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Management of Hyperglycemia in Acute Stroke How, When, and for Whom?

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Current acute therapies for ischemic stroke are limited. Only a small proportion of stroke patients are eligible to receive fibrinolytic therapy; clinical trials of neuroprotectant drugs have yielded disappointing results, and other potential interventions are at very early stages of development.

Against this background, coordinated stroke unit care is, however, of proven benefit; reduced mortality, institutionalization and dependency. Clinical trials demonstrating the benefit of stroke unit care have recognized the potential but unproven benefits that may be realized through rigorous physiological monitoring and intervention to correct derangements in the acute phase.

This review will discuss the complex relationship between hyperglycemia and stroke, with particular emphasis on the role of glycemic control in the acute stroke patient.

Whether acute hyperglycemia is a cause of neurological deterioration or an epiphenomenon, is a distinction pivotal in management of the stroke patient with hyperglycemia. Post-stroke hyperglycemia is common and, at least in nondiabetic individuals, is associated with a poorer stroke outcome when compared to normoglycemia.^{1,2} In a systematic review of observational studies examining the prognostic significance of hyperglycemia in acute stroke, the unadjusted relative risk of in-hospital or 30-day mortality was 3.07 (95% CI, 2.50 to 3.79) in nondiabetic patients and 1.30 (95% CI, 0.49 to 3.43) in those with diabetes.³ The relative risk of poor functional outcome in hyperglycemic nondiabetic patients was 1.41 (95% CI 1.16 to 1.73). Using MRI it has been demonstrated that in patients with acute perfusion diffusion mismatch within 24 hours of stroke onset, acute hyperglycemia correlates with reduced salvage of mismatch tissue from infarction, greater final infarct size, and worse functional outcome.⁴ As a consequence, not only has a causal relationship between hyperglycemia and poor outcome been assumed, but also a beneficial treatment effect from control of hyperglycemia (as reflected in local, national and international management

guidelines). Prospective trial data for such a treatment effect have been lacking and in the absence of randomized trial evidence, clinical practice has been guided by extrapolation of results from nonstroke populations that inform consensus guidelines.⁵ The absence of optimal quality evidence in this area has been recognized, and evidence derived from patients with acute stroke is becoming available. Recent data will be reviewed and discussed.

Diabetes or Poststroke Hyperglycemia?

Stroke is predominantly a disorder of older people in whom the prevalence of previously recognized type 2 diabetes is approximately 7%. Depending on the diagnostic criteria used, a further 7.7 to 14.8% of persons over 65 years of age may have previously unrecognized type 2 diabetes.⁶

In any given stroke population the prevalence of diabetes is approximately 8% to 20%, with a further 6% to 42% having evidence of previously unrecognized diabetes before the acute event.^{2,7–11} Such estimates are, however, complicated by the high prevalence of poststroke hyperglycemia; in one series of acute stroke patients it was estimated that up to 68% had poststroke hyperglycemia, defined by a plasma glucose concentration >6.0 mmol/L.²

It is possible that poststroke hyperglycemia is primarily a stress response in relation to stroke size and severity¹²; however, poststroke hyperglycemia is prevalent across all clinical subtypes and severities of stroke and is not restricted to those most severely affected.^{10,13} Although some studies have suggested that stress hyperglycemia may occur as a result of neuroendocrine dysregulation in response to insular cortex lesions,¹⁴ this finding has not been replicated by others.¹⁵ It remains unclear whether hyperglycemia arises as an epiphenomenon of stroke in general, as a consequence of specific anatomic involvement, or as a reflection of underlying dysglycemia.

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Insulin and Stroke Units: Current Practice

American and European guidelines advise active treatment of hyperglycemia. The criteria for implementation of insulin treatment vary, with European Stroke Initiative (EUSI) guidelines advising intervention if blood glucose exceeds 10 mmol/L, whereas the American Stroke Association (ASA) now advocates a threshold of 11 mmol/L.⁵ In an audit of acute neurological stroke care performed across 22 countries by the European Federation of Neurological Societies, the mean threshold of blood glucose concentration for intervention was 10.6 mmol/L, ranging from 7.4 to 14.0 mmol/L in different countries.⁶ The survey did not reveal the variation in practice among centers within individual countries, which we presume to be at least as great. The blood glucose level used to define poststroke hyperglycemia (PSH), and thus the level at which a worse stroke outcome is anticipated, also varies. Poststroke hyperglycemia has been defined using thresholds between 6.1 and 8.0 mmol/L, based on random or fasting blood glucose,^{10,16,17} with some studies including patients presenting up to 72 hours from ictus.¹⁶ Factors influencing PSH may include a variable combination of neuroanatomical, neuroendocrine, and general metabolic features. In addition, extraneous factors such as time from ictus to sampling, early feeding, and intravenous support will influence plasma glucose levels. A recent study examining the effect of blood glucose on infarct size as measured using MRI found that persistent hyperglycemia (defined as blood glucose ≥ 7.0 mmol/L) in the 72 hours after acute stroke was associated with an increase in infarct size and worse stroke outcome.¹⁸ The decision to intervene is made more complex by the risk of iatrogenic hypoglycemia during insulin treatment. This needs to be considered when selecting the most appropriate glucose level, the method and duration of insulin delivery, and the duration of glycemic monitoring.

A variety of methods of insulin administration exist, comprising continuous intravenous (IV) infusion, repeated subcutaneous dosing by sliding scale, or IV delivery of a reconstituted infusion containing insulin and dextrose with potassium supplementation (the GKI regime). Sliding scale regimens are largely reactive, correcting changes as and when they occur, whereas GKI regimens are largely proactive, predicting insulin requirements and maintaining euglycemia within a therapeutic range. Concurrent administration of insulin, potassium and glucose as a GKI infusion may theoretically reduce the risk of hypoglycemia arising as a result of device or infusion failure.

Maintenance of euglycemia can prove difficult in patients who are eating and drinking normally, as such patients tend to develop postprandial hyperglycemia before the insulin infusion rate is increased. Although both sliding scale and GKI regimes have attracted criticism in the literature,¹⁹ no clearly superior alternative has yet been reported.²⁰ The practical aspects and the safety profile of each method have been considered in different hospital settings including critical care, coronary care, general medical wards, and stroke units. In the absence of trial data sufficiently powered to examine the effect of insulin on clinical outcomes in a stroke population, trials of insulin infusions in other contexts (such as coronary and intensive care units) may yield some insights

into the potential effectiveness of methods of glucose lowering in stroke.

Insulin Use Outwith Stroke Units

A meta-analysis of 35 randomized controlled trials involving 8478 patients examined the effect of insulin on mortality in the hyperglycemic critically ill patient. Insulin was administered as a GKI Infusion in 86% of the studies, with 14% using intravenous insulin by pump. Studies were published between 1965 and 2002 and included patients primarily with acute myocardial infarction (MI). Combined data demonstrated that insulin decreased short-term mortality by 15% (RR 0.85; 95% CI, 0.75 to 0.97). Greatest benefit was noted in the surgical intensive care unit (ICU) population (RR, 0.58; 95% CI, 0.22 to 0.62), when the aim of therapy was glucose control (RR, 0.71; 95% CI, 0.54 to 0.93) and in patients with diabetes mellitus (RR, 0.73; 95% CI, 0.58 to 0.90).²¹ Two multicenter randomized controlled trials of GKI infusions in the context of acute MI have clouded the picture. The Diabetes-Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) trial failed to reproduce the initial promising results of the first DIGAMI trial.²² In contrast to the findings in DIGAMI, in DIGAMI 2 GKI with or without long-term insulin failed to demonstrate survival benefit over routine treatment, likely because of the failure to attain sustained glycemic control and a significant difference between treatment and placebo groups.²²

Additional results from the merger of 2 multicenter trials (The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation, and Estudios Cardiológicos Latin American Study Group: CREATE-ECLA) which randomized 20 201 patients within 12 hours of acute ST-elevation MI to GKI-infusion or placebo, found that GKI infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock.²³

The more recent publication of the large single center Leuven study that reported reduced mortality in a surgical intensive care unit population treated with insulin to achieve tight blood glucose control (4.4 to 6.1 mmol/L) has resulted in its adoption in many intensive care facilities.²⁴ Severe nosocomial infections, acute organ dysfunction, and critical illness neuropathy were prevented in patients treated with intensive insulin. When the same group examined the effect of insulin in 1200 patients admitted to a medical intensive care unit with similar targeted levels of glucose control, overall intensive care mortality was similar for both groups, with a suggestion of benefit of tight control emerging only in those patients who stayed in the intensive care unit for three or more days.^{25,26} Both trial results have recently been pooled to examine the controversies surrounding infusion duration, optimal blood glucose thresholds, and effect on specific subgroups. Intensive insulin therapy (IIT) reduced mortality for both the intention to treat population and for patients staying for >3 days, with no difference in patients resident for <3 days. Mortality was more significantly reduced in patients with a blood glucose <6.1 mmol/L when compared to patients with a blood glucose 6.1 to 8.3 mmol/L or >8.3 mmol/L, despite a greater risk of hypoglycemia.²⁶ Two recent European multicenter trials (Glucontrol²⁷ and NICE-

Sugar²⁸) have aimed to maintain tight glycemic control (4.4 to 6.1 mmol/L) in acutely ill patients. The Glucontrol trial was stopped early after recruitment of 1100 patients, because of a high rate of hypoglycemia in the intensive control group, and an association of hypoglycemia with increased mortality. In 488 patients recruited to the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial,²⁹ examining the effect of insulin in patients with severe sepsis and septic shock, patients receiving insulin had a 6-fold increased risk of significant hypoglycemia.

Although current evidence suggests that intensive glucose lowering may be necessary to achieve a treatment effect, recent evidence from the UK Glucose Insulin Stroke Trial (GIST-UK)³⁰ suggests that most acute stroke patients will only have mild to moderate increases in plasma glucose at presentation (median 7.6 mmol/L [IQR 6.7 to 9.0]) with minimal insulin requirement as a consequence. Therefore, in the management of acute stroke, intensive insulin regimens are likely to require significant carbohydrate loading and immediate supplemental feeding to reduce the risk of hypoglycemia.

Insulin Use in Brain-Injured Patients

Limited evidence exists on the action of insulin in humans with CNS injury. Post hoc analysis of 63 patients with isolated brain injury from the larger Leuven cohort of 1548 surgical ICU patients examined the effect of insulin therapy on intracranial pressure, diabetes insipidus, seizures, and long-term rehabilitation at 6 and 12 months follow-up. Both neurological and nonneurological morbidity was reduced in the insulin group.³¹ In a retrospective study of 960 patients with thromboembolic stroke, patients who had initial hyperglycemia that settled on repeated testing at 24 and 48 hours had similar mortality rates to patients with persistent euglycemia.³² Insulin, oral hypoglycemic agents, or both were used in 63.7% of patients with hyperglycemia after admission. These results suggested some association between blood glucose control and outcome, providing justification for prospective work in this area.

Recent Evidence in Stroke Patients

The GIST-UK study recruited patients with acute stroke and blood glucose between 6.1 and 17 mmol/L regardless of whether or not they were known to have diabetes, although insulin requiring patients with diabetes were excluded.³⁰ Patients were randomized to either control (normal saline) or a GKI infusion for 24 hours. The objective of the GKI treatment was to maintain capillary blood glucose between 4 and 7 mmol/L. The primary end point of the trial was mortality at day 90. The GKI regime in GIST-UK comprised 500 mls of 10% dextrose, 20 mmol KCL, and 16 U (initial) of soluble recombinant human insulin. At infusion initiation blood glucose monitoring was undertaken hourly until euglycemia was reached and then changed to 2-hourly. Insulin dosage escalations or reductions required bag disposal and adjustment attributable to the inflexibility of insulin titration independent of glucose, and the median number of bag changes over the 24 hours was 2 per patient. The GKI regime is therefore labor-intensive.

A total of 933 patients were recruited. Median time to infusion was less than 14 hours for both groups. Of the 464 acute stroke patients who were treated with the GKI infusion, 30% died within 90 days compared with 27.3% among the 469 patients who were randomized to receive saline solution ($P=0.37$). Similarly, no significant effect of GKI infusion on prevalence of severe disability at 90 days was identified. One unexpected finding was an effect of GKI infusion on blood pressure. Treatment with GKI was associated with significant decreases in blood pressure beyond that of medical therapy, with a mean fall in systolic blood pressure of 9.03 mm Hg. Although insulin is known to exert a vasodilatory effect on resistance vessels,³³ alternative explanations for this novel observation include the effect of potassium as part of the trial infusion or a pressor effect of alternate fluid therapy in the control arm. Despite the neutral result the trial remains the first large clinical trial of glucose modulation in acute stroke, and subsequent trials will be informed through its results. The trialists intended to recruit a proposed sample size of 2355 patients and as such the study was underpowered to detect the prespecified mortality difference between groups. As previously discussed, despite a glucose enrolment range of 6.0 to 17 mmol/L, the majority recruited had mild hyperglycemia; median blood glucose 7.8 mmol/L (6.8 to 9.2) in the GKI group and 7.6 mmol/L (6.7 to 8.8) in the placebo group. The effect of GKI on patients with moderate to severe hyperglycemia remains uncertain with current practice still being guided by consensus guidelines. In contrast to the previously published meta-analyses on insulin, which demonstrated benefit in patients when the goal of therapy was glucose lowering, GKI lowered glucose but the effect was only small (difference between GKI and saline group's 0.57 mmol/L) and glucose concentration fell spontaneously with IV saline alone. It is interesting to compare the neutral result of GIST-UK with the neutral result of DIGAMI II, which saw a 0.9-mmol/L difference in blood glucose between the insulin and placebo groups,²² whereby the positive DIGAMI study achieved a 2.1-mmol/L reduction in glucose.²¹ A posthoc analysis of GIST-UK investigating the safety of glucose lowering on outcome found that patients receiving GKI with a 2-mmol/L or more decrease in blood glucose between baseline and 24 hours had a higher mortality at 24 hours (34%^{53/154}) when compared to patients with a glucose reduction of less than 2 mmol/L over the same period (22%^{41/188}; $P=0.009$). The time window for targeted acute stroke therapy remains uncertain, although more recent neuroprotective and thrombolytic trials have adopted times limit of up to 6 hours from ictus to maximize opportunity to attenuate tissue injury.^{34,35} In the GIST-UK study only 8 patients were treated within 3 hours, with 108 patients being treated within 6 hours. No patients in GIST-UK received thrombolysis and as such any potential synergistic effect with GKI could not be assessed.

The timing of insulin treatment after stroke may not necessarily follow conventional windows for acute therapies, as the timeframes for hyperglycemia to evolve may be unrelated and dependent on other physiological and iatrogenic factors.

An alternative method of insulin administration using intravenous insulin at a variable rate adjusted for target glucose concentration of 5 to 8 mmol/L and run simultaneously with a crystalloid infusion of either normal saline or 5% dextrose was examined in a small randomized controlled pilot study. Patients within 24 hours of an acute ischemic stroke with hyperglycemia (8 to 20 mmol/L) were randomized to receive rigorous glycemic control or standard management for 48 hours. Twenty-five patients were recruited, 13 of whom were randomized to insulin infusion.³⁶ In a further study of IV insulin administration 24 patients within 12 hours of an acute ischemic stroke with blood glucose 9.4 to 22.2 mmol/L received insulin for a mean of 54 hours (range 17 to 72 hours). At least 1 episode of hypoglycemia occurred in 11 (46%) patients, with symptomatic hypoglycemia in 5 (21%).³⁷

Two further trials are examining the insulin administration in hyperglycemic acute ischemic stroke: the Glucose Regulation in Acute Stroke Patients Trial (GRASP),³⁸ which is continuing recruitment, and the Treatment of Hyperglycemia in Ischemic Stroke trial (THIS),³⁹ which has completed recruitment but not yet presented its results. In GRASP, patients with hyperglycemia (glucose >6.1 mmol/L) within 24 hours of symptom onset are randomized to tight glucose control (3.9 to 6.1 mmol/L), loose glucose control (6.1 to 11.1 mmol/L), or usual care. The insulin is delivered as a GKI infusion and titrated to capillary glucose. The primary outcome of the GRASP trial is rate of hypoglycemic events (glucose <3.05 mmol/L) and definitive information on clinical endpoints is not expected.

The THIS trial³⁹ is a randomized, multi-center trial which recruited patients with acute ischemic stroke within 12 hours of symptom onset to usual treatment (subcutaneous insulin four times daily) or aggressive treatment (continuous intravenous insulin to a target glucose range 6.1 to 7.2 mmol/L). The experimental interventions continued for 72 hours. The study recruited 45 patients, and as such it seems unlikely that any statistically significant effect on clinical end points will be discernible between groups.

Mechanisms of Injury and Potential Role for Insulin

Evidence derived from animal models shows that during acute focal and global ischemia, insulin therapy reduces ischemic brain damage and may be neuroprotective.⁴⁰ It is postulated that the neuroprotective action is exerted through insulin like growth factor (IGF) type receptors. Insulin and IGF-1 were found to reduce ischemic damage when injected directly into the brain ventricles.⁴¹ In a model of forebrain ischemia in rats, insulin not only reduced histological injury but improved neurobehavioural outcome.⁴² Insulin is also felt to exert an anticoagulant effect, through reduced thromboxane production⁴³ and decreased plasminogen activator inhibitor-1 activity.⁴⁴ The effect of insulin appears dependent on the model of ischemia and also the method of insulin administration. Studies examining the effect of insulin on infarct size in animal models of focal ischemia demonstrate differing results depending on the timing of insulin relative to ischemia, duration of ischemia, and blood glucose

level obtained. In a transient focal model of cerebral ischemia in rats, elevated blood glucose at the time of ischemia resulted in larger infarcts than those with a blunted glucose effect.⁴⁵ Development of hypoglycemia (mean blood glucose in the range 3.2 to 3.8 mmol/L) in a cat model using insulin resulted in larger infarcts and an increased death rate.⁴⁶ Table 1 summarizes the effect of insulin on infarct volumes in experimental models of focal ischemia.

There is evidence to support a beneficial effect of insulin administration to achieve euglycemia in both preclinical models of ischemia and in selected clinical scenarios.^{40,47} Animal studies indicate that this benefit is lost if hypoglycemia occurs.⁴⁸ Uncertainty remains as to whether insulin has an effect independent of its action to lower glucose and evidence exists of alternative mechanisms. In a rat model of transient forebrain ischemia insulin administered with glucose significantly reduced cortical and striatal neuronal necrosis in the presence of normoglycemia, suggestive of a neuroprotective effect of insulin independent of its hypoglycemic action.⁴⁹ Various methods of neuroprotection have been proposed, including a direct interaction with CNS tissue via a growth factor effect. Use of a continuous intraventricular infusion of low- and high-dose insulin or insulin like growth factor 1 (IGF-1) in a transient forebrain model of ischemia reduced neuropathological injury at 1 week compared to placebo.⁴¹ Other possible actions have been suggested: reduction of plasma free fatty acid (FFA) concentration occurs after GKI infusion in patients with MI.⁵⁰ This may be significant, as elevated FFA levels cause endothelial dysfunction.⁵¹ It has previously been demonstrated in vitro that insulin has an antiinflammatory effect on endothelial cells.⁵² Some supportive evidence from human studies exists: insulin infusion in patients with myocardial infarction reduced both C reactive protein and serum amyloid A protein at 24 and 48 hours compared to placebo.⁵³ One further mechanism underlying the antiinflammatory role of insulin relates to the release of NO. Insulin increases expression of nitric oxide (NO) synthase, the enzyme that generates NO. NO downregulates the expression of endothelial cell adhesion molecules as well as proinflammatory cytokines, resulting in vasodilatation and improved blood flow.⁵⁴ Insulin also has anabolic properties, with stimulation of skeletal muscle protein synthesis promoting tissue repair and potentially affecting rehabilitation.⁵⁵

The "glucose paradox of cerebral ischemia" questions why glucose, the main energy substrate for the brain, causes demise of brain tissue at the time of cerebral ischemia. Metabolism within penumbral tissue changes from aerobic to anaerobic glycolysis. Anaerobic metabolism is less energy efficient and produces lactate and unbuffered hydrogen ions. Experimental models have consistently shown that animals made hyperglycemic before induction of ischemia have higher levels of lactate than euglycemic controls.^{56,57} Hyperglycemia may initially be neuroprotective, with increased glucose available for metabolism and ATP production. Persisting anaerobic metabolism results in the development of intracellular acidosis. It has been shown using both pH-sensitive microelectrodes and ³¹P nuclear magnetic resonance spectroscopy that the brain pH of animals pretreated with

Table 1. Effect of Insulin on Infarct Volumes in Experimental Models of Focal Ischemia Using Permanent or Temporary Occlusion

Reference	Species	Site of Ischemia	Occlusion Type	Results
Yip et al ⁴⁵	Rat	MCAO	Temporary	Intraischemic normoglycemia resulted in significantly smaller infarct volumes than hypoglycemic rats
Zhu et al ⁴⁸	Rat	MCAO	Temporary	Insulin was not beneficial in reducing infarction size. The increased damage induced by insulin occurred in animals with very low blood sugars (2 to 3 mmol/l)
Hamilton et al ⁸³	Rat	MCAO	Temporary	Reduction in blood glucose to the low normal range (3 to 4 mmol/l) reduced infarction size, whereas insulin administration without hypoglycemia did not
Fukuoka et al ⁸⁴	Gerbil	UCCO	Temporary	Daily insulin injections without hypoglycemia resulted in least infarction on histology
Zhao et al ⁸⁵	Rat	MCAO	Temporary	Oedema formation was less in rats treated with insulin that resulted in normal blood glucose levels
de Courten-Myers et al ⁴⁶	Cat	MCAO	Temporary	Insulin induced hypoglycemia resulted in increased infarct size in cat survivors
			Permanent	Hyperglycemic cats receiving insulin had larger infarct sizes than cats receiving normal saline
Nedergaard et al ⁸⁶	Rat	MCAO	Permanent	Volume of infarction was decreased in hypoglycemic animals
Bomont et al ⁸⁷	Rat	MCAO	Permanent	Insulin treatment in diabetic rats significantly reduced infarct volume (by approximately 30%)
Izumi et al ⁸⁸	Rat	MCAO	Permanent	Insulin and magnesium chloride in combination maximally reduced infarct volume size
Izumi et al ⁸⁹	Rat	MCAO	Permanent	Insulin given after MCA occlusion reduced infarction volume without inducing sustained hypoglycemia
Kazan et al ⁹⁰	Rat	MCAO	Permanent	Infarct volume was significantly reduced for rats receiving insulin when compared to controls
Combs et al ⁹¹	Cat	MCAO	Permanent	No significant difference in infarct size between hyperglycemic rats and rats with hyperglycemia receiving insulin

MCAO indicates middle cerebral artery occlusion; UCCO, unilateral common carotid artery occlusion.

glucose is considerably more acidotic than saline treated controls.^{58,59} Acidosis may exacerbate penumbral injury through enhancement of free radical formation, activation of pH dependent endonucleases, and glutamate release with subsequent alteration of intracellular Ca^{2+} regulation and mitochondrial failure.^{60–63}

There is currently no direct proof that lactate is detrimental to the ischemic brain. In vitro work using murine hippocampal slices has shown that glucose and acidosis are detrimental to cells whereas lactate is not.⁶⁴ Using PET scanning it has been shown that lactate may be the preferred energy supply to the brain especially during times of stress.⁶⁵ This is relevant to the management of hyperglycemia in acute ischemic stroke patients. If the ischemic brain is dependent on lactate for its source of energy, targeted euglycemia may result in less glucose load to the brain and thus less substrate for anaerobic metabolism, therefore attenuated lactate production. Periinfarct depolarisations (PIDS) which contribute to infarct expansion in focal ischemia models were found to be more frequent⁶⁶ in a cat model of middle cerebral artery occlusion and associated with lower plasma glucose and a worse outcome.⁶⁷ The same group have demonstrated in a single patient with traumatic brain injury complete disappearance of cortical glucose dialysate coinciding with a period of hypoglycemia associated with an insulin infusion.⁶⁸ This is consistent with the effect of hypoglycemia on infarct progression in animal models and emphasizes importance of strict mon-

itoring in patients receiving insulin. The lower limit for glucose control in recent randomized trials is 3.9 to 4.0 mmol/L.^{30,37} It is possible that this figure may need to be revised upwards in future trials.

Patient Selection

Identification of appropriate patients that may benefit from glucose lowering therapy requires knowledge of the temporal profile of blood glucose post ictus. In patients with first blood glucose measurement an average of 2.5 hours after onset, glucose concentration increased in the first 12 hours after stroke in 68% of subjects, the increase correlating with greater stroke severity.⁶⁹ In the first 231 patients randomized to the placebo arm of the GIST-UK, mean blood glucose was lower at 8 hours after commencement of placebo infusion.³⁰ Using a continuous subcutaneous monitor measuring interstitial glucose over a 72-hour period, blood glucose decreased from a peak at 8 hours after stroke, reached its lowest level at 14 to 16 hours, reached a plateau, and then exhibited a further late hyperglycemic phase at 48 to 88 hours after stroke.⁷⁰ Elevated admission blood glucose after stroke may reveal latent dysglycemia. In a study of 62 patients screened at 3 months after an acute ischemic stroke when admission blood glucose was ≥ 6.1 mmol/L, 21% had diabetes mellitus and 37% had impaired glucose tolerance. A blood glucose ≥ 6.1 mmol/L and $\text{HbA}_{1c} \geq 6.2\%$ on admission had an 80% positive predictive value for diabetes at 12 weeks.⁷¹ Patients

Table 2. Relationship Between Admission Glucose Level and Outcomes in Clinical Trials of Anticoagulant and Thrombolytic Agents

Reference	Time Window	Therapeutic Agent	No. of Patients	Study Parameters	Results
TOAST ⁹²	<24 hours	Low molecular weight heparinoid vs placebo	1259	Relationship between admission blood glucose and clinical outcome	All strokes combined: (OR=0.82 for every 100 mg/dl increase in blood glucose; <i>P</i> =0.03) Non lacunar strokes (OR 0.74 for every 100 mg/dl increase in blood glucose; <i>P</i> =0.02)
NINDS rt-PA stroke trial ⁷⁶	<3 hours	Intravenous rt-PA vs placebo	624	NIHSS change of ≥ 4 at 3 months or a final score of 0 Symptomatic ICH at 36 hours*	OR of neurological improvement per 100 mg/dl increase in blood glucose=0.76 (0.61 to 0.95) (<i>P</i> =0.01) OR of SICH per 100 mg/dl increase in blood glucose=1.75 (1.11 to 2.78) (<i>P</i> =0.02)
PROACT II ⁹³	<6 hours	Intraarterial r-proUK+IV heparin vs IV heparin alone	180	Symptomatic ICH within 36 hours of treatment**	Patients receiving r-proUK with admission blood glucose >200 mg/dl experienced a 36% risk of SICH compared to 9% for those ≤ 200 mg/dl (RR 4.2; 95% CI 1.04 to 11.7) (<i>P</i> =0.022)
CLOTBUST ⁹⁴	<3 hours	Intravenous thrombolysis with randomisation to TCD or placebo	117	Interaction between admission glucose and ultrasound with respect to good clinical outcome (mRs 0 to 2)	High admission glucose predicted a lower probability of good outcome in the control group but not the active ultrasound group, as demonstrated by an interaction between glucose and treatment group (<i>P</i> =0.043)

TOAST indicates Trial of ORG 10172 in Acute Stroke Treatment; NINDS, National Institute of Neurological Disorders and Stroke; PROACT II, PROlyse for Acute Cerebral Thromboembolism; CLOTBUST, Combined Lysis Of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA; r-proUK, recombinant pro-urokinase.

*SICH defined as CT documented hemorrhage within 36 hours of treatment that was temporally related to clinical deterioration.

**Presence of ICH with neurological deterioration defined as an increase of ≥ 4 points on the NIHSS in comparison with the preangiography score within 36 hours of treatment initiation.

with “stress” hyperglycemia have an unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose levels ≥ 6.0 to 8.0 mmol/L of 3.07 (95% CI, 2.50 to 3.79) whereas in patients with diabetes it is 1.30 (95% CI, 0.49 to 3.43).⁷² The prevalence of established diabetes in studies examining the role of hyperglycemia on stroke outcome ranges from 7.4% to 33%.^{73,74} Identification of diabetes at presentation usually results in additional monitoring of blood glucose and a lower threshold for intervention to treat hyperglycemia: it may be that the apparent difference in outcome between known diabetic and simply hyperglycemic stroke patients is related to the lower threshold for intervention.

Hyperglycemia and Fibrinolytic Therapy

Restoration of cerebral blood flow with salvage of penumbral tissue is the aim of thrombolysis.⁷⁵ In a posthoc analysis of the NINDS study hyperglycemic patients had a significantly increased odds of symptomatic intracerebral hemorrhage and reduced odds of a good clinical outcome.⁷⁶

It is biologically plausible that recanalization may augment the injurious effect of hyperglycemia. Using transcranial Doppler ultrasound (TCD) to assess recanalization after thrombolysis in 73 patients, hyperglycemia was an independent predictor of poor outcome at 3 months in patients who recanalized but not in patients with permanent occlusion.⁷⁷ This finding may reflect the observation that early recanalization is associated with a larger penumbral area susceptible to the adverse effects of hyperglycemia.⁷⁸ Using MR to measure infarct progression in patients receiving intravenous

thrombolysis, infarct growth was more apparent in hyperglycemic patients compared to normoglycemic patients.⁷⁹

Acute hyperglycemia has recently been shown to predict nonrecanalization in the hyperacute phase of stroke⁸⁰ and is associated with poor outcome. Acute hyperglycemia may exert an antifibrinolytic effect through glycation of annexin II,⁸¹ and there is some suggestion that hyperglycemic patients may derive more benefit from adjunctive measures to enhance the lytic effect of rt-PA.⁸² On the basis of these findings it is plausible that maintenance of euglycemia at initial presentation and continued through to recanalization may enhance the effect of thrombolysis. Tables 2 and 3 summarize studies of the relationship between admission glucose level and outcomes in clinical trials of anticoagulant and thrombolytic agents and the effect of blood glucose on lesion volume progression measured using MRI surrogate markers in clinical studies of patients with acute ischemic stroke.

Conclusions and Recommendations

Although experimental evidence supports a causal relationship between hyperglycemia and adverse outcome after stroke, trial data do not yet support intervention with insulin. Current guidelines advise lowering of blood glucose but disagree on the threshold at which to intervene, and make no comment on specific insulin treatment regimes or treatment targets. The heterogeneity of the stroke population may mean that standard protocols should and cannot be applied to all patients. Nutritional intake varies between stroke patients, and adjustment for oral intake is difficult in the following stroke maintenance of the targeted glucose level. The impor-

Table 3. Effect of Blood Glucose on Lesion Volume Progression Measured Using MRI Surrogate Markers in Clinical Studies of Patients With Acute Ischemic Stroke

Reference	Time Window	No. of Patients	Study Parameters	Results
Baird et al ¹⁸	<24 hours	25	Correlation between mean blood glucose and infarct volume change	Mean blood glucose over 72 hours correlated with infarct volume change between acute and subacute DWI ($r \geq 0.60$, $P < 0.01$), and acute DWI and day 90 T2-MRI ($r \geq 0.53$, $P < 0.02$)
Parsons et al ⁴	<24 hours	63	The effect of hyperglycemia on patients with and without DWI/PWI mismatch	In 40/63 patients with mismatch, acute hyperglycemia (≥ 144 mg/dl) correlated with reduced salvage of mismatch tissue from infarction and greater final infarct size In patients with no mismatch acute blood glucose did not independently correlate with outcome measures
Ribo et al ⁹⁵	<6 hours	47	Hyperglycemia effect on DWI lesion growth relative to occlusion time	DWI lesion volume grew 2.7 times faster between baseline (pre rt-PA) and repeat imaging at 24 to 36 hours in those patients with hyperglycemia (glucose >140 mg/dl) during occlusion time. (1.73 vs 4.63 cm ³ /h of occlusion, $P = 0.07$). Occlusion time measured using TCD
Els et al ⁹⁶	<3 hours	31	Hyperglycemia effect on MRI infarct size at admission (DWI), day 3 (DWI) and day 7 (T2-MRI)	Change in lesion volume between day 3 (DWI) and day 7 (T2-weighted MRI) increased significantly in the hyperglycemic (admission blood glucose >178 mg/dl) group ($39.9 \pm 17.4\%$) vs the normoglycemic group ($27.1 \pm 14.1\%$) ($P < 0.05$)

DWI indicates diffusion weighted imaging; PWI, perfusion weighted imaging; TCD, transcranial Doppler.

tance and implications of early mobilization after stroke discourages the use of prolonged infusions, contrasting significantly with the immobile ventilated patient in intensive care receiving enteral or parenteral nutrition and the acute MI patient with staged mobilization. Extrapolation of animal data and case series suggest that hypoglycemia may increase final infarct size. Prevention of hypoglycemia is therefore important and requires strict monitoring, but the threshold at which hypoglycemia affects infarct progression is undetermined. Application of intensive monitoring is dependent on appropriate staffing of stroke units and adherence to set protocols. Different methods of insulin administration currently exist and are being tested in randomized clinical trials. The GIST-UK trial demonstrated that intervention with insulin in the form of GKI infusion cannot be recommended routinely. Many questions surrounding the role of glucose lowering therapy remain unanswered; is intravenous infusion of insulin at variable rate as opposed to the GKI infusion potentially beneficial to patients with hyperglycemia? What level of blood glucose is best for intervention? What is the therapeutic time window? Will identification of the penumbra with CT and MR imaging select appropriate patients? Is the effect of insulin infusion affected by early recanalization of occluded vessels? What effect would insulin have on outcome if it impedes early mobilization? How long should the insulin infusion last, with current knowledge of the variation in the natural history of blood glucose in stroke demonstrating an early and late peak? What level of monitoring is required and how feasible is that within the confines of an acute stroke unit and the patient-to-nurse staffing ratios available? Will more rigorous identification of hyperglycemia in the setting of acute stroke have implications for earlier detection underlying diabetes or impaired glucose tolerance? The challenges inherent in answering these questions are considerable, but

the potential impact on our ability to provide optimal management of stroke patients is greater still.

Disclosures

None.

References

- Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurol*. 2002;59:67–71.
- Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Prevalence of admission hyperglycemia across clinical subtypes of acute stroke. *Lancet*. 1999;353:376–377.
- Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
- Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 2002;52:20–28.
- Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. American Heart Association; American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655–1711.
- Thomassen L, Brainin M, Demarin V, Grond M, Toni D, Venables GS; EFNS Task Force on Acute Neurological Stroke Care. Acute stroke treatment in Europe: a questionnaire based survey on behalf of the EFNS task force on acute neurological stroke care. *Eur J Neurol*. 2003;10:199–204.

7. Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. *Arch Neurol*. 1985;42:661–663.
8. Melamed E. Reactive hyperglycemia in patients with acute stroke. *J Neurol Sci*. 1976;29:267–275.
9. Gray CS, Taylor R, French JM, Alberti KG, Venables GS, James OF, Shaw DA, Cartledge NE, Bates D. The prognostic value of stress hyperglycemia and previously unrecognized diabetes in acute stroke. *Diabet Med*. 1987;4:237–240.
10. Sprafka JM, Virnig BA, Shahar E, McGovern PG. Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival: the Minnesota Heart Survey. *Diabetic Med*. 1994;11:678–684.
11. Woo E, Ma JTC, Robinson JD, Yu YL. Hyperglycemia is a stress response in acute stroke. *Stroke*. 1988;19:1359–1364.
12. O'Neill PA, Davis I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke*. 1991;22:842–847.
13. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. *BMJ*. 1997;314:1303–1306.
14. Allport L, Butcher K, Baird T, MacGregor L, Desmond PM, Tress BM, Colman P, Davis SM. Acute stress hyperglycemia is associated with insular cortical ischemia. *Stroke*. 2004;35:248.
15. Moreton FC, McCormick M, Muir KW. Insular cortex hypoperfusion and acute phase blood glucose after stroke: a CT perfusion study. *Stroke*. 2007;38:407–410.
16. Oppenheimer SM, Hoffbrand B, Oswald GA, Yudkin JS. Diabetes mellitus and early mortality from stroke. *BMJ*. 1985;291:1014–1015.
17. Riddle MC, Hart J. Hyperglycemia, recognised and unrecognised, as a risk factor for stroke and transient ischemic attacks. *Stroke*. 1982;13:356–359.
18. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
19. Sawin CT. Action without benefit. The sliding scale of insulin use. *Arch Int Med*. 1997;157:489.
20. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Int Med*. 2004;164:2005–2011.
21. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenström A, Wedel H, Welin L. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57–65.
22. Malmberg K. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26:650–661.
23. Mehta SR, Yusuf S, Díaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L; CREATE-ECLA Trial Group Investigators. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA*. 2005;293:437–446.
24. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
25. Van den Berghe G. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449–461.
26. Van den Berghe G. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*. 2006;55:3151–3159.
27. Devos P. European glucose control study. www.glucontrol.org. Accessed March 28, 2007.
28. NICE-SUGAR study: <http://www.thegeorgeinstitute.org/iih/index.cfm?CBEB61E0-D192-95-F9-9C1E-6A2474B45DCC>. Accessed March 10, 2007.
29. Brunkhorst FM. Intensive insulin therapy in patients with severe sepsis and septic shock in associated with an increased rate of hypoglycemia—results from a randomized multicenter study (VISEP). *Infection*. 2005;33:19.
30. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartledge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406.
31. Van den Berghe G, Schoonheydt K, Bexx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurol*. 2005;64:1348–1353.
32. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. Decreased mortality by normalising blood glucose after acute ischemic stroke. *Acad Emerg Med*. 2006;13:174–180.
33. Cleland SJ, Petrie JR, Connell JC. Insulin action is associated with endothelial function in hypertension and type 2 diabetes. *Hypertension*. 2000;35:507–511.
34. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
35. Fisher M. Characterizing the Target of Acute Stroke Therapy. *Stroke*. 1997;28:866–872.
36. Walters MR, Weir CJ, Lees K. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycemic acute ischemic stroke patients. *Cerebrovasc Dis*. 2006;22:116–122.
37. Bruno A, Saha C, Williams LS, Shankar R. IV insulin during acute cerebral infarction in diabetic patients. *Neurol*. 2004;62:1441–1442.
38. Johnston KC. Glucose Regulation in Acute Stroke Patients Trial. <https://grasptrial.org/grasp/home.aspx>. Accessed 2 May 2007.
39. Treatment of hyperglycaemia in ischemic stroke trial. <http://www.strokecenter.org/trials/TrialDetail.aspx?tid=686>. Accessed August 28th 2007.
40. Auer RN. Insulin, blood glucose levels, and ischemic brain damage. *Neurol*. 1998;51:S39–S43.
41. Zhu CZ, Auer RN. Intraventricular administration of insulin and IGF-1 in transient forebrain ischemia. *J Cereb Blood Flow Metab*. 1994;14:237–242.
42. Wass CT, Scheithauer BW, Bronk JT, Wilson RM, Lanier WL. Insulin treatment of corticosteroid-associated hyperglycemia and its effect on outcome after forebrain ischemia in rats. *Anesthesiology*. 1996;84:644–651.
43. Davi G, Catalano I, Averna M, Notarbartolo A, Strano A, Ciabattini G, Patrono C. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med*. 1990;322:1769–1774.
44. Jain SK, Nagi DK, Slavin BM, Lumb PJ, Yudkin JS. Insulin therapy in type 2 diabetic subjects suppresses plasminogen activator inhibitor (PAI-1) activity and proinsulin-like molecules independently of glycemic control. *Diabet Med*. 1993;10:27–32.
45. Yip PK, He YY, Hsu CY, Garg N, Marangos P, Hogan EL. Effect of plasma glucose on infarct size in focal cerebral ischemia-reperfusion. *Neurol*. 1991;41:899–905.
46. de Courten-Myers GM, Kleinholz M, Wagner KR, Myers RE. Normoglycaemia (not Hypoglycaemia) optimises outcome from middle cerebral artery occlusion. *J Cereb Blood Flow Metabol*. 1994;14:227–236.
47. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2004;164:2005–2011.
48. Zhu CZ, Auer RN. Optimal blood glucose levels while using insulin to minimize the size of infarction in focal cerebral ischemia. *J Neurosurg*. 2004;101:664–668.
49. Voll CL, Auer RN. Insulin attenuates ischemic brain damage independent of its hypoglycemic effect. *J Cereb Blood Flow Metabol*. 1991;11:1006–1014.
50. Apstein CS, Taegtmeyer H. Glucose-insulin-potassium in acute myocardial infarction. *Circulation*. 1997;96:1074–1077.
51. Steinberg HO, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, Bayazeed B, Baron AD. Elevated circulating free fatty acid levels impair endothelium dependent vasodilatation. *J Clin Invest*. 1997;100:1230–1239.
52. Aljada A, Ghanim H, Saadeh R, Dandona P. Insulin inhibits NFκB and MCP-1 expression in human aortic endothelial cells. *J Clin Endocrinol Metab*. 2001;86:450–453.
53. Chaudhuri A, Janicke D, Wilson MF, Tripathy D, Garg R, Bandyopadhyay A, Calieri J, Hoffmeyer D, Syed T, Ghanim H, Aljada A, Dandona P. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment elevation myocardial infarction. *Circulation*. 2004;109:849–854.
54. Aljada A, Saadeh R, Assian E, Ghanim H, Dandona P. Insulin inhibits the expression of intercellular adhesion molecule-1 by human aortic endothelial cells through stimulation of nitric oxide. *J Clin Endocrinol Metab*. 2000;85:2572–2575.

55. Ferrando AA, Chinckes DL, Wolf SE, Matin S, Herndon DN, Wolfe RR. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Ann Surg*. 1999;229:11–18.
56. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurol*. 1982;32:1239–1246.
57. Anderson RE, Tan WK, Martin HS, Meyer FB. Effects of glucose and PaO₂ modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke*. 1999;30:160–170.
58. Siemkowicz E, Hansen AJ. Brain extracellular ion composition and EEG activity following 10 minutes ischemia in normo- and hyperglycemic rats. *Stroke*. 1981;12:236–240.
59. Widmer H, Abiko H, Faden AI, James TL, Weinstein PR. Effects of hyperglycemia on the time course of changes in energy metabolism and pH during global cerebral ischemia and reperfusion in rats: correlation of ¹H and ³¹P NMR spectroscopy with fatty acid and excitatory amino acid levels. *J Cereb Blood Flow Metab*. 1992;12:456–468.
60. Li PA, Shuaib A, Miyashita H, He QP, Siesjö BK, Warner DS. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. *Stroke*. 2000;31:183–192.
61. Siesjö BK, Bendek G, Koide T, Westerberg E, Wieloch T. Influence of acidosis on lipid peroxidation in brain tissues in vitro. *J Cereb Blood Flow Metab*. 1985;5:253–258.
62. OuYang YB, Mellergård P, Kristián T, Kristiánova V, Siesjö BK. Influence of acid-base changes on the intracellular calcium concentration of neurons in primary culture. *Exp Brain Res*. 1994;101:265–271.
63. Anderson RE, Tan WK, Martin HS, Meyer FB. Effects of glucose and PaO₂ modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke*. 1999;30:160–170.
64. Cronberg T, Rytter A, Asztely F, Söder A, Wieloch T. Glucose but not lactate in combination with acidosis aggravates ischemic neuronal death in vitro. *Stroke*. 2004;35:753–757.
65. Smith D, Pernet A, Hallett WA, Bingham E, Marsden PK, Amiel SA. Lactate: a preferred fuel for human brain metabolism in vivo. *J Cereb Blood Flow Metab*. 2003;23:658–664.
66. Gill R, Andine P, Hillered L, Persson L, Hagberg H. The effect of MK-801 on cortical spreading depression-induced calcium transients on neuronal viability in moderately hypoglycemic rats. *J Cereb Blood Flow Metab*. 1992;12:371–379.
67. Hopwood SE, Parkin MC, Bezzina EL, Boutelle MG, Strong AJ. Transient changes in cortical glucose and lactate levels associated with peri-infarct depolarisations studied with rapid sampling microdialysis. *J Cereb Blood Flow Metab*. 2005;25:391–401.
68. Strong AJ, Boutelle MG, Vespa PM, Bullock MR, Bhatia R, Hashemi P. Treatment of Critical care Patients with substantial acute ischemic or traumatic brain injury. *Crit Care Med*. 2005;33:2147–2149.
69. Christensen H, Boysen G. Blood glucose increases early after stroke onset: a study on serial measurements of blood glucose in acute stroke. *Eur J Neurol*. 2002;9:297–301.
70. Allport LE, Baird TA, Butcher KS, Macgregor L, Prosser J, Colman P, Davis S. Frequency and temporal profile of poststroke hyperglycemia using continuous glucose monitoring. *Diabetes Care*. 2006;29:1839–1844.
71. Gray CS, Scott JF, French JM, Alberti KG, O'Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. *Age Ageing*. 2004;33:71–77.
72. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
73. Cox NH, Lorains JW. The prognostic value of blood glucose and glycosylated haemoglobin estimation in patients with stroke. *Postgrad Med J*. 1986;62:7–10.
74. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med*. 1983;74:540–544.
75. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
76. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurol*. 2002;59:669–674.
77. Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, Codina A, Quintana M. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. *Stroke*. 2003;34:1235–1241.
78. Alvarez-Sabin J, Molina CA, Ribo M, Arenillas JF, Montaner J, Huertas R, Santamarina E, Rubiera M. Impact of admission hyperglycemia on stroke outcome after thrombolysis: risk stratification in relation to time to reperfusion. *Stroke*. 2004;35:2493–2498.
79. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Mönting J, Schumacher M, Lücking CH. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. *Cerebrovasc Dis*. 2002;13:89–94.
80. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, Quintana M, Alvarez-Sabin J. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke*. 2005;36:1705–1709.
81. Benz J, Hofmann A. Annexins: from structure to function. *Biol Chem*. 1997;378:177–183.
82. Martini SR, Hill MD, Alexandrov AV, Molina CA, Kent TA. Outcome in hyperglycemic stroke with ultrasound-augmented thrombolytic therapy. *Neurol*. 2006;67:700–702.
83. Hamilton M, Tranmer B, Auer RN. Insulin reduction of cerebral infarction due to transient focal ischemia. *J Neurosurg*. 1995;82:262–268.
84. Fukuoka S, Yeh H, Mandybur T, Tew J. Effect of insulin on acute experimental cerebral ischemia in gerbils. *Stroke*. 1989;20:396–399.
85. Zhao YJ, Yang GY, Domino EF. Acute ethanol effects on focal cerebral ischemia in nonfasted rats. *Alcohol Clin Exp Res*. 1997;21:745–748.
86. Nedergaard M, Diemer NH. Focal ischemia of the rat brain with special reference to the influence of plasma glucose concentration. *Acta Neuropathologica*. 1987;73:131–137.
87. Bomont L, MacKenzie ET. Neuroprotection after focal cerebral ischemia in hyperglycaemic and diabetic rats. *Neurosci Lett*. 1995;197:53–56.
88. Izumi Y, Roussel S, Pinard E, Seylaz J. Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. *J Cereb Blood Flow Metab*. 1991;11:1025–1030.
89. Izumi Y, Pinard E, Roussel S, Seylaz J. Insulin protects brain tissue against focal ischemia in rats. *Neurosci Lett*. 1992;144:121–123.
90. Kazan S, Karasoy M, Baloglu H, Tuncer R. The effect of mild hypothermia, mannitol and insulin induced hypoglycaemia on ischaemic infarct volume in the early period after permanent middle cerebral artery occlusion in the rat. *Acta Neurochir (Wien)*. 1999;141:979–987.
91. Combs DJ, Dempsey RJ, Kumar S, Donaldson D. Focal cerebral infarction in cats in the presence of hyperglycemia and increased insulin. *Metab Brain Dis*. 1990;5:169–178.
92. Bruno A, Biller J, Adams HP Jr, Clarke WR, Woolson RF, Williams LS, Hansen MD. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurol*. 1999;52:280–284.
93. Kase CS, Furlan AJ, Wechsler LR, Higashida RT, Rowley HA, Hart RG, Molinari GF, Frederick LS, Roberts HC, Gebel JM, Sila CA, Schulz GA, Roberts RS, Gent M. Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. *Neurol*. 2001;57:1603–1610.
94. Martini S, Hill M, Alexandrov A, Molina C, Kent T. Outcome in hyperglycemic stroke with ultrasound augmented thrombolytic therapy. *Neurol*. 2006;67:700–702.
95. Ribo M, Molina CA, Delgado P, Rubiera M, Delgado-Mederos R, Rovira A, Munuera J, Alvarez-Sabin J. Hyperglycaemia during ischaemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622.
96. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Mönting J, Schumacher M, Lücking CH. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. *Cerebrovasc Dis*. 2002;13:89–94.