High admission glucose is associated with poor outcome after endovascular treatment for ischemic stroke

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Stroke

CLINICAL AND POPULATION SCIENCES

High Admission Glucose Is Associated With Poor Outcome After Endovascular Treatment for Ischemic Stroke

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BACKGROUND AND PURPOSE: High-serum glucose on admission is a predictor of poor outcome after stroke. We assessed the association between glucose concentrations and clinical outcomes in patients who underwent endovascular treatment.

METHODS: From the MR CLEAN Registry, we selected consecutive adult patients with a large vessel occlusion of the anterior circulation who underwent endovascular treatment and for whom admission glucose levels were available. We assessed the association between admission glucose and the modified Rankin Scale score at 90 days, symptomatic intracranial hemorrhage and successful reperfusion rates. Hyperglycemia was defined as admission glucose ≥7.8 mmol/L. We evaluated the association between glucose and modified Rankin Scale using multivariable ordinal logistic regression and assessed whether successful reperfusion (extended Thrombolysis in Cerebral Infarction 2b-3) modified this association.

RESULTS: Of 3637 patients in the MR CLEAN Registry, 2908 were included. Median admission glucose concentration was 6.8 mmol/L (interquartile range, 5.9–8.1) and 882 patients (30%) had hyperglycemia. Hyperglycemia on admission was associated with a shift toward worse functional outcome (median modified Rankin Scale score 4 versus 3; adjusted common odds ratio, 1.69 [95% CI, 1.44–1.99]), increased mortality (40% versus 23%; adjusted odds ratio, 1.95 [95% CI, 1.60–2.38]), and an increased risk of symptomatic intracranial hemorrhage (9% versus 5%; adjusted odds ratio, 1.94 [95% CI, 1.41–2.66]) compared with nonhyperglycemic patients. The association between admission glucose levels and poor outcome (modified Rankin Scale score 3–6) was *J*-shaped. Hyperglycemia was not associated with the rate of successful reperfusion nor did successful reperfusion modify the association between glucose and functional outcome.

CONCLUSIONS: Increased admission glucose is associated with poor functional outcome and an increased risk of symptomatic intracranial hemorrhage after endovascular treatment.

Key Words: adult ■ cerebral infarction ■ glucose ■ odds ratio ■ reperfusion

In the acute phase of ischemic stroke, many patients have hyperglycemia, even if they do not have a history of diabetes mellitus.[1] Hyperglycemia is associated with poor functional outcome[2] and lower recanalization rates[3] in patients with ischemic stroke treated with intravenous thrombolysis. There are various mechanisms by which high glucose concentrations might exert a detrimental effect on the brain: hyperglycemia may induce brain injury because of intracellular acidosis in ischemic brain tissue, which leads to mitochondrial

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
EVT	endovascular treatment
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracranial hemorrhage

dysfunction.[4] Furthermore, hyperglycemia may stimulate the formation of reactive oxygen and nitrogen species, which can contribute to the development of reperfusion injury including cerebral edema and hemorrhagic transformation.[5]

Previous studies have assessed the association between serum glucose levels on admission and outcome in patients with stroke after endovascular treatment (EVT); however, these studies either had a small sample size or were performed in selected patient populations from randomized trials. Therefore, we sought to determine whether admission glucose is associated with radiological, functional, and clinical outcomes for patients treated in routine clinical practice with EVT.

METHODS

Study Design and Patient Selection

We used data from the MR CLEAN registry (Multicenter Registry of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), a prospective, nationwide registry of consecutive patients with acute ischemic stroke treated with EVT in the Netherlands. For the current study, we used data of all patients treated with EVT between March 2014 and November 2017 of whom the glucose concentration on admission was available. Other inclusion criteria were age ≥18 years, treatment in a center that had participated in the MR CLEAN trial, and presence of a large vessel occlusion of the anterior circulation (intracranial carotid artery/intracranial carotid artery-T, middle cerebral artery [M1/M2] or anterior cerebral artery [A1/A2]). No formal power calculation was performed for the purpose of this study.

EVT consisted of arterial catheterization with a microcatheter to the level of the occlusion, followed by mechanical thrombectomy, thrombus aspiration, or a combined approach, with or without delivery of a thrombolytic agent. The exact strategy for EVT was at the discretion of the treating physician. Patients with reperfusion at first angiography underwent only a diagnostic digital subtraction angiography without further intervention. In patients in whom intracranial access was not possible, only digital subtraction angiography was performed. All relevant imaging was analyzed by an imaging core laboratory, whose members were blinded to all clinical data except for the side of symptoms. An adverse event committee, consisting of 2 vascular neurologists and one neuroradiologist, evaluated the safety end points based on clinical data and reports from the imaging core laboratory. Detailed methods of the MR CLEAN Registry have been reported previously.[6]

Medical Ethic Committee Statement

The study protocol has been evaluated by the medical ethics committee of the Erasmus University Medical Center in Rotterdam and permission to carry out the study as a registry was granted (MEC-2014-235). They waived the need for written informed consent.

Outcomes and Definitions

The main outcome was functional outcome at 90 days, assessed with the modified Rankin Scale (mRS). The mRS score ranges from 0 (no symptoms) to 6 (death).[7] Other outcomes included poor functional outcome at 90 days (defined as mRS score of 3–6), mortality at 90 days, symptomatic intracranial hemorrhage (sICH), and other complications (new ischemic stroke, extracranial hemorrhage, stroke progression resulting in death or neurological deterioration, pneumonia, and other infections). Hyperglycemia was defined as the first glucose on admission of ≥7.8 mmol/L, in accordance with previous studies[8,9] and the criteria of the American Diabetes Association.[10] sICH was defined as death or neurological deterioration (an increase of ≥4 points on the National Institutes of Health Stroke Scale [NIHSS], assessed by the treating physician) associated to the hemorrhage (Heidelberg Bleeding Criteria).[11] Successful reperfusion was defined as extended Thrombolysis in Cerebral Infarction scores of 2b-3.[12] To achieve an extended Thrombolysis in Cerebral Infarction score of 2b-3, digital subtraction angiography needed to include both antero-posterior and lateral views post-EVT. If the lateral view was not available, the extended Thrombolysis in Cerebral Infarction score could be no higher than 2A. The extent of collaterals was graded on baseline CTA by the imaging core laboratory on a 4-point scale, with 0 for absent collaterals (0% filling of the occluded vascular territory), 1 for poor (>0% and ≤50% filling), 2 for moderate (>50% and <100% filling), and 3 for good collaterals (100% filling), as used previously.[13–15] Definitions of complications were as previously described.[6]

Statistical Analysis

We compared patients with hyperglycemia on admission with patients without hyperglycemia on admission. We also analyzed glucose as a continuous variable. We performed independent samples *t* test, Mann-Whitney *U* test, Fishers' exact test or χ^2 test as appropriate for intergroup comparison. For regression analyses, missing variables were imputed with multivariate imputation by chained equations with 5 imputations.

For the main outcome, we used multivariable ordinal logistic regression analysis to evaluate any shift toward poorer functional outcome on the mRS. For the remaining end points, we used multivariable binary logistic regression analyses. For the regression analyses with mRS and mortality as outcome, we adjusted for the following prognostic factors: age, sex, NIHSS at baseline, prestroke mRS, treatment with intravenous thrombolysis, systolic blood pressure, peripheral artery disease, prior stroke, collateral status, and onset-to-groin time. For the regression analyses with reperfusion and extracranial or intracranial hemorrhage as outcomes, we adjusted for the following prespecified prognostic factors: age, sex, NIHSS at baseline, treatment with intravenous

thrombolysis, anticoagulant use, antiplatelet use, and systolic blood pressure. The regression analyses for new ischemic stroke, pneumonia, and other infections were adjusted for age, sex, and NIHSS at baseline. To explore whether an association between hyperglycemia and poor outcome could be explained by an increased risk of sICH, we performed an analysis in which we additionally adjusted for sICH. We performed a sensitivity analysis restricted to patients without a history of diabetes mellitus, as previous studies have suggested that this group of patients has a worse outcome when presenting with hyperglycemia.[16]

We also analyzed admission glucose as a continuous variable (divided into deciles) to determine the association between admission glucose and mRS score at 90 days (dichotomized, with mRS score of 3–6 as poor functional outcome) and the probability of sICH using multivariable ordinal and binary logistic regression models, respectively. We determined whether the association was nonlinear by assessing the fit of models with or without restricted cubic splines using the likelihood ratio test. We set out to assess whether successful reperfusion, as a proxy for treatment with EVT, may result in reperfusion injury, which could be more severe in patients with higher glucose levels on admission. Therefore, we determined whether successful reperfusion modified the association between admission glucose and functional outcome at 90 days by adding a multiplicative interaction term in the model. We plotted the probability of poor functional outcome (mRS score of 3–6) and sICH, and we reported adjusted (common) odds ratios (ORs) with corresponding 95% CIs. Statistical analyses were performed using R software and R Studio (Version 3.6.1, R Foundation).

Data cannot be made available to other researchers, as no patient approval was obtained for sharing coded data, and sharing data would violate Dutch law. However, syntax and output files of statistical analyses will be made available upon reasonable request to the corresponding author.

RESULTS

Of the 3637 patients in the MR CLEAN Registry, we excluded 729 patients for the following reasons: age <18 years (n=9), posterior circulation ischemic stroke (n=172), EVT in a non-MR CLEAN trial center (n=177), and missing admission glucose levels (n=371; Figure 1). The median admission glucose was 6.8 mmol/L (interquartile range, 5.9–8.1). In total, 882 of 2908 (30%) patients had hyperglycemia on admission.

Patient and procedural characteristics at baseline are described in Table 1. Patients with hyperglycemia

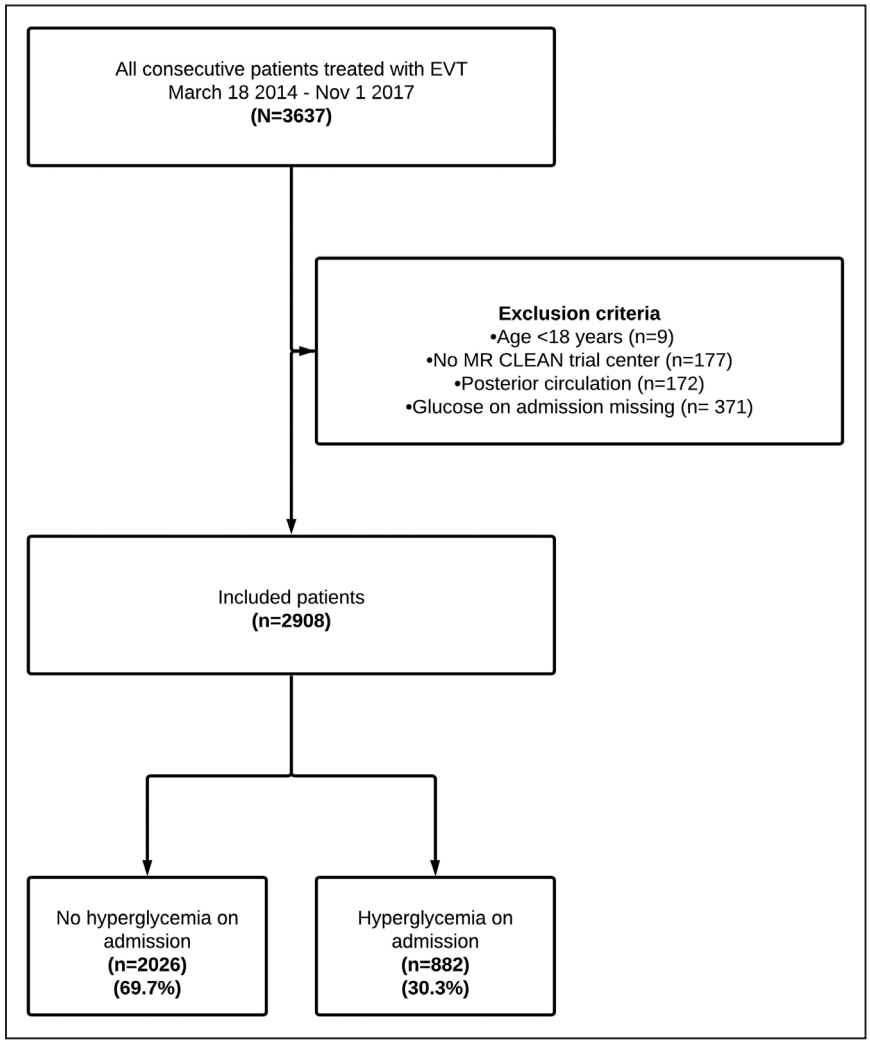

Figure 1. Flowchart of patient selection.
EVT indicates endovascular treatment; and MR CLEAN, Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands.

Table 1. Baseline and Procedural Characteristics

	Admission Hyperglycemia (n=882)	No Admission Hyperglycemia (n=2026)	*P* Value
Median age, y (IQR)	73 (64–81)	71 (59–80)	<0.001*
Male, n (%)	430/882 (49)	1082/2026 (53)	0.021*
Median glucose at admission, mmol/L (IQR)	9.1 (8.3–10.8)	6.3 (5.7–6.9)	NA
Mean systolic blood pressure (mm Hg±SD)†	153±24	149±25	<0.001*
Mean diastolic blood pressure (mm Hg±SD)‡	83±16	83±15	0.930
IV thrombolysis, n (%)	664/880 (76)	1522/2023 (75)	0.900
Median NIHSS at admission (IQR)§	16 (12–20)	15 (10–19)	<0.001*
Transfer patients, n (%)	446/882 (51)	1037/2026 (51)	0.759
Medical history			
Stroke, n (%)	163/882 (19)	317/2026 (16)	0.057
Atrial fibrillation, n (%)	205/874 (24)	471/1999 (24)	0.951
Diabetes mellitus, n (%)	315/876 (36)	150/2014 (7)	<0.001*
Hypertension, n (%)	533/862 (62)	968/1992 (49)	<0.001*
Peripheral artery disease, n (%)	77/870 (9)	187/1985 (9)	0.628
Prestroke mRS, n (%)			0.055
Prestroke mRS score 0	555/862 (64)	1381/1992 (69)	
Prestroke mRS score 1	126/862 (15)	242/1992 (12)	
Prestroke mRS score 2	181/862 (8)	368/1992 (8)	
Prestroke mRS score ≥3	113/862 (13)	216/1992 (11)	
Medication use			
Statin use, n (%)	373/866 (43)	628/1982 (32)	<0.001*
Anticoagulation use, n (%)	152/868 (18)	356/1991 (18)	0.812
Antiplatelet use, n (%)	306/875 (35)	580/2004 (29)	<0.001*
Process measures			
General anesthesia, n (%)	202/832 (24)	503/1906 (26)	0.244
Median duration from onset-to-groin in minutes (IQR)‖	205 (158–270)	191 (147–255)	<0.001*
Median duration of procedure in minutes (IQR)¶	60 (40–85)	56 (35–82)	0.010*
Imaging			
Occlusion location, n (%)			0.397
Intracranial ICA	41/850 (5)	107/1918 (6)	
ICA-T	193/850 (23)	385/1918 (20)	
M1	473/850 (56)	1126/1918 (58.7)	
M2	135/850 (16)	284/1918 (15)	
Other#	8/850 (1)	16/1918 (1)	
Collateral status, n (%)			0.029*
Grade 0	61/825 (7)	100/1901 (5)	
Grade 1	298/825 (36)	668/1901 (35)	
Grade 2	324/825 (39)	732/1901 (39)	
Grade 3	142/825 (17)	401/1901 (21)	
Extracranial carotid stenosis (50%–99%), n (%)	80/783 (10)	158/1767 (9)	0.307
Extracranial carotid occlusion, n (%)	91/783 (12)	193/1767 (11)	0.605
Median ASPECTS baseline (IQR)	9 (7–10)	9 (8–10)	0.604

ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; DSA, digital subtraction angiography; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Statistically significant.

†Missing values, n (%): 68 (2).

‡Missing values, n (%): 77 (3).

§Missing values, n (%): 40 (1).

‖Missing values, n (%): 13 (1).

¶Missing values, n (%): 255 (9).

#(M3/A1/A2).

on admission were older (73 versus 71 years; $P<0.001$) and less often male (49% versus 53%; $P=0.021$) than patients without hyperglycemia. Hyperglycemic patients more often had a history of diabetes mellitus (36% versus 7%; $P<0.001$) or hypertension (62% versus 49%; $P<0.001$). Patients with hyperglycemia had higher median NIHSS scores at baseline (16 versus 15; $P<0.001$) and longer median onset-to-groin-times (205 versus 191 minutes; $P<0.001$). Hyperglycemic patients had worse collateral scores. The prestroke mRS was similar in both groups. Decompressive hemicraniectomy for space-occupying edema was performed in 35/385 (9%) of hyperglycemic patients compared with 20/814 (2%, $P<0.001$) for nonhyperglycemic patients.

Hyperglycemia and Outcome

Patients with hyperglycemia on admission had worse functional outcomes at 90 days than patients without hyperglycemia (median mRS score of 4 versus 3; $P<0.001$). After adjustment, hyperglycemia remained associated with poor functional outcome (adjusted common odds ratio for a shift toward poor mRS score of 1.69 ([95% CI, 1.44–1.99]; Figure 2, Table 2).

Of all patients with hyperglycemia on admission, 250/841 (30%) had a good functional outcome (mRS score of 0–2) compared with 875/1892 (46%) of the nonhyperglycemic patients (adjusted odds ratio [aOR], 0.60 [95% CI, 0.49–0.74]; Table 2). Mortality at 90 days was higher for patients with hyperglycemia on admission (40% versus 23%, aOR 1.95 [95% CI, 1.60–2.38]). Hyperglycemic patients had a higher risk of sICH (9% versus 5%; aOR, 1.94 [95% CI, 1.41–2.66]). Patients with hyperglycemia on admission also more often had stroke progression (12% versus 8%; aOR, 1.44 [95% CI, 1.10–1.89]), pneumonia (15% versus 10%; aOR, 1.48 [95% CI, 1.16–1.88]), and other infections (5% versus 3%; aOR, 1.50 [95% CI, 1.03–2.19]). There were no differences in the rates of successful reperfusion (60% versus 63%; aOR, 0.94 [95% CI, 0.79–1.11]), or the other complications. Adjusting for sICH yielded similar results for functional outcome at 90 days (aOR, 1.62 [95% CI, 1.38–1.90]). The sensitivity analyses excluding patients with preexisting diabetes mellitus essentially also yielded the same results (Table I in the Data Supplement).

Glucose as a Continuous Variable and Outcome

Overall, higher admission glucose was associated with a shift toward poor functional outcome with an adjusted common odds ratio per increase of 1 mmol/L of 1.12 (95% CI 1.08–1.15). However, we observed that admission glucose as a continuous variable was nonlinearly associated with poor functional outcome (mRS score of 3–6) at 90 days (P likelihood ratio test <0.001; Figure 3). Upon further analysis, we found a J-shaped association between admission glucose and functional outcome with a nadir at 6 mmol/L and different associations for patients with admission glucose levels below 6, between 6 and 9, and levels exceeding 9 mmol/L. For patients with admission glucose below 6 mmol/L (n=746), a decrease in admission glucose level appeared associated with a shift toward poorer functional outcome (adjusted common odds ratio per 1 mmol/L decrease in glucose, 1.16 [95% CI, 0.95–1.41]), but this was not statistically significant. For patients with admission glucose between 6 and 9 mmol/L (N=1715) and higher than 9 mmol/L (N=447), there was a positive association between higher admission glucose levels and poorer functional outcome (adjusted common odds ratio per 1 mmol/L increase in glucose, 1.27 [95% CI, 1.17–1.37] and 1.06 [95% CI, 1.01–1.11], respectively). Successful reperfusion did not modify the association between admission glucose concentration and functional outcome (P value for interaction=0.295; Figure I in the Data Supplement).

Admission glucose as a continuous variable was nonlinearly associated with sICH in univariate analysis (P likelihood ratio test=0.037). However, after adjustment, the addition of splines no longer improved model fit (P likelihood ratio test=0.068; Figure 3). Higher admission glucose was associated with an increased probability

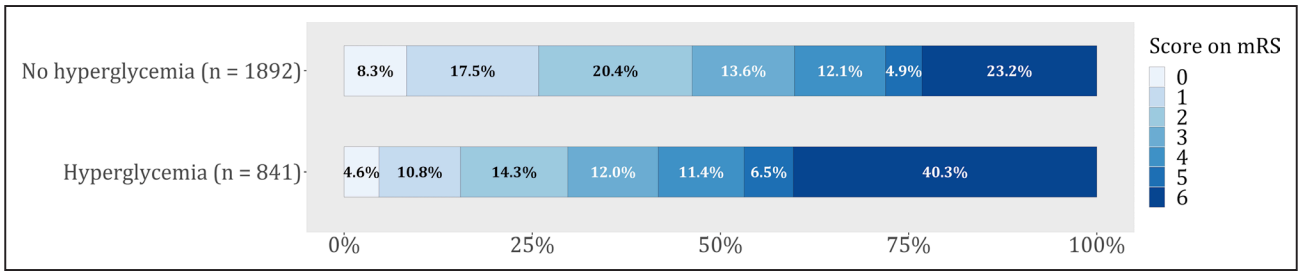

Figure 2. Functional outcome at 90 d.
Modified Rankin Scale (mRS) scores for patients with and without hyperglycemia on admission. A statistically significant difference between the 2 groups was noted in the overall distribution of mRS scores (adjusted common odds ratio, 1.69 [95% CI, 1.44–1.99]), indicating a shift toward poor functional outcome, with nonhyperglycemic patients as reference group.

Table 2. Outcomes and Complications

	Admission Hyperglycemia (n=882)	No Admission Hyperglycemia (n=2026)	Unadjusted (c)OR (95% CI)	Adjusted (c)OR (95% CI)
Outcomes				
Median mRS at 90 d (IQR)	4 (2–6)	3 (1–5)	2.03 (1.76–2.36)	1.69 (1.44–1.99)
Good functional outcome at 90 d, n (%)*	250/841 (30)	875/1892 (46)	0.51 (0.43–0.60)	0.60 (0.49–0.74)
Mortality at 90 d, n (%)	339/841 (40)	439/1892 (23)	2.12 (1.79–2.51)	1.95 (1.60–2.38)
Successful reperfusion, n (%)†	513/855 (60)	1241/1973 (63)	0.90 (0.77–1.06)	0.95 (0.80–1.12)
Complete reperfusion, n (%)‡	230/855 (27)	573/1973 (29)	0.91 (0.76–1.08)	0.91 (0.75–1.11)
Complications				
sICH, n (%)	82/882 (9)	92/2026 (5)	2.06 (1.51–2.82)	1.90 (1.40–2.56)
New ischemic stroke, n (%)	15/882 (2)	33/2026 (2)	1.03 (0.55–1.90)	1.05 (0.56–1.97)
Extracranial hemorrhage, n (%)	23/882 (3)	44/2026 (2)	1.24 (0.74–2.12)	1.02 (0.61–1.69)
Stroke progression, n (%)	102/882 (12)	162/2026 (8)	1.49 (1.15–1.95)	1.44 (1.10–1.89)
Pneumonia, n (%)	135/882 (15)	198/2026 (10)	1.61 (1.27–2.05)	1.48 (1.16–1.88)
Other infection, n (%)	47/882 (5)	65/2026 (3)	1.55 (1.07–2.24)	1.50 (1.03–2.19)

(c)OR indicates (common) odds ratio; eTICI, extended Thrombolysis in Cerebral Infarction; IQR, interquartile range; mRS, modified Rankin Scale; and sICH, symptomatic intracranial hemorrhage.

*Defined as mRS score 0–2.

†Defined as eTICI score of 2b-3.

‡Defined as eTICI score 3.

of sICH (aOR per 1 mmol/L increase, 1.11 [95% CI, 1.07–1.17]; Figure 4). In our model, patients with admission glucose levels of 12.0 mmol/L had a 7% (95% CI, 5%–10%) absolute probability of sICH, and in patients with a glucose concentration of 20.0 mmol/L this probability increased to 15% (95% CI, 9%–24%).

DISCUSSION

We found that hyperglycemia on admission (≥7.8 mmol/L) is associated with worse functional outcomes at 90 days, increased mortality, and an increased risk of sICH after EVT in patients with stroke in routine clinical

Figure 3. Admission glucose concentration as a continuous variable and the probability of poor functional outcome (modified Rankin Scale [mRS] score 3–6) at 90 d.

The association between glucose on admission and poor outcome (mRS score of 3–6) including 95% CI is shown. We observed a *J*-shaped curve with different associations based on glucose levels on admission. Overall, glucose level on admission was associated with a shift toward poor functional outcome with an adjusted common odds ratio (acOR) per 1 mmol/L increase of 1.12 (95% CI, 1.08–1.15). For patients with admission glucose under 6 mmol/L, glucose appeared associated with a shift toward poor functional outcome (acOR per 1 mmol/L decrease, 1.16 [95% CI, 0.95–1.41]), but this was nonsignificant. There was a significant association between glucose levels and poor functional outcome for patients with admission glucose between 6 and 9 (acOR, 1.27 per 1 mmol/L increase [95% CI, 1.17–1.37]) and a less pronounced association for patients with glucose levels on admission higher than 9 mmol/L (acOR, 1.06 per 1 mmol/L increase [95% CI, 1.01–1.11]).

Figure 4. Admission glucose concentration and the probability of symptomatic intracranial hemorrhage (sICH).
The association between glucose and the probability of sICH, including 95% CIs with admission glucose levels on the *x* axis and the probability of sICH on the *y* axis. We observed a linear relationship and an overall significant association between glucose and the probability of sICH (adjusted odds ratio per 1 mmol/L increase, 1.11 [95% CI, 1.07–1.17]).

practice. Further analysis showed a *J*-shaped association between admission glucose concentration and poor outcome, in which concentrations above 6 mmol/L were associated with poor outcome. By contrast, we found a linear association between admission glucose concentrations and the risk of sICH, with patients with an admission glucose concentration of 12 mmol/L on admission having an absolute risk of sICH of ≈7%, and this risk increased to 15% in patients with an admission glucose concentration of 20 mmol/L.

In our study, about one-third of patients had hyperglycemia on admission, which is comparable to proportions in previous studies.[17] Our findings are in line with those of previous studies that investigated the association between serum glucose on admission and functional outcome after EVT.[17,18] A subgroup analysis of the highly effective reperfusion using multiple endovascular devices (HERMES) collaboration showed that higher glucose levels on admission are associated with worse functional outcome and that glucose concentration modified the treatment effect of EVT, with smaller benefit for patients with glucose levels higher than 5.5 mmol/L. The authors suggested that, as patients treated with EVT have a higher rate of successful reperfusion compared with those not treated with EVT, these patients may be more prone to redox-mediated reperfusion injury associated with higher glucose levels resulting in decreased functional outcome. To address this in our study population, we analyzed whether successful reperfusion modified the association between admission glucose and functional outcome. Although we observed that the probability of poor functional outcome increased with admission glucose levels above 6 mmol/L, we did not find that successful reperfusion modified the association between admission glucose and functional outcome.

If a causal relation between hyperglycemia and poor outcome after stroke exists, lowering glucose concentrations may improve outcome. Previous trials failed to demonstrate that glucose lowering had a positive influence on outcome in patients with stroke.[19,20] The recent randomized SHINE trial (Stroke Hyperglycemia Insulin Network Effort) which compared intensive glucose lowering with standard treatment in 1151 patients with acute ischemic stroke found no difference in outcome at 90 days.[21] However, in this study, only a small proportion (13%) of patients underwent EVT. As patients with a large vessel occlusion have large ischemic areas, they are potentially more prone to reperfusion injury associated with higher admission glucose levels and may therefore benefit from intensive glucose lowering compared with standard treatment for hyperglycemia. The authors did not provide a subgroup analysis restricted to patients treated with EVT. Additionally, data on reperfusion rates were not available in SHINE and therefore the authors were unable to perform a subgroup analysis for patients with high glucose levels and successful reperfusion. In contrast to our observation, SHINE did not find a difference between the rates of ICH between the treatment groups. This discrepancy could be because of the fact that the admission glucose levels were similar between the groups and that glucose lowering could have been initiated too late to have an effect on the probability of ICH; because our study included only patients with a large vessel occlusion and thus more severe ischemic

strokes; or because of the smaller sample size of SHINE. Of course, it could also indicate that there is no causal relation between admission glucose and the occurrence of ICH.

We did not find that the association between high admission glucose and poor functional outcome was mediated by the occurrence of sICH, despite the association between higher admission glucose and an increased probability of sICH. All in all, it remains unclear whether high admission glucose levels play a causal role in increasing the probability on sICH or worse clinical outcome, but at least the absolute risk of sICH in patients with hyperglycemia can be taken into account when deciding whether or not perform EVT in a particular patient.

A *J*-shaped association between admission glucose and functional outcome has been reported in patients with ischemic stroke before EVT became routine clinical practice.[22] A similar association has also been described between blood pressure and functional outcome in patients with stroke treated with EVT.[23] The association between glucose under 6 mmol/L and functional outcome was not statistically significant in our study, although previous observational studies have suggested that patients with hypoglycemia had worse outcomes compared with normoglycemic patients.[24] The fact that we failed to demonstrate a significant association may be explained by the limited number of patients who presented with low admission glucose levels.

Pneumonia and other infections occurred more frequently in patients with hyperglycemia on admission. The association between hyperglycemia and the occurrence of infections has previously been described in patients with acute ischemic stroke.[25] However, it remains unclear whether poststroke infections explain the higher risk of a poor outcome as the authors of this study did not show evidence that the occurrence of poststroke infections mediates or explains the association between hyperglycemia on admission and poor functional outcome.

Patients in the hyperglycemia group had a longer median onset-to-groin time. This may be because of a slightly higher age, increased burden of comorbidities, and a trend toward worse prestroke mRS in this group. However, as we adjusted for these variables in the analyses, it is unlikely that this explains the results.

Our study has several strengths. The data presented in this study likely reflect daily clinical practice as they come from a nationwide, prospective registry of consecutive patients treated with EVT. Another strength is the large sample size of this study with only small numbers of missing data. Finally, all data on imaging and adverse events were centrally adjudicated. There are also several limitations. First, there were no data available on the use of glucose-lowering medication or on follow-up glucose levels. Therefore, we were unable to assess the dynamics of poststroke hyperglycemia although studies have suggested that persisting hyperglycemia is associated with infarct expansion and poor functional outcome.[26,27] Finally, we could not ascertain whether glucose levels were determined in venous or capillary samples and whether point-of-care testing was applied, which may influenced the measured glucose levels.[28]

CONCLUSIONS

The presence of hyperglycemia at admission is associated with an increased risk of poor functional outcome and sICH in patients with acute ischemic stroke who undergo EVT. Studies are warranted to determine whether patients treated with EVT may benefit from early intensive glucose-lowering therapy.

ARTICLE INFORMATION

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Supplemental Materials

Table I
Figure I

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