it is reasonable to think that the detrimental effects of hyperglycemia would persist beyond the first hours and its progress must be evaluated during the first days poststroke. In this respect, a retrospective study found a sustained increase of blood glucose levels during the first 12 hours after stroke, which occurred in all stroke subtypes and was greater in more severe patients.\(^1\) The development of continuous glucose monitoring devices has improved understanding of poststroke hyperglycemia. Thus, it has been shown that poststroke hyperglycemia is common and prolonged despite current guidelines-based treatment, and 2 hyperglycemic phases were identified: an early hyperglycemia phase within the first 8 hours affecting up to 50% of nondiabetic and 100% of patients with diabetes and a later phase 48 to 88 hours poststroke that affects 27% of nondiabetic and 78% of diabetic subjects.\(^2\) We have also found that patients with diabetes had higher glucose levels within the first 48 hours than patients without diabetes, but no significant differences in outcome between patients with diabetes and those without diabetes with hyperglycemia were found, suggesting that outcome is more related to the development of hyperglycemia \( \geq 155 \text{ mg/dL} \) than to the diagnosis of diabetes.

To our knowledge, our study is the first designed with the purpose of finding the capillary glucose threshold for poor outcome in patients with acute IS. Our study can be seen either as a confirmation or validation of the prediction capability of hyperglycemia or as an exploratory study of the best cutoff point. Approaches to finding admission serum glucose levels or mean blood glucose optimal concentrations

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**Figure 3.** This figure shows a prognostic classification tree provided to test the stability of the prognostic role of the maximum capillary glucose levels at any time within the first 48 hours if the statistical modeling assumptions are changed. It could be seen on the prediction probabilities, estimated by the proportion of patients with good outcome, that maximum capillary glucose levels at any time within the first 48 hours \( \geq 155 \text{ mg/dL} \) retains its prognostic value on this different model.
have recently been developed. In a multicenter study, admission serum glucose >166 mg/dL in patients without diabetes was associated with a more than 4-fold increase in case fatality compared with patients with serum glucose <103 mg/dL.18 On the other hand, in another study, mean blood glucose concentrations >186 mg/dL predicted 30-day case fatality in patients with diabetes and >114 mg/dL in patients without diabetes.19 However, it seems that mean blood glucose concentration is not a practical value for therapeutic purposes, and several limitations regarding the interpretation of admission glucose levels have been addressed2; most studies used a random glucose level obtained on admission, but other studies were based on fasting glucose levels obtained the morning after admission. Moreover, almost 20% of patients with normal glucose levels on admission could develop hyperglycemia later, as we demonstrated. Another limitation of previous studies on the prognostic influence of glycemia in acute IS is the operative definition of hyperglycemia. Most of them used predefined and arbitrary cutoff thresholds ranging from >108 mg/dL (6 mmol/L) to ≥150 mg/dL (8.3 mmol/L).3,4,6,7,17,20–25 In our study, both admission and capillary glucose levels ≥155 mg/dL at any time within the first 48 hours correlated significantly with poor outcome at 3 months, but the logistic regression analysis demonstrated the superiority of capillary glucose ≥155 mg/dL within the first 48 hours over isolated values of admission hyperglycemia. This approach is more relevant from a therapeutic point of view because this point could serve as a target concentration for starting active treatment with insulin.

To date, there are discrepancies in acute IS management guidelines. The European Stroke Initiative guidelines recommend starting insulin therapy when hyperglycemia is higher than 10 mmol/L (181 mg/dL),6,9 and the Stroke Council of the American Stroke Association recently recommend lowering the minimum threshold for insulin treatment from 300 mg/dL (2003 year guidelines)26 to 140 to 185 mg/dL (7.7 to 10.2 mmol/L), but these recommendations were based on consensus because data from interventional prospective studies were lacking.27 Although several randomized studies of insulin treatment in IS are ongoing,28,29 the published results of 2 clinical trials are controversial. Preliminary data of the Glucose in Ischemic Stroke Trial (GIST)30–32 suggested the safety and feasibility of glucose–potassium–insulin infusions with the objective of maintaining capillary glucose between 80 and 140 mg/dL. However, the recent report of final data showed no significant benefit on stroke outcome. This study has several limitations that prevent definite conclusions about the efficacy of intensive insulin therapy in patients with acute IS. First, a prettrial power calculation of sample size was not achieved; most patients included had baseline glucose levels <150 mg/dL (thus without hyperglycemia), and blood glucose was lowered by only 0.6 mmol/L.33 On the other hand, higher glucose levels reduction by aggressive treatment with continuous intravenous insulin in 46 patients with baseline glucose values ≥150 mg/dL was associated with nonsignificantly better outcomes in a recently published pilot trial (Treatment of Hyperglycemia in Ischemic Stroke).34 Although further clinical trials with this insulin regimen should be investigated to come to definite conclusions about the role of correcting hyperglycemia in patients with acute IS, this last trial included patients with a prespecified hyperglycemia criteria (≥150 mg/dL) and this point is quite close to that found in our study as independently associated with poor outcome.

We have to recognize several limitations of our study. This is a multicenter study conducted in Spain and the results do not necessarily represent a generalizable value in all populations. On the other hand, this is an observational study and although we found a negative association between capillary glucose levels ≥155 mg/dL at any time within the first 48 hours and stroke outcome at 3 months, no intervention was made that could support any intervention to lower blood glucose. The implicit suggestion that avoiding hyperglycemia >155 mg/dL would improve outcome should be tested in a clinical trial of intervention to avoid hyperglycemia.

In conclusion, capillary glucose levels >155 mg/dL at any time within the first 48 hours from stroke onset are associated...
with a higher risk of death and poor outcome in patients with acute IS independent of stroke severity, diabetes, admission glycemia, infarct volume, or age. This study provides first-time evidence from a prospective and multicenter study of a glucose level cutoff threshold for outcome in patients with acute stroke. This study has implications for future research because it gives a cutoff point of capillary glucose level that could serve as a reference in future interventional trials.

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Disclosures
None.

References
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