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Diabetes is an independent growth factor of ischemic stroke during reperfusion phase leading to poor clinical outcome

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Abstract

Objectives: Despite the success of recanalization by bridging therapy, about half of treated stroke patients remain disabled. While numerous reports propose clinical predictors of stroke clinical outcome in this context, we originally aimed to study pre-therapeutic factors influencing infarct growth (IG) and poor clinical outcome in strokes due to large vessel occlusion (LVO) successfully recanalized.

Materials and methods: We enrolled 87 consecutives successfully recanalized patients (mTICI: 2b/2c/3) by mechanical thrombectomy (\pm rt-PA) after stroke due to middle cerebral artery (M1) occlusion within 6 hours according to AHA guidelines. IG was defined by subtracting the initial DWI volume to the final 24h-TDM volume. Statistical associations between poor clinical outcome (mRS \geq 2), IG and pertinent clinico-radiological variables, were measured using logistic and linear regression models.

Results: Among 87 enrolled patients (Age(y): 68.4 \pm 17.5; NIHSS: 16.0 \pm 5.4), 42/87 (48,28%) patients had a mRS \geq 2 at 3 months. Diabetic history (OR: 3.70 CI95%[1.03;14.29] and initial NIHSS (/1 point: OR: 1.16 CI95%[1.05;1.27]) were independently associated with poor outcome. IG was significantly higher in stroke patients with poor outcome (+7.57 \pm 4.52 vs -7.81 \pm 1.67; p=0.0024). Initial volumes were not significantly different (mRS \geq 2: 16.18 \pm 2.67; mRS[0-1]: 14.70 \pm 2.30; p=0.1618). Explanatory variables of IG in linear regression were diabetic history (β : 21.26 CI95%[5.43; 37.09]) and NIHSS (β : 0.83 CI95%[0.02; 1.64]). IG was higher in diabetic stroke patients (23.54 \pm 1.43 vs -6.20 \pm 9.36; p=0.0061).

Conclusions: We conclude that diabetes leads to continued IG after complete recanalization, conditioning clinical outcome in LVO strokes successfully recanalized by bridging therapy. We suggest that poor tissular reperfusion by diabetic microangiopathy could explain this result.

Introduction

In stroke patients, clinical prognosis is conditioned by final infarct volume (1–3). In the setting of large vessel occlusion, ischemic core increases over time to the detriment of ischemic penumbra, depending mainly on quality of collaterality sustaining penumbra tissue until complete recanalization (4). So, final volume is determined by early recanalization and penumbra salvage (5). Bridging therapy (endovascular thrombectomy in addition to thrombolysis by rt-PA IV) leads to a significant improvement of the functional outcome within 6 hours of ischemic stroke due to higher recanalization rate of large vessel occlusion (6). Despite highest arterial recanalization rates (~72%), about half of the treated patients remain disabled at 3 months (6). This leads to the common assumption that recanalization is considered as necessary but not sufficient to determine the functional outcome at 3 months (7).

Because patients elected to these recanalization treatments in the 6 first hours are selected on initial volume (ASPECT score ≥ 6) (6), this radiological parameter is not determinant for clinical outcome in the literature (8). Thereby, clinical prognosis is conditioned by the fate of initial ischemic core after recanalization during reperfusion phase (5). Ischemic core is classically evaluated by initial diffusion-weighted imaging (DWI) hypersignal on magnetic resonance imaging (MRI) realized before recanalization treatment (9). Despite successful recanalization, increase of initial infarct core has been described, conditioning clinical prognosis (1,10). Apart from known factors influencing infarct growth before complete recanalization such as the quality of the collaterality (4,11), factors impacting infarct growth after complete recanalization are seldomly studied (10).

In this context, we aimed to determine the pretherapeutic explanatory clinico-radiological variables of infarct growth after successful recanalization. We studied a cohort of stroke patients successfully recanalized in the first 6 hours by mechanical thrombectomy for large vessel occlusion of anterior circulation.

Materials and methods

Patients and data collection

We enrolled patients admitted in mothership condition at the stroke unit of the University Hospital of Marseille (France) for an acute stroke (documented by MRI) due to a proximal occlusion of the middle cerebral artery successfully recanalized by mechanical thrombectomy within six hours of symptoms onset according to AHA guidelines (12), between January 1st,

2018 and October 31st, 2020. The success of the artery recanalization was assessed at the end of the endovascular procedure by a modified Thrombolysis In Cerebral Infarction (mTICI) score equal to 2b, 2c or 3, certified by a neuroradiologist.

Individual data were collected in the ischemic stroke registry of Marseille stroke unit. The registry includes demographic data (age, sex, past medical history), the pre-therapeutic clinico-radiological characteristics of ischemic stroke (baseline NIHSS, admission glycemia, initial MRI characteristics of ischemic stroke including Fazekas scale (13)), the therapeutic data (time to admission, time to thrombolysis IV by rt-PA, time to mechanical thrombectomy, mTICI score at the end of the mechanical thrombectomy), the clinico-radiological data at 24h (NIHSS, hemorrhagic transformation according to ECASS II classification (14)) and the neurological evaluation at 3 months (modified Rankin Scale, TOAST classification).

Stroke patients with no MRI at the admission, no CT at 24h or no mRS evaluation at 3 months follow up were excluded. Stroke patients with hemorrhagic transformation on CT, 24h after the admission, classified PH1&2 (Parenchymal Hemorrhage) according to the ECASS II classification (14) or a clinically symptomatic transformation (increase in NIHSS score of at least 4 points) were also excluded.

The research was conducted according to the principles of the Declaration of Helsinki. Ethics approval was obtained from the local institutional review board. The board waived the need for patient consent in this non-interventional study.

Analyzes of admission MRI and 24h CT-scan imaging

Pre-treatment MRI was performed using a commercially available echo planar instrument operating on a 1,5 T unit (Siemens Magnetom Sola 1,5T, Siemens 1,5T or Philips Ingenia 1,5T). The neuroimaging protocol for acute stroke in our hospital is composed of a diffusion weighted (DWI), apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery sequence (FLAIR), T2* gradient echo sequence and a time-of-flight MRA covering the circle of Willis. At 24h, a brain control imagery by CT-scan was performed to assessed final infarct volume and hemorrhagic complications classified according ECASS II classification.

Initial infarct on MRI and final infarct on CT scan were manually delineated by a single experienced neuroradiologist (QH) blinded from clinical data. Volumes (cm³) were calculated by the VOI tool of Siemens, using 2D-drawing and slice thickness.

The infarct growth (cm³) was calculated by the subtraction of the volume of the DWI hypersignal on admission MRI from the volume of final infarct on the 24h CT-scan. Because

final and initial volumes were compared for each patient individually, no normalization to whole brain volume was performed.

Statistical analysis

Continuous variables are presented adequately as the mean with standard deviation. Categorical variables are presented by absolute numbers (%). To evaluate the association between pre-therapeutic variables, radiological variables, and poor prognosis defined by mRS \geq 2 at 3 months, univariate (OR: unadjusted odd ratios) and multivariate (aOR: adjusted odd ratios) binary logistic regression models were used. A Chi-square test was used for binary variables and a t-Student test for continuous variables in univariate analysis. A threshold of $p < 0.05$ was considered as significant. The univariate analysis was completed by a multivariate analysis by using a backward stepwise logistic regression to determine independent factors associated with a poor prognosis. Variables associated with the prognosis in univariate analysis ($p < 0.1$) and the ones that were considered relevant by clinicians were included into the logistic regression model.

Linear regression model was performed to identify explanatory variables of infarct growth. In univariate analysis (β : unadjusted beta coefficient), explanatory variables which were correlated to infarct growth ($p < 0.1$) and variables considered as pertinent by clinicians were included into the linear regression model ($a\beta$: adjusted beta coefficient).

Optimal infarct growth threshold to predict clinical outcome was apprehended using a Receiver-Operating Characteristic curve (Youden Plot).

Statistical analyses were conducted using the STATA 10.0 statistical package.

Results

Characteristics of the studied population

Between January 1st, 2018 and October 31st, 2020, 617 patients were treated by mechanical thrombectomy in the Marseille stroke unit, 310 of whom (50.24%) were admitted in mothership condition. 274/310 (88.38%) had an acute proximal anterior circulation large vessel occlusion (carotid artery terminal occlusion, M1, proximal M2). After applying the inclusion and exclusion criteria, 87/617 patients (14.10%) were analyzed. (Table 1).

Characteristics of the studied population are described in Table 1. The studied population had a mean age of 68.43 ± 17.49 years and 39/87 (44.83%) were men. The mean time between onset of symptoms and hospital admission were 98.85 ± 54.85 minutes. The mean initial

NIHSS was 15.95 ± 5.38 . 24/87 (27.59%) patients had an internal carotid artery occlusion associated with a proximal middle cerebral artery occlusion. On the initial MRI (on average, achieved at 123.54 ± 55.22 min after symptoms onset), the mean hypersignal DWI volume was $15.41 \pm 16.29 \text{cm}^3$. 64/87 (73.56%) patients received IV thrombolysis before endovascular treatment (the average time between symptoms onset and rt-PA treatment was 144.34 ± 44.80 minutes). The average time for starting mechanical thrombectomy procedure after symptoms onset was 194.12 ± 56.62 minutes. At 24h, the mean NIHSS (evaluated by a neurologist) was 7.16 ± 6.18 . The average final infarct volume on 24h-CT was $15.03 \pm 32.33 \text{cm}^3$, a mean decrease of $0.39 \pm 23.08 \text{cm}^3$. 14/87 (16.09%) patients had on 24h-CT an asymptomatic hemorrhagic transformation classified HI (Hemorrhage infarction) 1 or 2, according to ECASS II classification.

At 3 months, the etiological stroke subtypes were determined using TOAST classification as follow: large vessel atherosclerosis (17/87 (19.54%)), cardioembolic origin (41/87 (47.13%)), others determined causes (3/87 (3.45%)) and undetermined causes (26/87 (29.89%)).

At 3 months, 45/87 (51.72%) had an excellent clinical outcome (mRS [0-1]) and 42/87 (48.28%) had a mRS [2-6]. 9/87 (10.34%) patients were deceased.

Pre-therapeutic variables and clinical outcome at 3 months

We performed an univariate analysis of all pretherapeutic variables to compare groups with excellent clinical outcome (mRS [0-1]) and bad clinical outcome (mRS [2-6]) (Table 1). Patients with a bad functional outcome at 3 months were more frequently diabetics (30.95% vs 8.89%; $p=0.0095$), with a higher clinical severity at admission evaluated by admission NIHSS (18.02 ± 5.04 vs 14.02 ± 4.99 ; $p=0.0004$), and a higher admission glycemia (1.47 ± 0.51 vs $1.26 \pm 0.26 \text{g/dL}$; $p=0.0221$) compared to the excellent outcome group. No statistical association was found with functional outcome for age ($p=0.0953$), time to hospital care ($p=0.7719$), time to IV thrombolysis administration ($p=0.3157$) or time to start the mechanical thrombectomy ($p=0.6904$), for an internal carotid artery occlusion ($p=0.8425$) and for initial DWI volume ($p=0.6771$).

According to methodology, patients with symptomatic hemorrhagic transformation or parenchymal hemorrhage (ECASS PH 1 & 2) were not included. No difference was found between two groups concerning hemorrhagic infarction (ECASS HI 1 & 2).

We noted that admission blood glucose was positively correlated to the diabetic history ($r=+0.57$; $p<0.0001$), in agreement with the fact that blood glucose admission was higher in diabetic patients (1.91 ± 0.57 vs 1.23 ± 0.22 ; $p<0.0001$).

The following variables were included in logistic regression model, according to methodology: age, NIHSS, diabetes and admission glycemia. The parameters independently associated with a poor functional outcome were the initial severity (NIHSS per 1 point increase: aOR: 1.16 CI 95% [1.050; 1.27]) and diabetic history (aOR: 3.70 CI 95% [1.03; 14.29]).

Evolution of the infarct volume and clinical outcome at 3 months

Then we compared the initial DWI volumes, final CT-scan volumes and infarct growth (final CT-scan volume – initial DWI volume) between patients with good (mRS [0-1]) and poor (mRS [2-6]) outcome. (Figure 1)

We found that infarct growth was significantly different between patients with good (mRS [0-1]) and poor (mRS [2-6]) outcome ($p= 0.0024$). Patients with good outcome presented a final volume on 24h-CTscan smaller than initial ischemic core on DWI (-7.82 cm^3 CI 95% [-11.17; -4.46]). On the contrary, patients with poor outcome presented a final volume on 24h-CT-scan greater than initial ischemic core on DWI ($+7.58 \text{ cm}^3$ CI95% [-1.56; +16.71]). Initial DWI volumes were not significantly different between two groups (mRS<2: 14.70 cm^3 CI95% [10.06; 19.35] and mRS \geq 2: 16.18 cm^3 [10.78; 21.57]).

The threshold of the volume of infarct growth discriminating for clinical outcome was calculated using ROC curve, at the Youden Plot. Infarct growth was a significant predictor of clinical outcome at 3 months (Area under the ROC curve: 0.701 CI 95% [0.594; 0.795]; $p=0.0003$). For a threshold of volume $\leq -1 \text{ cm}^3$ the predictive properties of an excellent outcome were: sensitivity 93.33% 95%CI [81.70; 98.50] and specificity 42.86% CI 95% [27.70; 59.00]. So, stroke patients with an increase of ischemic core after successful recanalization were associated with a higher risk of poor clinical prognosis.

Explanatory pre-therapeutic variables of infarct growth

Because infarct growth was associated with clinical prognosis, we realized a linear regression analysis to determine the pre-therapeutic variables explaining the infarct growth (Table 2). First, we measured association (unadjusted Beta coefficient) of all pretherapeutic variables with infarct growth. All following pretherapeutic variables were found significantly associated to infarct growth: diabetic history (β : 29.74 CI95% [19.03; 40.45], hbA1C (/%, β : 8.59 CI95% [4.86; 12.33], initial DWI volume (/cm³, β : 0.46 CI95% [0.18; 0.75], Fazekas score (β : 7.00 CI95% [1.16; 12.85]), NIHSS (β : 1.40 CI95% [0.52; 2.27]), admission glycemia (/g/L β : 15.02 CI95% [3.43; 26.61]). The various considered times (time to

admission, time to imaging, time to thrombolysis, time to groin puncture) were not explanatory variables of infarct growth. More, we observed that etiology subtypes according to TOAST classification were not explanatory variables of infarct growth.

Among these explanatory variables, only diabetic history (adjusted β : 21.26 CI95% [5.43; 37.09]) and NIHSS (adjusted β : 0.83 CI95% [0.02; 1.64]) were significantly associated to infarct growth after adjustment

We studied imaging parameters according to diabetes history (Figure 2). The diabetic patients compared to non-diabetic ones do not have significantly different initial DWI volume (21.55 ± 24.17 vs $13.92 \pm 13.56 \text{cm}^3$; $p=0.2254$), but the infarct growth ($+23.54 \pm 38.61$ vs $-6.20 \pm 11.97 \text{cm}^3$; $p=0.0061$) and final volumes (45.09 ± 61.57 vs $7.72 \pm 12.10 \text{cm}^3$; $p=0.0239$) were significantly higher.

Discussion

We demonstrated that diabetic history is an independent growth factor of ischemic core during the reperfusion phase leading to a poor functional outcome in patients successfully recanalized by bridging therapy in the six hours from stroke onset. Indeed, in stroke patients treated by mechanical thrombectomy for proximal middle cerebral artery occlusion, poor clinical outcome at 3 months was determined by diabetes history and continued growth of ischemic core despite the success of the recanalization. Originally, diabetes history was found in our study as a strong independent factor of the continued growth of ischemic core between pre-treatment MRI and control CT-scan at 24 hours supporting its deleterious role on reperfusion phase. If numerous reports propose clinical predictors of stroke clinical outcome in stroke patients treated by bridging therapy, we provide original data from clinico-radiological study allowing to associate the influence of these predictors on infarct growth.

Interestingly, we demonstrated in this cohort of stroke early recanalized patients by mechanical thrombectomy, that infarct growth during reperfusion phase (Area under the ROC curve: 0.701 CI 95% [0.594; 0.795]) was a predictive factor of clinical prognosis, while initial DWI volume is not. According AHA guidelines (12), stroke patients with symptomatic proximal middle cerebral artery occlusion treated by bridging therapy in six first hours from stroke onset were selected on the presence of ischemic penumbra. In this context, the presence of ischemic penumbra was apprehended by clinico-radiological evaluation associating clinical gravity (NIHSS \geq 6) and small ischemic core (ASPECTS \geq 6). So, in these selected stroke patients, initial DWI volume was not identified in the literature, nor in our study, as a predictor of clinical outcome (8). We found that continued infarct growth after

complete recanalization during reperfusion was significantly associated to worse prognosis according to literature (10). On the other hand, none, or negative infarct growth interpreting as the DWI initial regression (reversible ischemic core) after complete recanalization, was significantly associated to a good clinical outcome, as reported in previous studies (15,16).

In this study, diabetes history was found to be an independent predictor of poor clinical outcome (aOR: 3.70 CI 95% [1.03; 14.29]) and an independent growth factor of ischemic core during the reperfusion ($\alpha\beta$: 21.26 CI 95% [5.43; 37.09]). Because we found that continued infarct growth was associated to clinical prognosis, our results support that diabetes history leads to poor clinical outcome in recanalized stroke patients due to its deleterious effect on infarct growth during reperfusion (17,18). Because admission hyperglycemia is classically associated to poor clinical prognosis in ischemic stroke independently of diabetes status (17–23), our results obtained in this studied population of recanalized stroke patients are discussed. The underlying mechanisms of the deleterious effect of admission hyperglycemia remain unclear and could be mediated by diabetes status (17–19). Our results argue for the hypothesis that deleterious effects on infarct growth, and consequently on the clinical outcome, were mediated by the chronic metabolic disease and not acute hyperglycemia due to diabetes. First, diabetes history was found independent of admission hyperglycemia in multivariate analysis. Stress hyperglycemia in acute stroke was determined by diabetic status supporting by the strong correlation between admission hyperglycemia and diabetes history ($r=+0.59$). In our study, only two de novo diabetic patients were diagnosed at the end of the hospitalization in stroke unit. In most studies, considering diabetes status only based on medical history could be a methodological bias and could explain this ambiguity in results. Second, in stroke patients with diabetes history, 41% had a good long term glycemic control evaluated by $HbA1c \leq 7\%$ suggesting that deleterious effect on clinical prognosis and infarct growth was mediated by the chronic metabolic disease and not its acute control. Third, we found that cerebral microangiopathy quantified by Fazekas scale (13) was related to infarct growth in univariate analysis suggesting that the deleterious effect of diabetes was a consequence of chronic disease and not a consequence of admission hyperglycemia mediated by metabolic disease (24–26). Fourth, according to our results, chronic diabetes as a predictor of clinical outcome and infarct growth could support the failure of insulin therapy to improve the functional prognosis in acute phase (27,28).

We hypothesize that cerebral microangiopathy mediated by diabetes leads to poor tissular reperfusion after arterial recanalization (24–26). Vessel diameter is a major determinant of infarct growth. We assume that underlying mechanisms of cerebral microvascular damages of

diabetes might explain poor tissular reperfusion. This hypothesis is supported by the significant association between Fazekas scale and infarct growth. In literature, white matter hyperintensities, lacunes, cerebral microbleeds, perivascular spaces, cerebral atrophy, and microinfarcts are considered to be witness of structural microangiopathy associated with diabetes (29). Microvessel diameter reduction in diabetes is also due to arterial vasoreactivity dysfunction, caused by biochemical phenomena involving a disruption of regulatory systems (prostaglandins, nitric oxide) in diabetic patients (18,26,30). Despite arterial recanalization, diabetes could limit the reperfusion by an alteration in the caliber of the microcirculation in relation to the diabetic microangiopathy. Also, it is known that baseline cerebral blood flow is altered in diabetic patients, which could impact efficiency of reperfusion (29). Moreover, diabetes could be responsible of direct reperfusion lesions in hyperglycemic environment, related to the oxidative stress mediated by recanalization providing oxygen and glucose in an inadequate quantity for ischemia-related mitochondrial inertia (18). Another mechanism of infarct growth could be diabetes-linked chronic energetic failure, caused by mitochondrial dysfunction, enhanced by the cerebral vessel occlusion, similar to a negative preconditioning to cerebral ischemia (31).

This study has several limitations as its retrospective nature and the final volume calculated on a CT at 24h. A control MRI would have been beneficial to minimize the risk of contouring error of the ischemic lesion. Moreover, the difference between the thickness of slice of brain on CT-scan and size of voxel on brain MRI is a source of effect of partial volume and may disrupt the results. However, in order to minimize this risk, the analysis of ischemic lesion on CT was realized by the same experienced neuroradiologist blinded from clinical data. As this method was applied for the whole study population, this problem should not affect the result of the statistical analysis.

Conclusions

Originally, we conclude that diabetes leads to continued infarct growth after complete recanalization, influencing the clinical outcome. Poor tissular reperfusion by microangiopathic status could explain this result. We conjecture that alteration in the caliber of the microcirculation, alteration of arterial vasoreactivity or reperfusion lesion in hyperglycemic context might be at the origin of the deleterious effect of this chronic metabolic disease. This conclusion could explain the failure of ischemic stroke

neuroprotection targeting only admission hyperglycemia. In perspective, our results need to be supported by subsequent studies, focusing on impact of severity and duration of diabetes.

References

1. Yoo AJ, Chaudhry ZA, Nogueira RG, *et al.* Infarct Volume Is a Pivotal Biomarker After Intra-Arterial Stroke Therapy. *Stroke* 2012;43:1323-1330
2. Zaidi SF, Aghaebrahim A, Urra X, *et al.* Final Infarct Volume Is a Stronger Predictor of Outcome Than Recanalization in Patients With Proximal Middle Cerebral Artery Occlusion Treated With Endovascular Therapy. *Stroke* 2012;43:3238-3244.
3. Ribo M, Flores A, Mansilla E, *et al.* Age-adjusted infarct volume threshold for good outcome after endovascular treatment. *J NeuroIntervent Surg* 2014;6:418-422.
4. Jiang B, Ball RL, Michel P, *et al.* Factors influencing infarct growth including collateral status assessed using computed tomography in acute stroke patients with large artery occlusion. *International Journal of Stroke* 2019;14:603-612.
5. Cho T-H, Nighoghossian N, Mikkelsen IK, *et al.* Reperfusion Within 6 Hours Outperforms Recanalization in Predicting Penumbra Salvage, Lesion Growth, Final Infarct, and Clinical Outcome. *Stroke* 2015;46:1582-1589.
6. Goyal M, Menon BK, van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *The Lancet* 2016;387:1723-1731.
7. Maas MB, Kapinos G. Recanalization for large vessel stroke: Necessary but not sufficient for reperfusion. *Neurology* 2019;92:1127-1128.
8. van de Graaf RA, Samuels N, Chalos V, *et al.* Predictors of poor outcome despite successful endovascular treatment for ischemic stroke: results from the MR CLEAN Registry. *J NeuroIntervent Surg* 2021
9. Campbell BC, Purushotham A, Christensen S, *et al.* The Infarct Core is Well Represented by the Acute Diffusion Lesion: Sustained Reversal is Infrequent. *J Cereb Blood Flow Metab* 2012;32:50-56.
10. Man S, Aoki J, Hussain MS, *et al.* Predictors of Infarct Growth after Endovascular Therapy for Acute Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases* 2015;24:401-407.
11. Rocha M, Jovin TG. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke: Clinical and Research Implications. *Stroke* 2017;48:2621-2627.
12. Powers WJ, Rabinstein AA, Ackerson T, *et al.* Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early

- Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association *Stroke* 2019;50:e440-e441
13. Fazekas F, Chawluk J, Alavi A, *et al.* MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *American Journal of Roentgenology* 1987;149:351-356.
 14. Hacke W, Kaste M, Fieschi C, *et al.* Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *The Lancet* 1998;352:1245-1251.
 15. Yoo J, Choi JW, Lee S-J, *et al.* Ischemic Diffusion Lesion Reversal After Endovascular Treatment: Prevalence, Prognosis, and Predictors. *Stroke* 2019;50:1504-1509.
 16. Nagaraja N, Forder JR, Warach S, *et al.* Reversible diffusion-weighted imaging lesions in acute ischemic stroke: A systematic review. *Neurology* 2020;94:571-587.
 17. Kruyt ND, Biessels GJ, DeVries JH, *et al.* Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol* 2010;6:145-155.
 18. Luitse MJ, Biessels GJ, Rutten GE, *et al.* Diabetes, hyperglycaemia, and acute ischaemic stroke. *The Lancet Neurology* 2012;11:261-271.
 19. Piironen K, Putaala J, Rosso C, *et al.* Glucose and Acute Stroke: Evidence for an Interlude. *Stroke* 2012;43:898-902.
 20. Wang H, Zhang M, Hao Y, *et al.* Early Prediction of Poor Outcome Despite Successful Recanalization After Endovascular Treatment for Anterior Large Vessel Occlusion Stroke. *World Neurosurgery* 2018;115:e312-321.
 21. Wahlgren N, Ahmed N, Eriksson N, *et al.* Multivariable Analysis of Outcome Predictors and Adjustment of Main Outcome Results to Baseline Data Profile in Randomized Controlled Trials: Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). *Stroke* 2008;39:3316-3322.
 22. Goyal N, Tsivgoulis G, Pandhi A, *et al.* Admission hyperglycemia and outcomes in large vessel occlusion strokes treated with mechanical thrombectomy. *J NeuroIntervent Surg* 2018;10:112-117.
 23. Chamorro Á, Brown S, Amaro S, *et al.* Glucose Modifies the Effect of Endovascular Thrombectomy in Patients With Acute Stroke: A Pooled-Data Meta-Analysis. *Stroke* 2019;50:690-696.
 24. Ay H, Arsava EM, Rosand J, *et al.* Severity of Leukoaraiosis and Susceptibility to Infarct Growth in Acute Stroke. *Stroke* 2008;39:1409-1413.
 25. Henninger N, Lin E, Haussen DC, *et al.* Leukoaraiosis and Sex Predict the Hyperacute Ischemic Core Volume. *Stroke* 2013;44:61-67.

26. Poittevin M, Bonnin P, Pimpie C, *et al.* Diabetic Microangiopathy: Impact of Impaired Cerebral Vasoreactivity and Delayed Angiogenesis After Permanent Middle Cerebral Artery Occlusion on Stroke Damage and Cerebral Repair in Mice. *Diabetes* 2015;64:999-1010.
27. Bellolio MF, Gilmore RM, Ganti L. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Stroke Group, éditeur Cochrane Database of Systematic Reviews 2011
28. Ntaios G, Papavasileiou V, Bargiota A, *et al.* Intravenous Insulin Treatment in Acute Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International Journal of Stroke* 2014;9:489-493.
29. van Sloten TT, Sedaghat S, Carnethon MR, *et al.* Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *The Lancet Diabetes & Endocrinology* 2020;8:325-336.
30. Purkayastha S, Fadar O, Mehregan A, *et al.* Impaired Cerebrovascular Hemodynamics are Associated with Cerebral White Matter Damage. *J Cereb Blood Flow Metab* 2014;34:228-234.
31. Kwak SH, Park KS, Lee K-U, *et al.* Mitochondrial metabolism and diabetes: Mitochondria and diabetes. *Journal of Diabetes Investigation* 2010;1:161-169.

Tables

Table 1: Baseline characteristics of studied population

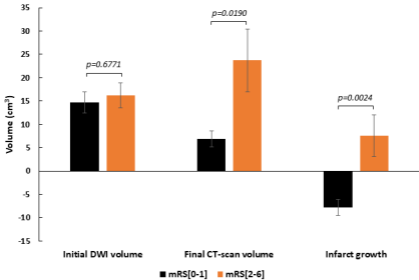
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

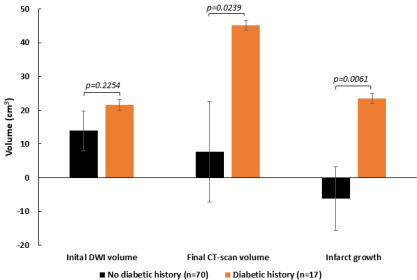
Table 2: Linear regression models of infarct growth.

Figures legends

Figure 1: Initial DWI volume, final CT scan volume and infarct growth (cm³) according to clinical outcome

Figure 2: Initial DWI volume, final CT scan volume and infarct growth (cm³) according to diabetic history





	All n=87	mRS [0-1] at 3 months n=45 (51.72%)	mRS [2-6] at 3 months n=42 (48.28%)	<i>p</i>
Demographic characteristics				
Age (years)	68.43±17.49	65.87±14.50	71.17±14.78	0.0953
Men	39 (44.83%)	19 (42.22%)	20 (47.62%)	0.6130
Medical History				
High Blood Pressure	47 (54.02%)	24 (53.33%)	23 (54.76%)	0.8937
Diabetic history	** 17 (19.54%)	4 (8.89%)	13 (30.95%)	0.0095
HbA1c (%)	6.11±1.18	5.86±0.66	6.39±1.55	0.0400
Dyslipidemia	33 (37.93%)	16 (35.56%)	17 (40.48%)	0.6364
Current Smoker	16 (18.39%)	8 (17.78%)	8 (19.05%)	0.8786
Atrial Fibrillation	18 (20.69%)	9 (20.00%)	9 (21.43%)	0.8694
Stroke/TIA	19 (21.84%)	10 (22.22%)	9 (21.43%)	0.9287
Coronaropathy	9 (10.34%)	4 (8.89%)	5 (11.90%)	0.6444
Vascular peripheral disease	3 (3.45%)	2 (4.44%)	1 (2.38%)	0.5981
Obesity	13 (14.94%)	8 (17.78%)	5 (11.90%)	0.4426
Treatments at admission				
Antithrombotic	37 (42.53%)	17 (37.78%)	20 (47.62%)	0.3535
Statin	22 (25.29%)	11 (24.44%)	11 (26.19%)	0.8515
Initial MRI characteristics				
Internal carotid occlusion	24 (27.59%)	12 (26.67%)	12 (28.57%)	0.8425
Initial DWI MRI volume (cm ³)	15.41±16.29	14.70±15.46	16.18±17.30	0.6771
Fazekas scale	1.25±1.08	1.16±0.12	1.36±0.88	0.2567
Clinical characteristics				
Initial NIHSS	*** 15.95±5.38	14.02±4.99	18.02±5.04	0.0004
Systolic Blood Pressure (mmHg)	149.63±25.94	148.00±27.09	151.29±4.23	0.5667
Diastolic Blood Pressure (mmHg)	82.08±15.31	81.62±13.03	82.56±17.48	0.7820
Cardiac frequency (bpm)	80.10±16.69	79.25±15.61	80.94±17.89	0.6698
Admission glycemia (g/dL)	* 1.36±0.41	1.26±0.26	1.47±0.51	0.0221
Treatments characteristics				
Time to admission (min)	98.85±54.85	97.14±8.76	100.63±8.23	0.7719
Time to initial MRI (min)	123.54±55.22	122.18±59.11	125.00±51.41	0.8124
Time to rtPA (min)	144.34±44.80	138.94±39.67	150.47±49.98	0.3157
Time to groin puncture (min)	194.12±56.62	191.42±59.38	196.76±54.50	0.6904
IV rt-PA treatment	64 (73.56%)	34 (75.56%)	30 (71.43%)	0.6627

Table 1: Baseline characteristics of studied population

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

	Non adjusted Beta [CI 95%]	<i>p</i>	Adjusted Beta [CI 95%]	<i>p</i>
Demographic characteristics				
Age (per one year)	0.13 [-0.21; 0.47]	0.444	-0.03 [-0.40; 0.33]	0.852
Men	4.43 [-5.47; 14.34]	0.376		
Medical History				
High Blood Pressure	5.57 [-4.28; 15.14]	0.264		
Diabetes	29.74 [19.03; 40.45]	<0.0001	21.26 [5.43; 37.09]	0.009
HbA1C (%)	8.59 [4.86; 12.33]	<0.0001	3.82 [-1.13; 8.76]	0.129
Dyslipidemia	- 1.05 [-11.25; 9.15]	0.838		
Current smoker	-6.90 [-19.59; 5.79]	0.283		
Atrial fibrillation	-3.30 [-15.50; 8.90]	0.592		
Stroke/TIA	1.94 [-10.04; 13.91]	0.749		
Coronaropathy	12.04 [-4.00; 28.09]	0.139		
Vascular peripheral disease	5.79 [-21.31; 32.89]	0.672		
Obesity	-6.64 [-20.45; 7.17]	0.342		
Treatments at admission				
Antithrombotic therapy	3.87 [-6.11; 13.85]	0.443		
Statin	2.34 [-9.04; 13.71]	0.684		
Initial MRI characteristics				
Carotid artery occlusion	-2.53 [-13.59; 8.53]	0.650		
Initial DWI MRI volume (cm ³)	0.46 [0.18; 0.75]	0.002	0.25 [-0.03; 0.53]	0.078
Fazekas scale	7.00 [1.16; 12.85]	0.019	3.92 [-2.27; 1.12]	0.211
Clinical characteristics				
Initial NIHSS	1.40 [0.52; 2.27]	0.002	0.83 [0.02; 1.64]	0.045
Systolic Blood Pressure (mmHg)	0.07 [-0.13; 0.27]	0.479		
Diastolic Blood Pressure (mmHg)	0.25 [-0.08; 0.58]	0.136		
Cardiac frequency (bpm)	0.04 [-0.30; 0.39]	0.813		
Admission glycemia (g/dl)	15.02 [3.43; 26.61]	0.012	-10.16 [-27.11; 6.80]	0.237
Treatments characteristics				
Time to admission (min)	-0.08 [-0.17; 0.01]	0.085		
Time to initial MRI (min)	-0.07 [-0.16; 0.02]	0.134		
Time to rtPA (min)	0.04 [-0.04; 0.12]	0.451		
Time to groin puncture (min)	-0.05 [-0.15; 0.05]	0.298		
IV rt-PA treatment	-8.99 [-20.05; 2.06]	0.110		

Table 2: Linear regression models of infarct growth.