












ORIGINAL ARTICLE

Association of diabetes mellitus and admission glucose levels with outcome after endovascular therapy in acute ischaemic stroke in anterior circulation

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Abstract

Background and purpose: We aimed to assess the association of diabetes mellitus (DM) and admission hyperglycaemia (AH), respectively, and outcome in patients with acute ischaemic stroke with large vessel occlusion in the anterior circulation treated with endovascular therapy (EVT) in daily clinical practice.

Methods: Consecutive EVT patients admitted to our stroke centre between February 2015 and April 2020 were included in this observational cohort study. Patients with versus without DM and with versus without AH (glucose ≥ 7.8 mmol/L) were compared.

Results: We included 1020 patients (48.9% women, median age = 73.1 years); 282 (27.6%) had DM, and 226 (22.2%) had AH. Patients with versus without DM less often showed successful reperfusion (odds ratio [OR]_{adjusted} = 0.61, $p = 0.023$) and worse 3-month functional outcome (modified Rankin Scale [mRS] = 0–2: 31.3% vs. 48%, OR_{adjusted} = 0.59, $p = 0.004$; death: 38.9% vs. 24.1%, OR_{adjusted} = 1.75, $p = 0.002$; mRS shift: $p_{\text{adjusted}} < 0.0001$; if moderate/good collaterals and mismatch, mRS = 0–2: OR_{adjusted} = 0.52, $p = 0.005$; death: OR_{adjusted} = 1.95, $p = 0.005$). If analysis was additionally adjusted for AH, only mRS shift was still significantly worse in patients with DM ($p_{\text{adjusted}} = 0.012$). Patients with versus without AH showed similar successful reperfusion rates and worse 3-month functional outcome (mRS = 0–2: 28.3% vs. 50.4%, OR_{adjusted} = 0.52, $p < 0.0001$; death: 40.4% vs. 22.4%, OR_{adjusted} = 1.80, $p = 0.001$; mRS shift: $p_{\text{adjusted}} < 0.0001$; if moderate/good collaterals and mismatch, mRS = 0–2: OR_{adjusted} = 0.38, $p < 0.0001$; death: OR_{adjusted} = 2.39, $p < 0.0001$). If analysis was additionally adjusted for DM, 3-month functional outcome remained significantly worse in patients with AH (mRS = 0–2: OR_{adjusted} = 0.58, $p = 0.004$; death: OR_{adjusted} = 1.57, $p = 0.014$; mRS shift: $p_{\text{adjusted}} = 0.004$). DM independently predicted recurrent/progressive in-hospital ischaemic stroke (OR = 1.71, $p = 0.043$) together with admission National Institutes of Health Stroke Scale score (OR = 0.95, $p = 0.005$),

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and AH independently predicted in-hospital symptomatic intracranial haemorrhage (OR = 2.21, $p = 0.001$). The association of admission continuous glucose levels and most outcome variables was (inversely) J-shaped.

Conclusions: Hyperglycaemia more than DM was associated with worse 3-month outcome in the patients studied, more likely so in the case of moderate/good collaterals and mismatch in admission imaging.

KEYWORDS

acute ischaemic stroke, admission glucose levels, diabetes mellitus, endovascular therapy, outcome

INTRODUCTION

Dysglycaemia in patients with acute ischaemic stroke (AIS) is common. On the one hand, high admission glucose levels may be due to underlying diabetes mellitus (DM) and thus a known risk factor, but on the other hand, they may also reflect a transient stress response following an AIS. A transient stress response is more likely in patients with severe stroke, with poor collaterals [1–4].

The mechanisms by which dysglycaemia can lead to harmful effects in AIS patients are numerous and involve altered blood–brain barrier permeability, impaired cerebrovascular reactivity in the microvasculature, increased lactic acid production in ischaemic tissues, antifibrinolytic effects, and increased vulnerability to reperfusion injury. These pathomechanisms facilitate infarct growth, brain oedema, and haemorrhagic transformation [5–7].

Even in times before endovascular therapy (EVT), it was shown that dysglycaemia versus normoglycaemia is associated with worse outcome in AIS patients treated conservatively or with intravenous thrombolysis (IVT) [1, 4, 8–18].

Several recent retrospective and a few prospective studies, post hoc analyses of randomized controlled trials (RCTs), and meta-analyses have also shown that dysglycaemia versus normoglycaemia is associated with worse outcome in AIS patients treated with EVT [2, 3, 7, 19–31]. Limitations of the studies to date are the rather limited sample size of each centre, the focus on some glycaemia parameters only, and/or the determination of the diagnosis of DM based only on medical history or intake of oral and subcutaneous antidiabetics, but not on HbA1c levels as a measure of chronic glucose control. Furthermore, no study has yet looked at collaterals combined with mismatch status in this patient group. Also, recurrent/progressive in-hospital ischaemic stroke was not a clinical outcome variable in most previous studies, only infarct growth in some [32, 33].

In the present study, we aimed to comprehensively investigate the association between DM and admission hyperglycaemia (AH), respectively, and outcome in AIS patients treated with EVT for large vessel occlusion (LVO) in the anterior circulation in an observational cohort from daily clinical practice at a tertiary care centre.

METHODS

Patients

Data for AIS patients treated from February 2015 to April 2020 were extracted and retrospectively analyzed, having previously been prospectively collected in the Bernese Stroke Centre registry. We included all AIS patients with acute LVO treated with EVT. AIS was defined according to the criteria of the American Stroke Association/American Heart Association (ASA/AHA) [34]. LVO was defined as acute vessel occlusion of the internal carotid artery (ICA), the carotid terminus, the proximal middle cerebral artery (MCA; M1 or M2 segment), or tandem occlusion (ICA and M1 or M2 segment of the MCA).

All patients were evaluated upon emergency department admission using a standardized AIS protocol that included medical history, clinical examination by a board-certified neurologist, laboratory blood tests, electrocardiography, and cranial imaging with computed tomographic (CT) and/or magnetic resonance (MR) arteriography. The decision for or against EVT was made on an individual basis by an experienced neurologist together with an experienced interventional neuroradiologist according to international as well as our institutional guidelines [35, 36]. EVT was performed as early as possible after the diagnosis was established, taking into account indications and contraindications. All patients underwent diagnostic digital subtraction angiography (DSA). The radiological data were evaluated by two independent neuroradiologists. After EVT, all patients were hospitalized in the stroke unit, or intermediate or intensive care unit of the Bernese Stroke Centre for at least 24 h or until death.

Follow-up CT and/or MR arteriography was performed 12–24 h after EVT and in the case of secondary neurological deterioration.

A 3-month follow-up was performed clinically by a board-certified neurologist or by telephone by a trained study nurse.

Pre-existing DM was determined if the HbA1c was $\geq 6.5\%$ at admission and/or patients were taking antidiabetics prestroke or at discharge [37]. AH was considered as admission glucose ≥ 7.8 mmol/L, in line with previous studies [2, 22–24]. All admission plasma glucose levels were measured in venous samples. Admission glucose levels were defined as glucose levels obtained upon emergency

department admission. However, if patients received any acute application of drugs correcting pathological glucose levels and/or initiation of intravenous thrombolysis before admission at our stroke centre, those glucose levels measured beforehand at the referring stroke unit were selected and defined as admission glucose levels. Patients who were missing either admission glucose or HbA1c levels were excluded from the study (Figure 1).

Reperfusion was evaluated with the modified Thrombolysis in Cerebral Infarction (mTICI) score [38]. Successful reperfusion (SR) was defined as mTICI = 2b/3. Collateral status was scored according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale on pre-EVT DSA [39]. Mismatch was categorized into basic profiles [40]. Recurrent/progressive in-hospital ischaemic stroke was defined according to ASA/AHA criteria, and in-hospital symptomatic intracranial haemorrhage (sICH) according to European Cooperative Acute Stroke Study II criteria [36, 41]. Death was classified as vascular if the patient died within 2 weeks of a vascular event. Functional outcome was graded according to the modified Rankin scale (mRS). mRS = 0–2 was defined as good and mRS = 0–1 as excellent outcome [42].

Statistical analysis

Statistical analysis was performed using SPSS 25.0 (IBM). In univariable analysis, χ^2 test and Fisher exact test was applied if appropriate for categorical variables and Mann-Whitney *U*-test for ordinal and continuous variables to compare baseline characteristics and outcome variables between patients with versus without AH, with

versus without DM, and with versus without HbA1c $\geq 6.5\%$. A two-tailed *p*-value < 0.05 was considered significant.

All variables with *p* < 0.05 were included in the stepwise multivariable binary logistic regression analysis for outcome analysis of SR, death at 3 months, and good outcome at 3 months and in ordinal regression analysis for mRS and mTICI shift analysis. To avoid overfitting, the maximum number of potential confounders in the models was restricted to approximately one tenth of the size of the smallest number of the outcome categories, and intermediate variables on a causal path from exposure to outcome were not adjusted for.

Stepwise logistic regression analysis was used to determine independent prediction by DM and AH of recurrent/progressive in-hospital ischaemic stroke and in-hospital sICH. The variables turning out to be less predictive than DM and AH were removed from the final model.

Sensitivity analyses were performed for patients with DM with versus without AH, for patients with AH with versus without DM, and for patients without DM with versus without AH.

For continuous admission glucose levels, probability of outcome was analyzed with binary logistic regression analysis. We determined whether the association was nonlinear by assessing the fit of models with restricted cubic splines using the likelihood ratio test.

Missing data were not imputed.

RESULTS

We included 1020 patients (499 [48.9%] women, median age 73.1 years) in this study. Median admission National Institutes of Health Stroke Scale (NIHSS) score was 14 (range = 0–36). Median

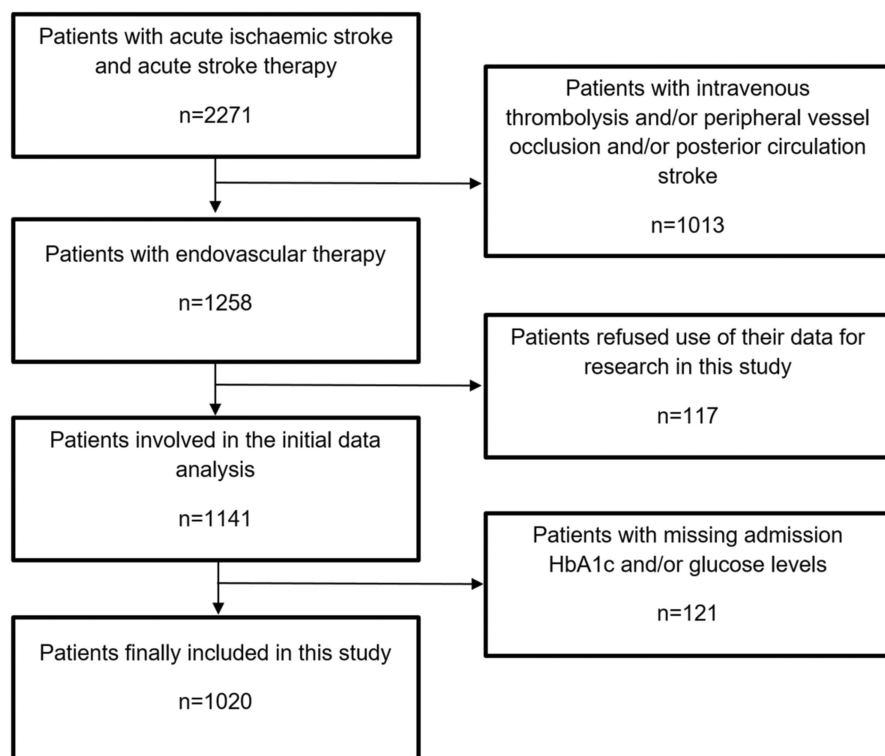


FIGURE 1 Flow chart of patients who met inclusion and exclusion criteria

time from known symptom onset to groin puncture was 195 (range = 61–1436) min, and 265 (26%) of all patients had a wake-up stroke or were found with unknown time of symptom onset. Median admission HbA1c and glucose levels were 5.7% (range = 4.1%–12.9%) and 6.6 mmol/L (range = 1.4–26.9 mmol/L), respectively.

Patients with versus without DM were older, more frequently suffered from arterial hypertension, hyperlipidaemia, coronary heart disease, and peripheral artery disease, were more frequently prescribed with antithrombotic agents prestroke, and were admitted with higher median NIHSS scores.

Patients with versus without AH were older, more frequently suffered from arterial hypertension, hyperlipidaemia, DM, and coronary heart disease, more frequently actively smoked or had stopped <2 years previously, and were admitted with higher median NIHSS scores.

Baseline characteristics are shown in [Table 1](#).

In univariable analysis, 187 (82.7%) patients with versus 697 (87.8%) patients without DM showed SR ($p = 0.049$), 37 (16.4%) versus 76 (9.6%) were dead at discharge from acute care ($p = 0.004$), and 82 (38.9%) versus 184 (24.1%) were dead at 3 months ($p < 0.0001$). Sixty-six (31.3%) patients with versus 366 (48%) without DM showed good outcome and 38 (18%) versus 245 (32.1%) excellent outcome at 3 months (each $p < 0.0001$). Rates of recurrent/progressive in-hospital ischaemic strokes and in-hospital sICH were similar in this group comparison ([Table 2](#)).

In univariable analysis, rates of SR and of recurrent/progressive in-hospital ischaemic strokes were similar in patients with versus without AH. Thirty-two (11.6%) patients with versus 41 (5.6%) patients without AH suffered an in-hospital sICH ($p = 0.001$), 47 (16.7%) versus 66 (8.9%) were dead at discharge from acute care ($p < 0.0001$), and 107 (40.4%) versus 159 (22.4%) were dead at 3 months ($p < 0.0001$). Seventy-five (28.3%) patients with versus 357 (50.4%) without AH showed good outcome and 43 (16.2%) versus 240 (33.9%) excellent outcome at 3 months (each $p < 0.0001$; [Table 2](#)).

In multivariable analysis, comparing patients without versus with DM, mTICI shift was similar, mRS shift at 3 months worse ($p < 0.0001$) for patients with DM, SR less likely (odds ratio [OR] = 0.61), death at 3 months more likely (OR = 1.75), and good outcome less likely (OR = 0.59), when analysis was adjusted for age, arterial hypertension, hyperlipidaemia, prestroke antithrombotic agents, and admission NIHSS score. If analysis was additionally adjusted for AH in this group comparison, mRS shift at 3 months was still worse ($p = 0.012$). However, there was no longer a significant difference concerning SR, and death and outcome at 3 months ([Table 3](#)). There was a more pronounced likelihood of outcome in patients with moderate or good collaterals and small core or target mismatch in admission imaging ([Table 3](#)). Further likelihood analyses of outcome are depicted in [Table 3](#).

DM turned out to independently predict recurrent/progressive in-hospital ischaemic stroke (OR = 1.71, 95% confidence interval [CI] = 1.02–2.87, $p = 0.043$) together with admission NIHSS score (OR = 0.95, 95% CI = 0.92–0.99, $p = 0.005$), but not in-hospital sICH (OR = 1.34, 95% CI = 0.78–2.30, $p = 0.294$; [Table S1](#)).

In multivariable analysis, comparing patients without versus with AH, mTICI shift was similar, mRS shift at 3 months worse ($p < 0.0001$) for patients with DM, SR similar, death at 3 months more likely (OR = 1.80), and good outcome less likely (OR = 0.52), when analysis was adjusted for age, arterial hypertension, hyperlipidaemia, actively smoking or having stopped <2 years previously, and admission NIHSS score. If analysis was additionally adjusted for DM in this group comparison, the difference concerning mRS shift, death, and good outcome at 3 months remained significantly different. There was a more pronounced likelihood of outcome in patients with moderate or good collaterals and small core or target mismatch in admission imaging ([Table 3](#)). Further likelihood analyses of outcome are depicted in [Table 3](#).

AH turned out not to independently predict recurrent/progressive in-hospital ischaemic stroke (OR = 1.55, 95% CI = 0.93–2.59, $p = 0.095$), but in-hospital sICH (OR = 2.21, 95% CI = 1.36–3.59, $p = 0.001$; [Table S1](#)).

Results of the group comparison with versus without HbA1c $\geq 6.5\%$ are shown in [Table 3](#) and [Tables S4–S5](#). Results of sensitivity analyses for patients with DM with versus without AH, for patients with AH with versus without DM, and for patients without DM with versus without AH are shown in [Tables 3](#) and [S2–S5](#).

Probability of outcome by continuous admission glucose levels showed a significant cubic association for SR ($p = 0.023$, $R^2 = 0.080$), for recurrent/progressive in-hospital ischaemic stroke ($p < 0.0001$, $R^2 = 0.154$), for death ($p = 0.002$, $R^2 = 0.120$), and for good ($p = 0.001$, $R^2 = 0.128$) and excellent outcome ($p = 0.005$, $R^2 = 0.105$) at 3 months, but not for in-hospital sICH ([Figure 2](#)). Probability of good outcome by continuous admission glucose levels for patients with moderate or good collaterals and small core or target mismatch in admission imaging are shown in [Figure 3](#).

DISCUSSION

Our study comprehensively elucidates the association of DM and AH with outcome after EVT at a tertiary care centre in an observational cohort of AIS patients with LVO in the anterior circulation treated in daily clinical practice.

In our study, between one fifth and one third of the patients suffered from DM and/or AH. Some previous studies have shown even higher rates [[21–24](#), [26–28](#), [32](#), [33](#)].

The main findings of our study are as follows. Patients with versus without DM less often showed SR and showed worse 3-month functional outcome. If analysis was additionally adjusted for AH, only mRS shift was still significantly worse in patients with DM. Patients with versus without AH showed similar SR rates and worse 3-month functional outcome. If analysis was additionally adjusted for DM, 3-month functional outcome remained significantly worse in patients with AH. DM was an independent predictor of recurrent/progressive in-hospital ischaemic stroke and AH of in-hospital ICH. The association of admission continuous glucose levels and most outcome variables was (inversely) J-shaped.

TABLE 1 Baseline characteristics of patients without and with diabetes mellitus and without and with admission hyperglycaemia (glucose ≥ 7.8 mmol/L)

| Baseline characteristics | No diabetes mellitus, <i>n</i> = 794 | Diabetes mellitus, <i>n</i> = 226 | <i>P</i> -value | No hyperglycaemia, <i>n</i> = 738 | Hyperglycaemia, <i>n</i> = 282 | <i>P</i> -value |
|---|--------------------------------------|-----------------------------------|-----------------|-----------------------------------|--------------------------------|-----------------|
| Age, years | 75 (18–101) | 78 (45–94) | 0.003 | 75 (18–101) | 78.3 (45–98) | 0.004 |
| Female | 400 (50.4%) | 121 (53.5%) | 0.401 | 366 (49.6%) | 133 (47.2%) | 0.487 |
| Vascular risk factors | | | | | | |
| Arterial hypertension | 553 (69.6%) | 207 (91.6%) | <0.0001 | 524 (71%) | 236 (83.7%) | <0.0001 |
| Hyperlipidaemia | 531 (66.9%) | 184 (81.4%) | <0.0001 | 503 (68.2%) | 212 (75.2%) | 0.029 |
| Actively smoking or stopped <2 years previously | 168 (21.2%) | 42 (18.6%) | 0.398 | 168 (22.8%) | 42 (14.9%) | 0.005 |
| Diabetes mellitus | 0 | 226 (100%) | <0.0001 | 80 (10.8%) | 146 (51.8%) | <0.0001 |
| Coronary heart disease | 168 (21.2%) | 88 (38.9%) | <0.0001 | 168 (22.8%) | 88 (31.2%) | 0.005 |
| Peripheral artery disease | 47 (5.9%) | 28 (12.4%) | 0.001 | 48 (6.5%) | 27 (9.6%) | 0.093 |
| Atrial fibrillation or flutter | 313 (39.4%) | 103 (45.6%) | 0.097 | 296 (40.1%) | 120 (42.6%) | 0.477 |
| Previous ischaemic stroke | 98 (12.3%) | 36 (15.9%) | 0.159 | 100 (13.6%) | 34 (12.1%) | 0.528 |
| Previous haemorrhagic stroke | 10 (1.3%) | 4 (1.8%) | 0.525 | 12 (1.6%) | 2 (0.7%) | 0.260 |
| Stroke aetiology | | | 0.195 | | | 0.107 |
| Cardiac embolism | 361 (45.5%) | 109 (48.2%) | | 342 (46.3%) | 128 (45.4%) | |
| Cervical artery dissection | 27 (3.4%) | 1 (0.4%) | | 26 (3.5%) | 2 (0.7%) | |
| Large artery atherosclerosis | 99 (12.5%) | 33 (14.6%) | | 90 (12.2%) | 42 (14.9%) | |
| More than one possible aetiology | 59 (7.4%) | 15 (6.6%) | | 58 (7.9%) | 16 (5.7%) | |
| Other determined aetiology | 46 (5.8%) | 8 (3.5%) | | 41 (5.6%) | 13 (4.6%) | |
| Unknown, complete evaluation | 94 (11.8%) | 26 (11.5%) | | 87 (11.8%) | 33 (11.7%) | |
| Unknown, incomplete evaluation | 108 (13.6%) | 34 (15%) | | 94 (12.7%) | 48 (17%) | |
| Independency before stroke, mRS = 0–2 | 663 (83.8%) | 178 (78.8%) | 0.076 | 609 (82.9%) | 232 (82.3%) | 0.824 |
| Prestroke antithrombotic agents | | | <0.0001 | | | 0.858 |
| Antiplatelets | 209 (26.3%) | 94 (41.6%) | | 213 (28.9%) | 90 (31.9%) | |
| NOAC | 49 (6.2%) | 15 (6.6%) | | 47 (6.4%) | 17 (6%) | |
| OAC | 54 (6.8%) | 16 (7.1%) | | 51 (6.9%) | 19 (6.7%) | |
| NOAC or OAC and antiplatelets | 12 (1.5%) | 6 (2.7%) | | 12 (1.6%) | 6 (2.1%) | |
| None | 470 (59.2%) | 95 (42%) | | 415 (56.2%) | 150 (53.2%) | |
| Prestroke oral antidiabetic agents ^a | | | <0.0001 | | | <0.0001 |
| Potentially hypoglycaemic | 0 | 27 (11.9%) | | 4 (0.5%) | 23 (8.2%) | |
| Nonhypoglycaemic | 0 | 79 (35%) | | 27 (3.7%) | 52 (18.4%) | |
| None | 794 (100%) | 120 (53.1%) ^b | | 707 (95.8%) | 207 (73.4%) | |
| Other prestroke drugs | | | | | | |
| Insulin treatment ^a | 0 | 40 (17.7%) | <0.0001 | 13 (1.8%) | 27 (9.6%) | <0.0001 |
| Lipid-lowering drugs | 192 (24.2%) | 100 (44.2%) | <0.0001 | 204 (27.7%) | 88 (31.2%) | 0.265 |
| Antihypertensives | 467 (58.9%) | 184 (81.4%) | <0.0001 | 455 (61.7%) | 197 (69.9%) | 0.016 |

TABLE 1 (Continued)

| Baseline characteristics | No diabetes mellitus, n = 794 | Diabetes mellitus, n = 226 | P-value | No hyperglycaemia, n = 738 | Hyperglycaemia, n = 282 | P-value |
|---|-------------------------------|----------------------------|---------|----------------------------|-------------------------|---------|
| Admission systolic blood pressure, mmHg | 157 (60–265) | 155 (80–253) | 0.316 | 155 (60–265) | 160 (80–253) | 0.073 |
| Admission NIHSS score | 13 (0–36) | 16 (0–36) | 0.002 | 12 (0–36) | 17 (0–36) | <0.0001 |
| Admission laboratory values | | | | | | |
| Glucose, mmol/l | 6.3 (1.4–11) | 8.8 (2.2–26.9) | <0.0001 | 6.1 (1.4–7.7) | 9.1 (7.8–26.9) | <0.0001 |
| Hyperglycaemia, glucose ≥ 7.8 mmol/L | 136 (17.1%) | 146 (64.6%) | <0.0001 | 0 | 282 (100%) | <0.0001 |
| HbA1c, % | 5.6 (4.1–6.4) | 6.9 (4.8–12.9) | <0.0001 | 5.6 (4.1–8.3) | 6.3 (4.8–12.9) | <0.0001 |
| HbA1c $\geq 6.5\%$ | 0 | 157 (69.5%) | <0.0001 | 43 (5.8%) | 114 (40.4%) | <0.0001 |
| Total cholesterol, mmol/l | 4.6 (2–10.7) | 4 (1.9–8.5) | <0.0001 | 4.5 (1.9–10.7) | 4.5 (2–8.5) | 0.833 |
| LDL, mmol/l | 2.5 (0.3–8) | 2.2 (0.5–6.4) | 0.001 | 2.4 (0.3–8) | 2.4 (0.5–6.4) | 0.734 |
| CRP, mmol/l | 3 (3–380) | 5 (3–198) | 0.053 | 3 (3–336) | 5 (3–380) | 0.059 |
| Wake-up stroke | 207 (26.1%) | 58 (25.7%) | 0.902 | 193 (26.2%) | 72 (25.5%) | 0.840 |
| Known onset to groin puncture time, min | 190 (70–1436) | 205 (61–1284) | 0.195 | 190 (70–1436) | 210 (61–1284) | 0.091 |
| Location of main acute vessel occlusion | | | 0.725 | | | 0.255 |
| ICA | 91 (11.5%) | 24 (10.6%) | | 86 (11.7%) | 29 (10.3%) | |
| Carotid-T | 58 (7.3%) | 22 (9.7%) | | 51 (6.9%) | 29 (10.3%) | |
| ICA and M1/2 segment of MCA | 60 (7.6%) | 20 (8.8%) | | 53 (7.2%) | 27 (9.6%) | |
| M1 segment of MCA | 382 (48.1%) | 106 (46.9%) | | 359 (48.6%) | 129 (45.7%) | |
| M2 segment of MCA | 203 (25.6%) | 54 (23.9%) | | 189 (25.6%) | 68 (24.1%) | |
| Collaterals | | | 0.004 | | | <0.0001 |
| Poor | 201 (25.3%) | 79 (35%) | | 177 (24%) | 103 (36.5%) | |
| Moderate | 287 (36.1%) | 83 (36.7%) | | 265 (35.9%) | 105 (37.2%) | |
| Good | 306 (38.5%) | 64 (28.3%) | | 296 (40.1%) | 74 (26.2%) | |
| Mismatch | | | 0.111 | | | 0.028 |
| None/malignant | 65 (10.1%) | 28 (15.7%) | | 61 (9.9%) | 32 (15.8%) | |
| Target | 315 (49%) | 81 (45.5%) | | 295 (47.7%) | 101 (49.8%) | |
| Small core | 263 (40.9%) | 69 (38.8%) | | 262 (42.4%) | 70 (34.5%) | |

Note: For categorical variables, the number of patients and percentage in parentheses are shown. For nonnormally distributed continuous and ordinal variables, median, and minimum and maximum range are shown (in parentheses). For normally distributed continuous and ordinal variables, average and SD are shown (in parentheses).

Abbreviations: CRP, C-reactive protein; ICA, internal carotid artery; LDL, low-density lipoprotein; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, new oral anticoagulants; OAC, oral anticoagulants.

^aPatients on no antidiabetics at discharge had significantly lower admission HbA1c levels (median = 6.6 vs. 7.2, $p = 0.014$).

^b $n = 16$ were on insulin treatment.

There was a more pronounced likelihood of good outcome in patients with moderate or good collaterals and mismatch in admission imaging.

The treatment of AIS patients and LVO in the anterior circulation changed a few years ago when several RCTs demonstrated that EVT (\pm IVT) is safe and leads to better outcomes compared to standard treatment, strongly predicted by SR [43, 44].

However, experimental studies on cerebral ischaemia have shown that SR contributes to detrimental effects of hyperglycaemia, and studies on IVT have yielded conflicting results [12–14].

Obviously, SR rates after IVT are lower than after EVT, and documentation of variable SR timing, speed, and extent are limited [2].

Abrupt SR, as occurs with EVT, has been shown to facilitate reperfusion injury and increase final infarct volume by up to 70% in preclinical studies [45]. Reperfusion injury is a condition in which restoration of blood supply to brain tissue following ischaemia or anoxia/hypoxia results in tissue destruction due to inflammation and oxidative damage from induced oxidative stress. Reperfusion injury has not been widely studied in clinical studies in AIS patients with SR after EVT [46]. However, high glucose levels may increase the

TABLE 2 Procedural and outcome characteristics of patients without and with diabetes mellitus and without and with admission hyperglycemia (glucose ≥ 7.8 mmol/L)

| Procedural and outcome characteristics | No diabetes mellitus, (n = 794) | Diabetes mellitus, (n = 226) | Unadjusted P-value | No hyperglycaemia, (n = 738) | Hyperglycaemia, (n = 282) | Unadjusted P-value |
|--|---------------------------------|------------------------------|--------------------|------------------------------|---------------------------|--------------------|
| EVT duration | 55 (9–412) | 50 (15–250) | 0.645 | 55 (9–412) | 51 (13–250) | 0.858 |
| Therapy modality | | | 0.414 | | | 0.097 |
| MT only | 400 (50.4%) | 110 (48.7%) | | 375 (50.8%) | 135 (47.9%) | |
| MT and IVT | 364 (45.8%) | 111 (49.1%) | | 333 (45.1%) | 142 (50.4%) | |
| MT and IAT | 30 (3.8%) | 5 (2.2%) | | 30 (4.1%) | 5 (1.8%) | |
| Stent retriever applied | 744 (93.7%) | 207 (91.6%) | 0.265 | 689 (93.4%) | 262 (92.9%) | 0.797 |
| Successful reperfusion | 697 (87.8%) | 187 (82.7%) | 0.049 | 644 (87.3%) | 240 (85.1%) | 0.365 |
| Recurrent/progressive in-hospital ischaemic stroke | 53 (6.7%) | 23 (10.2%) | 0.079 | 51 (7%) | 25 (8.9%) | 0.287 |
| In-hospital sICH | 52 (6.6%) | 21 (9.5%) | 0.147 | 41 (5.6%) | 32 (11.6%) | 0.001 |
| Duration acute care, days | 4 (0–83) | 4 (0–59) | 0.732 | 4 (0–83) | 4 (1–59) | 0.304 |
| Oral antidiabetics at discharge ^a | | | <0.0001 | | | <0.0001 |
| Potentially hypoglycaemic | 0 | 19 (8.4%) | | 5 (0.7%) | 14 (5%) | |
| Nonhypoglycaemic | 0 | 66 (29.2%) | | 20 (2.7%) | 48 (17%) | |
| None | 793 (99.9%) | 141 (62.4%) ^b | | 712 (96.5%) | 220 (78%) | |
| Insulin treatment at discharge ^a | 0 | 78 (34.5%) | <0.0001 | 24 (3.3%) | 55 (19.5%) | <0.0001 |
| Death at discharge | 76 (9.6%) | 37 (16.4%) | 0.004 | 66 (8.9%) | 47 (16.7%) | <0.0001 |
| Death causes | | | 0.711 | | | 0.747 |
| Vascular | 105 (57.1%) | 47 (57.3%) | | 92 (57.9%) | 60 (56.1%) | |
| Nonvascular | 19 (10.3%) | 11 (13.4%) | | 16 (10.1%) | 14 (13.1%) | |
| Unknown | 60 (32.6%) | 24 (29.3%) | | 51 (32.1%) | 33 (30.8%) | |
| mRS at 3 months | 3 (0–6) | 4 (0–6) | <0.0001 | 2 (0–6) | 4 (0–6) | <0.0001 |
| 0 | 106 (13.9%) | 17 (8.1%) | <0.0001 | 102 (14.4%) | 21 (7.9%) | <0.0001 |
| 1 | 139 (18.2%) | 21 (10%) | | 138 (19.5%) | 22 (8.3%) | |
| 2 | 120 (15.7%) | 28 (13.3%) | | 116 (16.4%) | 32 (12.1%) | |
| 3 | 112 (14.7%) | 25 (11.8%) | | 103 (14.5%) | 34 (12.8%) | |
| 4 | 80 (10.5%) | 25 (11.8%) | | 69 (9.7%) | 36 (13.6%) | |
| 5 | 22 (2.9%) | 13 (6.2%) | | 22 (3.1%) | 13 (4.9%) | |
| 6 | 184 (24.1%) | 82 (38.9%) | | 159 (22.4%) | 107 (40.4%) | |
| Good outcome at 3 months | 366 (48%) | 66 (31.3%) | <0.0001 | 357 (50.4%) | 75 (28.3%) | <0.0001 |
| Excellent outcome at 3 months | 245 (32.1%) | 38 (18%) | <0.0001 | 240 (33.9%) | 43 (16.2%) | <0.0001 |

Note: For categorical variables, the number of patients and percentage in parentheses are shown. For nonnormally distributed continuous and ordinal variables, median, and minimum and maximum range are shown (in parentheses). For normally distributed continuous and ordinal variables, average and SD are shown (in parentheses).

Abbreviations: EVT, endovascular therapy; IAT, intra-arterial thrombolysis with urokinase; IVT, intravenous thrombolysis with recombinant tissue plasminogen activator; mRS, modified Rankin Scale; MT, mechanical thrombectomy; sICH, symptomatic intracerebral haemorrhage.

^aPatients on no antidiabetics at discharge had significantly lower admission HbA1c levels (median = 6.7 vs. 7.2, $p = 0.003$).

^b $n = 32$ on insulin treatment and $n = 37$ dead.

likelihood not only of reperfusion injury but also of other heterogeneous effects [5, 6].

Several studies, most of which focused on AH or on a limited number of glycaemia parameters, have found that dysglycaemia

versus normoglycaemia is associated with worse outcome in AIS patients treated with EVT [2, 3, 7, 19–31]. In our study, as in other previous studies, most of which did not analyze patients with versus without DM separately but adjusted the analysis for this

TABLE 3 Outcome characteristics of patients according to different glycaemia parameters

| Putative predictive variables | Successful reperfusion | Death at 3 months | Independency at 3 months | mRS shift | mTICI shift |
|---|---------------------------------|----------------------------------|----------------------------------|----------------|---------------|
| Diabetes mellitus, with vs. without ^a | 0.61 (0.40–0.94), $p = 0.023$ | 1.75 (1.22–2.50), $p = 0.002$ | 0.59 (0.41–0.85), $p = 0.004$ | $p < 0.0001$ | $p = 0.296$ |
| | NA | 1.55 (1.04–2.29), $p = 0.031^b$ | 0.60 (0.41–0.89), $p = 0.011^b$ | $p = 0.001^b$ | NA |
| | 0.61 (0.35–1.04), $p = 0.071^c$ | 1.95 (1.23–3.11), $p = 0.005^c$ | 0.52 (0.33–0.82), $p = 0.005^c$ | $p < 0.0001^c$ | $p = 0.347^c$ |
| | 0.54 (0.32–0.91), $p = 0.020^d$ | 1.77 (1.12–2.79), $p = 0.014^d$ | 0.58 (0.36–0.93), $p = 0.025^d$ | $p = 0.002^d$ | $p = 0.142^d$ |
| | 0.64 (0.40–1.02), $p = 0.060^e$ | 1.42 (0.96–2.09), $p = 0.081^e$ | 0.78 (0.52–1.16), $p = 0.214^e$ | $p = 0.012^e$ | $p = 0.365^e$ |
| Admission hyperglycaemia [glucose ≥ 7.8 mmol/L], with vs. without ^f | 0.77 (0.51–1.16), $p = 0.206$ | 1.80 (1.29–2.50), $p = 0.001$ | 0.52 (0.37–0.72), $p < 0.0001$ | $p < 0.0001$ | $p = 0.601$ |
| | NA | 1.82 (1.27–2.62), $p = 0.001^b$ | 0.49 (0.34–0.71), $p < 0.0001^b$ | $p < 0.0001^b$ | NA |
| | 1.02 (0.60–1.75), $p = 0.942^g$ | 2.39 (1.60–3.57), $p < 0.0001^g$ | 0.38 (0.26–0.56), $p < 0.0001^g$ | $p < 0.0001^g$ | $p = 0.720^g$ |
| | 0.79 (0.51–1.22), $p = 0.291^d$ | 1.71 (1.20–2.42), $p = 0.003^d$ | 0.54 (0.38–0.77), $p = 0.001^d$ | $p < 0.0001^d$ | $p = 0.564^d$ |
| | 0.94 (0.59–1.48), $p = 0.774^h$ | 1.57 (1.10–2.25), $p = 0.014^h$ | 0.58 (0.40–0.84), $p = 0.004^h$ | $p = 0.004^h$ | $p = 0.926^h$ |
| Diabetes mellitus with vs. without admission hyperglycaemia [glucose ≥ 7.8 mmol/L] ⁱ | 1.59 (0.76–3.29), $p = 0.216$ | 1.71 (0.77–3.78), $p = 0.186$ | 0.61 (0.33–1.12), $p = 0.112$ | $p = 0.088$ | $p = 0.127$ |
| Admission hyperglycaemia ≥ 7.8 mmol/L with versus without diabetes mellitus ^j | 0.92 (0.46–1.83), $p = 0.805$ | 1.66 (0.84–3.29), $p = 0.149$ | 0.76 (0.42–1.37), $p = 0.360$ | $p = 0.162$ | $p = 0.513$ |
| No diabetes mellitus with vs. without admission hyperglycaemia [glucose ≥ 7.8 mmol/L] ^k | 0.76 (0.43–1.33), $p = 0.331$ | 1.48 (0.96–2.29), $p = 0.080$ | 0.59 (0.38–0.92), $p = 0.020$ | $p = 0.022$ | $p = 0.280$ |
| HbA1c $\geq 6.5\%$, with vs. without ^l | 0.51 (0.32–0.80), $p = 0.004$ | 1.62 (1.10–2.39), $p = 0.014$ | 0.70 (0.47–1.05), $p = 0.082$ | $p = 0.002$ | $p = 0.117$ |
| | 0.51 (0.30–0.86), $p = 0.011^e$ | 1.22 (0.80–1.87), $p = 0.353^e$ | 1.01 (0.65–1.59), $p = 0.932^e$ | $p = 0.199^e$ | $p = 0.135^e$ |

Note: Adjusted odds ratios (95% confidence interval) and p -values are shown.

Abbreviations: mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction; NA, not available; NIHSS, National Institutes of Health Stroke Scale.

^aAdjusted for age, arterial hypertension, hyperlipidaemia, prestroke antithrombotic agents, and admission NIHSS score.

^bAdjusted for variables in a and f; however, only patients with successful reperfusion.

^cOnly patients with moderate or good collaterals and with small core or target mismatch in admission imaging, adjusted for arterial hypertension, hyperlipidaemia, and prestroke antithrombotic agents.

^dAdjusted for variables in a and f, additionally adjusted for prestroke oral antidiabetics and insulin treatment.

^eAdjusted for variables in a and l, additionally adjusted for admission hyperglycaemia.

^fAdjusted for age, arterial hypertension, hyperlipidaemia, actively smoking or stopped <2 years previously, and admission NIHSS score.

^gOnly patients with moderate or good collaterals and with small core or target mismatch in admission imaging, adjusted for age, arterial hypertension, actively smoking or stopped <2 years previously, and admission NIHSS score.

^hAdjusted for variables in f, additionally adjusted for diabetes mellitus.

ⁱAdjusted for atrial fibrillation or flutter.

^jAdjusted for arterial hypertension, hyperlipidaemia, and admission NIHSS score.

^kAdjusted for age, actively smoking or stopped <2 years previously, and admission NIHSS score.

^lAdjusted for arterial hypertension, hyperlipidaemia, prestroke antithrombotic agents, and admission NIHSS score.

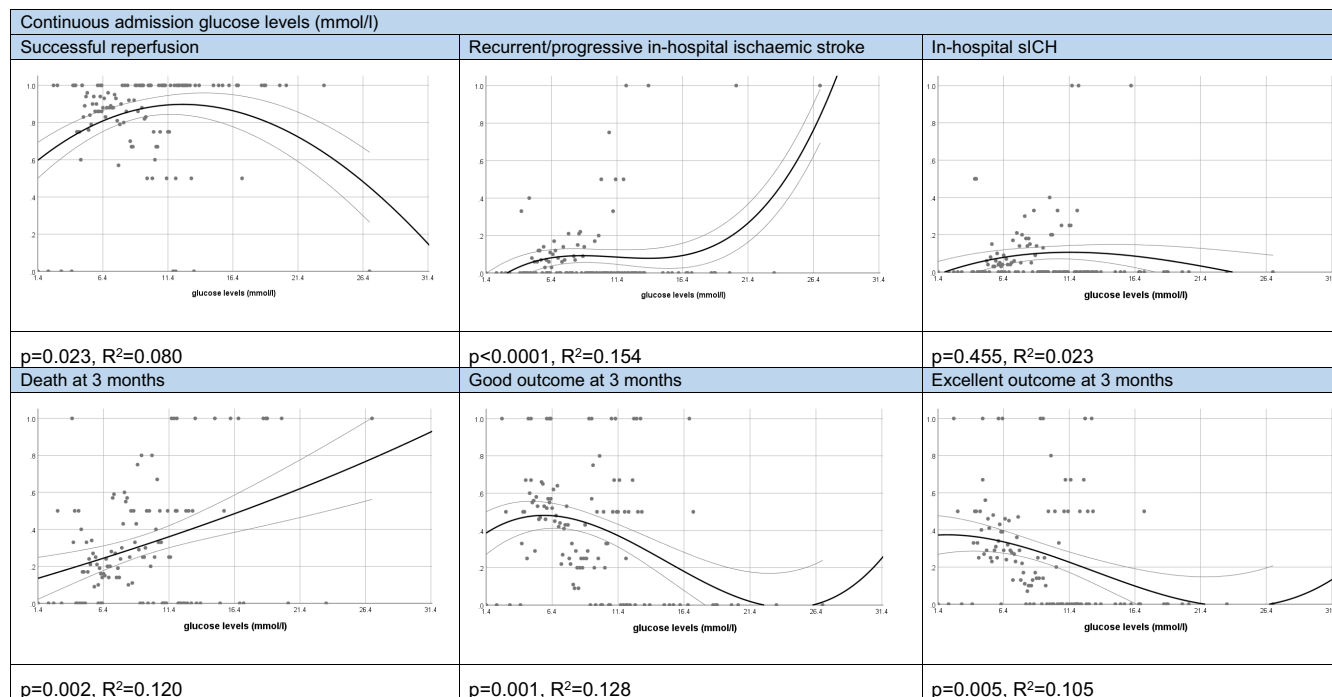


FIGURE 2 Probability of outcome by continuous admission glucose levels for all patients. sICH, symptomatic intracranial haemorrhage [Colour figure can be viewed at wileyonlinelibrary.com]

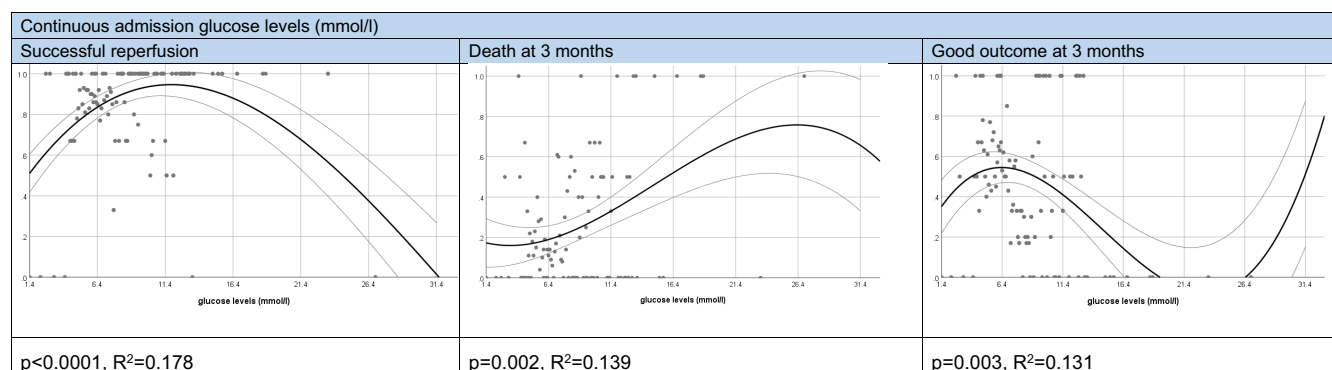


FIGURE 3 Probability of outcome by continuous admission glucose levels for patients with moderate or good collaterals and small core or target mismatch in admission imaging [Colour figure can be viewed at wileyonlinelibrary.com]

disease, AH seemed to be more important than DM in predicting poor outcome [7, 19–24, 26, 30, 31]. This underscores that AH may be a better poor prognostic marker for an eventful postprocedural course [3].

Most previous studies reported similar SR rates in AIS patients after EVT regardless of glucose levels but still worse functional outcomes and/or infarct growth in patients with versus without dysglycaemia at admission [2, 3, 7, 19, 21–27, 30]. Our adjusted study results are in line with these findings. The numerous detrimental effects of dysglycaemia at the capillary, cellular, and metabolic levels could explain these findings [5, 6].

Dysglycaemia has also been demonstrated to be a factor modifying penumbra, as it is associated with an altered “time is brain” concept, implying less salvageable tissue, faster progression of infarction, and worse collaterals [15, 18, 20, 25, 29, 31]. In patients

with moderate or good collaterals and a mismatch in admission imaging in our study, the likelihood of either a good or bad outcome was more pronounced.

Dysglycaemia also has procoagulant and antifibrinolytic effects that can compromise the effectiveness of IVT, but can be partly overcome with EVT [7, 13, 47]. This may explain why a stronger negative effect of dysglycaemia on functional outcome and/or infarct growth was found in AIS patients without SR after EVT in a few studies [2, 30]. Moreover, in some studies but not others, dysglycaemia was not only a negative prognostic factor but also a treatment modifier lowering the effectiveness of EVT [19, 21, 23, 27, 29]. Our study is in line with these findings.

Results about sICH in AIS patients treated with EVT with dysglycaemia are conflicting [2, 3, 7, 19, 21–27, 30, 31]. In our study, AH but not DM turned out to be an independent predictor of sICH.

If dysglycaemia is associated with poor outcome in AIS patients treated with EVT, the question arises whether acute treatment of dysglycaemia is beneficial and safe in these patients.

Previous RCTs in the pre-EVT era that assessed the benefit and safety of lowering glucose levels in AIS patients were unsuccessful [48, 49]. In the SHINE RCT, insulin treatment with intensive versus standard (target glucose levels of 4.4–7.2 mmol/L vs. 4.4–9.9 mmol/L) glucose control with treatment initiation within 12 h of symptom onset for up to 72 h in AIS patients with AH (glucose concentration of >6.1 mmol/L in patients with DM or ≥8.3 mmol/L in patients without DM) did not result in a different 3-month rate of good outcome [32]. There were similar admission glucose levels and sICH, recurrent/progressive ischaemic stroke, and mortality rates in both groups, but lower mean glucose levels achieved in the intensive versus standard treatment group (difference of 3.4 mmol/L). Severe hypoglycaemia, with potentially adverse neurological outcomes, only occurred in the intensive treatment group. The subgroup analysis of the few patients treated with EVT did not show different results regarding good outcome. The TEXAIS RCT has completed recruiting recently, and results are awaited. This trial compared exenatide (a GLP-1 receptor agonist that does not generally cause hypoglycaemia) to standard care in AIS patients with treatment initiation within 9 h of symptom onset. Probably, few AIS patients treated with EVT were included [33].

Interestingly, treatment with uric acid, which has antioxidant properties, improved 3-month functional outcome and reduced infarct growth without causing more sICH or more gout attacks in AIS patients treated with IVT (\pm EVT) in the URICO-ICUTS RCT [50]. This trial suggests that the detrimental effects of poor glucose control in AIS patients may be mitigated by antioxidants, which could be investigated in further studies.

In our study, only prestroke oral antidiabetics and insulin treatment were investigated, which did not significantly affect outcomes and were too heterogeneous in terms of agents for subgroup analyses to be performed. However, in a previous multicentre study, prestroke metformin was shown to be neuroprotective in patients with acute ischaemic stroke treated by IVT [51].

Strengths

We retrospectively examined a prospective database of a patient group as little as possible preselected at our tertiary care centre, which makes this study applicable for generalization in daily clinical practice. Also, we investigated and analyzed dysglycaemia from different points of view in this single study. In addition, the number of patients from a single centre in our study is considerable.

Limitations

The main limitation of this study is its retrospective analysis and monocentric design. Furthermore, patients were included over a

long period of time, during which guidelines, treatment strategies, and devices have evolved. Moreover, patients with missing admission HbA1c and glucose levels were excluded. Additionally, repeated glucose levels during hospitalization in acute care were not assessed; these have previously been shown to be helpful in predicting detrimental effects [11, 17]. Similarly, no data pertaining to periprocedural glucose-lowering measures were collected. Also, there are different reasons for elevated admission glucose levels [1–4]. Furthermore, we did not consider glucose levels that had already been collected in the ambulance. One percent of patients had received acute application of specific drugs correcting dysglycaemia before hospital admission. Moreover, previous studies have also found J-shaped associations [16, 23]. However, some results in our study were influenced by the small sample size of the outcome variables and by confounding factors and must be interpreted with caution.

CONCLUSIONS

Our data indicate that AH more than DM is associated with worse 3-month outcome in the patients studied, more likely so in the case of moderate/good collaterals and mismatch in admission imaging. Whether acute treatment of dysglycaemia is beneficial and safe in AIS patients treated with EVT remains an open question. Further studies should investigate a sufficiently large number of AIS patients, reperfusion, faster treatment algorithms, treatment options without hypoglycaemia risk, glucose target levels for treatment initiation, and optimal frequency of measurements of glucose levels. In addition, it would be interesting to study patients with DM separately from those with AH, as they are likely to respond differently to treatment.

AUTHOR CONTRIBUTIONS

Kotryna Genceviciute: Data curation (equal); formal analysis (equal); investigation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Martina B. Göddlin:** Data curation (equal); writing – review and editing (supporting). **Christoph C. Kurmann:** Data curation (equal); writing – review and editing (supporting). **Adnan Mujanovic:** Data curation (equal); writing – review and editing (supporting). **Thomas R. Meinel:** Data curation (equal); writing – review and editing (supporting). **Johannes Kaesmacher:** Data curation (equal); writing – review and editing (supporting). **David J. Seiffge:** Data curation (equal); writing – review and editing (supporting). **Simon Jung:** Data curation (equal); writing – review and editing (supporting). **Pasquale Mordasini:** Data curation (equal); writing – review and editing (supporting). **Urs Fischer:** Data curation (supporting); writing – review and editing (supporting). **Jan Gralla:** Data curation (equal); writing – review and editing (supporting). **Hakan Sarikaya:** Data curation (equal); writing – review and editing (supporting). **Barbara Goeggel Simonetti:** Data curation (equal); writing – review and editing (supporting). **Kateryna Antonenko:** Data curation (equal); writing – review and editing (supporting). **Roza M. Umarova:** Data curation (equal); writing – review and editing (supporting). **Lia Bally:** Conceptualization (supporting); data curation

(supporting); supervision (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Marcel Arnold:** Conceptualization (supporting); data curation (equal); supervision (supporting); writing – review and editing (supporting). **Mirjam R. Heldner:** Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (lead); visualization (equal); writing – original draft (equal); writing – review and editing (lead).

ACKNOWLEDGMENTS

We are grateful to the entire Bernese Stroke Team for its support. Open access funding provided by Inselspital Universitätsspital Bern.

CONFLICT OF INTEREST

M.B.G. reports grants from the Swiss Academy of Medical Sciences/Bangerter-Rhyner Foundation, Swiss Stroke Society, and Mittelbauvereinigung der Universität Bern as well as congress support from Pfizer. T.R.M. reports research support from the Bangerter Rhyner Foundation, Swiss National Science Foundation, and Swiss Heart Foundation. J.K. reports research support from the Swiss Academy of Medical Sciences, Bangerter Rhyner Foundation, Swiss Stroke Society, and Clinical Trials Unit Bern. P.M. reports research support from Siemens, Cerenovus, iSchemaview, Medtronic, and Stryker and is has received honoraria and consultation fees from Medtronic, Cerenovus, Phenox, and Microvention, paid to the institution. U.F. reports research support from Medtronic, Stryker, and CSL Behring. J.G. is a global principal investigator of STAR, Clinical Event Committee member of the PROMISE study, and principal investigator and consultant for the SWIFT DIRECT study and receives Swiss National Science Foundation grants for magnetic resonance imaging in stroke. K.A. reports research support from the Swiss National Science Foundation. M.A. reports personal fees from Bayer, Bristol-Myers Squibb, Medtronic, Amgen, Daiichi Sankyo, Nestlé Health Sciences, Boehringer Ingelheim, and Covidien. M.R.H. reports research support from the Bangerter Rhyner Foundation, SITEM Research Funds, Swiss Heart Foundation, and Swiss National Science Foundation and Amgen advisory board participation in 2020. No author reports any disclosures directly related to this article. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Raw data of all patients included in this study can be made available upon request to the corresponding author and after clearance by the local ethics committee.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The Bernese stroke registry was approved by the local ethics committee (KEK Bern 2016–01905) for quality control and research. Informed consent form was waived by the ethics committee, and patients were informed about the registry and the potential use of their data for research. In accordance with Swiss law, patients who refused the use of their data for research were excluded from

this analysis. This study complies with the Declaration of Helsinki. Data analyses followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Genceviciute K, Göldlin MB, Kurmann CC, et al. Association of diabetes mellitus and admission glucose levels with outcome after endovascular therapy in acute ischaemic stroke in anterior circulation. *Eur J Neurol*. 2022;29:2996-3008. doi: [10.1111/ene.15456](https://doi.org/10.1111/ene.15456)