Triage of stroke patients in the chain of acute stroke care

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Chapter 7

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

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ABSTRACT

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 (EVT).

Methods

From the MR CLEAN Registry, we selected consecutive adult patients with a large vessel occlusion of the anterior circulation who underwent EVT and for whom admission glucose levels were available. We assessed the association between admission glucose and the modified Rankin Scale (mRS) score at 90 days, symptomatic intracranial hemorrhage (sICH) and successful reperfusion rates. Hyperglycemia was defined as admission glucose ≥7.8 mmol/L. We evaluated the association between glucose and mRS using multivariable ordinal logistic regression and assessed whether successful reperfusion (eTICI 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 (IQR 5.9-8.1) and 882 patients (30%) had hyperglycemia. Hyperglycemia on admission was associated with a shift towards worse functional outcome (median mRS 4 vs 3; adjusted common OR 1.69; 95%CI 1.44-1.99), increased mortality (40% vs 23%; aOR 1.95; 95%CI 1.60-2.38) and an increased risk of sICH (9% vs 5%; aOR 1.94; 95%CI 1.41-2.66) compared to non-hyperglycemic patients. The association between admission glucose levels and poor outcome (mRS 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.

Conclusion

Increased admission glucose is associated with poor functional outcome and an increased risk of sICH after EVT.

INTRODUCTION

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 ischemic stroke patients treated with intravenous thrombolysis (IVT). There are various mechanisms by which high glucose concentrations might exert a detrimental effect on the brain: hyperglycemia may induce brain injury due to intracellular acidosis in ischemic brain tissue, which leads to mitochondrial 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 stroke patients following 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, 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 (LVO) of the anterior circulation (intracranial carotid artery [ICA/ICA-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 micro-catheter 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 (DSA) without further intervention. In patients in whom intracranial access was not possible, only DSA 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 two vascular neurologists and one neuro-radiologist, evaluated the safety endpoints based on clinical data and reports from the imaging core lab. 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 ranges from 0 (no symptoms) to 6 (death).[7] Other outcomes included poor functional outcome at 90 days (defined as mRS 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 NIHSS, assessed by the treating physician) associated to the hemorrhage (Heidelberg Bleeding Criteria)[11]. Successful reperfusion was defined as extended Thrombolysis in Cerebral Infarction (eTICI) scores of 2b-3.[12] To achieve an eTICI score of 2b-3, DSA needed to include both antero-posterior and lateral views post-EVT. If the lateral view was not available, the eTICI 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 chi-square 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 a shift towards poorer functional outcome on the mRS. For the remaining endpoints, 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, pre-stroke mRS, treatment with IVT, 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 pre-specified prognostic factors: age, sex, NIHSS at baseline, treatment with IVT, 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 at 90 days (dichotomized, with mRS 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 non-linear 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 would be more severe in patients with higher glucose levels on admission are more severely affected. 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 3-6) and sICH and we reported adjusted (common) odds ratios (ORs) with corresponding 95% confidence intervals (CI). 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.

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 [IQR] 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 on admission were older (73 vs 71 years, p<0.001) and less often male (49% vs 53%, p=0.021) than patients without hyperglycemia. Hyperglycemic patients more often had a history of diabetes (36% vs 7%, p<0.001) or hypertension (62% vs 49%, p<0.001). Patients with hyperglycemia had higher median NIHSS scores at baseline (16 vs 15, p<0.001) and longer median onset-to-groin-times (205 vs 191 minutes, p<0.001). Hyperglycemic patients had worse collateral scores.

The pre-stroke mRS was similar in both groups. Hemicraniectomy was performed in 35/385 (9%) of hyperglycemic patients compared to 20/814 (2%, p<0.001) for non-hyperglycemic patients.

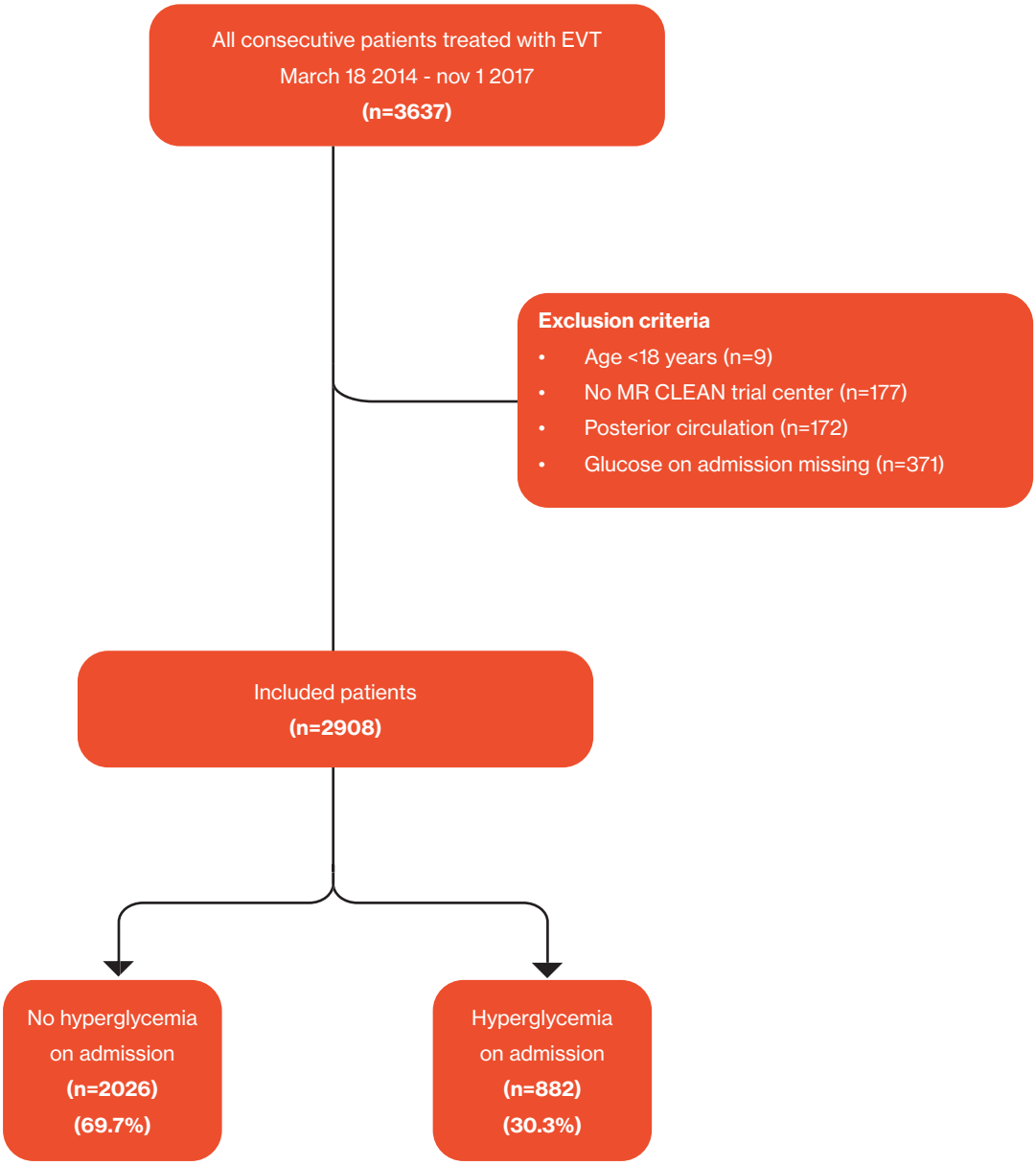


Figure 1.
Flowchart of patient selection

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 in years (IQR)	73 (64 – 81)	71 (59 – 80)	**<0.001**
Male, n (%)	430/882 (49)	1082/2026 (53)	**0.021**
Median glucose at admission in mmol/L (IQR)	9.1 (8.3 - 10.8)	6.3 (5.7 – 6.9)	NA
Mean systolic blood pressure (mmHg ± SD)[a]	153 ± 24	149 ± 25	**<0.001**
Mean diastolic blood pressure (mmHg ± SD)[b]	83 ± 16	83 ± 15	0.930
IV thrombolysis, n (%)	664/880 (76)	1522/2023 (75)	0.900
Median NIHSS at admission (IQR) [c]	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
Pre-stroke mRS, n (%)			0.055
Pre-stroke mRS 0	555/862 (64)	1381/1992 (69)	
Pre-stroke mRS 1	126/862 (15)	242/1992 (12)	
Pre-stroke mRS 2	181/862 (8)	368/1992 (8)	
Pre-stroke mRS ≥ 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)[e]	205 (158-270)	191 (147-255)	**<0.001**
Median duration of procedure in minutes (IQR)[f]	60 (40-85)	56 (35-82)	**0.010**

	Admission hyperglycemia (n=882)	No admission hyperglycemia (n=2026)	P-value
Imaging			
Occlusion location, n (%)			0.397
Intracranial ICA	41/850 (5)	107/1918 (6)	
ICA-T	193 /850 (23)	3851918 (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)	
Extra-cranial carotid stenosis (50-99%), n (%)	80/783 (10)	158/1767 (9)	0.307
Extra-cranial carotid occlusion, n (%)	91/783 (12)	193/1767 (11)	0.605
Median ASPECTS baseline (IQR)	9 (7-10)	9 (8-10)	0.604

IQR indicates interquartile range; SD, standard deviation; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; DSA, digital subtraction angiography; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score;
*Other: local interventionist ended the procedure before a thrombectomy attempt was made, despite a target occlusion being present.
†(M3/A1/A2)
Missing values, n (%): [a] 68 (2), [b]77 (3), [c]40 (1), [e]13 (1), [f]255 (9)

Hyperglycemia and outcome

Patients with hyperglycemia on admission had worse functional outcomes at 90 days than patients without hyperglycemia (median mRS 4 vs 3, p<0.001). After adjustment, hyperglycemia remained associated with poor functional outcome (adjusted common OR (acOR) for a shift towards poor mRS 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 0-2) compared to 875/1892 (46%) of the non-hyperglycemic patients (aOR 0.60, 95% CI 0.49-0.74, table 2). Mortality at 90 days was higher for patients with hyperglycemia on admission (40% vs 23%, aOR 1.95, 95% CI 1.60-2.38). Hyperglycemic patients had a higher risk of symptomatic ICH (9% vs 5%, aOR 1.94, 95% CI 1.41-2.66). Patients with hyperglycemia on admission also more often had stroke progression (12% vs 8%, aOR 1.44, 95%CI 1.10-1.89), pneumonia (15% vs 10%, aOR 1.48, 95%CI 1.16-1.88), and other infections (5% vs 3%, aOR 1.50, 95%CI 1.03-2.19). There were no differences in the rates of successful reperfusion (60% vs 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.

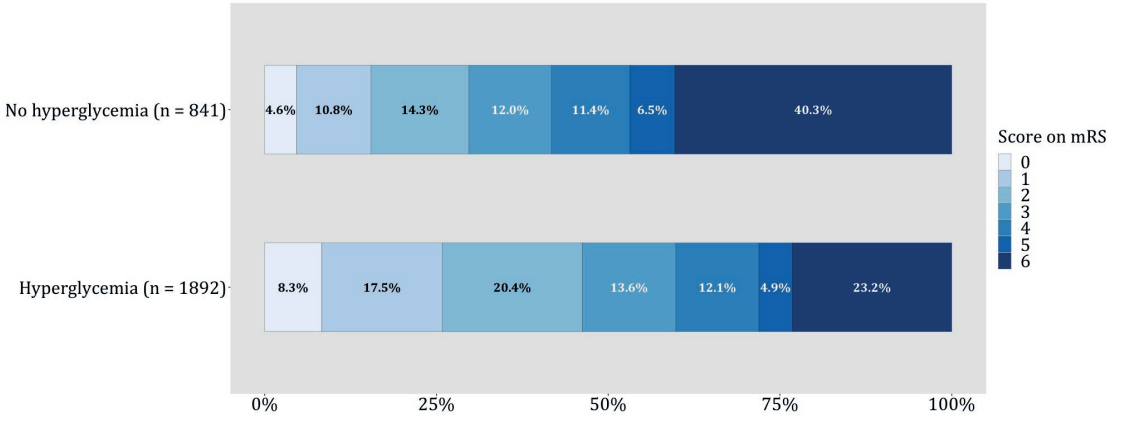


Figure 2.
Functional outcome at 90 days

Modified Rankin Scale (mRS) scores for patients with and without hyperglycemia on admission. A statistically significant difference between the two groups was noted in the overall distribution of mRS scores (adjusted common OR 1.69, 95% CI 1.44-1.99), indicating a shift towards poor functional outcome, with non-hyperglycemic 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 days (IQR)	4 (2–6)	3 (1–5)	2.03 (1.76-2.36)	1.69 (1.44-1.99)
Good functional outcome at 90 days, n (%)*	250/841 (30)	875/1892 (46)	0.51 (0.43-0.60)	0.60 (0.49-0.74)
Mortality at 90 days, 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; mRS, modified Rankin Scale; IQR, interquartile range; sICH, symptomatic intracranial hemorrhage; eTICI, extended Thrombolysis In Cerebral Infarction; SD, standard deviation.

*Defined as mRS 0-2 † Defined as eTICI score of 2b – 3 ‡Defined as eTICI score 3.

(aOR 1.62, 95%CI 1.38-1.90). The sensitivity analyses excluding patients with pre-existing diabetes mellitus essentially also yielded the same results (supplemental material Table I, https://www.ahajournals.org/journal/str).

Glucose as a continuous variable and outcome

Overall, higher admission glucose was associated with a shift towards poor functional outcome with an acOR 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 non-linearly associated with poor functional outcome (mRS 3-6) at 90 days (P-value 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 towards poorer functional outcome (acOR 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 (acOR 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, supplemental material Figure I, https://www.ahajournals.org/journal/str,)

Admission glucose as a continuous variable was non-linearly associated with sICH in univariate analysis (P-value likelihood ratio test = 0.037). However, after adjustment, the addition of splines no longer improved model fit (P-value likelihood ratio test = 0.068, figure 3). Higher admission glucose was associated with an increased probability of sICH (aOR per 1mmol/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%).

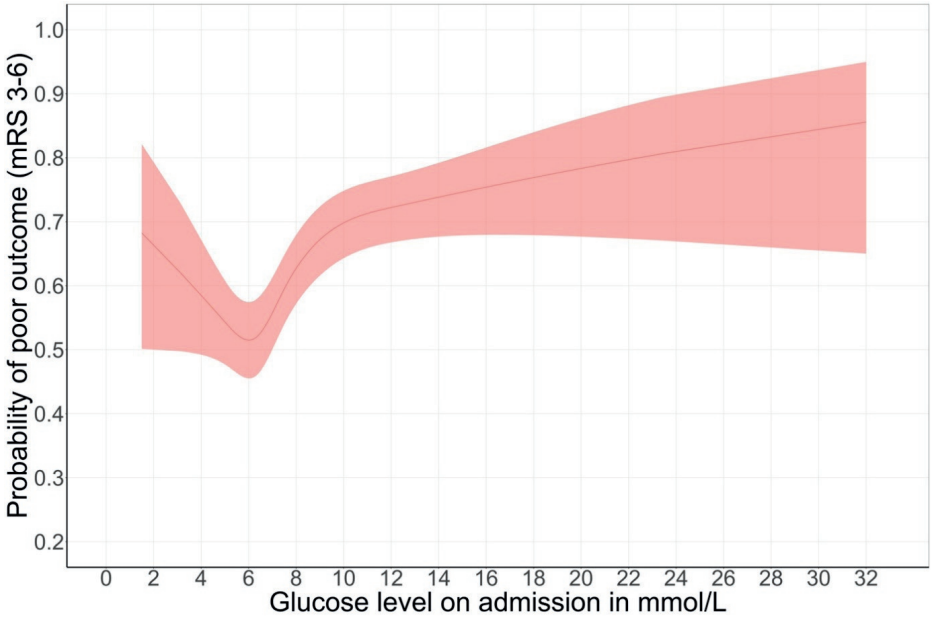


Figure 3.
Admission glucose concentration as a continuous variable and the probability of poor functional outcome (mRS 3-6) at 90 days

The association between glucose on admission and poor outcome (mRS 3-6) including 95% confidence intervals (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 towards poor functional outcome with an 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 towards poor functional outcome (acOR per 1mmol/L decrease 1.16 [95% CI 0.95 –1.41]), but this was non-significant. 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).

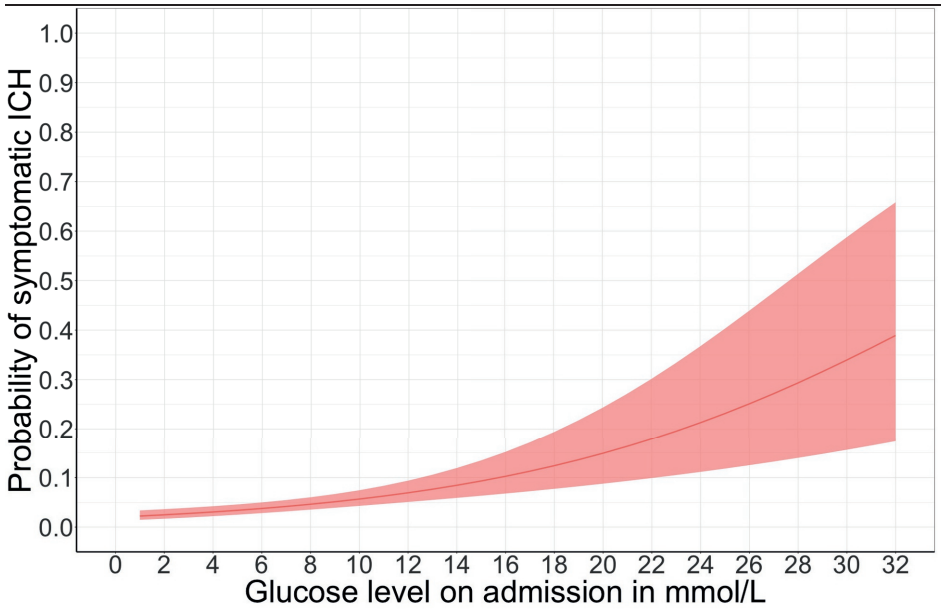


Figure 4.
Admission glucose concentration and the probability of symptomatic ICH

The association between glucose and the probability of symptomatic intracranial hemorrhage (sICH), including 95% confidence intervals 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 (aOR per 1 mmol/L increase 1.11, 95%CI 1.07-1.17).

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 stroke patients in routine clinical 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 approximately 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 HERMES 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 to 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. In order 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 stroke patients. [19,20] The recent randomized SHINE trial 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 LVO 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 to 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 due to 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 LVO 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 ischemic stroke patients before EVT became routine clinical practice.[22] A similar association has also been described between blood pressure and functional outcome in stroke patients 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 to 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 acute ischemic stroke patients.[25] However, it remains unclear whether post-stroke infections explain the higher risk of a poor outcome as the authors of this study did not show evidence that the occurrence of post-stroke infections mediates or explains the association between hyperglycemia on admission and poor functional outcome.

Patients in the hyperglycemia group had a longer median duration of onset-to-groin time. This may be due to a slightly higher age, increased burden of co-morbidities, and a trend towards worse pre-stroke mRS in this group. However, since 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 post stroke hyperglycemia while 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]

CONCLUSION

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.

REFERENCES

1. Christensen H, Boysen G. Blood glucose increases early after stroke onset: a study on serial measurements of blood glucose in acute stroke. *European Journal of Neurology*. 2002;9(3):297-301. doi:10.1046/j.1468-1331.2002.00409.x

2. Ahmed N. Association of Admission Blood Glucose and Outcome in Patients Treated With Intravenous Thrombolysis. *Archives of Neurology*. 2010;67(9):1123. doi:10.1001/archneurol.2010.210

3. Ribo M, Molina C, Montaner J, et al. Acute Hyperglycemia State Is Associated With Lower tPA-Induced Recanalization Rates in Stroke Patients. *Stroke*. 2005;36(8):1705-1709. doi:10.1161/01.str.0000173161.05453.90.9f

4. Anderson RE, Tan WK, Martin HS, Meyer FB. Effects of Glucose and PaO2 Modulation on Cortical Intracellular Acidosis, NADH Redox State, and Infarction inthe Ischemic Penumbra. *Stroke*. 1999;30(1):160-170. doi:doi:10.1161/01.STR.30.1.160

5. Martini SR, Kent TA. Hyperglycemia in Acute Ischemic Stroke: A Vascular Perspective. *Journal of Cerebral Blood Flow & Metabolism*. 2007;27(3):435-451. doi:10.1038/sj.jcbfm.9600355

6. Jansen IGH, Mulder MJHL, Goldhoorn R-JB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018:k949. doi:10.1136/bmj.k949

7. Swieten JCv, Koudstaal PJ, Visser MC, Schouten HJ, Gijn Jv. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607. doi:doi:10.1161/01.STR.19.5.604

8. Schut ES, Westendorp WF, De Gans J, et al. Hyperglycemia in bacterial meningitis: a prospective cohort study. 2009;9(1):57. doi:10.1186/1471-2334-9-57

9. Zuurbier SM, Hiltunen S, Tatlisumak T, et al. Admission Hyperglycemia and Clinical Outcome in Cerebral Venous Thrombosis. *Stroke*. 2016;47(2):390-396. doi:10.1161/strokeaha.115.011177

10. Anon. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. Jan 2019;42(Suppl 1):S13-s28. doi:10.2337/dc19-S002

11. Kummer Rv, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification. *Stroke*. 2015;46(10):2981-2986. doi:doi:10.1161/STROKEAHA.115.010049

12. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *Journal of NeuroInterventional Surgery*. 2014;6(2):83-86. doi:10.1136/neurintsurg-2013-010665

13. Berkhemer OA, Jansen IGH, Beumer D, et al. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke. *Stroke*. 2016;47(3):768-776. doi:10.1161/strokeaha.115.011788

14. Román LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *The Lancet Neurology*. 2018;17(10):895-904. doi:10.1016/s1474-4422(18)30242-4

15. Tan IYL, Demchuk AM, Hopyan J, et al. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. *American Journal of Neuroradiology*. 2009;30(3):525-531. doi:10.3174/ajnr.a1408

16. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress Hyperglycemia and Prognosis of Stroke in Nondiabetic and Diabetic Patients. *Stroke*. 2001;32(10):2426-2432. doi:10.1161/hs1001.096194

17. Chamorro Á, Brown S, Amaro S, et al. Glucose Modifies the Effect of Endovascular Thrombectomy in Patients With Acute Stroke. *Stroke*. 2019;50(3):690-696. doi:doi:10.1161/STROKEAHA.118.023769

18. Campbell BCV, Van Zwam WH, Goyal M, et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. *The Lancet Neurology*. 2018;17(1):47-53. doi:10.1016/s1474-4422(17)30407-6

19. Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *The Lancet Neurology*. 2007;6(5):397-406. doi:10.1016/s1474-4422(07)70080-7

20. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol*. May 2010;67(5):570-8. doi:10.1002/ana.21983

21. Johnston KC, Bruno A, Pauls Q, et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke. *JAMA*. 2019;322(4):326. doi:10.1001/jama.2019.9346

22. Ntaios G, Egli M, Faouzi M, Michel P. J-Shaped Association Between Serum Glucose and Functional Outcome in Acute Ischemic Stroke. 2010;41(10):2366-2370. doi:10.1161/strokeaha.110.592170

23. Anadani M, Orabi MY, Alawieh A, et al. Blood Pressure and Outcome After Mechanical Thrombectomy With Successful Revascularization. *Stroke*. 2019;50(9):2448-2454. doi:doi:10.1161/STROKEAHA.118.024687

24. Piironen K, Putaala J, Rosso C, Samson Y. Glucose and Acute Stroke. *Stroke*. 2012;43(3):898-902. doi:doi:10.1161/STROKEAHA.111.631218

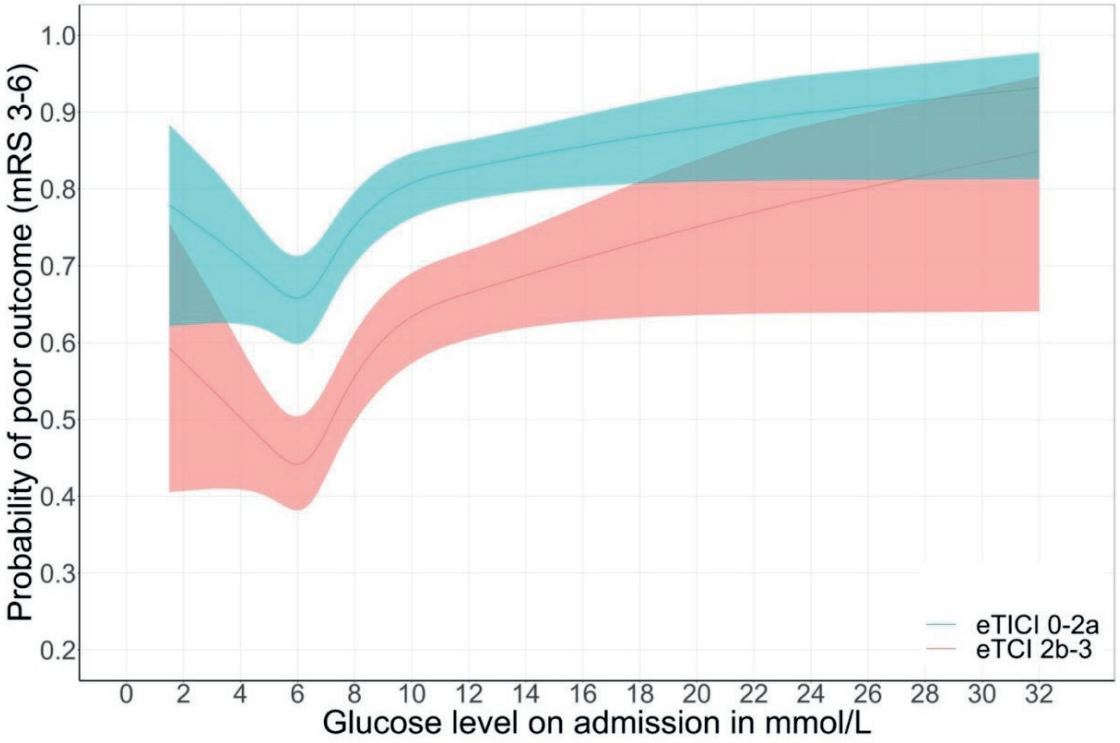
25. Zonneveld TP, Nederkoorn PJ, Westendorp WF, Brouwer MC, van de Beek D, Kruyt ND. Hyperglycemia predicts poststroke infections in acute ischemic stroke. *Neurology*. 2017;88(15):1415-1421. doi:10.1212/wnl.0000000000003811

26. Yong M, Kaste M. Dynamic of Hyperglycemia as a Predictor of Stroke Outcome in the ECASS-II Trial. *Stroke*. 2008;39(10):2749-2755. doi:10.1161/strokeaha.108.514307

27. Baird TA, Parsons MW, Phan T, et al. Persistent Poststroke Hyperglycemia Is Independently Associated With Infarct Expansion and Worse Clinical Outcome. *Stroke*. 2003;34(9):2208-2214. doi:10.1161/01.str.0000085087.41330.ff

28. Pereira AJ, Corrêa TD, De Almeida FP, et al. Inaccuracy of Venous Point-of-Care Glucose Measurements in Critically Ill Patients: A Cross-Sectional Study. 2015;10(6):e0129568. doi:10.1371/journal.pone.0129568

SUPPLEMENTAL



Supplemental Figure I:
Glucose as a continuous variable and the probability of poor functional outcome (mRS 3-6) according to reperfusion status

The effect of glucose on the probability of mRS 3-6, in patients with successful reperfusion (red line) vs no successful reperfusion (blue line), including 95% confidence intervals with serum glucose levels on admission on the x-axis and the probability of poor outcome on the y-axis. Successful reperfusion did not modify the association between glucose and functional outcome (P value for interaction = 0.295).