Impact of Admission Hyperglycemia on Stroke Outcome After Thrombolysis
Risk Stratification in Relation to Time to Reperfusion
José Alvarez-Sabín, MD, PhD; Carlos A. Molina, MD, PhD; Marc Ribó, MD; Juan F. Arenillas, MD, PhD; Joan Montaner, MD, PhD; Rafael Huertas, MD; Esteban Santamarina, MD; Marta Rubiera, MD

Background and Purpose—We evaluated the impact of admission hyperglycemia (HG) on stroke outcome in relation to the timing of reperfusion in patients treated with tissue plasminogen activator (tPA).

Methods—We studied 138 consecutive stroke patients with a documented middle cerebral artery (MCA) occlusion treated with intravenous tPA <3 hours of stroke onset. Serum glucose was determined at baseline before tPA administration. HG was defined as a glucose level >140 mg/dL. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at baseline and 24 hour. Transcranial Doppler monitoring of recanalization was conducted during the first 12 hour of stroke onset. mRS was used to assess outcome at 3 months.

Results—Median baseline NIHSS score was 17 points. At baseline, 42 (37.3%) patients were hyperglycemic and 96 (62.7%) normoglycemic. Reperfusion was achieved <3 hours of stroke onset in 32 (23%) patients, between 3 to 6 hours in 49 (36%), 6 to 12 hours in 15 (12%), and in 32 (23%) the MCA remained occluded at 12 hours. A logistic regression model revealed that baseline NIHSS score >16 points (odds ratio [OR], 3.32; 95% CI, 2.18 to 24.7; \( P=0.032 \)) and admission glucose level >140 mg/dL (OR, 5.65; 95% CI, 1.97 to 16.18; \( P=0.002 \)) independently predicted poor outcome (modified Rankin scale, 3 to 6) at 3 months. After adjusting by age, stroke severity, site of MCA occlusion, and degree of recanalization, the contribution of HG for poor outcome was higher as shorter the time to reperfusion. The highest odds for poor outcome related to HG corresponded to patients who recanalized <3 hour (OR, 3.1; 95% CI, 1.8 to 14.3; \( P=0.002 \)), as compared with those who recanalized between 3 and 6 hours (OR, 2.1; 95% CI, 1.1 to 16; \( P=0.034 \)) and between 6 to 12 hours (OR, 1.1; 95% CI, 0.7 to 21; \( P=0.43 \)). Moreover, baseline glucose level was negatively correlated \( (r=-0.45; P=0.001) \) with the degree of improvement in the NIHSS score at 24 hours after early (<3 hours) but not after delayed (>3 hours) or no recanalization.

Conclusion—The impact of admission HG on stroke outcome varies depending on the time to tPA-induced reperfusion. The detrimental effect of acute HG is higher after early than after delayed or no reperfusion. Ultra-early glycemic control before reperfusion may improve the efficacy of thrombolytic therapy. (Stroke. 2004;35:2393-2499.)

Key Words: hyperglycemia ■ outcome ■ stroke ■ thrombolysis

Thrombolytic therapy has been demonstrated to be effective in improving long-term outcome in stroke patients when given <3 hours of symptom onset.1 Rapid restoration of blood flow into the penumbra area before it is recruited into fully infarcted tissue may limit brain damage and disability after stroke. However, the beneficial effect of early reperfusion on stroke outcome may be hampered in part by a variety of factors including the extent of irreversible brain injury before recanalization, blood pressure changes during thrombolysis, and excessive glucose burden at the time of reperfusion.2,3

Hyperglycemia has been widely shown to exacerbate brain injury in a variety of animal models of focal cerebral ischemia by enhancement of intracellular acidosis in the ischemic penumbra,

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which leads to loss of ion homeostasis, mitochondrial dysfunction, and bioenergetic failure.4 Hyperglycemia has consistently increased infarct size in models of brief transient cerebral ischemia, but it had little or no effect on infarct size in models of severely prolonged or persistent ischemia without reperfusion.5,7 In humans, hyperglycemia has been shown to be detrimental in nonlacunar strokes, in which reperfusion may eventually occur, but not in lacunar strokes with little or no reperfusion.8 In stroke patients treated with tissue plasminogen activator (tPA), acute hyperglycemia has been shown to be an independent predictor of early neuro-

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logical worsening and poor long-term outcome.²,⁹ Moreover, hyperglycemia before reperfusion has been demonstrated to counterbalance, at least in part, the beneficial effect of tPA.¹⁰ However, the relative contribution of elevated glucose level on poor outcome according to the timing of recanalization has not previously been studied. Therefore, we aimed to evaluate the impact of hyperglycemia accelerating brain damage on stroke outcome by stratifying patients according to time to tPA-induced recanalization.

**Subjects and Methods**

Our target group consisted of patients with acute ischemic stroke admitted within the first 3 hours after symptom onset. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. A total of 456 consecutive patients with nonlacunar stroke involving the vascular territory of the middle cerebral artery (MCA) were evaluated between February 2001 and July 2003. Of these, 431 (94.5%) underwent urgent carotid ultrasound and transcranial Doppler (TCD) examinations. Sixty-two patients (14.4%) were excluded from the study because of insufficient acoustic temporal window for TCD examination. Three hundred ninety-eight patients had a documented MCA occlusion on TCD. Of these, 138 (34.7%) patients who fulfilled established criteria for intravenous t-PA treatment (0.9 mg/kg)¹ and with a documented MCA occlusion on TCD before therapy were included in the study.

On arrival to the emergency department, patients underwent standard neurological and cardiovascular examinations, electrocardiogram, blood chemistry, and noncontrast computed tomography (CT) before enrollment in the study. Serum glucose was determined in all patients before t-PA administration. Hyperglycemia was defined as admission blood glucose value >140 mg/dL. Blood pressure, temperature, and glucose levels were managed following the European Stroke Initiative recommendations.¹¹ In patients with suspected cardioembolic stroke, anticoagulant therapy was started in the absence of hemorrhagic transformation on the second CT performed at 36 to 48 hours. Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local ethics committee.

**TCD Assessment**

A standard TCD examination was performed in the emergency department on admission before t-PA administration (<3 hours). To assess the timing of arterial recanalization, TCD was repeated at 3, 6, and 12 hours of stroke onset. Baseline and follow-up studies were conducted by the same neurologist. The TCD examination was performed with standard 2-MHz pulsed-wave equipment. Flow velocities of the MCAs, the anterior cerebral arteries, and the posterior cerebral arteries were bilaterally recorded by the transtemporal approach. Proximal MCA occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm, accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery. Distal MCA occlusion was defined as a diffuse dampening of the mean flow velocity in the affected MCA ≥21% compared with the unaffected MCA.¹² Recanalization was diagnosed when a dampened flow appeared in a previously demonstrated proximal MCA occlusion (partial recanalization) or when a previous absent, minimal, or dampened flow came within the normal range (complete recanalization).¹²,¹³ The appearance of a low-resistance stenotic signal on follow-up was also considered complete recanalization.¹² No change in the abnormal waveforms indicated that no recanalization had occurred. According to the time of recanalization, patients were classified into 4 groups: <3 hours, 3 to 6 hours, 6 to 12 hours, or no recanalization.

**CT Studies**

On admission, all patients underwent a CT scan that was repeated at 36 to 48 hours to evaluate the presence of hemorrhagic transformation. Whenever a neurological worsening (National Institutes of Health Stroke Scale [NIHSS] decrease ≥4 points) occurred, an additional CT scan was immediately performed to rule out symptomatic intracranial hemorrhage. CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to clinical details, TCD, and laboratory data. Hypodensity on the pretreatment CT was retrospectively classified as absent, involving less than one third of the MCA territory, or involving one third or more of the MCA territory. The presence and type of hemorrhagic transformation were defined according to previously published criteria.¹⁴,¹⁵ Hemorrhagic infarction was defined as a petechial infarction without space-occupying effect, and parenchymal hematoma was defined as hemorrhage with mass effect.

**Clinical Assessment**

We assessed clinical status at baseline and 24 hours after symptom onset by means of the NIHSS, which was conducted by a stroke neurologist or a senior neurology resident not involved in obtaining sonographic information who was video-trained and certified for application of the NIHSS.¹⁶ Early neurological deterioration or improvement was defined as an increase or decrease of ≥4 points on the NIHSS score after 24 hours from baseline assessment.¹ An intracranial hemorrhage was considered symptomatic if the patient had clinical deterioration causing an increase of ≥4 points on the NIHSS and if the hemorrhage was likely to be the cause of neurological deterioration. The modified Rankin scale (mRS)¹⁷ was used to assess clinical outcome at 90 days. We defined poor outcome as mRS score ≥3.

**Statistical Analysis**

The analysis was performed with the use of SPSS 9.0 software (SPSS Inc). Statistical significance for intergroup differences was assessed by 2-tailed Fisher exact test and Pearson χ² test for categorical variables and Student t test and Mann–Whitney U test for continuous variables. The Spearman coefficient was applied to verify correlation between examined variables. A receiver-operating characteristic curve was applied to determine a cut-point of admission blood glucose that better-distinguishes between favorable and unfavorable outcome. The probability of poor outcome, dependence, and death at 3 months was assessed by forward stepwise logistic regression analysis on the basis of the maximum likelihood ratio. Variables with a value of P<0.1 on univariate testing were included. A level of P≤0.05 was accepted as statistically significant.

**Results**

We included in the study 138 patients (45% women), mean age 69±11.3 years (range, 24 to 90 years), with an acute MCA occlusion. Median NIHSS score on admission was 17 (range, 7 to 22), and mean time to treatment was 151 minutes from symptoms onset. The mean admission glucose level was 156 mg/dL (range, 84 to 369). Forty-two (37.3%) patients were hyperglycemic and 96 (62.7%) were normoglycemic. Baseline characteristics of the patients are shown in Table 1. Hyperglycemic patients were more likely to have history of diabetes mellitus than were normoglycemic patients. Stroke severity was unrelated to admission blood glucose levels.

On baseline TCD, 90 patients presented a proximal MCA occlusion and 48 a distal occlusion. In 26 patients, carotid ultrasound also revealed a severe cervical carotid artery stenosis or carotid occlusion. Recanalization was achieved within 3 hours of stroke onset in 32 (23%) patients, between 3 and 6 hours in 49 (36%), between 6 and 12 hours in 15 (12%), and in 32 (23%) the MCA remained occluded at 12 hours. Figure 1 illustrates the degree of artery reopening according to the time point of recanalization. Complete recanalization was seen in 20 (63%), 28 (61%), and 6 (38%) of patients who recanalized <3 hours, between 3 and 6 hours,
and between 6 and 12 hours, respectively. Moreover, the degree of artery reopening at different time points of recanalization was unrelated to admission glucose levels.

Clinical assessment revealed that 25 patients (18.1%) worsened, 64 (46.4%) improved, and 49 (35.5%) remained stable during the first 24 hours of admission. Admission blood glucose correlated negatively with the degree of neurological improvement at 24 hours ($r = -0.38; P = 0.001$). Figure 2 shows the relationship between glucose levels and the degree of neurological improvement according to the time of recanalization. Baseline glucose levels appeared strongly and negatively correlated ($r = -0.6; P = 0.02$) with the point improvement in the NIHSS score at 24 hours among patients who recanalized at <3 hours. However, the strength of this correlation decreased progressively as longer the time to artery reopening.

Symptomatic intracranial hemorrhage (ICH) within 48 hours of stroke onset occurred in 8 patients (5.8%). There was a trend toward higher baseline glucose level ($P = 0.083$) in patients with symptomatic ICH (171.2±31 mg/dL) than in those without symptomatic ICH (155.3±69 mg/dL). Furthermore, symptomatic ICH occurred in 0 of 32, 2 of 49 (4.1%), and in 4 of 15 (26.6%) patients who recanalized <3 hours, between 3 and 6 hours, and between 6 and 12 hours, respectively, and in 2 of 32 (6.5%) of those who remained occurred at 12 hours of stroke onset.

The median mRS score at 3 months was 3 points (interquartile range, 1 to 4 points). The mRS score was significantly lower in normoglycemic than in hyperglycemic patients ($P = 0.001$). Sixty-seven (49%) became functionally independent (mRS, 0 to 2 points) and 71 (51%) severely disable or died (mRS, 3 to 6 points) at 3 months. As shown in Figure 3, the rate of independence at 3 months varied depending on the time to reperfusion. Up to 72% of patients who recanalized <3 hours were functionally independent at 3 months, but only 18% of those who remained occluded within 12 hours presented a favorable long-term outcome. Among patients with a poor clinical outcome at 3 months, admission hyperglycemia was seen in 66%, 50%, 45%, and 42% of patients who recanalized <3 hours, between 3 and 6 hours, between 6 and 12 hours, and in those with persistent occlusion at 12 hours, respectively.

### Table 1. Demographic, Risk Factor Profile, and Baseline Clinical Findings of the Series

<table>
<thead>
<tr>
<th>Hyperglycemic, n=42</th>
<th>Normoglycemic, n=96</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71±11</td>
<td>68±9</td>
</tr>
<tr>
<td>Sex, male</td>
<td>31 (38%)</td>
<td>41 (63%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (47%)</td>
<td>32 (52%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (50%)</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>16 (15–19)</td>
<td>15 (14–19)</td>
</tr>
<tr>
<td>Right side, no.</td>
<td>23 (54%)</td>
<td>49 (51%)</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>206±54</td>
<td>126±14</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>158±21</td>
<td>158±37</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81±9</td>
<td>83±11</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.3±0.8</td>
<td>2.9±0.9</td>
</tr>
<tr>
<td>Early CT signs</td>
<td>22 (43%)</td>
<td>31 (58%)</td>
</tr>
<tr>
<td>HDMCA sign</td>
<td>21 (40%)</td>
<td>27 (53%)</td>
</tr>
<tr>
<td>Door-to-needle, min</td>
<td>73±14</td>
<td>75±26</td>
</tr>
<tr>
<td>Time-to-treatment, min</td>
<td>154±33</td>
<td>158±38</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>21 (50%)</td>
<td>52 (54%)</td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>9 (21%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>12 (29%)</td>
<td>27 (28%)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; CT, computed tomography; HDMCA, hyperdense middle cerebral artery.
Table 2 shows the relative contribution of different variables for poor outcome (mRS score, 3 to 6 points) at 3 months. Baseline stroke severity ($P<0.001$), admission glucose level ($P=0.031$), systolic blood pressure before treatment ($P=0.05$), and proximal MCA occlusion ($P=0.04$) were significantly associated with a poor outcome. However, a logistic regression model revealed that only baseline NIHSS score $\geq 16$ points (odds ratio [OR], 3.32; 95% CI, 2.18 to 4.7; $P=0.032$) and admission glucose level $>140$ mg/dL (OR, 5.65; 95%, CI, 1.97 to 16.18; $P=0.002$) independently predicted poor outcome (mRS, 3 to 6) at 3 months. These odds remained materially unchanged after exclusion of patients with symptomatic ICH.

After adjusting by age, stroke severity, site of MCA occlusion, and degree of recanalization, the contribution of hyperglycemia for poor outcome became higher as the time to reperfusion became shorter. The highest odds for poor outcome related to hyperglycemia corresponded to patients who recanalized $<3$ hours (OR, 3.1; 95% CI, 1.8 to 14.3; $P=0.002$), as compared with those who recanalized between 3 and 6 hours (OR, 2.1; 95% CI, 1.1 to 16; $P=0.034$), and between 6 and 12 hours (OR, 1.1; 95% CI, 0.7 to 21; $P=0.43$). The lowest odds for poor outcome related to hyperglycemia corresponded to patients who remained occluded at 12 hours (OR, 0.7; 95% CI, 0.1 to 23; $P=0.67$).

**Discussion**

The present study demonstrates that the impact of admission hyperglycemia on stroke outcome varies depending on the time to tPA-induced reperfusion. The detrimental effect of acute hyperglycemia is higher after early than after delayed or no reperfusion. Baseline glucose level negatively correlated with the degree of neurological improvement after reperfusion. Moreover, the strength of this correlation decreased over time to arterial occlusion, being significant only after early ($<3$ hours) recanalization. After adjusting by other potential confounders such as age, stroke severity, site of MCA occlusion, and degree of recanalization, the odds for poor outcome decreased progressively as longer the time to artery reopening. These observations are in line with experimental and human studies, indicating that the detrimental role of hyperglycemia is linked to the occurrence of recanalization and mainly exerted into the penumbra area. So, the shorter the time to reperfusion, the larger the extension of ischemic penumbra to be reperfused and the higher the contribution of hyperglycemia in accelerating the recruitment of ischemic brain tissue into infarction.

Hyperglycemia is frequently seen in the acute phase of ischemic stroke affecting up to 20% to 50% of patients at presentation. Even if an important proportion of these patients have diabetes, hyperglycemia may be also caused by stress mediated by the release of cortisol and norepinephrine in nondiabetic. High glucose levels induce anaerobic metabolism and free radical production, leading to direct membrane lipid peroxidation and cell lysis in the cerebral penumbra. However, it may cause cell injury indirectly by triggering intracellular biochemical cascades and increasing early gene expression like c-fos and cyclooxygenase-2.

A post hoc analysis of the National Institute of Neurological Disorders and Stoke (NINDS) trial demonstrated that admission blood glucose is associated with poor outcome and symptomatic ICH. Moreover, admission hyperglycemia has been consistently demonstrated to be associated with a lesser degree of neurological improvement and to be a powerful predictor of clinical worsening in stroke patients receiving thrombolytic therapy. Previous studies demonstrated that glucose levels higher that 140 mg/dL, may counterbalance the beneficial effect of tPA treatment in stroke patients. Moreover, the present study suggests that the impact of acute hyperglycemia on early clinical course and long-term outcome depends on the extent of ischemic penumbra to be reperfused, which, in turn, is closely related to the duration of arterial occlusion. Magnetic resonance imaging studies have demonstrated that the extent diffusion-weighted imaging/perfusion-weighted imaging mismatch, a surrogate of ischemic penumbra, decreases progressively over time from stroke onset to imaging. Further, admission hyperglycemia has
been shown to be associated with a higher degree of diffusion-weighted imaging lesion growth and with a lesser extent of penumbral tissue salvaged. We hypothesize that an excessive glucose burden at the time of reperfusion may accelerate the recruitment of penumbral tissue into infarction and that this effect decreases gradually as the extent of penumbra reduces over time of arterial occlusion. However, hyperglycemia would have little or no impact on tissue evolution and outcome after delayed or no recanalization. There are other alternative mechanisms contributing to a greater reperfusion injury in hyperglycemic patients at earlier time points of recanalization, such as greater reactive oxygen species production during reperfusion at shorter time points, which may promote a rapid expansion of ischemic damage.

The present study has some limitations. In our study, blood glucose was measured on admission before tPA administration. However, it may not accurately indicate the glucose burden that reaches the ischemic tissue at the time to reperfusion. This may be especially relevant after early administration of insulin, which might ameliorate the impact of admission hyperglycemia particularly in those patients who experienced delayed or no recanalization. However, persistent hyperglycemia has been shown to be a frequent phenomenon during the acute of stroke even after standard insulin therapy. Therefore, more aggressive glycemic control regimens are required such as glucose/potassium/insulin infusion, which has demonstrated to be a safe and effective approach to rapidly achieve euglycemia in patients with acute stroke.

In conclusion, the impact of admission hyperglycemia on stroke outcome varies depending on the time to tPA-induced reperfusion. The detrimental effect of acute hyperglycemia is higher after early than after delayed or no reperfusion. Ultra-early glycemic control before reperfusion may improve the efficacy of thrombolytic therapy.

Acknowledgments
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References

TABLE 2. Relative Contribution of Different Variables for Poor Outcome (mRS 3–6) at 3 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS 0–2, n=67</th>
<th>mRS 3–6, n=71</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±11</td>
<td>70±9</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex, male</td>
<td>36 (53%)</td>
<td>34 (63%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (53%)</td>
<td>31 (48%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (21%)</td>
<td>16 (23%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Statins treatment, no.</td>
<td>9 (13%)</td>
<td>7 (10%)</td>
<td>0.41</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>15 (11–18)</td>
<td>18 (16–20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right side, no.</td>
<td>37 (55%)</td>
<td>35 (49%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>156±54</td>
<td>206±94</td>
<td>0.031</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>145±21</td>
<td>172±37</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85±10</td>
<td>87±12</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.3±0.8</td>
<td>2.9±0.9</td>
<td>0.67</td>
</tr>
<tr>
<td>Early CT signs</td>
<td>25 (38%)</td>
<td>28 (43%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>35 (40%)</td>
<td>59 (83%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Door-to-needle, min</td>
<td>73±14</td>
<td>79±26</td>
<td>0.27</td>
</tr>
<tr>
<td>Time-to-treatment, min</td>
<td>151±34</td>
<td>158±32</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>39 (58%)</td>
<td>34 (47%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>10 (14%)</td>
<td>16 (23%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>18 (27%)</td>
<td>21 (30%)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin score.


**Editorial Comment**

**Prime Time for Proactive Blood Glucose Control?**

There is overwhelming evidence that hyperglycemia is detrimental in cerebral ischemia, not only from experimental research but also from an increasing number of clinical studies. Elevated admission glucose levels are associated with increased mortality and worse functional outcome from ischemic stroke. In human magnetic resonance imaging studies, tissue at risk will progress to infarction in the presence of high blood glucose level, and diffusion-weighted imaging lesion will grow even in recanalized patients receiving thrombolytic therapy. The mechanisms of hyperglycemia depend on reperfusion in patients receiving recombinant tissue plasminogen activator (rtPA) treatment. Moderately elevated admission blood glucose (≥140 mg/dL) emerged as the only independent predictor of poor outcome in patients recanalized by rtPA when controlled for stroke severity.

In a re-analysis of the National Institute for Neurological Disorders (NINDS) rtPA Trial, increased admission blood glucose level was independently associated with decreased odds for neurological improvement and the risk of symptomatic intracerebral hemorrhage was increased by 75% per each 100 mg/dL of blood glucose.

In accordance with these studies, the data from Helsinki showed an increased risk of hemorrhagic change by 42% per each mmol/L of admission blood glucose in a logistic regression model.

This year, Leigh et al found that in patients recanalized by rtPA, blood glucose was higher in those who deteriorated, compared with those who improved, and moderately elevated blood glucose was more common in those with poor outcome (OR, 5.67; P = 0.009). Of recanalized patients with elevated blood glucose and a poor outcome, the majority (55%) had diabetes as compared with those with good outcome (42%). From their earlier work, Alvarez-Sabin et al concluded that admission hyperglycemia is associated with a lesser degree of neurological improvement, greater infarct size, and worse outcome after rtPA-induced recanalization.

One limitation of the current study is the case series design with no randomization to intensive glucose lowering therapy. Stroke severity as well as timing of recanalization were unrelated to admission blood glucose levels, emphasizing that both the level blood glucose and stroke severity, as measured by National Institutes of Health Stroke Scale (NIHSS) score,
were independent predictors of poor outcome at 3 months. However, hyperglycemic patients were two times more likely to have diabetes (50%) than normoglycemic patients (25%). Although there was no difference in the proportion of diabetics in patients with good or poor outcome, it is impossible to completely exclude the possibility that diabetes with associated angiopathic end-organ manifestations would have partially explained the worse outcome in hyperglycemic patients with early recanalization.

The key result from this study is that even a moderate degree of admission hyperglycemia predicts poor outcome in patients recanalized by 6 hours after onset of stroke, and the blood glucose level has an inverse correlation with the degree of improvement in the NIHSS score at 24 hours only in patients recanalized within the first 3 hours, as demonstrated by transcranial Doppler ultrasound.

What are the clinical implications? Significantly decreased mortality by aggressive blood glucose lowering has already been proven in non-neurological intensive care, and has already been widely adopted.12 High admission blood glucose is certainly a risk factor for poor outcome in ischemic stroke patients receiving rtPA. Several questions remain unanswered, however. Does the risk disappear if blood glucose is rapidly lowered, or does it remain high because of a pre-existing metabolic disturbance at the cellular level? Should untreated hyperglycemia, with or without diabetes, be a relative contraindication to rtPA?

Finally, rapidly accumulating evidence inevitably casts some doubts on current guidelines recommending active treatment of only extreme degrees of hyperglycemia (European Stroke Initiative, >10 mmol/L; American Stroke Association, >300 mg/dL [16.63 mmol/L]).13 The relationship between admission hyperglycemia and worse outcome is supported by substantial evidence, both in diabetic and nondiabetic stroke patients.14,15 Although randomized therapeutic trials are still awaited,16 we should ask whether it is time for a more proactive blood glucose control.

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Perttu J. Lindsberg, MD, PhD

References
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