Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis

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**Objective:** Admission hyperglycemia has been associated with worse outcomes in ischemic stroke. We hypothesized that hyperglycemia (glucose >8.0 mmol/L), in the hyperacute phase would be independently associated with increased mortality, symptomatic intracerebral hemorrhage (SICH) and poor functional status at 90-days in stroke patients treated with intravenous (IV)-tPA.

**Research Design and Methods:** Using data from the prospective, multicenter Canadian Alteplase for Stroke Effectiveness Study (CASES), the association between admission glucose >8.0 mmol/L and mortality, SICH, and poor functional status at 90-days (modified Rankin Scale [mRS] >1) was examined. Similar analyses were conducted examining glucose as a continuous measure.

**Results:** Of 1098 patients, 296 (27%) had admission hyperglycemia, including 18% of those without diabetes mellitus and 70% of those with diabetes mellitus. After multivariable logistic regression, admission hyperglycemia was found to be independently associated with increased risk of death (adjusted RR 1.5 (CI95 1.2 to 1.9), SICH (adjusted RR 1.69 CI95 0.95 to 3.00) and decreased probability of a favorable outcome at 90 days (adjusted RR 0.7 CI95 0.5 to 0.9). An incremental risk of death, SICH and unfavorable 90-day outcomes was observed with increasing admission glucose. This held true for patients with and without diabetes mellitus

**Conclusions:** In this cohort of IV-tPA treated stroke patients, admission hyperglycemia was independently associated with increased risk of death, SICH and poor functional status at 90-days. Treatment trials continue to be urgently needed to determine if this is a modifiable risk factor for poor outcome.
Admission hyperglycemia has been associated with a worse functional outcome after ischemic stroke (1-3). Poor functional outcomes and increased mortality have been described in non-thrombolysed cohorts and increased rates of intracerebral hemorrhage (ICH) have been found in the few studies which exclusively examined patients treated with intravenous tissue plasminogen activator (IV-tPA) (4-6). Baseline hyperglycemia is found more commonly in patients with pre-existing diabetes mellitus, but is also present in a significant proportion of non-diabetic patients (1). A causal relationship between elevated glucose and worse outcomes has not yet been proven but current guidelines suggest that excessive hyperglycemia be treated in acute stroke patients (7). Trials of insulin therapy to treat hyperglycemia in acute stroke are ongoing (GRASP trial, www.grasptrial.org) and two smaller studies have been published showing equivocal results (8, 9).

The bulk of previous studies exploring the role of hyperglycemia in stroke have included only non-thrombolysed patients. Glucose values were measured beyond the hyperacute (≤3 hours) phase and several of these studies pooled ischemic and hemorrhagic strokes in their analyses (1-3, 10). The few studies of admission glucose in tPA-treated ischemic stroke patients have all been relatively small (largest 748 patients) (4-6, 11-15); some were retrospective (5, 14), examined only ICH (5) or short-term (< 30 days) outcomes (12, 14, 15), or included patients treated with IV tPA beyond 3 hours (6, 14) or with intra-arterial tPA (IA-tPA) (11). We sought to determine whether in a large national cohort of stroke patients treated with standard protocol IV-tPA, elevated admission glucose was associated with worse outcomes, particularly disability, death and symptomatic ICH (SICH).

**RESEARCH DESIGN AND METHODS**

Data prospectively collected in the Canadian Alteplase for Stroke Effectiveness Study (CASES) were analyzed (16). This was a national prospective cohort study that lead to the full approval of IV-tPA for acute ischemic stroke in Canada. Sixty sites across the country participated over a period of 2.5 years and where relevant, each center obtained institutional ethics approval for data collection. If patients were incapacitated by their stroke, next of kin provided informed consent. Patients were treated at the discretion of the site neurologist according to Canadian guidelines for intravenous thrombolytic treatment in acute stroke (17).

Baseline demographic data were obtained as were pre-treatment basic blood tests, data regarding timing of drug administration and stroke subtype as determined by the site investigator using the Oxfordshire Community Stroke Project (OCSP) classification. Baseline glucose was determined prior to IV-tPA administration, either by laboratory blood testing or from capillary blood. The particular method used was determined by the site’s own usual practice and not specifically recorded. The severity of the baseline neurological deficit was assessed with the National Institute of Health Stroke Scale (NIHSS) prior to treatment. The NIHSS is a validated 11-domain systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit, such that a higher score corresponds to a more severe deficit (mild 0-15, severe >15, maximum 42). The outcome was measured using the 5-point modified Rankin Scale (mRS) at 90 days by clinicians who were not necessarily blinded to patients' baseline glucose values. A favorable outcome was defined as a mRS score of 0–1.

All patients underwent a follow-up head computed tomography (CT) scan at 24–
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48 h. Baseline and follow-up CT scans were centrally reviewed by a stroke neurologist and neuroradiologist blinded to clinical information, and the Alberta Stroke Program Early CT Score (ASPECTS) was applied. ASPECTS is a validated 10-point score assessing the extent of infarction in strokes of the middle cerebral artery using non-contrast CT. A lower score suggests a more extensive area of infarction (minimum score 0) (18). Symptomatic ICH was defined as any hemorrhage documented on follow-up CT associated with a decline in neurological status within the first 24 h after thrombolytic treatment as judged by the site investigator, who was not blinded to clinical information. Asymptomatic ICH involved hemorrhage on follow-up CT without associated clinical deterioration.

The definition of admission hyperglycemia was pre-specified to be a serum glucose >8.0 mmol/L in accordance with other studies (10, 13, 19). As a primary analysis, patients were dichotomized into those with admission hyperglycemia and those without hyperglycemia and compared with regard to baseline characteristics, rate of SICH, functional outcome at 90 days and death. A secondary analysis examined the association of these outcomes with admission glucose as a continuous measure.

Role of the funding source: The CASES study was funded in part by the Canadian Stroke Consortium, the Canadian Stroke Network, the Heart & Stroke Foundation of Canada and Hoffmann-La Roche Canada Ltd. None of the sponsors had any role in the collection, analysis or interpretation of the data.

Statistical Analysis: Standard descriptive statistics were used to report the data. Fisher’s exact test and Student’s t test were used to compare the two groups. Both binomial regression and logistic regression were used to develop models for the three outcomes of interest depending upon use.

The large sample size provided sufficient power to perform multivariable analysis. For graphical descriptions, multivariable logistic regression was used to plot adjusted curves. For tabular description of risk ratios, multivariable binomial regression was used to identify predictors of outcome using a log-link function. The final models were all parsimonious models, meaning that variables that were not significant at p<0.05 or variables that showed no evidence of confounding were eliminated from the final models. Models were developed by backwards stepwise elimination beginning with the variables listed in table 1. Analyses were conducted using STATA 8.2 (Statacorp, College Station, TX, USA).

RESULTS

Baseline characteristics: Of 1135 patients enrolled in CASES, 1098 had adequate admission glucose data for inclusion in the current study. Of these patients, median age was 73 years, 45% were women, 96% had anterior circulation stroke and 16% had pre-existing diabetes mellitus. A glucose of 8.0 mmol/L corresponded to the 75th percentile and overall, 296 (27%) patients had admission hyperglycemia. Hyperglycemia was present in 70% of those with diabetes mellitus and 18% of those without diabetes mellitus. Hyperglycemic patients were older, more likely to be non-Caucasian, have atrial fibrillation, hypertension, congestive heart failure, coronary artery disease, known diabetes mellitus and less likely to be current smokers. The greater prevalence of co-morbid illness in the hyperglycemic group is likely explained by older age and the higher proportion of diabetes mellitus. There were no differences in sex, stroke subtype or baseline stroke severity between groups (Table 1). No relationship was observed between baseline serum glucose and baseline NIHSS score.

Symptomatic ICH, 90-day outcome and death: Rates of intracerebral hemorrhage,
90-day outcomes and mortality are shown in Table 2. A total of 49 (4.5%) patients suffered SICH. Among hyperglycemic patients, this proportion was 6.8% compared to 3.6% for non-hyperglycemic patients (p=0.03), resulting in an unadjusted risk ratio of 1.87 (CI95 1.07 to 3.25) for SICH in patients with baseline glucose >8.0mmol/L (Table 2). Multivariable regression attenuated this relationship somewhat yielding an adjusted risk ratio of 1.69 (CI95 0.95 to 3.00).

Clinical outcomes at 90-days, unadjusted for confounders, are shown in Figure 1. Only 80 (27.7%) hyperglycemic patients experienced a favorable functional outcome (mRS 0-1) compared to 316 (40%) non-hyperglycemic patients (P = 0.0002). The proportion of patients who were dead at 3 month follow-up was also significantly higher among patients with admission glucose >8.0mmol/L (30.8% v 18.7% p<0.0001). Unadjusted risk ratios for favorable outcome and death among hyperglycemic patients were 0.69 (CI95 0.56 to 0.85) and 1.64 (CI 95 1.31 to 2.06), respectively.

After multivariable regression, adjusted risk ratios were 0.7 (CI95 0.5 to 0.9) for favorable outcome and 1.5 (CI95 1.2 to 1.9) for death (Table 3). Multivariable analysis found that independent predictors of 90-day outcome and death were age, baseline NIHSS, baseline CT ASPECTS and admission glucose. Each of these had a comparable magnitude of association with outcome. When dichotomized as age >80 years, baseline NIHSS >15 and ASPECTS >7, unadjusted risk ratios for favorable functional outcome were 0.64 (CI95 0.52 to 0.80), 0.40 (CI95 0.32 to 0.48) and 1.53 (CI95 1.26 to 1.86), respectively. The negative association between admission glucose and functional outcome and death persisted even after exclusion of patients with SICH, a known independent predictor of death and disability after thrombolysis (4, 20). These relationships were not different for patients with and without diabetes mellitus (no evidence of an interaction effect).

Effect of stroke subtype and severity:
No heterogeneity was found with regards to the association between baseline hyperglycemia and a favorable clinical outcome when analyzed by OCSP stroke subtype ($\chi^2$ test, p=0.80) or when comparing mild strokes (NIHSS ≤5) and moderate-to-severe strokes ($\chi^2$ test, p=0.29), suggesting a deleterious effect of hyperglycemia on outcome regardless of stroke subtype or severity.

Admission glucose as a continuous measure: Using glucose as a continuous variable, the predicted probability of SICH adjusted for age, atrial fibrillation, onset-to-treatment time and sex was calculated and represented as a fractional polynomial estimate of best fit (Figure 2, panel A). An increasing probability of SICH was seen with increasing admission glucose values. Similarly, the predicted probability of death at 90-days according to admission glucose, adjusted for age, baseline NIHSS, CT ASPECTS, onset-to-treatment time and sex was calculated and represented using a linear least squares line of best fit (Figure 2, panel B). An increasing risk of death was found with increasing baseline glucose. Finally, the predicted probability of a favorable outcome at 90-days, adjusted for age, baseline NIHSS, CT ASPECTS, congestive heart failure, atrial fibrillation and diabetes mellitus was determined, yielding an inverse relationship between admission glucose levels and the probability of achieving an mRS of 0-1 (Figure 2, panel C). The predicted probability of a favorable outcome was also determined for only those patients with baseline glucose <8mmol/L. Even among these non-hyperglycemic patients, a linear decline in the probability of a good outcome was seen with increasing glucose levels.

CONCLUSIONS
This study further confirms the relationship between admission hyperglycemia and SICH, death and poor functional outcome in ischemic stroke patients treated with IV-tPA. Our findings bolster and expand upon those of previous studies, the majority of which examined smaller numbers of non-thrombolyzed stroke patients and some of which analyzed hemorrhagic and ischemic strokes together (1-3, 10).

Published studies of baseline hyperglycemia in stroke patients treated with thrombolysis have been few, generally small and often did not report 3 month outcomes (4, 6, 12-15). However, all have suggested an increased risk of poor outcome with elevated glucose, despite using different cutoff levels to define hyperglycemia (from 7.7 to 10 mmol/L) (4, 6, 12-15). One study included 312 tPA-treated patients from the original NINDS IV-tPA trial and analyzed these together with 312 placebo-treated patients (4). This study found that regardless of treatment assignment, as admission glucose level increased, the odds for a favorable outcome progressively decreased and the odds of SICH increased (4). A recent post-hoc analysis of 748 patients from ECASS-II, a trial of IV-tPA given within 6 hours of stroke onset, examined the prognostic value of hyperglycemia at baseline and 24 hours (6). Patients were classified into 4 groups: those with isolated baseline hyperglycemia, isolated 24-hour hyperglycemia, hyperglycemia persisting at both time points and persistent normoglycemia. Thrombolyzed (n=384) and non-thrombolyzed (n=364) patients were analyzed together. Interestingly, isolated baseline hyperglycemia was not found to independently predict poor outcome or ICH. In this study, the strongest predictor of poor outcome, death and ICH was persistent hyperglycemia at baseline and 24 hours, although this was only true in patients without known diabetes. The prognostic utility of hyperglycemia exclusively in those patients treated with IV-tPA cannot be drawn since this subgroup was not analyzed separately. Two other studies of tPA treated patients, one IV and the other IA, also found that elevated glucose was an independent predictor of ICH (5, 11).

What remains unclear is whether hyperglycemia is merely an epiphenomenon of underlying stroke severity, or if it is itself directly harmful to ischemic brain tissue. After adjusting for clinical stroke severity, a dose-response relationship between baseline glucose and unfavorable outcome is still suggested by our results and those of others (1, 4, 6, 10). There is ample animal literature suggesting plausible mechanisms by which glucose may exert a deleterious effect on ischemic brain, including cellular acidosis due to anaerobic glycolysis, enhanced free radical production, increased blood-brain barrier permeability, impaired mitochondrial function, influx of intracellular Ca$^{2+}$ and cellular edema (21).

However, non-causal explanations have also been proposed. Baseline hyperglycemia may represent an acute stress response from activation of the hypothalamic-pituitary-adrenal axis causing a rise in cortisol and catecholamines, and therefore may simply be indicative of underlying stroke severity. Furthermore, it may also be a result of injury or irritation of brain areas involved in glucose regulation, a theory supported by the association of hyperglycemia with strokes involving the insula (22). Finally, hyperglycemia may reflect previously undiagnosed diabetes mellitus.

The argument for causality is also further mitigated by the equivocal results of trials targeting aggressive glucose-lowering therapy in the acute phase after stroke (8, 9). No evidence to date supports the concept that ensuring strict post-stroke normoglycemia improves outcome. The GIST-UK trial was both stopped early and underpowered, but
suggested no difference in clinical outcome between patients randomized to glucose-potassium-insulin infusion to maintain glucose levels at 4-7 mmol/L over the first 24 hours and patients given saline without glucose-lowering interventions (9). The lack of benefit may be related to the relatively late initiation of therapy after stroke (median 14 hours) and the modest mean reduction in glucose achieved in the treatment arm (0.57 mmol/L).

Our prospective cohort study is the largest yet to report upon the effect of admission glucose exclusively in stroke patients treated uniformly with IV-tPA. It confirms the notion that post-stroke hyperglycemia is a predictor of death, worse functional outcome, and SICH in thrombolized patients. This association remains true regardless of stroke subtype or severity and in patients with and without diabetes mellitus. We acknowledge that our work has several limitations. First, it is an observational study. Nonetheless, the data were prospectively collected from a large number of representative patients drawn from 60 hospitals across Canada. Second, our results are based on only a single admission glucose value. Contrary to data for acute coronary syndromes arguing that dynamic changes in glucose are not prognostically significant (23), it has recently been suggested that change in glucose over the first 24 hours among stroke patients may provide additional prognostic value (6). However, use of a single baseline glucose value presumably underestimates potential harm, since patients with the highest admission glucose levels would have most likely been treated earlier and more aggressively with glucose-lowering therapies. Also, because thrombolytic treatment is necessarily rapid, a single admission glucose level has greater clinical utility for guiding acute treatment decisions. Third, we did not collect HbA1c values and so we do not have any measures of chronic dysglycemia. However, in acute coronary syndromes, HbA1c levels convey little short term prognostic value with respect to mortality (24). Fourth, the method of blood glucose determination was not uniform, with either capillary blood or laboratory glucose measurements used at different sites. Both methods have been shown to provide comparable results in critically ill patients (25). Fifth, we have no information regarding glycemic management during hospitalization or after discharge. Last, baseline differences between both groups may be potential confounders which cannot be entirely accounted for using statistical adjustments.

While it remains unclear whether correcting elevated glucose in the acute phase after ischemic stroke is beneficial, it is apparent that admission hyperglycemia rapidly identifies patients at higher risk for poor outcomes in whom glucose levels should be closely monitored.

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Author’s Contributions: AYP was involved in study conception and design,
interpreted the data, designed the tables and wrote and edited the manuscript.

SRM was involved in study conception and design, provided guidance for the Introduction and Discussion and reviewed and edited the manuscript.

TJ was involved in study conception and design, provided guidance for the Introduction and Discussion and reviewed and edited the manuscript.

WG was involved in study conception and design, provided guidance for the Introduction and Discussion and reviewed and edited the manuscript.

AMB was involved in study conception and design, reviewed and edited the manuscript.

MDH was involved in study conception and design, performed the statistical analyses, generated the figures and reviewed and edited as well as provided guidance for the entire manuscript.

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Table 1: Baseline patient characteristics

| Clinical variable                  | Baseline glucose ≤8.0 mmol/L (n=802) | Baseline glucose >8.0 mmol/L (n=296) | p value |
|------------------------------------|--------------------------------------|--------------------------------------|---------|
| Age (years, mean (SD))            | 69.7 (13.6)                          | 71.6 (12.0)                          | 0.03    |
| Sex (female, n (%))               | 370 (46.4)                           | 125 (42.7)                           | 0.3     |
| Caucasian race n (%)              | 699 (92.6)                           | 232 (86.2)                           | 0.003   |
| Vascular risk factors n (%)       |                                      |                                      |         |
| Hypertension                      | 369 (48.1)                           | 156 (57.4)                           | 0.009   |
| Diabetes mellitus                 | 50 (6.5)                             | 116 (42.6)                           | <0.001  |
| Atrial fibrillation               | 160 (20.9)                           | 74 (27.2)                            | 0.035   |
| Dyslipidemia                      | 141 (18.4)                           | 59 (21.7)                            | 0.25    |
| Current cigarette use             | 130 (16.9)                           | 29 (10.7)                            | 0.014   |
| Ischaemic heart disease           | 165 (21.5)                           | 89 (32.7)                            | <0.001  |
| Valvular heart disease            | 30 (3.9)                             | 9 (3.3)                              | 0.85    |
| Congestive heart failure          | 41 (5.3)                             | 31 (11.4)                            | 0.001   |
| Prior stroke/TIA                  | 170 (22.2)                           | 72 (26.5)                            | 0.16    |
| Pretreatment systolic BP (mm Hg, mean (SD)) | 151 (21.6)                           | 153 (21.8)                           | 0.18    |
| Pretreatment ASPECTS (median (SD))| 8                                    | 8                                    | 0.64    |
| Baseline NIHSS (median)           | 14                                   | 15                                   | 0.14    |
| Protocol violations, all causes n (%) | 113 (14.1)                           | 39 (13.2)                            | 0.77    |
| Onset-to-treatment time (minutes, mean (SD)) | 150 (37.2)                           | 150 (38.9)                           | 0.92    |
| OCSP stroke subtype n (%)         |                                      |                                      | 0.8     |
| Total anterior circulation        | 198 (26.4)                           | 82 (31.1)                            |         |
| Partial anterior circulation      | 481 (64.1)                           | 155 (58.7)                           |         |
| Posterior circulation             | 22 (2.9)                             | 13 (4.9)                             |         |
| Lacunar                            | 49 (6.5)                             | 14 (5.3)                             |         |

(not all percentages are calculated from the total number of patients because certain clinical variables were not available for all patients)

ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.

Table 2: Outcome at 90 days and symptomatic intracranial hemorrhage in hyperglycemic and non-hyperglycemic patients with unadjusted and adjusted risk ratios in hyperglycemic (baseline glucose >8 mmol/L) versus non-hyperglycemic patients (after multivariate logistic regression). Not all percentages are calculated from the total number of patients because certain outcome variables were not available for all patients.

| Outcome variable                  | Baseline glucose ≤8.0 mmol/L (n=802) | Baseline glucose >8.0 mmol/L (n=296) | P value | Risk Ratio (CI 95) |
|------------------------------------|--------------------------------------|--------------------------------------|---------|-------------------|
|                                   |                                      |                                      |         | Unadjusted        | Adjusted        |
| Intracerebral hemorrhage, n (%)   |                                      |                                      |         |                   |
| All                               | 213 (26.6)                           | 105 (35.5)                           | 0.007   | 1.87 (1.07 to 3.25) | 1.69 (0.95 to 3.00) |
| Symptomatic                       | 29 (3.6)                             | 20 (6.8)                             | 0.03    | (0.56 to 0.85)    | (0.5 to 0.9)    |
| Outcome at 90 days, n (%)          |                                      |                                      |         |                   |
| Excellent outcome (modified Rankin scale 0-1) | 316 (40)                             | 80 (27.7)                            | <0.001  | 0.69 (0.56 to 0.85) | 0.7 (0.5 to 0.9) |
| Death from all causes (modified Rankin scale 6) | 148 (18.7)                           | 89 (30.8)                            | <0.001  | 1.64 (1.31 to 2.06) | 1.5 (1.2 to 1.9) |

mRS, modified Rankin scale
Figure Legends

Figure 1: Patient outcome at 90-day follow-up by baseline glucose (unadjusted for other predictors of outcome)

mRS, modified Rankin Scale; mRS 0–1, excellent outcome; mRS 2–3, moderate disability; mRS 4–5, severe disability; mRS 6, dead.

Figure 2:
Panel A. Probability of symptomatic ICH by baseline glucose level. Quadratic polynomial line of best fit with range 95% confidence interval lines. Adjusted for age, baseline NIHSS score, gender, onset-to-treatment time and atrial fibrillation. For each increase of 1 mmol/l of serum glucose, the relative risk of symptomatic ICH rises by 10%.

Panel B. Probability of death by baseline glucose level. The line and confidence intervals are based upon a linear regression of predicted probability of death adjusted for age, baseline NIHSS score, gender, onset-to-treatment time and baseline CT ASPECTS score. For every 1 mmol/l rise in the baseline serum glucose, the probability death at 90 days increases by an absolute risk of 2%.

Panel C. Relationship between glucose and good outcome. The line and confidence intervals are derived from a fractional polynomial regression of baseline serum glucose and the predicted probability of good outcome adjusted for age, baseline NIHSS score, baseline CT ASPECTS, gender, onset-to-treatment time. For every increase of 1 mmol/l of baseline serum glucose, the relative risk of a good outcome falls by 12%.
Hyperglycemia and stroke outcome

90-day Outcome

Glucose < 8 mM
- mRS 0-1: 40.0
- mRS 2-3: 24.9
- mRS 4-5: 16.3
- Death: 18.7

Glucose >= 8mM
- mRS 0-1: 27.7
- mRS 2-3: 24.9
- mRS 4-5: 16.6
- Death: 30.8

0 20 40 60 80 100
percent

mRS 0-1 mRS 2-3 mRS 4-5 Death

Pr(SICH)

Pr(Death)

Pr(mRS 0-1)

Glucose (mmol/l)