Intravenous thrombolysis for acute ischemic stroke is still underused. Only 4% to 5% of all patients with ischemic stroke are currently treated with recombinant tissue plasminogen activator (rtPA). The limited use of rtPA is only partly attributable to the logistical demands of the narrow time window for treatment and current limitations of diagnostic accuracy. In a considerable number of patients, treatment is withheld foremost because of mild or improving stroke symptoms, but also because of safety concerns, especially the fear of symptomatic intracerebral hemorrhage (sICH).

sICH after intravenous treatment with rtPA is a potentially devastating event with a high mortality rate. As a consequence, international guidelines recommend excluding patients with an excessive bleeding risk from treatment with rtPA. Among other factors, acute and chronic damage of the microvasculature are thought to increase the risk of hemorrhage after rtPA. Most important risk factors for chronic microvascular injury are long-term arterial hypertension and chronically elevated glucose levels in diabetes mellitus.

Hemoglobin A1 (HbA1c) is a well-established marker for long-term elevated glucose level and is widely used for monitoring diabetic vascular damage, that is, the development of atherosclerosis and microangiopathic changes, such as retinopathy, nephropathy, and cerebral angiopathy of small vessels. In this analysis, we investigated the predictive value of HbA1c for sICH and clinical outcome in patients treated with rtPA for acute ischemic stroke.

Background and Purpose—Symptomatic intracerebral hemorrhage (sICH) is the most feared acute complication after intravenous thrombolysis. The aim of this study was to determine the predictive value of parameters of glycosylated hemoglobin A1 (HbA1c) on sICH.

Methods—In a retrospective single center series, 1112 consecutive patients treated with thrombolysis were studied. Baseline blood glucose was obtained at admission. HbA1c was determined within hospital stay. A second head computed tomography was obtained after 24 hours or when neurological worsening occurred. Modified Rankin Scale was used to assess outcome at 90 days.

Results—A total of 222 patients (19.9%) had any hemorrhage; 43 of those had sICH (3.9%) per Safe Implementation of Treatments in Stroke definition and 95 (8.5%) per National Institute of Neurological Disorders and Stroke definition; 33.2% of patients had a dependent outcome (modified Rankin Scale score 3–5). In univariate analysis history of diabetes mellitus, HbA1c, blood glucose, and National Institute of Health Stroke Scale score on admission were associated with any hemorrhage and sICH. In multivariate analysis National Institute of Health Stroke Scale score, a history of diabetes mellitus, and HbA1c were predictors of sICH per National Institute of Neurological Disorders and Stroke, and only HbA1c when Safe Implementation of Treatments in Stroke criteria were used.

Conclusions—In our study, HbA1c turns out to be an important predictor of sICH after thrombolysis for acute stroke. These results suggest that hemorrhage after thrombolysis may be a consequence of long-term vascular injury rather than of acute hyperglycemia, and that HbA1c may be a better predictor than acute blood glucose or a history of diabetes mellitus. (Stroke. 2013;44:00-00.)

Key Words: acute stroke ■ blood glucose ■ glycosylated hemoglobin ■ outcome ■ thrombolytic therapy ■ tissue plasminogen activator ■ symptomatic hemorrhage
Patients and Methods

Diagnostic and Treatment Protocol

We studied all consecutive patients with acute ischemic stroke admitted to the Neurological Department in Heidelberg and treated with intravenous rtPA between March 1998 and November 2011. Data were entered into our prospective stroke database, including age, sex, medical history, cardiovascular risk factors, time of symptom onset, time of start of rtPA treatment, National Institute of Health Stroke Scale (NIHSS) score on admission and discharge, laboratory data (including baseline glucose, HbA1c), stroke origin according to the following Trial of Org 10172 in Acute Stroke Treatment criteria: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion (lacunar), (4) stroke of other determined pathogenesis, and (5) stroke of undetermined pathogenesis, and Modified Rankin Scale at day 90.

Quantitative determination of HbA1c (%) was performed by high performance liquid chromatography within hospital stay (but within a maximum of 7 days). Computed tomographic (CT) or MRI scans were repeated at 20 to 36 hours after treatment or whenever a neurological worsening occurred.

sICH was assessed per Safe Implementation of Thrombolysis in Stroke (SITS)10 and National Institute of Neurological Disorders and Stroke (NINDS)11 criteria. Any ICH was defined as any blood on the follow-up CT scan.

Outcome Parameters

Outcome parameters included the occurrence of sICH within 24 hours, the occurrence of any ICH, mortality and functional outcome at 3 months, assessed by the Modified Rankin Scale: a score of 3 to 5 was defined as dependent outcome. Neurological assessment at follow-up was made by a trained stroke-neurologist or study nurse in the outpatient setting. If the visit could not be made, a standardized telephone interview for functional outcome was done.

Statistical Analysis

All analyses were performed using the SPSS version 19.0 software package. Data are expressed as median and range, and were compared by nonparametric tests because of deviation from normality in most instances. To assess correlations between baseline variables, Pearson Correlation or Spearman ρ was used as appropriate. Pearson χ² and Fisher exact tests were used to assess associations between categorized variables. Mann–Whitney U test was used to determine intergroup differences between continuous variables. We assessed for possible collinearity between the included variables by performing a linear regression model using multicollinearity diagnostic statistics for determining the variance factor, in which we included the independent variables from our final logistic regression model. No substantial multicollinearity was found.

A value of P≤0.05 was considered statistically significant. Univariate analysis was performed to find predictors for any bleeding and sICH (NINDS and SITS). Multivariate logistic regression backward analysis was used to analyze independent predicting factors for any hemorrhage, sICH, and clinical outcome. Receiver-operating characteristics were developed for sICH, any ICH, and mortality at 90 days. Areas under receiver-operating characteristics (c-statistic) and 95% confidence interval (CI) were calculated as a measure of predictive ability.

Results

We studied a total of 1112 patients (52.4% men). Baseline blood glucose values were available in 1110 patients and HbA1c in 1095 patients. Demographic and baseline characteristics, clinical, and biochemical data are given in Table 1.

Predictors of Any Hemorrhage and sICH

Any hemorrhage occurred in 222 of patients (19.9%); 43 of those had sICH (3.9%) per SITS definition and 95 (8.5%) per NINDS definition.

Time to treatment was not associated with an increased risk for any bleeding or sICH (for both, SITS and NINDS definition). In univariate analysis, higher NIHSS score was significantly associated with any bleeding (odds ratio [OR], 4.97; CI, 2.41–10.24; P<0.001) and sICH_NINDS (OR, 8.63; CI, 2.05–36.20; P=0.003). History of diabetes mellitus, blood glucose at baseline, and HbA1c were all significantly associated with sICH_NINDS (history of diabetes mellitus OR, 1.88; CI, 1.21–2.92; P=0.01; blood glucose OR, 2.10; CI, 1.01–4.40; P=0.05; HbA1c OR, 23.89; CI, 9.09–62.78; P<0.001). Blood glucose at baseline and HbA1c were significantly associated with any hemorrhage (blood glucose OR, 2.06; CI, 1.24–3.43; P=0.01; blood glucose OR, 2.10; CI, 1.01–4.40; P=0.05).

Table 1. Baseline Characteristics for the Studied Population Divided Into sICH per NINDS and SITS Criteria

<table>
<thead>
<tr>
<th></th>
<th>pts 1112</th>
<th>sICH NINDS pts 95</th>
<th>sICH SITS pts 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year (year)</td>
<td>74 (65–80)</td>
<td>75 (70–82) 95</td>
<td>73 (66–82) 43</td>
</tr>
<tr>
<td>OTT in hour (hour)</td>
<td>2.25 (1.75–2.92)</td>
<td>2.42 (1.97–3) 95</td>
<td>2.33 (1.83–2.67) 43</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>12 (7–17)</td>
<td>15 (10–19) 95</td>
<td>15 (10–18) 43</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.9 (5.4–6.5)</td>
<td>7.1 (6.3–8.4) 91</td>
<td>7.5 (6.8–8.9) 42</td>
</tr>
<tr>
<td>Blood glucose on admission, mg/dL</td>
<td>121 (105.0–148.25)</td>
<td>130 (108–166) 95</td>
<td>128 (110–165) 43</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>160 (144–175)</td>
<td>160 (141–175) 95</td>
<td>160 (140–171) 42</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>88 (80–97)</td>
<td>135 (80–95) 95</td>
<td>80 (74–90) 42</td>
</tr>
</tbody>
</table>

n (%)

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<tr>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>529 (47.5)</td>
<td>53 (55.8)</td>
<td>25 (58.1)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>894 (80.3)</td>
<td>82 (86.3)</td>
<td>37 (86)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>276 (24.8)</td>
<td>35 (36.8)</td>
<td>15 (34.9)</td>
</tr>
<tr>
<td>History of CHD</td>
<td>236 (21.2)</td>
<td>30 (31.6)</td>
<td>12 (27.9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>372 (33.4)</td>
<td>45 (47.4)</td>
<td>22 (51.2)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; HbA1c, hemoglobin A1; IQR, interquartile range; N, the number of patients with data available for the specific category; NIHSS, National Institute of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; OTT, onset to treatment; pts, patients; and sICH, symptomatic intracerebral hemorrhage.
HbA₁c OR, 20.51; CI, 11.28–37.31; \( P<0.001 \). Only HbA₁c was significantly associated with sICH \(_{\text{SITS}}\) (OR, 60.06; CI, 7.98–452.29; \( P<0.001 \)).

In multivariate analysis, HbA₁c was highly significantly associated with any hemorrhage and sICH, regardless of the definition used. NIHSS score on admission was associated with any hemorrhage and sICH \(_{\text{SITS}}\). A history of diabetes mellitus was significantly associated with sICH \(_{\text{SITS}}\). Data are shown in Table 2. In addition to this model, HbA₁c, blood glucose at baseline, and history of diabetes mellitus were individually included in separate models of multivariate analysis, excluding the other 2 parameters, respectively. These analyses showed a significant association of HbA₁c with any type of hemorrhage, and an significant association of diabetes mellitus with sICH \(_{\text{SITS}}\). Blood glucose at baseline was not statistical significantly associated with any type of hemorrhage.

The best cut point to predict sICH with NIHSS score was 12 points and with HbA₁c was 6.5% (Figure). The corresponding c-statistic was 0.65 for NIHSS score (CI, 0.60–0.71; \( P<0.001 \)) and 0.80 for HbA₁c (CI, 0.75–0.80; \( P<0.001 \)) to predict sICH per NINDS definition.

**Predictors of Clinical Outcome**

In the univariate analysis age (OR, 1.02; CI, 1.01–1.03; \( P=0.001 \)), NIHSS score on admission (OR, 1.089; CI, 1.067–1.112; \( P<0.001 \)), presence of atrial fibrillation (OR, 1.35; CI, 1.04–1.75; \( P=0.03 \)) and female sex (OR, 1.45; CI, 1.13–1.86; \( P=0.004 \)) were associated with dependent outcome (Modified Rankin Scale, 3–5). Blood glucose levels on admission (OR, 1.01; CI, 1.00–1.01; \( P=0.002 \)), age (OR, 1.08; CI, 1.06–1.10; \( P<0.001 \)), NIHSS score (OR, 1.15; CI, 1.12–1.18; \( P<0.001 \)), history of diabetes mellitus (OR, 1.76; CI, 1.25–2.48; \( P<0.001 \)), history of hypertension (OR, 1.88; CI, 1.11–3.02; \( P=0.01 \)), longer time to treatment (OR, 2.46; CI, 1.10–5.49; \( P=0.03 \)) sICH \(_{\text{SITS}}\) (OR, 23.88; CI, 11.22–50.82; \( P<0.001 \)), and HbA₁c (OR, 1.41; CI, 1.24–1.61; \( P<0.001 \)) were associated with mortality at 90 days.

In multivariate analysis, age (OR, 1.01; CI, 1.00–1.03; \( P=0.02 \)), NIHSS score (OR, 1.09; CI, 1.07–1.11; \( P<0.001 \)) on admission, and HbA₁c (OR, 1.31; CI, 1.15–1.46; \( P<0.001 \)) remained as predictors of dependent outcome (Modified Rankin Scale, 3–5). Furthermore, age (OR, 0.35; CI, 0.20–0.59; \( P<0.001 \)), time to treatment (OR, 3.02; CI, 1.13–8.06; \( P=0.03 \)), history of diabetes mellitus (OR, 1.57; CI, 1.02–2.43; \( P=0.04 \)), sICH \(_{\text{SITS}}\) (OR, 9.86; CI, 3.35–29.01; \( P<0.001 \)), and HbA₁c (OR, 1.45; CI, 1.25–1.69; \( P<0.001 \)) were independently associated with death at 90 days.

**Discussion**

Diabetes mellitus is often unrecognized in patients who had stroke, and its prevalence may be as high as 50%.12 Some studies suggest that patients with diabetes mellitus have more severe strokes with a higher mortality and poorer outcomes as compared with nondiabetics.13 Other studies question a direct association of diabetes mellitus and poor outcome, suggesting that rather the extent of acute and chronic complications of diabetes mellitus, that is, acute hyperglycemia and long-term macro- and microangiopathic changes, influences the course of stroke.14 Laboratory parameters of diabetes mellitus, which represent these 2 different aspects of diabetic complications, are acute blood glucose level and HbA₁c. Our study provides a differential analysis of these parameters in thrombolysis for acute stroke.

Hyperglycemia is a frequent finding in patients with acute stroke (=40%) within the first 6 hours after symptom onset.15,16 Although it does not necessarily reflect impaired glucose-tolerance, but may be a stress-response in many patients, it is more common in diabetics.15 Whereas experimental models of hyperglycemia in cerebral ischemia have yielded contradictory results,17,18 clinical studies have almost consistently shown an association of hyperglycemia with increased stroke severity, larger infarct volumes, early hemorrhagic transformation, poorer outcomes, and increased mortality, irrespective of a history of diabetes mellitus.14,19,20 The effect of hyperglycemia is even more evident after thrombolysis: (1) it is a well-known

**Table 2. Multivariate Analysis for Any Hemorrhage and sICH per SITS and NINDS Definition**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c, %</td>
<td>10.30</td>
<td>3.89–27.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS SITS</td>
<td>6.69</td>
<td>0.74–63.48</td>
<td>0.11</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.42</td>
<td>0.57–3.54</td>
<td>0.46</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>1.60</td>
<td>0.84–3.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Blood glucose at baseline</td>
<td>1.14</td>
<td>0.41–3.17</td>
<td>0.73</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>25.85</td>
<td>3.40–196.69</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Logistic regression: age, sex, OTT, NIHSS score, blood glucose, and HbA₁c as categorical variables.
inhibitor of fibrinolysis; and (2) may be especially harmful in reperfusion. Experimental and clinical studies also suggested hyperglycemia to predict hemorrhagic transformation. Glycosylation is the link between diabetes mellitus and microangiopathy, and HbA1c is the best established parameter for long-term diabetes mellitus control and microangiopathy, far more reliable than acute blood glucose.

We found HbA1c to be strong independent predictor for any hemorrhage and also for sICH regardless of the definition used, with a cutoff value of 6.5%. This is a new finding. Previous studies focused on hyperglycemia in the acute phase and the effect of hyperglycemia and diabetes mellitus on outcomes in patients treated by thrombolysis, but not on the bleeding risk.

A recent large retrospective study showed that patients with stroke with persistent hyperglycemia within 48 h have higher risk for sICH and poor outcome compared with normoglycemic patients. This indicates that persistently increased blood glucose might also play a role in the pathology of the hemorrhagic transformation. A recent study from the SITS registry identified 9 independent risk factors for sICH, among them blood glucose on admission. None of these studies analyzed the role of HbA1c as another possible risk factor for sICH.

In our population, a history of diabetes mellitus was also independently associated with sICH according to NINDS, but not with hemorrhage after thrombolysis according to other definitions. Blood glucose at baseline was not independently associated with hemorrhage after thrombolysis regardless of the definition used.

These findings may be explained by the hypothesis of cerebral microvascular damage as a major risk factor for sICH and HbA1c as a possible marker for chronically elevated blood glucose rather than pathophysiological mechanisms of acutely increased blood glucose. However, in our study, we only investigated blood glucose on admission, but not in the next hours or days. Therefore, this hypothesis remains speculative and does not contradict a possible role of increased blood glucose in sICH after thrombolysis. Furthermore, our data do not provide evidence that HbA1c is a better predictor for sICH than diabetes mellitus. Larger and prospective trials directly looking at these parameters are necessary to answer this question.

Whereas in our cohort HbA1c was also an independent predictor for dependent outcome, as shown in a previous study, blood glucose level on admission was not identified as a predictor for outcome in multivariate analysis in our study, which is in contrast to many previous studies. It may be speculated that this may be attributable to intensive treatment of hyperglycemia with insulin in our routine practice.

Although our study includes a large population providing data on different outcome parameters, it has several limitations. Although our data were collected in a prospective fashion, and outcome parameters were assessed blinded to the baseline and imaging parameters, data analysis has been done retrospectively, including all known possible bias of such an approach. In particular, statistical associations should be interpreted with caution before they are confirmed in prospective studies. Because the intention of our study was to assess the risk of ICH using clinical and laboratory parameters of glucose metabolism as prognostic criteria that are available in the emergency setting, we used a history of diabetes mellitus based on pre-existing diagnosis, medical records, medical history, or medical treatment. This includes the possibility of misdiagnosis, especially in those patients without a history of diabetes mellitus on arrival. Moreover, we did not collect data on the type of diabetes mellitus treatment.

Conclusions
Identifying patients who are at high risk of hemorrhagic complications is a key issue in improving patient selection and safety of thrombolytic treatment in stroke. Both HbA1c and blood glucose can nowadays be rapidly assessed in the acute setting by the use of point of care tests. The predicting value of
HbA1c concerning outcome and risk for sICH may be used as a tool for the selection of patients who require a more intensive monitoring or intensive care, but needs further evaluation in a prospective and multicenter study. More data are also needed on HbA1c as a predictor of outcome after thrombolysis, an effect, which seems independent of an increased bleeding risk.

Disclosures

None.

References

Glycosylated Hemoglobin A1 Predicts Risk for Symptomatic Hemorrhage After Thrombolysis for Acute Stroke

A. Rocco, P.U. Heuschmann, P.D. Schellinger, M. Köhrmann, J. Diedler, M. Sykora, C.H. Nolte, P. Ringleb, W. Hacke and E. Jüttler

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