Glycemic control in acute stroke: ‘balancing the risks’
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HYPERGLYCEMIA IN ANEURYSMAL SUBARACHNOID HEMORRHAGE: A POTENTIALLY MODIFIABLE RISK FACTOR

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ABSTRACT

Hyperglycemia after aneurysmal subarachnoid hemorrhage (SAH) occurs frequently and is associated with delayed cerebral ischemia (DCI) and poor clinical outcome. In this review we highlight the mechanisms that cause hyperglycemia after aneurysmal SAH and we discuss how hyperglycemia may contribute to poor clinical outcome in these patients. As hyperglycemia is potentially modifiable with intensive insulin therapy (IIT), we systematically reviewed the literature on IIT in aneurysmal SAH patients. In these patients IIT appears to be difficult to achieve in terms of lowering blood glucose levels substantially without an increased risk of (serious) hypoglycemia. Therefore, a large scale randomized trial is initiated to investigate the clinical benefit of IIT, phase II studies, possibly with the help of cerebral blood glucose monitoring by microdialysis, will first have to improve this therapy in terms of both safety and adequacy.
INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with high case morbidity and case fatality rates.\textsuperscript{3} Although these rates have decreased in the last decades, still 35% of aneurysmal SAH patients die within the first month after the hemorrhage.\textsuperscript{287} Prevention and treatment of neurological complications such as rebleeding, hydrocephalus and delayed cerebral ischemia (DCI) are obvious targets to improve prognosis. Besides neurological complications, patients with aneurysmal SAH often have cardiopulmonary and general medical complications that can influence outcome. Hyperglycemia in aneurysmal SAH patients is common and associated with poor clinical outcome.\textsuperscript{123,203-206,218,254} As treatment for hyperglycemia is available, it has attracted increasing attention as a target for intervention, although adequate and safe glycemic control is difficult to achieve in patients with aneurysmal SAH.

As hyperglycemia appears to be implicated in the pathway from aneurysmal SAH to poor clinical outcome, insight into these mechanisms may reveal new treatment options. We undertook a non-systematic literature search to provide an overview of the potential causes and consequences of hyperglycemia in aneurysmal SAH patients and to address the pathophysiological mechanisms that might link hyperglycemia to poor clinical outcome. Furthermore, we performed a systematic literature search to review studies on glycemic control in aneurysmal SAH patients. Finally, we provide directions for further trials and clinical management concerning glycemic control in this patient group.

MECHANISMS LEADING TO HYPERGLYCEMIA AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

In patients admitted within 72 hours from aneurysmal SAH, mean admission glucose is around 9 mmol/L, and around 3 out of 4 patients with aneurysmal SAH are hyperglycemic on admission.\textsuperscript{254} Studies that report on glucose levels during the first 1 or 2 weeks of the clinical course report that hyperglycemia persists with levels exceeding 7 to 8 mmol/L.\textsuperscript{123,204-206,218} In ischemic stroke, hyperglycemia on admission is also frequent.\textsuperscript{11} This is, at least in part, attributed to (unrecognized) abnormalities of glucose metabolism such as diabetes mellitus (DM) that is existent prior to the stroke in around one third of patients.\textsuperscript{36,38,288} As DM is not a risk factor for aneurysmal SAH,\textsuperscript{236,289} and as patients with SAH are relatively young, the proportion of aneurysmal SAH patients with pre-existent abnormalities of glucose metabolism is much smaller than in patients with ischemic stroke.

There are several explanations for the increased glucose levels in acute aneurysmal SAH patients. First, aneurysmal SAH is accompanied by the activation of the hypothalamic–pituitary–adrenal axis and the activation of the sympathetic autonomic nervous system.\textsuperscript{39} This activation results in an increase in the levels of stress hormones such as cortisol and catecholamines up to day 10 after the aneurysmal SAH.\textsuperscript{279,290} These hormones enhance glycogenolysis, gluconeogenesis, proteolysis and lipolysis, all resulting in excessive glucose production.\textsuperscript{43,44} Moreover, catecholamines inhibit glucose transport by inhibition of insulin binding, resulting in insulin resistance with hyperinsulinemia.\textsuperscript{45,46} Indeed, increased levels of cortisol are associated with increased levels of blood glucose in aneurysmal SAH patients.\textsuperscript{279} Second, aneurysmal SAH is accompanied by an increased inflammatory response with release of cytokines.\textsuperscript{291} Cytokines, in turn, have been linked directly to hyperglycemia and insulin resistance.\textsuperscript{54,55,291,292} In addition, cytokines stimulate the hypothalamic–pituitary–adrenal–axis, further increasing the stress...
response. Interestingly, an altered glucose metabolism and hyperglycemia can in turn also stimulate the inflammatory response, raising the question of what is the cause and what is the effect. Third, besides a central role in the stress reaction, the hypothalamus also has an important role in maintaining glucose homeostasis by reducing hepatic gluconeogenesis and increasing insulin sensitivity. Neuropathological studies show that the majority of acute aneurysmal SAH patients have hypothalamic lesions. Moreover, a recent study reported hypothalamic dysfunction in the acute phase of aneurysmal SAH, while the same study could not confirm previous findings of hypothalamic dysfunction at longer (years) follow-up. Whether acute hypothalamic dysfunction indeed contributes to hyperglycemia in aneurysmal SAH patients is currently unclear.

In conclusion, increased stress and inflammatory responses appear to be the most important contributors to hyperglycemia after aneurysmal SAH. Pre-existent abnormalities of glucose metabolism do not seem to have a prominent role in aneurysmal SAH patients and the role of hypothalamic dysfunction and impaired glucose homeostasis remains uncertain (figure 1, upper panel).

HYPERGLYCEMIA AND CLINICAL OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

Patients with hyperglycemia have an approximately threefold increased risk for poor outcome, and this appears unrelated to the different cut-off levels used to define hyperglycemia. The association between high levels of blood glucose and poor clinical outcome is more pronounced with persistent hyperglycemia than with hyperglycemia on admission. A recent study showed that aneurysmal SAH patients with persistent hyperglycemia are seven times more likely to have poor outcome than patients with normoglycemia, whereas in the same study isolated hyperglycemic events throughout the clinical course were not predictive of poor outcome.

HOW DOES HYPERGLYCEMIA AFFECT OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE?

Although several studies found that high levels of blood glucose in the acute phase of aneurysmal SAH are an independent risk factor for poor clinical outcome, this does not prove causality of that relation. Elevated levels of admission blood glucose for example could constitute no more than a marker of SAH severity rather than a causative factor leading to secondary damage and consequently poorer clinical outcome. Indeed, high levels of admission glucose are associated with more severe SAH. On the other hand, several experimental and imaging studies, as well as clinical observations, have highlighted mechanisms through which hyperglycemia may affect clinical outcome after aneurysmal SAH. (figure 1, lower panel). In critical illness in general, hyperglycemia on admission and during the clinical course is associated with various in-hospital complications such as respiratory failure, nosocomial infections and impaired wound healing, all of which are contributors to poor outcome. Several trials, also in aneurysmal SAH patients showed that IIT lowered these in-hospital complications. Another factor that could link hyperglycemia to poor outcome is DCI. The DCI occurs in approximately one-third of aneurysmal SAH patients, mostly between days 4-10, and can progress to irreversible cerebral infarction with subsequent poor clinical outcome. Patients with hyperglycemia on admission or during the clinical course develop DCI and
The association between admission hyperglycemia and DCI was weaker than that of persistent hyperglycemia and DCI, and the association between admission glucose and DCI did not persist after multivariable assessment in several studies. The fact that aneurysmal SAH patients with pre-existent DM are at an increased risk of DCI compared to aneurysmal SAH patients without pre-existent DM lends further support of a link between abnormalities of glucose metabolism and DCI in aneurysmal SAH patients.
The cause of DCI in aneurysmal SAH patients remains unclear, but various mechanisms have been proposed that may be influenced by hyperglycemia. One of these mechanisms is vasospasm, which is frequently seen in aneurysmal SAH patients. In vitro and in vivo studies have linked hyperglycemia to vascular tone by inhibition of vasodilatation and by increasing vasoconstriction. Vasodilatation is predominantly mediated by endothelium derived-nitric oxide. In vitro studies show that hyperglycemia reduces the production of nitric oxide by increasing the activity of Nicotinamide Adenine Dinucleotide Phosphate oxidase. In healthy individuals, glucose infusion for six hours reduces endothelium-dependent vasodilatation. Moreover, hyperglycemia is associated with the formation of vasoconstrictive prostaglandins and increased eicosanoid production, both resulting in vasoconstriction.

Although vasospasm is associated with the occurrence of DCI, it does not fully explain DCI. Several other mechanisms, of which micro-thrombosis and inflammation are the most prominent, appear to contribute to DCI. Hyperglycemia is closely linked to increased coagulation and decreased fibrinolysis, both of which enhance thrombin formation. In studies in healthy individuals, hyperglycemia stimulates coagulation by increasing platelet activation via thrombin-antithrombin complexes and the tissue factor pathway, and hyperinsulinemia decreases fibrinolytic activity by increasing plasminogen activator inhibitor. Besides interference with coagulation and fibrinolysis, hyperglycemia is also associated with an increase in pro-inflammatory transcription factors and pro-inflammatory cytokines. In aneurysmal SAH patients, several studies have linked markers of increased inflammation to the development of DCI. Once DCI is established in aneurysmal SAH patients, the most imminent danger is that potentially reversible ischemic tissue progresses to irreversible infarcted tissue. Experimental and clinical imaging studies in ischemic stroke show that hyperglycemia is associated with this progression. Although restoration of blood flow to ischemic tissue is essential, reperfusion itself can also induce injury: so-called reperfusion injury. The mediators of reperfusion injury are inflammation and oxidative stress. Markers of inflammation are associated with the progression of cerebral ischemia to infarction, and, in experimental stroke, inhibition of the inflammatory response reduces infarct size. As outlined earlier, hyperglycemia increases the inflammatory response, and may therefore exacerbate reperfusion injury. The other mediator of reperfusion injury, oxidative stress, results from an imbalance between the production and neutralization of reactive oxygen species. Reactive oxygen species have been shown to increase neuronal death and infarct volume. In experimental ischemic stroke, hyperglycemia increases the production of reactive oxygen species through the activation of proteine kinase C and through increased nicotinamide adenine dinucleotide phosphate production, thus promoting oxidative stress. In addition to increased reperfusion injury, hyperglycemia also promotes anaerobic glycolysis leading to the accumulation of lactic acid and a derangement in pH homeostasis. Both these processes have been proposed to contribute to increased brain injury. In support of a detrimental role of lactic acid is the finding that in patients with cerebral ischemia, hyperglycemia correlates with both an increased lactate production and with the progression from ischemic to infarcted tissue. In conclusion, a causal relation between hyperglycemia and poor outcome in aneurysmal SAH patients remains elusive, but in the sequence of events that occur after aneurysmal SAH, hyperglycemia may exert a detrimental effect by increasing secondary complications such as infection and cerebral ischemia, as well as by facilitating the progression from ischemia to...
irreversible infarction. Besides lowering of blood glucose levels with insulin, a more mechanistic approach with interventions directly aimed at the restoration of glucose homeostasis have potential clinical relevance. For example, pharmacological neutralization of cytokines was shown to revert insulin resistance, and inhibition of cortisol production prevented hyperglycemic aggravation of ischemic neuronal damage. These findings, however, are experimental and should not be extrapolated to the clinical setting.

GLUCOSE-LOWERING TREATMENT

STUDIES IN NON-ANEURYSMAL SUBARACHNOID HEMORRHAGE PATIENTS.

Before addressing glucose-lowering treatment in aneurysmal SAH patients, we first summarize current insights on this topic in other groups of critically ill patients because this provides relevant background information. In 2001, intensive insulin therapy (IIT) was implemented worldwide in ICU facilities after a landmark trial from Leuven demonstrated its clinical benefit in a surgical ICU. Several later trials could not confirm the previous positive findings. In one of these trials IIT was even associated with an increased risk of serious hypoglycemia (glucose <2.2 mmol/L) and subsequent poor clinical outcome. It remains unclear why these recent and earlier trials show conflicting results. One possible explanation is that in the time frame that separated these trials, the standards for hyperglycemia management in “regular care” had become more rigorous, thus decreasing the potential contrast with an IIT group in trials. Meanwhile, IIT is still recommended for patients admitted to an ICU, but the negative trials have emphasized the important drawback of IIT namely increased incidence of hypoglycemia. In stroke other than aneurysmal SAH, the UK Glucose Insulin in Stroke Trial (GIST-UK) failed to demonstrate a clinical benefit from glycemic control on clinical outcome. This trial, however, was stopped prematurely because of slow enrolment. Other limitations of the trial were a relatively short duration of treatment (24 hours) and a small contrast in mean glucose levels (0.57 mmol/L) between the intervention and control group.

STUDIES IN ANEURYSMAL SUBARACHNOID HEMORRHAGE PATIENTS

We performed a systematic literature search on glucose-lowering treatment in aneurysmal SAH patients. MEDLINE was searched on published studies from 1966 to February 2010 written in English, German, French, or Spanish. We used the medical subject headings (MeSH) and search terms “blood glucose” and “subarachnoid hemorrhage” truncated text words “hyperglyc(a)emia,” “glucose,” “subarachnoid,” ,“SAH,” “h(a)emorrhage,” and “bleeding” in different combinations. Studies describing a consecutive series of aneurysmal SAH patients that were treated with IIT and that reported glucose levels during IIT (i.e. not only admission glucose levels) could be included. When an article complied with the inclusion criteria but lacked information on parameters of hypoglycemia, we approached the authors to obtain these data. We hand-searched the bibliographies of all included articles and abstract books of the European and American stroke congresses held from January 2008 to October 2009. The MEDLINE search yielded 92 articles. Most articles were excluded because patients were not given IIT or because glucose levels during the clinical course were not reported (58). Other reasons for exclusion were non consecutive series (20), same population described (2) and non aneurysmal SAH patients described (6). No additional relevant studies were found by searching...
## Table 1 | Studies reporting on intensive insulin therapy in SAH patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>N</th>
<th>Intervention target (mmol/L)</th>
<th>Glycemic control parameters</th>
<th>Hypoglycemia parameters</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell311</td>
<td>Pilot, uncontrolled</td>
<td>55</td>
<td>5.0-7.0</td>
<td>75% assessments &lt;7.0</td>
<td>0.9% assessments &lt;3.5;</td>
<td>-</td>
</tr>
<tr>
<td>Bilotta312</td>
<td>randomized controlled trial</td>
<td>38</td>
<td>Controls: 4.4-12.2</td>
<td>Controls: 4.4-12.2</td>
<td>Controls: 4.4-12.2</td>
<td>6 months clinical outcome and vasospasm: no difference. Infection rate decreased with ITT (42 - 27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>IIT: 4.4-6.6</td>
<td>IIT: 4.4-6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latorre27</td>
<td>sequential comparison†</td>
<td>166</td>
<td>Pre-protocol: &lt;11.1</td>
<td>mean glucose: 8.9 (± 1.7)</td>
<td>2.4% of assessments &lt;3.9</td>
<td>3-6 months poor outcome decreased with IIT. (40.2 - 28.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>166</td>
<td></td>
<td>mean glucose: 8.0 (± 0.9)</td>
<td>12.7% of assessments &lt; 3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIT: 4.4-7.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiele313</td>
<td>sequential comparison†</td>
<td>343</td>
<td>Pre protocol: NR</td>
<td>median glucose: 6.7 [6.2-7.4]</td>
<td>1.5% patients ≥1 episode with glucose &lt;3.3</td>
<td>No effect on overall in-hospital mortality with ITT.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>491</td>
<td>IIT: 5.0-6.7</td>
<td>median glucose: 6.5 [6.0-6.9]</td>
<td>7.1% patients ≥1 episode with glucose &lt;3.3</td>
<td></td>
</tr>
<tr>
<td>Schlenck323</td>
<td>Prospective cohort</td>
<td>178</td>
<td>IIT: 4.4-7.8</td>
<td>mean glucose: 7.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Naidech314</td>
<td>Prospective Cohort</td>
<td>172</td>
<td>IIT: 4.4-6.1</td>
<td>mean glucose: 6.8 (± 0.8)</td>
<td>Mean lowest glucose: 4.7; one serious hypoglycemic event (&lt;2.2)</td>
<td></td>
</tr>
</tbody>
</table>

N: number of patients included; * these data were provided by the authors upon request; †: This means a comparison between a cohort before and a cohort after the introduction of intensive insulin therapy (IIT); NR: not reported [inter quartile range].
the bibliographies or abstract books. We identified six studies (listed in table 1); five cohort studies, of which two compared glucose levels before and after the introduction of IIT and one small randomized controlled trial.\(^{27,311-314}\) In all identified studies, patients were admitted to an ICU. Glucose levels targets varied somewhat between the studies with upper limits of glucose levels ranging from 6 to 7.8 mmol/L and lower limits ranging from 4.4 to 5.0 mmol/L. The cut-off level used to define hypoglycemia varied between studies (3.5 to 4.4 mmol/L). None of the studies reported neurological deterioration during hypoglycemia; however, the warning symptoms of hypoglycemia might be less clear in patients with aneurysmal SAH than in other patients, as these symptoms are similar to some stroke comorbidities.\(^{139}\) One uncontrolled pilot study showed that IIT was feasible but was accompanied by hypoglycemic episodes.\(^{311}\)

In the only randomized trial that was designed to test the applicability of IIT, 78 patients were enrolled. IIT reduced the mean glucose from 8.0 to 5.0 mmol/L, but increased hypoglycemic episodes from 3.5 to 10.5%.\(^{312}\) IIT reduced the infection rate from 42 to 27% (p<0.001), but did not improve clinical outcome, although the number of included patients was too small to reliably address this. Currently a phase II safety study with hypoglycemia as primary outcome by the same research group aims to randomize 800 neurosurgical ICU patients between IIT and regular care.\(^{240}\)

We identified two sequential observation studies comparing clinical outcome in aneurysmal SAH patients before and after the introduction of IIT.\(^{27,313}\) The first study (total n=332) used a prospective database, with retrospective review of patient characteristics and clinical outcome data.\(^{27}\) After the introduction of IIT, mean blood glucose levels decreased from 8.9 to 8.0 mmol/L, while the percentage of glucose measurements that fell in the hypoglycemic range increased from 2.4 to 12.7%. At baseline, IIT-treated patients more often had hypertension, DM and cerebral infarction. Still, clinical outcome was better in IIT-treated patients compared to non-IIT-treated patients (OR for poor outcome, 0.25; 95% confidence interval, 0.08 to 0.80), although this difference was not significant after adjusting for temporal trend, i.e. taking into account that other variables than IIT could improved clinical outcome. The second study that compared clinical outcome in aneurysmal SAH patients before and after the introduction of IIT was larger (N=834), but clinical data were collected retrospectively.\(^{313}\) IIT achieved only a small reduction in the mean glucose (0.2 mmol/L) and glucose measurements that fell in the hypoglycemic increased from 1.5 to 7.1%. In this study IIT was not accompanied by a reduction of in-hospital mortality. However, the study lacked data on baseline aneurysmal SAH severity, while patients receiving IIT more often had intraventricular or parenchymal hematoma, which suggests more severe aneurysmal SAH in this group. In conclusion, currently there is no evidence that hyperglycemia in aneurysmal SAH patients should be lowered actively. Moreover, IIT is accompanied by an increase in hypoglycemic episodes which should raise concerns about the safety of this therapy.

**RISK OF INTENSIVE INSULIN THERAPY: HYPOGLYCEMIA.**

As noted earlier, ITT is invariably accompanied by hypoglycemic episodes, which is posing a potential risk to aneurysmal SAH patients subjected to this therapy. The brain relies on the continuous delivery of glucose via the blood to maintain normal metabolic function. Moreover, various studies indicate that under conditions of acute brain injury glucose utilization is increased.\(^{315-317}\) Thus, it is conceivable that hypoglycemia on top of pre-existing cerebral damage and the increased glucose utilization is even more detrimental than for the
healthy brain (double hit theory).\textsuperscript{140} Besides simple deprivation of energy, another interesting explanation for hypoglycemia to be detrimental to the brain is the occurrence of cortical spreading depression (CSD), a slowly moving wave that leads to intracellular calcium overload and depression of synaptic activity.\textsuperscript{318} Such depolarization waves occur frequently in patients with aneurysmal SAH.\textsuperscript{319,320} In focal ischemia of nonhuman primates, even mild hypoglycemia promoted the occurrence of CSDs.\textsuperscript{319,320} More recently, in a patient with aneurysmal SAH, a severe cluster of CSDs was associated with (IIT induced) hypoglycemia.\textsuperscript{319,320} Interestingly, CSD can by itself also lead to the depletion of extracellular cerebral glucose levels thereby further jeopardizing brain tissue.\textsuperscript{321} Although IIT was never proven to be beneficial for neurologic critically ill patients, various IIT protocols, often with different glycemic targets, are being used on ICU’s worldwide also for this particular patient group (see Table 1). This has driven various research groups to investigate the metabolic consequences of IIT in patients with brain injury with the use of microdialysis.\textsuperscript{225,322-325} This technique, for which a micro-catheter is inserted into the brain parenchyma, allows \textit{in vitro} monitoring of regional brain metabolites such as glucose, lactate, glutamate and glycerol.\textsuperscript{326} Observations from these studies increase our understanding of regional metabolic changes in response to changes in serum blood glucose levels, and potentially contribute to rational glycemic targets that should be aimed for with IIT. Various studies have shown that brain injury, including aneurysmal SAH, is accompanied by metabolic derangements that indicate distress such as increased glutamate, glycerol and lactate/pyruvate ratio.\textsuperscript{317,322,324} In patients with traumatic brain injury, IIT induced low levels of blood glucose were associated with reduced cerebral glucose availability and increased prevalence of metabolic distress.\textsuperscript{317,324} For patients with aneurysmal SAH this association appears less clear. Various studies have shown that levels of systemic glucose do not necessarily correlate with cerebral glucose levels after aneurysmal SAH,\textsuperscript{322,323} although in the largest study, including 178 aneurysmal SAH patients, it was shown that when mean inpatient blood glucose levels exceeded 7.8 mmol/L, cerebral glucose levels also increased.\textsuperscript{323} The same group also reported that extracellular cerebral glucose levels decreased 3 hours after initiation of despite stable blood glucose levels.\textsuperscript{327} Moreover, episodes of low cerebral glucose occurred somewhat more frequent in IIT treated patients than in patients not treated with insulin.\textsuperscript{322,327} Unfortunately in these studies no episodes of serum hypoglycemia were monitored, which could have provided insight into cerebral metabolites during such condition. Recently, another group reported that abrupt reductions of blood glucose of more than 25% rather than an absolute decrease in blood glucose levels were associated with brain metabolic crisis (defined as an increased lactate/pyruvate ratio) occurring hours thereafter.\textsuperscript{328} Although the studies that used microdialysis are generally small, often retrospective and without randomization for patients with or without IIT, they do emphasize that IIT is not without risk. In this respect, especially the observations that low levels of serum glucose are sometimes also accompanied by low extracellular glucose levels and that abrupt reductions of glucose levels are accompanied by brain metabolic crisis should warrant caution in executing IIT in these patients.

**CONCLUSIONS AND FUTURE DIRECTIONS**

For a long time hyperglycemia was thought to be an adaptive beneficial response to critical illness to provide those organs that predominantly rely on glucose as metabolic substrate
such as the brain. With the publication of the landmark Leuven trials, however, this concept has changed dramatically and IIT was implemented worldwide for all kinds of critically ill patients, including patients with brain injury. It is important, however, to realize that today IIT was proven only in mono-center studies and for a subgroup of critically ill patients. In addition, more recently a large multicenter study could not prove a beneficial effect from IIT and IIT was even associated with an increased risk of severe hypoglycemia and subsequent poor clinical outcome. Therefore, although hyperglycemia, especially if persistent during the clinical course, clearly predicts poor clinical outcome in aneurysmal SAH patients, care should be taken in extrapolating previous positive data to aneurysmal SAH patients. The most recent guidelines for the treatment of aneurysmal SAH state that it is imperative to avoid hyperglycemia. However, it is unclear which glucose levels should be targeted and how this has to be accomplished. Only a large scale randomized controlled trial that investigated the clinical benefit of IIT in aneurysmal SAH patients will be able to resolve this issue.

Before initiating such a trial, however, it is important to improve glycemic control in phase II studies with special reference to safety. In these studies, focus should be not only on the lowering of glucose levels, but, and perhaps even more so, on the prevention of hypoglycemia related to this therapy. As for the question which glucose targets should be aimed at, there is no unambiguous answer. On the one hand, when IIT does not achieve a substantial lowering of blood glucose levels compared with standard ICU therapy this treatment is not likely to result in a clinical benefit. On the other hand, the most recent trials in non-aneurysmal SAH patients have shown that IIT targeting blood glucose levels in a low physiological range (4.4 to 6.1 mmol/L) is associated with serious hypoglycemic episodes (glucose < 2.2 mmol/L) and subsequent worse clinical outcome. A recent cohort study in aneurysmal SAH patients emphasized this, by demonstrating that not high, but IIT induced nadir levels of blood glucose, were associated with poor clinical outcome. Possibly, as in other critically ill patients, there is a U-shaped admission glycemia- mortality risk curve in aneurysmal SAH patients with both low and high blood glucose levels relating to worse outcome. Ideally, glucose levels in the flat part of this curve should be targeted. From the studies we identified, however, strict glucose control in aneurysmal SAH patients appears difficult to establish without a risk of (serious) hypoglycemia. The definition of an optimal and safe glycemic target range is as yet unclear and may not be uniform among patients and even vary for individual patients at various time points during the clinical course. Future studies that monitor brain metabolites with microdialysis and CSDs with electrocorticography could perhaps facilitate the identification of a safe glycemic range from a brain’s metabolic perspective, although this would not be easy to implement in clinical practice, as currently most ruptured aneurysms are treated with endovascular coiling, and the occurrence of a hydrocephalus, the other intervention providing the possibility to insert a microdialysis catheter, occurs in only 30% of patients. All studies we identified on ITT were performed in the ICU setting. Patients with clinically less severe aneurysmal SAH are sometimes admitted to a stroke unit. In contrast to an ICU, a stroke unit often lacks the highly intensive treatment facilities available on the ICU. For instance, the lack of direct access to frequent arterial blood glucose monitoring and fewer personnel per patient to execute laborious treatment algorithms could render glycemic control even more challenging than on the ICU facility. In view of this, if it is decided to actively lower treat hyperglycemia in aneurysmal SAH patients as is recommended by the guidelines, the
best advice seems to institute a multidisciplinary team, including stroke and diabetes experts to facilitate the implementation of glucose lowering protocols with the aim to lower blood glucose levels only if this can be done without subsequent hypoglycemia. Such a protocol should probably include close monitoring of blood glucose levels with a high rate of insulin adjustments (i.e. every one- or two hours). Continuous glucose monitoring devices that are now becoming available and the use of computerized treatment algorithms have the potential to facilitate this, but the safety of these devices will have to be investigated first.333

In conclusion, target levels of blood glucose will remain arbitrary until a randomized control trial has investigated the clinical benefit of IIT. Before such a trial can start, focus should be on how IIT can be improved both in terms of efficacy but perhaps more important in terms of safety.