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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: 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 02/2015-04/2020 were included in this observational cohort study. Patients with vs. without DM and with vs. without AH≥7.8mmol/l were compared.

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

ABBREVIATIONS

AH	admission hyperglycaemia
AIS	acute ischaemic stroke
CT	computed tomography
DM	diabetes mellitus
LVO	large vessel occlusion
MRI	magnetic resonance imaging
mRS	modified Rankin scale
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
RCT	randomized controlled trial
sICH	symptomatic intracranial haemorrhage
SR	successful reperfusion
TICI	Thrombolysis In Cerebral Ischaemia

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 vs. normoglycaemia is associated with worse outcome in AIS patients treated conservatively or with intravenous thrombolysis (IVT) [1, 4, 9-18].

Several recent retrospective and few prospective studies, post-hoc analyses of RCTs and meta-analyses have also shown that dysglycaemia vs. 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 endovascular therapy (EVT) for large vessel occlusion (LVO) in the anterior circulation in an observational cohort from daily clinical practice in a tertiary care centre.

METHODS

Patients

Data of 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 large vessel occlusion 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 (ICA-T), the proximal middle cerebral artery (M1- or M2-segment; MCA) 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 CT- and/or 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, intermediate or intensive care unit of the Bernese Stroke Centre for at least 24 hours or until death.

A follow-up CT- and/or MR-arteriography was performed 12 to 24 hours after EVT and in 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 ≥6.5% at admission and/or patients were taking antidiabetics pre-stroke or at discharge [37]. AH was considered as admission glucose ≥7.8mmol/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 and/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 (ASITN/SIR) 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, in-hospital symptomatic intracranial haemorrhage (sICH) according to ECASS 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 (SPSS Inc., Chicago, Illinois, USA). In univariable analysis, $\chi 2$ 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 vs. with AH, with vs. without DM and with vs. without HbA1c ≥6.5%. A 2-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 around 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 vs. without AH, for patients with AH with vs. without DM and for patients without DM with vs. 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.

Ethics 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 (ICF) was waived by the ethics committee, and patients were informed about the registry and the potential use of their data for research. In accordance to 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 reporting guidelines.

Availability of data and materials

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.

RESULTS

We included 1020 patients [499 (48.9%) women, median age 73.1 years] in this study. Median admission NIHSS score was 14 (0-36). Median time from known symptom onset to groin puncture was 195 (61-1436) minutes, 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% (4.1-12.9%) and 6.6 mmol/l (1.4-26.9 mmol/l), respectively.

Patients with vs. without DM were older, more frequently suffered from arterial hypertension, hyperlipidaemia, coronary heart disease and peripheral artery disease, were more frequently prescribed with antithrombotics pre-stroke and were admitted with higher median NIHSS scores.

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

Baseline characteristics are shown in table 1.

In univariable analysis, 187 (82.7%) patients with vs. 697 (87.8%) patients without DM showed less often SR (p=0.049), 37 (16.4%) vs. 76 (9.6%) were more frequently dead at discharge from acute care (p=0.004) and 82 (38.9%) vs. 184 (24.1%) at 3 months (p<0.0001). 66 (31.3%) patients with vs. 366 (48%) without DM showed good outcome and 38 (18%) vs. 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 vs. without AH. 32 (11.6%) patients with vs. 41 (5.6%) patients without AH suffered an in-hospital sICH (p=0.001), 47 (16.7%) vs. 66 (8.9%) were more frequently dead at discharge from acute care (p<0.0001) and 107 (40.4%) vs. 159 (22.4%) at 3 months (p<0.0001). 75 (28.3%) patients with vs. 357 (50.4%) without AH showed good outcome and 43 (16.2%) vs. 240 (33.9%) excellent outcome at 3 months (each p<0.0001) (table 2).

In multivariable analysis, comparing patients without vs. with DM, mTICI shift was similar, mRS shift at 3 months worse (p<0.0001) for patients with DM, SR less likely (OR 0.61), at 3 months death more likely (OR 1.75) and good outcome less likely (OR 0.59), when analysis was adjusted for age, arterial hypertension, hyperlipidaemia, pre-stroke antithrombotics and admission NIHSS score. If analysis was adjusted for AH in this group comparison additionally, mRS shift at 3 months was still worse (p=0.012). However, there was no significant difference anymore concerning SR, death and good

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%CI 1.02-2.87), p=0.043] together with admission NIHSS score [OR=0.95 (0.92-0.99), p=0.005], however, not in-hospital sICH [OR=1.34 (0.78-2.30), p=0.294] (table S1 in the Supplement).

In multivariable analysis, comparing patients without vs. with AH, mTICI shift was similar, mRS shift at 3 months worse (p<0.0001) for patients with DM, SR similar, at 3 months death 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 stopped <2 years and admission NIHSS score. If analysis was adjusted for DM in this group comparison additionally, 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 in the Supplement).

Results of the group comparison with vs. without HbA1c ≥6.5% are shown in table 3 and supplementary tables S4-5. Results of sensitivity analyses for patients with DM with vs. without AH, for patients with AH with vs. without DM and for patients without DM with vs. without AH are shown in table 3 and in table S2-5 in the Supplement.

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), good (p=0.001, R^2=0.128) and excellent outcome (p=0.005, R^2=0.105) at 3 months, however not for in-hospital sICH (figure 2). Probability of 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 and outcome after EVT in 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 vs. without DM showed less often SR and worse 3-month functional outcome. If analysis was adjusted for AH additionally, only mRS shift was still significantly worse in patients with DM. Patients with vs. without AH showed similar SR rates and worse 3-month functional outcome. If analysis was adjusted for DM additionally, 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. There was a more pronounced likelihood of outcome in patients with moderate or good collaterals and mismatch in admission imaging.

The treatment of AIS patients and large vessel occlusion in the anterior circulation changed few years ago when several randomized controlled trials (RCTs) demonstrated that EVT (+/- IVT) is safe and leads to better outcomes compared to standard treatment, strongly predicted by successful reperfusion (SR) [43, 44].

However, experimental studies on cerebral ischaemia have shown that SR contributes to detrimental effects of hyperglycaemia, while 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 it 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 an-/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 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 vs. 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 vs. without DM separately but adjusted the analysis for this 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 post-procedural 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 vs. 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]. Indeed, 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 vastly in line with these findings.

Results about sICH in AIS patients treated with EVT with dysglycaemia are conflicting [2, 3, 7, 19, 21, 7, 22-27, 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 vs. 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 hours of symptom onset for up to 72 hours 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, sICH, recurrent/progressive ischaemic stroke and mortality rates in both groups, but lower mean glucose levels achieved in the intensive vs. 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 which does not generally cause hypoglycaemia) to standard care in AIS patients with treatment initiation within 9 hours of symptom onset. Probably, few AIS patients treated with EVT got 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 (+/- 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 pre-stroke oral antidiabetics and insulin treatment were investigated, which did not significantly affect outcomes considerably and were too heterogeneous in terms of agents to perform subgroup analyses. However, in a previous multicentre study, pre-stroke 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 pre-selected 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, which have previously been shown to be helpful in predicting detrimental effects [11, 17]. Similarly, no data pertaining to peri-procedural glucose-lowering measures was collected. Also, there are different reasons for elevated admission glucose levels [1-4]. Furthermore, we did not consider glucose levels, which were collected in the ambulance already. 1% of patients have received acute application of specific drugs correcting dysglycaemia before hospital admission. Moreover, previous studies have also found *J*-shaped associations in comparable studies [16, 23]. However, some graphs 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 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 open. 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.

DECLARATIONS

Competing interests

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Authors' contributions

K Genceviciute, M Arnold and MR Heldner had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept, design and supervision: L Bally, M Arnold and MR Heldner.

Acquisition of data: All co-authors.

Extraction of data and statistical analysis: K Genceviciute and MR Heldner.

Analysis and interpretation: K Genceviciute and MR Heldner.

Drafting of the manuscript: K Genceviciute and MR Heldner.

Critical revision of the manuscript for important intellectual content: All co-authors.

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FIGURES LEGENDS

Figure 1. Flow chart of patients who met inclusion and exclusion criteria

Figure 2. Probability of outcome by continuous admission glucose levels for all patients

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

Table 1. Baseline characteristics of patients without and with diabetes mellitus and without and with admission hyperglycaemia ≥7.8mmol/l

Baseline characteristics	No diabetes mellitus (n=794)	Diabetes mellitus (n=226)	P-value	No hyperglycaemia (n=738)	Hyperglycaemia (n=282)	P-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 <2years	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
Pre-stroke antithrombotics			<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%)	
Pre-stroke oral antidiabetics [b]			<0.0001			<0.0001
Potentially hypoglycaemic	0	27 (11.9%)		4 (0.5%)	23 (8.2%)	
Non-hypoglycaemic	0	79 (35%)		27 (3.7%)	52 (18.4%)	
None	794 (100%)	120 (53.1%) [a]		707 (95.8%)	207 (73.4%)	
Other pre-stroke drugs						
Insulin treatment [b]	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
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
Hyperclycaemia ≥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≥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%)	

For categorical variables, the number of patients and percentage in brackets are shown. For non-normally distributed continuous and ordinal variables, median, minimum and maximum range are shown (in brackets). For normally distributed continuous and ordinal variables, average and standard deviation are shown (in brackets).
NOAC: new oral anticoagulants, OAC: oral anticoagulants, ICA: internal carotid artery, MCA: middle cerebral artery.
[a] n=16 were on insulin treatment. [b] Patients on no antidiabetics at discharge had significantly lower admission HbA1c levels (median 6.6 vs. 7.2, p=0.014).

Table 2. Procedural and outcome characteristics of patients without and with diabetes mellitus and without and with admission hyperglycemia ≥7.8mmol/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 [b]			<0.0001			<0.0001
Potentially hypoglycaemic	0	19 (8.4%)		5 (0.7%)	14 (5%)	
Non-hypoglycaemic	0	66 (29.2%)		20 (2.7%)	48 (17%)	
None	793 (99.9%)	141 (62.4%) [a]		712 (96.5%)	220 (78%)	
Insulin treatment at discharge [b]	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%)	
Non-vascular	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

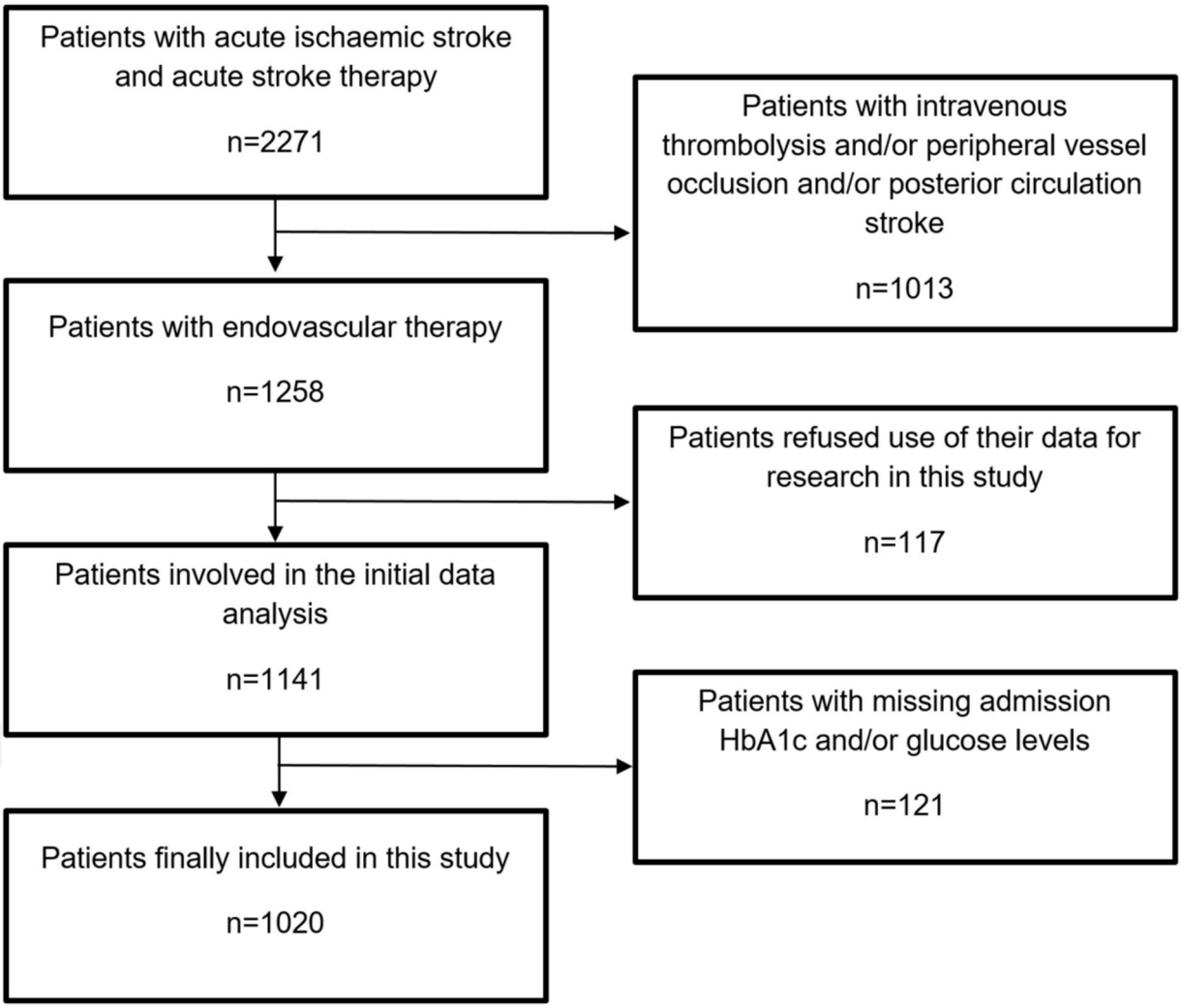
For categorical variables, the number of patients and percentage in brackets are shown. For non-normally distributed continuous and ordinal variables, median, minimum and maximum range are shown (in brackets). For normally distributed continuous and ordinal variables, average and standard deviation are shown (in brackets).

EVT: endovascular therapy, MT: mechanical thrombectomy, IVT: intravenous thrombolysis with rtPA, IAT: intraarterial thrombolysis with urokinase, sICH: symptomatic intracerebral haemorrhage, mRS: modified Rankin scale. [a] n=32 on insulin treatment and n=37 dead. [b] Patients on no antidiabetics at discharge had significantly lower admission HbA1c levels (median 6.7 vs. 7.2, p=0.003).

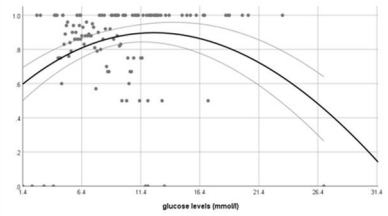
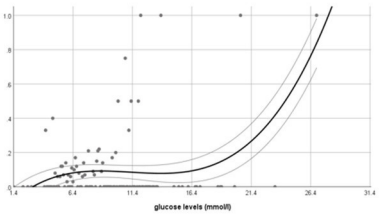
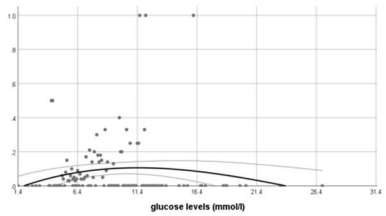
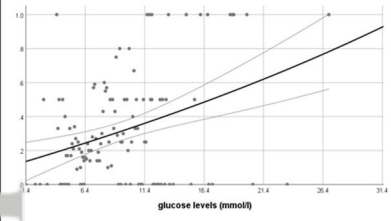
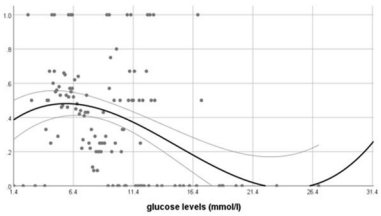
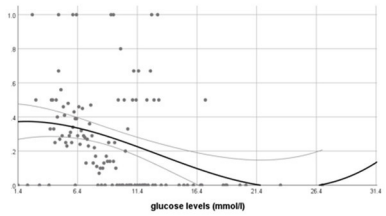
Table 3. Outcome characteristics of patients according to different glycaemia parameters

Putative predictive variables	Successful reperfusion	Death at 3 months	Independency at 3 months	mRS shift	mTICI shift
Diabetes mellitus [a] (With vs. without)	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 [g]	0.60 (0.41-0.89), p=0.011 [g]	p=0.001 [g]	NA
	0.61 (0.35-1.04), p=0.071 [h]	1.95 (1.23-3.11), p=0.005 [h]	0.52 (0.33-0.82), p=0.005 [h]	p<0.0001 [h]	p=0.347 [h]
	0.54 (0.32-0.91), p=0.020 [j]	1.77 (1.12-2.79), p=0.014 [j]	0.58 (0.36-0.93), p=0.025 [j]	p=0.002 [j]	p=0.142 [j]
	0.64 (0.40-1.02), p=0.060 [k]	1.42 (0.96-2.09), p=0.081 [k]	0.78 (0.52-1.16), p=0.214 [k]	p=0.012 [k]	p=0.365 [k]
Admission hyperglycaemia ≥7.8mmol/l [b] (With vs. without)	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 [g]	0.49 (0.34-0.71), p<0.0001 [g]	p<0.0001 [g]	NA
	1.02 (0.60-1.75), p=0.942 [i]	2.39 (1.60-3.57), p<0.0001 [i]	0.38 (0.26-0.56), p<0.0001 [i]	p<0.0001 [i]	p=0.720 [i]
	0.79 (0.51-1.22), p=0.291 [j]	1.71 (1.20-2.42), p=0.003 [j]	0.54 (0.38-0.77), p=0.001 [j]	p<0.0001 [j]	p=0.564 [j]
	0.94 (0.59-1.48), p=0.774 [l]	1.57 (1.10-2.25), p=0.014 [l]	0.58 (0.40-0.84), p=0.004 [l]	p=0.004 [l]	p=0.926 [l]
Diabetes mellitus with vs. without admission hyperglycaemia ≥7.8mmol/l [c]	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 ≥7.8mmol/l with vs. without diabetes mellitus [d]	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 ≥7.8mmol/l [e]	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 ≥6.5% [f] (With vs. without)	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 [k]	1.22 (0.80-1.87), p=0.353 [k]	1.01 (0.65-1.59), p=0.932 [k]	p=0.199 [k]	p=0.135 [k]

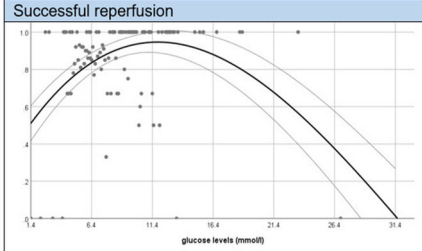
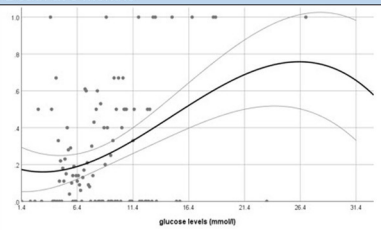
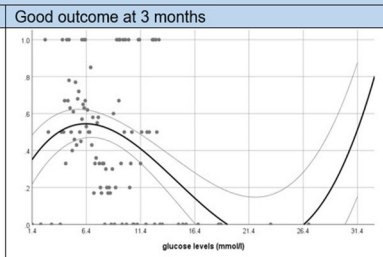
Adjusted odds ratios (95% CI) and p-values are shown. Adjusted for:
a) age, arterial hypertension, hyperlipidaemia, pre-stroke antithrombotics and admission NIHSS score
b) age, arterial hypertension, hyperlipidaemia, actively smoking or stopped <2years and admission NIHSS score
c) atrial fibrillation or flutter
d) arterial hypertension, hyperlipidaemia and admission NIHSS score
e) age, actively smoking or stopped <2years and admission NIHSS score
f) arterial hypertension, hyperlipidaemia, pre-stroke antithrombotics and admission NIHSS score
g) variables in a and b respectively, however, only patients with SR
h) only patients with moderate or good collaterals and with small core or target mismatch in admission imaging, adjusted for arterial hypertension, hyperlipidaemia, pre-stroke antithrombotics
i) only 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 <2years and admission NIHSS score
j) variables in a and b respectively, additionally adjusted for pre-stroke oral antidiabetics and insulin treatment
k) variables in a and f respectively, additionally adjusted for admission hyperglycaemia
l) variables in b, additionally adjusted for diabetes mellitus



ENE_15456_Figure1.jpg

Continuous admission glucose levels (mmol/l)		
Successful reperfusion	Recurrent/progressive in-hospital ischaemic stroke	In-hospital sICH
		
p=0.023, R^2=0.080	p<0.0001, R^2=0.154	p=0.455, R^2=0.023
Death at 3 months	Good outcome at 3 months	Excellent outcome at 3 months
		
p=0.002, R^2=0.120	p=0.001, R^2=0.128	p=0.005, R^2=0.105

ENE_15456_Figure2.jpg

Continuous admission glucose levels (mmol/l)		
Successful reperfusion	Death at 3 months	Good outcome at 3 months
		
p<0.0001, R^2=0.178	p=0.002, R^2=0.139	p=0.003, R^2=0.131

ENE_15456_Figure3.jpg

MANAGE-PD

Tool for Making Informed Decisions to **Aid Timely Management of Parkinson's Disease**

MANAGE-PD allows you to:

- Identify PD patients inadequately controlled on oral medications
- Determine which patients with PD may be adequately controlled on their current treatment regimen or may require changes to their treatment regimen

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MANAGE-PD is an AbbVie Inc. registered Medical Device. It is a collaborative research and development effort between AbbVie Medical Affairs and Health Economics and Outcomes, the Parkinson's Foundation and an international panel of Movement Disorder Specialists.

PD: Parkinson´s Disease

Parkinson's Foundation

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