Hyperglycemia (HG), a common phenomenon in all types of acute strokes, is increasingly considered as a potential therapeutic target in ischemic stroke because there is now strong evidence that high glucose levels are independent predictors of larger infarct size, poor clinical outcome, and higher risk of mortality.1 In the past few years this has led many acute stroke centers to initiate intensive insulin therapy (IIT) policies often modeled on intensive care unit practices. Unfortunately, the initial enthusiasm for IIT in the intensive care unit has disappeared because currently available evidence-based data fail to identify any clinical benefit at the time of continuing to outline the high risk of hypoglycemia.2 Furthermore, in the neurocritical care setting, the increased frequency of hypoglycemia may result in higher mortality.3 Finally, the UK Glucose Insulin in Stroke Trial (GIST-UK) failed to demonstrate any benefit from IIT in 933 patients with stroke.4 Five other small randomized trials were not powered to demonstrate a clinical benefit, but all showed that IIT induced a high risk of hypoglycemia in patients with acute stroke.5–10

It may be time for an interlude. As highlighted by others, there is a need for safer methods of improving glucose control before launching large randomized trials.1,11 We will also argue here that the proper design of large trials may require further experimental work and proof-of-concept human studies, which in turn may benefit from some results obtained in the past decade. It should be stressed that HG is a complex phenomenon in acute stroke and may result from known diabetes or undiagnosed diabetes, metabolic syndrome, acquired insulin resistance, stress response, and lesion size or its location. Furthermore, despite many theories, the mechanism of HG toxicity in acute stroke remains to be clearly elucidated.

Correlation Between HG and Stroke Outcome in Large Clinical Series

Admission HG in Ischemic Stroke
A 2001 systematic review reported that an admission glucose level >6 to 8 mmol/L was associated with higher in-hospital or 30-day mortality (relative risk, 3.07; 95% CI, 2.50–3.79) and poor functional outcome (relative risk, 1.41; 95% CI, 1.16–1.73) in nondiabetic patients with stroke.12 Many data have since accumulated from randomized trials and open cohorts. In randomized trials, admission HG considered as a continuous variable was an independent predictor of neurological outcome in the National Institute of Neurological Disorders and Stroke (NINDS), the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS),13 and the pooled analysis of the Stroke-Acute Ischemic NXY Treatment (SAINT) I and II trials14 but not in the European Cooperative Acute Stroke Study (ECASS) I and II trials.15,16 However, it was not associated with altered effectiveness of recombinant tissue plasminogen activator (rtPA) in the NINDS trial.13 Admission HG also predicted symptomatic intracerebral hemorrhage (SICH) in the NINDS13 and the Pro-Urokinase for Acute Cerebral Thromboembolism (PROACT) II trials17 but not in ECASS I and II.18 In PROACT II, categorization of glucose levels suggested that the risk of SICH increases >11 mmol/L. In Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR), which is the largest postmarketing rtPA register including 16 049 patients, admission HG was an independent predictor of good outcome and symptomatic hemorrhage. Moreover, in patients not undergoing any acute interventions, 1 study showed a linear increase in the risk of severe hemorrhagic transformation (parenchymal hematoma) of ischemic stroke related to increasing blood glucose.19

Interestingly, when glucose levels were considered as categorical variables, the cutoff values were lower for functional independence (>6.7 mmol/L) than for SICH (>10.0 mmol/L).20 The cutoff glucose values were lower in nondiabetic than in diabetic patients. In the GRASP register, admission HG (>8 mmol/L) was also independently associated, in nondiabetic and diabetic patients, with a lower rate of excellent outcome and a higher rate of SICH.21 Further modelization also suggests that cutoff glucose values are lower for excellent outcome than for SICH. In both registers,
admission HG was also an independent predictor of mortality. Lacunar stroke may be an exception because moderate HG (8–12 mmol/L) has been found to be associated with a good outcome,22 confirming an earlier finding.23

Prolonged HG in Ischemic Stroke
In the ECASS II trial, 24 hours or persistent hyperglycemia (>7.8 mmol/L) but not baseline HG were independent markers of poor outcome, death, and SICH in nondiabetic patients.16 Similar findings were reported in 3 large cohorts of patients using cutoff glycemia values varying between 7.2 and 8.6 mmol/L.24–26

Admission HG in Hemorrhagic Stroke
In a pooled analysis of 8 trials and 2164 patients with aneurysmal subarachnoid hemorrhage, the mean admission blood glucose level was 9.3 mmol/L and the OR for poor outcome associated with hyperglycemia was 3.1 (95% CI, 2.3–4.3).27 Evidence for the association of HG on clinical outcomes in spontaneous hemorrhagic stroke is more limited; few studies have found admission HG in nondiabetic patients with spontaneous hemorrhage to be independently associated with greater early, 30-day, or 3-month mortality,28–30 whereas in a recent study, only a history of diabetes mellitus, but not HG on admission, remained an independent predictor of death at 3 months.31

In summary, there is no doubt that HG at baseline and during the first days of ischemic stroke are independent predictors of death, poor outcome, and SICH after thrombolysis. However, the relationships are complex, probably reflecting the complexity of glucose regulation impairment in patients with acute stroke. The glycemic thresholds may be different in nondiabetic and diabetic patients and may be lower for predicting good outcome than increased risk of SICH. Finally, it should be stressed that these statistical relationships may not imply a causal relationship.

Experimental Evidence of Glucose Toxicity
A comprehensive review of all the putative mechanisms that may lead to HG toxicity in acute stroke is outside of the scope of this review. We concentrate on the data showing that HG may increase infarct size in experimental models of focal ischemia. The issue is complex, because in some experimental designs, HG appears to have a protective effect, although in most conditions, it is toxic.32,33 In rats with reversible middle cerebral artery (MCA) occlusion, HG reduces the duration of the therapeutic window for recanalization.34–36 In these studies, large infarcts already occur after 15 to 45 minutes of MCA occlusion in HG rats, whereas they only appear after 60 to 90 minutes in normoglycemic rats. The difference is dramatic because final infarct sizes are 5- to 10-fold larger in HG than in normoglycemic rats. In permanent MCA occlusion models, HG is associated with larger infarct size in species that have large penumbral areas in collaterally perfused regions such as cats or monkeys. Hence, after permanent MCA occlusion,37,38 the final infarct size affected 10% to 15% of the MCA territory in normoglycemic and 30% to 40% in HG cats. These effects are observed independently of the technique used to induce HG and are prevented by preischemic insulin infusion,32,33 strongly suggesting that HG has deleterious effects on focal ischemia models. The underlying mechanisms remain debated. Hyperglycemia may accelerate the transformation of ischemic penumbra into infarction as a result of lactate accumulation and acidosis, which can be directly toxic or trigger different mechanisms eventually leading to infarction. HG may also enhance reperfusion damage, although this remains challenged.36,39

To our knowledge, there is no experimental evidence that late postischemic HG has an effect on final infarct size or functional outcome. What has been shown is that early postischemic HG has a less deleterious effect than pre- or intraischemic hyperglycemia on final infarct size in rats and cats.34,38 Surprisingly, there are very few reports on the effect of postischemic insulin treatment in hyperglycemic animals. Two studies reported the results in 12 rats and 10 cats.38,40 Early death occurred in 5 of the 12 rats (presumably from severe hypoglycemia), which could not be included in the

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Table. Summary of Prospective, Randomized Controlled Trials That Report Clinical Outcome on Intensive Insulin Treatment in Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Definition of Hyperglycemia, mmol/L</th>
<th>Mean Plasma Glucose on Admission Treatment/Control Group, mmol/L ± SD</th>
<th>Outcome at 3 Mo Treatment/Control Group(s) (% of Patients in Each Group) P</th>
<th>Recruitment From Stroke Onset Within, H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staszewski⁶</td>
<td>50</td>
<td>7.0–10.0</td>
<td>8.3 (±0.9)</td>
<td>mRS 0–2 (1 mo) 46% vs 29%</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vs 8.1 (±0.8)</td>
<td>Death 4% vs 8%</td>
<td>0.50</td>
</tr>
<tr>
<td>Bruno⁶</td>
<td>46</td>
<td>&gt;8.3</td>
<td>14.4 (±4.4)</td>
<td>mRS 0–2 52% vs 47%</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vs 15.1 (±5.6)</td>
<td>Death 7% vs 0%</td>
<td>NS</td>
</tr>
<tr>
<td>THS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston⁴</td>
<td>74</td>
<td>&gt;6.1</td>
<td>9.3 (tight control; IQR, 7.9–12.7)</td>
<td>mRS 0–1 42% vs 25% vs 33%</td>
<td>NS</td>
</tr>
<tr>
<td>GRASP</td>
<td></td>
<td></td>
<td>9.3 (loose control; IQR, 7.4–12.3)</td>
<td>Death 13% vs 4% (tight vs conventional)</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.9 (conventional; IQR, 7.4–10.3; median)</td>
<td>25% vs 4% (loose vs conventional)</td>
<td>0.05</td>
</tr>
<tr>
<td>McCormick⁴</td>
<td>40</td>
<td>&gt;7.0</td>
<td>8.31 (±2.79)</td>
<td>mRS 0–2 (1 mo) 16% vs 13%</td>
<td>NS</td>
</tr>
<tr>
<td>SELESTIAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray⁴</td>
<td>933</td>
<td>6.0–17.0</td>
<td>7.8 (IQR, 6.8–9.2)</td>
<td>mRS 0–2 27% vs 29%</td>
<td>NS</td>
</tr>
<tr>
<td>GIST-UK</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

THIS indicates Treatment of Hyperglycemia in Ischemic Stroke; GRASP, Glucose Regulation in Acute Stroke Patients; SELESTIAL, Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic Acidosis; GISK-UK, UK Glucose Insulin in Stroke Trial; IQR, interquartile range; mRS, modified Rankin Scale; NS, nonsignificant; NR, not reported.

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histological analysis and the infarct size of the remaining rats was similar to those of the control group. Four cats had also an early death due to malignant MCA infarct and the insulin-treated group had the largest infarct size.

**Imaging Studies**

The few available imaging studies strongly suggest that the experimental toxicity of early HG also occurs in patients with acute stroke. A pioneering MRI study reported that HG reduced salvage of perfusion–diffusion mismatch tissue from infarction and resulted in greater infarct size, but had no deleterious effect in patients without penumbra. Furthermore, a higher glucose level was associated with greater lactate production, which in turn was independently associated with reduced salvage of penumbral tissue. In this study, glucose levels <7.0 mmol/L were associated with >80% of penumbra salvage and >8.0 mmol/L with <50% salvage. In another small series of patients treated with rtPA <3 hours and described as recanalized, patients with glucose levels >9.9 mmol/L had larger infarct growth on MRI.

Another study also showed that persistent HG was associated with larger MRI infarct growth at a later time. Ribo and coworkers further investigated this issue by studying diffusion-weighted imaging infarct growth in 30 rtPA-treated patients with initial intracranial arterial occlusion at the same time as monitoring arterial recanalization timing with transcranial Doppler. They found that high glucose level (>7.8 mmol/L) during arterial occlusion time was the best predictor of infarct growth, which was approximately 2.7 times faster in patients with HG. In this series, the time before arterial recanalization associated with poor outcome was only 3.5 hours in patients with HG, whereas it was 7.5 hours in patients with adequate glucose control. Recently, in a series of 94 patients with MRI-proven intracranial artery occlusion within 6 hours of stroke onset, infarct growth was independently predicted by the extent of ischemic penumbra, arterial recanalization, and baseline glucose >7.0 mmol/L. Infarct growth associated with HG was approximately 3-fold larger in nonrecanualized than in recanualized patients. These data are consistent with the association of HG with an increased transformation of penumbra into infarct and with a shorter time window for efficient penumbra salvage. This may explain that HG attenuates the effect of rtPA on infarct growth in the 3-to 6-hour window and does not affect rtPA efficiency in the much shorter time window of the NINDS trial. It remains to be proven that postischemic insulin treatment may limit infarct growth. This was not found in the Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic Acidosis (SELESTIAL) trial, although GKI decreased lactate accumulation at Day 3. Conversely the patients without arterial recanalization had larger infarct growth when treated by IIT.

The reperfusion lesion hypothesis is supported by 2 transcranial Doppler studies in rtPA-treated patients. In the first, HG predicted poor outcome in recanalized but not in nonrecanalized patients. In the second, the best correlation between early neurological outcome and glycaemia occurred in patients who recanalized earlier. However, the work presented here suggests that the statistical results are mainly driven by the progressive decrease of good outcome rate with increasing time to reperfusion in the normoglycemic group, whereas the HG group seems to have equally poor outcome independently of recanalization delay or occurrence. Therefore, although the reperfusion lesion hypothesis cannot be excluded, the data are also consistent with a shorter time window for efficient recanalization in patients with HG. HG may also reduce the rate of arterial recanalization, although this finding was not reproduced in other series.

In summary, the current imaging data in humans are consistent with the experimental results suggesting that baseline HG may increase infarct growth in the penumbral area and decrease the time window for efficient arterial recanalization. They do not rule out the existence of recanalization lesions. They also suggest, in agreement with large clinical studies, that the cutoff for “toxic” HG is low, approximately 7.0 mmol/L.

**Randomized Trials of IIT in Acute Stroke**

The available randomized controlled trials do not currently support the efficiency of IIT in acute stroke (Table).
GIST-UK trial was the only trial to be primarily designed to assess the effect on clinical outcome. The study enrolled 933 patients before being stopped due to slow enrolment. There was no trend toward better functional outcome (OR, 0.96; 95% CI, 0.70–1.32) for modified Rankin Scale >3 and OR, 0.84; 95% CI, 0.59–1.20 for Barthel Index <9) or decreased mortality (OR, 1.14; 95% CI, 0.86–1.5). The study had some major limitations that could solely explain the ineffectiveness of the IIT in acute stroke: only a very small difference of mean glucose level was achieved between the treatment and the control group (0.57 mmol/L), and the percentage of patients who reached the <7.0 mmol/L target glucose level was not specified. Furthermore, the median time for treatment was nearly 14 hours. Hypoglycemia occurred in 15.7% of the IIT patients but was not associated with a significant increase in mortality (32.9% versus 29.4%). A post hoc analysis did, however, find an increased mortality in patients on IIT who had a glucose decrease of >2 mmol/L (34% versus 22%; P = 0.009). The 6 other randomized controlled trials were not powered to detect a difference in clinical outcome measures. These studies enrolled 25 to 74 patients within 12 hours or 24 hours of stroke onset. There were no significant differences in functional outcome or mortality in these trials. The percentage of patients experiencing hypoglycemic episodes ranged from 8% to 76% in the IIT groups.

In summary, the available randomized controlled trials do not support the hypothesis that late postischemic IIT will improve functional outcome in patients with acute stroke, and they raise safety concerns. In addition, IIT imposes considerable strain on both patients and caregivers.

Hypoglycemia in Acute Stroke and Focal Ischemia
In contrast with the large amount of literature concerning HG in acute stroke, there are surprisingly little data published concerning hypoglycemia. One study reported a J-shaped association between serum glucose and functional outcome and suggested that glucose serum level <3.7 mmol/L may be associated with poor outcome. However, in this cohort of 1446 patients, only 4 had glucose level <3.7 mmol/L, suggesting that the results should be interpreted with caution and that spontaneous hypoglycemia is very rare in patients with acute stroke. This is confirmed in the SITS-ISTR register with only 2.3% of the patients with serum glucose level <4.4 mmol/L. Those patients had a similar mortality rate and functional outcome compared with patients with normoglycemia. Three of the randomized controlled trials reported the absence of relationship between outcome and hypoglycemia. These reassuring data must be taken with caution because in a neurocritical care unit, the institution of IIT imposes considerable strain on both patients and caregivers.

Conclusions and Future Directions
Despite the overwhelming evidence that HG is statistically associated with poor functional outcome, increased mortality, and increased risk of symptomatic hemorrhage in patients with acute stroke, the current randomized controlled trials do not support the use of IIT in clinical practice and we propose that it is time for an interlude. Further large clinical trials may benefit from more efficient and safer methods of improving glucose control. Further experimental work may be useful to investigate the relationships between HG and SICH, the impact of delayed postischemic glucose control, the downstream mechanisms of intraischemic HG toxicity, and the effects of hypoglycemic episodes on focal ischemia. Proof-of-concept human clinical and imaging studies may also be helpful to investigate the feasibility and the usefulness of very early and strict glucose control, because the current data suggest that HG may in humans like in experimental stroke shorten the therapeutic window of efficient recanalization and exacerbate the transformation of ischemic penumbra into infarction. Finally, it remains that HG in stroke is not monolithic. HG in diabetics and in nondiabetics is likely different in some ways and the causal relationship between HG and outcome has not yet been established with certainty in humans.

Disclosures
Drs Rosso and Samson received a research grant: Insulinfarct sgr06011 in the amount of >$10 000.

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Key Words: acute stroke | focal cerebral ischemia | hyperglycemia | insulin | outcome
Glucose and Acute Stroke: Evidence for an Interlude
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Stroke. 2012;43:898-902; originally published online February 16, 2012;
doi: 10.1161/STRKEAHA.111.631218
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
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